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Pretreatment brain connectivity during positive emotion upregulation predicts decreased anhedonia following behavioral activation therapy for depression

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ABSTRACT

Background: Neurobiological predictors of antidepressant response may help guide treatment selection and improve response rates to available treatments for major depressive disorder (MDD). Behavioral activation therapy for depression (BATD) is an evidence-based intervention designed to ameliorate core symptoms of MDD by promoting sustained engagement with value-guided, positively-reinforcing activities. The present study examined pre-treatment task-based functional brain connectivity as a predictor of antidepressant response to BATD.
Methods: Thirty-three outpatients with MDD and 20 nondepressed controls completed a positive emotion regulation task during fMRI after which participants with MDD received up to 15 sessions of BATD. We used generalized psychophysiological interaction analyses to examine group differences in pre-treatment functional brain connectivity during intentional upregulation of positive emotion to positive images. Hierarchical linear models were used to examine whether group differences in functional connectivity predicted changes in depression and anhedonia over the course of BATD.
Results: Compared to controls, participants with MDD exhibited decreased connectivity between the left middle frontal gyrus and right temporoparietal regions during upregulation of positive emotion. Within the MDD group, decreased connectivity of these regions predicted greater declines in anhedonia symptoms over treatment.
Limitations: Future studies should include comparison treatments and longitudinal follow-up to clarify the unique effects of BATD on neural function and antidepressant response.
Conclusions: Results are consistent with previous work showing BATD may be particularly effective for individuals with greater disturbances in brain reward network function, but extend these findings to highlight the importance of frontotemporoparietal connectivity in targeting symptoms of low motivation and engagement.

1. Introduction

Behavioral activation therapy for depression (BATD) is an intervention designed to ameliorate core symptoms of major depressive disorder (MDD) by promoting systematic engagement in valued activities and reductions in avoidance behaviors. The overarching goal of BATD is to increase contact with potential sources of positive reinforcement (Dimidjian et al., 2011). In line with the emerging science of neuroprediction to better match MDD patients to existing treatments (e.g., Langenecker et al., 2018; Pizzagalli et al., 2018), our recently completed open trial investigated neuroimaging predictors of BATD response (Walsh et al., 2017; Carl et al., 2016; Crowther et al., 2015). In a sample of MDD patients and nondepressed controls, we evaluated group differences in pre-treatment brain activation and

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connectivity during a reward-based task or at rest. For MDD patients enrolled in BATD, we then examined the extent to which these neuroimaging biomarkers explained the observed decreases in symptoms of depression and anhedonia over the course of treatment. Thus far, we have provided evidence that BATD may be most optimal for MDD patients with deficits in reward-related brain network function, with particularly robust effects on the core symptom of anhedonia.

An exploratory aim of our open trial study was to evaluate prediction of BATD response from pre-treatment brain connectivity during an emotion regulation task. MDD is characterized by emotion dysregulation, and much research to date has focused on addressing deficits in regulation of *negative* mood states. However, given that anhedonia is a defining feature of MDD (American Psychiatric Association, 2013), it is likely that deficits in *positive* emotion regulation may increase risk for or maintain MDD. Therefore, we hypothesize that positive emotion regulation disturbances may predict treatment outcome in response to BATD.

2. Methods

Full details of the study protocol and participants are described in Carl et al. (2016) and Walsh et al. (2017). The protocol was approved by local Institutional Review Boards and all participants provided written informed consent.

2.1. Participants

Participants with MDD were recruited via participant recruitment registries and listservs at Duke University and the University of North Carolina at Chapel Hill. Participants in the MDD group met DSM-IV criteria for a current episode of MDD using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (First et al., 2002). Control group participants did not meet criteria for a current or lifetime episode mood episode. Exclusion criteria included: 1) history of psychosis or mania; 2) active suicidal ideation, 3) evidence of organicity, 4) magnetic resonance imaging contraindication, 5) history of neurological injury or disease, 6) current pregnancy, and, in the MDD group, 7) current mood, anxiety, psychotic, or substance abuse disorder beyond unipolar MDD or dysthymia.

Thirty-eight outpatients with MDD (29% male; mean age = 33 (range = 21–45)) and twenty controls (30% male; mean age = 31 (range = 20–44)) were enrolled. Five MDD participants were excluded from analyses; two did not return for therapy after the pre-treatment fMRI session, and three were taking psychoactive medications. The final sample included 33 outpatients with MDD and 20 nondepressed control participants.

