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Research paper

Negative mood-induction modulates default mode network resting-state functional connectivity in chronic depression

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ABSTRACT

Background: The aim of this study was to investigate the effects of sad mood on default mode network (DMN) resting-state connectivity in persons with chronic major depressive disorder (cMDD).

Methods: Participants with a diagnosis of cMDD (n=18) and age, gender and education level matched participants without a diagnosis of depression (n=18) underwent a resting-state fMRI scan, before and after a sad mood induction. The posterior cingulate cortex (PCC) was used as a seed for DMN functional connectivity across the two resting-state measurements.

Results: Mood ratings decreased in both groups following the sad mood induction procedure. PCC connectivity with the parahippocampal gyrus, the superior temporal gyrus and the anterior inferior temporal cortex increased in cMDD patients following the sad mood induction, whereas it decreased in non-patient controls. PCC connectivity with the anterior prefrontal cortex and the precuneus decreased in cMDD patients following the sad mood induction, whereas it increased in non-patient controls.

Limitations: Limitations of this study include the relatively small sample size and lack of a clinical control group.

Conclusions: These findings are in line with neurobiological models of depression suggesting that the observed changes in DMN connectivity following the sad mood induction might reflect a failure to exert cognitive control over negative memory retrieval in patients with cMDD.

1. Introduction

Major depressive disorder (MDD) is a relatively common, psychiatric disorder that often takes a chronic course [1]. Recent efforts to understand the neuropathology of depression have focused on connectivity within or between brain networks that can be identified during rest for reviews see e.g.: [2,3]. The default mode network (DMN), a brain network which has well-documented associations with self-referential processing [4], rumination [3,5] and autobiographic memory [6], plays a key role in the neuropathology of MDD [7]. Numerous studies have now demonstrated that patients with MDD show increased DMN resting-state functional connectivity, compared to non-patient controls [2,8].

Although the finding of increased connectivity in the DMN of MDD patients is fairly consistent [2], connectivity within this network might not necessarily be stable. For example, a number of studies have shown that DMN connectivity in depression changes when symptoms improve following treatment with antidepressants [9]. Moreover, changes in mood states might also drive network dynamics. For example, studies in non-depressed [10] and remitted depressed [11] participants have shown that DMN connectivity can be modulated by a sad mood induction. Harrison et al. (2008) used a combination of autobiographical recall and classical music to induce a neutral (scan 1) or sad (scan 2) mood state in healthy participants. The authors found that the

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strength of DMN connectivity decreased in the sad vs. neutral mood induction condition [10]. Zamoscik et al. (2014) used a combination of autobiographical recall and classical music to induce sad mood in individuals with remitted depression and healthy controls. The authors found that individuals with remitted depression showed greater connectivity between the PCC and parahippocampal gyri following the sad mood induction compared to healthy controls [11].

Whereas these previous studies reveal important mechanisms as to how DMN connectivity can be modulated by a sad mood induction in healthy or previously depressed individuals, it is unclear how patients with a current MDD modulate connectivity in the DMN following a sad mood induction. Given that connectivity within the DMN is positively correlated with depressive chronicity [12], it is intriguing to study DMN connectivity following a sad mood induction in patients with chronic major depressive disorder (cMDD). Therefore, the aim of the present study was to investigate resting state connectivity of the DMN in patients with a current cMDD and matched non-patient controls before and after a sad mood induction.

Harrison et al. (2008) instructed participants to actively visualize and ruminate about the event recalled. The authors argued that the sad mood-induction might require more cognitive effort from their healthy participants whereas neutral recall might require less cognitive effort. Given previous findings of task induced deactivation of the DMN they expected that the sad vs neutral mood induction would lead to reduced DMN connectivity [10]. However, DMN connectivity in individuals with depression, compared to non-depressed individuals, is generally increased and immersing in a sad mood state might be less effortful for individuals with depression compared to non-depressed individuals. Moreover, the sad-mood induction that was used in the current study was conducted prior to scanning and did not require participants to engage in a task during scanning. Finally, as has been argued by Zamoscik et al. (2014) a negative mood induction can trigger increased self-referential processing in (remitted) depressed patients, increasing DMN connectivity. Based on these previous findings it is hypothesized that compared to non-patient controls, cMDD patients would show increased connectivity in the DMN following a sad mood induction.

