Are Anesthesia and Surgery during Infancy Associated with Decreased White Matter Integrity and Volume during Childhood?

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ABSTRACT

Background: Anesthetics have neurotoxic effects in neonatal animals. Relevant human evidence is limited. We sought such evidence in a structural neuroimaging study.

Methods: Two groups of children underwent structural magnetic resonance imaging: patients who, during infancy, had one of four operations commonly performed in otherwise healthy children and comparable, nonexposed control subjects. Total and regional brain tissue composition and volume, as well as regional indicators of white matter integrity (fractional anisotropy and mean diffusivity), were analyzed.

Results: Analyses included 17 patients, without potential confounding central nervous system problems or risk factors, who had general anesthesia and surgery during infancy and 17 control subjects (age ranges, 12.3 to 15.2 yr and 12.6 to 15.1 yr, respectively). Whole brain white matter volume, as a percentage of total intracranial volume, was lower for the exposed than the nonexposed group, 37.3 ± 0.4% and 38.9 ± 0.4% (least squares mean ± SE), respectively, a difference of 1.5 percentage points (95% CI, 0.3 to 2.8; $P = 0.016$). Corresponding decreases were statistically significant for parietal and occipital lobes, infratentorium, and brainstem separately. White matter integrity was lower for the exposed than the nonexposed group in superior cerebellar peduncle, cerebral peduncle, external capsule, cingulum (cingulate gyrus), and fornix (cres) and/or stria terminalis. The groups did not differ in total intracranial, gray matter, and cerebrospinal fluid volumes.

Conclusions: Children who had anesthesia and surgery during infancy showed broadly distributed, decreased white matter integrity and volume. Although the findings may be related to anesthesia and surgery during infancy, other explanations are possible. **(ANESTHESIOLOGY 2017; 127:788-99)**

GENERAL anesthesia (hereafter referred to as *anesthesia*) causes histopathologic and functional changes in the central nervous system (CNS) of late fetal and early neonatal animals,[1–6] associated with long-term behavioral changes, including deficits in learning and memory.[5] More than approximately 250,000 human infants in the United States have anesthesia annually.[7,8] The possibility that this exposure could result in abnormalities in CNS and cognitive development with lifelong consequences is concerning, but whether findings from animal studies apply to humans is uncertain.

Direct evidence about adverse effects on CNS and cognitive development of early anesthesia and surgery in humans is limited. Most relevant studies have examined behavioral outcomes. Earlier studies were summarized in a 2008 review.[9] More than 30 studies have been published since, some summarized in more recent reviews.[6] Many earlier studies did not focus specifically on anesthesia and included patients with major medical problems that might affect CNS or cognitive function, but many recent studies

What We Already Know about This Topic

- Anesthetics have neurotoxic effects in neonatal animals. However, neither volumes of white or gray matter in anatomically defined brain regions nor regional indicators of white matter integrity have been studied in relatively healthy children undergoing anesthesia and surgery.
- Magnetic resonance imaging at the ages of 12 to 15 yr was performed in children who had undergone anesthesia and surgery during infancy. Total and regional white and gray matter volumes and regional white matter integrity were determined.

What This Article Tells Us That Is New

- Children exposed to anesthesia and surgery during infancy had lower whole brain white matter volumes than control subjects. Regional white matter volumes and integrity were also reduced in the exposed children.
- Although white matter volumes and integrity were reduced in exposed children, no inference about causality can be made, and comorbid conditions may well have contributed to the structural changes that were observed on magnetic resonance imaging.

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focused on anesthesia and relatively broader or healthier populations or subgroups.[10–15] In some studies, under some circumstances, early anesthesia and surgery were associated with later impairments in academic achievement[10] or cognition,[13,14] or increased frequencies of learning disabilities[13] or developmental or behavioral disorders.[12] The overall pattern of results has been mixed, with some studies suggesting little or no adverse effects.[11,15]

Fewer studies have examined effects of exposure to anesthesia and surgery in children using neuroimaging. One study, using magnetic resonance imaging (MRI), found some associations of decreased cognitive test scores with altered gray matter volumes in certain regions in children with such exposure before their fourth birthday.[16] Another study, using functional MRI during a response inhibition test, found differences in activity in several regions in children exposed before their second birthday.[17] Other tangentially relevant neuroimaging studies involved regional anesthesia[18] or populations with frequent CNS problems unrelated to anesthesia, making it difficult to attribute any effects to sedative or anesthetic drugs.[19–25]

Previously we reported that a higher than expected percentage of children with anesthesia and surgery during infancy later showed very poor academic achievement, even among a subgroup with no potential confounding CNS problems or risk factors during infancy.[10] The present study assessed possible associations of anesthesia and surgery during infancy with later brain structure abnormalities among children with no potential confounding CNS problems or risk factors. We compared global and regional volumes of white and gray matter of children with anesthesia and surgery to otherwise similar but nonexposed control subjects. In addition, regional white matter measurements of fractional anisotropy and mean diffusivity were analyzed as indicators of diminished white matter integrity.[26]

We hypothesized that early anesthesia and surgery might be associated with decreased total and regional white and gray matter volumes and white matter integrity. Any such changes might be related to CNS neurotoxicity of early anesthesia found in animal studies, including apoptosis of oligodendrocytes and neurons.[1–6] Oligodendrocytes are essential in myelinating axons, of which white matter is largely composed; and correlative MRI and other evidence has been accumulating in recent years suggesting the involvement of myelin in cognition and learning.[27,28]

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Materials and Methods

Approval

The research and consent procedures were approved by the University of Iowa Institutional Review Board (Iowa City, Iowa).

Selection of Groups of Operations

Four groups of operations were selected for the research through a pilot study that attempted to identify operations that were often performed under anesthesia on otherwise healthy infants (*i.e.*, age younger than 1 yr) and for which sufficient numbers of cases were available for review: circumcision (older than 28 days), inguinal hernia repair and orchiopexy (with or without hernia repair), pyloromyotomy, and tympanostomy.

