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Plasma Polyunsaturated Fatty Acids and Regional Cerebral Glucose Metabolism in Major Depression

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Abstract

Deficiencies in polyunsaturated essential fatty acids (PUFA) are implicated in mood disorders, although mechanisms of action and regional specificity in the brain are unknown. We hypothesized that plasma phospholipid PUFA levels are correlated with regionally specific relative cerebral metabolic rates of glucose (rCMRglu). 29 medication-free depressed subjects were studied using [^{18}F]-fluoro-2-deoxyglucose positron emission tomography. Docosahexaenoic acid (22:6n-3), arachidonic acid (20:4n-6), and eicosapentaenoic acid (20:5n-3) were assessed as a percentage of total phospholipid PUFA (DHA%, AA%, EPA%, respectively). DHA% and AA% correlated positively with rCMRglu in temporoparietal cortex. In addition, DHA% correlated negatively with rCMRglu in prefrontal cortex and anterior cingulate. No correlations were seen with EPA%. Thus, under conditions of low plasma DHA, rCMRglu was higher in temporoparietal cortex and lower in anterior cingulate/prefrontal cortex. Opposing effects of DHA on these regions is a hypothesis that could be addressed in future prospective studies with n-3 supplementation. This pilot study is the first to demonstrate fatty acid- and regionally specific correlations in the brain between plasma PUFA and rCMRglu in humans.

INTRODUCTION

The major brain species of essential polyunsaturated fatty acids (PUFA) are docosahexaenoate (DHA, 22:6n-3) and arachidonate (AA, 20:4n-6). DHA, in particular, is important for normal brain development [1,2] and mature brain functioning [3]. Abnormal levels of PUFA also are implicated in mood disorders. Depressive episodes are associated with lower blood levels of n-3 PUFA in Major Depressive Disorder (MDD) [4–8] and Bipolar Disorder (BD) [9]. Higher ratios of n-6 to n-3 fatty acids are seen in MDD [4,6,10], in suicide attempters [11,12], in first-degree relatives of patients with BD [13], and in correlation with severity of manic symptoms [14]. Levels of n-6 fatty acid AA metabolites (prostaglandins) also are higher in MDD [15–19]. A functional opposition of n-3 and n-6 PUFA in mood disorders [20] is consistent with

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competition of n-3 and n-6 in regard to a number of biochemical processes [21,22], including long-chain PUFA production from precursors, breakdown to active metabolites, and membrane insertion. Meta-analysis of randomized controlled trials of EPA and DHA supplements in major depression found a large treatment effect size, as reported in treatment recommendations for n-3 fatty acids issued by the American Psychiatric Association. [23]

Although PUFA play a vital role in brain structure and performance, only a few studies have examined relationships between PUFA status and human brain functioning in healthy volunteers [24–28] or in subjects with mood disorders [29–33]. We therefore performed an exploratory study of correlations between plasma DHA and AA levels and rCMRglu in medication-free depressed adult subjects. Eicosapentaenoate (EPA, 20:5n-3) was included as a control, since EPA is a plasma precursor to DHA that is not found in brain in significant amounts. In designing the study, we made the assumption that DHA and AA are each in a steady-state equilibrium between plasma and brain, as brain DHA and AA levels come from circulating DHA and AA entering the brain, equaling their rate of consumption therein [34]. Synthesis of DHA and AA from precursors in the brain is minimal even under conditions of deficiency [34,35]. Dietary deficiency of n-3 PUFA has been shown to differentially alter regional brain PUFA concentrations in rats: frontal cortex [36–38] and temporal lobe [37] were among the regions with the largest depletion of DHA. In postmortem infants, erythrocyte membrane PUFA levels correlate positively with brain PUFA levels [39].

