Effects of Unpredictable Stress on Contextual Acquisition and Extinction in Mouse Models of Alzheimer's Disease

Madison Johnson[1,2], Taylor Jamali[1,2], Julia Peterman[1,3], Kelly Brice[1,3], Christopher Hagen[1,2], Jordon White [1,3]
Gary Boehm[1,3], and Michael Chumley[1,2]

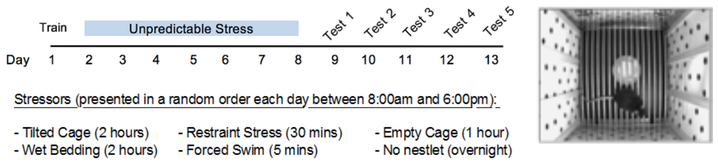
[1]Neurobiology of Aging Collaborative [2]Department of Biology and [3]Department of Psychology at Texas Christian University Fort Worth, TX 76129

Alzheimer's disease (AD) is a progressive form of dementia marked by decline in cognitive functioning and memory loss due to protein abnormalities in the brain. One early cognitive deficit seen in AD is a contextual acquisition deficit. However, evidence suggests that deficits in contextual extinction learning may present earlier than acquisition deficits. Extinction is a type of learning process by which the brain acquires information inconsistent with information it had previously learned, and gradually begins to accept this new information instead of the old information. As psychological stress has been linked with increased Alzheimer's markers, it is important to explore the interaction between stress and contextual learning.

Introduction

- Alzheimer's disease (AD) is a neurodegenerative disorder that affects nearly 5.5 million Americans, and there is currently no cure.
- AD is characterized by Aβ plaques and neurofibrillary tangles in the brain.
- Interestingly, psychological stress has been associated with increased inflammation, exacerbated amyloid pathology, and acquisition and extinction deficits in CFC male C57BL/6J mice.
- As the elderly face surmounting odds of AD, along with significant stress, research on how these interact and early diagnostic signs is especially relevant.

Methods



- Male C57BL/6J mice were divided into three groups – unpredictable stress (US), isolation, and group housed controls.
- All three groups were trained in a contextual fear conditioning paradigm.
- After training, the animals in the isolation and US groups were isolated in individual cages for seven days.
- In addition to living in isolation, the US group underwent seven days of variable, unpredictable stressors which include 2 hours of wet bedding, cage tilted at 45 degrees for 30 minutes, 30 minutes of restraint stress, 5 minutes of forced swimming in warm water, placement in an empty cage for one hour, and nesting material removal overnight. These stressors were applied in a random order every day for 7 days.
- On the eighth day, acquisition learning was assessed.
- Extinction learning was assessed on days nine through twelve.

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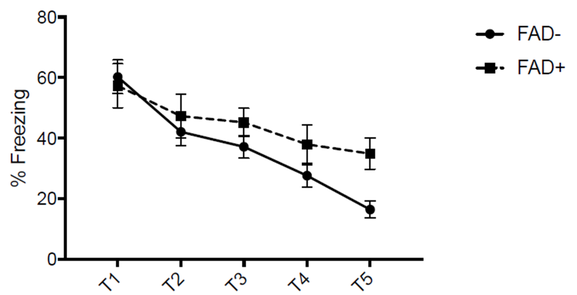
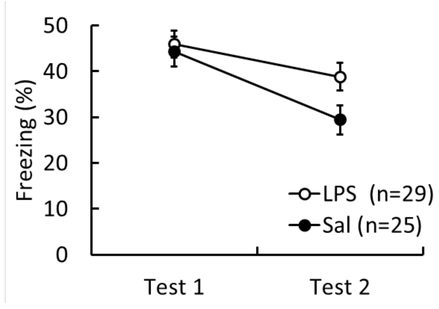
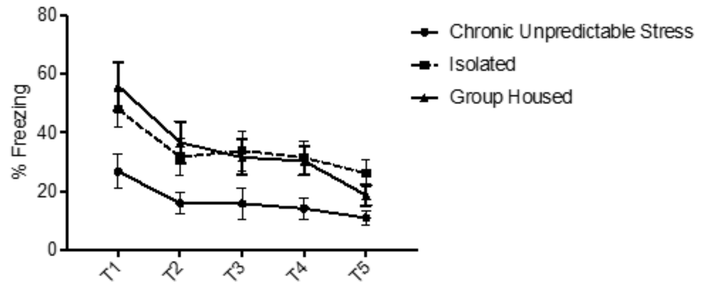
Results



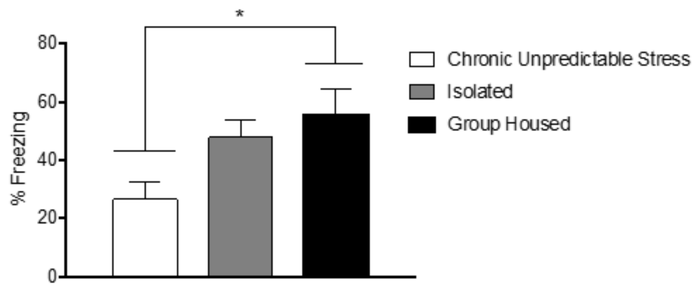
Effect of Genotype on Extinction Learning in 4 Month Old 5xFAD Mice. A repeated measures ANOVA revealed significant effect of test, $p \leq 0.001$, and a significant test*genotype interaction, p = .04, wherein FAD+ animals extinguished more slowly than did FAD- animals. There was also a significant linear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



Effect of 7 days of LPS Administration on Extinction Learning in C57BL6/J Mice. Results from CFC analysis demonstrate that LPS animals extinguished more slowly than saline animals.



Effect of Unpredictable Stress and Isolation on Extinction Learning in C57BL/6 Mice. A repeated measures ANOVA revealed a significant linear contrast effect of test, *p* = .031, but no significant interaction effect. There was also a significant between subjects effect, *p* = .018, such that unpredictable stress animals froze less than both isolated and group housed animals.



Effect of 7 days of Unpredictable Stress on Acquisition in C57BL/6 Mice. One-way ANOVA results from contextual fear conditioning demonstrate that unpredictable stress significantly impairs freezing behavior in acquisition, p = .014. Bars represent +/- SEM.

Conclusions

- Animals in the US group showed significant deficits in acquisition of contextual fear conditioning compared to isolated animals and group housed controls.
- There was no effect of US on extinction learning, as there was likely a floor effect due to impaired acquisition.

Future Directions

- Further research will investigate whether inflammation and biological markers of Alzheimer's disease are increased following unpredictable stress. This will include examining the inflammatory response to LPS after 6 days of unpredictable stress and exploring whether LPS-induced increases in hippocampal amyloid beta and resulting cognitive deficits are exacerbated by unpredictable stress.
- Additionally, given these data, further research may investigate the mechanisms behind these extinction effects and examine extinction learning in humans with early-onset and sporadic AD.