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Cerebral glucose metabolism in childhood onset schizophrenia

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Abstract

Decreased frontal cortical glucose metabolism has been demonstrated in adult schizophrenics both at rest and while engaging in tasks that normally increase frontal metabolism, such as the Continuous Performance Test (CPT). The authors tested the hypothesis that adolescents with childhood onset schizophrenia would also demonstrate hypofrontality while performing the CPT. Cerebral glucose metabolism was examined in 16 adolescents (mean age 14.1 ± 1.7) with onset of schizophrenia by age 12 (mean age at onset 9.9 ± 1.8) and 26 healthy adolescents selected to be similar in age, sex and handedness using positron emission tomography and ^{18}F-fluorodeoxyglucose. Patients with childhood onset schizophrenia made fewer correct and more incorrect identifications on the CPT. Region of interest analysis revealed no significant group differences in global cerebral glucose metabolism, but increased metabolic rate in supramarginal gyrus ($F = 6.74$, $P < 0.05$) and inferior frontal gyrus/insula ($F = 7.09$, $P < 0.05$) and decreased metabolic rate in middle frontal gyrus ($F = 6.72$, $P < 0.05$) and superior frontal gyrus ($t = 2.04$, $P < 0.05$) in schizophrenics. Comparison of effect sizes with an identically designed study of adult schizophrenics did not indicate

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more severe hypofrontality in childhood onset schizophrenia. Pixel-based analyses indicated a more complex pattern of group differences in cerebral metabolism with bilaterally increased cerebellar metabolic rate in childhood onset schizophrenics. These findings suggest that childhood onset schizophrenia may be associated with a similar, but not more severe, degree of hypofrontality relative to that seen in adult onset schizophrenia.

Keywords: Neurodevelopment; Hypofrontality; Cerebellum

1. Introduction

Schizophrenia is increasingly considered a neurodevelopmental disorder (Weinberger, 1995). For example, maldevelopment of neural circuitry integrating the activity of the frontal cortex with other brain areas has been hypothesized to underlie the poor performance of schizophrenic patients on measures of frontal lobe functioning, the failure of these patients to activate frontal cortical regions normally during these tasks, as well as the deficit symptoms common in this disorder (Berman et al., 1992; Siegel et al., 1993).

Examination of young adolescents with very early onset schizophrenia offers a rare opportunity to test neurodevelopmental hypotheses of schizophrenia. Studies of this population have demonstrated clinical continuity with adult onset schizophrenia (Russell, 1994), along with more severe premorbid impairments (Russell, 1994; Alaghband-Rad et al., 1995) and a more chronic course (Gordon et al., 1994), possibly reflecting a more severe developmental lesion. Neurobiologic studies of the NIMH childhood onset schizophrenia sample have also supported continuity between very early onset and adult onset schizophrenia (Jacobsen and Rapoport, in press).

Studies of cerebral glucose metabolism and blood flow in adult onset schizophrenics at rest have yielded inconsistent findings (Chua and McKenna, 1995), with some demonstrating reduced anterior to posterior ratios of metabolism in schizophrenia (Buchsbaum et al., 1984; DeLisi et al., 1985), others showing no group differences in frontal metabolism or blood flow (Wiesel et al., 1987; Ebmeier et al., 1995) and still others showing increased frontal metabolism in schizophrenia (Szechtman et al., 1988). Studies measuring glucose metabolism or blood flow during task performance have yielded somewhat more consistent findings, with hypofrontality being demonstrated while adult schizophrenics performed the Wisconsin Card Sorting Test (Berman et al., 1992), the Tower of London (Andreasen et al., 1992) and the Continuous Performance Test (Cohen et al., 1987; Siegel et al., 1993). Hypofrontality was demonstrated in a sample of older adolescent patients with schizophrenia (Chabrol et al., 1986) and has been particularly associated with negative symptoms (Andreasen et al., 1992; Siegel et al., 1993).

In the present study, cerebral glucose metabolism was examined in the NIMH childhood onset schizophrenia sample and compared to that of a matched group of healthy adolescents using positron emission tomography (PET) and ^{18}F-fluorodeoxyglucose (FDG). Subjects performed an auditory Continuous Performance Task (CPT) during FDG uptake which previously was found to be associated with decreased frontal metabolism in a sample of adult onset schizophrenics (Cohen et al., 1987). Given evidence for neurobiologic continuity between childhood onset and adult onset schizophrenia, we hypothesized that hypofrontality would also be observed in this sample and would be associated with negative symptoms. We further hypothesized that hypofrontality would be relatively more severe in childhood onset schizophrenics, possibly reflecting a more severe neurodevelopmental lesion leading to earlier illness onset.

2. Methods

2.1. Subjects

Sixteen schizophrenic adolescents were recruited for an ongoing study of childhood onset

schizophrenia (Kumra et al., 1996). Because this study involved a trial of clozapine, all patients had a history of poor response to or intolerance of at least two typical neuroleptics. Other inclusion criteria were: DSM-III-R diagnosis of schizophrenia, with onset of psychotic symptoms by age 12, premorbid full scale IQ of at least 70 and absence of active medical or neurologic disease. Diagnosis was determined using previous records, and clinical and structured interviews of the adolescents and their parents based on portions of the Schedule for Affective Disorders and Schizophrenia for School-Age Children — Epidemiologic Version (Puig-Antich et al., 1980) and of the Diagnostic Interview for Children and Adolescents Revised (Reich and Welner, 1988).

