Views on vulnerability

*Cognitive and neurobiological vulnerability during remission of Major Depressive Disorder*

Figueroa, C.A.

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Chapter 9

General Discussion
The aim of this thesis was to study cognitive and neurobiological vulnerability factors that are present when patients are in remission of recurrent MDD and could lead to a higher susceptibility of developing future depressive episodes. More specifically, we focused on dysfunctional attitudes, cognitive reactivity, rumination and changes in neural networks during rest. We also conducted an updated meta-analysis of resting-state functional connectivity (FC) aberrations in acute MDD using improved meta-analytic methods for fMRI analysis.

In this final chapter, we will first summarize the main results of this thesis and reflect on our findings. We will then discuss methodological considerations, describe clinical implications, and provide recommendations for future studies.

Summary of Main Findings

In Part 1 we explained the importance of studying vulnerability for new depressive episodes in patients remitted from recurrent MDD: the high rate of recurrences contributes greatly to the extensive burden of MDD. Discovering cognitive and neurobiological vulnerability factors and their interactions in patients who are remitted from recurrent MDD is a first step to 1) identify markers for recurrence risk, and 2) help to develop or alter preventative interventions for recurrence in MDD patients.

In Chapter 2 we described the protocol of the DELTA-Neuroimaging study. Baseline data from this study is used for Chapters 3, 6, 7 and 8. We studied remitted recurrent MDD-patients who were at high risk for recurrence because they had experienced two or more depressive episodes in their lifetime (median of four earlier episodes). These patients had not been using psychotropic medication (i.e. antidepressants) for more than 8 weeks.

Part 2 investigated the cognitive perspective of MDD vulnerability. In Chapter 3, we compared two measures of cognitive reactivity (CR): the change in Dysfunctional Attitude Scale (DAS) scores version A/B after sad mood-induction (DAS-change); and the self-report Leiden Index of Depression Sensitivity-Revised (LEIDS-R). We found that DAS-change was larger in remitted MDD patients when subjects filled in the DAS-B version before the mood-induction, followed by the DAS-A afterwards; compared to the group that filled in DAS-A before and DAS-B afterwards. This effect was opposite in controls. Further, the LEIDS-R and DAS-change scores were only correlated for participants that received the B-A version order. In contrast to DAS-change, scores on the other CR measure, LEIDS-R, were higher in remitted MDD than in controls. We conclude that the LEIDS-R is a more valid measure to assess depression vulnerability.

Next, in Chapter 4, we found that a higher LEIDS score predicted recurrence within a 3.5 year follow up in a sample of 116 remitted recurrent MDD patients (hazard ratio for a 20-point increase on the LEIDS = 1.46). Specifically, we found that every 20-point increase on this CR scale, with has
a total of 136 points, increased the risk of recurrence over the 3.5-year period with 10-15%. This is after correcting for two well established recurrence risk factors: previous depressive episodes and residual depressive symptoms. In contrast, the level of unprimed DAS-scores, before mood-induction, did not predict time to recurrence. We conclude that CR (measured by the LEIDS) might be a more important recurrent MDD vulnerability factor than unprimed dysfunctional attitudes. Further, particularly the rumination subscale appeared to be a stronger predictor of recurrence than the total LEIDS score. Certain sub-aspects of CR, including rumination, might thus be particularly strong recurrence predictors.

In Part 3 we examined the neurobiological perspective of MDD vulnerability.

In Chapter 5 we meta-analysed evidence of studies using resting-state seed-based FC to compare neural networks in patients with acute MDD to healthy controls. We used improved meta-analytic methods: Seed-based D-mapping (SDM) with Meta-analysis of Non Statistically-significant Unreported Effects (MetaNSUE). We did not find differences between MDD patients and controls in connectivity strength within- or between the Default Mode-, Fronto-Parietal-, Ventral Attention-, Limbic-, Somato Sensory- and Visual Network. For individual seed-regions, we found increased connectivity between Default Mode areas in MDD-patients, but these findings did not survive statistical corrections for conducting a large number of tests. In a conceptual stepwise confirmation analysis, we showed that the null results of our study (which conflicted with previous meta-analytical work) might be explained by our improved method. We conclude that our null results might relate to differences between fMRI studies, including heterogeneous patient populations and variability in preprocessing techniques and analysis methods.

