Published in final edited form as:

Psychiatry Res. 2015 December 15; 230(2): 447–453. doi:10.1016/j.psychres.2015.09.035.

First-Episode Bipolar Disorder is Associated with Erythrocyte Membrane Docosahexaenoic Acid Deficits: Dissociation from Clinical Response to Lithium or Quetiapine

Robert K. McNamara^{a,*}, Ronald Jandacek^b, Patrick Tso^b, Thomas J. Blom^a, Jeffrey A. Welge^a, Jeffrey R. Strawn^a, Caleb M. Adler^a, Melissa P. DelBello^a, and Stephen M. Strakowski^a

^aDepartment of Psychiatry and Behavioral Neuroscience, Division of Bipolar Disorders Research, University of Cincinnati College of Medicine, Cincinnati, OH 45267, USA

^bDepartment of Pathology, University of Cincinnati, Cincinnati OH 45237, USA

Abstract

Deficits in long-chain omega-3 (LCn-3) fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may be associated with the pathophysiology of bipolar disorder. However, LCn-3 fatty acid status at the initial onset of mania and its association with treatment response are not known. Erythrocyte membrane fatty acid composition was determined in first-episode bipolar manic or mixed ($n=40$) and healthy ($n=40$) subjects. Mood symptom ratings were obtained with the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale (HDRS). Erythrocyte fatty acid composition and clinical ratings were also determined within a sub-group of bipolar subjects following 8-week ($n=19$) or 52-week ($n=11$) open-label treatment with lithium or quetiapine. At baseline bipolar subjects exhibited significantly lower erythrocyte docosahexaenoic acid (DHA, 22:6n-3) composition compared with healthy subjects (–23%, $p<0.0001$). EPA (20:5n-3) and docosapentanoic acid (22:5n-3), and LCn-6 fatty acids including arachidonic acid were not different. Following 8- or 52-week treatment with lithium or quetiapine, YMRS and HDRS total scores decreased significantly whereas erythrocyte fatty acids including DHA did not change. These data indicate that selective erythrocyte DHA deficits coincide with the initial onset of manic symptoms, and reductions in mood symptoms following treatment are not mediated by changes in fatty acid status.

Keywords

Bipolar disorder; Mania; Lithium; Quetiapine; Arachidonic acid

*To whom correspondence should be addressed: Robert K. McNamara, Ph.D. Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, 260 Stetson Street, Cincinnati, OH 45219-0516, USA. PH: 513-558-5601, FAX: 513-558-4805, robert.mcnamara@uc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

A growing body of evidence suggests that lower habitual dietary intake of long-chain omega-3 (LCn-3) fatty acids, including eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), is associated with the pathophysiology of mood disorders including major depressive disorder (MDD) and bipolar disorder (McNamara, 2015). First, cross-national epidemiological surveys suggest that greater habitual dietary intake of fish/seafood, primary sources of preformed EPA and DHA, is associated with reduced lifetime prevalence rates of MDD (Hibbeln, 1998; Peet, 2004) and bipolar disorder (Noaghiul and Hibbeln, 2003). Second, cross-sectional studies suggest that greater habitual fish or fish oil intake is associated with reduced risk of developing depressive symptoms (Tanskanen et al., 2001; Timonen et al., 2004; Raeder et al., 2007; Lai et al., 2014). Third, meta-analyses of controlled supplementation trials reveal that fish oil is more effective than placebo for reducing depression symptom severity in MDD (Grosso et al., 2014) and bipolar disorder (Sarris et al., 2012). These and other findings suggest that habitual diets containing low amounts of LCn-3 fatty acids may increase risk for mood dysregulation.

Erythrocyte (red blood cell) membrane EPA and DHA composition is highly correlated with habitual intake of fish or fish oil (Sands et al., 2005; Flock et al., 2013) and represents a valid biomarker of LCn-3 fatty acid status (Harris et al., 2013). Case-control studies have consistently observed reduced erythrocyte EPA and/or DHA levels in adults and adolescents with MDD (Lin et al., 2010; Pottala et al., 2012; McNamara et al., 2014) and in medicated and medication-free bipolar subjects (Chiu et al., 2003; Ranjekar et al., 2003; Clayton et al., 2008; McNamara et al., 2010). Although depression frequently precedes the initial onset of mania (Skjelstad et al., 2010), it is not currently known whether LCn-3 fatty acid deficits coincide with the initial onset of mania or are a consequence of chronic illness and/or pharmacological treatments. For example, animal studies suggest that chronic exposure to mood-stabilizer (Rao et al., 2008; McNamara et al., 2008) or second-generation antipsychotic (McNamara et al., 2009, 2011) medications alter long-chain fatty acid membrane turnover and composition. Moreover, the relationship between LCn-3 fatty acid status and the initial response to pharmacologic treatments is unknown. While prior supplementation studies in medicated bipolar subjects suggest that increasing LCn-3 fatty acid status augments therapeutic efficacy (Stoll et al., 1999; Clayton et al., 2009), this relationship has not been evaluated prospectively from a medication-free baseline.

The primary objective of the present study was to compare erythrocyte fatty acid composition in first-episode bipolar manic and healthy comparison subjects. Based on existing evidence, our specific prediction was that first-episode bipolar subjects would exhibit significantly lower erythrocyte EPA and DHA levels compared with healthy subjects. We additionally investigated variables previously found to be associated with EPA and DHA status including gender (Giltay et al., 2004; Bakewell et al., 2006), body mass index (Sands et al., 2005), and cigarette smoking (Leng et al., 1994; Hibbeln et al., 2003). A second objective was to prospectively investigate the effects of 8- or 52-week treatment with either lithium or quetiapine on erythrocyte fatty acid composition and investigate associations with treatment response.

