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Prenatal and postnatal polybrominated diphenyl ether (PBDE) exposure and measures of inattention and impulsivity in children

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Abstract

Exposure to polybrominated diphenyl ethers (PBDEs) during fetal development may be associated with deficits in attention and impulse control. However, studies examining postnatal PBDE exposures and inattention and impulsivity have been inconsistent. Using data from 214 children in the Health Outcomes and Measures of the Environment (HOME) Study, a prospective pregnancy and birth cohort with enrollment from 2003–2006 in the Greater Cincinnati Area, we investigated the relationship of both prenatal and postnatal PBDE exposures with attention and impulse control. Serum PBDEs were measured at 16±3 weeks of gestation and during childhood at 1, 2, 3, 5, and 8 years. We assessed children's attention and impulse control using the Conners' Continuous Performance Test-Second Edition (CPT-II) at 8 years. We used multiple informant models to estimate associations of repeated PBDE measures with inattention and impulsivity. There was a

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pattern of associations between PBDEs and poorer performance on CPT-II measures of attention. For BDE-153, adverse associations extended to exposures at preschool and kindergarten ages; ten-fold increases in exposure were associated with higher omission errors (BDE-153 at 3 years: $\beta=4.0$ [95% CI: -2.4, 10.4]; at 5 years: $\beta=4.6$ [95% CI: -2.8, 12.0]; at 8 years: $\beta=4.1$ [95% CI: -3.4, 11.5]). Longer hit reaction times, indicated by the exponential part of the hit reaction curve, were also observed with 10-fold increases in BDE-153 during the prenatal period and throughout childhood (Prenatal: $\beta=15.0$ milliseconds (ms) [95% CI: -15.8, 45.8]; 5 years: $\beta=20.6$ ms [95% CI: -20.8, 61.9]; 8 years: $\beta=28.6$ ms [95% CI: -12.1, 69.4]). Significant impairment in discriminability, as indicated by detectability (d'), between targets and non-targets was also noted with 5 and 8-year PBDE concentrations. Associations between PBDEs and inattention significantly differed by child sex, with males performing more poorly than females with regard to omission errors and measures of reaction times. Collectively, these results do not strongly support that PBDEs are associated with poorer impulse and attention control among 8 year old children. However, there may be a possible relationship between prenatal and concurrent PBDEs and inattention, which requires additional research.

Keywords

Polybrominated diphenyl ether (PBDE); neurobehavior; inattention; impulsivity; attention; impulse control

1. Introduction

Since the 1970s polybrominated diphenyl ethers (PBDEs) were widely used as flame retardant additives in the manufacturing of polyurethane foams, furniture, car seats, and electronic equipment. PBDEs are not covalently bound to product materials, enabling them to escape material surfaces. In addition to ubiquitous exposure among pregnant women, this poses a particular risk for infants and young children who have a lower breathing zone than adults, often play on floors, and have frequent hand-to-mouth behaviors, all of which increases exposure to PBDEs in the air and house dust. These factors, in conjunction with PBDEs being transferred via the placental exchange and breast milk, have resulted in infants and toddlers having the higher PBDE concentrations compared with older children and adults (Schechter et al., 2005; Toms et al., 2008; Toms et al., 2009). While PBDEs have been phased out from the U.S. market, products containing them are still widely used in the home and office environment. With half-lives of up to 12 years in humans (Geyer et al., 2004), PBDEs remain a group of major environmental contaminants with potential health concerns.

PBDEs are neurotoxicants and early life exposure has been associated with adverse neurobehavior. PBDE exposure during fetal brain development is associated with deficits in cognitive function and behavior, including lower scores for full scale IQ (FSIQ), language, memory, reading, and executive function, as well as increased hyperactivity and attention problems (Chen et al., 2014; Cowell et al., 2015; Ding et al., 2015; Eskenazi et al., 2013; Gascon et al., 2011; Herbstman et al., 2010; Roze et al., 2009; Sagiv et al., 2015; Shy et al., 2011; Vuong et al., 2016; Zhang et al., 2017). In addition, postnatal exposure to PBDEs has also been associated with poorer FSIQ, slower processing speeds, inattention, and poorer

social skills, lending evidence to support that PBDE neurotoxicity also occurs during childhood, when the brain is continuing to undergo synapse pruning and myelination (Adgent et al., 2014; Eskenazi et al., 2013; Gascon et al., 2011; Hoffman et al., 2012; Sagiv et al., 2015).

Several studies have reported increased inattention and impulsivity among children from prenatal and postnatal exposures to PBDEs (Cowell et al., 2015; Eskenazi et al., 2013; Gascon et al., 2011; Hoffman et al., 2012; Roze et al., 2009). However, only two studies have examined PBDEs and inattention and impulsivity as assessed by the Conners' Continuous Performance Test-Second Edition (CPT-II) and reported differing results (Kicinski et al., 2012; Sagiv et al., 2015). To help solve this discrepancy and further our understanding of the impact of PBDE exposures on inattention and impulsivity, we examined both prenatal and postnatal PBDEs in relation to self-regulatory behaviors: attention and impulse control using the CPT-II.

2. Methods

2.1 Study population

From 2003–2006, the Health Outcomes and Measures of the Environment (HOME) Study, an ongoing prospective pregnancy and birth cohort, enrolled 468 pregnant women at 16±3 weeks of gestation from nine prenatal clinics in the greater Cincinnati, Ohio area. Details regarding inclusion and exclusion criteria, measurement of chemicals, and neurobehavioral assessments can be found elsewhere (Braun et al., 2017). The present study included 214 singletons who had measured PBDEs (prenatal and postnatal) and a CPT-II assessment at 8 years. The institutional review boards at the Cincinnati Children's Hospital Medical Center and the Centers for Disease Control and Prevention (CDC) approved this study.

