

Research paper

Sustained anterior cingulate cortex activation during reward processing predicts response to psychotherapy in major depressive disorder



Hannah Carl^a, Erin Walsh^b, Tory Eisenlohr-Moul^c, Jared Minkel^{c,d}, Andrew Crowther^e, Tyler Moore^c, Devin Gibbs^c, Chris Petty^f, Josh Bizzell^{c,f,g}, Gabriel S. Dichter^{c,d,e,f,g,*}, Moria J. Smoski^{a,d}

^a Department of Psychology & Neuroscience, Duke University, Durham, NC 27710, USA

^b Program on Integrative Medicine, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC 27599, USA

^c Department of Psychiatry, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC 27599, USA

^d Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham NC 27710, USA

^e UNC Neurobiology Curriculum, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC 27599, USA

^f Duke-UNC Brain Imaging and Analysis Center, Duke University Medical Center, Durham, NC 27710, USA

^g Carolina Institute for Developmental Disabilities, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC 27599, USA

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ABSTRACT

Background: The purpose of the present investigation was to evaluate whether pre-treatment neural activation in response to rewards is a predictor of clinical response to Behavioral Activation Therapy for Depression (BATD), an empirically validated psychotherapy that decreases depressive symptoms by increasing engagement with rewarding stimuli and reducing avoidance behaviors. **Methods:** Participants were 33 outpatients with major depressive disorder (MDD) and 20 matched controls. We examined group differences in activation, and the capacity to sustain activation, across task runs using functional magnetic resonance imaging (fMRI) and the monetary incentive delay (MID) task. Hierarchical linear modeling was used to investigate whether pre-treatment neural responses predicted change in depressive symptoms over the course of BATD treatment. **Result:** MDD and Control groups differed in sustained activation during reward outcomes in the right nucleus accumbens, such that the MDD group experienced a significant decrease in activation in this region from the first to second task run relative to controls. Pretreatment anhedonia severity and pretreatment task-related reaction times were predictive of response to treatment. Furthermore, sustained activation in the anterior cingulate cortex during reward outcomes predicted response to psychotherapy; patients with greater sustained activation in this region were more responsive to BATD treatment. **Limitation:** The current study only included a single treatment condition, thus it unknown whether these predictors of treatment response are specific to BATD or psychotherapy in general. **Conclusion:** Findings add to the growing body of literature suggesting that the capacity to sustain neural responses to rewards may be a critical endophenotype of MDD.

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1. Introduction

A defining symptom of MDD is anhedonia, the loss of interest or pleasure in previously rewarding activities (American Psychiatric Association, 2013). Major depressive disorder is characterized by decreased responsiveness to rewarding stimuli, including decreased anticipation of forthcoming rewards, reduced pleasure

derived from reward presentation, and impaired reward-based learning (Admon and Pizzagalli, 2015; Der-Avakian and Markou, 2012). Anhedonia may be more universally endorsed than other MDD symptoms (Hamilton, 1989) and is associated with risk for future depressive episodes (Wardenaar et al., 2012), a more chronic illness course (Moos and Cronkite, 1999; Spijker et al., 2001), and poorer treatment response to both pharmacologic (McMakin et al., 2012) and neurostimulation (Downar et al., 2014) interventions.

Functional neuroimaging studies have revealed that anhedonia is characterized by decreased responsiveness of mesocorticolimbic

* Corresponding author at: Department of Psychiatry University of North Carolina at Chapel Hill School of Medicine, CB 7155, Chapel Hill, NC 27599-7155, USA.

E-mail address: dichter@med.unc.edu (G.S. Dichter).

reward processing brain circuitry, including the dorsal and ventral striatum, and ventral lateral and midline prefrontal cortical areas (Dichter et al., 2012a; Stein, 2008; Zhang et al., 2013). This general pattern has been found in adolescent (Forbes et al., 2009; Gabbay et al., 2013) and adult populations (Epstein et al., 2006; Pizzagalli et al., 2009; Smoski et al., 2009) as well as in unipolar and bipolar presentations of MDD (Redlich et al., 2015), and is evident in remitted patients with a history of MDD (Dichter et al., 2012b; Schiller et al., 2013).

Altered functioning of the anterior cingulate cortex (ACC) in particular, which plays a central role in detecting the salience of external stimuli and in reward feedback monitoring (Seeley et al., 2007; Whitton et al., 2016), has been observed in patients with MDD during reward processing tasks (Diener et al., 2012; Knutson et al., 2008; Uhl et al., 2015; Yang et al., 2016). There is evidence of decreased functional connectivity between the ACC and the middle frontal gyrus (Wu et al. (2016)), the caudate (Admon et al., 2015), and dorsolateral and ventrolateral prefrontal cortices (Alexopoulos et al., 2013) in MDD. Further, a meta-analysis by Fu et al. (2013) found that increased pretreatment ACC activation was associated with response to a range of pharmacologic and cognitive interventions for MDD, highlighting the relevance of ACC functioning in MDD to understanding not only MDD pathophysiology but also to developing predictive models of antidepressant treatment response.

Given the centrality of anhedonia and reward processing deficits to MDD, responses to rewards may be promising endophenotypes to understand not only the pathophysiology of MDD, but also biomarkers of response to antidepressant treatments (Dichter et al., 2009; Lammers et al., 2000; Vrieze et al., 2013). Therefore, the purpose of this study was to investigate whether pretreatment neural responses to rewards are predictive of response to Behavioral Activation Treatment for Depression (BATD) psychotherapy using functional magnetic resonance imaging (fMRI). This intervention was originally developed to ameliorate symptoms of MDD by promoting interactions with potentially positive reinforcers and inhibiting avoidance behaviors as well as supporting sustained interaction with potentially rewarding activities (Hopko et al., 2003; Jacobson et al., 2001).

