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A preliminary study on prenatal polybrominated diphenyl ether serum concentrations and intrinsic functional network organization and executive functioning in childhood

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Background: The prenatal period is a period of vulnerability during which neurotoxic exposures exert persistent changes in brain development and behavior. Polybrominated diphenyl ethers (PBDEs), used as flame retardants in commercial products, are known to be developmental neurotoxicants. PBDEs were phased out of use in the United States a decade ago, but exposure remains widespread due to their release from existing products and biopersistence. Despite consistent animal and epidemiological evidence of developmental neurotoxicity, the neural substrates linking prenatal PBDE serum concentrations to impaired neurodevelopment are poorly understood. **Methods:** In the present study, we used resting state functional magnetic resonance imaging (fMRI) to examine associations between prenatal PBDE concentrations measured in maternal serum and intrinsic functional network organization (i.e., global and local efficiency; estimated using a graph-theoretical approach) in 5-year-old children (n = 34). We explored whether PBDE serum concentrations were associated with executive functioning (EF) assessed using a parent-report questionnaire (BRIEF-P) (n = 106) and whether changes in intrinsic functional network organization linked the association between prenatal PBDE serum concentrations and EF problems. **Results:** Children with higher prenatal PBDE serum concentrations showed: (a) increased global efficiency of brain areas involved in visual attention (e.g., inferior occipital gyrus) (β's = .01, FDR-corrected p's ≤ .05); (b) more reported EF problems (β's = .001, FDR-corrected p's ≤ .05). Higher global efficiency of brain areas involved in visual attention was associated with more EF problems (β's = .01, FDR-corrected p's < .05). **Conclusions:** Intrinsic functional network organization of visual attention brain areas linked prenatal PBDE concentrations to EF problems in childhood. Visual attention may contribute to the development of higher-order cognitive functions, such as EF, which could be explored in future studies. **Keywords:** Children; executive functioning; flame retardants; pregnancy; resting state fMRI.

Introduction

The developing human brain is vulnerable to environmental neurotoxicant exposure (Rodier, 1995). The brain must grow from a small strip of cells into an intricately connected network, which requires complicated maturational processes (e.g., neuron proliferation, synaptogenesis, apoptosis) to occur in the right order and at the right time (Rice & Barone, 2000; Tau & Peterson, 2010). Neurotoxic chemicals can disrupt these maturational processes, setting the stage for deviant developmental trajectories (Grandjean & Landrigan, 2014). Because of the exquisite timing of brain development, exposures during different developmental periods likely have different effects (Heyer & Meredith, 2017).

Polybrominated diphenyl ethers (PBDEs) are persistent, bioaccumulative organobromine chemicals used as flame retardants and found in consumer products such as fabrics, furniture, electronics, wire insulation, and infant products (Sjodin et al., 2008). There are a total of 209 possible PBDE congeners with varying bromination degrees and locations of the bromine atom on the diphenyl ether backbone (Bradner, Suragh, Wilson, et al., 2013). Widely recognized as developmental neurotoxicants, epidemiologic studies suggest that prenatal PBDE exposure may negatively impact executive functioning (EF), the cognitive processes that underlie goal-directed behaviors (Best, 2010). Specifically, children prenatally exposed to PBDEs exhibit attention problems (Eskenazi et al., 2013; Roze et al., 2009; Sagiv et al., 2015), impaired working memory (Sagiv et al., 2015), and impaired task switching (Sagiv et al.,

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2015). Brain areas subserving EF in children include the lateral prefrontal cortex (PFC), inferior and superior parietal cortex, and striatum (McKenna, Rushe, & Woodcock, 2017). Animal studies demonstrate that prenatal PBDE exposure disrupts the functioning and integrity of brain areas implicated in EF, including the PFC (Bradner, Suragh, & Caudle, 2013). To date, no study has examined the neural substrates linking the association between prenatal PBDE serum concentrations and EF problems in children. Understanding these neural substrates could ultimately inform programs to prevent exposure and reduce its adverse effects (Horton, Margolis, Tang, & Wright, 2014).

The goal of the present study is to examine the impact of prenatal PBDE serum concentrations on intrinsic functional organization of the brain in childhood, and to further explore whether intrinsic functional brain organization links the association between prenatal PBDE serum concentrations and EF problems in children aged 5 years. We acquired a resting state functional magnetic resonance imaging (rs-fMRI) scan to assess intrinsic functional connectivity (iFC) of children's brains and used graph theory (i.e., complex network) analyses (Rubinov & Sporns, 2010) to characterize children's whole-brain intrinsic functional network organization, focusing on measures of integration (i.e., global efficiency) and segregation (i.e., local efficiency) of the brain (Rubinov & Sporns, 2010). An rs-fMRI scan allows one to focus on iFC of distributed networks, instead of on isolated brain areas (Kelly & Castellanos, 2014). Furthermore, rs-fMRI is particularly useful in young children, since participants are not required to perform a demanding cognitive task.

Based on prior animal (Bradner, Suragh, & Caudle, 2013) and behavioral studies (Eskenazi et al., 2013; Roze et al., 2009; Sagiv et al., 2015), we expected that higher prenatal PBDE serum concentrations would be associated with altered intrinsic functional organization of brain networks involved in EF (e.g., lateral prefrontal cortex, parietal cortex, striatum). We hypothesized that children exposed to higher prenatal PBDE concentrations would show greater EF problems (Eskenazi et al., 2013; Roze et al., 2009; Sagiv et al., 2015). We further anticipated that altered intrinsic functional organization of brain networks involved in EF (e.g., prefrontal cortex, parietal cortex, striatum) would be associated with more EF problems in children. To our knowledge, associations between prenatal exposure to environmental toxicants and children's intrinsic functional network organization have not been investigated yet. Therefore, we proposed two opposing hypotheses regarding the altered intrinsic functional network organization we anticipated in children with higher PBDE concentrations, and examined positive and negative associations with PBDE concentrations. It may be hypothesized that children with higher prenatal PBDE concentrations show *decreased* intrinsic functional network organization, since PBDE concentrations are associated with executive dysfunction and children with disorders characterized by executive dysfunction (i.e., ADHD) show *decreased* global efficiency compared to typically developing children (Wang et al., 2009). Conversely, children with higher prenatal PBDE concentrations could also be expected to show *increased* intrinsic functional network organization, which may be considered a compensatory response to EF problems (cf. Hawkey, Tillman, Luby, & Barch, 2018; Plessen et al., 2006).

Methods

Participants

Participants were selected from an ongoing birth cohort study called the "Endocrine Disruption in Pregnant Women: Thyroid Disruption and Infant Development Study" consisting of 316 mother-child pairs (Horton et al., 2013). Pregnant women between the ages of 16–35 years were enrolled from two New York City prenatal clinics between September 2009 and December 2010. Enrollment and exclusion criteria are described in detail elsewhere (Horton et al., 2013). Briefly, inclusion criteria were: <20 weeks pregnant (based on reported date of last menstrual period and the earliest ultrasound) with a singleton pregnancy. Exclusion criteria included: medical complications (including chronic hypertension, diabetes, or epilepsy), and drug and/or alcohol abuse. From the 316 mother–child dyads enrolled in the cohort, 106 completed the 5-year-old follow-up which included a parent-report questionnaire to measure EF (BRIEF-P). From these, we selected 47 children to participate in a resting state fMRI study based on the following criteria: (a) age 5 years or older, (b) a maternal blood sample analyzed for PBDEs.

The Institutional Review Boards of Columbia University and the Icahn School of Medicine at Mount Sinai approved the study protocol; it was determined at the Centers for Disease Control and Prevention (CDC) that the agency was not engaged in human subjects' research. Written informed consent was obtained from all mothers of participating children.

