

Depressive-like Behaviour in a Humanized Knock-in Mouse Model of APOE, Amyloid, and Tau is Sex- & APOE Allele-specific

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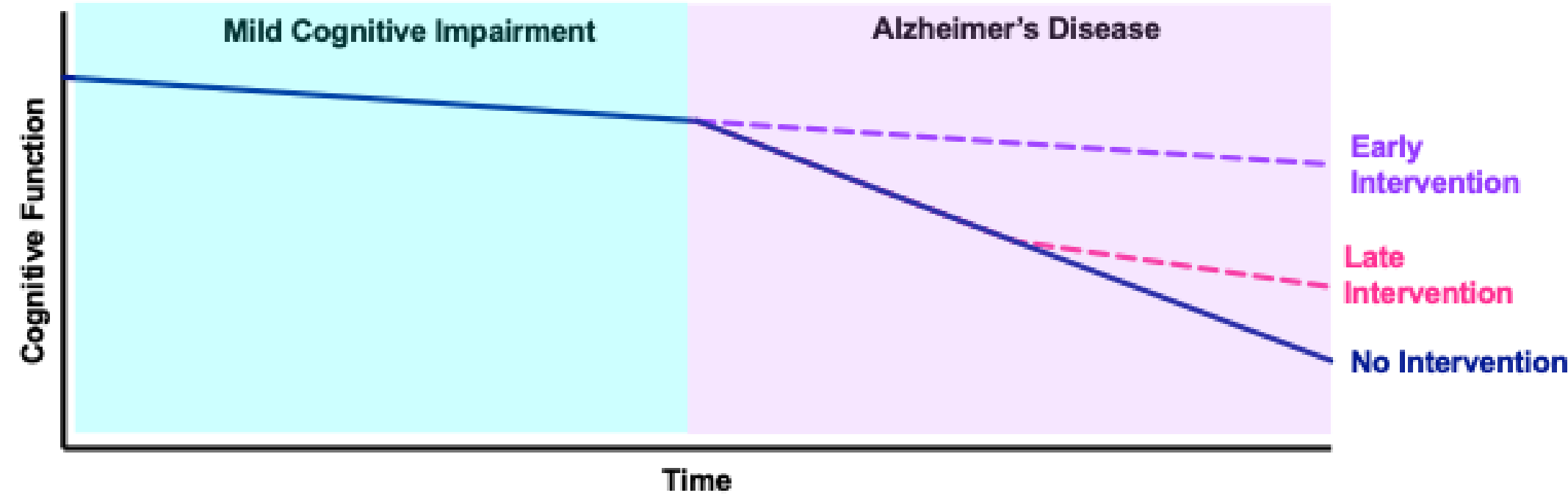
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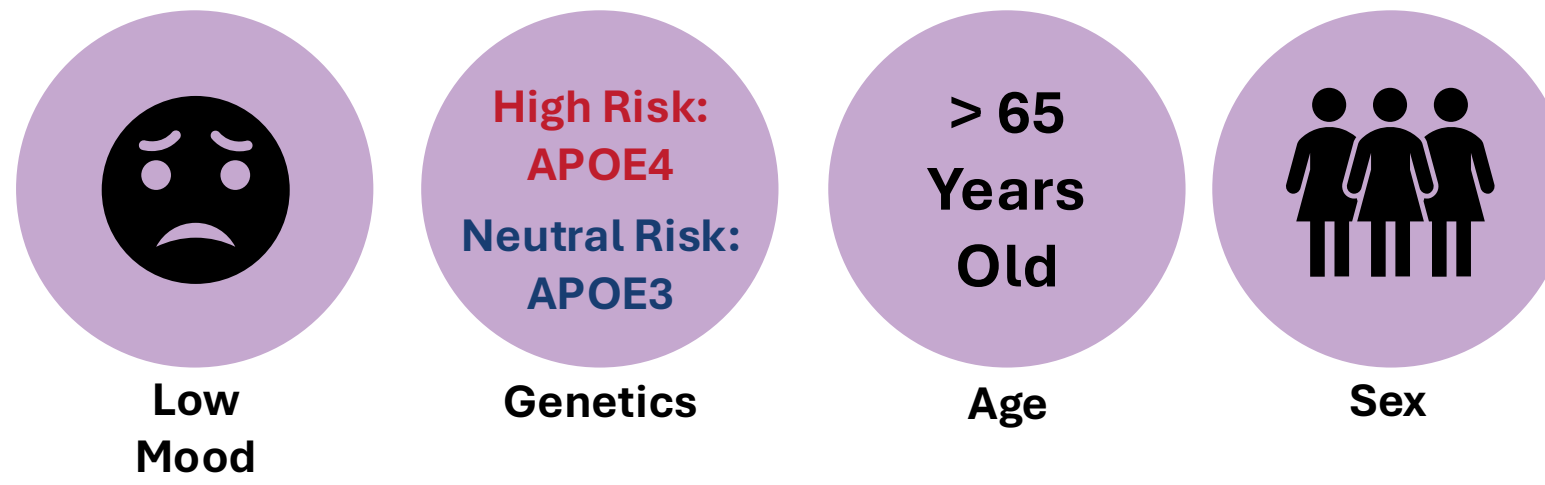
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Introduction

