The relationship between persistent organic pollutants and Attention Deficit Hyperactivity Disorder phenotypes: Evidence from task-based neural activity in an observational study of a community sample of Canadian mother-child dyads

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Abstract

Background: Prenatal exposure to persistent organic pollutants (POPs), widespread in North America, is associated with increased Attention Deficit/Hyperactivity Disorder (ADHD) symptoms and may be a modifiable risk for ADHD phenotypes. However, the effects of *moderate* exposure to POPs on task-based inhibitory control performance, related brain function, and ADHD-related symptoms remain unknown, limiting our ability to develop interventions targeting the neural impact of common levels of exposure.

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Objectives: The goal of this study was to examine the association between prenatal POP exposure and inhibitory control performance, neural correlates of inhibitory control and ADHD-related symptoms.

Methods: Prospective data was gathered in an observational study of Canadian mother-child dyads, with moderate exposure to POPs, including polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs), as part of the GESTation and the Environment (GESTE) cohort in Sherbrooke, Quebec, Canada. The sample included 87 eligible children, 46 with maternal plasma samples, functional magnetic resonance imaging (fMRI) data of Simon task performance at 9–11 years, and parental report of clinical symptoms via the Behavioral Assessment System for Children 3 (BASC-3). Simon task performance was probed via drift diffusion modeling, and parameter estimates were related to POP exposure. Simon task-based fMRI data was modeled to examine the difference in incongruent vs congruent trials in regions of interest (ROIs) identified by meta analysis.

Results: Of the 46 participants with complete data, 29 were male, and mean age was 10.42 ± 0.55 years. Increased POP exposure was associated with reduced accuracy (e.g. PCB molar sum rate ratio = 0.95; 95% CI [0.90, 0.99]), drift rate (e.g. for PCB molar sum $\beta = -0.42$; 95% CI [−0.77, −0.07]), and task-related brain activity (e.g. in inferior frontal cortex for PCB molar sum $\beta = -0.35$; 95% CI [−0.69, 0.02]), and increased ADHD symptoms (e.g. hyperactivity PCB molar sum $\beta = 2.35$; 95% CI [0.17, 4.53]), supporting the possibility that prenatal exposure to POPs is a modifiable risk for ADHD phenotypes.

Discussion: We showed that exposure to POPs is related to task-based changes in neural activity in brain regions important for inhibitory control, suggesting a biological mechanism underlying previously documented associations between POPs and neurobehavioral deficits found in ADHD phenotypes.

1. Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most common childhood neurobehavioral disorders and is associated with a range of long-term negative outcomes, including increased risk for substance use, mood and anxiety disorders, motor vehicle accidents, difficulties with educational achievement and employment status (Sayal et al., 2018; Kupper et al., 2012; Geffen and Forster, 2018). Evidence of benefits of ADHD treatment are more often found in shorter-compared to longer-term follow ups (Arnold et al., 2015), suggesting that long-term sequelae of ADHD persist. During childhood, ADHD creates a significant economic burden for families via increased medical and indirect costs related to absenteeism and reduced productivity (Gupte--Singh et al., 2017). Improved understanding of modifiable risk factors of ADHD could elucidate paths to reducing both the personal and societal burden of this highly prevalent condition.

Studies examining the heritability of ADHD via family, twin and adoption studies, estimate a heritability rate at 74%–88% (Faraone and Larsson, 2019), however, heritability estimates from genome wide association studies (GWAS) are much lower, e.g. 22% (Demontis et al., 2019). The "heritability gap" between estimates from family compared to GWAS studies suggests that the environment may play an important role in ADHD risk. Observations of increasing prevalence rates of ADHD (Sayal et al., 2018; Vasiliadis et al., 2017; Visser et al., 2014) may also suggest that environmental exposures contribute to ADHD, although increased diagnosis and awareness of neurodevelopmental disorders contribute to these observations (Huffling et al., 2016; Lam et al., 2017; Landrigan et al., 2012).

Persistent organic pollutants (POPs), including polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs), are toxic chemicals once widely used in plastics, electrical equipment and flame retardants. Prenatal exposure to PCBs and PBDEs is associated with neurobehavioral deficits related to ADHD in observational studies, including reductions in inhibitory control and attention, and increased externalizing behaviors and ADHD symptoms based on teacher reports (Eubig et al., 2010; Verner et al., 2015; Sagiv et al., 2010, 2015; Stewart et al., 2003, 2005; Jacobson and Jacobson, 2003; Vreugdenhil et al., 2002; Vuong et al., 2018; Eskenazi et al., 2013; Herbstman et al., 2010; de Water et al., 2019). Therefore, prenatal exposure to POPs may be a modifiable risk for ADHD and related behavioral phenotypes.

In recognition of the toxicity of these chemicals, global treaties have banned or slowed the production of many POPs in over 90 countries (e.g. the Stockholm Convention (Stockholm Convention. In:, 2001)). However, POPs persist for long periods, bioaccumulate and move up the food chain (Guo et al., 2019; Norstrom et al., 2010). Due to the persistence of these chemicals, as well as the consumption of animal products in which POPs have bioaccumulated (e.g. meat, fish and dairy (Norstrom et al., 2010)) and the continued release of POPs from existing products (e.g. electronics and furniture (Peltier et al., 2012)), exposure continues to occur, despite the slowing production of POPs. Widespread exposure has been observed in North America, with recent studies finding the majority of the population exposed to PCBs (Singh et al., 2019; Xue et al., 2014) and near universal PBDE exposure (Harley et al., 2010; Rawn et al., 2014).

