

# INNOVATE

## EVIDENCE-BASED MENTAL HEALTH RESEARCH



### **Bridging Structural and Functional Maps of the Brain**

Molecular interactions throughout the brain determine thoughts, feelings, behaviors, learning and memory and when these interactions go awry mental illness can result. Some of the most important molecular interactions occur at the synapse, or the point of connection between two neurons. The hundreds of trillions of connections throughout the brain are of particular interest to Kimberley McAllister, professor of neurology and neurobiology, physiology and behavior at UC Davis and one of five investigators funded by the UC Davis BRAIN-STIM program. McAllister and her team have developed a new approach to study synapse dynamics that identifies the molecular signature

of synapses of known age and strength. Their funded project is titled, “The functional synaptome: a novel screen for molecular signatures of functional synaptic state to bridge connectomics and large-scale recordings in mapping the brain.”

#### **Psychiatric Disorders**

Psychiatric disorders affect 1 in 5 people in the United States. “Mental illness isn’t about someone’s personal strength, but rather it’s about molecules and their interactions,” McAllister stated. We know that a constant balance of synapse formation, stabilization and elimination is essential for a healthy brain. “It is increasingly clear that abnormalities in the molecular composition of synapses are central to psychiatric and neurologic brain disorders,” McAllister said. “Identifying disease-specific changes in the molecular composition of synapses may allow us to better diagnose these disorders and identify knowledge-

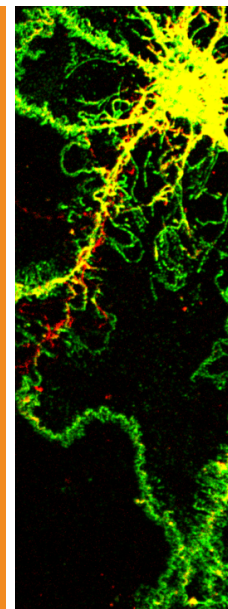
based therapies aimed at ameliorating their underlying synaptic defects.”

#### **The Connectome and the Functional Synaptome**

The connectome, or the map of all connections in the brain is a main goal of the BRAIN Initiative. McAllister’s work goes one step further to identify molecular signatures of strong vs. weak synapses, stable vs. newly formed synapses and active vs. inactive synapses to bridge the functional map with the structural map of the brain. “To achieve the objectives of the BRAIN Initiative, there is a critical, unmet need to place the connectome in the context of functional circuit dynamics” said McAllister. Her team aims to develop an assay that will allow the identification of molecular signatures of synapses in a range of functional states. If successful, there is potential to identify specific molecules that can

*“At UC Davis incredibly creative minds have the chance to intersect with the leading edge of technology to enable experiments we couldn’t even dream of a decade ago. It has been theorized for some time that the brain is not simply a bunch of static on/off connections. Dr. McAllister will directly test the molecular changes that neurons undergo as they figure out how to up- and down-regulate the strength of synapses in a constantly changing environment. Such knowledge is essential to understanding how the system works, how it adapts to change, and how we may gain better control over strategies for therapeutic interventions.”*

*-Paul FitzGerald, Ph.D.  
Dean’s Endowed Chair for Medical Research, UC Davis*



be targeted in the development of new drugs to repair synaptic dynamics.

### **Understanding Activity and Strength of Neurons**

Is there a molecular signature for a strong versus a weak synapse? McAllister aims to find out using an approach that places two neural networks in competition against each other for a common target.

The project uses microfluidics, which uses tiny channels to grow neurons in chemically isolated environments and guide interactions. Picture three chambers, two outer chambers connected to a central chamber by tiny channels, the size of a single axon. The central chamber contains a blue neuron. The outer chambers contain either a red neuron or a yellow neuron. The red and yellow neurons have axons that grow towards the center blue neuron. When the red neuron connects to the central blue neuron through the microfluidic channels the postsynaptic site will turn purple, but if the source were the yellow neuron it would turn green. The neurons in the outer chambers are altered pharmacologically to be either

strong or weak. The team can then see which connections came from active versus inactive inputs and then use a new approach called array tomography to identify the molecules that comprise each type of synapse, which will be the functional signature.

During development the brain creates, stabilizes and eliminates neuronal connections. If these connections form improperly it can result in communication deficits, aberrant behavior, obsessions, or inappropriate attention. Some connections in the brain drive cell function more than others, that is why the connectome alone cannot explain what goes on in the brain. Not all synapses are created equal, and the functional information that investigators gather may be able to explain why. “Neurotechnologies will drive innovation and answer fundamental questions,” explained McAllister.

### **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. McAllister’s project aligns with this goal by providing critical information about the brain’s circuits.

The team includes Kimberley McAllister, Stephen Smith, James Trimmer, Deb Van der List, and postdoctoral fellows Myka Estes, Alex Sood.

### **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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