Early diagnosis of Alzheimer's disease (AD) is critical for enabling earlier and more effective interventions that may help prevent severe cognitive decline



AD has several **key risk factors** that may support early diagnosis and facilitate early intervention prior to severe cognitive decline



- Mood changes and/or depression often precede AD diagnosis, suggesting that alterations in affect may occur during a prodromal phase of AD prior to severe cognitive decline and memory loss¹
- Carriers of the apolipoprotein E4 (APOE4) allele are at increased risk of AD compared with apolipoprotein E3 (APOE3) carriers¹. In AD, APOE4 carriers experience earlier cognitive decline¹, more severe pathology¹, and more adverse responses to treatments compared to non-carriers².
- Combining APOE4 genetic screening with assessment of depression/mood changes may improve identification of AD-risk individuals who could benefit from early intervention
- Women are at higher risk than men, with female APOE4 carriers showing the greatest risk of AD¹

Mouse models are essential for developing early interventions for AD, enabling evaluation of the safety, efficacy, and optimal timing of treatments aimed at preventing severe cognitive decline.

Can AD-relevant mouse models recapitulate the genetic and affective risk indicators observed in human AD?

Two key limitations hinder progress towards answering this question

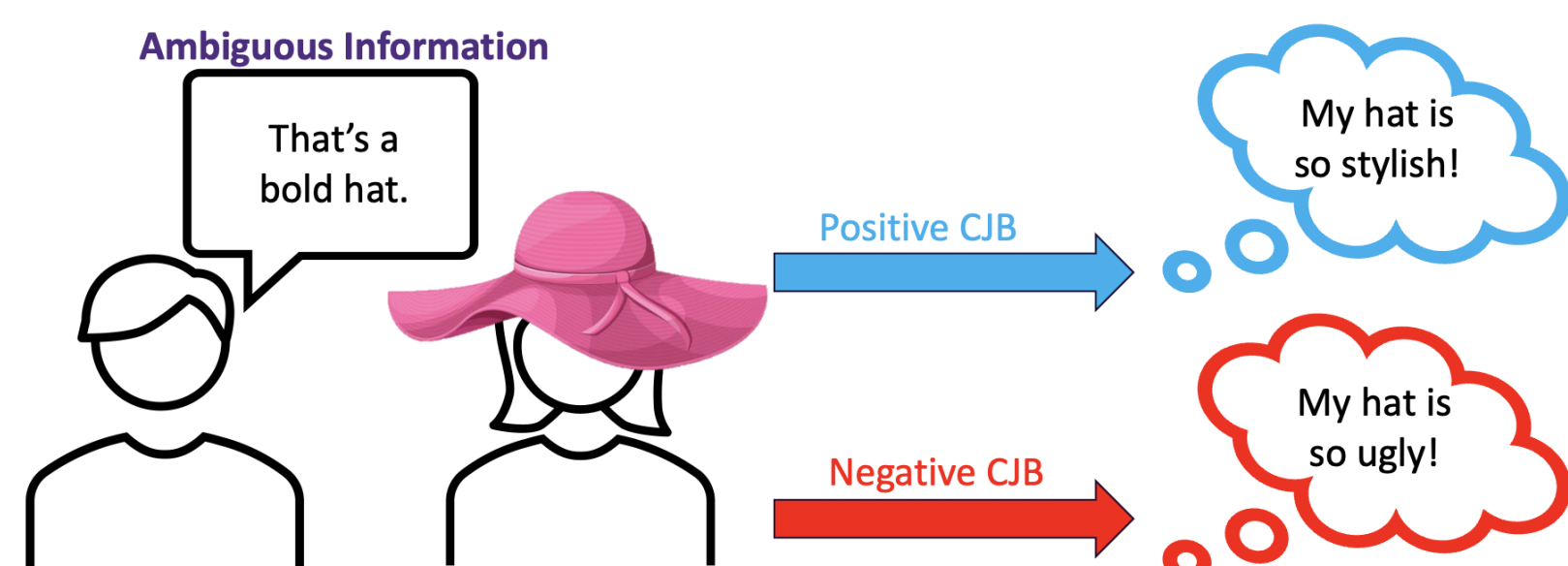
1. Traditional AD mouse models often fail to recapture the slow progressive nature of AD, and the APOE4 genetic risk for AD

