Cerebral ventricular volume and temperamental difficulties in infancy. The Generation R Study

Sabine J. Roza, MD; Paul P. Govaert, MD, PhD; Maarten H. Lequin, MD, PhD; Vincent W.V. Jaddoe, MD, PhD; Henriette A. Moll, MD, PhD; Eric A.P. Steegers, MD, PhD; Albert Hofman, MD, PhD; Frank C. Verhulst, MD, PhD; Henning Tiemeier, MD, PhD

Roza — The Generation R Study Group and Department of Child and Adolescent Psychiatry; Govaert, Moll — Department of Pediatrics; Lequin — Department of Radiology; Jaddoe — The Generation R Study Group and Departments of Pediatrics and of Epidemiology; Steegers — Department of Obstetrics and Gynecology; Hofman — Department of Epidemiology; Verhulst — Department of Child and Adolescent Psychiatry; Tiemeier — Departments of Child and Adolescent Psychiatry and of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands

Background: Numerous studies have provided evidence for subtle deviations in brain morphology in children with psychiatric disorders, but much less is known about the onset and developmental trajectory of these deviations early in life. We sought to determine whether variances in cerebral ventricular size in fetuses and newborns are associated with temperamental difficulties in infants. **Methods:** Within a population-based cohort study, we measured the size of the lateral ventricle of the fetus' brain twice during pregnancy. We used 3-dimensional cranial ultrasound to measure the cerebral ventricular volume of infants at age 6 weeks. We then related the size of the cerebral ventricular system to temperamental dimensions at age 3 months using the Mother and Baby Scales, and at age 6 months using the Infant Behavior Questionnaire for a total of 1028 infants. **Results:** The size of the lateral ventricle of the fetuses in midpregnancy was not related to temperamental difficulties in infants; however, smaller lateral ventricles in late pregnancy were associated with higher activity levels at the age of 6 months. Infants with smaller ventricular volumes at age 6 weeks experienced higher activity levels, more anger or irritability and poorer orienting later in infancy. Children with the lowest ventricular volumes scored on average 0.15 (95% confidence interval 0.06–0.23, $p = 0.001$) points higher (23%) on activity levels than children with the highest ventricular volumes. **Conclusion:** Variations in ventricular size before and shortly after birth are associated with temperamental difficulties. Some of the morphologic differences between children with and without psychiatric disorders may develop very early in life.

Contexte : De nombreuses études ont produit des données montrant des écarts subtils de la morphologie du cerveau chez les enfants atteints de troubles psychiatriques, mais on en sait moins au sujet de l'apparition et de l'évolution de cet écart dans les débuts de la vie. Nous avons cherché à déterminer s'il y a un lien entre des variations de la taille des ventricules du cerveau du fœtus et du nouveau-né et des difficultés caractérielles chez les nourrissons. **Méthodes :** Dans le contexte d'une étude de cohortes représentatives, nous avons mesuré la taille du ventricule latéral du cerveau du fœtus 2 fois au cours de la grossesse. Nous avons utilisé l'échographie crânienne tridimensionnelle pour mesurer le volume du ventricule du cerveau de nourrissons âgés de 6 semaines. Ensuite, chez 1028 nourrissons au total, nous avons établi un lien entre la taille du système ventriculaire cérébral et des aspects caractériels à 3 mois en utilisant les échelles de la mère et de l'enfant, et à 6 mois, le questionnaire sur le comportement du nourrisson. **Résultats :** Il n'y avait pas de lien entre la taille du ventricule latéral du fœtus au milieu de la grossesse et des difficultés caractérielles chez les nourrissons, mais on a toutefois établi une association entre des ventricules latéraux plus petits à la fin de la grossesse et une plus grande activité à 6 mois. Les nourrissons qui avaient un volume ventriculaire plus faible à 6 semaines étaient plus actifs, plus colériques et irritables, et s'orientaient plus mal plus tard au cours de la petite enfance. Les enfants qui avaient les volumes ventriculaires les plus faibles ont obtenu en

Correspondence to: Dr. H. Tiemeier, Erasmus Medical Center, Department of Child and Adolescent Psychiatry, PO Box 2060, 3000 CB Rotterdam, the Netherlands; h.tiemeier@erasmusmc.nl

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moyenne 0,15 (intervalle de confiance à 95 % 0,06–0,23; p = 0,001) points de plus (23 %) quant au niveau d'activité que les enfants qui avaient les volumes ventriculaires les plus élevés. **Conclusion :** On établit un lien entre des variations de la taille des ventricules avant la naissance et peu après et des difficultés caractérielles. Certaines des différences morphologiques entre les enfants qui ont des troubles psychiatriques et ceux qui n'en ont pas peuvent faire leur apparition très tôt au début de la vie.

