
THE NEURAL EXPOSOME TOP PRIORITIES WORKING
GROUP: REPORT TO THE NATIONAL ADVISORY
NEUROLOGICAL DISORDERS AND STROKE COUNCIL

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EXECUTIVE SUMMARY

Neurological diseases and disorders are now the world's leading cause of disability and the second leading cause of death, surpassing heart disease, cancer, and infectious diseases, including COVID (Collaborators, 2024). There is, therefore, an urgent need for effective prevention, treatment and rehabilitation strategies for nervous system dysfunction. Over 25 years of significant investment in genetic research has identified the cause of only a few neurological diseases and disorders but has revealed that many, including some of the most common, disabling and deadly, such as stroke, Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS) and pain, are among the least heritable of major medical disorders (van Dongen et al., 2012). Both genetic and non-genetic evidence have led to the general scientific consensus that many, if not most, neurological diseases and disorders are not due solely to genetic causes but rather arise from complex interactions between genetic susceptibilities and environmental risk factors (Nussbaum and Ellis, 2003; Carlsson et al., 2021; De Miranda et al., 2022).

Investing in research to identify and understand environmental factors that influence nervous system health offers the exciting possibility of meaningfully decreasing the burden of neurological disease by controlling exposures – it is far easier to change our environment than our genetics. However, the development of effective, scientifically defensible clinical and public health strategies focused on exposure control is currently stymied by critical gaps in our understanding of environmental factors that increase risk for adverse neurological outcomes or, conversely, increase neurological resiliency. The potential payoff of closing this gap is enormous: a 1% reduction in AD spares 5,000 Americans and their families annually; a 1% reduction in PD would save Medicare \$250 million annually, which equals NIH's annual spending on Parkinson's research (Yang et al., 2020; AA-Report, 2023; Alzheimer's_San Diego, 2024; NIHRePORT, 2024; NINDS, 2024). Increased understanding of the environmental factors that influence brain health is also likely to provide novel, actionable insights regarding clinical and public health strategies for preventing neurological disorders outright, slowing their progression, and lessening their severity of disease.(WHO, 2022)

A myriad of environmental factors, including the physical and social environments in which people live and the impact of these environments on their opportunities and health behaviors influence brain health and aging (WHO, 2022). Some of these environmental exposures can begin as early as *in utero* and may lead to diseases years, decades, or generations later. Capturing all of the environmental exposures experienced by an individual to identify those that modify disease risk is a major challenge because socioeconomic factors and geographical specificities typically vary across the life span and are often cumulative in effect (Lefevre-Arbogast et al., 2024). There is an increasing recognition of the potential for exposomics to meet this challenge by enabling the systemic and comprehensive analysis of the environmental factors to which an individual is exposed during their lifetime, e.g., their exposome.

The term “exposome” was coined in 2005 by Christopher Wild (Wild, 2005) in an effort to draw attention to the need to characterize environmental exposures with the same scientific rigor and precision that was at the time being applied to the analysis of the human genome. Exposomics has continued to mature over the past two decades, prompting the convening of an international group of experts at the Banbury Center at Cold Spring Harbor Laboratory in December 2023 to reach a consensus definition of exposome and exposomics (Report, 2024). This group agreed to define exposome as “the integrated compilation of physical, chemical, biological and social

influences that impact biology” and exposomics as “the transdisciplinary field aimed at discovering how the exposome influences biology and health”.

The neural exposome encompasses the diverse array of factors that influence brain health and neurological disease, including factors that are exogenous (e.g., originating from outside the organism such as environmental contaminants, climate, noise and light), behavioral (e.g., lifestyle, stress), and endogenous (e.g., microbiome, metabolism, pre-existing medical conditions) (Tamiz et al., 2022). The study of the neural exposome is complicated by the brain's dynamic and adaptive nature, characterized by continual change as a function of experience across the life course. Additionally, just as genetic variants often interact to influence genetic disease risk, combined exposures from across the life course are likely to have interactive effects on brain health (Tamiz et al., 2022). In addition to efforts focused on specific individual exposures, interventional strategies that target multiple factors may be expected to have greater effectiveness when multiple factors contribute additively or synergistically to risk of neurological dysfunction. Further complexity stems from the fact that exposures or events that occur in early life may not manifest until later in life and are likely cumulative over the life span (Migliore and Coppede, 2022; Tamiz et al., 2022).

Leveraging exposomics to understand neurological health and dysfunction is an exciting concept, yet logistically daunting. How does one analyze the totality of environmental influences across an individual's life span? Currently, we lack the capacity to do that, but recent advances in technology are enabling initial steps in that direction and the field is poised to advance rapidly with strategic investments. Bold vision has proven time and again to yield significant scientific advances. The human genome and human microbiome were once equally daunting. With the launch of the Human Genome Project, human genetic studies rapidly progressed within a few years from the laborious study of one-polymorphism-at-a-time to the mapping of the human genome, the invention of genotyping arrays and the identification of the genetic structure of complex diseases. Similarly, microbiome studies were limited to culturing one microorganism at a time until the introduction of next generation sequencing, which enabled profiling of entire metagenomes (trillions of microorganisms per individual site) of thousands of individuals at once. The advent of genomics, and then metagenomics revolutionized brain research; exposomics will similarly catalyze major advances that will complement and significantly extend the genetic work.

The neural exposome is arguably vaster than the human genome or microbiome, but recent advances in geospatial technologies and high-resolution mass spectrometry (HRMS) are already enabling investigators to study hundreds to thousands of chemical features and to link changes in these features to the underlying biology and chemistry (Lefevre-Arbogast et al., 2024). The potential for exposomics to yield novel and meaningful insights into the pathogenesis and prevention of neurological diseases is illustrated by recent exposomic studies of PD and AD. Until the mid-1990s, PD was thought to be primarily environmental in origin. Individual factors that increased risk (e.g., pesticides and the solvent trichloroethylene) or conferred protection (e.g., nicotine and coffee) have been known for decades (Bellou et al., 2016); however, relatively little could be discerned about disease pathophysiology from this knowledge. The recent application of exposomics to examine combined effects of PD risk factors led to the realization that a substantial proportion of PD may be prevented by removing exposure to known modifiable risk factors, such as pesticides (Payami et al., 2023). Recent HRMS-based pilot studies (with generally < 50 participants) have begun to identify novel

exogenous and endogenous chemicals associated with increased PD and AD risk (Agin et al., 2020; Niedzwiecki et al., 2020; Chang et al., 2023). For example, bis(2-ethylhexyl)phthalate, a commonly used plasticizer, was detected at higher levels in the cerebrospinal fluid of patients with Lewy body disease than patients with AD (Agin et al., 2020), while the profiles of phthalates, dietary long-chain unsaturated fatty acids, and gut-derived indole metabolites detected in the hair of patients with AD differed from that of healthy individuals (Chang et al., 2023).

Exposomics will not only enable discovery of novel, modifiable risk factors, but also mechanistic understanding of how environmental factors interact with each other and with susceptibility genes to determine individual risk of neurological disease. Genome-wide gene-environment interaction studies (GWIS) of nicotine in a *Drosophila* model of pesticide-induced PD discovered the SV2C (synaptic vesicle 2C) gene and this discovery was validated in GWIS of smoking and PD (Hill-Burns et al., 2013). These findings of interactions between risk factors triggered mechanistic studies that revealed SV2C modulates dopamine release and is disrupted in PD (Dunn et al., 2017). GWIS also identified GRIN2A (glutamate receptor NMDA subunit 2A) as the gene that modulates the protective effect of coffee in PD (Hamza et al., 2014). Interestingly, GRIN2A is also associated with schizophrenia, epilepsy, and developmental delay/intellectual disability (Shepard et al., 2024), raising questions as to what factors cause a single gene to have such varied phenotypes? The most likely answer is the combined effects of the type of mutation, site of expression, and variation in the exposome, as evidenced by the interaction of GRIN2A with coffee in PD. The field of exposomics is poised to rapidly advance understanding of the combined interactive effects of multiple environmental factors with each other and with the genome.

Emerging research on another component of the exposome, the gut microbiome, is revealing more of the missing pieces in the pathophysiology of complex neurological diseases and disorders. Nearly all inflammatory and immune-related conditions, which includes many neurological conditions, involve the microbiome. Many nervous system disorders, PD, AD, autism, and multiple sclerosis involve a dysbiotic gut microbiome. Collaborative research is making strides in deciphering the composite effects of the human genome, gut metagenome and exposome in neurological disease risk. For example, experiments in mice showed curli, an amyloid encoded by *E. coli*, caused pathologic aggregation of α -synuclein in the gut leading to parkinsonian features (Sampson et al., 2020). Another group showed pathogen infection in the gut induced a parkinsonian phenotype in PINK1 $-/-$ mice (Matheoud et al., 2019). Parkinsonian phenotypes in these animals responded positively to the PD drug, levodopa, and could be ameliorated by vagotomy to prevent the spread of pathology from the gut to the brain. Independently, metagenome-wide association studies (MWAS) in humans revealed vast dysbiosis of the gut microbiome in PD patients, including overabundance of *E. coli* and opportunistic pathogens (Wallen et al., 2022). Moreover, the relative abundance of opportunist pathogens correlated with genetic variations that determine expression levels of α -synuclein (Wallen et al., 2021). These examples of interactions between exogenous environmental factors (pathogens) and endogenous environmental factors (gut microbiome and genetic susceptibility factors) that influence expression of PD phenotypes provide powerful proof of concept for the value of collaborative studies that integrate human and animal models and use exposomics to examine multiple factors. Investigators are already successfully leveraging the potential of exposomics to generate novel insights into neural health and disease – imagine what can be accomplished with the infrastructure and support of a Neural Exposome Initiative.

Based on its collective knowledge of the research landscape, the NINDS Council Working Group on Neural Exposome Top Priorities (NEXT WG) identified the following critical scientific gaps that need to be addressed to significantly advance understanding of how the neural exposome influences nervous system health and disease.

- Which environmental factors increase risk of neurological disease? Which increase neurological resiliency? Are there disease- or disorder-specific exposomes? Are there common ones?
- Many of the same exogenous, behavioral, and endogenous factors are associated with increased risk of diverse neurological diseases. What determines whether an individual exposed to a given environmental factor experiences increased risk of stroke vs. AD vs. epilepsy, etc.? What is the relative contribution of an individual's genetic substrate vs. their exposomic profile in determining neurological outcomes in response to an environmental stressor?
- How do environmental factors interact with each other and with the genome to influence neurological disease risk?
- Are specific life-stages uniquely sensitive to specific environmental factors?
- What is the cumulative risk to brain health of exposure to multiple factors and how do exposures earlier in life influence disease risk later in life?

Guided by these critical scientific gaps and building on the aforementioned examples of momentum and lines of promising research in exposomics, the NEXT WG identified six priority areas to guide NINDS investment in neural exposome research for the next 5 to 10 years.

- 1) **Identify exposomic factors that influence neurological health:** Several critical data gaps emerged that cut across disciplines and the research spectrum (basic, pre-clinical, clinical, implementation science, public health, etc.). These include:
 - *The identification of specific environmental factors that influence brain health and the context (e.g., vulnerable life stages, co-exposures, modifiers) that modifies neurological outcomes associated with these exposures.*
 - *The need to shift towards research that assesses the composite effect of multiple exposures on multiple biological targets in order to develop an understanding of the interactive effects of multiple exposomic factors on brain health and their cumulative effects across the lifespan.*
 - *Researching the neurological effects of climate change.*
 - *Developing approaches for leveraging socio-biological research to promote brain health equity.*
- 2) **Conduct fundamental mechanistic research to determine how these factors influence neurological health:** NINDS should leverage its leadership in fundamental neuroscience research to advance mechanistic research on the neural exposome with the goal of identifying novel mitigation targets. High priority research areas include:
 - *Defining the biological underpinnings of neurological resiliency across the life course and elucidate how environmental factors promote or undermine resilience.*
 - *Developing a mechanistic understanding of how diverse environmental factors promote neurological dysfunction and how they interact with each other and with the genome to promote neurological disease.*
 - *Identifying the mechanism(s) by which diseases in other organ systems (especially cardiovascular, hepatic, pulmonary, and epithelial) influence neurological diseases.*

- 3) **Evaluate exposomic factors in human/population research studies:** Public health, clinical, and interventional research studies are needed to identify neural exposome risk factors in diverse cohorts and to develop and test interventional strategies to mitigate such risks. Action items include:
 - *Identify environmental risk factors that promote neurological diseases in diverse human cohorts to elucidate exposome-genome and exposome-epigenome interactions of relevance to brain health.*
 - *Assess the impact on neurological health of policy/community interventions that modify exposomic factors. For example, identify and leverage “natural” experiments, such as changes in public policy, natural disasters, varying levels of toxicant exposure, etc. that alter exposures for specific populations.*
 - *Develop and test strategies to mitigate exposures, including studies to better understand, assess, and expand neurological resilience.*

- 4) **Create a multi-disciplinary pool of investigators to assess the neural exposome:** The transdisciplinary nature of exposome research requires supporting and building highly skilled multi-disciplinary teams that include clinical neurologists, basic scientists with expertise in studying how environmental stressors influence the nervous system, toxicologists, bioinformaticians, data scientists, etc. Action items include:
 - *Provide support for training and education in multi-disciplinary exposomics to researchers at all career stages.*
 - *Recognize outstanding educators in neural exposomics.*
 - *Incentivize interdisciplinary research teams and team science approaches.*
 - *Support the integration of exposomic expertise into ongoing human cohort studies (i.e., provide supplemental funding for established cohort studies to add exposomic expertise to the project).*
 - *Ensure review panels have the appropriate interdisciplinary expertise to evaluate exposome-focused research, including exposome-wide association studies.*
 - *Communicate the importance of advancing neural exposome research: (1) Update the NINDS’s website and other communication materials, including the mission statement, to convey NINDS’s commitment to understanding the influence of the environment on brain health, e.g., neural exposomics; and (2) Educate the public, policy makers, clinicians, researchers, disease communities, and journalists in the role the environment plays in brain health.*

- 5) **Develop resources and tools to assess the neural exposome:** Exposomic research, by definition, will require interdisciplinary approaches across all biological levels. This will result in the generation and integration of large, complex datasets or “big data.” Currently, the existing research platforms and tools are predominantly in the early development stage. Even those that are relatively well-developed have not been extensively leveraged to investigate neurological diseases. To significantly advance neural exposome research in a meaningful time frame, it will be critical for NINDS to invest in the development of research resources and tools, a goal more likely realized by leveraging ongoing efforts. Action items include:
 - *Biorepositories and data repositories: Understanding early life environment is critical but difficult to reconstruct in adult research studies. Infrastructure that enables the collection and storage of relevant biological samples and the addition of life course exposome data to existing deeply phenotyped biorepositories will be needed to advance neural exposome research in the near to mid-term.*
 - *Infrastructure: (1) Invest in core research to develop the infrastructure needed to provide technical and methodological support to facilitate neural exposome research; and (2)*

Convene and fund a working group to foster data access and to address technical and cultural issues that impede data access and sharing.

- *New model systems: The models widely used currently for neurological research are either not amenable to high throughput screening needed to accelerate the identification of potential environmental risk factors for neurological disease and/or require expression of human transgenes to observe human-relevant disease phenotypes. Two opportunities to address these issues in the near to midterm would be to leverage: (1) new approach methodologies (NAMs), e.g., in silico, in vitro and simple organisms to screen environmental stressors for those that converge on mechanistic pathways underlying the pathogenesis of neurological disease; and (2) non-human animals with spontaneous neurological diseases comparable to human neurological diseases, e.g., companion animals with epilepsy, stroke or age-related dementia, to examine the impact of the shared exposome on disease incidence and progression.*

6) **Foster collaborations and partnerships to accelerate and amplify efforts:** Trans-NIH, interagency, and cross-sector partnerships are needed to fully realize the potential positive impact of neural exposomics on human health.

- *Seek opportunities to expand existing human cohorts to include measures of neurological health and to incentivize ongoing studies of brain health to add exposomic measures.*
- *Seek input and advice from other NIH Institutes and Centers and other agencies that have experience building infrastructure and tools for collecting, managing and analyzing high content data.*
- *Support cross-institute research projects to fund neural exposome research that leverages the experience/mission of the NINDS and partner institute.*
- *Collaborate with NCATS's CTSA program to incentivize clinical research on the role of environmental exposures on progression and expression of neurological disease.*
- *Build partnerships with government agencies that track and/or set standards for environmental quality (e.g., EPA, NOAA, FDA, USGS, NASA satellites).*
- *Support an exposome ontology in part by leveraging existing systems/studies, e.g., engage in interagency/cross-sector efforts to establish a national (global) toxicant registry with exposure (e.g., air pollution, herbicides and pesticides, nanoplastics) mapped to specific geographic units and a national (global) monitoring program).*

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ACRONYM KEY

AD: Alzheimer's disease
ADHD: attention deficit hyperactivity disorder
ALS: amyotrophic lateral sclerosis
CDC: Centers for Disease Control and Prevention
COVID-19: coronavirus disease 2019
CTSAs: Clinical and Translational Science Awards (supported by NCATS)
DOHaD: Developmental Origins of Health and Disease
ELSI: Ethical, Legal and Social Implications
EPA: Environmental Protection Agency
EWAS: exposome-wide association study
FDA: Food and Drug Administration
GWAS: genome-wide association study
GWIS: genome-wide gene-environment interaction studies
HHS: Department of Health and Human Services
HRMS: high-resolution mass spectrometry
IDDRCs: Eunice Kennedy Shriver Intellectual & Developmental Disabilities Research Centers (supported by NICHD)
NAMs: new approach methodologies
NANDS Council: National Advisory Neurological Disorders and Stroke Council
NASA: National Aeronautics and Space Administration
NCATS: National Center for Advancing Translational Sciences/NIH
NEXT: Neural Exposome Top Priorities
NHANES: National Health and Nutrition Examination Survey/CDC
NIA: National Institute on Aging/NIH
NICHD: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development/NIH
NIDCD: National Institute on Deafness and Other Communication Disorders/NIH
NIEHS: National Institute of Environmental Health Sciences/NIH
NIH: National Institutes of Health
NIH BRAIN Initiative®: NIH Brain Research Through Advancing Innovative Neurotechnologies® Initiative
NIMH: National Institute of Mental Health/NIH
NIMHD: National Institute on Minority Health and Health Disparities/NIH
NINDS: National Institute of Neurological Disorders and Stroke/NIH
NIOSH: National Institute for Occupational Safety and Health/CDC
NOAA: National Oceanic and Atmospheric Administration
NSF: National Science Foundation
ONETOX: Office of Neural Exposome and Toxicology
PD: Parkinson's disease
RFI: Request for Information
SchARE: Science Collaborative for Health Disparities and Artificial intelligence bias Reduction (supported by NIMHD)
SNPs: single nucleotide polymorphisms
WG: Working Group
WHO: World Health Organization
USGS: United States Geological Survey

INTRODUCTION

Background

In 2022, the [National Institute of Neurological Disorders and Stroke \(NINDS\)](#) established the [Office of Neural Exposome and Toxicology Research \(ONETOX\)](#) to support a new emphasis on neural exposome research within the NINDS mission (Tamiz et al., 2022). The overall goal of ONETOX is to enhance basic, translational, and clinical research on the effect of the neural exposome on nervous system diseases and disorders by fostering more collaborative research within the neuroscience research community and across the NIH. ONETOX provides information and tools to help break down barriers to research between different scientific disciplines, which can be used to establish productive team science for targeted funding opportunities. Because of the large number and different kinds of exposures within the neural exposome that occur across the lifespan, ONETOX collaborates across the NINDS and with many different Institutes and Centers across the NIH to obtain a full understanding of how these exposomic factors affect brain and nervous system health.

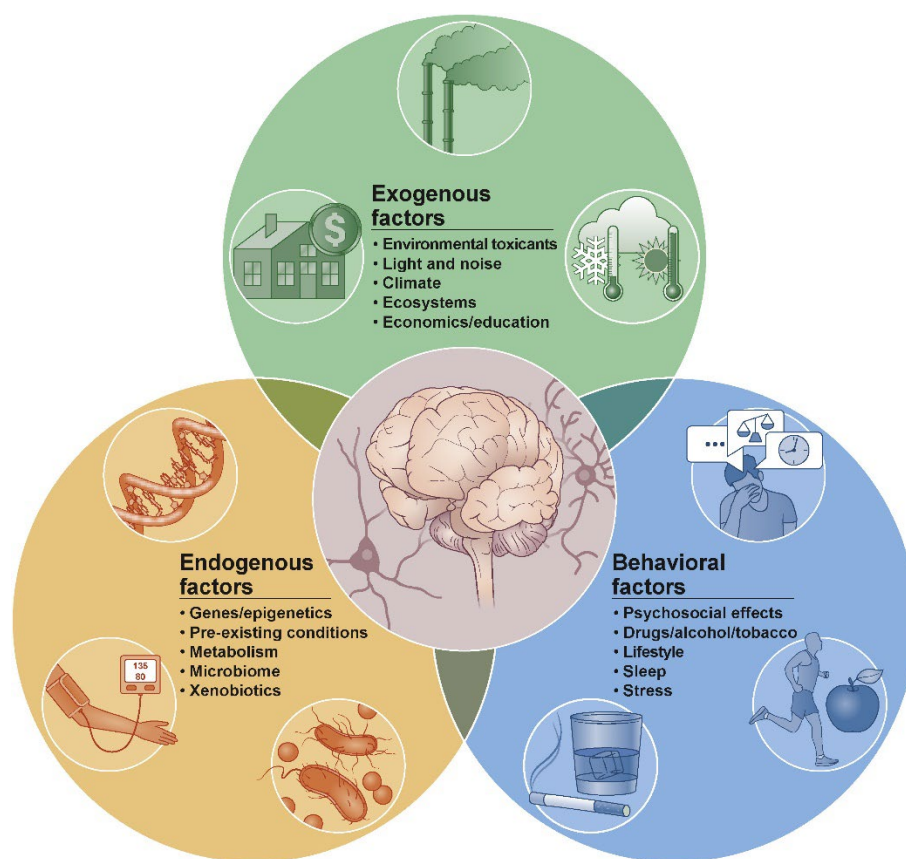


Figure 1: Infographic displaying the three exposomic factors in large circles—Exogenous, Endogenous, and Behavioral—that have an impact on neurological disease and disorders, and overall nervous system health. Exogenous factors include environmental toxicants, light and noise, climate, ecosystems, and economics/education. Endogenous factors include genes/epigenetics, pre-existing conditions, metabolism, microbiome, and xenobiotics. Behavioral factors include psychological effects, drugs/alcohol/tobacco, lifestyle, sleep, and stress (Tamiz et al., 2022).

To guide near- and medium-term efforts to cultivate neural exposome research, NINDS has embarked on a two-phased effort to identify research priorities in this area. Phase one, which began in 2023, has been conducted by a working group of the [National Advisory Neurological Disorders and Stroke \(NANDS\) Council](#) called the [Neural Exposome Top Priorities Working Group \(NEXT WG\)](#), composed of investigators with basic, pre-clinical, and clinical research expertise in neurobiology, diverse neurological conditions, and exposomic research (see [Appendix A](#) for NEXT WG charge and roster). Phase two will be conducted by an internal NINDS working group led by ONETOX and comprised of program staff across all extramural research divisions, who will develop an implementation strategy.

Charge to the NEXT Working Group

The NEXT WG was charged with identifying the most tractable and highest impact research opportunities across the three exposomic categories of exogenous, endogenous, and behavioral factors (Figure 1), including near (1-3 years) and medium-term priorities (3-10 years). The working group was additionally asked to advise on strategies for engaging interdisciplinary teams as well as the tools and resources needed to cultivate neural exposome research.

Process

From November 2023 to July 2024, the NEXT WG met six times as a full group and several more times in subgroups to review and discuss the current state of neural exposomic research, learn about current NIH and other federal exposome research programs, and develop research priorities. The WG advised on and participated in two NINDS-sponsored mini-workshops: [Team Science to Advance Neural Exposome Research](#) on February 29, 2024 (see [Appendix B](#) for workshop summary), and [The Right Tools and Resources for Neural Exposome Research](#) on April 19, 2024 (see [Appendix C](#) for workshop summary).

In addition to input from consultants and workshop speakers ([Appendix D](#)), the workgroup reviewed several analyses and background materials, including results of literature scans, an analysis of NIH's portfolio of research grants related to the neural exposome, and compiled information on efforts (i.e., federal programs, workshops, trainings, funding opportunities) related to the exposome and the neural exposome (see [Appendix E](#)). Public input was gathered at various points in the process, including a 2022 Request for Information (RFI) on Interdisciplinary Research Opportunities that Bridge Neuroscience and Environmental Health Science ([NOT-NS-22-076](#); see [Appendix F](#) for summary), input from mini-workshop participants, and a 2024 RFI on the WG's Draft Priorities ([NOT-NS-24-102](#); see [Appendix G](#) for RFI responses). Additionally, the working group presented their draft priorities at a webinar held on July 15, 2024, which included open discussion time for comments and questions from the public (see [Appendix H](#) for public comments). NINDS advertised the RFIs, the mini-workshops, and the webinar on draft priorities widely through the NIH Guide (for the RFIs), social media, the NINDS homepage, the ONETOX webpage, and email notifications sent to several NIH and NINDS contact lists, which include researchers, trainees, research organizations, nonprofit organizations, and other interested members of the public.

