ORIGINAL ARTICLE

Asperger Syndrome

A Proton Magnetic Resonance Spectroscopy Study of Brain

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Background: Asperger syndrome (AS; an autistic disorder) is associated with impaired social skills and obsessional/repetitive behavior. Patients with autism have significant abnormalities in the frontal lobe and frontoparietal connectivity. Nobody has examined the relationship between abnormalities in the frontal and parietal lobes and clinical symptoms in people with AS.

Methods: We used in vivo proton magnetic resonance spectroscopy to examine neuronal integrity of the medial prefrontal and parietal lobes in 14 non–learning-disabled adults with AS and 18 control subjects (of similar sex, age, and IQ). We obtained measures of the prefrontal lobe in 11, the parietal lobe in 13, and both lobes in 10 subjects with AS. We measured concentrations and ratios of *N*-acetylaspartate (NAA), creatine and phosphocreatine (Cr+PCr), and choline (Cho). Levels of NAA, Cr+PCr, and Cho are indicators of neuronal density and mitochondrial metabolism, phosphate metabolism, and membrane turnover. Frontal metabolite levels were correlated with scores on the Yale-Brown Obsessive Compulsive Scale and the Autism Diagnostic Interview.

Results: Subjects with AS had a significantly higher prefrontal lobe concentration of NAA ($z=-3.1$; $P=.002$), Cr+PCr ($z=-2.2$; $P=.03$), and Cho ($z=-2.9$; $P=.003$). Increased prefrontal NAA concentration was significantly correlated with obsessional behavior ($\tau=0.67$; $P=.005$); increased prefrontal concentration of Cho, with social function ($\tau=0.72$; $P=.02$). We found no significant differences in parietal lobe metabolite concentrations.

Conclusion: Subjects with AS have abnormalities in neuronal integrity of the prefrontal lobe, which is related to severity of clinical symptoms.

Arch Gen Psychiatry. 2002;59:885-891

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PEOPLE WITH high-functioning autistic disorder (autism and Asperger syndrome [AS]) are not learning disabled (mentally retarded), but they exhibit characteristic impairments in social skills and obsessional/repetitive behavior.[1] A consensus exists that the clinical features of autistic disorder are strongly genetic[2-4] and associated with brain dysfunction,[5] but the neurobiological basis of autistic symptoms is unknown. The frontal lobe may be critically involved because, in nonautistic populations, damage to or dysfunction of the prefrontal cortex is associated with autistic-like social deficits and obsessional/repetitive behavior.[6] Also, people with autism are reported to have significant differences in frontal lobe metabolic maturation,[7] anatomy,[8] function,[9] and connectivity to parietal lobe.[10] However, the relationship between abnormalities in the frontal and parietal lobes and clinical symptoms in people with autistic disorder is poorly understood.

One technique for addressing this question is in vivo magnetic resonance spectroscopy (MRS), because it can be used to quantify neuronal integrity. Phosphate 31–labeled MRS quantifies phosphate-containing compounds that reflect high-energy phosphate and membrane phospholipid metabolism. In contrast, proton (^{1}H)–MRS provides spectra that can be used to measure *N*-acetylaspartate (NAA)-, creatine and phosphocreatine (Cr+PCr)–, and choline (Cho)- containing substances. *N*-acetylaspartate is present in high concentration in gray matter and neurons, and its synthesis is closely correlated with mitochondrial energy metabolism. Therefore, NAA is often used as a measure of neuronal density and/or mitochondrial function.[11] In contrast, Cr+PCr and Cho concentrations are used as measures of phosphate metabolism and membrane turnover, respectively.[11-18] A ^{31}P-MRS study[19] reported that young people with autism had a hypermetabolic energy state in the frontal lobe and that fron-

tal hypermetabolism and undersynthesis of neuronal membranes were related to performance of verbal and executive function tasks. In contrast, ^{1}H-MRS studies detected no abnormalities in neuronal integrity of the parietal[20] or the frontal lobe in people with autism,[21] but they reported lower levels of NAA in the cerebellum.[21] These MRS studies were important first steps; however, to our knowledge, nobody has examined subjects with AS using ^{1}H-MRS or has related clinical symptoms to neuronal integrity.

Obsessional/repetitive behavior is recognized as a core clinical symptom in people with autistic disorder.[22] For example, (1) obsessional interests are a major diagnostic feature of autistic spectrum conditions in *DSM-IV*.[23] (2) Repetitive behaviors have been considered an integral part of the syndrome since the classic description by Kanner.[24] (3) Rutter[25] stated that "ritualistic and compulsive phenomena are very common in autism. . . . . It is not uncommon for them to develop into frankly obsessional symptoms," and Baron-Cohen and Wheelwright[26] reported that up to 92% of children with autism display obsessional behaviors. Damage to or dysfunction of the prefrontal lobe is associated with stereotyped, obsessional, and ritualistic behavior in the general population, and abnormalities in frontal lobe development may account for these symptoms in people with autism.[6] However, this issue has never been investigated in people with AS. Therefore, we used ^{1}H-MRS to study the frontal and parietal lobes in subjects with AS who were otherwise healthy, and we related frontal metabolic measures to obsessional/repetitive behavior. Also, we performed a post hoc analysis relating frontal metabolic measures to global clinical symptoms as measured by the Autism Diagnostic Interview–Revised (ADI-R).[27]

