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Functional Neuroimaging of State, Course, and Symptom Specificity in Affective Psychopathology

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Chapter 3

Depressive-state dependency of brain activation during emotional memory formation: a longitudinal functional MRI study

Submitted as: Hui Ai, Esther M. Opmeer, Jan-Bernard C. Marsman, Dick J. Veltman, Nic J.A. van der Wee, André Aleman, Marie-José van Tol. Longitudinal functional brain changes in MDD during emotional memory encoding: effects of depressive state and load.

Abstract

Background: The importance of the hippocampus and amygdala for disrupted emotional memory formation in depression is well recognized, but whether abnormal activation of these structures is state-dependent and is subject to enduring depressive symptoms is unclear.

Methods: Forty patients with a diagnosis of major depressive disorder (MDD) and twenty-nine healthy controls (HC) who underwent functional magnetic resonance imaging at baseline (S1) and two year follow-up (S2) were recruited from the longitudinal Netherlands Study of Depression and Anxiety (NESDA). At both time points, participants performed an emotional word encoding and recognition task. At S2, twenty-one patients showed symptomatic remission and nineteen were actively depressed.

Results: Larger symptom improvement was associated with increased activation the right anterior hippocampus extending to the amygdala during encoding of positive words. Furthermore, a group \times time analysis including remitted patients, actively depressed patients and HC indicated that remitted patients showed normalization of activation during encoding of emotional words in this region, with no activation change in HC. No relation between emotional word encoding and percentage of months with depressive symptoms in-between scan moments was observed. Results were independent of medication-use and psychotherapy.

Conclusion: Using a longitudinal design we showed that hippocampal-amygdalar activation during positive memory formation is moderated by the depressive state in MDD, with normalization of response upon naturalistic remission but not by depression duration. Thus, we suggest that hippocampal activation is a state-dependent characteristic, which is not subject to functional 'scarring'. Evaluating the neural correlates of clinical outcome may potentially help identify candidate biomarkers for clinical response.

Introduction

Major depressive disorder (MDD) is a prevalent psychiatric disorder associated with high morbidity and mortality, frequently characterized by a chronic or relapsing/remitting course (Kessler *et al*, 2005). An emotional memory bias has been proposed as a key factor for the development and maintenance of MDD (Ai *et al*, 2015; Disner *et al*, 2011; Everaert *et al*, 2015; Leppänen 2006). This emotional memory bias has been suggested to be a state-independent phenomenon in cross-sectional studies: better memory for negative information and worse memory for positive information have been reported in patients both during an acute depressive state and during remission (reviewed by Bradley and Mathews 1988; Elliott *et al*, 2010). In addition, high neurotic individuals have been found to show an increased negative memory bias (Chan *et al*, 2007), which may underlie their vulnerability to a depressive episode. However, a cross-sectional design does not allow for firm inferences on state-dependency characteristics of emotional memory biases in depression. Longitudinal treatment studies have mostly found memory bias to resolve upon recovery after treatment (Calev *et al*, 1986; Peselow *et al*, 1991), although results were not consistent (Sternberg and Jarvik 1976). Identifying state-dependent markers of MDD may constitute a first step in understanding mechanisms of recovery versus maintenance of depression and may aid in choice of interventions (Maalouf *et al*, 2012; Mayberg 1997).

In healthy individuals, it has been suggested that the amygdala facilitates memory processing of emotional stimuli by modulating hippocampus activation (Dolcos *et al*, 2004; LaBar and Cabeza 2006). In a previous study from our group, we observed hyperactivation of the anterior hippocampus/amygdala during encoding of negative information in actively depressed patients and not in remitted patients (van Tol *et al*, 2012), suggesting that this hyperactivation is state-dependent. However, others have found that amygdalar/hippocampal hyperactivation is also present in remitted patients and therefore likely independent of the depressive state (Ramel *et al*, 2007). During encoding of positive information, hyperactivation of the anterior hippocampus/amygdala (Arnold *et al*, 2011) and hypoactivation of the posterior hippocampus (van Tol *et al*, 2012) have also been revealed as state-independent phenomena. Activation of other brain regions associated with encoding of emotional material (e.g., dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), anterior cingulate cortex (ACC) and insula) was also inconsistently associated with state-dependency (Arnold *et al*, 2011; Kerestes *et al*, 2011; Okada *et al*, 2009; van Tol *et al*, 2012; Van Wingen *et al*, 2010). These ambiguous findings illustrate the limitations

of cross-sectional designs to elucidate depressive-state dependency of brain functioning.

Longitudinal treatment studies have demonstrated both decreases (Fu *et al*, 2004; Sheline *et al*, 2001) as well as increases (Goldapple *et al*, 2004; Neumeister *et al*, 2006; Ritchey *et al*, 2011; Victor *et al*, 2010) in activation and/or metabolism in the amygdala/hippocampus after successful short-term pharmacological (Fu *et al*, 2004; Sheline *et al*, 2001; Victor *et al*, 2010) and cognitive behavioral treatment (Fu *et al*, 2008; Goldapple *et al*, 2004; Ritchey *et al*, 2011) during affective processing or rest. However, effects of symptom improvement on memory processing have not been studied to date. Nevertheless, a large recent multi-modal imaging study failed to show an association between the amygdala and hippocampus responsivity and the therapeutic response to the antidepressant duloxetine during emotional processing (Fu *et al*, 2015). Critically, treatment studies are designed to investigate the short-term mechanisms mediating clinical improvement and therefore might not purely inform us on the correlates of the naturalistic symptomatic state.

Longer duration of depression has been associated with more severe structural and functional abnormalities, related to glucocorticoid-dependent toxic effects of stress (Fossati *et al*, 2004). Studies have indeed confirmed that a longer duration of depressive symptoms was associated with volume loss, especially in the hippocampus (Frodal *et al*, 2008; MacQueen *et al*, 2003; Schmaal *et al*, 2015), which may result in explicit memory deficits (Sapolsky 2000). Recently, medial prefrontal involvement during processing of certain self-related memory has been revealed to differentiate individuals at high-risk for developing MDD from remitted MDD patients (Young *et al*, 2015), suggesting that memory deficits might be a consequence of having experienced a depressive episode. However, to our knowledge, it has not yet been investigated whether longitudinal functional brain changes are related to duration of depression.