The following section contains the NEXT WG's findings and recommendations on priorities for advancing neural exposomic research at NINDS. NINDS staff coordinated working group meetings, produced background analyses and summaries, and facilitated drafting the final report; however, the priorities and ideas expressed in the body of the report were solely developed by NEXT WG members. This report is being delivered to the NINDS Council on September 4, 2024. After review and acceptance by the full Council, the report will be made available to the public on the NINDS ONETOX webpage.

NEXT WORKING GROUP PRIORITIES AND RATIONALE

The NEXT WG's complete list of priorities and action items are detailed below and organized under six overarching priority areas: 1) Identify environmental factors that influence neurological health, 2) Conduct fundamental mechanistic research to determine how these factors influence neurological health, 3) Evaluate environmental risk factors in human/population research studies, 4) Create a multi-disciplinary pool of investigators to assess the neural exposome, 5) Develop resources and tools to assess the neural exposome, and 6) Foster collaborations and partnerships to accelerate and amplify efforts.

Identify exposomic factors that influence neurological health

Several critical data gaps emerged that cut across disciplines and the research spectrum (basic, pre-clinical, clinical, implementation science, public health, etc.). These include:

- *The identification of specific environmental factors that influence brain health.* As discussed in the Executive Summary, both genetic and non-genetic evidence support a significant role for environmental factors in determining individual risk for neurological disease. However, which of the myriad exogenous, endogenous, and behavioral factors to which humans are exposed confer increased risk for nervous system function, or conversely, increase neurological resiliency, remains largely unknown (Lefevre-Arbogast et al., 2024). While there has been significant research to identify modifiable risk factors for several neurological diseases and disorders with significant public health impact (e.g., stroke, epilepsy, autism, ADHD, PD, and AD), the research coverage for any given disease or disorder has been uneven (e.g., PD research has been heavily weighted towards environmental contaminants; AD research, towards lifestyle factors), and for many others (e.g., pain), there is a significant paucity of information regarding environmental risk factors. Reducing exposure to environmental risk factors is clearly feasible as evidenced by the success of public health efforts to reduce cigarette smoking and policy efforts in the U.S. to reduce air pollution. However, compelling evidence causally linking specific environmental risk factors to neurological disease will be required to develop targeted interventional strategies, to inspire clinicians, public health officials and individuals to significantly change behavior and to motivate policy and law makers to change standards.

Two complementary strategies should be pursued to address this data gap. The first is unbiased screening studies to discover previously unknown environmental risk factors for neurological disease. The second is focused studies to evaluate the risk potential of specific categories of environmental pollutants of increasing public health concern because of their known neuroactive properties and/or widespread human exposure,

including air pollution, water pollution, including water disinfection byproducts, pesticides and persistent organic pollutants, plasticizers and micro/nanoplastics, and neurotropic infectious agents.

- *Understanding the interactive effects of multiple exposomic factors on brain health and their cumulative effects across the lifespan.* To date, most research on environmental risk factors has largely focused on single exposures and/or a limited set of biological effects from exposure to environmental risk factors. However, at any given time, humans are exposed to complex mixtures of exogenous, endogenous, and behavioral risk factors. It is well established that the biological impact of a chemical can differ significantly when it is administered singly vs. as part of a chemical mixture (Bloch et al., 2023). Further, there are multiple examples of chemical toxicity being altered by co-exposure to non-chemical environmental stressors. For example, carriers of the hepatitis B virus who are also exposed to aflatoxin show a 60-fold increase in the incidence of liver cancer (Sylla et al., 1999). In the context of the nervous system, maternal stress has been shown to alter the response to developmental lead exposure (Cory-Slechta et al., 2008; Tamayo et al., 2017).

The biological impact of multiple exposures on the nervous system is understudied. To move towards a truly exposome approach, NINDS should develop strategies for incentivizing and enabling multi-factor research studies that assess the composite effects of multiple factors on broad arrays of biological targets (e.g., microbiome, genome, epigenome, lipidomics, transcriptome, metabolome). The technology currently exists to conduct studies that interrogate multiple environmental risk factors and assess multiple biological responses. One of the earliest examples of an exposome-wide association study (EWAS) used National Health and Nutrition Examination Survey (NHANES) targeted chemical biomarker data to rank order associations linked to type 2 diabetes in a manner similar to genome wide association study (GWAS) analysis of single nucleotide polymorphisms (SNPs) (Patel et al., 2010). Findings included higher risk of type 2 diabetes with higher serum polychlorinated biphenyls (PCB) levels. More recently, polyexposomic risk scores analogous to polygenic risk scores were generated to identify 2-chloroacetophenone, low food access, neighborhood deprivation and reduced access to fitness centers as four exposome measures associated with COVID 19 severity (Hu et al., 2023). Other EWAS studies have used multiple geospatial maps rather than chemical assays, such as a recent study in the Netherlands (Ohanyan et al., 2024). Exposome analysis has been applied to questionnaire data on environment as well (Lloyd et al., 2024).

Like all 'omic analyses, correction for false discovery rates is needed and replication in independent populations is mandatory to validate true positives. Because the exposome varies with time and is life stage specific, replication should factor in the life stage of the discovery sample. There are no examples yet of EWAS studies that have comprehensively measured the chemical, physical, social, and biological exposomes from conception to death, or even from conception to a given life stage. Child health studies hold the most promise for a truly exposome-wide approach since the life stages that would need to be covered would be more feasible than a neurodegeneration study in which the exposome would need to be measured from approximately 1940 to today. The existence of biobanks from large cohorts such as the Framingham that were enrolled decades ago may be able to partly address a life course EWAS for neurodegeneration. For child health, the Environmental influence on Child Health

Outcomes (ECHO) program holds considerable resources and promises for EWAS studies across the chemical, physical, social, and biological exposome domains as such data are being collected along with multiple phenotypes including neurodevelopment and Autism. Although the field is still young and does not yet capture the full exposome, a larger proportion can now be captured than even 5 years ago and the ability to get closer and closer to measuring the exposome is rapidly advancing. We note that genomic research from 20 years ago captured a much smaller portion of the genome than genomics today and that actively funding EWAS research will accelerate innovation in integrating different exposure measures (nontargeted/targeted, social, geospatial, etc.) study design, informatics, statistical analysis, replication and functional testing of candidate environmental factors that are discovered and replicated.

- *Researching the neurological effects of climate change.* Arguably one of the most significant challenges we currently face is climate change, which is having far-reaching effects on social structures and diverse biological systems. Evidence from field and laboratory studies of non-human animals has documented significant behavioral changes in these organisms in response to the unprecedented pace of environmental change caused by climate change. A central research question in current ecology research is what cellular, molecular and circuit-level processes underlie the altered behaviors induced by climate change with the goal of using this information to develop predictive frameworks to describe which neurobiological systems may be resilient or vulnerable to rapidly changing ecosystems (MichaieI and Bernard, 2022).

Increasing evidence demonstrates that climate change is also affecting human health and wellbeing through impacts of extreme weather events on social structures, worsening air quality, changes in the spread of infectious diseases and the attendant increased use of pesticides to combat them, threats to food and water quality and quantity, and adverse effects on mental health. The elevated temperatures such as we are experiencing in the summer of 2024 are having direct effects on human health. For example, there are many incidents of heat-related deaths around the world, including tragedies like the recent pilgrimage to Mecca (Schmidt, 2023). There is also emerging evidence that many neurological disorders are exacerbated by excess heat (Sisodiya, 2024; Sisodiya et al., 2024). Individuals with Dravet syndrome are very temperature-sensitive, as are individuals with multiple sclerosis, but high temperature environments also increase stroke risk and worsen Parkinson's (Sisodiya et al., 2024). Cognitive performance even in healthy young adults can be compromised at high temperatures (Coudeville et al., 2022). In humans, the heat stress response to environmental temperature includes a vast array of effects in the nervous system (Bouchama et al., 2023). Individuals who developed heatstroke showed overexpression of 9000 genes when compared to individuals subjected to the same extreme desert heat who did not develop heatstroke (Bouchama et al., 2023; Mundel, 2023). Thus, although humans have robust physiological mechanisms that aid in maintaining constant brain and body temperature, when those mechanisms are overwhelmed, the human nervous system shows temperature "crashes" akin to those observed in crabs and lobsters (MichaieI and Bernard, 2022).

There are many outstanding questions regarding the direct and indirect effects of climate change on nervous system health at the physiological and behavioral levels. This is a large, complex topic, and exposomic approaches have the potential to begin to unravel some of the issues by enabling integration of multiple biological responses to a complex environmental stressor.

- *Developing approaches for leveraging socio-biological research to promote brain health equity.* Many neurological diseases disproportionately impact racial/ethnic minorities, especially in the United States and the socioeconomically disadvantaged worldwide (Barnes and Bennett, 2014; Mayeda et al., 2016; Maestre et al., 2024). Recent research strongly suggests that the adverse social exposome accounts for at least some of this increased risk. Disadvantaged populations in any society are more likely to reside in areas of adverse social exposome, which often have fewer health-promoting resources, sub-standard housing, poorer public infrastructure, increased life-stressors such as criminal activity, and increased exposure to environmental contaminants, such as air pollution, noise pollution and toxic chemicals (Moore and Diez Roux, 2006; Smith et al., 2017; Kind and Buckingham, 2018). Generally, the association of adverse social exposome with health and disease is distinct from—and sometimes greater than—the association of individual-level socioeconomics or behaviors with health and disease (Ludwig et al., 2011; Ludwig et al., 2012; Kind and Buckingham, 2018).

The social exposome is fundamentally modifiable, so holds great promise as an actionable pathway towards disease mitigation. Furthermore, improved mechanistic understanding of how the adverse social exposome interacts with biology to produce disease holds promise for unlocking sociobiological mechanisms to inform new fundamental discovery and intervention. Multi-domain indices of disadvantage can be used to quantify the social exposome, and the most commonly used of these in the US is the Area Deprivation Index or 'ADI', freely available through the Neighborhood Atlas® (Kind and Buckingham, 2018). The ADI uses 17 US Census and American Community Survey poverty, education, housing and employment indicators to characterize the social exposome. Higher ADI areas have a greater degree of adverse social exposome. Within the US, high ADI neighborhoods are primarily located in urban core, tribal communities and rural areas, and these areas also have higher rates of disease, disability and early death, independent of individual-level factors. Residence in a high ADI neighborhood is strongly associated with poorer brain health. Adverse social exposome as measured by high ADI has been strongly linked to poorer cognitive function, faster cognitive decline and increased clinical dementia diagnosis across multiple studies (Lang et al., 2008; Hunt et al., 2020; Hunt et al., 2021; Tsoy et al., 2021; Dintica et al., 2023; Wong et al., 2023; Peterson et al., 2024). High ADI has also been linked to smaller total brain volume and smaller hippocampal volume on MRI, and greater post-mortem AD neuropathology burden (Hunt et al., 2020; Powell et al., 2020; Powell et al., 2022). Life course studies suggest that exposure to high ADI neighborhoods in childhood may be particularly linked to markers of poorer brain health in mid- and late-life.

Additional detailed life-course study is needed to further clarify the association between adverse social exposome and neurodegenerative diseases to determine the fundamental socio-biological mechanisms that underlie these findings. This is a pathway of inquiry which may potentially unlock new pathways towards therapy and risk mitigation, and better define how the life course exposome contributes to brain health disparities.

Conduct fundamental mechanistic research to determine how these factors influence neurological health

A major focus for the NINDS should be developing the basic biological understanding of how exogenous, endogenous, behavioral, and social factors interact to influence neurological health and disease. Investment in observational research in humans to establish human-relevant exposures coupled with mechanistic research that utilizes human-relevant exposures, including in cellular, animal, and human as well as computational models, is critical to understanding why different individuals exposed to the same environmental stressors (e.g., air pollution) exhibit radically different neurological outcomes. For example, Parkinson's is more common in men than in women and this is reflected in the relative susceptibility to the PD-associated environmental toxicant, rotenone (De Miranda et al., 2019). This sex difference appears to be due to less rotenone-induced neuroinflammation and more efficient proteostasis in females. As another example, ALS and PD are linked to common environmental exposures but exhibit different neurological outcomes – why? In this context, mechanistic research should provide insights into interventional strategies to mitigate adverse neurological outcomes, slow disease progression and/or promote neurological resiliency. For example, it has been found that inhibition of Leucine Rich Repeat Kinase 2 (LRRK2) protects against several PD-associated environmental toxicants (Ilieva et al., 2024). Moreover, similar strategies may be useful to prevent or delay PD (Rocha et al., 2022). High priority research includes:

- Defining the biological underpinnings of neurological resiliency and vulnerability across the life course and elucidating how environmental factors promote or undermine resiliency. Neurological resiliency refers to the ability of humans to adapt to extreme stress without developing neuropsychiatric disorders (Russo et al., 2012). A similar concept is cognitive resiliency, which refers to “the capacity of the brain to maintain cognition and function despite the presence of aging and disease” (Stern et al., 2023). For example, studies to correlate neuropathologic changes with premortem cognitive function have demonstrated that cognitive health can be maintained despite the accumulation of high levels of neuropathology (Zhang et al., 2023). Understanding the biological underpinnings of neurological/cognitive resiliency has significant implications for interventional strategies to preserve neurological function even in the face of neurological disease and/or extreme environmental stress.

There is growing evidence that neurological and cognitive resiliency are modulated by environmental factors. For example, psychosocial risk factors such as depression, loneliness, and chronic distress increase risk of dementia independent of impacts on typical pathologic features (amyloid plaques, tau tangles, Lewy bodies, or infarcts) (Wilson et al., 2007a; Wilson et al., 2007b), indicating the existence of yet-to-be discovered mechanisms that degrade resiliency. Other factors (e.g., education, cognitive stimulation, socialization, sense of purpose, physical activity) function in a protective manner to increase (or maintain) resiliency, enabling the brain to compensate for brain pathologies and maintain cognitive function. There is also evidence indicating that lifestyle factors (e.g., diet, exercise, sleep, and social activities) and exposures to environmental pollution (e.g., air pollution, excessive light or noise, toxic chemicals) can influence neurological resiliency. However, the physiological mechanisms by which environmental factors alter neurological

resilience remain largely unknown. Addressing this data gap will inform therapeutic strategies for mitigating environmentally-induced neurological disease.

- Developing a mechanistic understanding of how diverse environmental factors interact with each other and with the genome to promote neurological disease. As discussed earlier, humans are exposed to complex mixtures of exogenous, endogenous and behavioral risk factors, and it is well established that the biological impact of any given environmental factor can be altered by co-exposure to another environmental factor (Bloch et al., 2023) and by the genetic substrate of the exposed individual (Keil-Stietz and Lein, 2023). While many mechanisms have been proposed to explain how such interactions modify physiological outcomes (e.g., xenobiotic metabolism, epigenetics, convergence of different factors on critical signaling pathways) (Bloch et al., 2023; Keil-Stietz and Lein, 2023), there remains a critical lack of data regarding this question particularly in the context of the nervous system.

NINDS investment in mechanistic research is needed to understand the biological basis for the effects of risk and protective factors on brain health and to determine whether associations are causal in nature (Tamiz et al., 2022). This knowledge would also enable the development of a predictive framework for identifying exposure scenarios that pose risks for specific neurological outcomes and for identifying those individuals at increased risk for developing nervous system dysfunction. Areas that would benefit from research investment include:

- Mechanisms underlying interactive effects between social/behavioral factors with exogenous/endogenous factors;
 - The mechanisms mediating the neurological impacts of complex mixtures of chemicals, including complex environmental mixtures like air and water pollution; and
 - Mechanistic studies of how environmental stressors interact with other 'omic factors, e.g., the genome, epigenome, microbiome, transcriptome, and metabolome, to influence individual risk of neurological disease.
- Identifying the mechanism(s) by which diseases in other organ systems influence neurological diseases. It is increasingly appreciated that there is bidirectional communication between the brain and most if not all organ systems in the human body that influences neurological function and disease, e.g., the gut-brain axis (Castells-Nobau et al., 2024), the lung-brain axis (Park and Lee, 2024), the liver-brain axis (Yang et al., 2024). For example, vascular pathology is widely acknowledged as a contributing factor to the development of AD and related dementias (Gorelick et al., 2011). A mechanistic understanding of how disease in peripheral organs influences the development and/or progression of neurological disease and how impacts of environmental factors on peripheral organs modify crosstalk with the brain to promote neurological disease, or conversely, neurological resiliency would further inform interventional strategies.

Evaluate exposomic factors in human/population research studies

Public health, clinical, and interventional research studies are needed to identify neural exposome risk factors in diverse cohorts and to develop and test interventional strategies to mitigate such risks.

An in depth understanding of neural exposome risk factors across a diverse population is necessary to inform and accelerate the identification of new disease modifying therapies and prevention efforts and support more innovative clinical trials. Environmental factors, including chemical pollutants, dietary factors, and psychosocial stressors, interact with genetic predispositions and other biological factors in complex ways. By studying diverse cohorts, researchers can capture a wide range of exposures and genetic backgrounds, enhancing the generalizability and applicability of findings. Such studies enable the identification of population-specific risk factors and protective factors, which are crucial for understanding the full spectrum of neural exposome impacts. Additionally, investigating diverse cohorts helps address health disparities by identifying vulnerable populations and tailoring interventions to their specific needs (Woods-Burnham et al., 2021).

Developing and testing interventional strategies to mitigate neural exposome risks requires a robust evidence base that only human research can provide. Interventions, whether behavioral, pharmacological, or policy-based, must be grounded in a thorough understanding of the causal pathways linking environmental exposures to neural outcomes. Additionally, exposure and response to neural exposome risk factors vary widely among individuals. Use of diverse cohorts will allow for the examination of these pathways in real-world settings, accounting for the complexity and variability inherent in human populations. Furthermore, testing interventions in diverse cohorts ensures that strategies are effective across different demographic groups, increasing the likelihood of successful implementation and public health impact.

Action items include:

- Identify exposome risk factors in neurological diseases in diverse human cohorts, including understanding exposome-genome and exposome-epigenome interactions. Such work is particularly important for research on the Developmental Origins of Health and Disease (DOHaD). There is currently insufficient mechanistic data available to understand how environmental stressors (endogenous, exogenous, and behavioral) interact with each other or with underlying genetics to determine individual risk. These interactions are crucial because they reveal how environmental exposures influence genetic expression and epigenetic modifications, potentially triggering or exacerbating neurological conditions. For example, evidence continues to suggest a relationship between air pollution and dementia, with gene-environment interactions now being investigated (Peters et al., 2019). Recent work has also shed light on how environmental factors impact nervous system health by interacting with each other and influencing gene expression. For instance, environmental enrichment enhances recovery after spinal cord injury through processes involved in redox signaling (De Virgiliis et al., 2020). Sophisticated research approaches are also needed that can assess how the life course exposome contributes to disparities (over and above individual-level factors) in brain health equity, including how the adverse social exposome influence biology to produce disease. This could be done by engaging with existing comprehensive longitudinal cohorts, such as the NIH “All of Us” study or the Environmental influences on Child Health Outcomes (ECHO) program. By comprehensively studying these interactions, NINDS can identify critical points of intervention and develop targeted prevention and treatment strategies. Understanding these intricate relationships will also contribute to personalized

medicine approaches, ensuring that interventions are tailored to individual genetic and environmental profiles.

- Assess the impact on neurological health of policy/community interventions that modify exposomic factors. For example, identify and leverage “natural” experiments, such as changes in public policy, natural disasters, etc. that alter exposures for specific populations. Assessing the impact of policy and community interventions on neurological health is essential for understanding how large-scale environmental modifications affect brain health outcomes. For instance, studying the neurological effects of reduced air pollution following the implementation of clean air policies can reveal significant insights into how environmental regulation benefits brain health. Similarly, analyzing the cognitive and neurological impacts on communities that experience natural disasters, such as hurricanes, floods, or forest fires, which can result in sudden changes in water and air quality, can provide critical data on the immediate and long-term effects of such exposures (Saulnier et al., 2017; Sandifer and Walker, 2018).
- Develop and test strategies to mitigate exposures, including studies to better understand, assess, and expand resilience. By identifying effective mitigation strategies, such as reducing exposure to pollutants or improving nutrition, researchers can directly address the root causes of neurological diseases and enhance public health. Moreover, studying resilience can reveal protective factors and coping mechanisms that help buffer against environmental stressor, providing valuable insights for designing interventions that strengthen these defenses. Adoption of this comprehensive approach would not only aim to prevent the onset of neurological conditions but also improve overall well-being and quality of life.

Create a multi-disciplinary pool of investigators to assess the neural exposome

The transdisciplinary nature of exposome research requires supporting and building highly skilled multi-disciplinary teams that include clinical neurologists, basic scientists with expertise in studying how environmental stressors influence the nervous system, toxicologists, bioinformaticians, data scientists, etc.

Neural exposome research is inherently complex and involves understanding a multitude of interactions between a wide array of environmental exposures and their impact on health (Sakowski et al., 2024), thus necessitating collaboration from multidisciplinary teams (Zhang et al., 2021). These interactions span multiple scientific domains, necessitating expertise from diverse fields. Each discipline provides critical insights and tools, enabling a comprehensive approach to identifying and analyzing the myriad of factors that contribute to health outcomes. For instance, basic scientists can elucidate the biological mechanisms underlying these interactions, while bioinformaticians and data scientists can manage and analyze vast datasets required to uncover meaningful patterns and associations. Supporting and building these multi-disciplinary teams needs to be a priority for NINDS. By investing in training programs, collaborative grants, and infrastructure that facilitates cross-disciplinary research, NINDS will enhance the capacity of researchers to address the complex challenges inherent in exposome research and accelerate scientific discovery.

There is a critical need for multi-disciplinary exposome center programs across the US. Therefore, a major goal should be for NINDS to leverage existing programs that have been effective in promoting interdisciplinary research, such as the NIH BRAIN Initiative® and the Office of Neural Exposome and Toxicology (ONETOX) that is already located within the NINDS. Additionally, the Center for Innovative Exposomics at Columbia University Irving Medical Center is an established model of a local, national, and international intellectual hub for multiple stakeholders invested in exposomic research.

Action items include:

- *Provide training and education in exposomics.* Investigators with deep expertise in specific neurological disease often lack training in exposomics, which limits their ability to fully understand and study the environmental factors contributing to these conditions. By offering targeted training programs and educational opportunities, NINDS can equip investigators with the skills in exposomics needed to study and analyze environmental interactions and their impacts on the brain. A particular focus could be the development of templates of how to conduct exposomic research in studies of neurological diseases. This investment in education will lead to more innovative research and ultimately better health outcomes.
 - Establish graduate and postdoc training grants on multi-disciplinary exposome research.
 - Develop educational opportunities for investigators at all levels of training (especially early stage) to broaden their skill set and orientation to examine the role of the environment in brain health.
 - Recognize outstanding educators in neural exposomics.
- *Cultivate interdisciplinary research teams and team science research approaches.* By leveraging existing programs as a template, which have proven effective in promoting interdisciplinary collaboration, such as the NIH BRAIN Initiative®, NINDS can create a vibrant research ecosystem that includes experts from various fields. This approach enhances networking, promotes transparency, and integrates broader scientific expertise, leading to the application of new research techniques, tools, and approaches. Recognizing that some of the most impactful collaborators may be outside the traditional neurology and exposome field, NINDS can accelerate groundbreaking research by incorporating diverse perspectives and fostering creative problem-solving.
 - Attract new talent by supporting neural exposome projects that deliberately require different disciplines to work together (e.g., neuroscientists, computational metagenomics experts, geographers). This could include individuals with specific technical expertise who may or may not be in neuroscience, such as computational metagenomics experts for microbiome studies or geographers with geospatial modeling expertise. As above, NINDS could offer training grants to encourage cross-disciplinary work.
 - Support the integration of exposomic expertise into ongoing human cohort studies (i.e., provide supplemental funding for ongoing cohort studies to add exposomic expertise to the project).
 - Ensure review panels have the appropriate interdisciplinary expertise to evaluate exposome-focused research, including exposome-wide association studies.

