Extra-axial CSF relationships to infant brain structure, cognitive development, and risk for schizophrenia

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Abstract

Background—Increased volume of extra-axial cerebrospinal fluid (EA-CSF) is associated with autism spectrum disorder diagnosis in young children. However, little is known about EA-CSF development in typically developing children or in children at risk for schizophrenia.

Methods—3T magnetic resonance imaging scans were obtained in typically developing children (TD; N=105) and in children at risk for schizophrenia (SCZHR; N=38) at ages 1 and 2 years. EA-CSF volume and several measures of brain structure were generated, including global tissue volumes, cortical thickness (CT), and surface area (SA). Cognitive and motor abilities at 1 and 2 years were assessed using the Mullen Scales of Early Learning.

Results—In the TD children, EA-CSF volume was positively associated with total brain volume, gray and white matter volumes, and total surface area at ages 1 and 2 years. In contrast, EA-CSF volume was negatively associated with average CT. Lower motor ability was associated with increased EA-CSF volume at age 1. EA-CSF was not significantly increased in SCZHR children compared to TD children.

Conclusions—EA-CSF volume is positively associated with overall brain size and cortical surface area, but negatively associated with CT. Increased EA-CSF is associated with delayed motor development at 1 year of age, similar to studies of children at risk for autism, suggesting that increased EA-CSF may be an early biomarker of abnormal brain development in infancy.

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Infants at risk for schizophrenia did not exhibit significantly increased EA-CSF, suggesting that increased EA-CSF could be specific to neurodevelopmental disorders with an earlier onset, such as autism.

Keywords

infancy; MRI; early brain development; high-risk; schizophrenia; extra-axial cerebrospinal fluid

Introduction

Cerebrospinal fluid (CSF) provides mechanical and immunological protection to the brain by playing a vital role in brain homeostasis through the transportation of water, ions, and proteins (1). CSF, produced in the choroid plexuses, flows through the ventricles, cisterns, and into the subarachnoid space, delivering growth factors, peptides, and proteins (2). CSF flow also plays a critical role in the elimination of toxic waste; therefore, an abnormality in CSF absorption can be damaging to the developing brain (3, 4). Proper development of the neocortex is highly dependent upon proper CSF production and absorption (5, 6). Extra-axial CSF (EA-CSF), or excessive CSF in the subarachnoid space, tends to be associated with accelerated head growth (7) and is thought to be caused by a disruption in CSF absorption during the first year of life when CSF production is increased (7,8). Enlarged volume of the EA-CSF space has been found in high risk infants and toddlers who develop autism, a finding that has been replicated three times (6, 7, 9). While there is evidence that EA-CSF volume is associated with risk for autism, nothing is known about the normal variation of EA-CSF volume in typically developing (TD) children and its relation to brain structure. Although ASD has a stronger genetic liability, ASD and schizophrenia have similar underlying pathogenic mechanisms are present at different times and are influenced by similar genetic and environmental factors (10–13). Patients with schizophrenia often have increased CSF associated with increased lateral ventricles and widened sulci but such changes later in life may be related to degenerative changes (14, 15). It is unknown whether EA-CSF volume is increased in infants at risk for schizophrenia (SCZHR) at ages 1 and 2 years.

Our study had two objectives. First, we examined the relationship of EA-CSF volume to structural brain development, and cognitive development in a cohort of typically developing children at ages 1 and 2 years. Second, based on our previous finding that male neonates at risk for schizophrenia have enlarged lateral ventricles, suggesting that ventricle enlargement arises during prenatal brain development and maybe an early structural biomarker of risk (16), we hypothesized that EA-CSF would be increased in infants at risk for schizophrenia and would be associated with deficits in cognitive development.

Methods and Materials

Participants

This study was approved by the biomedical institutional review board of the University of North Carolina at Chapel Hill and is part of the UNC Early Brain Development Study (16–18). Mothers were initially recruited for a fetal ultrasound, and offspring returned after birth

and at ages 1 and 2 years for MRI and cognitive assessment visits. Participants were excluded at enrollment due to a fetal abnormality on ultrasound, major medical illness or pregnancy complication, or active substance use during pregnancy at the time of enrollment. Infants were excluded from this analysis if they had any major medical illness, a neonatal intensive care unit stay of greater than 24 hours, gestational age of birth fewer than 32 weeks, or an abnormality on MRI other than a minor intracranial hemorrhage (ICH), which is common in the neonatal period (19). Mothers with schizophrenia or schizoaffective disorder were also enrolled in a related study (16), and assessed with the Structured Clinical Interview for DSM-IV Axis Disorders (SCID) (20). Typically developing (TD mothers were screened with a modified SCID questionnaire. Each mother's past medical records were reviewed, and a final diagnosis was assigned by two board-certified psychiatrists (author JHG; LFJ). There were 140 TD and 33 SCZHR subjects after excluding subjects who failed quality control procedures (see Methods: Neuroimaging Protocol). Demographic variables for all subjects are reported in Table 1. There was a subsample of 24 TD subjects that with longitudinal data at ages 1 and 2 years.