In the present study, using a longitudinal within-subject design, we aimed to investigate 1) whether activation of the amygdala and hippocampus during emotional memory encoding in a naturalistic sample of MDD patients is dependent on the depressive state; and 2) whether changes in brain responsivity to emotional information relates to the time with symptoms during this interval. Participants underwent functional magnetic resonance imaging (fMRI) twice, with approximately two years in between. We hypothesized that change in depressive state is associated with a change in activation between S2 and S1 in the anterior hippocampus/amygdala, especially during negative word encoding. In addition, we hypothesized that changes of brain activation in the hippocampus/amygdala

complex during memory encoding of emotional information in patients with MDD would be influenced by depressive load (i.e., percentage of months with depressive symptoms) between the measurements.

Methods and materials

Participants

Participants were recruited from the ongoing neuroimaging sub-study of Netherlands Study of Depression and Anxiety (NESDA) (Penninx *et al*, 2008) and underwent functional magnetic resonance imaging (fMRI) scanning at the University Medical Center Groningen (UMCG), Academic Medical Center (AMC), and the Leiden University Medical Center (LUMC). As a longitudinal naturalistic study, NESDA has been designed as an eight year longitudinal cohort study with measurements at baseline, one-, two-, four-, and eight-year follow-up, with MRI-measurements performed in a subsample at baseline and two-year follow up. The ethical review boards of each participating center approved the study and all participants gave written informed consent.

Exclusion criteria for all participants in the NESDA neuroimaging study at baseline were: age under 18 or over 57 years; current alcohol or substance abuse; presence or history of a neurological or somatic disorder with possible effects on the central nervous system; general 3T MRI contraindications; hypertension; psychiatric medication other than selective serotonin reuptake inhibitors (SSRIs) or infrequent use of benzodiazepines (oxazepam or diazepam, maximum of three times a week, max 20 mg and not within 48 hours before scanning). Exclusion criteria for the second measurement at two-year follow-up (S2) were identical, with the exception of the age criterion. From a cohort perspective, we were less strict on exclusion based on type of medication used (see Table 1 for details). Findings of cross-sectional differences on the baseline measurement (S1) and associations with subsequent course were published elsewhere (Ai *et al*, 2015; van Tol *et al*, 2012).

Complete behavioral data and fMRI data at both S1 and S2 were available of 64 MDD patients and 39 healthy controls. At S1, all patients fulfilled the criteria for a diagnosis of major depressive disorder (MDD) with a half-year recency based on the Composite International Diagnostic Interview (CIDI life time - version 2). An additional diagnosis of social anxiety disorder (SAD), panic disorder (PD) and/or generalized anxiety disorder (GAD) at either S1 or S2 was allowed (See Table 1 for details). For the current analyses, we included only patients who were in a depressive state at S1 defined as a Montgomery-Åsberg Depression Rating Scale (MADRS) score larger than 10 (Zimmerman *et al*, 2004), which resulted in the

inclusion of 40 patients. Ten healthy controls (HC) were excluded based on their current depressive state evaluated by their MADRS scores (MADRS>10, indicative of depressive symptomatology, n=1) and unreliable task performance (n=9; Figure 1). This resulted in the inclusion of 29 HC without any current or life-time DSM-IV diagnosis at both S1 and S2 (Figure 1).

Task paradigm

All participants performed the same event-related, subject-paced, emotional word encoding and recognition task during both fMRI scanning sessions. During the encoding phase, 20 blocks containing 160 stimuli (positive/ neutral/ negative words and baseline trials; 40 each) were pseudo-randomly presented. Participants were instructed to evaluate whether the word was positive, negative or neutral by pressing the right, middle and left button, respectively. During baseline trials, participants were asked to press the corresponding button to indicate the direction of the arrow. After a retention interval of 10 minutes during which the structural T1 scan was acquired, the retrieval phase began during which 120 encoding target words, 120 distracter words and 40 baseline words were presented in 20 pseudo-randomized blocks. Participants were instructed to indicate whether they had seen, had not seen, or probably had seen the word. Emotional words in the valence categories were matched based on length, frequency in the Dutch language and complexity.

