Neural correlates of self-referential processing and implicit self-associations in chronic depression

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ABSTRACT

Background: Patients with depression tend to process negative information with regard to the self (i.e. self-referential processing). A better understanding of the neural underpinnings of self-referential processing in patients with depression is clinically important as it can inform on potential treatment targets.
Method: This fMRI study sought to study the neural correlates of self-referential processing in patients with chronic major depressive disorder (cMDD) (n=17) and non-patient controls (n=18) using a passive processing paradigm. Stimuli consisted of positive, negative, negative depression related and neutral personality trait words or non-words. Participants were instructed to indicate whether a presented word was an existing word or a non-word while undergoing an fMRI scan. Participants also completed an explicit and an implicit measure of positive and negative self-associations outside the scanner.
Results: Non-patient controls had relatively increased activity in the medial prefrontal cortex (mPFC) during processing of negative depression related vs. neutral words whereas patients with cMDD had relatively decreased activity. Non-patient controls had relatively increased dorsolateral prefrontal cortex (dlPFC) activity during processing of positive vs. neutral words whereas patients with cMDD had relatively decreased activity. Explicit but not implicit self-associations with depression related words were associated with neural activity in the mPFC and the dlPFC. Limitations: The study did not include a clinical control group and therefore the specificity of findings remains unknown. Conclusions: The distinct neural processing of emotional self-relevant stimuli in the mPFC and the dlPFC in patients with cMDD might represent an emotional blunting response towards negative self-relevant stimuli.

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1. Introduction

Patients with depression often show increased self-referential processing, defined as the experience of stimuli "as strongly related to one's own person" (Northoff, 2007, p.3) Functional neuroimaging studies in patients with depression have emphasised the importance of cortical midline structure (CMS) abnormalities during self-referential processing (for reviews see: Lemogne et al. (2012) and Nejad et al. (2013)). Whereas some studies found increased activity in the medial prefrontal cortex (mPFC) in depressed patients vs. non-patient controls during self-referential processing (Lemogne et al., 2009; Yoshimura et al., 2010) other studies found evidence for an opposite pattern (Grimm et al., 2009).

Previous neuroimaging studies on self-referential processing in depressed patients required participants to explicitly make a judgment regarding the self-relatedness of a stimulus (i.e. explicit processing paradigms). For example, in one study participants were instructed to judge whether a presented stimulus was self-

related or not (Lemogne et al., 2011). As acknowledged by the authors, one drawback of instructing participants to engage in self-referential processing is that such instructions elicit 'controlled' rather than more 'automatic' self-referential processing (Lemogne et al., 2011). According to cognitive theories, patients with depression tend to automatically process schema congruent information (Segal, 1988). Passive processing paradigms might therefore more closely resemble the way in which persons with depression process positive and negative information. Neural correlates of these more automatic aspects of self-referential processing can be studied by presenting participants with depression with either schema congruent information (i.e. negative stimuli) or schema incongruent information (i.e. neutral or positive stimuli) during fMRI.

On a behavioural level, self-associations can also be assessed explicitly and implicitly. Explicit assessment of self-associations requires participants to reflect upon their own self and to make an explicit judgment about the self. Yet, schematic information processing operates on an automatic, implicit level (Segal, 1988). Implicit rather than explicit self-associations might therefore more closely be related to neural correlates of self-referential processing. Given that the duration of a depressive episode (i.e. chronicity) is associated with stronger implicit negative self-associations (Elgersma et al., 2013) it is intriguing to study negative self-associations and the neural correlates of self-referential processing in patients with chronic depression.

