Published in final edited form as:

Prostaglandins Leukot Essent Fatty Acids. 2011 ; 84(3-4): 79–83. doi:10.1016/j.plefa.2010.12.001.

Reduction in Perseverative Errors with Adjunctive Ethyl-Eicosapentaenoic Acid in Patients with Schizophrenia: Preliminary Study

R. Reddy¹, S. Fleet-Michaliszyn², R. Condray^{3,4}, J. K. Yao^{3,4}, M. S. Keshavan⁵, and R. Reddy^{3,4}

¹University of Toledo School of Medicine, Toledo, OH, USA

²University of Arizona, Tucson, AZ, USA

³University of Pittsburgh, Pittsburgh, PA, USA

⁴VA Pittsburgh Healthcare System, Pittsburgh, PA, USA

⁵Harvard University, Boston, MA, USA

Summary

Introduction—Patients with schizophrenia have significant cognitive deficits, generally resistant to conventional treatment. This preliminary study examined the effects of ethyl-eicosapentanoate (EPA) on executive function in early-course patients.

Patients and Methods—Patients with schizophrenia were given, after informed consent, 2 g of EPA daily for 24 weeks, in an open-label study. The Wisconsin Card Sort Test (WCST) was administered at baseline, weeks 4, 12 and 24.

Results—The 27 patients, with a mean duration of illness of 4.2 years, were all receiving atypical antipsychotics; treatment remained unchanged for the study. Perseverative errors – the key measure derived from WCST – were significantly reduced from baseline mean of 28.2 errors to 18.4 errors at week 24. Positive symptoms also improved significantly. There were no correlations between EPA levels and any clinical or other neuropsychological measures.

Conclusion—These findings suggest that EPA has procognitive effects for patients with schizophrenia, but controlled trials are required.

INTRODUCTION

There is a substantial body of literature on the nature and consequences of cognitive deficits in schizophrenia [1], highlighting the presence of a broad array of neurocognitive deficits such as selective attention [2], working memory [3], language production [4] and comprehension [5]. Cognitive impairments are now recognized as a core feature of the illness, although this notion had its origins with Kraepelin and Bleuler over a century ago

© 2010 Elsevier Ltd. All rights reserved.

Reprint requests: Ravinder Reddy, MD, WPIC, University of Pittsburgh, 3811 O'Hara Street, Pittsburgh, PA 15213, USA (Tel: 412-246-5640; Fax: 412-246-5640; reddy@upmc.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.

(Nuechterlein and Asarnow, 1989). Cognitive deficits are detectable prior to the onset of florid psychosis [6], even when positive and negative symptoms are resolved [7], and present even in the highest functioning patients [8].

Neurocognitive deficits have significant impact on the outcome of patients with schizophrenia. For example, fewer than 15% of patients with schizophrenia are competitively employed [9;10], over 70% of patients do not live independently, and poorly functioning social networks are common [11]. A large proportion of the variance in functional outcome is explained by differences in neurocognition [12]. Cognitive deficits can be thought of as “rate limiting factors” in a patient’s ability to retain, acquire, or re-learn skills [13]; amongst these, deficits in executive functioning are consistently associated with difficulties in independent living and occupational success [14;15;16]. Executive functions are higher-order cognitions that are necessary for goal-directed behavior requiring mental flexibility, problem solving and planning capabilities that are necessary to managing uncertainties in the real world.

Because of the serious consequences of cognitive deficits in schizophrenia increasing attention has been paid to their treatment, which include pharmacological and cognitive remediation approaches [17]. While the earlier (typical) antipsychotics are effective in controlling positive symptoms, they are wanting with regard to cognitive deficits; in fact, worsening of cognitive deficits has been observed [18]. The newer (atypical) antipsychotics may modestly benefit cognitive deficits [17;19]. Thus, there is an urgent unmet need for the treatments that reduce the severity of cognitive deficits in schizophrenia. New molecular targets may be one avenue to redress this deficiency [19] [20].

