Views on vulnerability

Cognitive and neurobiological vulnerability during remission of Major Depressive Disorder
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General Introduction
The impact of depression

Imagine feeling down most of the day, every day. Imagine that the things you once enjoyed no longer give you any pleasure. Imagine that just trying to get through the day feels too overwhelming a challenge. For periods lasting for weeks, months or even years, you cannot summon up any hope of ever feeling better. For people suffering from Major Depressive Disorder (MDD), a severe mental health disorder, struggles of this nature are a bitter daily reality.

Mental health disorders are very common and account for about a third of the world’s disability due to illness amongst adults. Of all mental illnesses, Major Depressive Disorder (MDD) is ranked as the single largest contributor to global disability; affecting approximately 4.5% of the world population in 2015.

Depression, with its core symptoms of sad mood and anhedonia - the (near-complete) absence of enjoyment, motivation, and interest - has a profound impact on almost all aspects of everyday functioning for the afflicted. What’s more, it also affects the people, both adults and children, close to them. Besides the psychological suffering and impairments, MDD is associated with disturbances in inter-personal relationships, decreased marital satisfaction and substantial impairments at work. These include decreased productivity, increased risk of absenteeism, lower income and increased risk of unemployment.

Additionally, depression has been linked to a range of poor physical health outcomes: patients with MDD have worse health for various diseases including diabetes, cardiovascular disease and HIV. Moreover, MDD has also been associated with an increased mortality risk. Furthermore, from an economic perspective, the cost of MDD is very high. In the Netherlands, the direct costs, including healthcare and non-medical services, were estimated at 1.6 billion a year in 2015 making depression one of the most expensive diseases. The indirect costs, related to patients’ loss of productivity, were estimated at 1.8 billion a year. A recent study predicted that both direct and indirect costs of all mental disorders including MDD will double by 2030.

Considering the large individual, inter-personal, societal and economic impact of MDD as described above, it is no exaggeration to consider this disease as one of the greatest global health problems of our time.

Risk of developing MDD episodes

In the general worldwide population, the estimated lifetime prevalence of developing MDD is ~11%. For some individuals, the lifetime risk of ever developing MDD is higher than for others, i.e. they are a-priori more vulnerable. For instance, parental depression is one of the strongest risk factors for developing MDD. Having a parent with depression has been associated with a three-fold increase in the risk of developing a depressive episode over a 30-year follow up.

In cases where an individual has been depressed once, the probability of developing a new episode (recurrence) rises above 40% with higher rates in clinical samples than in community samples. The risk of recurrences increases with each new depressive episode.
After 3 previous episodes, it may rise to 90% after 10-15 years in clinical samples. This means that in a substantial subset of patients, MDD is characterized by a recurrent course in which episodes of remission and recurrence follow each other intermittently. On average, individuals with recurrent depression will have four separate depressive episodes during their lifetime. This group of recurrent MDD patients is the population we focus on in this thesis.

In order to prevent recurrence, pharmacotherapy is often continued in current clinical practice after (partial) remission from an acute episode. However, antidepressants have many side effects, which is one of the reasons that they are discontinued prematurely. Problematically, after discontinuation of antidepressants there is no prolonged protective effect against recurrence. For cognitive behavioural therapy (CBT), a psychological treatment that challenges negative thought patterns, the long-term outcomes are more positive. For instance, recent meta-analysed evidence from 16 trials showed that CBT led to a reduction in recurrence rates that was maintained for 2 to 6 years after CBT (typically 10 to 20 sessions). Unfortunately, even with treatments that are effective, the rates of new episodes remains substantial.

Further, at the individual level it is not clear what the best prevention treatments are. Predictors of recurrence

Though there is a substantial body of literature on possible risk factors for recurrence, the research outcomes are not entirely consistent. Among clinical factors, the number of previous episodes is one of the most consistent predictors for recurrence. Additionally, the remaining level of residual depressive symptoms when patients are in remission is a quite consistent risk-factor. There is also evidence that psychological and neurobiological aberrations might be associated with increased risk for recurrence in remitted patients. However, there is still a gap in knowledge when it comes to the importance of cognitive and neurobiological substrates for recurrence vulnerability. Additionally, recurrence risk is commonly assessed from a separate viewpoint of either neurobiological abnormalities (e.g. brain structure/function) or psychological abnormalities (e.g. dysfunctional thinking patterns/emotional processing). The two perspectives are not often combined.

