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Altered fatty acid concentrations in prefrontal cortex of schizophrenic patients

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Abstract

Background—Disturbances in prefrontal cortex phospholipid and fatty acid composition have been reported in schizophrenic (SCZ) patients, often as percent of total lipid concentration or incomplete lipid profile. In this study, we quantified absolute concentrations (nmol/g wet weight) of several lipid classes and their constituent fatty acids in postmortem prefrontal cortex of SCZ patients (n = 10) and age-matched controls (n = 10).

Methods—Lipids were extracted, fractionated with thin layer chromatography and assayed.

Results—Mean total lipid, phospholipid, individual phospholipids, plasmalogen, triglyceride and cholesteryl ester concentrations did not differ significantly between the groups. Compared to controls, SCZ brains showed significant increases in several monounsaturated and polyunsaturated fatty acids in cholesteryl ester. Significant increases or decreases occurred in palmitoleic, linoleic, γ -linolenic and n-3 docosapentaenoic acid in total lipids, triglycerides or phospholipids.

Conclusion—These changes suggest disturbed prefrontal cortex fatty acid concentrations, particularly within cholesteryl esters, as a pathological aspect of schizophrenia.

Keywords

fatty acids; lipids; phospholipids; brain; prefrontal cortex; postmortem; schizophrenia; composition; concentrations

1. INTRODUCTION

Schizophrenia (SCZ) is a mental disorder characterized by distortions in the perception of reality (Ross, Margolis, Reading, Pletnikov, & Coyle, 2006), which manifest as psychotic episodes involving hallucinations, delusions and / or thought disorder (Wong & Van Tol, 2003). SCZ affects approximately 0.5–1.0 % of the world's population, and is associated with cognitive impairment, diminished emotional expression and poor quality of life (Ross et al., 2006).

The pathological causes of SCZ are not agreed upon, although one proposed contributing factor is disturbed brain lipid metabolism (Horrobin, Glen, & Vaddadi, 1994). In support of this suggestion, P-31 magnetic resonance spectroscopy (MRS) studies reported an increase

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in choline glycerophospholipid (ChoGpl) and phosphatidylinositol (PtdIns) concentrations, as well as increased phosphomonoester or phosphodiester products of phospholipid synthesis / breakdown in postmortem frontal cortex of SCZ patients relative to controls (Deicken et al., 1994; Komoroski et al., 2001; Komoroski, Pearce, & Mrak, 2008; Miller et al., 2012; Pettegrew et al., 1991; Stanley et al., 1994; Williamson et al., 1991). These changes were not confirmed by a later study, however (Pearce, Komoroski, & Mrak, 2009). Thalamic concentrations of sphingomyelin and phosphatidylcholine were reported decreased, and of phosphatidylserine (PtdSer) increased in SCZ patients (Schmitt et al., 2004). Minimal or no changes in absolute phospholipid concentrations were reported in hippocampus (Hamazaki, Choi, & Kim, 2010), caudate region (Yao, Leonard, & Reddy, 2000), amygdala (Hamazaki, Hamazaki, & Inadera, 2012) or cingulate gyrus (Landen, Davidsson, Gottfries, Mansson, & Blennow, 2002a), suggesting region-specific changes in brain phospholipid metabolism.

An increase in frontal cortex but not hippocampus membrane fluidity was reported in SCZ patients, also suggesting region-specific changes in membrane lipid composition and possibly in enzymes that regulate fatty acid turnover within membrane phospholipids (Eckert, Schaeffer, Schmitt, Maras, & Gattaz, 2011). In agreement with this suggestion, fractional concentrations (i.e. percent of total fatty acids) of the main brain polyunsaturated fatty acids (PUFAs), arachidonic acid (AA, 20:4n-6) and docosahexaenoic acid (DHA, 22:6n-3), were reported to be reduced (McNamara et al., 2007) or unchanged (Horrobin, Manku, Hillman, Iain, & Glen, 1991) in prefrontal cortex total lipids of SCZ patients. AA-containing ChoGpl absolute concentration, DHA fractional concentration in phosphatidylinositol (PtdIns) and docosapentaenoic acid (n-6 DPA, 22:5n-6) fractional concentration in PtdSer and PtdIns were increased in prefrontal cortex of SCZ patients compared to controls (Horrobin et al., 1991; Matsumoto et al., 2011), suggesting phospholipid-specific changes in fatty acid composition. An increase in postmortem frontal cortex activity of DHA-releasing calcium-independent phospholipase A₂ (iPLA₂)-VIA, and a decrease in temporal / frontal cortex and caudate putamen activity of AA-releasing calcium-dependent phospholipase cPLA₂-IVA was reported in SCZ patients (Ross, Turenne, Moszczynska, Warsh, & Kish, 1999), supporting the reported changes in AA and DHA composition and membrane fluidity (Eckert et al., 2011; Horrobin et al., 1991; McNamara et al., 2007; Yao et al., 2000). Minimal changes in fatty acid concentrations were reported in other brain regions, including hippocampus (Hamazaki et al., 2010), amygdala (Hamazaki et al., 2012), cingulate gyrus (Landen et al., 2002a) or the caudate region, in which AA and linoleic acid (18:2n-6) fractional concentrations were reduced (Yao et al., 2000).

The cholesteryl ester pool is also affected in SCZ. Horrobin et al. reported a 43% decrease in the cholesteryl ester pool, and a 46–86% decrease in AA, DHA and linoleic acid absolute concentrations within cholesteryl esters, in frontal cortex of SCZ patients compared to controls (Horrobin et al., 1991). Cholesteryl ester is a precursor to free cholesterol and cholesterol oxidation products that were reported to increase after kainate-induced excitotoxicity (Kim, Jittiwat, Ong, Farooqui, & Jenner, 2010; Ong et al., 2010). Cholesterol oxidation products were reported to facilitate kainate-induced neurotransmitter release by increasing intracellular calcium concentrations, and to induce apoptosis by inducing the pro-inflammatory NF-kappa-B and protein kinase B (Akt) transcription pathway in rat pheochromocytoma-12 cells (Jang & Lee, 2011; Ma, Zhang, Farooqui, Chen, & Ong, 2010).

In many of the postmortem studies, the reported lipid profile was incomplete, or fatty acid concentrations were expressed as fractional concentrations (i.e. percentage of total fatty acids) rather than per gram tissue wet weight, protein or phosphorous. Changes in fatty acid concentrations may not be accurately reflected by using fractional concentrations, particularly if the respective total lipid pool is altered (Taha & McIntyre Burnham, 2007), as

has been reported in the phospholipid pool of SCZ patients (Deicken et al., 1994; Komoroski et al., 2001; Komoroski et al., 2008; Miller et al., 2012; Pettegrew et al., 1991; Williamson et al., 1991). Also, a change in one fatty acid reflects in the opposite direction in another, thereby limiting data interpretation and comparison between studies.

To comprehensively test the hypothesis that schizophrenia is associated with disturbed brain lipid metabolism, we quantified lipid concentrations, per gram brain wet weight, in postmortem prefrontal cortex (Brodmann area 10) of control and SCZ patients. We chose prefrontal cortex because of reported disturbances in lipid composition, membrane fluidity and PLA₂ activity in this region (Deicken et al., 1994; Horrobin et al., 1991; Komoroski et al., 2001; Komoroski et al., 2008; Matsumoto et al., 2011; McNamara et al., 2007; Pettegrew et al., 1991; Williamson et al., 1991; Yao et al., 2000), and because we wanted to compare our results to those on postmortem prefrontal cortex from bipolar disorder and Alzheimer's disease patients, to determine whether changes in lipid concentration were specific to one disease over the other (Igarashi et al., 2010; Igarashi et al., 2011). We also expressed our data as fractional concentrations (percent of total fatty acids) to compare our findings with other studies that reported fractional fatty acid concentrations in prefrontal cortex (Horrobin et al., 1991; McNamara et al., 2007).

2. Materials and Methods

2.1. Materials

Lipid standards were obtained from NuChek Prep (Elysian, MN, USA) or Sigma-Aldrich (St. Louis, MO, USA). Other solvents and reagents were purchased from Sigma-Aldrich or Fisher Scientific.

2.2. Postmortem brain samples

This study was approved by the Institutional Review Board of the McLean Hospital (Belmont, MA) and by the NIH Office of Human Subjects Research (Protocol No. #4380). Frozen prefrontal cortex (Brodmann area 10) from ten diagnosed schizophrenic patients and ten age-matched controls was provided by the Harvard Brain Tissue Resource Center (McLean Hospital, Belmont, MA) under PHS grant R24MH068855 awarded to J.S. Rao. The pH of the brain samples was measured by the method of Harrison et al. (Harrison et al., 1995). The RNA integrity number (RIN) was measured as previously described (Rao, Kellom, Reese, Rapoport, & Kim, 2012). Age, postmortem interval, reported cause of death, medication taken at the time of death, pH and RIN are provided in Table 1.

