

## **Determining the function of local inhibitory circuits in the synaptic dynamics of hippocampal pyramidal neurons during learning and memory.**

### Introduction:

The memories of the events we experience during our lives shape who we are. In mammals, the ability to learn and recall life's episodes is dependent on the hippocampus, where coordinated activity of excitatory and inhibitory neurons generates representations of life's episodes. It is thought that during this process excitatory and inhibitory neurons re-arrange their connectivity to support the formation of memories of such episodes. Yet, it is largely unknown how learning shapes the connectivity of hippocampal neurons and how changes in connectivity influence learning and memory.

### Project description:

The use of two-photon microscopy during the past years has revolutionized cellular and systems neuroscience as it allows investigating neurons and glia with high spatial and temporal resolution in live subjects in a relatively non-invasive fashion. Specifically, two-photon microscopy has been very instrumental in investigating how connections between neurons change in live animals as they become adult and learn. However, due to its location deep in the brain, the hippocampus has been inaccessible to two-photon microscopy. To solve this limitation, we have developed deep-brain two-photon microscopy and demonstrated that this technique allows tracking thousands of connections between hippocampal neurons in live mice over weeks to months.

The generous funding of the Schram foundation will enable us to use deep-brain two-photon microscopy to investigate how connections of excitatory and inhibitory neurons in the CA1 hippocampal region of mice change as new memories are formed and to study how these changes in connectivity support the subsequent recall of these memories.

In addition, we will focus the mechanisms by which interneurons modulate synaptic dynamics and learning and memory. We will use current molecular and cellular biological techniques to control the activity of inhibitory neurons in hippocampal CA1 and study the function of these neurons in learning and memory. At the same time, we will investigate how changes in the activity of these inhibitory neurons affect neuronal connections in the same mice as they learn and remember.

This work will clarify the mechanisms underlying acquisition and recall of episodic memories and, for the first time, establish a direct correlation between structural changes of inhibitory and excitatory neuronal circuits in the hippocampus and learning and memory.