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Original Article

Neurodevelopmental impact of prenatal regional or general anaesthesia: An ambidirectional pilot cohort study

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ABSTRACT

Background: Up to 2% of pregnant women undergo non-obstetric surgery, yet literature on the long-term effects of prenatal anaesthesia exposure is scarce and conflicting. This study aimed to assess executive functions in children born to mothers exposed to general anaesthesia (GA) or regional anaesthesia (RA) for non-obstetric surgery during pregnancy, compared with children born to women who did not undergo surgery. The second aim was to assess executive functions, considering potential confounding factors affecting brain development.

Methods: This single-centre ambidirectional pilot cohort study included children born between 2011 and 2018 at Caen Normandy University Hospital, with retrospective identification of children born to mothers exposed, or not, to GA or RA during pregnancy. Children with a diagnosed neurodevelopmental disorder were excluded. Neurodevelopmental outcomes were assessed using the Behaviour Rating Inventory of Executive Function (BRIEF) parental questionnaire. Analyses included potential confounding factors. We conducted an analysis of variance (ANOVA) between the three groups for the primary outcome and univariate ANOVAs to study the influence of confounders on BRIEF scoring.

Results: Ninety-four children (6.3–10.3 years old) were studied: children born to mothers exposed to GA (n = 40), RA (n = 13), and the control group (n = 41). No difference in BRIEF scores was observed among the groups. No confounding factors influenced this result.

Conclusions: This study is the first to compare neurodevelopmental outcomes in children born to mothers exposed, or not, to RA or GA during pregnancy. No difference in BRIEF scores was observed. Larger studies with detailed executive function analyses and daily life habits are needed.

Abbreviations: ADHD, Attention deficit hyperactivity disorder; ANOVA, Analysis of variance; ASD, Autism spectrum disorders; BMI, Body mass index; BRI, Behavioural regulation index; BRIEF, Behaviour Rating Inventory of Executive Function; CI, Confidence interval; DBP, Diastolic blood pressure; ENT, Ear, nose, and throat; GA, General anaesthesia; GEC, Global executive composite; h, Hours; HB, Hyperbaric; HR, Hazard ratio; IQR, Interquartile range; IR, Incidence rate; IV, Intravenous; IS, Inconsistency scale; kg, Kilograms; MD, Mean difference; mg, Milligrams; MI, Metacognition index; mL, Millilitres; min, Minutes; ng, Nanograms; PONV, Postoperative nausea and/or vomiting; RA, Regional anaesthesia; SBP, Systolic blood pressure; SD, Standard deviation; SpO_2, Peripheral oxygen saturation; TCI, Target-controlled infusion; WA, Weeks of amenorrhea; WHO, World Health Organization; y.o., Years-old; µg, Micrograms.

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1. Introduction

In Western Countries, up to 2% of pregnant women need to undergo non-obstetric surgery [1]. Most procedures are due to emergencies (82%), and almost half occur during the second trimester of pregnancy [2]. Between 70 to 97% of these procedures are performed under general anaesthesia (GA) [1,3,4].

As a large part of the human brain development occurs *in utero* [5], several preclinical studies, mainly in rodents, investigated the possible consequences of prenatal anaesthesia exposure on the developing brain [6–9]. Our previous translational study highlighted the possible behavioural and cerebral structural consequences of early GA exposure during childhood observed in mice and right-handed humans [10]. In humans, GA exposure was associated with reduced emotional control and right prefrontal gyrus volume. However, clinical studies on prenatal exposure are scarce [11–13], and their results are conflicting. Bleeser's study in 2022 did not find an association between prenatal anaesthesia and neurodevelopmental outcomes [12], whereas Ing's studies in 2021 and 2024 found that prenatal exposure to GA was associated with some impaired neurodevelopmental outcomes [11,13]. The neurodevelopmental effects attributed to GA could actually be the consequence of a combination of direct effects of anaesthetic agents, imbalance of physiological parameters during anaesthesia, and/or neuroinflammation related to nociceptive surgical stimuli or sepsis [14,15]. However, the human developing brain is not exposed to general anaesthetic agents when surgery is performed under regional anaesthesia (RA). In a recent retrospective study, GA for non-obstetric surgery during pregnancy was considered a posteriori avoidable in over 30% of cases [16].

We performed an ambidirectional pilot cohort study, with 1) a retrospective identification of children born from mothers who were either exposed to anaesthesia (under GA or RA) for non-obstetric surgery during pregnancy or did not undergo any surgery during pregnancy and 2) a prospective evaluation of neurodevelopmental outcomes of their children using parental questionnaires as the first aim of the study. We therefore used the Behaviour Rating Inventory of Executive Function (BRIEF) score in all children [17]. The second aim was to assess the possible effects of currently known or suspected confounding factors affecting the developing brain (including the child's current weekly estimated screen time exposure) on the BRIEF scores in these three groups.

2. Methods

2.1. Ethics approval

This was a single-centre, ambidirectional, pilot cohort study including all pregnant women who underwent non-obstetric surgery and delivered at Caen Normandy University Hospital over an 8-year period (2011–2018). It was approved on May 22nd, 2022, by the Research Ethics Committee of Caen Normandy University Hospital (CLERS identification number: 3851) and was performed in accordance with the Declaration of Helsinki (2013). In accordance with the Ethics Committee decision, mothers provided written consent to the use of their medical data during pregnancy and childbirth. In addition, parents or legal guardians provided written consent to the use of their children's medical data.

2.2. Recorded data

Women who underwent surgery during pregnancy were identified through the electronic medical recording system (M-CrossWay, Ivry-sur-Seine, France) of the Caen University Hospital from January 1st, 2011, to December 31st, 2018. The children born from these mothers who were exposed – or not – to surgery during pregnancy were identified through the same electronic medical recording system of the Caen University Hospital.

2.3. Population

Three groups of patients were defined as follows:

- General anaesthesia group (GA-group): Children born between 2011 and 2018 at the Caen University Hospital from mothers who underwent non-obstetric surgery under GA during pregnancy.
- Regional anaesthesia group (RA-group): Children born between 2011 and 2018 at the Caen University Hospital from mothers who underwent non-obstetric surgery under RA during pregnancy.
- Control group: Children born between 2011 and 2018 at the Caen University Hospital from mothers who did not undergo any surgery during pregnancy. Children included in this group were born on the same day as those of the RA-group (a birth before, or a birth after).

2.4. Exclusion criteria

- Refusal of either parent or legal guardian to allow their child's participation.
- Children with a pathology identified as an independent risk factor altering cognitive development: neonatal hypoxia, neurological disease, neuromuscular disease, complex cardiac disease.
- Children with a confirmed or suspected genetic syndrome.
- Preterm-born children (*i.e.*, born before 37 weeks of amenorrhea).
- Caesarean section delivery.
- Presence of a diagnosed neurodevelopmental disorder (autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD) at the time of testing.

2.5. Retrospective data collection

Retrospective data were collected on an anonymized form from the electronic medical records. The accuracy of data was confirmed during the parental phone call interview (see Prospective data collection section below).

2.5.1. Collected data for mothers

Mothers' demographic characteristics included socio-economic status (as defined by the French National Institute of Statistics and Economic Studies, Institut National de la Statistique et des Études Économiques, www.insee.fr), history of chronic diseases and allergy, characteristics of pregnancy and related complications, medication and drug use during pregnancy as well as labour-related data (epidural analgesia, hypotension *etc*).