All schizophrenic subjects (six girls, 10 boys), age 12–18 (mean ± S.D. 14.2 ± 1.7) were pubertal (mean Tanner score of 3.8 ± 1.2, range 2–5). The mean age at the time of onset of psychotic symptoms was 9.9 ± 1.8 years (range 6–12 years). On average, patients had undergone 26.0 ± 18.5 months of neuroleptic therapy and 7.6 ± 10.4 months of hospitalization prior to this study. Mean vocabulary and block design subtest scores from the Wechsler Intelligence Scale for Children — Revised (WISC-R) (Wechsler, 1974) obtained on study entry were 5.3 ± 3.5 and 7.2 ± 2.9, respectively. Three subjects could not undergo intellectual assessment due to the severity of their psychotic symptoms. Mean height and weight for the sample was 161.8 ± 10.9 cm and 61.8 ± 12.2 kg, respectively. Schizophrenic subjects were medication free for an average of 19.5 ± 5.9 (range 9–32) days prior to PET scanning. Two subjects were medication free fewer than 14 days.

Twenty-six normal adolescents with a mean age of 15.1 ± 1.6 participated in the study as comparison subjects. Medical, neurologic and psychiatric illnesses and learning disabilities were screened for by history from parents and by structured interviews using the Diagnostic Interview of Children and Adolescents (DICA) (Herjanic and Reich, 1982) and the DICA-Parent Version administered to parents. Nineteen of the normal subjects had a sibling with Attention Deficit–Hyperactivity Disorder (ADHD) who had participated in a separate study (Zametkin et al., 1993). The normal group included 15 girls and 11 boys, with a mean Tanner stage of 4.1 ± 1.1, mean weight of 57.0 ± 12.9 kg and, for 25 comparison subjects, mean height of 165.0 ± 12.3 cm and mean vocabulary and block design subtest scores of 12.3 ± 2.4 and 13.0 ± 2.5, respectively. Subtest scores were obtained using the WISC-R and the Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981), where appropriate.

Handedness was determined using the 12 handedness items of the Physical and Neurological Examination for Subtle Signs (Denckla, 1985). Twenty-three normal subjects and 11 schizophrenic subjects were right handed. Parents of all subjects provided written informed consent and subjects provided assent for participation in the study. Subject preparation for the PET scan included multiple explanations of the procedure and an opportunity to visit the scanner prior to the procedure. This study was approved by the NIMH Institutional Review Board.

2.2. *Positron emission tomography*

PET scanning was performed using a previously described method designed to minimize radiation exposure to subjects (Zametkin et al., 1993). Beginning a few minutes prior to an injection of 33.7–50.3 MBq of FDG (dose calculated to not exceed 500 mrem to critical organs), all subjects performed a 30-min computerized auditory CPT with eyes patched during FDG uptake. Subjects were asked to press a button each time they identified the lowest intensity of three tones presented in random order. CPT stimulus duration was 1 s, interstimulus interval was 3 s and proportion of targets was 33%.

Subjects voided after the 30-min uptake period, to decrease radiation exposure to the bladder, and were positioned in the scanner where two interleaved sets of 15 slices (30 total) were obtained for each subject, with the lowest slice level 8 mm above and parallel to the canthomeatal line. Scanning duration for each set was 20 min. Tracer input curves were calculated from blood samples drawn through a radial artery catheter in all subjects except four patients with schizophrenia who tolerated only intravenous catheter

placement. No subject under 12 years of age or weighing under 33 kg was scanned. Scanning of patient and normal subjects was interleaved over a 4-year period.

2.3. Image analysis

Raw pixel values were converted into glucose metabolic rates (rCMRglu, in mg/min per 100 g) (Brooks, 1982) and regional rates of glucose metabolism were then measured by an independent rater, blind to diagnosis, for 60 standard ROIs distributed within five planes (Fig. 1). Global glucose metabolic rate was calculated by averaging values for glucose metabolism across all gray matter rich areas of the cortex sampled. Regional rates of glucose metabolism were normalized by dividing each subject's absolute glucose metabolic rate for the ROI by their global metabolic rate.

An exploratory analysis was also conducted in which between-group differences were assessed using Statistical Parametric Mapping (SPM), version 1995 (Friston et al., 1991). After each image was transformed into a standard stereotactic space (Talairach and Tournoux, 1988), images were smoothed using a $10 \times 10 \times 6$-mm Gaussian filter. Differences in global glucose metabolic rate were controlled for using proportional scaling. Between-group comparisons were performed on a pixel-by-pixel basis, with the resulting value of t for each pixel being transformed to a z score. Group differences in relative glucose metabolic rate were considered significant if they corresponded to a z score greater than 2.58 (or $P \leq 0.005$, not corrected for multiple comparisons).

2.4. Assessment of negative symptoms

Schizophrenic subjects were rated using the Scale for the Assessment of Negative Symptoms (Andreasen, 1983) at the end of the drug-free period. Interrater reliability (intraclass correlation coefficient, ICC), based on ratings of ten patients by two sets of child psychiatrists at two points in the study (one rater consistent across both assessments), ranged between 0.81 and 0.92.

