
Proton Spectroscopy in Medication-Free Pediatric Attention-Deficit/Hyperactivity Disorder

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Background: *The frontal–striatal pathway has been previously implicated in the neuropathology of attention-deficit/hyperactivity disorder (ADHD). Hence, we used proton magnetic resonance spectroscopy (¹H-MRS) to examine metabolite levels in the prefrontal cortex of children with ADHD.*

Methods: *Nine age- and gender-matched case-control pairs were examined, ages 7 to 16 years. A long-echo ¹H-MRS scan was acquired from the right prefrontal cortex and left striatum in all subjects. Compounds that can be visualized with ¹H-MRS include N-acetyl-aspartate (NAA), glutamate/glutamine/γ-aminobutyric acid (Glx), creatine/phosphocreatine (Cr), and choline compounds (Cho).*

Results: *Frontal–striatal glutamatergic resonances were elevated in the children with ADHD as compared to healthy control subjects. No differences were noted in NAA, Cho, or Cr metabolite ratios.*

Conclusions: *These findings suggest that frontal–striatal Glx resonances may be increased in children with ADHD in comparison with healthy control subjects. Biol Psychiatry 2003;53:184–187 © 2003 Society of Biological Psychiatry*

Key Words: Attention-deficit/hyperactivity disorder, striatum, prefrontal cortex, glutamate, spectroscopy

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a serious mental and public health problem. Children with ADHD have high levels of hyperactivity, impulsivity, or inattentiveness, which significantly impairs their family, school, and social functioning (American Psychiatric Association 1994). Prevalence estimates of ADHD have ranged from 1% to 20%, with an average prevalence between 3% and 6% (Greenhill 1998). Regarding the

neurobiology of pediatric ADHD, work is still in the early stages. The frontal–striatal circuit is the most consistently implicated in attentional disorders. Reductions in striatal activity have been noted previously in subjects with ADHD (Lou et al 1989; Teicher et al 2000; Vaidya et al 1998). The cingulate gyrus has also demonstrated reduced activity in ADHD (Bush et al 1999; Castellanos et al 1994; Rubia et al 1999). Hence, there is some evidence for neuronal dysfunction in these brain regions. The principal aim of this study was to examine children near the onset of their illness to investigate the neurochemistry of ADHD and how it differs from children with no psychiatric illness. We hypothesized that spectral profiles of children with ADHD would differ from control subjects. Recent developments in neuroimaging technology allow for the direct, safe, in vivo, noninvasive monitoring of brain neurochemistry via proton magnetic resonance spectroscopy (¹H-MRS). Compounds that can be identified in ¹H-MRS brain studies include the neuronal marker, N-acetyl-aspartate (NAA) (Birken and Oldendorf 1989), glutamine/glutamate/γ-aminobutyric acid (Glx), creatine/phosphocreatine (Cr), choline compounds (Cho), and myo-inositol (ml). Should specific MRS profiles be found for ADHD, this tool has the potential for aiding the clinician in making a sometimes-difficult diagnosis. Until we better understand the neurochemistry of this circuitry, we are limited in our understanding of how metabolic disturbances of this region are linked with symptom expression in ADHD.

Methods and Materials

Study Group

Subjects were recruited from clinical programs and through advertisements. All subjects and one of their parents gave informed consent for the study after a full explanation of the procedures, in accordance with the Research Ethics Board approval process provided by the Izaak Walton Killam (IWK) Health Center. A board-certified psychiatrist (NC) established diagnosis based on Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL) criteria. All data are reported as mean ± SD unless otherwise specified. Nine subjects (6 male, 3 female) aged 7–16 years with

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Table 1. Demographic and Clinical Data on Pediatric Attention-Deficit/Hyperactivity Disorder Subjects

ID	Gender	Age (Years)	Previous medication	Time off medication	Comorbid	Learning disability	Subtype
1	M	10	None	NA	ODD	Mild	Combined
2	F	9	MPH (10 mg b.i.d.)	48 hours	None	Mild	Combined
3	M	16	MPH (30 mg morning)	48 hours	None	No	Combined
4	M	11	MPH (10 mg/day)	3 weeks	None	Mild	Inattentive
5	M	11	Dexedrine (5 mg b.i.d.)	1 week	ODD	No	Combined
6	F	8	MPH (5 mg b.i.d.)	3 weeks	ODD	Moderate	Combined
7	F	9	Dexedrine (5 mg b.i.d.)	72 hours	ODD	None	Combined
8	M	8	MPH (5 mg b.i.d.)	3 weeks	ODD	None	Combined
9	M	7	MPH (5 mg morning, 2.5 mg at noon)	48 hours	ODD	Mild	Combined

M, male; F, female; MPH, methylphenidate; ODD, oppositional defiant disorder.

