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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

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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.

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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

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reduction of memory for positive information (e.g. Bower, 1981; Ellwart et al., 2003; for a direct comparison 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 Irlé, 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 have 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

Nijmegen Medical Center. Control participants were recruited via advertisement and from an online participation system operated by the university.

For an overview of participants characteristics see Table 1. All participants were right-handed, physically healthy and did not use any medication. Exclusion criteria were a history of severe somatic diseases, current or past alcohol or substance abuse/dependency, current psychotropic drug use, and postmenopausal phase. Pregnancy, claustrophobia, and metal implants were also exclusion criteria. Participants with psychiatric diagnoses other than MDD as assessed with the Mini International Neuropsychiatric Interview (M.I.N.I) (Sheehan et al., 1998) were excluded. All remitted patients met criteria for a DSM-IV-TR (American Psychiatric Association, 2000) diagnosis of unipolar MDD in the past, but not at the moment of scanning. Diagnoses were established by use of the revised Structural Clinical Interview for DSM (SCID-I;

mood section) (First et al., 1996). In addition, former patients were required to obtain scores in the minimal symptom range ($HDRS_{17} < 10$) and consider themselves as fully remitted. To avoid potential confounds of chronicity, we included only patients with less than three depressive episodes in the past.

Informed consent was obtained from all participants. They were paid about 50€ and their travel expenses for participation. The study protocol was approved by the local ethical committee (CMO region Arnhem-Nijmegen, The Netherlands, Nr. 2007/084).

2.2. Measures

We assessed psychopathology by Dutch versions of the

- (a) The Structured Clinical Interview for DSM-IV Disorders (SCID) (First et al., 1996).

Table 1

Demographic, clinical, and neuropsychological characteristics of remitted MDD patients and healthy control participants.

	Remitted patients N = 14			Healthy controls N = 14		Group effect ^a p ^b
	Mean	SD	%	Mean	SD	
Demographic variables						
Age	28.79	10.03		27.71	8.80	.77
Sex (male/female)	0/14			0/14		1.00
Handedness (left/right)	0/14			0/14		1.00
Educational level (1–5) ^b	4.71	0.73		5.00	0.00	.15
Clinical variables						
HDRS 17-item score	5.29	3.71		0.64	0.93	**
STAI State Mean	37.57	9.11		30.71	6.45	*
Trait Mean	49.14	12.90		29.93	6.89	**
Total Mean	86.71	16.83		60.64	11.30	**
Life events	7.21	5.04		4.64	2.41	.10
PANAS Positive Affect (PA)	25.86	6.10		33.57	4.97	**
Negative Affect (NA)	15.14	9.23		11.07	2.16	.12
Patient characteristics						
No. of episodes	2.29	0.83				
Age of onset (years)	19.21	6.13				
Time since last MDE (month)	16.67	14.32				
Previous AD treatment	8/14		57.14			
Previous Psychotherapy	6/14		42.85			
Neuropsychological variables						
Intelligence estimate						
DART-IQ	90.64	4.72		91.36	5.29	.71
Memory						
AVLT immediate recall	58.21	7.02		55.93	5.78	.36
Delayed recall	12.43	1.87		12.57	1.87	.84
Recognition	29.86	0.36		29.64	0.63	.28
Attention and psychomotor speed						
DSST Code	85.50	13.77		91.71	14.52	.26
DCT Copy	126.64	8.11		127.29	8.07	.84
Executive functioning						
STROOP Card 1	45.57	8.22		45.71	8.96	.97
Card 2	53.71	6.14		54.50	12.20	.83
Card 3	75.50	10.91		82.93	37.76	.49
Verbal Fluency						
Animals	26.38	5.20		27.71	7.22	.59
Letter N	14.23	3.65		15.93	4.76	.31

MDD, major depressive disorder; HDRS, Hamilton Rating Scale for Depression; STAI, State Trait Anxiety Inventory; PANAS, Positive and Negative Affect Scale; MDE, major depressive episode; DART, Dutch version of the National Adult Reading Test; AVLT, Dutch version of the Auditory Verbal Learning Test; DSST, Digit Symbol Substitution Test; DCT, Digit Copying Test.

^a One way analysis of variance (ANOVA) * $p < .05$; ** $p < .01$.

^b Educational level is coded level 1 to 5 (5 = academic), according to the Dutch education system (Loozen and Post, 1991).