2.2 PBDE exposure assessment

Blood samples were collected for the measurement of PBDEs from pregnant women at enrollment and their children at 1, 2, 3, 5, and 8 years. Sera were separated and stored at -70 °C until measurement of PBDE congeners (-17, -28, -47, -66, -85, -99, -100, -153, -154, -183, and -209 [postnatal only]) using gas chromatography/isotope dilution high-resolution mass spectrometry (Jones et al., 2012; Sjödin et al., 2004). Details about PBDE measurements, including quality assurance, procedures for measurements below the limit of detection, and lipid adjustment can be found elsewhere (Vuong et al., 2017). Briefly, for PBDE concentrations that were less than the limit of detection (LOD), values were substituted with LOD/ 2 (Hornung and Reed, 1990). Standardization of PBDE concentrations to serum lipid levels is still considered an appropriate method for examining PBDEs and has been reported to perform well in simulation studies (Chevrier, 2013; O'Brien et al., 2016). Detection frequencies of BDE-28, -47, -99, -100, and -153 by child age can be found in Supplemental Table S1. Limited serum availability at 1–3 years resulted in lower sample sizes at these ages. Of the children who completed the CPT-II (details below), a total of 214 had prenatal serum PBDE concentrations available and 82, 66, 66, 136, and 185 had PBDE concentrations at 1, 2, 3, 5, and 8 years, respectively. To increase our power, we applied multiple imputation using the Markov Chain Monte Carlo (MCMC)

method using SAS 9.4 to estimate missing PBDE concentrations for children who had at least one measurement of childhood PBDEs. Rather than estimating a single PBDE concentration for each missing time point, multiple imputation replaces the missing concentration with a set of plausible values that represent the uncertainty of the true missing value. We generated 100 sets of plausible PBDE estimates using imputation models that take into account available individual level PBDE concentrations as well as group level concentrations. We included the following auxiliary variables in the imputation models based on their correlation with childhood PBDEs ($p < 0.05$): maternal blood lead concentrations and serum polychlorinated biphenyls ($\Sigma_{15}\text{PCBs}$) during pregnancy, household income, marital status, whether the child was breastfed, the Home Observation for Measurement of the Environment Score, $\log_{10}$ -transformed prenatal and childhood PBDEs, and neurobehavioral assessments of children at 8 years (FSIQ and externalizing behaviors score) (Bodner, 2008). Neurobehavioral assessment scores were included to prevent estimated associations to be biased toward the null (Enders, 2010).

2.3 Conners' Continuous Performance Test-II (CPT-II)

We used the CPT-II to measure inattention and impulsivity at 8 years. The CPT-II is a computer generated vigilance test that consists of a rapid presentation of continuously changing stimuli (letters of the Latin alphabet) that appear one at a time for 250 milliseconds (ms) (Conners, 1992). Children were instructed to press the spacebar when letters other than "X" appeared on the screen (i.e., target, Go Trials), but avoid pressing the spacebar when the letter "X" appeared on the screen (i.e., non-target, No-go Trials). The assessment takes ~14 minutes and consists of 360 letters. The assessment was completed in a quiet room in our research clinic to avoid distractions.

The CPT-II generates several indices, including omissions, (i.e., the number of times the spacebar was not pressed when letters other than "X" were presented) and commissions (i.e., the number of times the spacebar was pressed when the letter "X" was presented) (Table 1). Errors of omission (missing targets) reflect inattention and errors of commission (responding to non-targets) indicate impulsivity. Hit reaction time (HRT) is the overall mean RT for correct responses. Short and long HRTs may be associated with impulsivity and inattentiveness, respectively. Fitting an exponentially-modified Gaussian distribution to the HRT yields tau (τ), the exponential component of the distribution or positive skew. Larger τ values correspond with longer HRTs and indicate inattention. Detectability, d' , reflects perceptual sensitivity to targets and the ability to discriminate between letter "X" and others, with lower values indicating worse performance. Response bias is a function of the ratio of target to non-target stimuli, with lower values indicating a "risky" response style by responding too much to non-target stimulus. CPT-II indices of commission and omission errors, HRT, as well as perceptual sensitivity have been shown to differentiate ADHD children from non-ADHD children (Epstein et al., 2003; Losier et al., 1996). We examined T-scores (population mean 50 and standard deviation 10) for omissions, commissions, HRT, d' , and response bias as well as τ (in ms) as endpoints.

2.4 Statistical Analyses

Multiple informant models were used to estimate β s and 95% confidence intervals (CIs) between $\log_{10}$ -transformed lipid-adjusted prenatal and postnatal PBDE concentrations (BDE-28, -47, -99, -100, -153, and Σ PBDEs) and continuous CPT-II measures at 8 years in each of the 100 imputed datasets (Horton et al., 1999; Litman et al., 2007). These models allow for repeated PBDE concentrations throughout childhood to be included within one model and therefore allowed us to examine PBDE neurotoxicity at different exposure time points, spanning from *in utero* to school-age. We are also able to statistically test if associations between PBDE exposure and CPT-II measures differs according to exposure measurement timing. The reported β estimates for PBDEs are an average of separate multiple informant models from the 100 imputed datasets as recommended by Rubin's Rules (Rubin, 1987). Standard errors were calculated by combining the within imputation variance and the between imputation variance. While not all of the interaction terms (PBDEs $\times$ age) had a $p < 0.10$, we presented all β estimates separately for each exposure window for consistency. Covariate selection was based on results from bivariate analysis examining their relationship with CPT-II measures ($p < 0.10$). We adjusted for the following covariates (measured at study enrollment): maternal age (<25; 25–34; 35 years), race/ethnicity (Non-Hispanic White; Non-Hispanic Black and others), marital status (married/living with partner; not married/living alone), maternal smoking status (non-smoker; environmental tobacco smoke; active smoker) and alcohol consumption during pregnancy (never; <1/month; >1/month), maternal IQ (Wechsler, 1999), maternal depression at enrollment (minimal/mild; moderate/severe) (Beck et al., 1996), parity (nulliparous; primiparous; multiparous), child sex (male; female), household income (<\$40,000; \$40,000–\$79,999; \$80,000), and Home Observation for Measurement of the Environment score (<40; 40–44; 45–49; 50–54; 55–59; 60–64; 65–69; 70–74; 75–79; 80–84; 85–89; 90–94; 95–99; 100), a measure of the quality of the caregiving environment. Maternal education, serum Σ_{15} PCBs, drug use, vitamin supplementation during pregnancy, employment, and insurance were also considered as possible covariates, but failed to meet our criteria of $p < 0.10$. To determine whether associations were modified by child sex, interaction terms between PBDEs (continuous), child sex (categorical), and child age (categorical), as well as all 2-way interactions, were included in the models. Effect measure modification by child sex was considered present if $p < 0.10$. We used the original non-imputed data for generalized additive models (GAMs) to examine potential nonlinearity. We additionally assessed linear trend using tertiles of PBDEs, with tertile 1 as the referent group. Linear trend was assessed using the median value of each tertile as a continuous variable in the models (Greenland, 1995).

