Chapter 9

General Discussion
9. GENERAL DISCUSSION

The aim of this thesis was to examine whether cognitive and vascular risk factors for depression were associated with the neural and clinical expressions of depression, and whether depression subgroups would show stronger associations than depression as unitary construct. The following paragraphs give a short overview of the main results.

First, the neural correlates of emotional processing abnormalities in depressed patients were examined. Chapter two addressed emotional valence in a meta-analysis, and showed that emotional brain circuits showed altered activation patterns at multiple processing nodes, previously implicated in emotional appraisal, monitoring and generating the bodily emotional response. Limbic brain areas (appraisal and response) were overactive for negative emotional cues, but underactive for positive emotional cues. In contrast, frontal areas (monitoring) were underactive for negative emotional cues, but overactive for positive emotional cues. Chapter three showed in an empirical MRI patient study (DIP) that self-evaluative processing modulates activation abnormalities as well, but in a very specific place: the dorsomedial prefrontal cortex. No circuit-level abnormalities were found. Thus, both valence and self-relatedness of emotional cues modulated activation abnormalities in depression.

Next, neural correlates of cognitive and vascular risk factors for depression were examined in the NESDA MRI cohort. Both cognitive and vascular risk was found to modulate alterations in emotional brain circuits. In chapter four, cognitive vulnerability was related to activation in limbic areas (appraisal and response) in depressed and non-depressed participants. Participants with high vulnerability but without psychiatric diagnosis showed surplus frontoparietal (monitoring) activation. In chapter five, comorbidity of depression and hypertension was associated with smaller gray matter volumes in mid and anterior cingulate cortex. These areas are involved in generating the bodily emotional response. Remarkably, depression was not associated with smaller gray matter volumes in participants without hypertension. In the chapters four and five, stronger effects were found for depression subgroups with the respective risk factors than for depression diagnosis or for depression severity.

Finally, it was examined whether cognitive and vascular risk factors are associated with the clinical expression of depression in epidemiological studies (MIND-IT, NESDA, INSTEL). Both types of risk factor were associated with cognitive symptom
levels, although in opposite directions. In chapter six, depression after myocardial infarction (vascular risk factor) was characterized by less cognitive symptoms, and a higher age of onset compared to depression in mental health care. However, the group differences in symptom profile were explained by differences in age of depression onset. In chapter seven, cognitive vulnerability was prospectively associated with higher cognitive symptom levels, and the interaction between cognitive vulnerability and life stress was stronger for cognitive than for somatic symptoms. Moreover, depression course predicted long-term cognitive vulnerability levels in primary care patients in chapter eight. Patients with an unfavorable course after enhanced treatment showed highest cognitive vulnerability levels after one year. Thus, vascular and cognitive risk factors explain at least some of the heterogeneity in the clinical presentation of depression.

9.1. The emotional brain in depression

Over time, the search for the emotional brain has expanded from a search for specialized brain areas to a search for interacting brain networks. The results presented in this thesis fit well into this trend. The frontolimbic system has been identified in the literature as a constellation of brain areas that are involved in emotional processing and show altered activation patterns in depressed patients. The literature frequently described nodes at the amygdala, anterior cingulate, ventro- and dorsolateral prefrontal cortex (Disner et al., 2011; Leppanen, 2003; Phillips et al., 2003). The work presented in this thesis confirms the role of these areas, and provides more insight into the functional implications of the alterations.

The results in chapter two of largely similar circuitry for negative and positive emotional cues were striking, given the stark difference in valence. It is, however, increasingly being acknowledged that the amygdala can be activated by a wide range of emotional stimuli, including stimuli that are generally viewed as positive (e.g., happy faces). This led to the hypothesis for the amygdala as relevance detector in the brain (Sander et al., 2003). In depressed patients, amygdala hyperactivation has been observed for negative emotional cues. In contrast, for positive emotional cues, the amygdala is less active (chapter two). Also, self-evaluation of emotional cues did not elicit any activation differences in the amygdala (chapter three). An interesting hypothesis in line with the hypothesized role as “relevance detector” is that a shift in amygdala responsiveness away
from positive and toward negative cues induces a corresponding shift in the allocation of attention, which drives real-life perception of the environment.

