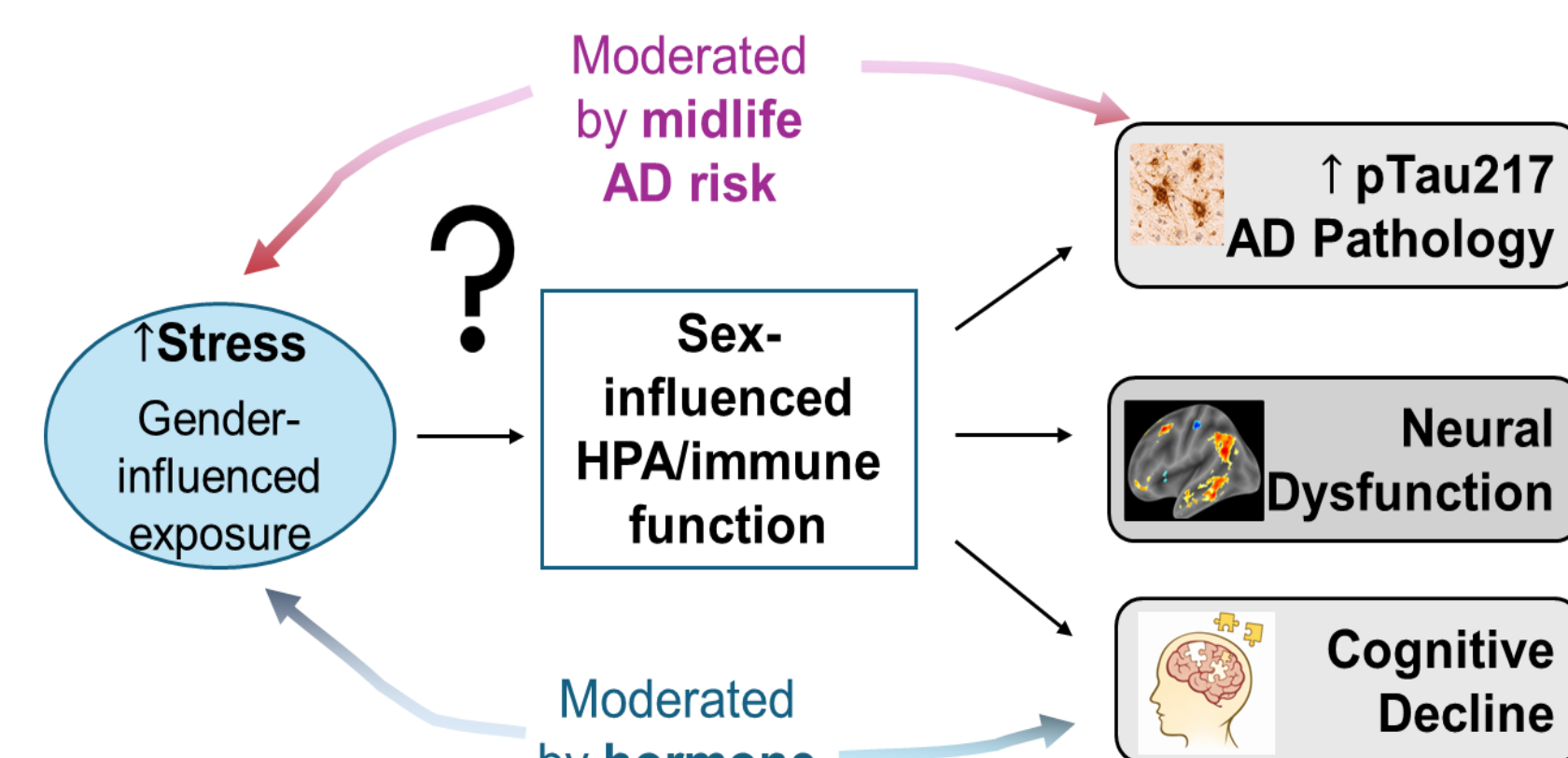


BACKGROUND

- Does menopause-related estrogen loss interact with gender-influenced stress to amplify the impact of mid-life AD risks on AD pathology, neural dysfunction, and cognitive decline?

