

Major depressive disorder (MDD) is one of the most widespread mental disability. Current therapies of MDD are suboptimal, with only one third of patients responding to first line treatment, and a majority failing to achieve full remission. These deficiencies highlight the urgent need of designing improved therapeutic strategies, driven by understanding the biological basics of the disease.

Previous studies identified lowered expression of genes encoding synaptic proteins and decreased number of synapses in the brains of MDD patients. These changes were prominent particularly in the prefrontal cortex, a brain center integrating response to stress. Similar changes were observed in rodent models of chronic stress. On the other hand, antidepressants, including fast-acting ketamine, were shown to rescue stress-induced synaptic deficits in rodent PFC. These studies suggest that restoration of the plasticity of synaptic connectivity represents crucial mechanisms for successful outcome of antidepressant treatment. However, mechanisms underlying neural circuit remodeling in stress and depression remain unclear.

Our previous work showed that astrocytes may be a long-overlooked cell type contributing to the disease. We found that expression of astrocyte-specific genes known to control developmental synapse formation and elimination was downregulated in prefrontal cortex of MDD patients and in rodents exposed to chronic stress. In mice, these changes were largely prevented by astrocyte-specific elimination of glucocorticoid receptors. Our data suggest a hitherto unknown mechanism of synapse loss in MDD where astrocytes play a crucial role: stress-induced downregulation of astrocyte-specific genes controlling synaptic connectivity.

In the current project, we will employ state-of-the-art neurobiological tools to directly test this hypothesis. First, we will use a recently developed method enabling precise genetic manipulation in a single cell type and defined brain regions. Second, to visualize the impact of this intervention, we will perform longitudinal *in vivo* imaging of dendritic spines – anatomical structures hosting synapses. Third, for detailed evaluation of the effects of genetic modification, we will obtain 3D-reconstruction of previously imaged brain regions with electron microscopy. Fourth, we will adopt the method established at the Max Planck Institute in Munich, enabling automated tracking of 60 voluntary behaviors of rodents, including social interactions, controlled by the PFC.

In summary, using the modern approaches for genetic modifications, imaging and high-throughput analysis of behavior, we expect to obtain a significant progress in understanding of contribution of astrocytes to remodeling synaptic connectivity in brain regions affected in depression. We envisage that our data will form the basis for developing new strategies of psychiatric diseases.