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# Abnormalities in the fatty acid composition of the postmortem orbitofrontal cortex of schizophrenic patients: Gender differences and partial normalization with antipsychotic medications

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**Abstract**

Previous studies have observed significant abnormalities in the fatty acid composition of peripheral tissues from drug-naïve first-episode schizophrenic (SZ) patients relative to normal controls, including deficits in omega-3 and omega-6 polyunsaturated fatty acids, which are partially normalized following chronic antipsychotic treatment. We hypothesized that postmortem cortical tissue from patients with SZ would also exhibit deficits in cortical docosahexaenoic acid (DHA, 22:6n-3) and arachidonic acid (AA; 20:4n-6) relative to normal controls, and that these deficits would be greater in drug-free SZ patients. We determined the total fatty acid composition of postmortem orbitofrontal cortex (OFC) (Brodmann area 10) from drug-free and antipsychotic-treated SZ patients ($n=21$) and age-matched normal controls ($n=26$) by gas chromatography. After correction for multiple comparisons, significantly lower DHA (−20%) concentrations, and significantly greater vaccenic acid (VA) (+12.5) concentrations, were found in the OFC of SZ patients relative to normal controls. Relative to age-matched same-gender controls, OFC DHA deficits, and elevated AA:DHA, oleic acid:DHA and docosapentaenoic acid (22:5n-6):DHA ratios, were found in male but not female SZ patients. SZ patients that died of cardiovascular-related disease exhibited lower DHA (−31%) and AA (−19%) concentrations, and greater OA (+20%) and VA (+17%) concentrations, relative to normal controls that also died of cardiovascular-related disease. OFC DHA and AA deficits, and elevations in oleic acid and vaccenic acid, were numerically greater in drug-free SZ patients and were partially normalized in SZ patients treated with antipsychotic medications (atypical>typical). Fatty acid abnormalities could not be wholly attributed to lifestyle or postmortem tissue variables. These findings add to a growing body of evidence implicating omega-3 fatty acid deficiency as well as the OFC in the pathoaetiology of SZ, and suggest that abnormalities in OFC fatty acid composition may be gender-specific and partially normalized by antipsychotic medications.


*Keywords:* Schizophrenia; Postmortem brain; Docosahexaenoic acid (DHA); Arachidonic acid; Prefrontal cortex; Antipsychotic

## 1. Introduction

The principal omega-3 polyunsaturated fatty acid in the mammalian brain, docosahexaenoic acid (DHA,

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22:6n-3) comprises ~15% of total fatty acid composition, and the principal omega-6 polyunsaturated fatty acid arachidonic acid (AA, 20:4n-6) comprises ~10% of total fatty acid composition. Both DHA and AA preferentially accumulate in synaptic membranes where they exert opposing effects on the phosphoinositide-protein kinase C signal transduction pathway and multiple clinically-relevant down-stream neurochemical processes (reviewed in McNamara et al., 2006a). Because mammals cannot synthesize omega-3 or omega-6 polyunsaturated fatty acids *de novo*, they are entirely dependent on dietary sources to procure and maintain adequate peripheral and central tissue concentrations. Cross-national and cross-sectional epidemiological surveys (Christensen and Christensen, 1988; Mellor et al., 1995; Peet, 2003) and intervention trials (Arvindakshan et al., 2003a,b; Emsley et al., 2002; Mellor et al., 1995; Peet et al., 2001, 2002) suggest that dietary omega-3 fatty acid deficiency may increase symptom severity in SZ patients. Moreover, drug-naïve first-episode psychotic patients exhibit significant deficits in omega-3 and omega-6 fatty acid concentrations in their red blood cell (RBC) membranes, suggesting that omega-3 and omega-6 fatty acid deficits *precede* illness onset, and both DHA and AA concentrations are partially normalized following chronic antipsychotic treatment leading to symptomatic improvement (Arvindakshan et al., 2003a,b; Evans et al., 2003; Khan et al., 2002; Reddy et al., 2004).

Primate studies have demonstrated that RBC and cortical DHA concentrations both decrease in response to dietary deficits in omega-3 fatty acid intake, albeit at different rates (RBC>Cortex; Anderson et al., 2005; Connor et al., 1990). To date, three studies have investigated the fatty acid composition of postmortem brain tissue from SZ patients. Horrobin et al. (1991) found that DHA and AA concentrations were lower in the cholesterol ester fraction of the frontal cortex of antipsychotic-treated SZ patients. Yao et al. (2000) found that AA (−14%), but not DHA (−11%), concentrations were significantly lower in the postmortem caudate nucleus of antipsychotic-treated SZ patients. Landen et al. (2002) did not find significant alterations in individual fatty acid concentrations, including DHA or AA, in the postmortem cingulate cortex of antipsychotic-treated SZ patients. These postmortem studies have four notable limitations: (1) SZ patients were being treated with antipsychotic medications that have been found to partially normalize DHA and AA deficits in peripheral tissues of SZ patients (Arvindakshan et al., 2003a,b; Evans et al., 2003; Khan et al., 2002), (2) normal controls were predominantly elderly subjects, and fatty acid concentrations have been found to vary as a function of age at death in human postmortem brain tissue (Carver et al., 2001; Gershbein et al., 1985; McNamara et al., in press), (3) these studies combined male and female SZ patients, and gender differences in brain fatty acid composition (Gershbein et al., 1985; McNamara et al., in press) and SZ epidemiology and psychopathology (Hafner, 2003) have been reported, and (4) these studies employed a relatively small number of SZ patients ($n$=7–11), and may have been underpowered to detect moderate changes in fatty acid concentrations.

In the present study, we determined the total fatty acid composition of postmortem orbitofrontal cortex (Brodmann area 10) from drug-free and antipsychotic-treated male and female SZ patients ($n$=21) and age-matched male and female healthy controls with no history of psychiatric illness ($n$=26). The OFC was selected as the region of interest because it has reciprocal connections with the amygdala, hippocampus, nucleus accumbens, and hypothalamus (Kringelbach and Rolls, 2004), and is thought to play an important role in cognitive and emotional processes relevant to SZ psychopathology (Bechara, 2004; Kringelbach, 2005; London et al., 2000). Previous neuroimaging studies have observed cortical thinning and/or reductions in OFC volume in patients with SZ relative to normal controls (Andreasen et al., 1997; Crespo-Facorro et al., 2000; Goldstein et al., 1999; Gur et al., 2000; Kuperberg et al., 2003; Pantelis et al., 2003), and postmortem studies have found alterations in the expression of multiple genes in the SZ OFC suggestive of synaptic pathology (Akil et al., 1999; Garey et al., 2006; Glantz and Lewis, 1997; Karson et al., 1999; Knable et al., 2004; Meador-Woodruff et al., 1997; Torrey et al., 2005). Our primary hypothesis was that DHA and AA concentrations would be significantly lower in the postmortem OFC of SZ patients, and that these deficits would be greater in drug-free SZ patients.

## 2. Methods

### 2.1. Postmortem brain tissues

Frozen, unfixed, postmortem OFC (Brodmann area 10) from normal (no psychiatric illness) male and female controls ($n$=26) and age-matched male and female patients with DSM-IV defined SZ ($n$=21) were used. Brain tissue was generously provided by the Stanley Research Foundation Neuropathology Consortium (Torrey et al., 2000) and the Harvard Brain Tissue