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The Relationship of Exposure to Anesthesia on Outcomes in Children with Isolated Oral Clefts

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Abstract

This study evaluated the relationship between exposure to anesthesia and previously identified differences in cognitive functioning, growth, and volumetric brain measures among a sample of children, adolescents, and young adults with isolated oral clefts (iCL/P). Data from a cross-sectional study was combined with a retrospective chart review. Data was obtained for 87 participants with iCL/P (55% male), ranging from 7.5 to 27 years old (mean = 15.78 [SD = 4.58]). Measures of interest included cognitive functioning, growth measures, and brain volumes. Number of surgeries and time under anesthesia were obtained through systematic medical record review. Potential sex and cleft type differences in exposure as well as relationships between anesthesia exposure and outcome measures were evaluated. Participants with isolated cleft lip and palate had more surgeries and were under anesthesia longer. For participants with isolated cleft lip only, more surgeries were correlated to lower verbal IQ and higher frontal lobe volume.

Keywords

Anesthesia; Cleft Lip and/or Palate; Magnetic Resonance Imaging; Neuropsychology

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Author Contributions

ALC, JG, and PN conceived the study. ALC and PN participated in study design. ALC contributed to the acquisition of data. ALC, JG, and PN participated in the analysis of the data. ALC, JC, RB, and PN contributed to the interpretation of data. ALC and JG drafted the manuscript, and JC, RB, and PN critically revised the manuscript for important intellectual content. The final version was approved by all authors.

Declaration of Conflicting Interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study was approved by the Institutional Review Board at the University of Iowa. Informed consent was obtained by all legal adults and from legal guardians of minor participants. Verbal and/or written assent (depending on age) was provided by all minor participants.

Over the past two decades, research on the growth and development of people with isolated, or non-syndromic, oral clefts (cleft lip and/or palate; iCL/P) has been expanding. Identification of increased risk for later behavioral and cognitive deficits, including ADHD,^{1–3} social withdrawal,^{4–7} and learning disabilities,^{8–11} has sparked interest in possible factors of etiology. Early work has focused on medical and social factors related to cleft (i.e., speech and hearing difficulties,^{12–14} social stigma¹⁵). However, inconsistent findings and continued unexplained variability^{16,17} in performance has led to another etiological theory.

The cells that make up our face and skin arise from the same cells that later form our brain.¹⁸ Because there is a disruption in the development of craniofacial structures leading to oral clefts, it is hypothesized that similar disruption of migration may also occur in the cells that create the brain.^{19–21} This abnormal development would be minor, but could be another factor in the etiology of behavioral and cognitive sequelae. Following this theory, research has evaluated the brain development of people with iCL/P as well as the relation to measures of behavior and cognition. Structural MRI studies have found volumetric brain differences in infants²² and children/adolescents²⁰ in comparison to age and sex-matched unaffected control participants. As a whole, this body of research suggests abnormal brain development where brain volume is globally smaller in childhood, with slower white matter maturation (myelination) and regional reductions in the frontal lobe and borderline enlargement of the occipital lobe.²⁰ These differences have been correlated to measures of attention and hyperactivity,² general cognition,²³ expressive language skills,²⁴ reading,⁹ and speech articulation.²⁵

Conversely, a key criticism to this theory is an equally growing body of literature on the impact of anesthesia on brain development. The use of anesthetic agents for many surgical procedures is nearly universal, as these agents are generally regarded as safe when appropriately administered and monitored by adequately trained medical personnel. However, in recent years, significant concerns regarding the long-term safety of these agents have emerged after findings from experimental animal studies revealed extensive neuroapoptosis (neural cell death) with associated learning deficits after early-life exposure to anesthetic agents.²⁶ Subsequent retrospective studies of large population-based samples suggest that children who have had multiple exposures to surgical anesthesia have increased rates of learning disabilities,^{27,28} language and abstract reasoning deficits,²⁹ an increased frequency of very poor performance on measures of academic achievement,³⁰ and behavioral difficulties.^{31,32} There is also some evidence associating just a single exposure to general anesthesia within the first three years of life to residual cognitive impairments.^{29,30} Recent work by Backeljaaw and colleagues³³ found that early exposure was associated with subtle, but significant decreases in language comprehension and performance IQ, which was further associated to volumetric differences in regional gray matter. However, other studies do not support clinical evidence regarding the impact of early anesthesia exposure on long-term cognitive functioning in humans,³⁴ as there have been conflicting studies yielding mixed results³⁰ or no association.³⁵

