Rhythmic PV Interneuron Gating of Behavioral Timescale Synaptic Plasticity: A Mechanism of Cognitive Impairment in Temporal Lobe Epilepsy

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Abstract:

Temporal lobe epilepsy (TLE) frequently causes hippocampus-dependent cognitive impairment that is not fully corrected by seizure control, indicating mechanisms beyond recurrent ictal activity. Behavioral timescale synaptic plasticity (BTSP) enables CA1 pyramidal neurons to associate synaptic inputs with dendritic plateau potentials across seconds, supporting rapid memory encoding; however, how its broad temporal window excludes irrelevant inputs remains unclear. We hypothesize that parvalbumin-positive (PV) interneurons provide rhythmic perisomatic inhibition around plateau events, organizing pyramidal-cell membrane potential and spike timing to constrain the BTSP window and preserve input selectivity, whereas disrupted PV timing after TLE produces BTSP rule mismatch and memory impairment. In pilocarpine-induced TLE mice, our preliminary studies identified deficits in object-recognition and spatial memory accompanied by altered CA1 theta/gamma activity and abnormal spike–theta phase organization. Single-nucleus transcriptomics and immunofluorescence further revealed changes in PV interneuron synaptic programs, population recruitment, and spatial organization. We established an ex vivo CA1 BTSP induction and time-window assay and developed a simplified computational model incorporating eligibility traces, plateau-associated instructive signals, and inhibitory gating. With inhibitory strength held constant, shifting PV-gating phase displaced the effective BTSP association region, while increased timing jitter elevated the ratio of extra-window to within-window synaptic weight change by approximately 17%, indicating reduced selectivity. We will combine PV-specific optogenetics, whole-cell recording, in vivo electrophysiology, and object–location–context memory testing to distinguish inhibitory-amount from timing-dependent effects and test causal rescue in chronic TLE. This framework links PV timing, BTSP temporal precision, and epilepsy-related cognitive dysfunction across molecular, cellular, network, and behavioral levels.

Keywords:

Temporal lobe epilepsy, Behavioral timescale synaptic plasticity, Parvalbumin interneuron, Rhythmic inhibition, Hippocampal CA1, Cognitive impairment.