Knowing me, knowing you
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Summary and Discussion
The emotional self in schizophrenia and bipolar disorder

The aim of this thesis was to shed more light upon the neural basis of the cognitive processes involved in social cognitive and emotional functioning. The neural correlates of the ability to understand other people’s thoughts and actions, Theory of Mind (chapter 2), the ability to regulate the emotions induced by negative events (chapter 5) and the ability to reflect upon one’s own traits and characteristics (chapter 6) were discussed. Disruptions in such amazingly complex processes can result in problems in social interactions. Patients with chronic psychiatric disorders often present with such problems. To unravel the nature of these impairments the behavioral performance and neural activation patterns in people with vulnerability for psychiatric disorders (chapters 3 and 5) as well as in patients with chronic psychiatric disorders (chapters 4 and 5) were examined. Finally, in the chapters 7 and 8, poor insight as a possible consequence of these impairments was discussed.

Theory of Mind and the brain

In chapter 2, the neurobiological pillars of understanding the beliefs and intentions of others, also referred to as Theory of Mind (ToM), was investigated. In this chapter, we elaborated on this process of understanding by distinguishing between inhibiting your own perspective and taking the perspective of someone else. This distinction was already proposed by Vorauer and Ross (1999) and was tested by Samson and colleagues (2005) in patients with lesions in the right inferior frontal gyrus (IFG). We tested the neural basis of this two-component theory in healthy subjects by means of fMRI. To our knowledge, this was the first time the two-component of theory was empirically tested with fMRI. We demonstrated an important role for the bilateral inferior frontal gyrus (IFG) for the inhibition of self-perspective. We additionally demonstrated that the second ToM component, taking the perspective of someone else, relies on the activation of the left superior temporal gyrus (STG), the temporoparietal junction (TPJ) and the middle temporal gyrus (MTG). Besides investigating the ToM sub-processes, we tested whether simple response inhibition would share neural resources with this self-inhibition process. We found that such simple motor response inhibition (withholding to push a button upon presentation of a cue just before the response would be given) showed overlapping activation with self-inhibition in the bilateral IFG.

Disentangling such a complex process as ToM can provide valuable information for research on impairments in ToM. More fundamental knowledge on the sub-processes of ToM, may enable us to understand which sub-processes are hampered in patients with psychiatric disorders, who often present with ToM impairments. Therefore, we investigated in chapter 3 the inhibition of self-perspective in psychosis prone subjects. Psychosis prone (PP) individuals report some subclinical symptoms of psychosis, but do not seek treatment for these symptoms. Behavioral results showed that high PP subjects performed as well as low PP subjects on self-inhibition as well as other-perspective taking. However, the
pattern of brain activation revealed increased activation for high PP subjects in the left IFG, the area that we demonstrated in chapter 2 to be important for the inhibition of your own perspective. At the same time, these high PP individuals did not show any differences on simple response inhibition, neither on behavioral performance nor on brain activation. We suggested that in a more complex process such as ToM, there is more contextual information that needs to be inhibited, while in the simple motor response inhibition task, just withholding a response upon the presentation of a cue was required. Individuals who are prone to psychosis may need to put more effort in inhibiting contextual information, which is reflected in increased brain activation. In real life, situations are even more complex and have much more contextual information than in our experimental task, while no explicit instructions to mentalize are given. We suggested in chapter 3 that the inhibition of such complex information that is part of your own perspective may be more effortful for high PP subjects and this may be even more problematic for psychiatric patients. Some studies showed that training patients on simple cognitive tasks can improve their performance on other more complex tasks (Fisher et al., 2010; Haut et al., 2010; Subramaniam et al., 2010) and can even result in increased brain activation for these more complex tasks (Haut et al., 2010; Subramaniam et al., 2010). Such results suggest that we may improve ToM in subjects with impairments in ToM by training them on inhibiting their own perspective, and perhaps even by training them on simple motor response inhibition alone.

