Fatty acids in context
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Discussion

Summary of our findings
In this fourth Part we tested relationships between fatty acid metabolism and the two other pathophysiological aspects in MDD introduced in Part III: neuroendocrinological stress and emotional processing. We observed relations with both mechanisms. In detail, evening cortisol was negatively associated with fatty acid unsaturation and peroxidation in two independent cohorts and EPA supplementation decreased cortisol reactivity. The findings from our neuroimaging study revealed that arachidonic acid was associated with reactivity of the amygdala (a main emotional processing structure) in response to emotional faces.

These studies of the relationships between fatty acid metabolism and other pathophysiological aspects in MDD can be seen as first explorations of neurometabolic network alterations. We think that further integration of diverse data sources, leading to investigation of pathophysiological alterations beyond the disciplinary boundaries, will lead to richer but also more complex phenotyping. The additional information on the relations between nodes in a network may contain important discriminative power. This richer phenotyping could more precisely delineate the affected pathophysiological pathways, and thereby detect the rate limiting steps. For example, edges in a neurometabolic network that strongly differ from the healthy situation, may lead to network instability and thereby perturbation of homeostasis. Collaboration and development of advanced analytical approaches is mandatory to overcome the "many variables, small $N$" problem that may result when applying a richer phenotyping to an inherently limited number of affected subjects that can be studied.

Relation with other literature
The literature on the relation of fatty acids and other pathophysiological aspects in psychiatric disorders as MDD is burgeoning. Besides the above main aspects, fascinatingly, fatty acids have also been associated with a wide variety of other pathophysiological aspects. For example, they are precursors of endocannabinoids, sphingolipids, and lipid oxidation products (lipoxins) as resolvins, maresins, and protectins. Endocannabinoids are neuromodulatory lipids derived from omega-6 arachidonic acid, and thought to be involved in mood regulation, psychosis and addiction vulnerability. (Neuro)protectin D1 is an oxidative derivative from the omega-3 fatty acid DHA, and has anti-apoptotic and thereby neuroprotective properties.

In addition, our own research investigated the associations between fatty acid metabolism and alterations in folate/one-carbon metabolism, which we do not cover in detail in the current thesis. In brief, in our DELTA-study we observed lower folate in recurrent MDD-patients, together with lower vitamin B6 and higher homocysteine during depressive episodes, without effects of antidepressants. Transdiagnostically, these findings partly correspond with our findings in PTSD, where we also found elevated homocysteine. This is important because it stresses the possible transdiagnostic nature of one-carbon metabolism findings. Of note, lower folate and vitamin B6 together with higher homocysteine are thought to reflect increased risk for cardiovascular disease. Interestingly, regarding the association with fatty acid metabolism, folate was significantly positively associated with EPA in our
DELTA-study, also after correction for confounders. This may reflect the role of one-carbon metabolism to deliver carbon groups for the elongation of long chain fatty acids as EPA. Moreover, the association between homocysteine and DHA was significantly less negative in patients compared to controls.\textsuperscript{212} This corroborates hypothesized cross-links between folate and fatty acid metabolism, and may additionally suggest that these cross-links are partly differentially regulated in MDD compared to the healthy state. Given that these are one of the first investigations of these cross-links in psychiatric populations, replication is warranted.

Next to these associations with one-carbon metabolism, fatty acids can exert nutrigenomic effects and thereby regulate gene-expression. As an example, several fatty acids and their oxidative derivatives are endogenous ligands to peroxisome proliferator-activated receptors (PPARs), important transcription factors for regulation of metabolism and cellular development.\textsuperscript{231} These nutrigenetics effect may also contribute to the observed association between dietary fatty acid intake and MDD. Finally, fatty acids have been reported to influence the gastrointestinal microbiome, which has also been suggested to play a role in MDD pathophysiology.\textsuperscript{232}

Taken together, due to their essential (patho)physiological nature, fatty acids seem to exert extensive cross-links with a wide range of other pathophysiological aspects. These cross-links may explain the associations of fatty acid alterations and fatty acid intake with disease, and suggest that fatty acids may exert a wide range of potentially beneficial effects. Nevertheless, the relevance of this mostly preclinical data should be tested in clinical samples, in order to see to what extent these relationships of fatty acid metabolism with other pathophysiological aspects are consistently altered in MDD and/or related psychiatric disorders. If so, in the end, such knowledge could provide ways to develop new treatment targets and/or markers to personalize prognosis and/or treatment.

**Conclusion**

The results regarding associations of fatty acid metabolism with cortisol and amygdala reactivity to emotional faces presented in this Part largely corroborated the hypothesized relations of fatty acid metabolism with neuroendocrinological stress and emotional processing. Besides providing insight in MDD pathophysiology, these relations between fatty acid metabolism and other mechanisms could be used to predict treatment response to antidepressants. In addition, the observed relations could be used to attempt to modify HPA-axis activity through fatty acid supplementation. In the next Part of this thesis, we will investigate the clinical implications of these relations, by testing the clinical effects of fatty acid supplementation in MDD. Further research elucidating the complex relations between different pathophysiological pathways, applying a multi- and interdisciplinary approach, will help to further translate this knowledge into the clinic.
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