

TOX-AD: NEUROMETABOLIC NETWORK REORGANIZATION IN AD MOUSE MODELS EXPOSED TO METAL/METALLOID



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BACKGROUND

Alzheimer's Disease (AD) is a multifactorial disease in which metal/metalloid neurotoxins are suspected modifiers of AD pathobiology. However, the molecular mechanisms underlying gene-by-environment (GxE) interactions during aging remain unclear, underscoring the importance of investigating the exposome in AD pathobiology. Thus, we hypothesize that arsenic (As), cadmium (Cd), and lead (Pb) exposures alter neural connections and their roles in cognition and disease, thereby potentiating AD pathogenesis in a toxicant-specific, neurodevelopment-sensitive, and age-dependent manner.

METHODS

MODEL-AD humanized mouse models (B6J.hAPOE3.hAβ.hMAPT, B6J.hAPOE4.hAβ.hMAPT) were exposed to As, Cd, or Pb via drinking water at human-relevant concentrations (e.g., 20, 50, and 200 ppm, respectively). After exposure, we performed neuroimaging (PET/CT) to assess amyloid-β (Aβ) deposition and neuro-metabolism. Mice were euthanized, perfused, and tissues were harvested. Brains were hemisected for further analysis. Using covariance analysis and consensus clustering, we evaluated functional connectivity changes across AD stages by computing whole-brain entropy, degree distribution, nodal connection strength, and clustering coefficients from ¹⁸F-FDG images. Finally, we analyzed ¹⁸F-FDG and ¹⁸F-AV45 separately for positive and negative regional correlations.