Whereas the amygdala initially received most research attention, the work presented in this thesis most consistently identifies the anterior cingulate cortex as deviant in depression (in chapters two - five). It is important to note that the amygdala and anterior cingulate cortex are both part of the salience network, which also includes the fronto-insular cortex (Seeley et al., 2007; Hamilton et al., 2012). Nodes in all of these structures showed higher activation in depressed patients for negative cues and lower activation for positive cues in chapter two. Therefore, this pattern of activation alterations may apply to the entire salience network. However, this hypothesis should be confirmed with a network analysis approach.

No network-level activation or connectivity abnormalities were found during self-reflection task performance in depressed patients, whereas self-reflection did target the networks of interest (chapter three). Connectivity alterations may be dependent on task execution, whereby emotional tasks might be most sensitive for detecting salience abnormalities, external orienting tasks for detecting default mode abnormalities, and cognition-emotion paradigms for detecting cognitive control abnormalities. More research is needed to link resting state alterations to specific cognitive processes, and to identify important nodes such as the dorsal nexus (Sheline et al., 2010).

9.2. Vascular vulnerability in depression

There is a bidirectional association between (cardio)vascular disease and depression. There may be causal influences in both directions, and in addition shared risk factors play a role. Therefore, a comorbid vascular disease and depression subgroup is influenced by many factors, and the stage of vascular pathology is likely to be important. More specifically, in a hypertension subgroup, vascular disease might be in such an early stage that the contribution of depression to vascular disease is larger than the contribution from vascular disease to depression. In a myocardial infarction subgroup, the high number of first depression onsets suggests that the vascular disease has a fair influence on depression.

The vascular depression hypothesis is focused on the direction of association from vascular diseases to depression. It selectively identifies patients with late-onset
depression or a worsening of depression course after vascular disease onset, and the concept is mostly supported by research into white matter hyperintensities (Taylor et al., 2013). Chapter five shows volumetric reductions of gray matter in a vascular depression subgroup, in a very early stage of vascular disease. These reductions likely reflect a sum of stress reactivity predisposition, and acquired damage attributable to stress and hypertension. The findings make an important contribution to the vascular depression literature because they implicate gray matter, and suggest that the complexity of bidirectional associations and shared risk factors in vascular depression may partly have a neural basis.

The chapters examining a vascular depression subgroup described convergent and divergent findings regarding depression phenomenology. Consistent with the vascular depression hypothesis, both studies found that comorbid vascular disease was associated with higher age at depression onset. However, the study into comorbid hypertension found an increased severity of depression whereas the study into comorbid myocardial infarction found a decreased severity in the vascular disease subgroup. NESDA sampling was aimed at including depressed patients, and therefore hypertension patients with undiagnosed depression were likely underrepresented in the study, which may explain part of this difference.

Although it was previously suggested that illness factors contribute to high somatic symptom levels in myocardial infarction patients, no such elevation was found in chapter six or seven. Elevated somatic symptom levels have been found in comparison with a population sample, suggesting that the effect is restricted to the lower range of symptoms (Thombs, 2010). Furthermore, it should be noted that measures of depressive symptoms may differ in their sensitivity to detect the somatic symptom elevations associated with illness factors (Delisle et al., 2012). The relative excess of depression onsets after myocardial infarction is remarkable. Whereas neurobiological factors might be involved, the results are also consistent with the concept of MI as a very severe stressor, capable of eliciting depression in low-vulnerable individuals. Future research should focus on the interplay of vulnerability for stress and vascular disease across disease stages.
9.3. **Cognitive vulnerability in depression**

In this thesis all the relevant chapters (e.g., 5,7,8) confirmed a bidirectional association between cognitive vulnerability levels and depressive symptoms. Cognitive vulnerability was high in individuals with recent life stress, and in individuals with a diagnosis of depression compared to individuals without these characteristics. In addition, a prospective study confirmed that cognitive vulnerability predicted higher depressive symptoms in depressed and non-depressed participants. On the other hand, alleviation of depressive symptoms was accompanied by a reduction in cognitive vulnerability, whereas an unfavorable course of depression predicted higher long-term cognitive vulnerability levels. There is an increasing interest in the bidirectional relationship between cognitive vulnerability and depression (see for instance Lagrange et al., 2011; Calvete et al., 2013). The most important and positive implication of these results is that cognitive vulnerability is not entirely fixed, and possibly can be manipulated in either way.

