HHS Public Access

Author manuscript

Environ Int. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

Environ Int. 2020 January ; 134: 105212. doi:10.1016/j.envint.2019.105212.

Functional Connectivity of the Reading Network is Associated with Prenatal Polybrominated Diphenyl Ether Concentrations in a Community Sample of 5 Year-Old Children: A preliminary study.

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Abstract

Genetic factors explain 60 percent of variance in reading disorder. Exposure to neurotoxicants, including polybrominated diphenyl ethers (PBDEs), may be overlooked risk factors for reading problems. We used resting-state functional magnetic resonance imaging (rs-fMRI) to examine associations between prenatal PBDE concentrations and functional connectivity of a reading-related network (RN) in a community sample of 5-year-old children (N=33). Maternal serum PBDE concentrations (ΣPBDE) were measured at 12.2±2.8 weeks gestation (mean±SD). The RN was defined by 12 regions identified in prior task-based fMRI meta-analyses; global efficiency

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

(GE) was used to measure network integration. Linear regression evaluated associations between ΣPBDE, word reading, and GE of the RN and the default mode network (DMN); the latter to establish specificity of findings. Weighted quantile sum regression analyses evaluated the contributions of specific PBDE congeners to observed associations. Greater RN efficiency was associated with better word reading in these novice readers. Children with higher ΣPBDE showed reduced GE of the RN;ΣPBDE was not associated with DMN efficiency, demonstrating specificity of our results. Consistent with prior findings, ΣPBDE was not associated word reading at 5-years-old. Altered efficiency and integration of the RN may underlie associations between ΣPBDE concentrations and reading problems observed previously in older children.

Keywords

Environmental Exposure; Neuroimaging; fMRI; Polybrominated Diphenyl Ether; Reading; Reading Disorder

1. Introduction

In the United States, roughly 2 million children have a specific learning disability (National Center for Education Statistics 2018); of these, 80 percent have a reading disorder (RD; Lerner 1989; Shaywitz 1998). These children are at increased risk for school failure, depression, anxiety, substance use, and unemployment (National Center on Addiction and Substance Abuse 1999; Cummings et al. 2000; Foorman 2003; McNulty 2003). Although research on the etiology of RD has focused largely on endogenous factors, such as genetics and intelligence (Vellutino et al. 2004; Willcutt et al. 2010), these factors explain only about 60 percent of the variance in RD (Hensler et al. 2010). Exogenous, modifiable environmental factors such as exposure to neurotoxicants, including polybrominated diphenyl ethers (PBDEs), may be overlooked risk factors for RD.

PBDEs are a class of bioaccumulative, halogenated compounds once widely used as flame retardants and still found in consumer products such as fabrics, furniture, electronics, wire insulation, and infant products (Harley et al. 2010; Peltier et al. 2012). Although phased out of use in the U.S. over the last two decades, continued PBDE exposure occurs through release from existing products and biopersistence in the environment. PBDE exposure results from inhalation or ingestion of household dust or contaminated food and accumulates in adipose tissue (Peltier et al. 2012). Studies indicate near universal exposure to PBDEs in the U.S. with 97 percent of American adult samples in the nationally representative National Health and Nutrition Examination Survey (NHANES) having detectable PBDE levels in blood (Harley et al. 2010). Additionally, the detection of selected brominated flame retardants (PBDE47, 99, 100, 153, and PBB153) varied from 87% to 100% in 75 pregnant women (NHANES; (Woodruff et al. 2011). Widespread exposure in pregnant women is concerning, as experimental models demonstrate that PBDEs vary in their ability to cross the placental barrier (Frederiksen et al. 2010) and are increasingly recognized as developmental neurotoxicants (Costa et al. 2014; Dingemans et al. 2011).

Animal models suggest that prenatal PBDE concentrations are associated with structural and functional alterations in the brain (Dingemans et al. 2011) and with impaired learning

(Branchi et al. 2002; Cheng et al. 2009; Dingemans et al. 2011; Rice et al. 2009; Viberg et al. 2006). Prenatal exposure to PBDEs may disrupt brain development through indirect action (e.g., disruption of thyroid hormone) or direct mechanisms including oxidative stress and DNA damage (Costa et al. 2014). PBDEs may interfere with neuronal differentiation (Schreiber et al. 2010), synaptogenesis (Xing et al. 2009), and myelination (Howdeshell 2002), all of which are critically important for healthy brain development (Tau and Peterson 2010). In the first MRI study of the impact of prenatal PBDE concentrations on human brain function, we have recently shown that higher concentrations of PBDEs in prenatal maternal serum are associated with altered global efficiency of brain areas supporting visual attention and impaired executive functioning (de Water et al. 2019). Epidemiologic evidence demonstrates associations between maternal PBDE concentrations and adverse neurodevelopmental outcomes across childhood, including reductions in cognitive capacity (Chen et al. 2014; Eskenazi et al. 2013), language capacity detected as early as age 2 and as late as age 12 years (Ding et al. 2015; Eskenazi et al. 2013), and visual memory in early adolescence (Cowell et al. 2018). In a longitudinal study of reading, the sum concentration of four prenatal PBDEs congeners (47, 99, 100, and 153) was not significantly associated with reading scores at age 5, but an inverse association between PBDE and reading scores was observed in the same children by age 8 (Zhang et al. 2017). Together, these findings suggest that the trajectory of language and visual memory development, and the skills supported by these abilities, such as reading, may be adversely affected by prenatal PBDE exposure, and that this process may unfold over time through a complex cascade of events.