Cognitive Assessments

The Mullen Scales of Early Learning is composed of five Scales- Gross Motor, Visual Reception, Fine Motor, Receptive Language, and Expressive Language (21). Each scale has developmental tasks to capture the functionality of distinct behavioral skills. The Mullen Early Learning Composite (ELC) is calculated using the sum of the standardized T-scores from four of the Scales, excluding Gross Motor. The Mullen was administered at ages 1 and 2 years by experienced testers who were blind to the high-risk status of subjects. Raw scores were used for the analysis of the independent Scales. The assessment date for each subject was included as a covariate in statistical analyses to account for any sample drift or variability due to changes in test administrators during the 10-year data collection period (22).

Neuroimaging Protocol

MR Image Acquisition—Scans were acquired on Siemens 3T scanners during natural sleep (Allegra scanner and TIM Trio; Siemens Medical Solutions, Erlangen, Germany). Before scanning, infants were swaddled, fed, and fitted with ear protection. Neonatal structural T1-weighted (T1w) a 3-D magnetization prepared rapid gradient echo sequence (N=99) was acquired on Allegra (N=89) and Tim Trio (N=10) scanners during the initial phase of the study (MP-RAGE, TR=1820ms, TE=3.75–4.38ms, Flip Angel=7°, Spatial Resolution=1x1mm^2, Slice thickness= 1mm). At ages 1 and 2 years, T1-weighted images were acquired using a 3-D magnetization prepared rapid gradient echo sequence (MP-RAGE, TR=1880–1900ms, TE=3.74–4.38ms, Flip Angel=7°, Spatial Resolution=1x1mm^2, Slice thickness= 1mm) on both Allegra (N=153) and Tim Trio scanners (N=22). Neonatal proton density and T2-weighted images (T2w) low-angle shot sequence (N=89) were acquired on the Allegra scanner used turbo spin-echo sequences (TSE, TR=5480–6200, TEl=20ms, TE2=119ms, Flip Angel=150°, Spatial Resolution=1x1mm^2, Slice thickness= 1.5–2). Neonatal T2 images acquired on the Tim Trio scanner (N=10) with a 3DT2 SPACE protocol (TSE, TR=3200ms, TE=406ms, Flip Angle=120°, Spatial Resolution=1,1mm^2, Slice Thickness=l). Additional proton density and T2w images acquired at ages 1 and 2

years on the Allegra scanner (N=153) used turbo spin-echo sequences (TSE, TR=7380–7590ms, TE1=20ms, TE2=119ms, Flip Angle=150°, Spatial Resolution=1.25, 1.25mm^2, Slice Thickness=1.5–1.95). T2w images were also acquired on the Tim Trio scanner (N=22) with a 3DT2 SPACE protocol (TSE, TR=3200ms, TE=406ms, Flip Angle=120°, Spatial Resolution=1,1mm^2, Slice Thickness=1).

MR Image Processing—Images were processed using a standard protocol which included removing the cerebellum and brain stem from all images (18, 23, 24). All T1w and T2w images were corrected for intensity inhomogeneity by applying N4 based bias correction (25). T2w images were re-sampled to 1x1x1mm^3 if necessary. Brain tissue was classified into gray matter, nonmyelinated white matter, myelinated white matter, and CSF in neonates using an automatic, atlas-moderated expectation maximization segmentation tool (18). T2w images were used for the 1 year and 2 years tissue segmentations of CSF, gray and white matter, utilizing an automatic brain tissue segmentation tool similar to the neonatal tissue segmentation (26–28). ITK SNAP, a semi-automated 3D segmentation tool, was used to trace lateral ventricles, yielding 3D segmentations and volumetric outputs for all ages (18). All images were assessed for quality and the presence of motion, utilizing a four-scale quality rating system that was used to determine the suitability of MR images.

We employed an adapted analysis workflow to define EA-CSF in the subarachnoid space using only T2w images due to the improved CSF contrast in the T2w images as compared to T1w images. This quantitative protocol allows us to measure EA-CSF utilizing automatic tissue and CSF segmentation (applied to the T2w data), as well as additional prior masks of the lateral, third, and fourth ventricles. A ventral boundary was also defined to measure the region of the brain that has the most EA-CSF in the subarachnoid space in the dorsal region of the brain, consistent with Shen et al. (9). The volume of the EA-CSF was quantified for each subject. A visual quality check system, based on Shen et al. (2017), was implemented to evaluate the quality of segmentations. The output was visually checked to observe if the subarachnoid space was accurately segmented, meaning there was no overestimation of segmentation into brain tissue or skull and no underestimation where EA-CSF found in the subarachnoid space was not included in the segmentation. All segmentations were given a score of 0–3, where 0 indicated no abnormalities in segmentations, 1 indicated minor under- or overestimation of EA-CSF in one region, 2 indicated moderate under or overestimation in multiple regions, and 3 showed either significant over-estimation or under-estimation of segmentation in the subarachnoid space that could not be manually edited. Only subjects with a score of 0 or 1 were included in this study. At age 1 year, 108 of 115 eligible subjects had a passing rating of 0 or 1; at age 2 years, 67 subjects of 85. Eligible subjects included participants who had global tissue volumes, Mullen Scales scores, passing quality EA-CSF segmentations, and were not excluded for major medical illness or psychiatric history.

