

## THE RESTING BRAIN AND OUR SELF: SELF-RELATEDNESS MODULATES RESTING STATE NEURAL ACTIVITY IN CORTICAL MIDLINE STRUCTURES

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**Abstract**—The resting brain shows high neural activity in various regions, the default-mode network, chief among them the cortical midline structures (CMS). The psychological correlate of high resting state neural activity in CMS remains however unclear though speculatively it has been associated with processing of internally-oriented self-relatedness. We used functional MRI to examine internally-oriented self-relatedness during the resting state period. This was indirectly done by letting subjects perceive emotional pictures followed by a fixation cross; the very same pictures were then rated subjectively according to their degree of self-relatedness in a postscanning session. This allowed us to correlate the picture ratings of self-relatedness with signal changes in the subsequent resting state period, i.e. fixation period. The emotional pictures' degree of self-relatedness parametrically modulated subsequent resting state signal changes in various CMS, including ventro- and dorsomedial prefrontal cortex and posterior cingulate cortex. This modulation could be distinguished from effects of emotion dimensions (e.g. valence, intensity) and evoked effects of self-relatedness during the stimulus period itself the latter being observed rather in subcortical regions, e.g. amygdala, ventral striatum, and tectum. In sum, our findings suggest that resting state neural activity in CMS is parametrically and specifically modulated by the preceding stimulus's degree of self-relatedness. This lends further support to the presumed involvement of these regions in processing internally-oriented self-relatedness as distinguished from externally-oriented self-relatedness. © 2008 IBRO. Published by Elsevier Ltd. All rights reserved.

**Key words:** self, cortical midline structures, subcortical, resting state, fMRI.

Recent observations indicate high neural activity during the resting state in our brain which is interpreted as some kind of intrinsic neural activity; this concerns a specific set

of brain regions, the default-mode network, chief among them the cortical midline structures (CMS) including the medial orbitofrontal cortex (MOFC), ventro- and dorsomedial prefrontal cortex (VMPFC, DMPFC) and the posterior cingulate cortex (PCC) (Raichle et al., 2001; Raichle and Gusnard, 2005; Gusnard and Raichle, 2001; Vincent et al., 2007; Raichle and Snyder, 2007; Fox and Raichle, 2007). The CMS shows high resting state neural activity while demonstrating predominant task-related reductions in signal changes, e.g. negative BOLD responses (NBR), across a broad range of cognitive tasks (Shulman et al., 1997; Raichle et al., 2001; Raichle and Gusnard, 2005; Gusnard and Raichle, 2001; Damoiseaux, 2006). This raises the question for the psychological correlate of high resting state neural activity in CMS. Recent studies demonstrated involvement of the CMS during tasks requiring distinction between self- and non-self-related stimuli (Phan et al., 2002, 2004a; Fossati et al., 2003; Ochsner et al., 2002, 2004; Ochsner and Gross, 2005; Gusnard et al., 2001; Lieberman et al., 2004; Satpute and Lieberman, 2006; D'Argembeau et al., 2005; Gillihan and Farah, 2005; Keenan et al., 2001; Mitchell et al., 2005; Kelley et al., 2002; Schmitz et al., 2004; Schmitz and Johnson, 2006; Vogeley et al., 2004; Christoff et al., 2003; McKiernan et al., 2006; D'Argembeau et al., 2005; Johnson et al., 2002; Moran et al., 2006; Macrae et al., 2004, see Northoff and Bermpohl, 2004; Northoff et al., 2006 for reviews). The origin of neural activity in CMS during self-related processing remains however unclear. Either CMS neural activity is directly evoked by the degree of self-relatedness of external stimuli and is thus visible during the presentation of external stimuli, in which case one may speak of externally-oriented self-relatedness, or CMS neural activity represents an intrinsic resting state activity related to rather internally oriented self-related processes, reflecting a surveillance of internal states such as emotional responses. More specifically, internal stimuli like those from one's body and cognitions may also be present during the resting state period and may possibly account for high resting state activity (see Northoff et al., 2006; Wicker et al., 2003). This however raises the question of how these internally-oriented stimuli with a high degree of self-relatedness are linked to external stimuli with different degrees of self-relatedness. One possible way would be that resting state neural activity during internal stimuli is modulated by the neural activity induced by external stimuli and their respective degree of self-relatedness. In this case CMS neural activity could be indirectly modulated but would not be directly induced by the degree of self-relatedness of exter-

\*Corresponding author. Tel: +49-391-6714234; fax: +49-391-6715223. E-mail address: georg.northoff@medizin.uni-magdeburg.de (G. Northoff). Abbreviations: CMS, cortical midline structure; DMPFC, dorsomedial prefrontal cortex; fMRI, functional magnetic resonance imaging; MOFC, medial orbitofrontal cortex; PCC, posterior cingulate cortex; VMPFC, ventromedial prefrontal cortex.

nal stimuli; one would then expect that the stimulus's degree of self-relatedness modulates CMS signal changes in the subsequent resting state more than in the period of stimulus presentation itself.

A recent PET study by D'Argembeau et al. (2005) demonstrated overlapping activation in the VMPFC during the stimulus period, e.g. while subjects were thinking self-referential thoughts, and resting state. This and other (McKiernan et al., 2006) studies indicate that high resting state neural activity in CMS may correspond to continuous self-related processing. If this holds true, the CMS may be crucially involved in what may be called internally-oriented self-related processing as distinguished from externally-oriented self-relatedness. Implicit self-related processing comprises surveillance of predominantly internal states including both emotional (e.g. bodily) and cognitive (e.g. ruminations) processes without becoming of aware of them as such as resulting also in what is called mind wandering (Mason et al., 2007). While explicit self-related processing refers predominantly to external stimuli, e.g. to the extent to which I relate a certain stimuli to myself resulting in awareness of myself as self, e.g. self-consciousness (Northoff et al., 2006).

Direct empirical support for the association of high CMS resting state neural activity with internally-oriented self-relatedness is however lacking. This may in part be due to the methodological difficulty to register internally oriented self-relatedness during rest without violating and confounding the resting state by task-related activity changes in response to external stimuli. One possible though indirect strategy to escape this dilemma is to investigate the effects of stimulus-related different degrees of self-relatedness on CMS neural activity in the subsequent resting state period. A more or less analogous methodological strategy has recently been successfully employed in investigating the effects of prior cognitive tasks on the resting state networks' functional connectivity (see Waites et al., 2005; Fair et al., 2007; Scheibe et al., 2006). However, the effects of the stimulus's degree of self-relatedness on subsequent resting neural activity remain to be investigated.

The aim of our study was to examine neural activity during internally-oriented self-relatedness. This could be done only indirectly by investigating the effects of externally-oriented and thus stimulus-associated self-relatedness on neural activity in the subsequent resting period. Using functional magnetic resonance imaging (fMRI), subjects perceived emotional pictures whose degree of self-relatedness was evaluated in a postscanning session in order to avoid cognitive confounds during scanning which by themselves may induce changes in resting state neural activity (see Taylor et al., 2003; Grimm et al., 2006; Walter et al., in press). In orientation on subjective ratings, the perceived stimuli were divided into high and low self-related stimuli whose differential effects on signal changes during the subsequent resting state period were investigated. In addition to such categorical analysis, we also investigated parametric modulation of resting state neural activity by the stimulus's degree of self-relatedness. To

exclude confounding effects of emotion dimensions in both analyses, we controlled for emotional intensity and emotional valence. To exclude simple carryover-effects from the stimulus period, e.g. externally-oriented self-related processing, to the resting state, e.g. internally-oriented self-related processing, within the same region, we controlled for effects occurring during the period of stimulus presentation by performing exclusive masking analysis. To control for confounding effects of emotion dimensions like valence and intensity, we performed regression analyses with the subjects' ratings of these emotion dimensions and compared them directly with the effects of the very same pictures' degree of self-relatedness on CMS resting state signal changes.

Our results show that the prior stimulus's degree of self-relatedness modulates subsequent resting state neural activity in CMS regions including VMPFC, DMPFC and PCC. These modulatory effects on internally-oriented self-relatedness could clearly be distinguished from those associated with emotion dimensions and the stimulus period, e.g. externally-oriented self-relatedness. Hence, our results lend support though indirectly to the assumed involvement of CMS resting state neural activity in processing internally-oriented self-relatedness as distinguished from externally-oriented self-relatedness. However, since the relationship between resting state period and self-relatedness could here be investigated only indirectly via modulatory effects from the preceding picture period, we cannot exclude that both internally- and externally-oriented self-relatedness may be processed in CMS. Instead of exclusive relation between internally- and externally-oriented self-relatedness one may assume dynamic balance between both with internally-oriented processing predominating in the resting state and externally-oriented processing during stimulation.

