Schizophrenia Research 195 (2018) 168–175

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Omega-3 fatty acid supplementation may prevent loss of gray matter thickness in the left parieto-occipital cortex in first episode schizophrenia: A secondary outcome analysis of the OFFER randomized controlled study

Tomasz Pawełczyk [a,*], Ewa Piątkowska-Janko [b], Piotr Bogorodzki [b], Piotr Gębski [c], Marta Grancow-Grabka [d], Elżbieta Trafalska [e], Natalia Żurner [c], Agnieszka Pawełczyk [a]

[a] Department of Affective and Psychotic Disorders, Medical University of Lodz, Czechosłowacka 8/10, 92-216 Lodz, Poland
[b] Institute of Radioelectronics and Multimedia Technology, Warsaw University of Technology, Nowowiejska 15/19; 00-665 Warsaw, Poland
[c] Scanlab Medical Diagnostics, ul. Przedzalniana 66, 90-338 Lodz, Poland
[d] Central Teaching Hospital, Adolescent Ward, Medical University of Lodz, Czechosłowacka 8/10, 92-216 Lodz, Poland
[e] Department of Nutrition Hygiene and Epidemiology, Medical University of Lodz, ul. Jaracza 63, 90-251 Lodz, Poland

ARTICLE INFO

Article history:
Received 13 June 2017
Received in revised form 28 July 2017
Accepted 8 October 2017
Available online 2 November 2017

Keywords:
Docosahexaenoic acid
Eicosapentaenoic acid
Magnetic resonance imaging
Antipsychotics
Neurodegeneration
Neuroprotection
Randomized controlled trial

ABSTRACT

The aim of the study was to assess changes in cortical thickness related to the use of n-3 polyunsaturated fatty acids (PUFA) as add-on therapy in patients with first episode schizophrenia. A double-blind randomized controlled study was conducted using a 26-week intervention composed of concentrated fish oil containing 2.2 g/d of eicosapentaenoic (EPA) and docosahexaenoic acid (DHA) or placebo (olive oil). Participants underwent MRI scanning twice to assess changes in cortical thickness: at the beginning and at the end of intervention. Data of suitable quality was obtained from 29 participants. The T1-weighted images for each participant were analyzed using FreeSurfer methodology for longitudinal pipeline. Significant differences in cortical thickness loss were observed between the groups in the parieto-occipital regions of Brodmann areas 7 and 19 of the left hemisphere, dysfunctions in which may be involved in schizophrenia symptomatology. The results of the study support the previous observations carried out in older individuals and patients with mild cognitive impairment, indicating that n-3 PUFA may have neuroprotective properties, especially at early stages of neurodegenerative diseases, such as schizophrenia. If replicated, the results of the present study may encourage clinicians to consider n-3 PUFA as a promising addition to antipsychotics for long-term treatment of schizophrenia.

1. Introduction

Structural brain abnormalities are well established in schizophrenia. Magnetic resonance imaging (MRI) studies frequently show reduced brain volume and cortical thickness in patients with schizophrenia, especially of the fronto-temporal and hippocampal regions of the brain, as well as lateral ventricle enlargement, even in individuals at high clinical risk of schizophrenia (Benetti et al., 2013) and at early stages of the disease (Hýža et al., 2016). Moreover several studies have shown these changes to be progressive over time, with different loss patterns at every stage of the disease (Bois et al., 2016; Torres et al., 2016). It has been found that brain volume loss is partly related to disease severity, expressed as the number and frequency of relapses leading to excitotoxicity induced by glutamatergic overactivity, or by oxidative stress related to dopaminergic stimulation (Ho et al., 2011). There is also accumulating data suggesting a link between brain tissue loss and intensive antipsychotic therapy (Ahmed et al., 2015; Fusar-Poli et al., 2013). However, that extent to which these changes can be attributed to the pathological processes underlying the disease and the consequences of antipsychotic therapy is still a matter of debate (Andreasen et al., 2013; Goff et al., 2017). Studies also indicate the magnitude of brain volume loss to be directly related to worse clinical outcome (van Haren et al., 2008).

Deficiencies of n-3 polyunsaturated fatty acid (n-3 PUFA) levels have repeatedly been observed in schizophrenia, especially at early stages of disease (van der Kemp et al., 2012). MRI studies suggest that n-3 PUFA may be related to neuroprotective effects in patients with schizophrenia (Wood et al., 2010) and bipolar disorder (Hirashima et al., 2004),

* Corresponding author at: Czechosłowacka 8/10, 92-216 Lodz, Poland.
E-mail addresses: tomasz.pawelczyk@umed.lodz.pl (T. Pawełczyk), janko@ire.pw.edu.pl (E. Piątkowska-Janko), piotr@ire.pw.edu.pl (P. Bogorodzki), piotr.gebski@umed.lodz.pl (P. Gębski), elzbieta.trafalska@umed.lodz.pl (E. Trafalska), agnieszka.pawelczyk@umed.lodz.pl (A. Pawełczyk).

https://doi.org/10.1016/j.schres.2017.10.013
0920-9964/

leading to decreased brain water proton transverse relaxation times (T2), which was shown to be indicative of increased neuronal membrane fluidity, and hence, increased neuronal health. A study of schizophrenia showed n-3 PUFA supplementation to have neuroprotective effects in hippocampi (Wood et al., 2010), and a bipolar study showed T2 reductions across the whole brain (Hirashima et al., 2004).

Both the disease itself and, possibly, treatment with antipsychotics are known to be related with GM loss (Ahmed et al., 2015; Fusar-Poli et al., 2013; Goff et al., 2017; Ho et al., 2011). The aim of the present study, therefore, is to confirm whether the use of adjunctive n-3 PUFA therapy, with its neuroprotective effects, may preserve this cortical volume loss in patients with schizophrenia.

2. Materials and methods

A scan dataset of patients enrolled to a randomized clinical trial was employed. The aim of the trial was to assess the efficacy of n-3 PUFA supplementation to antipsychotics in patients with first episode schizophrenia.

2.1. Study participants

All the participants were inpatients admitted to the Psychiatric Clinics of the Central Teaching Hospital, Medical University of Lodz and the wards of the Babinski Memorial Hospital, Lodz, Poland. The inclusion and exclusion criteria have been reported elsewhere (Pawełczyk et al., 2015). The participants were part of the study group formed for the randomized placebo-controlled trial (OFFER) (Pawełczyk et al., 2016), whose aim was to investigate the efficacy of augmentation with concentrated fish oil containing 2.2 g of n-3 PUFA, i.e. eicosapentaenoic (1320 mg) and docosahexaenoic acid (880 mg) (EPA + DHA), in 71 drug-naive or early-treated first-episode schizophrenia patients.

Seventy-one individuals were enrolled in the study. Thirty-six were randomly assigned to the EPA + DHA group and 35 to the placebo group. The treatment groups were similar in terms of demographic variables and baseline characteristics (Table 1).