Cortical thickness (CT) and surface area (SA) measurements were obtained from an image analysis pipeline described by Li et al. (2016) (29). Topologically corrected white matter segmentations for each hemisphere were tessellated into a triangular surface mesh that is deformed to obtain the inner, central, and outer surfaces under Laplacian field deformation. (26). CT is measured as the average distance of the minimum distance from the inner to middle surfaces and the minimum distance from outer to inner surface. And SA is based on

the central cortical surface located in the middle between the inner and outer surfaces. CT and SA anatomical parcellations included 78 cortical regions of interests that were obtained using the Automated Anatomical Labeling atlas (30). The average CT, the mean of all regions, and total SA, the sum of all regions, were calculated for each subject at each time point. Quality control was performed on the surface reconstructions and included manual edits if necessary.

Statistical Analyses

Linear models were used to analyze the relationship between the response variable (EA-CSF) and other brain tissue and cognitive measures and high-risk status. The r-squared, t-statistic (t), degrees of freedom (DF), standard deviation (sd), mean, median, minimum, maximum, and p-values (p) were calculated for all analyses. To observe if gender and high-risk status differences are present, regressions with gender and the interaction of gender with EA-CSF as predictors, and regressions with group and the interaction of group with EA-CSF as predictors were performed. The significance level was set at an alpha of 0.05. FDR correction was performed for associations of EA-CSF with regional CT and SA. Linear model analyses were done with SAS, version 9.4.

Results

Distribution of EA-CSF in TD subjects

The distribution of EA-CSF at ages 1 and 2 years are shown in Figure 1. The mean volume of EA-CSF increased slightly between 1 and 2 years in the cross-sectional samples (Table 2a). In the longitudinal sub-sample (N=24), there was a similar increase of EA-CSF from 1 year (mean= 78,568 mm^3; sd= 12,582) to 2 years (mean= 89,062 mm^3; sd= 14,874). EA-CSF at age 1 was highly correlated with EA-CSF at age 2 years (r = 0.585, p = 0.003; Figure S1).

EA-CSF Relationship to Brain Tissues Volumes in TD subjects

EA-CSF was significantly and positively correlated with brain tissue volumes at each age, with larger EA-CSF associated with overall intracranial volume, gray matter, white matter, total cerebrospinal fluid (Table 2a). EA-CSF was also correlated with total ventricle volumes at 2 years (Table 2a). Since EA-CSF volumes were positively correlated with total CSF at each age, we explored the relationship of EA-CSF to CSF at birth and found that it was positively and significantly related at ages 1 and 2 years (Table 2a). Scatter plots of these associations can be seen in Figure 2.

EA-CSF Relationship to Surface Area and Cortical Thickness in TD subjects

Total SA was positively related to EA-CSF at 1 year and 2 years (Table 2a). EA-CSF had a positive relationship to regional SA, with 50 significant cortical regions at age 1 year (37 remained significant after FDR corrections) and 29 regions at 2 years (0 remained significant after FDR corrections) (Table S1 and Figure 3). In contrast, EA-CSF had a significant relationship with average CT at 1 year, with larger EA-CSF associated with smaller cortical thickness (Table 2a). Similarly, 35 of the 36 significant regions had significantly smaller CT correlated with larger EA-CSF at 1 year (25 remained significant after FDR corrections;

Table S2 and Figure 3). There were a few regional CT relationships present at 2 years and none remained significant after FDR correction.

EA-CSF Relationship to Mullen Scales of Early Learning in TD subjects

Larger EA-CSF was significantly related to lower gross motor scores at age 1 year (p=0.005; F(3,78)=4.68) (Table S3, Figure S2). Interactions of gender with EA-CSF revealed female subjects had the same significant relationship and the same pattern of lower scores associated with larger EA-CSF volume at age 1 year (p=0.001; t(78)=−3.38) (Table S3). Male subjects exhibited the same pattern as the overall and female groups, though the relationship was not significant (Table S3). At age 2 years, there was no significant relationship between EA-CSF and any Mullen score (Table S3). Scatter plots of these relationships can be seen in Figure S3.

Since CT and SA measures are correlated to EA-CSF development, we also explored whether EA-CSF predicted motor scores at age 1 beyond CT and SA and found that EA-CSF did significantly predict GM at age 1 beyond CT and SA. Also, EA-CSF also predicted fine motor scores beyond SA (Table S4).

