

Alzheimer's disease (AD) is a neurodegenerative disease currently affecting 5.5 million Americans. Moreover, the disease prevalence is expected to rise to 16 million by 2050. People with AD share common neurological pathologies, mainly consisting of buildup of A $\beta$  protein fragments and tau proteins, which correspond with a deterioration of memory and cognition in patients afflicted with AD. Previous research from our lab has shown that when mice are chronically stressed through social isolation, they have an increased number of hippocampal A $\beta$  plaques. The goal of this project was to determine whether the stress-induced increase in A $\beta$  plaques could be prevented through exposure to physical exercise alone, or to exercise and an enriched environment throughout the period of isolation.

## Introduction

- Currently there is no cure or preventative treatment for AD [1]
- Chronic stress is believed to worsen plaque deposition, leading to more severe cognitive dysfunction in AD patients [2]
- Our lab has shown that AD mice that are chronically stressed through social isolation, as opposed to typical group housing, show a decrease in cognitive function and increase in A $\beta$  plaques
- Previous research has found that exercise and/or enriched environment (EE) can help lead to neuronal changes corresponding to an improvement in cognitive function [3,4]
- We hypothesize that exercise and EE can help decrease the onset of cognitive impairments in AD mice exposed to social isolation

## Methods

- Alzheimer's transgenic (5xFAD+) and wild type mice (5xFAD-) were housed in isolation or group housing for 3 months
- The follow up had 3 groups: isolation alone, enriched environment and exercise (EE), and exercise wheel only (EX)
- EE cages contained cognitively stimulating objects including wire mesh climbing walls, PVC pipe tunnels, plastic and paper huts, steel climbing chains, wooden sticks, extra nesting material, and exercise wheels
- EE objects were rearranged every 3-4 days, with one object exchanged, to maintain environmental novelty
- After 3 months, animal learning was assessed in a contextual fear-conditioning (CFC) paradigm and tissue was collected
- Hippocampal slices were collected, stained, and viewed under a Confocal microscope. A $\beta$  plaques were counted for comparison between groups



