Functional Magnetic Resonance Imaging Correlates of Emotional Word Encoding and Recognition in Depression and Anxiety Disorders

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Background: Major depressive disorder (MDD), panic disorder, and social 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.

Methods: We used functional magnetic resonance imaging during the performance of an emotional word encoding and recognition paradigm in patients with MDD (n = 51), comorbid MDD and anxiety (n = 59), panic disorder and/or social anxiety disorder without comorbid MDD (n = 56), and control subjects (n = 49). In addition, we studied effects of illness severity, regional brain volume, and antidepressant use.

Results: Patients with MDD, prevalent anxiety disorders, or both showed a common hyporesponse in the right hippocampus during positive (>neutral) word encoding compared with control subjects. During negative encoding, increased insular activation was observed in both depressed groups (MDD and MDD + anxiety), whereas increased amygdala and anterior cingulate cortex activation during positive word encoding were observed as depressive state-dependent effects in MDD only. During recognition, anxiety patients showed increased inferior frontal gyrus activation. Overall, effects were unaffected by medication use and regional brain volume.

Conclusions: Hippocampal blunting during positive word encoding is a generic effect in depression and anxiety disorders, which may constitute a common vulnerability factor. Increased insular and amygdalar involvement during negative word encoding may underlie heightened experience of, and an inability to disengage from, negative emotions in depressive disorders. Our results emphasize a common neurobiological deficiency in both MDD and anxiety disorders, which may mark a general insensitivity to positive information.

Key Words: Emotional memory, fMRI, major depressive disorder, memory function, panic disorder, social anxiety disorder

Major depressive disorder (MDD), panic disorder (PD), social anxiety disorder (SAD) are among the most prevalent and most frequently co-occurring psychiatric disorders in adults (1,2). 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 (2). Until recently, morphological and functional brain alterations in anxiety and depression have rarely been studied in concert, although several studies have now indicated shared functional and structural abnormalities in regions associated with emotion processing (3–6).

MDD, PD, and SAD have been associated with similar biases in processing syndrome-specific information such as negative, threat, or stress-eliciting words or pictures (7–11). Also, MDD has been associated with abnormalities in processing mood-incongruent (i.e., positive) information (12), 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 (13–15), which might reinforce negative mood and could contribute to a chronic course of the disorder (16). Whether anxiety disorders are also associated with memory biases for positive information is unclear. Moreover, it is as yet unknown whether comorbid depression-anxiety (CDA) resembles MDD or anxiety disorders in performance and regional brain activation during emotional memory processes or should be considered a sum of its parts.

To date, neuroimaging studies in MDD have predominantly focused on processing of negative information and have demonstrated differential involvement of the amygdala, hippocampus, anterior cingulate gyrus, and lateral prefrontal cortex (4,5,17–20), supporting the hypothesis of altered involvement of subcortical and prefrontal regions during emotion processing in depression (21,22). However, 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 (16,23) and ventrolateral prefrontal cortex (23) and ventral striatum (24,25), has been associated with positive information processing. Only van Wingen et al. (26) have studied memory for positive and neutral faces in MDD, and they demonstrated altered involvement of the amygdala and fusiform gyrus. In PD, SAD, and generalized anxiety disorder (GAD) studies focusing on the processing of (social) threat-related material reported increased prefrontal (4,11,27–29), hippocampal (11), and amygdalar (4,11,29,30) activation, but effects on emotional memory formation have, to our knowledge, not been studied yet.

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In this study, we investigated unique and shared functional magnetic resonance imaging (fMRI) correlates of mood-congruent and mood-incongruent information processing in MDD in frequently co-occurring anxiety disorders and in the comorbid condition during an emotional word memory paradigm. On the basis of 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 lateral and medial prefrontal “regulatory” brain regions during hypothesized biased memory formation and recollection, while testing for the effects of comorbidity and also controlling for variations in regional brain volume (3). 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 control subjects. Furthermore, in MDD, we hypothesized increased activation of the amygdala, hippocampus, insula, and decreased activation of lateral prefrontal regions during encoding and recognition of negative information, whereas decreased activation of amygdala, hippocampus, and medial prefrontal regions was expected during positive word encoding and recognition, relative to control subjects. 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.

