Fatty acids in context

Neurometabolic perspectives on depression vulnerability

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This thesis describes our research on the role of fatty acids in depression and related psychiatric disorders. It focuses on fatty acids in their pathophysiological context, by studying the relations between fatty acid metabolism and other aspects as neuroendocrinological stress and emotional processing. In addition, it provides a clinical translation by showing ways in which fatty acids may be used to improve treatment.

This general introduction first addresses depression as an important health problem, and subsequently identifies opportunities to reduce its burden of disease. Next, the contribution of the current thesis will be explained by describing its scope, aims and outline.

**WHY DEPRESSION?**

Of all diseases that plague mankind, psychiatric disorders including depression, schizophrenia and posttraumatic stress disorder (PTSD), currently cause by far the most disability, and together with cardiovascular disease (CVD) they are also responsible for most lost life years. Among the psychiatric disorders, depression accounts for the greatest disability, being responsible for the highest burden of all diseases in high-income countries, and being expected to cause the second-highest burden worldwide in 2030. No doubt, depression is one of the largest challenges currently facing our society.

Interestingly, there is continuing debate regarding the definition of depression. Almost everybody feels down once in a while. However, within psychiatric research, depression is usually relatively strictly defined as Major Depressive Disorder (MDD), using the syndromic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association. In brief, these criteria are only fulfilled if a person experiences at least one of two core symptoms (depressed mood and anhedonia) for most of the day, almost every day for at least two consecutive weeks, with at least five symptoms in total together with additional symptoms as insomnia, weight loss, or suicidal thoughts. Importantly, in order to fulfill the criteria, these symptoms must cause clinically meaningful impairment or distress almost every day.

Even when these relatively strict criteria are being used, MDD still is a widespread mental disorder, with estimated worldwide prevalences of 4.3% annually and 11.1–14.6% during lifetime. Next to personal existential grief for patients, their families and caregivers, MDD also impacts society on a whole. Currently, MDD’s (in)direct annual excess costs constitute approximately 1% of the gross domestic product in high-income countries. Below, three main reasons for this overwhelming burden of disease will be further explained: limited efficacy of available treatment options, high recurrence rates and considerable cardiovascular comorbidity.
CAUSES OF DISEASE BURDEN FOR DEPRESSION

Limited efficacy of treatment options
Although publicly disputed every now and then, several treatments for MDD show effectiveness in large meta-analyses. Although effect sizes are modest, a wide range of psychotherapeutic (e.g. cognitive behavioral or interpersonal psychotherapy) and pharmacological [e.g. antidepressants as selective serotonin reuptake inhibitors (SSRIs)] options are available that work better than the already large placebo response.\textsuperscript{11-17}

Nonetheless, treatment is still far from ideal. For example, 30–40\% of MDD patients do not respond to currently available treatment options, and it currently takes several weeks to determine that a treatment does not work.\textsuperscript{18} Disappointingly, available treatment options did not substantially improve during the last decades. Moreover, and more alarmingly, several pharmaceutical companies have even abandoned psychiatric drug development, because of high failure rates of new compounds.\textsuperscript{19,20} While some new treatments are currently being tested, it could be seen as exemplary that hope is highest for a drug (ketamine) that has already been on the market for decades for other indications.\textsuperscript{21,22}

High recurrence rates
Another important reason for MDD’s burden is its recurrent course,\textsuperscript{6} as already indicated by Kraepelin \textit{et al.}\textsuperscript{23} and formulated by Angst \textit{et al.}:\textsuperscript{24} ‘Single episodes are extremely rare if the period of observation is significantly extended’. The incidence of recurrences\textsuperscript{*} varies depending on study-characteristics.\textsuperscript{26-28} While previously a distinct disease entity has been suggested called recurrent MDD (more related to bipolar disorder), population studies show that recurrence is generally widespread in MDD with $\geq$40–75\% lifetime recurrence in patients recovered from a first depressive episode,\textsuperscript{29-32} with even higher rates in clinical samples.\textsuperscript{23,24} In a 10-year follow-up study of a cohort of recurrent MDD-patients that experienced $\geq$2 depressive episodes in the last five years, we previously showed an overall 90.3\% recurrence-rate.\textsuperscript{25,36} During lifetime, MDD-patients are estimated to experience about five MDD-episodes on average.\textsuperscript{5,34}