We further assumed that PUFA can influence brain functioning in part through effects on glucose utilization in a regionally specific manner, since rats on a diet low in n-3 PUFA exhibited 30–50% decreases in DHA in membrane phospholipids and a 30% decrease in relative regional cerebral glucose utilization (rCMRglu) in brain regions studied (fronto-parietal cortex, hippocampus and suprachiasmatic nucleus). [40] Furthermore, in primary cultures of astrocytes from neonatal mice, AA, but not palmitic or arachidic acids, had a time- and concentration-dependent effect of increasing 2-deoxy-D-[1-3H]glucose uptake. [41] One potential mechanism for effects of PUFA deficiency on brain glucose metabolism is post-transcriptional reduction of glucose transport: n-3 deficient rats exhibited decreased immunoreactivity of the glucose transporter GLUT1 but not the corresponding mRNA message in cerebral cortex homogenates and brain microvessels. [42] GLUT1 mediates glucose uptake into astrocytes, where glucose is metabolized to lactate that, upon release, forms the primary energy substrate utilized by neurons. [43]

The primary objective for using this correlative paradigm in a limited sample was to identify brain regions vulnerable to dietary deficiencies in PUFAs. Our hypothesis was that lower levels of DHA would correlate with glucose metabolism in brain circuits known to be implicated in the pathophysiology of depression. Although erythrocyte PUFA levels provide a more long-term measure of subjects' nutritional state, we studied plasma phospholipid PUFA for a cross-sectional assessment of PUFA dietary status, an approach that has been successfully utilized in animal and human studies [4,6,44].

MATERIALS AND METHODS

All subjects (N=29) gave written informed consent as approved by the Institutional Review Board of the New York State Psychiatric Institute, Columbia University. They were drawn from patients presenting for evaluation and treatment for depression in the context of a research study of the biology of mood disorders. At study entry, subjects met DSM-IV criteria [45] for a current major depressive episode in context of major depressive disorder (N=23) or bipolar disorder (N=6) based on the Structured Clinical Interview for DSM-IV [46], with scores greater than 15 on the clinician-rated 17-item Hamilton Depression Rating Scale (HDRS) [47,48]. Subjects also completed the Beck Depression Inventory (BDI) [49], a subjective self-

assessment of depression severity. Subjects were free of medical illness based on history, physical examination and laboratory tests and had not taken psychotropic medications for at least 14 days prior to PET studies (6 weeks for fluoxetine and 4 weeks for oral antipsychotics) with the exception of lorazepam, which could be taken for up to 3 mg daily during the washout phase, but not in the 3 days before scanning. We note that some subjects have been included in other FDG-PET studies with different objectives [12,50–54].

Baseline fasting plasma samples were drawn before 10 AM on the day of the PET scan, stored at −80°C, and shipped on dry ice to the National Institute of Mental Health, where levels were determined for PUFA in phospholipids according to the following protocol. Total plasma lipids were extracted by a method modified from Folch and colleagues [55]. Samples were aliquoted into 2 mL $CHCl_3$, 1 mL BHT-MeOH, and a known quantity of 23:0 methyl ester as an internal standard. One milliliter of 0.2 mol/L Na_2HPO_4 was added after brief vortexing. The samples were capped under N_2 and vortexed again. After centrifugation, $CHCl_3$ was removed and dried under N_2. Total plasma phospholipids were separated using solid phase extraction as previously described [56]. The phospholipid fraction was methylated with BF_3-MeOH for 60 min [57]. Samples were kept cold and under N_2 throughout analysis to prevent oxidation. Gas chromatography was performed on a Hewlett-Packard (HP) 5890 series II with a flame ionization detector, an autosampler, and a FFAP capillary column (J&W Scientific). Peaks were identified using authentic standards (NuChek Prep, Elysian, MN). Fatty acids were quantified by comparison to peak areas of the 23:0 internal standard. When subjected to thawing and refreezing, within- and between-run coefficients of variance were less than 0.3% and 5%, respectively.