- *Communicate the importance of advancing neural exposome research.* Public trust is essential for the success of epidemiological and clinical studies, which rely on individuals providing detailed personal information and remaining engaged over time (Slegers et al., 2015). By clearly articulating the potential benefits of exposome research, NINDS can encourage active involvement and collaboration across key stakeholders. Transparent communication can also enhance the understanding and acceptance of research findings, leading to more informed decision-making by policy makers, better care by clinicians, and increased advocacy by disease communities. The commitment of NINDS to a holistic engagement strategy is critical for advancing the field of neural exposome research and achieving meaningful health outcomes.
 - Update the NINDS's website and other communication materials, including the mission statement, to convey NINDS's commitment to fostering neural exposomics.
 - Educate the public, policy makers, clinicians, researchers, disease communities, and journalists in the role the environment plays in brain health. For example, the Human Exposome Assessment Platform (HEAP) project created a set of 14 personas, fictional characters created to represent groups of real people, to define and introduce the concept of the exposome to target audiences (Coombs et al., 2023).

Develop resources and tools to assess the neural exposome

Exposomic research, by definition, requires interdisciplinary approaches across biological, geographical, physical, chemical and social domains. While exposomic research generates “big data” these data are more difficult to integrate than genomics because, unlike genomics, there is no single measurement type (e.g., base pair sequences) that defines exposomics. Types of data vary from large numbers of chemicals derived from bioassays to temporal spatial models using grids and street addresses to quantify weather or air quality, to personal monitors that track location and local environments, to questionnaires about past life experiences. When combined, all these measures capture the underlying complexity and time varying nature of the human exposome. The challenge is not the need for a new technology, but rather methodologies that can bring these measures together in human health studies (Wright et al., 2018; Zhang et al., 2021; Wright, 2022). Fortunately, exposomic data scientists have been able to leverage the substantial data architectural resources created for genomic analysis to develop statistical and machine learning methods to create tools for mining nontargeted assay data, administrative databases (census, health departments, real estate data, etc.), NASA satellite remote sensing data, and even social media platforms. Further, statistical methods for complex, time varying mixtures of environmental factors have been developed that create vectors or indices of combined exposures as predictors of health outcomes (Liu et al., 2018; Gennings et al., 2020; Rosato et al., 2022; Yu et al., 2022).

The primary issue today is not the need to develop tools, it is the siloed nature of existing tools and resources. Many data science tools can be “cross purposed” i.e., statistical methods such as Weighted Quantile Sum (WQS) regression developed for chemical mixture can be applied to “mixtures” of social environment (i.e. racism, stress, religiosity, resilience) (Kachen et al., 2022; DeSerisy et al., 2023). Further, geospatial modeling techniques such as satellite remote sensing used in air pollution monitoring can be applied to models of climate change (e.g., flooding,

pollen, heat waves) (Carrion et al., 2021; Mpakairi et al., 2024; Solaimani et al., 2024; Wang et al., 2024). Nontargeted chemical assay methods are now being combined with targeted methods to create hybrid assays and widely used metabolomics databases, such as METLIN (Tautenhahn et al., 2012; Dennis et al., 2017; Marasco Junior et al., 2022), no longer are limited to endogenous metabolites but contain over 500,000 environmental chemicals, and a growing number of laboratories now use "metabolomics" platforms to profile PFAS, phthalates, acrylates, flame retardants, and many other environmental chemicals. *Tabulation and collation of existing methods into a centralized resource is what is needed* so that advances do not continue to reside in silos. Such an effort towards integration of large, complex exposomic data sets would identify key exposomic factors that drive risk for neurological disease. Because these tools were developed in the environmental, chemical, geographical and social sciences, they have not been extensively leveraged to investigate neurological diseases in studies that would benefit from adding exposomic measures. To significantly advance neural exposome research in a meaningful time frame, it will be critical for NINDS to invest in programs that scale up the use of these tools as well as collaborate in the integration of exposomic research resources and methods to make them more easily accessible to non-exposomic researchers. Training neuroscientists in exposomic methods is a key step in achieving these goals long term. Promoting collaboration is a more immediately achievable goal that can be realized by leveraging ongoing efforts (i.e., extant research programs in Parkinson's, ALS, autism) and incentivizing cross-disciplinary collaborations by neuroscientists, clinical researchers and epidemiologists with exposomic scientists.

The following action items would accelerate neural exposomic research:

- *Leverage Biorepositories and Data Repositories*: Collection of biosamples is expensive and time consuming. Using extant repositories could discover important exposomic factors for neurological disease in a shorter and less costly manner. Understanding early life environment is critical but difficult to reconstruct in adult research studies. Using extant biosamples collected decades earlier can rapidly inform research on the Developmental Origins of Health and Disease (DOHaD) as it pertains to neurologic disease. A potential solution is to leverage studies and biorepositories with biospecimens from childhood with longitudinal follow-up to adult life. Examples include the National Perinatal Collaborative and the Framingham Heart Study, which can potentially reconstruct environments *from 50+ years ago* and link early life environment to existing adult neurologic disease, especially common disorders such as dementia. With regards to rarer diseases, such as ALS, new methods using teeth to reconstruct past exposure in infancy and late fetal life can be leveraged by incentivizing brain banks to collect teeth in addition to brain post mortem (Figueroa-Romero et al., 2020). Likewise, hair contains exposome data that has been linked to future onset of autism (Austin et al., 2022). Hair is simple to collect and represents exposure data that goes back in time for several months. It can be leveraged to reconstruct the environment that existed near the time of death, which may provide important clues for palliative care of neurologic diseases.
 - Prospectively, patients recruited to studies should be asked to provide consent to a diverse range of biosamples, e.g., blood, urine, cerebrospinal fluid, from which to quantify environmental exposures, e.g., metals, pesticides and assess biological consequences beyond genomics. Infrastructure (inventories, sample collection method and age at collection details, etc.) that

enables the addition of life course exposome data to existing deeply phenotyped biorepositories will be needed to provide research resources in the near to midterm. The NIEHS Human Health Exposure Analysis Resources (HHEAR) program has substantial expertise in leveraging extant biomarkers for exposomic research and could provide guidance on resources needed.

- Support efforts to develop, validate, and harmonize exposome assays, metrics, and measurement approaches across the life course (e.g., early-life and occupational exposures). Nontargeted assays are run with a variety of different mass spectrometry techniques and pipelines. At present there is no equivalent of proficiency testing for nontargeted assays that has become standard practice for targeted exposure assays. Partnering with NIEHS on efforts to standardize nontargeted assays for interlaboratory comparison is needed.
- Employ assays and exposure models to measure current and prior exposure to toxicants. There are many well-developed tools to measure environmental exposure, including:
 - Wearables, personal monitors, m-health apps, Ecological Momentary Assessment (Zhang et al., 2020).
 - Satellite remote sensing of climate, air pollution, green space, walkability, and built environment as well as models of social environment that employ spatial modeling techniques (e.g., area deprivation index) derived from multiple data sources (e.g., Census tract, crime statistics, American Community Survey, Esri).
 - *In vivo* brain imaging modalities for measuring biomarkers of exposure and effect in the brain. MRI uses nuclear magnetic resonance, a method used for metabolomics, albeit with lower resolution than mass spectrometry. Further, neurotoxic metals, such as manganese, have unique MRI signals. More research into leveraging the distribution of chemical data from MRI may provide insights into environmental exposures.
 - Biomarkers that can be measured in accessible body fluids and tissues, e.g., brain-derived extracellular vesicles in blood and urine, epigenetic assays of placenta, and chemicals in shed baby teeth or adult teeth collected postmortem.
 - The use of photos can be a source of social environment or nutrition data. Research on mining social media platforms for content using natural language processing or other Machine Learning methods can provide novel data on the social environment.
- Define biosamples and measures that should be uniformly collected and applied across the exposome field to enable aligned, harmonized study and assessment. At a minimum, blood (plasma or serum) and urine are needed at multiple life stages. Ideally, deciduous and adult teeth, hair and nails should be collected as well. Stool and saliva can be used both for microbiome analysis but also for analysis of environmental chemicals.
- Define resources/approaches to collect and analyze life-course geospatial data to better delineate the role of place in neurologic disease. There are many methods existing but few efforts to compare them. Air pollution is an excellent example of multiple teams creating models with little comparison of their relative performance.

- Develop templates or guidelines to assist investigators not trained in exposomics with integrating relatively low-cost add-on collection of biospecimens (what specimens to collect, how to collect/store samples) and how to find exposome geospatial variables (ambient temperature, air quality, occupation of patient) into the design of clinical and other population-based studies. *At a minimum a home address history is needed for all participants in research studies. Occupation, work address and school address would also be collected routinely.* It is difficult to over-emphasize how valuable an address history is for an exposome study.
- There is an urgent need for integrative pathway analyses for assessing the impact of multiple environmental perturbations on an individual's nervous system – harness machine learning and artificial intelligence (AI).
- **Infrastructure:** Invest in core research to develop the infrastructure needed to provide technical and methodological support to facilitate neural exposome research.
 - Convene and support a working group to foster data access and to address technical and cultural issues that impede data access and sharing.
 - Develop guidelines and invest in tools for sample collection, storage, and analysis, including harmonization of protocols for laboratory and data analyses.
 - Develop guidelines and invest in the development of geospatial modeling including additional uses for remote sensing, drones, spatial mapping of soil, water and air quality, and social determinants of health.
 - Develop guidelines for neural exposome research that address ethical, legal, and social implications (ELSI) related to personal protections, privacy, community trust in science, etc. This should be done soon as exposomics is being applied more and more and ethical issues will likely come to the fore.
 - Patient portal and data management platforms: Develop secure data management platforms that enable linking of a variety of data, including (but not limited to) demographic, questionnaire, geographic, exposome phenotyping data, and/or electronic medical records, for each participant in real-time for a variety life course focused research.
 - Registries: Robust, diverse clinical registries are needed to generate a large pool of patients from which to recruit for prospective neural exposome studies. Ensure the inclusion of diverse populations to allow for varied genetic backgrounds and sampling of assorted biomes.
- **Develop new model systems:** Even extant data should be re-evaluated to ensure that it represents the human exposome. Experiments should leverage what is known about relative dose, age at exposure and combinations of exposures that exist in real life human populations.
 - Leverage recent advances in new approach methodologies (*in silico*, *in vitro*, simple model organisms) to screen environmental stressors to identify those that converge on mechanistic pathways underlying the pathogenesis of neurological disease. See for example the National Academy of Sciences, Engineering, and Medicine's Workshop on New Approach Methods (NAMs) for Human Health Risk Assessment (NASEM, 2021).
 - Leverage spontaneous neurological diseases in non-human models that are comparable to human neurological diseases, e.g., companion animals with epilepsy, stroke or age-related dementia, to examine the impact of the shared exposome on disease incidence and progression. Since companion animals

share the environment with humans, and there are many studies demonstrating that the same exposomic approaches used in humans can be readily adapted to dogs and cats, e.g., wearable monitors (Matheson et al., 2024) they offer the unique opportunity to examine the impact of the shared exposome on neurological disease incidence and progression. This may be particularly advantageous for neurodegenerative diseases given the shorter lifespan of dogs and cats relative to humans.

Foster collaborations and partnerships to accelerate and amplify efforts

Thirty-five years ago, the genomics landscape was small. Outside of Mendelian genetic diseases, there was relatively little genetics research conducted for complex diseases with multiple causes. This is because there were no tools to discover genetic risk factors in the 1980s and early 1990s. The Human Genome Project changed all of that and today all 27 NIH Institutes and Centers fund genomics research, even NIEHS. This transformation came about because of partnerships that were trans-NIH, interagency, and cross-sector including the private sectors. These partnerships were critical for the success of the Human Genome Project. A similar partnering effort directed at exposomics is needed to fully realize the potential positive impact of neural exposomics on human health. Like the Human Genome Project, a Human Exposome Map Project can best be achieved through public-private partnerships and collaboration among all the ICs as well as other federal agencies, such as EPA, USGS, NASA and NOAA among others. Such a project would be a catalyst for new data science tools in exposure analysis, functional testing of results for mechanisms of action, data visualization, search engines and harmonization methods. Further, if we are to apply exposomics broadly, we will need a common ontology and publicly available tools and databases that researchers can use to apply, analyze and understand exposomic data. Collaboration across disciplines, government agencies and the private sector (Google, Metabolon, etc.) is key.

Action items for NINDS include:

- Seek opportunities to expand existing studies to integrate exposomic research. This includes expanding existing human cohorts to include measures of neurological health, e.g., add brain health to NIH's "All of Us" or leverage NIEHS's Human Health Exposure Analysis Resources (HHEAR). In addition, existing studies of human brain health should be incentivized to add exposomic measures (assays, exposure models, social environment, etc.).
- Seek input and advice from other NIH institutes and other agencies that have experience building infrastructure and tools for collecting, managing and analyzing high content multidimensional data. Particularly pertinent examples are the NIH BRAIN Initiative® (analyze/adopt their approach for focusing initially on developing tools and teams and once these in place, shift focus to basic research), NSF (deep expertise in data science), and the National Toxicology Program (structured to integrate/harmonize toxicologic research expertise across the NIEHS, NIOSH, EPA, FDA and has expertise in high-throughput screening approaches).
- Offer supplements to awards administered by other NIH ICs that focus on neurologic health (e.g., IDDRCs [NICHD], NIDCD, NIMH, NIA) to integrate measures of the exposome.
 - Support cross-institute research projects to fund neural exposome research that leverages the experience/mission of the NINDS and partner institute.

- Collaborate with NCATS's CTSA program to incentivize clinical research on the role of environmental exposures on progression and expression of neurological disease.
- Promote Small Business Innovation Research (SBIR) grants to develop novel exposome methodologies (social, chemical, physical and biological).
- Engage in interagency/cross-sector efforts to establish a national (global) toxicant registry with exposure (e.g., air pollution, herbicides and pesticides, nanoplastics) mapped to specific geographic units and a national (global) monitoring program.
 - Support an exposome ontology in part by leveraging existing systems/studies like ChemID, databases for air pollution that use satellites measuring haziness [AOD], EPA pollutant monitoring systems and database of toxic waste sites, NIMHD's SchARe program (social determinants of health data), NIEHS Human Health Exposure Analysis Resources (HHEAR) Program, the Collaborative Perinatal Study, and the CDC National Health and Nutrition Examination Study (NHANES).
 - Review the Gene Ontology program (GeneOntology, 2024) to learn from their experience.
 - Build partnerships with government agencies that track and/or set standards for environmental quality (e.g., EPA, NOAA, FDA, USGS, NASA satellites). Leverage their ongoing work that maps environment and link to address history of study participants.

NANDS COUNCIL FEEDBACK AND ACCEPTANCE OF THE NEXT WORKING GROUP'S RECOMMENDED PRIORITIES

The NEXT WG presented their recommended priorities to the NANDS Council on September 4, 2024. This section summarizes the subsequent discussion and feedback from the Council members.

The Council reinforced many of the WG's findings, agreeing that the scope of exposomics is far-reaching but affords the potential to substantially expand our ability to understand, treat and even prevent neurological disorders. That is, understanding how exposures contribute to disease has the potential to enable the design of therapeutics to address the disease while also working to reduce exposures in the first place. It will also require a broadening of approach. Studying one exposure at a time will not be sufficient. Rather, humans experience multiple exposures simultaneously and consequently, to understand the impact on disease, must be studied together. For example, one could imagine characterizing the risk factors for dementia for a particular geography. Doing so will demand investigators work with members of the community to identify the multitude of stressors and exposures to which individuals with or at risk for dementia have been exposed.

One theme of discussion was that there are many active or ongoing efforts that NINDS could leverage to expand exposomic research capabilities. While much needs to be done to cultivate exposomic research going forward, the scientific community is well-positioned to make progress in neural exposome research right now. There are several databases and patient cohort studies that already contain key exposomic data. Furthermore, there are existing technologies such as

artificial intelligence and machine learning to integrate clinical neurological history with exposure history.

There was also consensus that there are opportunities to leverage existing databases and cohort studies. NINDS and NIH lead several initiatives that make biosamples available to the neuroscience research community. The [NIH NeuroBioBank](#) is an NIH-supported resource that hosts human post-mortem brain tissue and related biospecimens as well as genome-wide genotyping and whole genome sequence (WGS) data. While NINDS does not have the capacity to support data and biosample repositories for the hundreds of diseases in its mission space, it can for some. One example is the [BioSEND repository](#), which contains biosamples as well as genomics data from more than 10,000 individuals across a range of neurological and neuropsychiatric diseases and disorders, including PD, AD/ADRDs, Huntington's disease, and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, among others. Other large publicly-funded cohorts include the [NIH All of Us Research Program](#) and the [UK Biobank](#), which contain comprehensive health data of hundreds of thousands diverse individuals. These datasets could be better harmonized and linked with other datasets of environmental factors. Another opportunity is to expand other NIH efforts that are not yet addressing neurological disease. For example, there may be subject cohorts for non-neural diseases that have collected detailed exposure histories. These could be expanded to add neurological data, potentially through supplemental funding to ongoing grants. Finally, one idea discussed was to explore natural variation world-wide in exposure patterns to study neurological disease incidence patterns and potential association hotspots.

The NINDS Council reinforced that NINDS is a leader in mechanistic neuroscience research and is well-positioned to pursue expanding studies using *in vivo* models, *in vitro* models, and NAMs, again through supplements as well as other award mechanisms, to draw out causal relationships between exposures and disease pathology. This is reasonably tractable in the context of single, high-exposure events. But even lower-dose chronic exposures may be addressable through new technologies. High resolution geospatial mapping will be essential to assess environmental risk factors, such as pesticide exposure or air pollution, across space and time. These exposures can be precisely mapped to geographical locations for cross-reference with other data, for example census data. Another opportunity to characterize lifetime exposure is afforded by teeth, which act as an exposure integrator. It is now possible to assess exposure history by profiling the proteomic distribution across different layers of tooth enamel. Similarly, exposure to lipophilic compounds may be assessed by analyzing fatty tissue (e.g., adipocytes). Finally, the Council agreed that NINDS should incorporate more measures of socioeconomic exposures and address how exposures influence epigenetic changes and characterize such exposures within specific time windows across the lifespan.

Overall, the NINDS Council expressed enthusiasm for the WG's recommended priorities, underscoring the potential for exposomics to reveal causes and contributors to neurological disease, facilitate disease prevention and mitigation strategies, and how this may ultimately reduce healthcare burden and costs. The NINDS Council voted unanimously to accept the report.

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APPENDIX A: National Advisory Neurological Disorders and Stroke (NANDS) Council Working group on Neural Exposome Top Priorities (NEXT) Charge and Roster

Charge to the NANDS Council Working Group

The Neural Exposome Top Priorities Working Group (NEXT WG) is charged with recommending research priorities to guide NINDS's neural exposome programmatic efforts for the next 5-10 years. The NEXT WG should identify the most tractable and highest impact research opportunities across the three exposomic categories (exogenous, endogenous, and behavioral factors), including near (1-3 years) and medium-term priorities (3-10 years). The WG will also provide recommendations on best practices for engaging neuroscientists and promoting neural exposome research in the NINDS mission space and what tools and resources are needed (or could be leveraged) to cultivate neural exposome research.

The NEXT WG will prepare a final report to present to the NANDS Council in open session on September 4, 2024.

Working Group Composition

The Working Group includes two members of the NANDS Council and is composed of investigators with basic, pre-clinical, and clinical research expertise in neurobiology, diverse neurological conditions, and exposomic research. For example, Working Group members include field-leading scientists who study the influence on neurologic function and disease of environmental toxins, climate, social and built environments, behavioral factors (e.g., psychosocial stress and lifestyle factors), and 'omics-related mechanisms (i.e., microbiome, metabolome, epigenome), among other topics. WG members bring additional expertise in exposome methodologies and technological applications, interdisciplinary science and collaboration, and a broad array of neurological disease mechanisms.

Roster

[Pam Lein, PhD](#) (Chair)

University of California, Davis

[Gina Poe, PhD](#) (Member of NANDS Council)

University of California, Los Angeles (UCLA)

[Ekemini Riley, PhD](#) (Member of NANDS Council)

Aligning Science Across Parkinson's (ASAP)

[Deborah Cory-Slechta, PhD](#)

University of Rochester Medical Center

[Ray Dorsey, MD](#)

University of Rochester Medical Center

Richard L. Doty, PhD

University of Pennsylvania

Eva Feldman, MD, PhD

Michigan Medicine

Tim Greenamyre, MD, PhD

University of Pittsburgh

Amy J. H. Kind, MD, PhD

University of Wisconsin

Eve Marder, PhD

Brandeis University

Gary Miller, PhD

Columbia University

Haydeh Payami, PhD

University of Alabama at Birmingham

Robert O. Wright, MD, MPH

Icahn School of Medicine at Mount Sinai

APPENDIX B. Team Science to Advance Neural Exposome Research Workshop Summary

National Institute of Neurological Disorders and Stroke Neural Exposome Top Priorities Working Group (NEXT WG)

MINI WORKSHOP ON TEAM SCIENCE TO ADVANCE EXPOSOME RESEARCH

February 29, 2024

Revised on October 15, 2024



This meeting summary was prepared by Rose Li and Associates, Inc., under contract to the National Institute of Neurological Disorders and Stroke (NINDS). The views expressed in this document reflect both individual and collective opinions of the meeting participants and not necessarily those of NINDS. Contributions to this summary by the following individuals are gratefully acknowledged: Bethany Stokes, Maya Sapiurka, Nancy Tuvesson.

Acronym List

ADRD	Alzheimer’s disease and related dementias
AOP	Adverse Outcome Pathways
BRAIN	Brain Research Through Advancing Innovative Neurotechnologies®
BTS	Big Team Science
CIAO	Modeling the Pathogenesis of COVID-19 Using AOP Framework
COMBINE	Collaborative Opportunities for Multidisciplinary, Bold, and Innovative Neuroscience
CRedit	Contributor Roles Taxonomy
NANDS	National Advisory Neurological Disorders and Stroke
NEXT WG	Neural Exposome Top Priorities Working Group
NIEHS	National Institute of Environmental Health Sciences
NINDS	National Institute of Neurological Disorders and Stroke
ONETOX	Office of Neural Exposome and Toxicology
PEDP	Plan for Enhancing Diverse Perspectives
PI	principal investigator
SCI	spinal cord injury
UCLA	University of California, Los Angeles

Meeting Summary

Opening Remarks

Overview of the NANS Council NEXT WG

Pam Lein, PhD, University of California, Davis, NEXT WG Chair

The National Advisory Neurological Disorders and Stroke (NANDS) Council Working Group for Neural Exposome Top Priorities (NEXT) was established by the National Institute of Neurological Disorders and Stroke (NINDS) in order to recommend neural exposome research priorities and better integrate exposomic research into NINDS's mission. The NEXT WG was charged with identifying the most tractable and highest impact research opportunities across the three exposomic categories (exogenous, endogenous, and behavioral factors), including near (1-3 years) and medium-term priorities (3-10 years).

Following the NEXT WG's recommendations, an internal NINDS working group will develop an implementation plan. This process is being informed by two mini-workshops; today's meeting and a second on "The Right Tools and Resources for Exposome Research" to be held on April 19, 2024, from 1:00 to 4:30 pm ET. Following the two mini-workshops, the NEXT WG will hold an open meeting in summer 2024, to share and hear feedback on a draft set of research priorities, before reporting the final recommendations to the NANDS Council on September 4, 2024.

Overview of NINDS Exposome Research

David Jett, PhD, NINDS, Office of Neural Exposome and Toxicology (ONETOX)

NINDS aims to advance fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease for all people. The exposome was defined in 2005 as all environmental exposures that affect the genome, but this definition has since expanded to include all non-heritable traits that affect gene expression across the lifespan. Understanding the exposome can help researchers develop holistic and personalized approaches to disease prevention. NINDS established ONETOX with the goal to advance the understanding of multiple causes of neurological illness in order to enable the development of more effective interventions. Initial focus areas of ONETOX include exogenous (e.g., chemical exposures, climate change, health inequities), endogenous (e.g., gene-environment interactions, microbiome, metabolome), and behavioral factors (e.g., psychosocial effects, substance abuse, lifestyle) that can impact neurological conditions.

Exposome studies are becoming more prominent in the literature. In one study, researchers found that providing an environmental-enrichment cage to rats enabled increased regeneration of the dorsal root ganglion following nerve transection. Another study identified various exposome factors that impact cardiovascular disease burden. Research underscoring the importance of the exposome has grown in recent years, with many workshops focused on the topic also calling for more collaborations between neuroscience and environmental researchers. In addition, NINDS and the National Institute of Environmental Health Sciences (NIEHS) released a Request for Information on interdisciplinary research opportunities to bridge neuroscience and environmental science and received many responses calling for more analytical tools and resources, as well as methods to reduce barriers to collaboration. There is a trans-NIH Environmental Neuroscience Working Group, co-chaired by NINDS and NIEHS to help coordinate neural exposome efforts and identify opportunities for IC collaborations.

Opportunities in exposome research include using new human, geospatial, and biomarker data from studies, biobanks, and wearables; implementing innovative tools, databases, training, and technology; and employing team science approaches that have been successfully implemented in various NIH and federal programs. NINDS has begun to support studies that have expanded their scope to investigate the exposome's contribution to Alzheimer's disease (AD) and related dementias (ADRD) and plans to begin similar studies on other diseases in their mission space, such as Parkinson's disease and spinal cord injury (SCI). Several other NINDS funding opportunities focused on neural exposome topics have been published, including some targeted at specific topics (e.g., child health outcomes, climate change, toxic exposures in ADRD).

