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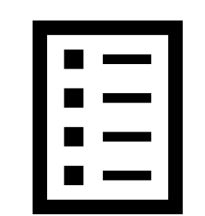
Background

- Female *APOE* ϵ 4 carriers face greater Alzheimer's disease (AD) risk, more severe pathology, and faster cognitive decline¹⁻⁴.
- However, it is unclear whether *APOE* ϵ 4-related differences in female brain health and cognition are detectable at **midlife (40-65 years)**, the age when AD-related pathological changes begin to accumulate and intervention holds most promise.
- Existing midlife *APOE* ϵ 4 studies have yielded mixed findings, likely due to the insensitivity of neuropsychological tests and a failure to account for **female sex**⁵⁻⁶.
- We investigated whether female *APOE* ϵ 4 carriers (ϵ 4+) and non-carriers (ϵ 4-) exhibited midlife differences in **episodic memory**, assessed using an experimental task.
- To determine whether *APOE* ϵ 4-related differences in episodic memory were driven by AD pathology, we included two plasma biomarkers in our analyses: **A β 42/40 ratio** and **p-tau231**.

Methods



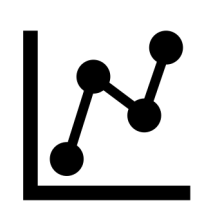
Sample: 129 cognitively unimpaired, middle-aged females (40-65 years), all recruited as part of the BHAMM Study (38 ϵ 4+, 91 ϵ 4-). No difference in demographics except for parental history of AD (42.1% ϵ 4+ vs. 24.2% ϵ 4-).



Episodic memory task: Encoding: faces presented in one of four quadrants. Retrieval: recall face and its spatial location. Six possible responses: new, remember + no location, remember + location(s). Load manipulated (easy, hard).



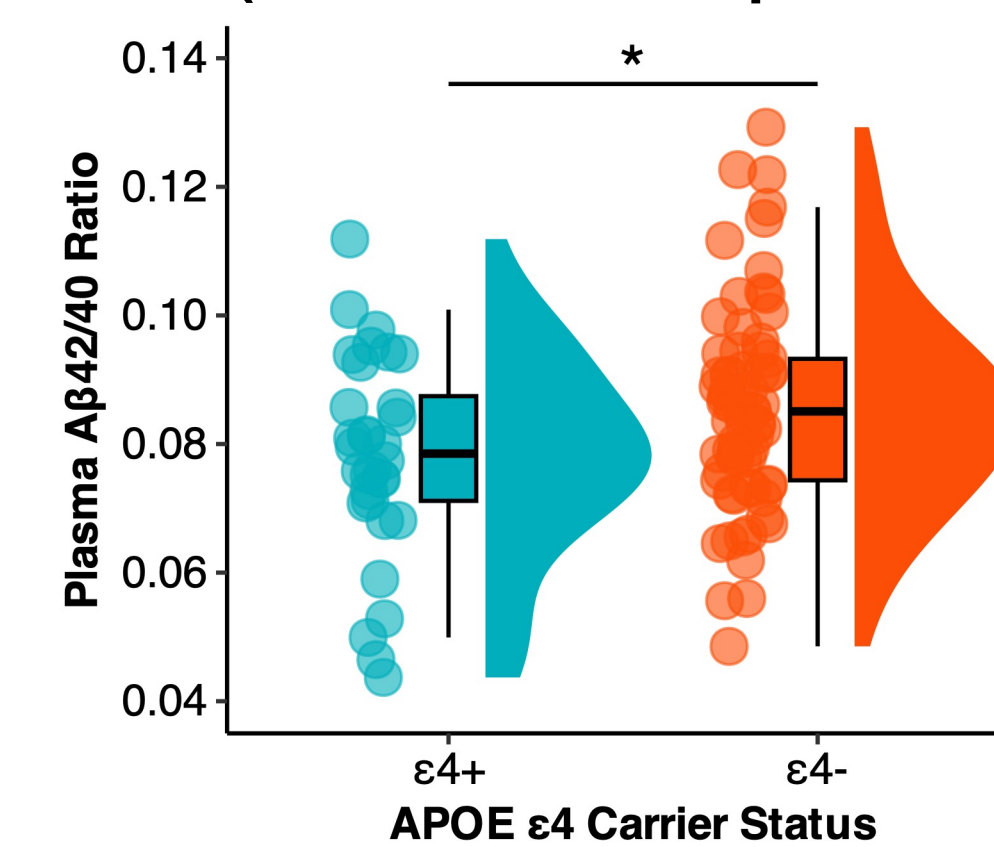
Plasma biomarkers: Performed on Simoa HD-X Analyzer. Plasma A β 42/40 ratio quantified using the Neurology 4-Plex E assay, plasma p-tau231 quantified using in-house Simoa assays developed at the University of Gothenburg. In total, $n = 101$ had A β 42/40, $n = 100$ had p-tau231.



