A global perspective on the influence of environmental exposures on the nervous system

Desire Tshala-Katumbay1,2,3, Jean-Claude Mwanza4, Diane S. Rohlman5,6, Gladys Maestre7 & Reinaldo B. Oriá5,8

Economic transitions in the era of globalization warrant a fresh look at the neurological risks associated with environmental change. These are driven by industrial expansion, transfer and mobility of goods, climate change and population growth. In these contexts, risk of infectious and non-infectious diseases are shared across geographical boundaries. In low- and middle-income countries, the risk of environmentally mediated brain disease is augmented several fold by lack of infrastructure, poor health and safety regulations, and limited measures for environmental protection. Neurological disorders may occur as a result of direct exposure to chemical and/or non-chemical stressors, including but not limited to, ultrafine particulate matters. Individual susceptibility to exposure-related diseases are modified by genetic, epigenetic and metagenomic factors. The existence of several uniquely exposed populations, including those in the areas surrounding the Niger Delta or north western Amazon oil operations; those working in poorly regulated environments, such as artisanal mining industries; or those, mostly in sub-Saharan Africa, relying on cassava as a staple food, offers invaluable opportunities to advance the current understanding of brain responses to environmental challenges. Increased awareness of the brain disorders that are prevalent in low- and middle-income countries and investments in capacity for further environmental health-related research are positive steps towards improving human health.

ENVIRONMENTAL EXPOSURE AND BRAIN HEALTH

LMICs are home to around 80–85% of the world’s population1. Of these 5.8 billion people2, 1 billion remain in extreme poverty, living below the US$1.25 per day poverty line3. Around 3 billion people do not have piped drinking water in their home and 173 million people rely on the direct use of surface water. Without proper sanitation, about one billion consume unhygienic water4. Of these 5.8 billion people2, 1 billion remain in extreme poverty, living below the US$1.25 per day poverty line3. Around 3 billion people do not have piped drinking water in their home and 173 million people rely on the direct use of surface water. Without proper sanitation, about one billion continue to defecate in gutters, in the open bush or in open water bodies4. Wildfires and deforestation are commonplace and drought and floods, possibly due to climate change, degrade the existing farming systems and create food insecurity5–7. Armed conflicts and population displacements impose a toll on human life8. Industrial expansion coexists with an unprecedented rise in artisanal mining and unprotected labour9. In some instances, normal urbanization operations, such as road construction and quarantines (for example during Ebola outbreaks in the Democratic Republic of the Congo) have created conditions that exacerbated the risk of environmental exposure and brain disease10. Flawed regulations compounded by a lack of infrastructure set the stage for

1Department of Neurology, Oregon Health & Science University, Portland, Oregon, 97239, USA. 2National Institute of Biomedical Research, 1197 Kinshasa I, Congo. 3National Institute of Biomedical Research, University of Kinshasa, 825 Kinshasa XI, Congo. 4Department of Ophthalmology, University of North Carolina at Chapel Hill, North Carolina 27599, USA. 5Occupational and Environmental Health, The University of Iowa, Iowa 52242, USA. 6Oregon Institute of Occupational Health Sciences, Oregon Health and Science University, Portland, Oregon, 97239, USA. 7G.H. Sergievsky Center, Columbia University Medical Center, New York, New York 10032, USA. 8Department of Morphology and Institute of Biomedicine, Faculty of Medicine, Federal University of Ceará, Fortaleza 60020, Brazil. Correspondence should be addressed to D. T-K. e-mail: tshalad@ohsu.edu.

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environmental degradation and pollution to pose serious threats — of a chemical or non-chemical nature — to human health. The degradation of local ecosystems leads to the creation of ‘microenvironments’ that have a high risk of harmful exposures, often resulting in unique challenges and increased risk of human disease (Fig. 1).

**HIGH-RISK POPULATIONS AND MICROENVIRONMENTS**

Risk of exposure-related brain disease is determined by age, gender and microenvironments created by natural disasters in which economic, social and cultural determinants of health often have important roles. One example of a profit-mediated environmental risk is that caused by the oil industry through accidental spills or mismanagement of oil operations. For instance, crude oil operations have polluted large areas of rainforests, including streams and rivers in Ecuador, Peru and Colombia. The population of Nigeria has faced similar challenges owing to reoccurring oil spills as a result of ageing, ill-maintained or sabotaged pipelines in the Niger Delta. The impact of such man-made and preventable natural disasters on human health has yet to be determined. Effects on human health will depend on the type and composition of the spilled oils, which often contain a mixture of polycyclic hydrocarbons that are known to be toxic to the nervous system. Oil spills arise owing to reasons, such as a lack of vigilance, neglect of necessary health and safety checks, or sometimes even promotion of commercial interests at the expense of communities. Symptoms of acute exposure to raw oil include consistent episodes of headache, nausea, dizziness and fatigue. Chronic effects include psychological disorders, endocrine abnormalities and genotoxic effects.