## EXPERIMENTAL PROCEDURES

### Subjects

We investigated 15 female and male subjects (seven females, eight males; age:  $24.4 \pm 2.72$ , mean  $\pm$  S.D., min: 21, max: 31). All were right-handed as assessed by the Edinburgh Inventory for Handedness (Oldfield, 1971). After detailed explanation of the study design and potential risks all subjects gave written informed consent. The study was approved by the institutional review board of the Otto-von-Guericke University of Magdeburg.

### Experimental stimuli and design

Photographs from the International Affective Picture System (University of Florida, Miami Beach, FL) (Lang et al., 1999) were shown to the subjects for a duration of 5 s. Picture sets were counterbalanced across subjects as well as within each subject according to the two categories emotional and neutral. For exact matching procedures see previous work of our group (Northoff et al., 2004; Grimm et al., 2006). The paradigm consisted of eight runs with emotional and neutral pictures. In the respective runs pictures were presented in a randomized order and subjects were instructed to view the pictures passively. An arbitrary button press was requested to assure a constant level of attention during picture viewing. Reaction times from picture onset to button press were measured. At the time of scanning, subjects were not aware

of any post-scanning ratings. Half of the pictures were preceded by an expectancy period with a duration of 4 s, in which the type (emotional or neutral) of the following picture was indicated by a white arrow on a dark background pointing to different directions. An upward pointing arrow was followed by an emotional picture and a downward pointing a neutral picture. The other half of the pictures were presented directly after a fixation cross, which was presented after every picture for 8.5 s and served as a baseline condition and allowed the subjects to recover from the emotional stimulation. The non-pictorial stimuli (arrows, fixation cross) were of equal size, color, and luminance and were centered on a black background. A total of 256 trials were presented in the eight runs. The different types of IAPS pictures and expectancy tasks were pseudorandomized within and across the eight runs. Prior to the experimental session, subjects were familiarized with the paradigm by completing a test run. During fMRI, pictures were projected automatically via a computer and a forward projection system on a screen placed at the end of the subject's gurney. Subjects lay supine in the scanner and viewed the screen through a mirror positioned on the head coil. Subjects were asked to keep their eyes open and fixate the middle of the screen in front of them. They were asked not to move finger, head or body during picture presentation and viewing with the exception of the button press for the response. For this button press the reaction times were measured.

### Behavioral ratings

Subjective ratings of self-relatedness and emotional dimensions (valence, intensity) were made on a visual analog scale ranging from 0 to 9. These ratings were made immediately afterward in a postscanning session in order to avoid cognitive influences during scanning which can confound neural activity during emotional perception (Taylor et al., 2003; Grimm et al., 2006). Self-relatedness was assessed using the question 'How much do I personally associate with or relate to this picture?' (translated from German) and ranged from 'low personal association' (1) to 'high personal association' (9). Subjects were instructed to re-experience the picture with regard to themselves. Rather than evaluating the picture with regard to the distinction between self and non-self, they were instructed to rate the personal association based on the strength of their subjective or personal experience of themselves while viewing the pictures. Prior to beginning the task, the participants were also explicitly asked what they understood by 'personal association' which was then explained in the way the concept was to be used here, i.e. as subjective and experiential (Northoff et al., 2006). This was done to exclude other potential meanings of 'personal association' like for example imagination of oneself in the picture, recollection of associated autobiographical memories, introspection or observation of themselves while viewing the picture, or evaluation of self-relevance. What was most important here was to establish experimental conditions that minimized predominantly cognitive-evaluative tendencies as, for example, might be required by recollection of autobiographical memories, imagination, etc. Since even our post-scanning evaluation with the question 'How much do I personally associate with or relate to this picture?' requires some at least implicit cognitive-evaluative elements, we did not attempt to monitor that psychological dimension during the scanning session itself.

In order to validate ratings of self-relatedness and their relation to emotion dimensions, we tested the very same pictures and ratings in another group of subjects ( $n=13$ ) which will we will here refer to as 'the behavioral control group.' In addition to self-relatedness, we also evaluated experienced emotional valence and intensity states in our subjects. Valence was assessed using the question 'How unpleasant/pleasant is that picture?' and ranged on a continuum from 'negative' to 'positive' on a 1–9 point Likert scale. Emotional intensity was assessed using the question 'How intense is this picture?' and ranged on a continuum from

'low' (1) to 'high' (9) (see Supplementary Fig. 1). Since we did not include a measure of 'dominance' (or 'urgency') in our postscanning ratings, we relied on the given standard IAPS ratings for this dimension. We considered this as justified since our subjects' ratings for emotional valence and intensity did not differ significantly from standard IAPS norms, and the concept of 'dominance' is the most difficult for subjects to understand.

Based on individual subjects' rating, we distinguished between high (7–9 on the visual analog scale), medium (4–6 on the visual analog scale), and low (1–3 on the visual analog scale) categories in our analysis of self-relatedness. We then analyzed ratings of emotional valence and intensity to these same three categories of self-relatedness so that these measures could be inter-related. In sum, we performed ANOVA and post hoc *t*-tests to directly compare ratings of emotion dimensions between the three different categories of self-relatedness. Finally, we performed Pearson product moment correlation analysis of self-relatedness with emotion dimensions.

### fMRI acquisition

Data acquisition was conducted on a 1.5 T General Electric Signa scanner using a standard head coil. Imaging procedures included collection of (a) structural high resolution images (rf-spoiled GRASS sequence 60 slices sagittal, 2.8 mm thickness), (b) T1-weighted anatomic images coplanar with the functional images (23 slices, aligned to the plane connecting the anterior and posterior commissure axis covering the whole head in oblique axial orientation), (c) inversion recovery T1-weighted echo planar images coplanar with the functional images and (d) echo planar functional images sensitive to BOLD contrast (402 sequential acquisitions, 23 slices with 3.125 mm in-plane resolution, 5 mm thickness, 1 mm gap; T2\*-weighted gradient echo sequence: TR 2s, TE 40 ms). The first seven images were discarded due to T1 saturation effects. Subjects were positioned in the scanner and the head was immobilized with foam peaces and a Velcro strip around the forehead. By a mounted mirror on the head coil a screen was visible, on which stimuli were projected using a LCD projector.

### Image analysis

Image processing and statistical analyses were carried out using MATLAB 6.5.1 (The Mathworks Inc., Natick, MA, USA) and SPM2 (statistical parametric mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk>) (Friston et al., 1995) and included realignment, normalization and smoothing. Statistical parametric maps were first generated for baseline after high self-related pictures versus baseline after low self-related pictures for each subject by using a general linear model. Random effects analysis was used to determine each subject's voxel-wise activation in baseline after high self-related (when compared with low self-related) pictures. For the entire group of 15 subjects, significant clusters of activation were determined by using the threshold  $P<0.001$  (uncorrected),  $k>10$ . Partial correlation analysis was conducted along the recommendations by SPM (<http://www.mrc-cbu.cam.ac.uk/Imaging/spm.html>). Individual subject's rating values of self-relatedness, valence and intensity for each picture presented in fMRI were entered as regressors in the design matrix. First, the correlation for each dimension (self-relatedness, valence, intensity) associated with the preceding picture with neural activity of the subsequent baseline period was calculated. This was followed in a second step by direct comparison of self-relatedness with valence and intensity respectively. The level of statistical significance was again set to  $P<0.001$  (uncorrected),  $k>10$ . Correlation curves were extracted from original SPM data. Time courses and bar diagrams using Marsbar program were calculated for high, medium, and low levels of self-relatedness. We then compared signal changes of high–low differences for self-relatedness with those of high–low differences of emotional intensity and the



positive–negative differences of emotional valence. Third, in order to distinguish between effects of self-relatedness on neural activity during the baseline period and those during the picture presentation, we performed exclusive masking analyses as established in SPM2. Specific effects of self-relatedness during the baseline period were calculated by exclusively masking the contrast 'Baseline after High Self pictures>Baseline after Low Self pictures' with the contrast 'Pictures High Self>Pictures Low Self.' While specific effects of self-relatedness during picture presentation were calculated by exclusively masking the contrast 'Picture after High Self pictures>Picture after Low Self pictures' with the contrast 'Baseline High Self>Baseline Low Self.' The level of statistical significance was set in both analyses to  $P<0.001$  (uncorrected),  $k>10$  using a threshold of  $P<0.05$ , uncorrected for the mask image. Please note that masking procedure does not impact on the statistical analysis for the respective contrasts. The masking procedure rather concerns the visualization of the SPM map. Voxels that survived the threshold  $P<0.05$  uncorrected for the mask contrast were not displayed in the figure. Most importantly, no region was excluded a priori by the masking procedure.

