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Hilar interneuron vulnerability distinguishes aged rats with memory impairment.

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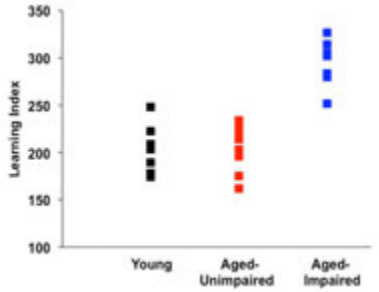
INTRODUCTION

- Previous data indicates that excess hippocampal activity is associated with memory impairment in aged rats and elderly humans, including individuals with amnestic mild cognitive impairment[1,2].
- Inhibitory control by interneurons is vital for maintaining appropriate levels of excitation in the hippocampus.
- Here we investigated the condition of hippocampal interneurons in relation to cognitive impairment in a rat model of neurocognitive aging.

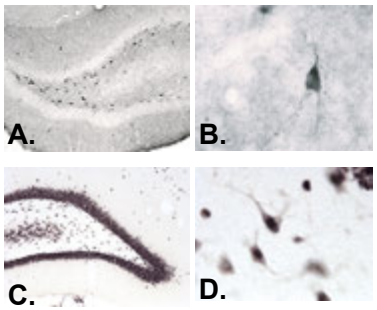
Questions:

1. Is there a loss of GAD67 expressing hippocampal interneurons in relation to cognitive function with age?
2. Are any decreases in GAD67 expressing interneurons the result of neuronal loss?

- Young and aged rats were behaviorally characterized using a version of the spatial water maze and a learning index score, which is an assessment of memory performance that is dependent on the hippocampus (Gallagher *et al.*, 1993)[3]
- GAD67 and NeuN expressing neurons were stereologically quantified using the MBF Stereo Investigator system with the optical fractionator method applied.



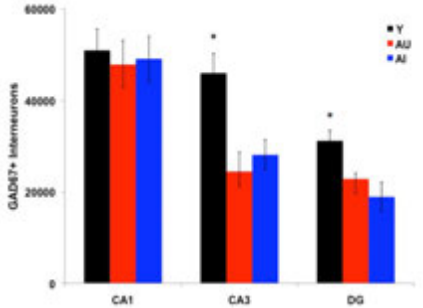
Set of behaviorally characterized young and aged animals used to obtain stereological counts of GAD67 and NeuN immunoreactive neurons.



A-D. Representative immunohistochemical staining for GAD67 and NeuN in the rat dentate hilus (A.) GAD67 10X, (B.) GAD67 100x, (C.) NeuN 10x, (D.) NeuN 100x.

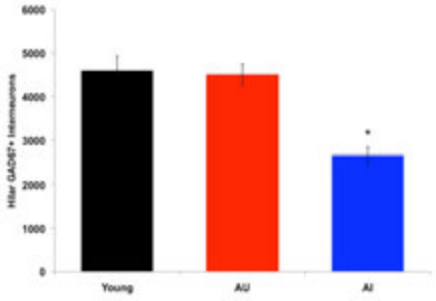
GAD67 RESULTS

1 Age-related decrease in GAD67+ interneurons is subregion specific



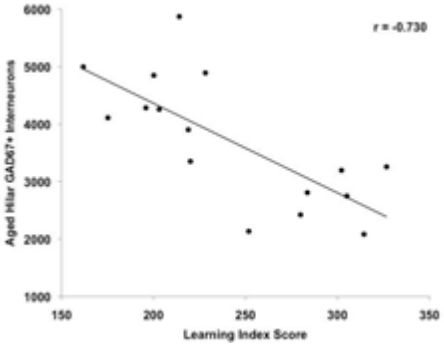
*p<0.05. Error bars= + 1 SE.

2 Hilar GAD67+ interneurons are reduced in the dentate hilus only in AI rats

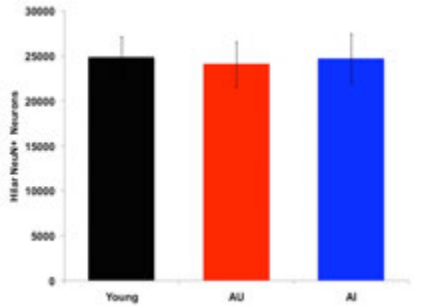


*p<0.05. Error bars= + 1 SE.

3 Decreased number of GAD67+ hilar interneurons correlates with worse spatial memory among aged rats



4 Total hilar neuron number is preserved in aged rats with spatial learning deficits



*p<0.05. Error bars= + 1 SE.

Conclusions

- **GAD67+ interneurons are not uniformly decreased in the aged rat hippocampus; the decline is subregion specific and localized to the CA3 and DG**
- **Hilar GAD67+ interneuron decline distinguishes aged rats with memory impairment**

- ✓ **Here we have shown an age-related decline in hippocampal interneuron integrity, which is specific to subregions that have previously been shown to exhibit excess levels of activity in the aged rat and human hippocampus in conditions of memory impairment**
- ✓ **The decline in hilar interneuron integrity that distinguishes aged rats with memory impairment highlights a population of interneurons known to be vulnerable in ApoE4 models**
  - **apoE4 knock-in mice show an age-related decrease in the number of hilar GAD67+ interneurons that is greater than the loss observed with age alone[4]**
- ✓ **While aging represents the greatest risk factor for Alzheimer's Disease (AD), having an ApoE4 genotype confers the greatest additional risk for sporadic AD**
  - **The hilar interneuron decline selectively observed in aged animals with memory impairment may represent a phenomenon in normal aging that is permissive for pathological conditions**

REFERENCES

1. Wilson, I.A., et al., *Age-associated alterations of hippocampal place cell are subregion specific.* J. Neurosci, 2005. **25**(29): p. 6877-86.
2. Yassa, M.A., et al., *High-resolution structural and functional MRI of hippocampal CA3 and dentate gyrus in patients with amnestic Mild Cognitive Impairment.* Neuroimage, 2010. **51**(3): p. 1242-52.
3. Gallagher, M., R. Burwell, and M. Burchinal, *Severity of spatial learning impairment in aging development of a learning index for performance in the Morris water maze.* Behav Neurosci, 1993. **107**(4): p. 618-26.
4. Andrews-Zwilling, Y., et al., *Apolipoprotein E4 causes age- and Tau-dependent impairment of GABAergic interneurons, leading to learning and memory deficits in mice.* J Neurosci, 2010. **30**(41): p. 13707-17.