



Brain imaging of the self – Conceptual, anatomical and methodological issues [☆]

Georg Northoff ^{a,*}, Pengmin Qin ^{a,1}, Todd E. Feinberg ^{b,c,d}

^a *Mind, Brain Imaging and Neuroethics, University of Ottawa Institute of Mental Health Research (IMHR), 1145 Carling Avenue Ottawa, ON, Canada K1Z 7K4*

^b *Albert Einstein College of Medicine, United States*

^c *Yarmon Neurobehavior Center, United States*

^d *Beth Israel Medical Center, United States*

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ABSTRACT

In this paper we consider two major issues: conceptual–experimental approaches to the self, and the neuroanatomical substrate of the self. We distinguish content- and processed-based concepts of the self that entail different experimental strategies, and anatomically, we investigate the concept of midline structures in further detail and present a novel view on the anatomy of an integrated subcortical–cortical midline system. Presenting meta-analytic evidence, we show that the anterior paralimbic, e.g. midline, regions do indeed seem to be specific for self-specific stimuli. We conclude that future investigation of the self need to develop novel concepts that are more empirically plausible than those currently in use. Different concepts of self will require novel experimental designs that include, for example, the brain's resting state activity as an independent variable. Modifications of both conceptual and anatomical dimensions will allow an empirically more plausible account of the relationship between brain and self.

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1. Introduction

The problem of the self has been investigated extensively in neuroscience using most notably brain imaging (Gillihan & Farah, 2005; Legrand & Ruby, 2009; Metzinger & Gallese, 2003; Northoff & Bermpohl, 2004; Northoff et al., 2006). Comparing self- vs. non-self-specific stimuli, brain imaging studies observed neural activity changes in various medial cortical regions including the perigenual anterior cingulate cortex (pACC), dorsomedial prefrontal cortex (MPFC) and the posterior cingulate cortex (PCC) (Kelley et al., 2002; Mitchell, Banaji, & Macrae, 2005; Northoff & Bermpohl, 2004; Northoff et al., 2006; Platek et al., 2006; Uddin, Iacoboni, Lange, & Keenan, 2007; Yaoi, Osaka, & Osaka, 2009; Zhu, Zhang, Fan, & Han, 2007). The results obtained in single studies were however contradicted by recent meta-analyses on imaging studies of the self (Gillihan & Farah, 2005; Legrand & Ruby, 2009) which do not support the specific association of medial cortical regions, i.e., the cortical midline structures (CMS) (Northoff & Bermpohl, 2004) with self-specific stimuli. Instead, they demonstrated that these regions may also be implicated in processing non-self-specific stimuli as, for instance personal familiar stimuli (Gillihan & Farah, 2005; Seger, Stone, & Keenan, 2004) or task-specific requirements like general evaluation (Legrand & Ruby, 2009).

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* Corresponding author. Address: Mind, Brain Imaging and Neuroethics, University of Ottawa Institute of Mental Health Research (IMHR), Room 6959, 1145 Carling Avenue, Ottawa, ON, Canada K1Z 7K4.

E-mail address: georg.northoff@rohcg.on.ca (G. Northoff).

¹ These authors have contributed equally.

However, the association of familiarity and task-specific requirements with the cortical midline structures during presentation of self- and non-self-specific stimuli remains to be investigated.

In addition to the cortical midline structures, neural processing of self-specific stimuli has recently been also associated with resting state activity in the default-mode network (DMN) (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle et al., 2001). Since the regions of the DMN strongly overlap with those of the cortical midline structures, some authors speak even of 'default-self' arguing that the self may be more or less identical with the high resting state activity observed in these regions (Boly et al., 2008; Christoff, Ream, Geddes, & Gabrieli, 2003; David et al., 2007; Golland et al., 2007; Gusnard, Akbudak, Shulman, & Raichle, 2001; Wicker, Ruby, Royet, & Fonlupt, 2003). If so the self may be assumed to be based purely on internal processing, i.e., the brain's resting state activity, and thus distinguished from external processing, i.e., stimulus-induced activity. While there is some indirect support for the regional overlap in especially the pACC between resting state activity and neural activity induced by self-specific stimuli (D'Argembeau et al., 2005; Schneider et al., 2008), direct experimental demonstration is thus far lacking. This may also be due in part to the methodological difficulty of measuring resting state activity in relation to self-specific stimuli with the latter violating the former.

There may be several reasons why the data regarding the neuroanatomical basis of the self conflict. One of them may be that differing neuroscientific and philosophical concepts of the self. (Legrand & Ruby, 2009; Northoff et al., 2006) may yield different results regarding its underlying anatomy. What exactly is meant by self when we for instance compare the neural effects of judging self- and non-self-specific stimuli? There may be other concepts of self which require a different experimental design. One possibility would be to determine if the self as judged by its internal contents is already present in the resting state independent of externally presented stimuli. This is suggested by the strong overlap between cortical midline structures (CMS) and the DMN.

Another issue is that how we organize and interpret the hierarchical structure of brain anatomy with reference to the concept of anatomically "midline structures" has special relevance for our understanding of the neuroanatomy of the self. Feinberg (2009, *this issue*) suggests that the neural hierarchy is organized along an anatomically medial–lateral or central–peripheral dimension. This results in anatomically concentric rings that extend the length of the neuroaxis from sub-cortical to cortical zones (Feinberg, *this issue*). According to this organization, the medial (interoself) system corresponds to the innermost rings and is related to self-related and homeostatic processes, the lateral (peripheral) system is anatomically related to the outer rings and subserves exterosensorimotor processes, and the middle rings represent an integrative system that mediates between the other two. Rostrally, the cortical midline regions (Northoff & Bermpohl, 2004; Northoff et al., 2006) are in part paralimbic regions that correspond to the medial- inner rings. It would be of interest to see how the imaging data map onto this medial-inner and lateral outer distinction.

Third, in addition to conceptual and anatomical issues, we need to consider some methodological issues. When observing the effects of self- and non-self-specific stimuli current imaging studies treat the self as independent variable on neural activity, while the neural activity itself as measured with fMRI is considered the dependent variable. This informs us about neural activity related to the stimulus itself, e.g., the stimulus-induced activity but it may not provide any insight into the brain's intrinsic activity, e.g., its resting state activity, and how it modulates the stimulus-induced activity, e.g., rest–stimulus interaction (Northoff, Qin, & Nakao, 2010). However as there is strong overlap between stimulus-induced activity in CMS and resting state activity in the DMN, one may need to consider the latter, e.g., the resting state activity, in experimental designs. To do that, however, we may need to modify our current methodological and experimental approaches to the self in brain imaging studies.

