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Mood related insights : functional and structural MRI studies in depression and anxiety disorders

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CHAPTER 3

EMOTIONAL WORD ENCODING AND RECOGNITION IN DEPRESSION AND ANXIETY DISORDERS

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SUMMARY

Background: Major depressive disorder (MDD), panic disorder, social anxiety disorder, and generalized anxiety disorder are among the most prevalent and frequently co-occurring psychiatric disorders in adults and may be characterized by a common deficiency in processing of emotional information. We aimed to identify the unique and shared functional magnetic resonance imaging correlates of emotional word memory processes in depression and anxiety, controlling for comorbidity and illness severity.

Methods: Fifty-one patients with MDD (MDD), 59 with comorbid MDD and anxiety, 56 patients with a diagnosis of an anxiety disorder (panic disorder, social anxiety disorder and/or generalized anxiety disorder) without MDD and 49 controls performed an emotional word encoding and recognition paradigm during functional magnetic resonance imaging. We tested for the effects of current psychopathological status on the Blood-oxygen-level-dependent response and performance during task execution. Post-hoc we tested for the effects of illness severity, regional brain volume, and anti-depressant use.

Results: Patients with MDD, comorbid depression-anxiety, and anxiety disorders without MDD showed a common hypo-response in the right hippocampus during positive (>neutral) word encoding compared with controls. Also, MDD showed depressive state-independent hyperactivation of the insula, and depressive state-dependent hyperactivation of the amygdala, striatum, and prefrontal cortex during negative encoding. Recognition was associated with increased activation of prefrontal regions, related to illness severity in comorbid depression-anxiety and anxiety without MDD. Overall, effects were unaffected by SSRI use and regional brain volume.

Conclusion: Our findings indicate that hippocampal blunting during positive word encoding is a generic effect in depression and anxiety disorders, independent of illness severity, medication use, and regional volume, that may constitute a common vulnerability for MDD and anxiety disorders. MDD is additionally characterized by increased sensitivity for negative words as reflected in increased insular, amygdalar, striatal, and prefrontal response during encoding. The present results emphasize the current distinction between MDD and anxiety disorders (with and without comorbid MDD) with respect to processing of mood-congruent information, although a generic hippocampal hypo-response to positive words may mark a general insensitiveness to positive information in both MDD and anxiety disorders.

Major depressive disorder (MDD), panic disorder, social anxiety disorder, and generalized anxiety disorder are among the most prevalent and most frequently co-occurring psychiatric disorders in adults (Gorman, 1996; Ressler & Mayberg, 2007). Because of this high comorbidity and because MDD and anxiety disorders respond to the same treatment strategies, it has been suggested that they may share a similar etiology (Ressler & Mayberg, 2007). Recently, we reported on shared anatomical abnormalities in the anterior cingulate cortex in MDD and anxiety disorders (van Tol et al., 2010) supporting this suggestion. In contrast, it has been proposed that MDD with and MDD without comorbid anxiety should be considered distinct diagnostic groups in view of their course trajectories (Penninx et al., 2011). However, in studies investigating the neurobiology of depression and anxiety, comorbidity is rarely explicitly studied.

Major Depressive Disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder have been associated with similar biases in processing syndrome specific information such as negative, threat, or stress eliciting words or pictures (Grant & Beck, 2006; Leppanen, 2006; Musa, Lepine, Clark, Mansell, & Ehlers, 2003; van den Heuvel et al., 2005b; Watkins, Martin, & Stern, 2000). Also, MDD has been associated with abnormalities in processing mood-incongruent (i.e. positive) information (Burt, Zembar, & Niederehe, 1995), reflective of anhedonia (i.e. loss of the capacity to experience pleasure), the MDD core-symptom next to lowered or sad mood. These biases could lead to biased memory formation (Coles & Heimberg, 2002; Coles, Turk, & Heimberg, 2007; Wagner et al., 1998), that might reinforce negative mood and could contribute to the course of the disorder (Elliott et al., 2002). Whether anxiety disorders are also associated with memory biases for positive information is unclear. Moreover, whether comorbid depression-anxiety resembles MDD or anxiety disorders in performance and regional brain activation during emotional memory processes, or should be considered a sum of its parts, is to our knowledge, unknown.

Neuroanatomical models of MDD propose that symptoms such as lowered mood may result from dysregulation of subcortical and (para)limbic regions on the one hand, and dorsal and lateral cortical regions on the other hand (Mayberg, 1997; Phillips et al., 2003b). (Para)limbic regions, such as the amygdala, insula, and ventromedial prefrontal regions, have been associated with emotional appraisal of information. Dorsal and lateral cortical regions, including dorsomedial-, dorsolateral-, and ventrolateral prefrontal (PFC) regions, are predominantly linked to regulatory control over subcortical and (para)limbic regions, possibly via the medial PFC and anterior cingulate cortex (ACC) (Johnstone et al., 2007). Neuroimaging studies in MDD have predominantly focused on processing of negative information, and demonstrated differential involvement of the amygdala, hippocampus, ACC, lateral PFC (Bremner, Vythilingam, Vermetten, & Charney, 2007; Bremner, Vythilingam, Vermetten,

Vaccarino, & Charney, 2004; Hamilton & Gotlib, 2008; Roberson-Nay et al., 2006), supporting the hypothesis of altered involvement of subcortical and prefrontal regions for memory processing of mood-congruent information. Yet, few studies have explicitly tested for the effect of mood-incongruent content on memory formation in MDD, although a blunted response in areas linked to reward processing such as the ventromedial PFC (Elliott et al., 2002; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005a), ventrolateral PFC (Keedwell et al., 2005a), and ventral striatum (Epstein et al., 2006; Heller et al., 2009) has been associated with positive information processing. Only van Wingen et al. (2009) studied memory for positive and neutral faces in MDD. They demonstrated altered involvement of the amygdala and fusiform gyrus during memory formation, and differential involvement of the amygdala, fusiform gyrus, inferior frontal gyrus, orbitofrontal cortex, and posterior cingulate gyrus during retrieval. In panic disorder, social anxiety disorder, and generalized anxiety disorders, studies focusing on the processing of (social) threat related material reported increased prefrontal (Maddock, Buonocore, Kile, & Garrett, 2003; Monk et al., 2006; Nitschke et al., 2009; van den Heuvel et al., 2005b), hippocampal (van den Heuvel et al., 2005b),and amygdalar (Nitschke et al., 2009; Stein et al., 2002; van den Heuvel et al., 2005b) activation, but effects on emotional memory formation have, to our knowledge, not been studied yet.

In the present study, we investigated unique and shared functional magnetic resonance imaging (fMRI) correlates of mood-congruent and mood-incongruent information processing in MDD and frequently co-occurring anxiety disorders during an emotional word memory paradigm. Based on the overlap in their phenomenology, neurobiology, and information processing bias, and to capitalize on our sample size, we incorporated the anxiety disorders within one group. We focused on involvement of (para)limbic 'appraisal' and dorsal and lateral cortical 'regulatory' brain regions during hypothesized biased memory formation and recollection, while testing for the effects of the comorbidity of depression and anxiety disorders. We hypothesized better recognition performance for negative words (relative to neutral), and worse recognition performance for positive words (relative to neutral) in MDD compared with controls. Furthermore, in MDD, we hypothesized increased activation of the amygdala, hippocampus, insula, and decreased activation of prefrontal regions during encoding and recognition of negative information, whereas decreased activation of amygdala, hippocampus, striatal and medial PFC regions was expected during positive word encoding and recognition, relative to controls. We investigated whether this pattern generalizes to anxiety disorders with and without comorbid MDD and to what extent emotional word memory is affected by severity of depression and anxiety.

PARTICIPANTS

Three-hundred-one native Dutch speaking participants (233 outpatients with a half year diagnosis of MDD and/or PD and/or SAD and/or GAD, and 68 controls) recruited from the observational Netherlands Study of Depression and Anxiety (NESDA) were included and underwent magnetic resonance imaging in the Leiden University Medical Center (LUMC), Academic Medical Center (AMC) Amsterdam, or University Medical Center Groningen (UMCG). The Ethical Review Boards of each participating center approved this study. All participants provided written informed consent. Detailed information on participant recruitment and inclusion criteria can be found in the supplemental material.

TASK PARADIGM

We employed an event-related, subject-paced, word encoding- and recognition paradigm (Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2003). During the encoding part, participants were asked to classify 40 positive, 40 negative, and 40 neutral words according to their valence. Words were presented pseudo-randomized together with 40 baseline trials in 20 blocks of eight words. After a retention interval of ten minutes, participants were asked to complete a word recognition task. This task consisted of the 120 old encoding target words and 120 new distracter words, and 40 baselines. During baseline trials participants had to indicate the direction of arrows (<<left,<<middle>>,right>>). Words were presented pseudo-randomized in 20 blocks of 14 words. Subjects had to indicate whether they have 'seen' (i.e.,remembered) the words previously, 'probably have seen it' ('know'), or 'haven't seen it' (rejection). Participants' responses and response times were registered through two magnet-compatible button boxes. A detailed description of the task is given in the supplemental material.