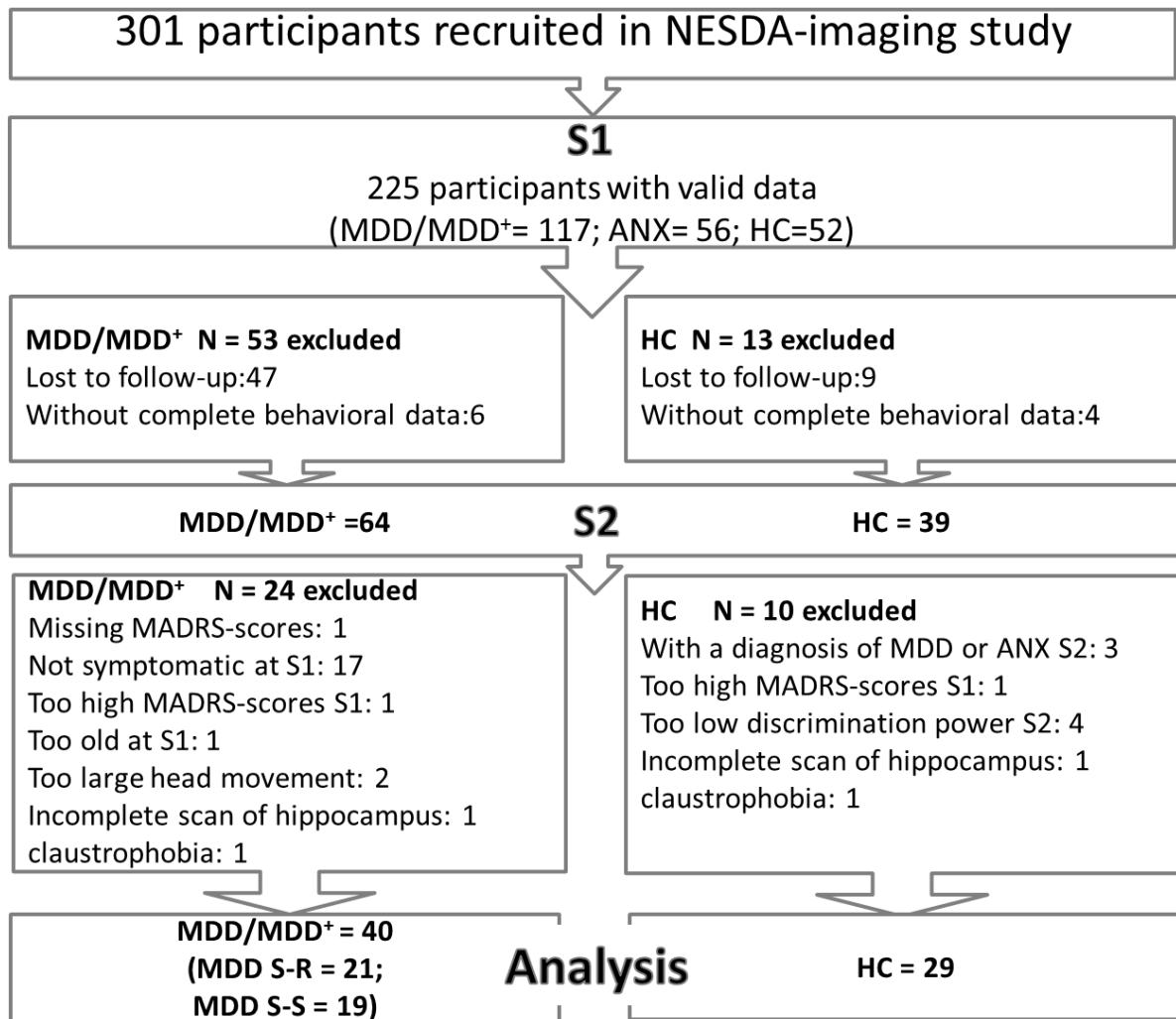
fMRI data acquisition

Neuroimaging data were collected with 3T Philips MR-scanners located in Leiden, Groningen and Amsterdam. A SENSE-6 channel head coil was used at S1 in Amsterdam. A SENSE-8 channel head coil was used in Groningen and Leiden at both S1 and S2 and in Amsterdam at S2. In Groningen, echo planar imaging (EPI) volumes of 39 slices were acquired using a T2*- weighted gradient echo sequence (TR = 2300 ms, TE = 28 ms, matrix size: 64 × 64, plane resolution: 3 × 3 mm, slice thickness: 3 mm) at S1 and the EPI slice setting was changed into 35 slices at S2. In Leiden and Amsterdam, 35 axial slices were obtained using a T2*- weighted gradient echo sequence (TR = 2300 ms, TE = 30 ms, matrix size: 96 × 96, plane resolution: 2.29 × 2.29 mm, slice thickness: 3 mm) at S1 and S2. Transversal slices were acquired parallel to the anterior commissure-posterior commissure plane (no gap) in interleaved order.

In addition, a high-resolution anatomical MRI was obtained with a sagittal 3D gradient-echo T1-weighted sequence for each participant (TR = 9 ms, TE = 3.5 ms, matrix size: 256 × 256, voxel size: 1 × 1 × 1 mm, 170 slices).

Figure 1. Flow chart of recruitment of participants. In total, 21 symptom-improved patients, 19 non-improved patients and 29 healthy controls were included in final analysis.

MDD, major depressive disorder; MDD⁺, depression combined with an additional diagnosis of social anxiety disorder, panic disorder and/or generalized anxiety disorder; ANX, anxiety; S1, baseline measurement; S2, second measurement; MADRS, Montgomery–Åsberg Depression Rating Scale; HC, healthy control; S-R, symptomatic-remitted MDD patients; S-S, symptomatic-symptomatic MDD patients.



Data analysis

Independent variables

Firstly, to test for the correlation between symptom change and brain activation change over time, a symptom change score representing the difference in depressive severity between S1 and S2 was calculated for each depressed patients (i.e., MADRS S2 – MADRS S1). Furthermore, to be able to investigate whether changes in behavior and brain activation following symptomatic change represented normalization (i.e., in comparison to the HC group), we divided the patients in two groups: a group of MDD-patients who changed from symptomatic (S) at S1 to remission (R) at S2 (S-R; MADRS-scores S2≤10; n=21, Figure 1) and a group of MDD-patients who were symptomatic at both S1 and S2 (S-S; MADRS-scores S2>10; n=19). Depressive load was defined by presence of depressive symptoms per month for the duration of the interval between S1 and S2 using the life chart interview (Lyketsos *et al*, 1994) administered at S2. Participants had to rate the severity of depressive symptoms per month and only symptoms with small to severe burden were taken as indication of presence of symptoms. Percentage of months experiencing depressive symptoms was calculated per patient (depressive load).

Clinical variables and behavioral data

Effects of symptom change and depressive load on demographic, psychometric assessment and behavioral data were analyzed in IBM SPSS software (SPSS v.22.0, IBM). We employed analyses of variance (ANOVA), Chi-square tests and *t*-tests where appropriate for demographic and psychometric data with a significance level of $p<.05$, two-tailed.

For the behavioral data, reaction times (RT) and accuracy for successfully encoded words (hits and false alarms) (Tulving 1985) were calculated. We calculated performance difference scores for both RTs and accuracy (S2-S1). We firstly investigated the relation between symptom change scores and RT- and accuracy difference scores over time in patients. Age, years of education were included as covariates. After that, we conducted a group (3; HC, MDD S-R, MDD S-S) × valence (3; positive, negative, neutral) × time (2; S1, S2) repeated measures ANCOVA, with age and years of education as covariates to test for main effects and interactions of group, valence, and time. In case a significant main- or interaction effect was detected ($p<.05$), post hoc *t*-tests were conducted at a significance level of $p<.05$ (two-tailed), Bonferroni corrected for multiple comparisons.

