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Research Review: Environmental exposures, neurodevelopment and child mental health – new paradigms for the study of brain and behavioral effects

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Abstract

Background—Environmental exposures play a critical role in the genesis of some child mental health problems.

Methods—We open with a discussion of children's vulnerability to neurotoxic substances, changes in the distribution of toxic exposures, and co-occurrence of social and physical exposures. We address trends in prevalence of mental health disorders, and approaches to the definition of disorders that are sensitive to the subtle effects of toxic exposures. We suggest broadening outcomes to include dimensional measures of autism spectrum disorders, attention deficit hyperactivity disorder, and child learning capacity, as well as direct assessment of brain function.

Findings—We consider the impact of two important exposures on children's mental health: lead and pesticides. We argue that longitudinal research designs may capture the cascading effects of exposures across biological systems and the full-range of neuropsychological endpoints. Neuroimaging is a valuable tool for observing brain maturation under varying environmental conditions. A dimensional approach to measurement may be sensitive to subtle sub-clinical toxic effects, permitting the development of exposure-related profiles and testing of complex functional relationships between brain and behavior. Questions about the neurotoxic effects of chemicals become more pressing when viewed through the lens of environmental justice.

Conclusions—Reduction in the burden of child mental health disorders will require longitudinal study of neurotoxic exposures, incorporating dimensional approaches to outcome assessment and measures of brain function. Research that seeks to identify links between toxic exposures and mental health outcomes has enormous public health and societal value.

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Keywords

Mental health; environmental influences; neuropsychology; brain development

Introduction

The environment is now known to be a powerful determinant of child health, with increasing evidence that some chemicals are particularly toxic to the human brain. This evidence, documenting links between exposures and neurodevelopmental damage, was comprehensively reviewed by Grandjean and Landrigan in 2006 (Grandjean & Landrigan, 2006) and updated in 2014 (Grandjean & Landrigan, 2014). The authors identified more than a dozen industrial chemicals that can be reliably classified as known developmental neurotoxicants, and postulated that there are thousands of potential neurotoxicants that remain untested in humans (Grandjean, Satoh, Murata & Eto, 2010, Slotkin & Seidler, 2012; Grandjean, 2013). The story of exposures to such hazardous chemicals, dubbed the 'chemical brain drain' (Grandjean & Landrigan, 2014), frequently begins with observations of adult clinical toxicity, followed much later by worrisome findings of child or even fetal subclinical toxicity, occurring at exposure levels previously thought to be safe (Needleman, 2000; Landrigan & Goldman, 2011). Neurotoxicants are relevant to mental health generally but particularly when mental health is conceptualized in relation to neurodevelopmental disorders as introduced in DSM-5.

The developing brain is particularly vulnerable to toxic chemical exposures, as exemplified by lead and selected pesticides, and this sensitivity is likely greatest in utero and throughout early childhood (Grandjean, 2013). From the animal literature, we know that, during these critical periods of brain development, low exposures that would have little or no adverse effect in adults can cause permanent disruptions in normal maturational processes (Rice & Barone, 2000). Although it is more difficult to establish causality in human populations, strategies such as sibling designs or the incorporation of genetic variants that modulate toxicant metabolism in a natural experiment can clarify the likelihood of causal effects (Lewis, Relton, Zammit & Smith, 2013). The central nervous system disruptions associated with some toxic chemical exposures may have far-reaching effects on socioemotional adjustment, educational success, and quality of life. Adverse child outcomes that have been associated with early chemical exposures highlight the entire neurodevelopmental spectrum, including intellectual disability, autism spectrum disorder (Landrigan, Lambertini & Birnbaum, 2012), ADHD (Sagiv et al., 2012a; Sagiv et al., 2012b, Boucher et al., 2012; Froehlich, Anixt et al., 2011), motor delays (Lucchini, Guazzetti et al. 2012; Roze, Meijer et al., 2009), and learning disabilities (Zhang, Baker et al., 2013; Khan, Wasserman et al., 2012; Kofman, Berger, Massarwa, Friedman, & Jaffar, 2006), to more subtle deficits, such as slightly lowered IQ and subclinical learning or attention problems (Rauh, Arunajadai et al., 2011; Yolton, Dietrich, Auinger, Lanphear, & Hornung, 2005; Cho, Frijters, Zhang, Miller & Gruen, 2013). We now know that even small cognitive deficits can have important consequences for long-term academic success and productivity, particularly when viewed at the level of impacts on society (Bellinger, 2009; Gould, 2009). A recent review showed that the magnitude of total IQ losses attributable to lead, pesticides, and other neurotoxic

exposures was comparable to, or greater than, the IQ deficits associated with major pediatric medical events such as preterm birth, traumatic brain injury, brain tumors, and congenital heart disease (Bellinger, 2012). Furthermore, the antisocial behavior, violence, and substance abuse associated with early-life exposures to some neurotoxic chemicals are extremely costly to individuals and society (Schwartz, 1994; Nevin, 2007; Gould, 2009). Thus, continued scrutiny of these associations is extremely important.

While increasing numbers of epidemiologic and clinical studies continue to explore links between neurotoxic exposures and child mental health, new research findings need regular evaluation in the context of secular changes in the definition and prevalence of child psychopathology as well as changes in the environmental distribution of neurotoxic substances. The present review begins with a brief discussion of children's unique vulnerability to neurotoxic substances. Secondly, we review changes over time in the distribution of toxic environmental exposures, including the often neglected issue of the co-occurrence and potential interactions between social and physical environmental exposures. Thirdly, we address trends in the prevalence of mental health and neuropsychological disorders, and new approaches to the definition of disorders that may be more sensitive to the subtle effects of toxic exposures. Fourthly, we argue for the further broadening of outcomes in neurotoxicology studies to include (a) measures of brain function, and (b) increased attention to the domains of learning capacity, attention deficit hyperactivity disorder, and autism spectrum disorder—outcomes with important implications for understanding child psychological well-being. Finally, in light of the changing landscape, we reconsider the impact of two important environmental exposures on children's mental health and neuropsychological development: lead and pesticides.

Our selection of lead and pesticides to illustrate links between toxicant exposures and mental health outcomes aims to illustrate important principles, not to imply that the study of these two neurotoxicants is sufficient. The growing public health problem of widespread exposure in the general population to a range of synthetic chemicals, plasticizers and other endocrine disrupting or neurotoxic compounds is a relatively recent source of concern to the medical and public health communities, especially with respect to the potential for early and persistent brain compromise (Genius, 2008). As yet, only a few industrial chemicals (e.g., lead, methylmercury, polychlorinated biphenyls, arsenic, and toluene) are widely recognized contributors to neurodevelopmental disorders and subclinical brain dysfunction. According to a review by Grandjean and Landrigan (2006), another 200 chemicals are associated with clinical neurotoxoic effects in adults, but have not yet been fully tested in relation to children, so that we are lacking the high level of proof required for regulation. The high volume of new chemicals that are being introduced annually and the urgent need for updated safety standards have severely strained the capacity of the U.S. EPA to manage the risk assessment process (U.S. Government Accountability Office,2008; U.S. EPA, 2009: McCarthy & Copeland, 2015).

