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NEUROIMAGING

Longitudinal hippocampal iron accumulation predicts episodic memory in presymptomatic Alzheimer's disease with additional influences of tau and APOE geneotype

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Abstract

Background: Elevated brain iron deposition is recognized as a characteristic of normal aging and neurodegenerative diseases, particularly Alzheimer's disease (AD), where it correlated with amyloid-β plaques and neurofibrillary tangles. Our study aimed to investigate the relationship between longitudinal changes in hippocampal iron deposition and episodic memory, and how this relationship is impacted by AD pathology and APOE4 allele carriership.

Method: We measured longitudinal changes in brain iron levels using quantitative susceptibility mapping (QSM)-MRI (see Figure 1), in a cohort of old adults at risk of AD (N =143, 102 females, 41 males; mean age = 67.7 ± 5.0 years; longitudinal duration = 2.7 ± 0.4 years). Cognition was assessed using the RBANS. Plasma was collected from all participants at a single time point (Time 2, T2) and p-tau181 measured using in-house single-molecule arrays. We examined the relationship between iron accumulation and memory, the mediating effect of plasma p-tau181. We also investigated how APOE4 status moderates the relationship between iron deposition and plasma p-tau181.

Result: Hippocampal iron levels demonstrated a significant increase over time (t(142)=2.45, Cohen's d=0.21, p = 0.016). Changes in iron levels were significantly negatively correlated with memory performance (β=-0.223, p = 0.009, Figure 2A), and positively associated with plasma p-tau181 (β=0.217, p = 0.011, Figure 2B). Plasma p-tau181 were also negatively associated memory (β=−0.207, p = 0.015, Figure 2C). Furthermore, p-tau181 mediated the relationship between hippocampal iron increases

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and memory performance, accounted for 16.2% of the total association (β = −0.034, p = 0.045, CI: −0.09 to -0.004, Figure 2D). APOE4 status moderated the impact of increased hippocampal iron on plasma p-tau181 levels (β =0.431, p = 0.021, CI: 0.06 to 0.8, Figure 3).

Conclusion: These findings underscore the unique effect of hippocampal iron accumulation on cognition, which is additionally impacted by AD pathology. Further, we find a novel association in APOE4 carriers, wherein increases in iron interact with AD pathology, which highlights the need for early detection and intervention strategies tailored to APOE4 carriers. This work deepens our understanding of the interplay among iron dysregulation, tau pathology, and APOE4, offering a promising avenue for precision-based approaches to AD risk assessment and therapeutic development.