Selection and Recruitment of Patients

Department of Anesthesia (University of Iowa, Iowa City, Iowa) billing records were searched for male patients within the targeted current age range (table 1) who had anesthesia for one or more of the four groups of operations during infancy. To recruit potential control subjects who were not exposed to anesthesia and surgery during infancy, University of Iowa Hospitals and Clinics medical charts were searched for male inpatients or outpatients within the targeted current age range. For patients exposed to anesthesia and surgery during infancy, the entire population was considered; for the much larger population of potential control subjects, pseudorandomly selected samples for different ages within the targeted current age range were considered. Preliminary review of the hospital electronic medical charts was conducted to exclude patients who certainly or almost certainly did not meet the inclusion–exclusion criteria (*e.g.*, who had CNS problems or risk factors during infancy; table 1). For some patients exposed to anesthesia and surgery, who had already been considered for participation in a previous study,[10] medical history information from that study was also reviewed.

Letters inviting participation in the study were sent to parents of patients. The hospital mailing addresses for parents were frequently out of date because of the length of time between the date of surgery and the present. Current mailing addresses and telephone numbers were sought through Internet searches and the MetroNet database of Experian, a credit reporting agency. If interested, parents telephoned a research assistant for additional information and preliminary screening. Those who were eligible and interested in participating were subsequently seen for in-person screening of the patient and one of his parents. Compensation was provided for participation. During in-person screening, following written informed consent of the parent and consent (age 13.0 yr or older) or assent (age less than 13.0 yr) of the patient, we obtained demographic and medical history information concerning the patient from the parent and handedness (Edinburgh Handedness Inventory[29]), drug use

Table 1. Exclusion Criteria

Contraindications to magnetic resonance imaging (*e.g.*, certain types of metal in the body or claustrophobia)
Current age < 12.0 yr or > 15.25 yr*
Current severe systemic diseases†
Current use of psychotropic or other prescribed medications that could affect the results of neuroimaging or cognitive function‡
Dental braces (which would interfere with neuroimaging)
Female§
History at birth or before the first birthday of any of 18 types of prespecified conditions or procedures defined as central nervous system disorders or potential risk factors for subsequent developmental or cognitive dysfunction‖; or other medical problems during infancy or later that might significantly affect central nervous system or cognitive development unless they were considered possible sequelae of anesthesia and surgery (*e.g.*, attention-deficit/hyperactivity disorder, learning disorders, and developmental delays)†
History of serious psychopathology (*e.g.*, schizophrenia or mood disorder) based on the C-DISC, medical records, and parental report
Left or mixed handedness (*i.e.*, Edinburgh Handedness Inventory score of ≤ 40)
Nonnegligible use of alcohol or illicit drugs
Residence > 150 miles from University of Iowa Hospitals and Clinics
Substantial uncorrected auditory or visual impairments

*This age range was chosen to assess very long-term effects of anesthesia and surgery during infancy; to minimize problems with excessive subject motion in the scanner, entailing loss of data, which are substantially more prevalent in younger children; and to be wide enough to ensure feasibility of recruiting enough subjects but narrow enough to reduce age-related variability. †Medical problems were evaluated by two anesthesiologist coinvestigators for a joint decision on inclusion and exclusion. ‡Chronic use of stimulants to control symptoms of attention-deficit/hyperactivity disorder was permitted. §Females were excluded because they constituted only a small percentage of patients who had anesthesia and surgery during infancy.[10] ‖The conditions or procedures are listed in table 2 of a previous report.[10]

C-DISC = National Institute of Mental Health Diagnostic Interview Schedule for Children, C-DISC Version IV.

history, and psychiatric (National Institute of Mental Health Diagnostic Interview Schedule for Children, C-DISC Version IV[30]) information from the patient. Information from the telephone and in-person screening, the hospital electronic and paper medical charts, and additional medical history information from other hospitals and physician offices (which was obtained whenever relevant) were extracted in prespecified formats, including information pertaining to inclusion–exclusion criteria (table 1), comparability of patients exposed to anesthesia and surgery and control subjects, and history of anesthesia and surgery.

Selective Recruitment of Control Subjects

To achieve comparability of the groups of patients exposed to anesthesia and surgery and control subjects, some prospective control subjects were excluded based on age, race, ethnicity, household income, and medical history characteristics that were unrepresentative of the patients exposed to anesthesia and surgery. No patients exposed to anesthesia and surgery were excluded to achieve comparability. Patients exposed to anesthesia and surgery and an equal number of comparable control subjects were scheduled for structural MRI (as well as functional MRI and additional cognitive testing after MRI, the results of which will be reported separately). Recruitment of control subjects was then stopped.

Structural MRI

The subject was initially familiarized with the scanner environment and procedures in a Psychology Software Tools MRI Simulator (Psychology Software Tools, Inc., USA). Anatomic and diffusion tensor imaging (DTI) (together taking 19 min) was performed on a Siemens TIM Trio 3.0T MRI Scanner (Siemens, Germany) with a 12-channel head array. Anatomic imaging included three-dimensional T1-weighted images collected in the coronal plane using an Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) sequence (echo time [TE] = 3 ms; inversion time = 900 ms; repetition time [TR] = 2,530; flip angle = 10°; field of view [FOV] = 256 × 256 × 240 mm; matrix = 256 × 256 × 240; parallel imaging implementation = 2; bandwidth = 220 Hz/pixel) and three-dimensional T2-weighted scans collected in the coronal plane (TE = 430 ms; TR = 4,800 ms; FOV = 256 × 256 × 224 mm; matrix = 256 × 256 × 160; parallel imaging implementation = 2; bandwidth = 592 Hz/pixel). Two-dimensional DTI data were acquired using a twice refocused echo-planar spin-echo sequence in the axial plane (TE = 92 ms; TR = 12,000 ms; FOV = 256 × 256 mm; matrix = 128 × 80; bandwidth = 1,396 Hz/pixel; b value = 1,000 s/mm^2; no. of directions = 30).

