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ABSTRACT

Background: Pregnant women are ubiquitously exposed to organic solvents, such as glycol ethers. Several studies suggest potential developmental neurotoxicity following exposure to glycol ethers with a lack of clarity of possible brain mechanisms.

Objectives: We investigated the association between urinary levels of glycol ethers of women during early pregnancy and motor inhibition function of their 10- to 12-year-old children by behavioral assessment and brain imaging.

Methods: Exposure to glycol ethers was assessed by measuring six metabolites in urine (< 19 weeks of gestation) of 73 pregnant women of the PELAGIE mother-child cohort (France). Maternal urinary levels were classified as low, medium, or high. Children underwent functional magnetic resonance imaging (fMRI) examinations during which motor inhibition function was assessed with a Go/No-Go task. Analyses were performed using linear regression for task performance and generalized linear mixed-effect models for brain activation, FWER-corrected for multiple testing at the spatial cluster level. Confounders were considered by restriction and *a priori* adjustment.

Results: Higher maternal butoxyacetic acid (BAA) urinary concentrations were associated with poorer child performance ($\beta = -1.1$; 95% CI: -1.9, -0.2 for high *vs* low). There was also a trend for ethoxyacetic acid (EAA) towards poorer performance ($\beta = -0.3$; 95% CI: -0.7, 0.01). Considering inhibition demand, there were increased activity in occipital regions in association with moderate EAA (left cuneus) and moderate methoxyacetic acid (MAA) (right precuneus). When children succeeded to inhibit, high ethoxyethoxyacetic acid (EEAA) and moderate phenoxyacetic acid (PhAA) levels were associated with differential activity in frontal cortex, involved in inhibition network.

Discussion: Prenatal urinary levels of two glycol ether metabolites were associated with poorer Go/No-Go task performance. Differential activations were observed in the brain motor inhibition network in relation with successful inhibition, but not with cognitive demand. Nevertheless, there is no consistence between performance indicators and cerebral activity results. Other studies are highly necessary given the ubiquity of glycol ether exposure.

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1. Introduction

The use of organic solvents is widespread in industries, mainly to dissolve other substances without altering them or themselves. Although glycol ethers represent only 4% of solvent consumption in France, pregnant women are ubiquitously exposed to these chemicals according to French and European biomonitoring data (AFSSET, 2008; Fromme et al., 2013; Garlantézec et al., 2013; Béranger et al., 2017). For instance, metabolites of glycol ethers have been detected in at least 90% of urine samples of pregnant women in the PELAGIE cohort (2002–2006) (Béranger et al., 2017). Glycol ethers are oxygenated solvents which are highly miscible in oil and water. Their use is authorized in both occupational and domestic products and they are present in various products, such as paint, varnish, and ink, as well as cosmetics and agrochemicals. There are several possible routes of exposure (dermal, pulmonary or oral), depending on their formulation and context of use (AFSSET, 2008).

Organic solvents can pass the placental barrier and the developing blood-brain barrier (Grandjean and Landrigan, 2006). The developing brain is sensitive to its environment and solvent exposure during critical growth phases could result in neurobehavioral effects later in life (Julvez and Grandjean, 2009a; Rice and Barone, 2000). Several studies have investigated the association between prenatal exposure to solvents and the neurodevelopment of children. In an occupational setting, Eskenazi et al. did not find any association between prenatal solvent exposure and child behavior at 3.5 years of age, but exposed children (n = 92) started walking slightly earlier (Eskenazi et al., 1988). A Canadian study reported lower language scores and graphomotor abilities in exposed three- to seven-year-old children (n = 61), suggesting impaired cognitive and neuromotor function (Till et al., 2001a,b). Nevertheless, in 2004, a similar study of three- to nine-year-old children (n = 64) showed an association between prenatal solvent exposure and cognitive (processing speed, memory), motor (dexterity and visual-motor coordination), and behavioral (hyperactivity/impulsivity) scores (Laslo-Baker et al., 2004). In 2005, Till et al. reported reduced visual acuity in infants prenatally exposed to solvents (n = 59) (Till et al., 2001a,b; Till et al., 2005). In 2013, Pelé et al. investigated effects of occupational exposure to solvents during pregnancy and child behavior at two years of age in a population-based cohort (n = 1278) (Pelé et al., 2013). Women were asked to report the frequency (never, occasional, regular) of occupational contact with products known to contain solvents and classified as occasionally or regularly exposed if they reported occasional or regular exposure, respectively, to at least one product. They observed an association between occasional and regular solvent exposure at work and higher attention deficit/hyperactivity and aggression scores. These studies all investigated exposure to solvents in occupational settings for which levels of exposure are likely to be higher than that of the general population. In addition, these studies dealt with different solvent mixtures (mainly petroleum or halogenated solvents, except for that of Pelé et al. in which women were mainly exposed to oxygenated solvents). In 2017, Beranger et al. investigated the specific effects of glycol ethers on neurodevelopment in a population-based mother-child cohort. The authors reported that six-year-old children with the highest level of *in-utero* exposure to glycol ethers had lower verbal comprehension and copying scores (n = 204) (Béranger et al., 2017). These findings are original and supported by only a few animal studies on rats, suggesting that learning ability and neurochemistry are affected after prenatal exposure to low levels of 2-methoxyethanol or 2-ethoxyethanol (Nelson et al., 1984; Nelson and Brightwell, 1984).

Apart from Till et al. and Eskenazi et al., these studies all reported learning disabilities or behavioral alterations. These cognitive processes are supported by executive functions, in particular inhibitory control (Bari and Robbins, 2013; Diamond et al., 2007). Inhibitory control is critical for learning ability (Bari and Robbins, 2013) and difficulties in the ability to control impulses and inhibit a prepotent response are related to various conditions, such as attention deficit hyperactivity disorder (Willcutt et al., 2005) and poor academic performance (Diamond et al., 2007). In healthy subjects, the efficiency of inhibition during childhood is a strong predictor of future academic and professional outcomes (Moffitt et al., 2011).

In light of the adverse effects observed in children, we investigated potential effects on inhibitory control in a general population-based cohort and look further into possible neural underpinnings suggested by the literature. We hypothesize that investigating functional brain processes while children are engaged in specific cognitive tasks suspected to be affected by glycol ethers could provide finer tools.

Thus, we aimed to investigate the suspected neurotoxicity of glycol ethers after prenatal exposure on the inhibitory control of 10- to12-year-old children from a population-based mother-child cohort using motor inhibition task during functional magnetic resonance imaging (fMRI) and neuropsychological tests.