Ethyl-eicosapentanoate (EPA) is one of a class of omega-3 fatty acids (O3FA) which are potent neuroactive lipids by virtue of their obligatory role in key functional systems, including membrane fluidity and transmembrane ion channels, neurotransmitter receptor binding, signal transduction, immune-inflammatory processes, and in the case of mitochondrial membranes the electron-transport chain. Together these wide-ranging effects mediate neurochemical integrity and cognition [21;22]. The effects of O3FA are largely expressed through membrane physicochemical dynamics, eicosanoid production and gene expression. Thus, even small decrements in membrane O3FA composition can lead to alterations in these systems, many of which have been observed in schizophrenia, including in dopamine and serotonin neurotransmission, eicosanoid production and membrane fluidity [23].

The evidence for O3FA deficits in schizophrenia has been consistent in both chronic treated patients [24;25] and in drug-naïve first-episode patients [26]. Additionally, there is evidence for decreased O3FA in the brain from postmortem studies by our group [27] and others [28;29]. Moreover, clinical outcome is better in those patients who have improvement in erythrocyte essential fatty acid levels [30;31].

The findings to date from studies of O3FA treatment in schizophrenia have generally been encouraging [31]. Studies with positive results have utilized EPA rather than DHA, which has not yielded positive results [32]. This preliminary open-label study was conducted to examine whether O3FA supplementation would in fact show any benefit in executive functioning, or other cognitive domains.

PATIENTS & METHODS

Subjects were enrolled into a 24-week open-label add-on supplementation of ethyl-EPA trial if they met DSM-IV criteria for schizophrenia or schizoaffective disorder, were between 18 and 45 years old, either sex and any ethnicity; had a duration of illness $\leq$ 9 years, had illness

severity of moderate or higher on the CGI, and were on stable antipsychotic treatment for 1 month. Subjects were excluded if they had any other DSM-IV Axis I diagnosis, or significant drug or alcohol use in the previous month, or significant medical illness requiring systemic treatment or neurologic disorders.

Supplementation

After signing informed consent, subjects received 2 g of ethyl-EPA in 4 × 500 mg capsules daily, supplied by Laxdale Ltd. (now Amarin Neuroscience Ltd.) at no cost to patients. The 2g/day dose of EPA was chosen based on results from a dose-finding study conducted by Peet et al [32] who found it most efficacious relative to 1g or 4g/d. Patients remained under the care of their treating psychiatrist, with no attempts to modify or influence the treatment they received. “Pill count” was conducted to establish adherence.

Neurocognitive assessments

The computerized version of the WCST was used to assess executive functioning, thus minimizing rater bias. Initially, four stimulus cards are presented. The subject is given a “stack” of additional cards and asked to match each one to one of the four stimulus cards, without being told how to match the cards, but is told whether a particular match is right or wrong. The sorting is rule-based – shape, number, or color. If the subject successfully sorts a specific number of consecutive trials the rule is changed without knowledge of the subject. The results are: number of categories achieved, number of trials, number of errors, number of perseverative errors, percentage perseverative errors. Neurocognitive functions were assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [33].

Clinical assessments

The Positive and Negative Symptom Scale (PANSS) [34] and Global Assessment Scale (GAS) [35] were administered at baseline and 4, 12 and 24 weeks.

RBC Membrane Fatty Acid Assay

The assays were conducted batch-wise, blind to any clinical data, including the sequence of sample collection. The methyl esters of fatty acids and dimethyl acetals of fatty aldehydes are analyzed on a Hewlett-Packard Model 5890A capillary gas chromatograph (GC) equipped with a hydrogen flame ionization detector [27;36]. Peaks on the chromatograms are identified by comparing the retention times with those of standard mixtures and are verified by a Hewlett-Packard GC-Mass Spectrometer.