In Chapter 6 we calculated Default Mode Network (DMN) dominance over the Task Positive Network during resting state. We compared remitted recurrent MDD patients to healthy controls and examined associations of DMN dominance with self-report rumination. Contrary to our expectations, DMN dominance was not increased in remitted recurrent MDD patients compared to controls. Further, higher DMN dominance did not correlate with greater levels of rumination in remitted patients. We conclude that higher DMN dominance and its association with rumination is not present in remitted MDD patients at high risk for recurrence.

In Chapter 7, we examined resting-state FC of the DMN in remitted recurrent MDD patients and controls after a neutral and a sad mood-induction. After sad compared to neutral mood, remitted-MDD patients did not show an increase in FC between the posterior DMN and the hippocampus, whereas controls did. Lower posterior-DMN-hippocampus connectivity was associated with higher cognitive reactivity and rumination, which we interpreted as a measure of recurrence vulnerability. We conclude that aberrant pDMN-hippocampus connectivity and its associations with CR and rumination is a neural vulnerability marker in remitted MDD.
In Chapter 8 we calculated dynamic FC using a recently developed method: the Leading Eigenvector Dynamics Analysis (LEiDA) in remitted recurrent MDD and controls. This method has the advantage of measuring fluctuations in FC at every time-point and can detect when the same underlying FC-states occur again. We observed that remitted MDD-patients showed a decreased ability to access an FC-state consisting of frontal areas, Default Mode, Salience and striatum areas. Previous studies have shown that these areas are important for cognitive control, self-referential processing, salience detection and emotional processing respectively. Not only did this FC-state appear less and lasted shorter during the scan, but remitted patients were also less likely to switch to a smaller FC-state consisting of prefrontal areas. Interestingly, the duration of this state increased more in remitted MDD than in controls after a sad mood induction. We interpret this as a compensatory mechanism of remitted individuals to regulate brain activity in sad mood. We conclude that a decreased ability to access a clinically relevant control network during neutral mood might be a neural vulnerability factor during remission of MDD.

In summary, the results presented in Chapter 3, 4, 7 and 8 provide support for remaining cognitive and neural network abnormalities in patients remitted from recurrent MDD. In contrast, in Chapter 6 we did not find evidence for Default Mode Network dominance as a neural vulnerability factor in remitted MDD. Further unexpectedly, in our meta-analysis in Chapter 5 we did not observe overall resting-state neural network abnormalities in acute MDD.

Interpretation of findings
Below we will provide a further interpretation of our main findings following the cognitive and neurobiological perspective. We will then discuss methodological considerations and clinical implications and provide recommendations for future studies.

Part 2. Cognitive vulnerability
Overall, our results show support for remaining cognitive vulnerability in patients with remitted recurrent MDD (who were not taking antidepressants) and for predictive relationships between these cognitive factors and recurrence. Our findings also point to methodological caveats of measuring this vulnerability.

Dysfunctional attitudes after sad mood-induction
The differential activation hypothesis proposes that dysfunctional attitudes are latent when patients are in remission of depression, but that they can become reactivated after stress and/or low mood. This activation process is conceptualized as cognitive reactivity (CR).2,3 Contrary to this theory, in Chapter 3 we observed that changes in the dysfunctional attitude scores (DAS-change) after mood induction, were low and comparable for remitted recurrent MDD and controls.
Further analyses however indicated that this measurement might not be representative of true CR levels: DAS-change scores depended on the version order of the DAS administration (A-B or B-A). We only observed higher CR scores for remitted MDD who had the B-A version order. We explain this in Chapter 3.

We think that DAS-change after mood-induction, which has been the most common measurement to assess CR so far, might not be a valid operationalization of the CR construct.

**LEIDS scores**

Scores on a different more recent measure of CR, the Leiden Index of Depression Sensitivity-Revised (LEIDS-R) were indeed higher in remitted recurrent MDD patients than in controls. Further, the magnitude of the difference in scores between the groups was high (large effect-size). Importantly, the methodological issues that affect DAS-change do not apply to this questionnaire: it only has one version and does not require a complicated mood-induction procedure.