PARTICIPANTS AND METHODS

PARTICIPANTS

Subjects with AS were recruited through local support groups and our clinical research program in autism. We studied 14 high-functioning men with AS, with a mean (SD) age of 30 (9) years and a mean (SD) Full-Scale IQ (FSIQ) of 97 (14). Ten subjects were right-handed and 4, left-handed. A diagnosis of AS was made using the criteria of the *International Classification of Diseases, 10th Revision*[28] by a team consisting of 3 psychiatrists (H.D.C., D.G.M.M., and G.M.) and a psychologist (P.H.). We included subjects with no reported language delay and who met autistic criteria for social and obsessional behavior. It was also possible to apply the ADI-R[27] in 12 subjects with parental informants.

Control subjects were recruited locally by means of advertisement and included 18 men with a mean (SD) age of 32 (8) years and a mean (SD) FSIQ of 102 (8). Fourteen were right-handed and 4, left-handed. No control had past or present mental health problems or physical disorders that affected brain function.

All participants in the study underwent structured physical and psychiatric examination[29,30] (for the presence of a *DSM-IV* Axis I or II disorder[23]), and clinical magnetic resonance imaging. Participants were excluded if they had a history of psychiatric disorder (other than AS), head injury, toxic exposure, diabetes, hypertension, cardiovascular disease, abnormal results of routine blood tests, alcohol or other drug abuse, a clinically abnormal finding on routine magnetic resonance imaging, or a medical disorder associated with autistic symptoms (eg, epilepsy). We measured the FSIQ using the Wechsler Adult Intelligence Scale–Revised[31]; obsessional/repetitive behavior, the Yale-Brown Obsessive Compulsive Scale[32]; and handedness, the Annett Questionnaire.[33] No participants were taking medication at the time of the study, although 2 subjects with AS had previously received psychotropic medication for obsessional behavior and symptoms of anxiety (a selective serotonin reuptake inhibitor in one, and a benzodiazepine in the other). We found no significant differences between subjects with AS and controls in age, FSIQ, handedness, or education. Research was approved by the local research ethics committee, and all participants provided informed written consent.