Image 1. Enriched Environment

## Histochemistry

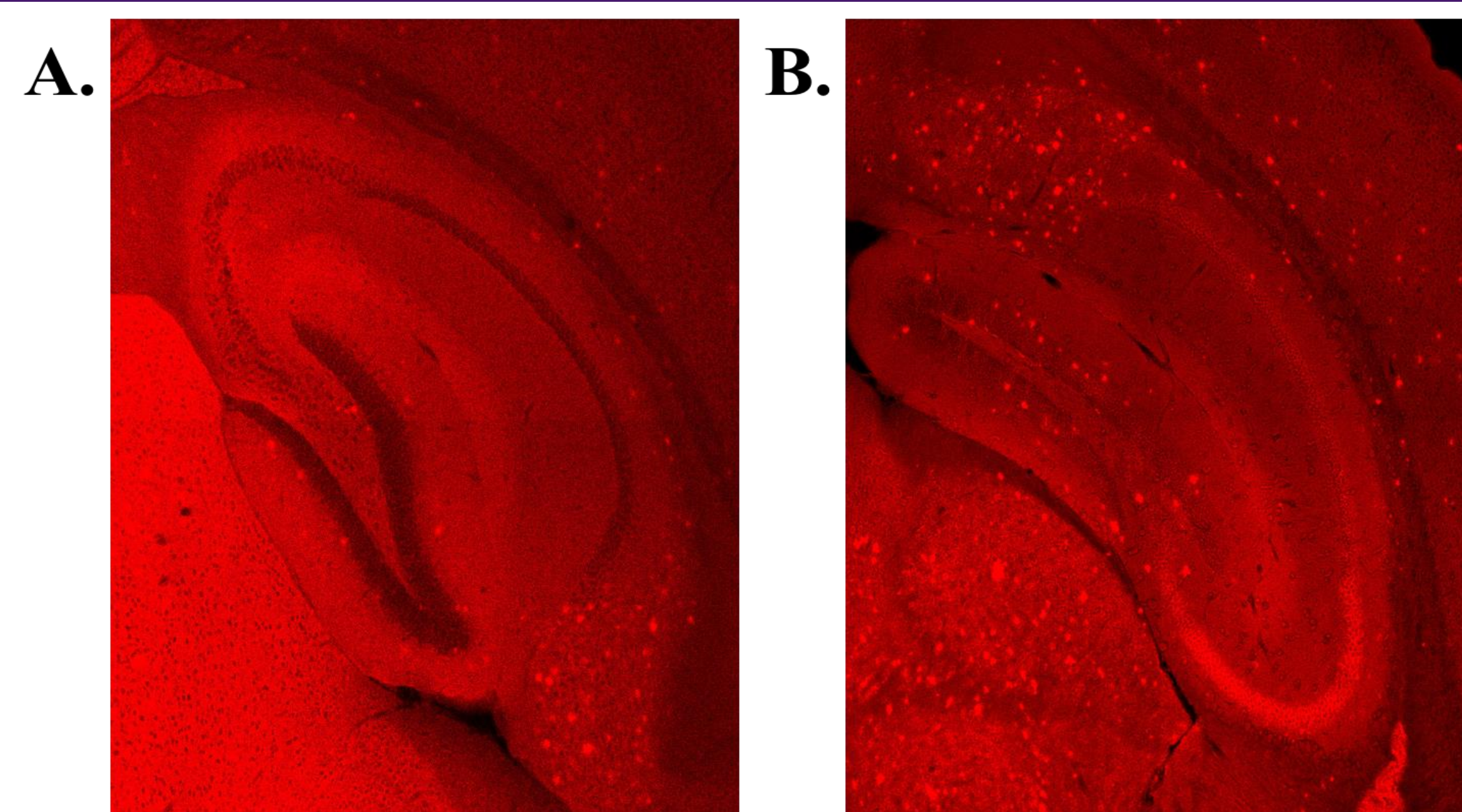
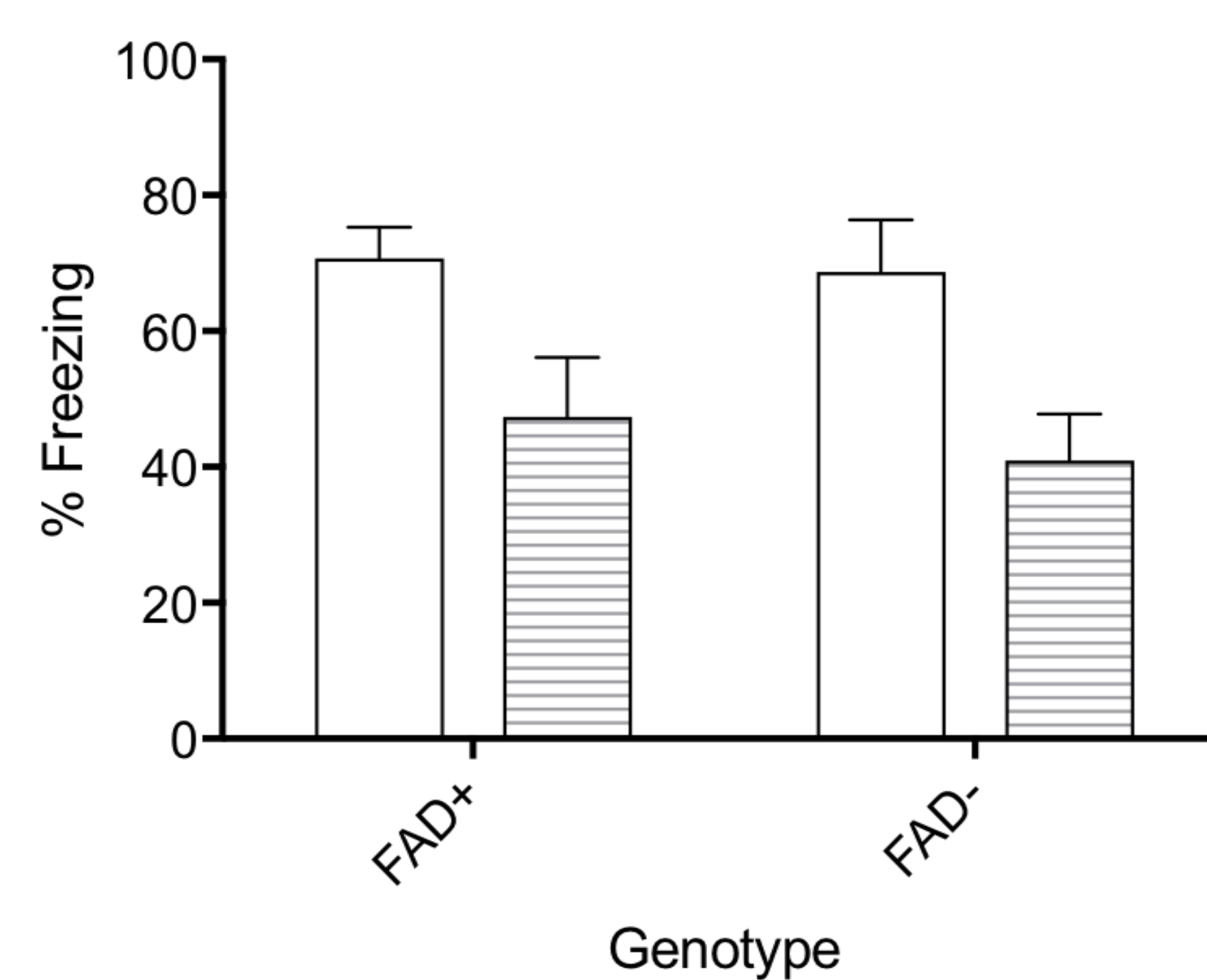


