

# Relative Contributions of Brain Aging Pathologies to Cognitive Impairment in Alzheimer’s Disease



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## Context

Alzheimer’s disease (AD) often co-occurs with multiple brain aging pathologies affecting cognition. However, the relative contribution and interaction of neurodegeneration, small vessel disease, and glymphatic dysfunction remain poorly understood.

### Objective

We aimed to investigate the independent and relative associations of MRI biomarkers from these systems with cognitive performance along the AD spectrum.

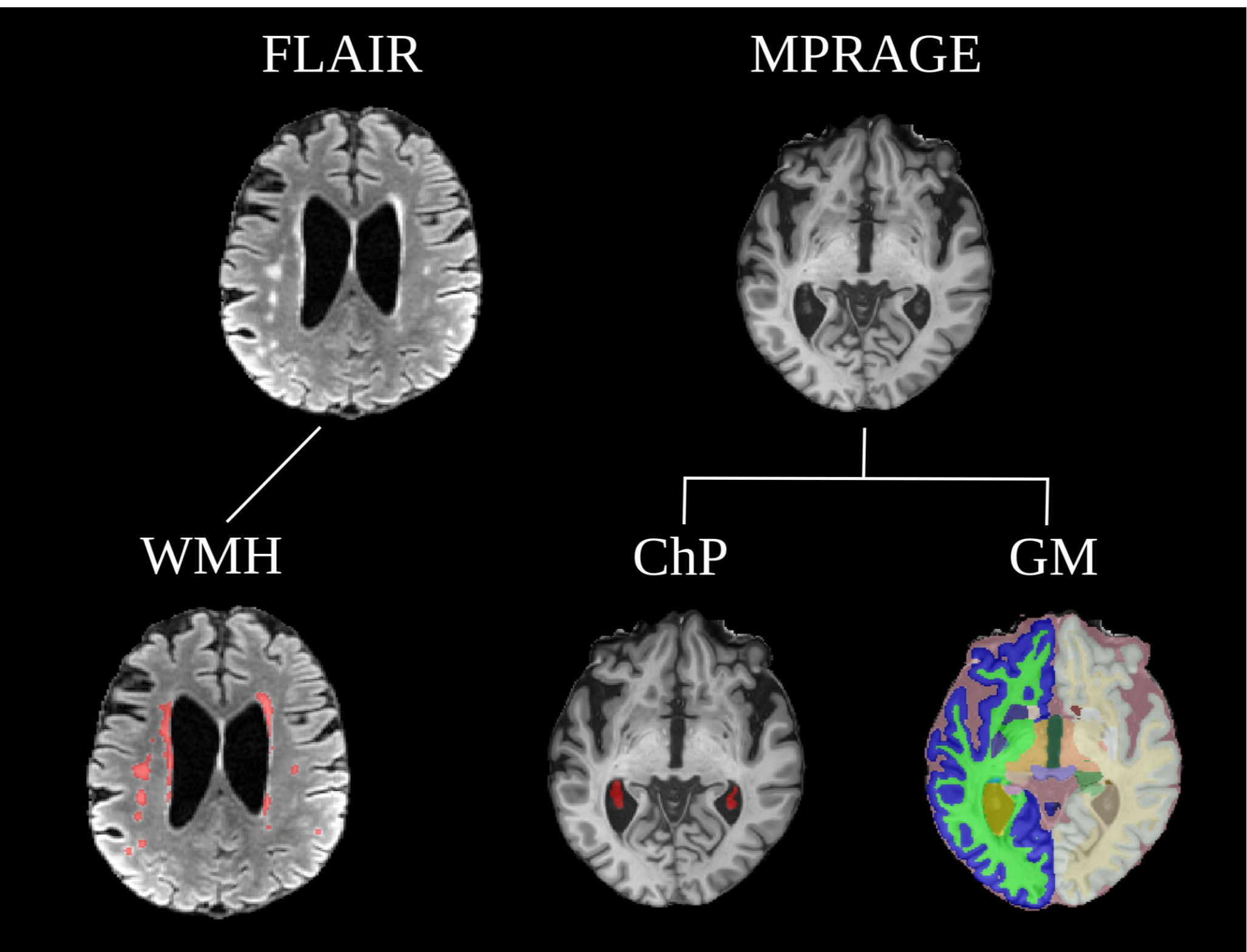
## Methods

### MRI analysis:

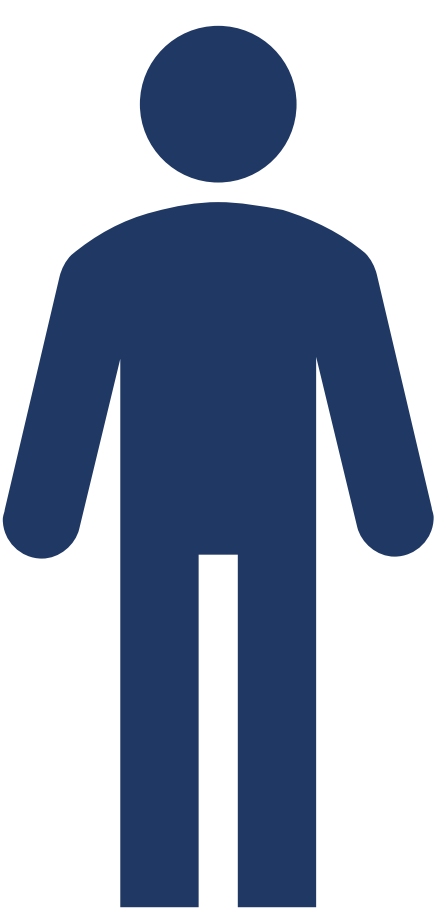
- Gray Matter (GM)** volume segmented on T1w-MPRAGE image using MRI synthseg<sup>1</sup> from FreeSurfer
- White Matter Hyperintensities (WMH)** segmented on T2-FLAIR using FLAMeS<sup>2</sup>
- Choroid Plexus (ChP)** segmented on T1w-MPRAGE using Deep Learning UNet<sup>3</sup>

