Cesarean Delivery Impacts Infant Brain Development

ORIGINAL RESEARCH

PEDIATRICS

Background and Purpose: The cesarean delivery rate has increased globally in the past few decades. Neurodevelopmental outcomes associated with cesarean delivery are still unclear. This study investigated whether cesarean delivery has any effect on the brain development of offspring.

Materials and Methods: A total of 306 healthy children were studied retrospectively. We included 3 cohorts: 2-week-old neonates (cohort 1, \( n = 32/11 \) for vaginal delivery/cesarean delivery) and 8-year-old children (cohort 2, \( n = 37/23 \) for vaginal delivery/cesarean delivery) studied at Arkansas Children’s Hospital, and a longitudinal cohort of 3-month to 5-year-old children (cohort 3, \( n = 164/39 \) for vaginal delivery/cesarean delivery) studied independently at Brown University. Diffusion tensor imaging, myelin water fraction imaging, voxel-based morphometry, and/or resting-state fMRI data were analyzed to evaluate white matter integrity, myelination, gray matter volume, and/or functional connectivity, respectively.

Results: While not all MR imaging techniques were shared across the institutions/cohorts, post hoc analyses showed similar results of potential effects of cesarean delivery. The cesarean delivery group in cohort 1 showed significantly lower white matter development in widespread brain regions and significantly lower functional connectivity in the brain default mode network, controlled for a number of potential confounders. No group differences were found in cohort 2 in white matter integrity or gray matter volume. Cohort 3 had significantly different trajectories of white matter myelination between groups, with those born by cesarean delivery having reduced myelin in infancy but normalizing with age.

Conclusions: Cesarean delivery may influence infant brain development. The impact may be transient because similar effects were not observed in older children. Further prospective and longitudinal studies may be needed to confirm these novel findings.

Abbreviations: BMI = body mass index; DMN = default mode network; FA = fractional anisotropy; ICA = independent component analysis; IQ = intelligence quotient; MWF = myelin water fraction; RS-fMRI = resting-state fMRI; TFCE = threshold-free cluster enhancement; TBSS = Tract-Based Spatial Statistics; VBM = voxel-based morphometry

Cesarean delivery has become increasingly prevalent throughout the world.\(^1\) In the United States, about one-third of all births are by cesarean delivery,\(^2\) a 60% increase from the rate in 1996.\(^3\) Elective cesarean delivery without a medical indication is not uncommon\(^4,5\) and contributed to a considerable percentage (8%) of the increase of cesarean deliveries in recent years.\(^6\) In addition, the large range of cesarean delivery rates across hospitals\(^7\) suggests that practice variation, a modifiable factor, also played an important role in the increased prevalence of cesarean delivery. The World Health Organization recently reassessed available evidence and concluded that cesarean delivery should ideally be undertaken only when medically necessary, acknowledging that the relationship between the cesarean delivery rate and pediatric outcome is unclear.\(^1\) An important aspect to con-
Consistently different between groups for both TBSS and RF-fMRI and therefore included as a covariate in the analysis.

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For each cell in the table, the first row is for the DTI TBSS study, the second row is for the RS-fMRI study.

Not available for 1 subject with vaginal delivery.

Defined as gestational age at birth plus postnatal age at MRI.

Consistently different between groups for both TBSS and RF-fMRI and therefore included as a covariate in the analysis.

Appendix.

To test whether cesarean delivery has significant effects on infant brain development and whether these effects persist into and throughout childhood, we analyzed advanced brain MR imaging data in 3 cohorts of healthy children—cohort 1: two-week-old neonates with well-documented pregnancy and infant perinatal profiles; cohort 2: eight-year-old children who had undergone a suite of neuroimaging examinations at Arkansas Children’s Hospital included DTI evaluation of brain white matter and T1-weighted high-resolution structural images for voxel-based morphometry (VBM) evaluation of brain gray matter volume. Demographic information for subjects with valid DTI (n = 35/21 for vaginal and cesarean delivery, respectively) and VBM data (n = 36/21 for vaginal and cesarean delivery, respectively) is presented in Table 2.

