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Three-dimensional mapping of the lateral ventricles in autism

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Abstract

In this study, a computational mapping technique was used to examine the three-dimensional profile of the lateral ventricles in autism. T1-weighted three-dimensional magnetic resonance images of the brain were acquired from 20 males with autism (age: 10.1 ± 3.5 years) and 22 male control subjects (age: 10.7 ± 2.5 years). The lateral ventricles were delineated manually and ventricular volumes were compared between the two groups. Ventricular traces were also converted into statistical three-dimensional maps, based on anatomical surface meshes. These maps were used to visualize regional morphological differences in the thickness of the lateral ventricles between patients and controls. Although ventricular volumes measured using traditional methods did not differ significantly between groups, statistical surface maps revealed subtle, highly localized reductions in ventricular size in patients with autism in the left frontal and occipital horns. These localized reductions in the lateral ventricles may result from exaggerated brain growth early in life.

Keywords

Autism; Lateral ventricles; Brain; MRI

1. Introduction

Autism is a developmental disorder characterized by social deficits, impaired communication, and restricted and repetitive patterns of behavior (American Psychiatric Association, 2000). There is strong evidence that autism has a neurobiological basis, and while many studies suggest that total brain volume is increased in children with autism, there is disagreement about whether this enlargement in brain volume persists into adulthood or whether it is limited to childhood (Nicolson and Szatmari, 2003).

The overall excess in brain volume in patients with autism may result from abnormally high rates of growth for both gray and white matter in early childhood (Courchesne et al., 2001;

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Herbert et al., 2003; Hazlett et al., 2005, 2006). This early hypertrophy might be expected to influence the volume or shape of the lateral ventricles, but magnetic resonance imaging (MRI) studies of lateral ventricular anatomy in autism have yielded inconsistent results. Several studies have reported an increase in lateral ventricle volume (Piven et al., 1995; Howard et al., 2000; Palmen et al., 2005) or area (Gaffney et al., 1989), while other studies using MRI (Filipek et al., 1992; Hardan et al., 2001; McAlonan et al., 2002) or computed tomographic imaging (Campbell et al., 1982; Harcherik et al., 1985; Creasey et al., 1986; Jacobson et al., 1988) have found no difference in the total volume of the lateral ventricles between patients and controls. Among those studies which controlled for group differences in brain size, a majority found no group differences in ventricular size (Campbell et al., 1982; Harcherik et al., 1985; Jacobson et al., 1988; Hardan et al., 2001; McAlonan et al., 2002), although two studies did find an increase in ventricular size even after correcting for brain size (Gaffney et al., 1989; Palmen et al., 2005).

Factors related to subject selection may have contributed to the inconsistency of these past studies. However, each of these studies assessed the ventricles in autism with traditional volumetric methods, examining only the total volume (or area) of the lateral ventricles. Total volume measures can be insensitive to anatomical shape variability and are unlikely to identify subtle regional differences in anatomy between groups. As such, regional methods, which can examine more localized abnormalities in the ventricles, may be more appropriate. These regional differences may provide important clues about the nature and location of the aberrant brain growth in autism. Only one study to date has used this approach: Bigler et al. (2003) examined the temporal horns of the lateral ventricles specifically, and noted a non-significant trend for patients with normal head sizes (i.e., without macrocephaly) to have smaller temporal horns than controls (P=0.09). Other regional methods that can examine more highly localized abnormalities in the ventricles may reveal irregularities that would remain undetected by traditional volumetric analyses. Three-dimensional (3D) anatomical mapping methods, which have not previously been used in studies of the lateral ventricles in autism, may be beneficial for detecting subtle regional morphological abnormalities. Unlike traditional volumetric methods, surface mesh models and statistical maps can provide better anatomical localization of group differences in lateral ventricular morphology while preserving information on subtle variability patterns within groups (Thompson et al., 2004a,b). Surface-based anatomical modeling is complementary to voxel-based statistical methods that assess differences in tissue types at each voxel of stereotaxic space. The shape modeling approach works by averaging the geometry of the anatomical models across subjects, rather than comparing segmented images. These computational methods have detected regional alterations of ventricular morphology in conditions such as schizophrenia and Alzheimer's disease, and have associated ventricular shape changes with immunological decline and psychomotor impairment in HIV/AIDS (Narr et al., 2006; Thompson et al., 2004a, 2006). Ventricular maps have also been used to quantify the effects of progressive brain atrophy, and relate them to deteriorating cognitive function in longitudinal scans of patients with dementia (Thompson et al., 2004a).

In the present study, we used computational mapping methods to visualize shape and volume abnormalities of the lateral ventricles in autism. Given reports of early rapid growth of the brain in autism (Courchesne et al., 2001, 2003; Hazlett et al., 2005), we hypothesized that patients with autism would have localized ventricular abnormalities, although the direction of the effect (smaller or larger) was not predicted *a priori*. Because of the relative ease of ventricular measurement in T1-weighted brain images, we were interested in determining the 3D profile of ventricular shape differences associated with autism, which might provide important clues regarding the nature and timing of the abnormal neurodevelopment in the disorder.

2. Methods

2.1. Subjects

Twenty males with autism (age: 10.1±3.5 years; range: 6-17 years) were included in the study. The diagnosis of autism was made using the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994), the Autism Diagnostic Observation Schedule (ADOS-G; Lord et al., 2000), and clinical observation. All patients met DSM-IV-TR criteria for autism (American Psychiatric Association, 2000) as well as ADI-R and ADOS-G algorithm criteria. Patients were also assessed using the Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III) or the Leiter International Performance Scale. Exclusionary criteria for patients included a non-verbal IQ below 70, a seizure disorder or any other neurological condition, or a known cytogenetic abnormality. All patients had a physical examination prior to participation in this study, including measurement of height, weight, and head circumference. Handedness was determined by clinical observation and the report of the patients and their parents. At the time of the scan, 10 patients were being treated with psychotropic medication: six were taking stimulants, three were receiving dopamine antagonists, two were taking selective serotonin reuptake inhibitors, and one was being treated with a cholinesterase inhibitor. Among the 10 patients who were not taking medications at the time of the study, six were medication-naïve, three had discontinued their previous medications at least 4 weeks before imaging, and one subject who had been treated with a stimulant had discontinued it 1 week before his scan.

