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Research paper

# Fatty acid concentrations in patients with posttraumatic stress disorder compared to healthy controls

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ABSTRACT

*Background:* Although fatty acid (FA)-supplementation studies are currently being implemented, in fact little is known about FA-profiles in posttraumatic stress disorder (PTSD). Therefore, the present study aimed at comparing FA-concentrations between PTSD-patients and healthy controls.
*Methods:* A cross-sectional study comparing a mixed-gender sample of 49 patients with PTSD due to civilian trauma to 46 healthy controls regarding erythrocyte FAs including docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), arachidonic acid (AA), and nervonic acid (NA).
*Results:* DHA was found to be significantly lower in PTSD-patients compared to controls after adjusting for sociodemographic and dietary factors ($p = 0.043$). Additionally, exploratory analyses showed lower vaccenic acid ($p = 0.035$) and eicosatrienoic acid ($p = 0.006$), but higher erucic acid ($p = 0.032$) in PTSD-patients. The effect of erucic acid remained after adjustment for sociodemographic factors ($p = 0.047$); with the additional adjustment for dietary factors none of these FAs were found to be significant.
*Limitations:* Statistical power for differences with small effect sizes was limited, and dietary assessment could be optimized.
*Conclusions:* We found little evidence for a considerable role of FA-metabolism in PTSD. Apart from lower DHA after adjusting for confounders, no differences were observed in the hypothesized long-chained polyunsaturated FA-concentrations. Additionally, we found few alterations in the long-chained monounsaturated FAs, which may be explained by dietary factors. Nevertheless, the observed small effect sizes and limited extent of the alterations emphasize the importance of further investigating the assumed role of FA-metabolism and its underlying mechanisms in PTSD, before implementing further FA-supplementation studies.



## 1. Introduction

The vast majority of the general adult population will experience a potentially traumatic event; about nine percent of the affected people will develop posttraumatic stress disorder (PTSD). PTSD implies great personal and societal suffering (de Vries and Olff, 2009; Kessler et al., 2003; Kessler et al., 2012), leading to an invalidating disease burden worldwide (Baxter et al., 2014; Wittchen et al., 2011). Complex biopsychosocial mechanisms determine who will develop PTSD after trauma and who is rather resilient (Christopher, 2004; Southwick et al., 2014). A better understanding of these mechanisms may help to improve preventive interventions aimed to preclude development of PTSD (Olff et al., 2013).

One important mechanism underlying PTSD-development may be fatty acid (FA)-metabolism. Long chain polyunsaturated fatty acids (LCPUFAs) are the main components of neuronal membranes, which makes them essential for normal brain functioning (Bourre, 2005). Consequently, FAs already derived much scientific attention in other major psychiatric disorders like depression and schizophrenia (Assies et al., 2010; Medema et al., 2015), providing evidence for altered FA-profiles in these disorders. However, FA-profiles may also be relevant for PTSD, because – as outlined below – FAs are found associated with other pathophysiological mechanisms in PTSD, including sympathetic activity (Matsumura et al., 2012; Pitman et al., 2012), the hypothalamic-pituitary-adrenal (HPA) axis (Mocking et al., 2013a; Mocking et al., 2015; Olff

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et al., 2006; Rohleder et al., 2001; Yehuda et al., 1995), endocannabinoids (Bitencourt et al., 2014; Lafourcade et al., 2011; Marsicano et al., 2002; Meijerink et al., 2013; Neumeister, 2013), neuronal survival and plasticity (Beltz et al., 2007; Calderon and Kim, 2004; Kawakita et al., 2006; McNamara, 2013; Peters et al., 2013; Pitman et al., 2012), white matter integrity (Daniels et al., 2013; Peters et al., 2013), inflammation (Assies et al., 2014; Baker et al., 2012), and oxidative stress (Michels et al., 2014; Miller and Sadeh, 2014; Ng et al., 2008; Tsaluchidu et al., 2008).

For example, omega-3 PUFAs including eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3) have been found to (I) lower sympathetic activity (Delarue et al., 2003; Hamazaki et al., 2005), (II) increase brain-derived neurotrophic factor (BDNF) (Rao et al., 2007), and (III) be associated with hippocampus and amygdala gray matter volume (Conklin et al., 2007; Samieri et al., 2012), that are all implicated in PTSD-pathogenesis (Frijling et al., 2014; Frijling et al., 2015; Pitman et al., 2012). For example, promoting hippocampal neurogenesis may be of particular importance in PTSD-patients to enhance the impaired extinction learning. Moreover, EPA and arachidonic acid (AA, 20:4 n-6) are precursors for eicosanoids that regulate and stimulate inflammation, respectively (Assies et al., 2014). Of note, chronic immune activation is commonly observed in PTSD (Baker et al., 2012). Furthermore, the omega-9 monounsaturated fatty acid (MUFA) nervonic acid (NA; C24:1 n-9) may be important in myelin biosynthesis as it is found in white matter sphingolipids (Assies et al., 2010). NA decrease may therefore explain white matter reductions in PTSD. Finally, due to their double bonds, PUFAs determine neuronal membrane fluidity and peroxidizability, which are important for membrane functioning and oxidative stress susceptibility/regulation, respectively (Mocking et al., 2012). Of note, increasing evidence suggests a role for oxidative stress in PTSD-pathogenesis (Ng et al., 2008; Tsaluchidu et al., 2008), e.g. as a result of life style (including poor diet or smoking) or psychological stress (Assies et al., 2014).