2. Concepts of the self and their experimental realization

2.1. Content-based concepts of the self

The question of the self has been one of the most salient problems throughout the history of philosophy, psychology and neuroscience (Gallagher, 2000; Gallagher & Frith, 2003; Metzinger & Gallese, 2003; Northoff, 2004). For example, William James distinguished between a physical self, a mental self, and a spiritual self. These distinct selves even may be related to distinct brain regions (Churchland, 2002; Dalgleish, 2004; Damasio, 1999, 2003a, 2003b; Gallagher, 2000; Gallagher & Frith, 2003; Keenan, Wheeler, Platek, Lardi, & Lasseonde, 2003; Kelley et al., 2002; Kircher & David, 2003; Lambie & Marcel, 2002; LeDoux, 2002; Marcel & Lambie, 2004; Northoff & Bermpohl, 2004; Panksepp, 1998a, 2003; Stuss, Gallup, & Alexander, 2001; Turk, Heatherton, Macrae, Kelley, & Gazzaniga, 2003; Turk et al., 2002; Vogeley & Fink, 2003).

Damasio (1999) and Panksepp (1998b), Panksepp (2003) suggest a "proto-self" that corresponds more or less to James's physical self. The "proto-self" is supposed to outline one's body in affective and sensory-motor terms and is associated with subcortical regions like the PAG, the colliculi and the tectum (Panksepp, 2007). Such bodily self-related sensorimotor contents resemble William James's description of the physical self. A variant of such sensorimotor-based self has recently been suggested by Legrand and Ruby (2009). Based on the phenomenological distinction between reflexive, e.g., cognitive, and pre-reflexive, e.g., pre-cognitive self-awareness, they associate the latter with sensorimotor rather than cognitive contents (Legrand & Ruby, 2009). This emphasis on sensorimotor functions is in agreement with their assumption of embodiment as crucial for reflexive and thus cognitive functions (Legrand, 2005). Following their sensorimotor-based concept of self, they assume that the neural structures underlying sensorimotor functions including sensorimotor feedback loops are crucially involved in generating a sense of self, e.g., pre-reflexive self-awareness. This hypothesis remains to be experimentally tested.

In addition to sensorimotor and bodily contents, mental contents are regarded as specific for the self. What has recently been described as the “minimal self” (Gallagher, 2000; Gallagher & Frith, 2003) or “core or mental self” (Damasio, 1999) might roughly correspond to James’ concept of mental self. The “core or mental self” builds upon the “proto-self” in mental terms and is associated with regions including the thalamus and the ventromedial prefrontal cortex (see for instance Damasio, 1999, 2003a). Instead of sensorimotor and bodily contents of the ‘proto-self’, the mental self is defined by its mental contents and their associated cognitive contents. For instance, one’s own name may be considered a mental content that is specifically related to the self as part of the mental self, and therefore the mental self is not restricted to parts of one’s own body nor their underlying substrate. Instead, the mental self may also concern stimuli from the outside of the body and person. The central feature is not ownership (as in the case of the body) but rather the designation of certain stimuli as being either self or non-self-specific. Since the judgment of stimuli as either self- or non-self-specific is the guiding experimental paradigm in most current imaging studies, they presuppose in part the concept of the mental self (see below).

Finally, a more extended concept of the self may be defined. Here the self is not based on either sensorimotor or mental contents as the ‘proto- and the mental self’ but rather on its autobiographical contents. The inclusion of autobiographical memories further entails the concept of time, more specifically the subjective experience of time and episodic memory with its extension into past, present and future. Philosophically, the concept of the autobiographical self overlaps with the concept of personal identity and the question of temporal continuity. This is reflected in, for instance, Damasio’s (1999) “autobiographical self” and Gallagher’s (Gallagher, 2000; Gallagher & Frith, 2003) “narrative self” in that both rely on linking past, present, and future events thereby resembling James’ concept of a spiritual self. Since the autobiographical dimension impacts the ability to judge specific stimuli as either self- or non-self-specific, many of the current paradigms in brain imaging presuppose an ‘autobiographical self’. The concepts of self assumed in many imaging studies therefore amounts to an admixture of mental and autobiographical self. Taken together, the self is defined here on the basis of various contents. The proto-self presupposes bodily contents. The mental self is determined by one’s own mental contents. Finally, the autobiographical self presupposes autobiographical contents and distinguishes them from heterobiographical contents. These different contents provide the basis for current neuroscience to ‘neuralize’ the self, and provide the basis to investigate whether different self-specific contents are associated with different brain regions.

2.2. *Process-based concepts of the self*

What remains unclear, however, is what unites the different content-based concepts of self? One common denominator is that the stimuli are often characterized as self-referential and entail self-referential processing that is considered common to the aforementioned distinct concepts of self. This has also been described as ‘self-related’ or ‘self-relevant’ processing (Churchland, 2002; Dalgleish, 2004; Gallagher, 2000; Gallagher & Frith, 2003; Keenan et al., 2003; Kelley et al., 2002; Lambie & Marcel, 2002; LeDoux, 2002; Marcel & Lambie, 2004; Northoff & Bermpohl, 2004; Turk et al., 2002, 2003). In this particular group of studies subjects were presented pictures, faces, words, or tones, and had to evaluate whether they were personally related to them or not. Faces, for instance, were presented from the own person, relatives, family members, and other non-related famous and non-famous persons. Subjects had to decide upon the degree of the stimuli’s closeness to the own person. Another example is the way we perceive pictures of ourselves or close friends vs. pictures of completely unknown people or pictures of our houses where we spent our childhood vs. pictures of any unknown house, etc. Such comparisons are possible in different sensory modalities. Self-relatedness is here understood and presupposed in a cognitive sense that implies that one becomes aware of one’s self once one sees the stimulus.

The experimental designs in current imaging studies focus on the judgment of specific contents, be they sensorimotor/bodily, mental or autobiographical. This judgment task implicates self-awareness or self-consciousness, the ability to become aware of that stimulus being specific or non-specific. Imaging studies thus combine a content-based view of the self, be it bodily, mental or autobiographical, with the recruitment of higher-order cognitive functions required in the task. Legrand and Ruby (2009) have criticized the latter. They argue that the imaging results may be confounded by a general non-specific evaluation function and influenced by the judgment required in these imaging studies.