All models were re-examined using the original, non-imputed data to determine whether our conclusions differed between imputation-based and non-imputation-based models. We additionally adjusted for blood lead levels at 8 years to check if any of the observed associations were driven by this neurotoxicant (Chen et al., 2005; Lanphear et al., 2005). Lastly, we adjusted for breastfeeding (yes/no) in the statistical analyses. These additional adjustments were completed in both the original, non-imputed dataset and the imputed-dataset.

3. Results

3.1 PBDE concentrations

BDE-47 was the most abundant congener, with a geometric mean (GM) concentration of 21.7, 59.1, 66.0, 46.9, 30.5, and 20.3 ng/g lipid at the prenatal period, 1, 2, 3, 5, and 8 years, respectively Supplemental Table S1. Σ PBDE concentrations increased after birth, peaking at 2 years and subsequently declining until 8 years where concentrations were similar to that during the prenatal period. Most PBDE congeners followed a similar pattern; however, concentrations of BDE-153 continued to gradually increase from gestation up to age 5 years.

3.2 Participant characteristics

Prenatal Σ PBDE concentrations were higher among mothers who were younger, non-Hispanic black or others, of lower income, active smokers, experiencing moderate to severe depression, not married or living alone, and whose Home Observation for Measurement of the Environment score was <40 (Table 2). Maternal serum cotinine was positively correlated with prenatal Σ PBDE concentrations. Children who were non-Hispanic white, had a family income >\$40,000, and had a Home Observation for Measurement of the Environment score 40, and who had mothers that were married or living with a partner had lower omission errors. Commission scores were higher for children who were non-Hispanic white and whose mothers consumed alcohol during pregnancy and were married or living with a partner. HRT was longer among non-Hispanic blacks and others, males, and children of active smoking and environmental tobacco smoke exposed mothers. Maternal IQ was negatively correlated with prenatal Σ PBDE concentrations and omission scores.

3.3 CPT-II measures of inattention and impulsivity

A pattern of higher omission errors was observed with increased BDE-153 concentrations throughout childhood, although the 95% CIs included the null value (Table 3). Ten-fold increases in BDE-153 concentrations at 3, 5, and 8 years were associated with an increase of 4.0 [95% CI: -2.4, 10.5], 4.6 [95% CI: -2.8, 12.0], and 4.1 [95% CI: -3.4, 11.5] points in omission errors, respectively. In contrast, most of the findings yielded associations which were null, but there were some inverse associations. In particular, prenatal BDE-28 was associated with lower omission errors at 8 years (β =-3.2 [95% CI: -10.3, 3.9]).

We observed a pattern between concurrent PBDE concentrations and tau, with a positive non-significant association for all congeners as well as total PBDEs. Interestingly, BDE-153 concentrations at every exposure window were associated with increases in tau, albeit not statistically significant. Ten-fold increases in prenatal and postnatal BDE-153 concentrations were estimated to increase tau by ~15 ms and 20–29 ms, respectively. As an example, a scatter plot and smoothed spline regression also depicted an overall positive association between BDE-153 concentrations at 8 years and tau (Figure 1). When we examined the association between tertiles of 8 year BDE-153 concentrations we observed increases in tau in both the second (β =15.1 ms, 95% CI -30.5, 60.8) and third tertile (β =6.9 ms, 95% CI -36.5, 50.3) compared to the first tertile of BDE-153 concentration.

3.4 CPT-II measures of signal detection

Significant decreases in discriminability between targets and non-targets (d') were observed with 10-fold increases in BDE-100 concentrations at ages 5 ($\beta=-3.0$ [95% CI: -6.0, -0.1]) and 8 years ($\beta=-2.8$ [95% CI: -5.6, -0.1]) and Σ PBDE concentrations at age 5 years ($\beta=-3.4$ [95% CI: -6.5, -0.3]) (Table 4). Serum concentrations of PBDEs were not related to a “risky” response style as measured by response bias.

3.5 Child sex differences

Child sex significantly modified associations between PBDEs at 8 years and omission errors ($p_{\text{interaction}} < 0.10$) (Figure 2). For example, increased omission errors were observed in males, while decreased omissions were observed among females with 10-fold increases in concentrations of concurrent BDE-28 (Males: $\beta=7.9$ [95% CI: -1.7, 17.4]; Females: $\beta=-9.9$ [95% CI: -21.5, 1.8]), BDE-99 (Males: $\beta=6.2$ [95% CI: -1.3, 13.7]; Females: $\beta=-2.3$ [95% CI: -9.7, 5.0]), and Σ PBDEs (Males: $\beta=6.8$ [95% CI: -1.4, 15.1]; Females: $\beta=-3.1$ [95% CI: -11.6, 5.3]). Male children also had significant increases in tau with 10-fold increases in BDE-28 ($\beta=75.4$ ms [95% CI: 18.6, 132.1]) and BDE-153 concentrations ($\beta=48.4$ ms [95% CI: 3.8, 93.1]), while a null association was found in females (data not shown).

3.6 Sensitivity analyses

Additionally adjusting for blood lead concentrations at 8 years and whether the child received breastmilk in the imputed and original, non-imputed dataset yielded similar findings. Examining original, non-imputed concentrations of prenatal and postnatal PBDEs did not substantially change our conclusions (Supplemental Table S2). Aside from BDE-28, PBDEs at 8 years were associated with more omission errors, though results were still not statistically significant. In addition, concentrations of PBDEs during fetal development and at 8 years had a consistent pattern of associations, with larger tau values, indicating longer reaction times and thus inattention. The positive association between BDE-153 exposure during multiple time points during childhood and tau were no longer present for exposure windows at 1–3 years, which may be due to the lower number of available children with measured concentrations. In addition, BDE-153 exposure during childhood (except at 1 year of age) was also associated with more omission errors. Lastly, for detectability, we continued to observe statistically significant associations between PBDEs at 8 years, but only marginally significant associations with exposures at 5 years.

