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CHAPTER 5



WHOLE BRAIN FUNCTIONAL CONNECTIVITY DURING
EMOTIONAL WORD CLASSIFICATION IN MEDICATION
FREE MAJOR DEPRESSIVE DISORDER

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Background: Evaluating emotional information involves coordinated activity of prefrontal and subcortical brain regions that may be compromised in Major Depressive Disorder (MDD). This study tested whether patients with MDD show altered functional connectivity during the processing of emotional information with a set of independently derived brain networks that in previous research have shown high correspondence with different task demands, including stimulus salience and emotional processing.

Methods: Twenty-five medication-free MDD patients and 25 right-handed matched controls performed an event-related, subject-paced emotional word evaluation task during functional magnetic resonance imaging. Data were analyzed with a dual regression approach using eight independently derived template independent component networks. First, a time series was estimated for each template per subject. Next, a subject-specific weighted spatial map of brain connectivity with that template was created based on the time series created in the first regression step. Individual spatial connectivity maps were used to evaluate between-group differences using permutation tests.

Results: In patients with MDD, we observed decreased functional connectivity of the medial prefrontal cortex, ventrolateral prefrontal cortex, and ventral striatum with a network that has previously been associated with stimulus salience and emotional task execution compared with controls. Within MDD, results were unrelated to illness severity, but related to the number of words evaluated as positive. No other independent component networks showed between-group differences.

Conclusion: The decreased connectivity of prefrontal and ventral-striatal regions with the salience network during emotional word evaluation confirms the hypothesis of a relative (para)limbic-cortical decoupling that may serve to explain abnormal emotional regulation in MDD.

Failure to adaptively process emotional information is one of the key features of Major Depressive Disorder (MDD). The ability or tendency to continuously evaluate significant stimuli in our surroundings provides us with the ability to limit the magnitude or duration of negative emotions, thus allowing us to devote attention and resources to other important needs or goals. Equally, the capability to “lift oneself up” by evaluating stimuli in a positive manner provides one of the primary motivations needed in an active and productive day-to-day life. Anhedonia, a fundamental aspect of MDD, may in large part reflect an inability to engage in such positive emotional appraisal. Animal research and neuroimaging studies with humans indicate that adaptive appraisal of emotional stimuli depends on intact interactions between (para)limbic and subcortical brain structures, and dorsal and lateral prefrontal cortical (PFC) areas (Ochsner et al., 2004; Phillips et al., 2003a; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). A reduction in the coordinated engagement of such neural systems is one possible mechanism underlying MDD.

Processing external (and internal) emotional information involves the perception of a stimulus (e.g., word, picture, bodily sensation) and appraisal of this stimulus for its content, meaning, and significance. Any negative or positive emotional state resulting from this process of primary appraisal can subsequently be increased or decreased in amplitude through continuing reappraisal of the stimulus or situation. Circuits responsible for these processes may include perception areas (visual cortex, auditory cortex, sensory cortex), areas associated with initial evaluation of or conditioned responding to potentially salient information (amygdala, ventral striatum, insula) and areas supporting more elaborate cognitive appraisal and top-down control such as dorsal and lateral prefrontal cortex (Ochsner et al., 2009; Urry, van Reekum, Johnstone, & Davidson, 2009; Wager et al., 2008).

Functional magnetic resonance imaging (fMRI) studies that have specifically tested the connectivity of (para)limbic and prefrontal regions in MDD suggest abnormal connectivity of the amygdala (Anand et al., 2005; Chen et al., 2008; Cullen et al., 2009), thalamus (Anand et al., 2005), frontal regions (Lemogne et al., 2009; Sheline, Price, Yan, & Mintun, 2010) including the ACC (Anand et al., 2005; Cullen et al., 2009; Sheline et al., 2010) and parietal regions (Bluhm et al., 2009; Sheline et al., 2010; Zhou et al., 2010) during emotional paradigms (Anand et al., 2005; Chen et al., 2008; Lemogne et al., 2009) and without any externally cued task (the so called resting state) (Bluhm et al., 2009; Cullen et al., 2009; Sheline et al., 2010). However, these studies used seed-based analyses where signal from one brain region is correlated with signal from other voxels in the brain or a (set of) predefined brain region(s). Such approaches only allow to test for connectivity based upon a limited number of seed regions (e.g. the amygdala), potentially missing important information about the involvement of broadly interconnected regions throughout the brain. Further, choosing a seed region is rather arbitrary and may be biased when the seed region