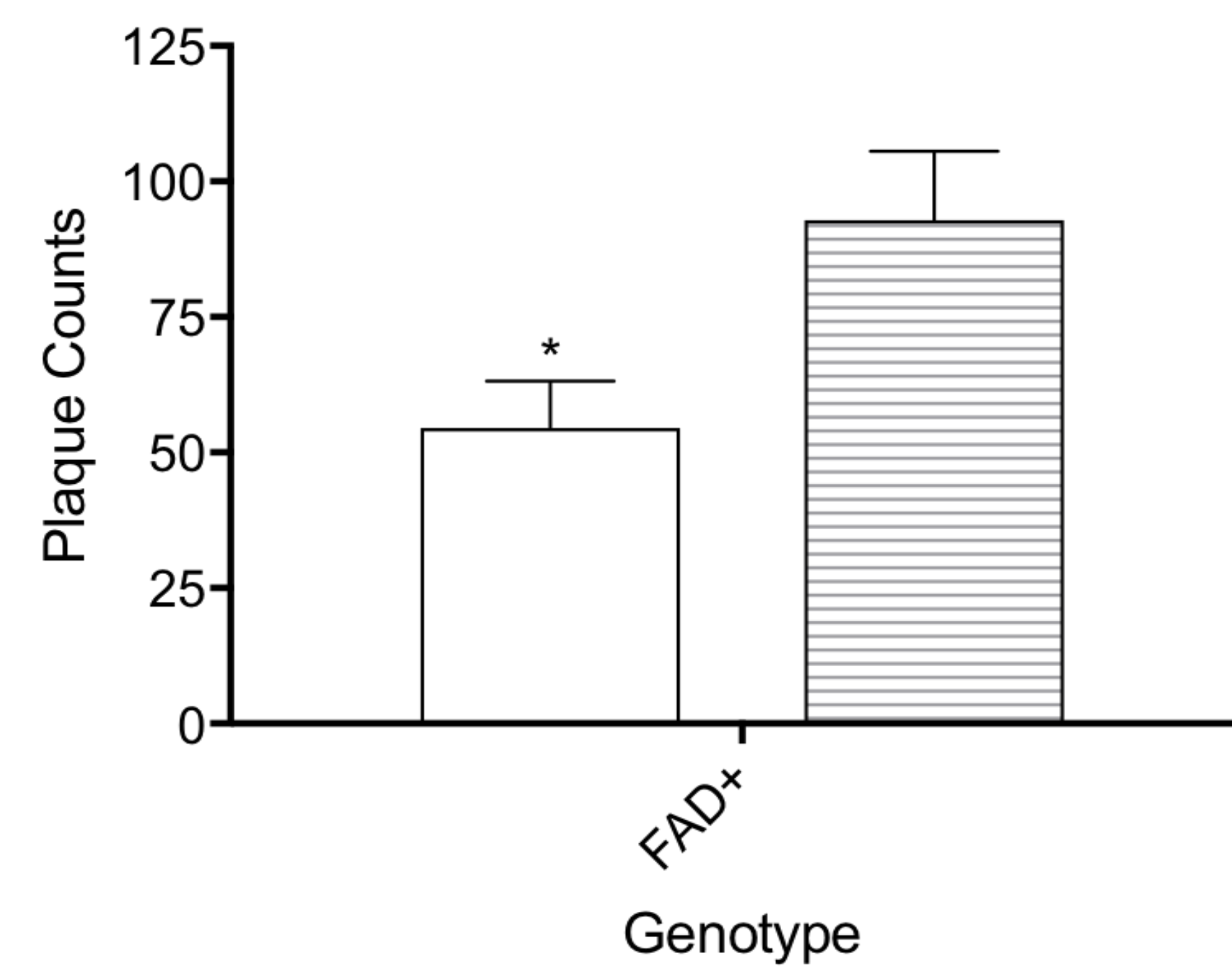
Figure 1. Representative images of plaques in the hippocampus of 5xFAD+ animals group housed (A) and isolated for 3 months (B).