PBDE serum concentrations

Maternal blood (10 ml) was collected by sterile venipuncture during the first half of pregnancy at a regularly scheduled prenatal blood draw (M = 12.2 weeks gestation, SD = 2.8 weeks). Blood was collected in silicon-coated (i.e., PBDE-free) vacutainers provided by the Centers for Disease Control and Prevention (CDC) to avoid contamination. Aliquots of 2 ml serum from each subject were sent to the CDC for measurement of PBDEs and serum lipids (total triglycerides and cholesterol). Serum PBDEs were measured using isotope dilution high resolution mass spectrometry on a MAT95XP DFS (ThermoFisher; Bremen, Germany) instrument. Serum lipids were measured via commercially available test kits from Roche Diagnostics Corporation (Indianapolis, IN). Details of the analytical methods, including quality control, reproducibility, and limits of detection are provided elsewhere (Sjodin et al., 2004). Serum samples were available for all participants. We measured concentrations of PBDE congeners 17, 28, 47, 66, 85, 99, 100, 153, 154, 183, and 209. For the current analyses, we included congeners with concentrations > limit of detection (LOD) in at least 50% of participants (Cowell et al., 2015). Thus, we focused on congeners 28 (55.9% of participants >LOD), 47 (100% of participants >LOD), 99 (85.3% of participants >LOD), 100 (88.2% of participants

>LOD), and 153 (100% of participants >LOD). These five congeners were significantly correlated with each other (*r*'s .74–.99, all *p*'s < .01). Concentrations below the LOD were substituted by the LOD divided by the square root of 2 (Hornung & Reed, 1990). Lipid adjusted PBDE concentrations (ng/g lipid) were used in analyses.

Executive functioning

One parent of each child completed the Behavior Rating Inventory of Executive Function–Preschool Version (BRIEF-P) (Gioia, Espy, & Isquith, 2003), approximately 4 months prior to the neuroimaging study (median = 4.3 months; range = 0.3–10.8 months). The BRIEF-P was completed by all but one parent of the children who participated in the rs-fMRI study, and an additional 65 parents of children who did not complete the rs-fMRI study. Thus, BRIEF-P data was available for a total of 106 children (43% girls) (*median age at administration* = 5.07 years, range = 3.90–6.02 years *SD* = 0.31 years). The BRIEF-P is a 63-item rating scale designed to assess everyday behaviors associated with specific domains of executive functioning in children aged 2–5 years. Parents are asked to rate how often their child displayed problems with specific behaviors in the past 6 months; on a scale ranging from never (0), sometimes (1) to often (2). Ratings are summed; higher BRIEF-P scores indicate more reported executive functioning problems. The BRIEF-P consists of 5 scales: Inhibit (i.e., Inhibition), Shift (i.e., Task switching), Emotional Control, Working memory, and Plan/Organize (i.e., Planning and Organizing). Scales can be combined to create an overall score [Global Executive Composite (GEC); sum of all 5 scales] and 3 summary indexes: Inhibitory Self-Control Index (ISCI; Inhibit + Emotional control), Flexibility Index (FI; Shift + Emotional Control), and Emergent Metacognition Index (EMI; Working Memory + Plan/Organize). The BRIEF-P overall score and summary indexes demonstrate excellent test–retest reliability (*r*'s = .80–.95) and adequate to high internal consistency (Cronbach's α = .70–.90) (Sherman & Brooks, 2010). The BRIEF-P demonstrates high validity, in that children with psychiatric disorders characterized by executive dysfunction (i.e., Attention Deficit Hyperactivity Disorder; ADHD) show higher scores than typically developing children (Ezpeleta & Granero, 2015), and BRIEF-P scores are significantly correlated with performance on objective cognitive tasks measuring EF (Garon, Piccinin, & Smith, 2016). EF measured in preschool is strongly correlated with EF measured in later childhood (Gooch, Thompson, Nash, Snowling, & Hulme, 2016; Mazzocco & Kover, 2007).

We used the *T* scores (i.e., transformation of raw scores, providing an index of a child's score relative to children of the same age and gender) for the GEC, ISCI, FI, and EMI in analyses. *T* scores have a mean of 50 and standard deviation of 10; *T* scores ≥ 65 are considered clinically significant. As scores were positively skewed (all Kolmogorov–Smirnov statistics > .9; *p*'s ≤ .031), we applied a reciprocal root transform to meet assumptions of normality for the statistical models and to reduce the influence of outliers.

MRI data collection

MRI data were collected using a 3T Philips Achieva scanner equipped with an 8-channel (SENSE-head-8) coil, located at the Columbia University Department of Radiology. We measured children's intrinsic functional connectivity of the brain at rest, by administering a 5 min resting state fMRI scan (single-shot EPI Gradient Recalled (GR) sequence, TR = 2,000 ms, TE = 25 ms, 150 volumes, 44 slices, no slice gap, sequential ascending slice acquisition, flip angle = 72°, acquisition matrix = 80 × 80, field of view = 24 cm, voxel size = 3 mm^3). For registration purposes, we collected two anatomical MPRAGE scans (duration: 3 min 46 s per scan; TR = 10 ms, TE = 4.936 ms, 165 slices, slice thickness = 1 mm, slice gap = 1 mm flip angle = 8°, acquisition matrix = 256 × 256, field of view = 25.6 cm). At the time of acquisition, each anatomical scan was visually inspected for motion artifacts by the MRI technician, if both scans contained visible artifacts additional scans were collected until one scan without visible artifacts was collected. For registration, we used the first collected scan without visible artifacts.

Resting state fMRI data preprocessing

47 children were enrolled in the neuroimaging study; 42 children completed at least one scan (i.e., structural scan or resting state fMRI scan). We included data from 34 children (*median age* = 5.57 years, range = 5.13–5.83 years; *SD* = 0.22 years; 18 girls) in analyses (see Appendix S1 for reasons for exclusion).

Data were preprocessed using FEAT Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The first two volumes were discarded to allow for T1-equilibration effects. We performed motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), slice-timing correction using Fourier-space time-series phase-shifting, nonbrain removal using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of 6 mm FWHM, and high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 100.0s). Registration of functional images to participants' high-resolution structural images was carried out using FLIRT (Jenkinson & Smith, 2001). Given the participants' young age, we created a study-specific template by averaging participants' high-resolution structural images, and we registered this study-specific template to standard space (MNI-152 template) using FNIRT nonlinear registration (Andersson, Jenkinson, & Smith, 2007a, 2007b). Participants' functional and high-resolution structural images were subsequently registered to this standard space, study-specific template using FNIRT. Using Anatomical CompCor (aCompCor; Behzadi, Restom, Liau, & Liu, 2007), we estimated and regressed out white matter and cerebral spinal fluid (CSF) noise (five principal components). In order to reduce motion artifacts, we included 24 motion parameters (Friston, Williams, Howard, Frackowiak, & Turner, 1996) as nuisance regressors at the single-subject level, and volumes exceeding > 0.5 mm relative FD were regressed out (i.e., motion scrubbing) (Chai, Ofen, Gabrieli, & Whitfield-Gabrieli, 2014).

Graph theory analyses

Using the CONN functional connectivity toolbox (version 17.c; Whitfield-Gabrieli & Nieto-Castanon, 2012), we parcellated participants' gray matter (excluding the cerebellum) into 638 similarly sized regions (Crossley et al., 2013).

We characterized the properties of children's intrinsic functional network organization by computing the global efficiency (i.e., integration) and local efficiency (i.e., segregation) of their brains, which reflect opposing demands of the brain (Rubinov & Sporns, 2010). Global and local efficiency metrics show excellent test–retest reliability (*r*'s .90–.95) (Whitfield-Gabrieli & Nieto-Castanon, 2012), including in children as young as 4 years of age (Paldino, Chu, Chapieski, Golriz, & Zhang, 2017). A more detailed description of the graph theory analyses is provided in Appendix S1.