Introduction

In the last 2 decades, numerous studies have investigated the associations between anatomic brain structure and child and adolescent psychiatric disorders.[1] Childhood psychiatric disorders, such as attention-deficit hyperactivity disorder (ADHD), autism and childhood-onset schizophrenia, are hypothesized to be neurodevelopmental in origin,[2,3] although the underlying mechanisms that contribute to their development are yet unknown. Subtle changes in the brain may make individuals more vulnerable to affective disorders.[1] In spite of the large number of studies that have used neuroimaging techniques to identify childhood psychiatric disorders, the findings thus far have been inconsistent,[1,4,5] mainly owing to methodologic problems such as heterogeneity of disorders, small samples, different control groups and confounding because of pharmacotherapy.

Nonetheless, the studies have shown correlations between measures of brain structure and neurodevelopmental disorders. For example, the most consistent structural abnormalities described in children with autism are enlarged total brain size[6–8] and reduced corpus callosum size.[9] Furthermore, abnormalities in the amygdala, hippocampus and cerebellum have been frequently reported in autistic children.[7] It has been reported that the total brain size of children with ADHD is about 5% smaller than that of children of the same age and sex who do not have ADHD.[10] Distributed subtle anomalies in the brains of children with ADHD have been described, in particular in the prefrontal cortices, right caudate, corpus callosum and cerebellar regions.[11–13]

Findings have been inconsistent with regard to the volume of the ventricular system, which is considered to be one of the general parameters of brain development.[14] One study suggested that children with autism had enlarged lateral ventricles compared with children who did not have autism,[15] whereas other studies did not report a statistical difference.[16] Castellanos and colleagues[10] described a slower increase in lateral ventricular volume in children with ADHD compared with children who did not have the disorder. Similarly, case series involving children with schizophrenia reported enlarged ventricles,[4,17,18] a finding that is also consistent in adult patients with schizophrenia.[19] However, it should be noted that lateral ventricular volume increases robustly with age in healthy children, which adds to the complexity of interpreting changes in ventricular volume in patient populations.[20]

It is unclear whether the subtle changes in the brains of children with psychiatric disorders emerge before the onset of symptoms or whether they are compensatory or adaptive changes of the nervous system. To elucidate whether and when the development of the brain is disturbed in children with psychiatric disorders, imaging techniques should be used to study progressively younger groups of children without disease at the time of imaging.[21] Such studies have been conducted in groups of children (e.g., children born prematurely) at high risk of psychiatric disorders. Their results have shown that enlarged ventricles are very common in premature infants and are related to neurodevelopmental outcomes in the first years of life.[22–25] Furthermore, mild ventricular enlargement in fetuses has been associated with ADHD, autism and learning disorders.[26] However, studies involving patients at high risk for psychiatric disorders cannot distinguish brain damage due to prematurity, pharmacotherapy and mechanical ventilation from subtle changes in the developing brain due to genetic predisposition or environmental factors.

One aspect of social and emotional behaviour that can be measured early in life is temperament. Temperament is conceptualized as the constitutionally based individual differences in reactivity and self-regulation, which are influenced over time by heredity, maturation and experience.[27] Numerous studies have argued that temperament plays a role in the etiology and persistence of behavioural problems in childhood and adolescence.[28–30] Precursors of behavioural problems include susceptibility to anger and hostility in infancy and early childhood.[31] For example, ADHD symptom scores in kindergarten are predicted by irritability, anger, high activity levels and difficulties with inhibitory control in preschool-age children.[32] Another study reported that children aged 7 years who had been classified as "high reactive" (i.e., vigorous motor activity combined with distress and crying) at the age of 4 months were more likely to have anxious symptoms than those who had been classified as "low reactive."[33]

We sought to examine the association between ventricular size and temperamental difficulties in 1028 infants. We hypothesized that ventricular volumes of children with a more difficult temperament at age 3 months and 6 months would differ significantly from the ventricular volumes of children without temperamental problems.

Methods

Study population

We conducted our study within a subgroup of the ongoing Generation R Study, which follows participants from fetal life until young adulthood in Rotterdam, the Netherlands. The Generation R Study previously has been described in detail.[34,35]

We selected fetuses and infants from the general population, and conducted detailed prenatal ultrasound assessments in 1232 pregnant women. This subgroup was racially homogeneous, which prevented confounding or effect modification based on ethnic origin. We did not define any other inclusion or exclusion criteria for participation in this subgroup. All children included in our study were born between February 2003 and August 2005.

We measured ventricular size twice during pregnancy and once postnatally at the age of 6 weeks. We used 3-dimensional ultrasound as the imaging technique because, when compared with magnetic resonance imaging, ultrasound has been shown to provide valid volume measurements of the ventricular system.[36] We performed fetal ultrasounds to measure cerebral ventricles during midpregnancy and late pregnancy. We then obtained data on temperament at ages 3 months and 6 months using postnatal questionnaires.

