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Polyunsaturated fatty acid composition and childhood adversity: Independent correlates of depressive symptom persistence

William H. Coryell[a,*], Douglas R. Langbehn[b], Andrew W. Norris[c], Jian-Rong Yao[d], Lilian N. Dindo[e], Chadi A. Calarge[f]

[a] Department of Psychiatry, University of Iowa Carver College of Medicine, 500 N Road, Suite 2-205 MEB, Iowa City, IA 52242-1900, USA
[b] Department of Psychiatry, University of Iowa Carver College of Medicine, 500 N Road, Suite 1-290 MEB, Iowa City, IA 52242-1900, USA
[c] Department of Pediatrics, University of Iowa Carver College of Medicine, 285 N Road, 1270B CBRB, Iowa City, IA 52242-1900, USA
[d] Department of Pediatrics, University of Iowa Carver College of Medicine, 285 N Road, 1270 CBRB, Iowa City, IA 52242-1900, USA
[e] Department of Psychiatry, Baylor College of Medicine, Houston, TX, USA
[f] Department of Psychiatry and Pediatrics, Baylor College of Medicine, Houston, TX, USA

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ABSTRACT

Childhood experiences, personality, and polyunsaturated essential fatty acid (PUFA) composition have all been shown to affect the likelihood of depressive symptoms. Few studies have addressed relationships between these factors in their influence on the occurrence or course of depressive symptoms. The following analysis was designed to do so. Subjects, 15–20 years old, had either begun antidepressant treatment within the preceding month (n = 88), or had never taken psychiatric medications (n = 92). Baseline assessments included a structured diagnostic interview, the self-completed Multiphasic Personality Questionnaire, and a determination of plasma PUFA phospholipid composition. Depressive symptom levels were assessed at baseline and again at 4, 8 and 12 months. Omega-3 composition and general childhood trauma scores were unrelated to each other but both correlated, in predicted directions, with negative emotionality. Low omega-3 composition and history of childhood trauma were associated with persistence of depressive symptoms during follow-up, largely through their effects on negative emotionality. Negative emotionality appears to comprise a final common pathway to depressive disorder through which the diverse risk factors of childhood adversity and low omega-3 composition are expressed.

1. Introduction

Many ecological and therapeutic studies have demonstrated the importance of polyunsaturated fatty acids (PUFA) to risks for (Lin et al., 2010; Assies et al., 2010; Marx et al., 2015; Horikawa et al., 2016; Beydoun et al., 2015), and recovery from (Mocking et al., 2015, 2016), depressive disorders. PUFAs are important components of neuronal membranes and particular PUFA deficits adversely affect both the serotonergic and dopaminergic systems (Hibbeln et al., 1998; de la Presa Owens and Innis, 1999). In addition, most PUFAs in the omega-3 series are anti-inflammatory, while those in the omega-6 series are pro-inflammatory (Calder, 2006). A balance in the PUFAs favoring the omega-6 component is therefore associated with increases in pro-inflammatory cytokines and, as an apparent consequence, with increased risks for depressive symptoms (Pascoe et al., 2011).

PUFA measurements at one point reflect not only an individual's concurrent dietary habits, but also that person's activity of desaturases and elongases, enzymes responsible for the interconversion to effector omega-3 and omega-6 fatty acids (Lemaitre et al., 2011). Therefore, a single PUFA measure is likely to predict, at least to some degree, future values and thus to have prognostic weight for the course of depressive illness. Most prospective studies that have examined relationships between baseline dietary omega-3 intake and incident depressive disorder have failed to find them, however (Hakkarainen et al., 2004; Kesse-Guyot et al., 2012; Sanchez-Villegas et al., 2007; Lucas et al., 2011). Another reporter identified a group of adolescents with MDD who had failed to respond to a six-week trial of SSRI antidepressants and found clear deficits in docosahexaenoic acid (DHA) levels relative to those of a nested control group (McNamara et al., 2014). The majority went on to achieve remission of symptoms in a ten-week trial of DHA and eicosapentanoic acid (EPA). Several that did not exclude individuals with depressive disorders at baseline, and that could therefore be considered

* Corresponding author.
E-mail addresses: william-coryell@uiowa.edu (W.H. Coryell), douglas-langbehn@uiowa.edu (D.R. Langbehn), andrew-norris@uiowa.edu (A.W. Norris), jian-rong-yao@uiowa.edu (J.-R. Yao), lilian.dindo@bcm.edu (L.N. Dindo), chadi.calarge@bcm.edu (C.A. Calarge).

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studies of prevalence rather than incidence, did find association between omega-3 dietary intake and depressive morbidity during follow-up (Beydoun et al., 2015; Astorg et al., 2008; Colangelo et al., 2009). Only two prospective studies have employed direct measures of PUFA composition as potential predictors of depressive morbidity. One found no relationship between baseline serum phospholipid PUFA measures and the occurrence of depressive illness as revealed by records of antidepressant prescriptions (Astorg et al., 2009). In contrast, a much smaller, case-control report found significantly higher ratios of omega-6 to omega-3 concentrations among women who developed post-partum depression in comparison to those who did not (De Vriese et al., 2003).

Several additional prospective studies are germane if suicidal behavior is viewed as a proxy for depressive illness. Sublette (Sublette et al., 2006) found higher ratios of omega-6 to omega-3 composition in patients who attempted suicide during follow-up and Lewis (Lewis et al., 2011) reported lower DHA composition in a large sample of active duty military service members who later committed suicide in comparison to demographically-matched control individuals.