## Results



□ Group Housed  
\* ▨ Isolated

Figure 2. Three months of isolation stress leads to decreased freezing in CFC. Isolated animals froze significantly less than group housed animals regardless of genotype



□ Group Housed  
▨ Isolated

Figure 3. Three months of isolation stress leads to increased plaques in FAD+ mice. There was significant differences in hippocampal plaque counts between isolated and group housed animals.

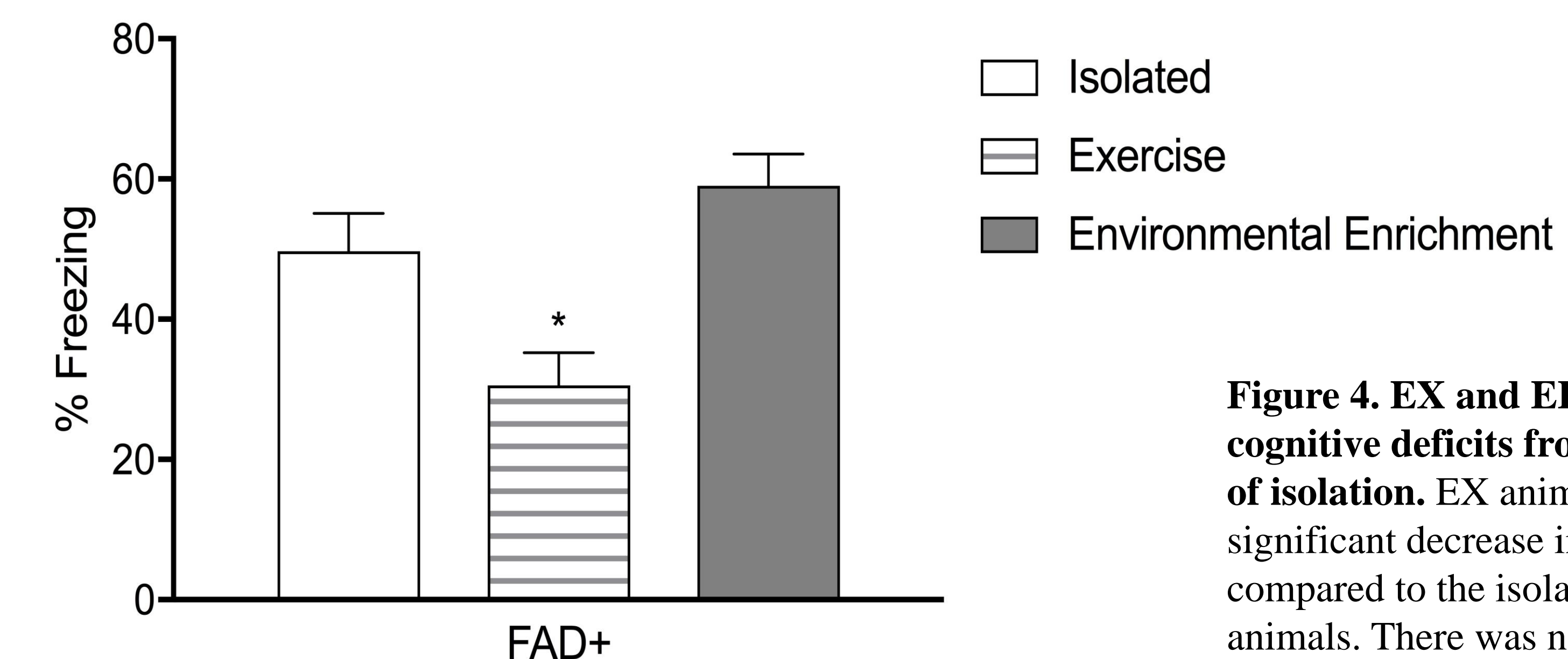


Figure 4. EX and EE did not alleviate cognitive deficits from three months of isolation. EX animals showed a significant decrease in % freezing time compared to the isolated and EE animals. There was no significant difference between EE and isolated animals.

