# Segmental Brain Volumes and Cognitive and Perceptual Correlates in 15-Year-Old Adolescents with Low Birth Weight

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**Objective** To determine whether preterm very low birth weight (VLBW) or term born small for gestational age (SGA) adolescents have reduced regional brain volumes. We also asked which perinatal factors are related to reduced brain volume in VLBW adolescents, which regional brain volumes are associated with cognitive and perceptual functioning, and if these differ between the groups.

**Study design** Fifty adolescent preterm VLBW (≤1500 g) births and 49 term SGA births (birth weight <10th percentile) were compared with 57 normal-weight term births. An automated MRI segmentation technique was used. Cognitive and perceptual functions were evaluated by WISC-III and Visual Motor Integration (VMI) tests.

**Results** The VLBW group had reduced volumes for thalamus and cerebellar white matter ($P < .002$). The SGA group had smaller total brains, and proportionally smaller regional brain volumes. Cerebellar white matter in the VLBW, hippocampus in the SGA, and cerebral cortical in the control group were volumes that significantly predicted cognitive and perceptual functions.

**Conclusions** We speculate that white matter injury may explain the impaired cognitive and perceptual functioning in the prematurely born, whereas hippocampal injury may be related to cognitive dysfunction in term SGA adolescents. *(J Pediatr 2009;155:848-53)*.

Being prematurely born and/or small for gestational age (SGA) are recognized risk factors for motor impairment as well as for cognitive and behavioral deficits later in life.[1,2] Although it has been difficult to ascertain any specific pattern of brain abnormalities as the underlying cause of individual impairment, a reduction in regional brain volume near term in the preterm infant is a predictor of later cognitive outcome.[3,4] Studies using an MRI scan suggest that abnormal cerebral findings in preterm infants persists into adolescence,[5] especially as it pertains to white matter injury.[6,7] Another group of infants believed to be susceptible to slight brain dysfunction are those born SGA at term.[8] In previous studies, we did not find an increased rate of structural brain abnormalities[9] or changes in white matter diffusion[10] in the same cohort of SGA adolescents as was included in the current study. Their cognitive and perceptual scores were inferior to those of the control group, so we investigated whether their function could be reflected in differences in regional brain volumes.

The first aim was to examine whether preterm VLBW and/or term SGA adolescents had reduced regional brain volumes when compared with the control group. Our hypothesis was that being born preterm affects specific regional brain volumes, whereas being born term at a low birth weight results in a smaller overall brain but with no reduction in specific regional brain volume. We further questioned whether brain development in prematurely born adolescents was related to known perinatal risk factors. Our third aim was to determine if a reduction in brain volume influences the association between brain volume and cognitive and perceptual function. We used an automated MRI segmentation technique specifically designed to classify the brain across many structures.[11] The brain volumes we were most interested in were cerebral cortical and white matter, hippocampus, amygdale, thalamus, and cerebellar cortical and white matter.

| | |
|---|---|
| ICV | Intracranial volume |
| IQ | Intelligence quotient |
| SGA | Small for gestational age |
| VLBW | Very low birth weight |
| VMI | Developmental test of visual-motor integration |

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Funding information available at www.jpeds.com (Appendix). A.M.D. and B.F. are funded by CorTechs Labs, Inc. A.M.D. has equity in CorTechs Labs, Inc. The other authors declare no conflicts of interest.

