Review

Psychopathology and pathophysiology of the self in depression — Neuropsychiatric hypothesis

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Received 27 August 2006; received in revised form 8 February 2007; accepted 11 February 2007
Available online 26 March 2007

Abstract

Background: The question of the self has intrigued philosophers and psychologists for a long time. More recently distinct concepts of self have also been suggested in neuroscience more specifically in neuroimaging.

Aims: The aim here is to apply these findings to abnormalities of the self in depression and to develop neuropsychiatric hypothesis.

Methods and results: Patients with depression suffer from an increased self-focus, attribution of negative emotions to the self, and increased cognitive processing of the own self. We assume that in major depressive disorder (MDD), the abnormal self-focus may be related to altered neural activity in the ventral cortical midline structures (CMS), the one-sided attribution of negative emotions to the self with neural activity in the amygdala and the ventral striatum/N. accumbens, and the abnormal cognitive processing of one’s self with reciprocal modulation between ventral CMS and lateral prefrontal cortical regions.

Conclusions: It is concluded that the transdisciplinary investigation of the self between neuroscience, psychiatry and philosophy yields novel insights into the psychopathology and pathophysiology of the self in depression as well as into the neurophilosophical concept of the self in general.

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Keywords: Self; Depression; Cortical midline structures

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doi:10.1016/j.jad.2007.02.012
1. Introduction

The question of the self has been one of the most salient problems throughout the history of philosophy and more recently also in psychology and neuroscience (James, 1892; Panksepp, 1998; Damasio, 1999; Gallagher, 2000; Stuss et al., 2001; Gillihan and Farah, 2005; Kelley et al., 2002; Lambie and Marcel, 2002; LeDoux, 2002; Turk et al., 2003; Damasio, 2003; Gallagher and Frith, 2003; Keenan et al., 2001; Kircher and David, 2003; Panksepp, 2003; Vogeley and Fink, 2003; Northoff, 2004; Northoff and Berrmpohl, 2004; Northoff et al., in press; Metzinger, 2003). The question of the self is not only of philosophical and neuroscientific interest but also highly relevant in psychiatry. Recent investigations have predominantly focused on abnormalities of the self in schizophrenia and its so-called ego-disturbances (Kircher and David, 2003). In contrast, abnormalities of the self in other psychiatric disorders have rather been neglected so far. We here want to focus on the self and its abnormalities in depression, particularly in depression. The aim of the paper is to develop predictions or hypotheses about the possible neural basis of abnormalities of the self in depression. In a first step, I want to define the concept of self making it suitable and applicable to neuroscience and psychiatry. The second step characterizes the psychopathology of the self in depression focusing on three particular characteristics, increased self-focus, attribution of negative emotions to the self, and increased cognitive processing of the own self. The third step consists in discussing recent findings in healthy subjects from predominantly imaging studies about the possible neural basis of the self. The focus is here on the neural basis of the three characteristics, self-focus, attribution of emotions to the self, and cognitive processing of one’s self. In a fourth step, these findings in healthy subjects are related to current imaging studies in depression. By combining psychopathological changes in the self and imaging data from both healthy and depression, I develop neuropsychiatric hypotheses that reflect assumptions about the possible neural basis of the three characteristics of the abnormal self in depression, increased self-focus, attribution of negative emotions to the self, and increased cognitive processing of the own self. I will also discuss possible empirical study designs that may possibly allow to further explore the neural basis of the self in depression. It should be noted that due to the wide span and the transdisciplinary character of the current investigation, many interdisciplinary details in the different sections cannot be spelled out and discussed in an appropriate detail and length. At the very end I will also discuss some implications for the neurophilosophical concept of the self, e.g., whether the self is a higher-order cognitive function, e.g., self-awareness, or rather a particular type of process of formatting and coding incoming stimuli.

2. Definition and concept of the self in neuroscience

Damasio (1999, 2003) and Panksepp (1998, 2003) suggest a “proto-self” in the sensory and motor domains, respectively, which resembles William James’s description of the physical self. Similarly, what has been described as “minimal self” (Gallagher, 2000; Gallagher and Frith, 2003) or “core or mental self” (Damasio, 1999, 2003) might correspond more or less to James’ concept of mental self. Finally, Damasio’s (1999, 2003) “autobiographical self” and Gallagher’s (2000), Gallagher and Frith’s (2003) “narrative self”
strongly rely on linking past, present, and future events with some resemblances to James’ spiritual self.

