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Permalink
https://escholarship.org/uc/item/9239t4k0

Journal
Neuroimage, 21(4)

ISSN
1053-8119

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Publication Date
2004-04-01

Peer reviewed
1H MRSI evidence of metabolic abnormalities in childhood-onset schizophrenia

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Received 18 September 2003; revised 12 November 2003; accepted 13 November 2003

In adult schizophrenia, magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) have revealed volumetric and metabolic defects in multiple brain regions, among them the anterior cingulate, frontal cortex, striatum, thalamus, parietal cortex, and frontal and parietal white matter. This study used proton magnetic resonance spectroscopic imaging (1H MRSI) to identify potential metabolic abnormalities in these regions in childhood-onset schizophrenia. 1H MRSI was acquired at 1.5 T and 272 ms echo time in 11 children and adolescents with schizophrenia (aged 7–18 years; seven boys, four girls; all but two medicated) and 20 age-matched healthy controls (10 boys, 10 girls). Absolute levels of N-acetyl compounds (NAA), creatine plus phosphocreatine (Cr), and choline compounds (Cho) were compared among groups in each region. In schizophrenic patients relative to controls, Cr was 14.3% higher in superior anterior cingulate (mean of left and right hemispheres). Cho was higher in superior anterior cingulate (30.3%), frontal cortex (13.3%), and caudate head (13.5%). In the thalamus, there was also a diagnosis-by-gender interaction, whereby NAA was lower in patients for male but not for female subjects. Elevated Cr suggests abnormal local cell-energy demand and elevated Cho is consistent with a prior proposal that patients with early-age-onset schizophrenia exhibit phospholipid membrane disturbances. Low NAA may reflect diminished neuronal integrity.

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Keywords: Anterior cingulate; Frontal cortex; Striatum; Childhood-onset schizophrenia; Magnetic resonance spectroscopy

Introduction

Noninvasive magnetic resonance techniques reveal effects of schizophrenia on the living brain. In adult schizophrenia (reviewed in Lawrie and Abukmeil, 1998; McCarley et al., 1999; Wright et al., 2000), structural magnetic resonance imaging (MRI) has uncovered volumetric and morphometric abnormalities in multiple brain regions, including anterior cingulate, frontal cortex, thalamus, and striatum; regions also implicated, though less strongly, include parietal and occipital cortices and frontal and parietal white matter. Cortical and white matter volumes are often below normal (Lawrie and Abukmeil, 1998; McCarley et al., 1999; Wright et al., 2000), while subcortical nuclei can be larger or smaller than normal, depending in part on neuroleptic treatment (Keshavan et al., 1998; Lang et al., 2001). Proton magnetic resonance spectroscopy (1H MRSI) and proton magnetic resonance spectroscopic imaging (1H MRSI) have documented metabolic abnormalities in many of the same regions (reviewed in Bertolino and Weinberger, 1999; Deicken et al., 2000b; Delamillieure et al., 2000; Kegeles et al., 1998; Keshavan et al., 2000), including below-normal levels of N-acetyl compounds (NAA) or below-normal ratios of NAA to choline plus phosphocreatine (NAA/Cho) or to choline compounds (NAA/Cho). Above-normal Cr has been reported in parietal white matter (Auer et al., 2001), while 31P MRS has measured elevated temporal and parietal phosphocreatine (Blüml et al., 1999; Fuku- zako et al., 1999; Volz et al., 1998). Above-normal Cho or Cho/Cr have also been found in anterior cingulate (Yamasue et al., 2002), frontal lobes (Block et al., 2000; Buckley et al., 1994; Cecil et al., 1999), thalamus (Auer et al., 2001), basal ganglia (Fujimoto et al., 1996; Shioiri et al., 1996), and parietal white matter (Auer et al., 2001).

