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Novel PET tracer [11C]-CS1P1 Reveals Connection Between Peripheral and Central Inflammation in the Presence of Amyloid-β

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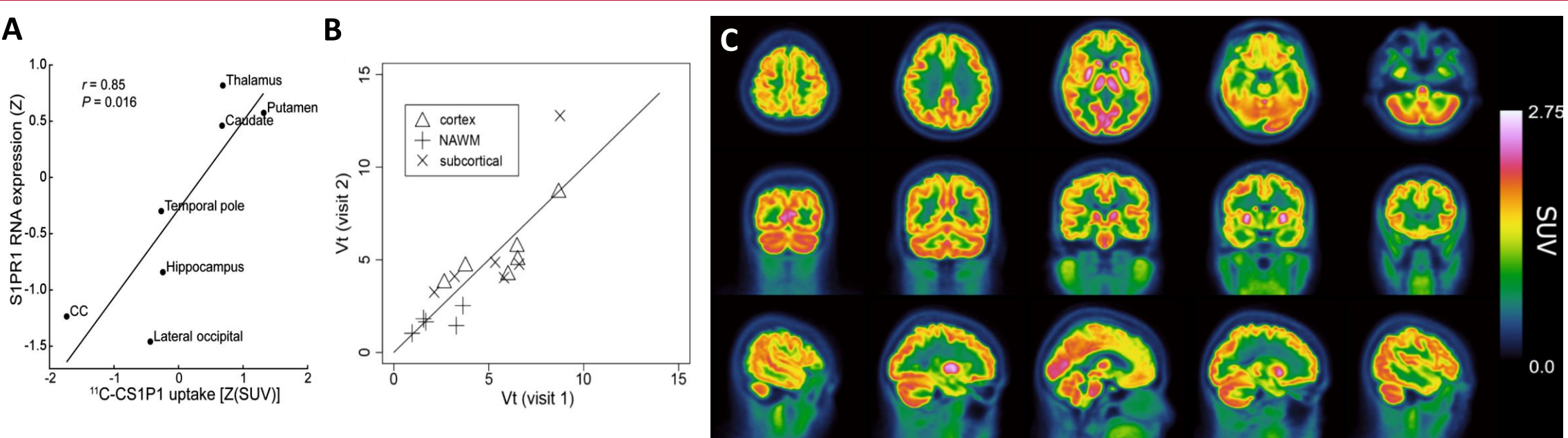


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Intro: Neuroinflammation as a potential biomarker for ADRDs

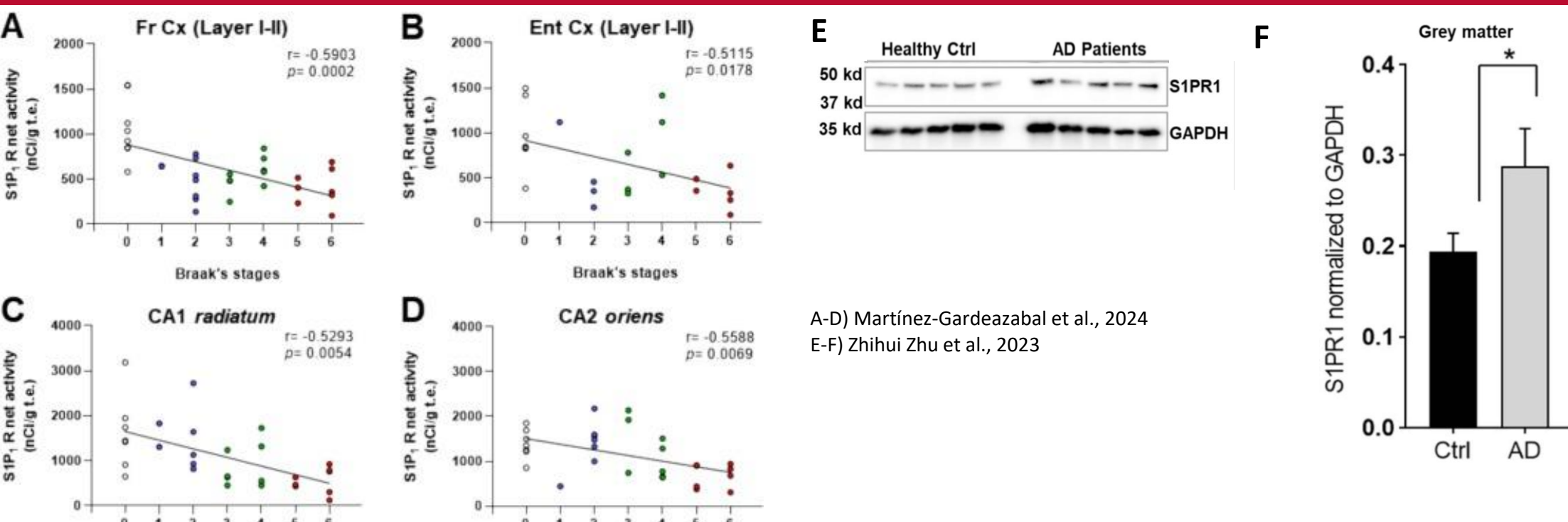
- Neuroinflammation is hypothesized as a protective response to increased amyloid-beta (Aβ), involving activation of microglia via cytokine signaling pathways.
- When vascular injury is combined with AD pathology, it can accelerate Aβ and tau accumulation, increasing neuroinflammation, and result in earlier and more severe cognitive symptoms.
- Despite this, there is not a validated spatial tool to visualize neuroinflammation *in vivo* in AD patients.