Microenvironments in which the population has a higher susceptibility to exposure-related diseases have also been created by extreme poverty and natural disasters, including drought and flooding that can degrade soils, plants and farming operations. The burden of conventional neurodevelopmental stressors (for example, lead) on children is exacerbated by unique environmental challenges, including malnutrition and enteric infections and, possibly, a diet of neurotoxicant-containing plants such as cassava (Manihot esculenta; also known as tapioca), the grass pea Lathyrus sativus or the seeds from the cycad plants, which are all known to be associated with a high burden of neurodevelopmental stressors at a population level.

Populations with unique exposures and risks include those living in the tropical cassava belt of Angola, the Central African Republic, Cameroon, Congo, Tanzania, Uganda, Nigeria and Mozambique; those reliant on L. sativus as a staple food in Ethiopia, Eritrea, India and Bangladesh; and the people of the Pacific Island Guam or the Japanese Kii Peninsula where the rates of environmentally linked syndromes such as amyotrophic lateral sclerosis-parkinsonism–dementia complex (ALS/PDC) have been declining for reasons that have yet to be uncovered.

The impact of early childhood diseases that lead to a vicious cycle of enteric infections and malnutrition has been underestimated and neglected, especially in areas that lack acceptable levels of hygiene and sanitation and that have reduced accessibility to vaccines and antimicrobials. This has caused clinically silent, chronic–illness–related effects, which jeopardize the child’s full cognitive development. This vicious cycle establishes what is called environmental enteropathy, a mostly subclinical condition (even without diarrhea) caused by various degrees of intestinal barrier dysfunction, luminal–to–blood intestinal bacterial translocation, low–grade local and systemic inflammation, and disrupted innate intestinal immune responses that may affect growth and cognition and possibly lead to neurodegeneration as well as liver, and metabolic diseases later in life.

Adolescents in LMICs experience a higher burden of exposures (in contrast with those in high-income countries), primarily because of the childhood labour crisis. Although there are regulations and international agreements restricting child labour, often there are exceptions for certain industries, notably the growing agricultural industry, one of the most hazardous industries worldwide. In this context, adolescent workers are at risk of exposure to agrochemicals as pesticides and other work-related threats include exposure to organic solvents in work that involves painting and manufacture, to toxic metals and fine particulate matters in artisanal mining, and to heat andambient air pollution while working long hours and outside. Exposure to

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**Table 1 | Heavy metals and exposure-related outcomes**