The focus on the role of making judgments raises the role of self-consciousness or self-awareness. This is because the various tasks applied in these studies required subjects to make explicit reference to some aspects of themselves and to consciously access and monitor representational content about one’s self. Since subjects must reference themselves in self-consciousness or self-awareness, one may speak of ‘self-referential processing’. Due to the fact that it requires self-consciousness or self-awareness, self-referential is assumed to involve higher-order cognitive functions, the “highest” and most advanced forms of cognitive processing, out of which the self emerges at the pinnacle of the psychological and neural hierarchy (Feinberg, 2000, 2001a, 2001b). On the philosophical level, such higher-order view of self-referential processing corresponds to predominantly cognitive accounts of the self and subjectivity as it has for example been advanced by Kant and the German school of idealism.

What are the alternatives? Experimentally, we need to replace “judgment” by a less cognitive task as for instance by mere perception of self-specific and non-self-specific stimuli. This strategy has been pursued by some single studies (Northoff et al., 2009; Qin et al., 2010; Schneider et al., 2008). In one, subjects were shown either emotional pictures (Northoff et al., 2009; Schneider et al., 2008) or their own name (Qin et al., 2010) and instructed to not make any judgment. This experimental design therefore does presuppose a judgment or general evaluation function. Interestingly, in both cases various cortical midline structures as well as subcortical regions were found to be active during the self-specific stimuli. This

indicates that the neural activity in these regions may not be related to the general evaluation function or judgment itself (Legrand & Ruby, 2009).

In addition, neural activity in the CMS may also be independent of the consciousness of the self, e.g., self-consciousness. Qin et al. (2010) demonstrated neural activity in various cortical midline regions during perception of the subject's own name in patient's in vegetative state (Qin et al., 2010). These results indicate first that the self may be processed independent of full consciousness, and second that the neural activity in the CMS may not be related to consciousness itself whether it is the consciousness of the self or the non-self.

In summary, imaging results have demonstrated that the neural activity in the CMS is not specific for self-specific stimuli. Hence, distinction between self- and non-self-specific contents could not be mapped onto a corresponding anatomical distinction in the cortex. At the same time however, neural activity in the CMS may not be associated with judgment/general evaluation function or consciousness either. This means that the neural activity in the CMS cannot be accounted for by a specific function be it judgment/general evaluation or consciousness. This raises the question: What is the neural activity in the CMS specific for if it is neither self-specific contents nor a general evaluation function nor consciousness? Rather than being specific for a specific content (bodily, mental, autobiographical) or a specific function (judgment/general evaluation, consciousness), neural activity in the CMS may be assumed to be specific for a specific process. Conceptually, this entails a shift from a content- or function-based concept of self to a process-based view of the self. Neural activity in the CMS may then be determined by a specific process that is instantiated when being confronted with both self- and non-self-specific stimuli. What could this specific process be?

2.3. Psychological and experimental characterization of self-related processing

Any stimuli, be they bodily, mental or autobiographical, must first be related to the organism in order for the latter to be able to access the former as a specific content be it self- or non-self-specific in perception or judgment. The constitution of any content thus may be traced back to a specific relation between the stimulus and the organism which must itself be mediated by a specific process in order to yield any kind of content, be it bodily, mental, or autobiographical.

The process that establishes a relation between the organism and a stimulus is called *self-related processing*. It is distinguished from its cognitive counterpart, *self-referential processing*, that takes the contents be they bodily, mental or autobiographical as given (and preexisting). Self-related processing concerns stimuli that are experienced as strongly related to one's own person. A definition of self-related 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 (2005) and others' (Legrand, 2005; Legrand & Ruby, 2009) describe as "prereflective" whereas our current focus is less on associated cognitive and reflective functions. As such we distinguish self-related processing from what is commonly called "insight" which we consider to presuppose cognitive and reflective functions rather than simply pure subjective and phenomenal aspects (Metzinger & Gallese, 2003; Zahavi, 2005).

Self-related processing (SRP), can neither be associated with the "self-as-object" nor the "self-as-subject"; instead, it makes this distinction first and foremost possible in that it allows to distinguish between subject and object and hence between both concepts of the self. SRP must consequently be regarded more basic and fundamental than both subjective, i.e., phenomenological, and objective, i.e., neuroscientific, concepts of the self. As we will see in the following, characterization of SRP as non-cognitive, affective, basic and fundamental is central in constituting subjectivity and objectivity. Neither SRP nor the implied sense of self can be equated with any kind of content like self-specific contents as distinguished from non-self-specific ones or subjective-experiential contents as distinguished from objective-observational ones. Instead, SRP may conceptually be determined rather as process that first and foremost makes the distinction between different kinds of contents with different degrees of self-relatedness possible.

Considered in this way, the neural mechanisms underlying SRP can no longer be regarded the neural correlates, e.g., the sufficient conditions, of the self. Instead, the neural mechanisms underlying SRP may only be considered a necessary condition which is not sufficient by itself to constitute a self with its self-specific contents. SRP may only be a necessary but non-sufficient condition of the self that as such enables and predisposes but not executes the self. One may consequently characterize the neuronal mechanisms underlying SRP no longer as neural correlates but rather as 'neural predisposition' of the self. This entails that methodologically we may need to tap into those neural mechanisms and processes that precede those we currently focus our attention within the context of our current designs. More specifically, this means that we may need to shift our attention from the perception or judgment of self- and non-self-specific contents to those mechanisms that precede, e.g., enable and predispose those very contents. Neuronally, this entails that we may need to shift our attention from stimulus-induced activity as related to self- and non-self-specific stimuli to the resting state activity itself and its interaction with the former amounting to rest–stimulus interaction (Northoff et al., 2010). This shift in the methodological focus would be well compatible with the above described overlap between CMS during self-specific stimuli and the high resting state activity in the DMN. Hence, our focus may need to shift from stimulus-induced activity to the brain's intrinsic activity, its resting state activity, and how the latter interacts with the former, e.g., rest–stimulus interaction (see also Northoff et al., 2010).

