CHAPTER 1

General introduction
In our daily lives, we encounter many emotional events, leading to changes in our emotional state. Although our emotions fluctuate, most of us have the ability to control our emotions to a proper level, which refers to an ability of emotion regulation (ER). Problems during ER are seen in patients with different psychiatric disorders, including bipolar disorder (BD), schizophrenia (SZ) and major depressive disorder (MDD). One of the severe consequences of dysfunctional ER in the situation of emotionally overwhelming events could be committing suicide. Suicidality is a severe symptom in many psychiatric disorders, but particularly associated with depression. In the first part of the present thesis, we investigated the neural correlates underlying ER and suicidal behavior/ideation in psychiatric patients.

Furthermore, in the second part of this thesis the neural correlates during self-reflective processing in BD and SZ were investigated. Self-reflection refers to the cognitive process to judge whether certain information, for instance traits and attitudes, are related to the self or not (van der Meer et al., 2010). This ability of reflection on the self helps people to make insight in the social positioning of the self in relationship to others. This may be of importance for social cognition, because reflection on the self may be associated with inference of other’s information (e.g., intentions), especially close others (Mitchell et al., 2005). Self-reflection has indeed been associated with social functioning and quality of life (Dimaggio et al., 2008; Lysaker et al., 2005). Problems with self-processing are common in BD patients (Ghaznavi and Deckersbach, 2012; Lyon et al., 1999) and SZ patients (Holt et al., 2011; Murphy et al., 2010; van der Meer et al., 2013). In part II of this thesis, we tried to unravel the neural correlates underlying self-reflection in patients with BD and SZ, which might provide insight in the shared and unique neural mechanisms between these two disorders during self-processing.

**Psychiatric disorders**

In this thesis, we investigated two common mood disorders (i.e., BD and MDD) and schizophrenia (SZ). These disorders have been shown to be leading contributors to global burden of diseases (Whiteford et al., 2013), not only resulting in burden for patients themselves (e.g., problems of functioning in occupations and interpersonal relationships, emotional pain), but also for family members (e.g., psychological stress) and society (e.g., direct financial costs of medical care and indirect costs due to unproductivity and loss of work).
In our daily lives, we encounter many emotional events, leading to changes in our emotional state. Although our emotions fluctuate, most of us have the ability to control our emotions to a proper level, which refers to an ability of emotion regulation (ER). Problems during ER are seen in patients with different psychiatric disorders, including bipolar disorder (BD), schizophrenia (SZ) and major depressive disorder (MDD). One of the severe consequences of dysfunctional ER in the situation of emotionally overwhelming events could be committing suicide. Suicidality is a severe symptom in many psychiatric disorders, but particularly associated with depression. In the first part of the present thesis, we investigated the neural correlates underlying ER and suicidal behavior/ideation in psychiatric patients. Furthermore, in the second part of this thesis the neural correlates during self-reflective processing in BD and SZ were investigated. Self-reflection refers to the cognitive process to judge whether certain information, for instance traits and attitudes, are related to the self or not (van der Meer et al., 2010). This ability of reflection on the self helps people to make insight in the social positioning of the self in relationship to others. This may be of importance for social cognition, because reflection on the self may be associated with inference of other’s information (e.g., intentions), especially close others (Mitchell et al., 2005). Self-reflection has indeed been associated with social functioning and quality of life (Dimaggio et al., 2008; Lysaker et al., 2005). Problems with self-processing are common in BD patients (Ghaznavi and Deckersbach, 2012; Lyon et al., 1999) and SZ patients (Holt et al., 2011; Murphy et al., 2010; van der Meer et al., 2013). In part II of this thesis, we tried to unravel the neural correlates underlying self-reflection in patients with BD and SZ, which might provide insight in the shared and unique neural mechanisms between these two disorders during self-processing.