Task-based and resting state functional magnetic resonance (fMRI) studies have identified a left hemisphere reading network (RN) composed of left inferior frontal, temporo-parietal, and occipito-temporal regions that support normal reading (Koyama et al. 2011; Martin et al. 2015). Adults and children with disordered reading show altered activation of these regions during reading and reading-related tasks (Richlan et al. 2009; Willcutt et al. 2010) and disrupted functional connectivity of these circuits at rest (Koyama et al. 2013). Further, in graph theoretical analyses of the RN, greater network efficiency associated with better reading skill in typically developing 8–14 year old children (Smith et al. 2018). Reduced network efficiency among adults with reading disorder has been documented across several imaging modalities, including task-based fMRI, magnetoencephalography, and electroencephalography (Dimitriadis et al. 2013; Fraga Gonzalez et al. 2016; Smith et al. 2018; Vourkas et al. 2011). Increased network efficiency is thought to reflect greater integration between spatially disparate but functionally connected brain regions that contribute to reading skill.

Given the difficulties inherent in conducting MRI with young children, few studies have examined the connectivity of the reading circuit in very young children who are in the early stages of learning to read (i.e., 5–6 years of age), but the extant literature points to structural and functional connectivity of the reading circuit in young children. One study reported that increases in functional connectivity between left inferior parietal cortex (IPC) and inferior frontal cortex (IFC) during a phonological task paralleled increases in reading skill from 5 to 8-years-old (Yu et al. 2018). Maternal reading fluency was associated with connectivity of the future reading circuit during a story-listening task in 4 year-old girls (Horowitz-Kraus et al. 2018) as well as with functional connectivity between a language network and regions

that support reading in 4 year-old girls (Greenwood et al. 2019). In addition, studies of structural connectivity suggest that reduced fractional anisotropy (FA) in white matter tracts linked to reading ability (including the arcuate fasciculus [AF], and the superior and inferior longitudinal fasciculi [SLF, ILF]) characterize children at risk for reading problems, and that increases in FA parallel increases in reading skill from 5 to 8 years of age (Vanderauwera et al. 2017; Wang et al. 2017).

The current study represents a first step in examining associations between prenatal PBDE concentrations, emerging reading skills, and resting state functional connectivity within the brain networks that support reading, in a sample of 5-year-old children enrolled in a longitudinal birth cohort study. We designed the current study to examine: 1) RN connectivity in a community sample of 5-year-old children; 2) associations between RN connectivity and reading skill (i.e., Word Identification); and 3) whether maternal serum PBDE concentrations were associated with altered RN connectivity and reading skill. We also explored which PBDE congeners most contributed to altered RN connectivity and reading skill. Given prior task-based fMRI and structural connectivity studies (Vanderauwera et al. 2017; Wang et al. 2017; Yu et al. 2018), we hypothesized that young children would show resting state connectivity between RN regions (identified in studies of adults and school age children) even before the onset of formal reading instruction and that this connectivity would associate with reading skill. Given that significant associations between prenatal PBDE and reading skill have been detected at age eight, but that associations were not significant at age five (Zhang et al. 2017), we hypothesized that PBDE concentrations would be associated with RN connectivity at age 5 but not with reading skill at age 5. Last, to assess the specificity of these potential findings, we evaluated associations between prenatal PBDE concentrations and connectivity within the Default Mode Network (DMN), a key network that is evident early in development and is not associated with PBDE or reading skill. We hypothesized that exposure would not be associated with connectivity within the DMN.

2. Methods

2.1 Participants

Forty-seven children were selected from an ongoing longitudinal birth cohort of 316 mother-child pairs (Horton et al. 2013) to participate in a single-day visit including an MRI scan and a reading assessment. The sample of 47 subjects included in this pilot study were enrolled from the parent cohort during years 2009–2010. This sample includes all participants who 1) were between 5–6 years of age, 2) completed their 5 year study visit, 3) had available maternal blood sample for PBDE analysis, and 4) responded to recruitment strategies implemented in the study (i.e., invitation by research assistant during 5 year visit and/or saw a flyer describing the study in the study office). Forty-two children completed the functional scan. Children were excluded from statistical analyses due to excessive head motion during the functional (n=4 with less than 3 minutes of data with <0.5 mm relative framewise displacement) or structural (n=4 with visible motion artifact in the MPRAGE) scan or extreme PBDE values more than five standard deviations above the mean (n=1). Thus, 33 children with complete data were included in the current analyses. The Institutional Review

Boards of Columbia University, the Icahn School of Medicine at Mount Sinai and the Centers for Disease Control and Prevention (CDC) approved the study. Written informed consent was obtained from all mothers of participating children.

