

Cell-Type-Specific Alterations in Hippocampal Formations in APOE4 Mice

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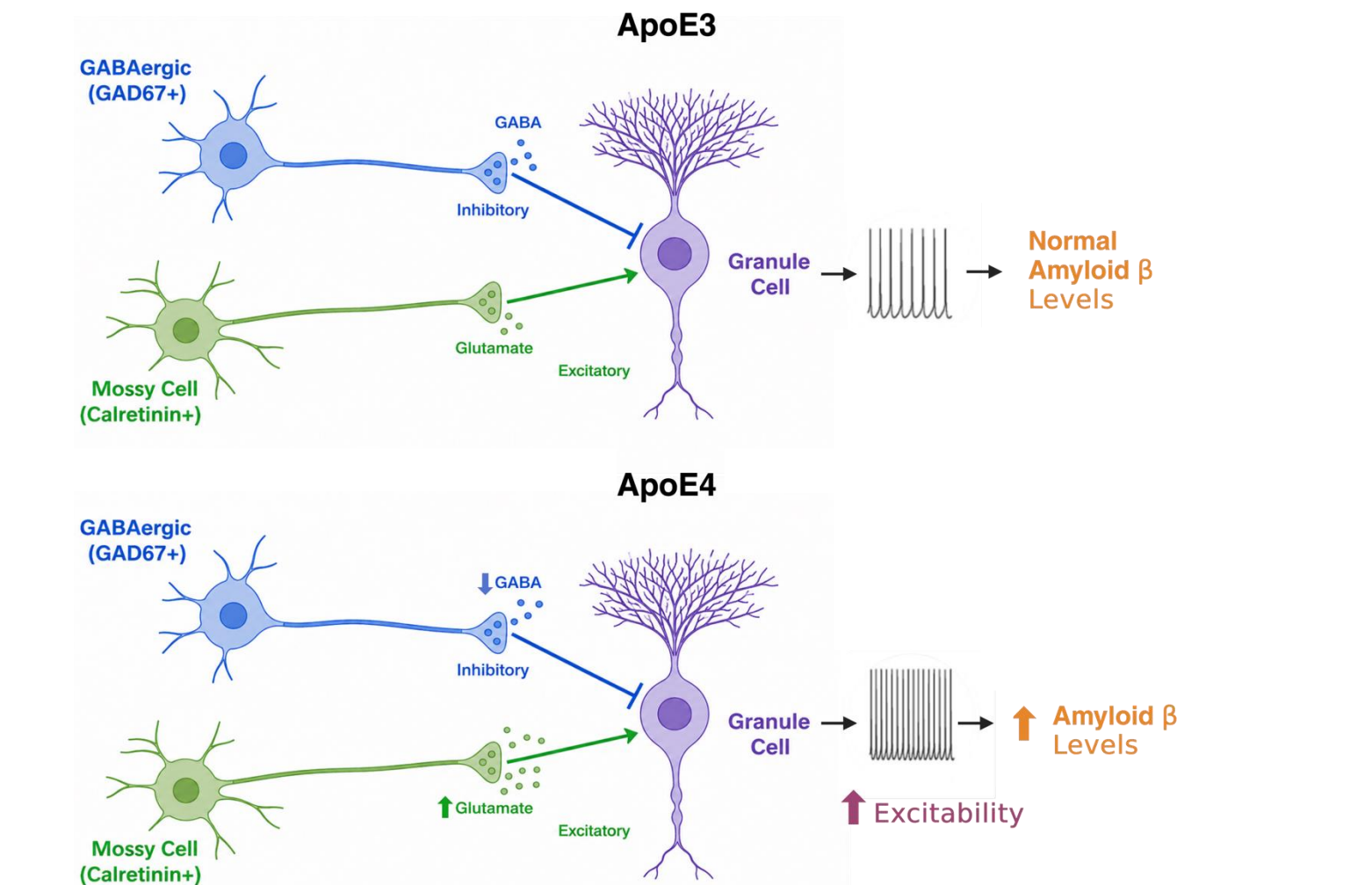
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Background Information

