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Relation of Neural Structure to Persistently Low Academic Achievement: A Longitudinal Study of Children with Differing Birth Weights

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Abstract

Objective—Children with very low birth weight (VLBW; <1500g) are at risk for academic underachievement, although less is known regarding the developmental course of these difficulties or their neural basis. This study examined whether cerebral tissue reductions related to VLBW are associated with poor patterns of growth in core academic skills.

Method—Children born <750 g, 750–1499 g or >2500 g completed measures of calculation, mathematical problem solving and word decoding at several time points spanning middle childhood and adolescence. Espy, Fang, Charak, Minich and Taylor (2009) used growth mixture modeling to identify two distinct growth trajectories (growth clusters) for each academic domain: an average achievement trajectory and a persistently low achievement trajectory. In this study, 97 of the same participants underwent MRI in late adolescence. MRI measures of cerebral tissue volume were used to predict the probability of low growth cluster membership for each domain.

Results—After adjusting for whole brain volume, each 1cm³ reduction in caudate volume was associated with a 1.7 – 2.1 fold increase in the odds of low cluster membership for each academic domain. Each 1mm² decrease in corpus callosum surface area increased these odds approximately 1.02 fold. Reductions in cerebellar white matter volume were associated specifically with low calculation and decoding growth while reduced cerebral white matter volume was associated with low calculation growth. Findings were similar when analyses were confined to the VLBW groups.

Conclusions—Volumetric reductions in neural regions involved in connectivity, executive attention and motor control may help to explain heterogeneous academic growth trajectories amongst children with VLBW.

Keywords

Very low birth weight; preterm; development; academic achievement; MRI

With advancements in neonatal intensive care, major forms of neural pathology, including cystic periventricular leukomalacia (PVL) and severe intraventricular hemorrhage (IVH), now are identified in fewer than 10% of infants born very preterm (<32 weeks gestation) and/or very low birth weight (VLBW; Hintz & O'Shae, 2008; Ment, Hirtz, & Huppi, 2009; Volpe, 2009c). However, magnetic resonance imaging (MRI) has revealed a more diffuse and subtle form of white matter abnormality extending into the deep cerebral white matter regions in over 50% of these infants by term equivalent age (Inder, Wells, Mogridge, Spencer, & Volpe, 2003; Stewart et al., 1999). A large proportion of neonates with VLBW also show reductions in cortical gyration and gray and white matter density, increased cerebrospinal fluid volume, and a thinning of the corpus callosum relative to infants born full term (Ajayi-Obe, Saeed, Cowan, Rutherford, & Edwards, 2000; Boardman et al., 2006; Inder, Warfield, Wang, Huppi, & Volpe, 2005; Inder et al., 2003). Sophisticated diffusion weighted tensor imaging methods have elaborated on these macrostructural findings, indicating reduced anisotropy of water diffusion in central white matter areas, suggestive of damage to commissural and association fibers (Counsell, Allsop, et al., 2003; Counsell, Rutherford, Cowan, & Edwards, 2003; Huppi et al., 2001; Mathur, Neil, & Inder, 2009). Additionally, neuropathological studies suggest gliosis, neuronal loss, and axonal degeneration in the subcortical and cerebellar regions (Volpe, 2009b, 2009c).

With maturation, normal patterns of white and gray matter development continue to be perturbed in a large proportion of VLBW survivors. Volumetric reductions in global neural tissue, cerebral white matter, and cerebral gray matter have been observed across childhood and adolescence (de Kieviet, Zoetebier, van Elburg, Vermeulen, & Oosterlaan, 2012; Gimenez et al., 2006; Nagy et al., 2003; Nosarti, Allin, Frangou, Rifkin, & Murray, 2005), with the corpus callosum, caudate, basal ganglia, thalamus, cerebellum, and temporal and parietal lobes being particularly vulnerable (Ball et al., 2012; Boardman & Dyet, 2007; Martinussen et al., 2009; Nagy et al., 2009; Peterson et al., 2000). Indeed, evidence suggests that the epigenesis of neural development may be fundamentally altered by adverse perinatal events associated with VLBW. Based on MR images obtained at ages 8 and 12 years, Ment et al. (2009) showed that normal age-related decreases in gray matter volume were less pronounced in children with VLBW relative to full-term peers, whereas typical developmental increases in white matter density were 3-fold lower in the VLBW group. Correspondingly, between late adolescence and young adulthood, Parker et al. (2008) found that the mean volume of the cerebellum decreased by 3% in participants born <33 weeks GA whereas it remained constant for full-term participants. Gray and white matter reductions appear to occur in a dose-dependent manner with decreasing birth weight and gestational age (Davis et al., 2011; Kapellou et al., 2006).

The implications of these neural abnormalities for outcome are as yet unclear, but they likely have substantive impact on long-term development. The spectrum of neurodevelopmental impairments associated with VLBW and its accompanying medical complications ranges from global cognitive impairment and cerebral palsy to behavior problems and relatively selective deficits in visuo-spatial skills and executive function (Anderson et al., 2003; Hack et al., 1994). These negative consequences are manifest across various environmental contexts, but their economic impact is particularly great in the educational arena (Petrou et al., 2006). Across international cohorts, 20–60% of children born VLBW require special education services and experience grade repetition (Hack et al., 1994; Klein, Hack, & Breslau, 1989; Rickards, Kelly, Doyle, & Callanan, 2001; Ross, Lipper, & Auld, 1991; van Baar, van Wassenae, Briet, Dekker, & Kok, 2005). Discrepancies on standardized mathematics and literacy tests are generally in the range of .5 to .75 *SDs* below children born full term and increase as a function of decreasing birth weight (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Breslau, Johnson, & Lucia, 2001;

Grunau, Whitfield, & Davis, 2002). Rates of specific learning difficulty, defined either by a low score cut-off criterion or a discrepancy between IQ and achievement, also are 2–3 fold higher among children with VLBW compared with normal birth weight controls (Litt, Taylor, Klein, & Hack, 2005; Pritchard et al., 2009). Difficulties in the area of mathematics are particularly common, even after controlling for general cognitive abilities (Klein et al., 1989; Litt et al., 2005; Pritchard et al., 2009; Taylor, Espy, & Anderson, 2009; Taylor, Klein, et al., 2011). However, academic difficulties are by no means characteristic of all individuals born VLBW. Substantial heterogeneity in developmental outcome and individual variation in development over time among children with VLBW make it difficult to target early interventions to those most in need.

Two major limitations of extant studies warrant attention. First, few studies of children with VLBW have assessed academic achievement repeatedly to capture change and stability over time (although see Saigal, Hoult, Streiner, Stoskopf, & Rosenbaum, 2000; Schneider, Wolke, Schlagmuller, & Meyer, 2004, as exceptions). Because cross-sectional designs are unable to distinguish transient academic delays from sustained achievement deficits, they are less able to identify the children who are least responsive to ongoing instruction. Repeated measures designs are in keeping with best practice in special education, which stresses the need for continued progress monitoring to determine whether children are making gains in response to typical instruction and more intensive interventions for those who do not show expected gains (Kauffman, Nelson, Simpson, & Mock, 2011). Second, researchers often employ variable-centered statistical approaches (Muthen & Shedden, 1999), which focus on individual or net correlations between specific perinatal variables and mean outcome scores. This approach to analysis constrains the statistical power to define mechanisms of influence, given tremendous variability in the medical experiences, risk factors contributing to VLBW, and socio-familial environments of children with VLBW.