Before entering the scanner, subjects gazed at a uniform visual stimulus (cross hairs) in a dimmed, quiet room during the first 15 min of the 45 min ^{18}FDG distribution phase. After another 15 minutes of resting quietly, they were transferred to the scanner, where they lay supine. The head was positioned with the lowest scanning plane parallel to and approximately 1.0 cm above the canthomeatal line. Head movement was minimized with an individually customized thermoplastic mask. A Siemens ECAT EXACT 47 scanner (in plane spatial resolution 5.8 mm, axial resolution 4.3 mm FWHM at center) acquired a 60-min emission scan in 2D mode as a series of twelve 5-min frames. The attenuation correction was based on a 15-min ^{68}Ge/^{68}Ga transmission scan. Images were reconstructed with a Shepp radial filter, cutoff frequency of 35 and a ramp axial filter, cutoff frequency of 0.5.

Image preprocessing included automated image coregistration [58] to align the 12 frames within each PET scan [59] that were then summed and transformed into MNI standard stereotaxic atlas space. Each image was smoothed by applying an isotropic 12 mm Gaussian kernel, to increase the signal to noise ratio.

To control for between-subject differences in total PUFA, we measured DHA, AA, and EPA as a percentage of total phospholipid PUFA (DHA%, AA%, EPA%). Statistical analyses of associations between individual PUFA and relevant demographic and clinical characteristics were conducted using SPSS Version 11.0.1 for Mac OS X (Chicago: SPSS Inc). Continuous demographic/clinical variables were independently tested for correlation with initial levels of DHA%, AA%, EPA%, using Pearson's r; for each categorical variable, differences between PUFA means were independently tested using Student's t.

Independent, voxel-level analyses were performed to determine correlations between rCMRglu and DHA%, AA%, and EPA%, with adjustment for nuisance variables that correlated with or trended toward correlation with individual PUFA concentrations: age, sex, and diagnosis (MDD vs. BD). Analyses were performed using the general linear model with Statistical Parametric Mapping (SPM2; Institute of Neurology, University College of London, London,

England) implemented in Matlab 6.5, Release 13, service pack 1 (The Mathworks Inc, Natick, Mass) [60]. Global normalization with proportional scaling was applied to control for global cerebral rates of glucose metabolism and other global effects. For all analyses, voxel intensity and cluster extent thresholds were set *a priori* to P<0.01 and P<0.05, respectively, after correction for multiple comparisons by SPM. In some *post-hoc* exploratory analyses, cluster extent (but not voxel intensity) thresholds were relaxed as described in the text in order to detect additional trends. All SPM analyses included diagnosis (MDD vs BD), sex, and age as covariates/cofactors. No adjustments were made for smoking status or body mass index, neither of which correlated with PUFA levels. As described above, results were corrected for multiple comparisons of the voxel-wide analyses, but they were not further corrected for multiple analyses with individual PUFA, since lipid variables are not independent. Regional labelling was accomplished using the SPM-generated MNI coordinates for significant clusters, transformed by algorithm [61] into Talairach space and entered into the Talairach Client (University of Texas Health Science Center, San Antonio).[62]

RESULTS

Clinical Outcomes

Observed mean plasma PUFA levels (μg/ml ± SD) were as follows: total phospholipid fatty acids, 1040.2 ± 217.0; DHA, 36.9 ± 15.9; AA, 113.6 ± 34.6; EPA, 6.6 ± 3.0. Total plasma phospholipid PUFA correlated with individual PUFA: DHA, $r = 0.71$, $p < 0.000$; AA, $r = 0.85$, $p < 0.000$; EPA, $r = 0.53$, $p = 0.003$; this potential confound was controlled for by expressing individual PUFA as a percentage of total PUFA. Observed mean percentages of total phospholipid fatty acids were: DHA% 3.4 ± 1.2; AA% 10.8 ± 2.0; EPA% 0.6 ± 0.2.

