



## Review

## How is our self related to midline regions and the default-mode network?

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## ABSTRACT

The problem of the self has been of increasing interest in recent neuroscience. Brain imaging studies have raised the question of whether neural activity in cortical midline regions is self-specific and whether self-specific activity is related to resting state activity (RSA). A quantitative meta-analysis that included 87 studies, representing 1433 participants, was conducted to discuss these questions. First, the specificity of the self (e.g. hearing one's own name, seeing one's own face) was tested and compared across familiar (using stimuli from personally known people) and other (non-self–non-familiar, i.e. strangers and widely-known figures) conditions. Second, the relationship between the self and resting state activity, as reflected by the default-mode network (DMN), was tested. The results indicated that the perigenual anterior cingulate cortex (PACC) is specifically involved in self-processing when compared to familiarity, other, and task/stimulus effects. On the contrary, other midline regions, i.e., medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC) were functionally unspecific as they were recruited during the processing of both self-specific and familiar stimuli. Finally, the PACC was recruited during self-specific stimuli and this activity overlapped with DMN activity during resting state, thus distinguishing the self-related processing from both that of the familiar and other conditions. Taken together, our data suggest that our sense of self may result from a specific kind of interaction between resting state activity and stimulus-induced activity, i.e., rest–stimulus interaction, within the midline regions.

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## Introduction

The problem of the self has been one of the most pertinent problems in the history of philosophy and has now entered also psychology and neuroscience (Brewer and Weber, 1994; Markus and Kunda, 1986; Metzinger and Gallese, 2003; Northoff and Bermpohl, 2004) and more recently also in psychology (Rogers et al., 1977) and neuroscience (Gillihan and Farah, 2005; Legrand and Ruby, 2009; Northoff and Bermpohl, 2004; Northoff et al., 2006). What is the problem of the self? The problem of the self has both conceptual and empirical dimensions. Conceptually, different concepts of the self like process- and entity-based (Northoff et al., 2006) as well as sensorimotor- and cognitive-based (Legrand and Ruby, 2009) concepts of self can be distinguished. While empirically, i.e., neuronally, the problem of the self consists in the neuronal mechanisms including the kind of regions and networks as for instance cortical midline structures have often been highlighted to be specific for the self (Gillihan and Farah, 2005; Legrand and Ruby, 2009; Northoff and Bermpohl, 2004).

Although numerous studies have indicated that cortical midline structures were involved in the self-processing (Kelley et al., 2002; Mitchell et al., 2005; Northoff and Bermpohl, 2004; Northoff et al., 2006; Platek et al., 2006; Uddin et al., 2007; Yaoi et al., 2009; Zhu et al., 2007), the consideration of confounding factors such as familiarity (Gillihan and Farah, 2005) and tasks effect (Legrand and Ruby, 2009) in studies about self-processing means that the neural basis of the self is still unclear. Since studies have also indicated an apparent overlap between the self and default-mode network (DMN), the relationship between the self and default-mode network (or resting state) draws more attention recently.

The aim of the present study was twofold. First, we aimed to detect the brain regions involved in self-specificity, compared with personal familiar people and strangers. Our hypothesis was that self-specific stimuli recruit neural activity in cortical midline structures and predominantly in anterior ones. Second, we aimed to compare the regions implicated in self-specificity with the ones showing high resting state in the DMN. Based on previous studies (D'Argembeau et al., 2005; Schneider et al., 2008; Whitfield-Gabrieli et al., 2011), we hypothesized that there would be strong regional overlap between self-specificity and DMN resting state activity in especially the anterior cortical midline structures. In order to pursue these aims, we performed a coordinate-based meta-analysis (Multilevel Kernel Density Analysis (MKDA) (Wager et al., 2009)) to detect the brain regions involved in self-specificity, compared with personal familiar people and strangers, and to detect the relationship between self-specificity and resting state in the DMN. This MKDA is a standard method which has often been successfully used in various types of meta-analysis of imaging studies (Fan et al., 2011; Salimi-Khorshidi et al., 2009; Wager et al., 2009; Wang et al., 2010).

The self-reference effect was demonstrated in a key behavioral study in which words related to the self were shown to be better remembered than other non-self-related words (Rogers et al., 1977). Comparing self- vs. non-self-specific stimuli, brain imaging studies observed neural activity changes in various medial cortical regions like the perigenual anterior cingulate cortex (PACC), medial prefrontal cortex (MPFC) and

the posterior cingulate cortex (PCC) (Kelley et al., 2002; Mitchell et al., 2005; Northoff and Bermpohl, 2004; Northoff et al., 2006; Platek et al., 2006; Uddin et al., 2007; Yaoi et al., 2009; Zhu et al., 2007). This has led to the assumption that self-related processing may be specifically mediated by cortical midline structures (CMS) (Northoff et al., 2006). Furthermore, many studies have demonstrated a predominant involvement of the anterior CMS (e.g., ACC) in the processing of self-specific stimuli (D'Argembeau et al., 2005, 2007; Feinberg et al., 2010; Feinberg, 2009; Gusnard and Raichle, 2001; Han et al., 2009; Modinos et al., 2009; Ochsner et al., 2005; Zhu et al., 2007). Most of the previous brain-imaging results were obtained by comparing activations related to the presentations of self-specific stimuli to those of familiar or unfamiliar-non-self (i.e., other) stimuli. In the present study, the concept of familiarity refers to the use of stimuli related to people that the participants personally knew, such as the voices or faces of family, friends, or colleagues. While stimuli related to widely-known/famous/unfamiliar people may activate semantic memories, those related to personally familiar people may involve the triggering of more autobiographical memories and/or emotions (Gillihan and Farah, 2005). Based on this, the condition termed 'other' in the present study includes those stimuli related to the former group (i.e., non-self-non-familiar).

In contrast to these studies, recent review papers of the self (Gillihan and Farah, 2005; Legrand and Ruby, 2009) point out that processes other than self-related processing may account for neural activity changes in cortical midline structures during the presentation of self-specific stimuli. Processes like familiarity (Gillihan and Farah, 2005) or task-related requirements like judgment or some general evaluation (Legrand and Ruby, 2009) that are supposedly implicated in self-specific stimuli are instead suggested to underlie neural activity changes in CMS. However, these hypotheses (i.e. self as familiarity or judgment/general evaluation) remain to be tested empirically.

In the cortical midline structures, neural processing of self-specific stimuli has also been associated with regions implicated in the default-mode network (DMN) (Buckner et al., 2008; Buckner and Vincent, 2007; Raichle et al., 2001). Compared with resting state activity, cognitive tasks typically induce deactivation in the DMN. This brain network is believed to reflect one default mode of brain function (Raichle et al., 2001). The DMN includes cortical midline structures (e.g., ACC and PCC) and lateral cortices (e.g., TPJ) that are functionally connected with each other during resting state conditions (Fox et al., 2005). Due to the overlap in activity between regions that are suggested to be involved in self-relatedness processing and DMN regions (D'Argembeau et al., 2005; Schneider et al., 2008), some even speak of a so-called "default self" arguing that the self may be more or less identical with the resting state activity observed in DMN regions (Beer, 2007; Boly et al., 2008; Christoff et al., 2003; David et al., 2007; Golland et al., 2007; Gusnard et al., 2001; Wicker et al., 2003).

Previous studies showed that the resting state activity in the DMN could affect the subsequent stimulus-induced activity in corresponding sensory cortices, so called "rest-stimulus interaction" (Northoff et al., 2010). Regarding the role of the DMN in rest-stimulus interactions and the overlap seen with self-specific processing, self-specific stimuli could be hypothesized to induce a special type of rest-stimulus interaction when generating our sense of the self (compared to non-self-related

stimuli). However the special form of rest–stimulus interaction between self-specific stimuli and resting state activity in the DMN remains to be investigated.