These MRS findings yield insights into possible brain mechanisms of schizophrenia. Low NAA is consistent with diminished neuronal integrity (Birken and Oldendorf, 1989; Urenjak et al., 1992, 1993), including possible mitochondrial dysfunction (Petroff et al., 2003). High Cr may reflect disturbed energy metabolism of neurons and/or glia, based on the well-known role of creatine and phosphocreatine in ATP transduction (Siesjö, 1978). Since multiple choline compounds are involved in neuronal and glial phospholipid metabolism (Aiken and Gillies, 1996), elevated Cho may imply disturbed membrane “turnover” (Gill et al., 1990; Gupta et al., 2000; Miller et al., 1996; Speck et al., 1996). Auer et al. (2001)
have interpreted elevated Cho as supportive of the “membrane hypothesis” of schizophrenia (Fenton et al., 2000; Horrobin et al., 1994). They have suggested that earlier onset occurs in patients with more severe phospholipid disturbances (Auer et al., 2001). Childhood-onset schizophrenia is thought of as a more severe form of schizophrenia (Asarnow and Asarnow, 1994) and by definition emerges relatively early in life. MRI abnormalities have been found in many of the same brain regions in childhood-onset schizophrenia as in adult schizophrenia (reviewed in Hendren et al., 2000; Mehler and Wannke, 2002; Rapoport et al., 2001; Sowell et al., 2000). The proposal of Auer et al. (2001) implies that, of the three 1H MRS metabolic defects seen in adult schizophrenia, low NAA, high Cr, and high Cho, elevated Cho should be especially prominent in patients with childhood-onset schizophrenia. Some MRS research (Bertolino et al., 1998, Brooks et al., 1998), including work from this laboratory (Thomas et al., 1998), suggests anterior cingulate and frontal metabolite abnormalities in childhood-onset schizophrenia, including below-normal NAA/Cr. The number of patients with childhood-onset schizophrenia examined with 1H MRS to date, however, is small, implying a need for more investigation. Further, most studies in adult- and childhood-onset schizophrenia acquired 1H MRS from one or two isolated sites. Most reported results as ratios to Cr (an inherently ambiguous format) rather than as absolute metabolite levels. And few determined the tissue composition (gray matter, white matter, CSF) of the 1H MRS volumes acquired.

We undertook an exploratory 1H MRSI study on a small number of children and adolescents with childhood-onset schizophrenia and age-matched healthy controls. Absolute levels of NAA, Cr, and Cho were measured in anterior cingulate, frontal cortex, thalamus, and striatum, as well as in parietal and occipital cortices and frontal and parietal white matter, accounting for 1H MRS voxel tissue composition. Based on the above-cited MRI and MRS literature and the proposal of Auer et al. (2001), we hypothesized below-normal NAA and above-normal Cr and Cho in each of these regions. Other regions known to show structural and metabolic abnormalities in schizophrenia, such as the mesial temporal lobes (Levitt et al., 2001; Matsumoto et al., 2001a,b), were outside the scope of this investigation.

### Methods

**Subjects**

The study was conducted under the supervision of the UCLA Human Subjects Review Board. Informed consent was obtained from all parents or legal guardians, and written assent was obtained from all children before participation. Eleven patients with childhood-onset schizophrenia (7–17.5 years; mean age ± SD, 12.3 ± 3.8 years; seven boys, four girls) were recruited. Patients had to have a DSM-IV diagnosis of schizophrenia, absence of neurologic or other nonpsychiatric illness, and onset of symptoms by age 14 to be included. Diagnoses were based on a structured interview using the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997). Current medication and medication history for patients are listed in Table 1. Twenty healthy control children and adolescents (6.8–16.3 years; mean age ± SD, 11.7 ± 2.9 years; 10 boys, 10 girls) were recruited from public and private schools in the community. These subjects were screened for psychiatric, neurologic, or developmental disorders by developmental history and K-SADS-PL (Kaufman et al., 1997) interviews with parent and child. Subjects were excluded from the normal sample if they met criteria for any lifetime significant medical disorder or Axis I mental disorder. Subject ascertainment and diagnosis are detailed in Asarnow et al. (2001). Several patients and no controls had first-degree relatives with history of schizophrenia or other psychiatric illness.

