Mitigating Stress-Driven Potentiation of Amyloid Pathology via Frequency-Specific Audiovisual Flicker Stimulation

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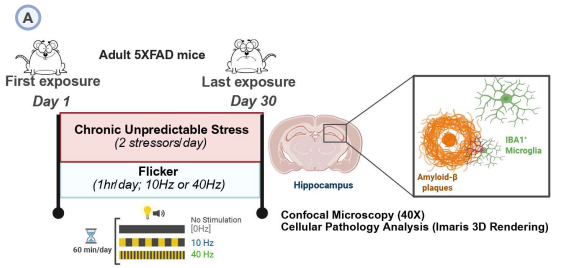
Background

Psychological stress can more than double the risk of neurodegenerative disease. Our lab recently showed that audiovisual flicker, rhythmic light and sound stimulation at specific frequencies, ameliorates pathology under conditions of stress or neurodegeneration alone.

However, its effects have not been examined where these conditions intersect.

To address this gap, we use chronic flicker intervention to test whether it can mitigate stress-induced exacerbation of Alzheimer's disease related pathology.

Paradigm



AV Flicker ↓ Undesirable Weight Gain in Males

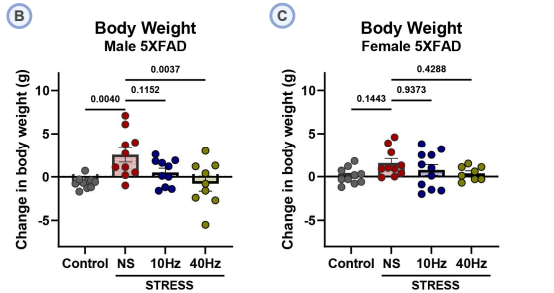
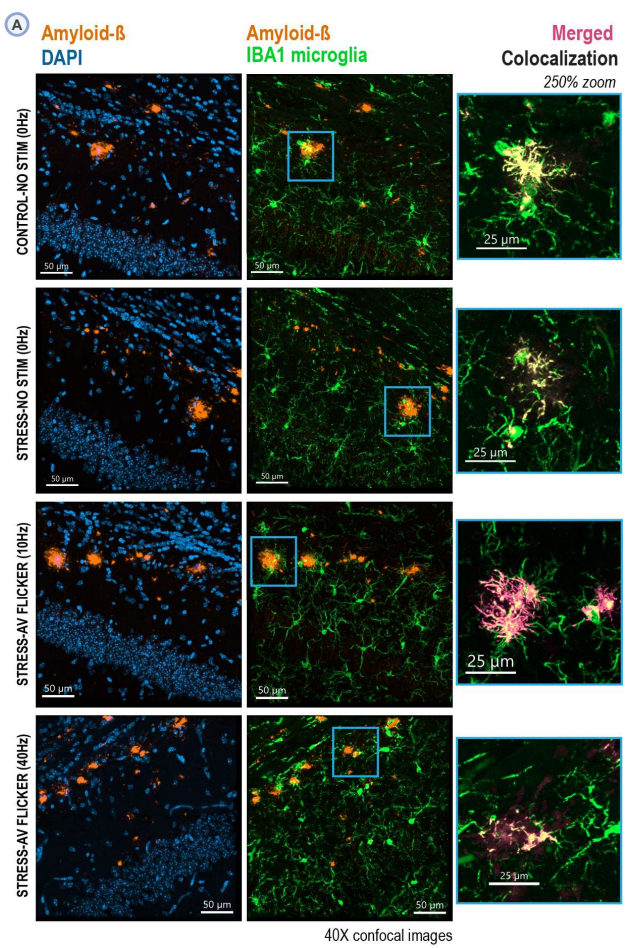
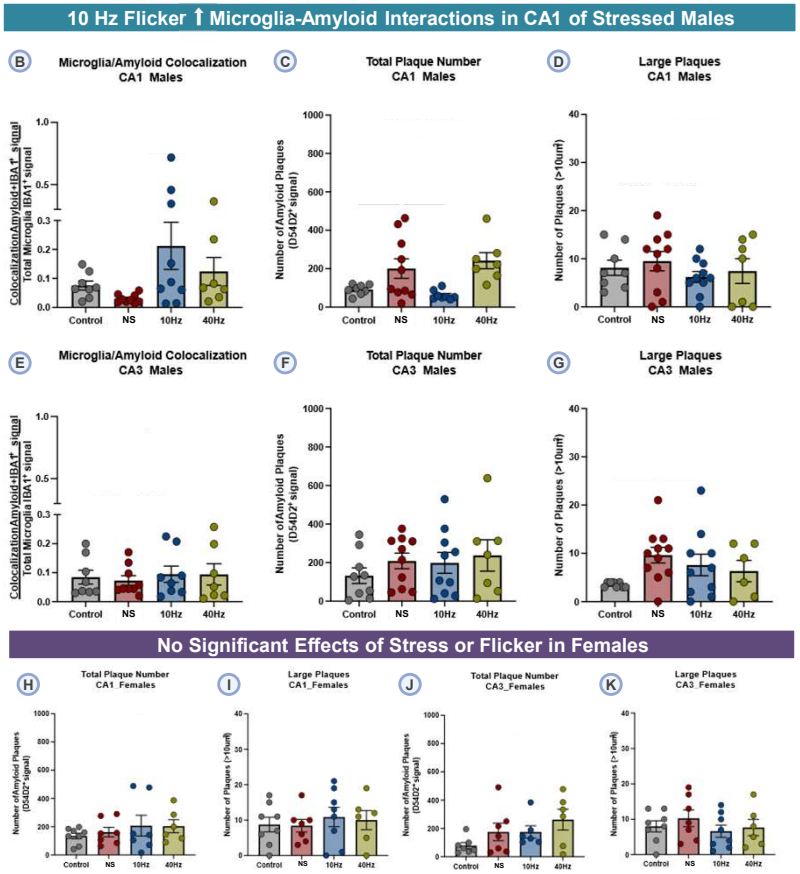


