Chapter 1
General introduction
The focus of this thesis is on functional neuroimaging of affective processing in psychiatric disorders. In the first part of this thesis, I present a prospective and a longitudinal functional magnetic resonance (fMRI) study on affective processing to investigate whether brain abnormalities 1) could predict the long-term course of depression; 2) depend on the clinical depressive state and progress with enduring depressive course. In the second part of the thesis, I focus on symptom specific neural abnormalities in depression, namely suicidality, and on distinctive abnormalities in emotion regulation in psychiatric disorders characterized by affective dysregulation: schizophrenia and bipolar disorder. Because depression is associated with a high suicidal risk, I sought to unravel 3) whether neural correlates of affective and cognitive control could be a candidate marker of suicidality. Finally, I investigated 4) the temporal markers of brain activation during emotion regulation in schizophrenia and bipolar disorder. In this introduction, an overview of the clinical characteristics, prevalence, illness course and symptom specificity in depression will be presented first. Then, the neurobiological models of affective processing in psychiatric disorders will be briefly reviewed. Finally, I will introduce the aims and outline of this thesis.

**Major depressive disorder (MDD)**

*Clinical characteristics and prevalence*

MDD is a psychiatric disorder characterized by enduring sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration (See Box I for Diagnostic and Statistical Manual of Mental Disorders-version 5 [DSM-5] for MDD) (American Psychiatric Association 2013). Currently, MDD is a leading cause of disability worldwide, with an estimate of more than 350 million people affected (Marcus et al, 2012). Recently, the World Mental Health survey by the World Health Organization reported that the lifetime prevalence of major depressive episode (MDE) across the world ranges from 6.5% (People’s Republic of China) and 6.6% (Japan) to 21.0% (France) and 19.2% (the USA) (Bromet et al, 2011; Kessler and Bromet 2013). Average twelve-month prevalence rates range from 5.5% to 5.9% (Bromet et al, 2011).

Social-demographic factors such as sex, age, and marital status are associated with depression (Kessler and Bromet 2013). Women typically have a two-fold higher risk of MDD compared to men (Van de Velde et al, 2010). The typical age of onset of depression is in the early to mid twenties (Kessler and Bromet 2013) and prevalence decreases with age (Andrade et al, 2003). Being separated or divorced predicts significantly higher rates of major depression compared to being currently married.
Box I. Diagnostic Criteria for Major Depressive Disorder [DSM-5]

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 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 attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, 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 worthlessness 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 cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A–C represent a major depressive episode (MDE).

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizoaffective disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

(Andrade et al, 2003). Moreover, MDD has a high comorbidity with anxiety disorders (Lamers et al, 2012; Zimmerman et al, 2014). Current and life-time comorbidity rates between MDD and anxiety disorders range from 40-80%. Comorbidity of anxiety and MDD associates with a specific pattern of vulnerability, such as childhood trauma, neuroticism, severity and duration of symptoms (Lamers et al, 2012).
**Course of depression**

The course of MDD is very heterogeneous, ranging from a single-episode, through remission followed by relapse (or recovery by recurrence), to a chronic course. Frank et al. (1991) have provided some criteria for defining depressive course (Table 1). The DSM-5 (American Psychiatric Association, 2013) defines remission as a period of two or more months free of symptoms, or with only one or two symptoms less than to a mild degree. Chronic depression is defined as a continuous depressed mood (for most of the day, for more days than not) lasting for more than two years.

**Table 1. Definitions of depressive course**

<table>
<thead>
<tr>
<th>Key Terms</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Episode</td>
<td>Defined as having a certain number of symptoms for a certain period of time, fully symptomatic.</td>
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<tr>
<td>Remission</td>
<td>Partial remission: the individual is no longer fully symptomatic, but displays more than minimal symptoms. Full remission: a brief period (2–8 weeks), where the individual is asymptomatic, with no more than the presence of minimal symptoms.</td>
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<td>Response</td>
<td>A partial or full remission due to a treatment intervention</td>
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<tr>
<td>Recovery</td>
<td>Defined as a full remission, symptom free for a certain length of time (&gt; 8 weeks). It denotes a recovery from an episode.</td>
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<td>Relapse</td>
<td>An early return of symptoms following a positive response, meeting full syndrome criteria that occurs during the period of remission</td>
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<tr>
<td>Recurrence</td>
<td>Refers to a new episode, which can only occur during/following a recovery</td>
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Represented from Richards (2011); Original data from Frank et al. (1991).

