

Self-referential processing in our brain—A meta-analysis of imaging studies on the self

Georg Northoff,^{a,b,*} Alexander Heinzl,^c Moritz de Greck,^b Felix BERPpohl,^{a,d}
Henrik Dobrowolny,^b and Jaak Panksepp^e

^aDepartment of Neurology, Harvard University, Cambridge, MA 02138, USA

^bDepartment of Psychiatry at Otto-von-Guericke University of Magdeburg, Germany

^cDepartment of Nuclear Medicine, University of Duesseldorf, Germany

^dDepartment of Psychiatry and Psychotherapy, University Medicine Berlin, Charité Campus Mitte, Germany

^eScience Department of VCAPP, College of Veterinary Medicine, Washington State University, Pullman, WA 99164-6520, USA

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The question of the self has intrigued philosophers and psychologists for a long time. More recently, distinct concepts of self have also been suggested in neuroscience. However, the exact relationship between these concepts and neural processing across different brain regions remains unclear. This article reviews neuroimaging studies comparing neural correlates during processing of stimuli related to the self with those of non-self-referential stimuli. All studies revealed activation in the medial regions of our brains' cortex during self-related stimuli. The activation in these so-called cortical midline structures (CMS) occurred across all functional domains (e.g., verbal, spatial, emotional, and facial). Cluster and factor analyses indicate functional specialization into ventral, dorsal, and posterior CMS remaining independent of domains. Taken together, our results suggest that self-referential processing is mediated by cortical midline structures. Since the CMS are densely and reciprocally connected to subcortical midline regions, we advocate an integrated cortical–subcortical midline system underlying human self. We conclude that self-referential processing in CMS constitutes the core of our self and is critical for elaborating experiential feelings of self, uniting several distinct concepts evident in current neuroscience.

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* Corresponding author. Laboratory of Neuroimaging and Neurophilosophy, Department of Psychiatry, Otto-von-Guericke University of Magdeburg, Leipziger Strasse 44, 39120 Magdeburg, Germany. Fax: +49 391 6715223.

E-mail address: georg.northoff@medizin.uni-magdeburg.de (G. Northoff).

URL: www.nine3.com/gnorthoff/ (G. Northoff).

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Introduction

The question of the self has been one of the most salient problems throughout the history of philosophy and more recently also in psychology (Gallagher, 2000; Gallagher and Frith, 2003; Metzinger and Gallese, 2003; Northoff, 2004). For example, William James distinguished between a physical self, a mental self, and a spiritual self. These distinctions seem to reappear in recent concepts of self as discussed in neuroscience (Panksepp, 1998a,b, 2003, 2005b; Damasio, 1999; Gallagher, 2000; Stuss et al., 2001; Churchland, 2002; Kelley et al., 2002; Lambie and Marcel, 2002; LeDoux, 2002; Turk et al., 2002; Damasio, 2003a,b; Gallagher and Frith, 2003; Keenan et al., 2003; Kircher and David, 2003; Turk et al., 2003; Vogeley and Fink, 2003; Dalgleish, 2004; Marcel and Lambie, 2004; Northoff and BERPpohl, 2004). Damasio (1999) and Panksepp (1998a,b, 2003) suggest a “proto-self” in the sensory and motor domains, respectively, which resembles William James’s description of the physical self. Similarly, what has been described as “minimal self” (Gallagher, 2000; Gallagher and Frith, 2003) or “core or mental self” (Damasio 1999) might correspond more or less to James’ concept of mental self. Finally, Damasio’s (Damasio 1999) “autobiographical self” and Gallagher’s (Gallagher, 2000; Gallagher and Frith, 2003) “narrative self” strongly rely on linking past, present, and future events with some resemblances to James’ spiritual self.

The distinct concepts of self differ in the class of stimuli and their specific material or content reflecting what is called different domains. The “proto-self” refers to the domain of the body, whereas the “autobiographical self” reflects the domain of memory. Other concepts of self like the emotional self (Fossati et al., 2003, 2004), the spatial self (Vogeley and Fink, 2003; Vogeley et al., 2004), the facial self (Keenan et al., 2000, 2001, 2003), the verbal or interpreting self (Turk et al., 2003), and the social self (Frith and Frith, 1999, 2003) refer to further domains.

What remains unclear, however, is what unites these distinct concepts of self allowing us to speak of a self in all cases. In this article, we assume that processing of stimuli as self-referential, self-referential processing, is common to the distinct concepts of self in the different domains. This has also been described as ‘self-related’ or ‘self-relevant’ processing (Craig and Hay, 1999; Kelley et al., 2002; Schore, 2003; Turk et al., 2003; Northoff and Bermpohl, 2004; Phan et al., 2004a,b). Self-referential processing concerns stimuli that are experienced as strongly related to one’s own person. Typical examples are the way we perceive pictures of ourselves or close friends versus pictures of completely unknown people or pictures of our houses where we spent our childhood versus pictures of any unknown house, etc. Such comparisons are possible in different sensory modalities. Without going deeply into abstract philosophical considerations, we would like to give a brief theoretical description of what we mean by the terms ‘experience’, ‘strongly related’, and ‘to one’s person’. ‘Experience’ refers to phenomenal experience such as, for example, the feeling of love, the smell of a rose, or the feeling of mineness. Thus, we focus on the subjective aspect of experience that is described as the “phenomenal aspect” (Block, 1996; Chalmers, 1996). The subjective aspect of experience as prereflective is often distinguished from its reflective or cognitive aspects (see also Fig. 5). The latter refer to veridical information processing and objective reasoning. Being in love from that point of view refers to psychological questions concerning motivation and causes for the emotional state (Block, 1996; Chalmers, 1996). Our definition of self-referential processing by experience implies a focus on the implicit, subjective, and phenomenal aspects (to feel or experience self-referential stimuli) what Kircher and David (2003) call “self-qualia” and Zahavi (2003) describe as “prereflective” (Legrand, 2003; Gallagher and Zahavi, 2005; Legrand, 2005), whereas our focus is less on associated cognitive and reflective functions (see also Fig. 5) allowing to make it explicit (to know about or to be aware of stimuli as self-referential). As such, we distinguish self-referential processing also from what is commonly called “insight” which we consider to presuppose cognitive and reflective functions rather than simply pure subjective and phenomenal aspects (Kircher and David, 2003).

The term ‘strongly related’ points out the process of associating and linking intero- and exteroceptive stimuli with a particular person. The main feature here is not the distinction between diverse sensory modalities but rather the linkage of the different stimuli to the individual person, i.e., to its self. What unifies and categorizes stimuli in this regard is no longer their sensory origin but the strength of their relation to the self (this is what Kircher and David (2003) call ‘ipseity’). The more the respective stimulus is associated with the person’s sense of belongingness, the more strongly it can be related to the self. We assume that the strength of the self-stimulus relation cannot be determined in absolute terms but only relatively since it depends on the respective context (which includes autobiographical, social, spatial, and various other factors). The process of relating stimuli to the self can thus not be considered an isolated process but rather an embedded process that depends on the respective environmental context (Clark, 1999; Northoff, 2004). The self-stimulus relation results in what has been called “mineness”. Lambie and Marcel (2002) speak of an “addition of the ‘for me’” by means of which that particular stimulus becomes “mine” resulting in “mineness” (Metzinger, 2003).

The self is usually characterized by a more intense emotional subjectivity which points out that stimuli are considered in more value-laden ways. When objects and events are viewed through the

‘eyes’ of the self, stimuli are no longer simply objective aspects of the world, but they typically become emotionally colored, and thereby more intimately, related to one’s sense of self. Another feature of the self is that it is characterized in relation to both physical and psychological stimuli. Physical stimuli include those from one’s own body such as face, arms, interoceptive bodily functions, etc., whereas psychological stimuli encompass propositional knowledge about one’s self including episodic memories as well as more subtle evaluations such as perspectives on one’s body image, worthiness, etc. (Gillihan and Farah, 2005). Psychological self-referential stimuli were, for example, investigated by Kelley et al. (2002) in a trait adjective judgment task. In that study, participants were asked to judge trait adjectives (for example, ‘polite’) as to whether they properly described the participants themselves (self-referential), the current U.S. President (other-referential), or a given case (case-referential). Self-referential processing might not only concern verbal stimuli but also those from other psychological or physical domains like for example autobiographical, emotional, motor, and facial stimuli.

Finally, we do not necessarily wish to imply that the reflective self constitutes a substantial material entity; there may even be no fixed entity behind the continuously ongoing self-referential processing what James called the “stream of thought” (James, 1892). Instead, here, we characterize the self by an individual’s relation to stimuli in the world and thus by self-referential stimuli. The reflective self is not considered as a fixed and isolated entity but as a context-dependent and thus embedded process. This process is manifest in subjective experience—the self we consider here is an experiential self that mediates ownership of experience (Zahavi, 2003; Gallagher and Zahavi, 2005; Legrand, 2005). Our presupposition in this paper is that self-referential processing constitutes the “experiential self” which can be considered to be a way that one reflects on one’s experiences in a very fundamental way. Below, this processing there may be a more fundamental core self that is more strictly a prereflective and rather affective representation of internal and external stimuli including their subjective (or phenomenal) experience as such that is essential for any reflective awareness to become possible (Panksepp, 1998a,b; Damasio, 1999).

Recently, the question of self has also become a topic in neuroimaging. Though current studies remain unable to account for all the distinct and subtle aspects of self-referential processing discussed above, they at least are able to reveal various regions in association with self-related tasks (see also Legrand, 2005) for advancing a similar argument about the discrepancy between empirical designs and conceptual distinctions). In addition to various regions in our brains’ medial cortex (see below for details), a variety of other regions like ventro- and dorsolateral prefrontal cortex, lateral parietal cortex, bilateral temporal poles, insula, and subcortical regions, including brain stem, colliculi, periaqueductal gray (PAG), and hypothalamus/hypophysis, have been observed to be activated during self-related tasks (LeDoux, 1996; Gazzaniga, 1998; Panksepp, 1998a,b, 2003, 2005b; Damasio, 1999; Damasio, 2003a,b; Gallagher, 2000; Rolls, 2000a,b; LeDoux, 2002; Gallagher and Frith, 2003; Keenan et al., 2003; Kircher and David, 2003; Vogeley and Fink, 2003; Gillihan and Farah, 2005). This regional heterogeneity raises the question of so-called core regions being commonly involved in the different self-related tasks. In addition to lateral cortical and subcortical regions, several neuroimaging studies report involvement of various medial cortical regions. These include the medial orbital prefrontal cortex (MOFC), the ventromedial prefrontal cortex (VMPFC), the sub/pre- and supragenual anterior

cingulate cortex (PACC, SACC), the dorsomedial prefrontal cortex (DMPFC), the medial parietal cortex (MPC), the posterior cingulate cortex (PCC), and the retrosplenial cortex (RSC) (see also Fig. 5 in Gillihan and Farah, 2005). Recently, these regions have been subsumed under the term cortical midline structures (CMS) (see Fig. 1) and characterized as an anatomical and functional unit (Northoff and Bermpohl, 2004). What remains unclear, however, is whether activation in CMS is related to self-referential processing per se or to some task-specific processes reflecting the respective sensory–perceptual processing domains (Gillihan and Farah, 2005). If the CMS are associated with self-referential processing per se, activation in these regions should be observed in self-related tasks across all domains and sensory modalities, remaining task-independent. In the converse case, activation in CMS should occur only in self-related tasks in specific cognitive domains (or even sensory modalities) but not in other domains (or sensory modalities), showing task dependence or specificity.