How though can we include the resting state activity of the brain and its impact on stimulus-induced activity, e.g., rest–stimulus interaction (Northoff et al., 2010), as variables in our experimental design? One way is to manipulate the level of resting state activity itself by for instance opening or closing the eyes (Logothetis et al., 2009; Raichle, 2010) and see how it impacts the neural processing of self- and non-self-specific stimuli and thus their stimulus-induced activity. While this has

been done in predominantly the sensory domain (see Northoff et al. (2010) for a recent review), it remains to be shown in the case of the self. Experimentally, this implies a reversal in our assignment of dependent and independent variable. The self is no longer the independent variable but rather the dependent one while the brain's resting state activity becomes the independent variables. Both rest–stimulus interaction and stimulus-induced activity are then dependent variables. While being fully aware of the methodological challenges, this though remains to be done (Fig. 1).

3. Anatomy of the self and subcortical–cortical integration

3.1. Neuroanatomy: radial-concentric organization and subcortical–cortical systems in the brain

Many imaging studies on the self demonstrated involvement of cortical midline structures like the VMPFC, the PACC, the DMPFC and the PCC in the neural processing of self-specific stimuli (Northoff et al., 2006). The self-specificity of the neural activity in the CMS has been questioned on several grounds. At the same time the concept of cortical midline structures has been extended to include subcortical midline regions (Feinberg, 2009; Northoff & Panksepp, 2008; Panksepp & Northoff, 2009). Consecutively, an integrated subcortical–cortical midline system has been proposed as specific for the self. This raises the question for the anatomical and functional continuity between subcortical and cortical regions that may be crucial for the self.

Nieuwenhuys proposed there is a medial–lateral organization in subcortical regions that are located concentrically or radially around the aqueduct, with progressive extension from medial to lateral locations (Nieuwenhuys, 1996; Nieuwenhuys, Veening, & van Domburg, 1988/89; Nieuwenhuys, Voogd, & Van Huijzen, 2007). Based on various distinct features (see below), he distinguished the subcortical regions into three distinct territories, core, median and lateral paracore, and lateral regions which, despite being closely interconnected, can be distinguished from each other. Core subcortical regions refer to those regions that are located in direct proximity to the aqueduct and may thus be described as paraventricular or periaqueductal. These regions include the PAG, the pontine central gray, the medial hypothalamus, the septum, the parabrachial nuclei and the dorsal vagal complex. While the subcortical median paracore regions are located directly adjacent to the core regions; subcortical median paracore regions include the series of raphe nuclei, the lateral hypothalamus, the bed nucleus of the stria terminalis. These are closely connected to the bilateral paracore regions that include the ventral tegmental area (VTA), the locus coeruleus, the substantia nigra, the nucleus reticularis.

Based upon this organization, Feinberg proposed that these regions can be thought as of a series of concentric rings (Feinberg, 2009, this issue). The inner rings (core and paracore regions), can be distinguished from the outer (lateral-peripheral) rings with respect to their fibers (myelinated or unmyelinated), biogenic amines (serotonin, noradrenaline/adrenaline, dopamine, histamine), circumventricular organs, gonado-steroid receptors, and coherent behavior (e.g., as induced by localized electrical stimulation of the brain) (see Nieuwenhuys (1996, pp. 560–567) and Feinberg (2009) for details). According to Nieuwenhuys and co-workers, the core and paracore regions functionally are characterized by their involvement in processing interoceptive stimuli and regulating the body's homeostatic milieu, vegetative-autonomic functions, and a

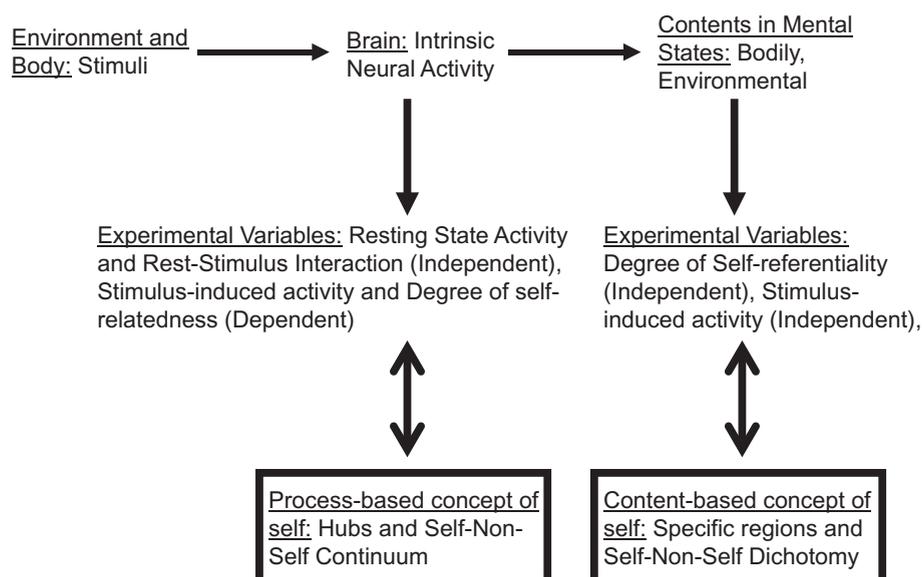


Fig. 1. Content- and process-based concepts of the self and the brain.

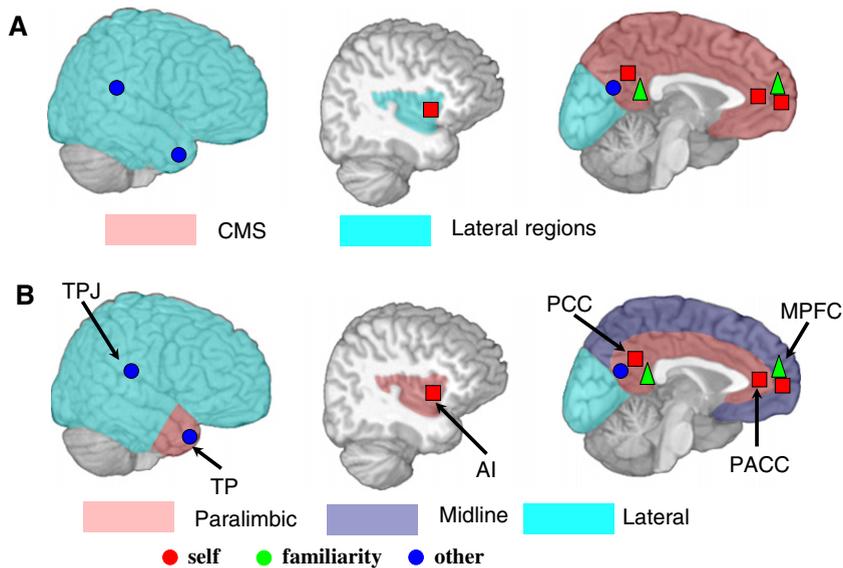


Fig. 2. (A) The traditional medial–lateral twofold anatomical dichotomy. Red: CMS; Cyan: lateral regions. (B) Threefold anatomical distinction. Red: paralimbic; Blue: Midline; Cyan: lateral. Red square represent the regions activated under self condition in meta-analysis; Green triangle represent the regions activated under familiarity condition in meta-analysis; Blue dots represent the regions activated under other condition in meta-analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

variety of specific emotional and motivational processes. These medial structures are distinguished in Feinberg’s scheme from the lateral or peripheral rings that are concerned with exteroceptive and sensorimotor stimuli.