Reports from the 4th Pediatric Anesthesia NeuroDevelopment Assessment team (PANDA) Symposium³⁶ indicate that “there is still not sufficient cause to significantly alter practice

primarily because of fear of neurotoxic effects.” (pg 394). It was recently reported that a single exposure to general anesthesia before the age of 3 years old did not have any statistically significant impact on IQ scores in later childhood.³⁷ However, there are gaps in the research (e.g., evaluation of dosing and repetition, specific agents, and psychological risk/benefit for children with stigmatizing defects with delaying surgery) that need to be addressed. It is hoped that these results and from two ongoing studies (i.e., MASK study³⁸ and the GAS trial) will help provide more insight and guidance. So far, the GAS trial has published results of cognitive outcome at 2 years of age with no significant differences between infants who received regional versus sevoflurane-based general anesthesia.³⁹

The consistent concerns of 1) early exposure during key neurodevelopmental time periods and 2) increased exposure (through a higher number of surgeries or longer time in surgery) make the study of exposure to anesthesia a primary concern for children with an oral cleft. Treatment typically involves numerous surgeries that start in infancy and continue through adolescence, as well as use of screening methods that also require sedation (e.g., MRI or other imaging procedures). In a review article, Laub and colleagues specifically relates the research on potential neurotoxicity of anesthesia to children with cleft.⁴⁰ The authors have also conducted a systematic literature review of this research, which was presented at the American Cleft Palate Association Annual Meeting.⁴¹ In both reviews, the authors discussed evidence based on animal models and human studies, suggesting that there is a possibility of neurotoxicity related to early anesthesia exposure and this is highly relevant given the current treatment protocols of children with oral clefts. There has been one published study that examines the impact of surgical exposure to anesthesia on academic achievement of children with isolated cleft lip and/or palate (iCL/P). Clausen and colleagues⁴² used population data from a Danish registry to determine potential relationships between number of surgeries and academic achievement as measured by standardized assessments. It was found that cleft type had a significant impact on outcomes (those with cleft palate only (iCP) performed lower), but number and timing of operations were not associated with academic performance. The authors acknowledged that “potential neurotoxic effects due to anesthetic agents ... cannot be completely excluded” (pg 1).

The important role of surgical intervention in the treatment of oral clefts and its otolaryngological sequelae, mounting evidence of subtle cognitive impairments in children with CL/P, and the question as to whether these cognitive impairments may be attributed to anesthesia exposure warrant the current study. Previous research on brain development in people with non-syndromic oral clefts has not adequately accounted for the possibility that rather than stemming from a genetic cause (shared with the oral cleft), abnormal brain development that has been found may be due to 1) the number of surgeries or 2) length of time in surgery that patients must go through as part of their treatment of the cleft early in development. The purpose of the current study is twofold: 1) Provide preliminary data regarding cleft type and sex differences in exposure to anesthesia during the first 7 years of life and 2) Evaluate the relationship between exposure to anesthesia, and previously identified areas of difference, including: cognitive, growth, and volumetric brain measures among a sample of children and adolescents with non-syndromic oral clefts.²⁰ Primary analysis will focus on children with iCL/P as a whole, and exploratory analyses will evaluate possible cleft type and sex differences in these relationships. It is hypothesized that children

with cleft lip and palate (iCLP) will have the highest number of surgeries and longest exposure, given the higher complexity of their diagnosis. Further, it is hypothesized that exposure to anesthesia will be significantly correlated to cognitive, growth, and volumetric brain outcome measures.

Patients and Methods

Participants

Data was obtained from a longitudinal study of brain development and neuropsychological performance in children, adolescents, and young adults with cleft. Please refer to Nopoulos et al²⁰ for detailed information on recruitment, consent, and protocol administration. The original sample (ages 7 – 17 years old) consisted of 148 children (74 iCL/P and 74 unaffected control) assessed between November of 2002 through November of 2005. In an extension to this study, one hundred and one of the original sample returned for longitudinal assessment (39 iCL/P and 62 unaffected control). An additional 78 new participants were also evaluated as part of this extension (ages 7 – 30 years old; 54 iCL/P and 24 unaffected control). Because the purpose of the current study was to focus on exposure to anesthesia for participants with iCL/P and because complete medical information was not available for the majority of the control sample, only data from participants with iCL/P was included in the current study.

