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Abnormal fatty acid pattern in the superior temporal gyrus distinguishes bipolar disorder from major depression and schizophrenia and resembles multiple sclerosis

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ABSTRACT

This study investigated the fatty acid composition of the postmortem superior temporal gyrus (STG), a cortical region implicated in emotional processing, from normal controls ($n=15$) and patients with bipolar disorder (BD, $n=15$), major depressive disorder (MDD, $n=15$), and schizophrenia (SZ, $n=15$). For comparative purposes, STG fatty acid composition was determined in a separate cohort of multiple sclerosis patients (MS, $n=15$) and normal controls ($n=15$). Compared with controls, patients with BD, but not MDD or SZ, exhibited abnormal elevations in the saturated fatty acids (SFA) palmitic acid (16:0), stearic acid (18:0), the polyunsaturated fatty acids (PUFA) linoleic acid (18:2*n*-6), arachidonic acid (20:4*n*-6), and docosahexaenoic acid (22:6*n*-3), and reductions in the monounsaturated fatty acid (MUFA) oleic acid (18:1*n*-9). The total MUFA/SFA and 18:1/18:0 ratios were lower in the STG of BD patients and were inversely correlated with total PUFA composition. MS patients exhibited a pattern of fatty acid abnormalities similar to that observed in BD patients including elevated PUFA and a lower 18:1/18:0 ratio. Collectively, these data demonstrate that BD patients exhibit a pattern of fatty acid abnormalities in the STG that is not observed in MDD and SZ patients and closely resembles MS patients.

1. Introduction

Emerging evidence suggests that mood and psychotic disorders are associated with a dysregulation in polyunsaturated fatty acid (PUFA) homeostasis. Specifically, case-control studies have repeatedly found that patients with major depressive disorder (MDD, Lin et al., 2010), bipolar disorder (BD, Chiu et al., 2003; McNamara et al., 2010), and schizophrenia (SZ, van der Kemp et al., 2012), exhibit significant deficits in omega-3 PUFAs, including docosahexaenoic acid (DHA, 22:6*n*-3) and/or the omega-6 PUFA arachidonic acid (AA, 20:4*n*-6) in red blood cell (RBC) membranes. Independent meta-analyses of controlled LC*n*-3 fatty acid intervention trials observed a significant advantage of omega-3 PUFAs over placebo for the treatment of depressive symptoms in patients with MDD (Appleton et al., 2010; Freeman et al., 2006; Lin and Su, 2007; Martins, 2009; Sublette et al., 2011) or BD (Sarris et al., 2012). Accumulating evidence also suggests that omega-3 PUFA treatment may have benefits for positive and negative symptoms in patient with or at ultra-high risk for developing schizophrenia (Amminger et al., 2010; Arvindakshan et al., 2003; Emsley et al., 2002). These and other data suggest that a dysregulation in PUFA homeostasis secondary to omega-3 PUFA deficiency may represent a modifiable pathophysiological mechanism associated with mood and psychotic symptoms.

The primary PUFAs found in mammalian brain gray matter are AA and DHA, and preferentially accumulate in synaptosomal, astrocytic, and mitochondrial fractions (Jones et al., 1996; Suzuki et al., 1997) where they are acetylated into the *sn*-2 position of membrane phospholipids (Lee and Hajra, 1991). DHA and AA are mobilized by different phospholipase A_2 (PLA_2) isozymes (Farooqui and Horrocks, 2004), and once mobilized exert opposing effects on signal transduction and inflammation pathways (McNamara et al., 2006; Rao et al., 2007). Although RBC AA and DHA compositions are positively correlated with postmortem frontal cortex AA and DHA compositions in adult human subjects (Carver et al., 2001), case-control studies have not consistently observed reductions in AA and/or DHA compositions in the postmortem frontal cortex or anterior cingulate gyrus of patients with SZ (Horrobin et al., 1991; Landén et al., 2002; McNamara et al., 2007a; Yao et al., 2000; Taha et al., 2013), BD (McNamara et al., 2008a; Igarashi et al., 2010), or MDD (Conklin et al., 2010; McNamara et al., 2007b, 2013; Tatebayashi et al., 2012). Moreover,

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postmortem studies have not observed major alterations in AA or DHA in medial temporal lobe structures including the amygdala (Hamazaki et al., 2012), hippocampus (Hamazaki et al., 2010), and entorhinal cortex (Hamazaki et al., 2013) of psychiatric patients. While there are several clinical and postmortem variables that may contribute to these discrepancies (McNamara and Jandacek, 2011), prior clinical neuroimaging (Umhau et al., 2009) and animal (Dullemeijer et al., 2008; Diau et al., 2005; Xiao et al., 2005) studies have observed significant brain regional differences in DHA and AA incorporation rates and composition.