Psychiatric disorders

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In order to classify a syndrome of symptoms as BD, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994), patients have to have experienced different emotional episodes, including at least one manic or hypomanic episode and often experienced one or several major depressive episode(s) (Table 1). The present thesis focused on BD I and BD II, which requires presence of at least one manic episode or only one or more hypomanic episode(s), respectively. Notably, mood disturbances are a common feature across episodes, indicating an essential role of ER in BD (Phillips et al., 2003b). SZ is characterized by a range of symptoms, including positive psychotic symptoms (hallucinations and delusions), negative symptoms (e.g., flat affect) and/or disorganized (verbal) behavior (Table 2). In addition, for the diagnosis of MDD, presence of at least one major depressive episode is required (Table 1), which should not be explained by other psychiatric disorders (e.g., schizophrenia, schizoaffective disorder, schizophreniform disorder).

Currently, there is a discussion in the literature whether BD and SZ are two separate disorders or two variations on the same disorder continuum. Both similarities and discrepancies between BD and SZ have been reported in the literature. Similarities include shared risk genes, psychotic and emotional symptoms, impaired cognitive and social functioning, and brain structural alterations (Arnone et al., 2009; International Schizophrenia Consortium et al., 2009; Lichtenstein et al., 2009; Rowland et al., 2013a; Schretlen et al., 2007). On the other hand distinctions have also been highlighted, in the first place in clinical presentation as recognized by their separate classification in all editions of the DSM (American Psychiatric Association, 1994) and in cognitive (Krabbendam et al., 2005) and neurobiological differences (Schnack et al., 2014). In the present thesis, we tried to shed more light on the comparison between BD and SZ, from the perspective of ER and self-reflective processing.

Table 1 Diagnostic criteria for episodes of bipolar disorder (reproduced from the DSM-IV)

<table>
<thead>
<tr>
<th>Diagnostic criteria for Major Depressive Episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at</td>
</tr>
</tbody>
</table>
least one of the symptoms is either (1) depressed mood or (2) loss of
interest or pleasure. **Note:** Do not include symptoms that are clearly due to
a general medical condition, or mood-incongruent delusions or
hallucinations.

1. Depressed mood most of the day, nearly every day, as indicated by
   either subjective report (e.g., feels sad, empty, or hopeless) or
   observation made by others (e.g., appears tearful). (Note: In children
   and adolescents, can be irritable mood.)

2. Markedly diminished interest or pleasure in all, or almost all, activities
   most of the day, nearly every day (as indicated by either subjective
   account or observation).

3. Significant weight loss when not dieting or weight gain (e.g., a change of
   more than 5% of body weight in a month), or decrease or increase in
   appetite nearly every day. (Note: In children, consider failure to make
   expected weight gain.)

4. Insomnia or hypersomnia nearly every day.

5. Psychomotor agitation or retardation nearly every day (observable by
   others; not merely subjective feelings of restlessness or being slowed
down).

6. Fatigue or loss of energy nearly every day.

7. Feelings of worthless or excessive or inappropriate guilt (which may be
   delusional) nearly every day (not merely self-reproach or guilt about
   being sick).

8. Diminished ability to think or concentrate, or indecisiveness, nearly every
day (either by subjective account or as observed by others).

9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal
   ideation without a specific plan, or a suicide attempt or a specific plan for
   committing suicide.

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social,
   occupational, or other important areas of functioning.

D. The episode is not attributable to the physiological effects of a substance
   (e.g., a drug of abuse, a medication) or a general medical condition (e.g.,
The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 month or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

**Diagnostic criteria for Manic Episode**

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) are have been present to a significant degree:
   1. Inflated self-esteem or grandiosity;
   2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep);
   3. More talkative than usual or pressure to keep talking;
   4. Flight of ideas or subjective experience that thoughts are racing;
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli);
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation;
   7. Excessive investment in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The symptoms do not meet criteria for a Mixed Episode.

D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

**Note:** Manic-like episodes that are clearly caused by somatic antidepressant
treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.

### Diagnostic criteria for Hypomanic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 4 days, that is clearly different from the usual nondepressed mood.

B. During the period of mood disturbance, three (or more) of the following symptoms (four if the mood is only irritable) have persisted and have been present to a significant degree:
   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli).
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
   7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.

