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ORIGINAL INVESTIGATION

Reduced negative BOLD responses in the default-mode network and increased self-focus in depression

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Abstract

Objectives. Functional imaging studies in major depressive disorder (MDD) indicate abnormal resting state neural activity and negative blood oxygenation level-dependent (BOLD) responses (NBRs) in regions of the default-mode network (DMN). *Methods.* Since activity in DMN regions has been associated with self-relatedness, we investigated neural activity in these regions during self-related emotional judgement and passive picture viewing in 25 patients with MDD and 25 healthy controls in an event-related fMRI design. *Results.* Behaviourally, MDD subjects showed significantly higher ratings of self-relatedness that also correlated with depression symptoms such as hopelessness. Neuroimaging results in MDD patients showed significantly lower negative BOLD responses (NBRs) in anterior medial cortical regions during judgement of self-relatedness while posterior medial regions showed increased NBRs. Unlike in healthy subjects, the anterior medial cortical NBRs were no longer parametrically modulated by the degree of self-relatedness in MDD patients. *Conclusions.* Our findings suggest that reduced NBRs in the anterior regions of the default-mode network may signify decoupling from self-relatedness in MDD patients with the consecutive abnormal increase of self-focus.

Key words: *Default-mode network, negative BOLD responses, major depression, self-related processing, event-related fMRI*

Introduction

Anterior and posterior medial cortical regions are part of the default-mode network (DMN) that is characterized by high activity in the resting state and negative blood oxygenation level-dependent (BOLD) (NBRs) during various emotional–cognitive tasks (Raichle et al. 2001; Raichle and Gusnard 2005; Fox et al. 2007; Raichle and Snyder, 2007; Buckner et al. 2008). Psychologically, high resting state activity in the DMN has been associated with various processes like mind wandering and random thoughts (Mason et al. 2007). Providing a unitary framework by tracing these various processes back to one common underlying process, high resting state neural activity in the DMN has been assumed to mirror self-related processing (Northoff et al. 2006). Self-related processing concerns the appraisal of stimuli strongly related to one's own person (Metzinger and Gallese 2003; Northoff and Bermpohl 2004). Self-relatedness of stimuli is usually assessed by a rating of the personal association based on the strength of the subjective or personal experience of subjects (Northoff et al. 2006; Schneider et al. 2008). Studies in healthy subjects showed overlapping neural activity in the ventromedial prefrontal cortex (VMPFC) during stimulus-induced and resting state activity (d'Argembeau et al. 2005; McKiernan et al. 2006) and modulation of medial cortical regions' resting state activity by the prior stimulus' degree of self-relatedness (Schneider et al. 2008). Anterior and posterior medial cortical regions are also recruited during stimulus-induced self-relatedness (Gusnard et al, 2001; Kelley et al. 2002; Phan et al. 2004; Ochsner et al. 2005; Moran et al. 2006;

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Schmitz and Johnson 2006; d'Argembeau et al. 2008) and self-referential processing of emotional stimuli (Yoshimura et al. 2009). Accordingly, these regions have anatomically been characterized as cortical midline structures (CMS) and psychologically by self-relatedness (Kelley et al. 2002; Northoff and Bermpohl 2004; Northoff et al. 2006). More specifically, high resting state activity in the CMS may be crucial in constituting our sense of self and consecutively in becoming aware of one's self (McKiernan et al. 2006).

Imaging studies in major depressive disorder (MDD) reported increased cerebral blood flow/glucose metabolism at rest in regions of the DMN including the sub/pregenual anterior cingulate cortex (PACC), the medial prefrontal cortex including ventro- and dorsomedial prefrontal cortex (VMPFC, DMPFC), and the posterior cingulate cortex (Mayberg et al. 1999;Videbech 2000; Mayberg 2002, 2003; Phillips et al. 2003; Greicius et al. 2007). In accordance with such increased resting state activity, significantly reduced negative BOLD responses (NBRs) during emotional stimulation in MDD patients were observed in both anterior (PACC, VMPFC) and posterior medial cortical (posterior cingulate cortex, PCC) regions (Frodl et al. 2009; Grimm et al. 2009). Self-referential processing in acute and remitted MDD patients is associated with abnormal activity of the medial prefrontal cortex (Lemogne et al. 2009, 2010). A recent study by Johnson et al. (2009) not only showed less deactivation in DMN regions during self-reflection, but also provided first evidence for a dissociation of anterior and posterior medial cortex in MDD depending on the focus of self-relevant thought. The psychological or more specifically psychopathological and clinical significance of increased resting state activity and reduced NBRs in anterior and posterior medial cortical regions remains unclear though.

Clinically, MDD patients can be characterized by strong ruminations, enhanced self-blame, abnormal coupling of the self with negative emotions, and increased attention to one's self (Treynor 2003; Grunebaum et al. 2005; Rimes and Watkins, 2005) which can be described as increased self-focus. Increased self-focus is characterized by heightened attention on internal perceptual events (Ingram et al. 1990; Pyszczynski et al. 1991) as well as enhanced self-reflection with a repetetive and passive focus on one's negative emotions (Mor and Winquist 2002; Treynor 2003; Northoff 2007).