2.2 PBDE Measurement

PBDEs were measured in maternal serum collected by sterile venipuncture at a regularly scheduled prenatal blood draw during the first or second trimester of pregnancy (median = 12.2 weeks gestation, standard deviation = 2.8 weeks). Complete details pertaining to the sample collection and analysis of PBDE congeners in this cohort have been previously published (Horton et al. 2013). To avoid contamination, blood was placed in PBDE-free silicon-coated vacutainers provided by the Centers for Disease Control and Prevention (CDC). PBDEs and serum lipids (total triglycerides and cholesterol) were measured at the CDC using isotope dilution high resolution mass spectrometry on a MAT95XP DFS (ThermoFisher; Bremen, Germany) and 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 available in prior publications (Sjodin et al. 2004a). PBDE congeners 17, 28, 47, 66, 85, 99, 100, 153, 154, 183, and 209 were measured. Consistent with prior studies (Horton et al. 2013) congeners with concentrations > limit of detection (LOD) in at least 80% of participants included congeners 47, 99, 100 and 153 (% > LOD = 100%, 84.8%, 87.9% and 100%, respectively). Median LODs for PBDE 47, 99, 100, and 153 were 1.20, 0.70, 0.50, and 0.50 ng/g lipid, respectively. Concentrations below the LOD were substituted by the LOD divided by the square root of 2 (Hornung 1990) and PBDE concentrations were lipid adjusted as described previously (Sjodin et al. 2004b). For statistical analyses, we considered PBDE 47, 99, 100, and 153 and computed the ΣPBDE representing the sum of the lipid-adjusted concentrations of congeners 47, 99, 100 and 153.

2.3 Reading Assessment

A comprehensive reading assessment was administered by a trained research assistant on the day of the visit, prior to the MRI scan. Administration and scoring were reviewed by a licensed psychologist. Children completed measures of reading readiness (Woodcock Reading Mastery Test [WRMT-2], Letter Identification; Woodcock 1998); and basic reading skill (WRMT-2, Word Identification; Woodcock 1998). In addition, the protocol assessed cognitive skills that might contribute to the acquisition of reading skill: verbal learning (Wide Range Assessment of Memory and Learning, 2nd edition, Sound Symbol Learning; Sheslow 2003); Woodcock Johnson Test of Cognitive Abilities, 3rd edition, Visual Auditory Learning; Woodcock et al. 2001) and phonological processing (Comprehensive Test of Phonological Processing, 2nd edition, Elision and Sound Matching; Wagner et al. 2013). These measures were intended for analysis in a separate study of brain-behavior associations in very young children, who presumably would be in the early stages of learning to read. A measure of intellectual functioning, Wechsler Preschool and Primary Scales of Intelligence (Wechsler 2012), including verbal and non-verbal IQ was also available from the parent study. The current study focused on associations between brain connectivity and basic reading skill and, thus, analyzed only word reading as measured by performance on the Word Identification subtest. Letter Identification was not examined due to lack of variability

(<10 percent of the participants had performance at 1 standard deviation below the mean). Word Identification had sufficient variability, but was not normally distributed. Probability-probability plots demonstrate normal distribution of the Word Identification residuals, therefore it was included as a continuous variable in parametric tests.

2.4 Resting State fMRI Data Acquisition and Preprocessing

Five minutes of resting state fMRI data were acquired on a 3T Philips Achieva scanner. Data were acquired with an 8-channel head coil using a single-shot EPI Gradient Recalled (GR) sequence (TR = 2000ms, TE = 25 ms, 150 volumes, 44 slices, no slice gap, sequential ascending slice acquisition, flip angle = 72°, acquisition matrix =80x80, field of view = 24cm, voxel size = 3mm3). For registration purposes two anatomical MPRAGE scans were collected (duration: 3 min 46 s per scan; TR =10 ms, TE = 4.936 ms, 165 slices, slice thickness = 1 mm, slice gap = 1mm flip angle = 8°, acquisition matrix =256 x 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.

