Skin Ceramide Alterations in First-episode Schizophrenia Indicate Abnormal Sphingolipid Metabolism

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There is considerable evidence for specific pathology of lipid metabolism in schizophrenia, affecting polyunsaturated fatty acids and in particular sphingolipids. These deficits are assumed to interfere with neuronal membrane functioning and the development and maintenance of myelin sheaths. Recent studies suggest that some of these lipid pathologies might also be detected in peripheral skin tests. In this study, we examined different skin lipids and their relation to schizophrenia. We assessed epidermal lipid profiles in 22 first-episode antipsychotic-naïve schizophrenia patients and 22 healthy controls matched for age and gender using a hexan/ethanol extraction technique and combined high-performance thin-layer chromatography/gas-chromatography. We found highly significant increase of ceramide AH and NH/AS classes in patients and decrease of EOS and NP ceramide classes. This is the first demonstration of specific peripheral sphingolipid alterations in schizophrenia. The results support recent models of systemic lipid pathology and in particular of specific sphingolipids, which are crucial in neuronal membrane integrity. Given recent findings showing amelioration of psychopathology using fatty acid supplementation, our findings also bear relevance for sphingolipids as potential biomarkers of the disease.

Key words: sphingolipids/ceramides/schizophrenia/epidermis/brain white matter/omega-3 fatty acids

Introduction

Schizophrenia is assumed to be a neurodevelopmental disorder, in which genetic and environmental factors contribute to abnormalities in the synaptic connectivity of specific brain areas. There is now accumulating evidence that disturbance of glycerophospholipid and sphingolipid metabolism is a potentially crucial factor in the development and progression of this disorder.1,2 While neuropathological and postmortem studies have shown abnormalities of oligodendrocytes related to myelination, a process dependent on specific sphingolipids,3 there are also in vivo brain imaging studies showing altered membrane phospholipid turnover and white matter abnormalities.4-6

The rationale for linking central nervous system (CNS) and skin pathologies in schizophrenia is based on several factors considering the structural biology of specific lipids present in both tissue types. First, both contain significant quantities of specific sphingolipids essential for specific cellular functions. In the case of the CNS, they affect development and maintenance of myelin sheaths. Secondly, skin tests might provide a means of testing systemic lipid pathology in vivo. Third, alterations of cytosolic phospholipase A2 (PLA2), a specific group of enzymes regulating phospholipid turnover, have likewise been shown in postmortem and peripheral blood studies in schizophrenia and are highly correlated to the niacin skin test.7 Therefore, detection of skin lipid abnormalities might also serve as a potential biomarker of the disease tracking pathologies related to the disorder.

Based on our previous studies on skin markers of phospholipid pathology in schizophrenia,8,9 we aimed to extend these studies examining the composition of specific skin lipids and their association with schizophrenia.

The structural backbone of both organs (CNS and skin) are, in fact, lipids, ie., 60% of the dry weight of the CNS,1 10% of the epidermis, and more specifically, 50% of stratum corneum as the upper part of the epidermis.10 Lamellar sheets present in the intercellular spaces of the stratum corneum are composed of approximately equimolar concentrations of free fatty acids, cholesterol, and ceramides. Ceramides are produced by keratinocytes and extruded in the stratum granulosum/stratum...
corneum interface. They are critical in maintaining the morphological integrity of the stratum corneum and the epidermal barrier function of the skin. Representing the main intercellular domain, skin lipids are a structurally heterogeneous and complex group of sphingolipids containing derivatives of sphingosine bases in amide linkage with a variety of fatty acids. Differences in chain length, type and extent of hydroxylation, saturation, etc. are responsible for the heterogeneity of the epidermal sphingolipids. Today 11 classes of ceramides are distinguished according to the sphingoid base (sphingosine [S], phytosphingosine [P], and 6-hydroxysphingosine [H]) or dehydro sphingosine (DS) attached to a nonhydroxy (N), α-hydroxy (A), or ω-hydroxy (EO) long-chain free fatty acid.\textsuperscript{11,12} In conjunction with the other stratum corneum lipids, they form ordered structures.\textsuperscript{13} Separation and real-time detection of the stratum corneum ceramide classes became possible in one run using high-performance thin-layer chromatography (HPTLC) combined with automated multiple development (AMD) techniques.\textsuperscript{14} Ceramide species with C26 and/or C28 fatty acid chains were the most abundant ones in Cer [NP], Cer [NH], Cer [AP], and Cer [AH]. The main component of Cer [AS] is C16. The omega-esterified ceramide classes Cer [EOS], Cer [EOP], and Cer [EOH] contain mostly species with ω-hydroxylated fatty acids >C30, esterified to linoleic acid, which is unsaturated. Also in the case of Cer [NS] fatty acids >C30 appear, suggesting an analogy to the omega-esterified ceramides. The importance of sphingolipids as structure maintaining domain and the high proportion of polyunsaturated long-chain fatty acids (PUFA) in different ceramide classes (Cer [EOS], Cer [EOP], and Cer [EOH]) resembles in many aspects the situation in the brain.\textsuperscript{15}