Facilitators and Barriers of Team Science

Better Together: Team Science Theory to Practice

Cory Kelly, PhD, NINDS

Team science is an emerging field that originated at NIH in the 1990s as the National Cancer Institute worked to employ transdisciplinary approaches to cancer research, treatment, and care. Dr. Michelle Bennet's Collaboration and Team Science Field Guide in 2010

(<https://ombudsman.nih.gov/collaborationTS>) served as the first set of guidelines for team science and set the foundation for future collaborations. Team science research has grown over the past few decades, but ongoing efforts are needed to further encourage diverse perspectives, disciplinary insights, integration insights, and community based participatory research. Qualities contributing to team science include clearly organizing and structuring team composition and roles, intentionally including all members - particularly trainees - and addressing early in the process that conflict is plausible. Barriers include integration of new and unfamiliar teams and processes, discipline-based differences, project management, and the need for more incentive and reward systems. Team science also necessitates the integration of diverse perspectives in order to address individual biases and facilitate community-based participatory research.

Successful team science programs must define a purposeful project methodology, a process for overcoming challenges, and resource allocation strategies. Teams can also use a logic model to monitor progress, inputs, outputs, and outcomes. Stages of team development include forming (i.e., when the members first convene), storming (i.e., when teams discover teamwork can be difficult), norming (i.e., when group begins to function as a team), performing (i.e., when the team begins functioning as a high-performance team), and adjourning (i.e., when the team's task is complete). In the forming stage, team members must define organizational structure, team composition, and roles, whereas the norming stage focuses more on harmonizing outcomes, overcoming cross-institutional barriers, and planning for the project. Teams in the performing stage must adjudicate credit assignments, including authorship of publications and other rewards and performance recognition. Overall, team science is an opportunity to facilitate more interdisciplinary research that enhances understanding of human disease.

Supporting Team Science: Creating the New NINDS COMBINE Program

Karen David, PhD, NINDS and BRAIN Initiative

The Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative 2025 Report underscored the importance of team science by emphasizing how many innovative findings will result

from projects that bridge fields, which is a key principle of team science. NINDS developed the Strategic Team Research Mechanism (STReM) Workgroup to identify how other NIH institutes and centers are supporting team science through funding opportunities. To produce more team science opportunities at NINDS, the RM1 Collaborative Opportunities for Multidisciplinary, Bold, and Innovative Neuroscience (COMBINE) program was established. Unlike P01 or R01 grant mechanisms, the COMBINE program requires funded studies to have an integrative component. Projects supported by the COMBINE program must be bold, impactful, and challenging, with a simple and focused single goal that can only be achieved through interdisciplinary science. COMBINE program applications must have 3-6 principal investigators (PIs) with distinct expertise and perspectives, a management plan, clear milestones, and a commitment to diversity, equity, and inclusion (e.g., Plan for Enhancing Diverse Perspectives [PEDP]). Applicants should also describe their resources for coordination, the shared vision of the partnership, mechanisms of credit assignment for team members, and approaches to coordination and communication. NINDS has selected the first six COMBINE projects, which include studies on a variety of neuroscience topics.

Question & Answer Session

Can you expand on what you mean by data management?

Drs. David and Cory confirmed that data management refers to how teams may each bring different types of data and datasets to a team science project that will need to be harmonized, combined, or integrated in some way. Outlining how data will be shared and combined across contributing laboratories should be included in a data management plan.

How did you review COMBINE submissions?

Dr. David emphasized the importance of using a special emphasis panel for reviewing applications. This panel should be trained in or have experience with team science. Dr. Cory added that the COMBINE program selected study section members with expertise in team science.

Are the currently funded COMBINE program projects across institutions? Do they require sub-contracts?

Dr. Cory noted that the COMBINE program does not require teams to be at different institutions; teams can include groups from different institutions or groups at the same institution but different departments. The main requirement is that there be 3-6 PIs, each of whom are equally involved in the project.

Teams Science Presentations

An Affair to Remember: How Adverse Outcome Pathways Catalyzed Interdisciplinary Collaboration During Pandemic Times

Laure-Alix Clerbaux, Joint Research Centre, European Commission

Over the past few decades, the toxicology field has begun a paradigm shift in chemical risk assessments from observing endpoints in a whole organism to investigating a comprehensive understanding of mechanisms. This shift led to several new frameworks for chemical risks assessments, including the Adverse Outcome Pathways (AOPs)—which outlines a sequence of events that leads to an adverse outcome (e.g., disease presentation at the population level). The AOP framework can be used as a collaborative tool to synthesize current knowledge and gaps. Teams can also use the AOP-Wiki tool to collaborate and propose updates to a project's AOP framework.

Early in the pandemic, the Modeling the Pathogenesis of COVID-19 Using AOP Framework (CIAO) was established with global participation from more than 75 scientists with different disciplinary expertise, including regulation, pharmacology, systems biology, and food safety. CIAO resulted in the development of several AOP frameworks, including one focused on the mechanistic involvement of olfactory neuroepithelium in short-term anosmia. Using AOP frameworks, CIAO investigators discovered that SARS-COV-2 can damage the olfactory epithelium, leading to anosmia; however, anosmia is short term because of the neuroepithelium's regenerative abilities. This project also evaluated modulating factors related to anosmia, including gut dysbiosis and inflammation. Understanding these modulating factors is critical because different factors may lead to similar outcomes, which can help identify shared mechanisms and possible treatments. Through the efforts of CIAO, researchers highlighted the need for unified terminology to enhance interdisciplinary communication among team members. They also emphasized the importance of defining a common goal and terms for collaboration, and instating strong but agile central organization to ensure the project's success. CIAO is a successful example of the use of the AOP framework in bridging disciplines to facilitate discovery.

Question & Answer Session

Were participants in CIAO paid?

Dr. Clerbaux confirmed that CIAO participation was voluntary and not paid.

Fails and (Some) Successes in Team Neuroscience

Jae Lee, PhD, MS, University of Miami School of Medicine

No cure or therapeutics exist for spinal cord injuries (SCIs). Dr. Lee's laboratory seeks to improve understanding of post-SCI wound healing process, which involve the development of fibrotic scars surrounded by neural cells, glial astrocytes, and microglia. Wound healing involves several pathways, each with their own critical contribution to the overall response to SCI; thus, team science collaborations are imperative to studying wound healing response. Team science fosters creativity and innovation by exposing team members to disciplines they do not regularly encounter, fostering the development of innovative ideas, and bring people together with diverse expertise to solve big picture problems.

Dr. Lee outlined several challenges that can arise when forming collaborations without key team science principles in place, such as mismatched expectations (ill-defined roles), poor communication (lack of regular meetings), lack of significant history working together, lack of staff and trainee engagement, and a drift in scientific interest. With these challenges in mind, he initiated his next collaborative project with team science principles integrated into each step. He identified the need for additional expertise, particularly in cell growth and drug delivery, to understand the wound healing process. He engaged with two long-time colleagues: Dr. Nagi Ayad of Georgetown University, who specializes in cancer biology, and Dr. KiBum Lee of Rutgers University, who specializes in drug delivery systems and chemical biology. Together, this team developed a grant application that sought to use their combined expertise and shared goals to facilitate cell type-specific treatment for SCI. Dr. Lee attributes the successes of this partnership to a shared vision and defined roles and expectations to keep the team engaged and avoid drift in interest. The project had a detailed statement of work with quarterly milestones modified as needed by the team members. Effective communication was achieved by adopting regular and ad hoc meetings, as well as by using meeting platforms such as Slack for informal communication, and by

capturing meeting minutes. Working in a team takes about 20% more effort than working alone, thus that extra time needs to be taken into consideration when planning the project.

In summary, team science enhances creativity and innovation by exposing members to diverse disciplines, fostering innovative ideas, and uniting individuals with varied expertise to tackle complex problems. Challenges in team science include mismatched expectations, poor communication, and drifting scientific interests. To integrate team science principles into successful projects leveraging team members combined skills and goals require: 1) a shared vision and defined roles, 2) effective communication through regular and ad hoc meetings, use of platforms like Slack, and 3) meticulous project planning with adaptable milestones. Team science requires more effort than solo work.

Question & Answer Session

Were team meetings conducted in person or virtually?

Dr. Lee confirmed that biweekly meetings were conducted virtually, primarily via Zoom, but annual meetings were and will continue to be conducted in person.

Recognizing and Rewarding Contributions to Large-Scale Collaborations

Heidi Baumgartner, PhD, Stanford University and ManyBabies

ManyBabies is a collaborative program established in 2015 to improve reproducibility, replicability, and generalizability, and best practices in developmental psychology research. The program has since grown to include 647 contributors from 265 institutions across 50 countries and 26 collaborative projects. ManyBabies has integrated Big Team Science (BTS) principles, including the use of collaborative study design and consensus-based best practices. Benefits to using BTS approaches also include increased diversity of team members and patient populations, large sample sizes and highly powered studies that enable investigation of sources of variability, the use of reproducible analytical pipelines, and open sharing of data, code, and study materials. A major challenge to using BTS approaches is the need for handling disagreements, which can be overcome by defining consensus, using a neutral arbiter, and allowing for some dissenting opinions.

Individuals may be incentivized to participate in BTS projects because it enables network building, it expands the scope of projects an individual pursues, and it can increase a researcher's number of publications and thus, lead to career advancement. Authorship requirements for specific journals can vary significantly. Indeed, they can differ on fundamental issues such as whether an author needs to have been involved in writing the manuscript and if all authors are accountable for all the work in the paper or just the part that is relevant to them. Dr. Baumgartner and her team have developed several publications on how BTS collaborations can introduce challenges to the current varying authorship criteria (e.g., defining and documenting authorship-worthy contributions for large groups). Ambiguity regarding authorship disproportionately harms underrepresented and early career researchers; thus, large teams must institute a frequently updated collaboration agreement with clearly defined roles and requirements. These kinds of agreements can benefit small teams as well as big teams. Documenting contributions can be improved by use of the Contributor Roles Taxonomy (CRediT), a system that defines 14 categories of tasks (e.g., primary writing, editing, data curation). ManyBabies requires team members to report their individual contributions through an online survey in accordance with the CRediT categories. These survey reports are processed and transparently presented on the ManyBabies website to track program progress and work. Tenzing is a web tool that can output formatted summaries of

author contributions appropriate for a wide variety of journals. In the future, would be desirable to build a searchable database of the network of author contributions in the vein of IMDB.

The major takeaways are: 1) transparency is key, 2) make decisions on how you will handle disagreement as early as possible, 3) Document decisions in a living Collaboration Agreement that is shared with all contributors. Lastly, the principles of BTS also apply to “small team science” collaborations.

Question & Answer Session

How is authorship order determined for publications with large author lists? Can CRediT be used for that?

Dr. Baumgartner noted that each ManyBabies project has a core leadership team that determines the first and last authorship positions. Researchers that led WGs or other subteams related to their projects are typically listed immediately following the first author; the remaining contributors will be listed in alphabetical (or some other predetermined) order after the subteam leaders. In addition, the CRediT report explains what each individual contributed to the project.

Would contributors know their place in the authorship order before they agree to join the team?

Dr. Baumgartner confirmed that the ManyBabies' Collaboration Agreement will outline a potential order so that contributors have a relative expectation of recognition. However, the authorship order likely changes throughout manuscript development and knowing the inevitability of these changes and having the Collaboration Agreement that details the method for determining authorship order is important for managing staff expectations.

Neural Exposomics Is a Team Science

L. Michelle Bennett, PhD, Roger Schwarz & Associates, Inc., and LMBennett Consulting

Both team science and the field of neural exposomics require (1) integration of frameworks from basic to clinical research and various disciplines, (2) incorporation of team science principles into collaborations, (3) productive conflict, (4) collaboration to solve complex scientific challenges, and (5) a community of practitioners interested in furthering the field of exposomics. Dr. Bennett emphasized the importance of building purposeful collaborations by establishing team values, designing teams to maximize effectiveness and productivity, and recognizing that some of the most impactful collaborators may not be in the exposome field. She stressed that NINDS can support team science collaborations by guiding funded researchers to collaborate effectively, involving experts in team science on review panels, and fostering interdisciplinary engagement in exposomics.

Dr. Bennett emphasized the significance of involving diverse team members in exposomics research, as it necessitates a blend of various methods, perspectives, disciplines, vocabularies, expertise, and experiences. Effective management of these differences can spark creativity and innovation, while poor management can pose challenges. Utilizing team science in exposomics is vital for fostering innovation and discovery. Collaborations should include clear agreements outlining expectations for participation and recognition to ensure fruitful partnerships.

Panel Discussion

Moderator: Gina Poe, PhD, University of California, Los Angeles (UCLA)

Panelists: Beate Ritz, MD, PhD, UCLA, and Rosalind Wright, MD, MPH, Icahn School of Medicine at Mount Sinai

Why is team science important in neural exposome research?

Drs. Ritz and Wright emphasized how team science can accelerate innovative research in ways that would not be possible otherwise. Many projects evolve as discoveries are made; the subsequent research directions may require additional knowledge and expertise, which enables team members to gain broader scientific expertise and engage new or prior collaborators to help explore a pathway forward.

Dr. Ritz underscored how much more enjoyable research projects are when they employ team science principles and engage new contributors. Team science also helps integrate researchers across the full biomedical research spectrum, as she put it “from cells to populations,” meaning from investigators that study animal and cellular models to those that engage with patient communities and broad populations. Exposure to new disciplines and ideas can foster discoveries, the application of new research techniques/tools/approaches, and new directions for understanding human health, as well as enable the sharing of perspectives that some researchers may not hear in their usual fields of study.

Dr. Wright emphasized the need for other areas of science. Engagement in team science leads to development of richer scientific expertise for individual scientists and trainees. She noted that besides genetics, environmental exposures were not enough and found the need for social factors, and so on. The need for transdisciplinary team science was essential. She noted the transdisciplinary research at the NIH’s National Center for Accelerating Translational Science (NCATS) has been very successful, especially with respect to training the next generation of biomedical scientists to conduct team science. Team science lends itself to tackling big scientific questions.

What are the main challenges to team science?

Dr. Ritz noted that identifying the right team members is often the biggest challenge for team science. Many investigators may rely on colleagues they are familiar with rather than those that have the correct expertise and experience for a given project. It helps to have strong leadership (e.g., Department Chairs) who believe in the value of team science. Another significant challenge is the difficulty associated with initiating and maintaining engagement outside of one’s discipline; Dr. Ritz encouraged investigators to communicate in ways that are more easily translatable to other fields, such as not overusing field-specific jargon and acronyms.

Dr. Wright noted that meetings like this one are where researchers of disparate disciplines meet each other and find potential collaborators. She emphasized the importance of bringing junior researchers into team science conversations early. In large groups, junior members may have more difficulty being recognized or involved, compared to more senior leaders. Leadership and senior team members must actively involve junior members and ensure that their contributions are rewarded. Dr. Ritz added that annual meetings in which all supporting junior and senior researchers can present on their contributions to a program, or across programs, can help better engage researchers within interdisciplinary teams and show how each member contributes to the field’s efforts. Dr. Poe reinforced the need to involve junior

scientists, noting that team science provides an excellent opportunity to engage researchers with diverse perspectives and backgrounds.

Dr. Ritz discussed how important it is that research institutions embrace team science and find new ways to give credit to researchers for their work, which requires a cultural change in the way that individual scientific contributions are recognized in academic settings and in scientific journals. NIH's use of multi-PI grants has made a positive impact in this respect, but more progress is needed. One example where academic leadership and ranking efforts may overlook members of a team are on multi-PI grants that, for administrative reasons, include a sole Contact PI. In some cases, the Contact PI may be the only investigator (and institution) that gets credited for the grant when the reality is that all of the investigators/institutions on the grant contribute equally. Dr. Poe noted that NIH could have a positive influence on how scientific journals approach co-authorship recognition, for example by encouraging journals to include more information on the specific contribution of each author listed on an article.

The field needs a short article on best practices in team science and future directions. If we were to write such an article, what should we include?

Panelists emphasized that many best practices have been shared during today's meeting, including those provided by the COMBINE program and each speaker. Each of these practices should be included in such an article. Best practices in data tools and computational methods, including for example the application of Artificial Intelligence (AI) approaches, should also be highlighted.

Open Discussion

Dr. Poe invited all meeting participants to participate in an open Q&A session.

How do we engage specific but highly different disciplines (e.g., environmental science, neuroscience)?

In order to engage and encourage the development of complex transdisciplinary teams, Dr. Lein recommended providing funding for facilitating team science and involving leaders with proven success in conducting team science to help promote such funding opportunities and guide new teams. She emphasized that this is a time when team science is experiencing a swell of attention in publications and research studies, and many institutions are embracing the concept that team science is going to be essential in solving grand challenges in science. She added that trans-institute funding opportunities may encourage teams across NIH institutes, as well as mitigate the burden of supporting an expensive field of research (i.e., exposomics). Dr. Baumgartner noted the team science field needs funding opportunities to develop centralized infrastructure that could support multiple projects, instead of needing to re-develop infrastructure after each new project is formed and funded.

Dr. David noted that the BRAIN Initiative has opted to be prescriptive in funding opportunities that multiple disciplines must collaborate on a proposed project, and to identify specific targeted disciplines. Dr. Poe emphasized the challenge of reviewing multi-disciplinary grant applications, and that there's a clear need to find and integrate team science experts into grant review panels; Dr. David agreed, noting the BRAIN Initiative's use of special emphasis panels to ensure that reviewers have sufficient expertise to evaluate proposals.

Dr. Wright highlighted the NIH Environmental Influences on Child Health Outcomes (ECHO) program as a good model of successful trans-disciplinary exposome research where neuroscientists are working alongside environmental researchers and populations scientists.

Dr. Lein noted that the interdisciplinary nature of exposomic science suggests that trans-NIH and interagency partnerships (e.g., with the National Science Foundation) are critical. Dr. Jett agreed and said that IC collaborations are increasing and there's growing appreciation across NIH institutes that these kinds of partnerships are worthwhile endeavors.

Who should be involved in exposomics research? How can we engage nontraditional partners outside of the academic space (e.g., the public)?

Dr. Ritz emphasized the importance of engaging the community, patient advocates, and patients themselves in research teams and noted that NIEHS has mandated community engagement in its funding opportunities, particularly in Center grants. This requires true dialogue between scientists and community.

Dr. Wright noted that exposomics is a field that affects all people and that showing communities how this topic affects them can help improve engagement and involvement in exposome research. Dr. Amy Kind added that the exposomics field may eventually need to study communities as interventions themselves because studies have observed that communities can become resilient to specific health outcomes.

Appendix: Workshop on Team Science to Advance Neural Exposome Research Agenda

February 29, 2024

1:00 pm	Welcome, Opening Remarks, and Housekeeping Meeting Moderator: Neel Druv, PhD, NINDS Overview of the NANDS Council NEXT WG Pamela Lein, PhD, University of California, Davis Overview of NINDS Exposome Research David Jett, PhD, NINDS
1:30 pm	Facilitators and Barriers to Team Science Better Together: Team Science Theory to Practice Cory Kelly, MS, NINDS Supporting Team Science: Creating the New NINDS COMBINE Program Karen David, PhD, NINDS
1:55 pm	Break
2:00 pm	Team Science Presentations An Affair to Remember: How Adverse Outcome Pathways Catalyzed Interdisciplinary Collaboration During Pandemic Times Laure-Alix Clerbaux, PhD, Joint Research Centre, European Commission Fails and (Some) Successes in Team Neuroscience Jae Lee, PhD, MS, University of Miami School of Medicine Recognizing and Rewarding Contributions to Large-Scale Collaborations Heidi Baumgartner, PhD, Stanford University
3:00 pm	Break
3:05 pm	Team Science Presentations, Continued Neural Exposomics is a Team Science Michelle Bennett, PhD, LMBennett Consulting and Roger Schwarz & Associates, Inc.
3:25 pm	Panel Discussion Moderator: Gina Poe, PhD, University of California, Los Angeles (UCLA) Panel: Beate Ritz, MD, PhD, UCLA, and Rosalind Wright, MD, MPH, Icahn School of Medicine at Mount Sinai

APPENDIX C. The Right Tools and Resources for Neural Exposome Research Workshop Summary

National Institute of Neurological Disorders and Stroke Neural Exposome Top Priorities Working Group (NEXT WG)

MINI WORKSHOP ON THE RIGHT TOOLS AND RESOURCES FOR NEURAL EXPOSOME RESEARCH

April 19, 2024

Revised on October 15, 2024



This meeting summary was prepared by Rose Li and Associates, Inc., under contract to the National Institute of Neurological Disorders and Stroke (NINDS). The views expressed in this document reflect both individual and collective opinions of the meeting participants and not necessarily those of NINDS. Contributions to this summary by the following individuals are gratefully acknowledged: Gina Castelvechi, Maya Sapiurka, Nancy Tuveeson.

Acronym List

AD	Alzheimer's disease
AI	Artificial intelligence
ALS	Amyotrophic lateral sclerosis
BioSEND	BioSpecimen Exchange for Neurological Disorders
BRAIN	Brain Research Through Advancing Innovative Neurotechnologies®
CDE	Common data element
CDMRP	Congressionally Directed Medical Research Program
CTD	Comparative Toxicogenomics Database
dbGaP	Database of Genotypes and Phenotypes
DNA	Deoxyribonucleic acid
EPA	Environmental Protection Agency
FAIR	Findable, accessible, interoperable, and reusable
FITBIR	Federal Interagency Traumatic Brain Injury Research
FTD	Frontotemporal dementia
HEAL	Helping to End Addiction Long-Term®
HHEAR	Human Health Exposure Analysis Resource
HMRP	Health Monitoring Research Program
HOLC	Home Owner's Loan Corporation
ICs	Institutes and Centers
iNDI	Induced Pluripotent Stem Cell Neurodegenerative Disease Initiative
iPSC	Induced pluripotent stem cell
ME/CFS	Myalgic encephalomyelitis/chronic fatigue syndrome
ML	Machine learning
MOMRP	Military Operational Medicine Research Program
NANDS	National Advisory Neurological Disorders and Stroke
NEXT WG	Neural Exposome Top Priorities Working Group
NHCDR	National Institute of Neurological Disorders and Stroke Human Cell and Data Repository
NIEHS	National Institute of Environmental Health Sciences
NHP	Non-human primate
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
ONETOX	Office of Neural Exposome and Toxicology
PD	Parkinson's disease
RDT&E	Research, development, test, and evaluation
RNA	Ribonucleic acid
TERP	Toxic Exposures Research Program
TBI	Traumatic brain injury
TRL	Technology readiness level

Meeting Summary

Opening Remarks

Overview of the NANS Council NEXT WG

Neel Dhruv, PhD, NINDS

The National Advisory Neurological Disorders and Stroke (NANDS) Council was established by the National Institute of Neurological Disorders and Stroke (NINDS) to identify research priorities in the neural exposome relevant to NINDS' mission. The NANDS Council is developing a strategic plan for the neural exposome that aims to (1) define exposome research within the NINDS mission, (2) identify and prioritize areas of neural exposome research, (3) identify best practices for communicating with and engaging neuroscientists in exposome research, (4) identify best practices for fostering more collaboration between NINDS and other National Institutes of Health (NIH) institutes and centers (ICs), and (5) identify tools and resources that advance neural exposome research. To support strategic plan development, NANDS formed two strategic planning workgroups— (1) the Neural Exposome Top Priorities Working Group (NEXT WG) to identify research priorities and (2) the Internal NINDS Strategic Plan Development Committee to develop an implementation plan. [Today's meeting on tools and resources](#) will inform strategic plan development as will the [previous workshop on team science](#). After NEXT WG's final meeting in July 2024 to discuss findings from both workshops, NEXT WG will report its recommendations to NANDS on September 4, 2024. The Internal NINDS Strategic Plan Development Committee will then draft an implementation plan for NANDS to review by February 12, 2025.

Overview of NINDS Exposome Research

David Jett, PhD, Office of Neural Exposome and Toxicology (ONETOX), NINDS

Although genetics has provided insight into the etiologies of inherited disease, most health risk factors cannot be explained by genetics alone. In 2005, Dr. Christopher Wild coined the term “exposome” to encompass all environmental exposures across the lifespan. Characterization of the exposome can unlock a more holistic approach to disease prevention and personalized interventions.

The neural exposome consists of nonheritable factors that contribute to the complex etiologies of neurological disorders. These factors can be classified as (1) exogenous (e.g., environmental toxicants, climate, economics, education, light, noise); (2) endogenous (e.g., genetics, epigenetics, gene–environment interactions, microbiome, preexisting conditions); or (3) behavioral (e.g., psychosocial effects, lifestyle, drug and alcohol use, sleep, stress). NINDS established ONETOX to advance understanding of how these noninheritable factors contribute to neurological illness and to enable development of better interventions.