To extend this line of investigation, the present study determined the fatty acid composition of the postmortem superior temporal gyrus (STG) (Brodmann area 22) from patients with SZ, BD, or MDD. The STG plays a central role in emotional processing and social cognition (Allison et al., 2000; Arnsten and Rubia, 2012), and emerging neuroimaging and postmortem evidence has implicated the STG in the pathophysiology of SZ, BD, and MDD (Beasley et al., 2005, 2009; Fitzgerald et al., 2008; Nudmamud et al., 2003; Takahashi et al., 2009, 2010). Emerging evidence also suggests that patients with multiple sclerosis (MS) exhibit abnormal RBC (Homa et al., 1980; Navarro and Segura, 1989; Nightingale et al., 1990) and central white matter (Alling et al., 1971; Woelk and Borri, 1973; Wilson and Tocher, 1991) PUFA levels as well as elevated rates of MDD and BD (Byatt et al., 2011; Edwards and Constantinescu, 2004; Galeazzi et al., 2005; Joffe et al., 1987; Schiffer et al., 1986). We therefore additionally investigated the fatty acid composition of the postmortem STG in a separate cohort of MS patients and controls for comparative purposes.

2. Methods

2.1. Human postmortem brain samples

Frozen (−80 °C), unfixed, postmortem STG (Brodmann area 22) from patients with DSM-IV defined BD ($n=15$), SZ ($n=15$), and MDD ($n=15$), and demographically similar healthy controls (no psychiatric illness, $n=15$) were used. Frozen ~100 mg cortical samples were dissected from gray matter regions of the original frozen tissue chunk, and effort was made to avoid inclusion of white matter. Brain tissue was generously provided by the Stanley Research Foundation Neuropathology Consortium. Group demographic and tissue variables are presented in Table 1, and details regarding brain dissection parameters, axis I DSM-IV diagnoses, and criteria and incidence of ethanol and substance abuse severity have been detailed previously (Torrey et al., 2000). At the time of death, $n=5$ BD patients were receiving lithium, $n=5$ valproic acid, $n=2$ antipsychotic medications, and $n=3$ patients were medication-free. At the time of death, $n=12$ SZ patients were receiving antipsychotic medications and $n=3$ were medication-free, and $n=12$ MDD patients were receiving antidepressant medications and $n=3$ were medication-free. Normal-appearing STG tissues from patients with multiple sclerosis ($n=15$) and demographically similar controls ($n=15$) were generously provided by the UCLA Human Brain and Spinal Fluid Resource Center. Details regarding brain dissection and storage parameters, histopathological evaluations, and diagnostic criteria are available at http://brainbank.ucla.edu/tissue-research/protocols/.

2.2. Gas chromatography

Total fatty acid composition was determined using the saponification and methylation methods and gas chromatography (GC) procedure described previously (McNamara et al., 2008a). Samples were analyzed with a Shimadzu GC-2014 equipped with an auto-injector (Shimadzu Scientific Instruments Inc., Columbia MD). The column was a DB-23 (123-2332): 30 m (length), I.D. (mm) 0.32 wide bore, film thickness of 0.25 μM (J&W Scientific, Folsom CA). The GC conditions were: column temperature ramping by holding at 120 °C for one minute followed by an increase of 5 °C/min from 120 to 240 °C. The temperature of the injector and flame ionization detector was 250 °C. A split (8:1) injection mode was used. The carrier gas was helium with a column flow rate of 2.5 ml/min. Fatty acid identification was determined using retention times of authenticated fatty acid methyl ester standards (Matreya LLC Inc., Pleasant Gap PA). Analysis of fatty acid methyl esters is based on areas calculated with Shimadzu Class VP 4.3 software. Individual fatty acid composition data are expressed as weight percent of total fatty acids (mg fatty acid/100 mg fatty acids, wt% total). All samples were processed by a technician blinded to illness state.

We restricted our primary analysis to principal saturated fatty acids (myristic acid, C14:0; palmitic, C16:0; stearic, C18:0), monounsaturated fatty acids (cis-vaccenic acid, 18:1*n*-7; oleic acid, 18:1*n*-9; palmitoleic acid, 16:1*n*-7; mead acid, 20:1*n*-9), omega-6 PUFAs (linoleic acid, 18:2*n*-6; homo-γ-linolenic acid, 20:3*n*-6; arachidonic acid, 20:4*n*-6; adrenic acid [docosatetraenoic acid], 22:4*n*-6; docosapentaenoic acid, 22:5*n*-6), and the omega-3 PUFA docosahexaenoic acid (DHA, 22:6*n*-3). Together these 13 fatty acids comprise ~90% of total fatty acids in postmortem brain tissue, and the remaining fatty acids individually represent <2% of total fatty acids. We additionally determined total SFA composition (Sum: 14:0, 16:0, 18:0), total MUFA composition (Sum: 16:1*n*-7, 18:1*n*-7, 18:1*n*-9, 20:1*n*-9), and total PUFA composition (Sum: 18:2*n*-6, 20:3*n*-6, 20:4*n*-6, 22:4*n*-6, 22:5*n*-6, 22:6*n*-3), as well as product:precursor ratios as indices of stearoyl-CoA desaturase (18:1/18:0), delta6-desaturase (20:3*n*-6/18:2*n*-6), and delta5-desaturase (20:4*n*-6/20:3*n*-6) activities (Liu et al., 2009; McNamara et al., 2008b).