- (b) The Mini International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998).
- (c) Hamilton Depression Rating Scale (HDRS₁₇) (Hamilton, 1960).
- (d) Spielberger State and Trait Anxiety Inventory (STAI) (Spielberger et al., 1983).
- (e) Participants also filled in the Positive and Negative Affect Scale (PANAS) (Watson et al., 1988).
- (f) Stressful life events questionnaire (LEQ) (Holmes and Rahe, 1967).
- (g) Centre-intern general health questionnaire to assess scanner compatibility.
- (h) Edinburgh Handedness Inventory (EHI) (Oldfield, 1971).

Further, all participants were also tested with a standard neuropsychological battery:

- (1) Dutch Adult Reading Test (DART) (Nelson and Willison, 1991).
- (2) Digital symbol substitution test (DSST) and Digit copying test (DCT) of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955, 1981).
- (3) Dutch version of the Auditory Verbal Learning Test (AVLT) (Saan et al., 1986).
- (4) Stroop (Golden, 1978).
- (5) Verbal fluency task (Thurstone, 1938).

2.3. Procedure

During a first 2-hour meeting, participants filled in several questionnaires (general health questionnaire, Edinburgh Handedness Inventory, STAI trait, Stressful life-events questionnaire, PANAS). Subsequently, the clinical interviews (M.I.N.I., mood section of the SCID, HDRS) were taken to confirm former MDD diagnose or assignment to the healthy control group. Neuropsychological functioning was assessed using a neuropsychological test battery. During the second 2-hour appointment, all participants were given detailed written information regarding the scanning procedure including the memory and distraction task followed by a practice block inside the scanner, followed by the experimental task. After scanning, all participants filled in the state version of the STAI outside the scanner.

2.4. Experimental task

The experimental paradigm consisted of a free-recall task divided into 20 study-distraction-test cycles of approximately 3 min each. Breaks were interleaved after every five cycles. During the study phase, participants silently read and memorized lists of 12 sequentially presented words. During distraction, they were asked to count back in steps of 3 from a given random number between 80 and 100. This distraction period lasted 40 s and aimed at overriding active working memory. Participants were asked to count back silently, pressing a button for each step and only name the final number aloud when primed. Immediately following the distraction phase, participants were asked to report orally all words they could remember from the previous list within 30 s. All responses were digitally recorded and all stimuli were subsequently transcribed into 'later remembered' or 'later forgotten'. See Fig. 1 for schematic overview.

2.5. Stimuli

We used neutral, positive and negative Dutch words varying in length from five to thirteen letters (mean: 8.6 ± 2.2). They were derived and translated mainly from the Affective Norms for English Words list (ANEW) (Bradley and Lang, 1999). Dutch translations of 1050 words were rated by an independent group of students for their perceived emotional valence with a 15-point Likert scale varying from 'very negative' via 'neutral' to 'very positive'. The minimum number of ratings per word was 11, with an average of 15 ratings ($SD = 5$). Words were segregated into three categories: positive (mean rating of 11 or more), negative (mean rating of 5 or less) and neutral (mean rating between 7 and 9). For the present study, we selected the 160 most negative, the 160 most positive and 160 neutral words, previously also used in related experiments (e.g. Fitzgerald et al., 2009). All 480 words were divided into 40 sets of 12 words each, with 4 negative, 4 positive and 4 neutral words, out of which 20 sets and therefore 240 words were used per participant in a counterbalanced order. Moreover, the sets were assembled such that they did not differ significantly in word length, frequency of use (CELEX database) (Baayen et al., 1995), or type (i.e., adjectives, nouns and verbs). The stimuli were pseudo-randomly intermixed, such that there

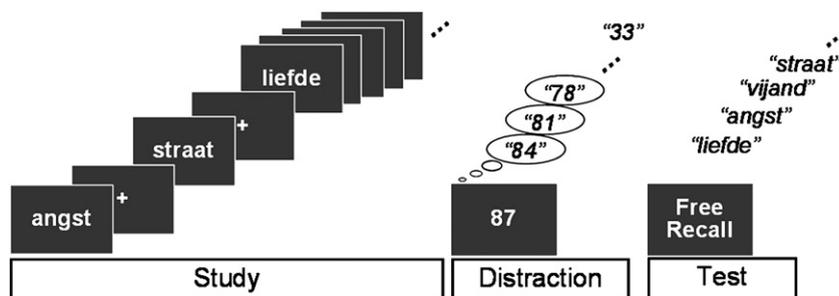


Fig. 1. Schematic overview of a single study run. Participants learn lists of 12 negative, neutral and positive words, whereby they silently count back by 3 for 40 s (pressing a button for every step and naming the last number aloud) and finally within 30 s name all words they remember from the previous list.

were no more than two consecutive words per valence. Words were presented in centred position for 500 ms with a random inter-stimulus interval (ISI) between 4 and 8 s, with 2 'null events' per block—i.e. 2 longer ISIs averaging 12 s per block.