What remains unclear, however, is what unites these distinct concepts of self allowing us to speak of a self in all cases. We assume that processing of stimuli as self-referential, self-referential processing, is common to the distinct concepts of self in the different domains. This has also been described as ‘self-related’ or ‘self-relevant’ processing (Kelley et al., 2002; Turk et al., 2003; Northoff and Berrmpohl, 2004; Northoff et al., in press; Craik and Hay, 1999; Schore, 2003; Phan et al., 2004). In these studies (Kelley et al., 2002; Turk et al., 2003; Northoff and Berrmpohl, 2004; Northoff et al., in press; Craik and Hay, 1999; Schore, 2003; Phan et al., 2004) subjects were presented stimuli, pictures, faces, words, or tones, and had to evaluate whether they were related to them or not. Faces, for instance, were presented from the own person, relatives, family members, and other non-related famous and non-famous persons. Subjects then had to decide upon the degree of the stimuli’s closeness to the own person and decide whether they have something to do with me or not. Another example is the way we perceive pictures of ourselves or close friends versus pictures of completely unknown people or pictures of our houses where we spent our childhood versus pictures of any unknown house etc. Such comparisons are possible in different sensory modalities. Self-relatedness is here understood and presupposed in a rather cognitive sense implying that one becomes aware of one’s self once one sees the stimulus. Self-relatedness in this higher-order cognitive sense can more or less be identified with self-awareness or self-consciousness as it is especially clear in recognition of one’s own face (see below in the Neurophilosophy of the self for further discussion). However, awareness of one’s self presupposes that there is a self at all since one cannot be aware of nothing in self-awareness. How is this self upon which self-awareness is based constituted? I here suggest that what I call self-related processing may be crucial in empirical terms for constituting our self. In the following I will focus on characterizing self-related processing as empirical process whereas in the final part of this papers, the neurophilosophy of the self I will discuss the implications of such an approach for our philosophical concept of the self.

What is self-related processing? Self-related processing concerns stimuli that are experienced as strongly related to one’s own person. Without going deeply into abstract philosophical considerations we would like to give a brief theoretical description of what we mean by the terms ‘experience’, ‘strongly related’, and ‘to one’s person’. ‘Experience’ refers to phenomenal experience such as, for example the feeling of love, the smell of a rose or the feeling of mineness. Thus we focus on the subjective aspect of experience that is described as the “phenomenal aspect” (Block, 1996; Chalmers, 1996). The subjective aspect of experience as prerreflective is often distinguished from its reflective or cognitive aspects. The latter refer to veridical information processing and objective reasoning. Being in love from that point of view refers to psychological questions concerning motivation and causes for the emotional state (Block, 1996; Chalmers, 1996). Our definition of self-related processing by experience implies a focus on the implicit, subjective, and phenomenal aspects (to feel or experience self-referential stimuli) what Kircher and David (2003) call “self-qualia” and Zahavi (2003) and others’ (Zahavi, 2003; Legrand, 2005; Gallagher and Zahavi, 2005) describe as “prerreflective” whereas our focus is less on associated cognitive and reflective functions allowing to make it explicit (to know about or to be aware of stimuli as self-related). As such we distinguish self-related processing also from what is commonly called “insight” which we consider to presuppose cognitive cognitive and reflective functions rather than simply pure subjective and phenomenal aspects (Kircher and David, 2003).

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

The self-stimulus relation results in what has been called “mineness”; Lambie and Marcel (2002) speak of an “addition of the ‘for me’” by means of which that particular stimulus becomes “mine” resulting in “mineness” (Metzinger, 2003).
3. Psychopathology of the self in depression

She sat by the window, looking inward rather than looking out. Her thoughts were consumed with her sadness. She viewed her life as a broken one, and yet she could not place her finger on the exact moment it fell apart. ‘How did I get to feel this way?’ she repeatedly asked herself. By asking, she hoped to transcend her depressed state; through understanding, she hoped to repair it. Instead, her questions led her deeper and deeper inside herself — further away from the path that would lead to her recovery. (cited from: 30, p.247)

This description of a depressed patient shows three crucial characteristics concerning the self which shall be discussed in further detail in the following (see also Fig. 1).

3.1. Increased self-focus

Similar to our patient, almost all depressed patients look rather inward than outward, they focus very much on themselves while no longer being able to shift their focus on others’ (see arrows towards the self in Fig. 1). Social–psychological theory speaks of self-focused attention as focus on internal perceptual events, that is, information from those sensory perceptions that react to changes in bodily activity (Ingram, 1990). Self-focus may also concern enhanced awareness of one’s present or past physical behaviour, that is, heightened cognizance of what one is doing or what one is like. This implies that the depressed subject’s attention is no longer focused on its relation to the environment and environmental events, as in healthy subjects, but rather on itself as the prime focus with the environment shifting into the background. One may speculate that in sensory terms, attention may shift from the exteroceptive sensory system that signals environmental events and the subject’s relation to the environment, to the interoceptive sensory system that processes stimuli from the subject’s body.

Empirical research clearly indicates heightened self-focus attention in depression. A variety of studies assessing self-focused attention and depression with diverse measures and methodologies all converge on the finding of an increased and perhaps prolonged level of self-focused attention in depression (Ingram, 1990). What remains however unclear is whether this increased self-focus is purely on the explicit, e.g., conscious level, as it is defined here, or whether it is already present on the implicit, e.g., unconscious level.