Associations between potentially relevant demographic and clinical characteristics and PUFA nutritional status are shown in Table 1. Patients were moderately depressed at study entry and time of scan; neither self-reported (BDI) nor clinician-evaluated (HDRS) measures of depression correlated with any PUFA levels. DHA% and AA%, but not EPA% correlated positively with age and showed a trend associated with sex: DHA% higher in males, AA% higher in females. DHA% was lower in subjects with bipolar disorder compared with MDD. Smoking has been shown to cause degradation of fatty acids [63] and has been associated with reduction in serum fatty acid levels [64]; however, plasma phospholipid levels of DHA% or AA% did not differ between smokers and nonsmokers in this study. Body mass index did not correlate with any fatty acid measures. Based on these findings, we therefore included age and diagnosis as covariates of no interest (nuisance variables) in the statistical parametric analyses; although an association with sex was only a trend, we chose the conservative approach of adjusting for it as well.

FDG-PET

Statistical parametric mapping results of PUFA correlations with rCMRglu (after adjustment for age, sex, and diagnosis and SPM correction for multiple comparisons) are presented graphically in Figure 1 and summarized in Table 2. Both AA% and DHA% correlated positively with rCMRglu in an area of right temporoparietal cortex that included precentral gyrus, superior temporal gyrus, and inferior parietal lobule. The correlated cluster extent (number of voxels) was about five times greater for AA% compared with DHA%, extending to include inferior frontal, fusiform, inferior temporal, inferior frontal, middle temporal, postcentral and lingual gyri; insula, posterior cingulate, claustrum, and bilateral cerebellum. AA% also correlated positively with rCMRglu in left superior and middle temporal gyri. There was no left-sided positive correlation of rCMRglu with DHA% at *a priori* significance thresholds. However, when the cluster extent significance threshold was lowered *post-hoc* to $p_{corrected} < 0.5$ ($p_{corrected}$ = p after correction for multiple comparisons), with voxel intensity

threshold maintained at $p_{corrected}$=0.01, positive correlation was found in the corresponding left precentral and superior temporal gyri (data not shown). There were no negative correlations of rCMRglu with AA%. However, DHA% correlated negatively with rCMRglu in left anterior cingulate, middle frontal, and inferior frontal gyri. At the less stringent significance for cluster extent threshold ($p_{corrected}$ <0.5), the negative correlation between DHA% and rCMRglu in anterior cingulate was also bilateral. As expected, neither positive nor negative correlations were seen with EPA%.

DISCUSSION AND CONCLUSIONS

This is the first study in depressed human subjects to examine the relationship between plasma levels of fatty acids known to have clinical effects on mood and the *in vivo* glucose metabolism of brain regions implicated in emotion processing. Currently there is significant interest in optimizing the levels and ratios of distinct subtypes of PUFA in depressed subjects, given the increasing usage of n-3 supplementation. We sought to identify neural targets for future research into PUFA effects on cognition and emotion regulation, by identifying specific brain regions that may be uniquely vulnerable to PUFA deficiencies. Results can be used to design region-specific cognitive tasks that can further refine our understanding of the impact of PUFAs on cognitive and emotional functioning.

We found that temporoparietal glucose usage correlated positively with both DHA% and AA %, indicating that individuals with lower PUFA levels have relative glucose hypometabolism in this region. Functions of the superior temporal gyrus include auditory processing [65], error processing in response inhibition tasks [66] and decision-making [67]. These effects may be mediated through connectivity with the limbic system [68,69], possibly by evaluating the emotional significance of auditory stimuli [70]. In humans, lower erythrocyte DHA correlates with lower scores on the Mini-Mental State Exam among Alzheimer's patients [71], while supplementation with DHA plus AA improves cognitive functioning in patients with MCI [72]. Prospective studies can be used in the future to test the hypothesis emerging from our findings, that low fatty acids may have an effect on depression-related cognitive problems, such as conflict resolution and decision-making, via decreased glucose metabolism in temporoparietal cortex.