Since the increased self-focus is characterized by increased attention and reflection upon one's self, one would assume close relationship of high resting state neural activity in CMS to the depressed patients' altered sense of self. Hence, increased resting state activity and reduced NBRs in MDD patients should be related to their increased self-focus. A recent study by Sheline et al. (2009) investigated the role of the DMN in MDD and observed stimulus-induced heightened activity during passive emotional picture viewing and a failure to normally down-regulate activity during the reappraisal of negative stimuli. It remains unclear though, whether the increased resting state activity in midline regions is related to self-relatedness. More specifically, the question is whether the reduced NBRs in MDD patients are related to their altered sense of self and thus their increased self-focus.

We therefore aimed to investigate whether self-related emotional judgement induces reduced NBRs in DMN regions of MDD patients and how these might be related to self-related processing. For that we applied a paradigm that tested for passive picture viewing and self-related emotional judgement. In a first step, we elucidated DMN regions by subtracting both viewing and judgment periods from resting state periods. These regions then served as functional localizers for further analyses where we, in a second step, compared differences in NBRs between healthy and MDD subjects during passive picture viewing and self-related emotional judgement. In a third step, we conducted parametric analyses by correlating the NBRs in these regions with the subjectively evaluated degree of self-relatedness (and other confounding variables like emotional intensity and valence).

Based on this methodological approach, we hypothesized first reduced NBRs during passive picture viewing and self-related emotional judgement in DMN regions in MDD and second a relationship of such reduced NBRs to patients' altered sense of self, i.e. their increased self-focus.

Materials and methods

Subjects

Subjects with an acute MDD episode (DSM-IV, American Psychiatric Association 1994) were recruited from the inpatient department of Psychiatry at the University of Zurich. Eligibility screening procedures included the 21-item Hamilton Depression Rating Scale (HDRS) (Hamilton 1960), the 21-item Beck Depression Inventory (BDI) (Beck 1961), the 20-item Beck Hopelessness Scale (BHS) (Beck 1974), that includes many items about one's self, and clinical laboratory tests. Diagnoses of depression were made by the participants' treating psychiatrists. Inclusion criteria were a score of at least 18 on the HDRS and the BDI. Exclusion criteria were major medical illnesses, histories of seizures, head trauma

with loss of consciousness, abnormal clinical laboratory tests and pregnancy. Additionally, patients who were actively suicidal, met criteria for any psychiatric disorder other than MDD, had a history of substance abuse or electroconvulsive therapy in the previous 6 months, or had a history of substance dependence were excluded from the study. Healthy subjects without any psychiatric, neurologic, or medical illness were self-referred from online study advertisements. The study was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the University of Zurichs' Institutional Review Board. All subjects gave written informed consent before screening. All subjects were right-handed as assessed with the Edingburgh Handedness Inventory (Oldfield et al. 1970). After applying the exclusion criteria above, fMRI scans from 27 depressed subjects and 25 healthy control subjects were processed. Of these scans, two could not be included in the analysis owing to structural abnormalities in the 3D T1-weighted anatomical scan (two depressed subjects). This resulted in usable fMRI data on 25 subjects with depression and 25 healthy control subjects.

Pictorial stimuli

Subjects viewed full-color pictures selected from the International Affective Picture System (IAPS) (Lang et al. 1999) with positive (IAPS norm ratings: 7.32 ± 2.06) and negative (IAPS norm ratings: 2.24 ± 2.67) valence. The picture sets were counterbalanced across all subjects as well as within each subject according to the two categories of valence as well as according to dominance, intensity, human faces and human figures. We used IAPS stimuli that were successfully applied in previous studies (Grimm et al. 2006, 2008) and also validated with regard to self-relatedness in healthy subjects (Northoff and Panksepp 2008; Schneider et al. 2008). The pictures were generated by Presentation® (Neurobehavioral Systems, Inc., Albany, CA, USA) and rear projected onto a projection screen positioned at the head end of the MRI scanner bore. Subjects viewed the screen through a mirror mounted on the head coil and responded by pushing a fiber-optic light sensitive keypress.

Experimental design

The fMRI design was "event related" with positive and negative stimuli alternating with a fixation control condition. The IAPS pictures were presented for 4 seconds. A total of 150 pictures was presented twice: once for passive picture viewing and once for self-related emotional judgement. During the viewing condition, subjects had to passively view the picture ("Passive Viewing": "PV") which was indicated by the letter "E" in one corner of the picture. Subjects had to arbitrarily press a button when a picture was presented. In case of the judgment condition, subjects had to judge the pictures with regard to their self-relatedness ("Self-Related Judgment": "SRJ"); this was indicated by the letter "B" in one corner of the picture. Pictures had to be judged as either self-related or not (yes–no option). Responses and reaction times were recorded. After the presentation of each picture, a resting period followed, where a fixation cross was presented for 6–8 s (6.0, 6.5, 7.0, 7.5, 8.0 s). This allowed the subjects to recover from the active tasks and, in addition, served as a baseline condition in order to distinguish between positive and negative BOLD responses (Stark and Squire 2001). The two different task conditions were pseudorandomized within and across six runs and their order counterbalanced across all subjects. Immediately after the fMRI session pictures were presented for a second time. Each of the 160 pictures (including 10 new ones for distraction) was followed by a task period which consisted of a concern rating (subjects had to rate whether they felt affected by the picture), dominance rating, intensity rating, valence rating and self-relatedness rating. All responses were given using a scale ranging from 1 to 9. The 10 new emotional pictures were matched in valence, intensity and dominance with those presented in the scanner. The mean of each of the five ratings was calculated for each subject. Analysis of postscanning ratings was conducted separately for positive and negative pictures. Postscanning ratings were conducted with 16 healthy controls and 15 depressed subjects, since some of the subjects did not consent to this investigation after the fMRI-scan.