2.3. Statistical analysis

To evaluate diagnostic group (CON, BD, MDD, SZ) differences in fatty acids and ratios, a one-way analyses of variance (ANOVA) was performed followed by post-hoc *t*-tests (two-tailed, $\alpha=0.05$). Analysis of gender effects was performed with a two-way ANOVA using gender (male, female) and diagnostic group (CON, BD, MDD, SZ) as the main factors. Parametric linear regression analyses were performed to determine the relationship between fatty acid composition and demographic (age at onset of illness, duration of illness, age at time of death) and postmortem tissue variables (brain pH, brain weight, postmortem interval, and days in freezer storage). Two-tailed *t*-tests ($\alpha=0.05$) were used to compare fatty acid levels in MS patients and controls. Statistical analyses were performed using GB-STAT (V.10, Dynamic Microsystems, Inc., Silver Springs MD).

Table 1
Demographic and tissue characteristics.

	Controls ($n=15$)	**BD** ($n=15$)	**MDD** ($n=15$)	**SZ** ($n=15$)	***p*-Value**[a]
Subject characteristics					
Age at death, mean ± S.D.	48.1 ± 10.7	42.3 ± 11.7	46.5 ± 9.3	44.5 ± 13.1	0.54
Gender (*n*)	6F,9M	6F,9M	6F,9M	6F,9M	–
Race (*n*)	14C,1AA	14C,1AA	15C	12C,3AS	–
Suicide	0	9	7	4	–
Age at onset, mean ± S.D.	–	21.5 ± 8.3	33.9 ± 13.3	23.2 ± 8.0	0.003
Duration of illness, mean years ± S.D.	–	20.1 ± 9.7	12.7 ± 11.1	21.3 ± 11.4	0.07
History of psychosis (*n*)	0	11	0	15	–
Tissue characteristics					
Brain hemisphere	7R/8L	8R/7L	6R/9L	6R/9L	–
Brain mass, mean grams ± S.D.	1501.0 ± 164.1	1441.0 ± 171.5	1462.0 ± 142.1	1472.0 ± 108.2	0.74
Postmortem interval, mean hours ± S.D.	23.7 ± 9.9	32.5 ± 16.1	27.5 ± 10.7	33.7 ± 14.6	0.15
Time in storage, mean days ± S.D.	338.3 ± 234.3	620.5 ± 172.3	434.1 ± 289.9	621.1 ± 233.1	0.003
Tissue pH, mean ± S.D.	6.3 ± 0.2	6.2 ± 0.2	6.2 ± 0.2	6.2 ± 0.3	0.62

Race: C=Caucasian, AA=African American, AS=Asian.

[a] One-way ANOVA.

3. Results

3.1. Postmortem variables

Among all subjects ($n=60$), there were no significant correlations between individual fatty acid levels and age at death, brain mass, postmortem interval, time in storage, or tissue pH. Among psychiatric patients ($n=45$), there were no significant correlations between fatty acid levels and age at illness onset or duration of illness.

3.2. Psychiatric groups

Analysis by diagnostic group found significant main effects for the SFAs palmitic acid (16:0) and stearic acid (18:0) and total SFA, oleic acid (18:1*n*-9) and total MUFA, the PUFAs linoleic acid (18:2*n*-6), arachidonic acid (20:4*n*-6), and docosahexaenoic acid (22:6*n*-3) and total PUFA (Table 2). There was also a significant main effect of diagnostic group for the 18:1/18:0, 20:3/18:2, 20:4/18:2, and 20:4/20:3 ratios. There were significant main effects for the total MUFA/SFA ratio, $F(3,59)=3.3$, $p=0.02$, the total SFA/PUFA ratio, $F(3,59)=2.8$, $p=0.04$, and the total MUFA/PUFA ratio, $F(3,59)=3.2$, $p=0.03$ (Fig. 1). Post-hoc analysis revealed that these fatty acids and ratios were significantly altered in BD patients compared with controls, and were not significantly altered in patients with MDD or SZ. Furthermore, SZ patients exhibited significant differences compared with BD patients for all of the fatty acids and ratios that differed between BD and controls with the exception of 20:4/18:2. Similarly, linoleic acid and DHA levels were significantly lower, and the 18:1/18:0, 20:3/18:2, and 20:4/18:2 ratios were significantly higher, in MDD patients compared with BD patients. In the two-way ANOVA, the main effects of gender and the diagnosis by gender interaction was not significant for any fatty acid or ratio. Among all subjects ($n=60$), total PUFA was inversely correlated with the MUFA/SFA ratio, the 18:1/18:0 ratio, and 18:1*n*-9 composition (Fig. 2). Among BD patients ($n=15$), total PUFA was inversely correlated with the MUFA/SFA ratio ($r=-0.95$, $p\leq 0.0001$), the 18:1/18:0 ratio ($r=-0.93$, $p\leq 0.0001$), and 18:1*n*-9 composition ($r=-0.95$, $p\leq 0.0001$).

