

Disentangling brain-region specific from global brain-wide microglial responses to pathologies of Alzheimer's disease

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Motivation:

- Most transcriptomic studies of Alzheimer's disease (AD) sample tissue from one brain region, and conclude cellular mechanisms of the entire brain.
- However, these cellular mechanisms could strongly differ from region-to-region, for instance, due to how co-occurring neurodegenerative diseases spread throughout the brain.
- Which cellular mechanism are region-specific vs. brain-wide?**

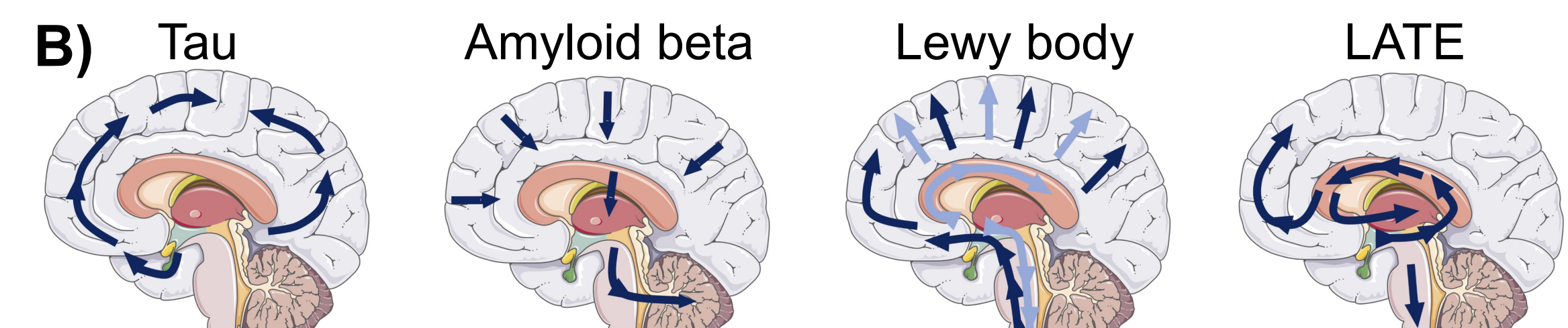
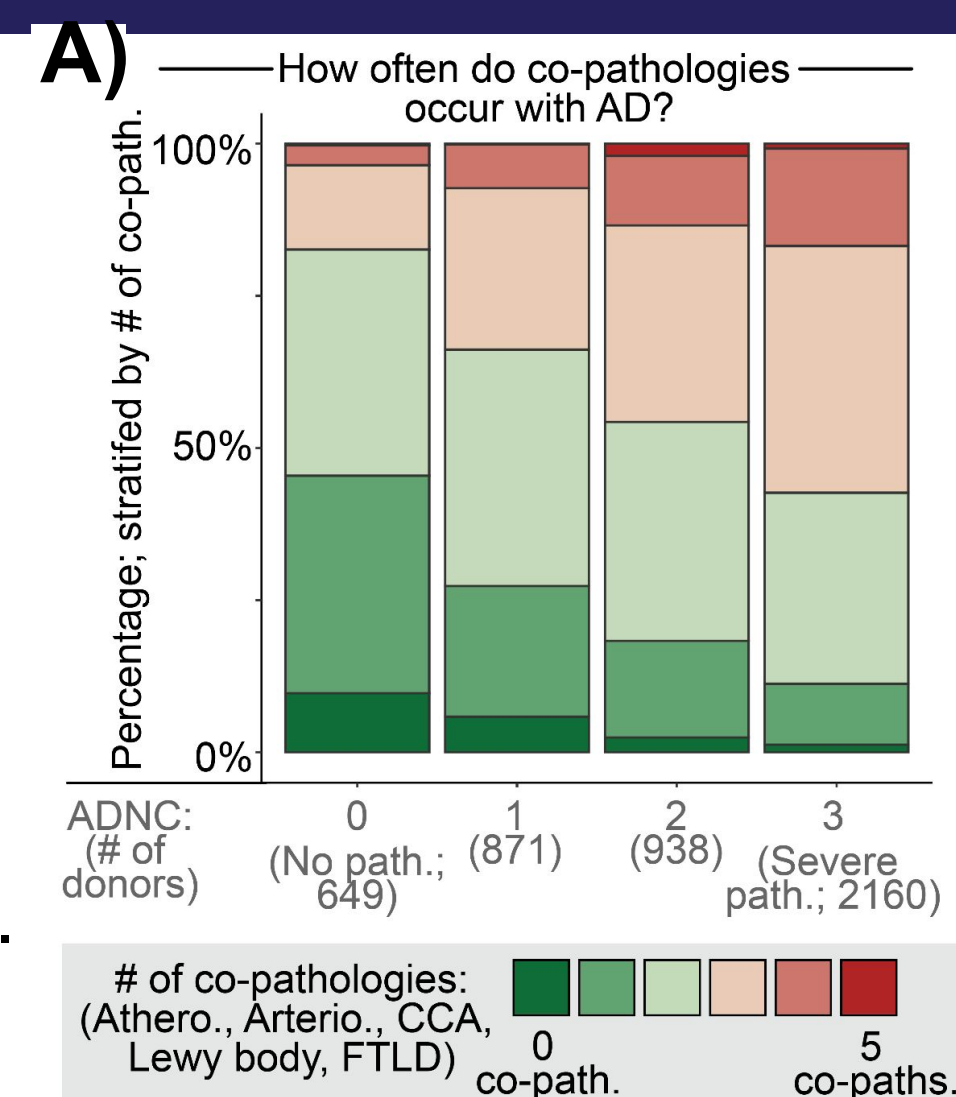
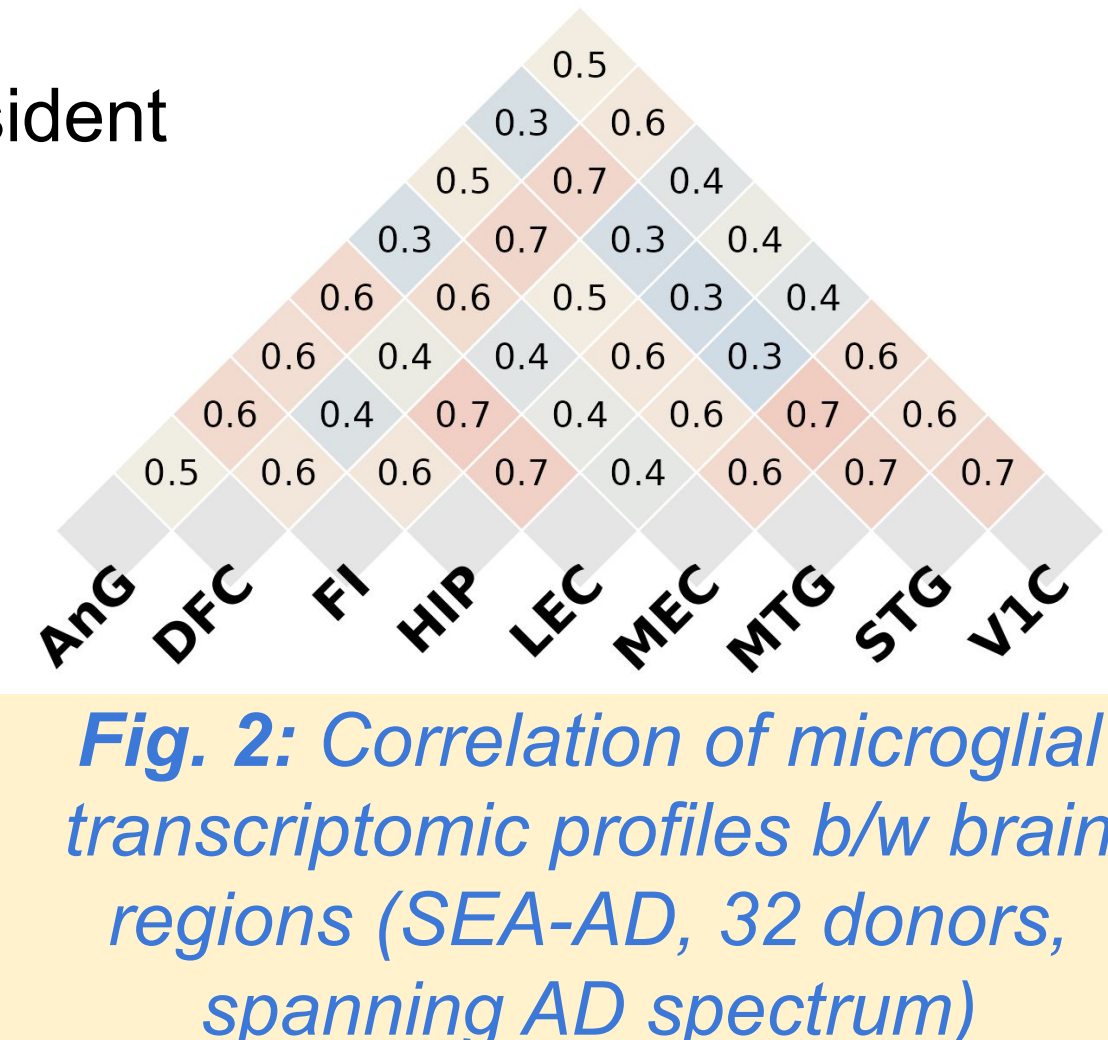