Twenty-two healthy male control subjects (age: 10.7±2.5 years) were recruited from the local community through advertisement and word of mouth. They were assessed with the Schedule for Affective Disorders and Schizophrenia-Childhood Version (Kaufman et al., 1997) to ensure that none had a major psychiatric disorder. Additionally, none had a personal history of neurological disorders. Controls were also assessed with the WISC-III or the Wechsler Abbreviated Scale of Intelligence, and a full-scale IQ of less than 70 was exclusionary.

This study was approved by the Health Sciences Research Ethics Board at the University of Western Ontario. The parents or legal guardians of all subjects provided written consent for participation in this study, while the subjects provided written assent.

2.2. Magnetic resonance imaging

All subjects were scanned on a 3.0 T head-only scanner (IMRIS, Winnipeg, Canada) with a quadrature head coil. All patient scans and the majority of control subject scans were acquired in the late evening.

Standard T1-weighted localizer images were acquired initially. Images used for volumetric analysis were then acquired using a T1-weighted 3D MP-RAGE (Magnetization Prepared Rapid Gradient Echo) sequence (TI=200 ms, TR=11 ms, TE=5 ms, flip-angle 12 degrees, total scan time: 8 min) with 1.2-mm isotropic voxels.

2.3. Image processing and analysis

Each brain volume was corrected for intensity inhomogeneities (Sled et al., 1998) and resliced into a standard orientation as follows. Twenty standard anatomical landmarks were identified by a trained operator (C.V.) in all three planes and matched with a set of corresponding point locations defined on the ICBM53 stereotaxic brain template (Mazziotta et al., 2001). These landmarks were used to compute a three-translation and three-rotation rigid-body transformation for each brain volume to align it to the standardized coordinate system of the ICBM53 average brain (Mazziotta et al., 2001). Each brain volume was reoriented to correct for head alignment and resampled to 1.0-mm isotropic voxels using trilinear interpolation. In addition, a second set of analyses was performed to adjust the data for overall differences in

brain scale. To do this, each brain was uniformly scaled into the ICBM53 stereotaxic space using a 9-parameter linear transformation, allowing the brain to be scaled to match the standardized average brain template. Because differences in overall brain scale were anticipated between patients and controls, analyses were performed both with and without global brain scaling.

2.4. Lateral ventricle modeling

The lateral ventricles were manually traced bilaterally by a single image analyst (C.V.) blind to diagnosis and hemisphere. The lateral ventricles were manually traced by following the CSF/gray or CSF/white tissue boundaries in the gray scale image volumes corrected for head-tilt and orientation (as described previously). The ventricles were traced in successive coronal brain slices and the digitized surface contours were displayed simultaneously in all three viewing planes to facilitate the accurate identification of neuroanatomic boundaries (see Fig. 1a,b). Contours were drawn on images magnified four-fold to allow sub-voxel precision and faithful tracking of small-scale features. Anatomical delineation was performed using a standardized ventricular segmentation protocol (Narr et al., 2001). Previous studies in our laboratory have demonstrated high interrater (Intraclass Correlation Coefficient (ICC)=0.91) and intrarater reliability (ICC>0.89) using this methodology (Narr et al., 2001, 2006). Partial volume effects of CSF with the adjacent white matter and hippocampal gray matter in the inferior horns made it difficult to identify them consistently; therefore, analysis was confined to the frontal and occipital horns of the ventricles. The posterior aspect of the atrium of the lateral ventricles was used as the boundary between the frontal and occipital ventricular horns. Volumes obtained from these tracings were retained for statistical analyses.

2.5. Anatomical surface averaging

Anatomical mesh modeling methods (Narr et al., 2001; Thompson et al., 2004a,b) were then used to match equivalent ventricular surface points, obtained from manual tracings, across subjects and groups (Fig. 1d,e). To match the digitized points representing the ventricle surface traces in each brain volume, the manually derived contours were made spatially uniform by modeling them as a three-dimensional parametric surface mesh (Fig. 1c). That is, the spatial frequency of digitized points making up the ventricular surface traces was equalized within and across brain slices. These procedures allow measurements to be made at corresponding surface locations in each subject that may then be compared statistically. The matching procedures also allow the averaging of ventricular surface morphology across all individuals belonging to a group (Fig. 1d) and they record the amount of variation between corresponding surface points relative to the group averages (Fig. 1e).

2.6. Mapping radial ventricular size

The three-dimensional parametric mesh models of each individual's lateral ventricles were analyzed to estimate the regional specificity of any group differences in ventricular volume. As in our prior work (Thompson et al., 2004a, 2006), a medial curve was defined as the three-dimensional curve traced out by the centroid of the ventricular boundary in each section (Fig. 1e). This medial curve, computed separately for each individual, threads down the center of each individual's ventricular model. The radial size of each ventricle at each boundary point was assessed by measuring the radial distances from homologous ventricular surface points to the central core of the individual's ventricular surface model. These distances can be thought of as a map of radial expansion or compression, assigning numbers to each ventricular boundary point, which record how far it is from the medial curve of the lateral ventricle (Fig. 1e). The distances of each ventricular surface point to its respective medial curve are represented on the ventricular surface as a map. Since all ventricular surfaces are represented using the same

parametric mesh structure, corresponding surface traces can be matched across subjects and averaged across a group, together with their associated distance measures.

2.7. Statistical analysis and permutation tests

Age, race, handedness, height, head circumference, the scaling factor needed to transform each brain volume into stereotaxic space, and intelligence quotients (verbal, non-verbal, and full-scale) were compared using *t*-tests or chi-squared analyses.