2.6. MRI data acquisition

Imaging data were acquired with a 1.5 T Siemens AVANTO MR scanner (Siemens, Erlangen, Germany), equipped with a standard Siemens 8-channel head coil (Phase Array Head Coil). Functional T2*-weighted blood oxygenation level-dependent (BOLD) images were acquired using echo-planar imaging (EPI), with each image volume consisting of 33 axial slices (3.4 mm, slice-gap = 0.34 mm, FOV = 212 mm, TR = 2190 ms, TE = 35 ms, FA = 90°, final voxel dimension = 3.3 × 3.3 × 3.4 and a bandwidth of 1628 Hz/Px). Anatomical MR scans were acquired using a T1-weighted MP-RAGE sequence (176 slices, voxel size: 1.0 × 1.0 × 1.0 mm, TR = 2250 ms; TE = 2.95 ms, FA = 15°).

2.7. Data processing and statistical analysis

Functional MRI data were processed using Statistical Parametric Mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London, UK). The first four EPI-volumes were discarded to allow for T1 equilibration, the remaining images were spatially realigned, slice-time corrected and co-registered to the participant's T1 scan, which was then used to normalize with the standard MNI template. Resulting images were smoothed using an 8 mm FWHM Gaussian kernel, and high-pass filtering removed low-frequency noise.

Statistical analysis was performed within the framework of general linear model (Friston et al., 1995). 'Later remembered' and 'later forgotten' stimuli were separately modelled for each of the word types (positive, negative, and neutral). The relevant parameter images were entered in a random-effects repeated measure ANOVA with a non-sphericity correction. Given that the purpose of the study was to investigate valence-specific effects in memory formation between the remitted patients and controls, we directly focused on the interaction of the factors Group, Recall and Valence. These statistical tests were investigated at an uncorrected p-value of 0.001 (if not otherwise stated) and were cluster corrected at the whole brain level ($p_{\text{corrected}} < 0.05$). Given clear *a priori* predictions of brain activation differences in the amygdala and hippocampus, we applied small volume correction (SVC) using anatomical region of interest (ROI) masks for bilateral amygdala and hippocampus from Brodman area atlas implemented in the SPM WFU Pickatlas toolbox (version 2.4) (Maldjian et al., 2003). Results in these areas were considered significant at $p_{\text{SVC}} < 0.05$.

3. Results

3.1. Participants characteristics

As can be seen from Table 1, the patients and controls did not differ on any demographical variable including the number of life events. Both groups did not show any significant differences on the neuropsychological measures

of intelligence (DART), memory (AVLT), attention (DSST), processing speed (DCT), executive functioning (STROOP) or verbal fluency suggesting that no global differences in neuropsychological performance could account for differences in neural activity related to emotional memory formation. Ten of the 14 former patients met the definition (Frank et al., 1991) for fully remitted depressed patients ($\text{HDRS}_{17} < 7$), four had a score in the minimal symptom range ($\text{HDRS}_{17} < 10$). Nevertheless all former patients considered themselves as fully remitted. As expected, patients reported more anxiety symptoms (STAI) and revealed less positive mood ratings (positive affect, PA, scale of the PANAS) compared to controls. To control whether our findings are based only on these mood differences, we conducted our subsequent analyses with the positive affect PANAS scores as covariate.

Patients experienced their first major depressive episode (MDE) at 19 years of age. However, the time interval since the last MDE (mean = 16.67 months) did not correlate with either the PANAS scores (PA: $p = .306$; NA: $p = .439$) or the HDRS ($p = .831$) scores.

3.2. Behavioural performance

Participants recalled about 42% of all words they were shown during the learning phases. An overview of the mean memory performance is given in Fig. 2. As is evident from this figure patients recall less positive words. However, a 2 (Recall: remembered vs. forgotten) × 3 (Valence: negative vs. neutral vs. positive) ANOVA with Group (remitted patients vs. controls) as between subject factor revealed no significant results. Thus, no general memory impairment, valence-specific facilitation or general emotional memory enhancement in either group was found.