2. Material and methods

2.1. Population

The PELAGIE (*Perturbateurs endocriniens: Etude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance*) mother-child cohort included 3421 women at the beginning of pregnancy (before 19 weeks of gestation) from three districts of Brittany (France) between 2002 et 2006 (Garlantézec et al., 2009). They were recruited from the general population by obstetricians, gynecologists, and ultra-sonographers at early visits for prenatal care. At inclusion, they completed a self-administered questionnaire about family, social, and demographic characteristics, diet, and lifestyle.

A sub-cohort of 265 children between 10 and 12 years of age was randomly selected for the present study to include 100 children, since we expected a participation rate below 50%. We actually invited 251 families. Children had to 1. be live-born singleton, 2. be delivered after 35 weeks of amenorrhea, 3. present no major condition at birth (neonatal hospitalization, hypoglycemia, five-minute Apgar score < 7) (Cartier et al., 2016), 4. present no prenatal exposure to tobacco, alcohol, or medical treatment during childhood which could affect neurodevelopment (methylphenidate, psychotropic or antiepileptic drugs, *etc.*) and 5. have a maternal urine sample collected at inclusion (minimum–maximum, 4–17; median, 10 weeks; interquartile range, 8–11) available for chemical analysis. Among the 251 families, 124 (46.4%) refused to participate or were lost to follow-up, 26 (9.8%) were excluded due to technical (braces) or medical reasons (meningitis, head trauma). Thus, 101 (38.1%) children participated in neuropsychological and functional MRI examinations.

Testing took place at the Clinical Investigation Unit of the Rennes University Hospital from November 2014 to November 2016. They were performed on Wednesdays out the French school holidays periods or during the all days of the week except week-end during holidays. Proceedings were standardized as much as possible: all MRI sequences were carried out at the beginning of the testing for almost two hours (45 minute-training and 1 h in the MRI scanner).

Urine samples were not available for 28 women because their samples were used for other urinary assays, resulting in 73 mother-child pairs (72.3%) for our study population (see Supplementary material, Fig. S.I). Parents completed a questionnaire about the environmental and health conditions of their child.

All parent and child participants provided written informed consent and the appropriate ethics committees approved the study (Committee for the Protection of Persons- n°2013-A01420-45, French Consulting Committee for the Treatment of Information in Medical Research, n°09.485, and the French National Commission for the Confidentiality of Computerized Data, n°909347).

Table 1
Alkoxycarboxylic acids measured in urine samples, precursors, and sources (AFSSET, 2008).

Alkoxycarboxylic acid (metabolite)	Glycol ethers (parent compound)	Sources
MAA	EG(D)ME, DEG(D)ME, TEG(D)ME	Cleaning agents
EAA	EG(D)EE, DEG(D)EE, TEGEE	Biocides, cleaning agents, cosmetics, drugs, paints
EEAA	DEGEE, TEGEE	Biocides, cleaning agents, cosmetics, drugs, paints
BAA	EGBE, DEGBE, TEGBE	Biocides, cleaning agents, cosmetics, paints
PhAA	EGPhE	Biocides, cosmetics, drugs
2-MPA	1PG2ME (β isomer)	Biocides, cleaning agents, paints

Abbreviations: BAA, 2-butoxyacetic acid; DEGBE, 2-(2-butoxyethoxy)ethanol; DEGDEE, 2-(2-Ethoxyethoxy)-1-ethoxyethane; DEGDME, 2-(2-Methoxyethoxy)-1-methoxyethane; DEGEE, 2-(2-ethoxyethoxy)ethanol; DEGME, 2-(2-methoxyethoxy)ethanol; EAA, ethoxyacetic acid; EEAA, ethoxyethoxyacetic acid; EGBE, 2-butoxyethanol; EGDEE, 1,2-Diethoxyethane; EGDME, 1,2-Diethoxymethane; EGEE, 2-ethoxyethanol; EGME, 2-methoxyethanol; EGPhE, 2-phenoxyethanol; MAA, methoxyacetic acid; 2-MPA, 2-methoxyproprionic acid; 1PG2ME, methoxy-propanol; PhAA, phenoxyacetic acid; TEGBE, 2-(2-(2-Butoxyethoxy)ethoxy)ethanol; TEGDME, 1,2-bis(methoxyethoxy)ethane; TEGEE, 2-(2-(2-ethoxyethoxy)ethoxy)ethanol; TEGME, 2-(2-(2-methoxyethoxy) ethoxy)ethanol.

2.2. Solvent exposure assessment

At inclusion, pregnant women returned a urine sample (first morning void) in a 10-mL test tube (95 × 16-mm polypropylene, with wing plug). Six alkoxycarboxylic acids (glycol ether metabolites) of the most commonly used glycol ethers in France at the time of inclusion (Table 1) were analyzed: methoxyacetic acid (MAA), ethoxyacetic acid (EAA), ethoxyethoxyacetic acid (EEAA), 2-butoxyacetic acid (BAA), phenoxyacetic acid (PhAA), and 2-methoxypropionic acid (2-MPA). Analyses were performed in 2013 (n = 54) and 2017 (n = 19) by gas chromatography–mass spectrometry (GC–MS) at the LABOCEA (Laboratoire public Conseil, Expertise et Analyse en Bretagne) with a limit of detection (LD) of 3 µg/L. Details of the chemical analysis procedures are described elsewhere (Béranger et al., 2017). We found no mean differences between the two series of measurements (see Supplementary material, Fig. S.II and Table S.1). Glycol ether metabolite levels were categorized into three groups. For clarity, we refer hereafter to low, moderate, or high levels. Values below the LD were imputed from a lognormal distribution (Jin et al., 2011).

2.3. Inhibition function

2.3.1. Task

Children completed a 10-minute task in the MR scanner. First, short practices were performed in front of a computer then in a mock MR scanner to provide the instructions and accustom the child to the scanner environment.

Motor inhibition function of the children was evaluated with a visual Go/No-Go task. This event-related task, adapted from Mostofsky et al. (2003), minimizes cognitive demands other than motor execution and response inhibition and can be easily performed in children (Réveillon et al., 2013; Suskauer et al., 2008). Green and red smileys were successively presented on a screen. Children were asked to press a button as quickly as possible when seeing a green smiley but had to refrain otherwise. The ratio of No-go cues (red smileys) over Go cues (green smileys) was 1:4, to elicit a dominant response. The task was implemented using *E*-Prime v.2.0.8 Professional (Psychology Software Tools, Pittsburgh, PA, USA) and presented using the Nordic Neurolab Solution (Nordic Neurolab, Bergen, Norway).