When considering the literature addressing reward processing in MDD, it is important to note that not all neuroimaging studies have consistently reported decreased neural response to rewards in MDD (Harvey et al., 2007; Knutson et al., 2008; Mitterschiffthaler et al., 2003; Schaefer et al., 2006). One recent conceptualization of hedonic capacity in MDD that potentially addresses such inconsistencies is that MDD may be characterized by decreased capacity to sustain response to rewards over time (Pizzagalli et al., 2008). In support of this framework, a recent emotion regulation study reported that participants with MDD demonstrated decreased capacity to sustain nucleus accumbens (NAcc) activity during conscious upregulation of positive emotions across the scan session (Heller et al., 2009). Furthermore, the degree of decrease in NAcc activity predicted the magnitude of self-reported positive affect in the MDD sample. In a follow-up study, Heller et al. (2013) reported that the magnitude of change in positive affect following two months of treatment with fluoxetine or venlafaxine was associated with sustained activation of the NAcc during upregulation of positive emotions.

Given that the capacity to sustain response to rewards may be a critical endophenotype of MDD, the present investigation examined whether overall neural activation, as well as the capacity to sustain neural activation in response to rewards predicted clinical response to BATD. We used the monetary incentive delay task (MID) because this reward task reliably elicits mesocorticolimbic activation and allows for dissociation of responses during reward anticipation and outcomes (Keedwell et al., 2005;

Mitterschiffthaler et al., 2003; Pizzagalli et al., 2005). By presenting two runs of the MID task, we were able to evaluate changes in neural activation from the first task run to the second task run as a potential predictor of response to BATD. Because previous investigations have shown linkages between anhedonia in MDD and decreased activation of the striatum (e.g., Pizzagalli et al., 2009; Stoy et al., 2012), we predicted that the capacity to sustain striatal activation would predict the magnitude of clinical response to BATD, with a particular emphasis on declines in symptoms of anhedonia. We are reporting results of connectivity analyses from this sample separately (Walsh et al. submitted for publication), and thus here we focus on analyses of task-based activation as a predictor of treatment response.

2. Materials and methods

2.1. Overview

The study protocol was approved by the Institutional Review Boards at Duke University Medical Center and the University of North Carolina at Chapel Hill, and all enrolled participants provided written informed consent. Participants with MDD were recruited via the Cognitive Behavioral Research and Treatment Program at Duke University Medical Center and nondepressed control participants were recruited via listservs at Duke University and UNC-Chapel Hill. Potential participants completed an initial brief phone screen, and those who passed the phone screen were clinically evaluated, including administration of the structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID; First et al., 2002) to assess for Axis I disorders, and completed the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) and Beck Depression Inventory-II (BDI; Beck et al., 1996). If still eligible, they were invited to participate in the MRI scan session. Participants with MDD then began psychotherapy. HAM-D scores were used to verify inclusion criteria, but only BDI scores are used in analyses. After their fMRI scans, MDD outpatients received an average of 11.67 (SD=4.40; range: 2–15) weekly sessions of Brief Behavioral Activation Treatment for Depression (BATD). Up to 15 sessions of BATD were offered. Early responders were given the option to end therapy after eight sessions and non-responders received the maximum number of sessions before being referred to the community for additional treatment.

2.2. Participants

Participants in the MDD group met DSM-IV criteria for a current episode of MDD and scored 15 or above on the HAM-D. Participants in the control group scored six or lower on the HAM-D and did not meet criteria for a current Axis I disorder or lifetime episode of a mood disorder. Exclusion criteria included: 1) In the MDD group: current mood, anxiety, psychotic, or substance abuse disorder beyond unipolar MDD or dysthymia, 2) history of psychosis or mania; 3) active suicidal ideation, 4) evidence of organicity, 5) magnetic resonance imaging contraindication (e.g., metal in body), 7) history of neurological injury or disease, and 8) current pregnancy.

Participants were paid for participating in the clinical assessment and neuroimaging sessions. Thirty-eight outpatients with MDD (11 male; mean (SD) age=33 (7.1)) and twenty matched controls (6 male; mean (SD) age=31 (8.8)) enrolled in the study. Two MDD participants did not return for psychotherapy after the first imaging session and were therefore excluded from all analyses since the objective of this study was to predict treatment response. Additionally, three MDD subjects taking psychoactive medications were excluded from analyses. Thus, the final sample

Table 1
Participant characteristics.

	MDD N=33		Con N=20		p
	Mean (SD)	Range	Mean (SD)	Range	
Sex (M/F)	11/22		6/14		.803
Age (yrs)	33.2 (6.5)	21–45	31.1 (8.82)	20–44	.315
NAART	111.28 (4.83)	99.2–117.3	112.03 (3.83)	102.6–118.1	.558
Pre-treatment BDI	25.27 (8.52)	9–44	1.1 (1.65)	0–5	< .0001
Previous Major Depressive Episodes	2.97 (1.79)	1–7	0	0	–
Duration Current Episode (months)	36.03 (77.82)	1–384	–	–	–

was 33 outpatients with MDD and 20 non-depressed control participants. Groups did not differ in age, estimated IQ (measured by the North American Adult Reading Test (Blair and Spreen, 1989; NAART), or gender distribution, p 's > .32 (see Table 1 for participant characteristics).

2.3. Monetary incentive delay (MID) fMRI task

Participants practiced the fMRI task outside the scanner prior to the scan session. During this practice session, participant-specific average reaction times were recorded and used to adjust target reaction times during the scan sessions. Each trial consisted of: (1) a 2000 ms cue that indicated whether a fast enough response (a “hit”) to the forthcoming target bulls-eye could result in a “reward” (a triangle) or “no reward” (a circle); (2) a delay period during which a crosshair was presented for 2000–2500 ms; (3) a target bulls-eye that required a speeded button press presented for up to 500 ms; (4) 3000 ms of feedback that indicated whether that trial resulted in a “reward” or not; and (5) a variable length ITI crosshair presented such that the total duration of each trial was 12 s. Trial types (i.e., potential reward or not) were aperiodic and pseudorandomly ordered (Knutson et al., 2000). Participants could win \$2 per trial, and feedback displayed the amount of money won on a given trial (e.g., “+\$2”). Coincident with this feedback, a cumulative count of the number of dollars won within the run was presented. Participants were instructed to respond to all target bulls-eyes as quickly as possible, and outcomes were contingent on reaction times. The task was adaptive such that participants were successful on approximately two-thirds of trials, regardless of individual differences in reaction times. Each 8-min run contained 40 trials: 20 were potential reward trials, 20 were non-reward trials. The top of Fig. 1 illustrates the MID task condition.