- This limitation can be addressed using **humanized targeted replacement mouse models** that recapture APOE4 genetic risk and the slow, progressive nature of AD³

2. Behavioural assays of mood in mice differ substantially from human mood assessments, limiting translation of affect-related findings from AD mouse models to patients with AD⁴

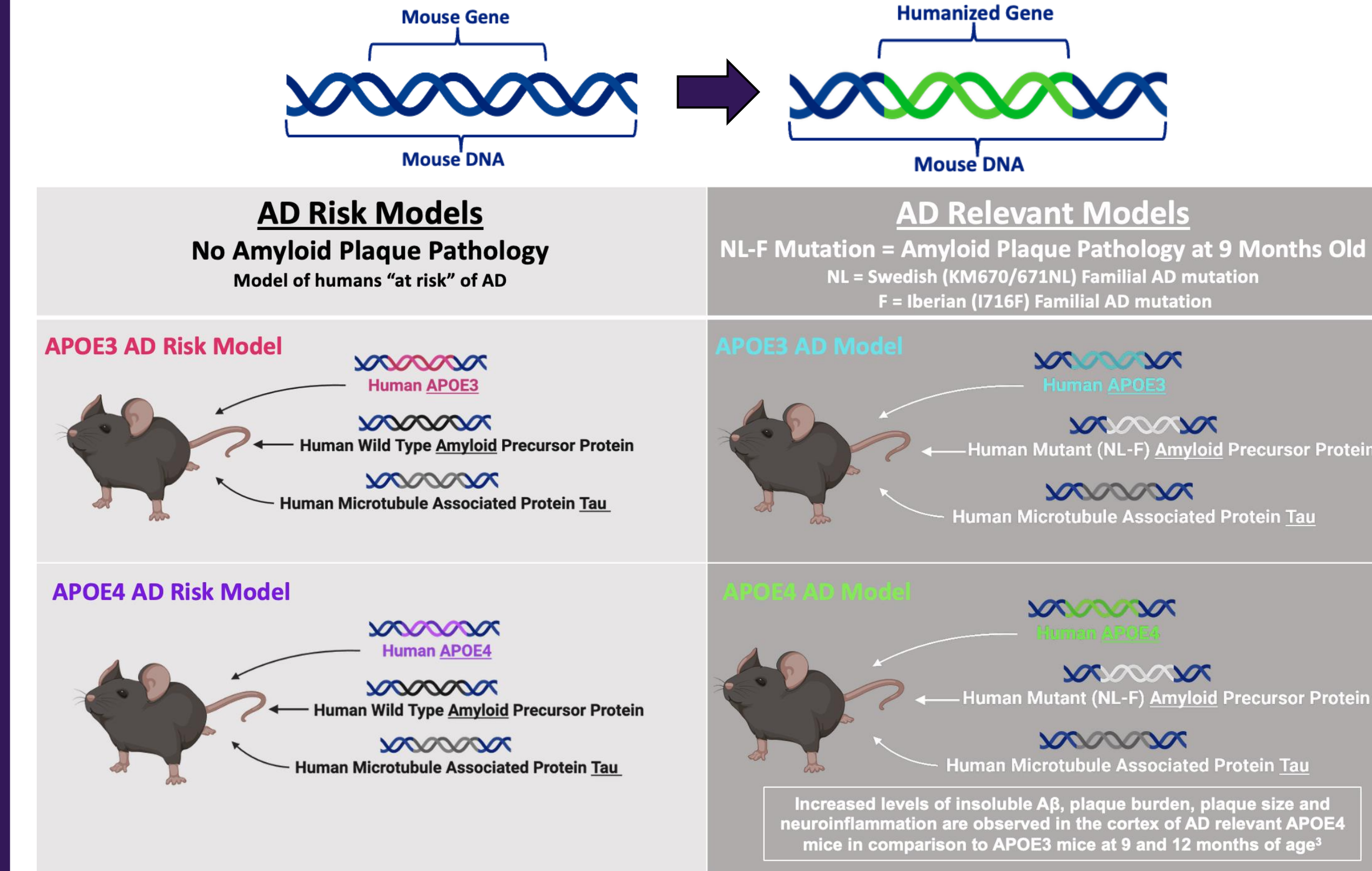
- This limitation can be addressed using **touchscreen-based tasks**, which provide a more translational approach to assess affect in mice and enable more direct comparisons with humans^{4,5}