## RESULTS

### Behavioral data

We divided postscanning ratings of self-relatedness and emotional intensity into three different categories, high (7–9), medium (4–6), and low (1–3) and, analogously, emotional valence ratings into negative (1–3), neutral (4–6) and positive (7–9) categories. The following values were obtained for self-relatedness: High ( $7.47\pm0.63$ ), medium ( $5.08\pm0.80$ ), and low ( $1.89\pm0.82$ ) (see also Supplementary Fig. 1a). Values were also obtained for emotional intensity (high ( $7.74\pm0.74$ ), medium ( $5.32\pm0.67$ ), and low ( $1.78\pm0.83$ )), and emotional valence (positive ( $7.51\pm0.63$ ), neutral ( $5.13\pm0.82$ ), and negative ( $2.01\pm0.82$ )).  $t$ -Tests revealed significantly higher emotional intensity in high than in medium ( $df=27$ ,  $t=4.62$ ,  $P<0.05$ ) and low ( $df=27$ ,  $t=9.58$ ,  $P<0.05$ ) self-related pictures (see Supplementary Fig. 1 for validation of self-relatedness ratings in a control group). Furthermore, high self-related pictures were significantly ( $df=28$ ,  $t=3.09$ ,  $P<0.05$ ) more associated with positive emotional valence ratings ( $5.57\pm1.23$ ) than with negative emotional valence (1–3) ( $3.94\pm1.64$ ). In order to further investigate the relationship of self-relatedness with emotion dimensions, we correlated self-relatedness ratings with those of emotion dimensions using Pearson product moment correlation. We obtained significant correlation of self-relatedness with emotional intensity ( $r=0.76$ ,  $t=16.19$ ,  $P<0.001$ ) but no significant correlation with emotional valence ( $r=0.22$ ,  $t=3.61$ ,  $P>0.05$ ). In order to further support these behavioral data on self-relatedness and emotion dimensions, we conducted the same evaluations with the same pictures in another group of subjects, 13 healthy subjects, and observed similar patterns of self-relatedness ratings and their association with emotion dimensions (see Supplementary Fig. 1).

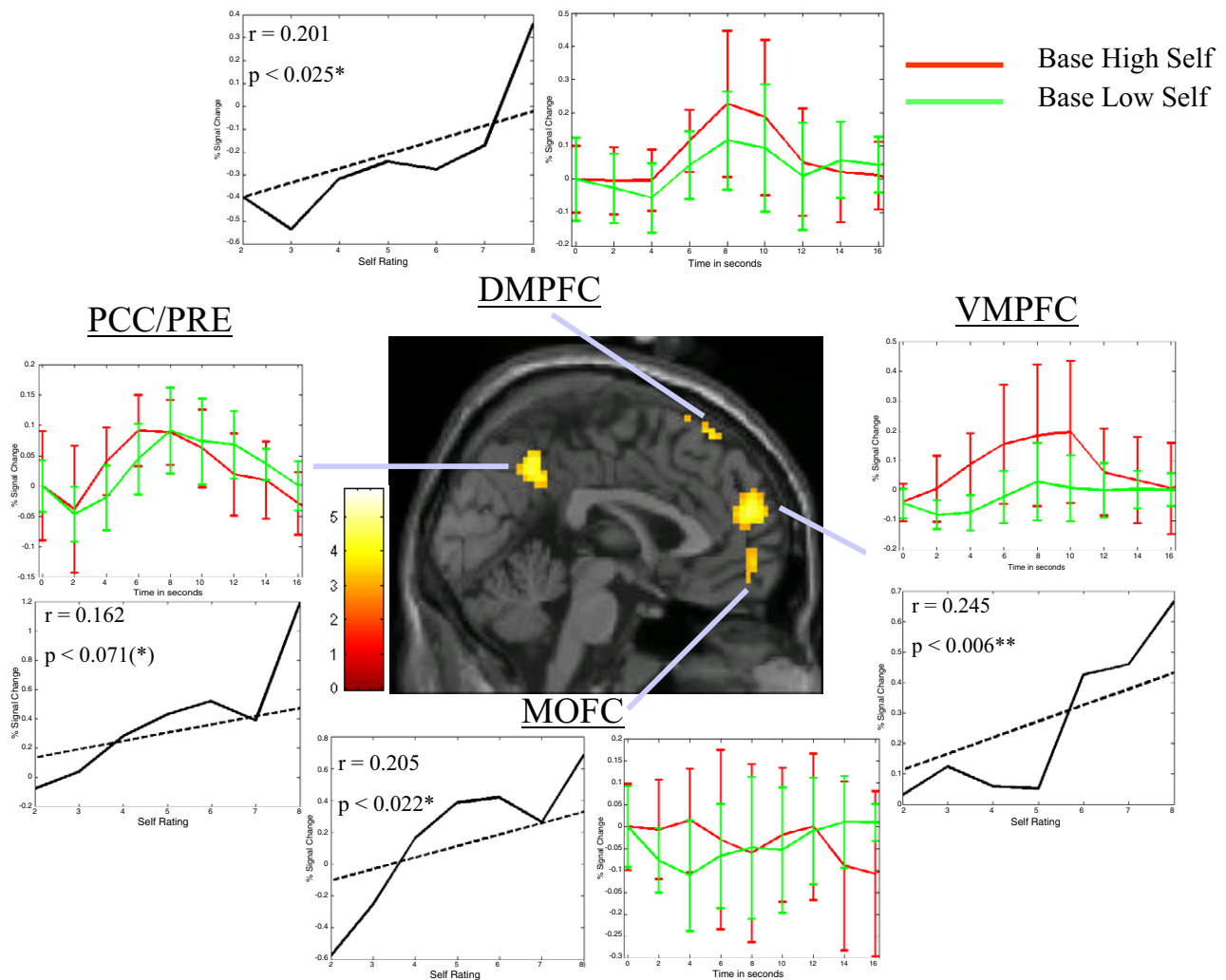
Reaction times (means $\pm$ S.D.) in the scanner, as calculated from an arbitrary button click to ensure vigilance, for all pictures was  $845\pm278$  ms. ANOVA ( $F=0.009$ ,  $P>0.05$ ) revealed no significant difference in reaction times between high ( $785\pm262$  ms), medium ( $845\pm272$  ms) and low ( $857\pm332$ ) self-related pictures. Reaction

times (means $\pm$ S.D.) were also calculated for high ( $831\pm295$  ms), medium ( $829\pm281$  ms) and low ( $817\pm321$  ms) emotional intensity as well as for high, i.e. more positive ( $819\pm281$ ), medium, i.e. less positive ( $831\pm298$  ms) and low, i.e. not at all positive ( $878\pm311$  ms) valenced pictures which both revealed no significant effects ANOVA (emotional intensity:  $F=0.219$ ,  $P>0.05$ ; emotional valence:  $F=0.131$ ,  $P>0.05$ ). This suggests that no robust differences in vigilance were evident as a function of degree to which pictures were deemed self-related during the course of the study.

### FMRI data

*Effects of stimulus's high and low self-relatedness on resting state signal changes.* We distinguished the baseline periods after high self-related pictures ('Baseline High Self') from the baseline periods following low self-related pictures ('Baseline Low Self'). This allowed us to categorically compare the effects of high- and low-self-related pictures on the subsequent baseline period. Baseline High Self induced significantly stronger signal intensities in the MOFC, the VMPFC, DMPFC and the PCC (adjacent to the precuneus) (and the right lateral posterior parietal cortex and the left anterior insula) compared with Baseline Low Self (see SPM maps and BOLD time courses in Fig. 1 and Table 1). The DMPFC finding is reported with caution, as it is located at the periphery of the prefrontal cortex and we cannot exclude an artifact. However, it should be noted that clusters of activation were projected on the MNI standard brain and extended into the cortex on a lower level of significance. SPM-based parametric regression analysis including postscanning ratings of self-relatedness as regressor yielded the following parametric relationship: The higher signal intensities in MOFC, VMPFC, DMPFC and PCC during the baseline period, the higher subjects rated the preceding pictures' degree of self-relatedness (see correlation curves in Fig. 1). These results indicate that high and low self-related stimuli differentially modulate CMS signal changes in the subsequent baseline period.