For recurrence prevention, antidepressants are an effective strategy that is most often used.\textsuperscript{25,37} However, unwillingness to take these antidepressants, non-adherence and discontinuation due to adverse effects limit their applicability.\textsuperscript{28-40} In addition, antidepressant effects cease after stopping taking them. As an alternative, preventive psychotherapies have been developed (e.g. preventive cognitive therapy and mindfulness-based cognitive therapy),\textsuperscript{41-49} which seem to produce more long-lasting beneficial effects that do remain after the therapy has stopped.\textsuperscript{35,51} Nevertheless, as mentioned earlier, recurrence-rates remain substantial (e.g. $>80\%$ in our preventive naturalistic add-on preventive cognitive therapy trial).\textsuperscript{35,36,51}

\* The terms relapse and recurrence are used in the literature and defined as new MDD-episodes within or after 6 months recovery, respectively. However, empirically there is no clear evidence for this distinction. We hereafter will name both ‘recurrence’ for clarity.
Considerable cardiovascular comorbidity

Cardiovascular disease (CVD), including coronary heart disease, stroke and peripheral arterial disease, is the most frequent cause of excess mortality in patients with severe psychiatric disorders, including MDD.\textsuperscript{52,53} Patients with severe psychiatric disorders have a doubled risk of dying from CVD, especially at an earlier age.\textsuperscript{52} Traditionally, the focus has been on schizophrenia, but CVD is of equal concern for patients with MDD.\textsuperscript{52-58} For example, also MDD confers a more than doubled prospective risk of CVD comorbidity.\textsuperscript{59,60}

On top of great personal suffering, CVD comorbidity in psychiatric disorders causes substantial excess societal costs. Patients with high CVD risk have a more complex presentation of their psychiatric disorders, including greater burden of disease, less favorable response to treatment and an adverse course and outcome.\textsuperscript{52,53} Moreover, CVD treatment in patients with psychiatric disorders has been shown to account for up to 70\% of their total treatment costs.\textsuperscript{61} Pathophysiological mechanisms underlying the mutual association between psychiatric disorders and CVD are complex and still largely unknown.

RESEARCH OPPORTUNITIES

Several research opportunities can be thought of that may lead to improved treatment strategies, reduction of MDD recurrence and prevention of CVD comorbidity. Thereby, these research opportunities may ultimately contribute to relieving MDD’s overwhelming burden of disease. Here we will discuss several possibilities to improve disease understanding, personalize treatment and prognosis, and augment treatment response.

Improve disease understanding

Although large advances have been made in clinical neuroscience in the last decade, patients with psychiatric disorders have largely yet to benefit from them. Nevertheless, the idea remains that if we would better understand MDD pathophysiology, we may discover new treatment targets. While we have come a long way since Hippocrates’ four humor theory, most drugs used nowadays for psychiatric disorders like MDD have been found by serendipity and were later, after further experimental research, based on one theory: the monoamine hypothesis. This hypothesis - derived from unexpected effects on mood of drugs that later proved to modulate neurotransmitters - focused on disturbances in the synaptic neurotransmission of monoamines as serotonin, dopamine and noradrenaline.\textsuperscript{62} While this monoamine hypothesis certainly has advanced the field of biological psychiatry and our understanding of MDD, it is increasingly being recognized that it does only tell a small part of the complex pathophysiological story.\textsuperscript{63,64}

More recent hypotheses suggest broader metabolic alterations that extend beyond monoamine metabolism.\textsuperscript{64-70} In general, based on genetic, biomarker and imaging studies, complex interacting metabolic pathways are being hypothesized to partly underlie - and be connected with - observed coexistent biological stress, inflammatory, and brain network alterations. However, the more detailed interconnectedness and relevance of these pathways have yet to be unraveled. Below, we will describe several strategies that could aid in improving disease understanding, including reducing heterogeneity (cross-sectionally and longitudinally) and applying a transdiagnostic approach.
Reduce heterogeneity