4. fMRI results

In an initial whole brain analysis for all participants we found a subsequent memory effect significant at trend-level, i.e. more activity for later remembered compared to forgotten words in left inferior frontal gyrus ($-38, 40, -12$; $p_{\text{corrected}} = .07$) at an uncorrected p-value of 0.005. The ROI analysis showed a

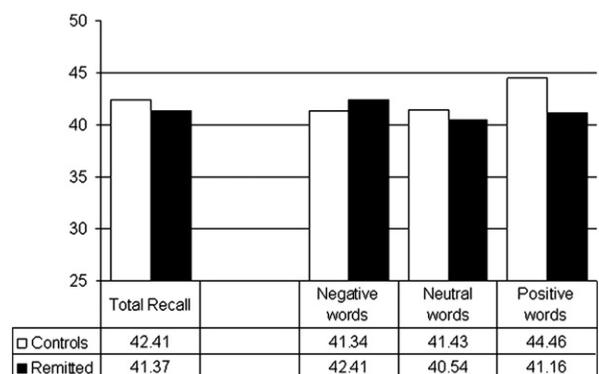


Fig. 2. Behavioural results (absolute recall rate and relative recall per valence in%).

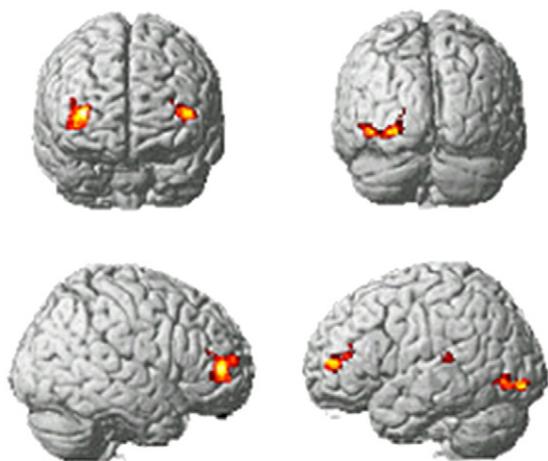


Fig. 3. Interactions between group, recall and valence (positive vs. neutral words). Only clusters significant at $p_{\text{corrected}} < 0.05$ are depicted.

significant activation of the left amygdala ($-18, -8, -14$; $p_{\text{SVC}} < .05$) and a trend-level activation within the left hippocampus ($-28, -12, -18$; $p_{\text{SVC}} = .07$). The analysis including the PANAS scores revealed the same regions and significant levels.

4.1. Group \times recall \times valence

Most important with respect to the experimental question, we wanted to investigate valence-specific effects in memory formation between remitted patients and controls. We therefore investigated whether there was a significant interaction between the factors Group, Recall and negative vs. neutral stimuli (Valence). This analysis did not give rise to any significant effects. However, the whole-brain analysis gave rise to a strong three-way interaction between the factors Group, Recall and positive vs. neutral Valence. This difference in successful memory formation for positive stimuli between groups was significant in a set of brain regions comprising medial frontal gyrus left ($-40, 52, 8$; $p_{\text{corrected}} < .05$) and right ($34, 44, 6$; $p_{\text{corrected}} < .005$), as well as right anterior cingulate gyrus ($6, 10, 28$; $p_{\text{corrected}} < .05$), and right posterior cingulate gyrus ($8, -58, 32$; $p_{\text{corrected}} < .05$), left superior temporal ($-42, -34, 12$; $p_{\text{corrected}} < .001$) and left fusiform gyrus ($-32, -62, -4$; $p_{\text{corrected}} < .005$). For an overview of the significant activations in this analysis see Fig. 3. Next, we further explored this interaction by comparing the subsequent memory effect between controls and patients separately for positive and neutral stimuli. While the between-group comparison for neutral stimuli did not give rise to any significant effects, the between-group comparison for the subsequent memory effects for positive stimuli confirmed that the aforementioned three-way interaction was based on an inverted subsequent memory effect in the remitted patient group compared to controls in right anterior ($6, 10, 30$; $p_{\text{corrected}} < .001$) and left posterior cingulate gyrus ($0, -54, 20$; $p_{\text{corrected}} < .05$) as well as right inferior frontal ($60, 14, 28$; $p_{\text{corrected}} < .005$) and left medial frontal regions ($-42, 46, 16$; $p_{\text{corrected}} < 0.02$ and $-24, -10, 54$; $p_{\text{corrected}} < .005$). Finally, the ROI analysis of amygdala and hippocampus showed that the subsequent memory effect related to positive stimuli for remitted patients was greater in the right amygdala/anterior