**On the regulation of emotions**

In chapter 4 of this thesis, we investigated another process important for dealing with society: the interpretation of emotional events and dealing with the emotional response that is evoked upon this event. We examined the ability to introspect upon feelings and putting these feelings into words, as well as strategies to cope with emotional events in patients with schizophrenia. We showed that schizophrenia patients reported problems with identifying their emotions, but we also showed that this was associated with levels of depression. This finding is difficult to interpret, but may indicate that schizophrenia patients have more problems with identifying their emotions when they are more depressed. This may be due to a general lack of motivation that is often observed in depression. An interpretation that is intuitively more appealing is that problems in identifying emotional feelings may result in a more depressed mood. That is, if the emotion cannot be identified it may be more difficult to reduce the negative affect through cognitive down-regulation. We also showed that schizophrenia patients reported to suppress their emotions more often than healthy controls, whereas healthy controls reported to more often reappraise these negative events. Perhaps due to these differing preferences for emotion regulation strategies, schizophrenia patients experience as much or even more negative affect (Kring & Neale, 1996; Myin-Germeys et al., 2000). Possibly, patients have more difficulty using the reappraisal strategy so they may cope with this
negative affect by suppressing their emotions. This is supported by the apparent flat affect, that is so often reported in these patients, in spite of these similar or even stronger subjective emotional experiences of these patients (Gur et al., 2006; Kring & Neale, 1996).

To understand the underlying neural mechanisms of these emotion regulation strategies we tested schizophrenia patients and first-degree relatives of schizophrenia patients with an emotional regulation task, while we measured brain activation. The inclusion of the first-degree relatives is especially interesting since they often present with similar, but less severe, cognitive impairments as patients without demonstrating symptoms of schizophrenia or medication effects (Keshavan et al., 2010; Phillips & Seidman, 2008). This study was described in chapter 5. Similar to our findings reported in chapter 4, we found that schizophrenia patients reported to use the suppression strategy more frequently than healthy subjects. Relatives reported to use suppression with a frequency somewhat in between healthy control subjects and patients. In addition, similar to the findings in chapter 4, we found that schizophrenia patients showed more problems with identifying their emotions, while relatives reported less problems with identifying than healthy control subjects.

The pattern of brain activation was measured for reappraisal as well as for suppression. Both emotion regulation strategies resulted in a reduction of negative affect in patients, relatives and healthy control subjects. However, the overall negative affect remained higher for both patients as well as for relatives compared to healthy control subjects. With regard to the reappraisal strategy, patients showed less activation than healthy controls in the reappraisal brain network (bilateral IFG, dorsomedial prefrontal cortex, inferior parietal lobe and the left insula). Conversely, relatives showed increased activation in this network (dorsomedial prefrontal cortex, posterior cingulate cortex, left dorsolateral prefrontal cortex and bilateral inferior parietal lobe).

Similarly, with regard to the suppression strategy, healthy controls deactivated the insula and the dorsal anterior cingulate cortex, while schizophrenia patients did not deactivate these areas. Such deactivation is consistent with previous findings in which activation of, amongst others, the dorsal anterior cingulate cortex and insula was negatively correlated with the intensity of the negative stimulus (Phan et al., 2005). Furthermore, Goldin et al. (2008) reported ventrolateral prefrontal cortex (vLPFC) activation for suppression. We replicated this finding and found vLPFC activation in suppression for both patients and healthy subjects. Goldin et al. (2008) suggested that this region is implicated in the down-regulation of insular activation to diminish emotional valence. This down-regulation may result in the suppression of sensory information from multiple modalities that is processed in the insula. We proposed that this may subsequently prevent the experience of an emotion. This interpretation is supported by research on posterior insula indicating its involvement in multimodal somatosensory processing (Craig 2002). Lesions of the posterior insula have shown to induce distortions in the recognition of sensory input and even to impaired self awareness of actions (Baier and Karnath 2008). Similarly,
Summary and discussion

the dorsal anterior cingulate has been related to emotional awareness (Lane et al., 1998a). We proposed in chapter 5 that deactivation of this area may eventuate in unawareness of the emotion, and thus successful suppression. Thus, the results suggest that even though patients are able to employ this suppression strategy, they are not able to reduce their negative affect to the level of healthy controls.

