

Why Some Brain Regions Rust: Identifying Biological Drivers of Regional Brain Iron Burden in Aging

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Introduction

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- Brain iron supports neuronal metabolism^{1,2}, but age-related increases in redox-active iron can promote oxidative injury and are implicated in cognitive decline and Alzheimer's disease^{3,4}.
- Brain iron accumulates unevenly with age⁵, but why some regions become iron **"hotspots"** remains unclear.
- Inflammation has been proposed as one contributor but shows inconsistent associations with MRI-indexed brain iron burden^{6,7}, prompting a search for additional contributors.
- Because mitochondria support heme metabolism and iron compartmentalization, age-related increases in mitochondrial stress may impair iron utilization and favor iron retention, particularly in regions with low tissue respiratory capacity.
- Our goals are:
 - Test whether regional tissue respiratory capacity (TRC; atlas-based⁸) and systemic mitochondrial stress contribute to brain iron hotspots in aging, independent of systemic inflammation.

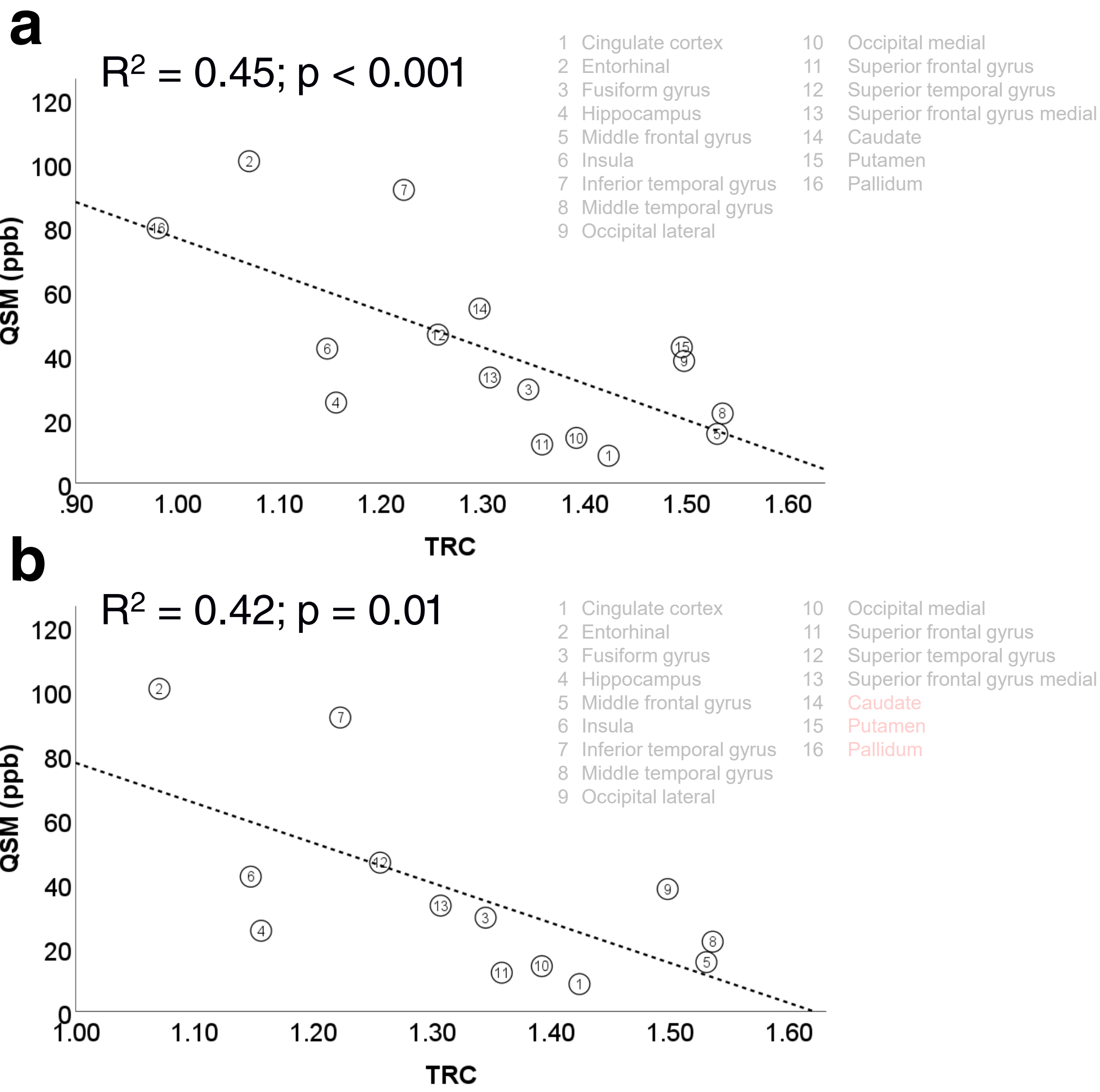
Methods

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- Thirty-nine healthy older adults:
 - 60-85 years (mean 71.1 years)
 - 24 women
 - Average MOCA score = 27.6
- Completed structural MRI, quantitative susceptibility mapping (QSM) for regional iron burden, and whole-plasma assays of the systemic mitochondrial stress markers: **GDF-15** and **FGF-21** and the pro-inflammatory markers **IL-1b**, **IL-6**, **IL-8**, **TNF-a**, and **IL-12p70**, each expressed as a composite score.
- Normative priors from the MitoBrainMap dataset (Mosharov et al., 2025)⁸ provided TRC for 16 gray-matter regions.
- Linear mixed-effects models tested whether lower TRC predicted higher iron in the same regions and whether systemic mitochondrial stress moderated this association, adjusting for age, sex, physical activity (CHAMPS Physical Activity Questionnaire for Older Adults), and the systemic pro-inflammatory composite.

