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Morphological features of the neonatal brain following exposure to regional anesthesia during labor and delivery

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ABSTRACT

Introduction: Recent animal and human epidemiological studies suggest that early childhood exposure to anesthesia may have adverse effects on brain development. As more than 50% of pregnant women in the United States and one-third in the United Kingdom receive regional anesthesia during labor and delivery, understanding the effects of perinatal anesthesia on postnatal brain development has important public health relevance.
Methods: We used high-resolution magnetic resonance imaging (MRI) to assess the effects of regional anesthesia during labor and delivery as part of a larger study of perinatal exposures on the morphological features of the neonatal brain. We mapped morphological features of the cortical surface in 37 healthy infants, 24 exposed and 13 unexposed to regional anesthesia at delivery, who were scanned within the first 6 weeks of life.
Results: Infants exposed to maternal anesthesia compared with unexposed infants had greater local volumes in portions of the frontal and occipital lobes bilaterally and right posterior portion of the cingulate gyrus. Longer durations of exposure to anesthesia correlated positively with local volumes in the occipital lobe.
Conclusions: Anesthesia exposure during labor and delivery was associated with larger volumes in portions of the frontal and occipital lobes and cingulate gyrus in neonates. Longitudinal MRI studies are needed to determine whether these morphological effects of anesthesia persist and what their consequences on cognition and behavior may be.

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1. Introduction

In 2007 and 2011 the U.S. Food and Drug Administration held advisory meetings to discuss emerging animal and human research suggesting that exposure to anesthetic agents during infancy and early childhood can be neurotoxic and produce long-term learning deficits [1,2]. The committee determined that further studies are needed to establish the dose and duration of anesthetic use that produces the neurotoxic effects reported in young animals and humans, and it recommended that elective surgeries requiring administration of anesthesia be delayed whenever possible in children younger than three years of age.

Brain development during early childhood represents a unique temporal window of potential vulnerability to the neurotoxic effects of anesthetic agents, as the major architectural features of the brain are established during prenatal and early postnatal life [3]. The brain grows most rapidly between the third trimester of gestation and the fourth postnatal month [3], primarily as a consequence of glial cell proliferation, but also of synapse formation and the arborization of axons and dendrites [4]. Neurons at this time also establish early functional circuits as foundations for the later emergence of more elaborate networks that support higher-order cognitive functions [5].

Prior studies have reported divergent neurobehavioral effects of neonatal exposure to anesthesia. Whereas several studies reported that exposure to anesthesia via maternal epidural and spinal block had no discernible short-term effects on neonatal behavior [6], several others suggested that anesthetic exposure during labor and delivery depresses neonatal sucking [7], muscle tone, and strength [8], albeit only transiently in some cases. None of these studies

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assessed the long-term neurodevelopmental effects of anesthetic exposure during labor and delivery.

Detection of anesthetic drug levels in the umbilical vein and artery at birth indicates that maternally administered regional anesthesia can reach the human fetus [9]. Although animal studies across many species have shown that exposure to anesthetic agents increases apoptosis [10,11] and the density of dendritic spines [12], to date no human studies have assessed the effects of *in utero* exposure to anesthesia on brain development.

The current study of healthy, full-term neonates was a naturalistic assessment of the correlates of regional (epidural or spinal) exposure to anesthesia with indices of local volume across the cerebral surface. Based on findings from animal studies, we hypothesized that exposure to regional anesthesia would be associated with altered measures of brain maturation.

2. Methods

2.1. Participants

Our cohort of 37 healthy infants was a subset of participants in a larger study of perinatal exposures on infant brain development. Pregnant women were recruited from 2005 to 2009 during the first to third trimester of pregnancy from prenatal clinics at New York Presbyterian Hospital, Columbia University Medical Center. Inclusion criteria for healthy infants included a maternal age at conception of 18–45 years, no major prenatal or delivery complications, gestational age ≥37 weeks, birth weight >10th percentile relative to the national standards, no major congenital anomalies, and an uncomplicated neonatal nursery course. Infants were excluded if the mother had a history of a chronic medical disease, used drugs of abuse, smoked cigarettes, or drank more than 1 ounce of alcohol during any trimester. Parents provided informed written consent for their infant to participate in the study including the magnetic resonance imaging (MRI) scan. Infants were imaged within the first 6 weeks of life. All study procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute.