Statistical Analyses

First, descriptive characteristics of the data were examined (e.g., means and variance). Means and variances were compared by the use of t-tests and F-tests, respectively. Correlative analyses of data were performed with the calculation of correlation coefficients (Pearson, normally distributed; Spearman, non-normally distributed). Continuous measures where appropriate, in contrast to categorical measures, were used in all analyses.

RESULTS

The sample comprised 21 male and 6 female patients. The mean age at study enrollment was 27.9 ± 8.4 years, years of education was 13.3 ± 2.3 , the age at onset of illness was 23.8 ± 6.5 years, and duration of illness was 4.15 ± 2.2 years.

Treatment conditions, safety and adherence

All patients were receiving atypical antipsychotic drugs (APDs), and remained on the same medications and doses for the duration of the trial. “Pill count” was conducted to establish adherence. No patient withdrew due to side-effects. Side effects were minimal and transient, comprising mild nausea and one instance of diarrhea. Taking capsules with food minimized nausea. No change in body-mass index (BMI) was found, in contrast to the modest increase found by Emsley and colleagues [37] over a shorter study period.

Neuropsychological measures

There was reduction in the key measure derived from the WCST - perseverative errors – from baseline of 28.2 ± 21.1 errors to 25.0 ± 23.0 errors at week 4, 17.1 ± 15.9 errors at week 12, and 18.4 ± 13.7 errors at week 24 (–11%, –40% and –35% respectively). The decrements in perseverative errors were statistically significant at weeks 12 and 24. WCST perseverative errors were not related to age, age of onset of illness, illness duration or years of education.

RBANS was administered at baseline and week 24 of EPA trial. There were no statistically significant differences across the five RBANS indices (attention, immediate memory, delayed memory, language, visuospatial/constructional) and total score, consistent with findings by Fenton et al [38].

Clinical measures

GAS scores rose significantly from baseline (52.0 ± 11.5) to end of study (61.1 ± 10.2), indicating significant overall level of improvement. Likewise, there were significant reductions in positive symptom subscale scores from baseline to week 24 (17.8 ± 5.5 v 14.1 ± 4.8 ; $t=4.5$, $P < .001$). However, there were no significant differences in negative and general psychopathology subscale scores of the PANSS across all time points.

Fatty Acid analyses

RBC membrane EPA levels were assessed to verify the adherence with EPA supplementation, as well as to determine whether there was incorporation of EPA into RBC membrane. There was a three-fold increase in mean EPA levels between baseline and 4 weeks, and 12 weeks, but there was no significant increase between 12 and 24 weeks (Table 1). Likewise, there was a significant increase in levels of docosapentaenoic acid (22:5n3) between baseline and 24 weeks. As expected, there were significant increases in total n-3 fatty acids, as well as total pentanenes. There were no significant changes in total saturated fats, monoenes, dienes, trienes, tetraenes, hexaenes, total n-6 fatty acids or total trans-fats.

Relations between RBC fatty acid levels and clinical assessments

There were no significant correlations between RBC levels of EPA, or other fatty acid measures and any clinical or neuropsychological data. Gender differences were not examined since there were fewer females than males.

DISCUSSION

The limitations of this study - the open-label design, small sample size and absence of a healthy control group - constrain the interpretation and implications of the study. To a limited extent, the weaknesses of the study are offset by the relatively long duration of the trial, the unchanged primary antipsychotic treatment for the duration of the trial, use of computerized WCST, and blind biochemical assays.