Imaging data preprocessing

For the fMRI data, preprocessing and task modeling were performed with Statistical Parametric Mapping software (SPM8, Wellcome Trust Center for Neuroimaging, <http://www.fil.ion.ucl.ac.uk/spm>) implemented in Matlab 7.8 (The Math Works Inc., Natick, MA, USA). Based on the hypotheses formulated in our cross-sectional study (van Tol *et al*, 2012), we only investigated the encoding session.

Before preprocessing, functional images were reoriented manually to the anterior-posterior commissure plane. Preprocessing consisted of slice timing, spatial realignment and co-registration of the anatomical image to the EPI image, spatial normalizing of the image to the standard Montreal Neurological Institute (MNI) space, reslicing to a $3 \times 3 \times 3$ mm voxel size and spatial smoothing with an 8 mm full-width at half maximum Gaussian kernel. To remove low frequency noise, a high-pass filter with a cut-off of 128 s was applied to the fMRI time-series.

First-level analyses

For each participant two first-level models were set up, one for S1 and one for S2. To minimize the effect of motion, the absolute scan-to-scan difference in both rotational and translational displacement after realignment was computed, and scans in which the displacement was larger than 0.9 mm compared to the previous scan were censored by modeling them as regressors (Siegel *et al*, 2014). Because we were interested in the valence effects and to be consistent with our previous reports (Ai *et al*, 2015; van Tol *et al*, 2012), we defined the following contrasts for each model: [*successfully encoded positive words* > *successfully encoded neutral words*] and [*successfully encoded negative words* > *successfully encoded neutral words*]. The difference between the two scan sessions was calculated for each contrast by subtracting the contrast image of the first scan from the second scan (S2-S1) for every participant using the ImCalc option implemented in SPM8. Consequently, positive activation indicates an increase of activation from S1 to S2 and negative activation a decrease of activation from S1 to S2.

Correlation with depressive state change

To test for the correlation between symptom change and brain activation change between two scan moments in patients, S2-S1 contrast maps were entered as dependent variables in a full-factorial model, with valence (positive>neutral encoding [S2-S1], negative>neutral encoding [S2-S1]) as a factor and symptom change (MADRS S2 – MADRS S1) as interacting covariate with valence. As we aimed to test for relations of symptom change with positive and negative encoding separately, and were not so much interested in the interaction of valence and state change, we chose to set up a full factorial model instead of a flexible factorial model.

To control for the confounding effects caused by variations within and between participants in coil, sequence and site, four dummy variables for scanning site (both times scanned in AMC; changed from AMC to LUMC; changed from LUMC to AMC; both times scanned in UMCG; both times scanned in LUMC) were defined as covariates of no interest. In addition, age and years of education at S1 were added as covariates.

To investigate whether our main results regarding state were related to depressive load, we repeated our analysis with depressive load (percentage of time with depressive symptom demeaned within group) as an additional covariate. In addition, to examine whether possible changes in activation were related to changes in anxiety severity at time of scanning, we repeated our analysis by adding difference in Beck Anxiety Inventory (BAI) scores (Beck *et al*, 1988) (S2>S1) as covariate. Finally, to test for the possible effect of medication use, we repeated our analysis by excluding SSRI-users at both S1 and S2. We also controlled for treatment factor by adding SSRI-use and psychotherapy use as covariates.

Next, to investigate whether changes in activation observed in our main correlational model represented normalization of regional activity and to test for stability of responses in HC, we set up a repeated measure ANCOVA with group (3; HC, improved MDD [S-R], non-improved MDD [S-S]) as between-subject factor and valence (2; positive>neutral encoding [S2-S1], negative>neutral encoding [S2-S1]) as within-subject factor. Scanning site, age and years of education were included as covariates. We applied the same mask and threshold for correction of results as our main analysis.

Correlation with duration of illness (depressive load)

We built a full factorial model with valence as factor (2; positive>neutral and negative>neutral) and depressive load as an interacting covariate with valence. Site (four dummy variables), age, years of education were added as covariates. We tested for the effects of depressive load during encoding of positive words and negative words separately. In a subsequent step, symptom change, medication use and psychotherapy use were added as covariates to statistically control for their possible confounding effects.

Statistical thresholding

Based on previous studies (see introduction), we *a priori* defined the bilateral hippocampus and amygdala as our regions-of-interest (ROI) and built one composite mask encompassing these regions. The regions were defined according to the automated anatomical labels of the Wake Forest University (WFU, Winston Salem,

North Carolina) Pick Atlas toolbox. Small volume correction for multiple comparisons was applied within the ROI. In accordance with our previous reports (Ai *et al*, 2015; van Tol *et al*, 2012), main effects and interactions (F-tests) were explored separately for positive and negative words at $p < .005$ uncorrected. *Post hoc* t-tests were regarded significant at a threshold of $p < .05$ family wise error (FWE) corrected at voxel-level (with an initial threshold of $p < .005$ uncorrected). Effects occurring outside the amygdala and hippocampus were explored at $p < .005$, but had to meet $p < .05$, FWE whole brain correction to be considered significant.

Results

Demographic characteristics

Demographics and clinical characteristics of all patients and healthy controls are summarized in table 1. Within patients, symptom change was not associated with age ($r = .28$, $p = .08$), years of education ($r = .14$, $p = .38$) or sex ($r_{\text{kendell's tau}} = .09$, $p = .56$). Moreover, it was not associated with medication use ($r_{\text{kendell's tau}} = .09$, $p = .55$) or psychotherapy use ($r_{\text{kendell's tau}} = -.13$, $p = .43$) between S1 and S2. In addition, symptom change was not related to anxiety severity at S1 (BAI-score S1; $r = -.03$, $p = .85$), depressive load in the five years before S1 ($r = .20$, $p = .22$), and the depressive load between S1 and S2 ($r = .29$, $p = .07$). However, symptom change of depression was correlated to change in anxiety severity (BAI-scores) ($r = .46$, $p = .003$) and depression severity at baseline (MADRS-S1; $r = -.34$, $p = .034$).

