

Brain Volume in Autism

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ABSTRACT

Increased brain size has been observed in individuals with autism with a wide range of cognitive functioning. The purpose of this investigation was to obtain measurements of the brain volume in a sample of nonmentally retarded autistic individuals. Magnetic resonance imaging scans from 16 nonmentally retarded individuals with autism and 19 male volunteer comparison subjects were obtained and the following structures were measured: third, fourth, and lateral ventricles and intracranial and cerebral volumes. Mean cerebral and third ventricle volumes in the autistic subjects were significantly greater than in the controls when adjusted for intracranial volume. No other significant results were found. Our finding of increased brain volume in autism is consistent with previous reports in the literature. Additional longitudinal neuroimaging and, more importantly, neuropathologic studies are warranted to provide a better understanding of the complexities underlying increased brain size in autism. (*J Child Neurol* 2001;16:421–424).

Autism is a neurodevelopmental disorder characterized by abnormalities in social skills and behavior, verbal and non-verbal communications, symbolic and imaginative play, reasoning, and related complex behavior.¹ Studies of brain structure have implicated several aspects of brain development involved in neuronal organization including the elaboration of dendritic and axonal ramifications, the establishments of synaptic connections, and cell death.² These developmental neuronal disturbances may lead to a wide range of anatomic abnormalities including changes in brain volume. Interestingly, there is mounting evidence using different methodologies that brain size in autism is, on average, increased.

Kanner, in his original description, pointed to the presence of large heads in some children with autism.³ Several subsequent studies have found an increase in fronto-occipital head circumference^{4–6} and macrocephaly.^{7,8} Neuropathologic studies have reported an increase in brain weight,^{9–12} more so in children than in adults.¹² Consistent with these reports, several neuroimaging studies have

reported an increase in brain size in autism.^{13–15} In a study of 15 high-functioning autistic men, the midsagittal supratentorial brain area was reported to be increased compared with a matched control group.¹³ A more recent study found an increase in total brain volume, which was the consequence of enlargement of parietal, temporal, and occipital regions but not the frontal lobe.^{14,15} This regional brain enlargement was consistent with another study reporting an increase in brain volume selectively involving pericallosal segments.¹⁶

The objective of the present investigation was to determine whether brain volume was increased in a sample of nonmentally retarded autistic individuals, as has been reported in several studies in generally lower functioning individuals. We hypothesized that, after adjustment for intracranial volume, the cerebral volume will be larger in the autistic group compared with controls. In an attempt to identify the potential contributors to the increase in brain size, the following structures were measured: third, fourth, and lateral ventricles.

METHOD

Subjects

Sixteen male subjects with autism were included in the study. The diagnosis of autism was established through expert clinical evaluation in accordance with accepted clinical descriptions of high-functioning autism¹⁷ and two structured diagnostic instruments, the Autism Diagnostic Interview¹⁸ and the Autism Diagnostic Observation Schedule.¹⁹ Inclusion criteria were (1) absence of mental retardation (Wechsler Full Scale and Verbal IQ > 70); (2) absence

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of known neurologic causes of the autistic syndrome such as tuberous sclerosis, neurofibromatosis, fragile X syndrome, inborn errors of metabolism, or acquired brain damage as determined by neurologic history, examination, and laboratory testing; (3) male gender; and (4) ability to provide (or a guardian capable of providing) informed consent. The study was confined to males because the sample size was too small to accommodate structural variability associated with gender. The age-appropriate version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) or the Wechsler Intelligence Scale for Children-Revised (WISC-R) was administered to measure IQ. The socioeconomic status of the family of origin was determined with a modification of the Hollingshead method and matched at group level.

The comparison group consisted of 19 healthy volunteer males recruited from the community through advertisements who met the following criteria: (1) neurologically and psychiatrically normal, without developmental learning or language disorders; (2) negative family history of autism, developmental disorders, or heritable neuropsychiatric disorders; and (3) good physical health. Twenty-two controls were originally recruited as 1:1 matches with autistic subjects with regard to gender, race, Full-Scale IQ (within 5 points), and age (within 6 months for subjects aged ≤ 17 years and within 1 year for those ≥ 18 years). However, a few subjects from both groups were excluded from analyses because of the inadequate quality of their magnetic resonance imaging scans. The resulting groups were matched for age, Full-Scale IQ, Performance IQ, Verbal IQ, education level, and the socioeconomic status of the family of origin (Table 1).