Fig. 1: A) Co-pathologies of AD are correlated with increased severity of AD (NACC data). **B)** Different pathologies spread along different routes, suggest the importance of distinguishing local-vs-global cellular mechanisms.

- We focus on microglia, the resident immune system of the brain.
- After correcting for baseline snRNA-seq gene expression, correlation b/w brain regions is only modestly positive – this suggests possible region-specific mechanisms.



Analysis workflow:

- Step 1:** Confirmatory factor analysis to derive MTG-specific burden
- Step 2:** Associate MTG-specific burden and global burden (Sinha, et al., 2023) to gene expression using NEBULA (He et al., 2021).

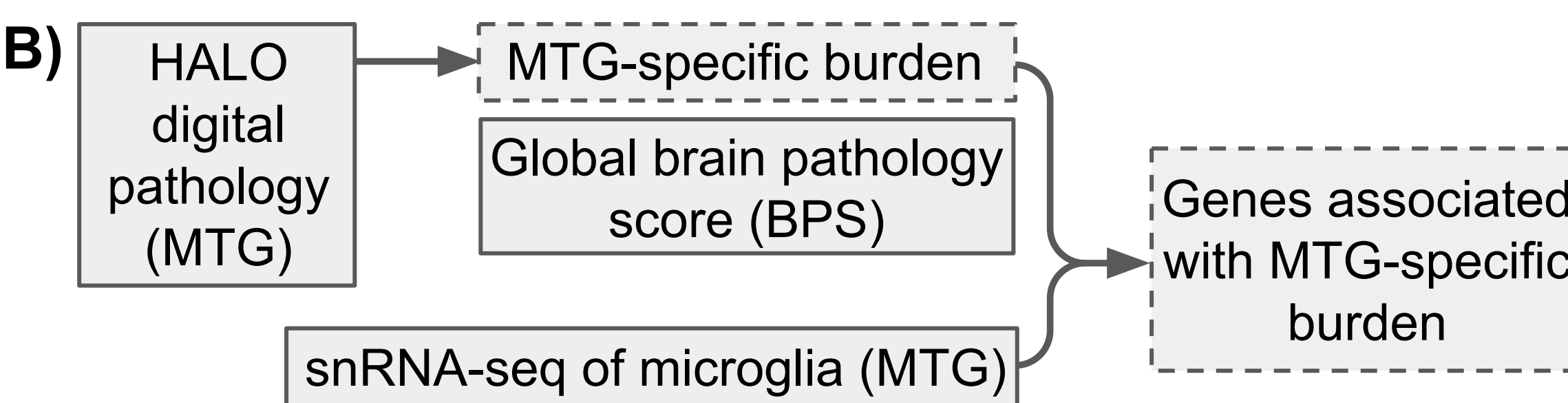


Fig. 4: A) Schematic of association b/w MTG burden and gene expression, adjusting for covariates. **B)** Flowchart of how HALO neuropathology and snRNA-seq is used.

Latent MTG burden:

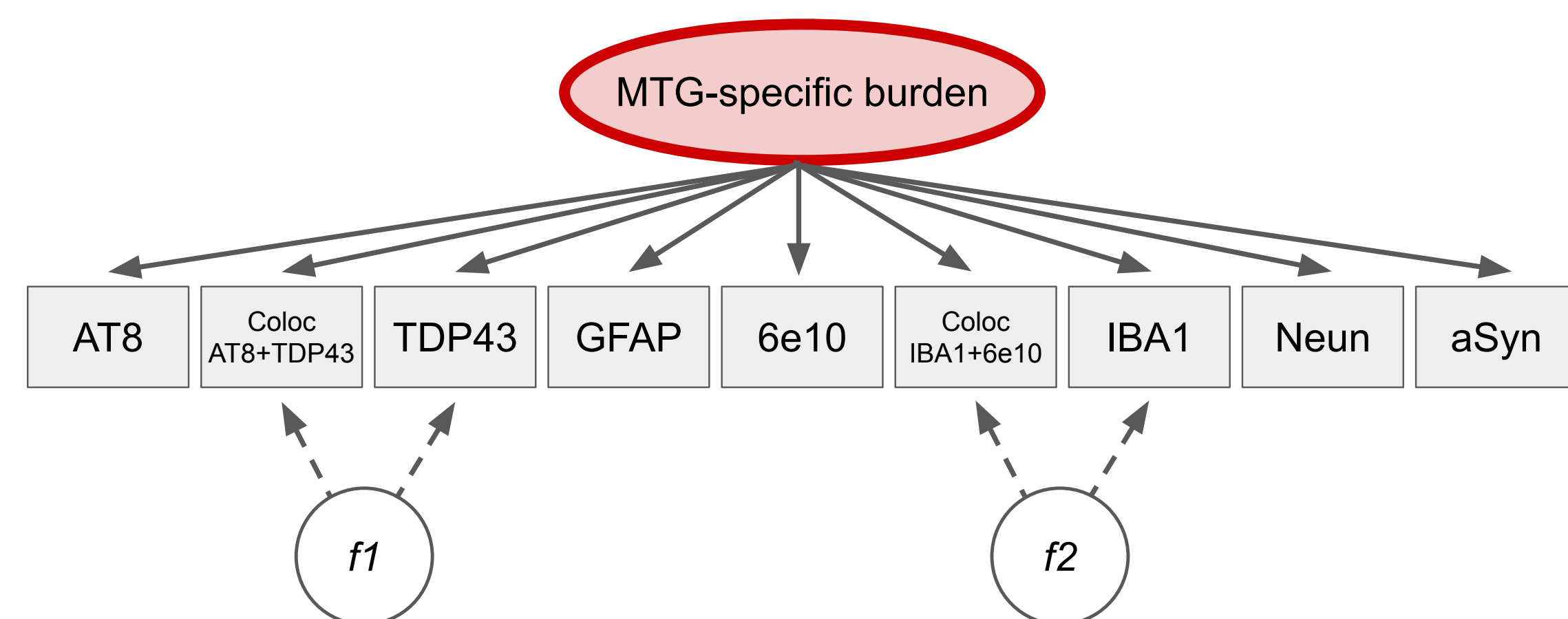


Fig. 5: Confirmatory factor analysis including 2 co-localization variables to improve model fit (CFI = 0.959, RMSEA = 0.058).

