LONGITUDINAL INVESTIGATION OF THE RELATIONSHIP BETWEEN OMEGA-3 POLYUNSATURATED FATTY ACIDS AND NEUROPSYCHOLOGICAL FUNCTIONING IN RECENT-ONSET PSYCHOSIS: A RANDOMIZED CLINICAL TRIAL

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Abstract

Alterations in polyunsaturated fatty acids (PUFAs), including omega-3 and omega-6, have been implicated in the pathophysiology of psychotic disorders, but little is known about their associations with neuropsychological functioning. The present study includes 46 recent-onset psychosis patients who participated in a larger (n=50) double blind, placebo-controlled

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randomized clinical trial comparing 16 weeks of treatment with either risperidone+fish oil (FO) (EPA 740mg and DHA 400mg daily) or risperidone+placebo and completed neuropsychological assessments at the baseline timepoint. We investigated the relationship between baseline omega-3 (i.e., eicosapentaenoic acid, EPA; docosapentaenoic acid, DPA and docosahexaenoic acid, DHA) and omega-6 (i.e., arachidonic acid, AA) PUFA with baseline MATRICS Consensus Cognitive Battery (MCCB) and Brief Psychiatric Rating Scale (BPRS) scores. Twenty-five patients had neuropsychological data available at 16 weeks following participation in the clinical trial, which included 12 patients assigned to risperidone+FO and 13 patients assigned to risperidone+placebo. At baseline both higher DHA and EPA correlated significantly with better social cognition after controlling for functioning on other neuropsychological domains, total BPRS score, AA level and substance use. Also, at baseline higher AA correlated significantly with hostility/uncooperativeness after controlling for DHA+EPA+DPA, overall neuropsychological functioning and substance use. Patients treated with risperidone+FO demonstrated a significant longitudinal increase in social cognition that was significantly higher at 16 weeks compared to patients treated with risperidone+placebo. DHA also correlated significantly with social cognition at the 16-week timepoint. This study provides novel evidence for a differential role of omega-3 vs. omega-6 PUFA in neuropsychological deficits and symptoms in recent-onset psychosis and its treatment.

Introduction

Polyunsaturated fatty acids (PUFA) are a broad class of bioactive lipids that are considered essential because they are not produced *de novo* and must be obtained from the diet. These essential fatty acids include alpha-linolenic acid (ALA) and linoleic acid (LA), which are short-chain precursors of omega-3 PUFA such as eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA), and omega-6 PUFA such as arachidonic acid (AA), respectively. These fatty acids cross the blood-brain barrier and influence cellular and inflammatory signaling and contribute to healthy brain development, aging, and neuronal resilience (Janssen and Kiliaan, 2014; McCusker and Grant-Kels, 2010; Rapoport, 2013). Omega-3 and omega-6 PUFA have a complex synergistic and antagonistic relationship (Lin et al., 2015; Luxwolda et al., 2011), and extant evidence indicates that an optimal ratio of omega-6 to omega-3 PUFA is important for mental health and cognitive functioning (Nelson and Raskin, 2019).

Several lines of evidence suggest that a deficiency in omega-3 PUFA may be relevant to the pathoetiology of schizophrenia. Animal studies have demonstrated that developmental deficits in brain DHA accrual can recapitulate behavioral and neurobiological features observed in schizophrenia (Li et al., 2015; Maekawa et al., 2017; McNamara et al., 2017; Zimmer et al., 2002). Meta-analyses have indicated that DPA, DHA and AA are lower in patients with schizophrenia compared to healthy controls (Hoen et al., 2013; van der Kemp et al., 2012), and several studies suggest that omega-3 and omega-6 PUFA are associated with clinical symptoms in psychosis (Berger et al., 2019; Kim et al., 2016; Kim et al., 2014; Medema et al., 2016; Pawełczyk et al., 2016; Sethom et al., 2010; Watari et al., 2010). Several clinical trials investigating omega-3 PUFA supplementation on symptoms in patients with multi-episode schizophrenia have reported negative findings (Emsley et al., 2006; Fenton et al., 2001; Peet and Horrobin, 2002), although improvement in overall symptom

severity (Emsley et al., 2002; Jamilian et al., 2014; Peet et al., 2001) and positive symptoms (Peet et al., 2001) has been observed. Consistent with clinical stage specific effects (Chen et al., 2014), more consistent evidence for reductions in overall symptom severity following omega-3 PUFA supplementation has been observed in first-episode psychosis patients (Pawełczyk et al., 2016; Peet et al., 2001; Robinson et al., 2019).

Neurocognitive impairment in schizophrenia is difficult to treat and these deficits portend a less favorable clinical outcome (Reynolds et al., 2018). There is therefore a need for alternative treatments that might enhance cognition in schizophrenia and associated psychotic disorders. Cross-sectional and intervention studies reported an association between omega-3 PUFA and cognitive functioning in healthy children and adults (Adjepong et al., 2018; Montgomery et al., 2013; Stonehouse et al., 2013) and healthy elderly subjects (Witte et al., 2014; Yuan et al., 2016; Yurko-Mauro et al., 2015; Zamroziewicz et al., 2017). Few studies, however, examined the relationship between either omega-3 or omega-6 PUFA and neurocognitive functioning in patients with psychosis. One cross-sectional study reported that the Brief Assessment of Cognition (BACS) composite score correlated significantly with EPA and DHA levels, which then predicted social functioning outcome in schizophrenia (Satogami et al., 2017). Another study revealed a significant inverse relationship between AA and semantic memory and general intelligence in unmedicated patients with chronic schizophrenia (Condray and Yao, 2011). Other data indicate that EPA treatment was associated with worse sustained attention among patients with low baseline PUFA levels (Bentsen and Landrø, 2018). In addition, general cognitive performance correlated significantly with the ratios of both omega-3 and DHA to total fatty acids among individuals at risk for psychosis (Ramsay et al., 2018).