Image Analyses

Global and regional measures of brain tissue composition and volume were analyzed. The fully automated structural imaging pipeline of the BRAINS software (AutoWorkup) was used.[31] A human observer blindly reviewed the images for technical quality before analysis and reviewed for pipeline failures. Briefly, this pipeline reoriented the T1-weighted images to achieve alignment along the anterior and posterior commissures and along the interhemispheric plane. The T2-weighted images were then aligned with the anterior/posterior commissure-aligned T1 images. Next, tissue classification was performed using a multispectral discriminant analysis method with automated training class selection to classify each voxel as gray matter, white matter, cerebrospinal fluid (CSF), or blood.[32] Subsequently, an atlas-based segmentation into regions (frontal, parietal, temporal, and occipital lobes; subcortical region; and cerebellum and brainstem) was performed.[33] Finally, a neural network segmentation was

performed to delineate the brain, including surface CSF.[34] Volume measurements for gray matter and white matter were then obtained for each region, as were volume measurements for total (ventricular and surface) CSF and total blood. Volume measurements were converted from voxels to physical units (cubic centimeters).

For the DTI data, quality assurance was first performed using DTIPrep[35] to eliminate diffusion gradients with artifacts while retaining the remaining high-quality diffusion-weighted images. Next, the diffusion-weighted images were coregistered to the b0 image to remove motion and eddy-current artifacts. The motion-corrected diffusion-weighted images were then coregistered to the anterior and posterior commissure aligned anatomic T1-weighted image generated as part of the structural image analysis using the b0 image. The resulting rigid body transformation was used to resample the diffusion-weighted image and to rotate the diffusion gradients.[36] Tensor estimation was then performed, and rotationally invariant scalar measures of fractional anisotropy and mean diffusivity were generated. Regional white matter measurements were made. The white matter regions measured corresponded closely with those listed in the description by Mori *et al.*[37] of their White Matter Parcellation Map, except that four regions in that listing were not distinguished (medial longitudinal fasciculus, inferior fronto-occipital fasciculus and/or uncinate fasciculus, inferior fronto-occipital fasciculus and/or inferior longitudinal fasciculus, and anterior commissure), and three other regions were distinguished (fornix [column/body], pontine crossing tract, and posterior thalamic radiation).

Statistical Analysis

The comparability of the groups (children exposed to anesthesia and surgery *vs.* control subjects) with respect to their own and their parents' characteristics was assessed by two independent samples Student's *t* tests for quantitative characteristics (*e.g.*, age) and Fisher exact tests for categorical characteristics (*e.g.*, ethnicity). Volumes of whole brain white matter, gray matter, CSF, and blood, as well as regional volumes of white matter and gray matter, were expressed as percentages of total intracranial volume (total white matter, gray matter, CSF, and blood combined). Adjusting tissue volumes for total intracranial volume has become standard practice in cross-sectional studies in recent years to reduce the influence of factors not associated with the mechanism of interest.[38] Left and right sides were analyzed separately, as well as combined. These measures, as well as fractional anisotropy and mean diffusivity of the white matter regions from DTI, were compared between groups by analysis of covariance, with subject's age at the time of MRI as the covariate. This analytical plan was developed before examination of the data by the first author in consultation with the authors, especially those with expertise in biostatistics (E.O.B.) and image analysis (V.A.M.), and another colleague experienced in pediatric structural image analysis (P.C.N.; see Acknowledgments). In addition, secondary analyses were performed to assess possible confounding effects among children exposed to anesthesia and surgery: those who had tympanostomy *versus* other surgeries were compared to assess chronic otitis media, and those who did or did not have *health issues*, defined as current chronic diseases or current or past attention-deficit/hyperactivity disorder, learning disorders, or developmental delays, were compared. Furthermore, to assess possible confounders, the primary between-group analyses of covariance were redone with health issues and low (less than $50,000) annual household income as additional covariates. A significance level of $P < 0.05$ with two-tailed tests was used for all of the analyses. Because of the preliminary, hypothesis-generating nature of this study, correction for multiple comparisons was not used. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

Results

Characteristics of Children and Their Parents

The numbers of subjects invited to participate who were screened and recruited, who had MRI, and whose MRI data were analyzable are shown in a flow diagram (fig. 1). For the eligible children with some analyzable MRI data (fig. 1), the age ranges were 12.3 to 15.2 yr for the 17 patients with anesthesia and surgery and 12.6 to 15.1 yr for the 17 control subjects. Characteristics of these children and their parents are shown in table 2.[39,40] Patients with anesthesia and surgery and control subjects did not differ significantly in age, years of education, ethnicity, race, total intracranial volume, height (which is potentially correlated with total intracranial volume), household income, or a number of characteristics related to their health status and history or their parents' education and employment. No patients with anesthesia and surgery or control subjects had a history of medical problems that were judged likely to have affected current brain structure, brain function, or cognition. Table 3 provides information about characteristics of exposures to anesthesia for the patients who were exposed during infancy, including the types of operations and anesthetics and the age at operation for the groups of operations during infancy selected for study, as well as additional exposures and durations of exposures.

Whole Brain Tissue-type Volumes

Total white matter volume, as a percentage of total intracranial volume, was lower in patients with anesthesia and surgery (least squares mean ± SE of 37.3 ± 0.4%; 95% CI, 36.5 to 38.2%) than control subjects (38.9 ± 0.4%; 95% CI, 38.0 to 39.7%; $P = 0.016$; fig. 2). The difference was 1.5 percentage points (95% CI, 0.3 to 2.8; *i.e.*, 1.5/38.9 = 3.9%) lower for the exposed than the nonexposed group. The corresponding difference for gray matter was negligible (0.2% difference), whereas that for CSF seemed large in percentage terms (17.3% higher in patients with anesthesia and surgery than control subjects) but was nonsignificant due to substantial variability (fig. 2).

