

Brain Age Models as Biomarkers of Neurodegeneration in Alzheimer’s Disease

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Brain age gap increased with clinical severity across cohorts. The in-house transformer provided the most complete separation of CN, MCI, and AD in OASIS-3 and was associated with cognitive performance.

BACKGROUND

Brain age prediction from structural MRI has emerged as a promising approach for detecting deviations from normative aging. The brain age gap (BAG), defined as predicted age minus chronological age, has been proposed as a marker of accelerated aging in neurological and psychiatric disorders. However, its validity as a clinical biomarker requires evaluation across different models, clinical groups, and independent populations.

We evaluated whether brain age models could detect differences in BAG across cognitively normal individuals, patients with mild cognitive impairment, and patients with Alzheimer’s disease, and whether BAG was associated with cognitive performance.

DATASETS

ADNI

- CN, EMCI/MCI, LMCI and AD
- External evaluation of public and in-house models
- T1-weighted MRI
- Cognitive assessment: MoCA

OASIS-3

- CN, MCI and AD
- Demographically matched clinical groups
- Cognitive assessment: MMSE

BRAIN AGE MODELS

T1-weighted MRI → Preprocessing → Deep Learning Models → Predicted Age → Brain Age Gap (BAG)

Chronological Age (65) → Predicted Age (68) → BAG (68 – 65 = 3)

Positive BAG: Accelerated brain ageing

Models: Pyment [2], BrainAgeNeXt [3], In-House Model

Model	MAE (yrs)	ME (yrs)
Pyment	3.7	-1.2
BrainAgeNeXt	3.9	-1.7
In-House	4.0	-0.4

DATA ANALYSIS

- Accuracy (MAE) assessed in CN participants
- BAG compared across groups (age-adjusted)
- Post-hoc tests corrected for multiple comparisons
- BAG vs cognition (MoCA / MMSE)

In-house: Global–local transformer

- Triplanar T1w input
- Multi-cohort training
- External test: ADNI & OASIS-3

RESULTS

Comparison of Clinical Groups in ADNI In-House Model

Brain Age Gap (BAG) by Clinical Group

Comparison of Clinical Groups in OASIS-3 In-House Model

Brain Age Gap (BAG) by Clinical Group

Association between BAG, cognition and Ethnicity

Higher BAG was associated with poorer cognitive performance across cohorts: lower MoCA scores in ADNI ($p = 0.03$ to $p < 0.01$) and lower MMSE scores in OASIS-3 ($\rho = -0.26$, $p < 0.001$). In ADNI, ethnicity also showed a small but significant association with BAG ($p < 0.01$), driven by White–Black and Latino–Black differences.

CONCLUSIONS

Brain age models distinguished cognitively normal individuals from patients with cognitive impairment and Alzheimer’s disease, supporting BAG as a group-level marker of neurodegenerative burden. The in-house model showed particularly good clinical stratification in the older OASIS-3 cohort, separating CN, MCI, and AD despite a slightly higher prediction error.

However, brain age estimates remained affected by age-related regression bias, with reduced accuracy in older individuals, and ethnicity showed a small but significant association with BAG in ADNI. The association between higher BAG and poorer cognitive performance further supports its clinical relevance. Overall, BAG is promising for group comparisons, but individual-level use will require improved age calibration, more diverse training data, and external validation.

REFERENCES

- Cole JH, Franke K. *Trends Neurosci.* 2017;40:681–690.
- Leonardsen EH, et al. *NeuroImage.* 2022;256:119210.
- La Rosa F, et al. *Imaging Neuroscience.* 2025;3.
- Aguzin Parrilli LJ, Belzunce MA. *Imaging Neuroscience.* 2026;4.

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