

Extinction Learning Deficits Precede Contextual Learning Deficits in 5xFAD Transgenic Mice



Alzheimer's disease (AD) is a progressive brain disorder marked by loss of memory and a decline in cognitive functioning due to protein abnormalities in the brain. One of the earliest symptoms of AD is the inability to retain new information, or acquisition. However, a previous study by Bonardi et al. (2011) has shown that APP/PS1 transgenic mice exhibit a deficit in extinction learning before they display a deficit in acquisition. The present study aims to determine if the same pattern exists in 5xFAD mice, despite the differing genetic mutations. The results indicate that 5xFAD mice, like APPswe mice, show a deficit in memory extinction before they exhibit a loss of memory acquisition in the CFC, or contextual fear conditioning, paradigm.

Introduction

- Alzheimer's disease (AD) is the most common form of dementia and affects over 5 million Americans. There is no known cure for AD.
- The disease is usually not diagnosed until severe symptoms and pathology have set in. We aim to better understand the early stages of Alzheimer's pathology through the use of the 5xFAD transgenic mouse model of AD.
- One of the early symptoms of AD is the loss of memory acquisition, or the ability to retain new information.
- Learning is assessed using Contextual Fear Conditioning (CFC), where the mice are introduced to a new environment and experience a mild aversive stimulus. When reintroduced to the context 24 hours later, mice that acquired a memory for the novel context freeze, an instinctive rodent fear response.
- After repeated trials of exposure to the environment in the absence of an aversive stimulus, the mice gradually freeze less. This is indicative of new learning of the environment not being associated with the stimulus, or extinction of the initial association.
- A previous study by Bonardi et al. (2011) has shown that APP/PS1 transgenic mice exhibit a deficit in extinction learning before they display a deficit in acquisition.
- Our hypothesis is that 5xFAD mice will display similar behavior to APPswe mice, experiencing extinction deficits earlier than acquisition deficits.

Methods



- Learning ability of Alzheimer's transgenic (5xFAD) mice was assessed in contextual fear conditioning test for six days.
- On the first day, mice underwent training two at a time in separate but identical environments with unchanging visual and olfactory stimuli. A single mild aversive stimulus was administered on training day.
- 24 hours later, the mice are reintroduced to the same environment for the same amount of time with no aversive stimulus. The rate of freezing is measured by a computer program.
- The testing phase is repeated for four more days, continuing to measure freezing with no aversive stimulus.

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Effect of Genotype on Extinction Learning in 3 Month Old 5xFAD mice. A repeated measures ANOVA revealed significant effect of test, $p \le 0.001$, and a marginally significant test*genotype interaction, p = 0.066, wherein FAD+ animals extinguished more slowly than did FAD- animals. There was also a significant linear contrast effect of test, $p \le 0.001$, and a significant test*genotype interaction, p = .04.

Conclusion

We hypothesized that 5xFAD transgenic mice would exhibit a deficit in extinction learning earlier than a deficit in memory acquisition. Our results supported our hypothesis:

- There were no significant differences in memory acquisition between FAD+ and FAD- mice for either age group.
- FAD+ animals extinguished significantly more slowly than FAD- mice for both of the tested age groups.

Mice expressing the 5xFAD gene persisted in their freezing behavior for a longer period of time than did the wild type mice. This indicates lower overall cognitive function because the FAD+ mice had more difficulty dissociating the environment from the aversive stimulus.

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Effect of Genotype on Extinction Learning in 4 Month Old 5xFAD mice. A repeated measures ANOVA revealed significant effect of test, $p \le 0.001$, and a significant test*genotype interaction, p = .04, wherein FAD+ animals extinguished more slowly than did FAD- animals. There was also a significant linear contrast effect of test, $p \le 0.001$, and a significant test*genotype interaction, p = .02.

Future Directions

- extinction prior to a loss of memory acquisition.

- symptoms have set in.



• Data from the contextual fear conditioning paradigm confirmed a deficit in memory

• Future studies would likely focus on the mechanism behind why this is the case. • Other possible experiments may study this same effect in LPS transgenic mice, or look at extinction learning in humans with early Alzheimer's disease.

• The results of this study are important because if we can better understand the early stage pathology of Alzheimer's disease, we can potentially treat patients before severe