Comparison between global and MTG-specific burden

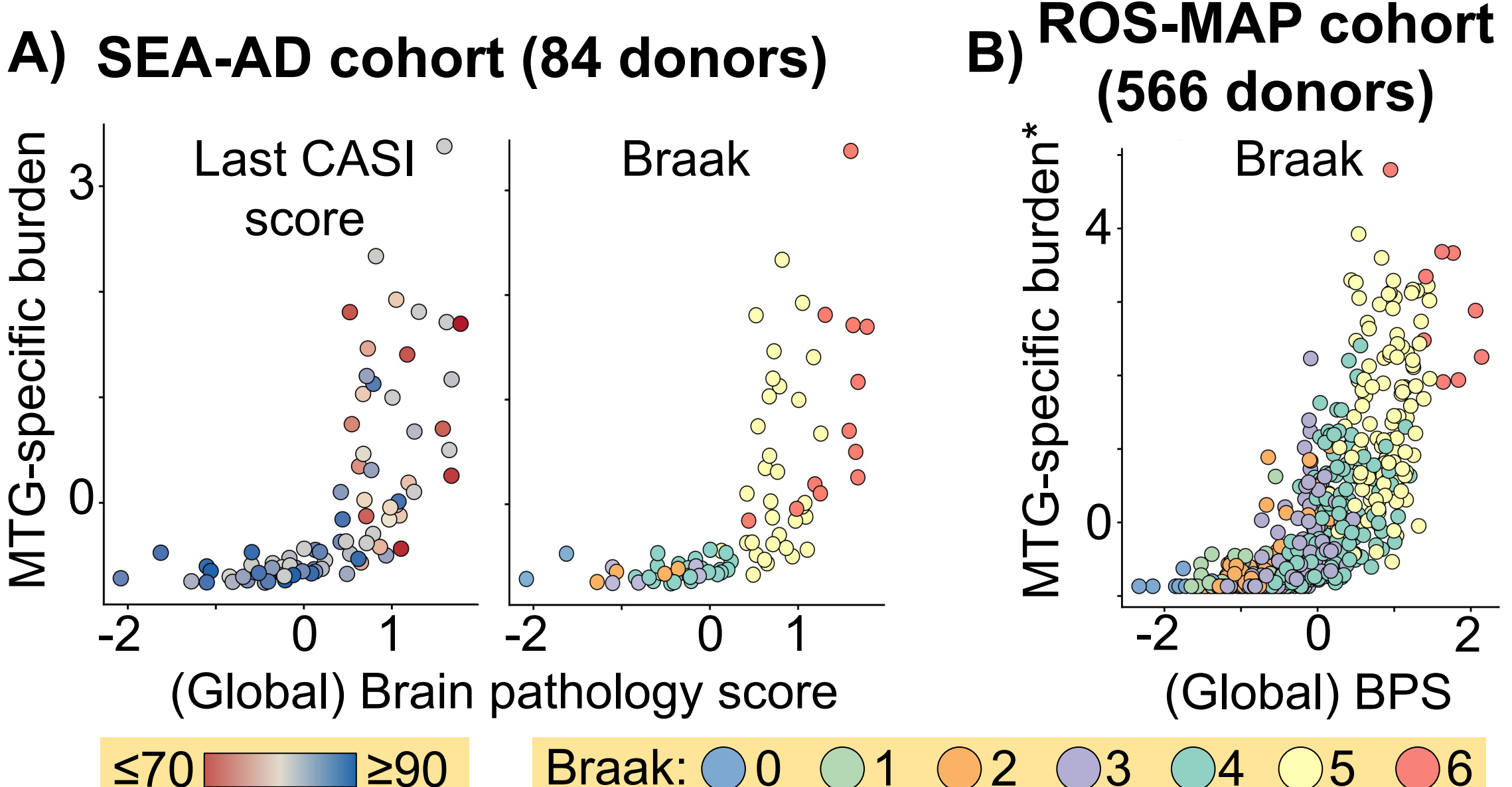


Fig. 6: A) SEA-AD cohort, showing last CASI score (Nested F-test p-value: 0.0581) or Braak. MTG is staged at Braak 4. The MTG-specific burden captures variability overlooked by the global BPS. **B)** Corroboration of the local-vs-global burden using ROS-MAP cohort. *Not exact replication is the quantified neuropathology is only amyloid and tau from the medial temporal cortex (MTC).

Associated genes:

- Key genes (*CHI3L1*, apoptosis; *SORL1*, phagocytosis; *CTSD*, lysosome) implicated as responding locally in MTG burden.