Data were preprocessed consistent with prior work (de Water et al. 2019) using FSL's FEAT Version 6.00 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The first two volumes were discarded to allow for the scanner to come to steady state. Preprocessing included realignment using MCFLIRT (Jenkinson et al. 2002) slice-timing correction, non-brain removal using Brain Extraction Tool (BET; Smith 2002) and spatial smoothing using a 6mm full-width half-maximum Gaussian kernel. Functional to T1 registration was performed using FLIRT (Jenkinson et al. 2002; Jenkinson and Smith 2001). Given the participants' young age, we used a study-specific template (average of all participants' structural images), which we registered to standard space (MNI-152) using FNIRT (Andersson et al. 2007a; 2007b). Participants' functional and structural images were then non-linearly registered to this MNI-space study-specific template.

2.5 First Level Models and Motion Correction.

First level general linear model analyses were run using the CONN fMRI Functional Connectivity Toolbox v 16.b (http://www.nitric.org/projects/conn/). Anatomical CompCor (aCompCor; Behzadi et al. 2007) was used to estimate and regress out white matter and cerebral spinal fluid (CSF) noise (five principal components). Band pass filtering was utilized (threshold=0.008–0.09 Hz). Six motion parameters and their first order derivatives were included as regressors to further reduce motion artifact (Friston et al. 1996). Volumes exceeding >0.5mm relative FD or frame-to-frame changes in global signal above a z-value of 3 were regressed out (i.e., motion scrubbing).

2.6 Reading Network Connectivity Measures

The reading network (RN) was defined by 12 regions of interest (ROIs; Table 1, Figure S3) identified in a prior task-based fMRI meta-analysis, and used in prior resting state fMRI studies of reading (Koyama et al. 2013). For control analyses, the DMN was defined by 9

ROIs (Table 1; Laird et al. 2009; Power et al. 2011). ROIs (6mm spheres) were made in MARSBAR (Brett et al. 2002) around the peak coordinates from these prior studies.

The mean of all pairwise correlations among each network's ROIs was used to summarize average network connectivity. Network efficiency was measured by global efficiency (GE), a graph theoretical measure of integration in the brain that reflects the average inverse value of the path length from each region of a network to all others; thus, higher GE values indicate greater network efficiency (Latora and Marchiori 2001; Rubinov and Sporns 2010). We evaluated GE rather than other graph metrics because we were specifically interested in within-network integration of the RN. GE was calculated in CONN separately for the RN and DMN for each participant using a fixed threshold (cost > 0.15) commonly used in graph theoretical analyses. In prior work, global efficiency shows excellent test-retest reliability at a 0.15 cost threshold (r's 0.90–0.95; Whitfield-Gabrieli and Nieto-Castanon 2012) in adults and in children as young as 4 years of age (Paldino et al. 2017). To ensure robustness of results, consistent with a prior study (Sheffield et al. 2016) average GE of the RN and of the DMN was evaluated across two additional cost thresholds that varied in small increments from the initial fixed value (0.125, 0.15, 0.175).

2.7 Statistical Analyses

Distributions of dependent and independent variables were examined (Figure S2). To address assumptions of parametric tests, the distribution of the residuals was examined through probability-probability plots for non-normally distributed variables. If these residuals were normally distributed, variables were not transformed. Cases with missing data were excluded from analyses. All tests were two-tailed and significance levels were set at $p < .05$.

A one-sample t-test was used to test whether average RN connectivity differed significantly from zero, i.e. to establish that this putative RN, identified previously in adults and older children, is also evident in this sample of young children. In addition, a paired sample t-test was used to test whether average RN connectivity differed significantly from that of a randomly generated 'network' (twelve 6mm spheres, centered on randomly generated peak coordinates, Table S1). Three linear regression analyses were then used to examine associations between GE of the RN, Word Identification, and ∑PBDE. Models included a priori a set of known potential confounders of brain connectivity (age, sex, birthweight, socio-economic status [SES], mean head motion, and global correlation) and of reading (sex, birthweight, SES, and Verbal IQ [VIQ]; (Hackman and Farah 2009; Simos et al. 2014; Uddin et al. 2011; Walhovd et al. 2012; Zuo et al. 2010). Specifically, (1) GE of the RN was tested as a predictor of Word Identification (age normed scores), controlling for sex, birthweight, reported annual household income (<$25,000; $25,000 – $50,000; >$50,000; as a proxy for SES), VIQ, mean head motion, and global correlation. (2) ∑PBDE was tested as a predictor of RN GE, controlling for age, sex, birthweight, reported annual household income, mean head motion, and global correlation. (3) ∑PBDE was tested as a predictor of Word Identification, controlling for sex, birthweight, reported annual household income, and VIQ. Control analyses evaluated associations between GE of the DMN and Word Identification or ∑PBDE to examine specificity of associations to the RN. To address the

effect of two potential outliers (one in PBDE 47 and one in PBDE 47, 100, and 153), an additional control analysis evaluated the association between average GE of the RN and ∑PBDE concentrations with the two potential outlier values manually replaced by the next highest score. All linear regression analyses were checked for normal distribution of residuals (Figure S1). Results of the regression analyses are presented as $\beta_{unstandardized}$ (β_u) and $\beta_{standardized}$ (β_{st}).

