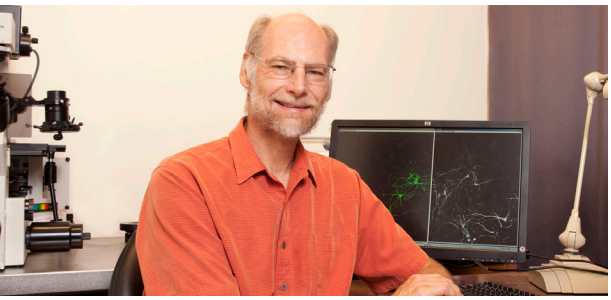
INNOVATE
EVIDENCE-BASED MENTAL HEALTH RESEARCH



Understanding Brain Connectivity on a Molecular Level

Johannes Hell, Ph.D., was awarded one of five BRAIN-STIM awards for the study "Detection of endogenous PSD-95, a-actinin and other proteins and their interactions in live cells by fluorescent peptides." The overarching goal of this study is to develop completely new tools that will help elucidate the molecular basis of how neurons communicate with each other.

Neurons are cells in the brain that receive, process, store, and relay information, ultimately defining who we are and how we process the world around us. Signaling between neurons involves axons, dendrites, synapses, neurotransmitters, action potentials and many other features. Axons transmit information that dendrites receive across a synapse. Here, a combination of electrical and chemical signals tells each neuron when to 'turn on' and send a message to other neurons. An electrical signal is sent though an action potential, which travels down the axon and stimulates the release of a small chemical compound called a neurotransmitter (e.g. glutamate). This neurotransmitter can either excite or inhibit the postsynaptic neuron (neuron #2) to send its own action potential and continue the message. Electrical signals converting to chemical signals is the basis for all brain activity.

The Synapse: 1 in 100,000,000,000,000

Let's look a little closer at one important component of neuronal signaling, the postsynaptic site. The postsynaptic site is where neurotransmitters bind, create a signaling cascade and either excite or inhibit the postsynaptic neuron. The majority (~80%) of neurons are excitatory, meaning they encourage action potentials to be sent and act like a green light. The type of neurotransmitter released by a cell determines if it will promote or inhibit the signal. The main excitatory neurotransmitter in the brain is glutamate. However, in order for glutamate to work its excitatory magic it must bind to a glutamate receptor (e.g. AMPA receptors) on the postsynaptic site. A protein called PSD-95 is responsible for anchoring glutamate receptors to the postsynaptic cleft and alpha-actinin is the protein that keeps PSD-95 at postsynaptic sites. So we know that glutamate leads to excitation after binding to AMPA receptors, AMPA receptors bind to PSD-95 and the stability of that connection determines the strength of the synapse. Strong synapses are related to long-term potentiation (LTP), which is the basis of learning and memory. Synapses are like muscles; the more they are used, through excitation, the stronger they get. Stronger synapses generally mean stronger memories, thus comes

"Fluorescent imaging of endogenous synaptic proteins in live brain tissue, such as PSD-95, in space and time will provide a crucial novel approach to advance our understanding how these proteins contribute to brain function."

-Johannes Hell, Ph.D., Professor of Pharmacology, UC Davis

the importance for understanding the interactions at the synapse.

Connections in the brain are either strengthened or weakened by signaling pathways leading to how we store information and learn new things. As important as synapse strength is for learning, dysregulation of synaptic strength can cause neural damage and is a component for most neurological disorders such as ADHD, Alzheimer's disease, schizophrenia, PTSD, stroke, epilepsy and others.

Hell's team is working on a revolutionary way to visualize the protein interactions at the synapse. The project's success would dramatically advance our understanding of the molecular basis of how postsynaptic AMPA receptor abundance is mediated by PSD-95 and alpha-actinin, which in turn is important not only for understanding learning and memory but also many different neurological and mental diseases in which AMPA receptor targeting is dysregulated. The team aims to understand the precise interactions that occur across the human brain's 100 trillion synapses and map brain connectivity on a molecular level.

Connections A-glow

This grant focuses on developing new technology for detecting proteins in a cell. Current methods are generally one of two. The first is using GFP, a fluorescent tag derived from jellyfish and the second is by using antibodies. Both methods have their benefits and their downfalls, but Hell envisions "a new technology that can circumvent most pitfalls." The new technology is based on fluorescent dyes.

Some dyes, like malachite green, will only send out florescence when bound to something. These dyes can be attached to a peptide, a small part of a protein, and will only glow when bound to a target protein. The team aims to identify peptides that bind specifically to PSD-95 or alpha-actinin. When the peptide binds to the protein it will act like turning on a light switch and the team will then be able to visualize PSD-95 and alpha-actinin interactions in live glutamatergic synapses.

One of the most arduous factors for achieving this goal is identifying a peptide that binds to PSD-95 or alpha-actinin specifically. This is where the expertise and collaboration between departments at UC Davis is of paramount importance. Kit Lam and Lin Tian from the Department of Biochemistry, James Ames in the Department of Chemistry and Vladimir Yarov-Yarovy in the Department of Physiology at UC Davis are key collaborators on this project.

Once the specific peptides for PSD-95 and alpha-actinin have been identified the team will work to label the interaction between the two proteins. The long-term goal is to be able to use this imaging technique in combination with CLARITY, a recent method developed to view whole brains translucently, to view synapses throughout the brain. Imagine all of the excitatory synapses in the brain labeled fluorescently within a transparent whole brain. This would be a revolutionary discovery in brain mapping.

The BRAIN Initiative

The BRAIN-STIM awards, co-funded by the Office of Research and the Behavioral Health Center of Excellence at UC Davis, were created in response to the White House BRAIN Initiative, whose goal is to map the structural and functional aspects of the brain. Hell explains, "This project could not be done without the BRAIN-STIM grant. There would be no funding for developing peptides that would specifically detect individual proteins. It is a high-risk project, but if it works it is also has a very high payoff." Hell's project aligns with this goal to map the interactions that occur at synapses throughout the brain.

Behavioral Health Center of Excellence at UC Davis

UC Davis launched the Behavioral Health Center of Excellence in October 2014 to advance mental health research and policy with initial funding from the Mental Health Services Act. The Innovate series highlights the Center's $4.3 million Research Pilot Award program.

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