Emotion, self and psychopathology

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CHAPTER 7

General discussion

Emotional dysfunction and alterations in self-related processing are common in patients with bipolar disorder (BD) and schizophrenia (SZ). As introduced in the General Introduction (**chapter 1**), the present thesis aimed to shed more light on the underlying neural correlates of these processes in both disorders. To achieve this, in the first part of this thesis, we examined the neural correlates of emotion regulation (ER) in BD and SZ patients, in terms of temporal dynamics (**chapter 2**), and BD and controls in terms of effective connectivity (**chapter 3**). Moreover, as a potential consequence of dysfunctional ER, and also a large problem in psychiatric patients, especially in Major Depressive Disorder (MDD), we tried to unravel the structural characteristics of suicidal risk (**chapter 4**). In the part two of the present thesis, we further investigated the brain activation and functional connectivity during self-reflection in BD and SZ patients (**chapter 5-6**). In this general discussion, I summarize the main results, followed by a brief discussion. I also address future perspectives and clinical implications.

Summary

Emotional dysregulation has consistently been observed in both BD and SZ, and is known to affect social and occupational functioning adversely. However, BD and SZ show different emotional symptomatology, with BD being featured with cycling between different mood states (e.g., mania/hypomania and depression) and SZ being characterized mainly by flat affect (American Psychiatric Association, 2013). On the other hand, both disorders may be characterized by increased levels of negative affect, increased use of emotion suppression and decreased use of reappraisal (Aleman and Kahn, 2005; Johnson et al., 2016). The investigation of the neural correlates of ER in BD and SZ patients may help unravel the shared and/or distinct neural pathophysiological mechanisms underlying their emotional symptomatology (part I of the present thesis). In **chapter 2**, we investigated the temporal dynamics (i.e., time course of hemodynamic responses) of the responses in the brain during ER (more specific: when applying cognitive reappraisal) in SZ and BD patients. The results showed that SZ patients were able to recruit, but not sustain activation in the ventrolateral prefrontal cortex (VLPFC) during reappraisal, an area that is assumed to be involved in detecting emotional salience information and need to regulate emotion, along with a lack of involvement of the dorsolateral prefrontal cortex (DLPFC), which is associated with implementing cognitive control to regulate

emotion during reappraisal. In contrast, BD patients demonstrated general blunted responses in these prefrontal areas (i.e., VLPFC and DLPFC) during ER. These results suggest differential neural mechanisms underlying deficient ER in SZ and BD (although our behavioral data did not show differences in the outcome of the ER). In SZ, disturbed ER may be due to a problem of sustaining activation important for signaling the need for ER, whereas ER problems in BD arise from an early deficit to recognize emotional salience in order to call upon ER control.

In **chapter 3**, the aim was to investigate the causal relationship (effective connectivity) within the ER circuit (i.e., DLPFC, VLPFC and amygdala) during reappraisal, particularly in BD patients. By applying dynamic causal modeling (DCM) which tests effective connectivity between brain areas, we found that BD patients had different effective connectivity from the DLPFC to amygdala. Specifically, during reappraisal, activation in the DLPFC decreased the activation in the amygdala in healthy controls (HC). However, BD patients, compared to HC, showed a weaker and actually absence of modulatory effects of reappraisal on DLPFC-amygdala connectivity. These findings indicate disturbed prefrontal top-down control over negative emotions in BD patients.

Suicide is a potential catastrophic consequence of dysfunctional ER. Therefore, the aim of **chapter 4** was to search for structural neural correlates for suicidal risk (i.e., SI and SA) in patients suffering from MDD. Such correlates could ultimately, if replicated consistently, serve as biomarkers. We found reduced grey matter (GM) volumes in the DLPFC extending to the VLPFC in relation to presence of suicidal risk (SI and SA combined), with no significant contribution from the effects of presence of SI or SA alone. Therefore, we propose that reduced DLPFC/VLPFC volumes might represent trait-like vulnerability risk for future suicide, which may be related to dysfunctional ER and problems with inhibition of suicidal behavior.