F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

**Note:** Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar II Disorder.
**Table 2** Diagnostic criteria for schizophrenia (reproduced from the DSM-IV)

<table>
<thead>
<tr>
<th>Diagnostic criteria for schizophrenia</th>
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</thead>
<tbody>
<tr>
<td>A. <strong>Characteristic symptoms</strong>: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):</td>
</tr>
<tr>
<td>1. Delusions;</td>
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<td>2. Hallucinations;</td>
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<tr>
<td>3. Disorganized speech (e.g., frequent derailment or incoherence);</td>
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<tr>
<td>4. Grossly disorganized or catatonic behavior;</td>
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<tr>
<td>5. Negative symptoms, i.e., affective flattening, alogia, or avolition.</td>
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<tr>
<td>Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations or hallucinations consist of a voice keeping up a running commentary on the person’s behavior or thoughts, or two or more voices conversing with each other.</td>
</tr>
<tr>
<td>B. <strong>Social/occupational dysfunction</strong>: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).</td>
</tr>
<tr>
<td>C. <strong>Duration</strong>: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).</td>
</tr>
<tr>
<td>D. <strong>Schizoaffective and Mood Disorder exclusion</strong>: Schizoaffective Disorder and Mood Disorder with psychotic features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief</td>
</tr>
</tbody>
</table>
relative to the duration of the active and residual periods.

E. **Substance/general medical condition exclusion:** The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. **Relationship to a Pervasive Developmental Disorder:** If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

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**Emotion regulation**

BD and SZ have both shared (e.g., depressed mood) and distinct (elevated mood in BD, while flat affect in SZ) emotional symptoms, implying variations in ER. Studies investigating mechanisms underlying ER in BD and SZ patients may enable us with a better understanding of their emotional symptomatology.

Gross and Thompson (2007) proposed that emotion generation is composed of four steps, including attending to a situation, directing attention to certain cue(s), appraising the meaning of cue(s), and giving emotional responses in response to appraised cues (e.g., facial expression and physiological response). Depending on whether ER happens before or after emotional responses have been generated, ER strategies could be classified in antecedent-focused and response-focused strategies, respectively (Gross, 2001). In the present thesis, we were specifically interested in the antecedent-focused strategy reappraisal. Reappraisal is defined as reinterpreting the meaning of the stimulus to change its emotional intensity and connotation (Gross, 2001; Gross, 2002; Gross and John, 2003), and has been shown to be an adaptive ER strategy (Gross, 2002). Investigating reappraisal in both BD and SZ may provide information on the specific dysfunctions of ER in these disorders.

Previous studies have shown that compared to healthy individuals BD patients need more effort for reappraisal and show less success (Corbalan et al., 2015; Gruber et al., 2012; Morris et al., 2012), and SZ patients show less use of reappraisal (van der Meer et al., 2009). On the neural level, studies in healthy individuals have mainly shown involvement of the lateral and medial prefrontal cortex (PFC), and reduced activation in limbic affective areas (e.g., amygdala) (Buhle et al., 2014;
Diekhof et al., 2011; Kalisch, 2009). In contrast, increased but also decreased lateral PFC, as well as elevated amygdala activation during reappraisal have been observed in BD patients (Kanske et al., 2015; Morris et al., 2012; Townsend et al., 2013), although no activation deviations from healthy individuals have also been reported (Corbalan et al., 2015). For SZ patients, more consistent results of reduced involvement of the lateral prefrontal PFC compared to healthy individuals are reported (Morris et al., 2012; van der Meer et al., 2014). Altogether, previous studies demonstrate disturbed ER in BD and SZ patients both on the behavioral and brain activation level.

The aforementioned studies used functional magnetic resonance imaging (fMRI) to measure brain activation. Brain activation is measured as the mean blood-oxygen-level dependent (BOLD) signal. However, this BOLD signal is orchestrated across time, with activation in the prefrontal areas peaking in an early phase and activation in the amygdala in a late phase during reappraisal period (Goldin et al., 2008). It has not yet been investigated when during the full duration of reappraisal altered activation occurs in BD and SZ patients. Therefore, important information may be gained by investigating the temporal dynamics in addition to the average brain activation signal over time (which is done in the traditional general linear models). For this purpose, we investigated the temporal dynamics of brain activation during reappraisal in BD and SZ patients, which may provide a better understanding of the different and aberrant neural mechanisms underlying emotional symptomatology in BD and SZ (chapter 2).