The task was split into two runs of 5 min each. Each run consisted of 150 trials and four 10-second rest periods. A trial was the consecutive presentation of a smiley (duration of 200 ms) and a cross fixation point (duration of 1300 ms). A response was allowed until the next trial began, giving a constant inter-stimulus interval (ISI) of 1500 ms. Smileys appeared in a pseudo-random order: trials at the beginning of runs or following resting periods had to be Go cues. Go cues had to occur at least three times in a row and No-Go cues had to occur individually or at most two times in a row.

2.3.2. Performance

Child performance for the Go/No-Go task was evaluated by response latency (RLs, average reaction time for the correct answering of Go cues), commission rate (incorrect answers for the No-Go cues), and performance score (PS). Responses before 200 ms were considered to be anticipatory and were excluded from the indicator calculation (on average, < 1% of all cues). The accuracy of motor inhibition was assessed by the sensitivity index, *d′*, which subtracts the standardized (z score) commission rate from the standardized hit rate (correct answers for Go cues). The RLs and commission errors inversely correlated with each other (Spearman rho coefficient = −0.32, p = 0.01). Thus, we built a PS by subtracting the RLs from the accuracy of motor inhibition (*d′*), following standardization (Collignon et al., 2010).

$$d' = Z(hit\ rate) - Z(commission\ rate)$$
$$PS = Z(d') - Z(RLs)$$
$$(Z: standardized\ value)$$

Thus, children with the highest PS scores were considered to efficiently perform the task (fast with a high hit rate, with few commissions), whereas children with the lowest PS scores were slow and found it difficult to inhibit their response to No-Go cues. Performance indicators could not be recorded for one child (n = 72), due to technical issues with the recording.

2.3.3. Cerebral hemodynamic response related to the task

Neural activity related to motor inhibition was evaluated indirectly by blood oxygen-level dependent (BOLD) imaging.

Scanning was completed on a 3 T MR Scanner (Magnetom Verio, VB17, Siemens, Erlangen, Germany) using a 32-channel receiver head coil. Functional images were acquired using gradient echo-planar imaging (EPI) with repetition/echo times of 2500/30 ms, a 90° flip angle, and 110 volumes per run. Each volume was composed of 34 axially oriented 4 mm-interleaved slices, covering the whole brain. Scans with a voxel size of 2*2*4 mm^3 were based on a 110*110 acquisition matrix (220 × 220 mm^2 field of view (FOV)). Operators assessed image quality during the acquisition, two children who moved repeated the sequence. Learning effects are not expected for this task and we did not observe any improvement in performance during the two sessions.

High-resolution 3D anatomical images were obtained using T1-weighted MPRAGE at 1 mm^3 resolution for anatomical referencing (repetition/inversion/echo times: 1900/900/2.26 ms, 9° flip angle).

Image pre-processing is described in Supplementary material. Head movements were evaluated by six parameters calculated during the realignment step. Two children had head motion > 2 mm (in-plane size of an acquisition voxel) and their images were excluded from further analysis (n = 71).

The hemodynamic response was modeled from trials (Go cue and No-Go cue), implicit baseline (resting periods enabling recovery of the hemodynamic response and the time between trials), and motion

regressors using a canonical hemodynamic response function (HRF) and its temporal derivative. This HRF is the subtraction of two gamma functions. The first gamma function models the peak of intensity with a latency of 6 s and the second the undershoot during the recovery period with a latency of 16 s. The use of a temporal derivative allows for variations in peak latency, while providing comprehensive models for the response. Scanner drift was modeled with a discrete cosine transform (DCT) set (128-second cut off) and temporal autocorrelation was accounted for using an autoregressive AR(1) model over the whole brain. First, we modeled Go cue and No-Go cue, independently of the subject's response. Secondly, we modeled successful No-Go, failed No-Go and Go conditions. Maps were extracted for each condition and for each subject by voxel-wise multiple regressions estimated by the restricted maximum likelihood (ReML) method and then contrasted. Because we were investigating the ability to stop a planned response when it is no longer pertinent, we built two types of individual contrast images. First, we extracted "No-Go vs Go" activations, representing activation amplitudes that were higher for inhibition than motor tasks, when children perceived the inhibition demand. Secondly, we built contrast images for "Successful No-Go vs successful Go", when children were able to inhibit and stop their answers. Results for failed inhibition contrast "Failed No-Go vs successful Go" were reported for information (see Supplementary material, Table S.6).

There were no differences between the two runs for contrast estimate (at the uncorrected cluster level $p < 0.001$) or any performance indicators (at $p < 0.05$), allowing concatenation of the two runs.

2.4. Analysis strategy and statistical analyses

Multivariable linear regressions were built on performance indicators (log-transformed-reaction time, commission rate, and PS) to analyze the association with each categorical level of glycol ether metabolite. We used restricted cubic splines with log-transformed metabolite concentrations to assess a possible dose-response relation. When the assumption of linearity was assessed, we plotted urinary metabolite levels as continuous and reported their p-values as a trend test.

The hemodynamic response during the motor inhibition task was modeled by mixed effect generalized linear regressions to investigate the interaction between the category of prenatal exposure to glycol ethers and the effects of the motor inhibition task on cerebral activity. We did not have any *a priori* hypotheses on brain regions that could be differentially activated during the inhibition task across exposure levels, so we performed whole-brain analyses. Some regions are known to be part of the motor inhibition network (frontal and anterior cingular cortices and supplementary motor area (SMA)) regions (Mostofsky et al., 2003; Suskauer et al., 2008). Thus, we highlighted our results for these regions. Statistical significance was assessed for cluster-wise significance, defined by random field theory (FWER corrected $p = 0.05$) to account for 3D spatial autocorrelation, using an uncorrected one-sided cluster-defining threshold of $p = 0.01$ (Nichols and Hayasaka, 2003).

Maternal educational level ($<$ *vs* ≥ 3 years of post-secondary school attendance) and breastfeeding of the child ($\leq$ *vs* > 3 months) were included *a priori* in all regression models as potential confounders. A missing covariate value (maternal educational level, $n = 1$) was imputed by the mode of the distribution.

R software v.3.4.1 (https://www.R-project.org/) and SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) were used for data analysis.

3. Results

3.1. Population characteristics

Participant characteristics are presented in Table 2. Women included in the study had a median age of 30.4 years at inclusion. This population was highly educated (45.8% attended at least three years of post-secondary school) and reported few medical problems during pregnancy (2.7% reported high blood pressure, no diabetes). The children's median birth weight was 3430 g, 43.8% were breastfed for more than three months, and 38.4% were boys. Children attending follow-up were mainly right-handed (87.7%), attended mainly elementary school (74.0%) and had a median age of 10.8 years. We did not observe any differences for these characteristics between the study population and non-participants (see Supplementary material, Table S.2).