Each participant completed two functional imaging runs and reaction times were recorded as a behavioral index of motivation. Stimuli were presented using E-Prime presentation software v.1.1 (Psychology Software Tools Inc. Pittsburgh, PA) and displayed in the scanner through magnet-compatible goggles (Resonance Technology, Inc., Northridge, CA).

2.4. Brief Behavioral Activation Treatment for Depression (BATD)

As described previously, behavioral activation treatments have gained increasing interest since Jacobson et al. (1996) critical study of cognitive behavioral therapy in which behavioral activation proved equally effective as cognitive therapy in relieving symptoms of depression. At follow-up, behavioral activation appeared as effective as cognitive therapy in preventing relapse (Gortner et al., 1998), and a subsequent large-scale randomized trial found

that behavioral activation psychotherapy was equivalent to paroxetine in reducing symptoms in moderately to severely depressed individuals (Dimidjian et al., 2006). In parallel, Lejuez and Hopko developed Brief Behavioral Activation Treatment for Depression (BATD) (Lejuez et al., 2001). Although similar to previous behavioral activation approaches, BATD is unique in that it is shorter than traditional treatments (only 8–15 sessions) and does not require as extensive skills on the part of the therapist or the patient (Hopko et al., 2003). Treatment proceeds through a series of structured units that a) educate subjects about MDD and provide a rationale for the treatment approach; b) assess and monitor baseline activity levels; c) develop individualized goals according to subjects' values and initiate a multi-layered plan to achieve these goals; and d) monitor, support, and encourage accomplishing behavioral goals. BATD effectively reduces MDD symptoms and is well-tolerated in both outpatient (Hopko et al., 2005; Lejuez et al., 2001) and inpatient (Hopko et al., 2003) settings.

2.5. Treatment outcome measures

Treatment outcomes in the MDD group were evaluated by the Beck Depression Inventory-II (BDI; Beck et al., 1996), which was collected at the scan session, every two weeks during treatment, and at the last psychotherapy session. BDI scores of 0–13 indicate minimal MDD severity, 14–19 indicates mild MDD severity, 20–28 indicates moderate MDD severity, and 29–63 indicates severe MDD severity (Beck et al., 1996). The BDI provides an overall measure of MDD severity and includes items that tap multiple MDD symptom dimensions. We examined BDI total scores as well as BDI anhedonia subscale scores, derived from items 4, 12, 15, and 21 (Joiner et al., 2003).

2.6. Imaging methods

Functional images were acquired at the Duke-UNC Brain Imaging and Analysis Center (BIAC) on a General Electric (Waukesha, WI, USA) MR750 3.0 T scanner equipped with 50 mT/m gradients (200 T/m/s slew rate) and an 8-channel head coil for parallel imaging. High resolution T1-weighted anatomical images were acquired with 162 axial slices using a FSPGR pulse sequence (TR=7.584 ms; TE=2.936 ms; FOV=256 mm; image matrix=256 × 256; voxel size=1 × 1 × 1 mm; flip angle = 12°) and used for normalization and coregistration with the functional data. This structural image was aligned in a near axial plane defined by the anterior and posterior commissures. Whole-brain functional images were acquired using a spiral-in SENSE sequence (TR = 1500 ms; TE=30 ms; FOV=240 mm; image matrix, 64 × 64; flip angle=60°; voxel size, 3.75 × 3.75 × 4.0 mm; 34 axial slices) to reduce susceptibility artifacts and recover signal in orbital frontal regions (Pruessmann et al., 2001; Truong and Song, 2008). A semi-automated high-order shimming program ensured global field homogeneity.

2.7. Imaging data preprocessing

The first four volumes of each functional imaging dataset were discarded to allow for magnetic field stabilization. Data were preprocessed using FSL version 5.0.1 (Oxford Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Oxford University, U. K.). Timing files were converted to FSL compatible format and NIFTI image data files were generated. Preprocessing was applied in the following steps: (i) brain extraction for non-brain removal (Smith et al., 2004), (ii) motion correction using MCFLIRT (Smith, 2002), (iii) spatial smoothing using a Gaussian kernel of FWHM 5 mm, (iv) mean-based intensity normalization of all volumes by the same factor, and (v) high-pass filtering (Jenkinson

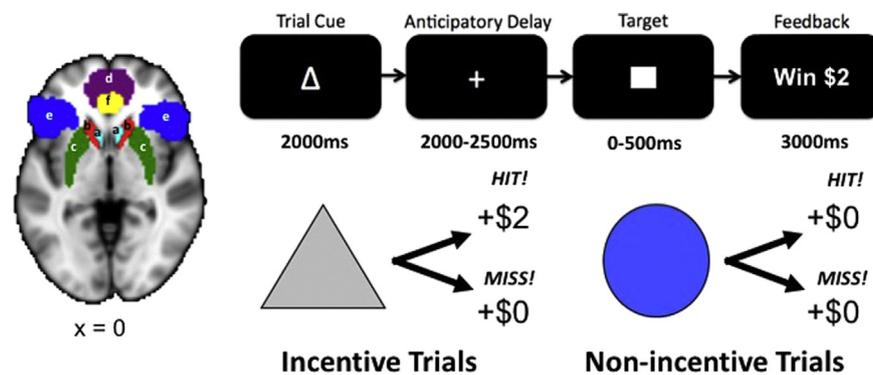


Fig. 1. **Left:** ROIs from Harvard-Oxford subcortical and cortical structural probabilistic atlases. a) Nucleus accumbens: light blue; b) caudate: red; c) putamen: green; d) frontal medial cortex: purple; e) orbitofrontal cortex: dark blue; f) anterior cingulate cortex: yellow. **Right:** The monetary incentive delay (MID) task presents a cue indicating whether money can be won, followed by an *anticipatory* phase, then a target, and feedback indicating whether or not money was won. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

