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Journal

Brain Imaging and Behavior, 11(5)

ISSN

1931-7557

Authors

Sullivan, Edith V

Lane, Barton

Kwon, Dongjin

et al.

Publication Date

2017-10-01

DOI

10.1007/s11682-016-9634-2

Peer reviewed

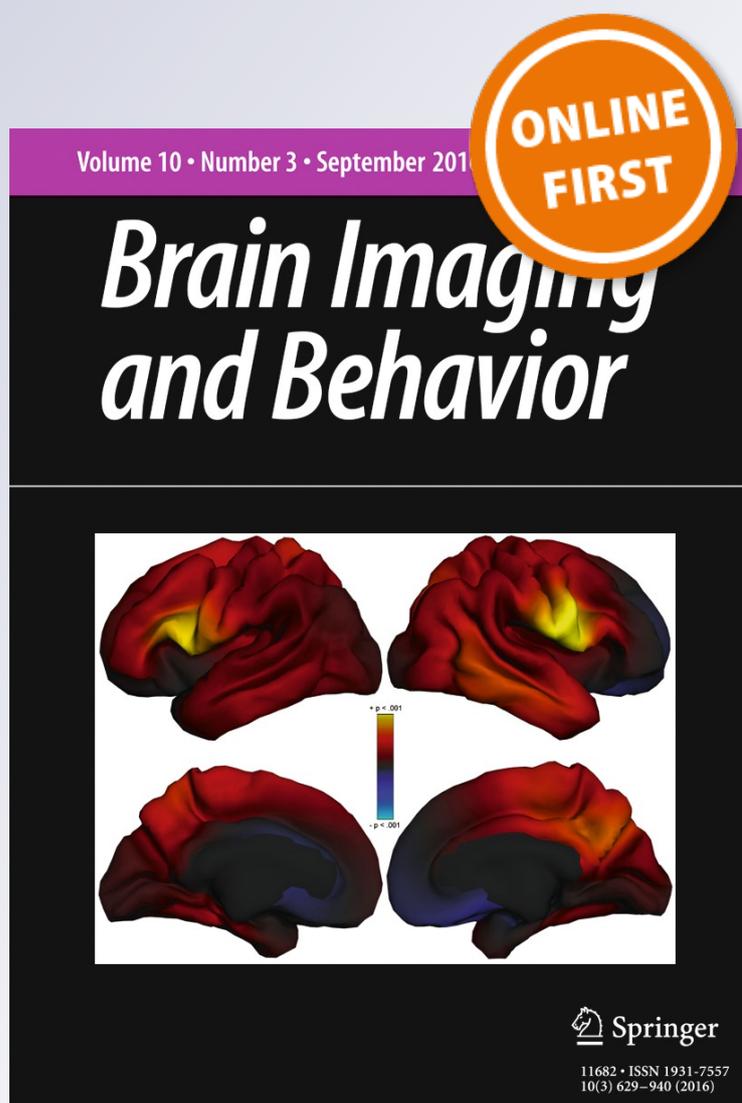
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**Brain Imaging and Behavior**

ISSN 1931-7557

Brain Imaging and Behavior  
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# Structural brain anomalies in healthy adolescents in the NCANDA cohort: relation to neuropsychological test performance, sex, and ethnicity

Edith V. Sullivan<sup>1</sup> · Barton Lane<sup>2</sup> · Dongjin Kwon<sup>1,3</sup> · M. J. Meloy<sup>4</sup> · Susan F. Tapert<sup>4</sup> · Sandra A. Brown<sup>4</sup> · Ian M. Colrain<sup>3</sup> · Fiona C. Baker<sup>3</sup> · Michael D. De Bellis<sup>5</sup> · Duncan B. Clark<sup>6</sup> · Bonnie J. Nagel<sup>7</sup> · Kilian M. Pohl<sup>1,3</sup> · Adolf Pfefferbaum<sup>1,3</sup>

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**Abstract** Structural MRI of volunteers deemed “normal” following clinical interview provides a window into normal brain developmental morphology but also reveals unexpected dysmorphology, commonly known as “incidental findings.” Although unanticipated, these anatomical findings raise questions regarding possible treatment that could even ultimately require neurosurgical intervention, which itself carries significant risk but may not be indicated if the anomaly is nonprogressive or of no functional consequence. Neuroradiological readings of 833 structural MRI from the National Consortium

on Alcohol and NeuroDevelopment in Adolescence (NCANDA) cohort found an 11.8 % incidence of brain structural anomalies, represented proportionately across the five collection sites and ethnic groups. Anomalies included 26 mega cisterna magna, 15 subarachnoid cysts, 12 pineal cysts, 12 white matter dysmorphologies, 5 tonsillar ectopias, 5 prominent perivascular spaces, 5 gray matter heterotopias, 4 pituitary masses, 4 excessively large or asymmetrical ventricles, 4 cavum septum pellucidum, 3 developmental venous anomalies, 1 exceptionally large midsagittal vein, and single cases requiring clinical followup: cranio-cervical junction stenosis, parietal cortical mass, and Chiari I malformation. A case of possible demyelinating disorder (e.g., neuromyelitis optica or multiple sclerosis) newly emerged at the 1-year NCANDA followup, requiring clinical referral. Comparing test performance of the 98 anomalous cases with 619 anomaly-free no-to-low alcohol consuming adolescents revealed significantly lower scores on speed measures of attention and motor functions; these differences were not attributed to any one anomaly subgroup. Further, we devised an automated approach for quantifying posterior fossa CSF volumes for detection of mega cisterna magna, which represented 26.5 % of clinically identified anomalies. Automated quantification fit a Gaussian distribution with a rightward skew. Using a 3SD cut-off, quantification identified 22 of the 26 clinically-identified cases, indicating that cases with percent of CSF in the posterior-inferior-middle aspect of the posterior fossa  $\geq 3SD$  merit further review, and support complementing clinical readings with objective quantitative analysis. Discovery of asymptomatic brain structural anomalies, even when no clinical action is indicated, can be disconcerting to the individual and responsible family members, raising a disclosure dilemma: refrain from relating the incidental findings to avoid unnecessary alarm or anxiety; or alternatively, relate the neuroradiological

**Electronic supplementary material** The online version of this article (doi:10.1007/s11682-016-9634-2) contains supplementary material, which is available to authorized users.

✉ Edith V. Sullivan  
edie@stanford.edu

<sup>1</sup> Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305-5723, USA

<sup>2</sup> Department of Radiology, Stanford University School of Medicine, Stanford, CA, USA

<sup>3</sup> Center for Health Sciences, SRI International, Menlo Park, CA, USA

<sup>4</sup> Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA

<sup>5</sup> Department of Psychiatry & Behavioral Sciences, Duke University School of Medicine, Durham, NC, USA

<sup>6</sup> Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

<sup>7</sup> Departments of Psychiatry and Behavioral Neuroscience, Oregon Health & Sciences University, Portland, OR, USA

findings as “normal variants” to the study volunteers and family, thereby equipping them with knowledge for the future should they have the occasion for a brain scan following an illness or accident that the incidental findings predated the later event.