Besides capturing cross-sectional differences between remitted MDD and controls, in Chapter 4 we observed that the LEIDS score (a previous version of the LEIDS-R) predicted recurrence over 3.5 years in a sample of 116 remitted patients. In contrast to the LEIDS, unprimed DAS scores did not predict time to recurrence. This suggests that higher dysfunctional cognitions, without priming of mood state, are less relevant for recurrence vulnerability than a rise in negative cognitive processes after sadness or stress. The latter is captured by the LEIDS.

Nevertheless, evidence for CR’s association with recurrence is still mixed: some previous studies showed that high CR, measured by the DAS-change, predicted quicker recurrence. Instead, other studies (that also used DAS-change) did not find evidence for its predictive value.

To our knowledge, this thesis is so far the only research to report CR as a recurrence marker using the LEIDS instead of DAS-change. We speculate that the methodological limitations of DAS-change as described before might in part explain why some studies that used A-B in randomized order or only A-B administration did not find an association between DAS-change and recurrence.

In addition to methodological differences, conceptual features of the two CR assessments might also partly account for the observed differences between the two measures. First, the LEIDS-R asks participants to respond to a series of statements whilst imagining how they would react when they feel down or sad, e.g. “When I feel down, I am more bothered by perfectionism”. Instead, DAS-change assesses self-reported change in dysfunctional thoughts, e.g. “I feel like a failure every time I make a mistake”, after an actual priming of sad mood. Also, relative to the DAS, the LEIDS-R also measures reactivity by cognitive processes, for example by rumination or avoidance included in LEIDS-R subscales. Thought processes, or operations, such as rumination are thought to aggravate low mood and further increase negative cognitions. In contrast, DAS-change

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i We found higher CR scores in remitted MDD for the B-A administration.
only measures a rise in plain negative cognitions (the cognitive products of the operations). It does not capture the processes that maintain the vicious cycles of low mood and negative thoughts.11

Taken together, our results indicate that on a cognitive level the risk of recurrence might stem from an easier activation of negative cognitive processes in the face of sadness or stressful triggers (i.e. higher CR). These cognitive-affective processes might be more important recurrence vulnerability factors than a higher level of plain dysfunctional cognitions.

Part 3. Neurobiological vulnerability

Globally, results of this thesis support the proposition that aberrations in resting-state neural networks are a neurobiological vulnerability in patients with remitted recurrent MDD. However, some of our findings did not follow our initial hypotheses. This complicates the interpretation of our results. We will reflect on this below.

Resting-state neural network aberrations in acute MDD

Besides studying patients remitted from MDD, here we also conducted a meta-analysis on resting-state abnormalities in acute MDD. We did this because findings in individual studies showed contradicting results. This interferes with the ability to make general conclusions about MDD as a disorder of neural network aberrations. We did not include remitted MDD in this analysis because there were not enough studies that examined remitted patients to properly conduct a meta-analysis. In contrast to neurobiological models of MDD12,13 and a previous meta-analysis14 our meta-analysis of seed-based resting-state FC in Chapter 5 showed no consistent resting-state neural network differences between acute MDD patients (n=1230) and healthy controls (n=1220).

Importantly, we used an improved meta-analytic approach that tackled methodological problems, which removed substantial biases that were introduced by previous approaches. Namely, we combined Seed-based D-mapping (SDM) with Meta-analysis of Non Statistically-significant Unreported Effects (MetaNSUE). In Chapter 5 we explain the main improvements of this method. Further, we show how addressing the methodological problems of earlier meta-analysis methods reduces the number of significant findings.

Our null results could mean that, unexpectedly, there are no functional differences in the brain during rest in patients with MDD compared to non-depressed controls. Alternatively, if there are abnormalities, seed-based resting-state fMRI might not be a suitable measure to elucidate these differences. However, we believe that more likely explanations of our results are underlying heterogeneity of examined patient populations and differences between methods of fMRI studies. Before we can make correct inferences about the importance of resting-state fMRI for the pathophysiology of MDD, methodological and clinical differences between fMRI studies need to be addressed in future studies.