et al., 2002). Functional images of each participant were co-registered to structural images in native space, and structural images were normalized into a standard stereotaxic space (Montreal Neurological Institute) for intersubject comparison. The same transformation matrices used for structural-to-standard transformations were then used for functional-to-standard space transformations of co-registered functional images. All registrations were carried out using an intermodal registration tool (Jenkinson et al., 2002; Smith et al., 2004). Voxel-wise temporal auto-correlation was estimated and corrected using FMRIB's Improved Linear Model (FILM; (Jenkinson and Smith, 2001)).

2.8. Regions of interest

Activation analyses used a region-of-interest (ROI) approach to target canonical reward processing regions. ROI's were the NAcc, caudate nucleus, putamen, frontal medial cortex, orbitofrontal cortex, and anterior cingulate cortex (including both rostral and dorsal subdivisions). These ROIs were defined using the Harvard-Oxford subcortical and cortical structural probabilistic atlases. Frontal medial cortex and anterior cingulate cortex were divided into left and right hemispheric regions using a custom MATLAB script. Additionally, a striatum ROI was constructed by combining the caudate nucleus, putamen, and NAcc masks. Results of whole-brain analyses are provided as Supplementary Materials.

2.9. fMRI data analysis

For each ROI and participant, condition- and run-specific mean parameter estimates reflecting activation were calculated and extracted using the Featquery tool within FSL separately for anticipation and outcome phases of the MID task. For the anticipation phase, the contrast of interest was potential win versus non-win trials; for the outcome phase, the contrast of interest was wins versus non-wins. Parameter estimates (reflecting activation intensity) were then analyzed via Group (MDD, Control) \times Run (run 1, run 2) repeated measures ANOVAs conducted for each ROI (main effects of Group derived from these models were used to evaluate whether groups differed in the overall level of activation, regardless of differences between runs). ROI's with significant Group \times Run interaction effects as well as significant decrease in activation between runs 1 and 2 were then queried to evaluate whether decreases in activation from run 1 to run 2 predicted response to BATD, measured as both BDI total scores and BDI anhedonia subscale scores.

2.10. Analysis of treatment outcomes

Data were analyzed in two-level hierarchical linear models, with people at level 2 and treatment weeks (i.e., assessments with the BDI) at level 1. Treatment week was utilized as a continuous time variable, and was uncentered. Study hypotheses were tested using models in which the current week's BDI score were predicted from: (1) current treatment week, (coefficient interpreted as the simple effect of treatment on BDI scores over time), (2) brain activation during run 1 (coefficient interpreted as the impact of run 1 activation on baseline BDI scores) (3) change in brain activation from run 1 to run 2 (calculated as run 1 minus run 2; coefficient interpreted as the impact of changes in activation on baseline BDI scores), (4) the interaction of brain activation in run 1 and treatment week (coefficient interpreted as the impact of baseline brain activation on the slope of a participant's trajectory of BDI change over time during treatment), and (5) the interaction of change in brain activation and treatment week (coefficient interpreted as the impact of changes in brain activation across runs on the slope of a participant's trajectory of BDI change over time during treatment). Inclusion of the run 1 functional connectivity predictors gives a specific meaning to the change predictors; that is, the change predictors represent only the degree of reduction in brain activation from run 1 to run 2. Preliminary unconditional growth models indicated significant between-person differences in both baseline BDI scores and in the slope of treatment week on BDI scores. Therefore, random effects were specified for both the intercept and the slope of treatment week on BDI scores. It is this variance in the slope of treatment week on BDI scores that will be explained using baseline fMRI activation magnitudes.

3. Results

3.1. Treatment response

Treatment resulted in significant reductions in BDI total scores (pretreatment mean (SD)=25.27 (8.52), post-treatment mean (SD)=14.73 (9.96), $p < .001$) and BDI anhedonia subscale scores (pretreatment mean (SD)=4.91 (2.26), post-treatment mean (SD)=2.87 (2.00), $p < .001$).

3.2. Pretreatment anhedonia as a predictor of treatment response

Because BATD targets motivation and reward-oriented behaviors, we examined whether severity of pre-treatment anhedonia predicted response to BATD. We observed a significant interactive effect of pre-treatment BDI anhedonia subscale scores and

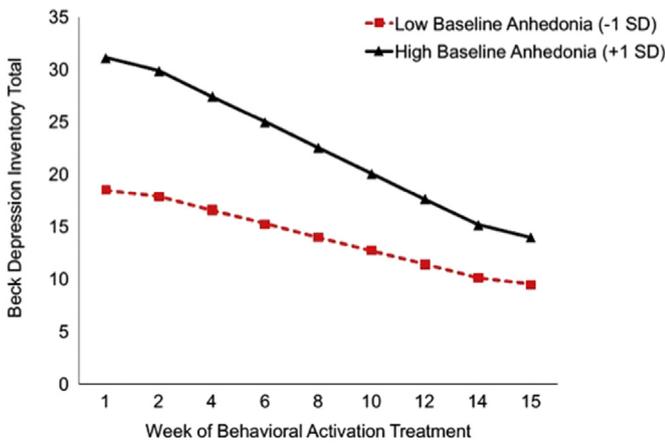


Fig. 2. Within the MDD group, higher levels anhedonia, measured by the BDI anhedonia subscale, at pretreatment predicted greater improvement in BDI total scores over the course of BATD treatment. The plot is a graphical illustration of the significant interaction between pre-treatment anhedonia and time predicting change in BDI scores from the HLM models. The lines represent the expectation for change in an individual who is one SD below the mean and one SD above the mean. Note the lines are model-based estimates and do not represent averages but rather ranges of anhedonia variability.