Associations between PBDE concentrations and Word Identification or GE of the RN were further evaluated with weighted quantile sum (WQS) regression, controlling for sex, birthweight, and mean motion. This method was employed to estimate associations between co-exposure to the four highly correlated PBDE congeners (PBDE 47, 99, 100 and 153) and Word Identification or GE of the RN. WQS can assess the overall impact of the mixture and identify the contribution of each individual congener to the overall impact (Carrico 2015; Czarnota et al. 2015). The WQS index was constructed by summing the ranked concentrations (quintiles) of each individuals' exposures multiplied by the relative strength of each predictor variable's association with the outcome (Word Identification or GE). A higher WQS index reflects higher exposures to PBDEs related to the outcome, while a lower WQS index indicates either low exposures, or that the WQS index is unrelated to the outcome. Estimating the WQS index was performed across 100 bootstrap ensembles, thereby minimizing vulnerability to collinearity among predictors, and resulting WQS indices were tested in a traditional linear framework, as: $g(\mu) = \beta_0 + \beta_1\ WQS + z'\varphi$. G($\mu$) reflects an identity link function, given the continuous nature of the graph theory outcomes, β_0 reflects the model intercept, β_1 indicates the association between the WQS index and the outcome, and z' indicates a vector of covariates. All WQS models were tested using negative and positive constraints. Sensitivy analyses were conducted to test the resolution of quantiling using tertiles and quartiles.

3. Results

3.1 Participants

Thirty-three children (54% female; 82 % Hispanic, 12% Non-Hispanic White, 3% African-American, 3% Other) were included in the current analyses. Children included in the MRI study did not differ from those in the larger cohort in demographic characteristics or PBDE exposure (Tables 2 and 3, respectively). Neither individual PBDE congener concentrations nor reading levels differed between those who were (n=33) and were not (n=14) included in the rs-fMRI analyses (Table S2). The median age of children included in the study was 5.0 years. Children placed in the average range on Word Identification (mean=95.6; SD=15.3) relative to national norms (mean=100; SD=15). Prenatal PBDE concentrations are presented in Table 3. Concentrations of these four congeners were significantly intercorrelated (Spearman r's 0.41 – 0.92, all p's ≤ .015) and did not differ significantly between children included in these analyses and those in the parent cohort.

3.2 Reading Network

Among these participants, average RN connectivity was significantly greater than zero ($t(32)=9.478$, $p<.0001$) and significantly greater than the average connectivity of a randomly

generated ‘network’ (t(32)=4.632, p<.0001). Greater GE of the RN (mean=.274; SD=0.042) was associated with higher Word Identification scores (β_u =205.55, β_{st}=0.57, 95% confidence interval β_{st} [CI]: 0.001, 1.13; t(27)=2.09, p=.050; Figure 1b). Greater GE of the RN was similarly associated with higher Word Identification scores averaged across three cost thresholds (β_u=233.1, β_{st}=0.57, CI β_{st}: 0.03, 1.11; t(27)=2.21, p=.039; Table S3). GE of the DMN was not associated with performance on Word Identification (β_u=101.56, β_{st}=0.21, CI β_{st}: −0.26, 0.68; t(27)=0.938, p=.360).

3.3 PBDEs and Reading

Greater prenatal ΣPBDE was associated with lower adjusted GE of the RN at a fixed cost threshold of 0.15 (β_u=−0.001, β_{st}=−0.55, CIβ_{st}: −1.01, −0.09; t(30)=−2.50, p=.02; Figure 1c), indicating that a 10 ng/g lipid increase in ΣPBDE concentration was associated with .01 lower GE. ΣPBDE was similarly associated with lower average adjusted GE of the RN averaged across three cost thresholds (β_u=−0.001, β_{st}=−0.68, CIβ_{st}: −1.13, −0.24; t(30)= −3.19, p=.004; Table S4). This association remained significant after adjusting values of two potential outliers (β_u=−.001, β_{st}=−0.42, CIβ_{st}: −0.27, −0.003; t(30)=−2.539, p=.018). ΣPBDE did not associate with GE of the DMN (β_u<0.001, β_{st}=0.16, CIβ_{st}: −0.51, 0.82; t(30)=0.479, p=.636) or with performance on Word Identification (β_u=−0.20, β_{st}=−0.24, CIβ_{st}: −0.84, 0.35; t(27)=−1.60, p=.124).