The present study examined associations between omega-3 (i.e., EPA, DPA, DHA) and omega-6 (i.e., AA) PUFA and neuropsychological and symptom measures in a cohort of recent-onset psychosis patients. In addition, 25 patients completed both baseline and follow-up neuropsychological assessments following participation in a double-blind randomized placebo controlled 16-week clinical trial comparing the efficacy of risperidone + placebo vs. risperidone + fish oil (FO) on overall clinical functioning (Robinson et al., 2019). We used erythrocyte membrane fatty acid composition (mg fatty acid/100 mg fatty acids) in this study because it is a more reliable biomarker of habitual dietary fatty acid intake compared to plasma (Harris & Thompson, 2010). We predicted that lower total omega-3 PUFA (i.e., EPA+DHA+DPA), lower omega-3 index (i.e., EPA+DHA), a higher level of AA and a higher ratio of AA to total omega-3 PUFA (i.e., AA/(EPA+DHA+DPA) would be associated with greater symptom severity and worse neuropsychological functioning. We further tested the hypothesis that adjuvant treatment of risperidone with FO would be associated with better neuropsychological functioning compared to patients treated with risperidone + placebo.

METHODS AND MATERIALS

Subjects

The present study includes 46 (35M/11F) recent-onset psychosis patients (mean age = 21.5 years, SD = 5.3) who participated in a larger (n=50) double-blind placebo-controlled

randomized clinical trial comparing 16 weeks of treatment with either risperidone + FO (EPA 740 mg and DHA 400 mg daily) or risperidone + placebo and completed neuropsychological assessments at baseline. Patients were recruited from the Zucker Hillside Hospital, a large acute care non-for-profit psychiatric facility in New York between June, 2013 to September, 2015. Twenty-five patients had neuropsychological data available at 16 weeks following participation in the clinical trial, which included 12 patients assigned to risperidone + FO and 13 patients assigned to risperidone + placebo.

Patient diagnoses were based on the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-I/P) (First et al., 1994) supplemented by information from clinicians and, when available, family members. Patients met DSM-IV criteria for schizophrenia (n = 31), schizophreniform disorder (n = 9), psychotic disorder NOS (n = 1), schizoaffective disorder (n = 1), or bipolar disorder with psychosis (n = 4). Eight patients met DSM-IV criteria for an alcohol use disorder and 18 patients were diagnosed with a cannabis use disorder. All patients received a physical exam and laboratory screening to rule out medical/neurologic causes for their psychotic episode. Ten patients were antipsychotic drug-naïve at the time of consent and the remaining 36 patients had a median exposure of 4.5 days of antipsychotic treatment (range = 1 to 240 days). Duration of untreated psychotic symptoms was 93.7 weeks (range = 2 to 574). Total Brief Psychiatric Rating Scale score (BPRS) at the time of study entry was 41.6 (SD = 6.4). The study was approved by the Northwell Health Institutional Review Board. Written informed consent was obtained from all individuals, and from a parent or legal guardian in the case of minors. Written assent was obtained from all minors.

Inclusion criteria were: (1) current DSM-IV-defined diagnosis of schizophrenia, schizophreniform, schizoaffective disorder or bipolar disorder assessed using the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-I/P) (First et al., 1994); (2) does not meet DSM-IV criteria for a current substance-induced psychotic disorder, a psychotic disorder due to a general medical condition, delusional disorder, brief psychotic disorder, shared psychotic disorder, or major depressive disorder with psychotic features; (3) current positive symptoms rated 4 (moderate) on one or more of these BPRS items: conceptual disorganization, grandiosity, hallucinatory behavior, unusual thought content; (4) in an early phase of illness as defined by having taken antipsychotic medications for a cumulative lifetime period of 2 years or less, (5) age 15 to 40 years; (6) competent and willing to sign informed consent; and (7) for women, negative pregnancy test.

Exclusion criteria were: (1) serious neurological or endocrine disorder or any medical condition or treatment known to affect the brain; (2) any medical condition requiring treatment with a medication with psychotropic effects; (3) significant risk of suicidal or homicidal behavior; and (4) cognitive or language limitations, or any other factor that would preclude participants providing informed consent.

Treatment Trial

A detailed description of the overall treatment trial (registration ID: NCT01786239) and study results using the primary clinical outcome measure, total BPRS score, is provided in Robinson et al (2019). Briefly, all participants received open-label risperidone for 16

weeks with half assigned randomly to receive FO and the other half to placebo in a double-blind manner. Randomization was conducted on a 1:1 basis stratified by sex and length of antipsychotic exposure (< versus   16 weeks) by the study biostatistician using a computer generated randomization list. Patients and all staff providing treatment and conducting clinical and neuropsychological assessments were blind to randomization.

The FO and matching placebo (a soybean/corn blend) capsules were manufactured by Ocean Nutrition Canada. Each FO capsule contained 370 mg EPA and 200 mg DHA as well as 2 mg/g tocopherol. Participants took one randomized capsule in the morning and one capsule in the evening so that the total daily dose was 740 mg of EPA and 400 mg of DHA. If participants were receiving an antipsychotic prior to study entry, it was terminated and risperidone initiated and titrated according to the following flexible dosing schedule: 1 mg qhs days 1–3; 2 mg qhs on day 4 and 3 mg on day 7 with the possibility of an increase up to 6 mg over the subsequent weeks, if needed. Risperidone dosage was increased until participants responded or until side effects precluded further increases.

Allowed concomitant medications included benztropine mesylate; lorazepam, propranolol, and if lorazepam was contraindicated for insomnia treatment, zolpidem or rozerem. We dichotomized individuals who received at least one dose of benztropine mesylate or lorazepam vs. those who did not receive these medications during the trial in subsequent analyses.

Neuropsychological and Clinical Assessments

Patients received the MATRICS Cognitive Consensus Battery (MCCB) (Kern et al., 2008; Nuechterlein and Green, 2006) and the Brief Psychiatric Rating Scale – Anchored version (BPRS-A) (Woerner et al., 1988). The MCCB includes the following neuropsychological domains: speed of processing, verbal learning, visual learning, working memory, attention/ vigilance, reasoning/problem solving, and social cognition as well as a composite measure of overall functioning. There were missing data for three patients on the social cognition domain and three patients on the attention/vigilance domain at baseline. Twenty-five patients had neuropsychological data available at 16 weeks following participation in the clinical trial, which included 12 patients assigned to risperidone+FO and 13 patients assigned to risperidone+placebo. For the symptom measures we formed BPRS factor scores as defined in prior studies (Robinson et al., 2019; Ventura et al., 2000), which included negative symptoms, positive symptoms, depression/anxiety, and hostility/uncooperativeness. A total BPRS score was formed by summing the individual items.