treatment week in predicting change in BDI total scores ($\gamma_{\text{ANHEDONIA} \times \text{TREATMENTWEEK}} = -.16$, $SE = .035$, $t(173) = -4.60$, $p < .0001$) such that patients with higher pre-treatment BDI anhedonia subscale scores showed greater reductions in BDI total scores over time, though total BDI scores remained higher after treatment in patients with greater BDI anhedonia subscale scores. This pattern is illustrated in Fig. 2. Pseudo R^2 calculations (Raudenbush and Bryk, 2002, p. 85) indicated that baseline BDI anhedonia scores accounted for 43% of the between-person differences in the effect of treatment week on BDI total scores.

3.3. Pretreatment behavior as a predictor of treatment response

Fig. 3(a) illustrates MID reaction times from MDD and control groups separated by task run as well as trial type (reaction time

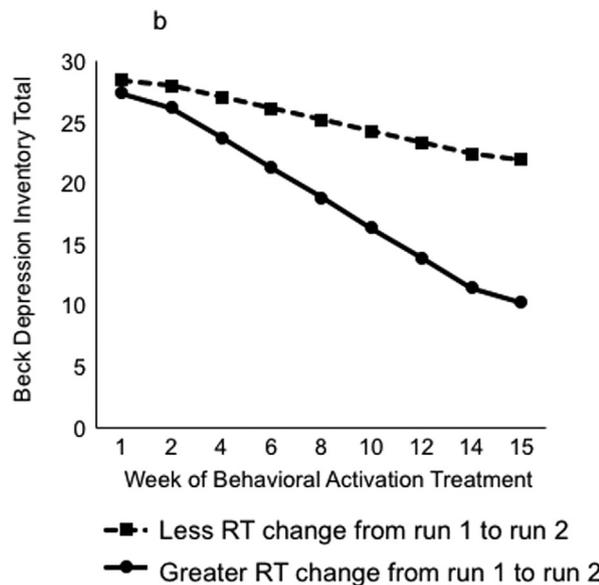
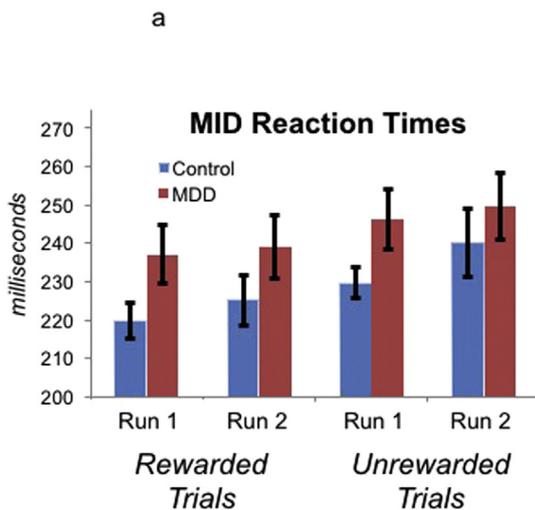


Fig. 3a: Average reaction times during the MID task, separated by group (MDD, Control), run (run 1, run 2), and trial type (rewarded, unrewarded). **3b:** Within the MDD group, greater change in reaction times during reward trials (i.e., faster response at run 2) at pretreatment predicted greater reductions in BDI total scores and anhedonia scores (not shown) over the course of BATD treatment. The plot is a graphical illustration of the significant interaction between pre-treatment depression and time predicting change in BDI scores from the HLM models. The lines represent the expectation for change in an individual who is one SD below the mean and one SD above the mean. Note the lines are model-based estimates and do not represent averages but rather ranges of RT variability.

data were unavailable for one MDD participant). These data were analyzed via a Group (MDD, Control) \times Trial (Rewarded, Unrewarded) \times Run (Run 1, Run 2) ANOVA with Group as a between subjects factor and Trial and Run as within subjects factors. The omnibus Group \times Trial \times Run interaction was not significant, multivariate $F(1,50) = 1.66$, $p > .20$. Additionally, the Trial \times Run interaction was not significant, multivariate $F(1,50) = 0.44$, $p > .50$, the Group \times Trial interaction was not significant, multivariate $F(1,50) = 0.33$, $p > .50$, and the Group \times Run interaction was not significant, multivariate $F(1,50) = 1.20$, $p > .25$. There was a main effect of run, multivariate $F(1,51) = 5.00$, $p < .03$, reflecting that across groups and trial types, RTs were faster during run 1 than run 2, and a main effect of trial type, multivariate $F(1,50) = 54.56$, $p < .0001$, reflecting that across groups and runs, RTs were faster for rewarded than unrewarded trials, but no main effect of Group, $F(1,50) = 1.66$, $p > .20$. Finally, t -tests revealed that within the MDD and Control groups separately, there were no significant reaction time differences between run 1 and run 2 (for both rewarded and unrewarded trials), p 's $> .40$, and that Groups did not differ on reaction times to either trial type during run 1 or run 2, p 's $> .05$. Fig. 4.

Change in RTs during scanning was, however, a significant predictor of response to treatment in the MDD group, as illustrated in Fig. 3(b). Greater change in RTs from run 1 to run 2 during reward trials was associated with greater declines in BDI total and BDI anhedonia subscale scores during treatment (BDI total score: $\gamma_{\text{RT CHANGE} \times \text{TREATMENTWEEK}} = -.02$, $SE = .001$, $t(185) = -2.41$, $p = .02$; BDI anhedonia subscale score: $\gamma_{\text{RT CHANGE} \times \text{TREATMENTWEEK}} = -.004$, $SE = .001$, $t(182) = -2.24$, $p = .03$). That is, MDD participants who exhibited increased speed (i.e., greater decline in RT) from run 1 to run 2 during reward trials showed greater reductions in symptoms following BATD. Pseudo- R^2 calculations indicated that change in RTs from run 1 to run 2 accounted for 15% of the between-person variance in the within-person effect of treatment week on BDI total scores, and 17% of the between-person variance in the within-person effect of treatment week on BDI anhedonia subscale scores.