Vulnerability of the developing child

Children are fundamentally more vulnerable than adults to toxic chemicals in their environment (Faustman, Silbernagel, Fenske, Burbacher & Ponce, 2000; Thompson, 2004;

Landrigan, Kimmel, Correa, & Eskenazi, 2004; Dourson, Chernly, & Schuenplein, 2002). They have disproportionately heavier exposures to chemicals, reflecting their higher metabolic rate and therefore greater consumption of food, water and air per pound of body weight. Furthermore, children are undergoing rapid growth and development, especially in the central nervous system, and these processes are accompanied by windows of great plasticity and vulnerability. In addition, immature metabolic pathways render children less able than adults to break down and excrete toxic compounds. The identification of developmental periods during which an exposure is likely to be highest and have the greatest effect has implications for dose-response relationships over time and for risk assessment tolerances at different stages of maturation. Because multiple biological mechanisms participate in the relevant pathophysiologic processes, some neurodevelopmental pathways may be activated or disturbed at lower levels of exposure than others. As a result, apparently 'safe' levels of exposure for some pathways may be toxic for other pathways.

Secular changes in patterns of neurotoxic exposures

Over the past 50 years, there have been broad-scale improvements in the physical and chemical environment, including improved sanitation and clean drinking water. At the same time, there have also been dramatic increases in the production of new chemicals, largely synthetic, including plastics, pesticides, building materials, antibiotics, flame retardants and synthetic hormones (Grandjean, Satoh, Murata & Eto, 2010; Grandjean & Landrigan, 2014). Each neurotoxic exposure has its own unique history of use, regulatory action and patterns of exposure. As described below in relation to lead and pesticides, changes in the population-level distribution of exposures, often as a result of regulatory policies, may represent a reduction in the total burden of risk to children, without addressing differential neurodevelopmental risk to groups of children who vary by age and susceptibility.

Ideally, regulatory decisions for chemicals are based on the weight of the scientific evidence. However, regulatory action often lags years behind the science, at least partly as a function of social and economic interests (Rosner & Markowitz, 2005; Markowitz & Rosner, 2003). For example, removal of lead from gasoline was a slow process occurring over a 20-year period from 1975 to 1996, despite the fact that the U.S. Environmental Protection Agency had released a report in 1972, citing the evidence that lead was associated with adverse health outcomes (U.S. EPA, 1972). There has likewise been some tightening of pesticide safety standards, consistent with research showing adverse pesticide effects at lower, sub-clinical exposure levels (e.g., Rauh, Arunajadai et al., 2011; Engel, Wetmur et al., 2011; Bouchard, Chevrier et al., 2011). Given that the timing of exposure likely influences the toxicity of the effect of these subclinical exposures, and that effects involve multiple biological pathways (at the cellular, neural systems, and neurobehavioral levels), traditional toxicological methods of risk assessment based on classic monotonic dose-response relationships may fail to capture the complexities of these effects.

Common to many neurotoxic exposures is their *disproportionate* distribution across population groups, with most inequities falling along racial and socioeconomic lines (Brulle & Pellow, 2006). For example, current cases of lead poisoning are disproportionately concentrated in poor minority communities in the United States (Landrigan, Rauh & Galvez,

2010). With respect to pesticides, farm families and migrant worker communities now carry the heaviest burden (Curwin, Hein et al., 2005; Arcury, Strambi, Novelli, Lunghini & Bozzi, 2007). This disproportionately heavy exposure of poor and minority populations to toxic chemicals, contaminated air and water, and other environmental hazards has been termed *environmental injustice* (Landrigan, Rauh & Galvez, 2010; Birnbaum, Zenick & Brance, 2009). Infants and children, because of their unique biological vulnerabilities and age-related patterns of exposure, are especially vulnerable to the health impacts of environmental injustice.

Finally, the neuropsychological effects of toxic exposures are likely amplified by psychosocial adversity both in utero and during early development. This further increases the risk disparity among different groups of children, because disadvantaged populations with disproportionate chemical exposures are also more likely to experience a range of potentially stressful living conditions, including substandard housing, poor nutrition, neighborhood crime, and inadequate health care (e.g., Rauh, Landrigan & Claudio, 2008; Mohhai, Lantz, Morenoff, House & Mero, 2009). Such adverse conditions carry their own risk, resulting in damage to the developing brain--a phenomenon now termed ‘toxic stress’ (Shonkoff & Garner, 2012). Moreover, the exacerbation of chemical risk by social risk has now been demonstrated at both the individual level and the community levels (Clougherty, Levy et al., 2007; Rauh, Whyatt et al., 2004; Morello-Frosch & Shenassa, 2006; Boyle & Cordero, 2005; Rauh, Landrigan & Claudio, 2008; Cory-Slechta, Virgolini et al., 2008). Therefore, while low level exposures to toxic chemicals are widespread and of general concern, it is important to realize that these risks must be understood in their psychosocial context.

Shifting patterns in the definition, identification and prevalence of child neurodevelopmental and mental health disorders

Rates of identification of some child developmental and mental health conditions, particularly autism, attention-deficit/hyperactivity disorder, and developmental disabilities, have increased dramatically over the past few decades and even further, in just the past decade, in the U.S. and some other developed nations (Boyle & Cordero, 2005; CDC, 2012). Such apparent changes in prevalence over time are at least partly due to increased reporting of a disorder and/or modifications in diagnostic criteria, but true increases in incidence are also possible. In California, a 600% increased incidence in autism was observed among children up to 5 years of age for births from 1990 to 2001, yet only one-third of the rise could be explained by identified factors such as changing diagnostic criteria and a younger age at diagnosis (Hertz-Picciotto & Delwiche, 2009).

Accurate assessment of the contribution of newly emerging neurotoxic exposures to any real increase in mental health disorders will depend upon a clearer understanding of other influences and real changes in the distribution or expression of psychopathology over time. It is currently estimated that 13–20% of children living in the United States experience a mental disorder in a given year (Bloom, Cohen & Freeman, 2009). Prevalence estimates for specific mental health categories for U.S. children aged 3–17 years were recently provided

in a comprehensive report from the Centers for Disease Control and Prevention (CDC, 2013). ADHD was the most frequent diagnosis (6.8%), followed by behavioral or conduct problems (3.5%), anxiety (3.0%), depression (2.1%), autism spectrum disorders (1.1%), and Tourette syndrome (0.2%). Among adolescents aged 12–17 years, rates for illicit drug use disorder, alcohol use disorder and cigarette dependence ranged from 2.8% to 4.7%. Overall, the number of children with a mental disorder increased with age, with the exception of autism spectrum disorders, which was highest among 6 to 11 year old children. Boys were more likely than girls to have ADHD, behavioral or conduct problems, autism spectrum disorders, anxiety, Tourette syndrome, and cigarette dependence. Among adolescents, boys were more likely than girls to die by suicide, and girls were more likely than boys to have depression or an alcohol use disorder.

Prevalence estimates for clinical diagnoses at different ages are key to understanding how early mental health problems affect longer-term developmental trajectories. National Health Interview Survey (NHIS) data show that rates of childhood disability have increased from 2% in 1960 to 8% in 2010 (Halfon, Houtrow, Larson & Newacheck, 2012). Although childhood disability due to physical conditions has declined, there was a 21% increase in frequency of disabilities related to neurodevelopmental or mental health problems. For the first time since the NHIS began tracking childhood disability in 1957, the rise in reported prevalence was highest (28.4%) among socially advantaged families.