is based at least partially on the data being analyzed (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009). Independent component analysis (ICA), on the other hand, is a multivariate data-driven approach that allows studying whole-brain intrinsic connectivity. Using ICA, functional data is decomposed into a set of independent spatial maps and their associated time series which can then be compared between conditions. It is now established that a highly consistent set of component maps can be identified across multiple studies and human samples (Beckmann, DeLuca, Devlin, & Smith, 2005; Biswal et al., 2010; Damoiseaux et al., 2006). Recent evidence suggests that such independent component maps depict networks of brain regions that co-activate when particular categories of tasks or cognitive processes are being performed (Smith et al., 2009), including perception, motor processing, cognition, and emotional processing.

So far, whole brain ICA approaches for analyzing functional imaging data have been sparingly applied in MDD. There is some evidence, based on resting-state ICA that prefrontal networks are altered in MDD, though some studies have indicated increased (Greicius et al., 2007) while others have revealed decreased (Veer et al., 2010) connectivity. However, the lack of a specific task during resting-state studies means that brain activation and connectivity may be influenced by a variety of perceptual, emotional or cognitive processes preceding or during the resting state session (Harrison et al., 2008; Pyka et al., 2009; Waites, Stanislavsky, Abbott, & Jackson, 2005). Also, differences in cortico-limbic connectivity in MDD might become more apparent when studied during tasks that tap into cortico-limbic processes. So far, to our knowledge, no study attempted to investigate whole-brain connectivity during execution of an emotional task in MDD.

In this study we tested whether depressed patients showed different patterns of connectivity in distributed networks during emotional processing compared with controls, using a subset of independently derived brain networks that are involved in perception, and emotional appraisal and regulation. We used a set of template independent component networks (ICNs) derived from a resting state study using healthy individuals (Beckmann et al., 2005). These ICNs also show strong correspondence to a set of spatial components estimated in a meta-analysis of the BrainMap database, which consists of activation maps from nearly 30,000 subjects engaged in a wide variety of tasks (18). We hypothesized that prefrontal and limbic connectivity within these template networks, specifically those found previously to become active during emotion tasks, would be reduced in a group of individuals with MDD compared to a sample of matched healthy controls.

PARTICIPANTS

Twenty-five right-handed medication-free patients with a half-year diagnosis of MDD (16 female; age range: 20-52), with no past or present diagnosis of comorbid anxiety disorders were selected from the Netherlands Study of Depression and Anxiety (NESDA, see supplemental material) neuroimaging study. Diagnoses according to Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) algorithms were established using the structured Composite International Diagnostic Interview (CIDI) – lifetime version 2.1 (Robins et al., 1988), administered by a trained interviewer. The control group consisted of 25 age, sex, handedness, scan-center and education matched healthy control participants also recruited through NESDA (HC; 17 female; age range: 21-54), who 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. Exclusion for all participants in this analysis were: 1) a history of major internal or neurological disorder, 2) dependency or recent abuse (past year) of alcohol and/or drugs, 3) hypertension, 4) left handedness, 5) general MR-contraindications.

TASK PARADIGM

We employed an event-related subject-paced word encoding paradigm (Daselaar et al., 2003), programmed in E-prime software (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Forty positive, 40 negative, 40 neutral study words, and 40 baseline trials were presented in a pseudo-randomized order in 20 blocks of eight words. Each block consisted of two negative words, two positive words, two neutral words, and two control words. Words were matched for length (ranging from three to twelve letters) and frequency of use. The task was paced by the subject, but each word was presented with a maximum duration of 5 sec. Subjects had to indicate whether they thought the word presented was positive, negative, or neutral to them (response options were displayed at the bottom of the screen). Control words were '<< left', '<< middle>>', and 'right >>' and participants were instructed to press the corresponding button. This task was part of a word recognition paradigm. Therefore, the task started and ended with three filler words to protect for the 'primacy-recency' memory effect.