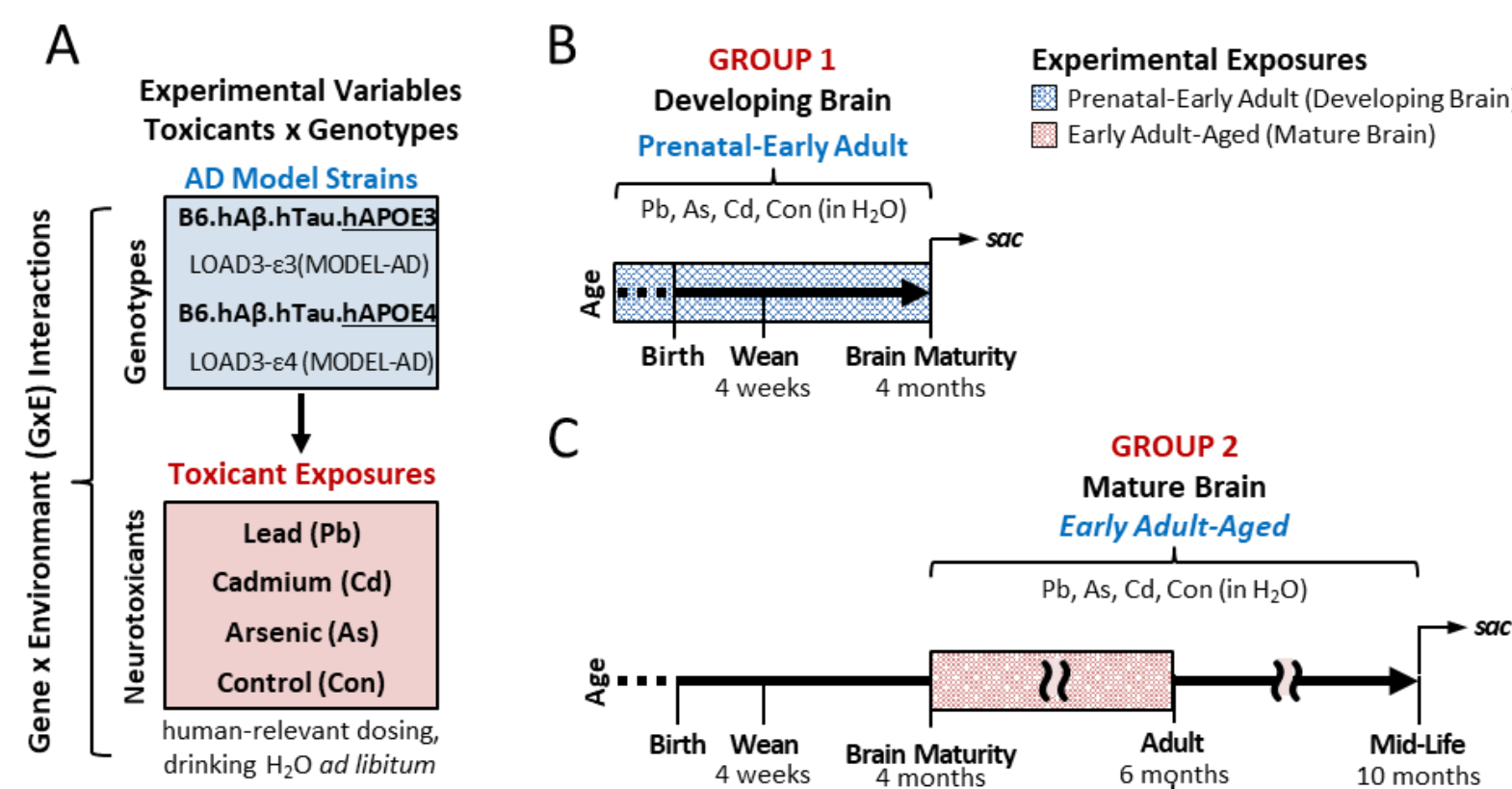
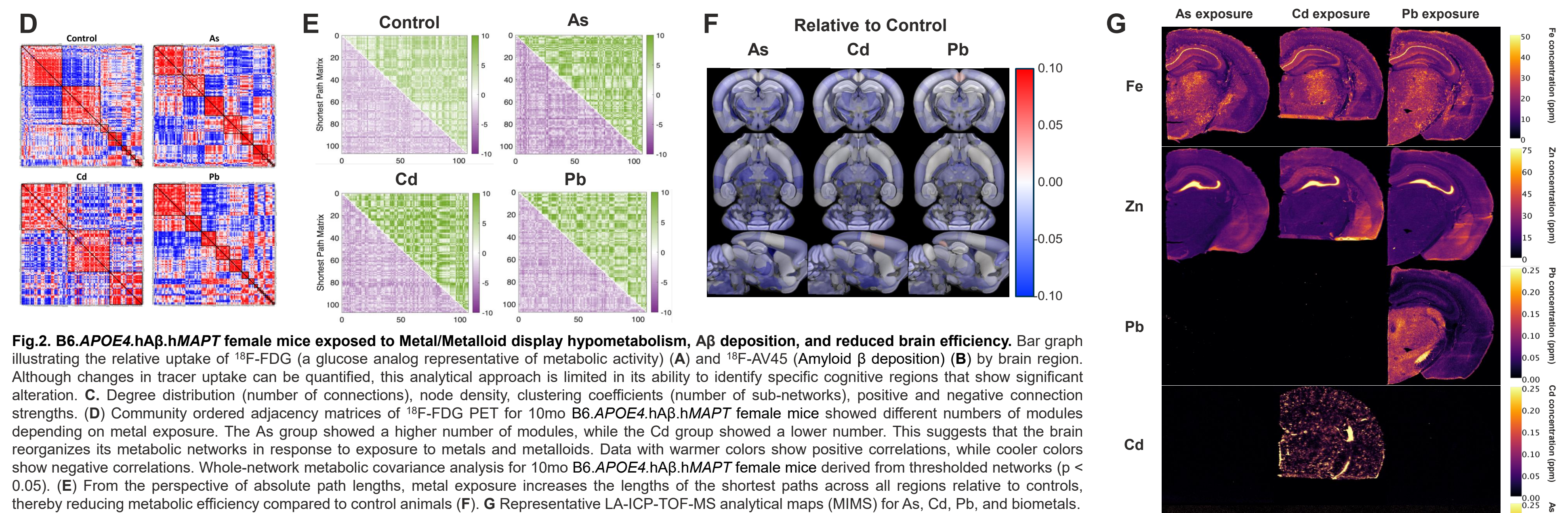