Analyses were limited to only those participants with iCL/P who had medical records with documentation on surgeries and exposure to anesthesia. From the total sample (original and extension), brain, cognitive, and chart review data was available for 87 participants with iCL/P. Forty-four (51%) were included in the original Nopoulos et al²⁰ article. The remaining participants were included in the extended portion. Return data was used for 10 participants from the original study who had poor quality MRI scan at their first visit. Visit 1 data was used for 33 new participants (See Figure 1). For the combined sample, 48 participants were male (55%). Forty-eight had isolated cleft lip and palate (iCLP; 31 unilateral, 16 bilateral, 1 unspecified), 20 had isolated cleft lip only (iCL; 17 unilateral and 3 bilateral), and 19 had isolated cleft palate only (iCP; 12 soft palate and 7 hard and soft palate). Participants ranged in age from 7.50 to 27.25 years old (mean = 15.78, standard deviation = 4.58; see Table 1).

Measures

Primary outcome measures for the current study include the cognitive, growth, and brain measures that were found to be discrepant between children with oral cleft and unaffected controls in the original study, variables without significant group differences were not included.²⁰ The only cognitive variable included is Verbal IQ (VIQ) from the Wechsler Intelligence Scales (WISC-III⁴³ for participants ages 7 – 17 and WAIS-III⁴⁴ for participants 18 and older). Growth measures included height and head circumference. Volumetric brain measures of interest included: intracranial volume (ICV), total brain tissue (total white matter and total gray matter), total cerebral volume (total frontal and total occipital volume), subcortical structures (caudate, putamen, and globus pallidum), and cerebellar volume. In the original study, children with iCL/P were found to have significantly lower IQ

(specifically Verbal IQ), shorter height, smaller head circumference, and smaller volumetric brain measures. However, occipital lobe volume was larger in participants with iCL/P. Socioeconomic status (SES) is included as a covariate for all analyses. SES was measured with a modified Hollingshead⁴⁵ scale based on parental education and income, with lower values reflecting higher SES. Mid-way through the original study, there was a change in MRI scanner at the facility where testing took place; 47 participants in the current sample were imaged using a 1.5-T GE Signa magnetic resonance scanner (General Electric, Milwaukee, Wisconsin) and the rest were scanned on a 1.5-T Siemens Avanto scanner (Siemens AG, Muenchen, Germany). Therefore, scanner is included as a covariate for all analyses utilizing brain measures.

Systematic medical record reviews were conducted on all charts available to identify the predictor measures: 1) number of surgeries and 2) hours of exposure to anesthesia. For each subject, every recorded surgery up to the date of participation was tallied. For each surgery, the hours of exposure to anesthesia were also recorded; this was not available for 8 participants. Given the large age range and the fact that children with oral clefts often have surgeries into adolescence and adulthood, only surgeries prior to the age of 7 years old (the age of the youngest participants) were included for analysis to avoid confounding of age (e.g., older children having more surgeries recorded).

Analyses

Preliminary Analyses—Univariate ANOVAs were run to evaluate any possible main effects of cleft type or sex on number of operations or hours of exposure to anesthesia. The possible interaction of type and sex was also evaluated.

Primary Analyses—Partial Pearson correlations were conducted to evaluate the relationship between number of operations and hours of exposure to anesthesia to the previously identified cognitive, growth, and brain variables of interest. To control for growth across the wide age range, ratios of head circumference and global brain measures to height and regional brain measures to cerebrum volume were calculated. All analyses controlled for age and socioeconomic status (SES), and correlations with brain measures also controlled for scanner. Because of the exploratory nature of this study, Bonferroni correction was not utilized despite the numerous comparisons evaluated.

Exploratory Analyses—Two additional sets of correlations were conducted: (1) Relationships evaluated for participants split by sex and (2) Relationships evaluated for participants split by cleft type (iCL, iCP, and iCLP).