Part of the observed brain activation abnormalities in depressed patients were linearly associated with cognitive vulnerability. Of note, these associations were only found for negative emotional cues. The nodes that were associated with cognitive vulnerability in both depressed and non-depressed participants belonged to the salience network. Salience network dysfunction in emotional processing might thus constitute a trait that predisposes to affective psychopathology (for more recent evidence in this direction implicating the amygdala node of the salience network, see Swartz et al., 2015). In participants without a psychiatric diagnosis, high cognitive vulnerability levels were associated with increased activation in nodes from the frontoparietal control network. One might speculate that non-depressed participants with high cognitive vulnerability levels recruit this network to counterbalance increased salience activation. Tentatively connecting this to cognitive theory, increased salience activation might reflect schema activation, whereas increased control activation might reflect schema suppression (see Farb et al., 2015 for an interesting novel perspective towards vulnerability processes over the course of disorder that is largely supported by the findings presented in this thesis).

The results for cognitive vulnerability as a stress sensitivity measure were mixed. In chapter 4, recent life stress was not associated with brain activation abnormalities during emotional processing, not even in individuals with high cognitive vulnerability levels. However, in this chapter vulnerability was measured after stress experience. The
vulnerable individuals in which stress activated a negative processing schema, likely also self-reported higher cognitive vulnerability. In contrast, a prospective design demonstrated that negative life events were predictive of depressive symptoms in vulnerable individuals, but not at all in individuals with low cognitive vulnerability. These findings strengthen the conceptualization of cognitive vulnerability as a stress sensitivity marker (Hammen, 2015). Remarkably, a multitude of cognitive vulnerability dimensions were prospectively associated with depressive symptom levels in individuals that were non-depressed and did not experience stress, and thus cognitive vulnerability may convey more risk than merely stress sensitivity.

The value of cognitive theory has been challenged, because opponents have reasoned that cognitive vulnerability is not truly a trait vulnerability factor and argued that remitted patients are hard to distinguish from never-depressed individuals. Cognitive reactivity has been put forward as a more trait-like and more informative vulnerability marker (Segal et al., 2006). In chapters four and seven, the results provide just as much support for the hopelessness model of cognitive vulnerability (highlighting experienced control and negative self-associations) as for cognitive reactivity as vulnerability marker. The combined results from chapters four, seven and eight support a state-trait vulnerability model that is characterized by absolute changes in cognitive vulnerability associated with disease state, but also relative stability over long periods of time. Conceptually, the observed increases in cognitive vulnerability after depression onset could be interpreted as reflecting schema activation and kindling processes. The negative schemata might stay fully activated and cognitive vulnerability may become integral to depression over time (Van der Zanden et al., 2014). More research is needed into the factors that contribute to stability and change of cognitive vulnerability (for an overview and discussion of this topic, see Evraire et al., 2014). The results in chapter eight suggest that although cognitive vulnerability is difficult to manipulate, it could potentially be a valuable treatment target.

9.4. Critical considerations

Several limitations should be acknowledged for the evaluation of the results presented in this thesis. Conceptually, it is difficult to draw a line between a vulnerability factor that is activated by stress or negative mood states and a symptom of depression. Excessive
feelings of worthlessness and guilt have been studied as examples of negative self-associations, but as cognitive depression symptoms as well. The fact that residual symptoms are a powerful predictor for the relapse and recurrence of depression complicate research into cognitive vulnerability. During analysis, it was observed (chapter five, data not shown) that the predictive power of cognitive symptoms dramatically decreased by including cognitive vulnerability dimensions as predictors, indicating that partly the same variation between individuals is captured. The clinical and research value of the cognitive vulnerability concept lies in the theoretical rationale and in the description of a verifiable, quantifiable, and modifiable process. Therapeutic benefits may be more readily obtained by interventions directed at a more nuanced and complete interpretation of events, than at sadness per se.