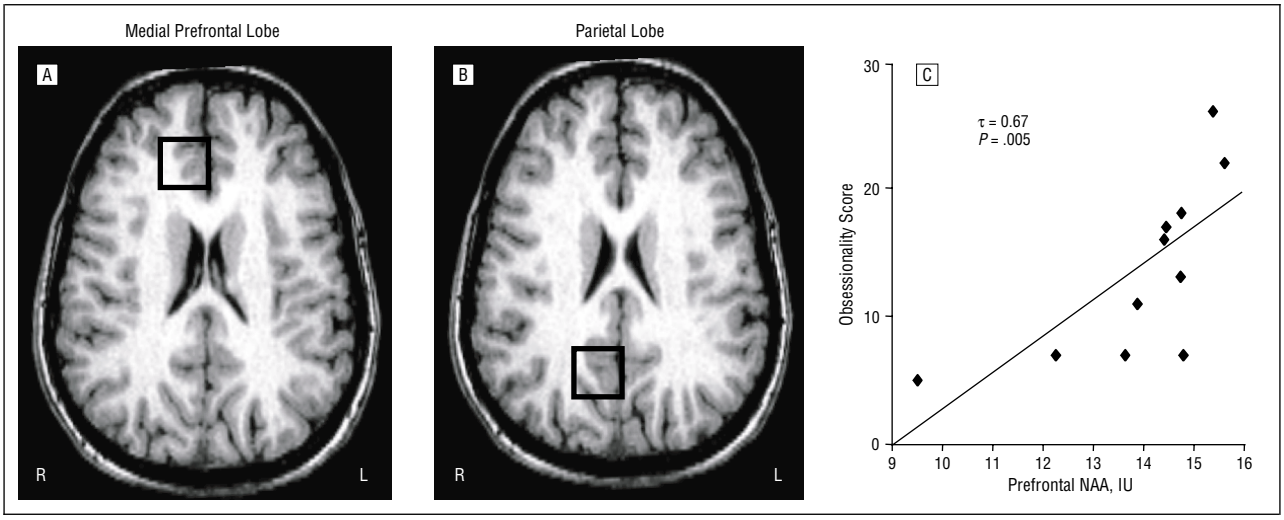
SCANNING PROTOCOL

Subjects with AS and controls underwent scanning using a 1.5-T system (GE Signa; General Electric, Milwaukee, Wis). An 8.5-mL voxel of interest (VOI) was positioned in the right medial prefrontal lobe and incorporated white and gray matter from the superior and medial prefrontal gyri, and a portion of the anterior cingulate (placed at one third of the distance between the anterior commissure and frontal pole and one half of the distance between the dorsal and orbital margins of the prefrontal lobe, located medially) (**Figure**). An additional 8.5-mL VOI was located in the right medial parietal lobe, including the precuneus, and contained gray and white matter (placed at one half of the distance from the posterior commissure to the back of the brain, and one third of the vertical distance from the anterior commissure–posterior commissure line to the vertex). An 8.5-mL point resolved selective spectroscopy (point-resolved selective spectroscopy [PRESS] spectrum (echo time, 136 ms; repetition time, 2000 ms; 256 averages) was obtained from each voxel after chemical shift selective [CHESS] water suppression. The MRS data were analyzed using SAGE/IDL software (General Electric). Concentrations of metabolites were determined using derived metabolite peak areas and documented relaxation characteristics of these neurochemicals at 1.5 T with the total water signal of the VOI.[34] Data of sufficient quality to be analyzed were obtained from the prefrontal voxel in 11 subjects with AS and 18 controls, and from the parietal voxel in 13 subjects with AS and 14 controls. Of those we studied, 10 subjects with AS and 7 controls underwent frontal and parietal spectroscopy. We were unable to obtain data from both regions in all participants owing to technical difficulties (eg, problems "shimming" or participants wanting to withdraw).

Differences in lobar brain volume and/or proportions of white and gray matter and cerebrospinal fluid (CSF) in the MRS VOI may confound group differences in metabolite concentrations. Thus, to ensure that differences in regional brain volume or tissue composition did not account for metabolic differences between subject groups, we acquired a 3-dimensional inversion-recovery prepared spoiled-grass data set at the same time that we acquired spectroscopic data. These data covered the whole head (124 slices; 1.5-mm slice thickness) and were used for manual tracing of lobar brain matter volume using Measure software[35] and previously described methods.[29] Also, the position of the MRS VOI relative to the spoiled-grass volume was determined automatically using in-house software, and we analyzed each MRS VOI using SPM (statistical parametric mapping) software (available at: http://www.fil.ion.bpmf.ac.uk/spm) to determine the percentage of gray and white matter and CSF composition.

STATISTICS

We analyzed the data masked to subject status using SPSS software (SPSS Inc, Chicago, Ill). We compared between-group dif-



Location of voxels of interest (VOIs) in a proton magnetic resonance spectroscopy (^{1}H-MRS) study of metabolite concentrations and ratios. A, An 8.5-mL VOI was positioned in the right medial prefrontal lobe and placed one third of the distance between the anterior commissure and frontal pole and one half of the distance between the dorsal and orbital margins of the prefrontal lobe, located medially. B, An additional 8.5-mL VOI was located in the right medial parietal lobe and was placed at one half of the distance from the posterior commissure to the back of the brain and one third of the vertical distance from the anterior commissure–posterior commissure line to the vertex. R indicates right; L, left. C, Relationship between prefrontal *N*-acetylaspartate (NAA) concentration and score on the Yale-Brown Obsessive Compulsive Scale in patients with Asperger syndrome (n=11).

ferences in handedness using χ^2 tests, and demographic variables, hand-traced volume of brain matter in the frontal and parietal lobes, tissue proportions of the VOI, and metabolite concentrations and ratios using the Mann-Whitney test. To further investigate whether our findings were confounded by differences in tissue proportions of the VOIs, we compared metabolite concentrations using analysis of covariance (covarying for percentages of gray and white matter and CSF).

To determine whether our data were driven by participants for whom we were not able to perform parental interviews or by sampling heterogeneity, we performed a further between-group analysis after restricting the inclusion criteria to include only those subjects with AS for whom ADI-R scores were available (n=11) and participants who had data available from the prefrontal and parietal lobes (10 subjects with AS vs 7 controls).

Finally, we related the concentrations of metabolites that were significantly different in subjects with AS (ie, frontal NAA, Cr+PCr, and Cho) to obsessional/repetitive behavior using the Kendall τ. Also, we performed a post hoc exploratory analysis on the relation between abnormalities in frontal neuronal integrity and global severity of clinical symptoms by correlating scores on the ADI-R to frontal metabolite concentrations. Results are reported as significant when $P<.05$ (2-tailed).

RESULTS

Compared with controls, subjects with AS had a significantly higher prefrontal concentration of NAA, Cr+PCr, and Cho (**Table**); but we found no significant between-group differences in the ratios of NAA/Cr+PCr, NAA/Cho, and Cho/Cr+PCr. These results were unchanged when we included only those people for whom ADI-R scores were obtainable. When the analysis was restricted to subjects who underwent prefrontal and parietal spectroscopy, the difference in Cho concentration did not remain significant ($z=-0.98$; $P=.90$).

We found no significant differences between subjects with AS and controls in concentrations or ratios of NAA, Cho, or Cr+PCr within the parietal lobe. This finding also remained true for the restricted analyses.

We found no significant between-group difference in the volume of the frontal and parietal lobes or in the percentage of gray or white matter or CSF content of the MRS VOIs. Our results remained significant in the frontal lobe and nonsignificant in the parietal lobe when we corrected for tissue proportion of the VOI using analysis of covariance.

Subjects with AS had significantly higher scores on the Yale-Brown Obsessive Compulsive Scale. Within this group, prefrontal NAA concentration was significantly positively correlated with the severity of obsessive/repetitive behavior ($\tau=0.67$; $P=.005$) (Figure). The result remained significant when we excluded the 2 subjects with the lowest and the highest NAA concentrations and Yale-Brown Obsessive Compulsive Scale scores ($\tau=0.55$; $P<.04$). Post hoc analysis demonstrated a significant correlation between social impairment (the communication domain of the ADI-R and frontal Cho concentration ($\tau=0.72$; $P=.02$).