In each group, four patients did not agree to have MRI scans at baseline. Claustrophobia or psychotic anxiety prevented the acquisition of MRI data in three patients allocated to the EPA + DHA group and five patients in the placebo group. Five patients from the EPA + DHA group and six patients from the placebo group did not take a second MRI scan at t1 = 26 weeks. Forty-four (41%) patients completed two MRI scans: 24 from the EPA + DHA group and 20 from the placebo group. Finally, difficulties with distinguishing white and gray matter due to poor quality of data prevented analysis in six patients allocated to the EPA + DHA group and nine in the placebo group. The patient flow diagram shows the history of participant inclusion and exclusion at different stages of the study (Fig. 1).

The analysis was performed using complete and high quality MRI data of 29 patients: 18 allocated to the EPA + DHA group and 11 to the placebo group. The difference in drop-out rate between groups was not statistically significant (Fisher exact test; $p = 0.149$). A reasonable percentage of patients completed both MRI scans, especially considering the active psychotic symptoms present in both groups of participants at the beginning of the study and the high level of cooperation needed to acquire high-quality MRI data.

The trial procedures were explained verbally and in writing to all eligible patients. All participants provided written informed consent prior to study enrollment. Consent was obtained from parents or guardians for participants under 18 years of age. The study was approved by the Ethics Committee of the Medical University of Lodz and was carried out in accordance with the Declaration of Helsinki.

2.2. Structural MRI acquisition

Structural MRI data was acquired at both baseline and follow-up on a GE Signa HDi 1.5 T MRI scanner using identical MRI protocols. For each individual, a two-dimensional pilot scan was used to identify the anterior commisure–posterior commisure (AC-PC) line followed by a 3D HiRes scan (Spoiled Gradient echo, TR = 16 ms, TE = 5.2 ms; flip angle 20°) with anisotropic voxel 0.45 × 0.48 × 1.50 mm and whole brain coverage. Gross pathology was excluded after visual inspection by an experienced neuroradiologist blinded to the subject group.

2.3. Image processing

The T1-weighted images for each subject were analyzed using FreeSurfer methodology for longitudinal pipeline, as described by Martin Reuter (Bernal-Rusiel et al., 2013; Reuter et al., 2012). The FreeSurfer longitudinal pipeline was run on the results obtained from the 29 subjects using the first baseline scan and the six-month repeat scan. The FreeSurfer longitudinal pipeline (version 5.3) takes the T1w image at *n*-timepoints, creates an average T1w image, and on this average image, creates the WM and pial boundary as described above. These initial surfaces are used as a starting point for a deformable model algorithm at all *n*-timepoints. In this case, $n = 2$ (Dale et al., 1999). For longitudinal processing, for each subject with images at more than one time point, the average image was used to create a within-subject template using robust inverse consistent registration. Each subject's template was then used to initialize the longitudinal image processing to increase the reliability and statistical power when measuring changes in the brain over time (Xu et al., 2014).

Both analyses were carried out: comparison between groups (EPA + DHA vs placebo) at a single time point using a scan segmented according to the Desikan-Kiliany Atlas defined by FreeSurfer, and longitudinal analysis using FreeSurfer longitudinal pipeline. For scan–rescan analysis, the symmetrized percentage change (SPC) was calculated at each vertex as the rate of thickness change with respect to the average thickness; SPC = rate/mean, where rate = (thickness 2 − thickness 1)/(time2 − time1) and mean = 0.5 × (thickness 1 + thickness 2).

2.4. Statistical analysis

A general linear model was applied at each surface vertex (for FreeSurfer) to determine the effect of group membership (EPA + DHA or placebo) on the change in measurement parameter, controlling for age and gender. FreeSurfer's statistical analysis tool utilized a Monte-Carlo permutation cluster analysis, a significance value of 0.05, a cluster threshold of 0.05, and 10,000 random permutations (Reuter et al., 2012).

3. Results

3.1. Study sample

No difference in MRI gray matter thickness was observed between the groups at the beginning of the study, which indicates that the process of patient exclusion was not biased. The treatment groups were similar in terms of socio-demographic variables and baseline characteristics (Table 1). Antipsychotic use at baseline and change in antipsychotic use, presented as chlorpromazine equivalents, is shown in Table 1. The mean rate for adherence with study intervention, based on pill count and self-report, was 83.2% (SD = 17.4) in the EPA + DHA group and 78.9% (SD = 16.6) in the placebo group (Student *t*-test; $t = 1.096$; $p = 0.277$). The use of medications and adherence to medications are reported in detail elsewhere (Pawełczyk et al., 2016).

Table 1
Characteristics of patients included in cortical thickness analysis.

Characteristic	EPA + DHA (1) (N = 18)	Placebo (2) (N = 11)	*p*
Age, mean (SD)	23.06 (4.9)	22.0 (3.77)	0.547
Male sex, N (%)	12 (66.7)	7 (63.6)	1.0[&]
Duration of untreated psychosis, mean (SD), mo	2.97 (3.63)	2.45 (3.75)	0.909
Family history of schizophrenia, N (%)	7 (38.9)	4 (36.4)	1.0[&]
Education level, N (%)			0.555[Ψ]
Elementary	6 (33.3)	5 (45.5)	
Vocational	1 (5.6)	0 (0)	
Secondary	7 (38.9)	4 (36.4)	
Bachelor's degree	1 (5.6)	2 (18.2)	
Master's degree	3 (16.7)	0 (0)	
Years of education, mean (SD)	13.36 (3.22)	13.77 (2.7)	0.726
Marital status, N (%)			0.512[Ψ]
Married	0 (0)	0 (0)	
Single	16 (88.9)	11 (100)	
Divorced	2 (11.1)	0 (0)	
Place of living, N (%)			1.0[&]
Alone	3 (16.7)	2 (18.2)	
With family	15 (83.3)	9 (81.8)	
Employment, N (%)			0.238[Ψ]
Employed	3 (16.7)	2 (18.2)	
Not employed	9 (50.0)	2 (18.2)	
Sheltered workshops	0 (0)	0 (0)	
During education	6 (33.3)	7 (63.6)	
Tobacco use, N (%)	6 (33.3)	3 (27.3)	1.0[&]
Income category, % of average wages, N (%)			0.299[Ψ]
<10	0 (0)	0 (0)	
10–20	7 (38.9)	2 (18.2)	
21–30	3 (16.7)	4 (36.4)	
31–40	3 (16.7)	2 (18.2)	
41–50	0 (0)	2 (18.2)	
51–60	3 (16.7)	1 (9.1)	
>60	2 (11.1)	0 (0)	
Energy consumption, median (IQR) [kCal]	2458.91 (1536.3)	2301.24 (1214.8)	0.369[#]
PUFA consumption, median (IQR) [g]	16.8 (13.9)	10.3 (7.0)	0.07[#]
CPZ eq., median (IQR)[a]	100 (252,5) $n = 8$	260 (175.0) $n = 5$	0.502[#]
Antipsychotic-naïve patients, N (%)	10 (55.6)	6 (54.5)	1.0[&]
Antipsychotics at baseline, N (%)			
Aripiprazole	1 (12.5)	0 (0.0)	0.681[Ψ]
Risperidone	3 (37.5)	2 (40.0)	
Olanzapine	1 (12.5)	2 (40.0)	
Quetiapine	2 (25.0)	1 (20.0)	
Sulpride	0 (0.0)	0 (0.0)	
Amisulpride	1 (12.5)	0 (0.0)	
Change in antipsychotic use during the study - presented as change in CPZ eq., median (IQR)	310.0 (280.0)	450 (600.0)	0.497[#]
CDSS score, mean (SD)	8.22 (6.3)	7.73 (5.93)	0.836
CGI-S score, mean (SD)	5.72 (0.57)	5.64 (0.81)	0.741
GAF score, mean (SD)	28.28 (7.09)	29.09 (8.26)	0.78
PANSS score, mean (SD)			
Positive	21.94 (4.76)	23.64 (6.31)	0.419
Negative	26.28 (3.54)	23.36 (7.12)	0.193
General	48.5 (5.47)	48.36 (6.76)	0.953
Total	96.72 (9.01)	95.64 (13.49)	0.796
Global brain volumes (cm^3), mean, (SD)			
CSF (baseline)	95.7 (26.4)	99.2 (18.4)	0.65[*]
WM (baseline)	458.1 (53.3)	442.1 (75.6)	
GM (baseline)	614.7 (65.1)	602.6 (89.0)	
CSF (follow-up)	92.7 (24.7)	103.1 (20.6)	0.24[*]
WM (follow-up)	457.7 (53.9)	450.3 (62.8)	
GM (follow-up)	614.6 (67.1)	600.5 (72.1)	