2.3. Brain lipid extraction and separation of lipid classes

Total lipids were extracted from frozen postmortem brain tissues by the Folch method (Folch, Lees, & Sloane Stanley, 1957). They were separated into phospholipid or neutral lipid subclasses using thin layer chromatography (TLC) on silica gel-60 plates (EM Separation Technologies, Gibbstown, NJ, USA). Phospholipid classes (ethanolamine glycerophospholipid (EtnGpl), phosphatidylinositol (PtdIns), phosphatidylserine (PtdSer), and choline glycerophospholipid (ChoGpl)) were separated using chloroform:methanol:glacial acetic acid:water (60:50:1:4, by vol) (Skipski, Good, Barclay, & Reggio, 1968). Neutral lipid subclasses (cholesteryl esters, triacylglycerol, unesterified fatty acids, cholesterol, and total phospholipids) were separated using heptane: diethylether: glacial acetic acid (60:40:3, by vol) (Skipski et al., 1968). The bands were scraped into test-tubes and used to prepare fatty acid methyl esters (FAMES) or to determine phosphorus or plasmalogen phospholipid concentrations as previously described (Igarashi et al., 2010; Igarashi et al., 2011). Before methylation, an internal standard (di-17:0 PC for phospholipids or 17:0 for unesterified fatty acids) was added to each tube. FAMES were analyzed on an

Agilent gas-chromatography system (6890N, Agilent Technologies, Palo Alto, CA, USA) equipped with an SPTM-2330 fused silica capillary column (30 m × 0.25 mm i.d., 0.25 µm film thickness) (Supelco, Bellefonte, PA, USA) and a flame ionization detector.

2.4. Triglycerides and cholesteryl esters determination

Total triglyceride and cholesteryl ester concentrations were derived by dividing the sum of fatty acids in each fraction by 3 and 1, respectively.

2.5. Phospholipid measurements

Total and individual phospholipid concentrations were quantified using a phosphorus assay involving perchloric acid digestion and spectrophotometric quantification at 797 nm (Rouser, Fkeischer, & Yamamoto, 1970).

2.6. Plamalogen measurements

Concentrations of the plasmenylethanolamine (PlsEtn) and plasmenylcholine (PlsCho), were determined on the separated EtnGpl and ChoGpl TLC bands by the iodine uptake method (Gottfried & Rapport, 1962).

2.7. Statistical analysis

We screened for outliers and tested assumptions of normality and homogeneity of variance with the Shapiro-Wilk and Levene tests, respectively, using SPSS 12.0 (SPSS Inc, Chicago, IL, USA). Since statistical assumptions of normality were met, an unpaired Student's t-test was applied. For all statistical tests, the alpha level of significance was set at 0.05. We did not perform corrections for multiple comparisons because this was an exploratory study involving a small number of postmortem samples, designed to detect changes (if any) in lipid composition in SCZ subjects. We also used different methods to confirm statistically significant changes in the different lipid pools. For instance, changes in total phospholipids paralleled those in phospholipid subfractions; changes in total lipids were reflected within the neutral lipid pool consisting of cholesteryl esters, triglycerides, phospholipids and free fatty acids.

3. RESULTS

3.1. Age, PMI, pH and RIN

Table 1 shows age, pH, postmortem interval (PMI) (RNA integrity number) RIN and drug history of each control and SCZ subject. Mean age (control, 49.7 ± 14.3 ; SCZ, 59.1 ± 13.8 years), pH (control, 6.3 ± 0.3 ; SCZ, 6.4 ± 0.2), PMI (control, 20.6 ± 5.0 ; SCZ, 22.1 ± 4.3 hours) and RIN (control, 6.9 ± 0.6 ; SCZ, 6.8 ± 0.8) did not differ significantly between the groups. With regard to medication history at the time of death, no control was on prescription medication whereas the SCZ subjects were on an antipsychotic (n = 8), mood stabilizer (n = 1) or antidepressant (n = 1) (Table 1).

3.2. Prefrontal cortex lipid concentrations

Mean concentrations (nmol/g wet weight) of total phospholipid, individual phospholipids (EtnGpl, ChoGpl, PtdIns and PtdSer), plasmalogens (PlsEtn and PlsCho), cholesteryl ester and triglycerides did not differ significantly between SCZ and controls subjects (Table 2).

3.3 Prefrontal cortex fatty acid absolute and fraction concentrations

Table 3-A summarizes mean concentration of unesterified fatty acids and esterified fatty acids in total lipids, phospholipid, triglyceride and cholesteryl ester. In total lipids, concentrations of palmitoleic acid (16:1n-7), LA and n-3 docosapentaenoic acid (DPA,

22:5n-3) were significantly higher by 42%, 35% and 46%, respectively, in SCZ frontal cortex than controls. Palmitoleic acid and n-3 DPA were also significantly higher in total phospholipid. In triglycerides, γ -linolenic acid (20:3n-6) was significantly reduced by 3.5 fold. Cholesteryl ester concentrations of LA, AA, n-6 DPA, n-3 DPA and DHA were 4.0, 3.8, 3.0, 4.3, 2.5 fold higher in SCZ compared with controls ($p < 0.05$). Unesterified concentrations of 16:1n-7, LA, AA and eicosapentaenoic acid (EPA, 20:5n-3) were 1.3 – 5 fold higher in SCZ subjects compared to controls ($p < 0.05$).

Previous studies reported reduced percent composition (i.e. fraction of net fatty acid concentrations) of AA and DHA in frontal cortex of SCZ patients. To compare our results with these reports, we transformed our absolute concentration data (nmol/g wet weight) into fractional concentrations, by dividing the concentration of each fatty acid by the net fatty acid concentration in each lipid pool (Table 3-B). In agreement with one previous report, we found significant reductions in total lipid AA and DHA fractional concentration in SCZ compared to controls (McNamara et al., 2007). DHA was reduced also in total phospholipid by 20% ($p < 0.05$). In triglycerides, the fractional concentration of 20:3n-6 was reduced (4-fold), whereas that of AA and n-3 DPA was increased by 1.6 – 4 folds ($p < 0.05$). Cholesteryl ester fractional concentrations of 16:0 and stearic acid (18:0) were reduced, whereas oleic acid (18:1n-9), vaccenic acid (18:1n-7), AA and n-6 DPA were increased ($p < 0.05$). Within unesterified fatty acids, 18:1n-9, LA, EPA and n-3 DPA were significantly increased by 16%, 100%, 300% and 50%, respectively, in SCZ frontal cortex.

Significant differences were seen in esterified fatty acid concentrations within individual phospholipids (Table 4-A). The concentration of palmitic acid (16:0) was higher in ChoGpl (21%), PtdIns (57%) and PtdSer (95%) of SCZ frontal cortex compared to controls ($p < 0.05$). 16:1n-7 concentration was significantly increased (90%) in EtnGpl of SCZ subjects, as was 18:0 concentration in PtdIns (19%). LA concentration was significantly increased in EtnGpl (2.5 fold) and ChoGpl (1.4 fold), reflecting the increase seen in total phospholipid (Table 2). EPA concentration was significantly increased (3.5 fold) in PtdSer, whereas DHA was significantly decreased (42%) in PtdIns of SCZ subjects. Adrenic acid (22:4n-6) was significantly reduced by 29–37% in ChoGpl and PtdIns of SCZ frontal cortex.

Fractional concentrations within individual phospholipids were calculated from the absolute concentration data presented in Table 4-A. As indicated, fractional concentrations of 16:1n-7, LA and 20:3n-6 were significantly higher in EtnGpl of SCZ than controls. In ChoGpl, AA, 22:4n-6 and DHA were significantly reduced in SCZ by 22%, 40% and 32%, respectively. 16:0 was significantly increased in PtdIns and PtdSer of SCZ subjects (32–50%). 22:4n-6 was reduced in PtdIns, whereas EPA was increased in PtdSer ($p < 0.05$).

4. DISCUSSION

This study showed a number of statistically significant changes in prefrontal cortex lipid concentrations of SCZ patients compared with controls, particularly in cholesteryl ester fatty acids. Total and individual phospholipid, plasmalogen, cholesteryl ester and triglyceride concentrations (nmol per g wet weight) did not differ significantly between the groups. In SCZ subjects, significant increases in the absolute concentration (nmol per g wet weight) of esterified LA, AA, DHA, n-6 DPA, n-3 DPA, oleic acid and vaccenic acid occurred in cholesteryl ester, a quantitatively minor fraction of the total lipid pool. Statistically significant changes were seen in palmitate absolute concentration within EtnGpl, PtdIns and PtdSer (21–95% increase), and in esterified fatty acids including palmitoleic acid, linoleic acid, γ -linolenic acid and n-3 DPA, which increased or decreased in total lipids, triglycerides or total or individual phospholipids. AA and DHA absolute concentrations did not differ per g wet weight, but were reduced in total lipids, total phospholipid, ChoGpl or

PtdIns when expressed as fractional concentrations (percent of total fatty acids). The increases in 16:1n-7, LA, AA and EPA unesterified concentrations in SCZ subjects likely reflected differences in response to their ischemia-induced postmortem release from phospholipids.

