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Fatty acid composition in postmortem brains of people who completed suicide

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Objective: Cholesterol levels have been reported to be lower in suicidal patients, and alterations in blood levels of polyunsaturated fatty acids have been found in people with depression. Given that the evidence for the link between lipid metabolism and psychopathology thus far has almost exclusively hinged on alterations of these variables in blood, this study aimed to address whether similar alterations in fatty acids would be evident in the brains of people who complete suicide. **Methods:** Using gas chromatography, we measured 49 different fatty acids in the orbitofrontal cortex and the ventral prefrontal cortex of people who had completed suicide with (n = 16) and without (n = 23) major depression and in control subjects (n = 19) with no current psychopathology and whose cause of death was sudden. **Results:** Comparisons of fatty acids between the 3 groups did not reveal significant differences. **Conclusion:** Further research is required to better understand the link between fatty acids in the peripheral circulation and those in the central nervous system before determining whether fatty acids play a mediating role in suicidal behaviour.

Objectif : On a signalé des niveaux de cholestérol moins élevés chez les patients suicidaires et on a constaté des altérations des concentrations sanguines d'acides gras polyinsaturés chez les personnes atteintes de dépression. Étant donné que les preuves relatives au lien entre le métabolisme des lipides et la psychopathologie reposent jusqu'à maintenant presque exclusivement sur des altérations de ces variables du sang, l'étude visait à déterminer si des altérations semblables au niveau des acides gras seraient évidentes dans le cerveau de personnes qui se sont suicidées. **Méthodes :** Nous avons utilisé la chromatographie en phase gazeuse pour mesurer 49 acides gras différents dans le cortex orbitofrontal et le cortex préfrontal ventral de personnes qui se sont suicidées (n = 16) et de sujets (n = 23) sans dépression majeure et de sujets témoins (n = 19) qui n'avaient aucune psychopathologie courante et qui sont morts subitement. **Résultats :** Les comparaisons des acides gras entre les trois groupes n'ont pas révélé de différences significatives. **Conclusion :** Une recherche plus poussée s'impose pour mieux comprendre le lien entre les acides gras dans la circulation périphérique et ceux que l'on retrouve dans le système nerveux central avant de déterminer si les acides gras jouent un rôle de médiation dans le comportement suicidaire.

Introduction

There has been growing interest in investigating lipid metabolism in relation to normal central nervous system (CNS) development and function and in the possible role of lipid metabolism alterations in mental health problems such as suicidal behaviour and major depression (MD). Low levels of serum cholesterol have been linked to suicidality and violence in many different types of studies.[1,2] The data supporting the link come from studies correlating serum cholesterol measurements with violent or suicidal behaviours, or both, in psychiatric patients,[3–5] in people who attempt suicide[6–10] and in violent populations.[11–14] Data are derived from large cohort studies[15–20] and from studies in animals.[21–23] It remains unclear, however, how serum cholesterol might be involved in increasing the risk of suicidal or violent behaviour. It has been hypothesized that low serum cholesterol reflects reduced cholesterol content in the brain, specifically in brain cell membranes. This might impact on the serotonergic system, due to the lowering of the lipid microviscosity of the brain cell membranes.[24] Alternatively, reduced brain cholesterol might affect synaptic plasticity, because cholesterol is re-

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quired for synapse formation.[25] We previously reported our finding of significantly reduced cholesterol content in the frontal cortex of people who had completed suicide using violent, compared with nonviolent, methods.[26] This observation led us to question whether there are alterations in other lipid classes in the brains of people who had completed suicide. This is a particularly relevant question given some recent reports suggesting that polyunsaturated fatty acids (PUFAs) may play a role in suicidality.

In an epidemiological survey of 1767 subjects from the general population in Finland, those who frequently ate fish — which is a rich source of omega-3 fatty acids — were found to have a significantly lower risk of suicidal ideation compared with people who ate fish less frequently.[27] Extending the link with suicidality beyond dietary assessments to actual measures of fatty acids in the blood, Huan and colleagues[28] conducted a case-control study in China of 100 people who had attempted suicide and 100 hospital admission control subjects and found that those who had attempted suicide had significantly lower levels of omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in the total phospholipid fraction of red blood cells (RBCs). Similarly, in a study of patients with depression monitored for suicide attempt over a 2-year period, survival analysis revealed that lower proportions of omega-3 fatty acids, particularly DHA, in plasma were predictive of suicide attempt.[29] Not all studies have found a link between suicidality and fatty acids. A large cohort study of 29 133 men observed for up to 8 years did not find a link between dietary consumption of fatty acids and death from suicide.[30] Since the substantiation supporting the link between fatty acids and suicide is scarce, more research is warranted, especially considering growing evidence emphasizing the relation between fatty acids and mood disorders.

Several studies have shown a link between low blood levels of omega-3 fatty acids, or an elevated omega-6–to–omega-3 ratio, and depressive disorders, including MD, bipolar disorder and postpartum depression[31–35] (see Parker and others[36] for review). Maes and colleagues[33] found that patients with MD had higher omega-6–to–omega-3 ratios and lower omega-3 levels in serum cholesteryl ester fractions, compared with healthy control subjects. Similarly, Edwards and colleagues[32] found an association between low omega-3 levels in RBC membranes and severity of depression. Epidemiological studies worldwide have revealed inverse correlations between fish consumption and depressive disorders.[37–39] These findings have led researchers to investigate the possibility of using dietary omega-3 supplements as a treatment for depression. Double-blind randomized controlled trials of PUFA supplementation in patients with bipolar disorder or MD have typically used EPA, DHA or both as an adjunct to standard treatment, and most[40–45] — but not all[46–48] — have reported improvements in mood in the PUFA supplement groups, as reflected in reduced scores on depression rating scales. Overall, the evidence points to an association between alterations in PUFAs and depression, but it is apparent that a clearer picture of the possible mechanisms by which PUFAs might influence depressive symptoms is necessary before applying the findings to a clinical setting and concluding that supplementation is safe and effective.

