Fatty acids in context
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Discussion of emotional processing

Summary of our findings
In sum, we showed that unmedicated depressed and remitted patients with MDD or bipolar disease showed transdiagnostic differences and similarities in emotional processing and related brain activity depending on the symptomatic state of the disease. In the remitted state, only bipolar patients showed impaired emotion regulation, associated with increased dorsolateral prefrontal cortex activity. During the depressed state, patients with bipolar disease performed worse than those with MDD on sad emotion regulation but better on happy emotion regulation, and they demonstrated significantly less rostral anterior cingulate activity while regulating happy compared with sad emotions. These transdiagnostic differences and similarities in emotional processing and related brain activity contribute to disease understanding, and if replicated they may ultimately be used to reduce heterogeneity and thereby improve diagnostic classification of mood disorders patients.

Relation with other literature
Emotional processing remains a concept at the heart of MDD. Functional MRI studies on emotional processing provide increasing evidence for the importance of a network perspective.\(^222,223\) The field moved from modern phrenology (assessing sizes and activities of specified brain regions) to a circuits/network/connectomics approach. Meta-analyses corroborate reduced connectivity within frontoparietal control systems, together with an imbalanced connectivity with other networks involved in emotional processing.\(^149,150,224\) However, transdiagnostic meta-analysis question the specificity of these alterations for MDD.\(^227\)

In the DELTA-neuroimaging study, we showed that daily real-life dynamics in positive and negative affect were related to brain network organization in remitted recurrent MDD, as recently published in *Neuropsychopharmacology*.\(^228\) In brief, remitted recurrent MDD patients, compared to healthy controls, were less stable in symptoms related to negative affect and these dynamics were associated with differences in information processing within and between specific functional brain subnetworks. These results are a first step to gain a better understanding of how emotion fluctuations in real-life are represented in the brain and provide insights in emotional processing vulnerability profiles of MDD.

Several additional investigations are going on to gain further insight in alterations in brain functioning and structure associated with emotional processing biases in MDD. Especially the use of novel analytical approaches will ensure that data will be used efficiently. These new analytical techniques hopefully work around important statistical concerns about false-positive findings in MRI findings.\(^229\) These statistical concerns may explain the limited or even absent clinical translation of MRI in psychiatry.\(^230,231\) Nevertheless, ultimately MRI may be used to inform clinicians on clinical course, and provide targets to modulate it. Some aspiring ideas have already been put forward. For example, resting state fMRI was able to predict outcome of electroconvulsive therapy in MDD with ~85% sensitivity and specificity.\(^232\) Functional MRI responses to emotional faces predicted naturalistic course of MDD with up to 73% accuracy.\(^233\) Finally, resting state functional connectivity distinguished
MDD from BD with ~70% accuracy. However, accuracies are usually not high enough for clinical implementation yet, even if they can be replicated. ‘Smarter’ combination and integration of data may result in more clinically usable tools.

Clinical translation of emotional processing theories have also been attempted using neuropsychological test batteries quantitatively measuring biases in emotional processing without relying on expensive MRI techniques. For example, in *Neuropsychopharmacology* we described our use of an emotional processing test battery to test the depressogenic effects of the smoking cessation drug varenicline. A lack of effects of varenicline on this sensitive emotional processing battery in non-smoking participants suggests that any clinical depressogenic effects are caused by successfully stopping smoking itself. On the contrary, the same emotional processing battery proved to be able to detect the clinically relevant depressogenic effects of rimonabant. Moreover, in the DELTA-Neuroimaging study we currently test whether emotional processing alterations seen in remitted MDD can predict recurrence, and efforts to predict antidepressant response from emotional processing are underway.

**Conclusion**
Disturbances in emotional processing are an essential feature of MDD. These emotional processing alterations seem associated with imbalances in brain network connectivity, mainly between controlling frontoparietal and limbic ventral networks. Neuropsychological emotional processing test batteries are being used to predict clinically relevant outcomes. Transdiagnostic studies suggest limited specificity and inconsistencies remain, which may be improved by statistically robust replication. Nevertheless, initial aspiring findings show that neuroimaging correlates of emotional processing still has great potential to increase disease understanding and thereby reduce heterogeneity and personalize medicine.

**Overall conclusion**
In this third Part we described our research on two main pathophysiological aspects in MDD: neuroendocrinological stress and emotional processing. Research in both areas showed interesting alterations, but important inconsistencies remain. Initial initiatives to use these pathophysiological aspects to personalize treatment and/or prognosis or as targets for interventions have been made, but are not robust enough yet for clinical implementation.

Interestingly, these two aspects have both been hypothesized to be (patho)physiologically linked with fatty acid metabolism. Nevertheless, most studies investigated these aspects in isolation. Taking these links between pathophysiological aspects into account could provide an important way to improve consistency in findings. In the next Part of this thesis, we will explain the possible links with fatty acid metabolism, and present our data investigating these links.
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