Using the WQS mixtures approach, the weighted PBDE index was inversely associated with GE of the RN. For every quintile-increase in the exposure index, a −0.01 (95% confidence interval: −0.02, −0.003) reduction in reading network GE was detected (p=.006). Congeners 47 and 153 particularly contributed to GE (weight> 79% and 16%, respectively; Table S5). The contributions of PBDE congeners 99 and 100 to this association were negligible (weights ≤ 3%). The PBDE mixture was not associated with performance on Word Identification (β_u=−0.0001, p=.40). Models including tertiles and quartiles yielded similar results (Table S6). Using positive constraints yielded no significant results.

4. Discussion

To our knowledge, this is the first MRI study to examine associations between prenatal PBDE concentrations and architecture of the RN. In this community sample of 5-year-old children, we detected connectivity in the RN, and increased GE of the RN was associated with better word reading. Consistent with our hypotheses, higher prenatal PBDE concentrations were associated with decreased GE of the RN. Increased prenatal PBDE concentrations, however, were not associated with reading ability among these five-year-old children. This pattern of results suggests that prenatal PBDE exposure may affect the trajectory of individual reading achievement in part by altered functional architecture of the RN, which onsets before the manifestation of overt reading deficits. Notably, similar results were observed across two different statistical approaches; traditional linear regression using the sum of four PBDEs and WQS regression representing a weighted index of PBDEs.

Global efficiency of the RN associated positively with word reading, and inversely associated with prenatal PBDE concentrations. Higher GE is thought to reflect greater integration within a network or across the brain (Rubinov and Sporns 2010). In the current

study we examined GE within the RN. Our findings are consistent with prior findings in older children suggesting greater efficiency of the RN associates with better reading, extending our understanding of the efficiency of the RN to younger ages than previously studied. Further, we detected a significant inverse association between prenatal PBDE concentrations and GE of the RN, suggesting that exposure alters network integration. Such integration may rely on optimal pruning, synaptogenesis, and myelination, which is programmed during fetal brain development (Tau and Peterson 2010) and thus is particularly vulnerable to prenatal neurotoxic exposure. Consistent with this view, experimental models point to reduced neuronal cell differentiation and altered synaptogenesis and myelination after PBDE exposure (Schreiber et al. 2010; Viberg et al. 2006; Xing et al. 2009) Follow-up analyses revealed that this association was driven mainly by PBDE-47, consistent with experimental evidence demonstrating that PBDE-47 reduces long-term potentiation in mouse hippocampus (Dingemans et al. 2007). Further, among 9- and 14-year old children enrolled in a birth cohort study, sustained exposure to PBDEs during childhood were associated with reduced visual memory and attention skills (Cowell et al. 2018), both of which may contribute to acquisition of reading skill. These associations were strongest for PBDE-47.

Prenatal PBDE concentrations were not associated significantly with word reading at age 5. This result is consistent with prior findings that point to associations between prenatal PBDE exposure and reduced reading skill at age 8 but *not* age 5 (Zhang et al. 2017). Considered in the context of our finding that prenatal PBDE concentrations are inversely associated with architecture of the RN, this pattern suggests that the action of PBDE on the developing brain may lead to downstream reading problems. The influence of PBDE on the developmental trajectory of reading skill may not be detected behaviorally at very young ages. This underscores the need to use functional imaging techniques to study effects of neurotoxicants on trajectories of child brain development, prior to the onset of learning and achievement problems.

Nodes of the distributed RN exhibited significant within-network connectivity, and increased GE of the RN were associated with better reading skill in 5-year-old children. These findings extend the small extant literature examining task and structural connectivity of the RN in young children to include connectivity at rest. Prior studies report that increases in reading skill from age 5 to 8 are paralleled by increasing functional connectivity between left IPC and left IFG, posterior occipitotemporal cortex, and angular gyri during a phonological task (Yu et al. 2018) and increasing fractional anisotropy of the AF, SLF, and ILF (Wang et al. 2017). Moreover, infants at risk for dyslexia already show reduced fractional anisotropy of the AF that is associated with early language skill (Langer et al. 2017). These findings suggest that environmental influences, such as prenatal exposure to neurotoxicants, may have substantial effects on the maturation of this network beginning in utero.

Our study has several limitations. First the sample size is small relative to neuroimaging studies of adults, and may have led to overfitting of models; well powered studies with larger sample sizes are required to confirm these findings. Given the relatively small sample size, non-significant findings between prenatal PBDE and reading skills may represent a

Type II error. Although animal research has demonstrated associations between gestational exposure to PBDEs and changes in sexually dimorphic brain regions (Faass et al. 2013), with effects on sexual maturation that persist into adolescence (Lilienthal et al. 2006), our sample size does not allow us to assess sex-specific effects of PBDE exposure on reading. Further, our PBDE biomarker acts only as a proxy for fetal exposure during gestation and does not account for sustained exposure in childhood, and we did not have a measure of postnatal exposure in these children. Both prenatal and postnatal periods may be vulnerable to developmental neurotoxicity of PBDEs (Cowell et al. 2018), however in our prior work (Cowell et al, 2018) we report that concentrations of PBDE in cord plasma (representing prenatal exposure) and plasma from blood samples taken at postnatal age 2 are not correlated (Spearman's ρ: PBDE-47: −0.03, PBDE-99: 0.04, PBDE-100: 0.21, PBDE-153: 0.26). Last, we were unable to assess any potential unique effects of children's bilingualism on their reading or brain function. Future studies should include larger sample sizes, expand follow-up to include longitudinal assessments of the exposure and the outcome, and address sex-specific associations. That we obtain significant results using a range of cost thresholds for graph measures, and using two different statistical approaches supports the robustness of our findings, despite the small sample size.

