Self-referential processing influences functional activation during cognitive control: an fMRI study

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Rostral anterior cingulate cortex (rACC) plays a central role in the pathophysiology of major depressive disorder (MDD). As we reported in our previous study (Wagner et al., 2006), patients with MDD were characterized by an inability to deactivate this region during cognitive processing leading to a compensatory prefrontal hyperactivation. This hyperactivation in rACC may be related to a deficient inhibitory control of negative self-referential processes, which in turn may interfere with cognitive control task execution and the underlying fronto-cingulate network activation. To test this assumption, a functional magnetic resonance imaging study was conducted in 34 healthy subjects. Univariate and functional connectivity analyses in statistical parametric mapping software 8 were used. Self-referential stimuli and the Stroop task were presented in an event-related design. As hypothesized, rACC was specifically engaged during negative self-referential processing (SRP) and was significantly related to the degree of depressive symptoms in participants. BOLD signal in rACC showed increased valence-dependent (negative vs neutral SRP) interaction with BOLD signal in prefrontal and dorsal anterior cingulate regions during Stroop task performance. This result provides strong support for the notion that enhanced rACC interacts with brain regions involved in cognitive control processes and substantiates our previous interpretation of increased rACC and prefrontal activation in patients during Stroop task.

Keywords: fMRI; rostral anterior cingulate; cognitive control; emotion; self-referential processing; functional connectivity; major depression

INTRODUCTION

The rostral anterior cingulate cortex (rACC) is involved in controlling affective states and plays a major role in the psychopathology of major depressive disorder (MDD). In healthy controls, it has been found to be of major relevance in tasks involving self-reflection, such as reflecting about one’s own future (Sharot et al., 2007), thinking about hopes and aspirations (Johnson et al., 2006) and during sad mood induction using autobiographical scripts (Liotti et al., 2000).

In patients with MDD, the activity of rACC has been often shown to be altered in the resting state condition as well as during performance of cognitive and affective tasks (Wagner et al., 2006; Drevets et al., 2008; Walter et al., 2009; Yoshimura et al., 2010). This aberrant activity in rACC seems to be associated with depressed mood and cognitive impairments. Moreover, depressed patients are often characterized by difficulties in disengaging from self-focusing and inhibiting context-relevant self-related information, e.g. negative self-relevant thoughts, which in turn may lead to disturbed attention in cognitively demanding tasks (Siegle et al., 2002; Joormann and Gotlib, 2008). These difficulties have been related to a putative dysfunction in rACC and adjacent ventromedial prefrontal cortex.

Furthermore, rACC represents a central node within a brain network subserving processing of emotional and motivational stimuli. This brain network often seems to ‘deactivate’ during cognitive tasks, which has led to the suggestion that self-reflective thoughts may be a common ‘default mode’, when individuals are not otherwise engaged (Gusnard et al., 2001). All of the putative functions in the ‘default mode network’ (DMN), such as beliefs, remembering the past as well as planning the future are self-referential in nature (Buckner et al., 2008). A failure in the inhibition of these processes may lead to an interference with cognitive task performance, as often seen in patients with depression.

In agreement with this assumption, neuropsychological studies provided evidence that depressive subjects had deficient cognitive inhibition and enhanced interference sensitivity when performing tasks tapping cognitive control functions (Ottowitz et al., 2002). The Stroop-Color-Word Test (Stroop task; Stroop, 1935) is an established neuropsychological task taxing inhibitory cognitive control and has been consistently shown to activate the fronto-cingulate network (Peterson et al., 1999). Therefore, in order to investigate the neural basis of cognitive inhibition processes in patients with MDD, we used the Stroop task in our previous functional magnetic resonance imaging (fMRI) study (Wagner et al., 2006). The main finding was that undemcitated depressed patients were unable to suppress rACC activation during Stroop task performance in contrast to healthy controls. We interpreted this result in terms of an inability of patients to inhibit affective interferences, which may arise from the enhanced self-referential processing (SRP) during the execution of the Stroop task. However, the postulated interfering effect of enhanced SRP due to the increased activation in DMN and especially in rACC on cognitive control processes has not been explicitly investigated yet. To specifically test this assumption, we conducted this fMRI study in healthy controls, in which we used affective self-referential statements referring to dysfunctional depressive thinking as well as non-affective neutral statements and the cognitive Stroop task. Based on our previous study, the main hypothesis was that negative SRP is associated with an increased sustained activation in rACC, which leads to an increased fronto-cingulate activation during the Stroop task performance. To test this hypothesis, we investigated the network associated with the activation in rACC during SRP and during the Stroop task with univariate and functional connectivity fMRI analyses.