2. Methods

2.1. Participants

Bipolar subjects experiencing a first mixed or manic episode (n=40; n=20 women, n=20 men) were consecutively recruited from the inpatient psychiatric units of the University of Cincinnati Medical Center and Cincinnati Children's Hospital Medical Center. Healthy subjects with no history of a *DSM-IV* Axis I disorder (n=40; n=20 women, n=20 men) were recruited from the greater Cincinnati area. Diagnoses were made with the Structured Clinical Interview for *DSM-IV*, patient version (SCID-I/P)(First et al., 1995). Symptom ratings were obtained with the Young Mania Rating Scale (YMRS)(Young et al., 1978) to assess mania and the 28-item Hamilton Depression Rating Scale (HDRS)(Hamilton, 1960) to assess depression. Both groups were assessed by board-certified psychiatrists with established inter-rater reliabilities (kappa >0.9). Eligible bipolar subjects met *DSM-IV* criteria for type I bipolar disorder, manic or mixed, had a baseline YMRS total score >20, had 3 months of lifetime antidepressant medication exposure, had no more than two prior episodes of major depression, and were between 15 and 35 years of age (subjects under 18 years were required to rate at least 4 on the Duke Tanner Pubertal Self Rating scale). Bipolar subjects were excluded from participation if they had a history of mental retardation or an estimated IQ total score of <85 determined by the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), had a positive urine pregnancy test (in women), or had any substance use disorder within the past three months established with the SCID-I/P in conjunction with the Addiction Severity Index. Cigarette use in the last 30 days was also determined. All subjects provided written informed consent, or if under 18 years of age assent plus consent from a legal guardian. This study was approved by the Institutional Review Boards of University of Cincinnati Medical Center and Cincinnati Children's Hospital Medical Center.

2.2. Treatments

Following baseline evaluations, bipolar subjects were pseudorandomly assigned to open label treatment with either lithium or quetiapine and erythrocyte fatty acid composition and clinical ratings repeated at week 8 or week 52. The quetiapine target dose was 400–600 mg and the lithium target dose was based on achieving serum levels of 0.8–1.2 meq/L achieved in most subjects by doses in the range of 600–1800 mg/day.

2.3. Erythrocyte fatty acid composition

Whole venous blood (4 ml) was collected into EDTA-coated BD Vacutainer tubes, and centrifuged at 4°C for 20 min (1,500 xg). Plasma and buffy coat were removed and erythrocytes washed 3 times with sterile 0.9% NaCl and stored at –80°C. Total erythrocyte membrane fatty acid composition was determined with a Shimadzu GC-2010 equipped with an auto-injector (Shimadzu Scientific Instruments Inc., Columbia MD), using the direct saponification method described previously (McNamara et al., 2010, 2014). The column was a DB-23 (123–2332): 30m (length), I.D. (mm) 0.32 wide bore, film thickness of 0.25 µM (J&W Scientific, Folsom CA). The carrier gas was helium with a column flow rate of 2.5 ml/min. Fatty acid identification was determined using retention times of authenticated fatty acid methyl ester standards (Matreya LLC Inc., Pleasant Gap PA). Analysis of fatty acid methyl esters was based on areas calculated with Shimadzu Class VP 4.3 software. The

lower limit of detection with a threshold area of 500 and a 1 μ l injection volume was approximately 200 ng of an individual fatty acid. Data are expressed as weight percent of total fatty acids (mg fatty acid/100 mg fatty acids) which we have previously found in pilot studies to be highly correlated with fatty acid total mass (μ mol/g). Samples were processed by a technician blinded to group assignment.

2.4. Statistical analysis

Group differences in demographic variables were evaluated using unpaired *t*-tests for continuous variables and Chi-square tests for dichotomous variables. Homogeneity of variance was confirmed using Bartlett's test. For the baseline fatty acid analysis we employed Bonferroni correction for multiple comparisons ($\alpha=0.05/17$ comparisons = 0.003). Categorical assessments were used to determine the percentage of subjects with an 'omega-3 index' (EPA+DHA weight percent of total fatty acids) of ≥ 4.0 percent (Chi-square test). Analysis of interactions with demographic variables was performed with a two-way ANOVA. Baseline-endpoint changes in symptom ratings (YMRS, HDRS) were evaluated with unpaired *t*-tests. Pearson correlation coefficients were used to evaluate relationships among baseline or endpoint erythrocyte fatty acid composition and manic (YMRS) and depression (HDRS) symptom severity scores as well as baseline-endpoint change in symptom ratings. Differences between correlation coefficients were determined using the Fisher *r*-to-*z* transformation. For primary outcome measures, effect size was calculated using Cohen's *d*. Using Mplus v6.12 software (Muthen & Muthen, Los Angeles CA), mediation analyses were conducted to estimate: 1) whether selected fatty acid levels mediated variation in YMRS and HDRS scores between groups at baseline, and 2) whether baseline-endpoint changes in YMRS and HDRS scores were mediated by baseline-endpoint changes in fatty acid levels. Bootstrapping was used to estimate confidence intervals on model parameters, including estimates of the indirect (mediated) effects via selected fatty acid levels. All statistical tests were two-tailed ($\alpha=0.05$).

3. Results

3.1. Subject characteristics

Baseline demographic characteristics of both groups are presented in Table 1. Although both groups were similar, significantly more bipolar subjects (45%) reported cigarette use in the past 30 days compared with healthy subjects (17.5%, $p=0.01$). Eleven bipolar subjects and none of the healthy subjects had a lifetime history of attention deficit hyperactivity disorder (ADHD). The mean YMRS total score for bipolar subjects was significantly greater than healthy subjects ($p = 0.0001$, $d = 5.9$), and the mean HDRS total scores significantly greater for bipolar subjects than healthy subjects ($p = 0.0001$, $d = 2.1$).

3.2. Baseline measures

3.2.1. Erythrocyte fatty acid composition—Group erythrocyte fatty acid compositions are presented in Table 2. Erythrocyte DHA composition (-23% , $p = 0.0001$, $d = 1.0$) was significantly lower in bipolar than healthy subjects, and there was a trend for lower EPA ($p=0.08$, $d = 0.42$) but not docosapentaenoic acid (DPA, $22:5n-3$) ($p=0.64$). The sum of LCn-3 fatty acids (EPA+DPA+DHA, -15% , $p=0.0002$, $d = 0.87$) and EPA+DHA

('omega-3' index)(-20%, $p = 0.0001$, $d = 1.0$) were significantly lower in the bipolar group. A significantly greater number of bipolar subjects (93%) exhibited an omega-3 index (EPA +DHA) of 4.0 percent (range: 1.7–4.9%) compared with healthy subjects (67%, range: 2.4–7.5%)($p=0.01$). Erythrocyte arachidonic acid (AA, 20:4 n -6) composition did not differ between groups ($p=0.89$), and the AA/DHA (+22%, $p = 0.0001$, $d = 0.97$) and AA/EPA +DHA (+22%, $p = 0.0001$, $d = 1.0$) ratios were significantly greater in bipolar subjects. There was a trend for a higher AA/EPA ratio in bipolar subjects (+11%, $p=0.05$). Other major saturated and monounsaturated fatty acids did not differ between groups.