2.5. Statistical analysis

Group differences on demographic and performance variables and global glucose metabolic rate were assessed with chi-square analyses and t-tests for independent samples. Normalized ROI data were examined using repeated measures analysis of variance (ANOVA) with diagnosis as a between-subjects factor and side as a within-subjects factor. Significant interactions ($P < 0.05$) were further examined with Bonferroni post-hoc t-tests. Diagnostic differences for midline ROIs were assessed using t-tests. Pearson correlation coefficients were used to examine relationships between symptom ratings and metabolic rates for ROIs showing group differences within the schizophrenic group and between CPT performance and metabolic rates for these ROIs within both groups.

Chi-square analyses, t-tests, ANOVA and Pearson correlation coefficients were computed using SAS (SAS Institute Inc., 1989).

3. Results

There were no significant differences between schizophrenic and normal subjects in age, height, weight, Tanner stage, sex, handedness, or hand used to button press during the CPT. The groups did differ in mean vocabulary and block design subtest scores ($t = 7.19$, d.f. = 36, $P < 0.0001$ and $t = 6.32$, d.f. = 36, $P < 0.0001$, respectively). Due to intermittent failure of the computer recording CPT performance, performance data were recorded for only 13 schizophrenic and 20 normal subjects, although all subjects performed the task. For the subgroups from which CPT data were collected, schizophrenic subjects had significantly fewer CPT hits (schizophrenic subjects = 83.5 ± 63.0, normal subjects = 139.6 ± 40.7, $t = 3.11$, d.f. = 31, $P < 0.01$) and significantly more CPT false alarms (schizophrenic subjects = 65.9 ± 54.7, normal subjects = 8.6 ± 6.9, $t = 4.67$, d.f. = 31, $P < 0.001$).

3.1. Region of interest analysis

Global cerebral glucose metabolism in childhood onset schizophrenics (14.13 ± 2.11 mg/min

