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Midsagittal Magnetic Resonance Imaging of Autism

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Since recent reports suggest structural brain abnormalities in autistic patients, we analysed magnetic resonance imaging (MRI) scans of autistic children. Planimetric measurements were done on midsagittal MRI scans, produced with a 0.5 T superconducting magnet. Scans of 13 'high-level' autistic subjects were compared with 35 control MRI scans, read as anatomically normal by a neuroradiologist. Corpus callosal, fourth ventricular, cerebellar, cerebral, and cranial areas were measured. The fourth ventricle was found to be significantly larger in the autistic group. No other areas in the midsagittal scans differed statistically between groups. Results suggest that structures defining the fourth ventricle are anatomically altered in autistic patients.

Past investigations of brain anatomy and morphology in autistic children have yielded variable results. A pneumoencephalography study found dilated left anterior ventricular horns in autistic patients (Hauser *et al*, 1975). Computerised tomography (CT) scan studies present variable results. Several studies found significant parenchymal or ventricular abnormalities in autistic subjects (Damasio *et al*, 1980; Caparulo *et al*, 1981; Campbell *et al*, 1982; Gillberg & Svendsen, 1983); however, there were several equivocal or even negative CT studies as well (Rosenbloom *et al*, 1984; Prior *et al*, 1984; Harcherik *et al*, 1985; Creasey *et al*, 1986).

Likewise, autopsy studies offer conflicting evidence of brain abnormalities in autism (Williams *et al*, 1980; Bauman & Kemper, 1985). A Harvard group reported neuropathological gross and microscopic abnormalities of limbic structures, fourth ventricle, and cerebellum in an autistic 'brain' (Bauman & Kemper, 1985). The same group also reported abnormalities of fourth ventricle and cerebellum in autistic patients studied by CT scan (Bauman *et al*, 1985). Recently a group from UCLA reported cerebellar changes found in a number of post-mortem examinations of autistic patients (Ritvo *et al*, 1986).

Magnetic resonance imaging (MRI) offers several advantages over X-ray CT, especially in investigating the posterior fossa. There is no skull artifact in MRI as found in CT; further, MRI offers multiplanar imaging, whereas CT imaging currently is limited to transverse scans. Considering the reports indicating anatomical abnormalities in autistic brains, we felt it would be of interest to investigate the gross brain morphology of autistic children, by MRI. Thus, we wish to report our initial analysis of the midsagittal MRI scans of autistic children.

Method

Subjects

MRI scans were obtained on 13 autistic patients, seen at the University of Iowa Hospitals, who were diagnosed by the American Psychiatric Association DSM-III criteria. Age, sex, and IQ are given in Table I. IQs were mostly assessed by WISC-R (however, in one case by the Leiter and another by the Merrill-Palmer). Eleven patients were right-handed, one was left-handed, and one was mixed-handed. One patient had generalised tonic clonic seizures and was taking anticonvulsants. Two autistic patients had *café au lait* spots on physical examination, and thus had neurofibromatosis diagnosed by a paediatric neurologist. None of the patients, however, had major structural abnormalities on MRI scans.

The control group was ascertained from the records at the MRI centre. Records were examined of patients aged 4 to 19, who were referred to MRI at the same time as the autistic patients were, and whose MRI scans were read anatomically as 'normal' by the consulting neuroradiologist. Hospital records, and sometimes treating physicians, were consulted to determine significant behavioural problems or developmental delays; control patients with mention of these problems were excluded from this study. There were 35 scans of patients in childhood and adolescence that met criteria.

The control patients were referred for MRI scanning for a variety of reasons; these included a past history of histiocytosis X, headaches, Duane's syndrome, congenital optic atrophy, and others. One control child had neurofibromatosis, diagnosed by *café au lait* spots. Two control children had psychomotor seizures and were taking anticonvulsive medications. Age and sex of the controls are given in Table I. IQs and handedness of the children who served as controls were unknown; however, as mentioned, children with significant learning and developmental abnormalities were excluded from the study.

The control group used in the study is a 'medical' control group. Although it appears that this group is devoid of patients with autism, it may be argued that a 'non-medical' normal control group should be ascertained. However, for a pilot study the 'medical' control group seems adequate,

TABLE I
Demographic data of the autistic and control groups

	Autistic group	*Control group*
Number	13	35
Age range	5–22	4–19
Mean age[1] (± s.d.)	11.3 ± 4.7*	12.0 ± 5.2*
IQ range	60–135	—
Mean IQ (± s.d.)	84.9 ± 26.7	—
Males	10 (77%)	21 (60%)

1. Age data in the groups were tested independently for skewness. The null hypothesis of no skewness was not rejected.
*NS (*t*-test).

especially considering the ethical issues of exposing normal children to a procedure that may require sedation. Moreover, since the medical control group was referred to the same hospital as the autistic group, referral bias would be controlled.

Procedures

The MRI scans were done on a 0.5 tesla superconducting magnet, Picker Vista MR. Scans were recorded on transparent film with a 14 cm to 4 cm scale reduction. Most of the autistic children were sedated with chloral hydrate, 50–100 mg/kg. No problems were encountered during these scanning procedures.

The midsagittal scans were projected from a photographic condenser, life size, on to a digitising tablet (Houston Instruments, Hipad) interfaced to a microcomputer (IBM PC/AT) for digitisation and area measurements. Planimetric measurements were calculated by computeraided design software (Autocad, by Autodesk). Scans were digitised three times by two investigators. The digitising was done blind to diagnostic group. Areas measured by planimetry included corpus callosum, fourth ventricle, cerebellum, cerebrum, and cranium.