The general aim of our study was to investigate the relationship between brain activity related to the processing of self-specific, personally familiar, and other (non-self and non-familiar) stimuli. This also included the investigation of general non-specific task-related requirements as well as their relationship to neural networks showing high resting state activity, i.e. the DMN. Our specific aims were thus twofold. The first aim consisted in detecting the possible regional differences and overlap between self-specific, personally familiar and other stimuli (non-self-specific and non-personal-familiar) while at the same time accounting for unspecific task- and stimulus-related effects. Following the results from previous studies, we hypothesized that anterior cortical midline structures may be involved in self-related processing when compared to the regions recruited during the perception of personally familiar and other stimuli. The second aim consisted in detecting the relationship between self-specificity and resting state in DMN. Based on the previous results, we hypothesized an overlap in neural activity in anterior midline regions like the PACC between stimulus-induced activity during self-specificity and resting state activity in the DMN. We hypothesized this to be special for self-specific stimuli as distinguished from familiar and other (e.g., non-self and non-familiar) stimuli.

In order to investigate our aims, we conducted a quantitative meta-analysis (Multilevel Kernel Density Analysis (MKDA) (Wager et al., 2009)) based on the coordinates of the peak voxels reported in the previous studies. The present study focused on the recent brain imaging studies using self-specific, personally familiar, and other stimuli and those on resting state activity in the DMN. Our meta-analysis focused first on the regions implicated in self-specific, familiar and other stimuli, along with DMN activity, followed by direct statistical comparison between the four conditions. In order to exclude unspecific task- and stimulus-related effects, we also controlled for task- and stimulus-dependent effects independent of the four conditions. Two kinds of tasks were investigated in the present study: one involving evaluation of whether the stimuli were self- or non-self-specific; the other pertaining to the strict recognition of stimuli related to faces, names, bodies and/or voices. Two kinds of stimuli were investigated, word stimuli (e.g. trait adjectives), and face stimuli (e.g. one's own face, or other familiar or unfamiliar faces or). Finally, as a first step towards investigating the potential interaction between stimulus-dependent conditions (self-specificity, familiar and other) and resting state activity in the DMN, we plotted the regional activation clusters during the self-specific, familiar and other stimuli against those from the resting state activity.

## Method

### *Determination and operationalization of concepts*

#### *Operationalization of the concept of self*

Gillihan and Farah (2005) define the self on the concept of self-knowledge, dividing the self into two branches: physical and psychological. The concept of the physical self reflects the knowledge of the body, including its separate parts (e.g. face, arms), as well as the body as a whole. The concept of the psychological self reflects the knowledge ingrained in episodic memories (past experiences), semantic memories (traits about oneself), and the first-person perspective experience. In sum, Gillihan and Farah (2005) describe the self as an agent which is regarded as the integration between physical and psychological selves. Alternately, one may also presuppose a broader definition of the self that includes not only these physical and psychological dimensions, but also the person's relationship to specific stimuli in the environment. Heinzl et al. (2006) and Northoff et al. (2009), for instance, used one task in which participants were asked to evaluate the degree of relevance and personal meaning to emotional pictures (Heinzl et al., 2006; Northoff

et al., 2009). It is this broader sense of self-specificity that is presupposed here; in other words, self-specificity as a specific relation between the organism and stimuli – with the latter including physical-bodily, psychological-cognitive/mental and exteroceptive-sensory stimuli.

#### *Operationalization of the concept of familiarity*

In the present work, we consider the concept of familiarity in terms of personally familiar stimuli, meaning that a person has been in direct, real and personal contact with the stimulus, be it a person, place or thing. This excludes the notion of familiarity that refers to famous persons with whom one has never had a personal encounter. As noted above, personal familiarity may involve more autobiographical memories and emotional responses while a familiarity with famous or widely-known individuals, for instance, may rather recruit semantic memories (Gillihan and Farah, 2005). These difference have been demonstrated in terms of both behavior and neural activity in previous studies (Gobbini et al., 2004; Leibenluft et al., 2004; Sugiura et al., 2006; Sugiura et al., 2009; Zhu et al., 2007). For example, Zhu et al. (2007) indicated that activations related to personal familiarity overlapped strongly with the regions implicated in the self which, in contrast, did not overlap with the brain regions recruited during the presentation of widely-known/famous people (Zhu et al., 2007). Consequently, we have presupposed that the definition of familiarity is that which regards personally familiar stimuli and is distinguished from stimuli related to the familiarity of famous or widely-known people, these being included under the 'other' condition.

#### *Operationalization of the concept of non-self–non-familiarity (the 'other' condition)*

Given the above mentioned distinction between widely-known/famous people/strangers and personally familiar people, the results of the widely-known/famous people and strangers were included in one independent condition, referred to as the 'other' condition (or non-self–non-familiar). Furthermore we included studies using the third-person perspective (Vogetley et al., 2001, 2004) or other agency tasks (David et al., 2006; Ruby and Decety, 2001) because these tasks do not presuppose the distinction between self and other nor any special perception or experience of the self.

#### *Operationalization of the resting state (i.e., "default-mode network condition"; DMN)*

The brain network that shows high resting state activity and task-induced deactivation (TID) when comparing active tasks with passive conditions/or resting state (Mazoyer et al., 2001; Shulman et al., 1997) has been called the default-mode network (Raichle et al., 2001). Task induced deactivations in the DMN can be found in a wide range of cognitive tasks using verbal and nonverbal stimuli, as well as auditory and visual stimuli (Buckner et al., 2008). Besides TID, the DMN can also be delineated by analyzing resting state functional connectivity (Fox et al., 2005; Fransson, 2005; Greicius et al., 2003) through the use of, for instance, independent component analysis (ICA) (Greicius et al., 2009). Since the exact functional relationship between TID and functional connectivity in the DMN is not clear at this point, we have focused here only on those studies probing the DMN by TID. This led us to exclude resting state studies on functional connectivity and resting state studies utilizing ICA/PCA. Furthermore, because the relationship between the DMN and mind wandering is not clear, the foci noted in studies of mind wandering (Christoff et al., 2009) were also not used in the present study.

#### *Literature search and coordinate selection*

Based on our first hypothesis we included three kinds of stimulus-dependent conditions in our meta-analysis. First, we included studies with contrasts focusing on self-specific stimuli, comparing them with non-self-specific stimuli; this made up the self condition. Second, we

included another set of studies focusing on personally familiar stimuli compared to non-personally familiar and self-specific stimuli. Thirdly, to make up the 'other' condition, we included the results from the comparison between other stimuli (non-self specific and non-personally familiar stimuli) and self-specific and personally familiar stimuli (see [Table 1](#) for detailed information). The inclusion of these three sets of studies allowed us to investigate the relationship among self, familiarity and other (see below for a more detailed description of inclusion and exclusion criteria).

In addition to the three stimulus-dependent conditions (i.e. self, familiarity and other), we also included a fourth default-mode network condition which included studies showing high brain activity during the resting state. In particular, we included those studies that subtracted task-dependent effects from a resting state condition, thus eliciting task-induced deactivation or negative BOLD responses (see below for more detailed description of inclusion and exclusion criteria). This in turn allowed us to address our second hypothesis regarding the relationship between self-specificity and resting state.