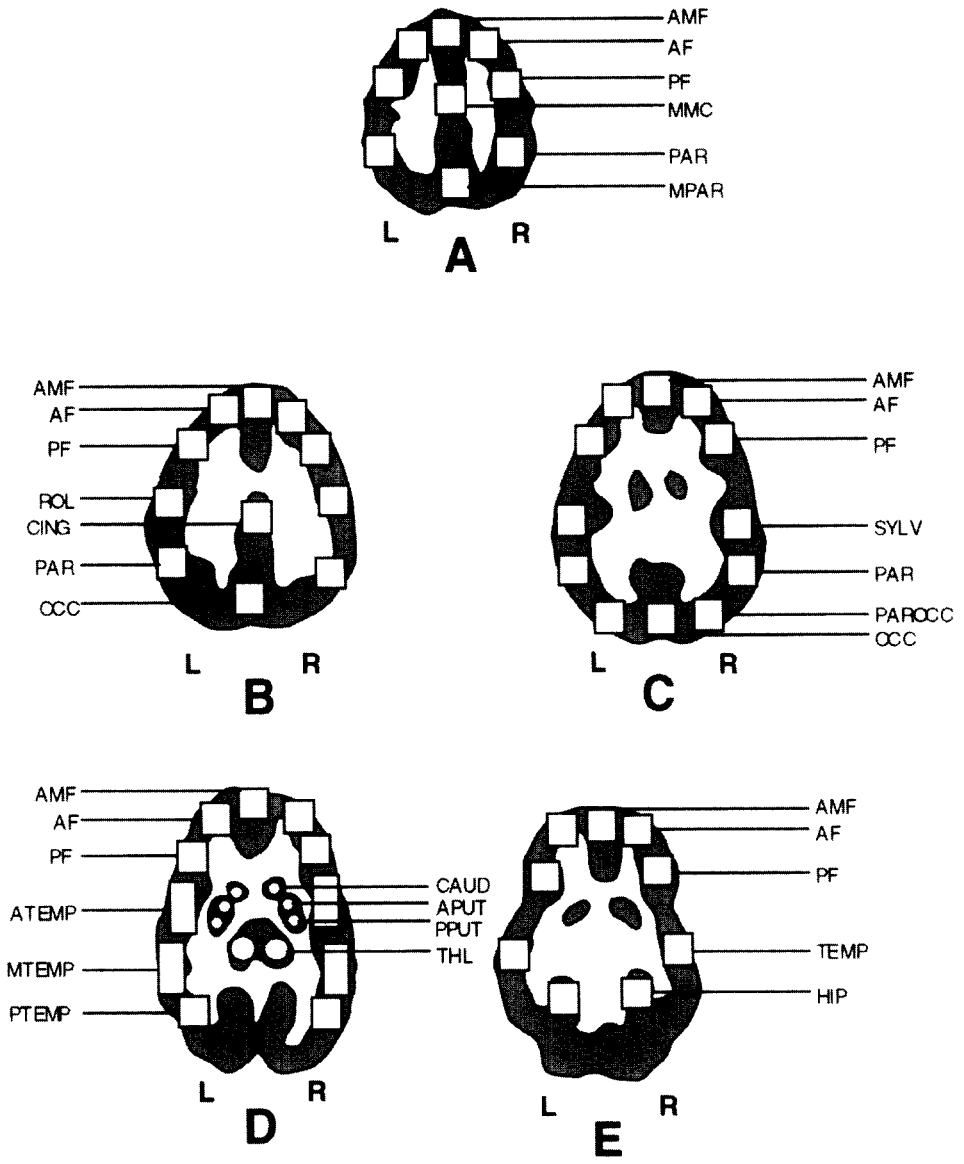

Fig. 1. Template of regions of interest (area of square = 49 pixels). A through E correspond to the five transaxial planes examined; A plane at 94 mm, B plane at 84 mm, C plane at 67 mm, D plane at 53 mm and E plane at 40 mm above the canthomeatal line; L = left, R = right. AMF = anterior medial frontal; AF = anterior frontal; PF = posterior frontal; MMC = mid medial cortex; PAR = parietal; MPAR = medial parietal; ROL = rolandic; CING = middle cingulate; OCC = occipital; SYLV = sylvian; PAROCC = parietal occipital; ATEMP = anterior temporal; MTEMP = middle temporal; PTEMP = posterior temporal; THAL = thalamus; CAUD = caudate; APUT = anterior putamen; PPUT = posterior putamen; TEMP = temporal; and HIP = hippocampus.

per 100 g) did not significantly differ from that in the normal subjects (14.01 ± 2.39 mg/min per 100 g). Mean normalized glucose metabolic rates for each region examined in schizophrenic and normal adolescents are shown in Table 1 along with the results of the repeated measures ANOVA.

Schizophrenics had significantly greater meta-

bolic rate than normal subjects in the parietal region of plane B (supramarginal gyrus) and in the posterior frontal region of plane E (inferior frontal gyrus/insula) and significantly lower metabolic rate than normal subjects in the anterior frontal region of plane C (middle frontal gyrus) and the anterior medial frontal (superior frontal gyrus).

Table 1
Relative glucose metabolic rate in cortical regions of $n = 16$ adolescents with childhood onset schizophrenia and $n = 26$ normal adolescents[a]

Regions	Schizophrenic adolescents			Normal adolescents			
	Left	Right	Medial	Left	Right	Medial	Comment
A plane							
Anterior medial frontal			0.99 ± 0.08			1.01 ± 0.06	
Mid medial cortex			1.00 ± 0.09			1.03 ± 0.10	
Occipital			1.10 ± 0.10			1.09 ± 0.09	
Anterior frontal	1.07 ± 0.09	1.04 ± 0.08		1.02 ± 0.09	1.04 ± 0.08		
Posterior frontal	1.06 ± 0.05	1.06 ± 0.08		1.06 ± 0.07	1.06 ± 0.07		
Parietal[b]	1.08 ± 0.13	1.02 ± 0.10		1.03 ± 0.07	1.06 ± 0.10		S: L > R, N: L = R
B plane							
Anterior medial frontal			0.98 ± 0.06			1.00 ± 0.07	
Cingulate			1.01 ± 0.08			0.98 ± 0.09	
Occipital			1.13 ± 0.14			1.10 ± 0.09	
Anterior frontal[c]	1.05 ± 0.10	1.00 ± 0.09		1.05 ± 0.05	1.03 ± 0.07		L > R
Posterior frontal	1.08 ± 0.06	1.11 ± 0.09		1.06 ± 0.11	1.09 ± 0.12		
Rolandic	0.93 ± 0.09	0.93 ± 0.15		0.91 ± 0.07	0.91 ± 0.07		
Parietal[d]	1.04 ± 0.07	1.00 ± 0.07		0.98 ± 0.06	0.98 ± 0.09		S > N
C plane							
Anterior medial frontal			0.99 ± 0.08			0.98 ± 0.06	
Occipital			1.10 ± 0.15			1.07 ± 0.07	
Anterior frontal[e]	1.00 ± 0.07	0.99 ± 0.09		1.05 ± 0.05	1.04 ± 0.06		S < N
Posterior frontal	1.15 ± 0.09	1.12 ± 0.10		1.11 ± 0.10	1.10 ± 0.09		
Sylvian[f]	0.98 ± 0.07	0.93 ± 0.07		0.99 ± 0.07	0.96 ± 0.06		L > R
Parietal	1.00 ± 0.09	1.00 ± 0.08		0.99 ± 0.08	0.98 ± 0.07		
Parietal–occipital[g]	0.88 ± 0.12	0.82 ± 0.09		0.88 ± 0.07	0.85 ± 0.08		L > R
D plane							
Anterior medial frontal			0.96 ± 0.10			0.94 ± 0.07	
Anterior frontal	1.02 ± 0.08	1.00 ± 0.08		1.03 ± 0.07	1.02 ± 0.06		
Posterior frontal	0.98 ± 0.06	0.96 ± 0.14		0.97 ± 0.07	1.01 ± 0.08		
Anterior temporal	0.97 ± 0.10	0.97 ± 0.10		1.00 ± 0.07	1.01 ± 0.06		
Middle temporal	0.96 ± 0.10	0.92 ± 0.08		0.97 ± 0.06	0.96 ± 0.06		
Posterior temporal	0.88 ± 0.10	0.85 ± 0.10		0.90 ± 0.06	0.87 ± 0.05		
Caudate	0.98 ± 0.10	0.92 ± 0.10		0.96 ± 0.10	0.94 ± 0.09		
Anterior putamen	1.03 ± 0.13	1.00 ± 0.16		1.00 ± 0.22	0.98 ± 0.13		
Posterior putamen	1.00 ± 0.15	0.97 ± 0.13		1.00 ± 0.13	0.95 ± 0.11		
Thalamus	0.96 ± 0.13	0.97 ± 0.11		0.98 ± 0.12	0.99 ± 0.13		