The aim of the present article is to investigate whether there are core medial cortical regions that are commonly involved in self-related tasks across different cognitive domains and sensory modalities. For that purpose, we review neuroimaging studies with self-related tasks in different domains employing different stimuli such as trait adjectives, memories, emotions, and movements. We assume that there may be common regions in all such studies and that these core regions might predominantly be situated in cortical midline structures. Based on our hypothesis, we focus on reported involvement of medial cortical region in a series of relevant imaging studies. In addition, we test for functional specialization within the CMS using cluster and factor analysis. We assume that functional specialization within the CMS is not oriented on specific cognitive or perceptual domains but rather on some other principles like for example how meaningful a stimulus is to an individual. We will also shed some light on anatomical and functional linkage of CMS to

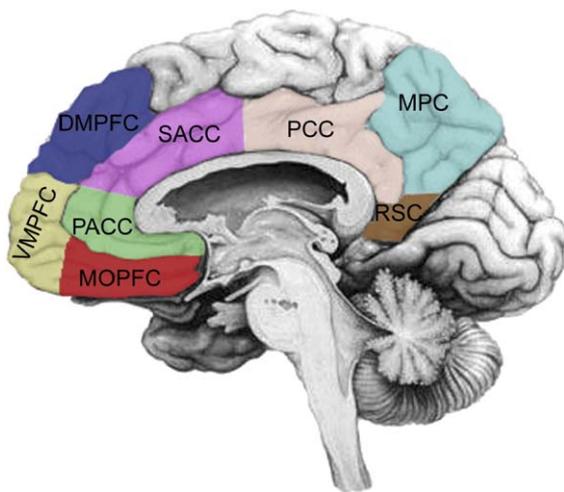


Fig. 1. Schematic illustration of cortical midline structures. The regions referred to as cortical midline structures (CMS) (BA = Brodman areas) in this article include the following areas. MOPFC = medial orbital prefrontal cortex (BA 11, 12); VMPFC = ventromedial prefrontal cortex (BA 10, 11); PACC = pre- and subgenual anterior cingulate cortex (BA 24, 25, 32); SACC = supragenual anterior cingulate cortex (BA 24, 32); DMPFC = dorsomedial prefrontal cortex (BA 9); MPC = medial parietal cortex (BA 7, 31); PCC = posterior cingulate cortex (BA 23); RSC = retrosplenial cortex (BA 26, 29, 30). Note that there are no clear anatomically defined borders between the different regions.

subcortical midline regions and the role of both systems in constituting the multitudes of selves that have been proposed in the literature. This is complemented by discussing the linkage of self-referential processing in CMS to higher-order processing in lateral prefrontal cortical regions. Finally, we briefly discuss our results and their implications within the context of neurophilosophical conceptions of the self.

Methods and results

Study selection

We analyzed 27 PET and fMRI studies on self-related tasks published between 2000 and 2004 (see Table 1). We used a rather broad and unspecific definition of self-related tasks describing all tasks where some material or content had to be related to the persons themselves, i.e., their own selves. Studies included only those with healthy subjects, whereas those on neurological or psychiatric disorders were excluded. The following inclusion criteria were applied:

1. Only studies measuring neural activity in the whole brain were included, whereas studies reporting only selected regions of interest were excluded.
2. Only studies comparing self- and non-self-related tasks were included; studies with lack of a non-self-related control task were excluded.
3. Presentation of results has been limited to regional activation changes (as revealed by task comparison or image subtraction method, parametric designs, or brain–behavior correlations). Data on changes in functional or effective connectivity have been excluded from statistical analysis but are reported in the text.
4. Only activation data were included in the relevant analysis, whereas deactivation data were not considered. If more than one coordinate per condition was reported, the three most significant activation coordinates were included in the meta-analysis. This was done to account for extended activations as well as activations in different brain regions. Restricting the analysis to one coordinate per study might have occluded overlapping foci of activation. As a result, a total of 324 coordinates (108 x coordinates, 108 y coordinates, 108 z coordinates) were included. For studies in which coordinates referred to the Montreal Neurological Institute (MNI) standard brains, a conversion of the coordinates to Talairach space was performed according to the method developed by M. Brett (<http://www/mrc-cbu.cam.ac.uk/Imaging/mnispace.html>).
5. In order to avoid debate concerning what can be considered neural activity of “significant” magnitude, we included all signal changes that the authors of individual papers have labeled “significant”. These changes were based on peak voxel maxima effects regardless of cluster extent.
6. Following our hypothesis, we distinguished between different domains. Self-related tasks in the verbal, the spatial, the facial, the memory, the motor, the social, and the emotional domain were distinguished. The social domain included activations from two comparisons, those where self-related tasks activated differently from other-related tasks as well as those where both tasks activated common regions. Finally, we included studies comparing first- and third-person perspectives which also mirror

Table 1
Summaries of studies included in this review

Study	Method	<i>n</i>	Experimental paradigm	Specific contrast	Modality
D'Argebeau et al., 2005	PET	13	Reflection about personality traits	Own vs. other's personality traits	Mental
Christoff et al. (2003)	fMRI	12	Simple matching task of geometric shapes	Internally vs. externally generated information	Visual
Ehrsson et al. (2004)	fMRI	17	Rubber hand illusion	Synchronous vs. asynchronous	Visual
Farrer and Frith (2002)	fMRI	12	Driving a circle with a joystick	Own vs. experimental driving	Visual
Farrer et al. (2003)	PET	8	Presentation of a virtual hand	Full control vs. non-control	Visual
Fossati et al. (2003)	fMRI	14	Encoding of positive and negative trait adjectives	Self vs. other	Visual
Fossati et al. (2004)	fMRI	14	Retrieval of personality traits	Personality traits semantic vs. phonemic condition	Visual
Gusnard et al. (2001)	fMRI	24	Attention and judgment	Internally vs. externally cued attention	Visual
Iacoboni et al. (2004)	fMRI	13	Movie clips of social interactions	Two persons vs. single person	Visual
Johnson et al. (2002)	fMRI	11	Judgments about abilities and traits	Own vs. other's judgments	Auditorily
Kelly et al. (2002)	fMRI	24	Trait adjectives	Own vs. other's trait adjectives	Visual
Kircher et al. (2000)	fMRI	6	Personality traits	Own vs. other's personality traits	Visual
Kjaer et al. (2002)	PET	7	Reflection on personality traits and physical appearance	Reflection on own vs. other's personality/physical traits	Mental
Lou et al. (2004)	PET	13	Retrieval of personality trait adjectives	Self vs. other	Visual
Macrae et al. (2004)	fMRI	22	Personality adjectives	Self vs. non-self descriptive/remember vs. forgotten	Visual
Ochsner et al. (2004)	fMRI	24	Reference of negative emotional pictures	Self-focus vs. situation-focus	Visual
Phan et al. (2004a,b)	fMRI	12	Evaluation of self-relatedness of emotional pictures	Correlation between emotion and self-relatedness	Visual
Platek et al. (2004, 2005)	fMRI	5	Presentation of faces	Self face vs. famous face	Visual
Ruby and Decety (2001)	PET	10	Imagination of action	First- and third-person perspective	Visual and auditory
Ruby and Decety (2003)	PET	10	Believing and thinking	Third- vs. first-person perspective	Mental
Ruby and Decety (2004)	PET	10	Imagination	First- vs. third-person perspective	Mental
Schmitz et al. (2004)	fMRI	19	Trait adjectives	Third- vs. first-person perspective	Visual
Seger et al. (2004)	fMRI	12	Decisions about liking of food	Own vs. other's feelings	Visual
Vogeley et al. (2001)	fMRI	8	Theory of mind (TOM) and self perspective (SELF)	Other's vs. own feelings	Visual
Vogeley et al. (2004)	fMRI	11	Counting red balls	Self vs. other evaluation	Visual
Zysset et al. (2002)	fMRI	13	Evaluative judgment	Self and other's evaluation	Visual
Zysset et al. (2003)	fMRI	18	Judgement of items	Self vs. other's decisions	Visual
				Self and other's decisions	Visual
				Self vs. theory of mind (TOM)	Visual
				Theory of mind (TOM) vs. SELF	Visual
				Theory of mind (TOM) and SELF	Visual
				Own vs. avatars/other's perspective	Visual
				Evaluative vs. episodic and semantic judgment	Visual
				Evaluative vs. semantic	Visual

the distinction between self- and non-self-related tasks (Ruby and Decety, 2001, 2003, 2004; Vogeley et al., 2004).

7. Since, in addition to specific domains, we were also interested in the question of self-related tasks in different sensory modalities, we coded for the sensory mode in which the respective stimuli were presented.

Statistical analysis

The standard coordinates of activation peaks, *x*, *y*, and *z*, reported by individual studies were plotted onto medial and lateral

views of a 3-D canonical brain image (SPM 2002, Welcome Department of Cognitive Neurology; derived from the MNI brain template). We calculated the mean *x*, *y*, and *z* coordinates for each domain and for all domains taken together. All regions showing $x < 25$ or $x > -25$ were designated as medial regions. We chose a rather liberal criterion for medial regions in order to reveal whether activated regions are located really in the midline (see average values) or rather in lateral medial regions of one particular hemisphere. We first compared the means of all coordinates from all domains against 0 using *t* test. We then compared the means of the three coordinates between the different domains using one-way

ANOVA and post-hoc *t* tests. To further exclude possible association of specific domains with particular coordinates, we applied two-way ANOVA for repeated measurement with the within-subjective factor coordinate (*x*, *y*, *z*) and the between-subjective factor domain (emotional, etc.).