Functional imaging

Measurements were performed on a Philips Intera 3T whole-body MR unit equipped with an eight-channel Philips SENSE head coil. Functional time series were acquired with a sensitivity encoded (Pruessmann et al. 1999) single-shot echo-planar sequence (SENSE-sshEPI). The following acquisition parameters were used in the fMRI protocol: TE (echo time) = 35 ms, FOV (field of view) = 22 cm, acquisition matrix = 80×80, interpolated to 128×128, voxel size: $2.75 \times 2.75 \times 4$ mm^3, SENSE acceleration factor $R = 2.0$. Using a midsaggital scout image, 32 contiguous axial slices were placed along the anterior–posterior commissure (AC–PC) plane covering the entire brain with a TR = 3000 ms ($\theta = 82°$). The first three acquisitions were discarded due to T1 saturation effects.

Statistical analysis

Behavioural data. Reaction times and judgments (self-relatedness rating) were analysed in a multivariate ANOVA with the factors group (healthy subjects/MDD patients), valence (positive/negative pictures) and task (PV/SRJ). Postscanning ratings of concern, dominance, valence, intensity, and self-relatedness were analysed in a group × valence ANOVA. We performed multivariate ANOVAS where we included the different substance-classes of psychotropic medication (SSRIs, tricyclica, benzodiazepines, etc.) as well as age as covariates while the dosage of the medication was not considered in the analysis. The association between the altered sense of self-relatedness and psychopathological parameters was analyzed by correlating the individual scores of postscanning self-relatedness ratings with the individual scores of the BHS using Spearman correlation analysis.

FMRI data. FMRI data were analyzed using MATLAB 6.5.1 (The Mathworks Inc., Natick, MA, USA) and SPM2 (Statistical parametric mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). Functional data were corrected for differences in slice acquisition time, realigned to the first volume, corrected for motion artifacts, mean-adjusted by proportional scaling, normalized into standard stereotactic space (template provided by the Montreal Neurological Institute), and spatially smoothed using an 8-mm FWHM Gaussian kernel. The time series were high-pass filtered to eliminate low-frequency components (filter width 128 s) and adjusted for systematic differences across trials. Statistical analysis was performed by modeling the different conditions (passive viewing (PV), judgment of self-relatedness (SRJ), and fixation cross (rest)) convolved with a haemodynamic response function (HRF) as explanatory variables within the context of the general linear model on a voxel-by-voxel basis. Realignment parameters were included as additional regressors in the statistical model. A fixed-effect model at a single-subject level was performed to create images of parameter estimates, which were then entered into a second-level random effects analysis. To to get an overview over all regions showing NBRs, the contrast images of all subjects of each group (depressed subjects and control subjects) were included in a one-sample *t*-test (threshold $P < 0.001$, uncorrected and at least 10 active voxels). FMRI analysis focused on the comparison of passive viewing and judgment of self-relatedness with the resting condition (fixation cross). Then ROI analyses were performed to further investigate NBRs and to correlate them with self-relatedness and psychopathological parameters. We did not attend to differences between positive and negative emotional stimuli, since the main focus of our study was on the investigation of NBRs as induced by the judgment of self-related stimuli and not on the distinction between the processing of positive and negative stimuli. No subject had to be excluded due to susceptibility artifacts or significant signal dropout. Age and psychotropic medication were included as covariates in the analyses. For the ROI analyses of peak voxels, coordinates which were obtained in the analysis of the entire sample (Table I) were selected. Regions of interest were functionally defined by centering spheres on the respective peak voxels with a radius of 3 mm. Analyses were carried out for the DMPFC (–22, 30, 40), PACC (–2, 34, –2), precuneus (–8, –66, 22), and VMPFC (4, 48, –4). For the ROI analyses, percent signal changes for the different conditions were extracted for each subject separately using Marsbar (http://marsbar.sourceforge.net/). To detect the association of signal changes in response to self-related judgment with psychopathological parameters and postscanning ratings, the correlation between the individual scores of the BHS, the individual scores of postscanning ratings and signal changes in the regions of interest was analyzed in a post-hoc, region-of-interest analysis using Marsbar (see above). Subjects' individual scores were correlated with signal changes during rest > judgement of self relatedness using using Pearson correlation analysis.

Results

Subjects

Groups did not differ significantly in age (controls: 32.4 years; MDD: 37.0 years; *t*-test $P = 0.09$) or in gender distribution (controls: 12 women, 13 men; MDD: 9 women, 16 men; χ^2 $P = 0.39$). The mean HDRS score was 26.8 (SD 7.1), the mean BDI score 26.6 (SD 9.1) and the mean BHS score 31.08 (SD 5.2) in the depressed group, indicating that patients were severely depressed and showed self-abnormalities with increased attribution of negative emotions to ones' self as hallmark of an increased self-focus. The mean duration of the current episode was 8.1 weeks (SD 8.4), the number of previous depressive episodes 2.2 (SD 1.5), and the duration of the depressive disease 3.6 years (SD 3.9). Regarding exposure to psychotropic medications, two of the 25 depressed subjects were not taking any when investigated. Twenty-three depressed subjects were taking one or more medications from the following classes: antidepressants (19 subjects; SSRIs/SNRIs: 15 subjects (escitalopram 10–20 mg, venlafaxine 150–300 mg,

Table I. Signal changes in healthy and depressed subjects during the resting condition when compared to all other conditions, Passive Viewing and Self-related Judgment.

