Knowing me, knowing you
van der Meer, Elisabeth

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Self-reflection and the brain: a theoretical review and meta-analysis of neuroimaging studies with implications for schizophrenia

Lisette van der Meer, Sergi Costafreda, André Aleman, Anthony S. David

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Abstract

Background Several studies have investigated the neural correlates of self-reflection. In the paradigm most commonly used to address this concept, a subject is presented with trait adjectives or sentences and asked whether they describe him or her. Functional neuroimaging research has revealed a set of regions known as Cortical Midline Structures (CMS) appearing to be critically involved in self-reflection processes. Furthermore, it has been shown that patients suffering damage to the CMS, have difficulties in properly evaluating their problems and often overestimate their capacities and performance.

Method Building on previous work, a meta-analysis was conducted of published fMRI and PET studies on self-reflection.

Results The results showed that two areas within the medial prefrontal cortex (MPFC) are important in reflective processing, namely the ventral (v) and dorsal (d) MPFC.

Conclusions In this paper a model is proposed in which the vMPFC is responsible for tagging information relevant for ‘self’, whereas the dMPFC is responsible for evaluation and decision making processes in self- and other-referential processing. Finally, implications of the model for schizophrenia and lack of insight are noted.
Introduction

The aim of this paper is to review the literature on self-reflection, and in particular its differentiation from other-reflective processing, by means of a meta-analysis of the fMRI and PET studies published so far on the subject. We will present a model of self-reflection and the brain based on the results of the meta-analysis. The discussion will be expanded to encompass the literature on failure of self-reflection processes, in particular in schizophrenia patients who may be viewed as having important problems in this area (Addington et al., 2006; Baird et al., 2006; Carter et al., 2001; 2007). Recent neuroimaging evidence (Park et al., 2008; Taylor et al., 2007) suggests that processes relying upon these Cortical Midline Structures (CMS), a set of regions encompassing the posterior cingulate cortex (PCC), the medial prefrontal cortex (MPFC) and the anterior cingulate cortex (Northoff & Bermpohl, 2004), may be affected in this patient group. Finally, the possible role for self-reflection abilities in illness awareness in schizophrenia patients will be discussed.

The study of self has become increasingly popular in cognitive neuroscience over the past decade (Kircher and David, 2003). Several studies have investigated the neural correlates of self-reflection or self-referential processing. In the literature these terms are used interchangeably and refer to the evaluation process used to decide whether certain environmental cues apply to one’s self or not. Technically, self-referential processing is a broader concept in which all information that somehow refers to oneself is processed and encompasses subconscious as well as conscious processing. Self-reflective processing on the other hand implies a conscious process in which a decision is made regarding oneself.

Having an accurate representation of one’s traits, abilities and attitudes is important in evaluating one’s own behavior and comparing it with the behavior of other human beings. The most commonly used paradigm to address this concept in experimental and neuroscientific research uses self-reflection in which subjects are presented with trait adjectives or sentences and are asked whether the trait or sentence applies to them. Results have consistently pointed to a role of the CMS in these self-reflection processes, but this has not allayed misgivings regarding the concept of self-reflective processing (Gillihan & Farah, 2005) and whether the processing of self-reflective information is substantially different from the processing of information concerning other people. Finally, it has also been shown that patients who have suffered damage to the CMS have difficulties in properly evaluating their problems and often overestimate their capacities as well as their performance particularly on cognitively demanding operations (Schmitz et al., 2006).

Neural correlates of self-reflection and the Cortical Midline Structures

Most studies investigating self-reflection processes have found evidence for medial pre-frontal cortex (MPFC), posterior cingulate cortex (PCC) and anterior cingulate cortex (ACC) involvement in distinguishing self-related information from non self-
related information. Even though these studies report a similar functional anatomy, the precise involvement of the component structures is debated. One of the first studies looking at the neural correlates of the ‘self-reference effect’, using PET was by Craik et al. (1999). The self-reference effect refers to the finding that people tend to remember words when processed in relation to themselves better than words processed more generally [see Symons and Johnson (1997) for a meta-analysis]. Craik et al. (1999) found that the retrieval of self-referential information is mediated by the right prefrontal areas including the MPFC, whereas the encoding of such information is similar to the encoding of information about others and is mediated mainly by the left prefrontal areas. This effect was replicated using fMRI by Kelly et al. (2002) and Johnson et al. (2002) who studied self-reflection by means of a paradigm in which subjects were presented auditorily with short questions, each entailing a trait, attitude or ability (e.g. ‘I am a good friend’). As a control condition, they used simple questions entailing general semantic knowledge (e.g. ‘You need water to live’). The authors found anterior MPFC (aMPFC) and PCC activation in the self-reflection condition. The studies by Craik et al. (1999), Kelley et al. (2002) and Johnson et al. (2002) were followed up by a number of other studies using similar paradigms and reporting similar areas of activation. Macrae et al. (2004) demonstrated that activation in MPFC regions corresponded to self-reflective judgments and memory performance related to self descriptive trait words. Fossati et al. (2003) were specifically interested in the processing of emotionally valenced words in self-reflection. They presented positive and negative traits words and found dMPFC and PCC activation in a self vs. baseline contrast. Interestingly, this dMPFC activation was not specific to either positive or negative stimuli but rather it was present regardless of valence. Gusnard et al. (2001) and Johnson et al. (2005) found only MPFC activation in a similar contrast in which subjects were asked to introspect either in response to pleasant/unpleasant visual stimuli or color preference respectively. Johnson et al. (2006) similarly used an introspection paradigm in which subjects ruminated on hopes and duties in comparison with a condition without self-reference and found MPFC and PCC activation.

