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Long-term influence of normal variation in neonatal characteristics on human brain development

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Et al.

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It is now recognized that a number of cognitive, behavioral, and mental health outcomes across the lifespan can be traced to fetal development. Although the direct mediation is unknown, the substantial variance in fetal growth, most commonly indexed by birth weight, may affect lifespan brain development. We investigated effects of normal variance in birth weight on MRI-derived measures of brain development in 628 healthy children, adolescents, and young adults in the large-scale multicenter Pediatric Imaging, Neurocognition, and Genetics study. This heterogeneous sample was recruited through geographically dispersed sites in the United States. The influence of birth weight on cortical thickness, surface area, and striatal and total brain volumes was investigated, controlling for variance in age, sex, household income, and genetic ancestry factors. Birth weight was found to exert robust positive effects on regional cortical surface area in multiple regions as well as total brain and caudate volumes. These effects were continuous across birth weight ranges and ages and were not confined to subsets of the sample. The findings show that (*i*) aspects of later child and adolescent brain development are influenced at birth and (*ii*) relatively small differences in birth weight across groups and conditions typically compared in neuropsychiatric research (e.g., Attention Deficit Hyperactivity Disorder, schizophrenia, and personality disorders) may influence group differences observed in brain parameters of interest at a later stage in life. These findings should serve to increase our attention to early influences.

neurodevelopmental | anterior cingulate | cortical area | magnetic resonance imaging

The neurodevelopmental origins of lifespan behavioral and mental health outcomes are increasingly recognized. Recently, variance in cognitive functioning and psychopathology in adulthood have been traced back to fetal development and growth (1). Early environmental conditions interact with the genome of the fetus in producing a range of characteristics, including health and physical stature. Effects may be observed on immediate as well as long-term development. For instance, maternal nutritional deficits can induce persistent changes in metabolism within the offspring (2) Hence, brain development throughout childhood and adolescence (and beyond) may be influenced by factors that occur in utero. Cognitive functioning and behavioral problems, such as in Attention Deficit Hyperactivity Disorder, personality disorders, and schizophrenia (3, 4) as well as other psychopathology (5) with an established neural basis, have been linked with fetal growth and adversity. However, normal variation in birth weight, one of the most commonly used indicators of fetal growth and perinatal health, is substantial, even among typically developing individuals. A healthy full-term baby can range in weight from 2.5 to 4.5 kg. The question is whether this range relate to brain development in the years and decades to come.

The long-term impact of early life development on human health and function may be understood in terms of a special ability of the fetus or child to adapt and respond to environmental conditions by long-lasting regulatory change, in part documented to take place through changes in gene expression (6). This adaptation has been coined fetal programming or developmental plasticity (7). Although numerous studies have documented relations between lower birth weight and coronary heart disease and diabetes (1), little is known about the effect of normal variation in human fetal growth on brain development. The relationship between birth weight, gestational age, and later neurocognitive function has been documented primarily in prematurely born and growth-restricted children. In these clinical groups, lower birth weight is associated with long-term deficits in brain and cognitive development (8–11), including continued perturbation of trajectories of cortical development in late childhood and early adolescence (12). Effects of intrauterine growth restriction (IUGR), the major human pregnancy condition leading to reduced birth weight, are not always clearly distinguished from the effects of premature birth. These conditions may occur together, and both result in very low birth weight and risk of injury to or abnormal development of the CNS (9, 13–16). However, the resulting brain developmental characteristics can be expected to at least, in part, differ. Adverse effects on brain and neurodevelopment over and above the effects in children born

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prematurely with an appropriate weight for gestational age have been found for prematurely born infants with IUGR (17, 18). Indeed, it has been suggested that birth weight rather than gestational age has a predominant impact on brain development (17, 19). Infants with IUGR have smaller cortical volumes and surface area at birth and term equivalent age, relating to poorer neurobehavioral scores (13, 18).