COMMENT

In this relatively small study, we did not obtain spectra from both brain regions in all participants, and we did not include subjects with classic autism (ie, abnormalities in language development and learning disability). Moreover, although our correlation of prefrontal measures and obsessional/repetitive behavior was planned a priori, our correlation with ADI-R scores was not (and so this latter result may be spurious). However, we used nonparametric statistical tests, and our results remained significant when we dropped potential outliers; also, we found no significant between-group differences in any demographic variable we measured. None-

^{1}H-MRS in Subjects With Asperger Syndrome and Control Subjects*

	Subjects With AS	Controls	*z* Score	*P* Value
Demographic variables				
No. of participants	14	18	NA	NA
Total ADI-R score	41 (8)	1 (1)	–4.485	.001
YBOC score	13 (6)	1 (1)	–4.843	.001
Age, y	30 (9)	32 (5)	–1.124	.26
FSIQ	97 (14)	102 (8)	–1.464	.14
Prefrontal voxel				
No. of participants	11	18	NA	NA
NAA concentration, IU	13.9 (1.7)	11.7 (2.1)	–3.146	.002
Cr + PCr concentration, IU	10.4 (1.5)	9.0 (1.7)	–2.247	.03
Cho concentration, IU	3.3 (0.7)	2.5 (0.6)	–2.922	.003
Gray matter, %	45.6 (5.7)	42.4 (10.8)	–0.292	.77
White matter, %	47.8 (8.4)	49.8 (8.6)	–0.450	.65
CSF, %	6.6 (3.5)	7.8 (4.8)	–0.383	.70
Right frontal lobe volume, mm^3	279 (29)	278 (37)	–0.449	.67
Parietal voxel				
No. of participants	13	14	NA	NA
NAA concentration, IU	13.2 (1.1)	13.2 (0.8)	–0.121	.90
Cr + PCr concentration, IU	9.8 (0.8)	9.9 (0.9)	–0.534	.59
Cho concentration, IU	2.3 (0.3)	2.3 (0.3)	–0.680	.50
Gray matter, %	42.9 (8.9)	41.8 (11.1)	–0.340	.73
White matter, %	50.2 (12.3)	53.3 (13.8)	–0.559	.58
CSF, %	6.9 (4.2)	4.9 (2.9)	–1.214	.23
Right parietal lobe volume, mm^3	150 (20)	139 (20)	–0.534	.62

*Unless otherwise indicated, data are given as mean (SD). ^{1}H-MRS indicates proton magnetic resonance spectroscopy; AS, Asperger syndrome; NA, not applicable; ADI-R, Autism Diagnostic Interview–Revised; YBOC, Yale-Brown Obsessive Compulsive Scale; FSIQ, Full-Scale IQ; NAA, *N*-acetylaspartate; Cr + PCr, creatine and phosphocreatine; Cho, choline; and CSF, cerebrospinal fluid.

theless, we need to repeat our study in a larger group, to acquire data from multiple brain regions within the same subject and to determine whether our findings generalize across the whole spectrum of autistic disorders.

Obsessional/repetitive behavior is recognized as a core clinical symptom in patients with autistic disorder.[22-26] However, the relation between obsessional behavior in autistic disorder and obsessive-compulsive disorder (OCD) in the general population is poorly understood. Bolton et al[4] argued that OCD might index an underlying liability to autism because a significantly higher prevalence of OCD is found in the relatives of subjects with autism, and individuals with OCD are more likely to exhibit autistic-like social impairments than controls. Also, in subjects with autism, treatment with selective serotonin reuptake inhibitors significantly reduces obsessive/compulsive symptoms[36] and repetitive thoughts and behavior[37] (similar to OCD in the general population). Nonetheless, others reported that obsessions and compulsions in patients with autism have different characteristics from those displayed by patients with OCD.[38,39] For example, obsessions in people with OCD are usually seen as ego-dystonic (typically involving thoughts of harm and contamination), whereas people with autistic disorder are significantly more likely to hoard and order[39] and to have obsessions about how things work.[26] To our best knowledge, nobody has directly compared the neurobiological associates of obsessional/repetitive behavior in people with AS and those with OCD in the general population. However, studies of OCD in non-AS populations using positron emission tomography and single-photon emission computed tomography described significantly increased glucose metabolism and/or blood flow in the prefrontal cortex. Moreover, some researchers reported that in patients with OCD, increased absolute glucose metabolism correlated with the severity of OCD.[40,41] We also found evidence that increased NAA concentrations are associated with obsessional behavior in subjects with AS. One potential explanation for this increase in NAA concentration involves differences in mitochondrial, and hence glucose, metabolism. Thus, similar to patients with OCD, obsessional symptoms in people with AS may be related to metabolic differences in the prefrontal lobe. However, we also found that our subjects with AS had a significantly higher frontal lobe concentration of NAA that was significantly positively correlated with more severe obsessional/repetitive behavior, whereas other researchers reported that patients with OCD had a decreased NAA concentration that negatively correlated with symptom severity.[42] Thus, it is unclear whether the neurobiological basis of obsessional behavior in subjects with AS differs from that in OCD, and further studies are required to address this issue directly.