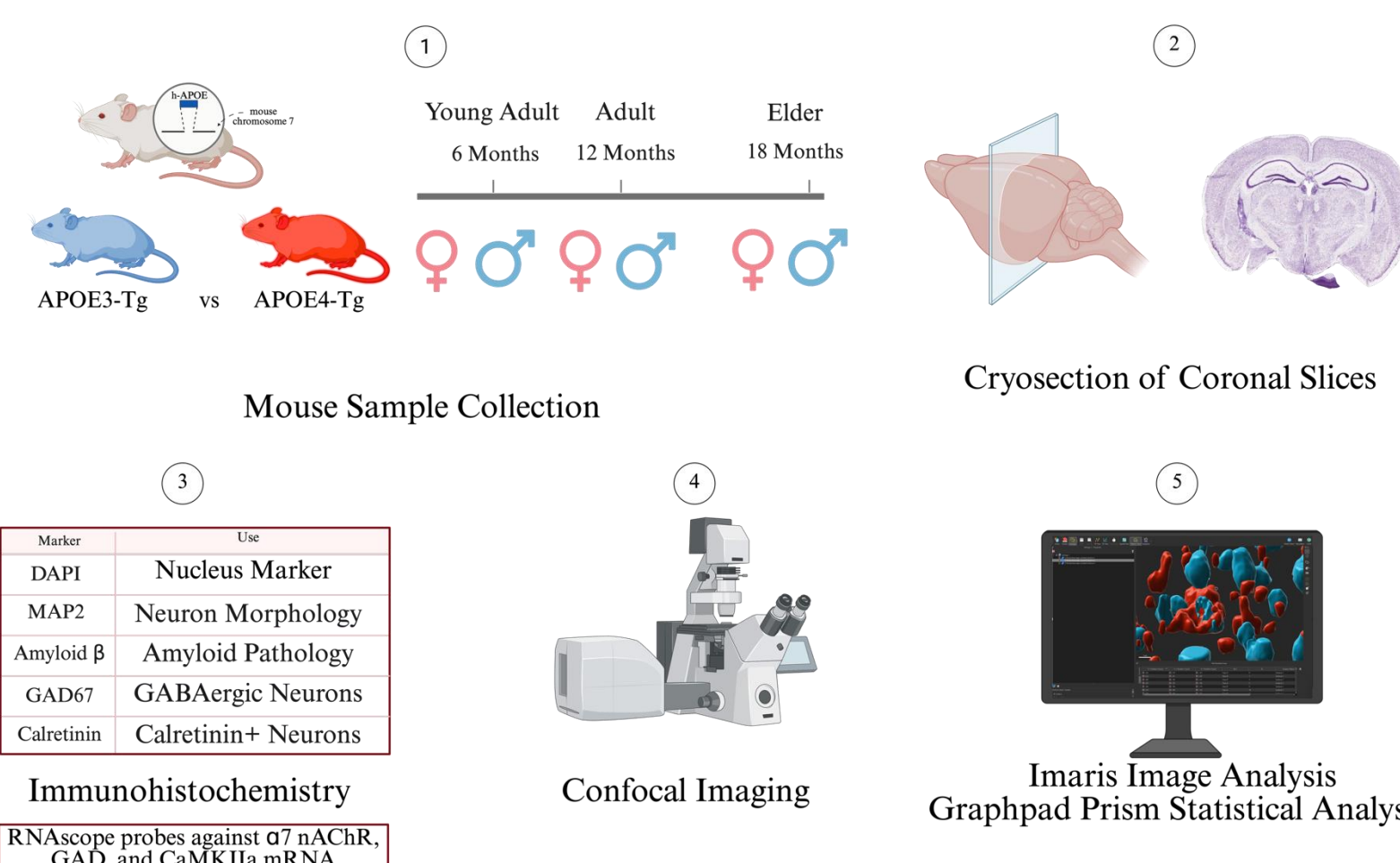
Alzheimer's disease (AD) is a progressive neurodegenerative disorder and a major public health challenge, affecting more than 7 million Americans. It is characterized by cognitive decline, particularly in memory, attention, and executive function, and is associated with high morbidity and mortality. Hallmark features of AD include amyloid-beta plaque accumulation and neurofibrillary tangles, along with related pathological processes such as mitochondrial dysfunction, impaired autophagy, and degeneration of cholinergic pathways. Cholinergic projections are especially important for learning and memory, including projections from the medial septum to the hippocampus, a region critical for memory formation. This pathway is of particular interest because the hippocampus shows some of the earliest and most prominent pathological changes in AD. Degeneration of hippocampal cholinergic input may therefore contribute to early hippocampal dysfunction and memory impairment in the disease. Understanding how cholinergic circuit disruption interacts with other AD-related mechanisms may help identify targets for therapeutic intervention.

Hypothesis

The granule cells of APOE4 mice receive increased glutamate inputs and decreased GABA inputs, resulting in neuronal hyperexcitability and amyloid β accumulation compared with APOE3 mice.



Methods



Hippocampal neuronal loss in APOE4 female mice.