Thickness measures improve the localization of deficits but may be less sensitive to differences in the length of the ventricles. Traditional volumetric measures may thus be more sensitive than thickness maps for detecting group differences in some instances, while thickness maps may be more sensitive in others. Therefore, we used both traditional volumetric methods and statistical maps in order to compare the ability of both methods to detect ventricular abnormalities among patients with autism.

Ventricular volumes measured using traditional volumetric methods were compared between groups using repeated measures Analysis of Variance, with diagnosis as the between-subjects factor and side (left and right) and ventricular region (frontal and occipital) as repeated measures. This analysis was applied to both the raw and scaled ventricular volumes (i.e., both before and after controlling for group differences in brain size through scaling; see section on brain size correction below). Although the two groups differed significantly in IQ scores, we chose not to use IQ scores as a covariate as reductions in IQ may reflect the neurobiological abnormalities underlying autism (Cochrane, 1957). Further, IQ scores were not correlated with ventricular volumes for both groups. Although the age range in this study was wide, we did not covary for age in the analyses as ventricular volumes were not correlated with age in either group or when the two groups were combined.

The possible effects of psychotropic medications on ventricular volumes determined from traditional measures in patients with autism were assessed with a repeated measures Analysis of Variance. This analysis was similar to the analysis described above with the exception that the between-groups factor consisted of three levels (patients receiving medication, patients not receiving medication, and controls).

To evaluate regional differences in ventricular volume as indexed by measures of ventricular radial distance, Student's *t*-tests were performed at equivalent locations on the ventricular surface maps. Uncorrected *t*-values and their corresponding two-tailed probability values were mapped onto the averaged ventricular surface models of the entire group and displayed in three dimensions in scaled and raw space.

For tests of overall volume differences and for statistical mapping of surface-based measures, a two-tailed alpha level of $P<0.05$ was used as the significance threshold. However, for statistical mapping, comparisons were made at thousands of ventricular surface points. Permutation testing was therefore used to confirm the overall significance of the statistical mapping results, adjusting for multiple comparisons. This accounts for the spatial autocorrelation of the residuals of the statistical model while adjusting for the multiple comparisons implicit in conducting multiple statistical tests at each point on a surface (Nichols and Holmes, 2002). For permutations, the assignment of subjects to diagnostic groups was randomized 100,000 times, performing statistical tests at each hippocampal surface point for each random assignment. Using a threshold of $P<0.05$, uncorrected, the number of significant results between patients with autism and controls in the actual data was compared to the number of significant results produced during the permutation testing to produce a corrected overall significance value for each map. This ensures that any reported patterns of group differences were not observed by chance alone.

2.8. Brain size correction

For statistical mapping of ventricular surface parameters, image volumes and the ventricular contours were mapped into stereotaxic space, adjusting for differences in brain size. However, uncertainty exists as to whether or not brain size corrections increase or decrease error variance for region of interest comparisons (Arndt et al., 1991; Mathalon et al., 1993). To allow for either possibility, we built the same anatomical maps and performed the same comparisons using raw ("descaled") ventricular volumes, which were derived by dividing each ventricular volume by the scaling factor used to transform it to the ICBM53 average brain. To descale the three-dimensional maps created previously, the inverse of the global scaling transformation matrix was applied to the ventricular surface points. A least squares rigid transform with 6 parameters (without scaling) was then applied to the resulting ventricular traces to align them rigidly with the ICBM53 average brain dataset. Maps of group differences were created both before and after adjusting for any individual and group differences in brain size.

3. Results

3.1. Subjects

The groups did not differ significantly in terms of age, race, height, head circumference, or total brain volume (see Table 1). While there was no significant difference in non-verbal IQ between the two groups, patients did have a significantly lower verbal IQ ($P<0.0007$) and full-scale IQ ($P=0.02$). Consistent with previous studies (Escalante-Mead et al., 2003), there was a significantly greater proportion of left-handed subjects in the patient group ($P=0.007$).

3.2. Ventricular volume

Using traditional volumetric methods with the scaled images, repeated measures ANOVA did not reveal any significant main effects of diagnosis ($F_{1,40}=3.1$, $P=0.09$) or interactions of diagnosis-by-ventricular region ($F_{1,40}=0.2$, $P=0.7$), diagnosis-by-side ($F_{1,40}=0.7$, $P=0.4$), or diagnosis-by-ventricular region-by-side ($F_{1,40}=1.2$, $P=0.3$) in the overall volumetric measures (see Table 2). The pattern of results was similar when the descaled (native space) images were used.

Repeated measures ANOVA used to determine the effects of medication on the results from traditional volumetric measurements did not reveal a significant main effect of group (patients receiving medication, patients not receiving medication, and controls). There were no significant group-by-side or group-by-ventricular region-by-side interactions. There was a significant group-by-ventricular region interaction ($F_{2,39}=3.4$, $P=0.04$), but post-hoc univariate tests did not reveal any significant differences among the three groups.

3.3. Ventricular distance maps

The statistical maps revealed several localized group differences in the size of the lateral ventricles after scaling (i.e., after controlling for total brain volume; see Fig. 2). Patients with autism exhibited localized reductions in regional ventricular volumes in the right and left frontal and occipital horns of the ventricles as well as in the mid-portion of the left lateral ventricle (*red colors* in Fig. 2a,b,c). Permutation tests on these specific regions of interest to control for multiple testing confirmed the significant local volume reduction in the left frontal ($P=0.03$) and occipital horns ($P=0.02$; *white colors* in Fig. 2d,e,f). Although the other regions did not reach statistical significance after permutation testing, there was a non-significant trend for localized reduction in the right frontal horn to be significantly greater among the patients ($P=0.052$). The native space maps (i.e., descaled) were essentially identical to the scaled maps, and so are not reported here.

