Department of Health and Human Services
Part 1. Overview Information

Participating Organization(s)

National Institutes of Health (NIH (http://www.nih.gov))

Components of Participating Organizations

National Institute of Mental Health (NIMH (http://www.nimh.nih.gov))

Funding Opportunity Title

Understanding and Modifying Temporal Dynamics of Coordinated Neural Activity (R01 Clinical Trial Optional)

Activity Code

R01 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=r01&Search.x=0&Search.y=0&Search_Type=Activity) Research Project Grant

Announcement Type

Reissue of PAR-17-466 (https://grants.nih.gov/grants/guide/pa-files/PAR-17-466.html)

Related Notices

None

Funding Opportunity Announcement (FOA) Number

PAR-18-555

Companion Funding Opportunity

PAR-18-554 (https://grants.nih.gov/grants/guide/pa-files/PAR-18-554.html), R21 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=r21&Search.x=0&Search.y=0&Search_Type=Activity) Exploratory/Developmental Grant

Number of Applications

See Section III. 3. Additional Information on Eligibility.

Catalog of Federal Domestic Assistance (CFDA) Number(s)

93.242

Funding Opportunity Purpose

A rich body of evidence suggests that optimal cognitive, affective, and social processes are associated with highly coordinated neural activity. These findings suggest that oscillatory rhythms, their co-modulation across frequency bands, spike-phase correlations, spike population dynamics, and other patterns might be useful drivers of therapeutic development for treatment of cognitive, social, or affective symptoms in neuropsychiatric disorders. This funding opportunity supports projects that test whether modifying electrophysiological patterns during behavior can improve cognitive, affective, or social processing. Applications must use experimental designs that incorporate active manipulations to address at least one, and ideally more, of the following topics: (1) in animals or humans, determine which parameters of neural coordination, when manipulated in isolation, improve particular aspects of cognitive, affective, or social processing; (2) in animals or humans, determine how particular abnormalities at the genomic, molecular, or cellular levels affect the systems-level coordination of electrophysiological patterns during behavior; (3) determine whether in vivo, systems-level electrophysiological changes in behaving animals predict analogous electrophysiological and cognitive improvements in healthy persons or clinical populations; and (4) use biologically-realistic computational models that include systems-level aspects to understand the function and mechanisms by which oscillatory and other electrophysiological patterns unfold across the brain to impact cognitive, affective, or social processing. This FOA uses the R01 grant mechanism, whereas its companion funding opportunity seeks shorter, higher-risk R21 grant applications.

Key Dates

Posted Date

January 02, 2018

Open Date (Earliest Submission Date)

January 5, 2018

Letter of Intent Due Date(s)

Not applicable.

Application Due Date(s)

Standard dates (//grants.nih.gov/grants/guide/url_redirect.htm?id=11111) apply, by 5:00 PM local time of applicant organization. All types of non-AIDS applications allowed for this funding opportunity announcement are due on these dates.

Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.

AIDS Application Due Date(s)

Standard AIDS dates (//grants.nih.gov/grants/guide/url_redirect.htm?id=11112) apply, by 5:00 PM local time of applicant organization. All types of AIDS and AIDS-related applications allowed for this funding opportunity announcement are due on these dates.

Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.

Scientific Merit Review

Standard dates (//grants.nih.gov/grants/guide/url_redirect.htm?id=11113) (http://grants1.nih.gov/grants/funding/submissionschedule.htm#reviewandaward) apply.

Advisory Council Review

Standard dates (//grants.nih.gov/grants/guide/url_redirect.htm?id=11113) (http://grants1.nih.gov/grants/funding/submissionschedule.htm#reviewandaward) apply

Earliest Start Date

Standard dates (//grants.nih.gov/grants/guide/url_redirect.htm?id=11113) apply.

Expiration Date

January 8, 2021

Due Dates for E.O. 12372

Not Applicable

Required Application Instructions

It is critical that applicants follow the Research (R) Instructions in the SF424 (R&R) Application Guide (//grants.nih.gov/grants/guide/url_redirect.htm?id=12000), except where instructed to do otherwise (in this FOA or in a Notice from the *NIH Guide for Grants and Contracts* (//grants.nih.gov/grants/guide/)). Conformance to all requirements (both in the Application Guide and the FOA) is required and strictly enforced. Applicants must read and follow all application instructions in the Application Guide as well as any program-specific instructions noted in Section IV. When the program-specific instructions deviate from those in the Application Guide, follow the program-specific instructions. **Applications that do not comply with these instructions may be delayed or not accepted for review.**

There are several options available to submit your application through Grants.gov to NIH and Department of Health and Human Services partners. You **must** use one of these submission options to access the application forms for this opportunity.

1. Use the NIH ASSIST system to prepare, submit and track your application online.

   Apply Online Using ASSIST

2. Use an institutional system-to-system (S2S) solution to prepare and submit your application to Grants.gov and eRA Commons (http://public.era.nih.gov/commons/) to track your application. Check with your institutional officials regarding availability.

3. Use Grants.gov (../ApplyButtonSplash.cfm?oppNum=PAR-18-555) Workspace to prepare and submit your application and eRA Commons (http://public.era.nih.gov/commons/) to track your application.

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Part 2. Full Text of Announcement

Section I. Funding Opportunity Description

Purpose

The purpose of this funding opportunity announcement (FOA) is to lay the groundwork for developing systems-level neuroscience interventions into treatments for cognitive, affective, or social deficits in psychiatric disorders. A rich body of knowledge exists regarding the systems-level coordination of temporal patterns of electrophysiological activity in the brain. One key principle that has emerged from basic systems-level neuroscience is that brain rhythms appear to be necessary for normal cognition, including phase-amplitude coupling of slow and fast rhythms, spike-phase correlations such as hippocampal theta precession, and the re-activation of previously experienced neural activity on specific oscillatory frequencies. On the clinical side, cognitive symptoms in particular are among the least tractable and most disabling problems across a wide range of brain disorders, including autism and schizophrenia, because they affect the ability to live independently, such as holding a job and managing a bank account. Almost none of the existing treatments for neuropsychiatric illnesses were developed for the purpose of modulating systems-level coordination of neural activity, yet this is the level at which brain processes such as attention, memory, and social processing emerge. Even for medications that are based on a rational understanding of single-gene disorders, such as Fragile X, Rett, or Angelman syndromes, it has been surprisingly difficult to ameliorate cognitive, affective, or social symptoms in patients with these disorders. However, these medications act at the molecular level, and they might not have a useful effect at the systems level. Therefore, it might be advantageous and even necessary to begin to address cognitive, affective, and social domains of function with a greater consideration of the systems-level electrophysiological patterns, and to test whether modulating these patterns can improve function. The key idea is to evaluate any intervention, whether pharmacological or not, at the systems level rather than exclusively at the molecular level. Evaluating interventions at the systems level might be helpful regardless of whether the interventions themselves are at the genetic, molecular, or cellular level via pharmacology or gene editing, or whether the intervention is at the systems level such as electrical or magnetic stimulation. The purpose of this FOA is to seek applications that use active manipulations to address at least one, and ideally more, of the following points: (1) in animals or humans, determine which parameters of neural coordination, when manipulated in isolation, improve particular aspects of cognitive, affective, or social processing; (2) in animals or humans, determine how particular abnormalities at the cellular or molecular level, such as specific receptor dysfunction, affect the coordination of electrophysiological patterns during behavior; (3) determine whether in vivo, systems-level electrophysiological changes in behaving animals predict analogous electrophysiological and cognitive improvements in normal humans or clinical populations; and (4) use systems-level computational modeling to develop a principled understanding of the function and mechanisms by which oscillatory and other electrophysiological patterns unfold across the brain (cortically and subcortically) to impact cognitive, affective, or social processing.