One factor that is thought to complicate studies into the pathophysiology of MDD is the suggested heterogeneity of patients that get the diagnosis and consequently enter the studies. Based on DSM-criteria, theoretically, 2437 possible different combinations of symptoms could lead to the diagnosis MDD, with a large number of combinations that even show no mutual overlap in criteria.71 Despite acknowledgement of this conceptual heterogeneity, it has been proven difficult to define clinically useful subgroups of patients.72 Several subdivisions based on clinician views or data-driven methods have been developed, but are not routinely clinically applied yet. Also the most studied subdivision of atypical versus melancholic depression seems to have limited clinical relevance thus far,73,74 and evidence regarding the longitudinal stability of these subtypes is mixed.75,76

If we would be able to study a more homogeneous set of patients, it is expected that it will become easier to find consistent and specific pathophysiological alterations. Recent research efforts aim at focusing on endophenotypes,77 e.g. through the Research Domain Criteria (RDoC) initiative,78 or try to define subgroups based on biological factors.79 It has yet to be investigated to what extent these efforts to reduce MDD heterogeneity and resulting subtypes prove to be clinically useful.

Another way to reduce heterogeneity is stratification according to disease stage. It is increasingly being acknowledged that MDD is a chronic disorder, with periods of remission followed by frequent relapses and/or recurrences and in several cases chronic depression as an end-stage.34,80-82

Given this chronic, recurrent course, from a pathophysiological perspective it is interesting and useful to differentiate between trait factors (that remain present during remission and possibly constitute vulnerability for recurrence) versus state factors (which are only present during an MDD-episode). If we could (longitudinally) study the changes in patients during depressive episodes compared with remission, we may differentiate between trait and state factors. Although remitted MDD-patients have already been studied for a number of years,34 most studies still investigated MDD only cross-sectionally during the acute phase.

Apply a transdiagnostic approach

Comorbidity between psychiatric disorders is the rule rather than the exception, i.e. ~45% of people with a psychiatric disorder also receive an additional diagnosis.83 This may suggest that pathophysiological processes are (at least partly) shared.84,85 In line with this idea, research in biological psychiatry suggests alterations that are shared between different comorbid psychiatric disorders, e.g. MDD and schizophrenia. If we could compare patients with different disorders in a transdiagnostic approach, we might thereby improve our biological understanding of the relation between conceptually different, but often comorbid, psychiatric disorders.

Personalize treatment and prognosis

Next to development of new treatment targets, improved disease understanding could also lead to personalization of treatment and prognosis. At the moment, clinicians have to deal with a limited understanding of the processes underlying treatment response or recurrence.
If we would better understand these processes, we could think of ways to predict beforehand which patients will respond to what treatment or have the highest chance of recurrence.

**Predict treatment response**

Biological factors might not only predict onset of disease, but might also help the clinician to select the optimal treatment for patients.\textsuperscript{36} Knowing which patient will respond to what treatment could lead to immediate selection of the most effective treatment, instead of the currently applied trial- and-error approach. Some studies have already attempted to formulate such (bio)marker panels in a personalized/precision psychiatry approach, but these are not routinely clinically applied yet. For example, in *Molecular Psychiatry* we described our investigations to test whether we could use a genetic factor [a polymorphism in the serotonin transporter gene promoter region (5HTTLPR)] to predict response to cognitive therapy in preventing recurrence in remitted patients with recurrent MDD.\textsuperscript{36}

**Predict recurrence**

Recurrent depressive episodes seem to cluster in subpopulations of MDD-patients. This suggests that overall, most MDD-episodes occur in a distinct group of persons with a high differential vulnerability for MDD. If we could *a priori* identify these patients at high risk for recurrence,\textsuperscript{36} this would provide excellent opportunities for specific, indicated, (secondary) prevention to lower recurrence rates in these highly recurring cases, and thereby greatly reduce the overall number and possibly also the severity of subsequent MDD-episodes and thereby the overall burden caused by MDD.\textsuperscript{86}