Intro: [11C] – CS1P1 is a novel PET tracer for neuroinflammation



- Current neuroinflammatory PET tracers bind to TSPO, but these have relatively low brain permeability and high nonspecific and plasma protein binding, which result in a low signal-to-noise ratio and low specificity in PET images.
- [11C]-CS1P1 (CS1P1) is a novel PET tracer targeting sphingosine-1-phosphate receptor 1 (S1PR1), a receptor expressed on all immune cells.
- Brier et al. show CS1P1 standard uptake value (SUV) is highly correlated with S1PR1 mRNA expression across brain (A).
- CS1P1 volume of distribution (Vt) is consistent between two visits that are three months apart (B).
- Friedrichsen et al. show CS1P1 is expressed globally, with elevated uptake in the grey matter (C).

Intro: S1PR1 is dysregulated in postmortem AD tissue

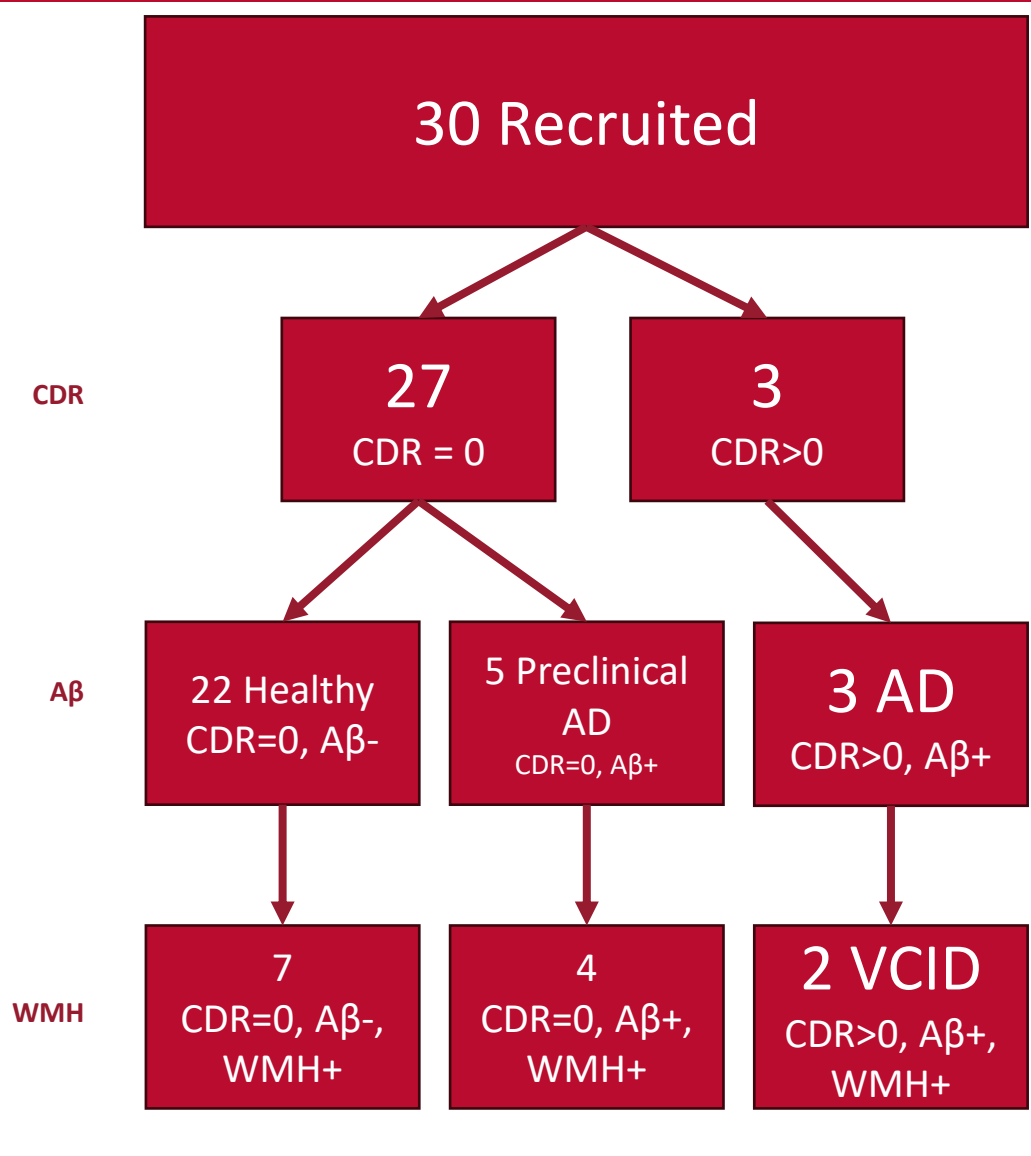


- A postmortem human tissue study by Martínez-Gardeazabal et al., 2024 found net decreases in S1PR1 expression in the frontal cortex (A), entorhinal cortex (B), and the hippocampus (C,D) with AD progression.
- Layer-specific analyses found elevated S1PR1 in Braak stages 1-2 in the frontal cortical layers V-VI, the frontal cortex white matter, and the temporal cortex white matter.
- Contrarily, this 2023 study by Zhu et al. found elevated S1PR1 in the grey matter of AD patients (E-F).
- This study also finds that the 5xFAD mouse has elevated S1PR1 and found that adding Aβ to a culture of mixed glia cells elevates S1PR1.

Methods

Objective: We will use the novel CS1P1 PET tracer to examine S1PR1 signaling dysregulation in AD.

- Participants underwent T1, FLAIR, CS1P1 PET, and PiB PET imaging
- FreeSurfer-7 extracted ROIs
- TruE-NET identified white matter hyperintensities (WMH) from T1/FLAIR
- PET processed through PUP (30-60 min post-injection)
- PiB SUVs used cerebellum-cortex reference and (CL=20) for Aβ classification
- CS1P1 used body-weighted SUVs
- WMH >3000mm³ defined vascular injury
- Plasma proteins (IL6, TNF, CRP) quantified via NULISaseq CNS 120 panel
- Multivariable linear regression in cognitively normal participants (CDR=0) examined Aβ, WMH, and inflammation effects on CS1P1, controlling for age and sex