Dimensional versus categorical approaches and research domain criteria (RDoC)

Toxic exposures have multiple effects on neural, cognitive, social and emotional function, yet such effects can be subclinical, often failing to reach diagnostic criteria for any single disorder. The current categorical framework (American Psychiatric Association, DSM-5, 2013) does not capture subclinical effects on neurobiological systems that may be altered by chemical exposures. Further, despite efforts to add severity codes to DSM-5, this framework does not effectively map degree of disorder, including dimensional variation in co-occurring symptoms that cut across diagnostic categories. As a result the DSM framework is often inadequate to assess the magnitude of a dose-response relationship. Since the effects of environmental exposures can often be observed across a range of symptoms and biological pathways, the dimensional severity or dose-response magnitude of effect may actually be a more important research question than ‘caseness’ itself (Rose, 1985; Sagiv, Kalkbrenner & Bellinger, 2015). Because subclinical effects are more common than clinical diagnoses, overreliance on diagnostic categories as endpoints for environmental exposures may result in under-identification of meaningful toxic effects, potentially resulting in misclassification of outcomes (Sagiv, Kalkbrenner & Bellinger, 2015).

Dimensional approaches to understanding psychopathology, including sub-phenotypes or endophenotypes (e.g., Swanson, Kinsbourne et al., 2007), complement the categorical approach and may provide greater sensitivity than diagnostic approaches in neurotoxicity studies. While this approach has been longstanding in the field, it is notable that a renewed focus on dimensional constructs at the national level is proposed via the Research Domain Criteria Project (RDoC), developed by the National Institute of Mental Health (Cuthbert & Kozak, 2013; Cuthbert, 2014; Morris & Cuthbert, 2012). The goal of RDoC is to provide a

biologically-valid framework for understanding mental disorders, and to accelerate the integration of approaches in genetics, neuroscience, and behavioral science (Cuthbert & Insel, 2013; Morris, Rumsey & Cuthbert, 2014)—an emphasis that is well suited to the study of neurotoxicity. RDoC research thus starts with basic mechanisms as a way to understand homogeneous symptom sets that cut across multiple disorders. RDoC lends itself to the use of phenotypic dimensions, enabling us to develop neuropsychological profiles of children with various exposures and then to study the trajectory of development over time. Co-variation of symptoms, interactions, and nonlinearities are more easily explored using continuous outcomes. Such an approach improves statistical power, reduces bias due to diagnostic misclassification (Sagiv, Kalkbrenner & Bellinger, 2015), facilitates trajectory analyses (Insel, Cuthbert et al., 2010), and is inherently translational. Despite some controversies, this approach promises to further inform the study of links between neurotoxic exposures and child mental health.

Broadening outcome measures in neurotoxicology research

Neurodevelopmental domains deserving more attention in toxicology studies

Although intellectual development (IQ) has been widely studied in relation to neurotoxicants, learning disability (LD), autism spectrum disorders (ASD), and attention deficit hyperactivity disorder (ADHD)—all domains with increasing prevalence--have received somewhat less attention. These foci are particularly important now that DSM-5 has placed ADHD in a neurodevelopmental cluster with learning disabilities, autism spectrum disorders, and intellectual disability. Furthermore, such neurodevelopmental domains are well-suited to a dimensional approach, allowing for the study of dose-response effects on degree of impairment, along including subclinical findings. Here, we briefly introduce the rationale for including such domains in future neurotoxicology studies; later, we review the emerging evidence for lead and pesticide effects on these domains.

Etiologic research on Learning Disabilities (LD) has focused largely on endogenous factors, such as genetics, intelligence, and specific cognitive abilities, with scant attention to the influence of exogenous environmental factors on the manifestation of learning and achievement problems (Vellutino, Fletcher, Snowling, & Scanlon, 2004). Several studies have demonstrated that toxic exposures are associated with decreases in performance on achievement tests, using continuous outcome measures (Yolton, Dietrich, Auinger, Lanphear & Hornung, 2005; Cho, Frijters, Zhang, Miller & Gruen, 2013), yet little is known about the neurobiological pathways by which these exposures alter performance. The evidence for potentially causal associations of environmental factors with LD comes from experimental work and some mechanistic human studies. Animal studies demonstrate that the neural systems supporting memory and learning are particularly vulnerable to prenatal neurotoxic exposures (Roy, Seidler & Slotkin, 2002; Hyman, 2010). In humans, toxic exposures during critical developmental windows may yield alterations in the maturational trajectory of discrete brain-based circuits that produce distinct learning and achievement processes in otherwise healthy children. For example, single-word reading is supported by a well-defined left hemisphere neural circuit that is disrupted in dyslexia (Richlan, 2012). The maturation of this neural circuit may be affected by a neurotoxic exposure, producing idiopathic

learning problems, but the nature and developmental timing of these possible exposure effects have yet to be examined. Research linking toxic exposures to LDs could potentially yield a unique set of environmentally-associated learning problem phenotypes. Because exposures to some neurotoxic conditions are potentially modifiable, the potential identification of neurotoxic determinants of learning and achievement problems (including reading and math) has important public health implications for treatment and the development of primary prevention strategies.

Autism spectrum disorders (ASD) constitute a major public health problem affecting one in 68 children (CDC, 2013). To date, we lack a clear understanding of the causes of ASD despite its serious social impact. Based on the most recent reviews of the role of environmental toxicants in the etiology of ASD (e.g., Rossignol, Genuis & Frye, 2014; Suades-González, Gascon, Guxens, & Sunyer, 2015; Talbott, Marshall et al., 2015), a number of classes of chemicals have been identified as potential contributors, including pesticides, phthalates, polychlorinated biphenyls (PCBs), solvents, air particulates ($PM_{2.5}$), traffic-related pollutants, ozone, and heavy metals, with the strongest evidence found for air pollutants and pesticides. Current findings are tempered by at least three issues—all of which suggest future directions for neurotoxicology research in the mental health arena. First, environmental exposures implicated in ASD typically occur in mixtures, so it is difficult to disentangle the effects of specific compounds or the potentiating effects of joint exposures. Efforts to identify etiologic chemicals will require sophisticated statistical techniques to accommodate the challenges posed by co-occurrence in complex mixtures (Hastie, Tibshirani & Friedman, 2009). Second, most extant studies have relied on population-level estimates; possible confounding by socioeconomic status and place of residence is a concern, because both sociodemographic conditions may be related to ASD case ascertainment and other potential causal risk factors (Weisskopf, Kioumourtzoglou & Roberts, 2015). Studies including biomarkers of exposure have yielded less consistent findings, smaller sample sizes, and have tended to focus on heavy metals, reporting higher concentrations in blood, urine, hair, brain or teeth of children with ASD compared with controls. Other biomarker studies have found solvent, phthalate and pesticide levels to be associated with ASD. Third, since the involvement of genetic abnormalities in ASD is well-accepted, the etiology of ASD may involve, at least in a subset of children, complex interactions between genetic factors and specific environmental toxicants. Carefully designed genetic studies, including attention to critical periods of development, are needed to lend weight to possible causal links in this arena.