Before and after the word encoding-recognition task, we monitored anxiety levels using a Visual Analogue Scale (VAS) (Huskisson, 1974) ranging from zero to 100.

ADDITIONAL PSYCHIATRIC MEASUREMENTS

Severity of depression and anxiety at the day of scanning was assessed using Dutch versions of the Beck Anxiety Inventory (BAI) (Beck et al., 1988), the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979), the Inventory of Depressive Symptomology (IDS) (Rush et al., 1986), and the Fear Questionnaire (FQ) (Marks & Mathews, 1979).

IMAGE ACQUISITION

Imaging data were acquired using Philips 3-tesla MRI-systems (Best, The Netherlands) located at the LUMC, AMC, and UMCG, equipped with SENSE-8 (LUMC and UMCG) and SENSE-6 (AMC) channel head coils. For each subject, echo-planar images were obtained using a T2*-weighted gradient echo sequence (repetition time [TR]=2300ms; echo time [TE]=30ms [UMCG: 28 ms], matrix size: 96x96 [UMCG: 64x64], 35 axial slices [UMCG: 39], interleaved

acquisition, 2.29x2.29mm in-plane resolution [UMCG: 3x3mm], 3mm slice thickness). Anatomical imaging included a sagittal 3-dimensional gradient-echo T1-weighted sequence (TR=9ms, TE=3.5ms; matrix 256x256; voxel size: 1x1x1mm; 170 slices).

STATISTICAL ANALYSIS

Psychometric and performance data were analyzed with SPSS (SPSS Inc, Chicago, Illinois, USA). Functional imaging data were preprocessed and analyzed using Statistical Parametric Mapping software (SPM5; http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab 7.1.0. (The MathWorks Inc., Natick, MA, USA). To test for effects of the diagnosis, groups were formed based on current psychopathology and comorbidity. To test for the effects of depressive state, we formed subgroups based on current IDS score: 1) remitted (IDS 0-13), 2) mildly depressed (IDS 14-25), and 3) moderately to severely depressed (IDS>25) (Muller et al., 2000). Age and education were added to each model to account for variance related to these factors.

Performance

Abbreviations and descriptions of performance indices are listed in Table 1. Proportions Correctly Recognized words (pCREC), proportions False Alarms (pFA), and old/new discriminant accuracy (d';=pCREC - pFA) were calculated, overall and per valence (i.e. positive, negative, neutral).

Effects of diagnosis on recognition performance were analyzed for pCREC_all, pFA_all, and d'_all using ANCOVAs. Repeated-Measures analyses of covariance (ANCOVAs) were performed to test for interaction of valence and diagnosis, and valence and depressive state, on task performance. Deviation response times [(pos/neg) – neutral] of SCR and CREC were calculated and entered in multivariate analyses of covariance (MANCOVAs) to test for effects of diagnosis/depressive state on response times. Age and years of education were entered as covariates in each analysis. Significance for behavioral analyses was set at $p<.05$, and post hoc paired tests (T-test or Mann-Whitney [U]) were Bonferroni-corrected for multiple comparisons (p_{crit}).

Imaging data

Preprocessing included reorientation of the functional images to the anterior commissure, slice time correction, image realignment, registration of the T1-scan to the mean image, warping to Montreal Neurological Institute (MNI)-space as defined by the SPM5 T1-template, reslicing to 3x3x3mm voxels and spatial smoothing using an 8-mm FWHM Gaussian kernel. Subject movement greater than 3mm in more than one direction resulted in exclusion of the data. Next, data were analyzed in the context of the General Linear Model (Friston et al., 1995). Haemodynamic responses to each stimulus were modeled with a delta function convolved with a synthetic haemodynamic response function and modulated using response times. The model included regressors for

Abbreviations

Encoding phase		
SCR	Subsequent Correct Recognition	a word, presented during the encoding phase, that is correctly recognized during the subsequent recognition phase
Recognition phase		
CREC	Correct RECognition	correct recognition of a previously encoded word
CREJ	Correct REJection	correct recognition of a newly presented word as a new word
FA	False Alarm	incorrect indication of a newly presented word as a previously encoded word
MISS	Miss	incorrect indication of a previously encoded word as a new word
PROB	Probably seen/known	indication that a word is 'probably seen'
All		
p/prop	proportion	
rt	response time in seconds	
BL	baseline	
d'	old/new discrimination accuracy	(pCREC)-(pFA)
Affixes		
_all	all words, irrespective of valence	
_pos	positive words	
_neg	negative words	
_neu	neutral words	

encoding[1] and recognition[2] parameters. In addition, filler words, error- and no-response trials were included as a regressor of no interest. Low-frequency noise was removed by applying a high-pass filter (cut-off: 128s) to the fMRI time-series at each voxel. Owing to the small proportion of recognition trials that were responded to with a 'know' response, these responses were treated as 'remembered' and consequently added to either CREC or FA.

Following the summary statistics approach, contrast images for 'SCR_pos > SCR_neu', 'SCR_neg > SCR_neu', 'CREC_pos >CREC_neu', and 'CREC_neg> CREC_neu', were calculated per subject on a voxel-by-voxel basis and entered into second-level analyses for between-group comparisons (MANCOVA) with age and education as covariates. Additionally, 'center' was added as a regressor by means of two dummy variables. We repeated the analysis after omission of the SSRI-users. We contrasted positive and negative SCR/CREC trials to neutral SCR/CREC trials to avoid inclusion of signal related to familiarity processes which might be expected when contrasting against the repetitive lower level baseline. We tested for the effects of anxiety severity on encoding and recognition related activity by performing a linear regression analysis with BAI scores as regressor of interest, and age, IDS scores, and center as covariates, masked with a binary mask derived from the relevant main effect at $p<.05$.

We defined the following areas of interest: hippocampus, amygdala, dorsal medial PFC (Brodmann area (BA) 8 and 9), ventromedial PFC (BA 10), dorsolateral PFC (BA 8, 9 and 46), OFC (BA 11), IFG (BA 44, 45, and 47), ACC (BA 32 and 24), striatum, and insula (BA 13).

The main effects of task are reported at a threshold of $p<.05$, corrected for Family Wise Error (FWE) at the voxel level, unless specified otherwise. To restrict

1 SCR_pos, SCR_neg, SCR_neu, SMISS_pos, SMISS_neg, SMISS_neu, BL. (SMISS=subsequently missed)

2 CREC_pos, CREC_neg, CREC_neu, CREJ_pos, CREJ_neg, CREJ_neu, FA_pos, FA_neg, FA_neu, MISS_pos, MISS_neg, MISS_neu, BL. (CREJ=correct rejections; MISS=misses)

the search for significant effects to voxels which were identified in the main effect, group comparisons were masked with the orthogonal relevant main effect (across groups) at p<.05 (uncorrected). Group by task interaction effects (F-tests) were inspected at p<.005, uncorrected and post-hoc t-tests had to meet p<.05, FWE voxel wise corrected for the spatial extent of the volume of interest, to be considered significant. For this small volume correction, we used the Automated Anatomical Labeling atlas (Maldjian, Laurienti, Kraft, & Burdette, 2003), implemented in the WFU-Pick Atlas toolbox (Wake Forest University School of Medicine). For non-ROIs, a voxel level threshold of p<.05 FWE whole brain corrected was set a priori.

The statistical toolbox Biological Parametric Mapping (Wake Forest University School of Medicine, 2010) was used to test whether between-group effects were affected by variations in regional gray matter volume (Casanova et al., 2007). We used individual modulated gray matter images derived from the T1 scans (for a description and results of the optimized voxel based morphometry procedure, see van Tol et al. (2010)). Gray matter images were normalized to standard MNI space and resliced to 3x3x3 mm voxels.

SAMPLE CHARACTERISTICS

Group characteristics are listed in Table 2. Our final sample for the present report consisted of 215 participants, 51 with a diagnosis of MDD and no anxiety disorders (MDD), 59 patients with MDD and anxiety disorder(s) (comorbid depression-anxiety [CDA]), 56 patients with one or more anxiety disorder (panic disorder, social anxiety disorder, generalized anxiety disorder), but no MDD (ANX), and 49 controls. A description of excluded data sets is given in the supplemental material. Importantly, no selective drop out of data over diagnosis was observed ($X^2(3)=1.39$; $p=.71$).