hippocampus ($16, -10, -16$; $p_{\text{SVC}} < .05$). All whole brain and ROI results are comparable on regions and level of significances when including PANAS score as covariate. Investigation of the mean beta-values shows that the effect arises due to inverted bar graphs for positive words in the patient group, probably suggesting more default network activation interfering with memory. See Fig. 4a and b for examples of inverted effect in the anterior cingulate gyrus and the right amygdala.

5. Discussion

In the present study we investigated whether there is any evidence for altered neural processing during emotional memory formation in female patients with remitted depression compared to a group of matched controls. Despite the absence of behavioural differences, we found altered neural processing during successful memory for positive words. Given the behavioural results, this effect is probably not simply related to quantitative but rather qualitative differences present during remission from depression.

The neuropsychological results suggest that there was no global difference between patients and controls supporting the idea that remitted patients early in the course of depression do not yet show chronic neuropsychological deficits (for a review see Kessing, 1998), and therefore general neuropsychological deficits are eliminated as potential confounding factors. Most relevant, the neuropsychological memory test (AVLT) revealed no memory impairment within the patient group. Consistently, there was also no difference in general experimental memory performance between the groups. These findings are in line with most other studies that investigated memory performance in the early course of MDD (Basso and Bornstein, 1999; Fossati et al., 2004a; MacQueen et al., 2002). Some behavioural studies suggested that depressed patients show impaired memory for positive material (Burt et al., 1995). In remission, a facilitated negative memory is only observed after mood induction, but impaired memory for positive material remains (Teasdale and Dent, 1987). In the present study, valence-specific behavioural memory biases are absent, which can be explained by the euthymic mood state and the relatively small sample size. The remitted patient group still revealed subtle, however not clinically-relevant changes in mood reporting less positive affect (PANAS), compared to the control group that may have accounted for the slight decrease in recall for positive words, which however did not reach significance. In line with this notion, patients still reported more depressive (HDRS) and anxious (STAI) symptoms than controls. Levels of negative affect (PANAS) were comparable to healthy controls supporting the remission state. Given this remission state it is not surprising that they do not show a negative memory bias as acutely depressed patients often do. The absence of memory performance differences, however, is advantageous for interpreting the imaging results, because differences in performance may change the observed neural effects (Morcom et al., 2007).

When investigating patients early in the course of MDD, this raises the possible risk of including subjects that subsequently develop a bipolar rather than a unipolar course with the confound of a different underlying pathophysiology.