*Comparison between effects of stimulus's self-relatedness and emotion dimensions on resting state signal changes.* In order to exclude the effects of emotion dimensions as possible confounds, we directly compared effects of self-relatedness with those of emotion dimensions (valence, intensity) on signal changes in the subsequent baseline period. Self-relatedness correlated significantly stronger with baseline period signal intensities in VMPFC (including pregenual anterior cingulate), DMPFC, PCC and dorsomedial thalamus when compared with emotional intensity (see SPM map in Fig. 2 and Table 1). The very same regions also showed significantly stronger correlation with self-relatedness than with emotional valence. We then calculated the differences in signal percent changes between high and low self, positive and negative valence and high and low intensity and statistically compared these differences with each other. This yielded significantly higher high–low differences for self-relatedness when compared with high–low differences of emotional



**Fig. 1.** Effects of self-relatedness ratings on neural activity during the subsequent baseline period. The SPM maps show the categorical comparison between the baseline periods following high self-related pictures and the baseline periods following low self-related pictures (Base High Self>Base Low Self). The sagittal view depicts the right hemisphere; the threshold of significance is set to  $P<0.001$  (uncorr),  $k>10$ . See below and Table 1 for exact coordinates. BOLD curves (x axis: time locked to baseline onset (t0), y axis: % signal change) are plotted separately for baseline following high (red curve) and low (green curve) self-related pictures. The DMPFC finding is reported with caution, as it is located at the periphery of the prefrontal cortex and we cannot exclude an artifact. However, it should be noted that clusters of activation were projected on the MNI standard brain and extended into the cortex on a lower level of significance. We also plotted the correlation curves between % signal change (y axis) and the degree of self-relatedness (based on visual analog scale ranging from 0 to 9 with the extreme values, 0 and 9, cutoff; x axis); the original data points as obtained by partial correlation analysis and the regression curve are shown. Correlation values are based upon Spearman correlation analysis (\*  $P<0.05$ , \*\*  $P<0.005$ , (\*)  $P<0.05-0.1$ ). Abbreviations and MNI coordinates (x,y,z,Z): DMPFC (close to premotor cortex and BA 8) (−3,24,66,3.09), MOFC (bordering to the VMPFC) (0,57,−6,2.94), VMPFC (bordering to the DMPFC) (−3,57,24,3.74), PCC/PRE=Precuneus (−3,−54,39,3.84). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

intensity and positive–negative difference of emotional valence in the abovementioned regions; i.e. VMPFC, DMPFC, PCC and dorsomedial thalamus (see bar diagrams in Fig. 2). These results indicate that CMS modulation during the baseline period is specifically associated with self-relatedness rather than with emotion dimensions.

*Distinction between stimulus's effects of self-relatedness during the resting state period and those during the stimulus period.* In order to exclude simple carryover-effects from the preceding period of stimulus presentation to the subsequent resting state within the same region, we

exclusively masked the contrast 'Baseline High Self>Baseline Low Self' with the contrast 'Picture High Self>Picture Low Self.' This procedure revealed regional signal changes in VMPFC, DMPFC, PCC (bordering to the precuneus), and left DLPFC (see SPM map and BOLD time courses in Fig. 3a and Table 2). Signal changes in these regions are specifically modulated by self-relatedness in the baseline period as distinguished from effects of self-relatedness during the picture period. These regions showed significantly stronger high–low self differences during the baseline period than during the picture period (see bar diagrams in Fig.

**Table 1.** Modulation of signal changes in the subsequent baseline period by preceding stimulus-related effects of self-relatedness

	Baseline correlated with self-relatedness from preceding picture ( $P<0.001$ , $k\geq 10$ )	Baseline after High Self Picture>Baseline after Low Self Picture ( $P<0.001$ , $k\geq 10$ )	Baseline correlated with self-relatedness from preceding picture>Baseline correlated with Emotional Intensity from preceding picture ( $P<0.001$ , $k\geq 10$ )
Right lateral parietal cortex	4.42 (45–81 12)	4.07 (45–81 9)	
Left lateral parietal cortex	3.50 (–42–81 0)		3.29 (51–72 36)
Left anterior insula	3.91 (–51 18–6)	3.25 (–51 21–9)	
MOFC	3.75 (0 54–15)	2.94 (0 57–6)	
PCC/precuneus		3.84 (–3–54 39)	3.46 (–3–36 42)
VMPFC		3.74 (–3 57 24)	3.13 (3 51 3)
Left dorsolateral prefrontal cortex		3.51 (–39 18 54)	
DMPFC		3.09 (–3 24 66)	3.89 (6 54 42)
Dorsomedial thalamus			3.62 (0 0 0)
Left temporal superior gyrus			3.41 (–54–30 6)
Right temporalis superior gyrus			3.28 (60 3–6)

Shown are the regional coordinates that were obtained in categorical comparison between the baseline periods following high self-related pictures and the baseline periods following low self-related pictures (Base High Self>Base Low Self) by themselves and in comparison to emotional intensity as well as the results for parametric analysis of self-relatedness. Foci were identified with a global height threshold of  $P<0.001$  uncorrected for multiple comparisons and an extent threshold of  $k=10$  voxels. Numbers represent the x, y, z coordinates and the Z-values.

3a). Though this analysis yielded the same regions as demonstrated in Fig. 1, the data described here in Fig. 3a were now able to control for possible carryover effects from the stimulus period to the subsequent resting state period within the same regions, e.g. the CMS.

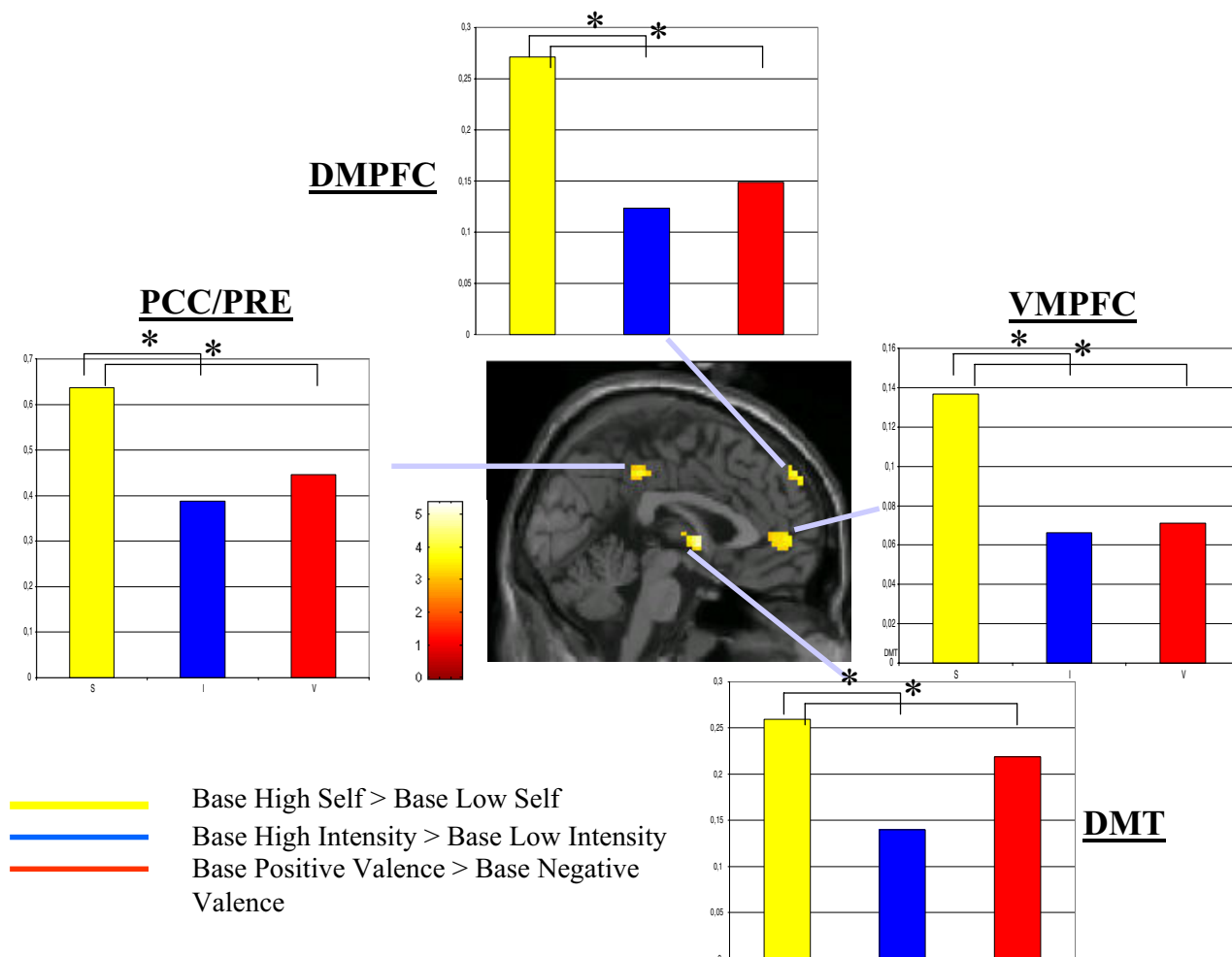
In order to reveal the regions directly associated with stimulus-period-related effects of self-relatedness, we masked the contrast 'Picture High Self>Picture Low Self' with the contrast 'Baseline High Self>Baseline Low Self.' Regions specifically associated with modulation of self-relatedness during the picture period were MOFC, VS/NACC, right amygdala and tectum (see SPM map and BOLD time courses in Fig. 3b and Table 2). These regions showed significantly stronger high–low self differences during the picture period than during the baseline period (see bar diagrams in Fig. 3b). It should be noted that the masking procedure was undertaken for the whole brain and also included the MOFC. We observed MOFC activation when the contrast 'Pictures High Self>Pictures Low Self' was exclusively masked with the contrast 'Baseline after High Self pictures>Baseline after Low Self pictures.' This finding indicates that MOFC activation was present during the picture but not the rest period. Taken together, these results indicate differential involvement of subcortical and cortical regions in self-related processing (except the MOFC) between the actual stimulus period and the subsequent resting state period.