In this thesis we will study and integrate both perspectives: cognitive psychology and neurobiology. Combining both the cognitive perspective and the neurobiological perspective may lead to a clearer and more complete overview of interacting factors of recurrence vulnerability. Ultimately, such an integrative approach might improve the development of more effective interventions and facilitate the exploration into (bio)-markers as predictors of successful treatment. This more holistic approach has the final aim to tailor interventions to an individual’s underlying processes of recurrence vulnerability.

Below we will describe current theories of psychological and neurobiological vulnerability in remitted depression and outline the research questions and aims of the separate chapters of this thesis.
Cognitive perspective of MDD vulnerability

Depressive schemas and negative thinking styles have been proposed as key aspects of cognitive vulnerability in MDD. They are expected to continuously be important vulnerability features during remission of MDD. Important concepts herein are Dysfunctional Attitudes, Cognitive Reactivity and Rumination. We will elaborate on these below:

I. Dysfunctional Attitudes

The first and still one of the most influential models of cognitive vulnerability, Beck’s cognitive model of depression, proposes that the acute phase of MDD is characterized by high levels of negative beliefs about oneself, the world and the future. These so called dysfunctional attitudes or schemas comprise beliefs such as “if I fail at my work then I am a failure as a person”, or “I cannot trust other people because they might be cruel to me.” They are thought to be formed early in life as a result of negative life events or stressful circumstances. In combination with current difficult experiences they might increase the susceptibility of developing a first episode of depression. Further, according to Beck’s model, a high level of dysfunctional attitudes interferes with information processing at the level of attention, interpretation and memory.

II. Cognitive Reactivity

Theories of cognitive vulnerability propose that patients who are remitted from MDD no longer exhibit the increased levels of dysfunctional attitudes that characterize the acute phase of MDD. However, sad mood and/or mild stressors might easily re-activate dysfunctional attitudes when patients are in remission. The level of these cognitions can be measured by the self-report Dysfunctional Attitudes Scale (DAS). Cognitive reactivity (CR) refers to the process of mood-linked increases in negative cognitive patterns. According to the differential activation hypothesis, the link between negative mood and dysfunctional cognitions is established during earlier episodes of depression and strengthens with every experienced episode. In this theory, it is assumed that patients become more vulnerable to recurrence after each episode, and new episodes are triggered by progressively milder stressors. Therefore, CR has been suggested as an important factor for recurrence of MDD.

III. Rumination

Another well known cognitive vulnerability factor is rumination, defined as a repetitive trait like response style to distress. Rumination is characterized by the content of thoughts; which are related to one’s sad mood or depression. As rumination constitutes a rise in negative thinking activated by sad mood or stress, it can be considered a sub-concept of CR. During rumination, one is caught in narrowing and repeating thoughts focused on causes and consequences of sad mood or depression. Inherent to rumination is that this process tends to strengthen and reinforce itself: negative thoughts precipitate sad mood and in turn sad mood exacerbates negatives thoughts. Thus, once caught in the ruminative process, it can be very difficult to break this vicious cycle.
With respect to recurrence prediction, dysfunctional attitudes, rumination and CR have all been identified as predictors of MDD-recurrence. However, especially for rumination this has sparsely been examined. Further, for DAS and CR results as predictors are not always consistent. The studies that examined CR all used its most common measurement: a change in dysfunctional cognitions after an experimental induction of a sad mood (DAS-change). To measure DAS-change, parallel versions of the DAS (A and B) are often used. This approach is taken to avoid biased scores due to filling in the same questionnaire twice within approximately 10 minutes. However, it has been suggested that the A and B forms might not be interchangeable. This leads to unreliable change scores. Additionally, CR can also be measured by a self-report questionnaire: the Leiden Index Depression Sensitivity (LEIDS). The predictive value for recurrence of this questionnaire has not been assessed before, to our knowledge.