To distinguish between different subregions within the CMS, we employed the following analysis. We applied a hierarchic cluster analysis using quadratic Euclidean distance and Ward linkage rules. To test for different solutions, we applied three-, four-, and five-cluster solutions to our data set. We then statistically compared the different clusters within each solution among each other using two-way ANOVA with the factors cluster (number of clusters within each solution) and coordinates (*x*, *y*, *z*). This was done to test for statistical difference between the clusters within each cluster solution. We then performed Chi-square analysis to test for possible associations of the obtained clusters with specific domains. Finally, we applied another test for yielding subgroups within our data set, namely principal component analysis using varimax rotation.

Results of statistical analysis

t test for all coordinates from all domains when compared to 0 revealed no significant difference for the *x* coordinate ($t(107) = -1.867$, $P = 0.065$). Despite the rather liberal entrance criterion for the *x* coordinate ($x < 25$ or $x > -25$), the means did not differ significantly from 0. Moreover, the means and SDs (-2.06 ± 11.49) and the confidence interval (95% confidence interval: -4.26 – 0.13) show that despite the liberal entrance criterion *x* coordinates are located closely to 0 and thus to cortical midline (see also Figs. 2A and B). Similarly, the means of all *y* coordinates did not show a significant difference when compared to 0 ($t(107) = 1.932$, $P = 0.056$), though it was closer to a significant level than the *x* coordinate and showed a higher SD and confidence interval (means \pm SD = 8.51 ± 45.78 ; 95% confidence interval: -0.22 – 17.24). Finally, the means of all *z* coordinates revealed a significant difference when compared to 0 ($t(107) = 12.116$, $P = 0.0000$) (means \pm SD = 27.77 ± 23.82 ; 95% confidence interval: 23.23 – 32.31).

In a second step, we compared the means of coordinates between the different domains. One-way ANOVA revealed no significant difference between the different domains for *x* coordinate ($F(7) = 0.829$, $P = 0.566$), for the *y* coordinate ($F(7) = 0.483$, $P = 0.845$), and for the *z* coordinate ($F(7) = 1.766$, $P = 0.103$). These results suggest that there is no significant difference in all three coordinates between the

different domains (see also Fig. 2B). The two-way repeated measures ANOVA including the within-subjects factor coordinates (three levels: *x*, *y*, *z*) and the between-subjects factor

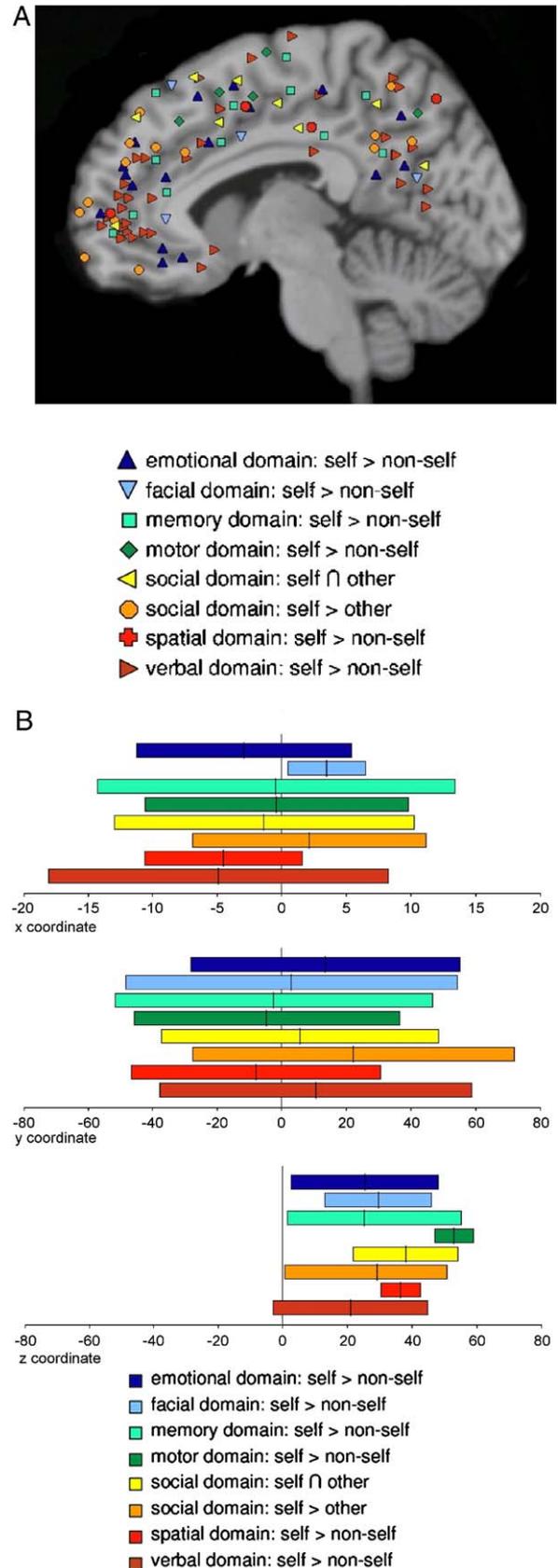


Fig. 2. (A) Activation in CMS observed in imaging studies during self-related tasks in different domains. Outcome of a meta-analysis of CMS foci of activation reported in 27 fMRI studies published between 2000 and 2004. These studies investigate brain activity during self-related tasks in different domains (emotional domain—dark blue, facial domain—light blue, memory domain—light green, motor domain—dark green, social domain: self and other—yellow, social domain: self vs. other—orange, spatial domain—red, verbal domain—brown). Medial activations ($-25 < x < 25$) are superimposed on a sagittal slice of an anatomical MRI scan at $x = -6$. Note the pattern of activations in all domains throughout anterior and posterior CMS. (B) Graphic representation of means and ranges of *x*, *y*, and *z* coordinates during self-related tasks. The figure shows the range of the coordinate values for all domains (mean \pm standard deviation; colors are the same as in A). Statistical analysis showed no significant differences between the domains. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

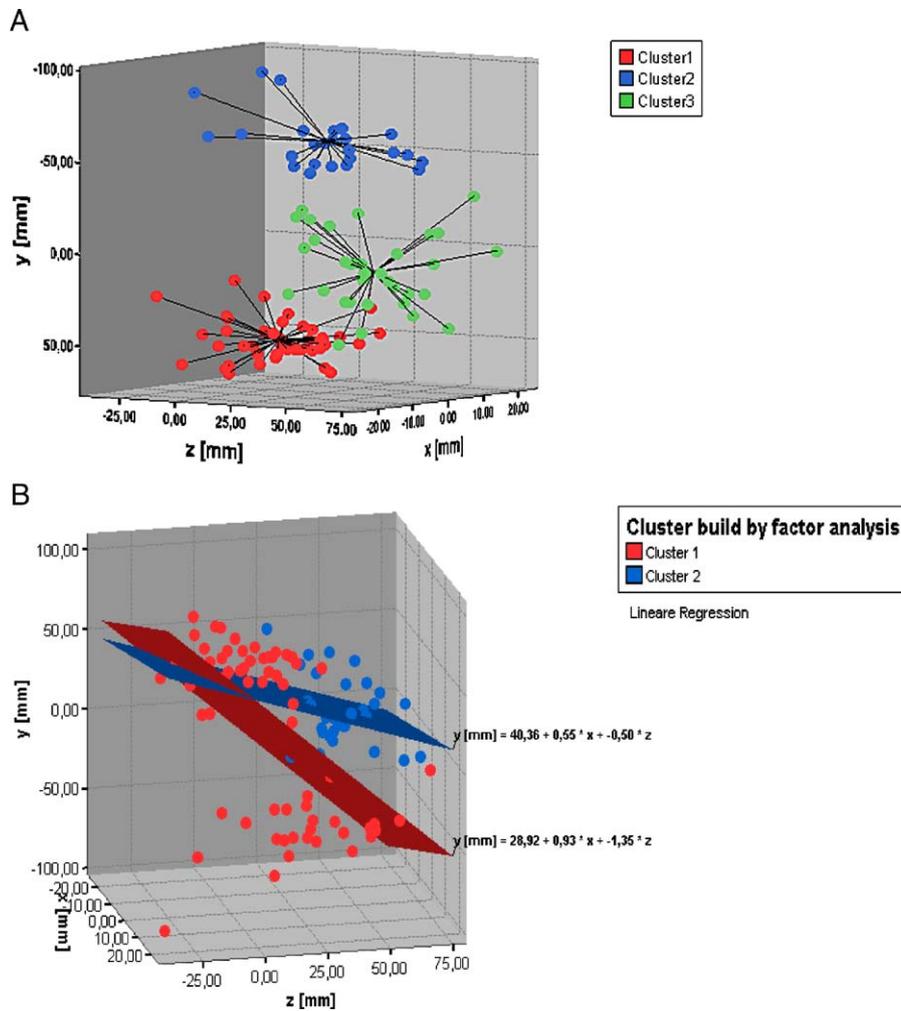


Fig. 3. Graphic representation of localizations of clusters (A) and factors (B) in three-dimensional space. (A) shows the localization of the three clusters from the three-cluster solution in three-dimensional space as obtained in statistical analysis. (B) shows the components including the respective data points as obtained in principal component analysis using varimax rotation.

domains (8 levels) revealed no significant difference between the different domains with respect to the coordinates ($F = 0.582$; $P = 0.769$; explained variance = 3.9%; power = 0.24). The fact that we did not obtain any significant result in either ANOVA (one-way and two-way) suggests that there is no association between specific domains and particular coordinates.

The hierarchic cluster analysis revealed the following results. All cluster solutions, the 3-, 4-, and 5-cluster solutions, yielded three reliable clusters with more or less similar anatomical localization within the CMS (see Figs. 3 and 4). The three-cluster solution yielded the following results. The first cluster showed the coordinates (means \pm SD) in $x = -2.07 \pm 10.28$, $y = 48.78 \pm 11.11$, $z = 7.45 \pm 14.02$ (44 data points) which is anatomically located in the VMPFC/PACC; the second cluster showed the coordinates in $x = -3.30 \pm 10.96$, $y = -61.19 \pm 13.39$, $z = 31.20 \pm 21.16$ (26 data points) which is anatomically located in the PCC/precuneus; and the third cluster showed the coordinates in $x = -1.20 \pm 13.20$, $y = 9.58 \pm 21.39$, $z = 48.91 \pm 12.42$ (38 data points) which is anatomically located in the DMPFC/SACC (see also Figs. 3A and 4). The two-way repeated measures ANOVA, including within-subjects factor coordinates (three levels: x , y , z) and the observed clusters within the 3-cluster solution, revealed a highly significant

difference between the three different clusters ($F = 101.139$; $P = 0.000$; explained variance 65%; power = 1.00). Finally, Chi-square analysis did not yield any significant association between the three clusters with any of the domains ($\chi^2 = 16.1$; $P = 0.308$).