To address these limitations, Espy, Fang, Charak, Minich and Taylor (2009) employed growth mixture modeling (GMM) to identify distinct clusters or groups of children with different growth trajectories for core academic skills. GMM extends on traditional growth curve modeling by relaxing the assumption that all participants show a similar pattern of growth. Instead, GMM empirically identifies the number of distinct patterns of growth present in the data set. Participants then are assigned probabilistically to identified growth trajectory clusters based on their individual patterns of growth. Thus, the starting point for analysis is the individual's unique developmental trajectory as opposed to a pre-defined risk group. GMM groups children with similar patterns of growth so that the researcher can then determine which background factors may drive these similarities. Thus, the technique is particularly relevant for examining groups of children with heterogeneous experiences and outcomes. In a sample of children with birth weights ranging from 440 to 4600g, Espy et al. (2009) identified two growth trajectory clusters for the domains of mathematical calculation, applied problem solving, and reading respectively: 1) *a typically-developing (average) cluster*, characterized by average academic achievement across time, a faster rate of acceleration and an earlier peak in skill development; and 2) *a poorly achieving (low) cluster*, characterized by a persistent lag in performance across all study time points and a later peak in achievement growth. The probability of being classified into the low achieving clusters for mathematical calculation and problem solving increased as a function of decreasing birth weight, while increasing days of ventilation in the neonatal period were associated with an increased probability of low achievement in all three achievement domains.

Although Espy et al.'s (2009) findings are of interest in helping to specify groups of children with distinct academic trajectories as well as the risk factors that increase children's likelihood of making poor academic progress, their study did not address the neural bases of

these growth patterns. Nosarti et al. (2008) suggested that the effects of VLBW and its accompanying medical risk factors are mediated in part by their direct impact on the developing brain and there is now encouraging evidence that MRI may have prognostic utility in predicting poor cognitive outcome within groups of children born VLBW. Qualitative and quantitative MRI measures obtained at term equivalent age correlate with general cognitive ability (Peterson et al., 2003; Woodward, Anderson, Austin, Howard, & Inder, 2006), as well as executive control and working memory through middle childhood (Beauchamp et al., 2008; Clark & Woodward, 2010; Edgin et al., 2008). Similarly, cross-sectional studies have revealed associations of volumes of the caudate, hippocampus, cerebellum, and thalamus with IQ, visuo-motor performance, language, and executive control (Abernethy, Cooke, & Foulder-Hughes, 2004; Allin et al., 2001; Gimenez et al., 2006; Isaacs et al., 2000; Nosarti et al., 2005; Taylor, Filipek, et al., 2011). In one study, white matter volume and corpus callosum area explained as much as 70% of the variance in IQ among adolescents born very preterm (Northam, Liegeois, Chong, Wyatt, & Baldeweg, 2011).

Notably, findings from the few studies that have examined associations between MRI-based measures of neural structure and academic achievement in VLBW cohorts have been mixed. For example, in an early MRI study, Stewart et al. (1999) reported no significant relations between qualitative ratings of white matter abnormality and concurrent reading achievement in adolescents born VLBW, despite the fact that 55% of the VLBW sample showed white matter abnormalities. Similar null findings were reported by Gaddlin et al. (2008), who also employed qualitative ratings of white matter abnormality. In contrast, using volumetric tissue segmentation, Allin et al. (2001) reported significant associations between children's cerebellar volumes and their reading scores. While differences in findings across the above studies potentially reflect different samples, analytic techniques, and regions of interest, they also highlight a clear need for further research to clarify whether volumetric reductions in specific subcortical and cortical areas may be of relevance for long-term development in different domains of academic achievement. The person-centered GMM approach may increase the power to detect such relations, by first grouping children with like trajectories of academic skill growth, and then relating the probability of cluster group membership to variation in neural structure.

The objective of this study was to examine relations between volumetric cerebral MRI measures taken during adolescence and Espy et al.'s (2009) previously-derived growth trajectory clusters for letter-word identification (decoding), calculation and mathematical problem solving. Although data on academic skill development pre-dated administration of MRIs in the sample, study of the relation of brain structure to academic growth trajectories is justified by the persistence of brain abnormalities through childhood and adolescence in children with VLBW (Ment et al., 2009b). The sample included children with <750 g birth weight, children with 750–1499 g birth weight VLBW, and term-born normal birth weight (NBW, >2500 g) controls. We hypothesized that volumetric reductions in central subcortical and cerebellar regions known to be particularly vulnerable in children born VLBW would increase the likelihood of low achieving growth trajectories and thus help to explain the significant relations of VLBW to poor academic growth.

Method

Participants

Participants were drawn from the original sample of 201 children described in Taylor et al. (Taylor, Klein, Minich, & Hack, 2000; Taylor, Minich, & Hack, 2004). The majority (93%) of surviving children born <750 g (extremely low birth weight; ELBW) and admitted to tertiary neonatal intensive care units between July 1, 1982 and December 31, 1986 in the

six-county region surrounding Cleveland, Ohio, were recruited for a longitudinal study. These children were individually matched for birth date (within 3 months), race and sex to a child born 750 g – 1499 g (VLBW) from the same hospital and a term-born normal birth weight (NBW, >2500 g) child from the same school. Participants completed developmental assessments through middle childhood. During late adolescence, a subset of the participants ($N = 108$) consented to cerebral MRI scanning. Of these, 97 (48% of original sample) had complete data, including all covariates necessary for the GMM analysis. There were no significant differences between children included in the current analyses and those who were not included in terms of sex, race, or IQ at study entry; or perinatal characteristics, including the proportion in each birth weight group, length of hospitalization, bronchopulmonary dysplasia (BPD), defined as oxygen dependence for 36 weeks corrected age, or severe abnormality on neonatal cranial ultrasound, defined as grade III/IV IVH, PVL, ventricular enlargement, or shunted hydrocephalus. However, the included sample were of higher socioeconomic status (SES), as measured by the Four-Factor Hollingshead Index, $t(199) = 1.98, p = .05$.

Table 1 describes the perinatal and social background characteristics of the 97 children for whom complete data were available. There were no significant differences among the birth weight groups in the distributions of sex, race, age at MRI scanning, or SES. However, mean IQ, prorated according to Sattler's method (Sattler, 1992) from the Vocabulary and Block Design Tests of the Wechsler Intelligence Scale for Children, 3rd Edition (Wechsler, 1991), was lower in the VLBW groups and, as expected, children in these groups were more likely to have experienced a variety of perinatal adversities.

Procedures and Measures

Assessment of academic achievement—All procedures for the study were approved by the University Hospitals Case Medical Center Institutional Review Board and written, informed consent was provided by legal guardians prior to participation. Children initially were assessed at early school age ($M = 7.0$, range 5.7 to 9.8 years). They returned for follow-up assessments at a mean of 4.3 years later ($M (SD) = 11.3 (1.4)$ years) and annually for four subsequent assessments (at M ages 12.3 (1.2), 13.24 (1.2), 14.2 (1.2) years and 16.8 (1.1)), although there was a wide age range at each follow-up due to the variability in age at initial assessment. Although sample retention varied across different phases of the study, there were no significant differences between the birth weight groups in age at each follow-up point (see Espy et al., 2009 and Taylor et al., 2004 for further details). At each follow-up assessment, children completed three subtests from the Woodcock-Johnson Test of Achievement - Revised (WJ-R; Woodcock & Johnson, 1989), with the resultant Rasch-derived w scores used in GMM analyses. *Calculation* is a paper-based measure of children's ability to solve written arithmetic problems. The problems are presented in order of increasing difficulty and the child is required to complete as many of them as possible. *Applied Problems* assesses children's ability to apply mathematical knowledge to every-day story-based problems. *Letter-Word Decoding* assesses the ability to read single words of increasing difficulty. The WJ-R was standardized on a geographically diverse sample. Chosen subtests have high internal reliability and correlate well with other measures of achievement, supporting their validity.