MR Imaging Data Acquisition and Analysis

The data acquisition and analysis were based on established protocols at Arkansas Children’s Hospital and Brown University and were similar to those in previous publications.16–23 Details are provided in On-line Appendix.
Statistics

For the comparison of demographic/anthropometric/neuropsychological data between delivery mode groups in cohorts 1 and 2, Wilcoxon rank sum tests were used for numeric parameters and Fisher exact tests (or χ² tests) were used for categorical variables. For the voxelwise comparison of DTI parameters in Tract-Based Spatial Statistics (TBSS; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS) analysis and RS-fMRI parameters, independent t tests were used after confirming normal distribution of data and testing for equality of variance, and general linear model univariate analyses were used to compare differences, with covariates controlled. For the VBM analyses of regional gray matter volume, 2-sample t tests with unequal variance were performed with multiple-comparison correction to control for family-wise error. P < .05 family-wise error—corrected was regarded as significant. For cohort 3, the Gompertz function parameters for the MWF curve of the 6 regions were compared between delivery groups using nonparametric tests, with significance defined as P < .001.

Potential confounders were controlled as covariates in statistical analyses. Specifically, for cohort 1, the TBSS and RS-fMRI dual-regression analyses were performed, respectively, when there were no potential confounders added as covariates; when adding demographic parameters that were consistently different between groups (P ≤ .05 for both the TBSS and the RS-fMRI subsets) as covariates (gestational weight gain, infant sex, and birth length); and when adding an additional 2 parameters that were known potential confounders identified by our previous studies (gestational age at MR imaging and maternal body mass index [BMI] at early pregnancy) as covariates. For the post hoc ROI comparisons, significances with and without controlling for all of these 5 covariates were both evaluated. For cohort 2, the TBSS and VBM analyses were performed without adding covari-
ates and then were repeated with age, sex, and infant diet added as covariates. Socioeconomic variables were not included as covariates because of incomplete data (group comparison on the available data did not show group differences other than mother’s income).

RESULTS

The demographic/anthropometric/neuropsychological parameters are listed in Tables 1–3 for the 3 cohorts. For cohort 1, the 2 groups of neonates did not differ with respect to mother’s age, maternal IQ, and body fat percentage at early pregnancy, infant gestational age at MR imaging, birth weight, head circumference, and diet at 2 weeks of age. There was a trend toward differences in maternal BMI measured at 12 weeks of pregnancy (significant for the subjects included in the TBSS analysis but not significant for the subjects included in the RS-fMRI analysis). There were group differences in the mother’s gestational weight gain, infant sex, and birth length. For cohort 2, the 2 groups of 8-year-old children did not differ in any demographic or family socioeconomic status measures except for mother’s income. The neuropsychological test scores including IQ, language skills, and memory index were also not significantly different between groups. For cohort 3, the 2 groups of children did not differ in birth weight, birth length, maternal education, number of scans per child, and mean inter-scan period. However, the cesarean delivery group had a higher maternal age and slightly lower gestational age at birth.

Imaging Findings for Cohort 1. DTI TBSS revealed widespread white matter regions in the frontal, parietal, and temporal lobes that had higher fractional anisotropy (FA) values (P < .05, corrected for voxelwise multiple comparisons) when no covariates were added. B. Group differences (P < .05, corrected for the voxelwise multiple comparisons) when no covariates were added. C. Trend of group differences (P < .15, corrected for the voxelwise multiple comparisons) when an additional 2 potential confounders (gestational age at MR imaging and maternal BMI at early pregnancy) were included as covariates. D. Illustration of ROIs selected for further post hoc analysis. E. Group comparison of mean FA values in these white matter ROIs. L indicates left; R, right; ACR, anterior corona radiata; ALIC, anterior limb of internal capsule; PLIC, posterior limb of internal capsule; AF, arcuate fasciculus; BCC, body of the corpus callosum; SAF, short association fibers; SCR, superior corona radiata; asterisk, P < .05 without controlling for covariates; double asterisks, P < .05 with and without controlling for covariates.

FIG 1. DTI TBSS results for the comparison of FA values between 2-week-old neonates born by cesarean delivery or vaginal delivery in cohort 1. Green represents major white matter tracts in the brain; orange shows voxels that have different FA values between groups. A. Group differences (P < .05, corrected for the voxelwise multiple comparisons) when no covariates were added. B. Group differences (P < .05, corrected for the voxelwise multiple comparisons) when 3 demographic parameters that were different between groups (gestational weight gain, infant sex, and birth length) were added as covariates. C. Trend of group differences (P < .15, corrected for the voxelwise multiple comparisons) when an additional 2 potential confounders (gestational age at MR imaging and maternal BMI at early pregnancy) were included as covariates. D. Illustration of ROIs selected for further post hoc analysis. E. Group comparison of mean FA values in these white matter ROIs. L indicates left; R, right; ACR, anterior corona radiata; ALIC, anterior limb of internal capsule; PLIC, posterior limb of internal capsule; AF, arcuate fasciculus; BCC, body of the corpus callosum; SAF, short association fibers; SCR, superior corona radiata; asterisk, P < .05 without controlling for covariates; double asterisks, P < .05 with and without controlling for covariates.
the cesarean delivery group (Fig 2B). After controlling for potential confounders (3 demographic parameters that differed between groups and 2 more parameters known to influence neonatal brain development), the differences were more prominent with a larger cluster in the precuneus and additional bilateral regions in the parietal lobes involved (Fig 2B). ROI analysis of mean z scores in the precuneus (see Fig 2C for an illustration of the ROI selection) confirmed lower functional connectivity (P < .05, corrected for the voxelwise multiple comparisons) when excluding or including potential confounders as covariates (Fig 2D). No other meaningful functional components obtained from the ICA showed significant group differences in the dual-regression analyses.