 10.1016/j.jpeds.2009.06.015

## Methods

In a follow-up study of 15-year-old children, we examined 2 groups with low birth weights, that is, prematurely born infants with very low birth weight (VLBW) and term SGA births. These groups were compared with a group of term normal-weight births. The VLBW children were admitted to the neonatal intensive care unit at the University Hospital in Trondheim (the referral hospital) from 1986 to 1988. The SGA and control group children were the second or third births to mothers living in the Trondheim area. They were enrolled before gestational week 20 in a multicenter study conducted between January 1986 and March 1988 and followed prospectively through pregnancy. Details of the study design and population have been previously published.[12]

VLBW was defined as birth weight ≤1500 g. Because of imaging artifacts from dental braces, the MRI results of 5 adolescents were excluded, leaving 50 VLBW adolescents (26 boys and 24 girls) for the morphometric brain analyses. Cerebral palsy was diagnosed in 6 of the 50 adolescents, that is, 5 cases of diplegia and 1 of hemiplegia, of whom all but 1 could walk. There were no major visual or hearing impairments in any of the adolescents who were examined using MRI.

SGA was defined as birth weight <10th percentile adjusted for gestational age, sex, and parity. Fifty SGA adolescents had MRI examinations. Because of imaging artifacts, 1 subject was excluded, leaving 49 MRI investigations (20 boys and 29 girls) for the morphometric analysis of the brain. Cerebral palsy (diplegia) was diagnosed in 1 SGA adolescent.

In the control group, 65 adolescents had MRI examinations. Because of imaging artifacts, 8 MRI scans were excluded, leaving 57 MRI investigations (22 boys and 35 girls) for the morphometric studies.

### Perinatal Factors in the VLBW Group

The perinatal factors investigated were intrauterine growth and the use of antenatal steroids, days on the ventilator, and days after birth used to regain the actual birth weight. Before delivery, 25 mothers in the VLBW group received steroids to enhance fetal lung maturation. To explore the influence of intrauterine growth on brain development, we calculated individual standard deviation scores ($Z$ scores) for birth weight. This score represents the departure from the mean weight for sex, gestational age, and singleton[13] or multiple births.[14] Twenty-six infants had mechanical ventilation, with a mean duration on the ventilator of 7 days. The VLBW neonates regained their birth weight after 3 to 39 days. Other perinatal risk factors such as premature rupture of the membrane and intraventricular hemorrhage were not investigated because there were too few infants with these characteristics (eg, 4 infants or fewer).

### MRI Studies

MRI studies were performed using a 1.5-T Siemens Symphony Sonata (Siemens AG, Erlangen, Germany). The imaging for the morphometric analysis was a 3D inversion recovery prepared at a fast low flip angle gradient echo sequence (MP-RAGE) with 128 sagittal partitions, 1.33-mm slice thickness, TR between inversion pulses of 2730 ms, TR/TE/flip angle/TI: 7.1 ms/3.45 ms/7°/1000 ms, an acquisition matrix of 256 × 192 × 128, square FOV of 256 mm, NEX 1, and an acquisition duration of 8.5 minutes.

We used the technique for the automated labeling of human brain structures as developed by Fischl et al.[11] The volume for total brain and white matter and a series of gray matter structures were obtained. This technique uses whole brain segmentation and the automated labeling of neuroanatomical structures, with the correction for the partial volume effect performed by estimating the percentage of each voxel occupied by each tissue class that borders it, based on image intensity and class means. The technique is based on a set of manually labeled brains as a training set to compute prior probabilities and class statistics. A sample of the segmentation is shown in the **Figure**.

### Clinical Tests

Total intelligence quotient (IQ) was estimated using 2 subtests of the Wechsler Intelligence Scales (WISC-III): Vocabulary and Block design tests.[15] To estimate verbal and performance IQ, we administered the Arithmetic and Vocabulary subtests and the Block design and Picture Arrangement subtests, respectively.[16]

The Developmental Test of Visual-Motor Integration comprises 27 geometric designs with an increasing order of difficulty that must be copied, matched (visual perception test; VMIv), and traced (motor coordination test; VMIm), respectively. Scores were given according to the manual,[17] and raw scores were used.