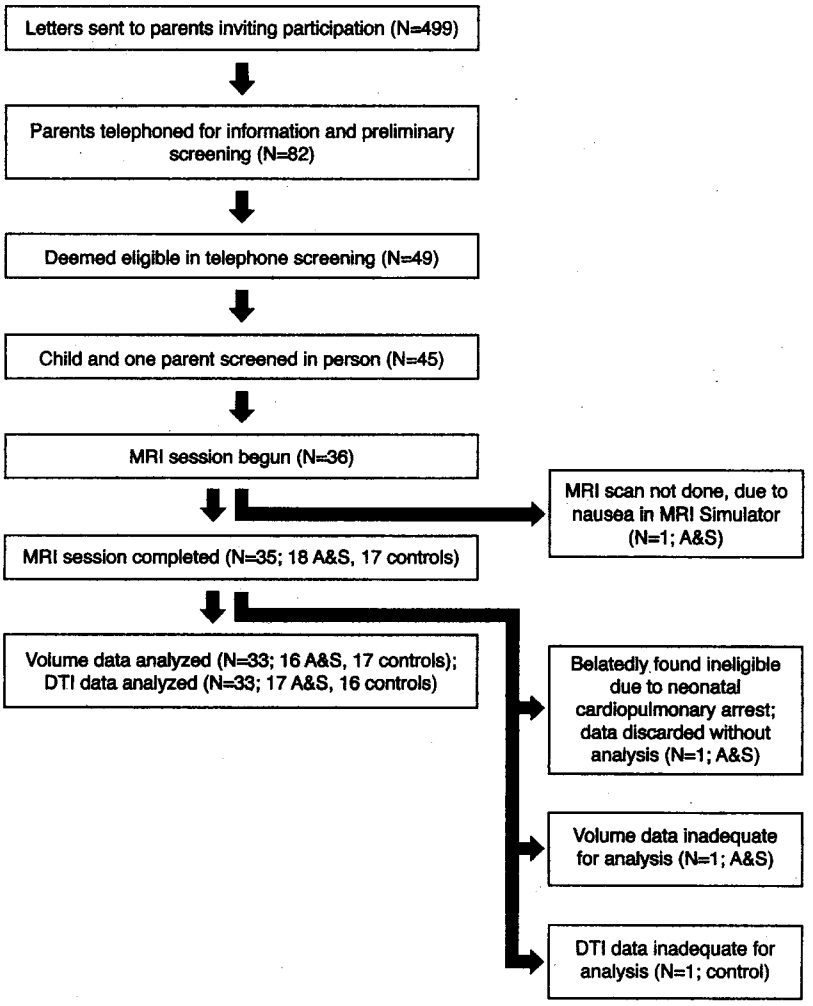

Fig. 1. Numbers of subjects invited to participate who were screened and recruited, who had MRI, and whose MRI data were analyzable. A&S = anesthesia and surgery; DTI = diffusion tensor imaging; MRI = magnetic resonance imaging.

Regional White Matter Volumes

Table 4 shows white matter volumes as percentages of total intracranial volume. The smaller total white matter volume associated with anesthesia and surgery was significant for both left and right sides separately. For left, right, and/or both sides combined, anesthesia and surgery were associated with significantly smaller white matter volumes in the parietal and occipital lobes, the infratentorium as a whole, and the brainstem. In contrast to the 12 significant differences showing associations of anesthesia and surgery with lower white matter volumes in table 4, there were none in the opposite direction; and corresponding analyses of gray matter volumes showed no associations with anesthesia and surgery.

Diffusion Tensor Imaging

Diminished white matter integrity in many disease and injury processes is typically associated with decreased fractional anisotropy and/or increased mean diffusivity.[26] In DTI, all of the significant differences associated with anesthesia and surgery were in the directions associated with diminished white matter integrity, including six decreases in fractional anisotropy and three increases in mean diffusivity (table 5); none were in the opposite directions. These associations occurred in the left and/or right superior cerebellar peduncle, cerebral peduncle, external capsule, cingulum (cingulate gyrus), and fornix (cres) and/or stria terminalis.

Possible Confounders

Among children exposed to anesthesia and surgery, there were some differences in the outcome measures between those who had tympanostomy *versus* other surgeries (n = 5 and 12, respectively; table 3) and between those who did or did not have health issues (n = 10 and 7; table 2); results not shown. However, only one of these differences (for health issues, white matter volume of the infratentorium, left and right sides combined) corresponded with any of the differences associated with anesthesia and surgery (table 4, second footnote). When the primary between-group analyses were redone with health issues and low income as additional covariates, 81% (17 of 21) of the significant effects (tables 4

Table 2. Characteristics of Children and Their Parents

Variable	Anesthesia and Surgery	Control Subjects
Age, yr	13.9±0.9	13.8±0.8
Education, yr	8±1	7±1
Education (father), yr	14±3	15±4
Education (mother), yr	15±3	14±2
Total intracranial volume, cc	1,493.4±116.9	1,515.5±133.7
Height, cm	169±12	167±12
Ethnicity		
Hispanic	1 (6)	1 (6)
Not Hispanic	16 (94)	16 (94)
Race		
White	16 (94)	17 (100)
Not white	1 (6)	0 (0)
Annual household income		
< $50,000	4 (24)	2 (12)
$50,000 to $74,999	1 (6)	3 (18)
$75,000+	12 (71)	12 (71)
Employment status (father)*		
Employed	15 (94)	17 (100)
Not employed	1 (6)	0 (0)
Employment type (father)*		
Professional, managerial, or comparable	9 (56)	11 (65)
Not professional, managerial, or comparable	6 (38)	6 (35)
Retired	1 (6)	0 (0)
Highest diploma or degree (father)		
None	1 (6)	0 (0)
High school/GED, but not bachelor's	10 (59)	8 (47)
Bachelor's or above	6 (35)	9 (53)
Employment status (mother)		
Employed	14 (82)	17 (100)
Not employed	3 (18)	0 (0)
Employment type (mother)		
Professional, managerial, or comparable	7 (41)	9 (53)
Not professional, managerial, or comparable	7 (41)	8 (47)
Homemaker or student	3 (18)	0 (0)
Highest diploma or degree (mother)		
None	0 (0)	0 (0)
High school/GED, but not bachelor's	8 (47)	10 (59)
Bachelor's or above	9 (53)	7 (41)
ASA PS category		
I	13 (76)	16 (94)
II	4 (24)	1 (6)
Charlson Comorbidity Index score[35]		
0	14 (82)	17 (100)
1–2	3 (18)	0 (0)
Surgical risk score[36]		
0	17 (100)	17 (100)
Current chronic disease		
No	13 (76)	16 (94)
Yes	4 (24)	1 (6)
Current and lifelong chronic disease		
No	14 (82)	17 (100)
Yes	3 (18)	0 (0)
Current or past ADHD, learning disorders, or developmental delays		
No	8 (47)	13 (76)
Yes	9 (53)	4 (24)