Several important risk factors for depression were not studied in this thesis, such as neuroticism. This personality trait reflects emotional instability, and the tendency to experience negative affect and arousal quickly, and decrease it slowly (Ormel et al., 2013). Vulnerability / stress reaction is one of the subcomponents of neuroticism, largely corresponding to cognitive vulnerability. Neuroticism is a more distal and encompassing risk factor for depression than cognitive vulnerability, and has been shown to be less specific for depressive disorders. Moreover, neuroticism is less explicit with regard to the process that causes dysfunction. On the other end of the spectrum, rumination is considered to be a subcomponent of cognitive vulnerability, and also of self- and emotion-regulation. It is generally defined as the process of repetitively thinking about distress, negative affect, and unattained goals when facing a stressor, in a more state-like fashion than cognitive vulnerability (Smith & Alloy, 2009). Accordingly, it is more proximal to depression than cognitive vulnerability. Despite the conceptual differences, many of the findings for the neural and clinical expression of depression could also apply to neuroticism and rumination.

The studied cognitive/affective and somatic symptom dimensions are rooted in the cognitive model, and, though well-researched, their validity is mainly based on theoretical grounds. Although the symptom dimensions identified in the NESDA study roughly correspond to the traditional cognitive and somatic symptom dimensions (Beck et al., 1996), a substantial anxiety facet is present in the IDS somatic symptom dimension that was not previously recognized (e.g. arousal, panic, and phobic symptoms). This
makes the results of chapter six and seven difficult to compare. Data-driven analyses confirmed symptom profiles that are characterized by low cognitive symptoms in chapter six. However, data-driven techniques have more consistently identified low-severity classes that are additionally differentiated by separate core symptoms, which may suit profiles from chapter six as well (Van Loo et al., 2012). The inconsistencies in dimensions and profiles across samples and measures suggest that vulnerability factors may have more promise for subtyping depression.

Finally, there are several methodological limitations to the work presented in this thesis. The main limitation is that the majority of chapters cover cross-sectional research designs, and therefore no firm conclusions regarding directionality and etiology can be drawn from these chapters. Further, MRI research is often characterized by low power, and consequently there is a large risk of false negatives in MRI studies (Button et al., 2013). The stringent criteria for multiple comparison corrections that are typically employed in the field contribute to this problem. The inconsistent results reported by studies in the meta-analysis (chapter two) suggest that the effect sizes for activation abnormalities in depressed patients may be smaller than generally assumed. Chapter three showed few regional activation alterations in depressed patients for a self-reflection task, in a relatively small sample. Results were very consistent with previous findings, and reducing the number of comparisons with network-based analyses did not change the results. Still, larger samples and meta-analyses may implicate more nodes than currently established.

9.5. Future directions for etiological and clinical research

With regard to vascular depression, one interesting avenue for further research lies in delineating the pathways to depression in more detail. The neural correlates of vascular depression might comprise gray and white matter abnormalities in brain areas regulating emotional and stress responses, possibly depending on the stage of vascular disease (white matter more prominent in a later disease stage). It would be interesting to study how these structural abnormalities relate to alterations in brain activation and physiological responses to emotional cues. So far, very few studies have addressed these questions in cardiovascular disease patients. Furthermore, it would be interesting to study biomarkers predicting cognitive and somatic symptom dimensions in vascular disease
patients. Inflammatory cytokines may be more strongly related to depression in late-life and vascular depression subgroups - particularly driven by somatic symptoms (Poole et al., 2011; Naudé et al., 2013; 2014).

With regard to the cognitive vulnerability concept, the ecological validity of measures could be improved by measuring interpretations in real-life situations rather than self-reported general response tendencies. To establish a trait-like negative cognitive style, a multitude of measurements is required. This could be achieved with a daily diary study. A major advantage of this design is that it allows investigation of changes within the individual during stress exposure, rather than examining differences between individuals that did or did not experience stress. This would allow research into the temporal dynamics of schema activation, by investigating the interplay between event appraisals and negative affect. As a result, individual differences in the content of dysfunctional appraisals may become apparent. This offers new perspectives for personalized identification of treatment targets, and evaluation of treatment mechanisms at a very high temporal resolution.