We conducted our study in accordance with the World Medical Association Declaration of Helsinki, and we received approval from the Medical Ethics Committee of the Erasmus Medical Center in Rotterdam. We obtained written informed consent from all participants.

Determinants

Trained sonographers carried out fetal ultrasound examinations during mid- and late pregnancy. The median gestational age (and range) for these examinations were 21 (19–23) weeks for midpregnancy and 30 (28–33) weeks for late pregnancy. Online measurements included head circumference (the outer perimeter of the fetus' skull) and the atrial width (the widest diameter of the atrium) of one of the lateral ventricles. Both were measured in an axial plane. High intra- and interobserver reproducibility have been reported for both methods of measurement.[37,38]

We performed postnatal cranial ultrasounds with the Voluson 730 Expert (GE Healthcare), a commercially available multifrequency electronic transducer that could be used for 3-dimensional volume acquisition. We positioned the probe on the anterior fontanelle, and placed a volume box at the level of the interventricular foramen in a symmetric section of the crown. We scanned a pyramid-shaped volume of the brain tissue and measured the volume of the lateral ventricular system offline. This method was described elsewhere in detail.[39] We quantified in millilitres the volume of the frontal horn of the lateral ventricle, ventricular body and ventricular trigone on both sides. Four raters manually traced the left and right ventricles. For reliability analyses, each rater segmented 20 images twice. All 4 then rated the images of another 20 children. The intra- and interobserver reliability of the volumetric measurements was very high, partly owing to the high variance in ventricular volume within our population.

Infant temperament

Mothers completed the Mother and Baby Scales (MABS)[40,41] for their children at age 3 months and the Infant Behavior Questionnaire — Revised (IBQ-R)[27] at age 6 months. We used the 2 infant scales of the MABS: infant irritability and alertness. The assessment scales ranged from 0 to 75 for irritability and from 0 to 40 for alertness. The irritability scale consisted of 15 items (e.g., "My baby has fussed before settling down"), and the alertness scale consisted of 8 items (e.g., "When I talk to my baby, (s)he seems to take notice"). We rated each item on a 6-point scale in which 0 indicated "not at all" and 5 indicated "very much/often." A higher score on the irritability scale indicated more difficult behaviour, whereas a higher score on the alertness scale indicated less difficult behaviour.

We chose 6 of 14 scales on the IBQ-R because use of the complete instrument, which includes 191 items, was not feasible within our multidisciplinary study with numerous assessments. The 6 scales we chose were activity level, distress to limitations, fear, duration of orienting, falling reactivity and sadness. We judged these to be of particular importance, from a clinical perspective, for the most prevalent behavioural disorders in childhood. Activity levels related to gross motor activity and squirming. Distress to limitations referred to negative emotionality and reaction to frustrating situations. Fear included rejection of new objects and persons. Duration of orienting comprised attention and distractibility. Falling reactivity referred to the rate of recovery from peak distress or frustration. Finally, questions about sadness related to lowered mood due to personal suffering or object loss. We rated each item on a 3-point scale in which 0 indicated "never present," 1 indicated "sometimes present" and 2 indicated "often present." Our scale was adapted from the original 7-point scale because participants of a pilot study seldom used the extreme positions on the scale and because reducing the number of options would not result in significant loss of information.[42] Higher scores on all but falling reactivity indicated more difficult behaviour. We calculated the scores for each scale by dividing the sum of the items by the number of completed items. Because traits could be consolidated into a smaller number of dimensions,[29] we grouped distress to limitations, recovery from distress and irritability into irritability or anger. We grouped fear and sadness into behavioural inhibition. We grouped duration of orienting and alertness into orienting.[43] We did not group activity level into one of these categories because it represented the approach or positive affect dimension.

Covariables

We considered variables related to socioeconomic status, psychosocial stressors, and obstetric and neonatal variables as possible confounders. Furthermore, we adjusted our associations for other known determinants of infant temperament, including sex, age, maternal psychopathology and maternal self-esteem. We obtained information on the date of birth, birth weight and sex of the infant from community midwife and hospital registries at the time of birth. We established gestational age using the fetal ultrasound examinations within the Generation R Study. During the postnatal visit at age 6 weeks, we measured the fronto-occipital circumference of the head in centimetres. We determined maternal age, maternal educational level and parity at the time of enrolment. To assess maternal psychopathology during midpregnancy and at 3 months postpartum, we used the Brief Symptom Inventory (BSI).[44,45] We assessed family functioning using the 12-item General Functioning subscale of the

McMaster Family Assessment Device.[46] We measured long-lasting difficulties using a 12-item checklist.[47] We assessed maternal self-esteem in late pregnancy using the Rosenberg Self-Esteem Scale.[48] Community midwife and hospital registries at birth yielded information on mode of delivery and Apgar scores. We classified the mode of delivery as cesarean section, spontaneous vaginal delivery or instrumental vaginal delivery.

