Journal of Affective Disorders 164 (2014) 50–56

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Preliminary communication

# Neural response to reward anticipation in those with depression with and without panic disorder

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ARTICLE INFO

*Article history:*
Received 14 March 2014
Accepted 11 April 2014
Available online 19 April 2014

*Keywords:*
Major depressive disorder
Reward anticipation
Panic disorder
Anterior cingulate cortex

ABSTRACT

*Background:* One of the hallmark features of major depressive disorder (MDD) is reduced reward anticipation. There have been mixed findings in the literature as to whether reward anticipation deficits in MDD are related to diminished mesolimbic activation and/or enhanced dorsal anterior cingulate activation (dACC). One of the reasons for these mixed findings is that these studies have typically not addressed the role of comorbid anxiety, a class of disorders which frequently co-occur with depression and have a common neurobiology.

*Methods:* The aim of the current study was to examine group differences in neural responses to reward anticipation in 40 adults with either: (1) current MDD with no lifetime diagnosis of an anxiety disorder (MDD-only), (2) current MDD with comorbid panic disorder (MDD-PD), or (3) no lifetime diagnosis of psychopathology. All participants completed a passive slot machine task during a functional magnetic resonance imaging (fMRI) scan.

*Results:* Analyses indicated that there were no group differences in activation of mesolimbic reward regions; however, the MDD-only group exhibited greater dACC activation during the anticipation of rewards compared with the healthy controls and the comorbid MDD-PD group (who did not differ from each other).

*Limitations:* The sample size was small which limits generalizability.

*Conclusions:* These findings provide preliminary support for the role of hyperactive dACC functioning in reduced reward anticipation in MDD. They also indicate that comorbid anxiety may alter the association between MDD and neural responding to reward anticipation.



## 1. Introduction

Major depressive disorder (MDD) is one of the world's most common illnesses and currently affects over 16% of the general population (Hasin et al., 2005; Kessler et al., 2003). Enormous personal and societal costs are associated with MDD, and it is predicted that depression will be the leading global cause of poor health by 2030 (Lépine and Briley, 2011). Despite the high prevalence and devastating impact of MDD, its underlying neurobiology is still not well understood. Consequently, there is a growing need to elucidate neural processes which contribute to depressive disorders in hopes of identifying biomarkers for outcomes and developing more targeted interventions.

A large body of evidence suggests that individuals with depression exhibit reward processing deficits (Epstein et al., 2006; Pizzagalli et al., 2009a; Wacker et al., 2009; see Bylsma et al., 2008 for a review). It is important to note, however, that reward processing is a broad construct and can be divided into two distinct, temporal components – reward anticipation and reward consummation (Berridge and Robinson, 2003; Gard et al., 2006). Reduced reward anticipation, or a diminished tendency to expect and/or approach rewards, has long been argued to be a core feature of depressive disorders (Davidson, 1998; Meehl, 1975), and this premise has been supported by numerous behavioral and psychophysiological studies (Treadway et al., 2009; Shankman et al., 2013). A recent study has also suggested that the broad reward-related abnormalities in depression are primarily driven by deficits in reward anticipation and not reward consummation (Sherdell et al., 2012).

Across human and animal imaging studies, the mesolimbic dopaminergic pathway has been most often implicated in reward

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http://dx.doi.org/10.1016/j.jad.2014.04.019
0165-0327/

anticipation (see Haber and Knutson, 2010). The pathway originates in the ventral tegmental area (VTA) and projects to the nucleus accumbens (NAc) of the ventral striatum, as well as the dorsal striatum, amygdala, and medial prefrontal cortex (Knutson et al., 2001; Tsurugizawa et al., 2012). Several neuroimaging studies have demonstrated that individuals with depression exhibit reduced activation in mesolimbic regions during reward anticipation compared to healthy controls. For example, using a 'Wheel of Fortune' decision-making task, Smoski et al. (2009) found that relative to controls, MDD participants showed decreased activation in the right caudate during reward anticipation. In a separate study, using a monetary incentive delay task (MID), Pizzagalli et al. (2009b) reported that MDD participants displayed reduced activation in the left putamen while anticipation a reward.

In addition to hyporesponsivity in mesolimbic structures, researchers have speculated that the reward processing deficits in MDD may also be associated with hyperresponsivity of cortical regions associated with conflict monitoring (Liu et al., 2011). Depressed individuals expect positive outcomes to a lesser extent than non-depressed individuals (Alloy and Ahrens, 1987; Beck and Clark, 1988), which is thought to create an affective conflict (or incongruence) during reward anticipation. Affective conflict has repeatedly been shown to be associated with enhanced dorsal anterior cingulate cortex suggesting that this region may also be associated with reward anticipation deficits in individuals with depression (dACC; Botvinick et al., 1999; Ochsner et al., 2009; Shackman et al., 2011). In line with this hypothesis, Knutson et al. (2008) reported that depressed and non-depressed individuals both exhibited activation of the ventral striatum (including the NAc) during anticipation of reward, but those with MDD displayed significantly greater dACC activation compared with controls. In other words, hyperactive dACC activity, and not hypoactive mesolimbic activity, differentiated the depressed and non-depressed participants.

