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Developing topics

From genes to cognition: *Octodon degus*, an animal model for AD translational research

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Abstract

Background: *Octodon degus* (*O. degus*), a long-lived rodent, provides us with a unique opportunity to search for molecular pathways that are associated with enhanced longevity in mammals. This rodent from Chile spontaneously develops an analog of sporadic AD at behavioral and neurobiological levels. It is a diurnal rodent that makes wide use of spatial memory to find and hide food. This cognitive ability is thought to be rooted in what is commonly known as the GPS of the mammalian brain, a collection of structures centred around the hippocampus and neighbouring cortical areas. A fraction of the aged *O. degus* population not only exhibits amyloid-beta oligomers, tau hyperphosphorylation, neurofibrillary tangle formation, cell death and cognitive decline but also several other conditions comorbid to AD like diabetes mellitus type 2, macular and retinal degeneration and atherosclerosis.

Method: In this study, we used the *Octodon degus*. Behavioural assessment of a population (N = 150) of *degu* was performed using the tests of daily living (burrowing test, marble burying and nesting), Novel Object Recognition and the Open Field. All Degus were chronically implanted with a four-tetrode microdrive, which was originally developed for mice (Versadrive-4, Neuralynx, USA).

Result: These model features call for research efforts to be put on studying the degu GPS from both the basic and applied science perspectives, with a multilaboratory and multidisciplinary perspective. In response to this, we here present the first multidisciplinary study including i) Recording 69 CA1 principal cells while O. degus explored a 1 m wide square environment, finding that O. *degus* exhibited extreme *place cell behaviour*. ii)We performed a genome-wide association study in *O. degus* and report the identification of SNVs in genes associated with AD (APP, BACE1, MAPT, Psen1 and Psen2, grn and SORL1. iii) Some of the variants identified in AD associated genes showed significant association with behavioural performance in Hardy-Weinberg equilibrium.

Conclusion: All together these findings provide an important path toward the understanding how AD related mutations in the *O. degus* prove this model to be an important translational tool for aging and Alzheimer's research.

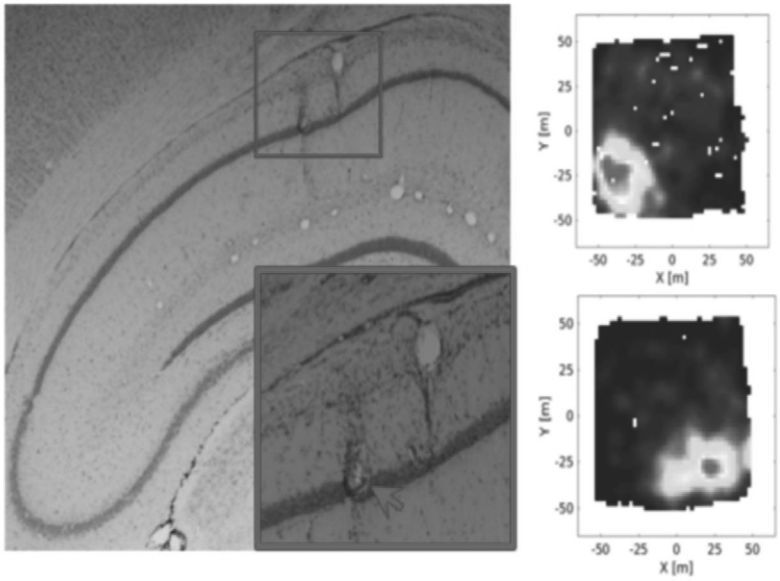

Figure shows Place cells in hippocampal CA1 of O. degus. Left: Representatative example of histological preparations showing the final position of one recording tetrode (red arrow) and the trace left on the same brain section by a second neighboring tetrode. Right: Two representative examples of place cell spatial maps with high spatial information rate and stability. Each example shows the firing rate of one CA1 pyramidal neuron (color coded, with red indicating maximum firing rate and blue indicating no activity) as a function of the position of the animal in the open field arena.

FIGURE 1