As with the reported association between serum cholesterol and suicidality, it is important to address whether fatty acid alterations observed in the peripheral circulation are also evident in the brain. This has not been investigated in studies examining fatty acids in relation to either suicidality or MD, despite the suggested crucial role of omega-3 fatty acids in brain functioning.[49–51] Given what is known about the relation between cholesterol and fatty acids in the blood and given the evidence suggesting that these parameters are related to suicidality and depression, respectively, disruptions in PUFAs (particularly omega-3 and omega-6) might also be expected in the brains of people who complete suicide. We therefore measured fatty acids in brain tissue from people who had completed suicide and control subjects to explore possible fatty acid profile alterations in those who completed suicide, with and without MD.

Methods

Subjects

Brain tissue samples used in this study were obtained from the Quebec Suicide Brain Bank (QSBB) in collaboration with the Quebec Coroner's Office. We included in this study 39 men who died by suicide. Of these, 16 had a diagnosis of MD. We considered this group separately from the remaining 23 subjects who had completed suicide and who did not have MD, given the evidence linking peripheral fatty acid alterations to MD.[32–34] The control group comprised 19 men who died suddenly from causes that had no direct influence on brain tissue. Cause of death was ascertained by the coroner's office. Toxicological screening with either body fluid or tissue samples was performed to assist in determining the cause of death; thus, information on drug and alcohol use at the time of death was available for some subjects. There were no signs of prolonged agonal state in any of the deaths, nor was there any evidence of neurodegeneration or other abnormalities in any of the brains.

Psychological autopsies were performed to obtain information on psychiatric history, medical history and other relevant clinical and sociodemographic data, as previously described.[52,53] The *Structured Clinical Interview for the DSM-IV* (SCID-I)[54] was administered to 1 or more informants of the deceased. SCID-I assessments, case reports, coroner's notes and medical records were reviewed by a panel of clinicials to obtain consensus psychiatric diagnoses. Approval for this study was granted by our local institutional review board, and written informed consent was obtained from each participating family of the deceased before the subject's inclusion in the study.

Fatty acid analysis in brain tissue

Whole brains were processed and sectioned as previously outlined[55] and kept frozen at –80°C. The average period between death and brain tissue collection was approximately 25 hours. The brain tissue specimens used for the analysis of

fatty acid content were dissected from 2 regions of the frontal cortex from the left hemisphere of all subjects. Samples were obtained from the orbitofrontal cortex (Brodmann's area [BA] 11) and ventral prefrontal cortex (BA 47), because these 2 frontal cortical regions have been shown to play a role in suicidality[56]; we have reported significantly lower cholesterol content in people who used violent, compared with nonviolent, methods to complete suicide in these 2 regions.[26] A small portion of grey matter approximately 100 to 300 mg (wet weight) in size was carefully dissected at 4ºC from each frontal region and stored in a plastic vial kept at –80ºC.

Each brain tissue sample was weighed while frozen just before homogenization on ice in saline containing 0.005% (weight/volume) butylated hydroxy-toluene (BHT). An aliquot of homogenate was lipid-extracted with 2:1 chloroform:methanol (volume/volume)[57] and internal standard and BHT. The samples were agitated at room temperature for 1 hour and centrifuged; the inferior phase containing the lipid fraction was recovered and evaporated under a fine stream of nitrogen. $NaOCH_3$ was added, and the samples were left at room temperature for 30 minutes before hydrochloric acid-methanol was added. After a 5-minute wait at room temperature, boron trifluoride$_3$-methanol was added and the samples were incubated at 100°C for 20 seconds. Saline was then added. The samples were centrifuged at room temperature to recover the superior phase for analysis by gas chromatography (GC), as previously described,[58] using the Varian 8400 GC Autosampler system (Cole-Parmer, Ill., Vernon Hills), with helium as the carrier gas, a flow rate of 1.0 mL/min and a coupled flame ionization detector. The fatty acids were identified by comparison with the expected retention times of known standards and were analyzed with Galaxie Chromatography Data System software (Varian Inc., Palo Alto, Calif.). The amount of each fatty acid in the brain sample is expressed either as µmol/g (wet weight) of brain tissue or as a percentage of total fatty acids. An aliquot of homogenate was also taken for cholesterol analysis, as previously described.[26]

Statistical analyses

Differences in dichotomous variables were analyzed with Pearson's chi-squared test or Fisher's exact test, and continuous variables were compared with 1-way analysis of variance (ANOVA) or 2-tailed Student's *t* test. Pearson's correlation coefficient was used to test for correlations among continuous variables. We used SPSS version 11 to conduct statistical analyses.

Results

Table 1 shows the main characteristics of the subjects included in this study, with the people who had completed suicide divided into 2 groups according to the absence or presence of a diagnosis of MD within the 6 months before death.

In total, 49 different species of fatty acids were measured in each sample, using GC. Although the principal fatty acids of

Table 1: Subject characteristics

Characteristics	Group; no. of subjects (and %)*†		
	Control subjects (*n* = 19)	Completed suicide, no MD (*n* = 23)	Completed suicide, with MD (*n* = 16)
Mean age, yr‡	36.7 (11.5)	34.8 (10.4)	33.9 (11.0)
Postmortem interval, hr§	24.0 (6.2)	26.6 (9.7)	24.8 (6.1)
Brain tissue pH¶	6.4 (0.3)	6.3 (0.3)	6.5 (0.4)
Causes of death			
Cardiac related	11 (57.9)	—	—
Hanging	—	12 (52.2)	11 (68.8)
Car accident	5 (26.3)	—	—
CO poisoning	—	5 (21.7)	2 (12.5)
Drug overdose	2 (10.5)	2 (8.7)	1 (6.3)
Respiratory failure	1 (5.3)	—	—
Drowning	—	1 (4.3)	1 (6.3)
Cutting	1 (4.3)	—	—
Firearm	—	1 (4.3)	1 (6.3)
Present axis I diagnosis**	5 (35.7)	10 (76.9)	16 (100)
Major depression	—	—	16 (100)
Substance misuse	4 (28.6)	7 (53.8)	10 (62.5)
Past axis I diagnosis††	6 (42.9)	10 (76.9)	14 (87.5)
Major depression	3 (15.8)	—	11 (68.7)
Substance misuse	5 (35.7)	8 (61.5)	10 (62.5)
Axis II diagnosis	—	7 (53.8)	6 (37.5)

*Unless otherwise indicated.
†Percentages are given according to the number of subjects for whom the data were available.
‡$p = 0.74$.
§$p = 0.57$.
¶$p = 0.42$.
**Diagnosis of at least 1 axis I disorder within the 6 mo before death.
††Diagnosis of at least 1 axis I disorder in the past, excluding the 6 mo before death.

