

Iron dysregulation is associated with cognitive and functional decline independently of amyloid Pathology in AD

Jonghyun Bae, Zhaoyuan Gong, Noam Y. Fox, Nathan Zhang, Angelique de Rouen, Aaliya Taranath, Mustapha Bouhrara
Magnetic Resonance Physics of Aging and Dementia (MRPAD) Unit, Laboratory of Clinical Investigation, National Institute on Aging



National Institutes
of Health

Motivations

- Iron is an essential metal ion, but increasing evidence suggests age-related iron overload
- In AD, excess iron has been linked to amyloid pathology
- Iron-devoid plaques suggest iron dysregulation and amyloid pathology may be independent process

Aim: 1. To Characterize **iron accumulation** patterns across **clinical AD continuum** using large-cohort QSM
2. To Determine whether iron-driven cognitive and functional decline operates **independently of amyloid pathology**

Methods

Cohort Demographics

	N	Sex (N) F M	Age Mean SD
CN	296	202 94	70.0 8.8
CI	223	120 103	72.0 8.4



Cognitively Normal (CN) and Cognitively Impaired (CI; MCI (N=185) and AD(N=38)) subjects

- Quantitative Susceptibility Mapping:** Higher **iron** content increases tissue susceptibility, reflected as **elevated QSM** values

Multi-Echo Gradient Echo Sequence, 5 Echoes,
TE1=6.71ms, ΔTE=3.91, Res.=0.52×0.52×1.8
Processed with ROMEO, V-SHARP, and QSM-Net

- Amyloid PET:** CENTILOIDS used for overall Amyloid burden

Statistics Modeling

Single Biomarker LMER

$CDR-SB_{ij} \sim Age_i + Sex_i + Diagnosis_i + Time_{ij} \times Amyloid_i$
 $CDR-SB_{ij} \sim Age_i + Sex_i + Diagnosis_i + Time_{ij} \times QSM_i$

Multivariable LMER

$CDR-SB_{ij} \sim Age_i + Sex_i + Diagnosis_i + Time_{ij} \times QSM_i + Time_{ij} \times Amyloid_i$

Results

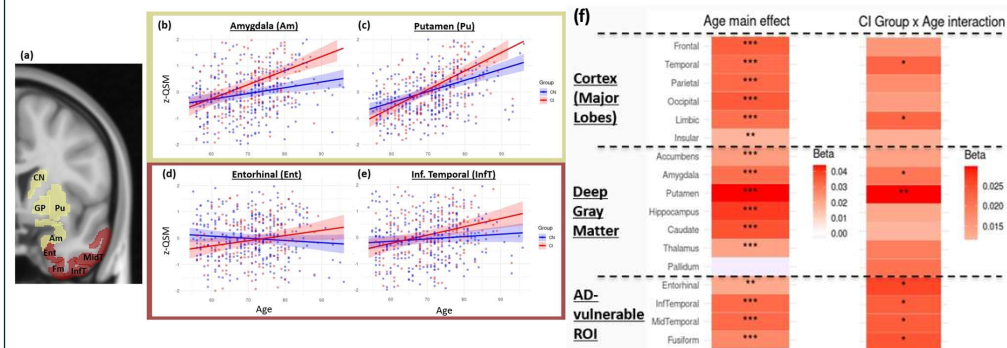


Figure 1. (a) Region of Interests (ROIs) on a structural MRI template. (b–e) CI (red) shows steeper age-related iron accumulation than CN (blue) across representative ROIs. (f) Age effects on iron were widespread; CI × Age interactions were concentrated in deep gray matter and AD-vulnerable cortical regions.

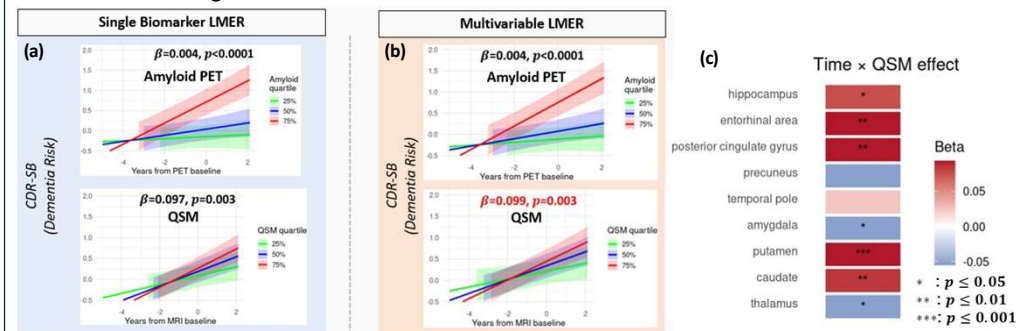


Figure 2. (a) Entorhinal QSM and amyloid PET each predict dementia risk (CDR-SB). (b) QSM remains significant after controlling for amyloid ($\beta=0.099$, $p=0.003$), indicating an amyloid-independent effect of iron on cognition. (c) Time × QSM interactions reveal region-specific iron effects on cognitive decline.

Conclusions

- Advanced age** was associated with **greater iron accumulation** in DGM and AD-vulnerable regions, particularly for CI
- Higher baseline iron burden predicted faster cognitive and functional decline, **independent of amyloid burden**, suggesting an additional pathological pathway
- Iron is a promising **prognostic biomarker** for trial enrichment, mechanistic investigation, and **therapeutic targeting** via iron chelation

This research was supported by the Intramural Research Program of the National Institutes of Health (NIH).

- CI group exhibits **more rapid** increase in QSM value (high iron) than CN

- Advanced age** moderates iron increase **more strongly** in CI than CN, particularly in DGM and AD-vulnerable regions

- Both elevated amyloid burden and high iron levels predict accelerated dementia risk

- Iron levels **independently predicted** cognitive decline after controlling for amyloid