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The Moderating Role of Physical Activity on Hippocampal Iron Deposition and Memory Outcomes in Typically Aging Older Adults

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Abstract

Physical activity (PA) is linked to better cognitive and brain health, though its mechanisms are unknown. While brain iron is essential for normal function, levels increase with age and when excessive, can cause detrimental neural effects. We examined how objectively measured PA relates to cerebral iron deposition and memory functioning in normal older adults. 68 cognitively unimpaired older adults from the UCSF Memory and Aging Center completed neuropsychological testing and brain MRI, followed by 30-day Fitbit™ monitoring. MRI Quantitative Susceptibility Mapping (QSM) quantified iron deposition. PA was operationalized as average daily steps. Linear regression models examined memory as a function of hippocampal QSM, PA, and their interaction. Higher bilateral hippocampal iron deposition correlated with worse memory but was not strongly related to PA. Covarying for demographics, PA moderated the relationship between bilateral hippocampal iron deposition and memory such that the negative effect of hippocampal QSM on memory performances was no longer significant above 9,120 daily steps. Physical activity may mitigate adverse iron-related pathways for memory health.

Keywords

Quantitative Susceptibility Mapping; physical activity; iron deposition; hippocampus; memory; healthy aging

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1. INTRODUCTION

Cognitive aging trajectories are heterogeneous and complex, ranging from stability and even increasing skills to significant decline and dementia. Despite its widespread impact as a leading cause of chronic disability and dependency in older adults, dementia does not represent typical changes in the biological aging process and is not an inevitable consequence of aging (Qiu & Fratiglioni, 2018). Thus, identification of factors that impact cognitive aging outcomes, particularly those that may be modifiable, is an important area of research. The alterable nature of lifestyle behaviors makes them a promising target for primary prevention against cognitive impairment, particularly in the absence of available efficacious disease-modifying treatments for all-cause dementia. A recent cross-sectional study of risk factor prevalence in US adults cited that 41.0% of the nationwide dementia population has a diagnosis associated with modifiable lifestyle factors (Lee et al., 2022). Of the 12 lifestyle indices assessed, one of the top risk factors was physical inactivity. Physical activity is consistently associated with greater cognitive performance and brain aging outcomes (Barnes et al., 2003), as well as reduced incidence of dementias such as Alzheimer's disease (AD) (Buchman et al., 2012). As such, physical activity is widely supported as a lifestyle modification for older adults (Livingston et al., 2020). However, the precise biological mechanisms linking physical activity and exercise to brain health are still under investigation. Identification and thorough understanding of these biological mechanisms are essential to develop precise risk-stratification approaches for physical activity recommendations and identifying novel therapy targets (Möller et al., 2019).

A key measure of interest that may contribute to our understanding of the neurobiological mechanisms of physical activity is brain-based iron accumulation. As the most abundant paramagnetic agent in the human brain, iron plays a critical role in normal brain function. Iron is essential for brain homeostasis, including oxidative metabolism, formation and maintenance of neural networks, and myelin synthesis (Acosta-Cabronero et al., 2013). Importantly, increased brain iron deposition with age has been evidenced in both in-vivo cross-sectional (Daugherty & Raz, 2013); (Haacke et al., 2005) and longitudinal studies (Daugherty et al., 2015); Daugherty & Raz, 2016). While brain iron accumulation occurs during typical aging, dysregulation of iron can lead to highly elevated levels with detrimental effects. Excessive iron accumulation is thought to encourage spontaneous, neurotoxic release of free iron, which can then catalyze the formation of highly reactive radical species. This process is associated with exacerbated oxidative stress and increased cell predisposal to neuronal death (Acosta-Cabronero et al., 2016), as well as propagation of myelin breakdown and neurodegeneration (Khattar et al., 2021).

Through a variety of MRI-based methods, advancing technology has enabled the ability to quantify brain iron deposition in-vivo, especially as it relates to cognition. Cerebral iron deposition accumulation with age has been shown to be associated with poorer cognitive outcomes. MRI-based estimates of brain iron concentrations correlate with age-related differences in cognition cross-sectionally (Hosking et al., 2018), and such findings are also reflected in longitudinal studies of cognitive decline in aging (Daugherty et al., 2015). Indeed, elevated cerebral iron load, particularly in the hippocampus, has been associated with poorer overall cognitive performances (Chen et al., 2021) and predicts accelerated

