



Hypothalamic Synaptic Vulnerability in Alzheimer's Disease



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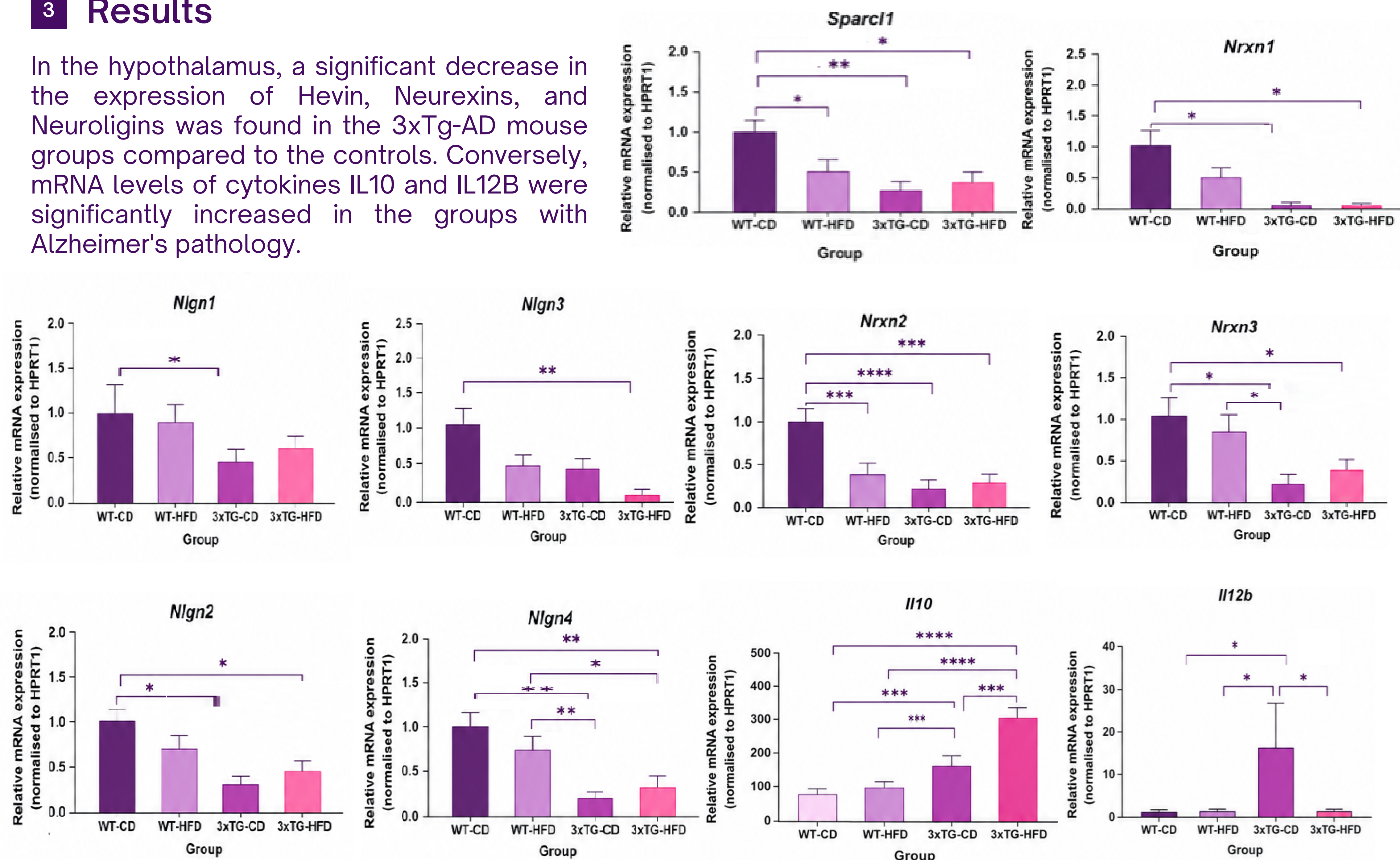
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1 Introduction

Background: Alzheimer's disease (AD) is the most common and lethal dementia globally, characterized by early synaptic loss that precedes irreversible cognitive decline. The stability of neuronal connections depends on synaptic processes mediated by adhesion proteins such as Hevin (SPARCL-1), neurexins and neuroligins NRXN/NLGN. Hevin acts as a fundamental bridge that organizes glutamatergic synapses by interacting with the trans-synaptic NRXN/NLGN complex. Insulin resistance (IR), exacerbated by environmental factors, is directly associated with synaptic dysfunction and increased neurotoxicity, thereby accelerating the progression of Alzheimer's disease (AD)