3.3. Medication effects

To investigate the potential contribution of medications, we additionally compared fatty acids that were found to be altered in BD subjects (Table 2) following separation of BD patients into those that were drug-free ($n=3$) or were being treated with lithium ($n=5$) or valproic acid ($n=5$) at time of death. There was a significant main effect of treatment for all fatty acids and ratios with the exception of the 20:4/18:2 ratio (Table 3). Drug-free BD patients exhibited greater stearic acid and arachidonic acid levels compared with controls, and patients treated with lithium did not exhibit significant alterations in any fatty acid or ratio. In contrast, BD patients treated with valproic acid exhibited robust and significant alterations in all fatty acids and ratios compared with controls. After the removal of the $n=5$ BD patients treated with valproic acid, palmitic acid ($p=0.04$), stearic acid ($p=0.001$), linoleic acid ($p=0.03$), AA ($p=0.01$), and DHA ($p=0.04$) remained significantly elevated, and oleic acid remained significantly reduced ($p=0.02$), compared with controls. Moreover, the 18:1/18:0 ($p=0.01$) and 20:3/18:2 ($p=0.02$) ratios remained significantly reduced compared with controls, whereas the 20:4/18:2 ($p=0.1$) and 20:4/20:3 ($p=0.2$) ratios were not significant.

3.4. Multiple sclerosis

The STG from MS patients exhibited significantly higher levels of the SFAs myristic acid (14:0), palmitic acid (16:0), and stearic

Table 2
STG fatty acid composition.

Fatty acid[a]	Controls ($n=15$)	BD ($n=15$)	MDD ($n=15$)	SZ ($n=15$)	*p*-Value[b]
Saturated fatty acids (SFA)					
Mystic acid (14:0)	0.4 ± 0.026	0.4 ± 0.130	0.3 ± 0.09	0.3 ± 0.036	0.49
Palmitic acid (16:0)	16.9 ± 1.71	18.6 ± 1.15**	17.5 ± 1.90	16.9 ± 1.98##	0.029
Stearic acid (18:0)	18.4 ± 0.63	19.5 ± 0.69***	19.0 ± 0.96	18.6 ± 0.95##	0.003
Total SFA	35.8 ± 2.3	38.5 ± 1.6***	36.0 ± 2.82##	36.9 ± 2.91#	0.014
Monounsaturated fatty acids (MUFA)					
Vaccenic acid (18:1*n*-7)	3.8 ± 0.43	3.4 ± 0.38	3.6 ± 0.65	3.8 ± 0.440	0.090
Oleic acid (18:1*n*-9)	19.4 ± 3.1	16.1 ± 2.2**	18.1 ± 3.6	19.1 ± 2.92##	0.019
Palmitoleic acid (16:1*n*-7)	0.6 ± 0.076	0.5 ± 0.101	0.5 ± 0.077	0.5 ± 0.082	0.72
Mead acid (20:1*n*-9)	1.1 ± 0.49	0.7 ± 0.31	0.9 ± 0.51	1.0 ± 0.34	0.118
Total MUFA	24.8 ± 3.8	20.6 ± 2.8**	24.4 ± 4.82##	23.1 ± 3.6	0.019
Polyunsaturated fatty acids (PUFA)					
Linoleic acid (18:2*n*-6)	0.5 ± 0.19	0.8 ± 0.25**	0.5 ± 0.112##	0.6 ± 0.171#	0.0036
Homo-γ-linolenic acid (20:3*n*-6)	0.9 ± 0.23	0.9 ± 0.14	0.8 ± 0.17	0.9 ± 0.17	0.53
Arachidonic acid (20:4*n*-6)	8.2 ± 1.01	9.5 ± 0.75***	9.0 ± 1.73	8.3 ± 1.042##	0.015
Adrenic acid (22:4*n*-6)	6.0 ± 0.61	5.6 ± 0.47	6.0 ± 0.30	6.1 ± 0.74	0.19
Docosapenaenoic acid (22:5*n*-6)	1.5 ± 0.48	1.8 ± 0.45	1.5 ± 0.47	1.3 ± 0.51	0.044
Docosahexaenoic acid (22:6*n*-3)	9.4 ± 2.9	12.3 ± 1.8**	10.4 ± 2.81#	9.7 ± 3.21#	0.027
Total PUFA	27.4 ± 3.6	31.2 ± 2.3**	27.6 ± 4.32##	28.9 ± 3.6	0.015
Ratios					
18:1/18:0	1.1 ± 0.20	0.8 ± 0.13**	1.0 ± 0.251#	1.0 ± 0.222##	0.014
20:3/18:2	1.8 ± 0.58	1.2 ± 0.40**	1.6 ± 0.461#	1.7 ± 0.492##	0.0066
20:4/18:2	17.3 ± 4.2	13.8 ± 4.4*	16.8 ± 3.61#	14.9 ± 3.6	0.050
20:4/20:3	9.5 ± 1.9	11.5 ± 2.1*	10.9 ± 2.5	9.2 ± 1.82##	0.010

[a] Values are mean composition (g/100 g) ± S.D.
[b] One-way ANOVA.
* $p\leq 0.05$ vs. controls.
** $p\leq 0.01$ vs. controls.
*** $p\leq 0.001$ vs. controls.
# $p\leq 0.05$ vs. BD.
$p\leq 0.01$ vs. BD.