### Cognitive scores:

Mini-Mental State Examination (MMSE), and composite z-scores for memory, language, visuospatial, executive functions and global cognition



## Results

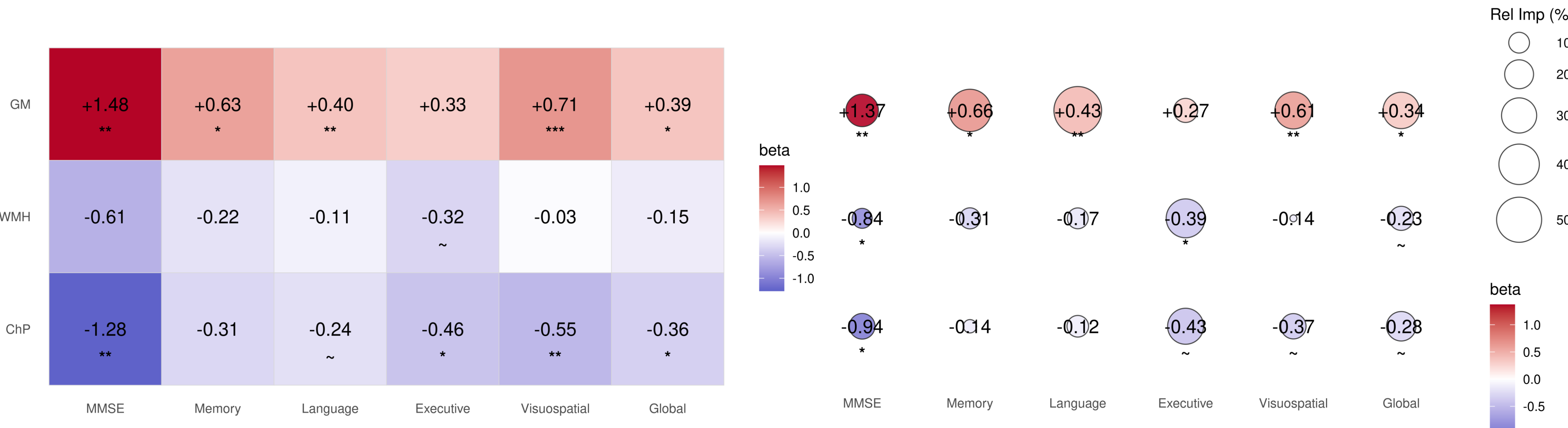


### We included:

85 amyloid-positive individuals spanning

- Cognitively normal (CN — 8),
- Mild cognitive impairment (MCI — 55),
- Alzheimer’s disease dementia (ADD — 22) stages

| Characteristic           | CN<br>N=8       | MCI<br>N=55     | ADD<br>N=22     | p-value |
|--------------------------|-----------------|-----------------|-----------------|---------|
| Age, mean (std)          | 75 (7)          | 72 (8)          | 68 (9)          | 0.014   |
| Female, n (%)            | 6 (75%)         | 32 (58%)        | 13 (59%)        | 0.7     |
| Education level, n (%)   |                 |                 |                 | 0.9     |
| 1                        | 0 (0%)          | 6 (11%)         | 3 (14%)         |         |
| 2                        | 1 (13%)         | 10 (18%)        | 4 (19%)         |         |
| 3                        | 7 (88%)         | 39 (71%)        | 14 (67%)        |         |
| MMSE, mean (std)         | 28.8 (0.9)      | 26.2 (1.8)      | 19.3 (3.4)      | <0.001  |
| Memory, mean (std)       | 0.06 (0.6)      | -3.17 (2.03)    | -4.45 (1.63)    | <0.001  |
| Language, mean (std)     | -0.36 (0.64)    | -0.94 (0.83)    | -2.42 (1.29)    | <0.001  |
| Executive, mean (std)    | 0 (0.56)        | -0.95 (1.34)    | -2.7 (1.84)     | <0.001  |
| Visuospatial, mean (std) | -0.19 (0.83)    | -0.67 (1.10)    | -3.42 (3.29)    | <0.001  |
| Global, mean (std)       | -0.12 (0.41)    | -1.37 (0.84)    | -3.36 (1.55)    | <0.001  |
| GM, mean (std)           | 0.347 (0.008)   | 0.343 (0.011)   | 0.336 (0.009)   | 0.008   |
| WMH, mean (std)          | 0.001 (0.001)   | 0.005 (0.010)   | 0.007 (0.010)   | 0.11    |
| ChP, mean (std)          | 0.0018 (0.0003) | 0.0019 (0.0004) | 0.0020 (0.0003) | 0.3     |



### Univariable analysis<sup>+</sup>:

- GM** is the most consistent predictor of cognitive performance
- WMH** shows marginal association with executive performance
- ChP** demonstrate broad association pattern

### Multi-variable analysis<sup>+</sup>:

- GM** remained the dominant predictor
- WMH** showed domain-specific effects
- ChP** demonstrated weaker independent associations

<sup>+</sup> Adjusted for age, sex assigned at birth, and education level

## Conclusions

- Among the MRI measures examined, **Cortical volume loss** showed the strongest association with cognitive performance across domains, except for executive function
- Vascular pathology contributes selectively**, with a stronger impact on executive dysfunction
- Glymphatic dysfunction has broad univariable effects but weaker independent contribution**, highlighting its likely indirect or shared role with broader brain aging processes

**Overall**, results supports a **multi-system framework**, with neurodegeneration as the dominant clinical determinant