Results

Preliminary Analyses

Evaluation of differences in number of operations resulted in a significant main effect for cleft type ($F(2, 81) = 5.449, p = 0.006$). Participants with iCLP underwent more operations before the age of 7 years in comparison to participants with iCL (mean difference 95% CI = -2.838 to $-0.224, p = 0.014$) and this difference nearly reached significance in comparison

to participants with iCP (mean difference 95% CI = -2.836 to 0.054, $p = .063$). A similar pattern was found for hours of exposure to anesthesia, where there was a main effect for cleft type ($F(2, 73) = 14.033$, $p < 0.001$). Participants with iCLP were under longer in comparison to participants with both iCP and iCL (mean difference 95% CI = -7.100 to -1.165 ($p = .003$) and -7.724 to -2.529 ($p < .001$), respectively). There was not a significant main effect for sex or interaction of sex and cleft type for either number of operations ($F(1, 81) = 1.112$, $p = .295$ and $F(2, 81) = 1.561$, $p = .216$, respectively) or number of hours of exposure to anesthesia ($F(1, 73) = 1.540$, $p = .219$ and $F(2, 73) = 0.611$, $p = .545$, respectively). (See Figure 2).

Primary Analyses

Results of all Partial Pearson correlations are presented in Table 2. For the single cognitive outcome measure, VIQ, there were no significant correlations to number of operations or hours of exposure to anesthesia for the group as a whole. Of the two growth measures, neither height nor head circumference were correlated to number of operations or hours of anesthesia. Similarly, global brain variables were not significantly correlated to number of operations or hours of anesthesia. Of the regional brain variables, increased frontal lobe volume was significantly correlated to more surgeries for the sample as a whole ($r = .233$, $p = .033$). This relationship was not significant for hours of exposure to anesthesia ($r = .133$, $p = .251$).

Exploratory Analyses

When split by sex, neither number of operations nor hours of exposure to anesthesia was correlated to any of the cognitive, growth, or volumetric brain measures.

When split by cleft type, number of operations was negatively correlated to VIQ for participants with iCL, where more operations was related to lower VIQ ($r = -.696$, $p = .001$). For those with iCP, this relationship reached a trend level ($r = -.433$, $p = .082$) and was nonsignificant for those with iCLP. The relationship of VIQ to hours of exposure to anesthesia was not significant for any cleft type. Relationships to growth and global brain measures were not significant when split by cleft type. Regionally, increased frontal lobe volume was significantly related to increased number of operations ($r = .651$, $p = .005$) and hours of anesthesia ($r = .583$, $p = .023$) for participants with iCL. There were no significant relationships with regional brain volume measures for participants with iCP or iCLP.

A post-hoc correlation was run to evaluate the possible correlation of VIQ and frontal lobe volume for those with iCL. After controlling for age, SES, and scanner, the Pearson correlation was significant ($r = -.671$, $p = .003$) where decreased VIQ was associated with increased frontal lobe volume.

Discussion

Preliminary analyses on rates of surgery and hours of exposure to anesthesia found no sex differences, but there were significant cleft type difference. Participants with iCLP had a higher number of operations and more hours of anesthesia than participants with iCL and

iCP. This finding is consistent with other reports⁴² and is not surprising, given the higher complexity for those with iCLP compared to iCL and iCP.

The primary purpose of this study was to evaluate the possible relationship anesthesia exposure may have to previously identified outcomes in cognition, growth, and brain development in children with iCL/P. When the relationship of exposure to anesthesia to key cognitive, growth, and brain variables was assessed, there was one significant correlation for the total sample (87 children with clefts of various types); more surgeries were related to larger frontal lobe volumes. While one significant finding out of 13 outcome measures may be due to Type I error, the specification to the frontal lobe is of particular interest for this population.

The structure of the frontal lobe has previously been shown to be abnormal in subjects with iCL/P. Importantly, there is a change in developmental trajectory of the frontal lobe in which during childhood this region is proportionately small²⁰ and later in adulthood is found to be proportionately enlarged (especially the cortex).¹⁹ Normally, the cerebral cortex undergoes substantial decrement in volume, particularly between ages 10–16 due to programmed synaptic elimination.⁴⁶ The differential trajectory of iCL/P suggests that the later maturational changes of pruning are less robust. Is it possible that a high number of surgeries early in life has a pathological impact on the pruning of frontal gray matter among children with iCL/P? Further research is required to explore the possible connection of surgeries and later development.