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

1. Only data (brain activity coordinates) from healthy adult 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 the studies based on region of interest (ROI) analyses were excluded.
3. All reported cluster maxima from the relevant contrasts in each study were included in the meta-analysis. Cluster volumes were not considered due to variance in the reporting of this information between studies.
4. The activity coordinates generated by the data-processing based on the whole brain from each single study were included while the activity coordinates generated by the data-processing based on the regions of interests were not included.
5. Data related to brain activity revealed by task comparisons and brain imaging data (fMRI, PET) – other data (behavior, ERP) correlations – were included. In contrast, fMRI data about functional connectivity were not considered.
6. Coordinates reported in the space of the MNI template or the atlas of Talairach and Tournoux were included, the latter being converted to MNI space.

See the following information for each condition:

#### Self condition

We included 57 recent papers about self-specific processing (see [Table s1a](#)). We used a broad definition of self-related tasks that encompassed all tasks where some material or content had to be related to the person themselves. 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. In addition, we obtained a number of studies from a previous corresponding meta-analysis ([Northoff et al., 2006](#)). 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 (see [Supplementary Table 1a](#) for more information). The following contrasts were employed in the single studies: self vs. personal familiarity, self vs. control/baseline, self vs. widely-known people, first-person perspective vs. third-person perspective and self vs. other (agency task). The coordinates of the brain regions involved in correlation between self evaluation and BOLD signal were also included (See [Table 1](#)). The coordinates that showed significantly stronger brain activity comparing the self condition with other conditions (even all the condition showing deactivation compared with the baseline) in the single studies were included.

#### Familiarity condition

According to the difference between personally 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 ([Table s1b](#)). Studies involving famous/widely-known people were included in the other condition. 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. widely-known people (See [Table 1](#)). The coordinates that showed significantly stronger brain activity in the personal familiarity condition when compared with the other condition in single studies were included. Coordinates that showed common brain activity for self and familiarity ([Vanderwal et al., 2008](#)) were also included in the familiarity condition, with these not being included in the self condition (because we assumed that the common regions for self and familiarity represent the personal familiarity of the stimuli).

#### Other condition

The other condition included 23 recent papers that came from both the self condition and the familiarity condition ([Table s1c](#)). These studies employed trait adjective judgment about widely-known people, agency, name recognition of widely-known people, recognition of widely-known people's faces, or retrieval of trait adjectives related to widely-known people; additionally, third-person perspective tasks and the other agency tasks were used as a control condition in some studies about self and familiarity. The 'other' condition included the following

**Table 1**  
Contrasts included in each condition.

| Self condition                                      | Familiarity condition                        | Other condition                                    | DMN condition                                     |
|---|--|--|---|
| Self vs. personal familiarity                       | Personal familiarity vs. self                | Widely-known people vs. self                       | Working memory                                    |
| Self vs. control/baseline                           | Personal familiarity vs. baseline            | Widely-known people vs. baseline                   | Stroop, visuospatial                              |
| Self vs. widely-known people                        | Personal familiarity vs. widely-known people | Widely-known people vs. personally familiar people | Paired associates learning                        |
| 1PP vs. 3PP   | Personal familiarity vs. stranger            | 3PP vs. 1PP  | Judgment of personally related adjectives         |
| Self vs. other (agency task)                        |  | Other vs. self (agency task)                       | Semantic memory retrieval and mental calculations |
| Correlation between self-evaluation and BOLD signal |  | Widely-known people vs. stranger                   | Arrow direction judgment                          |

Note: 1PP: first person perspective; 3PP: third person perspective.

contrasts from the single studies: widely-known people vs. self, widely-known people vs. stranger/baseline, widely-known people vs. personally familiar people, third person perspective vs. first person perspective and other vs. self (agency task) (See Table 1). The coordinates that showed significantly stronger brain activity when comparing the other condition with the self and familiarity conditions were also included.

#### *Default-mode network (DMN)*

The DMN condition included 24 papers investigating those regions that showed stronger brain activation during the resting state when compared to tasks (Table S1d). Most of the DMN studies recruited in the present study employed active rather than passive tasks. The tasks included those involving working memory, stroop, visuospatial paired associates learning, judgment of personally related adjectives, semantic memory retrieval and mental calculations, and arrow direction judgment (See Table 1). All these tasks required the participants to concentrate on the task requirements and hence to recruit their attention. We used the following keywords to find studies for the DMN condition: “fMRI” or “PET” with “default-mode” or “task induced deactivation”. In addition, we included some studies from previous meta-analyses that included investigation of the default-mode network (Mazoyer et al., 2001; Spreng et al., 2009).

#### *General statistical analysis*

We used Multilevel Kernel Density Analysis (MKDA) (Wager et al., 2009), a voxel-wise coordinate based meta-analytic program, to process the current data on brain imaging studies. In MKDA, the coordinates were treated as the location of activation, and the coordinates from a single contrast in each study make up a particular statistical contrast map (SCM); therefore, the number of relevant contrasts performed in each study will be reflected by the number of SCMs created and used. The main aim of MKDA is to reconstruct a map of significant regions for each statistical contrast map within each study and subsequently analyze the consistency and specificity of these activations across all the studies in the neighborhood of each significant 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). Those coordinates in Talairach Space were translated into MNI space. The coordinates from the same contrast make up one special SCM, and the coordinates in each SCM are considered as one spherical kernel with radius = 10 mm. This means that the voxels within 10 mm around the coordinates were regarded as activated, the value of these voxels being thresholded at a maximum of 1. This contributed to the construction of 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 subjects and the kind of data analysis which was used in each study (random or fixed). The current version of MKDA weights each SCM by the square root of the number of the subjects; in addition, the SCM from studies using fixed effects analysis are down weighted by a factor of 0.75. We did not consider the z-scores of the single studies because they are not provided by all studies and their inclusion has been shown affect the replicability of activation across studies, hence making interpretation more difficult (Kober et al., 2008; Wager et al., 2009). Only 60% percent of the included studies reported the  $k$  threshold that was used in them, with many studies also not reporting the volume of activation clusters. For this reason the cluster size was not controlled for in the present meta-analysis. The weighted average of the indicator maps was compared with the maximum proportion of activated comparison maps expected under the null hypothesis such that there was no coherent spatial consistency across the SCMs. During the calculation a random effects

analysis was used. To threshold the data, MKDA uses a threshold derived from a 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 (although stability is typically seen after 2000) (Wager et al., 2009). We report the results from the height imaging in which the threshold is set to  $p < 0.05$ , corrected across the whole brain.

Regarding the comparison between two conditions in the MKDA, separate maps are constructed for each of the two task conditions and subtracted to yield difference maps. The same procedure is employed in the course of the Monte Carlo randomization: The locations of contiguous activation blobs (coordinates in MKDA) are randomized, providing simulated null-hypothesis conditions from which a threshold for significant differences is established. In the Monte Carlo MKDA difference maps, the relative frequency of activation in a given region will be compared with the overall frequencies in other respective regions of the brain. As such, a very reliable concentration of the coordinates in one area for one task condition will shift the marginal activation frequencies for this task condition. Thus, for task types with relatively few coordinates, there need not be a greater absolute probability of activating a region to achieve a significant density for that region relative to other task types (Wager et al., 2009).

#### *Specific statistical analysis*

We conducted our meta-analysis in several steps. First, we conducted the meta-analysis for each condition (i.e. self, familiarity, other, and DMN) separately to reveal those brain regions associated with each condition. This was followed by a second step in which we compared the four conditions by conducting subtraction analyses in MKDA. Thereby the following subtractions were conducted: self vs. familiarity, self vs. other, self vs. default-mode network, familiarity vs. other, familiarity vs. default-mode network, other vs. default-mode network, default-network vs. self, default-network vs. familiarity, default-network vs. other. We then used the activation map for each condition to find the overlap between self and familiarity, between self and other, and between self and the DMN. The aim of this approach is to show the relationship between self and other conditions. This overlap analysis was conducted by AFNI (Cox, 1996).

