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Abnormal body perception and neural activity in the insula in depression: An fMRI study of the depressed "material me"

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Abstract

Objectives. In addition to affective-cognitive symptoms, patients with major depressive disorder (MDD) suffer from somato-vegetative symptoms, suggesting abnormal interoceptive awareness of their "material me". While recent imaging studies have extensively investigated affective-cognitive symptoms in MDD, the neural correlates of somato-vegetative symptoms and abnormal interoception remain unclear. Since the "material me" has been especially associated with the anterior insula in healthy subjects, we hypothesized abnormalities in this region during interoceptive awareness in MDD. *Methods.* We therefore investigated behavioural and neural correlates of interoception in healthy and depressed subjects using the Body Perception Questionnaire (BPQ) and a well established heartbeat perception task in fMRI. *Results.* MDD patients showed significantly higher scores in the BPQ and reduced neural activity during rest periods, particularly in the bilateral anterior insula. In contrast to healthy subjects, BPQ scores no longer correlated with activity during rest periods in the anterior insula. Both BPQ scores and left anterior insula signal changes correlated with depression severity. *Conclusions.* We demonstrate for the first time abnormal body perception and altered activity in the insula during rest in MDD. Our results suggest that these behavioural and neural abnormalities are closely related to these patients' somato-vegetative abnormalities and their abnormal "material me".

Key words: *Major depressive disorder, functional magnetic resonance imaging, awareness, insular cortex, self concept, mind-body relations*

Introduction

Patients with major depressive disorder (MDD) can be characterized by abnormalities in both mental and physical aspects of their self (Northoff 2007). Abnormalities in the mental self include abnormal emotions and cognitions like ruminations, self-blame, and increased association of their self with negative emotions (Ingram 1990; Treynor 2003; Rimes and Watkins 2005; Frodl et al. 2007; Northoff 2007); whilst alterations in the physical self are reflected in various persisting somato-vegetative symptoms, along with an apparent hyperawareness of bodily changes (Beck et al. 1961; Garcia-Cebrian et al. 2006; Nyboe Jacobsen et al. 2006). Patients with

MDD can thus be described as suffering from major abnormalities in their "material me".

Recent imaging studies of MDD have indicated an association of the mental aspects of the self – i.e., its emotional and cognitive abnormalities – with altered neural activity in the medial cortical regions, particularly the dorsomedial prefrontal cortex (Northoff 2007; Grimm et al. 2009a). In contrast, the neural correlates of the abnormal physical aspects of the self in MDD remain to be explored.

The physical aspect of our self (Panksepp 1998; Damasio 1999; Gillihan and Farah 2005; Northoff et al. 2006, for the distinction between mental and physical aspects of the self) has been conceptualized

as our "bodily or proto-self" (Panksepp 1998; Craig 2002, 2003, 2004). Craig (Craig 2002, 2003, 2004) characterizes the "bodily or proto-self" as perception and awareness of one's body, with him describing this interoceptive awareness as the "material me". Consistent with the basics of the James-Lange theory of emotion and Damasio's somatic marker hypothesis, he describes the representation of the interoceptive body in the anterior insula as essential for subjective feelings from the body and for emotional awareness. This "material me" is thought to be predominantly mediated by neural activity in the right anterior insula (Craig 2002, 2003, 2004, 2009). This has recently been further supported by imaging studies that have identified the anterior insula as a key region in interoceptive awareness (Critchley et al. 2004, 2005; Pollatos et al. 2007).

The neural correlates of abnormal somato-vegetative symptoms and interoceptive awareness in MDD remain unclear however. Early PET, and more recent MRI studies, do show alterations to the insula in MDD, but these studies have been concerned only with the resting state or exteroceptive perception (Mayberg 2002; Mayberg 2003; Fitzgerald et al. 2008). Emotional-cognitive stimulation has also been seen to induce abnormal neural activity in the insula in MDD (Mayberg 2002; Mayberg 2003; Phillips et al. 2003a,b; Keedwell et al. 2005; Paulus and Stein 2006; Fitzgerald et al. 2008). In contrast, studies targeting the insula specifically during interoceptive awareness, as distinguished from resting periods, exteroceptive awareness and affective components (as they are present in, for instance, pain perception; Bar et al. 2007; Strigo et al. 2008a,b) remain to be reported.

The aim of our study was to investigate the changes in neural activity in the insula during interoceptive awareness and their relation to abnormal body perception in MDD. Since previous findings demonstrated neural abnormalities in the insula during resting periods and exteroceptive, i.e. emotional-cognitive, stimulation (see above), we also investigated signal changes in the insula during both rest periods and exteroceptive stimulation. Our main focus was thus not on the activity of the rest period itself, but on the modulation of interoception and exteroception by the rest period. Based on the above mentioned findings, we hypothesized abnormal neural activity in specifically the anterior insula in MDD, as well as abnormal body perception, as measured by the Body Perception Questionnaire (BPQ; Porges 1993). To induce neural processing of interoceptive awareness, we applied a modified and well established heartbeat perception task and compared it with activity during rest periods and tone perception mirroring exteroceptive awareness (Critchley et al. 2004; Pollatos et al. 2007).

Methods

Depressed subjects and healthy controls

We studied 22 psychiatric in-patients suffering from major depressive disorder (MDD), diagnosed according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders (4th edition); American Psychiatric Association 1994), using functional magnetic resonance imaging (fMRI). Patients with MDD were recruited in an acute state from either the Department of Psychiatry at the University of Magdeburg or from the state hospital of Uchtspringe. Eligibility screening procedures included the 21-item Beck Depression Inventory (BDI; Beck et al. 1961) and the 20-item Beck Hopelessness Scale (BHS; Beck et al. 1974). Diagnoses of depression were made by the participants' treating psychiatrists. Inclusion criteria were a score of at least 16 on the BDI, while exclusion criteria were major medical illnesses, histories of seizures, metallic implants, a history of substance dependence, head trauma with loss of consciousness, pregnancy and criteria for any psychiatric disorder other than MDD.