Specific collected data concerning mothers who underwent non-obstetric surgery during pregnancy: clinical characteristics and vital signs at admission (as reported by the anaesthesiologist in charge of the procedure), emergency or elective procedure status, type and duration of the surgical procedure, anaesthetic data including hypotension during surgery, anaesthetic drugs administered and dosage, and postoperative hospitalization data.

2.5.2. Collected data for children

Data concerning foetal and neonatal condition and course, child's characteristics, and medical history were collected.

2.6. Prospective data collection

All prospective data were collected from October 9th, 2023, to February 23rd, 2024, by two independent investigators (VC and CS) who interviewed the mothers using a standardized questionnaire through a phone call. The standardized questionnaire was designed by a cognitive psychologist and an anaesthesiologist (NP, JPS).

2.6.1. Children's executive functions assessment: Behaviour Rating of Executive Function (BRIEF) questionnaire

The BRIEF questionnaire (Hogrefe, 2013) is a validated parental questionnaire assessing the executive functions of children aged from 5 to 18 years old [17] through 86 questions grouped into 8 scales: inhibition, flexibility, initiation, emotional control, working memory, planning/organization, material organization, and monitoring. The obtained global scale provides information regarding subtle and subclinical changes in various executive functions.

2.6.2. Collected data for mothers

Self-rated health and self-reported anxiety during pregnancy were collected.

2.6.3. Collected data for parents' demographics

Parents' marital status, child smoke exposure, and psychiatric and/or psychological follow-up for one of the parents were collected.

2.6.4. Children's medical history

Surgery under GA during childhood, history of any hospitalization, and history of medical pathologies (including neurodevelopmental, otolaryngological, and neurological) were collected.

2.6.5. Children's cognitive functioning in daily life

Children's academic difficulties, experiences of traumatic life events (defined as a history of domestic violence and/or school harassment), children's well-being in daily life (at home, at school, and during extracurricular activities), and average weekly screen time exposure were collected.

2.7. Outcomes

2.7.1. Primary outcome

The BRIEF score described above was the primary outcome compared among the three groups.

2.7.2. Secondary outcomes

The influence of several confounding factors currently known or suspected to have a potential impact on neurodevelopment outcomes and therefore alter the BRIEF score in children born from mothers who were exposed to anaesthesia (GA or RA groups) for non-obstetric surgery during pregnancy *vs.* children from mothers that did not undergo any surgery during pregnancy (control group) was evaluated.

2.8. Sample-size determination

To evaluate the statistical validity of this analysis, we performed an a priori power analysis using G*Power software version 3.1 (Düsseldorf, Germany) with a mixed 3×8 design with the group as the between-subject factor (GA-group *vs.* RA-group *vs.* the control group) and the 8 BRIEF sub-group scales. The analysis indicated that a study sample size of a minimum of 27 participants, *i.e.*, 9 patients per group, was sufficient to detect a medium effect size ($f = 0.30$) with a power of 0.80 and an alpha level of 0.05.

2.9. Statistical analyses

2.9.1. Descriptive data

Categorical variables are expressed as numbers and percentages. Continuous variables are expressed as mean ($\pm$ standard deviation ($\pm$ SD)) in case of normal distribution or as median (1st–3rd interquartile range (IQR)) in case of non-normal distribution or a discrete variable. Normality was assessed using the Shapiro-Wilk test. We conducted all post hoc comparisons using chi-2 test in case of significant difference among the three groups.

2.9.2. Primary outcome

Statistical analysis was conducted to assess the BRIEF T-score in children born to mothers exposed to anaesthesia (GA or RA groups) for non-obstetric surgery during pregnancy, and the children born to mothers who did not undergo any surgery during pregnancy (control group). Because these scores were derived from the same questionnaire, we conducted a two-factor repeated-measure analysis of variance (ANOVA) that included the 2 BRIEF indexes (*i.e.*, the metacognition index (MI) and the behavioural regulation index (BRI)) and their 8 sub-group scales. The group (*i.e.*, GA-group, RA-group, or control group) was used as the between-subject factor, while the BRIEF T-score, its two indexes, and their eight sub-group scales, were included as within-subject factors.

2.9.3. Secondary outcomes

The confounding factors, enlisted below, currently known or suspected to have an potential impact on neurodevelopment were included in the BRIEF scoring analyses using a univariate ANOVA: mothers' age, mother's and father's university level, household income, urban *vs.* rural housing, psychological follow-up of one or the two parents, separated parents, mother's parity, self-reported anxiety during pregnancy, smoking during pregnancy, epidural analgesia, duration of surgery, intraoperative hypotension (defined as systolic blood pressure (SBP) <100 mmHg during surgery), nadir of systolic and diastolic blood pressure during surgery, child's gender, child's age at survey date, surgery under GA during childhood, traumatic life events, and current weekly screen time exposure ≥ 2 h.

The current weekly screen time exposure was submitted to ANOVAs with the group (*i.e.*, GA-group, RA-group, or control group) used as the between-subject factor.

2.9.4. Post hoc analyses

Post hoc analyses were performed if significant differences were found for the primary and secondary outcomes.

All analyses were performed using JASP software version 0.16.4 (Amsterdam, The Netherlands).

3. Results

3.1. Flowchart

Among the 124 eligible pregnant mothers, 93 underwent a GA and 31 a RA. A total of 184 children were eligible for this study: 94 children in the GA group (1 twin pregnancy), 33 children in the RA group (2 twin pregnancies), and 62 children in the control group. After applying the exclusion criteria, 54 (57%), 20 (61%), and 21 (34%) patients were excluded from the GA, RA, and control groups, respectively. Neurodevelopmental disorders were more common in children prior to exclusion in the GA and RA groups compared to the control group, respectively: 3/94 in the GA-group (incidence rate (IR), 3%; 95% confidence interval (CI), 1.0%–10.0%), 3/33 in the RA-group (IR, 9%; 95% CI, 3.1%–26.7%), and 0/62 in the control group (IR, 0%; 95% CI, 0%–4.8%) (see Flowchart in the Fig. 1).