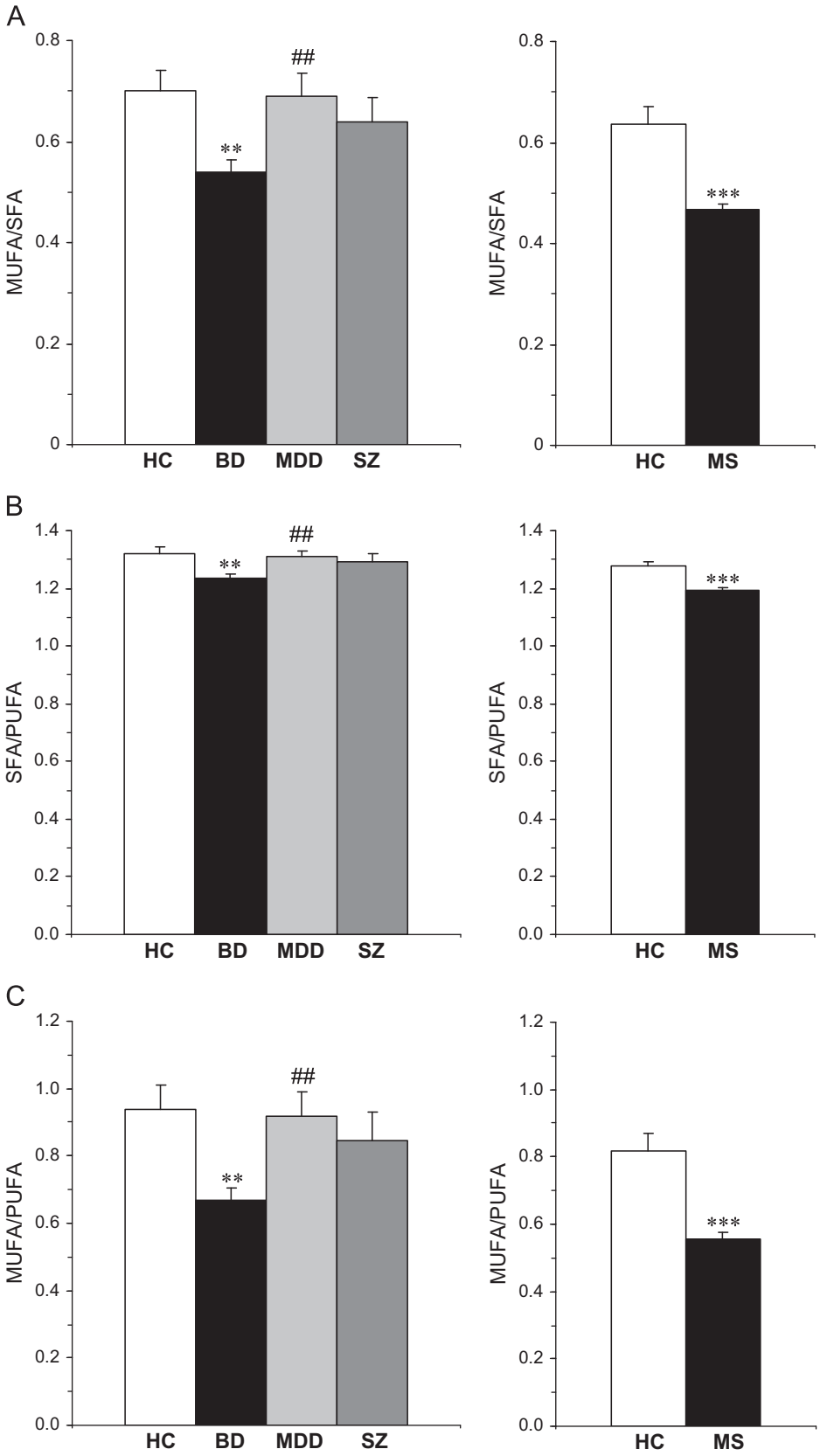

Fig. 1. The MUFA/SFA ratio (A), the SFA/PUFA ratio (B), and the MUFA/PUFA ratio (C) in the STG of healthy controls (HC, $n=15$), and patients with BD ($n=15$), MDD ($n=15$), or SZ ($n=15$) (left column), and in the STG of healthy controls (HC, $n=15$) and patients with MS ($n=15$) (right column). Values are mean ratio ± S.E.M. $^{*}p \leq 0.01$, $^{***}p \leq 0.001$ vs. HC, $^{\#\#}p \leq 0.01$ vs. BD.

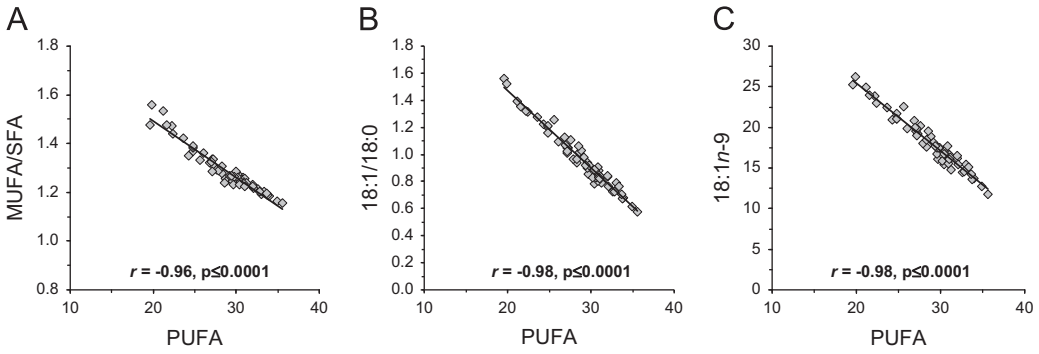

Fig. 2. Correlation between total polyunsaturated fatty acids (PUFA) and the MUFA/SFA ratio (A), the 18:1/18:0 ratio (B), and 18:1*n*-9 (C) in the STG among all subjects ($n=60$). Pearson correlation coefficients and associated *p*-values (two-tailed) are presented.