Northoff et al. (2004) reviewed the literature on self-processing and neuroimaging and discussed the role of the CMS in self processing. They discussed each area separately and came to the conclusion that different areas within the CMS represent different functions, such as representation, monitoring, evaluation and integration. However, their review focused on the processing of self only. Many other recent studies have included an ‘other’ condition in which the subject is asked to reflect upon another person, either an unfamiliar person, a relative, close friend or someone famous, while presented with trait words (D’Argembeau et al., 2007; Gutchess et al., 2007; Heatherton et al., 2006; Kelley et al., 2002; Macrae et al., 2004; Ochsner et al., 2005; Schmitz et al., 2004; Schmitz et al., 2006; Zhu et al., 2007), trait

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2 The terms ventral and dorsal medial frontal cortex are not always well defined in the literature. In this paper, a dividing line will be placed along Talairach’s z-coordinate of 20. The area above will be referred to as dMPFC, whereas the area underneath will be referred to as vMPFC [see Van Overwalle (Van Overwalle, 2009) and Krueger et al. (2009)]. This roughly corresponds to Brodmann’s areas 9 for dMPFC and 10 and 11 for vMPFC (Northoff et al., 2006).
sentences (Modinos et al., 2009a; Pfeifer et al., 2007), or when instructed to introspect upon emotional pictures (Jenkins et al., 2008; Ochsner et al., 2004) or food preference (Seger et al., 2004). The involvement of the MPFC (Johnson et al., 2005; Macrae et al., 2004; Modinos et al., 2009a; Ochsner et al., 2004; Schmitz et al., 2004; Schmitz et al., 2006; Zhu et al., 2007) and PCC, precuneus (Heatherton et al., 2006; Johnson et al., 2006; Modinos et al., 2009a; Ochsner et al., 2004; Schmitz et al., 2006; Seger et al., 2004) in self-reflective processing is broadly confirmed. However, regarding ‘other’-reflective processing and the extent to which this differs from self-reflective processing, the literature does not yield a consensus.

Even though most studies report differences in self vs. other processing, the brain region that is mostly reported to be functionally associated specifically with self-processing is referred to as MPFC (D’Argembeau et al., 2007; Gutchess et al., 2007; Heatherton et al., 2006; Jenkins et al., 2008; Kelley et al., 2002; Modinos et al., 2009a; Ochsner et al., 2004; Pfeifer et al., 2007; Zhu et al., 2007), while the same studies report this area to be involved in other processing as well. Additional areas that are reported to be involved specifically in self-processing are the anterior cingulate cortex (D’Argembeau et al., 2007; Heatherton et al., 2006; Modinos et al., 2009a; Ochsner et al., 2005; Zhu et al., 2007), dorsolateral PFC (dLPFC) (Schmitz et al., 2004), superior parietal regions (Seger et al., 2004) and lateral temporal regions (Kjaer et al., 2002; Lou et al., 2004). The observation that the involvement of the MPFC is reported for self as well as other-processing indicates that there is a need to be more specific regarding the areas within the MPFC that are involved in either self- or other-processing or both.

Some studies suggest that a functional distinction should be made between the vMPFC and the dMPFC (Frith & Frith, 1999; Gusnard et al., 2001; Northoff et al., 2006; Northoff & Bermpohl, 2004; Schmitz & Johnson, 2007) in which the dMPFC might process the non-emotional, and the vMPFC the more emotional content of the information. However, most studies mentioned above do not make this explicit distinction. Hence we still do not have a definitive answer to the question formulated by Gillihan and Farah (2005), namely, does the processing of self-referential information in the brain indeed differ as compared to the processing of other-referential processing? And if so, which brain areas are functionally involved in these processes?

To this end, a meta-analysis was conducted to integrate and extend the published findings. The aim was to get a more objective and quantitative picture of which regions are involved in self-referential processing specifically and those which are implicated in other-referential processing. The neuroimaging meta-analysis software algorithm that was applied allows visualization and precise localization of foci of activation that are consistent across the majority of studies.
Materials and Methods

Articles included in the meta-analysis were identified through a literature search using the search terms ‘self AND (reflect* OR referen*) AND (fMRI OR "functional magnetic resonance imaging" OR PET OR positron emission tomography)’ in PubMed until November 2008. Furthermore, the references of the selected papers were searched for additional papers on self-reflection and neuroimaging that did not appear in the PubMed search. A total of 20 out of 29 PET or fMRI studies were selected based on the inclusion criteria below, resulting in a total of 16 and 17 studies for the self > baseline and the self > other contrasts, respectively. All studies included in the meta-analysis are presented in table 1 (self > baseline) and table 2 (self > other).

