Tinnitus and Cognitive Decline:
Multi-Omics Approach to Precision Medicine (TINNOMICS)

Background and Rationale

Tinnitus, the perception of sound without external stimuli, affects approximately 740 million adults worldwide, with prevalence increasing with age. It is frequently associated with sensorineural hearing loss, anxiety, depression, headache or sleep disorders, making it a complex and multifactorial condition. More than 90% of tinnitus cases co-occur with age-related or noise-induced hearing loss, leading to distress, functional impairment, and a growing economic burden on healthcare systems.

Beyond its auditory impact, emerging evidence suggests a bidirectional relationship between tinnitus and cognitive decline (CD). Chronic tinnitus can impair attention and working memory, as patients allocate cognitive resources to suppress phantom auditory perceptions. Conversely, individuals with pre-existing cognitive impairments, particularly age-related decline and mild cognitive impairment (MCI), may be more vulnerable to severe tinnitus. This interplay suggests shared neurobiological pathways that remain poorly understood.

Despite the increasing recognition of this link, the integration of genomics, neurophysiology, and AI-driven diagnostics in tinnitus and cognitive decline research remains limited. This project aims to leverage cutting-edge genomic and neurofunctional tools to improve early detection, risk stratification, and personalized interventions for individuals with tinnitus-related cognitive decline.

Objectives

Aligned with Horizon Europe's Destination 5, this project will integrate genomic profiling, neurophysiological markers, and AI-based predictive analytics to:

1. Validate Findings in a European Cohort: Replicate genetic, electrophysiological, and cognitive findings from previous European research projects in an independent cohort to ensure reproducibility, scalability, and clinical translation across diverse populations.
2. Unlock Genomic Insights: Conduct whole genome sequencing (WGS) re-analysis to identify rare genetic variants linked to severe tinnitus and cognitive decline, particularly those involved in neuronal connectivity and neuroplasticity.
3. Develop AI-Driven Digital Biomarkers: Integrate electrophysiological (Auditory Brainstem Responses (ABR) and Middle Latency Response (AMLR)), audiological, and psychometric data into machine-learning algorithms to predict individuals at risk of tinnitus-related cognitive impairment.
4. Advance Precision Medicine Approaches: Perform deep phenotyping in tinnitus patients using clinical, electrophysiological, and cognitive assessments to refine patient subgroup classification and guide personalized treatments.

Innovative Approach and Technological Advances

Our approach combines multi-omics data, neurophysiology, and AI-driven analytics to redefine tinnitus-related cognitive decline research:

1. Genomic Profiling and Functional Validation
   - Advanced genomic analysis of tinnitus patients from the UNITI cohort, identifying rare genetic variants influencing neuronal excitability and axonal connectivity.
   - Functional validation through induced pluripotent stem cell (iPSC)-derived auditory neurons from patients with severe tinnitus, assessing abnormalities in neuronal excitability, oxidative stress, mitochondrial health, and neuroinflammatory responses.
2. AI-Driven Digital Biomarkers
   - Integration of electrophysiological (brainstem auditory evoked potentials, middle-latency responses), audiological, and psychometric data into a machine-learning predictive model.
   - AI-driven pattern recognition algorithms to identify subgroups at high risk of cognitive decline, enabling early intervention strategies.
3. Validation in a European Cohort
   - Replication of genetic, neurofunctional, and cognitive markers in an independent cohort to confirm robustness and reproducibility.
   - Multi-center recruitment across Europe to ensure findings are generalizable across populations.

Preliminary Data and Funding
This project builds upon prior work developed in major EU-funded initiatives:

1. **European School for Interdisciplinary Tinnitus Research (ESIT, MSCA-ITN-722046)** – Established a pan-European tinnitus patient database, enabling genomic and clinical research.
2. **UNITI (Horizon 2020; Grant 848261)** – Developed a predictive model for personalized tinnitus treatments, integrating genetic, clinical, and psychological data. Our preliminary analysis of 380 patients revealed a correlation between high Tinnitus Handicap Inventory (THI) scores, high-frequency hearing loss, and mild cognitive impairment.
3. **TIGER (GNP-182, Gender-Net Co-Plus, co-funded by La Caixa Foundation and H2020-SC1-2019-848261)** – Focused on genetic research in tinnitus, identifying rare variants in ANK2, TSC2, and AKAP9 in severe tinnitus patients, which were replicated in a Swedish cohort but not in a broader epilepsy cohort.
4. **eCOST Action TINNET (BM1306)** – Created the largest tinnitus-specific genetic dataset in Europe.

Our group performed gene burden analysis (GBA) in Spanish patients with extreme tinnitus phenotypes, identifying novel genetic variants in *ANK2, CACNA1E*, and *NAV2*, which are highly expressed in the auditory cortex, hippocampus, and limbic system. We also derived iPSC models from patients, revealing abnormal neuronal clustering and increased axonal projections in mature auditory neurons carrying *ANK2* mutations.
This extensive research infrastructure and data availability provide an unparalleled foundation for expanding genetic, neurophysiological, and AI-driven studies in tinnitus and cognitive decline.

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Main ArchiFun theme involved:

- **Neurosciences and cognition.**

Proposed collaboration within ArchiFun network (not mandatory at this stage):

Proposed list of secondments (not mandatory, but recommended if known already):