The lack of change in total and individual phospholipid concentrations is in agreement with one (Pearce et al., 2009), but not other studies that reported changes in concentration of various phospholipid subclasses in postmortem SCZ frontal cortex (Deicken et al., 1994; Komoroski et al., 2001; Komoroski et al., 2008; Pettegrew et al., 1991; Williamson et al., 1991). Differences in study outcomes may be related to differences in analytical methodology. In prior reports, MRS was used to quantify phospholipid concentrations, whereas in this study, phospholipids were quantified by gas chromatography and a phosphorous assay, which measure the sum of fatty acids and the net phosphorous amount per phospholipid, respectively. MRS and gas-chromatography have been shown to yield inconsistent lipid profiles (Thomas, Cunnane, & Bell, 1998), which can also be exacerbated by study differences in tissue brain bank source, method of tissue collection, duration of post-mortem interval, disease severity or drug history. Our finding of no significant change in major polyunsaturated fatty acid absolute concentrations in phospholipids (e.g. AA, DHA) or in individual phospholipid concentrations is consistent with one study which reported no change in hippocampal absolute concentrations (pmol per μg protein) of phospholipid species or of major fatty acids esterified within phospholipid subclasses (Hamazaki et al., 2010). It is possible, however, that our sample size ($n = 10$ / group) was too small to detect significant changes in prefrontal cortex phospholipid or PUFA concentrations. Thus, our findings need to be confirmed in larger postmortem studies.

The significant increases in LA, AA, DHA, n-6 DPA, n-3 DPA, oleic acid and vaccenic acid in cholesteryl esters is opposite to the reported reductions in AA, DHA and LA cholesteryl ester concentrations in SCZ frontal cortex (Horrobin et al., 1991). Differences in study outcomes are difficult to reconcile, but may be attributed to other study confounders such as cause of death, disease duration, medication history or diet. However, the fact that changes in cholesteryl ester absolute fatty acid concentrations were found in this study and the Horrobin et al. study, suggests disturbed cholesteryl ester metabolism in SCZ patients. Although cholesteryl ester is a minor lipid pool in the brain (~0.3% of brain total lipids), it is a precursor to oxidized cholesterol products (Kim et al., 2011c; Kim et al., 2010) that can cause neuronal death by increasing intracellular calcium concentrations and inducing apoptosis via activation of the NF-kappa-B and Akt pro-inflammatory pathways (Jang et al., 2011; Ma et al., 2010). Cholesteryl ester turnover and concentration in brain is regulated by acyl-coenzyme A: cholesterol acyl transferase-1, which is upregulated during excitotoxic brain injury (Kim et al., 2011c; Kim et al., 2010). Thus an increase in cholesteryl ester fatty acid concentration and possibly turnover in SCZ may reflect the excitotoxicity and neuronal loss reported in SCZ patients (Deicken, Pegues, & Amend, 1999; Landen, Davidsson, Gottfries, Mansson, & Blennow, 2002b; Rao et al., 2012). Future studies should explore the involvement and targeting of acyl-coenzyme A: cholesterol acyl transferase-1 in SCZ.

The significant increases in phospholipid palmitoleate and n-3 DPA, and decreases in PtdIns DHA and adrenic acid ChoGpl and PtdIns, suggest disturbed fatty acid metabolism and phospholipid remodelling in SCZ patients. Since fatty acids such as n-6 DPA and DHA are released from membrane phospholipids by selective phospholipase A₂ enzymes (cPLA₂-IVA for n-6 DPA and iPLA₂-VIA for DHA; Igarashi et al., 2012; Strokin, Sergeeva, & Reiser, 2003) that are functionally coupled to G-protein receptors (Basselin, Ramadan, & Rapoport, 2012), changes in their concentration reflect disturbed G-protein neuroreceptor signaling. This is consistent with findings in postmortem brain from SCZ patients suggesting hypoglutamatergic and hyperdopaminergic neurotransmitter signalling, in association with

neuronal loss and disease worsening over time (Davidsson et al., 1999; Landen et al., 2002b; Moghaddam & Javitt, 2012; Rao et al., 2012).

Prefrontal cortex absolute concentrations (nmol per g wet weight) of AA and DHA did not differ significantly between the groups, but were reduced in total lipid, ChoGpl or PtdIns when expressed as fractional concentrations (percentage of total fatty acids). This decrease is in agreement with one study that showed reduced AA and DHA fractional concentrations in total lipid orbitofrontal cortex total lipids of SCZ patients compared to controls (McNamara et al., 2007), but differs from another study that reported increased DHA fractional concentration in frontal and cerebral cortex PtdIns and no change in ChoGpl (Horrobin et al., 1991). Fractional concentration changes are difficult to interpret because a change in one fatty acid may be secondary to changes in others. In this study, changes in AA and DHA fractional concentrations were an artefact of changes in other fatty acids (16:1n-7 and n-3 DPA) that were increased per g brain wet weight and also as a fractional percent of total fatty acids. The fact that absolute concentrations (nmol per g wet weight) of DHA were not changed argues against a suggested DHA deficit in SCZ prefrontal cortex (McNamara et al., 2007). Also, n-6 DPA, a marker of DHA deficiency that increases in response to reduced plasma and brain DHA concentration in rats (Kim, Rao, Rapoport, & Igarashi, 2011a), did not significantly differ between SCZ and control brains.

Activity of AA-releasing cPLA₂-IVA and DHA-releasing iPLA₂-VIA was reported decreased and increased, respectively, in frontal cortex of SCZ patients relative to controls (Ross et al., 1999), suggesting disturbed AA and DHA metabolism. This suggestion is further supported by one study that showed increased prefrontal cortex (Brodmann area 10) mRNA and protein of AA-selective cPLA₂-IVA and cyclooxygenase-2 (COX-2) (Rao, 2010). COX-2 converts both AA and DHA into bioactive pro-inflammatory or anti-inflammatory metabolites (Groeger et al., 2010). Another study found no change in COX-2 mRNA in Brodmann area 46 of SCZ patients. In the future, region-specific changes in AA or DHA metabolism if they occur could be quantified in human subjects with positron-emission tomography (PET) using [1-(11)C]AA, [20-(18)F]AA or [1-(11)C]DHA (Pichika et al., 2012; Thambisetty et al., 2012; Umhau et al., 2009). Also, because cPLA₂-IVA is functionally coupled to dopaminergic and glutamatergic neuroreceptors (Basselin, Chang, Bell, & Rapoport, 2005; 2006; Ramadan et al., 2011; Ramadan et al., 2010), which were shown to be altered in postmortem prefrontal cortex of SCZ patients (Rao et al., 2012), in vivo brain imaging using PET could be used to estimate disturbed neuroreceptor signaling in SCZ patients (Pichika et al., 2012; Thambisetty et al., 2012).

It would be worthwhile to assess whether the observed changes in fatty acid concentrations in SCZ patients occur in other brain regions reported to be involved in disease pathology, such as the hippocampus (Altshuler, Casanova, Goldberg, & Kleinman, 1990; Haijma et al., 2012; Solowij et al., 2012; Suddath, Christison, Torrey, Casanova, & Weinberger, 1990). In this study, we focused only on the prefrontal cortex because of reported signaling and anatomical abnormalities in that region in particular (Beasley, Zhang, Patten, & Reynolds, 2002; Rajkowska, Selemon, & Goldman-Rakic, 1998; Rao et al., 2012; Selemon, Rajkowska, & Goldman-Rakic, 1998) and because many of the reported changes in lipid composition were found in prefrontal cortex but not other areas (see Introduction) (Deicken et al., 1994; Komoroski et al., 2001; Komoroski et al., 2008; Miller et al., 2012; Pettegrew et al., 1991; Williamson et al., 1991). It is possible that phospholipid or fatty acid concentrations in other affected brain regions are altered as well, or change with disease progression as reported recently by Miller et al. (Miller et al., 2012).

The control phospholipid, plasmalogen, triglyceride, cholesteryl ester and fatty acid concentrations in this study are comparable to published concentrations (per gram wet

weight) in prefrontal cortex (Igarashi et al., 2010; Igarashi et al., 2011). The distribution of fatty acids within individual phospholipids also is in agreement with previous postmortem studies, with AA being highly concentrated in ChoGpl and PtdIns, and DHA being enriched in EtnGpl and PtdSer (Igarashi et al., 2010; Igarashi et al., 2011). This confirms the accuracy and reproducibility of our analytical methods, in which an internal standard was used for quantitation.