PROCEDURE

MR imaging was performed in one of the three participating centers, 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 center approved this study. All participants provided written informed consent after having received written information about the study.

Severity of depression and anxiety on the day of scanning was assessed using Dutch versions of the Beck's Anxiety Inventory (Beck et al., 1988), the Montgomery Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979),

and the Inventory of Depressive Symptomatology (Rush et al., 1986). Before the word encoding task, self-rated anxiety levels were monitored using a Visual Analogue Scale ranging from 0 to 100. The words paradigm was performed as part of a larger functional imaging session, including a visuospatial planning task (van Tol et al., 2011), an emotional faces paradigm (Demenescu et al., 2011), and resting-state imaging (Veer et al., 2010).

IMAGE ACQUISITION

Imaging data were acquired using Philips 3-tesla MR-systems (Best, The Netherlands) located at the LUMC, AMC, and UMCG Neuroimaging Center, equipped with a SENSE-8 (LUMC and UMCG) and a SENSE-6 (AMC) channel head coil, respectively. For each subject, echo-planar images (EPI) were obtained using a T2*-weighted gradient echo sequence (repetition time [TR]=2300 ms, echo time [TE]=30ms [UMCG: TE=28 ms], matrix size: 96x96 [UMCG: 64x64], 35 axial slices [UMCG: 39 slices], interleaved acquisition, 2.29x2.29mm in-plane resolution [UMCG: 3x3mm], 3mm slice thickness). EPI's were scanned parallel to the anterior-posterior commissure plane. Scan session length was dependent on the subjects' pace of completing the task and varied between 128 and 240 volumes. Anatomical imaging included a sagittal 3D gradient-echo T1-weighted sequence (TR=9 ms, TE=3.5 ms; matrix 256x256; voxel size: 1x1x1mm; 170 slices).

STATISTICAL ANALYSIS

Imaging data acquired during the word encoding task were processed using FSL software (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl, (Smith et al., 2004)). Preprocessing of the fMRI images was carried out using FEAT (fMRI Expert Analysis Tool) Version 5.98, implemented in MELODIC Version 3.10. The following processing steps were applied: motion correction, slice timing correction, non-brain removal, spatial smoothing using a Gaussian kernel of 5 mm full width at half minimum, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=150 s). Next, the functional images were registered to MNI-152 standard space (T1 standard brain averaged over 152 subjects; Montreal Neurological Institute, Montreal, QC, Canada) using a two-step registration from functional to high resolution structural T1 image to MNI template. Normalized 4D data sets were resampled to 4 mm isotropic voxels to reduce computational burden in the subsequent analysis steps.

Resampled and normalized data sets from both MDD patients and HCs were then entered into a dual regression analysis (Beckmann, Mackay, Filippini, & Smith, 2009) using the set of eight standard independent component networks (ICNs) as described in detail in Beckmann et al. (2005). In the dual regression procedure, two stages of multiple linear regression analyses are performed. 1) A time series is estimated for each ICN template per subject, using the subject's

functional data as the predicted variable and the set of spatial ICNs as predictors; 2) A subject-specific weighted spatial map is created using the time series created in [1] as predictors of the participant's functional data. The resulting spatial maps represent an unbiased measure of the degree to which BOLD signal fluctuations in each voxel covary with each ICN time series for each subject separately. More simply, each participant's spatial map for a given ICN can be considered a voxelwise map of the strength of functional connectivity with that ICN.

To assess main effects across both groups of functional connectivity within each ICN, individual spatial maps were included in a one-sample t-test performed separately for each ICN. To assess group differences in functional connectivity within each ICN, individual spatial maps were compared in an independent samples t-test performed separately for each ICN. All results are reported at $p < .05$, family wise error corrected for multiple comparisons using permutation tests (# permutations=5000) with cluster-mass thresholding (voxelwise threshold: $z = 2.3$) (Hayasaka & Nichols, 2003).