Table 3
Medication effects in BD patients.

Selected fatty acids[a]	Controls ($n=15$)	Drug-free ($n=3$)	Lithium ($n=5$)	Valproate ($n=5$)	*p*-value[b]
Fatty acids					
Palmitic acid (16:0)	16.9 ± 1.7	18.8 ± 1.0	17.7 ± 1.2	19.4 ± 0.86**	0.016
Stearic acid (18:0)	18.4 ± 0.63	19.6 ± 1.07*	19.1 ± 0.57	19.7 ± 0.58**	0.0034
Oleic acid (18:1*n*-9)	19.4 ± 3.1	15.6 ± 2.7	17.7 ± 1.9	14.8 ± 1.9**	0.015
Linoleic acid (18:2*n*-6)	0.5 ± 0.19	0.8 ± 0.25	0.7 ± 0.31	0.9 ± 0.25**	0.043
Arachidonic acid (20:4*n*-6)	8.2 ± 1.01	9.7 ± 0.56*	8.9 ± 0.61	10.0 ± 0.75**	0.0030
Docosahexaenoic acid (22:6*n*-3)	9.4 ± 3.0	12.6 ± 2.3	10.9 ± 1.4	13.5 ± 1.7*	0.022
Ratios					
18:1/18:0	1.1 ± 0.20	0.8 ± 0.18	0.9 ± 0.12	0.8 ± 0.12**	0.010
20:3/18:2	1.9 ± 0.58	1.2 ± 0.60	1.4 ± 0.36	1.0 ± 0.36**	0.015
20:4/18:2	17.3 ± 4.2	12.4 ± 5.4	14.2 ± 5.7	12.7 ± 4.1*	0.132
20:4/20:3	9.5 ± 1.9	12.0 ± 2.2	10.0 ± 2.0	13.1 ± 1.6**	0.0087

[a] Values are mean composition (g/100 g) ± S.D.
[b] One-way ANOVA.
* $p \leq 0.05$.
** $p \leq 0.01$ vs. controls.

acid (18:0) and total SFA, higher levels of the PUFAs linoleic acid (18:2*n*-6), arachidonic acid (20:4*n*-6), and docosahexaenoic acid (22:6*n*-3) and total PUFA, and significantly lower levels of the MUFA oleic acid (18:1*n*-9) and total MUFA, compared with controls (Table 4). The 18:1/18:0, 20:3/18:2, and 20:4/18:2 ratios we all significantly lower in MS patients, as were the MUFA/SFA, SFA/PUFA, and MUFA/PUFA ratios (Fig. 1). Among all subjects ($n=30$), total PUFA was inversely correlated with the MUFA/SFA ratio ($r=-0.96$, $p \leq 0.0001$), the 18:1/18:0 ratio ($r=-0.95$, $p \leq 0.0001$), and 18:1*n*-9 composition ($r=-0.91$, $p \leq 0.0001$).

4. Discussion

This cross-sectional study investigated the fatty acid composition of the postmortem STG from patients with BD, MDD, and SZ. We found that patients with BD, but not MDD or SZ, exhibited significantly greater SFA and PUFA levels and significantly lower MUFA levels compared with controls. STG fatty acid abnormalities were more robust in BD patients treated with valproic acid and were attenuated in patients treated with lithium. Nevertheless, removal of BD patients treated with valproic acid did not substantially alter the results, and a prior rat study found that chronic valproic acid treatment, resulting in therapeutically-relevant plasma concentrations, did not significantly alter brain SFA or MUFA concentrations (Bazinet et al., 2005a). Additionally, the MUFA/SFA and 18:1/18:0 ratios were significantly lower in the STG of BD patients and were inversely correlated with total PUFA composition. Remarkably, MS patients exhibited a pattern of fatty acid abnormalities in the STG that was very similar to that observed in BD patients, including greater SFA and PUFA levels lower MUFA levels. Collectively, these data demonstrate that BD patients exhibit a pattern of fatty acid abnormalities in the STG that is not observed in MDD and SZ patients and closely resembles MS patients.