MRI Protocol—MRI images were acquired with a Siemens 1.5 T Vision MRI system. After T1-weighted fast low angle shot scout images had been obtained, a sagittal three-dimensional T1 weighted magnetization-prepared rapid gradient echo (MP-RAGE) sequence was acquired using the following parameters: TR/TE = 9.7/4.0 msec, flip angle = 12 degrees, FOV = 25 cm, matrix = 200×256 , slice thickness = contiguous 1.25 mm and NEX = 1, with an imaging time of about 9 minutes for the MP-RAGE.

The MRI images were processed on Sun Microsystems computer workstations by technicians who were masked to birth status. Morphometric analyses were performed according to an established protocol, entailing positional normalization along the axis of the anterior and posterior commissures, segmentation, and calculation of hemispheric regional volumes (Filipek et al., 1997; Taylor, Filipek, et al., 2011). Semi-automated segmentation was performed on coronal images in the Cardviews program (Caviness, Meyer, Makris, & Kennedy, 1996; Filipek, Richelme, Kennedy, & Caviness, 1994) using intensity contour mapping and differential intensity color algorithms. Each subcortical structure was segmented on a slice-by-slice basis using intensity information from the MPRAGE images and then subsequently labeled. For more global volumetric measures, data were segmented and labeled into gray matter, white matter, and cerebrospinal fluid tissue classes on a slice-by-slice basis. Total brain volume was partitioned into the cerebrum, ventricular system, cerebellum, and brainstem. The cerebrum was portioned further into neocortical gray matter, cerebral WM and subcortical gray matter. Subcortical structures of interest included the caudate, lenticular nucleus (putamen and pallidum), amygdala, hippocampus, and thalamus. Volumes were calculated by multiplying slice thickness by the number of voxels for each segmented/labeled structure or tissue class. Corpus callosum surface area was measured on a single midsagittal slice and thus independently of white matter volume. The error of this manual segmentation method is approximately 5% for large structures and 10% for structures $<60 \text{ mm}^3$ and results are reproducible (Filipek et al., 1997). Previous analyses revealed significant associations between birth weight group and brain structure, with the $<750 \text{ g}$ group showing mean reductions in volume across almost all neural regions (cerebral white matter, neocortical gray matter, cerebellar gray and white matter and corpus callosum surface area) and the $750\text{--}1500 \text{ g}$ group showing regionally specific reductions in neocortical gray matter and thalamus volumes and corpus callosum surface area relative to NBW children (Taylor, Filipek, et al., 2011).

Statistical Methods

Membership in the poor- or average-achieving clusters for each of the three academic domains (calculation, applied mathematical problem solving, and letter-word decoding) was determined by GMM on the full sample, as described in Espy et al (2009). Briefly, linear or quadratic growth curve models were fit for each academic domain under the assumption that all individuals were drawn from a single population with common growth parameters (i.e. a common growth intercept, slope, and acceleration for all children in the study). Then this assumption of a single population was relaxed and the number of clusters with distinct growth trajectories was determined by fixing or freeing growth parameters and examining resultant statistical fit indices, including Bayesian Information Criteria, entropy, and the bootstrap likelihood ratio test. Clusters were validated by examining relations to specific covariates (birth weight, neuropsychological test scores, and a summary socio-familial risk score). Finally, subjects were assigned to either the average or the poor latent growth clusters based on their posterior probabilities using multinomial logistic regression in GMM. In this study, logistic regression analyses were used to predict the probability of membership in the low relative to the average growth trajectory clusters for calculation, problem solving and decoding based on whole brain volume (wbv) and on the volumes of key cerebral structures after controlling for age at MRI scanning and sex. Relations between regional structures and low growth cluster membership were examined both with and without additional adjustment for wbv. All analyses were repeated with NBW children excluded to determine whether neural structure could explain variability in growth trajectories within the VLBW group.

Results

Relation of Birth Weight Groups to Achievement Cluster Membership

For the calculation domain, 0% of the NBW group, 12.5% of the VLBW group, and 55.9% of the ELBW group showed a low as opposed to an average growth trajectory, $\chi^2(2) = 31.31$, $p < .001$. Corresponding proportions were 9.7%, 21.9% and 47.1% for problem solving, $\chi^2(2) = 12.14$, $p = .002$, and 6.1%, 18.8% and 32.4% for decoding, $\chi^2(2) = 6.93$, $p = .031$. Over one quarter of the children with ELBW (29.4%) showed low achievement trajectories in all 3 achievement domains ($\chi^2(2) = 15.59$, $p < .05$), with Bonferroni-adjusted contrasts indicating that this proportion was significantly higher than in the NBW (0%) or VLBW (6.3%) groups. Notably, however, 65.6% of children with VLBW and 41.2% of children with ELBW showed average growth in every domain, highlighting the variability in achievement trajectories among children with VLBW.

Correlations between Perinatal Risk Factors and Regional Cerebral Volumes

Table 2 presents partial correlations between continuous birth weight and regional cerebral tissue volumes in the full sample after controlling for sex and age at MRI scanning, and both prior to and after adjustment for wbv. Robust linear associations were evident between decreasing birth weight and decreasing wbv in adolescence, as well as between decreasing birth weight and decreasing regional subcortical gray matter, amygdala, caudate, thalamus, and cerebellar white matter volumes after accounting for wbv (see Taylor, Filipek, et al., 2011 for similar findings). Additionally, decreasing birth weight was associated with an increase in the volume of the lateral ventricles and with reduced total surface area of the corpus callosum.

Similar relations were evident when specific medical risk factors were correlated with cerebral volumes within the VLBW groups. In particular, gestational age and days on ventilation were robustly correlated with total cerebral white matter and caudate volume as well as with corpus callosum surface area after accounting for sex, age at MRI and wbv. Severe neonatal ultrasound abnormalities were associated with reduced cerebral white matter volume and increased cerebral gray matter volume only after accounting for wbv. Unlike gestational age and days on ventilation, severe ultrasound abnormalities were not associated with reduced caudate volume or corpus callosum surface area. After additional control for all other clinical risk factors, gestational age continued to correlate with corpus callosum surface area ($r = .43$, $p = .001$); days on ventilation correlated with reduced cerebral white matter ($r = -.42$, $p = .002$) and increased cerebral gray matter ($r = .37$, $p = .006$); and severe neonatal cerebral ultrasound abnormalities correlated with increased lateral ventricle volume ($r = .36$, $p = .001$), and reduced cerebral ($r = .36$, $p = .017$), and cerebellar white matter ($r = -.33$, $p = .015$; see footnote to Table 2). Note that the clinical variables presented in Table 2 were selected on the basis of conceptual importance and/or because they were key predictors of academic growth cluster membership in Espy et al. (2009). Findings clearly highlight the relations between cerebral tissue volumes, decreasing birth weight and associated clinical risk.

