

Cognition and Brain Structure Following Early Childhood Surgery With Anesthesia

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abstract

BACKGROUND: Anesthetics induce widespread cell death, permanent neuronal deletion, and neurocognitive impairment in immature animals, raising substantial concerns about similar effects occurring in young children. Epidemiologic studies have been unable to sufficiently address this concern, in part due to reliance on group-administered achievement tests, inability to assess brain structure, and limited control for confounders.

METHODS: We compared healthy participants of a language development study at age 5 to 18 years who had undergone surgery with anesthesia before 4 years of age ($n = 53$) with unexposed peers ($n = 53$) who were matched for age, gender, handedness, and socioeconomic status. Neurocognitive assessments included the Oral and Written Language Scales and the Wechsler Intelligence Scales (WAIS) or WISC, as appropriate for age. Brain structural comparisons were conducted by using T1-weighted MRI scans.

RESULTS: Average test scores were within population norms, regardless of surgical history. However, compared with control subjects, previously exposed children scored significantly lower in listening comprehension and performance IQ. Exposure did not lead to gross elimination of gray matter in regions previously identified as vulnerable in animals. Decreased performance IQ and language comprehension, however, were associated with lower gray matter density in the occipital cortex and cerebellum.

CONCLUSIONS: The present findings suggest that general anesthesia for a surgical procedure in early childhood may be associated with long-term diminution of language abilities and cognition, as well as regional volumetric alterations in brain structure. Although causation remains unresolved, these findings nonetheless warrant additional research into the phenomenon's mechanism and mitigating strategies.



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WHAT'S KNOWN ON THIS SUBJECT: Permanent neuronal deletion and neurocognitive impairment after anesthetic exposure in animals raised substantial concern that similar effects occur in children. Human studies were equivocal but have not combined structural and intelligence tests in otherwise healthy children after childhood anesthesia.

WHAT THIS STUDY ADDS: Anesthetic exposure for surgery did not lead to measurable neuronal elimination in brain regions previously identified in animals. However, language comprehension and performance IQ were decreased in exposed children and associated with decreased gray matter, primarily in posterior brain regions.

Worldwide, millions of young children undergo seemingly uneventful surgeries with anesthesia every year. However, recently observed subsequent behavioral abnormalities and diminished academic performance have raised significant concerns regarding the safe use of anesthetics in children.¹ The phenomenon's etiology remains under investigation; however, animal studies in a variety of species have demonstrated widespread neuronal cell death, permanent neuronal deletion, alterations in dendritic architecture, or long-term learning and memory impairment after exposure to all commonly used anesthetics (most recently reviewed in Lin et al²). Because anesthetics are potent modulators of excitatory and inhibitory neurotransmission, the assertion that anesthetic exposure may interfere with proper development of the immature brain is not entirely implausible. Exposure during sensitive neurodevelopmental periods early in life could interfere with refinement of neuronal networks and lead to long-term functional abnormalities.³

Given the ubiquitous use of anesthetics in modern medicine, epidemiologic data have tried to ascertain whether these agents have lasting effects on cognitive function in children. Although several studies found an association with learning, language, or behavioral abnormalities, others were unable to identify an abnormal neurologic phenotype (as reviewed in Lei et al⁴). This discrepancy may be due, in part, to the diverse outcome measures, such as group-administered achievement tests, school records, individually administered tests, or billing and diagnostic codes for behavioral disorders. Many studies were not able to adjust for potent confounders of cognitive performance, such as gender⁵ or socioeconomic status,⁶ and access to anesthetic records to verify exposure duration, specify drug use, and exclude untoward events was frequently unavailable. Furthermore, no data are currently available regarding brain

structural effects of anesthetic exposure in early childhood. Research in rodents has identified permanent neuronal deletion in certain brain regions, such as the retrosplenial cortex and thalamus,⁷ which may be linked to their subsequently observed neurobehavioral abnormalities.⁸

To address whether surgical anesthetics as used in otherwise healthy children have long-term effects on cognition, language, and brain structure, volunteers of an existing study of language development with a history of exposure to surgery with anesthesia before their fourth birthday were matched to unexposed control subjects for age, gender, handedness, and socioeconomic status (all important confounders of cognition and brain structure). Anesthesia records were reviewed to quantify exposure and to exclude intraoperative events, such as hypotension, bradycardia, or hypoxemia. Validated, individually administered assessments for language development and intelligence were compared between exposed and unexposed subjects. In addition, brain structure (as assessed by using MRIs) was compared between the groups.

METHODS

Study Population

Study subjects were drawn from an existing cross-sectional MRI database that includes 5- to 18-year-old volunteers lacking any history of neurologic or psychological illness, head trauma with loss of consciousness, previous or current use of psychostimulant medication, diagnosis of a learning disability, premature birth before 38 weeks' gestation, or abnormalities observed during a clinical neurologic examination.^{5,9} Subjects were included in the exposed group if they had any documented surgery with anesthesia in their medical record

before their fourth birthday. Control subjects were matched to the most appropriate anesthesia-exposed subject according to gender, handedness, age, and socioeconomic status, if they lacked any documented evidence of anesthesia exposure in their medical charts.

Neuropsychological Assessment

All study participants underwent a battery of individually administered neurocognitive tests that included the Oral and Written Language Scales (OWLS),¹⁰ as well as the Wechsler Intelligence Scale for Children-Third Edition¹¹ or the Wechsler Adult Intelligence Scale-Third Edition,¹² as appropriate for age.

MRI

Magnetic resonance image acquisition was performed without anesthesia or sedation by using a Biospec 30/60, 3-T MRI scanner with SK330 head gradient insert (Bruker Corporation, Billerica, MA).