1. Only studies in which the whole brain was measured were included in the meta-analysis.
2. Studies were only included when a paradigm was used in which the subject had to decide whether or not a trait word or sentence was applicable to the self or to another (predefined) person.
3. Studies were only included when reporting a self versus baseline contrast and/or a self versus other contrast.
4. All studies reporting a self > baseline contrast included a self condition where the subject was asked to self-reflect and a baseline condition not involving self-processing.
5. All studies reporting a self > other contrast included a self condition where the subject was asked to self-reflect and an ‘other’ condition in which the subject was asked to reflect upon another person.
6. Studies reporting a self versus non-self contrast, but not including a non-self semantic baseline were excluded from the meta-analysis.
7. Only studies using auditory or visually presented trait words or sentences were included in the meta-analysis. Studies using facial stimuli or emotive pictures were excluded from the meta-analysis.
8. Only activation data and not deactivation data were included in the meta-analysis.

Two contrasts will be explored in this meta-analysis, a self > baseline contrast and a self > other contrast. The self > baseline contrast included peak activation data from 14 fMRI studies and 2 PET studies (see table 1). All studies reported a self condition in which the subject is asked to self-reflect and a baseline condition not involving self-processing. The self > other contrast included peak activation data from 15 fMRI studies and 2 PET studies (see table 2). The exclusion of 9 out of 29 studies was mainly a result of criteria 2 and 3.
Statistical analysis

Parametric voxel-based meta-analysis [PVM; (Costafreda et al., 2009)] was employed to determine the brain areas where the studies identified in the literature search reported activations with a degree of consistency that could not be explained by chance alone. Briefly, PVM compares the observed distribution of reported activations across studies with a spatial null distribution reflecting the null hypothesis that the activations reported by each study have been generated at random locations across brain regions.

Based on this null model, a brain map representing the probability of observing a given degree of concordance across studies by chance alone is computed, and thresholded to reveal the areas of above chance concentration of activations across studies using the false discovery rate \[q=5\%\], (Benjamini & Hochberg, 1995)]. The purpose of the method is therefore to determine a cut-off point above which a certain foci overlap across studies is deemed statistically significant, in the sense of unlikely to have been generated by chance. The PVM method requires only the pre-specification of a smoothing parameter, which is here defined by a radius of 10 mm around each reported focus of activation. Each individual study map contribution to the final concordance map is weighted by the square root of its sample size. PVM implements a random effects model, whereby each study is assigned its own specific signal and noise function, thus reflecting that studies may differ due not only to random error, but also because of differences in equipment, analysis methods and subject population. Random effects modeling across studies results in better generalization of potential findings, and it is equivalent to the random effects approach for multisubject analysis in neuroimaging (Mumford & Nichols, 2006). It also provides an easily interpretable summary statistic, the percentage of studies reporting activation in the vicinity of a given voxel. Using simulated and real meta-analysis data, this approach has been shown to be a valid and powerful technique for neuroimaging meta-analysis (Costafreda et al., 2009). The software has been implemented in R, and it is available from the second author.

Results

The results of this meta-analysis are presented in figures 1 (self > baseline) and 2 (self > other). Tables 3 (self > baseline) and 4 (self > other) summarize brain regions that were revealed by this meta-analysis. The self > baseline contrast yielded four clusters (see table 3). A first large cluster with 58% and 55% of the studies reporting activation in this area included the Posterior Cingulate/Precuneus (BA23/30) and the Cuneus (BA 18), respectively. A second large cluster, with a similar 58% and 51% of concordance among studies showed Frontal Superior Medial (BA10) and Anterior Cingulate (BA32) activation, respectively. Thirdly, a cluster including left Frontal Superior areas (BA9) and Frontal Superior Medial (BA9) showed 44% and 37% of concordance among studies, respectively. Finally, a cluster, with 38% of the studies
Table 1. Studies included in the meta-analysis. Contrast self > baseline.