In addition to ER problems, both BD and SZ have been implied to involve alterations in self-processing, which may be particularly relevant to those that have experienced psychosis (Brookwell et al., 2013). The investigation of self-processing in BD and SZ might aid our understanding of the neural mechanisms underlying affective and non-affective psychosis. A well-validated task for investigating self-processing is a self-reflection task in which participants have to reflect on statements about person characteristics and indicate whether they are applicable to themselves. Accordingly, the part II focused on another aim of this thesis: to investigate the neural

correlates of self- and (close) other-reflection in BD and SZ. In **chapter 5**, we show that BD patients had reduced involvement of the posterior cingulate cortex (PCC) extending to the precuneus during other-reflection compared to HC, with no differences between BD and SZ patients and between SZ patients and HC. Based on the suggested role of the PCC/precuneus during reflective processing in autobiographical memory retrieval/processing and its involvement in emotional processing, this result might imply a disturbance in integrating emotion and memory information in relation to close others in BD patients. In addition, a disorder-specific correlation was found between this PCC/precuneus activation during other-reflection and cognitive insight in SZ patients only, but not in BD patients.

In **chapter 6**, we investigated the functional connectivity underlying self- and other-reflection in BD and SZ patients, by applying generalized psycho-physiological interaction (gPPI). We did so because areas involved in reflective-processing, including the cortical midline structures (CMS) and insula, have been suggested to work in a network, which we wanted to examine in more detail during the performance of the self/other-reflection task. Compared to HC, BD patients had decreased functional connectivity between the CMS nodes (anterior cingulate cortex [ACC], ventromedial prefrontal cortex [VMPFC] and insula) and the caudate head during self-reflection, which might be associated with difficulties in linking reward to self-reflection. However in SZ patients, decreased functional connectivity between the ventral-anterior insula and precuneus/ PCC during other-reflection was observed compared to HC, which could possibly point to a problem in integrating autobiographical memory and emotional awareness related to close others. These differential functional connectivity patterns between BD and SZ during reflective processing might contribute to their differences in clinical symptomatology.

Emotion regulation

Neural correlates of cognitive reappraisal

In the first part of this thesis, we focused on cognitive reappraisal, which is an adaptive ER strategy by forming new interpretations for emotional stimuli in order to adjust emotional intensity (Gross, 2001; Gross, 2002; Gross and John, 2003). Meta-analyses have consistently shown involvement of the lateral and medial part of the prefrontal cortex (PFC) during cognitive reappraisal. In healthy individuals the DLPFC and VLPFC show the strongest activation during reappraisal while reduced activity is

observed in limbic affective areas especially the amygdala (Buhle et al., 2014; Diekhof et al., 2011; Kalisch, 2009). Interaction between the PFC and limbic affective areas have been suggested to be essential for ER, in which the PFC is supposed to perform inhibitory top-down control over limbic affective areas (Ochsner and Gross, 2005; Ochsner et al., 2012; Phillips et al., 2003a). Within the PFC especially the DLPFC has been suggested to play an important role in top-down control during reappraisal (Kohn et al., 2014; Phillips et al., 2008b), with an important role in maintaining reappraisal goals and implementing reappraisal to change emotional responses (Kohn et al., 2014; Ochsner and Gross, 2005; Ochsner et al., 2012; Wager et al., 2004). Regarding the ER role of the VLPFC, it has been suggested that this areas is not involved in cognitive control *per se*, but plays an intermediate role between top-down prefrontal control and bottom-up emotional processing from limbic affective areas, by evaluating the emotional information and signaling the need for ER (Kohn et al., 2014).

Cognitive reappraisal in bipolar disorder

By investigating the temporal features of brain activation of the ER circuit in BD patients, we found that BD patients had generally blunted responses in the DLPFC, with a late but non-sustained involvement of this area during reappraisal (**chapter 2**). In addition, during reappraisal, we showed impaired cognitive control over emotional pictures from the DLPFC to the amygdala in BD patients compared to HC (**chapter 3**). These results suggest that BD patients have difficulties in top-down prefrontal control over negative emotions, although they might make regulatory attempts (late response in the DLPFC). The disturbed cognitive control from the DLPFC may be due to reduced evaluation of the emotional information denoted by a lack of early VLPFC involvement during reappraisal observed in BD patients (**chapter 2**), while a presumed indirect control via the VLPFC seems preserved (i.e., no differences from healthy individuals in the effective connectivity from the VLPFC to the amygdala; **chapter 3**). Altogether, we propose that insufficient (initiation of) prefrontal cognitive control over emotional responses might underlie the deficient ER in BD patients.