### Statistical Analysis

Descriptive analyses included bivariate plots, calculation of percentiles, and means and standard deviations. First, we studied the association of brain volume with the independent variables of interest. We used multivariate linear regression with the following 7 volumes as the dependent variables: cerebral cortical volume and white matter volume, hippocampal volume, amygdale volume, thalamus volume, cerebellar cortical volume, and white matter volume. The predictor variables were sex, age at scan, and study group (SGA, VLBW, or control group). We also studied the relationship of proportional volume with respect to sex, age, and study group. Thus, the proportional volume for each subject was calculated as the volume of a specific area, divided by the total intracranial volume. As shown in the results, analyses that compared study groups were controlled for sex and age at the time of the scan. Second, we sought to identify the strongest perinatal predictors of brain volume among VLBW births. To address this goal, we analyzed the VLBW group separately, used stepwise linear regression, and controlled for gestational age, sex, age at scan, and intracranial volume. We used $P$ values of .05 and .10 to enter or remove, respectively. In these analyses, we considered the amount of days on a ventilator, days used to regain birth weight, use of antenatal steroids, and the $Z$ score of birth weight as potential predictors. Finally, to identify the relationship between

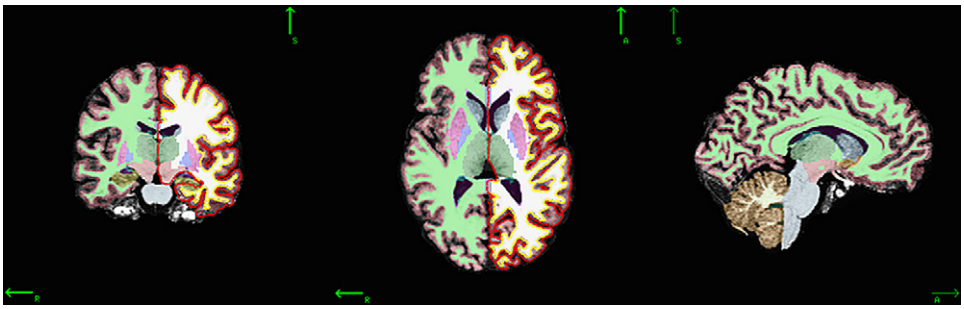

**Figure.** A sample of automated segmentation of brain volumes on one of the subjects. **Left and middle**, Segmentation and surface representation left side; **right**, segmentation.

cognitive and perceptual test scores and brain regions, we conducted separate analyses within subject groups using stepwise linear regression and again controlled for sex, age at scan, and intracranial volume. We used the same *P* values to enter and remove as in the above analyses. For all regression analyses, diagnostics included the investigation of potential colinearity, influential points, and normality and residual plots.

The regional committee for medical research ethics approved the study protocol, and written informed consent was obtained from the adolescents and their parents.

## Results

The VLBW subjects had significantly lower gestational age than the control subjects (Table I). Birth weight, *Z* score of birth weight, and head circumference were significantly reduced in the VLBW and SGA groups. The VLBW adolescents were approximately 4 to 5 months younger than the control adolescents when they were scanned.

The brain volume of the 3 study groups are presented in Table II (available at www.jpeds.com). The differences in brain structures were explored in relation to the total intracranial volume, with proportions of brain volume still associated with age. As a result, after making the correction for sex and group, the cerebral cortical volume was negatively associated ($F = 10.31$, $P < .01$) and the cerebral white matter positively associated ($F = 14.21$, $P < .001$) with age at scan. Further, girls had relatively larger hippocampus and cerebellum white matter than boys ($F = 15.04$, $P < 0.001$; $F = 12.46$, $P < 0.005$, respectively, when corrected for age and group). When adjusted for age at scan and sex, the VLBW group had smaller volumes for thalamus and cerebellar white matter in relation to total volumes than did the control group (thalamus: $P < .001$; cerebellar white matter: $P < .002$). For the SGA group, the average proportional volume for each cerebral region was similar to that found in the control groups, but in general the volumes were smaller.