Statistical analysis

In order to examine the associations of intrinsic functional network organization with prenatal PBDE serum concentrations and parent-reported executive functioning in childhood, we performed a series of Weighted Quantile Sum (WQS) regression analyses (Czarnota, Gennings, & Wheeler, 2015), using

SAS version 9.4. WQS is a statistical approach developed to examine associations between co-exposure to multiple, highly correlated environmental toxicants with health outcomes. This method can be used to estimate the total exposure burden associated with a mixture of correlated factors, and identify influential compounds in the mixture. WQS reduces multicollinearity issues associated with highly correlated congeners, and has increased power compared to performing separate analyses for each congener (Gennings et al., 2013). Using WQS, we estimated a weighted linear PBDE exposure index, in which the weights are empirically estimated using bootstrap sampling (n = 100 bootstrap samples) (Czarnota et al., 2015; Gennings et al., 2013). The use of bootstrapping during parameter estimation reduces errors in effect estimation caused by high correlation (i.e., collinearity) among congeners (Czarnota et al., 2015; Gennings et al., 2013). We developed three models to examine associations between prenatal PBDE serum concentrations and outcomes in children (see Appendix S1 for more details): (a) PBDE index and intrinsic functional network organization (global and local efficiency; n = 34); (b) PBDE index and EF (n = 106); (c) BRIEF-P index and intrinsic functional network organization (n = 33). An FDR correction (a = 0.05) was used for all models (model 1: 638 comparisons, model 2: 4 comparisons, and model 3: 10 comparisons), and covariates included home environment and support, maternal education and child gender (only models 1 and 3).

Results

Demographic characteristics

Maternal and child demographic characteristics and child BRIEF-P scores are presented in Table 1. Prenatal PBDE concentrations are presented in Table S1 (online supporting information). There were no significant differences between the participants who were included in the rs-fMRI analyses (n = 34), the participants with BRIEF-P data who did not complete a rs-fMRI scan (n = 73) and the larger cohort (n = 209) in the sociodemographic and PBDE serum concentration measures (all p's $\geq$ .12; see Tables 1 and S1). Furthermore, among the children with BRIEF-P data, those who were included in the rs-fMRI analyses did not differ from those who were not included in these analyses in terms of BRIEF-P scores (all p's $\geq$ .45). The majority of children scored within the normal range on the BRIEF-P scales; only 9%–15% of subjects had T scores above the cutoff for clinically significant scores ($T \geq 65$) on the different BRIEF-P scales.

Model 1: PBDE index and intrinsic functional network organization

Increases in the PBDE WQS index were associated with *increases* in global efficiency of brain areas involved in learning and visual attention (see Table S2 and Figure 1), including the hippocampus, lingual gyrus, inferior occipital gyrus (2 regions; Brodmann areas 18 and 19), superior occipital gyrus, inferior temporal gyrus, and middle temporal

Table 1 Sociodemographic characteristics of the participants of the parent cohort who did not participate in the study described here (n = 209) and of participants with BRIEF-P data who did not provide resting state fMRI data (n = 73) and those with resting state fMRI data included in the analysis (n = 34)

Characteristic	Full cohort (n = 209)[a] Median (IQR) or %	Subjects with BRIEF-P data (n = 73) Median (IQR) or %	Subjects with resting state fMRI data (n = 34) Median (IQR) or %	p[c]
Maternal ethnicity (%)				
African-American	7.7	2.7	3	.12
Non-Hispanic White	24.5	17.8	12.1	
Hispanic	62.5	72.6	84.8	
Other	5.3	6.8	0	
Maternal education (%)				
<High school	17.4	12.5	14.7	.61
High school	24.6	19.4	29.4	
College	58.0	68.1	55.9	
Child gender (%)				
Female	43.4	41.2	52.9	.51
Male	56.6	58.8	47.1	
Birth weight (g)	3330 (650)	3298 (551)	3310 (550)	.89
HOME (total score)[b]	67.5 (13.8)	66 (12.5)	66.5 (9.5)	.61
BRIEF-P (T score)				
GEC		50 (19.5)	45 (17.5)	.72
ISCI	N/A	49 (19.0)	46 (15.5)	.75
EMI		49 (21.5)	49 (19.5)	.64
FI		45 (16.5)	47 (18)	.45

BRIEF-P, Behavior Rating Inventory of Executive Function–Preschool Version); EMI, Emergent Metacognition Index (i.e., Planning/Organizing and Working Memory); FI, Flexibility Index (i.e., Shifting); GEC, Global Executive Composite (i.e., Overall executive functioning); ISCI, Inhibitory Self-Control Index (i.e., Inhibition).

[a]All participants, minus the participants included in the BRIEF-P analyses (n = 106) and one participant who provided resting state fMRI data, but no BRIEF-P data.

[b]Complete HOME data was available for 109 participants.

[c]Differences in the distribution of categorical variables were tested using Chi-Square tests, while differences in continuous variables were compared using Kruskal–Wallis tests (for Birth weight and HOME) and a Mann–Whitney U test (BRIEF-P).

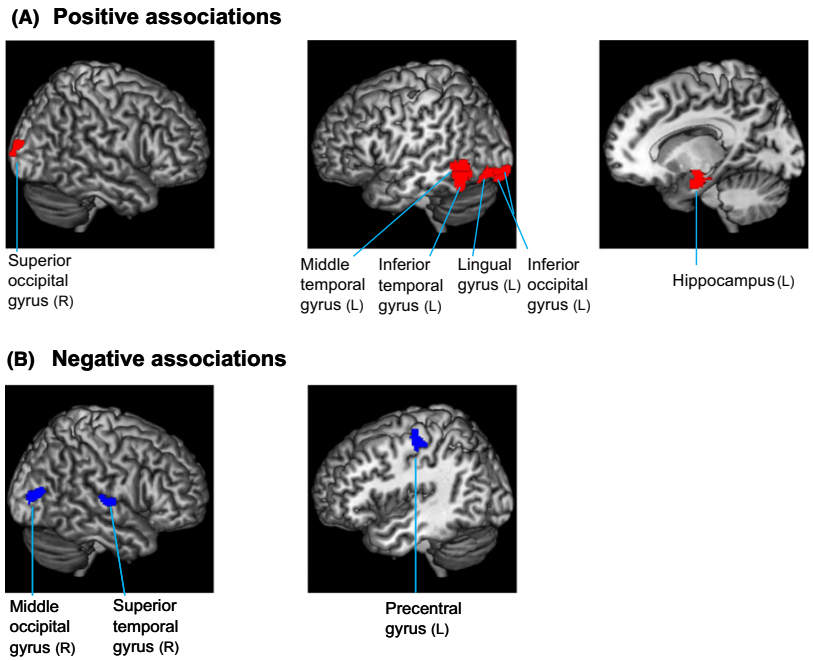

Figure 1 Brain areas showing significant associations (FDR-corrected $p \leq .05$; adjusted for child gender, maternal education, and HOME) between the PBDE index (comprised of congeners 28, 47, 99, 100, 153) and global efficiency (i.e., intrinsic functional network organization) of children's brains. *Note*. Figure 1A shows brain areas that were positively associated with the PBDE index. Figure 1B shows brain areas that were negatively associated with the PBDE index. L, left hemisphere; R, right hemisphere. 638 analyses were performed (FDR-corrected $p \leq .05$), one for each brain region of the parcellation atlas

gyrus. Children who were exposed to higher prenatal PBDE levels (as estimated by the WQS index) in utero showed increased global efficiency of these brain areas at age 5 years.

Increases in the PBDE WQS index were associated with *decreases* in global efficiency in the middle occipital gyrus, precentral gyrus, and superior temporal gyrus, regions involved in visual, sensorimotor, and auditory processing respectively.

All PBDE congeners comprising the WQS index contributed to the global efficiency of these brain areas, and the contribution (i.e., weight) of different congeners differed by brain area (see Table S3). Congeners 28 and 99 particularly contributed to global efficiency of brain areas involved in learning and memory (e.g., hippocampus), while congener 100 strongly contributed (weights > 70%) to the global efficiency of visual areas (i.e., inferior occipital gyrus and lingual gyrus), and congeners 28 and 153 particularly contributed to global efficiency of sensorimotor areas (i.e., precentral gyrus and superior temporal gyrus).