decline on tests of memory and executive functions even in cognitively normal older adults (Zachariou et al., 2020). Associations are also demonstrated between hippocampal iron deposition and declarative memory. In healthy older adults, lower declarative memory scores have been linked to both higher hippocampal iron concentration and smaller hippocampal volume (Rodrigue et al., 2013), while longitudinal spatial memory improvement was predicted by lower baseline hippocampal iron levels and larger parahippocampal volumes (Daugherty & Raz, 2017). In clinical comparative studies, hippocampal iron deposition distinguished AD patients from healthy controls as measured through quantitative phase imaging (Ding et al., 2009) and a combination of ferritin iron accumulation and associated hippocampal tissue damage (Raven et al., 2013). Iron has been recognized as a significant source of oxidative stress that contributes to AD progression, and disruption to brain iron metabolism is postulated to influence AD pathogenesis (Honda et al., 2004). Based on supporting hippocampal iron accumulation and memory relationships and associations between altered brain iron metabolism and neurodegenerative disease (Schenck & Zimmerman, 2004), we pursued a study of brain iron deposition as a biomarker for neural and cognitive decline using Quantitative Susceptibility Mapping (QSM). Major reservoirs of iron in the human brain including ferratin and neuromelanin pigments create local field distortions in the presence of a magnetic field that can be detected at submillimeter resolutions (Möller et al., 2019). This novel, MRI-based technique sensitively measures in-vivo iron deposition via relaxation and magnetic susceptibility of brain tissue.

As an effect of its metabolic activity, density of oxidizable substrates, and generally low antioxidant defense, the brain is highly susceptible to oxidative stress (García-Mesa et al., 2016). Physical activity, on the other hand, is linked to reduced oxidative stress, greater white matter integrity, and maintained myelin content (el Assar et al., 2022). Regular physical activity has been shown to increase cell and tissue endurance to oxidative stress, vascularization, and neurotrophin synthesis, processes that are closely related to neurogenesis, memory improvement, and brain plasticity (Radak et al., 2010). By promoting increased activity of enzymatic antioxidants, physical activity leads to heightened resistance to oxidative stress-related diseases, including cardiovascular and neurodegenerative disorders such as Alzheimer’s and Parkinson’s disease (Kim et al., 2015). Despite the overlap of potential neurobiological targets, it is currently unknown how physical activity may associate with age-related iron deposition and related cognition changes.

To explore this relationship, our study evaluated 68 cognitively normal older adults who completed 30-days of Fitbit monitoring, neuropsychological assessment, and brain MRI including QSM and diffusion tensor imaging (DTI). Our primary study aim was to characterize associations among hippocampal iron deposition, memory outcomes, and physical activity in a cohort of cognitive unimpaired older adults. We hypothesized that: 1) greater hippocampal iron deposition would correlate with worse memory outcomes and 2) increased levels of physical activity would directly relate to lower iron deposition and/or that increased levels of physical activity would attenuate the negative relationship between age-related iron deposition and memory performance.

2. MATERIALS AND METHODS

2.1 Participants

Participants included 68 community-dwelling, cognitively unimpaired older adults ages 55 and older that were enrolled in the UCSF Memory and Aging Center's Brain Aging Network for Cognitive Health (BRANCH). All participants received a clinical dementia rating (CDR) of 0. To be included in the current study, participants completed neuropsychological testing and brain MRI scans, followed by Fitbit™ physical activity monitoring for 30-days. Participants were medically screened for a history of the following conditions: Drinking two or more alcoholic beverages a night, Substance Abuse, Epilepsy, Brain Tumors, Multiple Sclerosis, Parkinson's Disease, Post-traumatic Stress Disorder, Schizophrenia, Sleep Apnea, Major Depression, Anxiety Disorder, Head injury with loss of consciousness, Surgery requiring anesthesia in the past 6 months, Stroke, Cancer (and treatment), Eye surgery, Severe vision deficits (e.g. cataracts, macular degeneration), Colorblindness, High Blood Pressure, High Cholesterol, and Diabetes. The aforementioned cardiovascular health risk factors were noted in participant health history, but not exclusionary to participation. BRANCH exclusion criteria included history or current evidence of the following conditions: large vessel stroke, diagnosis of DSM-5 major psychiatric disorders, multiple sclerosis, symptomatic neurodegenerative disease (e.g., Parkinson's disease), epilepsy, significant memory concerns or related diagnoses, active substance abuse, hepatitis C, HIV, syphilis, blindness, or deafness. This study was approved by the UCSF Institutional Review Board and all participants provided written, informed consent.

2.1.2 Participant Characteristics—In the study sample of 68 cognitively unimpaired older adults, 56% were female and 85% identified as non-Hispanic White. On average, participants were 78.5 years old and reported 18.2 years of education. Participants averaged 7,319 steps per day. Additional participant demographic characteristics are displayed in Table 1.