Table 2: Fatty acid composition in grey matter samples taken from the orbitofrontal cortex (BA 11) and ventral prefrontal cortex (BA 47) of control subjects (*n* = 19), subjects without MD who completed suicide (*n* = 23) and subjects with MD who completed suicide (*n* = 16)

	Group; mean (and SD)							
	BA 11*				BA 47*			
Fatty acid	C	S	D	*p* value	C	S	D	*p* value
7:0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)		0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	
8:0	0.08 (0.04)	0.08 (0.02)	0.10 (0.07)	0.55	0.08 (0.03)	0.08 (0.03)	0.09 (0.04)	0.35
9:0	0.13 (0.06)	0.13 (0.04)	0.15 (0.11)	0.60	0.13 (0.06)	0.12 (0.04)	0.14 (0.05)	0.73
10:0	0.74 (0.37)	0.65 (0.22)	0.75 (0.26)	0.47	0.73 (0.36)	0.72 (0.28)	0.79 (0.35)	0.80
11:0	0.05 (0.05)	0.03 (0.02)	0.05 (0.04)	0.08	0.02 (0.01)	0.02 (0.01)	0.04 (0.04)	0.09
12:0	0.22 (0.11)	0.20 (0.06)	0.22 (0.08)	0.75	0.21 (0.10)	0.21 (0.06)	0.24 (0.10)	0.51
13:0	0.06 (0.07)	0.03 (0.04)	0.10 (0.21)	0.20	0.02 (0.03)	0.02 (0.01)	0.04 (0.10)	0.26
14:0	0.63 (0.09)	0.63 (0.06)	0.67 (0.10)	0.23	0.62 (0.08)	0.62 (0.04)	0.65 (0.07)	0.35
15:0	0.15 (0.07)	0.13 (0.01)	0.14 (0.03)	0.33	0.16 (0.07)	0.14 (0.01)	0.14 (0.02)	0.30
16:0 (palmitic)	21.61 (0.90)	21.32 (1.46)	20.46 (2.54)	0.13	21.32 (1.66)	21.08 (0.96	21.22 (0.88)	0.82
17:0	0.35 (0.15)	0.32 (0.06)	0.34 (0.08)	0.60	0.36 (0.14)	0.33 (0.05)	0.35 (0.06)	0.58
18:0 (stearic)	18.92 (0.59)	18.96 (0.55)	19.09 (1.10)	0.77	18.91 (0.52)	18.83 (0.54)	19.03 (0.55)	0.52
19:0	0.06 (0.02)	0.06 (0.02)	0.06 (0.03)	0.67	0.07 (0.02)	0.06 (0.01)	0.06 (0.02)	0.39
20:0	0.10 (0.02)	0.10 (0.01)	0.13 (0.11)	0.31	0.10 (0.02)	0.10 (0.01)	0.11 (0.02)	0.78
22:0	0.07 (0.08)	0.05 (0.01)	0.06 (0.03)	0.69	0.05 (0.01)	0.05 (0.02)	0.05 (0.01)	0.99
24:0	0.68 (0.68)	0.53 (0.56)	1.02 (1.02)	0.13	0.24 (0.12)	0.41 (0.50)	0.47 (0.76)	0.39
Total saturated	43.84 (1.13)	43.20 (1.50)	43.35 (2.33)	0.37	43.04 (2.18)	42.80 (1.43)	43.42 (1.12)	0.52
11:1	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)		0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	
12:1	0.00 (0.00)	0.00 (0.00)	0.01 (0.01)	0.14	0.00 (0.00)	0.00 (0.00)	0.01 (0.01)	0.87
13:1	0.01 (0.02)	0.01 (0.01)	0.01 (0.01)	0.37	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)	0.58
14:1	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.64	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.69
15:1	0.06 (0.21)	0.02 (0.02)	0.03 (0.04)	0.46	0.02 (0.03)	0.02 (0.02)	0.03 (0.04)	0.34
16:1	1.96 (1.35)	2.01 (0.99)	1.67 (1.14)	0.65	1.99 (0.97)	2.01 (1.36)	2.05 (1.35)	0.99
17:1	0.01 (0.03)	0.01 (0.01)	0.01 (0.02)	0.60	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)	0.37
18:1n-7	3.72 (0.34)	4.09 (0.65)	3.92 (0.59)	0.10	4.25 (1.08)	4.35 (0.84)	4.09 (0.58)	0.67
18:1n-9 (oleic)	14.78 (1.47)	16.16 (3.25)	15.99 (2.06)	0.17	15.89 (5.29)	16.72 (2.73)	16.19 (1.88)	0.75
18:1n-12	0.13 (0.06)	0.15 (0.06)	0.18 (0.14)	0.32	0.14 (0.06)	0.15 (0.03)	0.15 (0.04)	0.78
20:1n-9	0.78 (0.30)	0.87 (0.48)	0.97 (0.33)	0.34	0.91 (0.53)	0.93 (0.39)	0.90 (0.33)	0.97
20:1n-12	0.04 (0.03)	0.07 (0.05)	0.06 (0.04)	0.16	0.06 (0.03)	0.05 (0.03)	0.05 (0.04)	0.69
20:1n-15	0.21 (0.89)	0.01 (0.02)	0.01 (0.02)	0.38	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)	0.52
22:1n-9	0.34 (0.64)	0.20 (0.09)	0.21 (0.12)	0.43	0.21 (0.12)	0.21 (0.07)	0.23 (0.12)	0.84
24:1n-9	0.15 (0.47)	0.06 (0.07)	0.05 (0.04)	0.46	0.03 (0.01)	0.04 (0.02)	0.04 (0.03)	0.27
Total monounsaturated	22.21 (2.27)	23.66 (4.26)	23.13 (2.79)	0.38	23.52 (6.66)	24.51 (3.64)	23.76 (2.31)	0.77
16:1T9	0.18 (0.06)	0.21 (0.12)	0.17 (0.09)	0.40	0.22 (0.12)	0.22 (0.09)	0.21 (0.06)	0.96
18:1T9	0.06 (0.03)	0.07 (0.02)	0.08 (0.05)	0.38	0.07 (0.03)	0.07 (0.01)	0.07 (0.02)	0.83
18:1T7	0.13 (0.09)	0.14 (0.08)	0.16 (0.09)	0.59	0.84 (3.18)	0.14 (0.09)	0.15 (0.08)	0.40
18:2TT	0.01 (0.00)	0.01 (0.00)	0.01 (0.01)	0.67	0.01 (0.00)	0.01 (0.00)	0.01 (0.00)	0.75
Total trans	0.37 (0.13)	0.43 (0.14)	0.41 (0.15)	0.43	1.13 (3.16)	0.43 (0.10)	0.44 (0.07)	0.40
18:3n-3 (ALA)	0.06 (0.04)	0.10 (0.19)	0.07 (0.03)	0.63	0.07 (0.07)	0.07 (0.03)	0.08 (0.04)	0.74
20:3n-3	0.02 (0.03)	0.01 (0.02)	0.03 (0.04)	0.11	0.01 (0.01)	0.01 (0.02)	0.01 (0.02)	0.96
20:5n-3 (EPA)	0.03 (0.01)	0.04 (0.04)	0.03 (0.02)	0.78	0.03 (0.03)	0.03 (0.02)	0.03 (0.01)	0.74
22:3n-3	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)		0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	
22:5n-3	0.42 (0.09)	0.41 (0.11)	0.42 (0.10)	0.93	0.38 (0.09)	0.38 (0.08)	0.40 (0.06)	0.89
22:6n-3 (DHA)	15.12 (1.09)	14.48 (2.42)	14.64 (2.17)	0.58	14.42 (2.99)	14.66 (2.28)	14.77 (1.54)	0.90
Total omega-3	15.65 (1.09)	15.03 (2.49)	15.19 (2.15)	0.61	14.92 (3.09)	15.14 (2.34)	15.28 (1.57)	0.91
18:2n-6 (LA)	0.62 (0.12)	0.61 (0.11)	0.66 (0.21)	0.57	0.66 (0.19)	0.63 (0.13)	0.64 (0.07)	0.79
18:3n-6	0.03 (0.03)	0.01 (0.01)	0.04 (0.07)	0.12	0.02 (0.03)	0.01 (0.02)	0.03 (0.05)	0.23
20:2n-6	0.34 (0.58)	0.29 (0.54)	0.28 (0.47)	0.92	0.11 (0.03)	0.11 (0.03)	0.11 (0.05)	0.77
20:3n-6	0.87 (0.14)	0.86 (0.16)	0.95 (0.13)	0.18	0.84 (0.15)	0.83 (0.15)	0.90 (0.13)	0.28
20:4n-6 (AA)	9.63 (0.77)	9.29 (1.06)	9.41 (1.25)	0.57	9.21 (1.16)	9.05 (0.79)	9.08 (0.60)	0.82
22:2n-6	0.02 (0.01)	0.04 (0.05)	0.02 (0.02)	0.10	0.03 (0.02)	0.03 (0.02)	0.03 (0.02)	0.80
22:4n-6 (DTA)	6.22 (0.36)	6.38 (0.52)	6.38 (0.48)	0.50	6.32 (0.84)	6.24 (0.55)	6.10 (0.41)	0.58
Total omega-6	17.73 (1.34)	17.47 (1.13)	17.73 (1.64)	0.78	17.18 (1.04)	16.90 (0.95)	16.90 (0.77)	0.56
20:3n-9 (ETA)	0.19 (0.03)	0.21 (0.05)	0.19 (0.03)	0.16	0.21 (0.05)	0.21 (0.05)	0.20 (0.05)	0.77
Total polyunsaturated	33.57 (1.72)	32.71 (2.99)	33.11 (3.24)	0.60	32.32 (3.45)	32.25 (2.36)	32.38 (1.66)	0.99
Total FA μM/g brain	1031715 (120558)	1015712 (174385)	1029297 (200593)	0.95	1096350 (164122)	1050181 (166827)	1038491 (121144)	0.49