The PBDE WQS index was not significantly associated with the measure of segregation (i.e., local efficiency) of children's intrinsic functional brain networks.

Model 2: PBDE index and executive functioning

A higher PBDE WQS index was significantly associated with increases in BRIEF-P GEC, FI, and ISCI scores, indicating more reported EF problems (see Table S4). The association between the PBDE WQS index and BRIEF-P EMI scores approached significance (FDR-corrected $p = .065$). PBDE congeners 28 and 99 contributed primarily to the BRIEF-P scores; the combined weights of these congeners were ≥82% for each BRIEF index (see Table S4).

Model 3: BRIEF-P index and intrinsic functional network organization

We examined whether a BRIEF-P WQS (comprising the GEC, ISCI, FI, and EMI) index was associated with global efficiency of the 10 brain regions that were significantly associated with the PBDE WQS index (Model 1). Increases in the BRIEF-P WQS index were associated with increases in global efficiency of the lingual gyrus and inferior occipital gyrus (two regions; Brodmann areas 18 and 19 (see Figure 2 and Table S5). The ISCI (i.e., Inhibition) and FI (i.e., Shifting) indexes contributed most to global efficiency of these areas; combined weights for these indexes were ≥74% for all brain areas (see Table S5).

Discussion

In the present study, we examined whether: (a) prenatal PBDE serum concentrations, expressed as a weighted index (congeners 28, 47, 99, 100, and 153) using WQS regression (Czarnota et al., 2015; Gennings et al., 2013), are associated with intrinsic

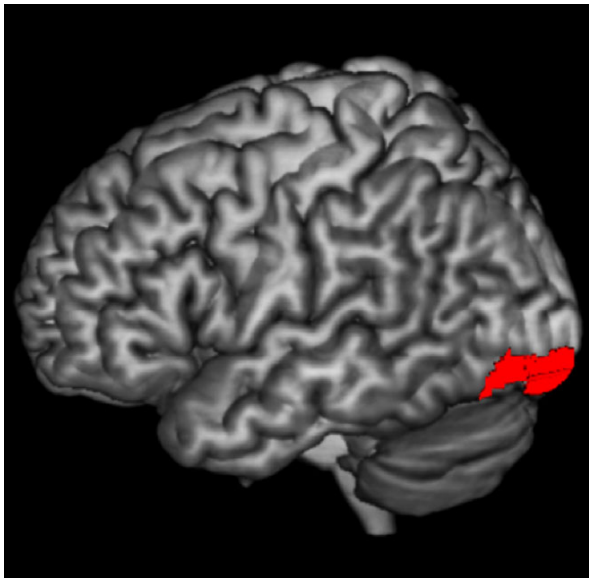

Figure 2 Associations between global efficiency of children's brains and parent-reported executive functioning (BRIEF-P). *Note*. We performed weighted quantile sum (WQS) analyses, to examine associations between a weighted linear BRIEF-P index (Overall executive functioning, Planning/organizing and Working memory, Shifting and Inhibition) and global efficiency of children's brains. We performed separate WQS analyses (FDR-corrected $p \leq .05$; adjusted for child gender, maternal education and HOME) for the 10 brain areas that were significantly associated with the PBDE index (see Figure 1). The brain areas depicted in red are the three brain areas that were significantly associated with the BRIEF-P index: left lingual gyrus and left inferior occipital gyrus (two regions)

functional network organization (i.e., global efficiency and local efficiency) in 5-year-old children; (b) prenatal PBDE serum concentrations are associated with children's reported EF problems at 5 years; and (c) children's intrinsic functional network organization is associated with their reported EF problems.

Prenatal PBDE serum concentrations are associated with global efficiency and EF problems

Our three main findings suggest that: (a) children with higher prenatal PBDE serum concentrations showed increased global efficiency of brain areas involved in memory (hippocampus) (Ofen, Chai, Schuil, Whitfield-Gabrieli, & Gabrieli, 2012) and visual attention (lingual gyrus, inferior and superior occipital gyrus, posterior inferior and middle temporal gyrus) (Mayer et al., 2007), and decreased global efficiency of brain areas involved in sensorimotor functions (precentral gyrus) (Ugur et al., 2005) and visual (middle occipital gyrus), and auditory processing (superior temporal gyrus) (Mendoza, 2011); (b) children with higher prenatal PBDE serum concentrations showed more reported EF problems, including poor inhibition and shifting; (c) children who showed increased global efficiency of brain areas involved in visual attention (lingual gyrus, inferior occipital gyrus), showed more reported EF problems.

Contrary with our a priori hypotheses, global efficiency of the PFC, parietal cortex and striatum did not link prenatal PBDE concentrations to EF problems in children. Instead, increased global efficiency of the lingual gyrus and inferior occipital gyrus was associated with prenatal PBDE concentrations and reported EF problems. A recent meta-analysis showed that the inferior occipital gyrus is consistently recruited during EF tasks in children, particularly during inhibition tasks (McKenna et al., 2017). The inferior occipital gyrus and lingual gyrus are further recruited during both visual attention tasks (Lidzba, Ebner, Hauser, & Wilke, 2013) and inhibition tasks (Booth et al., 2003) in children. Visual attention and inhibition skills are correlated in children (Bartgis, Thomas David, Lefler Elizabeth, & Hartung Cynthia, 2008; Gerardi-Caulton, 2001). Visual attention in infancy predicts inhibition and other EF skills in childhood (Cuevas & Bell, 2014; Vaughan Van Hecke et al., 2012), suggesting that visual attention may be a basic cognitive function required to develop higher-order cognitive functions, such as EF.

When examined as a mixture, all five PBDE congeners contributed to the global efficiency of children's brains and to their reported EF problems. However, the contribution (i.e., weight) of each congener differed by outcome. While variability in weights for different outcomes may complicate interpretation of the results, we demonstrated that different congeners show region-specific associations with brain organization and the behaviors supported by these brain regions. Congeners 28 and 99 particularly contributed to children's EF. Congener 100 strongly contributed to the global efficiency of visual brain areas (i.e., inferior occipital gyrus and lingual gyrus), while congeners 28 and 153 particularly contributed to global efficiency of sensorimotor areas (i.e., precentral gyrus and superior temporal gyrus). Even though the concentrations of the five different congeners were highly correlated in the current study (*r*'s ranging between .74 and .99), previous studies have shown that different congeners are associated with different cognitive functions (Herbstman et al., 2010; Zhang et al., 2017). It may be hypothesized that different congeners affect the function of different thyroid hormones (Herbstman et al., 2010; Zhang et al., 2017), and receptors for these hormones are expressed in distinct brain regions (Constantinou, Margarity, & Valcana, 2005). Future molecular neuroscience studies should test this hypothesis.

These findings are consistent with prior behavioral studies showing that prenatal PBDE serum concentrations are associated with impaired EF (Cowell et al., 2015; Herbstman et al., 2010; Sagiv et al.,

2015). Several mechanisms might explain why prenatal PBDE serum concentrations are associated with changes in intrinsic functional network organization and EF problems. PBDEs can cross the placental and fetal blood-brain barriers (Dassanayake, Wei, Chen, & Li, 2009), exerting neurotoxic effects on the developing brain, including dopamine dysfunction (Madia et al., 2004), oxidative stress (Madia et al., 2004), and impaired synaptic plasticity (Kodavanti & Derr-Yellin, 2002). Additionally, PBDEs impair brain development by disrupting maternal thyroid hormone levels, which are crucial for fetal brain development throughout pregnancy (Wier & Farley, 2006).