In summary, our findings show that in children as young as 5 years of age connectivity within the RN is present, and increased GE of this network is associated with better word reading. We have also demonstrated in this preliminary study that GE of this network appears vulnerable to prenatal PBDE exposure. Word reading was not associated with prenatal PBDE concentrations; however, it seems likely that PBDE-related alterations of network architecture may underlie downstream effects of prenatal PBDE on reading, as has been shown in the few prior studies of such exposure. Our findings further underscore the importance of examining prenatal and early-life exposure to environmental neurotoxicants when studying etiologic factors in reading disorder, and the potential importance of identifying neurobiological markers that influence and predict cognitive and behavioral outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

This work was supported by funding from the National Institute for Environmental Health Sciences (K23ES026239 to A.E.M., R00 ES020364 to M.K.H; R21 ES016610-01 to R.W.)

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Highlights

- Polybrominated Diphenyl Ethers (PBDEs), used as flame retardants, cross the placenta
- Prenatal PBDE exposure predicts reduced efficiency of the brain's reading network
- Efficiency of the brain's reading network predicts word reading in 5 year-olds
- Prior findings show PBDE exposure predicts reading problems in 8 year-old children
- PBDE may represent an overlooked factor in the etiology of reading problems

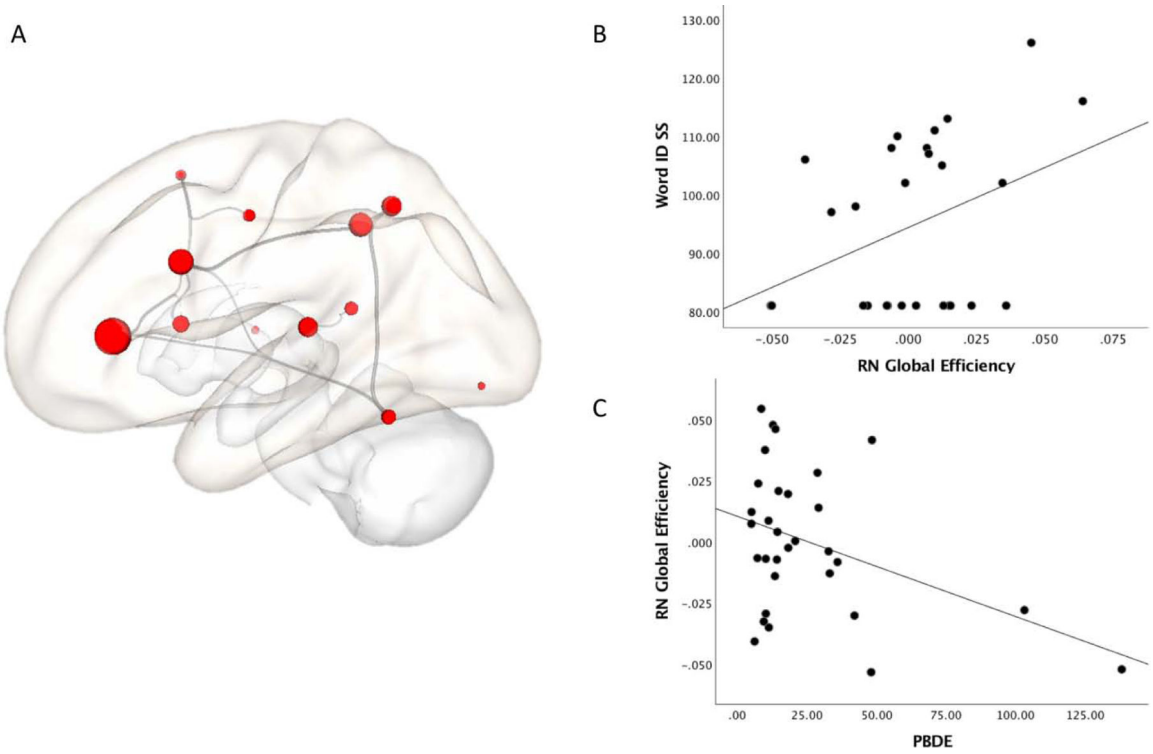

Figure 1.