BA = Brodmann's area; MD = major depression; SD = standard deviation; C = control subjects; S = people without MD who completed suicide; D = subjects with MD who completed suicide; ALA = alpha-linolenic acid; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; LA = linoleic acid; AA = arachidonic acid; DTA = docosatetraenoic acid; ETA = eicosatrienoic acid; FA = fatty acid.
*Values for fatty acids are expressed as a percentage of the grand total of all fatty acids measured, except in the final row, where the mean total of all fatty acids measured is given as micromoles per gram (wet weight) of brain tissue for each group.

interest were the omega-3 and omega-6 PUFAs, statistical comparisons were performed for all the fatty acids measured. No significant differences were found for any of these fatty acids when compared among control subjects, people who had completed suicide without MD and those who had MD and who completed suicide for either of the 2 brain regions examined (Table 2). No significant differences were revealed when the 2 suicide groups (with and without MD) were combined and then compared with control subjects (data not shown). Table 2 summarizes the values for the different fatty acids measured, and Table 3 compares relevant fatty acid ratios and desaturase activity indices.

In view of the association that has been reported among depression, cardiovascular disease and low levels of omega-3 fatty acids,[59] we considered that any alterations in fatty acids in people with MD who completed suicide might be masked owing to similar alterations that could be present among the control subjects who died from cardiac-related problems. To test for this, the control group was divided into 2 groups according to the cause of death: cardiac related (n = 11) and noncardiac related (n = 8). Fatty acids measured in each brain region were compared between the 2 control group subsets, and the same set of ANOVA comparisons summarized in Table 2 were repeated. None of these comparisons revealed any significant differences between groups (data not shown), suggesting that the cardiac-related deaths in the control group would not confound the results.