3 Results

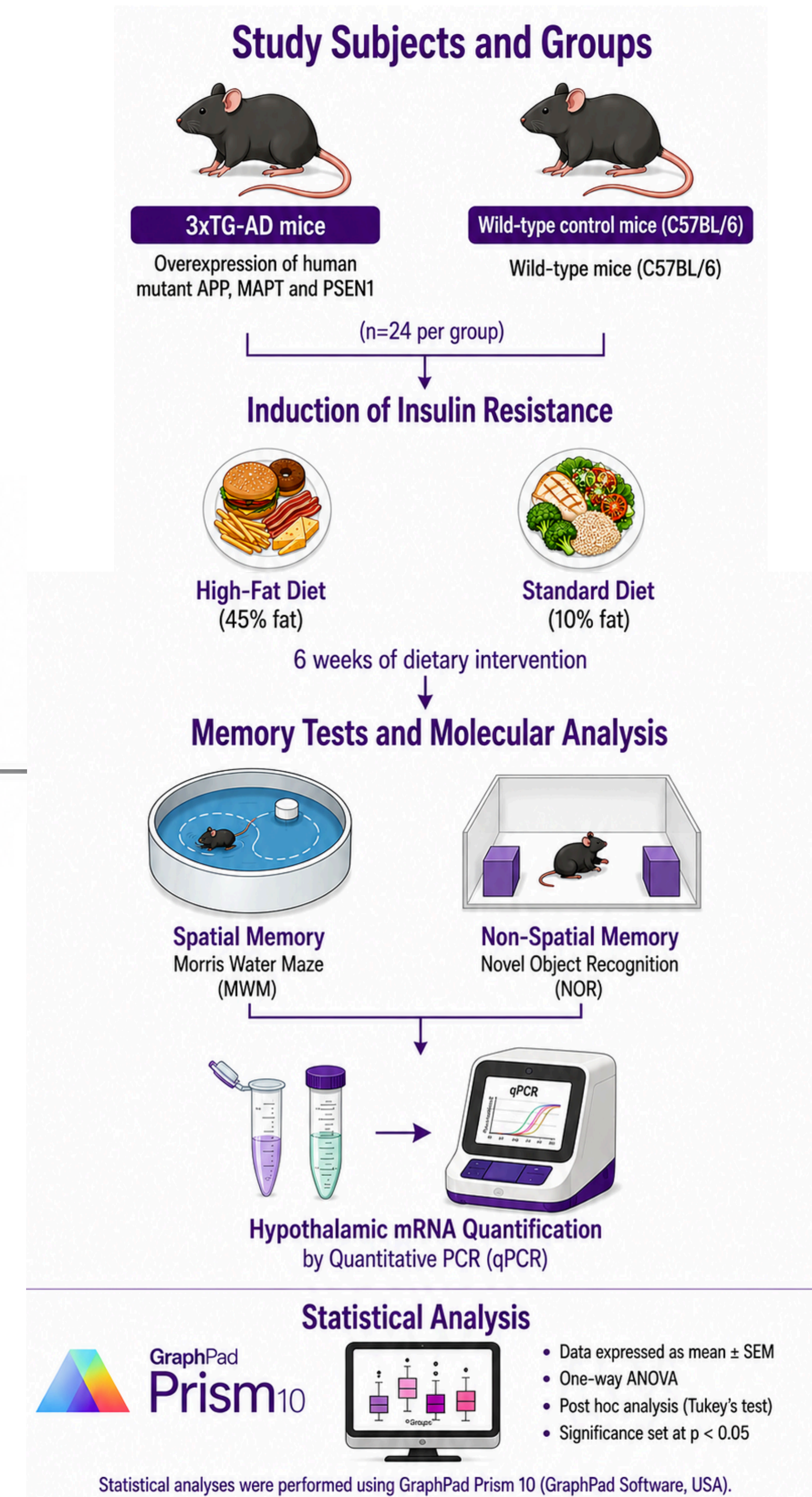
In the hypothalamus, a significant decrease in the expression of Hevin, Neurexins, and Neuroligins was found in the 3xTg-AD mouse groups compared to the controls. Conversely, mRNA levels of cytokines IL10 and IL12B were significantly increased in the groups with Alzheimer's pathology.



4 Conclusion

Diet-induced insulin resistance alters the molecular integrity of the synapse and promotes a neuroinflammatory environment in key regions such as the hypothalamus. The downregulation of the Hevin-NRXN-NLGN axis and the increase in inflammatory markers IL10 and IL12B constitute a critical synaptic vulnerability in AD. Therefore, therapeutic strategies designed to preserve the binding and function of this protein complex they could represent a novel and promising approach to halting cognitive decline in the early stages of the disease.

2 Methods



- WT-SD (Wild-type, Standard Diet)
- WT-HFD (Wild-type, High-Fat Diet)
- 3xTG-SD (3xTG-AD mice – Standard Diet)
- 3xTG-AD-HFD (3xTG-AD mice – High-Fat Diet)

ANOVA con Turkey's test, valores de *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

5 References

Astrocytic Hevin/SPARCL-1 Regulates Cognitive Decline in Pathological and Normal Brain Aging - Cabral-Miranda - 2025 - Aging Cell.
Iang Z, Liu B, Lu T, Liu X, Lv R, Yuan K, et al. SGK1 drives hippocampal demyelination and diabetes-associated cognitive dysfunction in mice. Nat Commun. 17 de febrero de 2025

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