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects (N)</th>
<th>Method</th>
<th>Contrast</th>
<th>Brain region</th>
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<tbody>
<tr>
<td></td>
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<td>vmPFC</td>
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<tr>
<td>1</td>
<td>Schmitz et al. 2006</td>
<td>Healthy control subjects (15)</td>
<td>fMRI</td>
<td>Self ref. trait adjectives &gt; valence trait adjectives</td>
</tr>
<tr>
<td>2</td>
<td>Johnson et al. 2005</td>
<td>Healthy control subjects (17)</td>
<td>fMRI</td>
<td>Internal subject decision making &gt; external subject decision making</td>
</tr>
<tr>
<td>3</td>
<td>Johnson et al. 2002</td>
<td>Healthy control subjects (11)</td>
<td>fMRI</td>
<td>Self evaluative statements &gt; general knowledge statements</td>
</tr>
<tr>
<td>4</td>
<td>Johnson et al. 2006</td>
<td>Healthy control subjects (19)</td>
<td>fMRI</td>
<td>Self-reflection cues (preceded by essay writing) &gt; distraction cues</td>
</tr>
<tr>
<td>5</td>
<td>Johnson et al. 2006</td>
<td>Healthy control subjects (19)</td>
<td>fMRI</td>
<td>Self-reflection cues (NOT preceded by essay writing) &gt; distraction cues</td>
</tr>
<tr>
<td>6</td>
<td>Lou et al. 2004</td>
<td>Healthy control subjects (13)</td>
<td>PET</td>
<td>Self ref. trait adjectives &gt; nr of syllables trait adjectives</td>
</tr>
<tr>
<td>7</td>
<td>Schmitz et al. 2004</td>
<td>Healthy control subjects (19)</td>
<td>fMRI</td>
<td>Self ref. trait adjectives &gt; valence trait adjectives</td>
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<tr>
<td>8</td>
<td>Seger et al. 2004</td>
<td>Healthy control subjects (12)</td>
<td>fMRI</td>
<td>Self food liking &gt; nr vowels food name</td>
</tr>
<tr>
<td>9</td>
<td>Fossati et al. 2003</td>
<td>Healthy control subjects (10)</td>
<td>fMRI</td>
<td>Self ref. trait adjectives &gt; generally desirable trait</td>
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<tr>
<td>10</td>
<td>Heatherton et al. 2006</td>
<td>Healthy control subjects (30)</td>
<td>fMRI</td>
<td>Self ref. trait adjectives &gt; Trait words upper/lower case</td>
</tr>
<tr>
<td>11</td>
<td>Modinos et al. 2009</td>
<td>Healthy control subjects (16)</td>
<td>fMRI</td>
<td>Self evaluative statements &gt; general knowledge statements</td>
</tr>
<tr>
<td>12</td>
<td>Zhu et al. 2007</td>
<td>Healthy western subjects (13)</td>
<td>fMRI</td>
<td>Self ref. trait adjectives &gt; Trait words upper/lower case</td>
</tr>
<tr>
<td>13</td>
<td>Zhu et al. 2007</td>
<td>Healthy Chinese subjects (13)</td>
<td>fMRI</td>
<td>Self ref. trait adjectives &gt; Trait words bold/light faced character</td>
</tr>
<tr>
<td>14</td>
<td>Craik et al. 1999</td>
<td>Healthy control subjects (8)</td>
<td>PET</td>
<td>Self ref. trait adjectives &gt; generally desirable trait</td>
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<td>Yoshimura et al. 2008</td>
<td>Healthy control subjects (21)</td>
<td>fMRI</td>
<td>Self ref. trait adjectives &gt; difficulty defining trait adjective</td>
</tr>
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<td>16</td>
<td>Ochsner et al. 2005</td>
<td>Healthy control subjects (17)</td>
<td>fMRI</td>
<td>Self reference trait adjectives &gt; nr of syllables trait adjectives</td>
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<tr>
<td>Study</td>
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<td>dLPFC</td>
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<td>1 D’argembeau et al. 2007</td>
<td>Healthy Control subjects</td>
<td>fMRI</td>
<td>self reference trait adjectives &gt; other trait</td>
<td>left right</td>
</tr>
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<td>2 Ochsner et al. 2005</td>
<td>Healthy Control subjects</td>
<td>fMRI</td>
<td>Self reference trait adjectives &gt; other trait</td>
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<tr>
<td>3 Lou et al. 2004</td>
<td>Healthy Control subjects</td>
<td>PET</td>
<td>self reference trait adjectives &gt; other trait</td>
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<tr>
<td>4 Schmitz et al. 2004</td>
<td>Healthy Control subjects</td>
<td>fMRI</td>
<td>self reference trait adjectives &gt; other trait</td>
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<td>5 Kelley et al. 2002</td>
<td>Healthy Control subjects</td>
<td>fMRI</td>
<td>self reference trait adjectives &gt; other trait</td>
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<tr>
<td>6 Seger et al. 2004</td>
<td>Healthy Control subjects</td>
<td>fMRI</td>
<td>food liking self &gt; food liking other</td>
<td></td>
</tr>
<tr>
<td>7 Heatherton et al. 2006</td>
<td>Healthy Control subjects</td>
<td>fMRI</td>
<td>self reference trait adjectives &gt; other trait</td>
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<tr>
<td>8 Kjaer et al. 2002</td>
<td>Healthy Control subjects (7)</td>
<td>PET</td>
<td>self reference trait adjectives &gt; other trait</td>
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</tr>
<tr>
<td>9 Jenkins et al. 2008</td>
<td>Healthy Control subjects</td>
<td>fMRI</td>
<td>Opinion question self &gt; opinion question other</td>
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<tr>
<td>10 Modinos et al. 2009</td>
<td>Healthy Control subjects</td>
<td>fMRI</td>
<td>self evaluative statements &gt; other evaluative</td>
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<td>11 Zhu et al. 2007</td>
<td>Healthy Chinese subjects</td>
<td>fMRI</td>
<td>self reference trait adjectives &gt; other trait</td>
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<td>12 Zhu et al. 2007</td>
<td>Healthy western subjects</td>
<td>fMRI</td>
<td>self reference trait adjectives &gt; other trait</td>
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<td>13 Gutchess et al. 2007</td>
<td>Healthy aged subjects (17)</td>
<td>fMRI</td>
<td>self reference trait adjectives &gt; other trait</td>
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<td>14 Gutchess et al. 2007</td>
<td>Healthy young subjects (19)</td>
<td>fMRI</td>
<td>self reference trait adjectives &gt; other trait</td>
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<tr>
<td>15 Vanderwal et al. 2008</td>
<td>Healthy Control subjects (20)</td>
<td>fMRI</td>
<td>self reference trait adjectives word pairs &gt; other trait adjectives word pairs</td>
<td></td>
</tr>
<tr>
<td>16 Pfeiffer et al. 2007</td>
<td>Healthy Control subjects</td>
<td>fMRI</td>
<td>self evaluative statements &gt; other evaluative</td>
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<tr>
<td>17 Yoshimura et al. 2008</td>
<td>Healthy Control subjects</td>
<td>fMRI</td>
<td>self reference trait adjectives &gt; other trait</td>
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reporting activation in this area included the Left Inferior Frontal, Orbital part (BA47), the Left Temporal pole (BA38) and the Left Insula (BA48).