Methods and Materials

Participants

Three hundred and 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 control subjects) recruited from the observational Netherlands Study of Depression and Anxiety (NESDA) (31) were included and underwent magnetic resonance imaging in the Leiden University Medical Center (LUMC), Academic Medical Center (AMC) University of Amsterdam, or University Medical Center Groningen (UMCG). The ethical review boards of each participating center approved this study. All participants provided written informed consent. A detailed description of the MRI sample has been provided elsewhere (3) but can also be found in Supplement 1.

Task Paradigm

We used an event-related, subject-paced, word-encoding and recognition paradigm (32). 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 10 min, participants were asked to complete a word-recognition task. This task consisted of the 120 old encoding target words and 120 new distracter words, as well as 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 Supplement 1.

Before and after the word encoding and recognition task, we monitored anxiety levels using a visual analogue scale (33) ranging from 0 to 100. The encoding–recognition paradigm was part of a larger imaging session (Supplement 1).

Additional Psychiatric Measurements

Severity of depression and anxiety at the day of scanning was assessed using Dutch versions of the Beck Anxiety Inventory (BAI) (34), the Montgomery–Åsberg Depression Rating Scale (MADRS) (35), the Inventory of Depressive Symptomatology (IDS) (36), and the Fear Questionnaire (FQ) (37).

Image Acquisition

Imaging data were acquired using the Philips 3-Tesla MRI system (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 = 2300 msec; echo time = 30 msec [UMCG: 28 msec], matrix size: 96 × 96 [UMCG: 64 × 64], 35 axial slices [UMCG: 39], interleaved acquisition, 2.29 × 2.29 mm in-plane resolution [UMCG: 3 × 3 mm], 3-mm slice thickness). Anatomic imaging included a sagittal three-dimensional gradient-echo T1-weighted sequence (repetition time = 9 msec; echo time = 3.5 msec; matrix 256 × 256; voxel size: 1 × 1 × 1 mm; 170 slices).

Statistical Analysis

Psychometric and performance data were analyzed with SPSS (SPSS Inc., Chicago, Illinois). Functional imaging data were preprocessed and analyzed using Statistical Parametric Mapping software (http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 7.1.0 (The MathWorks, Natick, Massachusetts). To test for effects of diagnosis, groups were formed based on current psychopathology and comorbidity. Depression common effects (MDD_yes/no) were tested by pooling MDD and CDA and contrasting these with the pooled ANX patients and healthy control (HC) subjects. A similar approach was followed to test for anxiety common effects (ANX_yes/no: [ANX and CDA vs. MDD and HC]). 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) (38). Age and education were added to each model to account for variance related to these factors. Standardized effect sizes (Cohen’s $d$) were Bonferroni-corrected for multiple comparisons. To test for effects of depression and anxiety common effects, and their interaction with valence during an emotional word memory paradigm. On the basis of overlap in their phenomenology, neurobiology, and information during encoding and recognition, relative to control subjects. 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.

Performance Data. Proportions (p) hits, proportions False Alarms, and old/new discriminant accuracy ($d' = p_{Hits} – p_{FalseAlarms}$) (40) were calculated, overall and per valence (i.e., positive, negative, neutral).

Repetitive-measures analyses of covariance were performed to test for the effect of diagnosis, disorder common effects, depression and anxiety common effects, and their interaction with valence on task performance ($p_{Hits\_all}$, $p_{FalseAlarms\_all}$, and $d'\_all$) and response times during encoding and recognition. Significance for behavioral analyses was set at $p < .05$, and post hoc pairwise tests (t test or Mann–Whitney U) were Bonferroni-corrected for multiple comparisons ($p_{cor}$).