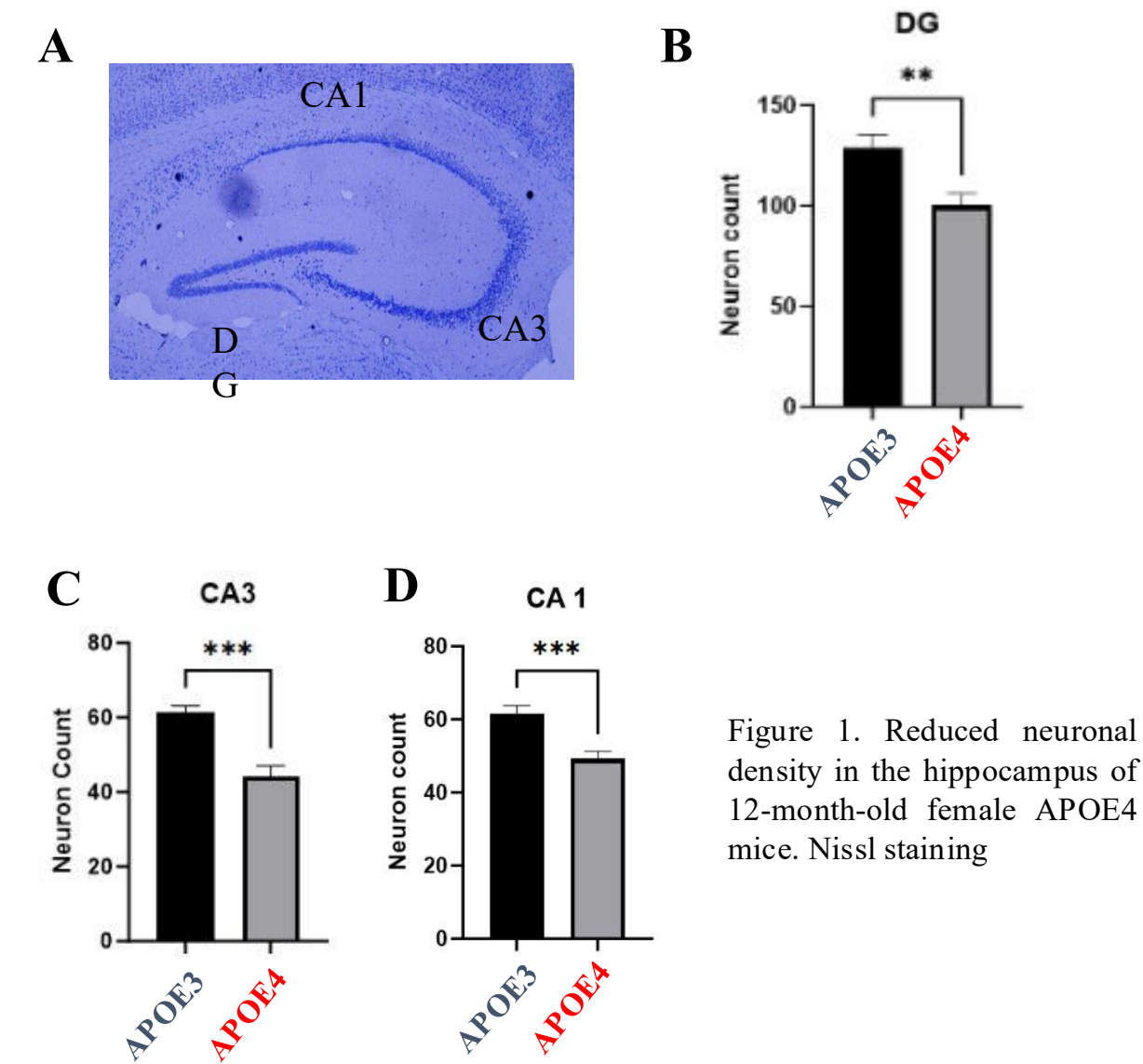


Figure 1. Reduced neuronal density in the hippocampus of 12-month-old female APOE4 mice. Nissl staining

Significant loss of cholinergic neurons in the medial septum of APOE4 mice.

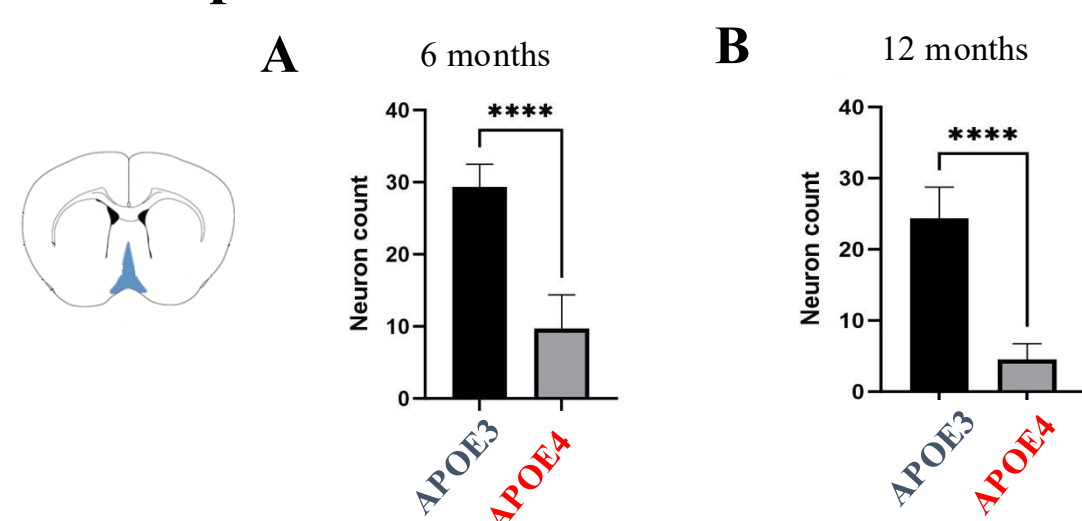


Figure 2. Age-dependent loss of cholinergic neurons in female APOE4 mice.

The expression of $\alpha 7$ nAChR mRNA decreased in APOE4 dentate granule cells and hilar GABAergic interneurons.