CDSS – The Calgary Depression Scale for Schizophrenia. CGI-S – The Clinical Global Impressions Severity Scale. PANSS – The Positive and Negative Syndrome Scale. GAF – Global Assessment of Functioning Scale; N – number of observations in a population, SD – standard variation, mo -month, yr -year; CPZ Eq. – Equivalent doses of chlorpromazine.

[a] Among patients treated with antipsychotics at baseline.

[&] Fisher's Exact Test.

[#] Based on Mann-Whitney *U* test.

[Ψ] Based on Chi^2 test.

[*] Multivariate analysis for global metrics inclusive of GM, WM, and CSF between groups.

3.2. Imaging

Comparisons between study groups at a single time point (baseline and follow-up) revealed no statistically significant differences. The results are shown in Table 1. Longitudinal analysis using multiple comparison correction revealed significant group differences in cortical thinning among study groups. The placebo group demonstrated significantly greater cortical thickness loss in the parieto-occipital cortex of the left hemisphere on the border of Brodmann areas 7 and 19 than the EPA + DHA group. The exact location of the significant differences in cortical thickness between groups is shown in Fig. 2, and its talairach coordinates are presented in Table 2. A symmetrized percentage change

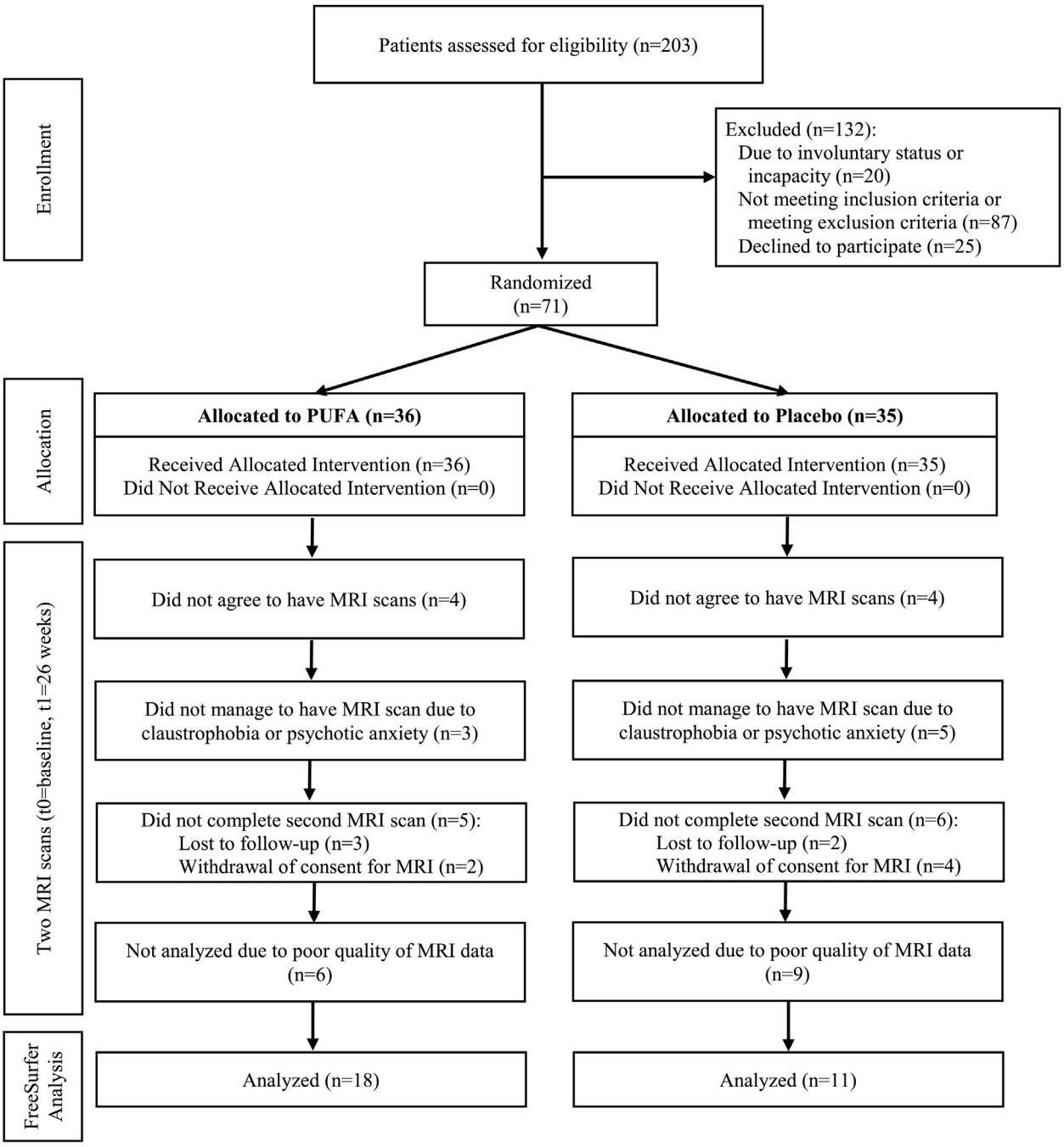

Fig. 1. Consort flow diagram. Abbreviations: PUFA – polyunsaturated fatty acids; MRI – magnetic resonance imaging.

between study groups in the left parieto-occipital cortex (Brodmann area 7 and 19) is shown in Fig. 3. The exclusion of a single outlying observation in the placebo group did not influence the overall significance of differences in SPC between study groups in the maximum of the left parieto-occipital cortex (Brodmann area 7 and 19).

