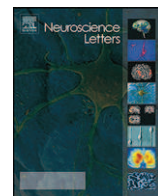




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Are emotions associated with activity during rest or interoception? An exploratory fMRI study in healthy subjects

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ABSTRACT

Imaging studies investigating the default-mode network (DMN) of the brain revealed the phenomenon of elevated neural responses during periods of rest. This effect has been shown to be abnormally elevated in regions of the DMN concerning mood disorders like major depressive disorder (MDD). Since these disorders are accompanied by impaired emotional functioning, this leads to the suggestion of an association between activity during rest conditions and emotions, which remains to be demonstrated in a healthy and clinical population. Controlling for interoceptive processing, a process often closely connected to emotional functioning, we here demonstrate in an fMRI study of 30 healthy subjects the connection between activity during rest conditions in regions of the DMN and emotions in a psychologically, regionally, and stimulus specific way. Our findings provide further insight into the psychological functions underlying rest activity. Our findings in healthy subjects may also have future implications for a better understanding of mood disorders.

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The significance of the high level of activity displayed by certain regions of the brain during rest is a topic of increasing interest [26,34]. Central amongst these regions are those termed the default-mode network (DMN). This network consists mainly of cortical midline structures [17,35] and includes, for example, the perigenual anterior cingulate cortex (PACC), posterior cingulate cortex (PCC) as well as the ventro- and dorsomedial prefrontal cortex (VMPFC, DMPFC) [11,15,16]. The DMN displays a deactivation from its level of activity at rest in response to attention-requiring tasks (task-induced deactivations, TID).

Several studies have suggested that the DMN, or components of the DMN, are connected to emotional functioning [18,29]. This hypothesis is supported by the observation that a number of psychiatric disorders characterised by a deficit in emotional processing – such as major depressive disorder (MDD) and social phobia – are associated with an alteration in DMN functioning [14,39].

Emotional processing has, however, also been associated with interoceptive processing [6,7,27,31]. The attention-requiring

nature of interoceptive tasks means that such processing can be assumed to induce a deactivation in the DMN (i.e., TID). This, in conjunction with the dual association of emotions with activity during rest and interoception, thus raises the question as to whether the link between emotion and activity in the DMN described above is due to a relationship between emotion and activity during rest itself, or whether the observed relationship is instead a result of emotion-induced interoceptive activity within the DMN.

In order to investigate this issue in an exploratory study with healthy subjects, we utilised a combination of fMRI and measures of emotions and bodily awareness. A well-established fMRI paradigm for interoceptive processing [8,32] was slightly modified to include an operationalisation of resting-state (via fixation cross) within an event-related design [39]. This design allowed the BOLD signal observed during rest, and intero-/exteroception (TID) to be related to the measures of emotions and bodily awareness.

Based on the DMN-related findings described above, it was hypothesised that emotional processing would be related to the level of rest activity within the DMN. In addition, it was further hypothesised that there would be no relationship between emotions and intero- or exteroceptive induced activity in these regions, as based on the assumption that it is the induced activity during rest itself in these regions that is tied to emotion, rather than any task-induced signal changes.

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We studied 30 subjects (15 females) with no psychiatric, neurological, or medical illness using fMRI. In order to evaluate the status of the subjects, they were questioned about psychiatric, neurological, or medical diseases as well as the use of psychoactive substances using a custom-made semi-structured clinical questionnaire. Participants were recruited from the University of Magdeburg and the local community. The study was approved by the local ethics committee and all participants gave written informed consent before participating in this study. Subjects were compensated for their participation.

The fMRI design was based on a paradigm introduced by Pollatos et al. [32] and Critchley et al. [8]. Subjects were presented with three separate conditions: an interoceptive task, an exteroceptive task, and rest periods (fixation) – in a pseudo-randomised order. For a detailed description of the paradigm, see [Supplementary Fig. 1a](#) or Wiebking et al. [39], where a separate dataset and independent analysis are presented.

Intelligence was assessed through the nonverbal LPS-3 [19] and verbal MWT-B [21] tests.