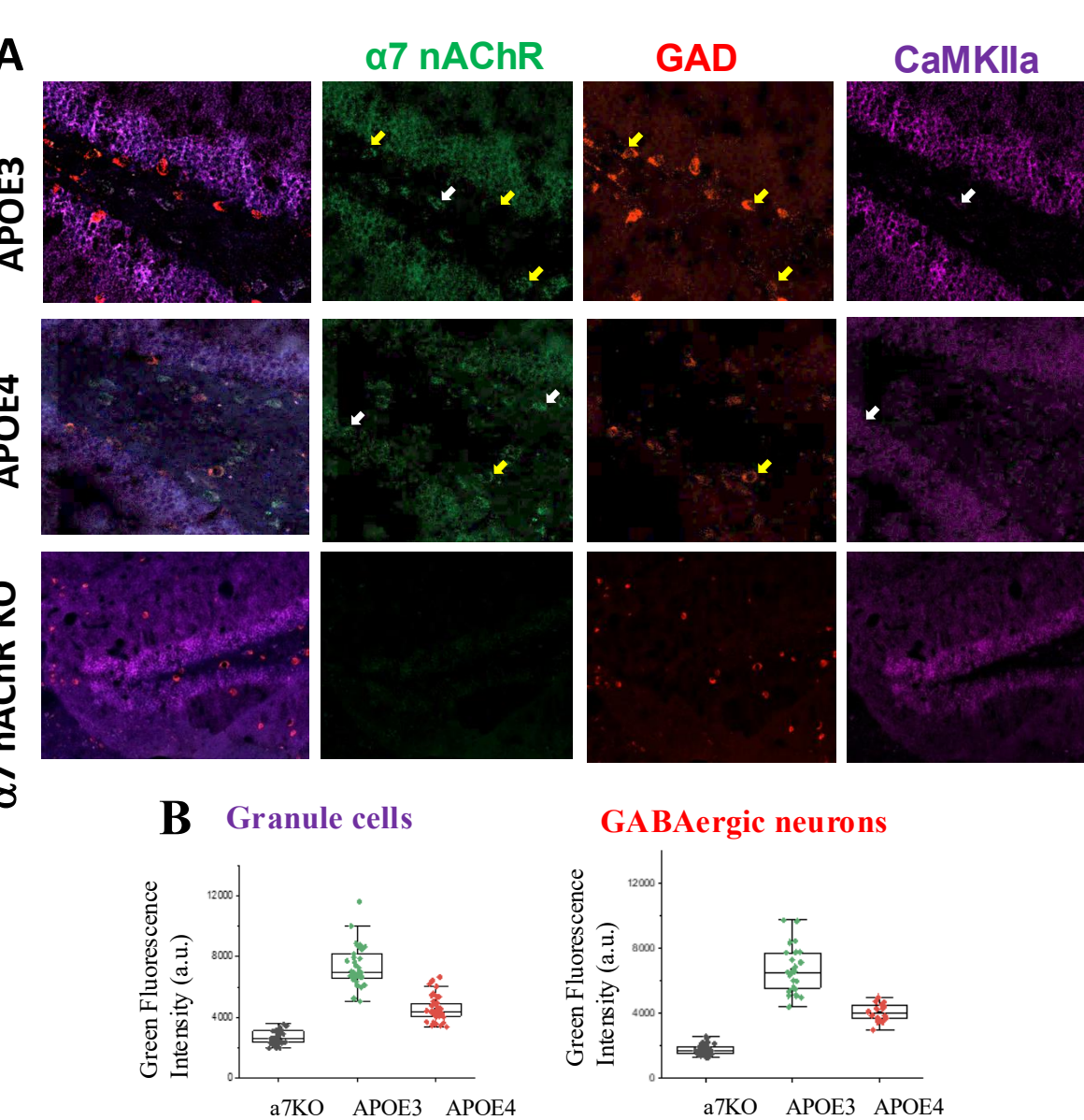


Figure 3 Expression of $\alpha 7$ nAChR, GAD, CaMKIIa in $\alpha 7$ nAChR KO, APOE3, and APOE4 mice. (A) Representative RNAseq images. (B) Statistical analysis of Granule Cells and GABAergic neurons.