We also observed that DHA% but not AA% correlated negatively with rCMRglu in frontal cortex and anterior cingulate; that is, subjects with low DHA% had relative glucose hypermetabolism in these areas. Speculatively, if DHA has inhibitory effects in the anterior cingulate and areas of prefrontal cortex, then DHA deficiency could result in disinhibition of these regions, both of which have been implicated in regional brain studies of MDD (reviewed in [73]). Previous research suggests these regions may be particularly sensitive to PUFA concentrations: 1) Postmortem studies of orbitofrontal cortex found lower DHA content in females with MDD [32] and lower DHA and AA content in subjects of both sexes with BD [33] compared with age-matched normal controls. 2) In healthy volunteers, higher dietary intake of DHA and EPA was associated with regionally-specific higher gray matter volume in the subgenual anterior cingulate, as well as in right amygdala and right hippocampus. [28]

The observed positive temporoparietal correlation and negative anterior cingulate/prefrontal correlation of rCMRglu with DHA% could indicate cross-talk between these regions. Superior temporal gyrus is known from animal studies to have neuroanatomical connections with anterior cingulate/prefrontal cortex [69,74–79]. Functional connectivity analyses in primates also have shown that prefrontal cortex exerts inhibitory control over temporal cortex [77,80]. The opposite directionality of the correlative effects we observed in these regions is consistent with human studies in which increased prefrontal cortical activity is coincident with decreased

temporal cortical activity in patients with prefrontal cortical lesions [81,82] and in patients with schizophrenia [83,84].

With regard to the laterality of our findings, the meaning of positive right temporoparietal correlation and negative left anterior cingulate/prefrontal correlation of rCMRglu with DHA % is unclear. As the PUFA/rCMRglu correlations were bilateral at a lower significance threshold, the apparent laterality may not have physiological importance. On the other hand, laterality of anatomy and function has been proposed to be a characteristic of the healthy brain that is diminished in conditions of n-3 PUFA deficiency, as observed in rat striatum. [85] Our findings are consistent with this notion, as the correlative effects indicate that the greater the concentrations of PUFAs, the greater the unilateral regional changes in rCMRglu. This particular contralateral regional pairing also has been observed in context of structural changes in subjects with remitted geriatric depression, who were found to have smaller volumes of right middle temporal gyrus and larger left cingulate gyrus volumes. [86]

The lack of correlations with EPA% was expected, as EPA is not expressed in appreciable amounts in brain and therefore acted as a control for spurious findings. Since there was no comparison group, it was not possible to determine whether the observed associations are specifically related to mood disorders. However, the anterior cingulate-prefrontal cortical circuitry has repeatedly been implicated in mood regulation [51,87–91], including Brodmann area 32 [51,54,89,92], a region negatively correlated with DHA% in our study.

The study employed a between-subjects, rather than a between-groups, design, for two reasons. First, the primary hypothesis was parametric rather than categorical: that as dietary levels of PUFA increased, changes in glucose usage would vary in a PUFA subtype-specific way in brain regions known to mediate depression. A categorical comparison of depressed to non-depressed subjects would have obscured these more nuanced findings. Second, evidence supports the hypothesis that the brains of depressed patients are different, even after recovery from depression, from never-depressed healthy subjects.[93,94] Differences in activity found in a categorical comparison of these two groups might reasonably be ascribed to baseline differences rather than PUFA levels. To improve interpretability of this initial study, we therefore used correlation between ecologically valid parametric variation in PUFA levels and glucose utilization in a relatively monolithic population, although we acknowledge that within major depression, clinical and biological heterogeneity exists.