<table>
<thead>
<tr>
<th>Heavy metal</th>
<th>Source of exposure</th>
<th>Susceptibility window</th>
<th>Neurological outcomes</th>
<th>Proposed mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead⁹⁻¹⁹</td>
<td>Lead-containing dust, lead-based paints, soil, drinking water, air, leaded gasoline, toys and lead-containing sweets</td>
<td>Lifelong</td>
<td>Visual and verbal memory decline, intellectual deficits, decline in executive functioning (fine motor function, hand-eye coordination and reaction time) and hyperactivity in children</td>
<td>Disruption of neurotransmitter release and function, and prenatal disruption of neuronal migration and differentiation; aggravating factors include poor nutrition (deficiency in iron, zinc and calcium) and younger age</td>
</tr>
<tr>
<td>Mercury⁷⁸,⁸⁰</td>
<td>Mining industry, power plants, crematoria, coal, charcoal industry, and contaminated food (mostly sea food) and water</td>
<td>From neural development to neurulation, and adolescence</td>
<td>Ataxia in adults and language, attention, and visuospatial performance deficits in children</td>
<td>Oxidative stress or impairment of intracellular calcium and glutamate homeostasis</td>
</tr>
<tr>
<td>Arsenic⁸⁰,⁸¹</td>
<td>Contaminated food and drinking water, air and arsenic-based treatments</td>
<td>5–15 years</td>
<td>Impaired selective and focused attention and long-term memory in children, and sensorimotor polyneuropathy</td>
<td>Oxidative stress or disruption of metabolism of neurotransmitters</td>
</tr>
<tr>
<td>Copper⁴³</td>
<td>Contaminated drinking water and food, uncoated copper cookware and infant formula containing copper</td>
<td>Children Those over 65</td>
<td>Alzheimer’s disease, OCD, ADHD, antisocial behaviour and anxiety in children</td>
<td>Oxidative stress, microglia cell activation or promotion of α-synuclein and fibril formation</td>
</tr>
<tr>
<td>Cobalt⁴２,⁴³</td>
<td>Contaminated drinking water and food, inhalation of dust containing cobalt particles in various industries</td>
<td>Prenatal, young children and the elderly</td>
<td>Optic, auditory and peripheral neuropathy, motor deficits and verbal memory loss</td>
<td>Alteration of mitochondrial oxidative phosphorylation or depletion of neurotransmitters</td>
</tr>
<tr>
<td>Cadmium⁴⁴</td>
<td>Fumes or dust, cigarette smoke, and contaminated food and water</td>
<td>Prenatal, young children and the elderly</td>
<td>Antisocial behaviour and attention impairment in children, parkinsonism and peripheral neuropathy</td>
<td>Oxidative damage and neurotransmitter disruption</td>
</tr>
<tr>
<td>Manganese⁷⁶,⁷⁹</td>
<td>Airborne as fumes, aerosols or suspended particulate matter and contaminated water</td>
<td>Childhood and the elderly</td>
<td>Reduced IQ, impaired verbal learning and working and immediate memory in children, and Parkinson-like symptoms</td>
<td>Disruption of mitochondrial respiratory chain reaction; aggravating factors include iron deficiency and impaired biliary excretion (liver injury or disease)</td>
</tr>
<tr>
<td>Aluminium⁴⁴</td>
<td>Contaminated air, water, food, cosmetics (such as antiperspirants), metal industries and pharmaceuticals</td>
<td>Lifelong</td>
<td>Alzheimer’s pathology in the form of neurofibrillary tangles</td>
<td>Disruption of mitochondrial respiratory chain reaction or inflammation; zinc deficiency acknowledged as an aggravating factor</td>
</tr>
</tbody>
</table>

ADHD, attention-deficit hyperactivity disorder; OCD, obsessive compulsive disorder.
Exposure-related brain damage may result from chemical and/or non-chemical stressors. Damage to the nervous system often leads to a range of bilateral and symmetrical motor and/or sensory symptoms. Behavioural problems, cognition deficits and psychiatric illness may also occur. Non-chemical stressors include, but are not limited to, psychological stress, heat, noise, fine and ultrafine particulate matter (FUPM), and waterborne, airborne or foodborne pathogens that may occur under the conceptual framework shown in Fig. 1. Chemicals with neurotoxic potential that people are commonly exposed to are listed in Tables 1–3. Mixed exposure, for example chemical–covered FUPM from industrial emissions; co-exposure to chemical and non-chemical stressors; and repeated and multiple exposure can occur, creating a complex human environmental exposome.

Brain damage linked to chemical exposure may result from chemicals interfering with neurotransmission through molecular mimicry or reacting with crucial biomolecules and causing incorrect function (for example, protein or DNA adduction and/or crosslinking). For both chemical and non-chemical exposures, the mechanisms of brain damage may include injury to the vascular system (for example, fine particulate matter induced vascular pathology), systemic dyshomeostasis (for example, cadmium-induced kidney disease) and hormonal imbalance (for example, through endocrine disruption; Table 1).

The susceptibility to exposure-related disease is, however, determined by mechanisms of functional genetics, epigenetics and metagenomics at the interface between risk factors and neurological outcomes (Fig. 2).

It is increasingly acknowledged that genetic and epigenetic factors, including the effect of maternal stress on brain function, influence the effect of environmental exposure. For example, the E4 allele of the APOE gene that is reportedly associated with higher risk of late–onset Alzheimer’s disease, although not in people from sub-Saharan Africa and with a mild association among Hispanic people, is associated with protection against early childhood diarrhoea and its related cognitive
impairments. One example of gene–environment interactions is the relationship between air pollution components and the gene encoding the MET receptor tyrosine kinase. Several studies have implicated MET as an autism risk gene. Stratiﬁcation of the risk conferred by a functional promoter variant in this gene (rs1858830) and by local trafﬁc–related air pollution (regional particulate matter less than 10 micrometres in diameter and nitrogen dioxide exposure) revealed signiﬁcant multiplicative interaction between the risk genotype and the air pollution exposure.