Neurobiological perspective of MDD vulnerability

Over the last three decades, psychiatry research has seen great advances in the study of brain activity and its changes during psychiatric disorders. Promising developments in the field of neuroscience have led Thomas Insel, the former director of a prominent federal agency for research on mental disorders - the National Institute of Mental Health - to commend that “mental disorders can be addressed as disorders of brain circuits” and “dysfunction of these circuits can be identified with the tools of clinical neuroscience”. One of these tools is functional magnetic resonance imaging (fMRI), currently one of the most commonly used neuroimaging methods. It is a non-invasive technique based on the ‘blood oxygenation level–dependent’ (BOLD) contrast that captures a local vascular effect in response to neuronal activation. Thereby, it provides an indirect measure of neural activity. The vast majority of fMRI research has focused on task-based fMRI, which examines how the brain responds to cognitive or affective tasks and how this differs in psychiatric disorders.

Mainly in the last decade, resting-state functional connectivity (rs-FC) has also become very widely employed. This is in part because it does not require any task paradigm and at the same time provides valuable information about the brain’s psychological architecture. Here, rest implies that subjects are not engaged in a task, but lie in the scanner for a period of usually 5-10 minutes with their eyes closed or while staring at a fixed point. Further, they are instructed to let their minds wander but not to fall asleep.

Rs-FC represents the level of co-activation between the functional data collected over time of anatomically separated brain regions during rest. This is believed to reflect functional communication between these regions. Importantly, differences in communication patterns, i.e. decreased or increased FC in various neural networks, have been linked to altered psychological functions that might characterize psychiatric diseases. For instance, over the last decade a growing number of studies have linked MDD to FC changes in multiple ‘resting-state networks’,
thought to be involved in cognitive and affective processing (see Mulders and colleagues\textsuperscript{59} and Kaiser and colleagues\textsuperscript{60} for a review and meta-analysis of resting-state FC aberrations, respectively).

This large body of literature on resting-state neural network aberrations increases our knowledge of MDD’s neurobiology. Nevertheless, until now we still lack clinically relevant biomarkers that can be used as reliable and valid diagnostic or prognostic tools for MDD. Further, most resting-state fMRI studies examined acutely depressed patients. Therefore, it is not well known if resting-state FC aberrations that are present during the acute phase of MDD also exist during remission of depression. If so, they might also be associated with vulnerability for recurrence.

It has been proposed that the Default Mode Network (DMN), a network that has an important role in introspective thoughts, might have a particularly important role in the pathophysiology of recurrent MDD.\textsuperscript{29}

Multiple studies have indicated that altered resting-state connectivity of the DMN, and an inability to deactivate the DMN during attentional/emotional tasks, may reflect pathological self-referential processing and increased rumination in acute MDD.\textsuperscript{29,61} Importantly, these types of DMN aberrations have not only been identified in acutely depressed subjects, but also in subjects vulnerable to MDD, including the offspring of parents with MDD.\textsuperscript{62} These findings - combined with the notion that DMN activity might be related to cognitive risk-factors for recurrence as rumination and cognitive reactivity - led Marchetti and colleagues\textsuperscript{29} to hypothesize the following: vulnerability during MDD-remission might specifically relate to dominance in activity or increased connectivity of the DMN over the ‘Task Positive Network’ (TPN) during resting-state. Here the DMN represents passive introspective attention whereas the TPN serves external awareness and cognitive effort as planning and problem solving.

More recent studies have confirmed the presence of DMN aberrations in remitted MDD patients compared to controls during tasks\textsuperscript{63,64} and resting-state.\textsuperscript{65} Reflective of cognitive reactivity, three studies that used mood-induction paradigms reported that sad mood increased connectivity or activity in DMN-areas in remitted-MDD.\textsuperscript{66-68} Further, one study showed that this increase was related to higher rumination,\textsuperscript{68} and another study found that increased DMN activity predicted recurrence.\textsuperscript{66}

However, the number of studies that examined remitted MDD is still sparse and most studies included participants on antidepressants.

