Résumé du projet de thèse *(1 page maximum, en anglais)*
Indiquer la participation de chaque co-directeur et structure dans la gestion du projet. Please indicate explicitly the specific contribution of each supervisor to the PhD project.

Epilepsy is the second most common neurological disease in humans. Seizures can be triggered by sensory stimuli, for instance in "reflex epilepsies". Triggering stimuli can range from a simple flash of light in photosensitive epilepsies, particularly common in human epilepsies, to more complex sensory stimuli, for example in musicogenic epilepsies. Rodents with audiogenic seizures (AS) present tonic and/or clonic seizures triggered by exposure to a brief and intense sound. Repeated exposure to a sound over several days allows the expansion of an initially subcortical epileptic network implying mainly brainstem auditory nuclei into a more diffuse network also involving cortical regions (a phenomenon called "kindling"). This animal model is thus particularly interesting for studying the relationships between sensory perception and ictogenesis (generation of a seizure) and epileptogenesis (development of an epileptic network). The anatomical site (subcortical or cortical) where these two processes take place is still subject of debate, and the literature provides conflicting data.

Our main objective will be to elucidate the anatomical structures necessary and/or sufficient for the initiation of epileptogenesis and ictogenesis in response to sound, and to determine the dynamics of cortical activation in response to sound exposure, in mice with AS.

Our main hypothesis, based on published data in mice with AS, is that epileptogenesis begins in subcortical structures, and spreads progressively to the cortex with repeated sound exposure (kindling), enabling cortical ictogenesis at the end of the audiogenic kindling. In other words, sound integration at the level of the inferior colliculi would be necessary and sufficient to initiate the first AS and audiogenic kindling, while the auditory cortex activation would be sufficient (but not necessary) to trigger AS after kindling. This hypothesis is original in that it gives a large role to subcortical structures in triggering the epileptic process, which to some extent goes against the more conventional view of epilepsy as a predominantly "cortical" process.

This PhD project aims to explore these questions by bringing together two teams with complementary expertise: Brice Bathellier's laboratory (Institut de l'Audition, Institut Pasteur), specialized in the cortical dynamics of auditory perception and Vincent Navarro's (co-supervisor, Institut du Cerveau, Sorbonne Université), expert in the mechanisms of epileptogenesis.

We will use optogenetic techniques to specifically activate and/or inhibit the main subcortical (inferior colliculi) and cortical structures of the central auditory pathways, and we will study the impact on AS triggering and audiogenic kindling. Optogenetic techniques will bring a high degree of spatial, temporal, and cell-type specificity in neuronal network modulation. We will also use 2-photon calcium imaging to study the dynamics of cortical activation during AS with single-cell resolution, to identify specific cortical patterns of activation which would be in favor of a cortical ictogenesis.

The laboratory experiments will take place in Brice Bathellier's laboratory at Institut de l'Audition, which is fully equipped for optogenetic and 2-photon calcium imaging experiments in mice. Vincent Navarro's laboratory will provide expertise in the assessment of epileptic seizures in mice and help interpret intracranial EEG traces. Supervision and direction of the PhD thesis and experiments will be shared between the two labs.

The results of this research, beyond helping to understand the mechanisms of epileptogenesis and ictogenesis, and the reciprocal relationships between epilepsy and sensory perception, could also help identify anatomical structures to target in neurostimulation protocols, currently gaining ground in the management of patients suffering from epilepsy.