Imaging Data. fMRI data preprocessing and task modeling details can be found in Supplement 1. Contrast images for Subsequent_Hits_positive > Subsequent_Hits_neutral and Subsequent_Hits_negative > Subsequent_Hits_neutral, resulting from the encoding phase, and Hits_positive > Hits_neutral, and Hits_negative > Hits_neutral, resulting from the recognition phase, were calculated per subject on a voxel-by-voxel basis and entered into second-level analyses for between-group comparisons. Additionally, “site” was added as a regressor by means of two dummy variables. We repeated the analysis after omission of the selective serotonin reuptake inhibitor (SSRI) users. We defined the following regions of...
interest (ROIs): hippocampus, amygdala, medial prefrontal cortex, inferior frontal gyrus (IFG), anterior cingulate cortex (ACC), and insula. To test for the interaction of diagnosis and valence, we set up a 4 (diagnosis) × 2 (valence; positive vs. neutral and negative vs. neutral) factorial design with age, education, and scan site as covariates for encoding and recognition separately. To follow up on these effects and to test for depression-specific (MDD_yes/no) and/or anxiety-specific (ANX_yes/no) effects, we set up two 2 × 2 analyses of variance per valence (i.e., positive vs. neutral and negative vs. neutral), with one factor including HC and ANX and one factor accommodating the depression groups (MDD and CDA), as did Etkin and Schatzberg (5). We reran these models after excluding the remitted patients, based on cutoff scores of 13 on the IDS (38) and 10 on the BAI (41).

We restricted the search for significant effects to voxels that were identified in the main effects (Table S2 in Supplement 1) by masking the group comparisons with the orthogonal relevant main effect (across groups) at p < .05 (uncorrected). To test for the effects of depression severity within MDD and CDA, we set up one factorial design for each valence for encoding and recognition separately. Group-by-task interaction effects and effects of depression severity (F tests) were analyzed at p < .005 uncorrected, and post hoc t tests had to reach p < .05, familywise error (FWE) voxelwise-corrected for the spatial extent of the volume of interest, to be considered significant. For this small volume correction, we used the Automated Anatomical Labelling atlas (42), implemented in the WFU Pick Atlas toolbox (Wake Forest University School of Medicine, Winston-Salem, North Carolina; http://www.fmri.wfubmc.edu/cms/software). For non-regions of interest, a voxel-level threshold of p < .05 FWE whole brain corrected was set a priori. We tested for the effects of anxiety severity on encoding- and recognition-related activity by performing a linear regression analysis with anxiety scores as regressor of interest, and age, depression severity scores, and site as covariates, masked with a binary mask derived from the relevant main effect at p < .05, uncorrected.

The statistical toolbox Biological Parametric Mapping (http://www.fmri.wfubmc.edu/cms/software) was used to test whether between-group effects were affected by variations in regional gray matter (GM) volume (http://www.fmri.wfubmc.edu/cms/software). We used individual modulated GM images derived from the T1 scans (for a description and results of the optimized voxel-based morphometry procedure, see van Tol et al.) (3). Also, we calculated mean volumes of structures containing significant activation effects, based on the anatomic automatic label templates, to correct for large-scale volumetric variations.

Results

Sample Characteristics

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 (PD, SAD, and/or GAD) but no MDD (ANX), and 49 control subjects. Groups were matched for age, education (years), sex, handedness, and scan site. Within diagnostic groups, SSRI users did not differ from antidepressant nonusers regarding scan site, sex, age, education, scan interval, onset and severity of depression and anxiety, and recurrence of depressive episodes in MDD and CDA (Table S1 in Supplement 1). Group characteristics and statistics are listed in Tables 1 and 2. A detailed description of included and excluded data sets is given in Supplement 1. Importantly, no selective drop out of data over diagnosis was observed ($\chi^2(3) = 1.39; p = .71$). Behavioral results are summarized in Figure 1.

fMRI Results: Encoding

Effect of Diagnosis. A group (4) by valence (2) 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 control subjects during positive encoding only and was most strongly observed in the MDD (t(207) = 4.39, $d_{Cohen's} = .61$) and ANX groups (t(207) = 3.40, $d_{Cohen's} = .47$; see Figure 2A and Table 3). Comorbid depression-anxiety showed this hypoactivation below threshold ($Z = 2.7, p_{FWE} = .01, p_{uncorrected} = .004$; t(207) = 2.87, $d_{Cohen's} = .40$). The hippocampal hypoactivation was not explained by regional volume, illness severity (Figure 2A, bottom), or 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). No interactions of valence and group were observed in other regions of interest.

