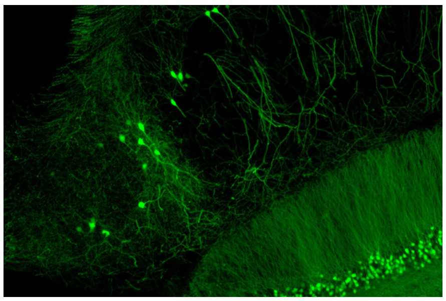
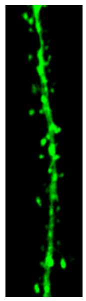
INNOVATE
EVIDENCE-BASED MENTAL HEALTH RESEARCH





A Dynamic Organ

The scientific community and much of the public have come to an agreement that the brain changes in response to sensory stimuli, just as muscles grow in response to exercise. The advent of "brain games" to improve cognitive function has made the concept of the brain as a dynamic organ a mainstream one. Learning is a particularly useful application of the dynamic brain. "When we learn, our brain not only changes in its function, but it also changes its structure," stated Karen Zito, associate professor of Neurobiology, Physiology and Behavior in the Center for Neuroscience at UC Davis. Zito studies how the structure of the brain changes in response to stimuli using advanced imaging techniques.

When we learn, sensory experiences come into the brain via our senses. Signals are sent through the brain via electrical activity. This electrical activity can shape neurons by stimulating the growth of new connections and strengthening existing ones. Just as sensory experiences can shape these connections, they can also be altered by disease. Neurological and psychiatric disorders like epilepsy and schizophrenia involve problems in the connection of the brain's neural circuits. Zito received one of 23 Research Pilot Awards from the Behavioral Health Center of Excellence at UC Davis for the study, "Analyzing Functional Plasticity with Synaptic Resolution Using a Novel Genetically Encoded Sensor." This project aims to understand the mechanisms that drive neural circuit modifications during learning and in disease, and to facilitate the development of targeted interventions for people with mental illnesses.

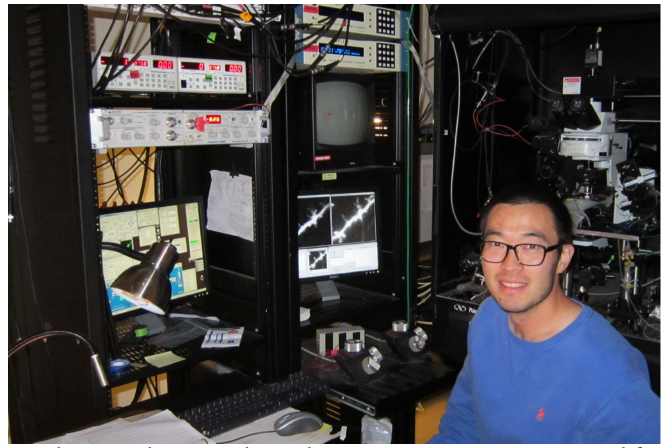
Excitable New Sensors

Neurons have axons and dendrites that they use to send and receive information through electrical signals. Additionally, dendrites have tiny protrusions called spines that grow and shrink depending on their inputs. Zito's project looks at these connections in real time, in living neurons, to discover how they change in response to experience, not only at the level of the individual neuron, but at each synaptic site.

Zito and colleagues use green fluorescent dye to mark neurons and see their shape and structure. Then, using a novel genetically encoded glutamate integrator coupled with a photoconvertible fluorescent protein, individual synapses change from green to red when they bind to glutamate, the main excitatory neurotransmitter in the brain. This causes the points on the neuron that have received a signal to change from green to red. The scientists can then see where neurons are talking to each other and how they respond to changes in stimuli, such as those received during a seizure as experienced in epilepsy.

"This project brings together researchers working at different levels of analysis in order to rapidly translate discoveries into treatments available to the community."

-Karen Zito, Ph.D.
Associate Professor, Center for Neuroscience



Graduate student Wonchan Oh uses a custom microscope vital for this project.

Structure and Function of Neural Circuits

Synaptic plasticity, or the ability for synapses to change in structure or function in response to neural activity, is tightly linked to learning and memory. Epilepsy is associated with enhanced neural activity, which causes new structures to form. When the brain transitions to an epileptic state, synaptic and neural circuit changes occur that current technologies are only able to probe on a global scale. Zito and her team's novel genetically encoded sensors enable monitoring these structural and functional changes at individual synapses. The visualization and localization of the modifications in brain structure that lead to changes in cognition and behavior can be transformative for the development of new therapies to treat epilepsy and other brain disorders.

Future of New Treatments

The team is able to expose brain slices to seizure-inducing convulsants and then monitor the localization of synaptic activity as the synapses change from green to red. By comparing the distribution and density of the red signal in these brain slices to those treated with novel therapeutic drugs, they will be able to more accurately predict the efficacy of new treatments.

"Ultimately, our future goal is to implement our novel sensors broadly to study the activity-dependent mechanisms that drive circuit changes in diverse neurological disorders," Zito said.

Multidisciplinary Team

"It would have been very difficult to embark upon this project without the BHCOE pilot awards. This project brings together researchers working at different levels in order to rapidly translate discoveries into treatments available to the community," stated Zito.

The interdisciplinary team includes Dr. Lin Tian, assistant professor in the Department of Biochemistry and Molecular Medicine at UC Davis, who brings chemical and protein engineering expertise, and Dr. Michael Rogawski, professor in the Department of Neurology at UC Davis, whose experience as a clinician researcher is invaluable for developing novel therapeutic techniques. Pilot funding allows the team to be truly innovative and pursue high-risk, high-reward research while bridging silos in the scientific community.

Educating the Next Generation

Beyond her work in the lab, Dr. Zito passionately educates future generations of neuroscientists. She teaches undergraduate and graduate courses as a faculty member in the College of Biological Sciences and she also organizes activities for grade school students through Brain Awareness Week. She strongly believes that by bringing awareness about scientific research and discovery in brain science, we can inspire the next generation.

Front image: dendrites and dendritic spines on hippocampal neurons filled with green fluorescent dye

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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