We tested the hypotheses that first-episode schizophrenia (FES) patients show abnormalities in those lipids crucial for maintaining intact skin structure and function.

**Methods**

**Subjects**

From a total population of 28 (19 male/9 female) FES patients, all meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for schizophrenia or schizophreniform disorder, and 49 (31 male/18 female) healthy control subjects, we carefully matched a group of 22 FES patients (15 male/7 female) and 22 controls for age and gender. This was done because previous studies revealed significant influence of epidemiologic covariates on skin structure and skin physiology.\textsuperscript{16} Apart from the criteria age and gender selection of participants related to the lowest possible atopic dermatitis score according to the Erlanger Atopic Dermatitis Score.\textsuperscript{17} Patients were admitted consecutively to the Department of Psychiatry of Jena University Hospital. Diagnoses were made by 2 independent board-certified experienced psychiatrists (S.S. and H.S.) and were further supported by structured clinical interview, SCID-IV.\textsuperscript{18} Psychiatric symptoms were assessed using the Scale of Assessment of Negative Symptoms (SANS), the Scale of Assessment of Positive Symptoms (SAPS), the Brief Psychiatric Rating Scale (BPRS), and the Symptom Check List 1990 revised (SCL90-R). All patients have never been treated with antipsychotic agents before measurement. Twelve patients received sporadic doses of lorazepam (maximum 2 × 2.5 mg/d).

All controls were recruited by newspaper advertisements and reimbursed for their travel expenses. They underwent detailed semi-structured interviews to exclude a current or previous history of psychiatric disorders.

General exclusion criteria for both groups were: any current or previous history of skin diseases (eczema, atopic dermatitis, and psoriasis), recent treatment with steroids, or nonsteroidal anti-inflammatory drugs (eg, acetylsalicylic acid).

The study was approved by the Research Ethics Committee of Friedrich-Schiller-University Jena. All subjects gave written informed consent prior to participation in the study.

**Measurement of Skin Lipids**

Skin lipids were extracted using an n-hexane/ethanol (2:1) washout technique, and profiles were determined by HPTLC and gas chromatography (GC)/mass spectrometry (MS).\textsuperscript{14} This well-validated technique enables harvesting skin lipids without invasive biopsy.

**Extraction of Skin Lipids.** A cylindrical glass ring (internal diameter: 4 cm, covering 12.56 cm²) was firmly pressed onto the skin and thereafter filled with 10 ml of n-hexane/ethanol (2:1, vol/vol) solution. The duration of solution/skin contact under ongoing rotary stir movements was 5 minutes. Subsequently, 3 ml aliquots were separated.

