Published in final edited form as:

J Psychiatr Res. 2011 January ; 45(1): 44–46. doi:10.1016/j.jpsychires.2010.04.029.

Investigation of Postmortem Brain Polyunsaturated Fatty Acid Composition in Psychiatric Disorders: Limitations, Challenges, and Future Directions

Robert K. McNamara¹ and Ronald Jandacek²

¹Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH

²Department of Pathology, University of Cincinnati, Cincinnati OH

A growing number of case-control studies have investigated the fatty acid composition of postmortem brain tissue from patients with psychiatric disorders, including schizophrenia (Hamazaki et al., 2010; Horrobin et al., 1991; Landen et al., 2002; McNamara et al., 2007a; Yao et al., 2000), bipolar disorder (Hamazaki et al., 2010; Igarashi et al., 2010; McNamara et al., 2008a), major depressive disorder (Conklin et al., 2010; Lalovic et al., 2007; McNamara et al., 2007b), and suicide (Lalovic et al., 2007; McNamara et al., 2009). Of particular interest are the principal brain omega-3 and omega-6 polyunsaturated fatty acids, docosahexaenoic acid (DHA, 22:6n-3) and arachidonic acid (AA, 20:4n-6) respectively, because prior case-control studies have observed significant erythrocyte membrane DHA and/or AA deficits in psychiatric patients. However, results from different postmortem brain studies have been inconsistent, with some studies finding DHA and/or AA deficits whereas others have not. These disparate findings serve to highlight a number of important extraneous variables and methodological issues, frequently not accounted for, that may directly influence postmortem cortical DHA and AA composition, and help inform interpretation of these findings. Furthermore, accounting for such variables will help guide the design of future postmortem fatty acid studies.

While matching groups for postmortem tissue variables, including postmortem interval, freezer storage duration, and pH, is critical, potential differences in oxidative defenses in postmortem brain tissue from psychiatric patients may nevertheless artificially lead to lower postmortem DHA and AA levels despite matching these variables. Additionally, tissue dissection from frozen cortical tissue blocks may introduce a high degree of variability. For example, DHA is concentrated in synaptic membranes, and frontal white matter DHA composition (~2%) is a small fraction of frontal gray matter DHA composition (~15%). It is therefore important to obtain cortical samples that are as uniform as possible in terms of gray and white matter content. Additionally, imaging studies have found that psychiatric disorders are associated with accelerated gray matter loss. Therefore, the observed reductions in DHA composition in postmortem brain tissue may simply reflect reductions in

© 2010 Elsevier Ltd. All rights reserved.

Robert K. McNamara, Ph.D., Department of Psychiatry, University of Cincinnati College of Medicine, 260 Stetson Street, Cincinnati, OH 45219-0516, PH: 513-558-5601, FAX: 513-558-4805, robert.mcnamara@uc.edu; Ronald Jandacek, Department of Pathology, University of Cincinnati College of Medicine, 2170 East Galbraith Road, Cincinnati, OH 45237, PH: 513-558-5492, FAX: 513-558-4800, ronald.jandacek@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.

gray matter/synaptic density. Arguing against this interpretation, however, is the finding that a marker of synaptic density (synaptophysin) was found to be reduced in the postmortem cingulate of schizophrenic patients whereas DHA levels were not different (Landen et al., 2002). Nevertheless, these issues represent important challenges to the investigation of fatty acid composition in postmortem brain.

One frequently overlooked extraneous variable is the influence of chronic treatment with antipsychotic, mood stabilizer, and/or antidepressant medications prior to death. Emerging data from preclinical studies indicate that chronic exposure to antidepressant, mood-stabilizer, and antipsychotic medications influence cortical AA and/or DHA turnover, metabolism, and/or composition (Lee et al., 2007; McNamara et al., 2009b; Rao & Rapoport, 2009). Furthermore, those postmortem studies that have investigated the effects of prior medication exposure have observed a partial or full normalization of AA and/or DHA levels in patients treated with antipsychotic and/or mood stabilizer medications (Hamazaki et al., 2010; McNamara et al., 2007a, 2008a). In view of data indicating a positive correlation between erythrocyte and postmortem cortical DHA and AA compositions, it is also relevant that a prospective longitudinal case-control study similarly found that erythrocyte DHA and AA deficits observed in medication-naïve first-episode psychotic patients at baseline were normalized following 6-month treatment with risperidone or olanzapine (Evans et al., 2003). However, the majority of published postmortem studies did not account for, or were underpowered to evaluate the influence of, prior medication exposure. In view of the prevalence of pharmacotherapy in the treatment of these disorders, obtaining postmortem brain tissues from medication-naïve or medication-withdrawn patients represents an important challenge for future studies.