Our findings – particularly the associations between PBDE concentrations and organization of the inferior occipital gyrus, lingual gyrus, and superior temporal gyrus – are also consistent with the findings of studies that explored associations between early-life exposure to other environmental toxicants and brain function. Recently, we demonstrated that the lateral occipital gyrus showed reduced intrinsic functional connectivity with the insula in children with higher prenatal manganese concentrations (de Water et al., 2018). Yuan et al. (2006) showed that childhood lead levels were associated with increased activity of the superior temporal gyrus during a language task. Prenatal exposure to marijuana was associated with reduced intrinsic functional connectivity between the inferior occipital gyrus and caudate in infants (Grewen, Salzwedel, & Gao, 2015), while prenatal exposure to tobacco smoke was associated with increased activity of the lingual gyrus during an auditory attention task in adolescents (Jacobsen, Slotkin, Mencl, Frost, & Pugh, 2007).

Increased global efficiency: a positive or negative outcome?

We found that children with higher prenatal PBDE serum concentrations showed *increased* global efficiency of brain areas involved in visual attention (lingual gyrus and inferior occipital gyrus), which was in turn associated with more reported EF problems. Conversely, children with disorders characterized by executive dysfunction (i.e., ADHD) show *decreased* global efficiency compared to typically developing children in the lingual gyrus (Wang et al., 2009), and integration of brain networks increases (i.e., increased global efficiency) with development in typically developing individuals (Fair et al., 2007). We performed exploratory seed-to-voxel analyses (see Figures S1 and S2) to test whether the increased global efficiency of the lingual gyrus and inferior occipital gyrus we observed, may reflect atypical connectivity of these brain regions. Independent of PBDE serum concentrations, we found that the lingual gyrus and inferior occipital gyrus seeds were connected to the occipital cortex, temporal gyrus, and cerebellum. However, in children with higher PBDE serum concentrations, the inferior occipital gyrus was also connected to brain areas involved in EF, including the PFC and insula. Thus, the increased global efficiency we observed in children with higher PBDE serum concentrations could reflect atypical connectivity, which may be considered a compensatory response to EF problems (cf. Hawkey et al., 2018; Plessen et al., 2006). It must be noted that these exploratory seed-to-voxel analyses did not survive correction for multiple comparisons and should therefore be replicated in future studies.

PBDE concentrations: comparison to prior studies

Amongst the PBDE congeners measured, two congeners (47 and 153) were detected in 100% of maternal serum collected during pregnancy, and four congeners (47, 99, 100, and 153) were detected in >85% of subjects. Median PBDE concentrations in our study were higher than in prior European and Asian studies of pregnant women (Roze et al., 2009; Zhang et al., 2011), but 2–3 times lower than in earlier US studies (Cowell et al., 2015; Herbstman et al., 2010; Sagiv et al., 2015), likely reflecting the fact that PBDE regulations have been effective in reducing PBDE exposure, and that the EU regulated and phased out PBDEs earlier than the United States (EC, 2003; EPA, 2015). Exposure to PBDEs occurs through ingestion of house dust and diet (Stapleton, Kelly, Allen, McClean, & Webster, 2008); we previously showed that higher PBDE concentrations were particularly associated with greater use of household electronics and consumption of solid dairy and processed meat in this cohort (Horton et al., 2013).

Strengths and limitations

This study has several strengths. We used WQS regression, which reduced the multidimensionality and collinearity of our data, and enabled us to identify differential contributions of individual PBDE congeners to brain and behavioral outcomes. Additionally, we used a whole-brain, data-driven approach (i.e., graph theoretical network analyses) to identify children's intrinsic functional network organization, which provided an unbiased and comprehensive overview of children's functional connectivity.

Several limitations of the current study must be noted as well. We measured intrinsic functional network organization and EF problems at a single timepoint. Future longitudinal studies should measure these variables at multiple timepoints to assess whether changes in intrinsic functional network organization predict changes in EF, or the other way around. While we controlled for child sex in our analyses, we had limited statistical power to examine child gender as an effect modifier, which has been

reported in prior studies (Sagiv et al., 2015). Future studies should extend our preliminary findings by using larger samples with diverse demographic characteristics, which would allow one to adjust for residual confounders that may affect serum PBDE concentrations (e.g., household smoker status). We used parent-report measures of EF. While parent-report measures correlate significantly with objective cognitive tasks of EF in some studies (Garon et al., 2016), future research should ideally include both parent-reported measures and objective cognitive tasks to optimally assess EF in daily life and in controlled settings respectively. Children who were excluded from the resting state fMRI analyses because of excessive head motion, showed more EF problems than children who were included in these analyses (see Table S6). This is consistent with other studies demonstrating that children with impaired EF (i.e., children with ADHD) show more head motion during resting state fMRI scans than typically developing children (Di Martino et al., 2013). Exclusion of children who show excessive head motion is critical to ensure that the results are not biased by head motion (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Van Dijk, Sabuncu, & Buckner, 2012). However, exclusion of these children in our study may have reduced the variability in EF, possibly attenuating associations with EF. Finally, we measured PBDE concentrations in maternal serum once during pregnancy. The fetal brain is particularly vulnerable to exposure to environmental toxicants, as the fetal blood-brain barrier provides only partial protection against toxicants, and disruption of neuronal maturational processes can have lasting consequences (Grandjean & Landrigan, 2014; Rice & Barone, 2000; Tau & Peterson, 2010). Furthermore, PBDEs disrupt maternal thyroid function, and maternal thyroid hormones play a critical role in fetal brain development (Wier & Farley, 2006). However, postnatal PBDE exposure is also associated with impaired neurodevelopment (Eskenazi et al., 2013; Sagiv et al., 2015), although associations between prenatal PBDE concentrations and neurodevelopment have been reported when controlling for postnatal PBDE concentrations (Eskenazi et al., 2013; Sagiv et al., 2015). Future researchers should aim to include multiple measures of PBDE concentrations throughout pregnancy and early childhood, in order to identify windows of vulnerability, during which exposure is particularly harmful.

Conclusions

To conclude, we found that prenatal PBDE serum concentrations are associated with more EF problems and changes in intrinsic functional network organization of brain areas involved in memory, sensorimotor function and visual attention in children. Further, these changes in intrinsic functional network organization of brain areas involved in visual attention were associated with more EF problems. Future studies should extend these findings by conducting longitudinal studies with multiple measures of PBDE serum concentrations throughout pregnancy and childhood, and multiple measures of brain changes and EF (using parent-report and cognitive tasks) throughout childhood and adolescence. Given the prevalence of PBDEs, regulations should be implemented to reduce the release of PBDEs from existing household products.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Supplementary materials.
Table S1. Distribution of maternal polybrominated diphenyl ether (PBDE) concentrations among the participants of the parent cohort who did not participate in the study described here (n = 209) and of participants with BRIEF-P data who did not provide resting state fMRI data (n=73) and those with resting state fMRI data included in the analysis (n=34).
Table S2. Associations between the weighted PBDE index (comprised of congeners 28, 47,99,100,153; measured in maternal blood) and intrinsic functional network organization (i.e., global efficiency) of children's brains at age 5 (n = 34).
Table S3. Estimated weights for each congener included in the weighted PBDE index (28, 47,99,100,153; measured in maternal blood), reflecting the congener's contribution to global efficiency of children's brains at 5 years (n = 34).
Table S4. Associations between the weighted PBDE index (28, 47,99,100,153; measured in maternal blood) and BRIEF-P at 5 years (n = 106), and estimated weights for each congener.
Table S5. Associations between the weighted BRIEF-P index (Overall executive functioning, Planning/organizing and Working memory, Shifting and Inhibition) and global efficiency of children's brains at 5 years (n = 33), and estimated weights for each BRIEF-P scale.
Table S6. Comparison of participants included in the rs-fMRI analyses (n = 34) and those who were excluded from these analyses (n = 13).
Figure S1. Seed-to-voxel connectivity for the left lingual gyrus and two left inferior occipital gyrus seeds across all subjects (n = 34), FDR-corrected $p < .05$.
Figure S2. Correlations between the left inferior occipital gyrus seed (Brodmann area 18) and weighted PBDE index, $p < .001$, with an extent threshold of 20 voxels.