The four-cluster solution showed the following results. The first cluster showed the coordinates in $x = -4.0 \pm 13.06$, $y = -53.0 \pm 45.22$, $z = 37.0 \pm 22.26$ (29 data points; PCC/precuneus); the second cluster showed the coordinates in $x = -2.61 \pm 8.92$, $y = 49.08 \pm 48.18$, $z = 7.59 \pm 20.26$ (44 data points; VMPFC/PACC); the third cluster showed the coordinates in $x = 1.37 \pm 8.82$, $y = -67.06 \pm 44.98$, $z = -20.37 \pm 31.55$ (2 data points; occipital); the fourth cluster showed the coordinates in $x = -1.94 \pm 11.99$, $y = 15.43 \pm 42.56$, $z = 50.86 \pm 24.74$ (33 data points; SACC). The two-way repeated measures ANOVA, including within-subjects factor coordinates (three levels: x , y , z) and the obtained clusters (4 clusters), revealed a significant difference between the four different clusters ($F = 211.83$; $P = 0.000$; explained variance 80%; power = 1.00). Finally, the Chi-square analysis did not yield any significant association between the four clusters and particular domain ($\chi^2 = 19.77$; $P = 0.536$).

The five-cluster solution showed the following results. The first cluster showed the coordinates in $x = 0.52 \pm 13.06$, $y = 16.19 \pm$

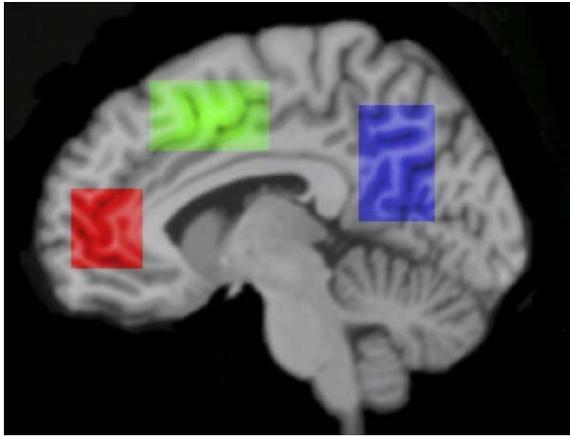


Fig. 4. Localization of the clusters from the three-cluster solution in the cortical midline structures. The figure shows the anatomical localization of the three clusters from the three-cluster solution, as visualized in three-dimensional space in Fig. 3A, in the cortical midline structures. The colors correspond to the ones shown in Fig. 3A, the bars within each cluster reflect the standard deviations from the y and z coordinates obtained in statistical cluster analysis. Note the distinction between the VMPFC/PACC, the DMPFC, and the PCC/precuneus which might correspond to functional specialization within the CMS. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

45.22, $z = 50.37 \pm 22.26$ (32 data points; SACC); the second cluster showed the coordinates in $x = 22.33 \pm 9.28$, $y = -88.75 \pm 46.79$, $z = -38.00 \pm 20.40$ (1 data point; Cerebellum); the third cluster showed the coordinates in $x = -3.37 \pm 8.82$, $y = -47.06 \pm 44.98$, $z = 42.37 \pm 31.55$ (23 data points; PCC/precuneus); the fourth cluster showed the coordinates in $x = -1.94 \pm 11.99$; $y = -49.43 \pm 42.56$; $z = 7.86 \pm 24.74$ (44 data points; VMPFC/PACC); the fifth cluster showed the coordinates in $x = -9.77 \pm 8.02$; $y = -71.87 \pm 59.64$; $z = 17.03 \pm 22.31$ (8 data points; occipital). The two-way repeated measures ANOVA, including within-subjects factor coordinates (x , y , z) and observed clusters, revealed a significant difference between the different clusters ($F = 234.68$; $P = 0.000$; explained variance 82%; power = 1.00). Finally, the Chi-square analysis did not yield any significant association between the five clusters and particular domains ($\chi^2 = 26.36$; $P = 0.551$).

The factor analysis revealed two factors, which correspond to areas in the 3-D space. Two components were obtained (the first component explained 65.1% of the variance; the second component explained 34.9%; thus, the total explained essentially 100% of the variance). Based on the two components obtained, we calculated another 2 clusters associating them with the different data points. The absolute value of each component load specifies uniquely whether each respective data point belongs (absolute value for component 1 < absolute value for component 2) to either cluster 1 or cluster 2. As such, we were able to obtain the function of the regression area for the two clusters. The regression area for cluster 1 was $y = 28.92 + 0.93 * x - 1.35 * z$ and for cluster 2, $y = 40.36 + 0.55 * x - 0.50 * z$. As can be seen in the graphics (see Fig. 3B), three groups of data points (lower red, upper red, blue) can be distinguished from each other corresponding to localization in VMPFC/PACC, SACC/DMPFC, and PCC/precuneus. This lends further support to our results from cluster analysis. The two-way repeated measures ANOVA included within-subjects

factor coordinates (three levels: x , y , z), and the obtained clusters revealed most significant differences between the different clusters ($F = 17.731$; $P = 0.000$; explained variance = 14.3%; power = 0.987). The Chi-square analysis did not reveal any significant association between the two clusters and particular domains ($\chi^2 = 5.385$; $P = 0.613$).

Imaging studies and the self

Self-referential processing in the verbal domain

Several studies have investigated verbal tasks in relation to the self. For example, Kelley et al. (2002) investigated a trait adjective judgment task comparing self-, other-, and case-referential adjectives (see Introduction for more complete description). They demonstrated that the VMPFC and the DMPFC were selectively engaged in the self-related condition. Employing auditorily delivered statements, Johnson et al. (2002) compared judgments about one's own abilities, traits, and attitudes (such as 'I can be trusted') to a semantic judgment task. The self-referential condition was associated with activation in VMPFC, DMPFC, and PCC/RSC relative to the control condition. Another mode of stimulation was applied by Kjaer et al. (2002). Instead of relying on sensory presentation of verbal items, they asked the subjects to mentally induce thoughts reflecting on one's own personality traits and physical appearance. Self-referential conditions (personality traits, physical appearance) induced activation in various CMS including VMPFC, PACC, DMPFC, SMA, and precuneus when compared to non-self-referential conditions (i.e., thoughts about a famous person, the Danish Queen). They also observed increased functional connectivity between SACC and precuneus during self-referential conditions. An analogous method of mental stimulation with thoughts was applied by D'Argembeau et al. (2004). These authors observed a positive correlation between blood flow in the VMPFC and the degree of self-referentiality of thoughts (D'Argembeau et al., 2004).

Taken together, all these studies (Johnson et al., 2002; Kelley et al., 2002; Kjaer et al., 2002; D'Argembeau et al., 2004) observed involvement of CMS in self-referential tasks, although they relied on different modes of verbal task presentation (visual, auditory, mental/thoughts). This suggests that neural activity in the CMS during verbal self-referential processing remains independent of the respective sensory modalities and might therefore be called supramodal.

Self-referential processing in the spatial domain

Self-referential processing in the spatial domain refers to the centeredness of an individual's multidimensional and multimodal space upon one's own body. This provides egocentric information about one's own body and its spatial context which needs to be distinguished from allocentric information about other body's spatial contexts. This has first been investigated in navigational tasks (Maguire et al., 1998, 1999; Vogeley and Fink, 2003). Key regions for egocentric navigation involved posterior CMS like MPC and PCC as well as other regions like the right inferior parietal cortex and the temporal cortex. The relevance of the MPC and the right lateral parietal cortex in egocentric processing of one's own body's spatial context can also be derived from studies of patients with right parietal lesions (Marshall and Fink, 2001; Vogeley and Fink, 2003).

These patients show spatial neglect with impairments in tracking changes in egocentric spatial relationships.

The involvement of these regions in self-referential processing in the spatial domain is further supported by a recent study by Vogeley et al. (2004). They investigated subjects in fMRI while perceiving a virtual scene including an avatar and red balls in a room. The task for the subjects was to count the red balls by taking either the avatars perspective (third-person perspective; TPP) or one's own perspective (first-person perspective; FPP). According to the authors, the crucial difference is that TPP necessitates an additional translocation of the egocentric viewpoint from FPP to TPP. Counting the balls in FPP revealed decreased reaction times and higher accuracy compared to the identical task in TPP. Moreover, counting in FPP (when compared to counting in TPP) induced activation in anterior and posterior CMS like VMPFC, PACC, DMPFC, PCC, and RSC as well as in other regions including the bilateral left inferior and medial temporal gyrus, the right anterior insula, and the right postcentral gyrus.

Self-referential processing in the memory domain

Memorizing, i.e., encoding and retrieving self-referential stimuli, is reflected in episodic and autobiographical memory (see Maguire, 2001 and especially Gilboa, 2004 for a comparison of both). Macrae et al. (2004) investigated the retrieval of visually presented self- and non-self-related adjectives describing personality traits. They performed a double analysis with grouping retrieved items in two ways, remembered versus forgotten and self-descriptive versus non-self-descriptive. Remembered items induced activation in DMPFC, left LPFC, and bilateral hippocampus/parahippocampal gyrus when compared to forgotten items, while the self-descriptive versus non-self-descriptive contrast revealed activation in the DMPFC. Both contrasts involved the DMPFC suggesting that retrieval performance and self-relevance interact in this particular region.

The interaction between retrieval and self-reference might be particularly crucial in autobiographical memory. Accordingly, previous imaging studies during autobiographical memory retrieval show involvement of the DMPFC and/or the VMPFC (Fink, 1996; Maddock, 1999; Maddock et al., 2003; Piefke et al., 2003; Gilboa, 2004). In addition, autobiographical memory has a strong emotional component. This has been investigated by Fossati et al. (2003, 2004) who investigated the encoding and retrieval of visually presented positive and negative self-related personality trait adjectives (semantic and phonemic conditions served as controls). Both the encoding and the correct retrieval of self-encoded personality traits engaged the DMPFC, in particular, the right DMPFC. According to the authors, recruitment of the DMPFC suggests that the same process, i.e., self-referential processing, might operate at both encoding and retrieval to relate personality adjectives to one's own self.

The relation between anterior and posterior CMS as well as their relation to other regions has been investigated in a recent PET-TMS study by Lou et al. (2004). Episodically retrieved (visually presented) personality trait adjectives were either related to their own person, to their best friend, or to the Danish Queen. Retrieval of self-related adjectives induced activation in the DMPFC and the PCC/precuneus as well as in the right and left inferior parietal cortex, the left ventrolateral prefrontal cortex (VLPFC), and the middle temporal cortex

including the hippocampus. Analysis of functional connectivity revealed significant interaction between anterior (DMPFC) and posterior (MPC, PCC, precuneus) CMS as well as between anterior CMS and other regions (LPFC, inferior parietal, middle temporal). Based on a complementary TMS study (Lou et al., 2004), the authors conclude that the MPC might be a nodal region in mediating interaction between CMS and other lateral cortical regions during episodic retrieval of self-related adjectives (see also Seger et al., 2004 whose results show specific involvement of the MPC (and the PCC) during self-referential processing in the verbal domain).