We do not suggest that neurobiological differences occur only in the frontal lobe of patients with AS. Damasio and Maurer[6] proposed that autism is due to dysfunction of the mesolimbic brain areas (ventromedial prefrontal cortex, medial temporal lobe, striatum, and limbic thalamus), and patients with autism exhibit impairments in higher cognitive functions subserved by these brain regions.[43-45] Neuropathological studies of patients with autism reported neuronal abnormalities in the cerebral cortex, cerebellum, and limbic system.[46,47] In vivo studies of

brain anatomy described widespread abnormalities in brain morphometry and cerebral gyrification,[48,49] but increasingly point to the pathoaeotiogical importance of mesolimbic and subcortical structures.[50-53] Studies of brain metabolism and blood flow in autistic disorder using positron emission tomography reported delayed metabolic maturation of the prefrontal cortex[7] and reduced functional associations between the frontal and parietal regions at rest,[10] reduced prefrontal and anterior cingulate metabolism during attentional and verbal learning tasks,[51,54] and reduced medial prefrontal blood flow during theory-of-mind tasks.[9] Recent functional magnetic resonance imaging studies of patients with autism reported reduced activation in the amygdala when making emotional judgments of eyes[55]; in the amygdala and cerebellar, mesolimbic, and temporal lobe cortical brain regions when processing facial emotion[56]; and in the temporal lobe during facial recognition tasks.[57] Our findings further support the position that the frontal lobe is implicated in autistic disorder and suggest that previous reports of differences in frontal metabolism and function are associated with differences in neuronal integrity.

We found that frontal, but not parietal, metabolite concentrations were significantly increased in adults with AS. Thus, the frontal lobe may be more affected than the parietal lobe in AS, and/or our findings may result from regional differences in brain maturation because human brain development continues into adult life and occurs at different times in different brain areas.[58,59] For example, the frontal lobe matures relatively late compared with the rest of the brain in synaptic pruning,[60] myelination,[61] and acquisition of adult patterns of glucose metabolism.[62] Also, postadolescent brain development is associated with a significant reduction in gray matter volume of the frontal cortex, with relatively little change in other brain regions (including the parietal lobe).[58] Thus, maturation of the frontal lobe is normally delayed relative to other brain areas, and so may continue to display a pathologic process in adulthood that was more generalized in earlier life.

Previous MRS studies of neuronal integrity in subjects with autism are in disagreement. A ^{31}P-MRS study of high-functioning autistic adolescent boys and young men that used surface coils reported that young patients with autism had a hypermetabolic energy state in the frontal lobe when measures from the right and left hemispheres were combined.[19] In contrast a ^{1}H-MRS study of the frontal lobe in 9 children with autism and 5 of their siblings[21] reported no significant difference in NAA concentrations, but reported preliminary evidence of lower levels of NAA in the cerebellum. A ^{1}H-MRS study of 28 learning-disabled children with autism (9 with epilepsy) detected no abnormalities in the neuronal integrity of the parietal lobe.[20] We found significant differences in the frontal, but not the parietal, lobe concentration of NAA, Cr+PCr, and Cho in non–learning-disabled adults who were otherwise healthy and who had no significant differences in the volume or gray-white matter composition of the VOIs we assessed. Thus, the results of our study and those of other MRS studies most likely disagree owing to differences in the technique used for data acquisition and, thus, the amount and/or type of tissue sampled (eg, the use of surface coils does not allow visualization of the tissues studied) and the age, intelligence, and physical health of the study subjects.

We found that concentrations of all frontal metabolites were increased in the subjects with AS. This finding may result from differences in regional brain volume and brain tissue composition of the VOIs we studied, because brain tissue composition changes after adolescence,[58] and the relative concentrations of NAA, Cho, and Cr may differ in gray and white matter.[63] For example, autopsy studies reported that the gray-white matter ratio varies from 2.26 to 2.38[64,65] at 3 years of age to about 1.3 at 20 years of age.[66] Moreover, some researchers have reported a higher NAA and Cho signal intensity in gray than in white matter, whereas others report the opposite. The Cr signal intensity is typically higher in gray than in white matter.[63] However, the regional brain volumes and gray-white matter ratio in the people we studied were similar to those in previous reports.[29,66,67] Also, we found no significant between-group differences in age, in regional brain volume, or in the proportion of gray and white matter and CSF contained in the MRS VOIs. Thus, our measures of regional brain volume and VOI tissue proportion are most likely reliable, and our results cannot be fully explained by these potential confounders.

Our results may be explained by differences in tissue density and/or metabolism. For example, the increased NAA and Cr+PCr concentrations we found in our subjects with AS suggest an increased density of metabolically active neurons in the prefrontal lobe or a hypermetabolic state.[11] If the increase in NAA concentration reflects an increase in neuronal density, it should be unaffected by treatment, whereas if it reflects a metabolic abnormality, this may reverse with treatment (as severity of obsessive/repetitive behavior was related to NAA concentration). We suggest that abnormalities in neuronal density/metabolism most likely result from differences in frontal maturation, because NAA concentration rapidly increases as the brain develops and decreases in adulthood,[11] and neuropathological studies of patients with autism reported abnormalities in neuronal development.[47] The Cho-related compounds are components of neuronal cell membranes and are found in highest concentration in neuroglia and myelin sheaths.[68] Thus, differences in the Cho concentration may indicate differences in neuroglial number or neuronal membrane turnover and/or may be linked to hypermetabolism involving phosphatidylcholine via the action of phospholipase A_2. In humans, membrane turnover is increased by abnormal patterns of neuronal activation,[69] and a significant elevation in CSF ganglioside concentration (an important component of neuronal membranes) has been reported in patients with autism.[70] Thus, differences in neuronal membrane turnover and signal transduction provide the most parsimonious explanation for the increased Cho concentration that we found in subjects with AS.