Relations of Brain Volumes to Achievement Growth Cluster Membership

Table 3 shows the β values and odds ratios (*OR*) with associated confidence intervals, for membership in the low relative to the average calculation, applied problem solving, and decoding clusters as a function of decreasing cerebral tissue volumes. Results are shown after adjustment for sex and age at MRI scanning and both before and after accounting for wbv. In the calculation domain, a 1cm^3 decrease in wbv corresponded with a 1.01 fold increase in the odds of poor relative to average calculation growth, $p = .004$. After accounting for this association with wbv, a 1cm^3 decrease in caudate nucleus volume

increased the odds of being a member of the poor calculation cluster relative to the average growth cluster by a factor of 1.94 ($p = .010$) a 1cm^3 decrease in cerebellar white matter volume increased the odds by 1.17 ($p = .038$), and a 1cm^3 decrease in cerebral white matter volume increased the odds by 1.02, $p = .050$. Similarly, a 1mm^2 decrease in the surface area of the corpus callosum increased the odds of being in the poor calculation cluster by a factor of 1.02, $p < .001$, with this relation explaining as much as 20% of the variance in group membership after adjustment for wbv. Although decreasing subcortical gray matter ($p = .002$), amygdala ($p = .015$), hippocampus ($p = .010$), thalamus ($p = .012$) and cerebellar cortex ($p = .010$) volumes also were associated with an increasing probability of falling into the low growth cluster, these relations were attenuated after statistical adjustment for wbv. Conversely, decreasing neocortex volume decreased the likelihood of membership in the low calculation growth cluster, although only after accounting for wbv ($p = .036$), indicating an inverse relation between relative volume of the neocortex and progress in written computation.

In terms of applied mathematical problem solving, a 1cm^3 decrease in wbv increased the odds of falling into the poor relative to the average growth cluster by 1.01 ($p = .018$). Each 1cm^3 decrease in caudate volume doubled the odds of falling into the poor relative to the average growth cluster after accounting for wbv ($p = .002$). Reduced subcortical gray matter volume ($p = .021$) and corpus callosum surface area ($p = .015$) were also associated with increased odds of poor progress in problem solving after accounting for wbv. Reductions in cerebral white matter ($p = .022$), gray matter ($p = .043$), hippocampus ($p = .010$), thalamus ($p = .013$), and lenticular nucleus ($p = .030$) volumes were associated with membership in the low problem solving cluster only prior to adjustment for wbv.

For decoding, reduced wbv was associated with poor growth cluster membership ($p = .018$). Similarly, decreased caudate ($p = .034$) and cerebellar white matter ($p = .045$) volumes and reduced surface area of the corpus callosum ($p = .015$) corresponded with a greater likelihood of showing a poor growth trajectory, whereas decreasing cerebral gray matter ($p = .029$) and neocortex ($p = .018$) volumes decreased the likelihood of poor growth. All of these relations remained significant after adjustment for wbv. Reductions in cerebral white matter ($p = .005$), subcortical gray matter ($p = .011$), lenticular nucleus ($p = .036$), hippocampus ($p = .018$), and cerebellar cortex ($p = .020$) volumes were associated with membership in the low decoding cluster only prior to adjustment for wbv. Findings were similar when all of the above logistic regressions were repeated with SES included as a covariate.

Next, we examined the probability of showing a poor pattern of development in any of the 3 academic domains relative to average growth in all domains (1 = poor growth in at least one domain, 0 = average growth for all 3 domains) based on regional cerebral volumes. After accounting for age at MRI scanning, sex, and wbv, decreases in the volumes of the following regions were associated with a greater probability of poor development across any of the 3 achievement domains: subcortical gray matter, $OR = 1.15$ ($CI = 1.03 - 1.28$), $p = .010$; caudate, $OR = 2.02$ ($CI = 1.30 - 3.14$), $p = .002$, and hippocampus, $OR = 1.90$ ($CI = 1.14 - 3.17$), $p = .014$. Similarly, a 1mm^2 decrease in the surface area of the corpus callosum increased the probability of poor development across all domains by a factor of 1.01 ($CI = 1.00 - 1.01$), $p = .002$. Figures 1 and 2 illustrate the predicted probability of poor growth in at least 1 domain as a function of decreasing caudate volume and decreased corpus callosum surface area after accounting for sex, age at MRI and wbv.

Relations of Regional Brain Volumes to Achievement Growth Cluster Membership within the Sample of Children Born VLBW

Table 4 describes the associations between regional cerebral volumes and growth cluster membership when analyses were confined to the ELBW and VLBW groups. As shown, the associations were similar to those reported for the whole sample. After accounting for sex, age at MRI and wbv, decreases in cerebral white matter ($p = .015$), caudate ($p = .032$), and corpus callosum ($p = .001$) tissue increased the probability of low calculation growth 1.02 – 1.8 fold. Conversely, reduced neocortex volume relative to wbv reduced the odds of low calculation cluster membership ($p = .009$). For problem-solving, reduced caudate volume increased the probability of low growth ($p = .045$). Finally, reductions in cerebral white matter ($p = .041$), caudate ($p = .034$), and corpus callosum ($p = .023$) tissue increased the probability of low decoding growth, whereas reduced cerebral gray matter ($p = .018$) and neocortex ($p = .015$) volumes relative to wbv reduced the likelihood of poor decoding growth. Although many of these associations were attenuated after additional control for gestational age or days on ventilation, the association between reduced corpus callosum surface area and poor calculation growth remained significant.

Discussion

To our knowledge, this study is one of the first to demonstrate links between neural structure and specific longitudinal patterns of growth in academic skills in children with different birth weight groupings. A unique strength of the study is the use of sophisticated GMM analysis to isolate clusters of children who not only show low academic performance on one occasion, but whose learning trajectories across middle childhood deviate markedly from their peers. Espy et al. (2009) previously showed that the odds of following these atypical achievement trajectories increased in a dose-dependent manner with decreasing birth weight and increasing ventilation requirements. However, birth weight and ventilation are only proxy measures for the known neurological effects of VLBW and premature birth. The use of in vivo measures of neurological structure in the current study provides direct support for the importance of cerebral integrity in canalizing learning trajectories within this vulnerable population.

Several neural regions were related to children's achievement trajectories, particularly subcortical structures proximal to the periventricular regions that are vulnerable to insult in children with VLBW. The majority of these effects were attenuated after adjustment for wbv, suggesting that the general reduction in cortical volume reported in studies of VLBW samples may be partially responsible for poor academic achievement (de Kieviet et al., 2012). The association of decreased wbv with increased likelihood of poor academic progress in all domains in the present sample adds to this evidence. Nonetheless, adjustment for wbv highlighted associations of academic growth with relative volumes in specific regions of interest. Subcortical gray matter volumes were related to patterns of development in problem solving, while higher cerebellar white matter volume increased the probability of average calculation and reading trajectories. However, the strongest and most consistent associations were found for the caudate and corpus callosum, a 1cm^3 reduction in the volume of the caudate approximately doubling the odds of low achievement across all domains assessed and a 5mm^2 reduction in the surface area of the corpus callosum corresponding to a 5 fold increase in these odds, after accounting for wbv. Notably, caudate and cerebellar white matter volumes and corpus callosum surface area were also highly correlated with birth weight, gestation and other medical risk factors prevalent in the VLBW group, suggesting that the integrity of these neural regions helps to explain well-established relations between decreasing birth weight and poor academic performance. Moreover, relations between these structures and group membership were found within the group of VLBW sample even when excluding children with NBW. Therefore, variations in the

volume of these neural structures appear to be a principle mechanism contributing to heterogeneous developmental pathways within the population of children with VLBW.

