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Prenatal exposure to organophosphorus pesticides and childhood neurodevelopmental phenotypes

Melissa A. Furlong[a,*], Amy Herring[b], Jessie P. Buckley[c], Barbara D. Goldman[d], Julie L. Daniels[a], Lawrence S. Engel[a], Mary S. Wolff[e], Jia Chen[e], Jim Wetmur[f], Dana Boyd Barr[g], Stephanie M. Engel[a]

[a] Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, United States
[b] Department of Statistical Science and Global Health Institute, Duke University, United States
[c] Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health, United States
[d] Department of Psychology and Neuroscience & FPG Child Development Institute, University of North Carolina at Chapel Hill, United States
[e] Department of Environmental Medicine and Public Health, Mount Sinai School of Medicine, United States
[f] Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, United States
[g] Department of Environmental Health, Rollins School of Public Health, Emory University, United States

ABSTRACT

Prenatal exposure to organophosphorus pesticides (OPs) has been associated with different neurodevelopmental outcomes across different cohorts. A phenotypic approach may address some of these differences by incorporating information across scales and accounting for the complex correlational structure of neurodevelopmental outcomes. Additionally, Bayesian hierarchical modeling can account for confounding by collinear co-exposures. We use this framework to examine associations between prenatal exposure to OPs and behavior, executive functioning, and IQ assessed at age 6–9 years in a cohort of 404 mother/infant pairs recruited during pregnancy. We derived phenotypes of neurodevelopment with a factor analysis, and estimated associations between OP metabolites and these phenotypes in Bayesian hierarchical models for exposure mixtures. We report seven factors: 1) Impulsivity and Externalizing, 2) Executive Functioning, 3) Internalizing, 4) Perceptual Reasoning, 5) Adaptability, 6) Processing Speed, and 7) Verbal Intelligence. These, along with the Working Memory Index, were standardized and scaled so that positive values reflected positive attributes and negative values represented adverse outcomes. Standardized dimethylphosphate metabolites were negatively associated with Internalizing factor scores ($\hat{\beta}$ − 0.13, 95% CI − 0.26, 0.00) but positively associated with Executive Functioning factor scores ($\hat{\beta}$ 0.18, 95% CI 0.04, 0.31). Standardized diethylphosphate metabolites were negatively associated with the Working Memory Index ($\hat{\beta}$ − 0.17, 95% CI − 0.33, − 0.03). Associations with factor scores were generally stronger and more precise than associations with individual instrument-specific items. Factor analysis of outcomes may provide some advantages in etiological studies of childhood neurodevelopment by incorporating information across scales to reduce dimensionality and improve precision.

1. Introduction

Prenatal exposure to organophosphorus pesticides (OPs) has been associated with impaired neurodevelopment in both urban (Engel et al., 2016, 2011; Rauh et al., 2006) and agricultural populations (Eskenazi et al., 2007). Specifically, prenatal OP exposure has been associated with measures of cognition, including lower IQ scores and lower scores on the Bayley Scales of Infant Development Mental Development Index (Engel et al., 2016; Eskenazi et al., 2007; Rauh et al., 2006); developmental delay (Liu et al., 2015, 2016); as well as various measures of behavior, including impaired social responsiveness (Furlong et al., 2014); indicators of Pervasive Developmental Disorder (Eskenazi et al., 2007); and inattention (Marks et al., 2010).

Although the literature linking prenatal OP exposure to neurodevelopment is robust, the exact nature of the neurodevelopmental deficit imparted by OPs is difficult to determine based on the existing evidence. Typically, studies have considered only a single component of neurodevelopment at a time, such as IQ or behavior. However, there are major conceptual advantages in jointly modeling domains of neurobehavioral development (Rauh and Margolis, 2016; Robinson, 2012).

* Correspondence to: University of Arizona, PO Box 245163, Tucson, AZ 85724-5163, United States.
E-mail address: mfurlong@email.arizona.edu (M.A. Furlong).

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Accounting for the interrelations between developmental domains is more clinically relevant because neurological functions are mutually dependent. For example, higher-level inhibitory control – typically considered to be a component of executive functioning – relies on more basic processing speed capability, which is typically measured in intelligence tests (Ridderinkhof and van der Molen, 1997). By jointly considering behavior, cognition, and executive functioning, we may also better characterize patterns of deficits in neurodevelopment (Castellanos et al., 2006; Mattison and Mayes, 2012; Sinzig et al., 2008) that result from OP exposure, which may ultimately provide insights into etiological pathways. Disruptions to an underlying process may have cascading effects upon other biological processes, which could result in the clustering of behaviors into phenotypes. For instance, OPs can negatively influence serotoninergic and dopaminergic processing (Aldridge et al., 2005a, 2005b, 2004; Slotkin and Seidler, 2008; Venerosi et al., 2010). Serotonin, in turn, can influence aggression, other problematic social behaviors, depression, and Attention Deficit Hyperactivity Disorder (Cadoret et al., 2003; Eley et al., 2004; Zoroğlu et al., 2002). Animal and human studies do support that OPs may be associated with these outcomes (Bouchard et al., 2010; Eskenazi et al., 2007; Furlong et al., 2014; Middlemore-Risher et al., 2010; Ricceri et al., 2003, 2006). Other biological mechanisms, such as oxidative stress (Soltaninejad and Abdollahi, 2009), DNA damage (Mehta et al., 2008), and long lasting impacts on the dopaminergic systems (Aldridge et al., 2005b), may have downstream effects on a variety of outcomes that could coalesce into a phenotypic presentation of traits.