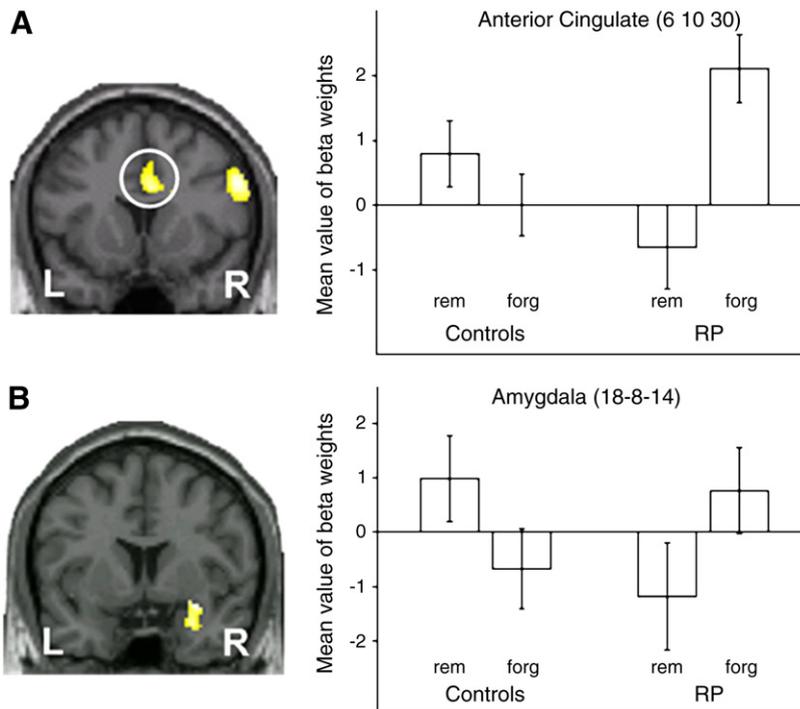


Fig. 4. Interactions between group and recall of positive words for A) whole brain activation of the right anterior cingulate and B) the anterior hippocampus/amygdala region of interest (RIO) with plots of the respective beta-values. The two plots show exemplary that the beta-values for remitted patients and controls show an inverted pattern for subsequently remembered and forgotten positive words. RP: remitted patients; rem: subsequently remembered words; forg: subsequently forgotten words. Left is left and right is right.

Note, that we tried to detect possible signs of mania with particular care when screening our patients with the structured interviews (SCID, M.I.N.I.). Moreover, given the relatively small prevalence of bipolar depression (lifetime women <1%), compared to the great prevalence of unipolar depression (lifetime women >20%), the possible chance to unintentionally measure bipolar instead of unipolar patients is relatively small. Therefore, we feel confident that our results are not crucially confounded by masked bipolar diseases.

During general successful memory formation, our functional MR imaging results support the well-known engagement of inferior frontal regions as well as amygdala and hippocampus, which has extensively been discussed elsewhere (for review see LaBar and Cabeza, 2006). That the activation of inferior frontal gyrus and the hippocampus only reached trend-level significance is probably due to the relative small sample size. However, we were particularly interested in investigating the neural underpinnings of valence-specific differences in successful memory formation between groups. Indeed, we found in the patient group that successful memory formation for positive words was associated with altered neural activity in a network comprising medial and inferior frontal regions, anterior and posterior central gyrus as well as amygdala.

The psychological processes involved in recognition of the emotional significance of a stimulus and the neural substrates of these processes in healthy individuals are relatively well defined. After analysis of the visual features in the visual cortex, emotion recognition and emotional responses take

place within the amygdala, insula, orbitofrontal cortex and ventral striatum (Phillips et al., 2003a). Emotion regulation, however, is associated with the anterior cingulate, and dorsolateral and dorsomedial prefrontal cortex, regions that are also relevant for memory formation. Our findings of prefrontal regions showing differences between patients and controls during successful memory formation for positive words are in line with other studies of depression showing abnormal levels of activity in prefrontal regions (Drevets, 2000; Phillips et al., 2003b; van Wingen et al., 2010) suggesting a difference in prefrontally-mediated monitoring mechanisms. Activity in left inferior frontal gyrus (IFG) has a long history of being linked to conceptual semantic processes during successful memory formation (Gabrieli, 1996; Wagner et al., 1998), in particular for verbal information (Buckner et al., 1999; Fletcher and Henson, 2001). Labelling of emotionally-valenced stimuli requires the recruitment of semantic networks in addition to the affective neural network. Our results suggest that additionally medial frontal regions combined with the anterior cingulate cortex that plays a prominent role in monitoring affective responses and are more engaged during the successful formation of positive memories in remitted patients.

The role of the amygdala in depression has been investigated mainly during sad mood (Hamilton and Gotlib, 2008; Ramel et al., 2007) and has shown an increased engagement during mood-congruent memory formation. Recently, van Wingen et al. (2010) reported first evidence that patients remitted from depression exhibit an altered neural processing during memory formation for positive faces

within the amygdala. Using verbal material of positive, negative and neutral valence, our data provide the additional evidence that even when less biologically salient stimuli and no mood induction are employed, patients who are clinically remitted from depression still show evidence for an altered processing of positive information during successful encoding.