The significant changes in esterified fatty acid absolute concentrations might be attributed to antipsychotic medications that the SCZ patients were taking at the time of death. None of the controls was on medication, whereas seven of ten SCZ patients were on risperidone and one was on clozapine. However, both drugs were reported to have no effect on rat brain fatty acid concentrations (Levant, Crane, & Carlson, 2006; Modi et al., 2012). Clozapine, like the other atypical antipsychotic olanzapine, was reported to reduce brain AA incorporation in rats, suggesting effects on fatty acid kinetics in the absence of major changes in concentrations (Cheon et al., 2011; Modi et al., 2012).

Although PMI, pH, RIN and age are similar between control and SCZ subjects, diet, duration of drug exposure, substance abuse, smoking status, gender, pregnancy and liver disease history are uncontrolled factors that may have altered brain lipid concentrations. Our sample size was too small to allow statistical control for gender as a covariate. We do not have information on diet composition, substance abuse, smoking status, pregnancy or liver disease. With regard to diet, one study reported higher saturated fatty acid and total PUFA intakes, but no differences in α -linolenic acid, eicosapentaenoic acid or DHA consumption, in SCZ patients compared to population standards derived from the National Health and Nutrition Examination Surveys (Cycle III) (Strassnig, Singh Brar, & Ganguli, 2005). Individual n-6 PUFA concentrations were not reported (Strassnig et al., 2005). Differences in saturated fatty acid and PUFA intakes can influence brain fatty acid metabolism (Rapoport, Igarashi, & Gao, 2010). Supporting a link between diet and brain fatty acid metabolism is evidence from several epidemiological and double-blinded randomized trials showing an inverse association between dietary EPA and DHA intake and the risk of psychosis (Amminger et al., 2010; Berger et al., 2007; Hedelin et al., 2010).

As in bipolar disorder and Alzheimer's disease, the postmortem SCZ brain shows neuroinflammation (Fillman et al., 2012) and upregulated AA metabolizing enzymes, including cPLA₂-IVA and COX-2 (Kim, Rapoport, & Rao, 2011b; Rao, 2010; Rao, Harry, Rapoport, & Kim, 2010; Rao, Rapoport, & Kim, 2011). The changes in prefrontal cortex cholesteryl ester fatty acid concentrations in schizophrenia are similar to changes reported in prefrontal cortex of bipolar disorder and Alzheimer's disease patients (Igarashi et al., 2010; Igarashi et al., 2011). Unlike the bipolar or SCZ brains, however, Alzheimer's disease patients show more profound changes in prefrontal cortex lipid concentrations, characterized by reductions in choline plasmalogen and phospholipid AA and DHA absolute concentrations (Igarashi et al., 2011).

In summary, we found several statistically significant changes in prefrontal cortex esterified fatty acid absolute concentrations (nmol per g wet weight) in the cholesteryl ester lipid pool and in esterified palmitate, palmitoleic acid, linoleic acid, γ -linolenic acid and n-3 DPA, within total lipids, triglycerides or total or individual phospholipids of SCZ patients compared with control brain. The decrease in AA and DHA fractional concentrations, although consistent with one previous report (McNamara et al., 2007), reflected increased 16:1n-7 and n-3 DPA absolute concentrations, suggesting that absolute measurements using internal standards should be used in future postmortem studies. Our results suggest subtle lipid disturbances in schizophrenia. PET imaging of SCZ and control patients with radiotracers might be used to determine whether regional disturbances in AA or DHA

metabolism exist, in relation to disease severity, progression and clinical management with antipsychotics.

Abbreviations

AA	arachidonic acid
BD	bipolar disorder
ChoGpl	choline glycerophospholipid
COX	cyclooxygenase
DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
EtnGpl	ethanolamine glycerophospholipid
FAME	fatty acid methyl ester
GC	gas chromatography
cPLA₂	cytosolic phospholipase A ₂
iPLA₂	calcium-independent phospholipase A ₂
MRS	magnetic resonance spectroscopy
PET	positron-emission tomography
PtdIns	phosphatidylinositol
PtdSer	phosphatidylserine
sn	stereospecifically numbered
PlsEtn	plasmeneylethanolamine
PlsCho	plasmeneylcholine
RIN	RNA integrity number
sPLA₂	secretory phospholipase A ₂
TLC	thin layer chromatography

References

- Altshuler LL, Casanova MF, Goldberg TE, Kleinman JE. The hippocampus and parahippocampus in schizophrenia, suicide, and control brains. *Arch Gen Psychiatry*. 1990; 47:1029–1034. [PubMed: 2241505]
- Amminger GP, Schafer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, Mackinnon A, McGorry PD, Berger GE. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *Arch Gen Psychiatry*. 2010; 67:146–154. [PubMed: 20124114]
- Basselin M, Chang L, Bell JM, Rapoport SI. Chronic lithium chloride administration to unanesthetized rats attenuates brain dopamine D2-like receptor-initiated signaling via arachidonic acid. *Neuropsychopharmacology*. 2005; 30:1064–1075. [PubMed: 15812572]
- Basselin M, Chang L, Bell JM, Rapoport SI. Chronic lithium chloride administration attenuates brain NMDA receptor-initiated signaling via arachidonic acid in unanesthetized rats. *Neuropsychopharmacology*. 2006; 31:1659–1674. [PubMed: 16292331]
- Basselin M, Ramadan E, Rapoport SI. Imaging brain signal transduction and metabolism via arachidonic and docosahexaenoic acid in animals and humans. *Brain Res Bull*. 2012; 87:154–171. [PubMed: 22178644]

- Beasley CL, Zhang ZJ, Patten I, Reynolds GP. Selective deficits in prefrontal cortical GABAergic neurons in schizophrenia defined by the presence of calcium-binding proteins. *Biol Psychiatry*. 2002; 52:708–715. [PubMed: 12372661]
- Berger GE, Proffitt TM, McConchie M, Yuen H, Wood SJ, Amminger GP, Brewer W, McGorry PD. Ethyl-eicosapentaenoic acid in first-episode psychosis: a randomized, placebo-controlled trial. *The Journal of clinical psychiatry*. 2007; 68:1867–1875. [PubMed: 18162017]
- Cheon Y, Park JY, Modi HR, Kim HW, Lee HJ, Chang L, Rao JS, Rapoport SI. Chronic olanzapine treatment decreases arachidonic acid turnover and prostaglandin E(2) concentration in rat brain. *J Neurochem*. 2011; 119:364–376. [PubMed: 21812779]
- Davidsson P, Gottfries J, Bogdanovic N, Ekman R, Karlsson I, Gottfries CG, Blennow K. The synaptic-vesicle-specific proteins rab3a and synaptophysin are reduced in thalamus and related cortical brain regions in schizophrenic brains. *Schizophr Res*. 1999; 40:23–29. [PubMed: 10541003]
- Deicken RF, Calabrese G, Merrin EL, Meyerhoff DJ, Dillon WP, Weiner MW, Fein G. 31phosphorus magnetic resonance spectroscopy of the frontal and parietal lobes in chronic schizophrenia. *Biological psychiatry*. 1994; 36:503–510. [PubMed: 7827212]
- Deicken RF, Pegues M, Amend D. Reduced hippocampal N-acetylaspartate without volume loss in schizophrenia. *Schizophr Res*. 1999; 37:217–223. [PubMed: 10403193]
- Eckert GP, Schaeffer EL, Schmitt A, Maras A, Gattaz WF. Increased brain membrane fluidity in schizophrenia. *Pharmacopsychiatry*. 2011; 44:161–162. [PubMed: 21710408]
- Fillman SG, Cloonan N, Catts VS, Miller LC, Wong J, McCrossin T, Cairns M, Weickert CS. Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia. *Mol Psychiatry*. 2012
- Folch J, Lees M, Sloane Stanley GH. A simple method for the isolation and purification of total lipides from animal tissues. *J Biol Chem*. 1957; 226:497–509. [PubMed: 13428781]
- Gottfried EL, Rapport MM. The biochemistry of plasmalogens. I. Isolation and characterization of phosphatidyl choline, a pure native plasmalogen. *J Biol Chem*. 1962; 237:329–333. [PubMed: 13900748]
- Groeger AL, Cipollina C, Cole MP, Woodcock SR, Bonacci G, Rudolph TK, Rudolph V, Freeman BA, Schopfer FJ. Cyclooxygenase-2 generates anti-inflammatory mediators from omega-3 fatty acids. *Nat Chem Biol*. 2010; 6:433–441. [PubMed: 20436486]
- Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS. Brain Volumes in Schizophrenia: A Meta-Analysis in Over 18 000 Subjects. *Schizophr Bull*. 2012
- Hamazaki K, Choi KH, Kim HY. Phospholipid profile in the postmortem hippocampus of patients with schizophrenia and bipolar disorder: No changes in docosaheptaenoic acid species. *J Psychiatr Res*. 2010
- Hamazaki K, Hamazaki T, Inadera H. Fatty acid composition in the postmortem amygdala of patients with schizophrenia, bipolar disorder, and major depressive disorder. *Journal of psychiatric research*. 2012
- Harrison PJ, Heath PR, Eastwood SL, Burnet PW, McDonald B, Pearson RC. The relative importance of premortem acidosis and postmortem interval for human brain gene expression studies: selective mRNA vulnerability and comparison with their encoded proteins. *Neurosci Lett*. 1995; 200:151–154. [PubMed: 9064599]
- Hedelin M, Lof M, Olsson M, Lewander T, Nilsson B, Hultman CM, Weiderpass E. Dietary intake of fish, omega-3, omega-6 polyunsaturated fatty acids and vitamin D and the prevalence of psychotic-like symptoms in a cohort of 33,000 women from the general population. *BMC Psychiatry*. 2010; 10:38. [PubMed: 20504323]
- Horrobin DF, Glen AI, Vaddadi K. The membrane hypothesis of schizophrenia. *Schizophrenia research*. 1994; 13:195–207. [PubMed: 7841132]
- 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, Kim HW, Gao F, Chang L, Ma K, Rapoport SI. Fifteen weeks of dietary n-3 polyunsaturated fatty acid deprivation increase turnover of n-6 docosapentaenoic acid in rat-brain phospholipids. *Biochim Biophys Acta*. 2012; 1821:1235–1243. [PubMed: 22142872]