3.2.2. Relationship with potential confounding variables—For DHA the interaction term for group by smoking status was not significant ($p=0.85$). DHA levels did not differ between bipolar subjects that smoked ($n=18$) compared with those that did not smoke ($n=22$)($p=0.09$), and both non-smokers (-16%, $p=0.01$) and smokers (-26%, $p=0.0007$) exhibited significantly lower DHA levels compared with non-smoking healthy subjects ($n=33$). BMI was not significantly correlated with DHA levels among bipolar ($r = +0.11$, $p=0.54$), healthy ($r = +0.02$, $p=0.92$), or all subjects ($r = +0.07$, $p=0.57$). Age was not significantly correlated with DHA levels among bipolar ($r = -0.03$, $p=0.86$), healthy ($r = -0.11$, $p=0.48$), or all subjects ($r = -0.04$, $p=0.75$). While the group by gender interaction was not significant for DHA ($p=0.22$), there was a significant main effect of gender: all women ($n=40$) exhibited higher DHA levels compared with all men ($n=40$)(+12%, $p=0.03$). Bipolar subjects with (-26%, $p=0.004$) and without (-21%, $p=0.0006$) ADHD exhibited similar DHA deficits compared with healthy subjects, and the two groups did not differ from each other ($p=0.46$).

3.2.3. Associations with baseline symptom severity—YMRS total scores were not correlated with DHA in bipolar ($r = +0.04$, $p=0.80$) or healthy ($r = -0.12$, $p=0.49$) subjects, and a significant inverse correlation was observed when both groups were combined ($r = -0.43$, $p = 0.0001$). Similarly, YMRS total scores were positively correlated with the AA/DHA ($r = +0.41$, $p = 0.0001$) and AA/EPA+DHA ($r = +0.42$, $p = 0.0001$) ratios only when both groups were combined. YMRS total scores were not correlated with EPA ($r = +0.03$, $p=0.83$), arachidonic acid ($r = +0.04$, $p=0.73$), or the AA/EPA ratio ($r = +0.16$, $p=0.17$) among all subjects or among only bipolar or healthy subjects. HDRS total scores were inversely correlated with DHA ($r = -0.35$, $p=0.002$) and positively correlated with the AA/DHA ($r = +0.39$, $p=0.0004$) and AA/EPA+DHA ($r = +0.38$, $p=0.0005$) ratios among all subjects, but not among only bipolar or healthy subjects. HDRS total scores were not correlated with EPA among all subjects ($r = -0.04$, $p=0.72$) or among only bipolar ($r = +0.24$, $p=0.13$) or healthy ($r = -0.07$, $p=0.66$) subjects and the differences between correlation coefficients was not significant ($p=0.19$). However, arachidonic acid was positively correlated with HDRS total scores among bipolar subjects ($r = +0.31$, $p=0.05$), but not among healthy subjects ($r = -0.07$, $p=0.66$) or all subjects ($r = +0.16$, $p=0.15$), though the differences between correlation coefficients was not significant ($p=0.09$). The AA/EPA ratio was not correlated with HDRS total scores among all subjects ($r = +0.04$, $p=0.72$) or among only bipolar ($r = -0.26$, $p=0.15$) or healthy ($r = +0.07$, $p=0.66$) subjects. In the mediation analysis, the standardized indirect effects from group membership to

YMRS and HDRS scores via any of the selected baseline fatty acid levels or ratios (DHA, AA, AA/DHA EPA+DHA, AA/EPA+DHA) were all less than $r = 0.02$ (all $p > 0.5$).

3.3. Treatment effects

3.3.1. 8-weeks—Within-subject erythrocyte fatty acid data were obtained at baseline and week 8 from $n=19$ bipolar subjects ($n=8$ lithium, $n=11$ quetiapine). YMRS total scores decreased significantly following 8-week treatment with lithium ($p=0.0001$) or quetiapine ($p=0.0001$) (Fig. 1A). HDRS total scores decreased significantly following 8-week treatment with lithium ($p=0.03$) or quetiapine ($p=0.02$). There were no significant alterations in any fatty acid including DHA (Fig. 1C) or AA (Fig. 1E) following 8-week treatment with lithium (Table S1) or quetiapine (Table S2), or when both treatments were combined ($n=19$) (Table S3). Among bipolar subjects treated with lithium, baseline DHA levels were not significantly correlated with baseline-endpoint change in YMRS ($r = +0.09$, $p=0.83$) or HDRS ($r = -0.06$, $p=0.88$) total scores. Among bipolar subjects treated with quetiapine, baseline DHA levels were not significantly correlated with baseline-endpoint change in YMRS ($r = -0.41$, $p=0.21$) or HDRS ($r = -0.09$, $p=0.79$) total scores. Among all bipolar subjects treated with lithium or quetiapine ($n=19$), baseline DHA levels were not significantly correlated with baseline-endpoint change in YMRS ($r = -0.29$, $p=0.23$) or HDRS ($r = -0.12$, $p=0.61$) total scores or endpoint YMRS ($r = +0.28$, $p=0.24$) or HDRS ($r = -0.07$, $p=0.78$) total scores. In the mediation analysis, the standardized indirect effects from baseline-endpoint change in YMRS or HDRS via any of the selected baseline fatty acid levels or ratios (DHA, AA, AA/DHA EPA+DHA, AA/EPA+DHA) were all less than $r = 0.02$ (all $p > 0.5$).

3.5.2. 52-weeks—Within-subject erythrocyte fatty acid data were obtained at baseline and week 52 from $n=11$ bipolar subjects ($n=3$ lithium & $n=8$ quetiapine). A subset of these patients ($n=3$ lithium & $n=5$ quetiapine) were also included in the 8 week analysis. Baseline YMRS ($p = 0.0001$) (Fig. 1B) and HDRS ($p=0.0003$) total scores decreased significantly following 52-week treatment. There were no significant alterations in any fatty acid including DHA (Fig. 1D) or AA (Fig. 1F) following 52-week treatment with lithium or quetiapine (Table S4). However, there was a trend for an increase in DPA (22:5 $n-3$)(+23%, $p=0.04$) and a reduction in the LC $n-6$ /LC $n-3$ ratio (-15%, $p=0.05$). Among all bipolar subjects ($n=11$) neither baseline DHA levels ($r = +0.11$, $p=0.74$) nor baseline-endpoint change in DHA ($r = +0.35$, $p=0.29$) were significantly correlated with baseline-endpoint change in YMRS total scores. Similarly, neither baseline DHA levels ($r = +0.32$, $p=0.33$) nor baseline-endpoint change in DHA ($r = +0.23$, $p=0.26$) were significantly correlated with baseline-endpoint change in HDRS total scores. In the mediation analysis, the standardized indirect effects from baseline-endpoint change in YMRS or HDRS via any of the selected baseline fatty acid levels or ratios (DHA, AA, AA/DHA EPA+DHA, AA/EPA+DHA) were all less than $r = 0.02$ (all $p > 0.5$).

