Funding Opportunity Announcement

Leveraging Cognitive Neuroscience Research to Improve Assessment of Cancer Treatment Related Cognitive Impairment

PAR-16-212 (R01) & PAR-16-213 (R21)

Webinar Questions and Answers

Q. The FOA encourages the applications of cognitive neuroscience theory and task paradigms developed in the last three decades for improved measurement and assessment of acute and late-term cognitive changes following cancer treatment. Does that mean that traditional clinical neuropsychological batteries should not be included?

A. The traditional batteries, or certainly parts of those batteries, should be included as a comparison to the newer cognitive neuroscience paradigms. This would be one of the comparisons that would be critical to determine whether the cognitive science paradigms can do a better job than traditional assessment tools in predicting problems and how.

Q. To what extent are proposals that focus on both cognitive and social affective changes in response to cancer treatment of interest or are relevant to the FOA?

A. Social and affective changes as a function of cancer treatment are not a primary focus of the FOA. However, to the extent that social, and particularly, affective changes may be informative as a contributor to cognitive impairment, then its measurement may be looked at favorably. For example, in cases like depression, there may be good reason to measure and control for this variable to determine whether the effect of treatment is "purely a cognitive affect."

Q. Must the NIH cognitive toolbox battery be included as a control?

A. No. The NIH Cognitive toolbox does not need to be included as a control. It is offered as an option, in part, because of its brevity and ease of administration. If one found that the cognitive neuroscience paradigms performed no better than certain parts of the toolbox, that would be useful information. In any case, researchers do not have to include this toolbox in their applications.

Q. Do you have any preference about the cancer sites that must be studied?

A. There are certain sites that are more relevant to chemo-brain phenomena, but we are not taking a position on any specific sites being studied. However, it must be a non-CNS malignancy and be treated with systemic chemotherapy and/or hormone blocker therapies or molecularly targeted therapies, such as monoclonal agents. Most data collected to date are for breast cancer. There are also results on lymphomas and some other sites. There are some incentives to cancer sites that have not been studied as much as breast cancer.

Q. Are applications exclusively to be focused on the effects of systemic chemotherapy?

A. Although we anticipate the lion's share of applications will pertain to systemic chemotherapy, investigators are not restricted to it. The questions about cognitive effects of cancer treatments also pertain to hormone blocker treatments, such as Tamoxifen,

aromatase inhibitors, and other molecularly targeted therapies. We still do not know a great deal about the effects of those treatments on cognition, but there are some reports and plausible biological pathways that indicate there are cognitive effects. Researchers could also look at other forms of treatment such as monoclonal agents, which are not well-studied. An investigator's decision will depend on the availability of the patients and the kind of regimen that they receive. We expect that drug combinations may be most common. It will be important for investigators to justify why they have selected certain agents, or why they have selected a combination of drugs to study. While it would be ideal to disaggregate the different factors and the different treatments, it will not always be possible.

Q. How concerned should we be about patient burden if we expect applicants to compare traditional neuropsychological and cognitive neuroscience tasks?

A. There needs to be some attention to these considerations, but it will depend largely on the goals or aims of the investigator. Because traditional neuropsychological inventories can take more than an hour or so to administer, a couple of testing sessions may be needed. Sessions can be administered on iPads or remotely (e.g., outside a lab, in a hospital or clinic), which could minimize participant burden. Participant burden and effects of fatigue are legitimate concerns, but we think they can be strategically overcome.

Q. For the determination of near-term versus late-term effects of treatment, is the question of whether the cognitive or cancer-related cognitive impairment is near-term or late-term a required analysis?

A. We would encourage long-term or late-term effects assessment, but in some contexts, that will not be relevant or possible. It will depend on the application making clear that meaningful conclusions can be drawn about the effects of treatment based on the follow-up period selected. We suspect that long-term effects are what most patients and clinicians are most concerned about. But the short-term effects, or acute effects, can also be very important for medical treatment, adherence, etc. Assessment of late-term effects would be very appealing but not essential. There also is a need for longitudinal data about late cognitive effects in preclinical studies, but whether that is a feasible question will depend on the applicants' specific aims, chemo-agent, the kind of cognitive testing, the species, etc. There will be preclinical studies for which the assessment of late cognitive effects will not be feasible.