For investigating the ability to recognise emotions, we used the Florida Affect Battery (FAB) [3]. The FAB is a research tool that was designed to investigate disturbances in the perception of emotional signals (facial and prosodic affect) under a variety of task demands. In order to apply a comparable auditory emotional task in relation to the exteroceptive task in the scanner, we concentrated only on subtest 8a. This consists of a set of 15 semantically neutral sentences (e.g.: ‘The chairs are made of wood’) spoken in emotional tones of voice. The sentences are all approximately the same length and were recorded by an experienced actress in five different emotional intonations: happy, angry, sad, fearful and neutral. Each affect was presented three times. Subjects were asked to verbally label the emotional prosody of each item.

The Body Perception Questionnaire (BPQ) [33] was also used in order to test for the individuals’ awareness and manner of processing bodily changes. It includes 4 subscales, e.g. for bodily awareness, with subjects scoring their answer on a 5-point scale (ranging from never to always). Since the resting-state network has been associated with depressive symptoms we also applied the 20-item Beck Hopelessness Scale (BHS) [1].

Scans were performed on a 3-T whole body MRI system (Siemens Trio, Erlangen, Germany) using an eight-channel head coil. Slices were acquired parallel to the AC-PC plane in an odd-even interleaved acquisition order. Thirty-two T2*-weighted echo planar images per volume with BOLD contrast were obtained (matrix: 64 × 64; FoV: 224 × 224 mm; spatial resolution: 3.5 × 3.5 × 4 mm; TE = 30 ms; TR = 2000 ms; flip angle = 80°). Functional data were recorded in four scanning sessions containing 290 volumes per session for each subject. The first five volumes were discarded due to saturation effects.

The fMRI data were pre-processed and statistically analysed by the general linear model approach [13] using the SPM2 software package (spm2, <http://www.fil.ion.ucl.ac.uk>) and MATLAB 6.5 (The Mathworks Inc., Natick, MA, USA). For a detailed description of the pre-processing see Wiebking et al. [39].

All three conditions (rest, intero-/exteroception) were included in the SPM model as separate events without their response phases. Regionally specific condition effects were tested by employing linear contrasts for each subject and different conditions. The resulting contrast images were submitted to a second level random-effects analysis. Here, one-sample *t*-tests were used on images obtained for each subjects’ volume set and different conditions. To control for the multiple testing problem we performed a familywise error rate correction [2,25]. The anatomical localisation of significant neural responses in our main contrast [rest > intero-/exteroception] ($P < 0.01$, FWE-corrected, $k > 10$) was assessed with reference to the

standard stereotactic atlas by superimposition of the SPM maps on a standard brain template provided by SPM2.

In a second step, the BOLD signals were analysed. Applying sphere-shaped regions of interest (ROI, radius 5 mm), we extracted fMRI signal timecourses from regions of the DMN, as identified using the contrast [rest > intero-/exteroception] (VMPFC: –2, 52, –4, DMPFC: –2, 52, 40, PCC: 6, –48, 24) using the MarsBaR toolbox (<http://www.sourceforge.net/projects/marsbar>). Using a custom PERL script, fMRI signals were corrected for baseline shifts (applying a linear baseline correction algorithm) as well as normalised (dividing each value through the average fMRI signal of the time from –6 s to 30 s). The normalised average fMRI signal of the time-points –2 s and 0 s was then subtracted from each single fMRI value. This procedure ensured that all timecourses start from 0% signal change at 0 s. For each subject, mean fMRI signal changes for each of the three conditions were calculated by averaging the normalised fMRI signal values from 4 s to 10 s. For inter-subject statistical analysis, these values were Pearson-correlated (SPSS 17.0) with subjects’ behavioural scores.

Following the recommendations of Kriegeskorte et al. [20], we also used independent coordinates (midline rather than right or left as criterion; except the DMPFC, see Table 1a). As described above, we calculated percent signal changes in similar regions found to be involved in mind-wandering and Pearson-correlated them with the behavioural test results. Independent coordinates were taken from Christoff et al. [5] and transferred from Talairach in MNI coordinates using the WFU-pickatlas [22,37].