**Keywords** Brain anomaly · Dysmorphology · Development, adolescence · Incidental findings

## Introduction

Morphometric heterogeneity of brain structure is evident from large-scale neuroimaging studies of healthy individuals and is salient during the adolescent years of development. The range of normal variation includes structural anomalies that are traditionally considered as clinically, neurologically, and neuropsychologically asymptomatic. The incidence of these anomalies ranges widely, from 4 % to 80 %, when including samples drawn retrospectively from clinical cases with MRI whose diagnoses were ultimately deemed non-serious (Gupta and Belay 2008; Bredlau et al. 2012; Famini et al. 2011; S. Gupta et al. 2010; Potchen et al. 2013; Roth et al. 2012) and, not surprisingly, was substantially higher in the elderly (Morris et al. 2009). When restricted to prospective MRI studies of research participants selected by rigorous exclusionary medical, neuropsychological, psychiatric, and other behavioral factors, the incidence of anomalies detected on clinical readings has a more restricted range, 4 % and 19 % (Gur et al. 2013; Morris et al. 2009; Reneman et al. 2012; Cramer et al. 2011; Hartwigsen et al. 2010; Kaiser et al. 2015; Li et al. 2015; Nagy and Jonsson 2009; Weber and Knopf 2006), with greater sensitivity of detection with higher image resolution and MR field strength (Morris et al. 2009).

Of anomalies detected, few cases are referred for further clinical investigation and typically indicate treatable disorders, such as a focal mass or tumor, multiple sclerosis, and Chiari I malformation. Rarefied samples derived from systematic screening procedures do not exclude brain structural anomalies. Unreported to date, however, are data on neuropsychological test performance of individuals with MRI anomalies, such as posterior fossa findings, subarachnoid and pineal cysts, ventriculomegaly, and gray matter heterotopias. Despite the growing number of prospective studies of brain development and the multifactorial data collected in large samples (Raznahan et al. 2011; Sowell et al. 2004; Sullivan et al. 2011; Storsve et al. 2014; Shaw et al. 2008; Wierenga et al. 2014; Raznahan et al. 2010; Bava et al. 2010) (for review, Stiles and Jernigan 2010; Giedd et al. 2014; Toga et al. 2006), it remains unknown to what extent brain structural anomalies considered normal variants have functional ramifications. Providing data to fill this lacuna was one goal of this study.

Structural anomalies reported often involve the posterior fossa. Chiari I malformations and Dandy-Walker cysts have functional correlates that are likely screened behaviorally (Barkovich et al. 1989). By contrast, mega cisterna magna, which are prevalent in studies of normal participants (Gur et al. 2013), are considered functionally silent (Adam and Greenberg 1978). This assertion, however, has not been examined objectively with cognitive and motor testing. Further, although attempts have been made to quantify mega cisterna magna using landmarks and area measurements (Adam and Greenberg 1978; Barkovich et al. 1989), quantitative volumetric approaches have not been reported. A second goal of this study was to devise an objective, quantitation of posterior fossa CSF volume and to test its relation to neuropsychological test performance.

Use of high-resolution, 3 T images has revealed anomalies in brain structure not visible with lower power imaging and has identified anomalies in nearly 3 times as many healthy subjects compared with lower field-strength data (Morris et al. 2009). Thus, use of high-field, high-resolution protocols in ongoing and future MRI studies of healthy brain development will undoubtedly uncover more instances of normal morphology and abnormal anatomy, i.e., dysmorphology (Kaiser et al. 2015). Given the burden that knowledge of brain structural anomalies imposes on parents and participants, having quantitative data about the functional correlates of these anomalies should contribute to objectivity and direction in relating diagnostic information and to ethical considerations regarding whether and how to report findings (Wolf et al. 2008; Illes 2008; Kumra et al. 2006; Di Pietro and Illes 2013).

The findings presented herein are based on data from our previous publication (Pfefferbaum et al. 2015), which reported regional volume differences in cortical gray matter and white matter across the adolescent age range using high-resolution 3 T MRI, and initially noted an 11.4 % incidence of clinically-identified, neuroradiological anomalies in the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA) cohort of 833 youth, all of whom were deemed healthy and eligible for study entry before radiological readings (Brown et al. 2015). The current report provides an extensive analysis of the clinical findings by comparing cognitive and motor performance of adolescents with brain structural anomalies against performance by their counterparts without anomalies using test data from our earlier publication (Sullivan et al. 2016); examining the distribution of demographic descriptors (age, sex, ethnicity, and body mass index [BMI]) associated with each anomaly; and quantifying the infratentorial volume in all participants with the goal of using a quantitative approach to identify and measure mega cisterna magna, which occurred in one quarter of the sample with brain structural anomalies. These analyses addressed two critical questions: 1) Are incidental findings of little to no consequence cognitively or motorically, or alternatively, do these clinical readings have functional correlates with quantitative neuropsychological testing? 2) Can detection of

dysmorphology be enhanced by objective, quantitative measurement? The second question targeted mega cisterna magna.

## Methods

### Participants

Neuroradiological review of research-quality structural brain MRI collected on 3 T scanners was conducted on the entire group of 833 adolescents who were recruited for the longitudinal NCANDA study: 808 with MRI of adequate quality and structural integrity for automated cortical quantification (Pfefferbaum et al. 2015) (674 adolescents who met alcohol and drug use criteria for no/low consumption and 134 adolescents who exceeded those criteria; for details, see Brown et al. 2015); 23 adolescents with structural anomalies precluding automated cortical quantification; and 2 adolescents who were excluded from the NCANDA cohort because of brain structural abnormalities requiring clinical followup. One additional adolescent with a normal reading at baseline developed a lesion detected at the 1-year followup examination requiring clinical assessment; his baseline, but not followup, neuropsychological data were included for norm construction. Anomalies were detected in 77 of the no/low alcohol and drug exposure group and 21 of the exceeds-criteria group; only data from the no/low group were used as the normal standard against which to test scores of the anomalies group (Fig. 1).

Participants were divided into two groups based on presence or absence of clinically detected, MRI structural anomalies: 98 cases at baseline plus 1 identified at followup and 619 cases in the no/low drinking group without MRI anomalies. These two groups were characterized by age, sex, pubertal stage using the self-assessment Pubertal Development Scale (PDS) (Petersen et al. 1988), body mass index (BMI) adjusted for age and sex, socioeconomic status (SES) determined as the highest education achieved by either parent (Akshoomoff et al. 2014), and ethnicity by primary heritage (Caucasian, African-American, Asian). Relative to the no anomalies group, the anomalies group was older by about half a year and had proportionately more boys than girls, but no other reviewed characteristics distinguished in the two groups (Table 1).