Prior task-based neuroimaging research documents POP exposure-related differences in neural activation between exposed and non-exposed groups in observational studies (Chu et al., 2019; White et al., 2011). However, only two such studies exist, and they have been limited by small sample sizes (12 and 21 participants, respectively), by restricting analyses to groups exposed to high levels of POPs (due to environmental disaster or high seafood diets), and by only including male participants. Thus, the effects of moderate POP exposure on brain function remain unknown, limiting our ability to develop interventions targeting the neural impact of common levels of POP exposure.

We addressed the limitations outlined above by evaluating the association between moderate prenatal exposure to POPs and neural activation during inhibitory control performance in a larger sample of 46 male and female children 9–11 years of age in the GESTation and the Environment (GESTE) cohort in Sherbrooke, Quebec, Canada, an ongoing prospective birth

cohort of mother-child dyads, moderately exposed to POPs. Inhibitory control was measured via fMRI imaging of the Simon Task, a widely used task that has been found to engage brain regions important for inhibitory control (Hart et al., 2013; Norman et al., 2016), including the inferior frontal cortex (IFC), supplementary motor area (SMA) and anterior insula (AI) (McKenna et al., 2017). Meta-analyses have found decreased activity in IFC, SMA and AI in children with ADHD compared to typically developing children (TDC) (Hart et al., 2013; Norman et al., 2016).

To probe the relationship between POP exposure and inhibitory control, we modeled task performance using the hierarchical drift diffusion model (HDDM version 0.8.0) (Wiecki et al., 2013) estimating latent components of inhibitory control, including the rate at which information is extracted from stimuli and incorporated into decision-making (drift rate) and the level of response caution/impulsivity (boundary separation) (Ratcliff et al., 2016). In line with previous studies of ADHD, we hypothesized that higher levels of POP exposure would be related to reductions in drift rate (Karalunas et al., 2012, 2014; Metin et al., 2013) and that higher levels of POP exposure and deficits in performance would be associated with reduced brain activity in regions important for inhibitory control.

2. Methods

2.1. Study population

Participants were recruited as part of the GESTation and the Environment (GESTE) cohort in Sherbrooke, Quebec, Canada. Between 2007 and 2009, women were recruited during the first trimester of pregnancy and at delivery ($n = 800$). More specifically, 400 mothers were recruited during pregnancy (mean gestational week = 12 weeks, SD = 2.96 weeks), and 400 mothers were recruited at delivery. Maternal blood was collected at delivery to measure levels of POPs, including PCBs and PBDEs from plasma. Participants were followed up over 3 additional waves. Wave 4 is currently being collected, with children aged roughly between 9 and 11 years old. During Wave 4, children were assessed via behavioral measures including performance on the Simon task while undergoing functional magnetic resonance imaging (fMRI), and clinical measures, including parental report of clinical symptomology on the Behavioral Assessment System for Children 3 (BASC-3). Of the 800 mothers recruited during pregnancy and at delivery, 87 of their children provided Simon Task performance at Wave 4, 69 of these participants had analyzed maternal blood plasma samples, collected at delivery, 63 were assessed with the BASC-3, 51 had adequate Simon task performance (>50% accurate while responding to both congruent and incongruent trials), and 46 of these participants had MRI data without artifacts or excessive head motion (flow chart in Fig. S1 in supplement). All 46 participants were assessed with BASC-3 at the Wave 4 follow-up. Three of the 46 participants with adequate MRI data had taken ADHD medication within the last 3 months. Caregivers were asked to withhold this medication on the day of the MRI. Parents provided written informed consent at all waves, and children provided assent at Wave 4. Study protocols were approved by the institutional review boards of the University of Sherbrooke, Quebec, Canada, and Columbia University, New York, New York. This study followed the reporting guideline provided by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

2.2. Exposure assessment

Maternal blood samples (10 mL) were collected at delivery in Sodium/Heparin Vacutainer Hemogard glass tubes (Becton-Dickinson, San Jose, CA). Whole blood was separated into components, and plasma was frozen at −20 °C in decontaminated Supelco glass storage tubes (Supelco, Inc, Bellefonte, Pennsylvania). Maternal plasma concentrations of four PBDE congeners (BDE-47, BDE-99, BDE-100, and BDE-153) and three PCB congeners (PCB-138, PCB-153, and PCB-180) were analyzed using solid-phase extraction and gas chromatography-electron capture negative ionization mass spectrometry (Serme-Gbedo et al., 2016; Abdelouahab et al., 2013). The limit of detection (LOD) was established at 0.1 pg/μL for PBDEs and at 0.02 pg/μL for PCBs. Values below the LOD were replaced by LOD divided by the square root of 2 (Baccarelli et al., 2005). Total plasma lipids were measured in maternal blood at delivery with the Phillips method (Phillips et al., 1989).

2.3. Image acquisition

Children ages 9–11 were scanned with a 3-T whole-body scanner using a 32-channel head coil (Ingenia; Philips Healthcare), providing T1-weighted structural and functional images (TR = 1075 ms, 290 vol per participant). Images were acquired on a Phillips Healthcare Ingenia 3 T whole-body scanner with a 32-channel head coil. For the T1-weighted structural scans, the imaging parameters were: T1 3D TFE (Turbo Field Echo) pulse sequence, 8° flip angle, FOV 240 mm, matrix size 240 × 240, slice thickness 1 mm. For task-based MRI, echoplanar images were collected with the following parameters: TR = 1075 ms, TE = 30 ms, 55° flip angle, single excitation per image, FOV 240 mm, matrix size 80 × 80, slice thickness 3 mm, 48 slices. Three runs of 290 vol were collected for each participant.