Analysis of Anesthesia Records

Anesthesia records were analyzed by a pediatric anesthesiologist to extract end-tidal carbon dioxide concentrations, peripheral oxygen saturations, systolic blood pressures, heart rates, and the durations meeting age-appropriate Pediatric Advanced Life Support criteria for hypotension and bradycardia, respectively.¹³ Volatile anesthetic exposure was quantified into minimum alveolar concentration over time (ie, MAC-hour).¹⁴

Data and Statistical Analysis

All data are shown as mean \pm SD. Group comparisons of neurocognitive data were performed by using paired *t* tests followed by false discovery rate error correction for multiple comparisons with SAS version 9.3 (SAS Institute, Inc, Cary, NC). Statistical significance was accepted at $P < .05$.

To assess structural effects of surgery with anesthesia, anatomic data were analyzed by using voxel-based

morphometry after transformation to the standardized Montreal Neurological Institute reference frame.¹⁵ First, a region of interest was created for the thalamus and retrosplenial cortex (as defined by using Brodmann areas 26, 29, and 30), which have previously been found to be vulnerable in animals.⁷ To examine whether surgery with anesthesia affected gray matter volume in this region, each voxel in the region of interest was tested for significance after adjustment for multiple comparisons by using Bonferroni's correction at the $P < .05$ level.

In an unbiased analysis, we next examined potential interactions between neurocognitive performance and regional brain volume by creating a statistical model that estimated brain volume as a function of 3 variables: group, neurocognitive testing score, and group \times neurocognitive testing score. Total intracranial brain volume was used as a covariate of no interest. Voxel-based analyses were performed by using a multiple regression design controlling for total brain volume. Each voxel in the normalized brain images was tested for the significance of differences at a $P < .001$ level.

The study methods are described in more detail in the Supplemental Materials.

RESULTS

Fifty-three eligible subjects were identified by their medical records and matched to 53 control subjects. Telephone verification for additional exposures (or lack thereof) in previously exposed or control subjects was only successful for 26 or 29 individuals, respectively. One matched pair was excluded from the image analysis because of unsatisfactory quality of the MRI. Cohort characteristics are presented in Table 1. Boys were expectedly overrepresented because they more frequently require surgery at a younger age.

TABLE 1 Characteristics of Study Groups and Neurocognitive Testing

Characteristic	Anesthesia (n = 53)	Control (n = 53)
Gender		
Female	20 (38)	20 (38)
Male	33 (62)	33 (62)
Primary handedness		
Right	51 (96)	51 (96)
Left	2 (4)	2 (4)
Age at MRI scan, mo	128 \pm 44	128 \pm 44
Family income, \$		
<35 000	8 (15)	6 (11)
35 000–45 000	7 (13)	11 (21)
45 001–65 000	24 (45)	24 (45)
65 001–75 000	6 (12)	5 (10)
>75 000	8 (15)	7 (13)

Data are presented as total number (percentage of total) or mean \pm SD.

Most children (75%) in the exposed group underwent 1 surgical procedure before their fourth birthday, typically between 1 and

2 years of age (Table 2). At the time of surgery, which occurred between 1986 and 2003, all children were classified as American Society of Anesthesiologists' physical status 1 or 2, meaning that they were either healthy or had only mild systemic disease. Anesthesia records with legible anesthetic doses were available for 48 patients. Cumulative volatile anesthetic exposures, expressed as equipotent doses for sevoflurane, isoflurane, or halothane alone, or for combinations, varied from 0.2 to 3.8 MAC-hours; 88% of anesthetics also included nitrous oxide. Additional drugs administered intraoperatively included analgesics, such as morphine and fentanyl. Vital signs remained within normal limits or were only briefly abnormal (Table 2); none of the records

TABLE 2 Characteristics of Anesthetic Exposure and Surgery

Frequency of anesthetics and duration			
No. of exposures	Patients	Duration	Range
1	n = 40	30 \pm 30	5–170
2	n = 11	29 \pm 34	6–120
3	n = 2	17 \pm 8	15–50
Anesthesia start to anesthesia end, min		37 \pm 37	5–170
Age at first procedure		1.5 \pm 0.9 y	1 d–3.8 y
Type of surgeries (surgical subspecialties, includes multiple surgeries)			
ENT	53		
General surgery	16		
Urology	8		
Ophthalmology	2		
Orthopedics	1		
Cardiac	0		
Neurosurgery	0		
Other	1		
Anesthetic doses		Dose	Range
Volatile anesthetic, MAC-h	n = 48	1.0 \pm 0.7	0.2–3.1
Morphine, mg/kg	n = 15	0.1 \pm 0.03	0.07–0.18
Fentanyl, μ g/kg	n = 7	3.8 \pm 3.0	1–10
Ketamine, mg/kg	n = 2	2.8 \pm 0.3	2.6–3.0
Droperidol, mg/kg	n = 1	0.01	NA
Midazolam, mg/kg PO	n = 1	0.5	NA
Documented vital signs			
Lowest documented SBP, mm Hg		86 \pm 14	60–120
Lowest documented heart rate, min ⁻¹		125 \pm 26	60–170
SpO ₂ , %		99 \pm 2	90–100
Time bradycardic per PALS, min	n = 0	NA	NA
Time hypotensive per PALS, min	n = 7	6 \pm 2	5–10
Time EtCO ₂ <25 mm Hg, min	n = 1	90	NA
Time EtCO ₂ 25–29 mm Hg, min	n = 3	23 \pm 12	10–30
Time EtCO ₂ 30–35 mm Hg, min	n = 2	30 \pm 0	NA

Unless otherwise indicated, data are presented as mean \pm SD or number (percentage of total). ENT, ears, nose, and throat; EtCO₂, end-tidal carbon dioxide; MAC-h, minimum alveolar concentration over time; NA, nonapplicable; PALS, Pediatric Advanced Life Support guidelines; PO, by mouth; SBP, systolic blood pressure; SpO₂, peripheral oxygen saturation.

