PhD PROJECT PROPOSAL

Functional heterogeneity of hippocampal fast oscillations for memory processing

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Abstract (10 lines)*

The hippocampal region plays a pivotal role in episodic memory formation through collective neuronal discharges organized as cell assemblies or hippocampal Sharp Wave Ripples (SPW-Rs). While the classical view presents SPW-Rs as the result of the discharge of a canonical hippocampal circuit, our recent experimental observations in the mouse reveal distinct SPW-R profiles, suggesting the involvement of diverse neuronal subcircuits. Our hypothesis posits the existence of various SPW-R classes, each representing unique neuronal networks and functional processes. To investigate this, we will employ a suite of advanced machine learning techniques, including deep neural networks, and develop computational models of hippocampal networks. Our aim is to characterize the diversity of SPW-Rs, identify associated neural substrates, and elucidate the role of inter-area feedback loops in shaping the heterogeneity of SPW-R events.

Keywords*

memory, neural processing, signal analysis, machine learning, classifiers, hippocampal circuitry

Scientific question and Objectives (10 lines)*

This project aims to develop a novel classification framework for hippocampal Sharp Wave Ripples (SPW-Rs) utilizing advanced artificial neural networks. The presumed function of SPW-Rs is to integrate and consolidate the memory of recent experience. The typical electrographic signature of hippocampal SPW-Rs has been interpreted as evidence for the involvement of a canonical neuronal circuit, replaying at fast time scale the sequences of awake neuronal discharges. Departing from this traditional view, our recent observations reveal a surprising diversity in the electrographic signatures of SPW-Rs, strongly suggesting the local integration of distinct sets of inputs. Through the application of cutting-edge signal processing and machine learning techniques, we will characterize this previously overlooked diversity of SPW-Rs, uncovering their potential associations with specific neural circuits. In parallel, we will develop and refine computational models of the involved neural networks to better understand the functional consequences in terms of neuronal processing.

*: Mandatory

Proposed approach (experimental / theoretical / computational) and research plan (20 lines)*

This project integrates data analysis and computational approaches to investigate the diversity of hippocampal Sharp Wave Ripples (SPW-Rs). We will analyze simultaneous silicon probe recordings of neuronal activity from the Entorhinal Cortex, CA3, and CA1 regions of adult mice in a virtual reality set-up, during both rest and active behavioral states (wheel running in the head-fixed configuration). Variational Autoencoders (VAEs) with convolutional and/or transformer networks will be employed to classify experimentally recorded CA1 SPW-Rs based on their unique electrographic signatures. Subsequently, non-linear dimensionality reduction techniques like UMAP will be utilized to analyze cell assemblies and sequences associated with each class of CA1 SPW-Rs. This will enable the identification of distinct cell assemblies preferentially linked with specific SPW-R profiles, providing crucial insights into the functional integration of hippocampal processing during these events.

In parallel, we will develop computational models of hippocampal networks to systematically investigate the impact of different connectivity motifs and synaptic strengths on the generation and characteristics of SPW-Rs. These models will consist of spiking neurons with diverse connectivity patterns, reflecting the anatomical and physiological characteristics of the hippocampal circuitry. To analyze the dynamics of these models, we will employ the Fokker-Planck approach, a powerful mathematical framework for studying stochastic processes in complex systems. This approach will allow us to characterize the probability distributions of network states and identify the key factors that contribute to the expected diversity of ripple events in the model.

By integrating these analysis and computational approaches, we will gain a comprehensive understanding of the mechanisms underlying the diversity of hippocampal SPW-Rs, bridging the gap between cellular and network-level processes.

Interdisciplinarity and Implication of the two labs (15 lines)*
(In this section the collaboration of the two laboratories will be explained in details to explain why the project cannot be conducted by one team alone)

This project embodies a unique interdisciplinary collaboration, drawing upon the complementary expertise of X. Leinekugel in experimental neuroscience and Hervé Rouault in theoretical and computational neuroscience. Dr. Leinekugel brings extensive experience in electrophysiological recordings, behavioral analysis, and the study of hippocampal function, while Dr. Rouault possesses deep expertise in neural network modeling, machine learning, and information processing. This synergistic partnership will drive the project forward, enabling us to address fundamental questions about the neural mechanisms underlying episodic memory in the mammalian brain.
Computational approaches, fueled by the rapid advancements in computing power, are increasingly crucial for unraveling the complexities of neural systems. This project leverages a diverse array of computational techniques, including: machine learning classifiers, such as Variational Autoencoders (VAEs) with convolutional and/or transformer networks, non-linear dimensionality reduction, spiking neuron network models and analytical approaches. By integrating these diverse computational approaches with rigorous experimental data, this project pioneers an interdisciplinary framework to unravel the intricacies of neural processing during episodic memory formation.

Specify with whom the person recruited will collaborate and on what aspects *
The recruited person will become an integral member of our highly interactive and collaborative

*: Mandatory

research team. Despite being located in separate laboratories, we maintain close and frequent interactions, with weekly meetings and regular student exchanges. The successful candidate will have the opportunity to collaborate closely with both PIs throughout the project. For data analysis and the design of neural network models, the candidate will work closely with both PIs. For the more analytical and computational aspects of the project, including the development and analysis of spiking neuron models and the application of the Fokker-Planck formalism, the candidate will have more intensive interactions with Dr. Rouault.