## DISCUSSION

We here demonstrate modulatory effects of stimulus-associated degree of self-relatedness on neural activity in the subsequent resting state in various CMS including the VMPFC, the DMPFC and the PCC. Since the resting state effects of self-relatedness could clearly be distinguished from effects of self-relatedness during the stimulus period and effects of emotion dimensions in both stimulus-period and resting state, our results lend supportive evidence though preliminary to our assumption that high CMS resting

state neural activity modulates predominantly internally-oriented self-relatedness as distinguished from externally-oriented self-relatedness.

Various studies demonstrated that stimuli with high self-relatedness modulate neural activity in CMS during the stimulus period (Phan et al., 2002, 2004a,b; Fossati et al., 2003; Ochsner et al., 2002, 2004; Ochsner and Gross, 2005; Gusnard et al., 2001; Lieberman et al., 2004; Satpute and Lieberman, 2006; Northoff et al., 2006; D'Argembeau et al., 2005; Gillihan and Farah, 2005; Keenan et al., 2001; Mitchell et al., 2005; Kelley et al., 2002; Schmitz et al., 2004; Schmitz and Johnson 2006; Vogeley et al., 2004; Christoff and Gabrieli, 2000; Christoff et al., 2003; McKiernan et al., 2006; Moran et al., 2006; Macrae et al., 2004; Johnson et al., 2002; Ochsner et al., 2004; see Northoff and Bermppohl, 2004 and Northoff et al., 2006 for review). Using PET, D'Argembeau et al. (2005) observed that neural activity in the VMPFC showed common overlapping activation during the stimulus period, e.g. when subjects were instructed to think self-referential thoughts, and the resting state (see also McKiernan et al., 2006). This suggests that the CMS may primarily mediate internally-oriented self-relatedness rather than externally-oriented self-relatedness since otherwise they would not be active in the resting state. Taken together, it therefore remains unclear which aspect of self-relatedness is mediated by the CMS, internally- or externally-oriented self-relatedness. Our results indicate for the first time that the CMS mediate internally-oriented self-relatedness rather than externally-oriented self-relatedness which seems to be mediated rather by subcortical midline regions. One should however keep in mind that these results provide only indirect evidence because of a basic methodological problem, the difficulty of how to register self-relatedness without violating the resting state. One possible strategy to escape this methodological dilemma is to investigate the modulatory effects of prior stimulus-associated self-relatedness on subsequent resting state neural activity and, at

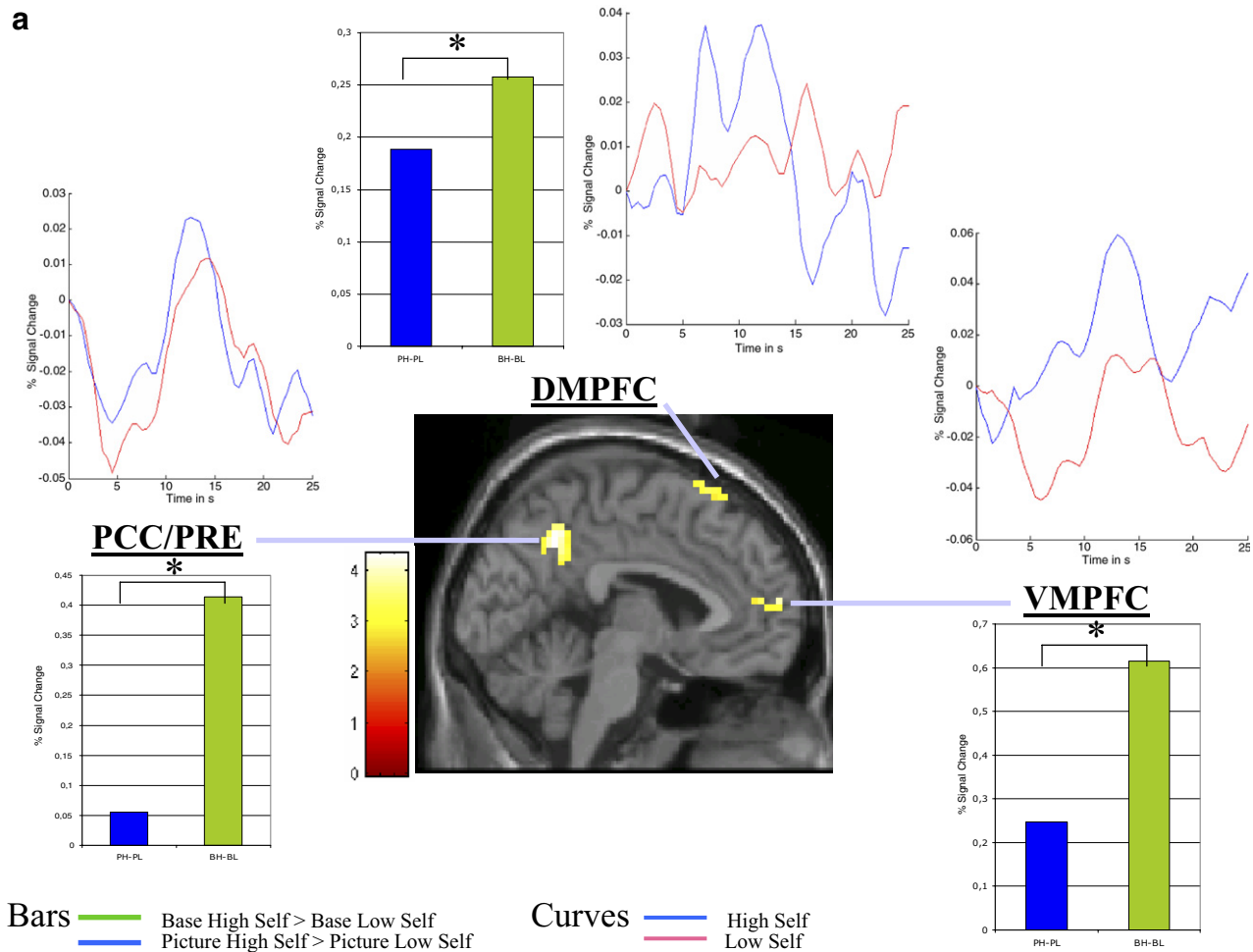


**Fig. 2.** Differential effects between self-relatedness ratings and emotion dimension ratings (valence, intensity) on neural activity during the subsequent baseline period. Based on regression analysis, the SPM map shows the contrast Baseline self-relatedness > Baseline emotional intensity. The sagittal view depicts the right hemisphere; the threshold of significance is set to  $P < 0.001$  (uncorr),  $k > 10$ . See below and Table 1 for exact coordinates. The bar diagrams show the differences in signal percent changes (during baseline period) between high (e.g. positive for emotional valence) and low (e.g. negative for emotional valence) ratings for all three self-relatedness and emotional intensity and valence. Asterisks represent statistically significant differences in signal intensities ( $P < 0.05$ ) between self-relatedness, valence and intensity ratings, e.g. between their respective high–low (e.g. positive–negative for emotional valence) differences. Abbreviations and MNI coordinates (x,y,z,Z): DMPFC (6,54,42,3.89), VMPFC (bordering to the pregenual anterior cingulate cortex) (3,51,3,3.13), PCC/PRE=Precuneus (–3,–36,42,3.46), DMT=Dorsomedial thalamus (0,0,0,3.62), L=Left.

the same time, to avoid both cognitive confounds like judgments (see Taylor et al., 2003; Grimm et al., 2006). Moreover, the task during the stimulus period should avoid any cognitive confounds since these may lead to possible carryover-effects from the actual stimulus period to the subsequent resting state period within the same region. Though a more or less analogous strategy has recently been successfully employed in investigating the effects of prior cognitive tasks on resting state network functional connectivity (Waites et al., 2005), effects of the stimulus's degree of self-relatedness on the subsequent resting state neural activity remain to be demonstrated. Pursuing such strategy, we could demonstrate differential signal changes in CMS during the subsequent resting state period following high and low self-related stimuli. Most importantly, these modulatory effects of the preceding stimulus's degree of self-relatedness on subsequent resting state neural

activity could clearly be distinguished from effects of self-relatedness during the stimulus period and effects of emotion dimensions (valence, intensity) in both stimulus-period and resting state. Modulation of resting state neural activity may consequently be considered specific for the preceding stimulus's degree of self-relatedness rather than its emotional valence and intensity. This in turn lends support to the presumed involvement of the CMS in specifically modulating internally-oriented self-relatedness rather than externally-oriented self-relatedness. One should however be careful in assuming exclusive internally-oriented self-related processing since due to the indirect nature of our investigation, we cannot exclude that resting state modulation may also reflect dynamic balance between internally-externally-oriented self-related processing. Hence, further investigation of the relationship between internal and external self-relatedness is necessary.