The second contrast that was studied was the self > other (see table 4) and yielded only one large cluster with a concordance of 35%-49% between studies showing Anterior Cingulate (BA24/32), concordance 49 %, Frontal Mid Orbital (BA10), concordance 48%, Frontal Superior Medial (BA10), concordance 43% and left Mid/Superior Frontal (BA10/46), concordance 35%, activation.
Discussion

Cortical Midline Structures

The areas that were most consistently activated across studies in this meta-analysis largely converge with what one would expect from individual studies that investigated self-reflection. Regarding self-reflection > baseline the integration of the published evidence leaves it beyond doubt that the Cortical Midline Structures (CMS) are associated with self-processing. However, this meta-analysis also pointed to other areas that have not been particularly highlighted before in relation to self-processing, although they were evidently activated in most individual studies: the insula, temporal pole and Inferior Frontal Cortex (orbital part). Furthermore, this meta-analysis demonstrates that a clear distinction can be made in activation patterns for self-reflective and other-reflective processing.

As to the role of the CMS, the meta-analysis shows that areas consistently activated included the vMPFC, dMPFC, PCC and ACC (see figure 1). We speculate that a functional distinction should be made between these areas. Based on the meta-
analysis and the reviewed literature, it is proposed that the dMPFC and PCC are not only involved in the processing of self-relevant information, but rather are involved in the evaluation and decision making process of whether a certain stimulus is applicable to the self or to another person (dMPFC) and the consultation of autobiographical memory (PCC). In contrast, the vMPFC is specifically involved in the processing of self-referential stimuli and not in the processing of other referential stimuli. Other studies that have previously suggested a functional distinction between the vMPFC and dMPFC have focused on self-reflective processes only and have not discussed other-reflective processing. In a study by Gusnard et al. (2001) an increased activation in the dorsal MPFC in the self-referential condition as compared to the non self-referential condition was demonstrated. Importantly, the authors found a decrease in activation in the ventral MPFC in both conditions. They suggest that dorsal MPFC activation is increased when processing self-referential stimuli or when engaging in introspective activities. Regarding the ventral MPFC, they suggest that this area is engaged in processes in which salience of stimuli is assessed. Furthermore, they suggest that the function of the vMPFC should be distinguished from the function of the orbito-MPFC. Through the oMPFC, the vMPFC receives sensory information from inside and outside the human body (Barbas, 1993; Carmichael & Price, 1995; Rolls & Baylis, 1994). Besides its connections with the oMPFC, the vMPFC is intimately connected to the limbic system (Ongur & Price, 2000). These interconnections suggest that the vMPFC plays a key role in emotional processing (Bush et al., 2000; Drevets & Raichle, 1998; Simpson et al., 2000). Bechara et al. (1997) more specifically proposed that the vMPFC is responsible for the coupling of emotional and cognitive processes regarding decision making, which might involve constant monitoring of the internal and external world (Elliott et al., 2000).

The dorsal MPFC area on the other hand, has been hypothesized to be involved specifically in self-referential processing (Frith & Frith, 1999). In line with these suggestions, Northoff et al. (2006) and Northoff and Bermpohl (2004) postulated that the dMPFC is important in the evaluation of self-referential stimuli, whereas the PCC is responsible for the integration of autobiographical information and emotional information regarding the ‘self’. Finally, Schmitz et al. (2006), demonstrated evidence for a vMPFC-Nucleus Accumbens-Insula-Amygdala network responsible for the affective component of decision making regarding the self. Furthermore, they provided evidence for a dMPFC-dorsolateral PFC-Hippocampus network which is involved in the cognitive control or monitoring of decisions regarding the self. Recently, Schmitz et al. (2007) proposed that the vMPFC is particularly important in detecting the self-relevance of the perceived stimulus, while the role of the dMPFC is of a more introspective nature.