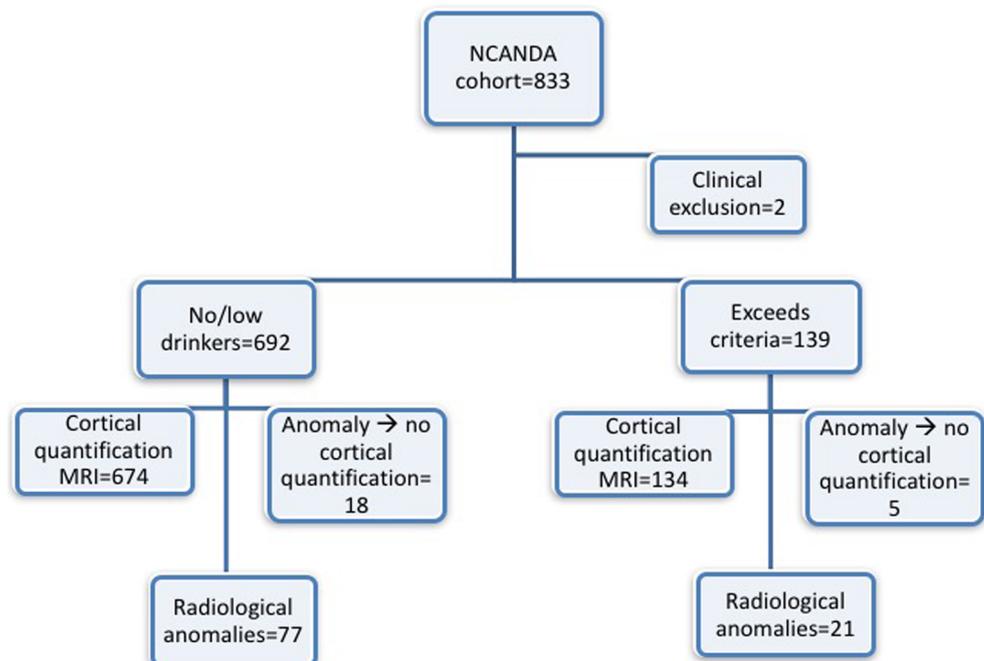
All youth participated in an informed consent process with a research associate trained in human subject research protocols. Adult participants or the parents of minor participants provided written informed consent before entering in the study. Minor youth provided assent before participation. The Institutional Review Boards of each site approved this study, and each site followed this procedure to obtain voluntary informed consent or assent, depending on the age of the participant.

### MRI Acquisition for Clinical Readings

T1-weighted, 3D MRI data sets were collected in the sagittal plane on systems from two manufacturers: 3 T General Electric (GE) Discovery MR750 at three sites (216 from

**Fig. 1** Flow chart of counts of NCANDA MRIs with and without brain structural anomalies identified on neuroradiological readings

### NCANDA MRIs with and without anomalies on neuroradiological readings



**Table 1** Demographics by group

Characteristic	Anomalies group	No anomalies No/low group	$\chi^2$ or t-value	p-value
Sex (M, F)	59, 39	296, 323	4.708	0.03
Age (mean $\pm$ SD)	16.5 (2.42)	15.7 (2.33)	3.298	0.001
PDS (mean $\pm$ SD)	3.2 (0.67)	3.1 (0.71)	1.410	n.s.
BMI (mean $\pm$ SD)	22.0 (3.93)	22.1 (4.48)	0.155	n.s.
SES (mean $\pm$ SD)	17.0 (2.51)	16.8 (2.44)	0.909	n.s.
Ethnicity			4.411	n.s.
Caucasian	79	451		
African American	7	90		
Asian	11	67		
Other	1	11		
Data Collection Site			6.133	n.s.
University of Pittsburgh	10	86		
SRI International	28	116		
Duke University	19	134		
Oregon Health & Science University	15	124		
University of California, San Diego	26	159		

Range: 1 = prepubescent, 5 = adult

PDS Pubertal Development Scale, SES socioeconomic scale = highest educational level of any parent

UCSD; 166 from SRI; 176 from Duke) and 3 T Siemens TIM TRIO scanners at two sites (125 from University of Pittsburgh; 150 from Oregon Health & Sciences University). The GE sites used an Array Spatial Sensitivity Encoding Technique (ASSET) for parallel and accelerated imaging with an 8-channel head coil and acquired a Inversion Recovery-Spoiled Gradient Recalled (IR-SPGR) echo sequence (TR = 5.904 ms, TI = 400 ms, TE = 1.932 ms, flip angle = 11°, NEX = 1, matrix = 256  $\times$  256, FOV = 24 cm, slice dimensions = 1.2  $\times$  0.9375  $\times$  0.9375 mm, 146 slices). The Siemens sites used a 12-channel head coil and parallel imaging and temporal acceleration with iPAT and acquired an MPRAGE sequence (TR = 1900 ms, TI = 900 ms, TE = 2.92 ms, flip angle = 9°, NEX = 1, matrix = 256  $\times$  256, FOV = 24 cm, slice dimensions = 1.2  $\times$  0.9375  $\times$  0.9375 mm, 160 slices).

### Clinical readings

Readings of all studies from all five collection sites were conducted on T1-weighted MRI by one board-certified neuroradiologist (B.L.) with ~40 years of experience in clinical and research investigations. Images were displayed with Osirix v.5.6 on an iMac with a 27-in. screen. Although the age range was known, MRIs were read prospectively by the neuroradiologist, who was blind to specific age, sex, ethnicity, and collection site. Neuroradiological readings were performed for the purpose of detecting clinically significant anomalies or abnormalities, and such were reported to the site-specific principal investigators for followup with the participant and family, depending on the age of the participant.

Mega cisterna magna were defined on sagittal T1-weighted images as bounded by the torcular superiorly, the bony posterior fossa posteriorly, the medulla and cerebellum anteriorly, and a line drawn at the superior margin of C-1 inferiorly. This inferior margin was chosen rather than the foramen magnum itself due to many cases with mega cisterna magna clearly extending below foramen magnum.

### Automated quantification of mega cisterna magna CSF volumes

In addition to visually-based clinical readings, 828 of the initial 833 scans were adequate for detection of cisterna magna by volumetric quantification of the posterior cistern, which is located in the cerebellomedullary cistern and positioned posterior to the medulla oblongata, and inferior and posterior to the cerebellum and exclusive of the 4th ventricle. Accordingly, a cisterna magna region of interest (ROI) was defined as that portion of the posterior fossa below an axial plane at the level of the posterior medullary velum of the 4th ventricle and extending laterally 20 mm on either side of the midline. To avoid inclusion of the 4th ventricle, CSF and tissue anterior to a coronal plane drawn at the medullary velum extending 12 mm inferiorly was excluded. For each subject, this ROI was registered to his or her T1-weighted image and the contents segmented into CSF and tissue. The final metric for the volume of the posterior cistern was the percent of CSF in the defined ROI. The volume of the entire posterior fossa was also defined by registration to a laboratory standard (Pfefferbaum et al. 2015), and the radiologist-measured area was expressed as a percent of the posterior fossa volume.

### Neuropsychological tests

Adolescents were administered a test battery comprising performance measures from the University of Pennsylvania Web-based Computerized Neurocognitive Battery (WebCNP) ([webcnp.med.upenn.edu/](http://webcnp.med.upenn.edu/)) (Gur et al. 2012; Gur et al. 2010) and traditional neuropsychological tests. Composite performance accuracy scores were expressed as standardized Z-scores, based on performance by the 619 adolescents in the no/low drinking group without anomalies, for 7 functional domains (Abstraction, Attention, Emotion, Episodic Memory, Working Memory, Balance, General Ability), and then applied to the scores of adolescents in the MRI anomalies group. Scores were also adjusted for age, sex, ethnicity, and site. Full descriptions of the tests appear elsewhere (Sullivan et al. 2016).

