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Authors
O'Neill, J
Levitt, J
Caplan, R
et al.

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^{1}H MRSI evidence of metabolic abnormalities in childhood-onset schizophrenia

Joseph O'Neill,[a,*] Jennifer Levitt,[a] Rochelle Caplan,[a] Robert Asarnow,[a,b] James T. McCracken,[a] Arthur W. Toga,[c] and Jeffry R. Alger[d]

[a] *Division of Child and Adolescent Psychiatry, University of California at Los Angeles, Los Angeles, CA 90095, USA*
[b] *Department of Psychology, University of California at Los Angeles, Los Angeles, CA 90095, USA*
[c] *Laboratory of Neuroimaging, University of California at Los Angeles, Los Angeles, CA 90095, USA*
[d] *Department of Radiology, Brain Research Institute, and Ahmanson-Lovelace Brain Mapping Center, University of California at Los Angeles, Los Angeles, CA 90095, USA*

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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 (s^{1}H MRSI) to identify potential metabolic abnormalities in these regions in childhood-onset schizophrenia. ^{1}H 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-of-onset schizophrenia exhibit phospholipid membrane disturbances. Low NAA may reflect diminished neuronal integrity.

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 (^{1}H MRS) and proton magnetic resonance spectroscopic imaging (^{1}H 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 creatine plus phosphocreatine (NAA/Cr) or to choline compounds (NAA/Cho). Above-normal Cr has been reported in parietal white matter (Auer et al., 2001), while ^{31}P MRS has measured elevated temporal and parietal phosphocreatine (Blüml et al., 1999; Fukuzako 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)

* Corresponding author. Division of Child and Adolescent Psychiatry, University of California at Los Angeles, NPI 47-417A, 760 Westwood Plaza, Los Angeles, CA 90024-1759. Fax: +1-310-206-4446.
E-mail address: joneill@mednet.ucla.edu (J. O'Neill).
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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 Warnke, 2002; Rapoport et al., 2001; Sowell et al., 2000). The proposal of Auer et al. (2001) implies that, of the three ^{1}H 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 ^{1}H MRS to date, however, is small, implying a need for more investigation. Further, most studies in adult- and childhood-onset schizophrenia acquired ^{1}H 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 ^{1}H MRS volumes acquired.

We undertook an exploratory ^{1}H 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 ^{1}H MRSI 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.

Table 1
Age, gender, IQ, concurrent and past medication, and propofol sedation during MR acquisition for schizophrenic subjects

Age (years)	Gender	IQ	Medication	History	Sedation
7.0	m	96	risperidone	imipramine, risperidone, olanzapine	yes
8.8	m	95	amphetamine salts, risperidone	none	yes
11.1	m	70	none	none	yes
11.9	m	101	fluoxetine, risperidone	none	no
15.8	m	–	clozapine, lithium, ziprasidone	divalproex, gabapentine, lithium, thiothixene, olanzapine, risperidone, sertraline	yes
16.6	m	99	clonazepam, risperidone, trazadone	divalproex, quetiapine, ethosuximide, zonisamide	yes
17.5	m	107	benztropine, risperidone	none	no
8.6	fm	–	clozapine	none	yes
9.6	fm	87	none	none	no
11.5	fm	84	benztropine, paroxetine, risperidone	none	no
16.7	fm	111	clozapine	none	no

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/^{1}H MRSI acquisition

MR methods were as described in Gupta et al. (2000) with modifications. MRI and ^{1}H 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 mm^2 in-plane resolution]. This sequence

yielded proton-density-weighted images. These images were used to identify the neuroanatomic structures within which individual ^{1}H MRSI voxels were selected during post-processing and to provide the proton-density intensity values to which ^{1}H 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-recalled echo (SPGR) sequence (TR/TE = 24/9 ms; 1.2-mm contiguous partitions; 0.94 × 0.94 mm^2 in-plane resolution). This sequence yielded T1-weighted images used for MRI tissue segmentation. Finally, multislice ^{1}H MRSI (Duyn 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 mm^2 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 ^{1}H 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 representative gray matter, white matter, CSF, and non-brain tissue were selected manually within each subject's T1-weighted volume. An intensity-based algorithm separated the MRI into gray matter, white matter, CSF, and non-brain component volumes. Interrater correlation coefficients of 0.94–0.98 have been assessed for these methods (Sowell et al., 1999). The gray matter, white matter, and CSF component volumes were then coregistered (Woods et al., 1993) onto the axial proton-density-weighted MRI volume, which was already in register with the ^{1}H MRSI volume.