- Igarashi M, Ma K, Gao F, Kim HW, Greenstein D, Rapoport SI, Rao JS. Brain lipid concentrations in bipolar disorder. *Journal of psychiatric research*. 2010; 44:177–182. [PubMed: 19767014]
- Igarashi M, Ma K, Gao F, Kim HW, Rapoport SI, Rao JS. Disturbed choline plasmalogen and phospholipid fatty acid concentrations in Alzheimer's disease prefrontal cortex. *Journal of Alzheimer's disease : JAD*. 2011; 24:507–517.
- Jang ER, Lee CS. 7-ketocholesterol induces apoptosis in differentiated PC12 cells via reactive oxygen species-dependent activation of NF-kappaB and Akt pathways. *Neurochem Int*. 2011; 58:52–59. [PubMed: 21035514]
- Kim HW, Rao JS, Rapoport SI, Igarashi M. Regulation of rat brain polyunsaturated fatty acid (PUFA) metabolism during graded dietary n-3 PUFA deprivation. *Prostaglandins Leukot Essent Fatty Acids*. 2011a; 85:361–368. [PubMed: 21880477]
- Kim HW, Rapoport SI, Rao JS. Altered arachidonic acid cascade enzymes in postmortem brain from bipolar disorder patients. *Mol Psychiatry*. 2011b; 16:419–428. [PubMed: 20038946]
- Kim JH, Ee SM, Jittiwat J, Ong ES, Farooqui AA, Jenner AM, Ong WY. Increased expression of acyl-coenzyme A: cholesterol acyltransferase-1 and elevated cholesteryl esters in the hippocampus after excitotoxic injury. *Neuroscience*. 2011c; 185:125–134. [PubMed: 21514367]
- Kim JH, Jittiwat J, Ong WY, Farooqui AA, Jenner AM. Changes in cholesterol biosynthetic and transport pathways after excitotoxicity. *Journal of neurochemistry*. 2010; 112:34–41. [PubMed: 19860851]
- Komoroski RA, Pearce JM, Griffin WS, Mrak RE, Omori M, Karson CN. Phospholipid abnormalities in postmortem schizophrenic brains detected by 31P nuclear magnetic resonance spectroscopy: a preliminary study. *Psychiatry research*. 2001; 106:171–180. [PubMed: 11382539]
- Komoroski RA, Pearce JM, Mrak RE. 31P NMR spectroscopy of phospholipid metabolites in postmortem schizophrenic brain. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*. 2008; 59:469–474. [PubMed: 18306399]
- Landen M, Davidsson P, Gottfries CG, Mansson JE, Blennow K. Reduction of the synaptophysin level but normal levels of glycerophospholipids in the gyrus cinguli in schizophrenia. *Schizophrenia research*. 2002a; 55:83–88. [PubMed: 11955966]
- Landen M, Davidsson P, Gottfries CG, Mansson JE, Blennow K. Reduction of the synaptophysin level but normal levels of glycerophospholipids in the gyrus cinguli in schizophrenia. *Schizophr Res*. 2002b; 55:83–88. [PubMed: 11955966]
- Levant B, Crane JF, Carlson SE. Sub-chronic antipsychotic drug treatment does not alter brain phospholipid fatty acid composition in rats. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006; 30:728–732. [PubMed: 16442197]
- Ma MT, Zhang J, Farooqui AA, Chen P, Ong WY. Effects of cholesterol oxidation products on exocytosis. *Neurosci Lett*. 2010; 476:36–41. [PubMed: 20380872]
- Matsumoto J, Sugiura Y, Yuki D, Hayasaka T, Goto-Inoue N, Zaima N, Kunii Y, Wada A, Yang Q, Nishiura K, Akatsu H, Hori A, Hashizume Y, Yamamoto T, Ikemoto K, Setou M, Niwa S. Abnormal phospholipids distribution in the prefrontal cortex from a patient with schizophrenia revealed by matrix-assisted laser desorption/ionization imaging mass spectrometry. *Analytical and bioanalytical chemistry*. 2011; 400:1933–1943. [PubMed: 21461619]
- 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]
- Miller J, Drost DJ, Jensen E, Manchanda R, Northcott S, Neufeld RW, Menon R, Rajakumar N, Pavlosky W, Densmore M, Schaefer B, Williamson P. Progressive membrane phospholipid changes in first episode schizophrenia with high field magnetic resonance spectroscopy. *Psychiatry Res*. 2012; 201:25–33. [PubMed: 22284150]
- Modi HR, Taha AY, Kim HW, Chang L, Rapoport SI, Cheon Y. Chronic clozapine reduces rat brain arachidonic acid metabolism by reducing plasma arachidonic acid availability. *J Neurochem*. 2012
- Moghaddam B, Javitt D. From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology*. 2012; 37:4–15. [PubMed: 21956446]