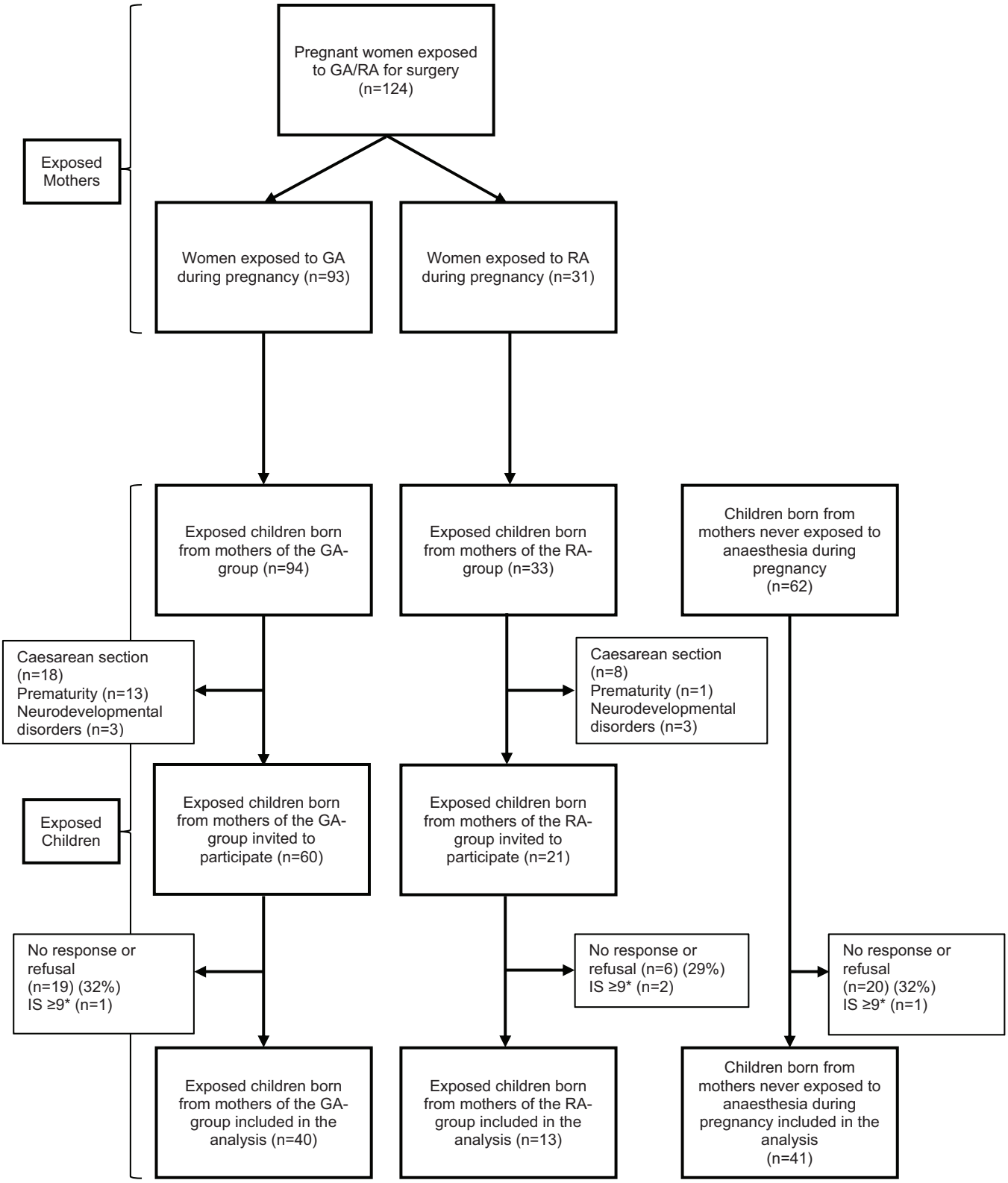

Fig. 1. Flowchart.
Abbreviations: GA, general anaesthesia; RA, regional anaesthesia.
* IS ≥ 9, Inconsistency scale ≥9: indicates an inconsistent way to which the respondent answered similar BRIEF items, thus classifying the assessed BRIEF scores of the concerned child as unreliable.

3.2. Baseline characteristics

Baseline characteristics of the 94 patients finally included are presented in Table 1.

Age of children at questionnaire was: 9.3 (7.4–10.3) years-old (y.o.), 7.5 (6.3–8.9) y.o., and 8.0 (6.3–9.4) y.o. in the GA, RA, and control groups, respectively (p = 0.17). A similar percentage of children had undergone at least one instance of surgery under general anaesthesia before the study: 20%, 23% and 24% in the GA, RA, and control groups, respectively (p = 0.89).

More mothers of the anaesthesia-exposed groups reported anxiety during pregnancy (45% and 31% in the GA and RA groups, respectively) compared to the control group (7%) ($p < 0.001$). Mothers of the GA group also had a significantly higher consumption of anxiolytics during pregnancy ($p = 0.001$) compared to the two other groups. The mothers exposed to RA received significantly more antibiotics during labour compared to the GA group (p = 0.03). Father's university level was significantly lower in the RA-group compared to the GA-group and the control group (p = 0.03).

3.3. Peri-operative data and characteristics of the anaesthesia-exposed groups

Peri-operative data available in the anaesthesia-exposed groups (*i.e.*, mothers of the GA and RA groups) are presented in Table 2.

Mean gestational age at surgery was 19 (± 10) weeks of amenorrhea (WA) in the GA-group and 21 (± 12) WA in the RA-group. Duration of surgery was 40 (22–60) minutes (min) in the GA-group and 20 (10–30) min in the RA-group.

More mothers of the GA group experienced more intraoperative episodes of hypotension compared to RA group mothers ($p < 0.001$), as well as more severe intraoperative hypotension (p = 0.018). Moreover, the duration of intraoperative hypotension was longer in the GA-group 20 (± 13) min compared to the one of the RA group 5 (± 0) min, although not significantly (mean difference (MD), 14.84 min; 95% CI, −0.75–30.42; $p = 0.06$). However, when accounting for the available data in the subgroup of mothers who received spinal anaesthesia for surgery (n = 3), the indicence of intraoperative hypotension was higher (2/3) (IR, 67%), and intraoperative hypotension was no longer significative when compared to the GA group (OR, 1.22; 95% CI, −1.35–3.80; $p = 0.33$). Mothers of the GA group received significantly more postoperative analgesics (steps 2 and 3 of the WHO ladder) compared to the RA group mothers.

Intraoperative drugs and types of surgeries for the GA group are presented in Tables 3 and 5.

In the GA group, the most common surgeries were intra-abdominal surgeries (68%).

Intraoperative drugs and types of surgeries for the RA group are presented in Tables 4 and 6.

In the RA group, the most common surgeries were orthopaedic procedures (62%).

RA consisted of peripheral nerve block in 70% of cases and spinal anaesthesia in 30 % of cases.

3.4. Primary outcome

The BRIEF score was not significantly different between all three groups (p = 0.48) (Table 7).

3.5. Secondary outcomes

The recorded confounding factors currently known or suspected to have a potential impact on neurodevelopment did not influence the BRIEF score as evaluated by univariate statistical analysis (Table 8).

Children's current weekly screen time exposure was 10.9 (±6.4) hours (h), 13.0 (±9.4) h, and 7.7 (±5.3) h in the GA, RA, and control groups, respectively. ANOVA analysis revealed that the children's current weekly screen time exposure was significantly different between the three groups (p = 0.02).

3.6. Post hoc analyses

No significant differences were found anymore for the children's current screen exposure time between all three groups after considering the following confounding factors: mother's university level, parental status: separated, household income, child's age, and extracurricular activities (all adjusted $p > 0.05$).

No significant differences were found either for the different screen exposure times and the BRIEF scores.

4. Discussion

This ambidirectional pilot cohort study is the first to compare the neurodevelopmental outcomes of children born to mothers exposed to RA or GA for non-obstetric surgery during pregnancy with those of children whose mothers had not been exposed to surgery and anaesthesia during pregnancy. We first assessed their executive functions with the BRIEF parental questionnaire, taking into account the influence of potential known or suspected confounding factors on neurodevelopment. Even after considering these factors, our results did not reveal any difference in gross executive functions between children exposed to prenatal anaesthesia (RA or GA) and those who were not exposed.

Our study did not reveal any difference in the BRIEF scores between the three groups of children evaluated. In the same way, Bleeser's study did not show any difference in the BRIEF score of children born to mothers exposed to GA for surgery during pregnancy, compared with children born to mothers not exposed to surgery [12]. It is possible that the differences in results between postnatal exposure to GA and prenatal exposure are linked to the regulation of uterine circulation. Although autoregulation of uterine blood flow has not been demonstrated, there is a local increase in oxygen extraction when uterine blood flow decreases, which may counterbalance its adverse effects [18]. However, in Ing et al. recent study, prenatally exposed children were more likely than unexposed children to receive a diagnosis of a disruptive or internalizing behavioural disorder (HR, 1.31; 95% CI: 1.23–1.40) [13]. For secondary outcomes, an increased hazard of attention-deficit/hyperactivity disorder (ADHD) (HR, 1.32; 95% CI, 1.22–1.43) and autism spectrum disorders (ASD) (HR, 1.31; 95% CI, 1.05–1.64) was observed. In our study, patients with a diagnosed neurodevelopmental disorder (*i.e.*, ADHD and ASD) were excluded because we considered that these disorders would alter the BRIEF score validity. However, when looking at the cases excluded from the study, we observed that neurodevelopmental disorders were more common in children in the GA and RA groups compared to the control group, with an IR (Incidence Rate) of 3% (IR, 3/94; 95% CI, 1.0%–10.0%), 9% (IR, 3/33; 95% CI, 3.1%–26.7%), and 0% (IR, 0/62; 95% CI, 0%–4.8%), respectively, this could be explained by the small number of patients initially available for inclusion in the RA-group (n = 33), allowing for sampling fluctuation bias.

