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Research report

Rose or black-coloured glasses? Altered neural processing of positive events during memory formation is a trait marker of depression

Jennifer F. Arnold [a,b,*], Daniel A. Fitzgerald [b,d], Guillen Fernández [b,e], Mark Rijpkema [b], Mike Rinck [d], Paul A.T.M. Eling [c], Eni S. Becker [d], Anne Speckens [a], Indira Tendolkar [a,b]

[a] Radboud University Nijmegen Medical Centre, Department of Psychiatry, The Netherlands
[b] Radboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging, The Netherlands
[c] Radboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour, Centre for Cognition, The Netherlands
[d] Radboud University Nijmegen, Behavioural Science Institute (BSI), The Netherlands
[e] Radboud University Nijmegen Medical Centre, Department of Neurology, The Netherlands

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ABSTRACT

Background: Valence-specific memory enhancement is one of the core cognitive functions that causes and maintains Major Depressive Disorder (MDD). While previous neuroimaging studies have elucidated the neural underpinnings of this emotional enhancement effect in depressed patients, this study aimed at detecting processing biases that are maintained throughout remission while patients were euthymic.
Methods: Fourteen medication-free women remitted from unipolar MDD and 14 matched controls were scanned while learning negative, positive, and neutral words, which were subsequently tested with free recall.
Results: The two groups did not differ in memory performance and showed no neural differences during successful encoding of neutral or negative words. However, during successful encoding of positive words, patients exhibited a larger recruitment of a set of areas, comprising cingulate gyrus, right inferior- and left medial-frontal gyrus as well as the right anterior hippocampus/amygdala.
Limitations: Restriction to female participants may limit the generalization of the findings.
Conclusion: Female MDD patients in clinical remission exert greater neural recruitment of memory-related brain regions when successfully encoding positive words, suggesting that neural biases related to memory formation of positive information do not entirely normalize. Further research is needed to establish whether this processing bias during successful memory formation of positive information is predictive for future relapse thereby offering the possibility to develop more focused therapeutic interventions to specifically target these processes.

1. Introduction

Memory facilitation for emotional events is a well-recognized phenomenon with clear advantages in adaptive behaviour (McGaugh, 2004). While enhancement of emotional information has been shown for positive information in healthy participants (Bradley et al., 1995; Denny and Hunt, 1992), depressed individuals have demonstrated an opposite enhancement of emotional memory for negative information or

* Corresponding author. Radboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 24 36 68236; fax: +31 24 36 10989.
E-mail address: J.Arnold@donders.ru.nl (J.F. Arnold).

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reduction of memory for positive information (e.g. Bower, 1981; Ellwart et al., 2003; for a direct comparision between anxiety and depression see for example Rinck and Becker, 2005). This so-called mood-congruent memory bias is thought to be one of the core cognitive processes that causes and maintains depression (Hasler et al., 2004). Sad mood at time of encoding might be one of the contributing factors for this memory bias in depressed patients (Teasdale and Dent, 1987). For this reason, previous behavioural studies investigating mood-congruent memory bias have been conducted either while patients were acutely depressed or while patients in remission underwent experimental induction of sad mood (Miranda et al., 1990; Scher et al., 2005; Teasdale and Dent, 1987).

In recent years, functional magnetic resonance imaging (fMRI) has identified brain regions involved in mood-congruent memory formation in depression and suggests abnormal processing during emotional memory encoding in the amygdala, hippocampus, and certain prefrontal regions (Bremner et al., 2007; Bremner et al., 2004; Hamilton and Gotlib, 2008; Ramel et al., 2007; Roberson-Nay et al., 2006; van Wingen et al., 2010). The important role of medial temporal lobe structures in mediating mood-congruent memory bias is not surprising given their core function in declarative memory and emotion (LaBar and Cabeza, 2006). Furthermore, structural imaging studies in MDD show enlarged amygdala volume (e.g. Frodl et al., 2002; van Eijndhoven et al., 2009) and reduced hippocampal volume (e.g. Lange and Irle, 2004; MacQueen et al., 2002). In line with behavioural experiments on mood-congruent memory in depressed patients, the role of the amygdala has mainly been investigated during sad mood (Hamilton and Gotlib, 2008; Ramel et al., 2007). Hamilton and Gotlib (2008) showed that the right amygdala was more active and showed greater functional connectivity with the hippocampus and caudate/putamen in fourteen acutely depressed patients compared to twelve healthy controls during encoding of subsequently remembered negative but not neutral or positive stimuli. Moreover, severity of depression was significantly correlated with memory-related activation of the right amygdala. Along the same lines, Ramel et al. (2007) investigated fourteen participants with remitted depression compared to matched controls. Following sad mood induction, bilateral amygdala response during encoding of emotional words predicted increased recall of negative self-referent words for a subset of remitted participants.