TABLE 3 Neurologic Testing Scores for Children Previously Exposed to Surgery With Anesthesia at Age <4 Years or Matched Control Subjects

Test	Exposed (n = 53)	Control (n = 53)	Difference (Exposed – Control)	P	Adjusted (FDR) P
OWLS listening comprehension	101.2 ± 12.9	107.2 ± 11.5	–6 ± 16.9	.013	.039
OWLS oral expression	108.1 ± 13.3	111.4 ± 15.5	–3.3 ± 21.2	.257	.257
OWLS oral composite	104.7 ± 12.2	110.1 ± 13.8	–5.5 ± 19.2	.043	.065
WISC/WAIS verbal	111.6 ± 12.7	114.9 ± 13	–3.3 ± 18	.183	.22
WISC/WAIS performance	108.3 ± 14.5	114.7 ± 13.1	–6.4 ± 17.7	.011	.039
WISC/WAIS full scale	110.9 ± 13.4	116.3 ± 13.1	–5.4 ± 17.9	.034	.065

Data are presented as mean ± SD. FDR, false discovery rate error correction for multiple comparisons; WAIS, Wechsler Adult Intelligence Scale-Third Edition; WISC, Wechsler Intelligence Scale for Children-Third Edition.

documented major intraoperative complications or cardiac arrests.

Mean cognitive test scores, regardless of anesthetic exposure, were within population norms (Table 3). However, previously exposed children consistently scored lower than the unexposed matched control group in all tests and subcategories, with significantly lower scores observed for performance IQ (Fig 1) and OWLS listening comprehension (Fig 2). However, no group differences in gray matter volume were detected in the thalamus or retrosplenial cortex, 2 brain regions with substantial neuronal elimination in immature rodents after an anesthetic exposure (Fig 3).

To identify potential structural correlates of the observed diminished performance IQ and OWLS listening

scores, an unbiased analysis was performed, and associated decreased performance IQ with decreased gray matter volume was measured in exposed subjects for anterior cerebellum and parts of the frontal lobe, as well as the lingual gyrus and occipital lobes (Brodmann areas 18 and 19), compared with their unexposed control subjects (Fig 4 [blue], Table 4). In contrast, the sign of the interaction term was reversed in the rolandic operculum, right frontal lobe (precentral and postcentral gyrus), and Brodmann area 43 (Fig 4 [red], Table 4), potentially indicating that increased volume in these brain regions after exposure may be associated with the relatively lower performance IQ compared with control subjects.

Figure 5 exemplifies this correlation

of performance IQ and gray matter volume for a representative voxel in the lingual gyrus of the occipital lobe, comparing previously exposed children with their unexposed matched subjects.

A similar analysis found an interaction between decreased OWLS listening scores and decreased regional gray matter volume in parts of the right lingual gyrus and occipital and temporal lobes, as well as parahippocampal gyrus postexposure, compared with previously unexposed children (Fig 6, Table 5).

No associations of volumetric changes in white matter and neurocognitive performance scores were observed.

DISCUSSION

Concerns for neurobehavioral disorders and abnormalities in brain function caused by environmental chemical exposure during early brain development have recently been extended to anesthetics and sedatives, which are administered to millions of young children worldwide.^{1,16} Many surgical procedures early in life treat life-threatening conditions, avert serious health complications, or improve

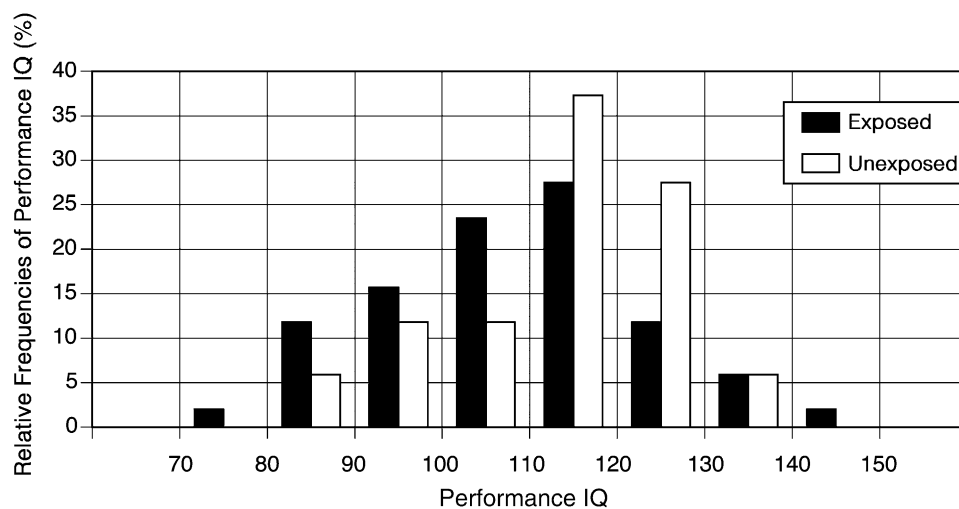


FIGURE 1

Frequency distribution for Wechsler performance IQ for children previously exposed to general anesthesia for surgery at age <4 years (n = 53) and unexposed control subjects matched for age, gender, handedness, and socioeconomic status (n = 53).