Of note, in the rest of the chapters of this thesis we eliminated some clinical heterogeneity (though not all, see methodological reflections) by studying an MDD sub-type: patients who
are remitted from recurrent depression (two or more previous episodes) and are not taking antidepressants.

**Default Mode Network dominance**

In Chapter 6 we examined dominance of the Default Mode Network (DMN) over the Task Positive Network and its association with rumination in remitted recurrent MDD and controls.\(^{15}\) In contrast to the hypothesis of Marchetti and colleagues,\(^ {16}\) the mean level of DMN dominance was not higher in remitted MDD patients (around 50% in both groups). Further, DMN dominance was not correlated with levels of rumination (measured by the Ruminative Response Scale).

One previous study by Hamilton and colleagues\(^ {15}\) used this particular metric, but in acutely depressed patients. Interestingly, the authors also did not observe differences in *mean* levels of DMN dominance between patients with acute MDD and controls. Instead, they found that a greater level of DMN dominance was associated with higher levels of maladaptive, depressive rumination and lower levels of adaptive, reflective rumination in MDD patients. Because DMN dominance was associated with maladaptive rumination in MDD but not in controls, the authors suggested that DMN dominance might comprise different psychological functions in these groups. In other words, although the relative dominance of the DMN might not differ between acutely depressed patients and controls it might only be related to rumination in MDD patients. Instead, in controls dominance of the DMN might be associated with other (more neutral or positive) thought processes.

There are a few possible explanations of our null results: first, the association of DMN dominance with rumination represents a state factor of MDD in contrast to a recurrent MDD trait or vulnerability factor; second, the association between DMN dominance and rumination is only observed after a priming of a sad mood, when ruminative thinking patterns (presumably) become more activated in remitted MDD. Third, this methodological approach, in which it is assumed that the brain exists only of two networks dominating in activity over time (DMN and TPN), is a gross simplification of brain activity during resting-state. Therefore it might not be a sensitive measure to detect subtle differences between remitted patients and non-depressed controls.

**The effect of sad mood-induction**

In Chapter 7 we examined the effect of a sad mood-induction on resting-state FC of the DMN in remitted recurrent MDD. To maximize the effect of the induction, we asked participants to re-experience one of the saddest events in their lifetime in as much detail as possible before they participated in a resting-state scan (see Chapter 7 for more details). In controls, but not in remitted MDD, we observed increased posterior DMN (pDMN) connectivity to a cluster consisting mostly of the hippocampus after sad vs. neutral mood-induction. Moreover, we found that less pDMN-hippocampus connectivity was associated with significantly higher levels of CR, rumination and trend-wise with DAS scores. We interpreted these findings as being related to the phenomenon of overgeneral autobiographical memory processing in remitted MDD. This indicates that a failure to
increase connectivity between the DMN and the hippocampus after sad autobiographical recall is a neural vulnerability factor. We hypothesize that through its associations with cognitive reactivity and rumination, this neural vulnerability after sad autobiographical recall might predispose patients to new depressive episodes.

Interestingly, in this analysis we did not observe any differences between patients and controls during neutral mood. Instead, we found that the effect of a sad mood-induction on functional connectivity of the DMN was not the same for remitted-MDD and controls (significant group x mood-induction interaction). This suggests that aberrations in neural networks are subtle in remitted patients compared to controls and need to be triggered by a sad mood. The latter is in line with the differential activation hypothesis. Unexpectedly, we did not observe increased FC between the DMN and hippocampus after sad mood-induction, which was reported by a previous study of Zamoscik and colleagues. Instead, there was no change in remitted MDD patients in connectivity between the DMN and hippocampus, whereas there was an increase in controls.

The effect of sad mood or stress on neural networks might depend on what type of paradigm is used. For instance, Zamoscik and colleagues measured FC-differences during sad mood-induction whereas we examined FC after the procedure (i.e. while recovering from a sad mood-induction). Various stages of measuring FC (i.e. during or after the mood-induction) might have different effects on neural network connectivity. For instance, negative thoughts might be quickly triggered after sadness or stress, whereas it might take longer for reactive processes (as over general memory) to become activated.