^{1}H MRSI post-processing

After Fourier transform, each subject's ^{1}H MRSI volume underwent sine-bell spatial filtering, 2.0-Hz lorenztian temporal-domain apodization, and automated polynomial baseline fitting using home-written software in the Interactive Data Language (IDL). ^{1}H MRSI voxels with lipid signals exceeding the NAA signal (i.e., those having a substantial contribution from non-brain tissue), with NAA signal-to-noise ratio less than 2.0, with line width greater than 10.0 Hz, or with other detectable artifact (e.g., aliased extracranial lipid signals arising from movement), were rejected manually. Peak intensities were integrated for *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.

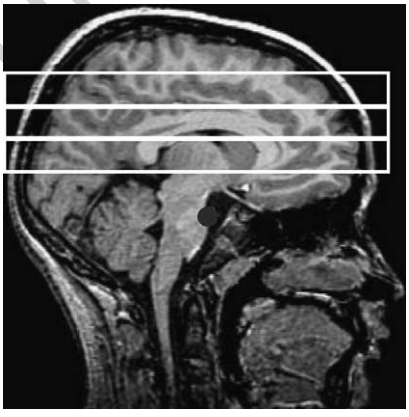

Fig. 1. Sagittal T1-weighted MRI of brain of a 9.6-year-old schizophrenic girl showing positioning of three ^{1}H MRSI acquisition slices.

MRI/^{1}H MRSI co-processing

Using the coregistered axial proton-density-weighted MRI to identify anatomy, an individual ^{1}H 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 ^{1}H MRSI voxel were calculated from the coregistered gray matter, white matter, and CSF MRI component volumes using home-written IDL software. ^{1}H 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;

Kelly and Murray, 2000) for childhood- and adult-onset schizophrenia, it was not deemed advisable to remove effects of IQ statistically. Nine childhood-onset schizophrenic patients and no healthy controls were taking atypical neuroleptics (and, in some cases, other agents; Table 1) at time of MRI/^{1}H MRSI acquisition. Therefore, to assess potential effects of neuroleptic medication, for each significant finding, a one-way ANOVA was performed post hoc comparing medicated to unmedicated patients. Six childhood-onset schizophrenic patients (Table 1) and no healthy controls were under propofol sedation at time of MRI/^{1}H MRSI acquisition. Therefore, to assess potential effects of propofol sedation, for each significant finding, an additional post hoc one-way ANOVA was performed comparing sedated to unsedated patients.

Results

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 ^{1}H MRSI voxel in the head of the right caudate nucleus of a 9.6-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.

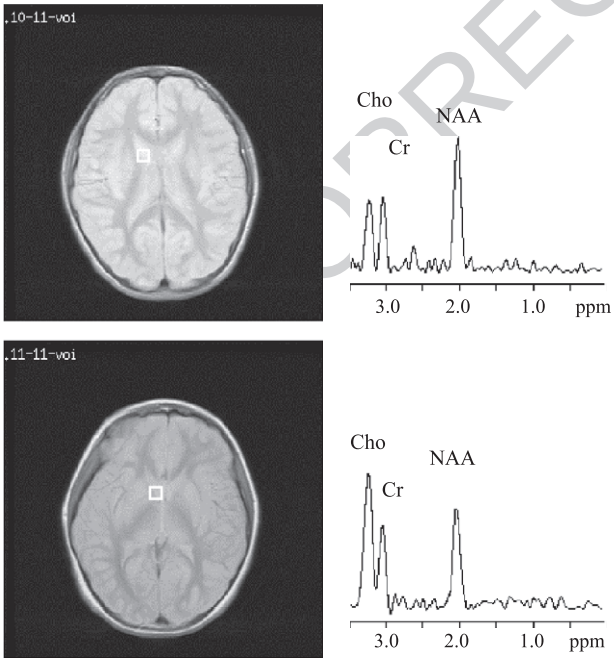

Fig. 2. Axial proton-density-weighted MRI section of brain of healthy 10.2-year-old girl showing location of single ^{1}H MRSI voxel sampled in the head of the right caudate nucleus (top, left). ^{1}H MR spectrum obtained in sampled voxel after post-processing, featuring major peaks for NAA, Cr, and Cho (top, right); same for the 9.6-year-old schizophrenic girl shown in Fig. 1 (bottom). Note elevated Cho and Cr intensities relative to NAA in patient.