MATERIALS AND METHODS

Subjects

Thirty-four subjects (age: mean = 24.1 ± standard deviation (s.d.) = 6.35; range: 18–51; 28 females) recruited from the Friedrich Schiller University community participated in the experiment.
All participants were screened for the presence of current psychiatric disorder using the German version of the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) and a semi-structured interview, by which neurological and past psychiatric diseases were assessed. None of the subjects fulfilled the criteria of Major Depression Disorder according to the International Classification of Diseases 10th revision.

None of the subjects reported a present or past history of drug abuse. Subjects had no present or past history of neurological or other clinically significant disorders. The participants were right-handed according to the modified version of the Annett handedness inventory (Briggs and Nebes, 1975) and reported normal or corrected-to-normal vision. Informed written consent was obtained in accordance with the protocols approved by the ethics committee of the University of Jena prior to conducting the study and all subjects received an allowance of 10 Euro per hour in return for their participation. Depressive symptoms were assessed with the Beck Depression Inventory (BDI) in order to relate them to brain activation in rACC. Subject had a mean BDI score of 4.91 with s.d. = 4.51 ranging from 0 to 16. In two participants, there were missing values regarding the BDI scores. According to the German version of BDI, a total score of over 18 indicates possible depression and warrants an additional clinical evaluation as confirmation (Hautzinger et al., 1994). Therefore, none of the participants in this study showed clinically relevant symptoms of depression. The variation in BDI scores in this study can therefore be considered as a normal variation in symptoms assessed by BDI.

Paradigm design

SRP task

The paradigm, which was used in this study, was developed and validated in a pilot study with 20 inpatients with MDD and 20 matched healthy controls. Based on the pilot study, negative and positive self-referential statements were chosen, which were able to discriminate between depressive patients and healthy controls. Moreover, neutral self-referential statements were used in this study, which did not significantly differ between patients with MDD and healthy controls in this pilot study. Affective self-referential statements were drawn from a variety of sources, including adaptation of Velten’s mood induction statements (Velten, 1968) and the Cognitive Triad Inventory (Beckham et al., 1986). Parts of these statements were used in previous studies of our group to induce negative affect in healthy subjects as well as in patients with MDD (Terhaar et al., 2009; Wagner et al., 2009; Köbele et al., 2010). Thus, we used 20 negative self-referential statements in this study dealing with negative view about the own self, e.g. ‘I consider myself to be a loser’, and 20 positive self-referent statements related to the positive view about the own self, such as ‘I have a lot of positive qualities’. Finally, 20 neutral statements were presented describing one’s traits or attitudes such as ‘I prefer to spend money instead of saving it’. Subjects were asked to judge positive, negative and neutral self-referential statements on a four-point scale, as to whether they properly described the participants themselves. All stimuli were matched according to the word number and length (no significant differences in the mean number) as well as syntax.

Stroop task

The manual version of the Stroop task was described in detail in our previous article (Wagner et al., 2006). In brief, the Stroop task consisted of two conditions: a congruent and an incongruent condition. In the congruent condition, color words were presented in the color denoted by the corresponding word; in the incongruent condition, color words were displayed in one of three colors not denoted by the word. This target stimulus was presented in the center of the display screen. Two possible answers (color words in black type) were presented below it (in the lower visual field) in order to minimize contextual memory demand. The subjects had to indicate as fast as possible the type of color by pressing one of two buttons (with index or middle finger), which corresponded spatially to both possible answers.

Paradigm timing

The whole paradigm consisted of 60 self-referential statements and 60 Stroop stimuli, which were presented in a pseudorandomized order and combination: each of 10 negative, 10 positive and 10 neutral self-referential stimuli were combined with each of 30 congruent Stroop stimuli to one trial, the other 10 negative, 10 positive and 10 neutral self-referential stimuli were combined with 30 incongruent Stroop stimuli. The detailed timing of the paradigm is illustrated in Figure 1. To minimize cognitive processes and brain activations due to task-switching costs, we introduced, prior to the presentation of each self-referential statement and Stroop stimulus, a task-specific cue for a short time (Verbruggen et al., 2007). Furthermore, to guarantee that subjects concentrated on the reading of the statements, the self-referential statement was presented during the first 3.5 s without and during the last 3 s with a digit bar with four possible responses. To be able to separate BOLD signal due to processing of self-referential from Stroop stimuli, a variable fixation baseline from 6 to 8 s with temporal jittering was introduced within each single trial. Single trials were separated by a variable temporally jittered fixation baseline varying from 6.5 s to 11 s in duration.