Groups were matched for age, education (years), sex, handedness, and scan center. Patient groups did not differ in number of patients using an SSRI. All patient groups showed higher scores on the Montgomery Åsberg Depression Rating Scale (MADRS) scores, Inventory of Depressive Symptomology (IDS), Beck Anxiety Inventory (BAI), and Fear Questionnaire (FQ) than controls (all: U>34;p<.001). Additionally, the comorbid depression-anxiety group showed higher depression (MADRS and IDS) and anxiety scores (BAI) than the MDD and ANX groups, both at the time of scanning (T2) and at the time of the NESDA baseline interview (T1) (all: U>425; P<.001). Also, the comorbid depression-anxiety group showed higher FQ scores than the MDD group (U=486; p<.001), but not than the ANX group (U=1026.5; p=.94). Within diagnostic groups, SSRI-users did not differ from antidepressant non-users in scan center, sex, age, education, scan interval, onset and severity of depression and anxiety, and recurrence of depressive episodes in MDD and comorbid depression-anxiety patients- (see Table S-1). Finally, within the depressed groups (MDD and

TABLE 2: CLINICAL CHARACTERISTICS OF THE TOTAL SAMPLE (N=215)

Depressive Symptomatology; BAI=Becks Anxiety Inventory; FQ=Fear Questionnaire; VAS=Visual Analogue Score; pre: before word encoding task; post: after word recognition task; T1=time of NESDA baseline measurement; T2=time of MRI measurement; interval=interval between T1 and T2.
Available data: MDD: IDS_T2 available of 49 patients, BAI_T2 available of 48 patients, FQ_T2 available of 45 patients, MADRS available of 48 patients, VAS available of 50 patients; CDA: IDS_T2 available of 58 patients, BAI_T2 available of 57 patients, FQ_T2 available of 46 patients, MADRS available of 57 patients, IDS/BAI/FQ_T1 available of 57 patients; ANX: IDS_T2 available of 54 patients, BAI_T2 available of 53 patients, FQ_T2 available of 45 patients, MADRS available of 54 patients; HC: IDS_T2 available of 48 participants, BAI_T2 available of 48 participants, FQ available of 44 participants.

		MDD	**CDA a**	**ANX b**	**HC**	*H*	*F*	*U*	X^2	*df*	*p*
N		51	59	56	49						
gender	male/female; N	20/31	21/38	14/42	19/30				*3.17*	*3*	*.366*
scan site	amc/lumc/umcg; N	15/18/18	21/24/14	16/16/24	18/21/10				*8.32*	*6*	*.215*
handedness	left/right; N	5/46	3/56	5/51	4/45				*.98*	*3*	*.806*
SSRI use	yes/no; N	11/38	23/35	15/37	-				*3.83*	*2*	*.15*
age	in years; mean ± sd	36.37 ± 10.14	36.47 ± 11.22	34.73 ± 8.78	38.94 ± 9.97		*1.53*			*3,214*	*.21*
education	in years; mean ± sd	12.96 ± 2.71	12.49 ± 2.92	13.04 ± 3.4	13.8 ± 2.54		*1.80*			*3,214*	*.15*
MADRS	total score; mean ± sd	12.58 ± 8.94	19.26 ± 8.77	11.11 ± 8.38	.88 ± 1.55	*110.97*				*3*	*<.001*
	range	0-33	0-43	0-35	0-6						
IDS T1	total score; mean ± sd	27.0 ± 9.87	32.68 ± 9.35	23.55 ± 11.02	5.19 ± 3.47	*112.7*				*3*	*<.001*
IDS T2	total score; mean ± sd	17.78 ± 10.26	28.67 ± 10.29	19.46 ± 10.14	4 ± 3.71	*110.85*				*3*	*<.001*
	range	1-39	5-55	4-49	0-17						
	rem/mild/mod_sev; N	19/17/15	3/21/35	-	-						
BAI T1	total score; mean ± sd	10.37 ± 6.44	19.44 ± 8.07	15.33 ± 8.98	1.81 ± 3.14	*113.64*				*3*	*<.001*
BAI T2	total score; mean ± sd	7.69 ± 6.14	18.46 ± 8.96	14.28 ± 9.43	2.23 ± 2.55	*105.27*				*3*	*<.001*
	range	0-26	1-46	1-42	0-10						
FQ	total score; mean ± sd	18.78 ± 12.96	35.39 ± 18.62	36.09 ± 21.41	9.16 ± 7.57	*68.57*				*3*	*<.001*
	range	0-45	6-78	3-84	0-29						
VAS_pre	mean ± sd	25.52 ± 22.07	34.44 ± 22.21	38.18 ± 25.19	23.98 ± 20.55	*12.92*				*3*	*.005*
VAS_post	mean ± sd	18.14 ± 18.11	26.63 ± 21.66	29.89 ± 21.86	17.12 ± 16.40	*14.24*				*3*	*.003*
interval	in days; mean ± sd	59.48 ± 28.59	62.85 ± 33.78	74.62 ± 35.38	65.47 ± 28.16	*6.43*				*3*	*.09*
onset MDD	age in years; mean ± sd	26.51 ± 10.22	24.19 ± 11.2	-	-	*1.85*				*1*	*.18*
onset ANX	age in years; mean ± sd	-	19.24 ± 10.99	14.85 ± 11.06	-	*5.73*				*1*	*.02*
recurrence MDD	single/recurrent episode; N	20/31	25/34	-	-				*.11*	*1*	*.737*
ANX (PD, SAD, GAD)	diagnosis in lifetime: N	10	59	56	0						-
	diagnosis in past year: N	2	59	56	0						-
MDD	diagnosis in lifetime: N	51	59	35	0						-
	diagnosis in past year: N	51	59	4	0						-

comorbid depression-anxiety), the remitted, mildly and moderately to severely depressed groups did not differ in age, education, and sex. See Table S-2 for characteristics of the MDD and comorbid depression-anxiety subgroups. Between T1 and T2, the remitted and mildly depressed subgroups showed a decrease in symptom scores; currently moderately to severely depressed groups showed stable symptom scores.

BEHAVIORAL RESULTS

Classification behavior, memory performance, and response times are summarized in Table S-3.

Classification behavior: An interaction of diagnosis and valence was observed on classification behavior ($F_{6,388}$=3.67,*p*=.001,η^2=.05): during the encoding task, MDD classified fewer words as positive and more words as neutral, compared with controls. This effect was observed trend-wise in the ANX group, but not in comorbid depression-anxiety group. No effect of group on classification of negative words was observed.

Recognition accuracy: No effect of diagnosis was found on memory performance (all F<.74;*p*>.53) and no effect of group x valence was observed for correctly recognized words, false alarms and d' (all F<.84;P>.54).

Response times: Analysis of response times revealed an interaction of diagnosis and valence on response times ($F_{6,418}$=2.41;*p*=.03,η^2=.03): controls showed shorter response times when encoding positive words than MDD patients. This effect was observed independent of illness severity in the MDD group, and in the moderately and severely depressed comorbid depression-anxiety group[3]. Also, MDD patients showed longer response times when recognizing positive than neutral words, an effect that was absent in controls. No effect of valence on response times was observed in anxiety disorders without MDD, and results were unaffected by anxiety severity. Results are summarized in Figure-1. Results remained unchanged after omission of the SSRI-users.

3 Only three CDA patients were remitted at time of scanning (see Table 2). Therefore, we left the remitted CDA group out of the severity analyses.

FMRI RESULTS

FWE corrected main effects of the contrast 'SCR_pos>SCR_neu' and 'SCR_neg>SCR_neu' reflecting encoding related activity are listed in Table S-4. At a more liberal voxel-threshold of *p*<.001, uncorrected, the left ventral putamen/striatum, right hippocampus, amygdala, insula, and bilateral fusiform gyri also showed activation during encoding. No whole brain FWE corrected effects of 'CREC_pos>CREC_neu' and 'CREC_neg>CREC_neu', reflecting recognition related activity, were observed. At *p*<.001, uncorrected, emotional recognition was associated with activation of the left inferior frontal gyrus and dorsomedial PFC. Interactions of task and diagnosis and effects of illness severity are listed in Table 3.

FIGURE 1: RESPONSE TIMES PLOTS

Error bars showing mean ± se for response times in seconds (s) for SCR per valence for MDD, CDA, ANC, and HC (top figure); CREC per valence for MDD, CDA, ANC, and HC (middle figure); SCR per valence for CDA_mild, CDA_mod/sev, and HC (bottom figure).