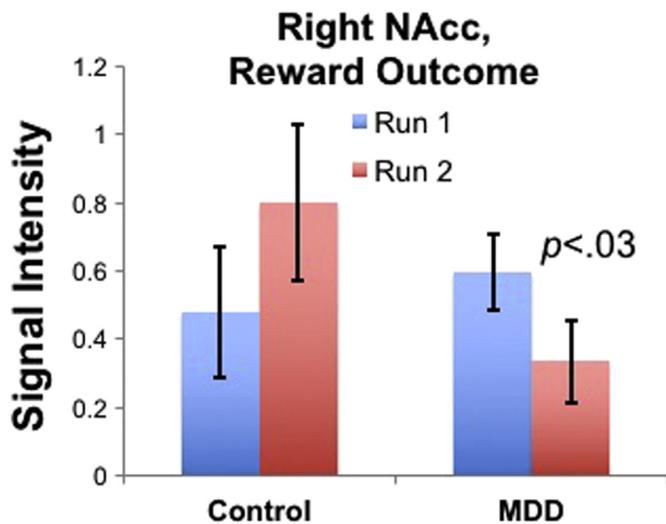


Fig. 4. Signal intensity in the right nucleus accumbens (NAcc) during reward outcomes averaged by groups and task runs. The Group (MDD, Control) \times Run (run 1, run 2) interaction term in this region was significant, $p < .04$, as was the effect of Run in the MDD group alone, $p < .03$.

3.4. Predicting treatment response from fMRI results

As described earlier, task-related activations were analyzed by deriving parameter estimates for each ROI that were analyzed via Group (MDD, Control) \times Run (run 1, run 2) repeated measures ANOVAs separately during the anticipation and outcome phases of

the MID task. Table 2 presents main effects and interactions between Group and Run as well as t -tests comparing groups and runs for each ROI. As can be seen from Table 2, during both phases of the task, there were no main effects of Run, of Group, or Group \times Run interaction for any ROI. There were a number of regions that showed a reduced capacity to sustain activation (i.e., greater decreases from run 1 to run 2) in the MDD group: in the anticipation phase, this was evident in left ACC, right ACC, left putamen, left striatum, and right striatum, and in the outcome phase this was evident in the same regions as well as left NAcc, right NAcc, right caudate, right FMC, left OFC, and right putamen. However, the only region in which these declines in sustained activation were moderated by Group status was in the right NAcc during reward outcomes. We then used hierarchical linear modeling (HLM) to examine whether group differences in sustained activation of the NAcc predicted response to BATD. HLM revealed that changes in right NAcc activation from run 1 to run 2 during reward outcomes were not predictive of treatment response.

To more fully explore potential neural predictors of treatment response, we also ran HLM models predicting treatment response from overall activation (averaged across runs) and sustained activation (changes from run 1 to run 2) even if the Group \times Run interaction term was not significant. These models revealed that ACC activation during reward outcomes predicted treatment response, as illustrated in Fig. 5(b). The significant model reflected that the capacity to sustain activation (i.e., less decrease) from run 1 to run 2 was associated with greater reductions in BDI total scores during treatment ($\gamma_{\text{CHANGE IN ACTIVATION}} \times \text{TREATMENTWEEK} = .46, SE = .20, t(200) = 2.38, p = .02$. Pseudo- R^2 calculations indicated that change in ACC activation from run 1 to run

Table 2

Group \times Run MANOVAs and t -tests within groups and runs. NAcc: nucleus accumbens, ACC: anterior cingulate cortex, FMC: frontal medial cortex, OFC: orbitofrontal cortex.