This meta-analysis suggests that this vMPFC involvement may be concerned with the affective processing of self-relevant information. However, in contrast to the suggestions of Schmitz et al. (2007), the results suggest that the involvement of the dMPFC is not unique to self-reflective processing but rather this region is important
for reflective processing on a broader scale. Furthermore, Mitchell et al. (2006) compared activations when subjects reflected upon ‘similar others’ compared to ‘dissimilar others’ and demonstrated activation in the vMPFC for the former and dMPFC activation for the latter condition. Thus the proposed dichotomy between the vMPFC and the dMPFC (Mitchell et al., 2006; Schmitz & Johnson, 2007; Schmitz et al., 2006) is supported by this meta-analysis which enables it to be taken one step further. The results diverge from Schmitz et al. (2007; 2006) when the second contrast of this meta-analysis is taken into account. When comparing self > other reflection processes, no involvement of the dMPFC was found, but the vMPFC and vACC seem to be the core regions. This suggests that the dMPFC is important in reflection processes per se. We suggest that the vMPFC and the vACC activation are related to a more affective process, namely the processing of self-relevant information. According to Northoff and Bermpohl (2004) and Northoff et al. (2006), an emotional component is inherent to self-processing. That is, they look upon emotional stimuli as being mentally significant and thus essential for decision making regarding the self. They proposed a continuum of self-relevance and an involvement for the vMPFC in coding the information for self-relevance: the more self-relevance, the more emotional, the greater the activation of the vMPFC. Moran and colleagues (2006) demonstrated by means of an affective self-reflection paradigm that activation of dMPFC is indeed independent of valence. This is in contrast to vACC activation, which was attenuated when the stimulus was negative and related to the self and heightened when the stimulus was positive and related to the self. This perhaps explains why these areas are less active in other reflection processes since when judging another person, it is less important to the self-image whether the stimulus is positive or negative. Similar results were found by Yoshimura et al. (2008) and Fossati et al. (2003) confirming the affective role of the vMPFC and vACC in self-reflective processing. A number of studies do report ACC activation in an other vs. baseline contrast (Heatherton et al., 2006; Kelley et al., 2002; Ochsner et al., 2005; Pfeifer et al., 2007; Seger et al., 2004; Zhu et al., 2007). When these findings are combined with the results of this meta-analysis, it seems that the ACC is involved in both self- and other-reflective processing. However, since ACC activation is present in the self > other contrast, this suggests that this area is more active in self- than in other-reflective processing and that the amount of activation in the ACC may be a indicator for self-specificity. Unfortunately, due to the limited number of studies reporting data on this contrast, this could not be included in the meta-analysis.

Interestingly, recent studies in patients with schizophrenia suggest that specifically the vMPFC shows abnormal activation in emotional tasks (Harrison et al., 2007; Park et al., 2008; Taylor et al., 2007). This may imply that these patients experience difficulties in self-reflection, resulting in an inaccurate representation of their traits, abilities and attitudes and thus hampering the evaluation of their own behavior and the comparison with the behavior of others.
Anterior Paralimbic Regions

Besides CMS activation, this meta-analysis showed insula, temporal pole and IFC orbital part activation in the self versus baseline contrast (see figure 1). These structures are functionally interrelated and, together with the ACC, have been suggested to form a circuit involved in representing and processing internal affective bodily states (Mega et al., 1997). A role that can be linked to self-processing and has often been associated with the temporal pole is Theory of Mind processing (Frith & Frith, 1999; Moriguchi et al., 2007). It has been shown that damage to the temporal pole region can result in an impairment in the use of knowledge a person has on the behavior of others and on situations associated with this behavior (Funnell, 2001). Damasio (2004) suggested that the temporal pole unites information from different modalities and by this defines unique situations and individuals. It is possible that this unification of information does not just occur when judging other individuals, but also when bits of information about one’s self are processed.

Regarding the insula, Damasio (1999) suggested that it plays a role in the representation of the current bodily state of the organism, also called ‘protoself’. Anatomically, the insula is highly connected with the limbic system and with the prefrontal cortex and is believed to play a key role in the integration of viscerosomatic information (Mayberg et al., 1999), that is, transient bodily states. Insula activation has been reported in studies on, amongst others, agency (Ruby & Decety, 2001), self-related episodic memory (Fink et al., 1996), self- and familiar face processing (Kircher et al., 2001) and food preference processing (Seger et al., 2004). Furthermore, it has recently been demonstrated that the insula is involved in decision-making processes on affective stimuli (Craig, 2009; Grabenhorst et al., 2008).

Finally, activation in the orbital part of the IFC was found. The IFC is commonly activated in the encoding of verbal information (Buckner et al., 1999). According to Kelley et al. (2002), this region is activated in self-reflective processing due to semantic encoding processes. These processes are more thorough when processing self-relevant information than simple baseline processing, simply because it is likely to be more important to later recall information about oneself.