The present postmortem study has several important limitations. First, there was no information available regarding the diets (i.e., PUFA intake) in the months preceding death, and it is therefore not possible to investigate whether the observed STG fatty acid abnormalities were associated with diet. Second, we used fatty acid composition data versus absolute fatty acid concentration data. However, we have previously found that fatty acid composition and concentration data are highly correlated, particularly for fatty acid ratios (McNamara et al., 2008a). Third, as with all postmortem brain studies, a number of clinical, lifestyle, and postmortem variables may contribute to the present findings (McNamara and Jandacek, 2011). Although time in storage for the BD samples was greater than controls, there were no significant correlations between time in storage and individual fatty acid levels. Moreover, the SZ samples had similar time in storage as BD samples but did not exhibit any significant fatty acid abnormalities. These findings suggest that the greater time in storage did not contribute to the fatty acid abnormalities observed in the STG of BD patients. Fourth, the small number of patients in each diagnostic group ($n=15$) may not be representative of all patients with these psychiatric disorders, and replication of the present findings in a different cohort will be required to confirm the present findings. Despite these limitations, the present study employed a well-characterized set of brain tissues and provides comparative postmortem data to guide future studies using alternative approaches including neuroimaging (McNamara, 2013; Umhau et al., 2009).

Table 4
MS Demographics and STG fatty acid composition.

Fatty acids[a]	Controls ($n=15$)	MS ($n=15$)	p-Value[b]
Subject & tissue characteristics			
Age at death, mean ± S.D.	53.1 ± 8.9	54.1 ± 7.0	0.76
Gender (n)	6F,9M	7F,8M	0.49
Postmortem interval, mean h ± S.D.	24.3 ± 8.7	19.0 ± 7.6	0.16
Saturated fatty acids (SFA)			
Mystic acid (14:0)	0.4 ± 0.03	0.3 ± 0.16	0.0001
Palmitic acid (16:0)	17.6 ± 1.15	20.3 ± 0.53	0.0001
Stearic acid (18:0)	18.6 ± 0.63	20.6 ± 0.58	0.0001
Total SFA	36.7 ± 1.71	41.0 ± 0.67	0.0001
Monounsaturated fatty acids (MUFA)			
Vaccenic acid (18:1n-7)	3.6 ± 0.31	3.3 ± 0.31	0.01
Oleic acid (18:1n-9)	18.1 ± 2.27	15.3 ± 1.24	0.003
Palmitoleic acid (16:1n-7)	0.6 ± 0.08	0.6 ± 0.26	0.67
Mead acid (20:1n-9)	1.0 ± 0.48	0.9 ± 0.54	0.90
Total MUFA	23.2 ± 2.95	19.1 ± 1.43	0.0009
Polyunsaturated fatty acids (PUFA)			
Linoleic acid (18:2n-6)	0.6 ± 0.20	1.1 ± 0.29	0.0002
Homo-γ-linolenic acid (20:3n-6)	1.0 ± 0.22	1.0 ± 0.17	0.99
Arachidonic acid (20:4n-6)	8.7 ± 0.68	10.2 ± 0.60	0.0001
Adrenic acid (22:4n-6)	5.8 ± 0.58	5.5 ± 0.48	0.22
Docosapenaenoic acid (22:5n-6)	1.6 ± 0.49	1.6 ± 0.38	0.86
Docosahexaenoic acid (22:6n-3)	10.4 ± 2.46	15.2 ± 1.11	0.0001
Total PUFA	28.9 ± 2.38	34.5 ± 1.39	0.0001
Ratios			
18:1/18:0	1.0 ± 0.15	0.7 ± 0.07	0.0004
20:3/18:2	1.9 ± 0.69	1.0 ± 0.31	0.002
20:4/18:2	16.6 ± 4.19	10.3 ± 3.35	0.002
20:4/20:3	9.3 ± 1.82	10.8 ± 2.25	0.12

[a] Values are mean composition (g/100 g) ± S.D.
[b] Two-tailed t-tests.

The observation that the STG of BD patients exhibited greater DHA and AA composition compared with controls was not predicted based on prior studies finding lower DHA and/or AA levels in RBCs (Chiu et al., 2003; McNamara et al., 2010) and the postmortem prefrontal cortex (McNamara et al., 2008a) of BD patients. Indeed, the fatty acid abnormalities observed in the STG of BD patients are opposite to what we observed in the prefrontal cortex (McNamara et al., 2008a). These data, and the prior finding of no fatty acid abnormalities in temporal lobe structures including the amygdala (Hamazaki et al., 2012) and hippocampus (Hamazaki et al., 2010) of BD patients, suggest that the peripheral and central fatty acid abnormalities are not uniformly observed across different cortical and subcortical regions. It is of interest, therefore, that a human positron emission tomography (PET) study found lower DHA incorporation rates in the temporal cortex compared with other cortical regions (Umhau et al., 2009), and that plasma DHA levels are positively correlated with glucose metabolism in the STG, and negatively correlated with glucose metabolic rates in the frontal cortex, of medication-free MDD patients (Sublette et al., 2009). Moreover, animal studies have found that DHA incorporation rates are lower in the temporal cortex compared with the frontal cortex (Diau et al., 2005; Dullemeijer et al., 2008). Together, these observations suggest that the fatty acid abnormalities observed in the STG of BD and MS patients may be attributable in part to localized abnormalities in the enzymes that mediate fatty acid biosynthesis and/or phospholipid incorporation.