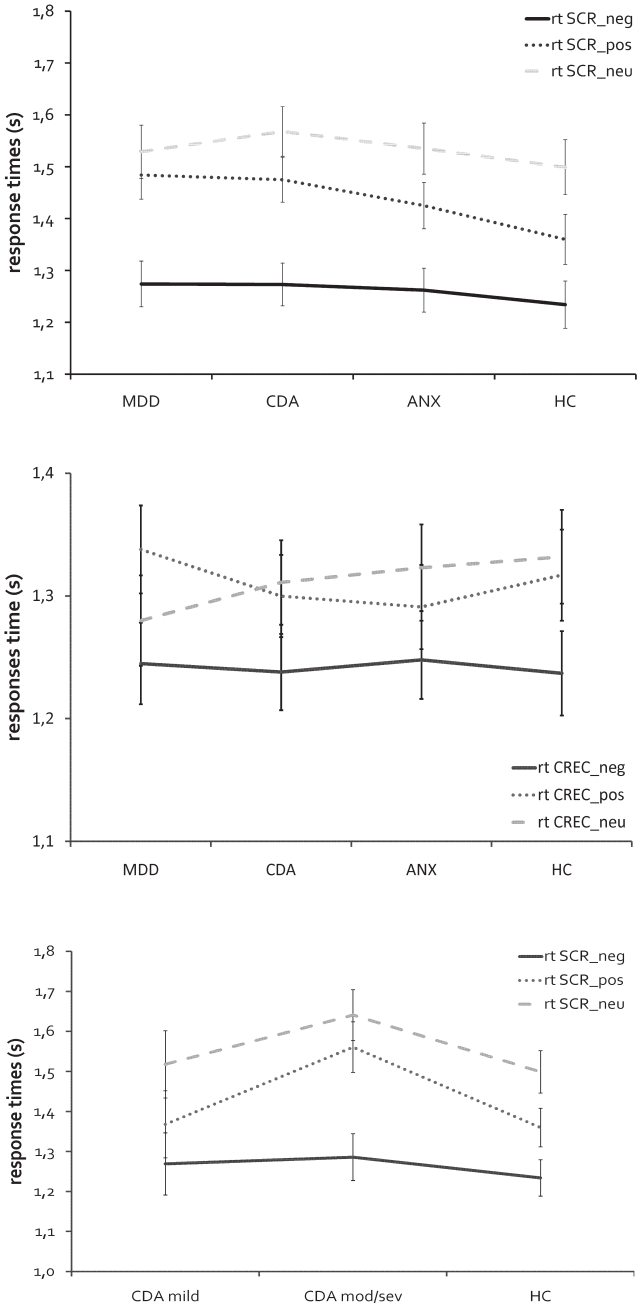


TABLE 3: MAIN EFFECTS OF DIAGNOSIS AND EFFECTS OF ILLNESS SEVERITY ON EMOTIONAL MEMORY

for the contrasts 'SCR_pos > SCR_neu', 'SCR_neg > SCR_neu', 'CREC_pos > CREC_neu', and CREC_neg > CREC_neu. Results are reported at $p_{FWE} < .05$, corrected for volume of Anatomic Automatic Label (AAL); BA = Brodmann Area; side=hemisphere; L=left; R=right. [] gray matter volume corrected Z-values and corresponding *p*-values are printed between brackets. ** significant at *p*<.001, uncorrected

Emotional word encoding

positive words > neutral words; encoding

			MNI-coordinates					
regions	side	BA	x	y	z	T	Z	P_{SVC_FWE}
MDD<HC								
hippocampus	R	n/a	33	-18	-12	4.19 [4.17]	4.14 [4.08]	.003 [.005]
ANX<HC								
hippocampus	R	n/a	33	-24	-9	3.80 [3.77]	3.76 [3.70]	.027 [0.034]
MDD_mod/sev>HC								
anterior cingulate cortex	L	24	-3	3	39	3.75	3.65	.03

negative words > neutral words; encoding

			MNI-coordinates					
regions	side	BA	x	y	z	T	Z	P_{SVC_FWE}
MDD>HC								
insula	L	13	-33	12	-15	3.52 [3.33]	3.49 [3.23]	.048 [.11]
MDD_mod/sev>HC								
anterior hippocampus/amygdala (lateral)	R	n/a	33	-9	-18	3.36	3.29	.045
caudate head	L	n/a	-6	12	0	3.54	3.46	.028
superior prefrontal gyrus	R	8	24	18	48	3.47	3.39	.15 **
putamen	R	n/a	33	9	0	3.33	3.26	.052 **

Emotional word recognition

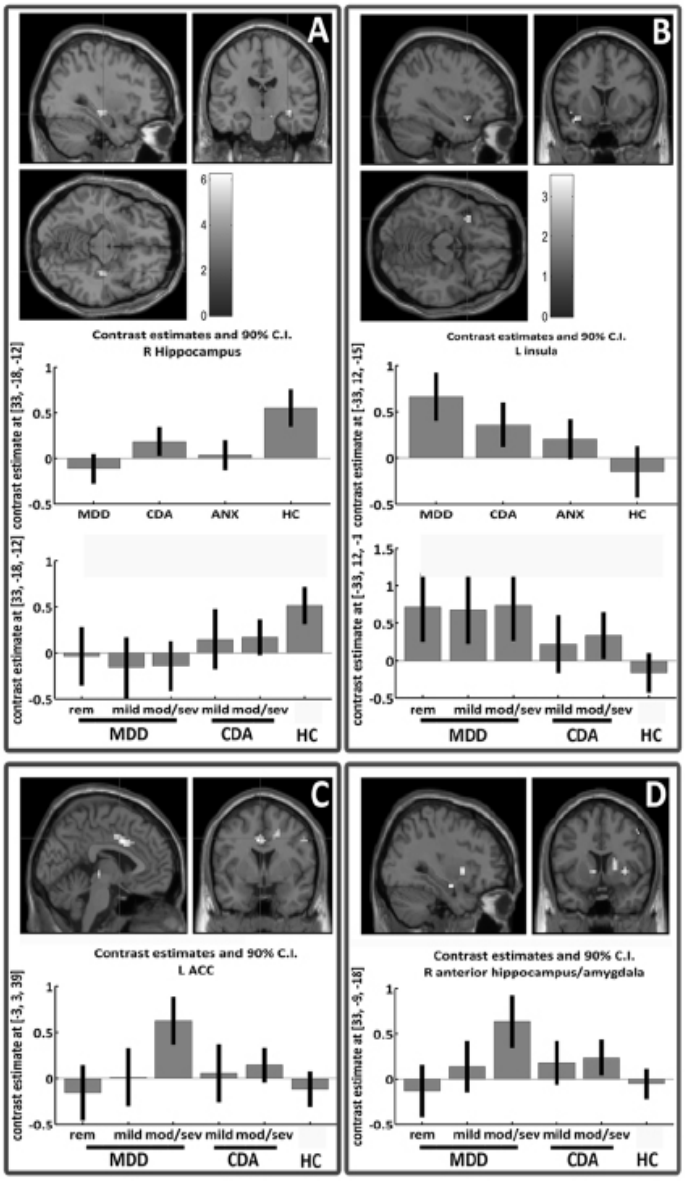
positive words > neutral words; recognition

			MNI-coordinates					
regions	side	BA	x	y	z	T	Z	P_{SVC_FWE}
ANX>MDD								
inferior frontal gyrus	L	45	-54	18	21	4.29 [3.76]	4.24 [3.69]	.004 [.045]
CDA_mod/sev>HC								
middle frontal gyrus	L	10	-30	48	3	3.94	3.84	.023
middle frontal gyrus	L	8	-45	12	45	3.71	3.62	.046

negative words > neutral words; recognition

			MNI-coordinates					
regions	side	BA	x	y	z	T	Z	P_{SVC_FWE}
negative correlation of BAI within CDA								
middle/inferior frontal gyrus	R	46	36	42	15	5.38	4.75	.001

FIGURE 2:
EFFECTS OF DIAGNOSIS AND ILLNESS SEVERITY ON ENCODING



A) Effects of groups (F statistics) on 'SCR_pos>SCR_neu' overlayed (top) and 90% confidence intervals (C.I.) centered at the right hippocampus showing contrast estimates of diagnosis (middle) and depression severity subgroups within MDD and CDA, and HC (bottom);
B) Effect of MDD>HC on 'SCR_neg>SCR_neu' (Z-statistics) (top) and 90% confidence intervals (C.I.) centered at the left ventral insula showing effects of group (middle) and effects of depression severity within MDD and CDA, and HC (bottom);
C) Effects of MDD_mod/sev> HC on 'SCR_pos>SCR_neu' (Z-statistics) (top) and 90% confidence intervals (C.I.) centered at the left ACC showing contrast estimates of depression severity subgroups within MDD and CDA, and HC (bottom);
D) Effects of MDD_mod/sev> HC on SCR_neg>SCR_neu' (Z-statistics) (top) and 90% confidence intervals (C.I.) centered at the right anterior hippocampus/amygdala showing contrast estimates of depression severity subgroups within MDD and CDA, and HC (bottom). Plots centered at the left caudate nucleus, right putamen, and right superior PFC showed similar effects (plots not shown).
Z- and F-statistics are displayed on mean T1 SPM5 template at $p<.005$, uncorrected. Effects on positive encoding are displayed in the left boxes, effects on negative encoding in the right boxes.