### Statistical analysis

Group differences in demographic variables were tested with  $\chi^2$  or t-tests. Comparison of mega cisterna magna measurements was done with Pearson correlations. Other analysis tools were the General Additive Model (GAM) (Wood 2006, 2011; Hastie and Tibshirani 1990, 1986) and analysis of variance (ANOVA) from the “mgcv” package in R Version 3.1.0 [<http://www.r-project.org/>], testing for the value of the effect of group (no MRI anomaly vs. MRI anomalies) with nonlinear

age (thin plane spline with 3 knots) and 3 covariates—site, ethnicity, and sex—to predict neuropsychological test scores.

$$GAM : performance_i \sim \beta_0 + S_1(age_i) + \beta_2 site_i + \beta_3 ethnicity_i + \beta_4 sex_i + \beta_5 group_i + \epsilon_i$$

The GAM was used for two major comparisons: the group of 619 no/low drinking adolescents without anomalies versus the total group of 98 anomalies and versus the group of 26 M cisterna magna cases.

## Results

### Incidental findings on clinical neuroradiological readings

Clinical neuroradiological readings of all 833 MRI studies at baseline identified noteworthy anomalies in 98 individuals (Table 2). On average, the group with the anomalies was older by about 1 year and had a significantly higher ratio of male-to-female participants than the no anomalies group, but the groups did not differ in PDS, BMI, SES. In addition, both groups had similar ethnicity and site distributions (Table 1). Notable was the large number of participants with mega cisterna magna and subarachnoid cysts (Table 2). Adolescents who had exceeded criteria for alcohol consumption had a

**Table 2** Frequency and type of anomalies identified on readings by a clinical neuroradiologist

Clinical reading	Count	Age (SD)	Age range	Male, Female	No-low, Exceeds
Mega cisterna magna	26	16.7 (3.06)	12.8–21.9	22, 4	24,2
Subarachnoid cysts (primarily temporal and frontal)	15†	16.2 (1.34)	13.8–18.1	8, 7	12,3
Pineal cysts	12	17.1 (1.60)	14.2–19.7	4, 8	9,3
White matter anomalies and callosal cysts	12	15.8 (2.68)	12.9–19.3	6, 6	7,5
Tonsillar ectopias	5	16.5 (2.40)	12.5–17.5	2, 3	4,1
Very prominent perivascular spaces	5	15.0 (1.95)	13.3–17.9	5, 0	5,0
Gray matter heterotopias	5	15.0 (2.56)	13.1–19.4	1, 4	5,0
Pituitary masses (primarily cysts)	4	19.6(0.61)	19.0–20.4	1, 3	3,1
Abnormally large or asymmetrical lateral ventricles	4	16.4 (1.48)	15.3–18.3	2, 2	2,2
Cavum septum pellucidum	4†	17.4 (3.67)	13.4–19.3	2, 2	1,3
Developmental venous anomalies (DVA)	3	16.5 (0.90)	15.5–17.3	3, 0	2,1
Severe cranio-cervical junction stenosis (10 mm)	1	13.8	—	1, 0	1,0
Large midline vein	1	16.8	—	0,1	1,0
*Right parietal cortical mass (3 cm)	1	16.7	—	1, 0	1,0
*Bilateral tonsillar herniation with medullary distortion (Chiari 1 malformation)	1	16.9	—	1, 0	1,0
Possible demyelinating disorder at 1 year followup	1	13.3	—	1, 0	1,0

N = 98/833 individuals, yielding 11.8 % incidence

\*After referral for clinical followup by collection site investigators, excluded from study

†one girl in each of these two categories also had primary white matter anomalies and thus are included in both counts

higher than expected representation in three categories of anomalies: white matter and callosal cysts, cavum septum pellucidum, and ventricular enlargement (Table 2). A.P. and E.V.S. then reviewed the MRIs of all individuals to judge whether the structural anomalies would interfere with automated quantification of cortical, subcortical, or white matter tissue morphometry (reported elsewhere, Pfefferbaum et al. 2015) and identified 23 cases for exclusion: 13 cysts, 3 white matter anomalies, 2 developmental venous anomalies, 4 heterotopias, and 1 large lateral ventricles with cyst (Fig. 2).

Three adolescents were referred for clinical neurological or neurosurgical consultation for evidence of the following: severe cranio-cervical junction stenosis (10 mm), right parietal cortical mass (3 cm), and bilateral tonsillar herniation with medullary distortion (Chiari 1 malformation); the latter two were excluded from the NCANDA sample (Fig. 3). At the 1-year followup study, a potentially demyelinating lesion consistent with neuromyelitis optica or multiple sclerosis emerged in an additional adolescent, whose MRI showed no evidence of abnormality at baseline (Fig. 4).

### Clinical readings and quantification of mega cisterna magna CSF volumes

Initial clinical readings identified mega cisterna magna (Fig. 5) in 21 male and 3 female youth across the age range studied, 12 to 21 years. Of these, most were Caucasian, none was African American, and 2 youth were in the exceeds-drinking criteria group (Table 3).

A frequency histogram, constructed for the automated volumes expressed as percent CSF of the posterior fossa ROI, of the total group of 828 cases was fit with a single Gaussian distribution with a mean of 13.7 % (SD = 2.69 %) and a significant skew toward the higher values; full fit was best achieved with two Gaussian distributions (Fig. 5). Although volumes were not related to ethnicity, CSF volume percentages were larger in boys than girls ( $t = 5.978$ ,  $p = 0.0001$ ) and larger in older adolescents ( $t = 3.402$ ,  $p = 0.0007$ ). A 4SD cut-off subtended a range from 24.4 % to 47.3 % of the cisterna magna ROI CSF and included 32 of the 828 adolescents, where 17 of these 32 were clinically identified mega cisterna magna. The remaining 9 of the total group of 26 clinically identified cases excluded from the 4SD cut-off ranged from 16.2 % to 23.9 % CSF on quantification and included 2 of the 4 female youth with mega cisterna magna readings. A 3SD cut-off identified 52 with large posterior fossa CSF volumes, subtending a range from 21.7 % to 47.3 %, and included 22 of the 26 clinically identified cases (see below). The remaining 4 cases identified by clinical but not automated assessment ranged from 16.2 % to 21.3 % CSF (Fig. 5).

In addition to the initial clinical review, B.L. visually re-reviewed the T1-weighted images of 41 cases that included the 24 originally deemed mega cisterna magna plus 15 with an average CSF percentile ranking of 95 %. This led to inclusion of 2 more, clinically-defined cases. B.L. also manually drew the outline of the mega cisterna magna region on the midsagittal slice on these cases to determine its area for comparison with the volumetric measurement (Fig. 4). Correlation of the volumetric and manual area measures, corrected for the infratentorial volume, yielded modest relations for the total group of 41 cases ( $r = 0.54$ ,  $p = 0.0002$ ) and the clinically determined group of 26 M cisterna magna ( $r = 0.47$ ,  $p = 0.015$ ).