3.2. Association of the self with negative emotions

Another characteristic of the description above is the attribution of negative emotions to the own self (see arrows from negative emotion to self in Fig. 1). The own self is associated with abnormal sadness, guilt, mistakes, inabilities, death, illness, etc. which may ultimately result in paranoid delusions. A recent study investigating symptom clusters in the Beck Depression Inventory (BDI) observed three BDI factors among them the self-blame factor (Grunebaum et al., 2005). Interestingly, patients with depression with previous suicide attempts showed significantly higher scores on the BDI self-blame factor than those depressive patients without suicide attempts. Moreover, the self-blame factor significantly correlated with the total number of suicide attempts and with known risk factors for suicidal behaviour. Such self-blame possible results from the association of the self with predominantly negative emotions in depression whereas these patients remain apparently unable to attribute positive emotions to their self.

3.3. Increased cognitive processing of the own self

Our patient typically suffers from increased cognitive processing, she thinks about herself and her mood and tries desperately to discover the reasons for that and thereby gets only deeper and deeper into the depressed mood (see arrows from negative cognitions to the self in Fig. 1). This cognitive processing of the own self is described as rumination as a method of coping with negative mood that involves self-focused attention with self-reflection as well as a repetitive and passive focus on one’s negative emotions (Treynor et al., 2003). On the basis of a rumination scale, Treynor et al. (2003)
suggest a two factor model of rumination. They call the first factor reflection which describes a purposeful turning inward to engage in cognitive problem solving to alleviate one’s depressive problems. The second factor is best described as brooding as passive comparison of one’s current situation with some unachieved standard oriented on others’ and thus on what psychodynamically can be called the ideal-self (Boeker et al., 2000). Corresponding to the first factor, reflection, Rimes and Watkins (2005) suggest an increased analytical self-focus in depression which they define as thinking analytically ‘about’ oneself and one’s symptoms; such increased analytical self-focus is related to the increased ratings of the self as worthless and incompetent and ratings of depressed mood. They distinguish the increased analytical self-focus from what they call experiential self-focus defined as focusing on the direct experience of one’s thoughts, feelings and sensations in the present moment. In contrast to the increased analytical self-focus, the experiential self-focus tends to be rather low and decreased in depression since these patients do no longer experience themselves and their self as such. Due to such imbalance between analytical and experiential self-focus, one may speculate that experiential access to their own self could be blocked by the predominance of self-centred cognitions reflecting the increased analytical self-focus. What is meant here by analytical self-focus may correspond more or less to what I call self-awareness or self-consciousness whereas experiential self-focus may refer to the characteristics of self-related processing (see above). Analytical and experiential self-focus may thus describe distinct aspects of the self, the former one pointing out higher-order cognitive function and the latter phenomenal aspects, which Hertel and Messidi (2006) demonstrated to interact with each other since negative self experience, e.g., the experiential self-focus, may induce increased rumination reflecting the analytical self-focus.

4. Neuroscience of the self

4.1. Self-focus and ventral CMS

Recently, the question of self has also become a topic in neuroimaging. Though current studies remain unable to account for all the distinct and subtle aspects the self discussed above, they at least are able to reveal various regions in association with self-related tasks (see also Legrand, 2005 for advancing a similar argument about the discrepancy between empirical designs and conceptual distinctions). In addition to various regions in our brains’ medial cortex (see below for details), a variety of other cortical and subcortical regions like ventro- and dorsolateral prefrontal cortex, lateral parietal cortex, bilateral temporal poles, insula, and subcortical regions including amygdala, ventral striatum/N. accumbens, brain stem, colliculi, periaqueductal gray (PAG), and hypothalamus/hypophysis have been observed to be activated during self-related tasks (Panksepp, 1998; Damasio, 1999; Gallagher, 2000; Gillihan and Farah, 2005; LeDoux, 2002; Damasio, 2003; Gallagher and Frith, 2003; Keenan et al., 2001; Kircher and David, 2003; Panksepp, 2003; Vogeley and Fink, 2003; Northoff, 2004; Northoff and Bermpohl, 2004; Northoff et al., in press; Gazzaniga, 1998; Rolls, 2000; Wicker et al. 2003).

This regional heterogeneity raises the question of so-called core regions being commonly involved in the different self-related tasks. In addition to lateral cortical and subcortical regions, several neuroimaging studies report involvement of various medial cortical regions. These include the medial orbital prefrontal cortex (MOFC), the ventromedial prefrontal cortex (VMPFC), the sub/pre- and supragenual anterior cingulate cortex (PACC, SACC), the dorsomedial prefrontal cortex (DMPFC), the medial parietal cortex (MPC), the posterior cingulate cortex (PCC), and the retrosplenial cortex (RSC). Recently, these regions have been subsumed under the term cortical midline structures (CMS) (see Fig. 2) and characterized as an anatomical and functional unit (Northoff and Bermpohl, 2004; Northoff et al., in press). Among these various regions, the ventral CMS including the medialFig. 2. Schematic presentation of anterior cortical midline structures. MOPFC = medial orbital prefrontal cortex, VMPFC = ventromedial prefrontal cortex, DMPFC = dorsomedial prefrontal cortex, SACC = supragenual anterior cingulate cortex, PACC = perigenual anterior cingulate cortex.
orbitofrontal cortex (MOFC), the ventromedial prefrontal cortex (VMPFC), and the sub- and pregenual part of the anterior cingulate cortex (PACC) are of particular interest (see Fig. 2). These ventral regions are densely connected with the amygdala, the ventral striatum/N. accumbens and other basal ganglia, all primary exteroceptive sensory modalities, and further subcortical regions (midbrain, brain stem) implicated in interoceptive processing (Ongur and Price, 2000). This connectivity pattern suggests that neural activity in the ventral part of the CMS could be involved in linking both extero- or interoceptive stimuli with respect to their self-relatedness. This is supported by a recent study (D’Argembeau et al., 2005), which observed a significant correlation of neural activity in the ventral CMS, i.e., on the junction between MPOFC, VMPFC, and PACC with the degree of self-relatedness of thoughts. Taken together, these results lend us to suggest that the ventral CMS are involved in coding the self-relatedness of stimuli thereby representing them as self-related. This is also well compatible with clinical observations in patients with lesions in ventral CMS who remain unable to develop a coherent model of their own self (Damasio, 1999; Schore, 2003).