Evidence also suggests that these relationships may extend beyond pathology, with positive associations between birth weight in the normal range and childhood intelligence quotient (IQ) (20). However, some data indicate that the observed associations may be explained largely by family characteristics rather than specific intrauterine effects (21). Some twin results also hint that the association between birth weight and childhood IQ may be mediated by genetic factors (22).

Regardless of the nature of the association, to the extent that birth weight is a meaningful perinatal health indicator, one could expect relations also with normal variation in brain development. A study of twins born, on average, slightly prematurely and within the lower but normal birth weight range did not find a relationship between birth weight and MRI-derived brain volumes at age 9 y (23). However, another recent study with healthy 6-y-old boys born at term reported birth weight and gestation influence on striatal volumes and motor responses (24). Very recently, it was reported that birth weight variation within monozygotic twin pairs was accompanied by significant differences in IQ and brain anatomy (25). The work by Raznahan et al. (25) concluded that greater birth weight within the normal range conferred a sustained and generalized increase in brain volume, which in the cortical sheet, was specifically driven by altered surface area rather than cortical thickness. This twin study by Raznahan et al. (25) also reported that anatomical, although not cognitive, findings were largely replicated in dizygotic twins and unrelated singletons. Effects of normal variance, however, have not previously been investigated in a large sample of singletons heterogeneous with regard to age, sex, socioeconomic status, and ethnicity. In the present study, we used data from 628 individuals ages 3–21 y participating in the Pediatric Imaging, Neurocognition, and Genetics (PING) Study (see below), yielding a heterogeneous sample recruited through geographically dispersed sites in the United States. The relationship between birth weight, cortical thickness, and surface area as well as striatal and total brain volumes was investigated, controlling for variance in age, sex, household income, and genetic ancestry factors (GAFs) (*SI Methods*). Striatal volumes were targeted in addition to the cortical and global brain measures because of the known role of the striatal circuitry in attention and executive function along with its established vulnerability to pre- and neonatal conditions, including low birth weight (9, 24, 26, 27). Based on the above reviewed relationships, we tentatively hypothesized that birth weight would be positively associated with morphometric measures of later brain development. Four questions were asked. (*i*) Does birth weight exert a long-term influence on brain development? (*ii*) If so, is the influence of birth weight equal throughout the normal continuum, or is there a greater influence at the extremes of the normal distribution? (*iii*) Is the influence of birth weight similar across age in childhood and adolescence, or are catch-up effects seen? (iv) Are brain characteristics influenced by birth weight related to executive function performance scores?

Results

Cortical Surface Analyses. Cortical analyses vertexwise across the surface were performed with general linear models to investigate relations of birth weight to regional cortical area and thickness, controlling for variation in age, sex, household income, and GAF as well as scanner used. When a commonly used approach to correct for multiple comparisons was used [false discovery rate (FDR) < 5%], minute effects of birth weight were observed on cortical thickness. However, significant positive relationships between birth weight and area were observed across large parts of the cortical surface (Fig. 1). On the medial surface of the brain, effects were seen bilaterally in the rostral anterior cingulate, retrosplenial, paracentral, precuneus, superior frontal and medial orbitofrontal cortices, parahippocampal, and fusiform gyri. On the lateral brain surface, bilateral effects extended from parsorbitalis to cover parts of lateral orbitofrontal cortices, and there were also effects in the rostral middle frontal, inferior parietal, and superior and middle temporal cortices as well as in the pre- and postcentral gyri. A few somewhat more scattered unilateral effects were also seen. Medially, effects extended into the caudal anterior cingulate in the left but not right hemisphere, whereas superior and orbitofrontal effects were more pronounced in the right than left hemisphere. Lateral effects were also more pronounced in the left orbitofrontal cortex, but otherwise, lateral effects also seemed slightly more extensive in the right hemisphere, covering somewhat larger temporal and parietal areas. Because the use of FDR for correction for multiple comparisons may influence the detection of specific effect sites, the full range of effects uncorrected at $P < 0.05$ is also shown in Fig. S1. Uncorrected, effects were somewhat more extensive, but the general pattern described was similar. A scatter plot of the relationship between birth weight and anterior cingulate area (partial $\beta = 0.19$, $P < 0.0001$) is shown in Fig. 2*A*. It appears from the plot that the low birth weight cases were not disproportionately influencing the relationship and that the relationship between cortical area and birth weight was also monotonous. The relationship between birth weight and anterior cingulate area remained virtually identical when excluding the low birth weight (1,500–2,499 g) cases (partial $\beta = 0.18$, $P < 0.0001$).