2.4. MRI preprocessing and approaches to head motion during scanning

To prepare fMRI data for first level analyses, the following steps were taken. First, a trained researcher visually inspected each structural image and the functional images from each run. For every functional task-based run, a separate 5 vol run was collected with reversed phase-encoded blips, providing a sequence of images with geometric distortions in the opposite direction. FSL's topup function was used to estimate and correct the susceptibility-induced off-resonance field (Smith et al., 2004).

Following distortion correction, the following preprocessing steps were taken in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/): slice timing correction, realignment, coregistration, segmentation, normalization and smoothing. We took several steps to limit the influence of in-scanner head motion on results. First, volumes with more than 0.5 mm framewise displacement were excluded from analyses. In addition, the six time-dependent motion parameter estimates output from registration, and the squares of the motion parameters and temporal derivatives were applied in multiple linear regression to remove the "nuisance" effects captured in these 24 parameters from the fMRI data (Friston et al., 1996; Power et al., 2012, 2014). Finally, subjects with more than 30% of volumes with more than 0.5 mm framewise displacement were excluded from analyses. The Statistical Parametric Mapping (SPM 12) software package was used for preprocessing as well as for first- and second-level analyses of task-based brain activity (see Statistical Analyses below) (Penny et al., 2011).

2.5. Task-based fMRI assessment

Inhibitory control was measured via the Simon spatial in-compatibility task, first developed in the 1960s, which has been widely used to examine inhibitory control, the neural correlates of inhibitory control, and neural and behavioral differences between children with and without an ADHD diagnoses (Hart et al., 2013; McKenna et al., 2017; LeMay and Simon, 1969; Simon and Reeve, 1990; Lu and Proctor, 1995; Mullane et al., 2009; Liu et al., 2004; Cespon et al., 2020). Stimuli were presented using EPRIME software (E-Prime 3, 2016) across three runs. White arrows pointing left or right were displayed against a black background to the left or right of a central white fixation cross. Participants were asked to report which direction the arrow was pointing while ignoring which side of the screen the arrow was presented on. Trials were either congruent: the stimulus pointed to the same side of the screen it was presented on, or incongruent: the stimuli pointed to the opposite side of the screen. Each run consisted of 22 congruent and 22 incongruent trials, counterbalanced to include equal numbers of trials presented on the left and right (Fig. S2 in the supplement).

2.6. Drift diffusion modeling of Simon Task performance

The drift diffusion model (DDM) uses the accuracy and the distribution of reaction times from task performance to model cognitive processes involved in decision making. The DDM assumes that on each trial of the Simon Task, perceptual evidence is accumulated until it reaches an evidence threshold and a response is made. The rate of evidence accumulation is modeled as the drift rate v, and the level of response caution is modeled by the boundary separation parameter, a. Parameters were estimated separately for congruent and incongruent trials. Model fits were validated by checking whether the posterior predictive distribution could reproduce key features of the subject- and group-level response distributions – e.g. mean reaction times and error rates.

2.7. Clinical outcomes

The BASC-3, collected via parent ratings (BASC-PRS), was used to assess clinical outcomes relevant to ADHD phenotypes during the same visit that task fMRI data were gathered (Reynolds CRK, 2015). T-scores from BASC-3 clinical indices, clinical scales, and content scales were used, including the ADHD Probability Index, Attention Problems, Hyperactivity, and Executive Functioning.

2.8. Covariates

All models were adjusted for covariates hypothesized to either confound the relationship between exposures and outcomes, or to add precision to effect estimation. The covariates used to adjust models include child age and estimated IQ percentile (assessed via the full scale Wechsler Intelligence Scale for Children V (Wechsler, 2014)), child sex, maternal age at birth, parity (first born vs not first born), breastfeeding (yes/no), maternal total plasma lipids at delivery, maternal education as a proxy measure of socioeconomic status (college vs no college), maternal BMI, maternal self-reported smoking during pregnancy (yes/no) and maternal alcohol use during pregnancy (yes/no). Missing covariate data were imputed with the median and mode for continuous and categorical variables, respectively. Differences in covariate distributions between our study sample (after imputing missing data) and the rest

of the cohort were determined using chi-square goodness of fit tests for binary variables and two-sample t-tests for continuous variables (see Table S2 in the supplement). In a sensitivity analysis, all models were repeated with lipid standardization (congeners were expressed as nanogram of exposure per gram of lipid, before being scaled and centered) rather than including total lipids as a covariate.

3. Statistical analysis

3.1. Exposures and outcomes

In addition to modeling each PCB or PBDE congener individually, we created sum variables by adding the molar concentrations of all PCBs or PBDEs. Both molar sums and individual PCB or PBDE congeners were modeled in units of standard deviations from the mean (z-scores). We constructed a pairwise Pearson correlation matrix for all exposures (Fig. S3 in supplement). We estimated associations of each PCB and PBDE congener as well as their molar sums with Simon task accuracy using trials-based quasi-Poisson models. In separate models for congruent and incongruent trials, we set the total number of trials as the offset and modeled the number of correctly answered trials as the outcome. Using linear regressions, we modeled the associations of PCB and PBDE congeners as well as their molar sums with the a and v parameters from the DDM, MRI brain activity, and BASC-PRS scores. While parameter estimates derived from hierarchical models are not independent, recent work indicates that this is not a problem for subsequent correlation analyses (Katahira, 2016). We additionally investigated non-monotonic associations and mixture interactions using Bayesian kernel machine regression (BKMR) (Bobb et al., 2015). We report two outputs from BKMR. First, univariate associations of each congener with each BASC-PRS outcome modeled with penalized splines to assess non-monotonic associations. In univariate models, all other PCB and BDE congeners are fixed to the 50th percentile. Second, we report interactions of each congener with the rest of the mixture. In this method, for each congener, we modeled the associations of being at the 75th percentile compared to the 25th percentile of exposure with each BASC-PRS outcome. These models were repeated three times with all other congeners fixed to the 25th, 50th, and 75th percentiles. Any congener having different associations with the BASC-PRS outcomes depending on the fixed level of the other congeners would be interpreted as an interaction with the mixture. A sensitivity analysis accounting for ADHD medication found no meaningful differences (see supplement). Statistical analyses were conducted with R 4.1.0 (R: A language and environ, 2017).