4. Discussion

The present study found that first-episode bipolar manic subjects exhibited significant erythrocyte DHA deficits compared with demographically similar healthy subjects. The

observed erythrocyte DHA deficit in first-episode mania is consistent with previous case-control studies investigating erythrocyte fatty acids in bipolar disorder (Chiu et al., 2003; Ranjekar et al., 2003; Clayton et al., 2008; McNamara et al., 2010). The selective reduction in DHA is also consistent with our previous report in medication-free bipolar disorder (McNamara et al., 2010) and a more recent study that used plasma (Pomponi et al., 2013). Although we did not observe significant erythrocyte EPA deficits in bipolar subjects, which is consistent with some (Chiu et al., 2003; McNamara et al., 2010) but not all (Ranjekar et al., 2003; Clayton et al., 2008) previous studies, there was a non-significant trend for lower levels ($p=0.08$). We did not observe significant erythrocyte AA deficits which is consistent with most (Ranjekar et al., 2003; Clayton et al., 2008; McNamara et al., 2010) but not all (Chiu et al., 2003) previous studies. It is notable that prior case-control studies observed significant erythrocyte AA and DHA deficits in medication-naïve first-episode psychosis (Hoen et al., 2013), and deficits in AA but not DHA in individuals at ultra-high risk for psychosis (Rice et al., 2015), suggesting that AA deficits may be more closely associated with risk for psychosis versus mania. Extant cross-sectional evidence therefore suggests that bipolar disorder is associated with significant DHA deficits, and the present results demonstrate that DHA deficits coincide with, and may precede, the initial onset of manic symptoms.

It is notable that the fatty acid precursors of DHA including EPA (20:5 n -3) and DPA (22:5 n -3) were not significantly lower in mania. This finding suggests that the DHA deficit cannot be attributed to lower activities of delta-6 and delta-5 desaturase enzymes which mediate EPA and DPA biosynthesis from alpha-linolenic acid (ALA, 18:3 n -3) (Reardon and Brenna, 2013). This observation is further supported by the finding that LC n -6 fatty acids including arachidonic acid (AA, 20:4 n -6) were not significantly lower in bipolar disorder. Selective DHA deficits are however consistent with impaired peroxisome function which is required for the final biosynthesis of DHA from fatty acid precursors (Wanders, 2013). For example, individuals with peroxisomal biogenesis disorders also exhibit significant deficits in erythrocyte DHA but not fatty acid precursors of DHA (i.e., DPA) (Martinez, 1994; Moser et al., 1999). However, even healthy human subjects exhibit negligible ALA→DHA and EPA→DHA biosynthesis (Brenna et al., 2009), and we recently found that first-episode manic subjects do not exhibit other lipid abnormalities characteristic of peroxisomal biogenesis disorders (McNamara et al., 2014). Alternatively, elevations in lipid peroxidation may contribute to erythrocyte membrane DHA deficits (Khan et al., 2002), although we recently found that first-episode manic subjects exhibit reduced indices of lipid peroxidation (Andreazza et al., 2015). While reduced levels of DHA in erythrocyte membranes may be a consequence of elevations in calcium-independent phospholipase A₂ (iPLA₂) activity, prior studies suggest that blood iPLA₂ activity is lower (Ikenaga et al., 2015) or not different (Ross et al., 2006) in bipolar patients. Therefore, extant evidence would suggest that the observed erythrocyte membrane DHA deficits cannot be wholly attributed to impaired biosynthesis or elevated membrane cleavage or degradation.

While a limitation of the present study is that we did not administer a diet questionnaire to determine habitual fish intake, previous studies have demonstrated that erythrocyte DHA levels are linearly correlated with dietary fish or fish oil intake (Sands et al., 2005; Flock et

al., 2013). Therefore, it is possible that the lower DHA levels observed in first-episode mania may reflect dietary deficits in preformed DHA. This is supported in part by the observation that erythrocyte DHA levels increase significantly in bipolar subjects following supplementation with fish oil containing preformed DHA (Wozniak et al., 2007; Clayton et al., 2009). The latter finding also suggests that patients with bipolar disorder are not impaired at absorbing DHA from the gut or at incorporating DHA into erythrocyte membrane phospholipids. The present findings and prior evidence that fish oil supplementation can reduce manic and depression symptom severity in bipolar youth (Wozniak et al., 2007; Clayton et al., 2009) provide a strong rationale to correct low DHA levels in subjects with or at high-risk for bipolar disorder.

Some prior studies observed inverse correlations between DHA and/or EPA, and positive correlations between the AA/EPA ratio, and depression symptom severity in unipolar depression (Adams et al., 1996; Edwards et al., 1998), and the plasma free AA/EPA ratio was positively correlated with manic symptom severity in a small sample of medication-free subjects (Sublette et al., 2009). Consistent with our previous study in medication-free bipolar disorder (McNamara et al., 2010), the present study found that neither DHA nor EPA were significantly correlated with manic or depression symptom severity among bipolar subjects at baseline. However, we did observe a positive correlation between AA and depression, but not manic, symptom severity at baseline. Although we observed a trend for a higher baseline AA/EPA ratio in bipolar disorder, this did not correlate significantly with either manic or depression symptom severity. While these findings suggest that DHA is poorly correlated with manic and depression symptom severity, the uniformly low DHA levels observed in the bipolar subjects may have precluded more robust associations.

Based on evidence from animal studies suggesting that chronic exposure to mood-stabilizer medications including lithium (Rao et al., 2008; McNamara et al., 2008) or second-generation antipsychotics (McNamara et al., 2009, 2011) alter membrane fatty acid turnover and composition, a second objective of the present study was to prospectively investigate the effects of 8- or 52-week treatment with either lithium or quetiapine on erythrocyte fatty acid composition and to determine associations with treatment response. We found that neither 8- nor 52-week treatment with quetiapine or lithium significantly altered erythrocyte fatty acid composition despite significant reductions in mood symptom severity. Moreover, the baseline-endpoint reductions in manic and depressive symptoms were not mediated by changes in DHA levels. This finding does not support a prior prospective study which found that the erythrocyte DHA deficits observed in first-episode psychosis were normalized following 6 month treatment with olanzapine or risperidone in association with reductions in psychotic symptoms (Evans et al., 2003). Nevertheless, the present prospective data suggest that the DHA deficits previously observed in medicated bipolar disorder subjects cannot be wholly attributed to long-term medication exposure.