**Imaging Findings for Cohort 2.** DTI TBSS analysis did not show any clusters or imaging voxels with significant white matter FA value differences between children born by cesarean or vaginal delivery. Likewise, VBM did not show any clusters or imaging voxels with significant regional gray matter volume differences between groups. Excluding/including potential confounders (age, sex, infant diet) as covariates did not change the results.

**Imaging Findings for Cohort 3.** Significantly different brain developmental trajectories were observed for the 2 groups (Fig 3). Specifically, at ~3 months of age, the MWF for the infants born by vaginal delivery was higher (indicating better myelination) in the frontal, temporal, parietal, and occipital white matter and the body of corpus callosum compared with those born by cesarean delivery. The differences of MWF in white matter regions between groups were consistent during infancy but gradually decreased and were not observable at age ~3 years or beyond when the MWF for both groups reached the same plateau.

**DISCUSSION**

The imaging results from cohort 1 showed striking differences in brain structural connectivity (measured by DTI-TBSS) and functional connectivity (measured by RS-fMRI) in 2-week-old healthy neonates born by cesarean delivery compared with vaginal delivery, whereas measured imaging parameters (structural connectivity and brain volume) in 8-year-old healthy children in cohort 2 did not differ. These novel findings provide the first-ever evidence that cesarean delivery may be associated with a shift in brain development, at least during early infancy. Considering the potential importance of these findings and the post hoc nature of our analyses using data derived from a larger study, we sought confirmation in a separate cohort (cohort 3) in which imaging results from a different institution were evaluated with the investigator blinded to findings from cohorts 1 and 2. The study in cohort 3 confirmed the delivery mode–associated differences in brain white matter development during infancy and was consistent in showing that differences dissipated with age. The differences in white matter development (as reflected by FA and MWF values) during infancy associated with delivery mode were widespread in both cohorts 1 and 3, involving the frontal, temporal, and parietal lobes and the corpus callosum, but not the cerebellum; the latter is one of the first regions to be myelinated, usually before birth. The differences were not prominent beyond age ~3 years, when myelination in most brain white matter regions approaches completion. Differences in resting-state functional connectivity were observed for the DMN network for neonates in cohort 1, while at this age most brain functional networks are still being developed.

Birth mode–associated brain developmental differences were not observed in later childhood (ie, 8-year-old healthy children in cohort 2 and 5-year-old healthy children in cohort 3). One possibility is that the differences were ameliorated during the years of postnatal development. Myelination for the cesarean delivery children may eventually catch up with that in children delivered vaginally when the developmental curve reaches a plateau after

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**FIG 2.** Resting-state fMRI analyses of functional connectivity in the DMN in 2-week-old neonates in cohort 1. A. The DMN for vaginal and cesarean delivery groups obtained from respective independent component analysis (ICA). B. Regions in which the vaginal delivery group had higher functional connectivity (z score) in the DMN than the cesarean delivery group (P < .05, corrected for the voxelwise multiple comparisons) when excluding or including potential confounders as covariates. C. Illustration of ROI (precuneus selected) for further post hoc analysis. D. Comparison of the mean z score values in the precuneus between the 2 groups. Double asterisks indicate P < .05 with and without controlling for covariates.
the first few years of life. In addition, breastfeeding (which reportedly promotes brain development in children\textsuperscript{20,22,29}) may have driven enough changes to offset differences caused by cesarean delivery. Another possibility is the influence of the environment. While age, sex, and infant diet were included as covariates in cohort 2 and socioeconomic parameters were, in general, not different for the 2 groups in cohort 3, extensive exposures to environmental factors (childhood diet, social enrichment, or other aspects) may have contributed to changes in neurodevelopment with long-term effects stronger than birth mode. For example, cognitive development in healthy children has been associated with breakfast consumption\textsuperscript{30} and composition,\textsuperscript{31} physical activity,\textsuperscript{32} television-viewing time,\textsuperscript{33} and sleep duration.\textsuperscript{34} Many of these variables during childhood are difficult to quantify and were not considered in our study of older children. Recent population studies showed an increased risk of autism spectrum disorder and attention deficit/hyperactivity disorder associated with cesarean delivery that did not persist if using sibling controls\textsuperscript{11,35} and partially confirmed the confounding factors of family environment during childhood. In addition, while advanced and quantitative imaging methods were used in the evaluation of children’s brain development in our study, it is possible that early brain structural differences associated with delivery mode introduced variations in brain function that could be apparent, for example, in the association of brain responses with stimulus-related information-processing.

