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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.