2.2 Measures

2.2.1 Fitbit Metrics—All participants wore a Fitbit™ Flex 2 for 30 continuous days following research visits. Fitbit monitoring was conducted observationally during waking hours. All Fitbit accounts were linked to Fitabase, a platform specifically tailored to wearable research data management. All de-identified participant Fitbit data were then exported from Fitabase and quality checked (QC), which included removing individual days with fewer than 100 steps from analyses to control for nonadherence and only including participant monitoring data if there were ≥ 14 days of available data (Paolillo et al., 2022; VandeBunte et al., 2022). Day-level step count data were aggregated into mean total daily steps for each participant.

2.2.2 Quantitative Susceptibility Mapping—All participants completed brain MRI using a Siemens Prisma 3T scanner located at the UCSF Neuroscience Imaging Center. The calculation of Quantitative Susceptibility Mapping (QSM) necessitated the acquisition of Gradient Echo sequences using Fast Low Angle Shot (FLASH) with a series of eight

echo times T2* [4,9,14,19,24,29,34,39]~ms and a flip angle of 15°. The acquisition matrix used was 0.9×0.9×2.0~mm3. All the images were registered in a QSM group template using Advanced Normalization Tools (ANTs) group template registration (Avants et al., 2009). Every single subject transformation was checked in the group template. The ROIs were extracted from an atlas registered in the group template space.

To compute tissue magnetic susceptibility maps based on gradient echoes, we used the STI-suite (Li et al., 2014). In summary, the application unwraps the measured phase images and removes contributions caused by background susceptibilities using a Laplacian-based method. A customized group template was generated from subject susceptibility maps by linear and non-linear registration template generation using Large Deformation Diffeomorphic Metric Mapping framework (Avants et al., 2008). Native subjects' susceptibility maps were geometrically normalized to the group template and smoothed in the group template. The applied smoothing used a Gaussian kernel with 8~mm full width half maximum. Every step of the transformation was carefully inspected from the native space to the group template. Susceptibility values of regions of interest were averaged and extracted from the Desikan atlas.

Our primary QSM outcome of interest was bilateral hippocampal iron deposition, calculated as an average of lateral hippocampal iron deposition. While there are a relatively limited number of studies specific to hippocampal iron deposition, increased understanding of brain iron metabolism, relationship of iron to neurodegeneration, and availability of novel iron-dependent MRI methods support using brain iron accumulation as a potential biomarker for cognitive decline (Schenck & Zimmerman, 2004). We chose the hippocampus as a target due to previously reported findings that higher levels of hippocampal iron deposition correlate with decreased memory performance (Spence et al., 2020) and randomized controlled exercise trials implicating the hippocampus in older adults (Chapman et al., 2013; Erickson et al., 2011).

To determine the specificity of hypothesized relationships to hippocampal QSM, we also calculated a secondary QSM composite reflecting subcortical iron deposition to serve as a control region. Subcortical iron deposition was computed by averaging lateral iron deposition regional values across the caudate, thalamus, putamen, and globus pallidus.

2.2.3 Structural Neuroimaging—Given that iron deposition is linked to white matter dysregulation, we aimed to determine the specificity of QSM models, independent of white matter integrity. Therefore, DTI fractional anisotropy (FA) was used to adjust for white matter integrity in QSM analyses.

Participants completed magnetic resonance imaging (MRI) using a Siemens Prisma 3T scanner. Whole brain T1-weighted images were acquired sagittally using magnetization prepared rapid gradient-echo sequence (TR/TE/TI = 2300/2.9/900 ms, $\alpha = 9°$) with field of view of 160 × 240 × 256 mm and isotropic voxel resolution of 1 mm3.

Diffusion weighted images were acquired via a Single-shot spin-echo planar imaging sequence with the following parameters: 69 axial slices with in-plane resolution of 2.0 mm

and slice thickness of 2.0 mm (isotropic voxel); TR/TE 2420/72.20 ms; flip angle = 85°, 2 volumes B=0 s/mm2 with opposite phase encoding (AP/PA), 10 volumes, and 3 multi-shells with 96 non-collinear diffusion sensitization directions at b=2500 s/mm2, 48 directions at B=1000 s/mm2, and 30 directions at B=500 s/mm2, with an integrated parallel acquisition techniques (iPAT) acceleration factor of 2 and multi-band acceleration factor of 3.