Neural Exposome Funding Opportunities Supported by ONETOX

- Clinical Relevance of the Linkage Between Environmental Toxicant Exposures and Alzheimer's Disease and Related Dementias ([PAR-22-048](#))
- Environmental Influences on Child Health Outcomes Program (multiple notices)
- Climate Change and Health ([NOT-ES-22-006](#))
- Research on Biopsychosocial Factors of Social Connectedness and Isolation on Health, Wellbeing, Illness, and Recovery ([PAR-21-349](#) and [PAR-21-350](#))

- Role of Environmental Stress in the health Inequities of Alzheimer’s Disease-Related Dementias ([RFA-NS-24-024](#))
- Impact of the Microbiome Gut-Brain Axis on Alzheimer’s Disease and Alzheimer’s Disease Related Dementias ([PAR-22-211](#))
- NINDS Mission Relevant Pain Research ([NOT-NS-22-050](#))
- Administrative Supplements to Support Research Infrastructure on Exposome Studies in AD/ADRD ([NOT-AG-22-022](#))
- Center for Exposome Research Coordination to Accelerate Precision Environmental Health ([RFA-ES-23-010](#))

NINDS Biospecimen/Cell/Tissue and Data Resources

Rebecca Price, PhD, NINDS

Christine Swanson-Fischer, PhD, NINDS

Drs. Rebecca Price and Christine Swanson-Fischer provided an overview of data and biosample resources relevant to neural exposome studies.

NINDS Human Cell and Data Repository

The NINDS Human Cell and Data Repository (NHCDR) is a biobank that stores and distributes patient- and healthy control–derived fibroblasts and induced pluripotent stem cells (iPSCs). Cell lines are distributed globally with clinical and genetic information available via an [online catalog](#). Patient-derived cell lines contain genetic mutations related to neurological diseases, including AD, amyotrophic lateral sclerosis (ALS), ataxia-telangiectasia, dystonia, frontotemporal degeneration, Huntington’s disease, Lewy body dementia, mild cognitive impairment, myotonic dystrophy, Parkinson’s disease (PD), spinal muscular atrophy, and spinal-bulbar muscular atrophy. NHCDR has engineered some of these patient-derived cell lines to remove the neurological disease–related mutations. In addition to maintaining and growing its biobank, NHCDR aids research groups collecting peripheral blood mononuclear cells or skin biopsies for subsequent derivation of iPSCs.

BioSpecimen Exchange for Neurological Disorders

The BioSpecimen Exchange for Neurological Disorders ([BioSEND](#)) is a biofluid sample repository that can also bank and distribute patient-derived cell lines. Currently available sample types include whole blood, plasma, serum, peripheral blood mononuclear cells, DNA, RNA, cerebrospinal fluid, saliva, and urine from individuals with neurological diseases such as PD, Lewy body dementia, Huntington’s disease, traumatic brain injury (TBI), spinocerebellar ataxia, frontotemporal dementia (FTD), and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). In addition to distribution services, BioSEND biobanks samples from clinical studies. BioSEND charges customers for initial sample kits and shipping fees but covers storage and distribution costs of these samples.

Because biosamples are not renewable, BioSEND’s Biospecimen Resource Access Committee reviews applications for biosample research. The Committee accepts applications on a rolling basis and convenes six times per year. After approval, BioSEND ships blinded samples to researchers and unblinds them after the research group completes its planned analyses. BioSEND then requires the research group to share these data with the repository.

NINDS Human Genetics Resource Center

The [NINDS Human Genetics Resource Center](#) houses DNA samples and lymphoblastoid cell lines along with their associated genomic data stored in the database of Genotypes and Phenotypes (dbGaP). Available DNA samples and cell lines were collected from individuals with cerebrovascular disease, dystonia, epilepsy, motor neuron disease, Parkinsonism, and Tourette Syndrome. NINDS-funded investigators collect these samples and cells and submit them to the Center with clinical data in common data elements ([CDEs](#)).

NIH NeuroBioBank

The [NIH NeuroBioBank](#) aims to democratize, modernize, and standardize human brain tissue banking and accessibility. The NeuroBioBank requires applications to access brain and spinal cord tissues, which are donated by individuals with disorders within the mission space of the NINDS, National Institute of Mental Health, the National Institute on Aging.

NINDS-Supported Data Resources

NINDS-supported data resources are listed below.

- The Federal Interagency Traumatic Brain Injury Research (FITBIR) [Informatics System](#) contains data from TBI studies.
- The [Map](#) (ME/CFS) repository contains data from CFS studies.
- The [PD Biomarkers Program](#) repository contains data from PD studies.
- The [Accelerating Medicines Partnership® Parkinson's Disease](#) repository contains data from PD studies.
- The Helping to End Addiction Long-Term® ([HEAL](#)) Initiative repository contains data related to drug addiction, particularly opioid addiction.
- The [Biomarkers for Vascular Contributions to Cognitive Impairment and Dementia](#) data repository contains data related to vascular dementia.
- The Advancing Research and Treatment in Frontotemporal Lobar Degeneration (ARTFL)-Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS) Longitudinal Frontotemporal Lobar Degeneration ([ALLFTD](#)) consortium repository contains data on FTD.
- The Enhancing Neuro Imaging Genetics Through Meta Analysis ([ENIGMA](#)) repository contains data on brain structure and function in neurological diseases.
- NINDS makes its [clinical trial data](#) available on its website.
- The Data Management and Coordinating Center of the Rare Diseases Clinical Research Network [hosts data](#) from various rare disease studies, including an ALS natural history study.
- The [Precision Medicine Platform](#) offers access to diverse datasets, including results from stroke clinical studies, and enables collaborative analysis of these datasets in a cloud-based environment.
- The Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative [Cell Census Network](#) is a comprehensive reference with data from diverse cell types from human, mouse, and nonhuman primate (NHP) brains.
- The [BRAIN Initiative Cell Atlas Network](#) is a comprehensive atlas of human brain data.
- The [Neuroscience Multi-Omic Data Archive](#) is a data repository that stores and disseminates omics data from BRAIN Initiative projects.

NIH Resources Not Directly Funded by NINDS

Other NIH resources not directly funded by NINDS with data and biosamples relevant for exposomics include the following:

- The National Centralized Repository for Alzheimer's Disease and Related Dementias ([NCRAD](#)), which is a National Institute of Aging–funded biorepository of samples collected from individuals with AD/ADRD.
- The National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site ([NIAGADS](#)), which is a data repository containing genetic information from individuals with AD/ADRD.
- The Exposomics for Characterization of Environmental Drivers of AD ([EXCEL AD](#)), which is a community dashboard aimed at standardizing exposome science.
- The [AD Knowledge Portal](#), which contains data from various AD studies.
- The NIH Common Fund [Metabolomics Workbench](#), which contains various tools for analyzing metabolomic data.
- The NIH Common Fund [Data Ecosystem](#), which coordinates access and analysis of a variety of Common Fund datasets.
- The National Institute of Diabetes and Digestive and Kidney Diseases [Central Repository](#), which houses both data and biosamples that may be of interest to researchers using metabolomic and gut microbiome data for their exposome studies.
- The iPSC Neurodegenerative Disease Initiative ([INDI](#)), which is an intramural program developing and disseminating isogenic iPSC lines engineered to contain mutations implicated in neurodegenerative diseases.

Discussion

Is there a single place where people can find a full list of NIH data and biosample resources?

Dr. Price noted that information on NINDS repositories is available on the [NINDS website](#). Presentations from NINDS staff that outline these resources at different conferences and workshops are also a useful strategy for educating researchers on available resources. Dr. Swanson-Fischer advised that NINDS grant applicants contact their program officers regarding relevant resources. NINDS has formed a working group to implement a new data management and sharing plan and has also created materials to assist in identifying useful repositories for deposition of data, samples, and cell lines, including privacy linkages using global unique identifiers.

Which repository has blood or cerebrospinal fluid from sports players, military personnel, and people exposed to pesticides who are not diagnosed with a particular disease?

Dr. Price explained that FITBIR contains data from military personnel focused on TBI and will eventually host data from TBI and chronic traumatic encephalopathy studies in individuals who play competitive sports. The National Institute of Environmental Health Sciences ([NIEHS](#)) may have repositories relevant to pesticide exposures. Dr. Swanson-Fischer explained that other non-NINDS data and samples, such as those housed at Boston University and those collected under the [Million Veterans Program](#), may also provide useful military personnel data.

Do existing PD biosamples have associated data on pesticide exposures?

Dr. Swanson-Fischer noted that PD biosamples available through NINDS resources have some associated CDEs related to lifestyle exposures.

The NIEHS Exposure Science and the Exposome Program: Creating Tools and Resources for Exposomics

Yuxia Cui, PhD, NIEHS

The National Institute of Environmental Health Sciences (NIEHS) hosted the “Accelerating Precision Environmental Health: Demonstrating the Value of the Exposome” workshop series in 2022 to discuss methodologies and approaches that lend themselves to the field of exposomics. Discussants determined that animal and *in vitro* models could be used to prioritize exposures and data measures that will eventually scale to large populations. Successful exposomic research also requires data sharing and harmonization across both basic biology and epidemiological studies to support cross-study analyses. In addition, artificial intelligence (AI)/machine learning (ML) enables integration of diverse exposomic data and subsequent analyses that can inform public health policies and help address health disparities.

Human Health Exposure Analysis Resource

The NIEHS Exposure Science and Exposome Program oversees the Human Health Exposure Analysis Resource (HHEAR) to provide an infrastructure for expanding exposure analyses to advance understanding of the impact of environmental exposures on human health throughout the life course. The HHEAR Exposure Assessment Laboratory Network generates exposure data, and these data generation activities are managed by the HHEAR Coordinating Center.

NIEHS develops tools and technologies (e.g., geospatial sensing, remote sensing, computational modeling, wearable sensors, biomarkers, biosensors) for use in comprehensive and systematic exposure assessments to achieve more accurate evaluations of exposure-disease associations and understand how novel gene–environment interactions contribute to disease etiology. HHEAR provides researchers with state-of-the-art exposure analysis, expert consultation, and data science support. The HHEAR [Data Center Web Portal](#) contains publicly available data from 32 studies, including 8 studies related to neurologic or cognitive development indications.

Comparative Toxicogenomics Database

[The Comparative Toxicogenomics Database](#) (CTD) is a free public resource with manually curated toxicology literature from PubMed. The main goal of CTD is to understand how exposure to environmental chemicals affects human health. There are more than two million chemical-gene interactions created. By using findable, accessible, interoperable, and reusable (FAIR)-controlled vocabularies and a relational database with nine data types—anatomy, chemicals, pathways, diseases, exposures, organisms, genes, gene ontology and phenotypes, and references—CTD enables computational predictive network modeling and empowers users to generate testable hypotheses.

Trans-NIH Initiative for Exposome Research Coordination

In support of the Trans-NIH Initiative for Exposome Research Coordination, NIH will fund a Center for Exposome Research Coordination from 2024 to 2029 ([RFA-ES-23-010](#)). This funding will support development of a commonly agreed upon research framework for exposomics as well as a resource of exposome technologies and methodologies. Funding recipients will build a global exposome research community and foster national and international collaborations, particularly with the European Union–funded International Human Exposome Network.

EPA's Computational Exposure Science Tools and Resources on a Path to the Neural Exposome

Timothy J. Buckley, PhD, Center for Computational Toxicology and Exposure, EPA

The Environmental Protection Agency ([EPA](#)) focuses on exposure science using risk assessments to support management decisions. Exposure science and exposomic research have some overlapping characteristics—both accommodate assessment of nonchemical stressors and transcend individual chemical approaches. Dr. Buckley described two examples of EPA activities relevant to exposome research.

Interaction of Tree Canopy Exposure with Depressive Symptoms

EPA collaborated with the NIEHS Sister Study to assess the effects of tree canopy presence on depressive symptoms in women. EPA analyzed a subsample within Homeowner's Loan Corporation (HOLC) cities from a national prospective cohort of women aged 35-74, controlling for covariates such as individual-level demographics and medication for depression. EPA researchers found that tree cover was associated with reduced odds of having depressive symptoms, with the strongest association observed in redlined neighborhoods ([Link to the manuscript](#)).

Computational Chemical Exposure Science

Computational chemical exposure science relies on the integration of chemical curation, a data development framework, and modeling to provide a comprehensive understanding of chemical exposure. For chemical curation, EPA's [CompTox Chemistry Dashboard](#) is the most comprehensive accounting of anthropogenic chemical landscape with more than 1.2 million chemicals. These data include chemical identifications, structures, and metadata that undergo rigorous quality assurance procedures. These data enable linkages and the integration of chemicals with hazard and risk and are available for computational, regulatory, and public use. In the future, EPA will continue to expand the CompTox Chemistry Dashboard to include polymers, mixtures, and ambiguously defined substances as well as continuing to add data from non-targeted analyses.

Dr. Buckley presented on data development activities such as advanced informatics, data mining, ML, and data collection, organization, integration, and access. Exposure databases developed using similar frameworks include [ChemExpoDB](#), [Chemical and Products Database](#), [Molecular Modeling Database](#), and [Concentration versus Time Database](#). Future computational data development research at EPA will focus on data from different occupational settings.

Eighty Pounds of Light Stuff: Building a Rational Exposure Assessment Toolkit

Valerie Adams, PhD, Defense Centers for Public Health-Aberdeen

The Toxicology Directorate at the Defense Centers for Public Health-Aberdeen supports the Strategic Environmental Research and Development Program and Environmental Security Technology Certification Program in their support of research, development, test, and evaluation (RDT&E) activities for sustainable alternatives, conservation, and mitigation and clean-up military technology development. RDT&E phases occur early in the technology acquisition process. The Toxicology Directorate uses a phased approach to evaluate toxicity with levels of effort scaled to budget activity and technology

readiness levels (TRLs).^{*} In addition to outlining Toxicology Directorate activities, Dr. Adams provided information on military research programs with research related to the exposome.

Toxic Exposures Research Program (TERP)

The [Congressionally Directed Medical Research Program](#) (CDMRP) funds high-risk, high-reward projects that address critical research gaps to benefit not only military service members, but also military retirees, service members' families, and civilians. The Toxic Exposures Research Program, one of 36 programs within CDMRP, supports research on various military relevant exposures, including Gulf War illness, burn pits, airborne hazards, neurotoxin exposures, prophylactic medications, pesticides, organophosphates, and toxic industrial chemicals, materials, metals, and minerals. Respondents to a Request for Information identified poorly defined exposures, difficulty monitoring exposures, lack of access to samples, and overall lack of data as critical challenges to the Program's research. To address these challenges, respondents recommended promotion of collaborative research, funding for a diverse array of exposures, funding for foundational research projects, funding for exposure assessment research, and facilitation of data access and data analytics tools.

Military Operational Medicine Research Program

The [Military Operational Medicine Research Program](#) (MOMRP) contains some research objectives relevant to exposome research. The main objective for MOMRP's Environmental Toxic Exposures Research is to prevent illness and optimize performance when operating in toxic environments. Relevant technical objectives include (1) identify and develop assays for verified biomarkers of exposures to military-relevant chemicals, materials, or mixtures (TRL1-3); (2) identify, improve, and demonstrate technology for rapid screening of toxic chemicals and materials (TRL3-5); and (3) provide novel health or toxicological data to fill data gaps for military-relevant chemicals, materials, and environmental hazards to advise on exposure limits and guidelines. To address the first technical objective, MOMRP is supporting the identification of biomarkers of exposure from per-and-polyfluoroalkyl substances (PFAS), sulfur dioxide, and jet fuel exhaust. To address the second technical objective, MOMRP supports assessments of silicone-based sensors, development of rapid screens of neurotoxic agents, establishment of a zebrafish toolbox for rapid toxicity screening, and assessment of pulmonary disease using *ex vivo* and *in vitro* systems. MOMRP will address the third technical objective with future funding opportunities.

Development of Health Monitoring Research Programs

Dr. Adams outlined considerations and challenges for the development of Health Monitoring Research Programs (HMRPs). An HMRP should collect data across three critical domains: biological samples and specimens, environmental signatures, and behavioral and social determinants. Potential sources of biological data include electronic health records from the Veterans Affairs and the Department of Defense (DOD) Individual Longitudinal Exposure Record, periodic surveys, and biorepositories. DOD environmental sampling studies can provide critical environmental exposure data.

Collection of biological samples and data for HMRPs likely requires novel approaches. Biological data are collected from service members upon entry into the military and during pre- and post-deployment.

^{*} TRL1-3 describes novel concepts and emerging technologies. TRL4-6 describes applied research that translates findings to solutions for military problems. TRL5-8 is comprised of prototype maturation and demonstration activities. TRL9 describes technology production and distribution.

HMRPs will need to develop data management plans and collection procedures in accordance with Good Laboratory Practice and to consolidate electronic health records for longitudinal analyses. HMRPs will also need to use incentives, reminders, and social media to strengthen participation and retention.

Notably, while chemical sensors and devices enable collection of exposure data, these technologies should not create an excessive physical burden for military personnel who are already carrying a significant amount of gear. The design of these sensors should account for military end users.

Common Data Elements at NIH

Robin Taylor, MLIS, National Library of Medicine

A Common Data Element (CDE) is a standardized, precisely defined question or variable, along with a predetermined set of permissible responses. These elements are employed consistently across diverse studies to maintain uniformity in collecting data. NIH recommends the use of CDEs to make research data adhere to findable, accessible, interoperable, and reusable (FAIR) principles. CDEs facilitate data interoperability, promoting secondary analyses, meta-analyses, and collaborations across various study designs, diseases, and disorders. Additionally, they enable data aggregation across multiple projects, boosting statistical power, strengthening scientific rigor, and minimizing data discrepancies. In addition, already developed CDEs reduce time and costs to investigators for data collection and facilitate subsequent data harmonization.

NIH Common Data Element Governance

The NIH Scientific Data Council formed the NIH CDE Governance Committee, comprised of eight members across NIH ICs. The Council charged the CDE Governance Committee to (1) decide whether submitted CDEs meet criteria that merit their designation as NIH-endorsed CDEs, (2) work closely with the National Library of Medicine (NLM) on processes for depositing NIH-endorsed CDEs in the NIH CDE Repository, and (3) review efficacy of CDE review processes annually. Importantly, committee members do not judge the scientific merits of CDEs. Instead, the research groups developing them are responsible for judging their scientific merits. The criteria for NIH endorsement are (1) clear definition of variable and measured with prompt and response, (2) documented evidence of reliability and validity, (3) human- and machine-readable format, (4) recommended or designated by a recognized NIH body, and (5) clear licensing and intellectual property status, preferably open source.

The workflow or the process starts with an NIH group submitting a CDE or group of CDEs. The CDE Governance Committee initially checks whether the submission is ready for review. Then, NLM performs quality assurance of CDEs while working with the submitter to address any gaps and correct errors. After passing quality assurance, the CDE Governance Committee conducts a full review. This review also includes collaboration between the committee and submitter to address revisions. After approval, NIH publishes the CDE to its repository. The NIH CDE Repository contains 171 NIH-endorsed CDEs and 24,158 total CDEs that were recommended by NIH groups prior to the formation of the CDE Governance Committee. CDEs have a lot of meta data associated with them and are readily available. A typical CDE record contains the following information: CDE name and definition, question text, data type, submitter, permissible values, concept and terminology codes, other identifiers, and related content. Form records are comprised of bundled CDEs that require use of the full bundle for CDE validity. Form records contain similar information to CDE records as well as copyright and licensing information.

Processes for Developing New Common Data Elements

Ms. Robin Taylor outlined the steps involved in the creation of new CDEs. First, relevant stakeholders, including research funders, regulatory agencies, and professional societies, decide to develop CDEs for a specific research initiative. Next, experts select existing CDEs or develop new CDEs with broader community engagement for further input. After finalization of CDE definitions, the chosen CDEs are reviewed and approved by a convening organization. This organization then incentivizes or mandates the use of CDEs by funding grantees. However, use of NIH-endorsed CDEs is not currently required for NIH grantees. Notably, the CDE development process at NINDS, which follows these steps, takes approximately 18 months. NINDS collaborates with other NIH ICs and federal agencies to develop CDEs and ensure alignment with international data standards whenever possible.

Widespread use of CDEs requires careful coordination across the research community to avoid duplication of efforts and to ensure investigators and other staff understand how to use and develop CDEs. CDE educational resources from NIH include [Common Data Elements: Standardizing Data Collection](#), [NINDS Common Data Elements](#), and [Standardize Your Research Data with NIH CDE Repository](#) courses. Use of CDEs at the beginning of a research initiative is critical for ensuring data interoperability.

Discussion

What are the criteria for bundling CDEs?

Ms. Taylor clarified that CDE bundles must be used together. A general example of a bundle is one CDE that is a number without units and a second CDE that contains the unit of measure.

How are identically named CDEs handled within the NIH CDE Repository?

NIH allows reuse of CDEs in its repositories by different research groups when definitions have slightly different wording. If definitions are significantly different, then the CDEs are not identical. NIH groups should search existing CDE resources prior to developing new CDEs.

Panel Discussion

Moderator: Ekemini Riley, PhD, Coalition for Aligning Science

Panelists: Darryl Hood, PhD, Ohio State University, and Caleb E. Finch, PhD, University of Southern California

What are your initial reactions to today's presentations?

Dr. Finch drew parallels between the complexities of the exposome and the multiplicity of cigarette smoke compound effects on carcinogenesis. In addition, multiple exposures can create synergistic effects on health outcomes. For example, the interaction of air pollution and cigarette smoke was super-additive compared to singular exposures. Therefore, the social and environmental contexts underlying chemical exposures are critical for understanding the exposome and the use of novel animal models.

Dr. Hood emphasized the importance of studying the cumulative nature of chemical and nonchemical exposures. While the workshop presentations highlighted multiple critical challenges for the field of exposomics, the scientific community appears especially well prepared to establish CDEs that are critical for large-scale analyses and team-based science necessary for progress in exposomics.

What are some must-have tools and resources for exposomic research that can focus on exposure synergies, social contexts, and cumulative exposures?

Dr. Hood noted that while understanding interactions between chemical and nonchemical stressors from conception to death appears daunting, a framework that accounts for both endogenous and exogenous exposures can establish a common baseline lexicon supportive of collaborative research.

Dr. Finch recalled that most experimental exposomic research has been conducted on rodents. While *in vitro* models may provide some valuable information, animal models are still critical for understanding the realities of chemical exposures, particularly those involving the lungs. Researchers need to broadly discuss and identify additional animal models for exposomic research. Humanized transgenic mice may be useful for answering certain exposome research questions (e.g., using transgenic APOE4 mice to understand the gene–environment interactions between the APOE4 gene and air pollution). Epigenetic assays beyond direct DNA methylation, such as assays measuring histone methylation and acetylation, are critical for understanding the molecular mechanisms by which these exposures impact health outcomes. NHPs may be necessary to more accurately recapitulate the human exposome; smaller NHPs such as the dwarf lemur should be considered in addition to rhesus macaques. However, researchers likely cannot use animal models to study some exposures with critical effects on lifespan and dementia age of onset, such as socioeconomic status and education.

Dr. Cory-Slechta emphasized that the future of the exposome field requires a cumulative exposure framework that integrates exposures over time to understand disease risk. In addition, with the multitude of chemical exposure databases, researchers can identify multiple exposures that increase risk for a particular health outcome and subsequently test which exposures have the highest magnitudes of effect to inform subsequent policy changes.

Dr. Cui emphasized the need for technology platforms to support the collection of exposure data. With a near-infinite number of relevant exposures for health outcomes, collection of exposure data becomes cost prohibitive when separate assays are needed for each chemical. Instead, platforms that test for multiple exposures can reduce costs and time investment. Animal studies can help researchers prioritize exposures for future study in humans, and surveys can help collect historical exposure data for epidemiological studies. Notably, the design of these surveys should minimize burden on participants while maximizing collection of useful data.

Could organoids be a useful in vitro model for exposomics?

Dr. Cory-Slechta noted that *in vitro* approaches are generally inappropriate for testing effects of social exposures such as resource deprivation and poverty. In addition, *in vivo* models are necessary for identifying the most sensitive endpoints to specific exposures.

What are some of the challenges researchers will face in the field of exposomics? How can we use AI to address these challenges?

Dr. Riley reminded workshop participants that AI is only as good as the data used to train the algorithms. Dr. Hood added that current underrepresentation of equity inputs into AI/ML models can result in the perpetuation of disproportional health outcomes. Data for large-scale analyses across studies need to be of high quality and aligned via CDEs. In addition, Dr. Poe emphasized the public trust required for epidemiological study participation and provision of detailed personal information. The scientific community needs to prioritize data privacy and earn this public trust. Although many social exposures

are difficult to model using animal models, Dr. Hood cited the use of the presence or absence of environmental enrichment to model poverty in rodents.

Dr. Finch cited three generation effects of certain exposures, such as lead. Therefore, exposomics should study an expanded time domain for life courses, beginning at the conception of an individual's mother.