Table 1 (*Continued*)

Regions	Schizophrenic adolescents			Normal adolescents			
	Left	Right	Medial	Left	Right	Medial	Comment
E plane							
Anterior medial frontal[h]			0.92 ± 0.07			0.97 ± 0.07	S < N
Anterior frontal	1.00 ± 0.09	0.95 ± 0.07		1.02 ± 0.08	1.01 ± 0.08		
Posterior frontal[i]	1.05 ± 0.09	1.06 ± 0.08		0.99 ± 0.08	1.02 ± 0.08		S > N
Temporal	0.96 ± 0.08	0.94 ± 0.08		0.93 ± 0.08	0.91 ± 0.08		
Hippocampus[j]	0.75 ± 0.09	0.77 ± 0.05		0.78 ± 0.07	0.75 ± 0.06		

[a]Regional metabolic rates divided by global metabolic rate; analysis of variance, d.f. = 1,40; S = schizophrenic, N = normal subjects.
[b]Diagnosis by side interaction; $F = 8.14$, $P < 0.01$.
[c]Main effect of side; $F = 7.88$, $P < 0.01$.
[d]Main effect of diagnosis; $F = 6.74$, $P < 0.05$.
[e]Main effect of diagnosis; $F = 6.72$, $P < 0.05$.
[f]Main effect of side; $F = 5.16$, $P < 0.05$.
[g]Main effect of side; $F = 7.95$, $P < 0.01$.
[h]$t = 2.04$, d.f. = 40, $P < 0.05$.
[i]Main effect of diagnosis; $F = 7.09$, $P < 0.05$.
[j]Diagnosis by side interaction; $F = 6.08$, $P < 0.05$; post-hoc tests not significant.

Metabolic rate was greater on the left side than on the right across groups in three regions, including the anterior frontal region of plane B (middle frontal gyrus) and the sylvian and parietal occipital regions of plane C (sylvian fissure and parietal/occipital junction). Two regions showed group differences in metabolic asymmetry (diagnosis by side interactions). Post-hoc tests showed that for the parietal region of plane A, metabolic rate was greater on the left in schizophrenic subjects and did not differ in normal subjects. For the hippocampal region of plane E, post-hoc tests were not significant.

When ANOVA was repeated with the subset of 13 schizophrenic and 20 normal subjects for which performance data were available, all diagnostic differences were lost except that for the posterior frontal region of plane E where schizophrenic subjects continued to show significantly greater metabolic rate than normal subjects. Given this inability to detect group differences between the subgroups for which performance data were available, further analyses controlling for performance were not conducted.

Within the schizophrenic group, metabolic rates of the brain regions showing group differences were not significantly correlated with SANS total score, duration of illness, total number of months that patients had received antipsychotic medication prior to study entry, or CPT hits (*P*-values ranging from 1.00 to 0.12). CPT false alarm rate was significantly negatively correlated with metabolic rate of the right parietal region of plane B among schizophrenic subjects ($r = -0.62$, $n = 13$, $P < 0.05$) and significantly positively correlated with metabolic rate of this region among normal subjects ($r = 0.73$, $n = 20$, $P < 0.001$). Among schizophrenic subjects CPT false alarm rate was also significantly positively correlated with metabolic rate of the right posterior frontal region of plane E ($r = 0.57$, $n = 13$, $P < 0.05$). There were no significant correlations with CPT hit rate among normal subjects.

3.2. Statistical parametric mapping

The results of the SPM analysis are shown in Table 2 and in Fig. 2 and reveal a more complex pattern of group differences in cerebral glucose metabolism. Schizophrenic subjects were found to have decreased metabolic rate in the right superior, middle and medial frontal gyrus, right rectus gyrus, cingulate gyrus, and right and left superior temporal gyri. Schizophrenic subjects were also

found to have increased metabolic rate in the left inferior, middle and medial frontal gyrus, right superior and medial frontal gyrus, right and left inferior temporal and fusiform gyrus and right parietal lobe. In addition, metabolic rate was decreased in the right and left caudate and increased in the right and left putamen and thalamus for the schizophrenic group.

Table 2
Statistical parametric mapping: foci of group differences in relative cerebral glucose metabolic rate for $n = 16$ adolescents with childhood onset schizophrenia and $n = 26$ normal adolescents at $P \leq 0.005$