CONCLUSIONS

We found that subjects with AS have a significant increase in the concentrations of NAA, Cho, and Cr+PCr. In healthy human brain development, postnatal neuro-

nal membrane turnover is high, and childhood is associated with increasing brain concentrations of NAA and Cr+PCr, which then reduce to adult levels by the late teenage years.[71,72] Thus, our findings imply that in AS, these developmental increases in metabolite concentrations fail to down-regulate, and this failure is related to some clinical symptoms in adulthood. Further studies are needed of brain development and aging across the spectrum of people with autistic disorder.

Submitted for publication October 10, 2000; final revision received November 14, 2001; accepted December 7, 2001.

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REFERENCES

1. Wing L. The autistic spectrum. *Lancet*. 1997;350:1761-1766.
2. Bolton P, Rutter M. Genetic influences in autism. *Int Rev Psychiatry*. 1990;2:67-80.
3. Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, Rutter M. Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol Med*. 1995;25:63-77.
4. Bolton PF, Pickles A, Murphy M, Rutter M. Autism, affective and other psychiatric disorders: patterns of familial aggregation. *Psychol Med*. 1998;28:385-395.
5. Frith U. *Autism and Asperger Syndrome*. New York, NY: Cambridge University Press; 1991.
6. Damasio AR, Mauer RG. A neurological model for childhood autism. *Arch Neurol*. 1978;35:777-786.
7. Zilbovicius M, Garreau B, Samson Y, Remy P, Barthelemy C, Syrota A, Lelord G. Delayed maturation of the frontal cortex in childhood autism. *Am J Psychiatry*. 1995;152:248-252.
8. Piven J, Arndt S, Bailey J, Andreasen N. Regional brain enlargement in autism: a magnetic resonance imaging study. *Am J Child Adolesc Psychiatry*. 1996;35:530-536.
9. Happe F, Ehlers S, Fletcher P, Frith U, Johansson M, Gillberg C, Dolan R, Frackowiak R, Frith C. "Theory of mind" in the brain: evidence from a PET scan study of Asperger syndrome. *Neuroreport*. 1996;8:197-201.
10. Horwitz B, Rumsey JM, Grady CL, Rapoport SI. The cerebral metabolic landscape in autism: intercorrelations of regional glucose utilization. *Arch Neurol*. 1988;45:749-755.
11. Clark JB. N-acetyl aspartate: a marker for neuronal loss or mitochondrial dysfunction. *Dev Neurosci*. 1998;20:271-276.
12. Gill SS, Thomas GT, Van Bruggen N, Gadian DG, Peden CJ, Bell JD, Cox IJ, Menon DK, Iles RA, Bryant DJ. Proton NR spectroscopy of intracranial tumours: in vivo and in vitro studies. *J Comput Assist Tomogr*. 1990;14:497-504.
13. Koller KJ, Zacsek R, Coyle JT. N-acetyl-aspartyl-glutamate: regional levels in rat brain and the effects of brain lesions as determined by a new HPLC method. *J Neurochem*. 1984;43:1136-1142.
14. Davie CA, Hawkins CP, Barker GJ, Brennan A, Tofts PS, Miller DH, McDonald WI. Serial proton magnetic resonance spectroscopy in acute multiple sclerosis lesions. *Brain*. 1994;117(pt 1):49-58.
15. Bruhn H, Frahm J, Gyngell ML, Merboldt KD, Hanicke W, Sauter R. Cerebral metabolism in man after acute stroke: new observations using localized proton NMR spectroscopy. *Magn Reson Med*. 1989;9:126-131.
16. Nishizuka Y. The molecular heterogeneity of protein kinase C and its implications for cellular regulation. *Nature*. 1988;334:661-665.
17. Berridge MJ, Irvine RG. Inositol phosphates and cell signalling. *Nature*. 1989;341:197-205.
18. Shetty UH, Schapiro MB, Holloway HW, Rapoport SL. Polyol profiles in Down syndrome: myo-inositol, specifically, is elevated in the cerebrospinal fluid. *J Clin Invest*. 1995;95:542-546.
19. Minshew NJ, Goldstein G, Dombrowski SM, Panchalingam K, Pettegrew JW. A preliminary ^{31}P MRS study of autism: evidence for undersynthesis and increased degradation of brain membranes. *Biol Psychiatry*. 1993;33:762-773.
20. Hashimoto T, Tayama M, Miyazaki M, Yoneda Y, Yoshimoto T, Harada M, Miyoshi H, Tanouchi M, Kuroda Y. Differences in brain metabolites between patients with autism and mental retardation as detected by in vivo localized proton magnetic resonance spectroscopy. *J Child Neurol*. 1997;12:91-96.
21. Chugani DC, Sundram BS, Behen M, Lee ML, Moore GM. Evidence of altered energy metabolism in autistic children. *Prog Neuropsychopharmacol Biol Psychiatry*. 1999;23:635-641.