The group of 30 subjects had a mean age of 33.73 years (± 11.62 SD) and a mean time in education of 16.05 years (± 2.42 SD), with no sex differences. Their mean score for verbal intelligence was 114.23 (± 13.56 SD) and for nonverbal intelligence 118.40 (± 14.53 SD). Emotional tests included the BHS and the FAB.8a, with mean scores of 4.6 (± 3.9 SD) and 91.78 (percent correct answers ± 8.87 SD), respectively. The BPQ showed a total score of 199.03 (± 50.24) and for the subscale of bodily awareness a score of 107.80 (± 38.78).

We firstly tested the validity of our paradigm by analysing the contrast [interoception > exteroception] ($P < 0.05$, FWE corrected, $k > 10$), comparing relevant regions with those obtained from the same contrast by Critchley et al. [8]. As detailed in [Supplementary Table 1b](#), this yielded almost identical regions, demonstrating that our modified paradigm can be considered to be valid.

Since we included the rest condition as a separate condition, we were able to calculate in a second step the main contrast [rest > intero-/exteroception] ($P < 0.01$, FWE corrected, $k > 10$), which showed significant signal changes in the VMPFC, DMPFC, and PCC (see Fig. 1 and [Supplementary Table 1a](#)) mirroring regions implicated in the DMN (Table 1a).

With the rest periods used here being rather short in comparison to the periods used in the majority of resting-state studies, we compared the regions identified by the main contrast with those obtained in a study by Fox et al. [12], which measured activity during rest over a time interval of 5 min. In addition, we compared our regions with the ones obtained in a comparable study by Christoff et al. [5]. Corresponding regions provide evidence that our rest periods show an acceptable representation of the resting-state (Table 1a).

Calculating percent signal changes in regions of the DMN obtained by the main contrast revealed task-induced deactivations (TID) during both intero- and exteroceptive processing ([Supplementary Table 1a](#)). Small positive BOLD responses (PBR) were observed in these regions during the rest condition (see also BOLD curves in Fig. 1).

The observed signal changes in the regions identified in the main contrast were then correlated with the results of the emotion-related psychological tests. This revealed negative correlations between signal changes during rest (i.e., PBR) with scores of the

Table 1

Regions of the DMN identified by the contrast [rest > intero-/exteroception] ($P < 0.01$, FWE corrected, $k > 10$) and their comparison with regions of the DMN from two other studies [5,12] can be seen in the upper part of the table. Below, different kinds of neural responses (rest, intero-/exteroception; mean fMRI values) in regions of the DMN (VMPFC, DMPFC, PCC) and their correlations with psychological measures of emotion (FAB: Florida affect battery, BHS: Beck hopelessness scale) are shown (** $P < 0.01$, * $P < 0.05$, (*) $P < 0.1$).

Region	Rest > Intero-/exteroception (x, y, z)	Default mode network (Fox et al. [12]) (x, y, z)	Mind wandering (Christoff et al. [5]) (x, y, z)
(a)			
VMPFC	−2, 52, −4	−3, 40, 0	−4, 50, −6
DMPFC	−2, 52, 40	–	–
PCC	6, −48, 24	−2, −39, 38	−6, −56, 42

(b)

(b)

