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Neuroimaging is a novel tool to understand the impact of environmental chemicals on neurodevelopment

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Abstract

Purpose of review—The prevalence of childhood neurodevelopmental disorders (ND) has been increasing over the last several decades. Prenatal and early childhood exposure to environmental toxicants is increasingly recognized as contributing to the growing rate of NDs. Very little is known about the mechanistic processes by which environmental chemicals alter brain development. We review recent advances in brain imaging modalities and discuss their application in epidemiologic studies of prenatal and early childhood exposure to environmental toxicants.

Recent findings—Neuroimaging techniques (volumetric and functional magnetic resonance imaging (MRI), diffusor tensor imaging (DTI), magnetic resonance spectroscopy (MRS)) have opened unprecedented access to study the developing human brain. These techniques are non-invasive and free of ionization radiation making them suitable for research applications in children. Using these techniques, we now understand much about structural and functional patterns in the typically developing brain. This knowledge allows us to investigate how prenatal exposure to environmental toxicants may alter the typical developmental trajectory.

Summary—MRI is a powerful tool that allows in vivo visualization of brain structure and function. Used in epidemiologic studies of environmental exposure, it offers the promise to causally link exposure with behavioral and cognitive manifestations and ultimately to inform programs to reduce exposure and mitigate adverse effects of exposure.

Keywords

Neuroimaging; children; environmental toxicant; MRI; neurodevelopment

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INTRODUCTION

Neurodevelopmental disorders (ND) involve impaired functioning of the neurological system and include learning disabilities, speech and language impairment, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorders. Recent estimates suggest 12% of children in the United States are affected by neurodevelopmental disorders [1]. A review of data from the National Health Interview Survey demonstrated a 16% increase in the prevalence of childhood disabilities throughout the last decade; much of this increase related to greater prevalence of NDs [2].

Although the origin and development of NDs reflect complex interactions among genetics, nutrition, social influences, and physical environment, growing evidence suggests increasing rates of NDs may be associated with early life exposure to chemical toxicants [3]. Brain development is based on an exquisitely choreographed sequence of cellular events, including neuronal/glial genesis, differentiation, migration, synaptogenesis, and synaptic pruning. These processes make the developing brain inherently more vulnerable to insult than the adult brain. Environmental toxicants can interfere with these developmental processes [4-6]; seemingly minor environmental exposures at critical stages may alter the developmental trajectory of the growing brain, programming long lasting adaptive or maladaptive traits.

Although an expanding list of environmental toxicants has been implicated in the growing number of children with ND [7], we understand little about anatomic and mechanistic processes by which chemicals alter brain development. Recent advances in neuroimaging techniques have opened unprecedented access to study the developing human brain. Magnetic resonance imaging (MRI) allows in-vivo visualization of brain anatomy, function, blood flow, and metabolite concentrations. It is non-invasive and free of ionization radiation making it suitable for research applications in children. MRI findings are increasingly accepted biomarkers of pathology in many neurological diseases that may provide clues to understanding the role environmental toxicants play in NDs.

In this paper, we review MRI studies of children and young adults following prenatal or early childhood exposure to neurotoxic exposures: lead, pesticides, and environmental tobacco smoke. These studies provide a framework for using MRI to understand the mechanisms through which neurotoxic exposures affect brain development and subsequent functional outcomes in children. Mechanistic knowledge of structural and functional changes in the brain following exposure to environmental toxicants offers promise to causally link exposure with behavioral or cognitive manifestations and ultimately to inform programs to prevent exposure and mitigate the adverse effects of toxic exposures.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging uses the body's natural magnetic properties to produce detailed images of any part of the body. The MRI signal derives from hydrogen atoms of water molecules. The nucleus of each hydrogen atom contains a positively charged proton with an intrinsic spin around an axis. When placed in a strong magnetic field, the protons' axes align with the magnetic field. This alignment creates a magnetic vector oriented along the axis of

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the MRI scanner. This magnetic vector is considered to be in a low energy state. The application of a short radiofrequency (RF) pulse excites protons into a higher energy state. When this pulse is turned off, these protons will precess through the magnetic field at characteristic frequencies and emit RF signals detected with a nearby coil. The magnitude of this signal decreases over time, relaxation, depending on tissue type. Differential relaxation mechanisms are generated through various programs (called pulse sequences) that control the timing of RF pulses and other magnetic fields. The power of MRI lies in its ability to generate high contrast images through these pulse sequences.