Table 2
^{1}H MRSI levels of *N*-acetyl compounds (Institutional Units) at multiple brain sites

Region	Diagnosis	Mean ± SD		ANCOVA		
		Left	Right	*df*	*F*	*P*
Superior anterior cingulate	schizophrenia	7.2 ± 1.9	6.3 ± 1.5	1,21	1.7	ns
	control	6.1 ± 1.6	6.0 ± 1.5			
Inferior anterior cingulate	schizophrenia	5.7 ± 2.2	5.7 ± 1.7	1,24	0.12	ns
	control	6.0 ± 1.6	5.7 ± 1.7			
Frontal cortex	schizophrenia	8.0 ± 0.5	7.5 ± 0.4	1,15	0.74	ns
	control	7.8 ± 1.6	8.2 ± 1.1			
Parietal cortex	schizophrenia	7.3 ± 0.9*	7.6 ± 1.5	1,16	0.39	ns
	control	8.2 ± 1.0	7.6 ± 1.4			
Occipital cortex	schizophrenia	7.9 ± 2.0	7.6 ± 0.9	1,23	0.11	ns
	control	7.4 ± 1.0	7.3 ± 1.1			
Caudate head	schizophrenia	4.1 ± 1.5	4.5 ± 1.3	1,22	0.31	ns
	control	4.6 ± 1.6	3.8 ± 1.4			
Caudate body	schizophrenia	6.3 ± 1.9	5.1 ± 1.5	1,22	0.014	ns
	control	6.1 ± 1.0	5.0 ± 1.5			
Putamen	schizophrenia	5.9 ± 2.0	5.4 ± 1.3	1,24	1.0	ns
	control	5.4 ± 1.8	5.1 ± 1.6			
Thalamus	schizophrenia	6.9 ± 2.0	6.4 ± 1.2	1,22	3.2	ns
	control	7.0 ± 1.2	7.0 ± 1.0			
Frontal white matter	schizophrenia	7.2 ± 1.5	6.8 ± 2.4	1,22	0.017	ns
	control	7.3 ± 1.5	6.7 ± 1.7			
Parietal white matter	schizophrenia	9.5 ± 1.3	8.4 ± 1.2	1,21	0.52	ns
	control	9.9 ± 1.9	8.6 ± 2.4			

* $P < 0.05$ vs. controls (left only; ANOVA). ANCOVA is repeated-measures with between-subjects variable diagnosis, within-subjects variable hemisphere, and covariates age and sex.

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

t3.1 Table 3
t3.2 ^{1}H MRSI levels of creatine + phosphocreatine (Institutional Units) at multiple brain sites