Region	Test		Signal changes resting-state	Signal changes interoception	Signal changes exteroception
VMPFC (−2, 52, −4)	FAB 8a	<i>r</i> <i>P</i>	−0.42 ^{a,*} 0.02	−0.27 0.15	0.03 0.86
	BHS	<i>r</i> <i>P</i>	0.32(*) 0.09	−0.25 0.18	−0.39* 0.03
	BPQ_body	<i>r</i> <i>P</i>	0.02 0.92	0.16 0.40	−0.04 0.83
	BPQ_total	<i>r</i> <i>P</i>	−0.03 0.86	0.13 0.48	0.01 0.96
VMPFC (−4, 50, −6) Christoff et al. [5]	FAB 8a	<i>r</i> <i>P</i>	−0.4* 0.03	−0.25 0.19	0.05 0.78
	BHS	<i>r</i> <i>P</i>	0.24 0.203	−0.27 0.14	−0.43* 0.02
	BPQ_body	<i>r</i> <i>P</i>	0.003 0.99	0.19 0.31	−0.07 0.73
	BPQ_total	<i>r</i> <i>P</i>	−0.02 0.93	0.19 0.32	−0.04 0.83
DMPFC (−2, 52, 40)	FAB 8a	<i>r</i> <i>P</i>	−0.46* 0.01	0.10 0.96	−0.62 0.75
	BHS	<i>r</i> <i>P</i>	0.28 0.14	−0.28 0.13	−0.10 0.59
	BPQ_body	<i>r</i> <i>P</i>	−0.21 0.26	0.28 0.28	−0.16 0.40
	BPQ_total	<i>r</i> <i>P</i>	−0.18 0.35	0.18 0.33	−0.04 0.82
PCC (6, −48, 24)	FAB 8a	<i>r</i> <i>P</i>	−0.42 ^{a,*} 0.02	−0.09 0.65	0.00 1.00
	BHS	<i>r</i> <i>P</i>	0.35* 0.05	−0.31 0.10	−0.20 0.29
	BPQ_body	<i>r</i> <i>P</i>	−0.15 0.44	0.20 0.30	0.00 1.00
	BPQ_total	<i>r</i> <i>P</i>	−0.15 0.44	0.15 0.44	−0.01 0.97
PCC (−6, −56, 42) Christoff et al. [5]	FAB 8a	<i>r</i> <i>P</i>	−0.53** 0.003	−0.22 0.24	−0.18 0.33
	BHS	<i>r</i> <i>P</i>	0.22 0.25	−0.16 0.41	−0.28 0.13
	BPQ_body	<i>r</i> <i>P</i>	−0.19 0.31	0.03 0.86	0.01 0.10
	BPQ_total	<i>r</i> <i>P</i>	−0.18 0.34	0.06 0.77	0.15 0.44

^aA partial correlation between FAB.8a and signal changes in VMPFC and PCC remained significant when controlling for BHS. Significance level of * $P < 0.05$ also remained on this level when excluding 2 subjects scoring <75% correct answers in the FAB.8a, except for the independent region of the PCC (changing to (*) $P < 0.1$). P =significance (2-tailed), r =Pearson-correlation.

FAB.8a (Fig. 1a–c, Supplementary Fig. 1b) and positive correlations with BHS scores (Table 1b). A high FAB score indicates that the subject's ability to identify emotions correctly is good, while high scores in the BHS indicate depressive symptoms concerning emotional expectation/future.

To look closer at the specificity of the association between emotions and induced activity during rest in regions of the DMN, we distinguished between stimulus, regional and psychological specificity. To test for the latter association, we correlated these signal

changes with results of the BPQ, which tests for awareness of bodily changes. No significant correlation was observed (Table 1b). In a further step we conducted a partial correlation using the individual's BHS scores as co-variables. No change in the correlation between activity during rest and FAB.8a was observed. To test for stimulus specificity, we correlated all three measures (FAB.8a, BHS and BPQ) with TID in regions of the DMN. There were two negative correlations between exteroceptive signal changes in the VMPFC and BHS, whereas no significant relationships concerning intero-