Region	Coordinates (X,Y,Z)			z	Side	Brodmann area (comment)
Schizophrenics < normal subjects						
Frontal cortex	0	22	28	3.77	Midline	32 (anterior cingulate g)
	−2	2	36	3.57	L	32
	12	40	−16	3.13	R	11 (medial front/rectus g)
	28	52	12	2.84	R	9/10 (middle frontal g)
	16	62	16	2.80	R	9/10 (superior frontal g)
	2	58	12	2.77	R	10 (medial frontal g)
	24	44	36	2.77	R	9 (superior/middle front g)
	16	60	4	2.76	R	10 (medial frontal g)
	30	48	24	2.69	R	9/10 (sup/middle front g)
	−30	56	16	2.66	L	10 (sup/middle front g)
Temporal lobe	52	0	4	3.35	R	22 (superior temp g)
	60	−26	8	3.22	R	22/42 (superior temp g)
	58	−52	20	3.20	R	22
	58	−14	12	3.15	R	22/42
	−46	−4	4	3.16	L	22
	40	−10	−4	3.34	R	Insula
	54	−56	28	2.87	R	22/39 (superior temp g)
	38	−12	8	2.85	R	Insula
	56	−14	−24	2.81	R	20/21 (inf temp/fusiform g)
	−30	18	8	2.70	L	Insula
Parietal lobe	−60	−20	16	2.88	L	40 (postcentral gyrus)
	54	−42	36	2.79	R	40 (inf parietal lobule)
	−60	−24	24	2.63	L	2/40 (postcent g/inf par lobule)
Occipital lobe	26	−84	16	2.94	R	18/19 (middle occipital g)
Subcortical nuclei	8	12	8	3.45	R	Caudate
	4	8	0	3.05	R	Caudate
	−12	2	16	2.92	L	Caudate
	−8	12	4	2.79	L	Caudate
Cerebellum	46	−70	−16	3.11	R	
	54	−50	−20	2.96	R	
Schizophrenics > normal subjects						
Frontal cortex	−38	32	4	4.93	L	45/46/47 (inferior front g)
	−38	22	−4	4.33	L	47 (inferior front g)
	8	24	44	4.21	R	8 (superior/medial front g)
	−38	−4	36	3.04	L	4 (precentral gyrus)
	−26	14	44	2.92	L	6/8 (middle frontal gyrus)
	−16	40	−8	2.85	L	10/11 (medial front/rectus g)
	14	48	16	2.74	R	9 (medial frontal gyrus)
	18	44	0	2.73	R	9/32 (medial frontal gyrus)

Table 2 (*Continued*)

Region	Coordinates (X,Y,Z)			z	Side	Brodmann area (comment)
Temporal lobe	44	−34	−12	4.41	R	20/37 (inf temp/fusiform g)
	54	−44	−4	3.15	R	21/37 (inf/middle temp g)
	−42	−8	−20	4.04	L	20 (inferior temp g)
	−56	−36	8	3.11	L	22 (superior temp g)
	−56	−64	4	3.10	L	37 (inf/middle temp g)
	44	−22	−20	2.93	R	20 (inf temp/fusiform g)
	−56	−16	−12	2.90	L	21 (middle temporal g)
	−44	−40	−12	2.79	L	37 (fusiform gyrus)
	−44	−32	16	2.60	L	22 (superior temporal g)
Parietal lobe	40	−8	20	4.34	R	43 (precentral g)
	40	−20	24	4.28	R	2 (postcentral g)
	38	−12	36	3.80	R	4 (postcentral g)
	4	−56	24	3.89	R	23/31 (post cingulate g)
	4	−62	16	3.52	R	23/31
	−4	−54	24	3.13	L	23/31
Occipital lobe	10	−76	8	2.70	R	18 (lingual gyrus)
	−42	−86	0	2.66	L	18 (inferior occipital g)
	−20	−88	−12	2.64	L	17/18 (lingual/fusiform g)
	4	−102	0	2.61	R	17/18 (lingual gyrus)
Subcortical nuclei	18	−26	4	4.34	R	Thalamus
	18	−12	12	3.49	R	Thalamus
	22	−20	−4	3.12	R	Putamen
	−22	−28	0	3.02	L	Thalamus
	−22	10	−8	2.66	L	Putamen
	20	8	12	2.61	R	Putamen
Cerebellum	26	−74	−28	5.52	R	
	−10	−56	−16	5.07	L	
	20	−60	−24	4.79	R	
	−34	−70	−16	3.12	L	

Notes: R = right, L = left, front = frontal, temp = temporal, par = parietal, g = gyrus, sup = superior, inf = inferior, post = posterior.

SPM analysis also indicated that cerebellar metabolic rate was bilaterally increased in schizophrenics. This finding did not change when the analysis was repeated after excluding the three schizophrenic subjects who had the most movement artifact, identified by visual inspection of PET scans prior to transforming them into standard stereotactic space.

ROI sampling of the left and right cerebellum from one slice [corresponding to level 0° − 12, atlas of Matsui and Hirano (1978)] confirmed this group difference. ANOVA using normalized glucose metabolic rates revealed significantly greater cerebellar metabolic rate for schizophrenic subjects ($F = 11.42$, d.f. = 1,40, $P < 0.01$) and significantly greater metabolic rate on the left side for this structure ($F = 5.55$, d.f. = 1,40, $P < 0.05$).

4. Discussion

In this first study of cerebral glucose metabolism in childhood onset schizophrenia, findings from the ROI analyses provide some limited support for the hypothesis of hypofrontality in this disorder. ROI analysis revealed decreased metabolic rates for the schizophrenics in two frontal lobe regions, one of which, the anterior frontal region of plane C, also showed decreased metabolic rate in a sample of later onset schizophrenics studied in an identically designed study conducted by

Cohen et al. (1987). The remaining region showing decreased metabolic rate for childhood onset schizophrenics is analogous to, but one plane lower than, regions found to have decreased metabolic rate in adult schizophrenics in the above-mentioned study. Notably, the posterior frontal region of plane E which showed increased metabolic rate in childhood onset schizophrenics also showed increased metabolic rate in a subgroup of adult schizophrenics with poor auditory CPT performance in the study by Cohen et al. (1987). Relative to the childhood onset schizophrenics in the present study, this poorly performing subgroup made a comparable number of CPT hits but fewer CPT false alarms.