4. Discussion

The findings in this study do not strongly support the hypothesis that PBDEs are associated with impaired attention and impulse control in children. Although associations were not statistically significant, higher omission errors were found with increased concentrations of childhood BDE-153. There was a similar pattern between prenatal and concurrent PBDE concentrations and tau; children with higher prenatal and concurrent PBDE concentrations had a greater proportion of slow reaction times (tau). It should be noted that increasing tau values were found with BDE-153 concentrations at all exposure windows. Additionally, adverse associations between BDE-153 and omission errors were not limited to 8 year concentrations; they span throughout childhood exposure windows. Adverse associations

with BDE-153 at multiple time points from prenatal to childhood may be due to its higher fat deposition and it being more difficult to metabolize and excrete than the other congeners (Staskal et al., 2006). We also observed significant impairment in discriminability between targets and non-targets with postnatal BDE-100 and Σ PBDE concentrations.

Self-regulatory behaviors, including attention and impulse control, have been examined in seven epidemiologic studies for associations with PBDE exposure; four reporting on postnatal PBDEs (Cowell et al., 2015; Eskenazi et al., 2013; Gascon et al., 2011; Hoffman et al., 2012; Kicinski et al., 2012; Roze et al., 2009; Sagiv et al., 2015). The ability to maintain attention for a prolonged period of time while resisting distractions internally and externally is important for daily life. Sustained attentional control is associated with academic performance and everyday functioning activities, including driving (Schmidt et al., 2009; Steinmayr et al., 2010).

The neurotoxicity of PBDEs may result from thyroid hormone disruption, because they are structurally similar to thyroxine and have endocrine disrupting properties. Thyroid hormones influence proper development of tissues, synapses, and dendrites, and myelination of the central nervous system. Thyroid hormone disruption may result in irreversible mental impairments. Other biologic mechanisms for neurotoxicity include inducing neuronal apoptosis through oxidative stress, reducing cell migration and differentiation into neurons and oligodendrocytes, interfering with signal transduction, and altering the cholinergic system and neurotransmitter release and function (Costa et al., 2014; Costa and Giordano, 2007; Dingemans et al., 2011; Schreiber et al., 2010). PBDEs may also affect GABAergic and glutamatergic neurotransmitter systems in the frontal cortex (Bradner et al., 2013). Since GABA is a major neurotransmitter in the brain, an imbalance could disrupt the excitation-inhibition neuronal activity and result in deficits in cognitive processes as well as over excitation, hyperactivity, and impulsivity behaviors. Attention and impulse control are strong correlates of hyperactivity, aggression, socio-emotional behaviors, and academic skills (Lonigan et al., 2017).

There have been a number of epidemiologic studies that have examined PBDEs and inattention and impulsivity, of which two have examined prenatal concentrations (Cowell et al., 2015; Roze et al., 2009), three have examined postnatal concentrations (Gump et al., 2014; Hoffman et al., 2012; Kicinski et al., 2012), and three have investigated both gestational and childhood exposures (Eskenazi et al., 2013; Gascon et al., 2011; Sagiv et al., 2015). Most studies have reported a statistically significant association between prenatal PBDEs and attention problems in children, including the CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas) Study (Eskenazi et al., 2013; Sagiv et al., 2015), the New York City cohort (Cowell et al., 2015), and the Groningen infant COMPARE (Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens) Study (Roze et al., 2009). In the CHAMACOS Study, prenatal Σ_4 PBDE concentrations (barring BDE-28 used in our Σ PBDEs) were associated with higher errors of omission at 5 years and later when children were 9 and 12 years (Eskenazi et al., 2013; Sagiv et al., 2015). In addition, significant attention problems were observed between postnatal Σ_4 PBDEs and several measures of inattention when children were 7 years of age (Eskenazi et al., 2013). In a New

York City birth cohort, maternal serum BDE-47 and BDE-153 concentrations were associated with attention problems at 4 years (Cowell et al., 2015). Roze et al. (2009) reported similar results, where prenatal BDE-47 concentrations were significantly inversely correlated with sustained attention at 5–6 years. In contrast, null associations were observed between cord serum BDE-47 concentrations and attention deficit symptoms in a Menorca birth cohort (Gascon et al., 2011). While our study findings do not fully support our hypothesis, we did observe a pattern of results that are suggestive of a possible relationship between higher prenatal PBDE concentrations and inattention in children that has been reported in a majority of the previous literature.

Results from epidemiologic studies examining the association between postnatal PBDE concentrations and inattention are not as consistent. Positive associations between childhood PBDEs and attention problems were observed in two cohorts. BDE-47 concentrations at 4 years were associated with more attention problems at 4 years in the Menorca birth cohort (Gascon et al., 2011) and concurrent Σ_4 PBDEs were associated with attention problems at 7 years in the CHAMACOS Study (Eskenazi et al., 2013). The findings in the current study indicate a pattern of associations that is similar to the previous two studies. We observed positive, although non-significant, associations between concurrent PBDEs and increased inattention in children at 8 years, which may indicate a possible adverse relationship between postnatal PBDEs and attention control in children. However, a number of studies have reported contradictory findings. Null associations were observed between 9 year Σ_4 PBDE concentrations and CPT-II measures when children were 9 and 12 years in the CHAMACOS Study (Sagiv et al., 2015). In addition, a cross-sectional study of Flemish adolescents found null associations between concurrent PBDE concentrations and errors of omission (Kicinski et al., 2012). No relation was also reported in a cross-sectional study of 43 children in Oswego County, New York between child serum PBDEs at 9–11 years and reaction times or false alarm rates (Gump et al., 2014). Lastly, while we did not find an association between PBDEs and impulsivity, a positive association was observed in a North Carolina cohort between PBDEs measured three months postpartum in breastmilk and impaired impulse control (Hoffman et al., 2012).