**Ceramide Analysis.** A volume of 3 ml of each lipid extract was dried under a nitrogen stream at 50°C; the residue was dissolved in 1 ml chloroform/methanol 2:1 (vol/vol) and stored at −30°C until further use. The separation of lipids was performed by HPTLC. Samples were applied to HPTLC plates using an Automated TLC Sampler 4 (ATS4, Camag, Muttenz, Switzerland). The development of the plates was carried out using an AMD 2 apparatus (Camag). A gradient with decreasing polarity was used to separate the different lipid species. Postchromatographic derivatization was carried out by immersing the dried plates for 20 seconds into an aqueous solution of 10% CuSO₄, 8% H₃PO₄, and 5% methanol and subsequent charring in a drying oven for 20 minutes at 160°C. The developed plates were scanned using a TLC Scanner 3 (Camag) at a wavelength of 546 nm. Peak areas of the resulting densitograms were integrated and quantified using winCATS software (CAMAG).
Fatty Acid Analysis. A volume of 3 ml of each lipid extract was used after adding D31-stearic acid as internal standard. This mixture was dried under a nitrogen stream at 50°C; the residue was dissolved in 1 ml chloroform/methanol 2:1 (vol/vol) and stored at −30°C until further use. The separation of lipids was performed as described for ceramide analysis using AMD-HPTLC. No postchromatographic derivatization was carried out. Free fatty acids were recovered by scraping off the corresponding band from the HPTLC plate and subsequent extraction under sonication using a mixture of n-hexane/methanol 95:5 (vol/vol). The sample was then centrifuged and dried under nitrogen. For GC experiments, the residue was dissolved in 100-μl ethyl acetate. GC/MS experiments were carried out on a Varian GC (Palo Alto) coupled to a Magnum mass spectrometer (Thermo Fisher, Bremen, Germany). The separation of the free fatty acids was carried out on an Optima-5 GC column (Macherey-Nagel, Dueren, Germany). The fatty acids were esterified prior to the injection using trimethylsulphonium hydroxide. In order to elute the analytes, a temperature program from 80°C to 280°C was applied. Helium was used as carrier gas. The pyrolysis products were identified by MS on the Magnum ion trap mass spectrometer equipped with electron impact ionization.

Chemicals. The solvents ethanol, ethyl acetate, n-hexane, chloroform, and acetone were obtained from Merck (Darmstadt, Germany) as High-performance liquid chromatography grade. Ceramide standards were provided by Degussa (Düsseldorf, Germany). All other lipid standards were obtained from Sigma Aldrich (Munich, Germany).

Data Analysis
Investigating main factors of influence, we performed as a first step a general linear model including “group” as main categorical variable (between-subject factor) and “nicotine” or “cannabis use,” and “storage time” as covariates. Differences in smoker/nonsmoker and cannabis user/noncannabis user distribution between groups were tested using the chi-square test. Age was compared by group using t test after testing for normal distribution.

Cross-sectional comparison of each skin lipid component between patients and matched controls was performed using ANCOVA including age and gender as covariables in every analysis. For methodological reasons, every analysis was performed only in relative values (%) of lipid parameters. Percentage quotations of lipids represented the relative amount of the total lipids.

In order to explore a possible association between age or psychopathological ratings and skin lipid parameters, Pearson correlation coefficients were calculated.

To further explore an underlying common pattern of ceramide profile in FES patients possibly different to the ceramide profile in healthy people, a factor analysis (FA) was calculated for all 7 single ceramide classes.

Common FA seeks for the least number of factors explaining the common variance (correlation) of a set of variables. In our data set, FA was used to describe the variability among observed, correlated variables (7 single ceramides) in terms of a potentially lower number of unobserved, uncorrelated variables called factors. The a priori assumption of this exploratory FA was that any observed ceramide value may be associated with any factor. We expected that variations in these factors mainly reflect the variations in the observed values of the 7 ceramides and that the information about the interdependencies between the observed variables gained by these factors can be used to understand the different alterations of single ceramides between patients and controls. The factor loadings are the correlation coefficients between the observed ceramide values and the calculated factors. Analogous to Pearson’s r, the squared factor loading is the percentage of variance in that ceramide value explained by the factor. Therefore, in our last step of data analysis, we compared factor loadings instead of observed ceramide values between patients and controls using t test after initial testing for normal distribution.

The statistical analysis was performed using STATISTICA software (version 10, StatSoft, Europe). The minimum sample size was calculated based on previous studies by Farwannah and coworkers14 including data obtained by the methodology used in the present study.