3.2. fMRI analyses

Following distortion correction, standard preprocessing was performed in SPM12 (Penny et al., 2011). First-level analyses were performed for each participant using the general linear model function in SPM 12 (Penny et al., 2011). For correct trials only, BOLD contrast data were modeled separately for congruent and incongruent trials. To examine condition-related differences in neural activity, a contrast modeling incongruent minus congruent trials was created. Inhibitory control is associated with brain activity in the right IFC (rIFC), SMA and right AI (rAI), and differences in brain activity between TDC and children with ADHD performing inhibitory control tasks have been found in these regions (Hart et al., 2013;

Norman et al., 2016; McKenna et al., 2017; Aron et al., 2014). Therefore, we created 5 mm ROI spheres of these regions based on coordinates (Table S1 in the supplement) from a meta-analysis of TDC aged 6–12 performing inhibitory control tasks using MarsBaR (Brett et al., 2002). Incongruent minus congruent activity was extracted from each of these three ROIs. To determine if significant inhibitory control-related activity was present within each ROI, one sample t-tests, two-sided, were performed with SPSS 26(IBM SPSS, 2019), with an FDR correction to account for multiple comparisons. The relationship between exposure and brain activity was examined in ROIs with significant inhibitory control-related activity using linear regressions controlling for the covariates described above.

4. Results

Characteristics of the study population and covariates are reported in Table 1. Compared to the rest of the cohort, our study sample had significantly reduced maternal smoking during pregnancy and increased breastfeeding (Table S2 in the supplement). The Simon effect was found among our sample of 46 children (29 male; mean age 10.42 ± 0.55); in other words, participants performed more accurately ($t_{45} = 2.27$ $p = 0.03$) and more quickly ($t_{45} = 4.29$, $p < 0.01$) on congruent compared to incongruent trials.

Because POP exposures followed a lognormal distribution, we present the geometric mean (GM) and standard deviation (GSD) for each congener (Table 2). Pearson correlations POP congeners were observed, and are reported in Fig. S3 in the supplement. High correlations between PCB-138, PCB-153, and PCB molar sum ($r2 > 0.95$) were found, while correlations between PCB-180 and all other PCBs were substantially lower ($r2 < 0.50$).

4.1. Exposure and Simon Task performance

PCBs and PBDEs were associated with decreased Simon Task accuracy on congruent trials (Fig. 1; the numeric data used in the figures can be found in tables in the supplement). Standard deviation unit increases in the molar sums of PCB and BDE exposures were separately associated with approximately 5% and 6% decreased accuracy on congruent trials, respectively (PCB rate ratio = 0.95; 95% CI [0.90, 0.99]; BDE rate ratio = 0.94; 95% CI [0.90, 0.99]). Increases in PCB-138, PCB-153, BDE-99, BDE-100, and BDE-153 were similarly associated with decreased accuracy on congruent trials, while PCB-180 and BDE-47 were not.

On incongruent trials, no exposures were associated with accuracy.

We observed similar patterns of association between exposures and DDM drift rate parameters (Fig. 1). On congruent trials, each one standard deviation unit increase in the molar sum of PCB exposure was associated with a 0.42-point decrease ($\beta = -0.42$; 95% CI [−0.77, −0.07]), and each standard deviation unit increase in the molar sum of BDE exposure was associated with a 0.45-point decrease ($\beta = -0.45$; 95% CI [−0.80, −0.10]) in the drift rate parameter. We observed similar trends with PCB-138, PCB-153, BDE-47, and BDE-99, while there were no associations of PCB-180, BDE-100 and BDE-153 with drift rate. Neither PCBs nor PBDEs were associated with drift rate on incongruent trials, or with boundary separation on congruent or incongruent trials.

4.2. Exposure and Simon Task-Related brain activity

Because PCBs and PBDEs were associated with Simon task performance, we hypothesized that they may also affect task-related brain activity in regions previously implicated in inhibitory control. Significant FDR corrected incongruent minus congruent activity was found in the rIFC ($t_{45} = 2.57$, $p = 0.01$), and the rAI ($t_{45} = 2.40$, $p = 0.02$), but not the SMA. Mirroring their associations with Simon task accuracy, PCB-138 (β =−0.38; 95% CI [−0.71, −0.06]), PCB-153 (β = −0.33; 95% CI [−0.63, −0.02]), and the molar sum of PCBs (β = −0.35; 95% CI [−0.69, −0.02]) were associated with decreased rIFC brain activity, while PCB-180 was not (Fig. 2). No PBDEs were associated with rIFC brain activity, but increased BDE-153 exposure was associated with decreased activity in the rAI (β = −0.41; 95% CI [−0.75, −0.07]). No other exposures were associated with brain activity in the rAI.