- Ong WY, Kim JH, He X, Chen P, Farooqui AA, Jenner AM. Changes in brain cholesterol metabolome after excitotoxicity. *Mol Neurobiol*. 2010; 41:299–313. [PubMed: 20140539]
- Pearce JM, Komoroski RA, Mrak RE. Phospholipid composition of postmortem schizophrenic brain by 31P NMR spectroscopy. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*. 2009; 61:28–34. [PubMed: 19097198]
- Pettegrew JW, Keshavan MS, Panchalingam K, Strychor S, Kaplan DB, Tretta MG, Allen M. Alterations in brain high-energy phosphate and membrane phospholipid metabolism in first-episode, drug-naïve schizophrenics. A pilot study of the dorsal prefrontal cortex by in vivo phosphorus 31 nuclear magnetic resonance spectroscopy. *Archives of general psychiatry*. 1991; 48:563–568. [PubMed: 1898445]
- Pichika R, Taha AY, Gao F, Kotta K, Cheon Y, Chang L, Kiesewetter D, Rapoport SI, Eckelman WC. The Synthesis and In Vivo Pharmacokinetics of Fluorinated Arachidonic Acid: Implications for Imaging Neuroinflammation. *J Nucl Med*. 2012
- Rajkowska G, Selemon LD, Goldman-Rakic PS. Neuronal and glial somal size in the prefrontal cortex: a postmortem morphometric study of schizophrenia and Huntington disease. *Arch Gen Psychiatry*. 1998; 55:215–224. [PubMed: 9510215]
- Ramadan E, Basselin M, Taha AY, Cheon Y, Chang L, Chen M, Rapoport SI. Chronic valproate treatment blocks D2-like receptor-mediated brain signaling via arachidonic acid in rats. *Neuropharmacology*. 2011; 61:1256–1264. [PubMed: 21839100]
- Ramadan E, Rosa AO, Chang L, Chen M, Rapoport SI, Basselin M. Extracellular-derived calcium does not initiate in vivo neurotransmission involving docosahexaenoic acid. *J Lipid Res*. 2010; 51:2334–2340. [PubMed: 20388940]
- Rao JS. Overlapping Molecular Neuropathology in Post-Mortem Frontal Cortex from Bipolar Disorder and Schizophrenic Patients. *Neuropsychopharmacology*. 2010:S1–S77. [PubMed: 21140541]
- Rao JS, Harry GJ, Rapoport SI, Kim HW. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. *Mol Psychiatry*. 2010; 15:384–392. [PubMed: 19488045]
- Rao JS, Kellom M, Reese EA, Rapoport SI, Kim HW. Dysregulated glutamate and dopamine transporters in postmortem frontal cortex from bipolar and schizophrenic patients. *J Affect Disord*. 2012; 136:63–71. [PubMed: 21925739]
- Rao JS, Rapoport SI, Kim HW. Altered neuroinflammatory, arachidonic acid cascade and synaptic markers in postmortem Alzheimer's disease brain. *Transl Psychiatry*. 2011; 1:e31. [PubMed: 22832605]
- Rapoport SI, Igarashi M, Gao F. Quantitative contributions of diet and liver synthesis to docosahexaenoic acid homeostasis. *Prostaglandins Leukot Essent Fatty Acids*. 2010; 82:273–276. [PubMed: 20226642]
- Ross BM, Turenne S, Moszczynska A, Warsh JJ, Kish SJ. Differential alteration of phospholipase A2 activities in brain of patients with schizophrenia. *Brain Res*. 1999; 821:407–413. [PubMed: 10064828]
- Ross CA, Margolis RL, Reading SA, Pletnikov M, Coyle JT. Neurobiology of schizophrenia. *Neuron*. 2006; 52:139–153. [PubMed: 17015232]
- Rouser G, Fkeischer S, Yamamoto A. Two dimensional then layer chromatographic separation of polar lipids and determination of phospholipids by phosphorus analysis of spots. *Lipids*. 1970; 5:494–496. [PubMed: 5483450]
- Schmitt A, Wilczek K, Blennow K, Maras A, Jatzko A, Petroianu G, Braus DF, Gattaz WF. Altered thalamic membrane phospholipids in schizophrenia: a postmortem study. *Biol Psychiatry*. 2004; 56:41–45. [PubMed: 15219471]
- Selemon LD, Rajkowska G, Goldman-Rakic PS. Elevated neuronal density in prefrontal area 46 in brains from schizophrenic patients: application of a three-dimensional, stereologic counting method. *J Comp Neurol*. 1998; 392:402–412. [PubMed: 9511926]
- Skipski VP, Good JJ, Barclay M, Reggio RB. Quantitative analysis of simple lipid classes by thin-layer chromatography. *Biochim Biophys Acta*. 1968; 152:10–19. [PubMed: 4296328]

- Solowij N, Walterfang M, Lubman DI, Whittle S, Lorenzetti V, Styner M, Velakoulis D, Pantelis C, Yucel M. Alteration to hippocampal shape in cannabis users with and without schizophrenia. *Schizophr Res.* 2012
- Stanley JA, Williamson PC, Drost DJ, Carr TJ, Rylett RJ, Morrison-Stewart S, Thompson RT. Membrane phospholipid metabolism and schizophrenia: an in vivo ³¹P-MR spectroscopy study. *Schizophr Res.* 1994; 13:209–215. [PubMed: 7841133]
- Strassnig M, Singh Brar J, Ganguli R. Dietary fatty acid and antioxidant intake in community-dwelling patients suffering from schizophrenia. *Schizophr Res.* 2005; 76:343–351. [PubMed: 15949667]
- Strokin M, Sergeeva M, Reiser G. Docosahexaenoic acid and arachidonic acid release in rat brain astrocytes is mediated by two separate isoforms of phospholipase A2 and is differently regulated by cyclic AMP and Ca²⁺. *Br J Pharmacol.* 2003; 139:1014–1022. [PubMed: 12839876]
- Suddath RL, Christison GW, Torrey EF, Casanova MF, Weinberger DR. Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *N Engl J Med.* 1990; 322:789–794. [PubMed: 2308615]
- Taha AY, McIntyre Burnham W. Commentary on the effects of a ketogenic diet enriched with omega-3 polyunsaturated fatty acids on plasma phospholipid fatty acid profile in children with drug-resistant epilepsy. *Epilepsy Res.* 2007; 76:148–149. discussion 150–141. [PubMed: 17851039]
- Thambisetty M, Gallardo KA, Liow JS, Beason-Held LL, Umhau JC, Bhattacharjee AK, Der M, Herscovitch P, Rapoport JL, Rapoport SI. The utility of (11)C-arachidonate PET to study in vivo dopaminergic neurotransmission in humans. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism.* 2012; 32:676–684. [PubMed: 22167235]
- Thomas EL, Cunnane SC, Bell JD. Critical assessment of in vivo ¹³C NMR spectroscopy and gas-liquid chromatography in the study of adipose tissue composition. *NMR in biomedicine.* 1998; 11:290–296. [PubMed: 9802471]
- 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]
- Williamson P, Drost D, Stanley J, Carr T, Morrison S, Merskey H. Localized phosphorus ³¹ magnetic resonance spectroscopy in chronic schizophrenic patients and normal controls. *Archives of general psychiatry.* 1991; 48:578. [PubMed: 1898225]
- Wong AH, Van Tol HH. Schizophrenia: from phenomenology to neurobiology. *Neurosci Biobehav Rev.* 2003; 27:269–306. [PubMed: 12788337]
- Yao JK, Leonard S, Reddy RD. Membrane phospholipid abnormalities in postmortem brains from schizophrenic patients. *Schizophr Res.* 2000; 42:7–17. [PubMed: 10706981]

Table 1

Characteristics of control and SCZ patients

Control				SCZ						
SEX	Age	pH	PMI	RIN	SEX	Age	pH	PMI	RIN	Medications
F	55	5.80	24.00	7.7	F	75	6.08	21.40	7.6	RSP
M	55	6.53	23.00	6.6	M	65	6.55	22.3	6.0	CLO
M	65	6.42	21.30	6.4	M	35	6.25	25.6	7.6	VPA
M	35	5.97	20.00	7.7	F	45	6.26	15.7	6.0	TZ
M	35	6.05	20.50	6.6	F	71	6.65	21.7	7.6	RSP
M	65	6.33	25.00	6.4	M	55	6.52	16.1	6.0	RSP
M	65	6.39	20.90	7.7	F	80	6.14	25.7	7.5	RSP
F	45	6.74	24.20	6.6	M	55	6.28	28.8	6.1	RSP
F	25	6.40	7.40	6.4	M	55	6.36	24.5	7.6	RSP
M	52	6.40	20.10	6.9	M	55	6.45	18.7	6.0	RSP

CLO, clozapine; Li+, Lithium; RSP, Risperidone; TZ, Trazadone; VPA, valproate SZ, schizophrenic subjects; PMI, postmortem interval; RIN, RNA integrity number.

Table 2

Lipid concentrations in postmortem prefrontal cortex from control and SCZ subjects

Lipid	Control	SCZ
	nmol/g brain wet weight	
Total phospholipids	37933 ±12674	44711±9448
Ethanolamine glycerophospholipid	14858±4857	17813±4085
msp;Choline glycerophospholipid	14643±5131	16844±3499
msp;Phosphatidylserine	5922±2195	7388±2157
msp;Phosphatidylinositol	2512±969	2627±271
Plasmalogens		
msp;Plasmenylethanolamine	7654±5773	7897±5077
msp;Plasmenylcholine	3993±1812	5352±3836
Cholesteryl ester	2.3±3.7	1.3±0.6
Triglycerides	69.2±38.7	71.2±42.4

Mean ± SD, n = 10 for controls, 10 for SCZ patients

*
p < 0.05 by unpaired t-test

Esterified and unesterified fatty acid concentrations (nmol per g wet weight) in postmortem prefrontal cortex from SCZ patients and control subjects