Because of past research reporting sex and cleft type differences in outcomes among children with iCL/P, exploratory analyses were run to evaluate if there were group differences in these relationships. However, because of the small sample sizes, results of these exploratory results must be interpreted with caution. While there were no significant relationships identified when the sample was split by sex, significant correlations were found when the sample was split by cleft type. Significant relationships only emerged for those participants with iCL. Specifically, higher exposure was related to both decreased VIQ and increased frontal lobe volume. The finding of lower VIQ is consistent with research in both children and adults.^{20,23} More importantly, the enlargement of frontal lobe gray matter is considered ‘pathological enlargement’ as it was shown that the larger the frontal lobe volume the lower the IQ. Given that the current sample is of an older age range, the finding of enlarged frontal lobes associated with lower VIQ is a replication of previous findings in adults with iCL/P²³ and consistent with the interpretation that it is a pathologic structural change.

It is interesting that findings were non-significant for participants with iCLP (with the most surgeries and longest exposure). This may provide further evidence of the limited impact anesthesia exposure may have on children. As noted by Clausen and colleagues,⁴² it was cleft type that was the strongest predictor of academic achievement outcomes. Perhaps other genetic, biological, or environmental factors have a stronger effect on cognitive and neurological development than anesthesia exposure.

These results should be interpreted with caution. This was an extended sample including participants slightly older than the original study.²⁰ The older age of some participants may have weakened possible relationships between exposure and outcome variables. The wide age range also means that different protocols for anesthesia were likely used. The oldest participants were born in the early 1980's and the youngest participants were born in the early 2000's. Additionally, medical chart reviews for some of the original sample did not provide needed information on surgeries or anesthesia exposure. Inclusion of that information may have had an impact on the results. As with all studies utilizing medical record review, there is also the risk of uncharted data or information from other institutions not being included (this could result in under-estimates of exposure). There is no control comparison for this study; many of the controls from the original study were treated at other hospitals, so medical records were unavailable to the authors. Furthermore, this study involved retrospective chart review. Measures of exposure to anesthesia were limited to what was available within medical records. It is possible that other measures of anesthesia exposure (e.g., type of medication) may have yielded different results. Finally, only information on surgeries was included in the chart review. Instances where a child may have been sedated for imaging procedures were not included, so length of exposure may be under-represented for some participants.

The relationship between anesthesia exposure and outcomes is undoubtedly complex, with numerous confounding factors. Additionally, it is unclear to what extent the potential risks of surgery/anesthesia exposure may be outweighed by the benefits of surgery and the costs of delaying or denying procedures.⁴⁷ For example, untreated otitis media is associated with hearing loss. When hearing loss occurs during early developmental timeframes, it can lead to delays in both language and reading development. Work like this continues to be needed as we strive to learn more about the practices we utilize with our patients and how to best meet their needs while minimizing risks. It is hoped that this study will set the groundwork for more research evaluating outcomes in connection to factors of early treatment. This should include prospective studies that utilize a pre- and post-surgery design, with detailed records of exposure to anesthesia (including age at exposure, type of anesthetic used, and length of surgery), neuroimaging measures, and cognitive assessment. Larger sample sizes will be required to fully evaluate possible sex and cleft type differences. Such research will increase understanding of the etiology of cognitive and neurodevelopmental differences among children with iCL/P and help guide treatment decisions.

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Figure 1.

Inclusion of participants from the original (Nopoulos et al., 2007) article and the extension study. *Return data was used for 10 participants to supplement missing or poor quality MRI data from their initial visit.

Figure 2.

A) Number of Operations and B) Hours of Anesthesia Before 7 Years Old by Sex and Cleft Type. *Higher than iCL, $p < .05$. ^Higher than iCP, $p < .05$. note: iCL = Isolated Cleft Lip Only, iCP = Isolated Cleft Palate Only, iCLP = Isolated Cleft Lip and Palate.

Table 1

Age, Socioeconomic Status, Verbal IQ, Number of Operations and Hours of Anesthesia Before 7 Years Old by Sex and Cleft Type.