### Neuropsychological test performance in groups and single cases

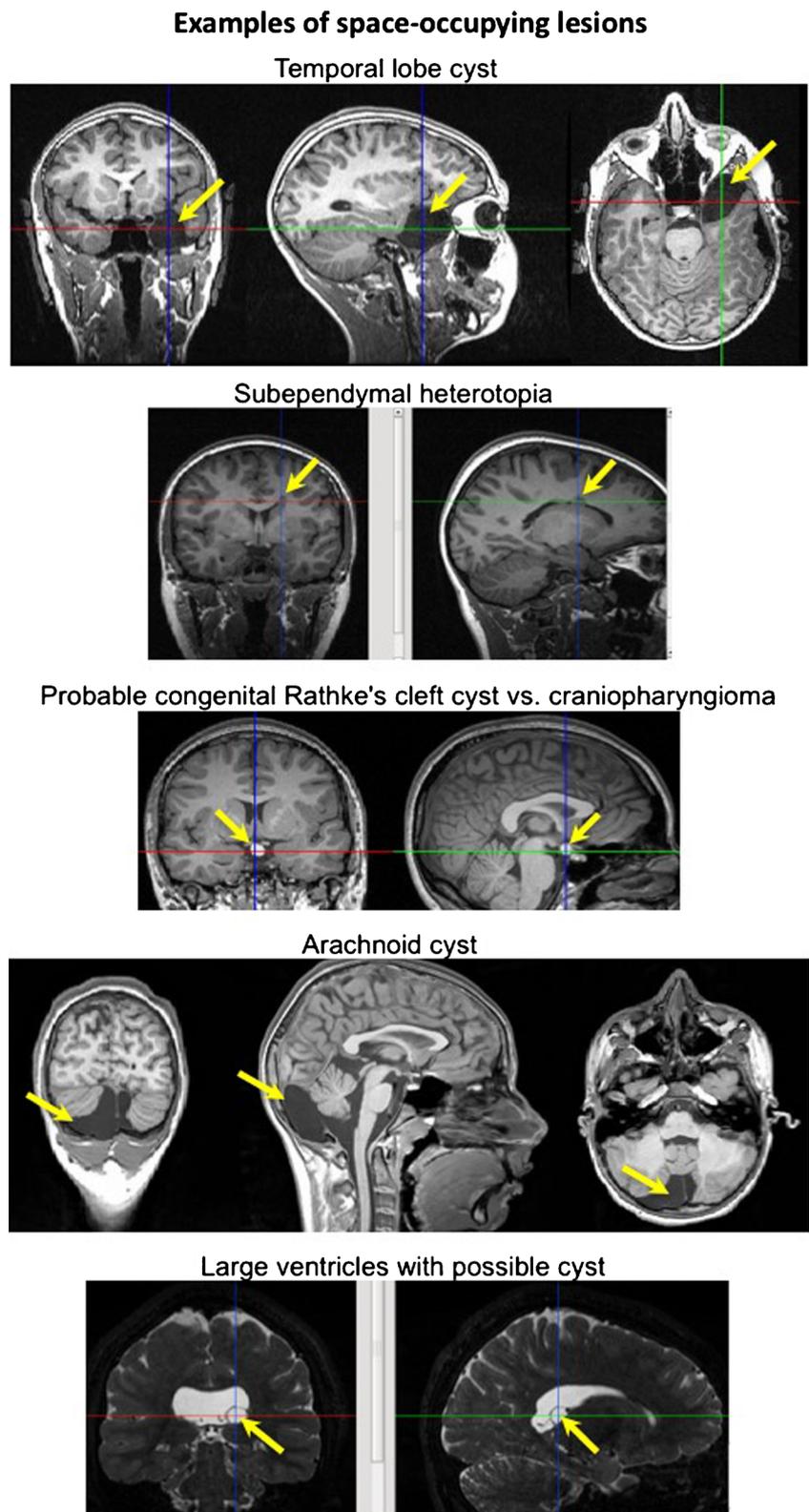
The total anomalies group achieved lower Attention and Motor speed scores than the no anomalies group, but none of the accuracy measures distinguished the groups (Supplemental Tables 1 and 2). These differences were not clearly attributed to any one anomaly subgroup, including the group of 26 mega cisterna magna, whose speeded performance did not differ significantly from the no anomalies group. Consideration of the four ataxia scores comprising the Balance composite score indicated normal performance by the mega cisterna magna group, with mean Z-scores ranging from  $-0.18$  to  $0.27$ .

To seek potential differences in performance by the no/low group and exceeds criteria for alcohol group with radiological anomalies, differences between pairs of groups were tested and revealed the following significant effects. Consistent with the differences observed in the total group of anomalies, the no/low only group with anomalies achieved lower scores than the no/low group without anomalies on the same two speed scores, although the difference was significant for Motor ( $t = -3.412$ ,  $p = .00068$ ) but not Attention ( $t = -1.822$ ,  $p = .069$ ) scores (Fig. 6). By contrast, the adolescents with anomalies and higher alcohol consumption did not differ from the no/low anomaly-free group on any speed measure, possibly because of low statistical power.

Consideration of performance by individuals revealed the following. Of the youth with mega cisterna magna, four participants, all from the no/low drinking group, had a Balance composite score of at least  $-1.0$  SD below average. An additional 9 cases, also in the no/low group, achieved balance scores below  $-1.0$  SD on at least one of the ataxia measures comprising the Balance composite score (Supplemental Tables 1 and 2).

Other scores of note (at least  $-1.0$  SD from average) were detected in individuals in the four diagnostic categories with single cases (Supplemental Tables 1 and 2); none exceeded the alcohol or drug use criteria. The youth with the large midline vein performed below  $-1.0$  SD on the Episodic Memory accuracy score and Working Memory speed score. The youth

**Fig. 2** Examples of space-occupying lesions



with the crano-cervical junction stenosis performed below  $-1.0$  SD on measures assessing Emotion accuracy and Attention, Motor, and Working Memory speeded responses (Supplemental Tables 1 and 2).

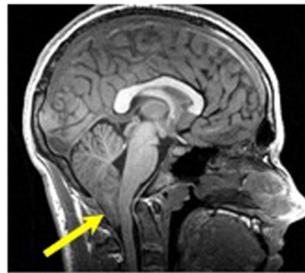
## Discussion

Prospective MRI study aimed at tracking developmental trajectories of brain structure in ostensibly healthy participants

**Fig. 3** Abnormalities referred for clinical followup

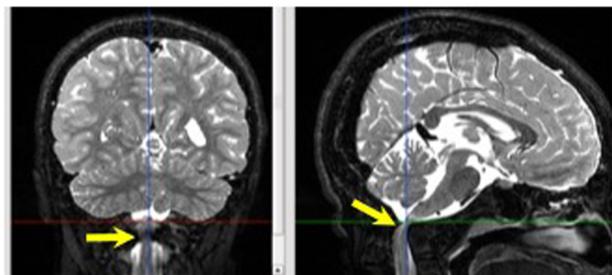
### Cases referred for clinical followup