Dynamic Functional Connectivity

In Chapter 8, we used a novel method, the Leading Eigenvector Dynamics Analysis, to examine dynamic FC. We found that remitted MDD patients showed a lower probability and duration of an FC-state consisting of frontal networks (FN), the Default Mode Network (DMN), the striatum (Str) and the Salience Network (SN) (which we refer to as the FN-DMN-Str-SN state). Importantly, this FC-state includes clinically relevant areas; involved in regulating cognitive control and attention, self-referential processing, salience-detection and emotion processing, respectively. Based on the functions that have been associated with these networks, our findings might reflect reduced cognitive control to disengage attention from negative self-referential information and effectively process emotions in remitted MDD. In support of this, attentional control difficulties have been linked before to deficiency in cognitive control networks and with disturbances in the DMN and cortico-limbic pathways (see Marchetti and colleagues and de Raedt and colleagues for reviews). Therefore, we hypothesize that our results indicate a decreased ability to access a clinically relevant control network involved in the interplay between external attention and self-referential/emotional processing in remitted MDD patients.

Interestingly, in contrast to results of our static FC analysis (and the differential activation hypothesis) here we observed larger differences between remitted MDD and controls in neutral mood. Moreover, after a sad mood-induction we found a larger increase in duration of the FN-
DMN-Str-SN state in remitted MDD-patients compared to never-depressed controls, which did not change in duration of this FC-state.

We speculate that remitted individuals attempt to increase the activation of this FC-state during sad mood and recovery from sad mood as a mechanism to regulate brain activity. This supports our hypothesis that this FC-state is relevant for processes associated with mood and emotions in remitted MDD. Although we did not test this, we hypothesize that during daily stressors it might take more effort for remitted patients than for controls to access this FC-state and to effectively deal with stress and negative thoughts. Therefore, a decreased ability to access this state in neutral mood could be associated with instability of affect, defects in cognitive control, and eventually the occurrence of and/or time to recurrence. These questions remain to be investigated in future analyses.

Importantly, to our knowledge this is the first study that examined the effect of a mood manipulation on dynamic FC states. Because this is such a new field, it should be further examined how sad mood or stress changes dynamic FC, and also what the differential effect of a mood-induction is on static FC.

Of note, comparing the results of this dynamic FC analysis to static FC is challenging. After all, these methods examine different FC features. Although this is not yet clear because it is still a new method, the LEIIDA might allow the detection of distinct and perhaps more transient FC characteristics. As a first illustration of this assertion, the differences between remitted MDD patients and controls in occurrence and time spent in the FN-DMN-Str-SN state are in the order of several percentage-points (4.6% compared to 7.2%) and several seconds (3.8 compared to 5.1 out of 420 seconds). It seems likely that when FC is averaged over larger time periods (5-10 minutes in the case of static FC), the small differences in occurrence and duration of (clinically relevant) FC-states are also averaged; and will therefore not be detected. We know that FC of the brain likely changes over the course of seconds. LEIIDA captures these changes over time. Though this is not well known yet, it has been suggested that dynamic FC changes might better explain a subject’s flexible adaptive behaviour and thoughts to their environment.

Within the follow up study of DELTA neuroimaging, we will determine the stability of these effects across different phases of illness and assess the predictive value of these neural factors for recurrence of depression. Further, follow up analyses could assess more thoroughly whether neurobiological recurrence risk factors are indeed reflective of certain cognitive/psychological risk profiles in remitted MDD.

Methodological Reflections
We already discussed several methodological problems of the individual studies in this thesis. In the following section we elaborate on some more generic methodological considerations.
Measuring Cognitive Reactivity

Considering the methodological problems of the DAS-change measurement as discussed in Chapter 3 we advise against the use of mood-inductions with A/B DAS administration in research and clinical settings. In contrast to DAS-change, studies have consistently reported that LEIDS-R scores were higher in remitted-MDD than in controls (i.e. more than 10 studies, see Solis and colleagues\(^9\) for an overview). LEIDS-R based CR might therefore be a more valid vulnerability measure. Future studies should confirm if the LEIDS-(R) and its subscales is a stable predictor of time to recurrence.