The whole paradigm was implemented using Presentation software (http://www.neurobs.com/) running on a PC, which was connected to a video projector. The visual stimuli were projected on a transparent screen inside the scanner tunnel, which could be viewed by the subject through a mirror system mounted on top of the MRI head coil. The subjects’ responses were registered by an MRI-compatible fiber optic response device (Lightwave Medical Industries, Canada) with four buttons on a keypad for the right hand.

MRI parameters

Functional images were recorded on a 3 Tesla whole-body scanner (MAGNETOM Trio, A Tim System; Siemens, Erlangen, Germany) with a 12-channel head matrix coil by using a whole-brain T2*-weighted Echo Planar Imaging (EPI) sequence, covering a volume of 48 parallel slices with 2.7 mm slice thickness and an isotropic voxel size of 2.7 × 2.7 × 2.7 mm³. Repetition Time (TR) was 2700 ms, Echo Time (TE) 30 ms, the flip angle was α = 90° and the Field Of View (FOV) was 192 mm × 192 mm (matrix 72 × 72). Parallel imaging (GRAPPA) with acceleration factor of 2 and 30 reference lines was used. One run with 600 volume acquisitions was collected from each participant. In addition, a high-resolution structural scan was acquired for co-registration using a three-dimensional (3D) Magnetization Prepared Rapid Gradient Echo (MP-RAGE) sequence with 192 contiguous axial slices of 1 mm thickness (TR 2300 ms; TE 3 ms; flip angle 9°; matrix size 256 × 256; isotropic voxel dimensions of 1 × 1 × 1 mm³).

Functional data analyses

Data preprocessing

The first four EPI images were discarded from further analysis to avoid T1 saturation effects. The functional images were preprocessed with the statistical parametric mapping software (SPM8, Wellcome Department of Cognitive Neurology, London, UK). Pre-processing included slice timing correction using the middle image of the volume as reference slice and 3D motion correction, i.e. rigid body realignment to the mean of all images. It was ensured that head movement was below 3 mm and 3° for each participant. Subsequently,
Family Wise Error (FWE) correction. All MNI coordinates were only. This analysis was corrected for multiple comparisons using the workflow created by means of the WFU Pickatlas (http://fmri.wfubmc.edu) of the whole cingulate cortex, whole brain level and a spatial extent threshold according to the extension of the task, individual movement parameters were entered as covariates into the design matrix as estimated during the realignment step. All regressors were convolved with a model of the Haemodynamic Response Function (HRF). Contrast images for each single regressor against baseline were calculated for each subject.

### Statistical analysis

#### Univariate analysis

The single-subject contrasts were submitted to the second-level group analyses with subject as the random-effect variable. For the analysis of the brain networks involved in SRP, a one-way analysis of variance (ANOVA) with three levels of the factor VALENCE, i.e. negative, positive and neutral self-related items, was performed. Two different contrasts were of interest: comparison of the negative SRP trials with the neutral SRP and Stroop-related activation after neutral self-referential stimuli was used. With this implementation of the PPI analysis, significant SPM activations of a particular area would reflect changes in functional connectivity between the source area (i.e. rACC) and the activated regions associated with the Stroop task depending on prior valence of SRP.

### RESULTS

#### Behavioral results

**SRP task**

The mean score for negative SRP items was mean = 1.49 (s.d. = 0.38), for positive SRP items M = 3.16 (s.d. = 0.46) and for the neutral SRP items mean = 2.77 (s.d. = 0.18). These responses were significantly different from each other (P < 0.0001), indicating a significant difference...
in response patterns between neutral and affective items as well as between positive and negative items.

Responses for negative SRP items negatively correlated with responses for positive SRP items ($r = -0.79$, $P < 0.0001$). Furthermore, negative SRP score positively correlated with the BDI score ($r = 0.79$, $P < 0.0001$), indicating a good criterion validity of SRP items to measure depression-specific attitudes.