4. Discussion

4.1. Summary of the results and relevance of the location

The study showed decreased cortical thickness loss related to concentrated fish oil supplementation (EPA + DHA) in comparison with placebo in schizophrenia patients treated with antipsychotics. The differences were observed in the left parieto-occipital cortex, specifically Brodmann areas 7 and 19, i.e. the cortical areas located near the temporo-parieto-occipital junction (TPOJ), which integrates information from both the external environment and from within the body (Abu-Akel and Shamay-Tsoory, 2011). The TPOJ is also involved in self-other distinctions: the process impaired in schizophrenia and one of the key features of the disease. Brodmann area 7 is known as a somatosensory association cortex, and is believed to play a role in visuomotor coordination, semantic categorization tasks and temporal context recognition (Burke et al., 2008). Brodmann area 19 is described as associative visual cortex and takes part in the detection of light

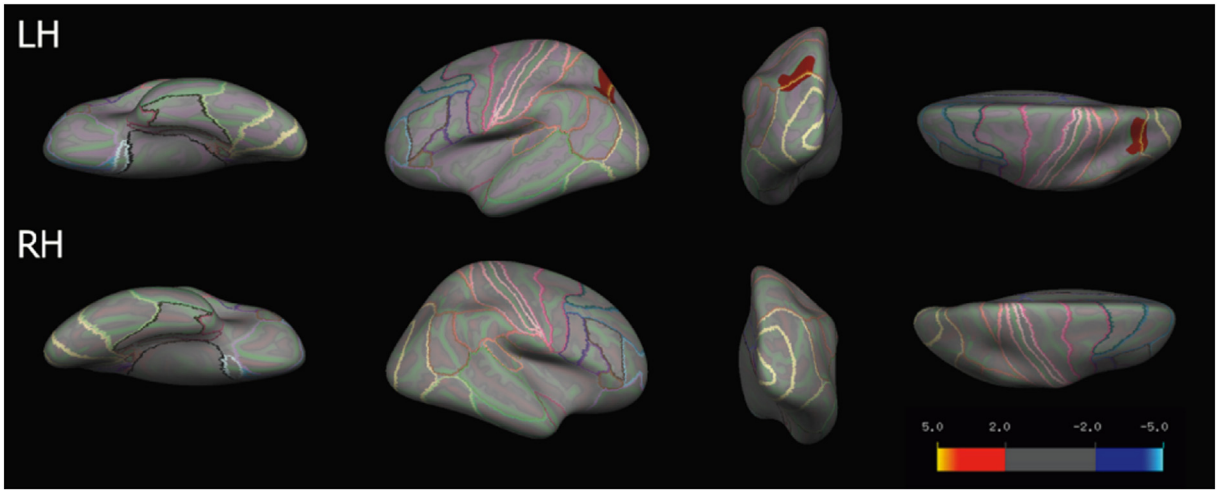

Fig. 2. Area with significant SPC differences between EPA + DHA and Placebo group (marked with red). This is an area in left hemisphere on the border BA7 and BA19. The significance in the display is a −log(10) *p*-value. LH – left hemisphere, RH – right hemisphere. Color bar description: Orange/yellow represent significant change in SPC in EPA + DHA group than Placebo group, blue represents greater change in SPC in Placebo then EPA + DHA group.

intensity, feature attention and pattern detection, and is involved in spatial working memory (Jahshan et al., 2017; Seymour et al., 2013). Many of these functions, such as visuo-motor coordination, attention, pattern detection and working memory, are known to be impaired in schizophrenia (Zai et al., 2017).

It is worth mentioning that both Brodmann areas found to be protected by the concentrated fish oil (BA 7 and 19) are involved in saccadic movement control (Cieslik et al., 2016; Parks et al., 2015). This function is considered an endophenotype of schizophrenia impaired not only in patients diagnosed with schizophrenia but also in their family members and people at increased clinical risk of schizophrenia development (Ross et al., 1998). Summing up, the present study indicates that the subjects who received n-3 PUFA demonstrated reduced cortical thickness loss in the cortical areas that control functions known to be impaired in schizophrenia.

4.2. Discussion of the results with previous studies

The effect of n-3 PUFA on cortical thickness when administered as add-on therapy to antipsychotics has not previously been assessed in patients with schizophrenia using a randomized controlled study approach, therefore, this is the first RCT study to investigate changes in cortical thickness during intervention with n-3 PUFA in first-episode schizophrenia patients. However, due to a lack of similar results from previous studies, it is not possible to compare our present findings with those from earlier studies.

Generally, previous studies with different study designs (cross-sectional, prospective longitudinal and retrospective) indicate that a habitual diet consisting of higher n-3 PUFA intake has a beneficial effect on cortical structure and function in healthy people (McNamara et al., 2017). Supplementation trials are scarce and have typically addressed the influence of EPA + DHA on cortical structure using MRI in healthy older subjects (mean age 64 years) (Witte et al., 2014), people with mild cognitive impairment (MCI) (Köbe et al., 2016) or have examined the effect of DHA on the cortical structure of patients diagnosed with Alzheimer's disease (Quinn et al., 2010). It was shown that DHA supplementation (2 g/d, 18 months) in patients with mild to moderate Alzheimer's disease (mean age 76 years) did not alter the rate of atrophy in total brain volume or hippocampal volume, or ventricular enlargement compared with placebo (Quinn et al., 2010). A second controlled study demonstrated that 26-week supplementation with fish oil (1.5:1 EPA/DHA – 2200 mg/d) compared with placebo (sunflower oil), significantly attenuated decreases in gray matter volume in the left hippocampus, precuneus, superior temporal lobe, inferior parietal lobe and postcentral gyri, and the right middle temporal gyrus in a cohort of healthy older adults (Witte et al., 2014). Finally, a recent MRI controlled study showed that 24-week therapy with fish oil supplementation (1.5:1 EPA/DHA – 2200 mg/d) combined with aerobic exercise, and cognitive stimulation attenuated frontal, parietal, and cingulate cortex gray matter volume reductions compared to controls (Köbe et al., 2016).