Region	Side	Rest > All pictures	Rest > Passive Viewing	Rest > Self-related Judgment
DMPFC	L	–22, 30, 40 3.88	–20, 34, 48 3.50	–24, 30, 42 4.24
PACC	L/R	–2, 34, –2 4.94	2, 34, 6 5.27	0, 36, 0 4.14
VMPFC	R	4, 48, –4 5.04	2, 52, 2 5.44	4, 50, –4 4.48
Precuneus	L	–8, –66, 22 3.83	–6, –66, 24 4.07	
Superior temporal gyrus	R	68, –22, –4, 5.57	68, –22, –4, 4.82	68, –24, –2, 6.19
Superior temporal gyrus	L	–54, –32, 0 4.05	–64, –28, –4 5.31	–56, –30, 0 4.00
Caudate nucleus	R	22, 22, 18 5.30	22, 20, 18 5.17	20, 18, 20 5.08
Caudate nucleus	L	–20, 20, 18 5.71	–20, 18, 18 5.54	–20, 20, 18 5.56
Parietal cortex	R	58, –60, 34 6.07	56, –60, 36 6.14	60, –58, 32 5.92
Parietal cortex	L	–56, –64, 32 5.53	–56, –64, 32 6.18	–56, –64, 32 4.39

All Pictures (comprised of Passive viewing and Self-related judgement); Rest, resting condition (fixation cross); DMPFC, dorsomedial prefrontal cortex; PACC, pregenual anterior cingulate cortex; VMPFC, ventromedial prefrontal cortex. The global height threshold for within-group comparisons (Healthy and MDD pooled in one group) was set to $P < 0.001$ uncorrected, the extent threshold to $k = 10$ voxels for all contrasts. The values in the table represent maximum z values with peak voxel coordinates in the MNI stereotactic space.

duloxetine 60–90 mg); TCAs: five subjects (amitryptiline 75–250 mg, clomipramine 75–250 mg)), antipsychotics (five subjects), anxiolytics (six subjects) and mood stabilizers (lithium: three subjects). None of the control subjects were taking any psychotropic medications at the time of the investigation.

Behavioural data

Intrascanner ratings (reaction times and self-related judgments). There was a significant effect of group ($F(1) = 216.61$, $P < 0.001$), task ($F(1) = 2419.21$, $P < 0.001$), and valence ($F(1) = 29.07$, $P < 0.001$) on reaction times, while there were no interactions between these factors. Post hoc *t*-tests demonstrated faster reaction times in healthy subjects in PV ($t = –12.52$, $P < 0.001$) as well as in SRJ ($t = –8.05$, $P < 0.001$). Reaction times in both groups were faster in positive pictures ($t = 4.57$, $P < 0.001$) and PV ($t = –48.99$, $P < 0.001$). Concerning the self-related judgments there was a significant group effect ($F(1) = 120.62$, $P < 0.001$) and valence effect ($F(1) = 20.21$, $P < 0.001$), but again no interaction effects. Differences in intrascanning self-related judgement between groups concerned positive ($t = 7.67$, $P < 0.001$) as well as negative pictures ($t = 8.75$, $P < 0.001$), which both were rated significantly more self-related by the MDD patients. There was a significant correlation between self-related judgement for negative pictures and the score of the BHS ($r = 0.85$, $P < 0.05$). Inclusion of age and psychotropic medication as co-variates did not have any influence on the results from group comparisons. The results are indicative of a consistent psychomotor impairment and show an increased tendency to relate emotional stimuli to the own self in patients with MDD thus supporting the assumption of an increased self-attribution as hallmark of an increased self-focus.

Postscanning ratings. There was a significant effect of participant group (Healthy, MDD) on ratings of intensity ($F(1) = 20.52$, $P < 0.001$). Picture valence (positive, negative) had a significant effect on ratings of concern ($F(1) = 173.45$, $P < 0.001$), valence $F(1) = 4776{,}14$, $P < 0.001$), intensity $F(1) = 99.78$, $P < 0.001$) and self-relatedness ($F(1) = 602.39$, $P < 0.001$). There was a significant interaction effect between the factors group and picture valence for intensity $F(1) = 7.89$, $P < 0.005$) and self-relatedness ($F(1) = 10.41$, $P < 0.001$). Post hoc *t*-tests demonstrated, that negative pictures were rated significantly more intense ($t = -5.37$, $P < 0.001$) and self-related ($t = -3.63$, $P < 0.001$) by the depressive patients, while there were no differences between groups for ratings of intensity and self-relatedness of positive pictures. In healthy subjects we found a correlation between valence ratings

and self-relatedness ratings for positive ($r = 0.57$, $p < 0.05$) but not for negative pictures. In MDD patients the opposite pattern was observed: a correlation between valence ratings and self-relatedness ratings for negative ($r = 0.63$, $p < 0.05$) but not for positive pictures (Figure 1). Inclusion of age and psychotropic medication as co-variates did not have any influence on the results from group comparisons. Results support the assumption of an increased self-attribution specifically with regard to negative emotions in MDD.