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Key points

- Higher prenatal flame retardant concentrations were associated with more parent-reported executive functioning problems in children.
- Higher prenatal flame retardant concentrations were associated with increased global efficiency of visual attention areas of the brain in children.
- Increased global efficiency of visual attention brain areas was associated with more parent-reported executive functioning problems in children.

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Online Supporting Information

Appendix S1.

Resting state fMRI data exclusion

13 subjects were excluded from the resting state fMRI analyses. 5 participants did not complete a single MRI scan (either a structural scan or resting state fMRI scan) due to claustrophobia or being unable to remain still in the scanner. 4 additional participants were unable to complete a structural (i.e., MPRAGE) scan that was free of visible motion artifacts and did not complete a resting state fMRI scan; 4 participants were excluded because they showed excessive head motion during the functional scan, which has been shown to affect intrinsic functional connectivity metrics (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Van Dijk, Sabuncu, & Buckner, 2012). We used the fsl_motion_outliers tool (implemented in FSL version 6.00) to determine volumes that were corrupted by excessive motion, which we defined as relative framewise displacement (FD) > 0.5 mm (Chai, Ofen, Gabrieli, & Whitfield-Gabrieli, 2014). The four participants were excluded from analyses because removal of these motion-corrupted volumes resulted in having less than 3 minutes (90 volumes) of useable data (Yan et al., 2013). In total, 34 participants (18 girls) were included in all rs-fMRI analyses described in the main text, with a mean of 110 included volumes per child. We compared PBDE concentrations and BRIEF-P scores of the 34 subjects included in the rs-fMRI analyses and the 13 subjects who were excluded from these analyses (see Table S6). While there were no significant differences in PBDE concentrations, subjects who were excluded from the rs-fMRI analyses showed significantly higher BRIEF-P scores (indicating more EF problems) on 3 of the 4 indexes. However, among the 34 subjects included in the rs-fMRI analyses, head motion (both

mean relative FD and the number of volumes with relative FD >0.5mm) was not significantly correlated with PBDE concentrations or BRIEF-P scores (all *p*'s >0.45).

Graph theory analyses

We computed bivariate correlations between the time series of all 638 atlas regions for each participant, creating a region-to-region connectivity matrix for each participant. To ensure that all brain regions had the same number of connections, we imposed a threshold for these connections at a cost value (i.e., the proportion of connections) of 0.15, which provides excellent test-retest reliability (*r*'s 0.90-0.95) for global and local efficiency metrics (Whitfield-Gabrieli & Nieto-Castanon, 2012). All thresholds were two-sided, considering both positive and negative correlations. The supra-threshold connections define an adjacency matrix characterizing a graph with nodes (i.e., the brain regions included in the atlas) and edges (i.e., the strength of the connections between the nodes).

We computed global and local efficiency for each atlas region and each participant. *Global efficiency* is a measure of integration of the brain and refers to the average inverse shortest path length from one node to all other nodes in the graph (Latora & Marchiori, 2001; Rubinov & Sporns, 2010). It is considered a better measure of integration than related graph theoretical measures (e.g., average path length) (Achard & Bullmore, 2007). *Local efficiency* is a measure of segregation of the brain and refers to the average global efficiency within a local subgraph consisting only of the neighbors of a given node (Latora & Marchiori, 2001; Rubinov & Sporns, 2010).

Weighted Quantile Sum (WQS) regression analyses

Weights were constrained between 0 and 1, and to sum to 1, to provide a scaled unit for comparison. In estimating weights, PBDE congener concentrations were ranked in quintiles to scale concentrations across congeners and to reduce the influence of extreme values. Since the weights sum to 1, the weight for each congener indicates the relative contribution of each congener to the outcome. We a priori hypothesized that all congeners would have effects in the same direction (i.e., harmful effects), thus justifying the use of a single WQS index comprised of all 5 congeners. Each WQS index is estimated for a specific outcome (i.e., global efficiency) and estimates the contribution of different congeners to that specific outcome.

A positive and significant ($p < 0.05$) weighted PBDE index indicates that PBDE serum concentrations are associated with an increase in the outcome measure (e.g., global efficiency of a specific brain area), whereas a significant and negative index indicates that PBDE exposure is associated with a decrease in the outcome measure.

We developed three models to examine associations between prenatal PBDE serum concentrations and outcomes in children:

1) **PBDE index and intrinsic functional network organization.** To examine the association between lipid adjusted prenatal PBDE serum concentrations and intrinsic functional network organization of children's brains ($n = 34$), we estimated a weighted linear PBDE index (comprised of congeners 28, 47, 99, 100 and 153), and tested whether this index was associated with global and local efficiency of children's brains. We performed separate analyses for each of the 638 brain regions included in the parcellation atlas we used, and for global and local efficiency separately. Given that socioeconomic status (SES) and sex impact brain function and functional connectivity in children (Hackman & Farah, 2009; Zuo et al., 2010), particularly in

brain areas supporting EF (Hackman & Farah, 2009; Zuo et al., 2010), we included maternal education (< high school, high school, > high school), home environment stimulation and support (Home Observation for Measurement of the Environment (HOME) inventory) (Bradley, Caldwell, & Corwyn, 2003) and child sex as covariates. An FDR correction (a = 0.05) was used to control for the number of brain regions (n = 638) we examined.

2) **PBDE index and EF.** To examine the association between lipid adjusted prenatal PBDE serum concentrations and parent-reported executive functioning in childhood (n = 106), we tested whether the weighted linear PBDE index was associated with the BRIEF-P. HOME score and maternal education were included as covariates. Given that sex-stratified t-scores were used for these outcome variables, sex was not included as a covariate in this model. We performed separate analyses for the total BRIEF-P score (i.e., GEC) and each of the three summary indexes (ISCI, EMI, FI), and applied an FDR correction (a = 0.05) to control for the number of comparisons (n =4).

3) **BRIEF-P index and intrinsic functional network organization.** To examine the association between parent-reported executive functioning and intrinsic functional network organization in childhood (n = 33), we estimated a weighted linear BRIEF-P index (comprised of the GEC, ISCI, EMI and FI indexes), and tested whether this weighted index was associated with the graph theory metrics of brain areas that were significantly associated with the weighted PBDE index in model 1. While we consider the BRIEF-P an outcome (and not a predictor), estimating a BRIEF-P WQS index allowed us to reduce the 4 highly correlated (r's 0.78-0.95; p's <0.001)

components of the BRIEF-P into a single index and to estimate the unique associations of different EF components (i.e., inhibition, shifting, planning/organizing and working memory) with global and local efficiency. We performed separate analyses for each brain region and for global and local efficiency. HOME score, child sex and maternal education were included as covariates. An FDR correction (a = 0.05) was used to control for the number of brain regions we examined (n = 10).

Exploratory post-hoc seed-to-voxel analyses

In order to explore whether associations between the WQS PBDE index and global and local efficiency reflect atypical connectivity to specific brain regions in children with higher prenatal PBDE serum concentrations, we performed posthoc seed-to-voxel analyses, using the CONN functional connectivity toolbox (version 17.c). We selected seeds that were shown to be significantly associated with the WQS PBDE index in model 1 and with the BRIEF-P index in model 3. First, we examined which voxels significantly (FDR-corrected p <0.05) correlated with each seed region across all subjects, in order to explore which brain regions are normally correlated with each seed in 5-year-old children. Then we examined whether the PBDE WQS index (comprising congeners 28, 47, 99, 100, 153) was correlated with seed-to-voxel connectivity for each seed region. We performed this second analysis using both an FDR-corrected threshold ($p < 0.05$), and an uncorrected threshold ($p < 0.001$, with an extent threshold of 20 voxels) to optimally balance Type-I and Type-II errors (Lieberman & Cunningham, 2009).