Values are mean ± SD for continuous variables and number of subjects (percentage of subjects) for categorical variables for the children who had anesthesia and surgery during infancy (N = 17) and control subjects (N = 17). Values are for the child except where father or mother is indicated. $P > 0.10$ for all differences between groups by t tests for continuous variables and Fisher exact tests for categorical variables. Children with ASA PS category II, Charlson Comorbidity Index score[35] > 0, and/or current chronic disease had the following current conditions (which, however, were not causing any significant ongoing problems): asthma (1 patient), chronic kidney disease/hydronephrosis (2 patients), scoliosis (1 patient), and migraine (1 control subject). ADHD, learning disorders, and developmental delays were counted based either on parental report or diagnoses in medical charts and were not included as chronic disease above, although some children (3 patients and 0 control subjects) had both.

*One deceased father was omitted.

ADHD = attention-deficit/hyperactivity disorder; ASA PS = American Society of Anesthesiologists Physical Status Classification System; GED = General Educational Development certificate.

and 5), including total white matter volume, remained significant (table 4, first footnote; table 5, footnote).

Discussion

Differences between Groups

Patients with anesthesia and surgery differed from control subjects in showing broadly distributed, decreased white matter integrity and volume. White matter volume (relative to total intracranial volume) was decreased for the brain overall and several regions separately, including parietal and occipital lobes, infratentorium as a whole, and brainstem. White matter integrity was decreased in several limbic, corticocerebellar loop, and other regions, including superior cerebellar peduncle, cerebral peduncle, external capsule, cingulum (cingulate gyrus), and fornix (cres) and/or stria terminalis. These findings might conceivably reflect long-term effects in humans related to anesthesia-induced apoptosis of oligodendrocytes in animals.[1–3] Extensive myelination proceeds gradually during human infancy.[41] If human infants experience anesthesia-induced apoptosis of myelin-producing oligodendrocytes,[28] long-lasting effects on white matter integrity and volumes might occur. Other possibilities include long-lasting effects of anesthesia-induced neuroapoptosis. Changes due to apoptosis during infancy might also conceivably lead to developmental delays associated with more pronounced changes in white matter integrity

Table 3. Characteristics of Exposures to General Anesthesia

Variable	Data
Groups of operations during infancy selected for study	
Operations (No. of patients)	
Circumcision (older than 28 d)	8 (47)
Tympanostomy	5 (29)
Pyloromyotomy	3 (18)
Orchiopexy (with or without hernia repair)	1 (6)
Volatile and gaseous anesthetics (No. of patients)*	
Nitrous oxide	16 (94)
Sevoflurane	10 (59)
Isoflurane	7 (41)
Halothane	4 (24)
Desflurane	1 (6)
Age at operation (d)	190 ± 127
Additional exposures to general anesthesia (No. of patients)	
Later during infancy, at UIHC†	2 (12)
After infancy, at UIHC‡	6 (35)
After infancy, not at UIHC§	5 (29)
Duration of exposures to general anesthesia, min	
For groups of operations during infancy selected for study	62 ± 36
For all exposures during infancy	68 ± 45
For all exposures during and after infancy at UIHC‖	124 ± 137

Values are mean ± SD for continuous variables and number of subjects (percentage of subjects) for categorical variables for the children exposed to anesthesia and surgery during infancy (N = 17).

*Some patients received more than one volatile and gaseous anesthetic. Other anesthetic, sedative, or analgesic drugs administered were morphine, propofol, and sodium thiopental; each was administered to N = 1 (6%). †Each patient had one additional exposure, and these were at UIHC (for otolaryngologic examination or myringotomy/excision of benign lesion). ‡Each patient had one to three additional exposures (for adenoidectomy, cystourethroscopy, excision of frenum, excision of lesion of tongue, insertion of gastrostomy tube, tonsillectomy, or tympanostomy). §These patients each had one additional exposure (for adenoidectomy, excision of onychocryptosis, tympanostomy, or urethral ablation). ‖Durations were unavailable for exposures at facilities other than UIHC.

UIHC = University of Iowa Hospitals and Clinics.

and volumes later during childhood. Major, regionally specific brain remodeling, including overall increasing white matter and decreasing gray matter volumes, occurs during the age range at which we performed MRI.[42]

Possible Cognitive Impact of White Matter Changes

Recent MRI and other studies have suggested involvement of white matter changes (likely including myelin changes) in cognition and learning.[27,43] Various previous studies, some summarized in reviews,[43–45] suggest that the integrity of the regions in which we found significantly decreased white matter integrity associated with anesthesia and surgery contributes to higher cognitive, rather than exclusively sensorimotor, functions. This includes the corticocerebellar loop regions.[44,45] Among these cognitive functions are aspects of learning and memory. The fornix (the major outflow tract from the hippocampus) is particularly relevant to memory.[46] The regions showing decreased white matter integrity in our study seem broadly consistent with trends in both animal and human studies for long-lasting consequences of early anesthesia to occur more at a cognitive or behavioral level than a sensorimotor level, with prominent effects on learning and memory.[5,14] Contrariwise, the only prospective randomized human study of cognitive deficits associated with general anesthesia and surgery during infancy showed no deficits,[11] and exposure durations were brief and comparable to our study, making the cognitive relevance of our white matter findings unclear.