Relatives instead show an increased activation of the dorsomedial prefrontal cortex. Activation in the dMPFC has been suggested to inhibit amygdala activation (Baron et al., 2010; Furlong et al., 2010; Goldin et al., 2008; Iidaka et al., 2010; Moses-Kolko et al., 2010). The increased activation in relatives suggests a compensatory activation necessary for down-regulation of the amygdala. However, this compensation is still not enough to decrease negative affect to the extent healthy unaffected control subjects do. Thus at some point between a vulnerability for psychosis and fully developing a psychiatric disorder, compensatory mechanisms may be employed to normalize response to emotion evoking stimuli.

In both chapter 4 as well as in chapter 5 we described compensatory activation in brain networks that are recruited for the inhibition of self-perspective and the regulation of emotions, respectively. This increased effort conjoined with the higher overall negative affect reported in chapter 5 may induce more stress in vulnerable individuals in social situations. While for relatives the literature reports that the pattern of brain activation varies from increased, to decreased, to similar activation compared to healthy controls, this pattern of brain activation shifts towards decreased activation in first-episode patients (Fusar-Poli et al., 2007). Thus, compensatory mechanisms seem to be less available once the transition to psychosis has been made. Nevertheless, training patients on cognitive tasks has resulted in an increase in brain activation related to cognitive control (Haut et al., 2010; Subramaniam et al., 2010), but also to areas related to emotional and self-processing, such as the ventral and dorsal MPFC (Subramaniam et al., 2010).

Self-reflective processing

The importance of the ventral and dorsal MPFC in social cognitive and emotional processing also emerges from the meta-analysis that was described in chapter 6. In this chapter we demonstrated the importance of the ventral and dorsal MPFC in self-reflective processing. Besides these areas, the anterior and posterior cingulate cortex (ACC and PCC) proved to be of great importance for self-reflective processing. In this meta-analysis we suggested that the vMPFC is specifically concerned with the affective processing of self-relevant information. More detailed investigation of self-reflective processing by comparing it with other-reflective processing revealed the involvement of only the vMPFC and vACC as core regions. The overlapping activation of dMPFC in self as well as other processing suggests that the dMPFC is important in reflection processes per se and not necessarily specific for self-reflection.

Based on the meta-analysis, we proposed a model for self-reflective processing (see figure 3, pp113). Both the vMPFC and ACC are important in affective
processing. We suggested that the ACC may be essential for directing attention to the self, while the vMPFC, through its anatomical connections with the limbic system (Young et al., 1994), may be responsible for tagging the stimulus when it is relevant for oneself (Northoff et al., 2006; Northoff & Bermahl, 2004). Anatomical connections have also been reported between the vMPFC and the dLPFC (Ghashghaei and Barbas, 2002), an area that is important for working memory performance and temporal organization of behavior (Hermann and Wyler, 1988; Corcoran and Upton, 1993; Upton and Corcoran, 1995; Haut et al., 1996; Fuster, 1997, 2000; Goldstein et al., 2004; Buchsbaum et al., 2005; Gilbert et al., 2006). The dLPFC exerts executive control on the vMPFC, which in turn influenced the limbic system (Phelps, 2006).

The insula and PCC keep the individual informed on the internal bodily state and autobiographical memory respectively. The dMPFC is then involved in the final evaluation process on the applicability of the stimulus (Northoff et al., 2006; Northoff & Bermpohl, 2004), but not only for the self also for others. This functional distinction between the vMPFC and the dMPFC has been investigated by Mitchell et al. (2006) who showed that the vMPFC was activated in ‘similar others’, but not in ‘dissimilar others’, which supports the proposed dichotomy between the vMPFC and the dMPFC. In chapter 5 of this thesis we demonstrated a role of the dMPFC in the regulation of emotions. This suggests that the dMPFC may not only be important for decision making with regard to self- and other-reflection, but may be involved in decision making on emotional stimuli in general. However, the area with the dMPFC important for emotion regulation seems to be more posterior than the area important in self and other reflection implying a different functional role for both processes.

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. In chapter 6 we argued that if self-reflective processing in schizophrenia patients is impaired, one would expect a deviant pattern of activation in self-reflective processing networks, leading to impaired self-evaluative processing and reduced awareness of mental illness.

