PhD PROJECT PROPOSAL

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How are cognitive maps affected in a mouse model of ASD ?

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Abstract (10 lines)*

Autism Spectrum Disorders (ASD) are neurodevelopmental conditions with diverse causes, leading to symptoms such as impaired social interaction, and repetitive behaviors. Individuals with ASD experience **sensory processing** and **cognitive impairments**, which may be linked to **dysfunctions in the hippocampus**—a brain region that organizes sensory information into cognitive maps to support memory and spatial navigation. A mismatch between external information and the local neural network dynamics in the hippocampus might result in incorrect mental representations, contributing to ASD symptoms. In mice, active exploration and experience-dependent plasticity begin around the end of the 2nd postnatal week (onset of vision and hearing). At this stage, hippocampal neurons start forming **cognitive maps** to represent the world in the form of **neuronal sequences**. We aim to determine when and how neuronal sequences are affected in ASD leading to a distort mental representation. To do so, we will combine 2-photon imaging with computational models to test how ASD-driven changes in excitation/inhibition balance and synaptic plasticity affect the formation, stability of neuronal sequences.

Keywords*

Hippocampus, Development, 2-photon calcium imaging, computational models, excitation/inhibition balance, ASD, neural dynamics

Scientific question and Objectives (10 lines)*

The project aims to investigate how early structural and functional disruptions in hippocampal circuits impact the formation and stability of cognitive maps. Analysis tools will be initially developed to extract and quantify neuronal sequences from imaging data, focusing on their timing, stability, and cell-type-specific dynamics. Experimental results will inform computational circuit models designed to simulate how ASD-related changes in synaptic plasticity and in excitation/inhibition balance impair network functionality. In turn, model predictions about circuit dysfunction will be validated through experimental approaches (see figure below). By integrating experimental and computational methods, the project seeks to uncover the mechanisms underlying ASD-related impairments in the hippocampus.

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

Wet lab: In this project, we will use a combination of transgenic mice, virus injections, anatomical analysis and large scale longitudinal (following same neurons days after days) *in-vivo* two-photon imaging. We will benefit from a newly deep-learning based algorithm (developed in the team, see Denis et al., 2020) and analysis pipeline

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(see ratsifandrihamanana et al., 2024) to analyze these recordings and characterize neuronal activity. To complement this computational approach, we benefit from the expertise of the Dr Lorenzo Fontolan to predict and modeled our data.

Dry lab: Under the co-supervision of Dr. Fontolan, computational tools will be developed to analyze neuronal sequences from imaging data. These tools will incorporate dimensionality reduction, clustering, and other advanced techniques to extract meaningful activity patterns. Circuit models will simulate how ASD-associated disruptions in excitation/inhibition balance and synaptic plasticity influence the formation, coherence, and functionality of these neuronal patterns. Model predictions will guide experimental manipulations, providing mechanistic insights into hippocampal circuit dysfunction.

The successful candidate will receive comprehensive training in state-of-the-art experimental techniques, including longitudinal *in-vivo* imaging. They will also gain experience in computational methods for detecting and analyzing neuronal sequences, as well as in developing and applying circuit models to understand hippocampal network dynamics. This interdisciplinary approach, combining experimental and computational strategies, offers a unique and valuable research experience.

Interdisciplinarity and Implication of the two labs (15 lines)*

The project investigating the emergence of cognitive maps in ASD necessitates the combined expertise of both experimental and computational approaches, making collaboration between the two laboratories indispensable. Picardo's lab provides critical insights into hippocampal development through cutting-edge techniques like *in-vivo* two-photon microscopy, electrophysiological recordings, and behavioral assays. These methods generate detailed data on neural dynamics and anatomical changes in ASD mouse models. However, interpreting these complex datasets requires a robust theoretical framework, which is where Fontolan's lab plays a pivotal role. Lorenzo's expertise in building computational models of brain circuits is essential for analyzing neural activity and identifying the principles underlying network dysfunction. Ultimately, a computational model will allow us to generate stable hypotheses about hippocampal mechanisms affected in ASD. The iterative process of hypothesis generation, model refinement, and experimental validation cannot be fully realized by either lab alone. **Together, this collaboration integrates data-driven experimentation with a modeling framework, allowing for a deeper understanding of hippocampal circuitry and its role in ASD.**

Specify with whom the person recruited will collaborate and on what aspects *

The recruited individual will actively collaborate with both Dr. Michel Picardo and Dr. Lorenzo Fontolan, engaging in complementary aspects of the project that seamlessly integrate experimental and computational approaches.

Within Dr. Picardo's team, the focus will be on experimental techniques, including *in-vivo* two-photon imaging and electrophysiological recordings, which will provide the critical data required for computational analyses. The student will work closely with two PhD students from the lab who are experts in two-photon imaging and animal behavior, fostering a collaborative and skill-enhancing environment.

In Dr. Fontolan's group, the emphasis will shift to computational tools and models. The student will develop methods to extract neuronal sequences and assemblies from imaging data and refine computational models to investigate how changes in excitation/inhibition balance and synaptic plasticity

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influence hippocampal network dynamics. They will benefit from a collaborative setting that includes a postdoc and two PhD students specializing in neural network modeling.

Together, these interactions will provide a robust, interdisciplinary framework for the recruited individual, offering a rich and supportive environment to develop expertise in both experimental and theoretical aspects of scientific research.

PhD student's expected profile*

We are looking for a creative, motivated candidate with keen interests in Neuroscience at the system/circuit level. Ideally, the candidate would have a biological background, preferably with hands-on two-photon calcium imaging experience. In addition, familiarity with quantitative methods in neuroscience and basic coding skills is desirable. Enthusiasm for interdisciplinary research and willingness to learn new techniques are required for this project to succeed.

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

No

Two to five references related to the project*

Dard et al., 2022 DOI: 10.7554/eLife.78116
Ratsifandrihamanana et al., 2024 DOI: 10.1016/j.xpro.2023.102760
Majumder et al, 2023 DOI: https://doi.org/10.1101/2023.08.09.552699 (preprint)

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

Picardo team : Dard et al., 2022 DOI: 10.7554/eLife.78116
Ratsifandrihamanana et al., 2024 DOI: 10.1016/j.xpro.2023.102760
Fontolan team : Finkelstein et al. 2021 DOI : https://doi.org/10.1038/s41593-021-00840-6
Vaissiere et al. 2024 DOI : https://doi.org/10.1101/2023.09.27.559787 (now accepted at Nat. Comm.)

Project's illustrating image