Notably, most of our BD patients were emotionally stable at scanning, as they were in a euthymic phase, which might imply that the neural disturbances during ER represent a trait-like vulnerability. Emotional negativity in general (e.g., negative

attitudes towards events, negative self-attributions) and emotional lability have been found to be robust components related to BD (Johnson et al., 2016). Therefore, it would be interesting for future studies to link the temporal pattern and disturbed DLPFC-amygdala effective connectivity in BD patients to the occurrence of their emotional disturbances seen in episodes of disease (e.g., depression and mania severity) and cycling frequencies of these episodes.

Cognitive reappraisal in schizophrenia

Previous activation studies of reappraisal with typical general linear model (GLM) fMRI analysis (i.e., averaging blood-oxygen-level dependent [BOLD] responses over time) have demonstrated reduced activation in the VLPFC in SZ patients compared to HC (Morris et al., 2012; van der Meer et al., 2014). Given the role of the VLPFC during ER of recognizing emotional information, the reduced VLPFC activation in SZ patients may indicate reduced recognition of the emotional contents. However, SZ patients have been found to have comparable or even elevated subjective emotional experience compared to healthy individuals (Cohen and Minor, 2010; Kring et al., 1993; Kring and Moran, 2008). Our findings of temporal patterns of brain activation in the VLPFC during reappraisal in SZ patients appear to elucidate this discrepancy. Specifically, our results showed that the activation in the VLPFC was only present in an early phase, suggesting a failure of sustained activation (**chapter 2**). Furthermore, we did not find reliable involvement of the DLPFC during reappraisal using this particular task in this group of SZ patients. Given the respective hypothesized roles of the DLPFC (i.e., maintaining and exerting reappraisal) and VLPFC (i.e., recognizing emotional salience to signal regulating emotions) during ER, these results may indicate that SZ patients are able to recognize emotional information properly, but show a disturbance in sufficiently maintaining the emotional information in order to initiate (and hence maintain) the top-down frontal control (reflected by the lack of DLPFC activation). This difficulty in reappraisal might lead to use of more maladaptive ER strategies in SZ patients, such as suppression (van der Meer et al., 2009), which might be associated with flat affect commonly observed in SZ. We did not observe behavioral differences in ER between patients and HC, which indicates that the task was not too difficult for the patients.

Suicidal risk

Dysfunctional ER would affect one's well-being in many aspects, and one of the possibly severe consequences may involve experiencing psychological pain and hopelessness, which can trigger suicidal thoughts and behavior (Rajappa et al., 2012). In **chapter 4**, we investigated the structural correlates of suicidality in patients with major depressive disorder (MDD), comparing MDD patients with and without suicidal risk. Our results showed smaller GM volumes in the DLPFC extending to the VLPFC in relation to presence of current SI and/or a history of SA compared to PC. Although the relationship between altered brain structures and changes in function needs more research, given that the DLPFC/VLPFC is important for cognitive control (Miller, 2000; Miller and Cohen, 2001), and has been involved in top-down control of emotion (Buhle et al., 2014), we propose that smaller DLPFC/VLPFC volumes might underlie emotional dysfunction in SRP. This is in line with the suggestion that dysfunctional ER is an important mechanism underlying suicidal behavior (Aleman and Denys, 2014).

Moreover, we found that in patients with presence of current SI only, there were no statistically significant associations with brain structural alterations. It should be noted that severity of current SI was mild in our SRP and we had insufficient power in our comparisons to detect small effects. SI has been suggested to precede SA (Jollant et al., 2011; Mann, 2003), and transition from SI to SA is proposed to be essential in understanding suicidal behavior. In this perspective, SI progresses from mild form to severe SI, and finally into SA (Klonsky et al., 2016). In this way, SA would occur only when severity of SI reaches sufficient level. This implies that our results of no observable structural alterations in relation to presence of SI might be due to insufficient SI severity in our SRP or lack of statistical power. Future research should study this relationship in more detail, including longitudinal designs. This might help to find potential structural biomarkers at an early phase.