FMRI data

Signal intensities in default-mode network. In order to reveal DMN regions, we pooled both healthy and depressed subjects and searched for all signal intensities that were larger during fixation cross when compared to all other conditions (resting condition > all pictures as comprised of resting condition > passive viewing and resting condition > judgment of self-relatedness). This yielded signal intensities in the dorsomedial prefrontal cortex (DMPFC), the pregenual anterior cingulate cortex (PACC), the VMPFC, the precuneus, the bilateral superior temporal gyrus (STG), the bilatateral parietal cortex, and the bilateral caudate nucleus (see Table I). Using regions of the default-mode network as functional localizers, we then compared regional signal intensities between healthy and depressed subjects in anterior and posterior DMN regions. MDD subjects showed significantly lower negative BOLD responses (NBRs) in DMPFC, PACC, and VMPFC during both passive viewing and judgment of self-relatedness (Figure 2). The precuneus showed significantly higher NBRs in MDD during both conditions, but much more pronounced during judgment of self-relatedness (Figure 2). Taken together, our data indicate abnormal NBRs in various regions of the default-mode network in MDD with anterior medial

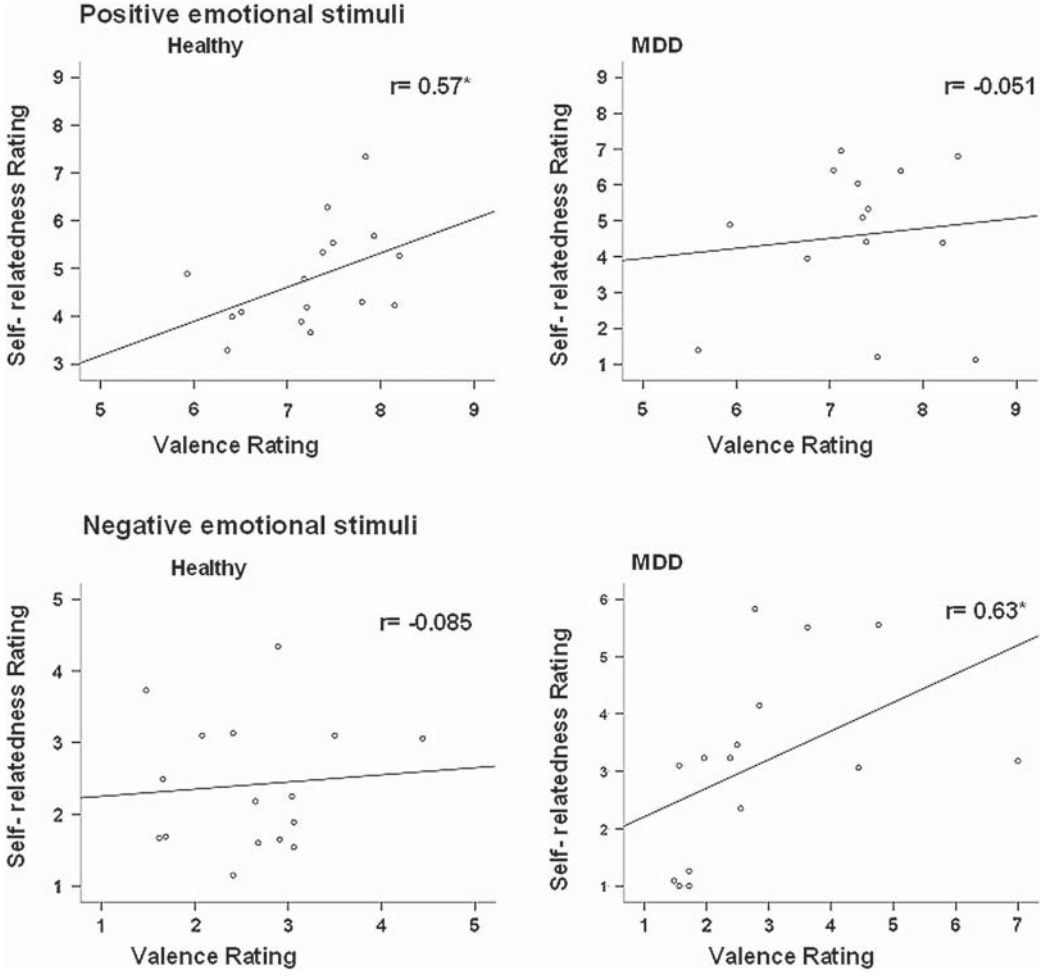

Figure 1. Correlation between valence ratings and self-relatedness ratings in healthy and depressed subjects. Correlation between valence ratings and self-relatedness ratings for positive and negative emotional pictures. While in healthy subjects there was a correlation between valence and self-relatedness ratings for postive, but not for negative emotional pictures, there was an opposite pattern in MDD (*$P < 0.05$). MDD, major depressive disorder.

