Brain development is a complex and sensitive to adverse conditions process, its disorders can have very serious consequences that can last a lifetime. One of the most common neurodevelopmental disorders is autism spectrum disorder (ASD). Symptoms of ASD include deficits in social-emotional reciprocity and repetitive, restricted behavior patterns that vary widely in severity. Currently, 1 in 100 children are diagnosed with ASD, but a significant number of patients receive the diagnosis much later in life. Despite this prevalence, there is no approved targeted drug, and available therapies focus on alleviating coexisting symptoms, not treating the disorder. Importantly, up to 30% of people with ASD do not receive any form of treatment. That's why it's so important to study the neuronal circuits underlying ASD, as this can lead to the development of better treatments and more tailored screening tools and diagnostic tools.

ASD profoundly affects the hippocampal formation (HPC) and the dentate gyrus (DG) with the ventral HPC being especially important due to its role in social behavior and memory. Cognitive inflexibility, increased preoccupation with minutiae, and unrestrained fixation on fine details, seen in ASD, may result from an imbalance between two hippocampal processes: pattern separation and pattern completion. Pattern separation involves transforming similar inputs into less similar outputs, ensuring distinct memories remain discernible. Conversely, pattern completion reconstructs complete stored representations from partial inputs, facilitating memory retrieval associated with familiar cues. Pattern separation takes place within the granule cell layer of the DG, where incoming information from the entorhinal cortex undergoes pattern separation, ensuring that only valuable and relevant input is transmitted to the hippocampal CA3 field, where pattern completion occurs. Excessive pattern separation may impede the normal integration of environmental information, causing individuals to focus too much on individual contextual and sensory features at the expense of understanding the “big picture”.

Proper pattern separation relies on DG interneurons, which regulate granule cell activity. Many studies have reported reduced numbers of specific DG interneuron populations in ASD. Moreover, DG interneurons are sensitive to neuropeptides such as oxytocin (OXT) and relaxin-3 (RLN3), though their influence on DG function remains unexplored. Both OXT and RLN3 are confirmed to play roles in social behaviors. OXT, in particular, has been extensively studied as a potential treatment for ASD, with its receptors located in the ventral HPC being crucial for discriminating social stimuli. Additionally, chronic activation of the RLN3 receptors (RXFP3) in the ventral HPC, reduces social interactions.

To verify the hypothesis, a series of experiments will be conducted using advanced neuroscience methods. Interneurons of the ventral DG carrying RXFP3 or OXT receptors (OXTR) will be studied for their electrophysiological properties and abundance. The course of pattern separation in ASD and the effect of RXFP3 and OXTR activation on this process will be studied at the neuronal network level. In addition, behavioral experiments using genetically modified animals will verify the role of NI neurons, which innervate the ventral DG and are sensitive to OXT, in the expression of social preference. The data obtained from the planned studies could greatly enhance our understanding of the neuronal mechanisms underlying ASD. In particular, the planned studies have the potential to elucidate the role of the OXT/OXTR and RLN3/RXFP3 systems in the pattern separation within the DG and in the regulation of social preferences in ASD and physiological conditions.