Fatty acids in context
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**Overall discussion**

In this discussion we will first provide a summary of findings and then relate them to relevant scientific literature. Finally, we will provide a conclusion of this Part.

**Summary of findings**

Due to their essential dietary nature and abundance in the brain, fatty acids may have an important role in structural and functional (patho)physiology of neurons, which is expected to contribute to psychiatric disorders like MDD. MDD is associated with lower omega-3 fatty acid concentrations and a higher omega-6 to omega-3 ratio. In our DELTA study, we observed various alterations in fatty acid concentrations, mainly consisting of lower concentrations of long chained fatty acids and higher concentrations of short chained fatty acids among all fatty acid classes (saturated, monounsaturated, and polyunsaturated), that were state-independent. This indicates that fatty acid alterations in recurrent MDD represent a trait that extends beyond the omega-3 and omega-6 polyunsaturated fatty acids, i.e. also involves alterations in saturated, monounsaturated and other polyunsaturated fatty acids.

In addition, we showed that fatty acid results differed when expressing them as percentages or absolute concentrations, and provided ways to choose between these presentation methods. In short, when effects of a certain fatty acid relative to the total amount of fatty acids can be expected, one should use percentages, otherwise absolute concentrations seem more useful. Furthermore, we showed that indices can be used to describe overall fatty acid patterns. For example, recurrent MDD patients showed highly significantly lower overall fatty acid unsaturation and chain length, which also proved to be bimodally distributed. This is important because it may suggest two biologically determined subtypes of the disease, each with their own pathophysiology. In search of a causal factor for this bimodal distribution we investigated the FABP2-genotype. An FABP2-polymorphism could not explain the bimodal distribution, but did influence fatty acid concentrations and thereby CVD-risk in MDD.

Overall, these findings increase our understanding of the possible role of fatty acids in MDD pathophysiology, and provide ways to reduce heterogeneity in study samples by better subgrouping patients on the bases of biological factors. In addition, findings provide part of an explanation for the high cardiovascular comorbidity rates: a polymorphism in the FABP2-gene influenced CVD-risk trough an effect on fatty acid metabolism. In the next paragraph we will discuss the relation with relevant studies by other groups.

**Relation with other literature**

A metabolomics analysis in the large Netherlands Study of Depression and Anxiety (NESDA) showed that lower omega-3 DHA was one of the only two metabolites (out of 231) that was associated with MDD, which is corroborative with our findings. In general, later studies mainly kept focusing on omega-3 and to a lesser extent omega-6 fatty acids, without testing overall fatty acid patterns in other fatty acid classes. This may be because omega-3 and -6 fatty acids are considered to be essential, and are hypothesized to have a more bioactive role than other fatty acids, as described in the introduction of this Part. Nevertheless, our observations of patterns of fatty acid alterations in MDD that extend beyond the omega-3 and -6 classes and include alterations in saturated and monounsaturated fatty acids may be of pathophysiological importance, e.g. given the interactions between fatty acids in the membrane and differences in effects of their lipid peroxidation products. Indeed, studies...
that tested other fatty acids in MDD mostly corroborate our findings that alterations extend beyond the omega-3 and -6 classes and are also found in saturated and monounsaturated fatty acid subclasses.\textsuperscript{111-114}

Methodologically, although most studies still assess and test the different fatty acids individually, some additional efforts have been made to better capture overall fatty acid patterns, e.g. using structural equation modeling.\textsuperscript{115,116} These efforts also show that fatty acid alterations in MDD can be better conceptualized as patterns, instead of deficiencies in one or two individual omega-3 or -6 fatty acids. In addition, the omega-3 index has been developed to describe fatty acid abnormalities.\textsuperscript{111,117} While this index has the advantage of reference values derived from large cardiovascular studies, it merely consists of the summation of red blood cell EPA and DHA concentration percentages, omitting overall fatty acid alteration patterns. Therefore, metabolomics and lipidomics studies will need to find more advanced ways of data reduction given the even larger number of individually measured metabolite concentrations (e.g. from 30 to >800 metabolites including various oxylipins).\textsuperscript{118}

Regarding nutrigenetics and nutrigenomics factors as \textit{FABP2} covered in chapter 3, attention for the effects of genes on nutrition and vice versa is quickly increasing.\textsuperscript{87,119} The paucity of research on the \textit{FABP} family in psychiatry did show that \textit{FABP4}, mainly expressed in adipocytes and macrophages, has been associated with MDD,\textsuperscript{120} particularly the atypical subtype.\textsuperscript{121} With our results, we showed a first indication of the nutrigenetic effects of \textit{FABP2} on CVD-risk in MDD through modulation of gut fatty acid uptake. This may be an interesting way to develop personalized nutritional interventions to reduce CVD-risk in MDD. Nevertheless, the complexity of nutrigenetic and -genomic interactions has yet to be fully discovered. Clinical applications including gene-based nutraceuticals are being developed, but it seems too early for clinical implementation yet.\textsuperscript{122,123}

**CONCLUSION**

This second Part showed that fatty acids have important structural and functional physiological roles in the brain and the rest of the body. Epidemiological and biological evidence links fatty acids to MDD and related psychiatric disorders. Indeed, our data shows that pathophysiology of (recurrent) MDD seems to involve alterations in fatty acid metabolism that extend beyond lower omega-3 fatty acid concentrations.\textsuperscript{150} Bimodal distributions of overall lowered fatty acid unsaturation and chain length suggest a yet unknown dichotomous underlying factor that may subdivide patients.\textsuperscript{3} The nutrigenetics factor \textit{FABP2} could not explain these bimodal distributions, but did influence fatty acid concentrations and thereby CVD-risk.\textsuperscript{3} Nevertheless, methodological issues like expression of fatty acid results and dealing with missing data may have influenced fatty acid research findings, for which we provided statistical solutions: indices and multiple imputation. Because the basic physiological role of fatty acids involves extensive theoretical relations with other pathophysiological aspects, in the next Part of this thesis we will introduce two potentially related pathophysiological aspects of MDD: neuroendocrinological stress and emotional processing. Subsequently, we will clinically test the relations between these other aspects and fatty acid metabolism in Part IV.


62. AMELIA II: A Program for Missing Data 2010.