Q. Is the funding opportunity announcement relevant to pediatric populations?

A. These PARs do not seek to support pediatric or a mix of pediatric and adult. We are interested in adult populations, ages 18 and older.

Q. Are preclinical studies an emphasis in this FOA?

A. The preclinical studies and clinical studies are both relevant; we are not emphasizing one over the other.

Q. Cognitive neuroscience-informed tests largely focus on the computerized assessment of skills that can distinguish selective attention and memory. Can you provide examples of cognitive neuroscience tests other than computerized?

A. In the FOA we invite the use of other instruments to assess brain activity (e.g., electrophysiology) to identify impaired cognitive processes. While we think most neuroscience paradigms will be computerized, there may be tasks that are much more oriented toward brain activity that is coincident with performing a cognitive task. Please contact Dr. Jerry Suls at jerry.suls@nih.gov or 240-276-6811 if you would like to discuss further.

Q. Would biological mechanisms be relevant as part of assessing the cognitive impact of cancer and treatment?

A. Absolutely. Identifying mechanisms of action as a function of chemo-agents or hormone blockers, etc., helps to clarify what cognitive process has been impaired. Biological mechanisms and their measurement are relevant but not essential for patient studies. Mechanisms are likely to play a major role in the preclinical study applications, where you can interrogate specific mechanisms in an experimental model.

Q. Other than test length, how do you clarify or distinguish between cognitive science tests and neuropsychological tests?

A. In standard clinical neuropsychology tests, with some exceptions, a poor performance on a test often implicates a composite of cognitive operations, so it is difficult to determine exactly where the impairment lies. Cognitive neuroscience paradigms can often probe more deeply about the source of the performance problem. For example, some neuropsychological test batteries can identify that a patient has a problem with memory but not whether it is long-term memory, short-term memory, or working memory, or all three. A well-developed cognitive science test can often differentiate far better than a neuropsychological test battery because it often requires looking at patterns of performance across different tests. The problem is that other factors may vary across the tests. We are not contending that all components of cognition are capable of being dissected at the current stage of cognitive neuroscience. A good place to find appropriate cognitive neuroscience tests is the consortium called the Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia (CNTRACS). It has a website that describes these paradigms for different aspects of cognition and subcomponent processes. There has been some incorporation of cognitive-neuroscience paradigms in functional brain imaging studies but little attempt to test the use of these paradigms for diagnostic purposes.

Q. Is it expected that the cognitive science tests that are proposed in these applications must have already been used in clinical samples of some type, or would more experimental cognitive science tests that might be used in healthy or normative samples be appropriate if they are scientifically justified?

A. Experimental cognitive tests are appropriate for this FOA.

Q. Is this funding mechanism appropriate for behavioral experiments in animal models, for examining mechanisms of cognitive impairment with chemotherapy?

A. Yes, if there is an aim and results that bear on whether the procedure could identify a potentially specific component of cognition that is impaired by chemotherapy.

Q. Is a standard battery expected in preclinical or animal model studies relevant to the FOA?

A. A standard battery is not expected in preclinical applications. However, it would be critical to justify the use of a cognition, learning, or memory paradigm for animals that can identify the specific processes that are not functioning properly. The use of a complete battery is not necessary.

Q. Would you expect that battery or that choice of either behavioral experiments or paradigms that are used in a preclinical model to have some ecological or translational relevance to human processes?

A. Absolutely. They should have some translational relevance and ecological validity. In most of the preclinical work that I am aware of, you can almost always find evidence for ecological validity. However, this should be specified in the application.

Q. Will grants be reviewed by special emphasis panel (SEP)? If so, will there be human and animal reviewers included in the peer-review group?

A. The grants will be reviewed by a special emphasis panel. There certainly will be strong recommendations to have reviewers with expertise in clinical and preclinical studies. We also anticipate that a SEP will have representation by cognitive scientists, clinical oncologists, psycho-oncologists, clinical neuropsychologists, and animal modelers. An applicant can request specific types of expertise on his or her cover letter to help ensure an adequate peer review of his or her application.

Q. Is there a funding limit to this FOA?

A. Because this is not a Request for Application (RFA), there are no specific limits set for this funding opportunity. The limitations will be based on how well the applications score in the review process. However, these are PARs, which means they do get a special review panel with relevant expertise to this particular set of questions and areas of research, both clinical and preclinical. In addition, these FOAs will remain active for a three-year period.