GABAergic neuron count in APOE4 and APOE3 mice

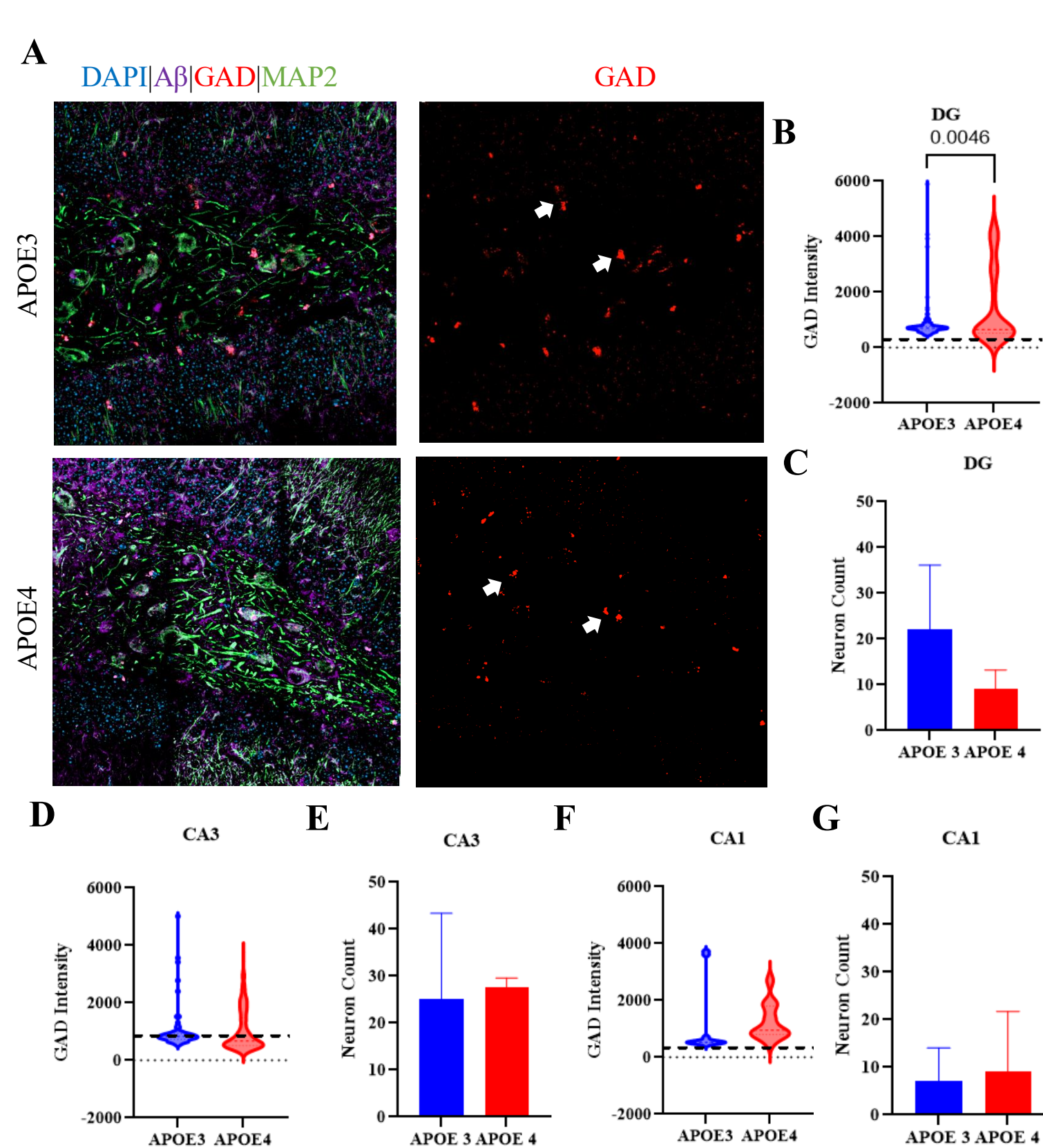


Figure 4. Distribution of GAD (glutamate decarboxylase) in APOE3 and APOE4 mice. (A) Representative images of GAD67+ GABAergic neurons in the dentate gyrus (DG) region showing intracellular Amyloid β staining. (B), (D) and (F) showing the distribution of Amyloid β intensity. (C), (E), and (G) Quantification of GAD67+ neuronal count demonstrating differences between APOE3 and APOE4 mice.

Increased intercellular Amyloid β accumulation in GABAergic neurons of 12-month female APOE4 and APOE3 mice