Although there is substantial evidence that the LEIDS-R is a clinically relevant construct, we cannot be fully certain that it measures CR or some other psychological construct. One possible way to strengthen the proposition that the LEIDS-R is a measure of CR is to examine its associations with actual fluctuations in participants’ thoughts and mood after daily negative events. This might for example be assessed by ecological momentary assessments.\(^23\) In support of this, an unpublished study showed that LEIDS-R scores indeed correlate with changes in negative thoughts after stressful events during the day.\(^24\)

Measuring resting-state FC

fMRI can provide valuable information about spontaneous activity of functional networks without having to use complex task paradigms. However, a limitation inherent to resting-state fMRI is that actual thoughts and psychological processes that take place during the scan cannot be assessed. A prerequisite of the resting-state is that subjects are free to let their minds wander without being instructed to engage in a task or certain behaviour. This means that subjects could be engaged in various thought processes during the scan. Additionally, retrospective recall of thoughts in itself is susceptible to bias. Therefore, we cannot make precise inferences about what psychological mechanisms directly cause the observed connectivity group difference in Chapter 6 and 7 of this thesis.

With regards to resting-state analysis procedures, there is a wealth of methods available to analyse resting-state FC and there is no real consensus on the ‘best’ preprocessing and analysis pipelines. Importantly, the use of different thresholding procedures, preprocessing methods, software packages and even operating systems\(^25\) might all lead to substantial differences in results.\(^26,27\) To illustrate, Carp and colleagues (2012) found that there were almost 7000 different analysis pipelines available to analyse an fMRI data-set. Importantly, these different pipelines led to a great degree of flexibility in sizes and location of observed effects.\(^26\) In the case of potential ‘cherry picking’, i.e. reporting only preprocessing and analysis pipelines that lead to significant findings, this high analytical flexibility can result in an increased rate of false positive findings and non-reproducibility of results.\(^28\)

Considering the above, the diversity in preprocessing techniques and analysis methods of studies included in our meta-analysis in Chapter 5 could be a source of bias that contributes to the observed inconsistencies between studies. Unfortunately, in our meta-analysis we were unable
to reliably correct for variation in preprocessing and analysis techniques because the included studies used a many different steps and methods.

Examining remitted recurrent MDD patients

A strength of our study is that we included participants in stable remission and free of antidepressants. This allowed us to examine recurrent MDD vulnerability factors that are unaffected by the symptomatology of acute MDD and effects of medication (antidepressants in particular). Further, by including never disordered controls without a familial history of MDD we maximized the contrast between groups for the detection of vulnerability factors.

However, our design does not allow us to test whether the observed vulnerability factors were already present before a first episode of depression or are specific to patients with (remitted) recurrent MDD. We did not compare our sample to patients with a first lifetime depressive episode and patients with recurrent MDD when they are depressed. This type of contrast would have provided us more certainty about the specificity of the studied factors to remitted recurrent MDD. However, the unique repeated measures design of DELTA-neuroimaging, in which patients are tested once more when they experience a recurrence of depression, will ultimately allow us to further differentiate between specific trait and state factors of recurrent MDD.

Additionally, in our sample there will be patients who are more resilient and more vulnerable to a quicker recurrence within our study population. This possible source of heterogeneity might in part explain why the neurobiological differences in remitted MDD compared to controls were subtle in Chapter 7 and 8, or even absent in Chapter 6.

The follow-up component of the DELTA-neuroimaging will allow us to further explore whether the identified neural vulnerability markers are also predictors of recurrence risk.

Clinical implications

In Chapter 3 and 4, we showed that high CR measured with the LEIDS is a recurrent MDD vulnerability factor. This cognitive mechanism could be a meaningful target for recurrence prevention. Though this needs to be confirmed by future work, Mindfulness Based Cognitive Therapy (MBCT) might be particularly useful for reducing CR. MBCT is a psychological therapy that has shown promise for recurrence prevention. In essence, MBCT makes participants become aware of thoughts that arise in reaction to sad mood, and teaches subjects to respond to these thoughts in a non-judgemental way. Thereby, this treatment helps patients to halt or disengage from negative cognitive patterns before the CR process becomes fully activated.