Dr. Adams noted that future exposure studies should discern the differential effects of chronic, low-level exposures versus intermittent, moderate- to high- level exposures of the same chemicals. In addition, laboratories need to design exposure testing strategies that include reference chemicals to support inter-laboratory experimentation and interpretation across studies. Dr. Poe added that inter-laboratory experimentation and collaboration also require a shift in scientific research culture to incentivize data sharing.

How do we train the next generation of researchers in the field of exposomics?

Dr. Swanson-Fischer explained that Dr. Gary Miller (Columbia) has assembled an exposome bootcamp course. Democratization, standardization, and increased data accessibility can also help the next generation of scientists as they design and perform secondary analyses on existing data.

To what extent are NIH exposome programs interacting with European research groups?

Dr. Cui explained that NIH interacts with exposome research groups internationally at various conferences and workshops, but these interactions have remained informal until recently. By supporting a Center for Exposome Research Coordination, NIH aims to support international collaborative exposome studies, particularly with research groups in the European Union and Japan. Dr. Jett also noted researcher interest in exposomics in Africa.

Appendix: Right Tools and Resources for Neural Exposome Research Workshop Agenda

April 19, 2024

1:00 pm	Welcome, Opening Remarks, and Housekeeping Meeting Moderator: Neel Dhruv, PhD, NINDS Overview of the NINDS Council NEXT WG Neel Dhruv, PhD, NINDS Overview of NINDS Exposome Research David Jett, PhD, NINDS
1:30 pm	NINDS Biospecimen/Cell/Tissue and Data Resources Rebecca Price, PhD, Program Manager, NINDS Christine Swanson-Fischer, PhD, Program Director, NINDS
1:55 pm	Break
2:00 pm	The NIEHS Exposure Science and the Exposome Program: Creating Tools and Resources for Exposomics Yuxia Cui, PhD, NIEHS
2:20 pm	EPA's Computational Exposure Science Tools & Resources on a Path to the Neural Exposome Timothy J. Buckley, PhD, Center for Computational Toxicology and Exposure, EPA
2:40 pm	Eighty Pounds of Light Stuff: Building a Rational Exposure Assessment Toolkit Valerie Adams, PhD, Defense Centers for Public Health-Aberdeen
3:00 pm	Break
3:05 pm	Common Data Elements at NIH Robin Taylor, MLIS, National Library of Medicine
3:25 pm	Panel Discussion Moderator: Ekemini Riley, PhD, Coalition for Aligning Science Panel: Darryl Hood, PhD, Ohio State University, and Caleb E. Finch, PhD, University of Southern California
4:25 pm	Adjourn

APPENDIX D. Consultants and Speakers

The following individuals gave presentations to the NEXT WG and participated in meeting discussions:

[Yuxia Cui, PhD](#), Health Scientist Administrator, Exposure, Response, and Technology Branch, National Institute of Environmental Health Sciences

[Suzana Petanceska, PhD](#), Director, Office for Strategic Development and Partnerships, Division of Neuroscience, National Institute on Aging

[Richard Benson, MD, PhD](#), Director, Office of Global Health and Health Disparities

[Cheryse Sankar, PhD](#), Program Director, Office of Global Health and Health Disparities

The Right Tools and Resources for Neural Exposome Research Mini Workshop Presenters:

The following individuals presented at the virtual workshop ([see also presenter bios](#)):

Valerie Adams, PhD, DABT, Senior Biologist, Defense Centers for Public Health – Aberdeen, Defense Health Agency, United States Department of Defense

Timothy J. Buckley, PhD, Senior Advisor for Exposure Characterization and Modeling, Center for Computational Toxicology and Exposure, U.S. Environmental Protection Agency

Yuxia Cui, PhD, Health Scientist Administrator, Exposure, Response, and Technology Branch, National Institute of Environmental Health Sciences

Caleb E. Finch, PhD, Professor, Gerontology and Biological Sciences, ARCO/William F. Kieschnick Chair in the Neurobiology of Aging, University of Southern California

Darryl Hood, PhD, Professor and Dean's Fellow for Diversity, Equity and Inclusive Excellence, Environmental Health Sciences, Ohio State University

Rebecca Price, PhD, Program Manager, Movement Disorders and Neurodegeneration, National Institute of Neurological Disorders and Stroke

Chris Swanson-Fischer, PhD, Program Director, Movement Disorders and Neurodegeneration, National Institute of Neurological Disorders and Stroke

Robin Taylor, MLIS, Lead for the NIH Common Data Elements Repository, National Library of Medicine

Team Science to Advance Neural Exposome Research Mini Workshop Presenters:

The following individuals presented at the virtual workshop ([see also presenter bios](#)):

Heidi Baumgartner, PhD, Research Scholar, Stanford University, Executive Director, ManyBabies

L. Michelle Bennett, PhD, Principal and Owner, L.M. Bennett Consulting, LLC

Laure-Alix Clerbaux, PhD, Senior Researcher, Institute of Experimental and Clinical Research University Catholic of Louvain, Belgium

August 20, 2024

Karen David, PhD, Program Director, Division of Neuroscience and NIH BRAIN Initiative, National Institute of Neurological Disorders and Stroke

Cory Kelly, MS, Advisor for Research Operations and Program Implementation, Division of Extramural Activities, National Institute of Neurological Disorders and Stroke

Jae K. Lee, PhD, Christine E. Lynn Distinguished Professor in Neuroscience, University of Miami School of Medicine

Beate Ritz, MD, PhD, Distinguished Professor of Epidemiology, Environmental Health, and Neurology, University of California, Los Angeles

Rosalind Wright, MD, MPH, Horace W. Goldsmith Professor of Pediatrics, Icahn School of Medicine at Mount Sinai

APPENDIX E. Selected Neural Exposome Research Efforts

This document provides a list and links to programs, workshops, conferences, webinars, trainings, and funding opportunities related to the exposome and the neural exposome.

NIH Exposome and Neural Exposome Programs

NINDS

- ONETOX [The Neural Exposome Program webpage](#)

National Institute on Aging (NIA)

- [Exploring the Role of the Exposome in Aging and Age – Related Diseases](#)

National Institute of Environmental Health Sciences (NIEHS)

Exposure Biology and the Exposome

- [Genes, Environment, and Health Initiative](#)
- [Health and Exposome Research Center: Understanding Lifetime Exposures \(HERCULES\)](#)
- [Human Health Exposure Analysis Resource \(HHEAR\)](#)
- The Virtual Consortium for Translational and Transdisciplinary Environmental Research ([VICTER](#))
- The [Environmental Health Sciences Core Centers](#)
- Comparative Toxicogenomics Database ([CTD](#))

NIH All of US Program

- [Linking environmental data with health outcomes to develop precision environmental health \(partnership with NIEHS\)](#)

National Cancer Institute

- The Breast Cancer and the Environmental Research Program ([BCERP](#))

NIH Common Fund

- [NIH Common Fund's Metabolomics Program](#)

Fogarty International Center

- [Global Environmental and Occupational Health Initiative](#) (GEOHealth)

Other Federal Agency Exposome Programs

- [National Amyotrophic Lateral Sclerosis \(ALS\) Registry \(CDC/ATSDR\)](#)
- [CDC National Report on Human Exposure to Environmental Chemicals](#)
- [CompTox Chemicals Dashboard NORMAN: Exposome-Explorer \(EPA\)](#)
- [Total Exposure Health: An Innovation in Precision Health \(U.S. Air Force\)](#)

International Programs

- [The European Human Exposome Network](#)
 - [Horizon Europe. Work Programme 2023-2024](#)
- [The Japan Environment and Children's Study \(JECS\)](#)

Workshops, Conferences, Symposia, Webinars, and Trainings

The Neural Exposome

- [Environmental Neuroscience: Advancing the Understanding of How Chemical Exposures Impact Brain Health and Disease--A Workshop \(2020, NASEM\)](#)
- [Exploring the Neurological Exposome \(European Commission\)](#)
- [ANA2022 Presidential Symposium Spotlight: Frances Jensen, MD | Environmental Neurotoxicology](#)
- [ASENT 2022 ANNUAL MEETING Virtual Neuroscience and Neurotherapeutics Conference.](#)
- [2024 Japan – USA Exposome Symposium. Aging and the Exposome: Research Implications for Alzheimer’s Disease and Related Dementia](#)
- [NINDS OPEN Stage Webinar: The Neural Exposome - HOW NINDS is Supporting exposomic Research](#)
- [NINDS Workshop: Team Science to Advance Neural Exposome Research \(NINDS 2024\)](#)
- [NINDS Workshop: The Right Tools and Resources for Neural Exposome Research \(NINDS 2024\)](#)
- [NINDS Webinar: NINDS Neural Exposome Top Priorities \(NEXT\) Working Group Strategic Planning Open Session](#)
- [2024 Society for Neuroscience Conference. What Does the Microbiome Tell Us About Prevention and Treatment of AD/ADRD?](#)

The Exposome

- [2024 USA Exposome Symposium. Children’s Health, Environmental Justice and the Exposome \(Mount Sinai and Meharry Medical College\)](#)
- [2023 USA – European Exposome Symposium. Exposomic Approaches to Prevent the Health Impacts of Climate Change \(Mount Sinai and the University of Brescia\)](#)
- [The Exposome Boot Camp: Measuring Exposures on an Omic Scale \(2023, Columbia University\)](#)
- [Accelerating Precision Environmental Health: Demonstrating the Value of the Exposome \(2022, NIEHS\)](#)
- [Advancing Environmental Health Equity Through Implementation Science \(2022, NIEHS\)](#)
- [The URBANOME paradigm: Exploring the urban exposome to co-create urban interventions for better health and wellbeing \(2022\).](#)
- [Integrating Exposomics into the Biomedical Enterprise. The Banbury Center, Cold Spring Harbor Laboratory \(meeting by invitation only\).](#)

Recent NIH Neural Exposome Funding Opportunities

Issued by The National Institute of Neurological Disorders and Stroke (NINDS)

- [PAR-22-048](#): Clinical Relevance of the Linkage between Environmental Toxicant Exposures and Alzheimer's Disease and Related Dementias (R01; Clinical Trial Not Allowed)
- [PAR-22-211](#): Impact of the Microbiome Gut-Brain Axis on Alzheimer's Disease and Alzheimer's Disease Related Dementias (R01; Clinical Trial Not Allowed)
- [RFA-24-024](#): Role of Environmental Stress in the Health Inequities of Alzheimer's Disease-Related Dementias (R01; Clinical Trial Not Allowed)
- [NOT-NS-22-050](#): NINDS mission relevant Pain Research
- [PAR-24-249](#): Interaction Between Environmental Factors and Lewy Body Dementia (R01; Clinical Trial Not Allowed)
- [PAR-24-270](#): ADRD Risk and Disease Following Nervous System Exposures at Biological Interfaces with the Environment (R01 - Clinical Trial Not Allowed)

Collaboration Between NINDS and Other NIH Institutes

NIH Office of the Director (OD)

- Several Environmental Influences on Child Health Outcomes ([ECHO Program](#)) Notices of Funding Opportunities (NOFOs)

Office of Behavioral and Social Sciences Research (OBSSR)

- [PAR-21-349](#): Research on Biopsychosocial Factors of Social Connectedness and Isolation on Health, Wellbeing, Illness, and Recovery (R01; Basic Experimental Studies with Humans Required)
- [PAR-21-350](#): Research on Biopsychosocial Factors of Social Connectedness and Isolation on Health, Wellbeing, Illness, and Recovery (R01; Clinical Trial Not Allowed)

National Institute of Environmental Health Sciences (NIEHS)

- [NOT-ES-22-006](#): Climate Change and Health
- [RFA-ES-23-007](#): Exploratory Grants for Climate Change and Health Research Center Development (P20; Clinical Trial Optional)
- [RFA-ES-23-010](#): Center for Exposome Research Coordination to Accelerate Precision Environmental Health (U24 Clinical Trial Not Allowed)

National Institute of Aging (NIA)

- [NOT-AG-22-022](#): Notice of Special Interest (NOSI): Administrative Supplements to Support Research Infrastructure on Exposome Studies in Alzheimer's Disease (AD) and AD-Related Dementias (ADRD)

National Institute on Minority Health and Health Disparities (NIMHD)

- [PAR-24-110](#): Interventions to Reduce Sleep Health Disparities PAR-24-110 (R01 - Clinical Trials Optional)

Issued by Other NIH Institutes and Centers

National Institute of Aging (NIA)

- [RFA-AG-24-011](#): Research Coordinating Center on the Exposome and Alzheimer's Disease and Related Dementias: Elucidating the Role of Social and Behavioral Determinants of Health (U24 Clinical Trial Not Allowed)
- [RFA-AG-24-021](#): Understanding Gene-Environment Interactions in Brain Aging and Alzheimer's Disease (AD) and AD-Related Dementias (ADRD) (U01 Clinical Trial Not Allowed)
- [RFA-AG-24-022](#): Quantifying the Impact of Environmental Toxicants on Alzheimer's Disease (AD) and AD-Related Dementias (ADRD) Risk in Cohort Studies (U01 Clinical Trial Not Allowed)
- [RFA-AG-24-023](#): Preclinical Studies to Characterize the Impact of Toxicants on Brain Aging and Alzheimer's Disease (AD) and AD-Related Dementias (ADRD) (U01 Clinical Trial Not Allowed)

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

- [RFA-DK-22-036 / RFA-DK-23-001](#): A Consortium for Gut-Brain Communication in Parkinson's Disease (U24 Clinical Trial not allowed)

National Center for Complementary and Integrative Health (NCCIH)

- [PAR-24-239](#): Enhancing Mechanistic Research on Precision Probiotic Therapies (R33 Clinical Trial Optional)

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

- [RFA-DK-22-036](#): A Consortium for Gut-Brain Communication in Parkinson's Disease (U01 Clinical Trial Not Allowed)

APPENDIX F. Request for Information on Interdisciplinary Research Opportunities that Bridge Neuroscience and Environmental Health Science: Summary of Responses

NIH Guide Notice Number: [NOT-NS-22-076](#)

Release date: March 8, 2022

Closing date: May 7, 2022

Project Summary

This Request for Information (RFI) sought input on challenges and opportunities for interdisciplinary research to understand the role of internal and external factors on neuronal health. The RFI outcomes will help determine research priorities, develop recommendations for resource allocation, ensure fair grant review, facilitate collaborative research within research institutions as well as among academia, industry, and government agencies, seek effective implementation of scientific findings, leverage on existing research resources, and perform outreach to disseminate information.

Project Origins and Goals

The newly federally mandated Office of the Neural Exposome and Toxicology (ONETOX) at the National Institute of Neurological Disorders and Stroke (NINDS) was created in 2022 to support basic, translational, and clinical research on the effect of internal, external, and behavioral exposures across the lifespan affecting the nervous system, the neural exposome¹⁻². The ONETOX aims to foster collaborative research and to provide information and tools to help break down barriers to research between different scientific disciplines to understand how exposomic factors contribute to neurological disease and disorders. The RFI sought input from the government, industry, academia, and the public on challenges and opportunities for interdisciplinary research between neuroscientists, environmental health scientists, and scientists from other disciplines to understand the impact of the exposome on neuronal health. The responses will identify priority research and resources to understand how environmental factors contribute to neurological disorders.

Project activities, team, and participants

The RFI was a collaborative effort between the National Institute of Neurological Disorders and Stroke ([NINDS](#)) and the National Institute of Environmental Health Sciences ([NIEHS](#)), with the support from other Institutes or Centers (ICs, NIA, NICHD, NIDA, NCCIH, OBSSR, and ORWH). The RFI was advertised through diverse NIH/NINDS/NIEHS listservs, and it was open to the public from March 8, 2022, to July 11, 2022. The responses to the NIH/ONETOX RFI were submitted through the official web form and followed NIH guidelines. This document summarizes the responses.

Project Outcomes

There were 64 responses from 57 individuals and 7 groups or foundations. The primary contacts represented diverse fields including neuroscientists (44.12), environmental health scientists (14.71%), toxicologists (13.24%), clinicians (5.88%), individual/family member

affected by a neurological condition (2.94%), patient advocate group members (1.47%), other interested parties (7.35%; basic scientist, science policy, small business). Seven respondents did not identify specialty (10.29%). Based on the information provided, 37 academics institutions, of which, 34 were from the USA and 3 internationals, one representing a USA government agency, and 3 USA non-profit organizations were represented in the RFI. Within the USA, most responses were from the East coast, the Midwest, and the southeast. The following summary represents common issues cited as important to the neural exposome community.

NIH restructuring and funding. An extremely common theme was that respondents believe government funding agencies are a major barrier to understanding the contribution of environmental toxicants to adverse neurological outcomes across the life span. Changing the culture at NIH **to recognize the environment as an important driver of human health** could be achieved by 1) using inclusive language in FOAs and RFIs. Two respondents commented that the options offered in the RFI question about field of study should include more than one field, 2) incentivizing interdisciplinary research by NIH at National Society Conferences, 3) Expanding the scope of NIH funded centers, such as the Udall Centers, to include environmental studies and epidemiology, 4) increasing institutional collaboration and funding from different NIH agencies supporting neurologic disease and environmental exposure research, 5) providing clear and consistent expectations and objectives for interdisciplinary teams, 6) conveying to the reviewers the NIH commitment to funding this research area, 7) release RFIs and educational materials to increase participation in studies, and 8) creating dedicated special emphasis panels and appropriately membered study sections with expertise in toxicology, environmental health, epigenetics, neurology, basic and clinical research to evaluate research projects at all levels.

The highest number of responses was related to increased funding mechanisms fostering new and existing interdisciplinary and multi-institutional partnerships, infrastructure, equipment, technologies, increase participants enrollment, basic science and preclinical studies, disease models, administrative supplements, and data analysis. These mechanisms will allow relationship building and knowledge, technology, and data sharing. Respondents were interested in funding for all behavioral outcomes as expressions of CNS function: cognitive, affective, regulatory, motor, and sensory, as well as gene-environment interactions and how individual genetic differences define neural damage by environmental toxicants.

The traditional 5-year R01 funding was believed to be impractical and insufficient to study toxicants impact of on aging, cognitive deficiencies, and mental health across the lifespan using larger-scale longitudinal studies, imaging, and phenotyping. Some respondents suggested to implement Center or Program Project Grants mechanisms, such as the Virtual Consortium for Translational and Transdisciplinary Environmental Research (VICTER) grant mechanism and the Environmental Health Sciences Core Center, at NIEHS. Another suggestion was to develop an Environmental Neuroscience Center program based on successful programs such as the Breast Cancer and the Environmental Research Program (BCERP)

Several respondents indicated that expanding Principal Investigator's eligibility to other disciplines besides neuroscience and environmental sciences (e.g., geology, oceanology, geography) as well as engaging Professor Emeritus will incentivize new and existing collaborations. In addition, there is interest on the inclusion of a) Black, Indigenous, and People of Color (BIPOC) and their communities and BIPOC researchers to ensure research maximizes its benefits to address ethical issues to reduce environmental health disparities and promote environmental justice; b) institutions in urban poverty areas to interact with their neighborhoods;

c) exposure monitoring strategies in countries with populations with unique exposure; and d) research in low- and middle-income countries (LMIC).

Opportunities related to the effects of environmental exposures on neurodevelopment, aging, late-onset neural diseases, substance abuse, and complementary and integrative approaches. Early-life exposures pose a high risk of developing neurodevelopmental, mental health, and/or late-onset neurological disorders. Environmental factors are preventive/rectifying targets; however, respondents acknowledged challenges to perform clinical/preclinical studies addressing the cumulative environmental neurotoxicity affecting the nervous system, behavior, and cognition due to difficulty in 1) establishing causal links between environmental exposures and clinical outcomes; 2) identifying the most impactful environmental exposures; and 3) big data integration from statistical modeling, omics, environmental measurements, and electronic technology. There was high interest in incorporating social structures as determinants to neurological diseases as they influence exposure, physical activity, housing/indoor/community level exposures, and they might act synergistically with genetic phenotypes to increase disease susceptibility. Numerous respondents felt that mental health is a key outcome of environmental health and should be considered to understand substance abuse. Respondents support an exposomic framework, life course, and reverse translational research approach to include environmental and occupational exposures, social determinants of health, and neuropsychiatric measures. The responders provided a comprehensive list of topics and approaches to develop high-risk-high-reward ideas and to increase collaborative efforts to advance this field:

- Identification of sensitive time windows of exposures, molecular and cellular mechanisms, and chemicals and stressors (concentrations, mixes, acute/chronic and repeated exposures) impairing cognition and neurodegeneration.
- Identification of causal and mechanistic links between genetic variability, genome-exposome-wide associations, gene-environment interactions, and epigenetic memory with neurodevelopmental, neurobehavioral, and psychiatric outcomes.
- Identification of the link between toxic developmental exposures, gender differences, and endocrine endpoints in neural disruptions.
- Study of the relationship among nutrition, toxicants, commensal microbes, and neurological health using longitudinal or repeated measures.
- Determination of accurate disease prevalence/incidence/disease rate information.
- Address multiple neurological phenotypes in epidemiological studies of sporadic neurodegenerative disorders seeking associations with environmental factors.
- Identification of cross-generational environmental exposures linked to familial disorders.
- Use and development of exposure techniques and methodologies such as a) wearable sensors, b) high-dimensional exposure measurements, c) single-cell analytical methods, d) artificial intelligence, bioinformatics, *in silico* toxicology, and geographic data, and e) biomonitoring maternal exposure levels during pregnancy, exposures in human cerebrospinal fluid, agricultural or domestic animals, and f) targeted and non-targeted analyses, omics analyses, and brain imaging.
- Study of brain shrinkage and biological processes implicated in vascular risk and metabolic disorders later in life resulting from long-time toxic occupational exposures.
- Study of mitochondria dysfunction.
- Association of toxicants (environmental neurotoxins, trace metals/elements, mycotoxins) with psychosocial, lifestyle factors, cognitive impairment, and neurodegeneration.
- Impact of environmental stressors in specific neural cell types, immune response, and glia

- Study of Tau/amyloid in response to environmental stressors.
- Inclusion of outcomes such as intermediate brain, cognitive, and educational attainment resulting in long-term psychosocial functioning, and risk for substance use and other mental health disorders emerging in late adolescence and adulthood.
- Modification of the present model from a disease-oriented to a prevention approach to address mental health in urban, suburban, and ex-urban settlements.
- Identification of interactions and the cumulative effect of socio-demographic vulnerability, structural racism, and health disparities in communities and other contributors such as nutrition and environmental justice in the context of environmental gradients (soil, air, water). Use of this framework to identify the most at-risk groups for poor outcomes from environmental exposures.
- Implementation of models of participatory action research with community and patient outreach and engagement to tackle health disparities in neurological, mental health, and behavioral outcomes, risk management and implementation.
- Use of urban water surveillance information to distinguish between individual and neighborhoods' environmental measurement.
- Identification of rapid and safe agents for environmental bioremediation.
- Collection of health care data from stroke centers and integrating it with local environmental metrics into stroke center certification.
- Use of complementary and integrative health approaches (e.g., mindfulness, yoga) and environmental interventions (e.g., green corridors, noise reduction) for stress resilience.
- Investigation of the microbiome as a mediator of environmental chemical effects on neurodevelopmental and neurological outcomes and a potential intervention.
- Understanding of the impact of environmental stressor on aquatic and terrestrial biomes and its relation to gut microbiome, metabolism, and mental health.
- Assessment of climate change/heat/CO₂ on the evolving nature of pollutants.

Diverse interdisciplinary teams are needed to understand the environmental impact on neurological diseases. Respondents believe a major limitation to advance the neural exposome field is that most researchers work in silos with only few having environmental science and neuroscience expertise. Teams should be comprised of basic scientist and clinicians with diverse backgrounds, career stages, institutions, countries, tools, ideas. The formation of a consortium of scientists in different fields and realms (industry, academia, and government agencies) would establish and validate protocols with modern technologies meeting key parameters of repeatability, reproducibility, sensitivity, and specificity of neurotoxicological testing. Collaborations between clinically oriented researchers and government agencies will facilitate to identify causes, prevention, and treatment of environmentally related neurological diseases. Neural exposomic research teams should be comprised by the following expertise:

- *To guide study design:* biostatistics, environmental health science, epidemiology, genomics, social sciences, urban planning.
- *To assess exposure and exposure dose:* industrial hygiene, mixtures analysis pharmacokinetics, toxicology.
- *To interpret neurological and psychological outcomes:* behavioral neurology, developmental neurology, endocrinology, gerontology, neuroimaging, neurology, neurotoxicology, pathology, pediatrics, psychiatry, and psychology.
- *To understand pathophysiological mechanisms:* basic science, biochemistry, chemistry, data science, genetics, immunology, neuroscience, physics, physical chemistry.
- *To regulate scientific findings implementation:* Formation of a consortia consisting of academia, industry, and government agencies.