#### Chiari 1 malformation

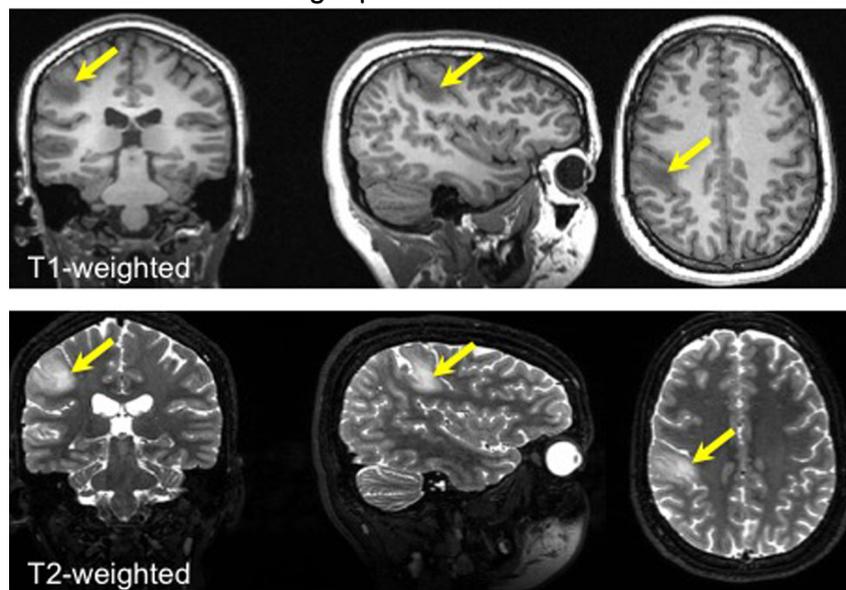


Bilateral tonsillar herniation with medullary distortion

#### Cranio-cervical junction stenosis



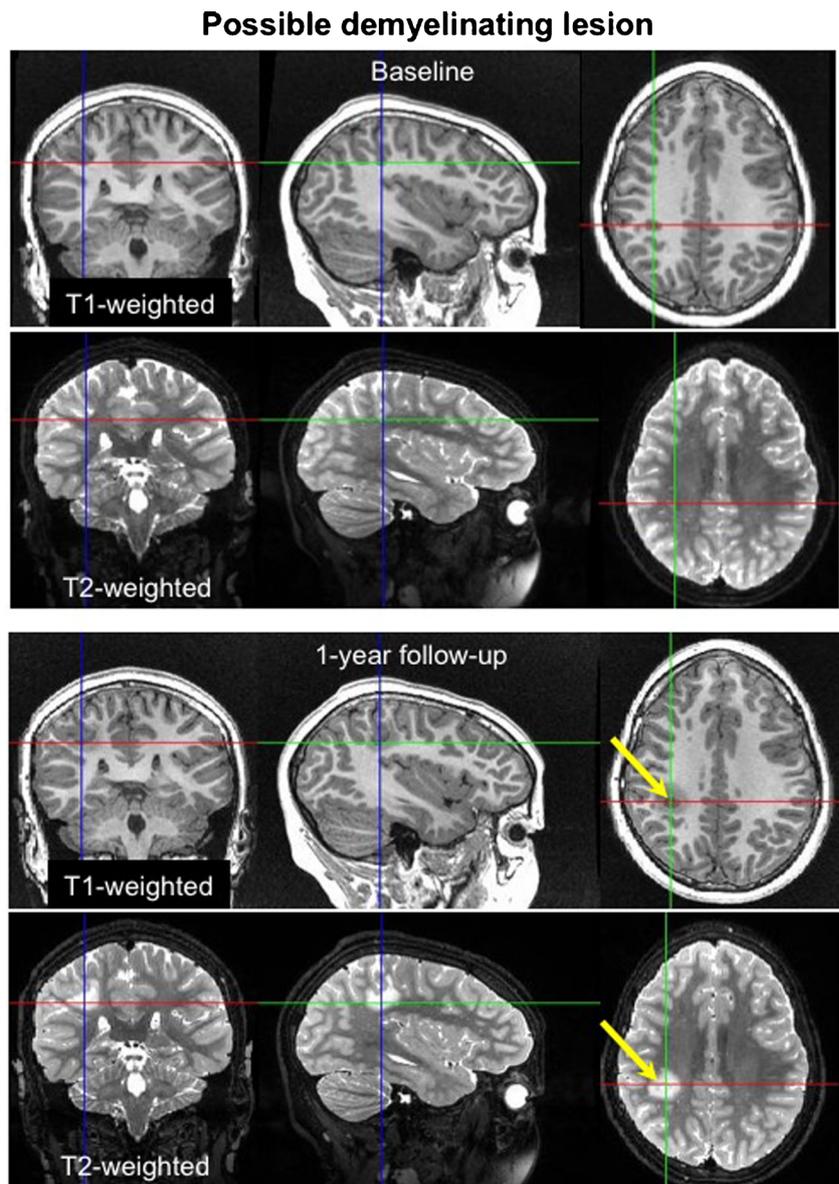
#### Right parietal cortical mass



has revealed novel findings both in terms of normal morphological ontogeny and unexpected, incidental findings reported to occur in about 4 to 19 % of well-screened adolescents. Clinical MRI readings of the NCANDA cohort of 833 adolescents, age 12 to 21 years, identified an 11.8 % incidence of anomalies (98 individuals), represented proportionately across the 5 sites and major ethnicities. Of all anomalies identified, only 4 radiological diagnoses were deemed to require neurological or neurosurgical followup: cranio-cervical junction stenosis, parietal cortical mass, Chiari I malformation, and

possible demyelinating disease consistent with neuromyelitis optica or multiple sclerosis. A few sex differences were noted: more boys than girls had mega cisterna magna and prominent perivascular spaces, whereas more girls than boys had pineal cysts, pituitary masses, or gray matter heterotopias. Mega cisterna magna occurred mainly in Caucasian boys of the NCANDA cohort; none was detected in African Americans. This ethnicity difference was also noted in the University of Pennsylvania cohort with respect to its category of “cerebellar findings,” which included mega cisterna magna. The

**Fig. 4** A case of possible demyelinating disease, consistent with neuromyelitis optica or multiple sclerosis, which was not visible at the baseline MRI