PhD student's expected profile*

We seek a highly motivated PhD student with a robust background in physics and/or computational approaches, particularly in signal analysis and machine learning. Previous experience with electrophysiological recordings can be appreciated but is not required. The ideal candidate should demonstrate a keen interest in probing fundamental questions within the field of neuroscience and possess a curiosity-driven approach to interdisciplinary research. This position offers a unique opportunity for the selected candidate to bridge the gap between theoretical insights and experimental observations, contributing to groundbreaking discoveries in the realm of neural circuit processing and memory formation.

Is this project the continuation of an existing project or an entirely new one? In the case of an existing project, please explain the links between the two projects (5 lines)*

This project is an entirely new project, although based on experimental observations made in former experimental projects.

Two to five references related to the project*

1. Buzsáki, G. (2015). Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. Hippocampus 25, 1073-1188.
2. Gedankien, T., Gotman, J., et al. (2022). A consensus statement on detection of hippocampal sharp wave ripples and differentiation from other fast oscillations. Nat Commun 13, 6000.
3. Girardeau, G., Benchenane, K., Wiener, S.I., Buzsaki, G., and Zugaro, M.B. (2009). Selective suppression of hippocampal ripples impairs spatial memory. Nature Neuroscience 12, 1222-1223.
4. Valeeva, G., Janackova, S., Nasretdinov, A., Rychkova, V., Makarov, R., Holmes, G.L., Khazipov, R., and Lenck-Santini, P.-P. (2018). Emergence of Coordinated Activity in the Developing Entorhinal–Hippocampal Network. Cerebral Cortex 29, 906-920.
5. Donoso, J. R., Schmitz, D., Maier, N., & Kempter, R. (2018). Hippocampal ripple oscillations and inhibition-first network models: frequency dynamics and response to GABA modulators. *Journal of Neuroscience*, *38*(12), 3124-3146.

Two main publications from each PI over the last 5 years*

X. Leinekugel

1. Dubanet, O., Ferreira Gomes Da Silva, A., Frick, A., Hirase, H., Beyeler, A., and Leinekugel, X. (2021). Probing the polarity of spontaneous perisomatic GABAergic synaptic transmission in the mouse CA3 circuit in vivo. Cell

reports 36.
2. Carreño-Muñoz, M.I., Medrano, M.C., Ferreira Gomes Da Silva, A., Gestreau, C., Menuet, C., Leinekugel, T., Bompart, M., Martins, F., Subashi, E., Aby, F., et al. (2022). Detecting fine and elaborate movements with piezo sensors provides non-invasive access to overlooked behavioral components. Neuropsychopharmacology 47, 933-943.

H. Rouault
1. Dard RF, Leprince E, Denis J, Rao Balappa S, Suchkov D, Boyce R, Lopez C, Giorgi-Kurz M, Szwagier T, Dumont T, Rouault H, Minlebaev M, Baude A, Cossart R, Picardo MA. (2022). The rapid developmental rise of somatic inhibition disengages hippocampal dynamics from self-motion. Elife 11:e78116
2. Kim SS, Rouault H, Druckmann S, Jayaraman V. (2017). Ring attractor dynamics in the Drosophila central brain. Science 356(6340):849-853

Project's illustrating image

Figure 1

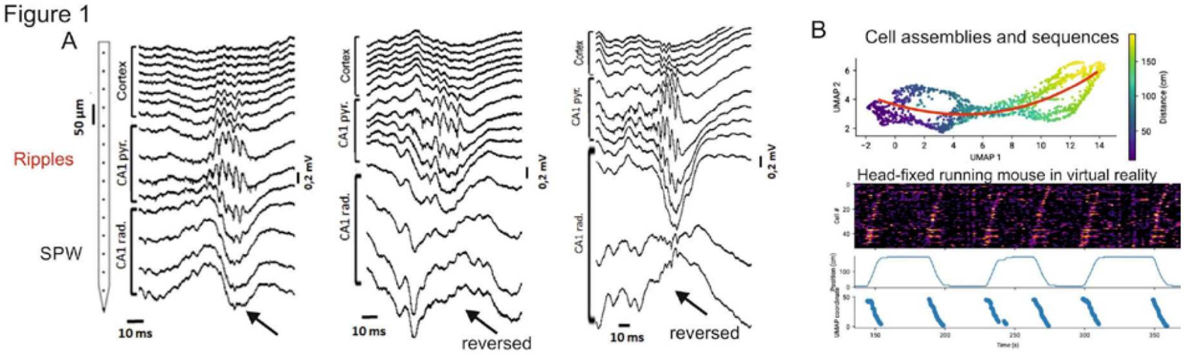

Fig1 A. SPW-Ripples recorded with a 16-sites silicon probe (50µm vertical separation) in the CA1 area of head fixed adult mice alternating locomotion and rest on a running wheel show a variety of SPW profiles, including "reversed" SPWs. B. Dimensionality reduction techniques allow to identify spike sequences throughout active behavior and their replay during SPW-Rs.