**Schizophrenia, social cognition, emotional processing and the brain**

In chapters 2, 5 and 6 we described brain areas involved in processes of self-inhibition, emotion regulation and self-reflection, respectively. When the activation patterns for self-inhibition, the reappraisal strategy of emotion regulation and self-reflective processing are compared (see figure 1), it becomes clear that there is one particular area of overlap between these processes, the left insula and the left IFG, also called ventrolateral prefrontal cortex [vLPFC; cf. Ochsner and Gross (2005)] (see figure 1a). The vLPFC has been implicated in processes of both cognitive and affective control (Ochsner, 2005). Ochsner and Gross (2005) suggested that the vLPFC is most importantly involved in the evaluation process of emotional stimuli and the subsequent actions through the connection with limbic structures such as the
amygdala and the nucleus accumbens. In addition, Craig (2009) reviewed the functional role of the anterior insula and concluded that this region is not only involved in the awareness of bodily sensations, but also in subjective feelings and self-awareness.

![Figure 1](image)

**Figure 1.** Overlapping brain activation for self-inhibition, self-reflection and reappraisal. X, y, z refer to the slices that are displayed at respectively sagittal, coronal and axial view. A, **top panel:** Activation patterns for healthy controls only, with in yellow the activation for self-inhibition, in red the activation for reappraisal, in green the activation for self-reflection. B, **bottom panel:** Activation pattern for healthy controls and schizophrenia patients. In yellow the activation patterns for healthy controls for self-inhibition and in green the activation pattern in healthy controls for self-reflection. In purple the decreased activation for schizophrenia patients for reappraisal, which falls within the area of overlap between self-inhibition, self-reflection and reappraisal.

Interestingly, the area of overlap between the tasks described in chapter 2, 5 and 6 is precisely the region in which schizophrenia patients showed less activation than HC when they reappraised a negative picture (see figure 1b). Other studies related a decrease of activation in this same region in schizophrenia patients to impairments in discriminating self generated from externally generated stimuli (Allen et al., 2004), recognizing the own face (Kircher et al., 2007), self-body perception (Orbach et al., 1966; Traub et al., 1967), the ability to integrate subcortical
somatic and cortical information (Anders et al., 2009), and short-term emotional memory (Royer et al., 2010). Thus, a decrease of activation seems to reflect a range of impairments not only in the processing of self, but also in the regulation of emotional stimuli. Petrides (2005) described the functional and anatomical organization of the vLPFC and proposed that this area projects to dLPFC as well as limbic and sensory regions.

Functionally, Petrides concluded that the vLPFC has a distinct role in the selection, comparison and judgments of stimuli. A study that compared activation related to cognitive and emotional control revealed that an area within the vLPFC, which is similar to the area revealed by our data was less activated in patients, is important in both networks (Seeley et al., 2007). Craig (2009) suggested that this area is important in the translation between bodily sensations and the awareness of these sensations. This may be true for more basic unemotional sensory input as well as for more complex top down processes such as self-inhibition and down-regulation of emotional stimuli. The decreased activation in schizophrenia patients in the region of overlap for self-inhibition, reappraisal of emotional stimuli and self-reflection may reflect an impaired functioning of this region.

The multiple faces of insight

The awareness of self-related information, both sensory and emotional, relates to the concept of insight. The concept of insight refers to the awareness of the illness in general, but also to an awareness that one presents with symptoms related to a mental disorder and the awareness that one may need treatment to overcome such symptoms. The chapters 7 and 8 both showed that the concept of insight is not just related to cognitive, emotional or symptom dimensions alone. Instead these chapters demonstrated that for both patients with schizophrenia and bipolar disorder, insight is a multidimensional concept that is related to cognitive as well as emotional as well as symptom dimensions. In chapter 7, we specifically analyzed patients with a recent onset psychosis versus patients in a more chronic stage of the illness. It was demonstrated that this relationship was most prominent in patients who suffered multiple episodes. This is also reflected in the number of hospitalizations which was significantly related to insight. That is, the more hospitalizations, the worse the insight or vice versa. Moreover, we investigated the role of social cognition in impaired insight with a Theory of Mind task and an emotion recognition task. We found that better performance on both social cognitive tasks was related to better insight. This finding confirms the idea that insight is not just related to neurocognitive or clinical factors, but also to factors that are important in social interaction.