Longitudinal clinical studies have suggested that more than 50% of patients with an MDE (see Box I) recover within one year (Barkow et al, 2003; Eaton et al, 2008) and that the substantial proportion of those who do not recover have a higher chance of developing a chronic course (Lamers et al, 2012). Moreover, recurrence is very common in patients with MDD even after recovery, with most of them showing recurrence within five years after reaching recovery and with recurrence rate increasing over time (Keller et al, 2007). Life-time prevalence is almost three times higher than the 12-month prevalence, suggesting that at least one-third to one-half of MDD individuals experience recurrence in a given year (Kessler and Bromet 2013). Recurrence rates over 15 years in clinical samples have been estimated at 85% and in the general population at 35% (Hardeveld et al, 2010). Clinical factors such as previous episodes of MDD and residual symptoms are more important to predict recurrence than are demographic factors (Hardeveld et al, 2010). In addition, more
than 10% of MDD patients develop a chronic course (Eaton et al, 2008; Gotlib and Hammen 2008). Comorbidity with other disorders and the presence of certain symptoms such as severe fatigue, loss of interest, insomnia, suicidal thoughts and physical symptoms are predictive of a chronic course of depression (Barkow et al, 2003; Gilchrist and Gunn 2007).

Although descriptions of depressive course are provided by Frank et al. (1991) and the DSM-5, they are based on observation of behaviors and experiences and not necessarily relevant to biological abnormalities. It is still not clear why some MDD patients recover, while others experience an enduring unfavorable course. Identifying neural markers of the natural course of depression would facilitate early detection and intervention in order to minimize cumulative effects, thus preventing relapse or an enduring course of depression (Clark et al, 2009).

**Suicidal behavior in depression**

As mentioned above, certain symptoms such as suicidality could predict an unfavorable course in depression. The suicide rate is almost eight times higher in people with mood disorders than in the general population (Bostwick and Pankratz 2014). More than half of depressed patients express suicidal ideas and one-third of patients with suicidal ideas progress to commit a suicidal act (Kessler et al, 1999; Nock et al, 2008). Despite the high correlation between MDD and suicide, some depressive patients develop suicidal behaviors, while others do not. Moreover, Aleman and Denys (2014) proposed defining suicidality as a distinct disorder, because it can occur independently and may not be responsive to effective treatment of depressive symptoms. However, it remains unclear whether suicidality can be viewed as a distinct disorder in terms of neurobiological dysfunction as well. Therefore, investigating the neural substrate that is specific for suicidality in depression may help to further differentiate the distinct mechanism of suicidality from depression.

**Neural models in affective psychopathology**

In recent decades, studies of emotional and cognitive processing in depression have provided a body of evidence regarding the behavioral and neural bases of emotional and cognitive processing disturbances. The most consistent finding is the presence of a cognitive emotional bias, represented by enhanced attention and memory for negative emotional information and diminished attention/memory for positive emotional information (Beck 2008; Disner et al, 2011; Gotlib and Joormann 2010; Leppänen 2006). Biases in attention and memory may have some consequences such
as inflexible appraisals, which hamper the selection of deliberate reappraisals to regulate emotions (Siemer and Reisenzein 2007). In this section, I will introduce some important neuroanatomical models proposed to explain the affective disturbances observed in depression (See Box II).

**BOX II. Neurobiological Models of Psychiatric Disorders**

A cognitive-neurobiological model proposed by Disner (2011) in an attempt to integrate the cognitive model of depression (Beck, 1967; Beck *et al.*, 2002) with more recent structural and functional neuroimaging findings, suggests that a specific neural substrate underlies biases in perception, attention and memory in depression. In this model, two compartments of processing are involved: a bottom-up (limbic-cortical) pathway that starts from hyper-responsivity in the limbic system (especially in amygdala) and continues through the subgenual part of the anterior cingulate cortex (ACC), caudate, putamen, nucleus accumbens and hippocampus to the prefrontal (cortical) regions (PFC). A top-down (cortical-limbic) pathway begins with reduced activation of prefrontal cognitive control areas and proceeds to inhibit the top-down control through thalamus and ACC to subcortical regions. The bottom-up pathway is unrestrained by top-down cognitive control, which may enhance the cognitive biases and prolong the depressive course.