Handedness

Handedness was assessed using a modified version of the Edinburgh Inventory (Oldfield, 1971) consisting of twenty items. The total number of right and left hand items were scored, and the laterality quotient was computed yielding a total laterality quotient for each participant that ranged from +1.00 (totally dextral) to −1.00 (totally nondextral). Participants with a laterality quotient greater than .70 were classified as dextral (n=34), and the rest as nondextral (n=12).

Erythrocyte fatty acid composition

Whole venous blood was collected into EDTA-coated BD Vacutainer tubes and centrifuged for 20 min (1,500 xg, 4°C). Plasma and the platelet rich interface were removed, and erythrocytes washed three times with 0.9% saline and stored at −80°C. Erythrocyte total fatty acid composition was determined using the saponification and methylation methods described previously (McNamara et al., 2010; Metcalfe et al., 1966). Briefly, the sample was saponified with methanolic sodium hydroxide and fatty acids methylated with BF_3 methanol to yield fatty acid methyl esters that were extracted in hexane and used for analysis. Samples were analyzed with a Shimadzu GC-2014 equipped with an auto-injector (Shimadzu Scientific Instruments Inc., Columbia MD). The column was a DB-23 (123–2332): 30m (length), I.D. 0.32 mm wide bore, film thickness of 0.25 μM (J&W Scientific, Folsom CA). 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. Fatty acid composition (mg fatty acid/100 mg fatty acids) was computed by a technician blind to group assignment. Two cases were determined to have outlying values on AA (> 3SD from the mean) at baseline and were excluded from analyses. Twenty-five patients had PUFA data available at 16 weeks following participation in the clinical trial, which included 10 patients assigned to risperidone+FO and 10 patients assigned to risperidone+placebo.

Statistical Analysis

Independent groups t-tests or chi-square analysis was used to compare the 2 treatment groups on distributions of demographic variables. We used Pearson product moment correlations to investigate the relationship between total omega-3 PUFA and neuropsychological functioning on the MCCB and BPRS scores. To minimize Type-I error we limited our initial analyses to investigation of (1) the ratio of AA/(EPA+DHA+DPA), (2) total omega-3 PUFA (i.e., DHA+DPA+EPA) for consistency with another study investigating magnetic resonance imaging correlates of fatty acids (Lyall et al submitted), (3) omega-3 index (EPA+DHA) and (4) AA. We further restricted initial analyses to overall neuropsychological functioning and total BPRS score. Only significant correlations were followed by post-hoc correlations investigating individual omega-3 PUFA or neuropsychological domains.

We used the method of Meng and colleagues (Meng et al., 1992) as implemented in the statistical online program, Cocor (Diedenhofen and Musch, 2015), (http://comparingcorrelations.org) to test the null hypothesis that (following r to z transformations) two correlation coefficients were not significantly different from each other in the same sample of individuals. Correlations were computed between predictor variables (X_1 or X_2) and a single common dependent variable (Y). In these analyses predictor variables were either neuropsychological domains or symptom scores whereas an individual PUFA (EPA, DPA, DHA or AA) served as the dependent measure.

Neuropsychological domains that correlated significantly with PUFA at the baseline time point were subsequently investigated in the clinical trial using a linear mixed model in an intention-to-treat analysis. Specifically, we focused on social cognition as the outcome

measure with group, age, sex, and group*time interaction included as covariates. The correlation between time points was modeled using compound symmetry. We then compared adjusted least square means for the group x time interaction between groups at baseline and follow-up using two-sample t-tests. We also investigated the potential impact of allowed concomitant medications on neuropsychological functioning.

RESULTS

Baseline demographic, clinical, and PUFA data are provided for the entire sample in Table 1. None of the variables in Table 1 differed significantly between treatment groups at baseline. There were no significant differences in the number of weeks patients were treated with risperidone + FO (mean =15.75, SD=1.08) vs. risperidone + placebo (mean = 15.90, SD=.89). There was no significant interaction between treatment group and dropout at 16 weeks in baseline distributions of age, sex, handedness, age at first psychotic symptoms, total BPRS score or neuropsychological domains.

The ratio of AA/(EPA+DHA+DPA) correlated significantly with worse overall neuropsychological functioning (r=−.33, df=38, p=0.045). Post-hoc Pearson correlations revealed a significant negative correlation between this ratio and social cognition (r=−.54, df=39, p<.001) that was statistically stronger compared to the correlation between this ratio and the other 6 domains of NP functioning. The examination of EPA+DHA+DPA versus AA levels separately revealed a significant positive correlation between overall neuropsychological functioning and EPA+DHA+DPA (r = .32, df=39, p=0.04), but not with AA. Post-hoc tests indicated that EPA+DHA+DPA correlated significantly and positively with social cognition (r=.58, df=42, p<0.001; figure 1) and that this correlation was statistically significantly stronger compared to the correlations between EPA+DHA+DPA and the other 6 domains of NP functioning. In addition, the omega-3 index (i.e., EPA+DHA) was significantly correlated with social cognition (r-.63, df=42, p < .001) and this correlation was statistically significantly stronger compared to the correlations between this index and the other 6 domains of NP functioning.

We investigated which individual omega-3 PUFA contributed to the significant correlation between EPA+DHA+DPA and social cognition. There were significant positive correlations between social cognition and DHA (r=0.57, df=43, p<0.001; figure 2A) and EPA (r=0.51, df=42, p<0.001; figure 2B), but not with DPA. The correlations between social cognition and DHA and EPA were statistically significantly stronger compared to the correlation of social cognition with DPA. The correlations between social cognition and DHA (r=0.57, df=32, p<0.001) and EPA (r=0.39, df=32, p=0.025) remained statistically significant when we controlled for functioning on the other 6 neuropsychological domains, total BPRS score, AA level and substance use diagnosis using partial correlation analysis.