Statistical analysis

To examine whether nonresponse to the 3-month and 6-month questionnaires was selective, we compared core data on children for whom we obtained information on ventricular volume and temperament with data on eligible children for whom we were not able to obtain this information.

We analyzed the associations between ventricular size and temperamental dimensions using multivariable linear regression models. First, we used log transformation of the data on postnatal ventricular volume to satisfy the assumption of normality. We used log or square root transformation of the data on the temperamental dimensions of fear, falling reactivity and alertness to achieve normality or constant variance. Next, we derived standard deviation scores for both determinants and outcomes to compare regression coefficients for transformed and nontransformed outcomes. Because the regression coefficients were not straightforward to interpret, we defined quartiles of ventricular volume and used analyses of covariance to compare the mean scores of nontransformed scales among the quartiles. We controlled all associations for head circumference when we measured the size of the ventricle because information about ventricular size was difficult to interpret without placing it in the context of overall head size.

We selected covariables as a result of exploratory analyses, and included them in our analyses if effect estimates of ventricular size changed meaningfully (> 5%). We excluded colinear covariables to avoid instability of the models. For example, maternal self-esteem, family functioning and long-lasting difficulties were highly correlated to maternal psychopathology and had no additional confounding effect on the association between ventricular size and infant temperament. Other variables, such as maternal smoking, alcohol consumption, single parenthood, financial difficulties, obstetric or perinatal complications (e.g., Apgar score, mode of delivery, birth weight, gestational diabetes, maternal hypertension, pre-eclampsia), child anthropometrics and child birth order, did not confound the association between ventricular volume and infant temperament. Therefore, we did not include these variables in our final models.

We performed a post-hoc Bonferroni adjustment for the multiple hypotheses regarding different temperamental scales per outcome in infants at ages 3 months and 6 months. When determinants and outcomes correlated highly, the conservatism of the Bonferroni adjustment increased, and the power of detecting effects owing to association was reduced. Because the ventricular measurements were highly correlated, we chose to correct for 2 hypotheses at age 3 months and for 6 hypotheses at age 6 months. We tested whether interaction terms of ventricular size and sex were significant at $\alpha = 0.05$. Measures of association are presented with their 95% confidence intervals (CIs).

We performed our analyses using the Statistical Package of Social Sciences version 11.0 for Windows (SPSS Inc.).

Results

Study population

The 1232 mothers who participated in our study delivered 1244 babies (1 intrauterine fetal death, 2 neonatal deaths). We performed fetal ultrasounds to measure cerebral ventricles for 692 singleton fetuses during midpregnancy and for 1186 singleton fetuses during late pregnancy. We performed additional postnatal cranial ultrasounds of sufficient quality for 778 infants. Of the children for whom we obtained information on cerebral ventricles (n = 1233), data on temperament were available for 939 infants at the age of 3 months and for 769 infants at the age of 6 months. We were unable to obtain data on temperament because of withdrawn consent for postnatal questionnaires (n = 49), logistical problems in sending out the postnatal questionnaires (n = 113 for the 3-month questionnaire, n = 273 for the 6-month questionnaire) and nonresponse (n = 128 for the 3-month questionnaire, n = 138 for the 6-month questionnaire). Twenty mothers participated with 2 children each (twins or siblings). We randomly excluded 1 of the siblings to avoid biases due to paired data. We included a total of 1028 children (82.6% of 1244) in one or more of our analyses.

Table 1 presents the characteristics of participating children and their parents. Half (50.2%) of the infants were boys. Birth weight and the circumference of the head at the gestational ages of 20 and 30 weeks, and at the postnatal age of 6 weeks, were larger among boys than girls. The median gestational duration was 40.1 weeks (range 28–43 wk). In total, 40 of 1028 children (3.9%) were born before 37 weeks. The mean maternal age at the time of enrolment was 31.8 years (range 18–46 yr). Of all participating children, 637 (62%) were the first-born children in their families. The mean measurements of atrial width of the lateral ventricle (and standard deviations [SD]) were 5.8 mm (1.2 mm) in midpregnancy, 5.3 mm (1.7 mm) in late pregnancy and –0.26 mm (0.7 mm) for the log transformation of data on postnatal ventricular volume. We found that the volume of the left ventricle was on average higher (median 0.44 mL, range 0.1 mL–1.6 mL) than that of the right ventricle (median 0.36 mL, range 0.1 mL–1.3 mL). Intraobserver intraclass correlation coefficients varied from 0.989 to 0.993 for the right ventricle and from 0.992 to 0.997 for the left ventricle. Interobserver intraclass correlation coefficients were 0.950 for the right ventricle and 0.981 for the left ventricle.