4. Discussion

To our knowledge, this is the first study to use computational mapping methods to investigate ventricular abnormalities in autism. While traditional methods did not reveal any significant group differences in total or regional ventricular volume, computational methods revealed highly localized reductions in volume in the left frontal and occipital horns of the lateral ventricles in patients with autism. This difference remained significant both with and without controlling for total brain size. Patients also had a strong trend for a localized deficit in volume in the right frontal horn.

As discussed earlier, previous MRI studies of the ventricles in autism have yielded inconsistent results. In contrast to the computational mapping methods used here, these earlier studies examined the total volume of the ventricles using traditional methods of analysis. Such an approach may be less sensitive than computational methods that permit examination of regional shape differences. As seen in previous studies of Alzheimer's disease and HIV/AIDS (Thompson et al., 2004a, 2006), computational maps, in conjunction with permutation testing, have more power than traditional volume measurements to detect group differences that are spatially heterogeneous and that do not affect the entire volume of a structure uniformly. If deficit patterns are not spatially uniform, computational shape mapping is more likely to detect deficits that volumetric measures may miss. Therefore, computational mapping methods make it possible to detect subtle regional abnormalities in the lateral ventricles even in the absence of global volumetric differences, as in the present study. The lower power of traditional volumetric measures may explain why studies using them have had inconsistent results, with the majority finding no significant group differences, as was noted here as well.

The spatial localization of volumetric abnormalities of the lateral ventricles provided by computational mapping methods permits possible insight into the brain regions potentially involved in the pathophysiology of autism and the timing of the aberrant neurodevelopment in the disorder. A highly localized reduction in the volume of the lateral ventricles suggests compression by associated white and/or gray matter. Aberrant, excessive brain growth during the first few years of life would be expected to lead to an exaggeration in head circumference, which has been reported frequently in autism (Lord, 2006). However, if this exaggerated brain growth continues after the sutures have closed, then a reduction in size of the lateral ventricles would be a potential result. This reduction in size would be most apparent in ventricular regions anatomically related to those brain regions with the greatest amount of aberrant growth after the close of the sutures. While most human sutures do not close until adulthood, the metopic, or frontal suture, closes by approximately age two (Cohen, 1993). Several authors have reported that the regions with the most abnormally increased volume in autism are frontal gray and white matter (Carper and Courchesne, 2005; Carper et al., 2002; Herbert et al., 2004). The regional reduction in the volume of the frontal horn of the left ventricle (and the strong trend to a regional reduction in the right frontal ventricular volume) could therefore be a reflection of excessive frontal growth. Similarly, the regional reduction in the size of the left occipital horn could be secondary to excessive growth of the temporal or occipital lobes, which has been noted in some studies of autism (Piven et al., 1996; Hazlett et al., 2006).

Alternatively, the reduction in size of the left frontal horn could be related to abnormalities of the caudate nucleus. While this could be secondary to the use of antipsychotic medications by some patients (Chakos et al., 1994), this seems unlikely given that ventricular size did not differ between patients taking medication and those not receiving medication. However, a recent meta-analysis of volumetric brain imaging studies in autism noted that patients had an increase in caudate volume (Stanfield et al., in press), suggesting that this also could potentially have resulted in a regional reduction of the frontal horn of the ventricles.

Patients in this study had a larger ventricular occipital horn on the left side, while controls showed the opposite. While this could be related to abnormalities of asymmetry reported in other brain imaging studies of autism (e.g., Herbert et al., 2002), statistical assessment of asymmetry did not show significant group differences.

The results of this study should be interpreted cautiously due to several limitations. The sample size in this study was relatively small and thus there may have insufficient power to detect group differences of lesser magnitude than those seen here. The lack of female subjects also limits the conclusions that can be drawn. However, given the known gender differences in the prevalence and severity of autism (Yeargin-Allsop et al., 2003), and in the developmental trajectory of the lateral ventricles (Giedd et al., 1997), the inclusion of males only in this study may have highlighted group differences by removing gender variables affecting the size of the ventricles. A number of patients in the present study were taking psychotropic medication, which could potentially have influenced the results. This seems unlikely, however, as MRI studies of other patient groups taking similar medications to those used in patients with autism have not reported reductions in the size of the lateral ventricles (Kumra et al., 2000; Peterson et al., 2001; Scherk and Falkai, 2006). Additionally, control subjects in the present study did not differ on traditional ventricular measures from patients receiving medication and medication-free patients, further suggesting that the results of this study are not solely due to the effects of psychotropic medication. However, given the small sample size and the diversity of medications used by the subjects in the patient group, possible effects of medications on the results cannot be ruled out conclusively. Although we assessed handedness in our subjects, it was not done using an objective measure.

The methodology used here requires some manual interaction with the images to trace the lateral ventricles whereas some other methods, such as voxel-based morphometry, are completely automated. If automated ventricular segmentation methods become as reliable as manual tracing, these shape analysis methods may be efficiently extended to larger samples. We are currently validating more automated approaches for creating these surface maps (Carmichael et al., 2007). In this study, a 9-parameter global scaling transform was applied to each individual brain, to match the standardized average brain template. Although, in our sample, there were no systematic group differences in overall brain volume, we still performed brain scaling to adjust for the large inter-individual variability in brain scale, which can make it easier to detect subtle group differences in brain substructures, such as the ventricles. However, it is possible in principle that a 9-parameter scaling can introduce effects due to possibly independent scalings along each of the 3 cardinal axes. To examine whether this scaling transformation may have affected the inferences made regarding volume reductions based on the maps, we also created non-scaled maps, as in our past studies (e.g., Thompson et al., 2005a,b), in which the individual datasets were brought into mutual alignment using a rotational alignment but no scaling. To do this, the 9-parameter scaling transformation matrix was inverted, applied to the surface meshes, and a 6-parameter rigid-body alignment was then applied to align the surface meshes before averaging and group comparison. As noted in Section 3, the non-scaled maps were essentially the same, so the maps are not shown.