Given our findings that PUFA status is correlated with regional brain glucose utilization, additional studies are warranted to compare PUFA-rCMRglu associations in depressed subjects *vs.* healthy volunteers, since PUFAs have been implicated in the etiology and treatment of depression [4–20]. Another interesting approach would be exploration of associations between PUFA status, rCMRglu, and clinical characteristics such as depression subtype, severity and suicidal ideation. Future studies should also consider associations with other neurobiological systems related to depression. Especially promising targets for study are the monoaminergic and hypothalamic-pituitary-adrenal axis (HPA) systems, as they are functionally linked with each other, with depression etiology, and with PUFA metabolism. [95,96]

As the results of this study are correlational, they do not demonstrate causal relationships among the variables. Thus, one possible meaning of our findings is that peripheral PUFA concentrations affect regional brain function. However, alternative explanations are that brain activity is affecting peripheral PUFA levels, or that both PUFA levels and rCMRglu are changing in response to an unknown third variable. As an example of the second hypothesis, limbic system activity could trigger HPA axis activation, which is known to have effects on fatty acid desaturase genes [97], and could thus regulate peripheral production of highly

unsaturated fatty acids from precursors. If this was the case, we might have observed changes in the EPA/rCMRglu correlations; however, lack of EPA effects does not prove that other PUFAs were not affected in this way. Dietary assessments were not performed in this study; therefore, this study does not address whether differences in subject plasma PUFA levels are due to dietary intake or metabolic differences [98]. In this study, we limited our objectives *a priori* to the study of specific polyunsaturated fatty acids on the basis of their probable clinical significance for depression. However, it would be useful in future studies to examine the full complement of PUFA in relation to regional brain activity.

Conclusions

This is the first study utilizing FDG-PET to explore relationships between plasma levels of essential PUFA and regional human brain activity during a major depressive episode. Correlations were seen between plasma PUFA levels and rCMRglu in regions including prefrontal cortex, cingulate gyrus, and temporoparietal cortex, brain regions that have been previously implicated as key players in the neurocircuitry of depression. Some distinct differences between DHA% and AA% correlational patterns were observed. Taken together, these findings suggest that future neuroimaging studies are warranted, to prospectively examine effects of n-3 supplementation on rCMRglu in depressed and healthy individuals.

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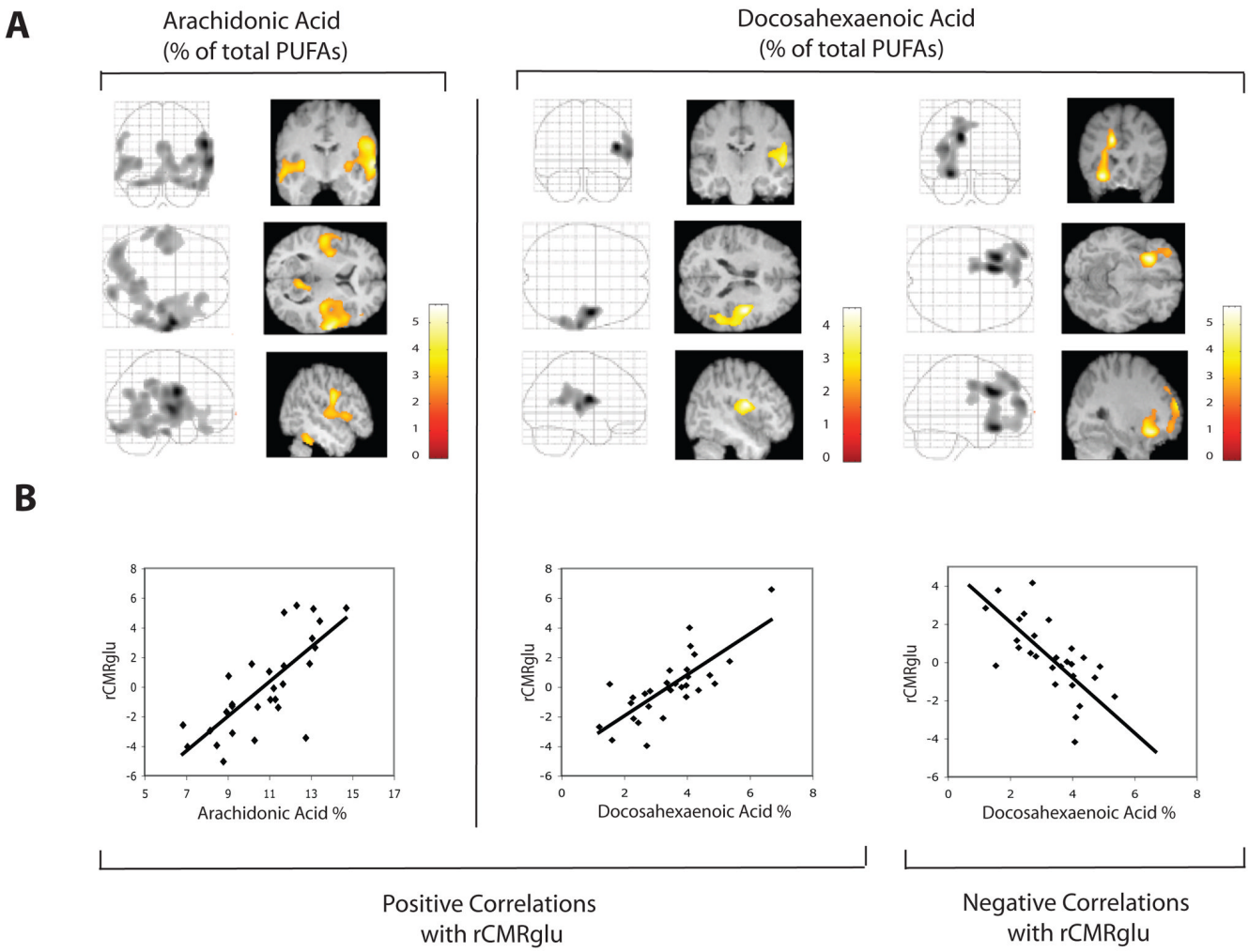

