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Omega-3 polyunsaturated fatty acid supplementation and white matter changes in major depression

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ABSTRACT

White matter abnormalities are implicated in major depressive disorder (MDD). As omega-3 polyunsaturated fatty acids (PUFAs) are low in MDD and affect myelination, we hypothesized that PUFA supplementation may alleviate depression through improving white matter integrity. Acutely depressed MDD patients ($n = 16$) and healthy volunteers (HV, $n = 12$) had 25-direction diffusion tensor imaging before and after 6 weeks of fish oil supplementation. Plasma phospholipid omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and omega-6 PUFA arachidonic acid (AA) levels were determined before and after supplementation using high-throughput extraction and gas chromatography and expressed as a percentage of total phospholipids (PUFA%). Fractional anisotropy (FA) was computed using a least-squares-fit diffusion tensor with non-linear optimization. Regression analyses were performed with changes in PUFA levels or Hamilton Depression Rating Scale scores as predictors, voxel-wise difference maps of FA as outcome, covariates age and sex, with family-wise correction for multiple comparisons. Increases in plasma phospholipid DHA% (but not EPA% or AA%) after fish oil predicted increases in FA in MDD but not HV, in a cluster including genu and body of the corpus callosum, and anterior corona radiata and cingulum (cluster-level $p < 0.001$, peak *t-score* $= 8.10$, $p = 0.002$). There was a trend for greater change in FA in MDD responders over nonresponders ($t = -1.874$, $df = 13.56$, $p = 0.08$). Decreased depression severity predicted increased FA in left corticospinal tract and superior longitudinal fasciculus (cluster-level $p < 0.001$, peak *t-score* $= 5.04$, $p = 0.0001$). Increased FA correlated with increased DHA% and decreased depression severity after fish oil supplementation suggests therapeutic effects of omega-3 PUFAs may be related to improvements in white matter integrity.

1. Introduction

Major Depressive Disorder (MDD) is one of the top five causes of disability worldwide (Ustun et al., 2004), with a lifetime prevalence of approximately 10–18% (Williams et al., 2007; Kessler et al., 2003). The cause of MDD is not known, although aberrant neurocircuitry and factors affecting brain health are active areas of research. Linking a causal mechanism to a treatment may help improve prognosis.

Abnormalities in white matter observed in MDD include hyperintensities seen on structural magnetic resonance imaging (MRI) (Coffey et al., 1990, 1993) and reduced myelin integrity as measured using magnetization transfer imaging (Gunning-Dixon et al., 2008). Similarly, *post-mortem* histopathologic studies have found altered deep white matter staining in MDD (Thomas et al., 2002, 2003; Regenold et al., 2007). White matter abnormalities could lead to diminished functional connections between brain regions and thereby contribute to depression symptomatology.

Microstructural changes of white matter within neural

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networks can be detected using diffusion tensor imaging (DTI) to quantify fractional anisotropy (FA), a measure of the directionality of water diffusion (Basser, 1995; Le Bihan et al., 2001). Healthy white matter generally has high anisotropy, because water movement in myelinated nerve fibers is primarily in the direction of the axon fiber bundles (Le Bihan et al., 2001).

Abnormalities in FA of prefrontal (Shimony et al., 2009; Yang et al., 2007; Zou et al., 2008), temporal (Yang et al., 2007; Nobuhara et al., 2006), and parietal (Zou et al., 2008) cortex and in anterior cingulate (Bae et al., 2006) are reported in MDD compared with healthy volunteers (HV). One large DTI study ($n = 132$) that found differences between MDD and HV in regions including splenium, genu and body of the corpus callosum, superior longitudinal fasciculus, and anterior corona radiata, also found a negative correlation between depression severity and white matter integrity (Cole et al., 2012). In elderly depressed patients, FA impairment is associated with executive dysfunction (Murphy et al., 2007). First-episode, medication-naïve (Ma et al., 2007; Li et al., 2007; Wu et al., 2011) adults demonstrate similar deficits in frontal and parietal white matter, which negatively correlate with severity of the depressive symptoms (Zou et al., 2008). Adolescent MDD patients likewise exhibit white matter abnormalities and low FA in subgenual anterior cingulate cortex and amygdala (Cullen et al., 2010).

One determinant of white matter health is the balance of lipids in the brain. For example, polyunsaturated fatty acids (PUFAs), key components of phospholipids in cell membranes, comprise 35% of lipids in the brain (Benatti et al., 2004) and are critical for nervous system development and functioning (Luchtman and Song, 2013; Lauritzen et al., 2001; Gerster, 1998; Singh, 2005; Spector, 1999). Highly unsaturated long-chain PUFAs arachidonic acid (AA, 20:4n-6) and docosahexaenoic acid (DHA, 22:6n-3), are the major constituents of brain PUFAs, and have been implicated in psychiatric illness, including major depression (Lin et al., 2010), bipolar disorder (Rapoport, 2014; Sublette et al., 2004) and suicide risk (Huan et al., 2004; Lewis et al., 2011; Sublette et al., 2006). Eicosapentaenoic acid (EPA, 20:5n-3), although present in considerably lower quantities in brain as a result of its rapid β-oxidation and metabolism (Chen et al., 2009, 2011; Chen and Bazinet, 2015), also is reported to have specific effects related to neuropsychiatric conditions (Beier et al., 2014; Martins, 2009; Martins et al., 2012; Sublette et al., 2011a; Lin et al., 2012; Ross et al., 2007).

Given that both reduced white matter integrity and lower omega-3 PUFAs are seen in MDD, we hypothesized that supplementation with omega-3 PUFAs would cause increased FA in MDD greater than HV, and that increased FA would correlate with improvement in depression symptoms. We used DTI in a prospective study to test effects of fish oil supplementation for 6 weeks on white matter integrity in MDD compared with HV, and to generate brain maps of correlations of FA with 1) plasma phospholipid PUFAs and 2) depression severity.