EA-CSF Relationship to High-Risk Status

Figure 1 shows the distribution of EA-CSF at ages 1 and 2 years in the SCZHR group. EA-CSF was not related to risk for schizophrenia at age 1 (mean (SD) TD: 78,831 mm^3 (13,492); SCZHR: 82,574 mm^3 (17,146) t(106) = −1.15; p = 0.252) or age 2 (TD: 85,286 mm^3 (14,636); SCZHR: 80,104 mm^3 (16,543) t(65) = 1.24; p = 0.219). At years 1 and 2, EA-CSF was significantly and positively correlated with brain tissue volumes in the SCZHR, with larger EA-CSF associated with overall intracranial volume, gray matter, white matter, total cerebrospinal fluid, cerebrospinal fluid at birth and total surface area (Table 3). Average cortical thickness was negatively related at age 1 year (Table 3). These associations can be observed in scatterplots (Figure 2).

EA-CSF relationships with brain structure in SCZHR

To determine if the SCZHR group had significantly different EA-CSF/brain structure relationships compared to the TD group, we used a linear model with group, brain tissue, and the interaction as predictors. At age 1 year, there were highly significant relationships EA-CSF with CSF at birth, gray matter, CSF, Average CT, intracranial volume, and total SA in the overall (TD and SCZHR), TD, and SCZHR separately (Table S5). There is no significant group dependence of these relationships. EA-CSF with total ventricular volume was highly significant in the SCZHR group but only trending in the TD group with a trend towards group dependence of this relationship. WM is highly significant in each group and overall, and there is significant group dependence of this relationship.

At age 2 years, intracranial volume, gray matter, white matter, CSF, total SA, and average CT had highly significant relationships to EA-CSF in each group and the overall group (Table S5). There were no significant group differences. There is a significant group dependence of the relationship of EA-CSF with CSF at birth relationship with a stronger relationship in the SCZHR group (Table S5).

EA-CSF Relationship to Neonatal Intracranial Hemorrhage

We explored the association of neonatal intracranial hemorrhage (ICH) with EA-CSF and found no significant relationships. In TD children, neonatal ICH was not associated with EA-CSF at 1 year (ICH=19 of 82; r=−0.143, p=0.199) or 2 years (ICH= 13 of 49; r=−0.268, p=0.063). In the SZCHR group, neonatal ICH was not associated with increased EA-CSF at 1 year (ICH=2 of 26; r=−0.313, p=0.119). At age 2 years, no SCZHR subjects had neonatal ICH.

Discussion

This is the first study of EA-CSF volume in the developing brain of TD children. We found that EA-CSF was highly and positively correlated to overall brain size, including cerebrospinal fluid, gray, and white matter volumes. Increased EA-CSF is also associated with reduced cortical thickness at age 1 year. Cortical thinning has also been found in the frontal lobe of school-age children with mild to moderate cases of increased EA-CSF, and widespread thinning has been associated with severely increased EA-CSF when compared to control subjects (32). We found that increased EA-CSF is associated with delayed gross motor development at 1 year of age, a relationship also observed in children at risk for autism (7, 9). The relationship with reduced cortical thickness and gross motor development was not present at age 2 years, suggesting that in TD children, the association is age-dependent. While increased EA-CSF is present in children with autism and at risk for autism, we did not find increased EA-CSF in SCZHR children. Additionally, group dependences of EA-CSF volume relationships to brain tissue volumes were non-significant except for white matter at age 1 and CSF at birth at age 2. This suggests that increased EA-CSF is not a general feature of all neuropsychiatric disorders and may be specific to those with earlier onset (e.g., autism) rather than those with later onset (e.g., schizophrenia), though our study is limited by small SCZHR sample size and additional studies are necessary.

Increased EA-CSF has been linked to many terms including benign enlargement of the subarachnoid space, external hydrocephalus, benign subdural hydrocephalus, enlargement of the subarachnoid spaces, and extra axial fluid collections (33). This condition is distinct from frank hydrocephalus and is often found in children who have a head circumference that exceeds the expected growth rate. Neuroimaging studies of clinically defined EA-CSF typically find enlarged subarachnoid space, enlarged brain, and sometimes mildly enlarged ventricles (34–38). The etiology of this increase in EA-CSF is unknown, though a common theory suggests immature arachnoid villi cause a disruption in the absorption of CSF (35). These villi tend to mature around 18 months, and interestingly, growth and development of these infants tend to normalize around 2 years of age. This increase is often described as benign, and most patients are untreated because symptoms tend to resolve spontaneously in childhood (33). However, in some cases of gross hydrocephalus, surgical procedures are often necessary to relieve pressure. Hydrocephalus presents in a heterogeneous manner, which is probably a result of its heterogeneous etiology. Four genes have been linked to hydrocephalus that are associated with different cellular processes, including cell adhesion and cell polarity. However, the mechanisms related to these genes do not provide a clear

understanding of the mechanisms driving the disorder (37). There are also non-genetic causes of increased CSF in the subarachnoid space like infection, trauma or hemorrhage occurring perinatally or prenatally.

