Abstract for the general public

The balance between excitatory and inhibitory signals in the brain, known as the excitation/inhibition (E/I) balance, plays a crucial role in normal brain function. When this balance is disrupted, it can lead to abnormal activity in neural networks, which is often seen in neurological and psychiatric conditions like autism spectrum disorder (ASD) and schizophrenia. These disorders can cause altered sensitivity to sensory stimuli, which can be attributed to an E/I imbalance in circuits between the cerebral cortex and the thalamus, which are responsible for processing sensory information. In the brain, the E/I balance is maintained by inhibitory signals originating in a structure called the thalamic reticular nucleus (TRN). However, we still have limited knowledge about how the development and maintenance of E/I balance in the corticothalamic-TRN circuitry are regulated.

Recent research from our group has shown that a transcription factor called TCF7L2, which is known to be associated with neuropsychiatric disorders like ASD and schizophrenia, plays a role in shaping the electrical properties of thalamic neurons. Based on these findings, and my observation that TCF7L2-deficient thalamic neurons show reduced mechanisms of inhibition of action potentials, I propose that TCF7L2 is involved in establishing the E/I balance in the connections between the TRN and thalamus.

To test this hypothesis, I have designed a project which will investigate the effect of *Tcf7l2* removal (knockout) from the thalamus during early postnatal development on the E/I balance. I will concentrate on studying the corticothalamic-TRN somatosensory pathway, which is a well-described circuit in the brain. The project aims to answer the following questions: (i) How does the knockout of *Tcf7l2* from the thalamus affect the electrical activity and processing of excitatory and inhibitory signals in the corticothalamic-TRN circuit (Tasks 1 and 2)? and (ii) What are the consequences of thalamic *Tcf7l2* knockout on the functioning of inhibitory (GABAergic) connections in the corticothalamic-TRN circuit (Tasks 3, 4 and 5)?

To address these questions, I will use various approaches such as electrophysiology, electron microscopy, biochemistry, and molecular biology. First, (1) I will assess the electrical properties of the TRN and thalamic neurons using a technique called patch-clamp, suited for recording of an electrical activity of single neurons. Next, (2) I will combine light-based stimulation method and patch-clamp technique to understand the specific effects of excitatory and inhibitory inputs on thalamic neurons. Using electron microscopy, (3) I will examine the structure of the inhibitory synapse connecting the thalamus and the TRN. Additionally, (4) I will investigate the concentration of a neurotransmitter called GABA, which is involved in inhibitory signaling, by sampling extracellular GABA levels in awake mice using microdialysis and high-performance liquid chromatography. Finally, (5) I will analyze the protein composition of the inhibitory synapse in the thalamus by quantifying the levels of enzymes and receptors involved in GABA signaling.

The results obtained from this project will provide insights into the role of TCF7L2 in establishing the E/I balance in the corticothalamic-TRN circuit and shed light on the underlying mechanisms. Understanding these processes within the somatosensory circuit will also serve as a foundation for extrapolating these findings to higher-order circuits in the thalamus. Ultimately, this research may contribute to the development of a mouse model to study thalamic impairments in the E/I balance associated with neuropsychiatric disorders.