Table 3A

Fatty Acid	Total lipids		Total phospholipid		Triglycerides		Cholesteryl ester		Unesterified fatty acid	
	Control	SCZ	Control	SCZ	Control	SCZ	Control	SCZ	Control	SCZ
nmol/g brain wet weight										
16:0	13863 ± 3090	15179 ± 1428	14027 ± 4102	15294 ± 2013	64 ± 36	35 ± 37	34.8 ± 9.2	31.6 ± 11.9	221 ± 103	260 ± 95
16:1n-7	391 ± 106	556 ± 131**	396 ± 148	571 ± 152*	7 ± 13	3 ± 3	2.1 ± 1.9	2.3 ± 0.8	6 ± 4	14 ± 7*
18:0	16940 ± 3782	18040 ± 1702	14669 ± 3889	14975 ± 4242	44 ± 14	69 ± 67	38.4 ± 12.2	59.0 ± 36.0	360 ± 173	392 ± 146
18:1n-9	13572 ± 3519	15833 ± 2803	12868 ± 4284	14562 ± 6022	39 ± 31	39 ± 28	15.0 ± 7.1	54.6 ± 50.1*	138 ± 82	208 ± 93
18:1n-7	3505 ± 1130	4463 ± 1011	2476 ± 745	2689 ± 1096	8 ± 8	9 ± 6	4.6 ± 2.3	16.0 ± 15.8*	62 ± 33	77 ± 34
18:2n-6	700 ± 180	942 ± 272*	562 ± 202	667 ± 262	16 ± 13	15 ± 10	4.7 ± 2.0	18.7 ± 17.9*	13 ± 7	25 ± 14*
20:3n-6	687 ± 199	853 ± 240	567 ± 168	760 ± 277	7 ± 3	2 ± 2***	5.4 ± 3.1	6.0 ± 2.9	15 ± 7	23 ± 16
20:4n-6 (AA)	6343 ± 1414	6619 ± 543	5810 ± 1574	5320 ± 1944	11 ± 11	15 ± 9	8.6 ± 3.6	32.9 ± 30.5*	185 ± 105	243 ± 124
20:5n-3	42 ± 10	69 ± 62	36 ± 17	151 ± 294	0 ± 0	1 ± 1	0.3 ± 0.1	0.4 ± 0.2	1 ± 0	5 ± 3**
22:4n-6	4771 ± 1268	5682 ± 1199	3663 ± 1208	3273 ± 1830	6 ± 8	13 ± 16	5.6 ± 3.4	11.4 ± 12.4	50 ± 76	95 ± 119
22:5n-6	1058 ± 351	1128 ± 399	908 ± 319	993 ± 535	1 ± 0	2 ± 3	0.9 ± 0.6	2.7 ± 2.1*	6 ± 3	8 ± 6
22:5n-3	356 ± 140	521 ± 118*	183 ± 84	416 ± 319*	0 ± 0	1 ± 2	0.3 ± 0.2	1.3 ± 1.3*	2 ± 2	4 ± 2
22:6n-3 (DHA)	9754 ± 2527	9695 ± 1239	8171 ± 2374	7052 ± 2596	5 ± 4	10 ± 8	9.1 ± 6.1	22.4 ± 15.9*	52 ± 31	66 ± 32
SUM	71981 ± 16694	79581 ± 7811	64336 ± 17733	66724 ± 17336	208 ± 116	214 ± 127	129.7 ± 35.0	259.2 ± 185.7	1111 ± 512	1420 ± 568
Total n-6	13559 ± 3043	15224 ± 1713	11510 ± 3062	11013 ± 3949	41 ± 22	48 ± 27	25.2 ± 9.3	71.7 ± 62.5*	268 ± 117	394 ± 202
total n-3	9796 ± 2533	9764 ± 1236	8207 ± 2389	7203 ± 2333	5 ± 4	11 ± 9	9.4 ± 6.0	22.7 ± 16.0*	53 ± 32	71 ± 35
total saturated	30803 ± 6813	33219 ± 2938	28695 ± 7731	30269 ± 5442	107 ± 49	104 ± 71	73.2 ± 16.8	90.6 ± 46.2	581 ± 275	652 ± 238
total monosaturated	17468 ± 4533	20852 ± 3612	15740 ± 4982	17822 ± 6795	54 ± 47	50 ± 37	21.7 ± 8.9	72.8 ± 66.0*	207 ± 118	299 ± 132
n-6/n-3	1.4 ± 0.1	1.6 ± 0.2*	1.4 ± 0.2	1.5 ± 0.3	11.9 ± 7.6	7.6 ± 4.6	5.3 ± 7.3	2.9 ± 1.1	8.0 ± 10.9	5.7 ± 2.0
AA/DHA	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.0	0.7 ± 0.2	2.5 ± 0.9	2.8 ± 2.1	2.3 ± 3.7	1.3 ± 0.6	3.5 ± 0.5	3.7 ± 0.4

Mean ± SD, n = 10 for controls, 10 for SCZ patient.

* p<0.05,

** p<0.01,

p<0.001 by unpaired t-test.

Esterified and unesterified fatty acid fractional concentrations (percent of total fatty acid concentration) in prefrontal cortex from SCZ patients and control subjects

Table 3B

Fatty Acid	Total lipids		Total phospholipid		Triglycerides		Cholesteryl ester		Unesterified fatty acid	
	Control	SCZ	Control	SCZ	Control	SCZ	Control	SCZ	Control	SCZ
% of total fatty acids										
16:0	19.4 ± 0.8	19.1 ± 1.0	21.8 ± 1.1	25.3 ± 12.2	31 ± 4	19 ± 12 *	28.1 ± 9.1	15.8 ± 6.7 **	19 ± 4	18 ± 2
16:1n-7	0.5 ± 0.1	0.7 ± 0.2 *	0.6 ± 0.1	1.0 ± 0.6	2 ± 4	1 ± 1	1.8 ± 2.0	1.3 ± 0.7	1 ± 0.1	1 ± 0.3 **
18:0	23.6 ± 1.0	22.7 ± 1.1	23.1 ± 2.6	22.2 ± 1.8	24 ± 7	27 ± 16	29.3 ± 3.9	24.5 ± 5.3 *	32 ± 6	28 ± 3
18:1n-9	18.7 ± 1.1	19.8 ± 2.1	19.6 ± 2.4	20.4 ± 6.6	17 ± 6	20 ± 7	11.0 ± 3.5	18.4 ± 5.0 **	12 ± 3	14 ± 2 *
18:1n-7	4.8 ± 1.0	5.6 ± 1.0	3.9 ± 0.6	3.9 ± 1.7	3 ± 1	5 ± 2	3.4 ± 1.0	5.3 ± 1.6 **	5 ± 1	5 ± 1
18:2n-6	1.0 ± 0.2	1.2 ± 0.4	0.9 ± 0.2	1.0 ± 0.3	7 ± 4	8 ± 3	3.6 ± 1.1	6.4 ± 3.8	1 ± 0.3	2 ± 1 **
20:3n-6	1.0 ± 0.2	1.1 ± 0.2	0.9 ± 0.2	1.3 ± 1.2	4 ± 3	1 ± 0 **	4.0 ± 2.3	2.9 ± 1.4	1 ± 1	2 ± 0.5
20:4n-6 (AA)	8.9 ± 0.6	8.3 ± 0.5 *	9.1 ± 0.6	7.5 ± 2.7	5 ± 2	8 ± 3 *	6.5 ± 2.0	11.3 ± 3.8 **	16 ± 4	17 ± 3
20:5n-3	0.1 ± 0.02	0.1 ± 0.1	0.1 ± 0.02	0.4 ± 1.2	0.1 ± 0.1	0.2 ± 0.1	0.2 ± 0.2	0.2 ± 0.1	0.1 ± 0.05	0.3 ± 0.2 **
22:4n-6	6.5 ± 0.6	7.1 ± 0.9	5.7 ± 1.1	4.5 ± 2.2	4 ± 7	5 ± 4	4.4 ± 2.2	3.7 ± 1.5	7 ± 16	7 ± 8
22:5n-6	1.5 ± 0.5	1.4 ± 0.5	1.5 ± 0.5	1.4 ± 0.7	0.3 ± 0.2	1 ± 1	0.7 ± 0.3	1.0 ± 0.3 *	1 ± 0.2	0.5 ± 0.2
22:5n-3	0.5 ± 0.1	0.7 ± 0.1 **	0.3 ± 0.1	0.9 ± 1.4	0.1 ± 0.1	0.4 ± 0.2 **	0.3 ± 0.2	0.4 ± 0.2	0.2 ± 0.1	0.3 ± 0.1 *
22:6n-3 (DHA)	13.5 ± 0.9	12.2 ± 1.4 *	12.7 ± 0.9	10.1 ± 3.6 *	2 ± 1	5 ± 5	6.6 ± 3.4	8.9 ± 1.9	4 ± 1	5 ± 1
Total n-6	18.9 ± 0.9	19.1 ± 0.7	18.0 ± 1.5	15.8 ± 3.8	20 ± 8	23 ± 5	19.2 ± 5.0	25.2 ± 6.3 *	26 ± 14	28 ± 7
Total n-3	13.6 ± 0.9	12.3 ± 1.4 *	12.8 ± 0.9	10.5 ± 2.6 *	2 ± 1	5 ± 5	6.9 ± 3.4	9.1 ± 1.9	5 ± 1	5 ± 1
Total saturated	43.0 ± 1.2	41.8 ± 1.6	44.9 ± 2.3	47.5 ± 11.0	55 ± 9	46 ± 8 *	57.4 ± 6.6	40.3 ± 11.4 **	51 ± 9	46 ± 5
Total monosaturated	24.1 ± 1.8	26.1 ± 2.8	24.1 ± 2.3	25.3 ± 7.1	23 ± 8	26 ± 10	16.2 ± 3.9	25.0 ± 5.8 **	18 ± 4	21 ± 3

Mean ± SD, n = 10 for controls, 10 for SCZ patient.