In this study, a computational mapping strategy was used to visualize patterns of localized ventricular contraction in children with autism. The greatest abnormalities were noted in the left frontal and occipital horns. Shape and computational mapping may reveal the spatial pattern of ventricular deficits with greater visual and statistical power than traditional volumetric methods and may thus provide important insights into the timing of neurodevelopmental abnormalities in autism. Future studies are required to confirm these differences in larger samples, and longitudinal studies will be needed to assess whether ongoing developmental changes in the ventricles among patients with autism differ from those seen in typically developing children and adolescents.

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References

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Vol. 4th Edition. Text revision. APA; Washington, D.C: 2000.

Arndt S, Cohen G, Alliger RJ, Swayze VW. Problems with ratio and proportion measures of imaged cerebral structures. Psychiatry Research. Neuroimaging 1991;40:79–89. [PubMed: 1946842]

Bigler ED, Tate DF, Neeley ES, Wolfson LJ, Miller MJ, Rice SA, Cleavinger H, Anderson C, Coon H, Ozonoff S, Johnson M, Dinh E, Lu J, Mc Mahon W, Lainhart JE. Temporal lobe, autism, and macrocephaly. American Journal of Neuroradiology 2003;24:2066–2076. [PubMed: 14625235]

Campbell M, Rosenbloom S, Perry R, George AE, Kricheff II, Anderson L, Small AM, Jennings SJ. Computerized axial tomography in young autistic children. American Journal of Psychiatry 1982;139:510–512. [PubMed: 7065302]

Carmichael OT, Kuller LH, Lopez OL, Thompson PM, Dutton RA, Lu A, Lee SE, Lee JY, Aizenstein HJ, Meltzer CC, Liu Y, Toga AW, Becker JT. Ventricular volume and dementia progression in the Cardiovascular Health Study. Neurobiology of Aging 2007;28:389–397. [PubMed: 16504345]

Carper RA, Courchesne E. Localized enlargement of the frontal cortex in early autism. Biological Psychiatry 2005;57:126–133. [PubMed: 15652870]

Carper RA, Moses P, Tigue ZD, Courchesne E. Cerebral lobes in autism: early hyperplasia and abnormal age effects. NeuroImage 2002;12:1038–1051. [PubMed: 12202091]

Chakos MH, Lieberman JA, Bilder RM, Borenstein M, Lerner G, Bogerts B, Wu H, Kinon B, Ashtari M. Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. American Journal of Psychiatry 1994;151:1430–1436. [PubMed: 7916539]

Cochrane WG. Analysis of covariance: its nature and uses. Biometrics 1957;13:261–281.

Cohen MM Jr. Sutural biology and the correlates of craniosynostosis. American Journal of Medical Genetics 1993;47:581–616. [PubMed: 8266985]

Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, Chisum HJ, Moses P, Pierce K, Lord C, Lincoln AJ, Pizzo S, Schreibman L, Haas RH, Akshoomoff NA, Courchesne RY. Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. Neurology 2001;57:245–254. [PubMed: 11468308]

Courchesne E, Carper R, Akshoomoff N. Evidence of brain overgrowth in the first year of life in autism. Journal of the American Medical Association 2003;290:337–344. [PubMed: 12865374]

Creasey H, Rumsey JM, Schwartz M, Duara R, Rapoport JL, Rapoport SI. Brain morphometry in autistic men as measured by volumetric computed tomography. Archives of Neurology 1986;43:669–672. [PubMed: 3488051]

Escalante-Mead PR, Minshew NJ, Sweeney JA. Abnormal brain lateralization in high-functioning autism. Journal of Autism and Developmental Disorders 2003;33:539–543. [PubMed: 14594334]

Filipek PA, Richelme C, Kennedy DN, Rademacher J, Pitcher DA, Zidel S, Caviness VA. Morphometric analysis of the brain in developmental language disorders and autism. Annals of Neurology 1992;32:475.

Gaffney GR, Kuperman S, Tsai LY, Minchin S. Forebrain structure in infantile autism. Journal of the American Academy of Child and Adolescent Psychiatry 1989;28:534–537. [PubMed: 2768148]

Giedd JN, Castellanos FX, Rajapakse JC, Vaituzis AC, Rapoport JL. Sexual dimorphism of the developing human brain. Progress in Neuro-Psychopharmacolology & Biological Psychiatry 1997;21:1185–1201.

Harcherik DF, Cohen DJ, Ort S, Paul R, Shaywitz BA, Volkmar FR, Rothman SL, Leckman JF. Computed tomographic brain scanning in four neuropsychiatric disorders of childhood. American Journal of Psychiatry 1985;142:731–734. [PubMed: 3859227]

Hardan AY, Minshew NJ, Mallikarjuhn M, Keshevan MS. Brain volume in autism. Journal of Child Neurology 2001;16:421–424. [PubMed: 11417608]

Hazlett HC, Poe MD, Gerig G, Smith RG, Provenzale J, Ross A, Gilmore J, Piven J. Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. Archives of General Psychiatry 2005;62:1366–1376. [PubMed: 16330725]

Hazlett HC, Poe MD, Gerig G, Smith RG, Piven J. Cortical gray and white brain tissue volume in adolescents and adults with autism. Biological Psychiatry 2006;59:1–6. [PubMed: 16139816]

Herbert MR, Harris GJ, Adrien KT, Ziegler DA, Makris N, Kennedy DN, Lange NT, Chabris CF, Bakardjiev A, Hodgson J, Takeoka M, Tager-Flusberg H, Caviness VS Jr. Abnormal asymmetry in language association cortex in autism. Annals of Neurology 2002;52:588–596. [PubMed: 12402256]

Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Lange N, Bakardjiev A, Hodgson J, Adrien KT, Steele S, Makris N, Kennedy D, Harris GJ, Caviness VS Jr. Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. Brain 2003;126:1182–1192. [PubMed: 12690057]

Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, Sanders HA, Kennedy DN, Caviness VS Jr. Localization of white matter volume increase in autism and developmental language disorder. Annals of Neurology 2004;55:530–540. [PubMed: 15048892]