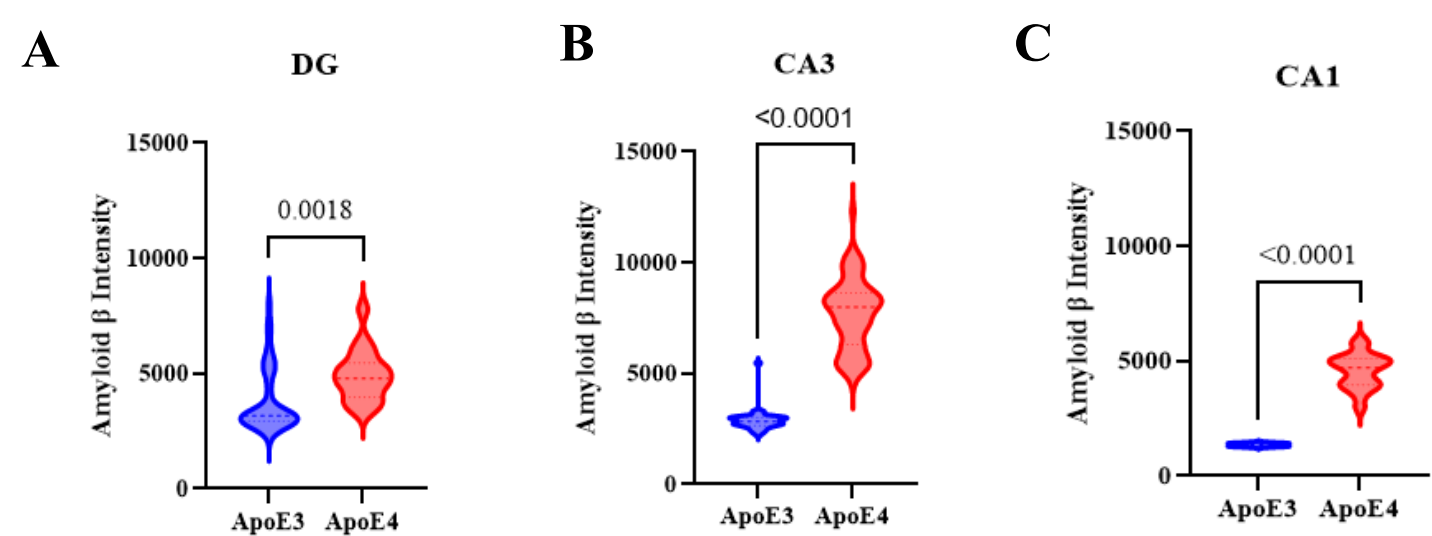


Figure 5. Distribution of Amyloid β in the CA1, CA3, and DG regions of APOE3 and APOE4 mice.

Increased Amyloid Accumulation in GABAergic neurons of 12-month Female Mice in Hippocampal Dentate Gyrus

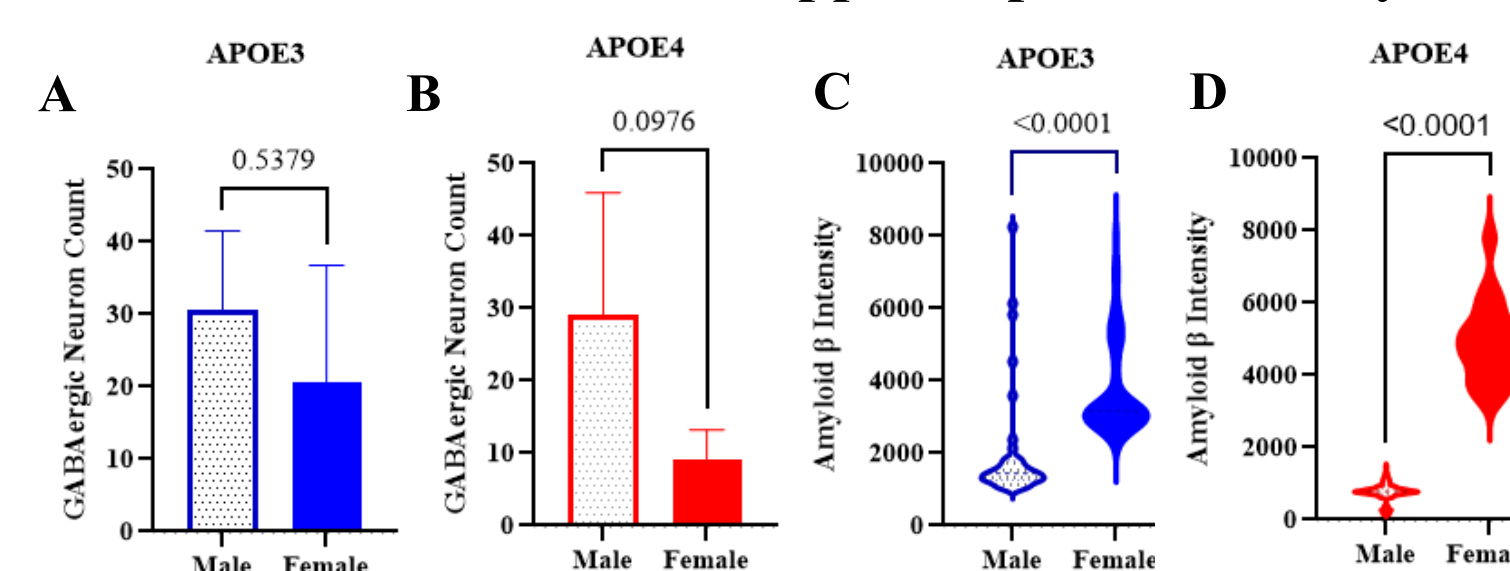


Figure 6. GABAergic neuron count and Amyloid β accumulation in Male and Female Mice. (A) and (B) shows APOE3 Male and Female mice at 12-months. (C) and (D) show APOE4 Male and Female mice at 12 months