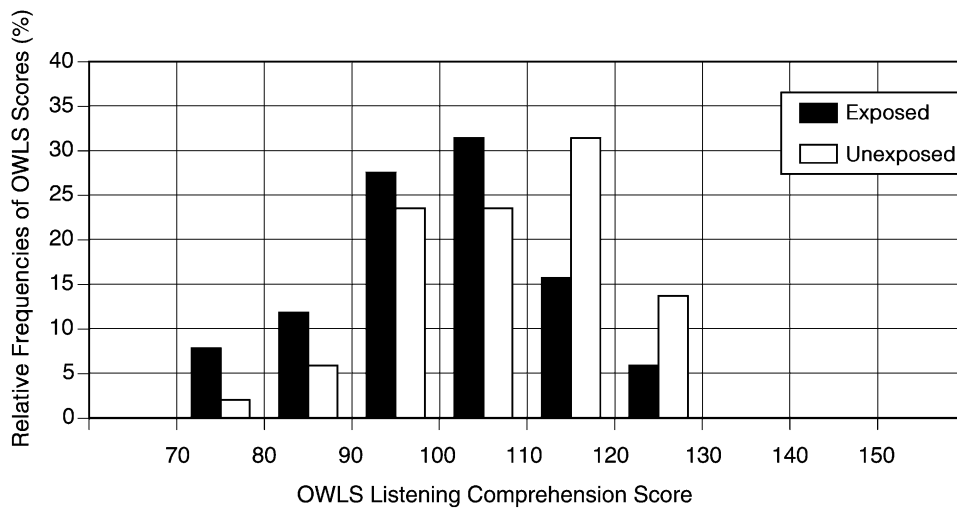


FIGURE 2 Frequency distribution of OWLS listening comprehension scores for children aged <4 years previously exposed to general anesthesia for surgery ($n = 53$) and unexposed control subjects matched for age, gender, handedness, and socioeconomic status ($n = 53$).

quality of life and therefore cannot be easily postponed or avoided. Neurotoxic effects of all commonly used anesthetics and sedatives have now

been found in a wide variety of animal species, and postexposure learning impairments have been documented in rodents and nonhuman primates.^{8,17}

Accordingly, the present study assessed the effects of early childhood anesthesia for surgery on long-term cognitive function and

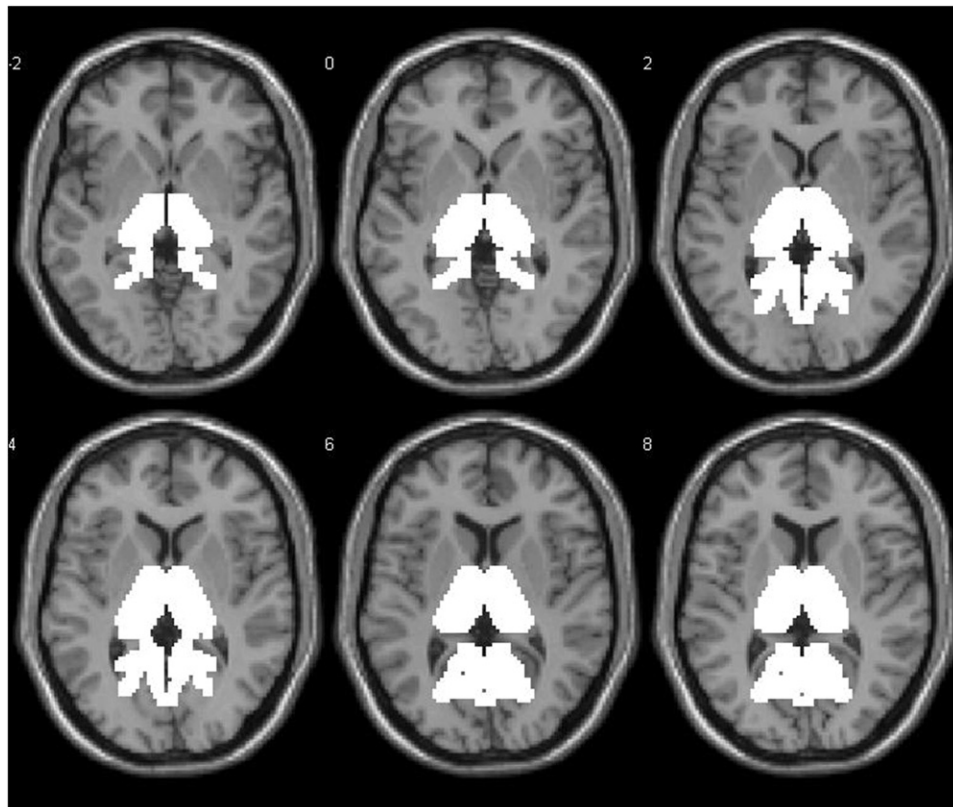


FIGURE 3 Group comparison of gray matter volume after surgery with anesthesia in children aged <4 years that focused on the thalamus and retrosplenial cortex, 2 brain regions previously identified in immature rodents to be particularly vulnerable to immediate neuronal cell death and long-term neuronal elimination. T1-weighted image sections in a representative brain are shown with the superimposed white-colored region of interest used for volumetric group comparison.