Thus far, the limited research that applied such a prospective approach in remitted MDD-participants investigated several factors as predictors of recurrence. While associated with MDD onset, demographics (e.g. gender) generally do not predict recurrence; clinical and social factors appear to be more predictive. Regarding clinical factors, the number of previous episodes is among the strongest predictors,\textsuperscript{87} together with residual depressive symptoms during remission.\textsuperscript{32} In addition, MDD family history, comorbid disorders, age of onset and duration and severity of the last episode have been suggested as predictors.\textsuperscript{28,32,88-94} Furthermore, personality characteristics (coping style and personality traits) and social factors (experiencing daily hassles) have been found to be predictive, although findings remain largely inconsistent. In addition, we showed that the presence of sustained medically unexplained symptoms increased recurrence risk in remitted patients with recurrent MDD. As an example of a relevant biological factor, we previously described that a gene-environment interaction between a methylenetetrahydrofolate reductase (MTHFR) polymorphism and having experienced traumatic childhood events could also predict prospective recurrence.\textsuperscript{95} Despite all these factors, in our previous study 71% of the variance in time to recurrence remained unexplained.\textsuperscript{96,97} Moreover, only few actual predictive factors were potentially modifiable.

This large proportion of variance in recurrence rates that remains unexplained may be because the pathophysiology behind these factors’ predictive properties for recurrence remains far from understood. For example, residual symptoms predict recurrence in the short-term but seem less predictive for the long-term recurrence-rate.\textsuperscript{98} This indicates that residual symptoms may not constitute a vulnerability trait, but reflect an earlier episode not
yet in full remission or rather represent the early initiation of a new episode. In addition, the predictive effect of previous episodes can be explained due to scarring (increasing vulnerability directly resulting from experiencing previous episodes) or high premorbid vulnerability (more pre-existing abnormalities leading to more previous episodes and new recurrences). From the prediction perspective, these differences might seem a merely academic question. However, identifying the mechanisms underlying MDD-recurrence is essential to discover better potential targets for innovative preventive interventions to increase resilience.

**Augment treatment outcomes**

A final opportunity to reduce MDD’s burden may be to augment the outcome of treatment by increasing therapy response. For example, if we could find new modifiable factors that predict response to antidepressants, we could find ways to influence these factors and thereby increase therapy effectiveness. Next to combination of antidepressants, currently available augmentation strategies include the addition of lithium, antipsychotics, psychotherapy and/or neurostimulation, with some evidence for effectiveness. Next to these augmentation strategies, the metabolic thyroid hormone triiodothyronine ($T_3$) has been tested as an augmentation strategy, with mixed results.

Nevertheless, the number of patients that show non-response or even resistance to the available treatment options remains considerable, which leaves ample opportunities for improvement. If we would better understand the mechanisms leading to non-response, we may develop new augmentation strategies to increase response rates. In addition, specific profiles of pathophysiologically linked predictors may guide clinicians which augmentation strategy may be most useful for each individual patient. These new strategies may also include non-pharmacological interventions including lifestyle modification, e.g. physical activity or dietary improvements.

**SCOPE OF THIS THESIS**

In sum, despite continuous research and clinical efforts, MDD is one of the largest health challenges currently facing mankind. Treatment options are limited, recurrence occurs often, and patients suffer from a high cardiovascular comorbidity. Opportunities to reverse this bleak perspective may lie in improving disease understanding, personalizing prognosis and treatment, and finding ways to augment treatment response.

To this end, this thesis will focus on fatty acids and their relation with other pathophysiological mechanisms in MDD, in order to investigate whether they can be used to improve disease understanding, personalize treatment and prognosis, and/or augment therapy response. Thereby, the ultimate aim is to contribute to a reduction in MDD’s burden of disease by showing ways to increase treatment efficacy, reduce recurrence rates, and minimize cardiovascular comorbidity.