One point that should be mentioned was that the self condition included 57 papers while other three groups included about 23 papers. To balance the number of studies, we randomly selected 23 papers from the 57 papers on the self to make up four sub groups of self-specific studies. We performed meta-analyses for the self condition based on the total 57 papers as well as for each sub-group respectively and found that the PACC and MPFC were the most consistent findings among the results (Supplementary Fig. 1). We then used the sub-group 1 and the total group of the self studies to do the contrast with other three conditions (familiarity, other and DMN). The results of the sub-group 1 were consistent with the results of total group (Fig. 2 and Supplementary Fig. 2). Since the results of the subgroups were consistent with the ones of the total group, we show and refer to the results of the latter in the following.

Our third step focused on controlling for the possible unspecific effects of both tasks and stimuli independently of the conditions themselves. To do this the following analyses were conducted across the three conditions (self, familiarity, other). The first task effect we targeted was judgment or evaluation of stimuli as required in many studies on self, familiarity and other. To control for the effects of judgment/evaluation, we performed the meta-analysis based on brain regions in the contrasts between the judgment of self, familiarity or other in trait adjectives and the judgment of syllables (or other condition-unspecific) features of the same words (remaining aware that this may not necessarily be the proper control condition to test for task-effects; see the limitation section in the discussion). The second

kind of task often required in studies on self, familiarity and other is recognition, concerning predominantly name, body, face and voice recognition. We thus calculated a meta-analysis based on the contrast between the recognition of self, familiarity and widely-known names/bodies/faces/voice and the perception of stranger names/bodies/faces (three studies used the fixation cross or smoothed face as their reference condition) in order to account for the specific task-effects of recognition.

In addition to the task-effects, we also aimed to control for the unspecific effects of the stimuli independent of their characterization of self, familiarity or other. In order to account for the unspecific effects of words as stimuli, we did contrasts between words indicating specific contents – such as self, familiarity and other – and words indicating non-specific contents (unrelated to self, familiarity or other, such as word font). Alternatively, many studies on self, familiarity and other use faces rather than words. In order to control for the unspecific effects of faces as stimuli, we compared all contrasts involving faces in the categories of self, familiar and those involving widely-known with stranger faces (as well as fixation and blurred face).

This was followed by plotting all three stimulus-dependent conditions (i.e. self, familiarity and other) against the DMN, taken to represent the resting state activity during the experiment (Northoff et al., 2010). More specifically, we compared each condition against the DMN and set the former relative to the latter. This allowed us to directly compare the brain activity pattern induced by the three stimulus-dependent conditions against the DMN.

In a fourth step of our analyses we aimed to validate our results obtained in MKDA. In order to show that the observed results do not stem from the specific method of analyzing meta-analytic data, we employed another voxel-wised coordinate based meta-analytic program, specifically the most recent version (Eickhoff et al., 2009) of the activation likelihood estimation toolbox (ALE) (Laird et al., 2005; Turkeltaub et al., 2002). The use of ALE allowed us to validate our MKDA results in an independent way. In ALE the reported foci are regarded as a 3D Gaussian probability (a sphere in MKDA) distribution to capture the spatial uncertainty that is based on the subject and between-template variance associated with each focus. The data analysis was also based on MNI space. The studies were also weighted by the number of subjects in each study, but can not be weighted by fixed or random effects. The probabilities of the activation foci in each study were combined with each voxel, resulting in a modeled activation map (MA map). Combining all the MA maps generated a voxel-wise ALE score. The spatial relationship between foci in a given experiment was assumed to be fixed and ALE results were assessed against a null-distribution of random spatial association between experiments. The reported results were  $p < 0.05$ , FDR corrected with volume ( $\text{mm}^3$ ) larger than 100.

Both MKDA and ALE are popular software suites for brain imaging meta-analyses; we have used the MKDA in the main manuscript because MKDA can calculate contrasts between different conditions (e.g., self vs. familiarity) while the revised ALE does not allow for a direct comparison between conditions.

## Results

### *Regional characterization of the four conditions: self, familiarity, other, DMN*

In the first step, we searched for those regions implicated in each of the four conditions of interest. During the self condition, the meta-analysis yielded activated clusters in several midline regions (including the PACC, MPFC and PCC), as well as in regions such as the left anterior insula and right inferior frontal gyrus (IFG) (see Fig. 1A and Supplementary Table 2). To rule out a possible bias in the selection and grouping of studies on the self, we also conducted the same analysis with different numbers of studies and obtained similar results (see Supplementary Fig. 1).

The familiarity condition revealed activated clusters in the MPFC and PCC, but not in the PACC (see Fig. 1B and Supplementary Table 2). 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 (L-TP) (see Fig. 1C and Supplementary Table 2). Finally, regions in the DMN included anterior and posterior midline regions (e.g., PACC, PCC), the right posterior insula, and the bilateral TPJ (see Fig. 1D and Supplementary Table 2).

The results for each condition were consistent with those obtained using ALE, which showed similar, and some additional, regional activations when compared to results obtained with MKDA (Supplementary Fig. 3).

### *Comparison between the four different conditions (self, familiarity, other, DMN)*

In order to directly compare our four conditions with each other, we conducted various subtraction analyses in MKDA. Subtracting the familiarity condition from the self condition lead to activation clusters in the PACC and right inferior frontal gyrus (IFG); similar results were yielded when subtracting the 'other' condition from the self condition. Finally, we also subtracted the DMN condition from the self condition, which yielded activation clusters in the MPFC and right IFG (see Fig. 2A, Supplementary Table 3). To rule out a possible bias in selection and grouping of studies on the self, we also conducted the same analysis with different numbers of studies on the self and obtained the same results (see Supplementary Fig. 2).

We then subtracted the self condition from the familiarity condition, yielding posterior regions, i.e. the PCC and the left TPJ (although, the latter had a cluster size smaller than 10 voxels). Comparing the familiarity condition with the other condition resulted in significant differences in midline regions like the MPFC and the PCC. Finally, subtracting the DMN condition from the familiarity condition yielded significant differences in the PCC (Fig. 2B, Supplementary Table 3).

The other (non-self–non-familiar) condition was then compared with the self condition. This yielded significant differences in posterior regions like the left temporal pole, the PCC and the right TPJ. Comparing other to familiarity led to significant differences in more or similar posterior regions, i.e. the left temporal pole, the precuneus and the right TPJ. Finally subtracting the DMN from the other condition led to significant differences in the same posterior regions, the temporal pole and the PCC (see Fig. 2C, Supplementary Table 3).