Depression- or Anxiety-Specific and Common Effects per Valence. Planned comparisons per valence revealed no anxiety- or depression-specific effects during positive encoding but confirmed the interaction of MDD_yes/no × ANX_yes/no in the hippocampus ($F(1,207) = 16.98, Z = 3.87$), also when all remitted MDD, CDA, and ANX patients were excluded from the analysis ($F(1,161) = 14.95, Z = 3.60$).

During successful negative encoding, however, a depression specific effect was observed in the left insula ($F(1,207) = 11.68, Z = 3.17$), showing increased left insular activation in MDD and CDA relative to HC, which was most strongly observed when MDD and CDA were contrasted versus HC ($t(207) = 3.51, d_{Cohen's} = .49$; Figure 2B and Table 2) and occurred subthreshold when contrasted against HC and ANX ($p_{FWE} = .078$). This effect was observed independent of SSRI use. Removing all remitted patients from the analysis did not change the insular effect ($t(161) = 3.61, Z = 3.53, p_{FWE} = .04, d_{Cohen's} = .57$) but revealed a depression-specific effect in the right IFG [Montreal Neurological Institute (MNI) coordinate: x = 48 y = 50 z = 12], $P(1,161) = 12.88, Z = 3.33$ and left amygdala (MNI coordinate: x = -21 y = -3 z = -18], $F(1,161) = 10.42, Z = 2.97$) during negative word encoding: MDD and CDA patients demonstrated increased activation of these areas compared to ANX and HC IFG: Z = 3.51, $p_{FWE} = .049, d_{Cohen's} = .67$; amygdala: Z = 3.30, $p_{FWE} = .012, d_{Cohen's} = .53$; see Figure 3C). No anxiety-specific effects were observed.

Effects of Illness Severity. Within MDD, an effect of depressive state (remitted/mild/moderately severe) severity was observed in the left ACC [Brodmann’s area 32; $F(2,142) = 8.37, Z = 3.37$] during positive word encoding: moderately/severely depressed MDD patients showed increased ACC activation compared with control subjects ($t(142) = 3.75, Z = 3.65, d_{Cohen's} = .63$; Figure 3A). The omnibus test, including mild and moderately/severely depressed CDA patients, was also significant ($F(5,142) = 5.54, Z = 2.70$) and confirmed that the effect was specific for moderately/severely depressed MDD patients without comorbid ANX. No effect of depression severity was observed in the moderately/severely depressed patients (linear regression analysis). Also, no effect of depression severity was observed in CDA, and no correlation of anxiety severity was observed within groups during positive word encoding.

Within MDD, an effect of depression severity on negative word encoding was observed in the right anterior hippocampus/amygdala ($F(2,142) = 6.42, Z = 2.80$; Figure 3B): moderately to severely depressed MDD patients showed hyperactivation of this region compared with remitted patients ($t(142) = 3.51, Z = 3.43,$

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Table 1. Clinical Characteristics of the Total Sample (N = 215)

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<th>ANX</th>
<th>HC</th>
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<th>F</th>
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<td>25/34</td>
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Available data: MDD: IDS_T2 available for 49 patients; BAI_T2 available for 48 patients; FQ_T2 available for 45 patients; MADRS available for 48 patients; ANX available for 50 patients; CDA: IDS_T2 available for 58 patients; BAI_T2 available for 57 patients; FQ_T2 available for 46 patients; MADRS available for 57 patients; IDS/BAI/FQ_T1 available for 57 patients; ANX: IDS_T2 available for 54 patients; BAI_T2 available for 53 patients; FQ_T2 available for 45 patients; MADRS available for 54 patients; HC: IDS_T2 available for 48 participants; BAI_T2 available for 48 participants; FQ_T2 available for 44 participants.

