Concept Clearance

Branch: Genes, Environment and Health

Council Period: 06/2025

Concept Title: Impact of environmental exposures on gut-brain signaling in neurological conditions

Introduction

Background:

The gut microbiome describes the collective genomes of the trillions of bacterial cells that reside within the gastrointestinal tract. Microbiota produce metabolites that impact human host cells in a myriad of ways through metabolic and immune pathways, contributing to host homeostasis. As a natural interface between host cells and environmental perturbations, the gut microbiome is instrumental in the protection from xenobiotic insults, and in mediation of the adverse effects of environmental factors on the host. Further characterization of the role microbes play in modulating chemical exposure, and the role exposures play in shaping the human microbiome and integral host pathways may provide valuable insight into the prevention or amelioration of the adverse effects of chemical exposure.

The interaction of the gut microbiome with the central nervous system has been an area of growing interest in the neuroscience community. The gut-brain axis consists of all bidirectional communication between the intestine and the central nervous system, and it's becoming increasingly apparent that the gut microbiome facilitates many of the signaling pathways that make up this network, either through direct stimulation of the vagus nerve, production of neuroactive microbial metabolites, or through promotion of neuroinflammation. Clinical associations and studies in animal models suggest mechanistic involvement of gut microbial regulation in the pathogenesis of various neurological disorders, including Parkinson's disease, Alzheimer's disease, and autism spectrum disorder. Given the growing evidence of the role for environmental exposures in neurological disorders, pursual of the gut microbiome and the gut-brain axis as targets for prevention and intervention warrants further exploration.

NIEHS has led a series of workshops highlighting the gut-brain axis as a promising archetype for realizing the capacity of the gut microbiome to modulate host response to chemical exposures. Collectively, these meetings underscored how exposures and the microbiome impact the brain across the lifespan, showcased multiple model systems that can be leveraged to answer these questions, and emphasized the need for more mechanistic data on target pathways linking these complex systems. Additionally, participants discussed opportunities for gut-focused detection, prevention, and intervention strategies to decrease etiological risk, slow progression, or possibly reverse neurological condition(s).

With the increased appreciation of precision environmental health for advancing predictive toxicology, as promoted in the 2025-2029 NIEHS Strategic Plan, it is a crucial time to substantiate the ability of human microbiomes to offer insight into interindividual variability in neurologic toxicity, pathogenesis, and therapeutic responses. Focused investment in the convergence of exposures, the gut microbiome, and neurological pathways is needed to ultimately take the science from characterization and association to more actionable data.

Research Goals and Scope

The overarching goal is to expand and leverage the role of the gut microbiome-brain axis for improved detection, prevention, and intervention strategies for environmental exposure-induced neurological diseases. Given this objective, impactful projects would require strong interdisciplinary collaboration.

The scope of this program would be inclusive of a wide range of neurological outcomes given overlapping gut-brain signaling pathways and the prevalence of comorbidities. For conditions where the environmental exposure-gut-brain connection is less defined (bipolar disorder, schizophrenia, etc.), investigators may generate necessary preliminary data and robust hypotheses to bolster intervention studies. Others, for which there is greater evidence for a toxicant-gut-neurological outcome association (Parkinson's disease, Alzheimer's disease, etc.), researchers would focus efforts on experimentally addressing detection, prevention, or intervention in the context of the stated hypotheses**.**

Categories of research supported by this program may include:

- refinement or development of models, methods, and tools that have not been previously leveraged or positioned for the study of gut-brain axis in the context of environmental health
- expanding knowledge of how other systems (liver, lung, etc.) interact with the gut-brain-exposure paradigm
- impact of exposures on neuroactive metabolites (including neurotransmitters) produced from gut microbiota that affect brain function
- development of molecular biomarkers for disease onset and progression derived from microbiome metabolomics
- combined effects of genetic, epigenetic, and environmental factors on regulation of the gut-brain axis
- mechanistic and observational studies in samples from patients with known exposure histories to determine the modifiable effects of microbiota composition and function
- pre-clinical approaches for testing pre- and probiotics and other interventions that reduce onset and progression of a toxicant-induced neurological condition

Justification

NIEHS staff is considering strategies to stimulate interdisciplinary collaborative research on how environmental exposures impact gut-brain signaling to develop interventions for neurological conditions. During the development of this program other NIH institutes that have expressed interest in participating include NIMH, NIA, NIDDK and NINDS.

Funding opportunities for this program are applicable to 2025-2029 NIEHS Strategic Plan Research Areas of Emphasis #2 (Precision Environmental Health) and #3 (Mechanistic Biology and Toxicology).

Proposed Timeline:

Council Concept Clearance: June 2025
RFA Release Date: October 2025
Application Due Date: January 2026
Peer Review Date: March 2026
Council Review Date: June 2026
Earliest Anticipated Start Date: July 2026