The data for one depressed subject was excluded from the analysis due to structural abnormalities identified in their anatomical scan. A further four depressed subjects were excluded due to motion artefacts. Usable fMRI data was thus available for a total of 17 depressed subjects. Behavioural test results were not available for two depressed subjects.

The group of depressed subjects (11 female and six male subjects, all right-handed) revealed a mean age of 41.88 ($\pm$ 12.1 SD) and mean educational years of 15.44 ($\pm$ 2.84 SD). Mean scores for verbal intelligence (MWT-B; Lehrl 1995) were 111.35 ($\pm$ 9.86 SD) and for nonverbal intelligence (LPS-3; Horn 1983) 108.77 ($\pm$ 13.56 SD). The mean BHS score was 32.13 ($\pm$ 4.45 SD), the mean BDI score 29.93 ($\pm$ 8.56 SD), and the mean score for the clinician rated Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg 1979) was 26.07 ($\pm$ 8.48 SD), indicating that patients were moderately depressed. Seventeen depressed subjects were taking one or more antidepressants from the following pharmacological classes: six subjects SSRIs, five subjects NaSSAs, 10 subjects NARIs/MAOI/others. None of the control subjects were taking any psychotropic medications at the time of the investigation.

Our healthy control group consisted of 17 subjects (11 female and six male subjects, all right-handed) with no psychiatric, neurological, or medical illness. They had a mean age of 37.59 ($\pm$ 12.84 SD) and mean educational years of 15.44 ($\pm$ 2.71 SD). Their mean score for verbal intelligence was 117.47 ($\pm$ 14.28 SD) and for nonverbal intelligence 117.56 ($\pm$ 16.93 SD). The healthy group was thus

well-matched to the patient group for group size, sex, age, years of education, and verbal and general intelligence. Groups did not differ significantly in gender distribution, age, verbal/ nonverbal intelligence or years of education.

The study was approved by the local ethics committee and all participants gave written informed consent before participating in this study.

Paradigm

The event related fMRI design was based on a paradigm introduced by Pollatos and Critchley (Critchley et al. 2004; Pollatos et al. 2007) which involves subjects counting intero- and exteroceptive stimuli in the form of heartbeats and tones. The paradigm was altered from the form originally described by Pollatos and Critchley in order to make it more suitable for use with a depressed population. A number of conditions were excluded (specifically, the presence or absence of a feedback delay, and a modulated tone) in order to make the paradigm less complicated and to reduce the time that patients spent in the scanner. Subjects were thus presented with three separate experimental conditions – an interoceptive task, an exteroceptive task, and rest periods – in a pseudo-randomised order.

During the interoceptive conditions, subjects were asked to silently count their own heartbeat for as long as the task-type indicator (a dark coloured heart on a light background) was displayed (9–13 s). After each interoceptive task presentation subjects were asked to report the number of heartbeats counted via a simple visual analogue scale (4 s). The indicator on the scale was moved by the subject to the labelled position representing the number of beats that they counted (left and right button presses corresponding to left and right on the scale). This feedback component allowed subject's attendance to the task to be monitored.

Exteroceptive conditions were indicated by a dark coloured musical note symbol on a light background (9–13 s). During such tasks subjects had to silently count the number of tones heard during the period that the task-type indicator was visible. Two different tones were presented, alternating with each of the fours scanning runs, each with a duration of 200 ms; a length that is comparable to the average duration of the sound of a heartbeat. In order to make the difficulty of both the intero- and exteroceptive tasks closely comparable, tones were presented at an individually determined volume that meant they were, like the heartbeat, just audible. The general presentation frequency of the tones was adapted to correspond to each subject's pulse-rate, with the individual onset time of the tones being jittered by 200 ms from this general frequency in order to control for habituation effects. As with the interoceptive task, subjects were asked to report after each exteroceptive trial the number of tones heard via a visual analogue scale (4 s).

Rest conditions were indicated by a dark cross on light background (9–13 s). Subjects were instructed to relax and reduce any cognitive work during these periods.

The total experiment consisted of 4 runs of 9.6 min (290 volumes), with each condition being presented 48 times in total. The paradigm was executed on an ordinary desktop personal computer running the software package "Presentation" (Neurobehavioral Systems, http://www.neurobs.com). Visual stimuli were projected via an LCD projector onto a screen visible through a mirror mounted on the headcoil. Auditory stimuli were presented via the scanner loudspeaker.

Behavioural tests

To assess body perception, we applied after fMRI measurement the Body Perception Questionnaire (BPQ; Porges 1993), which includes several factors: The awareness subscale (A) of the BPQ includes 45 items. Subjects should imagine how aware they are of their body processes and rate their awareness. In the second subscale (S: stress response, 10 items), subjects are asked to imagine being in a very stressful situation and rate their awareness of perceived changes due to stress. The third subscale, autonomic nervous system reactivity (ANSR), requires that subjects answer 27 items about their own autonomous nervous system reactions. Finally, the stress style (SS) subscale contains 12 items and evaluates the manner in which the subject responds to stress. All ratings are made on a five-point Likert scale.

fMRI data acquisition and analysis

Functional measurements were performed on a 3-Tesla whole body MRI system (Siemens Trio, Erlangen, Germany) with echo planar imaging (EPI) using an eight channel head coil. The slices were acquired parallel to AC–PC plane in an odd-even interleaved acquisition order. 32 $T2^*$-weighted echo planar images per volume with blood oxygenation level-dependent (BOLD) contrast were obtained (matrix: 64×64; 32 slices per volume; FoV: 224×224 mm; spatial resolution: $3.5 \times 3.5 \times 4$ mm; TE $= 30$ ms; TR $= 2000$ ms; flip angle $= 80°$). Functional data were recorded in four scanning runs, each containing 290 volumes. The first five volumes were discarded due to saturation effects.