Explorations of the clinical characteristics of the symptom remitted (S-R) and symptomatic (S-S) patient groups confirmed that S-R and S-S groups were of comparable age, sex, and years of education and no differences with the HC groups were observed ($p > 0.05$; Table 1). At S1, the patient groups did not differ on SSRI-use, psychotherapy-use, comorbidity, MADRS-scores, and BAI-scores ($p > 0.05$; Table 1). At S2, as expected, MADRS-scores and BAI-scores were lower in the S-R group compared to the S-S group ($p < .001$; Table 1). There were no group differences between the two patient groups on depressive load in the five years before S1 (i.e. months with depressive symptoms) and depressive load between the two measurements (i.e., percentage of time with depressive symptoms) (Table 1). Whereas use of SSRIs and benzodiazepines was not different between patient groups, at S2 more S-R patients had however received psychological care than S-S patients ($p = .04$; Table 1).

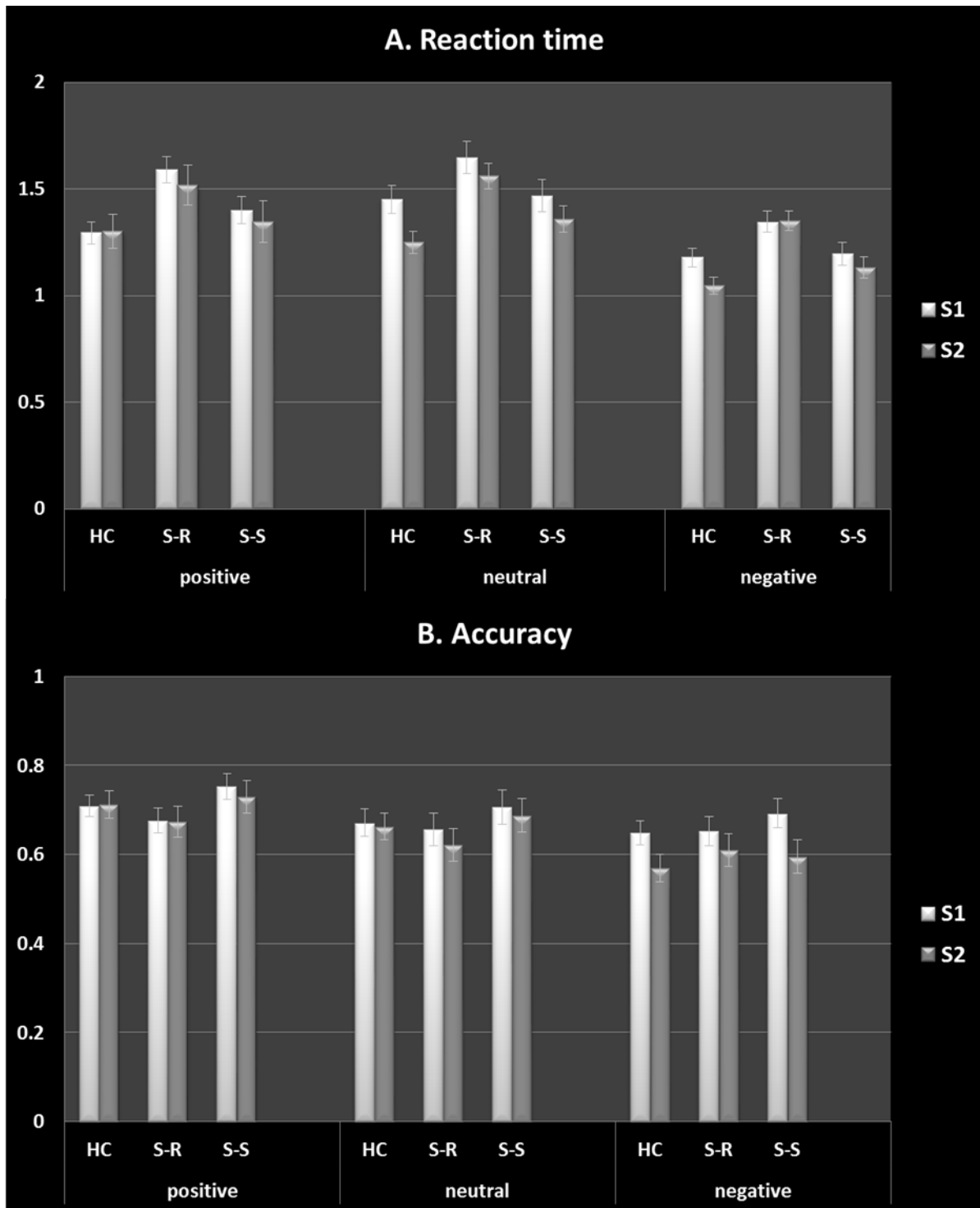
Table 1. Demographics.

	HC	S-R	S-S	F	t	χ^2	p
N	29	21	19	-	-	-	
Site S1(AMC/LUMC/UMCG) (N)	15/9/5	9/9/3	7/7/5	-	-	1.9	.75
Site S2(AMC/LUMC/UMCG) (N)	13/11/5	8/10/3	7/7/5	-	-	-	.84
Sex (male/female) (N)	10/19	8/13	9/10	-	-	.81	.67
Age, mean (SD)	40.28(9.81)	37.71(9.49)	40.00(11.64)	.42	-	-	.66
Years of education, mean (SD)	14.59(2.80)	12.57(2.42)	13.37(3.73)	2.89	-	-	.06
Months interval, mean (SD)	21.85(1.37)	22.57(1.28)	22.11(1.70)	1.47	-	-	.24
MADRS_S1, mean (SD)	1.10(1.70)	18.71(5.10)	21.79(7.45)	128.1	-	-	<.001 ^{aa}
MADRS_S2, mean (SD)	.62(1.17)	4.52(2.94)	19.68(6.28)	156.2	-	-	<.001 ^{ab}
MADRS_S2>S1, mean (SD)	-.48(1.52)	-14.19(5.22)	-2.11(7.65)	-	-5.88	-	<.001 ^{ab}
BAI_S1, mean (SD)	2.10(2.65)	13.33(7.67)	14.63(9.75)	25.39	-	-	<.001 ^{aa}
BAI_S2, mean (SD)	2.14(1.99)	8.48(6.16)	14.53(9.17)	24.81	-	-	<.001 ^{ab}
Depressive load between S1 and S2, mean (SD)	-	.44(.39)	.60(.42)	-	-1.24	-	.22
Months with depressive symptom before S1, mean (SD)	-	18.57(15.71)	21.47(15.61)	-	-.59	-	.56
Comorbidity_S1(MDD/MDD ⁺) (N)	-	8/13	5/14	-	-	.63	.43
Comorbid SAD (N)	-	8	5	-	-	-	-
Comorbid PD (N)	-	8	8	-	-	-	-
Comorbid GAD (N)	-	8	10	-	-	-	-
Age of depressive onset, mean (SD)	-	25.62(11.52)	23.11(9.62)	-	.73	-	.47
Psychotherapy-use_S1, mean (SD)	-	5/16	5/14	-	-	.03	.86
Psychotherapy-use_S2, mean (SD)	-	11/10	4/15	-	-	4.18	.04 ^c
SSRI-use_S1(yes/no) (N)	-	9/12	6/13	-	-	.54	.46
SSRI-use_S2(yes/no) (N)	-	9/12	7/12	-	-	.15	.69
Benzodiazepine_S1(yes ^d /no) (N)	-	3/18	1/18	-	-	.90 ^e	.33
Benzodiazepine_S2(yes/no) (N)	-	0/21	3 ^f /16	-	-	4.7 ^e	.09