To summarize, the results of supplementation studies in older patients suggest that n-3 PUFA may be effective in attenuating cortical

Table 2
Location of the maximum differences in spc between EPA + DHA group and placebo.

No	Max	VtxMax	Size (mm^2)	TalX	TalY	TalZ	NVtxs	Annotation
1	2.0132	71	988	−19.2	−68.2	37.4	1883	superiorparietal

Spc - symmetrized percentage change; EPA - eicosapentaenoic; DHA -hocosahexaenoic; Max indicates the maximum −log10 (*p*-value) in the cluster; VtxMax is the vertex number at the maximum; Size - surface area (mm^2) of cluster; Tal (XYZ) is the talairach (MNI305) coordinate of the maximum; NVtxs - number of vertices in cluster; Annotation – location according to Desikan-Kiliany Atlas.

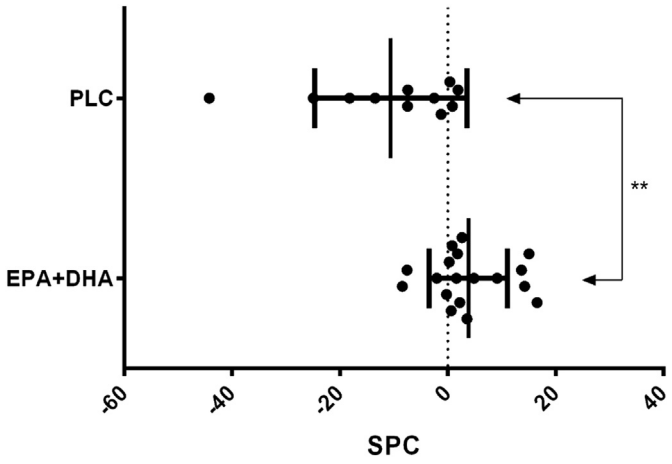

Fig. 3. Figure shows symmetrized percentage change (mean ± SD) between study groups in the maximum of the left parieto-occipital cortex (Brodmann area 7 and 19), which is depicted in detail on Fig. 2. SPC - symmetrized percentage change; ** - $p < 0{,}01$ (two-tailed, Mann-Whitney *U* test; U = 30).

thickness loss when used as prophylaxis in healthy individuals, or at early stages of neurodegenerative processes such as MCI as a prodrome of Alzheimer's disease. The postulated mechanism for the neuroprotective effects of n-3 PUFA may be related to its known immunomodulatory properties (Calder, 2013), as well as its ability to stimulate oxidative stress defense mechanisms (Liu et al., 2014; Pawełczyk et al., 2017) and inhibit apoptosis (Sadli et al., 2012; Suphioglu et al., 2010). The results of the current study indicate that n-3 PUFA possesses neuroprotective properties at early stages of neurodegenerative diseases such as schizophrenia.

Previous controlled studies of patients with schizophrenia do not examine the effects of n-3 PUFA on cortical thickness. More studies have described changes in white matter related to n-3 PUFA content. A significant correlation was found between total erythrocyte PUFA concentration and fractional anisotropy of a fronto-temporal white matter tract in a small group ($n = 12$) of first-episode schizophrenia patients (Peters et al., 2009). The authors concluded that n-3 PUFA may be necessary for the myelinating activity of oligodendrocytes or for myelin maintenance. The above results were later replicated in a larger group of patients ($n = 30$) (Peters et al., 2013). The authors conclude that white matter integrity is related to n-3 PUFA concentration in erythrocytes.

Animal studies have been used to address the topic of n-3 PUFA influence on cortical thickness; however, only one placebo-controlled study has been published (Cutuli et al., 2016). The authors assess the effects of eight-week n-3 PUFA supplementation on structural brain changes of aged mice using high-resolution MRI (Cutuli et al., 2016). The authors report significant increases of gray matter volume in the hippocampus, medial prefrontal cortex and the retrosplenial cortex of the mouse brain. Moreover, the observed increase in gray matter volume correlated significantly with improvement in cognitive task performance. In a previous study, the same group of researchers found that n-3 PUFA supplementation of aged mice was related to improved hippocampal cognitive functions which occurred in the context of enhanced cellular plasticity and reduced neurodegeneration (Cutuli et al., 2014). n-3 PUFA supplementation elevated hippocampal neurogenesis and dendritic arborization of newborn neurons, increased neuronal volume and density, as well as microglial cell number; however, it also decreased apoptosis, astrocytosis and lipofuscin accumulation in the hippocampus. The increased levels of blood acetyl-L-carnitine and brain n-3 PUFA concentrations found in n-3 PUFA supplemented mice also indicated effective neuroprotection. Our present findings seem to be supported also by recently published observations that a Mediterranean-style diet was related to increased cortical thickness (Staubo et al., 2017) and higher total brain volume (Luciano et al., 2017) in a large Scottish cohort.

4.3. Possible mechanism

Being an essential constituent of neuronal membranes and substrates of biologically-active compounds, n-3 PUFA is involved in wide range of cellular mechanisms; this variety may explain the results of the present study. Previous studies suggest that the potential underlying mechanism of GM changes induced by n-3 PUFA may be related to (a) neuroprotective properties (Begum et al., 2013; Wood et al., 2010), (b) increased neuronal membrane fluidity leading to changes in neurotransmission (Patrick and Ames, 2015), (c) modulation of the inflammatory response (Calder, 2015) with the production of resolving and anti-inflammatory cytokines, together with EPA and DHA derivatives such as maresins and neuroprotectins (Sansbury and Spite, 2016; Serhan et al., 2015), (d) enhancement of the antioxidative intracellular defense system (Berger et al., 2008; Liu et al., 2014; Smesny et al., 2015;), (e) reduction of dopamine and glutamate toxicity (Berger et al., 2008; Pu et al., 2013), (f) enhancement of neural plasticity (Bazan et al., 2011; McNamara et al., 2015). The above-mentioned mechanisms may slow the neurodegenerative processes observed in schizophrenia, and stimulate neuroprotective changes leading to macroscopic changes in cortical thickness.

4.4. Clinical importance

It is well established that cortical thickness loss occurs during the course of schizophrenia, even during the early stages of the disease. Moreover, there is accumulating evidence that GM loss in schizophrenia is related not only to the degenerative effects of the illness, its severity and the duration of untreated psychosis, but possibly also to the cumulative dose of antipsychotics (D2-blockers) (Fusar-Poli et al., 2013; Ho et al., 2011) which nowadays constitute the mainstay of effective schizophrenia therapy (Goff et al., 2017). The results of the present study suggest that n-3 PUFA possesses protective properties. If replicated, these results may offer promise for patients by acting as an additional form of therapy which is rather safe and well tolerated.