In contrast to the positive relations noted above, higher volumes of the neocortex were associated with *lower* odds of falling into the average growth clusters for calculation and decoding, although only after controlling for wbv. Additionally, clinical risk factors such as days on ventilation and severe ultrasound abnormalities were correlated with increased neocortex volumes within the VLBW group after adjusting for wbv. Longitudinal MRI studies have shown that typical brain development entails a linear *decrease* in gray matter volume in the frontal, parietal and cortical regions relative to wbv, concomitant with gradual increases in white matter (Giedd et al., 1999; Sowell, Trauner, Gamst, & Jernigan, 2002). This evidence suggests that a higher ratio of cortical gray matter relative to wbv may in fact indicate atypical myelination or less maturity in cortical development, potentially explaining the inverse relation of neocortical gray matter reductions to low academic growth.

Findings are consistent with those from cross-sectional designs relating structural MR-based measures to outcome in children born VLBW. Volumetric measures of caudate structure previously have been associated with IQ and hyperactivity ratings in school-aged and adolescent cohorts born VLBW (Abernethy et al., 2004; Abernethy, Palaniappan, & Cooke, 2002; Nosarti et al., 2005). Interestingly, the caudate also has been implicated in ADHD, rates of which are approximately 3 times higher amongst children born VLBW than in the general population (Bhutta, Cleves, Casey, Craddock, & Anand, 2002; Qiu et al., 2009; Tripp & Wickens, 2009). Although the caudate has long been recognized to play a role in movement, newer evidence highlights its central role in learning and memory consolidation (Wickens, 2009). In particular, the caudate is involved in memory for habits and stimulus-response mapping, suggesting that it would be important in the acquisition of academic skills and in remembering which particular procedure to apply when completing an academic task. The caudate also appears to play a key role in executive control and spatial response learning, with lesions to this structure in animals producing behavioral impairments on go-no-go and delayed alternation-type tasks (Grahn, Parkinson, & Owen, 2009; White, 2009). Impairments on such executive tasks have been found in a number of VLBW samples across different ages (Anderson et al., 2003; Clark & Woodward, 2010; Espy et al., 2002; Mulder, Pitchford, Hagger, & Marlow, 2009; Taylor, Minich, Bangert, Filipek, & Hack, 2004). Given that executive control is also known to be an important predictor of academic achievement (Clark, Sheffield, Wiebe, & Espy, in press; Espy et al., 2004; Welsh, Nix, Blair, Bierman, & Nelson, 2010), it is not surprising that reduced caudate volumes would be an important contributor to poor academic achievement over time.

Similarly, the corpus callosum was implicated in all three of the academic domains tested in this study and remained a robust predictor of low calculation cluster membership within the VLBW group even after adjustment for gestational age and clinical risk factors. Thinning of the corpus callosum is a commonly reported finding in children with VLBW (Volpe, 2009a), as was replicated in this sample. Reduced corpus callosum area on structural MRI is likely a global marker for white matter integrity, which is known to be compromised by VLBW, possibly due to the vulnerability of developing oligodendroglia during the second and third trimesters of pregnancy (Dammann, Drescher, & Veelken, 2003; Ment, Hirtz, et al., 2009). Reductions in cerebral connectivity associated with white matter disruption are likely to slow processing and communication between neural regions, perhaps making it difficult for children to keep up with the barrage of information presented in a classroom context where academic skills are acquired. For instance, current theories of reading development stress the interhemispheric transfer of information for successful integration of the multiple cognitive skills demanded by reading, with MR studies indicating reduced corpus callosum areas and reduced fractional anisotropy (FA; restriction of water diffusion associated with axonal

tract development and myelination) in the corpus callosum amongst children with reading disabilities (Fine, Semrud-Clikeman, Keith, Stapleton, & Hynd, 2007; Odegard, Farris, Ring, McColl, & Black, 2009). Interestingly, these findings parallel DTI studies in children born VLBW, which also indicate reduced FA in the corpus callosum (Nagy et al., 2003; Skranes et al., 2007).

Cerebellar white matter volume was related to developmental trajectories in reading and calculation. The cerebellum has received recent attention as a particularly vulnerable structure in children born VLBW, this vulnerability appearing to stem from the rapid proliferation and migration of granule cells between 20 and 40 weeks GA (van Soelen et al., 2010; Volpe, 2009b). Independent of overt cerebellar hemorrhage and infarction, there is increasing evidence for trophic effects on the cerebellum associated with injury or disruption to central white matter regions, which likely affect the connectivity of cerebellar-parietal and cerebellar-prefrontal feedback loops (Limperopoulos et al., 2007; Shah, Anderson, & Carlin, 2006; Volpe, 2009b). In the current study, for instance, severe neonatal cerebral ultrasound abnormalities were associated with reduced cerebellar white matter volume, perhaps indicating that injury to periventricular white matter regions in infancy may have ongoing implications for cerebellar development. Notably, the cerebellum receives input from the prefrontal cortex via the basal ganglia and tends to be activated during executive inhibitory control tasks (Lawrence et al., 2009; Rubia et al., 2006). Combined with results suggesting that the caudate is an important predictor of academic achievement, findings suggest that alterations to fundamental cerebellar-striatal-prefrontal circuits involved in executive and motor control may contribute to long-term difficulties across different academic domains, as defined by the poor trajectory clusters. Previously published findings from this cohort also showed that cerebellar and caudate volumes, as well as corpus callosum surface area, were correlated with concurrent measures of memory, IQ, perceptual-motor organization and executive control after accounting for wbv (Taylor, Filipek, et al., 2011). Therefore, these regions appear to be implicated in several neuropsychological skills that broadly support learning.

In keeping with the fact that some neural regions (i.e. the caudate and corpus callosum) were related to trajectory cluster membership across all domains, over half of the children (56%) who fell into a low achievement trajectory cluster for one academic domain also showed poor growth in another domain. The diffuse neural abnormalities observed in many children with VLBW may account for effects on multiple academic abilities. For instance, reductions in the surface area of the corpus callosum and in the integrity of white matter in this region may be a marker for global learning difficulties. Reduced connectivity associated with this white matter reduction is likely to decrease connectivity between neural regions and slow information processing, with cascading effects for learning in multiple domains.

Given that MRIs were administered in late adolescence, it is not possible to determine whether neural reductions associated with decreasing birth weight preceded or were coincident with poor academic progress. It is possible that poor learning through childhood either precipitated or contributed to neural differences in adolescence. However, because brain abnormalities in children with VLBW are evident at birth and persist throughout childhood and adolescence (de Kieviet et al., 2012), the abnormalities observed in this sample likely were present during the period over which growth in academic skills was assessed. It should also be acknowledged that the sample in this study represented a subset of the original sample and that participants in this MRI sample were of higher SES than those who could not be located or who declined, potentially limiting the generalizability of findings. Nonetheless, in the previous study by Espy et al. (2009), which included the majority of the sample, there was no evidence that environmental or learning opportunities contributed to growth cluster membership. Finally, the longitudinal nature of the study

inevitably means that the clinical experiences of the participants will differ from those of VLBW children currently receiving neonatal intensive care. For instance, rates of ultrasound abnormality and SGA are higher than those reported in more recent studies. While this does confer the advantage of being able to examine outcomes for these more rare clinical risk factors, it will be important to determine whether findings can be extrapolated to more recently born children who may have benefited from advances in neonatal intensive care over the past two decades.