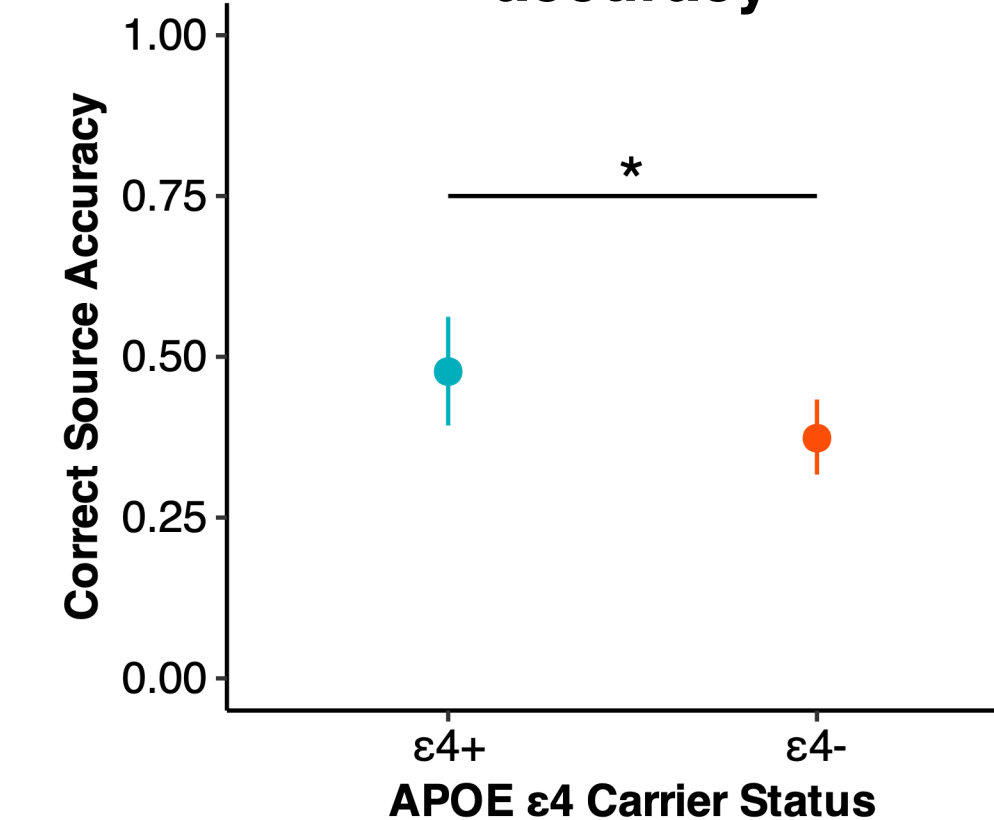
Analyses: Two binary task measures: correct source (CS), correct rejections (CR). Data analyzed using generalized linear-mixed effects models (GLMMs) with logit-link functions. Fixed effects: task difficulty (easy, hard), *APOE* ϵ 4 carrier status (ϵ 4+, ϵ 4-), AD plasma biomarker(s), interactions. Age included as covariate.