Anatomical MRI—Anatomical MRI generates static measurements of morphological brain features by discriminating between gray matter, white matter, and cerebrospinal fluid (CSF). Images are formed from three dimensional volume elements called voxels. Each voxel is assigned a single value based on the relaxation time of the tissue. The size of the voxel determines the spatial resolution or fineness of detail that can be distinguished in an image [8]. Clinically, anatomical MRI is used for medical diagnosis and staging of disease (e.g., identifying tumors); researchers use anatomical MRI to assess morphological features of the brain including whole brain volume, volumes of specific regions (e.g., frontal lobes, amygdala, hippocampus, basal ganglia), localized volumes of subregions (e.g. dentate gyrus of the hippocampus), and cortical thickness [9].

Diffusion Tensor Imaging—Diffusion Tensor Imaging (DTI) provides *in vivo* data on white matter integrity and fiber connectivity between brain structures by characterizing myelination patterns and neuroanatomical changes in white matter microstructure [10, 11]. Water molecules diffuse through brain tissue in isotropic (equal in all directions) fashion in cerebral spinal fluid and cell bodies but anisotropic (greater in one direction vs. other directions) in white matter tracts. Diffusional anisotropy is increased in regions where white matter is coherent, highly myelinated and tightly packed and decreased in areas where white matter is not as organized [12, 13]. By measuring the direction and flow of anisotropy within a voxel, DTI provides an estimate of the neural fiber connectivity within each voxel [12, 14-16]. DTI scans produce two kinds of data: an integrity measure, usually quantified using fractional anisotropy (FA) [17] which is linked to axon packing and myelination, and mean diffusivity (MD) reflecting water content and density. These vectors can then use used to perform tractography which produce graphics that represent the tracts in 3D space [18].

Functional MRI—Functional MRI (fMRI) provides an indirect measure of neuronal activity deriving its signal from changes in oxygenation states of blood. Blood Oxygen Level Dependent [19] imaging detects changes in the magnetic resonance signal at an active area as it is infused with oxygenated blood compared to inactive, deoxygenated blood [20]. Neuronal activation increases local deoxyhemoglobin concentration, which is rapidly followed by a surge of oxyhemoglobin through neurovascular coupling system. This surge of oxyhemoglobin leads to an increase of the MRI signal above baseline. Task-related fMRI compares regional activation during baseline and experimental tasks to identify regions that subserve specific task-related activity. Resting state fMRI (rsfMRI) measures activity in the brain when a subject is not performing an explicit task, and detects spontaneous synchronous activity between distant brain regions.

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Magnetic Resonance Spectroscopy—Magnetic resonance spectroscopy (MRS) determines chemical content in discrete brain regions by studying protons from metabolites including N-Acetyl Aspartate (NAA), choline [21], glutamate (Glu) and creatine [18]. The presence of these metabolites shields the resonant atoms of different metabolites of interest to varying degrees. Signals vary depending on the hydrogen positions within the compound. This shielding causes a characteristic shift in the observed resonance frequency and spectroscopic specific peak. The concentration of various molecules in specific brain regions is quantified based on the strength of the signal of each of these shifted frequencies. MR spectroscopy quantifies relative metabolite concentrations. The spectrum of different brain metabolites may reflect the functional status of neural structures: neurons, axons, glia; myelin; and cellular membrane [22]. For example, NAA is a component of axons and neurons while Cho reflects membrane turnover and indirectly myelination.