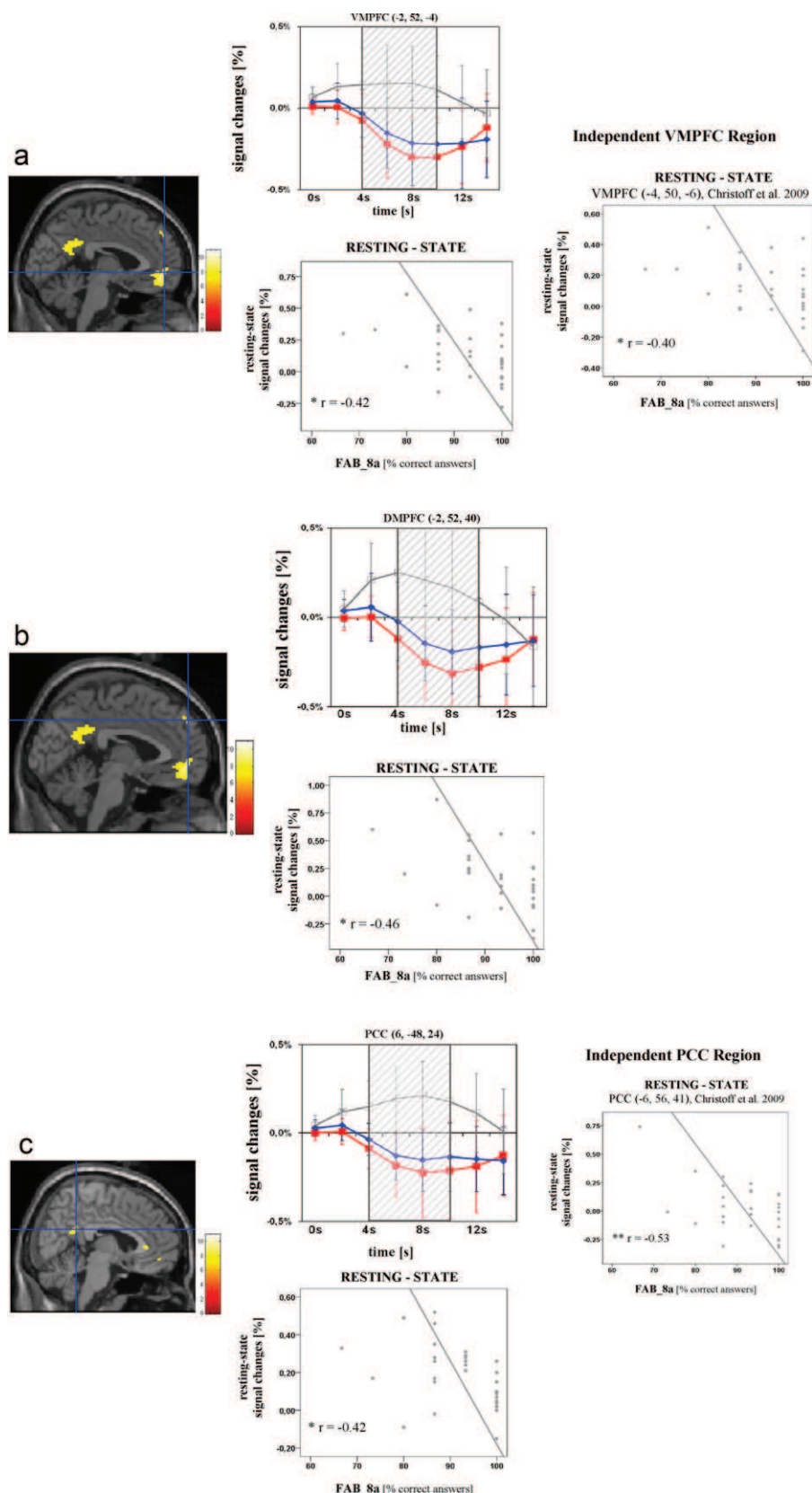


Fig. 1. SPM images show activity changes for the contrast [rest > intero-/exteroception] ($P < 0.01$, FWE corrected, $k > 10$) in (a) the ventromedial prefrontal cortex (VMPFC) ($x, y, z: -2, 52, -4$), (b) the dorsomedial prefrontal cortex (DMPFC) ($x, y, z: -2, 52, 40$), and (c) the posterior cingulate cortex (PCC) ($x, y, z: 6, -48, 24$). Timecourse images show the mean percent signal changes (\pm SD) in these same regions during rest (grey line), interoception (red line) and exteroception (blue line) conditions. Correlation graphs for each region show the intraregional relationship between percent signal changes during rest conditions and FAB.8a scores. The separate boxes in figure (a) and (c) show the same correlation using signal changes from an independent region, obtained in a similar imaging study ($*P < 0.05$). No independent region was available for the DMPFC (b). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

ceptive signal changes could be observed (Table 1b). Finally, to test for regional specificity, we correlated measures for emotions with interoceptive signal changes in interoceptive regions, which did not yield significant results for the main interoceptive regions (just for somatomotor areas, see Supplementary Table 1b).