Table 2
Characteristics of the population (n = 73).

Maternal and child characteristics		N (%)	Median (Q1;Q3)
Maternal characteristics (at inclusion)			
Age (in years)			30.4 (28.4;33.5)
Body Mass Index before pregnancy	($< 18.5\,kg/m^2$)	9 (12.3)	
	($18.5–25\,kg/m^2$)	51 (69.9)	
	($\geq 25\,kg/m^2$)	13 (17.8)	
Post-secondary school	(≤ 2 years)	39 (54.2)	
	(≥ 3 years)	33 (45.8)	
	Unknown	1	
High blood pressure (gestational or not; yes)		2 (2.7)	
Diabetes (gestational or not; yes)		0 (0)	
Subject characteristics			
Sex (boys)		28 (38.4)	
Gestational age (in weeks of amenorrhea)			40 (39;40)
Birth weight (in g)			3430 (3180;3800)
Breastfeeding (> 3 months)		32 (43.8)	
Parity	(single child)	10 (13.7)	
	(1 sibling)	35 (47.95)	
	(≥ 2 siblings)	28 (38.36)	
Age (in years)			10.8 (10.6;11)
Educational level	(Elementary school)	54 (74.0)	
	(Junior high school)	19 (27.0)	
Lateralization (right-hander)		64 (87.7)	

3.2. Urinary glycol ether metabolite levels

Each glycol ether metabolite was detected in the urine of at least 89% of the women, with median values from 15 (for EAA) to 275 µg/L (for PhAA) (Table 3). There were slight correlations between MAA and 2-MPA concentrations (Spearman rho coefficient = 0.32, p = 0.02) and PhAA and EEAA (rho = 0.17, p = 0.04) (see Supplementary material, Fig. S.II). EEAA, EAA, and 2-MPA levels also correlated with each other (EAA-EEAA, rho = 0.36; EAA-2-MPA, rho = 0.31; EEAA-2-MPA,

Table 3
Detection rates and median concentrations of glycol ether metabolites in maternal urine (n = 73). Abbreviations: BAA, 2-butoxyacetic acid; EAA, ethoxyacetic acid; EEAA, ethoxyethoxyacetic acid; MAA, methoxyacetic acid; 2-MPA, 2-methoxyproprionic acid; PhAA, phenoxyacetic acid.

Glycol ether metabolites	N (%) > LD	Median (µg/L) (1st tercile;2nd tercile)[a]	Max (µg/L)
MAA	71 (97.3%)	63 (52;83)	220
EAA	66 (90.4%)	15 (10;22)	169
EEAA	65 (89%)	31 (20;87)	7932
BAA	70 (95.9%)	30 (20;47)	558
PhAA	72 (98.6%)	275 (146;498)	43261
2-MPA	71 (97.3%)	20 (13;24)	192

LD = 3 µg/L.
[a] Before imputation.

Table 4
Go/No-Go task performance indicators (n = 72).

Indicators	Median (Q1;Q3)
Hit rate (in %)	98.4 (96.4;99.6)
Commission rate (in %)	23.1 (14.4;35.2)
Average reaction time (in ms)	393 (362;429)
Performance score	0.2 (−0.4;0.9)

rho = 0.33) but the correlations were not statistically significant (p = 0.50, p = 0.64, and p = 0.87, respectively).

3.3. Performance indicators and brain activation during the task

Children performed the Go/No-Go task with a median hit rate of 98.4%, 23.1% incorrect answers at No-Go cues, and response latency of 393 ms. The PS ranged from −9.9 to 2.1, with a median of 0.2 (Table 4).

For the "No-go *vs* Go" contrast in brain, children showed activation in regions known to be involved in the motor inhibition network: the anterior cingulate/SMA and the inferior and middle frontal regions of both hemispheres. This contrast was also associated with activated clusters in the right middle temporal region and brain structures of both hemispheres (parietal region, posterior lobe of cerebellum and caudate nucleus) (see Supplementary material, Table S.3). Similar activations were found with contrasts that took into account children's responses, *i.e.* "Successful No-Go vs successful Go" or "Failed No-Go vs successful Go" (see Supplementary material, Tables S.4 and S.5).

3.4. Prenatal urinary glycol ether metabolite levels and motor inhibition

We observed no association between commission rate and urinary levels of glycol ether metabolites (Fig. I), although there was a statistical trend for a lower commission rate for children whose mothers had high PhAA urinary levels (decrease of 6.4%, p = 0.09). Children whose mothers had moderate urinary EEAA levels had also a 0.08% faster reaction time than those whose mothers had low levels, but there was no statistically significant increase of the PS (p = 0.10). There was a statistical trend for a lower PS (decrease of 0.3 units, p = 0.06) with increasing concentrations of EAA in maternal urine. The highest levels of BAA were associated with a longer reaction time (increase of 0.08%, p = 0.04) and lower PS (decrease of 1.1 units, p = 0.02). Our results showed a linear dose-response relation between the children's PS and maternal urinary levels of BAA, when BAA concentrations were used as a continuous variable.

There were no statistically significant differences of activation for regions involved in the motor inhibition network (frontal and anterior cingular cortices and SMA) in association with motor inhibition demand for any urinary levels of glycol ether metabolites (Table 5). There was increased activation in occipital areas associated with moderate urinary levels of MAA and EAA. Children whose mothers had moderate levels of MAA exhibited higher activation in the right precuneus region and children whose mothers had moderate levels of EAA exhibited higher activation in the left cuneus region (Table 5 and Fig. II).

We found differential activities in opposite directions in brain regions related to inhibition network (frontal cortex) when children succeeded to inhibit in association with urinary levels of EEAA and PhAA but not with other glycol ether metabolites. There were decreased activities in left temporal (β = −0.96, 95% CI = [−1.23; −0.68]) and medial frontal regions (β = −1.1, 95% CI = [−1.47; −0.72]) associated with high levels of EEAA. We found increased activity in right inferior frontal region (β = 2.0, 95% CI = [1.2; 2.9]) in association with moderate levels of PhAA (Table 6 and Fig. III). These two findings were not observed when children failed to inhibit (see Supplementary material, Table S.6). Increased activations observed with motor inhibition demand in right precuneus and left cuneus (with MAA and EAA levels, respectively) were still found when distinguishing successful and failed inhibition but did not remain statistically significant after correction for multiple testing (Table 6 and Supplementary material, Table S.6).