Striatal and Total Brain Volume Analyses. Volumes of the putamen, pallidum, and caudate and total brain volume (TBV) were entered as dependent variables in regression analyses with age, sex, GAF, household income, and scanner and total birth weight, respectively, as simultaneous predictors. Birth weight was uniquely and positively associated with each volume (partial β for putamen: 0.11, $P = 0.006$; pallidum: 0.12, $P = 0.002$; caudate: 0.20, $P < 0.001$; TBV: 0.16, $P < 0.001$). These relationships also remained largely similar when excluding the low (1,500–2,499 g) birth weight cases (partial β for putamen: 0.09, $P = 0.022$;

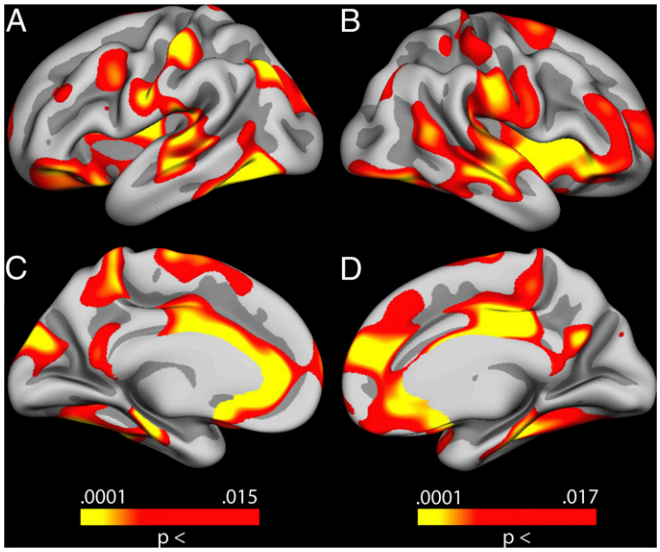

Fig. 1. Relationships of birth weight and cortical surface area, controlling for age, sex, GAFs, household income, and scanner, thresholded for multiple comparison corrections (FDR = 5%). (*A*) Lateral left hemisphere. (*B*) Lateral right hemisphere. (*C*) Medial left hemisphere. (*D*) Medial right hemisphere.

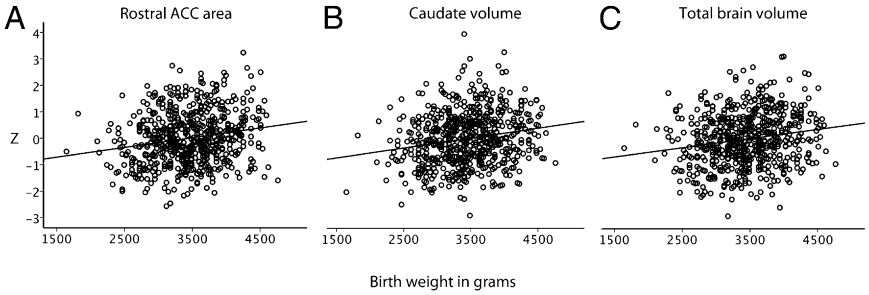

Fig. 2. Scatter plots showing the relationships between birth weight in grams (*y* axis) and neuroanatomical variables (*x* axis) averaged across hemispheres and residualized for age, sex, household income, GAFs, and scanner used. (*A*) Rostral anterior cingulate cortex area (R^2 = 0.04, P < 0.0001). (*B*) Caudate volume (R^2 = 0.04, P < 0.0001). (*C*) Total brain volume (R^2 = 0.03, P < 0.0001).