Investigation of clinical measures indicated that total BPRS score did not correlate significantly with either AA/(EPA+DHA+DPA), EPA+DHA+DPA or EPA+DHA, but correlated significantly with AA (r=0.34, df=44, p=0.024). Post-hoc analyses indicated that AA correlated significantly only with hostility/uncooperativeness (r=0.44, df=44, p=0.003; figures 3 and 4), and none of the other factor scores. The correlation between AA and

hostility was significantly stronger compared to the correlation of AA with negative symptoms. Furthermore, the correlation between AA and hostility remained statistically significant after controlling for EPA+DHA+DPA, overall neuropsychological functioning and substance use diagnosis using partial correlation analysis (r=.42, df=34, p=.01).

Omega-3 PUFA Changes

There were significant increases in omega-3 PUFA and reductions in AA among patients treated with risperidone + FO (Table 1): DPA (+72.6%; t=−6.99, df=9, p<.001), DHA (+56.2%; t=−4.48, df=9, p=.002), EPA (+281.7%; t = −4.91, df=9, p=.001) and AA (−0.9%; t=2.75; df=9, p=.022;). There were no significant changes (all ps > .05) in omega-3 PUFA in patients treated with risperidone + placebo (Table 1). In addition, at week 16, patients treated with risperidone + FO had significantly higher levels of DHA (t=−2.15, df=18, p=.046), EPA (t = −4.51, df=18, p<.001), DPA (t = −3.64, df=18, p=.002) and lower levels of AA (t = 3.01, df=18, p=.007) compared to patients treated with risperidone + placebo.

Neuropsychological Changes

Examination of within group changes of the adjusted least squares means from the linear mixed model analysis with intention-to-treat revealed a significant increase over time in social cognition among patients treated with risperidone + FO (t=−2.41, df=21.8, p=.025), but no significant change over time in social cognition among patients treated with risperidone + placebo (t=−.50, df=21.3, p=.62). Furthermore, patients treated with risperidone + FO had significantly (t = −2.27, df=58.8, p=.027) higher social cognition scores compared to individuals treated with risperidone + placebo at the 16 week follow-up timepoint. Group differences in social cognition at the follow-up timepoint were associated with a large effect size (Cohen's d > .90). There was no significant interaction between use of either lorazepam or benztropine with treatment group assignment for week 16 social cognition scores. Exploratory analyses did not reveal any significant group differences at follow-up for the other neuropsychological domains (ps>.05). At the 16-week timepoint there was a significant positive correlation between DHA and social cognition across both cohorts while controlling for functioning on the other 6 NP domains, total BPRS score and AA level (r=.71, df=5, p=.038; one-tailed).

Discussion

This study provides novel evidence for a differential role of omega-3 vs. omega-6 PUFA in recent-onset psychosis that may have implications for better understanding their roles in the pathophysiology of neurocognitive dysfunction in psychosis and its treatment. We found that EPA+DHA+DPA correlated significantly with social cognition and that the magnitude of this correlation was significantly stronger compared to the correlations of EPA+DHA+DPA with other neuropsychological domains. Lower levels of DHA and EPA were associated with worse social cognition even after controlling for functioning on other neuropsychological domains, overall symptom severity, AA level and substance use. In contrast, we found that AA correlated positively with hostility/uncooperativeness even after controlling for overall neuropsychological functioning, EPA+DHA+DPA level and substance use. We further demonstrate significant longitudinal increases in social cognition

among patients treated with risperidone + FO and that week 16 social cognition domain scores were significantly higher among patients treated with risperidone + FO compared to those patients treated with risperidone + placebo. At the 16 week follow-up timepoint we identified a significant positive correlation between EPA+DHA+DPA and social cognition performance across all participants, thus replicating findings at baseline.

Few studies have examined the relationship between omega-3 PUFA level and neuropsychological functioning at any stage of psychosis, although some evidence indicates that dietary intake of omega-3 PUFA may have beneficial effects on cognition in patients with affective disorders and schizophrenia (Knochel et al., 2015). Our finding that higher EPA and DHA correlated with better social cognition is broadly consistent with Satogami et al (2017) who reported that EPA and DHA levels were positively correlated with the composite score from the Brief Assessment of Cognition. In 2 cohorts of individuals at risk for psychosis the ratios of both omega-3 and DHA to total fatty acids was associated with cognitive performance (Ramsay et al., 2018). Clinical trials conducted in patients with schizophrenia reported either no effect when 3g ethyl EPA was administered daily on cognition (Fenton et al., 2001) and impairment in sustained attention when ethyl-EPA was administered alone to patients with low baseline PUFA (Bentsen and Landrø, 2018).

Although an initial study by Amminger et al (2010) reported that long-chain omega-3 PUFA reduced the risk of progression to psychotic disorder among individuals at ultra-high risk for psychosis, the subsequent NEURAPRO study failed to show benefits of n-3 PUFAs over placebo (McGorry et al., 2017). In this latter study, however, an increase in omega-3 PUFA was associated with better functioning and less severe psychopathology among these individuals at follow-up timepoints in the clinical trial (Amminger et al., 2020). Other studies reported lower EPA, DHA and AA in individuals at ultra-high risk for psychosis compared to age-matched healthy controls, which was associated with BMI in the patient group only (Alqarni et al., 2019) and that metabolic parameters in combination with a diet low in omega-3 predicted prodromal symptoms and poor role functioning among antipsychotic-free individuals at clinical high risk for psychosis (Cadenhead et al., 2019). Given differences in the consumption of omega-6 and omega-3 PUFA among individuals at ultra-high risk of psychosis and patients with first-episode psychosis compared to healthy controls (Pawełczyk et al., 2017), the examination of modifiable dietary factors and augmentation with omega-3 PUFA in relationship to clinical and neuropsychological functioning may be an important area for subsequent studies.

