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Prenatal and postnatal polybrominated diphenyl ether exposure and visual spatial abilities in children

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ABSTRACT

Polybrominated diphenyl ethers (PBDEs) are associated with impaired visual spatial abilities in toxicological studies, but no epidemiologic study has investigated PBDEs and visual spatial abilities in children. The Health Outcomes and Measures of the Environment Study, a prospective birth cohort (2003–2006, Cincinnati, OH), was used to examine prenatal and childhood PBDEs and visual spatial abilities in 199 children. PBDEs were measured at 16 ± 3 weeks gestation and at 1, 2, 3, 5, and 8 years using gas chromatography/isotope dilution high-resolution mass spectrometry. We used the Virtual Morris Water Maze to measure visual spatial abilities at 8 years. In covariate-adjusted models, 10-fold increases in BDE-47, −99, and −100 at 5 years were associated with shorter completion times by 5.2 s (95% Confidence Interval [CI] −9.3, −1.1), 4.5 s (95% CI −8.1, −0.9), and 4.7 s (95% CI −9.0, −0.3), respectively. However, children with higher BDE-153 at 3 years had longer completion times (β=5.4 s, 95% CI −0.3, 11.1). Prenatal PBDEs were associated with improved visual spatial memory retention, with children spending a higher percentage of their search path in the correct quadrant. Child sex modified some associations between PBDEs and visual spatial learning. Longer path lengths were observed among males with increased BDE-47 at 2 and 3 years, while females had shorter paths. In conclusion, prenatal and postnatal BDE-28, −47, −99, and −100 at 5 and 8 years were associated with improved visual spatial abilities, whereas a pattern of impairments in visual spatial learning was noted with early childhood BDE-153 concentrations.

1. Introduction

Polybrominated diphenyl ethers (PBDEs) were used extensively in a wide variety of commercial products, including building materials, electronics, polyurethane foams, and textiles, to retard, suppress, or inhibit combustion. PBDEs readily leach out from materials and have widespread environmental dispersion, bioaccumulating in virtually all abiotic and terrestrial compartments (Birnbaum and Staskal, 2004). Due to their high lipophilicity and long half-lives, accumulation of PBDEs in human tissue can last over 10 years depending on the congener (Geyer et al., 2004; Thuresson et al., 2006). BDE-47, −99, and −100 have half-lives up to 2–3 years, while BDE-153 has a half-life up to 12 years (Geyer et al., 2004). The phase-out of PBDEs started in 2004, but humans are continually exposed from older consumer products containing PBDEs. PBDE exposure begins during gestation from maternal transfer and continues postnatally via intake of breast milk and by direct routes of exposure, including inhalation and ingestion. PBDE concentrations have been reported to be highest among infants and toddlers due to breastfeeding, the frequency of hand-to-mouth behaviors, and the amount of time they spend in close proximity to the floor; levels in children and teenagers are several folds higher than those of adults (Jones-Otazo et al., 2005; Toms et al., 2008).

Prenatal and childhood PBDE exposure have been associated with

Abbreviations: ADHD, Attention deficit/hyperactivity disorder; CDC, Centers for Disease Control and Prevention; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; GM, Geometric mean; HOME Study, Health Outcomes and Measures of the Environment Study; LOD, Limit of detection; NHANES, National Health and Nutrition Examination Survey; NMDA, N-methyl-d-aspartate; PBDEs, Polybrominated diphenyl ethers; PCBs, Polychlorinated biphenyls; SD, Standard deviation

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decrements in cognitive function, impairments in executive function, increased attention deficit/hyperactivity disorder (ADHD) related behaviors and symptoms, and poorer motor coordination in children (Chao et al., 2011; Chen et al., 2014a; Eskenazi et al., 2013; Gascon et al., 2011; Herbstman et al., 2010; Hoffman et al., 2012; Roze et al., 2009; Sagiv et al., 2015; Shy et al., 2011; Vuong et al., 2016). The mechanism by which PBDEs exert their neurotoxic effects is unclear, but suspected mechanisms include disrupting thyroid hormone function (Costa and Giordano, 2007; Kodavanti et al., 2010; Szabo et al., 2009), altering the cholinergic systems (Dufault et al., 2005; Eriksson et al., 2002; Viberg et al., 2003a), causing oxidative stress (Belles et al., 2010; Cheng et al., 2009; Giordano et al., 2008; He et al., 2008), inducing cell apoptosis (Chen et al., 2014b; He et al., 2008, 2009b), impacting DNA methylation (Woods et al., 2012), and affecting neuronal proteins (e.g., CaMKII, GAP-43, synaptophysin, and tau) and N-methyl-d-aspartate (NMDA) receptors (Buratovic et al., 2014; Viberg et al., 2003b, 2008; Yan et al., 2012).

Visual spatial abilities, including learning and memory retention, contribute to overall cognitive ability and are necessary for successful everyday functioning. Visual spatial cognition is highly complex, requiring the processing of images and surroundings while focusing on pertinent details, suppressing those that are irrelevant, and manipulating mental representations to govern actions and decisions. No studies have examined the impact of prenatal and childhood PBDE exposures on visual spatial abilities, despite several animal studies reporting impairments in learning and memory with prenatal and postnatal PBDE exposure (Buratovic et al., 2014; Chen et al., 2014b; Cheng et al., 2009; He et al., 2011, 2009a; Viberg et al., 2003a, 2006; Woods et al., 2012; Yan et al., 2012). Further, several studies have found reduced visual spatial learning and memory retention in rats using the Morris Water Maze with PBDE exposure (Cheng et al., 2009; Eriksson et al., 2001; He et al., 2011, 2009a; Woods et al., 2012; Yan et al., 2012). Given that PBDE exposure coincides with critical periods of brain development, we examined the relations of prenatal and childhood PBDE exposure (measured at ages 1, 2, 3, 5, and 8 years) with visual spatial abilities in children at 8 years. We hypothesized that PBDE insults during gestation and early childhood (1–8 years) are associated with reduced visual spatial abilities.