2. Method

2.1. Participants

Eighteen patients with chronic major depressive disorder (cMDD) and 18 age, education level and gender matched non-patient controls participated in this study. Non-patient controls were also matched on left/right handedness except for one left handed patient who could not be matched with a left handed control participant. Patients were recruited from a specialized secondary care outpatient unit in the Netherlands (Riagg Maastricht) as part of a treatment study [13]. All patients were scanned before the start of the intervention phase of the treatment study. Non-patient controls were recruited via poster advertisements and a volunteer database. Participants were excluded if they had MRI contraindications.

Inclusion criteria for patients in the treatment study were a current diagnosis of cMDD defined as meeting Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria of major depressive disorder for ≥2 years, assessed with the Structured Clinical Interview for axis-I Disorders (SCID-I) by trained interviewers and a Beck Depression Inventory second edition (BDI-II) score of 20 or higher at study entry. Exclusion criteria for patients in the treatment study were the presence of bipolar disorder, psychotic disorders, alcohol or substance dependence, autism spectrum disorders, cluster-A or cluster-B personality disorder and acute suicide risk. One patient with co-morbid borderline personality disorder was not included in the treatment study but is included here. Use of antidepressant medication at study entry was an exclusion criterion, unless patients were stable on medications for three month or longer prior to study entry (n=10; 55.6%). Control participants meeting any current DSM-IV axis-I disorder or lifetime mood disorder, as assessed with the SCID-I interview were excluded.

Table 1
Demographic and clinical characteristics of the sample.

	cMDD (*N* =18)	Controls (*N* =18)	*t*-test (*p*-value)	χ2 (*p*-value)
Age, M (SD)	41.17 (17.53)	42.67 (18.73)	0.81	–
Gender, n (%)			–	1.00
female	13 (72.2)	13 (72.2)		
male	5 (27.8)	5 (27.8)		
Education level, n (%)			–	0.68
low	1 (5.6)	2 (11.1)		
medium	6 (33.3)	4 (22.2)		
high	11 (61.1)	12 (66.7)		
BDI-II score, M (SD)	30.50 (9.39)	2.67 (2.77)	< 0.001	–
# Previous episodes, M (SD)	3.38 (2.39)	–	–	–
Antidepressant use at baseline, n (%)	10 (55.6%)	–	–	–

Note. BDI-II = Beck Depression Inventory second edition; cMDD = chronic Major Depressive Disorder. Information on number of previous episodes was available from 16 patients.

The study protocol was approved by the medical ethical committee of the academic community hospital Maastricht, the Netherlands (Protocol ID/number: NL 31871.068.10). After complete description of the study to the participants, written informed consent was obtained. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Demographic and clinical characteristics of the sample are summarized in Table 1.

2.2. Procedure

This study used a mixed design with group (cMDD, non-patient controls) as between-subject factor and two fMRI runs (pre mood induction, post mood induction) as within subject factor. First, participants underwent a 6 min resting-state scan. Participants then rated their current mood along four visual analogue scales (VAS) ranging from 0 to 100 with higher scores representing more positive mood using an MR compatible joystick. The four VAS scales measured mood on a bipolar continuum between negative and positive, dull and glad, secure and anxious, and sad and happy. After the initial mood ratings, participants received the sad mood induction, consisting of mood suggestive music ("Adagio for Strings" by Samuel Barber played via headphones), played during the anatomical scan, in combination with autobiographical recall of a personal sad event (8 min). This standard protocol reliably induces short lasting sad mood-states [14] and the specific piece of music has successfully been used in our previous studies [15,16]. Directly after the sad mood induction, current mood-state was again assessed along the four VAS scales. Following this, participants underwent the second resting-state fMRI scan (6 min). After the second resting-state scan participants again rated their current mood-state on the four VAS scales.

2.3. Measures

2.3.1. Beck depression inventory

Depressive symptom severity was assessed using the Beck Depression Inventory second edition (BDI-II), a 21-item self-report instrument [17]. In the present study the Dutch version of the BDI-II was used which has been shown to have high internal consistency in a Dutch sample of psychiatric patients (Cronbach's α=0.92) and ade-