Based on MacLean’s and Nauta’s concept of the limbic system, Nieuwenhuys (1996) proposes the core–paracore system extends into the mesencephalon and diencephalon and is closely connected to the hypothalamus and various regions in the forebrain including the amygdala, septum, the hippocampus, and parahippocampal gyrus. This led to the concept of the ‘greater, distributed or extended limbic system’ (de Olmos & Heimer, 1999; Heimer, 2003; Morgane, Galler, & Mokler, 2005; Morgane & Mokler, 2006).

Feinberg (2009, this issue) proposed that this medial system further extends up the neural hierarchy into paralimbic regions that anatomically linked to emotional and motivational networks. These paralimbic areas include the lower parts of the orbitofrontal cortex, the perigenual, supragenual anterior cingulate cortex (PACC, SACC), the posterior cingulate cortex (PCC), the retrosplenial cortex (RSC), the temporal pole and the insula. Extending the radial–concentric organization into the subcortical mesencephalic level and its extensions into the forebrain as the starting point, Feinberg (2009) argues that the annular ring-like organization is preserved at the level of the cortex, the inner ring represented by medially located self-related systems and the outer ring represented by the exterosensorimotor systems. Feinberg also assumes a middle ring on the cortical level that is interposed between the inner and outer rings and thus between paralimbic and lateral cortical regions. He calls this the *integrative self-system* and it includes regions like the medial orbitofrontal cortex, the ventromedial and dorsomedial prefrontal cortex (VMPFC, DMPFC) and the medial parietal cortex (MPC) which have recently been subsumed under the concept of cortical midline structures (CMS) (Northoff & Bermpohl, 2004; Northoff et al., 2006). Since it is sandwiched between inner and outer rings and their involvement in intero- and exteroceptive processing respectively, Feinberg assumes this middle ring to account for integrating and linking both kinds of stimuli, i.e., intero–exteroceptive integration.² The CMS do grossly overlap with what especially in the imaging domain is often described as the default-mode network (DMN) that is supposed to be characterized by particularly high resting state activity, e.g., intrinsic activity (see above in chapter 1 of this part as well as Buckner et al., 2008; Raichle et al., 2001). How such high intrinsic or resting state activity in the CMS is related to intero–exteroceptive integration, as postulated by Feinberg, remains unclear though.

Taken together, the traditional medial–lateral twofold anatomical dichotomy is here challenged by a threefold anatomical distinction between three different concentric rings that extend from subcortical to cortical regions. These three rings can be characterized as paralimbic, heteromodal/CMS midline and exterosensorimotor/lateral regions.

² What though remains unclear whether such intero–exteroceptive integration on the cortical level corresponds to analogous processes on the level of the forebrain and the mesencephalon. One could for instance imagine that what is described as core system on mesencephalic level may extend into the paralimbic areas since both are located directly adjacent to the aqueduct/ventricle. While the median and lateral paracore regions on the mesencephalic level may correspond to the middle ring on the cortical level and thus cortical midline structures. Support comes here from the connectivity pattern. Cortical regions like the anterior cingulate (PACC, SACC, PCC), the caudal orbitofrontal cortex, the temporal poles and the insula are characterized by strong inputs from especially the subcortical core regions like the PAG (see Nieuwenhuys, 1996, p. 573). In contrast, the VMPFC and the DMPFC receive for instance strong input from especially the raphe nuclei as median paracore regions and the locus coeruleus as lateral paracore region (Morgane et al., 2005; Nieuwenhuys, 1996).

3.2. Correspondence between anatomical and conceptual distinctions

We now have two different anatomical distinctions on the cortical level (see Fig. 2a and b). There is the traditional one between medial and lateral regions. Medial regions include the PACC, SACC; VMPFC, DMPFC, PCC, MPC, and precuneus (see Fig. 2a) which, within the context of the self, have been subsumed under the concept of cortical midline structures (CMS) (Northoff & Bermpohl, 2004; Northoff et al., 2006). The CMS is distinguished from more lateral regions like the lateral prefrontal cortex and the lateral parietal cortex. The initial assumption was that the CMS are specific for self-relatedness which though as discussed is controversial. The question is whether there is a correspondence between anatomical and conceptual determination of the self as outlined above.

What can one do now to increase the match between anatomical and conceptual determination of the self? One can either modify the conceptual determination of the self as proposed above, and/or one can modify the anatomical determination of the self in terms of medial regions and the CMS as suggested by Nieuwenhuys, Mesulam and Feinberg. Rather than dividing cortical regions into medial and lateral ones, this model suggests a threefold distinction between paralimbic, medial heteromodal (CMS) and exterosensorimotor/lateral regions on the cortical level (see Fig. 2b). The medial regions and thus the CMS are no longer a homogenous anatomical entity but are split off instead into paralimbic regions (PACC, SACC, PCC) and the heteromodal (CMS) regions (VMPFC, DMPFC, Precuneus). Moreover, the insula which in the medial–lateral model is classified as lateral region is now considered part of the paralimbic system (see Feinberg, this issue). Hence, the same regions are classified and grouped in different ways in both anatomical models, the twofold medial–lateral model and the triadic paralimbic-heteromodal/CMS–exterosensorimotor/lateral model.

3.3. Meta-analysis of the self – methods

We conducted a descriptive meta-analysis of all recent studies on the self and matched the respective anatomical locations of self, familiarity and non-self onto both anatomical models. The concept of self was defined operationally as stimuli like specific words that were attributed a high degree of relevance to the self; familiar but not self-related stimuli such as famous faces, and other stimuli that were neither self-related nor familiar. Anatomically we were limited to focussing on cortical regions because data on subcortical regions and the self are sparsely available (Northoff et al., 2009; Schneider et al., 2008).