The work presented in this thesis took the approach to relate vulnerability factors for depression to neuroimaging measures and symptom dimensions. The somatic symptom dimension in particular did not discriminate well between the subgroups. It may therefore be valuable to reverse the research framework and reconstruct symptom dimensions on the basis of associations with neural correlates and vulnerability factors (for an example of this dimensional approach, see Oathes et al., 2015). If we conduct a thought experiment and imagine that in 1980 the DSM III committee decided not to include anhedonia as a (core) symptom of depression, would we replicate the present-day findings that emotional valence modulates activation abnormalities in depression? Would a primary deficiency in activation and connectivity in the salience network result in a different symptom profile than a primary dysfunction of the regulatory role of the cognitive control network? Importantly, such an approach would allow us to re-evaluate and adjust the diagnostic criteria, with the option to replace the least informative symptoms with more informative ones.

It is interesting that evidence-based treatments for depression such as antidepressant medication and cognitive behavioral therapy reverse many of the activation abnormalities observed in chapter two (Anthes, 2014; Ma, 2015). This has been
proposed to be a very early mechanism of action (Harmer et al., 2009). Meta-analysis has shown that increased activation in limbic areas (amygdala, striatum, insula and anterior cingulate cortex) before treatment commences predicts worse response to treatment (Fu et al., 2013). This is reminiscent of cognitive vulnerability; reduced by effective treatment, yet predictive of poor outcomes. The subgenual anterior cingulate cortex finding is close to the node that showed an association with cognitive vulnerability in chapter four. In late-life and late-onset depression, white matter hyperintensities have been associated with poor prognosis of depression. It would be of interest to study the effects of treatment for depression on brain imaging measures in cognitive and vascular depression subgroups, as well as study whether the inclusion of vulnerability and brain imaging measures might improve prediction models for treatment unresponsiveness (see Schmaal et al., 2014 for an example of a multifactorial clinical prediction model in NESDA, which is observational in nature).

One potential consequence of the multifactorial etiology and heterogeneous conceptualization of depression, is that it is impossible to find a treatment that works for each and every depressed individual. Antidepressant medication (e.g., SSRI/SNRI/TCA) and cognitive behavioral therapy are evidence-based treatments that will alleviate symptoms in around two thirds of depressed patients (Rush et al., 2006; also see Van der Lem et al., 2012). It might not be a realistic goal to search for a new treatment that will outperform established treatments in the aggregate of depressed patients. However, it could be a realistic goal to characterize subgroups of patients that do not respond to traditional treatment options, and identify novel treatment targets. The alternative treatments might have clinically relevant effects if they are beneficial only in the treatment-resistant subgroup.

Cognitive vulnerability was found to be associated with higher depression severity, comorbid anxiety and was higher after non-response to treatment in this thesis. In the literature, it has also been associated with an early depression onset, recurrence and chronicity of depression, and suicidality (Lau et al., 2004). Thus, targeting cognitive vulnerability might be worthwhile to reduce the burden of disease associated with depression. Several treatment alternatives offer potential for further investigation. The first is CBT optimized by diary study feedback. Other options in accordance with the imaging results presented in chapters two and four are attentional bias modification
(Browning et al., 2010), as well as transcranial magnetic stimulation at the left dorsolateral prefrontal cortex (Fox et al., 2013). The treatment objective would be to increase cognitive control over salience network nodes. The effects of treatment could be evaluated by comparing resting state scans before and after treatment, and activation and connectivity analyses to data from an emotion regulation task performed after treatment. The results from these analyses could be correlated with baseline levels and post-treatment reductions in cognitive vulnerability.

9.6. Concluding remarks

This thesis set out to examine whether cognitive and vascular vulnerability factors for depression are associated with heterogeneity in the neural and clinical expression of depression. The work from this thesis confirmed the important role of frontolimbic circuits in depression. The anterior cingulate was most consistently identified as node of deviance, and presumably plays an important role in the dysregulation of extended frontolimbic circuitry. Subgroups of depressed patients with high vascular and cognitive vulnerability for depression showed more pronounced neural abnormalities than the group of depressed patients as a whole. These results suggested that brain structural and activation abnormalities possibly signal individual differences in stress sensitivity. Finally, cognitive vulnerability and depressive symptoms were shown to adversely impact each other. Cognitive vulnerability may thus be a valuable target for interventions, which achieve beneficial outcomes by improving cognitive control over negative emotions.