The key finding of this preliminary study was the robust reduction (−40%) in perseverative errors from baseline to week 12, which was maintained at the approximately the same level for the next 12 weeks of the EPA trial. Since all patients were on adequate and stable doses of atypical antipsychotics throughout the study period, the observed improvement in executive functioning suggests that EPA provided additional benefits, beyond any potential procognitive effects of the APDs. It appears that the maximal improvement in executive functioning was achieved by 12 weeks, and the improvement was sustained for the duration of trial for an additional 12 weeks. This is in contrast to the study by Fenton and colleagues [38] who found no clinical or cognitive benefits of EPA in patients with schizophrenia. However, the dose of EPA was 3g/d, which may not be the optimal dose since Peet et al [32] found 1g/d and 4g/day to be suboptimal. Further, the study subjects had been ill for over two decades are largely refractory to treatment. As the authors themselves stated, “Thus, testing of omega-3 fatty acid supplementation among less severely ill patients earlier in their illnesses may be warranted. It is also possible that a different EPA dose or treatment duration might yield different results.”

A caveat about the findings is the susceptibility of the WCST to practice effects [39;40;41;42;43]. Thus the findings in the pilot study could be attributed to practice effects. The average 11% reduction in perseverative errors we observed at Week 4 is in agreement with the 17% reduction found by McGrath et al [41] on re-test at 4 weeks. In the 2-year prospective study of first-episode patients and matched controls described above Hill et al [44], there were no significant longitudinal effects in both groups, arguing against practice effects. Further, patients with schizophrenia show smaller practice effects [45;46]. The likelihood that additional reduction of 29% at week 12 is due entirely to practice effects is quite low. This notion is bolstered by the fact that there was no further error reduction during the additional 12 weeks of treatment, contrary to what would be expected if it was entirely due to practice effects.

No correlations were detected between membrane fatty acids and cognition. By contrast, Whalley et al [47] found, in a cohort born in 1936, that membrane O3FA and DHA/AA ratio were significantly correlated with scores on Ravens Progressive Matrices, Digit Symbol subtest, and Block design subtest (assesses executive function). The absence of a similar correlation in the present trial is likely due to the small sample size and testing EPA only. Alternatively, RBC membrane EPA may not reflect EPA uptake by the CNS, thus obscuring the correlation between a peripheral measure (RBC EPA) and a CNS-mediated event (executive functioning). It is also quite likely that EPA effects are mediated through secondary effects and processes, noted below, that are not reflected in RBC EPA levels.

The mechanism(s) of procognitive effects of EPA are as yet unknown. However there are several plausible candidate mechanisms [48], including the modulation of genes and proteins concerned with inflammation, apoptosis, neurotransmission, and neuronal growth and synapse formation [49], alteration of glutathione availability and modulation of the glutamine/glutamate cycle [50], rise in N-acetyl aspartate (NAA) brain levels after ethyl-EPA treatment [51], the mitochondrial NF-kappa B and c-Jun amino-terminal kinases (JNK) pathways [52]. Further, exposure to O3FA enhances synaptic plasticity by increasing long-term potentiation and synaptic protein expression to increase the dendritic spine density [53]. In aged rats, O3FA supplementation reverses age-related changes and maintains learning memory performance. Finally, O3FA have anti-oxidative stress, anti-inflammation, and anti-apoptosis effects, leading to neuron protection in the aged, damaged, and AD brain [53].

The improvement in positive symptoms with EPA supplementation has been reported previously [54], consistent with the findings of this study. However, in the absence of a

control group, this finding remains observational. There were no correlations between perseverative errors and other symptom measures, suggesting that the changes in executive functioning and positive symptoms were independent processes.

With a number of converging lines of evidence from human and animal studies supporting the notion that O3FA, including EPA, are likely procognitive compounds [20], and that there is an underlying theoretical framework supporting such a premise, particularly with regard to schizophrenia, there appears to be merit in conducting controlled trials that examine the effects of different doses and treatment duration, and post-treatment follow-up to determine the durability of cognitive gains.

Acknowledgments

The authors would like to thank Jack Haflett and John Jay Carroll for their assistance with biochemical assays.

Sources of support

This publication was supported by funds received from NIMH grants MH-46118 (RR), MH-58141 (JKY) and MH-45203 (MSK), VA Research Career Scientist Award (JKY), and the NIH/NCRR/GCRC grant #M01 RR00056.