4.3. Exposure and clinical outcomes

Several PCBs and one PBDE were associated with BASC-PRS scores (Fig. 2). Each standard deviation unit increase in prenatal PCB-180 exposure was associated with higher ADHD Probability Index (β = 2.54; 95%CI [0.19, 4.89]) and Hyperactivity t-scores (β = 3.37; 95%CI [0.77, 5.97]), while PCB molar sum was only associated with hyperactivity (β = 2.35; 95%CI [0.18, 4.53]). Increased prenatal BDE-153 exposure was associated with lower executive functioning scores (β = −2.34; 95% CI [−4.24, −0.43]). Neither PCBs nor PBDEs were associated with Attention Problems. Models results were not substantially different in sensitivity analyses with lipid standardization (Figs. S4 and S5). Univariate BKMR models suggested a non-linear, "inverted-U" relationship of PCB-153 with ADHD Probability Index, Hyperactivity, and Attention Problems (Supplemental Fig. S6). Associations of the remaining congeners with BASC-PRS scores were mostly linear, although there were some "threshold effects" in which linear dose-responses flattened out at higher levels of exposure. The relationships of each congener with each BASC-PRS outcome did not substantially differ when the rest of the mixture was set to the 25th, 50th, or 75th percentile of exposure, suggesting no interactions (Supplemental Fig. S7).

5. Discussion

This observational study found that in a prospective, community sample of Canadian mother-child dyads moderately exposed to PCBs and PBDEs, increased exposure was associated with increases in neurobehavioral deficits found in ADHD ($n = 46$), providing support for the possibility that prenatal exposure to POPs is a modifiable risk for ADHD phenotypes. As hypothesized, we found that increases in prenatal POP exposure were associated with decrements in accuracy and drift rate, and reduced task-related brain activity during an inhibitory control task in children aged 9–11. In addition, increased levels of prenatal POPs were associated with increased clinical symptoms of ADHD, including increased Hyperactivity t-scores and increased scores on the ADHD Probability Index. Results presented here are also consistent with studies of other POPs, such as per-and polyfluoroalkyl substances (PFAS), which have been found to have an inverse relationship with neurodevelopmental measures and cognitive performance (Wang et al., 2015; Goudarzi et al., 2016; Spratlen et al., 2020; Park et al., 2021). To the best of our knowledge, this is the first study to show that POP exposure is related to task-based changes in neural activity in

brain regions important for inhibitory control, suggesting a biological mechanism underlying previously documented associations between POP exposure and neurobehavioral deficits found in ADHD, including deficits in inhibitory control (Verner et al., 2015; Stewart et al., 2003, 2005; Jacobson and Jacobson, 2003).

Consistent with previous studies of ADHD (Karalunas et al., 2012, 2014; Metin et al., 2013), computational modeling revealed that POP-related decrements in accuracy were driven by slower drift rate, suggesting that POP exposure reduces the rate at which data can be extracted and incorporated into decision-making. Preclinical research in animal models has shown that POP exposure leads to impaired dopamine neurotransmission (Pessah et al., 2019; Seegal et al., 1991). In light of previous studies linking dopaminergic dysfunction to both ADHD and slowed drift rate, and ADHD medication (methylphenidate) with increased drift rate (Gold et al., 2014; Del Campo et al., 2011; Beste et al., 2018), these findings suggest a possible biological substrate for the observed POP-mediated decrements in task performance.

By examining the association between ADHD-related behaviors and symptoms with both the molar sums of PCBs and PBDEs and specific POP congeners, these results allow us to examine associations common across POP congeners as well as cases where a specific congener related to clinically relevant outcomes. Our data suggest that PCB and PBDE congeners have relatively uniform relationships with Simon Task behavoral indices, including accuracy and drift rate, but congener-specific relationships with ADHD-related clinical outcomes, such as the association between PCB-180 and the ADHD Probability Index and Hyperactivity t-scores on the BASC-3. However, differences between POP-Simon task performance associations and POP-ADHD symptom associations may be due to the Simon task measuring inhibitory control, and thus may track aspects of ADHD-*risk* more closely than the BASC-3, which measures clinical outcomes (Young et al., 2009). For example, inhibitory control, measured at age 5 has been shown to predict executive functioning in middle childhood (Berlin et al., 2003). Therefore, Simon task-based measures may reflect congener-specific associations with inhibitory control deficits more clearly than the BASC-3 scores we examined, which reflect ADHD symptomatology. In sum, congener specific results may reflect unique associations or the increased signal in the relationship between prenatal exposures and Simon Task performance compared to BASC-3 outcomes.

Prior studies have documented differential effects of specific POP congeners on neurobehavioral outcomes (Boix et al., 2011; Brun et al., 2021; Coburn et al., 2008; Usenko et al., 2015; Fernie et al., 2005). Specifically, prior work suggests that PCB-180 may relate to neural correlates and downstream outcomes differently than other PCB congeners. For example, pre-clinical work has shown that rats exposed prenatally to PCB-180 had increased extra-cellular dopamine in the nucleus accumbens, unlike rats who had been exposed to PCB-52 or PCB-138 (Boix et al., 2011). In addition, male rats prenatally exposed to PCB-180 also had reduced motor activity (Boix et al., 2011). In our study we found that, in contrast to other PCB congeners, prenatal exposure to PCB-180 was significantly associated with clinical outcomes measured on the BASC-3, but not with Simon task performance. Furthermore, it is possible that PCB-180 also had specific, unmeasured, neural effects in our sample that were associated with clinical problems indexed by BASC-3. Taken together,

these findings suggest that the specific neural effects of PCB-180 may have unique effects on ADHD symptoms.