We reconstructed the diffusion tensor images following principles from Basser and Pierpaoli (Basser & Pierpaoli, 1996). Diffusion imaging processing began with denoising (Veraart et al., 2016). Then, images were realigned to the primary volume of the sequence, using the FSL MCFLIRT algorithm (Jenkinson et al., 2002). Data reflecting absolute displacement parameters beyond 1mm were screened out and removed if necessary. Background voxels not considered as brain tissue were then masked out of the DWI volumes by applying a median Otsu function (Otsu, 1979). This function utilized the B0 acquisitions to provide a mask using Otsu thresholding with a 4mm radius and 4 iterations to minimize intra-class variance (Garyfallidis et al., 2014). We used the re-aligned diffusion images, the mask, and the b-vectors and b-values in the eddy current-induced distortions correction process (Andersson & Sotiropoulos, 2016). Angular parameters, output of the previous step, were used to correct the b-vector directions. Diffusion tensors were then fitted using Dipy (Garyfallidis et al., 2014) with a non-linear least-squares approach. To estimate diffusion, fractional anisotropy (FA) measures derived from the fitted tensor were reconstructed in the native space for quality control. Our primary DTI FA measures of interest were the uncinate fasciculus and fornix tracts, calculated as an average of left and right tracts.

To account for potential relationships between brain volume and iron deposition, we also calculated hippocampal brain volumes for use in our post-hoc QSM models. All T1-weighted images were visually quality checked and excluded for excessive motion or artifacts. Tissue segmentation was performed using SPM12's unified segmentation procedure (Penny et al., 2011). To create a study-specific template for warping individual participant T1-weighted images, we employed Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) (Ashburner, 2007). All images were normalized within the study-specific template space using nonlinear and rigid-body registration. Smoothing was performed using an 8-mm full width half maximum Gaussian kernel. To facilitate registration with a brain parcellation atlas, linear and nonlinear transformations between DARTEL's space and International Consortium of Brain Mapping (ICBM) space were applied. Volume quantification required transforming a standard parcellation atlas into ICBM space and summing all gray matter within parcellated regions of interest (Desikan et al., 2006). Total intracranial volume (TIV) was calculated as the sum of gray matter, white matter, and cerebrospinal fluid. We then examined TIV-adjusted hippocampal volume as a ratio of gray matter hippocampal volume to TIV.

2.2.4 Memory Performance—Participants completed a brief neuropsychological assessment battery. Given the previously reported utility of hippocampal QSM to detect changes in normal adults and reported relationships between physical activity and memory performances (Chieffi et al., 2017; Spence et al., 2020), we opted to focus on episodic memory as our primary cognitive outcome. Episodic memory was assessed via number of words recalled on the long delay free recall trial from the California Verbal Learning Test,

Second Edition (CVLT-II) (Beck et al., 2012). Sample-based z-scores were calculated and used as the primary measure of memory.

2.3 Statistical Analyses

First, Pearson correlations examined univariate associations of both bilateral and lateral hippocampal iron deposition with physical activity (daily steps) and memory (CVLT-II long delay free recall z-score). Univariate bilateral hippocampal iron deposition associations with age, sex, education, and DTI (uncinate fasciculus and fornix FA tracts) were also tested. Next, linear regression models examined memory as a function of hippocampal iron deposition, physical activity, and their interaction, covarying for age, sex, and education. We performed standard data diagnostics and found our model residuals to be normally distributed, with no suggested evidence of nonlinear patterns in the data. Post-hoc models were conducted to test both laterality and specificity of memory to hippocampal iron deposition. Left hippocampal, right hippocampal, and subcortical iron deposition were modeled, respectively. Secondary models covaried for hippocampal gray matter volume and FA levels of the uncinate fasciculus and fornix in order to account for possible effects of hippocampal gray and white matter integrity on hippocampal iron deposition. To follow up on interaction findings, we employed the Johnson-Neyman method (Johnson and Neyman,1936) to identify the specific level of physical activity at which the relationship between hippocampal iron deposition and CVLT-II long delay free recall z-scores was no longer statistically significant (False Discovery Rate adjusted).

3. RESULTS

Higher bilateral hippocampal iron deposition significantly correlated with worse memory performances (r = −0.34; $p = 0.01$; Figure 1). Lateralized correlations revealed a significant negative association between left hippocampal iron deposition and memory performance (r = −0.30, $p = 0.023$), but not between right hippocampal iron deposition and memory performance (r= −0.24; $p = 0.071$). Associations with education (r= −0.059, $p = 0.64$), age (r= 0.16, $p = 0.18$), sex (Cohen's d= 0.10, $p = 0.67$), fornix FA (r= −0.0058, $p = 0.96$, uncinate fasciculus FA (r= −0.024, $p = 0.84$), hippocampal volume (r= −0.21, $p = 0.086$), and physical activity (r = −0.18, $p = 0.14$) were not significant.

Adjusting for age, sex, and education, average daily steps significantly moderated the relationship between bilateral hippocampal iron deposition and memory performance (β = 0.37, $p = 0.013$, 95% CI = [0.08, 0.65]; Table 2), such that at higher levels of physical activity, the negative relationship between hippocampal iron deposition and memory was significantly attenuated (Figure 2A). To better characterize this attenuation, follow-up Johnson-Neyman analysis indicated that the negative relationship between bilateral hippocampal iron deposition and memory was reduced to a non-significant effect once a threshold of approximately 9,000 average total daily steps (9,120) was surpassed (Figure 2B).