Table 2 presents the associations between ventricular size and temperament at the age of 3 months. Ventricular size in mid- and late pregnancy was not related to temperament in 3-month-old infants; however, smaller ventricular volumes measured postnatally were associated with orienting at the age of 3 months. For each unit of decreased standard deviation related to lower ventricular volume, the infant alertness score also decreased by 0.10. This association remained statistically significant after we performed a Bonferroni adjustment. We found no significant differences between the sexes. Head circumference in late pregnancy was related to infant alertness only (β –0.01, 95% CI –0.01 to –0.00, p = 0.006). However, the associations between ventricular size and infant temperament could not be explained by head circumference.

We related ventricular size in midpregnancy, late pregnancy and at the age of 6 weeks to infant temperament at the age of 6 months (Table 3). We found that ventricular size in midpregnancy was not associated with infant temperament. In late pregnancy, smaller ventricular size predicted only higher activity levels at the age of 6 months. Postnatally, smaller ventricular volume was associated with both anger or irritability and with higher activity levels. For each unit of decreased standard deviation related to smaller ventricular volume at age 6 weeks, the activity level score at age 6 months increased by 0.18, and the infant distress to limitations score increased by 0.14. The rate of recovery from distress score decreased by 0.12. We found no significant associations between postnatal ventricular volumes with fear, sadness or duration of orienting. After performing the Bonferroni adjustment to establish more conservative alphas (α = 0.0083), we found that the associations between postnatal ventricular volume and activity levels and distress to limitations remained statistically significant. None of the interaction terms of ventricular size and sex was significant at α = 0.15. The circumference of the head at the age of 6 weeks was associated with distress to limitations (β = 0.06, 95% CI 0.00–0.12, p = 0.04); however, the measurement did not account for the association between ventricular size and infant temperament. Moreover, exclusion of children born prematurely (gestational age at birth < 37 wk, n = 40) did not change our results.

Internal consistencies for scores on the irritability and alertness scales were α = 0.75 for irritability and α = 0.64 for alertness. Figure 1 presents the adjusted mean scores on activity level, distress to limitations and sadness, per quartile of ventricular volume. Children with lower ventricular volumes scored on average 0.15 (95% CI 0.06–0.23, p = 0.001) points higher (23%) on activity levels compared with children with the highest ventricular volumes. The mean score on distress

Table 1: Characteristics of participants included in the analysis of association between cerebral ventricular volume and temperamental difficulties in infancy

Characteristic	Sex; median (95% CI)* Boys (n = 516)	Girls (n = 512)
Child		
Gestational duration, wk	40.3 (35.9–42.4)	40.1 (36.1–42.4)
Birth weight, g, mean (SD)	3567 (539)	3478 (540)
Apgar score 1 min after birth	9 (5–10)	9 (6–10)
Age at postnatal visit, wk	6.8 (4.4–12.3)	6.4 (4.4–12.0)
Head circumference at postnatal visit, mm, mean (SD)	390 (14.2)	383 (14.6)
Mother		
Age, yr, mean (SD)	31.6 (4.0)	32.0 (3.8)
Some higher education, %	63.8	66.1
Nulliparity, %	63.1	61.8
Mode of delivery, %		
Spontaneous vaginal	65.9	68.2
Instrumented vaginal	20.2	15.6
Cesarean section	13.9	16.2
Psychopathology, total score		
Midpregnancy	0.1 (0.0–0.8)	0.1 (0.0–0.7)
3 mo postpartum	0.1 (0.0–0.9)	0.1 (0.0–0.8)
Family functioning, according to mother, % pathological	2.7	4.5
Long-lasting difficulties, score	1.0 (0–8)	1.0 (0–9)
Self-esteem, score	4.53 (2.9–5.0)	4.53 (3.1–5.0)
Main determinants		
Width of the atrium in the lateral ventricle, mm, mean (SD)		
Midpregnancy	5.9 (1.1)	5.6 (1.2)
Late pregnancy	5.4 (1.8)	5.1 (1.7)
Ventricular volume, mL	0.84 (0.15–3.24)	0.76 (0.14–2.65)

CI = confidence interval; SD = standard deviation.
*Unless otherwise indicated.

Table 2: Associations between ventricular size and temperament at age 3 months observed in 912 infants*

Ventricular assessment (per unit of SD)	Irritability or anger, unsettled–irregularity (SD)† β (95% CI)§	p¶	R^2**	F††	Orienting, alertness–responsiveness (SD)†‡ β (95% CI)§	p¶	R^2**	F††
Prenatal								
Lateral ventricle in midpregnancy	–0.01 (–0.09 to 0.07)	0.8	0.29	5.0	–0.04 (–0.12 to 0.04)	0.3	0.22	2.7
Lateral ventricle in late pregnancy	–0.02 (–0.09 to 0.04)	0.5	0.30	9.4	0.03 (–0.03 to 0.10)	0.3	0.27	7.5
Postnatal								
Lateral ventricles at age 6 weeks‡‡	–0.08 (–0.16 to –0.00)	0.05	0.30	6.8	0.10 (0.01 to 0.18)	0.02	0.28	5.5