Self-referential processing in the emotional domain

Several studies investigating emotions observed activation in anterior CMS including the VMPFC, the ACC, and the DMPFC (see Phan et al., 2002 for an overview). Does this involvement of anterior CMS during emotions indicate self-referential processing? Phan et al. (2004a,b) investigated the degrees of self-referentiality during emotional processing. Subjects had to appraise the extent of personal association of emotionally salient pictures during fMRI. fMRI results were correlated with subjective ratings (after fMRI) appraising the degree of self-relatedness of the picture content in a visual analogue scale. Regions associated with self-relatedness were located in the CMS including VMPFC, PACC, and DMPFC, the latter two appearing only with increasing degrees of self-relatedness (other regions activated in relation to self-relatedness concerned the insula and the nucleus accumbens): The more self-related the picture content was appraised, the more activation was observed in these regions.

In another study (Fossati et al., 2003), subjects had to judge whether emotional, i.e., positive and negative personality, trait adjectives described themselves properly. For control, subjects were asked if the adjectives described generally desirable traits. The DMPFC and PCC were specifically activated during self-referential evaluation of words irrespective of their emotional valence. Ochsner et al. (2004) compared self-relevance of visually presented negative emotional pictures (self-focus) with alternative meanings for pictured actions and their situational contexts (situation-focus). They observed increased recruitment of the PACC/SACC in the self-focus and of right and left LPFC (VLPFC, DLPFC) in the situation-focus. This is in line with earlier studies (Gusnard and Raichle, 2001; Gusnard et al., 2001) where attention to self-referent emotional conditions induced neural activity in PACC/SACC, VMPFC, and DMPFC when compared to externally cued attention. A similar pattern of differential medial versus lateral prefrontal recruitment has been observed when participants either judged the valence of their own emotional responses to pictures or evaluated the valence of the emotion expressed by the central person displayed in those pictures (Ochsner et al., 2004). These results indicate that self-referential processing in the emotional domain especially involves the anterior CMS.

How can we disentangle emotion and self-referential processing? In addition to self-relatedness (see above), Phan et al. (2004a,b) also incorporated individual ratings of emotional intensity (or arousal) as a regressor in the analysis of functional activation data during evaluation of emotional pictures. Regions specifically activated in relation to subjective ratings of emotional intensity included the amygdala, the nucleus accumbens, and the insula; these regions clearly differ from the ones associated with appraisal of self-relatedness (see above). Similar results of a

relationship between neural activity in the amygdala (and other subcortical regions) and emotional intensity were obtained in both gustatory (i.e., unpleasant and pleasant taste; Small et al., 2003) and olfactory studies (unpleasant and pleasant odors; Anderson et al., 2003) studies.

While self-referential processing is apparently associated with CMS, emotion processing might predominantly take place in subcortical (and other cortical) regions including the insula, amygdala, brain stem, colliculi, and PAG (see also LeDoux, 1996, 2002; Panksepp, 1998a,b, 2003; Damasio, 1999). The often observed activation in anterior CMS across different emotion types and distinct induction methods (Phan et al., 2002; Murphy et al., 2003) might thus reflect the high degree of self-referentiality shared by all emotions rather than intrinsic emotion processing. This might also be reflected in reports of significant correlation of neural activity in anterior CMS with emotional valence (Anderson et al., 2003; Small et al., 2003; Heinzel et al., 2005) since evaluation of the latter presupposes self-reference.

Self-referential processing in the facial domain

One of the most important ways to identify one's own person is to recognize one's face and distinguish it from other persons' faces. Self-face recognition might thus presuppose self-referential processing in the facial domain. In a series of investigations applying visual presentation of own, others, and morphed faces, Keenan et al. (2000, 2001, 2003) suggested that self-face recognition is associated with processing in the right hemisphere and particularly the right LPFC. However, a more recent fMRI study observed activation in the DMPFC as well as in the right LPFC (and other regions like the temporal pole) during self-face recognition (Platek et al., 2004, 2005). Similarly, Kircher et al. (2000, 2001) observed co-activation in medial (ACC) and lateral prefrontal (left LPFC) regions when comparing own-face recognition with recognition of a morphed version of it and the partner's face (see also Sugiura et al., 2000). These findings suggest that medial cortical regions are involved in self-face recognition being co-activated with lateral prefrontal cortical regions.

Hemispheric lateralization in prefrontal cortex during self-face recognition remains an issue of debate. Keenan et al. (2000, 2001, 2003) associated self-face recognition with the right hemispheric lateral prefrontal cortex. In contrast, Turk et al. (2002, 2003) found left hemispheric dominance for self-face processing in a split-brain patient (see however Keenan et al., 2003 who report a patient with right hemispheric dominance for self-face processing). Therefore, Turk et al. (2002, 2003) speak of a so-called "left hemispheric interpreter in self-recognition": "This interpretive function of the left hemisphere takes available information from a distributed self-processing network and creates a unified sense of self from this input".

Self-referential processing in the social domain

The ability to assign and attribute mental states including emotions, thoughts, attitudes, and beliefs to other persons is referred to as 'theory of mind' (TOM) or mind reading (Baron-Cohen, 1995; Frith and Frith, 1999). This is central to any social interaction and makes communication possible. Interestingly, imaging studies during theory of mind tasks have been shown to involve anterior and posterior CMS like the VMPFC, the ACC, the DMPFC, and the MPC as well as other regions like the temporal

pole and the superior temporal sulci (Frith, 2002; Frith and Frith, 1999, 2003; Stuss et al., 2001; Vogeley et al., 2001; Kampe et al., 2003; Blakemore and Frith, 2004; Iacoboni et al., 2004; Platek et al., 2004, 2005).

Analogous involvement of especially the anterior CMS in both self- and other-person-referential processing has been observed in the verbal (Craig et al., 1999; Schmitz et al., 2004; Seger et al., 2004; as described above), emotional (see Wicker et al., 2003; Fitzgerald et al., 2004 who observe overlap between feeling and seeing of disgust in ACC and insula), and visceral (see Singer et al., 2004 who observed activation in ACC during experiencing and observing pain) domains.

How can CMS involvement in both self- and other-person referential processing be interpreted? According to the simulation theory of mind reading, the observer tries to covertly mimic one's mental state of the other person leading to shared mental states between observer and observed persons. Since in mind reading the others' mental states seems to resonate in the own mental state, it might be assumed that mind reading requires self-referential processing.

Self-referential processing in agency and ownership of movements

Self-referential processing is required in agency and ownership both characterizing the self in the motor domain. Agency describes the sense or feeling of being causally involved in an action. For example, the sense that I am the one who is causing something to move or that I am the one who is generating a certain thought in my stream of consciousness (Gallagher, 2000; Gallagher and Frith, 2003; Frith, 2002).

Farrer and Frith (2002) conducted PET studies investigating agency. In the agency condition, subjects had to draw a circle and mentally attribute the action seen on the screen to themselves. In the control condition, they also had to draw a circle but were shown that the action on the screen was driven by the experimenter. Being aware of causing the action was associated with activation in bilateral anterior insula, SMA, lateral premotor cortex, and primary sensorimotor cortex. In contrast, attributing action to another person promoted activity in the right inferior parietal cortex. These results were confirmed in a further study where subjects had to compare their own movements with those of a virtual hand (Farrer et al., 2003). Full control of the virtual hand was supposed to induce a sense of agency, whereas discrepancy between virtual hand and own movements leads to attribution of action to another person. The stronger the sense of agency, the greater activation was observed in the insula. Conversely, the weaker the sense of agency implying strong discrepancy, the greater the right inferior parietal lobe was activated.

Ownership describes the sense that I am the one who is undergoing an experience, for example, the sense that it is my body and not another person's body that is moving (Gallagher, 2000). Jeannerod (2003) speak of a "who system" enabling a subject to attribute an action to its proper owner. How can we distinguish agency and ownership? Agency describes a "sense of effort" corresponding to anticipatory mechanisms with pre-movement motor commands, i.e., forward mechanisms (Jeannerod, 2003). Ownership, in contrast, might rather indicate a "sense of effect" depending on sensory feedback mechanisms by means of which the consequences of the movements/action are related to the own person (Gallagher, 2000; Gallagher and Frith, 2003).

Ehrsson et al. (2004) investigated ownership in imaging. A perceptual illusion was used to manipulate feelings of ownership of a rubber hand presented in front of subjects lying in fMRI. After a short period, the majority of subjects had the experience that the rubber hand is their own hand reflecting the sense of ownership. To modulate the sense of ownership, the relation between their own hand and the rubber hand were varied according to different degrees of synchrony and congruency. The feeling of ownership of their own hand, as indicated by synchrony and congruency between both hands, induced increased activation in bilateral premotor cortex. In addition, the magnitude of activation in premotor cortex significantly correlated to the degree of ownership measured with a visual analogue scale. Other regions observed in studies of ownership include the ACC, motor cortex, cerebellum, and the posterior parietal cortex (see Jeannerod, 2003 for a summary of their own studies of motor ownership, as well as Blakemore et al., 2000; Blakemore, 2003 for studies of sensory ownership).

Self-referential processing, the CMS, and the self

Sensory processing and self-referential processing

Our review of neuroimaging studies reveals a set of commonly activated regions, within the extended CMS, during self-related tasks using a diverse set of sensory modalities. Activation in CMS must therefore be considered independent of the sensory mode within which the self-related stimuli were presented. Such sensory independence of neural activity in CMS can be observed in all domains. This is paradigmatically reflected in the emotional domain. Regardless of whether emotions were induced visually, auditorily, gustatory, or olfactorily, they all led to activation in CMS (see Phan et al., 2002; Anderson et al., 2003; Small et al., 2003). The same could be observed in the verbal and memory domains. Therefore, neural processing in CMS might be characterized by “supramodality”.

If neural processing in CMS is supramodal, these regions should receive afferent connections from all sensory modalities. In fact, the MOFC and VMPFC receive connections from all regions associated with primary and/or secondary exteroceptive sensory modalities (olfactory, gustatory, somatosensory, auditory, visual) (Barbas, 2000; Rolls, 2000a,b; Damasio, 2003a,b; Kringelbach and Rolls, 2004). Unfortunately, no imaging studies directly comparing the same self-related task in different sensory modalities have yet been reported.