We observed a significant difference in children's weekly screen exposure time between the three groups. However, in the post hoc analyses, no significant differences were found between all three groups after considering potential confounding factors.

One strength of our study is that it included many variables not considered in other studies [11,19,20], such as intraoperative

Table 1
Baseline characteristic.

		GA-group n = 40	RA-group n = 13	Control group n = 41	p value
Characteristics of pregnancy					
General characteristics					
	Age at delivery ≥ 30 y.o.	20 (50%)	6 (46%)	20 (49%)	0.97
	BMI	25.0 (20.8–29.0)	23.9 (19.9–26.3)	22.4 (21.1–24.5)	0.08
	Parity ≥ 1	25 (63%)	8 (62%)	23 (66%)	0.83
	Twin pregnancy	0	1 (8%)	0	**0.05**
	Allergies	8 (20%)	1 (8%)	3 (13%)	0.2
	History of depressed mood	9 (23%)	2 (15%)	3 (7%)	0.16
	Epilepsy	1 (3%)	0	0	0.51
	Thyroid problems	1 (3%)	0	0	0.51
	Pre-existing hypertension	1 (3%)	0	0	0.51
	Oncologic pathology	0	0	0	/
Pregnancy related pathologies					
	Preeclampsia	3 (8%)	0	0	0.12
	Gestational hypertension	0	0	0	/
	Gestational diabetes	6 (15%)	0	3 (7%)	0.23
	Gestational cholestasis	3 (8%)	0	1 (2%)	0.38
	Thyroid problems	2 (5%)	0	0	0.25
	Urinary tract infection	8 (20%)	2 (15%)	4 (10%)	0.43
In utero drug exposure		23 (58%)	6 (46%)	13 (32%)	0.07
	Smoking	9 (23%)	5 (38%)	14 (34%)	0.4
	Alcohol	1 (3%)	0	1 (2%)	0.85
	Marijuana	1 (3%)	1 (8%)	1 (2%)	0.61
	Opioid	2 (5%)	0	0	0.25
	Antiepileptic	2 (5%)	0	0	0.25
	Anxiolytic	15 (38%)	0	4 (10%)	**0.001**
	Antidepressant	1 (3%)	0	3 (7%)	0.4
	Insulin	2 (5%)	0	0	0.25
	Thyroid hormone	2 (5%)	0	0	0.25
	Antihypertensive drug	1 (3%)	0	0	0.51
Self-rated health during pregnancy[a]		4.4 (± 1.9)	5.0 (± 1.5)	5.0 (± 1.3)	0.22
Mother's self reported anxiety during pregnancy		18 (45%)	4 (31%)	3 (7%)	<**0.001**
Foetal condition and course					
Threat of premature birth		6 (15%)	2 (15%)	2 (5%)	0.28
	Prenatal corticotherapy	2 (5%)	1 (8%)	1 (2%)	0.68
	Tocolysis	6 (15%)	1 (8%)	2 (5%)	0.11
Sonographic anomaly during pregnancy		3 (8%)	2 (15%)	5 (12%)	0.66
	Oligoamnios	0	1 (8%)	1 (2%)	0.24
	Hydramnios	2 (5%)	0	0	0.25
Foetal anomaly		2 (5%)	1 (8%)	4 (10%)	0.72
	Foetal growth restriction or small for gestational age	0	1 (8%)	1 (2%)	0.24
	Macrosomia	1 (3%)	0	3 (7%)	0.4
	Other	1 (3%)	0	0	0.51
Labour					
Gestational age at birth (WA + days)		40 + 0 (± 3 + 1)	39 + 3 (± 3 + 4)	39 + 6 (± 4 + 6)	0.68
Antibiotherapy during labour		7 (18%)	7 (54%)	10 (34%)	**0.03**
Labour analgesia					
	Epidural analgesia	30 (75%)	9(69%)	34 (83%)	0.51
	Nitrous oxide-oxygen equimolar mixture	3 (7.5%)	0	4 (9.8%)	0.51
	None	10 (25%)	4 (31%)	6 (15%)	0.35
Episode of hypotension (SBP <100 mmHg) during epidural analgesia		3 (10%)	0	3 (8.8%)	0.62
Duration of hypotension (SBP <100 mmHg) during epidural analgesia (min)		8 (± 3)	0	5 (± 0)	0.27
Neonatal condition and course					
APGAR scores					
	APGAR (at 0 min)	10 (10 – 10)	10 (10 – 10)	10 (10 – 10)	0.71
	APGAR (at 3 min)	10 (10 – 10)	10 (10 – 10)	10 (10 – 10)	
	APGAR (at 5 min)	10 (10 – 10)	10 (10 – 10)	10 (10 – 10)	
Resuscitation at birth[b]		3 (8%)	1 (8%)	2 (5%)	0.87
pH at birth <7.2		5 (13%)	3 (23%)	7 (17%)	0.64
Birth weight (g)		3349 (± 394)	3319 (± 440)	3460 (± 456)	0.41

Table 1 (*Continued*)