There is also substantial evidence that preventive Cognitive Behavioural Therapy (CBT) is effective in reducing long-term recurrence (see Bockting and colleagues for an overview). A recent study directly compared CBT to MBCT and found that both were equally effective in reducing relapse rates within 24 months in 166 patients remitted from MDD. Regardless of the
treatment received, in both groups the patients that were resilient to recurrence showed higher levels of ‘decentering’, which is defined as the ability to view one’s thoughts and emotions as temporary products of the mind as opposed to accurate views of the self and the world. Thus, these treatments might particularly act by teaching metacognitive skills: skills that help individuals to regulate their negative thinking patterns.

We think that psychological treatments such as CBT or MBCT could further increase their effectiveness by focussing more specifically on targeting rumination and teaching metacognitive skills. This is corroborated by recent meta-analytical evidence showing that rumination focussed CBT (RF-CBT) is particularly effective in reducing rumination. Further, changes in rumination mediated symptom improvement.

Interestingly, in this thesis the LEIDS rumination subscale, which includes items such as - “When I feel sad, I spend more time thinking about the possible causes of my moods” - was a stronger predictor of recurrence than the total LEIDS score. We hypothesize that on a cognitive level, the activation of cycles of rumination (e.g. negative thoughts and negative mood) might be more important for the risk of recurrence than the precise content of maladaptive cognitions.

This also is in line with the metacognitive model of depression. This model proposes that MDD results from a problem of “overthinking”: inflexible and maladaptive response patterns as rumination and worry in response to cognitive events. It has been proposed that rumination is a maladaptive coping strategy, meaning that individuals (falsely) believe that repeatedly analysing their negative thoughts; feelings and failures might solve their perceived problems. In this regard, it might be the case that our finding of a reduced ability to access a clinically relevant control network in remitted MDD patients (Chapter 8) reflects a decreased use of these metacognitive skills to control negative self-referential processes. However, this remains speculative. Unfortunately, we did not use a questionnaire in our study that specifically measured metacognitive skills.

Furthermore, as we discussed in Chapter 6, a failure to recruit the hippocampus after sad autobiographical recall in remitted recurrent MDD possibly reflects overgeneral autobiographical memory. Rumination might be an underlying mechanisms of overgeneral memory and in turn, overgeneral memory might increase ruminative thoughts. Treatments that focus on rumination might thereby also target this vulnerability mechanism.

Recommendations for future studies

**Decreasing heterogeneity of investigated patient populations**

The heterogeneity of characteristics of MDD patients in research is very likely one of the reasons for the lack of the identification of reliable MDD biomarkers so far. Supportive of this, besides differences in antidepressant use, comorbidity and clinical course between patients (as discussed in Chapter 5) the diagnosis of MDD itself, as defined by the different versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM), is very heterogeneous. For instance, in current
clinical practice, it could be the case that two people who do not have a single symptom in common share a diagnosis of MDD. We propose that this clinical heterogeneity, in combination with the analytical flexibility of fMRI research that we described before, could have contributed to the absence in resting-state FC differences between MDD and controls in Chapter 5.

As a strategy to reduce clinical heterogeneity in MDD research, scientists have argued to step away from the sole comparison of groups based on DSM criteria and depression sum scores (i.e. comparing MDD patients to healthy controls). Instead, participants could also be studied based on dimensions of behavioural measures (such as cognitive control and emotion regulation) combined with neurobiological measures (e.g. fMRI and genetics). This could allow the detection of meaningful subtypes of depression, which might differ in neurobiology, treatment response and clinical course.

Interestingly, some advances using fMRI have recently been made to use a bottom-up approach for MDD diagnosis based on biological substrates. Drysdale and colleagues (2017) found that different patterns of dysfunctional FC involving fronto-striatal and limbic networks could subdivide MDD patients (n=1118) into subtypes of depression. These subtypes were partly associated with clinical symptom profiles (including anhedonia and anxiety). Importantly, this study showed a high classification accuracy (82–93%). Further, in an analysis of a subset of patients (n=154) these subtypes predicted response to treatment by Transcranial Magnetic Stimulation (TMS) of the dorsomedial prefrontal cortex. In detail, a subtype with reduced connectivity in fronto-amygdalar networks and high anxiety responded most strongly to TMS. These results provide some, albeit preliminary, evidence for the future use of fMRI to further delineate clinically and biologically meaningful MDD subtypes.