In addition to their exteroceptive connections, the CMS are densely connected to cortical and subcortical regions (insula, brain stem regions like hypothalamus, PAG, and colliculi) processing interoceptive sensory signals. These include the proprioceptive and vestibular senses, the visceral sense, and the sense of the internal milieu (Carmichael and Price, 1996; Price, 1999; Rolls, 2000a,b; Damasio, 2003a,b; Barbas, 2004). This is in accordance with results from imaging studies focusing on interoceptive signals of one’s own body (Craig, 2002, 2003, 2004; Wicker et al., 2003; Nagai et al., 2004). Studies investigating, for example, the regulation of heart beat, biofeedback arousal, relaxation, or the affective component of pain show activation sites in CMS like MOFC, VMPFC, and ACC (Craig, 2002, 2003, 2004; Wicker et al., 2003; Nagai et al., 2004; Singer et al., 2004) as well as in the respective cortical and subcortical regions (insula, brain stem regions like hypothalamus, hypophysis, PAG, and colliculi).

Due to these extensive exteroceptive and interoceptive connections, the anterior CMS and especially the MOFC and VMPFC have been characterized as polymodal convergence zones (Rolls, 2000a,b; LeDoux, 2002; Schore, 2003). Such polymodal convergence might provide the anatomical ground for directly assessing the different sensory stimuli according to their degree of self-referentiality: high degrees of self-referentiality seem to induce activation in CMS, whereas low degrees of self-referentiality are apparently accompanied by rather low levels of activation or even deactivation in CMS. Unfortunately, the exact mechanisms by which a purely sensory stimulus is transformed into a self-referential remain unclear. What seems to be clear however is that neural activity in CMS, especially in anterior CMS, must be considered crucial in transforming simple sensory processing into more complex self-referential processing (see also Fig. 5).

Cortical midline structures and subcortical midline regions

The CMS are densely and reciprocally connected to interoceptive midline regions in midbrain and brain stem like the periaqueductal gray (PAG), the superior colliculi (SC), and the adjacent mesencephalic locomotor region (MLR) as well as preoptic areas, the hypothalamus, the dorsomedial thalamus, and the bed nucleus of the stria terminalis (Holstege et al., 1996; Panksepp, 1998a,b). For example, the colliculi and the PAG are among the most richly connected areas of the brain; both receive afferents from several exteroceptive sensory regions (occipital, auditory, somatosensory, gustatory, and olfactory cortex) and, at the same time, afferents from other interoceptive subcortical regions (Holstege et al., 1996). In addition, the PAG and the colliculi are connected with the CMS (Dujardin and Jurgens, 2005). Since the same is true for the other subcortical midline regions mentioned, we suggest to speak of an integrated cortical–subcortical midline system which, of course, incorporates what MacLean (1990) called the limbic system.

How is such integrated cortical–subcortical midline system related to the self? Since they are involved in integrative processing of interoceptive bodily functions, the subcortical midline regions have been associated with what has been called “bodily-self” or “proto-self” (Strehler, 1991; Damasio, 1999; Parvizi and Damasio, 2001; Craig, 2002, 2003; Panksepp, 2003, 2005a). This reflects an archaic scheme of our own body; we envision that these ancient subcortical midline regions of the brain neurally instantiate a “virtual body” laid out in coherent viscerosomatic motor coordinates. This in turn serves as solid platform for basic instinctual–mental existence and the evolution of additional neuro-mental complexities with the emergence of additional “mental selves” (Panksepp, 1998a,b; Damasio, 1999).

We assume that the integrated cortical–subcortical midline system allows for the transformation of the “proto-self” into the “core or mental self” by linking sensory processing to self-referential processing. One might however argue that the “proto-self” already presupposes self-referential processing which might make distinction between both types of processing in different regions superfluous. Sensory processing in subcortical regions with the consecutive “bodily or proto-self” characterizes one’s own body functions but does not yet distinguish them from the ones of other bodies, i.e., other “bodily or proto-selves”. In contrast, self-referential processing allows for an active and explicit distinction between self- and non-self-related intero- and exteroceptive stimuli. We suppose that it is the active and explicit character of the distinction and its application to both intero- and exteroceptive

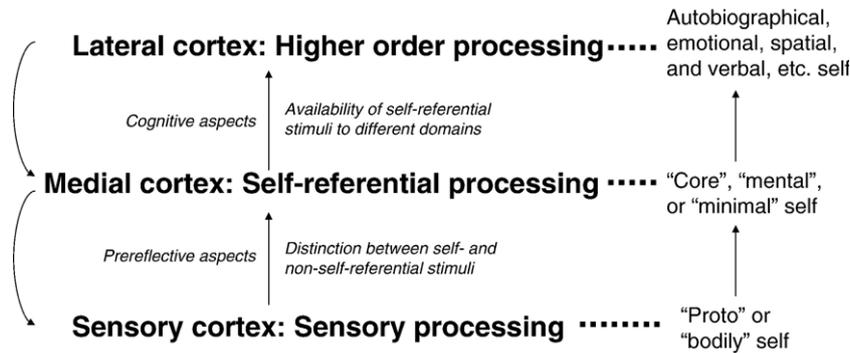


Fig. 5. Cortical localization and concepts of self. Schematic illustration of the relationship between cortical regions and concepts of self. On the right, we present different concepts of self, as suggested by different authors (Damasio, Panksepp, Gazzaniga, LeDoux, etc.). These concepts are related to sensory, self-referential, and higher-order processing with their respective cortical regions as shown on the left. Arrows showing upwards indicate bottom–up modulation, whereas downwards arrows describe top–down modulation. Note also the distinction between cognitive and pre-reflective aspects of self-referential processing.

stimuli that makes the difference between self-referential and direct sensory processing.

Finally, if self-referential processing is indeed based on and linked to sensory processing within the integrated cortical–subcortical midline system, one would assume concurrent activation in both subcortical and cortical midline regions in imaging studies employing self-related tasks. In addition to CMS, we therefore checked for subcortical activations in the studies reported above. Unfortunately, though visible on some of their fMRI images, most of the reported studies did not systematically investigate and report on subcortical regions. What would be needed in the future are studies investigating both cortical and subcortical regions during tasks self-referential processing (e.g., for an example of cortical–subcortical investigation, Wager et al., 2004). In addition, one should investigate functional and effective connectivity between cortical and subcortical midline regions. This would allow to specify their mode of interaction like for example top–down and bottom–up modulation (Heinzel et al., 2005; Panksepp, 2005a). We assume that interaction between top–down and bottom–up modulation in subcortical and cortical midline regions accounts for transforming the “bodily or proto-self” into the “core or mental self”.

Cortical midline structures as functional unit

Neural activity in the CMS was observed during self-related tasks across all domains. Verbal, memory, emotional, or social tasks related to the self were found to induce activation in the CMS. This suggests that CMS involvement reflects the self-related component, i.e., self-referential processing being common to all these tasks rather than the respective task-specific component, i.e., the domains. This was also supported by statistical results showing no significant difference in the x coordinate between the different domains. This suggests that the CMS can indeed be characterized by self-referential processing and subsequently as functional anatomical unit.

The CMS might be regarded as an anatomical unit for two reasons: (i) the different CMS regions show strong and reciprocal connections among each other; and (ii) the different CMS regions show a more or less (see below for discussion of differences) similar connectivity pattern to other cortical and subcortical regions (Barbas, 2000; Ongur and Price, 2000). This anatomical unit might provide the ground for what is here described as functional CMS

unit. Such functional unity is reflected in (i) co-activation among the different CMS regions as reported in a variety of different paradigms (see above as well as Northoff and Bermppohl, 2004) and (ii) strong functional and effective connectivity among CMS regions during self-referential tasks (Kjaer et al., 2002; Greicius et al., 2003; Lou et al., 2004). The results of our analysis strongly suggest that the CMS act as anatomical and functional unit during self-referential processing.

Another characteristic supporting our view of the CMS as functional unit is their peculiar physiological characteristics. The CMS show a high level of neural activity during resting conditions such as, for example, the fixation of a cross (Binder et al., 1999; Gusnard and Raichle, 2001; Gusnard et al., 2001; Mazoyer et al., 2001; Raichle et al., 2001). Therefore, the CMS have been characterized as ‘physiological baseline’ or ‘default mode’ of the brain (Gusnard and Raichle, 2001; Gusnard et al., 2001; Mazoyer et al., 2001; Raichle et al., 2001; Baars et al., 2003; Shulman et al., 2003, 2004). What is the psychological correlate of this ‘physiological baseline’? Exteroceptive stimuli, i.e., those from the environment, are (more or less) excluded in the resting state. In contrast, processing of interoceptive stimuli, i.e., those from the own body, should predominate in this state. If the CMS are associated with self-referential processing, their high resting neural activity should reflect continuous characterization of interoceptive stimuli as self-referential. Additional processing of exteroceptive self-referential stimuli might then enhance neural activity in CMS even further. However, this remains speculative since the exact relationship between self-referential processing of intero- and exteroceptive stimuli and its modulation by neural activity in CMS has not yet been explored.

These considerations suggest that a high resting level of neural activity in the CMS reflects processing of self-referential stimuli. This inclines us to speak of a “psychological baseline” indicating self-referential processing as the psychological correlate of the “physiological baseline” (Northoff and Bermppohl, 2004). If this is true, activation tasks requiring processing of non-self-referential stimuli should induce predominantly deactivation in CMS. As demonstrated in several studies, this indeed seems to be the case: non-self-referential cognitive tasks (reading and generation of nouns, coherence judgments, attribution of intention, judgment of stimulus pleasantness, discrimination of spatial attributes) elicit large signal decreases in CMS (Gusnard and Raichle, 2001; Gusnard et al., 2001; Raichle et al., 2001; Kelley et al., 2002;

Wicker et al., 2003; Northoff et al., 2004; Grimm et al., 2005). However, studies directly relating high resting neural activity in CMS to self-referential processing remain to be reported. Therefore, we remain unable to decide at this stage whether the high resting neural activity in the CMS reflects continuous self-referential processing and ultimately our subjective experience of a “continuous stream of subjective experience” or “phenomenal time” where past, present, and future are no longer divided but integrated (James 1892; Lloyd, 2002; Zahavi, 2003).

Functional specialization within the cortical midline structures

We also performed cluster and factor analyses across all activations in CMS reported in studies about self-relatedness. Taken together, these analyses revealed three different regional clusters within the CMS which could be characterized as ventral, dorsal, and posterior (see Figs. 3 and 4). We then tested whether these three regional clusters were associated with different domains. These analyses yielded negative results thus showing no association of particular domains with either ventral, dorsal, or posterior CMS regions. Accordingly, our results indicate that there is some functional specialization within the CMS though not in orientation on the different domains.

