We propose a 3 years long PhD project that proposes to investigate how HLRP function is altered in TLE condition, and its impact on the generation and the propagation of pathological activity, the alteration of physiological rhythmic activity and the associated behavioral deficits using a combination of multi scale cutting-edge techniques (see below for more details). The PhD will be jointly directed by C. Quairiaux (Geneva, CH) and V. Crépel and T. Marissal (Marseille, FRA), in two excellent working environments (INMED, CMU) surrounded by two wonderful landscapes (Western Alps, Parc National des Calanques).

Motivated candidates with a Master Degree should send their resume, cover letter and 2 references to thomas.marissal@inserm.fr and/or charles.quairiaux@unige.ch before mid-April 2021. Applicants will be interviewed by the prospective directors of the PhD during Spring 2021, then prospective PhD students will be auditioned by Neuroschool academic committee the 2 of June. PhD starts in Fall 2021.

Looking forward to reading your applications!

Thomas Marissal and Charles Quairiaux

State of the art

Temporal Lobe Epilepsy (TLE) is the most prevalent type of epilepsy in adults. Patient must cope with the generation of recurrent epileptic seizures, as well as numerous invalidating psychiatric and cognitive deficits. Even though the damaged hippocampus is still considered as a key actor in those pathological features, it is now postulated that TLE rather involves a network of altered brain structures within the temporal lobe and beyond. Last, a high fraction of patients with TLE are intractable to classical pharmacological treatments or even to surgery. Therefore, it appears particularly important regarding public health to understand better the pathological mechanisms underlying TLE in order to identify the targets for novel treatments. Using TLE rodent models, we particularly focus on a rare subset of inhibitory hippocampal long- range projecting neurons (HLRP), which is quite resistant to cell loss. In non-epileptic conditions, those HLRP neurons orchestrate behavior-related rhythmic activity in the hippocampus, and its coupling with other brain areas. Interestingly, those processes are deeply altered in the context of TLE. We hypothesize that an alteration of those long-range projecting inhibitory neurons might be critically involved in TLE pathology. A dysregulation of those inhibitory neurons may not only participate in the generation and the propagation of seizure, but also could interfere with functions normally handled by the hippocampus and the temporal lobe.

Objectives

The proposed PhD project proposes to investigate how HLRP function is altered in TLE condition, and its impact on the generation and the propagation of pathological activity, the alteration of physiological rhythmic activity and the associated behavioral deficits.

Methods

Experimentation on mice, in vitro and in vivo electrophysiological recordings (patch-clamp, EEG and/or multitrode recordings), neuronal manipulation techniques (using optogenetic and/or chemogenetic approaches) and behavioral testing.

Expected results

That ambitious project aims at unravelling a key mechanism of TLE pathology, and ultimately identifying a target for novel therapy for that disease via existing collaborations (Biotechs, clinic).

Feasibility

Project has been designed for 3 years. Every tool necessary for the project is routinely used by one or the other hosting lab, and projects using similar methodologies were already conducted in the last years (Marissal et al., 2018; Sheybani et al., 2018; 2019). The prospective student will be closely monitored by Drs. Valérie Crépel and Thomas Marissal (Marseille) for the study at the cellular level (patch-clamp,

specific neuronal manipulation, etc.), and by Dr. Charles Quairiaux (Geneva) for the experiments at the macroscopic level (in vivo local and large-scale neuronal recordings, etc.). Other team members with compatible expertise (histological analysis, electrophysiology, programming, etc.) will participate in the project when necessary.

Complementarity of the two laboratories

High. The two groups specifically study TLE, however they use distinct recording techniques at different biological scales (i.e. neuronal/local network aspects in Marseille, large-scale brain network levels in Geneva).

Expected candidate profile

Candidates should have a strong background in cellular neurobiology and should be familiarized with mouse experimentation.