Abbreviations: HC, healthy control; S-R, symptom-remitted MDD patients; S-S, symptomatic-symptomatic MDD patients; SAD, social anxiety disorder; PD, panic disorder; GAD, generalized anxiety disorder ^a HC differed from both patient groups, while the two patient groups did not differ; ^b All groups differed from each other; ^c significant at p<.05; ^d Infrequent use; ^e Likelihood Ratio; ^f Two patients used benzodiazepine frequently.

Figure 2. Performance of emotional memory task over time. (A) Reaction time for successfully encoded words at S1 and S2. Y-axis, reaction time. (B) Accuracy for successfully encoded words at S1 and S2. Y-axis, proportion correct remembered trials.

HC, healthy control; S-R, symptomatic-remitted MDD patients; S-S, symptomatic-symptomatic MDD patients; S1, baseline measurement; S2, second measurement.



Behavioral results

No correlations were found between depressive symptom change and changes in performance on memory of positive or negative words over time (i.e., RTs and accuracy) ($p > .05$). Group comparisons however indicated a main effect of group on the reaction time of successfully encoded words ($F(2,64)=7.44$, $p < .001$). At both time points, S-R patients showed slower responses to all words that were subsequently corrected recognized compared to S-S patients and HC (S-R>S-S, $p = .031$; S-R>HC, $p < .001$).

No main effect or interaction was found for accuracy of successfully encoded words.

fMRI results

Correlations with depressive state change

We observed that symptom change (MADRS at S2 - MADRS at S1) was negatively related to change in right hippocampal/amygdala activation during positive word encoding (MNI coordinates [$x=27$, $y=-4$, $z=-11$], $Z=3.97$, $p_{FWE}=.012$), but not during negative word encoding ($Z=2.73$, $p_{FWE}=.40$) (Table 2; Figure 3A). This means that larger symptomatic improvement coincided with larger changes in hippocampal activation related to the encoding of positive information during the interval.

Adding depressive load as covariate did not change the results ($Z=3.80$, $p_{FWE}=.022$). Also, results were not affected by including change in anxiety severity added as covariates to the model ($Z=3.77$, $p_{FWE}=.025$). After omission of SSRI-users ($n=18$; 7 patients used SSRIs at both S1 and S2, 8 only used SSRIs at S1, 3 only used SSRIs at S2) from the main model, the hippocampus-amygdala change in activation ceased to be significant ($Z=2.67$, $p_{FWE}=.43$). However, results were unaffected by adding SSRI-use or psychotherapy use as covariates ($Z=3.96$, $p_{FWE}=.013$ for SSRI-use; $Z=4.04$, $p_{FWE}=.010$ for psychotherapy use).

Post hoc group comparison

To follow-up whether hippocampal/amygdalar activation changes represented normalization, we explored brain activation during positive word encoding in a full-factorial model with MDD S-R, MDD S-S and HC. A main effect of group, representing activation differences between S1 and S2, was observed in the right anterior hippocampus extending to the amygdala (same area as found in the correlational analysis) (Table 3; Figure 3B). Explorative t -tests revealed that MDD S-R showed an increase in activation over time in the right hippocampus (MNI coordinates [$x=21$, $y=-7$, $z=-17$]), which was most pronounced during positive word

encoding ($Z=3.97$, $p_{FWE}=.011$), while MDD S-S did not ($p_{FWE}=.38$). This confirmed that increased activation in the right hippocampus/amygdala was associated with symptom remission. Changes in hippocampal activation were however not significantly different from HC (positive>neutral: MDD S-R>HC, $p_{FWE}=.44$). No difference in activation over time was observed for HC in the hippocampus/amygdala during both positive and negative word encoding. Moreover, no significant effect of group, valence or group \times valence was present in other brain regions ($p_{FWE}>.05$). Plotting of effects at S1 and S2 separately indicated that the increase in hippocampal activation in the MDD S-R represented a recovery to normal (Figure 3C). The effect during negative encoding was not explored because no such effects were observed for negative word encoding in the correlation analysis.

Correlations with depressive load

No correlation between percentage of time with depressive symptoms and changes in brain activation was observed across all MDD patients during positive>neutral and negative > neutral encoding. Adding depressive severity or medication/therapy use to the model did not change the effect.

Table 2. Correlation between state-change scores and brain activation changes across patients

Regions	MNI Coordinates									
Positive>neutral:										
negative correlation	k^a	k^b	Side	BA	x	y	z	T	Z	p_{FWE}
Hippocampus/amygdala	54	35	R	34	27	-4	-11	4.22	3.97	.012 ^c
Hippocampus/amygdala	33	13	L	20	-27	-16	-11	3.39	3.25	.122
Negative>neutral:										
negative correlation	k^a	k^b	Side	BA	x	y	z	T	Z	p_{FWE}
Hippocampus/amygdala	14	1	R	-	15	-7	-14	2.81	2.73	.401
Hippocampus/amygdala	2	1	L	-	-24	-13	-11	2.69	2.62	.483

^a. Cluster size in whole-brain analysis; ^b. Cluster size after small volume correction.