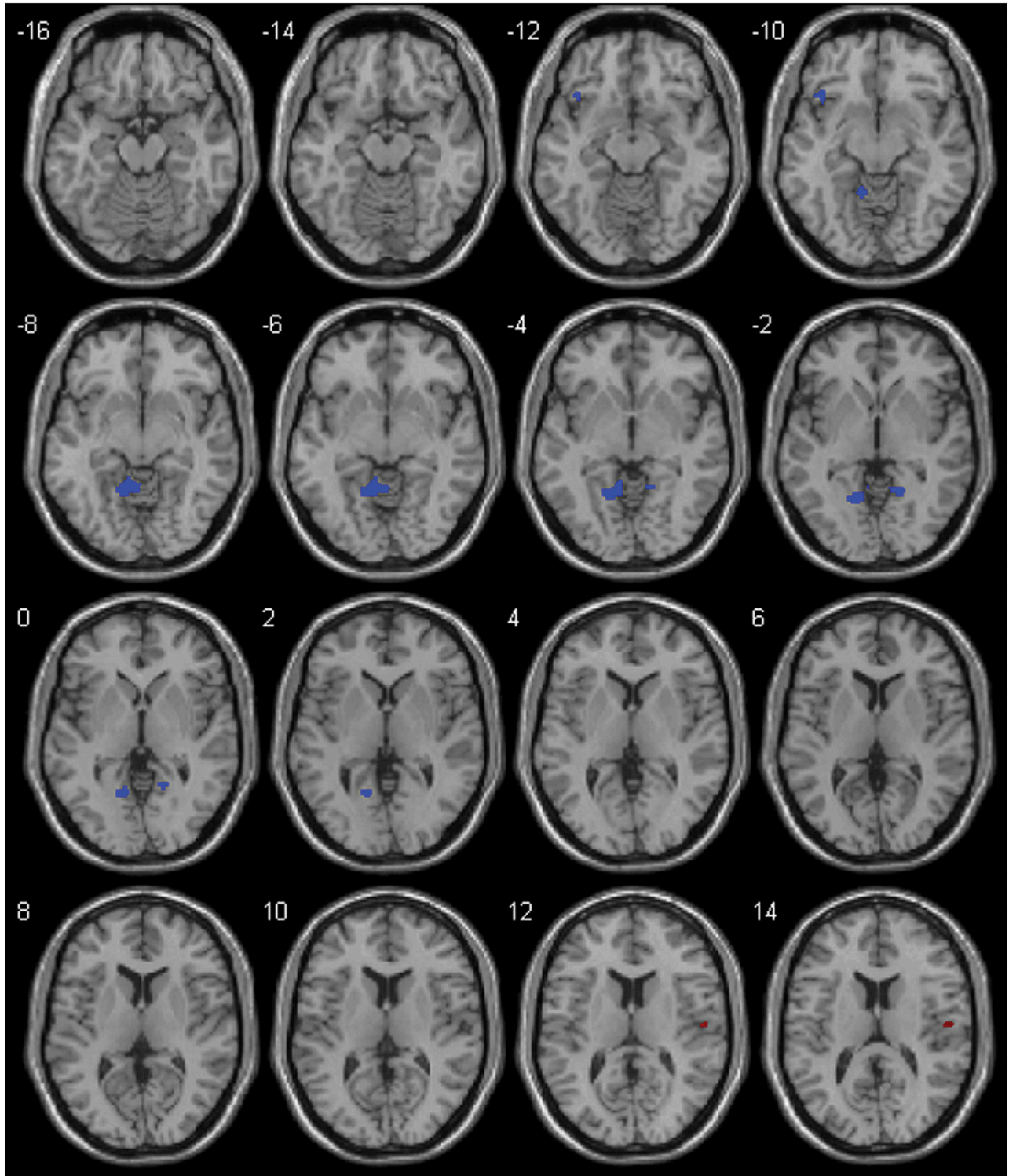


FIGURE 4

In children previously exposed to surgery with anesthesia before 4 years of age, diminished performance in individually administered tests of cognition may be associated with decreased gray matter volume in posterior brain regions, compared with unexposed control subjects. Normalized transverse, T1-weighted image sections through a normative brain with superimposed colored voxel clusters of regions demonstrating steeper correlations (blue) between decreased performance IQ and diminished regional gray matter volume for children who underwent surgery with anesthesia before their fourth birthday when compared with matched, unexposed peers. Areas were localized to the cerebellum, the occipital lobe/lingual gyrus, and the orbitofrontal cortex. A steeper correlation (red) between decreased performance IQ and increased regional gray matter volume for previously exposed children compared with unexposed control subjects was observed in small portions of the right cerebrum. Specific regions are identified by using their coordinates according to the Montreal Neurological Institute reference frame in Table 4. Data were adjusted for total intracranial brain volume, and voxels are only displayed for clusters of >10 voxels, tested at $P < .001$. Images are shown in neurologic orientation with the subject's right side facing the right side of the images.

TABLE 4 Regional Clusters of Gray Matter Demonstrating Steeper Negative or Positive Correlations (Peak Intensity) Between Decreased Performance IQ and Regional Volume in Exposed Children Compared With Matched, Previously Unexposed Children

Gray Matter Volume	Predominant Regions	Total No. of Voxels	Peak MNI Coordinates (x, y, z), mm	Peak Intensity
Decreased	Cluster 1	406	-10.5, -49.5, -7.5	-3.95
	Culmen	237		
	Cerebellum, anterior lobe	237		
	Left cerebellum	233		
	Left lingual gyrus	232		
	Left cerebrum	164		
	Occipital lobe	161		
	Left cerebellum	157		
	Lingual gyrus	145		
	Gray matter	56		
	Brodmann area 19	37		
	Brodmann area 18	18		
	Vermis	17		
Decreased	Cluster 2	63	16.5, -52.5, -3	-3.77
	Right lingual gyrus	57		
	Right cerebrum	56		
	Lingual gyrus	51		
	Occipital lobe	51		
	Gray matter	25		
Decreased	Cluster 3	54	-40.5, 19.5, -10.5	-3.76
	Frontal lobe	54		
	Inferior frontal gyrus	54		
	Left cerebrum	54		
	Left inferior frontal gyrus, orbital part	52		
Increased	Cluster 1	28	54, -13.5, 13.5	3.44
	Right cerebrum	28		
	Right rolandic operculum	28		
	Gray matter	20		
	Brodmann area 43	19		
	Postcentral gyrus	13		
	Parietal lobe	13		
	Precentral gyrus	12		
Frontal lobe	12			