Since the extracted signal changes, which derived from regions of interest (ROI) found in the second level analysis, served for further correlations, the problem of a selection bias occurs and thus a potential increase of the non-independence error. To test for statistical independence, in line with the recommendations made by Kriegeskorte et al. [20], Poldrack et al. [30] and Vul et al. [38], we used coordinates from a comparable study on mind-wandering by Christoff et al. [5]. Application of these midline coordinates (except the DMPFC, which they did not obtain) yielded again a negative correlation with FAB.8a (correlation graphs on the bottom right in Fig. 1a and 1c), which provides an independent confirmation of the above described results.

In an exploratory fMRI study with healthy subjects we demonstrate that measures of emotions correlate with induced activity during rest within regions of the DMN, including the VMPFC, DMPFC and PCC. In contrast, no relationship was seen between activity in these same regions during either intero- or exteroception (i.e., TID) and the measures of emotions. These findings in healthy subjects may have future implications for subjects with mood disorders, like MDD or social phobia, who show both abnormal emotional functioning and abnormally high activity during rest in the same regions as those identified in this study [14,16].

Our demonstration of a relationship between induced activity during rest within regions of the DMN and emotions, which was reduced here to identification of emotions, are in line with previous findings that show that emotions, as induced by the presentation of emotional stimuli, impact upon neural response changes in subsequent rest periods [18,29]. While these prior studies indicated some indirect relationship between emotions and DMN regions, it remained unclear whether this effect was mediated by non-task-related rest activity itself or by interoceptive activity associated with emotions. By distinguishing induced activity during rest (PBR) in DMN regions from both intero- and exteroceptively induced signal changes (TID) in the same regions, we were able to demonstrate psychological, regional, and stimulus specificity. Only emotional measures, and not bodily perception, were associated with PBR during rest indicating psychological specificity. Measures of emotions were only associated with activity during rest periods, but not with TID. This thus suggests a specificity of neural responses. Finally, we observed an association of emotions only with signal changes in DMN regions, but not with those in intero- and exteroceptive regions, thus being indicative of regional specificity.

Our findings in emotions complement recent observations in healthy subjects that associated activity of the DMN with various internally oriented functions like mind-wandering, episodic memory retrieval and self-relatedness [4,5,23]. This raises the question whether the observed relation between emotional functioning and induced activity during rest is mediated by psychological interaction with mind-wandering, episodic memory retrieval and self-relatedness rather than interoception. Such a psychological interaction between emotions and activity during rest remains to be directly demonstrated.

Moreover, the results of this exploratory study could serve for a better understanding of mood disorders. We could show that increases in rest activity in regions of the DMN are related to decreases in emotion perception (FAB.8a) and increases in hopelessness (BHS), although the latter point could not be replicated in independently selected regions. Since MDD patients are characterised by both deficits in emotional functioning as well as hopelessness, one could suggest a linkage between these deficits

and their abnormally increased rest activity, as observed in various imaging studies [11,16,24]. One would consecutively expect that MDD subjects may be at the upper extreme end of a continuous relationship between DMN activity and emotion abilities, which remains to be tested in future studies.

Several limitations need to be mentioned. By using the FAB, we could test only for one part of the broad processes of emotional functioning. Other emotional functions, like emotion recognition, were not included. Analogously, emotion measures were controlled only by measures of body perception since one condition addressed interoception. In the future one might want to include more cognitive functions and cognitive-emotional regulation strategies to achieve further neuropsychological specification. Since recent research underlined the impact of depression as well as anxiety symptoms on interoceptive awareness [10,28], future studies should also account for these interactive effects. Another major limitation is that correlations were not corrected for multiple comparisons.