One aspect of mood that can be assessed using touchscreens is **Cognitive Judgment Bias (CJB)**⁴. CJB measures systematic biases in interpreting ambiguous information, which reflects one's emotional state:



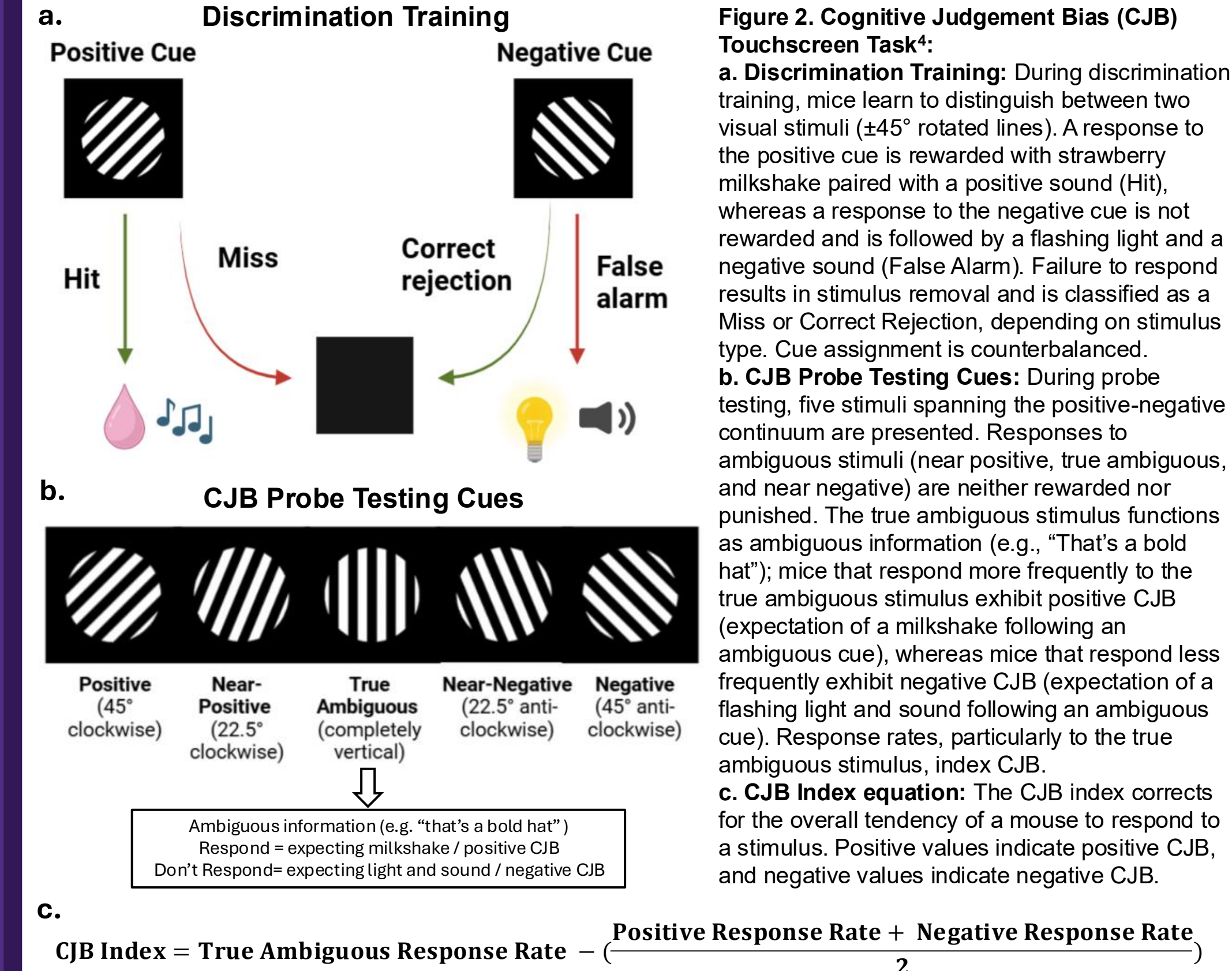
Humanized Targeted Replacement AD Relevant Mouse Models