Figure 1. Statistical parametric maps of regional cerebral metabolic rates of glucose metabolism correlated with plasma polyunsaturated fatty acid levels

Regional cerebral metabolic rates of glucose metabolism (rCMRglu) are shown correlated with plasma phospholipid docosahexaenoate and arachidonate as a percentage (DHA%, EPA%) of total phospholipid polyunsaturated fatty acids (PUFA). All analyses have been corrected for global cerebral rates of glucose metabolism, age, diagnosis (Major Depressive or Bipolar Disorder), and sex. **A.** Correlations are shown in orthogonal views in a 'glass brain' format (left panels) and also as superimposed on relevant MRI slices (right panels). Color scales indicate the strength (t score) of the correlations. **B.** Correlations are graphed at the cluster global maxima for DHA% (positive, $r = 0.77$, $p = 0.0005$; negative, $r = -0.77$, $p < 0.0000$) and AA% (positive, $r = 0.75$, $p < 0.0000$).

Table 1

Relationships Between Plasma Polyunsaturated Fatty Acid Levels and Clinical/Demographic Characteristics.

Correlation of PUFA Levels (% of Total Phospholipid FA) with Characteristic				
Characteristic	**Mean (SD)**	**Phospholipid PUFA**	**Pearson's r**	**p**
Age yrs	41.2 (12.4)	*DHA%*	0.37	**0.05**
		AA%	0.51	**0.004**
		EPA%	0.20	0.30
BMI	26.7 (5.0)	*DHA%*	0.03	0.87
		AA%	0.06	0.77
		EPA%	0.21	0.28
HDRS score	21.2 (5.0)	*DHA%*	− 0.05	0.80
		AA%	0.10	0.61
		EPA%	− 0.14	0.47
BDI score	32.1 (9.3)	*DHA%*	− 0.17	0.38
		AA%	0.04	0.85
		EPA%	− 0.14	0.48