RESULTS

Table 1 lists sample characteristics. MDD showed higher depression and anxiety scores than controls (MADRS, IDS, BAI: All $U > 38.5$; all $p < .001$). Between the NESDA interview (Time_1) and the MRI-session (Time_2) depressive symptom ratings decreased in MDD (IDS, $z = -3.35$, $p < .001$). At the time of scanning, eight MDD patients were in the remitted stage. No group difference was observed in the number of volumes acquired during the self-paced task ($F_{1,49} = .69$, $p = .41$). An interaction of valence classification and diagnosis was observed ($F_{1,2; 53,2} = 6.0$, $p < .05$, $\eta^2 = .12$): MDD patients indicated less words as 'positive' and more words as 'neutral' than the healthy controls ($F > 6.07$, $p < .05$) (figure 1), independent of illness severity. No effect of diagnosis on classifying negative words was observed and no interaction of diagnosis and valence occurred on response times.

As a check of overall fit of data to the template ICNs, we assessed main effects across groups of functional connectivity with each ICN to evaluate the spatial correlation pattern per template ICN. Overall, mean spatial maps over both groups (i.e., one sample t-tests per component) closely matched the template ICNs, although the components often included additional regions compared with the templates.

Comparison of spatial maps between the two groups showed decreased connectivity of the bilateral medial PFC, nucleus accumbens, caudate nucleus, right orbitofrontal cortex (OFC), and right putamen with a template network including the ventrolateral-PFC, dorsolateral PFC, anterior cingulate gyrus, medial PFC, cerebellum, and cuneus (Figure 2) in MDD compared with controls. This network had the strongest loading on emotion-related tasks in the

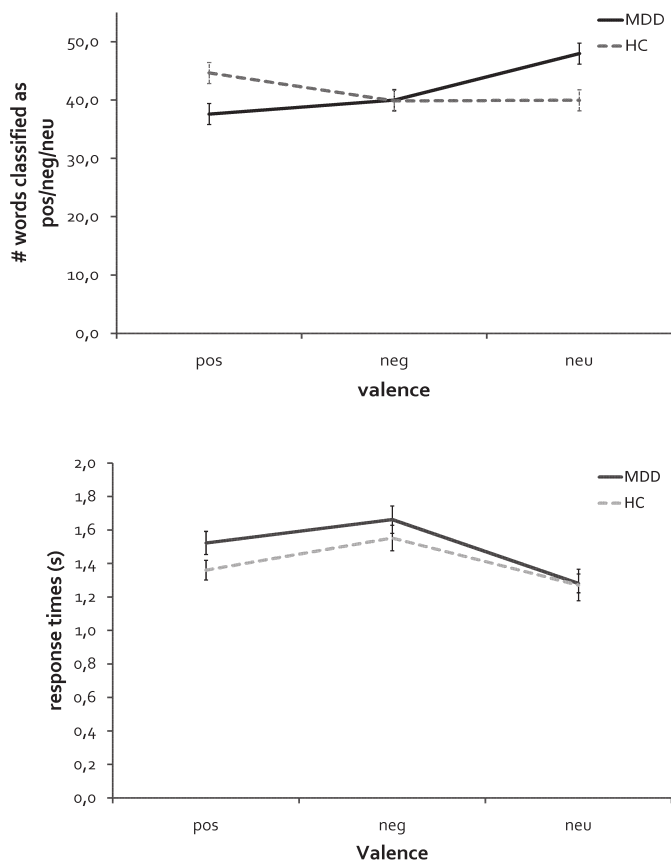
BrainMap database (Smith et al., 2009) and has previously been described as the salience network (Seeley et al., 2007). Therefore, we will refer to this network as the salience network for the remainder of this report.