Howard MA, Cowell PE, Boucher J, Broks P, Mayes A, Farrant A, Roberts N. Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. NeuroReport 2000;11:2931–2935. [PubMed: 11006968]

Jacobson R, Le Couteur A, Howlin P, Rutter M. Selective subcortical abnormalities in autism. Psychological Medicine 1988;18:39–48. [PubMed: 3363043]

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. Journal of the American Academy of Child and Adolescent Psychiatry 1997;36:980–988. [PubMed: 9204677]

Kumra S, Giedd JN, Vaituzis AC, Jacobsen LK, McKenna K, Bedwell J, Hamburger S, Nelson JE, Lenane M, Rapoport JL. Childhood-onset psychotic disorders: magnetic resonance imaging of volumetric differences in brain structure. American Journal of Psychiatry 2000;157:1467–1474. [PubMed: 10964864]

Lord, C. Autism spectrum disorders: phenotype and diagnosis. In: Moldin, SO.; Rubenstein, JLR., editors. Understanding Autism: From Basic Neuroscience to Treatment. Taylor and Francis Group; Boca Raton: 2006. p. 1-23.

Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. Journal of Autism and Developmental Disorders 1994;24:659–685. [PubMed: 7814313]

Lord C, Risi S, Lambrecht L, Cook EH Jr. Leventhal BL, DiLavore PC, Pickles A, Rutter M. The Autism Diagnostic Observation Schedule-Generic: a standard measure of social and communication deficits associated with the spectrum of autism. Journal of Autism and Developmental Disorders 2000;30:205–223. [PubMed: 11055457]

Mathalon DH, Sullivan EV, Rawles JM, Pfefferbaum A. Correction for head size in brain-imaging measurements. Psychiatry Research. Neuroimaging 1993;50:121–139. [PubMed: 8378488]

Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, Woods R, Paus T, Simpson G, Pike B, Holmes C, Collins L, Thompson P, MacDonald D, Iacoboni M, Schormann T, Amunts K, Palomero-Gallagher N, Geyer S, Parsons L, Narr K, Kabani N, Le Goualher G, Boomsma D, Cannon T, Kawashima R, Mazoyer B. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences 2001;356:1293–1322.

McAlonan GM, Daly E, Kumari V, Critchley HD, van Amelsvoort T, Suckling J, Simmons A, Sigmundsson T, Greenwood K, Russell A, Schmitz N, Happe F, Howlin P, Murphy DG. Brain

anatomy and sensorimotor gating in Asperger's syndrome. Brain 2002;125:1594–1606. [PubMed: 12077008]

Narr KL, Thompson PM, Sharma T, Moussai J, Blanton R, Anvar B, Edris A, Krupp R, Rayman J, Khaledy M, Toga AW. Three-dimensional mapping of temporo-limbic regions and the lateral ventricles in schizoprenia: gender effects. Biological Psychiatry 2001;50:84–97. [PubMed: 11526999]

Narr KL, Bilder RM, Woods RP, Thompson PM, Szeszko P, Robinson D, Ballmaier M, Messenger B, Wang Y, Toga AW. Regional specificity of cerebrospinal fluid abnormalities in first episode schizophrenia. Psychiatry Research. Neuroimaging 2006;146:21–33. [PubMed: 16386409]

Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Human Brain Mapping 2002;15:1–25. [PubMed: 11747097]

Nicolson R, Szatmari P. Genetic and neurodevelopmental influences in autistic disorder. Canadian Journal of Psychiatry 2003;48:526–537.

Palmen SJ, Hulshoff Pol HE, Kemner C, Schnack HG, Durston S, Lahuis BE, Kahn RS, Van Engeland H. Increased gray-matter volume in medication-naive high-functioning children with autism spectrum disorder. Psychological Medicine 2005;35:561–570. [PubMed: 15856726]

Peterson BS, Staib L, Scahill L, Zhang H, Anderson C, Leckman JF, Cohen DJ, Gore JC, Albert J, Webster R. Regional brain and ventricular volumes in Tourette syndrome. Archives of General Psychiatry 2001;58:427–440. [PubMed: 11343521]

Piven J, Arndt S, Bailey J, Havercamp S, Andreasen N, Palmer P. An MRI study of brain size in autism. American Journal of Psychiatry 1995;152:1145–1149. [PubMed: 7625461]

Piven J, Arndt S, Bailey J, Andreasen N, Palmer P. Regional brain enlargement in autism: a magnetic resonance imaging study. Journal of the American Academy of Child and Adolescent Psychiatry 1996;35:530–536. [PubMed: 8919716]

Scherk H, Falkai P. Effects of antipsychotics on brain structure. Current Opinion in Psychiatry 2006;19:145–150. [PubMed: 16612194]

Sled JG, Zijdenbos AP, Evans AC. A non-parametric method for automatic correction of intensity non-uniformity in MRI data. IEEE Transactions on Medical Imaging 1998;17:87–97. [PubMed: 9617910]

Stanfield AC, McIntosh AM, Spencer MD, Philip R, Gaur S, Lawrie SM. Towards a neuroanatomy of autism: a systematic review and meta-analysis of structural magnetic resonance imaging studies. European Psychiatry. August 30;2007 in pressElectronic publication ahead of print

Thompson PM, Hayashi KM, De Zubicaray GI, Janke AL, Rose SE, Semple J, Hong MS, Herman DH, Gravano D, Doddrell DM, Toga AW. Mapping hippocampal and ventricular change in Alzheimer disease. NeuroImage 2004a;22:1754–1766. [PubMed: 15275931]

Thompson PM, Hayashi KM, Simon SL, Geaga JA, Hong MS, Sui Y, Lee JY, Toga AW, Ling W, London ED. Structural abnormalities in the brains of human subjects who use methamphetamine. Journal of Neuroscience 2004b;24:6028–6036. [PubMed: 15229250]

Thompson PM, Dutton RA, Hayashi KM, Toga AW, Lopez OL, Aizenstein HJ, Becker JT. Thinning of the cerebral cortex in HIV/AIDS reflects CD4+ T-lymphocyte decline. Proceedings of the National Academy of Sciences 2005a;102:15647–15652.