Increased count of Calretinin-positive neurons in APOE4 mice compared to APOE3

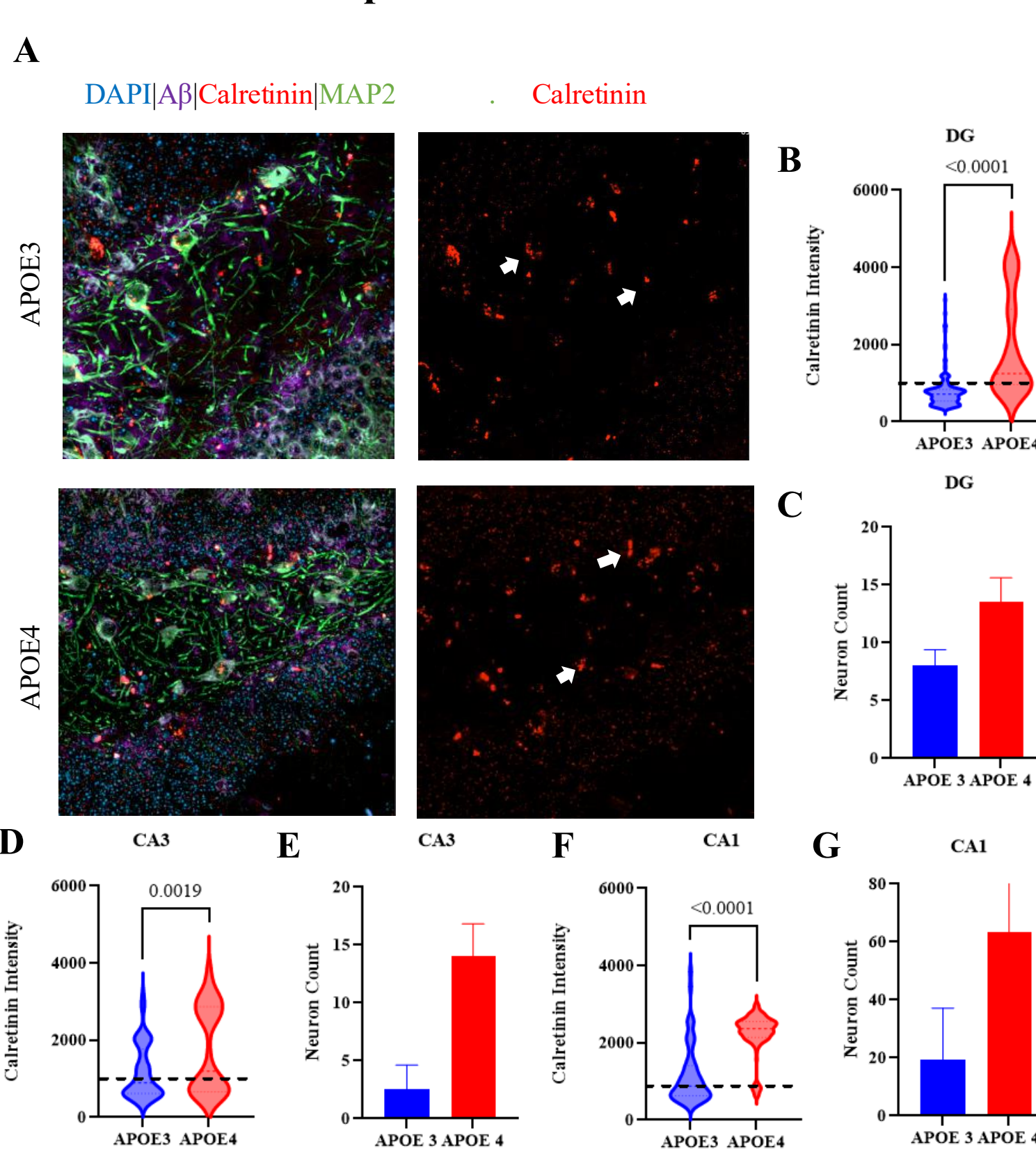


Figure 7. Distribution of CR+ (Calretinin) in APOE3 and APOE4 mice. (A) Representative images of CR+ neurons in the dentate gyrus (DG) region. (B), (D) and (F) showing the distribution of Amyloid β intensity. (C), (E), and (G) Quantification of CR+ neuronal count demonstrating differences between APOE3 and APOE4 mice.

Intercellular Amyloid β Accumulation of calretinin positive neurons of 12-month female APOE4 and APOE3 mice