**Fig. 3.** Regionally specific effects of self-relatedness on neural activity in the baseline period (a) and picture period (b). (3a) Specific effects of self-relatedness on neural activity during the baseline period controlled for effects of the preceding picture period. The images show regional signal changes that were elucidated by exclusively masking the contrast 'Baseline High Self>Baseline Low Self' with the contrast 'Picture High Self>Picture Low Self.' These regions show specific modulation of self-relatedness during the baseline period controlled for possible carryover effects from the preceding stimulus period within the same regions (which distinguishes this figure from Fig. 1 where we did not yet control for possible carryover effects). The sagittal view depicts the left hemisphere; the threshold of significance is set to  $P < 0.001$  (uncorr),  $k > 10$ . For the mask we set the level of significance to  $P < 0.05$  (uncorr),  $k > 10$ . See below and Table 2 for exact coordinates. The BOLD curves (x axis: time, y axis: % signal change) represent the curves for high (blue) and low (red) self-relatedness in those regions that were revealed in the above described exclusive masking analysis. Note that the BOLD curves are time-locked to the onset of the picture (0–4 s) rather than to the onset of the baseline, e.g. the fixation cross (from 4 s on). Bar diagrams show the high–low self differences in % signal change for the contrasts 'Picture High Self>Picture Low Self' (blue) and 'Base High Self>Base Low Self' (green) for the very same regions. Asterisks represent statistically significant differences ( $P < 0.05$ ) of the high–low self differences between the stimulus period and the baseline period. Abbreviations and MNI coordinates (x,y,z,Z): DMPFC (–6,24,69,3.20), VMFPC (–6,60,18,3.74), PCC/PRE=Precuneus (–3,–54,42,3.76). (3b) Specific effects of self-relatedness on neural activity during the picture period controlled for effects of the preceding baseline period. The images show regional signal changes that were elucidated by exclusively masking the contrast 'Picture High Self>Picture Low Self' with the contrast 'Base High Self>Base Low Self.' These regions show specific modulation of self-relatedness during the picture period. The sagittal view depicts the right hemisphere; the threshold of significance is set to  $P < 0.001$  (uncorr),  $k > 10$ . For the mask we set the level of significance to  $P < 0.05$  (uncorr),  $k > 10$ . See below and Table 2 for exact coordinates. The BOLD curves (x axis: time, y axis: % signal change) represent the curves for high (blue) and low (red) self-relatedness in those regions that were revealed in the above-described exclusive masking analysis. Note that the BOLD curves are time-locked to the onset of the picture (0–4 s) rather than to the onset of the baseline, e.g. the fixation cross (from 4 s on). Bar diagrams show the high–low self differences in % signal change for the contrasts 'Picture High Self>Picture Low Self' (blue) and 'Base High Self>Base Low Self' (green) for the very same regions. Asterisks represent statistically significant differences ( $P < 0.05$ ) of the high–low self differences between the picture period and the baseline period. Abbreviations and MNI coordinates (x,y,z,Z): MOFC (3,45,–12,3.66), VS/NACC=ventral striatum/nucleus accumbens (–6,–21,15,2.88), TECT=tectum (9,–30,–18,3.24), RAMY=right amygdala (18,–9,–15,2.86). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

Though our results indicate involvement of CMS resting state neural activity in internally-oriented self-relatedness, the exact mechanisms of such modulation remain unclear. Recent investigations (Fransson, 2005, 2006; Fox et al., 2005; Laufs et al., 2003) observed continuous signal fluctuations in

CMS during the resting state. Following our results, one may hypothesize that these CMS resting state signal fluctuations may be specifically modulated by the interaction of externally-oriented self-relatedness with internally-oriented self-relatedness. This however remains speculative and raises the ques-



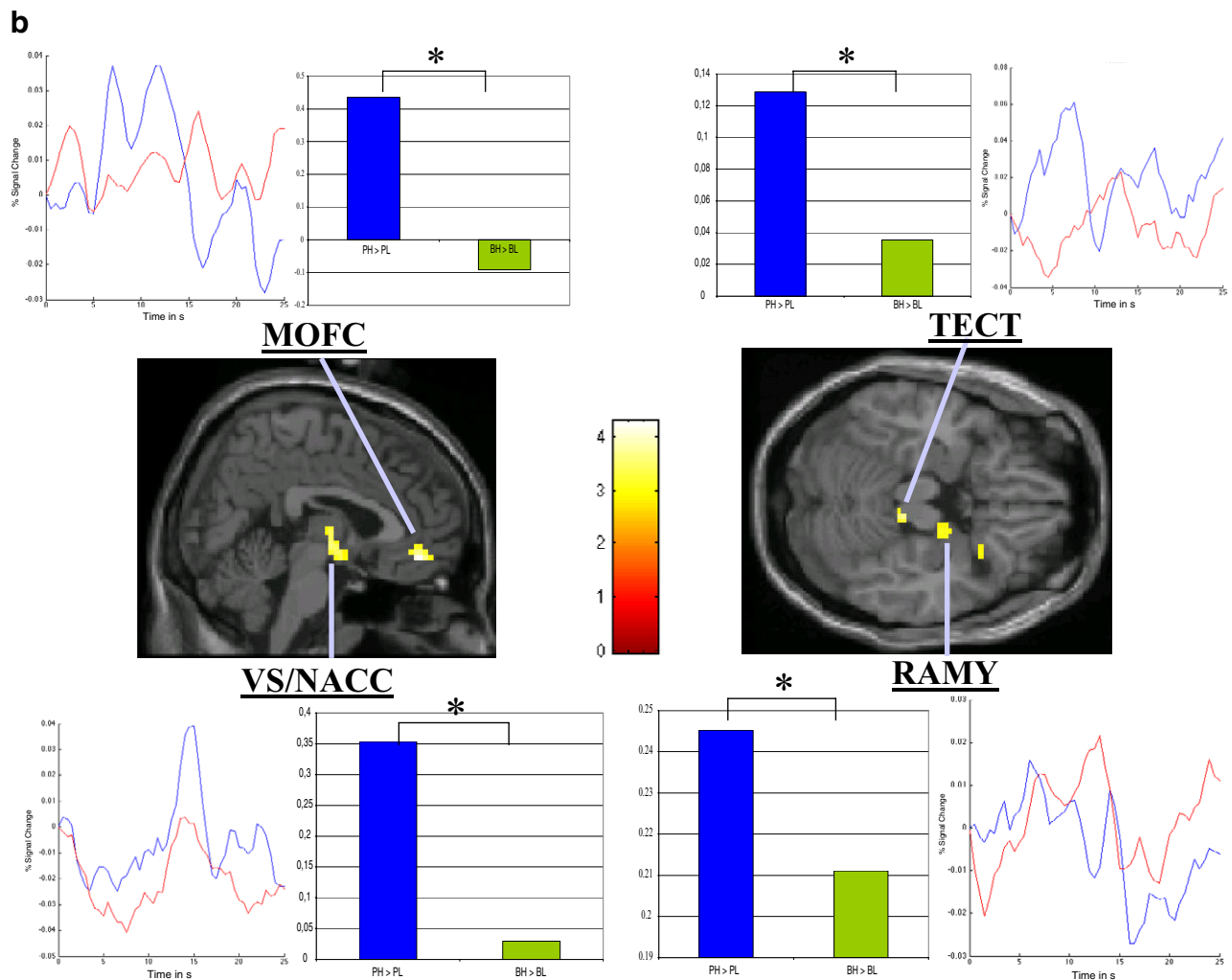


Fig. 3. (Continued).

tion for the neuronal mechanisms by means of which an external stimulus modulates intrinsic signal fluctuations in CMS. One possible neuronal mechanism how the stimulus's externally-oriented degree of self-relatedness might modulate resting state neural activity and thus internally-oriented self-relatedness could be by delaying stimulus-related neuronal activity. Such delayed neural activity changes would then, given the sluggishness of the BOLD response, extend and be measurable in the time period following the stimulus itself, e.g. the resting state period. In other terms, our observation of CMS resting state modulation by the stimulus's degree of self-relatedness could simply represent delayed or, more precisely, slowly occurring stimulus-related neural activity in these regions. This would be well in accordance with our observation of the late peak in BOLD curves at around 8–12 s in CMS in the resting state period rather than, as usual (and as observed in subcortical regions) peaking between 4 and 6 s. This suggests that the observed resting state modulation may not be attributed to the resting state itself, e.g. to internally-oriented self-relatedness, exclusively but rather to the CMS and their possible delayed neural reactivity with regard to the modulation of internally-oriented

by externally-oriented self-relatedness. To further investigate this hypothesis of delayed CMS neuronal reactivity and its specific association with the interaction between internally- and externally oriented self-relatedness, different designs using a more refined temporal differentiation between prior stimulus and subsequent resting period would be necessary.