Selection of studies: We included three kinds of stimulus-dependent conditions, i.e., single studies and their comparisons, in our meta-analysis. We included studies focusing on self-specific stimulus and compared them with non-self-specific stimuli, i.e., stimuli related to other personal familiar and non-personal familiar persons. This accounted for the self conditions. In addition we also included another set of studies that focused on personal familiarity by comparing personal familiar stimuli and non-personal familiar stimuli and self-specific stimuli. The third set of studies, the other condition, included the results from the comparison between other stimuli (non-self-specific and non-personal familiar stimuli) and self-specific and personal familiar stimuli. The inclusion of the three sets of studies allowed us to investigate the relationship between self, familiarity and other.

All the studies were selected from the search result in Pubmed from 1999 to August of 2009. Both the fMRI and PET results were included in the current meta-analysis. For all the four conditions, the following inclusion criteria were applied:

1. Only data (brain activity coordinates) from adult healthy subjects were included while those from neurological or psychiatric patients were excluded.
2. Only studies measuring brain activity in the whole brain were included while studies based on regions of interest (ROI) analysis were excluded.
3. All studies reporting significant activity changes in specific regions were included whereby only the coordinates of the peak voxel maxima were considered while we did not consider the volume of the activated clusters.
4. Significant activity coordinates within the whole brain were included as distinguished from region-of-interest-based meta-analyses (see for instance Northoff et al. (2006) who focused only on the midline regions).
5. Significant activation changes yielded by task (e.g., self- vs. non-self judgment)- and/or stimulus (e.g., self- vs. non-self-specific) comparison (image subtraction method, parametric designs and brain imaging (fMRI, PET)-other signal (behavior, ERP) correlations) were included. In contrast, data about functional connectivity were not considered.
6. The coordinates reported in the space of the MNI template or the atlas of Talairach and Tournoux were included.

See the following information for each condition:

Self condition: We included 57 recent papers about self-specific processing. 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. We used the following keywords to find the studies for the self condition: “fMRI” or “PET” with “self”, “self-related”, “self-relevant”, “own name”, “own face”, “autobiographical”, “First-person perspective” and “Agency” in the title or abstract of the studies. The tasks used in these papers included trait adjective judgment, retrieval of personality traits, face recognition, body recognition, personal thinking, name perception, autobiographical memory, own feeling, self-administered pain, person perspective tasks and agency tasks. The following contrasts were employed in the single studies: self vs. personal familiarity, self vs. control/baseline, self vs. public people, first-person perspective vs. third-person perspective and self vs. other (agency task). The coordinates that showed significantly

stronger brain activity comparing the self condition with other conditions (even all the condition showed deactivation compared with the baseline) in the single studies were considered. Finally, the coordinates of the brain regions showing correlation between self evaluation and BOLD signal were also included.

Familiarity condition: According to the difference between personal familiar people and famous people (Sugiura et al., 2009), our familiarity condition included 23 recent papers that investigated the neural effects of personally familiar people, e.g. participants' family, friends, classmates and relatives. We used the following keywords to find the studies for the familiarity condition: “fMRI” or “PET” with “familiarity”, “familiar name”, “familiar face”, and “familiar voice” in the title or abstract of the studies. The tasks adopted in the single studies on familiarity included face recognition, body recognition, voice recognition, trait adjective judgment and name recognition. The following contrasts were employed in the single studies: personal familiarity vs. self, personal familiarity vs. stranger/baseline and personal familiarity vs. public people. The coordinates that showed significantly stronger brain activity in personal familiarity condition when compared with the other condition in single studies were also included. Finally, the coordinates showing common brain activity for self and familiarity (Vanderwal, Hunyadi, Grupe, Connors, & Schultz, 2008) were also included in the familiarity condition. While the very same brain regions were not considered in the self condition (because we assumed that the common regions for self and familiarity represent the personal familiarity of self-specific stimuli).

Other condition: The other condition included 23 recent papers that came from both the self condition and the familiarity condition. These studies employed trait adjective judgment about public people, agency, public people's name recognition, public people's face recognition, or retrieval of public people's trait adjective, the third personal perspective tasks and the other agency tasks that were taken as control condition in the studies on self and familiarity. The other condition included the following contrasts in the single studies: public people vs. self, public people vs. stranger/baseline, public people vs. personal familiar people, third-person perspective vs. first-person perspective and other vs. self (agency task). The coordinates that showed significantly stronger brain activity comparing the other condition with the self and familiarity conditions in the single studies were included.

General statistical analysis: We used Multilevel Kernel Density Analysis (MKDA) (Wager, Lindquist, Nichols, Kober, & Van Snellenberg, 2009) to process our meta-analysis, a voxel-wise coordinates based meta-analysis on the brain imaging studies. In MKDA, the coordinates are treated as the location of the activation; the coordinates from one contrast in one study make up a particular statistical contrast map (SCM). The main aim of the MKDA is to reconstruct a map of significant regions for each statistical contrast map within each study, and analyze the consistency and specificity across all the studies in the neighborhood of each voxel.

In the following, the detailed method used in the present study will be described. The coordinates (peak activation) in each single study were transferred in MKDA to a standard brain from the Montreal Neurologic Institute as distributed with SPM2 software (Wellcome Department of Imaging Neuroscience, London, UK) and the coordinates from the same contrast will make up one special SCM. In order to integrate the coordinates in space, the coordinate in each SCM were considered as one spherical kernel with radius = 10 mm. This means that the voxels around the coordinates in 10 mm were regarded as activated, the value of these voxels were threshold at a maximum of 1. This contributed to construct one indicator map for each SCM where the value 1 in the voxel represented a coordinate (reported in the single study) in the neighborhood. The indicator maps were then weighted by the number of the subjects and the kind of data analysis (random or fixed). The current version of MKDA weights each SCM by the square root of the number of the subjects. Studies using fixed effects analysis let to w down-weighting of the SCM by a factor of 0.75. We did not consider the z-scores of the single studies because (i) they are not provided by all studies and (ii) their inclusion has been shown to confound with the replicability

Table 1

Comparison between the two- and three-fold anatomical characterizations with regard to meta-analytic results from self, familiarity and other.