4.5. Limitations

The present study has some limitations that need to be considered before formulating conclusions, the main one being a lack of any objective measure of adherence, since it was not possible to assess the concentration of n-3 PUFA in the red blood cells of study participants. To account for this, pill counts were taken and data concerning medication adherence was collected during every study visit. Another limitation is the low number of participants who provided MRI scans with acceptable quality allowing data analysis. The 26-week intervention period may be regarded as another limitation, as some patients may need more time to achieve cortical thickness changes visible on the macro scale.

The strengths of the study include its randomized, placebo-controlled design, blinding and its inter-rater reliability testing. Another strength, and novel aspect, is the composition of n-3 PUFA used, i.e. a 3:2 mixture of EPA and DHA, which has not yet been used in patients with first-episode schizophrenia: this dosage of PUFA supplementation was higher than that used in previous studies but low enough to ensure safety of intervention.

Further studies incorporating larger samples of patients are warranted, as well as studies aimed at describing the biological mechanisms underlying the observed protective effects of n-3 PUFA on cortical thickness loss in patients with first-episode schizophrenia.

4.6. Conclusions

The study shows that six-month add-on supplementation with n-3 PUFA may reduce cortical thickness loss in Brodmann areas 7 and 19 of the left hemisphere in patients with first-episode schizophrenia. The area protected by supplementation with n-3 PUFA is characterized by dysfunction in cases of schizophrenia and decreased cognitive performance. The neuroprotective properties of concentrated fish oils described in the present paper, together with reported earlier efficacy and low adverse effects profile, suggest that n-3 PUFA may be considered as a promising addition to antipsychotics for long-term treatment of schizophrenia.

Conflict of interest

Authors declare no conflict of interest.

Contributors

Author TP was responsible for literature searches, study design, patient's enrollment and clinical assessments, drafting the manuscript. Authors EP-J and PB took part in MRI data preparation, statistical analyses of MRI data, prepared MRI figures, and drafted parts of the manuscript related to MRI data processing and analysis. Author PG was responsible for data acquisition and drafting parts of the manuscript related to data acquisition. Author MG-G took part in literature searches, enrollment of patients and clinical assessment of patients. Author ET and NŻ took part in study preparation and clinical assessments of patients. All authors contributed to and have approved the final manuscript.

Funding body agreements and policies

This paper was supported by grant no. N N402 243435 obtained from the Polish National Science Centre.

Acknowledgement

The authors would like to express their special thanks to Prof. Jolanta Rabe-Jabłońska MD, PhD, the former head of the department who was deeply involved in study preparation, and who unfortunately died in May 2014.

References

Abu-Akel, A., Shamay-Tsoory, S., 2011. Neuroanatomical and neurochemical bases of theory of mind. Neuropsychologia 49:2971–2984. https://doi.org/10.1016/j.neuropsychologia.2011.07.012.

Ahmed, M., Cannon, D.M., Scanlon, C., Holleran, L., Schmidt, H., McFarland, J., Langan, C., McCarthy, P., Barker, G.J., Hallahan, B., McDonald, C., 2015. Progressive brain atrophy and cortical thinning in schizophrenia after commencing clozapine treatment. Neuropsychopharmacology 40:2409–2417. https://doi.org/10.1038/npp.2015.90.

Andreasen, N.C., Liu, D., Ziebell, S., Vora, A., Ho, B.-C., 2013. Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: a prospective longitudinal MRI study. Am. J. Psychiatry 170:609–615. https://doi.org/10.1176/appi.ajp.2013.12050674.

Bazan, N.G., Molina, M.F., Gordon, W.C., 2011. Docosahexaenoic acid signalolipidomics in nutrition: significance in aging, neuroinflammation, macular degeneration, Alzheimer's, and other neurodegenerative diseases. Annu. Rev. Nutr. 31:321–351. https://doi.org/10.1146/annurev.nutr.012809.104635.

Begum, G., Harvey, L., Dixon, C.E., Sun, D., 2013. ER stress and effects of DHA as an ER stress inhibitor. Transl Stroke Res 4:635–642. https://doi.org/10.1007/s12975-013-0282-1.

Benetti, S., Pettersson-Yeo, W., Hutton, C., Catani, M., Williams, S.C., Allen, P., Kambeitz-Ilankovic, L.M., McGuire, P., Mechelli, A., 2013. Elucidating neuroanatomical alterations in the at risk mental state and first episode psychosis: a combined voxel-based morphometry and voxel-based cortical thickness study. Schizophr. Res. 150: 505–511. https://doi.org/10.1016/j.schres.2013.08.030.

Berger, G.E., Wood, S.J., Wellard, R.M., Proffitt, T.M., McConchie, M., Amminger, G.P., Jackson, G.D., Velakoulis, D., Pantelis, C., McGorry, P.D., 2008. Ethyl-eicosapentaenoic acid in first-episode psychosis. A 1H-MRS study. Neuropsychopharmacology 33: 2467–2473. https://doi.org/10.1038/sj.npp.1301628.

Bernal-Rusiel, J.L., Greve, D.N., Reuter, M., Fischl, B., Sabuncu, M.R., Initiative, Alzheimer's Disease Neuroimaging, 2013. Statistical analysis of longitudinal neuroimage data with linear mixed effects models. NeuroImage 66:249–260. https://doi.org/10.1016/j.neuroimage.2012.10.065.

Bois, C., Levita, L., Ripp, I., Owens, D.C.G., Johnstone, E.C., Whalley, H.C., Lawrie, S.M., 2016. Longitudinal changes in hippocampal volume in the Edinburgh high risk study of schizophrenia. Schizophr. Res. 173:146–151. https://doi.org/10.1016/j.schres.2014.12.003.

Burke, L., Androutsos, C., Jogia, J., Byrne, P., Frangou, S., 2008. The Maudsley early onset schizophrenia study: the effect of age of onset and illness duration on fronto-parietal gray matter. Eur. Psychiatry 23:233–236. https://doi.org/10.1016/j.eurpsy.2008.03.007.

Calder, P.C., 2013. N-3 fatty acids, inflammation and immunity: new mechanisms to explain old actions. Proc. Nutr. Soc. 72:326–336. https://doi.org/10.1017/S0029665113001031.

Calder, P.C., 2015. Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. Biochim. Biophys. Acta 1851:469–484. https://doi.org/10.1016/j.bbalip.2014.08.010.

Cieslik, E.C., Seidler, I., Laird, A.R., Fox, P.T., Eickhoff, S.B., 2016. Different involvement of subregions within dorsal premotor and medial frontal cortex for pro- and antisaccades. Neurosci. Biobehav. Rev. 68:256–269. https://doi.org/10.1016/j.neubiorev.2016.05.012.

Cutuli, D., De Bartolo, P., Caporali, P., Laricchiuta, D., Foti, F., Ronci, M., Rossi, C., Neri, C., Spalletta, G., Caltagirone, C., Farioli-Vecchioli, S., Petrosini, L., 2014. n-3 polyunsaturated fatty acids supplementation enhances hippocampal functionality in aged mice. Front. Aging Neurosci. 6, 220. https://doi.org/10.3389/fnagi.2014.00220.