Combining various perspectives to assess recurrence vulnerability

The research presented in this thesis is limited to specific factors of cognitive and neurobiological vulnerability. It should be noted that many other factors, out of the scope of this thesis, might also show associations with risk of recurrence for patients recovered from MDD. For instance, attentional biases and affective instability have also been proposed as cognitive vulnerability factors of recurrent MDD. Similarly, besides aberrations in resting-state fMRI, a number of studies have also identified changes in brain activity during cognitive, emotional and reward-related processing tasks in remitted MDD. Recurrence risk of remitted patients is likely multifactorial and derives from various, interacting domains, including neurobiological, genetic, social and psychological factors, some of which are mentioned above.

As we described in Chapter 2, in the DELTA-neuroimaging study we employ a wide range of neuropsychological and cognitive task outside of- and within- the MRI scanner. Analyses that are being conducted or planned at the moment incorporate some of the measures mentioned above from this rich data set. The overarching conclusions from the DELTA-neuroimaging study will ultimately give us a more comprehensive and integrative overview of various domains of vulnerability for recurrence.
**Employing best practices in neuroimaging research**

Given the abundance of analytical pipelines for fMRI, a first best practice is the transparent and complete reporting of all analysis steps of a study. If applicable, this should also include information on the use of pipelines that were unsuccessful before obtaining the current results. Such a practice would allow readers to critically evaluate the strengths and limitations of the research and to more easily replicate the methods. Secondly, some generally established recommendations on analysis and preprocessing methods and avoiding statistical pitfalls could be determined and used as guides for researchers. And thirdly, tools that can assess risk of bias of individual resting-state fMRI studies should be developed to judge the methodological quality of studies.

Finally, the majority of neuroimaging meta-analyses that have been published up to now have calculated differences based on reported coordinates of peak effects and t/z scores. However, this results in a substantial loss of information compared to using the full statistical information from the between group statistical maps. We would urge more authors to make these maps available and/or share raw data of scans for the purpose of future meta-analyses and big data initiatives. This might lead to quicker discoveries and greater advances in cognitive neuroscience and psychiatry research.

**Examine the potential of FC markers for treatment**

Though still at its infancy, another interesting area of future research is the potential for FC markers as targets for treatments. For instance, it has been suggested that dynamic FC might be particularly susceptible to therapeutical manipulation. In this domain there might be a role for real time fMRI neurofeedback, a treatment aimed at teaching individuals to regulate activity of a specific region or connectivity within a network. The ultimate aim of this treatment would be to induce changes in psychological states. For instance, though this has not been examined before, it might be possible for subjects to increase the occurrence or duration of specific networks, or alter switching dynamics between networks. Similarly, it should be examined whether various forms of psychotherapy as MBCT and CBT or antidepressants might be able to modify the occurrence and persistence of certain FC-states.

**Conclusion**

The present thesis shows that patients remitted from depression, and at high risk for recurrence, exhibit multiple cognitive and neural disturbances. On a cognitive level, we can generally conclude that the activation of dysfunctional thinking processes in response to sadness or stress, captured by cognitive reactivity and rumination, are important vulnerability factors for recurrent MDD. Furthermore, cognitive reactivity and associated processes like rumination might represent a more prominent vulnerability than higher plain dysfunctional cognitions. Importantly, we show that the measurement of cognitive reactivity by the LEIDS can predict recurrence without a complex mood-induction procedure.
With regards to neurobiological vulnerability factors, we provide evidence that the DMN, Salience Network, Frontal network and striatum might all play important roles in neural vulnerability when patients are in remission of MDD. Furthermore, we show associations between neural aberrations in the DMN after a sad autobiographical mood-induction and rumination and cognitive reactivity. This suggests that this neural factor might be a marker of recurrence vulnerability. Combined, we conclude that on a psychological level, alterations in these neural networks and the interplay between them might reflect difficulty to disengage from negative self-referential information, including rumination. Future research should investigate whether the neural vulnerability factors that we identified indeed underpin cognitive risk factors and might predispose remitted patients to new MDD episodes.
REFERENCES