ADHD is the most common childhood neurodevelopmental disorder, with estimated prevalence rates in school-age children of 3%–8% (American Psychiatric Association, 2013; CDC, 2013). ADHD is associated with altered brain functioning and is characterized by an inability to focus on tasks, as well as impulsive hyperactive behavior, lethargic inattention, or both. The co-occurrence of ASD and ADHD supports the conceptualization of ADHD as a neurodevelopmental disorder, and argues for increased efforts to identify toxic substances with shared and distinct etiological effects on both ADHD and ASD (Musser, Hawkey et al., 2014). Not surprisingly, there is also high comorbidity of LD with ADHD, but again the etiologic basis for this comorbidity is not clear. Although ADHD has been well-studied, recent progress in its conceptualization has potential to further advance our understanding of

how neurotoxic exposures affect different subgroups of children, resulting in a range of ADHD type problems. For example, Fair et al. (2012) propose that (a) typically developing children can be classified into distinct neuropsychological subgroups with high precision, and (b) some of the heterogeneity in individuals with ADHD might be "nested" in this normal variation (Fair, Bathula, Nikolas & Nigg, 2012). This suggests that future studies seeking to identify links between toxic chemicals and ADHD-type problems will need to take into consideration the impact of exposures on the full range of ADHD subtypes and the neuropsychological domains that may account for this disorder (Nikolas & Nigg, 2013).

Brain-based indicators of neurotoxicity

The brain is inseparable from children's neurodevelopmental disorders like ADHD, ASD, Intellectual disability, and LD as well as other psychopathologies of childhood. Recently, several research groups are using Magnetic Resonance Imaging (MRI) in combination with epidemiologic studies to investigate the effects of toxic exposures on neurodevelopment and mental health. Such strategies can potentially detect sub-clinical biological changes at different time points in order to more completely describe the multifaceted complexities of development. MRI also permits *in vivo* visualization of many aspects of brain activity, with different imaging modalities yielding powerful information about brain structure, function, and connectivity within the same individuals. Several modalities are particularly well-suited for studies of neurotoxicity because (a) they capture aspects of brain activity that are known to be sensitive to environmental exposures, and (b) they detect disturbances that have been linked to functional developmental and mental health problems. Such tools thus provide more sensitive ways of detecting more subtle neurotoxicant effects, including subclinical changes.

Briefly, structural or anatomical MRI generates static measurements of brain morphology. Rather than estimating volumes of brain regions as was done in early MRI studies, surface morphometric techniques now allow for the comparison of cortical thickness or thinness in local regions as well as comparison of local surface perturbations such as inflections in local cortical surfaces (Bansal, Staib, Xu, Zhu & Peterson, 2007). Perhaps the most well-known modality of MRI is functional MRI (fMRI), which provides an indirect measure of neuronal activity by measuring changes in blood oxygenation level (BOLD signal). In task-related fMRI, a subject completes a task during scanning, and specific patterns of brain activation identify which brain regions are active and therefore relevant to the activity. Resting state fMRI (rsfMRI) captures spontaneous brain activity when the subject is not performing an explicit task. Brain regions that demonstrate strong coherence of neural activity (synchrony) are thought to be connected in functional networks (Matthews & Fair, 2015) and variations in these measures are widely associated with developmental psychopathology. Diffusion Tensor Imaging (DTI) measures white matter integrity and fiber connectivity. White matter tracts are myelinated tracts that connect distal and proximal regions in the brain. DTI measures connectivity between brain structures by measuring the direction of movement of water molecules through tissue (Watts, Liston, Niogi & Ulug, 2003; Casey, Tottenham, Liston & Durston, 2005) and are also associated with ADHD other neurodevelopmental conditions.

The potential value of MRI-based assessments of children who have been exposed to neurotoxic chemicals at different concentrations and at different points in development is only recently being explored, and will be discussed in relation to each of the illustrative chemical exposures. Briefly, such powerful tools will permit researchers to not only identify the direct structural, functional and metabolic effects of neurotoxic exposures on the brain, but also to determine how these brain-based changes mediate the impact of chemical exposures on neuropsychological symptoms and clinical outcomes over time. It will be fascinating to determine to what extent observed brain changes in child mental health disorders are related to neurotoxicant exposures. Most importantly, these tools have the potential to inform the development of biologically targeted, therapeutic interventions in response to evidence of neurotoxicity in the brain and behavioral realm.

The case of lead

Trends in environmental lead exposure

Childhood lead poisoning, an entirely preventable condition, is one of the most extensively studied childhood diseases of toxic environmental origin (CDC, 2000), accounting for about 0.6% of the global burden of disease (WHO, 2009). As a result of substantial efforts in the U.S. to remove lead from gasoline, paint, pigments, and solder (introduced above and elaborated here), the percentage of children aged 1–5 years with blood lead levels ≥10 μg/dL has dropped dramatically from 88% in 1976–1980, to 4.4% during 1991–1994, to 1.6% during 1999–2002, and to 0.8% during 2007–2010 (CDC, 2013). Currently, a blood lead level ≥5 μg/dL (down from ≥10 μg/dL) is defined as high. Despite these improvements, an estimated 535,000 U.S. children aged 1–5 years have levels ≥5 μg/dL based on the U.S. Census Bureau 2010 data, and about 25% of homes with children under age 6 still have a lead-based paint hazard. As described below, there is ample evidence that even low levels of exposure to lead are associated with neuropsychological deficits (e.g., Lanphear, Dietrich, Auinger, & Cox, 2000; Canfield, Henderson et al., 2003 Lanphear, Hornung et al., 2005; Jusko, Henderson et al., 2008), continuing to present excess, often unacceptable, risk for children. Lead exposure is now thought to be unsafe at any detectable level (Landrigan, 2000), yet nearly all children have detectable levels of lead in their body. Despite decades of evidence about the toxic impact of lead on children's mental health and development, lead continues to be added to paints, toys, cosmetics and other consumer products worldwide, at least partly due to the shift in manufacturing to lower income countries lacking effective environmental control policies.

We have failed to reach the *Healthy People 2020* objective of reducing mean blood lead levels for all children in the U.S.(U.S. Department of Health and Human Services, 2012), and differences between the mean blood lead levels of different racial/ethnic and income groups persist. Specifically, the difference between mean blood lead levels of non-Hispanic black children (1.8 μg/dL), compared with either non-Hispanic white (1.3 μg/dL) or Mexican American (1.3 μg/dL) children remains significant ($p<0.01$) (CDC, 2013). The difference in mean blood lead levels among children belonging to families with a poverty income ratio <1.3 compared with families with a poverty income ratio ≥1.3 is also significant (1.6 μg/dL versus 1.2 μg/dL, respectively [$p<0.01$]) (CDC, 2013). These

significant differences between the mean blood lead levels by race/ethnicity and income indicate a persistent disparity. According to the U.S. Environmental Protection Agency's definition of environmental justice, this unfair distribution of the lead burden is an example of environmental *injustice* (EPA, 2014). Such disparities can be traced to racial and income-related differences in housing quality, environmental conditions, nutrition, and other factors designed to control or eliminate lead exposure (CDC, 2012).

Vulnerability of children to lead

Children's greater risk of exposure to lead, as with many other toxic chemicals, reflects their typical hand-to-mouth behavior as well as their tendency to eat more food, drink more water and breathe more air per unit of body weight than adults (American Academy of Pediatrics Committee on Environmental Health, 2003). The major route of children's exposure to lead in the U.S. is through paint, via ingestion of lead-contaminated dust that forms inside homes from the flaking and chipping of older lead-based paint. Children between the ages of 1 and 6 years are at highest risk of lead exposure because normal exploratory behavior facilitates the transfer of lead dust from the environment into children's bodies. Furthermore, unlike many other neurotoxicants, lead can accumulate over time in a pregnant woman's bones, and then readily pass through the immature blood–brain barrier to the developing fetal brain. Having reached the brain, lead can interfere with growth and development, and this vulnerability extends from prenatal life into infancy and early childhood.