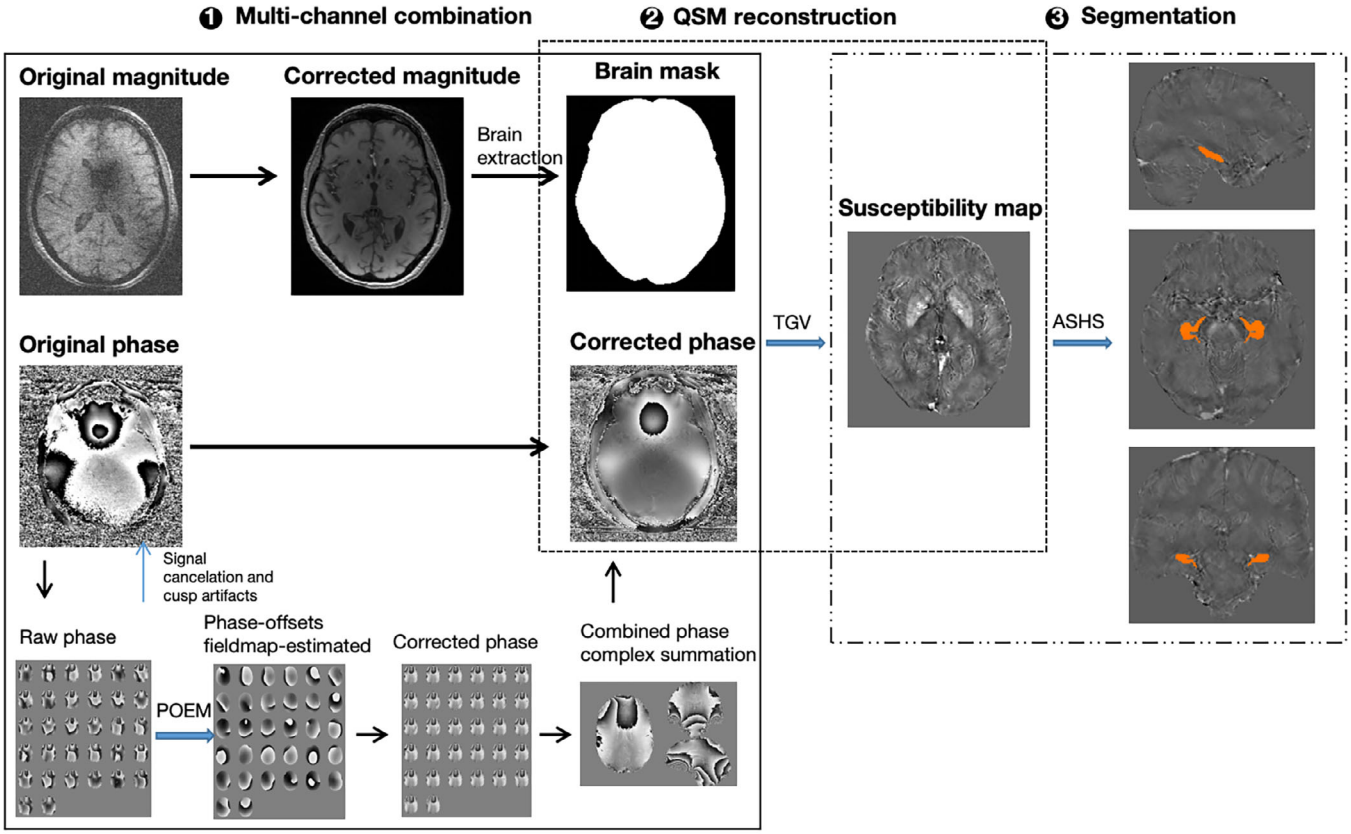

Figure 1. QSM preprocessing workflow. 1) Phase and magnitude images from the 32-channel receiver were combined to obtain offset-corrected phase images using POEM; 2) The corrected phase image and magnitude image were then used for QSM reconstruction to obtain QSM maps. QSM maps; 3) Hippocampal ROI obtain through ASHS package was registered to QSM space separately to quantify susceptibility value.

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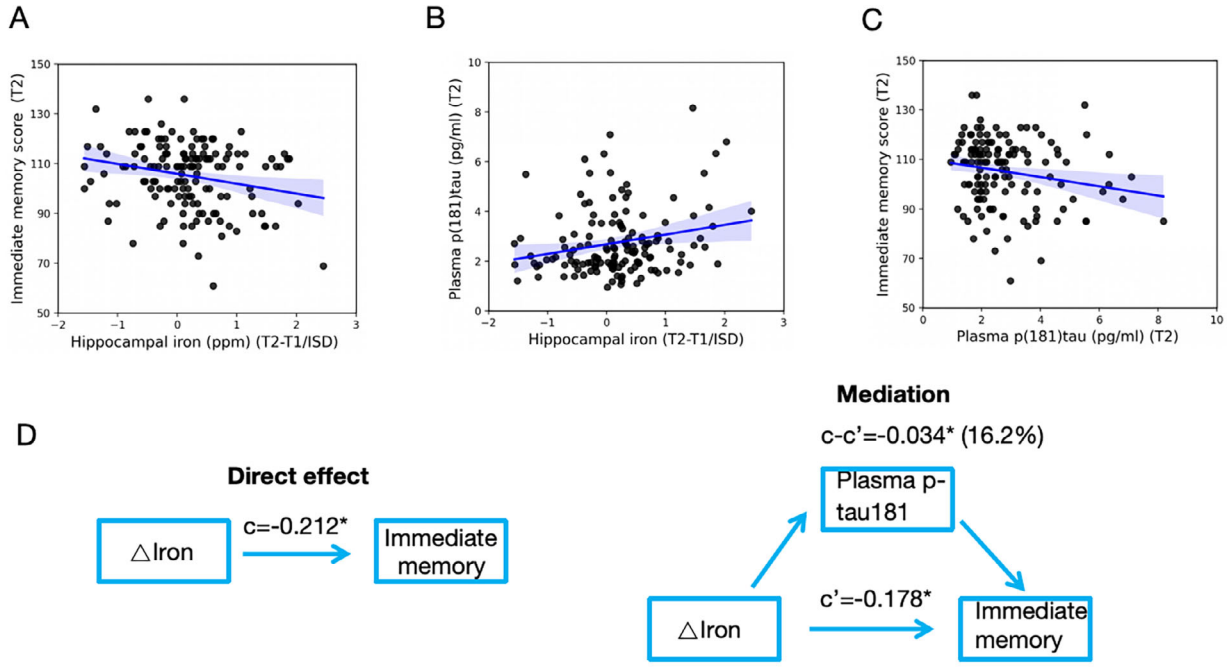