We found that increased EA-CSF had opposite relationships with CT and SA measures; greater EA-CSF was related to larger SA at ages 1 and 2 years and smaller CT at age 1 year. Gray matter measures can be parsed into CT and SA measures. However, CT and SA have distinct patterns of development within the first year of life (39). CT growth reaches approximately 97% of adult values at age 2 years, while surface expansion is robust and accounts for the majority of cortical volume growth after the first year of life. Additionally, thinner CT is observed in many regions of the frontal lobe in children with longer gestational periods, while larger SA is seen in later-born infants (40). These distinct patterns of development between how CT grows and SA and gray matter grow suggest the presented relation differences between these measures and EA-CSF. This suggests that the distribution of EA-CSF reflects overall brain size and that atrophy was not found in subjects with increased EA-CSF. Further research is needed to understand the possible genetic and environmental contributions affecting these relationships.

We found gross motor deficits were present with increased EA-CSF at age 1 year in our sample of TD subjects. Increased EA-CSF has been related to ataxia and seizures in infants from < 6 months to 2 years old (33, 41). Increased EA-CSF has also been related to motor deficits during infancy from approximately 5 to 12 months that tend to resolve around 1 to 3 years (33, 34, 42). Shen et al. (2017) found poorer motor ability in subjects with increased EA-CSF in infancy and decreased fine motor abilities at ages 2–4 years in children with autism, and we found a similar effect in TD infants.

Our study revealed no relationship to being at risk for schizophrenia and having increased EA-CSF. Although increased EA-CSF has been replicated in children diagnosed with autism, this is the first study to evaluate whether this biomarker is specific to autism or present in other disorders like schizophrenia (6, 7, 9). Patients with schizophrenia often have increased CSF associated with increased lateral ventricles, widened sulci, and increased subarachnoid spaces (14, 15). Researchers have found that the presentation of schizophrenia and measures of patients with the disorder is heterogeneous. Studies of high risk youth find cognitive deficits that progress with the onset of psychosis (43). Studies of the association of schizophrenia with dementia are inconsistent, though it is likely that abnormalities during early neurodevelopment can cause alterations in later development and aging (44). We previously found that male SCZHR neonates had enlarged lateral ventricles, suggesting that CSF distribution could be altered in this at-risk population (16). In this study, we did not find larger EA-CSF spaces in our sample of SCZHR, SCZHR showed a normal distribution of EA-CSF with no major outliers of increased or decreased EA-CSF volume, however, the sample size was small and in need of replication.

Historically, ASD and schizophrenia were thought to share similar mechanisms that present at different times during brain development (10). Theories suggest both of these disorders have neurodevelopmental origins. We know that genetic factors influence both disorders; ASD and schizophrenia share copy number variants, rare genetic abnormalities, and

candidate genes (10, 13). This indicates that ASD and schizophrenia may have some similar underlying pathogenic mechanisms that present at different times. Our observations of EA-CSF occurred at ages 1 and 2 years, after the 6month time-point of Shen's et al. (2013; 2017; 2018) studies. Future studies should determine if enlarged EA-CSF is present at 6 months of age in children at risk for schizophrenia, though our finding that neonatal CSF volume, highly correlated with EA-CSF in 1 year olds, is not significantly larger in high risk children, suggests that enlarged EA-CSF is not associated with risk for schizophrenia at early ages.

While this study has many strengths, there are several limitations that must be considered when interpreting results. It should be noted that the method to segment EA-CSF was not done exactly as Shen et al. (2013, 2017), though measures were taken to ensure the segmentations used in these analyses were done similarly and assessed for a high standard of quality. The analysis of children at high risk for schizophrenia had a small sample size and should be considered preliminary until replicated. Attrition occurred from 1 year to the 2-year-old imaging, and the imaging success rate is less at these ages, so the sample at each age was somewhat different; this may have contributed to age-related imaging findings.