Magnetic Resonance Imaging Scans

All imaging studies were performed with a General Electric Signa One instrument operating at a field strength of 1.5 Tesla. Imaging was conducted without sedation. The imaging protocol consisted of a T_1 -weighted (TR = 500 msec, TE = 20 msec) series: a coronal scout series of 5-mm image thickness (1-mm gap) for the purpose of identifying the midline plane, a sagittal series of 3-mm thickness (interleaved) parallel to the midline plane, and three-dimensional-axial spoiled gradient-recalled acquisitions in the steady state series of 2.5-mm thickness.

Image Analysis

Images were digitally transferred from the Signa System to a Macintosh work station, and the data were analyzed using the IMAGE software (version 1.45) developed by the National Institutes of Health,²⁰ which provides valid and reliable volume measurements of specific structures using a semiautomated histogram-based

segmentation approach.²¹ All measurements were made by A.H. and M.M., who were trained and reliable raters and were blind to subject status with regard to diagnosis. Intraclass correlation of interrater reliability ranged from 0.95 (intracranial volume) to 0.99 (cerebral volume). Intraclass correlation of intrarater reliability ranged from 0.93 (cerebral volume) to 0.99 (fourth ventricle volume). The investigator involved in the diagnosis (N.M.) was not involved in image selection or measurement.

Measurement of the Intracranial Volume

Axial images were first reformatted to produce coronal slices. The intracranial volume was calculated by summing up areas of successive coronal slices, including gray and white matter and cerebral spinal fluid volumes, and multiplying by the slice thickness. Images were traced along the diploe on the outside border of the brain excluding everything except dura, gray, and white matter. All of the frontal, parietal, temporal, and occipital cortices were included, in addition to the cerebellum, brain stem to the lower limit of the pons, pituitary gland, and optic chiasma.

Measurement of the Cerebral Volume and the Ventricles

The cerebral volume was calculated by summing up areas of successive coronal slices of the previously measured intracranial tracings, excluding cerebrospinal fluid, dura matter, the cerebellum, and the brain stem, and multiplying by slice thickness. The latter two structures were traced manually to exclude their volume. The third ventricle volume was calculated by summing up areas of successive coronal slices of the region of interest traced along the edge of this ventricle. Using a similar approach, the fourth and the lateral ventricles were measured.

Statistical Analysis

Inter-reliability and intrarater reliability were assessed by using the intraclass correlation coefficient ($N = 10$). Student's t -test (two-tailed) was employed to examine for mean differences between the autistic and comparison subjects. Analysis of covariance (ANCOVA) was used to examine differences in the regions of interest (cerebral, third, fourth, and lateral ventricle volumes) between autistic participants and comparison subjects after adjustment for intracranial volume. This approach (ie, ANCOVA) has been suggested and used as a method of analysis for dealing with potential confounders in structural imaging studies of the brain.^{15,22} Therefore, adjusting for intracranial volume is essential in light of the reports of increased head circumference reported in autism.⁴⁻⁸ Two-tailed tests were used for statistical significance, and alpha was set at $P < .05$.

Table 1. Demographic Information

	Autistics (n = 16)		Controls (n = 19)		t	P
	Mean	SD	Mean	SD		
Age (yr)	22.18	10.10	22.21	9.44	-0.01	.99
Full-Scale IQ	102.75	15.16	101.21	13.93	0.31	.75
Verbal IQ	106.12	16.16	101.58	13.84	0.90	.37
Performance IQ	100.00	13.23	99.89	12.53	0.02	.98
Education level	10.56	3.40	11.16	2.89	-0.56	.58
Socioeconomic status	3.87	1.45	3.52	1.22	0.77	.44

RESULTS

The mean raw values of cerebral volume, intracranial volume, and fourth and lateral ventricles between the two groups did not differ significantly. The volume of the third ventricle was significantly larger in the autistic group compared with the controls (Table 2). Mean cerebral volume and mean third ventricle volume in autistic participants were significantly larger than the control group when adjusted for intracranial volume (see Table 2). Due to the presence of an outlier with megalencephaly in the autistic group, the data were analyzed again without this participant, which did not lead to any change in the level of significance.

The participants were divided into two groups according to age (younger and older than 21 years), and the differences between the cerebral volume of the two groups remained significant in the younger group (autistic: $N = 11$, mean = 1430.86 cc, SD = 225.38; controls: $N = 13$, mean = 1335.13, SD = 106.32; $F = 4.328$, $df = [1,21]$, $P = 0.05$) but not in the older group when adjusting for intracranial volume (autistic: $N = 5$, mean = 1260.15 cc, SD = 116.65; controls: $N = 6$, mean = 1265.09, SD = 109.62; $F = 1.271$, $df = [1,8]$, $P = .92$).