2. Methods and materials

2.1. Sample

This study was approved by the Institutional Review Board of the New York State Psychiatric Institute in accordance with the latest version of the Declaration of Helsinki. After the procedures were fully explained, all subjects ($n = 28$) gave written informed consent to participate in this research study, which included a positron emission tomography (PET) scan component (not discussed here). At study entry, 16 depressed adults, ages 22–50, met DSM-IV criteria (American Psychiatric Association, 1994) for a current major depressive episode in context of major depressive disorder (MDD) without any history of psychosis, and no drug or alcohol abuse within the past 2 months or drug or alcohol dependence (except nicotine) within the past 6 months, based on the Structured Clinical Interview for DSM-IV (First et al., 1997). Patients were not actively suicidal, had not received electroconvulsive therapy within the past 6 months, and presented with scores between 16 and 25, inclusive, on the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967, 1960) at study entry. MDD participants were permitted to be on a single antidepressant or were medication-free and had no history of antipsychotic medications or mood stabilizers within 6 weeks; no washouts were performed. HV ($n = 12$) had no history of Axis I or Axis II illness. Participants in both groups did not have active medical illness based on history, physical examination and laboratory tests, and did not report more than occasional use of non-steroidal anti-inflammatory drugs (NSAIDs) or other medications known to interfere with the arachidonic acid pathway, including no use of omega-3 supplements within 3 months. Females were premenopausal. All participants were assessed for self-reported handedness.

2.2. PUFA supplementation

After the initial assessments and DTI scans, all participants received dietary supplementation daily with gelcaps containing a highly-purified, commercially available mixture of fatty acids from fish oil derived from anchovies, sardines and mackerel (OmegaLife-3, Unicity International, Inc., Orem, UT) for approximately six weeks. Participants took 4 gelcaps/day amounting to 4 g of total fish oil/d, including EPA, 1.6 g/d; DHA, 0.8 g; 0.8 mg saturated fat; inactive ingredients gelatin and glycerin; *d*-alpha tocopheryl 20 IU for stability; and orange oil to increase palatability. These doses and the EPA/(EPA + DHA) ratio of 67% EPA were consistent with those found effective in placebo-controlled, randomized clinical trials of fish oil supplementation as a treatment of depression (Sublette et al., 2011a). The six-week supplementation period was chosen in order to mitigate potential attrition over time, since it was important to obtain an additional scan at the end of the treatment; and taking into account several clinical trials that demonstrated separation from placebo as early as three (Nemets et al., 2002) or four (Peet and Horrobin, 2002; Su et al., 2003) weeks.

2.3. PUFA purification

Plasma from fasting blood samples was obtained within 3 weeks of the DTI scan and shipped on dry ice to the Nathan S. Kline Institute for Psychiatric Research (Orangeburg, NY) for biochemical analysis.

Plasma phospholipid PUFA levels were determined using a modified version of the rapid, high-throughput protocol of Glaser et al. (Glaser et al., 2010). Briefly, plasma proteins were precipitated in cold methanol, glycerophospholipid fatty acids were selectively esterified with sodium methoxide and acidified, and fatty acid methyl esters (FAMEs) were extracted in hexane. Separation and quantitation of FAMEs were accomplished via gas chromatography with flame ionization detection as described previously (Sublette et al., 2011b), and individual PUFA species are reported as a percentage of total plasma phospholipid PUFAs.

2.4. Image acquisition

MRI images were acquired on a 3.0T Signa Advantage system (GE Healthcare, Waukesha, WI, USA). Anatomical T1-3D images were acquired with the following parameters: echo time (TE) = 2.8 ms, repetition time (TR) = 7.1 ms, field of view (FOV) 256 × 256 mm^2, matrix size = 256 × 256, slice thickness = 1 mm

(voxel size 1 × 1 x 1 mm^3), number of slices = 178, with an acquisition time of 5 min. Diffusion images were acquired using a single-shot EPI (echo planar imaging) sequence. Scan parameters were as follows: TR = 14,000 ms, TE = 82 ms, flip angle 90°, slice thickness = 3 mm, Number of Excitation for signal averaging (NEX) = 1, FOV (field of view) = 240 × 240 mm^2, voxel dimensions = 0.95 × 0.95 × 3 mm, acquisition matrix = 256 × 256, b value = 1000 s/mm^2, and 25 collinear directions with 5 non-weighted images. DTI scan time was approximately 11 min.

2.5. Image processing

Each DTI image underwent a series of quality assurance tests for common artifacts, including ghost, ring, slice-wise intensity, venetian blind, and gradient-wise motion artifacts (Liu et al., 2010). Diffusion images were corrected for distortion induced by gradient coils and simple head motion using the eddy current correction routine from the FMRIB's Diffusion Toolbox (FSL, http://fsl.fmrib.ox.ac.uk/fsl/fsl-4.1.9/fdt/) with default settings. Following this, Camino (http://web4.cs.ucl.ac.uk/research/medic/camino/pmwiki/-pmwiki.php) (Cook et al., 2006) was used to estimate FA, computing the least-squares-fit diffusion tensor with non-linear optimization using a Levenburg-Marquardt algorithm, constrained to be positive by fitting its Cholesky decomposition. The individual FA maps were aligned into the up-sampled version (91 x 109 x 91 voxel, 2 × 2 × 2 mm^3/voxel) of the common FMRIB58 FA template (www.fmrib.ox.ac.uk/fsl/data/FMRIB58_FA) using FSL's FMRIB Nonlinear Image Registration Tool (FNIRT) (Andersson et al., 2007a, 2007b).