Voxel (volumetric pixel) is a 3-dimensional element, with an approximate volume of 2 mm³. Coordinates denote 3-dimensional location (left to right, posterior to anterior, and inferior to superior) of voxel cluster according to a standardized system based on the Montreal Neurological Institute (MNI) classification; peak intensity represents the maximum nuclear magnetic resonance signal intensity in a voxel cluster.

brain structure by comparing previously exposed children, whose anesthesia records were reviewed, versus matched unexposed control subjects to limit confounding of cognitive performance and structural assessment.

Language and intelligence were evaluated by using individually administered tests, and we found that all children, regardless of exposure, scored within population norms. However, compared with control subjects, lower scores were observed for OWLS listening comprehension and Wechsler performance IQ in

exposed subjects. Although these findings are seemingly in conflict with several previous studies demonstrating no effect on academic performance or learning deficits after a single anesthetic exposure,¹⁸⁻²¹ our findings are consistent with language deficits observed in healthy children after a single exposure to surgical anesthesia before 3 years of age.²² This finding seems to confirm that individually administered neurocognitive tests may be more sensitive for determining a potential neurologic phenotype after anesthetic exposure.²³ Moreover, the present

results extend the earlier observation of lower performance IQ in preschool-aged children with congenital heart disease after early life exposure to anesthesia and sedation²⁴ to healthy school-aged children and adolescents, with potentially greater prognostic importance for subsequent performance in adulthood. Although our study surprisingly demonstrated a larger effect size after a comparatively briefer exposure, these 2 studies are difficult to compare because of their substantial differences in comorbidity, acuity of surgery, age during and duration of exposure, and, importantly, control of confounders (eg, parental socioeconomic status and education).

Interestingly, a recent study in a patient cohort similar to ours showed long-term deficits in recollection memory years after surgery but failed to identify any effect on IQ.²⁵ Importantly, however, children in our study were matched for socioeconomic status, whereas exposed children in this previous study came from families with significantly higher income than their control subjects. Accordingly, a higher starting IQ trajectory in those exposed children could have masked the potentially deleterious effects of anesthetic exposure.

However, similar to the inherent weaknesses of all retrospective studies in this field (because truly randomized controlled studies and anesthetic exposures without indication are unethical), our findings cannot causatively link the observed neurocognitive abnormalities to any of a number of perioperative factors. In addition to the anesthetic exposure, potentially deleterious factors include surgery, the associated inflammatory process, pain, genetic or health-related predispositions, or the underlying indication for surgery, which may persist postoperatively.

It is important to note that most exposed children in our cohort

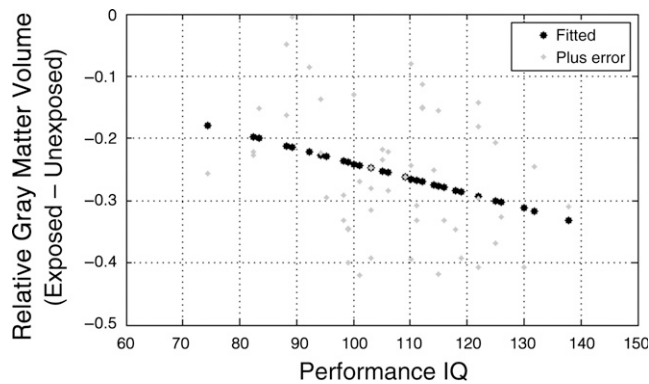


FIGURE 5

Graph of a representative, randomly selected voxel (coordinates $-30, 0,$ and $9,$ according to the Montreal Neurological Institute reference frame) from the 406-voxel cluster demonstrating a significantly steeper association between decreased performance IQ and reduced gray matter volume in previously exposed children compared with their matched unexposed control subjects. Light gray diamonds represent differences in gray matter volumes between exposed and matched control subjects ($n = 52$), plotted against the corresponding performance IQ. Black dots denote the corresponding value of performance IQ on a linear fitted curve for the entire cohort.

scored within the population norms and in aggregate performed better than the average population, making it difficult to determine the exact impact of diminished cognitive scores for the individual. Notably, neurocognitive abnormalities would not have been identified if the exposed children had only been compared with the overall population, as is common practice in this field of research. However, our findings may have significant societal relevance. The loss of 1 IQ point has been estimated to decrease an individual's lifetime earnings capability by \$18 000 (in 2008 dollar amounts).²⁶ Accordingly, a potential diminution in 5 to 6 IQ points after surgery, as observed here, may result in a lifetime loss of more than \$540 billion in the estimated 6 million children undergoing surgery every year in the United States alone.²⁷ Moreover, a potential population-wide downward shift of the IQ distribution could result in an increase in the number of very low performers (IQ <70) and concomitant reduction in the number of high performers, with dramatic societal implications.