Self- and other-reflection

Neural correlates of self- and other-reflection

The ability to judge whether certain information (e.g., traits and attitudes) applies to the self or not, referred to as self-reflection (van der Meer et al., 2010), is associated with social functioning and quality of life (Dimaggio et al., 2008; Lysaker et al., 2005; Mitchell et al., 2005). The cortical midline structures (CMS) and the

insula have been consistently shown to be activated during self-reflection, implying a network of brain areas associated with self-processing (Modinos et al., 2009; Northoff and Bermpohl, 2004; Northoff et al., 2006; van der Meer et al., 2010). Indeed, in healthy individuals, functional connectivity studies have demonstrated interactions within the CMS/insula circuit, as well as connections between the CMS/insula and other brain areas (Schmitz and Johnson, 2006; van Buuren et al., 2010; van Buuren et al., 2012), and as such represent the underlying neural mechanisms of normal self-reflection.

Self- and other-reflection in bipolar disorder

As described in **chapter 5,** BD patients did not show general activation differences compared to HC during self-reflection. However, regarding functional connectivity, there were reduced connectivities between the CMS/insula nodes (i.e., the ACC, VMPFC and insula) and the caudate head during self-reflection in BD patients compared to HC (**chapter 6**). The caudate has been considered as an area involved in action (Gerardin et al., 2004) and reward processing (Delgado et al., 2000; Delgado et al., 2004), but there also is accumulating evidence for a role of the caudate during self-reflection (Denny et al., 2012; Grigg and Grady, 2010; Moran et al., 2006). Furthermore, specifically for our observed caudate cluster (i.e., caudate head), a direct comparison between self-reflection and reward processing in healthy controls also revealed activation in the caudate head in both conditions (Enzi et al., 2009). Altogether, it might therefore be suggested that the connections between the CMS/insula nodes and the caudate head are associated with motivational influences on self-processing, which may be disturbed in BD-patients. This interpretation is in line with the observation that healthy individuals tend to attribute more positive than negative events to themselves (self-serving bias) (Mezulis et al., 2004), while BD patients showed smaller self-serving bias (**chapter 5**). Therefore, disturbed functional connectivity with the caudate head during self-reflection in BD patients may indicate that they experience less rewarding feelings during self-reflection, consistent with our behavioral finding of reduced self-serving bias in these patients. We should note, however, that this is a tentative interpretation and more research is needed to elucidate the precise role of this circuit in BD.

Besides the differences in functional connectivity during self-reflection, reduced activation in the PCC extending to the precuneus during other-reflection was

demonstrated in BD patients compared to HC (**chapter 5**). The PCC/precuneus has consistently been found to be activated during autobiographical memory processing (Fink et al., 1996; Maddock et al., 2001; Maguire and Mummery, 1999), therefore it has been suggested that its role during reflective processing is to retrieve autobiographical memory (van der Meer et al., 2010). Thus, reduced PCC/precuneus activation in BD patients might indicate a disturbance in coupling retrieved information from autobiographical memory to the stimuli related to close others, which might result in inaccurate evaluations on close others. This in turn might be associated with difficulties in social interaction with other people, as commonly seen in BD patients (Samame, 2013).

In summary, BD patients showed neural disturbances in self- and other-reflection compared to HC, with differences in functional connectivity during self-reflection (**chapter 6**) and in brain activation during other-reflection (**chapter 5**). Our results represent cross-sectional investigations in predominantly euthymic BD patients. It remains unknown whether the observed disturbances exist beforehand or are a consequence of previous episodes and how these disturbances develop over time. Therefore longitudinal approaches for BD are needed.