The mechanisms underlying the effects of cesarean delivery on early life brain development are not known and could not be directly addressed in the current studies. Although cesarean delivery is generally considered a safe procedure, both mother and neonate are directly or indirectly subjected to factors that differ significantly from vaginal delivery, such as anesthesia/analgesics, surgical incisions, labor, trauma, stress, and so forth. It is not unreasonable to assume that these factors could have significant effects on the neonate’s brain development. While speculative, we consider here a novel concept that associates cesarean delivery effects on neurodevelopment with an altered microbial environment. Several lines of evidence form the premise of this hypothesis. First, mode of delivery is a major determinant of gut microbiome composition in infants.\textsuperscript{36,37} Vaginally delivered neonates acquire bacterial communities resembling maternal vaginal microbiota, while cesarean delivery neonates have bacterial communities similar to those found on the skin surface,\textsuperscript{38} suggesting that the exposure to vaginal microbial environment during natural delivery is important for the initial establishment of neonate microbiota. Second, there is increasing evidence suggesting that gut microbiota modify central nervous system function and behavior, and microbiome-associated factors impact host immune activation, neural pathways, tryptophan metabolism and serotonin, gut hormone responses, and systemic exposures to bacterial metabolites.\textsuperscript{39} One or more of these events could, in theory, impact neurophysiology and development. A recent study of microbiota-deficient adult rodents showed differences in the regulation of genes linked to myelination and myelin plasticity in the prefrontal cortex, which was reversed by colonization with conventional microbiota.\textsuperscript{40} Third, a role for microglia and brain remodeling may be involved in response to the stressors and/or microbial-derived signals noted above.

One study in neonatal mice showed lower mitochondrial uncoupling protein 2 messenger RNA expression in the brain hippocampus associated with cesarean delivery.\textsuperscript{41} Uncoupling protein 2 expression during the early postnatal period is important for neuronal differen-
brain development (Fig 4). Further study on animal models is necessary, in turn modifying brain microglia activities that impact and/or the gut microbiome elicit a change in local signals of gut-brain cross-talk, in part, by using components from the Servier Medical Art Powerpoint image bank (https://smart.servier.com/), which is under an open-use Creative Commons license.

FIG 4. Illustration of a hypothetic model for mechanisms that drive differences in brains between infants with vaginal birth and cesarean delivery. Under this model, birth mode–associated changes to the gut microbiome lead to alterations in signals to the brain that regulate normal remodeling processes. Because microglia are implicated in this process, the model emphasizes this cell type as a major player in cell-cell cross-talk (red arrows) that modifies overall brain structure and function during the neonatal period. The model provides a theoretic framework for how birth mode contributes to normal neonatal brain development. The figure was generated, in part, by using components from the Servier Medical Art Powerpoint image bank (https://smart.servier.com/), which is under an open-use Creative Commons license.

The strengths of our approach include statistical analyses considering relevant covariates and reproducibility in 2 independent cohorts at different sites.

CONCLUSIONS

Studies separately conducted at 2 independent institutions revealed significant effects of cesarean delivery on infant brain development, including reduced white matter microstructural integrity, weaker resting-state functional connectivity, and less myelination. While obstetric situations necessitating cesarean delivery not addressed in this study could also be potential confounding factors, these novel findings may have important clinical practice implications, given the increasing global prevalence of cesarean delivery. Nevertheless, there is no evidence from the current study that the effects are long-lasting at the brain anatomic level, considering that different structural measurements across age were used and functional connectivity were not assessed in the older cohorts. Additional studies are needed that look specifically at the impact of delivery mode on short- and long-term brain biology, neurocognition, learning, and behavior phenotypes.

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