REFERENCES

- [1]. Heinrichs RW. The primacy of cognition in schizophrenia. *Am Psychol* 2005;60:229–242. [PubMed: 15796677]
- [2]. Nuechterlein KH, Dawson ME. Information processing and attentional functioning in the developmental course of schizophrenic disorders. *Schizophr Bull* 1984;10:160–203. [PubMed: 6729409]
- [3]. Goldman-Rakic PS. Working memory dysfunction in schizophrenia. *J Neuropsychiatry Clin Neurosci* 1994;6:348–357. [PubMed: 7841806]
- [4]. Barch DM, Berenbaum H. Language production and thought disorder in schizophrenia. *J Abnorm Psychol* 1996;105:81–88. [PubMed: 8666714]
- [5]. Condray R, van Kammen DP, Steinhauer SR, Kasperek A, Yao JK. Language comprehension in schizophrenia: trait or state indicator? *Biol Psychiatry* 1995;38:287–296. [PubMed: 7495922]
- [6]. Lencz T, Smith CW, McLaughlin D, Auther A, Nakayama E, Hovey L, Cornblatt BA. Generalized and specific neurocognitive deficits in prodromal schizophrenia. *Biol Psychiatry* 2006;59:863–871. [PubMed: 16325151]
- [7]. Bowie CR, Harvey PD. Cognition in schizophrenia: impairments, determinants, and functional importance. *Psychiatr Clin North Am* 2005;28:613–633. 626. [PubMed: 16122570]
- [8]. Wilk CM, Gold JM, McMahon RP, Humber K, Iannone VN, Buchanan RW. No, it is not possible to be schizophrenic yet neuropsychologically normal. *Neuropsychology* 2005;19:778–786. [PubMed: 16351353]
- [9]. Rosenheck R, Leslie D, Keefe R, McEvoy J, Swartz M, Perkins D, Stroup S, Hsiao JK, Lieberman J. Barriers to employment for people with schizophrenia. *Am J Psychiatry* 2006;163:411–417. [PubMed: 16513861]
- [10]. Hofer A, Baumgartner S, Bodner T, Edlinger M, Hummer M, Kemmler G, Rettenbacher MA, Fleischhacker WW. Patient outcomes in schizophrenia II: the impact of cognition. *Eur Psychiatry* 2005;20:395–402. [PubMed: 16171654]
- [11]. Magliano L, Fiorillo A, Malangone C, De Rosa C, Maj M. Social network in long-term diseases: a comparative study in relatives of persons with schizophrenia and physical illnesses versus a sample from the general population. *Soc Sci Med* 2006;62:1392–1402. [PubMed: 16162379]
- [12]. Velligan DI, Mahurin RK, Diamond PL, Hazleton BC, Eckert SL, Miller AL. The functional significance of symptomatology and cognitive function in schizophrenia. *Schizophr Res* 1997;25:21–31. [PubMed: 9176924]