Full-scale IQ of 9 of the 11 patients with childhood-onset schizophrenia was assessed (Table 1) using the Wechsler Intelligence Scale for Children-Revised (WISCR-R; Wechsler, 1974) and averaged 94.4 ± 12.6 (mean ± SD) across the group. This was significantly lower (F = 15.5; df = 1.28; P = 0.001; ANOVA) than the IQ of the control sample, 118.4 ± 16.2 (mean ± SD).

### MRI 1H MRSI acquisition

MR methods were as described in Gupta et al. (2000) with modifications. MRI and 1H MRSI of the brain were acquired in the same session lasting 1–1.5 h on a 1.5-T GE system (Signa Horizon 5.x) using a standard quadrature head coil. Six of eleven childhood-onset schizophrenic patients (Table 1) and no healthy control subjects were sedated with intravenous propofol anesthesia at time of scan. Dose and details of administration were determined by the staff anesthesiologist presiding. MR sequences were acquired from each subject in the following order. After initial localizer scout scan, axial fast spin-echo (FSE) MRI was acquired of the entire brain [repetition time (TR)/TE = 3000/13 ms; 3-mm contiguous slices; 0.94 × 0.94 mm² in-plane resolution]. This sequence was...
yielded proton-density-weighted images. These images were used to identify the neuroanatomic structures within which individual 1H MRSI voxels were selected during post-processing to provide the proton-density intensity values to which 1H MRSI metabolite resonance intensities were normalized as part of the process of absolute quantitation of metabolite levels. Next, a sagittal whole-brain volumetric acquisition was performed using a spoiled gradient-echoed spin (SPGR) sequence (TR/TE = 24/9 ms; 1.2-mm contiguous partitions; 0.94 × 0.94 mm² in-plane resolution). This sequence yielded T1-weighted images used for MRI tissue segmentation. Finally, multislice 1H MRSI (Duyan et al., 1993) was acquired using a 2D inversion-recovery sequence with CHESS (Haase et al., 1985) water-suppression [TR/inversion time (TI)/TE = 2300/170/272 ms; 1 average; 12-mm slice thickness; 10 × 10 mm² in-plane resolution, nominal voxel volume 1.2 cc] from three contiguous axial slices (Fig. 1). The first slice centered on the dorsoventral midplane of the basal ganglia, the second on the ventricles, and the third on the supraventricular brain. The latter two slices sampled wide areas of frontal, parietal, and occipital gray and white matter.

MR image processing

MRI scans were reviewed by staff radiologists to exclude subjects with structural or clinical abnormalities. MRI (and 1H MRSI) post-processing were conducted with operator blinded to subject diagnosis. Tissue segmentation of T1-weighted MRI has been described (Blanton et al., 2001). Briefly, 20 points each of subject diagnosis. Tissue segmentation of T1-weighted MRI has been described (Blanton et al., 2001) onto the axial proton-density-weighted MRI volume, which CSF component volumes were then coregistered (Woods et al., 2002) with N-acetyl compounds (NAA; 2.01 ppm), creatine plus phosphocreatine (Cr; 3.03 ppm), and choline compounds (Cho; 3.23 ppm). Lactate (Lac; 1.36 ppm) was not assayed since it was not always distinguishable from overlapping lipid resonances.