In chapter 8, insight was assessed in patients with bipolar disorder and it was demonstrated that similar to patients with schizophrenia, cognitive, emotional and clinical characteristics are all related to level of insight. We specifically investigated the relationship of these variables in patients with and without lifetime psychotic
features (LPF). We demonstrated that in patients with LPF specifically, the speed of processing is related to level of insight, suggesting that the faster the response, the lower the insight. We hypothesized that this may imply a relationship between impulsivity and jumping to conclusions and insight. The more time one takes to consider alternative explanations for abnormal experiences, the better the insight. However, the current data only point towards that direction and such a claim would require more supporting evidence.

Importantly, in chapter 8 we demonstrated that besides a relationship between neurocognition and insight as well as a relationship between clinical characteristics and insight, there is an additional role for emotional processing; more specifically, emotional learning. We suggested that the ability to pick up social cues from the environment is related to the ability to couple emotional and non-emotional stimuli. Impairment of such abilities may hamper attempts to use social and environmental information for reflecting upon oneself.

Clinical implications
In this thesis we focused on investigating the neural correlates of social cognitive and emotional processes such as ToM, self-reflection and emotion regulation in psychiatric patients. Understanding the neural correlates of impairments in these processes provides important information for understanding the social impairments in patients with schizophrenia and bipolar disorder. In addition, more fundamental knowledge will direct us towards the development of treatments specifically aimed to improve social functioning and illness insight. Based upon the results of this thesis, developing treatments that are aimed at cognitive and emotional control would be most appropriate. Indeed, preliminary results suggests that training schizophrenia patients on simple cognitive tasks can result in improvement on non-related social cognitive tasks as well as in increased activation in brain areas related to cognitive and social processes (Subramaniam et al., 2010). In addition, Haut et al. (2010) showed that training patients on cognitive tasks increased the activation in related brain areas. Mazza et al. (2010) showed that training schizophrenia patients with an emotion imitation treatment specifically targeted at improving social cognitive functioning, resulted in improved performance on all measures of social cognition. This was supported by pre and post measurements of neural activity measured with event related potentials (ERPs). Similarly, Eack et al. (2007) and Hogarty et al. (2006) demonstrated that cognitive enhancement therapy improves social cognitive processing. Finally, Lysaker et al. (2010a) as well as Pijnenborg and Aleman (2010) proposed a model for psychotherapeutic interventions in patients with schizophrenia, specifically aimed at the ability to self-reflect. If indeed self-reflective processing in patients with impaired insight is hampered, such an intervention may improve insight in these patients.

The combined results of chapters 2, 5 and 6 suggest an overlapping area in the left vLPFC extending to the insula that is important in processes related to self-
inhibition, self-reflection and emotion regulation (figure 1b). Moreover, we demonstrated that this area is less activated in patients with schizophrenia while reappraising negative pictures. These converging results suggest that perhaps the stimulation of this area may result in better performance for patients in different domains of social cognitive and emotional processing. One possibility for the stimulation of this area could be repetitive transcranial magnetic stimulation (rTMS). Even though the evidence is somewhat inconsistent, effective treatment of auditory verbal hallucinations (Cho & Strafella, 2009; Slotema et al., 2010; Vercammen et al., 2010b) and negative symptoms (Dlabac-de Lange et al., 2010) in patients with schizophrenia by means of rTMS has been reported. However, further research is needed to support the hypothesis that rTMS stimulation of the left vLPFC and insula may be effective in schizophrenia patients to improve social functioning. Especially since rTMS may only reach cortical areas as deep as one to two centimeters and thus may not reach the insula. New techniques of deep rTMS have been developed for stimulation of areas that lay deeper in the brain, such as the insula and thus may provide a solution for this issue (Roth et al., 2007).