		GA-group n = 40	RA-group n = 13	Control group n = 41	p value
Birth weight ≤2500g		0	0	1 (2%)	0.52
Neonatal jaundice		6 (15%)	1 (8%)	2 (15%)	0.29
Meconium inhalation		2 (5%)	0	0	0.25
Non-breast/bottle fed at 24 h		15 (38%)	7 (54%)	17 (41%)	0.58
Parents' demographics					
Parental status: separated		5 (13%)	3 (23%)	3 (7%)	0.3
Child smoke exposure		18 (45%)	8 (62%)	15 (37%)	0.28
Psychiatric/Psychologic follow-up for one of the parents		19 (48%)	4 (31%)	18 (44%)	0.57
Number of brothers/sisters		1.4 (± 0.8)	2.0 (± 1.4)	1.2 (± 0.7)	0.09
Household income ()		4315 (± 1465)	4138 (± 2465)	4663 (± 2063)	0.59
	<2500	3 (8%)	2 (15%)	4 (10%)	0.25
	2500–3999	13 (33%)	7 (54%)	10 (24%)	
	≥4000	24 (60%)	4 (31%)	27 (66%)	
Urban housing		23 (58%)	7 (54%)	23 (56%)	0.97
Housing tenure		33 (83%)	8 (62%)	33 (80%)	0.26
Mother's university level		35 (88%)	8 (62%)	33 (80%)	0.12
Father's university level		29 (73%)	4 (31%)	24 (59%)	**0.03**
Child characteristics and medical history					
Age at questionnaire		9.3 (7.4–10.3)	7.5 (6.3–8.9)	8.0 (6.3–9.4)	0.17
BMI		16.6 (15.1–18.6)	15.4 (15.1–17.8)	15.9 (14.8–16.8)	0.06
Sex (male/female)		43% / 57%	46% / 54%	54% / 46%	0.6
ENT pathology					
	Diagnosed deafness	3 (8%)	0	3 (7%)	0.25
	Obstructive sleep apnoea	1 (3%)	0	1 (2%)	0.68
Hospital care					
	Surgery under GA during childhood	8 (20%)	3 (23%)	10 (24%)	0.89
	Hospitalization during childhood	11 (28%)	3 (23%)	13 (32%)	0.82
	Total duration of hospitalizations during childhood	2.2 (± 2.5)	5.0 (± 6.1)	1.9 (± 2.0)	0.2
	Total duration of hospitalizations for medical reasons and/or surgery under GA during childhood	2.9 (± 3.1)	6.0 (± 5.3)	2.3 (± 2.2)	0.15
Childhood schooling and extracurricular activities					
Child's academic difficulties		11 (28%)	5 (38%)	9 (22%)	0.49
	Mathematics	2 (5%)	1 (8%)	1 (2%)	0.68
	French	8 (20%)	1 (8%)	4 (10%)	0.32
	Behaviour	4 (10%)	0	4 (10%)	0.5
	Others	10 (25%)	4 (31%)	7 (17%)	0.51
Extracurricular activities	Weekly physical activity	32 (80%)	10 (77%)	35 (85%)	0.72
	Other weekly extracurricular activities	8 (20%)	0	7 (17%)	0.22
Childhood traumatic experiences and well-being					
School harassment		3 (8%)	2 (15%)	8 (20%)	0.29
History of domestic violence in the household		4 (10%)	1 (8%)	1 (2%)	0.37
Traumatic life events		6 (15%)	3 (23%)	9 (22%)	0.68
Parents-rated well-being of the child[c]					
	Well-being at school	4 (3–4)	4 (3–4)	4 (3–4)	0.72
	Well-being at home	4 (3–4)	4 (3–4)	4 (3–4)	0.81
	Well-being during extracurricular activities	4 (3.5–4)	4 (3.25–4)	4 (3–4)	**0.05**
		35/40	Oct-13	36/41	

Data are presented as mean (±SD) or median (IQR) for quantitative data, qualitative data are presented as number of cases (percentage in brackets), unless specified otherwise.
Abbreviations: BMI, body mass index; ENT, ear, nose and throat; h, hours; kg, kilograms; min, minutes; SBP, systolic blood pressure; WA, weeks of amenorrhea; y.o., years-old.

[a] Classification: 1 = always bad, 2 = often bad, 3 = sometimes bad, 4 = sometimes good, 5 = often good, 6 = always good.

[b] Assisted ventilation or suction.

[c] Classification: 1 = bad, 2 = average, 3 = good, 4 = very good.

Table 2
Peri-operative data available in the anaesthesia-exposed groups.

		GA-group n = 40	RA-group n = 13	p value	Mean difference or OR
Clinical characteristics at admission					
Age of the mother at surgery (years)		29.3 (±5.1)	28.2 (±5.6)	0.53	1.07 [−2.23–4.42]
Known pregnancy at surgery		38 (95%)	10 (77%)	0.05	1.74 [−0.18–3.67]
Gestational week at surgery (WA + days)		19 + 3 (±10 + 1)	21 + 1 (±12 + 3)	0.54	1 + 5.0 [−3 + 6.0–7 + 2.2]
Pregnancy trimester at surgery					
	First trimester	8 (20%)	3 (23%)	0.44	0.18 [−1.32–1.69]
	Second trimester	23 (58%)	5 (38%)		0.77 [−0.51–2.05]
	Third trimester	9 (23%)	5 (38%)		0.77 [−0.58–2.11]
ASA Physical Status Classification					
	ASA = 1	1 (3%)	1 (8%)	0.5	1.18 [−1.67–4.03]
	ASA = 2	34 (85%)	12 (92%)		0.75 [−1.47–2.97]
	ASA = 3	4 (10%)	0		1.20 [−1.79–4.20]
	ASA = 4	1 (3%)	0		0.03 [−3.23–3.29]
Sepsis		5 (13%)	0	0.18	1.43 [−1.53–4.39]
Hemodynamic instability		1 (3%)	0	0.57	0.03 [−3.24–3.29]
Emergency procedure status		33 (83%)	9 (69%)	0.31	0.74 [−0.69–2.17]
Vital signs at admission					
Systolic blood pressure (mmHg)		122 (±12) (39/39)	120 (±8) (12/12)	0.7	1.43 [−6.05–8.91]
Diastolic blood pressure (mmHg)		68 (±12) (39/39)	71 (±12) (12/12)	0.36	3.55 [−4.20–11.30]
Mean blood pressure (mmHg)		85 (±10) (39/39)	87 (±9) (12/12)	0.6	1.75 [−4.86–8.36]
SpO_2 (%)		100 (99–100) (39/39)	100 (99–100) (12/12)	0.56	0.22 [−0.52–0.96]
Heart rate (bpm)		92 (±12) (39/39)	87 (±10) (12/12)	0.25	5.22 [−3.74–14.18]
Duration of surgery					
Duration of surgery (min)		40 (22–60) (39/39)	20 (10–30) (13/13)	0.13	14.00 [−4.19–32.19]
Surgery duration ≥ 60 min		11 (28%) (11/39) (28%)	3 (23%) (3/13) (23%)	0.75	0.24 [−1.23–1.70]
Hypotension during surgery					
Intraoperative hypotension (SBP <100 mmHg)		34 (85%) (34/39) (87%)	3 (23%) (3/12) (25%)	<**0.001**	3.02 [1.41–4.62]
Severe intraoperative hypotension (SBP <90 mmHg)		20 (62%) (20/36) (56%)	1 (8%) (1/12) (8%)	**0.02**	2.30 [0.10–4.51]
Duration of intraoperative hypotension (min)		20 ± 13 (34/36) (94%)	5 ± 0 (3/12) (25%)	0.06	14.84 [−0.75–30.42]
Postoperative hospitalization data					
Postoperative analgesics					
	WHO Step 1 postoperative analgesics	40 (100%)	13 (100%)	/	/
	WHO Step 2 postoperative analgesics	34 (85%) (34/39) (87%)	7 (54%) (7/13) (54%)	**0.01**	1.76 [0.32–3.20]
	WHO Step 3 postoperative analgesics	15 (38%) (15/38) (39%)	0 (0/13)	<**0.01**	2.89 [0.01–5.78]
Duration of hospitalization (days)		3 (2–4)	2 (1–2)	0.07	2.36 [−0.20–4.91]

Data are presented as n/N (% of non-missing data) or mean (±SD) or median (IQR) for quantitative data, qualitative data are presented as number of cases (percentage in brackets), unless specified otherwise.
Group comparisons are presented in mean difference, 95% confidence interval [CI] for quantitative data, or odds ratio (OR), [CI] for qualitative data.
Abbreviations: bpm, beats per minute; min, minutes; mmHg, millimetres of mercury; SBP, systolic blood pressure; SpO_2, peripheral oxygen saturation; WA, weeks of amenorrhea; WHO: World Health Organization.

maternal blood pressure. This physiological parameter is a potential confounding factor of the developing brain. Recently, Obiyo *et al.* published recommendations for maternal and foetal safety [21]. They recommended preserving maternal homeostasis and maintaining arterial blood pressure near baseline, while avoiding intraoperative hypotension, as it can decrease utero-placental circulation and threaten foetal homeostasis and development.