In addition, it is important to account for a number of life style variables that may influence DHA and AA composition. For example, long-term alcohol intake is associated with reductions of DHA in non-human primate cortex (Pawlosky et al., 2001), and we observed greater DHA deficits in the prefrontal cortex of bipolar patients and controls with high alcohol abuse severity compared with low alcohol abuse severity (McNamara et al., 2008a). In contrast, substance abuse severity and cigarette smoking were not found to substantially influence cortical DHA or AA composition (McNamara et al., 2007b; 2008a). Diet is also a critical variable because central tissue membrane DHA and AA levels are dependent on habitual dietary intake of *n*-3 and *n*-6 fatty acid precursors as well as preformed DHA and AA. The absence of dietary information for subjects prior to death represents a significant limitation of postmortem brain fatty acid studies. Furthermore, studies frequently employ control subjects that died from cardiovascular-related causes, and a habitual diet low in *n*-3 fatty acids is a risk factor for cardiovascular disease. Therefore, a control group largely comprised of such cases might be anticipated to exhibit lower postmortem brain DHA levels.

Accounting for gender is also important because preclinical studies have observed gender differences in brain DHA composition under controlled dietary conditions (McNamara et al., 2009c), and prominent gender by disorder interactions have been found for DHA composition in postmortem brain studies (McNamara et al., 2007a,b). For example, we found that cortical DHA deficits were greater in female (−32%) than male (−16%) patients with major depression (McNamara et al., 2007b), and a separate study did not observe cortical DHA deficits in exclusively male patients with major depression (Lalovic et al., 2007). In contrast, cortical DHA deficits were observed in male (−27%) but not female (−2%) patients with schizophrenia (McNamara et al., 2007a).

Lastly, age at death is an important variable because cortical DHA and AA composition has been found to decline significantly with advancing age in non-psychiatric control subjects

(McNamara et al., 2008b). Moreover, this age-related decline in cortical DHA and AA composition may be accelerated in psychiatric patients (Conklin et al., 2010; McNamara et al., 2007a). Furthermore, the childhood and adolescent period is associated with rapid changes in cortical DHA and AA composition (Carver et al., 2001), and these age-related changes may be blunted in patients with psychiatric disorders (McNamara et al., 2009a). Therefore, matching groups for age at death is imperative.

Data from preclinical studies in conjunction with emerging data from postmortem brain studies indicate that meaningful interpretation of fatty acid composition analyses requires accounting for age, gender, life style variables, including alcohol and diet, prior medication exposure, and multiple postmortem tissue variables including gray matter density. Many of the published results are based on a small sample size, precluding evaluation of the contribution of the multiple extraneous variables described above. Furthermore, studies with a small sample size may be underpowered to detect small to moderate group differences that may nevertheless be physiologically relevant. In view of the significant challenges and limitations associated with this approach, future studies combining peripheral measures of membrane AA and DHA status and neuroimaging techniques, including positron emission tomography (Sublette et al., 2009; Umhau et al., 2009) and magnetic resonance imaging (Conklin et al., 2007; McNamara et al., 2010), may provide an complimentary approach to investigate central fatty acid abnormalities in psychiatric disorders. Indeed, evidence from recent preliminary studies suggest that blood (erythrocyte, plasma) DHA and/or AA composition is correlated with central glucose metabolism (Sublette et al., 2009), functional cortical activity (McNamara et al., 2010), and potentially gray matter volumes in key limbic structures (Conklin et al., 2007).

References

- 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 Res Bull* 2001;56:79–85. [PubMed: 11704343]
- 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. *Neurosci Lett* 2007;421:209–212. [PubMed: 17574755]
- Conklin SM, Runyan CA, Leonard S, Reddy RD, Muldoon MF, Yao JK. Age-related changes of n-3 and n-6 polyunsaturated fatty acids in the anterior cingulate cortex of individuals with major depressive disorder. *Prostaglandins Leukot Essent Fatty Acids* 2010;82:111–119. [PubMed: 20060277]
- 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]
- Hamazaki K, Choi KH, Kim HY. Phospholipid profile in the postmortem hippocampus of patients with schizophrenia and bipolar disorder: No changes in docosahexaenoic acid species. *J Psychiatr Res*. 2010 Epub ahead of print.
- 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]
- Igarashi M, Ma K, Gao F, Kim HW, Greenstein D, Rapoport SI, Rao JS. Brain lipid concentrations in bipolar disorder. *J Psychiatr Res* 2010;44:177–182. [PubMed: 19767014]
- Landén M, Davidsson P, Gottfries CG, Månsson JE, Blennow K. Reduction of the synaptophysin level but normal levels of glycerophospholipids in the gyrus cinguli in schizophrenia. *Schizophr Res* 2002;55:83–88. [PubMed: 11955966]
- Lalovic A, Levy E, Canetti L, Sequeira A, Montoudis A, Turecki G. Fatty acid composition in postmortem brains of people who completed suicide. *J Psychiatry Neurosci* 2007;32:363–370. [PubMed: 17823652]