Because this FOA expects the inclusion of an active manipulation of a biological process, studies with human subjects will meet the NIH definition of a clinical trial. However, this FOA will only accept a subset of NIH-defined clinical trials, namely, mechanistic clinical trials (in addition to accepting research with animals). NIH defines mechanistic clinical trials as studies designed to understand a biological or behavioral process, the pathophysiology of a disease, or the mechanism of action of an intervention (see NOT-MH-18-004 (https://grants.nih.gov/grants/guide/notice-files/NOT-MH-18-004.html) for more detailed examples of mechanistic clinical trials). By contrast, this FOA will not accept studies whose purpose is to evaluate safety, clinical efficacy,

clinical effectiveness, management, and/or implementation of an intervention. Instead, these types of studies should be submitted to one of the NIMH FOAs that support clinical trials evaluating safety, clinical efficacy, clinical effectiveness, management and/or implementation. For more information, please refer to the Clinical Trials Funding Opportunity Announcements webpage (https://www.nimh.nih.gov/funding/opportunities-announcements/clinical-trials-foas/index.shtml#2).

All applicants are encouraged to contact Scientific/Research staff at NIMH before submitting a grant application.

Background

Cognition appears to emerge at the level of populations of neurons, with information represented and organized as action potentials and network events that are temporally coordinated across brain areas. For example, there have been notable advances in our basic understanding of the role of local field potential (LFP) oscillations and large-scale coordination of neural networks in learning and memory. In rodents, particular patterns of temporal dynamics have been shown to proportionally improve or worsen working memory, and particular LFP oscillatory bands predict episodic/relational learning. Theta phase precession is another well-known precise temporal code that might be required for optimal cognition, and the precise reactivation of neural activity during hippocampal sharp wave ripples is also a temporally coordinated representation that might be necessary for memory consolidation or decision making.

From a disease standpoint, electrophysiological aberrations exist in many brain disorders, and recent findings suggest that modulating electrophysiological patterns could potentially have therapeutic benefit. In schizophrenia, findings have suggested that systems-level electrophysiological endophenotypes are modifiable and that such modifications have the potential to improve cognition. In autism, the modest amounts of electrophysiological data that exist in patients and model organisms suggest that this disorder also has disruptions in temporal coordination of neural signals, and that electrophysiological patterns at the level of neural populations might represent an intermediate, modifiable phenotype. Furthermore, rationally-developed pharmacological interventions are being tested for autism spectrum disorders, whose effect on temporal dynamics of electrophysiological patterns might be instructive to examine, especially if the treatments are directed at the cognitive impairments that lead to significant functional deficits for some patients.

These basic and translational findings should be expanded to better understand the brain algorithms that implement learning, memory consolidation, attention, reasoning, affect regulation, and social interactions. Work in non-human primates is also highly encouraged, as it would provide a bridge between rodent and human work with regard to neuroanatomy and cognitive capabilities.

The underlying premise of this funding opportunity is that cognitive, affective, and social dysfunction may result in part from compromised systems-level electrophysiological patterns; that these patterns are necessary for normal brain function; and therefore, treatments whose goal is to improve these domains of function might be more effective if they improve the underlying aberrant electrophysiological patterns.

Research Objectives

Applications must address at least one, and ideally more, of the following topic areas:

Topic 1: Temporal dynamics of neural patterns that impact cognition, affect, or social behavior

In animals or humans, determine which aspects of temporal coordination of systems-level neural activity affect particular domains of function such as working memory, long-term memory, relational/spatial processing, attention, cognitive control, decision making, affect regulation, or social cognition. Projects should manipulate specific aspects of the electrophysiological patterns (e.g., the power of oscillatory frequencies during particular task periods, or the degree of phase-amplitude coupling of particular frequency pairs) to determine what parameters, if manipulated appropriately, might yield the most robust and reliable improvements in behavior. Active manipulations proposed in grant applications that address Topic 1 can consist of electrical or magnetic brain stimulation, optogenetics, pharmacological compounds including novel or existing medications if well justified, or other modalities. Novel interventions are encouraged if they might provide greater temporal and/or spatial resolution. It is expected that applications provide a strong scientific rationale for the specific biological

intervention chosen, and why it is expected to selectively alter electrophysiological measures in a particular direction. All projects should include measures of neural activity at the systems level during awake behavior.

Topic 2: Understanding how molecular aberrations lead to systems-level discoordination

In animals or humans, understand how particular abnormalities at the cellular or molecular level, such as glutamate or GABA receptor dysfunction, affect the coordination of electrophysiological patterns during cognitive, affective, or social processing. Single-gene disorders in particular, such as Fragile X or Rett syndromes, might be a good opportunity to study such mechanistic questions in the context of systems level dynamics, but the case can also be made for neuropsychiatric disorders of more heterogeneous etiology. The emphasis can be on discovering ways to rescue the systems-level discoordination with either molecular/cellular interventions (e.g., pharmacology, genomic interventions), or with neurophysiology manipulations such as patterned electrical or optogenetic stimulation. The outcomes should be measured at both the systems electrophysiology level and at the behavioral level.

Topic 3: Animal-to-human translation

Determine whether the changes in neural coordination patterns that improve cognition in animals predict analogous electrophysiological and cognitive improvements in normal humans and/or clinical populations. A key goal is to understand the translational value of systems electrophysiology in pre-clinical models, to know whether an electrophysiological pattern identified in a relevant model system is predictive of a similarly aberrant pattern in patients, and whether the effects of any interventions in animals are predictive of their effects in humans. Another goal is to characterize aberrant electrophysiological patterns during cognition in clinical patients, although electrophysiological recordings in humans, if there is no active intervention, should be accompanied by parallel work in animals that includes an active intervention. It is expected that, to the greatest extent possible, identical interventions (e.g., the same pharmacological compounds, or comparably patterned electrical stimulation in model animals and humans) and tasks (e.g., equivalent working memory tasks) will be used. A related question of interest is whether any existing or novel medications are able to modify neural coordination patterns, and whether this mediates any improvement in cognition, affect, or social interaction.