Lead exposure affects the developing brain through pharmacological and morphological mechanisms and is highly age and dose dependent (Silbergeld, 1992; Goyer, 1996). Animal studies have shown, at the pharmacologic level, that prenatal exposure to lead affects neurotransmitter receptor density and affinity; the type of neurotransmitter receptor change varies depending on the timing of exposure (Rossouw, Offermeier, & van Rooyen, 1987). At the morphological level, prenatal lead exposure delays structural development of the fetal cortex (Bull, McCauley, Taylor & Croften, 1983), and affects differentiation and synaptogenesis (Regan, 1989). Although it is more difficult to study potentially causal mechanisms in human studies, Mendelian randomization as mentioned earlier lends further weight to the causal evidence linking lead exposure to neurobehavioral outcomes in children (Nigg, Elmore, Natarajan, Friderici & Nikolas, in press).

Brain and behavioral consequences of lead exposure

The earliest studies of the adverse consequences of lead exposure focused on IQ (e.g., Needleman, Gunnoe et al. 1979), and showed that clinically asymptomatic children with elevated body lead burdens had a 4 to 5-point deficit in mean verbal IQ scores compared with children from the same communities with lower lead burdens. More recent studies have shown that the average IQ scores of children with levels of only 5–10 μg/dL are about 5 points lower than the IQ scores of children with levels less than 5 μg/dL (Canfield, Henderson et al., 2003), and these effect sizes persist into the school years (Jusko, henderson et al., 2008). The cognitive deficits associated with lead exposure are considered to be irreversible (Mazumdar, Bellinger et al. 2011; Dietrich, Ris, Succop, Berger & Bornschein, 2001; Bellinger, Stiles & Needleman, 1992; Wright, Dietrich et al., 2008); and it is generally

agreed that no safe level of exposure to lead exists (Grandjean, 2010; Lanphear, Hornung et al. 2005; Budtz-Jorgensen, Bellinger, Lanphear & Grandjean, 2013).

Early lead exposure has also been linked to conduct disorder, juvenile delinquency, drug use and incarceration (National Research Council, 1993; Sciarillo, Alexander & Farrell,1992; Needleman, McFarland, Ness, Fienberg & Tobin, 2002; Dietrich, Ris, Succopa, Bergerb & Bornscheina, 2001; Braun, Kahn, Froehlich, Auinger & Lanphear, 2006; Fergusson, Boden & Horwood, 2008; Nigg, Knottnerus et al., 2008; Wang, Chen et al., 2008; Ha, Kwon et al., 2009). Although externalizing behavior problems have been most frequently reported in relation to lead exposure, some studies have also found teacher-reported withdrawn behavior (e.g., Chiodo, Jacobson & Jacobson, 2004). Progress in our understanding of internalizing disorders in young children in general has lagged behind advances in the other areas of psychopathology in this age group, at least in part because such problems are less disruptive or visible to parents and teachers (Tandon, Cardeli & Luby, 2009). Recognizing and describing mood and anxiety disorders in children as a possible consequence of a toxic chemical exposure such as lead may benefit from the more flexible dimensional approach, as opposed to the more rigid diagnostic classifications.

Other deficits associated with prenatal exposure to lead include fine-motor skill problems as measured by slow finger tapping and reaction time, poor eye-hand coordination, and poor visuo-motor coordination skills (Chiodo, Jacobson & Jacobson, 2004; Needleman, Schell, Bellinger, Leviton & Allred, 1990), with some deficits persisting over time into adulthood, even at low levels of exposure (Mason, Harp & Han, 2014). Public health policy concerning lead has evolved steadily over the years in response to increasing scientific evidence that adverse effects are seen at very low levels of exposure.

Learning problems, ASD and ADHD associated with lead—Even very low levels of exposure to lead are associated with poorer school performance, marked by shortening of attention span, reading problems, attention deficit–hyperactivity disorder, and school failure (Needleman, Gunnoe et al., 1979; Bellinger, Stiles & Needleman, 1992). Analysis of data from more than 4800 children 6–16 years of age, who participated in the Third National Health and Nutrition Examination Survey in the U.S., found an inverse relationship between blood lead levels and math and reading scores at concentrations lower than 5μg/dl. In fact, the dose–response relationship between blood lead levels and loss of IQ was stronger at levels lower than 10μg/dl than at higher levels (Lanphear, Dietrich, Auinger & Cox, 2000). An international pooled analysis of data from multiple cohorts demonstrated that there are adverse effects below 10μg/dl and that the effects are steepest at the lowest levels of exposure (Lanphear et al., 2005). This non-monotonic dose-effect relationship has been confirmed by numerous investigators (Emory et al, 1999, 2003; Bellinger & Needleman, 2003; Wasserman, Factor-Litvak et al., 2003; Chiodo, Jacobson & Jacobson, 2004; Després, Beuter et al., 2005; Fraser, Muckle & Despres, 2006; Hu, Tellez-Rojo et al., 2006; Kordas, Canfield et al., 2006; Schnaas, Rothenberg et al., 2006; Tellez-Rojo, Bellinger et al., 2006; Chiodo, Covington et al., 2007; Surkan, Zhang et al., 2007).

Early studies showed an association between dentine lead, whole-tooth lead, hair lead, and symptoms of inattention (e.g., Bellinger, Leviton, Allred & Rabinowitz, 1994; Needleman,

Gunnoe et al., 1979). Subsequent studies reported associations between lead and attention deficit disorder and impulsivity (e.g., Brockel & Cory-Slechta, 1998; Wasserman, Staghezza-Jaramillo, Shrout, Popovac & Graziano, 1998), but virtually all of this work showed effects at lead levels much higher than current U.S. population averages. More recently, Nigg, Knottnerus et al. (2008) were the first to conduct a low-lead study in children formally diagnosed with ADHD by standardized methods, using sensitive exposure detection measures with limits 3–8 fold lower than previously used methods. Lead effects on ADHD are biologically plausible because lead disrupts midbrain dopamine and other neurotransmission circuitry (Cory-Slechta, 2005)--systems that are also implicated in ADHD (Nigg, 2006). Furthermore, since ADHD, like ASD, carries well-established genetic influences on susceptibility (Waldman & Gizer, 2006), it will be important to determine how lead may interact with that susceptibility (Purcell, 2002).

The role of lead in ASD has received less attention. In a recent study of autistic children (Adams, Audhya et al., 2013), the autism group had significantly higher levels of several metals including lead in their red blood cells (41%), and significantly higher urinary levels of lead (74%), thallium (77%), tin (115%), and tungsten (44%). Further, levels of several toxic metals were significantly associated with variations in the severity of autism for all three of the autism severity scales investigated.