Childhood adversity is a well-established antecedent of depressive illness (Scott et al., 2012; Hovens et al., 2010; Chapman et al., 2004). Moreover, among individuals with depressive disorder, those who have experienced such adversity have poorer outcomes (Hovens et al., 2012; Kim et al., 2013; Klein et al., 2008; Tunnard et al., 2014). While variables such as socio-economic status (SES) may influence both the likelihood of childhood adversity and subsequent dietary habits (Appleton et al., 2007), it may be that PUFA composition and childhood adversity measures are orthogonal in their relationships to the risk for, and course of, depressive illness. If both measures are independently predictive of greater depressive morbidity over time, their combination would be more predictive in at least an additive fashion. Even so, these two factors may share a common pathway in the causal route to depressive illness. A candidate for such a shared intermediary is neuroticism or negative affectivity.

Measures of neuroticism correlate with both the likelihood and the persistence of depressive symptoms. Separate studies have shown significant associations between neuroticism and both low PUFA (Conklin et al., 2007) intake or composition (Evans et al., 2012), and childhood adversity (Hengartner et al., 2015; Allen and Lauterbach, 2007). Notably, at least one study has shown that neuroticism mediated the relationship between cumulative lifetime adversity, inclusive of childhood adversity, and current depressive symptoms (Abravanel and Sinha, 2015). A demonstration that PUFA composition and childhood adversity have independent influences on neuroticism would have important implications for the mechanisms underlying depressive disorders.

2. Methods

2.1. Participants

Participants, 15–20 years old, who were within one month of starting a selective serotonin reuptake inhibitor (SSRI) (n = 88), or who were taking no psychotropic medication (n = 92), were enrolled from outpatient and inpatient clinical settings, as well as by e-mail solicitation and word of mouth, into a longitudinal observational study designed to examine the effects of SSRIs on bone mass (Calarge et al., 2014). Of those taking SSRIs, 25 (28.4%) were taking fluoxetine, 25 (28.4%) sertraline, 6 (6.8%) escitalopram and 2 (2.3%) paroxetine.

Those treated with other psychotropic medications over the preceding two years were excluded, though entry criteria permitted the use of benzodiazepines, antihistaminic agents, trazodone, α_2-agonists, mirtazapine, or stable doses of a psychostimulant. Other grounds for exclusion were the presence of eating disorders, substance dependence, pregnancy, significant medical or surgical history, the chronic use of medications potentially affecting bone metabolism (e.g., extended corticosteroid use), and plans to move out of state in the following year. The University of Iowa Institutional Review Board approved the study and adult participants provided informed consent. The parent/guardian of minor participants provided written informed consent while the minors gave written assent to the study.

2.2. Procedures

Trained research coordinators collected demographic and clinical data in an intake assessment battery that included the researcher-administered Inventory for Depressive Symptomatology (IDS), the NIMH Diagnostic Interview Schedule for Children (DISC-IV) (Shaffer et al., 2000), and an unstructured interview by a child psychiatrist (CAC). Parents of minors were also interviewed. Intake assessment included as well the Early Trauma Inventory – Self Report (ETISR) (Hyman et al., 2005; Bremner et al., 2007), a 19-item questionnaire covering general adverse life events that occurred before the age of 18. These included physical, sexual, and emotional abuse. Participants described their recent food intake with the Food Questionnaire (www.NutritionQuest.com), an instrument that required the subject to estimate their usual intake of a given food type over the preceding year.

Participants completed the Multidimensional Personality Questionnaire (MPQ) (Tellegen and Waller, 2008) at their first follow-up visit. The MPQ is a factor-analytically derived, broadband inventory of normal personality. It has 11 primary scales that load on three higher order factors: Positive Emotionality (Well-Being, Social Potency, Social Closeness, and Achievement), Negative Emotionality (Stress Reaction, Alienation, and Aggression), and Constraint (Control, Harm Avoidance, and Traditionalism). Negative emotionality correlates strongly with the construct of neuroticism from the NEO Personality Inventory (McCrae and Costa, 1987; Church, 1994). Because of the importance of neuroticism to the heritability (Kendler et al., 2006) and course (Wiersma et al., 2011) of depressive disorders, this measure was selected as a focus in the following analysis.

Raters arranged for face-to-face visits 4, 8 and 12 months after study entry. An Inventory of Depressive Symptoms (IDS) (Rush et al., 1996) at each in-person visit to assess depression symptom severity during the week prior to administration.

Samples for plasma PUFA composition assays were drawn under non-fasting conditions and stored at −80 °C. Storage times were up to two years but fatty acid composition in such samples have been shown to be stable across periods of 8–10 years (Matthan et al., 2010). Plasma lipids were extracted into chloroform-methanol (Folch et al., 1957) containing 0.01% (wt%) butylated hydroxytoluene as antioxidant. The phospholipid fraction was isolated by chromatography over aminopropyl silica gel. Fatty acids were methylated using acetyl chloride (Baack et al., 2012). Fatty acid methyl esters were separated by Hewlett-Packard model 5890 II gas chromatograph equipped with a DB23 column (30 m × 0.25 mm id; Agilent, Santa Clara, CA) and a flame ionization detector. Chromatograms of fatty acid methyl ester standard mixtures were obtained with each group of samples and the retention times of the standards were used to identify the fatty acids present in each phospholipid sample. Values are reported in mole %.

2.3. Data Analysis

To minimize risks for type 2 errors, analyses were limited, a priori, to those PUFA values that figure most prominently in the relevant literature, eicosapentanoic acid (EPA), decosahexanoic acid (DHA), arachidonic acid (AA) and the ratio of AA to the sum of EPA and DHA (AA/EPA + DHA). Natural log values were used for all analyses.

Analyses used both SPSS (version 22) and SAS 9.3. Group comparisons employed *t*-tests or one-way ANOVA as appropriate. IDS and negative emotionality scores were markedly skewed toward higher values and were therefore square root transformed when used as outcomes. Because we had no casual hypothesis for the relationship between PUFA composition and childhood adversity we simply described