Phospholipid PUFA Levels (% of Total Phospholipid FA) by Characteristic Status							
			Mean PUFA Level				
	N(%)	***PUFA***	***MDD***	***BD***	***t***	***df***	***p***
MDD (vs. BD)	23 (79)	*DHA%*	3.7 (1.1)	2.4 (1.0)	2.53	27	**0.02**
		AA%	11.0 (1.8)	10.0 (2.6)	1.12	27	0.27
		EPA%	0.6 (0.2)	0.6 (0.2)	0.11	26	0.91
			Male	***Female***			
Male	14 (48)	*DHA%*	3.8 (1.2)	3.1 (1.0)	1.75	27	0.09
		AA%	10.1 (2.0)	11.4 (1.9)	−1.74	27	0.09
		EPA%	0.6 (0.2)	0.6 (0.2)	0.87	26	0.39
			Smoker	***Non-smoker***			
Smoker	11 (38)	*DHA%*	3.0 (1.2)	3.6 (1.2)	1.43	27	0.16
		AA%	10.3 (2.3)	11.1 (1.8)	1.03	27	0.31
		EPA%	0.6 (0.1)	0.6 (0.3)	0.94	26	0.35

Bolded values significant at p<0.05. Data expressed in mean (SD) or N(%) as appropriate. Individual phospholipid fatty acid values shown as a percentage of total phospholipid fatty acids. Two-tailed Student's t-tests compare mean PUFA levels for each categorical variable, in columns labelled "+/− characteristic." Abbreviations: PUFA, polyunsaturated fatty acid; BMI, body mass index; HDRS, Hamilton Depression Rating Scale (17-item); BDI, Beck Depression Inventory; FA, fatty acid; MDD, Major Depressive Disorder; BD, Bipolar Disorder; DHA, docosahexaenoate; AA, arachidonate.

Table 2

Statistical Parametric Mapping of Correlations Between Plasma Polyunsaturated Fatty Acid Levels and Regional Cerebral Glucose Metabolism.

rCMRglu Analysis	Cluster- level $P_{corrected}$	Cluster Extent (voxels)		Anatomic Locations **Cluster Maxima	Brodmann Areas
Positively correlated with AA%	<0.001	10,402	Right	Precentral Gyrus**	6, 44
			“	Superior Temporal Gyrus	13, 22, 42
			“	Postcentral Gyrus	1
			“	Inferior Temporal Gyrus	20
			“	Insula	13
			“	Inferior Parietal Lobule	40
			“	Posterior Cingulate	29, 30
			“	Inferior Frontal Gyrus	11, 47
			“	Middle Temporal Gyrus	21
			“	Occipital Lobe, Lingual Gyrus	19
			“	Claustrum	
			“	Precuneus	31
			Left	Cerebellum, Posterior Lobe, Declive, Uvula	
			“	Cerebellum, Anterior Lobe, Culmen	
			Right	Cerebellum, Posterior Lobe, Declive, Tuber	
			“	Cerebellum, Anterior Lobe, Culmen	
	0.050	1,939	Left	Superior Temporal Gyrus**	22
			“	Middle Temporal Gyrus	21
				Claustrum	
Positively correlated with DHA%	0.033	2,137	Right	Precentral Gyrus**,	6
			“	Superior Temporal Gyrus	13, 22, 42
			“	Inferior Parietal Lobule	40
Negatively correlated with DHA%	< 0.001	4,957	Left	Cingulate Gyrus**,	24, 32

rCMRglu Analysis	Cluster- level $P_{corrected}$	Cluster Extent (voxels)	Anatomic Locations **Cluster Maxima	Brodmann Areas
			“ Middle Frontal Gyrus	10, 11
			“ Inferior Frontal Gyrus	47
			“ Superior Frontal Gyrus	8

Abbreviations: rCMRglu, regional cerebral rate of glucose metabolism; DHA% and AA%, docosahexaenoate and arachidonate, respectively, as a percentage of total phospholipid fatty acids; $p_{corrected}$, p values after Statistical Parametric Analysis (SPM2) correction for multiple comparisons.