4. Discussion

Our study shows differential performance during motor inhibition in children associated with their mothers' urinary glycol ether metabolite levels measured before 19 weeks of gestation. Higher maternal BAA urinary levels were associated with poorer performance of the child and increased reaction time. There was a linear trend of poorer performance in association with increasing levels of EAA. Moderate levels of EEAA in maternal urine were associated with a decreased reaction time, but no statistically significant difference in the PS score. There was no association between maternal urinary concentrations of metabolites and neural activity related to inhibition demand in regions involved in the motor inhibition network. We reported associations between increased child brain activation in the left cuneus and moderate levels of EAA and increased activity in the right precuneus and moderate MAA concentrations in maternal urine. We observed associations between decreased child brain activation related to successful inhibition in frontal regions, part of the inhibition network, and high levels of EEAA and between increased activity and moderate PhAA concentrations in maternal urine (Table 7).

No previous studies have used fMRI to investigate potential associations between prenatal exposure to solvents and motor inhibition function, but existing studies have evaluated associations between heavy *in-utero* exposure to a well-known solvent, namely alcohol, and brain activation during a motor inhibition task. The authors reported similar performance between exposed children and controls (n = 13/9 (Fryer et al., 2007), n = 8/17 (Kodali et al., 2017), n = 20/15 (O'Brien et al., 2013) and n = 21/21 (Ware et al., 2015)) aged 8 to 18 years, but observed differential brain activity in regions involved in motor inhibition (prefrontal, frontal, and cingular cortices). They also reported differential neural activity in regions involved in attention (parietal cortex, precuneus, cuneus, and caudate nucleus regions). Here, we used fMRI to investigate brain functioning during an inhibition task in association with glycol ether exposure in the general population. This technique provides excellent spatial resolution, giving the ability to investigate potential effects of exposure by fine brain regions of a few cubic millimeters. In addition, our study was based on a mother-child cohort (PELAGIE study), which gives the opportunity to measure glycol ether exposure before 19 weeks of gestation. The beginning of gestation is a key period for neurodevelopment and its disruption may result in short and long-term effects, such as behavioral and skill impairment (Julvez and Grandjean, 2009b; Rice and Barone, 2000). We used urinary biomarkers to estimate glycol ether exposure. Because glycol ethers are used in both occupational and household products, biomarkers enable the assessment of all sources of exposure, but without knowledge of the main route. We were also able to consider lifestyle and socioeconomic factors by restriction or adjustment. In particular, children whose mothers reported alcohol or tobacco consumption during pregnancy were not included in the study to eliminate two established risk factors of poorer neurodevelopment (Julvez and Grandjean, 2009b).

In their review, Bari and Robbins distinguished two major types of inhibitory control, cognitive and behavioral (Bari and Robbins, 2013). Here, the Go/No-Go task involves behavioral response inhibition with a motor component. This function appears in childhood and continues to mature into adolescence (Booth et al., 2003; Luna and Sweeney, 2006). All children understood and performed the Go/No-Go task well. Thus, response inhibition appeared to be well-established in our population of 10- to 12-year-old children. Performances in our study are similar to that reported during a similar Go/No-Go task with 8- to 13-year-old

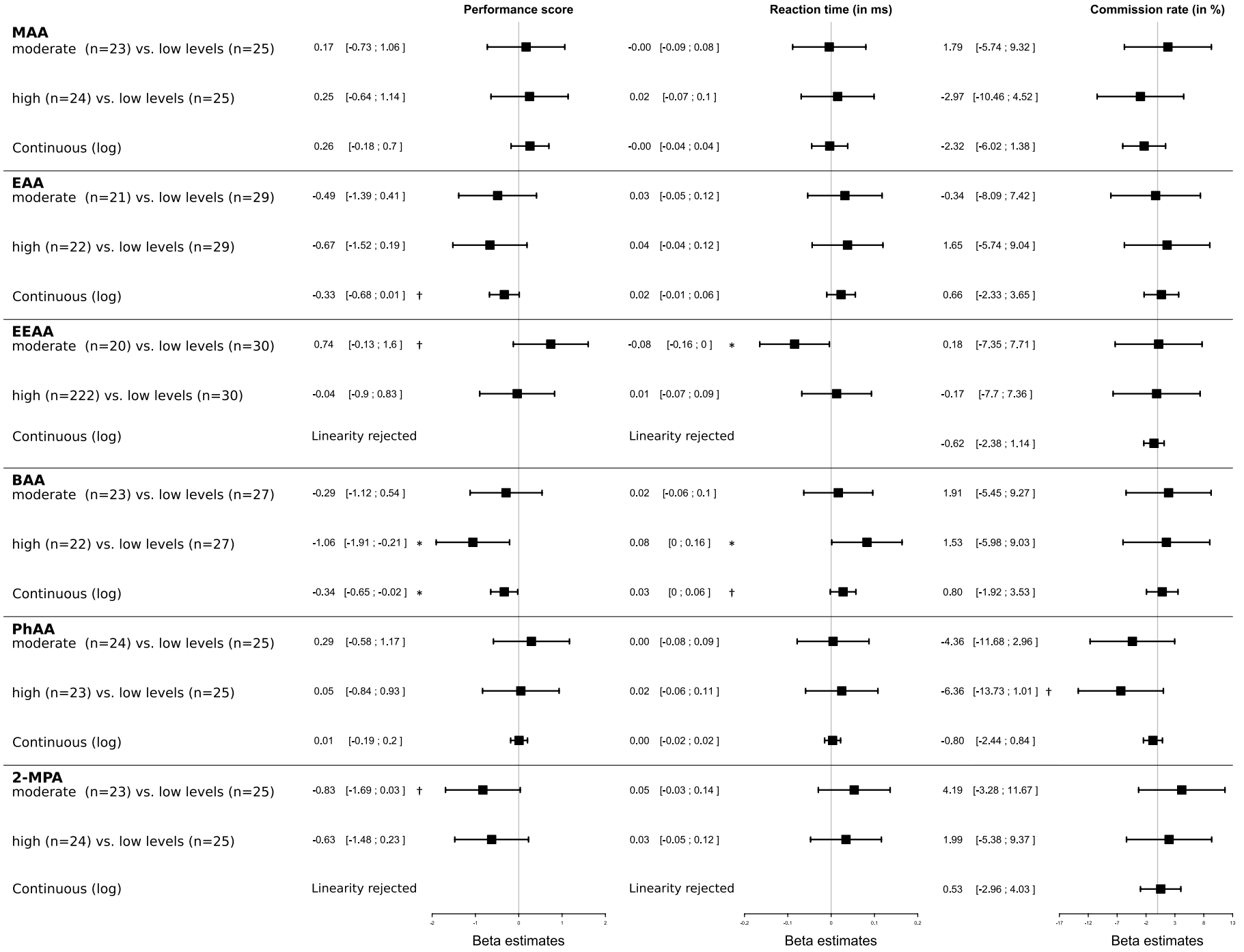

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Fig. I. Associations between glycol ether metabolite levels in maternal urine during pregnancy and performance indicators for the Go/No-Go task of their 10- to 12-year-old children (PELAGIE cohort, 2002–2017) (n = 72).
Abbreviations: BAA, 2-butoxyacetic acid; EAA, ethoxyacetic acid; EEAA, ethoxyethoxyacetic acid; MAA, methoxyacetic acid; 2-MPA, 2-methoxyproprionic acid; PhAA, phenoxyacetic acid; ref.: reference.
β (95% IC): estimated coefficient [95% confidence interval].
Adjusted for maternal educational level (< *vs* ≥3 years of post-secondary school attendance) and child's breastfeeding (≤ *vs* > 3 months).
*p ≤ 0.05, †: 0.05 < p ≤ 0.10.
a: Log-scale.
b: p-Value from linear trend-test.