pallidum: 0.11, P = 0.004; caudate: 0.19, P < 0.001; TBV: 0.17, P < 0.001). Scatter plots of the relationships between age, volume of caudate, and TBV are shown in Fig. 2 *B* and *C*. To investigate whether the striatal associations were specific, these regression analyses were also repeated with TBV as a regressor in addition to age, sex, GAF, household income, scanner, and total birth weight. This analysis rendered the putamen and pallidum relationships not significant (P > 0.10), but a unique relationship between birth weight and caudate volume remained (partial β = 0.11, P = 0.002).

Effects of Other Reported Pre- and Perinatal Conditions on the Observed Relationships. To tentatively investigate whether effects of birth weight were attenuated by other pre- and perinatal conditions, the above-described regression analyses for significant regions of interest (ROIs) were also repeated, including method of delivery (vaginal birth/cesarean section), gestational age at birth (36–42 wk), maternal smoking (yes/no), and maternal alcohol consumption (yes/no) as additional covariates entered separately. In no cases where a significant effect of birth weight was observed did any of these variables render the relationship not significant, and the effects on the neuroanatomical variables were generally not significant (P > 0.10). The only exception was an effect of method of delivery on rostral anterior cingulate area, where larger area was observed with cesarean section (standardized β = 0.09, P = 0.018). This finding did not, however, attenuate the relationship with birth weight, for which the effect size remained virtually identical (standardized β = 0.185 vs. 0.193, both P values < 0.0001) when method of delivery was included or not included in the analysis, respectively.

Analyses on Possibly Differential Effects of Birth Weight for Select Ranges and Ages. For selected ROIs showing a significant relationship to birth weight, putamen, palladium, caudate, TBV, and rostral anterior cingulate cortex area, regression analyses were also repeated, including (*i*) a quadratic birth weight term to investigate possible differential effects in select ranges of birth weight and (*ii*) an interaction term of birth weight and age to investigate possible differential effects of birth weight at different ages. In no case did the quadratic term or the interaction term exert a significant effect (P > 0.10). To further visualize comparisons of relationships across birth weights and ages, the standardized β values for these relationships were plotted for subgroups of the sample stratified by birth weight groups (low birth weight = 1,500–2,499 g, normal range (lower) = 2,500–3,499 g, normal range (higher) = 3,500–4,499 g; too few cases of high birth weight ≥ 4,500 g were available for analysis) in Fig. S2 as well as age groups (3–8, 9–14, and 15–21 y) (Table 1) in Fig. S3. Effects generally did not vary in a systematic fashion with select sample subgroups. Although there did seem to be somewhat stronger effects of birth weight on pallidum and caudate volumes within the low birth weight group, none of the differences among effects in this group and the others reached significance (P > 0.10).

Analyses on Relations to Performance Scores for Executive Function. Finally, we tested whether the fronto-striatal brain areas affected by birth weight were related to specific executive functions. The anterior cingulate is assumed to be the central structure in the major network responsible for resolving cognitive conflicts (28, 29), and we tested whether this region correlated with performance on a well-validated test of cognitive control, a version of the Erikson flanker test implemented in the National Institute of Health toolbox for Assessment of Neurological and Behavioral Function (30, 31) (*SI Methods*). Valid Flanker data were available for 522 participants, and we used reaction time in the incongruent condition, related to cognitive control, as the measure of interest. With GAF, MR site, sex, socioeconomic status, and age as covariates, better Flanker performance was significantly related to larger total anterior cingulate area [partial β = −0.092, P = 0.011, degrees of freedom (df) = 20, 502]. This effect was specific to cognitive control, because the relationship survived adding congruent reaction time as an additional covariate area (partial β = −0.064, P = 0.006, df = 21, 501); also, no relationship was observed in the congruent condition. Birth weight was positively related to total anterior cingulate area in this subsample (partial β = 0.14, P < 0.001, df = 20, 502). There were no significant effects of birth weight on Flanker performance. No significant effects were observed for the striatal volumes, with only a marginal effect observed for putamen (P = 0.062) when congruent reaction time was included as covariate.