This raises the question for the organizing principle of functional specialization within the CMS. The problem of domain versus process specificity has already been extensively discussed in the case of the lateral prefrontal cortex (Duncan and Owen, 2000; Goldman-Rakic, 2000; Levy and Goldman-Rakic, 2000; 2000; Owen, 2000; Petrides, 2000). Process specificity suggests a functional organization in orientation on specific functional processes (such as storage and manipulation of information in working memory) in different regions, independent from the processed contents. Domain specificity, in contrast, reflects a functional organization in orientation on the type of content (domains, such as verbal and spatial in working memory) in different regions, independent from the required processes.

What does this imply for the CMS? Since we could not observe any association of the three regional CMS clusters with a particular domain, we hypothesize some other principles than domain specificity guiding functional specialization within the CMS. This other principle might either be some specific processes being associated with neural activity in of the three subregions or some other yet unknown factor. We here suggest the first model of functional specialization within the CMS. It may be considered as analogous to the one of process specificity within the lateral prefrontal cortex. Ventral, dorsal, and posterior subregions in CMS, as revealed in cluster and factor analysis, might be associated with distinct processes in relation to self-referential stimuli. Before going into detail about the exact nature of these processes, it should be noted that our model of process specificity concerns only different subregions within the CMS; whereas it does not apply to the relationship between CMS and other cortical regions as it is for example the focus of Kircher and David (2003) assumption of domain specificity of self-referential processing.

The ventral part of the CMS includes the medial orbitofrontal cortex (MOFC), the ventromedial prefrontal cortex (VMPFC), and the sub- and pregenual part of the anterior cingulate cortex (PACC) (see Fig. 1). These ventral regions are densely connected with the amygdala, the basal ganglia including the striatum and the nucleus accumbens, all primary exteroceptive sensory modalities, and further subcortical regions (midbrain, brain stem) implicated in

interoceptive processing (Ongur and Price, 2000). This connectivity pattern suggests that neural activity in the ventral part of the CMS could be involved in linking both extero- or interoceptive stimuli with respect to their self-relatedness. This is supported by a recent study (D’Argembeau et al., 2005), which observed a significant correlation of neural activity in the ventral CMS, i.e., on the junction between MPOFC, VMPFC, and PACC with the degree of self-referentiality of thoughts. Taken together, these results lend us to suggest that the ventral CMS are involved in coding the self-relatedness of stimuli thereby representing them as self-referential. This is also well compatible with clinical observations in patients with lesions in ventral CMS who remain unable to develop a coherent model of their own self (Damasio, 1999; Schore, 2003).

What remains however unclear is the exact physiological correlate of the process of coding and representing self-relatedness in ventral CMS. The ventral CMS were shown to be exclusively modulated by deactivation during non-self-referential task demands (Gusnard et al., 2001). In contrast, dorsal and posterior parts of the CMS showed a wider range of neural modulation including both deactivation and activation. In these regions, self-referential task demands induced activation, whereas non-self-referential task demands induced deactivation. These findings suggest that coding and representing stimuli as self-referential in ventral CMS are apparently subserved by a special type of neural activity, i.e., deactivation which distinguishes it from other processes associated with other CMS parts.

The dorsal part of the CMS includes the dorsomedial prefrontal cortex (DMPFC) and the supragenual anterior cingulate cortex (SACC) (see also Figs. 2 and 4). Both are densely connected especially with the lateral prefrontal cortex (Ongur and Price, 2000). These anatomical interconnections may be considered as functionally reflected in the oft reported co-activation of all three regions in studies on cognition (Duncan and Owen, 2000; Ongur and Price, 2000). A recent meta-analysis of studies on the cognitive control of emotion characterized the dorsal prefrontal regions by reappraisal, evaluation, and explicit reasoning of emotional stimuli (Ochsner and Gross, 2005). We suggest that the dorsal CMS could be implicated in such processes, i.e., reappraisal and evaluation of self-related stimuli. This would be well compatible with the observed involvement of dorsal CMS in many studies on the self with a strong evaluative or judgmental component (see for example (Johnson et al., 2002; Kelley et al., 2002; Zysset et al., 2002). This could also account for the often observed involvement of the dorsal CMS in tasks involving other persons like for example in theory of mind (see above as well as Frith and Frith, 2003; D’Argembeau et al., 2005). Correspondingly, patients with lesions in dorsal CMS commonly show disturbances in social interactions (Damasio, 1999; Feinberg, 2001). Summing up, this suggests that reappraisal and evaluation presuppose that the respective self-referential stimuli embedded within (and compared to) the context of other stimuli including also non-self-related stimuli from other persons. If this is true, it indicates that reappraisal and evaluation of self-related stimuli occur within the social context of non-self-related stimuli. However, our assumption of differential roles of ventral and dorsal regions needs to be supported by studies directly comparing coding/representation and reappraisal/evaluation of self-related stimuli. Unfortunately, such studies are still unavailable so that our hypothesis must be considered preliminary.

Finally, our cluster and factor analyses revealed a posterior part within the CMS including the posterior cingulate cortex (PCC), the retrosplenial cortex (RSC), and the medial parietal cortex (MPC)

(see Figs. 3 and 4). These regions are densely connected with the hippocampus implicated in encoding and retrieving autobiographical memory. This suggests that the posterior CMS are centrally implicated in putting self-referential stimuli within a temporal context linking them to past self-referential stimuli. This is strongly supported by the often observed involvement of posterior CMS in studies on autobiographical memory (see above). It is worth considering whether the anterior and posterior CMS structures are more influential in negative and positive affective self-referential processing modes.

One methodological problem to consider consists in temporal limitation of fMRI. Since the posterior CMS as part of the “default mode” network show continuously high neural activity in the resting state (see above), self-referential processing should also be continuously ongoing. However, imaging techniques such as PET and fMRI rely on short and discrete modes of stimulation in time which are therefore designed to show discrete rather than continuous neural activity in CMS. Future studies should directly compare discrete and continuous modes of stimulation with self-referential stimuli. We would expect that discrete stimulation with for example exteroceptive self-related stimuli modulates the continuously ongoing self-referential processing of interoceptive stimuli in CMS. This would also require new techniques in analysis of fMRI data which consider the signal changes not in direct and thus discrete relation to stimuli but rather as expressions of continuous signals that are only modulated by external stimuli (see for example Lloyd, 2002).

A recent PET-TMS study demonstrated the particular role of the MPC (Lou et al., 2004). TMS on the MPC was used to disrupt neuronal circuitry during retrieval of self-related, i.e., episodic material; TMS showed clear and specific effects on retrieval performance of self-related items at around 160 ms after stimulus onset. In addition to putting self-referential stimuli within a temporal context, the MPC might also be implicated in relating them to the spatial context. The MPC is strongly connected with the lateral parietal cortex which has been associated with representing the own body in space (Vogeley and Fink, 2003; Vogeley et al., 2004). This makes it likely that the MPC mediates not only temporal but also (though rather indirectly) spatial contextualization of self-referential stimuli. This is well compatible with the fact that the lateral parietal cortex has also been observed to show increased neural activity during the resting state, thus forming together with the CMS what Raichle et al. (2001) called the “physiological baseline” or “default mode” (see above).

Self-referential processing and higher-order processing in lateral prefrontal cortex

In addition to the CMS, lateral prefrontal cortical regions were reported in imaging studies on self-related tasks. This was the case especially in those studies where a strong cognitive component was required (Christoff and Gabrieli, 2000; Christoff et al., 2003; Schmitz et al., 2004; Steele and Lawrie, 2004). For example, verbal tasks require linguistic abilities including deciphering the meaning of the word, verbal monitoring, and introspection (Frith et al., 1992; Gallagher, 2000; Gallagher and Frith, 2003). Higher cognitive abilities were also involved in many emotion and theory of mind tasks requiring, for example, judgments, inference, thoughts, and imagination (Phan et al., 2002; Northoff and Bermpohl, 2004; Northoff et al., 2004; Ochsner et al., 2004). This is particularly true in self-referential tasks in the facial domain requiring recognition

and identification of the own face (Keenan et al., 2000, 2001, 2003; Kircher et al., 2000, 2001; Turk et al., 2002, 2003; Platek et al., 2004, 2005). Finally, many memory tasks imply higher cognitive operation like encoding, retrieval, and recognition.

Higher cognitive functions require what we call “higher-order processing”. Though one might consider designation of stimuli which are self-referential a higher cognitive function by itself, we distinguish self-referential processing from higher-order processing. We assume that self-referential processing filters, selects, and provides those stimuli which are relevant for the self of a particular person. Only these stimuli, i.e., self-referential, are then elaborated further in higher-order processing, whereas stimuli characterized as non-self-referential are not available for higher-order processing. If this is true, self-referential processing must be regarded rather as intermediary between sensory and higher-order processing than a higher-order process by itself (see Fig. 5). However, this assumption remains speculative because the exact relationship between sensory, self-referential, and higher-order processing remains to be investigated.

Based on these considerations, we assume that the involvement of lateral prefrontal cortical regions reflects the interaction between self-referential processing and higher-order processing. Higher cognitive functions might be differentially modulated by self- and non-self-referential stimuli. For example, self-referential stimuli might enhance linguistic processing and consecutive activation in lateral prefrontal cortical regions in verbal tasks; whereas non-self-referential stimuli might not require analogous enhancement because they might not be further processed and expressed linguistically. Similarly, self-referential stimuli in memory tasks require stronger involvement of autobiographical encoding and retrieval when compared to non-self-referential stimuli. Finally, presentation of one’s own face might induce increased recruitment of cognitive functions like recognition and identification, thus leading to increased neural activity in lateral prefrontal cortex; whereas the very same functions remain on a rather low level, while the brain is processing the face of another person.

Finally, the involvement of lateral prefrontal cortex in higher-order processing raises questions about its interaction with the CMS. Recent studies indicate that the level of activation or deactivation in CMS might modulate the relationship between self-referential- and higher-order processing. Some studies reported activation (and increased functional connectivity) in anterior and posterior CMS during self-referential tasks with low cognitive load (Kjaer et al., 2002; Greicius et al., 2003; Wicker et al., 2003; Lou et al., 2004). Conversely, deactivation (and low functional connectivity) in CMS has been observed in tasks with high cognitive load and low degree of self-referentiality (Gusnard and Raichle, 2001; Gusnard et al., 2001; Raichle et al., 2001; Simpson et al., 2001a,b; Kelley et al., 2002; Greicius et al., 2003; Wicker et al., 2003; Vogeley et al., 2004). These findings suggest reciprocal modulation between self-referential- and higher-order processing: activation in CMS indicates that self-referential processing predominates with higher-order processing remaining in the background. In contrast, deactivation in CMS reflects increased higher-order processing, while self-referential processing shifts into the background. The assumption of reciprocal modulation between self-referential and higher-order processing is clearly compatible with the recent observation of reciprocal modulation between medial and lateral prefrontal cortex during emotional–cognitive interaction (Goel and Dolan, 2003; Northoff and Bermpohl, 2004; Northoff et al., 2004). Unfortunately, analogous

reciprocal modulation between medial and lateral prefrontal cortex has not yet been demonstrated for the interaction between self-referential- and higher-order processing.

