GABAergic behavioral timescale synaptic plasticity

In rapidly evolving modern neuroscience, particular attention has been given to the understanding of the intricate molecular, cellular, and network mechanisms that underpin learning and memory. Experimental studies have revealed that the process of encoding memory traces is primarily linked to modifications at synapses, the junctions where neurons communicate. These modifications are known as synaptic plasticity. Most research has centered on excitatory synapses, where changes can result in long-term strengthening (long-term potentiation, or LTP) or weakening (long-term depression, or LTD) of information transmission through the synapse.

However, the brain also contains inhibitory GABAergic synapses, which are found in nearly every brain structure. These synapses play a crucial role in generating brain rhythms and influencing cognitive processes. Additionally, they are targets for various drugs, including benzodiazepines, anesthetics, and neurosteroids. For a long time, it was believed that inhibitory synapses did not undergo long-lasting plastic changes, mainly serving to regulate the stability of neuronal networks by controlling the frequency and synchronization of action potentials. Recent discoveries, however, have overturned this belief, revealing various forms of long-term plasticity in inhibitory synapses *in vitro*. Moreover, changes in the strength of inhibitory synapses have been observed during learning in mice.

A key difference between the well-studied plasticity of excitatory synapses and the emerging understanding of inhibitory synapse plasticity lies in their mechanisms of induction. Inhibitory synapse plasticity is often heterosynaptic, meaning it requires prior plastic changes in neighboring excitatory synapses.

Current research into the plasticity of GABAergic synapses faces two significant challenges. Firstly, there are many different types of inhibitory neurons in the brain. For example, the hippocampus, which is crucial for spatial memory encoding, contains over 20 types of inhibitory interneurons forming GABAergic synapses. Secondly, the commonly used experimental methods for inducing plasticity in inhibitory synapses *in vitro* or in acute brain slices do not accurately reflect the conditions within the brain's neuronal networks, potentially leading to artifacts.

In the initial phase of this project, we aim to address these challenges in studying GABAergic plasticity. Our primary goal is to uncover physiologically relevant mechanisms for inducing GABAergic plasticity at the molecular, cellular, and network levels. Specifically, we plan to investigate the interactions between excitatory and various inhibitory synapses in the hippocampus. Understanding these mechanisms will provide insights into the foundations of inhibitory synapse plasticity.

While the discovery of Hebbian plasticity in excitatory synapses, which includes LTP and LTD, has been pivotal in understanding learning mechanisms, it does not fully explain associative learning. To address this gap, a new form of plasticity in excitatory synapses, known as Behavioral Time Scale Plasticity (BTSP), has been identified. In BTSP, the activity of one excitatory neuronal pathway triggers dendritic spikes, which subsequently strengthen all excitatory synapses that were active a few seconds before, during, and a few seconds after the dendritic spike. This allows for the strengthening of excitatory synapses over the duration of learning. Recent research has shown that BTSP plays a fundamental role in forming place cells in the hippocampus, essential for spatial memory in mice.

However, it remains unexplored whether the induction of BTSP in excitatory synapses affects nearby inhibitory synapses. In this project, we plan to investigate how BTSP induction influences the strength of various inhibitory synapses and to uncover the molecular and cellular mechanisms behind these forms of GABAergic plasticity. This will enhance our understanding of the role of inhibitory synapse plasticity as a key mechanism in learning and memory.