Targeted replacement of mouse genes with humanized genes:

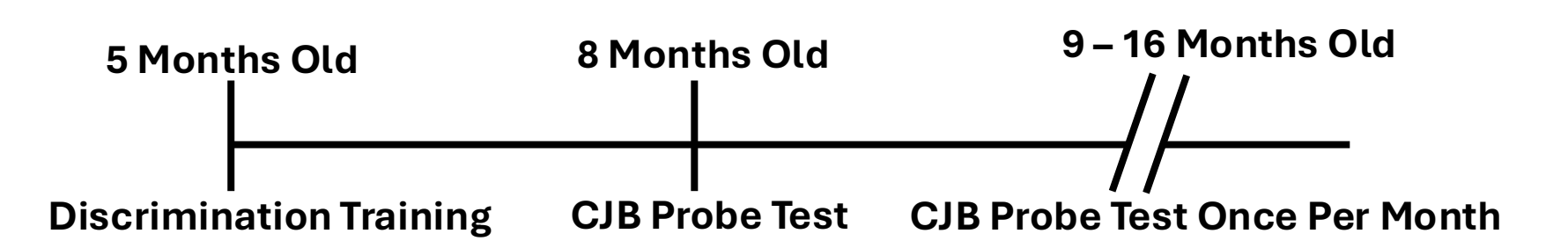


Hypothesis: Mice modeling APOE4-associated risk for AD, as well as mice expressing APOE4 in combination with amyloid pathology, will exhibit negative CJB, driven by APOE4 effects and amyloid-related neurodegeneration in brain regions involved in affective processing.