Table 1. Sample characteristics (n = 628) by age groups

	3–8 y (76 F, 87 M)		9–14 y (111 F, 148 M)		15–21 y (114 F, 92 M)	
	Mean	SD	Mean	SD	Mean	SD
Age (y)	6.4	1.7	12.1	1.8	17.6	1.8
Household income	6.7	2.4	7.0	2.2	6.8	2.5
Birth weight (g)	3,472	509	3,448	508	3,419	534
GAF (proportion)						
European	0.70	0.34	0.70	0.35	0.62	0.39
Native American	0.05	0.09	0.04	0.10	0.05	0.12
African	0.09	0.22	0.14	0.29	0.15	0.28
East Asian	0.15	0.29	0.10	0.23	0.14	0.31
Central Asian	0.01	0.04	0.01	0.06	0.03	0.14
Oceanic	0.01	0.03	0.00	0.02	0.00	0.01

ANOVA showed no significant differences in household income or birth weight across age groups. There was a higher proportion of European (P = 0.047) and Oceanic (P = 0.003) GAFs in the youngest age group compared with oldest age group and a higher proportion of males in the middle group compared with oldest group (P = 0.022). Household income is given on a scale from 1 to 12, where 1 < $5,000, 2 = $5,000–9,999, 3 = $10,000–19,999, 4 = $20,000–29,999, 5 = $30,000–39,999, and 6 = $40,000–49,999; thereafter, the increments are $50,000 for each successive category (i.e., 7 = $50,000–99,999 etc. and 12 = $300,000 and above). F, female; M, male.

Discussion

The present results indicate that aspects of normal child and adolescent brain development can be predicted by birth weight, the most widely used perinatal health indicator. Variance in birth weight did not exert differentially strong effects in select birth weight ranges in the present large healthy sample. Based on reports from pathological groups of prematurely born, dysmature, and growth-restricted children, one might be inclined to expect that particularly strong effects may be observed in the lower ranges. This expectation could be the case if, for instance, smaller newborns were more prone to subtle lesions or reductions in normal growth of neural processes or synapses (32). However, for none of the observed effects were nonlinear effects of birth weight observed.

The effect of birth weight on rostral anterior cingulate area was at least as strong in the normal (higher) birth weight groups as in the low and normal (lower) birth weight groups. However, it should be noted that some tendencies to systematically stronger effects on pallidal and caudate volumes were observed in the low birth weight group compared with the others. Although these effects were far from significantly different across groups, it should be noted that the low birth weight group in the present study was relatively small ($n = 23$) and limited to children with low (<2,500 g) but not very low (<1,500 g) birth weight. Hence, possible differential effects of birth weight on brain development for dysmature, low, and extremely low birth weight children should be investigated in other samples suited to this purpose. The same is true for children of higher than normal birth weight (>4,500 g), because data for too few high birth weight children ($n = 11$) were available for this subgroup to be included in the present analysis.

The present results show, however, that influence of birth weight on brain development is not limited to prematurely born or very low birth weight groups. In fact, although relations between birth weight and brain development have previously been the focus of pathology studies, the current results are more in line with epidemiological data from studies of fetal growth parameters. These epidemiological findings do indicate that fetal growth measures, including birth weight, are the most associated with later growth and adult height for those children born within the normal and most common gestational age range, namely 39–41 wk (33). Hence, it may be that a blurring of the relationships between fetal growth parameters and later brain development should rather be expected for dysmaturely and prematurely born children. Paradoxically and hitherto ignored, it is possible that the strongest relationships between perinatal characteristics and later brain development generally exist within the normal range.