Figure 1. A. Experimental paradigm. **B.** One-Way-Anova for flicker found a significant difference ($F = 5.831$, $p = 0.0024$). Bonferonni's multiple comparison test found a significant difference between Stress-No stim and Control ($p = 0.004$) and Stress-No stim and Stress-40Hz ($p = 0.0037$). **C.** No significance found in females.

Cellular Assessment





No Significant Effects of Stress or Flicker in Females

Figure 2. 10Hz flicker increases microglia colocalization with plaques and reduces overall plaque number in males. **A.** Representative images of each flicker condition (Control-NS, Stress-NS, Stress-10Hz, Stress-40Hz) of amyloid burden (left), microglia signal (middle), and colocalization (right). **(B-D.)** In the CA1 region of male mice. **B.** Colocalization is measured as the ratio of IBA1 signal overlapping with amyloid signal / total IBA1 signal. One-Way-Anova for flicker found a significant overall difference among the four groups ($F = 5.98$, $p = 0.0032$). Post hoc pairwise comparisons (Dunn's test) found a significant difference between Stress-40Hz and Stress-10Hz ($p = 0.030$), Stress-NS and Stress-10Hz ($p = 0.002$), Stress-10Hz and Ctrl-NS ($p = 0.0414$). **C.** Total Number of Plaques is measured as all amyloid signal. No significance found. **D.** Large plaques are plaques that are 10µm> in diameter. No significance found. **(E-G.)** In the CA3 region of male mice. **(E-F.)** No significance found. **G.** Kruskal-Wallis found a significant overall difference among the four groups ($\chi^2(3) = 9.38$, $p = 0.025$). Post hoc pairwise comparisons (Dunn's test) found a significant difference between Stress-NS and Ctrl-NS ($p = 0.022$). **(H-I.)** In the CA1 region of female mice. **(J-K.)** In the CA3 region of female mice. No significance found in any female measures.

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References

Franklin, et al. 2025; Martorell, Paulson, et al. 2019; Iaccarino, Singer, et al. 2016.

Conclusions

- Psychological stress exacerbates pathological and physiological outcomes in an Alzheimer's disease (AD) mouse model, with males showing greater vulnerability.
- Frequency-specific chronic audiovisual (AV) flicker mitigates several stress-induced effects, notably weight gain and hippocampal Aβ accumulation.
- 10 Hz AV flicker in males enhances microglial association with hippocampal plaques, suggesting a sex-dependent, frequency-specific microglial response that may underlie protection.

Future direction: Characterize effective engulfment of plaque material in microglia and other phagocytotic cells like astrocytes that may lead to protective cellular effects seen at 10Hz in males