Disease Models. With 85,000 chemicals in the consumer space, several respondents believe there is urgent to identify and prioritize neurotoxicants. Interdisciplinary teams could better decide which disease models are relevant to fill knowledge gaps in this field. Respondents were interested in alternative disease models to reduce cost and length of studies and to complement epidemiological and clinical studies with a) non-traditional animal models (*C. elegans*, *D. rerio*), b) *in vitro* models (pluripotent stem cells, heterologous transfection systems, and human neural adult stem cells), c) *in vivo* techniques (microfluidics, organ-on-a-chip/organoid-on-a-chip, multi-organ on a chip, 2D/3D platforms, and blood brain barrier modeling), and d) *in silico* models. Some respondents believe that well-controlled animal studies are useful to identify mechanisms involved in environmental adverse effects and replicating exposure profiles and mixtures in laboratory settings. However, they cautioned that genetic models mask the natural aging components, and that rodent and human brains are different. Companion animals and wildlife were suggested as useful spontaneous disease models. There was interest in using *in silico* approaches to study human standard clinical endpoints and biomarkers for socioenvironmental stress, to examine interventions for substance use, and to replace regulatory safety approval and long-term monitoring protocols, and guidelines by government agencies, for assessment of commercially available compounds currently based on animal tests. Non-human primate models could identify genetic susceptibilities to addiction, parental interactions and track neural network changes. Disease models complement epidemiological and clinical studies with:

- genome-wide association studies and identify targets and gene*environment interactions
- understanding neurotoxicity mechanisms and prioritize environmental toxicants,
- identifying semi chronic exposures across the lifespan,
- identifying what is the effect of environmental toxicants during critical developmental windows and to follow delayed effects during adulthood,
- developing and made widely available cell lines for neurodevelopmental-related research.

Cohorts. Multi-cohort studies would foster cross-collaboration and improve rigor and reproducibility of findings and to address the cross talk between neurological deficits, health disparities, and other exposomic factors including other diseases (e.g., cardiovascular and metabolic diseases). Several respondents suggested to:

- Leverage on well-characterized cohorts and/or existing large/nationwide studies and support new cohorts to collect key information and bio-samples longitudinally, incorporating neurological endpoints and environmental parameters, and perform sensitive assessments.
- Develop racially, ethically, geographically, socially, and economically diverse cohorts. Pool across multiple enrollment centers to power studies with low participation and/or diversity.
- Study populations with high exposure burdens to reduce study noise, to decrease inequality, and increase inclusion in research.
- Invest and collaborate with community groups working with underrepresented populations to ensure these groups are represented and included in the research process.

Rigorous Research. Respondents think that the current cross-sectional approaches in exposure assessment are insufficient and suggested to refine biological sampling and analysis, establish research standards and common nomenclature, and/or to create a national lab or a network of regional labs with standardized operating procedures and samples' collection and processing. Lack of interaction between neuroscientists and environmental scientists leads to misinterpreted published results. Interdisciplinary collaboration in neural exposome research will standardize preclinical and clinical approaches in the field to:

- link environmental, brain, and behavioral data.

- exchange data among government agencies.
- allow comparisons across different studies by considering sex, racial, and ethnic diversity.
- identify amount of exposure, duration time, sequestration and accumulation, route of ingestion and concentration range of various neurotoxicants to inform intervention.
- Identify the role of chemical toxicant mixtures on disease onset and progression.
- promote sophisticated biostatistical data analysis and informed interpretation of results.
- consider dietary, social, and cultural factors, and age-appropriate outcomes.
- include basic science and population research.
- facilitate reproducibility and comparison across studies
- increase translatability and efficiency of pre-clinical findings.

Biobanks and Data (sharing, processing, and protection). Several respondents advocated for the establishment of human samples biobanks with demographics and exposures data and enforceable data sharing policies from NIH-funded projects relevant to environmental neuroscience. However, secure mechanisms are needed to share Protected/Personal Health Information (e. g., residential or biological outcomes). Respondents emphasized the urgent need for biobanks infrastructure, imaging capabilities, and digital research to:

- collect and analyze brain-related data and to study gene-environment interactions for clinical and preclinical research,
- sharing and developing databases (e.g., chemical databases: chemical structures, physiochemical and biological properties, and toxicology data),
- integrate different types of external data (e.g., address pseudo-coded IDs in a secure server) with researchers' data (i.e., participant's personal information), and address ethical implications big data integration,
- support circuit-based outcomes such as linking neuroimaging data or well-established paradigms and self-report measures to the Research Domain Criteria (RDoC),
- annotate big data and develop *in silico* techniques to identify environmental neurotoxicants (e.g., the Comparative Toxicogenomics Database) with curated data for neuroscience,
- encourage a national effort to build and update geospatial exposomes across the US to link with electronic health records to identify regional risks and facilitate research nationally,
- develop lists of a) birth and aging cohorts with neurodevelopmental outcomes and b) comprehensive exposure and environmental data,
- pooling key elements from studies to achieve sufficient sample sizes.
- use multi-omics analysis to visualize each element and connect molecular network to integrate disease onset by deciphering phenotype differences,
- Biobanking samples (hair, skin) to temporally identify exposures. Robust data return and sharing policies.

Networking and Communication to promote interdisciplinary research. Several respondents suggested informal and formal settings to interact and promote interdisciplinary research for neural exposome, including symposia, forums, web-based tools, fellowships, establishing follow up meetings among grantees, and week-long retreats or workshops for basic scientist, clinicians, environmental scientists, patients, and caregivers with focus on:

- identifying and overcoming population research barriers: public reluctance to participate, diverse populations, and large cohorts,
- understanding biological mechanisms in the brain affected by chronic environmental exposures (pesticides/chemicals, algal blooms, nutritional) grounded in toxicology principles,
- facilitating novel prevention and intervention strategies,
- producing proposals and getting feedback to submit to funding agencies,

- ensuring productive collaborations last beyond the initial funding period,
- engaging patients and caregivers neural exposome interdisciplinary research,
- promoting preprints and publications in journals bridging neuro and environmental sciences,
- advertising interdisciplinary Request for Applications (RFAs) in NIH sites, and
- engaging researchers before funding opportunities are announced by sponsoring symposia with invited program officers and research teams to present joint pre-proposals.

Science dissemination and implementation. Defining the exposome and links to disease will guide government policy and education. Science dissemination and implementation are components of the scientific process. Several respondents urged to resource science dissemination, measures, implementation, intervention, and evaluation efforts to reduce exposures effects. Improved communication between scientists and health professionals regarding scientific issues, risks, and actions to inform their community is imperative. Ways to reduce barriers in accessing published manuscripts are to: 1) fund open access fees, 2) access PubMed electronic versions, or 3) require preprints deposition. Researchers voiced their frustration about the inefficient implementation of their studies to guide exposure standards for U.S. Government, patient education or clinical decisions. Lack of political will to act on scientific findings discourages scientists to join this field. It is essential to have more transparency on what data is necessary to design, translate, and execute efficient research programs on environmental toxicants. Science dissemination and implementation may be a funding incentive.

Education. Some respondents indicated early career education intervention could promote interdisciplinary collaborations by integrating medical school and graduate school curricula and encouraging early career investigators to focus on interdisciplinary work (e. g., exposures, neuroscience, clinical, environmental health science). In addition, key personnel in medical schools, such a vice-chair of environment and health, could serve as a liaison between the university and medical school.

Financial incentivization. One respondent suggested that loan forgiveness for neuroscientist looking to enter environmental health research would incentivize interdisciplinary research.

The research community has proposed numerous ways to promote interdisciplinary research among neuroscientist and environmental health scientists to study the effects of non-genetic stressors on the nervous system.

References

1. Wild, CP Cancer Epidemiol Biomarkers Prev. 2005 Aug;14(8):1847-50.
2. Tamiz, AP et. 2022 Apr 20;110(8):1286-1289.

APPENDIX G. Responses to Request for Information on Draft Strategic Priorities for Neural Exposome Research at NINDS

NOT-NS-24-102

This RFI sought comments and suggestions on the NEXT WG's draft neural exposome research priorities for the NINDS. This included identifying research gaps and opportunities, best practices for collaboration, and research tools that will advance neural exposome research. Responses to this RFI were received from July 5-31, 2024. Seventeen responses were submitted either electronically, using a web-based format, or by email to the ONETOX staff. The full text of each response is provided below, followed by a short summary of key points.

Response #1: This is an exciting prospect and significantly under studied since it doesn't fit easily into other institutes or programs. My expertise lies at the intersection of circadian rhythms/sleep, stress, and inflammation with a focus on how external perturbation of light/dark cycles impact these processes, how they interact with genetic predispositions, and the cellular/circuit mechanisms by which these effects occur. I would encourage including light as part of the exposome concept, particularly light cycles and light exposures at "incorrect" times of day and the impact of exposure to different wavelengths of light in the treatment of neurological disease. Primary effects on the circadian clock as well as secondary effects on processes such as sleep, neuroendocrine and neuroimmune function should be considered.

Summary: Include light exposure to the exposome concept affecting neurological diseases (timing and wavelengths, primary effects through circadian clock, and secondary effects on sleep, neuroendocrine, and neuroimmune functions.

Response #2: From epidemiological data, a clear leading factor is air pollution composed of PM2.5/NOx. Greater effort should be made in funding models looking mechanistically at this, with clear dose-response curves, chemical outputs, and suggested therapies for AD/ADRD. For example, aberrant protein S-nitrosylation and related redox reactions due to PM2.5/NOx is a vastly understudied area with regard to the air pollution exposome. Chemical biologists should be recruited to this effort, especially those with drug development academic facilities. Efforts should be made to link clinicians, neuroscientists, chemical biologists, structural biologists, medicinal chemists into a network or at least a large P01 or U01 coordinated effort to attack this problem in an interdisciplinary and comprehensive manner.

Summary: Include funding mechanistic models to explore air pollution composed of PM2.5/NOx. Investigate dose-response relationships, chemical outputs, and potential therapies for AD/ADRD. Promote interdisciplinary collaboration among clinicians, neuroscientists, and drug development experts.

Response #3: We write to you as stakeholders in the urgent mission to raise awareness of the significant risk of brain damage and disease caused by repetitive head impacts (RHI) in sports. Together, let us strive to save lives and prevent the tragic loss of children whose head impacts in sports result in suicide, erratic behavior, severe depression, or other forms of suffering that could have been avoided.

The evidence and knowledge necessary to enhance the care and quality of life for our nation's children and to educate those responsible for their wellbeing should be readily available. We believe it is important for everyone to understand there are risks in RHI, even if they do not result in a concussion diagnosis. Science has evolved. Here are the facts: Young athletes engaged in sports during their critical developmental years are significantly more susceptible to lifelong neurological impairments if they undergo repeated head or body impacts: * The ages between 8 and 13 are especially vulnerable, given the significant changes and maturation occurring in young brains. Statistics reveal an elevated risk of suicide, mental health issues, addiction, irrational behavior, and learning difficulties following brain trauma. These are national issues that can, in many cases, be mitigated by safeguarding a child's developing brain. Despite advances in sports safety equipment, improved playing standards, and enhanced coaching training, young players are still exposed to severe and unnecessary impacts to their developing brains. * It is a scientific fact that, due to the physiological structure of the brain, there are no known means of preventing subconcussive exposure through technology or equipment. We sincerely hope you look at exposure to contact sports, military, or domestic abuse as one of your factors. May we suggest a change to the death certificate to ask a question about contact sport history. It would go a long way in discovering poor outcomes for a RHI history.

Summary: Include repetitive head impacts from contact sports, military service, or domestic abuse as exposomic factor. Suggesting including contact sport history on death certificates to understand outcomes.

Response #4: Overall, the draft priorities were quite comprehensive and timely. One priority that I did not see well represented, however, is understanding sex differences in biological responses to the neural exposome. Sex differences to environmental exposures affecting brain development are the rule rather than the exception but are poorly understood at a mechanistic level. Almost every neurological disease has a sex bias in prevalence. There are sex differences in hormonal, genetic, and epigenetic biomarkers of neurologic diseases but the mechanisms to explain their differences are poorly understood. Despite the NIH mandate to consider sex as a biological variable, many research studies and publications still do not properly consider SABV. Therefore, research into sex differences in response to the neural exposome should be prioritized.

Summary: Prioritize sex differences in response to the neural exposome

Response #5: Perhaps it would be good to note that: "Very few diseases can be explained by genetics alone" or by a single factor or structure. This is why Engle formulated several decades ago the biopsychosocial model of disease stressing the broad interactions of biology, psychology and sociology. The Neural Eposome approach incorporates and updates this holistic real-world integration to go beyond biology and more fully embrace public health principles related to the social determinants of health and lifestyle factors.FYI: These comments come from the relatively recent CDC public health models for the dementias and for depression, which go beyond biology and a simple medical model.

Summary: Note or emphasize that "very few diseases can be explained by genetics alone or by a single factor or structure."

Response #6: I was grateful to attend the webinar on the 15th, and appreciate the hard work of the council. One thought that I came away with specifically is in regards to the development of new tools and models. One missing gap, to me, seems to be ability to translate human exposure data and outcomes effectively “back” into experimental models to test these outcomes. Emerging systems like human-derived organoids and organ-on-a-chip systems, or humanizing mice (with microbiome and or immune systems) might help to bridge the exposure data into more refined experimental systems. But certainly there must be other emerging technologies that could be leveraged. We can easily do many different exposures in experimental systems and can often measure exposures (or at least steady state levels) in humans, but effectively combining these into relevant experimental systems is a challenge. Support for multi-disciplinary teams and/or investigators wishing to incorporate a toxicological paradigm into their current neurological experimental pipeline might help to facilitate the development of more relevant, yet manipulatable, experimental systems.

Summary: Development of new tools and models: Ability to translate human exposure data and outcomes effectively "back" into experimental model to test outcome. Support for multi-disciplinary teams

Response #7: Humans are poisoned from cradle to grave due to the incessant use of a plethora of toxicants in their daily lives and workplace exposures. Babies are being born with upwards of 187 chemicals in their blood. (EWG) The plethora of research on pesticides and links to neurological diseases is not nearly enough as we do not know the synergistic effects of all the other onslaught of chemicals in our daily lives as contributing factors. In light of NINDS efforts to further research for the environmental links of toxicants to neurological diseases and disorders I would like for some critical areas of research be specified, and others be added where critically necessary. NINDS needs to consider pollution by consumers and the contribution to pollution by toxic consumerism as a neurotoxic insult. Neurotoxicity is characterized by symptoms that are not uncommon to a whole host of diseases, of which includes underfunded syndromes without diagnostic biomarkers. Symptoms of neurotoxicity may include memory problems, impaired control of limbs, bladder and bowels, migraines, headaches and sleep disorders, vision problems, muscle weakness and atrophy, along with anxiety and depression as a result of dealing with a chronic disease. The psychological issues normally arise out of the enormous stress, fear, and navigating a healthcare system utterly obtuse to how to diagnose, treat, and coordinate care for these patient populations, along with the dismissiveness and tormenting behavior of these professionals. These syndromes are potentially fatal and suffering is typically extreme; comparable or worse to cancer. The seriousness of which these syndromes are approached from a research perspective should be proportionate to quality of life. How quick does anxiety and depression set in with a cancer diagnosis? Yet, we don't question them as having a psychological condition. IT'S CANCER. People who have become very ill from exposures to everyday chemicals, such as perfumes, paint, pesticides and cleaning products are by no means struggling less to come to terms with a life turned upside down. Just because something is hard to quantify objectively does not mean it does not exist, no different than a headache. Psychological problems are the result of, not the cause of. Can we please move past this. There needs to be a huge focus on the products used in daily lives that contribute to neurotoxicity. People suffer serious chemical injuries to the brain and nervous system from workplace exposures and

various cocktails used in the home. Do we really need to research the environmental links to disease or get the medical community to accept it more and change course in how we treat those who suffer debilitating chronic conditions like Chemical Sensitivities? It is hard to research an already overabundance of chemicals being used on a daily basis let alone the synergistic effects. You can use the research on these exposure outcomes that's already been completed to sufficiently understand this relationship. Can we get to the acknowledgement and acceptance and move past on to the public service announcements on using the precautionary principle throughout their lives with everything they use inside and outside of the home and at work? Better use of funds could be to study the incidence rates of these illnesses to see if they are particular to regions and populations like autoimmune disease prevalence is higher in African American women. Understanding what professions have higher rates of illnesses like Gulf War Illness is related to military service. Large UK studies show nurses with higher rates of respiratory disease from disinfectant use in hospitals. Common diseases and disorders in common industries or professions could give you straight answers. Strategies to mitigate this should include increased stringency on IAQ guidelines and enforceable codes for public spaces, along with more awareness to the consumers. Please also reverse the GRAS for the over 80,000 chemicals registered with EPA. Many companies hide behind the fact they can use chemicals Generally Regarded As Safe and not have any duty to worry they may be causing harm.

Summary: Focus on products used in daily lives and occupational setting contributing to neurotoxicity and study the incidence rates of illnesses. Support strategies to mitigate daily exposures including increased stringency on IAQ guidelines and enforceable codes for public spaces, with more awareness to the consumers, and reverse of the GRAS for the over 80,000 chemicals registered with the EPA.

Response #8: This is a very exciting and much needed initiative. We appreciate the opportunity to comment and to propose that NINDS include a focus on the role of environmental neurotoxins and the neural exposome in adverse neurodevelopmental outcomes in the congenital heart disease (CHD) population. CHD are the most common developmental defects in humans, affecting 8 per 1,000 live births, and remain the leading cause of birth defect-associated illness and death. Improved survival after surgical repair of CHD has led to recognition that neurobehavioral disability, including cognitive dysfunction, impaired motor skills, language difficulties, and impaired attention and executive function, is the most common and potentially most disabling long-term adverse outcome for infants with CHD.¹ These developmental issues initially manifest during childhood and are associated with an increased risk of poor functional outcomes in adulthood; including, but not limited to, reduced educational achievement, lower levels of employment, and limited social engagement. Despite the efforts of multiple investigators and clinicians, there has been minimal progress in improving neurodevelopmental outcomes for these children over the past 20 years.²⁻⁴ For many years, studies of neurodevelopmental outcomes for children with CHD were focused on cardiac surgery; specifically on intraoperative management strategies.³ This focus was understandable inasmuch as these strategies are potentially modifiable and thus there were potential opportunities to improve outcomes. However, recent studies have shown that innate patient factors (prematurity, brain dysmaturity, genetic anomalies, maternal education, etc.) eclipse intraoperative factors as predictors of worse neurodevelopmental outcomes.^{1,3} Multiple investigations have shown that the currently recognized risk factors explain only 30-40% of the observed variation in outcomes for newborns with CHD, including neurodevelopment.^{3,5} To develop tools that more precisely predict individual risk and to create novel therapies, further efforts to better

understand and include other unrecognized factors are necessary. Emerging data suggest these include maternal-fetal, genetic, environmental, and other biophysiological variables, as well as social determinants of health. Identification of the factors and exposures underlying adverse neurodevelopmental outcomes is critical in the quest for novel, effective, and personalized therapies. There is increasing evidence that exposures to industrial chemicals (both health-care related exposures and during daily life) are associated with adverse cardiovascular and neurodevelopmental outcomes in CHD.⁶⁻¹⁰ We have shown that there are significant perioperative exposures to a variety of industrial chemicals (phthalates, phenols, volatile organic compounds, cyclohexanone) in neonates undergoing surgery for CHD, especially in relationship to the use of cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO).⁶⁻¹⁰ Increasing exposures to these chemicals have been associated with greater perioperative morbidity (phthalates) and worse neurodevelopmental outcomes (cyclohexanone).^{6,10} We have also demonstrated that during everyday life, toddlers with CHD are exposed to complex mixtures of chemicals (e.g., phthalates, phenols, parabens, pesticides), many of which are known or suspected endocrine disrupting compounds (EDCs) and neurotoxicants.⁸ Greater concentrations of biomarkers of exposure to these chemicals, especially phthalates, are associated with poorer performance for language and motor skills at 18 months of age after adjustment for known risk factors for adverse neurodevelopment outcomes. Interestingly, we identified a greater adverse effect in girls compared to boys. There is increasing evidence that children with CHD from disadvantaged neighborhoods have worse outcomes.^{11,12} We hypothesize that hazardous environmental exposures during fetal life and early childhood are greater in those from disadvantaged sociodemographic communities and may contribute to the observed disparate outcomes. The impact of the neural exposome in the CHD population must be considered from a developmental perspective. The impact of a neurotoxicant can differ depending on the developmental stage during which exposure occurs (i.e., “critical windows of vulnerability”), and that risk is modified by the presence or absence of biological, nutritional, and psychological factors which may vary over time.¹³ Perturbation of sensitive biological processes by exposure to environmental toxicants during distinct developmental periods increases the risk of later life adverse health outcomes, years, or even decades after exposure to the stressor.^{14,15} In addition, in utero life and the early postnatal period through the first two years of life are particularly important times for brain development.^{1,15} This developmental perspective is particularly important in the CHD population because neonates with complex CHD often require multiple cardiac operations with CPB, with associated prolonged hospitalizations and exposure to multiple medical devices, across their lifespan. In addition, the impact of exposure to complex mixtures of neurotoxicants must be considered.^{8,9,16} Longitudinal cohort studies should be created assessing the neural exposome for the CHD population beginning in fetal life and continuing post-natally into adulthood. Children with CHD are an especially vulnerable population and there is evolving evidence demonstrating the importance of early life environmental exposures as potentially modifiable mediators of adverse neurobehavioral outcomes across the lifespan. Targeting the neural exposome in the CHD population aligns with the important priorities of the NINDS’s efforts in neural exposome research: 1) Address critical knowledge gaps in the definition and understanding of the neural exposome and its impact on neurodevelopment and functional outcomes over the lifespan in the CHD population. 2) Understanding the interactive effects of vulnerable developmental windows with multiple chemical exposures on multiple biological targets/pathways, beginning in fetal life and extending over the lifespan in the CHD population. 3) Researching the neurological effects of known and emerging neurotoxic contaminants in the CHD population, especially in the context of neonatal exposures to complex chemical mixtures from medical

devices and in daily life. 4) Understanding the biological underpinnings of neurodevelopment disability across the life course in the CHD population and elucidation of how environmental factors promote or undermine better outcomes; including the contribution of the social exposome to adverse neurodevelopmental outcomes in the CHD population. 5) Developing and testing strategies to mitigate exposures to environmental toxins in children with CHD.

Summary: Propose that NINDS include a focus on the role of environmental neurotoxicants and the neural exposome in adverse neurodevelopmental outcomes in the congenital heart disease (CHD) population. Emphasis on developmental periods, daily life exposures, social influences, and develop strategies to reduce environmental toxin exposures.

Response #9: There have been enormous advances in geospatial modeling of the external environment that go far beyond air pollution. Newer models incorporate data from google images, real estate websites, social media, USGS, and satellite remote sensing models of climate, flooding and green space. A simple but powerful method to incorporate environment into extant genetic association studies for gene X environment interactions would be to link an address and work history to case and controls to such models. While biomarker data are needed as well, this is a first step in building a neural exposome map to inform how environment modifies genetic risk and can be an independent risk factor for neurologic diseases.

Summary: Support geospatial modeling to create a neural exposome map that shows how the environment influences genetic risk and independently contributes to neurological diseases.

Response #10: It is critical to also examine the role of early life exposome on infant and early childhood neurodevelopment. To date, most of the NINDS research portfolios mainly focus on adult neurodegenerative diseases, neglecting the role of environmental exposures on early life neurodevelopment, which is a critical risk factor for adult neurodegenerative diseases.

Summary: NINDS should support environmental exposures on early life neurodevelopment, which is a critical risk factor for adult neurodegenerative diseases.

Response #11: I suggest NINDS to strongly consider emphasizing the need to study mouse models of human neurodegenerative diseases exposed to environmental factors. There is growing evidence that the immune system of mice housed in clean facilities fails to mature and to reach target tissues, including the brain, to respond to damages. The lack of exposure to environmental factors may also impact the activity of microglia, the resident immune cells of the central nervous system. Hence, it may be necessary to study mice exposed to environmental factors that also affect humans to better translate discoveries made in the bench to the clinic.

Summary: Prioritize studying mouse models of human neurodegenerative diseases exposed to environmental factors, as the immune systems of mice in sterile environments may not mature properly or respond to brain damage effectively. This exposure is crucial for translating bench discoveries to clinical applications, given its impact on the activity of microglia, the brain's resident immune cells.

Response #12: The draft does a good job of explaining how pre-existing hypotheses will be tested but I would be interested to include an analysis of individual's "life stories" to cast a net wider than what we may think are contributing factors in the exposome. Individuals could record their history in their own words in any degree of detail they'd like. Prompts to include where they lived, what they did, who their friends were, fond memories, bad memories, etc. These stories could be auto-transcribed and evaluated using natural language processing and AI to look for latent patterns that may be non-obvious a priori.

Summary: Include an analysis of individual's "life stories" to cast a net wider than what we may think are contributing factors in the exposome. Data to be evaluated with natural language processing and AI to look for latent patterns.