Post-hoc laterality models showed similar effect sizes of right (β = 0.26, $p = 0.046$, 95% CI = [0.00, 0.51]) and left (β = 0.29, $p = 0.073$, 95% CI = [−0.03, 0.61]) hippocampal iron deposition interactions with physical activity on memory, suggesting that lateralization

of iron deposition did not appear to be driving our results. Our primary bilateral model remained statistically significant when further adjusting for hippocampal gray matter volume, such that the relationship between hippocampal iron deposition and memory performance appeared independent of hippocampal volume (β = 0.39, $p = 0.0073$, 95% CI = [0.11, 0.67]; Table 2). Post-hoc laterality models maintained similar effect sizes when adjusted for right (β = 0.24, $p = 0.060$, 95% CI = [−0.01, 0.49]) and left (β = 0.32, $p = 0.060$, 95% CI = [−0.01, 0.65]) hippocampal volumes, but did not reach statistical significance.

To understand specificity of estimates to hippocampal iron deposition, an additional model examined subcortical iron deposition. Subcortical iron deposition did not correlate with memory performance (r = −0.10, $p = 0.46$) nor was this relationship moderated by average daily steps (β = 0.06, $p = 0.63$, 95% CI = [−0.20, 0.33]). To additionally account for the potential influence of regional myelin levels and white matter integrity on hippocampal iron deposition, we further adjusted our bilateral model for DTI-measured integrity of the uncinate fasciculus and fornix white matter tracts. The significant interaction between average daily steps and bilateral hippocampal iron deposition on memory evidenced a similar effect size and persisted after covarying for DTI (β = 0.37, $p = 0.014$, 95% CI= [0.08, 0.65]; Table 2).

4. DISCUSSION

We found that hippocampal iron deposition negatively associated with memory performances and that physical activity significantly attenuated this adverse relationship in clinically normal older adults. Specifically, our analysis revealed that the adverse relationship between hippocampal iron deposition and memory performances only showed statistical significance below an average of 9,120 average daily steps. This threshold falls within 7,000–10,000 daily steps range that is consistently cited for its beneficial health outcomes, including cognitive aging (Del Pozo Cruz et al., 2022). Our sensitivity analyses also suggest that results were not driven by lateralized hippocampal iron deposition, were specific to iron deposition in the hippocampus, and were statistically independent of white matter integrity. Interestingly, we did not observe a strong direct relationship between physical activity levels and QSM, suggesting that activity may not be directly impacting production or clearance/metabolism of cerebral iron deposition. Nonetheless, ours are the first data to our knowledge characterizing the *in-vivo* relationships among cerebral iron deposition, objectively quantified physical activity, and cognition. We demonstrate the importance of targeting physical activity as a modifiable lifestyle factor that may help attenuate iron-related mechanisms of cognitive decline and serve as a primary prevention and/or behavioral intervention tool for individuals at risk for memory decline.

Highly elevated brain iron deposition has been shown to promote formation of reactive oxygen species (ROS) and act as a catalyst for oxidative stress and neuronal apoptosis (Auten & Davis, 2009). Based on our findings, the primary role of physical activity does not appear to be directly related to iron deposition levels. Physical activity may instead function by attenuating the detrimental cognitive outcomes *associated* with iron deposition. Although our data do not directly measure the molecular mechanisms underlying this attenuation

effect, literature suggests that physical activity may stimulate production of antioxidant promoters and myokines that protect against and/or respond to deposition-related oxidative stress (el Assar et al., 2022). For example, among a host of immune signals, exercise has been reported to upregulate nuclear factor erythroid 2-like 2(Nrf2), a major mediator of inflammation resolution (Sandberg et al., 2014). Following oxidative stress events, Nrf2 induces the expression of antioxidants and cytoprotective genes to protect against ROS-induced damage and provoke anti-inflammatory responses against stressors (Vomund et al., 2017). Additionally, irisin/FNDC5, an anti-inflammatory myokine expressed in skeletal muscle and brain tissue, is induced by physical activity. Irisin/FNDC5 also functions to decrease ROS production (Mancinelli et al., 2021) and has been shown to protect against metabolic stressors, including oxidative stress (Mazur-Bialy et al., 2018). Based on its ability to down-regulate ROS production in the brain and increase the level/activity of antioxidant enzymes in different brain regions, this may be a plausible mechanism by which physical activity can significantly attenuate oxidative stress in the brain and iron-deposition related homeostasis challenges (Radak et al., 2010; Simioni et al., 2018). Physical activity has been shown to improve antioxidant defenses in older adult individuals to levels comparable with young, sedentary subjects (Bouzid et al., 2018), emphasizing the potential of physical activity to mitigate age-associated impairments tied to iron accumulation, including cognition and memory. Through these means, physical activity may potentially offset iron deposition-related cognitive disruption by moderating the brain oxidative stress pathway.