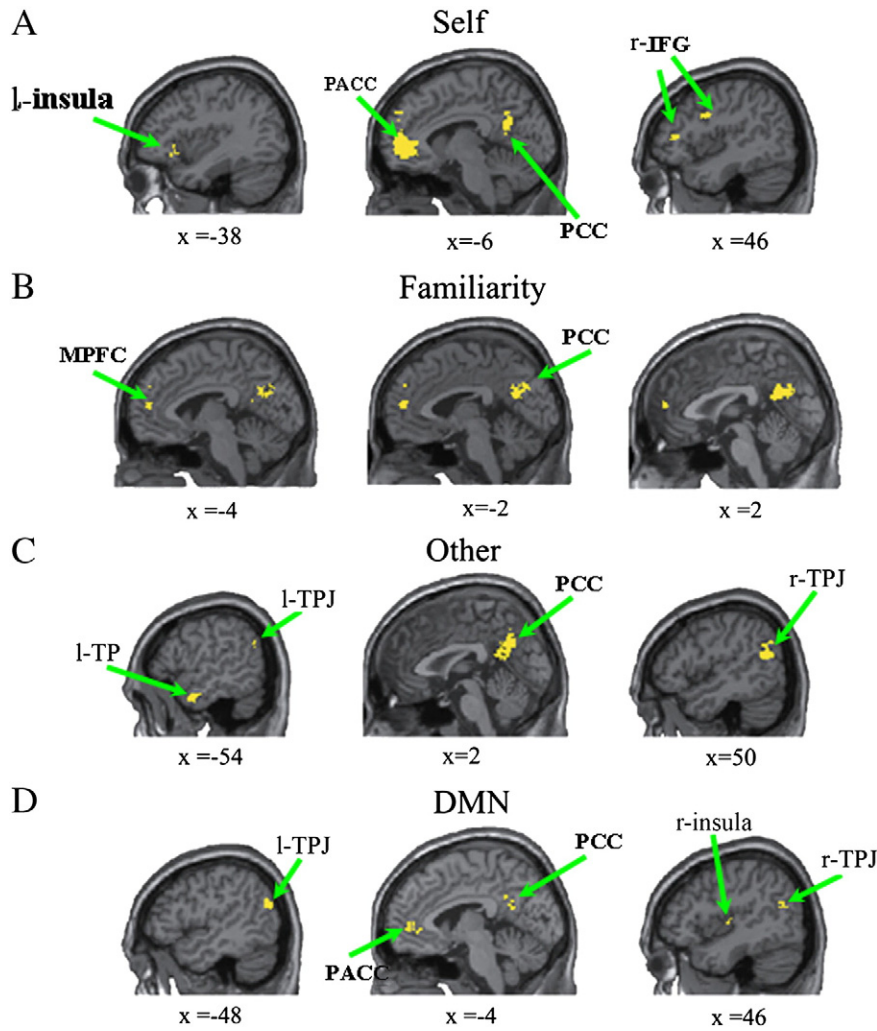
Finally, we subtracted the self from the DMN condition which yielded some differences in posterior regions, i.e. right posterior insula and left TPJ. Subtracting familiarity from the DMN condition yielded activation clusters in the PACC, PCC, and right posterior insula. Finally, comparing the DMN with the other condition showed a significant difference only in the PACC, right posterior insula and left TPJ. (Fig. 2D and Supplementary Table 3)

### *Overlapping between self and familiarity/the other/DMN*

The activation map of self, familiarity, other and DMN were used to uncover the overlap between the self and familiarity, overlap between self and other, and overlap between self and DMN. This showed that the activations related to self and familiarity overlapped in the MPFC and PCC (Fig. 3A); the self and the other in PCC (Fig. 3B); the self and DMN in PACC and PCC (Fig. 3C).

### *Control for unspecific task-(judgment, recognition) and stimulus-(words, faces) related effects*

In order to account for unspecific effects of the tasks and the stimuli themselves, independently of the respective conditions (self, familiarity,



**Fig. 1.** The activated clusters for four conditions. The activated clusters of the self, the familiarity, the other and the DMN conditions by using of MKDA ( $p < 0.05$ , corrected across the whole brain). MPFC, medial prefrontal cortex; PACC, perigenual anterior cingulate cortex; PCC, posterior cingulate cortex; l-TP, left temporal pole; l-insula, left insula; r-insula, right insula; l-TPJ, left temporoparietal junction; r-TPJ, right temporoparietal junction; r-IFG, right inferior frontal gyrus.

other), we conducted several analyses across the three conditions. To account for the task-effects of judgment/evaluation, we compared the judgment of self, familiarity and other with the judgment of syllables, uppercase letters, and so on; this yielded regional activation clusters in the left temporal pole, MPFC and PCC. To control for the task-effects of recognition, we compared the recognition of self, familiarity and widely-known names/bodies/faces with the recognition of stranger's names/bodies/faces, fixation and blurred face; this yielded activation clusters in the PCC and the right fusiform gyrus (the latter though with only 8 voxels) (Fig. 4A and Supplementary Table 4).

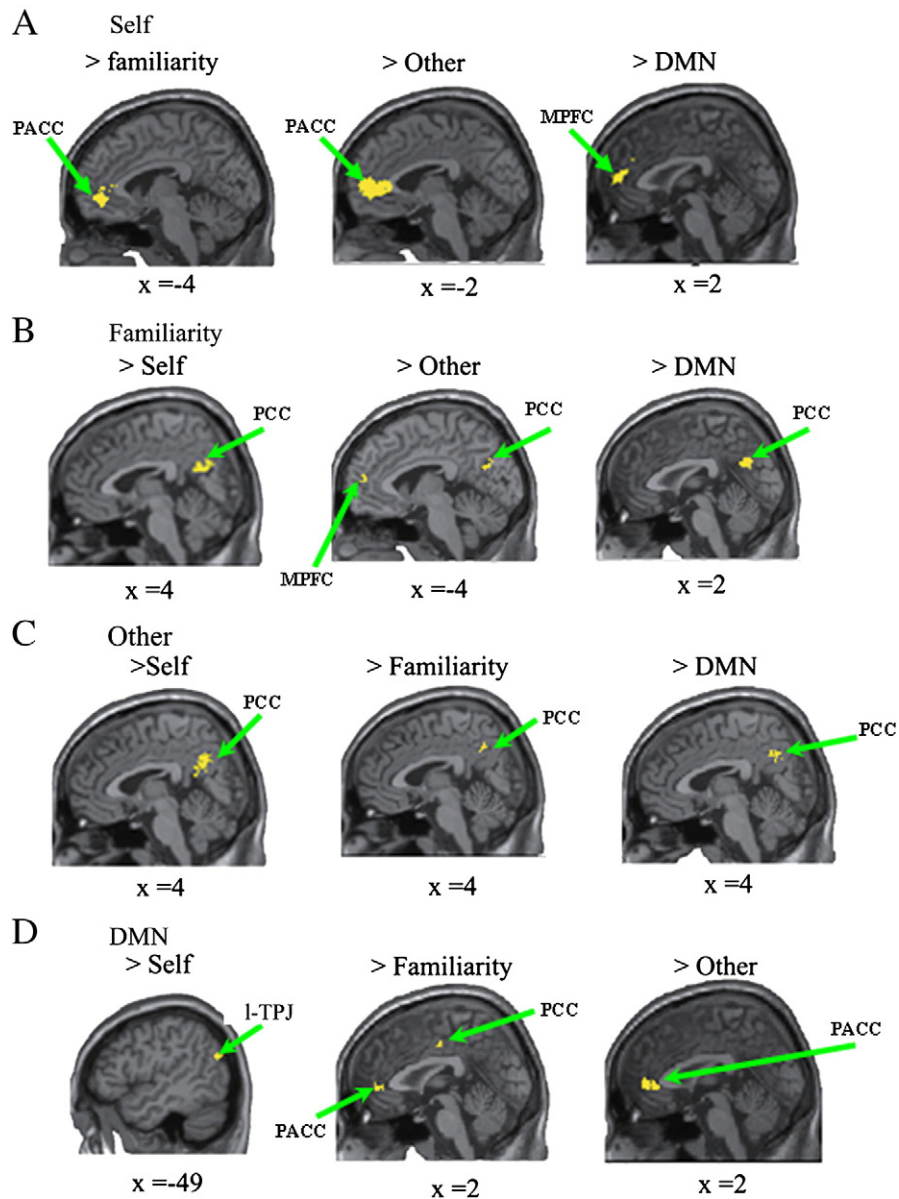
In addition to the task control, we also controlled for potential unspecific effects of the stimuli independent of their characterization of self, familiarity or other. First, we aimed to control for the unspecific effects of words by comparing words indicating the specific contents (like self, familiarity and other) with words indicating non-specific contents (unrelated to self, familiarity or other). This yielded activation clusters in bilateral temporal pole, PCC, bilateral TPJ, MPFC and left middle temporal gyrus. Second, we controlled for faces as stimuli and consecutively compared all faces of the self, familiarity and widely-known conditions with stranger faces (and fixation and smoothed face); this yielded activation clusters in the right fusiform gyrus (though with 8 voxels only) (Fig. 4B and Supplementary Table 5).