We similarly observed associations between specific PCB and PBDE congeners and neural activity in different brain ROIs: PCBs, but not PBDEs, contributed significantly to reductions in brain activity in rIFC, while only BDE-153 was significantly related to reduced brain activity in rAI. Again, these associations could reflect congener-specific relationships with brain activity, or alternatively, demonstrate that certain brain regions may be more sensitive indicators of neurobehavioral changes than others. While many associations did not reach significance, most congeners tended towards an association with reduced activity in both brain regions (except PCB-180), suggesting that with a larger sample, it is possible that other congeners would also be associated with reduced brain activity in IFC and AI. Lastly, univariate BKMR models suggested that PCB-153 had an inverted "u-shaped" non-linear relationship with ADHD clinical outcomes while most other congeners had linear associations (Supplemental Fig. S6), further underscoring how PCBs may have unique, congener-specific relationships with outcomes.

While, PCBs and PBDEs had an overall negative relationship with Simon task brain activity, only some congeners reached statistical significance. Furthermore, these were not generally the congeners that contributed significantly to clinical ADHD problems indexed by the BASC-3. Of the exposures that related to reduced inhibitory control-related brain activity, only the PCB molar sum was significantly related with the BASC-3 hyperactivity scale, but the association between hyperactivity and PCBs 138 and 153 was still in the expected direction. This discrepancy may be partially explained by a lack of power. For example, the PCB molar sum, PCB-138 and PCB-153 were all significantly associated with reduced activity in the rIFC, but not rAI, although they tended in the same direction. However, while the IFC and AI are both involved with inhibitory control, they also have dissociable roles: for example, activity in IFC, but not AI, has been found to predict individual differences in inhibitory control, while multivoxel patterns of activation in the AI, but not the IFC, can differentiate between correct and incorrect task performance (Cai et al., 2014). It is possible that these dissociable roles may help to explain why only PCBs were significantly associated with rIFC activity, and only one BDE congener was significantly associated with rAI activity.

We chose to allow our examination of brain activity to be hypothesis driven, and restricted analyses to ROIs defined by previous research in healthy children performing inhibitory control tasks. Therefore, it is possible that PCB-180 exposure related to neural activity in other brain regions not examined by this study, and that alterations in these unexamined brain regions during task performance relate to clinical symptoms. Future studies are required to determine if the differences between the effects of PCBs and PBDEs, and differences between congeners of PCBs and PBDEs observed here replicate in other samples. In addition, future work in non-human animals may be able to determine a more causal relationship between different POP types, and inhibitory control-related neural activity.

Replicating previous studies, this study found that POP exposure is linked with ADHD-related behaviors and symptoms (Verner et al., 2015; Sagiv et al., 2010; Stewart et al., 2005; Stewart et al., 2003; Jacobson and Jacobson, 2003; Vreugdenhil et al., 2002; Vuong et al., 2018; Eskenazi et al., 2013; Herbstman et al., 2010; Sagiv et al., 2015; de Water et al., 2019; Stockholm Convention. In:, 2001). Furthermore, results from this moderately exposed community sample may be more generalizable than previous studies, which were focused on highly exposed populations. Findings from this study may help future prevention, policy, and intervention efforts. More specifically, the following prevention efforts aimed at reducing the long-term negative effects of POP exposure could be explored in future research: targeting POPs in environmental cleanup efforts, altering eating guidelines during pregnancy to reduce POP exposure, and testing mothers at birth for POP levels to identify at-risk children.

Results from the current study are also consistent with research finding that exposure to other POPs, such as PFAS, has an inverse relationship with neurodevelopmental measures (Wang et al., 2015; Goudarzi et al., 2016; Spratlen et al., 2020). Pre-clinical research in rodents suggests that metabolic and elimination differences with POPs, including PCBs, PBDEs, and PFAS can be sex-dependent (Roth et al., 2021; Wu et al., 2013; Staskal et al., 2006). Therefore, examining if sex influences the relationship between POP exposure and ADHD phenotypes is an important goal for future research.

5.1. Strengths and limitations

Strengths of the present study include the measurement of POP exposure at birth in a cohort of prospectively followed children, in whom inhibitory control performance and related brain activity were measured at ages 9–11. While previous studies have documented a relationship between increased POP exposure and increased neurobehavioral deficits associated with ADHD, as well as POP-exposure related differences in brain activity, this study examined neural activity while performing a task used to assess inhibitory control in ADHD, allowing us to examine the relationship between prenatal POP exposure and childhood task-based brain activity. In addition, this study used computational modeling to elucidate the relationship between prenatal POP exposure and latent cognitive processes underlying inhibitory control during childhood.

While the present study accounted for key confounders, results could be influenced by unmeasured factors during the time between exposure and measurement of outcomes. It is possible that unknown genetic, social, cultural and familial factors could influence POP exposure. Finally, results could be prone to selection bias owing to loss to follow-up between recruitment and the Wave 4 visit, as well as differences in the rates of maternal smoking during pregnancy and breastfeeding between our study sample and the rest of the cohort.

6. Conclusions

By measuring the effects of prenatal POP exposure on inhibitory control task-related neural activity and performance, this study provides a plausible brain mechanism by which POP exposure may lead to neurobehavioral deficits found in ADHD. Computational modeling results revealed that, like ADHD, POP exposure slows drift rate on task performance.