Prior animal studies have found that chronic treatment with mood-stabilizer medications, including lithium and valproic acid, decrease AA, but not DHA, turnover in rat brain phospholipids (Bazinet et al., 2005b; Chang et al., 1996, 2001). Moreover, we reported that chronic lithium treatment increased AA, but not DHA, composition in different mouse brain regions (McNamara et al., 2008c). In the present study, AA and DHA compositions were significantly greater in the STG of BD patients treated with valproic acid, but not lithium, and AA was greater in drug-free BD patients. While these postmortem findings suggest that the overall increase in STG AA composition observed in BD patients cannot be uniformly attributed to treatment with mood-stabilizer medications, medication compliance at time of death is not known. Future PET studies will be required to more definitively address the effects of mood-stabilizers on human STG AA and DHA incorporation and turnover rates.

An unanticipated finding was that the STG of BD patients exhibited greater SFA levels and lower MUFA levels, and a significantly lower MUFA/SFA ratio. More specifically, we observed lower oleic acid (18:1n-9) composition and greater stearic acid composition (18:0), and a lower 18:1/18:0 ratio. Because chronic dietary oleic acid deficiency does not reduce rat brain oleic acid composition (Bourre et al., 1997), this abnormality may reflect reductions in local biosynthesis. Stearoyl-CoA desaturase (SCD1, delta9-desaturase) is the rate-limiting enzyme in the biosynthesis of oleic acid (18:1n-9) from stearic acid (18:0) (Paton and Ntambi, 2009). The human stearoyl-CoA desaturase gene (SCD1) is highly expressed in human brain and we previously reported that SCD1 mRNA expression was positively correlated with the 18:1/18:0 ratio in the postmortem prefrontal cortex of healthy controls (McNamara et al., 2008b). Although we previously found that SCD1 mRNA expression was not significantly altered in the postmortem prefrontal cortex of BD patients (Liu and McNamara, 2011), the fatty acid pattern observed in the STG of BD patients is consistent with reduced stearoyl-CoA desaturase activity. Furthermore, PUFAs decrease stearoyl-CoA desaturase expression at the level of transcription and mRNA stabilization (Ntambi, 1999), and we found that indices of stearoyl-CoA desaturase activity (18:1/18:0) and 18:1n-9 composition were both inversely correlated with PUFA composition. While these data suggest that the higher PUFA composition observed in the STG of BD patients may contribute to lower stearoyl-CoA desaturase activity and associated abnormalities in SFA and MUFA composition, additional studies investigating STG stearoyl-CoA desaturase mRNA and protein expression will be required to confirm this relationship.

Similar to BD patients, we also found that STG gray matter from MS patients exhibited greater SFA and PUFA levels, and decreased oleic acid levels, compared with controls. It is relevant therefore that oleic acid, a principal product of stearoyl-CoA desaturase activity, is enriched in human brain white matter (Wilson and Bell, 1993) and rat brain myelin (Bourre et al., 1997), and stearoyl-CoA desaturase expression is positively correlated with peripheral axonal myelination (Garbay et al., 1998). Furthermore, a prior postmortem study found that cortical white matter from MS patients exhibited greater SFA and PUFA levels, and lower oleic acid levels, compared with controls (Wilson and Tocher, 1991). Therefore, the lower oleic acid levels observed in the STG of BD and MS patients may be a consequence of reduced white matter within these gray matter tissue homogenates. This is supported in part by a prior postmortem brain study which found that increasing myelin content in postmortem cortical homogenates was positively associated with oleic acid levels (Tatebayashi et al., 2012).

It may also be relevant that the PUFA/MUFA ratio is elevated in cerebral white matter of the experimental allergic encephalomyelitis (EAE) marmoset model of MS which is associated with demyelination (Ohler et al., 2004). The latter finding suggests that the greater PUFA/MUFA ratio observed in the STG of BD and MS patients may be a

consequence of autoimmune demyelination processes. Interestingly, rates of BD among MS patients are greater than the general population (Edwards and Constantinescu, 2004; Joffe et al., 1987; Schiffer et al., 1986). Moreover, patients with or at risk for BD exhibit reduced white matter structural integrity and white matter volumes in the STG (Bellani et al., 2012; Chen et al., 2004; Jones et al., 2009; Mahon et al., 2013), as well as activated T cells (Breunis et al., 2003), elevated pro-inflammatory signaling (Padmos et al., 2008), and autoimmunity (Padmos et al., 2004). Elevated pro-inflammatory signaling in BD and MS may involve epigenetic modifications in inflammatory genes (Rao et al., 2012) as well as environmental factors (McNamara and Lotrich, 2012). Together, these data suggest that there maybe a relationship between inflammation-induced demyelination processes and the fatty acid abnormalities observed in the STG of BD and MS patients.

In summary, the present cross-sectional postmortem study demonstrates that abnormalities in STG fatty acid composition distinguish BD from SZ and MDD, could not be wholly attributed to treatment with mood-stabilizer medications, and were very similar to the abnormalities observed in the STG of MS patients. The fatty acid abnormalities observed in the STG of BD and MS patients may contribute to, or are a consequence of, common underlying pathological processes associated with white matter pathology including inflammation. Additional studies using alternative approaches including diffusion tensor imaging and PET are warranted to further investigate the relationship between peripheral markers of PUFA status and STG fatty acid incorporation and white matter structural integrity in patients with BD and MS.

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