Reelin as a Medial Temporal Lobe Marker of Age-Related Cognitive Decline in Male and Female Rats

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Abstract

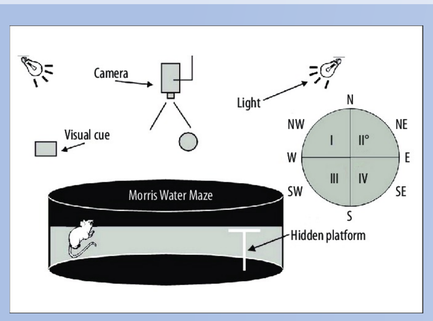
This study seeks to extend the findings from a well characterized model of age-related cognitive decline in male rats by expanding into the female population. Reduced reelin, a protein involved in adult synaptic plasticity, is implicated in hippocampal dependent memory impairment. Age impaired male and female rats experience a selective reduction of reelin mRNA in the lateral entorhinal cortex (LEC) and not the medial entorhinal cortex (MEC). This reduction of reelin can be correlated to hippocampal dependent memory impairment.

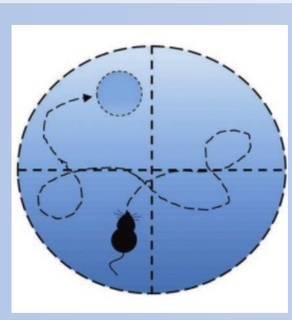
Background

- The entorhinal cortex together with the hippocampus form a vital circuit which plays a role in episodic memory.
- Neurons in layer II of the EC experience reduced synaptic connection to the hippocampus during age-related cognitive decline (Scheff et al. 2006).
- Reelin expression is reduced in the LEC but not the MEC of age-impaired humans and rat models.
- Decreased expression of reelin is implicated in impaired cognition and memory (Stranahan et al. 2010).

Methodology

- Young and aged rats (male n=35; female n=35) were subjected to the Morris water maze behavioral task. A learning index was generated by measuring the speed and accuracy of performance.
- The learning index was used to categorize the aged rats into aged-impaired (AI) and aged-unimpaired (AU) phenotypes.
- Hippocampal and EC tissue was labeled using immunohistochemistry as described in Stranahan et al. 2010.
- ImageQuant was used to measure reelin mRNA expression.





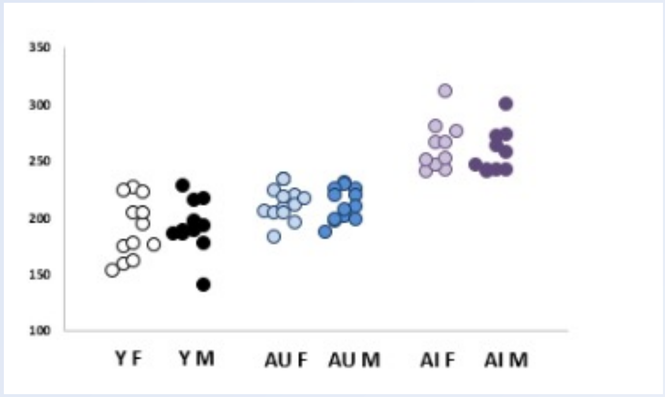


Fig a. Learning index scores for young, AU, and AI male and female rats

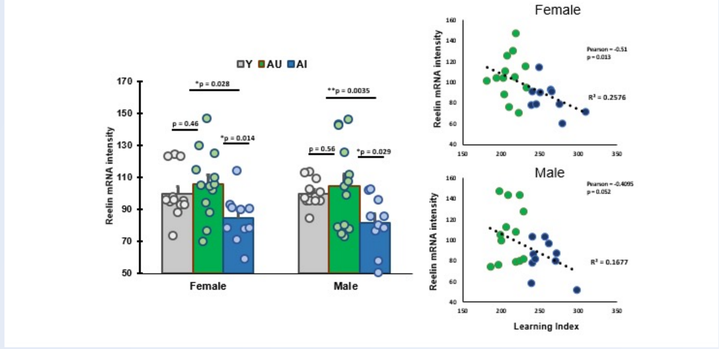


Fig b. Reelin mRNA intensity in the LEC of young, AU, and AI male and female rats

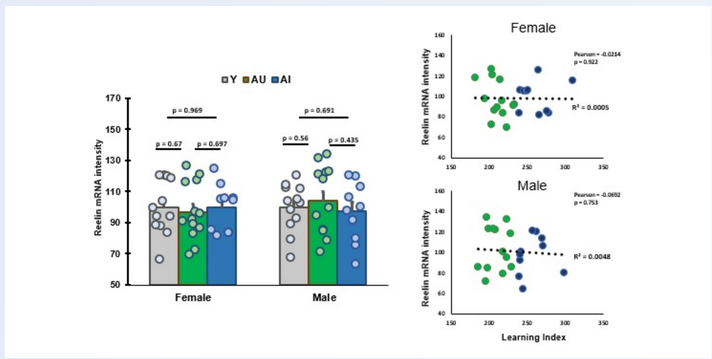


Fig c. Reelin mRNA intensity in the MEC of young, AU, and AI male and female rats

Results

- Aged female rats displayed the same aged-impaired and aged-unimpaired phenotypes previously found in male rats.
- No specific reduction in number of neurons in the EC of either male or female AI rats.
- Both the males and female populations show a similar negative correlation between reelin mRNA expression in the LEC and learning index scores (female: p=0.028; male: p=0.0035).
- Reelin mRNA expression in the MEC showed no correlation to hippocampal-dependent cognitive decline in either male or female populations (female: p=0.969; male: p=0.691).

Discussion

These findings, regarding male and female rats, can translate to the human population. Beyond increasing our knowledge of age-related cognitive decline in rats, our larger goal was to form a predictive model of cognitive decline that better models the human population.

In the future I would hope to expand this study to include the interneuron markers, glutamic acid decarboxylase (GAD) and somatostatin using the same behavioral task and categorization. Reduction of GABA-ergic interneurons in the hippocampus as part of normal aging may contribute to excess activity in this region. A disruption in the balance between excitation and inhibition has been implicated in age-dependent cognitive decline and impaired neuroplasticity. By measuring the number of GAD and somatostatin-immunoreactive neurons in the hippocampus, we can attempt to replicate these existing findings in female rats.

Sources and Acknowledgements

Stranahan AM, Haberman RP, Gallagher M. Cognitive decline is associated with reduced reelin expression in the entorhinal cortex of aged rats. Cereb Cortex. 2011 Feb;21(2):392-400. doi: 10.1093/cercor/bhq106. Epub 2010 Jun 10. PMID: 20538740; PMCID: PMC3020582.

Scheff SW, Price DA, Schmitt FA, Mufson EJ. Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment. Neurobiol Aging. 2006;27:1372–1384.

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