Draft Priorities for Neural Exposome Research at the NINDS: Recommendations from a Working Group of the National Advisory Neurological Disorders and Stroke Council

Background

The term "exposome," coined by Chris Paul Wild in 2005, encompasses "life-course environmental exposures" (Wild, C.P., 2005, Cancer Epidemiol Biomarkers Prev. 14(8):1847-50). Neural exposome research focuses on the noninheritable factors that influence neurological disorders, diseases, and damage to the brain and nervous systems, including those that may be affected by epigenetic changes. The National Institute of Neurological Disorders and Stroke (NINDS) seeks to promote neural exposomic research by engaging the neuroscience community across the basic-translational-clinical continuum to focus on the effects of exogenous (e.g., environmental toxicants and climate), endogenous (e.g., microbiome and epigenetic mechanisms), and behavioral (e.g., psychosocial stress and lifestyle) risk factors on neurological health and resilience (Tamiz AP, et al, 2022, Neuron. 110(8):1286-1289). In 2022, the NINDS established the Office of Neural Exposome and Toxicology Research (ONETOX) to support a new emphasis on neural exposome research within the NINDS mission.

To guide near- and medium-term efforts to cultivate neural exposome research, NINDS has embarked on a two-phased strategic planning effort. Phase one, which began in 2023, is being 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), which is composed of investigators with basic, pre-clinical, and clinical research expertise in neurobiology, diverse neurological conditions, and exposomic research (see Roster below). The NEXT WG is 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). The NEXT WG is also developing recommendations for engaging interdisciplinary teams and what tools and resources are needed (or could be leveraged) to cultivate neural exposome research. 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 plan.

Since November 2023, the NEXT WG has met five times as a full group and several more times in subgroups to review and discuss the current state of neural exposomic, identify research gaps and opportunities, and develop research priorities. Additionally, the WG participated in two NINDS-sponsored mini-workshops: Team Science to Advance Neural Exposome Research on February 29, 2024, and The Right Tools and Resources for Neural Exposome Research on April 19, 2024. This report contains the NEXT WG's draft priorities for advancing neural exposomic research at NINDS, which are being made available for public input via a Request for Information (NOT-NS-24-102) and an open session of the final meeting of the WG on July 15, 2024. Following public comment, the NEXT WG will deliver their final recommendations for neural exposome research priorities to the full NANDS Council on September 4, 2024, and the report will be made available to the public on the NINDS ONETOX webpage.

DRAFT Priorities Neural Exposome Research at NINDS

The NANDS Council Working Group on Neural Exposome Top Priorities (NEXT) has identified several draft priority areas to guide NINDS's efforts in neural exposome research for the next 5 to 10 years. The neural exposome is defined as the integrated compilation of the physical, chemical, biological, and social influences on nervous system function. Three areas were selected for special emphasis (*<u>*underlined and italicized in the larger list below*</u>):

- Shifting research studies from those that focus on single environmental exposures to research that assesses the composite effect of multiple exposures on multiple biological targets, with a focus on climate change that impacts external, internal, behavioral, and social stressors.
- Leveraging NINDS's global leadership in fundamental neuroscience to advance mechanistic research into how the exposome influences neurological health and resilience.
- Investigating the neurological impacts of environmental pollution, including known and emerging neurotoxic contaminants.

The NEXT WG's full list of draft priorities and action items are listed below and organized under the following themes: 1) Priority research areas to address key data gaps, 2) Mechanistic Research, 3) Public Health, Clinical, and Interventional Research, 4) Research Resources and Tools, 5) Research Workforce, and 6) Collaborations and Partnerships.

1) **Priority research areas to address key data gaps:** Several big-picture themes emerged that cut across disciplines and the research spectrum (basic, pre-clinical, clinical, implementation science, public health, etc.). Action items for NINDS include:
    - <u>*Emphasize understanding the interactive effects of multiple exposures on multiple biological targets/pathways**</u>. To date, most research on environmental exposures has largely focused on singular exposures and/or a limited set of biological effects from such exposures. To move towards a truly multi-omics approach, NINDS needs to enable multi-factor research studies that assess the composite effects of multiple exposures on broad arrays of biological targets (e.g., microbiome, genome, epigenome, lipidomics, transcriptome, metabolome). This is critical as exposomics reflects the real-life time varying complex mixtures that impact human health across the life-course.
    - <u>*Understanding and addressing the neurological effects of climate change**</u>. Specific topics include:
        - Temperature and extreme weather events – extremes and unpredictable swings in temperature are linked to several neurological diseases but they are understudied in the context of nervous system health.
        - Geographic and social disruption and displacement (and attendant social factors, e.g., food, housing, and economic insecurity), including displacement of wildlife (e.g., vector borne diseases).

- Indirect effects of climate change may also impact health (e.g., nutritional content of food, increased use of pesticides, effects of stress on mental health).

- *Researching the neurological effects of known and emerging neurotoxic contaminants, including:*
    - Pollution, including air, water, and ground pollution.
    - Pesticides and persistent organic pollutants – use and distribution are increasing with climate change and these environmental chemicals are understudied in the context of nervous system health.
    - Plastics, microplastics, nanoplastics.
- Leveraging socio-biological research to promote brain health equity, including:
    - Develop a "neurocentric" social exposome/social determinants of health tool kit that assesses social exposome measurement instruments (e.g., questionnaires on stress, hormone biomarkers, collated geospatial models of neighborhood stressors such as area deprivation index, crime statistics, built environment, neighborhood socioeconomic status, collection protocols for salivary cortisol rhythms, etc.) that researchers could employ to link to biological measures, such as epigenomic/transcriptomic assays.
    - Leverage other NIH efforts focused on behavioral and social factors to integrate impacts of external/internal factors on neurological outcomes.
    - Focused research to better define how the life course exposome contributes to disparities at the individual and community levels, including how the adverse social exposome influences biology to produce disease.

