Brown University
Providence, RI
Christopher Moore
$1,300,000

Discovery of dynamic processes that enable rapid and focal brain-body communication

The brain evolved to meet challenging biological needs, with the mammalian forebrain integrating lifelong experience, ongoing sensations, and future predictions. This powerful computation relies on the quality of body information received at moments of choice and learning. Brain vasculature contains a rich supply of such body signals, delivered in their native chemical format, but researchers view this pathway as sluggish and diffuse, unsuited to real-time behavior due to the blood-brain barrier (BBB). The recent discovery of Plume Events—rapid, local increases in BBB permeability timed to relevant behavioral events—suggest a dynamic solution for forebrain computation: brief vascular access when the risk is worth the information value. An investigator at Brown University and several of his collaborators will test key predictions, such as whether transient electro-calcium 'spikes' in vessels trigger these events, if Plume Events deliver impactful bio-active signals such as oxytocin, and if they are expressed across the forebrain. The collaborative team, bringing diverse computational and biological expertise, will also create a broader community for insight through colloquia and retreats focused on understanding this new discovery.

Dartmouth College
Hanover, NH
Michael Hoppa, Ahmed Abdelfattah
$1,000,000

Developing an optical technique to accurately measure membrane voltage

Recording the electrical activity of neurons at high spatial and temporal resolution is crucial for understanding brain function. Researchers are transforming this understanding by using fluorescent calcium-sensitive optical reporters to track neural activity across large populations of neurons. While neural circuits transmit information digitally through action potentials, the modulation of this flow is analog, dominated by rapid subthreshold voltage changes, which current imaging technology cannot capture. There are several challenges with optical voltage imaging, including photobleaching of intensity-based indicators, image blurring and motion artifacts, and the need for fast measurements and bright indicators due to sub-millisecond voltage changes. The aim of this project is to develop next-generation voltage indicators based on changes in the non-radiative decay rate of fluorescence lifetimes and use Fluorescence Lifetime Imaging Microscopy (FLIM) to enable absolute voltage measurements. This approach avoids photobleaching and blurring, making it ideal for voltage measurements at the cell membrane. The team will create a 4-D spatiotemporal FLIM microscope for rapid imaging and simultaneously image multiple ultrabright genetically encoded voltage sensors with distinct decay rates that are discernible by FLIM. FLIM-based voltage sensing could uncover new molecular mechanisms underlying neuronal excitability and other biological processes where voltage plays a role, such as insulin secretion in the pancreas and formation of biofilms by bacteria.

Massachusetts Institute of Technology
Cambridge, MA
Alison Ringel
$1,500,000

Understanding the role of T cells in healthy aging

Aging and related health issues are among our greatest public health issues. The accumulation of senescent cells, a state of permanent cell cycle arrest and inflammation, is an important driver of pathology. While molecular cues that trigger the onset of senescence are well-characterized, the natural mechanisms that restrain the accumulation of senescent cells are still poorly understood. An investigator at MIT proposed that the solution for clearing senescent cells will come from immunology. Recent studies have shown that CD8+ T cells actively clear senescent cells, using the same pathways by which they control viral infections and cancer. T cells are one of the only cell types in the body that can selectively destroy abnormal cells while leaving others intact, and they become less functional with advanced age. Thus, this investigator hypothesized that T cell dysfunction plays an active role in the aging process by enabling senescent cells to persist in tissues. Tools for studying antigen-specific immunity have not yet been introduced to aging research. Therefore, she proposed to develop novel animal models to enable the first studies that precisely identify senescence-associated antigens across tissues and time and to define how antigen-driven T cell responses control the progressive accumulation of senescent cells over lifespan at a mechanistic level.

Pennsylvania State University
State College, PA
Patrick Drew, Nicole Crowley, Nanyin Zhang
$1,200,000

The neural mechanism of nightmares

Dreams are amalgamations of recent and remote experiences mixed with fantastic and absurd elements. Sometimes dreams are nightmares, frightening experiences that can cause long-lasting distress. These unsettling thoughts during sleep can predict the development of many anxiety-related mental health conditions and even suicide, suggesting nightmares could be more than just a symptom, but rather a potential cause of brain disorders. However, their biological basis remains completely unexplored, and now a team of three neuroscientists at Penn State will develop a model of nightmares in mice. They will use converging pharmacological and optogenetic approaches to induce nightmares and will detect nightmare occurrence using both behavioral and neural markers. To uncover the biology underlying the generation of a nightmare, the molecular and circuit level changes caused by nightmares will be probed in sleep- and fear-related brain areas, as will the impacts of nightmares on brain network connectivity. The team will then recapitulate activity patterns in sleeping mice to recreate the behavioral signatures of nightmares. Finally, they will test if repeated replay of the nightmare-like activity during sleep can drive lasting, anxiety-like changes in behavior and brain connectivity.

University of California, Berkeley
Berkeley, CA
Nicholas Ingolia
$1,000,000

Systematic testing of sequence-function relationships in intrinsically disordered proteins

In the classical view, proteins fold into defined shapes that determine their function. However, almost a third of the human proteome is disordered and does not follow the rules established for folded proteins. Despite this, disordered regions of proteins play many essential roles, leaving a blind spot in our understanding of protein function. Disordered regions are prevalent in proteins that control mRNA translation and decay. These proteins are frequently mutated in neurodevelopmental and neurodegenerative diseases, making it difficult to predict the effects of mutations on disordered proteins. An investigator at UC Berkeley will learn how the sequence of a disordered protein determines its function in mRNA regulation through integrated high-throughput experiments and machine learning. The results from this project will aid in predicting the effects of genetic variants and cancer mutations affecting disordered regions. Disordered proteins exert their effects by binding to other proteins, achieving specificity without rigid sequence and structural constraints. The investigator's team will capture these interactions between disordered proteins and structured interaction partners and determine the molecular features underlying their specificity. In addition to answering fundamental questions about proteins, this research will inform strategies to strengthen or weaken these interactions therapeutically.

University of California, San Diego
La Jolla, CA
Vineet Augustine
$1,200,000

Understanding the interactions of the heart, brain, and immune system in heart attacks

Heart disease remains the leading cause of death worldwide, yet most treatments focus solely on the heart, overlooking the intricate neural network that influences it. An investigator at UCSD proposes treating myocardial infarction (MI) or heart attacks not just as isolated cardiac events, but as neuro-immunological disturbances driven by the interaction between the heart and brain. When ischemia (i.e., inadequate blood flow to tissues) occurs, the heart sends signals of tissue damage, hypoxia, and immune activation, which the brain interprets as acute stress. This triggers neural circuits to initiate an inflammatory response via the sympathetic nervous system, leading to maladaptive ventricular remodeling. To explore this interaction, the PI's team will employ a comprehensive strategy. Implanted probes will monitor real-time brain activity, while telemetry will track cardiac parameters such as heart rate, blood pressure, and body temperature. Single-cell and spatial transcriptomics of damaged heart muscle tissues will reveal molecular and immune mechanisms. By using opto- and chemo-genetic techniques, the team will activate cardiac sensory neurons. Advanced machine learning algorithms will decode neural states to enable closed-loop interventions. By combining cardiology, immunology, neuroscience, and machine learning, these studies could revolutionize cardiovascular care by leveraging the powerful connection between the heart and the brain.