The fMRI data were preprocessed and statistically analyzed according to the general linear model approach (Friston et al. 1995) using the SPM2 software package (spm2, http://www.fil.ion.ucl.ac.uk) running on MATLAB 6.5 (The Mathworks Inc., Natick, MA, USA). All functional images were slice time corrected with reference to the first slice acquired, corrected for motion artefacts by realignment to the volume taken nearest to the anatomical images, and spatially normalized to a standard T1-weighted SPM template (Ashburner and Friston 1999). Four MDD patients were excluded due to head-movements of more than 2 mm. The normalization was generated by warping the subject's T1-structural image to the T1-template provided by the MNI (Montreal Neurological Institute) and applying these parameters to all functional images. The images were resampled to $2 \times 2 \times 2$ mm and smoothed with an isotropic 6-mm full-width half-maximum Gaussian kernel. The time-series fMRI data were filtered using a high pass filter and cut-off of 128 s. A statistical model for each subject was computed by applying a canonical response function (Friston et al. 1998).

All three conditions (interoception, exteroception, and rest) were included in the SPM model as separate events. Regionally specific condition effects were tested by employing linear contrasts for each subject and each condition. The resulting contrast images were submitted to a second-level random-effects analysis by applying a one-sample *t*-test to the images created for all subjects in each condition. To control for the multiple testing problem we performed a false discovery rate correction (Nichols and Hayasaka 2003). The anatomical localization of significant activations was assessed with reference to the standard stereotactic atlas by superimposition of the SPM maps on the standard MNI brain template provided by SPM2.

Following the functional localizer approach (Saxe et al. 2006; Lamm and Decety 2008; Vul et al. 2008), we next determined the regions involved in interoception through the comparison between interoceptive and exteroceptive awareness (count heartbeat > count tones). In accordance with Goldstein and colleagues (Goldstein et al. 2007) we calculated this contrast for a combined group of healthy and depressed subjects ($n=34$). This was done to ensure that neither the group of healthy subjects nor the group of depressive subjects should be favoured and therefore have a dominant influence on the determination of the regions of interest (ROI). This contrast yielded significant signal changes in the bilateral anterior and middle insula. Spherical ROIs (radius 5 mm) were then located at the peak voxel within the left (*x*,*y*,*z*: –32,14,6) and right (36,16,6) anterior insula, and left (–42,12,-2)

and right (43,8,0) middle insula. Signal changes in these ROIs during interoception, exteroception and rest were then extracted using the Marseille Region of Interest Toolbox software package (MarsBaR 1.86, Brett et al. 2002, http://www.sourceforge.net/projects/marsbar).

Mean normalized fMRI signal values from 4 to 10 s of the BOLD response for each condition were first compared between healthy and depressed subjects (two-sample *t*-test, two tailed) using SPSS 16.0 (SPSS inc., Chicago, IL). In a second analysis, intero- and exteroceptive trials that followed a rest period were identified. The signal changes during these trials were thus assumed to represent the change from the baseline state; as opposed to those events which followed another trial type, which would represent a change from a stimulus-induced state. This allowed the effect of differences in resting-state activity on subsequent stimulus-induced signal changes to be characterised. These so-called baseline corrected signal changes were then compared between healthy and depressed subjects (two-sample *t*-test, two tailed). Finally, the signal changes during the rest condition were correlated with the subscales of the Body Perception Questionnaire (Pearson's, two-tailed).

Results

Behavioural data

MDD patients showed significantly higher scores in the Body Perception Questionnaire (BPQ) when compared to healthy subjects (see Figure 1a,b). This is true for the total score (*t*-test $P = 0.03$), as well as the subscores for stress response (S) (*t*-test $P = 0.001$), autonomic nervous system reactivity (ANSR) (*t*-test $P = 0.0001$) and stress style (SS) (*t*-test $P = 0.0001$). MDD patients did not differ significantly from healthy subjects in the BPQ subscore for awareness (A).

The BPQ stress style subscale scores correlated positively with total BDI scores ($r = 0.61$, $P < 0.05$). The higher the BPQ for stress style is, the higher the BDI scores and hence depression severity.

Signal changes during intero- and exteroceptive processing and rest in the insula

