Inhibitory mechanisms of memory reactivation

Episodic memory formation relies on neural assembly reactivation during hippocampal sharp-wave ripples (SPW-Rs). However, the circuit mechanisms governing the formation and stabilization of these assemblies remain poorly understood. Here, we introduce an approach to generate synthetic neural assemblies *in vivo*, enabling causal investigation of their emergence within hippocampal circuits. Using silicon probes with integrated micro-LEDs, we selectively coactivated groups of CA1 pyramidal neurons in behaving mice while performing large-scale electrophysiological recordings.

Across multiple stimulation protocols, only fast gamma–like bursting induced long-lasting assembly formation, as evidenced by increased pairwise co-firing, mutual information, and ICA-defined neuronal assemblies among coactivated neurons. Notably, other protocols that elicited comparable or stronger excitation during stimulation failed to produce persistent assemblies. Instead, fast gamma stimulation uniquely induced inhibitory responses during coactivation, enhancing interneuron responses via short-term facilitation at pyramidal-to-interneuron synapses.

This inhibitory enhancement persisted into subsequent sleep, where it selectively suppressed co-firing among unrelated neurons, thereby promoting the emergence and stabilization of induced assemblies. Consistent with this, assembly formation was characterized by cluster segregation within the network, combining increased population coactivation within stimulated assemblies with suppression of cofiring between different assemblies.

To generalize these findings, we examined spontaneously emerging assemblies in behaving mice. We observed both positive and negative coactivation signatures between CA1 pyramidal neurons, together with an enhanced inhibition in neurons with higher spatial information content during SPW-Rs. Finally, chemogenetic perturbation of CA1 interneurons reorganized population activity and disrupted memory reactivation, identifying inhibitory plasticity as a key mechanism organizing neural assemblies during memory consolidation.