Just as neurodevelopment is complex and multifaceted, so is human exposure to environmental chemicals (Stingone et al., 2017). Previous studies of OPs and neurodevelopment have generally not considered multiple chemical co-exposures, which may, if correlated, confound or alter the OP-neurodevelopment relationship (reviewed in (Bellinger, 2013)). Chemicals may be correlated with each other due to similar sources, such as plasticizers in consumer products, insecticides for pest control, or multiple compounds found in food due to production, delivery practices, or common dietary patterns (Engel and Wolff, 2013). In the Mount Sinai Children's Environmental Health Center, prenatal exposure to several potential neurotoxicants was measured, including OP pesticides, as well as pyrethroids, phthalates and environmental phenols (Barr et al., 2005; Berkowitz et al., 2003; Engel et al., 2011; Wolff et al., 2008). Exposure to these chemicals was widespread in this population due to the approved use of OP pesticides for residential pest control during this period, a city-wide pesticide spraying program to control West Nile Virus in the late 1990s and early 2000s (Gyure, 2009; Thier, 2001), and placement of phthalates and phenols in consumer products commonly used by reproductive aged women (Buckley et al., 2012).

In order to explore the impact of multi-dimensionality in both exposures and outcomes, we evaluate associations between OPs and neurodevelopmental phenotypes, while accounting for chemical co-exposures (specifically, phthalates, phenols, and pyrethroid pesticides). Since prior studies of OPs and neurodevelopment report subgroup heterogeneity (Engel et al., 2011; Furlong et al., 2014), we also consider possible sources of heterogeneity in associations due to race/ethnicity, child sex, and genetic variants in *PON1,* a gene which is involved in the detoxification of OPs.

2. Methods

2.1. Study Recruitment and Population

The Mount Sinai Children's Environmental Health Center is a prospective cohort study of 404 mother infant-pairs from New York City. We recruited women during prenatal visits at either the Mount Sinai Diagnostic and Treatment Center, which serves a predominantly East Harlem population, or one of two private practices on the Upper East Side of Manhattan. Eligible mothers were primiparous with singleton pregnancies, and delivered at the Mount Sinai Hospital between May 1998 and July 2001 (Berkowitz et al., 2003, 2004). Exclusions have been detailed elsewhere (Berkowitz et al., 2003; Engel et al., 2007). Mothers completed questionnaires during their third trimester that assessed a variety of sociodemographic, behavioral, and medical history characteristics. We also obtained maternal spot urine samples between 25 and 40 weeks of gestation (mean = 31.2 weeks).

We invited participants to return for follow-up visits with their child at ages 1, 2, 4–5, 6, and 7–9 years. At follow-up visits, mothers completed questionnaires describing sociodemographic features and developmental milestones. The Home Observation for Measurement of the Environment (HOME scale) (Bradley et al., 1989) was administered in the office at the 1 and 2 year follow-up visits. The HOME subscales include Involvement, Learning Materials, Organization, Acceptance, Responsivity, and Variety (descriptions provided in Appendix A).

2.2. Exposure biomarker measurements and PON1

Six dialkylphosphate metabolites, including three dimethylphosphate (DMP) and three diethylphosphate (DEP) metabolites, were analyzed in two batches between 2002 and 2003 at the Centers for Disease Control and Prevention (CDC). Quality control and laboratory methods have been published previously (Barr et al., 2005; Bravo et al., 2004).

Samples were also analyzed for 9 phthalate, 3 pyrethroid, and 5 phenol metabolites, using laboratory and quality control methods that have been described previously (Barr et al., 2010; Kato et al., 2005; Ye et al., 2005). Briefly, phthalates in urine were measured using automated sample preparation and an on-line solid-phase extraction method in conjunction with isotope dilution high-performance liquid chromatography/tandem mass spectrometry (SPE-HPLC-MS) (Kato et al., 2005). Urinary phenols were also measured using SPE-HPLC-MS (Ye et al., 2005). For the pyrethroids, an internal standard mixture of isotopically labeled 3-phenoyxbenzoic acid (3-PBA) and *trans*-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (*t*-DCCA) was used to spike 2 mL of urine, which was then incubated with Beta-glucuronidase/sulfarase to liberate the conjugated metabolites. Hydrolysates were extracted with OASIS HLB mixed-mode solid-phase extraction cartridges, which were then washed with 5% methanol in a 0.1% acetic acid solution. Metabolites were eluted with methanol. HPLC/MS was used to analyze the extracts. *t*-DCCA was quantified with isotope dilution calibration, while 3-PBA and *c*-DCCA were quantified using the labeled 3-PBA and labeled *c*-DCCA as internal standards (Barr et al., 2010).

Maternal *PON1* polymorphisms were measured using clamp-dependent and linking emulsion allele-specific polymerase chain reaction (Chen et al., 2005).

2.3. Child behavior, executive functioning, psychometric intelligence testing

We measured children's executive functioning and behavior at the 4, 6, and 7–9 year visits using parent report measures, and IQ at the 6 and 7–9 year visits using performance-based measures.

The Behavior Rating Inventory of Executive Functioning (BRIEF) is a parent-report assessment of children's problems with executive functioning over the past 6 months (Bodnar et al., 2007). Parents reported whether each behavior had been a problem on a 3-point scale (never, sometimes, and often). Validity studies report good reliability with high test-retest reliability (mean r_s = 0.81 for parents across scales) and internal consistency (Cronbach's alphas range from 0.80 to 0.98 across scales) (Gioia et al., 2000). Indices include the Behavioral Regulation Index and the Metacognition Index, both of which are age normed and combined to form the overall Global Executive Composite. Detailed descriptions of the indices and subscales are included in Appendix B.