In a first step, we identified the bilateral anterior and middle insula as being involved in interoception by investigating signal changes from the comparison between interoceptive and exteroceptive awareness in the contrast (count heartbeat > count tones) in all subjects, healthy and depressed ($n=34$), as described above (Methods). This is in accordance with the
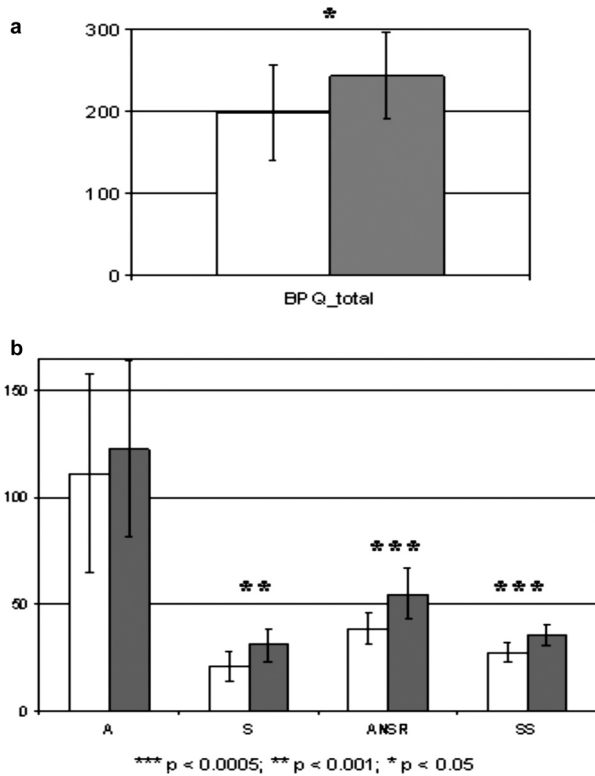
Figure 1. Results of the Body Perception Questionnaire (BPQ) for healthy (white bar) and depressive subjects (grey bar) (means ± SD). (a) Comparison of the total score of the Body Perception Questionnaire (BPQ_total); (b) comparison of the four subscores of the Body Perception Questionnaire. A, awareness; S, stress response; ANSR, autonomic nervous system reactivity; SS, stress style (1+2); total, total score.

regions obtained from the same contrast by Critchley et al. (2004), suggesting that our modified paradigm can be considered to be valid. Using the bilateral anterior and middle insula regions as functional localisers, we determined signal changes in these regions during interoceptive awareness (counting heartbeat), exteroceptive awareness (counting tones), and rest (fixation cross), and compared them between the two groups.

Signal changes during interoceptive processing - the heartbeat perception task - did not differ significantly between groups in the two relevant parts of the insula (see Figures 2a, b and c). This was independent of whether interoceptively associated signal changes were analyzed in relation to the preceding rest period or not (see Table I).

In contrast to interoceptive signal changes, signal changes during exteroceptive processing, the tone perception task, did differ significantly between both groups. Depressed subjects showed significantly reduced signal changes, with lower deactivation (i.e. smaller negative BOLD response), or even activation (i.e. switching to a positive BOLD response), in the left and right anterior insula when compared to healthy subjects (see Table I).

However, it cannot be excluded that such altered signal changes during exteroceptive processing might also be due to higher signal changes during the preceding rest period, which was rather long in our case (see above in the methods). This in turn might enhance the signal changes that are induced by subsequent exteroceptive stimulation. We therefore conducted a second analysis of the same data where we calculated exteroceptive signal changes as dependent on the level of signal change in the respectively preceding rest period (i.e. the fixation cross) for both healthy and depressed subjects. When these signal changes were then compared, depressed subjects no longer showed any significant difference from healthy subjects in the anterior and middle insula during exteroceptive processing (see Table I and Figure 2a–c). This suggests that the higher signal changes during exteroceptive processing yielded in the first analyses may be due to increased signal changes during rest periods.

Since the preceding rest period was shown to most likely affect signal changes during exteroceptive processing, we compared these signal changes themselves between both groups in the two relevant insula regions. MDD patients showed significantly lower deactivation (i.e. a reduced negative BOLD response) in the left anterior and middle (only marginally significant) insula, as well as in the right middle insula (see Figure 2a-c and Table I).

Taken together, our findings show abnormally reduced activity changes, i.e. a lower deactivation, during rest periods in the insula in MDD patients when compared to healthy subjects. In contrast, depressed patients showed no abnormalities in intero- and exteroceptive processing in the insula independent from rest periods.

Relationship between signal changes in the insula and body perception

Utilising the same regions of the insula as described above, we correlated signal changes during rest and intero- and exteroceptive processing with the scores in the BPQ (Body Perception Questionnaire) in healthy and depressed subjects.