Topic 4: Computational modeling

Develop a biologically realistic computational model to allow a principled understanding of the algorithms and mechanisms by which neural coordination patterns across brain areas affect cognitive, affective, and social processing. The computational models can cross levels, such as from the biophysical level to systems-level emergent properties, and they can also be top-down, such as mathematically describing and manipulating higher-order parameters of oscillatory coordination in relation to information processing and behavioral output. Projects that address the topic of computational modeling should also include work in animals or in humans, provide testable predictions, and be closely informed by the results.

There are two goals with this Topic. One goal is to reach a mechanistic understanding of how rhythmic patterns support information processing in the brain in the service of cognitive, affective, and social processing, and, relatedly, what algorithms are being implemented in the brain for each type of processing, including, but not limited to, spatial navigation, non-spatial relational processing (e.g., transitive inference), manipulation of items in working memory, social interaction, emotion regulation, decision making, and other cognitive domains of function. A second goal is to understand how modifying a neural pattern in one region of the network affects the patterns in other brain regions. This work can include modeling how brain stimulation at the scalp might affect oscillations and information processing subcortically (e.g., in the hippocampus), or in other cortical areas. The purpose of this is to understand network-level ramifications of local changes in oscillatory dynamics. Applications can address one or more of these goals.

Examples of research topics include, but are not limited to:

- An example of Topic 1 would be to conduct electrophysiological recordings in an animal relevant to neuropsychiatric disease during a spatial working memory task and to determine what systems-level aspects of the electrophysiological patterns could be modified to improve task behavior. The goal could be, for example, to examine whether theta precession, phase-amplitude coupling, sharp-wave ripples, or

other neural patterns are aberrant. Are there particular patterns of electrical stimulation that would improve theta precession, and would this improve spatial as well as non-spatial relational processing? What is the mechanism by which the changed neural pattern improves behavior? Methods for altering neural patterns could include pharmacological intervention, optogenetic methods, patterned electrical stimulation, or other methods, as long as the method allows for understanding what aspects of the temporal dynamics are the drivers of behavioral improvements, such as changes in amplitude of particular oscillatory frequencies, the co-modulation of particular frequencies, or other characteristics of oscillatory patterns and spike timing.

- Another example of Topic 1 would be to use patterned brain stimulation to test whether higher-level cognition could be improved in tasks such as transitive inference. For example, could sharp wave ripples be triggered to occur artificially, and might this improve an aspect of cognition? Can the fidelity of replay be improved? Work of this type would be especially encouraged in nonhuman primates because of more relevant brain anatomy and the possibility for more complex behavioral tasks.
- An example of Topic 2 would be to determine how over-activation of metabotropic glutamate signaling, or GABA receptor dysfunction in FMR1 knockout animals leads to particular changes in neural patterns and cognition, and which interventions could correct the systems-level neural coordination during an otherwise impaired behavior.
- An example of Topic 3 would be to test whether changes in neural coordination patterns in rodent models of relevant phenotypes predict similar intervention-induced changes in patients' EEG signals, during an equivalent behavioral task. The interventions in patients could be noninvasive brain stimulation (e.g., patterned transcranial magnetic or electrical stimulation) or medications. This type of work should also test whether the cognitive/behavioral improvements seen in rodents also predict improvements in patients.
- An example of Topic 4 would be to develop a biologically-realistic, computational model for predicting effects of noninvasive brain stimulation on particular frequencies of cortical and subcortical oscillations and how they interact across trial time and across brain areas.
- Another example of Topic 4 might be to model and experimentally test the effects of interneuron signaling on systems-level temporal dynamics.

In addition to addressing at least one of the four topic areas listed above, all applications under this FOA must also fulfill the following:

- All projects must employ active manipulations in awake, behaving vertebrate animals. The manipulations can consist of electrical or magnetic brain stimulation, optogenetics, genome editing, pharmacological compounds including existing or novel medications, or other modalities, but they cannot consist solely of behavioral manipulations. Biological manipulations can be tested in conjunction with behavioral training. In general, novel interventions are encouraged.
- All projects must provide a strong scientific rationale for the specific biological intervention chosen (pharmacological or otherwise), in particular whether the intervention can be expected to selectively alter a well-defined aspect of a systems-level temporal pattern in a particular direction (e.g., increasing the power of a specific oscillatory frequency).
- All projects must include in vivo, electrophysiological systems-level measures during behavior in each species. Computational/analytic work in particular is expected to reciprocally and iteratively interact closely with experimental work. The use of any non-mammalian species should be clearly justified, providing strong evidence that electrophysiological patterns during cognition are likely to generalize from animals to humans.
- EEG work must include spectral analyses.
- All projects must employ recording methods that detect neural activity directly, without relying on blood flow measures. All recording methods are expected to have the appropriate temporal resolution to address temporal dynamics of coordinated neural activity during cognition.

This FOA seeks to generate a mechanistic understanding of what aspects of neural coordination and patterning can be modified to improve cognitive, affective, and social processing. These findings are expected to eventually support the development of pharmacological, electrical, magnetic, or other types of interventions that can enhance cognitive, affective, or social processing sufficiently to improve real-life functioning for patients.

Protection of Human Subjects:

Applications with data collection plans that involve multiple respondent groups (e.g., clients/patients, therapists/providers, supervisors, administrators) should address provisions for human subject protections and consenting procedures for all participant groups, accordingly. The NIMH has published updated policies and guidance for investigators regarding human research protection and clinical research data and safety monitoring (NOT-MH-15-025). The application's Protection of Human Subjects section and data and safety monitoring plans should reflect the policies and guidance in this notice. Plans for the protection of research subjects and data and safety monitoring will be reviewed by the NIMH for consistency with NIMH and NIH policies and federal regulations.

See Section VIII. Other Information for award authorities and regulations.

Section II. Award Information

Funding Instrument

Grant: A support mechanism providing money, property, or both to an eligible entity to carry out an approved project or activity.

Application Types Allowed

New
Renewal
Resubmission
Revision

The OER Glossary (//grants.nih.gov/grants/guide/url_redirect.htm?id=11116) and the SF424 (R&R) Application Guide provide details on these application types.

Clinical Trial?

Optional: Accepting applications that either propose or do not propose clinical trial(s).