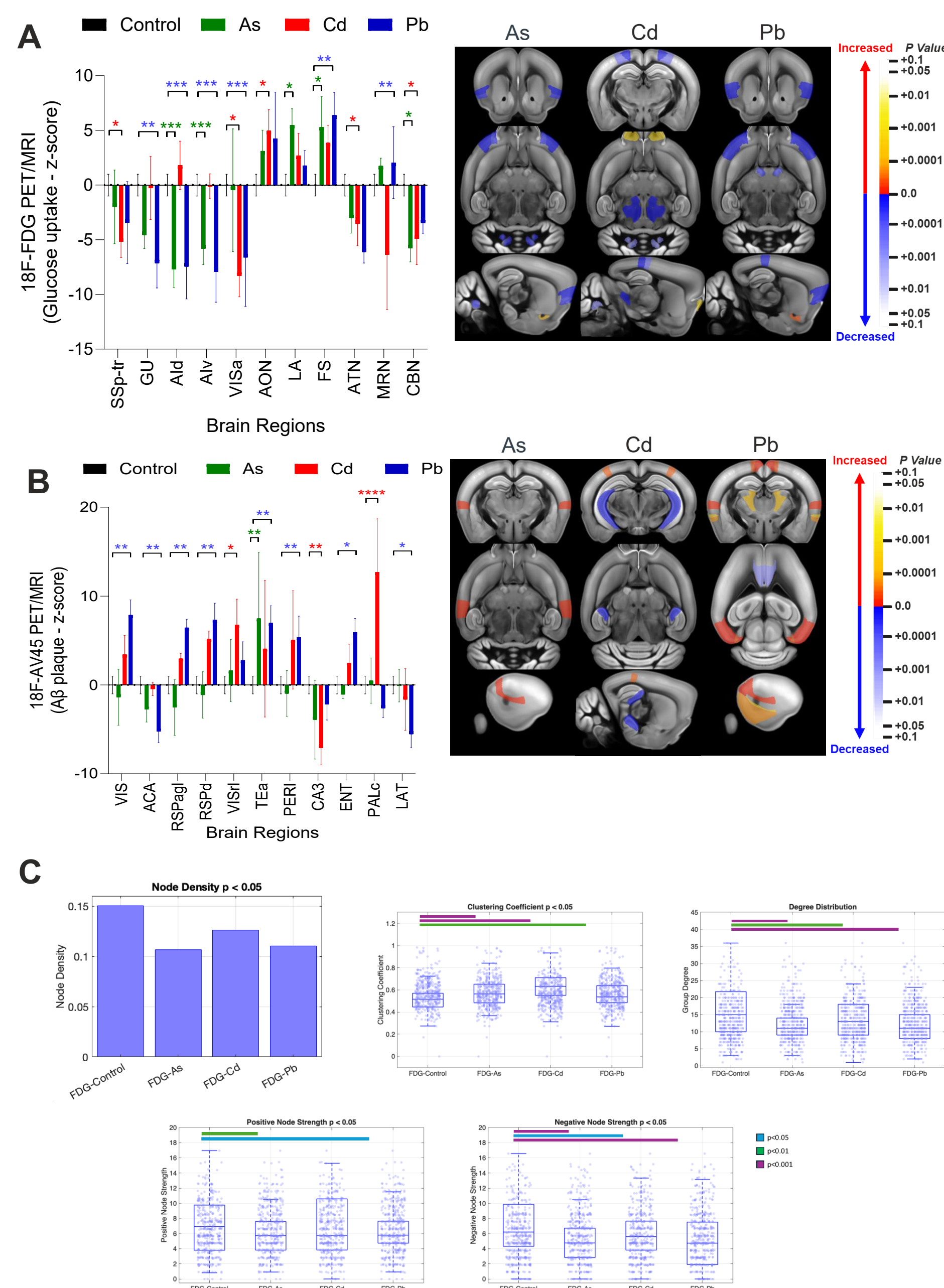