Anticipation phase							
ROI	Main Effect of Run (F (p))	Main Effect of Group (F (p))	Group \times Run (F (p))	Runs t -test in MDD group (t (p))	Runs t -test in Control Group (t (p))	Group t -test during Run 1 (t (p))	Group t -test during Run 2 (t (p))
Left NAcc	.61 (0.44)	.05 (0.82)	1.22 (0.27)	1.78 (0.08)	-.17 (0.86)	-.25 (0.80)	.65 (0.51)
Right NAcc	.05 (0.83)	.20 (0.66)	2.34 (0.13)	1.73 (0.09)	-.67 (0.51)	-.22 (0.82)	1.00 (0.32)
Left ACC	1.30 (0.26)	.08 (0.78)	1.63 (0.21)	2.07 (0.05)	-.08 (0.94)	-.89 (0.38)	.34 (0.74)
Right ACC	1.51 (0.22)	.01 (0.93)	1.40 (0.24)	2.19 (0.04)	.03 (0.98)	-.64 (0.52)	.43 (0.67)
Left caudate	.17 (0.68)	.23 (0.63)	1.38 (0.25)	1.54 (0.13)	-.39 (0.70)	-.05 (0.96)	.93 (0.36)
Right caudate	.26 (0.61)	.03 (0.86)	1.70 (0.20)	1.77 (0.09)	-.41 (0.69)	-.39 (0.70)	.80 (0.43)
Left FMC	.89 (0.35)	.28 (0.60)	1.38 (0.25)	.19 (0.85)	-1.33 (0.20)	-.43 (0.67)	1.05 (0.30)
Right FMC	.73 (0.40)	.08 (0.78)	1.88 (0.18)	.46 (0.65)	-1.26 (0.22)	-.79 (0.43)	.98 (0.34)
Left OFC	.52 (0.47)	.14 (0.71)	1.35 (0.25)	1.48 (0.15)	-.30 (0.77)	-.35 (0.73)	.83 (0.41)
Right OFC	.21 (0.65)	.40 (0.53)	1.05 (0.31)	1.34 (0.19)	-.31 (0.76)	.05 (0.96)	.96 (0.34)
Left putamen	1.99 (0.16)	.41 (0.52)	1.03 (0.32)	2.06 (0.05)	.24 (0.82)	-1.14 (0.26)	-.05 (0.96)
Right putamen	1.33 (0.25)	.16 (0.70)	1.16 (0.29)	1.90 (0.07)	.05 (0.96)	-.91 (0.37)	.18 (0.86)
Left striatum	1.36 (0.25)	.03 (0.87)	1.53 (0.22)	2.18 (0.04)	-.04 (0.97)	-.73 (0.47)	.39 (0.70)
Right striatum	.88 (0.35)	.02 (0.89)	1.77 (0.19)	2.10 (0.04)	-.21 (0.84)	-.71 (0.48)	.48 (0.64)
Outcome phase							
ROI	Main Effect of Run (F (p))	Main Effect of Group (F (p))	Group \times Run (F (p))	Runs t -test in MDD group (t (p))	Runs t -test in Control Group (t (p))	Group t -test during Run 1 (t (p))	Group t -test during Run 2 (t (p))
Left NAcc	.58 (0.45)	.20 (0.66)	2.20 (0.14)	2.00 (0.05)	-.40 (0.69)	-.37 (0.72)	1.23 (0.22)
Right NAcc	.02 (0.88)	.23 (0.64)	4.14 (0.04)	2.24 (0.03)	-.94 (0.36)	-.72 (0.48)	1.55 (0.13)
Left ACC	6.82 (0.01)	1.02 (0.32)	1.10 (0.30)	3.06 (0.005)	.95 (0.36)	-1.41 (0.17)	-.30 (0.76)
Right ACC	4.26 (0.04)	.04 (0.83)	1.25 (0.27)	2.64 (0.01)	.58 (0.57)	-.77 (0.45)	.40 (0.69)
Left caudate	.02 (0.89)	.48 (0.49)	3.05 (0.09)	1.45 (0.16)	-1.04 (0.31)	-.32 (0.75)	1.59 (0.12)
Right caudate	.81 (0.37)	.24 (0.63)	3.78 (0.06)	2.72 (0.01)	-.55 (0.59)	-.54 (0.59)	1.56 (0.13)
Left FMC	.36 (0.55)	.33 (0.57)	1.58 (0.21)	1.67 (0.10)	-.37 (0.72)	-1.25 (0.22)	.47 (0.64)
Right FMC	.42 (0.52)	.25 (0.62)	3.71 (0.06)	2.33 (0.03)	-.71 (0.49)	-1.66 (0.10)	1.01 (0.32)
Left OFC	1.33 (0.25)	.02 (0.90)	2.49 (0.12)	2.50 (0.02)	-.23 (0.82)	-.89 (0.38)	1.00 (0.33)
Right OFC	.87 (0.35)	.13 (0.72)	.93 (0.34)	1.70 (0.10)	-.02 (0.99)	-.23 (0.82)	.82 (0.42)
Left putamen	2.79 (0.10)	.74 (0.39)	1.29 (0.26)	2.36 (0.02)	.32 (0.75)	-1.16 (0.26)	.08 (0.93)
Right putamen	3.85 (0.06)	.30 (0.59)	1.10 (0.30)	2.50 (0.02)	.556 (0.58)	-.94 (0.35)	.23 (0.82)
Left striatum	1.36 (0.25)	.03 (0.87)	2.52 (0.12)	2.37 (0.02)	-.25 (0.81)	-.91 (0.37)	.88 (0.39)
Right striatum	2.70 (0.11)	.00 (0.98)	2.69 (0.11)	2.91 (0.01)	.00 (0.99)	-.81 (0.42)	.98 (0.33)

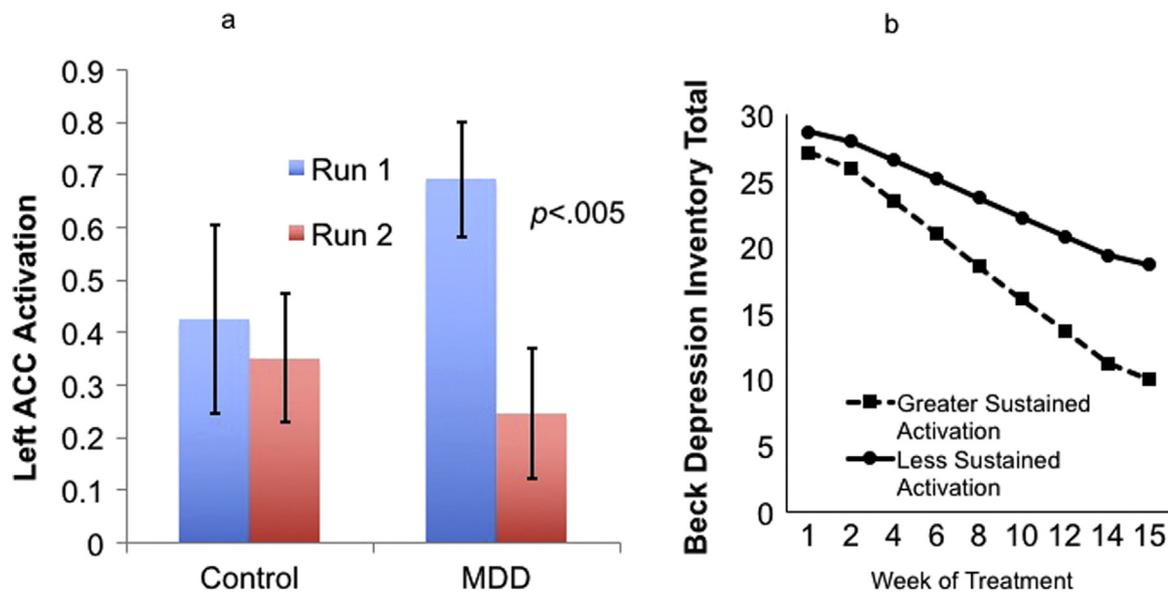


Fig. 5. a: Signal intensity in the left ACC during reward outcomes averaged by groups and task runs. The Group (MDD, Control) \times Run (run 1, run 2) interaction term in this region was not significant, but the effect of Run in the MDD group alone was significant, $p < .005$. **b:** Within the MDD group, decreased left ACC activation from run 1 to run 2 during reward outcomes predicted change in BDI total scores.