* p<0.05,

** p<0.01,

*** p<0.001 by unpaired t-test.

Table 4A

Esterified fatty acid concentrations (nmol per g wet weight) in individual glycerophospholipids in prefrontal cortex from SCZ patients and control subjects

Fatty Acid	EtnGpl		ChoGpl		PtdIns		PtdSer	
	Control	SCZ	Control	SCZ	Control	SCZ	Control	SCZ
	nmol/g brain wet weight							
16:0	1200 ± 378	1345 ± 192	10846 ± 2913	13179 ± 1306*	187 ± 47	294 ± 92**	171 ± 41	334 ± 102***
16:1n-7	64 ± 35	122 ± 40*	259 ± 77	318 ± 75	6 ± 3	6 ± 3	8 ± 3	9 ± 2
18:0	5485 ± 1492	5247 ± 493	3436 ± 889	3874 ± 482	1150 ± 266	1371 ± 172*	5113 ± 1470	6250 ± 1017
18:1n-9	2745 ± 990	3502 ± 900	6470 ± 2218	7855 ± 1425	166 ± 53	226 ± 97	1889 ± 783	2279 ± 870
18:1n-7	1159 ± 528	1610 ± 794	1724 ± 612	2136 ± 289	91 ± 32	114 ± 52	403 ± 174	519 ± 296
18:2n-6	97 ± 39	240 ± 106**	265 ± 71	381 ± 109*	15 ± 10	23 ± 11	19 ± 12	18 ± 5
20:3n-6	195 ± 69	270 ± 80*	173 ± 62	201 ± 54	35 ± 12	50 ± 20	68 ± 25	92 ± 29
20:4n-6 (AA)	2773 ± 869	3064 ± 372	1169 ± 383	1052 ± 143	860 ± 301	867 ± 304	260 ± 102	284 ± 71
20:5n-3	36 ± 32	24 ± 9	9 ± 4	20 ± 19	3 ± 3	2 ± 1	3 ± 2	7 ± 2***
22:4n-6	2644 ± 823	2443 ± 634	233 ± 44	165 ± 39**	116 ± 45	73 ± 33*	470 ± 173	497 ± 82
22:5n-6	493 ± 197	509 ± 201	58 ± 28	44 ± 14	20 ± 17	11 ± 4	252 ± 106	271 ± 91
22:5n-3	130 ± 56	152 ± 43	17 ± 8	5 ± 17	7 ± 3	5 ± 2	31 ± 18	29 ± 10
22:6n-3 (DHA)	4479 ± 1457	4296 ± 501	494 ± 178	397 ± 65	155 ± 84	90 ± 27*	1865 ± 803	1921 ± 446
SUM	21500 ± 6334	22823 ± 2619	25152 ± 7105	29650 ± 3224	2812 ± 813	3131 ± 649	10552 ± 3446	12508 ± 2240
Total n-6	6201 ± 1861	6526 ± 917	1898 ± 542	1842 ± 230	1047 ± 364	1022 ± 357	1069 ± 367	1161 ± 150
Total n-3	4515 ± 1466	4320 ± 499	502 ± 177	417 ± 57	158 ± 85	93 ± 27*	1868 ± 804	1928 ± 447
Total saturated	6685 ± 1817	6592 ± 610	14282 ± 3740	17053 ± 1718	1337 ± 305	1665 ± 231*	5284 ± 1509	6583 ± 1051*
Total monosaturated	3968 ± 1475	5233 ± 1530	8452 ± 2775	10309 ± 1526	264 ± 84	346 ± 150	2300 ± 949	2807 ± 972
n-6/n-3	1.4 ± 0.1	1.5 ± 0.2	4.3 ± 1.8	4.4 ± 0.5	7.1 ± 1.6	11.1 ± 3.2**	0.6 ± 0.1	0.6 ± 0.1
AA/DHA	0.6 ± 0.05	0.7 ± 0.1**	2.5 ± 0.4	2.7 ± 0.3	5.9 ± 1.5	9.6 ± 2.7**	0.1 ± 0.02	0.2 ± 0.04

Mean ± SD, n = 10 for controls, 10 for SCZ patient.

* p<0.05,

** p<0.01,

p<0.001 by unpaired t-test.

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Esterified fatty acid fractional concentrations (percent of total fatty acid concentration) in individual glycerophospholipids in prefrontal cortex from SCZ patients and control subjects

Table 4B

Fatty Acid	EtnGpl		ChoGpl		PtdIns		PtdSer	
	Control	SCZ	Control	SCZ	Control	SCZ	Control	SCZ
	% of total fatty acids							
16:0	5.8 ± 1.3	5.9 ± 0.5	44.3 ± 5.7	44.5 ± 2.1	7.1 ± 2.3	9.4 ± 2.2 *	1.8 ± 0.6	2.7 ± 0.8 *
16:1n-7	0.3 ± 0.1	0.5 ± 0.2 **	1.0 ± 0.2	1.1 ± 0.4	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.03	0.1 ± 0.02
18:0	26.6 ± 4.9	23.2 ± 2.7	14.0 ± 1.4	13.1 ± 0.6	42.7 ± 7.7	45.1 ± 8.8	49.8 ± 6.1	50.1 ± 2.5
18:1n-9	12.3 ± 2.2	15.2 ± 2.7 *	24.5 ± 5.4	26.3 ± 2.4	5.8 ± 0.7	6.9 ± 2.1	17.1 ± 3.6	17.8 ± 4.1
18:1n-7	5.1 ± 1.7	6.9 ± 3.0	6.7 ± 1.4	7.2 ± 0.9	3.2 ± 0.7	3.5 ± 1.1	3.6 ± 0.8	4.1 ± 2.2
18:2n-6	0.4 ± 0.1	1.1 ± 0.5 **	1.1 ± 0.3	1.3 ± 0.4	0.5 ± 0.3	0.7 ± 0.3	0.2 ± 0.1	0.1 ± 0.04
20:3n-6	0.9 ± 0.2	1.2 ± 0.3 *	0.7 ± 0.2	0.7 ± 0.2	1.2 ± 0.3	1.5 ± 0.4	0.6 ± 0.1	0.7 ± 0.2
20:4n-6 (AA)	12.9 ± 1.3	13.4 ± 0.7	4.5 ± 0.9	3.5 ± 0.3 *	29.0 ± 7.2	27.0 ± 6.5	2.4 ± 0.3	2.3 ± 0.4
20:5n-3	0.2 ± 0.1	0.1 ± 0.04	0.04 ± 0.04	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.02	0.03 ± 0.01	0.1 ± 0.02 **
22:4n-6	12.1 ± 1.3	10.7 ± 2.3	1.0 ± 0.4	0.6 ± 0.1 **	3.9 ± 0.9	2.2 ± 0.9 ***	4.4 ± 0.6	4.0 ± 0.3
22:5n-6	2.4 ± 0.8	2.3 ± 0.9	0.2 ± 0.1	0.2 ± 0.1 *	0.7 ± 0.4	0.4 ± 0.1 *	2.5 ± 0.8	2.3 ± 0.9
22:5n-3	0.6 ± 0.2	0.7 ± 0.2	0.1 ± 0.03	0.1 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.1	0.2 ± 0.1
22:6n-3 (DHA)	20.5 ± 2.1	18.9 ± 2.3	1.9 ± 0.5	1.3 ± 0.2 *	5.1 ± 1.8	2.9 ± 0.6 **	17.2 ± 3.5	15.5 ± 3.4
Total n-6	28.7 ± 2.5	28.6 ± 2.3	7.5 ± 0.6	6.2 ± 0.5 ***	35.4 ± 8.2	31.8 ± 7.2	10.1 ± 1.2	9.4 ± 0.9
Total n-3	20.6 ± 2.1	19.0 ± 2.2	1.9 ± 0.4	1.4 ± 0.2 **	5.2 ± 1.8	3.0 ± 0.6 **	17.2 ± 3.5	15.6 ± 3.4
Total saturated	32.5 ± 5.8	29.1 ± 2.8	58.3 ± 6.7	57.6 ± 1.9	49.9 ± 9.7	54.5 ± 9.1	51.6 ± 6.6	52.8 ± 2.1
Total monosaturated	17.7 ± 3.6	22.6 ± 4.8 *	32.3 ± 6.0	34.7 ± 2.2	9.3 ± 1.2	10.6 ± 3.2	20.8 ± 4.3	22.0 ± 4.3

Mean ± SD, n = 10 for controls, 10 for SCZ patient.

* p<0.05,

** p<0.01,

*** p<0.001 by unpaired t-test.