Response #13: I think that this is an excellent ONETOX draft. I would like to see an increased emphasis on the use of human pluripotent stem cell-derived NAMs, especially those that are scalable screening platforms, for investigating the exposome. Results from these systems, in conjunction with animal data, should form the basis of what is defined as toxin to the developing and adult nervous system.

Summary: Increased emphasis on the use of human pluripotent stem cell-derived NAMs, especially those that are scalable screening platforms.

Response #14: The proposal called for research on behavioral factors in neurological disease as one of three primary areas of research to focus on. It is not made clear in the proposal as to whether this research is on the outward behavior displayed by patients as a result of their illness, or behavior the patient is subjected to from others (ie. societal influences, trauma, etc). It is important to make this distinction because behavior that the patient displays is not a disease itself, but a symptom of an underlying pathological problem. Analyzing multiple exposure effects on multiple systems is extremely complicated. What is NINDS's plan to approach this, deep learning? I would argue that the number of variables being examined is so massive that it will be impossible to produce reliable data. Some exposures may have a stacking relationship in particular tissues/body systems and a negligible relationship in others. It will require a substantial amount of funding and an even greater amount of time to produce a reliable model. A more effective use of funds is simply to verify and distribute prior studies of single exposure relationships, which has largely been ignored and used when considering treatment options even less. Pivoting our healthcare system to a deep understanding of environmental relationships, in both diagnostics and treatments will have a massive impact and should be a top priority for the NIH. Why is climate change a focus? This seems to be a politically driven inclusion, rather than one born of scientific necessity. The effects of slight temperature change and increased precipitation will only have a mild effect on neurological disease at best. A much more appropriate focus would be to study geographical clusters of neurological disease. If there is a cluster near manufacturing plants, in urban areas, next to highways, at high elevations, cultural variations (heavier use of indoor chemicals & cleaning products in certain states), etc. this would be extremely interesting/informative, and useful for mitigating the largest risk factors. Exogenous factors need to be included in your list of biological targets: microplastics, heavy metals, radiation/radioactive substances, EMF (which needs to be measured in situ),

volatile chemical metabolites, nanoparticles, etc. These factors can be measured in blood and tissue, and are going to be more informative on disease states than endogenous factors such as genetics and microbiome. Additionally, biological targets should also include endogenous factors turned toxic/pathological, including autoantibodies/cytokines, protein aggregates, exosomes, connective tissue damage, and general histology. These may not be seen in your omics studies and are going to be key markers of disease progression and severity. This environmental research should also apply to diseases without neurological association (yet), including cancer, asthma, etc. because environmental research is such a poorly funded area of study relative to its significance. These studies also have particular relevance to Multiple Chemical Sensitivity, which affects 55 million Americans, has no diagnostic biomarkers or treatments, because it gets \$0 in NIH funding per year. This disease is extremely debilitating and potentially fatal if patients are over exposed. Studying this disease will also likely elucidate mechanisms to detoxify environmental exposures that are likely relevant to other neurological diseases. Specimen collection should also include autopsy studies. Some critical samples will be inaccessible, i.e. not all exposures are bioavailable in the blood, especially ones that cause neurological disease. Very large chunks of information needed to solve these diseases will be missing unless you do invasive biopsies/autopsies. There also needs to be a clear, and written priority for treating the pathologies that are being investigated, as well as how to educate doctors/the public on these findings. Just handling the discovery side of medicine and letting big pharma handle the treatment part is not sufficient or acceptable. Big pharma will only prioritize research of non-curable treatments that are costly, with no real concern of side effects or quality of life (or than getting it passed). They will skip over many effective treatment options because they are not patentable, or do not come in pill form.

Summary: 1) Clarify whether research on behavioral factors in neurological disease examines patients' outward behavior due to illness or the behavior they experience from societal influences and trauma. 2) Given the complexity of analyzing multiple exposure effects on various systems, it may be more effective to verify and share findings from studies on single exposure relationships. 3) Shift our healthcare system to prioritize understanding environmental relationships, as this will significantly impact diagnostics and treatments, and should be a top NIH priority. 4) Instead of focusing on climate change, prioritize studying geographical clusters of neurological diseases. 5) Include exogenous factors like microplastics, heavy metals, radiation, EMF, volatile chemical metabolites, and nanoparticles as biological targets. 6) Include endogenous factors that become toxic, such as autoantibodies, protein aggregates, exosomes, connective tissue damage, and general histology. 7) Extend environmental research to non-neurological diseases like cancer and asthma, as this area is underfunded relative to its importance. 8) Research Multiple Chemical Sensitivity, which affects 55 million Americans and lacks diagnostic biomarkers or treatments, as it receives no NIH funding and could reveal mechanisms for detoxifying relevant environmental exposures. 9) Specimen collection should include autopsy studies. 10) Clearly prioritize treating the pathologies being investigated and educate doctors and the public on these findings.

Response #15: As members of the Environmental Health Language Collaborative Data Harmonization Working Group, we are submitting comments in response to NOT-NS-24-102, Draft Strategic Priorities for Neural Exposome Research at NINDS. Briefly, the Environmental Health Language Collaborative was formed in 2021, to advance integrative environmental health research by promoting access, use and harmonization of data through interoperable terminologies and best practices. Our Data Harmonization Working Group focuses on critical issues related to facilitating and encouraging the use of harmonized

language, including (meta)data standards, to encourage data sharing and integration across diverse data resources. Exposomics research often requires the integration of diverse data types from multiple sources to enable comprehensive analysis and discovery of the environmental contributors to health. As such, we strongly encourage NINDS to incorporate the use of (meta)data standards, alignment with FAIR data principles (Findability, Accessibility, Interoperability and Reusability) and coordination and communication with other existing initiatives within NIH around data harmonization efforts into their strategic plan. As environmental health science investigators, we applaud NINDS' stated research priorities of examining interaction effects of multiple exposures on multiple biological targets/pathways and the multifactorial drivers and consequences of climate change. These complex analyses will require integrating fields from diverse data resources and potentially pooling across study populations to generate sufficient sample sizes and we are pleased to see a complementary priority within Research Resources and Tools that seeks the validation and potential harmonization of data around the exposomics data. We strongly recommend further development of this priority to go beyond lab assays and measurement approaches and extend to approaches for harmonization of existing data. There is a wide breadth of existing data that can be leveraged to address initial questions of the neural exposome, but only if those data are available and able to be successfully harmonized, pooled and analyzed. We believe NINDS should invest in developing and disseminating computational tools to assist in automated data harmonization, leveraging ontologies and other (meta)data standards, as well as expanding the existing (meta)data standards around features of the neural exposome. There are already a number of other NIH-based initiatives focused on (meta)data standards and tools for harmonization of data that would contribute to exposomics research efforts. These include the Human Health Exposure Analysis Resource, All of Us, and Environmental Influences on Child Health Outcomes. As such, we strongly encourage NINDS to pursue trans-NIH interagency and cross-sector partnerships around the use of (meta)data standards and data harmonization techniques within neural exposomics. We want to ensure consistent language across institutes and initiatives, in aims of a cohesive data ecosystem to drive exposomics research. By facilitating the use of (meta)data standards, fostering collaborative efforts and leveraging existing initiatives, NINDS can significantly enhance the impact and efficiency of neural exposome research. This integrated approach will not only promote a cohesive data ecosystem but also accelerate scientific discoveries that address the complex interactions between environmental exposures and neurological disorders.

Summary: Facilitating the use of (meta)data standards, fostering collaborative efforts and leveraging existing initiatives, NINDS can significantly enhance the impact and efficiency of neural exposome research.

Response #16: We are writing in response to your Request for Information (RFI) on the draft strategic priorities for neural exposome research. The concept of the exposome, encompassing all environmental exposures from conception onwards, is crucial for understanding the multifaceted influences on neural health and disease. The provided references highlight several key areas and approaches that align with and support the strategic priorities outlined by NINDS.

There is increased concern on the impact that prolonged exposure to apparently non-toxic doses of neurotoxicants during early development may have on children's health, possibly representing a major risk factor for neurodevelopmental disorders (NDs). The etiology of most NDs is unknown, but there is general agreement that they result from complex interaction between multiple genes conferring

vulnerability and adverse environmental factors. Exposures, whether chemical, physical, or microbiological, may act directly upon neural cells, interfering with critical processes of proliferation, migration, differentiation, synaptogenesis, programmed apoptosis and myelination, or may affect the expression of genes that regulate such embryonic/fetal/infant processes. They operate during sensitive periods of gestation by disrupting endocrine systems and altering the hormonal milieu necessary for fetal brain development. Moreover, environmental exposures could contribute to a dysregulated immune system that interacts at the molecular level with glial cells and astrocytes, creating a neuroinflammatory condition. Similarly, a lifetime of exposures, or even just early-life / in utero exposures can contribute to neurodegenerative diseases later in life. Systemic identification of chemicals and stressors that impair cognitive development and neurodegeneration is therefore needed. One holistic approach to do so is through Exposome Research.

The exposome encompasses the totality of human environmental (i.e., non-genetic) exposures, both internal and external, from conception to death, complementing the genome. It includes measuring the cumulative imprint of environmental influences and associated biological responses throughout the lifespan, including exposures from the environment, diet, behavior, and endogenous processes (Wild 2005, Wild 2009, Rappaport and Smith 2010, Wild 2011, Wild 2012). In a holistic way the exposome encompasses: 1) a life-time internal exposome including the microbiome, inflammation, and processes such as oxidative stress and lipid peroxidation, 2) the underlying external exposures such as environmental chemical, physical, and biological contaminants arising from indoor and outdoor environments, including occupation and lifestyle factors, and 3) the social, economic, ecological, and psychological factors that can affect chronic diseases (van Tongeren and Cherrie 2012). This integrative approach, combining untargeted approaches with targeted validation, requires a range of tools and techniques to capture the different domains of the exposome.

Many of these tools are already mature for deployment in community health studies, while others still require development. The last decade has seen rapid strides in various “omics” technologies to characterize downstream biological events in terms of profiles of hundreds or thousands of metabolites (metabolomics), proteins (proteomics), adductomics, immunomics, RNA expression (transcriptomics), histone modification and methylation profiles and micro- and other non-coding RNAs (epigenomics). Equally rapid development of material sciences and electronic technologies has enhanced our ability to measure and map exposures. These include, for example, sensors that measure a wide range of environmental pollutants, monitors for physiological parameters (i.e. blood pressure, heart rate, stress, physical activity, sleep patterns), GPS devices for monitoring location, mobile phones for dietary assessments and social interactions, and high resolution atmospheric models for predicting ground level pollutant levels, as well as high resolution mass spectrometry and deep sequencing, for adducts, and metabolic and epigenetic imprints. The ultimate goal is to understand the qualitative and quantitative relationships between exposures and their socio-demographic determinants and the profiles determined by the omics techniques. The challenge lies in the integrated analysis and statistical modeling of all the big data sets generated.

Critical knowledge gaps:

- Limited understanding of the cumulative effects of low-dose, chronic exposures to multiple environmental stressors on the human nervous system.

- Insufficient data on human-specific neurotoxicity pathways and their relevance to complex neurological disorders.
- Lack of validated biomarkers for early detection of neurotoxicity and prediction of long-term neurological outcomes in humans.

Key areas and approaches that align with and support the strategic priorities outlined by NINDS:

- Integration of the Neuro-exposome with the Human Exposome Project:

The Human Exposome Project, systematically explores and catalogs the exposure side of human health and disease. The envisioned Human Exposome Project will be more than a scaled exposomics approach, aiming to assess the totality of relevant exposures through ~omics of human body fluids and forming exposure hypotheses. In Hartung (2023) and Sillé et al (2024) we highlight how the Human Exposome Project aims to revolutionize our understanding of how environmental exposures affect human health by systematically cataloging and analyzing the myriad exposures individuals encounter throughout their lives. This initiative draws a parallel with the Human Genome Project, expanding the focus from genetic factors to the dynamic and complex nature of environmental interactions. The project leverages advanced methodologies such as omics technologies, biomonitoring, microphysiological systems (MPS), and artificial intelligence (AI), forming the foundation of exposome intelligence (EI) to integrate and interpret vast datasets. Key objectives include identifying exposure-disease links, prioritizing hazardous chemicals, enhancing public health and regulatory policies, and reducing reliance on animal testing. Characterization and integration of the Neuro-Exposome will be a key component of the Human Exposome Project.

- Enhanced Exposome Measurement and Analysis:

Investment in developing and standardizing methods for comprehensive exposome assessment, including advanced analytical techniques and bioinformatics tools for data integration and interpretation.

- Comprehensive Exposure Assessment:

Adopting a holistic approach to exposure assessment is essential. Utilizing advanced technologies such as high-resolution mass spectrometry (HRMS) can identify previously unknown polar organic compounds, offering a comprehensive analysis of environmental exposures impacting neural health. Sillé et al. (2020) emphasize the importance of HRMS in exposome research, demonstrating its potential in uncovering novel environmental contaminants.

- Mechanistic Understanding of Exposome-Neural Health Interactions:

o Research should focus on elucidating the mechanisms through which environmental exposures influence neural development and function. Hartung (2023) discusses the integration of multi-omics approaches, including genomics, epigenomics, and metabolomics, to uncover the biological pathways affected by environmental exposures. This mechanistic understanding is critical for identifying potential intervention points.

o Integration of multi-omics approaches (transcriptomics, proteomics, metabolomics) with advanced imaging techniques to elucidate mechanisms of neurotoxicity in human-derived systems.

- Longitudinal Cohort Studies:

Longitudinal studies are essential for capturing the dynamic nature of the exposome and its impact on neural health over time. Long-term cohort studies will provide insights into the cumulative effects of environmental exposures. These studies can inform strategies aimed at mitigating the adverse effects of harmful exposures.

- Artificial Intelligence for the Integration of Environmental and Biological Data:

- o Advanced data integration techniques are necessary to merge environmental exposure data with biological and health outcome data. Sillé et al. (2020) and Hartung (2023) highlight the potential of machine learning and artificial intelligence in managing and analyzing large datasets, facilitating the identification of critical exposure-disease relationships.

- o Hartung et al. (2023) highlights the potential impact of AI on a possible Human Exposome Project is so substantial that we should speak of exposome intelligence (EI) because this allows us to expand our limited current knowledge to the big unknown unknowns of threats to human health.

- o To establish the field of EI and facilitate implementation in the neuro-exposome field the following is needed:

- ♣ Bringing together the EI field, scoping the current landscape, definition of domains of the exposome, identifying challenges and knowledge gaps and establishing a framework to move forward.

- ♣ parison of existing EI models, benefits and limitations analysis, and development towards consensus approach.

- ♣ Establishing Best Practices principles for the EI field #1: including requirements for study designs for exposomics research, power calculators and domain-specific multiple correction procedures.

- ♣ Establishing Best Practices principles for the EI field #2: including strategies for quality assurance and quality control, replication and triangulation, standardization and harmonization.

- ♣ Establishing Best Practices for the EI field #3: including establishing validation criteria of EI, and criteria for the verification of exposure hypotheses.

- ♣ Determining the practical integration of EI with precision medicine.

- ♣ Evaluating the use of EI for regulatory purposes.

- Focus on Vulnerable Populations:

Prioritizing research on populations disproportionately affected by environmental exposures is crucial. It is important to address health disparities by studying how social determinants of health and environmental exposures intersect to influence neural outcomes. Understanding these interactions can guide targeted interventions to reduce disparities.

- Developmental and Lifespan Considerations:

- o Research should address critical windows of vulnerability, particularly during prenatal and early childhood periods, where exposures can have long-lasting effects on brain development and function.

- o Development and validation of human-relevant *in vitro* and *in silico* models for assessing neurotoxicity across the lifespan, with a focus on developmental neurotoxicity (DNT) and age-related neurodegenerative diseases.

- Policy and Public Health Implications:

Findings from exposome research should inform public health policies and interventions. Comprehensive assessment and mechanistic understanding of the exposome can guide regulations aimed at reducing harmful exposures and promoting neural health. Implementing evidence-based policies can help mitigate the burden of neurological disorders linked to environmental exposures.

- **Interdisciplinary Collaboration:**

Encourage collaborations between neuroscientists, toxicologists, epidemiologists, and social scientists to create a multidisciplinary approach to exposome research.

- **Strategies to enhance data sharing, integration and reproducibility:**

1. Promote the integration of exposome data with existing health databases and encourage data sharing to facilitate collaborative research efforts.
2. Create a centralized database for neural exposome research data, including raw data from *in vitro* assays, omics studies, and human biomonitoring.
3. Implement standardized reporting guidelines for exposome research in neurotoxicology research to improve reproducibility and facilitate meta-analyses.
4. Encourage pre-registration of study protocols and sharing of negative results to reduce publication bias.

Challenges are / there is a need for:

1. identification of (unknown) chemicals that cause neurodevelopmental disorders or neurodegeneration.
2. identification of sensitive windows of exposures that may lead to disease outcome.
3. identification of the causal associations among the human genome, environmental exposure and neurodevelopmental diseases.
4. identification of the effect of genetics and the signaling pathways which could modulate the detrimental effects of exposures
5. identification of the effect of cumulative exposure of compounds relevant to neurological disorders such as metals and specific persistent organic chemicals (e.g. organophosphate pesticides, PAHs)
6. identification of the interplay between genetic variability and co-exposure to environmental chemicals for extended periods of time and how this contributes to the development or exacerbation of central nervous system disorders during child development (neurodevelopmental disorders).
7. identification of the modifying effect of sociodemographic factors such as educational level of the parents, age of mother at birth and family SES; and dietary patterns, that can be beneficial and/or harmful for neurodevelopmental progress.
8. development of novel (wearable) devices that will monitor and measure personal exposures to toxicants via various routes (if possible throughout the course of many forming years).
9. integrated analysis and statistical modeling of all the big data sets generated.
10. Developing high dimensional analytical methods
11. With all the new omics and high dimensional data, there is a need for standardization and common nomenclature to enable to integrate and/or compare data from different studies
12. the ethical implications of integrated big data (e.g. for exposome or GEWAS) need to be considered to protect individuals from yet unknown future harm or discrimination.
13. Improved methods for measuring internal exposure and target organ concentrations of

environmental chemicals in humans.

Novel methodologies and approaches that will move the field forward:

1. Exposome research will aid with the systemic identification of chemicals that impair cognitive development and neurodegeneration
2. Genome-exposome-wide association studies (GEWAS) with adverse clinical and sub-clinical health outcomes.
3. Integrated exposome research will also inform personalized medicine for neurological disease.
4. Novel methods such as high dimensional and single-cell analysis will allow for teasing apart the contributions of different cell types and underlying pathways of disease.
5. High dimensional bioinformatics and *in silico* toxicology will integrate the results of the different 'omics' technologies aiming at connecting environmental exposure to disease outcomes and identify molecular signatures on different levels of biological organization to develop the relevant AOPs.
6. Artificial intelligence, advanced computational models and machine learning algorithms will aid in the integrated analysis of big data sets (e.g. related with exposome research / GEWAS) as well as with the identification of yet unknown compounds that cause neurological diseases.
7. Organoids and organoid intelligence (O.I.) combined with GEWAS approaches will aid in the discovery and validation of causal exposure sources and pathways for neurological disease.
8. Investigation of gene-environment interactions and epigenetic modifications in neural exposome research using human induced pluripotent stem cell (hiPSC) models.

Training needs and opportunities:

1. Develop interdisciplinary training programs that combine expertise in neuroscience, toxicology, bioinformatics, and computational modeling.
2. Provide workshops and courses on the design, implementation, and interpretation of Exposome and novel tools and models (incl. NAMs) for neurotoxicity assessment.
3. Create opportunities for early-career researchers to engage in collaborative projects that bridge traditional disciplinary boundaries in neural exposome research.

Potential partnerships:

1. Collaborate with the US Environmental Protection Agency (EPA) and the National Toxicology Program (NTP) to align neural exposome research with ongoing efforts to modernize toxicity testing.
2. Partner with patient advocacy groups and clinicians to ensure research priorities address the most pressing needs of individuals affected by neurological disorders.
3. Engage with international organizations (e.g., OECD, WHO) to harmonize approaches and share best practices in neural exposome research.

By considering these key areas, the NINDS can advance neural exposome research, contributing to the prevention and treatment of neurological disorders. The alignment of these research priorities with the NINDS mission will foster innovation and drive significant progress in understanding and mitigating the impact of environmental exposures on neural health.

Thank you for considering our input. We look forward to the continued advancement of neural exposome research and its contributions to public health.

Summary: Emphasize the critical role of environmental exposures from conception onwards in neural health and disease. Highlighting the impact of prolonged, low-dose neurotoxicant exposure on neurodevelopmental disorders, we stressed the need for a comprehensive approach, integrating omics technologies and longitudinal studies to uncover the mechanisms of neurotoxicity. Also advocate for including various exogenous and endogenous factors as biological targets, focusing on vulnerable populations, and leveraging advanced data integration and AI to enhance exposome research. By addressing these gaps and promoting interdisciplinary collaboration, NINDS can drive significant progress in understanding and mitigating the impact of environmental exposures on neural health.

Response #17: The working group priorities appear very promising. Looking at the effects of multiple variables, in multiple facets, is going to be key to developing the understanding of neurological disorders to the necessary depth required for effective treatments, and/or prevention. One component that did not appear to be included in any of the descriptions of the pollutants, toxins, etc. that will be analyzed was that of toxins ingested by diet. The US has dramatically different guidelines than the EU regarding what is allowed in the food and products individuals use and consume. This variability has the potential to be an impactful factor. The draft mentioned the differences in manifestations of diseases such as ALS and Parkinson's, but there should also be consideration as to why individuals exposed to the same environment, toxins, pollutants, etc. may or may not develop a disease such as ALS at all.

Summary: Include the impact of dietary toxins and investigate why some people exposed to the same environmental factors develop diseases. Take into consideration product guidelines by different countries.

APPENDIX H. Public Comments Provided at the NEXT WG Webinar on Draft Neural Exposome Research Priorities

1. I would like to offer brief comments advocating for a life-course approach that is inclusive of reproductive and pregnancy (including the placenta) as it influences the dynamic neural exposome across the life span. Three critical windows during which neuroplasticity changes have critical/sensitive effects based on gene-environment interactions: the first 1000 days, adolescence, and reproductive senescence. Addressing health disparities is the paramount challenge to offer healthcare equity with interventions that integrate prevention, rescue, and reparative strategies. Advocacy must emphasize women and children through DEI who will later experience toxic stressor interplay across the lifespan with transgenerational effects and consequences (Scher, Front. Neurology 2024).
2. A similar range of exposomic factors has been adopted by the World Federation of Neurology Environmental Neurology Specialty Group (ENSG). A global approach to this subject includes attention to natural, as well as synthetic, chemicals with neurotoxic potential, in normal and abnormal nutritional states. For example, environmentally tolerant plants like cassava and grass pea (i.e., complex chemical mixtures) are major sources of food on the African continent, and both induce pockets of highly prevalent irreversible neurological disease. ENSG incorporates the principles of One Health and Development Origins of Health and Disease.
3. One comment I have is the conceptual definition of 'mechanism'. Mechanism do not need to be only cellular/biological. Mechanisms can be social, physical, chemical, or psychological that respects the breadth of the factors you aim to study. For example, Snow discovered that the mechanism of a cholera epidemic (which affects the brain!) was a water pump, and removing its handle is the treatment. To foster interdisciplinary teams, a more open understanding of mechanism would encourage other specialists to engage. Has this line of thinking been considered?
4. In the interest of expanding the study of spontaneous disease in companion animals (which is an excellent idea), it will be important to include ensure veterinarians, veterinary residents, and veterinary clinician scientists are included in your opportunities for training grants, supplements, and research teams. It will also be important that there is well-represented veterinary/comparative expertise included in review panels. Also, neuropathologists can play a useful role in addition to neurologists.
5. In earlier slides, I got the impression that outcome measures of the exposome, in terms of molecular outcomes, were somewhat narrowly tailored to changes in gene expression and the epigenome. My question, therefore, is to what extent has the working group considered effects of the exposome on protein function that may not impact gene expression or epigenetic regulation, but nevertheless cause adverse neurological outcomes, which may or may not lead to gene/genome effects.
6. I would add that in urban environments there is a large amount of household pesticides used. In public housing, there is typically pest control, but many individuals go out and use pesticides on their own. Many studies have also shown that pesticides used in other countries can often be readily available in communities and have resulted in poisoning of children and individuals.
7. Consider for theme #6: partnership with NIH studies such as HEAL, ABCD and the Human Placenta project, philanthropy partnering with NIH such as the Allen Institute and Melinda Gates Foundation and the WHO focused on the 17 sustainable development goals particularly through the Global South.

8. A recent paper offers a strategy to research and discover factors underlying the etiology of long-latency neurodegenerative diseases: “Early-onset, conjugal, twin-discordant, and clusters of sporadic ALS: Pathway to discovery of etiology via lifetime exposome research.” <https://pubmed.ncbi.nlm.nih.gov/36860617/>