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Altered task-specific deactivation in the default mode network depends on valence in patients with major depressive disorder

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ABSTRACT

Background: Major depressive disorder (MDD) is a highly prevalent psychiatric condition in which patients often have difficulties regulating their emotions. Prior studies have shown that attention bias towards negative emotion is linked to activation in regions of the default mode network (DMN) in MDD individuals. Furthermore, MDD patients showed increased resting-state functional connectivity (FC) between the medial prefrontal cortex and other DMN structures.
Methods: Twenty-one MDD patients that currently experiencing depressive episodes and twenty-five healthy control participants performed the current emotional expectancy paradigm in a gradient-echo SENSE-SPIRAL fMRI. Whole brain and psycho-physiological interaction (PPI) analysis were applied to explore the task-related brain activity and FCs.
Results: Relative to healthy participants, we found MDD patients had greater activity in dorsal medial prefrontal cortex as a function of positive vs. neutral expectancy conditions. PPI results revealed a significant group difference of MDD patients having relatively decreased task-dependent decoupling from dorsal medial prefrontal cortex (DMPFC) towards posterior cingulate cortex (PCC) and parieto-occipital cortex during positive vs. neutral expectancy conditions, and patients exhibited a positive correlation between PPI (DMPFC and PCC) and anhedonia as measured via SHAPS during the same conditions.
Limitations: Modest sample size and lack of concurrent depressive episodes limit the generalizability of our findings.
Conclusions: In MDD patients, insufficient DMN decoupling might occur in response to positive expectancy conditions. Our findings are consistent with the hypothesis that high intrinsic DMN connectivity in MDD patients interfere with the down-regulation of intrinsic focus in order to incorporate information derived from external positive events.

1. Introduction

Major depressive disorder (MDD) is a highly prevalent psychiatric condition, typically characterized by persistent sadness and 'down states' that dominate patients' lives, wherein they lack interest in and happiness from pleasurable activities (anhedonia), and also experience energy exhaustion and often guilty feelings (Belmaker and Agam, 2008; Holtzheimer and Mayberg, 2011). Many of the depressive symptoms are related to the fact that MDD patients often have difficulties modulating emotion due to severe cognitive biases, in which their

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attention and memory retrieval are typically prone to negative emotional information (Disner et al., 2011; MacLeod et al., 2002).

Previous studies that focused on attentional bias in MDD found that patients showed impaired bottom-up emotional activation and top-down attentional control interactions (Mathews and MacLeod, 2005). While healthy control (HC) participants preferentially directed attention towards positive stimuli (Gotlib et al., 2004), MDD patients had difficulties shifting their attentional focus to positive stimuli (Clark et al., 1994; Disner et al., 2011). In the review of Holtzheimer and Mayberg (Holtzheimer and Mayberg, 2011), MDD patients were prone to negative states and once they entered those states, it was very difficult for them to shift back to positive states. And, Kellough and his colleagues found that individuals in depressive episodes showed increased attention towards negative stimuli and decreased attention towards positive stimuli (Kellough et al., 2008), supporting the emotional attention bias hypothesis.

Brain imaging studies have revealed that many brain regions responsible for mood regulation were functionally disrupted in MDD patients. For example, Shafritz and colleagues found that individuals with mood disorders required greater cognitive effort to divert attention away from negative stimuli, which was associated with activity in pregenual anterior cingulate cortex (pgACC) (Shafritz et al., 2006). Additionally, resting-state functional connectivity (FC) studies reported MDD patients showed abnormal signal fluctuations in ACC (Greicius et al., 2007; Zhang et al., 2016a), amygdala (Cullen et al., 2014; Kong et al., 2013) and medial prefrontal cortex (MPFC) (Bremner et al., 2002; Drevets, 2007; van Tol et al., 2014). Further, emotional attention bias has been linked to activation in MPFC, part of the default mode network (DMN) (Raichle et al., 2001) related to self-referential events and emotional processing (Gusnard et al., 2001). Grimm and colleagues showed that MDD was characterized by impaired deactivation in the anterior DMN during tasks (Grimm et al., 2009). What drives this impairment remains unclear. If MDD is characterized by biased attention, atypical attention focus may be a result of generally increased intrinsic coupling. MDD may also be characterized by atypical incorporation of explicit external information, such as increased sensitivity to actual negative stimuli. Alternatively, attentional bias may result from an inability to prepare for positive stimulation by reorienting attentional resources towards the environment.