Unchecked iron deposition is also hypothesized to detrimentally impact myelination (Todorich et al., 2009). While oligodendrocyte myelin production and maintenance does require consistent iron supply (Bartzokis et al., 2007), continual, substantial brain iron accumulation is associated with oxidative stress that promotes neurodegeneration and myelin breakdown as observed in Alzheimer's disease (Bartzokis, 2011). Oxidative injury and cyclic myelin degradation is further amplified when iron is released from oligodendrocytes during active demyelination (Haider et al., 2014). Although white matter integrity is known to decrease in both typical aging and dementia processes (Madden et al., 2012), recent RCTs demonstrated exercise-related effects on increased white matter plasticity (Mendez Colmenares et al., 2021) and integrity of white matter tracts (Bashir et al., 2021). In a recent cross-sectional observational study of older adults with cerebral small vessel disease and mild cognitive impairment, greater physical activity was linked to higher myelin content in whole-brain white matter (Boa et al., 2022). Preclinical animal studies of myelin have found that increased exercise can be beneficial for axonal myelination, including increasing myelin sheath maturation, thickness, and potentially regeneration (Feter et al., 2018), which we hypothesize may be true in humans. In the presence of iron deposition, targeting oxidative stress or myelin degeneration may therefore be potential mechanisms through which physical activity may moderate detrimental effects on memory performance. We attempted to account for myelin health by covarying our primary model for DTI FA. Given that we found the moderating effect of PA persisted even adjusting for DTI FA, our data suggest that physical activity relationships may be at least in part independent of gross white matter structure. Future studies capturing molecular markers of myelin health may help to parse out these hypothesized mechanisms.

This study also highlights important clinical implications for both MRI QSM and the application of physical activity for cognitive health. Given the observed specific relationship between hippocampal QSM and memory performance in unimpaired older adults, iron deposition measures through QSM may potentially serve as a pre-clinical indicator of neurodegeneration risk, consistent with emerging studies on this relatively novel MRI tool (Wang et al., 2017). Our findings in clinically normal older adults also underscore the potential utility of physical activity as a primary prevention tool against age-related cognitive changes. Physical activity may serve to mitigate the effects of elevated iron deposition on related cognitive changes, even prior to any form of clinical symptom onset. Taken together, these findings may inform a precision medicine approach to physical activity recommendations based on brain iron deposition levels.

Our study was not without limitations. Our relatively small sample size (n= 68) likely limited statistical power. This, as well as a restricted age range (56 to 93) may have impacted our ability to identify an expected relationship between hippocampal iron deposition and age. Considering our small sample size, we also wanted to keep the total number of comparisons in our models to a minimum and did not have robust data available for other measures of physical activity. This is a relevant area of study for future investigations. Given the observational nature of our study design, it is important to consider the role of reverse causality (i.e., accumulating iron deposition may result in lower physical activity engagement). It is likely that the relationship between physical activity and brain iron deposition levels are bidirectional with at least some contribution from reverse causality. Based on our cross-sectional design, it is not clear if iron deposition levels reflect longstanding brain differences that may impact subsequent physical activity engagement or vice versa. Future longitudinal studies will be essential for elucidating the temporal dynamics of how physical activity, iron deposition, and memory relate to one another over time. We also acknowledge that quantification of cerebral iron deposition and meaningful interpretation of QSM values is an emerging field of interest. Standardizing MRI-based QSM across scanners and study protocols is a barrier that has been reported on in the literature (Lancione et al., 2022) and will need to be continually addressed to promote large-scale, harmonized studies of this novel MRI metric. Although still in early, innovative stages, our study contributes to supporting the validity and wider effort understanding the utility of MRI QSM for future studies. Importantly, approximately 85% of our cohort identified as non-Hispanic White, which reinforces the field-wide need to accurately represent communities and racial groups that are insufficiently included in our research populations. We aim to replicate our findings in a larger, increasingly more ethnically and racially diverse group of older adults to determine generalizability of observed relationships.

5. CONCLUSIONS

As a modifiable lifestyle factor, physical activity continues to be an empirically supported target for primary cognitive health prevention in clinically normal older adults. Given these are the first known data to report on relationships among iron deposition, physical activity, and memory, this study innovatively utilizes QSM as an *in-vivo* method for exploring novel pathways that link lifestyle behaviors to cognitive health in humans. Clinically, our findings may offer support for utility of QSM for risk-stratification of exercise interventions.