Although intraoperative hypotension was more frequent in the GA group (85%) than in the RA group as a whole (23%) (OR, 3.02; 95% CI, 1.41–4.62; $p <$ 0.001), this difference was no longer significant when considering the subgroup of mothers who received spinal anaesthesia for surgery (67%). It highlights the importance of hemodynamic control during surgery under GA or neuraxial RA. In this study, we did not find any influence of intraoperative hypotension on BRIEF score comparisons (MD, 1.52; 95% CI, -8.10–11.15; $p =$ 0.25). However, even when taking the other numerous confounding factors into account, we did not find any changes in BRIEF score differences between all three groups. Another plus-value of our study is the use of anaesthetic data concerning the drugs used for GA and RA management [11,12]. Interestingly, GA for non-obstetric surgery during pregnancy is often avoidable. In one of our previous studies, based on a cohort of 106 non-obstetric surgeries performed under GA during pregnancy, a panel of 7 French experts (anaesthesiologists, gynaecological and digestive surgeons) highlighted that GA could have been avoided in over 30% of the cases, instead proposing RA to the patient [16]. After this pioneering study, more research will be

Table 3
Intraoperative drugs for the GA-group.

		GA-group n = 40
General		
	Duration of intubation (min)	80.0 (45.0–120.0)
		39/40 (98%)
Intraoperative drugs		
Paralysing agent		
	Succinylcholine (mg kg^{-1})	1.1 (± 0.1)
		33/39 (85%)
	Rocuronium (mg kg^{-1})	1.1 mg/kg, 1/39 (3%)
	Atracurium (mg kg^{-1})	0.6 (± 0.2)
		23/39 (59%)
Hypnotics		
	Propofol (mg kg^{-1})	4.1(± 1.3)
		36/39 (92%)
	Propofol TCI (ng mL^{-1})	4.5
		2/39 (5%)
	Etomidate (mg kg^{-1})	0.6
		2/39 (5%)
	Ketamine (mg kg^{-1})	0.3 (± 0.2)
		6/39 (15%)
	Thiopental; value (mg kg^{-1})	9.4
		1/39 (3%)
Morphinics		
	Sufentanil (µg kg^{-1})	0.3 (±0.0)
		29/39 (74%)
	Sufentanil TCI; value (ng mL^{-1})	0.3
		1/39 (3%)
	Remifentanil (mg mL^{-1})	2.4
		2/39 (5%)
	Remifentanil TCI (ng mL^{-1})	3.7 (± 1.3)
		5/39 (13%)
	Alfentanil (mg kg^{-1})	41.7 (± 13)
		3/39 (8%)
Intravenous anaesthetics		
	Lidocaine (mg kg^{-1})	3.0 (± 3.0)
		4/39 (10%)
Halogenated agents		
	Sevoflurane	18/39 (46%)
	Desflurane	12/39 (31%)
PONV medication		
	Dexamethasone	6/39 (15%)
	Ondansetron	1/39 (3%)
	Metoclopramide	1/39 (3%)
	Droperidol	6/39 (15%)
Vasopressors		
	Ephedrine (mg)	14.3 (± 6.9)
	Phenylephrine (µg)	396.7 (± 305)
	Norepinephrine	2/39 (5%)

Data are presented as n/N (% of non-missing data) or mean (± SD) or median (IQR) for quantitative data, qualitative data are presented as number of cases (percentage in brackets). Unless specified otherwise.
Abbreviations: IV = Intravenous, kg = kilograms, min = minutes, mg = milligrams, mL = millilitres, µg = micrograms, ng = nanograms, PONV = postoperative nausea and/or vomiting, TCI = Target Controlled Infusion.

Table 4
Intraoperative drugs for the RA-group.

		RA-group (n = 13)	p value*
Local anaesthetics			
	Ropivacaine	1/13 (8%)	/
	Mepivacaine	7/13 (54%)	/
	Chlorprocaine	1/13 (8%)	/
	HB Bupivacaine	3/13 (23%)	/
Adjuvants			
	Intrathecal sufentanil	2/13 (15%)	/
	Clonidine	1/13 (8%)	/
Hypnotics			
	Ketamine; value (mg kg^{-1})	0.2	0.48
		1/13 (8%)	
Morphinics			
	Remifentanil TCI; value (ng mL^{-1})	2.6	0.12
		1/13 (8%)	
	Alfentanil (mg kg^{-1})	5.9	1
		1/13 (8%)	
Vasopressors			
	Phenylephrine (µg)	75	0.17[a]
		2/12 (17%)	0.16

Data are presented as n/N (% of non-missing data)) or mean (±SD). Unless specified otherwise.
Abbreviations: HB, hyperbaric; kg, kilograms; mg, milligrams; mL, millilitres; µg, micrograms; ng, nanograms; TCI, Target Control Infusion.
Nota bene: Comparison for other drugs posology was not made possible due to $n < 2$ in the RA-group.
* p values are showed for comparison for parameters present in both the GA and RA groups.
[a] Comparison for phenylephrine posology between the GA and RA groups.

necessary to compare neurodevelopmental trajectories of GA and RA prenatally-exposed children, taking into account homeostasis physiology maintenance data.

The main limitation of our study is the small number of patients studied, although it was higher than the number estimated in the statistical power analysis. A refusal to participate around 30% was observed in the 3 groups; this could be explained by the announced length of the phone interview (around 30 min) during the first phone call. Further studies with larger numbers of patients will be needed. Moreover, BRIEF scores were based on parents' responses to a questionnaire and probably did not objectively reflect the children's cognitive abilities. Additionally, the present study, while taking into account a large number of covariates suspected to influence the developing brain, did not investigate the impact of prenatal anaesthetic exposure on other variables such as language learning or academic performance. Another caveat is the lack of brain imaging data associated with behavioural measures collected in children [10]. Finally, the time interval between prenatal anaesthetic exposure and neurodevelopmental evaluation could attenuate any potentially observed differences due to the influence over time of the potential known or suspected confounding factors on neurodevelopment as well as compensatory mechanisms in the human brain, such as neuroplasticity [22].

A more fine-grained analysis of the results obtained from experimental tasks, such as psychometric tests performed by the children themselves, will thus be necessary in the future to study whether maternal anaesthesia and/or surgery has any impact on their cognitive or emotional abilities. In particular, precise estimations of executive functions assessment seem essential, according to developmental psychology evidence suggesting that executive functions and self-control play a key role in childhood, for predicting physical health [23] and future academic performances [24]. As a matter of fact, IQ measures and BRIEF questionnaires are indeed probably not sensitive enough to assess the potential influence of anaesthesia on later cognitive abilities in children. This echoes with statements from parents who reported increased problems related to executive functions, behaviour, or even reading abilities in their child [25]. Moreover, even if it has been suggested that a child's IQ seems predictive of later school abilities [26], recent work has evidenced that fundamental school abilities are also strongly linked to executive functions [27]. One could argue that executive functions were already assessed in previous studies that aimed at investigating the impact of anaesthesia in children, thanks, for instance, to the Trail Making or the Wisconsin card sort tests [25]. Unfortunately, these executive tests mainly evaluate the cognitive flexibility process and do not provide indications regarding other executive functions, such as inhibitory control [28]. Given the importance of inhibitory control in daily life situations [29] and for school performances [30], future work will be needed to further

Table 5
Surgeries performed under general anaesthesia.

Intra-abdominal surgery	27 (68%)	Laparoscopy	21 (53%)	Appendicectomy	6 (15%)
				Cholecystectomy	3 (8%)
				Ovarian surgery	8 (20%)
				Explorative coelioscopy	4 (10%)
		Laparotomy	6 (15%)	Appendicectomy	1 (3%)
				Cholecystectomy	1 (3%)
				Digestive occlusion	1 (3%)
				Ovarian surgery	2 (5%)
				Splenectomy	1 (3%)
Urological surgery	8 (20%)	Obstructive pyelonephritis			5 (13%)
		Renal colic removal			3 (8%)
Ear nose and throat	1 (3%)	Correction of nasal fractures			1 (3%)
Other surgery indications	4 (10%)	Anal abscess			1 (3%)
		Vulvar abscess			2 (5%)
		Breast abscess			1 (3%)

Data are presented in number of cases (percentage in brackets).