Recently, van Wingen et al. (2010) investigated neural processing biases during emotional memory formation of positive and neutral faces. In addition to altered brain activity related to successful memory formation for positive faces in acute depression, they found altered neural activity following recovery—without an external mood induction. Though the results of van Wingen et al. (2010) were restricted to positive and neutral facial stimuli, they are in line with more global findings that neural processing of positive stimuli remains altered during clinical remission (Teasdale and Dent, 1987), including after treatment with an SSRI (Fu et al., 2007). Some authors have even suggested that in MDD, memory impairment for positive information seems to be the main problem (Burt et al., 1995), an effect which is preserved during recovery (Teasdale and Dent, 1987). Moreover, the results of van Wingen et al. (2010) suggest that even without a negative mood induction, neural processing deficits during memory formation for positive events are present in MDD patients.

The findings mentioned above have led to the idea that depressed individuals over-recruit a neural network involved more generally in enhancing memory for affective stimuli when activated by a stressor that engenders negative affect (Beck, 1971, 2008). However, the focus of these prior studies was placed on the striatal-limbic parts of a neural network thought to be involved in depression, leaving aside the potential role of prefrontal regions. Yet, Okada and colleague shave shown that during a verbal fluency paradigm, prefrontal activity of patients does not normalize after remission suggesting a state independent role of this brain region in processes that underlie verbal memory (Okada et al., 2009). Also general episodic memory deficits in depression have been linked to prefrontal dysfunction (Fossati et al., 2004b), which mediates strategic retrieval attempts and monitors their outcome (Buckner and Wheeler, 2001). Thus far, most of the previous research on memory biases was conducted in currently depressed individuals or using a sad mood induction, leaving it unclear whether patients with remitted depression really exhibit changes in emotional memory formation in a euthymic state. Should this be the case, memory biases may be even more important as vulnerability factors for the development of future episodes of depression distinct from a truly mood-state related memory bias (e.g. Gotlib and Krasnoperova, 1998) and should therefore receive special attention during treatment.

Therefore, in the present study we set out to elucidate the role of prefrontal and medio-temporal regions in emotional memory in remission of MDD. We investigated fourteen remitted medication-free depressive patients and fourteen matched healthy controls. Similar to Ramel et al. (2007), we used verbal material of different affective valence. Brain activity was measured by means of event-related functional MR imaging while participants were asked to memorize lists of mixed emotional and neutral words. In addition to whole-brain analysis, we used small volume correction analysis for the amygdala and hippocampus. The doubled prevalence of mood disorders in women (Kendler et al., 2006; Kendler et al., 1996) suggests a gender-specific pathophysiology; we thus included only female participants. In order to control for possible confounding effects of general neuropsychological deficits often found in depression, we included a broad neuropsychological assessment.

The setup of the study at hand was primarily intended to investigate neural activation differences with fMRI so that we took this into account when estimating the sample size. Therefore, we do not expect to find significant behavioural differences in any direction. However, we do expect to find altered neural activation patterns to emotional memory formation in our patient group. We hypothesize that this altered neural activation can be found not only in limbic but also prefrontal regions related to emotional memory.

2. Materials and methods

2.1. Participants

Fourteen women in remission from a Major Depressive Disorder (MDD) and 14 never-depressed women without a history of any psychiatric disorder participated in this study. Patients were recruited via newspaper advertisements, postings on depression-related websites and from the department of psychiatry of the Radboud University