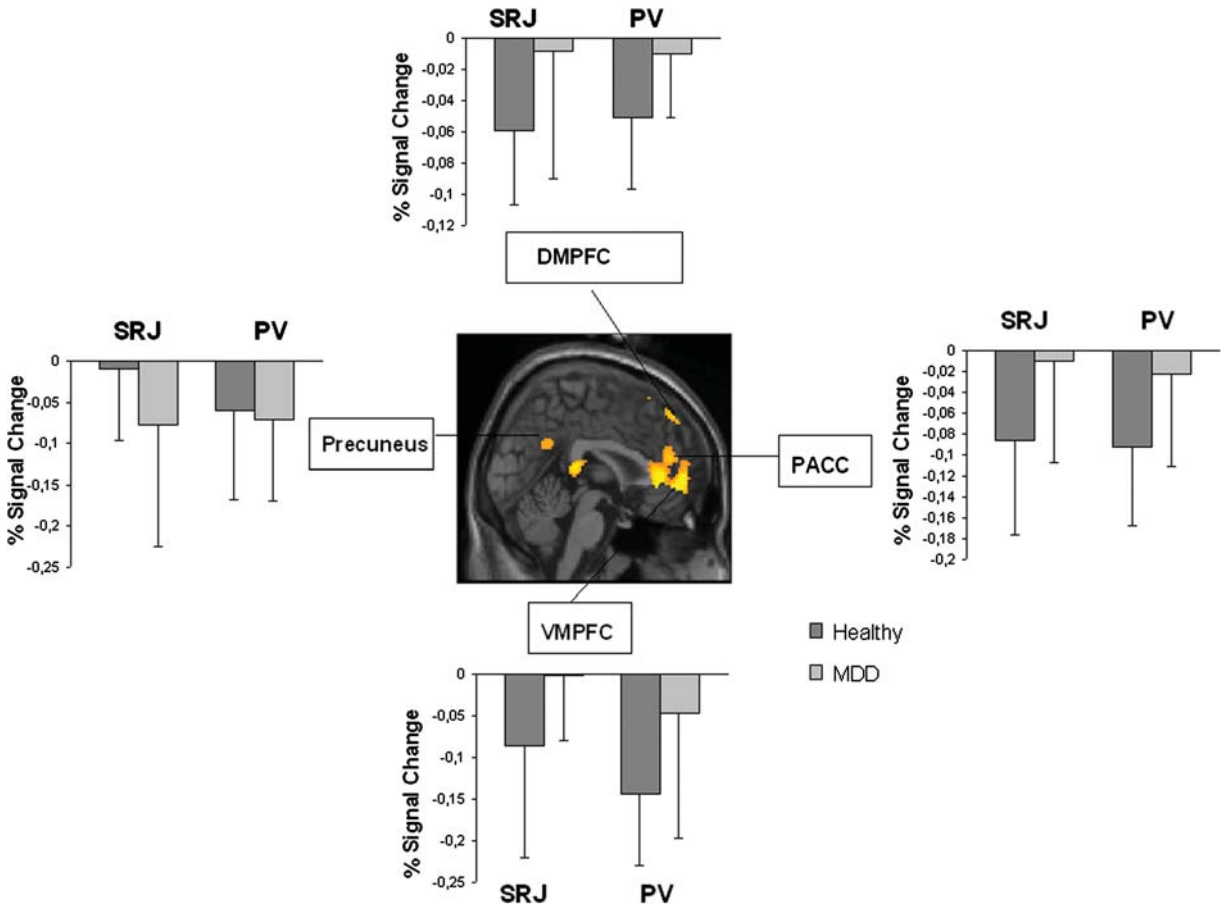

Figure 2. Signal changes in regions of the default-mode network during Self-related judgment and Passive viewing. The SPM image shows the statistical parametric (T) map for the contrast resting condition > all pictures (rest > all pictures) for all subjects (healthy and MDD), overlaid on a single subject's normalized brain in the MNI stereotactic space ($P < 0.001$; uncorrected; $k > 10$). The saggital view represents the left hemisphere. Bar diagrams show % signal changes in Self-related Judgment (SRJ) and Passive Viewing (PV) in healthy controls and MDD patients. Bar diagrams represent the % signal changes in DMPFC (–22, 30, 40), PACC (–2, 34, –2), VMPFC (4, 48, –4), and Precuneus (–8, –66, 22) for healthy controls and MDD. SRJ, Self-related Judgment; PV, Passive Viewing; DMPFC, dorsomedial prefrontal cortex; PACC, pregenual anterior cingulate cortex; VMPFC, ventromedial prefrontal cortex; MDD, major depressive disorder.

regions showing decreased NBRs and posterior medial regions showing increased NBRs.

Parametric modulation of default-mode network signal intensities by self-relatedness. To link the NBRs in the default-mode network to self-related judgment, subjective postscanning ratings of self-related judgment were correlated with signal intensities in the contrast rest > SRJ. Healthy subjects showed a significant correlation of signal intensities in the DMPFC (Figure 3): Stronger NBRs in the DMPFC ($r = 0.50$) were accompanied by lower ratings of self-relatedness. MDD patients showed no significant correlation of signal intensities, i.e. NBRs, in the DMPFC. In fact, the direction of correlation tended to be reversed. Hence, reduced NBRs during judgement of self-relatedness were no longer parametrically modulated by the degree of self-relatedness in MDD. Neither for healthy nor for MDD patients did we find a correlation between signal intensities in DMN regions with subjective postscanning ratings of valence, intensity or concern for positive or negative pictures.