MDD: Academic Medical Center at the University of Amsterdam; ANX: anxiety disorders; BAI: Beck Anxiety Inventory; CDA: comorbid depression-anxiety; FQ: Fear Questionnaire; GAD: generalized anxiety disorder; MADRS: Montgomery–Åsberg Depression Rating Scale; MDD: major depressive disorder; IDS: Inventory of Depressive Symptomatology; interval, interval between T1 and T2; HC: healthy controls; LUMC: Leiden University Medical Center; pre, before word encoding task; PD: panic disorder; post, after word recognition task; SAD: social anxiety disorder; SSRI: selective serotonin reuptake inhibitor; T1, time of Netherlands Study of Depression and Anxiety baseline measurement; T2, time of magnetic resonance imaging measurement; UMCNG, University Medical Center Groningen; VAS, visual analogue score.

MDD + SAD, n = 6; MDD + GAD, n = 13; MDD + PD, n = 12; MDD + PD + SAD, n = 7; MDD + SAD + GAD, n = 8; MDD + PD + GAD, n = 7; MDD + PD + SAD + GAD, n = 6.

SAD, n = 22; PD, n = 13; SAD + GAD, n = 2; PD + GAD, n = 2; SAD + PD, n = 13; SAD + PD + GAD, n = 4.

Significance at p < .05.

$\text{d}_{\text{Cohen's}} = .59$ and controls $t(142) = 3.36, Z = 3.29, d_{\text{Cohen's}} = .56$. However, the omnibus test did not reach significance [i.e., including the CDA subgroups; $F(5,142) = 2.20$], indicating that the effect observed in MDD could not be regarded as specific for the moderately/severely depressed MDD group. Within the moderately/depessed MDD patients, left amygdala activation was positively correlated with IDS severity [MNI coordinate: $x = -15, y = 0, z = -15$, $Z = 3.32, p_{\text{FWE ROI}} = .02, r = .78$], also when BAI scores were added as a covariate ($Z = 3.57$). During negative word encoding, no effect of depression and/or anxiety severity was observed within anxiety disorders, with or without comorbid MDD.

fMRI Results: Recognition

No main effect of diagnosis or a significant interaction of diagnosis x valence was observed at the set threshold. Planned comparisons on positive and negative versus neutral word recognition revealed an anxiety-specific effect in the left IFG (MNI coordinate: $x = -51, y = 24, z = -18$), $F(1,207) = 12.85, Z = 3.34$ during positive word recognition [neutral; ANX > non-ANX: $t(207) = 3.58, Z = 3.53, p_{\text{FWE ROI}} = .031, d_{\text{Cohen's}} = .50$; Figure 2C]. This effect ceased to be significant after excluding remitted patients. Furthermore, we did not find significant effects on negative recognition or illness severity effects during emotional word recognition.


### Discussion

In this study, we investigated the unique and shared fMRI correlates of mood-congruent and mood-incongruent word encoding and recognition in MDD and frequently co-occurring anxiety disorders, explicitly testing for the effects of their comorbidity and also controlling for symptom severity, regional brain volume, and SSRI use. Imaging results indicated that abnormal processing of positive information, as reflected in decreased hippocampal activation, may be regarded as a generic trait characteristic of both depression and anxiety disorders. State-dependent abnormalities during the processing of positive and negative emotional stimuli, on the other hand, were found to be specific for MDD and most pronounced in MDD patients without comorbid anxiety. Recognition of previously learned positive material was related to increased inferior frontal gyrus activation in patients with anxiety disorders only.

Our finding of a hyporesponse during positive encoding in the hippocampus in both MDD and anxiety, and trendwise in comorbid depression-anxiety, compared with control subjects was unexplained by regional volume, SSRI use, and illness severity. Given the important role of the hippocampus in episodic memory (43), recollection of previously learned material (44), and context-based memory (45,46), these results suggest decreased contextual coupling during semantic classification and simultaneous encoding of positive words in both depression and anxiety disorders. It is possible that 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 hypoactivation, and longer response times during classification. Our results are in agreement with recent findings of decreased speed in responding to positive self-relevant personality adjectives in MDD (47), as well as the mood-incongruent bias theory as proposed by Bower (48). Together, these findings suggest that positive content impedes encoding in MDD because of possible impairments in emotional recognition.