Our data further converge with animal studies reporting that omega-3 biostatus is associated with neuropsychological deficits targeting social interactions. Animal studies indicate that an omega-3 deficient diet across consecutive generations produce impairments on cognitive tasks (Bondi et al., 2014) that are improved following omega-3 PUFA administration (Chung et al., 2008; Fedorova et al., 2007), and omega-3 PUFA mitigate against the detrimental effects of chronic stress on cognitive functions (Trofimiuk and Braszko, 2013). Our data on social cognition are also consistent with animal studies indicating that dietary changes in PUFA ratios predicted developmental delays in a mouse model of autism spectrum disorder (van Elst et al., 2019) and that an EPA enriched diet was associated with less anxiety-like behavior in socially isolated rats (Oshima et al., 2018). Furthermore, maternal

DHA positively affected social behavior in offspring following weaning (Clouard et al., 2015) and prenatal exposure to lipopolysaccharides significantly decreased social interaction in the offspring of rats, which was reversed following omega-3 PUFA supplementation (Fortunato et al., 2017).

There may be several possible neural mechanisms through which omega-3 PUFA may exert beneficial effects on social cognition. It is known that omega-3 PUFA are abundant throughout the brain (Bentsen, 2017) with DHA being the most prominent and accounting for approximately 50% of neuronal membranes (Singh, 2005). Cell membranes of oligodendrocytes contain myelin and the phospholipid bilayers of this myelin sheath contain omega-3 PUFA that may play a role in their regulation (Chen et al., 2014; McNamara et al., 2017). It is conceivable that omega-3 PUFA could play a role in regulating brain functions associated with myelin integrity by enhancing brain plasticity and synaptic connections as well as facilitating anti-inflammatory effects. Prior studies (Peters et al., 2009; Peters et al., 2013), which have been replicated in an independent sample (Lyall et al., Submitted) are consistent with the hypothesis that omega-3 PUFA biostatus predicts putative white matter microstructural integrity as inferred from diffusion tensor imaging. Moreover, a controlled clinical trial found that omega-3 PUFA supplementation significantly improved executive functioning and regional white matter microstructural integrity and gray matter volume compared to placebo in healthy older adults (Witte et al., 2014). It should be acknowledged that despite the importance of DPA in brain regulation (Drouin et al., 2019) and its unique and shared overlap with DHA and EPA (Dyall, 2015), we did not find evidence to support an association between DPA and cognition in recent-onset psychosis. Despite growing evidence for a physiological role of DPA (Drouin et al., 2019), little is currently known, however, regarding the individual role of DPA in brain and cognitive functioning and thus, further studies are needed.

Alterations in AA associated with phospholipid metabolism have been hypothesized to play a key role in the neurobiology of schizophrenia (Skosnik and Yao, 2003; Yao and Reddy, 2002), but few studies have investigated their functional correlates. The finding that higher AA was associated with greater hostility/uncooperativeness in our cohort converges strongly with a prior study reporting that AA levels correlated positively with the hostility score from the Positive and Negative Syndrome Scale in 75 drug-free inpatients with schizophrenia (Watari et al., 2010). Another study provides partial support for the current findings in reporting that prior to interferon-alpha (IFN-α) therapy the ratio of AA/EPA+DHA correlated with subsequent increases in anger during treatment (Lotrich et al., 2013). Our data are consistent with the hypothesis that increased metabolism of AA early in the course of psychotic illness may contribute to hostility/uncooperativeness. The lack of association at follow-up suggests that AA levels may be affected by risperidone and/or omega-3 PUFA treatment.

The direction of our correlations suggests that lower omega-3 PUFA and higher AA in patients may be associated with less favorable neuropsychological and clinical outcomes, respectively. In this regard it should be acknowledged that prior studies investigating group differences in these PUFA have yielded inconsistent findings that further complicate interpretation. In a meta-analysis (Hoen et al., 2013) less AA was most robust in

antipsychotic-naive patients compared to healthy controls. However, in one of the largest studies to date (Medema et al., 2016), which was not included in this meta-analysis, higher DHA, DPA and AA were observed in 215 patients with psychosis and 187 siblings compared to 98 controls. The direction of our correlations is consistent with studies demonstrating that erythrocyte EPA+DHA is lower and that either AA or AA/EPA+DHA was higher in patients with schizophrenia compared to healthy controls (Arvindakshan et al., 2003; McNamara, 2013).

It is important to acknowledge that the relationship between omega-3 and omega-6 PUFA is complex and both synergistic and antagonistic effects have been identified (Lin et al., 2015; Luxwolda et al., 2011). For example, omega-6 PUFA deprivation was found to increase DHA loss within brain phospholipids and synergism between omega-3 PUFA and AA was evident at low omega-3 PUFA levels whereas AA could be suppressed at high (i.e., >8 g%) omega-3 levels (Luxwolda et al., 2011). We addressed this issue by examining a ratio incorporating these measures (i.e., AA/(EPA+DPA+DHA)) as well as examining absolute PUFA values. Although we found that lower AA/(EPA+DHA+DPA) correlated significantly with overall neuropsychological functioning, this relationship was driven primarily by EPA+DHA+DPA suggesting that omega-3 PUFA may be important in the identification of functional correlates in patients with recent-onset psychosis.

There are several study limitations that should be acknowledged. The sample was relatively small, especially in the follow-up groups and heterogeneous in terms of diagnosis, although all patients had a psychotic disorder. The social cognition domain from the MCCB was limited by a single measure, the Mayer-Salovey-Caruso Emotional Intelligence Test, although better performance on this task was associated with better psychosocial functioning on the Quality of Life Scale in a large cohort of patients in the schizophrenia spectrum (DeTore et al., 2018). Other measures of social cognition, including those assessing real world situations, are warranted in future studies (Pinkham et al., 2016). Because this study did not include a healthy comparison group we could not determine whether PUFA levels were abnormal at baseline in patients. We also acknowledge that a possible reason for the increase in DPA observed in this study is that EPA is a precursor of DPA and is converted via the enzyme elongase-5 (Drouin et al., 2019). Study strengths, however, include the randomized double-blind placebo-controlled design, well-characterized cohort of recent-onset psychosis patients, demographically and clinically similar treatment groups, and use of erythrocytes, which provide a better index of biostatus compared to plasma measures that can be highly variable and more prone to exogenous influences such as diet (Harris and Thomas, 2010).

In conclusion, we report that omega-3 and omega-6 PUFA are associated with social cognition and hostility/uncooperativeness, respectively, in patients with recent-onset psychosis. We further present preliminary evidence for improved social cognition in these patients following FO treatment compared with placebo. Taken together, omega-3 PUFA supplementation may represent a safe adjunctive treatment for social cognition deficits in psychosis and encourage additional investigation in a larger cohort.