Although there were widespread birth weight effects on cortical surface area, there were no effects on cortical thickness. One might ask whether the absence of a relationship between birth weight and cortical thickness may have been affected by previously reported nonmonotonous changes in cortical thickness in the presently studied age range (34). However, in the present sample with the present methods, only monotonous decrease in cortical thickness in the age range 3–21 y has been observed (35), making this explanation less likely. Rather, the present findings on birth weight being positively correlated with cortical surface area but not positively correlated with cortical thickness seem to correspond with findings from other studies of small for gestational age children born at term (36) and prematurely (18). The work by Dubois et al. (18) found greater effects of IUGR on surface than volume comparing IUGR infants with prematurely born normally grown as well as twin infants. They also found that cortical surface at birth correlated with neurobehavioral scores at term, indicating that this alteration of early brain development has functional consequences over time. The work by De Bie et al. (36) investigated small for gestational age children born at term, and it found that, although surface area was reduced, cortical thickness was increased in frontal areas. The present study is, however, from a sample with normal variation in birth weight and not suited to investigate possible differential effects of low birth weight on cortical thickness compared with surface area, and hence, this finding should be studied more in other samples.

It is noteworthy that, in monozygotic twins born at term, variation in birth weight was very recently reported to primarily affect cortical surface area rather than cortical thickness, a finding reported to be largely replicated in dizygotic twins and singletons (25). However, multiples have been shown to differ in brain development from singletons (18, 37). The work by Raznahan et al. (25) emphasized that effects appeared especially in late-maturing prefrontal and temporal cortices. In that study, however, effects were clearly more regionally restricted than in the present study. This restriction may be because of smaller sample sizes, but effects also seem only partially overlapping. Because the primary focus of that study was not singletons, location of effects in singletons was not specifically pinpointed or discussed. For instance, the work by Raznahan et al. (25) showed effects in the left but not right anterior cingulate and orbitofrontal cortex. Furthermore, the effects of the present study do not seem to be specific to late-maturing cortices; indeed, bilateral effects of birth weight are found in somatosensory and motor cortices, which are among the earliest to mature (38). The work by Raznahan et al. (25) speculated that surface area may be especially vulnerable to changes in progenitor cell division within the subventricular zone, relating these findings to a recent study showing that modest maternal calorie restriction altered the balance between rates of cell birth and apoptosis in midgestation baboon subventricular zone and reduced subplate neuronal network density (39). Although these findings are interesting, it is important to keep in mind that a lot of the present variation in birth weight must stem from differences in fetal growth potential and may have less to do with maternal diet.

The present results are consistent with a stable effect of birth weight on brain development across the current age range. This finding implies that differences present at birth constitute a continuous influence. The present findings on morphometric brain development are consistent with results from epidemiological studies showing that fetal growth, including birth weight, is associated with adult height (40), and although there is, of course, considerable variance in growth trajectories, the heavier newborns generally tend to become the taller children who tend to become the taller adults. This finding is likely also true for brain development, because cranial volumes are naturally associated with body size.

Beyond this result, the neural basis for the observed association is not clear. However, animal studies point to subtle neural influences of prenatal conditions. Factors that affect placental function and uterine and/or umbilical blood flow on a chronic basis may lead to restricted fetal growth. This effect can cause the brain, although relatively spared in relation to other organs, to be reduced in weight. The work by Rees et al. (32) points to chronic intrauterine insults compromising the growth of neural processes and synapses throughout fetal brains. Animal studies of chronic placental insufficiency have shown some relevance to neurodevelopmental disorders, and the observed effects on brain development have also been shown to persist with age (e.g., with reduced striatal volumes in adolescence) (41). Hence, the etiological background for the relationship between birth weight and brain development in the normal population could likely be twofold: it may, to some extent, be based on normal variation in body and brain size, but it also may be based on variations in prenatal conditions, yielding differences in optimality of early brain development persisting through childhood and adolescence and likely, also adulthood. However, it must be emphasized that the present relationship was found in a study of normal development, and any extrapolation to pathology cannot be done.