- Lee HJ, Rao JS, Ertley RN, Chang L, Rapoport SI, Bazinet RP. Chronic fluoxetine increases cytosolic phospholipase A(2) activity and arachidonic acid turnover in brain phospholipids of the unanesthetized rat. *Psychopharmacology (Berl)* 2007;190:103–115. [PubMed: 17093977]
- McNamara RK, Jandacek R, Rider T, Tso P, Richtand NM, Stanford K. Abnormalities in the fatty acid composition of the postmortem orbitofrontal cortex of schizophrenic patients: gender differences and partial normalization with antipsychotic medications. *Schizophr Res* 2007a;91:37–50. [PubMed: 17236749]
- McNamara RK, Hahn C-G, Jandacek R, Rider T, Tso P, Stanford K, Richtand NM. Selective deficits in the omega-3 fatty acid docosahexaenoic acid in the postmortem orbitofrontal cortex of patients with major depressive disorder. *Biol Psychiatry* 2007b;62:17–24. [PubMed: 17188654]
- McNamara RK, Jandacek R, Rider T, Tso P, Stanford K, Hahn G, 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 Res* 2008a;160:285–299.
- McNamara RK, Liu Y, Jandacek R, Rider T, Tso P. The aging human orbitofrontal cortex: Decreasing polyunsaturated fatty acid composition and associated increases in lipogenic gene expression and stearyl-CoA desaturase activity. *Prostaglandin Leukotrienes Essential Fatty Acids* 2008b;78:293–304.
- McNamara RK, Jandacek R, Rider T, Tso P, Dwivedi Y, Roberts RC, Conley RR, Pandey GN. Fatty acid composition of the postmortem prefrontal cortex of male and female adolescent suicide victims. *Prostaglandin Leukotrienes Essential Fatty Acids* 2009a;80:19–26.
- 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. *Schizophr Res* 2009b;107:150–157. [PubMed: 18993032]
- McNamara RK, Able JA, Liu Y, Jandacek R, Rider T, Tso P. Gender differences in rat erythrocyte and brain docosahexaenoic acid composition: Role of ovarian hormones and dietary omega-3 fatty acid composition. *Psychoneuroendocrinology* 2009c;34:532–539. [PubMed: 19046819]
- McNamara RK, Able J, 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. *Am J Clin Nutr* 2010;91:1060–1067. [PubMed: 20130094]
- Pawlosky RJ, Bacher J, Salem N. Ethanol consumption alters electroretinograms and depletes neural tissues of docosahexaenoic acid in rhesus monkeys: nutritional consequences of a low n-3 fatty acid diet. *Alcohol Clin Exp Res* 2001;25:1758–1765. [PubMed: 11781509]
- Rao JS, Rapoport SI. Mood-stabilizers target the brain arachidonic acid cascade. *Curr Mol Pharmacol* 2009;2:207–214. [PubMed: 20021459]
- Sublette EM, Milak MS, Hibbeln JR, Freed PJ, Oquendo MA, Malone KM, Parsey RV, Mann J. Plasma polyunsaturated fatty acids and regional cerebral glucose metabolism in major depression. *Prostaglandins Leukot Essent Fatty Acids* 2009;80:57–64. [PubMed: 19128951]
- Umhau JC, Zhou W, Carson RE, Rapoport SI, Polozova A, Demar J, Hussein N, Bhattacharjee AK, Ma K, Esposito G, Majchrzak S, Herscovitch P, Eckelman WC, Kurdziel KA, Salem N Jr. Imaging incorporation of circulating docosahexaenoic acid into the human brain using positron emission tomography. *J Lipid Res* 2009;50:1259–1268. [PubMed: 19112173]
- Yao JK, Leonard S, Reddy RD. Membrane phospholipid abnormalities in postmortem brains from schizophrenic patients. *Schizophr Res* 2000;42:7–17. [PubMed: 10706981]