DISCUSSION

In this study, the cerebral volume of a group of nonmentally retarded individuals with autism was, on average, enlarged when compared with a control group after adjusting for intracranial volume. This finding is concordant with several previous neuroimaging reports of increased brain volume.¹³⁻¹⁶ The increase in cerebral volume in younger but not in older subjects in this study is also consistent with neuropathologic studies reporting increased brain weight in individuals with autism,^{11,12} more so in children than in adults.¹² The findings of this study are also concordant with a number of studies reporting increased head circumference in autism.⁴⁻⁸ These studies revealed a fronto-occipital head circumference in the normal range at birth or shortly after with an increase to the above-average range by 4 years of age. This relationship with age, in addition to the one of brain weight with age, raises the issue of the influence of the continuing process of brain development in autism and suggests that postnatal processes are responsible for this abnormal rate of growth.

In the present study, there was no evidence of significant contribution of any brain compartment in the increased brain and head size. The volume of the third ventricle was found to be enlarged in the autistic group. This finding is consistent with one previous computed tomography scan report of increased size of this structure and not the lateral ventricles²³ in individuals with autism. This finding may suggest the presence of abnormalities in adjacent structures such as the thalamus. Interestingly, neuroimaging studies have pointed to abnormalities in the dentatohalamocortical pathway^{24,25} and functional impairment of the interaction between frontoparietal regions and the neostriatum and thalamus in autism.²⁶ This constellation of findings warrants further examination of the thalamus in autism using different technologies.

The pathophysiology of brain enlargement in autism is unclear, and several developmental processes are to be considered. Several distinct mechanisms have been suggested^{14,15}: increased neurogenesis, decreased neuronal death, increased production of non-neuronal brain tissues (ie, glial cells), and decreased synaptic pruning. The limited neuropathologic data available in the literature have not been conclusive in support of either a derangement of neurogenesis or a failure of the programmed cell death.^{10,27} Furthermore, postmortem studies have failed to show any abnormalities of gross brain structure, and myelination in autism has been found to be comparable to controls,¹¹ and no differences in glial cell number have been reported.²⁷ Last, the process of selective elimination of neuronal processes usually leads to reduced brain volume with maturation without alterations in overall head size. If the process is intact, one would expect a proportionate age-related reduction in brain volume in both healthy and autistic subjects, even if this was initially enlarged. Our preliminary observation of increased brain volumes adjusted for intracranial volume in autistic patients suggests that such a reduction may have partially or completely failed to occur in this developmental disorder. Such a defective synaptic pruning may predict increased synaptic density and decreased neuronal density in these subjects. Neuropathologic studies are needed to test these predictions.

The results of this study need to be interpreted with caution in light of the small sample size and the methodology used. The cerebral volume and the intracranial volume were nonsignificantly larger in the autistic group, and a larger

Table 2. Diagnosis Effect on Brain Volume

Volume	Autistics		Controls		t^*	P	ICV as Covariate	
	Mean	SD	Mean	SD			F^{**}	P
Intracranial	1742.14	237.25	1639.40	118.90	1.66	0.11	—	—
Cerebral	1377.51	210.25	1313.01	109.51	1.17	0.25	5.26	.03
Lateral ventricle	9.70	7.11	6.99	9.43	0.94	0.35	0.55	.46
Third ventricle	1.04	0.62	0.63	0.29	2.56	0.01	7.65	.01
Fourth ventricle	1.14	0.56	0.98	0.40	0.95	0.35	0.84	.37

*($df = 1, 33$); **($df = 1, 32$).

Volume is in cc.

ICV = intracranial volume.

sample size would have detected a statistical difference between the two groups. Furthermore, lobar measurements were not done to allow comparison with previous studies reporting regional brain enlargement in autism.¹⁵

In conclusion, the magnetic resonance imaging data in the present study show an average increase in brain volume consistent with the literature. Further research is needed to examine large sample sizes of different developmental ages with varying levels of severity of autism and more refined methodology. Moreover, longitudinal studies are warranted combining neuroimaging and fronto-occipital head circumference measurements to investigate clinical correlates associated with brain size and to determine whether brain volume could serve as some sort of biologic marker defining specific subgroups. Although increased brain size has been reported consistently, the exact mechanisms underlying this process remain obscure. Therefore, continued study of the brain in autism using histopathologic examination is critical to a better understanding of the complexities underlying the enlarged brain size in autism.