Table 6
Surgeries performed under regional anaesthesia.

Orthopaedic surgeries	8 (62%)	Upper limb surgery	Axillary nerve block	7 (54%)
		Lower limb surgery	Sciatic and femoral nerve blocks	1 (8%)
Digestive surgeries	3 (23%)	Inguinal hernia repair	Spinal anaesthesia	1 (8%)
		Pilonidal cyst	Spinal anaesthesia	2 (15%)
Gynaecological surgeries	1 (8%)	Vulvar abscess	Spinal anaesthesia	1 (8%)
Other surgery indications	1 (8%)	Scalp wound	Scalp nerves block	1 (8%)

Data are presented in number of cases (percentage in brackets).

Table 7
BRIEF scores among the three groups (GA-group, RA-group and control group).

	GA-group (n = 40)	RA-group (n = 13)	Control group n = 41	p value	Mean difference between GA and RA groups	Mean difference between GA and control groups	Mean difference between RA and control groups
BRIEF (Global executive composite T-score)	54.7 (±11.6)	56.8 (± 14.8)	52.8 (± 9.6)				
Metacognition index	56.2 (± 12.1)	59.1 (± 13.4)	55.2 (±12.0)	0.49	1.31 [−9.75–12.37]	2.27 [−5.42–9.97]	3.58 [−7.44–14.61]
Behavioural rating index	50.3 (± 11.1)	52.8 (± 14.8)	48.1 (± 10.8)	0.61	2.80 [−14.04–8.08]	0.93 [−6.77–8.63]	3.91 [−7.11–14.93]
Inhibition	51.1 (± 11.5)	54.4 (± 15.2)	50.9 (± 10.3)	0.62	3.26 [−10.52–17.04]	0.22 [−9.37–9.81]	3.48 [−10.26–17.22]
Flexibility	57.8 (± 12.4)	58.4 (± 10.1)	57.0 (± 13.4)	0.93	0.76 [−13.02–14.54]	0.72 [−8.87–10.32]	1.49 [−12.25–15.22]
Initiation	53.1 (± 11.3)	55.1 (± 14.1)	50.2 (± 9.5)	0.30	2.00 [−11.78–15.78]	2.83 [−6.76–12.42]	4.83 [−8.90–18.57]
Emotional control	56.5 (± 11.5)	59.4 (± 12.1)	55.2 (± 11.7)	0.50	2.89 [−10.89–16.67]	1.48 [−8.11–11.07]	2.89 [−10.89–16.67]
Working memory	55.6 (± 12.4)	53.6 (± 11.3)	52.1 (± 10.1)	0.38	1.98 [−11.79–15.76]	3.50 [−6.09–13.09]	1.52 [−12.22–15.26]
Planning/organisation	52.5 (± 11.6)	55.3 (± 12.3)	51.2 (± 9.4)	0.49	2.76 [−11.02–16.54]	1.33 [−8.26–10.92]	4.09 [−9.65–17.83]
Material organization	50.6 (± 9.4)	51.2 (± 14.8)	50.6 (± 9.6)	0.98	0.63 [−13.15 – 14.41]	0.01 [−9.58–9.61]	0.64 [−13.09–14.38]
Monitoring scale	50.3 (± 11.1)	52.8 (± 14.8)	48.1 (± 10.8)	0.40	2.52 [−11.26 – 16.30]	2.23 [−7.36–11.82]	4.75 [−8.99–18.49]

Data are presented as mean (± SD) or mean difference, 95% confidence interval [CI].

Table 8
Univariate associations of potential confounding factors with the BRIEF scores.

Confounding factor	BRIEF score	p value	Mean difference between GA and RA groups	Mean difference between GA and control groups	Mean difference between RA and control groups
Age ≥ 30					
	GEC	0.14	2.50 [−6.04–11.04]	2.02 [−3.92–7.94]	4.51 [−4.00–13.03]
	BRI - MI	0.11	2.53 [−5.49–10.56]	1.65 [−3.93–7.22]	4.18 [−3.82–12.18]
	BRIEF 8 subgroup-scales	0.12	1.92 [−4.56–8.39]	1.58 [−2.92–6.07	3.49 [−2.97–9.95]
Maternal university level					
	GEC	0.77	0.08 [−10.00–10.15]	3.48 [−4.91 – 11.87]	3.41 [−5.98–12.79]
	BRI - MI	0.66	0.16 [−9.33–9.65]	3.53 [−4.37–11.44]	3.37 [−5.47–12.21]
	BRIEF 8 subgroup-scales	0.73	0.13 [−7.52–7.78]	2.80 [−3.57–9.17]	2.67 [−4.46–9.80]
Paternal university level					
	GEC	0.11	5.08 [−4.18–14.33]	1.83 [−4.48–8.14]	6.91 [−2.11–15.92]
	BRI - MI	0.11	4.91 [−3.81–13.63]	1.43 [−4.51–7.38]	6.34 [−2.16–14.84]
	BRIEF 8 subgroup-scales	0.73	3.91 [−3.11–10.92]	1.43 [−3.35–6.21]	5.34 [−1.50–12.17]
Household incomes[a]					
	GEC	0.45	4.23 [−6.21–14.66]	2.66 [−5.59–10.90]	1.57 [−8.62–11.75]

Table 8 (*Continued*)