Conflicting results between epidemiologic studies may be due to differing neurodevelopmental assessments and ages as well as differing PBDE levels between cohorts. Only two studies used the CPT-II and the reported results were inconsistent (Kicinski et al., 2012; Sagiv et al., 2015). In the HOME Study, children were assessed at 8 years, which is more comparable to the CHAMACOS Study (9 and 12 years) than the Flemish study (13–17 years). Sustained attention improves with age, with an important period of development occurring between 6 and 8 years, followed by a plateau during middle childhood (Lewis et al., 2017). Tau is a highly sensitive indicator of attention deficits (Leth-Steensen et al., 2000; Tarantino et al., 2013) and has an incremental developmental trajectory throughout childhood (Lewis et al., 2017). The plateau after the essential period of development may partly explain null associations reported in the Flemish study of adolescents who may have cultivated their ability to focus on tasks that may not be intrinsically arousing. In the HOME Study, we observed a pattern of adverse associations between prenatal and concurrent Σ PBDEs in children prior to adolescence. In the CHAMACOS Study, significant increases in errors of omission were reported when examining prenatal Σ_4 PBDEs and repeated

measures at 9 and 12 years. However, null associations were reported with childhood Σ_4 PBDEs. It is unclear why conflicting results were observed with childhood PBDEs between the HOME Study and CHAMACOS Study. Differences between cohorts, including PBDE concentrations and cohort characteristics, could partially explain the discrepancies. The HOME Study had a lower GM of BDE-47 at age 8 years (20.3 ng/g lipid) compared to the CHAMACOS Study at age 9 years (35.2 ng/g lipid). In addition, the CHAMACOS Study consists of Mexican Americans in a farmworker community while our cohort is comprised of mainly non-Hispanic whites with a higher socioeconomic status. Lastly, we used multiple informant models that allowed for repeated measures of PBDEs, which was not used in previous studies.

We observed evidence that child sex may modify the association between PBDEs and CPT-II measures, suggesting that males may be more sensitive to PBDEs. Previously, normative differences between child sex have been reported on the CPT-II, with males more prone to impulsive errors and shorter HRTs (Conners et al., 2003). In our study, higher concurrent concentrations of PBDEs were associated with increased omission errors in males while decreasing associations in females. Males were also found to have higher tau values, or a larger proportion of slow reaction times, than females with increasing concurrent BDE-153 concentrations. Only one study reported a significant child sex difference between PBDEs and CPT-II measures, with males performing worse with errors of commission than females with increasing prenatal PBDEs (Sagiv et al., 2015); other studies have reported no modification by child sex (Gascon et al., 2011; Hoffman et al., 2012; Kicinski et al., 2012). As such, the presence of effect modification by child sex in the associations of PBDEs and attention remain unclear. Further, we observed inverse associations between concurrent PBDE concentrations and omission scores in females. It is uncertain whether the observed pattern of an increased omission score and tau values in males and a reduction in females is biologically supported by sexual dimorphism. Limited sample size, residual confounding, and environmental co-exposures could partially explain these divergent results.

Toxicology studies investigating postnatal PBDEs and modulation of attention are inconsistent. Acute postnatal exposure to mixture DE-71, consisting of BDE-47, -99, -100, -153, and -154, did not produce effects on attention or impulse control in rats (Driscoll et al., 2012; Dufault et al., 2005). However, rats who received chronic postnatal doses of DE-71, which is more similar to human exposure scenarios, had significant impairment in sustained attention and increased impulsivity (Driscoll et al., 2009). Similar results were observed with postnatal decaBDE (primarily BDE-209), with increased impulsivity in older, but not younger mice (Rice et al., 2009).

Our study had several strengths, including its prospective study design, long follow-up period, comprehensive adjustment of confounders, repeated assessments of PBDEs from *in utero* to school ages, and use of multiple informant models. We also used multiple imputation to estimate missing PBDE concentrations, thus fully utilizing the available exposure data. Imputation resulted in GMs that were comparable to the original measurements, with only slightly higher GMs at 2 and 3 years. Results from sensitivity analyses using non-imputed, original data also yielded similar conclusions of a pattern of associations that are suggestive of a possible adverse relationship between prenatal and

concurrent PBDEs and inattention in children. There is also suggestive evidence that exposure to BDE-153 occurring at other ages during childhood may also adversely influence attention in children based on a pattern of positive associations between BDE-153 and tau and omission errors, though none of these associations were statistically significant.

Our findings should be interpreted with caution for several reasons. First, although the results between the imputed datasets and the original dataset are overall similar, the observed trends are not always consistent. Second, we assume that the data were missing at random when we used multiple imputation, an assumption which may not be fully satisfied. Third, while we did not observe statistically significant associations, there was a pattern of higher omission errors with concurrent PBDEs. Although, the pattern was less consistent for prenatal and early childhood (aged 1–3 years) concentrations of PBDEs and CPT-II measures of inattention. Larger tau values (the proportion of slow reaction times) were observed with increasing concentrations of both prenatal and concurrent PBDEs. PBDEs at 5 and 8 years were also associated with poorer discriminability. Non-significant results may be due to our modest sample size. Fourth, CPT-II may only assess sustained attention, and does not fully examine selective, divided, and alternating attention (Lee, 2005). In addition, while selection bias may be an issue, children excluded due to missing assessments of PBDEs and CPT-II were comparable to those included in the study on all aspects of maternal, child, and household characteristics except maternal IQ and marital status. Baseline PBDE concentrations among mothers were also similar between those included and excluded from this study. Multiple comparisons may also be of concern, because we examined PBDEs at numerous time points. However, our models allowed us to collectively examine PBDEs, which greatly reduced the number of models. Residual confounding may also be a concern as HOME Study children from lower socioeconomic backgrounds had higher PBDE concentrations and lower CPT-II scores. Socioeconomic factors have also been reported to be a strong predictor of PBDE concentrations in child serum (Darrow et al., 2017). Lastly, due to high correlation between congeners and their long half-lives, we are not able to completely disentangle congener and exposure year specific associations with certainty.

5. Conclusions

PBDEs were not statistically associated with sustained attention or impulse control in a longitudinal cohort of children at 8 years. However, we observed a pattern of associations between pre- and postnatal PBDE concentrations and several measures of attentional control. Associations between BDE-153 concentrations and measures of omissions were particularly noteworthy. BDE-153 concentrations may be adversely associated with inattention in children at multiple exposure points from *in utero* through childhood. Further research is needed to determine whether PBDEs adversely affect other aspects of attention in children and the potential interaction between child sex and PBDE exposures.