In summary, we find that EA-CSF is associated with overall brain size in TD children, and is associated with reduced CT and lower gross motor scores at age 1 year, but not 2 years. EA-CSF was not increased in children at risk for schizophrenia, suggesting that increased EA-CSF is not present in infancy in all neurodevelopmental disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
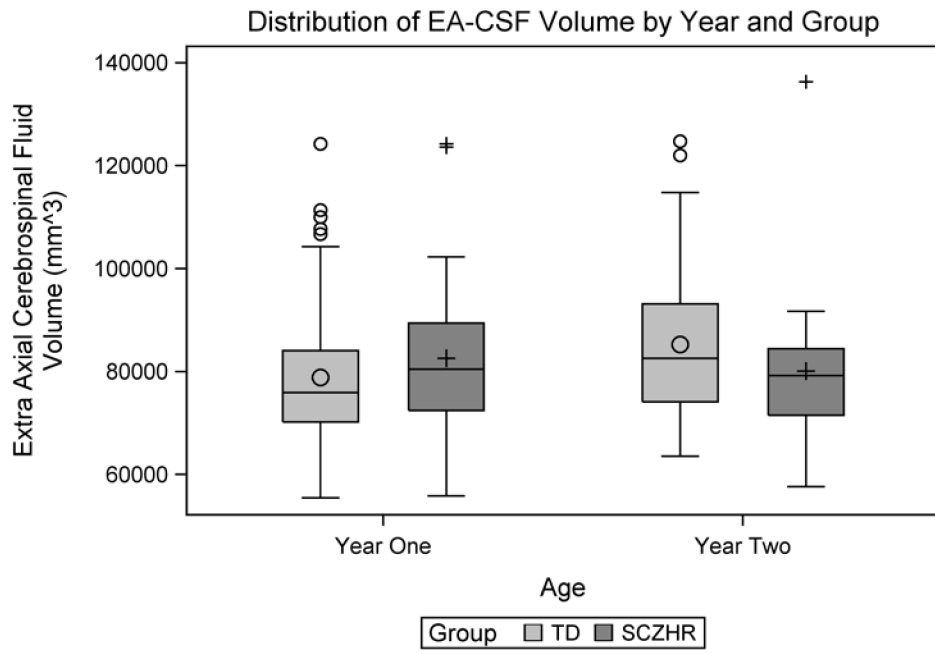Distribution of EA-CSF volume at ages 1 and 2 years.