It has been suggested that top-down control from the prefrontal areas to limbic affective areas (e.g., amygdala) plays an important role in successful reappraisal (Ochsner and Gross, 2005; Ochsner et al., 2012; Phillips et al., 2003a). Indeed, in healthy individuals, negative associations between activation in the lateral/medial prefrontal cortex and amygdala have been shown (Goldin et al., 2008; Ochsner et al., 2002; Phan et al., 2005; Urry et al., 2006), while BD patients show disturbed PFC-amygdala correlations compared to healthy individuals (Kanske et al., 2015; Morris et al., 2012; Townsend et al., 2013). Nonetheless, previous studies have not yet investigated the suggested directional relationships within the PFC-amygdala circuit in BD as compared to HC. Therefore, the aim of chapter 3 was to investigate the top-down directional relationships from the PFC to amygdala during reappraisal in BD.
Suicidal risk

Insufficient ability to regulate emotions can be associated with social problems and psychological distress, which ultimately affects one’s general well-being. One extreme consequence of this could be suicide. Indeed, dysfunctional ER has been suggested to play an important role in suicidal processes (Aleman and Denys, 2014; Jollant et al., 2011), by which individuals may regard suicide as a way to escape from emotional despair (Baumeister, 1990). Patients with a psychiatric disorder account for around 90% of people who commit suicide (Harris and Barraclough, 1997), especially patients with major depressive disorder (MDD) (Angst et al., 1999). As suicide might at one end of the spectrum of ER difficulties, in chapter 4, we as a first step investigated structural brain differences in relation to suicide, by comparing MDD patients with suicidal risk to patients with the same disorder characteristics but no suicidal risk and to healthy individuals.

Processes leading to suicide may start with suicidal ideation (SI), with or without suicide plans, which not in all cases though might finally end in a suicide attempt (SA) (Jollant et al., 2011; Klonsky et al., 2016; Mann, 2003). Both SI and SA have been found to be important predictors for future suicide (Fawcett et al., 1990; Hawton and van Heeringen, 2009; Kessler et al., 1999). Previous studies to structural differences have focused on structural alterations in suicide attempters (Ding et al., 2015; van Heeringen et al., 2014), revealing reduced grey matter (GM) volumes in areas related to ER (e.g., the lateral PFC). However, it remains unknown whether these observed structural changes are also associated with SI, since SA would imply occurrence of earlier SI (Klonsky et al., 2016). This requires investigating structural changes in relation to both SA and SI in one study. To our best knowledge, no such structural studies have been performed. Therefore, based on the Netherlands Study of Depression and Anxiety (NESDA), which is an ongoing longitudinal study in the Netherlands (Penninx et al., 2008; van Tol et al., 2010), we assessed structural brain alterations associated with suicidal risk (SI and/or SA) in MDD patients, by using a common method of assessing structural alterations (brain volumes), namely voxel-based morphometry (VBM) analysis (chapter 4).

Self-reflection

Problems with self-processing are prevalent in BD patients (Ghaznavi and Deckersbach, 2012; Lyon et al., 1999), which may be associated with awareness of
self in relation to others. This indicates the importance of investigating self-reflection in BD patients. In healthy individuals, it has consistently been found that during self-reflection, the dorsomedial prefrontal cortex (DMPFC), ventromedial prefrontal cortex (VMPFC), anterior cingulate cortex (ACC), and posterior cingulate cortex (PCC), which are referred to as the cortical midline structures (CMS), and the insula are involved (Modinos et al., 2009; Northoff and Bermpohl, 2004; Northoff et al., 2006; van der Meer et al., 2010). Furthermore, the CMS nodes have been suggested not to work independently, but to collaborate to contribute to self-reflection (Northoff and Bermpohl, 2004). In addition to this suggestion, a model of self-reflection (van der Meer et al., 2010) maintains that, self-reflective processing progresses in different stages. These start from directing attention to self-relevant features (ACC) that would be tagged as self-related subsequently (VMPFC), to integrating this with information of internal somaesthetic feedback (insula) and autobiographical memory (PCC). The final stage is an evaluation process to decide whether certain features describe oneself or not (DMPFC). Although further validation of this model is still needed, this model suggests that self-reflection areas may work together as a network. Indeed, it has been demonstrated that there are functional connectivities between nodes within the CMS circuit, as well as between CMS and areas outside the CMS during normal self-reflection (Schmitz and Johnson, 2006; van Buuren et al., 2010; van Buuren et al., 2012).