Discussion

This study investigated neural activity in the DMN during different emotional tasks in healthy subjects and patients with MDD in an event-related fMRI design. For passive picture viewing and self-related judgement of emotional stimuli (PV and SRJ), significant negative BOLD responses were found in the DMPFC, PACC, VMPFC, and precuneus in both groups. NBRs in various anterior medial cortical regions (PACC, DMPFC, VMPFC) were significantly reduced in MDD patients. Posterior medial cortical regions (precuneus) showed increased NBRs in MDD. NBRs in the DMPFC correlated with ratings of self-relatedness in healthy subjects, whereas this relationship was not found in MDD patients.

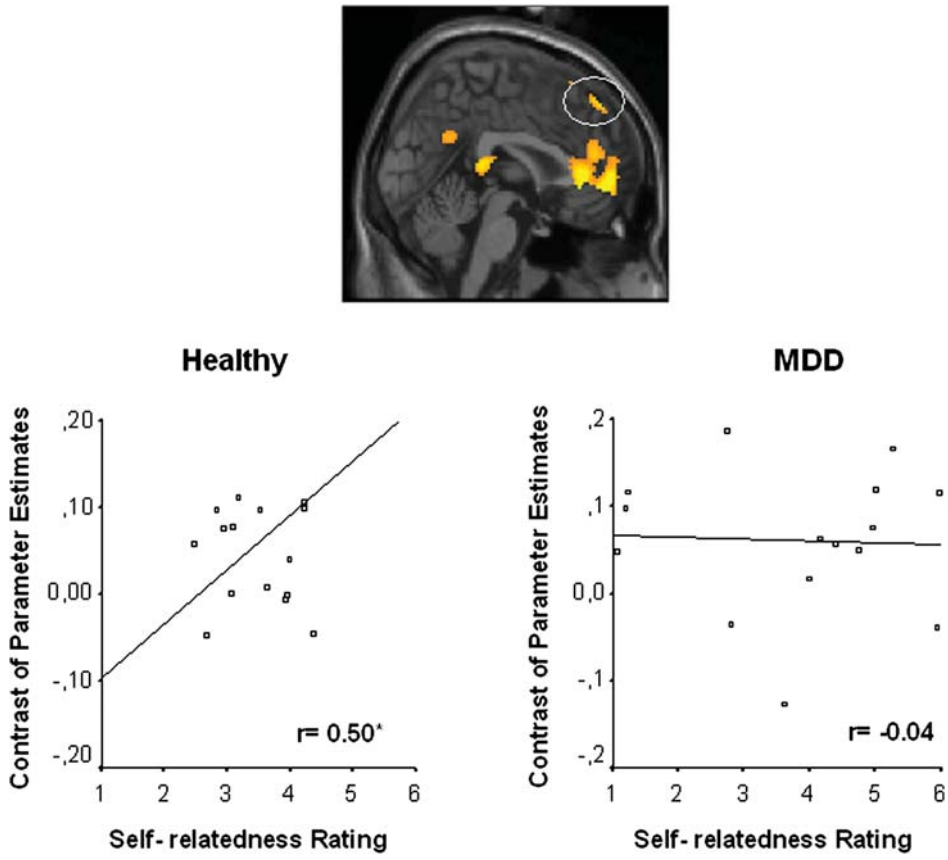

Figure 3. Parametric modulation of default-mode network signal intensities by self-relatedness. The SPM image shows the statistical parametric (T) map for the contrast resting condition > all pictures (rest > all pictures) for all subjects (healthy and MDD), overlaid on a single subject's normalized brain in the MNI stereotactic space ($P < 0.001$; uncorrected; $k > 10$). The saggital view represents the left hemisphere. The scatter plots show correlation between post-scanning ratings of self-relatedness and single-subject contrasts of parameter estimates for the contrast resting condition > Self-related Judgment (rest > SRJ) in the DMPFC (–4, 42, 50) for both healthy and depressed subjects ($^*P < 0.05$). DMPFC, Dorsomedial prefrontal cortex; MDD, major depressive disorder.

Behaviorally, MDD patients showed significantly higher degrees of self-relatedness when compared to the ratings of healthy subjects; this and the correlation between increased self-relatedness of negative stimuli and depressive symptoms such as hopelessness are well in accordance with clinical observations of an increased self-focus. Taken together, our findings demonstrate that altered NBRS in DMN regions in MDD may be related to the patients abnormally increased self-focus.

Clinically, MDD patients suffer from an altered sense of self including ruminations, self-blame, abnormal coupling of the self to negative emotions, and enhanced attention to the own self (Grunebaum et al. 2005) which we subsumed under the concept of increased self-focus (Northoff 2007). We were here able to confirm the increased self-focus on a behavioural level, since acute MDD patients showed significantly higher ratings of self-relatedness when compared to healthy subjects. Increased self-relatedness of negative stimuli also correlated with depressive symptoms such as hopelessness as measured with the BHS. Also, we were able to establish a direct relationship between NBRs and the degree of self-relatedness. Previous studies in healthy subjects (Schneider et al. 2008) suggest that high resting state neural activity in anterior and posterior cortical midline structures may specifically be related to self-relatedness as supposedly underlying diverse processes like mind-wandering, random thoughts, anticipation, and episodic memory retrieval that have been associated with the DMN (Mason et al. 2007; Raichle and Snyder 2007). If this holds true, one would expect the increased resting state activity in MDD to be associated with their increased self-focus. This is exactly what our findings of altered NBRs in CMS during self-related judgement and absent parametric modulation of signal changes by self-relatedness in MDD patients suggest.