Results
Demographic Parameters, Substance Use, and Psychopathology
No difference of age could be revealed between FES patients and controls (C) (mean ± SD: FES 23.27 ± 3.63, range 18–38 y; C 23.73 ± 3.63, range 18–33 y; T2 = 24.4; SANS 38.064). As expected, there were differences in nicotine and cannabis use between groups, indicating more intense substance consumption in patients. In FES patients, 13/22 (59.0%) used nicotine on a regular basis as compared with healthy controls 8/22 (36.3%), 6/ 22 (27.3%) casually used cannabis, in healthy controls only 2/22 (9.1%). Neither in terms of nicotine (Chi2 n. Pearson 3.436, P = .064) nor of cannabis use (Chi2 n. Pearson 2.97, P = .085), group difference of substance use reached significance but showed a marked trend. All FES patients showed moderate to severe psychotic symptoms at the time of assessment (total scores ± SD: SAPS 30 ± 24.4; SANS 38 ± 27.1; BPRS 44.75 ± 18.58; SCL90-R 90.39 ± 75.33).

General Effects: Covariance Analysis and of Cross-Sectional Comparison
Including all lipid components (total ceramides, cholesterol, free fatty acids, triglycerides, cholesterol esters, and total PUFA levels) and values of the single fatty acids
Finally, ceramides

All these mechanisms are not

\( P = .025 \), figure 4).

2,317, \( P < .001 \)) showed effects

5,36

0.270\%), "cannabis" (\( F_{3,40} = 1.681, 0.186\% \), and "blood pressure" (\( F_{3,40} = 1.021, n.s. \)) did not show significant influence. Of the included lipid and fatty acid components, only total ceramides (%) were significantly influenced by the factor group in this model (\( F_{3,36} = 271.264, P < .001 \)). The components cholesterol (%) (\( F_{3,36} = 1.297, 0.287\% \), free fatty acids (%) (\( F_{5,36} = 0.573, 0.720\% \), triglycerides (%) (\( F_{5,36} = 0.240, 0.942\% \), cholesterolesters (%) (\( F_{5,36} = 1.339, 0.270\% \), total PUFA content (%) (\( F_{5,36} = 1.889, 0.085\%)\), and single fatty acid values did not show significant effects.

Now we included all measured ceramide classes (Cer AH, Cer AP, Cer NH/AS, Cer EOH, Cer NP, Cer NS, and Cer EOS each in %) in this MANCOVA, using gender and age as covariables. A highly significant effect was revealed for total ceramides (%) (\( F_{3,40} = 548.728, P < .001 \), figure 1). In total PUFA levels (%) (\( F_{3,40} = 0.152, 0.923\% \), cholesterol (%) (\( F_{3,40} = 1.681, 0.186\% \), cholesterolesters (%) (\( F_{3,40} = 1.785, 0.165\% \), free fatty acids (%) (\( F_{3,40} = 0.536, 0.660\% \), and triglycerides (%) (\( F_{3,40} = 0.393, 0.758\% \), no significant effects could be found. Analyzing single ceramide classes in this model, the ceramides AH (%) (\( F_{3,40} = 3.112, P = .036 \), figure 2) and EOS (%) (\( F_{3,40} = 3.523, P = .023 \), figure 3) showed clear significant effects, the ceramides NH/AS (%) (\( F_{3,40} = 2.745, P = .055 \) and NP (%) (\( F_{3,40} = 2.824, P = .050 \) showed effects very close to the significance level, but the ceramides AP (%) (\( F_{3,40} = 1.775, n.s. \), EOH (%) (\( F_{3,40} = 1.025, n.s. \), and NS (%) (\( F_{3,40} = 0.981, n.s. \) showed no significant effects.

Analyzing correlations between all lipid and fatty acid parameters and potential covariates, only total ceramides (%) showed a moderate correlation with age (\( r = .622, P = .031 \). Single ceramides did not show statistically meaningful correlations with age. Correlation analysis between lipid parameters and ratings of psychiatric symptoms (SAPS, SANS, BPRS, and SCL90-R) could not elicit any association between skin lipid levels and severity of symptoms.

**Factor Analysis**

Being significantly different between groups, single ceramides showed inverse alterations. Whereas relative values of the ceramides AH and NH/AS were increased in FES patients, ceramides EOS and NP were significantly decreased in patients. To further explore this heterogeneity and searching for an underlying pattern, a FA was performed. Factor analyses are based on correlations between variables and allow uncovering a latent structure (dimensions) of a data set. The relation between the
extracted factors and single ceramide data is characterized by factor loadings, i.e., the correlation between a factor and this single ceramide. These factor loadings (Pearson correlation coefficients) were compared between groups using t test.