The present findings may take on additional significance in view of data indicating that DHA is the principal LCn-3 fatty acid found in cortical gray matter, and erythrocyte DHA is correlated with cortical gray matter DHA composition (Connor et al., 1990; Carver et al., 2001). We previously reported significant DHA deficits in the postmortem prefrontal cortex (BA10) gray matter of bipolar disorder (McNamara et al., 2008), and emerging evidence

from neuroimaging studies suggest that DHA status is correlated with corticolimbic structural and functional integrity (Conklin et al., 2007; Sublette et al., 2009; McNamara et al., 2010). Additionally, erythrocyte EPA and DHA composition is positively correlated with immune cell (i.e., monocyte) EPA and DHA composition (Browning et al., 2012), and cross-sectional studies have observed an inverse association between dietary or blood LCn-3 fatty acid levels and pro-inflammatory cytokine production (Pischon et al., 2003; Lopez-Garcia et al., 2004; Calder, 2008; Kalogeropoulos et al., 2010). It is notable therefore that elevated pro-inflammatory cytokine levels have been observed in bipolar disorder and are reduced following treatment with mood-stabilizer or antipsychotic medications in association with reductions in mood symptom severity (Maes et al., 1995; Knijff et al., 2007; Rapaport et al., 1999). Therefore, elevated immune-inflammatory signaling secondary to LCn-3 fatty acid deficits may contribute to mood symptoms, and reductions in pro-inflammatory signaling may mediate the therapeutic effects of medications independent of changes in LCn-3 fatty acid status. This suggestion is supported by our previous study which found that chronic risperidone treatment decreased constitutively elevated pro-inflammatory cytokine levels in LCn-3 fatty acid-deficient rats but did not alter erythrocyte EPA and DHA levels (McNamara et al., 2011). Additional studies are warranted to investigate whether pro-inflammatory cytokine levels mediate the association between low LCn-3 fatty acid status and mood symptoms in bipolar disorder.

In summary, this study demonstrates that individuals with first-episode bipolar mania exhibit significant erythrocyte DHA deficits compared with demographically similar healthy subjects. These data are consistent with prior case-control studies conducted in different countries, and add to a growing body of evidence implicating DHA deficiency in the pathophysiology and potentially pathoetiology of bipolar disorder. Additional prospective longitudinal studies are warranted to determine whether erythrocyte DHA deficits represent a valid prodromal risk biomarker. The present data additionally suggest that reductions in mood symptom severity following lithium or quetiapine treatment do not alter erythrocyte fatty acid levels and may instead be mediated through interrelated mechanisms including reductions in pro-inflammatory signaling cascades.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported in part by NIH/NIMH grant P50 MH077138 to S.M.S., R34 NIH/NIMH grant MH083924 to R.K.M and M.P.D (Co-PIs), and NIH/NIDDK grant DK59630 to P.T.; the NIH had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

References

- Adams PB, Lawson S, Sanigorski A, Sinclair AJ. Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. *Lipids*. 1996; 31:S157–S161. [PubMed: 8729112]

- Andreazza A, McNamara RK, Leffler J, Cullen K, Croarkin P, Geske J, Biernacka J, Frye M, DelBello MP. Lipid peroxidation biomarkers in adolescents with or at high-risk for bipolar disorder. *Bipolar Disorders*. 2015; 17:59–60.
- Bakewell L, Burdge GC, Calder PC. Polyunsaturated fatty acid concentrations in young men and women consuming their habitual diets. *British Journal of Nutrition*. 2006; 96:93–99. [PubMed: 16869996]
- Brenna JT, Salem N Jr, Sinclair AJ, Cunnane SC. International Society for the Study of Fatty Acids and Lipids ISSFAL. alpha-Linolenic acid supplementation and conversion to n-3 long-chain polyunsaturated fatty acids in humans. *Prostaglandins Leukotrienes & Essential Fatty Acids*. 2009; 80:85–91.
- Browning LM, Walker CG, Mander AP, West AL, Madden J, Gambell JM, Young S, Wang L, Jebb SA, Calder PC. Incorporation of eicosapentaenoic and docosahexaenoic acids into lipid pools when given as supplements providing doses equivalent to typical intakes of oily fish. *American Journal of Clinical Nutrition*. 2012; 96:748–758. [PubMed: 22932281]
- Calder PC. The relationship between the fatty acid composition of immune cells and their function. *Prostaglandins Leukotrienes & Essential Fatty Acids*. 2008; 79:101–108.
- Carver JD, Benford VJ, Han B, Cantor AB. The relationship between age and the fatty acid composition of cerebral cortex and erythrocytes in human subjects. *Brain Research Bulletin*. 2001; 56:79–85. [PubMed: 11704343]
- Chiu CC, Huang SY, Su KP, Lu ML, Huang MC, Chen CC, Shen WW. Polyunsaturated fatty acid deficit in patients with bipolar mania. *European Neuropsychopharmacology*. 2003; 13:99–103. [PubMed: 12650953]
- Clayton EH, Hanstock TL, Hirneth SJ, Kable CJ, Garg ML, Hazell PL. Long-chain omega-3 polyunsaturated fatty acids in the blood of children and adolescents with juvenile bipolar disorder. *Lipids*. 2008; 43:1031–1038. [PubMed: 18781353]
- Clayton EH, Hanstock TL, Hirneth SJ, Kable CJ, Garg ML, Hazell PL. Reduced mania and depression in juvenile bipolar disorder associated with long-chain omega-3 polyunsaturated fatty acid supplementation. *European Journal of Clinical Nutrition*. 2009; 63:1037–1040. [PubMed: 19156158]
- Conklin SM, Gianaros PJ, Brown SM, Yao JK, Hariri AR, Manuck SB, Muldoon MF. Long-chain omega-3 fatty acid intake is associated positively with corticolimbic gray matter volume in healthy adults. *Neuroscience Letters*. 2007; 421:209–212. [PubMed: 17574755]
- Connor WE, Neuringer M, Lin DS. Dietary effects on brain fatty acid composition: the reversibility of n-3 fatty acid deficiency and turnover of docosahexaenoic acid in the brain, erythrocytes, and plasma of rhesus monkeys. *Journal of Lipid Research*. 1990; 31:237–247. [PubMed: 2139096]
- Edwards R, Peet M, Shay J, Horrobin D. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. *Journal of Affective Disorders*. 1998; 48:149–155. [PubMed: 9543204]
- Evans DR, Parikh VV, Khan MM, Coussons C, Buckley PF, Mahadik SP. Red blood cell membrane essential fatty acid metabolism in early psychotic patients following antipsychotic drug treatment. *Prostaglandins Leukotrienes & Essential Fatty Acids*. 2003; 69:393–399.
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Biometrics Research Department. New York State Psychiatric Institute; 722 West 168th Street, New York, NY 10032: 1995. Structured Clinical Interview for DSM-IV Axis I Disorders- Patient Edition (SCID-I/P).
- Flock MR, Skulas-Ray AC, Harris WS, Etherton TD, Fleming JA, Kris-Etherton PM. Determinants of erythrocyte omega-3 fatty acid content in response to fish oil supplementation: a dose-response randomized controlled trial. *Journal of the American Heart Association*. 2013; 2:e000513. [PubMed: 24252845]
- Giltay EJ, Gooren LJ, Toorians AW, Katan MB, Zock PL. Docosahexaenoic acid concentrations are higher in women than in men because of estrogenic effects. *American Journal of Clinical Nutrition*. 2004; 80:1167–1174. [PubMed: 15531662]
- Grosso G, Pajak A, Marventano S, Castellano S, Galvano F, Bucolo C, Drago F, Caraci F. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. *PLoS One*. 2014; 9:e96905. [PubMed: 24805797]