Results: Aβ and WMH pathology modify S1PR1-mediated neuroinflammation

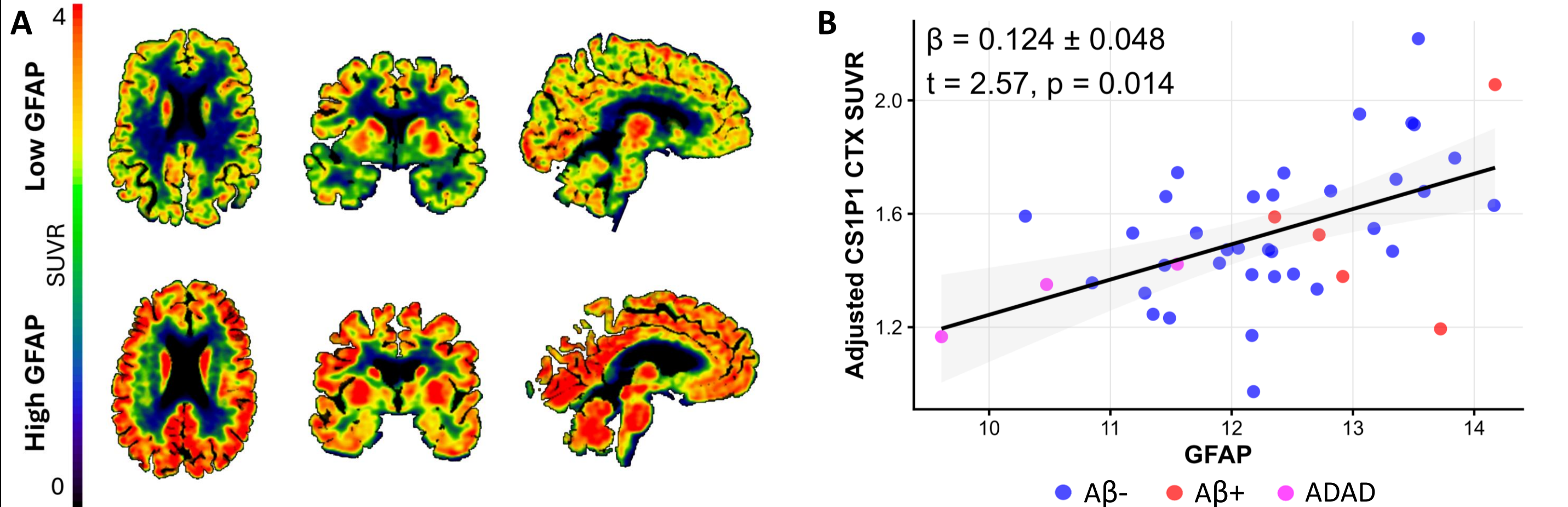


Figure 1: (A) Cognitively normal participants with elevated plasma GFAP have higher CS1P1 cortical uptake compared to cognitively normal participants with minimal lower plasma GFAP. (B) CS1P1 cortical SUVr is significantly associated with GFAP after adjusting for age, sex, and ptau-217.