Hippocampal blunting in untreated patients with MDD during a neutral episodic memory task has been previously described (17). We now demonstrated hippocampal blunting during positive encoding, unrelated to symptom severity, in MDD and patients with anxiety disorders. This finding supports previous behavioral studies that demonstrated a state-independent memory bias in MDD for positive stimuli only, whereas biases toward negative stimuli appeared to be state-dependent phenomena (49,50). The generic hippocampal blunting during encoding of positive words in MDD and anxiety disorders may be related to the shared symptoms of the diagnostic groups. According to the dimensional tripartite model of anxiety and depression (51), the factor “general distress” (also called “negative affect” or “negative emotionality”) describes symptoms of general psychological distress shared by MDD and anxiety disorders. Variations along this dimension of shared symptoms have, for example, recently been linked to specific features of hypothalamus-pituitary-adrenal axis functioning in depression and anxiety (52). From this perspective, our finding of decreased hippocampal activity during positive encoding in both depression and anxiety may be reflective of shared symptoms related to a general incapacity to disengage from negative emotional states and engage in more positive ones. This suggestion is in line with a recent redefinition of depressive pathology as a propensity to engage in, and a decreased capacity to disengage from, a negative mood state, rather than a negative mood per se (53), a concept that may also be relevant for common anxiety disorders.

In addition to these hippocampal trait-like abnormalities, moderately and severely depressed MDD patients were further characterized by over-recruitment of the dorsal ACC during encoding of positive information, an effect that was not observed in moderately/severely depressed CDA patients or mild or remitted MDD or CDA patients. In a previous report on largely the same sample, increased ACC activation was also observed in MDD during presentation of happy faces, although independent of illness severity (54). This over-recruitment of the dorsal cognitive subdivision of the ACC

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**Table 2. Between-Group Comparisons and Effects of Illness Severity on Emotional Memory**

<table>
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<tr>
<th>Regions</th>
<th>MNI Coordinates</th>
<th>k&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Side</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t</th>
<th>Z</th>
<th>p (FWE)</th>
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<td><strong>Positive Words &gt; Neutral Words</strong></td>
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<td><strong>Hippocampus</strong></td>
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<tr>
<td>Patients &lt; HC&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>33</td>
<td>−21</td>
<td>−12</td>
<td>4.03 (3.77)</td>
<td>3.95 (3.70)</td>
<td>.006 (.034)</td>
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<tr>
<td>MDD &lt; HC</td>
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<td>−18</td>
<td>−12</td>
<td>4.19 (4.17)</td>
<td>4.14 (4.08)</td>
<td>.003 (.005)</td>
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<tr>
<td>ANX &lt; HC</td>
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<td>−9</td>
<td>3.80 (3.77)</td>
<td>3.76 (3.70)</td>
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<td>3.45 (3.20)</td>
<td>.05 (.10)&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>MDD and CDA &gt; HC&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>3</td>
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<td>3.45 (3.20)</td>
<td>.05 (.10)&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>−18</td>
<td>3.36</td>
<td>3.29</td>
<td>.045</td>
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Main effects of diagnosis and effects of illness severity for the contrasts SCR<sub>pos</sub> > SCR<sub>neu</sub> and SCR<sub>neg</sub> > SCR<sub>neu</sub>. Results are reported at p<sub>FWE</sub> < .05, corrected for volume of anatomic automatic label (AAL).

<sup>a</sup>k, number of voxels at p < .001.

<sup>b</sup>When total hippocampal volume (divided by total GM) was added to the model, the hippocampus effect was still significant [t(204) = 4.06, Z = 3.98, p<sub>FWE</sub> = .006].

<sup>c</sup>When total left insular volume (divided by total GM) was added to the model, the depression common effect in the left insula became subthreshold [t(204) = 3.36, Z = 3.31, p<sub>FWE</sub> = .09].

<sup>d</sup>Subthreshold effect.
may be interpreted as engagement of extra-attentional re-
sources to classify mood-incongruent words in currently depressed 
patients because this effect was not observed during encoding of 
negative words. Because positive words might not be associated 
with a personally relevant state (56) in currently depressed patients,
additional ACC resources might be called on to resolve this classifi-
cation conflict (57).