Data were analysed by Pearson correlations, multivariate Hotteling's t^2, and univariate *t*-tests in appropriate applications. These statistical tests were done by the Statistical Package for the Social Sciences on a mainframe computer at the University of Iowa's Computing Center, and by SAS on mainframe at the University of Kansas.

Intra-rater correlations were calculated for the five areas. All three raters were above 0.93, with one exception; one rater had a intra-rater correlation of 0.84 of the callosal area.

Inter-rater correlations also indicated that the measures were consistent and reproducible: correlation for the corpus callosum area was 0.94 (average of the three Pearson's *r*); fourth ventricle, 0.96; cerebellum, 0.96; cerebrum, 0.97; cranium, 0.99.

Results

As seen in Table I, the two groups were not skewed in age distribution, and thus comparisons involving brain morphology between groups are valid. Also, there was no differences in results between the sexes by statistical analysis; thus, results (Table II) combine both sexes.

Using only brain areas, multivariate analysis of variance by Hotteling's t^2 was significant ($F = 3.24$; $P < 0.0106$). Univariate *t* tests were performed independently for each brain area measure (Table II). The results indicate that the fourth ventricle was significantly larger in the autistic group than in the control group. Cranium, cerebrum, and corpus callosum were not significantly different. The cerebellum was smaller in the autistic group, but the difference was not statistically significant.

Ratios were also analysed. Univariate *t*-tests revealed statistically significant differences for the fourth ventricle to cerebellum ratio (0.015 ± 0.006 in the autistic group and 0.009 ± 0.003 in the control group; $P < 0.001$) and the fourth ventricle to cerebrum ratio (0.014 ± 0.039 in the autistic group and 0.063 ± 0.025 in the control group; $P < 0.0002$). This indicates proportionally larger fourth ventricles in the autistic patients.

Discussion

Results of this study indicate that the MRI brain morphology of the autistic group was different from that of the control group. Specifically, on planimetrically analysed midsagittal MRI scans, the fourth ventricle of autistic children is larger than the same area of control children. The ratio of fourth ventricle to cerebrum also indicates that, proportionately, the fourth ventricle is larger in autistic children, and that the finding is not an artifact of larger brain size. Although there was a trend toward smaller cerebella in the autistic children, no other midsagittal areas measured differed statistically between autistic and control children.

Since this is a small sample size, the study needs replication not only with midsagittal views, but also with transverse and coronal images. However, if replicated, this finding, considered along with the autopsy and CT material, suggests strongly that the fourth ventricle is enlarged in autistic subjects.

The significance of an enlarged fourth ventricle finding is unclear. The fourth ventricle is related to the pons, cerebellum, and medulla. The midsagittal MRI scan images the ventricular length. This allows all portions of the fourth ventricle – inferior, middle, superior – to be seen. The superior portion of the fourth ventricle is bounded by the superior medullary velum and superior vermis in the roof, and the locus ceruleus and medial longitudinal fasciculus (MLF) of the upper pons in the floor. The middle fourth ventricle roof includes the cerebellar vermis and the central cerebellar nuclei; the floor of the middle part includes the MLF, and abducens (VI) and vestibulocochlear (VIII) nuclei. Finally, the inferior

TABLE II
Midsagittal areas (cm^2; mean ± s.d.) in autistic v. controls

	Austistics (n = 13)	*Controls (n = 35)*
Corpus callosum	5.89 ± 1.04	6.24 ± 1.37
Fourth ventricle*	1.51 ± 0.52	0.99 ± 0.33
Cerebellum	15.00 ± 2.46	16.39 ± 2.76
Cerebrum	105.48 ± 9.79	107.42 ± 12.00
Cranium	165.10 ± 14.77	170.23 ± 18.58

*Significant by *t*-test ($P < 0.002$).

medullary velum and the vermal nodulus define the roof of the inferior fourth ventricle, while the hypoglossal (XII) and vagal (X) nuclei, and MLF define the floor.

Of import are structures that have been implicated in autism, that define the fourth ventricle and, if altered, might alter the morphology of the ventricle. The central cerebellar nuclei have been reported to be aberrant in a neuropathological study of one 'autistic' brain (Bauman & Kemper, 1985). In another series of 'autistic' brains, there were widespread abnormalities in several cerebella (Ritvo *et al*, 1986). There are no anatomical studies of the brain stem to our knowledge. However, neurophysiological experiments suggest brain stem nuclei – especially areas in the pons (such as nucleus VIII) – are involved in autism (Ornitz, 1985). Thus, there is evidence that brain areas surrounding the fourth ventricle are involved with the clinical manifestations of autism; alterations in these discrete areas might then alter the space that they define, resulting in a relatively larger fourth ventricle.

Both brainstem and cerebellum have connections with, and affect function of, the limbic system, an area implicated in infantile autism. This suggests that widespread brain abnormalities, in neuronal circuits, are involved in autism. Although speculative, such abnormalities could be caused by aberrant development or early brain injury resulting in brain-tissue loss. Such brain-tissue loss would then result in the enlarged ventricular space.

This study indicates that in midsagittal MRI images, the fourth ventricle appears to be enlarged in autistic patients when compared with medical controls. This has several implications: replication is needed, with midsagittal and with other scanning orientations; and structures defining the fourth ventricle – the brainstem, the pons, and the cerebellum – deserve further morphological investigation in autism.

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