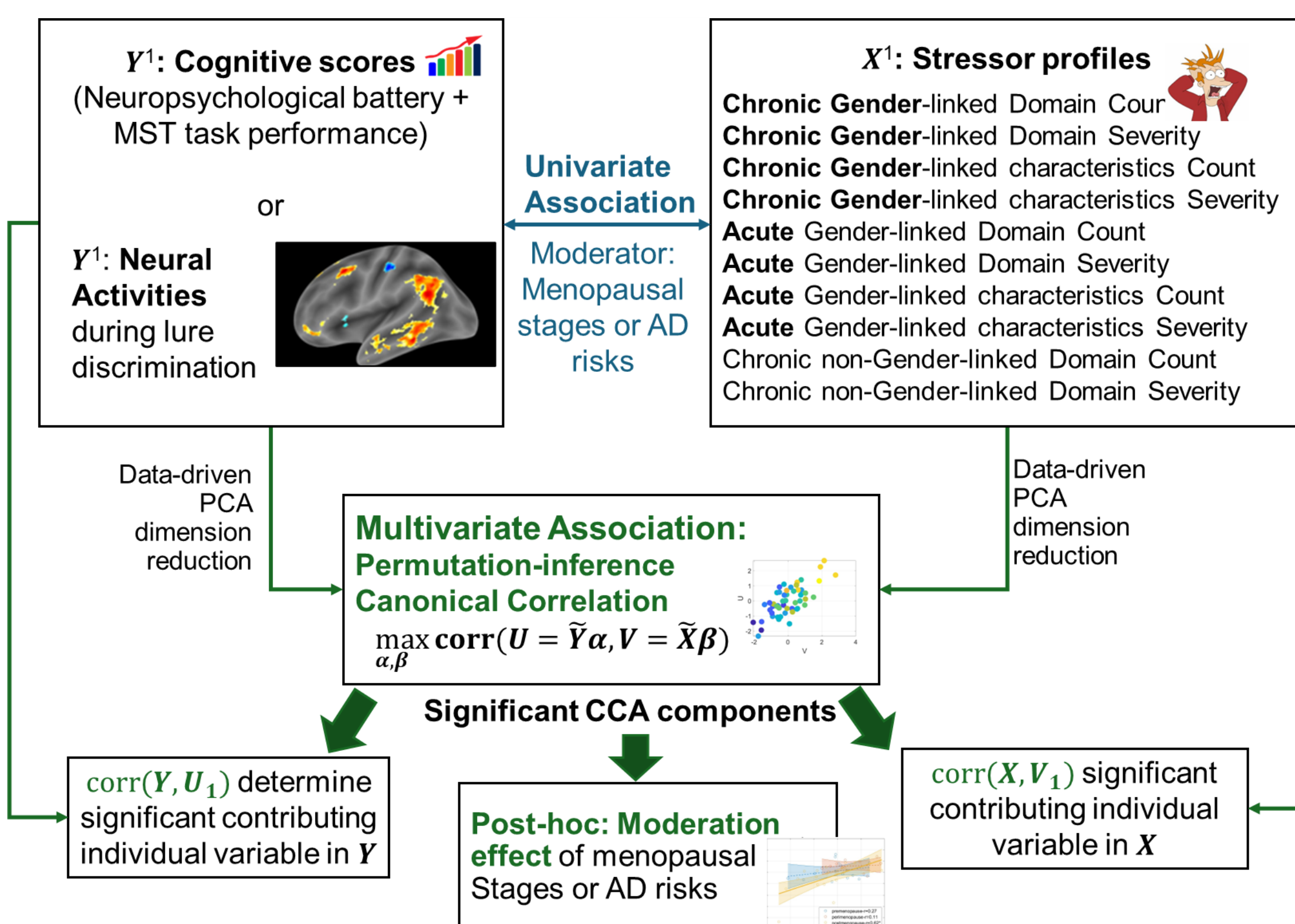