Previous, Tangentially Relevant MRI Studies of Brain Structure or Metabolism

Some previous MRI studies examined brain structure or metabolism in relation to anesthesia or surgery during childhood[16,18–21,25] or midazolam administration during neonatal care.[22,24] Two involved relatively healthy children,[16,18] but one is not pertinent because it involved regional anesthesia.[18] The pertinent study[16] involved children aged 5 to 13 yr who did or did not have anesthesia and surgery before age 4 yr. Decreased performance IQ and language comprehension were associated with lower gray matter volumes in portions of the occipital cortex and cerebellum in exposed children.

Two studies examined global or regional brain volumes or tissue types in very preterm[24,25] or low birth weight[25] infants. In one,[25] early surgery was associated with smaller total intracranial volume and deep nuclear gray matter volume as well as more frequent visually identified moderate or severe white matter injury, at term-equivalent age. In another study,[24] involving MRI early in life and again at term-equivalent age, higher cumulative doses of midazolam during neonatal care were associated with decreased hippocampal growth and increased mean diffusivity in a hippocampal region consisting primarily of gray matter. Midazolam administration was not associated with more frequent visually identified white matter injury after about a month of neonatal care, on average. An earlier study[22] involving some of these infants found no significant associations of fractional anisotropy or *N*-acetylaspartate/choline ratios in several white matter regions with cumulative doses of midazolam.

One study examined correlations of global and regional brain volumes and global tissue types with anesthetic exposure up to age 7 yr in patients with isolated oral clefts.[23] No correlations were significant overall; five subgroup analyses showed one significant correlation (with frontal lobe volume).

Approximately six studies of cardiac surgery in infants[19–21] included preoperative and postoperative brain MRI, but most did not analyze anesthetic effects. Two studies[19,20] examined anesthetic exposure and visually identified brain injury, including white matter injury, as predictors of neuropsychologic performance around the first birthday but did not examine whether anesthetic exposure influenced new postoperative brain injury. In another study,[21] ketamine supplementation influenced some measures of cerebral metabolism.

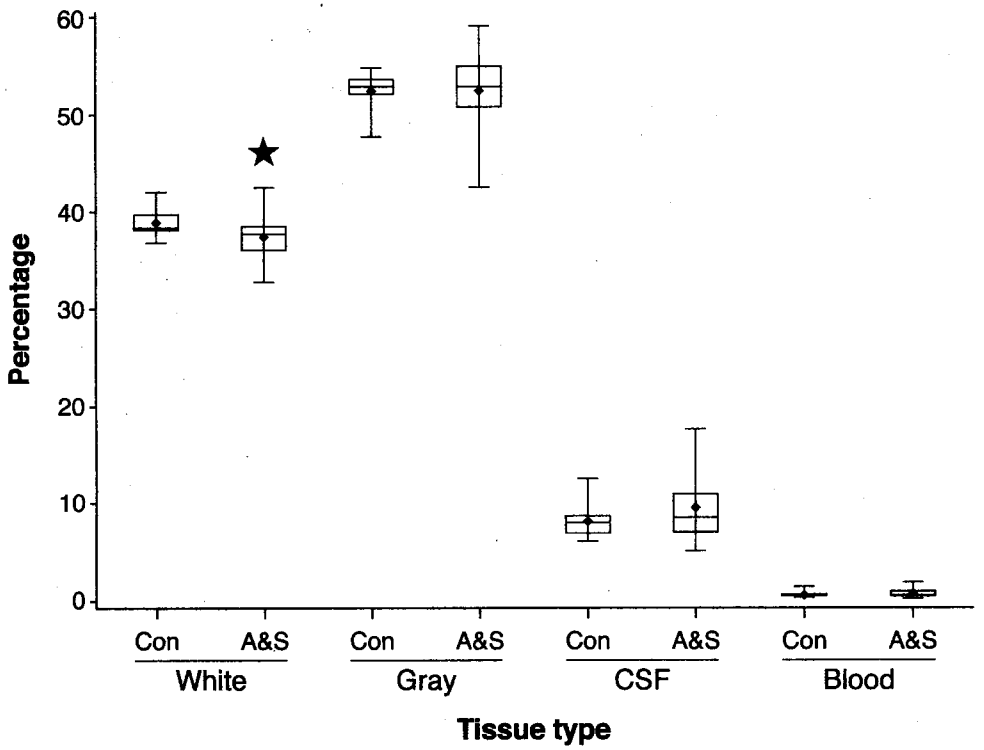

Fig. 2. Box plots of whole brain tissue type volumes as percentages of total intracranial volume. In each box plot, the least squares mean from analysis of covariance, adjusted for age, and the unadjusted mean (*i.e.*, without adjustment for age) are shown as a *plus sign* and *diamond*, respectively. The *five horizontal lines*, from *bottom* to *top*, show the unadjusted minimum, first quartile, median, third quartile, and maximum (with the *lines* showing the first and third quartiles forming the bottom and top of the box, respectively). The *star* indicates a difference between anesthesia and surgery and control subjects in analysis of covariance ($P = 0.016$; see text). The differences for gray matter, CSF, and blood were not significant. A&S = anesthesia and surgery; Con = control subjects; CSF = cerebrospinal fluid; Gray = gray matter; White = white matter.

We cannot state that our results agree or disagree with previous studies, considering the many differences in patient population and age, image analysis techniques, and other characteristics. Only global outcome variables in two studies,[23,25] and no regional outcome variables, matched any of ours.

Infants born very preterm or having isolated oral clefts or cardiac surgery[19–25] have high incidences of brain abnormalities, with multiple potential causes unrelated to anesthesia and surgery,[47–49] unlike our subjects, who had term births and comparatively healthy infancies. Moreover, infant cardiac surgery is associated with frequent, new postoperative brain injury, with multiple potential causes other than anesthesia.[48] Isolating anesthetic effects in such populations is challenging.