Seed-to-voxel analyses across all subjects

The lingual gyrus and inferior occipital gyrus seeds were correlated with occipital-temporal regions (see Figure S1), including the occipital pole, lateral occipital gyrus, fusiform gyrus, cerebellum, intracalcarine gyrus, hippocampus, parahippocampal gyrus, cuneus, inferior temporal gyrus and supracalcarine gyrus.

Correlation between PBDE WQS index and seed-to-voxel connectivity

At an FDR-corrected (p <0.05) threshold, the PBDE WQS index was not associated with seed-to-voxel connectivity from the lingual gyrus or inferior occipital gyrus seeds. However, at an uncorrected threshold (p<0.001, with an extent threshold of 20 voxels; Lieberman & Cunningham, 2009), the inferior occipital gyrus seed located in Brodmann area 18 showed altered connectivity with several frontotemporal and cerebellar regions in children with higher PBDE serum concentrations (see Figure S2). Specifically, children with higher PBDE serum concentrations showed increased connectivity between the inferior occipital gyrus seed and the cerebellum (MNI -26 -62 -24), and frontal pole/middle frontal gyrus (MNI -36 38 30). Further, children with higher PBDE serum concentrations showed decreased connectivity between the inferior occipital gyrus seed and the middle temporal gyrus (MNI -62 -18 -10) and insula (MNI -32 14 -16).

Supplementary Tables and Figures

Table S1.

Distribution of maternal polybrominated diphenyl ether (PBDE) concentrations among the participants of the parent cohort who did not participate in the study described here (n = 209) and of participants with BRIEF-P data who did not provide resting state fMRI data (n=73) and those with resting state fMRI data included in the analysis (n=34).

PBDE congener	**Full cohort (*n* = 209)[a]**	**Subjects with BRIEF-P data (*n* = 73)**	**Subjects with resting state fMRI data (*n* = 34)**	***p*[b]**
PBDE 28 (ng/g lipid)				0.25
25th percentile	0.35	0.28	0.35	
50th percentile	0.40	0.40	0.75	
75th percentile	0.95	1.20	1.40	
95th percentile	2.40	2.16	18.85	
PBDE 47 (ng/g lipid)				0.61
25th percentile	4.70	4.90	4.38	
50th percentile	7.70	8.00	9.20	
75th percentile	15.30	18.30	18.73	
95th percentile	35.20	35.18	462.55	
PBDE 99 (ng/g lipid)				0.65
25th percentile	0.90	1.00	0.90	
50th percentile	1.50	1.60	1.70	
75th percentile	2.75	3.00	4.13	
95th percentile	8.60	8.06	103.1	
PBDE 100 (ng/g lipid)				0.94
25th percentile	1.00	0.90	0.90	
50th percentile	1.70	1.50	1.80	

75th percentile	3.00	3.55	3.80	
95th percentile	8.35	9.47	101.8	
PBDE 153 (ng/g lipid)				0.85
25th percentile	1.70	1.75	1.73	
50th percentile	3.05	2.80	2.55	
75th percentile	5.38	4.80	6.15	
95th percentile	19.52	31.20	79.48	

Note. [a] All participants, minus the participants included in the BRIEF-P analyses (n = 106) and one participant who provided resting state fMRI data, but no BRIEF-P data. [b] Differences in PBDE concentrations were compared using Kruskal-Wallis tests.

Table S2.

Associations between the weighted PBDE index (comprised of congeners 28, 47,99,100,153; measured in maternal blood) and intrinsic functional network organization (i.e., global efficiency) of children's brains at age 5 (n = 34)

			MNI coordinates					
Brain region	**Brodmann area**	**Hemisphere**	**X**	**Y**	**Z**	***β***	***SE***	**FDR-corrected *p***
Hippocampus	35	Left	-21	-11	-19	0.01	0.004	0.043
Lingual gyrus	18	Left	-20	-90	-13	0.01	0.004	0.057
Inferior occipital gyrus	18	Left	-23	-93	-9	0.01	0.004	0.026
Inferior occipital gyrus	19	Left	-35	-82	-9	0.01	0.003	0.002
Middle occipital gyrus	19	Right	41	-80	12	-0.01	0.003	0.013
Superior occipital gyrus	18	Right	24	-91	12	0.01	0.004	0.026
Precentral gyrus	4	Left	-35	-20	59	-0.01	0.004	0.057
Inferior temporal gyrus	37	Left	-54	-60	-10	0.01	0.003	0.001
Middle temporal gyrus	37	Left	-54	-58	-1	0.01	0.004	0.051
Superior temporal gyrus	22	Right	58	-20	9	-0.01	0.004	0.057

Note. All results are corrected for child sex, maternal education and HOME. 638 analyses were performed (FDR-corrected $p \leq .05$); one for each brain region of the parcellation atlas. MNI coordinates refer to the center of mass of each brain region.

Table S3.

Estimated weights for each congener included in the weighted PBDE index (28, 47,99,100,153; measured in maternal blood), reflecting the congener's contribution to global efficiency of children's brains at 5 years (n =34)

Brain region	**Brodmann area**	**Hemisphere**	**Weight PBDE 28**	**Weight PBDE 47**	**Weight PBDE 99**	**Weight PBDE 100**	**Weight PBDE 153**
Hippocampus	35	Left	0.23	0.22	0.37	0.10	0.08
Lingual gyrus	18	Left	0.06	0.04	0.02	0.71	0.16
Inferior occipital gyrus	18	Left	0.06	0.01	0.04	0.73	0.16
Inferior occipital gyrus	19	Left	0.50	0.15	0.16	0.10	0.09
Middle occipital gyrus	19	Right	0.14	0.34	0.17	0.19	0.17
Superior occipital gyrus	18	Right	0.23	0.15	0.01	0.44	0.17
Precentral gyrus	4	Left	0.42	0.09	0.02	0.16	0.30
Inferior temporal gyrus	37	Left	0.14	0.23	0.11	0.33	0.19
Middle temporal gyrus	37	Left	0.02	0.39	0.35	0.10	0.15
Superior temporal gyrus	22	Right	0.26	0.04	0.13	0.12	0.45

Table S4.

Associations between the weighted PBDE index (28, 47,99,100,153; measured in maternal blood) and BRIEF-P at 5 years (n =106), and estimated weights for each congener

BRIEF-P	β	***SE***	***FDR-corrected p***	**Weight PBDE 28**	**Weight PBDE 47**	**Weight PBDE 99**	**Weight PBDE 100**	**Weight PBDE 153**
GEC	0.003	0.001	0.016	0.52	0.02	0.35	0.02	0.09
EMI	0.0002	0.0001	0.065	0.40	0.05	0.42	0.02	0.11
ISCI	0.003	0.001	0.036	0.58	0.02	0.25	0.03	0.13
FI	0.002	0.001	0.055	0.53	0.01	0.36	0.02	0.09

Note. BRIEF-P = Behavior Rating Inventory of Executive Function–Preschool Version; GEC = Global Executive Composite (i.e., Overall executive functioning); EMI = Emergent Metacognition Index (i.e., Planning/Organizing and Working Memory); ISCI = Inhibitory Self-Control Index (i.e., Inhibition); FI = Flexibility Index (i.e., Shifting). 4 analyses were performed (FDR-corrected $p \leq .05$). Natural log-transformed T scores were used as outcome variables.

Table S5.

Associations between the weighted BRIEF-P index (Overall executive functioning, Planning/organizing and Working memory, Shifting and Inhibition) and global efficiency of children's brains at 5 years (n =33), and estimated weights for each BRIEF-P scale

Brain region	β	***SE***	***FDR-corrected p***	**Brodmann area/ Hemisphere**	**Weight GEC**	**Weight EMI**	**Weight FI**	**Weight ISCI**
Lingual gyrus	0.01	0.004	0.038	18 / Left	0.03	0.10	0.78	0.09
Inferior occipital gyrus	0.01	0.004	0.028	18 / Left	0.07	0.10	0.44	0.39
Inferior occipital gyrus	0.01	0.004	0.028	19 / Left	0.06	0.12	0.29	0.53

Note. BRIEF-P = Behavior Rating Inventory of Executive Function–Preschool Version; GEC = Global Executive Composite (i.e., Overall executive functioning); EMI = Emergent Metacognition Index (i.e., Planning/Organizing

and Working Memory); FI = Flexibility Index (i.e., Shifting); ISCI = Inhibitory Self-Control Index (i.e., Inhibition). 10 analyses were performed (FDR-corrected $p \leq .05$).