We will present results from various studies. In order to improve readability, we provided a brief overview of each individual study in Table 1. Moreover, we will outline the structure of the different parts and chapters of this thesis on the following pages.
<table>
<thead>
<tr>
<th>Study</th>
<th>Acronym</th>
<th>Design</th>
<th>Included sample(s)</th>
<th>Measures used</th>
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</table>
| DELTA            | Depression Evaluation Longitudinal Therapy Assessment                | RCT on preventive cognitive therapy with nested prospective patient-control cohort follow-up | 1. Remitted recurrent MDD patients ($N \leq 187$)  
2. Matched controls ($N \leq 73$) | - Fatty acid metabolism  
- Cortisol  
- DHEAS  
- One-carbon metabolism  
- Genetics  
- Follow-up recurrence |
| DELTA- Neuroimaging | See above               | New inclusion round at 10-years follow-up of DELTA study, including $~90\%$ new participants | 1. Remitted recurrent unmedicated MDD patients ($N \leq 62$)  
2. Matched controls ($N \leq 41$) | - Daily mood using experience sampling method  
- MRI  
- Fatty acid metabolism  
- Cortisol  
- Follow-up recurrence |
| DELPHI           | Dose- Escalation Legitimate? Pharmacology and Imaging studies in depression | Prospective patient-control cohort follow-up with nested placebo-controlled paroxetine dose-escalation RCT | 1. Initially unmedicated depressed patients ($N \leq 70$)  
2. Matched controls ($N \leq 51$) | - Fatty acid metabolism  
- Cortisol  
- Amygala reactivity (fMRI)  
- C-reactive protein  
- Therapy response |
| DIADE            | Diagnostic Imaging of Affective Disorders using Emotion Processing  | Cross-sectional patient-control                                         | 1. Unmedicated MDD patients ($N \leq 42$)  
2. Unmedicated BD patients ($N \leq 35$)  
3. Healthy controls ($N \leq 36$) | - Emotion regulation task fMRI |
| Varenicline RCT  |                          | RCT                                                                     | Healthy non-smoking participants ($N \leq 41$) randomized to  
1. 7 days Varenicline  
2. 7 days placebo | - Cortisol  
- Emotional processing  
- Cognitive performance  
- Emotion potentiated startle |
| EPA RCT          |                          | RCT                                                                     | MDD patients with diabetes mellitus ($N \leq 25$) randomized to  
1. 12 weeks add-on EPA supplementation  
2. Placebo | - Fatty acid metabolism  
- Cortisol  
- Oxidative stress  
- One-carbon metabolism  
- Inflammation  
- Lipoproteins |
| MooDFOOD - Helius | Healthy Life In an Urban Setting                                  | Cross-sectional epidemiological, follow-up of cohort ongoing               | Subgroup of 5160 multi-ethnic participants | - Food frequency data  
- Neuroticism score on NEO-FFI |
| InChianti        | Invecchiare in Chianti  | Population-based cohort                                                | People from the general population ($N \leq 1453$) | - Fatty acid metabolism  
- One-carbon metabolism  
- Food frequency data  
- CES-D at 3, 6, and 9 years follow-up |
| PTSD study       |                          | Cross-sectional patient-control                                         | 1. Patients with PTSD ($N \leq 49$)  
2. Healthy controls ($N \leq 46$) | - Fatty acid metabolism  
- Cortisol  
- One-carbon metabolism |
| Schizophrenia: GROUP | Genetic Risk and OUtcome of Psychosis | Multisite, longitudinal, naturalistic cohort study                     | 1. Patients with non-affective psychotic disorder ($N \leq 215$)  
2. Siblings ($N \leq 187$)  
3. Controls ($N \leq 98$) | - Fatty acid metabolism |
| Meta-analyses    |                          | Three meta-analyses of RCT’s                                           | 1. Omega-3 fatty acids for MDD  
2. Omega-3 fatty acids for peripartum MDD  
3. Effects of omega-3 fatty acids on oxidative stress in humans | 1 & 2: Depressive symptoms  
3: Oxidative stress parameters |
Part II: Fatty acids - alterations in MDD