- [13]. Prouteau A, Verdoux H, Briand C, Lesage A, Lalonde P, Nicole L, Reinhartz D, Stip E. Cognitive predictors of psychosocial functioning outcome in schizophrenia: a follow-up study of subjects participating in a rehabilitation program. *Schizophr Res* 2005;77:343–353. [PubMed: 16085207]
- [14]. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 1996;153:321–330. [PubMed: 8610818]
- [15]. McGurk SR, Coleman T, Harvey PD, Reichenberg A, White L, Friedman J, Parrella M, Davis KL. Working memory performance in poor outcome schizophrenia: relationship to age and executive functioning. *J Clin Exp Neuropsychol* 2004;26:153–160. [PubMed: 15202535]
- [16]. Reed RA, Harrow M, Herbener ES, Martin EM. Executive function in schizophrenia: is it linked to psychosis and poor life functioning? *J Nerv Ment Dis* 2002;190:725–732. [PubMed: 12436011]
- [17]. Harvey PD, McClure MM. Pharmacological approaches to the management of cognitive dysfunction in schizophrenia. *Drugs* 2006;66:1465–1473. [PubMed: 16906778]
- [18]. Peuskens J, Demily C, Thibaut F. Treatment of cognitive dysfunction in schizophrenia. *Clin Ther* 2005;27(Suppl A):S25–37. [PubMed: 16198199]
- [19]. Gray JA, Roth BL. Molecular targets for treating cognitive dysfunction in schizophrenia. *Schizophr Bull* 2007;33:1100–1119. [PubMed: 17617664]
- [20]. McNamara RK. The emerging role of omega-3 fatty acids in psychiatry. *Prostaglandins Leukot Essent Fatty Acids* 2006;75:223–225. [PubMed: 16930969]
- [21]. Heinrichs SC. Dietary omega-3 fatty acid supplementation for optimizing neuronal structure and function. *Mol Nutr Food Res* 2010;54:447–456. [PubMed: 20112300]
- [22]. Yehuda S, Rabinovitz S, Mostofsky DI. Essential fatty acids are mediators of brain biochemistry and cognitive functions. *J Neurosci Res* 1999;56:565–570. [PubMed: 10374811]
- [23]. Yao JK, Reddy RD. Membrane pathology in schizophrenia: implication for arachidonic acid signaling. *ScientificWorldJournal* 2002;2:1922–1936. [PubMed: 12806131]
- [24]. Sethom MM, Fares S, Bouaziz N, Melki W, Jemaa R, Feki M, Hechmi Z, Kaabachi N. Polyunsaturated fatty acids deficits are associated with psychotic state and negative symptoms in patients with schizophrenia. *Prostaglandins Leukot Essent Fatty Acids*. 2010
- [25]. Yao JK, van Kammen DP. Red blood cell membrane dynamics in schizophrenia. I. Membrane fluidity. *Schizophr Res* 1994;11:209–216. [PubMed: 8193060]
- [26]. Reddy RD, Keshavan MS, Yao JK. Reduced red blood cell membrane essential polyunsaturated fatty acids in first episode schizophrenia at neuroleptic-naïve baseline. *Schizophr Bull* 2004;30:901–911. [PubMed: 15957200]
- [27]. Yao JK, Leonard S, Reddy RD. Membrane phospholipid abnormalities in postmortem brains from schizophrenic patients. *Schizophr Res* 2000;42:7–17. [PubMed: 10706981]
- [28]. Horrobin DF, Manku MS, Hillman H, Iain A, Glen M. Fatty acid levels in the brains of schizophrenics and normal controls. *Biol Psychiatry* 1991;30:795–805. [PubMed: 1751622]
- [29]. McNamara RK, Jandacek R, Rider T, Tso P, Hahn CG, Richtand NM, Stanford KE. Abnormalities in the fatty acid composition of the postmortem orbitofrontal cortex of schizophrenic patients: gender differences and partial normalization with antipsychotic medications. *Schizophr Res* 2007;91:37–50. [PubMed: 17236749]
- [30]. 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 Leukot Essent Fatty Acids* 2003;69:393–399. [PubMed: 14623492]
- [31]. Joy CB, Mumby-Croft R, Joy LA. Polyunsaturated fatty acid supplementation for schizophrenia. *Cochrane Database Syst Rev* 2006;3 CD001257.
- [32]. Peet M, Horrobin DF. A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. *J Psychiatr Res* 2002;36:7–18. [PubMed: 11755456]
- [33]. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol* 1998;20:310–319. [PubMed: 9845158]