2.6. Global tractography

We performed global tractography using findings from the FA analysis as a seed, in order to visualize regions of gray matter subserved by the white matter region where the change in FA (ΔFA) correlated positively with change in DHA% (ΔDHA%) among MDD but not HV. DTI was obtained after performing Insight Segmentation and Registration Toolkit (ITK, National Library of Medicine, http://www.itk.org)-based tensor reconstruction (Westin et al., 2002) on the preprocessed diffusion weighted images. The eddy-corrected diffusion weighted images were processed through MITK-Diffusion (Fritzsche et al., 2012), which implements the Gibbs Tracking Algorithm (Reisert et al., 2011), a global tractography method that reconstructs all brain fibers simultaneously while searching for a global optimum (Andersson et al., 2007b), and has outranked other tractography algorithms (Fillard et al., 2011). The subset of tracts that passed through the chosen seed were extracted, and brain regions connected via the extracted tracts were identified based on individual brain atlases derived from running Freesurfer's surface-based reconstruction pipeline (http://surfer.nmr.mgh.harvard.edu) on the T1-weighted anatomical image.

2.7. Statistical analyses

2.7.1. Sample

For demographic and clinical characterizations, MDD and HV groups were compared with respect to sex, age, race, body mass index (BMI), and income, and also with regard to plasma phospholipid PUFA concentrations before and after fish oil supplementation, and percentage change over the course of supplementation. Improvement in depression severity after supplementation was assessed with a paired *t*-test in HDRS scores within the MDD group. Within the depressed group, clinical responders were defined as having achieved at least a 50% improvement in HDRS scores over the course of supplementation. Analyses were performed using IBM SPSS Statistics (version 23, Armonk, NY).

2.7.2. Fractional anisotropy

For voxel-based analysis, an inclusion mask for white matter was created using the FA standard template by thresholding, which excluded all voxels with FA values > 0.2. Analysis was performed using Statistical Parametric Mapping (SPM8, v4290) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) with Matlab (version 7.14, Mathworks, Natick, Massachusetts) on a 64 bit iMac with OS X 10.7.5. For these analyses, all images were smoothed with an isotropic Gaussian kernel with full width half maxima (FWHM) = 2 mm. This relatively small FWHM was chosen as it adequately removed conspicuous noise without introducing any apparent partial volume effect. The Gaussian kernel was utilized as the FA images had a signal-to-noise ratio (SNR) greater than 2.0, a level at which the noise distribution is more nearly approximated by Gaussian than Rician distribution (Gudbjartsson and Patz, 1995).

A 2-way repeated measures ANCOVA was performed with the independent factors of diagnosis (2 levels, MDD vs. HV), and time point (2 levels: pre and post supplementation), dependent factor of FA, and age as a covariate.

For pre-post correlation analysis, pre-supplementation FA maps were subtracted from post-supplementation FA maps, and these voxel-wise difference maps were submitted to separate multiple regression analyses with post-supplementation minus pre-supplementation DHA%, AA%, or EPA% levels as predictor variables, covarying for age and sex. The PUFA change scores (ΔPUFAs) were tested and found to be normally distributed, so log-transformation was not required. For voxel-wise analyses, uncorrected $p < 0.01$ at voxel level and cluster-level $p < 0.05$ corrected for multiple comparisons with family-wise error (FWE), were used to determine statistical significance. Results were not further corrected for the multiple comparisons due to testing for three different PUFAs.

Additionally, separate regression analyses were performed in the MDD group with either pre-treatment HDRS as predictor, and pre-treatment FA as the outcome measure; or pre-post-supplementation change in HDRS (ΔHDRS) scores as predictor, and pre-to post-treatment ΔFA as the outcome measure. Age and sex were covariates of no interest using the same statistical thresholds as in the analyses with PUFAs as predictors. Post-hoc analyses compared responders to nonresponders with respect to ΔFA in the region of maximal correlation between ΔPUFAs and ΔFA.

Another *post-hoc* analysis quantified the observed brain regions that were common to ΔFA correlating with ΔHDRS, and ΔFA correlating with ΔDHA%. This was achieved by taking the intersection between the ΔFA by ΔHDRS and the ΔFA by ΔDHA% regression analyses. For this exploratory analysis, a less conservative *a priori* statistical threshold was set as uncorrected $p < 0.05$ at voxel level and FWE-corrected $p < 0.05$ at cluster level.

Additional exploratory analyses are found in the Supplemental Material, namely an assessment of radial and axial diffusivity, and a mediation analysis testing whether ΔFA mediated the association between ΔDHA% and ΔHamilton Depression scores after treatment.

3. Results

3.1. Sample

As detailed in Table 1, MDD and HV groups did not differ with respect to sex, age, or other demographic characteristics examined, although the MDD group trended toward a higher percentage of white participants. Participants were adults ages 22–50. Depressed participants had not taken psychotropic medications for at least 14

Table 1
Demographic and clinical characters of the research participants, including plasma phospholipid concentrations before and after fish oil supplementation.