In contrast to its effects on CMS neuronal activity during the resting state period, self-relatedness affected neural activity during the stimulus period rather in subcortical regions like the tectum, VS/NACC, and right amygdala (and the MOFC; see below for discussion). This is in accordance with previous studies implicating these regions in parametric modulation of self-relatedness during the stimulus period (Phan et al., 2004b; Northoff et al., *in press*). Our findings extend these observations by showing that self-relatedness modulates subcortical activity specifically during the stimulus period itself rather than during the subsequent resting state period. We consequently assume that subcortical regions mediate effects of self-relatedness during the presence of the actual stimulus itself thus reflecting what is called externally-oriented self-relatedness. Our observation of the clear temporal distinction between subcortical and cortical neural activity

**Table 2.** Differential effects of stimulus-related effects of self-relatedness on signal changes during the stimulus, e.g., picture period and the subsequent baseline, e.g., resting state, period

	Specific Baseline Self: Baseline High Self>Baseline Low Self (masked [excl.] by Picture High Self>Picture Low Self at $P=0.05$ ) ( $P<0.001$ , $k\geq 10$ )	Specific Picture Self: Picture High Self>Picture Low Self (masked [excl.] by Baseline High Self>Baseline Low Self at $P=0.05$ ) ( $P<0.001$ , $k\geq 10$ )
PCC/precuneus	3.76 (–3–54 42)	
VMPFC	3.74 (–6 60 18)	
DMPFC	3.20 (–6 24 69)	
Left dorsolateral prefrontal cortex	3.17 (–33 18 60)	
Left lateral prefrontal cortex	2.79 (–54 15 9)	
Left lateral parietal cortex	2.93 (–36–72 39)	
Right lateral parietal cortex		3.72 (48–69 0)
MOFC		3.66 (3 45–12)
Right lateral premotor cortex		3.29 (48–6 60)
Tectum/dorsal midbrain		3.24 (9–30–18)
Right amygdala/parahippocampal gyrus		2.86 (18–9–15)
Right superior temporal gyrus		3.17 (36 21–24)
Dorsomedial thalamus		3.19 (–3–15 6)
Ventral striatum/nucleus accumbens		2.88 (–6–21 15)

Differential effects of self-relatedness ratings on neural activity during the picture and subsequent baseline period. The table shows regional coordinates that were elucidated by exclusively masking the contrast 'Baseline High Self>Baseline Low Self' with the contrast 'Picture High Self>Picture Low Self.' These regions show specific, i.e., picture period independent, modulation of self-relatedness during the baseline period. In addition, the reverse is also shown, the regional coordinates that were elucidated by exclusively masking the contrast 'Picture High Self>Picture Low Self' with the contrast 'Base High Self>Base Low Self.' These regions show specific modulation of self-relatedness during the picture period. Foci were identified with a global height threshold of  $P<0.001$  uncorrected for multiple comparisons and an extent threshold of  $k=10$  voxels. Numbers represent the x, y, z coordinates and the Z-values.

changes might indicate that both subcortical and cortical mid-line networks may code distinct aspect of self-relatedness. Modulation of self-relatedness in subcortical regions during the stimulus period might signal the processing of the external stimulus's degree of self-relatedness, i.e. externally-oriented self-relatedness. This is supported by the fact that these subcortical regions have also been observed in previous studies on the self that directly relied on the stimulus properties (Phan et al., 2004a,b; de Greck et al., 2008; Northoff et al., in press) rather than on some cognitive task like judgment and evaluation, while the delayed neural activity changes in CMS might mirror the modulation of internally-oriented self-related processing in the resting state, as possibly represented by high CMS resting state neural activity, by the externally-oriented self-relatedness of the preceding stimulus.

How are these two aspects of self-relatedness, internally- and externally-oriented self-relatedness, linked together? Based on our data, one might speculate that the MOFC, that showed self-relatedness dependent neural activity changes in both stimulus and resting periods, might represent the neural link between internally- and externally-oriented self-relatedness. This would not only be in accordance with our results but also with the connectivity pattern of this region, a so-called convergence zone (Rolls et al., 1999), that receives numerous afferences from subcortical regions, where external stimuli are processed, and sends efferences to the other CMS where apparently internally-oriented self-relatedness may be represented. However, future studies employing designs that allow for temporal and psychological distinction between these aspects of self-related processing, e.g. internally- and externally-oriented self-relatedness, would be necessary to lend further support to this rather speculative hy-

pothesis. Another region that seems to show some peculiarities is the PCC where we could not find as clear-cut differentiation between high and low-self-relatedness during the resting state period as in the other regions, i.e. the anterior CMS. Due to their tight connections with the hippocampus, the PCC and the RSC have been implicated in episodic and autobiographical memory particularly in retrieving of these memories. Autobiographical memory retrieval may have also been present in the resting state period as induced and triggered by the preceding stimulus so that the PCC and the RSC may possibly account for integrating self-relatedness and autobiographical memory (see also Northoff et al., 2006). In contrast, the anterior CMS regions might be more involved in representing and monitoring self-relatedness be it internally- or externally-oriented. However, the possible different functional roles of the different CMS regions need to be addressed in future studies that for instance investigate the functional and temporal relationship between self-relatedness and autobiographical memory retrieval.

Some methodological issues should be mentioned. One problem consists in the baseline period. We presented a fixation cross which eventually may induce some neural activity by itself due to visual-cognitive processing so that our baseline period may not have mirrored a true resting state. Future studies may apply different baseline conditions with and without fixation cross. Another problem concerns the possibility of sustained activation. One may, for example, assume stimulus-dependent transient activation in subcortical regions while CMS regions may rather show sustained activation. What appears as baseline modulation may then be nothing but sustained activation originating in stimulus presentation and overlapping to the

baseline period, e.g. carryover effects. Sustained activation may, for instance, be assumed in the MOFC which may explain its occurrence in both resting state period and picture-period effect of self-relatedness. However, sustained activation can be excluded for VMPFC, DMPFC, PCC, and left DLPFC, since activation in these regions survived conservative exclusive masking with the contrast 'Picture High Self>Picture Low Self.' To control for overlapping of hemodynamic responses we separately modeled the periods of picture presentation and baseline in the SPM-analysis. By this means, we aimed to separate the temporal profiles of both. This has been shown for presentation times shorter than 2 s (Miezin et al., 2000; Friston et al., 1998). However, it cannot be excluded that the decorrelation only succeeded partially. A third problem is that, psychologically, high resting state neural activity might reflect random task-unrelated emotions (and cognitions) rather than a specific psychological process like self-related processing. Though we cannot completely exclude such random activity, the strong effects of self-relatedness on the subsequent resting state when compared with those of the emotion dimensions would argue against the assumption of at least totally random neural activity. Another option might be the process of mind-wandering which as recently demonstrated (Mason et al., 2007) also recruits cortical midline regions. Based on our results we would argue though rather speculatively that mind wandering is possible only on the basis of self-relatedness, e.g. implicit self-related processing. For that to be demonstrated, future studies might want to directly compare mind wandering and self-relatedness with regard to intero- and exteroceptive stimuli. Taken together, our data lead us to assume that the exteroceptive stimuli degrees of self-relatedness modulate neural activity in different regions of the subcortical–cortical midline network (subcortical, medial orbitofrontal, medial frontal and posterior) in different ways, e.g. immediate, sustained, and delayed. Furthermore, our data suggest that at least delayed modulation in CMS by self-relatedness may in part depend on the resting state or intrinsic neural activity in these regions and thus on the presumed internally-oriented self-relatedness.

## CONCLUSION

In sum, our data suggest that the prior stimulus's degree of self-relatedness parametrically modulates CMS neural activity in the subsequent resting state. Since such modulation could clearly be distinguished from effects of self-relatedness during the stimulus period and effects of emotion dimensions (valence, intensity) during both stimulus and resting state periods, our results provide indirect and preliminary evidence for involvement of CMS resting state neural activity in internally-oriented self-relatedness. Whereas the stimulus's externally-oriented self-relatedness may rather be processed in subcortical midline regions. Taken together, this lends strong support to the assumption that our brains' subcortical–cortical midline network is critically involved in distinct aspects of self-related processing like externally- and internally-oriented self-relatedness. Both internally- and externally-oriented self-relatedness and their possible inter-

action in MOFC may contribute to constitute, modulate and maintain our sense of self, e.g. what James (1982) called the 'stream of consciousness' and others' like Damasio (2003) and Panksepp (1998) described as 'core or mental self' and its modulation by the actual environment, e.g. the external stimuli's degree of self-relatedness.