MROI/H MRSI co-processing

Using the coregistered axial proton-density-weighted MRI to identify anatomy, an individual 1H MRSI voxel was selected within each of the following structures (in left and right cerebral hemispheres): superior anterior cingulate cortex, inferior anterior cingulate cortex; frontal cortex (i.e., any frontal cortex outside the cingulate), parietal cortex, occipital cortex; head of the caudate nucleus, body of the caudate nucleus, putamen, thalamus, frontal white matter, and parietal white matter. These structures were sites of suspected pathology in schizophrenia (see above). Volume percentages of gray matter, white-matter, and CSF in each selected 1H MRSI voxel were calculated from the coregistered gray matter, white matter, and CSF MROI component volumes using home-written IDL software. 1H MRSI voxels were sought that contained ≥75% gray matter for cortical gray matter sites; ≥75% white matter for white matter sites; and ≥50% gray matter for nuclear gray matter sites, but some voxels for some subjects fell below these threshold values. Systematic comparison revealed that there were no significant between-group differences in gray or white matter content at any site. Across two independent raters, both blind to diagnosis, reliability of the voxel-selection procedure was found to be ≥95%. Metabolite peak areas were adjusted for instrumental transmitter and receiver gains, normalized to MRI proton density intensity, and corrected for voxel CSF content. This yielded absolute metabolite levels—uncorrected for T1 and T2 relaxation—expressed in Institutional Units (IU).

Statistical analysis

NAA, Cr, and Cho absolute metabolite levels were analyzed using repeated-measures ANCOVA applied to each left–right structure pair with hemisphere as within-subjects factor and diagnosis as between-subjects factor. Gender and age were used as covariates to account for slight between-group differences in these two variables. This statistical model both accounted for the within-subject character of metabolite comparisons between left- and right-hemisphere homologous structures and tested explicitly for possible lateral asymmetries. Where significant interactions involving diagnosis and hemisphere and/or gender were uncovered, appropriate post hoc comparisons were undertaken using one-way ANOVA. Criterion for statistical significance was P < 0.05. Because this was an exploratory study with a priori hypotheses, Bonferroni correction for multiple comparisons was not applied.

The childhood-onset schizophrenic group had significantly lower IQ than the healthy control group. Since low IQ has been viewed as a cognitive symptom (Aylward et al., 1984; Frith, 1995) and a risk factor (Davidson and Weiser, 2000; Davies et al., 1998; 2001) 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029 2030 2031 2032 2033 2034 2035 2036 2037 2038 2039 2040 2041 2042 2043 2044 2045 2046 2047 2048 2049 2050 2051 2052 2053 2054 2055 2056 2057 2058 2059 2060 2061 2062 2063 2064 2065 2066 2067
Data quality

At this long TE (272 ms), MR spectra acquired from juvenile brains were typically of high quality, featuring prominent peaks for NAA, Cr, and Cho. Lac was generally not evident, but its presence cannot be excluded with certainty due to the aforementioned overlap with lipids. Fig. 2 shows a spectrum from a representative 1H MRSI voxel in the head of the right caudate nucleus of a 9.6-9.0-year-old female patient with schizophrenia compared to an analogous spectrum from a healthy 10.2-year-old girl. Cho and, to a lesser extent Cr, are visibly elevated, while NAA is lower in the schizophrenic spectrum. At this site, 8 of 11 subjects with schizophrenia had a Cho level above the healthy-control mean; for 5 of 11 it was 1 SD or more above.

Main effects of subject diagnosis on regional neurometabolite levels

Tables 2–4 list absolute levels of NAA, Cr, and Cho at all sites for both subject groups. The following differences (means of left- and right-hemisphere structures) between the childhood-onset schizophrenic group and the healthy control group were significant (ANCOVA). In superior anterior cingulate, Cr was 14.3% higher ($F = 5.0; df = 1,21; P = 0.04$) in patients than in controls. Cho was higher in patients than in controls in superior anterior cingulate (30.3%; $F = 9.6; df = 1,21; P = 0.006$), frontal cortex (13.3%; $F = 6.3; df = 1,15; P = 0.02$), and caudate head (13.5%; $F = 5.2; df = 1,23; P = 0.03$). No other main effects of diagnosis were significant.