	Self	Familiarity	Other (no-self and no familiarity)
<i>Paralimbic</i>			
Anterior	PACC, Insula	–	–
Posterior	PCC	PCC	PCC, TP
<i>Midline</i>			
Anterior	MPFC	MPFC	–
Posterior	–	–	–
Lateral	–	–	TPJ
<i>CMS</i>			
Anterior	PACC, MPFC	MPFC	–
Posterior	PCC	PCC	PCC
<i>Lateral regions</i>			
Anterior	Insula	–	–
Posterior	–	–	TPJ, TP

PACC: perigenual anterior cingulate cortex, PCC: posterior cingulate cortex, MPFC: medial prefrontal cortex, TP: temporal pole, TPJ: temporoparietal junction.

of activation across studies hence making interpretation more difficult (Kober et al., 2008; Wager et al., 2009). The weighted average of the indicator maps was subsequently compared with the maximum proportion of the activated comparison maps expected under the null hypothesis that there is no coherent spatial consistence across the SCMs. During the calculation, the random effects analysis was used. For the threshold, MKDA used the threshold derived from Monte Carlo Simulation of the global null hypothesis. The contiguous activated clusters of each SCM were identified, and were selected at random within a gray matter mask (smoothed to include an 8 mm border, derived from segmentation of the avg152T1.img template using SPM2). In the present study, we used 5000 Monte Carlo iterations (the results should be stabilize after 2000) (Wager et al., 2009). We conducted the meta-analysis for each condition separately, i.e., self, familiarity, and other, to reveal those brain regions specifically associated with each condition.

3.4. Meta-analysis of the self – results

During the self condition, the meta-analysis yielded activated clusters in the PACC, the MPFC and PCC as well as in other regions including the left anterior insula and right inferior frontal gyrus (IFG). The familiarity condition revealed activated clusters in MPFC and PCC but neither in PACC nor the insula. While the other condition yielded activation clusters only in posterior midline regions like the PCC and other temporal regions like the bilateral temporoparietal junction (TPJ) and left temporal pole (TP).

In a second step, we mapped these results onto both anatomical distinctions, the twofold medial–lateral one and the threefold paralimbic–midline–lateral one (see Fig. 2a and b and Table 1). This showed that both self and familiarity conditions were grouped together within the medial regions of the CMS without being distinguishable from each other. Moreover, the self condition also recruited a lateral region, the insula (see Fig. 2a and Table 1). Hence, the medial–lateral model can neither distinguish between self and familiarity grouping both in the same set of regions, the anterior CMS. Nor can it group the self coherently into the medial regions because it associates the self also with a lateral (as based on the traditional twofold model) region, the insula. Taken together, the medial–lateral anatomical determination fails to distinguish the self from both familiarity and lateral regions.

We then considered whether the data would fit the aforementioned paralimbic–heteromodal/CMS–exterosensorimotor/lateral triadic division. Using this model, studies on the self recruited the PACC and the insula are considered paralimbic regions; these regions were specific for the self as distinguished from both familiarity and other (see Fig. 2b and Table 1). In addition, studies on the self also recruited medial prefrontal regions (MPFC) including both VMPFC and DMPFC; there they though overlapped with the familiarity condition. Hence, unlike the paralimbic regions, the anterior midline regions turned out to be non-specific for the self. All three, self, familiarity and other mapped onto posterior paralimbic regions like the PCC and the temporal pole.

3.5. Meta-analysis of the self – discussion

The main results of our meta-analysis are: (i) no distinction of the self from familiarity in the medial–lateral model while both can be distinguished from each other in the threefold paralimbic–heteromodal/CMS–exterosensorimotor/lateral model; (ii) no specific association of the self with exclusively medial regions in the medial–lateral model because of recruitment of the insula which though in the threefold model is grouped among the paralimbic regions indicating self-specificity (see Feinberg, this issue); and (iii) anterior–posterior distinction with anterior regions being specific for self and/or familiarity as distinguished from other while posterior regions are recruited by all three. All three findings shall be discussed in more detail in the following.

We found the self could not be distinguished from familiarity in the medial–lateral model while it was specifically associated with anterior paralimbic regions in the threefold model. The PACC was specific for the self condition; this region was neither recruited during familiarity nor during other. While in the medial–lateral model the PACC is grouped with other medial regions, the MPFC, it is distinguished from them in the threefold model as paralimbic region as distinguished from midline regions. The threefold anatomical model thus matches better with our conceptual (and psychological) distinction between self and familiarity. One may consecutively regard the threefold anatomical model (Feinberg, 2009) to be more empirically plausible with regard to the self than the twofold model.

The threefold model considers the PACC to be different from medial prefrontal cortical regions like the VMPFC and DMPFC. As described above this is mainly based on cytoarchitectonic, neurochemical and connectional features. Our meta-analysis adds a psychological dimension to it by characterizing the PACC as specific for the self as distinguished from familiarity and other. Hence, the distinction of the anterior paralimbic regions from anterior midline regions in the threefold model is supported on psychological grounds.

Interestingly, the very same region, the PACC, shows hyperactivity in the resting state in patients with depression, e.g., major depressive disorders, as it has been demonstrated in both human patients and animal models of depression (Alcaro, Panksepp, Witzak, Hayes, & Northoff, 2010). While other medial prefrontal regions, the midline regions, do not display such hyperactivity in depression. Most importantly, depressed patients do indeed show an increased preoccupation with their own self (Northoff, 2007), the increased self-focus which indeed has been associated with the PACC and especially its resting state activity (Grimm et al., 2009). This lends further empirical support, e.g., psychiatric support, to the threefold anatomical model and its distinction between paralimbic and midline regions.

Considering the psychological and psychiatric evidence in favor of the distinction between anterior paralimbic from midline regions, this raises the question of the underlying physiological mechanisms. The PACC shows most consistently negative BOLD responses (NBR), e.g., deactivation, during stimulation in fMRI (Northoff et al., 2007). The physiological basis of such NBR in PACC remains however unclear. First, there is some evidence linking PACC with neural inhibition and gaba-ergic modulation which though needs to be explored in further detail. The issue here is whether this is really specific for the PACC as distinguished from other regions or whether it is rather specific for NBR in general independent of specific regions like the PACC. Muthukumaraswamy and Singh (2009) for instance demonstrated the association of GABA with NBR in visual cortex (Muthukumaraswamy & Singh, 2009). Moreover, the specific relationship of NBR to the self as distinguished from familiarity needs to be demonstrated in order to link PACC and the self. Interestingly, depressed patients show reduced NBR in PACC (Grimm, Boesiger et al., 2009) which is also decoupled from gaba-ergic modulation (Walter et al., 2009). How that is related to the increased self-focus in depression remains unclear.