- Hamilton M. A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1960; 25:56–61.
- Harris, WS.; von Schacky, C.; Park, Y. Standardizing methods for assessing omega-3 fatty acid biostatus. In: McNamara, RK., editor. *The Omega-3 Fatty Acid Deficiency Syndrome: Opportunities for Disease Prevention*. Nova Science Publishers, Inc; U.S.A: 2013. p. 385-398.
- Hibbeln JR, Makino KK, Martin CE, Dickerson F, Boronow J, Fenton WS. Smoking, gender, and dietary influences on erythrocyte essential fatty acid composition among patients with schizophrenia or schizoaffective disorder. *Biological Psychiatry*. 2003; 53:431–441. [PubMed: 12614996]
- Hibbeln JR. Fish consumption and major depression. *Lancet*. 1998; 351:1213. [PubMed: 9643729]
- Hoehn WP, Lijmer JG, Duran M, Wanders RJ, van Beveren NJ, de Haan L. Red blood cell polyunsaturated fatty acids measured in red blood cells and schizophrenia: a meta-analysis. *Psychiatry Research*. 2013; 207:1–12. [PubMed: 23068078]
- Ikenaga EH, Talib LL, Ferreira AS, Machado-Vieira R, Forlenza OV, Gattaz WF. Reduced activities of phospholipases A2 in platelets of drug-naïve bipolar disorder patients. *Bipolar Disorders*. 2015; 17:97–101. [PubMed: 25041493]
- Kalogeropoulos N, Panagiotakos DB, Pitsavos C, Chrysoshoou C, Rousinou G, Toutouza M, Stefanadis C. Unsaturated fatty acids are inversely associated and n-6/n-3 ratios are positively related to inflammation and coagulation markers in plasma of apparently healthy adults. *Clinica Chimica Acta*. 2010; 411:584–591.
- Khan MM, Evans DR, Gunna V, Scheffer RE, Parikh VV, Mahadik SP. Reduced erythrocyte membrane essential fatty acids and increased lipid peroxides in schizophrenia at the never-medicated first-episode of psychosis and after years of treatment with antipsychotics. *Schizophrenia Research*. 2002; 58:1–10. [PubMed: 12363384]
- Knijff EM, Breunis MN, Kupka RW, de Wit HJ, Ruwhof C, Akkerhuis GW, Nolen WA, Drexhage HA. An imbalance in the production of IL-1beta and IL-6 by monocytes of bipolar patients: restoration by lithium treatment. *Bipolar Disorders*. 2007; 9:743–753. [PubMed: 17988365]
- Lai JS, Hiles S, Bisquera A, Hure AJ, McEvoy M, Attia J. A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. *American Journal of Clinical Nutrition*. 2014; 99:181–197. [PubMed: 24196402]
- Leng GC, Smith FB, Fowkes FG, Horrobin DF, Ells K, Morse-Fisher N, Lowe GD. Relationship between plasma essential fatty acids and smoking, serum lipids, blood pressure and haemostatic and rheological factors. *Prostaglandins Leukotrienes & Essential Fatty Acids*. 1994; 51:101–108.
- Lin PY, Huang SY, Su KP. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. *Biological Psychiatry*. 2010; 68:140–147. [PubMed: 20452573]
- Lopez-Garcia E, Schulze MB, Manson JE, Meigs JB, Albert CM, Rifai N, Willett WC, Hu FB. Consumption of (n-3) fatty acids is related to plasma biomarkers of inflammation and endothelial activation in women. *Journal of Nutrition*. 2004; 134:1806–1811. [PubMed: 15226473]
- Maes M, Bosmans E, Calabrese J, Smith R, Meltzer HY. Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. *Journal of Psychiatric Research*. 1995; 29:141–152. [PubMed: 7666381]
- Martinez M, Mougan I, Roig M, Ballabriga A. Blood polyunsaturated fatty acids in patients with peroxisomal disorders. A multicenter study. *Lipids*. 1994; 29:273–280. [PubMed: 8177020]
- McNamara RK, Able JA, Jandacek R, Rider T, Tso P, Eliassen J, Alfieri D, Weber W, Jarvis K, DelBello MP, Strakowski SM, Adler CM. Docosahexaenoic acid supplementation increases prefrontal cortex activation during sustained attention in healthy boys: A placebo-controlled, dose-ranging, functional magnetic resonance imaging study. *American Journal of Clinical Nutrition*. 2010; 91:1060–1067. [PubMed: 20130094]
- McNamara RK, Able JA, Jandacek R, Rider T, Tso P. Chronic risperidone treatment preferentially increases rat erythrocyte and prefrontal cortex omega-3 fatty acid composition: evidence for augmented biosynthesis. *Schizophrenia Research*. 2009; 107:150–157. [PubMed: 18993032]
- McNamara RK, Jandacek R, Rider T, Tso P, Cole-Strauss A, Lipton JW. Differential effects of antipsychotic medications on polyunsaturated fatty acid biosynthesis in rats: Relationship with

liver delta6-desaturase expression. *Schizophrenia Research*. 2011; 129:57–65. [PubMed: 21458237]