Key Results

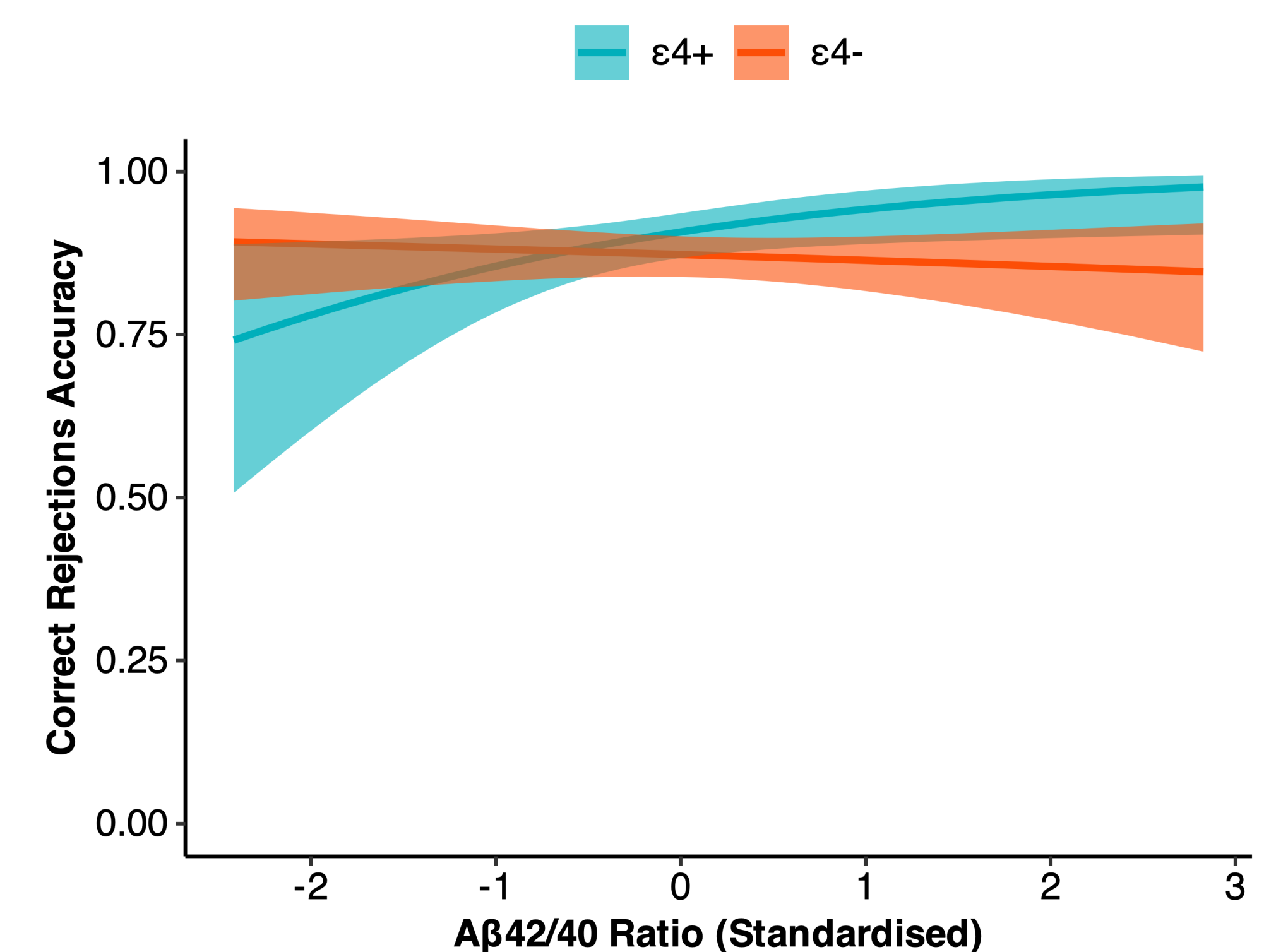
Female ϵ 4+ had lower plasma A β 42/40 (no difference in p-tau231)



Female ϵ 4+ exhibited better CS accuracy



Female ϵ 4+ with lower plasma A β 42/40 produced fewer CRs



Conclusions

- APOE* ϵ 4 enhanced vulnerability to A β , with lower plasma A β 42/40 ratio associated with lower CR accuracy in ϵ 4+.
- Independent of plasma A β 42/40 ratio, *APOE* ϵ 4+ showed higher CS accuracy, a possible example of antagonistic pleiotropy.
- Midlife may represent a transition period for female ϵ 4+, whereby the allele's phenotypic "advantages" are waning but still detectable and its detrimental (i.e., pathology-driven) effects are emerging.

References

¹Belloy et al. (2023), *JAMA Neurol.*; ²Altmann et al. (2014), *Ann. Neurol.*; ³Duarte-Guterman et al. (2021), *Psychoneuroendocrinology*; ⁴Hohman et al. (2018), *JAMA Neurol.*; ⁵Lancaster et al. (2017), *J. Int. Neuropsychol. Soc.*; ⁶Lissaman et al. (2025), *J. Prev. Alzheimer's Dis.*