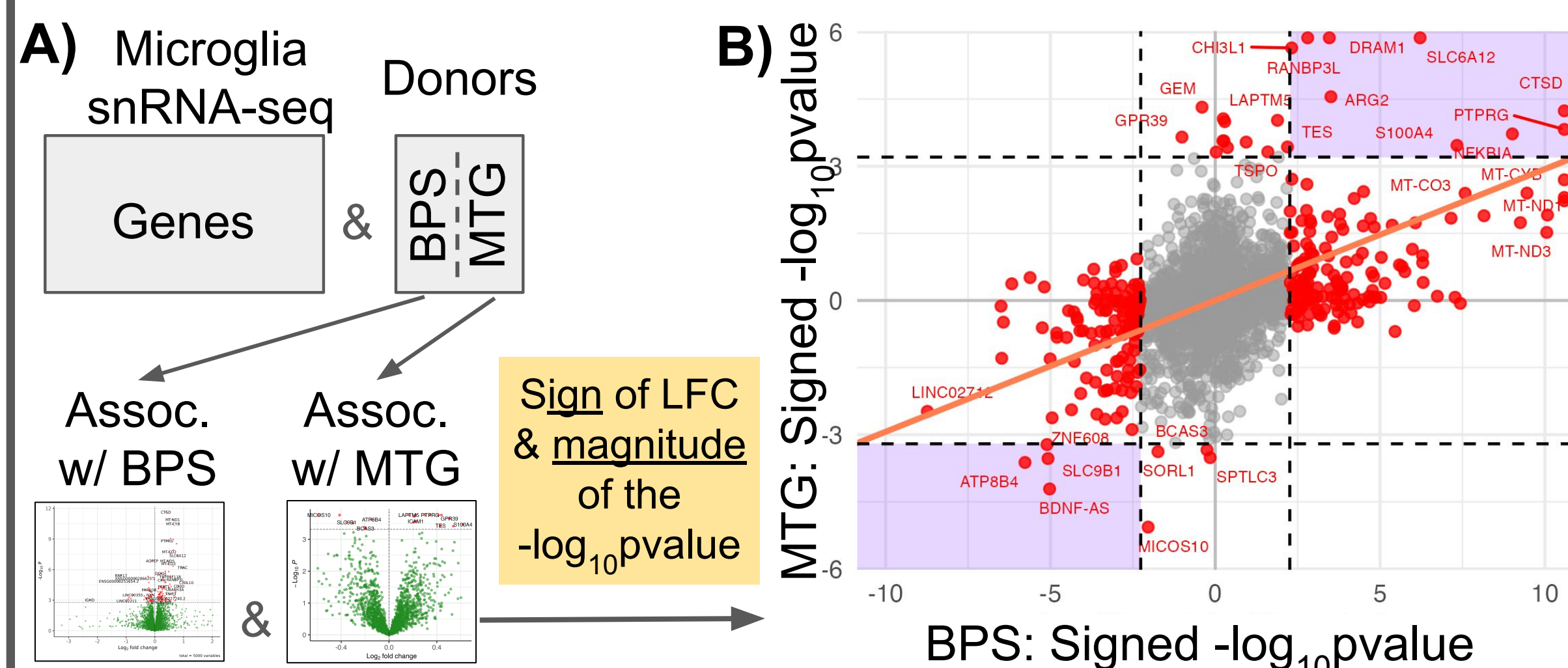


Fig. 7: A) Schematic of how we compare genes associated w/ (global) BPS or (local) MTG. **B)** Comparison of the gene associations. Dashed line denotes the signed FDR multiple-testing thresholding.