We exported the individual subject beta-values of the 8 sub-clusters (see Table 2) for this independent component network to SPSS to test for possible confounds. A one-way MANOVA confirmed the voxelwise analysis, with lower values in MDD than in controls ($F_{8,41}=2.86, p<.05, \eta^2=.36$). Adding age, education, and scan center (2 dummy variables) did not change the result ($F_{8,37}=2.35, p<.05, \eta^2=.34$). In a previous study, we reported on decreased inferior frontal gyrus and rostral anterior cingulate gyrus gray matter volumes in MDD (van Tol et al., 2010). As these regions are implicated in the salience network, we explored the relation between regional anterior cingulate cortex and inferior frontal gyrus volume and connectivity within the salience network. However, no correlation was observed ($r_{\text{Kendall's tau}}<.11, p>.26$). Moreover, connectivity of the medial PFC-striatal regions within the salience network was not associated with depression severity (IDS_T2: ($r_{\text{Kendall's tau}}=.02, p=.87$).

		MDD (n=25)	HC (n=25)	TABLE 1: SAMPLE CHARACTERISTICS
female	n	16	17	MDD: Major Depressive Disorder; HC: healthy controls; MADRS: Montgomery Åsberg Rating Scale; IDS: Inventory of Depressive Symptomatology; BAI: Beck Anxiety Inventory; VAS: Visual Analogue Scale; T1: time of the Netherlands Study of Depression and Anxiety baseline interview; T2: time of Magnetic Resonance Imaging session; # volumes: number of volumes acquired during the word classification task; # words_pos/neg/neu: number of words classified as positive, negative, or neutral; rt pos/neg/neu: response time of classifying positive/negative/neutral words.
amc/lumc/umcg	n	8/10/7	8/10/7	
age	years; mean (sd)	33.9 (9.9)	37.2 (10)	
education	years; mean (sd)	12.9 (2.6)	13.8 (2.3)	
recurrent MDD	N	15	-	
age of onset	years; mean (sd)	25 (11)	-	
MADRS	mean (sd)	14.4 (10.2)	.9 (1.7)	
	range	0 - 33	0 - 6	
IDS_T2	mean (sd)	19.2 (11.9)	3.8 (3.3)	
	range	2 - 39	0 - 11	
IDS_T1	mean (sd)	28.5 (10.5)	5.3 (2.8)	
	range	2 - 47	0 - 10	
BAI	mean (sd)	8.5 (7)	2.3 (2.2)	
	range	0 - 26	0 - 8	
VAS	mean (sd)	24.8 (20.4)	24 (22.3)	
	range	0 - 65	0 - 80	
# volumes	mean (sd)	168.8 (18.8)	163.9 (22.3)	
	range	128 - 207	138 - 240	
classification behavior				
# words_pos	mean (sd)	37.6 (9.5)	44.6 (9.7)	
# words_neg	mean (sd)	40 (2.5)	39.9 (6.8)	
# words_neu	mean (sd)	48 (10.2)	40 (9.8)	
rt pos	sec; mean (sd)	1.52 (.33)	1.36 (.28)	
rt neg	sec; mean (sd)	1.28 (.27)	1.27 (.44)	
rt neu	sec; mean (sd)	1.66 (.39)	1.55 (.36)	

FIGURE 1:

plots showing mean and standard errors for number of words classified as positive, neutral or negative (top), and response times in seconds during classifying words as positive, negative, and neutral (bottom).



We then explored whether connectivity was related to word classification behavior and response times. Within MDD, connectivity of the medial PFC with the salience network was positively correlated with the number of words classified as positive ($r_{\text{Kendall's tau}}=.33$, $p=.03$). Connectivity in the fronto-striatal areas was unrelated to response times during classification of positive, neutral and negative words ($r_{\text{Kendall's tau}}<.18$, $p>.25$). No significant between-group differences were observed for the other networks.