What remains however unclear is the exact physiological correlate of the process of coding and representing self-relatedness in ventral CMS. The ventral CMS were shown to be exclusively modulated by deactivation, e.g., signal decreases during non-self-related task demands (D’Argembeau et al., 2005; Gusnard et al., 2001). In contrast, dorsal and posterior parts of the CMS showed a wider range of neural modulation including both deactivation and activation. In these regions self-related task demands induced activation, e.g., signal increases, whereas non-self-related task demands induced deactivation. These findings suggest that coding and representing stimuli as self-related in ventral CMS is apparently subserved by a special type of neural activity, i.e., deactivation which distinguishes it from other processes associated with other CMS parts.

4.2. Association of the self with emotions and subcortical regions

Current social psychology distinguishes between implicit self-esteem, which is generally viewed as an efficient and automatic evaluation of the self that occurs unintentionally and without awareness, and an explicit self-esteem, which represents a more conscious deliberative cognitive assessment of the self (Greenwald and Farnham, 2000; Pinter and Greenwald, 2005; Koole et al., 2001). The implicit self-esteem may presuppose what I call self-related processing, the very basic process of relating stimuli to one’s organism (see above) whereas the explicit self-esteem implies higher-order cognitive function and thus self-awareness or self-consciousness.

Is there experimental evidence for such implicit self-esteem? One test tapping implicit self-esteem is the Implicit Association Task (IAT) which, based upon reaction time measures, assesses the degree of association between the self and positive versus negative concepts. Greenwald and Farnham (Greenwald and Farnham, 2000), for example, found that participants were much faster to respond when self-related items (e.g., their birth month) were paired with pleasant words than when self-related items were paired with unpleasant words. The IAT thus taps association of the self with emotional valences (and also other characteristics like gender) revealing predominantly positive emotions to be implicitly attributed to the self.

Several imaging studies investigating emotions observed activation in ventral CMS including the MOFC; VMPFC, and the PACC (Phan et al., 2002). Does this involvement of ventral CMS during emotions indicate self-related processing? Ochsner et al. (2004) compared self-relevance of visually presented negative emotional pictures (self-focus) with alternative meanings for pictured actions and their situational contexts (situation-focus). They observed increased recruitment of the PACC (and SACC) in the self-focus and of right and left LPFC (VLPFC, DLPFC) in the situation-focus. This is in line with earlier studies (Greenwald and Farnham, 2000; Gusnard and Raichle, 2001) where attention to self-related emotional conditions induced neural activity in PACC and VMPFC (and DMPFC) when compared to externally cued attention. A similar pattern of differential medial versus lateral prefrontal recruitment has been observed when participants either judged the valence of their own emotional responses to pictures or evaluated the valence of the emotion expressed by the central person displayed in those pictures (Ochsner et al., 2004). These results indicate that self-related processing in the emotional domain especially involves the ventral CMS.

Other studies show additional involvement of subcortical regions in self-relatedness of emotion processing. Phan et al. (2004), Lieberman et al. (2004) investigated the degrees of self-relatedness during emotional processing. Subjects had to appraise the extent of personal association of emotionally salient pictures during fMRI. FMRI results were correlated with subjective ratings (after fMRI) appraising the degree of self-relatedness of the picture content in a
visual analogue scale. Regions associated with self-relatedness were located in the CMS including VMPCF and PACC and the ventral striatum/N.accumbens the latter: The more self-related the picture content was appraised, the more activation was observed in these regions. A more recent study (Schneider et al., submitted for publication) demonstrates self-relatedness in positive emotions to be predominantly modulated by neural activity in the ventral striatum/N. accumbens and self-relatedness in negative emotions to be associated with neural activity in the right amygdala. In sum, subcortical regions like the N. accumbens mediating reward and associated feelings of pleasure, and the right amygdala, mediating negative emotions, have been observed to be implicated in both self-related and emotional processing (Phan et al., 2004, 2002; Schneider et al., submitted for publication). We therefore tentatively consider the right amygdala and the N. accumbens as convergence zones between self-related and emotional processing where the association of the self, e.g., self-related stimuli with positive and negative emotions may occur.