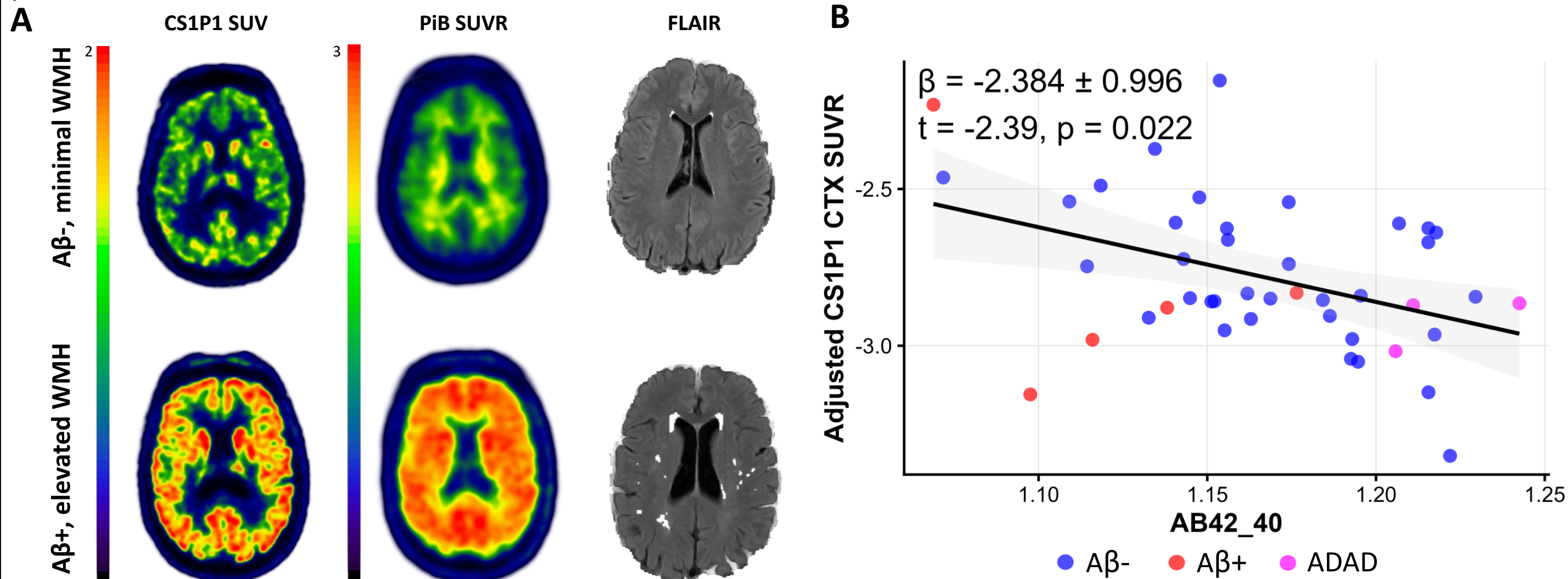


Figure 2: (A) Cognitively normal Aβ+ participants with elevated WMH have higher CS1P1 uptake compared to cognitively normal Aβ- participants with minimal WMH. (B) CS1P1 cortical SUVr is significantly associated with plasma Aβ42/40 after adjusting for age and sex.

Results: In a cognitively normal cohort, CS1P1 uptake is predicted by IL-6, Centiloid, and BMI