^c. Significant at $p<.05$ FWE corrected, voxel-level after small volume correction.

Figure 3. Brain activation during emotional word encoding. (A) Negative association between symptom change and hippocampal activation during positive word encoding. (peak MNI coordinate: $x=27, y=-4, z=-11$); (B) A main effect of group during emotional word encoding over time. (Contrast: main effect of group; $F=5.53, p<.005$ uncorrected; peak MNI coordinate: $x=21, y=-7, z=-17$); (C) Pattern of hippocampal activation (peak MNI coordinate: $x=21, y=-7, z=-17$) during encoding at S1 and S2. HC, healthy control; S-R, symptomatic-remitted MDD patients; S-S, symptomatic-symptomatic MDD patients; S1, baseline measurement; S2, second measurement.

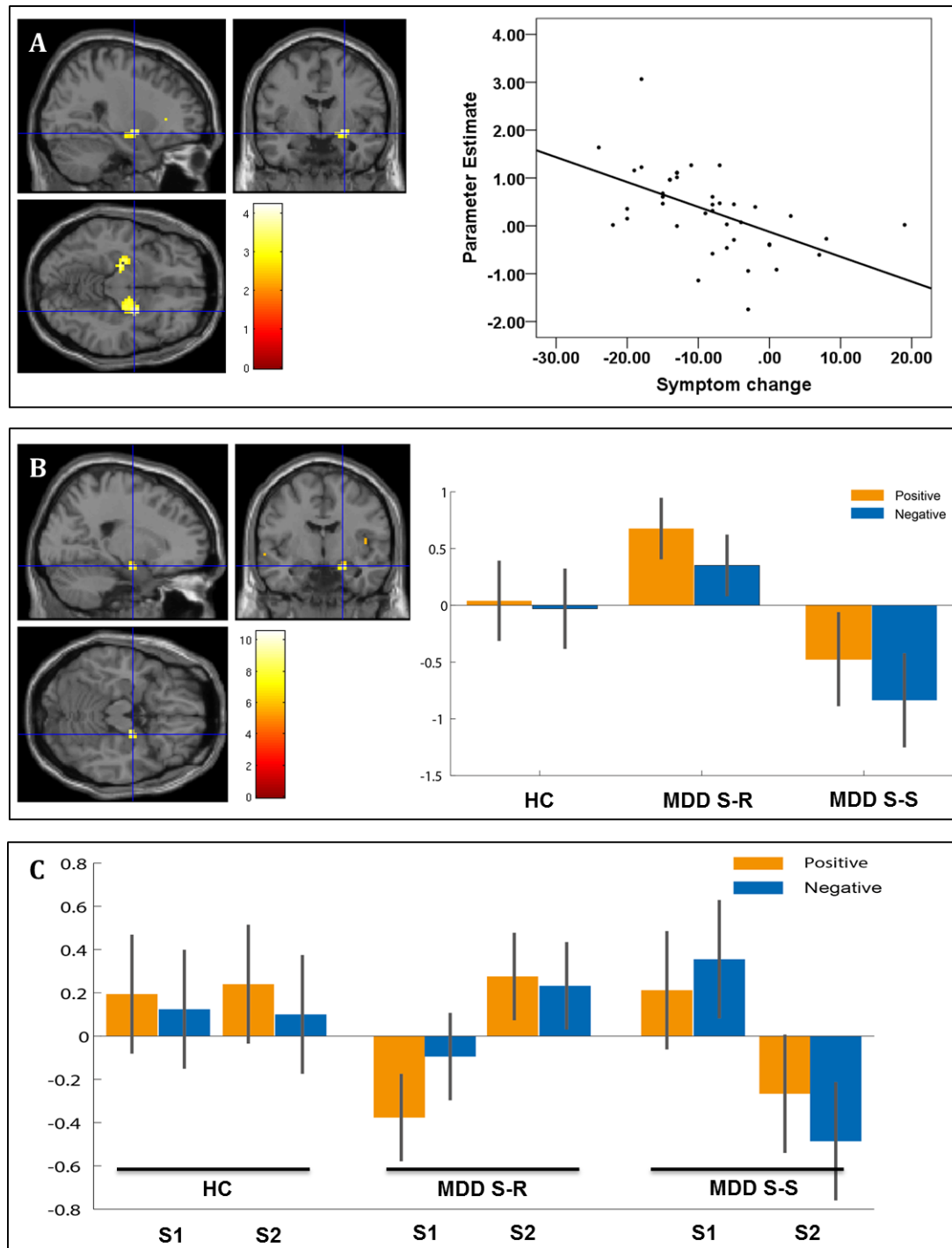


Table 3. Results of group (3) × valence (2) ANCOVA during emotional words encoding. Covariates are site, age and level of education. Dependent variable was the different brain activation between S1 and S2 (S2-S1).

Regions	MNI Coordinates									
Main effect of group_positive	<i>k^a</i>	<i>k^b</i>	Side	BA	x	y	z	F	Z	p
Hippocampus extending to amygdala	8	-	R	35	21	-7	-17	10.52	3.85	.001
Putamen	21	-	R	48	24	20	1	8.30	3.34	<.001
Medial frontal gyrus	11	-	R	9	12	56	34	7.99	3.27	.001
Inferior frontal gyrus	13	-	R	48	45	-7	13	7.46	3.13	.001
Post hoc t-test	<i>k^a</i>	<i>k^b</i>	Side	BA	x	y	z	T	Z	<i>p_{FWE}</i>
S-R>S-S_positive										
Hippocampus extending to amygdala	28	26	R	35	21	-7	-17	3.84	3.72	.026 ^c

Abbreviations: S-R, symptomatic-remitted MDD patients; S-S, symptomatic-symptomatic MDD patients.