4.3. Cognitive processing of the own self and reciprocal modulation in prefrontal cortex

In addition to the CMS, lateral prefrontal cortical regions were reported in imaging studies on self-related tasks. This was the case especially in those studies where a strong cognitive component was required (Christoff et al., 2003; Schmitz et al., 2004). For example, verbal tasks require linguistic abilities including deciphering the meaning of the word, verbal monitoring, and introspection (Gallagher, 2000; Gallagher and Frith, 2003). Higher cognitive abilities were also involved in many emotion and theory of mind tasks requiring, for example, judgments, inference, thoughts, and imagination (Northoff and Bermpohl, 2004; Northoff et al., in press; Phan et al., 2002; Ochsner et al., 2004). This is particularly true in self-related tasks in the facial domain requiring recognition and identification of the own face (Turk et al., 2003; Keenan et al., 2001; Kircher et al., 2000; Keenan et al., 2000).

Higher cognitive functions require what we call “higher-order processing”. Though one might consider designation of stimuli as a self-related higher cognitive function by itself, we distinguish self-related processing from higher-order processing. We assume that self-related processing filters, selects and provides those stimuli which are relevant for the self of a particular person. Only these stimuli, i.e., self-related, are then elaborated further in higher-order processing whereas stimuli characterized as non-self-related are not available for higher order processing. Based on these considerations, we assume that the involvement of lateral prefrontal cortical regions reflects the interaction between self-related processing and higher-order processing. Higher cognitive functions might be differentially modulated by self- and non-self-related stimuli. For example, self-related stimuli might enhance linguistic processing and consecutive activation in lateral prefrontal cortical regions in verbal tasks. Whereas non-self-related stimuli might not require analogous enhancement because they might not be further processed and expressed linguistically. Similarly, self-related stimuli in memory tasks require stronger involvement of autobiographical encoding and retrieval when compared to non-self-related stimuli. Finally, presentation of one’s own face might induce increased recruitment of cognitive functions like recognition and identification thus leading to increased neural activity in lateral prefrontal cortex. Whereas the very same functions remain on a rather low level while the brain is processing the face of another person.

Finally, the involvement of lateral prefrontal cortex in higher-order processing raises questions about its interaction with the CMS. Recent studies indicate that the level of activation or deactivation in CMS might modulate the relationship between self-related- and higher-order processing. Some studies reported activation (and increased functional connectivity) in anterior and posterior CMS during self-related tasks with low cognitive load (Wicker et al. 2003; Kjaer et al., 2002; Greicius et al., 2003; Lou et al., 2004). Conversely, deactivation (and low functional connectivity) in CMS has been observed in tasks with high cognitive load and low degree of self-relatedness (Wicker et al. 2003; Gusnard et al., 2001; Gusnard and Raichle, 2001; Raichle et al., 2001; Simpson et al., 2001). These findings suggest reciprocal modulation between self-related- and higher-order processing: Activation in CMS indicates that self-related processing predominates with higher-order processing remaining in the background. In contrast, deactivation in CMS reflects increased higher-order processing while self-related processing shifts into the background. The assumption of reciprocal modulation between self-related- and higher-order processing is clearly compatible with the recent observation of reciprocal modulation between medial and lateral prefrontal cortex during emotional–cognitive interaction (Goel and Dolan, 2003; Northoff et al., 2004; Grimm et al., 2006; Heinzel et al., 2005). Unfortunately, analogous reciprocal modulation between medial and lateral prefrontal cortex has not yet been demonstrated for the
interaction between self-related- and higher-order processing. In sum, there is some though rather indirect evidence for reciprocal modulation between medial and lateral prefrontal cortex during cognitive modulation of self-related processing.

5. Pathophysiology of the self in depression

After having described the psychopathology of the self in depression and having reviewed the current neuroscientific data about the self in healthy subjects, I now want to discuss possible neuropsychiatric hypotheses about the self in depression (see Fig. 3). On the basis of psychopathology and neuroscientific data, I want to develop predictions for the possible neural basis of alterations in the self in depression. This shall, of course, be discussed within the context of current neuroimaging data in depression thereby indicating specific design study designs for future neural investigation of the self in depression.