Finally, the concept of resting-state needs to be discussed. We here defined resting-state in a purely operational sense, i.e., as the absence of an active task [see 36 for a similar definition], realised in our design by a fixation cross. One may however argue that even viewing a cross may induce some activity, thus precluding a 'pure' resting-state. Another issue is the timing of rest periods. Investigations targeting functional connectivity in rest conditions use time intervals of 5 min in their designs [9,12]. In contrast, we were not interested in functional connectivity but rather in the induction of positive and negative BOLD responses in regions of the DMN during the three conditions of interest. This made it necessary to shorten the time interval and use 9–13 s periods of fixation cross as the rest condition. We are however aware that our results must be replicated for longer rest periods in order to be sure that they are not due to overlapping BOLD responses from preceding activation periods.

In conclusion, we demonstrate a relation between induced activity during rest in regions of the DMN and emotions, as distinguished from neural responses and psychological function associated with interoception. Demonstrating some degree of psychological, stimulus and regional specificity, our findings can serve for a better understanding of rest activity in both healthy and depressed subjects.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neulet.2011.01.012.

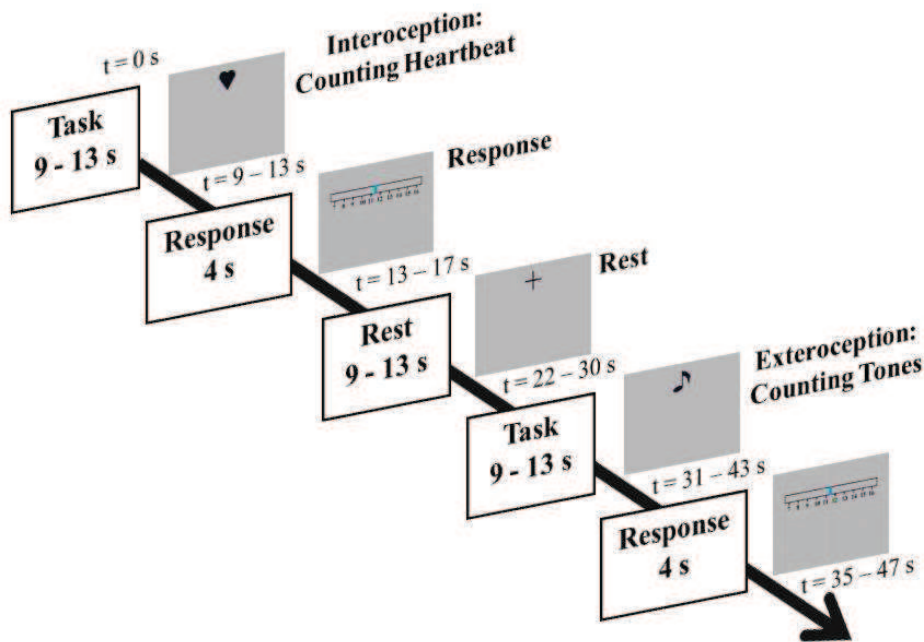
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Supplementary Figure 1

a)



The paradigm was based on a design, which was introduced by Pollatos and Critchley [8, 32]. Since the same paradigm was also applied to a separate subject group of depressed patients [39], it was altered in order to make it more suitable for the use with a depressed population, i.e. the paradigm was made less complicated and the time that patients spent in the scanner was reduced. In this paradigm, subjects were presented with three separate conditions: an intero- and an exteroceptive task, as well as rest periods – in a pseudo-randomised order.