Self- and other-reflection in schizophrenia

As described in **chapter 5**, we did not find activation differences during self- and other-reflection in SZ patients compared to HC. However, this result should be considered carefully, since previous studies have shown altered activation during self- and other-reflection in SZ patients (Bedford et al., 2012; Holt et al., 2011; Murphy et al., 2010; Pauly et al., 2013; Shad et al., 2012; van der Meer et al., 2013). We think this inconsistency might be due to our selection of SZ patients who had good insight (in order to match with BD patients on illness insight). This matching of SZ patients with good insight might represent a less severely ill group of SZ. In more severe SZ patients, lower PCC/precuneus activation during other-reflection would be expected, based on our finding of a positive correlation between PCC/precuneus activation in relation to close others and illness insight (**chapter 5**). Indeed, previously Van der Meer et al. (2013) showed reduced activation in the PCC/precuneus during other-reflection in SZ patients with a range of good and poor illness insight, compared to HC. Furthermore, we found reduced functional connectivity between the ventral-anterior insula and precuneus/PCC during other-

reflection in SZ patients compared to HC (**chapter 6**). Given the roles of the precuneus/PCC and ventral-anterior insula during reflective-processing of autobiographical memory processing (van der Meer et al., 2010) and emotional awareness processing (Craig, 2009; Kurth et al., 2010), respectively, the reduced ventral-anterior insula-precuneus/PCC connectivity in SZ patients may suggest disturbed information consultation of autobiographical memory and emotional awareness in relation to close others, leading to difficulties in other-reflection.

Altogether, in SZ patients, findings from our investigation of brain activation and functional connectivity suggest difficulties when reflecting on close others. This may result in problems with interacting with others, which might be associated with deficient social cognition, commonly observed in these patients (Penn et al., 2008). A more direct investigation with social functioning is needed, though, before strong conclusions are warranted.

Comparison between bipolar disorder and schizophrenia

The relationship between BD and SZ gains much attention and remains controversial. On the one hand, multifaceted evidence has shown many similarities between BD and SZ, including shared genetic vulnerability (International Schizophrenia Consortium et al., 2009; Lichtenstein et al., 2009), clinical symptomatology (e.g., psychotic symptoms) (American Psychiatric Association, 2013), psychological dysfunctions (e.g., difficulties in emotion regulation, cognitive functioning and social cognition) (Rowland et al., 2013a; Schretlen et al., 2007) and brain structure (Arnone et al., 2009). On the other hand, neural correlates (including brain activation and connectivity) have been shown to be different between these two disorders during multiple cognitive processes (e.g., executive function, language, and memory) (Whalley et al., 2012), and classification of multivariate patterns of GM anatomical differences (Schnack et al., 2014). Together with differences in clinical presentation, this corroborates the long-existing division between BD and SZ, which persists also in the most recent diagnostic and statistical manual (DSM-5). These results suggest both similarities and differences between BD and SZ. From a neuroscience perspective, a hypothesis has been proposed by Frangou (2014) that BD and SZ have shared disturbances in more superordinate processes/networks, while these two psychiatric disorders show differences on a macroscale level (e.g., different impairments in local area/subnetwork). In line with this suggestion, the

present thesis showed impaired ER and reflective-processing both in BD and SZ, while differential neural profiles were present within the corresponding circuits between BD and SZ (**chapter 2, 3, 5, 6**). Of note, both BD and SZ are heritable psychiatric disorders. Future research should further investigate the neural profiles of ER and reflective-processing in individuals at high risk for developing BD or SZ (e.g., first-level family members). This may provide more informative knowledge on the etiology of BD and SZ. Previous studies compared individuals with high risk for BD or SZ to patients with the same disorder. Adding to that, comparison between individuals at high risk for BD and individuals at high risk for SZ might provide more insights into similarities and putative differences.