Additional analyses were performed to determine whether certain perinatal factors predicted brain volumes in the VLBW adolescents. To start, we assessed the association between gestational age and brain structure using linear regression after controlling for sex and age at scan. The thalamus volume of the VLBW group was the only part of the brain significantly associated with gestational age ($P = .04$). Next, we assessed the potential association between brain volume and the antenatal administration of steroids, the *Z* score of birth weight, days needed to regain birth weight, and days on a ventilator. We controlled for gestational age, sex, and age at scan and found no significant association between antenatal steroids and brain volume. We did find an association between the number of days on the ventilator and the number of days used to regain birth weight; that is, 10 of the 11 individuals who took more than 3 weeks to regain their birth weight were on a ventilator. As a consequence, the number of days on the ventilator was not included in subsequent analyses. The *Z* score of birth weight was positively associated with the volumes of cerebral white matter ($P = .003$), thalamus ($P = .005$), and cerebellar cortical ($P = .02$) and white matter ($P = .002$). Moreover, the number of days needed to regain birth weight was negatively associated with cerebellar white matter volume. This was the difference in cerebellum white matter volume among those who took longer than 3 weeks to regain birth weight as compared with those who took less than 2 weeks ($P < .05$). After control for the additional effect of intracranial volume, no significant associations were found between the perinatal variables and regional brain volume.

The IQ scores were significantly lower in the VLBW group than in the control group: Total IQ was lower by approximately 11 points, verbal IQ by 11 points, and performance IQ by 20 points (Table III). The VMI, motor, and visual perception scores were also lower in the VLBW group than

**Table I. Group characteristics**

| | VLBW (n = 50) | SGA (n = 49) | Control (n = 57) |
|---|---|---|---|
| Sex (boys/girls) | 26/24 | 20/29 | 22/35 |
| Gestational age in weeks | 29.1 (2.7)* | 39.5 (1.1) | 39.6 (1.1) |
| Birth weight in grams | 1205 (233)* | 2915 (216)* | 3714 (486) |
| Z score of birth weight | -0.57 (1.44)* | -0.42 (0.30)* | 0.34 (0.96) |
| Head circumference at birth in cm | 27.1 (2.2)* | 33.8 (1.2)* | 35.4 (1.2) |
| MRI age in years | 15.2 (0.6)* | 15.6 (0.6) | 15.5 (0.5) |

Z score = (actual value−mean value)/SD, mean (SD).
*P < .01 compared with control group.

**Table III. Cognitive and perceptual scores: Mean (SD) and range**

| | VLBW (n = 50) | SGA (n = 49) | Control (n = 57) |
|---|---|---|---|
| IQ total | 87 (20) (48-126)* | 95 (15) (54-126) | 98 (15) (59-129) |
| IQ verbal | 82 (19) (42-117)* | 92 (17) (65-126) | 93 (16) (68-143) |
| IQ performance | 81 (28) (32-138)* | 95 (20) (44-135) | 101 (19) (52-130) |
| VMI | 20 (4) (10-26)* | 22 (3) (14-26) | 23 (3) (16-27) |
| VMIv | 23 (4) (13-27)* | 24 (3) (14-27) | 25 (3) (14-27) |
| VMIm | 21 (3) (14-27)* | 24 (2) (16-27) | 24 (2) (17-27) |

VMI, Visual-motor integration test; VMIv, visual perception test; VMIm, motor coordination test.
*$P < .05$ vs controls.

in the control group. No significant differences were observed between the SGA and control adolescents.

Each group was analyzed separately, with an adjustment for sex, age at scan, and total intracranial volume (Table IV). In the VLBW group, cerebellar white matter and hippocampus volumes predicted total and performance IQ. Cerebellar white matter volume predicted VMI scores and VMI visual perception test scores, whereas thalamus volume predicted VMI scores. In the SGA group, hippocampus volume predicted total and verbal IQ scores, whereas cerebral white matter and cerebral cortex volume predicted verbal IQ and VMI motor scores, respectively. In the control group, the cerebral cortical volume predicted all IQ measures. Hippocampus volume predicted both IQ and VMI scores, whereas thalamus volume predicted VMI visual perception scores.