Acknowledgments

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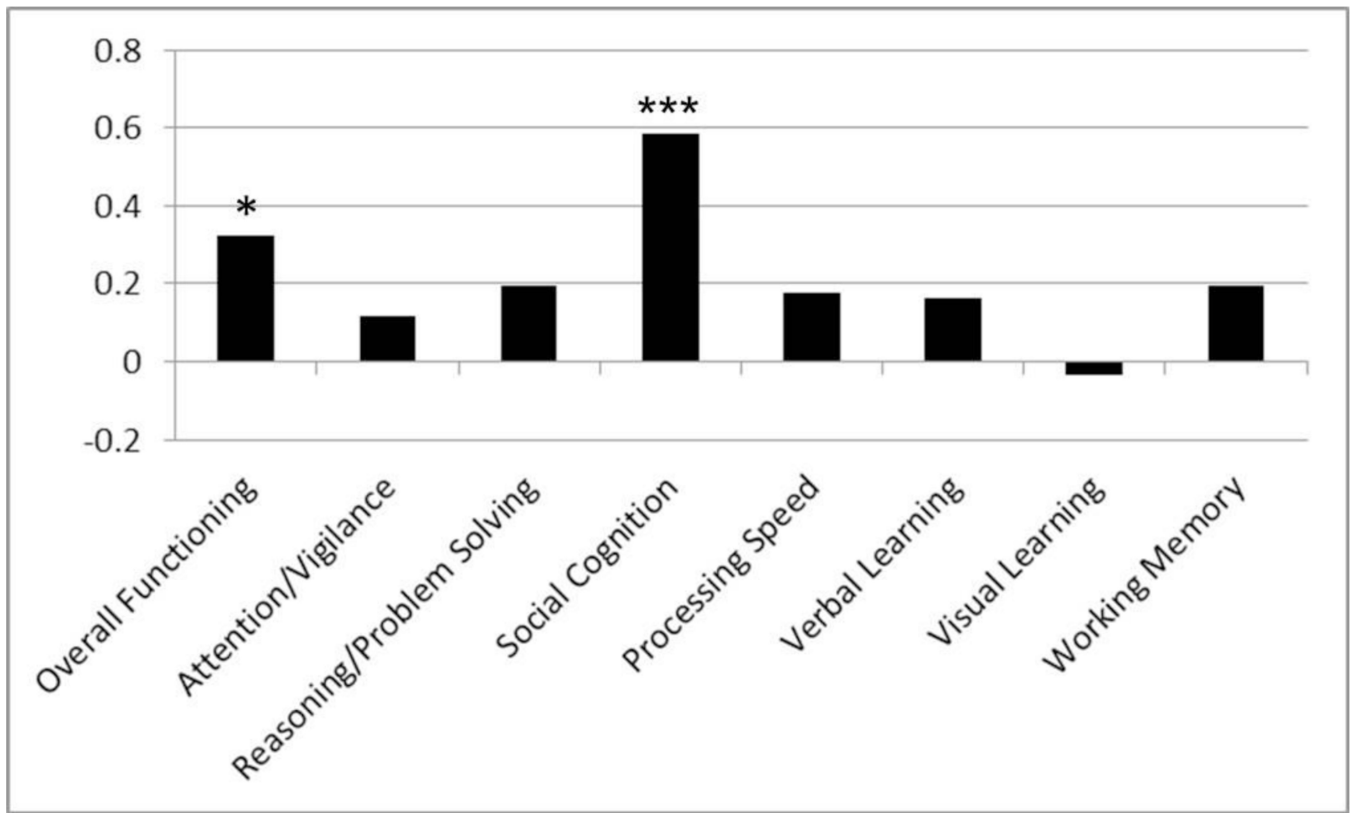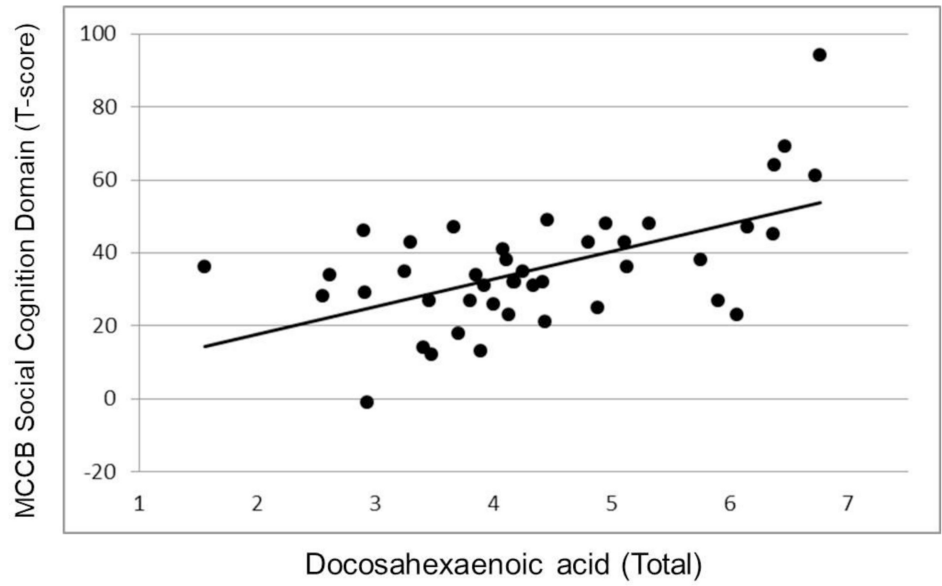
MATRICS Consensus Cognitive Battery Domain Score

Figure 1.
Correlation Coefficients between MATRICs Cognitive Consensus Battery and DHA + EPA + DPA.