However, no previous studies have shed light on neural mechanisms underlying self-reflection in BD patients. To this end, an important goal of the present thesis was to investigate neural activation during self-reflection in BD patients (chapter 5). Furthermore, SZ patients have demonstrated difficulties in self-reflection (Holt et al., 2011; Murphy et al., 2010; van der Meer et al., 2013). To explore whether any potential disturbed neural correlates in BD patients are unique characteristics of BD, we compared BD patients to SZ patients (chapter 5). Because of the network pattern of the CMS/insula areas, we further conducted generalized psychophysiological interaction (gPPI) analysis to investigate functional connectivity during self-reflection in BD and SZ patients (chapter 6). Moreover, in order to investigate whether findings are specific to self-reflection, we also included reflection on close others, which has been shown to be similar to self-reflection in many aspects (Murray et al., 2012; van der Meer et al., 2010) (chapter 5-6).
Outline of thesis

The primary aim of this thesis is to gain knowledge on the neural mechanisms underlying ER and self-reflection in BD, MDD and SZ. In part I of the present thesis, we focused on neural mechanisms underlying ER, and the structural basis of suicide, which might result from disturbances in ER. Specifically, in chapter 2, we investigated the temporal neural correlates of ER (reappraisal) in BD and SZ patients. Finite Impulse Response (FIR) modeling was conducted to measure temporal dynamics (i.e., shape and timing characteristics of the BOLD responses) during reappraisal. Based on the suggestion that top-down control from the prefrontal ER areas to amygdala is important for successful reappraisal, in chapter 3 we investigated whether this top-down control of the ER circuit was disturbed in BD patients. Directional relationships of the ER circuit were investigated with Dynamic Causal Modeling (DCM) analysis. Furthermore, as a possible consequence of dysfunctional ER, suicide is one of the most severe consequences in psychiatric disorders, especially major depressive disorder. Therefore, in chapter 4, we examined structural alterations in relation to both SI and SA in MDD patients. VBM analysis was applied to measure brain volumes in MDD patients with suicidal risk (presence of current SI and/or past SA), compared to MDD patients without suicidal risk (no SI and SA) and healthy individuals.

In part II of this thesis, the aim was to investigate self-reflective processing in BD and SZ patients. To achieve this, in chapter 5, we examined the brain activation during self-reflection, as well as close other-reflection in BD patients compared to SZ patients and healthy individuals. Adding to this activation study reported in chapter 5, we further studied the mechanisms of functional connectivity underlying self- and close other-reflection in BD and SZ patients (chapter 6).

Notably, chapter 4 was based on data from the Netherlands Study of Depression and Anxiety (NESDA) (van Tol et al., 2010), and chapters 2, 3, 5 and 6 were on data of the Study of Emotion, Self-insight and Self-evaluation (EMOZIE) (van der Meer et al., 2013). For each of the EMOZIE-based chapters, we selected different sub-samples, because not both tasks were available for all subjects and the different analysis methods lead to different exclusion criteria (i.e. DCM analysis [chapter 3] requires activation in certain areas on the individual level to select the time course; see Table 3 for an overview of the sample illustration). In addition, due to our specific research questions, all the studies described in this thesis include
planned comparisons. Of note, the power estimation of the NESDA and EMOZIE study were based on the primary outcome measures (van der Meer et al., 2013; van Tol et al., 2010).