We observed significantly reduced NBRs in anterior medial cortical regions during passive picture viewing and self-related judgement in MDD patients when compared to healthy subjects. This replicates earlier findings of ours of reduced NBRs

in these regions (Grimm et al. 2008). Taken together with previous resting state studies (Videbech 2000; Greicius et al. 2007), our finding further supports the assumption of abnormally high resting state activity in anterior medial cortical regions in MDD. Extending these findings, we here demonstrate that reduced NBRs are related abnormal self-related processes in MDD. Healthy subjects showed parametric modulation of signal changes in the DMPFC by the degree of self-relatedness, which was absent in MDD. One may consequently speculate whether such decoupling of self-relatedness from this region's neural activity may contribute to patients' increased self-focus. Due to such dissociation, MDD patients may no longer be able to down-modulate their high resting state and consecutively their abnormally high degree of self-relatedness in a fine-grained way so that they remain, metaphorically spoken, stuck in their own self. This interpretation, though preliminary and speculatively at this point, is well in accordance with the clinical observation that MDD patients remain unable to shift their focus from their own self back to the environment with consecutive withdrawal from others and the social environment.

In addition to reduced NBRs in anterior medial cortical regions, MDD patients also showed some alterations in posterior medial cortical regions, specifically the precuneus. Unlike anterior regions, the precuneus showed significantly increased NBRs during self-related judgement in MDD patients. Such dissociation indicates that the functional balance between anterior and posterior medial cortical regions may be altered in MDD. While anterior medial regions have been associated with anticipation of the future, posterior regions like the precuneus are crucial in retrieving past memories (Schacter et al. 2008). The here observed dysbalance between anterior and posterior medial regions with regard to NBRs during self-related judgment may indicate a shift in the functional balance between anticipation and retrieval and thus between future and past. Clinically, depressed patients show deficits in anticipating the future, as also tested for by the Beck Hopelessness scale, while at the same time suffering from increased retrieving and ruminating about past events (Northoff 2007). Though our finding of anterior-posterior medial cortical dysbalance in NBRs suggests functional dysbalance between anticipation and retrieval, this hypothesis remains rather speculative at this point awaiting further confirmation from studies linking anterior-posterior connectivity analysis to anticipation and retrieval. Since a previous study of ours in unmedicated MDD patients (Grimm et al. 2009) showed decreased NBRs in posterior medial regions, another conceivable explanation for the here reported increased NBRs might be a medication effect. Only two subjects of the investigated depressed sample were not taking any medication, which surely has to be considered a limitation of our study. Though we performed various analyses to account for possible medication effects, these cannot be excluded fully. It should however be mentioned that the results of reduced NBRs in anterior DMN regions in the present medicated MDD sample are consistent with those in an unmedicated sample (Grimm et al. 2009). However, investigation of NBRs in DMN regions and their relation to self-relatedness need to be conducted in unmedicated and at best in naïve MDD patients in the future.

Several further limitations need to be mentioned. One may argue that the judgement of self-relatedness of emotional stimuli did not concern self-relatedness but rather judgment of emotions. We instructed our subjects to focus on self-relatedness rather than the emotions depicted on the stimuli. This however does not rule out the emotional confound. One hint that our instruction was somehow successful can be seen in the finding that signal changes in medial cortical regions were parametrically modulated by the degree of self-relatedness, but neither by valence nor by concern, dominance or intensity in healthy subjects. It is clear though that future studies need to be conducted that directly compare both instructions, self-relatedness and emotion, with each other. This may then also shed further light on the interaction between self-relatedness and emotion (Moran et al. 2006; Northoff and Panksepp 2008) that as such was not the focus of the present study which was also the reason for not including neutral pictures as emotional control condition. One might also consider the difference in task difficulty a limitation of the study. While both passive picture viewing and self-related emotional judgement were associated with a button-press, only the judgement condition required a cognitive effort. This difference in task difficulty applies to both groups, though, and is therefore cancelled out when comparing healthy and MDD subjects. A final issue may concern our resting state period. We here presented a fixation cross that required subjects to keep their eyes open. One may argue that the duration of the fixation cross is not long enough to be considered a true resting state period, which might have to take 5 min or more for both psychological and methodological reasons (Greicius et al. 2007).

In conclusion, we here demonstrate evidence that altered NBRs in the default-mode network in acute MDD may be related to patients' increased self-focus. More specifically, we observed reduced NBRs in anterior medial cortical regions and increased NBRs in posterior medial cortical regions in MDD when compared to healthy subjects. These abnormal

NBRs no longer parametrically modulated the self-relatedness in MDD patients so that their increased degree of self-relatedness was decoupled from modulating resting state activity in anterior and posterior medial regions. Taken together, these findings suggest that the reduced NBRs in DMN regions of MDD patients might be associated with increased resting state neural activity and increased self-focus.

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Statement of Interest

None to declare.

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