Reading network (RN) connectivity, sum concentration of polybrominated diphenyl ethers (ΣPBDE ng/g lipid), and word reading. A) Regions of interest comprising the RN are depicted by red circles. The relative size of the circle reflects the global efficiency (GE) of the region (N=33). Scatterplots show: B) Positive associations between GE of the RN and standard scores on the Word Identification subtest of the Woodcock Reading Mastery Test (β_u=205.55, t(27)=2.09, p=.050), and C) Inverse associations between GE of the RN and ΣPBDE in maternal blood serum collected during the first half of pregnancy (β_u=−0.001, t(30)=−2.46, p=.022). SS = Standard score.

Table 1.

Regions of interest (ROI) defining the Reading Network (RN) and Default Mode Network (DMN).

ROI	Network	x	y	z
IOG	RN	−25	−87	−10
FFG	RN	−48	−57	−20
STG	RN	−53	−31	9
TPG	RN	−59	−45	15
IPL	RN	−40	−48	42
IPS	RN	−30	−58	48
PCG	RN	−48	−12	45
SMA	RN	−4	10	58
IFGop	RN	−51	10	10
IFGtr	RN	−48	32	6
MFG	RN	−44	10	30
THAL	RN	−10	−14	8
MPFC	DMN	1	55	−3
L AG	DMN	−44	−65	35
R AG	DMN	52	−59	36
PCC	DMN	−3	−49	13
PCUN	DMN	6	−59	35
ACC	DMN	−3	42	16
L MTG	DNM	−46	−61	21
R MTG	DMN	43	−72	28
L MFG	DMN	−35	20	51

Coordinates (x,y,z) represent peaks from prior studies. 6mm spheres were defined in MARSBAR around these peak co-ordinates. Abbreviations; L = left, R = right; ACC = anterior cingulate cortex, AG = angular gyrus, FFG = fusiform gyrus, IFGop = inferior frontal gyrus pars opercularis, IFGtr = inferior frontal gyrus pars triangularis, IPL = inferior parietal lobule, IPS = intraparietal sulcus, IOG = inferior occipital gyrus, MFG = middle frontal gyrus, MPFC = medial prefrontal cortex, MTG = middle temporal gyrus, PCC = posterior cingulate cortex, PCG = precentral gyrus, PCUN = precuneus, SMA = supplementary motor area, THAL = thalamus, TPJ = temporoparietal junction.

Table 2.

Demographic characteristics of 33 children included in MRI study.

	Participants with reading and MRI data (n=33)*	Participants with no MRI or reading data (n=259)**	*p-value*
Characteristic	**Mean (SD) or Median (IQR) or %**	**Mean (SD) or Median (IQR) or %**	
ΣPBDE (ng/g lipid, median)	12.30 (21.27)	11.30 (19.03)	.91
Sex (% female)	54.5%	38.6%	.11
Birth Weight (grams)	3219.8 (745.4)	3351.4 (489.2)	.19
Household Income (USD)			
< 25K	69.7%	60.6%	.20
25–50K	15.2%	10.0%	
> 50K	15.2%	29.3%	
VIQ	92.1 (15.1)	100.5 (19.7)	.03
Maternal Education			
< HS/GED	15.2 %	15.8%	.59
HS/GED	30.3%	23.6%	
1–4 years college	45.5%	42.1%	
> college	9.1%	17.8%	

Abbreviations; MRI = magnetic resonance imaging, SD = standard deviation, IQR = interquartile range, HS = high school, GED = General Educational Development, ΣPBDE - sum serum concentrations of polybrominated diphenyl ethers, VIQ = verbal intelligence quotient from Wechsler Preschool and Primary Scale of Intelligence.

*Missing; Birth weight (1), VIQ (3)

**Missing; Sex (32), Birth weight (32), VIQ (204), Maternal Education (2)

***Differences between two groups were compared using Student's T-test or Chi-Squared.

Table 3.

Distribution of PBDE concentrations (ng/g serum lipid) measured in maternal serum concentrations collected during pregnancy

	Subjects with resting state fMRI data (*n* = 33)	Full cohort (*n* = 259) *	*p-value***
PBDE congener (ng/g lipid)	**Median (range)**	**Median (range)**	
PBDE 47	9.20 (2.30–83.4)	7.70 (0.85–336.0)	.50
PBDE 99	1.70 (0.42–1.8)	1.40 (0.28–107.0)	.66
PBDE 100	1.80 (0.35–35.4)	1.60 (0.21–56.5)	.93
PBDE 153	2.40 (0.80–37.3)	3.00 (0.21–131.0)	.47

Abbreviations; PBDE = Polybrominated Diphenyl Ether.

* All participants, minus the participants included in the analysis.

** Differences in PBDE concentrations in MRI sample versus the full cohort were compared using Kruskal-Wallis tests.