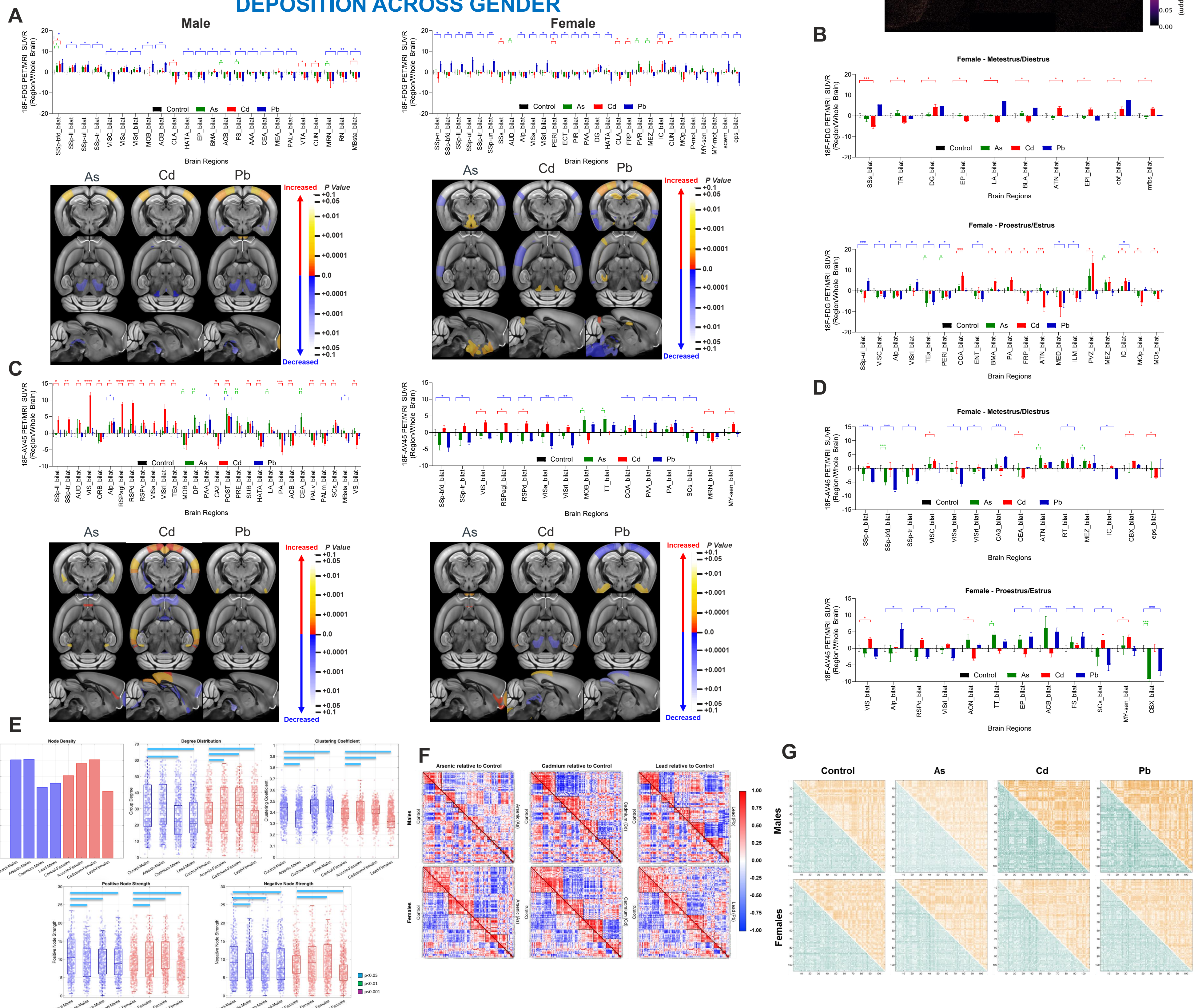
Fig. 1. Groups: **A.** 2 MODEL-AD strains (B6.APOE4.hAβ.hMAPT, B6.APOE3.hAβ.hMAPT) were exposed to Pb, Cd, As, or unspiked (control) drinking water at human-relevant toxicant doses during two clinically-relevant exposure windows: **B. Group 1** (developing brain: prenatal-to-early adult, 4 m.o.); **Group 2** (Brain maturity). All cohorts were evaluated for LOAD pathologies and phenotypes by MODEL-AD pipeline for cognition, frailty, neuroimaging, multi-omic analyses, hrMIMS brain mapping, and neuropathology for LOAD endpoints (ATN-V, NIA-AA framework, toxicant levels/distribution, and other LOAD-relevant metrics using a wide range of bioanalytical platforms).

RESULTS

ASSESSMENT OF METAL/METALLOID EXPOSURE IN NEURO-METABOLIC FUNCTION AND Aβ DEPOSITION



METAL/METALLOID EXPOSURE IN NEURO-METABOLIC FUNCTION AND Aβ DEPOSITION ACROSS GENDER



CONCLUSION

MODEL-AD mice exposed to metals/metalloids showed region-specific metabolic alterations in the brain and Aβ plaque deposition. These exposures revealed toxicant-specific neurometabolic alterations, enabling us to quantify and correlate them with similar disease signatures observed in human patients by assessing metabolic alterations in brain connectivity. Thus, investigating GxE interactions highlights the importance of integrating the exposome into the AD field and analyzing its progression with age.

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