ENCODING

Effect of diagnosis

A group by valence interaction was observed in the right hippocampus ($F_{3,418}$=7.21, Z=3.72). Post-hoc t-tests demonstrated that patients showed hypoactivation of the right hippocampus compared with controls during positive encoding only, and was most strongly observed in the MDD and ANX groups (See Figure-2A). Comorbid depression-anxiety showed this hypoactivation below threshold (Z=2.7, p_{FWE}=.21, $p_{uncorrected}$=.004). The hippocampal hypoactivation was not explained by regional volume, illness severity (Figure-2A_bottom), and SSRI use. Also, within the moderately to severely depressed MDD and CDA groups, hippocampal hypoactivation did not vary as a function of depression severity (r<|.14|, *p*>41). Next, we tested for the main effect of diagnosis on positive and negative word encoding separately. In addition to the hippocampal effect during positive encoding, an effect of group was observed on negative encoding in the left insula ($F_{3,418}$=4.34, Z=2.58). Post-hoc t-test showed increased insular activation in MDD relative to controls (Figure-2B), that was observed independent of SSRI-use and illness severity (Figure-2B_bottom), also within severity groups. This effect was not observed during positive word encoding.

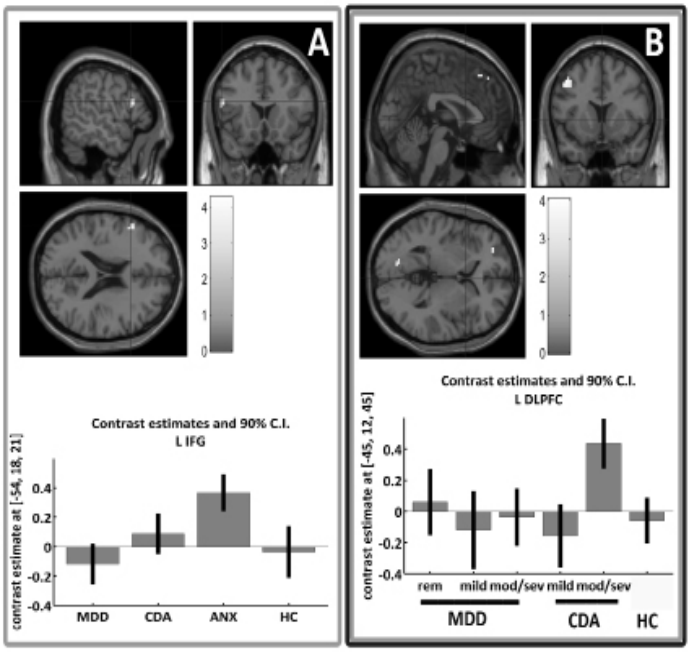
Effects of illness severity

Positive word encoding: Within MDD, an effect of depression severity was observed in the left ACC (BA 32; $F_{3,142}$=5.54, Z=3.02). A post-hoc t-test showed that compared to controls, moderately to severely depressed MDD patients showed increased ACC activation, whereas remitted and mild MDD patients and the comorbid depression-anxiety subgroups did not show this activation difference (Figure-2C). No effect of depression severity was observed in the comorbid depression-anxiety and ANX groups, and no correlation of anxiety severity was observed within groups. Moreover, within moderately to severely depressed MDD and comorbid depression-anxiety groups, ACC activation did not vary as a function of depression severity (r<-.19, *p*>.51).

Negative word encoding: An effect of depression severity on negative word encoding was observed in the right anterior hippocampus/amygdala, left caudate nucleus, right putamen, and right superior PFC (all $F_{3,142}$>4.47, Z>2.58; *p*<.005; Figure-2D): Post-hoc t-tests showed that moderately to severely depressed MDD patients showed hyperactivation of these regions compared with controls, although the superior PFC and right putaminal hyperactivation were observed subthreshold at p_{FWE}=.15 and p_{FWE}=.052, respectively. Within the moderately to severely depressed group, activation in these regions was unrelated to IDS and BAI scores (all r<|.36|, *p*>.20). No effect of depression and/or anxiety severity was observed within anxiety disorders, with or without comorbid MDD.

FIGURE 3:
EFFECTS OF DIAGNOSIS AND ILLNESS SEVERITY ON RECOGNITION

A) Effects of ANX>MDD on 'CREC_pos>CREC_neu' (Z-statistics) (top) and 90% confidence intervals (C.I.) centered in the left inferior frontal gyrus showing mean response per group (bottom);
B) Effects of CDA_mod/sev>HC on 'CREC_pos>CREC_neu' (Z-statistics) (top) and 90% confidence intervals (C.I.) centered in the left DLPFC (bottom) showing contrast estimates of depression severity subgroups within MDD and CDA, and controls. The frontopolar hyperactivation was observed on 'CREC_neg>CREC_neu' as well.
Z- and F-statistics are displayed on mean T1 SPM5 template at p<.005, uncorrected.



RECOGNITION

Effect of diagnosis

No significant interaction of diagnosis x valence occurred at the set threshold. For exploratory purposes, we tested for the effects of diagnosis on positive and negative word recognition separately. An effect of group was observed on positive word recognition in the left inferior frontal gyrus ($F_{3,418}$=6.91, Z=3.62; p<.001; Figure-3A). Post-hoc t-tests demonstrated that the ANX group showed hyperactivation of this region compared with MDD, and trend-wise compared with controls (Z=3.06; p_{FWE}=.17, $p_{uncorrected}$=.001). No effect of diagnosis was observed on negative word recognition.

Effects of illness severity

Within the comorbid depression-anxiety group, a main effect of illness severity on positive word recognition was observed on left superior PFC and left frontal pole activation ($F_{2,142}$>7.78, Z>3.23; Figure-3C): the moderately to severely depressed group showed increased activation of these regions compared with controls. However, this fronto-polar effect was also observed during negative word recognition, although subthreshold at p_{FWE}=.07. Also, within the comorbid depression-anxiety group, a negative correlation of Beck Anxiety Inventory (BAI) scores and activation of the right dorsolateral PFC was observed when Inventory of Depressive Symptomatology (IDS) scores were added to the

model (Figure-3B). No effect of illness severity was observed within the MDD and ANX group on positive or negative word recognition.

DISCUSSION

In this study, we investigated the unique and shared functional MRI correlates of mood-congruent and mood-incongruent word encoding and recognition in patients with MDD and frequent co-occurring anxiety disorders, explicitly testing for the effects of their comorbidity, and at the same time controlling for symptom severity, regional brain volume, and SSRI use.

Overall, we found no evidence for the hypothesized mood-congruent and mood-incongruent memory biases, as indicated by equal recognition accuracy for emotional words across diagnostic groups and controls. We demonstrated a depression related effect on response times during the encoding of positive words, unrelated to depressive state in MDD without comorbid anxiety, but related to current depressive state in patients with comorbid depressed-anxiety. Anxiety disorders without MDD were not associated with biases in memory or processing speed. Imaging results in MDD largely confirmed our hypothesis of differential involvement of (para)limbic and dorsal and lateral cortical areas during mood-congruent vs. mood-incongruent word encoding. Our results of increased processing times for positive information in MDD and currently depressed comorbid depression-anxiety are in concordance with the mood- incongruent bias theory as proposed by Bower (1981) and suggest that positive content impedes encoding and recognition in MDD.

In anxiety, no memory bias towards positive or negative material was found, consistent with previous studies (Coles & Heimberg, 2002). The absence of a mood-congruent bias in anxiety may be attributed to the low self-relevance of the words presented in our experiment, as previous research in panic disorder and generalized anxiety disorder demonstrated an attentional bias only when threat words with high self-relevance were presented (Coles et al., 2007). The absence of biases on recognition performance in mood and anxiety disorders has been described before (Banos, Medina, & Pascual, 2001; Bremner et al., 2004; van Wingen et al., 2009), although not consistently (Bradley et al., 1995; Epstein et al., 2006; Hamilton & Gotlib, 2008). Differences in findings could result from memory processes examined (e.g., strategic linking vs. priming; recognition vs. free recall) and task specifications, for instance length of the retention interval between encoding and recognition.

Our imaging result of a hypo-response during positive encoding in the hippocampus in both patients with MDD and anxiety disorders, and trend-wise in patients with comorbid depression-anxiety, compared with controls was unexplained by regional volume, SSRI use, and illness severity and therefore indicates a depression-anxiety generic phenomenon during encoding of positive words. Given the important role of the hippocampus in episodic

memory (Squire, Stark, & Clark, 2004), recollection of previously learned material (Daselaar, Fleck, & Cabeza, 2006), and context-based memory (Davachi, Mitchell, & Wagner, 2003; Ranganath et al., 2004), our results suggest decreased contextual coupling during semantic classification and simultaneous encoding of positive words in both depression and anxiety disorders. Possibly, mood-incongruent information is insufficiently recognized as positive information and subsequently connected less efficiently to (less) available memory 'nodes', as reflected in fewer words classified as positive, hippocampal hypo-activation, and longer response times. Hippocampal blunting in untreated patients with MDD during a neutral episodic memory task has been described before (Bremner et al., 2004). We now demonstrated hippocampal blunting during positive encoding in MDD and patients with anxiety disorders other than posttraumatic stress disorder. Also, we demonstrated that this hippocampal blunting is not specific to the moderately/severely depressive state, but is observed in the mild and (newly) remitted state as well. This finding supports previous behavioral studies that demonstrated a state independent memory bias in MDD for positive stimuli only, whereas biases towards negative stimuli appeared state dependent phenomena (Bradley & Mathews, 1988; Teasdale & Dent, 1987).