Limitations

This study was an observational study. There was limited success in contacting and recruiting patients, with resulting potential selection biases, and we cannot demonstrate causal relationships of white matter integrity and volume to anesthesia and surgery or distinguish influences of anesthesia *versus* surgery. Effects might be different with later or longer anesthesia and surgery or operations of higher complexity. The sensitivity of our volumetric and DTI measures to anesthetic effects in animal models is unclear. Some of the significant effects were small, and some 95% CIs only narrowly excluded 0. We did not adjust for multiple comparisons; even modest corrections would have rendered many of the significant effects nonsignificant. Our sample size, although comparable to many neuroimaging studies, was small and insufficient to permit meaningful investigation of specific types of anesthetics and surgeries, as well as duration of, and age at, exposure. (The tympanostomy analyses, however, suggested that our significant findings were not attributable to chronic otitis media.) With our sample size, statistical significance required an effect size of Cohen's d at or greater than 0.75 for whole brain white matter volume. Power at or greater than 0.9 would have required 28 subjects/group with the effect size that we observed (Cohen's $d = 0.89$; $\alpha = 0.05$, and a two-tailed test). The clinical significance of an effect of this magnitude associated with anesthesia and surgery is unknown. Larger samples will be needed to investigate this. This effect size may be compared with some extensively studied drug effects; for example, white matter atrophy is often considered a hallmark injury of alcohol use disorders, and the average effect size was 0.30 in a meta-analysis (maximum of 1.21 among the studies included).[38] As additional meta-analytic comparisons, average effect sizes were 0.17 (maximum = 0.80) for white matter

Table 4. White Matter Volumes as Percentages of Total Intracranial Volume

Region	A&S	Control Subjects	Difference	*P* Value
Left				
Cerebrum	15.4±0.2	15.9±0.2	0.5 (–0.1 to 1.1)	0.108
Frontal lobe	5.7±0.1	5.7±0.1	0.1 (–0.3 to 0.4)	0.668
Parietal lobe	3.7±0.1	3.9±0.1	0.2 (0.0 to 0.4)	**0.014***
Temporal lobe	2.6±0.1	2.7±0.1	0.1 (–0.0 to 0.3)	0.160
Occipital lobe	1.8±0.0	1.8±0.0	0.1 (–0.0 to 0.2)	0.135
Subcortical	1.8±0.0	1.7±0.0	–0.0 (–0.1 to 0.0)	0.445
Infratentorium	3.3±0.1	3.5±0.1	0.2 (–0.0 to 0.5)	0.062
Cerebellum	2.5±0.1	2.7±0.1	0.1 (–0.1 to 0.3)	0.177
Brainstem	0.7±0.0	0.8±0.0	0.1 (0.0 to 0.2)	**0.020**
Total	18.7±0.2	19.4±0.2	0.7 (0.1 to 1.3)	**0.031***
Right				
Cerebrum	15.5±0.2	16.0±0.2	0.5 (–0.0 to 1.1)	0.064
Frontal lobe	5.9±0.1	5.9±0.1	0.1 (–0.3 to 0.4)	0.685
Parietal lobe	3.6±0.1	3.9±0.1	0.3 (0.1 to 0.5)	**0.003**
Temporal lobe	2.6±0.1	2.7±0.1	0.1 (–0.0 to 0.3)	0.084
Occipital lobe	1.6±0.0	1.7±0.0	0.1 (–0.0 to 0.2)	0.115
Subcortical	1.8±0.0	1.8±0.0	–0.0 (–0.1 to 0.1)	0.677
Infratentorium	3.2±0.1	3.5±0.1	0.3 (0.1 to 0.5)	**0.012**
Cerebellum	2.5±0.1	2.7±0.1	0.2 (–0.0 to 0.4)	0.060
Brainstem	0.7±0.0	0.8±0.0	0.1 (0.0 to 0.2)	**0.007**
Total	18.7±0.2	19.5±0.2	0.8 (0.2 to 1.4)	**0.009**
Left + right				
Cerebrum	30.9±0.4	31.9±0.4	1.0 (–0.1 to 2.2)	0.081
Frontal lobe	11.5±0.2	11.7±0.2	0.1 (–0.5 to 0.8)	0.667
Parietal lobe	7.3±0.1	7.8±0.1	0.5 (0.2 to 0.8)	**0.004**
Temporal lobe	5.1±0.1	5.4±0.1	0.2 (–0.1 to 0.5)	0.104
Occipital lobe	3.4±0.1	3.5±0.1	0.2 (0.0 to 0.4)	**0.049***
Subcortical	3.6±0.0	3.5±0.0	–0.0 (–0.2 to 0.1)	0.539
Infratentorium	6.5±0.2	7.0±0.2	0.5 (0.1 to 1.0)	**0.024†**
Cerebellum	5.0±0.1	5.4±0.1	0.3 (–0.1 to 0.7)	0.097
Brainstem	1.4±0.1	1.6±0.0	0.2 (0.1 to 0.3)	**0.010**
Total	37.3±0.4	38.9±0.4	1.5 (0.3 to 2.8)	**0.016**

Least squares means and SEs from analysis of covariance, adjusted for age, are shown, along with the difference between anesthesia and surgery and control subjects, the 95% CI for the difference, and the *P* value. 0.0 represents values > 0 and < 0.05; –0.0 represents values > –0.05 and < 0. Corresponding unadjusted means and SDs are shown along with the above least squares means and SEs in a table in Supplemental Digital Content 1 (http://links.lww.com/ALN/B523). The whole brain is separated into the cerebrum and infratentorium, the cerebrum into the four lobes and subcortical region, and the infratentorium into the cerebellum and brainstem. Significant *P* values are in boldface (in all cases, means were lower for anesthesia and surgery than control subjects).

*These differences were not significant when health issues (see Statistical Analysis section for definition) and household income (less than $50,000) were controlled: left parietal, least squares mean ± SE, 3.6±0.1% for anesthesia and surgery and 3.8±0.1% for control subjects (*P* = 0.053), difference of 0.2 percentage points, 95% CI = –0.0 to 0.3; left total, 18.8±0.2% and 19.4±0.3%, respectively (*P* = 0.079), difference of 0.6 percentage points, 95% CI = –0.1 to 1.2; left plus right occipital, 3.4±0.1% and 3.5±0.1%, respectively (*P* = 0.096), difference of 0.2 percentage points, 95% CI = –0.0 to 0.4. †There was a significant difference corresponding with this one in the analysis among children exposed to anesthesia and surgery that compared those who did or did not have health issues, that is, lower values for those who did (least squares mean ± SE of 6.1±0.2%) than those who did not (6.9±0.3%; *P* = 0.048). The difference was 0.7 percentage points (95% CI = 0.0 to 1.5).