FIGURE 2:
SALIENCE NETWORK ACROSS PATIENTS AND CONTROLS AND BETWEEN GROUP DIFFERENCES

A) mean component across patients and controls together; B) differences between MDD and HC within the salience network showing decreased medial PFC, caudate nucleus, and nucleus accumbens connectivity in the MDD group. Results are displayed at $p < .05$, family wise error corrected. Right figures: mean and 95% confidence interval plots showing the mean connectivity strength in the nucleus accumbens (upper plot), caudate nucleus (middle plot), and medial PFC (bottom plot). A full-color image can be found on the supplementary sheet.

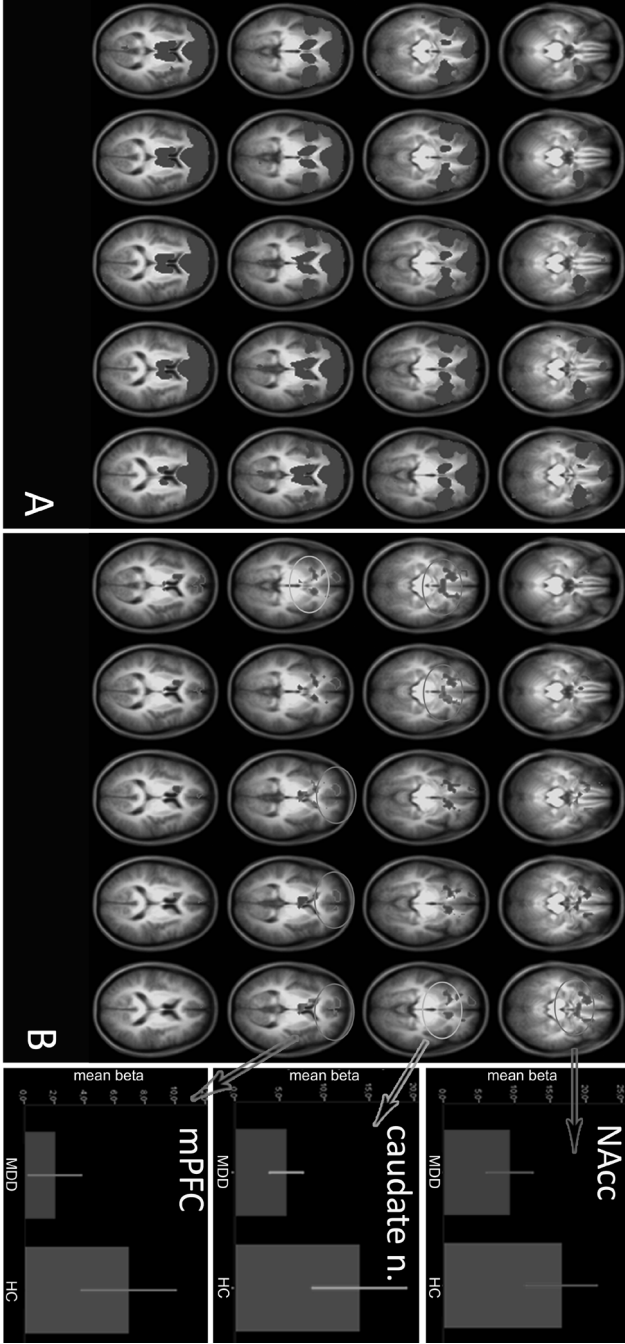


TABLE 2:
EFFECT OF DIAGNOSIS
ON CONNECTIVITY
WITH THE SALIENCE
NETWORK: MDD<HC

L=left hemisphere; R=right hemisphere; MNI: Montreal Neurological Institute coordinate system. Results are reported at $p<.05$, Family wise error corrected for multiple comparisons using permutation tests (# permutations=5000) of cluster-mass (voxelwise threshold: $z=2.3$).