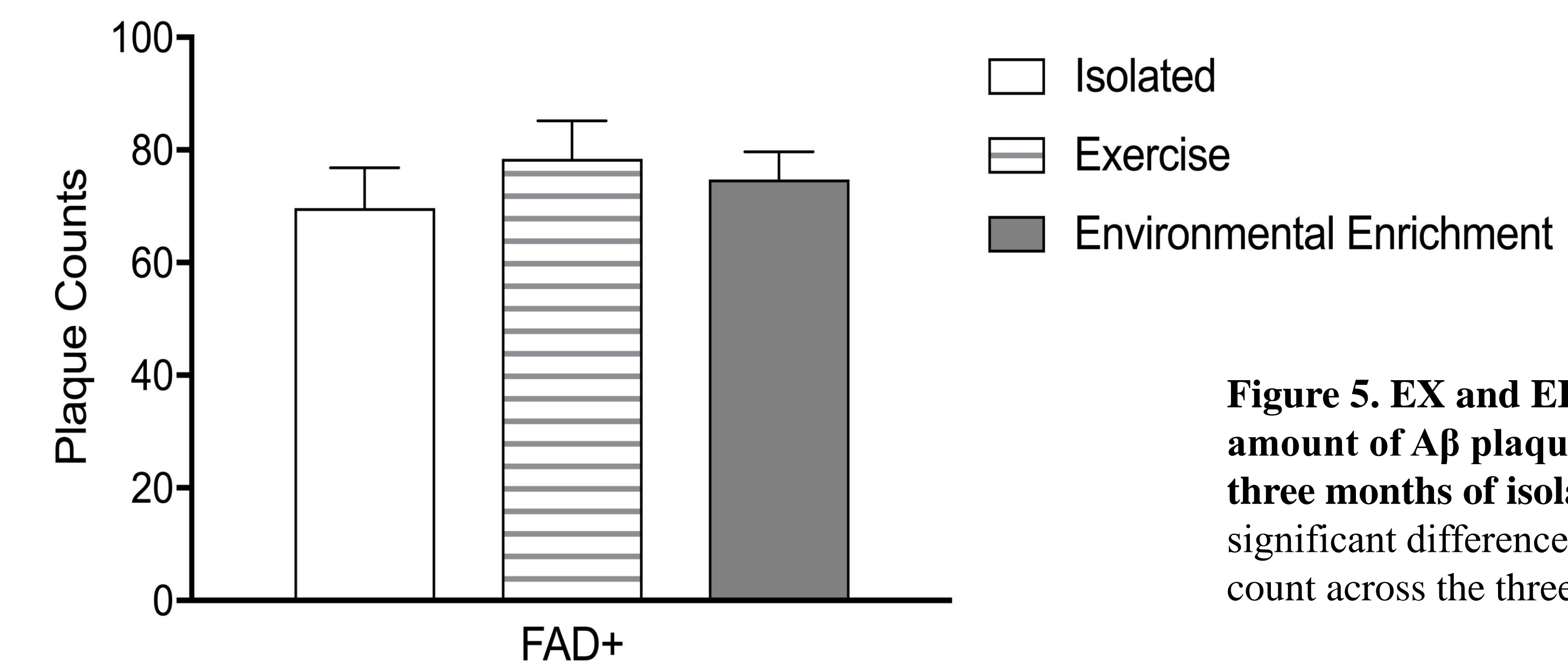


Figure 5. EX and EE had no effect on amount of A $\beta$  plaque formation from three months of isolation. No significant difference seen in A $\beta$  plaque count across the three groups.

## Conclusion

- Social isolation in 5xFAD+ mice leads to cognitive deficits and a significant increases in A $\beta$  plaque formation when compared to mice in group housing
- This cognitive impairment was so significant that exercise or enriched environment could not alleviate the effects
- Despite access to exercise and enriched environment, the mice did not demonstrate decreased production of A $\beta$  plaques as compared to isolation alone animals.
- This suggests that social isolation is detrimental to the extent that some therapeutic or preventative measures may not be effective

## Future Directions

- We are currently exploring the mechanism by which social isolation exacerbates plaque buildup and cognitive decline
- One such possibility is BACE1, the main beta secretase, involved in production of the A $\beta$  peptide, as a potential mechanism for the exacerbation
- EX and EE could be introduced earlier in their lifespan, or for a longer duration, to see if timing, and not the interventions themselves, was the reason for unsuccessful alleviation
- Pharmaceuticals could also be explored as an intervention

## References

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