ADHD and nine age- and gender-matched control subjects participated in this study. Mean age of onset for the ADHD subjects was 3.67 ± 1.41 years. All subjects were medication free at the time of the scan (see Table 1). Scans were conducted at the Queen Elizabeth II Health Sciences Center using a Siemens Magnetom Vision 1.5 Tesla scanner (Erlangen, Germany). Multi-slice scout images (axial, coronal, and sagittal planes) were used for voxel orientation. A long-echo ¹H-MRS spin echo (90°-180°-180°) procedure was used to acquire spectra from the right prefrontal cortex and the left striatum in this sample. Parameters were as follows: echo time = 135 msec, repetition time = 1500 msec, 1024 data points, acquisitions = 256, voxels = 4 cc (prefrontal cortex [PFC]) and 6 cc (striatum), time = 7 min (see Figure 1 for voxel placement). A trained MRS analyst (FPM) analyzed the data in a blind manner, using peak areas fit after zero filling, fast Fourier transformation, and Gaussian apodization. The quality of each spectrum was assessed in detail, and spectra displaying artifacts were not used. Hence, data from the striatum of two subjects were not used in the analysis.

Statistical analysis consisted of a two-tailed paired *t* test to determine differences between the age- and gender-matched sample. To correct for multiple comparisons (six comparisons),

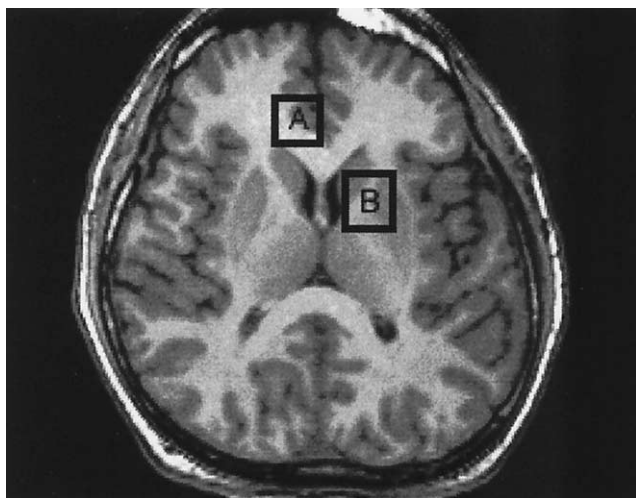


Figure 1. Voxel placement in (A) prefrontal cortex and (B) striatum.

α^1 was set at $p \leq .008$. We feel that close age and gender matching allows for a reduction in the potential confounds of gender and age on the data set. Correlations (two-tailed) between metabolites and age were also conducted.

Results

The two groups did not differ with regard to age [control group mean = 9.36 ± 1.66 , ADHD group mean = 9.60 ± 1.56 , $t(9) = 1.35$, $p = .21$]. Prefrontal and striatal NAA/Cr and Cho/Cr did not differ between groups (see Figure 2 for typical spectra). In the right PFC, Glx/Cr was significantly higher in the ADHD group as opposed to control subjects [control group mean = 0.30 ± 0.12 , ADHD group mean = 0.57 ± 0.23 , $t(8) = 3.55$, $p = .0075$]. In the left striatum, Glx/Cr demonstrated a trend for significant increase in Glx/Cr in the ADHD group [control group mean = 0.23 ± 0.07 , ADHD group mean = 0.41 ± 0.13 , $t(6) = 3.44$, $p = .014$]. Striatal glutamatergic ratios did not correlate with age in either group. In control subjects, prefrontal Glx ratios demonstrated a trend for positive correlation with age ($r = .67$, $p = .05$). Interestingly, prefrontal Glx/Cr ratios correlated positively with age of onset ($r = .74$, $p = .02$).

Discussion

Results of this study show an increase in the glutamatergic resonance in the right PFC and left striatum in ADHD children relative to healthy control subjects. In the prefrontal cortex, this resonance was correlated with age of onset of ADHD symptoms. Glutamatergic pathways, which are the major corticospinal neurons, have been shown to play a crucial neuromodulatory role in the striatum (Kalivas et al 1989; Taber and Fibiger 1993), a neuroanatomic region that may be especially relevant to ADHD. Glutamate modulates the release of neurotransmitters including dopamine and serotonin (Moghaddam 1993; Slotkin et al 1997). Alterations in the functioning of dopaminergic neurons could, therefore, result in glutama-