5.1. Increased self-focus and decreased deactivation in ventral CMS

Imaging studies in depression report abnormalities in ventral cortical midline regions including the PACC, the VMPFC and the MOFC in the resting state. Increased metabolism is observed especially in the PACC in therapy responders (Mayberg et al., 1999; Mitterschiffthaler et al., 2003; Dunn et al., 2002; Elliott et al., 1998). However, though resting state findings in these regions remain somewhat inconsistent, in total they indicate hypermetabolism in the ventral CMS (Mayberg, 2003; Phillips et al., 2003). Functional activation tasks (emotional, cognitive) showed either hypoactivity or hyperactivity in the PACC, VMPFC and the MOFC (Mayberg et al., 1999; Mitterschiffthaler et al., 2003; Dunn et al., 2002; Canli et al., 2004; Brody et al., 2001). Keedwell et al. (2005) demonstrated higher signal increases in the PACC, the MOFC and the VMPFC during happy stimuli in depressive patients whereas they showed lower signal increases in these regions during sad stimuli. Others showed lower MOFC signal increases in depression when exposed to emotional stimuli whereas higher signal increases were observed in the PACC and VMPFC and associated with good treatment response (Lawrence et al., 2004; Elliott et al., 2002; Kumari et al., 2003; Milak et al., 2005; Fu et al., 2004; Davidson et al., 2003). Taken together, ventral CMS show dysfunction with predominant hyperactivation (especially in the PACC) in depression during both resting state and emotional stimulation.

What however remains unclear is (i) how we can reconcile resting state and functional activation findings in depression, and (ii) the role of signal decreases as predominant mode of neural activity in ventral CMS during functional activation (see above). We predict that resting state hypermetabolism in depression might be reflected in abnormal hyperactivity in ventral CMS across all conditions thus remaining task-independent. Since the ventral CMS can apparently be characterized by predominant deactivation or signal decreases, we predict that such abnormal task-independent hyperactivity is due to decreased or lack of deactivation in depression. This is not only compatible with the nature

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Fig. 3. Psychopathology and pathophysiology of the self in depression.
of neural activity in ventral CMS but also with the task-independence of deactivation in general since the latter have been observed in various tasks depending only, if all, on the cognitive load (Gusnard and Raichle, 2001). Unfortunately, studies investigating deactivation in depression have not yet been reported. One may further question the origin of the lack of deactivation in depression. Is this due to decreased neuronal responsibility during cognitive tasks? Or is it due to an increased neuronal activity in the resting itself which then, due to the higher level, appears as decreased deactivation during cognitive tasks? Unfortunately, there are no studies currently which can decide this issue. The only hint may be the often reported hypermetabolism in the resting state as observed in PET studies, which would argue in favor of an increased resting state neural activity rather than for decreases in neural responsivity. This is not only important physiologically but also psychologically. Since the resting state neural activity in the CMS in general and especially in the ventral CMS has been associated with self-related processing and thus with the self (Northoff and Bermpohl, 2004; Northoff et al., in press), potentially increased resting state neural activity in depression could possibly underlie the increased self-focus in depression (see above). The increased neural activity in the ventral CMS during the resting state could then reflect increased self-related processing which could account for the increased self-focus in depressive patients and their consecutive inability to shift their focus away from their self to others’. This however remains purely speculative since both resting state and deactivations remain to be investigated in association with self-relatedness in depression. One may also expect a different balance between self-related processing of intero- and exteroceptive stimuli in depression, the former being designated as high self-related and the latter as low self-related. This could be tested by for instance directly comparing intero- and exteroceptive stimuli (for example, own and others heart beat) and letting subjects rate the degree of self-relatedness.

5.2. Association of the self with negative emotions and dysbalance in subcortical regions

Functional imaging studies revealed either hypo- or hyperactivity in the ventral striatum/N. accumbens and the right/left amygdala during positive and/or negative emotional stimulation in depression (Canli et al., 2004; Kumari et al., 2003; Lawrence et al., 2004; Surguladze et al., 2005). This suggests that changes in both regions the amygdala and the ventral striatum/N. accumbens are strongly involved in abnormally strong negative emotion processing and decreased positive emotion processing in depression. They may thus be involved in what has been called the “negative bias” as the restriction to negative emotion while excluding positive emotion (Mitterschiffthaler et al., 2003; Phillips et al., 2003). Based on these findings and the ones in healthy subjects, we predict that (i) changes in the amygdala may be associated with the attribution of predominantly negative emotions to the self in depression, and (ii) dysbalance between amygdala and ventral striatum/N. accumbens may be involved in the lack of attribution of positive emotions to the self in depression. However, these assumptions remain rather speculative since neither the association of experience of the self with neural activity in either cortical or subcortical regions has been investigated so far in depression. Nor are there any findings reported about the subcortical and cortical basis of attributing positive and negative emotions to the self in depression. Finally, investigation about functional and effective connectivity between the amygdala and the ventral striatum/N. accumbens are also missing in the same way as the connectivity analyses between these regions and the ventral CMS. Accordingly, our assumptions about possible involvement of subcortical regions in the abnormal attribution of positive and negative emotions to the self in depression remain purely speculative at present. One could for instance test this by letting subjects either rate emotional pictures with regard to self-relatedness or, even better, investigate the modulation of stimuli’s degree of self-relatedness by preceding positive and negative emotions.