	Male				Female			
	iCL N=10	iCP N=5	iCLP N=33	iCL N=10	iCP N=14	iCLP N=15		
Age								
Mean (SD)	15.46 (5.39)	12.00 (4.09)	16.98 (4.36)	15.21 (4.03)	15.01 (4.55)	15.71 (4.81)		
Min-Max	9.42 – 27.25	7.83 – 17.67	7.67 – 25.25	10.83 – 22.25	7.50 – 22.83	7.5 – 25.08		
Socioeconomic Status								
Mean (SD)	2.56 (0.50)	2.80 (0.45)	2.53 (0.54)	2.82 (0.33)	2.72 (0.80)	2.61 (0.60)		
Min-Max	2 – 3	2 – 3	2 – 4	2 – 3	2 – 4	2 – 4		
Verbal IQ								
Mean (SD)	109.70 (15.39)	101.40 (15.29)	107.33 (15.48)	102.30 (12.39)	106.29 (20.05)	107.27 (18.25)		
Min-Max	92 – 145	75 – 112	83 – 150	83 – 125	81 – 150	81 – 145		
Number of Operations								
Mean (SD)	2.10 (1.29)	3.20 (2.17)	4.52 (2.39)	2.80 (1.48)	2.00 (1.30)	3.47 (1.88)		
Min-Max	1 – 5	1 – 6	1 – 10	1 – 6	1 – 5	2 – 9		
Hours of Anesthesia								
Mean (SD)	3.68 (1.75)	6.12 (4.26)	9.71 (4.97)	4.01 (1.52)	3.56 (2.24)	8.24 (3.59)		
Min-Max	2.00 – 7.75	1.25 – 11.50	2.77 – 22.43	2.00 – 7.10	0.75 – 8.17	3.58 – 16.61		

* For Hours of Anesthesia, data was unavailable for 1 boy with iCL, 1 boy with iCP, 5 boys with iCLP, and 1 girl with iCL.

Table 2

Partial Pearson Correlations.

	Total		Split by Sex				Split by Cleft Type					
	NO [n=87]	HA [n=79]	Male [n=48]		Female [n=39]		iCL [n=20]		iCP [n=19]		iCLP [n=48]	
			NO	HA	NO	HA	NO	HA	NO	HA	NO	HA
VIQ	-.200	-.054	-.158	-.078	-.304	-.038	-.696 [^]	-.343	-.433	-.219	-.030	.048
Height	.105	.161	.149	.137	-.076	.030	-.234	.063	.115	.357	.134	.123
Head Cir.#	-.107	-.154	-.174	-.170	.018	-.115	.024	-.140	.224	-.016	-.181	-.175
ICV#	-.069	-.038	-.245	-.230	.185	.114	.099	.242	.391	.427	-.214	-.158
Total Tissue#	-.078	-.049	-.258	-.246	.146	.060	.118	.261	.375	.367	-.216	-.154
Total Gray#	-.071	-.039	-.246	-.232	.163	.100	.067	.204	.335	.350	-.221	-.152
Total White#	-.073	-.054	-.208	-.192	.088	-.020	.165	.289	.405	.346	-.158	-.121
Cerebrum#	-.066	-.039	-.244	-.234	.203	.127	.111	.244	.396	.432	-.214	-.172
Cerebellum#	-.029	-.023	-.170	-.211	.160	.175	-.014	-.023	.483	.436	-.189	-.111
Frontal% 233*	.133	.267	.126	.126	.114	.125	.651 [^]	.583*	.221	.324	.067	-.064
Occipital%	-.062	-.021	.048	.065	-.213	-.087	-.282	-.006	.287	.172	.017	.035
Caudate%	-.074	.027	-.043	-.026	.045	.265	.007	-.121	-.093	-.295	-.150	.007
Putamen%	-.106	.004	-.063	-.034	-.144	.047	-.113	-.004	-.213	-.397	-.156	.019
Globus%	.001	.044	.070	.109	-.289	-.161	-.345	-.366	-.158	-.400	.131	.139

NO = number of operations; HA = hours of anesthesia; VIQ = Verbal IQ. All comparisons include age and socioeconomic status as control variables and brain measures include scanner as control variables.

ratio to height.

% ratio to cerebrum.

^{*} p < .05.[^] p < .01.