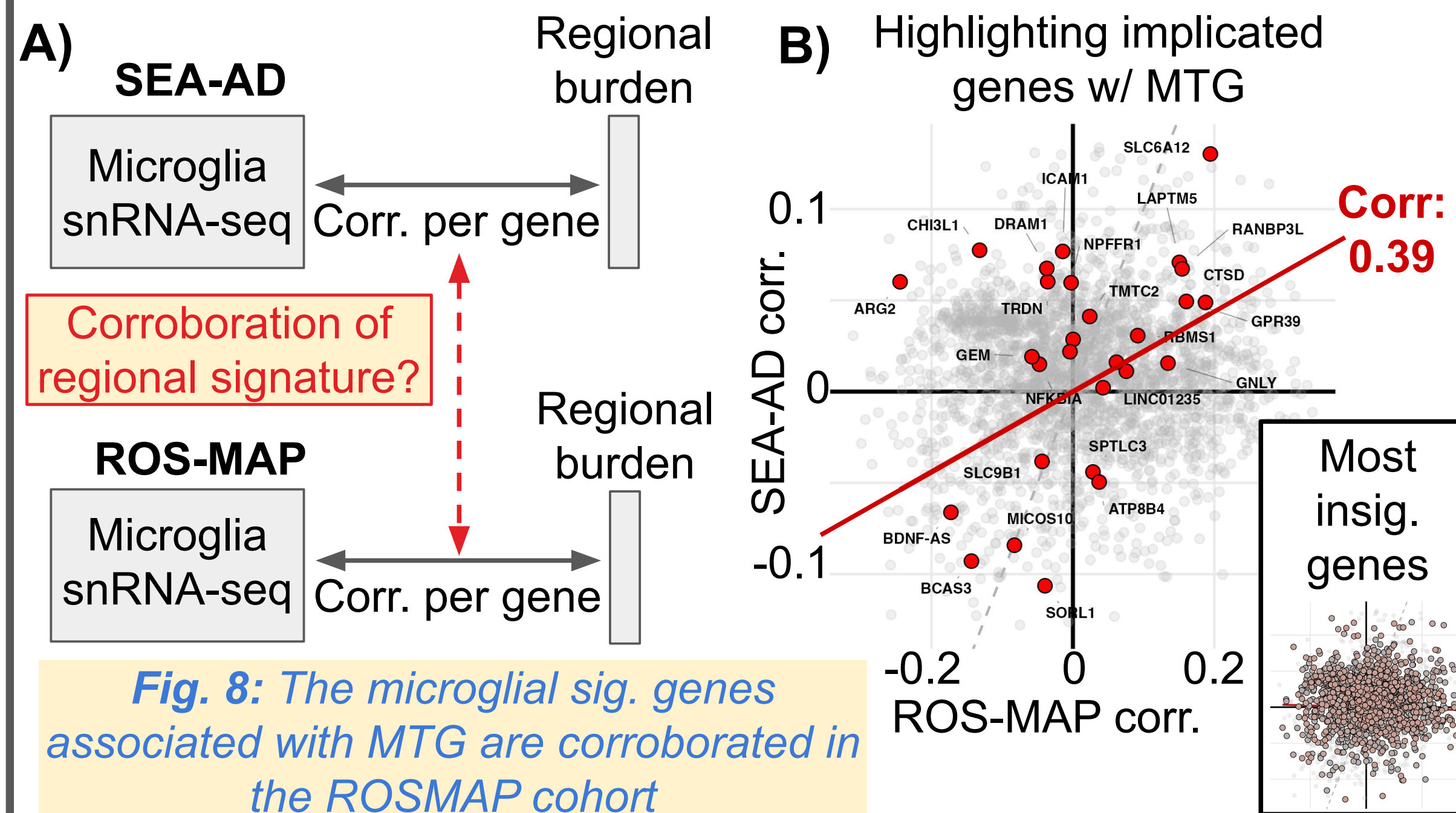


Fig. 8: The microglial sig. genes associated with MTG are corroborated in the ROSMAP cohort

Goal and dataset:

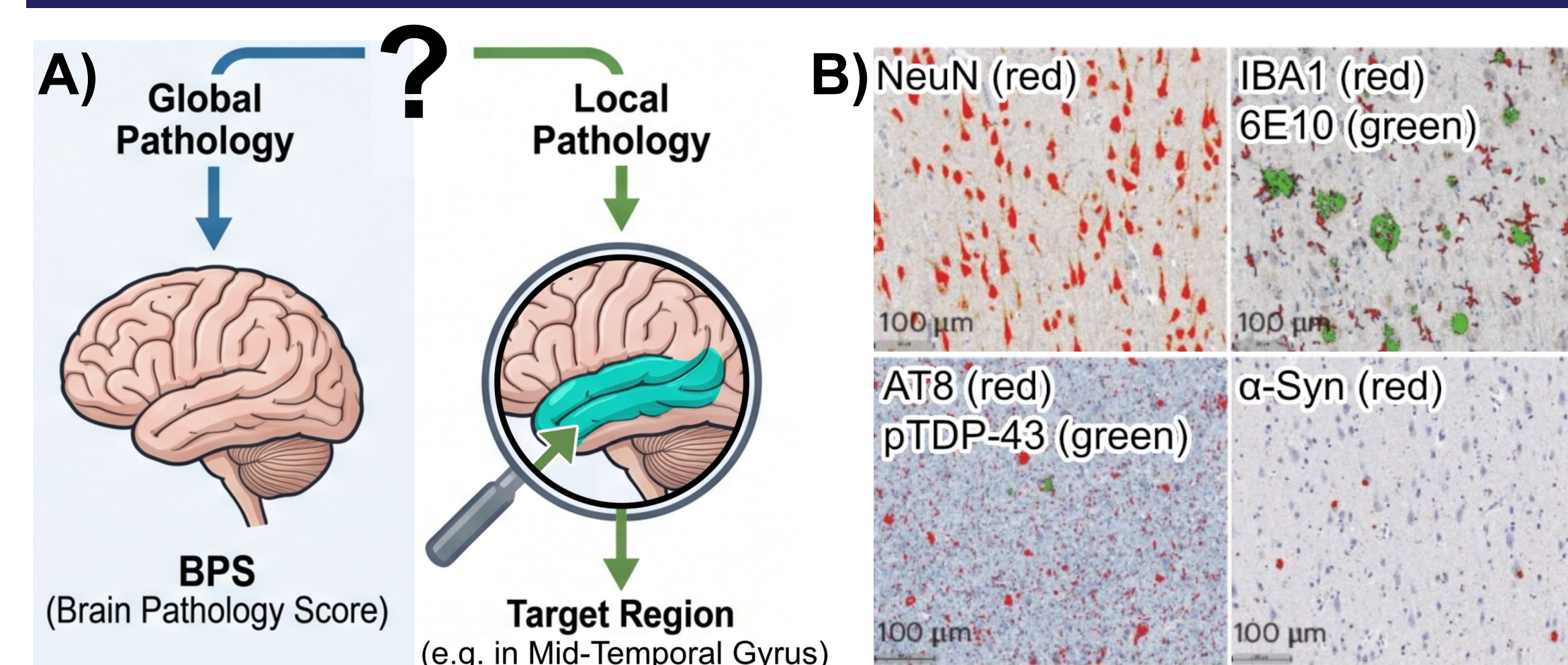


Fig. 3: A) Goal – distinguish microglial brain-wide mechanisms those localized to the MTG. **B)** Stainings used to derive the HALO quantitative neuropathology (% area in gray matter), GFAP not shown.