5.3. Increased cognitive processing of the own self and abnormal reciprocal modulation in prefrontal cortex

Recent functional activation studies reported not only hyperactivity in ventral CMS (see above) but also hypoactivity in the left dorsolateral prefrontal cortex (DLPFC) in depression during either emotional or cognitive processing (Mayberg, 2003; Phillips et al., 2003; Keedwell et al., 2005; Kumari et al., 2003; Davidson et al., 2003; Lawrence et al., 2004). Based on these observations, Phillips et al. (2003) and Mayberg (2003) suggest a model of altered reciprocal functional relationship between ventral medial and dorsal lateral prefrontal cortex in depression. This model of ventral–dorsal dissociation is based predominantly on findings in the resting state (and only partially on functional activation studies) showing hyperactivity in ventral prefrontal cortex (VMPFC, PACC) and hypoactivity in dorsal prefrontal cortical regions (left DLPFC) in acute depression.
The ventral–dorsal dissociation model is well compatible with opposite modulation between medial and lateral prefrontal regions as it has been described by reciprocal modulation in healthy subjects. Though ventral and dorsal prefrontal regions like the VMPC, the PACC and the DLPFC have been shown to be altered in depression (Elliott et al., 2002; Kumari et al., 2003; Milak et al., 2005; Fu et al., 2004; Davidson et al., 2003; Lawrence et al., 2004; Surguladze et al., 2005), ventral–dorsal dissociation with abnormal reciprocal modulation remains to be shown in depression. Based on current findings in healthy and depressed subjects, we predict that (i) reciprocal modulation may be abnormal in depression, and (ii) association of abnormal reciprocal modulation with abnormal emotional–cognitive interaction. The acute depressed patients may eventually be characterized by increased resting neural activity in the ventral CMS and accompanying decreased neural activity in the left DLPFC. We speculate that due to high neural activity in the resting state, depressed patients remain unable to reciprocally modulate the functional relationship between medial and lateral prefrontal cortex — the reciprocal modulation becomes abnormal because of such non-reactivity. Since, in healthy subjects, the reciprocal modulation is associated with emotional–cognitive interaction, we assume that the non-reactivity of the reciprocal modulation may be related to the depressed patients’ inability to unlock themselves from their increased analytical self-focus, the increased self-centred cognitions and ruminations about the own self, and to shift to what has been called the experiential self-focus (see above). However, since their have been no imaging studies yet about the neural correlates of the self and its modulation by cognitive processing in depression, these assumptions remain purely speculative. One could for instance directly compare perception and judgment of high and low self-related stimuli which may mirror the difference between experiential and analytical self-focus and then investigate the relationship between medial and lateral prefrontal cortex.

6. Neurophilosophy of the self: higher-order cognitive function versus basic formatting

In the following, I want to briefly discuss two often discussed alternatives in the concept of self which thus touches upon the philosophical issue of the concept of self. Is the self a higher-order cognitive function, e.g., self-awareness, or rather a kind of basic formatting and coding of incoming stimuli?

Most of the above described imaging studies (Kelley et al., 2002; Turk et al., 2003; Northoff and Bernpohl, 2004; Northoff et al., in press; Craik and Hay, 1999; Schore, 2003; Phan et al., 2004) implicitly presuppose a concept of self as self-consciousness or self-awareness. This is so because the various tasks applied in these studies required subjects to make explicit reference to some aspects of themselves and to consciously access and monitor representational content about one’s self. Since subjects must reference to themselves in self-consciousness or self-awareness, we speak of self-referential processing. Since it involves self-consciousness or self-awareness, self-referential processing is supposed to involve higher-order cognitive function, the “highest” and most advanced forms of cognitive processing, out of which the self emerges at the pinnacle of the psychological and neural hierarchy. On the philosophical level, such higher-order view of self-referential processing corresponds to predominantly cognitive accounts of the self and subjectivity as it has for example been advanced by Kant and the german school of idealism.

In contrast, I argue that such higher-order cognitive concept of the self and its definition by self-referential processing with self-consciousness or self-awareness is not compatible with current empirical data. The following observations argue against the concept of the self as higher-order cognitive function: (i) possibility of an implicit nonconscious, e.g., unconscious self, (ii) association of self-relatedness with both emotional and cognitive processing, (iii) equilibrium within the whole brain, e.g. between subcortical–cortical midline system and other brain regions including the lateral prefrontal cortex modulates the degree of self-relatedness, and (iv) abnormal balance between different levels of self processing in depression.

6.1. Implicit self

We assume self-related processing to include both unconscious and conscious processing of stimuli in relation to the self whereas, as defined above, self-referential processing describes only conscious processing — self-related processing may thus be considered more basic and wider than self-referential processing. Though direct empirical evidence is currently rather sparse (see above), subcortical and anterior cortical midline regions like the VMPC and the OMPF may be crucially involved in unconscious processing of self-related stimuli and thus in what we call self-related processing as distinguished from self-referential processing. Taken together, the possibility of an unconscious or implicit self in both psychological and
neuroanatomical terms suggest that the self cannot be restricted to self-consciousness or self-awareness which in turn argues against the concept of self as higher-order cognitive emergence. Instead, the self must be considered a more basic and wider function including both unconscious and conscious aspects. The subcortical–cortical midline system may then no longer be characterized by a “stream of consciousness (or self-referential processing)” in the sense of W. James’ description of the self but rather as “stream of (unconscious and conscious) self-related processing” which, according to the relationship to the rest of the brain, may remain unconscious or become conscious (see below).