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## REFERENCES

- Christoff K, Gabrieli JDE (2000) The frontopolar cortex and human cognition: evidence for a rostrocaudal hierarchical organization within the human prefrontal cortex. *Psychobiology* 28:168–186.
- Christoff K, Ream JM, Geddes LP, Gabrieli JD (2003) Evaluating self-generated information: anterior prefrontal contributions to human cognition. *Behav Neurosci* 117:1161–1168.
- Damasio A (2003) Feelings of emotion and the self. *Ann N Y Acad Sci* 1001:253–261.
- Damoiseaux JS (2006) Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A* 103:13848–13853.
- D'Argembeau A, Collette F, Van der Linden M, Laureys S, Del Fiore G, Degueldre C, Luxen A, Salmon E (2005) Self-referential reflective activity and its relationship with rest: a PET study. *Neuroimage* 25:616–624.
- de Greck M, Rotte M, Paus R, Moritz D, Thiemann R, Proesch U, Bruer U, Moerth S, Tempelmann C, Bogerts C, Northoff G (2008) Is our self based on reward? Self-relatedness recruits neural activity in the reward system. *Neuroimage* 39:2066–2075.
- Fair DA, Schlaggar BL, Cohen AL, Miezin FM, Dosenbach NU, Wenger KK, Fox MD, Snyder AZ, Raichle ME, Petersen SE (2007) A method for using blocked and event-related fMRI data to study "resting state" functional connectivity. *Neuroimage* 35:396–405.
- Fossati P, Hevenor SJ, Graham SJ, Grady C, Keightley ML, Craik F, Mayberg H (2003) In search of the emotional self: an fMRI study using positive and negative emotional words. *Am J Psychiatry* 160:1938–1945.
- Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 8(9):700–711.
- Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005) From The Cover: The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *PNAS* 102:9673–9678.
- Fransson P (2005) Spontaneous low-frequency BOLD signal fluctuations: An fMRI investigation of the resting-state default mode of brain function hypothesis. *Hum Brain Mapp* 26:15–29.
- Fransson P (2006) How default is the default mode of brain function? Further evidence from intrinsic BOLD signal fluctuations. *Neuropsychologia* 44:2836–2845.
- Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R (1998) Event-related fMRI: characterizing differential responses. *Neuroimage* 7:30–40.
- Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ (1995) Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp* 2:189–210.
- Gillihan SJ, Farah MJ (2005) Is self special? A critical review of evidence from experimental psychology and cognitive neuroscience. *Psychol Bull* 131:76–97.
- Grimm S, et al. (2006) Segregated neural representation of distinct emotion dimensions in the prefrontal cortex—an fMRI study. *Neuroimage* 30:325–340.

- Gusnard DA, Akbudak E, Shulman GL, Raichle ME (2001) Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci U S A* 98:4259–4264.
- Gusnard DA, Raichle ME (2001) Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci* 2:685–694.
- James W (1892) *Psychology*. New York: Henry Holt and Company.
- Johnson SC, Baxter LC, Wilder LS, Pipe JG, Heiserman JE, Prigatano GP (2002) Neural correlates of self-reflection. *Brain* 125:1808–1814.
- Keenan JP, Nelson A, O'Connor M, Pascual-Leone A (2001) Self-recognition and the right hemisphere. *Nature* 409:305.
- Kelley WM, Macrae CN, Wyland CL, Caglar S, Inati S, Heatherton TF (2002) Finding the self? An event-related fMRI study. *J Cogn Neurosci* 14:785–794.
- Lang PJ, Bradley MM, Cuthbert BN (1999) International affective picture system (IAPS) James, W (1892). *Psychology*. New York: Henry Holt and Company.
- Laufs H, Krakow K, Sterzer P, Eger E, Beyerle A, Salek-Haddadi A, Kleinschmidt A (2003) Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. *Proc Natl Acad Sci U S A* 100:11053–11058.
- Lieberman MD, Jarcho JM, Satpute AB (2004) Evidence-based and intuition-based self-knowledge: an fMRI study. *J Pers Soc Psychol* 87:421–435.
- Macrae CN, Moran JM, Heatherton TF, Banfield JF, Kelley WM (2004) Medial prefrontal activity predicts memory for self. *Cereb Cortex* 14:647–654.
- Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN (2007) Wandering minds: the default network and stimulus-independent thought. *Science* 315(5810):393–395.
- McKiernan KA, D'Angelo BR, Kaufman JN, Binder JR (2006) Interrupting the "stream of consciousness": an fMRI investigation. *Neuroimage* 29:1185–1191.
- Miezin FM, Maccotta L, Ollinger JM, Petersen SE, Buckner RL (2000) Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *Neuroimage* 11:735–759.
- Mitchell JP, Banaji MR, Macrae CN (2005) General and specific contributions of the medial prefrontal cortex to knowledge about mental states. *Neuroimage* 28:757–762.
- Moran JM, Macrae CN, Heatherton TF, Wyland CL, Kelley WM (2006) Neuroanatomical evidence for distinct cognitive and affective components of self. *J Cogn Neurosci* 18:1586–1594.
- Northoff G, Bermpohl F (2004) Cortical midline structures and the self. *Trends Cogn Sci* 8:102–107.
- Northoff G, Heinzel A, Bermpohl F, Niese R, Pfennig A, Pascual-Leone A, Schlaug G (2004) Reciprocal modulation and attenuation in the prefrontal cortex: an fMRI study on emotional-cognitive interaction. *Hum Brain Mapp* 21:202–212.
- Northoff G, Heinzel A, de Greck M, Bermpohl F, Dobrowolny H, Panksepp J (2006) Self-referential processing in our brain—a meta-analysis of imaging studies on the self. *Neuroimage* 31:440–457.
- Northoff G, Schneider F, Walter M, Bermpohl F, Heinzel A, Tempelmann C, et al. (2007) Differential parametric modulation of self-relatedness and emotions in different brain regions. *Hum Brain Mapp*, in press.
- Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD (2002) Rethinking feelings: an fMRI study of the cognitive regulation of emotion. *J Cogn Neurosci* 14:1215–1229.
- Ochsner KN, Gross JJ (2005) The cognitive control of emotion. *Trends Cogn Sci* 9:242–249.
- Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JD, Gross JJ (2004) For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage* 23:483–499.
- Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9:97–113.
- Panksepp J (1998) *Affective neuroscience: the foundations of human and animal emotions*. New York: Oxford University Press.
- Phan KL, Taylor SF, Welsh RC, Ho SH, Britton JC, Liberzon I (2004a) Neural correlates of individual ratings of emotional salience: a trial-related fMRI study. *Neuroimage* 21:768–780.
- Phan KL, Wager T, Taylor SF, Liberzon I (2002) Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* 16:331–348.
- Phan KL, Wager TD, Taylor SF, Liberzon I (2004b) Functional neuroimaging studies of human emotions. *CNS Spectr* 9:258–266.
- Raichle ME, Gusnard DA (2005) Intrinsic brain activity sets the stage for expression of motivated behavior. *J Comp Neurol* 493:167–176.
- Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. *Proc Natl Acad Sci U S A* 98:676–682.
- Raichle ME, Snyder AZ (2007) A default mode of brain function: a brief history of an evolving idea. *Neuroimage* 37(4):1083–1090.
- Rolls ET, Tovee MJ, Panzeri S (1999) The neurophysiology of backward visual masking: information analysis. *J Cogn Neurosci* 11:300–311.
- Satpute AB, Lieberman MD (2006) Integrating automatic and controlled processes into neurocognitive models of social cognition. *Brain Res* 1079:86–97.
- Scheibe C, Wartenburger I, Wüstenberg T, Kathmann N, Villringer A, Heekeren HR (2006) Neural correlates of the interaction between transient and sustained processes: a mixed blocked/event-related fMRI study. *Hum Brain Mapp* 27:545–551.
- Schmitz TW, Johnson SC (2006) Self-appraisal decisions evoke dissociated dorsal-ventral aMPFC networks. *Neuroimage* 30:1050–1058.
- Schmitz TW, Kawahara-Baccus TN, Johnson SC (2004) Metacognitive evaluation, self-relevance, and the right prefrontal cortex. *Neuroimage* 22:941–947.
- Shulman GL, Corbetta M, Buckner RL, Raichle ME, Fiez JA, Miezin FM, Petersen SE (1997) Top-down modulation of early sensory cortex. *Cereb Cortex* 7:193–206.
- Taylor WD, Steffens DC, McQuoid DR, Payne ME, Lee SH, Lai TJ, Krishnan KR (2003) Smaller orbital frontal cortex volumes associated with functional disability in depressed elders. *Biol Psychiatry* 53:144–149.
- Vincent et al. (2007) Intrinsic functional architecture in the anesthetized monkey brain. *Nature* 447:83–86.
- Vogele K, May M, Ritzl A, Falkai P, Zilles K, Fink GR (2004) Neural correlates of first-person perspective as one constituent of human self-consciousness. *J Cogn Neurosci* 16:817–827.
- Walter M, Matthä C, Wiebking C, Rotte M, Bogerts B, Heinze H-J, Northoff G (2007) Preceding attention and the dorsomedial prefrontal cortex: Process specificity versus domain dependence. *Hum Brain Mapp* Dec 10.
- Waites AB, Stanislavsky A, Abbott DF, Jackson GD (2005) Effect of prior cognitive state on resting state networks measured with functional connectivity. *Hum Brain Mapp* 24:59–68.
- Wicker B, Ruby P, Royet JP, Fonlupt P (2003) A relation between rest and the self in the brain? *Brain Res Brain Res Rev* 43:224–230.

## APPENDIX

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi: [10.1016/j.neuroscience.2008.08.014](https://doi.org/10.1016/j.neuroscience.2008.08.014).