Other potential confounders, such as age and postmortem interval, were also considered, and these variables were not found to significantly differ between the groups (Table 1). Further, correlations of age and postmortem interval with measures of the total fatty acids did not reveal any significant associations among these variables in both BA 11 (age r = –0.07, p = 0.60; PMI r = 0.05, p = 0.73) and BA 47 (age r = 0.11, p = 0.41; PMI r = –0.21, p = 0.14).

We obtained measures of the cholesterol content for each subject in both brain regions to determine whether there is a relation between fatty acids and cholesterol in the brain. Analyses revealed highly significant correlations between total cholesterol and total fatty acids in both BA 11 (Fig. 1) and BA 47 (Fig. 2).

Toxicological assessments revealing the presence of alcohol or drugs were found for too few subjects to make meaningful comparisons of the effects of these substances on fatty acid profiles. Exploratory comparisons of groups classified according to the presence or absence of a past or current diagnosis of alcohol or drug abuse or dependence, or axis II diagnosis (irrespective of subject status) did not reveal any significant associations between these diagnoses and fatty acids (data not shown).

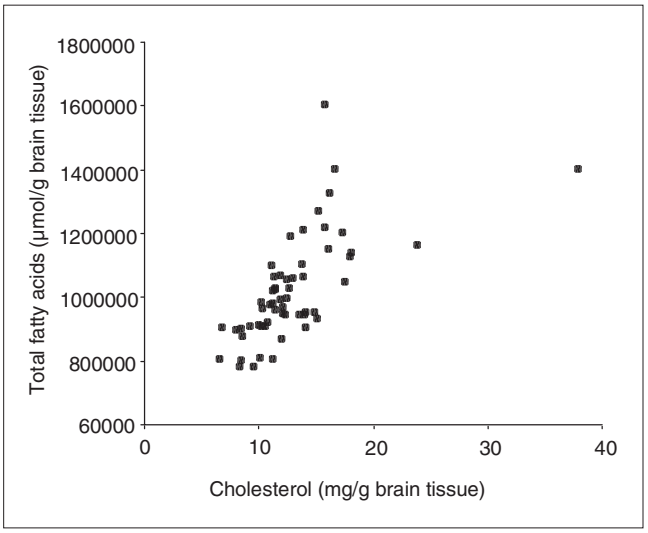

Fig. 1: Relation between total fatty acids and cholesterol in the orbitofrontal cortex (BA 11) for all subjects (n = 58). Significant correlation: r = 0.657, p < 0.0005. BA = Brodmann's area.

Table 3: Fattty acid ratios and desaturase activity indices in grey matter samples from the orbitofrontal cortex (BA 11) and ventral prefrontal cortex (BA 47) of control subjects (n = 19), subjects without MD who completed suicide (n = 23) and subjects with MD who completed suicide (n = 16)

	Group; mean (and SD)							
	BA 11				BA 47			
FA ratio or desaturase AI	C	S	D	p value	C	S	D	p value
Polyunsaturated/saturated	0.77 (0.04)	0.76 (0.05)	0.77 (0.1)	0.84	0.75 (0.06)	0.75 (0.04)	0.75 (0.04)	0.89
omega-6/omega-3	1.14 (0.12)	1.21 (0.32)	1.19 (0.17)	0.61	1.25 (0.57)	1.15 (0.26)	1.12 (0.14)	0.52
EFA/non-EFA	0.01 (0.001)	0.01 (0.002)	0.01 (0.002)	0.82	0.01 (0.003)	0.01 (0.001)	0.01 (0.001)	0.76
ALA/LA	0.1 (0.05)	0.17 (0.33)	0.11 (0.04)	0.57	0.1 (0.05)	0.1 (0.04)	0.12 (0.06)	0.64
ALA/EPA	2.29 (1.74)	2.39 (1.12)	2.46 (1.27)	0.94	3.06 (2.05)	2.79 (1.11)	3.39 (1.78)	0.54
EPA/DHA	0.002 (0.001)	0.003 (0.003)	0.002 (0.001)	0.72	0.007 (0.003)	0.007 (0.001)	0.007 (0.001)	0.73
DHA/AA	1.58 (0.17)	1.56 (0.21)	1.56 (0.17)	0.91	1.55 (0.26)	1.62 (0.25)	1.63 (0.16)	0.55
ETA/AA	0.02 (0.003)	0.02 (0.007	0.02 (0.004)	0.07	0.02 (0.01)	0.02 (0.007)	0.02 (0.007)	0.75
Δ6 desaturase AI = 20:3n-6/18:2n-6	1.47 (0.42)	1.47 (0.36)	1.52 (0.34)	0.88	1.38 (0.51)	1.37 (0.34)	1.40 (0.21)	0.95
Δ9 desaturase AI = 18:1n-9/18:0	0.78 (0.08)	0.86 (0.19)	0.84 (0.11)	0.23	0.89 (0.22)	0.89 (0.15)	0.85 (0.10)	0.72

BA = Brodmann's area; MD = major depression; SD = standard deviation; FA = fatty acid; AI = activity index; C = control subjects; S = subjects without MD who completed suicide; D = subjects with MD who completed suicide; EFA = essential fatty acids; ALA = alpha-linolenic acid; LA = linoleic acid; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; ETA = eicosatrienoic acid; AA = arachidonic acid.

Discussion

We measured fatty acids in brain tissue from people who had completed suicide partly as a follow-up to our study of cholesterol content in the brains of people who had completed suicide; we also wanted to investigate the relation among PUFAs, depression and suicidality beyond correlational studies in blood and add some insight into whether these alterations are apparent in the CNS. We measured 49 different fatty acids, and these values for all 3 groups overall fell into the range of those previously reported in brain tissue from normal subjects.[60,61] Also consistent with the literature is our finding of no correlation between age and total fatty acid content in our sample as a whole.[61,62] We did, however, find significant correlations between total fatty acids and cholesterol. Cholesterol levels and fatty acids are correlated in blood,[63] so it is not surprising that this relation is also found in the brain. We would therefore expect that the alterations in PUFAs — particularly omega-3 and omega-6 — observed in blood from patients with depressive disorders would similarly be found in brain tissue from patients with MD or suicidal ideation. Our findings do not support this idea.