Part II will cover fatty acids. Here we will introduce fatty acids and explain why they are our main focus. In addition, we will describe our results on fatty acid alterations in MDD. In chapter 1, we will provide solutions for statistical methodological issues in order to better grasp alterations in patterns of fatty acid alterations in MDD. Chapter 2 tests the presence of bimodal distributions in these fatty acid patterns. Chapter 3 investigates whether bimodal distributions can be explained by a nutrigenetic factor (fatty acid binding protein 2, involved in gut fatty acid uptake), and its influence on CVD risk. Finally, we will discuss these results in the light of other investigations of fatty acid metabolism. Thereby, we aim to show how fatty acids can be used to reduce MDD’s heterogeneity by disentangling state- and trait-effects, and so improve disease understanding. In addition, we will show the role of fatty acid metabolism in the development of CVD comorbidity in MDD.

Part III: Context - alterations in other pathophysiological aspects in MDD

In Part III, we will show our results of the investigations of alterations in two other main pathophysiological aspects in MDD that we will later relate to fatty acids in Part IV: neuroendocrinological stress and emotional processing. After first introducing neuroendocrinological stress, chapter 4 will show our results on hypothalamic-pituitary-adrenal axis trait and state effects in recurrent MDD for cortisol, and chapter 5 for dehydroepiandrosterone sulfate (DHEAS). We will then provide a brief overall discussion of our neuroendocrinological findings, followed by a short introduction of the other main pathophysiological aspect: emotional processing. Chapter 6 will describe our results from the DIADE study on brain activity differences during emotional processing between MDD, healthy controls and bipolar disorder. Subsequently we will provide a concise discussion of these findings on emotional processing in the light of other related findings by others and us. Finally, we will provide a brief overall discussion of these findings in the other pathophysiological aspects (neuroendocrinological stress and emotional processing). In particular, this third Part will address state-, trait- and medication-effects with the aim to improve disease understanding. In addition, opportunities to personalize treatment and prognosis will be presented.

Abbreviations used: RCT, randomized controlled trial; MDD, Major depressive episode; DHEAS, dehydroepiandrosterone; (f)MRI, (functional) magnetic resonance imaging; BD, bipolar disorder; EPA, eicosapentaenoic acid; NEO FFI, neuroticism-extraversion-openness five-factor inventory; CES-D, center for epidemiologic studies depression scale; PTSD, posttraumatic stress disorder.
Part IV: Fatty acids in context - relationships between fatty acids and other pathophysiological aspects

Part IV covers the relationships in MDD between fatty acids and the other two pathophysiological aspects discussed in Part III: neuroendocrinological stress and emotional processing. After a short introduction, we will describe our findings on the relationship between fatty acids and neuroendocrinological stress in chapters 7, 8, 9 and 10. Chapters 7 and 8 test this relationship in two independent samples of MDD-patients, while chapter 9 describes biological effects - including those on neuroendocrinological stress - of fatty acid supplementation in MDD-patients with comorbid CVD-risk factor diabetes mellitus. Chapter 10 describes our findings on the relationship between fatty acids and emotional processing (amygdala reactivity to emotional faces) in MDD-patients. Finally, we will provide a brief overall discussion. Investigation of the cross-links between fatty acids and related pathophysiological mechanisms in Part IV also aims at contributing to further disease understanding. Moreover, studies in Part IV will show examples of how this understanding can be used to personalize psychiatry, e.g. by predicting treatment response.

Part V: Clinical implications

Part V will examine whether fatty acids can be used to augment treatment outcome. We will first introduce this Part, chapters 11 and 12 will describe our meta-analyses on omega-3 fatty acid supplementation randomized placebo-controlled trials for MDD and peripartum depression, respectively. Chapter 13 provides a critical and cautionary note on fatty acid supplementation, particularly during pregnancy. Chapter 14 describes our meta-analysis on the effects of omega-3 fatty acid supplementation on oxidative stress, in order to gain a more nuanced view on the balance between potentially harmful and beneficial effects of supplementation. Finally, we will discuss these findings from a clinical and biochemical perspective.

Part VI: General discussion

Part VI will provide an overall summary and discussion of the findings presented in this thesis, in the light of related work by others and us.
REFERENCES


72. van Loo HM. *Data-driven subtypes of major depressive disorder.* University of Groningen; 2015.