Need help determining whether you are doing a clinical trial? (https://grants.nih.gov/grants/guide/url_redirect.htm?id=82370)

Funds Available and Anticipated Number of Awards

The number of awards is contingent upon NIH appropriations and the submission of a sufficient number of meritorious applications.

Award Budget

Application budgets are not limited but need to reflect the actual needs of the proposed project.

Award Project Period

The scope of the proposed project should determine the project period. The maximum project period is 5 years.

NIH grants policies as described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120) will apply to the applications submitted and awards made from this FOA.

Section III. Eligibility Information

1. Eligible Applicants

Eligible Organizations

Higher Education Institutions

- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education

The following types of Higher Education Institutions are always encouraged to apply for NIH support as Public or Private Institutions of Higher Education:

- Hispanic-serving Institutions
- Historically Black Colleges and Universities (HBCUs)
- Tribally Controlled Colleges and Universities (TCCUs)
- Alaska Native and Native Hawaiian Serving Institutions
- Asian American Native American Pacific Islander Serving Institutions (AANAPISIs)

Nonprofits Other Than Institutions of Higher Education

- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education)

For-Profit Organizations

- Small Businesses
- For-Profit Organizations (Other than Small Businesses)

Governments

- State Governments
- County Governments
- City or Township Governments
- Special District Governments
- Indian/Native American Tribal Governments (Federally Recognized)
- Indian/Native American Tribal Governments (Other than Federally Recognized)
- Eligible Agencies of the Federal Government
- U.S. Territory or Possession

Other

- Independent School Districts
- Public Housing Authorities/Indian Housing Authorities
- Native American Tribal Organizations (other than Federally recognized tribal governments)
- Faith-based or Community-based Organizations
- Regional Organizations
- Non-domestic (non-U.S.) Entities (Foreign Institutions)

Foreign Institutions

Non-domestic (non-U.S.) Entities (Foreign Institutions) **are** eligible to apply.
Non-domestic (non-U.S.) components of U.S. Organizations **are** eligible to apply.
Foreign components, as defined in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11118), **are** allowed.

Required Registrations

Applicant Organizations

Applicant organizations must complete and maintain the following registrations as described in the SF 424 (R&R) Application Guide to be eligible to apply for or receive an award. All registrations must be completed prior to the application being submitted. Registration can take 6 weeks or more, so applicants should begin the registration

process as soon as possible. The NIH Policy on Late Submission of Grant Applications (//grants.nih.gov/grants/guide/notice-files/NOT-OD-15-039.html) states that failure to complete registrations in advance of a due date is not a valid reason for a late submission.

- Dun and Bradstreet Universal Numbering System (DUNS) (http://fedgov.dnb.com/webform) - All registrations require that applicants be issued a DUNS number. After obtaining a DUNS number, applicants can begin both SAM and eRA Commons registrations. The same DUNS number must be used for all registrations, as well as on the grant application.
- System for Award Management (SAM) (https://www.sam.gov/portal/public/SAM/) (formerly CCR) – Applicants must complete and maintain an active registration, **which requires renewal at least annually**. The renewal process may require as much time as the initial registration. SAM registration includes the assignment of a Commercial and Government Entity (CAGE) Code for domestic organizations which have not already been assigned a CAGE Code.
    - NATO Commercial and Government Entity (NCAGE) Code (//grants.nih.gov/grants/guide/url_redirect.htm?id=11176) – Foreign organizations must obtain an NCAGE code (in lieu of a CAGE code) in order to register in SAM.
- eRA Commons (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123) - Applicants must have an active DUNS number and SAM registration in order to complete the eRA Commons registration. Organizations can register with the eRA Commons as they are working through their SAM or Grants.gov registration. eRA Commons requires organizations to identify at least one Signing Official (SO) and at least one Program Director/Principal Investigator (PD/PI) account in order to submit an application.
- Grants.gov (//grants.nih.gov/grants/guide/url_redirect.htm?id=82300) – Applicants must have an active DUNS number and SAM registration in order to complete the Grants.gov registration.

Program Directors/Principal Investigators (PD(s)/PI(s))

All PD(s)/PI(s) must have an eRA Commons account. PD(s)/PI(s) should work with their organizational officials to either create a new account or to affiliate their existing account with the applicant organization in eRA Commons. If the PD/PI is also the organizational Signing Official, they must have two distinct eRA Commons accounts, one for each role. Obtaining an eRA Commons account can take up to 2 weeks.

Eligible Individuals (Program Director/Principal Investigator)

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF424 (R&R) Application Guide.

2. Cost Sharing

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11126)

3. Additional Information on Eligibility

Number of Applications

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

The NIH will not accept duplicate or highly overlapping applications under review at the same time. This means that the NIH will not accept:

- A new (A0) application that is submitted before issuance of the summary statement from the review of an overlapping new (A0) or resubmission (A1) application.

- A resubmission (A1) application that is submitted before issuance of the summary statement from the review of the previous new (A0) application.
- An application that has substantial overlap with another application pending appeal of initial peer review (see NOT-OD-11-101 (//grants.nih.gov/grants/guide/notice-files/NOT-OD-11-101.html)).

Section IV. Application and Submission Information

1. Requesting an Application Package

Buttons to access the online ASSIST system or to download application forms are available in Part 1 of this FOA. See your administrative office for instructions if you plan to use an institutional system-to-system solution.

2. Content and Form of Application Submission

It is critical that applicants follow the Research (R) Instructions in the SF424 (R&R) Application Guide (//grants.nih.gov/grants/guide/url_redirect.htm?id=12000), except where instructed in this funding opportunity announcement to do otherwise. Conformance to the requirements in the Application Guide is required and strictly enforced. Applications that are out of compliance with these instructions may be delayed or not accepted for review.

For information on Application Submission and Receipt, visit Frequently Asked Questions – Application Guide, Electronic Submission of Grant Applications (//grants.nih.gov/grants/guide/url_redirect.htm?id=41137).

Page Limitations

All page limitations described in the SF424 Application Guide and the Table of Page Limits (//grants.nih.gov/grants/guide/url_redirect.htm?id=11133) must be followed.

Instructions for Application Submission

The following section supplements the instructions found in the SF424 (R&R) Application Guide and should be used for preparing an application to this FOA.

SF424(R&R) Cover

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Project/Performance Site Locations

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Other Project Information

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Senior/Key Person Profile

All instructions in the SF424 (R&R) Application Guide must be followed.

R&R or Modular Budget

All instructions in the SF424 (R&R) Application Guide must be followed.

R&R Subaward Budget

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS 398 Cover Page Supplement

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS 398 Research Plan

All instructions in the SF424 (R&R) Application Guide must be followed, with the following additional instructions:

Research Strategy:

Every application should address at least one of the four topic areas listed in Section I, "Funding Opportunity Description."