*Relationship between stimulus-dependent conditions (self, familiarity, other) and the resting state condition (DMN)*

In addition to the direct comparisons between the stimulus-dependent conditions (self, familiarity, other) with the resting state condition (DMN) (see above), we plotted all results obtained above onto a single brain.

First, for visually summarizing our results from the single conditions themselves, we plotted the activated spots from all four conditions, self, familiarity, other and DMN, onto a common brain. For anatomical delineations we also demarcated the midline regions like the PACC, the MPFC and the PCC (see Fig. 5A). Based on the single condition meta-analyses, both the self and DMN conditions showed activated clusters in PACC, both the self and familiarity conditions showed activated clusters in MPFC, and all four conditions showed activated clusters in PCC (Fig. 5A).

Since the DMN is supposed to experimentally reflect the resting state of the brain, we plotted the three stimulus-related conditions (self, familiarity and other) against the DMN. In a second step, we plotted the results from the various comparisons against the results from their comparisons with the DMN condition (and against each other) (see Fig. 5B).



**Fig. 2.** The activated clusters by contrasts between each condition. A: the self condition showed stranger activation than other three conditions; B: the familiarity condition showed stranger activation than other three conditions; C: the other condition showed stranger activation than other three conditions; D: the DMN condition showed stranger activation than familiarity and other, while DMN did not show significant stranger activation than self in MCS ( $p < 0.05$ , corrected across the whole brain).

There was overlap between the self-specific condition and the DMN probes in the PACC while familiarity condition and other condition (non-familiarity–non-self) did not recruit the PACC at all, with both showing significant differences when compared to DMN and self-specific stimuli.

In comparison, the PCC showed the reverse pattern, as stimuli related to familiarity and other conditions had a higher probability of recruiting this region when compared to the DMN condition, while the self condition did not differ from the DMN condition in this region.

In the MPFC, the self and familiarity conditions were significantly more likely to show activations when compared to the DMN and other conditions. While self and familiarity did not differ in MPFC recruitment, both conditions did differ significantly from the other and DMN conditions.

## Discussion

Our first main finding showed that the self condition recruited the PACC when compared to the familiarity and other condition. Concerning

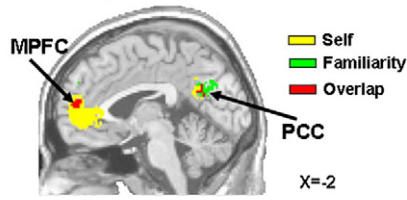
the other midline regions, there was either regional overlap of activations related to the self and familiarity conditions, as in the MPFC, or with both the familiarity and other condition, as in the PCC. This, in part, confirms our first hypothesis that the PACC, as an anterior midline region, is important for the self. Our second main finding concerns the regional overlap in activations between the self and DMN in the PACC and the PCC. Only stimuli related to the self resulted in activations which overlapped with those of the DMN in the PACC, while in the PCC, self, familiarity and other activations overlapped with those of the DMN. Taken together, our data show that the PACC shows more involvement in self-specific stimuli when compared to non-self (e.g. familiar and other) stimuli. Furthermore, activations of the PACC during self-specific stimuli overlap with the same region identified in the DMN, considered the central resting state network.

### *Regional difference between self-specificity and familiarity and other*

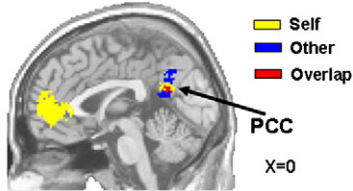
Our first findings show that the PACC is recruited during self-specific stimuli as distinguished from familiar and other stimuli. Activations



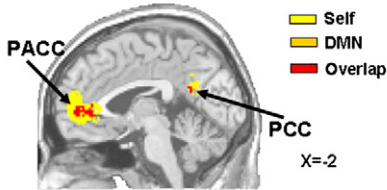
**A** Overlap between self and familiarity



**B** Overlap between self and other

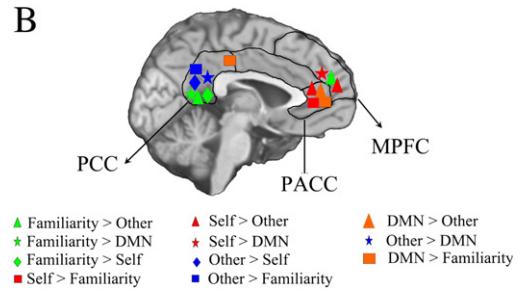
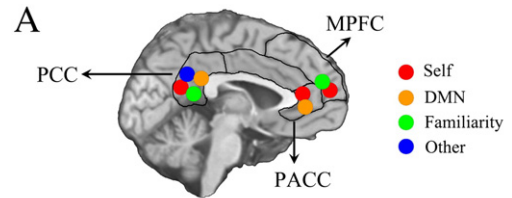


**C** Overlap between self and DMN



**Fig. 3.** Overlapping between the self and familiarity/the other/DMN. A. overlapping between the self and familiarity; B. overlapping between the self and the other; C. overlapping between the self and DMN.

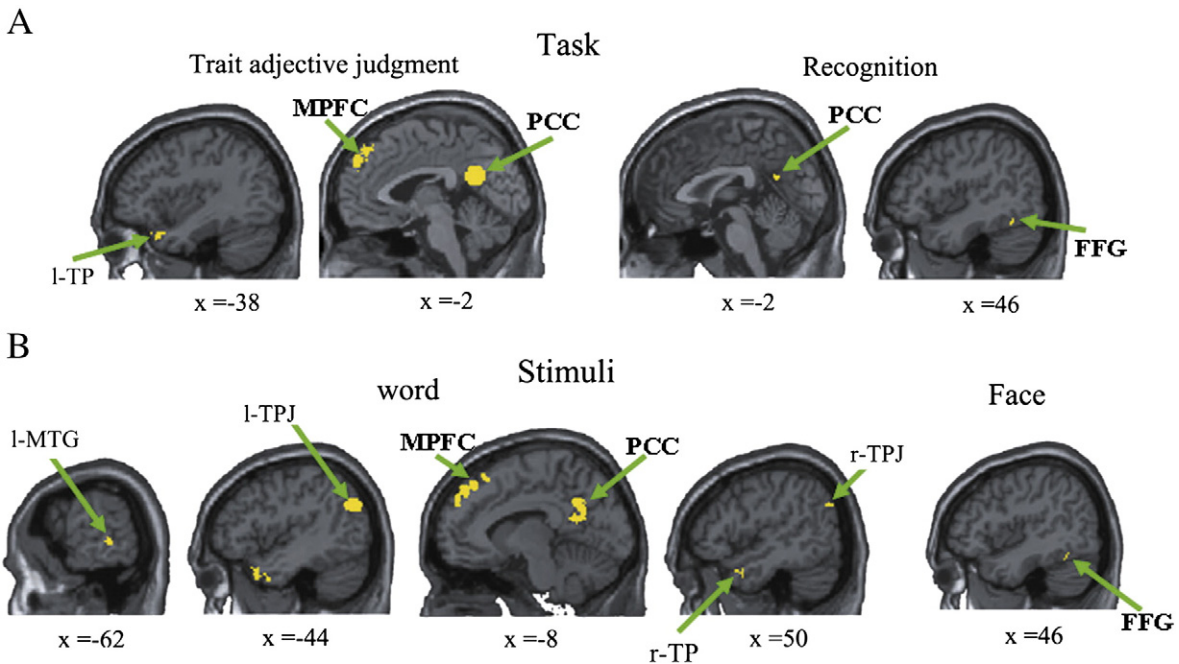
related to self-specific stimuli did overlap with those recruited during the presentation of familiar or other stimuli, i.e. in the MPFC and PCC. Our meta-analysis thus confirms our first hypothesis of the regional specificity of the self compared with familiarity and the other. In accordance with Gillihan and Farah's (2005) assumption, our results do indeed show strong regional overlap between self-specific and familiar stimuli as apparent in MPFC and PCC. However, contrary to their



