Closed-Loop Optogenetic Manipulation of Hippocampal Sharp-Wave Ripples

Final Report

Nicole Wang, Hu, Nicolas Dundov Muñoz, Nawal Zabouri, Mirna Merkler, Shuzo Sakata & Simon Schultz (PI)

1. Summary of the Project

Hippocampal sharp-wave ripples (SWRs) are brief, high-frequency population events that play a critical role in memory consolidation and decision-making. The project aimed to develop and optimise a **closed loop optogenetic system** capable of detecting SWRs in real time and manipulating their duration through precisely timed red-light stimulation targeted to CA1 pyramidal cell populations.

The work proceeded in two phases: a **calibration phase** to define stimulation parameters that reliably prolong SWRs, followed by a **behavioural phase** to test whether these same parameters enhance performance during a memory-demanding head-fixed alternation task. Calibration demonstrated that ripple duration could be reliably increased using bilateral ChrimsonR-mediated optogenetic stimulation at mid–high intensities (3–6 mW). However, during behaviour, identical parameters often reversed their effect—SWRs were truncated rather than prolonged, ripple occurrence rates decreased, and task performance did not improve.

The divergence between physiological calibration and behavioural outcomes highlighted the strong context-dependence of closed-loop neuromodulation, particularly regarding detection latency, brain state, and network excitability.

2. Brief Methodology

The project combined two phases. (1) Calibration**:** bilateral CA1 recordings and ChrimsonR-mediated optogenetic stimulation were used to test how light intensity (3-6 mW) and laterality (unilateral vs. bilateral) affected ripple duration, power, and interhemispheric synchrony. (2) Behavioural testing**:** optimal parameters from calibration: bilateral mid-high and 100 ms red-light pulses, were implemented in a real-time closed-loop system during a head-fixed spatial alternation task on a floating track. Ripple dynamics, fate, and task accuracy were compared with random-delay controls. This design enabled physiological calibration before behavioural validation.

3. Impact of the Project

3.1 Advancing Closed-Loop Neuroscience

This project makes several impactful contributions:

1. **Physiological Parameterisation of SWR Control.** The calibration data establish clear dose-response relationships and demonstrate that bilateral optogenetic stimulation can reliably and safely prolong SWRs. These findings provide an empirically grounded framework for designing ripple-modulation paradigms, filling an existing gap in standardised stimulation parameters.
2. **Identification of Critical Failure Modes in Behaviour**. The discovery that identical parameters can prolong SWRs during rest but truncate them during behaviour reveals crucial constraints on real-time neuromodulation. Factors including elevated detection latency, reduced early-window coverage (<30 ms), and theta-dominated locomotor dynamics all contribute to inconsistent effects. This insight helps the field move beyond simple parameter tuning toward a deeper understanding of **state-dependent neural responsiveness**.
3. **Design Rules for Future Closed-Loop Systems**. The work generates actionable guidelines that directly inform the next generation of closed-loop neuromodulatory experiments.

4. **Highlighting the Importance of Network State Alignment**. The project frames optimal stimulation not as a fixed set of parameters, but as **alignment between stimulation and appropriate physiological states.**

Overall, the project significantly advances our understanding of the constraints and opportunities inherent to real-time manipulation of memory-related neural events.

4. Contribution to the Neuromod+ Network Aims

The **Neuromod+ network** aims to accelerate neuromodulation innovation by integrating advanced neurotechnology, computational modelling, and translational neuroscience to develop more effective, personalised, and state-aware neuromodulatory interventions.

This project directly furthers these aims in multiple ways:

4.1 Developing State-Aware Neuromodulation

By demonstrating that SWR manipulation efficacy depends strongly on behavioural and network state, the project supports the neuromd+ focus on *adaptive, intelligent neuromodulation strategies*. The identification of latency, jitter, and state gating as critical factors provides a roadmap for closed-loop neuromodulators that respond dynamically to neural context.

4.2 Refining Real-Time Detection and Control Pipelines

The project advances the engineering of real-time neural interfaces by developing multi-feature SWR detection, demonstrating the importance of rapid processing pipelines, and establishing precision metrics (precision, recall, F1) for online event detection. These are foundational to the Neuromod+ goal of building robust and transparent neuromodulation systems.

4.3 Enabling Personalised and Target-Specific Neuromodulation

Ripple-targeted stimulation represents a **highly specific, physiologically grounded form of neuromodulation**, aligning directly with Neuromod+'s emphasis on precision targeting. The project's demonstration that stimulation must be aligned with individual event characteristics (e.g. amplitude percentile, temporal window) provides a model for personalised modulation strategies.

5. Outputs

1. RN Wang, J Hu, N Dundov Muñoz, N Zabouri, M merkler, S Sakata and SR Schultz (2025). Close-loop optogenetic manipulation of hippocampal sharp-wave ripples. Poster presentation at UK Symposium on Neuromodulation and Neurotechnology 2025 (UKSNN 2025), Newcastle, UK, November 2025.
2. RN Wang, J Hu, N Dundov Muñoz, N Zabouri, M merkler, S Sakata and SR Schultz (2025). Close-loop optogenetic manipulation of hippocampal sharp-wave ripples. To be presented at International Neuromodulation Society Conference, Lisbon, Portugal, May 9-14, 2026.