Traditionally, neuroimaging techniques have contributed to characterizing and combatting various neurological and psychiatric disorders. More recently, these techniques have been applied to begin to understand subtle alterations in normal developmental trajectories in the developing brain [8, 23-25]. Delineation of normal trajectories provides a necessary template to identify deviant patterns early in development [25]. When MRI techniques, are combined with neurologic/neuropsychological evaluation, studies can investigate mechanisms through which environmental toxicants impact neurodevelopment.

Applications to Children's Environmental Health

In this section, we review MRI studies of children and young adults following prenatal or early childhood exposure to neurotoxic exposures: lead, pesticides, and environmental tobacco smoke.

LEAD

Lead has been extensively studied and provides an excellent test case for MRI studies. Adverse neurologic outcomes associated with prenatal and/or early childhood lead exposure include lowered intelligence, behavioral problems, and diminished school performance [26-28]. In recent years, MRI studies have advanced our understanding of the mechanisms underlying the effects of lead exposure on neurological function. The first investigation to use MRI to investigate changes in the brain following lead exposure examined the MRS spectra of a lead-poisoned 10 year old compared to his unexposed age matched cousin [29]. The spectra of the lead-exposed child deviated from the expected pattern in all metabolite ratios analyzed. These results were confirmed in a cross-sectional study comparing 16 lead exposed subjects with 5 healthy, unexposed controls [30]. The MRS spectra obtained from the lead exposed group showed lower NAA/Cr ratios for gray matter, suggestive of neuronal loss.

The Cincinnati Lead Study (CLS) was the first longitudinal epidemiologic study to use MRI in a population well characterized for lead exposure [31]. Young adults with prenatal and early childhood lead exposure were invited to participate in an MRI follow-up. CLS investigators demonstrated that prenatal or early childhood lead exposure was associated with a variety of adverse effects on adult brain structure, organization, and function. Young

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adults demonstrate reductions in grey matter volume associated with increased prenatal and/or early childhood blood lead; the magnitude of loss increasing with age [32, 33]. The associations were most striking in frontal regions, particularly the anterior cingulate cortex and ventrolateral prefrontal cortex. Associations were stronger for males than females. No white matter volume changes were associated with childhood blood lead levels.

CLS Investigators further examined white matter connectivity using DTI. An analysis of 91 representative cohort members revealed lead associated reductions in fractional anisotropy (FA) [34]. Further investigation found that the changes in FA could be attributed to significant changes in radial diffusivity. Radial diffusivity primarily reflects alterations in the myelin sheath thickness and organizational characteristics. These finding suggests lead exposure disrupted the underlying neuronal network.

Incorporating MRS allowed CLS researchers to further investigate microscopic structural and chemical disruptions below the detection limits of conventional imaging modalities such as MRI. Cecil et al (2010) [35] employed MRS within the MRI examination to obtain *in vivo* measures of brain metabolites to reflect the functional status of neural structures. They demonstrated inverse associations between mean childhood blood lead levels and NAA and Cr concentrations in the basal ganglia and cerebral hemisphere and decreased Cho in the white matter of the frontal and parietal loves of the cerebral hemisphere.

These results, suggesting childhood lead exposure is associated with neuronal dysfunction in discrete anatomic regions, are consistent with behavioral studies suggesting cognitive, motor and behavioral effects of early childhood lead exposure. Note, the metabolic spectra were not consistent with results showing volume loss in medial frontal gray matter [32]. It is anticipated that volume loss would be associated with increased NAA. Lead therefore appears to affect both brain volume and metabolic content and likely has multiple mechanisms of action.