Figure 2: (A-C) Partial correlation analysis showed a significant negative association between changes in hippocampal iron levels and immediate memory, a positive association between changes in hippocampal iron levels and plasma p-tau181, and a negative association between plasma p-tau181 and immediate memory, these models include age, sex, education, APOE status, total intracranial volume, and hippocampal volume as covariates. (D) Flow chart illustration of the mediation analysis results (the model includes age, sex, education, APOE4 status, total intracranial volume and hippocampal volume as covariates); c represents the direct association strength between changes in iron level and immediate memory [β = –0.213, p=0.01, CI: –0.39 to –0.06]; c' is the association strength between changes in iron level and immediate memory accounting for the effect of plasma p-tau181 [β = –0.178, p=0.035, CI: –0.35 to –0.02]; c-c' is therefore the mediation effect of plasma p-tau181 [β = –0.034, p=0.045, CI: –0.09 to -0.004, plasma p-tau181 can explain 16.2% (β_{ratio}) of the effect of increased iron level on immediate memory]. The statistical significance of the mediation effect was tested with bootstrapping (10000 samples). (note: Longitudinal changes were calculated by dividing the difference between Time 2(T2) and Time 1(T1) values by the scan interval (T2-T1/ISD, Interval Scan Days).

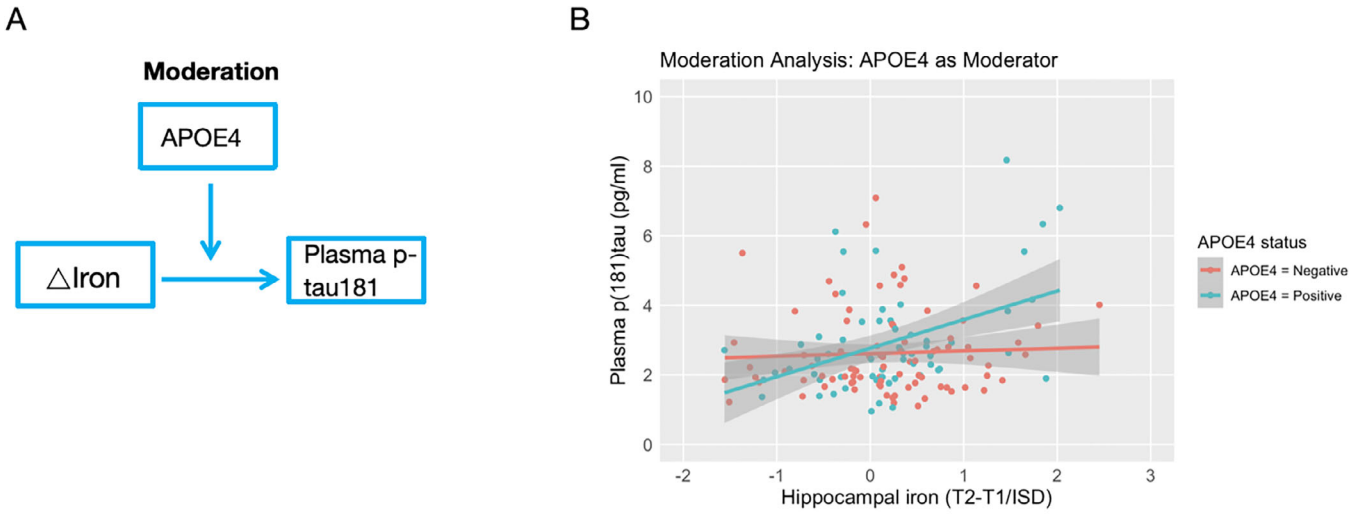

Figure 3: A) A flowchart illustrates the moderation analysis results. the model includes age, sex, education, total intracranial volume and hippocampal volume as covariates; B) plasma p-tau181 plotted as a function of changes in hippocampal iron. The translucent area around the regression line represents the 95% CI for the regression estimate. The statistical significance of the moderation effect was tested with bootstrapping (10000 samples). (note: APOE4 = positive (individuals carrying at least one APOE4))