2.2. Procedures and design

MDD and control groups participated in a pre-treatment MRI scan. Participants completed a number of different imaging protocols, some of which have been published (Walsh et al., 2017; Carl et al., 2016; Crowther et al., 2015). Following the pre-treatment scan, the MDD group began BATD psychotherapy. Up to 15 sessions of BATD were offered; participants received an average of 11.67 (SD = 4.40; range: 2–15) weekly sessions.

2.3. Positive emotion regulation task

During the scan, participants completed two runs of a positive emotion regulation task (similar to Smoski et al. (2013), but using positive images). Each trial began with a fixation cross (6 s) followed by presentation of a positive or neutral picture (Fig. 1A depicts timing and content of each trial). After initial picture display without regulation instruction (3–6 s, jittered), a visual regulation instruction was superimposed on the bottom of the picture, indicating the regulation strategy to use (3 s), followed by a brief delay (~3 s). Participants then rated post-trial affect using a visual analog scale (5 s; range of 1 = most negative to 4 = most positive). The task included two conditions: Passive Viewing ('view') and Positive Upregulation ('increase'). For the 'view' condition, which used both positive and neutral pictures, participants were instructed not to regulate their emotional response ("view images without trying to change the emotions that come"). For the 'increase' condition, which occurred only during positive images, participants were instructed to reinterpret the image to increase its positive impact. Specifically, participants were asked to "mentally placing themselves in the scene" or "interpret the image in a way that exaggerates the positive content". Two runs of 12 trials each were administered (4′42″ per run; 24 total trials), and there were 8 trials for each regulation condition.

Prior to the scan, participants practiced the regulation strategies with an experimenter until they could implement them without assistance. Task images were drawn from: (i) positive images from the International Affective Picture System based on normative positive ratings (Mikels et al., 2005) and (ii) a normed set of neutral images used in previous MDD imaging studies (e.g., Dichter et al., 2010).

2.4. Treatment outcome measures

Treatment outcomes were evaluated by the Beck Depression Inventory-II (BDI; Beck et al., 1996), collected at the scan session, every two weeks during treatment, and at the last psychotherapy session. The BDI provides an overall measure of MDD severity and includes items that tap MDD symptom dimensions. We examined BDI total scores, and BDI anhedonia subscale scores derived from items 4, 12, 15, and 21 (Joiner et al., 2003).

2.5. Imaging methods and fMRI preprocessing

Fully described in Walsh et al. (2017) and Supplement.

2.6. fMRI data analysis

The general linear model included the following regressors for each task event: "Increase" instructions (positive images), "View" instructions (positive and neutral images), and passive viewing of images (positive and neutral; pre-instructions). For the present study, we were most interested in examining differences in neural responses following instructions to intentionally increase positive emotion during a positive image vs. viewing a positive image without engaging in a specific strategy (Positive Increase Instructions > Positive View Instructions). Temporal derivatives and standard motion parameters (3 rotations, 3 translations) were included as covariates. To further control for excessive motion, we censored volumes that exceeded a framewise displacement threshold of 0.9 mm (i.e., head motion displacement occurring from one volume relative to the previous volume summing across linear and rotational displacements (Siegel et al., 2014)).

Task-based functional connectivity was evaluated using a generalized psychophysiological interaction (gPPI) approach (Cisler et al., 2014). Seed regions of interest (ROI) were selected to target canonical positive emotion regulation and reward processing regions (e.g., Kim and Hamann, 2007; Zhang et al., 2013). ROI seeds included the nucleus accumbens, caudate, putamen, frontal medial cortex, frontal pole, and middle frontal gyrus. ROIs were defined using the Harvard-Oxford subcortical and cortical structural probabilistic atlases. For each participant, mean fMRI timecourses (i.e., physiological regressors) were extracted from seed regions using fslmeants, then multiplied by each psychological variable of interest (i.e., task condition) to form the PPI interaction terms. The gPPI model included physiological and psychological regressors, as well as their interaction terms to describe the unique effect of these interactions above and beyond the main effects of seed timecourses and task conditions. Prior to performing group-level analyses, task runs were combined using a fixed-effects model.