Brain anomalies associated with lead—MRI has been used to better understand the mechanisms underlying the effects of lead exposure on neurological function. Studies of exposed children have found decreased brain volume, as well as altered myelination and axonal integrity (Cecil, Brubaker et al., 2008; Cecil, Dietrich et al., 2011; Brubaker, Schmithorst et al., 2009). The Cincinnati Lead Study (CLS) was the first longitudinal epidemiologic study to use MRI in a population well characterized for lead exposure (Bornschein, Hammond et al.,1985), demonstrating that prenatal or early childhood exposure was associated with a variety of adverse effects on adult brain structure, organization, and function. Young adults demonstrate reductions in grey matter volume associated with increased prenatal and/or early childhood blood lead, and the magnitude of loss increases with age (Cecil, Brubaker et al. 2008; Brubaker, Dietrich, Lanphear & Cecil, 2010). The associations were most striking in frontal regions, particularly the anterior cingulate and ventrolateral prefrontal cortices, and were stronger for males than females. CLS Investigators examined white matter connectivity using DTI, demonstrating associated reductions in fractional anisotropy (FA) (Brubaker, Schmithorst et al., 2009), and these changes were attributed to significant changes in radial diffusivity. Since radial diffusivity primarily reflects alterations in the myelin sheath thickness and organizational characteristics, these findings suggest that lead exposure disrupted the underlying neuronal network.

These results, among others, showing significant associations between childhood lead exposure and neuronal dysfunction in discrete anatomic regions and alterations in white matter connectivity, are consistent with behavioral studies suggesting cognitive, motor and behavioral effects of early childhood lead exposure. Lead thus appears to affect both brain volume, connectivity and metabolic content, and these disturbances very likely mediate observed deficits in cognition/learning, motor and behavioral function.

The case of pesticides

Trends in pesticide exposure

The World Health Organization estimates that approximately 3 million cases of pesticide poisoning occur annually, with approximately 220,000 fatalities (WHO, 2010). While much of this disease burden is occupationally related, there is also substantial exposure of children who often accompany parents to workplaces, live in farm regions, come in contact with post-application residue, and participate themselves in agricultural production, including pesticide application (Karr & Rauh, 2014). Daily, chronic low-level exposures to pesticides are more common today among children than acute pesticide poisonings. Children encounter pesticides in air, food, dust, and soil and on surfaces from lawn or garden applications, household insecticide use, pet applications, and agricultural product residues. Pesticides are purposefully applied directly to children's skin to treat lice or scabies, most often from the classes of pesticides known as pyrethroids, organochlorines or organophosphates. For most children, the majority of exposure comes from two sources: pesticide residues in the food supply, and home pesticide use. Broadcast applications of pesticides in indoor environments can leave residues in air, carpet, toys, and house dust that persist for months and herbicides applied on the lawn or garden can be tracked into the home by people and pets. For subgroups of children, such as farm families and children of migrant workers, proximity to agricultural production activities results in an especially heavy burden of exposure because regular pesticide applications, with periodic airborne drift, take place near their homes, schools, and play areas (Marks, Harley et al., 2010). As is the case for lead, the burden of exposure in the U.S. is now greatest for lower-income minority children, thus providing another example of environmental *injustice*.

Organophosphate pesticides—The class of pesticides known as organophosphate insecticides (OPs) poses a particularly serious health hazard because of their inherent acute toxicity and widespread use in residential pest control and food production. First registered in 1965 for agricultural and pest control purposes, chlorpyrifos (CPF) is a broad-spectrum, chlorinated OP. Prior to regulatory action by the Environmental Protection Agency (EPA) in 2000–2001, CPF applications were particularly heavy in urban areas, where the exposed populations included pregnant women (Whyatt, Camaan et al., 2002; Whyatt, Barr et al., 2003; Surgan, Congdon et al., 2002; Berkowitz et al., 2003). In a sample of pregnant women in New York City, detectable levels of CPF were found in 99.7% of personal air samples, 100% of indoor air samples, and 64%-70% of blood samples collected from umbilical cord plasma at delivery (Whyatt, Camaan et al., 2002; Whyatt, Camaan et al., 2005). In 2001, the U.S. EPA banned indoor residential use of CPF (U.S. Environmental Protection Agency, 2000; 2002), but continues to permit agricultural and commercial uses. Although the residential ban was effective in bringing down mean CPF blood levels among pregnant women in NYC (Whyatt, Rauh et al., 2004), pesticide metabolites continue to be detected in the urine of pregnant women and children living in farming communities across the U.S. from North Carolina to California (Bradman, Eskenazi et al., 2005; Accury, Grzywacz et al., 2007). Outside the U.S., pesticide use is common, partly due to U.S. product exportation (Romyen, Hawker & Karnchanasest, 2007).

Currently, diet is the most widespread source of children's OP pesticide exposure (Aprea, Strambi, Novelli, Lunghini & Bozzi, 2000; Lu, Toepel et al., 2006). In CDC's most recent Fourth National Report on Human Exposure to Environmental Chemicals, urinary concentrations of common OP insecticide metabolites were higher in the youngest age group sampled (age 6–11 years) than in older children and adults (Rohlman, Anger et al., 2001), largely because of high dietary consumption of apples, grapes, and carrots—all foods with OP pesticide residues. A recent study documented CPF levels by urinary metabolites in children, and found that an organic dietary intervention immediately reduced metabolites to nondetectable levels and remained nondetectable until conventional diets were reintroduced (Lu, Toepel et al., 2006).

Vulnerability of children to pesticides

OPs have been detected in amnionic fluid and are known to cross the placenta, posing a threat to the unborn child during a period of rapid brain development (Bradman, Barr et al., 2003). While OPs affect neurotransmission in adults, they act as neurodevelopmental disrupters in the fetal and neonatal brain. Much of the early evidence for neurotoxicity comes from animal studies; specifically, OPs inhibit AChE and overstimulate cholinergic targets in the developing brain, thereby disrupting normal patterns of neural cell proliferation and differentiation, axonogenesis, and synaptogenesis (Bigbee & Sharma, 2004). Noncholinergic mechanisms are also implicated in OP neurodevelopmental toxicity, involving disruption of neural cell development and neurotransmitter systems (Slotkin, 2004; Aldridge, Levin, Seidler & Slotkin, 2005), including the formation and activity of synapses in different brain regions (Barone, Das, Lassiter & White, 2000; Gupta, 2004; Qiao, Seidler, Tate, Cousins & Slotkin, 2003). These effects are seen at exposure levels well below the threshold for systemic toxicity caused by chlolinesterase inhibition in the brain (Dam, Seidler & Slotkin, 2003; Slotkin & Seidler, 2005). Moreover, evidence for extensive cellular toxicity in rodent models suggests that CPF produces long-term effects on brain structure and function that are likely irreversible (Slotkin, 2004).

As a body of work, these experimental findings have important implications for understanding the developmental neurotoxicity of CPF in children (Levin, Addy et al., 2002). First, the critical exposure period in which neuro-behavioral anomalies can be elicited likely extends through early postnatal brain development, suggesting multiple mechanisms by which CPF may alter the maturation of neural systems. Unlike most other cells in the body, neurons proliferate only during the first half of gestation. AChE-related and non-related effects of CPF disrupt neuronal proliferation and differentiation, axonal elaboration, synaptogenesis, and neurotransmitter specification, thereby likely reducing neuronal cell number and disturbances in axonal connectivity in specific brain regions and producing related abnormalities in behavior and cognition. Second, non-cholinergic mechanisms dominate the low-dose neurotoxic effects of CPF, and cholinesterase inhibition dominates its toxic effects at high doses. Third, traditional methods of risk assessment based on classic monotonic dose-response relationships may not be appropriate for CPF because of its multiple mechanisms of action. Fourth, the timing of exposure during development likely determines the specificity of the effects of CPF toxicity at the cellular, neural systems, and neurobehavioral levels.