Although independent effects of other perinatal variables on the observed birth weight–brain development relationships were not found in the present study, these variables may still play an important role. Information about these variables was based on parental and self report, and hence, it is vulnerable to biases in memory and social desirability. The present findings may, thus, relate to and interact with a number of pre- and perinatal variables, such as gestational age, maternal nutrition, smoking, and alcohol intake, that the present study is not well-suited to control for in a systematic manner. For instance, factors such as maternal gestational diabetes will impact the infant's birth weight, but we have no way of systematically controlling for this factor. Other factors and complications, such as preeclampsia, may influence the time of delivery and hence, birth weight. Although we have reports on gestational age, we have no way of systematically controlling for different factors influencing gestational age in the present sample. Furthermore, we have no possibility of knowing for most of the present birth weight range to what extent the weight reflects the individual fetal growth potential. This extent is hard to define, especially in the absence of longitudinal fetal growth charts, because a normal birth weight fetus can be growth restricted and a low birth weight fetus can have appropriate growth (42). The findings were derived from a large sample, and effect sizes were not very large: on the order of 4% of regional cortical area and caudate volume was explained by birth weight when influences of sex, GAF, and household income as well as study age and scanner were accounted. Effects were, however, found to be widespread and cover relatively large areas of the brain. Although it is a limitation that birth weight was also obtained by parental/self-report and not from medical records directly, the fact that these relationships were observed, despite such possible variables of noise, serves to underscore their relative robustness.

The present findings have important implications. First, aspects of child and adolescent brain development, which are, in all likelihood, predictive of lifespan brain characteristics, are related to individuals' weight at birth. In part, this result is likely associated with normal genetic differences in growth, and should not be expected to be particularly associated with cognition. Although a significant relationship was found between executive function performance scores and anterior cingulate area, there was no influence of birth weight on executive function. However, the present findings also underscore the importance of pre- and perinatal influences on brain development for the entire lifespan of individuals, and they should serve to increase our attention to researching and optimizing early influences. Second, relatively small differences in birth weight across groups compared in neuropsychiatric research may have a significant influence and cause group differences to be observed in brain parameters of interest. This result could be the case in schizophrenia (3, 43), Attention Deficit Hyperactivity Disorder (44–46), prenatal substance exposure (47), and personality disorders (48, 49) as well as other types of psychopathology (5), where differences in fetal growth or birth weight have been observed. The long-term consequences of these differences for brain development may be of significance to the neural basis of individual functional differences within the normal and clinical range. Additional research with longitudinal follow-up should aim to investigate to what extent such early life influences on brain development may interact with age and postnatal environmental influences.

Methods

Data used in the preparation of this study were obtained from the PING Study database (http://ping.chd.ucsd.edu). PING was launched in 2009 by the National Institute on Drug Abuse and the Eunice Kennedy Shriver National Institute of Child Health & Human Development as a 2-y project of the American Recovery and Reinvestment Act. Participants were recruited through local postings and outreach activities conducted in the greater metropolitan areas of Baltimore, Boston, Honolulu, Los Angeles, New Haven, New York, Sacramento, and San Diego. The human research protections programs and institutional review boards at the universities participating in the PING project approved all experimental and consenting procedures. All adult participants gave informed consent. For individuals under age 18 y, parental informed consent and subject assent, when appropriate, were obtained. Subjects were screened for history of major developmental, psychiatric, or neurological disorders, brain injury, or other medical conditions that affect development by means of self-report before scanning. Persons having contraindications for MR studies (such as metallic or electronic implants, claustrophobia, or pregnancy) were also excluded from participating. Individuals were also informed that, if a child was born at less than 36 wk of gestational age, they could not be included. At the time of data processing, a total of ~25 cases with incidental clinical findings had been reported across the nine PING Study sites, and these cases excluded from all analyses (35).