As shown in table 1, most of the variance was cleared by creating 3 factors: (1) cer AH and NP, (2) cer NH/AS and EOS, and (3) cer EOH and NS. Comparing factor loadings of these 3 factors between patients and controls, only factor 2 (including NH/AS and EOS) revealed a significant difference ($T_{42} = 2.317, P = .025$, figure 4).

**Discussion**

The aim of the present study was to use the skin (more specifically stratum corneum lipids of the epidermal layer) as a peripheral model to explore membrane lipid and sphingolipid alterations previously studied in certain brain regions and to explore these in a population of first-onset schizophrenia patients. Our main finding is a significant difference in the skin composition of ceramides between patients and controls, across several classes of ceramides (AH, NH/AS, NP, and EOS). The ceramide fraction of skin lipids as a whole was significantly decreased in patients suffering from FES. Some single ceramides (cer AH and NH/AS) were increased, whereas others (cer EOS and NP) were decreased in FES patients. These results support and extend findings of ceramide alterations in prefrontal gray and white matter postmortem tissue and in in vivo peripheral tissue (red blood cell membranes) as disease intrinsic factor of schizophrenia.

Although brain and skin are interrelated in some respects and although the skin is obviously easier accessible for in vivo lipid investigation than the brain, skin lipid components have not yet been investigated in populations of schizophrenia patients. Alterations of ceramides are of significant interest in understanding schizophrenia. First, ceramide metabolism is closely connected to fatty acid metabolism, as ceramides are generally composed of a sphingoid base and a fatty acid. Alterations of fatty acid (especially PUFA) metabolism in turn are a well-replicated finding in schizophrenia. Secondly, ceramides are found in high concentrations in the membranes of neurons and in myelin sheets of nerve fibers. In particular, such lipids are crucial to the maintenance of neuropil and its synaptic connections as well as oligodendrocyte dysfunction (ie, myelin-related) in schizophrenia. Furthermore, ceramides are one of the lipid fractions that form sphingomyelin, one of the major lipids in the lipid bilayers of lipid rafts, special membrane domains in synaptic membranes crucially involved in signal transduction, and recently discussed to be altered in schizophrenia. Finally, ceramides and other sphingolipids found in cell membranes are not purely structural elements; they also act as signaling molecules. The best-known functions of ceramides in terms of cellular signaling include the regulation of cell differentiation and proliferation, programmed cell death, and apoptosis. All these mechanisms are not only relevant in skin physiology but are also part of pathomechanisms implicated in schizophrenia.
In our population of FES patients, the changes across ceramide classes included both increase of cer AH and NH/AS as well as reduction of cer EOS and NP. This pattern might be explained by coexisting deficits in epidermal sphingolipid metabolism and compensatory processes.

According to our hypothesis, ceramide precursor synthesis and lipid processing could be disturbed as part of mechanisms involved in the pathogenesis of schizophrenia. Of the several major pathways of ceramide generation, the sphingomyelin-ceramide pathway is an evolutionarily conserved ubiquitous signal transduction system that regulates many cell functions. Sphingomyelin is hydrolyzed to ceramide by different sphingomyelinases. Ceramides in turn serve as second messengers in mediating cellular effects of cytokines and stress. Sphingomyelin (as 1 of the 4 common phospholipids found in the plasma membrane of cells) and sphingomyelinase are sensitive to extracellular signals leading to programmed cell death (apoptosis). While these findings are consistent with our hypothesis, ceramide precursor synthesis and lipid processing could be disturbed as part of mechanisms involved in the pathogenesis of schizophrenia. Of the several major pathways of ceramide generation, the sphingomyelin-ceramide pathway is an evolutionarily conserved ubiquitous signal transduction system that regulates many cell functions. Sphingomyelin is hydrolyzed to ceramide by different sphingomyelinases. Ceramides in turn serve as second messengers in mediating cellular effects of cytokines and stress. Sphingomyelin (as 1 of the 4 common phospholipids found in the plasma membrane of cells) and sphingomyelinase are sensitive to extracellular signals leading to programmed cell death (apoptosis).