SEA-AD cohort	84 donors total (snRNA-seq, HALO neuropath.)	Braak 0-2	3-4	5-6
Male (Med. age at death: 89)		4	11	18
Female (Med. age at death: 90+)		2	18	31

Microglial composition:

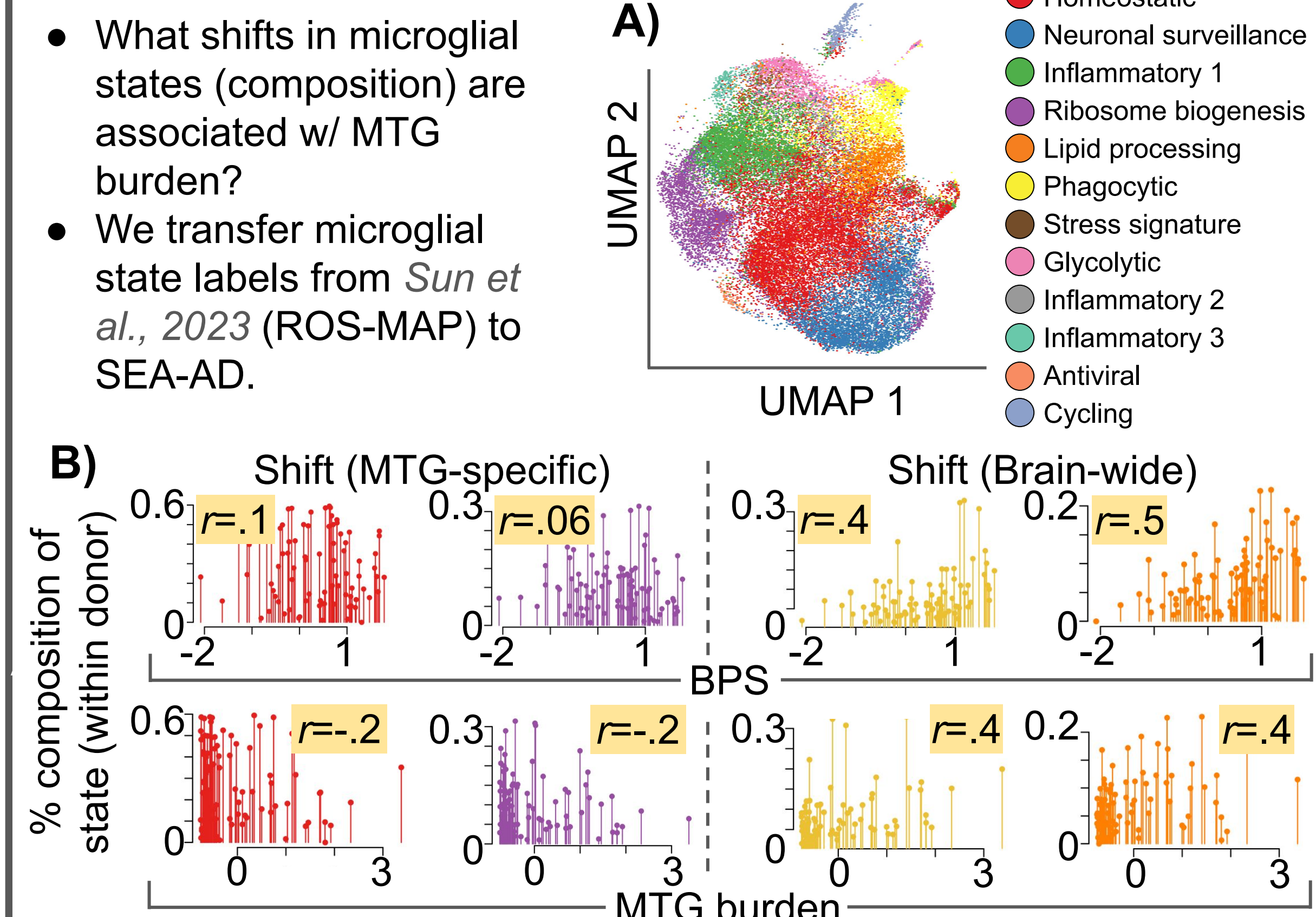


Fig. 9: A) Transferred microglial states in SEA-AD. **B)** Compositional shifts along BPS (global) or MTG burden (local), w/ Pearson corr. shown.