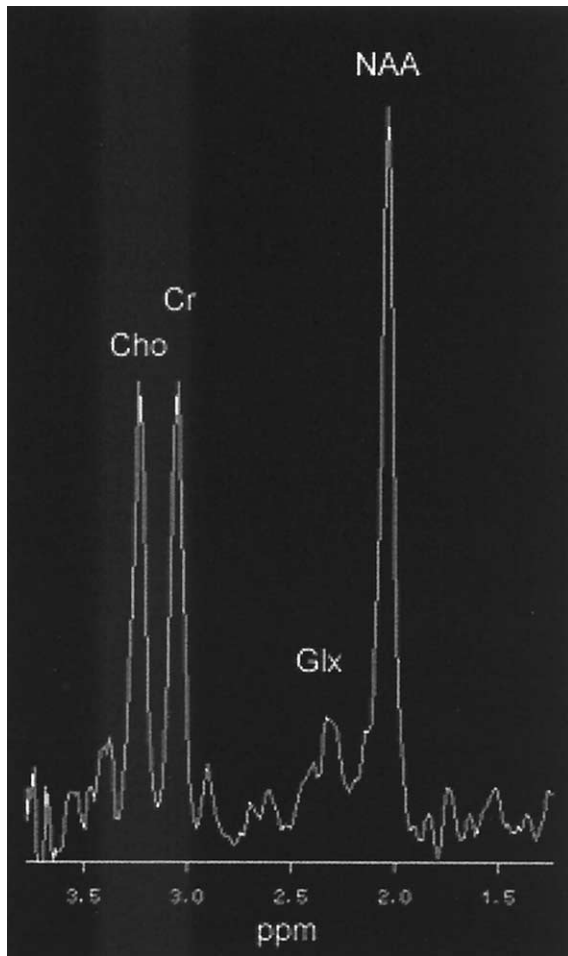


Figure 2. Sample spectra demonstrating NAA (N-acetylaspartate), Glx (glutamate/glutamine/ γ -aminobutyric acid), Cr (creatine/phosphocreatine), and Cho (choline compounds).

tergic pathway disruption in the striatum. Verma and Moghaddam (1998) found that, during basal conditions, metabotropic glutamate receptor activation facilitates striatal dopamine release, possibly through presynaptic, impulse-independent mechanisms; however, during conditions of hyperstimulation, activation of metabotropic receptors, in contrast to ionotropic receptors, reduces excess dopamine release. It should be noted that the measurement of glutamate with long-echo MRS is not optimal however, and a short-echo protocol would provide better resolution of the Glx resonance. As the influence of macromolecules is less with the method used here, long-echo may be useful for evaluating the Glx resonance in a simple way and hence, in the context of this exploratory investigation, we feel the Glx ratio findings are of interest.

Also of note is the lack of a significant difference in the NAA ratios in either the PFC or the striatum. Dysfunction in the right prefrontal region affecting inhibitory control

has been demonstrated previously (Pliszka et al 2000). Inadequate gating of sensory information in the striatum is believed to allow cortical input to capture and drive a self-sustaining loop. To our knowledge, there has been only one published ^1H -MRS study comparing five adult patients with the predominantly inattentive subtype of ADHD (ADHD-PI), five adult patients with the hyperactive-impulsive subtype of ADHD (ADHD-HI), and five control subjects (Hesslinger et al 2001). This study utilized a larger voxel size ($2\text{ cm} \times 2\text{ cm} \times 2\text{ cm}$), and an absolute quantitative metabolite measure as the index. Patients with ADHD-HI had significantly lower NAA levels in the dorsolateral PFC than control subjects and patients with ADHD-PI, supporting the hypothesis of neuronal abnormalities in the frontal cortex being associated with the pathophysiology of ADHD; however, they failed to demonstrate any differences in the striatum. This may be due to a lack of statistical power from the very small sample sizes used. The clinical relevance of neuronal disturbances in striatum, in terms of how such a dysfunction might cause ADHD, remains uncertain; however, one intriguing hypothesis is that dysfunction in this circuitry, which is known to play an important role in attentional regulation and response suppression, is disrupting the ability to inhibit context-inappropriate responses. To our knowledge, there has been no prior study of neuronal metabolites in the PFC and striatum in medication-free pediatric ADHD patients.

The primary limitation of this study is its small sample size. Another limitation of this study is the lack of absolute quantification of metabolites. The use of ratios, as done here, minimizes the error introduced by variable tissue composition and instrumental instability while allowing the evaluation of relative alterations in metabolites. Further experiments are under way to elucidate the exact mechanism of increase of the glutamatergic peaks and its relation to ADHD symptomatology.

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