**Stroop task**

The two-way ANOVA with the within-subject factors TASK (incongruent vs congruent Stroop condition) and VALENCE (Stroop task after negative vs positive vs neutral SRP conditions) revealed for the reaction time (RT), a significant main effect of TASK [$F(1,33) = 217.35$, $P < 0.0001$] indicating slower performance in the incongruent compared with the congruent condition. There was no significant main effect of VALENCE, but a TASK × VALENCE interaction [$F(2,66) = 5.52$, $P = 0.006$]. Post hoc t-tests revealed significantly prolonged RT for the congruent condition after presentation of negative compared with neutral SRP items ($t = 3.03$, $P = 0.005$) and significantly prolonged RT for the incongruent condition after presentation of neutral compared with positive SRP items ($t = 2.19$, $P = 0.035$).

In both Stroop conditions, high levels of accuracy were obtained in subjects. They showed in the incongruent condition after negative SRP items the worst performance in terms of the mean percentage of correct responses mean = 96.6% (s.d. = 5.38) and in the congruent condition after negative SRP items the best performance with mean = 98.8% (s.d. = 3.50) correct responses. There were no significant differences between single Stroop conditions with regard to the number of correct responses.

**fMRI results**

**Processing of negative SRP items vs neutral SRP items**

As depicted in Figure 2 and Table 1, subjects activated stronger during processing of negative SRP items in contrast to neutral SRP items, predominantly in the midline brain structures including lingual gyrus, posterior cingulate cortex (PCC), precuneus/superior parietal lobe (SPL) and the right rACC. Further brain areas involved were the right rostrolateral prefrontal cortex (RLPFC, Brodmann Area (BA)10), right inferior parietal lobe and right superior temporal gyrus (STG). Activation in the PCC and rACC both survived the FWE correction ($P < 0.05$) for multiple comparisons after applying the mask image of the whole cingulate cortex.
**Processing of positive SRP items vs neutral SRP items**

During processing of positive SRP items in contrast to neutral SRP items, subjects showed stronger activation in similar brain structures as during processing of negative SRP items including PCC and SPL (Figure 2 and Table 1). Further cluster of stronger activation during processing of positive SRP items included the left and right RLPCF extending to the left rACC. In addition, left insular cortex, left STG and the right precentral gyrus were strongly activated in comparison to the neutral SRP condition. Both the activation in the PCC and in the left rACC survived the FWE correction ($P < 0.05$) for multiple comparisons after applying the mask image of the whole cingulate cortex. However, although the activation in rACC during processing of negative SRP items was above the fixation baseline and thus represents a difference in activation level (Figure 1), the difference between the positive and neutral SRP condition in rACC/RLPFC activation is related to differences in deactivation level.

**Relationship to depressive symptoms**

Testing the relationship of the rACC activation during negative SRP condition with the degree of depressive symptoms, a significant positive correlation was detected between parameter estimates from the rACC and BDI scores ($r = 0.42$, $P = 0.016$) as well as with the sum score of negative self-referential judgments ($r = 0.39$, $P = 0.019$) as depicted in Figure 2. Parameter estimates drawn from other clusters of the contrast SRP negative vs SRP neutral, e.g. from the PCC or from the RLPCF, were not significantly correlated with BDI scores indicating the specificity of the relationship between rACC activation and depressive symptoms.

**Effects of SRP on brain activation during the Stroop task**

When testing the effect of prior presentation of negative SRP items on brain activation during Stroop task performance, we observed a significant main effect of VALENCE (negative vs neutral SRP) in the left rACC (BA 32, $x = -14$, $y = 39$, $z = 4$, $t = 4.91$ and $k = 62$), in PCC (BA 31, $x = 0$, $y = -53$, $z = 27$, $t = 3.97$ and $k = 253$), in the right inferior frontal gyrus (BA 47, $x = 36$, $y = 9$, $z = -17$, $t = 3.82$ and $k = 30$) and in the right precentral gyrus (BA 6, $x = 55$, $y = -3$, $z = -11$, $t = 3.89$ and $k = 31$) as illustrated in Figure 3. Only the activation in the rACC survived the FWE correction ($P < 0.05$) for multiple comparisons after applying the mask image of the whole cingulate cortex as well as across the whole brain. A significant TASK (congruent vs incongruent) by VALENCE (negative vs neutral SRP) interaction was only observed in the right STG (BA 21, $x = 56$, $y = -14$, $z = -1$, $t = 3.85$ and $k = 38$).

