2022 Buck Summer Scholar: Seth Talyansky

Hello! My name is Seth. I am twenty-one years old. I am a senior at Stanford University majoring in biology with a concentration in neurobiology. I am interested in understanding why brain health declines with age in the hope of learning how to mitigate debilitating and fatal neurological diseases. I also expect that a better knowledge of brain dysfunction will provide insights into the causes of the whole-body aging process, which increases risk of disease in all organ systems, as well as lead us to discover interventions that minimize these harmful effects.

At Stanford, I do research in the Greicius Lab in the School of Medicine, working with Professor of Neurology Michael Greicius and Quantitative Science Unit Assistant Director of Computational Biology Dr. Yann Le Guen on studying the genetic risk factors for Alzheimer's disease and other dementias. This summer at the Buck Institute, I am glad to be working with Professor Pejmun Haghighi and postdoctoral fellow Jill Farnsworth.

Human nerve cells connect to each other and muscle cells at synapses. The properties of these junctions are plastic, that is, adaptable. One kind of plasticity is homeostatic. This is the tendency of a synapse to preserve its overall function in the nervous system in response to changes in the presynaptic cell, such as an increased tendency of the neuron to fire, or in the postsynaptic cell, such as a loss of receptors for the signaling molecule on the muscle cell. Homeostatic plasticity is critical to normal nervous function, and impairment of this mechanism causes dysregulation of synaptic connections and has been widely observed under disease conditions. In the Haghighi Lab, we are studying precisely how homeostatic plasticity operates with an aim to uncover how its breakdown may in fact be a driver of age-related neurological disease.

We are working with the neuromuscular junction (NMJ) in the fruit fly *Drosophila,* a well-established model for human synapses. In flies, two main types of receptors at the muscle detect signals from the neuron: glutamate receptors (GluR) containing or lacking subunit IIA (GluRIIA). Eliminating GluRIIA-containing receptors induces homeostatic plasticity at the NMJ. This adaptation, which takes the form of reduced release of the signaling molecule from the neuron, is known to be triggered by a signal sent in reverse, from the muscle cell back to the neuron (termed the retrograde signal). One of the features of the GluRIIA-containing receptors is a robust ability to transmit calcium ions into the cell. Calcium is a prominent signaling molecule known to interact with many proteins and initiate many biological pathways inside cells.

We hypothesized that the decrease in calcium influx into the muscle, associated with loss of GluRIIA-containing receptors, induces the retrograde signaling from the muscle to the neuron. We tested this hypothesis by increasing calcium influx through GluRIIA-lacking receptors and investigating whether this would diminish the retrograde signal and homeostatic compensation. Our results so far have shown that this is indeed the case. Our work therefore suggests a key role for calcium signaling in the induction of homeostatic plasticity at synapses. As loss of synaptic homeostasis has been associated with many neurodegenerative diseases, our findings point to new therapeutic avenues.

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