Neurometabolite levels: interactions of subject diagnosis with cerebral hemisphere, gender, and/or age

ANCOVA revealed significant interactions involving diagnosis for NAA, Cr, and Cho. For NAA, there were several such interactions. In the thalamus, there was a significant diagnosis-by-gender interaction ($F = 6.2; df = 1,22; P = 0.02$). In post hoc ANOVA (Fig. 3), thalamic NAA was significantly lower in male patients than in female patients ($F = 19.5; df = 1,10; P = 0.002$) or in male controls ($F = 5.8; df = 1,16; P = 0.03$). NAA did not differ significantly between female patients and female controls ($F = 3.4; df = 1,12; P = ns$) or between female controls and male controls ($F = 0.74; df = 1,18; P = ns$). In caudate body, there was a
Table 3

<table>
<thead>
<tr>
<th>Region</th>
<th>Diagnosis</th>
<th>Mean ± SD</th>
<th>ANCOVA</th>
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<td></td>
<td>Left</td>
<td>Right</td>
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<td>2.7 ± 0.8</td>
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<tr>
<td>Caudate head</td>
<td>schizophrenia</td>
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<td>2.7 ± 0.8</td>
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<td>2.7 ± 0.8</td>
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<td></td>
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<td>2.8 ± 0.8</td>
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<td>3.1 ± 0.9</td>
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<td>Frontal white</td>
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ANOVA is repeated-measures with between-subjects variable diagnosis, within-subjects variable hemisphere, and covariates age and sex.

Table 4

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<td>control</td>
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ANOVA is repeated-measures with between-subjects variable diagnosis, within-subjects variable hemisphere, and covariates age and sex.

Fig. 3. Absolute levels in Institutional Units (IU; group means ± SD) of NAA in the thalamus (mean left and right) of male (rising stripes) and female (pink dots) childhood-onset schizophrenia patients and male (falling stripes) and female (plaid) age-matched healthy controls. NAA was 17.6% lower in male patients than in male controls (*P < 0.05, ANOVA) and 44.6% higher in female than in male patients (**P < 0.01, ANOVA).

The principal findings of this long-TE 1H MRSI study were: (1) above-normal levels of creatine plus phosphocreatine in superior anterior cingulate and (2) above-normal levels of choline com-

**Discussion**

Patients taking neuroleptic medication at time of study did not differ significantly from unmedicated patients for any of the above principal effects of diagnosis (all F < 0.40; df = 1.9; P = ns). Nor did patients sedated during MR scanning differ significantly from unsedated patients on these measures (all F < 3.9; df = 1.9; P = ns), with the exception of Cho in frontal cortex. Frontal cortex Cho was 34.5% higher in sedated than in unsedated patients (F = 8.2; df = 1.10; P = 0.02).

**Neurometabolic levels: effects of medication and sedation**

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The principal findings of this long-TE 1H MRSI study were: (1) above-normal levels of creatine plus phosphocreatine in superior anterior cingulate and (2) above-normal levels of choline com-
pounds in superior anterior cingulate, frontal cortex, and caudate, head in child and adolescent patients with childhood-onset schiz.
phrenia. These brain regions exhibit structural (Lawrie and Abuk-
meil, 1998; McCarley et al., 1999; Wright et al., 2000) and
metabolic (Bertolino and Weinberger, 1999; Deicken et al.,
2000b; Delamilleure et al., 2000; Kegeles et al., 1998; Keshavan
et al., 2000) abnormalities in adult schizophrenia. The present
findings suggest that metabolic disturbances exist in these regions
in childhood-onset schizophrenia as well.

The first major finding was above-normal Cr in superior
anterior cingulate. An earlier study from this laboratory (Thomas
et al., 1998) acquired single-voxel $^1$H MRS from a region labeled
“medial frontal cortex” that roughly overlaps with the “superior
anterior cingulate” of the present report. Detailed voluming studies
in progress in our laboratory suggest that both regions actually
contain a mix of anterior cingulate and superior frontal gyral tissue.