Our second main finding concerns the relationship between the insula and the self. The insula is characterized as a lateral region in the twofold medial–lateral model and distinguishes the insula from the PACC as medial region. In the twofold model the self-stimuli recruits both a medial region (PACC) and a lateral region (insula). In the threefold anatomical model (Feinberg, 2009, this issue), the insula is grouped as paralimbic region together with the PACC, and we found that both paralimbic regions, PACC and insula, were specific for the self as distinguished from both familiarity and other. Hence, the threefold anatomical distinction seems to match better with the conceptual distinction between self and familiarity than twofold anatomical model.

The specific involvement of the insula in self has recently been shown in two studies. The insula is closely involved in processing interoceptive stimuli from the body (Craig, 2002, 2004, 2009) which, following the threefold model, relays to the PACC. If the self is specifically associated with both insula and PACC, one would assume interoceptive processing to be crucially involved in the self and its distinction from familiarity. This supports Feinberg's (2009, this issue) proposal that the paralimbic regions mediate an interoceptive- and thus bodily-based self as distinguished from an exteroceptive- and environment-based self. However, neither the PACC nor the insula are exclusively and specifically involved in processing interoceptive stimuli. Rather both regions have been demonstrated in processing exteroceptive stimuli as for instance emotional stimuli with the insula showing positive BOLD responses (PBR) rather than NBR as the PACC (Phan, Wager, Taylor, & Liberzon, 2002). Therefore, neither the insula nor the PACC can be regarded to be specific for interoceptive stimuli as distinguished from exteroceptive ones. However, these regions may be critically involved in processing self-related and emotional stimuli.

The predominance of the above mentioned stimulus-induced NBR in the PACC indirectly indicates the level of resting state activity in that region. This level of resting state activity may be modulated by either exteroceptive or interoceptive stimuli presupposing what recently has been called rest–stimulus interaction (Northoff et al., 2010). However, while the interaction of the PACC resting state activity with exteroceptive stimuli has been demonstrated (Grimm et al., 2009), this remains to be demonstrated for interoceptive stimuli. Considering our meta-analytic findings here, one may assume that a specific interaction of the resting state activity in the PACC with intero- and exteroceptive stimuli may distinguish the self from familiarity and other. The self would then be generated by a specific rest–intero–extero interaction that may be mediated by a specific constellation of the neural activities in the insula and the PACC. Future studies could examine the functional connectivity and the constellation of signal changes, e.g., positive and negative BOLD responses (NBR, PBR) in the insula and the PACC.

Our third main finding consisted in the distinction between anterior and posterior regions with only the former being involved in self and familiarity. In contrast to anterior paralimbic regions, posterior paralimbic regions are involved in all three familiarity, self and other. This suggests that anatomically, the threefold anatomical distinctions between paralimbic, heteromodal/CMS and exterosensorimotor/lateral regions holds with regard to the self may hold for the anterior regions where self from familiarity and other are dissociable.

Therefore, the threefold anatomical distinction between paralimbic, heteromodal/CMS midline and exterosensorimotor/lateral regions may need to be complemented by the anterior–posterior dimension. Our findings from the meta-analysis underline the importance of considering the anterior–posterior distinction within the threefold anatomical model. Future anatomical investigation may reveal whether there are anatomical features, cytoarchitectonic, neurochemical, or connective (or others), that distinguish the anterior from the posterior regions especially within the paralimbic (and also the midline and lateral) regions.

What does all this entail for the concept of the self? Characterizing the self by a specific rest–intero–extero interaction presupposes the self as a specific process. The rest–intero–extero interaction describes a specific process rather than a particular content. If the self does indeed correspond to the process of rest–intero–extero interaction, one may also assume a continuous relationship between self, familiarity and other. This means that there is a continuous transition from self over familiarity to other. Such a “more-or-less” distinction of the process-based concept of self should be distinguished from the “all-or-nothing” distinction between self and non-self as is presupposed in the content-based concept of the self where the content is either self-related or not. What is specific about the PACC and insula with regard to the self may thus not be so much their exclusive anatomical involvement in the self but rather the kind of balance between resting state activity and interoceptive and exteroceptive stimulus processing. There is thus not ‘anatomical specificity’ but rather ‘processing specificity’ that makes the PACC and insula special nodes or hubs” in the neural network underlying self and familiarity. Such ‘processing specificity’ may in part also derive from the intimate connections of the PACC and the insula with the interself systems extending from hierarchically lower subcortical regions (Feinberg, 2009; this issue).

4. Conclusions

We here investigated two problems central in the imaging of the self, conceptual–experimental and anatomical issues. Conceptually, we distinguished between content- and process-based views of the self which were also shown to require different experimental approaches. The content-based view defines the self by specific contents (bodily, mental or autobiographical) and searches for the neural correlates of these contents and their respective stimulus-induced activity. The process-based view, in contrast, focuses on the processes that enable and predispose the constitution of these contents which can be traced back to the relation between stimuli and organism. The process-based view focuses on resting state activity and its impact on the neural processing of self- and non-self-specific stimuli, e.g., rest–stimulus interaction rather than on stimulus-induced activity. Methodologically, this requires a shift from the self as an independent to a dependent variable experimental designs.

Anatomically, we presented empirical evidence in favor of an anterior cortical paralimbic specificity for self-specific stimuli as distinguished from familiar and non-familiar non-self-specific stimuli. While this was the case for anterior paralimbic regions it could not be observed in posterior paralimbic regions. This supports a neuroanatomical dissociation between anterior and posterior midline, e.g., paralimbic regions, with regard to the self and its distinction from familiarity and other. Taken together, our findings support the view that the threefold anatomical distinction between paralimbic, heteromodal/CMS midline and exterosensorimotor/lateral regions is empirically more plausible with regard to the self than the traditional twofold distinction between medial and lateral regions. Moreover, the findings from our meta-analysis are more in line with a process- rather than a content-based concept of the self. However, both the empirical processes including the exact anatomical, physiological and functional characterization of the self as well as conceptual characterization of a process-based self need to be developed in further detail in the future.

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