Comparing both Stroop conditions after presentation of positive and negative SRP items, significantly higher Stroop task activations were detected in the left insula (BA 13, $x = -30$, $y = 6$, $z = 5$, $t = 3.72$, $k = 33$) after positive SRP items and significantly higher Stroop task activation in the left STG (BA 21, $x = -48$, $y = -25$, $z = -4$, $t = 4.19$, $k = 29$) after negative SRP items.

A significant TASK $\times$ VALENCE (negative vs positive) interaction was observed resulting predominantly in activations of ACC as well as bilaterally of the ventrolateral and RLPCF as depicted in Figure 4 and Table 2. The ACC activations passed the correction for multiple comparisons ($P < 0.05$) using the mask image of the cingulate cortex. This comparison indicates a BOLD signal increase from the congruent to incongruent condition after negative SRP condition in contrast to BOLD signal decrease from the incongruent to congruent condition after positive SRP condition (Figure 4). The opposite interaction contrast revealed no significant voxels.

**Functional connectivity: PPI analysis**

In order to examine the main hypothesis of the interfering effect of enhanced rACC activity during negative SRP on cognitive control brain areas, the PPI analysis revealed that during Stroop task performance rACC activity significantly interacted with predominantly left fronto-cingulate brain regions, i.e. with the dorsal ACC and the Ventrolateral Prefrontal Cortex (VLPCF) as well as with the left temporal and occipital gyrus in dependence on the VALENCE (negative vs neutral) of SRP before Stroop task presentation (Figure 5 and Table 3). The Dorsal Anterior Cingulate Cortex (dACC) cluster survived the cluster-level correction for multiple comparisons (FWE, $P < 0.05$) after masking with the whole cingulate cortex, although there was only a trend (FWE, $P = 0.06$) for FWE corrected statistical significance on the voxel-wise level.

### Table 1

<table>
<thead>
<tr>
<th>Region of activation</th>
<th>Right/Left</th>
<th>Brodmann’s area</th>
<th>Cluster size</th>
<th>Talairach coordinate</th>
<th>$t$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processing of positive SRP items &gt; neutral SRP items</td>
<td></td>
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<tr>
<td>Superior parietal lobe/precuneus</td>
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$^a$FDR cluster level corrected.

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Fig. 3  Brain regions showing significant BOLD signal difference comparing both Stroop conditions after presentation of negative vs neutral SRP statements (main effect of valence for Stroop task; \( P < 0.001 \) uncorrected, cluster threshold according to the expected number of voxels per cluster). The lower bar graph separately displays parameter estimates from the rACC cluster for both groups of healthy subjects split according to the median BDI value (BDI = 4). The error bars represent standard error of the mean.

Fig. 4  Brain regions showing significant BOLD signal in the TASK (incongruent vs congruent Stroop conditions) by VALENCE (presentation after negative vs positive SRP items) interaction (\( P < 0.001 \) uncorrected, cluster threshold according to the expected number of voxels per cluster). The error bars represent standard error of the mean.
Table 2  Maxima of regions showing significant ($P < 0.001$ uncorrected, cluster threshold according to the expected number of voxels per cluster) significant BOLD signal in the TASK (congruent vs incongruent Stroop conditions) by VALENCE (presentation after negative vs positive SRP items) interaction.

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$^a$FDR cluster level corrected.