Additional evidence for the genetic vulnerability of certain children to pesticide exposure, lending weight to the evidence for links between OP pesticides and developmental psychopathology, comes from several studies reporting greater adverse effects of prenatal organophosphate pesticide exposure on head circumference (Berkowitz, Obel et al., 2004), reflexes (Engel, Berkowitz et al., 2007) and early cognitive development among children of mothers with low paraoxonase 1 (PON1) (Engel, Wetmur et al., 2011). PON1 is a key enzyme in the metabolism of organophosphate pesticides (Costa, Li et al. 1999), and a biomarker of susceptibility to the toxic effects of organophosphate pesticides, both in animals (Costa, Richter et al. 2003), and in humans (Engel, Berkowitz et al. 2007; Engel, Wetmur et al., 2011; Eskenazi, Huen et al. 2010; Lee, London et al. 2003; Nielsen, McKean-Cowdin et al. 2010). Future Mendelian randomization studies can help us to better understand possible causal links between pesticides (or any neurotoxicant) and neurodevelopmental outcomes, but such studies are currently limited in the case of pesticides by the lack of information on genetic metabolism of these compounds.

Brain and behavioral consequences of pesticide exposure

Developmental problems in children exposed to pesticides were first reported more than 30 years ago among 4–5-year-olds living in a Mexican agricultural community exposed to high OP and organochlorine pesticides, as compared to children from a nearby community with low exposure (Guillette, Meza, Aquilar, Soto & Garcia, 1998). Exposed children showed disturbances in stamina, hand-eye coordination, drawing ability, and short-term recall, but the study did not include any validation of exposure using biomarkers. More recent birth cohort studies in both urban and agricultural settings, using biomarkers of exposure, have found significant associations between prenatal maternal OP exposure and deviant neonatal reflexes (Young, Eskenazi et al., 2005), overall neonatal neurological performance (Zhang, Han et al., 2014), mental/ motor deficits and pervasive developmental disorder at 2–3 years (Engel, Berkowitz et al., 2007; Rauh, Garfinkel et al., 2006), and attention problems at 3 ½ to 5 years of age (Marks, Harley et al., 2010). In these same cohorts, cognitive deficits have persisted to at least 7 years of age (Rauh, Arunajadai et al., 2011; Engel, Wetmur et al., 2011; Bouchard, Chevrier et al., 2011). Using data from the Nation Health and Nutrition Examination Survey, Bouchard et al. (Bouchard, Bellinger, Wright & Weisskopf, 2010) reported a 35% increase in the odds of developing ADHD with each 10-fold increase in urinary concentration of residue from OP exposure in children age 8–15 years, across the full range of exposures. This is an area where the RDoC approach to creating profiles of symptoms might complement and further inform the relationship between early exposure and ADHD-type behaviors, and could be even more informative than the diagnosis of ADHD ‘caseness’. Such early attention problems can be clinically persistent, putting children at risk for later psychiatric, neuropsychological, and academic difficulties. A recent study reports that children with prenatal exposure to chlorpyrifos are also likely to manifest moderate tremor in middle childhood, a disturbance that may underlie the frequently-reported symptom of poor hand writing among children with ADHD-type problems (Rauh, Garcia & Louis, 2015).

Although the evidence that OP pesticides are associated with adverse developmental outcomes is growing, some studies have reported weak or no associations between OP

exposure and behavioral outcomes (Eskenazi, Rosas et al., 2008). In some cases, prenatal but not postnatal exposures are associated with poor behavioral outcomes; further, increased exposure has been associated with enhanced performance, i.e., increased exposure to DAP was associated with higher scores on the Bayley Scales (Eskenazi, Marks et al., 2007). More prospective studies with larger samples of children and a more sophisticated approach to understanding the timing of exposure are needed to disentangle these seemingly contradictory results.

The issue of environment injustice is complicated in the case of pesticides, since more affluent groups may have greater access to fresh fruits and vegetables, a potential source of dietary pesticide residue. However, in its latest report, the Dietary Guidelines Advisory Committee, a panel at the U.S. government's Office of Disease Prevention and Health Promotion (CHHS, 2010), found that high levels of fruit and vegetable consumption are strongly or moderately associated with decreased risks of chronic diseases such as heart disease, high blood pressure, type 2 diabetes, obesity and cancer. The committee also found limited evidence that suggests that dietary patterns with high fruit and vegetable consumption may decrease the likelihood of congenital anomalies as well as neurological and psychological diseases. Therefore, to the extent that more affluent groups have greater access to fruits and vegetables, especially fresh produce, they have an advantage over less affluent groups. The argument here is that even eating conventionally produced fruits and vegetables (non-organic) is always healthier than not eating any fruits and vegetables (Roberts & Karr, 2012). Further, organic foods do have lower pesticide levels than conventional diets (Smith-Spangler, Brandeau et al., 2012). Perhaps more importantly, the exposure of less affluent groups, such as migratory workers and farm families, to pesticides through geographical proximity and occupational exposure remains a significant risk.

Brain anomalies associated with OP exposure—Only one study to date has investigated associations between CPF exposure and brain morphology using MRI (Rauh, Perera et al., 2012). In a sample of 40 children, 5.9–11.2 years, selected from a community-based cohort, high CPF exposure was associated with enlargement of superior temporal, posterior middle temporal, and inferior post-central gyri bilaterally, and enlarged superior frontal gyrus, gyrus rectus, cuneus, and precuneus along the mesial wall of the right hemisphere. Observed group differences reflected exposure-related changes in underlying white matter. Further, high exposure children did not show expected sex differences in the right inferior parietal lobule and superior marginal gyrus, and displayed reversal of sex differences in the right mesial superior frontal gyrus, consistent with disruption by CPF of normal behavioral sexual dimorphisms reported in animal models. High exposure children also showed frontal and parietal cortical thinning, and an inverse dose-response relationship between CPF and cortical thickness. This report suggests that prenatal exposure to CPF, at standard usage levels, is associated with structural changes in the developing human brain, in regions that subserve working memory, attention and executive function.

Learning problems, ASD and ADHD associated with OP pesticides—There is some evidence that specific learning problems are seen in OP-exposed children, in the absence of overall IQ deficits. These findings include problems with verbal learning and

memory; specifically, inability to sustain attention on learning tasks (Kofman, Berger, Massarwa, Friedman & Jaffar, 2006). Other studies, although not specifically designed to assess OP impact on LDs, have included neurocognitive tasks that are essential for the learning process. In a sample of Hispanic children living in an agricultural community (Lizardi et al., 2008), OP levels have been associated with speed of attention, sequencing, mental flexibility, visual search, concept formation, and conceptual flexibility. These results are consistent with other reports, from both human and experimental studies, documenting OP exposure effects on verbal abstraction, attention, and memory (Qiao, Seidler,Tate, Cousins & Slotkin, 2003; Slotkin, Levin & Seidler, 2006). Inclusion of LD assessment tools and more refined measures of attention and ADHD-type problems in future studies will add greatly to our understanding of how these exposures may affect educational success and longer-term social adjustment.