Elevated iron deposition confers risk for cognitive decline and neurodegenerative disease (Ravanfar et al., 2021). By encouraging physical activity, we aim to attenuate the clinical manifestation of accumulating brain iron deposition in aging adults. Beyond the scope of this study, future multimodal longitudinal RCTs that incorporate PA interventions, fluid biomarkers, and QSM will enable us to temporally capture in-vivo neurobiological changes that directly inform physical activity pathways and their specific mechanistic effects on human cognition.

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HIGHLIGHTS:

- Brain iron deposition occurs with age and increases risk for cognitive decline
- The role of physical activity on brain iron deposition is unknown
- Hippocampal iron deposition related to poorer memory in cognitively normal adults
- Physical activity attenuated the relationship between iron deposition and memory
- Physical activity may mitigate adverse iron-related pathways for memory health

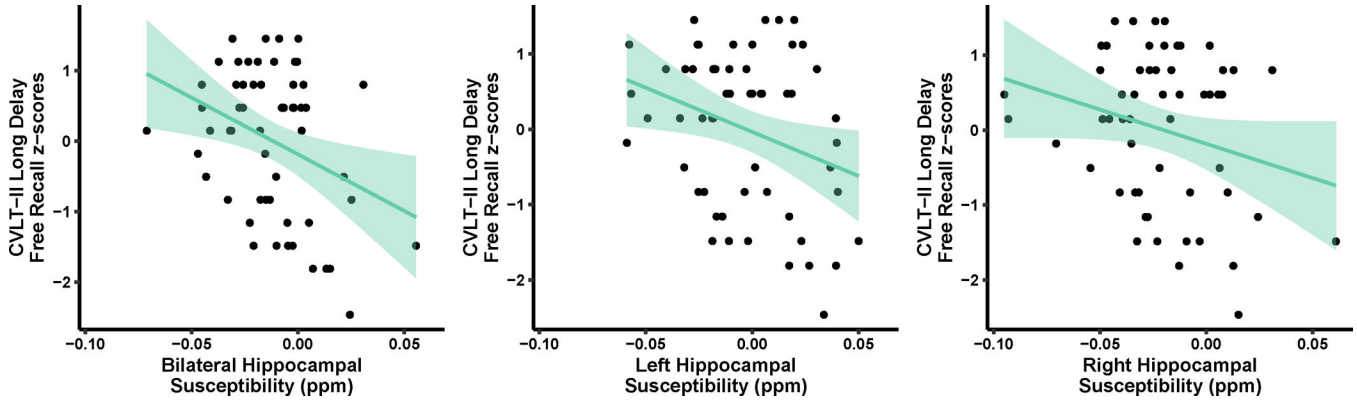

Figure 1.

There was a significant correlation between hippocampal iron deposition and memory. This was true for A) bilateral hippocampal iron deposition (r = −0.34; $p = 0.010$) and B) left hippocampal iron deposition (r = −0.30, $p = 0.023$), but not C) right hippocampal iron deposition (r = −0.24; $p = 0.071$).

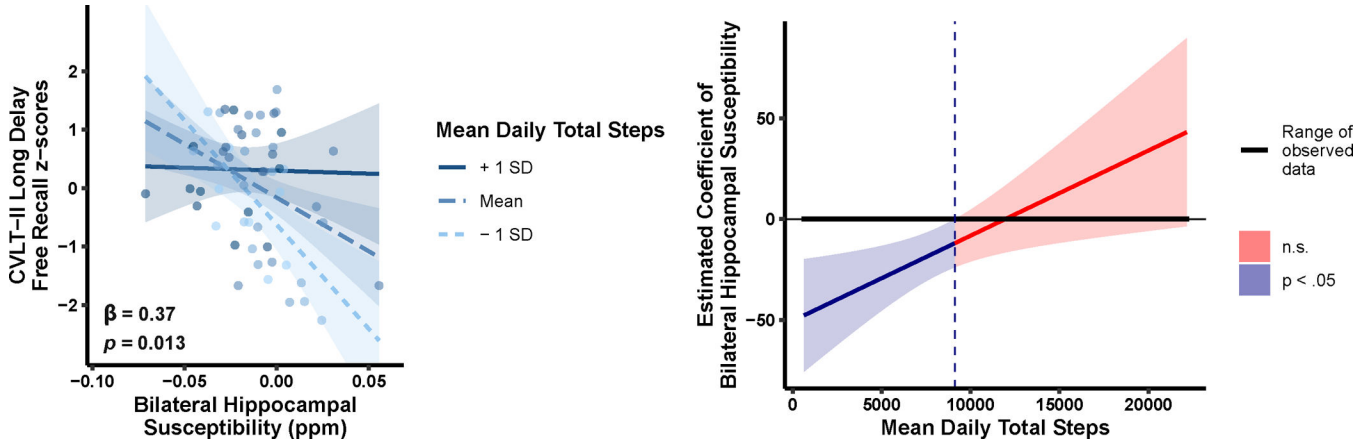

Figure 2.