This limbic-cortical inhibition model is a refinement of at least two other previous neuroanatomical models on depressive phenomenology proposed by Mayberg (1997) and Phillips *et al.* (2003). In Mayberg’s model, the dorsal neocortical system (dorsolateral PFC, hippocampus) mediating the sensory-cognitive aspect of MDD and ventral subcortical system (amygdala, insula, ventral striatum, thalamus and subgenual ACC) mediating vegetative and somatic aspect of MDD are proposed. Additionally, a regulatory hub (rostral cingulate) is highlighted to connect these two systems.

The model developed by Phillips *et al.* (2003) aimed to illustrate disturbances in emotional processing in a variety of psychiatry disorders. This model proposes that enhanced bottom-up regulation from a ventral system (amygdala, insula, ventrolateral PFC, ventral striatum) and weak top-down regulation from a dorsal system (dorsolateral PFC, dorsomedial PFC, ACC and hippocampus) are prominent features in MDD, which leads to abnormal appraisal of negative incoming information underlying depressed mood and anhedonia, which further reinforces the cognitive bias and perpetuate depression.

Moreover, this model suggests that, in schizophrenia, the pattern of structural and functional neural abnormalities in the ventral system may cause deficient emotion identification, and subsequent interpretation of all information as threatening, thereby result in specific negative and positive symptoms including flat emotion, anhedonia, persecutory delusions, and impaired social function. These maladaptive processes and
Continued BOX II.

negative symptoms might be maintained by abnormalities within the dorsal system, involved in reasoning, contextual processing, and effortful regulation of affective states. In contrast, the pattern of abnormalities in the ventral system in bipolar disorder has been posited to be associated with oversensitivity to emotional information and a disturbance to effectively regulate emotion, thus further resulting in certain manic and depressive symptoms, such as mood fluctuation, emotional burden, and distractibility.

Unlike the cyclical limbic-cortical inhibition models mentioned above, a recent neural model of negative bias in depression proposed a unidirectional pattern of neural substrates: signals from the limbic areas (amygdala and dorsal ACC) fail to project to the upward cortical-striatal-pallidal-thalamic circuit, leading to under-responsiveness to negative stimuli in the dorsal areas (dorsal striatum and dorsolateral PFC) (Hamilton, J.P. 2012). Furthermore, a temporal profile of affective processing in depression is suggested by this ascending trajectory, which implies that emotional significance is firstly registered as a sensory signal in the limbic system, and then proceeds through a higher-level upward circuit to the cognitive control cortical system for further interpretation and appraisal.

Aim and outline of this thesis

Current diagnoses in clinical psychiatry are based on clusters of symptoms and clinical course but virtually lack relevant biological measurements (Phillips 2012). Therefore, the application of basic and clinical neuroscience research for identifying pathophysiological biomarkers has been highlighted in the development of the recent released DSM-5 in order to facilitate early detection and effective diagnosis of psychiatric disorders (Charney et al, 2002). As one of the most important neuroimaging measures, fMRI examines a proxy measure of neural activity (i.e. changes in blood oxygen level-dependent or BOLD signal) under certain task requirements targeting different cognitive processes. It has been widely used to investigate the neural basis of cognitive and affective abnormalities in clinical populations, which might constitute potentially useful neural markers. However, there are still some remaining questions to be addressed.