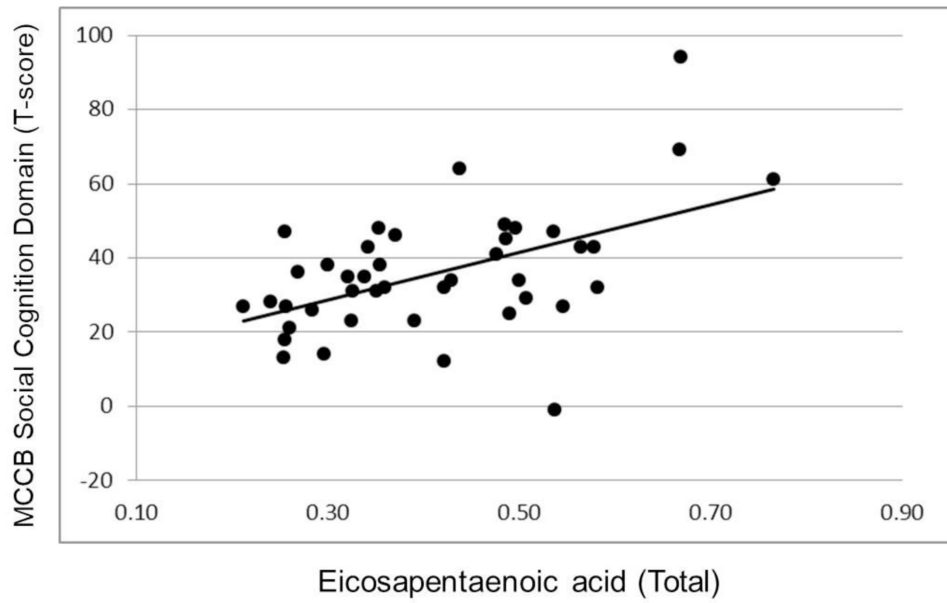<u>Notes</u>: * p < .05; *** p < .001

Panel A.

Panel B.

Figure 2.
Scatterplots of MATRICS Social Cognition Domain Score and Docosahexaenoic Acid
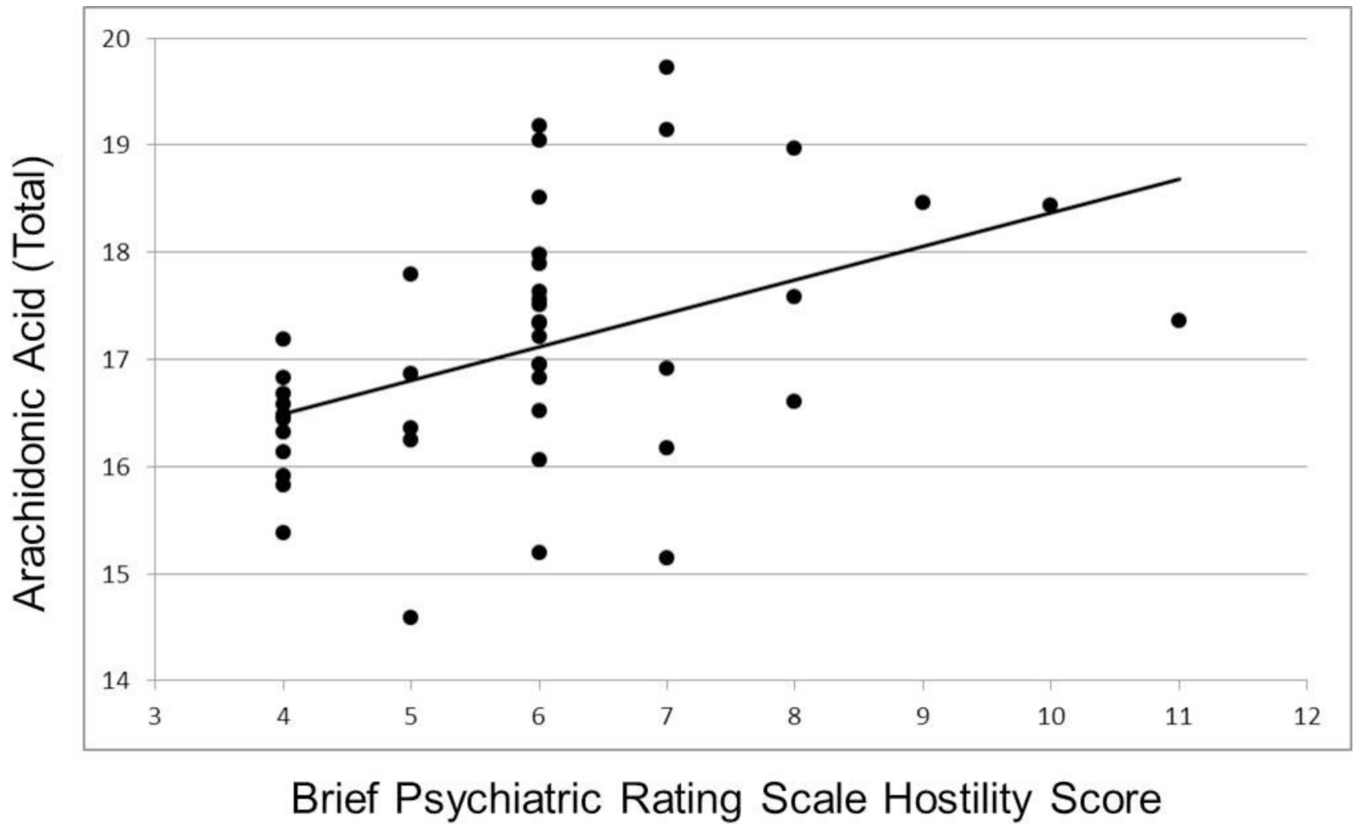(Panel A) and Eicosapentaenoic Acid (Panel B).