EA-CSF Relationships to Brain Tissues
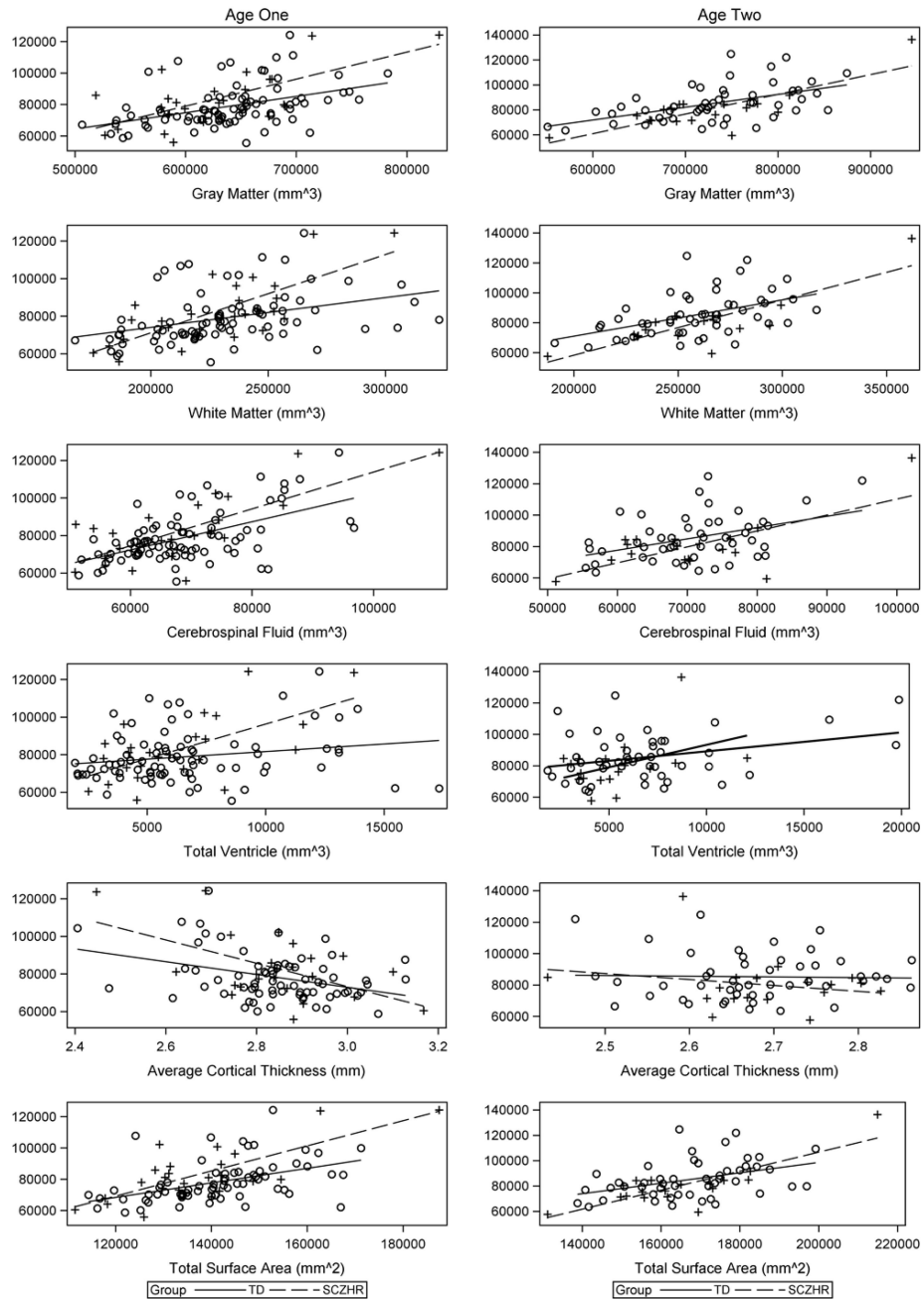
Figure 2.
EA-CSF volume relationships to gray matter, white matter, cerebrospinal fluid, and total ventricle volumes and average CT and total SA at ages 1 and 2 years.
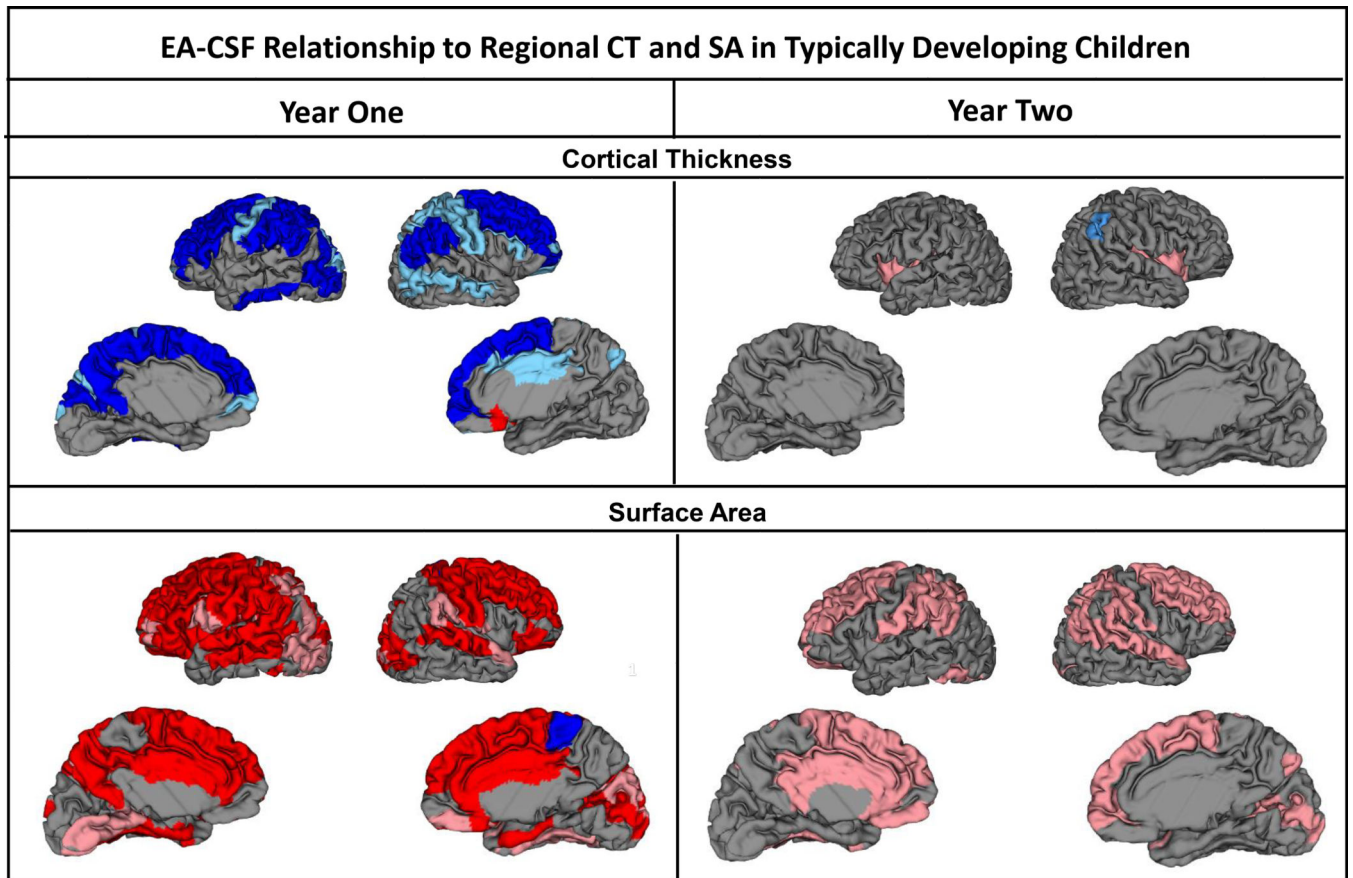
Figure 3.
Regional relationships of EA-CSF volume to CT and SA at 1 and 2 years. Pink represents a significant positive association, Red is significant after FDR correction. Light blue represents a significant negative association, Dark blue is significant after FDR correction.

Table 1.

Demographic variables for all subjects.