Thompson PM, Lee AD, Dutton RA, Geaga JA, Hayashi KM, Eckert MA, Bellugi U, Galaburda AM, Korenberg JR, Mills DL, Toga AW, Reiss AL. Abnormal cortical complexity and thickness profiles mapped in Williams syndrome. Journal of Neuroscience 2005b;25:4146–4158. [PubMed: 15843618]

Thompson PM, Dutton RA, Hayashi KM, Lu A, Lee SE, Lee JY, Lopez OL, Aizenstein HJ, Toga AW, Becker JT. 3D mapping of ventricular and corpus callosum abnormalities in HIV/AIDS. NeuroImage 2006;31:12–23. [PubMed: 16427319]

Yeargin-Allsop M, Rice C, Karapurkar T, Doernber N, Boyle C, Murphy C. Prevalence of autism in a US metropolitan area. Journal of the American Medical Association 2003;289:48–55.

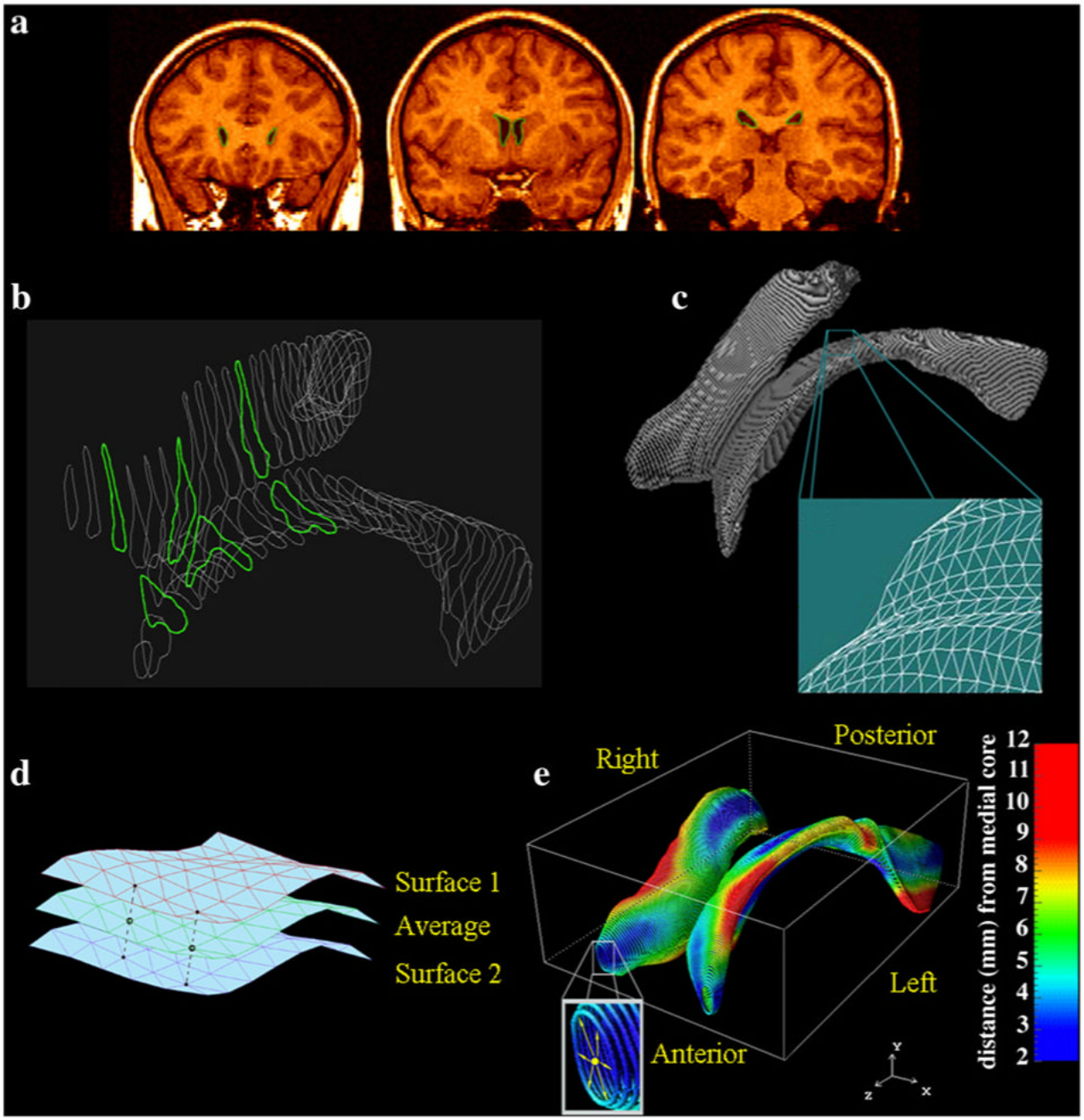

Fig. 1.

Ventricular surface modeling. The lateral ventricles were manually delineated on consecutive coronal magnetic resonance images (a and b) and converted into three-dimensional parametric surface meshes (c). Surfaces made up of spatially uniform triangular tiles were averaged across subjects in the same group to produce an average anatomical model (c). A medial curve, equidistant from each surface, was derived for each subject, and the radial size of the ventricles measured from the centerline to each surface point (e). Arrows in (e) represent vectors from the centerline to various points on the ventricular surface. These distance measures are then averaged across subjects at each boundary point (d) and plotted in color to produce a regional measure of radial expansion or contraction of the ventricles.