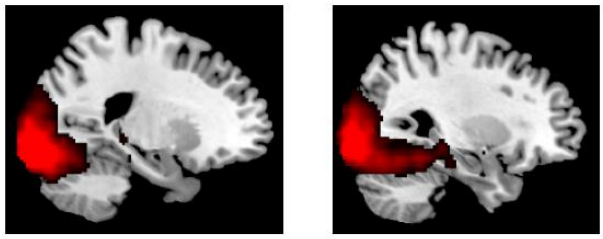
Table S6.

Comparison of participants included in the rs-fMRI analyses (n =34) and those who were excluded from these analyses (n = 13)

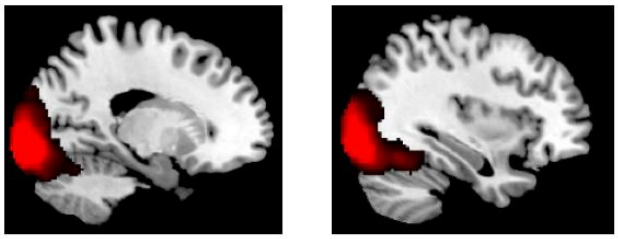
Measure	***Included in rs-fMRI analyses*** Median (IQR)	***Excluded from rs-fMRI analyses*** Median (IQR)	***p***
PBDE 28 (ng/g lipid)	0.75 (1.05)	0.35 (1.12)	0.50
PBDE 47 (ng/g lipid)	9.20 (14.35)	7.80 (16.5)	0.53
PBDE 99 (ng/g lipid)	1.70 (3.23)	2.20 (2.65)	0.55
PBDE 100 (ng/g lipid)	1.80 (2.90)	1.40 (2.40)	0.49
PBDE 153 (ng/g lipid)	2.55 (4.43)	2.90 (2.50)	0.43
BRIEF-P GEC T score	45 (17.5)	64 (17)	0.002
BRIEF-P EMI T score	49 (19.5)	62 (22.5)	0.001
BRIEF-P ISCI T score	46 (15.5)	61 (22)	0.005
BRIEF-P FI T score	47 (18)	57 (20)	0.09

Note. BRIEF-P = Behavior Rating Inventory of Executive Function–Preschool Version; GEC = Global Executive Composite (i.e., Overall executive functioning); EMI = Emergent Metacognition Index (i.e., Planning/Organizing and Working Memory); FI = Flexibility Index (i.e., Shifting); ISCI = Inhibitory Self-Control Index (i.e., Inhibition).

A Lingual gyrus seed



B Inferior occipital gyrus seed (Brodmann area 18)



C Inferior occipital gyrus seed (Brodmann area 19)

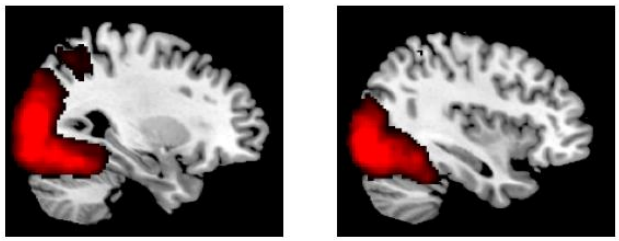


Figure S1. Seed-to-voxel connectivity for the left lingual gyrus and two left inferior occipital gyrus seeds across all subjects (n =34), FDR-corrected p< 0.05. The seeds are connected to areas in the bilateral occipital and temporal cortex and cerebellum.

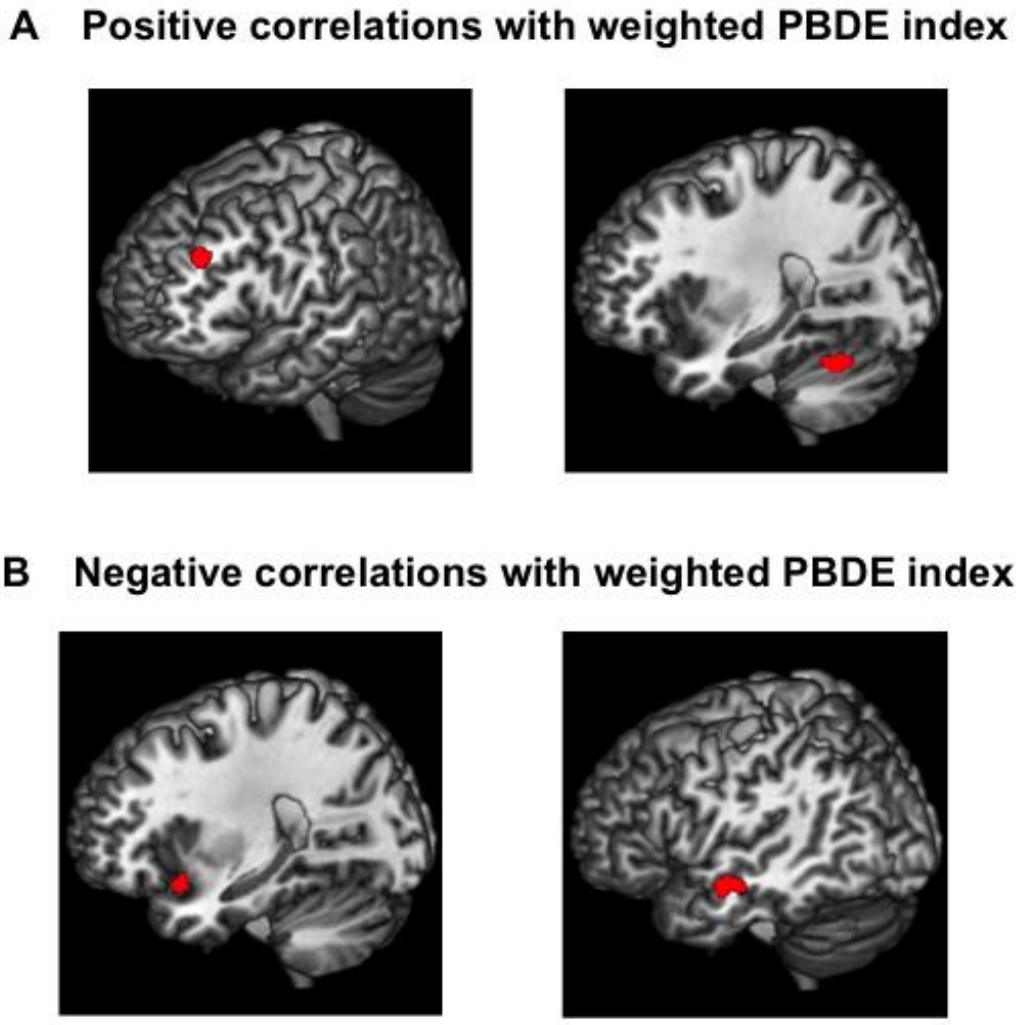


Figure S2. Correlations between the left inferior occipital gyrus seed (Brodmann area 18) and weighted PBDE index, $p < 0.001$, with an extent threshold of 20 voxels. A) positive correlations with the weighted PBDE (comprised of congeners 28, 47, 99, 100, 153) index, showing increased connectivity between the left inferior occipital gyrus seed and the left frontal pole (left panel) and left cerebellum (right panel) in children with higher prenatal PBDE serum concentrations. B) negative correlations with the weighted PBDE index, showing decreased connectivity between the left inferior occipital gyrus seed and the left insula (left panel) and left middle temporal gyrus (right panel) in children with higher prenatal PBDE serum concentrations.

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