t3.3 Region	Diagnosis	Mean ± SD		ANCOVA		
t3.4		Left	Right	*df*	*F*	*P*
t3.5 Superior anterior	schizophrenia	3.3 ± 0.9	3.0 ± 1.0	1,21	5.0	0.04
t3.6 cingulate	control	2.7 ± 0.6	2.8 ± 0.5			
t3.7 Inferior anterior	schizophrenia	3.0 ± 1.2	3.2 ± 0.9	1,23	0.016	ns
t3.8 cingulate	control	2.7 ± 0.9	2.6 ± 0.9			
t3.9 Frontal cortex	schizophrenia	2.9 ± 0.7	2.8 ± 0.4	1,16	0.027	ns
t3.10	control	2.6 ± 0.8	3.0 ± 0.7			
t3.11 Parietal cortex	schizophrenia	2.8 ± 0.8	2.9 ± 0.9	1,18	2.8	ns
t3.12	control	2.5 ± 0.4	2.6 ± 0.8			
t3.13 Occipital cortex	schizophrenia	2.9 ± 0.9	2.7 ± 0.5	1,25	0.066	ns
t3.14	control	2.4 ± 0.8	2.7 ± 0.8			
t3.15 Caudate head	schizophrenia	2.9 ± 0.7	2.7 ± 0.8	1,22	0.43	ns
t3.16	control	3.0 ± 0.8	2.3 ± 0.5			
t3.17 Caudate body	schizophrenia	3.2 ± 0.8	2.7 ± 0.8	1,25	0.048	ns
t3.18	control	3.0 ± 0.7	2.8 ± 0.8			
t3.19 Putamen	schizophrenia	2.8 ± 0.8	3.1 ± 0.9	1,24	1.0	ns
t3.20	control	2.6 ± 0.8	2.4 ± 0.9			
t3.21 Thalamus	schizophrenia	3.0 ± 0.8	2.9 ± 1.2	1,24	0.11	ns
t3.22	control	2.6 ± 0.6	2.6 ± 0.4			
t3.23 Frontal white	schizophrenia	2.4 ± 0.9	2.4 ± 0.4	1,23	0.12	ns
t3.24 matter	control	2.4 ± 0.8	2.5 ± 0.6			
t3.25 Parietal white	schizophrenia	2.8 ± 0.7	2.9 ± 0.9	1,23	0.041	ns
t3.26 matter	control	2.4 ± 0.8	2.6 ± 0.6			

t3.27 ANCOVA is repeated-measures with between-subjects variable diagnosis, within-subjects variable hemisphere, and covariates age and sex.

t4.1 Table 4
t4.2 ^{1}H MRSI levels of choline compounds (Institutional Units) at multiple brain sites

t4.3 Region	Diagnosis	Mean ± SD		ANCOVA		
t4.4		Left	Right	*df*	*F*	*P*
t4.5 Superior	schizophrenia	4.0 ± 1.3	4.4 ± 1.4	1,21	9.6	0.006
t4.6 anterior cingulate	control	3.2 ± 1.1	3.4 ± 1.0			
t4.7 Inferior	schizophrenia	3.7 ± 0.9	3.3 ± 0.8	1,24	1.1	ns
t4.8 anterior cingulate	control	3.5 ± 0.8	2.9 ± 1.1			
t4.9 Frontal	schizophrenia	3.5 ± 0.7	3.4 ± 0.9	1,15	6.3	0.02
t4.10 cortex	control	2.9 ± 0.9	3.0 ± 0.7			
t4.11 Parietal	schizophrenia	2.7 ± 0.8	2.5 ± 0.7	1,18	0.07	ns
t4.12 cortex	control	2.5 ± 0.7	2.4 ± 0.6			
t4.13 Occipital	schizophrenia	3.2 ± 0.9	2.5 ± 0.7	1,25	1.2	ns
t4.14 cortex	control	2.3 ± 0.8	2.4 ± 1.0			
t4.15 Caudate	schizophrenia	4.2 ± 0.8	4.2 ± 0.7	1,23	5.2	0.03
t4.16 head	control	4.0 ± 1.5	3.5 ± 0.8			
t4.17 Caudate	schizophrenia	3.1 ± 1.1	2.9 ± 0.6	1,24	0.55	ns
t4.18 body	control	3.2 ± 1.0	2.7 ± 1.2			
t4.19 Putamen	schizophrenia	3.4 ± 0.6	3.4 ± 1.0	1,23	0.072	ns
t4.20	control	2.4 ± 0.9	2.6 ± 0.7			
t4.21 Thalamus	schizophrenia	3.9 ± 1.3	3.5 ± 0.8	1,23	0.38	ns
t4.22	control	4.0 ± 0.9	3.7 ± 1.1			
t4.23 Frontal	schizophrenia	4.5 ± 1.3	4.1 ± 1.2	1,23	0.072	ns
t4.24 white matter	control	4.5 ± 1.4	4.2 ± 1.0			
t4.25 Parietal	schizophrenia	3.4 ± 1.1	3.3 ± 0.8	1,23	<0.0005	ns
t4.26 white matter	control	3.7 ± 1.2	3.5 ± 1.3			

t4.27 ANCOVA is repeated-measures with between-subjects variable diagnosis, within-subjects variable hemisphere, and covariates age and sex.