Cutuli, D., Pagani, M., Caporali, P., Galbusera, A., Laricchiuta, D., Foti, F., Neri, C., Spalletta, G., Caltagirone, C., Petrosini, L., Gozzi, A., 2016. Effects of Omega-3 fatty acid supplementation on cognitive functions and neural substrates: a voxel-based morphometry study in aged mice. Front. Aging Neurosci. 8, 805. https://doi.org/10.3389/fnagi.2016.00038.

Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. NeuroImage 9:179–194. https://doi.org/10.1006/nimg.1998.0395.

Fusar-Poli, P., Smieskova, R., Kempton, M.J., Ho, B.C., Andreasen, N.C., Borgwardt, S., 2013. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci. Biobehav. Rev. 37:1680–1691. https://doi.org/10.1016/j.neubiorev.2013.06.001.

Goff, D.C., Falkai, P., Fleischhacker, W.W., Girgis, R.R., Kahn, R.M., Uchida, H., Zhao, J., LIEBERMAN, J.A., 2017. The long-term effects of antipsychotic medication on clinical course in schizophrenia. Am. J. Psychiatry appiajp201716091016. https://doi.org/10.1176/appi.ajp.2017.16091016.

Hirashima, F., Parow, A.M., Stoll, A.L., Demopulos, C.M., Damico, K.E., Rohan, M.L., Eskesen, J.G., Zuo, C.S., Cohen, B.M., Renshaw, P.F., 2004. Omega-3 fatty acid treatment and T(2) whole brain relaxation times in bipolar disorder. Am. J. Psychiatry 161: 1922–1924. https://doi.org/10.1176/ajp.161.10.1922.

Ho, B.-C., Andreasen, N.C., Ziebell, S., Pierson, R., Magnotta, V., 2011. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Arch. Gen. Psychiatry 68:128–137. https://doi.org/10.1001/archgenpsychiatry.2010.199.

Hýža, M., Kuhn, M., Češková, E., Ustohal, L., Kašpárek, T., 2016. Hippocampal volume in first-episode schizophrenia and longitudinal course of the illness. World J. Biol. Psychiatry 17:429–438. https://doi.org/10.1080/15622975.2016.1199893.

Jahshan, C., Wynn, J.K., Mathalon, D.H., Green, M.F., 2017. Cognitive correlates of visual neural plasticity in schizophrenia. Schizophr. Res. https://doi.org/10.1016/j.schres.2017.03.016.

Köbe, T., Witte, A.V., Schnelle, A., Lesemann, A., Fabian, S., Tesky, V.A., Pantel, J., Flöel, A., 2016. Combined omega-3 fatty acids, aerobic exercise and cognitive stimulation prevents decline in gray matter volume of the frontal, parietal and cingulate cortex in patients with mild cognitive impairment. NeuroImage 131:226–238. https://doi.org/10.1016/j.neuroimage.2015.09.050.

Liu, Q., Wu, D., Ni, N., Ren, H., Luo, C., He, C., Kang, J.-X., Wan, J.-B., Su, H., 2014. Omega-3 polyunsaturated fatty acids protect neural progenitor cells against oxidative injury. Mar. Drugs 12:2341–2356. https://doi.org/10.3390/md12052341.

Luciano, M., Corley, J., Cox, S.R., Valdés Hernández, M.C., Craig, L.C.A., Dickie, D.A., Karama, S., McNeill, G.M., Bastin, M.E., Wardlaw, J.M., Deary, I.J., 2017. Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish cohort. Neurology 88:449–455. https://doi.org/10.1212/WNL.0000000000003559.

McNamara, R.K., Vannest, J.J., Valentine, C.J., 2015. Role of perinatal long-chain omega-3 fatty acids in cortical circuit maturation: mechanisms and implications for psychopathology. World J. Psychiatry 5:15–34. https://doi.org/10.5498/wjp.v5.i1.15.

McNamara, R.K., Asch, R.H., Lindquist, D.M., Krikorian, R., 2017. Role of polyunsaturated fatty acids in human brain structure and function across the lifespan: an update on neuroimaging findings. Prostaglandins Leukot. Essent. Fat. Acids https://doi.org/10.1016/j.plefa.2017.05.001.

Parks, N.A., Mazzi, C., Tapia, E., Savazzi, S., Fabiani, M., Gratton, G., Beck, D.M., 2015. The influence of posterior parietal cortex on extrastriate visual activity: a concurrent TMS and fast optical imaging study. Neuropsychologia 78:153–158. https://doi.org/10.1016/j.neuropsychologia.2015.10.002.

Patrick, R.P., Ames, B.N., 2015. Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar disorder, schizophrenia, and impulsive behavior. FASEB J. 29:2207–2222. https://doi.org/10.1096/fj.14-268342.

Pawełczyk, T., Grancow, M., Kotlicka-Antczak, M., Trafalska, E., Gębski, P., Szemraj, J., Żurner, N., Pawełczyk, A., 2015. Omega-3 fatty acids in first-episode schizophrenia - a randomized controlled study of efficacy and relapse prevention (OFFER): rationale, design, and methods. BMC Psychiatry 15:1 (15):97. https://doi.org/10.1186/s12888-015-0473-2.

Pawełczyk, T., Grancow-Grabka, M., Kotlicka-Antczak, M., Trafalska, E., Pawełczyk, A., 2016. A randomized controlled study of the efficacy of six-month supplementation with concentrated fish oil rich in omega-3 polyunsaturated fatty acids in first episode schizophrenia. J. Psychiatr. Res. 73:34–44. https://doi.org/10.1016/j.jpsychires.2015.11.013.

Pawełczyk, T., Grancow-Grabka, M., Trafalska, E., Szemraj, J., Pawełczyk, A., 2017. Oxidative stress reduction related to the efficacy of n-3 polyunsaturated fatty acids in first episode schizophrenia: secondary outcome analysis of the OFFER randomized trial. Prostaglandins Leukot. Essent. Fat. Acids (PLEFA) 121:7–13. https://doi.org/10.1016/j.plefa.2017.05.004.

Peters, B.D., Duran, M., Vlieger, E.J., Majoie, C.B., den Heeten, G.J., Linszen, D.H., de Haan, L., 2009. Polyunsaturated fatty acids and brain white matter anisotropy in recent-onset schizophrenia: a preliminary study. Prostaglandins Leukot. Essent. Fat. Acids 81: 61–63. https://doi.org/10.1016/j.plefa.2009.04.007.