- McNamara RK, Jandacek R, Rider T, Tso P, Dwivedi Y, Pandey GN. Selective deficits in erythrocyte docosahexaenoic acid composition in adult patients with bipolar disorder and major depressive disorder. *Journal of Affective Disorders*. 2010; 126:303–311. [PubMed: 20413162]
- McNamara RK, Jandacek R, Rider T, Tso P, Stanford K, Hahn CG, Richtand NM. Deficits in docosahexaenoic acid and associated elevations in the metabolism of arachidonic acid and saturated fatty acids in the postmortem orbitofrontal cortex of patients with bipolar disorder. *Psychiatric Research*. 2008; 160:285–299.
- McNamara RK, Rider T, Jandacek R, Tso P. Chronic risperidone treatment normalizes elevated pro-inflammatory cytokine and C-reactive protein production in omega-3 fatty acid deficient rats. *European Journal of Pharmacology*. 2011; 652:152–156. [PubMed: 21118685]
- McNamara RK, Strawn JR, Stahl L, Jandacek R, Tso P, Rider T, DelBello MP. Long-chain omega-3 fatty acid deficits in youth with or at high or ultra-high risk for bipolar disorder are not due to impaired peroxisomal function. *Biological Psychiatry*. 2014; 75:S319.
- McNamara RK, Strimpfel J, Jandacek R, Rider T, Tso P, Welge JA, Strawn JR, DelBello MP. Detection and treatment of long-chain omega-3 fatty acid deficiency in adolescents with SSRI-resistant major depressive disorder. *PharmaNutrition*. 2014; 2:38–46. [PubMed: 24772386]
- McNamara RK, Sullivan J, Richtand NM. Omega-3 fatty acid deficiency augments amphetamine-induced behavioral sensitization in adult mice: prevention by chronic lithium treatment. *Journal of Psychiatric Research*. 2008; 42:458–468. [PubMed: 17628596]
- McNamara, RK. Role of dietary fatty acids in mood disorders. In: Watson, R.; De Meester, F., editors. *Handbook of Lipids in Human Function*. American Oil Chemistry Society Press; U.S.A: 2015. p. 135-169.
- Moser AB, Jones DS, Raymond GV, Moser HW. Plasma and red blood cell fatty acids in peroxisomal disorders. *Neurochemical Research*. 1999; 24:187–197. [PubMed: 9972864]
- Noaghiul S, Hibbeln JR. Cross-national comparisons of seafood consumption and rates of bipolar disorders. *American Journal of Psychiatry*. 2003; 160:2222–2227. [PubMed: 14638594]
- Peet M. International variations in the outcome of schizophrenia and the prevalence of depression in relation to national dietary practices: an ecological analysis. *British Journal of Psychiatry*. 2004; 184:404–408. [PubMed: 15123503]
- Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Willett WC, Rimm EB. Habitual dietary intake of n-3 and n-6 fatty acids in relation to inflammatory markers among US men and women. *Circulation*. 2003; 108:155–160. [PubMed: 12821543]
- Pomponi M, Janiri L, La Torre G, Di Stasio E, Di Nicola M, Mazza M, Martinotti G, Bria P, Lippa S, Natili R, Pomponi MF. Plasma levels of n-3 fatty acids in bipolar patients: deficit restricted to DHA. *Journal Psychiatric Research*. 2013; 47:337–342.
- Pottala JV, Talley JA, Churchill SW, Lynch DA, von Schacky C, Harris WS. Red blood cell fatty acids are associated with depression in a case-control study of adolescents. *Prostaglandins Leukotrienes & Essential Fatty Acids*. 2012; 86:161–165.
- Raeder MB, Steen VM, Vollset SE, Bjelland I. Associations between cod liver oil use and symptoms of depression: the Hordaland Health Study. *Journal of Affective Disorders*. 2007; 101:245–249. [PubMed: 17184843]
- Ranjekar PK, Hinge A, Hegde MV, Ghatge M, Kale A, Sitasawad S, Wagh UV, Debsikdar VB, Mahadik SP. Decreased antioxidant enzymes and membrane essential polyunsaturated fatty acids in schizophrenic and bipolar mood disorder patients. *Psychiatry Research*. 2003; 121:109–122. [PubMed: 14656446]
- Rao JS, Lee HJ, Rapoport SI, Bazinet RP. Mode of action of mood stabilizers: is the arachidonic acid cascade a common target? *Molecular Psychiatry*. 2008; 13:585–596. [PubMed: 18347600]
- Rapaport MH, Guylai L, Whybrow P. Immune parameters in rapid cycling bipolar patients before and after lithium treatment. *Journal of Psychiatric Research*. 1999; 33:335–340. [PubMed: 10404471]
- Reardon, HT.; Brenna, JT. Microsomal biosynthesis of omega-3 fatty acids. In: McNamara, RK., editor. *The Omega-3 Fatty Acid Deficiency Syndrome: Opportunities for Disease Prevention*. Nova Science Publishers, Inc; U.S.A: 2013. p. 3-17.