**Table IV. Stepwise regression analyses: Results for functional outcomes, controlling for sex, age at scan, and total intracranial volume**

| Outcome | Volume (predictor) | Variances entered (No.) | Part R | *F* value | *P* value |
|---|---|---|---|---|---|
| VLBW | | | | | |
| IQ | | | | | |
| Step 1 | Cerebellar WM | 4 | 0.0588 | 5.03 | .0301 |
| Step 2 | Cerebellar WM | | | 7.24 | .0102 |
| | Hippocampus | 5 | 0.0492 | 4.56 | .0386 |
| IQ verbal | | | | | NS |
| IQ performance | | | | | |
| Step 1 | Hippocampus | 4 | 0.0900 | 7.25 | .0101 |
| Step 2 | Hippocampus | | | 11.66 | .0101 |
| | Cerebellar WM | 5 | 0.0906 | 8.59 | .0054 |
| VMI | | | | | |
| Step 1 | Cerebellar WM | 4 | 0.1435 | 8.62 | .0053 |
| Step 2 | Cerebellar WM | | | 9.26 | .0040 |
| | Thalamus | 5 | 0.0780 | 5.14 | .0286 |
| VMI v | | | | | NS |
| Step 1 | Cerebellar WM | 4 | 0.2076 | 13.65 | .0006 |
| VMI m | | | | | NS |
| SGA | | | | | |
| IQ | | | | | |
| Step 1 | Hippocampus | 4 | 0.1513 | 8.27 | .0062 |
| IQ verbal | | | | | |
| Step 1 | Cerebral WM | 4 | 0.1494 | 8.13 | .0066 |
| Step 2 | Cerebral WM | | | 7.92 | .0073 |
| | Hippocampus | 5 | 0.1066 | 6.53 | .0142 |
| | Cerebral WM | | | 7.92 | .0073 |
| IQ performance | | | | | NS |
| VMI | | | | | NS |
| VMI v | | | | | NS |
| VMI m | | | | | |
| Step 1 | Cerebral Cortex | 4 | 0.0637 | 4.24 | .0455 |
| Control | | | | | |
| IQ | | | | | |
| Step 1 | Cerebral Cortex | 4 | 0.0841 | 5.32 | .0251 |
| Step 2 | Cerebral cortex | | 0.0744 | 9.58 | .0032 |
| | Hippocampus | 5 | | 5.08 | .0286 |
| IQ verbal | | | | | |
| Step 1 | Cerebral Cortex | 4 | 0.1147 | 7.39 | .0089 |
| IQ performance | | | | | |
| Step 1 | Cerebral Cortex | 4 | 0.1099 | 7.30 | .00 |
| VMI | | | | | |
| Step 1 | Hippocampus | 4 | 0.0765 | 4.53 | 4.53 |
| VMI v | | | | | NS |
| VMI m | | | | | NS |
| Step 1 | Thalamus | 4 | 0.0764 | 4.49 | .0390 |

VMI, Developmental Test of Visual-Motor Integration; VMIv, visual perception test; VMIm, motor coordination test.