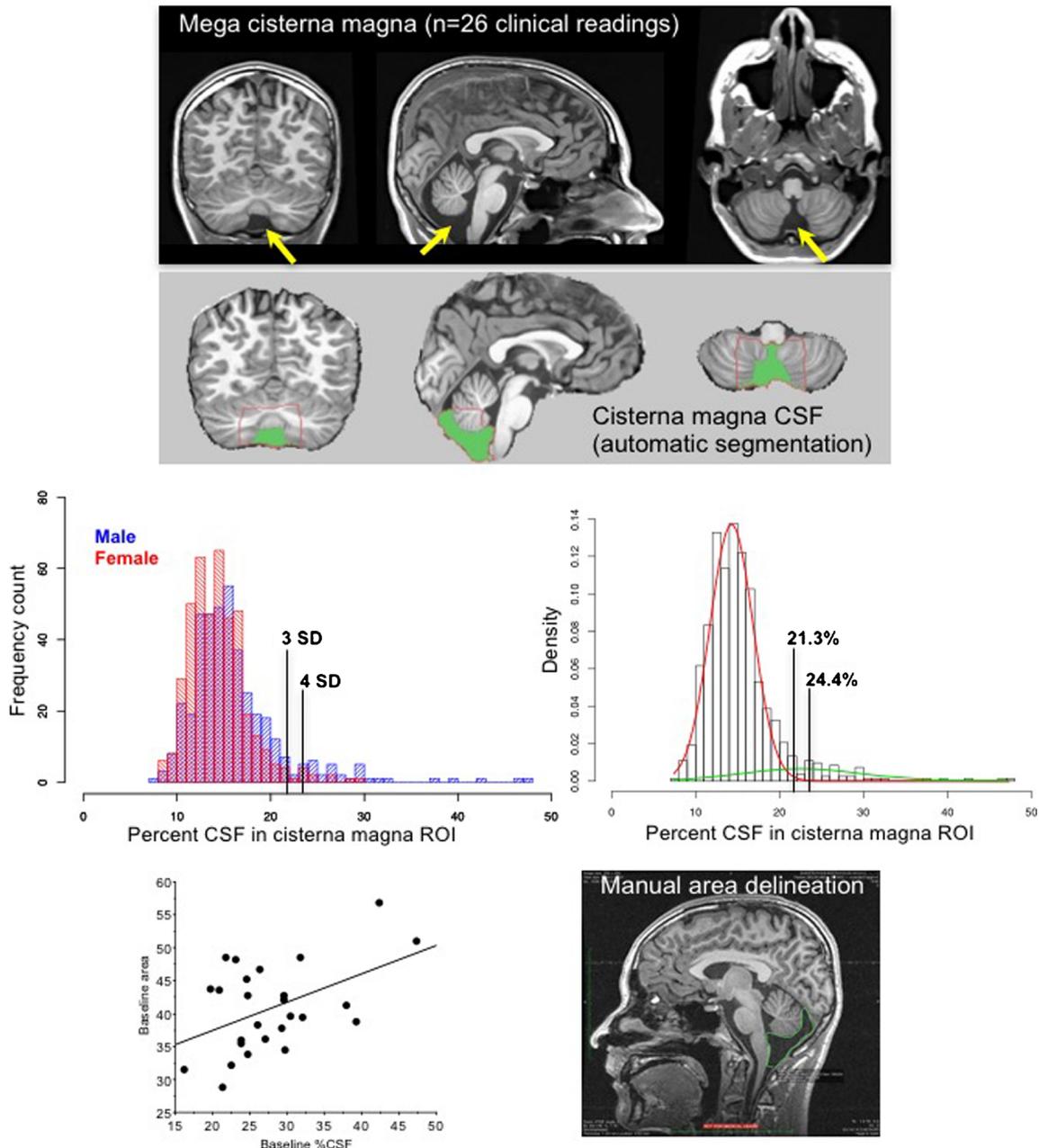
mainstay of incidental findings were not referred for clinical examination, a decision supported by other studies and ethical considerations that acknowledge the problem of introducing excessive concern to the affected individual and family for a “normal variant” of no clinical relevance (cf., Wolf et al. 2008). By contrast, that a serious abnormality of possible demyelinating disease emerged at the 1-year followup confirms the importance of continued neuroradiological monitoring of MRI in out years of longitudinal projects.

By definition, incidental findings are clinically silent. In challenge to this assumption, however, we examined performance on a neuropsychological test battery taken at the time of MRI acquisition. In general, the anomalous groups performed within the average range of performance by their counterparts free of structural brain anomalies, with few exceptions. Instances of low performance by the total group,

although not selective to any single diagnosis, involved speed rather than accuracy in responding on tests of attention and psychomotor speed. This pattern is similar to performance by individuals with mild closed head injury, which often result in modestly damped attention and psychomotor speed (e.g., Levin et al. 2013) and raises the possibility that these brain structural-functional correlations have a causal component. A further consideration is the genesis of the anomalies, many of which are likely to be congenital. If so, affected youth have had a lifetime to accommodate to the lesion both functionally and structurally.

The 11.8 % incidence of incidental findings in the NCANDA cohort compares well with other developmental MRI studies of a highly screened youth that report 4 % to 19 % incidences (Kaiser et al. 2015; Morris et al. 2009; Gur et al. 2013; Illes et al. 2004; Kim et al. 2002; Reneman et al.

### Quantification of cisterna magna



**Fig. 5** Top 3 images: An example of mega cisterna magna. Second row of 3 images: The same case with the cisterna magna region of interest outlined in red and CSF displayed in green. Third row of two histograms: Left = Percent CSF in the cisterna magna region of interest by frequency count in male and female youth. Right: Gaussian fit indicating that 3SD

marked 21.3 % and 4SD marked 24.4 % of the CSF in the cisterna magna ROI. Fourth row: Left: Correlation between the manually drawn areas and automatically determined volumes of the CSF in the region of interest. Right: An example of manual delineation of the region (green outlining)

2012). A close comparison is the University of Pennsylvania cohort of 1400 youth, age 8–21 years, randomly selected from a larger cohort of 9000 youth with a variety of pediatric disorders. As with the current study, those participants were scanned on a 3 T system, and structural images were reviewed by radiologists who identified 10.6 % anomalies (Gur et al. 2013). Nonetheless, fundamental differences distinguished

these study design. Specifically, the University of Pennsylvania study was conducted at a single site, data collection was accomplished on a single 3 T system, and recruitment was based in a hospital setting. By contrast, the NCANDA study was conducted at five, geographically distant sites, data were acquired on five different 3 T systems made by two different manufacturers, and recruitment was

**Table 3** Demographics by group for mega cisterna magna and no anomalies of no/low drinking group

Characteristic	Mega cisterna magna group	No anomalies No/low group†	$\chi^2$ or t-value	p-value
Sex (M, F)	22, 4	296, 323	11.882	0.0006
Age (mean $\pm$ SD)	16.7 (3.06)	15.7 (2.33)	2.226	0.0263
PDS (mean $\pm$ SD)	3.2 (0.75)	3.1 (0.71)	0.160	n.s.
BMI (mean $\pm$ SD)	21.5 (3.37)	22.1 (4.48)	0.692	n.s.
SES (mean $\pm$ SD)	17.4 (1.83)	16.8 (2.44)	1.223	n.s.
Ethnicity			7.665	0.0535
Caucasian	19	451		
African American	0	90		
Asian	6	67		
Other	1	11		
Data Collection Site			0.935	n.s.
University of Pittsburgh	3	86		
SRI International	6	116		
Duke University	4	134		
Oregon Health & Science University	6	124		
University of California, San Diego	7	159		

Range: 1 = prepubescent, 5 = adult

PDS Pubertal Development Scale

BMI Body Mass Index

SES socioeconomic scale = highest educational level of any parent

† from Table 1

community- and school-based (Brown et al. 2015). In contrast with our study, which had a referral rate of 4.1 % of the 98 anomalous cases, the University of Pennsylvania study referred 12 of 148 (8.1 %) cases for clinical followup and included younger participants (Gur et al. 2013).

