The Effects of Long-term Trazodone Administration on Object Recognition in the APP^{NL-F} Mouse Model of Alzheimer's Disease

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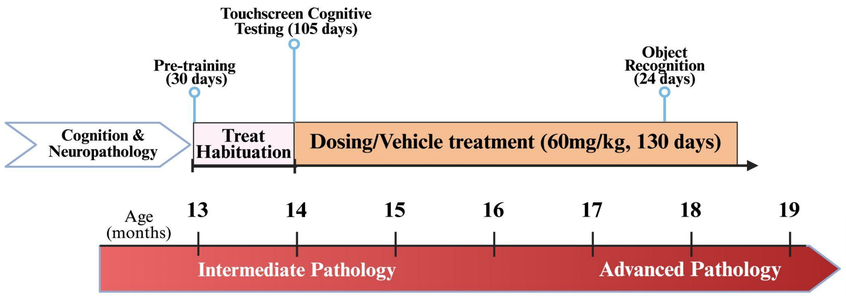
Introduction

- There is a bidirectional relationship between sleep and Alzheimer's disease (AD); in particular, slow-wave sleep (SWS) disruption is impacted by and contributes to amyloid-beta (Aβ) accumulation
- SWS disruption may contribute to progressive cognitive decline in AD
- Restoring SWS is a potential therapeutic target for slowing AD progression
- Trazodone is widely used off-label as a sleep aid; it improves SWS and may slow cognitive decline (James & Mendelson, 2004; La et al., 2019)
- **Aim**: Investigate the effects of trazodone on memory in a mouse model of AD

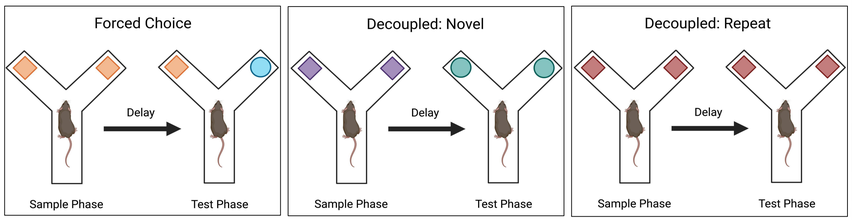
Methods

a. Experimental Timeline: Habituation, Dosing, and Cognitive Testing



- 13-month old APP^{NL-F} mice are placed on restricted feeding and a 11:13 hour light/dark cycle; they are habituated for ~30 days to voluntarily ingest a palatable treat containing trazodone or a vehicle (water), which occurs half an hour before their rest phase (Arai & Kent, 2025)
- After ~105 days of dosing and touchscreen testing (Lafayette Instruments), the mice undergo object recognition (OR) testing
- After cognitive testing, brain and blood collection occurred to assess pathology

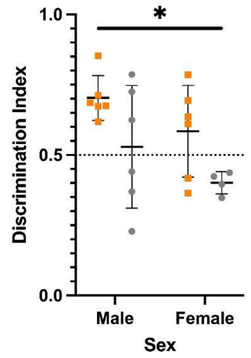
b. Object Recognition: Forced Choice and Decoupled Trials



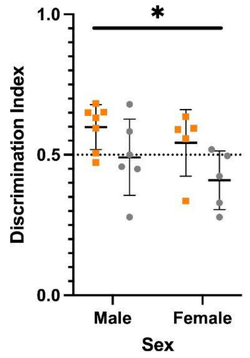
- Assesses OR using 1 hour and 24 hour delays
- Exploration time is measured and each phase lasts 5 minutes; mice that explored less than 3 seconds were excluded from analyses
- Objects are counterbalanced between treatment and sex; additional analyses suggest there is no bias between objects

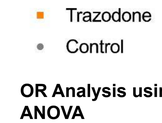
Results

a. Forced Choice 1 Hour



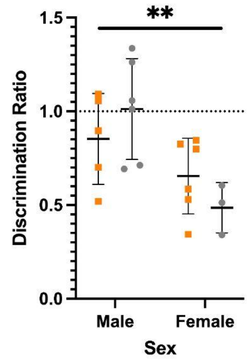
b. Forced Choice 24 Hour



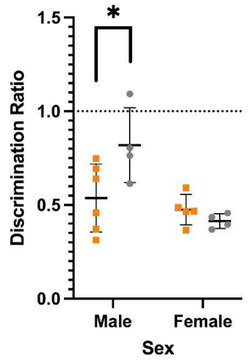


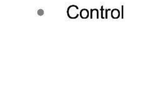
OR Analysis using 2-way ANOVA
Discrimination index=novel object exploration/test phase exploration. Forced choice 1 hour: main effect of treatment (p=0.0132; n=22); 24 hour: main effect of treatment (p=0.0177; n=23).