We did not find any significant differences among the control subjects and those who had completed suicide, with or without MD, in either of the 2 frontal cortical regions examined. Conversely, our results do not negate the existence of a link between fatty acids and depression or suicidality. It may be that the alterations in fatty acids in the peripheral circulation reported in previous studies are related to alterations in other substances in the CNS, with brain fatty acid levels not reflecting peripheral alterations. It is also possible that fatty acid alterations do not play a major role in suicidality, while they do in MD. The data linking fatty acids to suicidality are considerably less abundant than those for depression, and there have been some conflicting findings.[30,39] In particular, 1 study found no link between dietary intake of fatty acids and death from suicide in a large cohort observed for 8 years.[30] Perhaps suicide completion, representing a homogeneous or discrete phenotype within the suicidality spectrum, is not related to fatty acid alterations and the link is limited to suicidal ideation and mood disturbances, especially MD.

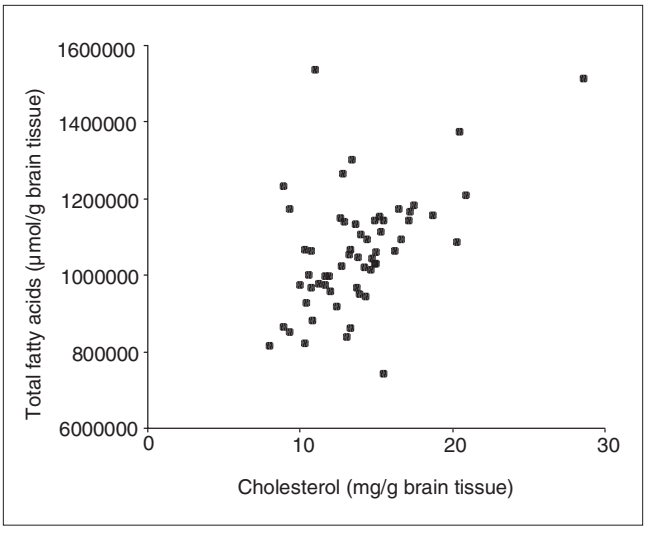

Fig. 2: Relation between total fatty acids and cholesterol in the ventral prefrontal cortex (BA 47) for all subjects (n = 58). Significant correlation: r = 0.512, p < 0.0005. BA = Brodmann's area.

A study by McNamara and colleagues[64] investigating the fatty acid composition in the postmortem orbitofrontal cortex of patients with major depressive disorder (MDD) did not find a significant difference in fatty acids examined between the patients who did and did not die by suicide, which agrees with our study findings. Although they found significantly reduced DHA in MDD patients, compared with psychiatrically normal control subjects, this finding was restricted to the female MDD patients. This raises the issue of possible sex effects, given that some studies have reported a link between decreased dietary fatty acid intake and depression among female subjects and not in males.[27,39] Our sample consisted entirely of men; thus we are unable to determine whether alterations in brain fatty acids would be present in female subjects who died by suicide.

In another study investigating fatty acids in postmortem brain tissue, Yao and colleagues[65] reported significantly lower amounts of saturated fatty acids and total PUFAs in brains from schizophrenia patients but did not find any significant differences in fatty acids in brains from patients with psychiatric disorders other than schizophrenia, compared with psychiatrically normal control subjects. Our results are in agreement with this aspect of their finding, although they did not provide information regarding the cause of death and specific diagnosis of psychiatric patients with no schizophrenia. The extent to which their findings might reflect a lack of association between alterations in postmortem brain fatty acids and suicide or MD cannot be assessed.

We could not address dietary effects in this study because we did not have data on dietary assessments before death, nor did we have access to blood samples for the analysis of fatty acids in the peripheral circulation. This information would have been interesting to examine in relation to our measures of fatty acids in the brain.

An alternative explanation for our observation of no significant difference in fatty acid measures among the 3 groups is that maybe our sample was not large enough to provide enough power to detect small alterations in the fatty acids. Another potential limitation is the inclusion of a small number of control subjects with a history of an axis I disorder (either MD or substance misuse). Although GC is a sensitive method, the extraction and purification steps required for its analysis are potential sources of error and could lead to problems determining the absolute amounts of fatty acids due to recovery losses. We controlled for this to a certain extent by considering relative amounts (i.e., percentage of total fatty acid) in our comparisons. Another potential source of error is the inclusion of different cell types present in varying proportions in the brain tissue homogenate that might contain different amounts of each of the fatty acids; this could mask any slight alterations in fatty acids present in the groups. These points reinforce the possibility that minor alterations in fatty acids in the membranes of specific cell types may play a role in suicidality,

particularly when considering the limited but growing knowledge about fatty acid biochemistry in the brain.

Fatty acids are important constituents of the brain cell membrane, with arachidonic acid and DHA being the most abundant PUFAs in the brain. The flexible nature of PUFAs contributes to the fluidity of the membrane, and alterations in membrane fluidity can lead to changes in the function of integral membrane enzymes, receptors and ion channels, with consequences to neurotransmission.[66] One hypothesis about the mechanism behind the relation between fatty acids and depression incorporates the notion that fatty acid alterations lead to changes in membrane fluidity that could affect the function of serotonin receptors or the transporter — a neurotransmitter system implicated in depression.[33] Also, they can activate transcription factors and therefore mediate cellular function via their effects on gene expression.[67] Additionally, fatty acids are released from the cell membrane by phospholipases and serve as precursors for eicosanoids, with resulting proinflammatory or antiinflammatory effects.[68] This has been cited as an alternative means through which fatty acids might play a role in MD. Specifically, an increased ratio of omega-6–to–omega-3 fatty acids could lead to increased production of proinflammatory cytokines, and an increased inflammatory response of the immune system has been linked to depression.[34] Given the diverse range of functional roles that fatty acids play in the brain, it is evident that alterations in fatty acids can have numerous effects on brain function and, thus, behaviour.