Characteristic	MDD ($n = 16$)			HV ($n = 12$)			Statistics		
							$\chi 2$	*df*	*p*-value
Sex (% male)	31.3%			41.7%			0.324	1	0.569
Race (% white)	68.8%			33.3%			3.458	1	0.063
[a]Handedness (% right)	80.0%			91.7%					0.605
[a]Tobacco use (% smokers)	12.5%			0%					0.492
	mean (SD)			*mean (SD)*			*t-score*	*df*	*p-value*
Age (yrs)	34.4 (8.2)			30.9 (7.9)			1.117	26	0.274
BMI (kg^*m^{-2})	25.1 (3.4)			25.7 (6.4)			−0.330	26	0.744
Education (yrs)	15.4 (2.2)			15.0 (1.8)			−0.710	26	0.484
	mean (SD)	*median*	*IQR*	*mean (SD)*	*median*	*IQR*	*z-score*		*p-value*
[b]Income (US $1000/yr)	41.1 (38.8)	26	52.7	23.2 (13.2)	19	16.7	−0.612		0.540
Plasma phospholipid PUFAs (w/w%)	*mean (SD)*			*mean (SD)*			*t-score*	*df*	*p-value*
Pre-supplementation									
DHA%	3.26 (0.81)			2.92 (0.53)			1.282	26	0.211
EPA%	0.72 (0.30)			0.73 (0.26)			−0.248	26	0.806
AA%	11.82 (2.39)			12.0 (1.62)			−0.228	26	0.821
Post-supplementation									
DHA%	4.90 (0.97)			4.28 (1.23)			1.510	26	0.143
EPA%	3.02 (1.86)			3.44 (2.43)			−0.522	26	0.606
AA%	10.36 (2.09)			10.52 (1.42)			−0.222	26	0.826
Percentage change									
ΔDHA%	159.81 (56.51)			148.38 (42.50)			0.586	26	0.563
ΔEPA%	488.47 (322.61)			553.82 (549.86)			−0.395	26	0.696
ΔAA%	88.85 (15.99)			88.66 (14.50)			0.033	26	0.974
FA (range:0–1)	*mean (SD)*			*mean (SD)*			*t-score*	*df*	*p-value*
Pre-supplementation	0.36 (0.02)			0.38 (0.01)			−1.994	26	0.057
Post-supplementation	0.36 (0.03)			0.38 (0.01)			−1.522	26	0.140

Abbreviations: AA%, DHA%, EPA%, arachidonic acid, docosahexaenoic acid, eicosapentaenoic acid, respectively, as a percentage of plasma phospholipids; df, degrees of freedom; FA, fractional anisotropy; HV, healthy volunteers; IQR, Inter-quartile range; MDD, major depressive disorder; PUFAs, polyunsaturated fatty acids; SD, standard deviation.
[a] Fisher's exact test (2-sided).
[b] Mann-Whitney test.

days prior to PET studies with the exception of three participants (one on sertraline, one on duloxetine, and one on mirtazapine plus clonazepam). MDD participants were mildly-moderately depressed at the time of the first PET scan (mean HDRS score = 17.8 ± 3.85 SD). Three MDD participants had a history of suicide attempt. Following fish oil supplementation, five participants were determined to be clinical responders, defined as ≥ 50% reduction in HDRS scores after PUFA supplementation. None of the responders were taking any antidepressant medications.

Supplementation caused significant increases in DHA% and EPA %, and decreases in AA%, that were comparable in magnitude in both MDD and HV groups (see Table 1). No group differences were observed in plasma phospholipid concentrations of PUFA before or after supplementation, nor did the magnitude of ΔPUFA differ between groups. Depressed participants improved significantly with supplementation (pre-supplementation HDRS mean score 17.8 ± 3.9; post-supplementation mean score 11.5 ± 5.9; *t-score* = 3.981, *df* = 15, $p = 0.001$); and the 31% who were responders had higher final DHA% levels than nonresponders ($t = 2.414$, $df = 14$, $p = 0.03$).

3.2. Fractional anisotropy

Group differences were seen in regional FA at the applied statistical thresholds after correction for age and sex, at both pre-supplementation (peak voxel, MNI -18, 38,-18, peak-level *t*-score = 5.97, observed cluster size = 1041 voxels, $p < 0.001$) and post-supplementation (peak voxel, MNI 24, 26,12, peak-level *t*-score = 3.90, observed cluster size = 263 voxels, $p = 0.026$) timepoints (Fig. 1). FA in MDD was lower than in HV in genu and splenium of corpus callosum, anterior corona radiata bilaterally, and right superior longitudinal fasciculus before supplementation (Fig. 1A). After supplementation, however, the regions of group difference were reduced in extent, such that only anterior corona radiata still showed lower FA in MDD than HV (Fig. 1B), suggesting a possible mitigation of abnormal FA by omega-3 PUFA treatment. There were no within-group differences between pre- and post-supplementation total FA in either MDD or HV (Table 1).

In regression models, for the depressed group, plasma phospholipid DHA% positively correlated with FA in the body of the corpus callosum prior to supplementation (peak voxel, MNI -10,-42,24, peak-level *t*-score = 5.27, observed cluster size = 679 voxels, cluster-level $p < 0.001$; Fig. 2A). After supplementation, the increase in plasma phospholipid DHA% correlated with increase in FA in MDD more anteriorly in a region encompassing genu and body of corpus callosum, and anterior corona radiata and cingulum bilaterally (peak voxel, MNI 4,20,12, peak-level *t*-score = 5.97, observed cluster size = 525 voxels, cluster-level $p < 0.001$; Fig. 2B).

In the depressed group, there were no correlations between baseline or post-supplementation HDRS scores and FA at those timepoints. However, ΔHDRS scores correlated positively with ΔFA in left corticospinal tract and longitudinal fasciculus (peak voxel, MNI -34, -26,62, peak-level *t*-score = 5.04, observed cluster size = 517 voxels, $p < 0.001$). This region overlapped with 17 percent of voxels from the cluster in which ΔDHA% correlated with ΔFA (Fig. 3).