### Table 1. Results of Factor Analysis (Varimax Rotation): The variance of the data set is cleared by creating 3 factors

<table>
<thead>
<tr>
<th>Ceramides</th>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AH</td>
<td>0.917662</td>
<td>0.270686</td>
<td>-0.038206</td>
</tr>
<tr>
<td>AP</td>
<td>-0.344511</td>
<td>-0.451501</td>
<td>-0.342872</td>
</tr>
<tr>
<td>NH/AS</td>
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<td>0.202567</td>
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<tr>
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<td>-0.090434</td>
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<tr>
<td>NP</td>
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<td>0.102109</td>
<td>0.005673</td>
</tr>
<tr>
<td>NS</td>
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<td>-0.110804</td>
<td><strong>0.728677</strong></td>
</tr>
<tr>
<td>EOS</td>
<td>0.194070</td>
<td><strong>0.798244</strong></td>
<td>0.421419</td>
</tr>
</tbody>
</table>

*Note: The highest factor loadings contributing to each factor are given in bold.*

Fig. 3. Box plot of ANCOVA results in ceramide EOS values (% of total skin lipids) showing group differences between schizophrenia patients and matched healthy controls.

FA revealed alterations of ceramide EOS and NH/AS to explain most of the variance (factor 2) related to group differences. Ceramide EOS in particular, being one of the most abundant ceramides of the skin, is the most important candidate based on its molecular structure. A sphingosine molecule is bound to a 30–40 carbon chain omega-hydroxy fatty acid, which is additionally esterified...
with the essential fatty acid linoleic acid (18:2 [n-6]). Linoleic acid, an omega-6 fatty acid, serves as precursor of dihomogamma-linolenic acid and arachidonic acid, the later being one of the most common and functionally most important fatty acids in the brain, and significantly decreased in schizophrenic patients. Therefore, the significant decrease of the entire ceramide fraction in patients and especially of ceramide EOS might be caused by the reduced availability of omega-6 fatty acids in schizophrenia. Increased levels of other ceramide classes might then be compensatory to the ceramide EOS deficit.

While these findings are consistent with our hypotheses, we need to consider that fatty acid deficits between groups did not reach significance; in particular, there was no significant difference in PUFA and arachidonic acid levels of the stratum corneum of the epidermal layer. Since initially these findings seemed at odds with well-established PUFA reductions, we also analyzed niacin skin data of this sample (data presented in online supplementary materials, method by Smesny et al), which provide an assessment of arachidonic acids and prosta-glandin availability in the subcutis layer. While we replicated the well-known deficit of flush response in schizophrenia patients, we also found highly significant positive correlations between niacin sensitivity and ceramide alterations. Reconciling these findings, we need to consider that our initial ceramide findings were obtained from upper skin layers of the stratum corneum, which do not relate to PUFA concentrations in that same upper layer but correlate with niacin-derived indicators of PUFA deficiency in the lower subcutaneous layers (which have previously been reported).

Using epidermal lipids as model for cerebral lipid abnormalities, our results further corroborate the reported membrane phospholipid abnormalities in FES. They are also the first direct evidence of sphingolipid abnormalities in never treated first acute onset schizophrenia. While alterations of membrane phospholipid synthesis and breakdown in schizophrenia have been shown repeatedly using in vivo 31P-magnetic resonance spectroscopy, cerebral alterations of sphingolipids (eg, sphingomyelin) were not accessible by direct in vivo measurement so far. However, there is also clear evidence for white matter abnormalities from diffusion tensor imaging studies, which are mostly interpreted as relating to myelin pathology and thus strongly suggesting a contribution of sphingolipid metabolism in schizophrenia pathophysiology. From our point of view, sphingolipid alterations in the brain and also in the epidermal layer of the skin of FES patients could be due to increased oxidative stress (due to excitotoxic glutamate/dopamine deregulation and/or genetically impaired antioxidative defense).

Finally, our results bear significance for an understanding of omega-3 fatty acid supplementation, a recently tested auxiliary experimental treatment strategy in schizophrenia. While shown to improve antioxidative defense, it might help to normalize sphingolipid metabolism, providing a biochemical explanation for the use of supplementation therapy as applied in recent clinical trials.
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Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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