^a. Cluster size in whole-brain analysis;

^b. Cluster size after small volume correction.

^c. Significant at $p < .05$ FWE corrected, voxel-level after small volume correction.

Discussion

In this longitudinal study, we examined changes over time in brain activation underlying symptom improvement and duration of depressive symptoms during emotional memory encoding in depressed patients. Symptom improvement was associated with increased response in the anterior hippocampus/amygdala to positive stimuli over time, but not to negative stimuli. Follow-up explorations indicated that increased activation related to symptom remission and that at S2, hippocampal/amygdalar responsivity returned to normal. Effects were unrelated to changes in anxiety severity, and psychotherapy-use, although the effect was smaller after excluding SSRI-users. However, no relation between percentage of time with depressive symptoms during the two-year follow-up and changes in hippocampal and amygdalar activation was observed. These results suggest that hippocampal activation during emotional memory formation is a state-dependent marker of depressive symptomatology, especially during positive word encoding. This indicates that symptomatic improvement is at least partially associated with normalization of limbic responsivity to emotional material, which could ameliorate

biased processing of new positive emotional information (Harmer *et al*, 2009). However, no support for functional 'scarring' following enduring symptom duration could be found.

We showed that activation in the anterior hippocampus/amygdala during positive word encoding is state-dependent in patients with MDD, as demonstrated by a negative correlation between symptom change and changes of activation as well as normalized activation in remitted patients at follow-up. This result was partly unexpected, as changes in hippocampal reactivity during negative encoding were hypothesized based on our previous cross-sectional observation that anterior hippocampal activation related to symptom severity in MDD patients (van Tol *et al*, 2012). In line with our expectations, no effects were observed in the posterior hippocampus, a region that we have previously found to show blunted activation in MDD, independent of illness severity (van Tol *et al*, 2012). The hippocampus has been proposed as a target for both antidepressant treatment and cognitive behavioral therapy (CBT) (Goldapple *et al*, 2004). Treatment studies have confirmed the importance of the hippocampus to various treatments by consistently indicating normalization of increased hippocampal activation during emotional processing after pharmacological treatment (Anand *et al*, 2007; Arnone *et al*, 2012b; Fu *et al*, 2004) and increased metabolism after CBT (Goldapple *et al*, 2004). In contrast, Ritchey *et al* (Ritchey *et al*, 2011) found an enhanced arousal response during emotional processing in the amygdala and hippocampus after CBT treatment. Our results were not affected by adding treatment use as a covariate to the model, although excluding the SSRI-users from the analyses made the effect non-significant. This might be due to a decrease in power because of the remaining limited sample size (n=22). Nevertheless, our observations suggest that increased hippocampal responsivity to positive material as previously observed following treatment (Fu *et al*, 2007; Victor *et al*, 2010; Wise *et al*, 2014), primarily relates to the remitted state instead of the mechanism of treatment. Of note, more remitted patients received psychological treatment than unremitted patients at S2. In light of this, increased hippocampal/amygdalar activation in symptom-remitted patients during positive word encoding, might partly reflect effects of psychological treatment. Nevertheless, only half of the sample received psychological care and hippocampal change was not related to psychotherapy use, suggesting that hippocampal/amygdalar activation change during positive word encoding might be at best a joint effect of remission after psychological treatment and naturalistic remission which might relate to the normalization of a mood-incongruent (i.e., positive) -processing bias.

The second aim of this study was to investigate whether depressive load (measured as percentage of months with depressive symptoms between scan moments) was associated with specific functional brain characteristics during emotional memory encoding. We found that depressive load was not correlated with changes of activation in the hippocampus, which indicates that the neurotoxic hypothesis might not be relevant to the functional change over time. To the best of our knowledge, no studies on the association between activation and symptom duration have been conducted yet. Nevertheless, previous cross-sectional and longitudinal studies suggested that hippocampal volume is negatively related to duration of illness in MDD, represented by number of episodes (MacQueen *et al*, 2003; Treadway *et al*, 2015) and duration of untreated illness (Sheline *et al*, 1999), though not consistently (Bremner *et al*, 2000). However, volumetric changes in the hippocampus have been linked to symptomatic improvement following treatment (Arnone *et al*, 2012a), suggesting state-dependency of hippocampal volume. Together with the cross-sectional studies which reported a state-dependent effect of hippocampal activation (Arnold *et al*, 2011; Milne *et al*, 2012; van Tol *et al*, 2012), our results indicate that functional change of the brain might be more related to the depressive state rather than the depressive duration.

Some limitations of our study should be noted. First, although a clear strength of our study is its longitudinal naturalistic design and we could control for activation changes in a healthy participant sample, the associations we found are correlational and do not imply causation. Second, despite the fact that we controlled for scanner site as a covariate and that groups did not differ in proportion of participants scanned in each site, different imaging parameters and head coils in different scanners and time moments might potentially caused variability on imaging acquisition. Third, although the longitudinal brain activation changes seemed to be unrelated to SSRI-use and that the observation that excluding SSRI-users made the effect subthreshold was likely due to a drop in power, a potential medication effect could not be excluded. Fourth, caution should be taken in interpreting our result as a true memory effect (i.e., hits-misses), because the number of error trials was too low to investigate this. Fifth, it is possible that the encoding processing was more explicit at S2 than at S1, because people at S2 could have remembered that they were asked which words were presented also during encoding phase. However, implicit and explicit memory processing have been suggested to be subject to the same encoding factors and can rely on similar perceptual processes and representations (Turk-Browne *et al*, 2006). Lack of difference over time in the HC group in our study supports this. Finally, although changes in anxiety severity were not correlated to the

change in brain activation, comorbid anxiety symptoms at both S1 and S2 could have caused some confounding effect on our results.

Conclusion

By characterizing longitudinal changes of activation in the anterior hippocampus/amygdala during emotional memory encoding, our study showed that the neural correlates of memory formation change with improvement of the depressive state, suggestive of a normalization of activation especially during positive encoding. However, enduring depressive load was not related to longitudinal changes in hippocampal-amygdalar activation. Together, we suggest that hippocampal activation is a state-dependent characteristic that is not subject to functional 'scarring'.

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