Findings highlight an urgent need for health campaigns and perinatal interventions to reduce the deleterious neurological impacts associated with VLBW/very preterm birth. NICU-based interventions show some promise, although tests of these interventions generally have been confined to 'low risk' samples (Als et al., 2004; McAnulty et al., 2009). Indeed, a meta-analysis indicates limited effectiveness of interventions developed for children with VLBW thus far (Orton, Spittle, Doyle, Anderson, & Boyd, 2009). Although the possibility of facilitating progress in these children by means of special education interventions remains untested, concrete mnemonic supports may help to reduce cognitive load and free working memory resources for learning in children with VLBW. Initial growth curve findings from Espy et al. (2009) showed that children in the poor academic clusters showed large discrepancies in performance even at the earliest follow up ages. These findings make it clear that children who are most at risk can be identified and targeted early in their school careers so that discrepancies are less likely to compound over time. Unfortunately, current research also suggests that a large number of VLBW children who exhibit early deficits in achievement are not receiving special education services that are designed to facilitate academic skill development (Taylor, Klein, et al., 2011). The implications of these poor growth trajectories for adult quality of life remain to be determined. Nonetheless, this paper clearly demonstrates the relevance of individual differences in brain structure for understanding heterogeneous academic pathways in children born VLBW.

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Figure 1. Probability of Membership in Low Growth Cluster for Any Academic Domain as a Function of Decreasing Caudate Volume in Late Adolescence (Corrected for Sex, Age at MRI and Whole Brain Volume).

Figure 2. Probability of Membership in Low Growth Cluster for Any Academic Domain as a Function of Decreased Corpus Callosum Surface Area in Late Adolescence (Corrected for Sex, Age at MRI and Whole Brain Volume)

Table 1
Socio-Demographic and Neonatal Characteristics of Participants Born ELBW, VLBW and NBW

<i>N</i>	<i>NBW M(n(SD))%</i>			<i>VLBW M(n(SD))%</i>			<i>ELBW M(n(SD))%</i>			<i>F/t/χ² (df)</i>		<i>p</i>
	31			32			34					
Age at study entry (years) ^a	7.92 (2.03)			7.07 (.91)			6.98 (1.07)			4.35 (2,94)		.02
Age at MRI (years)	16.95 (1.03)			16.76 (1.09)			16.89 (1.30)			.24 (2,94)		.79
Male sex	14 (45.2)			10 (31.3)			14 (41.2)			1.37 (2)		.51
Multiple Birth	0 (0)			6 (18.8)			6 (17.6)			6.51 (2)		.04
Race												
Black	14 (45.16)			19 (59.40)			21 (61.76)					
White	17 (54.84)			13 (40.6)			13 (38.24)			2.08 (2) ^b		.35
SES (at study entry) ^c	.11 (1.02)			.12 (1.14)			.04 (.91)			.06 (2,94)		.95
Primary caregiver education < high school	2 (6.5)			7 (21.9)			1 (2.9)			7.13 (2)		.03
IQ (at study entry) ^d	101.96 (14.70)			94.51 (14.53)			85.70 (15.92)			9.48 (2,94)		<.001
Birth weight (grams)	3445.61 (531.31)			1146.56 (223.54)			661.32 (76.70)			684.64 (2,94)		<.001
Gestational age (weeks)	>36			29.31 (2.29)			25.91 (1.64)			48.49 (1,64)		<.001
Length of hospitalization (days)	-			57.72 (42.48)			136.79 (84.42)			22.66 (1,64)		<.001
Days on ventilation	-			8.25 (17.37)			48.97 (53.41)			20.59 (2,94)		<.001
Apnea of prematurity	-			24 (75.0)			32 (94.1)			4.69 (1)		.03
Bronchopulmonary dysplasia (BPD) ^e	-			1 (3.1)			13 (38.2)			12.16 (1)		<.001
Hyperbilirunemia ^f	-			11 (34.4)			14 (42.4)			.45 (1)		.51
Septicemia	-			7 (21.9)			16 (47.1)			4.61 (1)		.03
Necrotizing Enterocolitis (NEC)	-			3 (9.4)			2 (5.9)			.29 (1)		.59
Small for gestational age (SGA) ^g	-			5 (15.6)			21 (61.8)			14.7 (1)		<.001
Ultrasound Abnormalities												
Mild abnormality ^h	-			4 (14.29)			8 (23.53)					
Severe abnormality ⁱ	-			6 (21.43)			11 (32.35)			2.52 (2)		.28

Note.

^a 6 additional children with NBW were recruited as matches for VLBW/ELBW children at the second follow up point; hence the greater variability in age at initial assessment for the NBW group.

^b Overall Chi-Squared Value for Group x Race.

^c SES: Hollingshead maternal education and occupational status z score.

^d BPD: oxygen dependence for >36 weeks.

^e IQ was prorated from the Vocabulary and Block Design subtests of the Wechsler Intelligence Scale for Children, 3rd Ed. (WISC-III, Wechsler, 1991) as described by Sattler (1992).

^f Hyperbilirubinaemia: maximal indirect serum bilirubin > 10mg/dL (171m/L).

^g SGA defined as <-2SD below mean for gestational age (Usher & McClean, 1969).

^h Grade I/II intraventricular hemorrhage.

ⁱ Grade III/IV Intraventricular hemorrhage, ventricular dilation or shunted hydrocephalus (periventricular leukomalacia, although also used to identify severe abnormality, was not documented for any of these children). Five children, two of whom showed severe cerebral ultrasound abnormalities as neonates, had neurosensory impairments, including 4 from the <750 g group (1 mild CP, 3 hearing loss) and 1 from 750–1499g group (visual impairment).

Table 2

Partial Correlations Between Birth Weight, Perinatal Risk Factors and Regional Cerebral Tissue Volumes Measured in Late Adolescence

	Birth Weight (Grams) ^a	Gestational Age ^b	Days on Ventilation ^b	Small for Gestational Age Status ^b	Septicemia ^b	Severe neonatal cerebral ultrasound abnormalities ^b
Cerebral white matter	.28**	.15 [†]	-.25*** ^{†††d}	-.17	-.18	-.16 ^{†††f}
Cerebral gray matter	.40***	-.10	.11 ^{††d}	-.30*	-.12 ^e	.17 [†]
Neocortex	.38***	-.13	.13 ^{††d}	-.29*	-.11 ^e	.18 [†]
Subcortical gray matter	.46*** ^{†††}	.18	-.15	-.25*	-.24	.03
Lateral ventricle	-.27*** ^{††}	-.16	.20	-.22	.20	.41*** ^{†††f}
Amygdala	.43*** ^{†††}	.10	.05	-.18	-.15	.16
Caudate	.46*** ^{†††}	.30*** ^{†††}	-.29*** ^{††}	-.41*** [†]	-.26*	-.12
Hippocampus	.24*	.14	-.23*	-.22	-.26*	-.03
Thalamus	.43*** ^{†††}	.11	-.04	-.07	-.20	-.06
Lentiform nucleus	.25*	.08	-.12	-.23	-.08	.25 ^{††f}
Corpus callosum (area)	.59*** ^{††††}	.53*** ^{†††††c}	-.39*** ^{†††}	-.29*	-.15	-.16
Cerebellar white matter	.37*** [†]	.26*	-.22	-.07	-.13	-.32*** ^{†††f}
Cerebellar cortex	.30**	.11	-.13	-.02	-.05	-.17
Whole brain volume	.38***	.01	-.05	-.28	-.13	.05

Note:

^a $n = 97$;

^b $n = 66$ (VLBW children only).