That regions showing decreased metabolism for the schizophrenics did not remain significant when a comparison of subjects with performance data was made suggests that the hypofrontality finding from the ROI analysis is not robust. Comparison of effect sizes observed by Cohen et al. (1987) with those seen in the present study did not indicate more severe hypofrontality for the childhood onset schizophrenics. Thus, while the similar pattern of cerebral metabolic abnormalities suggests similar underlying pathophysiology for childhood and adult onset schizophrenia, these data do not suggest that the earlier onset of symptoms in childhood onset schizophrenia results from a more severe neurodevelopmental lesion associated with more marked hypofrontality.

The left greater than right asymmetry of cerebral glucose metabolism seen across diagnostic groups in this study is consistent with findings from studies of adult subjects at rest (Gur et al., 1995) or engaging in tasks other than those that test visual attention (Berman and Weinberger, 1990). Tasks that assess visual attention, have been associated with the opposite (right greater than left) asymmetry (Berman and Weinberger, 1990), possibly reflecting predominantly right hemisphere mediation of visual attention.

In the present study, previously observed relationships between decreased frontal metabolism and negative symptoms were not observed. Given the small size of the schizophrenic group, this finding must be interpreted with caution.

The exploratory SPM analysis revealed a more complex pattern of group differences in cerebral metabolism and only subtle evidence of hypofrontality. In fact, most group differences in the frontal lobes did not survive SPM analysis conducted with the more stringent statistical threshold of $P < 0.001$. One exception was the anterior cingulate gyrus, a structure previously implicated in attention and in target detection (Posner and Petersen, 1990) and found to be hypometabolic in later onset schizophrenia (Tamminga et al., 1992; Siegel et al., 1993). This structure continued to show significantly decreased metabolic rate in childhood onset schizophrenics at more stringent statistical thresholds.

The thalamus, also implicated in attention (Posner and Petersen, 1990), has been shown to have increased metabolic rate in later onset schizophrenics who have been medication free for less than 6 months (Resnick et al., 1988), as was observed for the present sample of childhood onset schizophrenics using SPM analysis. Basal ganglia metabolic rate has been found to be decreased in never medicated (Buchsbaum et al., 1992a) and medication-free later onset schizophrenics (Resnick et al., 1988; Buchsbaum et al., 1992) and to increase during antipsychotic therapy, particularly in medication responsive patients (Rubin et al., 1991; Buchsbaum et al., 1992). Thus, while the observation of decreased metabolic rate in the caudate of childhood onset schizophrenics is consistent with observations in later onset schizophrenia, the increased metabolic rate seen in the putamen may not be.

While increased movement on the part of the schizophrenics cannot be ruled out as a cause of the group differences in cerebellar metabolic rate, the finding of increased metabolic rate in the cerebellum of schizophrenics is notable in light of recent evidence implicating the cerebellum in higher cortical processes (Kim et al., 1994). In healthy subjects, cerebellar activation has been demonstrated during task acquisition, with activation declining as performance of the task becomes more automatic (Jenkins et al., 1994; Raichle et al., 1994), possibly reflecting a shift in mental strategy (Fiez, 1996). Previous reports of cerebellar function in schizophrenia include one report of decreased cerebellar metabolism in rest-