During the course of this PhD project (which started in 2013) it became more apparent within the neuroimaging field that resting-state FC, which is commonly calculated as the average FC over a period of scanning (also referred to as ‘static FC’), does not remain stable during the scan. Instead, it exhibits dynamic fluctuations of connectivity patterns over time. Since the initial study that demonstrated the temporal dynamics of fMRI resting state-FC, Chang and Clover in 2010,\textsuperscript{69} a consequent body of research has started to investigate dynamic functional connectivity (dynamic FC).
In acute MDD, a number of studies have identified dynamic FC aberrations in neural networks including the DMN, the Frontoparietal network (with functions of cognitive control and attention) and the Salience Network (implicated in emotional processing and salience detection).\textsuperscript{70-72} To our knowledge, dynamic FC abnormalities remain to be assessed in remitted MDD.

**Aim of thesis**

The high risk of MDD recurrence has many consequences for individual patients, the people close to them, and society as a whole. Hence, there is a great need for a better understanding of vulnerability factors in individuals remitted from recurrent MDD. Understanding the vulnerability factors would be a first step in discovering (bio)-markers that might ultimately (1) aid the identification of markers for recurrence risk, and (2) help to develop or alter preventative interventions for recurrence in MDD patients.

The aim of this thesis is therefore to study cognitive and neurobiological vulnerability factors in remitted recurrent MDD that could contribute to a higher susceptibility of developing future depressive episodes.

In this thesis we use data of the ‘DELTA-Neuroimaging study’, a study of 69 remitted recurrent MDD-participants and 43 controls. Importantly, we aimed to maximize the contrast to detect vulnerability by comparing patients at high risk for recurrence (≥2 MDD episodes) to matched controls with no personal or familial history of MDD. These control participants are at low risk of developing any MDD episode across their lifetime.\textsuperscript{73} Further, to overcome methodological limitations of previous studies we examined patients who were not taking antidepressants for at least 4 weeks. This precludes possible confounding effects of medication on fMRI\textsuperscript{74,75} and cognitive measures.\textsuperscript{76}

Below we will outline the specific research questions of this thesis and how we use this data in each chapter:

**Research questions of this thesis**

This thesis consists of four parts. **Part 1** is a general introduction. It includes the current chapter and Chapter 2, which gives a comprehensive rationale behind studying patients remitted from depression as opposed to acutely depressed patients. We also outline the protocol of the DELTA-neuroimaging study. This cohort study examines MDD-recurrence risk at the level of symptomatology, affective neuropsychology, neural networks and endocrinology/metabolism. We use data of this study in Chapter 3, 6, 7 and 8.

Patients included in this study had not been using psychotropic medication (i.e. antidepressants) for more than eight weeks. This is important because antidepressants can confound results of resting-state functional connectivity (FC)\textsuperscript{74,75} and cognitive measures.\textsuperscript{76} As a second part of this
study (not part of this thesis) patients will also be followed up for 2.5 years to assess depressive recurrences in a longitudinal study.

In Part 2 we examine the cognitive perspective of MDD vulnerability. In Chapter 3, we first compare two measures of cognitive reactivity (CR) in remitted recurrent MDD and controls. We compare the change in Dysfunctional Attitude Scale (DAS) scores after sad mood-induction (DAS-change; the most common measurement of CR) to the self-report Leiden Index of Depression Sensitivity- Revised (LEIDS-R). We assessed DAS-change using the A and B versions of the DAS before and after mood-induction in randomized order (A-B or B-A). The LEIDS-R does not require the application of a mood-induction procedure. Instead, it asks participants how they would respond to a list of statements whilst they imagine that they are experiencing mild sadness.

Therefore we examine in this chapter whether (1) both DAS-change and the Leiden Index Depression Sensitivity-Revised (LEIDS-R) scores are higher in remitted recurrent MDD than in healthy controls, (2) if LEIDS-R and DAS-change scores are correlated and (3) if administration of the DAS A/B impacts DAS-change. We expect that both DAS-change and LEIDS-R scores are higher in remitted MDD than in controls and that these measures are correlated. Further, given previous reports that the A and B versions might not be fully interchangeable we expect that the administration of DAS A-B or B-A before and after mood-induction to influence DAS-change scores.