**Fig. 5.** Summary of the regional involvement in the four conditions based on their comparison. A: activated spots for single conditions; B: spots activated by comparisons between each other of four conditions. We here plotted all the above shown results onto one single brain. In first step we plotted the results from the single conditions onto one brain (A). While in a second step we plotted all results in relation to the brain's resting state activity thereby relying on the comparisons of the three stimulus-dependent conditions (self, familiar, other) with the DMN (B). MPFC (BA 8, 9, 10), PACC (BA 24, 25, 32), and PCC (BA 23, 31).

assumption, there is no complete overlap since the PACC was recruited only during self-specific stimuli but not during familiar ones.

Additionally, the results of the evaluation tasks effect also indicated brain activity in midline regions which lends empirical support to the assumption put forward by Legrand and Ruby (2009); they hypothesize a 'general evaluation system', and our investigation of task-related effects did indeed show recruitment of midline regions (i.e. MPFC and PCC/precuneus) during judgment/evaluation and recognition. Importantly, although regional activations related to the task-induced processing of trait judgment and recognition overlapped with those of the self, other regions (e.g. PACC) for the self did not necessarily show



**Fig. 4.** Activated clusters for task-specific effects of judgment and recognition. A. the activated clusters for task-related effects of judgment and recognition; B. activated clusters for stimulus-specific effects of words and faces.

any neural overlap with those task-related regions. However, it should be mentioned that this comparison controlled only for contents to be judged, but not for the judgment or recognition themselves and thus the task itself. Due to the lack of a proper control condition in the single studies, our meta-analytic comparisons remain unable to provide direct support for the assumption of a general evaluation system. Finally, the unspecific effects of the stimuli themselves, i.e. words and faces, also yielded activation clusters in the midline regions, which argue against exclusively task-related effects in these regions.

#### *Regional and functional differentiation in midline regions*

Despite their unspecific nature with regard to self-specific stimuli, the midline regions showed some regional and functional differentiation. The PACC showed strong overlap between self and DMN conditions, while it was less likely to be recruited in familiarity and other conditions. The MPFC, in contrast, showed a higher probability of being recruited during both self and familiarity when compared to DMN and other. This regional differentiation between the PACC and the MPFC suggests differential functional roles. While the PACC seems to be particularly involved in linking the self to the DMN and thus the brain's resting state activity (see below for more extensive discussion), the MPFC seems to be recruited during both familiarity and self as distinguished from the other. Taken together with the here observed involvement of the MPFC in unspecific task-effects of judgment/evaluation, this seems to suggest that this region may be involved in representing the stimulus as such in awareness, i.e., meta-representing, which is required in order to evaluate or judge the stimulus as self-referential (Northoff and Bermpohl, 2004; Northoff et al., 2006; Ochsner and Gross, 2005).

In contrast to anterior midline regions, the posterior midline regions like the PCC (as well as the TPJ and the temporal pole), showed a differential pattern. Here, the familiarity and other conditions showed increased probability of recruiting these regions, while self and DMN yielded decreased probability. This indicates that the posterior regions may be involved in functionally different processes when compared to the anterior midline regions. More specifically, the PCC may be involved in social processes like monitoring the environment and retrieving memories (Cavanna and Trimble, 2006; Gusnard and Raichle, 2001; Wagner et al., 2005) and the TPJ and the temporal pole in mind reading and social cognition (Decety and Lamm, 2007; Frith and Frith, 2006; Moriguchi et al., 2006; Van Overwalle, 2009; Van Overwalle and Baetens, 2009).

#### *Self and the default-mode network*

We observed a regional overlap between self and DMN conditions in the PACC. This is in accordance with previous studies (D'Argembeau et al., 2005; Gusnard et al., 2001; Schneider et al., 2008). Physiologically, the PACC region must be considered special among the DMN regions in that it shows particularly strong and almost exclusively negative BOLD response (NBR) rather than positive BOLD response (PBR) during task-induced stimulation in fMRI (Buckner et al., 2008; D'Argembeau et al., 2005; Gusnard et al., 2001; Mazoyer et al., 2001; Northoff et al., 2007; Shulman et al., 1997; Wicker et al., 2003). Previous studies have indicated that the DMN could affect external stimulus-processing, which can be termed rest-stimulus interaction (Northoff et al., 2010). One could consequently assume that self-specific and familiar/other stimuli interact differentially with the resting state activity in this region. The exact nature of such different kinds of rest-stimulus interactions remains unclear though. In addition one could hypothesize that such rest-stimulus interaction may be altered in psychiatric disorders. For instance there may be abnormal rest-stimulus interaction in patients with major depressive disorder (MDD), who show both an abnormally increased self-focus and abnormally increased PACC resting state activity (Grimm et al., 2009; Northoff, 2007); how this impacts their rest-stimulus interaction remains to be investigated though.

The anterior insula which has also been shown to be recruited during the processing of self-specific stimuli (Enzi et al., 2009; Modinos et al., 2009). Since the anterior insula is involved in interoceptive stimulus processing (Craig, 2004, 2009), and shows activity correlations with that in the PACC (Taylor et al., 2009), one may hypothesize that co-activation between the insula and the PACC may be crucial in constituting the self and assigning self-specificity to stimuli. One would consequently assume what may be called a trilateral interaction in the anterior insula and PACC between resting state activity, exteroceptive input and interoceptive input. This trilateral interaction may account for the self-special stimulus-rest interaction with DMN.

#### *Self as internal or external?*

The strong neural overlap between CMS during self-specific stimuli and the brain's resting state activity (e.g., as in the DMN) and self-related thoughts during resting state (Smallwood and Schooler, 2006) may argue in favor of an internal origin of the self. More specifically, the constitution of the self and consequently of stimuli as self-specific may rely on the internal resting state activity of the brain. Empirically, one could then assume that self-related processing may already occur in those psychological processes associated with the brain's resting state activity. For instance, self-related processing may operate during mind-wandering, where highly self-related contents have been suggested to dominate over low self-related ones (Smallwood and Schooler, 2006). Neuroscientifically, one would then expect mind-wandering to involve predominantly cortical midline regions, which has indeed been reported in a recent study (see (Mason et al., 2007), see though (Christoff et al., 2009) who also observed lateral regions during mind-wandering). Besides mind-wandering, self-related processing may also take place in other states associated with the brain's resting state activity, as for instance during dreaming; although this though remains to be shown.

However, some care must be taken with the current findings as they show only neural overlap, which does not yield any information about the exact processes underlying this overlap. The designation of stimuli as self-specific may recruit the very same process that may already be ongoing in the resting state. If so self-related processing may be at work not only during the presentation of self- and non-self-specific stimuli, e.g., stimulus-induced activity, but also in the resting state itself where it may operate on for instance cognitive contents.