Finally, in chapter 7, results from previous chapters (chapter 2–6) were integrated and discussed. Moreover, possible clinical implications of research in this thesis are addressed, along with some suggestions for future research.
### Table 3: Sample illustration in the EMOZIE-based chapters

<table>
<thead>
<tr>
<th>Variables</th>
<th>Chapter 2</th>
<th>Chapter 3</th>
<th>Chapter 5</th>
<th>Chapter 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HC</td>
<td>BD</td>
<td>SZ</td>
<td>HC</td>
</tr>
<tr>
<td>Number, N</td>
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<td>15</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Male/Female, N</td>
<td>10/5</td>
<td>6/9</td>
<td>12/4</td>
<td>9/5</td>
</tr>
<tr>
<td>Age (years), M (SD)</td>
<td>33.6(11.5)</td>
<td>39.9(12.5)</td>
<td>31.8(8.7)</td>
<td>33.6(11.5)</td>
</tr>
<tr>
<td>Education level, M (SD)</td>
<td>5.6(9)</td>
<td>6.1(7)</td>
<td>5.6(1.0)</td>
<td>5.6(9)</td>
</tr>
<tr>
<td>Intelligence</td>
<td></td>
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<tr>
<td>DART_correct, M (SD)</td>
<td>40.9(6.6)</td>
<td>42.7(3.9)</td>
<td>38.0(8.5)</td>
<td>40.9(6.6)</td>
</tr>
<tr>
<td>QIDS-SR, M (SD)</td>
<td>2.0(1.2)</td>
<td>5.3(5.4)</td>
<td>9.1(4.5)</td>
<td>2.0(1.2)</td>
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<td>YMRS, M (SD)</td>
<td>1.4(1.5)</td>
<td>1.8(1.7)</td>
<td>1.4(1.5)</td>
<td>1.3(1.5)</td>
</tr>
<tr>
<td>PANSS, M (SD)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Total</td>
<td>39.9(6.2)</td>
<td>53.4(13.9)</td>
<td>41.0(6.3)</td>
<td>40.8(6.3)</td>
</tr>
<tr>
<td>Positive</td>
<td>9.5(2.7)</td>
<td>12.4(4.8)</td>
<td>9.3(2.8)</td>
<td>9.5(2.6)</td>
</tr>
<tr>
<td>Negative</td>
<td>8.9(2.3)</td>
<td>14.3(4.8)</td>
<td>9.6(3.0)</td>
<td>9.6(2.9)</td>
</tr>
<tr>
<td>General psychopathology</td>
<td>21.5(3.6)</td>
<td>25.7(7.1)</td>
<td>22.1(3.5)</td>
<td>21.8(3.6)</td>
</tr>
<tr>
<td>Insight, M (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAI-E</td>
<td>22.3(2.1)</td>
<td>21.3(2.5)</td>
<td>22.2(2.1)</td>
<td>22.4(2.0)</td>
</tr>
<tr>
<td>BCIS_Cumposite score</td>
<td>7.3(4.7)</td>
<td>7.7(4.7)</td>
<td>7.7(4.2)</td>
<td>7.8(5.4)</td>
</tr>
<tr>
<td>BCIS_Self-reflectiveness</td>
<td>14.7(4.0)</td>
<td>15.3(4.0)</td>
<td>15.1(3.8)</td>
<td>15.1(4.4)</td>
</tr>
<tr>
<td>BCIS_Self-Certainty</td>
<td>7.4(2.5)</td>
<td>7.6(3.1)</td>
<td>7.3(2.4)</td>
<td>7.4(2.6)</td>
</tr>
</tbody>
</table>

Abbreviations: BCIS=Beck cognitive insight scale; BD=bipolar disorder; DART=Dutch Reading Test for Adults; HC=healthy controls; M=mean; PANSS=Positive and Negative Syndrome Scale; QIDS=Quick Inventory of Depressive Symptomatology; SAI_E=Schedule of Assessment of Insight-Expanded version; SD=standard deviation; SZ=schizophrenia; YMRS=Young Mania Rating Scale
Emotion regulation