In addition, all applications under this FOA are also expected to:

- Address a specific, definable aspect of systems-level temporal dynamics or coordination.
- Implement active manipulations in awake, behaving vertebrate animals or humans. The manipulation should be expected to selectively alter an electrophysiological parameter in a particular direction. The manipulations can consist of electrical or magnetic brain stimulation, optogenetics, pharmacological compounds including existing or novel medications, or other modalities, but they cannot consist solely of behavioral manipulations. Biological manipulations can be tested in conjunction with behavioral training. In general, novel interventions are encouraged.
- Include at least one scientific goal to see a measurable improvement in cognitive, affective, or social processing, even for basic research in normal/wildtype animals.
- Provide a mechanistic understanding of how neural coordination patterns unfold in the brain during healthy cognitive, affective, or social processing, or how the patterns are affected in disease states.
- Include behavioral tasks that would have real-life functional impact if they were improved in patients with neuropsychiatric disorders, such as memory, relational/spatial processing, attention, emotion regulation, or social interaction.
- Clearly justify the use of any non-mammalian species, and provide strong evidence that electrophysiological patterns during cognition will generalize easily from animals to humans.
- Include in vivo, neurophysiological systems-level measures during behavior in each species. Computational/analytic work in particular is expected to reciprocally and iteratively interact closely with experimental work. Computational work should test systems-level algorithms that underlie cognitive, affective, or social processing, such as modeling how increasing the amplitude of theta oscillations in one brain region affects oscillations in various frequency bands in other brain areas during spatial working memory.
- Include spectral analyses if EEG work is proposed.
- Employ recording methods that detect neural activity directly, without relying on blood flow measures. All recording methods are expected to have the appropriate temporal resolution to address temporal dynamics of coordinated neural activity during behavior.

Resource Sharing Plan: Individuals are required to comply with the instructions for the Resource Sharing Plans as provided in the SF424 (R&R) Application Guide.

Appendix:

Only limited Appendix materials are allowed. Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide.

PHS Human Subjects and Clinical Trials Information

Use only for applications with due dates on or after January 25, 2018. When involving NIH-defined human subjects research, clinical research, and/or clinical trials (and when applicable, clinical trials research experience) follow all instructions for the PHS Human Subjects and Clinical Trials Information form in the SF424 (R&R) Application Guide, with the following additional instructions:

If you answered "Yes" to the question "Are Human Subjects Involved?" on the R&R Other Project Information form, you must include at least one human subjects study record using the **Study Record: PHS Human Subjects and Clinical Trials Information** form or **Delayed Onset Study** record.

Study Record: PHS Human Subjects and Clinical Trials Information

All instructions in the SF424 (R&R) Application Guide must be followed.

Delayed Onset Study

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS Assignment Request Form

All instructions in the SF424 (R&R) Application Guide must be followed.

Foreign Institutions

Foreign (non-U.S.) institutions must follow policies described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11137), and procedures for foreign institutions.

3. Unique Entity Identifier and System for Award Management (SAM)

See Part 1. Section III.1 for information regarding the requirement for obtaining a unique entity identifier and for completing and maintaining active registrations in System for Award Management (SAM), NATO Commercial and Government Entity (NCAGE) Code (if applicable), eRA Commons, and Grants.gov

4. Submission Dates and Times

Part I. Overview Information contains information about Key Dates and times. Applicants are encouraged to submit applications before the due date to ensure they have time to make any application corrections that might be necessary for successful submission. When a submission date falls on a weekend or Federal holiday (https://grants.nih.gov/grants/guide/url_redirect.htm?id=82380), the application deadline is automatically extended to the next business day.

Organizations must submit applications to Grants.gov (//grants.nih.gov/grants/guide/url_redirect.htm?id=11128) (the online portal to find and apply for grants across all Federal agencies). Applicants must then complete the submission process by tracking the status of the application in the eRA Commons (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123), NIH's electronic system for grants administration. NIH and Grants.gov systems check the application against many of the application instructions upon submission. Errors must be corrected and a changed/corrected application must be submitted to Grants.gov on or before the application due date and time. If a Changed/Corrected application is submitted after the deadline, the application will be considered late. Applications that miss the due date and time are subjected to the NIH Policy on Late Application Submission.

Applicants are responsible for viewing their application before the due date in the eRA Commons to ensure accurate and successful submission.

Information on the submission process and a definition of on-time submission are provided in the SF424 (R&R) Application Guide.

5. Intergovernmental Review (E.O. 12372)

This initiative is not subject to intergovernmental review. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11142)

6. Funding Restrictions

All NIH awards are subject to the terms and conditions, cost principles, and other considerations described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120).

Pre-award costs are allowable only as described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11143).

7. Other Submission Requirements and Information

Applications must be submitted electronically following the instructions described in the SF424 (R&R) Application Guide. Paper applications will not be accepted.

Applicants must complete all required registrations before the application due date. Section III. Eligibility Information contains information about registration.

For assistance with your electronic application or for more information on the electronic submission process, visit Applying Electronically (//grants.nih.gov/grants/guide/url_redirect.htm?id=11144). If you encounter a system issue beyond your control that threatens your ability to complete the submission process on-time, you must follow the

Guidelines for Applicants Experiencing System Issues (//grants.nih.gov/grants/ElectronicReceipt/support.htm#guidelines). For assistance with application submission, contact the Application Submission Contacts in Section VII.

Important reminders:

All PD(s)/PI(s) must include their eRA Commons ID in the Credential field of the Senior/Key Person Profile Component of the SF424(R&R) Application Package**.** Failure to register in the Commons and to include a valid PD/PI Commons ID in the credential field will prevent the successful submission of an electronic application to NIH. See Section III of this FOA for information on registration requirements.

The applicant organization must ensure that the DUNS number it provides on the application is the same number used in the organization's profile in the eRA Commons and for the System for Award Management. Additional information may be found in the SF424 (R&R) Application Guide.

See more tips (//grants.nih.gov/grants/guide/url_redirect.htm?id=11146) for avoiding common errors.

Upon receipt, applications will be evaluated for completeness and compliance with application instructions by the Center for Scientific Review, NIH. Applications that are incomplete or non-compliant will not be reviewed.

Requests of $500,000 or more for direct costs in any year

Applicants requesting $500,000 or more in direct costs in any year (excluding consortium F&A) must contact a Scientific/ Research Contact at least 6 weeks before submitting the application and follow the Policy on the Acceptance for Review of Unsolicited Applications that Request $500,000 or More in Direct Costs as described in the SF424 (R&R) Application Guide.