The aim of the current study was to investigate the neural correlates of self-referential processing in patients with chronic major depressive disorder (cMDD) and matched non-patient controls using a passive processing paradigm. In addition, we examined explicit and implicit self-associations (assessed outside the scanner) with positive and negative personality traits in the same group of participants. We hypothesised that (1) patients with cMDD show a differential activation pattern in areas of the brain that have previously been associated with self-referential processing (i.e. CMS) during presentation of schema-congruent (negative and depression-related negative trait words) vs. schema incongruent (neutral or positive trait words) compared to non-patient controls; (2) neural activity in CMS is positively correlated with explicit and implicit self-associations of personality traits, as assessed outside the scanner.

2. Method

2.1. Participants

Eighteen patients with cMDD and 18 non-patient controls matched on age, gender, education level and left/right-handedness were recruited for this study. One left handed patient could not be matched to a left handed non-patient control and was therefore matched to a right handed non-patient control participant. After data acquisition, one cMDD patient had to be excluded because of technical problems with the MRI scans. The final sample analysed therefore comprised 18 non-patient controls and 17 patients with cMDD. The study protocol was approved by the medical ethical committee of the academic University Hospital Maastricht, the Netherlands and all participants enroled in the study signed written informed consent.

Patients were recruited from a specialized secondary mental health facility in the Netherlands (Riagg Maastricht) as part of a treatment study (Clinicaltrials.gov identifier: NCT01153867). Scanning of patients took place prior to the intervention phase of the study. Patients were included if they met the DSM-IV criteria for chronic Major Depressive Disorder (i.e. if they met the criteria for Major Depressive Disorder for two years or longer), assessed

with the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) and if they scored 20 or higher on the Beck Depression Inventory second edition (BDI-II), indicating moderate levels of depression. Patients were excluded if they were suicidal or if they fulfilled DSM-IV criteria for bipolar disorder, psychotic disorders, alcohol or substance dependence, autism spectrum disorders or cluster-A or cluster-B personality disorder as assessed with the SCID-II interview. One patient with co-morbid borderline personality disorder was included in error but is analysed here. Patients who took antidepressant medications were excluded, unless they were stable on medication for 3 months or longer prior to study intake. Nine (53%) patients with cMDD took antidepressant medication (8 SSRI's 1 TCA) and were stable on medication for at least 3 months, except for one patient for whom the medication dosage was adjusted two month prior to the study.

Non-patient controls were recruited via poster advertisements and a volunteer database. Non-patient controls were excluded if they met the DSM-IV criteria for a current axis-I disorder or any lifetime mood disorder.

Table 1 provides an overview of the demographic and clinical characteristics of the sample.

2.2. Materials

2.2.1. Beck Depression Inventory second edition

The Beck Depression Inventory second edition (BDI-II) is a 21-item self-report instrument assessing depressive symptom severity (Beck et al., 1996). In the present study depressive symptom severity during the past 7 days were assessed. The Dutch BDI-II that was used in the present study has good psychometric properties (van der Does, 2002).

2.2.2. Implicit task – single-category implicit associations test

A depression specific single-category implicit association test (SC-IAT) was used to assess implicit negative self-associations (outside the scanner). The task started with a practise block in which 12 positive and 12 negative words (attributes) were presented, followed by two test blocks. Test blocks included a third word category (self-stimuli). During the test blocks the self-stimuli shared a response key with either the positive or the negative attributes (counterbalanced). Each test block started with 12

Table 1
Demographic and clinical characteristics of the sample.

Measure	Patients (n=17)	Controls (n=18)	t-test (p-Value)	χ2 (p-Value)
Age, M (SD)	40.41 (17.77)	42.67 (18.73)	.72	–
Gender, n			–	.92
Female	12	13		
Male	5	5		
Education level, n			–	.80
Low	1	2		
Medium	5	4		
High	11	12		
BDI-II score	30.47 (9.68)	2.67 (2.77)	<.001	–
ADM use, n	9	–		
SSRI	8	–		
TCA	1	–		

Note. ADM=Antidepressant medication; BDI-II=Beck Depression Inventory second edition; SSRI=Selective Serotonin Reuptake Inhibitor; TCA=Tricyclic Antidepressant.