In addition, over-recruitment of the dorsal ACC during encoding of positive information was specifically observed in moderately and severely depressed MDD patients, and not in mild or remitted depressed patients. This over-recruitment of the dorsal cognitive subdivision of the ACC (Bush et al., 2000) may be interpreted as recruitment of extra attentional resources to classify mood- incongruent words in currently depressed patients, as this effect was not observed during encoding of negative words. As positive words might not be associated with a personally relevant state (Lemogne et al., 2009) in currently depressed patients, additional ACC resources might be called on to resolve this classification conflict (Kerns et al., 2004).

Related to encoding of negative words, exploratory analyses indicated a a trait-like effect of MDD was observed in the left ventral insula, that may reflect a general increased sensitiveness for negative information (Surguladze et al., 2010). It has been suggested that abnormal insula functioning in MDD reflects the presence of somato-vegetative symptoms and indicates an abnormal sense of the self (Wiebking et al., 2010). In addition, a depressive state dependent hyperactivation of the right anterior hippocampus/lateral amygdala, caudate head, and trend-wise right putamen, and superior frontal cortex was observed during encoding of negative words only, results that are in line with the report of Hamilton and Gotlib (2008). This finding suggests that an abnormal amygdalar response is related to depressive state, and the co-activation of the superior PFC and striatum implies increased recruitment of the dorsolateral PFC circuit (Mega & Cummings, 1994) that may mark a state dependent sensitivity for encoding negative information. Surprisingly, increased amygdalar/striatal/PFC activation was not observed in moderately to severely depressed comorbid

depression-anxiety patients. The finding of normal subcortical and PFC activity during encoding of mood-congruent stimuli in comorbid depression-anxiety is in concordance with behavioral studies (Grant & Beck, 2006; Musa et al., 2003; Tarsia, Power, & Sanavio, 2003), and it has been suggested that the presence of depressive symptoms in anxious patients abolishes the attentional bias. A possible explanation is that depression and anxiety are associated with hypo- and hyper-vigilant responses (Posner, Russell, & Peterson, 2005), respectively, when processing negative information, resulting in a net null effect.

In MDD, recognition of positive and negative words was unaffected in terms of BOLD responsiveness. Exploratory analyses in CDA patients indicated increased activation of left frontal pole and DLPFC during both negative and positive word recognition associated with depression severity. Moreover, in anxiety disorders without MDD left inferior frontal hyperactivation was observed during the recognition of positive words compared with MDD patients, and trend-wise compared with controls. This inferior frontal gyrus over-recruitment may indicate an increased need for attentional resources for correct response selection (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997), possibly due to less efficient encoding, as reflected in the hippocampal blunting during positive word encoding.

No effect of trait anxiety or depression was observed on recognition of negative words. However, as a function of depressive state, CDA patients showed increased activation of left frontal pole and DLPFC during both negative and positive word recognition. This valence non-specific effect suggests an increased demand for attentional and executive control during word recognition to maintain adequate task performance (van den Heuvel et al., 2003; Wagner, Koch, Reichenbach, Sauer, & Schlösser, 2006), related to illness severity. The moderately to severely CDA patients were characterized by higher depression and anxiety severity score than the moderately to severely MDD patients. This difference in illness severity may explain why we did not observe increased frontal recruitment during recognition in MDD patients without comorbid anxiety disorders.

In general our results were largely unaffected by variations in regional gray matter volume and inclusion of SSRI users, and no difference in activation in the reported regions was observed between SSRI-users and medication free patients (data not shown). Effects of SSRI treatment on amygdalar reactivity have been previously reported by Sheline et al. (2001) This latter result may be alternatively interpreted as an effect of successful treatment (i.e., remission), and therefore in line with our findings: only currently depressed MDD, and not remitted patients, showed increased anterior hippocampal and amygdalar responses to negative information.

In this study we included large and representative outpatient groups, excluded insufficient performers, could test for state and trait like effects, and were able to correct for possible confounds such as SSRI use and regional volume. However, several potential limitations should also be noted. First, the NESDA

strategy of recruiting through general practitioners and outpatient clinics across a wide range of disease severity and duration is likely to result in a representative sample but may also have increased variability (i.e., noise), without fully capturing the most severe end of the depressive spectrum. Second, on average, only approx. 15 per cent of the presented words were 'forgotten' (i.e., MISS). Therefore, the contrast 'recognized>forgotten' was underpowered and could not be calculated. Hence, caution should be taken when interpreting the results as purely reflecting memory related activity. However, we only analyzed signal related to events with a high probability of reflecting successful encoding and recognition related activity (i.e. SCR/CREC), and concentrated on valence effects during successful encoding and recognition which are likely to be subtle. Also, our strategy to control for type I error using an individual ROI approach rather than correcting for the overall search volume, although customary in imaging research, should be considered a potential limitation. Third, the negative words used in our study were not selected based on their relevance for mood and specific anxiety disorders, but had a negative connotation in general. We therefore could not examine encoding and recognition effects of disorder specific and non-specific negative words. Fourth, although similar 3-tesla systems were used at each site in this multi-center study, variability in image acquisition may have occurred due to minor differences in hardware (receiver coil), imaging parameters, and timing of software upgrades, but no systematic scanning site x diagnosis bias occurred. Finally, we aggregated the anxiety disorders in order to capitalize on our sample size and to compare the neural profile of these anxiety disorders with those observed in comorbid depression-anxiety and MDD. Therefore, no conclusions regarding the specific neural patterns of individual anxiety disorders within the ANX group could be drawn.

In conclusion, our results indicate that abnormal encoding of positive information is a shared feature of depression and anxiety, whereas abnormal encoding of negative information is a unique feature of MDD without comorbid anxiety. Hippocampal blunting during positive word encoding appeared as a common and state-independent neurophysiological phenomenon in depression and anxiety that may mark a general insensitiveness to positive information. At the same time, MDD is characterized by increased reactivity for negative words, reflected in an increased insular, amygdalar, striatal, and PFC response. With respect to their functional MRI profile during negative word processing, MDD with and without comorbid anxiety disorders should be considered separate groups. Possibly, comorbid depression-anxiety is primarily characterized by anxiety related functional neuropathology since the onset of anxiety disorders often precedes the manifestation of the first episode of MDD (Parker et al., 1999). Future studies should investigate whether individuals at high risk for depression and anxiety are characterized by abnormal processing of positive stimuli, as this may constitute a risk factor for mood and anxiety to be considered in prevention programs. Furthermore, we underline that current comorbid anxiety disorders should be controlled for when studying processing

of mood-congruent information in MDD.

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M.J. van Tol had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PARTICIPANT RECRUITMENT AND INCLUSION CRITERIA

Participants were recruited from NESDA (Netherlands Study of Depression and Anxiety), a large-scale multi-site longitudinal observational cohort study (Penninx et al., 2008). The rationale, methods, and recruitment have been described in detail elsewhere (Penninx et al., 2008). Out of the 2981 NESDA respondents (main sample, T1), participants aged between 18 and 57 years were asked to participate in the NESDA neuroimaging study (T2) if they met DSM-IV criteria for a half-year diagnosis of MDD and/or anxiety disorder (PD, SAD and/or GAD), or no lifetime DSM-IV diagnosis (i.e. healthy controls). At this interval, no specific intervention occurred. Exclusion criteria for patients were 1) the presence of axis-I disorders other than MDD, PD, SAD or GAD, 2) any use of psychotropic medication other than a stable use of selective serotonin reuptake inhibitors (SSRIs) or infrequent benzodiazepine use (i.e., equivalent to 2 doses of 10 mg of oxazepam 3 times per week or use within 48 hrs prior to scanning). Exclusion criteria for all NESDA-participants were: 3) the presence or history of major internal or neurological disorder 4) dependency or recent abuse (past year) of alcohol and/or drugs, 5) hypertension, 6) general MR-contraindications. Diagnoses were established using the structured Composite International Diagnostic Interview (CIDI) (Robins et al., 1988), administered by a trained interviewer. Healthy controls were currently free of, and had never met criteria for, depressive or anxiety disorders or any other axis-I disorder and were not taking any psychotropic drugs.