## Discussion

We found that low birth weight was associated with reduced brain volume in adolescents. Whereas prematurity was associated with a reduction in specific brain regions, term low birth weight was associated with a lower scaling of the brain. The age at scan was an important determining factor in regional brain volume, and our findings, which showed a decrease in cortical gray matter and an increase in white matter volume by age, are consistent with other reports.[18] The most common brain abnormality in premature infants is white matter injury, although this does not occur in isolation. Thus, in preterm infants a reduction in gray matter volume is reported in cortical gray matter[19] thalami and basal ganglia[20] as early as at term equivalent age. In these studies, the major predictors of volume reductions were white matter injury and gestational age at birth. Previous qualitative MRI studies of brain development of 6-year-old children in a subgroup of our adolescents indicated that a large proportion had periventricular leucomalacia.[21] Furthermore, the VLBW group in the current study had lower fractional anisotropy values on diffusion tensor imaging in widespread white matter tracts, possibly as a result of disorganization of fibers or axonal loss.[7] White matter injury impairs not only cerebral cortical development but also development of the remote cerebellum. Trophic interaction between the cerebrum and cerebellum is indicated by cerebellar growth failure with supratentorial white matter lesions.[22,23] Even though our adolescents had reduced thalamus and cerebellar white matter volume, they also tended to have reduced cerebral white matter volume. In preterm infants with white matter injury, neuropathological analyses reported the highest incidence of neuronal loss in the thalamus and, to a lesser extent, in the other gray matter regions.[24] Similar to the findings of preterm infants at term age,[20] we found a reduction in thalamus volume, and the lower the gestational age, the larger the reduction in volume. This volume reduction may be a consequence of an impaired interaction between the cerebrum and cerebellum but may also represent a primary thalamic injury. Neuronal loss in the thalamus and negative retrograde effects may therefore have contributed to impaired cerebellar growth. The question of why the more common neuronal

loss in the thalamus is related to the degree of immaturity and whether it is a primary or secondary injury is unclear. Our study suggests that the various volume reductions in premature infants as demonstrated at term equivalent age by others[20] persist into adolescence. However, because we have no neonatal imaging data, we were unable to identify the effect of primary destructive events and/or maturational disturbances on brain volume.

Several potentially adverse factors can influence brain development, including exogenous and endogenous insults such as ischemia, inflammation exitotoxcicity, free-radical attacks, and malnutrition. After control for the effect of intracranial volume, the association between growth (*Z* score of birth weight and days needed to regain birth weight) and regional brain volume in the preterm was no longer of significance to our study. It is possible, however, that such an influence would have been detected with larger numbers, and others have demonstrated the significant effect of nutrition on brain development.[25] In the growth-restricted preterm infant, a decrease in brain volumes and cerebral cortical[26] and hippocampus volumes was reported.[27] We found an association between the number of days on a ventilator and the number of days used to regain birth weight. The negative impact of poor weight gain on brain volume may be a marker of neonatal disease, as a reduction in brain volume has also been reported with prolonged oxygen requirements.[28]

Cognitive development is associated with the severity of white matter injury, which is the major mediator in altered cerebellar development in preterm infants.[29] A reduction in cerebellar white matter volume predicted impaired cognitive and perceptual functioning in our prematurely born infants. However, injury may damage both the cerebral and cerebellar white matter, and both regions may be co-markers of the insult. Therefore, studies to investigate the association between cerebellar white matter volume and cognitive outcome, with control for white matter injury in VLBW adolescents, is needed. Hippocampal volume was not reduced in the VLBW group. A previous report showed that only in premature infants who were exposed to white matter injury, to postnatal steroids, and to indomethacin treatment was the hippocampal volume reduced at term equivalent age.[4] This same study further reported a positive correlation between hippocampal volume and outcome for 2-year-old children. We also found an association between hippocampal volume and functional outcome but no reduction in hippocampal volume. We were unable to identify any adverse factors that were an influence on hippocampus volume. Again, it is possible that such an influence may have been detected in a larger study.

We found no reduction in hippocampus volume in the term SGA group. Animal studies have demonstrated that prenatal stress and fetal growth restriction result in fewer neurons in the hippocampus and cerebellum,[30] higher cortisol concentrations have been reported in growth restricted infants.[31] The vulnerability of the hippocampus may be more pronounced in early gestation, as premature intrauterine growth-restricted infants had a reduced hippocampus volume at term equivalent age, which in turn was associated with behavioral differences.[27] As a possible effect of growth restriction, our study has pointed out the importance of the hippocampus in predicting the cognitive outcome for term born adolescents.