Post Submission Materials

Applicants are required to follow the instructions for post-submission materials, as described in the policy (//grants.nih.gov/grants/guide/url_redirect.htm?id=82299). Any instructions provided here are in addition to the instructions in the policy.

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process. As part of the NIH mission (//grants.nih.gov/grants/guide/url_redirect.htm?id=11149), all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

In addition, for applications involving clinical trials:

A proposed Clinical Trial application may include study design, methods, and intervention that are not by themselves innovative but address important questions or unmet needs. Additionally, the results of the clinical trial may indicate that further clinical development of the intervention is unwarranted or lead to new avenues of scientific investigation

Overall Impact

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

Scored Review Criteria

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance

Does the project address an important problem or a critical barrier to progress in the field? Is there a strong scientific premise for the project? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

How well does the project fulfill each of the following questions:

- How likely are the active manipulations to lead to a measurable improvement in cognitive, affective, or social processing?
- How much will the work contribute, either experimentally or theoretically, to a mechanistic understanding of how neural coordination and patterns unfold in the brain?
- How much of a real-life functional effect would the type of cognition being studied (e.g., memory, relational/spatial processing, attention, etc.) have if it were improved in patients with neuropsychiatric disorders?
- Is the use of any non-mammalian species clearly justified, and how strong is the evidence that the electrophysiological patterns being studied will generalize easily from animals to humans?
- In addition, for applications proposing clinical trials

Are the scientific rationale and need for a clinical trial to test the proposed hypothesis or intervention well supported by preliminary data, clinical and/or preclinical studies, or information in the literature or knowledge of biological mechanisms? For trials focusing on clinical or public health endpoints, is this clinical trial necessary for testing the safety, efficacy or effectiveness of an intervention that could lead to a change in clinical practice, community behaviors or health care policy? For trials focusing on mechanistic, behavioral, physiological, biochemical, or other biomedical endpoints, is this trial needed to advance scientific understanding?

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or those in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

In addition, for applications proposing clinical trials

With regard to the proposed leadership for the project, do the PD/PI(s) and key personnel have the expertise, experience, and ability to organize, manage and implement the proposed clinical trial and meet milestones and timelines? Do they have appropriate expertise in study coordination, data management and statistics? For a multicenter trial, is the organizational structure appropriate and does the application identify a core of potential center investigators and staffing for a coordinating center?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

In addition, for applications proposing clinical trials

Does the design/research plan include innovative elements, as appropriate, that enhance its sensitivity, potential for information or potential to advance scientific knowledge or clinical practice?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

Does the project address at least one of the four topic areas listed in Section I, "Funding Opportunity Description"?

Does the project include in vivo electrophysiological recordings during awake behavior? Does it include active manipulations that are not only behavioral interventions, and can the manipulation be expected to alter an electrophysiological parameter in a particular direction?

If theoretical computational work is proposed, does it reciprocally and iteratively interact closely with experimental work? Will it test systems-level computational algorithms that underlie cognitive, affective, or social processing?

If EEG work is proposed, does it include spectral analyses, and not rely on event-related potentials (ERPs)?

Does the project employ recording methods that detect neural activity directly, without relying on blood flow measures, and which have the appropriate temporal resolution?

If the project proposes non-mammalian species, is this well justified? Are the findings likely to generalize to the mammalian brain?

In addition, for applications proposing clinical trials

Does the application adequately address the following, if applicable

Study Design

Is the study design justified and appropriate to address primary and secondary outcome variable(s)/endpoints that will be clear, informative and relevant to the hypothesis being tested? Is the scientific rationale/premise of the study based on previously well-designed preclinical and/or clinical research? Given the methods used to assign participants and deliver interventions, is the study design adequately powered to answer the research question(s), test the proposed hypothesis/hypotheses, and provide interpretable results? Is the trial appropriately designed to conduct the research efficiently? Are the study populations (size, gender, age, demographic group), proposed intervention arms/dose, and duration of the trial, appropriate and well justified?

Are potential ethical issues adequately addressed? Is the process for obtaining informed consent or assent appropriate? Is the eligible population available? Are the plans for recruitment outreach, enrollment, retention, handling dropouts, missed visits, and losses to follow-up appropriate to ensure robust data collection? Are the planned recruitment timelines feasible and is the plan to monitor accrual adequate? Has the need for randomization (or not), masking (if appropriate), controls, and inclusion/exclusion criteria been addressed? Are differences addressed, if applicable, in the intervention effect due to sex/gender and race/ethnicity?

Are the plans to standardize, assure quality of, and monitor adherence to, the trial protocol and data collection or distribution guidelines appropriate? Is there a plan to obtain required study agent(s)? Does the application propose to use existing available resources, as applicable?

Data Management and Statistical Analysis

Are planned analyses and statistical approach appropriate for the proposed study design and methods used to assign participants and deliver interventions? Are the procedures for data management and quality control of data adequate at clinical site(s) or at center laboratories, as applicable? Have the methods for standardization of procedures for data management to assess the effect of the intervention and quality control been addressed? Is there a plan to complete data analysis within the proposed period of the award?

If the project involves human subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks, and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of children, justified in terms of the scientific goals and research strategy proposed?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

In addition, for applications proposing clinical trials

If proposed, are the administrative, data coordinating, enrollment and laboratory/testing centers, appropriate for the trial proposed?

Does the application adequately address the capability and ability to conduct the trial at the proposed site(s) or centers? Are the plans to add or drop enrollment centers, as needed, appropriate?

If international site(s) is/are proposed, does the application adequately address the complexity of executing the clinical trial?

If multi-sites/centers, is there evidence of the ability of the individual site or center to: (1) enroll the proposed numbers; (2) adhere to the protocol; (3) collect and transmit data in an accurate and timely fashion; and, (4) operate within the proposed organizational structure?

Additional Review Criteria

As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

Study Timeline

Specific to applications proposing clinical trials

Is the study timeline described in detail, taking into account start-up activities, the anticipated rate of enrollment, and planned follow-up assessment? Is the projected timeline feasible and well justified? Does the project incorporate efficiencies and utilize existing resources (e.g., CTSAs, practice-based research networks, electronic medical records, administrative database, or patient registries) to increase the efficiency of participant enrollment and data collection, as appropriate?

Are potential challenges and corresponding solutions discussed (e.g., strategies that can be implemented in the event of enrollment shortfalls)?

Protections for Human Subjects

For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the Guidelines for the Review of Human Subjects (//grants.nih.gov/grants/guide/url_redirect.htm?id=11175).