Memory biases have been associated with depression and have been shown to be predictive of depressive course (Johnson et al, 2007). However, the current models on depression (See box II) are mostly focused on the neural correlates of processing
negative stimuli, but do not consider a bias for positive stimuli. Importantly, studies have found that the cognitive performance during processing of positive information was improved after using anti-depressants (Geschwind et al., 2011; Harmer et al., 2009; Norbury et al., 2009) and processing of positive information was predictive of treatment response (Geschwind et al., 2011), which implies an approach to identify neural markers of depressive course during processing of both positive and negative stimuli. Moreover, neuroimaging studies using fMRI have consistently indicated the importance of neural mechanisms for predicting remission following treatment, including morphology and functioning of the frontal regions (Heller et al., 2013; Langenecker et al., 2007; Ritchey et al., 2011), and limbic regions (Frodl et al., 2004; Fu et al., 2013; Langenecker et al., 2007). Although treatment studies could establish the effectiveness of a medication at various stages of depression, it is important to understand the natural course of depression because it is more akin to the every-day experience of patients and clinicians, and thus of ecological validity. In addition, a naturalistic prospective investigation could elucidate the neurocognitive mechanisms predicting long-term episodic stages of depression (Frodl et al., 2008) and facilitate early detection and intervention to minimize cumulative effects (Clark et al., 2009).

Therefore, in chapter 2, using a cross-sectional prospective design, we aimed to investigate the relationship between regional brain activation during both positive and negative word encoding and recognition related to the naturalistic course of depression.

As a key factor for the development and maintenance of MDD (Disner et al., 2011; Leppänen 2006), a mood-congruent memory bias has been shown in both depressed and remitted MDD patients. Despite that mood-congruent and mood-incongruent information have been shown to activate distinct areas during encoding and recognition (Fitzgerald et al., 2011; Van Wingen et al., 2010), it is unclear whether the limbic-cortical dysregulations proposed in these models represent stable abnormalities in depression, or are subject to changes in clinical state. Moreover, although Mayberg’s model describes the unique pattern of changes in brain activation with different treatments, no study has investigated how the brain changes within a naturalistic course of depression. Therefore in chapter 3, we reported a longitudinal fMRI study of emotional memory processing to clarify whether abnormal activation progresses further as a function of depressive load or may serve as state-dependent biomarkers of MDD course.

Structural and functional abnormalities during affective processing are associated with specific symptoms in psychiatric disorders in previous models (See Box II). However, the symptom specificity has not been thoroughly studied in
depression so far. Suicidal behavior is a common symptom in psychiatric disorders, especially in mood disorders such as MDD (Bernal et al, 2007; Haukka et al, 2008; Hawton and van Heeringen 2009; Nock et al, 2009). Similar to MDD patients in general, suicidal patients show abnormalities in emotion processing and cognitive control (Jollant et al, 2011). However, not all MDD patients show signs of suicidal ideation and attempts, and it is difficult to identify whether subjects with suicidal ideation with a diagnosis of MDD go on to make suicide plans or attempts. Elucidating the neurobiological factors related to suicidality (ideation or attempts) would not only help to identify biomarkers for development of suicidal behavior, but would provide valuable information for clinicians that guide assessment and treatment of depressive individuals with suicidal ideation. To this end, in chapter 4, we examined distinct mechanisms of emotion processing (emotional faces task) and executive functioning (Tower of London) at different stages of suicidality in depressed patients in order to identify the distinct mechanisms of suicidality.

As a core vulnerability factor in many psychiatric disorders, emotion dysregulation has been reported in both patients with bipolar disorder and schizophrenia, although strategies and underlying mechanisms may differ. Hypofrontality has consistently been found in SZ patients (Morris et al, 2012; van der Meer et al, 2014), suggestive of a failure to engage frontal regions during emotion down-regulation. In contrast, bipolar disorder has been associated with hyperfrontality (Morris et al, 2012) as well as hypofrontality (Townsend et al, 2013) during the down-regulation of negative emotions. Although these appear to indicate distinct patterns of brain activation during emotional control, it is unclear whether inefficient regulation in bipolar patients are due to the disability to perpetuate the initial frontal engagement during the whole process of effortful regulation, or due to a failure to engage frontal regulatory areas per se. Similarly, whether frontal control deficits are an early, late or constant characteristic in schizophrenia patients is unknown. The temporal feature from Hamilton’s model (See Box II) may be disrupted in depressed patients, leading to and a failure of reappraisal of negative information and a sustained negative bias. Hence, in chapter 5, we investigated the temporal profile of brain activation underlying cognitive emotion regulation (reappraisal) in patients with bipolar disorder and schizophrenia, which would be essential to understand how emotion dysregulation affects the distinct psychopathology of these two mental disorders.
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Functional neuroimaging of major depressive disorder: a meta-analysis and