Although our global assessment of the fatty acids in grey matter samples taken from 2 frontal cortical regions of men who had completed suicide did not reveal any significant alterations, the possible role of fatty acids in suicide and depression should not be dismissed and is worthy of closer examination. Future studies should focus on enzymes related to lipid metabolism in the brain, or on carrier proteins that are associated with the transport of lipids both in the CNS and into the brain from the peripheral circulation, since perhaps the blood fatty acid alterations linked to depression are reflected in CNS changes related to these factors rather than to the absolute quantities of fatty acids in the brain.

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References

1. Golomb BA. Cholesterol and violence: is there a connection? *Ann Intern Med* 1998;128:478-87.
2. Lalovic A, Turecki G. Cholesterol metabolism and suicidality. *Directions in Psychiatry* 2006;26:209-17.
3. Virkkunen M. Serum cholesterol in antisocial personality. *Neuropsychobiology* 1979;5:27-30.
4. Modai I, Valevski A, Dror S, et al. Serum cholesterol levels and suicidal tendencies in psychiatric inpatients. *J Clin Psychiatry* 1994; 55:252-4.
5. New AS, Sevin EM, Mitropoulou V, et al. Serum cholesterol and impulsivity in personality disorders. *Psychiatry Res* 1999;85:145-50.
6. Alvarez JC, Cremniter D, Lesieur P, et al. Low blood cholesterol and low platelet serotonin levels in violent suicide attempters. *Biol Psychiatry* 1999;45:1066-9.
7. Gallerani M, Manfredini R, Caracciolo S, et al. Serum cholesterol concentrations in parasuicide. *BMJ* 1995;310:1632-6.
8. Kunugi H, Takei N, Aoki H, et al. Low serum cholesterol in suicide attempters. *Biol Psychiatry* 1997;41:196-200.
9. Garland M, Hickey D, Corvin A, et al. Total serum cholesterol in relation to psychological correlates in parasuicide. *Br J Psychiatry* 2000;177:77-83.
10. Sarchiapone M, Roy A, Camardese G, et al. Further evidence for low serum cholesterol and suicidal behaviour. *J Affect Disord* 2000; 61:69-71.
11. Hillbrand M, Spitz RT, Foster HG. Serum cholesterol and aggression in hospitalized male forensic patients. *J Behav Med* 1995;18:33-43.
12. Repo-Tiihonen E, Halonen P, Tiihonen J, et al. Total serum cholesterol level, violent criminal offences, suicidal behavior, mortality and the appearance of conduct disorder in Finnish male criminal offenders with antisocial personality disorder. *Eur Arch Psychiatry Clin Neurosci* 2002;252:8-11.
13. Virkkunen M. Serum cholesterol levels in homicidal offenders. A low cholesterol level is connected with a habitually violent tendency under the influence of alcohol. *Neuropsychobiology* 1983; 10:65-9.
14. Mufti RM, Balon R, Arfken CL. Low cholesterol and violence. *Psychiatr Serv* 1998;49:221-4.
15. Lindberg G, Rastam L, Gullberg B, et al. Low serum cholesterol concentration and short term mortality from injuries in men and women. *BMJ* 1992;305:277-9.
16. Neaton JD, Blackburn H, Jacobs D, et al. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med* 1992;152:1490-500.
17. Zureik M, Courbon D, Ducimetiere P. Serum cholesterol concentration and death from suicide in men: paris prospective study I. *BMJ* 1996;313:649-51.
18. Partonen T, Haukka J, Virtamo J, et al. Association of low serum total cholesterol with major depression and suicide. *Br J Psychiatry* 1999;175:259-62.
19. Golomb BA, Stattin H, Mednick S. Low cholesterol and violent crime. *J Psychiatr Res* 2000;34:301-9.
20. Ellison LF, Morrison HI. Low serum cholesterol concentration and risk of suicide. *Epidemiology* 2001;12:168-72.
21. Muldoon MF, Kaplan JR, Manuck SB, et al. Effects of a low-fat diet on brain serotonergic responsivity in cynomolgus monkeys. *Biol Psychiatry* 1992;31:739-42.
22. Kaplan JR, Shively CA, Fontenot MB, et al. Demonstration of an association among dietary cholesterol, central serotonergic activity, and social behavior in monkeys. *Psychosom Med* 1994;56:479-84.
23. Penturk S, Yalcin E. Hypocholesterolaemia in dogs with dominance aggression. *J Vet Med A Physiol Pathol Clin Med* 2003;50:339-42.
24. Engelberg H. Low serum cholesterol and suicide. *Lancet* 1992;339: 727-9.
25. Mauch DH, Nagler K, Schumacher S, et al. CNS synaptogenesis promoted by glia-derived cholesterol. *Science* 2001;294:1354-7.
26. Lalovic A, Levy E, Luheshi G, et al. Cholesterol content in brains of suicide completers. *Int J Neuropsychopharmacol* 2007;10:159-66. Epub 2006 May 17.

