Request for Information (RFI) on Advancing Research in Fundamental Neuroscience (NINDS)
https://www.ninds.nih.gov/FN-RFI

Responses submitted by: Nicole C Rust, PhD

New ways that NINDS could better support FN:

Central to the mission of NINDS is figuring out 'What causes what?' with regard to nervous system function and dysfunction. In a recent community-based, collaborative effort, a number of us came together to generate 'A call for more clarity around causality in neuroscience' (Barack et al., Trends in Neuroscience (2022)). In that call, we introduced a number of suggestions to resolve the confusions about causality that are blocking progress in brain research. NINDS is well-positioned to act on one of those suggestions: supporting the creation of better conceptual frameworks for executing and interpreting brain perturbation experiments.

As we describe in our paper, recent progress on this topic has been made, but more work remains. One source of confusion is diaschisis - the change in the function of a brain area that results from the loss of its input due to perturbation in a distant brain area. This can happen in acute or chronic lesion studies, and when it does, it can lead to erroneous conclusions about function of the site of perturbation. We need better and more broadly agreed upon ways to disambiguate causal relationships in the brain, given its highly interconnected networks. Another challenge is randomization. While the importance of randomizing one variable relative to all others is conceptually clear, in practice this is often difficult to achieve. Modern perturbation methods such as targeted perturbation are powerful, but the results of these experiments can be difficult to interpret. To avoid erroneous conclusions, the causal relationships between the variables of interest needs to be carefully considered. In addition, given the complexities of inactivation and activation brain perturbation experiments, they should be regarded as one tool for inferring brain function but not prioritized at the expense of other approaches such as correlative measures.

In sum, NINDS can support fundamental neuroscience by supporting theoretical, computational and conceptual work targeted at understanding how to tease apart causal relationships in complex networks of the type that are reflected in the brain.

Issues that present obstacles or opportunities for the advancement of new areas of FN:

Because it is often difficult to anticipate what types of understanding of the brain will be most impactful, curiosity-driven research is an essential component of fundamental neuroscience. At the same time, contemporary neuroscience would benefit from a better concept of what types of understanding are missing from our current knowledge and what types of understanding are most likely to be impactful. Stated differently: of all possible questions that we might pursue, what should we prioritize learning about the brain next?

We all agree that a central goal of neuroscience is to determine 'What causes what?'. However, in the collaborative 'Call for clarity ..' mentioned above, we highlight that neuroscientists attach a diversity of concepts to the word 'cause' and consequently, neuroscience lacks a consensus vision for the path forward and its relationship to causality. For example, some fundamental researchers define causality in ways that lead them to target the brain areas that are most integral to brain function (such as the amygdala in the case of fear conditioning) with the implicit notion that understanding those will be most impactful in the longer term for treating brain dysfunction. Others define causality in broader ways that facilitate targeting many nodes along long causal chains with the understanding that clinical interventions can happen at any point (and sometimes even extend outside the brain where they can be targeted with behavioral interventions). Fundamental neuroscience has not arrived at consensus understanding of what it is that we are trying to achieve with regard to understanding 'What causes what?' and this is blocking progress. A better conceptual understanding of the relationships between different types of causes and different types of interventions would be very helpful for guiding fundamental neuroscientists toward research that will be impactful in the long-term.

Topic ideas for an NINDS FN workshop:

What types of fundamental knowledge about the brain are likely to be most impactful? Please see my response above to, 'Issues that present obstacles ...' A workshop exploring what it is that we are trying to achieve in fundamental neuroscience with regard to understanding 'What causes what?', and its relationship to laying the foundations for interventions in the longer term would be valuable for guiding fundamental neuroscientists toward research that will be impactful in the long-term.

Any additional comments related to Fundamental Neuroscience:

I want to express my gratitude for NINDS's wisdom in supporting Fundamental Neuroscience. As described by Isaac Asimov in his introduction to the 1974 book titled, 'The greatest adventure: Basic Research that shapes our lives':

"Today’s science is tomorrow’s solution — and tomorrow’s problems , too — and, most of all, it is mankind’s greatest adventure, now and forever."