The present finding suggests that elevated Cr may have contributed
to the below-normal NAA/Cr seen in patients with childhood-onset
schizophrenia, this region in Thomas et al. (1998), Auer et al.
(2001) have suggested that elevated Cr in schizophrenia signals
reduced cellular energy demand and may occur in response to
chronic use of dopaminergic agents. Several patients had been
treated with pharmacologics that influence the dopaminergic sys-
tems of the brain (Table 1). Elevated Cr may also reflect patho-
logically altered cellular energetics accompanying putative cell-
membrane disturbances in schizophrenia (see next paragraph).

The second major finding was above-normal Cho at three sites.
This is generally consistent with the notion of Auer et al. (2001)
that elevated Cho should be evident in schizophrenic patients with
younger age-of-onset. The Cho signal is thought to rise in tissues
undergoing enhanced throughput of phospholipid membrane con-
stituents, as during times of membrane build-up or degradation
(Gill et al., 1990; Speck et al., 1996). In this sense, the present
results support the notion of membrane abnormalities in schizo-
phrenia (Fenton et al., 2000; Horrobin et al., 1994) championed by
Auer et al. (2001). Unlike Auer et al. (2001), however, we
observed above-normal Cho in superior anterior cingulate, frontal
cortex, and caudate head, rather than in left thalami and left
parietal white matter. A recent report (Yamasue et al., 2002)
documents below-normal NAA/Cho and above-normal Cho/Cr
in the anterior cingulate in adult schizophrenia. Above-normal
Cho (Buckley et al., 1994) or Cho/Cr (Cecil et al., 1999) and
below-normal NAA/Cho (Block et al., 2000) have been found
previously in the frontal lobes in adult schizophrenia. Two
previous studies in adult-onset schizophrenia (Fujimoto et al.,
1996; Shoii et al., 1996) found above-normal Cho in the basal
ganglia. Bertolino et al. (1998) found (not significantly) 8–10% above-normal Cho/Cr in putamen in patients with childhood-onset
schizophrenia. Fukuzako et al. (1995), in contrast, did not find
differences between adults with schizophrenia and healthy con-
trols in Cho/Cr in left frontal lobe. Nor did Busillo et al. (2001)
find differences between adults with schizophrenia and healthy
controls in Cho in the caudate. These disparate findings exemplify
the difficulties in consistently replicating $^1$H MRS Cho findings in
schizophrenia (Deicken et al., 2000b). Putative brain Cho abnor-
malities in schizophrenia may occur in multiple brain regions and
the site or sites where they are most readily detected may vary
with subject population and/or with MRS technique. The present
long-TE $^1$H MRSI study using absolute metabolite quantitation
taking account of voxel tissue content suggests that Cho abnor-
malities do exist in childhood-onset schizophrenia. It is also
noteworthy that the cingulate, frontal cortex, and striatum form
neuronal circuits that participate in the execution of higher
behavioral functions that can be impaired in schizophrenia (Tekin
and Cummings, 2002). Thus, this study is consistent with a
common membrane disturbance besetting all three regions possi-
ably linked to the behavioral symptoms of childhood-onset schizo-
phrenia. At one site, frontal cortex, Cho was significantly higher
in propofol-sedated than in unsedated patients. Since more se-
verely symptomatic patients are more likely to require sedation, it
is thus unclear whether elevated frontal Cho is due to propofol
action or to severity of illness.

Since Cho and Cr are present in higher quantities in glia than in
neurons (Brand et al., 1993; Urenjak et al., 1993), Cr and Cho
tissue levels may index glial density or functional integrity (Gupta
et al., 2000; Miller et al., 1996). Alternative explanations of elevated Cr
and/or Cho in cingulate, frontal cortex, and striatum in the present
study may therefore be local glial cell proliferation, glial metabolic
hyperactivity, or abnormal composition of glial population. Prolif-
eration (or loss) of glial cells may in part underlie the gross
volumetric changes observed in striatal nuclei of patients with
schizophrenia with qualitative MRI (Corson et al., 1999; Hokama
et al., 1995; Keshavan et al., 1998; Shihabuddin et al., 2001).
Recent pathology studies reveal effects of schizophrenia on astro-
glia or oligodendrocytes in prefrontal cortex or white matter (Hof
et al., 2002, 2003; Rajkowska et al., 2002) and DNA microarray
investigation has found dysregulation of myelination-related genes
in schizophrenia (Hakak et al., 2001). Membrane activity, myelino-
genesis (or myelin degradation), and/or other glial activity may be
results of schizophrenia and/or of pharmacologic treatment. The
small number of patients and their heterogeneity with respect to
medication status and history (Table 1), however, preclude a
thorough analysis of potential pharmacologic influences on the
present findings.

