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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.

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-

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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.

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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±2.72, mean±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