Post-hoc analyses comparing MDD responders to nonresponders in the identified ΔDHA% − ΔFA correlation region found that 80% of responders (4/5) showed an increase in FA after supplementation, compared with only 45% (5/11) of non-responders (Fig. 4). The group difference between MDD responders and nonresponders was at a trend level in this small sample ($t = -1.874$, $df = 13.56$,

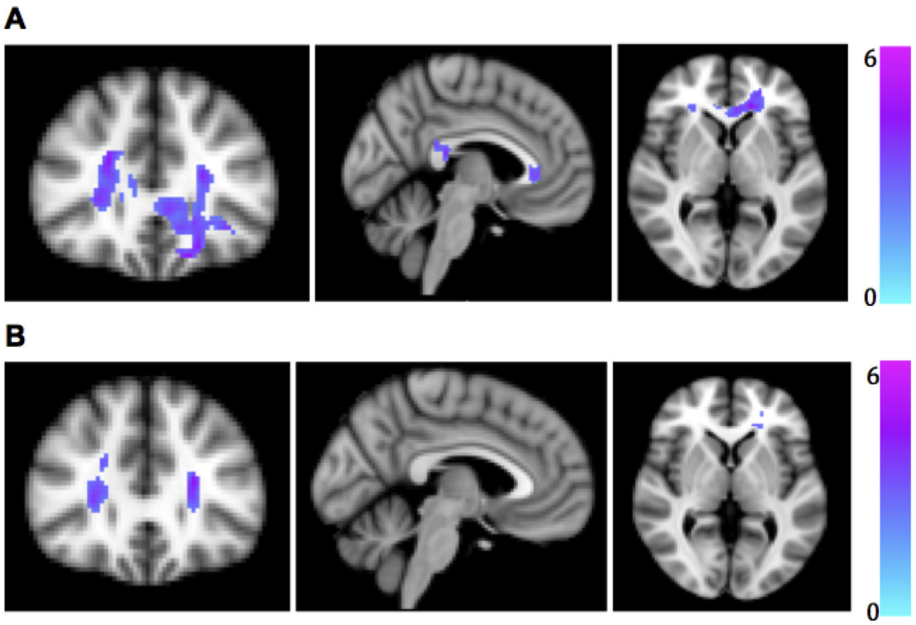

Fig. 1. Lower fractional anisotropy (FA) in patients with major depressive disorder compared to healthy volunteers (A) before and (B) after fish oil supplementation for six weeks. Affected regions are displayed on an MNI T1 template with corresponding t-score color bar.

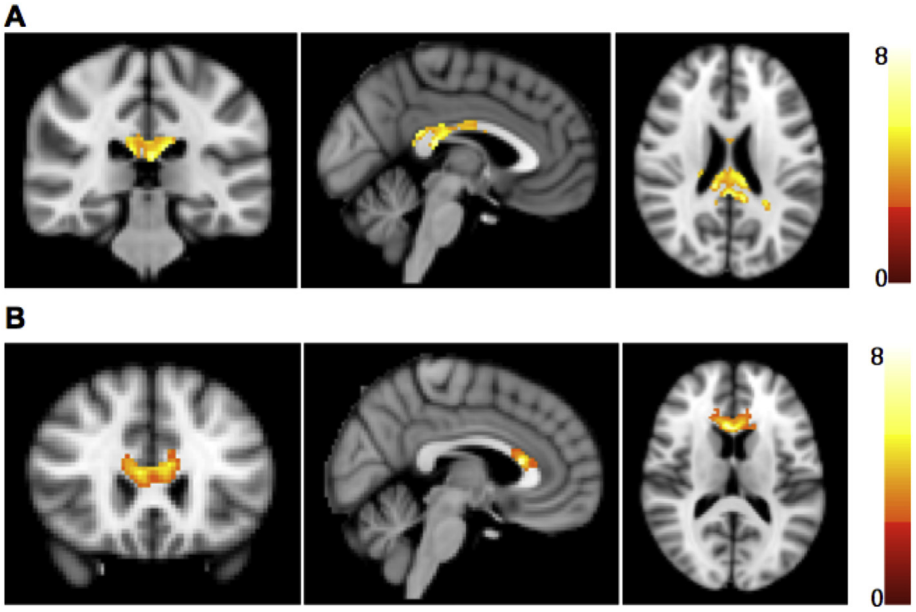

Fig. 2. Correlations between fractional anisotropy (FA) and plasma phospholipid docosahexaenoic acid as a percentage of total plasma phospholipid PUFAs (DHA%) in patients with major depressive disorder. A. FA positively correlates with DHA% before fish oil supplementation. B. Change in FA positively correlates with change in DHA% after fish oil supplementation. Affected regions are displayed on MNI T1 template with corresponding t-score color bar.

$p = 0.08$).

No correlations were seen between increased DHA% and ΔFA in the HV group. Neither AA% nor EPA% levels predicted changes in FA in either group.

3.3. Whole brain tractography

In the voxel cluster where increased DHA% correlated positively with increased FA in MDD (including portions of corpus callosum, anterior corona radiata, and cingulum) as a seed region, white matter tracts passing through the seed mapped bilaterally to cortical regions comprising rostral middle frontal and superior frontal gyri (Fig. 5).