Cognitive Judgement Bias (CJB) Touchscreen Task

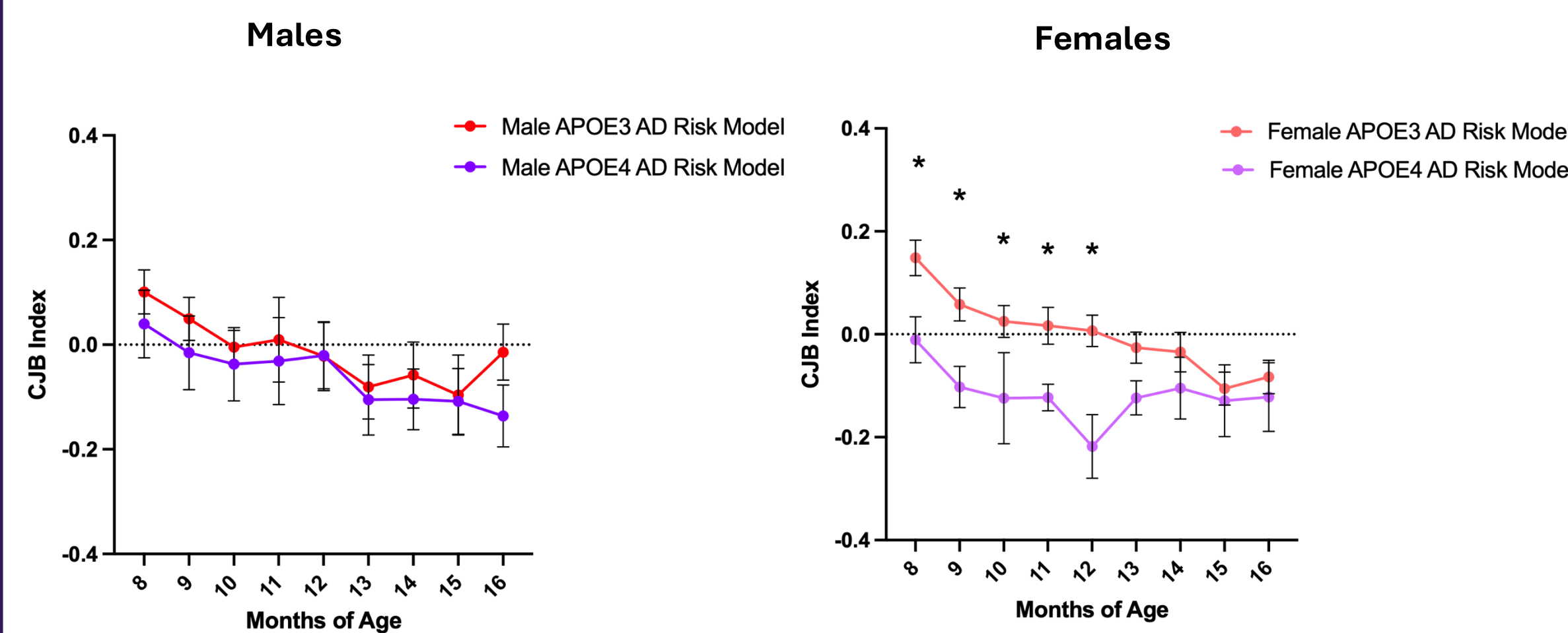


Timeline:



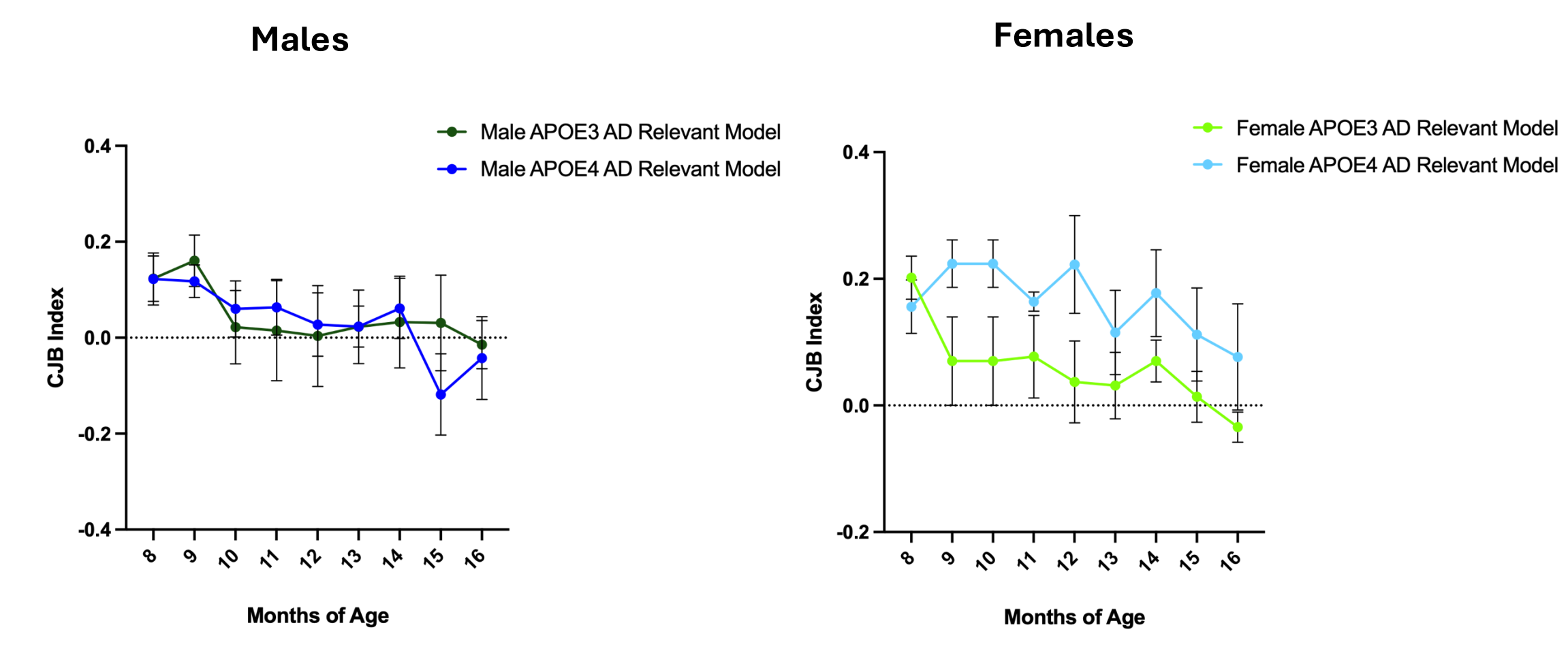
Affective Bias Across Mid and Late-Life Timepoints in AD Risk and AD Relevant Mouse Models

Female APOE4 Risk Model Mice Display Negative Affective Bias Across Multiple Mid-Life Timepoints



Analysis: Mixed Effects Model, * = p < 0.05

No Difference in CJB Between APOE3 and APOE4 AD Relevant Mouse Models Across Time



High CJB Index = Positive CJB
Low CJB Index = Negative CJB

Conclusion

Summary: In the AD risk model, female APOE4 mice exhibited a more negative affective bias than female APOE3 mice across multiple mid-life timepoints, indicating a sex- and genotype-dependent depressive-like phenotype. In the AD-relevant model, no CJB differences were observed between APOE3 and APOE4 mice, suggesting that amyloid pathology may mask APOE4-specific effects on CJB.

Conclusion: Negative CJB in the female APOE4 AD risk model reveals a sex-dependent depressive-like phenotype that precedes amyloid pathology, reflecting a potential early behavioural marker of AD risk in humans.

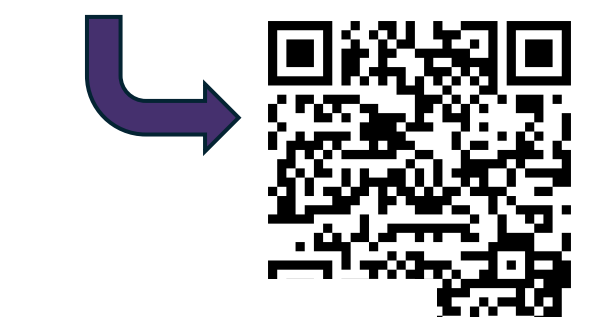
- Negative affective bias in the female APOE4 AD risk mouse model parallels human findings, where APOE4 genotype has been shown to predict depression in female AD patients⁶.**
- The female APOE4 risk model recapitulates early AD-relevant phenotypes observed in humans, supporting its utility for testing early interventions for female APOE4 carriers.

Significance/ Future Directions: The APOE4 risk model may be a viable model for testing early interventions for female APOE4 carriers. Screening human females with mid-life depressive symptoms for APOE4 genotype may help identify individuals at greatest risk for AD prior to severe cognitive decline.

References and Acknowledgments

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