Complete word encoding and recognition data (EPIs and e-prime output) were not available of 15 participants. Data of another 61 participants were excluded because of 1) bad quality of the EPI data acquired during encoding and/or recognition (n=22), 2) movement >3mm (n=6), 3) not enough coverage of the hippocampus and amygdala (n=4), 4) loss of voxels in the first level mask, owing to large inter-hemispheric frontal space (n=1), 5) very low discriminant power (i.e. d'=<.1; n=17) or >40 missing responses (n=7), indicating unreliable task involvement, 6) medication use (n=2; 1x mirtazepine, 1x corticosteroids), 7) MADRS scores of HC (n=2) that were indicative of possible depressive psychopathology (Muller et al., 2000). To obtain a good match on both age and education, data of another ten subjects (CDA patients: n=7; HC: n=3) had to be excluded. Characteristics of the CDA patients were: male/female: 2/5; mean (sd) age: 41.1 (4.8); mean (sd) years of education: 6.7 (1.6); mean (sd) IDS score: 24.7 (11.38), mean (sd) BAI: 13.7 (8.3). Of the three excluded healthy controls, 2 were female, mean (sd) age: 49.7 (4.2); mean (sd) years of education: 18 (0).

TASK PARADIGM

We employed an event-related, subject-paced, implicit word encoding- and recognition paradigm (Daselaar et al., 2003), programmed in E-prime software (Psychological Software Tools, Pittsburgh, PA). During the encoding part 40 positive, 40 negative, and 40 neutral words, and 40 baseline trials were presented in 20 blocks of eight words. Words were presented with an average ISI of 1026 ms (minimum, 1018 ms; maximum, 1035 ms). Within each block, two negative words, two positive words, two neutral words and two baseline trials were presented randomized. Over valence (i.e. negative, neutral, positive), words were matched for length (ranging from three to twelve letters) and frequency of occurrence in the Dutch language. The task was paced by the subject, but each word was presented with a maximal duration of 5 sec. During each stimulus presentation, response options were displayed at the bottom of the screen. Subject had to indicate whether they thought the word presented was positive, negative, or neutral to them. Baseline (BL) words were '<<left', '<<middle>>', and 'right>>' and participants were instructed to press the corresponding button. To protect against primacy and recency effects three filler (1 positive, 1 negative, 1 neutral) words were presented at the start and end of the encoding task. These filler words were not part of the subsequent recognition task. The recognition test phase consisted of the 120 old encoding target words and 120 new distracter words, and 40 baselines. Again, words were presented pseudo-randomized in 20 blocks of 14 words, each block containing two old and two new negative words, two old and two new positive words, two old and two new neutral words, and two baseline trials. 'Old' and 'new' words were matched on complexity, word length, and emotional intensity. Subjects had to indicate whether they have 'seen' (i.e. remembered) the words previously, 'probably have seen it' (i.e. know), or 'haven't seen it' (rejection). Interval between the encoding task and recognition task was 10 minutes. Participants' responses and response times were registered through two magnet-compatible button boxes. No feedback regarding the answers was provided.

The words encoding and recognition task was administered as part of a larger functional and structural imaging study, results of which will be reported elsewhere. The words task was administered as the second task in the session in all participants.

TABLE S-1: SSRI USERS VS SSRI-NON USERS WITHIN MDD, CDA, AND ANX

MADRS=Montgomery Asberg Depression Rating Scale; IDS=Inventory Depressive Symptomatology; BAI=Becks Anxiety Inventory; FQ=Fear Questionnaire; VAS=Visual Analogue Score; pre: before word encoding task; post: after word recognition task; T1=time of NESDA baseline measurement; T2=time of MRI measurement; interval=interval between T1 and T2.

		MDD		CDA		ANX	
		SSRI users	SSRI free subjects	SSRI users	SSRI free subjects	SSRI users	SSRI free subjects
N		12	39	24	35	17	39
gender	male/female; N	3/9	17/22	12/12	9/26	3/14	11/28
scan site	amc/lumc/umcg; N	5/4/3	10/14/15	8/10/6	13/14/8	5/4/8	11/12/16
SSRI use past	yes/no; N	n/a	6	n/a	5	n/a	3
age	in years; mean ± sd	39.6 ± 10	35.4 ± 10.1	36.9 ± 11.3	36.2 ± 11.4	36.5 ± 8.5	34 ± 8.9
education	in years; mean ± sd	13.4 ± 3.5	12.8 ± 1.5	12.1 ± 3	12.8 ± 2.9	12.4 ± 3.7	13.3 ± 3.3
MADRS	total score; mean ± sd	13.5 ± 7.7	12.3 ± 9.4	16.9 ± 7.6	21 ± 9.2	11 ± 8	11.2 ± 8.7
IDS T1	" "	25 ± 9.8	27.6 ± 9.9	30.1 ± 10.3	34.4 ± 8.4	24.3 ± 9.6	23.3 ± 11.7
IDS T2	" "	18.9 ± 7.6	17.4 ± 11.1	27.4 ± 9.4	29.5 ± 9.8	19.3 ± 9.2	19.5 ± 10.7
BAI T1	" "	10.3 ± 7.3	10.4 ± 6.2	19.2 ± 7.9	19.6 ± 8.3	15.9 ± 11.5	15.1 ± 7.9
BAI T2	" "	6.8 ± 5.4	8 ± 6.4	17.6 ± 1.9	19.1 ± 9.7	11.6 ± 7.8	15.6 ± 10
VAS_pre	mean ± sd	16.8 ± 18.5	28.3 ± 22.6	30.3 ± 17.4	37.3 ± 24.9	35.2 ± 26.4	39.5 ± 24.9
VAS_post	mean ± sd	19.1 ± 18.9	17.8 ± 18.1	21.6 ± 15.6	30.1 ± 24.6	28.1 ± 20	30.7 ± 22.4
interval	in days; mean ± sd	52.4 ± 22.4	61.7 ± 30.2	58.7 ± 21.3	65.7 ± 40.2	68.9 ± 37	77.1 ± 34.8
onset MDD	age in years; mean ± sd	28.9 ± 11.5	25.7 ± 9.8	24 ± 9.9	24.3 ± 12.2	19.6 ± 5.1	19.8 ± 6.6
onset ANX	age in years; mean ± sd	13 ± 5.6	19.1 ± 14.3	17 ± 12.2	17.2 ± 12.4	22.1 ± 13.3	17.4 ± 10.9
recurrence MDD	single/recurrent episode; N	6/6	14/25	11/13	14/21	n/a	n/a

TABLE S-2: CLINICAL CHARACTERISTICS IN MDD AND CDA SUBGROUPS, BASED ON CURRENT IDS SCORES

MADRS=Montgomery Asberg Depression Rating Scale; IDS=Inventory of Depressive Symptomatology; BAI=Becks Anxiety Inventory; FQ=Fear Questionnaire; VAS=Visual Analogue Score; pre: before word encoding task; T1=time of NESDA baseline measurement; T2=time of MRI measurement; interval=interval between T1 and T2. Rem=remitted depressed state at T2; mild=mild depressed state at T2; mod/sev=moderately to severely depressed state at T2. * significant within-group difference $p<.05$ (non-parametric related samples test).

		MDD rem	MDD mild	MDD mod/sev	CDA rem	CDA mild	CDA mod/sev
N		19	17	15	3	21	35
gender	male/female; N	9/10	7/10	4/11	1/2	6/15	14/21
scan site	amc/lumc/umcg; N	2/7/10	9/6/2	4/5/6	2/0/1	8/8/5	11/16/8
handedness	left/right; N	1/18	3/14	1/14	0/3	0/21	3/32
SSRI use	yes/no; N	3/16	6/11	3/12	2/1	8/13	14/21
age	in years; mean ± sd	36.3 ± 12.3	38.7 ± 7.7	33.9 ± 9.6	37.7 ± 7.4	37.6 ± 11.9	35.7 ± 11.3
education	in years; mean ± sd	13 ± 2.8	12.8 ± 2.7	13.1 ± 2.8	16 ± 3.5	12.8 ± 2.8	12 ± 2.8
MADRS	total score; mean ± sd	4.6 ± 4.8	13.6 ± 6.8	22.1 ± 7.6	2 ± 2.8	14.3 ± 5.5	23.1 ± 7.9
IDS T1	total score; mean ± sd	24.4 ± 11.6 *	26.2 ± 8.5 *	31.1 ± 8.1	18 ± 12.12	29.5 ± 8.5 *	35.7 8
IDS T2	total score; mean ± sd	6.7 ± 3.5	19.3 ± 3.9	30.2 ± 3.7	7 ± 2.7	21.8 ± 2.9	34.5 ± 6.8
BAI T1	total score; mean ± sd	10.4 ± 7.4 *	9.3 ± 5.5 *	11.6 ± 6.4	13.3 ± 8.6	18.1 ± 9.5 *	20.7 ± 7
BAI T2	total score; mean ± sd	3.3 ± 2.6	7.9 ± 5	13 ± 6.4	3 ± 1.7	15.7 ± 7.2	21.5 ± 8.4
FQ	total score; mean ± sd	13.2 ± 10.9	22.9 ± 11.1	21.3 ± 15.6	17.5 ± 9.2	32.9 ± 17.7	27.9 ± 19.1
VAS_pre	mean ± sd	24.7 ± 16.7	20.6 ± 25.5	32.1 ± 23.4	23 ± 32.5	32 ± 20.2	36.9 ± 22.8
interval	in days; mean ± sd	67.8 ± 30.7	46.4 ± 15	64.3 ± 33.7	66.3 ± 21.7	58.7 ± 21.9	65.1 ± 40.2
onset MDD	age in years; mean ± sd	25.5 ± 12.1	29.1 ± 9.7	24.7 8.4	19 ± 6	26.1 ± 11.4	23.5 ± 11.4
onset ANX	age in years; mean ± sd	-	-	-	16 ± 8.9	21 ± 11	18.4 ± 11.3
recurrence MDD	single/recurrent episode; N	5/14	7/10	8/7	0/3	10/11	15/20