4. Discussion

This is the first reported DTI study of PUFA supplementation effects on white matter in MDD. We found that white matter

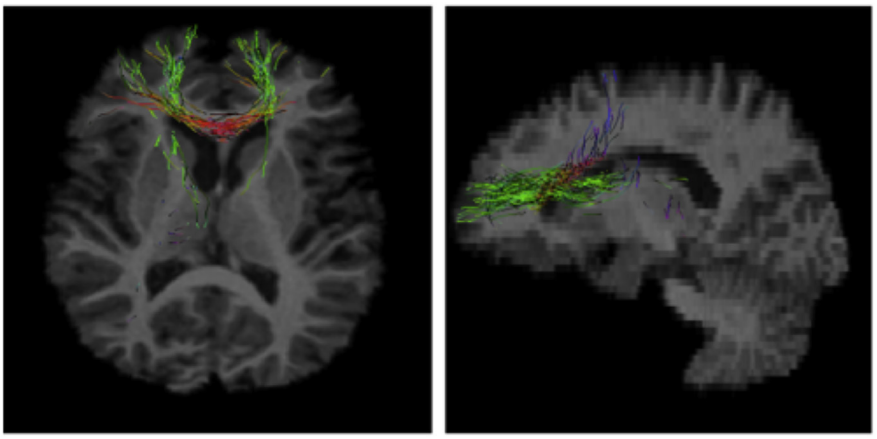

Fig. 3. Global tractography using seed regions in which change in fractional anisotropy correlated positively with change in plasma phospholipid docosahexaenoic acid as a percentage of total plasma phospholipid PUFAs (DHA%) for major depressive disorder. Tractography results from one representative healthy volunteer are shown here, superimposed on the same individual's structural MRI. Red – left to right; blue – inferior to superior; green – anterior to posterior.

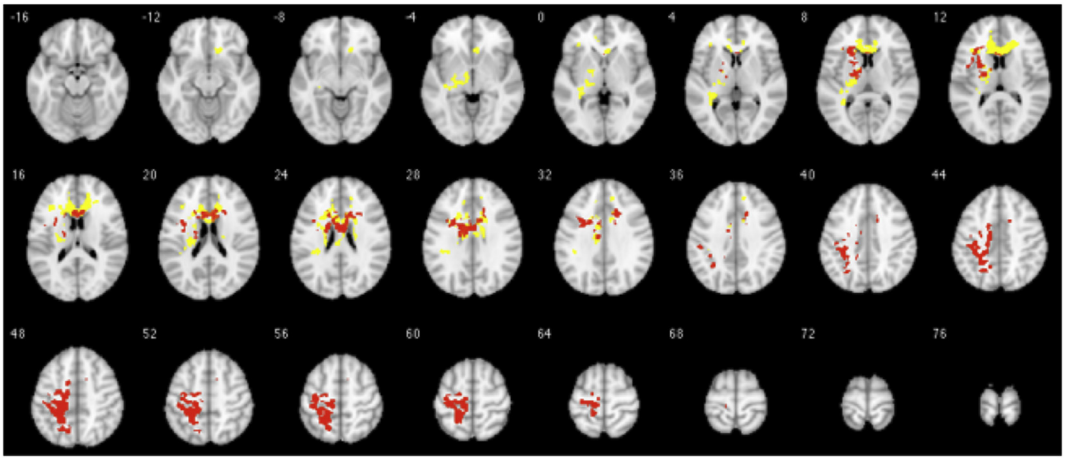

Fig. 4. Intersection between parametric brain maps of change in fractional anisotropy (ΔFA) correlated with change in plasma phospholipid docosahexaenoic acid as a percentage of total plasma phospholipid PUFAs (ΔDHA%) (yellow) and with change in depression severity scores (ΔHDRS) (red), in the MDD group. Depression severity is measured with the 17-item Hamilton Depression Rating Scale. Using xjView toolbox (http://www.alivelearn.net/xjview), SPM-derived t-score maps are superimposed on a series of transaxial slices [4 mm apart] of a coregistered anatomical MRI template. For this exploratory analysis, a less conservative statistical threshold was set *a priori* as uncorrected $p < 0.05$ at voxel level and FWE-corrected $p < 0.05$ at cluster level.

deficits in MDD, relative to HV, improved after six weeks of fish oil supplementation, as defined by increased FA in a single voxel cluster. Moreover, although changes were seen in plasma phospholipid levels of all three PUFAs, only the DHA% increases correlated with brain FA increases, and only in the MDD group, with a trend toward greatest FA increases in clinical responders. We also observed that the brain region in which improved depression correlated with increased FA overlapped with the region in which increased DHA% correlated with increased FA.

The pre-supplementation MDD deficits in FA relative to the HV group were not simply a function of lower baseline omega-3 PUFA levels in MDD, since although previous studies comparing MDD to HV found that depressed patients have lower omega-3 PUFA concentrations (Lin et al., 2010), in this sample MDD and HV had comparable levels prior to supplementation. This may have been due to the modest level of depression severity in this particular sample, as some studies have reported an inverse association between depression severity and plasma (Féart et al., 2008) or erythrocyte phospholipid (Adams et al., 1996) levels of EPA. Additionally, our sample had a low percentage of suicide attempters (2%), and suicide attempt history has been linked to lower EPA and DHA levels (Huan et al., 2004).

Although age-related decreases in FA have been reported [Salami et al., 2012], this potential confound was addressed by including age as a covariate in the analyses. Moreover, concern about age-related effects was mitigated by the fact that there were no participants over 50 yrs old.

Supplementation with fish oil was associated with a moderate antidepressant effect, as about one third of the patients were responders. Given the correlation observed between changes in FA and improvement in depression severity in the responder group, we could speculate that in a subset of depressed patients, clinical response to omega-3 PUFAs might depend on the degree of increase in FA. However, the lack of complete congruity between parametric maps of ΔFA correlating with ΔDHA% and ΔFA correlating with ΔHDRS suggests that other factors contribute. It is also possible that improved white matter integrity may relate to cognitive subdomains of depression symptoms not captured by the HDRS.