Inclusion of Women, Minorities, and Children

When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children to determine if it is justified in terms of the scientific goals and research strategy proposed. For additional information on review of the Inclusion section, please refer to the Guidelines for the Review of Inclusion in Clinical Research (//grants.nih.gov/grants/guide/url_redirect.htm?id=11174).

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following criteria: (1) description of proposed procedures involving animals, including species, strains, ages, sex, and total number to be used; (2) justifications for the use of animals versus alternative models and for the appropriateness of the species proposed; (3) interventions to minimize discomfort, distress, pain and injury; and (4) justification for euthanasia method if NOT consistent with the AVMA Guidelines for the Euthanasia of Animals. Reviewers will assess the use of chimpanzees as they would any other application proposing the use of vertebrate animals. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section (//grants.nih.gov/grants/guide/url_redirect.htm?id=11150).

Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmissions

For Resubmissions, the committee will evaluate the application as now presented, taking into consideration the responses to comments from the previous scientific review group and changes made to the project.

Renewals

For Renewals, the committee will consider the progress made in the last funding period.

Revisions

For Revisions, the committee will consider the appropriateness of the proposed expansion of the scope of the project. If the Revision application relates to a specific line of investigation presented in the original application that was not recommended for approval by the committee, then the committee will consider whether the responses to comments from the previous scientific review group are adequate and whether substantial changes are clearly evident.

Additional Review Considerations

As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact score.

Applications from Foreign Organizations

Reviewers will assess whether the project presents special opportunities for furthering research programs through the use of unusual talent, resources, populations, or environmental conditions that exist in other countries and either are not readily available in the United States or augment existing U.S. resources.

Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: (1) Data Sharing Plan (//grants.nih.gov/grants/guide/url_redirect.htm?id=11151); (2) Sharing Model Organisms

(//grants.nih.gov/grants/guide/url_redirect.htm?id=11152); and (3) Genomic Data Sharing Plan (GDS) (//grants.nih.gov/grants/guide/url_redirect.htm?id=11153).

Authentication of Key Biological and/or Chemical Resources:

For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.

Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

2. Review and Selection Process

Applications will be evaluated for scientific and technical merit by (an) appropriate Scientific Review Group(s) convened by the Center for Scientific Review, in accordance with NIH peer review policy and procedures (//grants.nih.gov/grants/guide/url_redirect.htm?id=11154), using the stated review criteria. Assignment to a Scientific Review Group will be shown in the eRA Commons.

As part of the scientific peer review, all applications:

- May undergo a selection process in which only those applications deemed to have the highest scientific and technical merit (generally the top half of applications under review) will be discussed and assigned an overall impact score.
- Will receive a written critique.

Applications will be assigned on the basis of established PHS referral guidelines to the appropriate NIH Institute or Center. Applications will compete for available funds with all other recommended applications submitted in response to this FOA. Following initial peer review, recommended applications will receive a second level of review by the appropriate National Advisory Council or Board. The following will be considered in making funding decisions:

- Scientific and technical merit of the proposed project as determined by scientific peer review.
- Availability of funds.
- Relevance of the proposed project to program priorities.
    - Adequacy of fit to at least one of the four topic areas described in Section I, "Research Objectives," namely, Topic 1: Temporal dynamics of neural patterns that impact cognition; Topic 2: Understanding how molecular aberrations lead to systems-level discoordination; Topic 3: Animal-to-human translation; or Topic 4: Computational modeling
    - Adequate selection of specific, definable aspects of systems-level neural coordination
    - Significance of the studied behavior or cognition.
- Compliance with resource sharing policies.

3. Anticipated Announcement and Award Dates

After the peer review of the application is completed, the PD/PI will be able to access his or her Summary Statement (written critique) via the eRA Commons (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123). Refer to Part 1 for dates for peer review, advisory council review, and earliest start date.

Information regarding the disposition of applications is available in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11156).

Section VI. Award Administration Information

1. Award Notices

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant as described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11157).

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization for successful applications. The NoA signed by the grants management officer is the authorizing document and will be sent via email to the grantee's business official.

Awardees must comply with any funding restrictions described in Section IV.5. Funding Restrictions. Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

Any application awarded in response to this FOA will be subject to terms and conditions found on the Award Conditions and Information for NIH Grants (//grants.nih.gov/grants/guide/url_redirect.htm?id=11158) website. This includes any recent legislation and policy applicable to awards that is highlighted on this website.

Additionally, ICs may specify any special reporting requirements for the proposed clinical trial to be included under IC-specific terms and conditions in the NoA. For example: If the proposed clinical trial has elevated risks, ICs may require closer programmatic monitoring and it may be necessary to require the awardee to provide more frequent information and data as a term of the award (e.g., to clarify issues, address and evaluate concerns, provide documentation). All additional communications and information related to programmatic monitoring must be documented and incorporated into the official project file. Individual awards are based on the application submitted to, and as approved by, the NIH and are subject to the IC-specific terms and conditions identified in the NoA. ClinicalTrials.gov: If an award provides for one or more clinical trials. By law (Title VIII, Section 801 of Public Law 110-85), the "responsible party" must register and submit results information for certain "applicable clinical trials" on the ClinicalTrials.gov Protocol Registration and Results System Information Website (https://register.clinicaltrials.gov). NIH expects registration of all trials whether required under the law or not. For more information, see http://grants.nih.gov/ClinicalTrials_fdaaa/

Institutional Review Board or Independent Ethics Committee Approval: Grantee institutions must ensure that the application as well as all protocols are reviewed by their IRB or IEC. To help ensure the safety of participants enrolled in NIH-funded studies, the awardee must provide NIH copies of documents related to all major changes in the status of ongoing protocols. Data and Safety Monitoring Requirements: The NIH policy for data and safety monitoring requires oversight and monitoring of all NIH-conducted or -supported human biomedical and behavioral intervention studies (clinical trials) to ensure the safety of participants and the validity and integrity of the data. Further information concerning these requirements is found at http://grants.nih.gov/grants/policy/hs/data_safety.htm and in the application instructions (SF424 (R&R) and PHS 398).

Investigational New Drug or Investigational Device Exemption Requirements: Consistent with federal regulations, clinical research projects involving the use of investigational therapeutics, vaccines, or other medical interventions (including licensed products and devices for a purpose other than that for which they were licensed) in humans under a research protocol must be performed under a Food and Drug Administration (FDA) investigational new drug (IND) or investigational device exemption (IDE).

2. Administrative and National Policy Requirements

All NIH grant and cooperative agreement awards include the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120) as part of the NoA. For these terms of award, see the *NIH Grants Policy Statement* Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (//grants.nih.gov/grants/guide/url_redirect.htm?id=11157) and Part II: Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities (//grants.nih.gov/grants/guide/url_redirect.htm?id=11159). More information is provided at Award Conditions and Information for NIH Grants (//grants.nih.gov/grants/guide/url_redirect.htm?id=11158).