Neurophilosophical perspectives on the brain and its selves

In addition to highlighting the empirical trends available through modern brain imaging, where one can rather clearly distinguish self-referential and non-self-referential information processing, we would briefly consider selected historical and philosophical issues that can help us better appreciate the complexity of relatively slippery concepts such as a basic self structure, self-reference, and potentially multiple selves in the human brain/mind. It is not transparent what all these concepts mean. Vigorous and provocative threads of thought in this area go back to William James' famous Chapter X in the *Principles* devoted to "The Consciousness of Self". For instance, while we have formulated our thinking around three interactive layers suggested by contemporary analyses: the proto, mental, and the autobiographical or narrative selves (Damasio, 1999), William James' tripartite discussion focused on a "material me", "social me", and "spiritual me". Neither the historical nor modern psychological approaches are obviously isomorphic with any known brain analysis.

As James emphasized, any discussion of the self needs to include distinctions between the self as subject, or the "I," and the self as the object, or the "Me", of experience. From his cognitively oriented perspective, James saw no need to postulate a stable core self to generate experience. Rather, he attempted to simplify the analysis by claiming that the "thought is the Thinker" (see more extensive discussion in Barresi, 2002). James stated: "The consciousness of Self involves a stream of thought, each part of which as 'I' can remember those which went before, know the things they knew, and care paramently for certain ones among them as 'Me,' and appropriate to these the rest". (James 1892). Since the stream of thought is constantly changing, for James, there was no reason to postulate any core process of selfhood beyond the stream itself, which since it was constantly changing, led to the possibility of a multiplicity of selves. At the same time, James would make statements that he recognized there were deeper issues to consider: "The nucleus of the 'me' is always the bodily existence felt to be present at the time" (Barresi, 2002). In our estimation, the most cogent way to distinguish self-referential from non-self-referential attitudes evaluated in most of the work we have summarized is that "the boundary between self and not-self is one's emotional attitude about an object or thought" (Barresi, 2002).

Variants of such themes have been elaborated extensively in the humanities, and tensions between types of analysis are evident in much of the literature, too vast to summarize here. For instance, philosophers of literature such as Mikhail Bakhtin (Bakhtin, 1973, 1990), who attempted to clarify how first- and third-person views may forever yield different perspectives on the same situation, were motivated as much by the difficulty of pursuing philosophical inquiry under Communist dogma where one had to often hide their deeper convictions within allegorical analyses. We are confronted by similar problems because modern mind scientists rarely ask the deep existential questions that need to be addressed in work related to the self. In a meta-analysis such as ours, we are unable to specify the extent to which each study included used self-reference more from a deep first-person emotional perspectives rather than perhaps a more third-person "theatrical" perspectives. Indeed, as Bakhtin emphasizes, perhaps it is difficult to ever be clear about such issues

because the dialogical mental flow is so uneven (Barresi, 2002). To the extent that we can judge such subtle issues, we would suggest that the default perspective most people would assume would be more of an unadulterated first-person affective perspective. Clearly, more work needs to be done on such subtle issues. However, without further analysis, it remains possible that several types of self-referential perspectives were mixed in the studies included in the present analysis.

More scientifically oriented thinkers like Hermans and colleagues (1999), who have focused on the fact that the higher cognitive self, in each individual, may take diverse perspectives, yielding a multitude of voices that can rapidly take different viewpoints (i.e., yielding the concept of "dialogical self"—intra-subjective selves that speaks to each other). This could lead to a variety of independent voices, taking different perspectives on the same situation. Such issues would be hard to disentangle in most brain imaging studies. We are not yet in a position to argue that the CMS provide the central integrative mechanism—a clearing-house—for all of the multiple self-referential perspectives. This would require the design of novel experiments where one experimentally tries to capture the activities of various semantically mediated selves operating independently of each other as they evaluate the same stimulus materials. This would be a major methodological challenge. Perhaps some progress could be made by using simple paradigms such as used in most of the studies summarized here in individuals that commonly exhibit dissociative states or those with multiple personality disorders. Such work would, of course, be remarkably difficult to implement since fMRI environments need strict temporal control over variables.

Methodological issues

There are many methodological issues that need attention in future work. Since psychologically oriented thinkers such as William James considered self-consciousness to ride in a continuous stream of thought, with the flow of different types of self-referential perspectives, more attention will eventually have to be placed on the temporal domain of different judgments that are made in various studies. It is possible that self-referential and non self-referential evaluations require different brain resources that cannot be recruited equally easily. Such concerns would require sophisticated phenomenological studies that remain to be implemented, but they could be very productive. This might, for example, allow investigators to bridge the gap between conceptual description of prereflective and cognitive aspects of self-referential processing (see above) on the one hand and the neglect of prereflective aspects in rather cognitively oriented self-related tasks employed in most current imaging studies on the other (Legrand, 2003). One attempt to account for distinct aspects of self-related information is the study by Lieberman et al. (2004). They compared intuition-based self knowledge, which is supposed to rely more on experience with rather automatic self-processing and evidence-based self knowledge. They observed activation in the VMPFC, the nucleus accumbens, and the amygdala during intuition-based self knowledge, whereas evidence-based self knowledge induced activation in lateral prefrontal cortex, hippocampus, and posterior parietal cortex. What remains however unclear is whether both types of self knowledge, intuition- and evidence-based, correspond to our distinction between prereflective and cognitive aspects of self-referential processing (see also Fig. 5).

Although we purposefully stayed away from studies that included psychiatric or neurological patients, such perspectives should eventually help us better understand what is being studied. Disorders of self-reference, such as are common in schizophrenia, might be important for understanding the degree to which “insight” is critical for some of the brain effects that have been observed in normals. Modern neuroscience has demonstrated that within the brain of schizophrenics there is a disconnection syndrome, especially one where cognitive and affective representations are no longer well integrated. One’s sense of ownership of experience is often disturbed, and feelings and thoughts no longer well coordinated, leading to delusions and deficits in insight. It will be most interesting when there are a sufficient number of self-referential studies in well-diagnosed psychiatric syndromes, which may yield cerebral *endophenotypes* that could eventually serve as empirically reduced indicators of psychological functioning.

Finally, the issue of CMS involvement in both self-related tasks and emotion processing must be discussed. Unfortunately, there are no studies available directly comparing both (see Phan et al. (2004a,b) for an exception). We would suggest that the present analysis highlights a major way in which the brain deals with information that is especially meaningful for the self from that which is less relevant for emotional concerns. The CMS system has been long implicated in emotional processing (MacLean, 1990), and we think that most self-referential processing of information is more affective than non-self-referential processing of the same information. This affective component might be crucial for the prereflective aspect of self-referential processing as distinguished from its rather cognitive aspects. In this way, self-reference may be distinguished from concepts such as “insight” which may be more the cognitive recognition of the relationships between world events (perhaps largely a left hemisphere function), which can secondarily have emotional ramifications (more a right hemisphere function). Indeed, we note that there is a vast literature that highlights how important the right hemisphere is for the processing of emotional information, which may yield an alternative to our concept of the CMS substrates of the self. As a provisional way to parse this overlap, we would suggest that it may turn out to be the case that the affective aspect of agency may be concentrated in CMS structures, while other less self-referential aspects of emotional information processing (prosody, facial actions, etc.) may be regulated by more lateral right hemisphere structures.

Conclusion

We assume self-referential processing to be at the core of what is called the self. Self-referential processing accounts for distinguishing stimuli related to one’s own self from those that are not relevant to one’s own concerns. As such, self-referential processing might be at the bottom of what has been called “mental or core self” (Damasio, 1999), “experiential self” (Lambie and Marcel, 2002; Zahavi, 2003), “prereflective self” (Gallagher and Zahavi, 2005; Legrand, 2005), or “minimal self” (Gallagher, 2000; Gallagher and Frith, 2003) (see also (Lambie and Marcel, 2002; Baars et al., 2003; Dalgleish, 2004; Marcel and Lambie, 2004).

It will be important to better relate such functions to gender, brain lateralization, and other critical psychological functions such as emotional valence, emotional arousal/intensity, and attention to

specific psychological events (Knutson et al., 2001; Phan et al., 2002; Murphy et al., 2003; Wager et al., 2003). Additionally, further conceptual discussion is needed to more precisely delineate the relationship between the empirical findings we have discussed with respect to the CMS, the theoretical concepts of the self, and the distinct (i.e., prereflective and cognitive) aspects of self-referential processing (see also Fig. 5).

The linkage of self-referential processing to higher-order processing might provide the ground for realizing and manifesting basic notions of self in different domains and consecutively in distinct behavioral patterns. Different concepts of self by different authors might correspond to the realization of the core self system in different domains. For example, Damasio assumes an “extended or autobiographical self” (Damasio, 1999); this might reflect the linkage of self-referential stimuli to the memory domain. Another example is the concept of an “interpreter” (Gazzaniga, 1998; Turk et al., 2003), a “narrative self” (Gallagher, 2000; Gallagher and Frith, 2003), or a “dialogical self” (Hermans, 1999; Dimaggio et al., 2003); these might reflect realization of the self in various verbal domains. Analogously, other authors speak of an “emotional self” (Fossati et al., 2003, 2004) or of a “spatial self” (Vogeley and Fink, 2003; Vogeley et al., 2004) which might correspond to the linkage of self-referential processing to the emotional and spatial realms respectively.

Due to the intermediary role of self-referential processing between sensory and higher-order cognitive processing, the CMS might be crucial in linking diverse functional regions of the brain such as subcortical and lateral cortical regions. As such, the CMS allow for both bottom–up and top–down modulation between sensory, self-referential, and higher-order processing (see also Fig. 5). This in turn could provide the basis for constituting a three-layer model of the self (sensory, experiential, higher-order cognitive) with multiple facets that can operate in many different life domains. The CMS might be a convergence zone for the many different concepts of self in current neural and mind sciences. As usual, there are more questions to be asked than have been answered, but current brain imaging data are remarkably consistent with the fact that the CMS is a major locus of control for the cerebral representations of self-referential processing. Of course, in the study of subjective experience, there are abundant ways to categorize processes and events. However, our review of imaging studies has revealed that a focus on CMS may facilitate the emergence of more unified views and thereby clarify psychological issues of ultimate concern that have long been resistant to analysis.

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