Our knowledge of the pathways that lead to late onset of exposure–related neurological disease is still sparse. Many studies suggest that the genetic and environmental causes of late onset diseases act in parallel and share common molecular mechanisms. A number of studies have supported the concept that early–life exposure to pollutants reprograms global gene expression in old age through epigenetic mechanisms. Variation in exposure response, even among individuals exposed to the same environment could be due not only to early–life exposures, but also to differences in genetic make up.

The extent and nature of exposures and related brain diseases in LMICs provide opportunities to explore and overcome the long reach that childhood exposure has into adulthood, as well as provide us with new advances in environmental health sciences.

Exposure–related neurological deﬁcits in LMICs range from peripheral neuropathies to a large number of acute, subacute or chronic central nervous system diseases. Deﬁcits may occur prenatally, during childhood or adolescence, and may be carried through to old age. Clinical implications include, but are not limited to, neural tube defects, learning disabilities, behavioural problems, psychiatric disorders, cognitive decline and the occurrence of distinct entities such as neurolathyrism, tropical ataxic neuropathy, ALS/PDC and kongzol.

The human microbiome may be of particular interest to the mechanistic understanding of exposure–related diseases in LMICs because it may inﬂuence the burden of heavy metals, the metabolism of food–borne neurotoxicants such as cassava cyanogens, and the outcome of enteric diseases in early life, including the child’s neurodevelopmental potential.

RESEARCH AND CAPACITY BUILDING

Recent advances in environmental health sciences have elucidated the myriad risk factors and mechanisms of brain damage that are associated with environmental exposures. The existence of uniquely exposed populations in LMICs offers invaluable opportunities to advance our current understanding of brain responses to environmental threats. In some instances, well–characterized neurotoxicants may be used as chemical probes to dissect the pathophysiology of the nervous system. However, challenges at the population level still remain, including setting exposure limits and developing metrics and methodologies to assess the long–term impact of environmental exposures on disease burden in LMICs and, therefore, globally. Climate change and mining of rare elements, which may include radioactive materials, present unpredictable risks, and should be added to the environmental health research agenda. The toll of such exposures on the global burden of disease may be efﬁciently addressed only through competent partnerships and alliances established on a global scale and focused on key areas and priorities (Box 1). Although there is evidence that some of these are already in place, more research and research capacity is needed to continue this agenda to improve human health, globally.

ONE HEALTH–GLOBAL HEALTH DIMENSIONS

Environmental degradation and contamination, changes in climate and ecosystems, and vector–borne pathogens or neurotoxicants are the primary environmental threats to human life and intellectual performance.

BOX 1 | INTERWOVEN RESEARCH AREAS AND INVESTMENT PRIORITIES IN GLOBAL ENVIRONMENTAL RESEARCH

- Epidemiology and statistical modelling for exposure and risk assessment in co–exposure and co–morbidty scenarios
- High–throughput ‘–omic’ methodologies
- Bioinformatics and knowledge management
- Development of diagnostic and remediation tools — validation and implementation of environmental sensors, detectors and biomonitoring of exposure and related outcomes
- Development of metrics and methodologies to assess the long–term impact of environmental exposures on neurological disease burden
- Understanding the pathways that lead to late onset of exposure–related neurological diseases
- Training and capacity building in the areas listed above
Humans, plants and animals adapt to environmental challenges, but some may overcome their adaptive capabilities and create imminent risks for all\(^\text{25}\). Strategies to promote human health will therefore require a serious commitment to trans-disciplinary work, plant and animal health and building capacity on a global scale\(^\text{26}\).

Figure 2 | Environmental framework and pathways to environmentally induced neurological disease in low- and middle-income countries. Susceptibility to neurological disease is determined at the interface between a particular exposure, epigenetic and metagenetic make up, and the presence of co-morbidities.

Figure 3 | Neurocognition deficits in konzo, a disease linked to eating cyanogenic cassava. a. Spasticity in a 14-year-old boy affected by konzo. b. Deficits in mental processing are evident from the results of a neuropsychological test.