2.2. Procedures

2.2.1. Measures

To determine whether mother-infant dyads were eligible for the study, we administered to all mothers a hospital screening survey that included questions on health, use of drugs of abuse, smoking, and alcohol. The Hollingshead Index of Social Status was estimated using the highest educational and current occupational levels attained by the parent(s) [13].

A neonatologist extracted from the clinical record obstetrical and neonatal data for the course of pregnancy, labor, and delivery, use of analgesia/anesthesia, laboratory data, and neonatal course (e.g., Apgar scores and physical exam).

The standard regional analgesia (A) and anesthesia (B) protocols used at New York Presbyterian Hospital are listed (STable 1 in the Supplement). Regional analgesia and anesthesia for labor and delivery refer to the use of local anesthetic and adjuvant drugs that at varying doses relieve pain or produce partial or complete loss of sensation in a localized area. Analgesia refers to the use of lower doses of the medication that provides pain relief with or minimal or no loss of sensation. Anesthesia refers to the use of higher doses of the medications that provide pain relief with loss of sensation. Because the terms are often used interchangeably and therefore for simplicity, we will use the term anesthesia to refer to analgesia and anesthesia.

2.2.2. MRI scanning

The infants were fed, swaddled, and given time to fall asleep. No sedatives were used. Foam ear plugs along with ear shields (Natus Medical Inc., San Carlos, CA) were applied to dampen scanner noise. MRI safe electrocardiography and pulse oximetry leads were placed and heart rate and oxygen saturation were continually monitored during the scan (InVivo Research, Orlando, FL). Infants were acclimated to the scanner environment and noise before the start of scanning. Scans were stopped at any signs of infant discomfort or changes in vital signs.

Images were obtained using a 3 Tesla GE Signa MRI scanner (Milwaukee, WI) and an 8-channel head coil. A 3-plane localizer was used to position the T2-weighted axial images parallel to the anterior–posterior commissure line. The T2-weighted images were acquired using a 2-dimensional, multiple-shot, fast spin echo pulse sequence that employed PROPELLER (Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction) to reduce motion artifacts in reconstructed MR images [14]. The pulse sequence parameters were repetition time = 10,000 ms; echo time = 130 ms; echo train length = 32; matrix size = 192 × 192; field of view = 190 × 190 mm; phase field of view = 100%; slice spacing = 1 mm; readout bandwidth = 83.33 KHz; number of acquisitions = 1 × 2 (i.e., two images are acquired and averaged off-line, allowing us to rescan one of the acquisitions if the infant moved). The voxel dimensions were 0.99 mm × 0.99 mm × 1 mm.

2.2.3. Image processing

The anatomical T2-weighted images for each infant were processed using a combination of automated and manual editing procedures (SFig.1 in the Supplement) that have been previously described [15]. Briefly, morphometric analyses were performed using ANALYZE 7.5 software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN) with operators blinded to infant characteristics. Large-scale variations in image intensity were removed [16]. Images were all aligned to a standard orientation using midline landmarks (anterior and posterior commissure and midsagittal plane) to correct for head rotation and tilt. We isolated the brain from nonbrain tissue using an isointensity contour function with manual edits that were confirmed by a second operator [17]. Connecting dura was removed manually on each slice in the sagittal view and confirmed in the orthogonal views. The brain was divided into hemispheres using a curvilinear plane positioned through standard midline landmarks. The cerebellum was removed where the peduncles join the brainstem, the brainstem was transected at the pontomedullary junction, and the brain was split into two hemispheres. The operator interrater reliability was assessed on 10 scans and intraclass correlation coefficients were greater than 0.95.

2.2.4. Deformation-based measures of brain morphology

We applied a rigorous, two-step procedure to select the brain of a single infant as the template to ensure that it was morphologically representative of the brains in our cohort (see Supplemental Materials). We calculated distances from the surfaces of each neonatal brain from the corresponding points on the surface of a template brain (SFig.1 in the Supplement) using previously validated methods [18] that permit fine-grained analyses of localized morphological features across the cerebral surface [19]. First we applied to each brain a similarity transformation consisting of seven parameters (three translations along the X, Y, and Z axes, three different rotations about the three axes, and one global scaling that scales the entire brain by the same amount along the three axes) to coregister each brain to the template while maximizing mutual information between the brains [20]. Second, we nonlinearly transformed each brain to the template using a high-dimensional, non-rigid warping algorithm based on fluid dynamics [21] so that

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