

Concept Clearance

Branch: Genes, Environment and Health

Council Period: 201801

Concept Title: Environmental Risks for Psychiatric Disorders

Introduction

Background: Every year, an estimated one in five adults in the US are affected by some mental illness, suffering conditions such as schizophrenia, major depression and bipolar disorder. The public health burden is immense, as these disorders represent the major cause of disability in the US and account for over \$300 billion in total national costs per year. Further, the societal burden of these diseases includes loss of work productivity, divorce, suicide, accidents and accidental drug overdoses. While the exact cause of most mental illnesses is unknown, the interaction between genetic susceptibility and environmental exposures is likely a contributing factor.

NIEHS has a long history of supporting many projects focused on how environmental exposures impact brain and behavioral endpoints. For example, since 1998 the NIEHS/EPA Children's Environmental Health and Disease Centers (or Children's Centers) have funded projects focused on trying to understand how environmental toxicants and living in unhealthy environments may contribute to dysfunction of the nervous system during development. Most recently, NIEHS has invested funds to solicit applications on understanding the environmental contributors to risk and expression of autism spectrum disorders (ASD; PAR-10-202). Despite a small but growing body of research in the NIEHS portfolio studying psychiatric conditions with early onset (e.g. ADHD, ASD), there has been a paucity of NIEHS-supported research examining psychiatric disorders with clinical symptoms emerging in later adolescence or early adulthood.

As emerging evidence over the past decade link toxicant exposure with central nervous system and behavior changes consistent with disorders ranging from schizophrenia to depression, it is important to understand how environment exposures can affect the underlying biological pathology of these disorders. In March 2017, NIEHS sponsored a workshop that brought together experts in the fields of psychiatry, fundamental neuroscience, human genetics, immunology and environmental health sciences to identify common pathways and mechanisms implicated in psychiatric disorders that are potential targets of environmental exposures. This meeting also highlighted opportunities for developing, adapting and harnessing the use of novel tools and resources from these diverse fields to study disorders with heterogeneous symptomology. However, a number of key data gaps emerged during the meeting, including (1) limited awareness and application of dimensional approaches to behavioral and neurobehavioral measures (e.g., Research Domain Criteria, RDoC) in the field of environmental health; (2) few existing human studies with reliable exposure and clinical measures, powered sufficiently to assess the association of exposure with psychiatric conditions or to uncover gene environment interaction; (3) incomplete understanding of inflammatory responses to diverse xenobiotics (e.g., diet, infectious agents, environmental chemicals) and how these may contribute to development of psychiatric conditions, and (4) uncertainties about the role of epigenetics as a potential mediator and/or biomarker in exposure-psychiatric disease associations. **Based on the opportunities and challenges identified in this workshop, NIEHS is in a unique position to encourage investigators to tackle many of these challenges and stimulate this understudied area of research.**

Research Goals and Scope

Vision for developing an NIEHS-supported program in psychiatric disorders

The overarching goal of the proposed program is to support innovative basic, epidemiological and interdisciplinary research to understand the role of and mechanisms by which environmental exposures disrupt normal brain and behavioral functioning to increase risk for psychiatric disorders. However, there are several obstacles that must be overcome to build an impactful and sustainable program in mental health at NIEHS, including (1) little history of interaction between the psychiatric research community and environmental health scientists, (2) inconsistent evidence for particular environmental exposures that are directly linked to a developing psychiatric condition, and (3) lack of awareness in the extramural community that environmental factors in the broad range of mental health disorders is of NIEHS interest (or assuming the topic falls exclusively under NIMH purview.)

To address these challenges, a multi-phased approach is proposed to systematically build the capacity and awareness of the new NIEHS program:

Step 1: PAR – To stimulate the interest of investigators in developing proposals that address a mechanistic understanding for the role of environmental factors in psychiatric disorder etiology and to provide a consistent review climate for those applications, one with a critical mass of expertise in psychiatric disorders as well as environmental health science/toxicology, a

Program Announcement (PAR) with a special review and multiple receipt dates is proposed. Investigators will be encouraged to go beyond strict diagnostic boundaries to examine dimensional aspects of psychopathology that may be associated with environmental exposures. A diversity of approaches and exposures of interest are needed to advance this field of research and will be solicited by the PAR, with the intent to have the broadest possible impact. Additional areas of interest that will be highlighted in the PAR include topic areas and challenges identified from the 2017 workshop discussed above, as well as additional key knowledge gaps in the field:

- Assessment of developmental neurotoxicant exposure and mental disorder risk in adulthood
- Investigation of multiple environmental factors (microbial pathogens such as viruses, diet substance use, exercise level, stress) in combination with toxicant exposures may protect or facilitate progression of a psychiatric condition
- Identification of common neuronal mechanisms and circuits underlying mental disorder susceptibility following environmental exposure
- Analysis of the interaction of environmental exposures, peripheral (e.g., gut) and central nervous system signaling on mood and mental health.

In conjunction with the PAR, a variety of other activities are planned to increase interaction between mental and environmental health communities, as well as increase the visibility of NIEHS in the field. First, NIEHS and NIMH Program staff are in the process of generating a post-meeting manuscript from the 2017 workshop on the data gaps and future directions for research when considering environmental factors in risk for mental disorders. Additionally, planning for seminars on environmental contributors to mental health at conferences where there is very little to no environmental scientist presence (e.g., American Psychiatric Association, Society for Neuroscience) are underway. It is also expected that annual in-person grantee meetings for awardees under the PAR will be planned so that investigators can meet each other and present their work.

Step 2 – R21 – As the research capacity, awareness and interest generated from the PAR builds in Step 1, we anticipate implementing a follow-up exploratory/developmental funding announcement through the R21 mechanism. The purpose of this targeted funding opportunity is to encourage mental health and environmental science experts to collaborate and propose “higher risk” projects where there is less evidence for an environmental exposure link (such as behaviors consistent with PTSD and bipolar disorders). When appropriate, it is expected that applications utilizing a basic mechanism approach will incorporate well-justified animal models of psychiatric disorders (e.g., deficit in pre-pulse inhibition of the startle reflex response in schizophrenia, forced-swim that models learned helplessness in depression) while applications with an epidemiology/human study approach will be encouraged to leverage existing data sets and cohorts.

Step 3 – R01 – The long-term vision of this new NIEHS program is to increase the number of investigators exploring the biological underpinnings of environmental factors in psychiatric disorders by expanding the use of existing cohorts/data sets in well characterized populations and/or advancing approaches for mechanistic studies in model systems. As the program matures in a 4-5 year timeframe (which will likely partially overlap with Step 2), an R01 announcement will be utilized for projects where there is a greater evidence for a toxicant association (e.g., chronic low level lead exposure and development of symptoms linked with depression/schizophrenia) and that warrant the extended (i.e., 5 year) period of funding.

Mechanism and Justification

As discussed above, NIEHS staff is proposing a multi-phased approach that takes advantage of PAR, R21 and R01 mechanisms to build the capacity and awareness of studying biological factors underlying the effects of environmental exposure in the context of psychiatric disorders. During the development of this program other NIH institutes that have expressed interest in participating include NIMH, NIDA and NIAAA. Therefore, the funding opportunity may be broadened (particularly at the Step 1 phase) to allow for proposals focused on the impact of nutrition, diet, stress, drugs of abuse and pharmacotherapies on psychiatric conditions.

Funding opportunities for this program are applicable to NIEHS Strategic Goal 1 (fundamental research), Goal 2 (exposure research) and Goal 4 (understanding how combined exposures affect disease pathogenesis).

Proposed Timeline for Step 1 (PAR, no set aside money requested):

RFA Release Dates: April 2018

Application Due Dates: July 2018, July 2019

Peer Review Dates: Fall 2018, Fall 2019

Council Review Dates: February 2019, February 2020

Earliest Anticipated Start Date: March 2019, March 2020

Proposed Timeline for Step 2 (R21, \$1.4 million per year to fund 4-5 awards)

RFA Release Date: April 2019
Application Due Date: July 2019, July 2020, July 2021
Peer Review Date: Fall 2019, Fall 2020, Fall 2021
Council Review Date: February 2020, February 2021, February 2022
Earliest Anticipated Start Date: March 2020, March 2021, March 2022

Proposed Timeline for Step 3 (R01)

Set aside funds requested and timing based on success of Steps 1 and 2, so TBD.