6.2. Implication of self-related processes in both emotional and cognitive processing

We already demonstrated association between self-related and emotion processing (see above); similarly, there is also some recent evidence for involvement of self-relatedness in cognitive processing of decision making. Johnson et al. (2002) investigated subjective decision making with (self-preference) and without (colour preference) and observed greater activation (or less deactivation) in the VMPFC and the ventral striatum/N. accumbens (and the DMPFC and RSC) in the former when compared to the latter. Neural activity in the midline structures is modulated by the degree of self-relatedness itself rather than by the cognitive involvement which was supposed to be the same across both tasks. This suggests that it is self-related processing itself rather than some associated cognitive functions that elicit and modulate neural activity in the default network. Further studies may show that the degree of neural activity is parametrically dependent on the degree of self-relatedness in a specific way as distinct from the degree of associated cognitive involvement. We therefore suggest that self-related processing cannot be considered a special higher-order cognitive function by itself like attention, memory, etc. This is also well in accordance with a recent review by Gillihan and Farah (2005) who could neither find psychological nor neural evidence in favour of a self as special higher-order cognitive function. What however is self-related processing? We assume self-related processing to provide a special code, format or mode by means of which sensory, emotional or cognitive stimuli become oriented towards the respective person. If this is true, self-related processing should be implicated in all kinds of processing in a very basic sense rather than emerging as higher-order cognitive or meta-cognitive function at the pinnacle of both.

6.3. Equilibrium within the whole brain

We already demonstrated that the self and self-related processing cannot be localized within one particular region but must be associated with the subcortical–cortical midline system as core network. In addition, we showed that this midline network interacts with other brain regions like the lateral prefrontal cortex so that the equilibrium within the whole brain (within its given context) must be associated with the self. The self can thus not be identified with a particular brain region but with the whole brain — our brain is our self. Since however the brain cannot be considered in isolation from our body, the brain is embodied (Northoff, 2004), our self is necessarily embodied. Furthermore, since the body is embedded within its respective environment, the embodied brain is also embedded within its environment. Our self can thus be identified with our embodied and embedded brain and thus with the relation between brain, body and environment.

How however was possible it to confuse the self with higher-order cognitive self-consciousness and to associate with particular brain regions rather than with the embodied and embedded brain? This may be a matter of perspectives and thus be traced back to epistemic matters. What from the observers’ perspective seems to appear as higher-order cognitive emergence, the self as based on self-referential processing since it is accessible only in self-consciousness or self-awareness, may be revealed as rather basic function from the hosts’ perspective in the gestalt of self-related processing. This means that what the observer exclusively associates with the highest neural regions, the prefrontal cortex, may be revealed as dynamic equilibrium between the subcortical and cortical midline and other regions in the hosts’ perspective. The self may then be associated with dynamic whole-brain equilibrium that modulates the degree of self-relatedness via task-independent deactivation rather than with specifically localizable higher-order cognitive brain regions.

6.4. Abnormal balance between different levels of self processing in depression

Patients with MDD suffer from increased self-focus as characterized by increased explicit reflection and cognition about the own self — one may speak of increased self-consciousness of hyper-self-awareness in MDD. In contrast, the experience of the own self as such without reflective conceptualization is decreased and the experience of the own body is increased. This clearly indicates that the self cannot be identified with self-consciousness or self-awareness but that there may be
different levels of self-processing ranging from unconscious to conscious levels. The peculiarity in MDD consists thus in the dysbalance between these different levels of self-processing which here, for pragmatic purposes, could not even be spelled out and described completely. We can therefore learn from MDD with its changes of self-processing on different levels that the self cannot be considered as higher-order cognitive concept but rather as format that encompasses different levels of processing.

7. Conclusion

The concept of self has originally been discussed in philosophy. Due to recent technical and empirical progress, the self has also become a topic of investigation in psychology and neuroscience. Findings in healthy subjects suggest that a subcortical–cortical midline system may be crucially involved in self-related processing thus providing the very basis of our self. Based on findings in both healthy and depressed subjects, we suggest that this subcortical–cortical midline system may be altered in depression which in turn may account for the different abnormalities of the self observed in these patients. However, due to lack of empirical imaging data about the self in depression, the present assumptions about the possible neural basis of self-abnormalities must be considered provisional, tentative and, in part, speculative. Though our empirical hypotheses must be considered rather carefully, it becomes clear that this transdisciplinary investigation, ranging from neuroscience over psychology and psychiatry to philosophy, generated novel ideas for future empirical study designs of the healthy and the depressed self as well as an alternative philosophical concept of the self. This will ultimately not only lead to a better understanding of our brain-based self in both empirical and conceptual regard but will also provide us better insight into the complex psychological and neural abnormalities of the self in depression with consecutive improvement of both diagnosis and therapy.

Acknowledgment

I thank H. Boeker for many thoughtful and inspiring discussions about the psychopathology and psychopathology of depression. The work was made possible by financial contributions from the Salus Foundation.

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