SRP in healthy subject

SRP was defined in this study as a concept, in which affective and non-affective information referring to oneself is processed and a decision is made regarding oneself. The majority of studies investigating self-referential processes compared self- with other-referential stimuli and found evidence for strong involvement of cortical midline structures, i.e. PCC, ventromedial (VMPFC, overlapping with rACC) and dorsomedial PFC (DMPFC) during processing of self-related information (Northoff et al., 2006; van der Meer et al., 2010). For example, Johnson et al. (2002) compared judgments about one’s own abilities, traits and attitudes to a semantic judgment task. The self-referential condition was associated with activation in VMPFC, DMPFC and PCC relative to the control condition. D’Argembeau et al. (2005) observed that VMPFC was more active during the self-referential than during other reflective tasks. A more differentiated view on brain structures involved in self- vs other-referential processing was reported in a recent review of van der Meer et al. (2010). The authors included 20 PET or fMRI studies on SRP into a meta-analysis and observed that the rACC was a key structure in processing self-related in contrast to other-related stimuli. The authors further suggested that rACC might be strongly involved in processing of affective self-relevant information. Moreover, according to this meta-analysis, brain activation in DMPFC and PCC did not seem to be specific for distinguishing self- vs other-reflection processes. DMPFC may be important in the cognitive evaluation of the self-relatedness of a stimulus, whereas PCC may be responsible for the integration of autobiographical information regarding the ‘self’. However, only very few studies explicitly investigated neurofunctional differences as a function of affective and non-affective self-relevant processing. Thus, by comparing self-referential statements of different valence, present findings extend previous work on SRP pointing out the anterior and posterior cingulate cortices during affective SRP. These results provide further support for the notion that DMPFC activation, which did not differ comparing affective with non-affective self-referential stimuli, may encode the self-relevance of information regardless of the valence. The higher PCC activation during processing of positive and negative SRP stimuli in contrast to neutral statements might be explained by the higher involvement of autobiographical information during processing of affective vs non-affective stimuli.

The new finding is that the rACC was differentially activated depending on the valence of the SRP stimuli. One possible explanation of the enhanced rACC activation during SRP of negative stimuli is that rACC specifically encodes negative valence of self-related stimuli. However, Sharot et al. (2007) reported enhanced rACC activation during processing of positive in contrast to negative future expectations. Moran et al. (2006) did not observe differences in rACC...
between negative and positive self-relevant adjectives. Furthermore, a positive relationship of the degree of rACC activation to depressive symptoms in this study speaks against this narrow interpretation of a specific rACC role in detecting and processing of negative self-relevant information.

**SRP in depressed patients**

A more suitable interpretation might be that rACC activation may reflect the degree of attention binding on self-referential stimuli. This is in accordance with the notion of Northoff et al. (2006), who proposed a continuum of self-relevance and involvement for the VMPFC/rACC in coding the information for self-relevance. Because an emotional component is inherent to self-relevant processing, greater activation of the rACC indicates stronger self-relevance and stronger emotional involvement during processing of negative SRP stimuli. We therefore suggest that in this study the rACC may reflect the degree of subjective salience of self-referential stimuli by assessing emotional and autobiographical information. This is further supported by the positive correlation between the total score of negative SRP judgments, BDI score and rACC activation, indicating a stronger subjective salience of dysfunctional self-relevant depressive statements in subjects with higher manifestation of depressive symptoms. Moreover, this interpretation fits well with the core feature of depressive patients, who are characterized by strong attentional bias toward self and especially toward negative aspects of the self. In this vein, Lemogne et al. (2010) underlined in a recent review the importance of medial prefrontal cortex in enhanced self-focus in patients with MDD and emphasized its putative negative impact on cognitive functions due to aberrant functional connectivity between dorsal and rACC. Furthermore, recent fMRI studies of Grimm et al. (2011) and Cooney et al. (2010) have consistently reported enhanced activation in the rACC due to increased self-focus and ruminative thinking. In addition, using trait words Lemogne et al. (2009) observed in depressed patients increased functional connectivity between the activation cluster in the medial frontal gyrus (near the rACC) and the left DLPFC as well as dACC in the self-judgment condition. This result provides strong evidence for the interaction between the self-referential and the ‘cognitive’ brain network, leading potentially to impaired cognitive performance in depressive patients.

**SRP and the ‘DMN’**

The rACC is a central part of the ‘DMN,’ which contains a set of medially located and interacting brain areas that are tightly functionally connected and distinct from other systems within the brain (Buckner et al., 2008). It was mostly observed to be active during resting states, when mind-wandering occurs and thoughts are directed toward internal processes such as SRP. During cognitive processing of external stimuli, such as visual cues brain region within DMN have been demonstrated to decrease activity. Li et al. (2007) explicitly tested the postulated interplay between DMN and ‘cognitive’ brain network using a go/no-go paradigm. Exploring brain activity on the trials that preceded errors, the authors observed that prior to errors regions within the default network (VMPFC and PCC) showed increased activity. These data suggest that cognitive task performance may be affected when the DMN is active. Although in this study high levels of accuracy were observed during Stroop task performance in all SRP categories, significant differences in RT could be observed after negative SRP stimuli relative to neutral SRP stimuli.