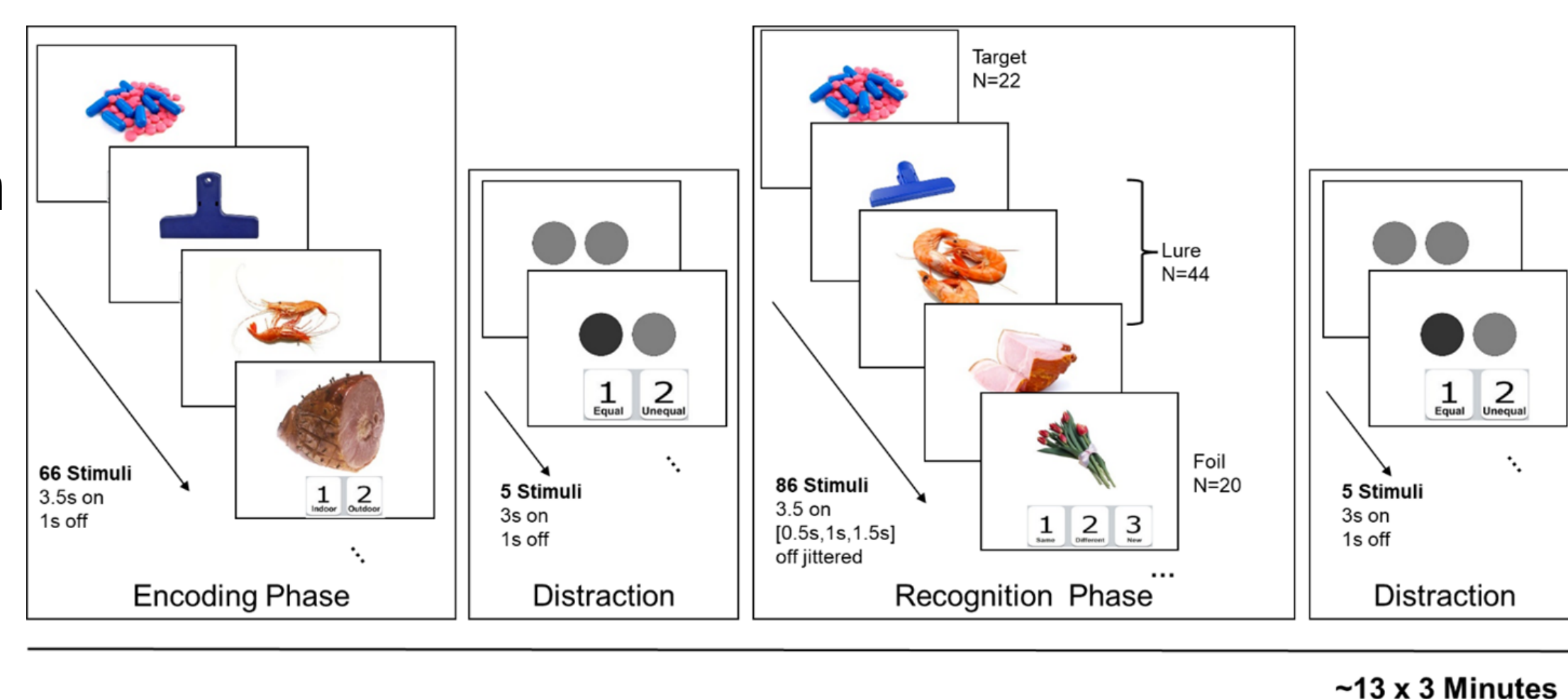