22. Rapin I. Introduction and overview. In: Bauman ML, Kemper TL, eds. *The Neurobiology of Autism*. Baltimore, Md: Johns Hopkins University Press; 1994:1-17.
23. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
24. Kanner L. Autistic disturbances of affective contact. *Nerv Child*. 1943;8:477-479.
25. Rutter M. Infantile autism and other pervasive developmental disorders. In: Rutter M, Hersov L, eds. *Child and Adolescent Psychiatry: Modern Approaches*. Malden, Mass: Blackwell Publishers; 1985:545-567.
26. Baron-Cohen S, Wheelwright S. "Obsessions" in children with autism or Asperger syndrome: content analysis in terms of core domains of cognition. *Br J Psychiatry*. 1999;175:484-490.
27. Lord C, Rutter M, Couteur A. Autism Diagnostic Interview–Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord*. 1994;24:659-685.
28. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research*. Geneva, Switzerland: WHO; 1993.
29. Murphy DG, DeCarli C, McIntosh AR, Daly E, Mentis MJ, Pietrini P, Szczepanik J, Schapiro MB, Grady CL, Horwitz B, Rapoport SI. Sex differences in human brain morphometry and metabolism: an in vivo quantitative magnetic resonance imaging and positron emission tomography study on the effect of aging. *Arch Gen Psychiatry*. 1996;53:585-594.
30. Murphy DGM, Mentis MJ, Pietrini P, Grady G, Daly E, Haxby JV, De La Granja M, Allen G, Largay K, White BJ, Powell CM, Horwitz B, Rapoport SI, Schapiro MB. A PET study of Turner's syndrome: effects of sex steroids and the X chromosome on brain. *Biol Psychiatry*. 1997;41:285-298.
31. Wechsler D. *Wechsler Adult Intelligent Scale Revised*. New York, NY: Psychological Corp, Harcourt Brace; 1987.
32. Goodman WK, Price L, Rasmussen S, Mazure C, Fleischmann R, Hill C, Heninger G, Charney D. The Yale-Brown Obsessive Compulsive Scale, I: development, use, and reliability. *Arch Gen Psychiatry*. 1989;46:1006-1011.
33. Annett N. A classification of hand preferences by association analysis. *Br J Psychol*. 1970;61:303-321.
34. Simmons A, Smail M, Moore E, Williams SCR. Serial precision metabolite peak area ratios and water references metabolite peak areas in proton MR spectroscopy of the human brain. *Magn Reson Imaging*. 1998;16:319-330.
35. Barta PE, Dhingra L, Royall R, Schwartz E. Improving stereological estimates for the volume of structures indentified in three-dimensional arrays of spatial data. *J Neurosci Methods*. 1997;75:111-118.
36. Gordon CT, State RC, Nelson JE, Hamburger SD, Rapoport JL. A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder. *Arch Gen Psychiatry*. 1993;50:441-447.
37. McDougle CJ, Naylor ST, Cohen DJ, Volkmar FR, Heninger GR, Price LH. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. *Arch Gen Psychiatry*. 1996;53:1001-1008.
38. Baron-Cohen S. Do autistic children have obsessions and compulsions. *Br J Clin Psychol*. 1989;28(pt 3):193-200.
39. McDougle CJ, Kresch LE, Goodman WK, Naylor ST, Volkmar FR, Cohen DJ, Price LH. A case-controlled study of repetitive thoughts and behavior in adults with autistic disorder and obsessive-compulsive disorder. *Am J Psychiatry*. 1995;152:772-777.
40. Insel TR. Toward a neuroanatomy of obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1992;49:739-744.
41. McGuire PK, Bench CJ, Frith CD, Marks IM, Frackowiak RS, Dolan RJ. Functional neuroanatomy of obsessive-compulsive phenomena. *Br J Psychiatry*. 1994;164:459-468.
42. Ebert D, Speck O, Konig A, Berger M, Hennig J, Hohagen F. 1H-magnetic resonance spectroscopy in obsessive-compulsive disorder: evidence for neuronal loss in the cingulate gyrus and right striatum. *Psychiatry Res*. 1997;74:173-176.
43. Rumsey JM, Hamburger SD. Neuropsychological divergence of high-level autism and severe dyslexia. *J Autism Dev Disord*. 1990;20:155-168.
44. Ozonoff S, Pennington BF, Rogers SJ. Executive function deficits in high-functioning autistic individuals: relationship to theory of mind. *J Child Psychol Psychiatry*. 1991;32:1081-1105.
45. Hughes C, Russell J, Robbins TW. Evidence for executive dysfunction in autism. *Neuropsychologia*. 1994;32:477-492.
46. Bauman ML, Kemper TL. Histoanatomic observations of the brain in early infantile autism. *Neurology*. 1985;35:866-874.

47. Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, Rutter M, Lantos P. A clinicopathological study of autism. *Brain*. 1998;121(pt 5):889-905.
48. Piven J, Berthier ML, Starkstein SE, Nehme E, Pearlson G, Folstein S. Magnetic resonance imaging evidence for a defect of cerebral cortical development in autism. *Am J Psychiatry*. 1990;147:734-739.
49. Courchesne E, Press GA, Yeung-Courchesne R. Parietal lobe abnormalities detected with MR in patients with infantile autism. *AJR Am J Roentogenol*. 1993; 160:387-393.
50. Piven J, Arndt S, Bailey J, Havercamp S, Andreasen NC, Palmer P. An MRI study of brain size in autism. .*Am J Psychiatry*. 1995;152:1145-1149.
51. Hazneder MM, Buchsbaum MS, Metzger M, Solimando A, Speigel-Cohen J, Hollander E. Anterior cingulate gyrus volume and glucose metabolism in autistic disorder. *Am J Psychiatry*. 1997;154:1047-1050.
52. Abell F, Krams M, Ashburner J, Passingham R, Friston K, Frackowiak R, Happe F, Frith C, Frith U. The neuroanatomy of autism: a voxel-based whole brain analysis of structural scans. *Neuroreport*. 1999;10:1647-1651.
53. Sears LL, Vest C, Mohamed S, Bailey J, Ranson BJ, Piven J. An MRI study of the basal ganglia in autism. *Prog Neuropsychopharmacol Biol Psychiatry*. 1999;23: 613-624.
54. Seigel BV Jr, Nuechterlein KH, Abel L, Wu JC, Buschsbaum MS. Glucose metabolic correlates of continuous performance test performance in adults with a history of infantile autism, schizophrenics, and controls. *Schizophr Res*. 1995;17: 85-94.
55. Baron-Cohen S, Ring HA, Wheelwright S, Bullmore ET, Brammer MJ, Simmons A, Williams SC. Social intelligence in the normal and autistic brain: an fMRI study. *Eur J Neurosci*. 1999;11:1891-1898.
56. Critchley HD, Daly EM, Bullmore ET, Williams SCR, Amelsvoort TV, Robertson DM, Rowe A, Phillips M, McAlonan G, Howlin P, Murphy DGM. The functional neuroanatomy of social behaviour: changes in cerebral blood flow when people with autistic disorder process facial expressions. *Brain*. 2000;123(pt 11):2203-2212.
57. Schultz RT, Gauthier I, Klin A, Fulbright RK, Anderson AW, Volkmar F, Skudlarski P, Lacadie C, Cohen DJ, Gore JC. Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. *Arch Gen Psychiatry*. 2000;57:331-340.
58. Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. *Nat Neurosci*. 1999;2:859-861.
59. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci*. 1999;2:861-863.
60. Huttenlocher P, Dabholkar A. Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol*. 1997;387:167-178.
61. Benes FM. Myelination of cortical-hippocampal relays during late adolescence. *Schizophr Bull*. 1989;15:585-593.
62. Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. *Ann Neurol*. 1987;22:487-497.
63. Pfefferbaum A, Adalsteinsson E, Spielman D, Sullivan EV, Lim KO. In vivo spectroscopic quantification of the N-acetyl moiety, creatine, and choline from large volumes of brain gray and white matter: effects of normal aging. *Magn Reson Med*. 1999;41:276-284.
64. Anton G. Gehirnvermessung mittelst des Kompensations-Polar-Planimeters. *Klin Wochenschrift*. 1903;16:1263-1267.
65. Jaeger R. Inhaltsberechnungen der Rinden-und-Mark substanz des Grosshirns durch planimetrische Messungen. *Arch Psychiatrie Nervenkrankheiten*. 1914; 54:261-272.
66. Miller AKH, Alston RL, Corsellis JA. Variation with age in the volumes of grey and white matter in the cerebral hemispheres of man: measurements with an image analyser. *Neuropathol Appl Neurobiol*. 1980;6:119-132.
67. Murphy DG, DeCarli C, Daly E, Haxby JV, Allen G, White BJ, McIntosh AR, Powell CM, Horwitz B, Rapoport SI, Schapiro MB. X-chromosome effects on female brain: a magnetic resonance imaging study of Turner's syndrome. *Lancet*. 1993; 342:1197-1200.
68. Miller BL, Chang L, Booth R, Ernst T, Cornford M, Nikas D, McBride D, Jenden DJ. In vivo 1H MRS choline: correlation with in vitro chemistry/histology. *Life Sci*. 1996;58:1929-1935.
69. Arai T, Jones CR, Rapoport SI, Weiss SR. Evidence for membrane remodeling in ipsilateral thalamus and amygdala following left amygdala–kindled seizures in awake rats. *Brain Res*. 1996;743:131-140.
70. Nordin V, Lekman A, Johansson M, Fredman P, Gillberg C. Gangliosides in cerebrospinal fluid in children with autism spectrum disorders. *Dev Med Child Neurol*. 1998;40:587-594.
71. Toft PB, Leth H, Lou HC, Pryds O, Henriksen O. Metabolite concentrations in the developing brain estimated with proton MR spectroscopy. *J Magn Reson Imaging*. 1994;4:674-680.
72. Kato T, Nishina M, Matsushita K, Hori E, Mito T, Takashima S. Neuronal maturation and N-acetyl-L-aspartic acid development in human fetal and child brains. *Brain Dev*. 1997;19:131-133.