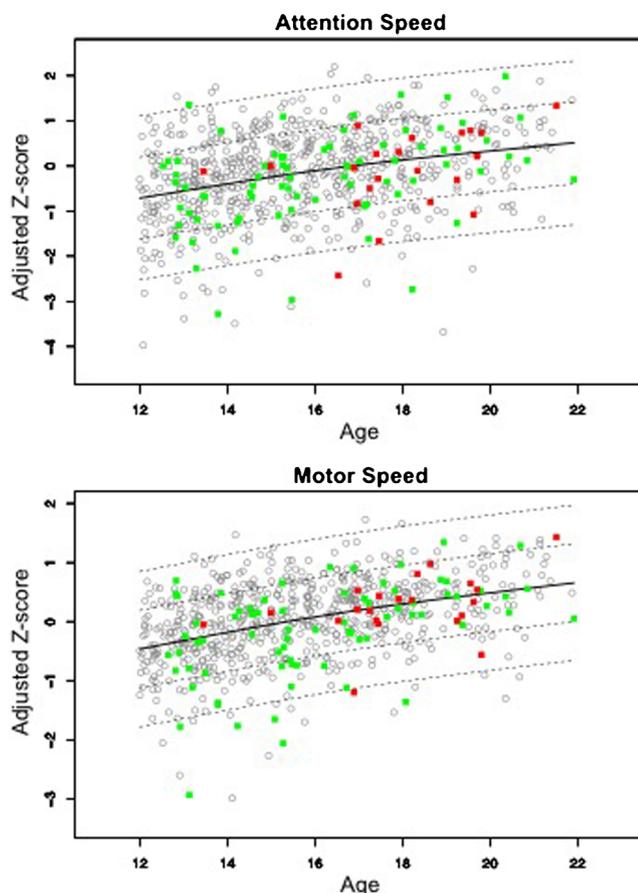
Mega cisterna magna was the most frequently identified anomaly, comprising 26.5 % of all anomalous cases, and was not associated with cognitive, motor, or postural stability deficits in the group. Their benign nature was described by Adam and Greenberg (Adam and Greenberg 1978), who noted that Gonsette and Andre-Balisaux (Gonsette and Andre-Balisaux 1968) coined the term “mega grande citerne” and made the point that cases described before their study presented with symptoms of posterior fossa disease requiring neurosurgery. By contrast, the 5 men and 6 women of 3000 cases in their series identified retrospectively with CT did not have such symptoms, albeit two had nystagmus and one had ataxia attributed to diphenylhydantoin or phenobarbital intoxication; two cases underwent surgery but with no change in symptoms, indicating lack of urgency or need for surgery. Later, Barkovich et al. (Barkovich et al. 1989) devised rules for quantitative measurement on MR images of posterior fossa CSF enlargement, including Dandy-Walker cysts, which are commonly accompanied by severe posterior fossa symptoms, and mega cisterna magna, which are typically asymptomatic. More recently, Yildiz and colleagues (Yildiz et al. 2006) used posterior fossa flow imaging to distinguish mega cisterna

magna from posterior fossa cysts, which can obstruct flow, cause hydrocephalus, and compress adjacent tissue. Examples of a posterior fossa cyst and a mega cisterna magna from the NCANDA sample are presented in Figs. 1 and 4.

In light of the high incidence of mega cisterna magna, we devised a volumetric approach for their identification and found that  $\geq 3SD$  threshold identified 22 of the 26 instances of clinically-defined mega cisterna magna, indicating that cases with the percent of CSF in the posterior inferior middle aspect of the posterior fossa  $\geq 3SD$  merit clinical review. This approach may be particularly valuable for detection of mega cisterna magna in study participants who are well screened for medical and psychiatric conditions, because the size of these anomalies is comparatively small. For example, in the NCANDA cohort the CSF/tissue ratio was 48.52 % of the maximum measured, whereas typically reported cases appear to be  $>50$  % CSF in posterior fossa (e.g., Barkovich et al. 1989).

Analysis of baseline MRI data from the NCANDA multi-site, longitudinal study revealed significant moderators of age-related, brain tissue differences in gray matter and white matter volume, cortical thickness, and cortical surface area marking adolescent neurodevelopment (Pfefferbaum et al. 2015). Whether youth with incidental findings follow the developmental trajectories measured in the non-anomalous counterparts remains open to longitudinal study and a challenge for automated quantification of primary brain morphometrics.

## Neuropsychological Test Performance



**Fig. 6** Scatterplots and regression line (solid black)  $\pm 1$  and 2 standard error of the regression lines of Attention speed and Motor speed test Z-scores, adjusted for sex, site, and ethnicity, showing poorer performance by the anomalies group [cases in the no/low group with anomalies (green squares) plus cases in the exceeds alcohol criteria group with anomalies (red squares)] than the no/low anomaly-free group (gray open circles)

In conclusion, even in a group of healthy, well-screened participants with normal brain structure at study entry, developmental anomalies will be found, and in some cases pathology will emerge in a sample of this size. The assertion that selective functionally silent, incidental anomalies detected through visual inspection by an experienced neuroradiologist are of no clinical relevance was largely supported by objective, quantitative cognitive and motor testing. The few exceptions involved speeded cognitive or motor responses, and these differences were not attributed to any one anomaly type. Use of a quantification scheme to detect mega cisterna magna, the anomaly occurring with the highest incidence, identified nearly 85 % of the clinically identified cases, and support complementing clinical readings with quantitative objective analysis. Of critical value is the continued radiological reading obtained through longitudinal study to enable followup of questionable anomalies and detection of emergent, clinically serious abnormalities. Discovery of asymptomatic brain

structural anomalies, even when no clinical action is indicated, can be disconcerting to the individual and responsible family members, raising a disclosure dilemma (cf., Wolf et al. 2008; Illes 2008; Kumra et al. 2006; Di Pietro and Illes 2013): refrain from relating the incidental findings to avoid unnecessary alarm or anxiety; or alternatively, relate the neuroradiological findings as “normal variants” to the study volunteers and family, thereby equipping them with knowledge for the future should they have the occasion for a brain scan following an illness or accident that the incidental findings predated the later event. Finally, it is critical to recognize that 1) research-grade MRI protocols are not FDA-approved, clinical-grade protocols and, therefore, cannot be used for definitive diagnosis and 2) a negative reading does not necessarily confirm absence of pathology.

### Compliance with ethical standard

**Funding** This work was supported by the U.S. National Institute on Alcohol Abuse and Alcoholism with co-funding from the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute of Child Health and Human Development [NCANDA grant numbers: AA021697 (A.P. + K.M.P.), AA021695 (S.A.B. + S.F.T.), AA021692 (S.A.B. + S.F.T.), AA021696 (I.M.C. + F.C.B.), AA021681 (M.D.D.B.), AA021690 (D.B.C.), AA021691 (B.N.)]. Additional funding supported E.V.S. (AA017168).

**Conflict of interest** The authors declare that they have no conflict of interest with the work reported herein.

**Informed consent** Informed consent was obtained from all individual participants, parents, or legal guardians who were majority, and assent from minors included in the study.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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