Although the direct translation of laboratory studies to clinical pediatric anesthesia practice remains complicated,²⁸ a permanent deletion

of up to 50% of brain cells observed in the thalamus and retrosplenial cortex of newborn rats after prolonged anesthetic exposure⁷ has been associated with abnormalities in learning in rodents.⁸ Even though the resolution of a 3-T MRI used in the present study cannot match these histologic cell counts in animals, a similarly dramatic reduction in gray matter volume in these regions should have been detectable but was not. This discrepancy could be related to differences in species, degrees of neuroplasticity, exposure times, or temporal relationship between exposure and structural assessment. In addition, our recent laboratory studies suggest another possibility: that brain regional vulnerability to anesthesia-induced neuronal abnormalities may depend on the regional maturational stage during exposure.²⁹ Laboratory research has shown that neurons are distinctly vulnerable to anesthetic exposure during a brief window early in their development³⁰; accordingly, brain regions are expected to be most susceptible to anesthesia-induced abnormalities at a time when they comprise the highest number of newborn neurons, which depends on age during exposure and differs

among regions.^{31,32} According to our exploratory analysis, subtle structural abnormalities (predominantly in the cerebellum, as well as in the occipital cortex and right frontal lobe) were associated with a decrease in performance IQ. This finding is consistent with our recent data in mice,²⁹ which showed that cerebellar neurons were specifically vulnerable to anesthesia-induced cell death if exposure occurred at an age when brain maturation was equivalent to that of human infants.³³ Moreover, cerebellar gray matter volume has previously been linked to nonverbal IQ,³⁴ and occipital cortex and lingual gyrus are associated with mathematical and advanced reading skills.^{35,36} Interestingly, similar to results in patients after their exposure in the present study, children with 22q11.2 deletion syndrome also experience reductions in gray matter density in the anterior cerebellum that are associated with deficits in performance IQ and language delay.³⁷

However, it is important to note that because we used a conservative approach to detect group differences, the identified regions were relatively small and the exploratory analysis would not survive correction for the tens of thousands of voxels across the entire brain volume, thereby increasing the risk of a type I error. Due to these limitations, we refrained from further structural analysis not linked to significant cognitive findings and suggest these findings should be interpreted with caution. However, to our knowledge, these observations represent the first structural assessment of the human brain after surgery with anesthesia early in life in otherwise healthy children, whereas a recent study in survivors of complex congenital heart surgery has linked brain injury observed on MRI with cognitive and language scores in critically ill infants.³⁸