- [34]. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261–276. [PubMed: 3616518]
- [35]. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 1976;33:766–771. [PubMed: 938196]
- [36]. Yao JK, van Kammen DP, Welker JA. Red blood cell membrane dynamics in schizophrenia. II. Fatty acid composition. *Schizophr Res* 1994;13:217–226. [PubMed: 7841134]
- [37]. Emsley R, Niehaus DJ, Oosthuizen PP, Koen L, Ascott-Evans B, Chiliza B, van Rensburg SJ, Smit RM. Safety of the omega-3 fatty acid, eicosapentaenoic acid (EPA) in psychiatric patients: results from a randomized, placebo-controlled trial. *Psychiatry Res* 2008;161:284–291. [PubMed: 18962989]
- [38]. Fenton WS, Dickerson F, Boronow J, Hibbeln JR, Knable M. A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. *Am J Psychiatry* 2001;158:2071–2074. [PubMed: 11729030]
- [39]. Basso MR, Bornstein RA, Lang JM. Practice effects on commonly used measures of executive function across twelve months. *Clin Neuropsychol* 1999;13:283–292. [PubMed: 10726600]
- [40]. Basso MR, Lowery N, Ghormley C, Bornstein RA. Practice effects on the Wisconsin Card Sorting Test-64 Card version across 12 months. *Clin Neuropsychol* 2001;15:471–478. [PubMed: 11935448]
- [41]. McGrath J, Scheldt S, Welham J, Clair A. Performance on tests sensitive to impaired executive ability in schizophrenia, mania and well controls: acute and subacute phases. *Schizophr Res* 1997;26:127–137. [PubMed: 9323343]
- [42]. McCaffrey RJ, Ortega A, Haase RF. Effects of repeated neuropsychological assessments. *Arch Clin Neuropsychol* 1993;8:519–524. [PubMed: 14591991]
- [43]. Goldberg TE, Keefe RS, Goldman RS, Robinson DG, Harvey PD. Circumstances under which practice does not make perfect: a review of the practice effect literature in schizophrenia and its relevance to clinical treatment studies. *Neuropsychopharmacology* 2010;35:1053–1062. [PubMed: 20090669]
- [44]. Hill SK, Schuepbach D, Herbener ES, Keshavan MS, Sweeney JA. Pretreatment and longitudinal studies of neuropsychological deficits in antipsychotic-naïve patients with schizophrenia. *Schizophr Res* 2004;68:49–63. [PubMed: 15037339]
- [45]. Gold JM, Rehkemper G, Binks SW 3rd, Carpenter CJ, Fleming K, Goldberg TE, Weinberger DR. Learning and forgetting in schizophrenia. *J Abnorm Psychol* 2000;109:534–538. [PubMed: 11016123]
- [46]. Goldberg TE, Goldman RS, Burdick KE, Malhotra AK, Lencz T, Patel RC, Woerner MG, Schooler NR, Kane JM, Robinson DG. Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? *Arch Gen Psychiatry* 2007;64:1115–1122. [PubMed: 17909123]
- [47]. Whalley LJ, Fox HC, Wahle KW, Starr JM, Deary IJ. Cognitive aging, childhood intelligence, and the use of food supplements: possible involvement of n-3 fatty acids. *Am J Clin Nutr* 2004;80:1650–1657. [PubMed: 15585782]
- [48]. Berger GE, Wood SJ, Pantelis C, Velakoulis D, Wellard RM, McGorry PD. Implications of lipid biology for the pathogenesis of schizophrenia. *Aust N Z J Psychiatry* 2002;36:355–366. [PubMed: 12060184]
- [49]. Menesi D, Kitajka K, Molnar E, Kis Z, Belleger J, Narce M, Kang JX, Puskas LG, Das UN. Gene and protein expression profiling of the fat-1 mouse brain. *Prostaglandins Leukot Essent Fatty Acids* 2009;80:33–42. [PubMed: 19138887]
- [50]. Berger GE, Wood SJ, Wellard RM, Proffitt TM, McConchie M, Amminger GP, Jackson GD, Velakoulis D, Pantelis C, McGorry PD. Ethyl-eicosapentaenoic acid in first-episode psychosis. A 1H-MRS study. *Neuropsychopharmacology* 2008;33:2467–2473. [PubMed: 18199999]
- [51]. Frangou S, Lewis M, Wollard J, Simmons A. Preliminary in vivo evidence of increased N-acetyl-aspartate following eicosapentanoic acid treatment in patients with bipolar disorder. *J Psychopharmacol* 2007;21:435–439. [PubMed: 16891338]