Healthy subjects showed significantly positive correlations of rest signal changes in the right anterior insula with the BPQ total, BPQ awareness and BPQ stress response scores (see Figure 3b and Table II). The less deactivation during the rest periods in the right anterior insula, the higher the BPQ scores indicating abnormal body perception. This relationship was not obtained in MDD subjects, where decreased deactivation in the insula was no longer related to body perception scores (see Figure 3b).
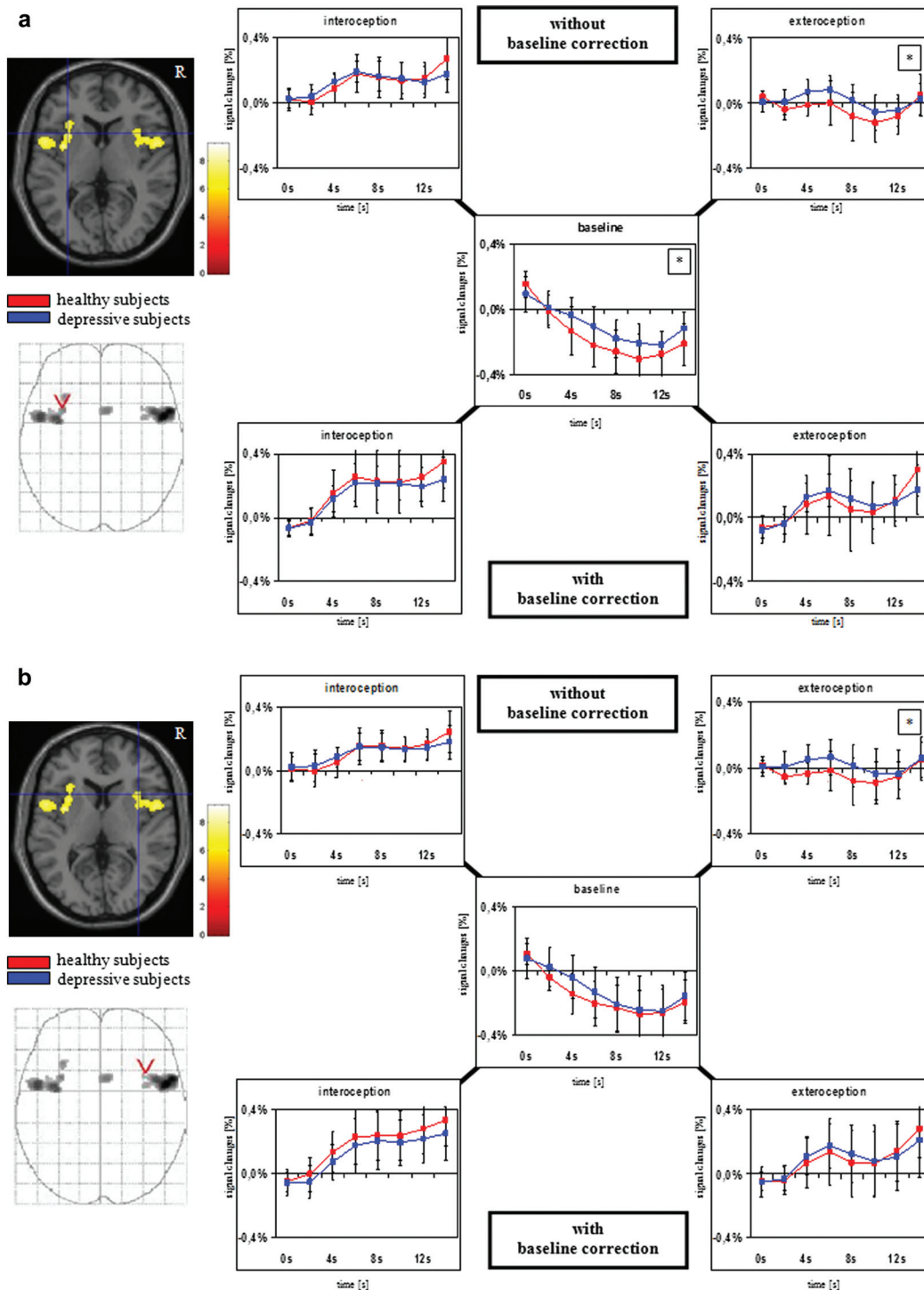
Figure 2. Comparison of interoceptive insular activity (SPM images) during intero- and exteroception (with and without baseline correction) and baseline between healthy (red lines) and depressive subjects (blue lines). SPM images show the comparison between interoceptive and exteroceptive awareness by the contrast (count heartbeat > count tones), $P < 0.01$, FWE corrected, $k>10$, $n=34$ subjects (17 healthy and 17 depressive subjects). BOLD curves (x axis: time in seconds, y axis: percent signal changes) are based upon regions of interest (ROIs) that are derived from this contrast. These are plotted separately for healthy (red lines, means ± SD) and depressive (blue lines, means ± SD) subjects and show baseline-corrected (i.e., signal intensities during interoception relative to the preceding baseline) and non-baseline-corrected (i.e., signal intensities during interoception independent of the preceding baseline) time courses for interoception and exteroception, as well as for rest periods. Figure 2a shows the results for the left anterior insula and Figure 2b for the right anterior insula.
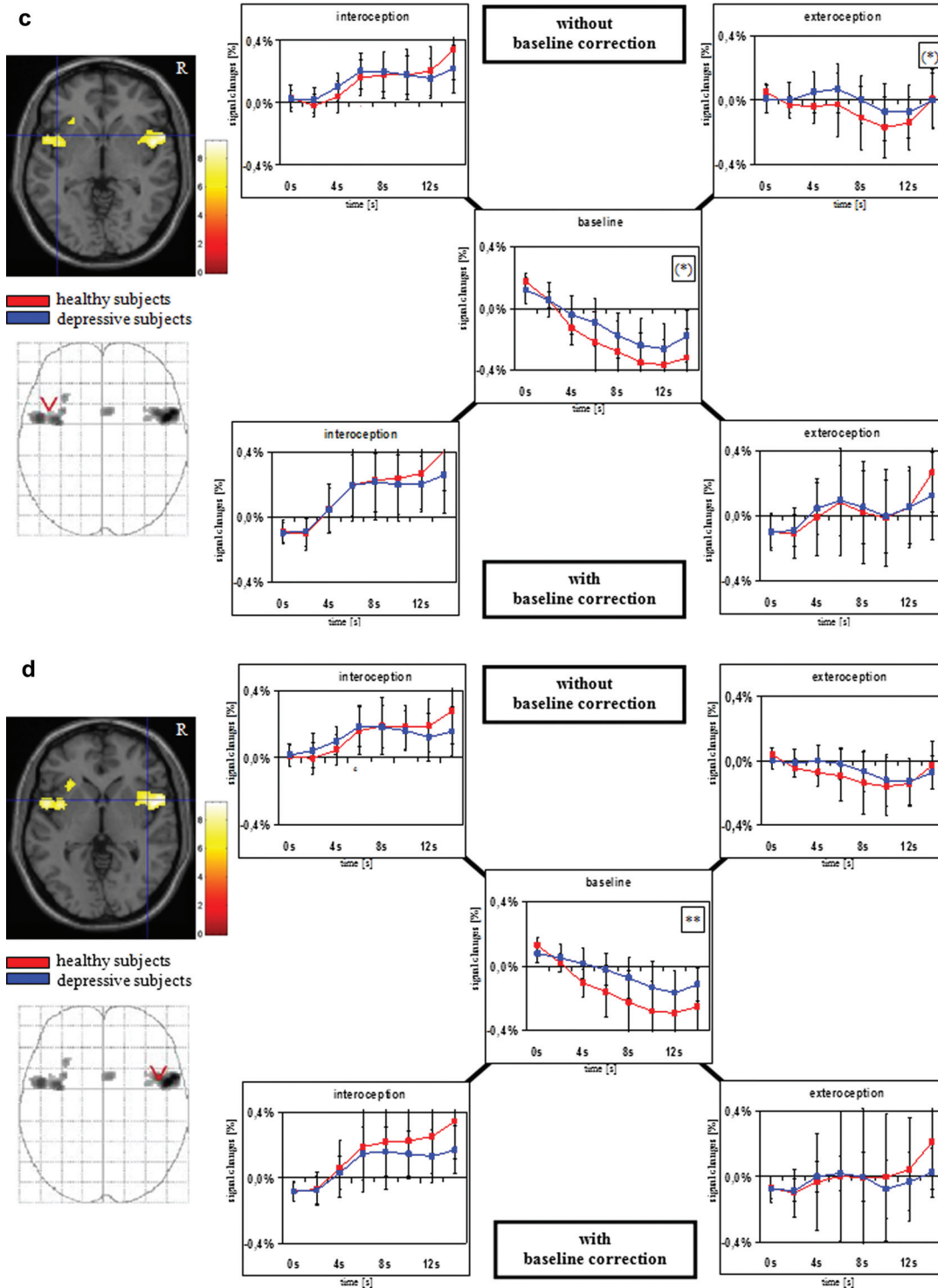
Figure 2 (*Continued*). Figure 2c shows the results for the left middle insula and Figure 2d for the right middle insula. Significant differences between both groups were obtained for exteroception without baseline-correction in the left and right anterior insula (*$P<0.05$), while this difference was no longer seen when baseline-correction was done. (a) Activation of left anterior insula (x,y,z: –32,14,6) in healthy and depressive subjects ($n = 34$); (b) activation of right anterior insula (x,y,z: 36,16,6) in healthy and depressive subjects ($n = 34$); (c) activation of left middle insula (x,y,z: –42,12,–2) in healthy and depressive subjects ($n = 34$); (d) activation of right middle insula (x,y,z: 43,8,0) in healthy and depressive subjects ($n = 34$).