CI = confidence interval; SD = standard deviation.
*The number of infants varied per measurement of ventricular size: 504 in midpregnancy, 894 in late pregnancy and 580 at age 6 weeks.
†Higher scores on alertness–responsiveness indicated less difficult behaviour, whereas a higher score on unsettled–irregularity indicated more difficult behaviour..
‡We used square root transformation for scores on this scale to satisfy the assumption of linearity.
§Values are regression coefficients (and 95% CIs) from multivariable linear regression and reflect the difference in z-score per unit of standard deviation in the measurements of the atrial width in lateral ventricles or in the measurements postnatal ventricular volume associated with temperamental scores. Models are adjusted for age, sex, gestational duration, circumference of the head at the time of measurement, maternal age, maternal educational level and maternal psychopathology
¶P value of ventricular size.
**Coefficient of multiple determination. This coefficient applies to the complete model.
††F-statistic with 9 degrees of freedom in the numerator. Degrees of freedom in the denominator were 497, 882 and 570 for irritability or anger, and 498, 885 and 571 for orienting. These F-statistics and degrees of freedom apply to the complete models, including covariates.
‡‡We used log transformation for ventricular volumes to normalize the distribution.

Table 3: Associations between ventricular size and temperament at age 6 months in 745 infants*

Ventricular assessment of lateral ventricle (per unit of SD)	Irritability or anger												Behavioural inhibition											
	Distress to limitations†				Falling reactivity†				Activity level				Fear†				Sadness†				Duration of orienting			
	β (95% CI)‡	*p*§	R^2¶	F**	β (95% CI)‡	*p*§	R^2¶	F**	β (95% CI)‡	*p*§	R^2¶	F**	β (95% CI)‡	*p*§	R^2¶	F**	β (95% CI)‡	*p*§	R^2¶	F**	β (95% CI)‡	*p*§	R^2¶	F**
Prenatal																								
Midpregnancy	–0.03 (–0.12 to 0.06)	0.5	0.21	2.7	0.04 (–0.05 to 0.13)	0.4	0.15	1.3	–0.07 (–0.16 to 0.02)	0.1	0.28	4.8	0.04 (–0.05 to 0.13)	0.4	0.24	3.5	–0.05 (–0.14 to 0.04)	0.3	0.16	1.5	0.05 (–0.04 to 0.14)	0.3	0.21	2.5
Late pregnancy	–0.06 (–0.13 to 0.02)	0.1	0.21	3.6	–0.01 (–0.09 to 0.07)	0.8	0.13	1.3	–0.09 (–0.17 to 0.02)	0.02	0.30	7.6	–0.06 (–0.14 to 0.02)	0.1	0.24	4.7	–0.06 (–0.14 to 0.02)	0.1	0.17	2.3	0.06 (–0.01 to 0.14)	0.1	0.20	3.2
Postnatal																								
Age 6 weeks††	–0.14 (–0.24 to 0.05)	0.004	0.26	3.4	0.12 (0.01–0.22)	0.03	0.16	1.3	–0.18 (–0.27 to 0.08)	0.004	0.30	4.9	–0.07 (–0.17 to 0.03)	0.2	0.24	3.0	–0.05 (–0.15 to 0.05)	0.3	0.19	1.8	0.01 (–0.09 to 0.11)	0.8	0.17	1.4

CI = confidence interval; SD = standard deviation.
*The number of infants varied per measurement of ventricular size: 516 in midpregnancy, 716 in late pregnancy and 411 at the age of 6 weeks.
†Higher scores on falling reactivity indicatd less difficult behaviour, whereas higher scores on the other dimensions indicated more difficult behaviour. We used square root transformation for scores on this scale to satisfy the assumption of linearity.
‡ Values are regression coefficients (and 95% CIs) from multivariable linear regression and reflect the difference in z-score per unit of standard deviation in the measurements of the atrial width in lateral ventricles or in the measurements postnatal ventricular volume associated with temperamental scores. Models are adjusted for age, sex, gestational duration, head circumference at time of measurement ventricle, maternal age, maternal educational level and maternal psychopathology.
§*p* value of ventricular size.
¶Coefficient of multiple determination. This coefficient applies to the complete model.
**F–statistic with 9 degrees of freedom in the numerator. Degrees of freedom in the denominator were 505, 707 and 433 for distress to limitations, 497, 696 and 425 for falling reactivity and 504, 707 and 431 for activity level. For fear, the degrees of freedom in the denominator were 511, 711 and 436, for sadness 509, 708 and 436, and for duration of orienting 502, 705 and 431. These F–statistics and degrees of freedom apply to the complete models, including covariates.
††Ventricular volumes were log-transformed to normalize the distribution.

to limitations for children with the lowest ventricular volumes was 0.09 (95% CI 0.01–0.17, $p = 0.03$) points higher (17%) than the mean score of those with the highest ventricular volumes. The difference in scores on sadness between children in these quartiles was not statistically significant (0.05 points, 95% CI –0.03 to 0.12, $p = 0.21$).