- [52]. Murck H, Manku M. Ethyl-EPA in Huntington disease: potentially relevant mechanism of action. *Brain Res Bull* 2007;72:159–164. [PubMed: 17352940]
- [53]. Su HM. Mechanisms of n-3 fatty acid-mediated development and maintenance of learning memory performance. *J Nutr Biochem* 2010;21:364–373. [PubMed: 20233652]
- [54]. Emsley R, Oosthuizen P, van Rensburg SJ. Clinical potential of omega-3 fatty acids in the treatment of schizophrenia. *CNS Drugs* 2003;17:1081–1091. [PubMed: 14661986]

Table 1

Distribution of fatty acids across Baseline and after Weeks 4, 12 and 24 after EPA supplementation (expressed as Mean $\pm$ SEM)

Fatty Acids	Baseline	Week 4	Week 12	Week 24	* p
Saturates	1579.1 $\pm$ 105.2	1826.1 $\pm$ 74.5	1564.5 $\pm$ 174.2	1587.5 $\pm$ 127.4	ns
Monoenes	544.1 $\pm$ 46.6	630.1 $\pm$ 43.8	474.5 $\pm$ 77.6	530.4 $\pm$ 63.0	ns
Dienes	306.0 $\pm$ 25.6	338.2 $\pm$ 28.5	259.0 $\pm$ 41.3	305.1 $\pm$ 40.6	ns
Trienes	42.0 $\pm$ 4.2	42.7 $\pm$ 5.8	35.5 $\pm$ 7.2	36.3 $\pm$ 6.7	ns
Tetraenes	320.4 $\pm$ 31.4	344.8 $\pm$ 43.8	250.8 $\pm$ 42.4	278.0 $\pm$ 51.0	ns
Pentaneenes	31.9 $\pm$ 3.4	62.6 $\pm$ 9.9	92.2 $\pm$ 20.7	80.6 $\pm$ 22.7	<0.5
Hexaneenes	70.8 $\pm$ 7.7	75.8 $\pm$ 15.0	66.4 $\pm$ 11.2	73.8 $\pm$ 15.8	ns
Total (n-6)	670.7 $\pm$ 59.6	728.7 $\pm$ 75.5	547.4 $\pm$ 90.0	621.5 $\pm$ 96.5	ns
Total (n-3)	106.1 $\pm$ 10.7	142.3 $\pm$ 22.9	161.1 $\pm$ 31.1	157.4 $\pm$ 34.3	<0.5
Total trans	45.9 $\pm$ 5.1	57.1 $\pm$ 5.9	32.8 $\pm$ 8.2	47.1 $\pm$ 5.4	ns
Specific fatty acids					
20:4n6	312.2 $\pm$ 30.5	335.9 $\pm$ 42.3	246.1 $\pm$ 41.8	272.6 $\pm$ 49.8	ns
20:5n3	12.9 $\pm$ 1.4	37.0 $\pm$ 5.9	49.2 $\pm$ 12.6	57.1 $\pm$ 13.0	<05
22:5n3	21.4 $\pm$ 2.4	33.0 $\pm$ 4.7	43.5 $\pm$ 8.7	38.4 $\pm$ 9.9	<05
22:6n3	70.8 $\pm$ 7.7	75.8 $\pm$ 15.0	66.4 $\pm$ 11.2	73.8 $\pm$ 15.8	ns

* p values for Baseline and Week 24 comparison