References

1. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised*. Washington, DC: American Psychiatric Association, 1987.
2. Aylward EH, Minshew NJ, Goldstein G, et al: MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. *Neurology* 1999;53:2145–2150.
3. Kanner L: Autistic disturbances of affective contact. *Nerv Child* 1943;2:217–250.
4. Bolton P, Macdonald H, Pickles A, et al: A case-control family history study of autism. *J Child Psychol Psychiatry* 1994;35:877–900.
5. Steg JP, Rapoport JL: Minor physical anomalies in normal, neurotic learning disabled, and severely disturbed children. *J Autism Child Schizophr* 1975;5:299–307.
6. Walker HA: Incidence of minor anomaly in autism. *J Autism Child Schizophr* 1977;7:165–176.
7. Bailey A, LeCouteur A, Gottesman I, et al: Autism as a strongly genetic disorder: evidence from a twin study. *Psychol Med* 1995;25:63–78.
8. Lainhart JE, Piven J, Wzorek M, et al: Macrocephaly in children and adults with autism. *J Am Acad Child Adolesc Psychiatry* 1997;36:282–290.
9. Bailey A, Luthert P, Bolton P, et al: Autism and megalencephaly. *Lancet* 1993;341:1225–1226.
10. Bailey A, Luthert P, Dean A, et al: A clinicopathological study of autism. *Brain* 1998;121:889–905.
11. Bauman ML, Kemper TL: Neuroanatomic observations of the brain in autism, in Bauman ML, Kemper TL (eds): *The Neurobiology of Autism*. Baltimore, Johns Hopkins University, 1994, 119–145.
12. Kemper TL, Bauman ML: Neuropathology of infantile autism. *J Neuropathol Exp Neurol* 1998;57:645–652.
13. Piven J, Nehme E, Simon J, et al: Magnetic resonance imaging in autism: Measurement of the cerebellum, pons, and fourth ventricle. *Biol Psychiatry* 1992;31:491–505.
14. Piven J, Arndt S, Bailey J, et al: An MRI study of brain size in autism. *Am J Psychiatry* 1995;152:1145–1149.
15. Piven J, Arndt S, Bailey, et al: Regional brain enlargement in autism: A magnetic resonance imaging study. *J Am Acad Child Adolesc Psychiatry* 1996;35:530–536.
16. Filipek PA, Richelme C, Kennedy CN, et al: Morphometric analysis of the brain in developmental language disorder and autism. *Ann Neurol* 1992;32:475.
17. Minshew NJ: Autism, in Berg BO (ed): *Principles of Child Neurology*. New York: McGraw-Hill, 1996, 1713–1730.
18. LeCouteur A, Rutter M, Lord C, et al: Autism Diagnostic Interview: A standardized investigator-based instrument. *J Autism Dev Disord* 1989;19:363–387.
19. Lord C, Rutter M, Goode S, et al: Autism Diagnostic Observation Schedule: A standardized observation of communicative and social behavior. *J Autism Dev Disord* 1989;19:185–212.
20. Rasband W: *NIH IMAGE Manual*. Bethesda, MD, National Institutes of Health, 1996.
21. Keshavan MS, Beckwith C, Bagwell W, et al: An objective method for edge detection in MRI morphometry. *Eur Psychiatry* 1994;9:205–207.
22. Arndt S, Cohen G, Alliger RJ, et al: Problems with ratio and proportion measures of imaged cerebral structures. *Psychiatr Res* 1991;40:79–89.
23. Jacobson R, Le Couteur A, Howlin P, et al: Selective subcortical abnormalities in autism. *Psychol Med* 1988;18:39–48.
24. Chugani DC, Muzik O, Rothermel R, et al: Altered serotonin synthesis in the dentatothalamocortical pathway in autistic boys. *Ann Neurol* 1997;42:666–669.
25. Muller RA, Chugani DC, Behen ME, et al: Impairment of the dentato-thalamocortical pathway in autistic men: Language activation data from the positron emission tomography. *Neurosci Lett* 1998;245:1–4.
26. Horowitz B, Rumsey JM, Grady CL, et al: The cerebral metabolic landscape in autism: Intercorrelations of regional glucose utilization. *Arch Neurol* 1988;45:749–755.
27. Coleman PD, Romano J, Lapham L, et al: Cell counts in cerebral cortex of an autistic patient. *J Autism Dev Disord* 1985;15:245–255.

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