* $p < .05$,

** $p < .01$

*** $p < .001$ after adjustment for sex and age at MRI;

[†] $p < .05$,

^{††} $p < .01$,

^{†††} $p < .001$ after adjustment for sex, age at MRI and whole brain volume;

- ^c $p < .05$ after adjustment for sex, age at MRI, wbv, days on ventilation, SGA, septicemia and severe ultrasound abnormalities;
- ^d $p < .05$ after adjustment for sex, age at MRI, wbv, gestational age, SGA, septicemia and severe ultrasound abnormalities;
- ^e $p < .05$ after adjustment for sex, age at MRI, wbv, gestational age, days on ventilation, SGA, and severe ultrasound abnormalities;
- ^f $p < .05$ after adjustment for sex, age at MRI, wbv, gestational age, days on ventilation, SGA, and septicemia.

Table 3

Probability of Membership in Average Academic Growth Trajectory Clusters for Calculation, Problem Solving and Decoding as a Function of Regional Cerebral Volumes in Late Adolescence

Cerebral Region	Adjusted for Age at MRI and Sex			Adjusted for Age at MRI, Sex and Whole Brain Volume				
	b^a	SE	OR (95% CI)	b	SE	OR (95% CI)	$R^2 \Delta^{(3)}$	
	Calculation Domain							
Cerebral White Matter	.017**	.005	1.017 (1.007 – 1.027)	.017*	.009	1.018 (1.000 – 1.035)	.04	
Cerebral Gray Matter	.006	.003	1.006 (.999 – 1.013)	–.015	3.413	.985 (.970 – 1.001)	.03	
Neocortex	.006	.004	1.006 (.999 – 1.013)	–.017*	.008	.983 (.968 – .999)	.04	
Subcortical Gray Matter	.132**	.042	1.141 (1.051 – 1.238)	.101	.057	1.106 (.989 – 1.237)	.03	
Lateral ventricle	–.019	.013	.981 (.956 – 1.007)	–.024	.014	.977 (.951 – 1.003)	.03	
Amygdala	.857*	.353	2.355 (1.178 – 4.709)	.479	.401	1.614 (.735 – 3.544)	.01	
Caudate Nucleus	.761***	.216	2.140 (1.402 – 3.268)	.660*	.258	1.935 (1.168 – 3.205)	.07	
Hippocampus	.594*	.229	1.810 (1.156 – 2.835)	.312	.270	1.366 (.805 – 2.318)	.01	
Thalamus	.224*	.089	1.251 (1.051 – 1.488)	.112	.110	1.118 (.902 – 1.387)	<.01	
Lenticular Nucleus	.262	.135	1.299 (.997 – 1.692)	.059	.160	1.061 (.775 – 1.453)	<.01	
Corpus Callosum (area)	.019***	.004	1.019 (1.010 – 1.028)	.018***	.005	1.018 (1.009 – 1.027)	.20	
Cerebellar White Matter	.203**	.068	1.225 (1.073 – 1.400)	.154*	.074	1.166 (1.008 – 1.348)	.04	
Cerebellar Cortex	.050*	.019	1.051 (1.012 – 1.092)	.032	.020	1.033 (.992 – 1.074)	.03	
Whole Brain Volume	.006**	.002	1.006 (1.002 – 1.010)					
			Problem-Solving Domain					
Cerebral White Matter	.010*	.004	1.010 (1.001 – 1.018)	.004	.008	1.004 (.988 – 1.019)	<.01	
Cerebral Gray Matter	.007*	.003	1.007 (1.000 – 1.013)	–.001	.029	.999 (.985 – 1.013)	<.01	
Neocortex	.007	.004	1.007 (1.000 – 1.014)	–.004	.007	.996 (0.983 – 1.010)	<.01	
Subcortical Gray Matter	.124**	.040	1.133 (1.048 – 1.224)	.129*	.056	1.138 (1.020 – 1.269)	.05	
Lateral ventricle	.003	.014	1.003 (.976 – 1.031)	.001	.014	1.001 (.974 – 1.030)	<.01	
Amygdala	.463	.300	1.589 (.883 – 2.861)	.129	.349	1.138 (.574 – 2.255)	<.01	
Caudate Nucleus	.756***	.207	2.131 (1.419 – 3.200)	.793**	.257	2.211(1.336 – 3.66)	.11	
Hippocampus	.555*	.215	1.742 (1.143 – 2.656)	.395	.256	1.485 (.899 – 2.452)	.02	

Cerebral Region	Adjusted for Age at MRI and Sex			Adjusted for Age at MRI, Sex and Whole Brain Volume		
	b^a	SE	OR (95% CI)	b	SE	OR (95% CI) $R^2 \Delta^{(3)}$
Thalamus	.210*	.084	1.234 (1.046 – 1.455)	.149	.104	1.161 (.946 – 1.424) .02
Lenticular Nucleus	.282*	.130	1.325 (1.027 – 1.709)	.162	.151	1.176 (.875 – 1.583) .01
Corpus Callosum (area)	.008**	.003	1.008 (1.003 – 1.013)	.007**	.003	1.007 (1.001 – 1.013) .06
Cerebellar White Matter	.094	.053	1.098 (.990 – 1.218)	.040	.062	1.041 (.922 – 1.174) <.01
Cerebellar Cortex	.009	.013	1.009 (.984 – 1.035)	-.012	.016	.988 (.956 – 1.020) <.01
Whole brain volume	.005*	.002	1.005 (1.001 – 1.008)			
Decoding Domain						
Cerebral White Matter	.014**	.005	1.014 (1.004 – 1.024)	.015	.009	1.015 (.997 – 1.034) .03
Cerebral Gray Matter	.004	.004	1.004 (.997 – 1.011)	-.018*	4.766	.982 (.966 – .998) .05
Neocortex	.004	.004	1.004 (.996 – 1.011)	-.020*	.008	.980 (.964 – .997) .06
Subcortical Gray Matter	.102*	.040	1.108 (1.024 – 1.199)	.076	.058	1.079 (.962 – 1.21) .02
Lateral ventricle	-.006	.013	.994 (.968 – 1.020)	-.009	.014	.991 (.965 – 1.018) <.01
Amygdala	.623	.345	1.864 (.948 – 3.666)	.286	.397	1.331 (.611 – 2.896) <.01
Caudate Nucleus	.614**	.207	1.848 (1.232 – 2.773)	.548*	.259	1.731 (1.042 – 2.875) .05
Hippocampus	.555*	.235	1.742 (1.099 – 2.761)	.354	.283	1.425 (.818 – 2.484) .02
Thalamus	.133	.086	1.142 (.965 – 1.351)	.000	.113	1.000 (.801 – 1.249) <.01
Lenticular Nucleus	.299*	.142	1.348 (1.020 – 1.781)	.159	.168	1.173 (.843 – 1.631) <.01
Corpus Callosum (area)	.009**	.003	1.009 (1.003 – 1.015)	.008*	.003	1.008 (1.002 – 1.014) .06
Cerebellar White Matter	.176**	.064	1.193 (1.053 – 1.352)	.144*	.072	1.154 (1.003 – 1.328) .04
Cerebellar Cortex	.040*	.017	1.041 (1.006 – 1.076)	.029	.019	1.029 (.992 – 1.067) .03
Whole brain volume	.005*	.002	1.005 (1.001 – 1.009)			

Note.