Methodological considerations and future perspectives

Sample characteristics

In the present thesis, we compared BD patients to SZ patients on the neural correlates during ER and self-related processing (**chapter 2, 3, 5, 6**). Because self-other distinctions may be of particular relevance for patients with a vulnerability to psychosis, we only included BD patients with a history of psychotic symptoms and matched the BD and SZ patients on illness insight to exclude alternative explanations for any group differences. However, this also induced potential limitations. First, because BD patients have preserved illness insight in general (Cassidy, 2010), the recruited SZ patients in this thesis were selected to have good levels of illness insight too, which might represent a less severe sub-group of the SZ population. Second, the BD patients might represent a more severe subgroup, due to the requisite of presence of psychotic symptoms somewhere in the past. By selecting these subgroups of patients, we are able to discuss the differences and similarities between these groups of SZ and BD patients, but we cannot easily generalize to the patients suffering from the full syndromes of SZ and BD. Although limited, there are indeed studies showing more severe impairments in cognitive functioning (Krabbendam et al., 2005) and emotional processing (Addington and Addington, 1998) in SZ patients than BD patients. Therefore, true differences between patients with BD and SZ in general might be underestimated. Furthermore, it is of importance to realize that our BD and SZ patients were predominantly stable at scanning, with only mild depressive and psychotic symptoms. This could help us to understand mechanisms underlying ER and reflective processing independent of influences from

acute emotional states and psychosis, which might pave the way to find trait-like biomarkers. However, this selection precludes definite conclusions about exaggeration or other differences between SZ and BD during episodes of their illness or differences induced by the different states of illness. Future studies may include patients during different mood states (e.g., depression, mania and euthymia), and with or without presence of acute psychosis into one study, which would be helpful in understanding the association between the neural correlates and illness course of BD and SZ and the state-trait differences. Although this type of research is very difficult to conduct in practice (e.g., it is very difficult for manic patients to lie still for a prolonged time in the MRI scanner), such investigation may be worth to attempt.

In addition, we had modest sample sizes of BD and SZ patients (**chapter 2, 3, 5, 6**). Although it has been suggested on statistical grounds that a sample size of approximately 16-20 may have sufficient power for typical effect sizes in neuroimaging studies (Landis and Koch, 1977; Thirion et al., 2007), replication in larger samples is necessary to permit generalization.

Finally, it should be noted that the present thesis was based on existing datasets. Specifically, the samples in **chapter 4** were sub-samples from the Netherlands Study of Depression and Anxiety (NESDA, neuroimaging study) (van Tol et al., 2010), and participants in **chapter 2, 3, 5, 6** were from the *Study of Emotion, Self-insight and Self-evaluation* (EMOZIE). Of note, the SZ sample in these studies was a sub-sample of the total sample included in the EMOZIE-study (see for total SZ sample, van der Meer et al., 2013), because these patients were matched on illness insight with the BD sample. Selecting these subsamples might increase the chance for type-II errors (false negative findings), because a reduction in number of participants reduces power to measure true differences. Therefore, future studies in larger samples are needed to replicate our findings.

Emotion regulation task

In **chapter 2-3**, an ER task was used to investigate neural correlates underlying cognitive reappraisal in BD and SZ patients. This task was adapted from the study of Ochsner et al. (2002), and we replicated prefrontal activation in areas consistently observed in previous meta-analysis studies on reappraisal (Buhle et al., 2014; Diekhof et al., 2011; Kalisch, 2009), supporting the validity of our ER task. However, we did not find decreased amygdala response during reappraisal, though

we indeed observed amygdala involvement during an earlier phase of viewing negative pictures (compared to viewing neutral pictures). This might be associated with our late cueing paradigm in which stimulus pictures were presented before regulation instructions were given. With this design of the task, direct automatic regulation might start immediately after the presentation of the stimulus, thus reducing the chance of finding differences associated with voluntary emotion regulation. On the other hand, this late cueing paradigm resembles situations in real life, where participants may already try to reappraise before voluntary regulation cues are presented or thought of, or the amygdala response gets habituated quickly since presentation of emotional stimuli (Ochsner et al., 2012). In future studies, it would be interesting to compare an early cueing paradigm (i.e., regulation instructions are presented before stimulus presentation) to a late cueing paradigm as we applied now, to test the generalizability of our ER results.