A model of self-reflection in the brain

To enhance the understanding of the mutual functional roles of the brain regions that emerge from this meta-analysis, we propose a model of self-processing in the brain (see figure 3). When a person is confronted with a situation in which decisions have to be made regarding the self or another person, firstly self-directed attention will modulate the manner in which the stimulus is processed. When attention is directed to the self, self-relevant features of the information will be filtered out and will be tagged. This information will be coupled to information gathered from the internal world, that is, from the affective bodily state. Furthermore, one needs to gather past information on the self in order to make an accurate decision, requiring autobiographical memory consultation. Lastly, evaluation and decision regarding the
applicability to the self or other has to be made.

Evaluations and decisions regarding another person might still call upon autobiographical memory and emotional processes since this person may be close to the self. However, as implied by the results of this meta-analysis, the information will not receive the self-relevance tags, which is so specific for self-processing. Thus, we distinguish two different pathways: (1) a pathway that includes processes similar for self- and other-reflective processing and (2) an additional pathway that is specific for self-reflective processing.

Regarding brain areas that are involved in the processes just described, the results of our meta-analysis suggest that the ACC may be important for directing attention to the self. Consequently, the vMPFC might be responsible for tagging the stimulus when it is relevant for self [cf. Northoff and Bermpohl (2004) and Northoff et al. (2006)]. Anatomically, the vMPFC is connected to the limbic system (Young et al., 1994) as well as the dLPFC (Ghashghaei & Barbas, 2002) - important for working memory performance and temporal organization of behavior (Buchsbaum et al., 2005; Corcoran & Upton, 1993; Fuster, 1997; Fuster, 2000; Gilbert et al., 2006; Goldstein et al., 2004; Haut et al., 1996; Hermann & Wyler, 1988; Upton & Corcoran, 1995). dLPFC exerts executive control on the vMPFC, through which in turn the limbic system is influenced (Phelps, 2006). The insula and PCC provide the individual with further information regarding the internal bodily state and memory.
respectively, while an evaluation and a decision concerning the applicability of the stimulus is likely to be finalized by the dMPFC [cf. Northoff and Bermpohl (2004) and Northoff et al. (2006)]. It may be expected that if any of these areas are damaged, this will hamper the gathering of information in one or more areas, resulting in defective or imperfect evaluation and decision-making.

As can be seen in figure 3, the dLPFC is not included in the model. Our interpretation of the data is that the main function for the dLPFC is its role in executive control. This function is not specific to the reflective network, whereas the proposed interplay between the other regions suggested in the model is specific to reflective processing.

When self-processing is hampered this can lead to major problems in the social domain, particularly in the domain of behavior modification in a social situation as well as in the recognition of social cues (Atkinson & Robinson, 1961). This typically is one of the major problems encountered by schizophrenia patients.

Implications for defective self-processing in schizophrenia

In the recent literature there has been an interest in these social cognitive deficits in schizophrenia patients, using paradigms such as ‘Theory of mind’ (TOM) or the capacity to put oneself in another person’s shoes (see Sprong et al. (2007) for a meta-analysis), self-monitoring (Carter et al., 2001), or emotional face recognition (Addington et al., 2006; Baird et al., 2006). One area that has received little attention is the relationship between schizophrenia and self-processing, in particular self-reflection.

Dimaggio et al. (2008) argued that to be able to recognize emotions in others, one needs to be able to recognize one's own emotions. That is, to be able to put oneself in another person’s shoes, one uses one’s own perspective as a basis for the interpretation (Carruthers, 2009). Importantly, the areas found in this meta-analysis come close to an area which has been labeled the anterior paracingulate cortex and which is thought to be of crucial importance for the formation of shared expectations in the own person and another agent (Gallagher et al., 2002; Gallagher & Frith, 2003; McCabe et al., 2001). This implies that the deficits in TOM could be based on deficits in self-reflective capacities. This is supported by findings of Corcoran and Frith (2003; 2005) who demonstrated a correlation between autobiographical memory retrieval and TOM performance in schizophrenia patients. Corcoran (2001) argued that when people try to infer a person’s mental state, they consult autobiographical memory as a basis for this attempt.

If self-reflective processing in schizophrenia patients is impaired, one would expect a deviant pattern of activation in self-reflective processing networks. FMRI data on an emotional stroop paradigm indeed shows abnormal activation in the vMPFC (Park et al., 2008; Taylor et al., 2007) The present meta-analysis shows that the vMFFC seems to be of particular importance when reflecting upon oneself as in the contrast self > other, implying that schizophrenia patients might experience
particular difficulties in self-reflection processes.

An interesting specification of impaired self-processing in schizophrenia patients may be the relationship between lack of illness awareness and self-reflective processing. When one experiences problems in reflecting external information upon oneself, this might lead to impaired insight in schizophrenia patients.

**Schizophrenia, insight and self-reflection**

Lack of insight is a widely recognized problem in clinically psychotic patients (Amador & David, 2004). Not only can this hamper the attempts of the clinician to help the patient, it also causes distress and feelings of frustration in family and friends. It is as yet unclear what causes unawareness of illness. Several studies have related lack of insight to reduced cognitive function and in particular cognitive set-shifting abilities [see Aleman et al. (2006) for a meta-analysis]. However, this accounts for a relatively small proportion of the variance in insight.