Neuroanatomically, our findings of abnormal FA in corpus

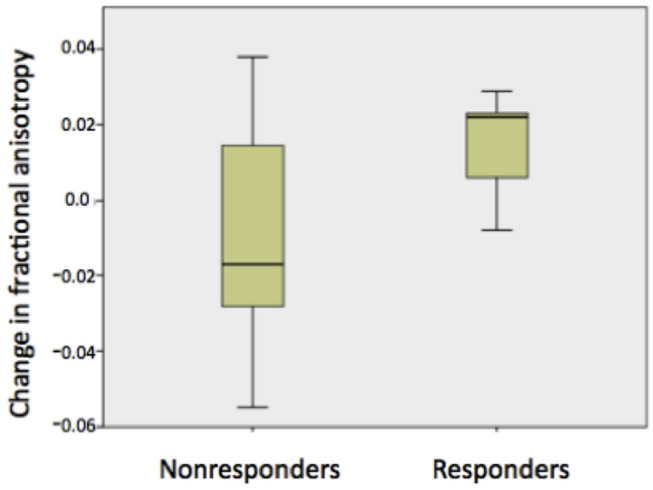

Fig. 5. Comparison of change in fractional anisotropy (ΔFA) between MDD clinical responders and nonresponders, in the region in which change in fractional anisotropy (ΔFA) correlated positively with change in plasma phospholipid docosahexaenoic acid as a percentage of total plasma phospholipid PUFAs (ΔDHA%). ($t = -1.874$, $df = 13.56$, $p = 0.08$).

callosum, anterior radiata and superior longitudinal fasciculus in major depression comport closely with previous results of Cole et al. (Cole et al., 2012). These structures mediate three different dimensions of communication within the brain: interhemispheric (corpus callosum), cortical–cortical (superior longitudinal fasciculus) and cortical-brainstem (anterior radiata). Structural changes in corpus callosum have been repeatedly implicated in depressive illness (Benedetti et al., 2011; Cyprien et al., 2011; Walterfang et al., 2009a, 2009b; Lyoo et al., 2002), and lower FA has been reported in MDD in the superior longitudinal fasciculus (Zou et al., 2008; Wu et al., 2011), a long association pathway running from parietal lobe to premotor and prefrontal cortices, including the dorsolateral prefrontal cortex. The relatively greater size of these three white matter tracts may confer a higher statistical power to detect FA changes there even in small samples. Future, larger studies might have the power to quantify more nuanced associations with respect to FA in finer white matter tracts.

The gray matter regions subserved by these tracts, as mapped out by whole brain tractography, also are consistent with our previous positron emission tomography (PET) findings in a separate sample of MDD, in which plasma phospholipid levels of DHA%, but not EPA%, correlated negatively with relative regional uptake of glucose (rCMRglu) in cingulate, middle frontal, inferior frontal, and superior frontal gyri (Sublette et al., 2009).

Among PUFAs tested, only increases in DHA% correlated with increases in FA in the MDD group, consistent with DHA's role as the predominant omega-3 species in brain. Rat studies indicate that although EPA and DHA enter the brain at similar rates, most of the EPA is rapidly β-oxidized, and is recycled into brain phospholipids to a much lower extent than DHA, resulting in a much higher DHA concentration in brain (Chen and Bazinet, 2015).

Counterintuitively, however, in clinical trials EPA appears to have greater therapeutic value than DHA, for acute treatment of major depression (Martins, 2009; Sublette et al., 2011a; Lin et al., 2012). Suggested explanations for EPA effects in depression have included its peripheral anti-inflammatory effects (Bhattacharya et al., 2007; Zhao et al., 2004), actions of EPA metabolites (Brooks et al., 2008), or direct effects on cerebral capillaries (Igarashi et al., 2013). However, in order to be consistent with both hypotheses that EPA is the active antidepressant agent *and* that brain DHA has effects on depression through increasing FA, we would need to postulate that increased peripheral EPA facilitates plasma DHA entry into brain in a manner superior to directly providing DHA supplements. This has not been proven, although it is true that most dietary EPA is taken up by the liver, where one fate is conversion to bioactive DHA (Igarashi et al., 2013). Alternatively, the explanation may lie in the relative proportions of *unesterified* DHA and EPA, not measured here, as unesterified PUFAs cross the blood–brain barrier most readily (Ouellet et al., 2009; Purdon et al., 1997).

Our ability to discern PUFA-related structural brain changes over a 6-week period is temporally consistent with another study (Hirashima et al., 2004), in bipolar disorder, in which omega-3 PUFA treatment of 4 weeks' duration resulted in MRI changes in brain water proton transverse relaxation times (T2), that, like DTI (Sakuma et al., 1991), reflect myelin content and changes in water environments (Whittall et al., 1997).

Studies in other psychiatric populations have found links between PUFA levels and white matter integrity. For example, total PUFA concentration correlated with FA in the bilateral uncinate fasciculus of young adult males with a recent-onset psychotic disorder (Peters et al., 2009). In a later study by the same group (Peters et al., 2013), lower total PUFA concentrations in men with early-phase psychosis correlated with lower FA in the corpus callosum, and bilateral parietal, occipital, temporal, and frontal white matter tracts. In contrast to our findings in MDD, in the group of psychotic males lower concentrations of arachidonic acid (AA), nervonic acid (24:1n-9), and docosapentaenoic acid (22:5n-3), but *not* DHA, directly correlated with lower FA (Peters et al., 2013).

