The role of the hippocampal-prefrontal cortex circuit in social memory, and its impairment in Rett syndrome mice

Inputs from the ventral hippocampus (vHIP) to the medial prefrontal cortex (mPFC) are implicated in several neuropsychiatric disorders. Here, we show that the vHIP–mPFC projection is hyperactive in the Mecp2 knockout mouse model of the autism spectrum disorder Rett syndrome, which has deficits in social memory. Long-term excitation of mPFC-projecting vHIP neurons in wild-type mice impaired social memory, whereas their long-term inhibition in Rett mice rescued social memory deficits. The extent of social memory improvement was negatively correlated with vHIP-evoked responses in mPFC slices, on a mouse-per-mouse basis. Acute manipulations of the vHIP–mPFC projection affected social memory in a region and behavior selective manner, suggesting that proper vHIP–mPFC signaling is necessary to recall social memories. In addition, we identified an altered pattern of vHIP innervation of mPFC neurons, and increased synaptic strength of vHIP inputs onto layer 5 pyramidal neurons as contributing factors of aberrant vHIP–mPFC signaling in Rett mice.