

Project Title: Neurogenesis, immunity, and inflammation in the auditory system

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Research Theme: Neuroinflammation, auditory disease, tinnitus, neural plasticity, neurogenesis, neurovascular interactions, choroid plexus, temporal bone marrow

Abstract

Tinnitus is an auditory disease characterized by the perception of phantom sounds. Although several risk factors are identified, no clear causative hypothesis for tinnitus exists yet, although several studies have identified the dorsal cochlear nucleus as a necessary station for tinnitus onset, similarly to spinal cord dorsal horn in chronic pain. Animals exposed to tinnitus-inducing stimuli but remaining free from tinnitus display differences, compared to animals developing tinnitus, in the activating ratio between dorsal cochlear nucleus and cerebellar floccular node. Moreover, tinnitus animals display a neurogenesis switch between the two structures (i.e. new cells are generated in the flocculus rather than the dorsal cochlear nucleus), and inflammatory stimuli (especially TNF-alpha) are able to affect the onset and development of tinnitus. Our works focuses on the auditory system responses in a noise trauma rat model of tinnitus. In particular, we are interested in two main problems:

- 1) Understanding the role of the 4th ventricle choroid plexus in tinnitus-related plasticity and neurogenesis. In the lateral ventricle, choroid plexus is essential in regulating adult neurogenesis, and recent data suggest a similar function for the 4th ventricle. We have developed a novel clarified brain-temporal bone preparation (Perin et al. 2019) to investigate the choroid plexus *in situ* and have found that it contacts the dorsal cochlear nucleus forming tight adhesion points (Perin et al. 2021); after cochlear damage, macrophages cluster between the surface of the plexus and of the nucleus. Moreover, the microvascular organization of the plexus (which we have started characterizing) suggests the presence of specialized districts for its different functions (bulk CSF secretion vs. immune cell trafficking). We are starting to dissect the role of plexus-derived factors and cells in dorsal cochlear nucleus cellular plasticity.
- 2) Reconstructing temporal bone immune activation in noise trauma. All kind of damage to the cochlea (including noise) results in a local inflammatory reaction involving several cell populations. However, the inner ear displays a blood-labyrinth barrier, which is analogous to the blood-brain barrier, and is encased in petrous bone, which isolates inner ear structures from the outside. By imaging cleared temporal bones, we have discovered that three conserved spots in the rat temporal bone contain bone marrow patches, adjacent to the cochlea, semicircular canals, and endolymphatic duct, respectively. By employing vascular markers, we are reconstructing the microvascular connections between these marrow patches and the inner ear, and plan to observe whether the immune cell trafficking from these marrow sites to the inner ear follows the same rules recently observed in the brain, where local bone marrow from cranial bones replenishes meningeal immune cells, which do not exit to the general circulation but mature locally.

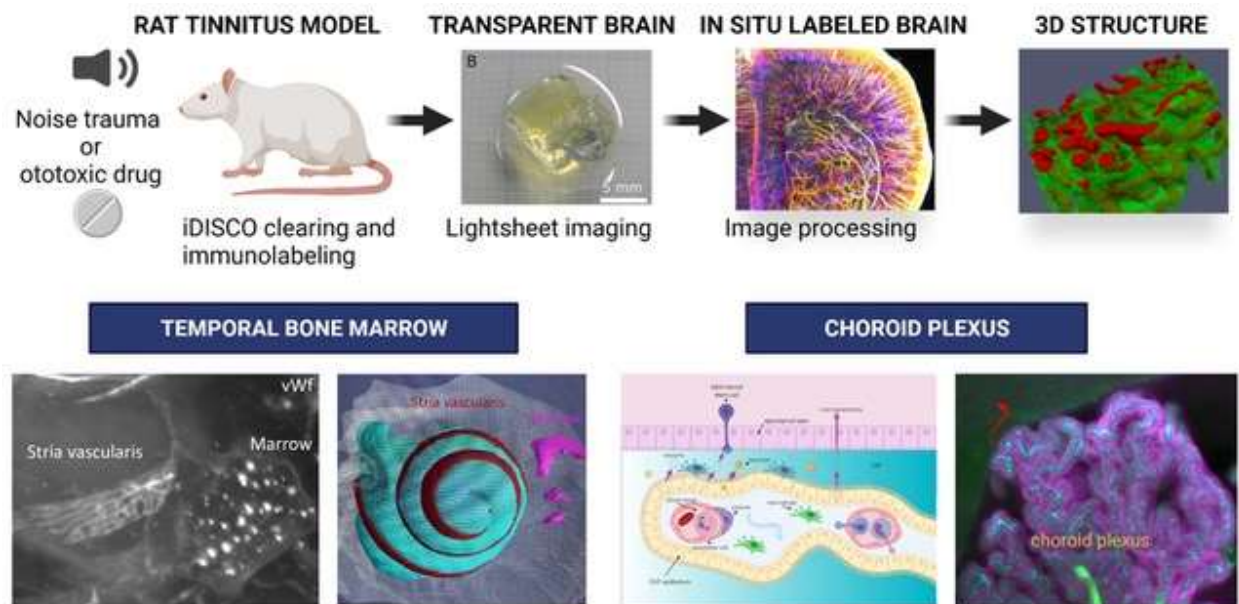
Methods: White-noise or frequency band noise trauma, auditory brainstem response, GPIAS tinnitus test, iDISCO+ tissue clearing, lightsheet imaging, image analysis.

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We want to understand the role of neuroimmune responses in tinnitus.

Tinnitus is an auditory problem related to maladaptive plasticity, neurogenesis, and neuroinflammation. Since the choroid plexus (which regulates adult neurogenesis) contacts the brain nuclei involved in tinnitus onset, and temporal bone marrow (which produces immune cells) is connected to the inner ear, we have developed a novel clarified brain-temporal bone preparation to investigate choroid plexus contacts with the auditory system and temporal bone immune cell trafficking in physiological and pathological conditions, and are starting to dissect the factors involved in tinnitus-related cellular plasticity.