Furthermore, our study did not observe complete neural overlap between activations related to the self and the DMN. Conceptually, this suggests that the self may not be completely reduced to and equated with the brain's intrinsic resting state activity and is henceforth not to be considered as being of a completely internal origin. Instead, the self may somehow also be tied to stimuli which trigger the recruitment of those regions showing high resting state activity, i.e., the DMN. If so, one would characterize the self neuroscientifically by a specific form of rest-stimulus interaction (Northoff et al., 2010), as described above, while psychologically this would further underline the above postulated relational nature of the self. The concept of self can then neither be associated with a purely internal origin, i.e., in the brain itself, nor with a purely external origin, i.e., in the environment. Instead, the self as a specific form of rest-stimulus interaction may defy any such distinction between internal and external origin and may rather consist in the intrinsic linkage or relation between them. Taken further, one may then speculate that any hypothesized internal-external dichotomy with regard to the origin of the self may be more related to our conceptualization of the self (and hence ultimately to the limitations in our knowledge and epistemic abilities) than to the self and the brain themselves.

#### *Other regions*

We also observed recruitment of two areas in the lateral prefrontal cortex (right inferior frontal gyrus) during self-specific stimuli. These regions have been associated with the self (Keenan et al., 2001; Platek et

al., 2008), and thus our results lend weight to their suggested relevance in the processing of self-specific stimuli. The lateral prefrontal cortex may account for some higher-order cognitive component like evaluation, recognition, or meta-awareness that unfortunately could not be fully excluded in our control for task-related effects (Platek et al., 2008; Uddin et al., 2007). One may consequently assume a specifically strong interaction of self-specific stimuli with task requirements that subsequently lead to increased activity in these regions.

One may speculate that the involvement of the DLPFC may be closely related to what cognitively is described as the meta-representation of originally non-self-specific stimuli, by means of which the subjects can then identify them as self-specific. This may pertain to what has been described above as self-referential processing, a higher-order cognitive process that allows the individual to reflect upon the mental content and its relationship to their own person. However, this assumption remains empirically and conceptually speculative at this point.

In addition to the DLPFC, we also observed the left anterior insula to be specific for the self. The insula has been associated with self-specific stimuli in recent studies (Enzi et al., 2009; Modinos et al., 2009), as distinguished from their rewarding properties (Enzi et al., 2009). Since the insula is heavily involved in interoceptive stimulus processing (Craig, 2004, 2009), one may suggest that the co-activation between insula and the CMS may be crucial in constituting the self and assigning self-specificity to stimuli. One would consequently assume what may be called a trilateral interaction in the CMS between resting state activity, exteroceptive input and interoceptive input. This trilateral interaction may account for what has been described above as self-related processing, the constitution of a relation of the environmental stimulus with the brain and the body of the respective organism. One may consequently consider self-related processing as a specific form of rest-(inter/extero) stimulus interaction whose exact mechanisms of neural coding remains unknown.

#### *Methodological contributions and limitations*

Our meta-analysis provides a significant step forward from previous ones (Gillihan and Farah, 2005; Legrand and Ruby, 2009; Northoff et al., 2006). First, unlike all three previous meta-analyses, we have tested for the effects of tasks and stimuli independent of whether they self-specific or not. This allows us to test the hypothesis that the neural activity observed in CMS is related to unspecific task- and/or stimulus-related effects rather than the self-specificity of the stimuli (see for instance (Legrand and Ruby, 2009)). Second, our meta-analytic design allowed us to test for the consistency of possible differences and similarities across the various studies between self and familiarity. Third, the meta-analytic approach allowed for a direct comparison of neural activity pattern changes during self-specific stimuli with the brain's resting state activity pattern — something that currently remains impossible to do in single studies. Fourth, our meta-analytic study pursued a whole-brain and most importantly a quantitative approach which distinguishes it from the recent reviews (Gillihan and Farah, 2005; Legrand and Ruby, 2009; Northoff et al., 2006) which allows us to make more substantial empirical claims.

This is not to neglect some limitations inherent in our meta-analytic approach. The variance of the tasks between the conditions may affect the interpretation of the results of the present meta-analysis. In order to test this task-variance effect, we randomly selected 23 papers from the 57 papers on the self four times, to make up four sub groups of self-specific studies. The types and distribution of tasks in the four subgroups should thus be different. The results indicated that four subgroup and total self condition show the similar activation pattern in midline regions (see Supplementary Fig. 1). Compared with familiarity, the other, and DMN condition, subgroup 1 of the self show the similar results as the total group (See Supplementary Fig. 2). This may indicate that the task-variance between different conditions did not affect the

results greatly. Another issue that we have to mention is that we did not consider the volume of the activated clusters in the source papers when we performed the meta-analysis. It is a shortcoming of the coordinate based meta-analysis technique that information concerning activation clusters (e.g., cluster size, location, shape) is lost during the analysis, compared with image-based meta-analysis that works with real activation maps (Salimi-Khorshidi et al., 2009). Compared with recent coordinate-based meta-analysis (Caspers et al., 2010; Fan et al., 2011; Kim, 2011; Sabatinelli et al., 2011), the present study selected the coordinates within different clusters from the total self condition randomly to make four subgroups, and got similar results. This may make the present results more convincing.

Furthermore, while we carefully validated our results by running the same analyses in an independent meta-analytic program, i.e., ALE, in addition to MKDA, we, as already mentioned above, were not able to fully exclude possible unspecific task- and stimulus-related effects. We did not control for the kind of design in MKDA being either an event-related experiment design or block experiment design. Unfortunately the same holds true for our control analysis of the unspecific stimulus-related effects, e.g., of words and faces, since neither study compared the effects of words/faces with those of non-words/non-faces as for instance single letters or smoothed face pictures. Due to these limitations, we cannot fully exclude unspecific task- and stimulus-related effects in our meta-analytic results.

#### **Conclusions**

We here report findings from a meta-analytic study on imaging studies of self, familiarity, other and resting state in DMN that allowed the direct comparison of the four conditions with each other without some of the methodological limitations inherent in single studies. Our results contribute to the current knowledge of the self in two ways. First, we here address for the first time the relationship between self and familiarity in a meta-analytic way. This is of major importance given that familiarity is always a major confounding factor in the studies about the self, with some authors arguing that the self is nothing but extreme familiarity. While our results indicate that the self overlaps with familiarity in MPFC and PCC, both conditions also differ from each other in the PACC. This suggests that self and familiarity cannot be regarded as identical.

The second main contribution of our meta-analysis is the relationship between the self and resting state activity in the DMN. Earlier studies by (D'Argembeau et al., 2005) and (Schneider et al., 2008) indicated an overlap between resting state regions and those implicated in the self. Our study provides further evidence for a direct overlap between rest and self in the anterior parts of the DMN, specifically in the PACC. Since this region shows high resting state activity and very consistent negative rather than positive BOLD responses, we assume a differential interaction of such high resting state activity with self- and non-self-specific stimuli. The self may then potentially be characterized by a specific type of what has recently been called 'rest-stimulus interaction' (Northoff et al., 2010). This remains to be investigated however.

Finally, we also investigated the relationship between the self and task-related general evaluation functions. It has been argued that the brain regions involved in self-processing are not specific for the self but are instead task-specific, implicating such a general evaluation function. We therefore tested in our meta-analysis for those regions related to the evaluation of stimuli as being self- or non-self-related. This demonstrated that the PACC was related to self-specific stimuli rather than to these task-related effects.

#### **Acknowledgments**

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.05.028.

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