Figure 3.
Scatterplot of Brief Psychiatric Rating Scale Hostility/Uncooperativeness Score and
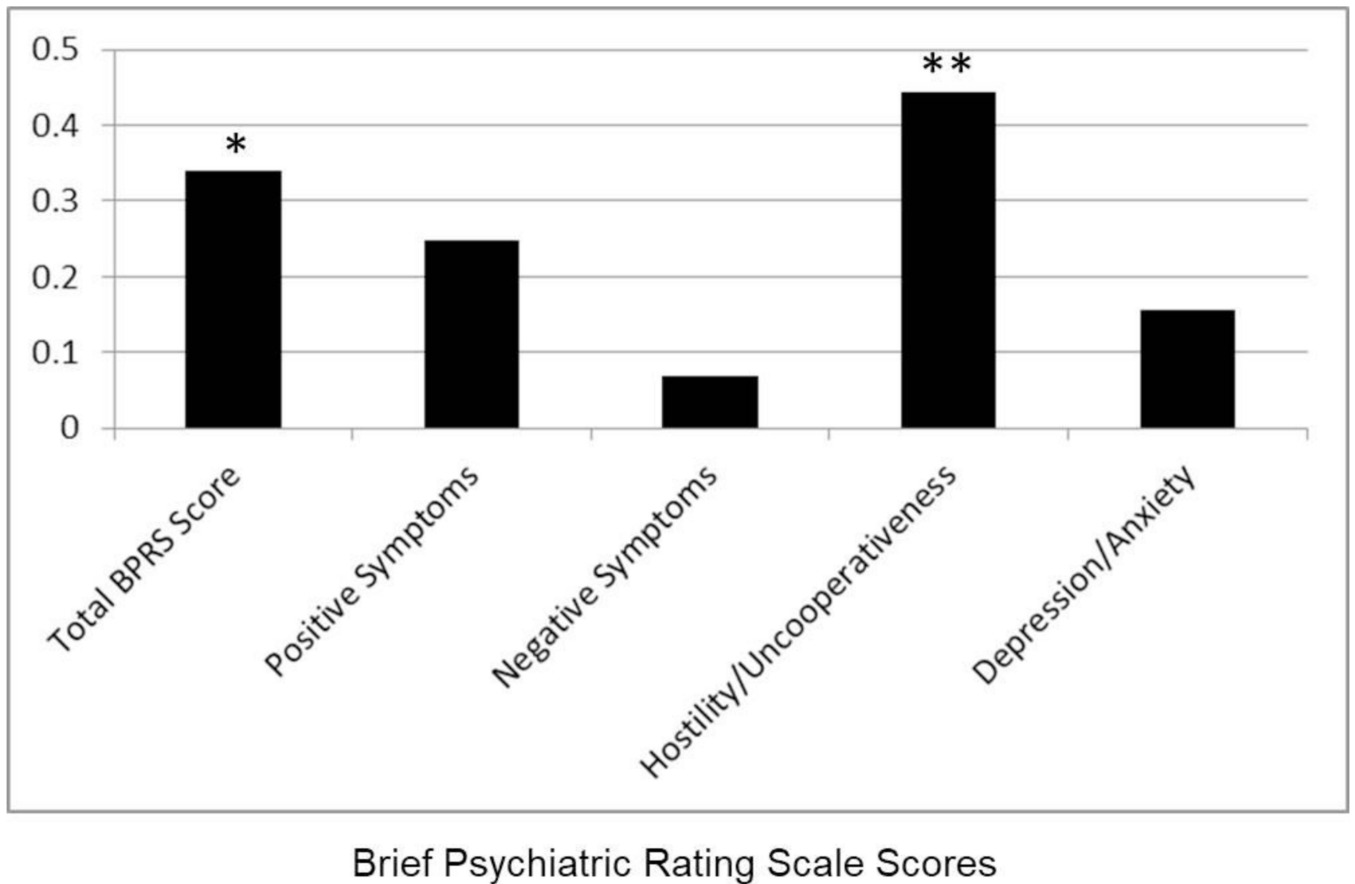Arachidonic Acid.

Brief Psychiatric Rating Scale Scores

Figure 4.
Correlation Coefficients between Brief Psychiatric Rating Scale Scores and Arachidonic
Acid.
Notes: * p < .05; ** p < .005

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Table 1.

Baseline and Follow-up Sample Characteristics.

Demographics	Risperidone + Fish Oil		Risperidone + Placebo	
Age (years)	22.7 (5.4)		21.3 (5.3)	
Sex (male, female)	17/6		18/5	
Education class [b]	3.6 (1.0)		3.8 (1.0)	
Laterality Quotient [c]	.49 (.77)		.62 (.60)	
	Baseline	Follow-up	Baseline	Follow-up
Clinical Data				
Depression/Anxiety	7.4 (2.8)	4.1 (1.6)	7.3 (3.1)	5.3 (2.8)
Hostility/Uncooperativeness	5.8 (1.4)	4.7 (1.0)	6.1 (1.8)	5.0 (1.6)
Negative Symptoms	4.9 (2.4)	4.6 (1.5)	4.9 (2.4)	5.8 (2.3)
Positive Symptoms	12.3 (2.1)	5.8 (2.1)	12.9 (2.2)	7.5 (3.4)
Total Score	41.0 (5.9)	24.4 (5.7)	42.2 (6.9)	30.0 (9.1)
Omega-3 PUFA [d]				
Eicosapentaenoic Acid (EPA)	.39 (.14)	1.3 (.61) [e]	.43 (.12)	.46 (.08)
Docosapentaenoic Acid (DPA)	2.2 (.51)	3.3 (.70) [e]	2.4 (.37)	2.4 (.29)
Docosahexaenoic Acid (DHA)	3.8 (1.3)	5.3 (1.6) [e]	4.0 (1.2)	4.0 (1.1)
Omega-6				
Arachidonic Acid (AA)	16.8 (1.2)	14.5 (2.4) [e]	17.3 (1.1)	17.0 (.81)
Omega-3 PUFA ratio				
AA/(EPA+DPA+DHA)	2.7 (.57)	1.6 (.47) [e]	2.6 (.51)	2.5 (.44)

Notes:

[a] Values are mean (SD) except sex;

[b] Education coded as follows: 5=less than high school education; 4=high school graduate; 3=some college, no degree, 2=college graduate, and 1=some graduate or professional schooling;

(c) handedness was assessed using a modified version of the Edinburgh Inventory (Oldfield, 1971) and ranged from +1.00 (totally dextral) to - 1.00 (totally nondextral);

(d) Fatty acid data expressed as weight percent of total fatty acids ((mg fatty acid/100 mg fatty acids) or ratio;

(e) Values are significantly (p < .05) different compared to baseline (fish oil + risperidone) and follow-up (risperidone + placebo) timepoints (see text for details).