In sum, literature seems to be supporting a role of FA-metabolism in PTSD. This in fact has led to randomized controlled trials supplementing omega-3 fatty acids to prevent PTSD after trauma, or examine its effects on PTSD-symptoms (Johnston, 2010; Marriott, 2013; Matsuoka et al., 2013b; Naylor and Marx, 2013). However, despite initial promising findings (Matsuoka et al., 2010; Nishi et al., 2012), effects of FA-supplementation in the context of PTSD are mostly negative. For example, importantly, a recent randomized placebo-controlled trial that tested the effects of omega-3 LCPUFA-supplementation in the prevention of PTSD showed a non-significant *doubled* incidence of PTSD in the intervention group compared to placebo (Matsuoka et al., 2015a). Moreover, Zeev et al. (Zeev et al., 2005) curtailed their small open-label study of omega-3 LCPUFA-supplementation in PTSD, because of possible deleterious effects as most patients showed mild to moderate tendencies towards worsening in PTSD-severity.

Given the several ongoing supplementation trials and considering the negative effects of LCPUFA-supplementation thus far (Matsuoka et al., 2015a; Zeev et al., 2005), it is noticeable that in contrast to most other psychiatric disorders little clinical research has been done into the role of FA-metabolism in PTSD-patients. Omega-3 LCPUFAs are generally supplemented with the idea to restore deficits in FA-concentrations that result because omega-3 LCPUFAs has to be obtained from diet since humans are incapable of de novo endogenous synthesis (Assies et al., 2014), and the modern Western diet is scarce in omega-3 LCPUFAs (Hallahan and Garland, 2005). However, to our knowledge, no study thus far compared FA-concentrations in PTSD-patients with controls to test whether such deficits actually exist. Some circumstantial evidence is available regarding FA-alterations in PTSD: Matsuoka et al. (2013a) found that AA and EPA levels were inversely associated with subsequent risk for developing PTSD, and Kalinic et al. (2014a) found in PTSD-patients that EPA was negatively associated with severity of PTSD-symptoms. Nevertheless, it remains to be elucidated whether PTSD-patients differ from healthy people in FA-concentrations, to see whether there actually exist FA-alterations that may need to be corrected with supplementation. If not, this may explain negative findings of FA-supplementation in PTSD thus far (Matsuoka et al., 2015a; Zeev et al., 2005), which besides being ineffective, may also lead to side effects (Assies et al., 2011; Ramsden et al., 2013).

Therefore, the aim of the present study was to investigate whether PTSD-patients differ in FA-concentrations compared to healthy controls. In a mixed-gender sample of patients with PTSD due to civilian traumatic events, we examined FA-concentrations in erythrocytes. We hypothesized that PTSD-patients would have lower concentrations of the PUFAs EPA, DHA, AA and MUFA NA compared to controls. Furthermore as measurements of overall FA-profiles, we compared patients and controls regarding FA-unsaturation, -chain length and -peroxidizability indices. Finally, we exploratively compared concentrations of other FAs of all FA-subclasses (e.g. omega-3, omega-9) between patients and controls.

## 2. Methods

### 2.1. Participants

We included 49 outpatients with PTSD due to a civilian trauma (e.g. accident, loss of loved one, sexual violence) recruited from our outpatient department and through newspaper advertisements, and 46 healthy controls recruited from newspaper advertisements and from personnel of the Academic Medical Center. Any current or lifetime mental disorder formed the exclusion criterion for controls. We excluded patients with past or present psychotic disorders, depressive disorders with psychotic symptoms or suicidal tendencies, bipolar disorders, psycho-organic syndromes and alcohol or drug dependency/ abuse according to the DSM-IV classification system (First et al., 2002). To reduce heterogeneity, we further excluded participants with medical conditions such as cardiovascular disease, diabetes mellitus, immunological disorders, psychical conditions known to cause endocrine changes, and those who were pregnant (all based on self-report and structured clinical interview). Patients were allowed psychotropic medication. Because the majority of the Dutch general population has experienced one or more potentially traumatic events (de Vries and Olff, 2009), trauma exposure formed no exclusion criterion for controls. The Medical Ethical Committee of the Academic Medical Center approved the study. We obtained written informed consent from all patients and controls. We did not pay subjects for their participation nor gave them any other benefits.

### 2.2. Materials and measures

#### 2.2.1. Clinical assessment

Trained psychologists or psychiatrists assessed the diagnosis of PTSD using the Structured Interview for Posttraumatic Stress Disorder (Davidson et al., 1989) and co-existing psychopathology using the Structured Clinical Interview for DSM-IV (First et al., 2002). We determined PTSD-symptom severity using the Impact of Event Scale-Revised (IES-R) (Creamer et al., 2003). Because depression frequently coexists with PTSD and is found associated with altered FA-concentrations (Assies et al., 2010), we assessed severity of depressive symptoms using the Beck Depression Inventory (BDI) (Beck and Beamesderfer, 1974). Both patients and controls filled out the IES-R and BDI questionnaires. When filling