Analyses of missing data showed that the birth weight of children for whom data on determinants or outcomes was not available was, on average, 119 g (95% CI 16 g–22 g) lower than the birth weights of children for whom data were available. The mothers of children for whom data were missing were 1.3 years (95% CI 0.5–2.1 yr) younger than those of children for whom data were available. In addition, 51.4% of the mothers of children for whom data were missing had completed some higher education compared with 64.9% of the mothers of children for whom data were available ($\chi^2_2 = 22.3$, $p < 0.001$). We found no differences between the 2 groups of children regarding median gestational duration or parental psychopathology. We found that ventricular sizes measured in midpregnancy, late pregnancy and postnatally at the age of 6 weeks did not differ between children for whom data on temperament were missing and those for whom data were available.

Discussion

We found an association between variation in brain morphology in fetuses and newborns and temperamental difficulties at ages 3 months and 6 months. Infants with a smaller cerebral ventricular system were more likely to have temperamental problems. Ventricular volume in infants was related to alertness at the age of 3 months. Furthermore, lower ventricular volume in infants was associated with more anger or irritability and higher activity levels at age 6 months. The size of the prenatal cerebral ventricular system was less strongly associated with infant temperament. Smaller ventricles in late pregnancy were related only to higher activity levels at age 6 months, and ventricular size in midpregnancy did not predict temperamental problems.

To our knowledge, our study was the first to attempt to relate brain morphology to behaviour within the normal population at such a young age. Early behavioural and emotional characteristics, or temperamental features, of very young children are thought to have a constitutional basis and form a relatively enduring makeup of the individual.[49] Temperamental traits have been frequently related to behaviour and psychopathology in childhood and later in life. Higher infant activity levels are related to outgoing activity and positive anticipation as well as impulsivity, anger or frustration and lower inhibitory control. Irritability and frustration in infancy predicted later externalizing negative affect[43] as well as oppositional and conduct problems.[29] Moreover, hostile and aggressive behaviour, anger and difficulties with inhibitory control are precursors of ADHD.[32] This suggests that the smaller ventricles observed among fetuses and infants in our study indicate a higher risk for developing externalizing psychopathology, including ADHD.

Most reports on ventricular volume and childhood psychiatric disorders described larger ventricles in patients with childhood-onset schizophrenia, autism, depression and eating disorders.[4] However, interpreting changes in ventricular volume in patient populations is complex, since studies involving children and adolescents with normal development reported robust increases of lateral ventricular volume with age.[20] The interpretation of this complexity would benefit from prospective studies in populations that are epidemiologically ascertained, which might help to identify the longitudinal trajectories of abnormalities in the brain that are related to illness.[21]

Our results indicated that lower ventricular volume in infancy may increase the risk of behavioural problems. This is consistent with the findings of Castellanos and colleagues,[10] who described a diminished age-related increase in lateral ventricular volume from ages 5–18 years in children with ADHD compared with children who did not have ADHD. Because knowledge on the maturation of the ventricular system is limited, we can only speculate about the underlying mechanism of the association between lower ventricular volumes and temperamental difficulties. It is possible that lower ventricular volumes are related to delayed or reduced apoptosis of overproduced neurons, which is one of the regressive phenomena that can occur during the development of the nervous system.[50,51] Another possible mechanism that explains the association between small ventricles and temperamental difficulties might be the reduced secretion of cerebrospinal fluid, which leads to a loss of the essential expanding pressure within the ventricular system that might determine brain morphology during its development.[52]

Small changes in brain development during prenatal and early postnatal life may be the consequence of several adverse environmental factors in utero. First, placental insufficiency may lead to chronic fetal hypoxia and to a shortage of other nutrients such as glucose and amino acids.[53] This not only leads to intrauterine growth restriction, but may also lead to altered brain structure and abnormalities in brain function.[54] Second, maternal smoking during pregnancy and maternal gestational stress have been shown to have direct negative effects on the developing brain.[55,56] These environmental factors have also been related to behavioural problems later in life.

Limitations

Although the effect sizes were small, the association between a lower ventricular volume and temperamental problems were consistent among children aged 3 months and 6 months. This association was pronounced for problems related to externalizing behaviour. However, several other methodologic considerations must be discussed.