- Rice SM, Schäfer MR, Klier C, Mossaheb N, Vijayakumar N, Amminger GP. Erythrocyte polyunsaturated fatty acid levels in young people at ultra-high risk for psychotic disorder and healthy adolescent controls. *Psychiatry Research*. 2015; 228:174–176. [PubMed: 25979466]
- Ross BM, Hughes B, Kish SJ, Warsh JJ. Serum calcium-independent phospholipase A2 activity in bipolar affective disorder. *Bipolar Disorders*. 2006; 8:265–270. [PubMed: 16696828]
- Sands SA, Reid KJ, Windsor SL, Harris WS. The impact of age, body mass index, and fish intake on the EPA and DHA content of human erythrocytes. *Lipids*. 2005; 40:343–347. [PubMed: 16028715]
- Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. *Journal of Clinical Psychiatry*. 2012; 73:81–86. [PubMed: 21903025]
- Skjelstad DV, Malt UF, Holte A. Symptoms and signs of the initial prodrome of bipolar disorder: a systematic review. *Journal of Affective Disorders*. 2010; 126:1–13. [PubMed: 19883943]
- Sobel ME. Asymptotic confidence intervals for indirect effects in structural equation models. *Sociological Methodology*. 1982; 13:290–312.
- Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, Cress KK, Marangell LB. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Archives of General Psychiatry*. 1999; 56:407–412. [PubMed: 10232294]
- Sublette ME, Bosetti F, DeMar JC, Ma K, Bell JM, Fagin-Jones S, Russ MJ, Rapoport SI. Plasma free polyunsaturated fatty acid levels are associated with symptom severity in acute mania. *Bipolar Disorders*. 2007; 9:759–765. [PubMed: 17988367]
- Sublette ME, Milak MS, Hibbeln JR, Freed PJ, Oquendo MA, Malone KM, Parsey RV, Mann JJ. Plasma polyunsaturated fatty acids and regional cerebral glucose metabolism in major depression. *Prostaglandins Leukotrienes & Essential Fatty Acids*. 2009; 80:57–64.
- Tanskanen A, Hibbeln JR, Hintikka J, Haatainen K, Honkalampi K, Viinamäki H. Fish consumption, depression, and suicidality in a general population. *Archives of General Psychiatry*. 2001; 58:512–513. [PubMed: 11343534]
- Timonen M, Horrobin D, Jokelainen J, Laitinen J, Herva A, Räsänen P. Fish consumption and depression: the Northern Finland 1966 birth cohort study. *Journal of Affective Disorders*. 2004; 82:447–452. [PubMed: 15555697]
- Wanders, RJA. Peroxisomal biosynthesis of omega-3 fatty acids and human peroxisomal diseases. In: McNamara, RK., editor. *The Omega-3 Fatty Acid Deficiency Syndrome: Opportunities for Disease Prevention*. Nova Science Publishers, Inc; U.S.A: 2013. p. 19-30.
- Wechsler, D. Wechsler Abbreviated Scale for Intelligence. Harcourt Brace, Inc; San Antonio, TX: 1999.
- Wozniak J, Biederman J, Mick E, Waxmonsky J, Hantsoo L, Best C, Cluette-Brown JE, Laposata M. Omega-3 fatty acid monotherapy for pediatric bipolar disorder: a prospective open-label trial. *European Neuropsychopharmacology*. 2007; 17:440–447. [PubMed: 17258897]
- Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry*. 1978; 133:429–435. [PubMed: 728692]

Highlights

- Long-chain omega-3 fatty acid status at the initial onset of mania and its association with medication response in first-episode bipolar disorder is not known.
- Bipolar subjects exhibited significantly lower erythrocyte docosahexaenoic acid (DHA, 22:6n-3) composition compared with healthy subjects.
- Following 8- or 52-week treatment with lithium or quetiapine, manic and depressive symptoms decreased significantly whereas erythrocyte fatty acids including DHA and AA did not change.
- Selective erythrocyte DHA deficits coincide with the initial onset of manic symptoms, and reductions in manic and depressive symptoms following treatment with lithium or quetiapine are not associated with changes in fatty acid status

Figure 1.

YMRS total scores (A,B), erythrocyte DHA (22:6n-3) composition (C,D), and erythrocyte AA (20:4n-6) composition (E,F) of first-episode bipolar subjects at baseline (BL) and following 8 week (A,C,E) or 52 week (B,D,F) treatment with lithium or quetiapine. Fatty acid data are expressed as weight percent of total fatty acids (mg fatty acid/100 mg fatty acids). Values are group mean $\pm$ S.D., and *P*-values for baseline-endpoint change are presented.

Table 1

Demographic and clinical characteristics of study participants

Variable ¹	Healthy (n=40)	Bipolar (n=40)	P-value ²
Age (years)	18.5 ± 4.2	17.8 ± 3.8	0.46
Gender (% male)	50	50	1.0
Race (n)			
Caucasian	25	31	0.22
African American	8	5	
Other	7	4	
Smoking status (current) (n)	7	18	0.01
BMI (kg/m ²)	25.9 ± 6.4	25.3 ± 6.6	0.69
ADHD (lifetime)(n)	0	11	0.001
YMRS Total Score	1.3 ± 1.9	25.5 ± 5.5	0.0001
HAMD Total Score	1.2 ± 1.8	15.7 ± 9.4	0.0001

¹Values are group mean ± S.D. or number of subjects (n).²Two-tailed *t*-test or Chi-square test

Table 2

Baseline erythrocyte fatty acid composition in healthy controls and first-episode bipolar subjects

Fatty Acid ¹	Healthy (n=40)	Bipolar (n=40)	P-value ²
<i>Saturated Fatty Acids</i>			
Palmitic acid (16:0)	17.6 ± 0.9	17.7 ± 1.0	0.63
Stearic acid (18:0)	17.1 ± 0.9	17.1 ± 0.8	0.92
<i>Monounsaturated Fatty Acids</i>			
Oleic acid (18:1n-9)	12.2 ± 0.9	11.8 ± 0.8	0.04
Vaccenic acid (18:1n-7)	1.3 ± 0.3	1.3 ± 0.2	0.75
<i>Polyunsaturated Fatty Acids</i>			
Linoleic acid (18:2n-6)	12.1 ± 1.5	11.6 ± 1.0	0.09
Homo-γ-linolenic (20:3n-6)	1.9 ± 0.4	2.0 ± 0.6	0.13
Arachidonic acid (AA, 20:4n-6)	17.6 ± 1.4	17.5 ± 1.7	0.89
Docosatetraenoic acid (22:4n-6)	4.5 ± 0.5	4.7 ± 0.7	0.04
Docosapentaenoic acid (22:5n-6)	1.0 ± 0.2	1.0 ± 0.2	0.94
Eicosapentaenoic acid (EPA, 20:5n-3)	0.33 ± 0.1	0.28 ± 0.1	0.08
Docosapentaenoic acid (22:5n-3)	2.3 ± 0.4	2.3 ± 0.4	0.64
Docosahexaenoic acid (DHA, 22:6n-3)	3.6 ± 1.0	2.8 ± 0.6	0.0001
EPA+DHA (Omega-3 Index)	3.9 ± 1.0	3.1 ± 0.7	0.0001
<i>Ratios</i>			
AA:DHA	5.2 ± 1.3	6.7 ± 1.7	0.0001
AA:EPA	58.9 ± 19.1	65.9 ± 20.2	0.05
AA:EPA+DHA	4.7 ± 1.1	6.0 ± 1.4	0.0001
LCn-6/LCn-3	4.1 ± 0.8	4.8 ± 0.8	0.0002

¹Values are group mean fatty acid composition (wt % total fatty acids) ± S.D.²Two-tailed *t*-test.