Recipients of federal financial assistance (FFA) from HHS must administer their programs in compliance with federal civil rights law. This means that recipients of HHS funds must ensure equal access to their programs without regard to a person's race, color, national origin, disability, age and, in some circumstances, sex and religion. This includes ensuring your programs are accessible to persons with limited English proficiency. HHS

recognizes that research projects are often limited in scope for many reasons that are nondiscriminatory, such as the principal investigator's scientific interest, funding limitations, recruitment requirements, and other considerations. Thus, criteria in research protocols that target or exclude certain populations are warranted where nondiscriminatory justifications establish that such criteria are appropriate with respect to the health or safety of the subjects, the scientific study design, or the purpose of the research.

For additional guidance regarding how the provisions apply to NIH grant programs, please contact the Scientific/Research Contact that is identified in Section VII under Agency Contacts of this FOA. HHS provides general guidance to recipients of FFA on meeting their legal obligation to take reasonable steps to provide meaningful access to their programs by persons with limited English proficiency. Please see http://www.hhs.gov/ocr/civilrights/resources/laws/revisedlep.html. The HHS Office for Civil Rights also provides guidance on complying with civil rights laws enforced by HHS. Please see http://www.hhs.gov/ocr/civilrights/understanding/section1557/index.html (http://www.hhs.gov/ocr/civilrights/understanding/section1557/index.html); and http://www.hhs.gov/ocr/civilrights/understanding/index.html (http://www.hhs.gov/ocr/civilrights/understanding/index.html). Recipients of FFA also have specific legal obligations for serving qualified individuals with disabilities. Please see http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html (http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html). Please contact the HHS Office for Civil Rights for more information about obligations and prohibitions under federal civil rights laws at http://www.hhs.gov/ocr/office/about/rgn-hqaddresses.html (http://www.hhs.gov/ocr/office/about/rgn-hqaddresses.html) or call 1-800-368-1019 or TDD 1-800-537-7697. Also note it is an HHS Departmental goal to ensure access to quality, culturally competent care, including long-term services and supports, for vulnerable populations. For further guidance on providing culturally and linguistically appropriate services, recipients should review the National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care at http://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=53 (http://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=53).

In accordance with the statutory provisions contained in Section 872 of the Duncan Hunter National Defense Authorization Act of Fiscal Year 2009 (Public Law 110-417), NIH awards will be subject to the Federal Awardee Performance and Integrity Information System (FAPIIS) requirements. FAPIIS requires Federal award making officials to review and consider information about an applicant in the designated integrity and performance system (currently FAPIIS) prior to making an award. An applicant, at its option, may review information in the designated integrity and performance systems accessible through FAPIIS and comment on any information about itself that a Federal agency previously entered and is currently in FAPIIS. The Federal awarding agency will consider any comments by the applicant, in addition to other information in FAPIIS, in making a judgement about the applicant's integrity, business ethics, and record of performance under Federal awards when completing the review of risk posed by applicants as described in 45 CFR Part 75.205 "Federal awarding agency review of risk posed by applicants." This provision will apply to all NIH grants and cooperative agreements except fellowships.

Cooperative Agreement Terms and Conditions of Award

Not Applicable

3. Reporting

When multiple years are involved, awardees will be required to submit the Research Performance Progress Report (RPPR) (//grants.nih.gov/grants/rppr/index.htm) annually and financial statements as required in the NIH Grants Policy Statement. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11161)

A final RPPR, invention statement, and the expenditure data portion of the Federal Financial Report are required for closeout of an award, as described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11161).

The Federal Funding Accountability and Transparency Act of 2006 (Transparency Act), includes a requirement for awardees of Federal grants to report information about first-tier subawards and executive compensation under

Federal assistance awards issued in FY2011 or later. All awardees of applicable NIH grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at www.fsrs.gov (//grants.nih.gov/grants/guide/url_redirect.htm?id=11170) on all subawards over $25,000. See the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11171) for additional information on this reporting requirement.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts from all Federal awarding agencies with a cumulative total value greater than $10,000,000 for any period of time during the period of performance of a Federal award, must report and maintain the currency of information reported in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently FAPIIS). This is a statutory requirement under section 872 of Public Law 110-417, as amended (41 U.S.C. 2313). As required by section 3010 of Public Law 111-212, all information posted in the designated integrity and performance system on or after April 15, 2011, except past performance reviews required for Federal procurement contracts, will be publicly available. Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75 – Award Term and Conditions for Recipient Integrity and Performance Matters.

Section VII. Agency Contacts

We encourage inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants.

Application Submission Contacts

eRA Service Desk (Questions regarding ASSIST, eRA Commons registration, submitting and tracking an application, documenting system problems that threaten submission by the due date, post submission issues)
Finding Help Online: http://grants.nih.gov/support/ (//grants.nih.gov/support/) (preferred method of contact)
Telephone: 301-402-7469 or 866-504-9552 (Toll Free)

Grants.gov Customer Support (//grants.nih.gov/grants/guide/url_redirect.htm?id=82301) (Questions regarding Grants.gov registration and submission, downloading forms and application packages)
Contact Center Telephone: 800-518-4726
Email: support@grants.gov (mailto:support@grants.gov)

GrantsInfo (Questions regarding application instructions and process, finding NIH grant resources)
Email: GrantsInfo@nih.gov (mailto:GrantsInfo@nih.gov) (preferred method of contact)
Telephone: 301-945-7573

Scientific/Research Contact(s)

Bettina D. Buhring, Ph.D.
National Institute of Mental Health (NIMH)
Telephone: 301-443-1576
Email: bettina.buhring@nih.gov (mailto:bettina.buhring@nih.gov)

Peer Review Contact(s)

Kirk Thompson
Center for Scientific Review (CSR)
Telephone: 301-435-1242
Email: kgt@csr.nih.gov (mailto:kgt@csr.nih.gov)

Financial/Grants Management Contact(s)

Terri Jarosik
National Institute of Mental Health (NIMH)
Telephone: 301-443-3858
Email: tjarosik@mail.nih.gov (mailto:tjarosik@mail.nih.gov)

Section VIII. Other Information

Recently issued trans-NIH policy notices (//grants.nih.gov/grants/guide/url_redirect.htm?id=11163) may affect your application submission. A full list of policy notices published by NIH is provided in the *NIH Guide for Grants and Contracts* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11164). All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120).

Authority and Regulations

Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR Part 52 and 45 CFR Part 75.

Weekly TOC for this Announcement (/grants/guide/WeeklyIndex.cfm?01-05-18)
NIH Funding Opportunities and Notices (/grants/guide/index.html)