Of multiple minor findings of the present study, we comment
on only one. This finding was that thalamic NAA was lower in
male patients with childhood-onset schizophrenia than in female
patients or in male controls. Multiple studies have found below-
normal NAA or NAA/Cr in the thalamus of adult patients with
schizophrenia (Auer et al., 2001; Deicken et al., 2000a; Ende et al.,
2001; Omori et al., 1997, 2000; but see Delamilleure et al., 2002).
These findings imply neuronal dysfunction in this nucleus in
schizophrenia, consistent with volumetric abnormalities in adult
(Ananth et al., 2002; Gilbert et al., 2001; Mehler and Warnke,
2002; Portas et al., 1998; Volz et al., 2000) and child (Kumra et al.,
2000; Sowell et al., 2000) patients with schizophrenia. The present
study also supports the notion of low thalamic NAA in schizo-
phrenia, but suggests that gender differences may be important in
child and adolescent patients with this disorder. Note that voxels
were sampled indiscriminately from all parts of the thalamus in the
present study, while recent findings in schizophrenia (Gilbert et
al., 2001) and other pediatric psychiatric conditions (Smith et al.,
in press) suggest that neurochemical concentrations vary regionally
within the thalamus. More precise MRI segmentation might allow
$^1$H MRSI effects in childhood-onset schizophrenia to be ascribed to
particular subnuclei within the thalamus.

This is an exploratory study with a small number of subjects.
Results should be confirmed on larger and more homogeneous
subject populations. There are several further limitations. Pharma-
cologic treatment, sedation during MR acquisition, and low IQ in
the patient, but not the control, group represent confounds in
interpreting the results. Effects ascribed to subject diagnosis may
in reality have been wholly or partially due to these other factors. In particular, in frontal cortex, Cho was significantly higher in sedated than in unsedated patients. Ideally, future studies should examine drug-naive patients who do not require sedation and compare them to lower-IQ healthy controls, although assembling such populations for this relatively rare disorder would represent a considerable experimental challenge and might exclude severely symptomatic patients in need of study. 1H MR spectra were acquired at long TE and were not fully relaxed. Subject tolerance and practical constraints on scanner time, however, did not permit us to undertake the repeated measurements required to correct metabolite levels for T1 and T2 effects. Therefore, between-group differences in absolute metabolite levels may reflect differences in tissue relaxation properties as well as differences in true metabolite concentrations. Abnormalities in relaxation properties, if extant, would represent a different kind of pathology than differences in concentrations, but would nonetheless be of interest in illuminating the neural bases of childhood-onset schizophrenia. A further limitation is that data post-processing did not take account of the point-spread function of MRSI.

Bearing its limitations in mind, the present study suggests that cell-membrane and/or cell-energetic metabolism are abnormal in anterior cingulate, frontal cortex, and striatum of childhood-onset schizophrenic patients. These results contribute to previously reported volumetric and metabolic effects in childhood- and adult-onset schizophrenia. Similarities with findings in adults may support a common etiology for childhood- and adult-onset schizophrenia.

521 Uncited reference

523 Shapleske et al., 2002

524 Acknowledgments

525 The authors thank Laura Heinichen, Leah Miner, David Fadale, and Mimi Lee for assistance with data acquisition and processing. Special thanks to Katherine Nan, PhD, for reviewing an earlier version of the manuscript. This research was supported in part by a Stanley Foundation Grant and by NARSAD grant # 015399 to Dr. Levitt.

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