PESTICIDES

Chlorpyrifos (CPF) is a broad-spectrum organophosphate (OP) insecticide. Once the most widely used insecticide to control indoor pests such as cockroaches, concerns of developmental neurotoxicity resulted in regulatory action to restrict the residential use of this compound [36]. CPF remains heavily used in agriculture, causing continued exposures of agricultural workers, residents of agricultural communities and the general population through consumption of CPF-treated products [37]. Acute toxicity is attributed to irreversible inhibition of the enzyme acetylcholinesterase [2], lower dose exposures appear to work through additional mechanisms including oxidative stress. Adverse effects of exposure have been documented in animal and human studies at exposure levels well below the threshold for AChE inhibition [38]. In epidemiologic studies, low-level exposure to chlorpyrifos during pregnancy has been associated with smaller head size [19], lower birth weight [39], deviate neonatal reflexes [40, 41], attention problems [42, 43], and neurodevelopmental anomalies resembling pervasive developmental disorders [43, 44] in children. Prenatal organophsophorous pesticide exposure is associated with significant reductions in subsequent childhood IQ [40, 45, 46].

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Recent work in animal models identifies neural mechanisms associated with the neurotoxic effects of prenatal CPF exposure. Subchronic exposure in pregnant rodents altered neurogenesis and neurotransmission in offspring [47-53]. Two recent studies showed regionally specific morphological effects on the brain targeting the septal nucleus, striatum, and somatosensory cortex as well as the hippocampus [51, 54]. Morphological changes correlated with later emergence of behavioral alterations [51]. One recent study exposed prepubertal guinea pigs to sub-lethal doses of chlorpyrifos and examined the metabolic and structural integrity of the brain [55]. While no significant anatomical differences were found between chlorpyrifos-exposed guinea pigs and control animals using MRI, MRS spectra showed decreases in hippocampal myoinositol concentrations in chlorpyrifos-exposed guinea pigs indicating altered astrocyte development.

To date, only one published study has investigated associations between prenatal CPF exposure and brain morphology in humans. This pilot study of subjects (ages 5 to 11 years) selected from an ongoing longitudinal birth cohort measured cortical surface volume using anatomical MRI in 20 children with high prenatal exposure to CPF (upper tertile of CPF concentrations measured in umbilical cord blood) to 20 controls with low prenatal exposure to CPF [37]*. Overall brain size did not differ significantly between exposure groups, after adjusting for age and height of child. The high CPF exposure group demonstrated regional enlargements of the cerebral surface in the superior temporal, posterior middle temporal, and inferior postcentral gyri bilaterally, and in the superior frontal gyrus, gyrus rectus, cuneus and precuneus along the mesial wall of the right hemisphere. Inward deformations were detected in the dorsal and mesial surfaces of the left superior frontal gyrus. Consistent with prior reports that CPF altered cognitive impairment, researchers reported a significant IQ x exposure interaction on cerebral surface measures; surface measures were significantly enlarged in the high CPF-group, particularly for those in the lower IQ scores.

The findings in humans are consistent with animal models demonstrating the neurotoxic effects of early developmental CPF exposure on glia and neurons. Regional enlargements observed in the high-CPF exposed subjects may be due to excessive astrocytic processing and perikaryal swelling [54]. Cortical thinning, as observed in the dorsal parietal, frontal and orbitofrontal cortices of the high-CPF children is consistent with the direct neurotoxic effects observed in rodents [51, 54].

ENVIRONMENTAL TOBACCO SMOKE

Despite national public health efforts to reduce rates of smoking in the US, nearly 20% of adults continue to smoke cigarettes. Epidemiologic studies demonstrate prenatal exposure to tobacco smoke is associated with negative neurologic outcomes across many functional domains. Prenatal exposure to environmental tobacco smoke is associated with cognitive delays at two years of age [56], lower scores on math and reading tests in the early school years [21, 57], and elevated risk for grade retention [58].

Animal models demonstrate that prenatal exposure to ETS affects the developing brain when nicotine crosses the placenta and binds with and stimulates nicotinic cholinergic receptors, mimicking the effects of acetylcholine neurotransmission[59]. Through this

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mechanism, prenatal exposure to ETS may affect processes such as cell replication, differentiation, growth, death, and sensitivity to future stimulation[60]. Notably, prenatal ETS exposure differentially affects structures that subserve learning, such as the hippocampus[61],[62]. Thus, prenatal exposure to ETS may contribute to anatomical and functional disturbances in brain development that contribute to the manifestation of neurodevelopmental disorders.