Sample. The sample used for the present analyses included scans from PING participants registered and processed at the University of California at San Diego by February 12, 2012. Only participants with cortical surface segmentations that passed quality check and for whom data on cortical thickness and area, household income, and birth weight were reported were included (n = 656). Among these participants, 20 children were reported to be multiplets (i.e., twins or triplets) and therefore, excluded. Children with gestational age of less than 36 wk were excluded from the present analyses. Furthermore, two participants were excluded based on reports of very low birth weight (<1,500 g). The final sample consisted of 628 children ages 3–21 y (mean = 12.4 y, SD = 4.6), and 301 children were female (Table 1). GAFs were calculated as a proportion of European, African, Native American, East Asian, Central Asian, and Oceanic decent based on genotype analysis, or when missing (n = 40), values from self-report were used to predict GAF (*SI Methods*). Each of nine US sites (*Methods*) contributed a range of 31–147 participants to the sample, and each site contributed to all age groups. Although surface data were available and surface analyses were conducted for 628 participants, ROI data were lacking for 10 participants, leaving an n = 618 for these analyses. Variance in scanner used, age, sex, household income, and GAF was controlled for in all analyses.

Information on other pre- and perinatal variables of interest was also gathered in PING, including method of delivery, gestational age at birth, and maternal smoking and alcohol consumption during pregnancy. However, with the exception of method of delivery, this information may not easily and objectively be remembered, obtained, and scored as birth weight. Hence, the significance of these variables in PING in relation to the present birth weight analyses should be considered with caution. For the 628 participants, method of delivery was listed as vaginal birth for 468 births and cesarean section for 157 births, whereas for 3 participants, this information was missing. Gestational age at birth was reported to be 36 wk for 51 participants, 37 wk for 35 participants, 38 wk for 77 participants, 39 wk for 83 participants, 40 wk for 191 participants, 41 wk for 49 participants, and 42 wk for 35 participants, whereas for 107 participants, this information was missing. For 528 participants, no alcohol consumption during pregnancy was reported, whereas for 34 participants, maternal alcohol consumption was listed; for 13 participants, this information was missing. For 586 participants, no smoking during pregnancy was reported, whereas for 29 participants, maternal smoking was reported; for 13 participants, this information was missing.

Imaging Data Acquisition. Across the nine sites and 12 scanners, a standardized multiple modality high-resolution structural MRI protocol was implemented involving 3D T1- and T2-weighted volumes and a set of diffusion-weighted scans (*SI Methods*). Data were acquired on all scanners to estimate relaxation rates and measure and correct for scanner-specific gradient coil nonlinear warping (50). Scanning duration for the T1 sequence was 8:05 min.

Image Processing. Image files in DICOM format were processed with an automated processing stream written in MATLAB and C++ by the UCSD Multimodal Imaging Laboratory. T1-weighted structural images were corrected for distortions caused by gradient nonlinearities (50), coregistered, averaged, and rigidly resampled into alignment with an atlas brain. Image postprocessing and analysis were performed using a fully automated set of tools available in the FreeSurfer software suite (http://surfer.nmr.mgh.harvard.edu/) (50–56). Volumetric subcortical segmentation and measurement were performed using validated automated procedures (57). Additional information is in *SI Methods*.

Statistical Analyses. The relationship of birth weight to indicators of brain development, including regional cortical area and thickness, striatal volumes,

TBV, and intracranial volume, were investigated, controlling for variations in age, sex, household income, and GAF as well as scanner used. Cortical analyses across the surface were performed with general linear models as implemented in FreeSurfer, and results were displayed on a semiinflated template brain that was thresholded by a conventional criterion for correction for multiple comparisons (FDR at 5% level) (58). To visualize effects, ROI regression plots were provided for select cortical and subcortical parcellations/segmentations for which values were averaged across hemispheres. Regression analyses for significant ROIs were also repeated, including method of delivery (vaginal birth/cesarean section), gestational age at birth (36–42 wk), maternal smoking (yes/no), and maternal alcohol consumption (yes/no). For ROIs showing effects of birth weight, regression analyses were rerun including quadratic birth weight terms to investigate possible differential effects in select ranges of birth weight. To investigate whether birth weight exerted differential effects on brain development at different ages, age and birth weight variables were standardized to the whole sample, and regression analyses with these variables, along with their interaction term (birth weight × age), sex, household income, GAF, and scanner, were repeated.

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