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Abbreviations

CDC	Centers for Disease Control and Prevention
CHAMACOS Study	Center for the Health Assessment of Mothers and Children of Salinas Study
COMPARE Study	Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogen Study
CPT-II	Conners' Continuous Performance Test-Second Edition
CI	confidence interval
d'	detectability
GAM	generalized additive model
HOME Study	Health Outcomes and Measures of the Environment Study
MCMC	Markov Chain Monte Carlo
PBDE	polybrominated diphenyl ether
PCB	polychlorinated biphenyls
HRT	hit reaction time
SD	standard deviation
τ	tau

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Highlights

- No statistically significant association was observed between PBDEs and inattention or impulsivity.
- A pattern of associations was observed between prenatal and concurrent PBDEs and inattention in children.
- BDE-153 at multiple exposure times was adversely associated with inattention.
- Males had higher omission errors and longer hit reaction times than females.
- Significant impairment in discriminability was observed with 5 and 8 year PBDEs.

Figure 1.

Scatter plot of child serum concentrations of BDE-153 at 8 years and tau (ms) at 8 years with generalized additive model curve fitting. Solid line represents that natural cubic spline of the covariate association and dotted lines represent 95% CIs. BDE-153 distribution is illustrated by vertical bars on the log₁₀-transformed x-axis. Model adjusted for maternal age, race/ethnicity, marital status, maternal smoking status, maternal alcohol consumption, maternal IQ, parity, child sex, maternal depression, household income, and Home Observation for Measurement of the Environment Score.

Figure 2.

Estimated score differences and 95% CIs in omission scores at 8 years by a 10-fold increase in polybrominated diphenyl ether concentrations in each exposure window by child sex, HOME Study. Asterisks indicate statistically significant p -value (<0.10) for effect measure modification by child sex. Models adjusted by maternal age, race/ethnicity, marital status, maternal smoking status, maternal alcohol consumption, maternal IQ, parity, maternal depression, household income, and Home Observation for Measurement of the Environment Score.

Table 1

Description of CPT-II measures

Measure	Description	Directionality for Poor Performance	Interpretation
Omissions	Number of times an individual did not respond to a target	↑	Inattention
Commissions	Number of times an individual incorrectly responds to a non-target	↑	Impulsivity
Hit Reaction Time	Mean overall reaction time for correct responses	↓	Impulsivity if reaction times are low
Tau (τ)	Mean of exponential component (tail of reaction time distribution that is fitted to an ex-Gaussian distribution).	↑	Inattention if reaction times are high
Detectability (d')	Ability to discriminate between letter "X" and other letters	↓	Increases in tau means larger proportion of slow reaction times
Response bias	Function of ratio of target to non-target stimuli and the individual's tendency to respond too little or too much relative to the actual distribution of the signal	↓	Lower scores suggest poorer discrimination between target and foil stimuli.
			Lower values indicate a greater percentage of responding than is required by the task parameters or a 'risky' response style

Table 2

Serum concentrations of ΣPBDE (ng/g lipid) and CPT-II measures at 8 years by maternal and child characteristics, HOME Study^a

	ΣPBDEs 16±3 weeks			ΣPBDEs 8 years			Omissions (T-score)		Tau (ms)	
	n	GM±GSD	n	GM±GSD	n	Mean±SD	n	Mean±SD	n	Mean±SD
All participants	214	40.1±2.4	198	43.6±2.2	214	61.2±19.6	175	212.7±93.0		
Age, years										
<25	57	47.7±1.9 *	54	40.1±2.2	57	64.6±22.8	44	199.9±85.2		
25–34	125	40.9±2.5	112	48.6±2.1	125	60.4±18.5	103	215.8±93.2		
35	31	27.9±2.5	31	34.2±2.3	31	58.4±17.2	27	224.4±105.8		
Race/ethnicity										
Non-Hispanic White	128	33.9±2.3 *	117	44.0±2.2	128	56.8±14.1 *	113	207.6±93.2		
Non-Hispanic Black and Others	85	52.3±2.4	80	43.1±2.2	85	67.8±24.4	61	223.5±92.8		
Family Income										
<\$40,000	90	51.0±2.2 *	84	46.0±2.2	90	65.1±23.8 *	65	207.3±86.0		
\$40,000–\$79,999	69	40.7±2.6	63	44.5±2.2	69	58.1±14.9	60	206.3±93.1		
\$80,000	54	26.9±2.2	50	39.0±2.1	54	58.6±15.9	49	229.2±101.8		
Maternal smoking status										
Non-smoker	179	37.6±2.4 *	164	44.7±2.2	179	60.2±18.8	151	211.0±94.1		
Environmental tobacco smoke	18	45.1±1.9	18	47.3±2.2	18	71.1±29.7	8	190.8±97.1		
Active smoker	16	78.2±2.1	15	30.6±2.0	16	61.0±10.4	15	246.2±77.6		
Maternal alcohol consumption										
Never	119	38.3±2.3	109	43.9±2.3	119	62.0±18.5	93	223.7±98.8		
<1 per month	63	42.8±2.5	61	42.9±2.0	63	60.9±22.4	55	211.0±83.6		
>1 per month	31	43.4±2.5	27	44.0±2.4	31	58.8±18.1	26	180.0±85.9		
Maternal depression										
Minimal/mild	192	38.2±2.6 *	176	44.4±2.1	192	60.4±18.5	156	209.6±92.3		
Moderate/severe	19	69.1±2.0	19	38.1±2.7	19	68.1±28.0	18	243.4±97.2		
Home Observation for Measurement of the Environment score										
40	123	34.0±2.4 *	113	43.4±2.2	123	57.3±13.5 *	105	209.2±88.0		
35–39	40	52.7±2.5	38	48.1±2.6	40	62.0±20.1	36	220.9±111.8		