Two reports demonstrate the neurotoxic effects of prenatal exposure to tobacco smoke using structural MRI to investigate changes in neuroanatomy. In a prospective epidemiologic study, maternal smoking throughout pregnancy was associated with thinning in superior frontal, superior parietal, lateral occipital, and precentral cortices [63], whereas maternal smoking in early pregnancy only (stopping after learning of the pregnancy), was not associated with reductions in cortical thickness. Importantly, maternal smoking throughout pregnancy was associated with affective problems, and this association was explained by thinning in the superior frontal and precentral cortices. In a retrospective study, adolescents exposed *in utero* to maternal smoking demonstrated thinning in orbitofrontal, middle frontal, and parahippocampal cortices relative to non exposed controls [64], somewhat consistent with findings from animal studies.

One report investigates the neurotoxic effects of exposure to tobacco smoke on fiber structure and connectivity in the brain using DTI [65]. Prenatal and adolescent exposure to tobacco smoke was associated with increases in regional fractional anisotropy in anterior cortex and subcortical structures. Adolescent smokers demonstrated changes in FA, regardless of prenatal exposure. However, adolescent smokers without prenatal exposure demonstrated unique increases in right internal capsule FA relative to adolescent non-smokers who were prenatally exposed, suggesting that the neurotoxic effects of nicotine exposure may be more deleterious in adolescence than in prenatal life, possibly because adolescence represents a critical period of white matter maturation [66].

Event related fMRI studies demonstrate that tobacco exposure is associated with changes in neurocircuitry that support learning and attention. Children who were prenatally exposed to tobacco showed greater activation during a working memory n-back task, in inferior parietal regions, whereas unexposed children showed greater activation in bilateral inferior frontal regions [67]*. Similar to many fMRI paradigms, all of the children were capable of the task and the differences in activation occurred in the context of correct responses, suggesting that exposed and unexposed children may use different brain regions when carrying out working memory tasks. Such findings may point to compensatory processes that mitigate toxic exposures, explaining in part population variability in response to chemicals. Prenatal or adolescent exposure to tobacco smoke was associated with decreased activation in neural circuits associated with auditory and visual attention in females, and the association was related to amount of exposure [68]. In males, however, the effect of exposure was detected in activations in neurocircuits that support auditory but not visual attention.

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Conclusion

MRI is a powerful tool that allows *in vivo* visualization of brain structure, chemical content, connectivity and function. Throughout the last decade, applications of MRI in infants, children and adolescents have improved our understanding of normal and abnormal trajectories in the developing brain. When used in epidemiologic studies of environmental exposure, MRI can provide insights on the mechanisms by which chemical cause toxicity and variable response in the general population to that exposure. While MRI offers a novel approach to understanding the mechanisms through which environmental exposures influence the increasing rate of NDs, the use of MRI in epidemiologic studies is still an evolving science and its applicability will likely increase as techniques are refined and improved. Finally, with regards to children, prospective study designs are needed both to determine the critical windows of vulnerability to exposure but also to appropriately assess the life stage specific developmental processes that MR scans assess, as normal development is a moving target changing with each life stage.

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Key points

- Prenatal and early childhood exposure to environmental toxicants may contribute to the growing rate of neurodevelopmental disorders
- Very little is understood about the mechanisms through which environmental toxicants interfere with brain development.
- Magnetic resonance imaging (MRI) is a powerful tool allowing *in vivo* visualization of brain structure and function
- MRI may provide the knowledge of structural and functional changes in the brain following exposure to environmental toxicants to causally link exposure with behavioral or cognitive manifestations and ultimately to inform programs to prevent exposure and mitigate the adverse effects of toxic exposures.