Together, these results support the possibility that prenatal POP-exposure could be a modifiable risk factor for ADHD phenotypes. Results from this study suggest novel approaches to prevention and intervention. Future research could determine if targeting POPs in environmental cleanup efforts could reduce the risk for ADHD phenotypes, if it is appropriate to change eating guidelines during pregnancy to reduce POP exposure, and if testing mothers at birth for POP levels could help identify at-risk children. Furthermore, future studies could examine the possibility that pharmacotherapies such as methylphenidate could treat POP-driven neurobehavioral deficits. Finally, future studies with larger sample sizes could help determine if the congener-specific results found here replicate reliably.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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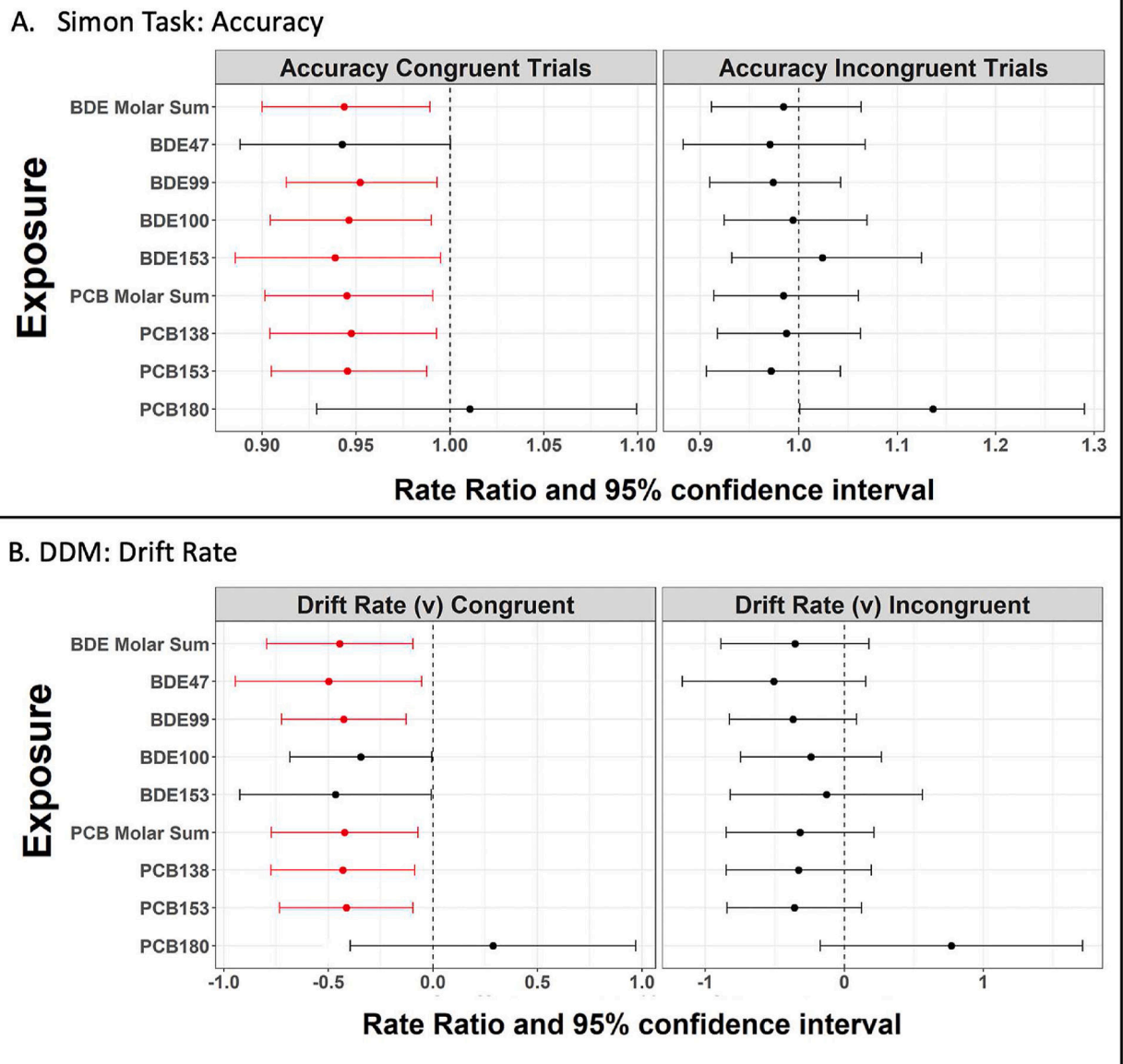
Fig. 1.
A) POP exposure was associated with accuracy on an inhibitory control (Simon) task, n = 46, according to quasi-Poisson models. B) Drift diffusion model parameters were estimated using the HDDM toolbox (n = 46). POP exposure was associated with drift rate on congruent, but not incongruent trials, according to linear regression analayses.
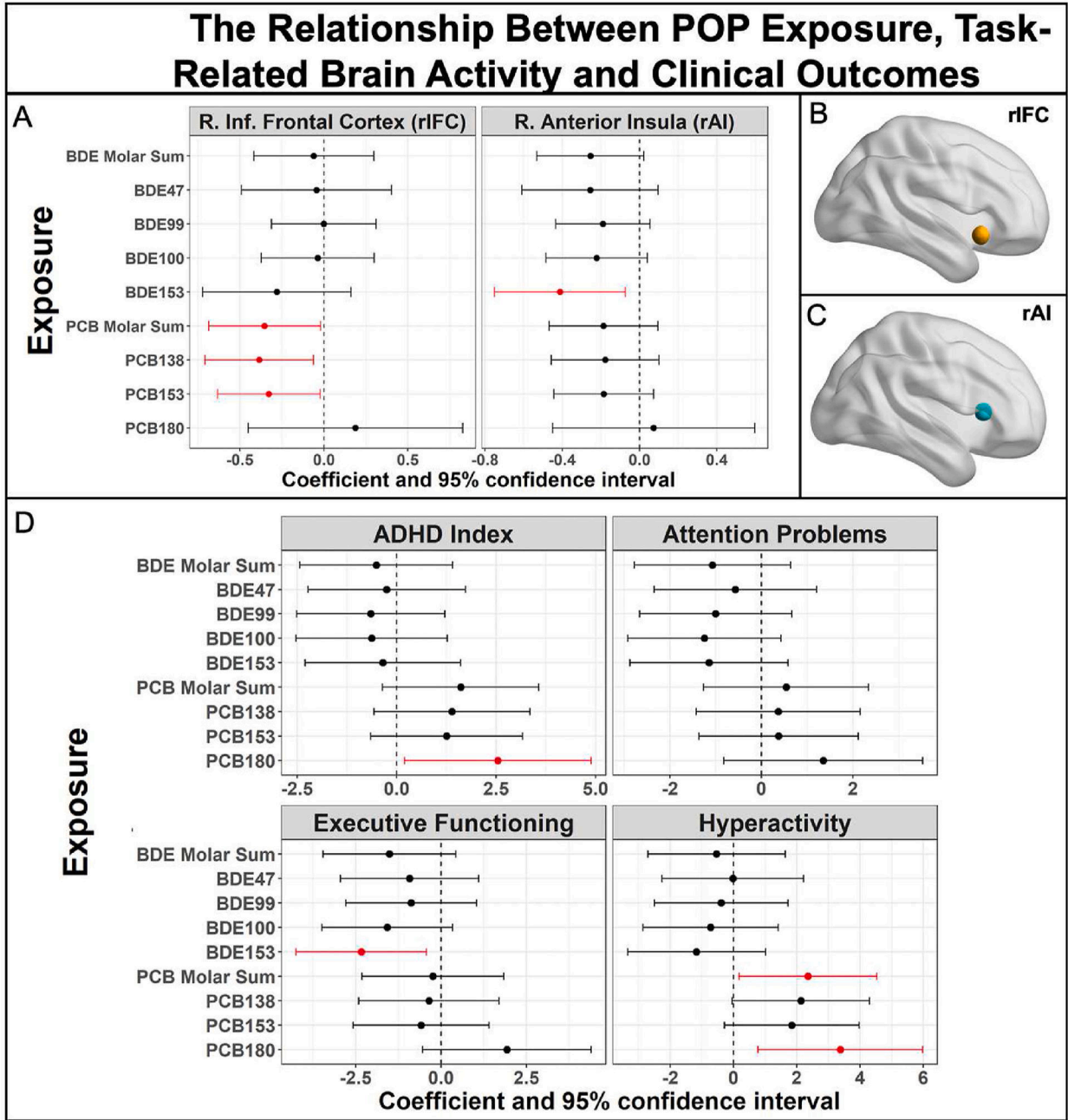
Fig. 2.