The importance of PUFA status to brain function may be due in part to the effects of PUFA composition on myelin. Studies in rats find that lower omega-3 PUFA intake causes abnormalities of myelin (Trapp and Bernsohn, 1978), and that omega-3 PUFA administration stimulates expression of myelin proteins (Salvati et al., 2008). Experimental traumatic brain injury studies in rodents support this link between PUFAs and myelination. Following spinal cord injury, white matter damage is prevented by injection of DHA; progressive protective effects are induced over a 6-week period, including increased synaptic formation and repair and reduced myelin damage (Ward et al., 2010). In addition, dietary supplementation with EPA and DHA prior to impact acceleration brain injury reduces the number of axons positive for beta amyloid precursor protein (APP), a marker of brain injury, at 30 days post-injury, to amounts comparable to those in uninjured rodents (Mills et al., 2011). Furthermore, a PUFA-enriched diet prevents post-injury loss of myelin, preserving the integrity of the myelin sheath, and maintaining the nerve fiber conductivity (Pu et al., 2013). In a different paradigm, maternal omega-3 fatty acid supplementation protects the neonatal rat brain from white matter injury due to lipopolysaccharide exposure (Tuzun et al., 2012).

Evidence from human populations also indicates a relationship between PUFA and myelination. In elderly people, dietary intake of fish with higher EPA and DHA concentrations was prospectively linked over a five-year interval to fewer sub-clinical infarcts and fewer white matter abnormalities on MRI (Virtanen et al., 2008), and plasma DHA levels were inversely associated with white matter hyperintensity volumes (a marker of white matter damage) and cognitive impairments, although inexplicably, depression weakened the association (Bowman et al., 2012). In a small ($n = 16$) prospective open intervention study of multiple sclerosis patients, dietary advice and omega-3 PUFA supplementation plus vitamins resulted in higher plasma omega-3 PUFA levels and a lower rate of exacerbations and decreased disability over a two-year period (Nordvik et al., 2000). EPA administration also has been found to reduce brain atrophy over 6–9 months in one case of a treatment-

resistant depressed patient (Puri et al., 2001) and in a small placebo-controlled study in patients with advanced Huntington's disease (Puri et al., 2002).

4.1. Limitations

Our findings should be interpreted cautiously in view of the small sample size of this study, although this is mitigated to some extent by its within-subject, prospective study design. The prospective nature of the study suggests that white matter changes are due to fish oil supplementation; however, we note that due to the lack of placebo group, we cannot rule out some other factor at work. Some group differences in PUFA and FA may have been undetected due to low statistical power. We were not able to parse out possible effects of medications taken by 3 patients in this small sample. The range of participants' ages is relatively narrow, so these results may not apply to older or younger populations. PUFA determinations were not made on the day of the DTI, which may add noise to the data. Dietary absorption might be affected by different formulations of omega-3 PUFAs, e.g. the bioavailability of triglyceride-associated PUFAs predominant in fish oil is reportedly lower than phosphoglyceride-associated PUFAs in as in krill oil (Kohler et al., 2015). However, krill meal, which also contains DHA and EPA bound to phospholipids, has similar bioavailability to fish oil, suggesting the triglyceride-phospholipid difference may not be the main arbiter of absorption (Kohler et al., 2015). Free (unesterified) fatty acids also have been suggested to have superior bioavailability (Davidson et al., 2012) but are a target for oxidation that may result in breakdown and in gastrointestinal side-effects (Schuchardt and Hahn, 2013). Other factors influencing bioavailability include food consumed with the supplements, matrix effects (e.g. capsule composition) and galenic formulation (oils vs. emulsion) (Schuchardt and Hahn, 2013). The relative importance of these factors for delivery of PUFAs into brain is unknown, as the primary circulatory carriers, lipoproteins and albumin, transport omega-3 PUFAs derived from both triglycerides and phospholipids [reviewed in (Liu et al., 2015)]. There is an inexact correspondence between plasma and brain concentrations, due to unmeasured effects of the blood–brain barrier. Different results might be obtained if PUFA status were assessed with different measures, such as plasma or erythrocyte levels, unesterified state, or percentage of total omega-3 PUFAs.

5. Conclusions

Our observations replicate previous findings that corpus callosum and anterior corona radiata are regions of vulnerability in MDD (Cole et al., 2012), and suggest that omega-3 PUFA supplements have restorative effects on white matter integrity that may relate to antidepressant efficacy in some patients. Additional, larger placebo-controlled studies are needed to replicate these findings and test whether omega-3 PUFA-induced enhancement of white matter integrity can cause improvements in specific depression symptoms such as cognitive deficits.

Conflicts of interest

Drs. Mann and Oquendo receive royalties for commercial use of the C-SSRS from the Research foundation for Mental Hygiene. Dr. Mann received past unrelated grants from Novartis and GSK. Dr. Oquendo received unrestricted educational grants and/or lecture fees from Astra-Zeneca, Bristol-Meyers Squibb, Eli Lilly, Janssen, Otsuka, Pfizer, Sanofi-Aventis, and Shire as well as financial compensation from Pfizer for the safety evaluation of a clinical facility, unrelated to the current manuscript. In addition, Dr. Oquendo's family owns stock in Bristol Myers Squibb. Other authors have no conflicts of interest to report.

Contributors

Mr. Chhetry and Ms. Hezghia contributed equally. Mr. Chhetry performed the image analyses and wrote the methods and results sections. Ms. Hezghia performed the literature search and wrote the first draft. Dr. Miller oversaw the image analysis and participated in interpretation of results. Dr. Lee was the statistician. Mr. Rubin-Falcone performed portions of the image analysis and wrote portions of the methods text. Mr. Cooper performed the biochemical analyses. Research participants were assessed through Dr. Oquendo's comprehensive assessment protocol, and Drs. Oquendo and Mann participated in interpretation of results. Dr. Sublette was the PI on the imaging protocol and oversaw project implementation, data analysis and interpretation. All authors participated in writing or critically reading, and editing of the manuscript.

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These data were presented previously as a poster at the 2014 Society for Biological Psychiatry Conference. Dr. Dongrong Xu performed a much-appreciated critical reading of the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2015.12.007.

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