Location	Center of Gravity (MNI)			No. of voxels
	x	y	z	
R orbitofrontal cortex	16	24	-4	102
L nucleus accumbens	-12	20	-8	70
R medial prefrontal gyrus, frontal poles	8	60	4	63
R caudate nucleus	4	4	6	20
R frontal pole/ventrolateral prefrontal gyrus	24	50	-12	7
L medial/superior prefrontal gyrus	-20	44	0	3
R ventral caudate nucleus	8	20	-4	1
R putamen	20	12	-8	1

DISCUSSION

In this study we investigated whole-brain functional connectivity in MDD during execution of an emotional word classification task using a subset of eight independently derived independent component networks. We demonstrated decreased functional connectivity of the medial PFC, putamen, caudate nucleus, OFC, and ventral striatum (including the nucleus accumbens) within the salience network in MDD as compared with healthy control participants. Results were unexplained by age, education, sex, and brain volume of regions implicated in the neuroanatomical profile of MDD. Moreover, within MDD, decreased functional connectivity of the fronto-striatal regions was unrelated to illness severity. No differences in functional connectivity were observed within any other network.

These results confirm the hypothesis that abnormal intrinsic connectivity of cortical and subcortical and (para)limbic regions during emotional processing is part of the functional pathophysiology of MDD. Our results indicate that this decreased coupling might not be a state phenomenon of MDD, but appears to be a trait-like phenomenon that continues into the (newly) remitted phase. Moreover, the decreased subcortical-cortical coupling was observed within the salience network, a network that has been found to specifically correlate with subjective emotional ratings (Seeley et al., 2007). Furthermore, the salience network is the only work of the Smith et al. (2009) study that showed a high load on emotional processes and tasks in a large scale meta-analysis of the BrainMap database, but also loads on sensory perception, including pain perception, working memory, explicit memory, cognition, and action inhibition (Smith et al., 2009). These processes are highly relevant for MDD symptoms such as sad mood, failure to stop negative thoughts, attentional deficits, and altered bodily sensations related to appetite and temperature.

Interestingly, we observed relative decoupling of the medial prefrontal cortex and striatum within the salience network in MDD. The medial prefrontal cortex is thought to be an important region for regulating emotional states through cognitive appraisal (Johnstone et al., 2007; Ochsner et al., 2009), self-referential processing (Lemogne et al., 2009), and affective conflict processing (Ochsner, Hughes, Robertson, Cooper, & Gabrieli, 2009). Moreover, the strength of connectivity in the medial prefrontal cortex and striatum was associated with positive word evaluation. Therefore, our findings indicate that the distributed network involved in cognitive appraisal, self-referential processing, and affective conflict processing is compromised in MDD, potentially related to the processing of positive information. The medial PFC has numerous connections with other regions that have been implicated in normal and abnormal mood regulation, including the striatum, thalamus, pallidum, and dorsal cortical areas, and therefore it has been suggested that the medial PFC may play an important role in moderating visceral processes related to emotions (Price & Drevets, 2010). Also, the nucleus accumbens, a part of the ventral striatum, showed lower connectivity with the salience network. This region receives projections from the amygdala, and further projects to the medial PFC and thalamus (Price & Drevets, 2010), and has been repeatedly associated with reward processing. Moreover, a failure to sustain activation in this region during upregulation of positive emotional states has been linked to anhedonia in MDD patients (Heller et al., 2009). This finding corroborates the present observation of diminished connectivity of the striatum with the salience network that was associated with positive word evaluation and suggests that decreased fronto-striatal coupling with the salience network may be specific to lacking a positive mood state. However, we were not able to investigate whether para(limbic)-cortical connectivity varied as a function of hedonic capacity or current mood state, as we did not include a measure specifically probing current mood state and anhedonia.

The present results are in concordance with the low-frequency seed-based correlation analysis of Anand et al. (2005), who showed decreased limbic-cortical connectivity of the pallido-striatum with the ACC during positive, negative, and neutral picture viewing in MDD. However, in this seed-based analysis, time series of only four seeds were included in the analysis and therefore connectivity of the striatal regions with other prefrontal regions could not be studied. Our results indicate that the decreased connectivity of the striatal regions during positive, negative, and neutral word classification extends to the dorsolateral PFC, inferior frontal gyrus, and dorsomedial PFC. Similar results have been observed in a small adolescent MDD sample during resting-state imaging, in which decreased connectivity of the subgenual ACC and a network including the rostral ACC, inferior frontal gyrus, medial frontal pole, and dorsolateral cortical areas was demonstrated, independent of illness severity (Cullen et al., 2009).