TRC vs Brain Iron

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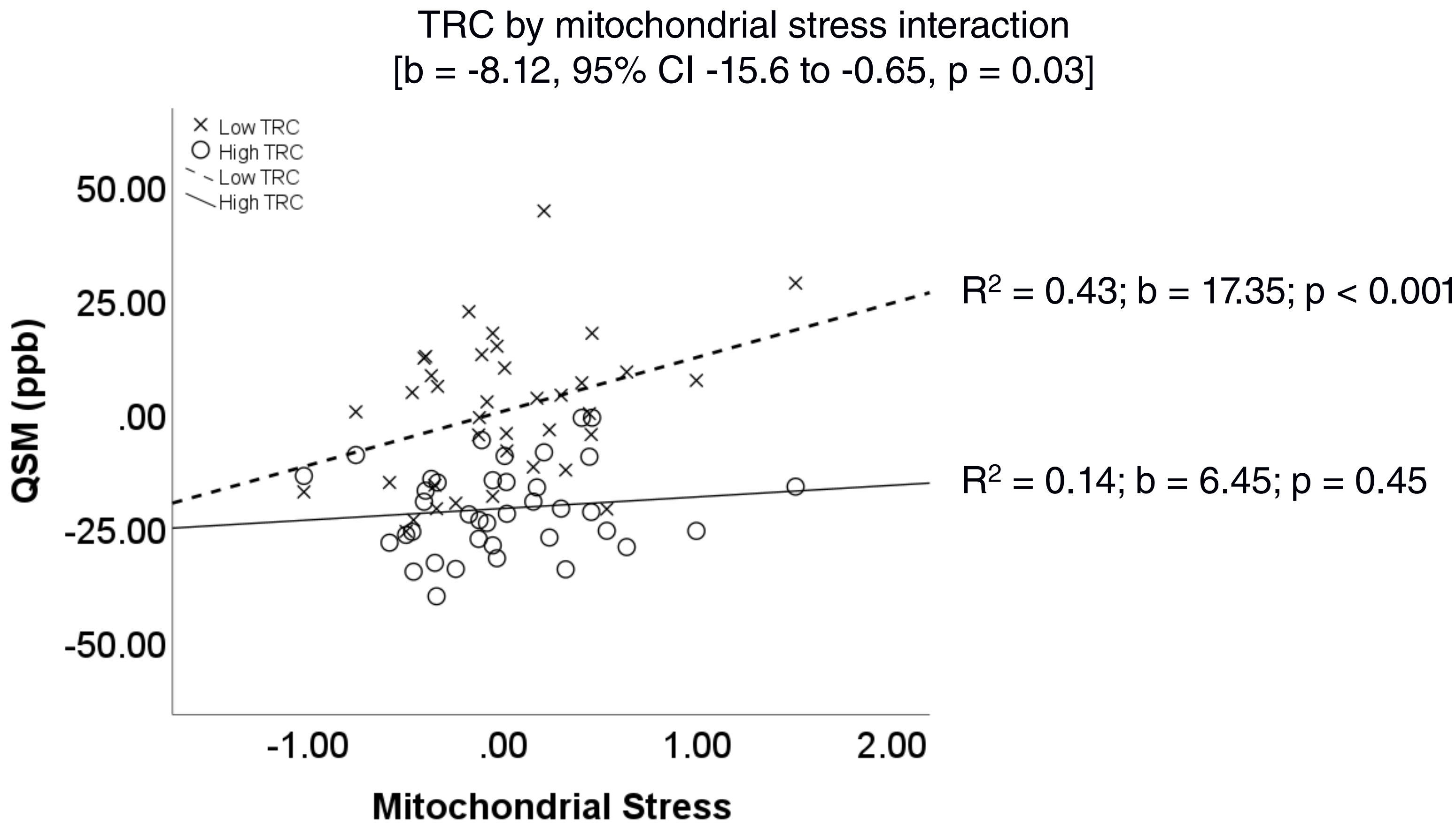
Associations between observed tissue respiratory capacity (TRC; MitoBrainMap-based) and QSM-indexed iron burden (susceptibility, parts per billion, ppb) across:

- (a) All 16 gray-matter regions available in the MitoBrainMap dataset.
- (b) The same regions excluding the caudate, putamen, and pallidum.

Linear mixed-effects models adjusted for age, sex, physical activity, and the systemic pro-inflammatory composite.

Systemic Mitochondrial Stress vs Brain Iron

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To visualize the significant TRC-by-mitochondrial-stress interaction from the linear mixed-effects model, regions were median-split into low- and high-TRC categories and QSM was averaged within each category. Associations are shown between the plasma marker-based mitochondrial stress composite and QSM (susceptibility, ppb), separately for the high- and low-TRC categories. The median split is for visualization only; all inference used continuous TRC. Values are standardized residuals after adjustment for age, sex, physical activity, and the systemic pro-inflammatory composite.

Conclusion

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- These preliminary findings suggest that low-TRC regions may experience greater age-related mitochondrial stress, increasing their vulnerability to iron retention.
- Pending replication with CNS-proximal mitochondrial stress markers, assessed in neuronal and astrocyte extracellular vesicles, these findings nominate regional mitochondrial respiratory phenotype as a marker of iron hotspots and mitochondrial stress as an actionable pathway for future iron-focused prevention studies.

References

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