Clinical implications

Understanding the neural correlates of ER in BD and SZ could provide insight in the mechanisms underlying the emotional symptomatology in these two disorders. Our fundamental research may aid in the development of future treatments targeting the emotional symptoms in BD and SZ. In our studies, BD patients showed disturbed prefrontal control over negative emotions during cognitive reappraisal. A recent study involving an extensive battery of emotion-related assessments reported that the use of an adaptive ER strategy (i.e., cognitive reappraisal) predicted lower levels of depression in a 12-month follow up in BD patients (Johnson et al., 2016). This might indicate that training of adequate reappraisal would be a meaningful intervention. However whether such training will also result in improvement of the aberrant findings as shown in this thesis remains to be shown in association with long-term outcomes. Moreover, the suggestion based on our results that a main difficulty for BD patients was to initiate reappraisal stemming from failed recognition of emotional salience, might indicate that focusing on emotion recognition during reappraisal training may be specifically more helpful for BD patients. Regarding reappraisal training in SZ patients, clinicians/psychotherapists may pay attention to the ability to sustain regulation, since we found that SZ patients could recognize emotional salience, but have difficulty in maintaining the information online sufficiently. Eventually, neurofeedback training, a method to provide participants real-time

feedback of brain activity in order to help control brain activity, might be an option (Sulzer et al., 2013).

Regarding self-other reflection, we proposed that BD may link less reward to the self during reflection on the self, in line with the behavioral observation that they had more negative than positive self-attributions. Cognitive behavior therapy (CBT) has been shown to improve positive self-evaluations (Goldin et al., 2013), and has been applied in BD, showing beneficial effects in medication adherence, reducing depression and preventing relapse (Deckersbach et al., 2016), however improvements in the ability to appreciate oneself during self-reflection needs further investigation. Therefore, CBT may be recommended for BD patients, especially in terms of increasing positive self-views, which might be more informative regarding long-term outcomes and should therefore be evaluated in addition to clinical outcomes. Furthermore, we found that both BD and SZ patients are disturbed in consulting/retrieving autobiographical memory when reflecting on close others. It remains to be demonstrated that an improvement in cognitive functioning, especially the memory component, might be advantageous regarding social functioning.

Some other potential clinical implications should also be mentioned. First, although whether BD and SZ are two separate disorders or not is still under discussion, the application of tailored interventions is encouraged, both between psychiatric disorders and as personalized approaches within each disorder. Based on the observed distinct neural mechanisms underlying ER and reflective processing between BD and SZ, when replicated, it would be interesting to develop tasks that could identify these distinctions in order to differentiate difficult diagnostic cases as belonging to a diagnostic group, but also to use these tests to guide the use of specifically aimed interventions. Second, it should be noted that although BD and SZ showed disturbed activation/connectivity during ER and reflective processing in some brain areas compared to HC, there were also brain areas that are previously associated with ER and reflective processing, but did not show impairments in activation/connectivity compared to HC. This indicates partly preserved functioning of ER and reflective processing in these patients, which might contribute to functional compensation for the disturbed brain areas/pathways. In this perspective, in addition to targeting impairments with interventions to improve functioning, an interesting approach might also be how to make use of the intact parts, which remains open for future research as well.

Concluding remarks

In this thesis, we provide a framework of ER and self- and other-reflection in BD and SZ. In part I, we observed that BD and SZ patients show differential temporal dynamics during cognitive reappraisal, with BD being disturbed in initiating reappraisal, while SZ patients showed normal early recruitment, but failed to sustain activation in areas important for emotional evaluation and signaling of the need to regulate. In patients with BD, we observed weaker prefrontal top-down control during regulating negative emotions. Consistent with the notion that suicidal risk (quantified by previous suicide attempts and current suicidal ideation) may be due to disordered emotion regulation, we observed that it was associated with structural brain alterations in parts of the ER circuit (e.g., DLPFC/VLPFC). This might provide insight in the search for potential structural biomarkers, which may ultimately contribute to suicide prevention. In part II, we found different correlates underlying self-evaluation in patients with BD versus SZ. Specifically, our results suggested reduced influence of motivational systems on self-reflection in BD patients. Based on the neural patterns we propose that both BD and SZ patients may have difficulties recruiting autographical memory (and emotional awareness for SZ patients) during reflecting on close others. Understanding these differences between BD and SZ patients might help to eventually develop better diagnostic procedures and more personalized treatments for BD and SZ.