c. Decoupled 1 Hour: Novel



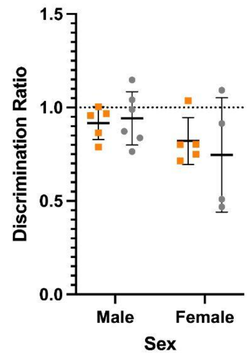
d. Decoupled 1 Hour: Repeat



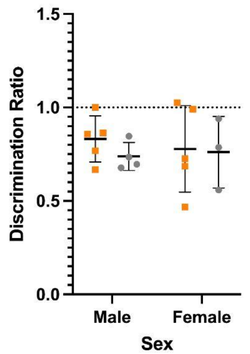


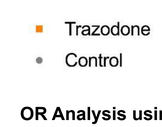
OR Analysis using 2-way ANOVA
Discrimination ratio=test phase exploration/sample phase exploration. Decoupled 1 hour novel: main effect of sex (p=0.0036; n=20); repeat: main effect of sex (p=0.0035; n=19) and interaction effect (p=0.0228). Bonferroni test reveals trazodone males outperform controls (p=0.0177).

e. Decoupled 24 Hour: Novel



f. Decoupled 24 Hour: Repeat



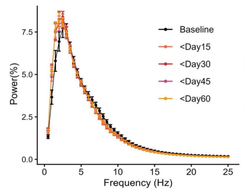


OR Analysis using 2-way ANOVA
Decoupled 24 hour novel: no significant results (n=20); repeat: no significant results (n=17).
Note: all data reported as mean ± SD

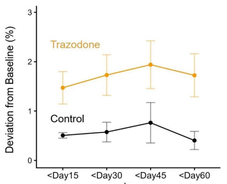
Discussion

- Trazodone improves OR performance in the forced choice paradigm for both the 1 hour and 24 hour delays
  - The decoupled 1 hour trials suggest that trazodone treated males have greater recollection of previously seen objects than control males
  - These results were not replicated in the 24 hour delays, likely due to overall poorer memory for longer delays in our aged AD mouse model
  - The sex differences seen in the decoupled data may be due to differences in Aβ pathology within the entorhinal and hippocampal regions of the brain
  - Overall OR memory improvements may be due to increased SWS, but further research on the mechanisms of trazodone must be conducted

a. SWS Power Spectra

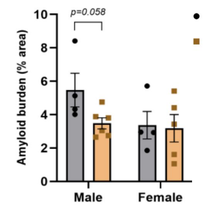


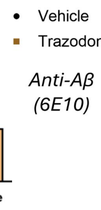
b. Slow Oscillations Deviations



Sleep analyses from 60 days of trazodone treatment (n=8) from ZT0-3
Trazodone changes the power spectra of SWS in APP^{NL-F} mice. Specifically of interest is increased power in SO band (0.5-1Hz). Data reported as mean ± SEM.

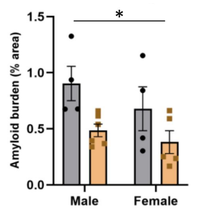
c. Entorhinal Aβ





Anti-Aβ (6E10)

d. Hippocampal Aβ



Analyses of neuropathology following 60d of treatment (N=19)
Samples collected between ZT12-14. Data points represent average for individual mice across 3 representative sections per region. Figure d. Amyloid burden (% area) in hippocampus, main effect of treatment ($p<0.05$). Data reported as mean ± SEM.

- **Limitations:** the results do not determine whether the mechanism in which trazodone improves OR is SWS or pathology dependent; the method is not as continuous or complex as human OR (Ennaceur, 2010)
- **Future directions:** incorporate a time delay less than 24 hours; determine the mechanisms in which trazodone impacts AD; avoid prolonged restricted feeding and/or other cognitive testing; ultimately ⟹ human studies

References

Acknowledgements

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