Table I. Percent signal changes of anterior and middle insula for healthy (*n*=17) and depressive (*n*=17) subjects. Interoceptive (Int.) and exteroceptive (Ext.) processes were analyzed in relation to the preceding rest period (with base correction) or not (without base correction).

	Healthy subjects Means ± SD	Depressive subjects Means ± SD	*P* value (two-tailed)
Anterior Insula, L			
Int. without base corr.	–	–	–
Ext. without base corr.	−0.054 ± 0.11	0.028 ± 0.08	0.02*
Rest	−0.231 ± 0.12	−0.13 ± 0.1	0.013*
Int. with base corr.	–	–	–
Ext. with base corr.	–	–	–
Anterior Insula, R			
Int. without base corr.	–	–	–
Ext. without base corr.	−0.057 ± 0.11	0.024 ± 0.097	0.03*
Rest	–	–	–
Int. with base corr.	–	–	–
Ext. with base corr.	–	–	–
Middle Insula, L			
Int. without base corr.	–	–	–
Ext. without base corr.	−0.085 ± 0.158	0.011 ± 0.123	0.055(*)
Rest	−0.242 ± 0.164	−0.137 ± 0.171	0.076(*)
Int. with base corr.	–	–	–
Ext. with base corr.	–	–	–
Middle Insula, R			
Int. without base corr.	–	–	–
Ext. without base corr.	–	–	–
Rest	−0.192 ± 0.132	−0.053 ± 0.111	0.002**
Int. with base corr.	–	–	–
Ext. with base corr.	–	–	–

**$P < 0.005$; *$P < 0.05$; (*) $P < 0.1$; – $P > 0.1$.

Signal changes during rest periods in the left anterior insula were also significantly positively correlated with BPQ stress response in healthy subjects; this no longer being the case in MDD patients (see Figure 3a and Table II). Instead, the reduced signal changes during rest periods correlated significantly with depression severity as measured with the BDI ($r = 0.57$, $P < 0.05$). The less deactivation during rest in the left anterior insula, the more severely patients experience their depressive symptoms (see Figure 3a). No significant correlation of BDI was observed with either the right anterior or middle insula.

Discussion

We here investigated body perception and neural activity in the insula as behavioural and neural measures of abnormal interoceptive awareness in depression. MDD subjects showed significantly higher body perception scores and lower signal changes during rest periods (i.e. reduced negative BOLD response) in the anterior and middle insula when compared to healthy subjects. It should be noted that a reduced negative BOLD-response may be due to either higher activity during rest periods or decreased neural activity. In contrast to healthy subjects, signal changes during rest periods in the anterior insula

were no longer parametrically related to body perception scores in MDD. Most interestingly, both abnormal body perception scores and reduced signal changes during rest periods in the left anterior insula correlated with depression severity, as measured with the Beck Depression Inventory (BDI; Beck et al. 1961). Taken together, our findings demonstrate abnormal body perception and modulation of exteroceptive processing by the activity during rest in the anterior insula in MDD, mirroring these patients' abnormal "material me".