	ΣPBDEs 16±3 weeks		ΣPBDEs 8 years		Omissions (T-score)		Tau (ms)	
	n	GM±GSD	n	GM±GSD	n	Mean±SD	n	Mean±SD
<35	34	51.3±2.3	31	43.6±1.9	34	69.7±27.2	23	203.2±91.1
Marital status								
Married/living with partner	157	36.2±2.4 *	144	43.4±2.1	157	58.9±17.1 *	134	211.5±95.3
Not married, living alone	56	54.6±2.1	53	44.3±2.4	56	67.5±24.4	40	218.7±86.3
Parity								
Nulliparous	96	37.4±2.2	85	45.7±2.3	96	60.9±19.7	82	215.9±88.2
Primiparous	66	41.8±2.3	63	44.4±2.1	66	55.9±19.6	52	200.8±95.4
Multiparous	51	44.3±2.9	49	39.3±2.2	51	63.4±19.6	40	223.6±100.4
Child sex								
Male	95	37.6±2.2	89	43.9±2.3	95	63.5±22.3	70	211.0±98.6
Female	119	42.2±2.6	109	43.4±2.1	119	59.3±16.9	105	213.9±89.6
	n	Pearson r	n	Pearson r	n	Pearson r	n	Pearson r
Maternal IQ								
(Mean±SD 105.5±15.2)	200	-0.19 *	187	-0.05	200	-0.15 *	163	-0.04
Maternal PCBs								
(GM±GSD 44.4±1.8 ng/g lipid)	187	-0.07	171	-0.04	187	-0.06	153	0.03
Maternal cotinine								
(GM±GSD 0.06±20.3 ng/mL)	209	0.35 *	193	-0.07	209	0.11	171	0.04

Abbreviations: GM, geometric mean; GSD, geometric standard deviation; SD, standard deviation.

* $p < 0.05$

Estimated score differences and 95% CIs in CPT-II measures of inattention and impulsivity at 8 years by a 10-fold increase in polybrominated diphenyl ether concentrations in each exposure window, HOME Study^a

	Exposure Year	BDE-28 β (95% CI)	BDE-47 β (95% CI)	BDE-99 β (95% CI)	BDE-100 β (95% CI)	BDE-153 β (95% CI)	ΣPBDEs β (95% CI)
Omissions	Prenatal	-3.2 (-10.3, 3.9)	-0.4 (-6.6, 5.8)	0.9 (-5.1, 6.9)	0.1 (-5.8, 6.0)	-0.4 (-5.8, 5.1)	-0.5 (-6.9, 6.0)
	1 year	0.6 (-6.3, 7.5)	-0.9 (-8.5, 6.6)	-0.4 (-7.1, 6.3)	0.7 (-6.7, 8.2)	1.1 (-5.3, 7.6)	-0.9 (-8.3, 7.7)
	2 years	0.1 (-8.3, 8.5)	-1.7 (-8.6, 5.3)	-1.8 (-8.2, 4.6)	-0.4 (-7.1, 6.4)	2.1 (-4.9, 9.1)	-1.2 (-8.6, 6.1)
	3 years	5.5 (-1.7, 12.7)	0.6 (-6.3, 7.6)	0.3 (-5.9, 6.5)	1.6 (-4.9, 8.0)	4.0 (-2.4, 10.5)	2.0 (-5.1, 9.1)
	5 years	0.5 (-6.6, 7.6)	-1.6 (-8.0, 4.7)	-1.6 (-7.5, 4.4)	2.2 (-4.6, 9.1)	4.6 (-2.8, 12.0)	0.2 (-7.1, 7.4)
	8 years	0.9 (-6.7, 8.4)	1.5 (-5.0, 8.0)	1.8 (-4.3, 7.9)	1.5 (-5.1, 8.0)	4.1 (-3.4, 11.5)	2.1 (-5.4, 9.6)
Commissions	Prenatal	0.5 (-2.5, 3.6)	0.6 (-2.0, 3.3)	0.5 (-2.1, 3.0)	0.5 (-2.0, 3.0)	0.2 (-2.1, 2.6)	0.7 (-2.1, 3.4)
	1 year	-0.3 (-3.1, 2.5)	-0.3 (-3.4, 2.7)	-0.6 (-3.4, 2.2)	-0.7 (-3.7, 2.3)	-0.7 (-3.4, 1.9)	-0.5 (-3.9, 2.9)
	2 years	0.2 (-3.1, 3.4)	0.1 (-2.7, 2.9)	-0.5 (-3.0, 2.1)	-1.0 (-3.7, 1.7)	-1.3 (-4.2, 1.5)	-0.2 (-3.3, 2.8)
	3 years	-0.5 (-3.6, 2.5)	-0.9 (-3.8, 2.0)	-1.3 (-3.8, 1.2)	-1.2 (-3.9, 1.4)	-1.0 (-3.8, 1.7)	-1.2 (-4.2, 1.8)
	5 years	-1.4 (-4.4, 1.7)	-0.9 (-3.7, 1.8)	-1.2 (-3.8, 1.3)	-1.8 (-4.8, 1.1)	-1.3 (-4.4, 1.9)	-1.5 (-4.6, 1.6)
	8 years	0.1 (-3.1, 3.3)	-0.6 (-3.4, 2.1)	-0.8 (-3.4, 1.7)	-1.1 (-3.9, 1.7)	-0.7 (-3.8, 2.5)	-0.7 (-3.9, 2.5)
HRT	Prenatal	-0.9 (-5.4, 3.6)	-0.2 (-4.2, 3.7)	0.9 (-3.0, 4.7)	0.4 (-3.3, 4.2)	0.8 (-2.6, 4.3)	0.5 (-3.5, 4.6)
	1 year	-0.3 (-4.5, 3.9)	-2.3 (-7.0, 2.3)	-1.5 (-5.6, 2.7)	-1.0 (-5.8, 3.8)	0.5 (-3.6, 4.5)	-2.5 (-7.5, 2.5)
	2 years	-0.5 (-5.9, 4.9)	-2.7 (-7.0, 1.6)	-2.1 (-5.9, 1.7)	-1.7 (-5.9, 2.6)	0.6 (-3.8, 5.0)	-2.9 (-7.5, 1.7)
	3 years	2.3 (-2.4, 7.0)	-1.2 (-5.6, 3.2)	-0.5 (-4.3, 3.3)	-0.7 (-4.8, 3.5)	1.3 (-2.9, 5.4)	-0.9 (-5.4, 3.6)
	5 years	1.9 (-2.6, 6.4)	-1.8 (-5.8, 2.3)	-1.3 (-5.1, 2.5)	-1.0 (-5.3, 3.3)	0.7 (-4.0, 5.5)	-1.5 (-6.1, 3.1)
	8 years	1.1 (-3.7, 5.8)	0.5 (-3.6, 4.6)	0.9 (-2.9, 4.8)	-0.2 (-4.4, 3.9)	0.4 (-4.3, 5.1)	0.01 (-4.7, 4.7)
Tau (ms)	Prenatal	15.7 (-24.0, 55.4)	7.5 (-27.3, 42.3)	11.3 (-23.1, 45.6)	10.9 (-21.7, 43.6)	15.0 (-15.8, 45.8)	17.1 (-18.7, 53.0)
	1 year	8.3 (-30.3, 46.8)	-9.3 (-54.3, 35.7)	-5.7 (-44.0, 32.6)	5.1 (-37.7, 47.9)	22.6 (-14.1, 59.4)	1.5 (-44.7, 47.8)
	2 years	-0.4 (-47.2, 46.4)	-7.6 (-46.4, 31.2)	-7.5 (-41.2, 26.1)	0.4 (-37.3, 38.2)	20.2 (-18.0, 58.3)	0.4 (-39.3, 40.1)
	3 years	8.8 (-31.8, 49.5)	0.6 (-38.8, 39.9)	-2.8 (-35.9, 30.4)	7.9 (-27.8, 43.6)	24.2 (-12.0, 60.4)	10.0 (-28.8, 48.8)
	5 years	2.6 (-37.3, 42.5)	-6.4 (-42.5, 29.8)	-7.2 (-41.3, 26.8)	5.7 (-33.2, 44.5)	20.6 (-20.8, 61.9)	1.4 (-39.1, 41.9)
	8 years	30.9 (-12.4, 74.2)	20.5 (-17.7, 58.7)	23.3 (-12.1, 58.8)	20.9 (-17.3, 59.1)	28.6 (-12.1, 69.4)	25.3 (-17.8, 68.4)