Peters, B.D., Machielsen, M.W.J., Hoen, W.P., Caan, M.W.A., Malhotra, A.K., Szeszko, P.R., Duran, M., Olabarriaga, S.D., de Haan, L., 2013. Polyunsaturated fatty acid concentration predicts myelin integrity in early-phase psychosis. Schizophr. Bull. 39:830–838. https://doi.org/10.1093/schbul/sbs089.

Pu, H., Guo, Y., Zhang, W., Huang, L., Wang, G., Liou, A.K., Zhang, J., Zhang, P., Leak, R.K., Wang, Y., Chen, J., Gao, Y., 2013. Omega-3 polyunsaturated fatty acid supplementation improves neurologic recovery and attenuates white matter injury after experimental traumatic brain injury. J. Cereb. Blood Flow Metab. 33:1474–1484. https://doi.org/10.1038/jcbfm.2013.108.

Quinn, J.F., Raman, R., Thomas, R.G., Yurko-Mauro, K., Nelson, E.B., Van Dyck, C., Galvin, J.E., Emond, J., Jack, C.R., Weiner, M., Shinto, L., Aisen, P.S., 2010. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA 304:1903–1911. https://doi.org/10.1001/jama.2010.1510.

Reuter, M., Schmansky, N.J., Rosas, H.D., Fischl, B., 2012. Within-subject template estimation for unbiased longitudinal image analysis. NeuroImage 61:1402–1418. https://doi.org/10.1016/j.neuroimage.2012.02.084.

Ross, R.G., Olincy, A., Harris, J.G., Radant, A., Adler, L.E., Freedman, R., 1998. Anticipatory saccades during smooth pursuit eye movements and familial transmission of schizophrenia. Biol. Psychiatry 44, 690–697.

Sadli, N., Ackland, M.L., De Mel, D., Sinclair, A.J., Suphioglu, C., 2012. Effects of zinc and DHA on the epigenetic regulation of human neuronal cells. Cell. Physiol. Biochem. 29:87–98. https://doi.org/10.1159/000337590.

Sansbury, B.E., Spite, M., 2016. Resolution of acute inflammation and the role of resolvins in immunity, thrombosis, and vascular biology. Circ. Res. 119:113–130. https://doi.org/10.1161/CIRCRESAHA.116.307308.

Serhan, C.N., Dalli, J., Colas, R.A., Winkler, J.W., Chiang, N., 2015. Protectins and maresins: new pro-resolving families of mediators in acute inflammation and resolution bioactive metabolome. Biochim. Biophys. Acta 1851:397–413. https://doi.org/10.1016/j.bbalip.2014.08.006.

Seymour, K., Stein, T., Sanders, L.L.O., Guggenmos, M., Theophil, I., Sterzer, P., 2013. Altered contextual modulation of primary visual cortex responses in schizophrenia. Neuropsychopharmacology 38:2607–2612. https://doi.org/10.1038/npp.2013.168.

Smesny, S., Milleit, B., Schaefer, M.R., Hipler, U.-C., Milleit, C., Wiegand, C., Hesse, J., Klier, C.M., Holub, M., Holzer, I., Berk, M., McGorry, P.D., Sauer, H., Amminger, G.P., 2015. Effects of omega-3 PUFA on the vitamin E and glutathione antioxidant defense system in individuals at ultra-high risk of psychosis. Prostaglandins Leukot. Essent. Fat. Acids 101:15–21. https://doi.org/10.1016/j.plefa.2015.07.001.

Staubo, S.C., Aakre, J.A., Vemuri, P., Syrjanen, J.A., Mielke, M.M., Geda, Y.E., Kremers, W.K., Machulda, M.M., Knopman, D.S., Petersen, R.C., Jack, C.R., Roberts, R.O., 2017. Mediterranean diet, micronutrients and macronutrients, and MRI measures of cortical thickness. Alzheimers Dement. 13:168–177. https://doi.org/10.1016/j.jalz.2016.06.2359.

Suphioglu, C., De Mel, D., Kumar, L., Sadli, N., Freestone, D., Michalczyk, A., Sinclair, A., Ackland, M.L., 2010. The omega-3 fatty acid, DHA, decreases neuronal cell death in association with altered zinc transport. FEBS Lett. 584:612–618. https://doi.org/10.1016/j.febslet.2009.12.013.

Torres, U.S., Duran, F.L.S., Schaufelberger, M.S., Crippa, J.A.S., Louzã, M.R., Sallet, P.C., Kanegusuku, C.Y.O., Elkis, H., Gattaz, W.F., Bassitt, D.P., Zuardi, A.W., Hallak, J.E.C., Leite, C.C., Castro, C.C., Santos, A.C., Murray, R.M., Busatto, G.F., 2016. Patterns of regional gray matter loss at different stages of schizophrenia: a multisite, cross-sectional VBM study in first-episode and chronic illness. Neuroimage Clin. 12:1–15. https://doi.org/10.1016/j.nicl.2016.06.002.

van der Kemp, W.J.M., Klomp, D.W.J., Kahn, R.S., Luijten, P.R., Hulshoff Pol, H.E., 2012. A meta-analysis of the polyunsaturated fatty acid composition of erythrocyte membranes in schizophrenia. Schizophr. Res. 141:153–161. https://doi.org/10.1016/j.schres.2012.08.014.

van Haren, N.E.M., Cahn, W., Hulshoff Pol, H.E., Kahn, R.S., 2008. Schizophrenia as a progressive brain disease. Eur. Psychiatry Schizophrenia as a progressive brain disease: 245–254. https://doi.org/10.1016/j.eurpsy.2007.10.013.

Witte, A.V., Kerti, L., Hermannstädter, H.M., Fiebach, J.B., Schreiber, S.J., Schuchardt, J.P., Hahn, A., Flöel, A., 2014. Long-chain omega-3 fatty acids improve brain function and structure in older adults. Cereb. Cortex 24:3059–3068. https://doi.org/10.1093/cercor/bht163.

Wood, S.J., Cocchi, L., Proffitt, T.-M., McConchie, M., Jackson, G.D., Takahashi, T., Pantelis, C., McGorry, P.D., Berger, G.E., 2010. Neuroprotective effects of ethyl-eicosapentaenoic acid in first episode psychosis: a longitudinal T2 relaxometry pilot study. Psychiatry Res. 182:180–182. https://doi.org/10.1016/j.pscychresns.2009.12.003.

Xu, Z., Shen, X., Pan, W., Initiative, Alzheimer's Disease Neuroimaging, 2014. Longitudinal analysis is more powerful than cross-sectional analysis in detecting genetic association with neuroimaging phenotypes. PLoS One 9, e102312. https://doi.org/10.1371/journal.pone.0102312.

Zai, G., Robbins, T.W., Sahakian, B.J., Kennedy, J.L., 2017. A review of molecular genetic studies of neurocognitive deficits in schizophrenia. Neurosci. Biobehav. Rev. 72:50–67. https://doi.org/10.1016/j.neubiorev.2016.10.024.