Our study has several limitations. The MRI data used in this study are

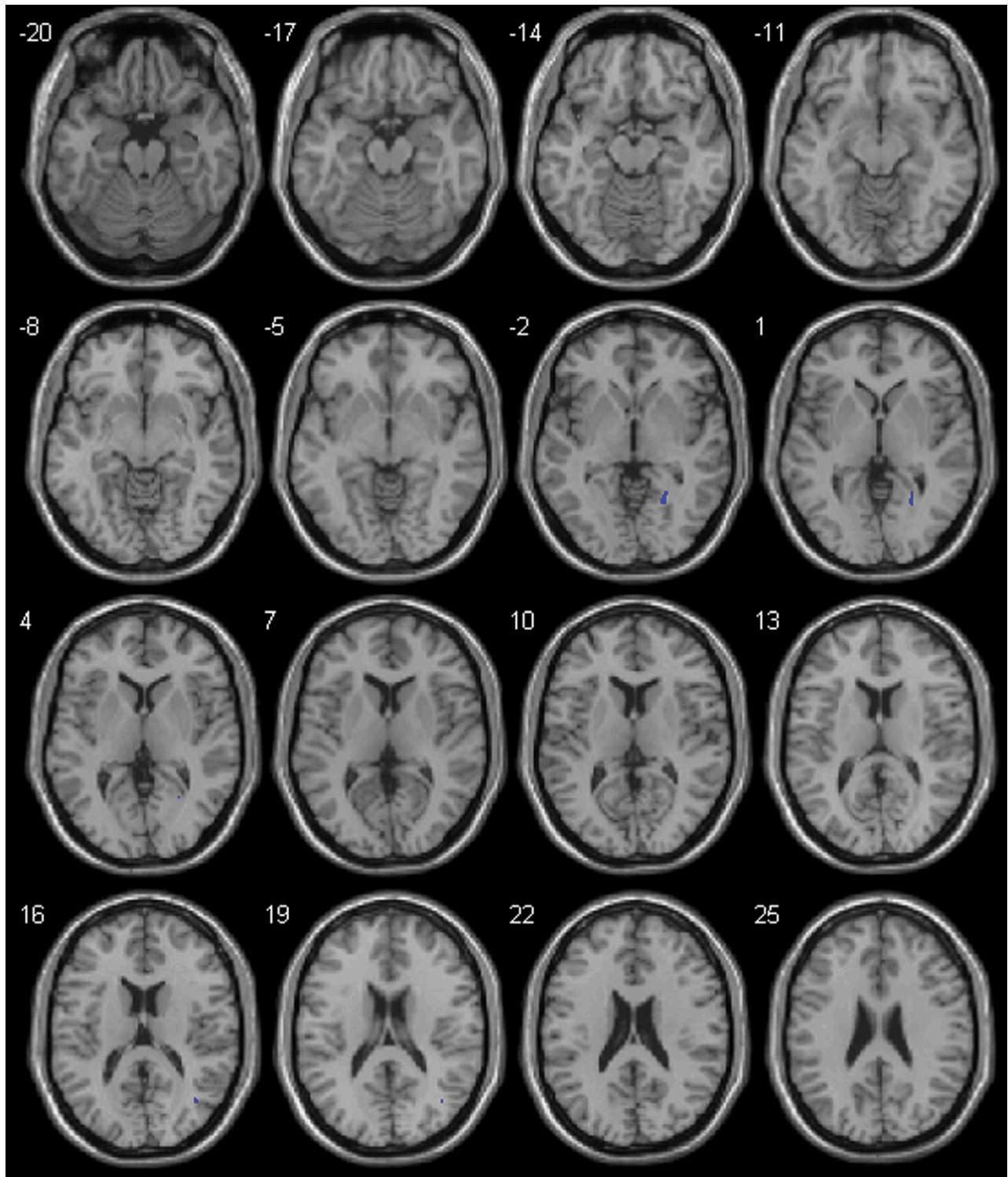


FIGURE 6

In children previously exposed to surgery with anesthesia before 4 years of age, an observed diminution of language performance may be associated with decreased gray matter volume in occipital and temporal brain regions, compared with unexposed control subjects. Normalized transverse, T1-weighted image sections through a normative brain with superimposed colored voxel clusters of regions demonstrating steeper correlation (blue) between diminished performance in OWLS listening tests and decreased regional gray matter volume for children who underwent surgery with anesthesia before their fourth birthday compared with matched, unexposed children. Areas were localized to the right occipital lobe, the lingual gyrus, the temporal lobe, and the parahippocampal gyrus. Specific regions are identified by using their coordinates according to the Montreal Neurological Institute reference frame in Table 5. No areas were identified demonstrating steeper positive correlations between OWLS scores and regional gray matter volume for exposed children compared with unexposed children. Data were adjusted for total intracranial brain volume, and voxels are only displayed for clusters of >10 voxels, tested at $P < .001$. Images are shown in neurologic orientation with the subject's right side facing the right of the images.

TABLE 5 Regional Clusters of Gray Matter Demonstrating Steeper Negative or Positive Correlations (Peak Intensity) Between Decreased OWLS Listening Score and Regional Volume in Exposed Children Compared With Matched, Previously Unexposed Children

Gray Matter Volume	Predominant Regions	Total No. of Voxels	Peak MNI Coordinates (x, y, z), mm	Peak Intensity
Decreased	Cluster 1	58	25.5, -55.5, 0	-3.79
	Right cerebrum	58		
	Right lingual gyrus	52		
	Occipital lobe	36		
	Lingual gyrus	28		
	Gray matter	17		
	Parahippocampal gyrus	15		
	Limbic lobe	15		
	Subgyral	13		
	Brodmann area 30	11		
Decreased	Cluster 2	15	39, -69, 18	-3.32
	Right cerebrum	15		
	Temporal lobe	15		
	Middle temporal gyrus	15		
	Right middle temporal	10		

Voxel (volumetric pixel) is a 3-dimensional element, with an approximate volume of 2 mm³. Coordinates denote 3-dimensional location (left to right, posterior to anterior, and inferior to superior) of voxel cluster according to a standardized system based on the Montreal Neurological Institute (MNI) classification; peak intensity represents the maximum nuclear magnetic resonance signal intensity in a voxel cluster.

between 8 and 11 years old. More contemporary imaging techniques might provide better resolution and improved sensitivity to subtle brain volumetric differences. Furthermore, the timing between the surgical procedure and the MRI scan and neurocognitive assessment varied from less than 2 to 15 years after surgery, which could have limited the extent of the detectable changes due to brain plasticity and repair. The study's sample size was relatively small, and the time interval since the original study made adequate follow-up difficult. Moreover, study participants were volunteered by their parents for the initial language assessment study, which could affect generalizability of the results to a broader population but did not influence the comparisons between the 2 study groups, which were drawn from the same cohort. As typical for surgery in infants and toddlers, many children in our study underwent surgery for chronic ear infections, which could potentially have influenced language development due to hearing impairment. However, surgery occurred at a younger age (ie, between 1 and 2 years) to prevent

long-standing hearing abnormalities. Moreover, recent, larger studies have not supported an association between chronic otitis and abnormalities in language development, academic performance, or IQ.^{39,40} The analysis of vital signs and anesthetic doses depended on the accuracy of documentation in the handwritten paper anesthesia records, which has been found to be discrepant from automated electronic recordkeeping systems.⁴¹ Surgery in our study and other, similar studies occurred before implementation of electronic recordkeeping systems. Accordingly, volatile anesthesia doses had to be calculated from the documented inspired anesthesia doses and may not be reflective of the true brain tissue concentration. Moreover, our study lacked power to compare different anesthetics with each other, which should be adequate if the comparable toxicity observed in animals translated to clinical practice.⁴²

Finally, the exclusion of neurologically grossly abnormal children from the entire cohort and our inability to confirm nonexposure in all control subjects

may have biased the study against finding a difference by mistakenly excluding children in whom anesthesia may have caused substantial impairment or by inadvertently including previously exposed children in the control group. In conclusion, the potentially deleterious effects of anesthetic exposure for surgery at a young age are a major concern for pediatric health. In order to control for several confounders of neurodevelopment, we used a matched-control design, which assigned previously exposed children with control subjects based on gender, age, handedness, and socioeconomic status.⁴³ We found that anesthetic exposure for surgery early in life did not lead to measurable neuronal elimination in brain regions previously identified in animals. However, language comprehension and performance IQ were decreased in exposed children, compared with their unexposed controls, and these functional abnormalities were associated with decreased gray matter volume, primarily in posterior brain regions. These provocative findings warrant additional research efforts to better define human applicability of animal data, to delineate the phenomenon's mechanisms, and to devise mitigating strategies for this potential dilemma for child health.

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ABBREVIATION

OWLS: Oral and Written Language Scales

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