TABLE S-3: TASK PERFORMANCE

Classification behavior: number of words classified as positive, neutral, and negative during the encoding phase. Mean proportion correct and response times for encoding and recognition indices. Abbreviations can be found in Table 1. A one-way ANCOVA showed no effect of diagnosis on proportion PROB responses (M_{old_words}= .13, sd=.09; F=.42, *p*=.74; M_{new_words}=.14, sd=.09; F=.23, *p*=.88). Therefore, we added the PROB trials to the CREC or FA and recalculated the proportion CREC and FA (and d'). * In the word encoding task, 42 positive, 42 neutral and 42 negative words (including the filler words) were presented.

Word classification*

			MDD	CDA	ANX	HC
# words classified	pos	mean ± sd	39.32 ± 9.95	41.45 ± 11.03	39.51 ± 8.8	44.62 ± 9.82
	neu	"	46.52 ± 10.74	42.04 ± 11.84	44.61 ± 11.37	40.21 ± 9.89
	neg	"	39.79 ± 2.80	40.81 ± 5.06	41.28 ± 5.27	40.40 ± 4.51

Memory performance

			MDD	CDA	ANX	HC
CREC	_all	prop; mean ± sd	.85 ± .08	.84 ± .09	.84 ± .09	.82 ± .11
	_neg	"	.84 ± .10	.84 ± .11	.84 ± .10	.82 ± .13
	_pos	"	.85 ± .10	.86 ± .09	.85 ± .11	.83 ± .12
	_neu	"	.84 ± .11	.83 ± .12	.84 ± .10	.79 ± .14
FA	_all	"	.26 ± .12	.25 ± .14	.25 ± .10	.25 ± .13
	_neg	"	.32 ± .12	.31 ± .15	.31 ± .12	.33 ± .16
	_pos	"	.28 ± .15	.27 ± .18	.27 ± .13	.28 ± .18
	_neu	"	.19 ± .11	.18 ± .16	.16 ± .09	.15 ± .10
d'	_all	"	.58 ± .14	.59 ± .14	.60 ± .12	.56 ± .12
	_neg	"	.52 ± .12	.53 ± .13	.53 ± .12	.50 ± .12
	_pos	"	.57 ± .17	.59 ± .18	.58 ± .15	.56 ± .18
	_neu	"	.65 ± .16	.65 ± .17	.68 ± .14	.64 ± .15

Response times

			MDD	CDA	ANX	HC
rt_SCR	_neg	in sec: mean ± sd	1.27 ± .26	1.28 ± .35	1.26 ± .28	1.23 ± .36
	_pos	"	1.49 ± .35	1.48 ± .39	1.42 ± .27	1.36 ± .31
	_neu	"	1.53 ± .33	1.58 ± .41	1.53 ± .38	1.49 ± .36
rt_CREC	_neg	"	1.24 ± .21	1.24 ± .23	1.24 ± .24	1.25 ± .27
	_pos	"	1.34 ± .27	1.31 ± .26	1.29 ± .23	1.32 ± .27
	_neu	"	1.28 ± .22	1.31 ± .27	1.32 ± .27	1.34 ± .29
rt_CREJ	_neg	"	1.46 ± .30	1.46 ± .34	1.44 ± .28	1.47 ± .32
	_pos	"	1.5 ± .31	1.52 ± .33	1.52 ± .29	1.49 ± .32
	_neu	"	1.38 ± .26	1.36 ± .30	1.41 ± .25	1.38 ± .26
rtFA	_neg	"	1.50 ± .49	1.49 ± .43	1.48 ± .46	1.49 ± .51
	_pos	"	1.66 ± .59	1.69 ± .65	1.57 ± .55	1.74 ± .76
	_neu	"	1.54 ± .54	1.90 ± .71	1.68 ± .67	2.04 ± .83
rtMISS	_neg	"	1.79 ± .62	1.98 ± .80	1.92 ± .69	1.84 ± .60
	_pos	"	1.97 ± .68	1.89 ± .68	1.91 ± .73	1.99 ± .68
	_neu	"	1.66 ± .65	1.62 ± .55	1.69 ± .57	1.77 ± .63
rtBL_enc		"	.83 ± .17	.81 ± .16	.79 ± .14	.83 ± .24
rtBL_rec		"	.78 ± .13	.79 ± .16	.76 ± .13	.76 ± .14

TABLE S-4: MAIN EFFECTS OF ENCODING OF POSITIVE AND NEGATIVE (VS. NEUTRAL WORDS)

Main effects of contrast 'SCR_pos>SCR_neu' and 'SCR_neg>SCR_neu' across groups (p<.05, FWE whole brain corrected); BA = Brodmann Area; side=hemisphere; L=left; R=right.

Main effect of SCR_pos>SCR_neu (whole brain FWE corrected)

			MNI-coordinates				
Regions	side	BA	x	y	z	T	Z
Frontal							
inferior frontal gyrus	L	45/47	-51	21	0	6.95	6.95
inferior frontal gyrus	L	44	-57	9	18	5.17	5.17
anterior cingulate gyrus	L	32	-3	45	-3	6.56	6.56
medial superior frontal gyrus	L	10	-3	57	0	6.32	6.32
medial frontal gyrus	L	10	0	60	18	5.96	5.96
middle frontal gyrus	L	6	-33	-9	57	5.94	5.94
middle frontal gyrus	L	6	-45	3	51	5.43	5.43
middle/superior frontal gyrus	R	6	27	-3	57	5.13	5.13
inferior frontal gyrus	R	44	51	6	30	4.94	4.94
precentral gyrus	L	4	-30	-24	48	4.87	4.87
temporal/parietal							
superior temporal gyrus/middel temporal gyrus	L	22/39	-51	-54	18	7.36	7.36
superior temporal gyrus/gyrus supramarginalis	L	39/40	-57	-51	30	5.61	5.61
middle temporal gyrus	L	37	-51	-66	3	5.11	5.11
posterior cingulate gyrus	L	31	-6	-54	27	5.66	5.66
inferior parietal lobule	R	40	45	-30	42	5.44	5.44
inferior parietal lobule	L	40	-39	-39	42	5.30	5.30
inferior parietal lobule	L	40	-45	-33	42	5.21	5.21
inferior parietal lobule	L	40	-42	-33	57	5.27	5.27
middle temporal gyrus	L	21	-48	-30	-6	5.03	5.03
inferior parietal lobule	L	40	-33	-48	57	4.83	4.83
other (subcortical)							
caudate nucleus	L		-9	-3	12	4.94	4.94

Main effect of SCR_neg>SCR_neu (whole brain FWE corrected)

			MNI-coordinates				
Regions	side	BA	x	y	z	T	Z
Frontal							
middle frontal gyrus	L	6	-30	-6	54	6.42	6.26
medial frontal gyrus	L	9	-6	51	24	5.67	5.56
inferior frontal gyrus	R	44	48	9	30	5.14	5.06
inferior frontal gyrus	L	44	-48	9	27	5.10	5.02
precentral gyrus	L	6	-39	3	36	5.08	5.00
inferior frontal gyrus	R	44	57	15	24	4.94	4.87
Temporal/Parietal							
inferior parietal lobule	L	40	-42	-42	39	7.28	7.06
inferior parietal lobule	L	40	-33	-48	42	6.86	6.68
supramarginal gyrus	L	40	-57	-48	27	6.35	6.20
middle temporal gyrus	L	21	-48	9	-27	6.42	6.27
middle temporal gyrus	L	21	-54	-3	-18	6.00	5.88
middle temporal gyrus	L	21	-57	-24	-6	5.99	5.87
inferior parietal lobule	R	40	45	-33	42	5.59	5.49
posterior cingulate gyrus	L	31	0	-48	24	5.53	5.43
middle temporal gyrus	L	39	-48	-63	6	5.19	5.11
inferior parietal lobule	R	40	33	-51	51	5.02	4.95
Occipital							
middle occipital gyrus	R	18	48	-63	-6	5.20	5.11
occipital gyrus	R	19	39	-81	0	5.19	5.10
middle occipital gyrus	L	19	-30	-78	21	5.08	5.00