		Typically Developing (N=107)		SCZHR (N=33)	t-test / Fisher Exact Test
Continuous Variables	N	Mean (SD)	N	Mean (SD)	p[a]
Birth Weight (g)	107	3445.32 (419.93)	33	3053.79 (605.55)	<.001*
Gestational Age at Birth (Days)	107	276.79 (9.28)	34	266.73(13.07)	<.001*
Postnatal Age at MRI at age One (Days)	82	381.21 (20.53)	26	388.31 (30.86)	.180
Postnatal Age at MRI at age Two (Days)	49	740.27(17.16)	18	768.00 (35.33)	<.001*
APGAR 5 minutes	107	8.85 (0.66)	33	8.76 (0.61)	.472
Total Income ($)	100	72938.12 (44106.61)	26	30529.62 (30926.58)	<.001*
Maternal Education (years)	107	16.44 (2.91)	33	10.48 (3.82)	<.001*
Paternal Education (years)	104	16.39 (3.32)	26	10.38 (3.54)	<.001*
Maternal Age at Birth (years)	107	29.79 (4.94)	32	27.28 (6.62)	.022*
Paternal Age at Birth (years)	104	31.24 (5.01)	25	34.40 (10.76)	.031*
Categorical Variables	N	n (%)	N	n (%)	p[b]
Sex	107		33		.692
Male		54 (50.47)		15 (45.45)	
Female		53 (49.53)		18 (54.55)	
Maternal Race	107		33		<.001*
African American		19 (17.76)		20 (60.61)	
Asian		4 (3.74)		1 (3.03)	
Caucasian		84 (78.50)		12 (36.36)	
Scanner at age One	82		26		.730
Allegra		71(86.59)		24 (92.31)	
Trio		11 (13.41)		2 (7.69)	
Scanner at age Two	49		18		.693
Allegra		43 (87.76)		15 (83.33)	
Trio		6(12.24)		3 (16.67)	

[a] t-test p-value

[b] Fisher Exact Test p-value

Table 2.

Brain Tissue Relationships to EA-CSF at ages 1 and 2 years in typically developing.

Continuous Variables	Year One (N=82)				Year Two (N=49)			
	Mean (SD)	R^2	Est.	p	Mean (SD)	R^2	Est.	p
EA-CSF (mm^3)	78830.59 (13491.83)	-	-	-	85285.73 (14635.93)	-	-	-
CSF at Birth (mm^3)	60213.59 (11805.56)[a]	.309	0.584	<.001*	59236.32 (11233.64)[b]	.107	0.431	0.048*
Intracranial (mm^3)	938899.07 (90378.31)	.211	0.069	<.001*	1061392.36 (108222.17)	.260	0.069	<.001*
Gray Matter (mm^3)	639499.57 (56240.98)	.187	0.103	<.001*	731709.03 (74139.13)	.270	0.103	<.001*
White Matter (mm^3)	230625.04 (31376.44)	.136	0.159	<.001*	258942.39 (28145.69)	.217	0.242	<.001*
CSF (mm^3)	68774.46 (10040.55)	.311	0.750	<.001*	70740.95 (8483.61)	.174	0.720	.002*
Total Ventricle (mm^3)	6552.18 (3301.14)	.039	0.807	.075	6830.35 (3878.06)	.102	1.205	.025*
Average CT (mm)	2.84 (0.14)[c]	.129	34039.4	.002*	2.68 (0.09)[d]	.001	−4414.55	.850
Total SA (mm^2)	141205.33 (12799.35)[c]	.213	0.465	<.001*	167593.47 (14747.69)[d]	.168	0.411	.004*

[a] n=56

[b] n=37

[c] n=7

[d] n=48.

Table 3.

Brain tissue relationships to EA-CSF at ages 1 and 2 years in SCZHR.

Continuous Variables	Year One (N=26)				Year Two (N =18)			
	Mean (SD)	R^2	Est.	p	Mean (SD)	R^2	Est.	p
EA-CSF (mm^3)	82573.58 (17144.59)	-	-	-	80104.17 (16543.21)	-	-	-
CSF at Birth (mm^3)	62477.00 (18298.30)[a]	.676	0.886	<.001*	64178.60 (13715.61)[b]	.617	1.250	.007*
Intracranial (mm^3)	917274.98 (108687.54)	.540	0.116	<.001*	1051756.09(129475.77)	.643	0.102	<.001*
Gray Matter (mm^3)	621378.09 (68767.12)	.475	0.172	<.001*	722166.33 (83084.18)	.629	0.158	<.001*
White Matter (mm^3)	227646.10 (30648.47)	.556	0.417	<.001*	259146.74(36889.80)	.678	0.369	<.001*
CSF (mm^3)	68250.79 (12971.67)	.553	0.983	<.001*	70443.02 (11168.81)	.469	1.015	.002*
Total Ventricle (mm^3)	6298.62 (2814.94)	.367	3.690	.001*	5394.44 (2398.89)	.171	2.850	.088
Average CT (mm)	2.84 (0.15)[c]	.293	62050.8	.006*	2.69 (0.09)	.046	−37746.3	.394
Total SA (mm^2)	137128.94(15848.73)[c]	.556	0.803	<.001*	164607.69 (18029.59)	.668	0.750	<.001*

[a] n=18

[b] n=10

[c] n=24.