A&S = anesthesia and surgery.

atrophy in medicated schizophrenics[50] and 0.53 (maximum = 1.05) for lower fractional anisotropy of the splenium of the corpus callosum in medicated and antipsychotic-naive schizophrenics combined.[51]

We excluded subjects with CNS problems or risk factors to avoid confounding effects of anesthesia and surgery. Subjects were exclusively male and mostly white, non-Hispanic, and reasonably healthy. Many were of fairly high socioeconomic status as reflected in household income and their parents' graduation from college and type of employment. They were similar in race and ethnicity (94% white, 6% Hispanic) but higher in socioeconomic status (median annual household income of $75,000 or more), compared with the Iowa population generally (91% white, 5% Hispanic or Latino, $52,716 income[52]) and patients who had anesthesia and surgery during infancy in our previous study.[10] The difference in socioeconomic status between studies suggests selection bias; higher-status compared with lower-status individuals may be more willing to undergo neuroimaging (which our previous study did not involve). Patients who differed from ours in any of these characteristics might show different effects of anesthesia and surgery.

Table 5. Decreased Fractional Anisotropy and Increased Mean Diffusivity Associated with Anesthesia and Surgery

White Matter Region and Side	Fractional Anisotropy				Mean Diffusivity (10^{-3} mm^2/s)			
	A&S	Control Subjects	Difference	*P* Value	A&S	Control Subjects	Difference	*P* Value
Superior cerebellar peduncle, right	0.35 ± 0.01	0.40 ± 0.01	0.05 (0.01 to 0.09)	**0.018**	1.32 ± 0.07	1.12 ± 0.07	−0.20 (−0.41 to 0.01)	0.056
Cerebral peduncle, right	0.48 ± 0.02	0.53 ± 0.02	0.05 (−0.01 to 0.12)	0.121	1.06 ± 0.05	0.89 ± 0.05	−0.17 (−0.30 to −0.04)	**0.015**
Cerebral peduncle, left	0.48 ± 0.02	0.55 ± 0.02	0.07 (0.01 to 0.14)	**0.027**	0.97 ± 0.04	0.86 ± 0.04	−0.11 (−0.22 to 0.00)	0.055
External capsule, left	0.34 ± 0.01	0.37 ± 0.01	0.03 (0.00 to 0.05)	**0.048***	0.77 ± 0.01	0.76 ± 0.01	−0.01 (−0.03 to 0.00)	0.136
Cingulum (cingulate gyrus), right	0.26 ± 0.02	0.35 ± 0.02	0.09 (0.03 to 0.15)	**0.006**	0.78 ± 0.01	0.76 ± 0.01	−0.02 (−0.04 to 0.00)	0.099
Cingulum (cingulate gyrus), left	0.29 ± 0.02	0.38 ± 0.02	0.09 (0.02 to 0.16)	**0.010**	0.78 ± 0.01	0.76 ± 0.01	−0.02 (−0.04 to −0.00)	**0.045**
Fornix (cres) and/or stria terminalis, right	0.40 ± 0.01	0.44 ± 0.01	0.04 (0.00 to 0.08)	**0.047**	0.94 ± 0.02	0.85 ± 0.02	−0.09 (−0.15 to −0.03)	**0.007**

Least squares means and SEs from analysis of covariance, adjusted for age, are shown, along with the difference between anesthesia and surgery and control subjects, the 95% CI for the difference, and the *P* value. 0.00 represents values > 0 and < 0.005; −0.00 represents values > −0.005 and < 0. Corresponding unadjusted means and SDs are shown along with the above least squares means and SEs in a table in Supplemental Digital Content 2 (http://links.lww.com/ALN/B524). Analysis was based on medians for subjects. Significant *P* values are in boldface. No significant differences between groups were observed on the left side for regions with only the right side listed above and *vice versa* or the other regions analyzed (see Materials and Methods section).

*This difference was not significant when health issues (see Statistical Analysis section for definition) and household income (less than $50,000) were controlled: least squares mean ± SE, 0.35 ± 0.01 for anesthesia and surgery and 0.37 ± 0.01 for control subjects (*P* = 0.115), difference of 0.02 (95% CI = −0.01 to 0.05).

A&S = anesthesia and surgery.

Although our exposed and nonexposed subjects were reasonably well-matched ($P > 0.10$) in the characteristics shown in table 2, there were nonsignificant differences in the directions of more health issues, annual household income under $50,000, and nonemployed parents associated with exposure. The groups may have differed in other, unevaluated characteristics (*e.g.*, household size and number of siblings). The observed white matter differences may have been confounded by such characteristics. There was some evidence of this (tables 4 and 5, footnotes).

Conclusions

Our findings of broadly distributed, decreased white matter integrity and volume associated with anesthesia and surgery in patients without other CNS problems or risk factors accord with concerns about the widespread use of anesthesia during infancy and early childhood. Our study cannot determine whether this association is causative. Our study design mandates caution in interpretation, and the findings should be considered tentative until further verification. Larger studies are needed to replicate our findings, control better for possible confounding characteristics, and evaluate the influences of other characteristics, for example, sex and duration of, and age at, anesthesia and surgery. We focused on anesthesia and surgery during infancy, but myelination and synaptogenesis continue after infancy in humans,[53] making time windows of risk for apoptosis of oligodendrocytes and neurons associated with anesthesia and surgery, and possible long-term correlates, uncertain. Additional studies should try to separate possible effects of anesthesia *versus* surgery by prospective, randomized controlled trials[11] or nonrandomized studies examining effects of anesthesia for nonsurgical procedures and surgical procedures varying in invasiveness.

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Competing Interests

The authors declare no competing interests.

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