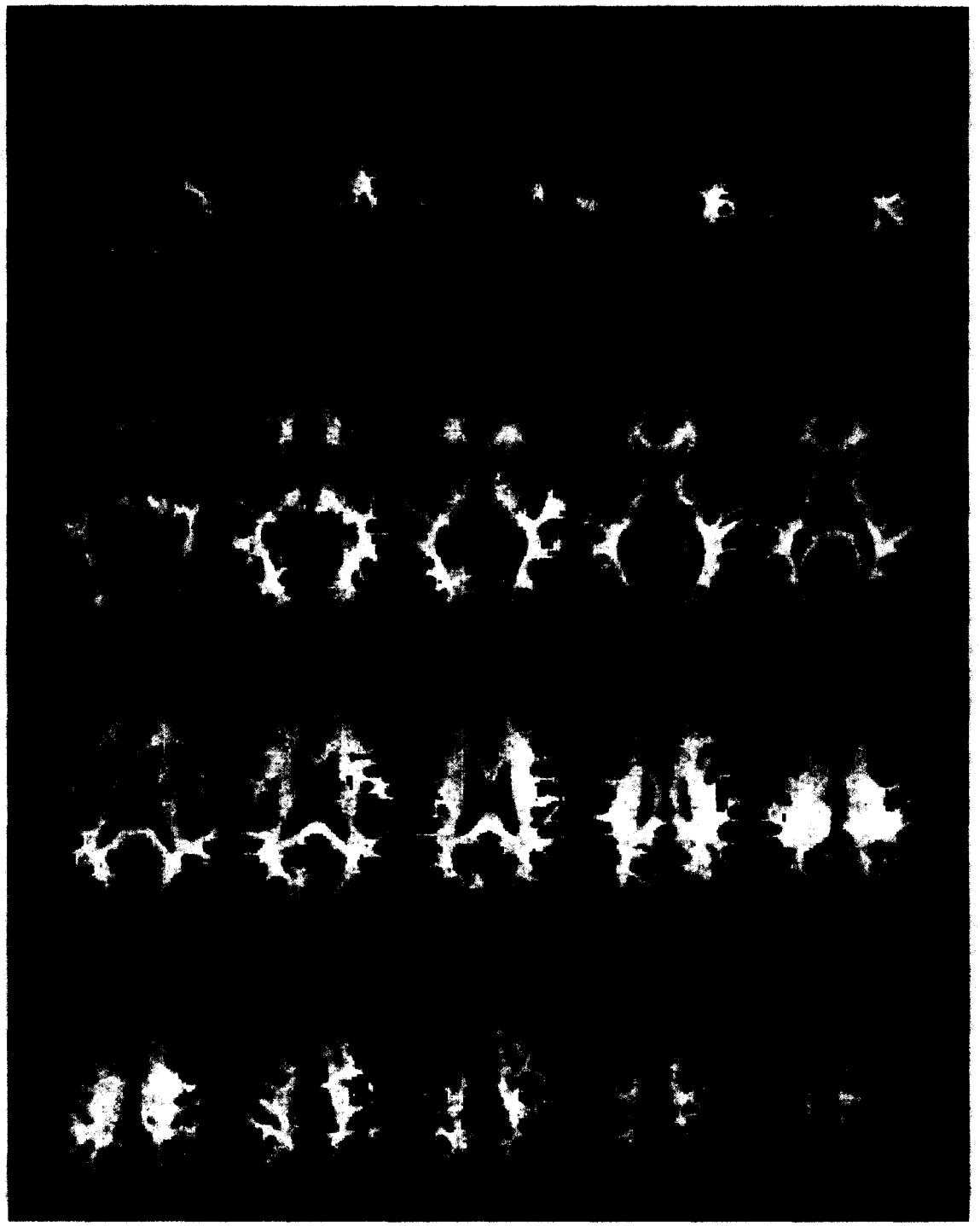

Fig. 2. Statistical parametric map showing pixel-based comparison of cerebral glucose metabolism for $n = 16$ adolescents with childhood onset schizophrenia and $n = 26$ healthy adolescents. For each pixel, t-values have been converted to z scores linked to a color scale where orange and blue indicate pixels for which schizophrenic subjects had, respectively, significantly higher and lower metabolic rate at $P \leq 0.005$. SPM data have been projected onto a standardized magnetic resonance image of a brain sliced transversely, parallel to the intercommissural (AC–PC) line, at levels corresponding to the atlas of Talairach and Tournoux (1988).

ing medicated adult patients (Volkow et al., 1992) and one report of greater increase in cerebellar blood flow in patients during activation conditions (Steinberg et al., 1995). More recently, dysfunction of a prefrontal–thalamic–cerebellar network was demonstrated in schizophrenics during practiced and novel memory tasks (Andreasen et al., 1996). These reports, together with observations from the present study, suggest that abnormal neural circuitry in schizophrenia includes the cerebellum, with persistent abnormal activation of the cerebellum possibly resulting from failure of patients to shift to more automatic strategies for performing the CPT.

4.1. Limitations

In an effort to fully explore the data gathered from this very unique sample of patients, multiple statistical tests were performed. This, however, increases the risk of Type I error such that the findings from this study should be viewed as preliminary and must await confirmation from future functional brain imaging studies of this population. In addition, while measuring counts from venous blood in four schizophrenic patients may have added variance to the patient data, comparison of counts measured from venous and arterial blood sampling in our lab has indicated no systematic bias in this additional variance.

Because most of the normal adolescents in this study did not undergo brain MRI, co-registration of MRI scans with PET scans was not possible, thus rendering the localization of group differences in metabolic rate more approximate. The inclusion criterion of previous non-response to typical antipsychotic medication may have selected for patients with greater brain abnormalities (Crow, 1985). However, phenomenologic similarities between the present sample and other samples of patients with childhood onset schizophrenia (Green et al., 1992; Russell, 1994) suggest that these findings apply generally to childhood onset schizophrenia.

Inclusion of 19 siblings of subjects with ADHD in the normal group also represents an important limitation of this study. Decreased frontal metabolism has been observed in both adults and adolescents with ADHD (Zametkin et al., 1990, 1993). However, a recent effort to replicate these findings in a different sample of normal and ADHD female adolescents failed to demonstrate differences in frontal metabolism between groups (Ernst et al., 1997). While none of the normal subjects in the present study met DSM criteria for current or previous ADHD and all were older than the maximum age before which symptoms must be present in order to be diagnosed with ADHD, any decrease in frontal metabolism in these normal subjects would have reduced the degree of hypofrontality observed in schizophrenic patients.

The significant group difference in CPT performance likely reflects the highly symptomatic state of the patients in this study. While CPT performance differences greatly complicate interpretation of group differences in brain metabolism, it is remarkable that even with the very poor performance of this sample the hypofrontality observed was not more severe than that observed in later onset schizophrenia.

Taken together, the findings of the present study suggest that hypofrontality in childhood onset schizophrenia is similar to, but not more severe than, the hypofrontality seen in adult onset schizophrenia. Thus, these findings provide some further evidence of neurobiologic continuity between childhood and adult onset schizophrenia. In addition, further evidence of the potential importance of the cerebellum in schizophrenic pathology was observed. Ongoing studies in this rare sample of children and adolescents, including gray/white segmentation and brain chemistry using magnetic resonance spectroscopy, may help to further elucidate early developmental triggers of schizophrenia.

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