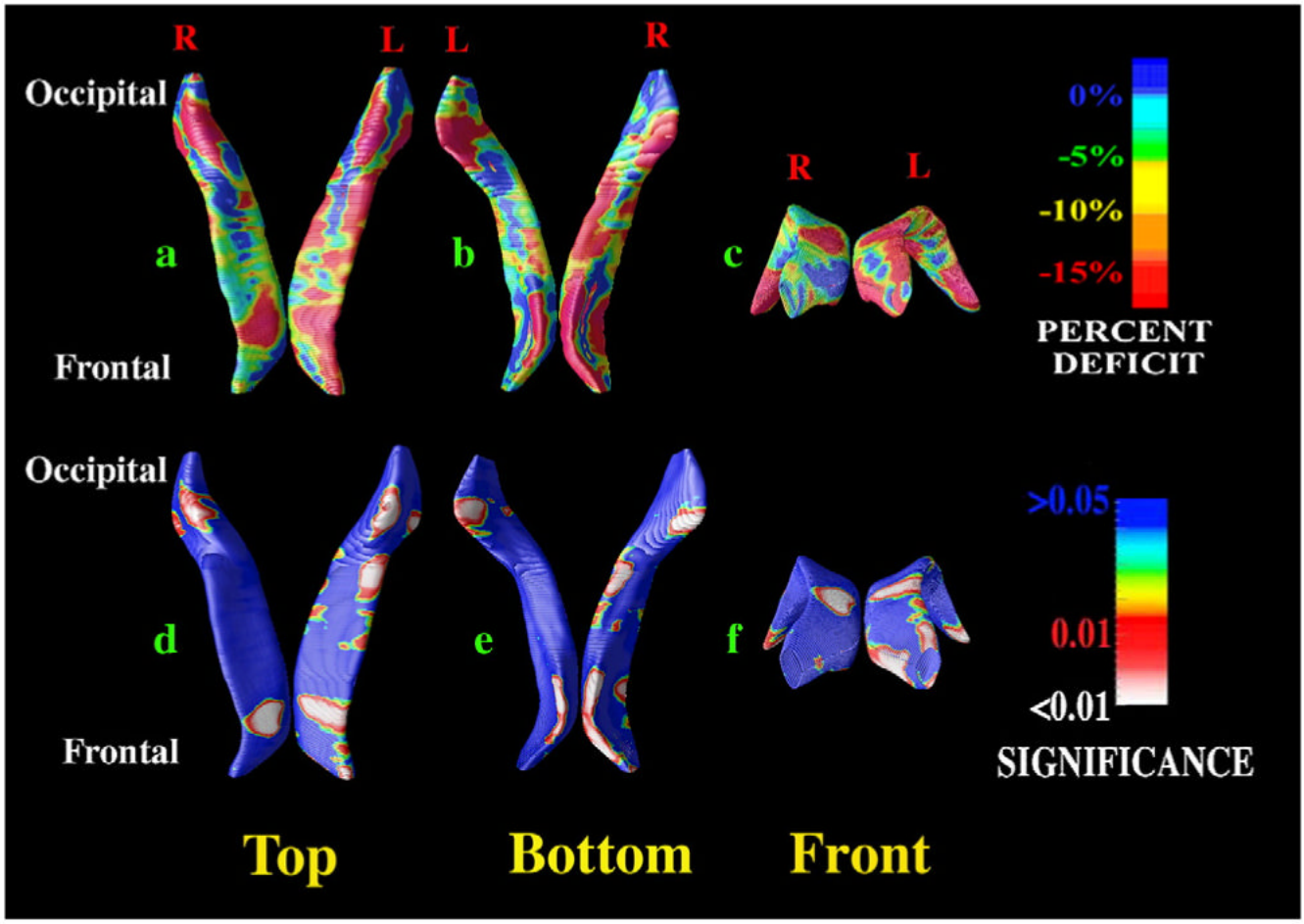

Fig. 2.

Scaled ventricular surface probability maps for patients with autism and controls. The upper row shows regions of volumetric reductions in patients with autism relative to controls (a-c, *red colors*). Significant localized reductions in ventricular size were detected in the frontal and occipital horns bilaterally as well as in the mid-portion of the left ventricle (d-f, *white colors*). After permutation testing to control for multiple comparisons, only the regional reductions in the left frontal (P=0.03) and occipital horns (P=0.02) remained significant, although there was a non-significant trend for a reduction in a portion of the right frontal horn as well (P=0.052). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1

Demographic characteristics of patients with autism and control subjects

Measures	Patients	Control subjects	Test statistic	*df*	*P*
	(*n*=20)	(*n*=22)			
Age (years)	10.1±3.5	10.7±2.5	t=0.7	40	0.5
Race (# Caucasian)	19	22	χ^2=1.1	1	0.3
Handedness (R:L)	14:6	22:0	χ^2=7.7	1	0.007
Height (cm)	145.5±20.0	146.2±13.1	t=0.1	36	0.9
Head circumference (cm)	55.4±2.7	54.9±1.8	t=0.7	40	0.5
Verbal IQ	90.8±11.1	104.8±10.6	t=3.8	33	0.001
Non-verbal IQ	97.8±14.4	101.5±11.6	t=0.9	38	0.4
Full-scale IQ	93.8±11.9	103.0±9.6	t=2.5	33	0.02

All continuous data presented as mean±standard deviation. Degrees of freedom vary across tests due to missing data for some subjects, e.g., the lack of a verbal or full-scale IQ for subjects tested using the Leiter International Performance Scale.

Table 2

Lateral ventricle volume, after scaling to control for brain size, in patients with autism and control subjects

Measure*	Patients (n=20)	Control subjects (n=22)
Total brain volume	1576.3±135.3	1572.8±104.2
Total ventricle	12.0±6.0	15.836±7.7
Left ventricle	6.3±3.6	8.4±3.9
Right ventricle	5.8±2.6	7.4±4.2
Left frontal horn	3.0±1.6	4.2±2.2
Left occipital horn	2.8±1.6	3.2±2.1
Right frontal horn	3.8±3.4	4.7±2.0
Right occipital horn	2.5±1.1	3.7±2.0

* Volumes are given in cc. All data are presented as mean±standard deviation.