In the present study we could not replicate findings of decreased connectivity

of the amygdala with hippocampal regions, or with orbitofrontal or medial PFC regions that have been observed in both task- and resting-state connectivity analyses (Johnstone et al., 2007; Hamilton & Gotlib, 2008; Matthews, Strigo, Simmons, Yang, & Paulus, 2008; Almeida et al., 2009; Lui et al., 2009; Veer et al., 2010). This discrepancy in findings could be the result of the template ICN method used. The independently derived ICNs used in this study did not include limbic regions and therefore detecting connectivity differences between (para)limbic and prefrontal regions is less likely than studies that use a limbic seed region. However, synchronicity between posterior visual regions and the amygdala was observed in the mean spatial maps of the lateral visual component across participants from both groups, but no differences were observed in this component, consistent with previous reports (Anand et al., 2005; Cullen et al., 2009).

In the present study, we used a new approach to study functional connectivity during the execution of an emotional word classification task. We used template ICNs to create subject specific component maps, based on the times series that best fit the weighted templates using the dual regression approach (Beckmann et al., 2009). This template-based dual regression approach has the advantage that templates are acquired independently of the data under study (Kriegeskorte et al., 2009). These template components have been found to be highly consistent and have been independently detected in a number of populations (e.g., Alzheimer's disease (Rombouts et al., 2009), MDD (Veer et al., 2010), healthy controls (Beckmann et al., 2005)). Overall, use of the template ICNs and dual regression approach resulted in highly consistent components across groups, even though the number of acquired brain volumes differed between participants. Indeed, a strength of this approach is that it is not limited to standard fMRI task paradigms with associated restrictions on the timing and number of trials, but can be used to study sustained engagement of brain networks over the duration of a task. Another advantage is that the template-ICN dual regression method allows for the study of connectivity across groups and tasks in a standardized and unbiased way, which is crucial for studies involving comparisons between clinical and non-clinical samples. Also, using the template ICNs should increase reproducibility of effects, due to the independence of the ICN templates in reference to the data under study. Taken together, we believe that this template-based dual regression method is a potent approach to study differences in functional connectivity during both rest and task paradigms, particularly when comparing across patient groups (or scan sessions in treatment studies) when an unbiased and reliable comparison is crucial.

Using an unbiased whole-brain functional connectivity approach, we showed decreased connectivity of medial prefrontal regions and ventral subcortical and paralimbic regions in MDD during the execution of an emotional word evaluation task with a distributed the salience network. Future studies should test the specificity and generalizability of our results to different MDD

sub-samples and different tasks. For example, medial PFC connectivity with the salience network was unrelated to illness severity but was related to the number of words as 'positive'. This finding might suggest that decreased fronto-striatal coupling within the salience network may be specific to lacking a positive mood state. Given the power of this technique to compare distributed patterns of connectivity in an unbiased way, future studies should also examine treatment-related changes of connectivity with the salience network.

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PARTICIPANTS

Participants were recruited from NESDA (Netherlands Study of Depression and Anxiety), a large-scale multi-site longitudinal observational cohort study. The rationale, methods, and recruitment have been described in detail elsewhere. (Penninx et al., 2008) In short, NESDA has been designed to be representative of those with depressive and anxiety disorders in different health care settings and stages of the developmental history. Therefore, the sample is stratified for setting (community, primary care, and specialized mental health) and set up to include a range of psychopathology. 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; N=301) if they met DSM-IV criteria for a half-year diagnosis of MDD and/or anxiety disorder (Panic Disorder, Social Anxiety Disorder, or Generalized Anxiety Disorder), or no lifetime DSM-IV diagnosis (i.e. healthy controls [HC]). Personality disorders were not obtained/screened for and so were not used in the inclusion/exclusion criteria, although persons with known personality disorders (either reported by psychiatrist or participant) were not included in the NESDA sample. The total MRI sample is described in detail elsewhere (van Tol et al., 2010).