Besides treatment for patients, one may discuss the practicality of the prevention of psychosis in individuals who are prone to psychosis either by genetic predisposition or otherwise. This is an ethical discussion since the majority of these individuals may not develop a psychotic episode at all. That implies that they do not need any intervention or psychotherapy. If one proceeds to therapeutic interventions in this group, one may unnecessarily stigmatize these individuals. Nevertheless, the group of subjects that do go on to develop a psychotic episode [about 10%; (Chapman et al., 1994; van Os et al., 2009)], may benefit from preventive interventions. In the development of the new version (5th edition) of the diagnostic and statistical manual (DSM), it is currently debated whether a Psychosis Risk Syndrome should be included in the manual. In this discussion, it is proposed that a psychotic illness is most effectively treated while still in an early stage. In chapters 3 and 5 we demonstrated abnormal brain activation in subjects prone to psychosis and relatives, respectively. Even though these subjects do show normal performance behaviorally, the increased activation does suggest increased effort. These individuals may benefit from psychotherapy or stress management (Preti & Cella, 2010).

Finally, insight is a relevant concept in the treatment of patients with psychiatric disorders. Level of insight is closely connected to treatment compliance (McEvoy, 2004). That is, patients who do not acknowledge their illness and the need for treatment are more likely to be non-compliant with their medication. It is important to note that insight is a multidimensional construct comprising three dimensions:, awareness of illness, symptom attribution and treatment compliance (David, 1990). In chapter 8 of this thesis we demonstrated that this multidimensional approach can also be applied in bipolar disorder. Patients may be aware in one

dimension, while they have impaired insight in another dimension. For example, patients who are compliant with their medication may not attribute their symptoms to their disorder (McEvoy, 2004). In addition, specifically in bipolar disorder impaired insight is related to misdiagnoses (Ghaemi, 2007). Patients tend to have better insight in or suffer more from their depressive episodes than in their (hypo)manic episodes, which may result in the patient not speaking about (hypo)manic symptoms and be misdiagnosed with unipolar depression. Moreover, we demonstrated that insight is related to cognitive, social and clinical characteristics in patients with schizophrenia as well as in patients with bipolar disorder (chapter 7 and 8 of this thesis). This relationship elucidated that directing treatment at only one of these factors is not sufficient to improve insight. Instead treatment should be directed at cognitive as well as emotional and clinical features.

**Future directions and concluding remarks**

The results of this thesis provide a framework for further investigation of social cognitive and emotional processes in schizophrenia and bipolar disorder. Currently, we are using this framework to examine the underlying mechanisms of impaired insight in these patients. We are assessing the neural basis of emotion regulation and self-reflection in patients with schizophrenia and bipolar disorder. Based upon the results presented in this thesis we expect to find a mediating effect of insight on brain activation in medial and lateral frontal as well as limbic regions. Besides the neural correlates of insight, we are investigating the relationship between meta-cognition and insight. Koren et al. (2004) demonstrated a large effect of meta-cognition on insight by means of an adapted Wisconsin Card Sorting Task (WCST). They asked patients to judge their own performance and found that this ability was highly related to levels of insight. In our current study we extended this task by providing the patient with feedback with regard to their performance. We expect that patients with good insight will be better at incorporating the feedback in their judgment on their performance, while patients with impaired insight will be less able to use this feedback. Furthermore, we are exploring whether impaired insight may be associated with functional and/or anatomical connectivity. Based upon the results of this thesis our expectations are mainly directed at connections between lateral frontal, medial frontal and limbic regions.

Besides investigating within group differences in schizophrenia patients and bipolar patients, we will examine between group differences as well. This will enable us to test whether differences between affective and non-affective psychosis can be observed in measures of social cognitive and emotional processing and corresponding brain areas. We specifically expect to find group differences in ventrolateral and ventromedial regions as well as limbic regions, since these areas are mostly involved in emotional processing.

Finally, the results of this thesis can be used in the development of clinical tools for improving social cognitive and emotional processing in patients with
schizophrenia and bipolar disorder. This may be the development of psychotherapy, but also other forms of treatment such as rTMS and medication targeting the brain areas involved in social cognitive and emotional processing.

In sum, this thesis has provided fundamental knowledge on social cognitive and emotional processes in healthy controls as well as schizophrenia patients which may lay the ground for the development of treatments specifically aimed at the improvement of these processes in patients. This fundamental knowledge can be the basis for such treatments and research should be conducted how to employ this knowledge in clinical settings.