According to previous studies, which reported that variations in intelligence are primarily caused by differences in gray matter volume,[32] the volume of gray matter, particularly cerebral cortical, and to a lesser degree thalamus and hippocampus volume, was associated with cognitive outcome in our control group. There are a number of brain characteristics other than volume that influence cognition and perception. Injury may damage both structure and functional processes but not necessarily in association with volume. Therefore, the associations we have reported between volume and functional outcome may only be co-markers of cerebral injury, although it was beyond the aim of our study to investigate whether significant perinatal factors could mediate the association between outcome and volumes.

This study was limited by the lack of information pertaining to regional brain volumes in the VLBW group. Our subjects did not undergo MRI examinations during their newborn period, and as a result the influence of white matter injury on regional brain structures could not be reported. We are also aware that SGA is a surrogate concept of intrauterine growth restriction. However, intrauterine growth is often inferred from size at birth, taking gestation into account. In our study, newborn infants with low birth weight who were not growth restricted may have been included, thus diluting any significant differences between the SGA and the control group.

We are aware that the correlation between brain regions and functions is not usually strong, and the differences in volume, although statistically significant, are still small. The rationale for not using multivariate analyses but instead to analyze each IQ volume separately was that there was already an a priori interest in some of these associations. We therefore performed separate stepwise analyses that were adjusted for sex, age at scan, and intracranial volume and found it inappropriate to adjust for multiple comparisons.

In summary, our study has demonstrated that premature birth has a deleterious effect on total brain size and on the increase of specific brain volumes, such as the thalamic and cerebellar white matter. The degree of immaturity appears to influence structural brain development in the prematurely born. No specific regional volume reduction was seen in the SGA term adolescents, although their total brain volume was smaller than in control subjects. We speculate that white matter injury may explain the impaired cognitive and perceptual functioning in the prematurely born, whereas hippocampal injury may be related to cognitive dysfunction in term SGA adolescents. ■

*We thank Cand Psychol Siri Kulseng of St Olavs University Hospital in Trondheim, Norway, for taking part in the clinical assessments of the adolescents.*

Submitted for publication Dec 15, 2008; last revision received May 5, 2009; accepted Jun 9, 2009.

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## Appendix

The study was supported by the Department of Laboratory Medicine, Children's and Women's Health, Faculty of Medicine, Norwegian University of Science and Technology, and by St Olavs University Hospital, Trondheim, Norway. The study was also supported by the US National Institutes of Health (NICHD contract No. 1-HD-4-2803 and No. 1-HD-1-3127; R01-NS39581, R01-RR16594, P41-RR14075, and R01-RR13609), the Mental Illness and Neuroscience Discovery (MIND) Institute, and in part by the Biomedical Informatics Research Network Project (BIRN, http://www.nbirn.net), which is funded by the National Center for Research Resources at the National Institutes of Health, USA (NCRR BIRN Morphometric Project BIRN002).

**Table II. Brain volumes in the 3 study groups**

| | VLBW (n = 50) | SGA (n = 49) | Control (n = 57) |
|---|---|---|---|
| Total intracranial volume | 1470 (163) | 1468 (129) | 1548 (118) |
| Cerebral cortical gray matter | 592 (70) | 587 (56) | 626 (56) |
| Cerebral white matter | 380 (64) | 389 (51) | 413 (43) |
| Hippocampus | 7.7 (0.9) | 8.0 (0.9) | 8.3 (0.8) |
| Amygdale | 3.3 (0.4) | 3.4 (0.4) | 3.5 (0.3) |
| Thalamus | 16 (2.3) | 17 (1.9) | 19 (1.5) |
| Cerebellar cortical gray matter | 118 (13) | 118 (12) | 124 (11) |
| Cerebellar white matter | 22 (3.6) | 23 (2.9) | 25 (3.0) |

Number of voxels ($cm^3$) – mean (SD) in each raw volume were measured.