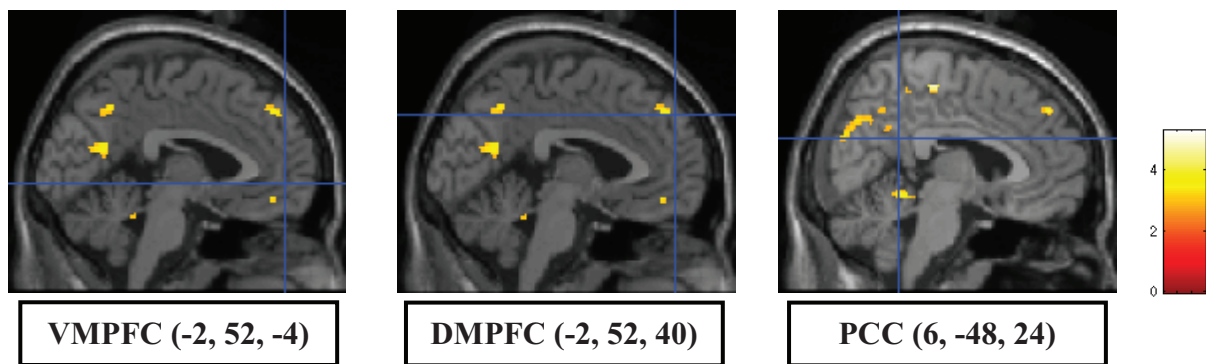
The task-type indicator for the interoceptive condition was a dark coloured heart on a light background. As long as it was displayed on the screen (9–13 s), subjects were asked to silently count their own heartbeat. Afterwards, subjects had to report the number of heartbeats counted via a simple visual 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.

Similarly, exteroceptive conditions were indicated by a dark coloured musical note symbol on a light background (9–13 s). During these conditions, as long as the task-type indicator was visible, subjects had to count silently the number of tones heard during this period. Afterwards, subjects were asked to report the number of counted tones, again via a visual analogue scale (4 s). Two different tones with a duration of 200 ms were presented. They were alternating with each of the four scanning runs. In order to make the difficulty of both tasks closely comparable, tones were presented at an individually determined volume (i.e. just audible, like the heartbeat). The general presentation frequency of the tones was adapted to correspond to each subject's pulse-rate. In order to control for habituation effects, the onset time of the tones was jittered by 200 ms from this general frequency.

Resting state conditions were indicated by a dark fixation 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 a 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.

b)



Supplementary Table 1

a)

Region (x, y, z)	Signal Changes Resting-State mean ± SD	Signal Changes Interception mean ± SD	Signal Changes Exteroception mean ± SD
VMPFC (-2, 52, -4)	0.1390 ± 0.20213	-0.2247 ± 0.20382	-0.1560 ± 0.21175
VMPFC (-4, 50, -6) Christoff et al. 2009	0.1277 ± 0.17370	-0.1940 ± 0.16592	-0.1097 ± 0.18178
DMPFC (-2, 52, 40)	0.1770 ± 0.28542	-0.2420 ± 0.19459	-0.1313 ± 0.21252
PCC (6, -48, 24)	0.1837 ± 0.16449	-0.1777 ± 0.18805	-0.1130 ± 0.13598
PCC (-6, -56, 42) Christoff et al. 2009	0.0123 ± 0.23018	-0.0963 ± 0.13890	-0.0663 ± 0.11716

b)

Regional Signal Changes Interception					
		FAB 8a	BHS	BPQ_body	BPQ_total
Insula Cortex (-40, 8, -4)	r P	-0.06 0.77	-0.16 0.41	0.27 0.16	0.22 0.24
Insula Cortex (52, 6, 0)	r P	0.001 1.0	-0.14 0.45	0.17 0.38	0.12 0.52
Anterior Cingulate Cortex (4, 10, 46)	r P	0.03 0.86	-0.29 0.12	0.18 0.33	0.24 0.20
Lateral Somatomotor Cortex (56, -22, 24)	r P	0.05 0.79	-0.12 0.53	0.08 0.66	0.55 0.81
Lateral Somatomotor Cortex (62, -20, 30)	r P	-0.44 0.02*	0.06 0.77	0.07 0.71	-0.09 0.63
Lateral Somatomotor Cortex (-58, -22, 20)	r P	0.15 0.42	-0.43 0.02*	0.04 0.82	0.03 0.90