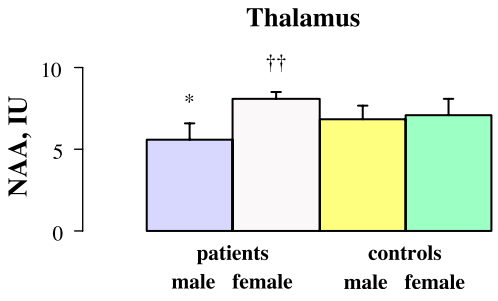

Fig. 3. Absolute levels in Institutional Units (IU; group means ± SD) of NAA in the thalamus (mean left and right) of male (rising stripes) and female (pink dots) childhood-onset schizophrenic patients and male (falling stripes) and female (plaid) age-matched healthy controls. NAA was 17.6% lower in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

significant three-way diagnosis-by-hemisphere-by-age interaction ($F = 5.4$; $df = 1,22$; $P = 0.03$). In parietal cortex, there were a significant diagnosis-by-hemisphere interaction ($F = 7.8$; $df = 1,16$; $P = 0.01$) and a significant diagnosis-by-hemisphere-by-gender interaction ($F = 6.3$; $df = 1,16$; $P = 0.02$). In post hoc ANOVA, NAA was significantly lower in patients than in controls in left ($F = 5.1$; $df = 1,23$; $P = 0.03$), but not in right ($F = 0.004$; $df = 1,23$; $P =$ ns), parietal cortex. For patients, NAA was lowest in left parietal cortex of males and highest in left parietal cortex of females; for controls, NAA was lowest in right parietal cortex of males and highest in right parietal cortex of females. For Cr in superior anterior cingulate, there were a significant diagnosis-by-gender interaction ($F = 5.0$; $df = 1,21$; $P = 0.04$) and a significant diagnosis-by-hemisphere-by-age interaction ($F = 5.0$; $df = 1,21$; $P = 0.04$). Cr was significantly higher in patients than in controls for males ($F = 4.6$; $df = 1,15$; $P = 0.05$), but not for females ($F = 0.67$; $df = 1,12$; $P =$ ns). For Cho, in superior anterior cingulate, there was a significant diagnosis-by-gender interaction ($F = 6.2$; $df = 1,21$; $P = 0.02$), whereby Cho augmentation was significant for male patients vs. male controls (35.3%; $F = 5.3$; $df = 1,15$; $P = 0.005$), but not for female patients vs. female controls (18.2%; $F = 0.62$; $df = 1,12$; $P =$ ns). In frontal cortex, there was also a significant diagnosis-by-gender interaction ($F = 4.8$; $df = 1,15$; $P = 0.04$) for Cho, whereby values were highest for male patients and lowest for female controls. No other interactions were significant.

Neurometabolite levels: effects of medication and sedation

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 ($F = 8.2$; $df = 1,10$; $P = 0.02$).

Discussion

The principal findings of this long-TE ^{1}H 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 schizophrenia. These brain regions exhibit structural (Lawrie and Abukmeil, 1998; McCarley et al., 1999; Wright et al., 2000) and metabolic (Bertolino and Weinberger, 1999; Deicken et al., 2000b; Delamillieure 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 systems of the brain (Table 1). Elevated Cr may also reflect pathologically 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 constituents, 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 schizophrenia (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 thalamus 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; Shioiri 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 controls in Cho/Cr in left frontal lobe. Nor did Bustillo 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 abnormalities 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 abnormalities 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 possibly linked to the behavioral symptoms of childhood-onset schizophrenia. At one site, frontal cortex, Cho was significantly higher in propofol-sedated than in unsedated patients. Since more severely 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 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. Proliferation (or loss) of glial cells may in part underlie the gross volumetric changes observed in striatal nuclei of patients with schizophrenia with quantitative 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 astroglia 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, myelinogenesis (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 Delamillieure 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 schizophrenia, 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. Pharmacologic 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-naïve 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. ^{1}H 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.

Uncited reference

Shapleske et al., 2002

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