On the brain activation level, a clear impact of enhanced activation in the DMN during processing of negative relative to neutral or positive self-referential stimuli on subsequent activation within the cognitive control network could be demonstrated in the univariate as well as in the functional connectivity analyses. This interfering effect seems to be strongly pronounced in subjects with a higher degree of depressive symptoms. The increased fronto-cingulate activation during Stroop task after negative SRP, as reflected in the results of the univariate task after negative SRP, as reflected in the results of the univariate and PPI analyses, may be the reason for rather moderate Stroop performance differences between single SRP valences.

These findings suggest that the inability to inhibit self-referential processes and to deactivate the DMN might be responsible for the often reported cognitive deficits in depressive patients. As we observed in our recent study (Wagner et al., 2008), volumetric abnormalities in the medial Orbitofrontal Cortex (OFC) might be one major factor influencing the patients’ reduced ability to deactivate the rACC and might be associated with its potentially chronically increased signal.

It should be noted that simple overlapping effect of rACC activation during SRP in terms of sustained activity on BOLD signal during Stroop task can be ruled out since there is a clear task effect with regard to the BOLD signal within the Stroop task after negative SRP condition as well as after single SRP conditions as illustrated in parameter estimates in Figures 4 and 5. Furthermore, BOLD signal in rACC during processing of self-referential stimuli was separable from the fixation baseline as illustrated in parameter estimates in Figure 2.

Moreover, it seems that during the SRP the right rACC tends to be strongly activated than during the Stroop task execution. An interesting question is whether there are functional differences in the rACC with regard to the side of activation. One explanation for the potential side differences in this study may be the choice of the statistical
threshold. Lowering the threshold to $P < 0.005$, we could observe that both the right and the left part of the rACC were activated during processing of the negative vs neutral self-referential statements. Another explanation may be that due to used fMRI resolution (i.e. 2.75 × 2.75 × 2.7 mm$^3$) and data processing strategy (e.g. spatial smoothing with 8 mm FWHM), neural activations in the left and right ACC may become at least partly indistinguishable. Thus, any reliable conclusions about the functional specialization within the left or the right rACC cannot be drawn from this study. This may explain why the majority of previous fMRI studies with depressed patients or with healthy controls using affective stimuli did not report the side of the rACC activation. First indications for potential lateralization differences in the ACC are provided by the study of Lutcke and Frahm (2008) using high-resolution fMRI. Improving the fMRI resolution may be promising to reveal potential differences in emotion regulation between the left and right ACC.

**Interplay between internally and externally focused processes**

Conceptualizing these results, we introduce a differentiation between internally and externally focused processes. According to Lieberman (2007), internally focused processes refer to mental processes that focus on one’s own or another’s mental interior, e.g. thoughts and feelings, whereas externally focused processes refer to mental processes that focus on one’s own or another’s physical and visible features and actions that are perceived through sensory modalities.

Evidence exists for a breakdown of the dynamic interplay between the internally and externally focused processes and the underlying brain circuits in patients with MDD. More precisely, depressed patients seem to have a strong shift in the direction of considerably increased internally focused processes, i.e. a strong shift in attention to the own self and a reduction in attention toward others and environment, which goes along with higher probability of occurrence of SRP and rumination (Joormann and Gotlib, 2008; Nolen-Hoeksema et al., 2008). Previous studies observed that brain regions mainly involved in processing of internally focused information are hyperactive in patients with MDD (Greicius, et al., 2007; Sheline et al., 2009). It was postulated that these brain areas interfere with brain regions mainly involved in processing of externally focused information, leading potentially to cognitive deficits and to difficulties in social relationships. The results of this study provide a model of how internally focused processes may interact with externally focused processes in the brain of MDD patients, emphasizing the crucial role of rACC in mediating these processes.

However, even if these data fit well with previous results in depressed patients, this model is limited by the fact that in this study only healthy subjects were investigated, who do not constitute a sample of individuals vulnerable to Major Depression. For instance, depressed patients are often characterized by structural brain changes in the fronto-cingulate network (Wagner et al., 2008), which we would not expect to observe in healthy subjects. Thus, these results should be viewed with caution regarding the generalization to psychopathology of Major Depression.

It will be therefore important and promising to use the SRP paradigm for investigating the neural basis of increased self-focus in patients with MDD and its direct impact on cognitive processes. Finally, it might be a promising target biomarker for psychotherapeutic or antidepressant response prediction.

**Conflict of Interest**

None declared.