children (average latency of 393 ms *vs* 407 ms, 98% *vs* 97.2% hit rate, and 23% *vs* 22% for commission errors) (Suskauer et al., 2008). Three main regions (the anterior cingulate, SMA, and inferior frontal gyri of both hemispheres) are involved in motor inhibition (Allman et al., 2006; Aron, 2007; Mostofsky et al., 2003). As expected, we observed cerebral activation in this network during inhibitory control demand ("No-Go *vs* Go" contrast). We also observed additional activation in other brain structures of both hemispheres (parietal, including the right cuneus and precuneus regions, temporal gyri, caudate nucleus, and posterior lobe of the cerebellum), also in 8- to 13-year-old children (Suskauer et al., 2008). These regions do not appear to be part of the motor inhibition network and may be related to attention and decision making processes (Behrmann et al., 2004; Grahn et al., 2008; Stoodley and Schmahmann, 2009).

Table 5
Associations between glycol ether metabolite levels in maternal urine during pregnancy and brain activation intensity during the Go/No-Go task of their 10- to 12-year-old children (PELAGIE cohort, 2002–2017) (n = 71).

Metabolite concentrations (in µg/L)	N	Frontal or cingular cortices		Brain regions outside frontal and cingular cortices		
		β (95% CI)	ext.	β (95% CI)	Region	ext.
MAA						
Low: < 52.4	26	Ref.		Ref.		
Moderate: [52.4–82.9]	23			1.3 (0.6, 1.9)*	R. precuneus	480
High: ≥82.9	22			0.6 (−0.01; 1.3)[a]	R. precuneus	480
EAA						
Low: < 9.7	29	Ref.		Ref.		
Moderate: [9.7–22]	22			1.7 (1.0, 2.3)*	L. cuneus	898
High: ≥22	20			0.06 (0; 1.1)[a]	L. cuneus	898
EEAA						
Low: < 19.8	30	Ref.		Ref.		
Moderate: [19.8–86.5]	21					
High: ≥86.5	20					
BAA						
Low: < 19.7	27	Ref.		Ref.		
Moderate: [19.7–47.1]	23					
High: ≥47.1	21					
PhAA						
Low: < 146.4	25	Ref.		Ref.		
Moderate: [146.4–498.1]	24					
High: ≥498.1	22					
2-MPA						
Low: < 13.2	26	Ref.		Ref.		
Moderate: [13.2–24.1]	21					
High: ≥24.1	24					

Abbreviations: BAA, 2-butoxyacetic acid; EAA, ethoxyacetic acid; EEAA, ethoxyethoxyacetic acid; ext.: extent (in voxels); MAA, methoxyacetic acid; 2-MPA, 2-methoxyproprionic acid; PhAA, phenoxyacetic acid; ref.: reference.
β (95% IC): estimated coefficient [95% confidence interval]. Empty cell: no statistically significant difference reported in this region.
Adjusted for maternal educational level (< *vs* ≥3 years of post-secondary school attendance) and child's breastfeeding (≤ *vs* > 3 months).
* FWER correction at cluster level, p < 0.05.
[a] Coefficient and confidence interval estimated for the statistically significant clusters determined for moderate levels of exposure.

One of our performance indicators to measure impulsivity was the proportion of commission errors, for which we observed no significant association between glycol ether exposures. We cannot eliminate the possibility that all children of our population, even those with problems concentrating, were able to focus for 10 min and that the task was too short to discriminate between the children. We observed that children making few commission errors tended to be slower. Thus, children with inhibition problems may also develop adaptive strategies, such as slowing their response speed.

We observed an association between increased maternal urinary levels of BAA and poorer PS, as well as increased reaction time, whereas the commission rate remained unchanged. Concentrations of BAA in maternal urine were not associated with differential neural activity during the task. If there is an association between BAA urinary levels and brain functioning, it is possible that our methodological choices (MRI sequence, sample size) did not allow to measure it. Urinary metabolite levels of BAA are weakly correlated with the concentration of other metabolites, although its parent compounds are used in the same products as the other glycol ethers measured in this study. BAA is the main metabolite of ethylene glycol butyl monobutyl ether (EGBE) and diethylene glycol butyl monobutyl ether (DEGBE), two glycol ethers widely used in Europe (2nd and 4th in commercialized volumes of glycol ethers during the study period). They are found in 20% of industrial paints and varnishes (DEGBE), 10% of biocides, and in cleaning products and cosmetic products (up to 0.2% in hair dyes). EGBE is well-known for its hemolytic properties, but not for neurotoxicity (AFSSET, 2008; INRS, 2011).

We observed weaker associations between maternal urinary levels of EAA or EEAA and motor inhibition indicators. There was a slight decrease in reaction time with moderate EEAA levels and decreased cerebral activities in inhibition network (in frontal cortex) when children succeeded to inhibit their answer with high levels of EEAA. There was a trend towards poorer performance with higher levels of EAA. There were no statistically significant associations between BOLD responses in brain regions involved in the motor inhibition network and urinary levels of EAA, but rather an association between urinary levels of these glycol ethers and an increased BOLD response in the left cuneus, a region involved in attention and reported in similar Go/No-Go studies (Cui et al., 2009; Suskauer et al., 2008). The cuneus is located in the occipital part of the brain and is involved in visual preprocessing (Rosen et al., 2018). The difference of brain activity in this region may be consistent with visual alterations reported by Till et al. in association with prenatal occupational exposure to solvents. EAA is a metabolite of EGEE, EGDEE, DEGEE, DEGDEE, and TEGEE. EAA levels are correlated with those of EEAA, which is also a metabolite of DEGEE and TEGEE. At the time of the study, these glycol ethers were found in paint, ink, cleaning products, and biocides (AFSSET, 2008; INRS, 2011). Some ethoxyethanol (EGEE) derivatives are recognized for their reproductive and developmental toxicity, but there are few studies on their neurotoxicity.