27. Tanskanen A, Hibbeln JR, Tuomilehto J, et al. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr Serv* 2001;52:529-31.
28. Huan M, Hamazaki K, Sun Y, et al. Suicide attempt and n-3 fatty acid levels in red blood cells: a case control study in China. *Biol Psychiatry* 2004;56:490-6.
29. Sublette ME, Hibbeln JR, Galfalvy H, et al. Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. *Am J Psychiatry* 2006;163:1100-2.
30. Hakkarainen R, Partonen T, Haukka J, et al. Is low dietary intake of omega-3 fatty acids associated with depression? *Am J Psychiatry* 2004;161:567-9.
31. Adams PB, Lawson S, Sanigorski A, et al. Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. *Lipids* 1996;31(Suppl):S157-S161.
32. Edwards R, Peet M, Shay J, et al. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. *J Affect Disord* 1998;48:149-55.
33. Maes M, Smith R, Christophe A, et al. Fatty acid composition in major depression: decreased omega-3 fractions in cholesteryl esters and increased C20: 4 omega 6/C20:5 omega 3 ratio in cholesteryl esters and phospholipids. *J Affect Disord* 1996;38:35-46.
34. Maes M, Christophe A, Delanghe J, et al. Lowered omega-3 polyunsaturated fatty acids in serum phospholipids and cholesteryl esters of depressed patients. *Psychiatry Res* 1999;85:275-91.
35. Peet M, Murphy B, Shay J, et al. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. *Biol Psychiatry* 1998;43:315-9.
36. Parker G, Gibson NA, Brotchie H, et al. Omega-3 fatty acids and mood disorders. *Am J Psychiatry* 2006;163:969-78.
37. Hibbeln JR. Fish consumption and major depression. *Lancet* 1998; 351:1213.
38. Hibbeln JR. Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *J Affect Disord* 2002;69:15-29.
39. Timonen M, Horrobin D, Jokelainen J, et al. Fish consumption and depression: the northern Finland 1966 birth cohort study. *J Affect Disord* 2004;82:447-52.
40. Stoll AL, Severus WE, Freeman MP, et al. Omega-3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999;56:407-12.
41. Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry* 2002;159:477-9.
42. Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry* 2002;59:913-9.
43. Su KP, Huang SY, Chiu CC, et al. Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. *Eur Neuropsychopharmacol* 2003;13:267-71.
44. Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. *Br J Psychiatry* 2006;188:46-50.
45. Nemets H, Nemets B, Apter A, et al. Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. *Am J Psychiatry* 2006;163:1098-100.
46. Marangell LB, Martinez JM, Zboyan HA, et al. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry* 2003;160:996-8.
47. Silvers KM, Woolley CC, Hamilton FC, et al. Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins Leukot Essent Fatty Acids* 2005;72:211-8.
48. Keck PE Jr, Mintz J, McElroy SL, et al. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol Psychiatry* 2006;60:1020-2.
49. Alan DD, Clemens F, Elbourne D, et al. A randomised controlled trial investigating the effect of n-3 long-chain polyunsaturated fatty acid supplementation on cognitive and retinal function in cognitively healthy older people: the older people and n-3 long-chain polyunsaturated fatty acids (OPAL) study protocol [ISRCTN72331636]. *Nutr J* 2006;5:20.
50. Bourre JM. Dietary omega-3 Fatty acids and psychiatry: mood, behaviour, stress, depression, dementia and aging. *J Nutr Health Aging* 2005;9:31-8.
51. Logan AC. Neurobehavioral aspects of omega-3 fatty acids: possible mechanisms and therapeutic value in major depression. *Altern Med Rev* 2003;8:410-25.
52. Kim C, Lesage A, Seguin M, et al. Patterns of co-morbidity in male suicide completers. *Psychol Med* 2003;33:1299-309.
53. Lesage AD, Boyer R, Grunberg F, et al. Suicide and mental disorders: a case-control study of young men. *Am J Psychiatry* 1994;151: 1063-8.
54. First MB, Spitzer RL, Gibbon M,et al. *Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition.* (SCID-I/P) New York: Biometrics Research, New York State Psychiatric Institute; 2002.
55. Sequeira A, Gwadry FG. Ffrench-Mullen JM, et al. Implication of SSAT by gene expression and genetic variation in suicide and major depression. *Arch Gen Psychiatry* 2006;63:35-48.
56. Turecki G, Briere R, Dewar K, et al. Prediction of level of serotonin 2A receptor binding by serotonin receptor 2A genetic variation in postmortem brain samples from subjects who did or did not commit suicide. *Am J Psychiatry* 1999;156:1456-8.
57. Folch J, Lees M, Sloane Stanley G. A simple method for the isolation and purification of total lipides from animal tissues. *J Biol Chem* 1957;226:497-509.
58. Lepage G, Levy E, Ronco N, et al. Direct transesterification of plasma fatty acids for the diagnosis of essential fatty acid deficiency in cystic fibrosis. *J Lipid Res* 1989;30:1483-90.
59. Frasure-Smith N, Lesperance F, Julien P. Major depression is associated with lower omega-3 fatty acid levels in patients with recent acute coronary syndromes. *Biol Psychiatry* 2004;55:891-6.
60. Julien C, Berthiaume L, Hadj-Tahar A, et al. Postmortem brain fatty acid profile of levodopa-treated Parkinson disease patients and parkinsonian monkeys. *Neurochem Int* 2006;48:404-14.
61. Skinner ER, Watt C, Besson JA, et al. Differences in the fatty acid composition of the grey and white matter of different regions of the brains of patients with Alzheimer's disease and control subjects. *Brain* 1993;116:717-25.
62. Soderberg M, Edlund C, Kristensson K, et al. Fatty acid composition of brain phospholipids in aging and in Alzheimer's disease. *Lipids* 1991;26:421-5.
63. Dewailly EE, Blanchet C, Gingras S, et al. Relations between n-3 fatty acid status and cardiovascular disease risk factors among Quebecers. *Am J Clin Nutr* 2001;74:603-11.
64. McNamara RK, Hahn CG, Jandacek R, et al. Selective deficits in the omega-3 fatty acid docosahexaenoic acid in the postmortem orbitofrontal cortex of patients with major depressive disorder. Biol Psychiatry 2007;62:17-24. Epub 2006 Dec 22
65. Yao JK, Leonard S, Reddy RD. Membrane phospholipid abnormalities in postmortem brains from schizophrenic patients. *Schizophr Res* 2000;42:7-17.
66. Murphy MG. Dietary fatty acids and membrane protein function. *J Nutr Biochem* 1990;1:68-79.
67. Wahle KW, Rotondo D, Heys SD. Polyunsaturated fatty acids and gene expression in mammalian systems. *Proc Nutr Soc* 2003;62:349-60.
68. Alessandri JM, Guesnet P, Vancassel S, et al. Polyunsaturated fatty acids in the central nervous system: evolution of concepts and nutritional implications throughout life. *Reprod Nutr Dev* 2004;44:509-38.