MDD patients showed significantly higher scores in body perception, as measured with the BPQ. Our observation of abnormal body perception is in accordance with previous findings of altered sensitivity and awareness of vegetative bodily changes in MDD (Stewart et al. 2001; Dunn et al. 2007; Strigo et al. 2008b). We were able to extend these findings by showing that different dimensions of body perception, such as stress response, autonomic nervous system reactivity and stress style, seem to be abnormally increased in depressed patients. This indicates abnormal body perception; although this may not concern awareness itself as we did not observe a significant difference in the awareness subscale of the BPQ. Future investigations of depressive subgroups may be needed to further detail their relationship with bodily awareness, with anxiety-dominated MDD patients,
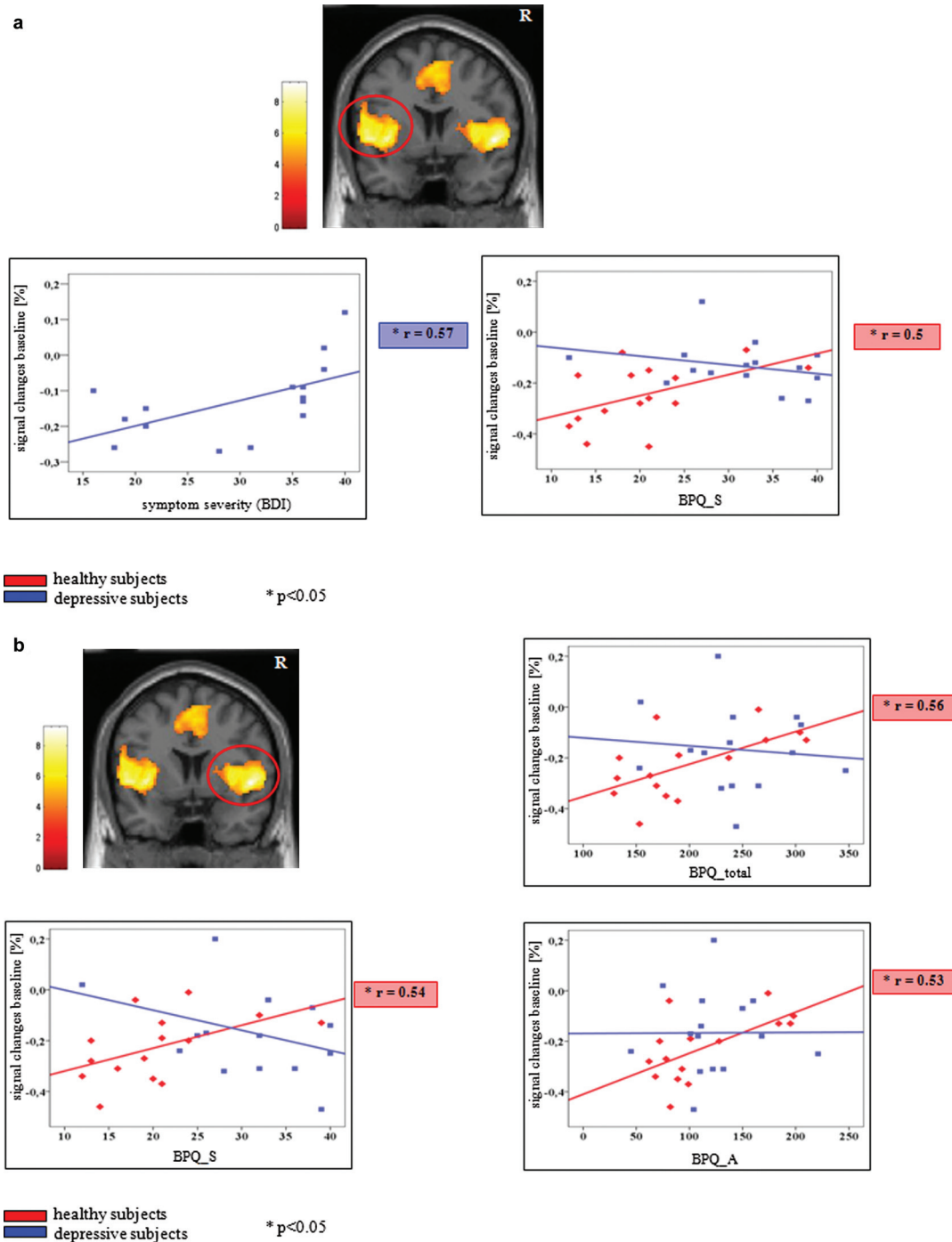
Figure 3. Correlation diagrams between left (a) and right (b) anterior insula activity during rest, Body Perception Questionnaire (BPQ) and Beck Depression Inventory (BDI). The SPM image shows the comparison between interoceptive and exteroceptive awareness (count heartbeat > count tones, $n = 34$). The threshold of significance is set to $P < 0.01$ (FDR corrected, $k > 10$). The diagrams show the correlation curves between percent signal changes of the left and right anterior insula during rest (y axis) and the scores of the Body Perception Questionnaire (BPQ, x axis). Healthy subjects (n=17, red lines) show significant correlations of the baseline signal changes in the right anterior insula (b) with the total score of the BPQ (BPQ_total), awareness (BPQ_A) and stress response (BPQ_S) (* $P < 0.05$). Depressive subjects ($n = 15$, blue lines), in contrast, showed no significant correlations between the BPQ in the right anterior insula (b). Baseline signal changes in the left anterior insula (a) show a significant correlation with stress response (BPQ_S) in healthy subjects, while the same regions correlated with depression severity in depressed subjects (*$P < 0.05$). The higher the signal changes in the left anterior insula during baseline, the more severe subjects scored their depressive symptoms.

Table II. Results of correlational analysis between signal changes in rest periods in different insular regions and subscores of the Body Perception Questionnaire (BPQ). white: healthy subjects, grey: depressive subjects.