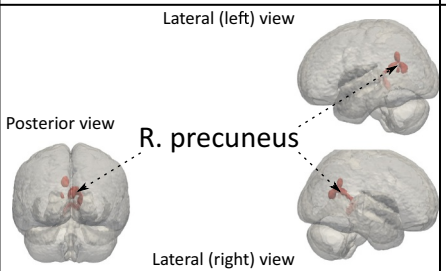
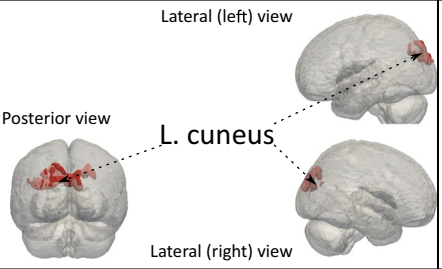
	1st tercile	2nd tercile (vs 1st)	3rd tercile (vs 1st)
MAA	Reference		*No statistically significant difference*
EAA	Reference		*No statistically significant difference*
EEAA	Reference	*No statistically significant difference*	*No statistically significant difference*
BAA	Reference	*No statistically significant difference*	*No statistically significant difference*
PhAA	Reference	*No statistically significant difference*	*No statistically significant difference*
2-MPA	Reference	*No statistically significant difference*	*No statistically significant difference*

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Fig. II. Summary of associations (estimated coefficients) between urinary glycol ether metabolite levels during pregnancy and brain activation during motor inhibition demand (n = 71)*.
Abbreviations: BAA, 2-butoxyacetic acid; EAA, ethoxyacetic acid; EEAA, ethoxyethoxyacetic acid; L.: left; MAA, methoxyacetic acid; 2-MPA, 2-methoxyproprionic acid; PhAA, phenoxyacetic acid; R.: right.
*FWER corrected-p < 0.05 with a one-sided uncorrected-p = 0.01 threshold.

There were an increased BOLD response in regions involved in shifting attention (precuneus) in association with moderate urinary levels of MAA (Cavanna and Trimble, 2006; Suskauer et al., 2008). MAA comes from the metabolism of EGME, EGDME, DEGME, DEGDME, TEGME, and TEGDME. Products containing > 0.5% EGME were prohibited in France before establishment of the PELAGIE cohort. EGDME, DEGDME, and TEGDME were banned in 2005 but DEGME and TEGME are still authorized and used in cleaning agents (AFSSET, 2008; INRS, 2011). Some methoxyethanol (EGME) derivatives are recognized for their reproductive and developmental toxicity, but there are few studies on their neurotoxicity.

We did not report any association between performance and urinary levels of PhAA, only a slight decrease of commission errors with increasing metabolite levels. There was also an increased activity in relation with moderate level of PhAA in inhibition network (frontal cortex) when children succeeded to inhibit their answer. EGPhE (parent compound of PhAA) is used as preservatives up to 1% in half cosmetic products in France, and some biocides and pharmaceutical products (AFSSET, 2008).

The possibly causal interpretation of our results is very limited by the lack of studies on the developmental neurotoxicity of glycol ethers, even mechanistic or *in-vivo* studies. In a previous epidemiological study from the PELAGIE cohort, Béranger et al. (2017) reported associations between maternal urinary concentrations of PhAA and verbal comprehension scores and EAA levels and visuospatial performance (n = 204), brain functions which could be controlled by cognitive inhibition. Here, we only observe an association between moderate PhAA metabolite levels and cerebral activity in frontal cortex and decreased commission rates with increasing levels of urinary biomarker. Outside inhibition network we observed increased activity in the left cuneus and a trend towards poorer performance with EAA metabolite concentrations. In contrast, we found associations between BAA levels in maternal urine and poorer inhibition performance and differential brain activity in relation with EEAA levels, although these glycol ether metabolites do not appear to be associated with poorer verbal comprehension or visuospatial abilities at six years of age (Béranger et al., 2017). An animal study has suggested behavioral alterations (learning and neuromuscular abilities) and variations of the cerebral concentrations of neurotransmitters (acetylcholine, norepinephrine, dopamine, and serotonin) in rats prenatally exposed to EAA and MAA through their parent

Table 6
Associations between glycol ether metabolite levels in maternal urines during pregnancy and activation intensity related to successful inhibition during the Go/No-Go task of their 10–12 years old children (PELAGIE cohort. 2002–2017) (FWER correction at cluster level. p < 0.05) (n = 70).

Metabolite concentrations (in µg/L)	N	Frontal or cingular cortices		Brain regions outside frontal and cingular cortices		
		β (95% CI)	ext.	β (95% CI)	Region	ext.
MAA						
Low: < 52.4	25	Ref.		Ref.		
Moderate: [52.4–82.9]	23			1.0 (0.3; 1.7)[a]	R. precuneus	480
High: ≥82.9	22					
EAA						
Low: < 9.7	29	Ref.		Ref.		
Moderate: [9.7–22]	21			0.7 (0.2; 1.4)[a]	L. cuneus	898
High: ≥22	20					
EEAA						
Low: < 19.8	30	Ref.		Ref.		
Moderate: [19.8–86.5]	20					
High: ≥86.5	20	−1.1 (−1.47; −0.72)	510	−0.96 (−1.23; −0.68)	Left temporal	499
BAA						
Low: < 19.7	27	Ref.		Ref.		
Moderate: [19.7–47.1]	23					
High: ≥47.1	20					
PhAA						
Low: < 146.4	25	Ref.		Ref.		
Moderate: [146.4–498.1]	24	2.0 (1.2; 2.9)	524			
High: ≥498.1	21					
2-MPA						
Low: < 13.2	25	Ref.		Ref.		
Moderate: [13.2–24.1]	21					
High: ≥24.1	24					

Adjusted for maternal educational level (< *vs* ≥3 years of post-secondary school attendance) and child's breastfeeding (≤ *vs* > 3 months). β [95% IC]: estimated coefficient [95% confidence interval]. ext.: cluster extent (in voxels). ref.: reference. Empty cell: no statistically significant difference reported in this region.
BAA. 2-butoxyacetic acid; EAA. ethoxyacetic acid; EEAA. ethoxyethoxyacetic acid; MAA. methoxyacetic acid; 2-MPA. 2-methoxyproprionic acid; PhAA. phenoxyacetic acid.
[a] Coefficient and confidence interval estimated for the statistically significant clusters determined for moderate levels of exposure in Table 5.