METHODS

- 82 women recruited from the Women's Alzheimer's Movement Center at Cleveland Clinic (Age:51.96[34,60]; Edu:16.79 [12,20])

Domain	Construct	Measure (Subjective)	Measure (Biomarker)	N / Visit
Stress	Stress exposure	Stress and Adversity Inventory (STRAIN) ¹	Salivary cortisol	N=81 (RV1)
Reproductive (HPG-axis)	Menopausal status	STRAW ² questionnaire	Salivary estradiol; Blood FSH	N=82 (RV1)
AD Risk	Midlife AD risk	Lancet early-mid life risk score ³ ; Family history	—	N=82 (RV1)
AD Pathology	Tau pathology	—	Blood pTau217	N=82 (RV1)
Cognition	Global cognition	PACC5 (MMSE, BVMT, ANT, FAS, SDMT)	—	N=78 (RV1)
Pattern Separation	MST performance	Lure discrimination	—	N=52 (RV2)
Neural Function	Task fMRI activity	—	LureCR-LureFA	N=52 (RV2)

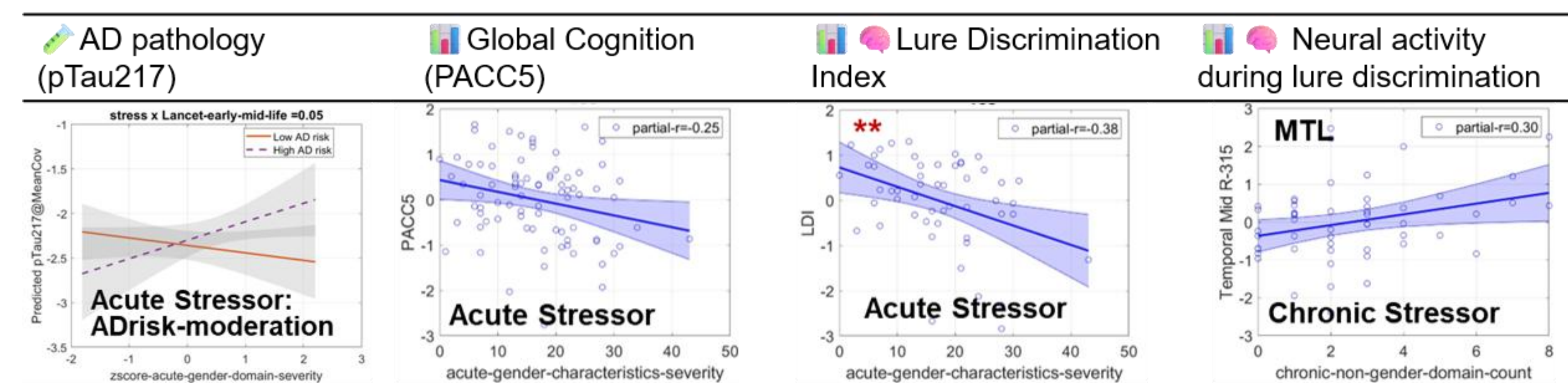
- Lure discrimination fMRI paradigm



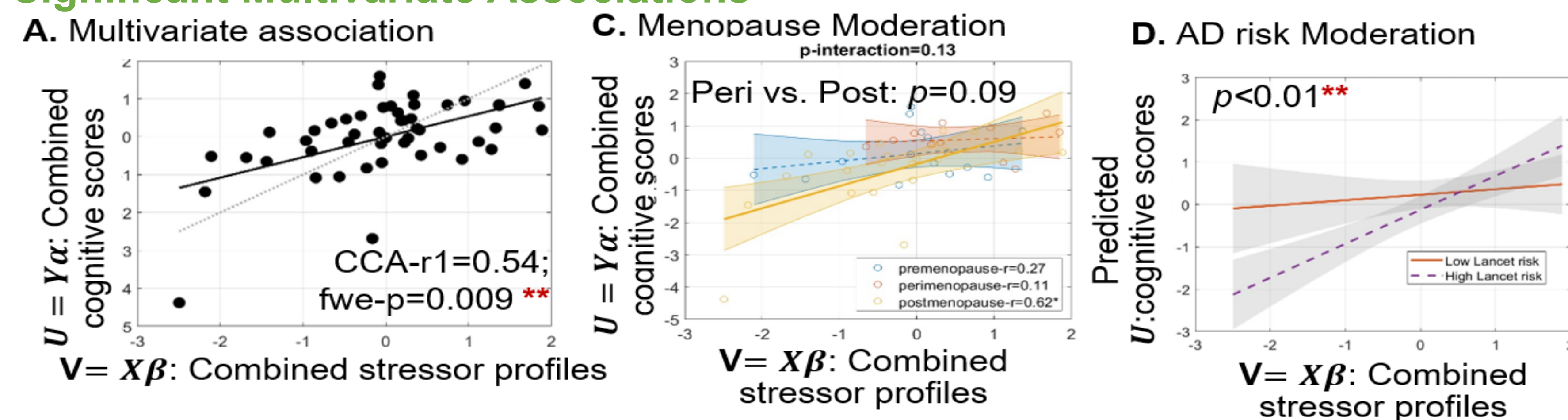
- Univariate regression and multivariate Canonical Correlation analysis pipeline⁴