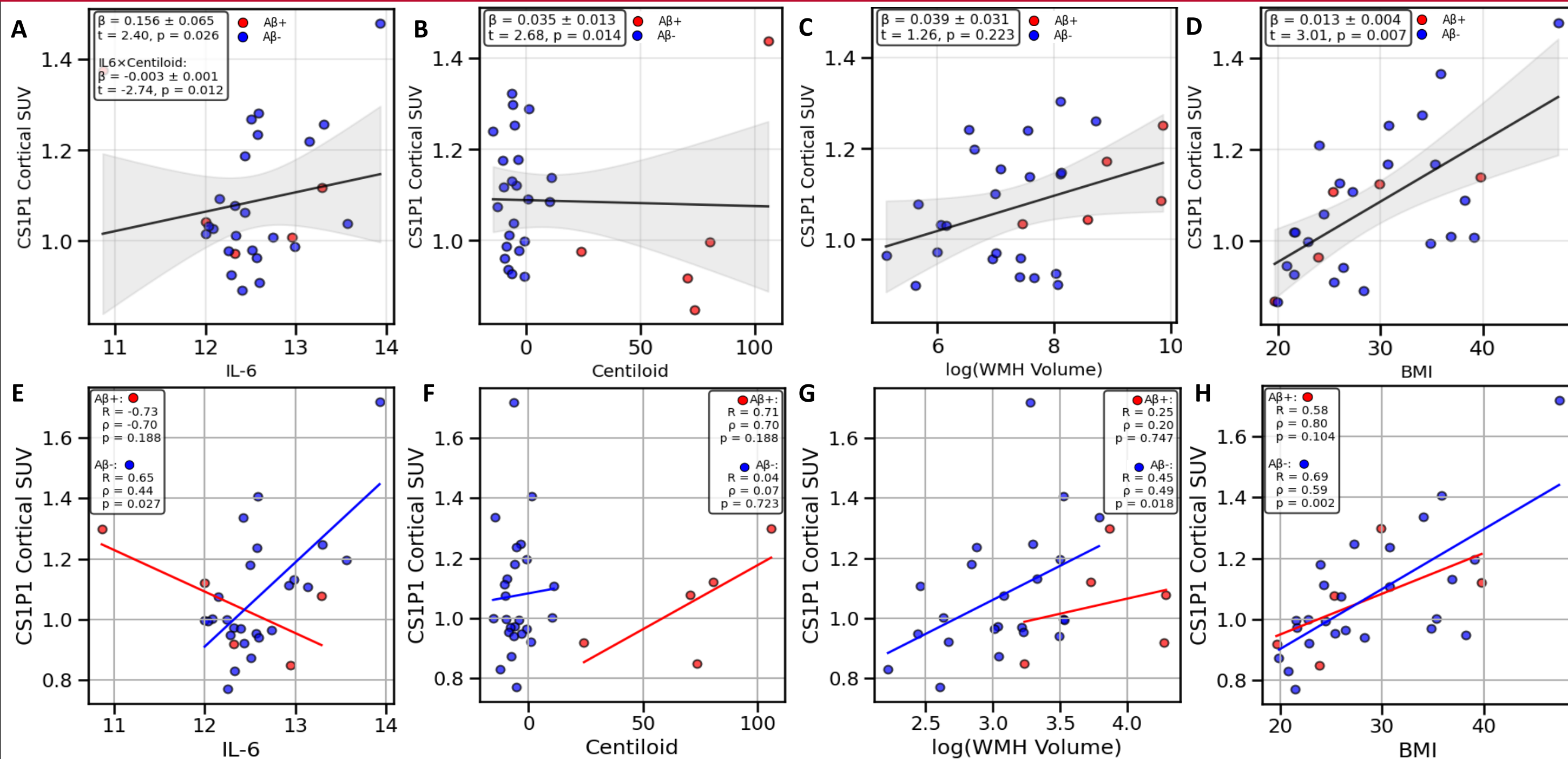


Figure 3: (A-D) shows multivariable linear regression with CS1P1~IL6*Centiloid + log(WMH volume) + BMI + Sex + Age. (E-H) shows a post-hoc Aβ stratified analysis of raw data.

- IL6 (A), centiloid (B&F) and BMI (D&H) were associated with increased CS1P1, while log-transformed WMH showed a positive trend (C).
- A significant IL6×centiloid interaction (A) indicates the positive IL6-CS1P1 association attenuates as Aβ burden increases.
- Stratified analyses revealed among Aβ- individuals, IL6 is positively correlated with CS1P1, whereas among Aβ+ individuals (n=5), this reversed (E).
- The stratified analysis shows a positive association between CS1P1 cortical SUV and log(WMH volume) only in the Aβ- group (G).