It is important to note that the findings from Knutson et al. (2008) have not been consistently replicated and several studies have found no difference in dACC activation between MDD and non-MDD participants during reward anticipation (e.g., Smoski et al., 2009, 2011). There are several potential explanations for these discrepant findings. First, there are important differences among task paradigms that examine reward anticipation that could impact neural responding. For instance, Knutson et al. (2008) used the MID task, a paradigm that requires participants to press a button in-order to gain or avoid losing money. As such, there was a behavioral component to their design which may be affected by the psychomotor deficits often seen in depressed individuals (Sobin and Sackeim, 1997). Smoski et al.'s (2009) task did not have a behavioral component but did contain aspects of decision-making, as participants were asked to choose between two options, with different probabilities of winning each trial. Importantly, no study to our knowledge has investigated the neural correlates of reward anticipation within currently depressed individuals using a task that does not require a motor response or decision (i.e., completely passive task).

The role of comorbid anxiety disorders is another factor that could contribute to prior mixed findings. Although depressive and anxiety disorders commonly co-occur (Kessler et al., 1996; Mineka et al., 1998), the effect of anxiety on neural responding during reward anticipation is poorly understood. In a sample of adolescents, it was previously demonstrated that like those with depression, anxious individuals displayed *reduced* activation in the striatum compared with controls (Forbes et al., 2006). Unlike those with depression, however, anxious participants also displayed enhanced orbital frontal cortex (OFC) activation. Bar-Haim et al. (2009) found that adolescents with elevated anxiety symptoms exhibited *enhanced* striatal response to reward anticipation relative to non-anxious youth. More recently, a study of adults reported no differences in neural responding during anticipation of rewards between controls and those with obsessive-compulsive-disorder (OCD; Choi et al., 2012). Given that these studies examined depression and anxiety separately, prior findings may not speak to the impact of MDD with comorbid anxiety. To date, there has been no study to our knowledge that has directly compared individuals with MDD-only and MDD with comorbid anxiety on neural responses to reward anticipation. Interesting, in the broader depression-anxiety psychophysiology literature, the findings are also mixed; however, several studies have found that having a comorbid disorder attenuates the typical response of the primary disorder (Weinberg et al., 2012; Kentgen et al., 2000). Thus, it is possible that a similar effect would be seen in investigations of neural responding.

Given the gaps in the existing literature, the aim of the current study was to examine neural responses to reward anticipation using functional magnetic resonance imaging (fMRI) in three groups: (1) current MDD, (2) current MDD with comorbid panic disorder (PD), and (3) no lifetime history of psychopathology. We used a completely passive, slot machine paradigm to attempt to reduce the role of motor responding on affective responses. We hypothesized that individuals with MDD-only would displayed reduced NAc/ventral striatum *and* enhanced dACC activation during reward anticipation relative to controls. Although there was very little existing data to inform our hypotheses about the effect of comorbid MDD and PD, we postulated that PD may moderate the relation between MDD and neural responding. Specifically, we speculated that the comorbid group would exhibit greater NAc/ventral striatum and reduced dACC activation relative to the MDD-only group.

## 2. Methods

### 2.1. Participants

The present study included 40 right-handed adults with: (1) current MDD with comorbid PD ($n=13$), (2) current MDD with no lifetime diagnosis of an anxiety disorder ($n=9$), and (3) no lifetime history of psychopathology ($n=18$). All participants were recruited from the community and enrolled in a larger study on emotional deficits in depression and anxiety (Shankman et al., 2013). Current and past diagnoses were made using the Structured Clinical Interview for *DSM-IV* (SCID; First et al., 1996). Participants in the comorbid group were allowed to have additional current or past anxiety disorders. Participants in the MDD-only group were required to have no current or past anxiety disorder. Interrater reliabilities of SCID diagnoses were conducted on a subset of participants and indicated perfect diagnostic agreement (all Kappas = 1.00). Individuals were excluded from the larger study if they had a lifetime diagnosis of a psychotic disorder, bipolar disorder, or dementia; were unable to read or write in English; had a history of head trauma with loss of consciousness; or were left-handed (as confirmed by the Edinburgh Handedness Inventory; range of laterality quotient: +20 to +100; Oldfield, 1971). All methods were approved by the local Institutional Review Board.

### 2.2. Procedure and reward anticipation task

After providing written informed consent, all participants completed a mock scan and a practice version of the experimental task. Approximately 7 days later, they returned for their fMRI scan. All scanning sessions took place between 7 am and 12 pm and