In Chapter 4 we examine if cognitive reactivity measured by the Leiden Index of Depression Sensitivity (LEIDS) questionnaire and unprimed dysfunctional attitudes (before a mood-induction) measured by the DAS questionnaire are predictors of time to depressive recurrence. We also analyse the predictive value of LEIDS subscales including the rumination subscale. We examine this in a cohort of 118 remitted MDD patients who were followed up for 3.5 years (a study performed prior to DELTA-neuroimaging). We expect that both higher LEIDS (including the rumination subscale) and unprimed DAS scores predict a shorter time to recurrence.

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

In Chapter 5 we conduct an updated meta-analysis of resting-state FC abnormalities in acute MDD. One of the reasons for the absence of clinically applicable resting-state fMRI derived biomarkers, is that overall, fMRI studies in depression have shown a diversity of results. That is, studies have reported findings in different regions and networks, and the same brain regions have shown conflicting effects of increased and decreased connectivity. Therefore, results of fMRI studies should be meta-analysed to gain a better overview of net connectivity differences. We could not conduct this analysis for remitted MDD because there were not enough studies available.

Unfortunately, commonly used meta-analysis methods for fMRI have important methodological limitations, particularly when applied to the most common analysis method:
‘seed based FC’. Seed-based FC measures correlations between an a-priori identified seed-region of interest with all other regions in the brain based on the time-series data of that seed-region.

To overcome the methodological problems of previous meta-analyses and provide an updated meta-analysis of resting-state seed-based FC aberrations in MDD, we used a novel meta-analytic approach: (1) Anisotropic Effect-Size Seed-based d Mapping (AES-SDM) and (2) Meta-Analysis of Studies with Non Statistically-Significant Unreported Effects (Meta-NSUE). AES-SDM is able to adequately integrate increased and decreased connectivity in the same image and allows inclusion of full, between groups, Statistical Parametric Maps (SPMs). This increases the power of the analysis. Moreover, Meta-NSUE can highlight effects that did not reach significance in the individual studies, but had an unknown specific effect-size. Neglecting these leads to biased effect-sizes. We examine intra and inter-network abnormalities and pairwise connections between individual regions.

With the findings of a previous meta-analysis on seed-based resting-state FC in mind, we expect to find large-scale differences in neural networks in MDD patients compared to controls.

In Chapter 6, we examine Marchetti and colleagues’ hypothesis of increased DMN dominance over the TPN and its association with rumination in remitted recurrent MDD. We conduct a replication of a previous study that showed a correlation between rumination and dominance of the DMN over the TPN in acute MDD patients. We test differences in levels of DMN dominance between remitted MDD and controls and correlate these scores to rumination. We expect that DMN dominance will be increased in remitted MDD relative to controls, and that greater DMN dominance is correlated with higher levels of rumination.

In Chapter 7 we examine FC during rest of the DMN in remitted MDD versus controls. We determine if deteriorations in mood lead to differential changes in neural network connectivity in these groups (in line with the differential activation hypothesis). We do this by analysing FC after a neutral and a sad mood-induction. Further, we correlate changes in DMN connectivity after sad mood-induction to self-reported rumination and CR. Considering previous evidence and theory, we expect an increase in DMN connectivity in remitted MDD compared to controls, which would further rise after a sad mood induction.

In Chapter 8, we use a recently proposed method that calculates dynamic FC. One of the most common ways to calculate dynamic FC is a ‘sliding-window analysis’. This consists of dividing the FC of the resting-state scan into multiple temporal windows, inside of which the pairwise FC of brain regions is calculated. However, the most important problem of the sliding window method is that results are strongly dependent on the chosen window length; which typically ranges from 8 to 240 seconds. At time of writing, it remains unknown what the optimal window length is. Therefore, we instead use the novel Leading Eigen Vector Dynamics analysis (LEiDA), which computes the phase coherence between bold signals at each recording frame. This method is
not affected by the methodological limitations related to window length. Using LEiDA we are able to characterize dominant FC-states of coherent activity in the brain, which emerge and dissolve during rest. We examine differences in occurrence, duration and switching profiles of these FC-states in remitted MDD patients compared to healthy controls, in both neutral and sad mood. As such, in this study, we do not constrict this analysis to one single region or network but examine characteristics of whole-brain connectivity patterns over time.

**Part 4** is a General discussion. It consists of **Chapter 9**, in which we summarize and discuss our findings, address methodological considerations, and present recommendations for future research.
REFERENCES