A) Inhibitory control task-based activity in right Inferior Frontal Cortex (rIFC) and right Anterior Insula (rAI) related to exposure to POPs, n = 46, according to linear regression analyses. B) A 5mm sphere in rIFC, based on a meta analysis of typically developing children performing inhibitory control tasks, from which task-based activity was extracted. C)A 5 mm sphere in rAI, based on the same meta analysis. D) Exposure to POPs were associated with ADHD related symptoms measured by the BASC-3,n = 63, according to linear regression analysis.

Table 1

Characteristics of study population in the GESTE cohort.

	Overall (N = 63)
Sex	
Female	23 (36.5%)
Male	40 (63.5%)
Child age at visit	
Mean (SD)	10.65 (0.42)
Range	9.61–11.45
Maternal age at delivery	
Mean (SD)	28.92 (4.78)
Range	19–40
Maternal education	
N-Miss	1
No college	23 (36.5%)
Some College	40 (63.5%)
Alcohol during pregnancy	
No	44 (69.8%)
Yes	19 (30.2%)
Smoked during pregnancy	
No	61 (96.8%)
Yes	2 (3.2%)
Parity	
First Born	31 (49.2%)
Not First Born	32 (50.8%)
Breastfeeding	
No	30 (47.6%)
Yes	33 (52.4%)
Maternal BMI	
N-Miss	3
Mean (SD)	25.21 (5.23)
Range	15.67–46.05
IQ (percentile) [a]	
Mean (SD)	60.03 (24.09)
Range	9.00–99.00

[a] A score in the 50 percentile = a standard score of 100, which is in the normal range.

Table 2

Levels of POP Exposure in the GESTE Cohort (Exposures in ng/ml).

	Overall (N = 63)	N (%)<LOD	Geometric mean (GSD)
Total lipids (g/L)			
N-Miss	1		
Mean (SD)	6.70 (1.24)		
Range	4.30–11.43		
BDE-47			
Mean (SD)	0.12 (0.16)	0 (0%)	0.06 (3.38)
Range	0.01–0.85		
BDE-99			
Mean (SD)	0.06 (0.11)	7 (11%)	0.02 (4.60)
Range	0.00–0.59		
BDE-100			
Mean (SD)	0.07 (0.11)	7 (11%)	0.03 (4.00)
Range	0.00–0.54		
BDE-153			
Mean (SD)	0.08 (0.10)	8 (13%)	0.04 (3.52)
Range	0.00–0.49		
PCB-138			
Mean (SD)	0.05 (0.08)	13 (21%)	0.02 (4.08)
Range	0.00–0.58		
PCB-153			
Mean (SD)	0.08 (0.12)	5 (8%)	0.05 (3.13)
Range	0.00–0.92		
PCB-180			
Mean (SD)	0.04 (0.04)	8 (13%)	0.02 (2.94)
Range	0.00–0.21		