Adjusted by maternal age, race/ethnicity, marital status, maternal smoking status, maternal alcohol consumption, maternal IQ, parity, child sex, maternal depression, household income, and Home Observation for Measurement of the Environment Score.

Table 4

Estimated score differences and 95% CIs in CPT-II measures of signal detection at 8 years by a 10-fold increase in polybrominated diphenyl ether concentrations in each exposure window, HOME Study^a

	Exposure Year	BDE-28 β (95% CI)	BDE-47 β (95% CI)	BDE-99 β (95% CI)	BDE-100 β (95% CI)	BDE-153 β (95% CI)	ΣPBDEs β (95% CI)
d'	Prenatal	-0.8 (-3.9, 2.2)	0.6 (-2.0, 3.2)	0.5 (-2.0, 3.0)	0.6 (-1.9, 3.1)	-0.1 (-2.4, 2.2)	0.4 (-2.4, 3.1)
	1 year	-0.02 (-2.9, 2.9)	-0.1 (-3.3, 3.1)	-0.3 (-3.0, 2.5)	-0.4 (-3.5, 2.6)	-0.8 (-3.5, 1.8)	-0.4 (-3.8, 3.1)
	2 years	1.1 (-2.2, 4.4)	-0.02 (-2.9, 2.9)	-0.6 (-3.1, 2.0)	-1.0 (-3.8, 1.8)	-1.5 (-4.4, 1.4)	-0.6 (-3.6, 2.5)
	3 years	0.003 (-3.1, 3.1)	-1.2 (-4.2, 1.9)	-1.4 (-4.0, 1.2)	-1.3 (-4.0, 1.5)	-1.1 (-3.8, 1.7)	-1.6 (-4.6, 1.5)
	5 years	-2.4 (-5.5, 0.7)	-2.5 (-5.3, 0.3)	-2.5 (-5.1, 0.05)	-3.0 (-6.0, -0.1)	-2.1 (-5.6, 0.7)	-3.4 (-6.5, -0.3)
	8 years	-2.5 (-5.6, 0.7)	-1.8 (-4.6, 0.9)	-1.6 (-4.2, 0.9)	-2.8 (-5.6, -0.1)	-2.5 (-5.6, 0.7)	-2.5 (-5.7, 0.6)
Response bias	Prenatal	0.7 (-2.3, 3.7)	1.0 (-1.6, 3.5)	1.8 (-0.7, 4.2)	0.4 (-2.1, 2.9)	0.2 (-2.1, 2.4)	1.0 (-1.6, 3.6)
	1 year	1.1 (-1.6, 3.7)	0.3 (-2.7, 3.4)	0.3 (-2.3, 2.9)	0.7 (-2.1, 3.6)	0.7 (-1.8, 3.1)	0.6 (-2.6, 3.9)
	2 years	1.2 (-2.0, 4.3)	0.3 (-2.4, 3.1)	0.1 (-2.3, 2.4)	0.4 (-2.2, 3.0)	0.9 (-1.8, 3.5)	0.4 (-2.5, 3.4)
	3 years	1.3 (-1.6, 4.2)	0.8 (-2.0, 3.7)	0.5 (-1.8, 2.8)	0.7 (-1.9, 3.3)	1.0 (-1.6, 3.6)	0.9 (-2.0, 3.8)
	5 years	1.0 (-1.8, 3.9)	0.8 (-1.7, 3.4)	0.6 (-1.8, 3.0)	1.1 (-1.7, 3.8)	1.1 (-1.8, 4.1)	0.9 (-2.0, 3.8)
	8 years	0.4 (-2.6, 3.4)	1.9 (-0.7, 4.4)	2.0 (-0.4, 4.4)	1.1 (-1.5, 3.6)	0.5 (-2.4, 3.5)	1.7 (-1.2, 4.7)

^a Adjusted by maternal age, race/ethnicity, marital status, maternal smoking status, maternal alcohol consumption, maternal IQ, parity, child sex, maternal depression, household income, and Home Observation for Measurement of the Environment Score.