We did not observe depression and anxiety generic abnormali-
ties during the encoding of negative words, a result that seems to 
be at odds with reports of increased amygdalar activation in anxiety 
and depression in (adolescent) patients. However, these studies 
used a fearful faces paradigm (4) and a conflict adaptation para-
digm (5), hampering direct comparisons. Nevertheless, a trait-like 
effect of MDD was observed in the left ventral insula during nega-
tive word encoding that was observed in the comorbid anxiety-depres-
sion group as well and may reflect a generally increased
sensitivity to negative information (58). It has been suggested that 
abnormal insula functioning in MDD is associated with the pres-
ence of somatovegetative symptoms and indicates an abnormal
sense of the self (59). Moreover, the insula is a key region in experi-
nencing emotions derived from bodily states and arousal (60,61) and
has been implicated in the salience network (62). Within this net-
work, the insula is considered an important hub for processing 
salient events for action to be initiated, including calling on atten-

![Figure 1. Behavioral plots. Positive words are in red, negative words are in blue, neutral words are in green. Plots show mean and standard errors. No disorder common effects, depression or anxiety common main effects, and no interaction of MDD_yes/no X ANX_yes/no were found on memory performance (all Fs < .157; p > .21), and no interaction of these factors with valence was observed for hits, false alarms, and d’ (all Fs < .50; p > .61). Classification behavior, memory performance, and response times are summarized in Table S2 in Supplement 1. (A) Classification behavior: (a) A disorder common (all patients vs. HC) effect was observed during classification of words (F(1,21,237.49) = 6.29, p = .009); patients classified more words as neutral and fewer words as positive compared with HCs (positive: t(198) = –3.1, p = .002, d_Cohen’s = .44; neutral: t(198) = 2.65, p = .009, d_Cohen’s = .38). (b) An interaction of MDD_yes/no, ANX_yes/no, and valence was observed (F(1,21,235.47) = 8.00, p < .001), which revealed that the difference in neutral and positive word classification was specific for depression (t(198) = 1.76, p = .04, d_Cohen’s = .25) and was not observed as a function of ANX_yes/no (t(198) = .09, p = .46, d_Cohen’s = .01). No effects on negative word classification were observed. (B) Response times. Analysis of response times revealed a valence × MDD_yes/no interaction effect (F(4,206) = 3.10, p = .017), but no disorder common or ANX_yes/no effects (F < 1.21, p > .31); increased response times during positive word encoding were observed in MDD and CDA compared with ANX and HC (t(213) = 2.02, p = .02, d_Cohen’s = .28; Figure 1B-a), although post hoc t test showed that MDD and CDA were slower than HC (t > 1.79, p < .04, d_Cohen’s > .35), but not to ANX (t < 1.07, p > .14, d_Cohen’s < .21; Figure 1B-b). Within diagnostic groups, this effect was observed independent of illness severity in MDD (Figure 1C-a), but only in the moderately and severely depressed CDA group (Figure 1C-b). Results remained unchanged after omission of the SSRI-users. ANX, anxiety disorder; CDA, comorbid depression-anxiety; HC, healthy controls; MDD, major depressive disorder; rem, remitted; mod/sev, moderate/severe.

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tional resources and regulating autonomic activity in reaction to salient stimuli (63). Increased activation in this region during negative word encoding may therefore indicate increased “marking” of the negative content and effort to regulate the autonomic activity elicited by negative events and explain the experience of increased negative emotions. Furthermore, a depressive state-dependent hyperactivation of the right anterior hippocampus/lateral amygdala, left amygdala, and right inferior frontal gyrus was observed during encoding of negative words only, results that are in line with those reported by Hamilton and Gotlib (19). Our results suggest that an abnormal amygdalar response may mark a state-dependent sensitivity for encoding negative information and, when interpreted in