2 accounted for 5.6% of the between-person variance in the within-person effect of treatment week on BDI total scores.

4. Discussion

The purpose of this study was to investigate whether neural responses to rewards were predictive of response to BATD, a treatment developed to ameliorate symptoms of MDD by promoting interactions with potentially positive reinforcers and inhibiting avoidance behaviors as well as supporting sustained interaction with potentially rewarding activities (Hopko et al., 2003; Jacobson et al., 2001). Specifically, we examined whether differences between MDD and control groups in the magnitude of activation in ROIs reflecting key reward processing brain regions predicted reductions in overall MDD symptoms and symptoms of anhedonia. We addressed this question by comparing groups' magnitude of activation during the first and second runs of the fMRI task. This analytic plan was developed on the basis of prior data indicating that positive affect in MDD is characterized by decreased capacity to sustain nucleus accumbens activity during positive emotion regulation (Heller et al., 2009) and that the endurance of NAcc activation and connectivity during positive emotion regulation predicted clinical response to antidepressant treatment (Heller et al., 2013).

The clinical effectiveness of BATD in the current study was consistent with prior trials (Dichter et al., 2009; Hopko et al., 2003): average BDI scores declined 10.54 points, a clinically meaningful response (Jacobson and Truax, 1991). However, there was considerable variability in response, highlighting the need to develop predictors of treatment response to maximize the efficacy of empirically validated treatments (Kapur et al., 2012).

We found symptomatic, behavioral, and neural predictors of response to treatment. First, patients with more severe pretreatment anhedonia responded better to BATD. Because anhedonia is associated with poorer treatment response to pharmacologic (McMakin et al., 2012) and neurostimulation (Downar et al., 2014) interventions, it may be that BATD is particularly well-suited to address the anhedonic symptoms of depression through targeting approach and avoidance behaviors. Second, patients who exhibited decreased reaction times (i.e., faster responses) while

making a speeded button press to receive a reward also fared better after treatment. Faster reaction to reward trials over time may reflect increased motivated responding (Pizzagalli et al., 2009), particularly when cues are provided (Mir et al., 2011). This finding suggests that BATD may also be an effective treatment for patients with greater capacity to anticipate incentives and/or relatively preserved hedonic responsiveness.

We had three central fMRI findings. First, contrary to previous reports, we found no group differences in brain activation responses using the MID task. This stands in contrast to previous reports of difference in MDD using the same task (Knutson et al., 2008; Pizzagalli et al., 2009). Although the precise reasons for these disparities are not clear, it may be that our region of interest analytic approach is one source of this difference. However, we did detect group differences in task responses when we considered differences in activation magnitudes between runs 1 and 2 of the task. Specifically, the MDD group showed decreased capacity to sustain activation in the right NAcc during reward outcomes relative to controls, highlighting the potential importance of hedonic endurance to understanding neural endophenotypes related to reward processing in MDD. The finding of altered NAcc activation during the outcome phase, but not the anticipation phase, is consistent with previous studies showing more robust effects in the caudate and NAcc during reward outcomes than reward anticipation (Pizzagalli et al., 2009) or reward predictions (Elliott et al., 2000; Ernst et al., 2005).

Finally, exploratory analyses revealed that sustained activation of the ACC (i.e., less change from run 1 to run 2) predicted better response to BATD, as evidenced by greater declines in total symptoms of depression. This finding is consistent with a prior report that MDD is characterized by reduced capacity to maintain frontostriatal activation and connectivity in the context of an emotion regulation task (Heller et al., 2009). The frontal medial cortex, including aspects of the ACC, is critically involved in controlling social approach–avoidance behaviors (Challis and Berton, 2015). Additionally, frontal medial regions of the prefrontal cortex are key components of neural circuits involved in detecting the motivational significance of external stimuli (Phan et al., 2005). Capacity to sustain ACC activation in the context of a reward may be a key predictor of response to a psychotherapy modality that specifically targets responding to motivationally salient aspects of

the environment.

The current study only included a single treatment condition, and it will be important in future research to evaluate the capacity for neural responses to rewards to predict differential clinical responses to different antidepressant treatment modalities. It will also be important to examine post-treatment neuroimaging to evaluate whether the brain regions that are predictive of treatment response are those that show recovery of functioning after treatment. Despite these limitations, the current study found symptomatic, behavioral, and neural predictors of response to BATD. Critically, the only neural predictor to emerge as significant was from a model that evaluated changes in neural activations from the first half to the second half of the reward task. This finding extends the emerging framework of MDD that emphasizes capacity to sustain neural responses to hedonic stimuli in the pathophysiology of the disorder (Heller et al., 2013; Heller et al., 2009) to the domain of treatment prediction. More generally, combined with our prior examination of resting state predictors of BATD response (Crowther et al., 2015), and emerging evidence addressing neural predictors of response to other antidepressant treatment modalities (see Dichter et al., 2014 for a review), these findings contribute to the growing body of literature addressing pre-treatment neuroimaging endophenotypes as predictors of antidepressant treatment response (McGrath et al., 2013). Given this suboptimal response rate to available MDD treatments, the identification of methods to match specific patients with the most appropriate, personalized treatment option is an important way to help relieve the societal burden of MDD (Kapur et al., 2012).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jad.2016.06.005>.

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