A possible new approach to the insight problem is to look at self-processing. So far, no studies have looked directly at the relationship between insight in psychosis and self-reflective processing, despite the apparent link. Patients, who experience difficulties in reflecting upon themselves, will most likely also have difficulty reflecting upon themselves in the light of their illness, symptoms and use of medication. In a paper by Ries et al. (2007) this train of thought was confirmed in individuals with Mild Cognitive Impairment. Individuals who had impaired insight, showed significantly attenuated activation of the CMS during self-appraisal. Importantly, the authors demonstrated that this relationship was not influenced by the cognitive impairment itself. In line with these findings Lysaker et al. (2005b) demonstrated that better metacognitive skills, such as the ability to think about one's own thoughts, were related to better insight in patients with schizophrenia. This concept is closely linked to the concept of ToM, namely to think about the thoughts and actions of another agent. Interestingly, some studies suggest that the capability to think about another agent thoughts does not imply full metacognitive capacities (McEvoy et al., 1993; Rockeach, 1964; Startup, 1997). These studies demonstrate that patients lacking insight into their own illness, were fully capable of recognizing the illness and symptoms in fellow patients. Thus as Wiffen and David (2009) proposed, self-reflective processing may make use of similar cognitive mechanisms as ToM processing, but this does not imply that these processes cannot be affected autonomously.

Several MRI studies have related lack of insight in schizophrenia to the structure of prefrontal sub-regions (Flashman et al., 2001; Shad et al., 2004; Shad et al., 2006), such as the dLPFC (Flashman et al., 2001; Shad et al., 2006), OFC (Flashman et al., 2001; Shad et al., 2006), MFG (Flashman et al., 2001), IFG (Sapara et al., 2007) and SFG (Sapara et al., 2007). Due to cognitive control on the medial PFC and thence the limbic system (Phelps, 2006) one might assume that the dLPFC does not only exert control in executive functioning or set-shifting, but also in more emotionally
related cognition including self-reflective processing. This reasoning is confirmed by a study by Schmitz et al. (2004) who found a relationship between bilateral dLPFC activation, MPFC activation and self-evaluative metacognition. Furthermore, a functional relationship between the dLPFC and the PCC, which has been associated with the storage of autobiographical memory (Andreasen et al., 1995; Maddock et al., 2001; Maguire & Mummery, 1999), is reflected in the dense connections between the dLPFC and the PCC (Petrides, 2005; Petrides & Pandya, 1999). As mentioned before, in the process of self-reflection, one needs to gather past information on the self in order to make an accurate decision, requiring autobiographical memory consultation.

Due to a deficit in cognitive control caused by dLPFC dysfunction, patients who lack insight may not only be impaired on more cognitive tasks, but also experience problems in self-reflective processing. In terms of the proposed model, due to an impaired controlling function of the dLPFC, the other areas important for self-evaluative and meta-cognitive problems, the vMPFC, dMPFC and PCC, will show sub-optimal functioning each leading to impaired self-evaluative processing and an unwillingness to accept that one is ill and needs treatment.

To test the validity of the proposed model, more research should be conducted looking at self-reflective processing and its neural correlates in patients lacking insight. This might guide us to the processes that are impaired in this patient group and give us a direction in which treatment should be directed in order to help these patients. The current proposal and meta-analysis of data from healthy subjects prepares the ground for such a project.

Limitations and directions for future research

One important drawback of meta-analysis is that it relies only on published data which is biased against negative results; often called the “file-drawer” problem. The central aim of fMRI meta-analysis, however, lies not on the aggregation of power across studies, but rather on its capacity to assess the reliability of findings across studies, thereby determining the location of an aggregate effect, and simultaneously reducing the likelihood of false positive reporting. It is arguable that this function-location aim is less affected by a file-drawer problem (Fox et al., 1998). However, no guarantee can be given that in addition to the significant regional effects reported here, other effects exist in other areas that have not been picked up by the meta-analysis because of low reproducibility across studies. On the other hand, the statistically significant meta-analysis results are very likely to represent true effects, even in the presence of a file-drawer problem (for a more detailed discussion of power, reliability and the limitations of fMRI meta-analysis (Costafreda et al., 2009).

In the current meta-analysis only two contrasts are included, self > baseline and self > other. Unfortunately, most studies suitable for inclusion in the meta-analysis did not report coordinates for a third contrast: other > baseline. Therefore, this process could not be discussed. Furthermore, readers should note that only self-reflection studies using trait words and sentences were included in the meta-analysis,
which limits the conclusions regarding self-processing in general. Finally, besides making a distinction between self- and other-reflective processing, a finer distinction may be that of distant and close others. Reflecting upon a close other may come closer to self-reflection and recruit the vMPFC, whereas reflecting upon a distant other should not. The presented model provides a theoretical framework by which these and similar hypotheses can be explicitly tested.

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