Journal of Affective Disorders 203 (2016) 204–212

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

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

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ARTICLE INFO

Article history:
Received 17 March 2016
Accepted 3 June 2016
Available online 4 June 2016

Keywords:
Major depressive disorder
Reward
Anhedonia
Functional magnetic resonance imaging
Nucleus accumbens
Psychotherapy

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.

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

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http://dx.doi.org/10.1016/j.jad.2016.06.005
0165-0327/

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; Ubl 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 (HAMD; 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. HAMD 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 HAMD. Participants in the control group scored six or lower on the HAMD 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