2) ***Mechanistic Research: NINDS should leverage its leadership in fundamental neuroscience to advance mechanistic research & identify mitigation targets*.***

A major focus for NINDS should be developing the basic biological understanding the ways internal, external, 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, amyotrophic lateral sclerosis (ALS) and Parkinson's disease are linked to common environmental exposures but exhibit different neurological outcomes – why? This mechanistic research should unlock avenues to design interventions that mitigate toxicity and/or disease progression. Action items include:

- Define the biological underpinnings of neurological resiliency across the life course and elucidate how environmental factors promote or undermine neurological resilience.

- Promote research on how diverse environmental factors interact to promote neurological disease:
    - Examine interactive effects between social and behavioral factors with external/internal factors.
    - Research complex mixtures of chemicals.
    - Identify mechanisms by which multiple environmental stressors interact with other 'omic factors—genome, epigenome, microbiome, transcriptome, metabolome—to influence individual risk of neurological disease.
- Identify mechanisms by which diseases in other organ systems (especially cardiovascular, hepatic, pulmonary, epithelial) influence neurological diseases.

3) **Public Health, Clinical, and Interventional Research:** Human 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 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 (i.e., DOHaD).
    - 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.
    - Develop and test strategies to mitigate exposures, including studies to better understand, assess, and expand resilience.

4) **Research Resources and Tools**: Exposomic research, by definition, will require interdisciplinary approaches across all biological levels. This will result in the generation and integration of large, complex data sets of big data to identify exposomic factors that drive individual risk for neurological disease. Currently, the existing research platforms and tools are predominantly in the early development stage. Even when well-developed, these tools 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 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. 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. Ideally, patients recruited to studies should prospectively provide, with consent, a diverse range of biosamples, e.g., blood, urine, cerebrospinal fluid, from which to quantify exposures, e.g.,

metals, pesticides and assess biological consequences. Infrastructure 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.

- Validation and harmonization of exposome assays, metrics, and measurement approaches across the life course (e.g., early-life and occupational exposures).
- Develop assays and exposure models to measure current and prior exposure to toxicants.
    - Wearables, monitors, m-health apps.
    - Climate, pollution, built environment and social environment spatial models.
    - In vivo brain imaging modalities for measuring biomarkers of exposure and effect in the brain.
    - Identify 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, chemicals in shed baby teeth, etc.
- Define biosamples and measures that should be uniformly collected and applied across the exposome field to enable aligned, harmonized study and assessment.
- Develop resources/approaches to collect and analyze life-course geo-spatial data to better delineate the role of place in neurologic disease.
- Develop templates or guidelines for integrating relatively low-cost add-on collection of biospecimens (what specimens to collect, how to collect/store samples) and exposome variables (ambient temperature, air quality, occupation of patient) into the design of clinical and other population-based studies.
- Urgent need for integrative pathway analyses for assessing the impact of multiple environmental perturbations on an individual's nervous system – harness machine learning and AI.

- Infrastructure: Investments in core research to develop the infrastructure needed to provide technical and methodological support to facilitate neural exposome research.
    - Develop guidelines and invest in tools for sample collection, storage, and analysis, including harmonization of protocols for laboratory and data analyses.
    - Develop guidelines for neural exposome research that address ELSI considerations 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.

- Developing new model systems:
    - Design novel 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 (https://www.nationalacademies.org/event/12-09-2021/new-approach-methods-nams-for-human-health-risk-assessment-workshop-1).
    - 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.

5) **Research Workforce:** The transdisciplinary nature of exposome research requires supporting and building highly skilled multi-disciplinary teams that include clinical researchers, basic scientists, bioinformaticians, data scientists, etc. Action items include:

- Train and educate:
    - 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:
    - Attract new talent by supporting neural exposome projects that deliberately require different disciplines to work together (e.g., neuroscientists, computational metagenomics experts, geographers, etc.).
    - 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:
    - 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.

6) **Institutional Collaborations and Partnerships:** 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, e.g., add brain health to NIH's "All of Us" or leverage NIEHS's Human Health Exposure Analysis Resources. In addition, studies of 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 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, and FDA and has expertise in high-throughput screening approaches).
- Offer supplements to awards administered by other NIH Institutes and Centers 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.
- Build partnerships with government agencies that track and/or set standards for environmental quality (e.g., EPA, NOAA, FDA, USGS, NASA satellites).
- Engage in interagency/cross-sector efforts to establish a national (global) toxicant registry with exposure (e.g., air pollution, herbicides and pesticides, nanoplastics, etc.) 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 ScHARe (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 to learn from their experience.

Acronym Key

ALS: amyotrophic lateral sclerosis

PD: Parkinson's disease

CDC: Centers for Disease Control and Prevention

CTSAs: Clinical and Translational Science Awards (supported by NCATS)

ELSI: Ethical, Legal and Social Implications

EPA: Environmental Protection Agency

FDA: Food and Drug Administration

HHS: Department of Health and Human Services

IDDRCs: Eunice Kennedy Shriver Intellectual & Developmental Disabilities Research Centers (supported by NICHD)

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

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

NINDS: National Institute of Neurological Disorders and Stroke/NIH

NIOSH: National Institute for Occupational Safety and Health

NOAA: National Oceanic and Atmospheric Administration

NSF: National Science Foundation

ScHARe: Science Collaborative for Health Disparities and Artificial intelligence bias Reduction (supported by NIMH)

WG: Working Group

USGS: United States Geological Survey

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