Given the inversion of the neural effect related to successful memory formation in the patient group, our data do not suggest that remitted patients simply require more neural activity to process positive words equally successfully. As a speculative note, positive words may not simply be more difficult to remember but rather induce task-irrelevant processing which has to be reduced to successfully form a specific memory trace (Henckens et al., 2009). The lack of differences in successful memory for negative words supports behavioural findings that the negative bias present in acute depression, normalizes in remission. Impaired recall of positive stimuli in acute depression has been demonstrated previously and does not seem to respond fully to antidepressant treatment (Fu et al., 2007). However during remission an altered processing for positive events during memory formation has not been shown yet and should be further investigated. It is commonly accepted that amygdala activity relates to successful encoding of emotional information (Cahill et al., 2001; Canli et al., 2000) and that it can modulate hippocampal activity during successful memory formation (Dolcos et al., 2005). Hence our data suggest that the decreased sensitivity of amygdala during successful encoding of positive information could also have a modulatory effect on the hippocampus, an effect we found to be significant at a trend level. Cognitive biases have been identified as critical cognitive factors in the etiology not only of depression but also of other emotional disorders. Earlier theories have suggested that attention, memory and interpretation biases should be even evident in affective disorders (Beck et al., 1985). However empirical studies did not support this hypothesis and show that only in depression explicit memory biases can be found (for a direct comparison between anxiety and depression see for example Rinck and Becker, 2005). Finally, these results are interesting in the light of our study sample characteristics. We only included women, which have a much higher risk of developing a mood disorder (Kendler et al., 2006; Kendler et al., 1996). Our gender-specific approach was supported by the findings of Ramel et al. (2007), showing that increased bilateral amygdala responses during encoding of valenced words was only demonstrated by female participants. In addition, older studies on healthy controls suggest sex differences in the hemispheric distribution of encoding-related amygdala activity, especially in relation to memory (e.g. Cahill et al., 2001). While previous functional imaging studies have not paid much attention to gender-specific effects on emotional memory formation, our results suggest that women who have been depressed before may remain vulnerable due to an impaired processing of positive stimuli during encoding. This should be investigated more fully in future studies.

In conclusion, rather than confirming a facilitation of the encoding of negative stimuli, we found evidence of an altered processing of positive stimuli in remitted female patients. Our results suggest that the neural activity within a brain circuit of

anterior and posterior regions involved in emotional memory formation is still altered in remission from depression and therefore may also influence the memory for personally meaningful positive events. From the clinic one knows that depressed patients in remission often underestimate positive aspects of their lives. Here, during use of non-self-referential positive words within an experimental task, we still see (Fig. 2) a non-significant decrease in memory for positive words compared to controls. One may speculate that events meaningful to the patient and accompanied with personal emotions, e.g. a conflict, birthday or vacation, could still reveal memories, biased towards forgetting the positive. However, the behavioural result following the found neural differences compared to never-depressed needs further investigation. This phenomenon might make formerly depressed patients vulnerable to new depressive episodes, because the in healthy humans investigated, often unrealistic but nevertheless pervasive optimism bias (Sharot et al., 2007) does not seem to normalize. We may further speculate on the basis of the inverted effects indicating more default network activation that former patients have difficulty to suppress self-referent thoughts, which in turn shifts attention away from relevant information and therefore results in forgetting (Sheline et al., 2009). In other words, remitted patients do process task irrelevant information of any kind within the regions demonstrating the reversed dm-effect when encoding positive words they later do not remember. Activations in these regions do not help encoding but instate hinder correct encoding. Therefore, increased activation here decreases the memory encoding success. This default mode network appears to be overactive in depression and the switching from introspective thoughts to cognitive tasks seems impaired (Sheline et al., 2009). For non-depressed, suppression of the default network or the self is possible in favour of get into the flow of a task. Former patients may fall into rumination reading positive words, maybe because associating personal shortcomings. When never-depressed controls forget information this seems to have different reasons, probably motivational differences between aim group and controls causes that both groups perform evenly well. Therefore, it might be that maintenance of negative schemas (Beck 2008, 1987) is not only the result of a focus on negative but also of a focus away from positive information during memory formation and could have important implications for prevention of recurrence of depression. Cognitive therapy (CT) focuses on reduction of symptoms by weakening or deactivating disorder-related maladaptive schemas and strengthening alternative, more positive modes of thinking. The neural correlates of CT are investigated in the recent years and have been found to target at comparable neural circuits, including anterior cingulate and prefrontal cortex (Clark and Beck, 2010). More recently developed therapeutic strategies, such as mindfulness based cognitive therapy (MBCT) (Kabat-Zinn, 1982) or positive psychology techniques might be also suited to improve the processing of positive stimuli. MBCT has been demonstrated, for example, to increase autobiographical memory specificity and reduces over-generalized memories (Heeren et al., 2009; Williams et al., 2000). Thus, it might be possible to influence emotional memory biases in depression, not only for experimental stimuli, but also with respect to personally meaningful

positive daily-life events, which are probably underestimated during remission from depression. Therefore, further research is required to shed light on the clinical relevance of this phenomenon.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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