Results: [11C]-CS1P1 links peripheral and CNS inflammation

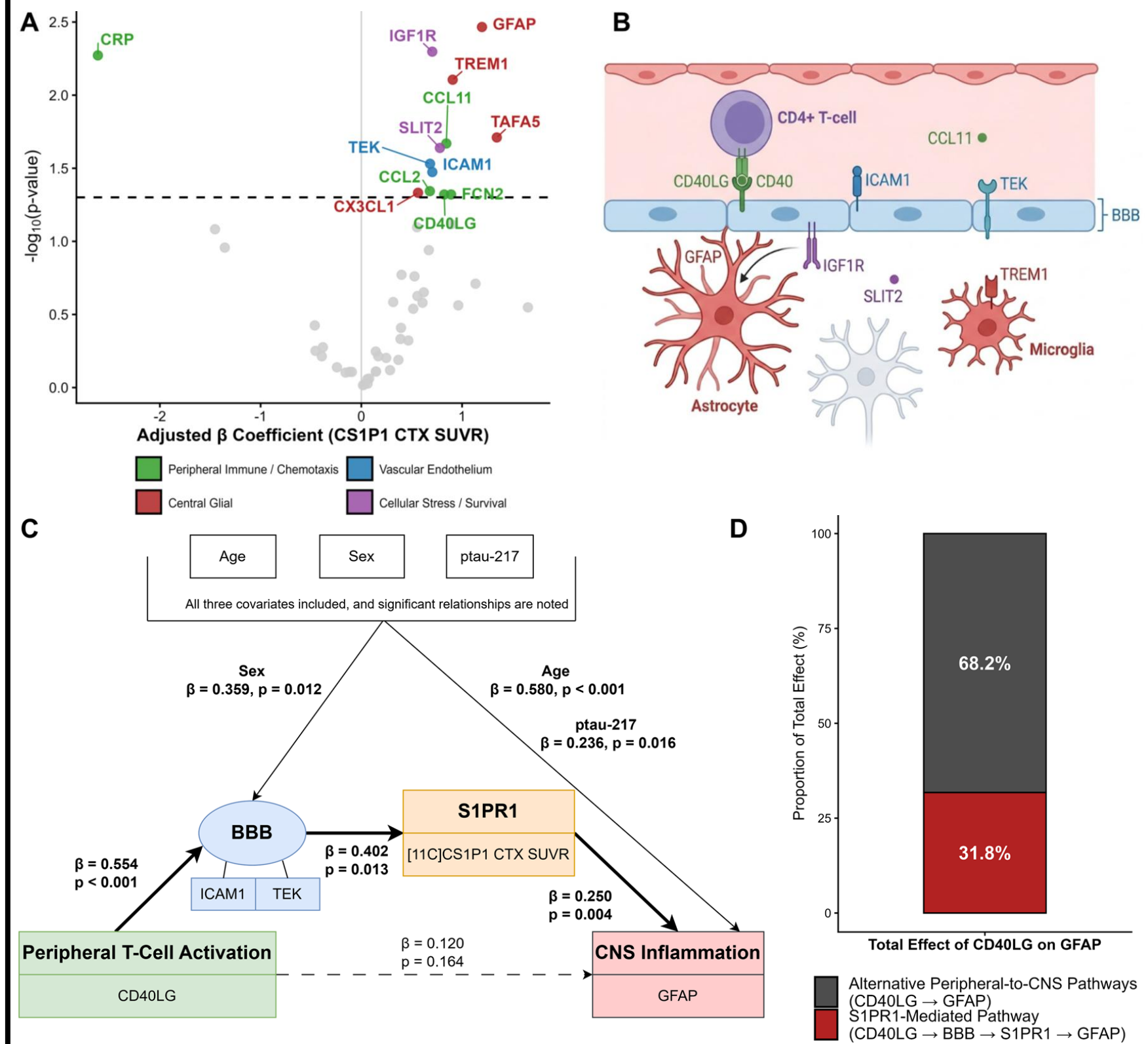


Figure 4: (A) Volcano plot of the differential abundance analysis highlighting peripheral immune, endothelial, and central glial markers that are significantly associated with CS1P1 cortical SUVr. (B) Schematic illustrating the localization of the protein signature across the blood-brain barrier (BBB). (C) Structural Equation Modeling (SEM) path diagram. The hypothesized sequential cascade is significant. (D) Mediation analysis estimates the S1PR1 pathway accounts for 31.8% of the total inflammatory drive from peripheral CD40LG to central GFAP.

Conclusions

- First in-human S1PR1 study found CS1P1 is associated with GFAP, a marker of reactive astrogliosis and observed elevated CS1P1 in cognitively normal participants with Aβ and WMH
- Significant IL6×centiloid interaction suggests peripheral inflammation and central neuroimmune responses decouple with Aβ pathology
- CNS S1PR1 positively correlates with plasma peripheral inflammatory markers, endothelial markers, and central glial markers, highlighting complex interplay between peripheral inflammation, Aβ, WMH, and sphingolipid metabolism
- This multimodal approach (CS1P1-PET, Aβ-PET, MRI, proteomics) provides unique insights into mixed pathologies and CNS S1PR1 activity

Limitations and Future Work

- Project includes a cross-sectional design with limited sample size, so results are preliminary and underpowered
- Future work will recruit more cognitively normal and impaired (CDR>0) participants with Aβ-PET and tau-PET to validate findings and explore CS1P1 associations with AD pathology
- Understanding S1PR1 relationships with Aβ and WMH is critical given existing FDA-approved S1PR1 modulators for MS may prevent AD and vascular dementia (Zhu et al., 2023).

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References

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