Confounding factor	BRIEF score	*p* value	Mean difference between GA and RA groups	Mean difference between GA and control groups	Mean difference between RA and control groups
	BRI - MI	0.41	4.15 [−5.69–13.98]	2.742 [−5.03–10.51]	1.40 [−8.19–11.00]
	BRIEF 8 subgroup-scales	0.46	3.26 [−4.67–11.19]	1.86 [−4.40–8.12]	1.40 [−6.34–9.13]
Urban housing					
	GEC	0.3	2.69 [−5.91–11.29]	1.50 [−4.51–7.52]	4.20 [−4.37–12.76]
	BRI - MI	0.16	2.82 [−5.21–10.84]	1.06 [−4.55–6.67]	3.88 [−4.12–11.87]
	BRIEF 8 subgroup-scales	0.27	2.06 [−4.47–8.58]	1.17 [−3.39–5.73]	3.22 [−3.27–9.72]
Psychological follow-up for parents					
	GEC	0.53	0.83 [−8.36–10.03]	1.93 [−4.12–7.97]	2.76 [−6.42–11.95]
	BRI - MI	0.53	0.83 [−8.36–10.03]	1.93 [−4.12–7.97]	2.76 [−6.42–11.95]
	BRIEF 8 subgroup-scales	0.52	0.64 [−6.35–7.63]	1.51 [−3.08–6.11]	2.15 [−4.82–9.13]
Separated parents					
	GEC	0.83	0.91 [−10.17–11.99]	1.14 [−9.31–11.59]	2.05 [−10.08–14.18]
	BRI - MI	0.77	0.91 [−10.17–11.99]	1.14 [−9.31–11.59]	2.05 [−10.08–14.18]
	BRIEF 8 subgroup-scales	0.87	0.96 [−7.46–9.38]	0.89 [−7.05–8.83]	1.852 [−7.37–11.07]
Parity ≥ 1					
	GEC	0.75	1.60 [−7.32–10.53]	2.40 [−3.76–8.56]	4.00 [−4.85–12.85]
	BRI - MI	0.64	1.60 [−6.79–10.00]	2.10 [−3.70–7.89]	3.698 [−4.62–12.02]
	BRIEF 8 subgroup-scales	0.72	1.17 [−5.61–7.95]	1.87 [−2.81–6.55]	3.04 [−3.68–9.75]
Self-reported anxiety during pregnancy					
	GEC	0.22	0.05 [−9.07–9.17]	0.60 [−8.51 – 9.70]	0.54 [−10.85 – 11.93]
	BRI - MI	0.17	0.05 [−8.52 – 8.62]	0.31 [−8.25 – 8.86]	0.36 [−10.35 – 11.06]
	BRIEF 8 subgroup-scales	0.22	0.03 [−6.91 – 6.96]	0.65 [−6.27 – 7.57]	0.67 [−7.98 – 9.33]
Smoking during pregnancy					
	GEC	0.2	0.33 [−8.84–9.50]	2.23 [−4.50–8.95]	2.56 [−6.26–11.38]
	BRI - MI	0.16	0.37 [−8.25–9.00]	1.90 [−4.43–8.22]	2.27 [−6.03–10.56]
	BRIEF 8 subgroup-scales	0.18	0.26 [−6.70–7.21]	1.73 [−3.37–6.83]	1.99 [−4.70–8.68]
Epidural analgesia					
	GEC	0.63	2.10 [−7.45–11.64]	0.34 [−7.17–7.84]	2.43 [−7.48–12.35]
	BRI - MI	0.58	2.47 [−6.52–11.45]	0.07 [−7.00–7.13]	2.40 [−6.94–11.73]
	BRIEF 8 subgroup-scales	0.61	1.64 [−5.61–8.89]	0.30 [−5.40–6.00]	1.94 [−5.59–9.47]
Duration of surgery (≥60 min[b])					
	GEC	0.86	1.56 [−7.90–11.02]	/	/
	BRI - MI	0.79	1.45 [−7.17–10.06]	/	/
	BRIEF 8 subgroup-scales	0.84	1.18 [−5.88–8.24]	/	/
Intraoperative hypotension (SBP <100 mmHg)[b]					
	GEC	0.25	1.52 [−8.10–11.15]	/	/
	BRI - MI	0.24	1.94 [−6.81–10.69]	/	/
	BRIEF 8 subgroup-scales	0.21	1.23 [−5.90–8.36]	/	/
SBP (nadir)[b]					
	GEC	0.27	4.25 [−3.36–11.86]	/	/
	BRI - MI	0.62	1.98 [−6.06–10.01]	/	/
	BRIEF 8 subgroup-scales	0.7	1.26 [−5.24–7.76]	/	/
DBP (nadir)[b]					
	GEC	0.31	3.94 [−3.72–11.60]	/	/
	BRI - MI	0.64	1.88 [−6.10–9.86]	/	/
	BRIEF 8 subgroup-scales	0.67	1.38 [−5.09–7.86]	/	/
Child gender					
	GEC	0.39	1.83 [−6.83–10.49]	2.11 [−3.93–8.15]	3.94 [−4.68–12.56]
	BRI - MI	0.39	1.92 [−6.25–10.09]	1.69 [−4.01–7.39]	3.61 [−4.52–11.74]
	BRIEF 8 subgroup-scales	0.37	1.41 [−5.17–7.99]	1.62 [−2.97–6.21]	3.02 [−3.52–9.57]
Child's age at survey date					
	GEC	0.47	2.33 [−6.46–11.11]	2.00 [−3.97–7.98]	4.33 [−4.52–3.17]
	BRI - MI	0.87	2.06 [−6.16–10.28]	1.67 [−4.07–7.40]	3.73 [−4.38–11.83]
	BRIEF 8 subgroup-scales	0.9	1.55 [−5.07–8.18]	1.58 [−3.04–6.20]	3.13 [−3.40 – 9.66]
Surgery under GA during childhood					
	GEC	0.32	5.26 [−5.06–15.57]	0.01 [−7.21–7.23]	5.25 [−4.86–15.35]
	BRI - MI	0.24	5.25 [−4.45–14.96]	0.59 [−6.19–7.38]	4.66 [−4.84–14.16]
	BRIEF 8 subgroup-scales	0.33	3.90 [−3.94–11.74]	0.06 [−5.43–5.54]	3.96 [−3.73–11.64]
Traumatic life events					
	GEC	0.1	3.36 [−7.06–13.78]	2.81 [−4.83–10.44]	0.57 [−9.41–10.52]
	BRI - MI	0.09	2.69 [−7.12–12.50]	2.02 [−5.17–9.21]	0.67 [−8.71–10.05]
	BRIEF 8 subgroup-scales	0.11	2.29 [−5.64 –10.22]	2.02 [−3.80–7.84]	0.271 [−7.32–7.86]
Weekly screen time exposure > 2 h					
	GEC	0.84	2.28 [−6.74–11.31]	0.86 [−6.72–8.43]	3.14 [−6.69–12.96]
	BRI - MI	0.8	2.39 [−6.11–10.89]	0.55 [−6.59–7.68]	2.94 [−6.32–12.19]
	BRIEF 8 subgroup-scales	0.87	1.70 [−5.16–8.56]	0.82 [−4.94–6.58]	2.52 [−4.95–9.99]

Data are presented as mean difference, 95% confidence interval [CI].
Abbreviations: BRI, behavioural regulation index; DBP, diastolic blood-pressure; GA, general anaesthesia; GEC, global executive composite; MI, metacognition index; SBP, systolic blood-pressure.
[a] Defined by three income scale: <2500, 2500–3999 and ≥4000.
[b] Variables only present in exposed groups to anaesthesia.

investigate the consequences of anaesthesia on this essential cognitive function, using, for instance Stroop task [31].

Finally, future works will need to conduct an earlier assessment of executive functions in children exposed to anaesthetic agents [22]. The use of functional imaging of the brain, detecting changes in the brain structure after exposure to anaesthesia [10], will also be needed in future works to investigate its effect on the developing brain.

5. Conclusion

In conclusion, the present study, which should be considered as a pilot study given the small number of children included, provides the first ambidirectional neurodevelopmental outcomes comparison between children born to mothers who underwent surgery under RA or GA during pregnancy with children whose mothers had no surgery during pregnancy. No difference in the BRIEF scores 6–10 years after exposure was observed between the three groups. These results pave the way for future investigations with finer granulometry to analyse executive functions, social behaviour, and daily life functioning.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article. The authors also confirm that the personal details of the patients and/or volunteers have been removed.

Ethics approval statement

ClinicalTrials.gov ID: NCT06052878.

Local ethics committee approval: Research Ethics Committee of Caen Normandy University Hospital (CLERS identification number: 3851).

Minor patient consent statement

Parental consent obtained, ACCPM consent form completed.

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CRediT authorship contribution statement

Vanja Courteille: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Côme Sauvage:** Formal analysis, Investigation, Writing - original draft. **Francis Veyckemans:** Methodology, Writing - review & editing, Supervision. **Shahad Albadri:** Writing - original draft. **Lorna Le Stanc:** Formal analysis. **Gilles Orliaguet:** Writing - review & editing. **Jean-Luc Hanouz:** Writing - review & editing. **Denis Vivien:** Writing - review & editing. **Nicolas Poirel:** Conceptualization, Methodology, Validation, Formal analysis, Writing - review & editing, Supervision. **Jean-Philippe Salaün:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial or personal relationships that could be viewed as influencing the work reported in this paper.

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