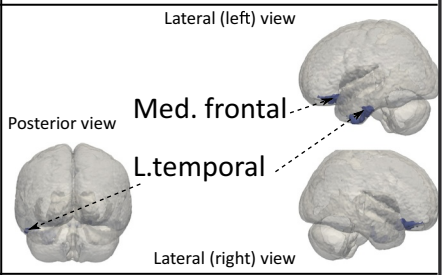
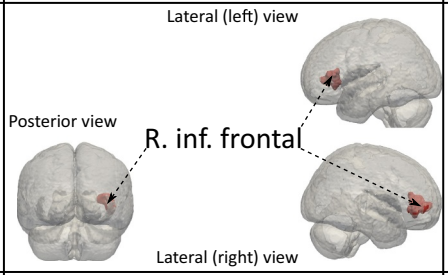
	1st tercile	2nd tercile (vs 1st)	3rd tercile (vs 1st)
MAA	Reference	*No statistically significant difference*	*No statistically significant difference*
EAA	Reference	*No statistically significant difference*	*No statistically significant difference*
EEAA	Reference	*No statistically significant difference*	
BAA	Reference	*No statistically significant difference*	*No statistically significant difference*
PhAA	Reference		*No statistically significant difference*
2-MPA	Reference	*No statistically significant difference*	*No statistically significant difference*

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Fig. III. Summary of associations (estimated coefficients) between urinary glycol ether metabolite levels during pregnancy and brain activation during successful inhibition (n = 70)*.
Abbreviations: BAA, 2-butoxyacetic acid; EAA, ethoxyacetic acid; EEAA, ethoxyethoxyacetic acid; L.: left; MAA, methoxyacetic acid; 2-MPA, 2-methoxyproprionic acid; PhAA, phenoxyacetic acid; R.: right.
*FWER corrected-p < 0.05 with a one-sided uncorrected-p = 0.01 threshold.

Table 7
Summary of the statistically significant associations between glycol ether metabolite levels in maternal urines during pregnancy and motor inhibition of their 10–12 years old children (PELAGIE cohort. 2002–2017).

Metabolite concentrations (in µg/L)	Performances	Brain activity	
		Inhibition network	Others brain regions
MAA			
Low: < 52.4	Ref.	Ref.	
Moderate: [52.4–82.9]			↗ R precuneus
High: ≥82.9			
EAA			
Low: < 9.7	Ref.	Ref.	
Moderate: [9.7–22]			↗ L cuneus
High: ≥22			
EEAA			
Low: < 19.8	Ref.	Ref.	
Moderate: [19.8–86.5]	↘ reaction time		
High: ≥86.5		↘ med frontal	↘ L temporal
BAA			
Low: < 19.7	Ref.	Ref.	
Moderate: [19.7–47.1]	↗ reaction time, ↘ PS score		
High: ≥47.1	↘ PS score		
PhAA			
Low: < 146.4	Ref.	Ref.	
Moderate: [146.4–498.1]		↗ R inferior frontal	
High: ≥498.1			
2-MPA			
Low: < 13.2	Ref.	Ref.	
Moderate: [13.2–24.1]			
High: ≥24.1			

(respectively EGEE and EGME), at doses that showed no effect on their mothers and equivalent to the US permissible limit (for EGME) or half the limit (for EGEE) (Nelson et al., 1984; Nelson and Brightwell, 1984). There are no existing studies on the possible developmental neurotoxicity of EGBE.

This study had some limitations. We cannot exclude a selection bias, although we did not find any difference in the characteristics of our study population and non-participants, limiting the risk that a confounder may predict participation. Moreover, we investigated subtle behavioral effects, which would be less sensitive to attrition bias than apparent clinical effects (Greene et al., 2011). BOLD imaging measures the ratio of deoxyhemoglobin to oxyhemoglobin to indirectly evaluate neural activity. This indicator is commonly used, but may vary depending on individual characteristics (blood flow, iron deficiency, *etc.*) (Ogawa et al., 1990). Moreover, the performance of inhibition is not determined solely by intensity of the hemodynamic response and could be explained by brain structure, connectivity, *etc.* Also, our exposure assessment is based on only one (first) morning void urinary sample collected before 19 weeks of gestation, and glycol ether metabolites have a short half-life, from several hours to several days (AFSSET, 2008). However, the high detection rate of glycol ether metabolites suggests that exposure was widespread and repeated. In addition, a previous study in the PELAGIE cohort found associations between the use of products containing solvents during early pregnancy and the urinary levels of four glycol ether metabolites (EAA, EEAA, BAA, and PhAA) (Garlantézec et al., 2012). Another cohort study highlighted the lack of information provided to French pregnant women concerning the prevention of exposure to reprotoxicants, including housekeeping products, and a French study suggested that cosmetics are generally used daily at home, including during pregnancy (Chabert et al., 2016; Ficheux et al., 2015). Thus, our results likely reflect regular individual exposure during the first trimester of pregnancy, a critical period for brain development. However, repeated samples would have been needed to ensure this hypothesis. Similarly, it is likely that our measurement did not capture intra-individual variability, over time, due to the rapid metabolism of glycol ethers. This produces non-differential measurement errors in the exposition estimation, which could have been limited by using repeated samples. Our study does not explore the effects of glycol ether exposure during late pregnancy or childhood, which could occur *via* various sources and exposure pathways, although human neurodevelopment is known to continue during childhood, until adolescence for maturation of the prefrontal cortex (Rice and Barone, 2000). Although we considered significant confounders and based our study on a homogeneous population, we cannot guarantee that our results were not affected by residual confounding. Thus, given that prenatal exposure to products containing solvents at work has been associated with problems related to the function of inhibition, we cannot exclude that our results may be explained by other solvents or chemicals present in these products (Laslo-Baker et al., 2004; Pelé et al., 2013; Till et al., 2001a,b). Then, we do not correct analyses for multiple comparisons with glycol ethers to protect against false negative results but we cannot rule out the possibility that some of them are due to chance. Finally, we cannot rule out the hypothesis of a lack of statistical power, especially for our whole-brain strategy.

5. Conclusion

Human exposure to glycol ethers is ubiquitous in our daily lives and might be of particular concern for pregnant women and developing fetuses. According to previous observational epidemiological studies, some glycol ethers have been suspected as neurodevelopmental toxicants, especially for learning abilities and behavioral development, while too few mechanistic studies supporting this possible effect exist. The present study provides new findings suggesting differential activations in the brain motor inhibition network in association with prenatal glycol ethers exposure. However, some results about specific glycol ether metabolites were unexpected regarding existing literature. Therefore, replication of these findings and deeper investigation on possible neural development changes are strongly required before drawing any conclusions or public health recommendations.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105163.

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