A) There was a significant interaction between bilateral hippocampal iron deposition and mean daily total steps on memory performance (β = 0.37, p = 0.013, 95% CI = [0.08, 0.65]). The interaction persisted when covarying for regional FA of uncinate fasciculus and fornix tracts (β = 0.37, p = 0.014, 95% CI = [0.08, 0.65]) and hippocampal volume (β = 0.39, p = 0.0073, 95% CI = [0.11, 0.67]).

B) The negative relationship between hippocampal iron deposition and memory performance was no longer significant when average physical activity was above a threshold of 9,120 daily total steps.

Table 1.

Participant Characteristics

n = 68	Mean (SD)	[Min, Max]
Age	78.5 (7.73)	[56.0, 93.0]
Education (years)	18.16 (1.83)	[12.0, 20.0]
Female n (%)	38 (56%)	
Race/Ethnicity n (%)		
Non-Hispanic White	58 (85%)	
Asian	7 (10%)	
Black/Other Race	3 (5%)	
Hippocampal Susceptibility (ppm)	−0.012 (0.0227)	[−0.071, 0.055]
Daily Total Steps	7319 (3873)	[641, 22153]
CVLT-II Long Delay Free Recall Raw Scores	11.7 (3.23)	[4.0, 16.0]

Table 2.

Bilateral Hippocampal Model Results

Bilateral Hippocampal Model							
Parameter	**Estimate**	**Std Error**	**Statistic**	**β**	**95% CI**		***p-value***
(Intercept)	−1.23	2.28	−0.54	0.05	−0.19	0.29	0.593
Bilateral Hippocampal Susceptibility	−50.34	14.8	−3.4	−0.39	−0.64	−0.14	0.001
Mean Total Steps	0.00011	0.000041	2.72	0.24	−0.04	0.52	0.009
Age	−0.0059	0.021	−0.28	−0.04	−0.3	0.23	0.779
Education	0.0059	0.067	0.09	0.01	−0.24	0.26	0.931
Gender	0.37	0.26	1.46	0.18	−0.07	0.43	0.151
Bilateral Hippocampal Susceptibility: Mean Total Steps	0.0042	0.0016	2.59	0.37	0.08	0.65	0.013
	Multiple R^2 = 0.2916, Adjusted R^2 = 0.2048						
Post-Hoc Model: Hippocampal Volume Adjusted							
Parameter	**Estimate**	**Std Error**	**Statistic**	**β**	**95% CI**		***p-value***
(Intercept)	−2.057	3.28	−0.63	0.07	−0.18	0.33	0.53
Bilateral Hippocampal Susceptibility	−52.87	16.03	−3.3	−0.32	−0.59	−0.05	0.0019
Mean Total Steps	0.00011	0.000044	2.46	0.18	−0.13	0.49	0.018
Age	−0.0037	0.027	−0.14	−0.02	−0.34	0.29	0.89
Education	0.0046	0.068	0.068	0.01	−0.25	0.27	0.95
Gender	0.31	0.28	1.14	0.15	−0.12	0.42	0.26
Bilateral Hippocampal Volume	0.25	0.4	0.63	0.09	−0.2	0.39	0.53
Bilateral Hippocampal Susceptibility: Mean Total Steps	0.0048	0.0017	2.81	0.39	0.11	0.67	0.0073
	Multiple R^2 = 0.3019, Adjusted R^2 = 0.1933						
Post-Hoc Model: DTI Adjusted							
Parameter	**Estimate**	**Sth Error**	**Statistic**	**β**	**95% CI**		***p-value***
(Intercept)	−3.45	3.44	−1.00	0.051	−0.20	0.30	0.32
Bilateral Hippocampal Susceptibility	−51.47	15.07	−3.42	−0.41	−0.68	−0.15	0.0013
Mean Total Steps	0.00011	0.000042	2.62	0.23	−0.05	0.51	0.012
Age	0.0014	0.024	0.057	0.0088	−0.30	0.32	0.95
Education	−0.0027	0.070	−0.039	−0.0050	−0.26	0.25	0.97
Gender	0.40	0.28	1.44	0.19	−0.08	0.46	0.16
FA Uncinate	1.69	5.10	0.33	0.046	−0.24	0.33	0.74
FA Fornix	2.67	4.02	0.67	0.10	−0.20	0.41	0.51
Bilateral Hippocampal Susceptibility: Mean Total Steps	0.0042	0.0017	2.54	0.37	0.08	0.65	0.014
	Multiple R^2 = 0.3028, Adjusted R^2 = 0.1842						