Figure 2: Effects of diagnosis on encoding and recognition. (A) Effects of diagnosis (patients < HC) on Subsequent_Hits_positive > Subsequent_Hits_neutral (Z statistics) overlaid (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) Depression common effect (MDD and CDA > ANX and HC) on Subsequent_Hits_negative > Subsequent_Hits_neutral (Z statistics; top) and 90% C.I. centered at the left insula showing contrast estimates of diagnosis (middle) and the absence of effects of severity within MDD and CDA (bottom) in comparison with HC. (C) Anxiety common effect (ANX and CDA > MDD and HC) on Hits_positive > Hits_neutral (Z statistics; left) and 90% C.I. (right) centered at the left inferior frontal gyrus (IFG) showing contrast estimates of diagnosis. Z and F statistics are displayed at p < .005, uncorrected. Effects on positive encoding are displayed in red boxes, effects on negative encoding in blue boxes, and effects on positive word recognition in green. ANX, anxiety disorder; CDA, comorbid depression-anxiety; HC, healthy controls; MDD, major depressive disorder; rem, remitted; mod/sev, moderate/severe.
may indicate increased salience detection and contextual coupling subserving enhanced learning of emotional 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 differences in regional brain volume. However, several potential limitations should also be noted. First, the Netherlands Study of Depression and Anxiety strategy of recruiting patients through general practitioners and outpatient clinics across a wide range of disease severity and duration (31) 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 approximately 15% of the presented words were “forgotten.” 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., subsequent_hits/hits) and concentrated on valence effects during successful encoding and recognition, which are likely to be subtle.

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 -nonspecific negative words. Fourth, although similar 3T systems were used at each site in this multicenter 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 × diagnosis bias occurred. Finally, we aggregated the anxiety disorders to capitalize on our sample size and compare the neural profile of these anxiety disorders with those observed in comorbid depression-anxiety and MDD. We chose this approach to focus on disorder common effects and are aware that caution should be taken when interpreting our results.

Figure 3. Effects of illness severity. (A) Effects of MDD_mod/sev > HC on Subsequent_Hits_positive > Subsequent_Hits_neutral (Z statistics; top) and 90% confidence intervals (C.I.) centered at the left anterior cingulate cortex (ACC) showing contrast estimates of depression severity subgroups within MDD and CDA, and HC (bottom). (B) Effects of MDD_mod/sev > HC on Subsequent_Hits_negative > Subsequent_Hits_neutral (Z statistics; top) and 90% C.I. centered at the right anterior hippocampus/amygdala showing contrast estimates of depression severity subgroups within MDD and CDA, and HC (bottom). (C) Depression common effects after exclusion of the remitted MDD, CDA, and anxiety patients (MDD and CDA > ANX and HC) on Subsequent_Hits_negative > Subsequent_Hits_neutral (Z statistics) in the left amygdala and right inferior frontal gyrus (left) and 90% C.I. showing contrast estimates of diagnosis (right). Z and F statistics are displayed at $p < .005$, uncorrected. Effects on positive encoding are displayed in red boxes, effects on negative encoding in blue boxes. ANX, anxiety disorder; CDA, comorbid depression-anxiety; HC, healthy controls; L, left; MDD, major depressive disorder; R, right; rem, remitted; mod/sev, moderate/severe.
results as the absence of anxiety-specific effects during encoding because this approach may have resulted in false-negative results. Post hoc comparisons of PD and SAD patients did not, however, reveal differences between groups.

In conclusion, our results indicate that abnormal hippocampal involvement during encoding of positive information is a shared feature of depression and anxiety, whereas abnormal insula involvement during negative word encoding is a depression common feature. Furthermore, amygdala activation during the encoding of negative information and ACC activation during positive encoding are unique state-dependent features of MDD without comorbid anxiety. Hippocampal blunting during positive word encoding appeared as a common and state-independent neurophysiologic phenomenon in depression and anxiety that may mark a general insensitivity to positive information. Future studies should investigate whether individuals at high risk for depression and anxiety (e.g., carriers of specific risk genes associated with affective disorders, offspring of patients with depression or anxiety disorders, abuse victims) are characterized by abnormal processing of positive stimuli because this may constitute a risk factor for mood and anxiety to be considered in prevention programs.

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