Several studies have been conducted to identify brain mechanisms contributing to emotional attention bias in MDD patients. Bermpohl and colleagues used the emotional expectancy task to investigate expectancy-induced modulation of emotional picture processing in HC group and MDD patients (Bermpohl et al., 2006). MPFC specifically regulated attentional modulation of emotion processing; they also found impairment of expectancy and perception interaction in dorsal MPFC (DMPFC) when MDD patients processed emotional pictures (Bermpohl et al., 2009). A limitation of this experimental design was that it did not distinguish positive or negative emotional expectancies, only investigating the effect of general, valence-unspecific emotional expectancy.

In the present study, we investigated neural correlates of biased attention in MDD patients using a similar paradigm as in Bermpohl's studies (with the addition of differentiated positive and negative expectancies) (Bermpohl et al., 2006, 2009). This investigation was motivated by two hypotheses: (1) MDD patients have impaired deactivation of DMPFC (anterior DMN) during expectancy of positive events and (2) an impaired decoupling on DMPFC and PCC (anterior – posterior DMN) for positive events expectancy. In this study, the impaired deactivation of DMPFC and the impaired decoupling on DMPFC and posterior cingulate cortex (PCC) are considered as a sign for a reduced positive bias (which is present in healthy subjects) and therefore in line with the negative attentional bias in MDD. We applied gradient-echo SENSE-SPIRAL fMRI a new fMRI sequence with expectancy emotion paradigm (Hypothesis 1). The SENSE-SPIRAL is a new fMRI sequence which can obtain high quality data in areas with low signal-to-noise ratios, such as the prefrontal cortex (Truong and Song, 2008). We used psychophysiological interaction (PPI) analysis to further investigate the FC alterations in MDD patients that related to our task findings (Hypothesis 2).

Table 1
Demographic characteristics of study participants.

	HC (n=25)	MDD (n=21)	Group effect P value
Gender (male/females)	16/9	13/8	0.522
Age (years)	39.28 ± 13.02	43.77 ± 10.83	0.203
HAMD	–	28.05 ± 8.04	–
MADRS	–	23.86 ± 8.58	–

2. Methods

2.1. Participants

Twenty-one MDD patients that currently experiencing depressive episodes and twenty-five age- and gender-matched HC participants performed the fMRI experiment. Patients were clinically diagnosed according to the ICD-10 criteria and severity was assessed using the 24-items Hamilton rating scale for depression (HAMD) and Montgomery-Asberg depression rating scale (MADRS) (Table 1). We used SHAPS for psychometric evaluation of anhedonia. Exclusion criteria were major non-psychiatric medical illness, history of seizures, prior electroconvulsive therapy treatments, illicit substance use or substance use disorders, and pregnancy. The exact number of previous depressive episodes was not available for all patients. The length of the current episode was between one and twelve months. All patients were medicated according to clinical standards with a selective serotonin reuptake inhibitor (SSRI), anti-psychotic medication, or a selective noradrenalin reuptake inhibitor (SNRI), tetracyclic antidepressant (TCA), or mood stabilizers. This study was approved by the ethics committee of Tianjin Medical University General Hospital, and all participants provided written informed consent to participate.

2.2. Expectancy and emotion task

The experiment was designed and administered using the Presentation software package (Neurobehavioral Systems, http://www.neurobs.com). Initially the fMRI Hardware System (Nordic NeuroLab, NNL) was used to project experimental stimuli onto a goggle screen worn by participants, and 8 MDD patients and 8 HC participants were tested in the goggle environment. Due to goggle dysfunction, 13 MDD patients and 17 HCs then performed the task through a mirror that located in the head coil and the stimuli were projected through a beamer into the mirror. We modeled the goggle/screen effect as a non-interest regressor in order to minimize the influence of experimental environment change.

The emotional expectancy paradigm is event-related design used visual cues and pictures with different valences (Fig. 1). A total of 60 pictures were selected from the International Affective Picture System (IAPS) (Lang et al., 2008), and pictures were divided into positive (n=20), neutral (n=20) and negative (n=20) pictures according to ratings of perceived valence (mean valence ratings: negative, 2.06 ± 0.54; neutral, 5.11 ± 0.52; positive, 7.68 ± 0.32). Pictures from this set were matched between valences with regard to number of people, situation complexity, and semantic content.

Each picture was presented for 4 s. Half of trials were preceded by an expectancy task predicting (with 100% validity) upcoming stimulus types; e.g., an upwards-pointing arrow indicated that a positive picture would follow (positive expectancy); a downward-pointing arrow indicated that a negative picture would follow (negative expectancy); a horizontal arrow indicated that a neutral picture would follow (neutral