RESULTS

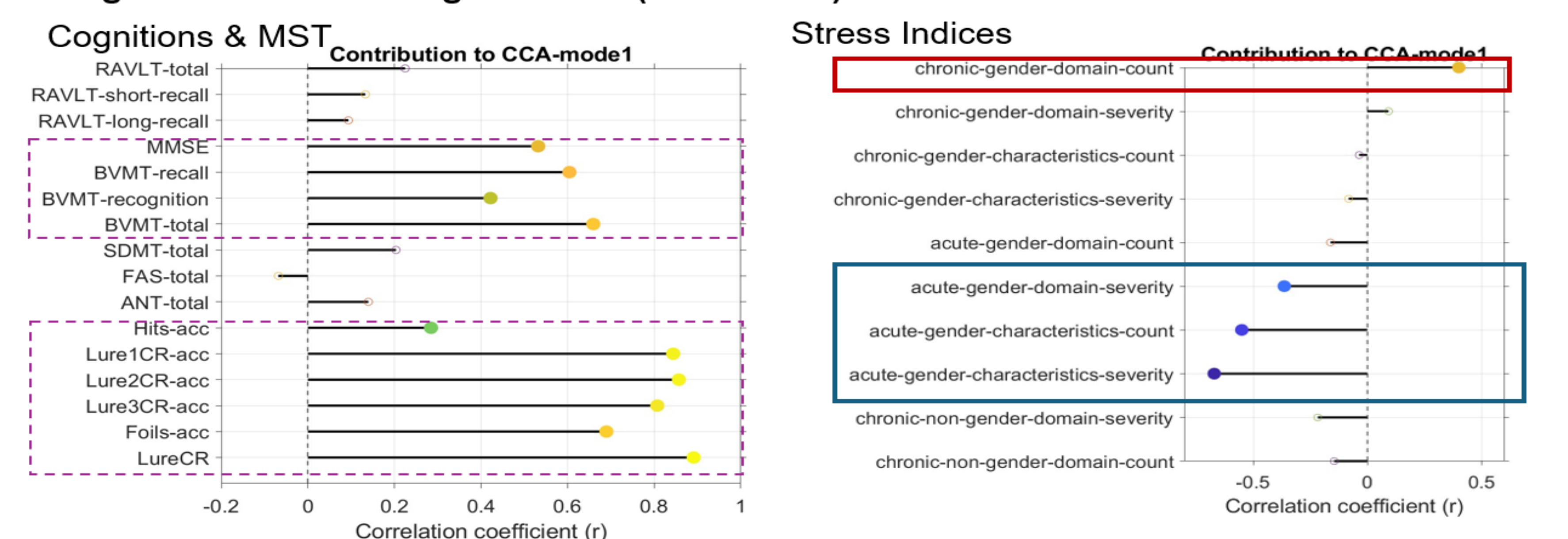
- Weak Univariate Associations



- Significant Multivariate Associations



- Significant contributing variables (filled circle)



CONCLUSIONS

- Acute stressors affect cognition while chronic stressors affect neural activities.
- Under similar levels of acute stress, individuals with higher early-to-midlife AD risk scores exhibit higher pTau217, poorer cognitive performance, no significant differences in LDI performances, but increased neural activities during LDI task.
- Multivariate models boost the statistical power and revealed more robust patterns:
 - Gender-linked stressors (both chronic and acute) significantly contribute to composite cognitive profiles, with trend-level moderation by menopausal stages and significant moderation by AD risk.

ACKNOWLEDGEMENTS

[1]. Slavich et al., 2018 *Psychosomatic Medicine* vol. 80 17–27; [2] Harlow et al., 2012 *Menopause* vol.19(4): 387-95; [3] Livingston et al., 2024 *Lancet* vol. 404 572-628.. [4]. Stark et al., 2013, *Neuropsychologia* 51, 2442–2449. & Yang et al., 2024, *Imaging Neuroscience* 2, 1–15. Research reported in this study was supported by NIA grants R01-AG074392 and RF1-AG071566. This study is additionally supported by The Women's Alzheimer's Movement Emerging Investigator Award at Cleveland Clinic; keep memory alive young scientist award, and private grants from the Peter and Angela Dal Pezzo funds, from Lynn and William Weidner, from Stacie and Chuck Matthewson and from E.L Wiegand foundation.