2. Materials and methods

2.1. Study participants and design

We enrolled 468 women in the Health Outcomes and Measures of the Environment (HOME) Study between March 2003 and February 2006 (Braun et al., 2016). The HOME Study is a prospective pregnancy and birth cohort in the Greater Cincinnati Area (Ohio, USA) in which pregnant women 16 ± 3 weeks of gestation were eligible to participate if they fulfilled the following criteria: 1) were at least 18 years of age; 2) lived in a house constructed prior to 1978 (a criterion related to the randomized trial examining lead and injury hazard reduction interventions); 3) intended to receive prenatal care and deliver in one of the nine collaborating obstetric practices and hospitals; 4) were HIV negative; and 5) did not take medications for seizures, thyroid disorders, or chemotherapy/radiation. Of the 390 women who remained to deliver live singleton infants, 199 mother-child pairs had at least one measure of PBDE concentration (prenatal and/or childhood) and an assessment of child visual spatial abilities at 8 years. The study protocol was approved by the Institutional Review Boards at the Cincinnati Children's Hospital Medical Center and the Centers for Disease Control and Prevention (CDC).

2.2. Assessment of prenatal and childhood PBDEs

Prenatal PBDEs were measured using maternal serum samples obtained at 16 ± 3 weeks of gestation. Serum samples were collected from children at 1, 2, 3, 5, and 8 years and used to measure concentrations of PBDEs during childhood. All serum samples were stored at −80 °C until analysis. Gas chromatography/isotope dilution high-resolution mass spectrometry was used to determine concentrations of BDE congeners −17, −28, −47, −66, −85, −99, −100, −153, −153, −183, and −209 (postnatal only) (Jones et al., 2012; Sjodin et al., 2004). The serum samples were extracted using automated liquid / liquid extraction with hexane/methyl *tert*-butyl ether after addition of internal standards and denaturation of serum proteins with hydrochloric acid (6M) and methanol (Jones et al., 2012; Sjodin et al., 2004). Each analytical batch of 24 unknowns included three quality control and method blank samples. PBDE values lower than the limit of detection (LOD), defined as 3 times the standard deviation (SD) of the method blanks or the lowest calibration standard point 0.5 pg/μL corresponding to 5 pg per sample (in the absence of detectable blanks), were substituted with LOD/√2 (Hornung and Reed, 1990). Percent detection for PBDEs by measurement timing are listed in Supplemental materials, Table S1. PBDE concentrations were lipid adjusted (ng/g lipid) based on measurements of triglycerides and total cholesterol using standard enzymatic methods (Phillips et al., 1989). The following congeners were included in our analysis of prenatal and postnatal PBDEs: BDE-28, −47, −99, −100, and −153. Of the HOME Study children who completed visual spatial assessments, 191, 76, 61, 61, 127, and 173 had PBDE concentrations available at 16 ± 3 weeks gestation, 1 year, 2 years, 3 years, 5 years, and 8 years, respectively. The number of measurements and detection frequencies of PBDE congeners at each age category are given in Table S1 (see Supplemental material, Table S1). Numbers of children at 1–3 years were considerably lower, because only a subset of children had available serum to measure PBDEs.

2.3. Visual spatial abilities

Visual spatial learning and memory retention were assessed at 8 years of age using the Virtual Morris Water Maze (Astur et al., 1998), a computerized version of the Morris Water Maze test that is used to measure spatial learning and navigation in rodents (Morris, 1981). The Virtual Morris Water Maze has been demonstrated to be an effective assessment of spatial learning in humans (Astur et al., 1998). The virtual environment is comprised of a circular pool contained within a square floor plan. Four distal cues of equal size were positioned at each of the walls. The platform lay at the center of the northeast quadrant under the water surface. Children were informed that the platform would remain stationary throughout the trials and were instructed to locate the hidden platform as quickly and efficiently as possible. In order to familiarize the children with the virtual environment, they were given four practice trials in which the platform was visible but no visual landmarks were displayed on the walls before the test began. Children could freely navigate between the four quadrants and control the speed of movement by manipulating the joystick. Movement was limited to forward, left, and right to mirror the natural movement of rodents. After the practice trials, a series of four blocks of four trials were administered with the location of the hidden platform and visual landmarks fixed. Children were randomly placed in different locations (north, east, south, and west) by one side of the pool wall at the start of each block of trials. Once the platform was reached, an audible cue would sound and the platform would become visible. Children were given a two second interlude prior to the onset of the next trial. The Virtual Morris Water Maze measures time (s) and distance (pool units) traveled from the start location to the platform for each trial. An average of time and distance for each set of blocks was used to assess visual spatial learning, with shorter times and distance traversed indicating superior performance.

Lastly, a 30-s probe trial was administered within the same virtual environment, but the platform was removed. Exploration continued for the duration of the trial as crossing the platform did not terminate the