	Awareness	Stress response	ANSR	Stress style (1+2)	Total score
Anterior Insula, L					
Rest, healthy	–	r=0.5	–	r=0.42	–
	–	P=0.044*	–	P=0.097(*)	–
Rest, depressive	–	–	r=−0.51	–	–
	–	–	P=0.054(*)	–	–
Anterior Insula, R					
Rest, healthy	r=0.53	r=0.54	–	–	r=0.56
	P=0.028*	P=0.027*	–	–	P=0.019*
Rest, depressive	–	–	–	–	–
	–	–	–	–	–
Middle Insula, L					
Rest, healthy	–	r=0.45	r=0.47	r=0.43	–
	–	P=0.068(*)	P=0.057(*)	P=0.087(*)	–
Rest, depressive	–	–	–	–	–
	–	–	–	–	–
Middle Insula, R					
Rest, healthy	–	–	–	–	–
	–	–	–	–	–
Rest, depressive	–	–	–	–	–
	–	–	–	–	–

*$P < 0.05$; (*)$P < 0.1$; – $P > 0.1$.
ASNR, autonomic nervous system reactivity.

for example, probably showing decreased awareness of the body (Pollatos et al. 2009).

Moreover, abnormal body perception correlated with depression severity as measured with the BDI. The more abnormally high body perception was, the more intensely and severely patients experience their depressive symptoms. This yields strong empirical support to the often made clinical observations of somato-vegetative symptoms, and of abnormal interoceptive awareness being an indicator of depressive symptoms and depression severity (Kirmayer 2001; Tylee and Gandhi 2005; Garcia-Cebrian et al. 2006; Nyboe Jacobsen et al. 2006).

MDD patients showed significantly reduced signal changes during rest in the insula, predominantly in the left anterior and middle insula. This is in accordance with early studies in MDD concerning rest periods that, using PET, also observed increased activity during rest in the insula (Mayberg 2002, 2003; Phillips et al. 2003a,b; Fitzgerald et al. 2008). In contrast, MDD patients did not show any abnormalities in this region during either intero- or exteroceptive stimulation when compared to healthy subjects. We were here able to extend these early observations by showing no changes during either intero- or exteroceptive stimulation independent of changes during rest periods. Although we did observe some abnormalities in the insula during the exteroceptive task, these could most likely be traced back to the reduced activity during rest rather than the exteroceptive stimulation itself, as revealed in our baseline corrected analysis. This underlines the

proposed abnormal rest-stimulus interaction in depressed patients, with, it is suggested, an abnormally high activity during rest periods leading to a reduced stimulus-induced change in activity.

Furthermore, reduced neural changes during rest periods in the left anterior insula correlated with depression severity. The smaller the deactivation during rest was, the more severely MDD patients experienced their depressive symptoms. This is in accordance with previous findings concerning both the insula and other regions, such as the ventro- and dorsomedial prefrontal cortex (Brody et al. 2001; Milak et al. 2005; Perico et al. 2005; Paulus and Stein 2006; Simmons et al. 2006; Stein et al. 2007; Grimm et al. 2009a, 2009b). Taken together, our findings provide strong evidence of reduced activity during rest periods in the left anterior insula and the relation of this to depressive symptoms.

Most importantly, our findings indicate decoupling of body perception from neural activity changes in the insula in MDD. In accordance with Craig's hypothesis of the right anterior insula mediating the "material me", rest activity in this region correlated with body perception, as measured with the BPQ, in healthy subjects. This was no longer the case in depressed subjects, where activity during rest periods in both right and left anterior insula no longer correlated with BPQ scores. Body perception and activity during rest thus seem to be dissociated or, better, decoupled from each other in MDD.

MDD patients' abnormal body perception and its relation to altered activity in the insula may be

interpreted as the inability of depressed subjects to shift their focus of perception/awareness from the own body to their environment. This could lead to increased interoceptive awareness, mirroring the abnormal "material me" of MDD patients.

Several limitations of our study need to be considered. Our patients were all medicated and therefore we cannot exclude medication effects. Hence, the same study may need to be conducted again in unmedicated MDD patients.

One may criticize that we did not include a true resting state period with scanning for about 5–10 min in the mere resting state. Instead, we only included 4–10-s long periods with fixation cross. This was done because our main purpose was to clearly separate signal changes associated with rest from those related to intero- and exteroceptive processing within the regions of interest. In order to do this we analysed the relative signal changes induced by intero- and exteroceptive processing in relation to the respectively preceding rest period, something that is not possible with a separate, long rest period. Future studies with a separate and longer resting state period will be necessary to investigate fully the relationship between the resting state network, the default-mode network (Raichle et al. 2001; Raichle and Gusnard 2005), and the interoceptive network and body perception. One may also argue that body perception itself does not account for what is called the "material self". The "material self" could only be investigated by explicitly testing for self-relatedness of one's body, which we did not do here. Hence, future studies are necessary that include both body perception and self-relatedness as implicit and explicit measures of the self with regard to the (inner and outer) body.

In conclusion, we here demonstrate the crucial relevance of the anterior insula to abnormal body perception and depression severity in MDD. MDD patients showed differing body perception scores and reduced activity during rest periods in the anterior insula specifically. Signal changes during rest in the anterior insula no longer correlated with BPQ scores in MDD patients, while they were related to depression severity. Taken together, our findings demonstrate abnormal body perception and reduced activity in the insula during rest periods, with the latter being decoupled from the former. This may account for the often observed somato-vegetative symptoms in MDD patients.

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Statement of interest

The authors report no conflict of interests.

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