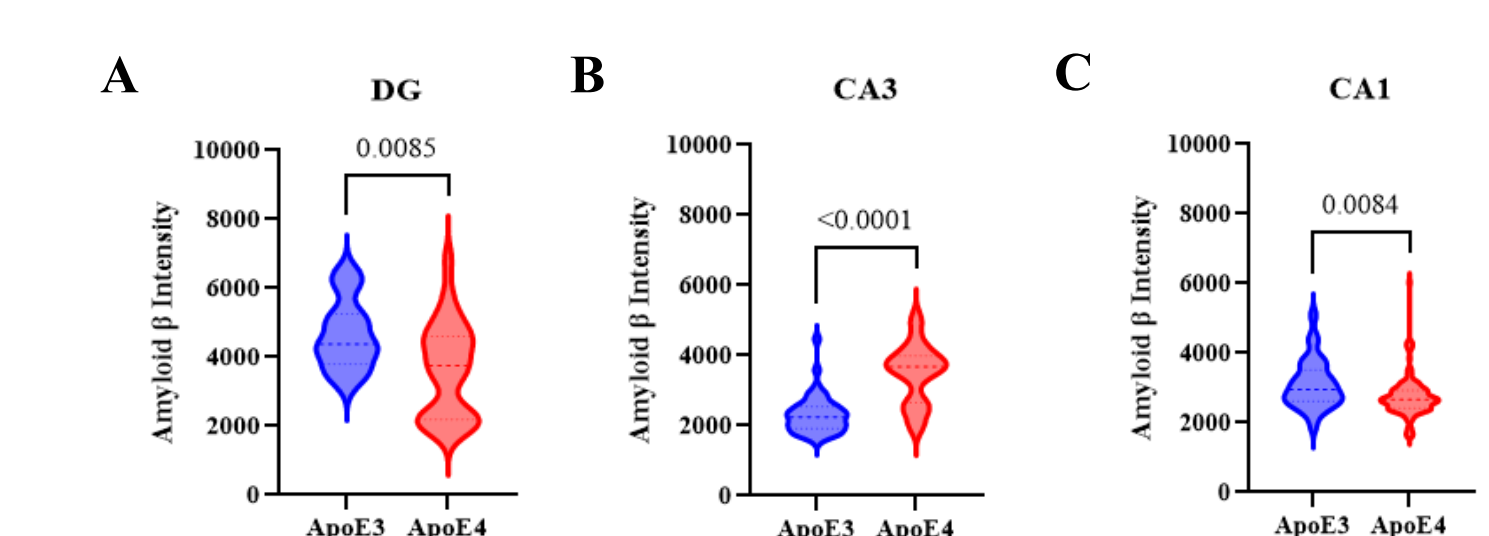


Figure 8. Distribution of Amyloid β in the CA1, CA3, and DG regions of APOE3 and APOE4 mice.

Increased Amyloid Accumulation in Calretinin-positive neurons of 12-month Female mice Hippocampal Dentate Gyrus

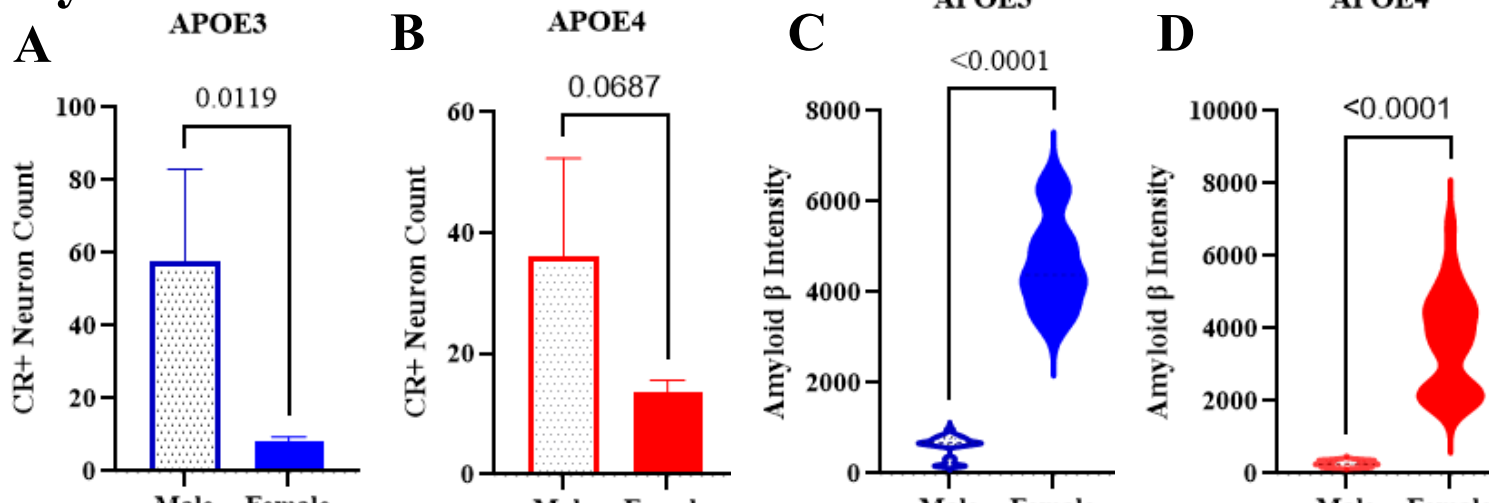


Figure 9. Calretinin-positive neuron count and Amyloid β accumulation in Male and Female Mice. (A) and (B) shows APOE3 Male and Female mice at 12-months. (C) and (D) show APOE4 Male and Female mice at 12 months

Summary

1. Increased intercellular Amyloid β in GABAergic neurons of APOE4 female mice

2. Hippocampal and medial septum cholinergic neuronal loss in APOE4 female mice

3. Decreased expression of $\alpha 7$ nAChR mRNAs in APOE4 dentate granule cells and hilar GABAergic interneurons

4. Increased Calretinin-positive neurons in DG, CA1, and CA3 in APOE4 female mice compared to APOE3 female mice

5. Increased Amyloid β in both GABAergic and Calretinin-positive neurons in hippocampus of both APOE3 and APOE4 female mice compared to male

Next Steps

1. Complete Timeline

2. Analysis of $\alpha 7$ nAChR; GABAergic and Calretinin+ Neurons

3. RNAseq Validation

4. Analysis of Human Samples

Acknowledgments

This project is supported by the RCMI program grant NIMHD U54MD012392 and NCCU RIPA Award, with additional funds from NIA25AG086122, DukeUNCADRC P30AG072958, and R245MH129791. The authors gratefully acknowledge S. Alex Marshall, Leon Coleman, Ping-An Li, Diego Correia, Zainab Afzal, and Jerry Yakel. Diagrams made in BioRender and Nissl Stain image from the Allen Brain Atlas.