* $p < .05$,

** $p < .01$,

*** $p < .001$;

^aThe average achieving class is the reference class, where a positive sign of b indicates that a 1 unit decrease in the volume of the cerebral structure is associated with a b unit increase in the log-odds of falling into the low achieving class;

² OR = Odds Ratio; CI = Confidence Interval;

³Change in Cox and Snell R^2 when cerebral tissue volume is entered into model including sex, age at MRI and wbv.

Table 4

Probability of Membership in Average Academic Growth Trajectory Clusters for Calculation, Problem Solving and Decoding as a Function of Regional Cerebral Volumes in Children with Very Low Birth Weight

Cerebral Region	Adjusted for Age at MRI and Sex			Adjusted for Age at MRI, Sex and Whole Brain Volume		
	<i>b^a</i>	<i>SE</i>	<i>OR (95% CI)</i>	<i>b</i>	<i>SE</i>	<i>OR (95% CI)</i>
Calculation Domain						
Cerebral White Matter	.015 ^{**} <i>b, c, d, e, f</i>	.005	1.015 (1.005 – 1.026)	.026 ^{*d, e, f}	.011	1.026 (1.005 – 1.048)
Cerebral Gray Matter	.002	.004	1.002 (.995 – 1.010)	-.025 ^{*b, c, e, f}	6.325	.976 (.957 – .995)
Neocortex	.002	.004	1.002 (.994 – 1.010)	-.026 ^{**b, c, e, f}	.010	.975 (.956 – .994)
Subcortical Gray Matter	.094 [*]	.045	1.098 (1.006 – 1.198)	.064	.064	1.066 (.941 – 1.208)
Lateral ventricle	-.007	.013	.993 (.969 – 1.019)	-.012	.013	.988 (.963 – 1.014)
Amygdala	.452	.363	1.571 (.772 – 3.199)	.171	.403	1.186 (0.539 – 2.612)
Caudate Nucleus	.624 ^{**} <i>b, c, d, e, f</i>	.228	1.867 (1.195 – 2.917)	.572 [*]	.266	1.772 (1.051 – 2.986)
Hippocampus	.414	.240	1.513 (.945 – 2.422)	.214	.282	1.238 (0.713 – 2.152)
Thalamus	.133	.098	1.142 (.943 – 1.383)	.011	.127	1.011 (.787 – 1.298)
Lenticular Nucleus	.212	.151	1.236 (.919 – 1.662)	.056	.181	1.058 (.741 – 1.51)
Corpus Callosum (area)	.016 ^{***} <i>b, c, d, e, f</i>	.005	1.016 (1.007 – 1.025)	.015 ^{**b, c, d, e, f}	.005	1.016 (1.006 – 1.025)
Cerebellar White Matter	.173 ^{*c, d, e, f}	.076	1.188 (1.025 – 1.378)	.139	.082	1.149 (.977 – 1.35)
Cerebellar Cortex	.036	.019	1.037 (.998 – 1.077)	.025	.020	1.025 (.985 – 1.067)
Whole brain volume	.004 ^{*b, c}	.002	1.004 (1.000 – 1.009)			
Problem-Solving Domain						
Cerebral White Matter	.009	.005	1.009 (.999 – 1.018)	.014 ^d	.009	1.014 (.996 – 1.033)
Cerebral Gray Matter	.001	.004	1.001 (.994 – 1.008)	-.014 ^d	.008	.986 (.970 – 1.003)
Neocortex	.000	.004	1.00 (.992 – 1.008)	-.016	.008	.984 (.968 – 1.001)
Subcortical Gray Matter	.090 ^{*e, f}	.044	1.094 (1.003 – 1.193)	.119	.066	1.126 (.989 – 1.282)
Lateral ventricle	.016	.017	1.016 (.984 – 1.050)	.014	.017	1.014 (.981 – 1.048)
Amygdala	.070	.322	1.072 (.571 – 2.013)	-.128	.363	.880 (.432 – 1.790)
Caudate Nucleus	.469 ^{*b, e, f}	.208	1.598 (1.063 – 2.402)	.511 ^{*e, f}	.255	1.667 (1.012 – 2.748)
Hippocampus	.419	.234	1.520 (.961 – 2.404)	.396	.283	1.485 (.853 – 2.587)
Thalamus	.162	.102	1.176 (.963 – 1.437)	.152	.132	1.164 (.899 – 1.507)

Cerebral Region	Adjusted for Age at MRI and Sex			Adjusted for Age at MRI, Sex and Whole Brain Volume		
	<i>b</i> ^a	SE	OR (95% CI)	<i>b</i>	SE	OR (95% CI)
Lenticular Nucleus	.257	.152	1.293 (.961 – 1.741)	.235	.185	1.265 (.881 – 1.817)
Corpus Callosum (area)	.007 ^{*b,e,f}	.003	1.007 (1.000 – 1.013)	.006 ^f	.003	1.006 (1.000 – 1.013)
Cerebellar White Matter	.094	.062	1.098 (.972 – 1.241)	.094	.062	1.098 (.972 – 1.241)
Cerebellar Cortex	.001	.014	1.001 (.974 – 1.028)	-.010	.017	.990 (.958 – 1.023)
Whole brain volume	.002 ^c	.002	1.002 (.998 – 1.007)			
Decoding Domain						
Cerebral White Matter	.014 ^{**b,c,d,e,f}	.006	1.015 (1.004 – 1.026)	.022 ^{*d,e,f}	.011	1.022 (1.001 – 1.044)
Cerebral Gray Matter	.003	.004	1.003 (.994 – 1.011)	-.023 ^{b,d,e,f}	5.587	.977 (0.958–0.996)
Neocortex	.002	.004	1.002 (.993–1.011)	-.024 ^{*b,d,e}	.010	.976 (0.957–0.995)
Subcortical Gray Matter	.085 ^{*c}	.045	1.089 (.996–1.19)	.040 [*]	.068	1.040 (0.911–1.188)
Lateral ventricle	-.001	.014	.999 (.972–1.028)	-.006	.015	0.994 (0.966–1.023)
Amygdala	.354	.378	1.425 (.679–2.989)	.017	.421	1.017 (0.445–2.324)
Caudate Nucleus	.693 ^{**b,c,d,e,f}	.255	1.999 (1.212–3.296)	.667 ^{*e}	.315	1.949 (1.051–3.616)
Hippocampus	.427	.253	1.532 (.932–2.518)	.201	.305	1.223 (0.672–2.225)
Thalamus	.089	.101	1.093 (.896–1.334)	-.089	.139	0.914 (0.696–1.202)
Lenticular Nucleus	.244	.162	1.276 (.929–1.752)	.072	.196	1.075 (0.732–1.579)
Corpus Callosum (area)	.010 ^{**b,c,d,e,f}	.004	1.01 (1.003 – 1.018)	.009 ^{*d,e,f}	.004	1.009 (1.001 – 1.017)
Cerebellar White Matter	.166 ^{*b,c,d,e,f}	.072	1.18 (1.025 – 1.359)	.132	.080	1.141 (0.976 – 1.334)
Cerebellar Cortex	.031	.017	1.032 (.998 – 1.066)	.021	.018	1.021 (0.986 – 1.058)
Whole brain volume	.005 [*]	.002	1.005 (1.000 – 1.009)			

Note

^{*} $p < .05$,

^{**} $p < .01$,

^{***} $p < .001$;

^b $p < .05$ with additional control for gestational age;

^c $p < .05$ with additional control for days on ventilation;

^d $p < .05$ with additional control for SGA status;

^e $p < .05$ with additional control for septicemia;

^f $p < .05$ with additional control for severe ultrasound abnormalities.