First, selective participation of healthier, more highly educated and older mothers may have impeded the detection of modest associations. We had no indication that the size of the lateral ventricle was different in children of younger and less educated women. The selective attrition of mothers with prenatally and perinatally complicated pregnancies could have led to bias. Their children may have had larger lateral ventricles postnatally owing to white matter damage or intraventricular hemorrhage and, in consequence, more behavioural problems. Therefore, we should be cautious in generalizing our findings to clinical populations such as children born prematurely.

Second, the lower resolution of ultrasound compared with magnetic resonance imaging necessitated manual tracing of ventricles and precluded tracing of other regions of the brain. However, our methods of ventricular measurement were highly reproducible, as indicated by high intra- and interobserver reliability scores.

Third, our use of questionnaires for mothers to report their children's temperamental traits may have introduced reporter bias.[57] However, we assumed this type of misclassification was nondifferential, since mothers were blinded to their

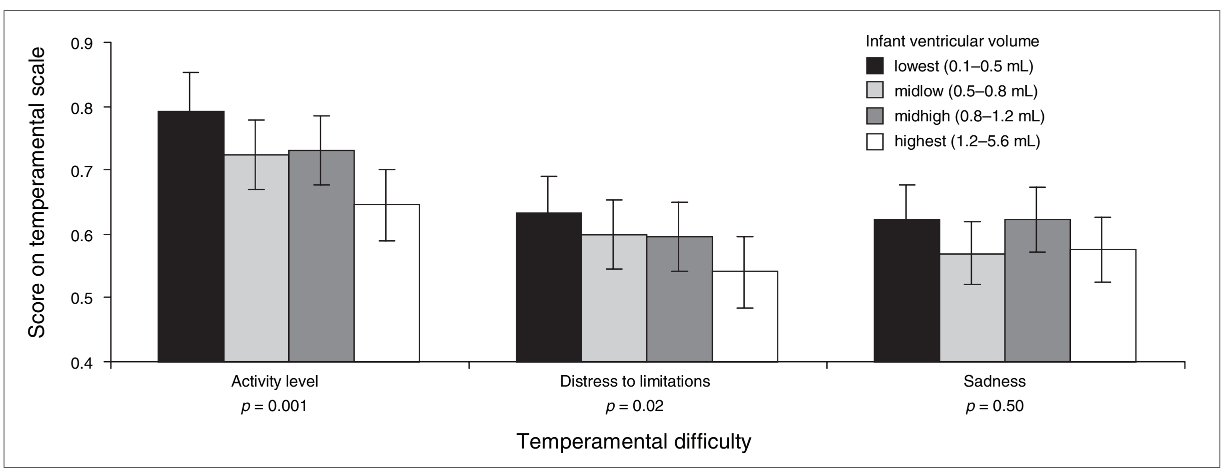

Fig. 1: Mean activity level, distress to limitations and sadness scores (on scales ranging from 0 to 2) associated with postnatal ventricular volume in 1028 infants. Values are estimated means and 95% confidence intervals, adjusted for age, sex, gestational duration, head circumference at the time of a 3-dimensional postnatal ultrasound, maternal age, maternal education level and maternal psychopathology.

infants' brain morphologies. Furthermore, we adjusted our associations for maternal psychopathology, which did not fully explain the associations between ventricular size and infant temperament. Although Seifer and colleagues[57] suggested that laboratory or home observations reliably and validly measured infant temperament and corresponded poorly with parent reports, maternal reporting of temperament took advantage of the primary caregiver's opportunity to observe her infant in different contexts.[27]

Fourth, the limited categories in our adapted version of the IBQ-R may have reduced the variation of temperamental scores. This would decrease our chance of detecting statistically significant effects.

Fifth, our study could not provide direct information on the developing trajectory of lateral ventricles throughout pregnancy and infancy because the 2-dimensional measurements of the atrium during pregnancy and the 3-dimensional measurement of the frontal horns and ventricular body after birth were not equivalent. We previously reported that a smaller size and a decreasing growth pattern of the width of the atrium in the lateral ventricle during pregnancy were predictive of lower ventricular volume in infancy.[39] However, our results suggest that postnatal measurement of ventricular size is superior to prenatal ventricle measurement in predicting infant temperament.

Finally, owing to the short time period between measurement of postnatal ventricular volume and assessment of temperamental outcome, inferences about cause and effect have to be made with caution.

Implications

Our study provides direct evidence that cerebral ventricular volume in infancy is related to temperamental difficulties. This suggests that the differences in brain morphology between children with and without specific psychiatric disorders could develop very early in life. Although it may be premature to speculate about clinical implications such as cranial ultrasound screening, our results suggested that it is worthwhile to follow up chance findings of very low ventricular volume in term infants, particularly when accompanied by maternal concerns about her child's temperamental difficulties. Future studies should address the development of brain structure from infancy onward in relation to emotional and behavioural problems in childhood and adolescence. Ideally, this should be investigated in large prospective studies involving the general population or patients at high risk for psychiatric disorders.

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