Evidence for adverse OP effects on reciprocal social behavior, as measured by degree of social responsiveness, has been reported in a multi-ethnic urban population at 7–9 years of age, particularly among males (Furlong, Engel, Barr & Wolff, 2014). Another recent study reported that proximity to OPs at some point during gestation, specifically 2nd trimester chlorpyrifos applications, was associated with a 60% increased risk for autism spectrum disorders (Shelton, Geraghty et al., 2014). Much of this evidence has been well-reviewed elsewhere (Polanska, Jurewicz & Hanke, 2013; Munoz-Quezada, Lucero et al., 2013; Gonzalez-Alzaga, Lacasana et al., 2013). Most research implicating pesticides in the etiology of autism comes from recent epidemiological studies in U.S. agricultural areas, specifically in families who live or work in proximity to areas treated with pesticides. Significant associations have been reported between prenatal exposure OP pesticides and autism diagnosis (Roberts, English et al., 2007) and maternally reported pervasive developmental disorder (Eskenazi, Marks et al., 2007). Although pesticides are biologically plausible contributors to autism, more research is needed to determine critical windows of exposure, neurotoxicity in the context of genetic susceptibilities, and the role of co-exposures, including chemical additives to pesticide compounds (Shelton, Hertz-Picciotto &,Pessah, 2012). Causes for the recent rise in autism diagnoses throughout the United States remain largely unknown. In California, a 600% increased incidence in autism was observed among children up to 5 years of age for births from 1990 to 2001, yet only one-third of the rise could be explained by identified factors such as changing diagnostic criteria and a younger age at diagnosis (Hertz-Picciotto and Delwiche 2009).

With respect to ADHD, Bouchard et al. (Bouchard, Bellinger, Wright & Weisskopf, 2010) reported a 35% increase in the odds of developing ADHD with each 10-fold increase in urinary concentration of residue from OP exposure in children age 8–15 years, across the full range of exposures. This is an area where the RDoC approach to creating profiles of symptoms might complement and further inform the relationship between early exposure and ADHD-type behaviors, and could be even more informative than the diagnosis of ADHD ‘caseness’. Such early attention problems can be clinically persistent, putting children at risk for later psychiatric, neuropsychological, and academic difficulties. A recent study reports that children with prenatal exposure to chlorpyrifos are also likely to manifest moderate tremor in middle childhood, a disturbance that may underlie the frequently-reported symptom of poor hand writing among children with ADHD-type problems (Rauh,

Garcia & Louis, 2015). Whether or not the ADHD-type deficits observed in children exposed to pesticides are identical (anatomically or functionally) with ADHD as identified by DSM-5 in the general population is unknown; nor is there any data concerning the persistence of such symptoms into middle childhood among children who were exposed prenatally or in early childhood. This is an important gap in the literature, with implications for treatment, as well as for regulatory standards.

Conclusions

In this review we first examined children's unique vulnerability to neurotoxic substances. We then described how the distribution, identification and definition of toxic environmental exposures, as well as mental health outcomes, have changed over time and shifted the burden of risk to different populations. As a consequence, we have also seen heightened risk associated with different patterns of co-exposure to both social and chemical toxicants. Third, we considered outcome measures that are likely to be sensitive to the subtle effects of toxic exposures, and argue that current trends in psychiatric research, calling for the use of dimensional rather than categorical models to describe health outcomes, are particularly well-suited to neuro-epidemiologic investigations aimed at understanding the etiology of children's neurodevelopmental disorders. Fourth, we presented our view that future neurotoxicology research will be further informed by the inclusion of additional mental health-related outcomes such as (a) measures of brain function, and (b) assessment of child learning capacity, ADHD and ASD. Finally, we discussed the history and impact of two important environmental exposures (lead and pesticides) on child mental health, reframing the discussion to consider shifts in population-based exposures and new approaches to outcome assessment.

Relevant to the role of environmental exposures in the etiology of neurodevelopmental disorders and mental health problems, but beyond the scope of this paper, are the many mechanistic and methodological challenges related to the interactive and potentially cumulative effects of toxic chemicals and social conditions. Approaches to measuring the combined effects of multiple exposures include toxicogenetic analysis (e.g., Mori, Kmoiyama et al., 2003), phased strategies (e.g., Menzie, MacDonell & Mumtaz, 2007), and complex mixtures analysis (e.g., Hastie, Tibshirani & Friedman, 2009). The difficulty arises when each exposure is low, but the cumulative effect of multiple exposures may be above the safe regulatory dose, as illustrated by a recent study of dietary sources of endocrine disrupting chemicals (Scheckter, Lorber et al., 2013). The task of identifying the etiologically-relevant compounds and/or mixtures associated with adverse health outcomes challenges standard regression-based techniques, due to the potentially strong correlation structure of the exposures as well as the hypothesized correlation between individual exposures and outcomes. The 'exposome' is a comprehensive term introduced to describe the totality of environmental exposures, as distinct from the genome (Wild, 2012), but this concept has yet to be applied to the etiology of neurodevelopmental and mental health disorders.

We argue that the adverse mental health consequences of exposure to toxic substances likely depend upon the complex effects of multiple chemical and social exposures on the

developing brain. Longitudinal research designs, with attention to the timing of exposures, are essential if we are to capture the cascading effects of early exposures across multiple biological systems and the full-range of neuropsychological endpoints. Neuroimaging at multiple time points, starting during the fetal period, will enable us to observe brain maturation under varying environmental conditions. Innovations in neuropsychological, physiological and behavioral assessments are sorely needed at the very earliest ages, as well as throughout childhood, including a range of performance-based indicators. At all ages, a continuous or dimensional approach to measurement across domains is not only likely to be sensitive to subtle sub-clinical toxic effects, but also permits the testing of complex functional relationships between brain and behavioral data. In addition, such an approach enables us to describe exposure-related profiles or phenotypes over time that may inform heterogeneity in children with specific mental health disorders (e.g., Fair, Bathula, Nikolas & Nigg, 2012).

Despite the public health policy response to scientific evidence that a number of environmental pollutants are toxic to the developing brain, including the examples of lead and pesticides, the problem of disproportionate exposure persists. Paradoxically, the overrepresentation of disadvantaged children in the most highly exposed groups often increases in response to regulatory activity, as more advantaged sectors of the population are protected. And of course, disproportionate exposures lead to social inequities in the mental health-related consequences of exposures—an example of environmental injustice.

Questions about how multiple exposures, the timing of exposures, and interactions of exposures with other social risk factors contribute to poor outcomes for children are scientifically important, but such questions become even more pressing when viewed through the lens of environmental justice. Any reduction in the burden of child mental health disorders (i.e., population attributable risk) that would be observed if we were to eliminate or reduce toxic exposures would be naturally limited, since most mental health problems are multiply determined by genetic and other risk factors. However, the important point is that this fraction of the excess risk for child mental health problems is *entirely preventable*. Research that seeks to identify links between toxic exposures and mental health outcomes is thus of enormous public health and societal value.

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Key points

- Environmental factors play a role in the origins of some child mental health disorders, as well as a range of subclinical neurodevelopmental deficits.
- The developing brain is particularly vulnerable to toxic chemical exposures, as exemplified by lead and pesticides, and this sensitivity is likely greatest in utero and throughout early childhood.
- Even at very low levels of exposure, toxic chemicals can have meaningful adverse effects on brain development and behavioral function, and these effects are often extremely costly to individuals and society.
- The inequitable distribution of environmental exposures in the population, resulting in a greater toxic burden among socially disadvantaged groups, is termed ‘environmental injustice’.
- We suggest broadening outcomes to include dimensional measures of autism spectrum disorders, attention deficit hyperactivity disorder, and child learning capacity, as well as direct assessment of brain function via neuroimaging.