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Associations between iron and mean kurtosis in iron-rich grey matter nuclei in aging

Jason Langley¹ · Kitzia Solis² · Vala Masjedizadeh³ · Murphy Shao^{1,4} · Ilana J. Bennett² · Xiaoping P. Hu^{1,3}

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Abstract

Objective Elevated kurtosis values have been observed in subcortical grey matter structures of patients with neurodegenerative diseases. Here, we examined relationships between iron measures and kurtosis in iron-rich subcortical grey matter structures. Please check and confirm the affiliation 4 for the author "Xiaoping P. Hu". Affiliation 4 for Xiaoping P. Hu was incorrect since he is not associated with that department. We have removed this affiliation. Thanks!

Materials and methods Multi-shell diffusion and multi-echo gradient echo acquisitions were used to derive mean kurtosis and iron measures (R_2^* and magnetic susceptibility), respectively, in subcortical grey matter nuclei and white matter tracts in a discovery cohort (110 healthy older and 63 younger adults) and replication cohort (72 healthy older adults). Please confirm if the author names are presented accurately and in the correct sequence (Ilana J. Bennett and Xiaoping P. Hu). Also, kindly confirm the details in the metadata are correct. Thanks for asking. We've checked and the names are presented accurately and in the correct sequence. We have corrected some details in the metadata - adding an affiliation to Murphy Shao (Department of Physics) and removing the Materials Science and Engineering affiliation for Xiaoping P. Hu. Is it possible to add an ORCID ID for Vala Masjedizadeh? His ORCID ID is 0009-0009-3692-2553. Everything else looks okay.

Results Iron-rich grey matter regions exhibited higher mean kurtosis, R_2^* , and magnetic susceptibility and white matter regions had lower mean kurtosis in the older adult group from the discovery cohort. In both cohorts, mean kurtosis was significantly correlated with R_2^* and magnetic susceptibility in iron-rich grey matter nuclei. No association was seen between signal-to-noise ratio and mean kurtosis in any grey matter region, indicating that the increase in mean kurtosis was not due to reduced signal-to-noise. As keywords are mandatory for this journal, please provide 3-6 keywords. I'm not sure where to put the keywords so I'll reply to the query with the keywords. Our keywords are: kurtosis, iron, grey matter, aging.

Conclusion Our findings indicate that kurtosis is associated with iron-sensitive metrics in iron-rich grey matter structures, suggesting that iron deposits may be contributing to kurtosis.

Keywords Kurtosis · Iron · Grey matter · Aging

Introduction

Diffusion-weighted magnetic resonance imaging (MRI) techniques have been used to study effects of normal aging [1–3] or disease [4–6] on brain tissue microstructure.

Diffusion tensor imaging (DTI) is a commonly used approach that approximates diffusion as a Gaussian process. However, the cells, organelles, and cell membranes that comprise tissue can impede diffusion and cause it to be a non-Gaussian process. Diffusion kurtosis imaging (DKI) is

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able to characterize non-Gaussian diffusion by relaxing this assumption [7] and measures the degree to which diffusion differs from a Gaussian process, known as kurtosis. Higher mean kurtosis (MK) values are thought to be indicative of more complex tissue microstructure [8, 9].

Application of DKI to aging has consistently revealed lower kurtosis values in white matter tracts of older adults relative to younger adults [10–15], consistent with evidence that aging is accompanied by degradation of white matter [16, 17], which would remove barriers to diffusion and manifest as lower MK [8, 18]. In contrast, conflicting results have been seen in subcortical grey matter nuclei, with lower MK in older than younger adults in the caudate and thalamus, but higher MK in older than younger adults in the putamen [11, 12]. Higher MK has also been seen in the globus pallidus, putamen, and substantia nigra in participants with neurodegenerative disorders (Parkinson's disease) relative to age-matched controls [19, 20]. Whereas the mechanism for this increase is unknown [19], its occurrence in grey matter nuclei that accumulate iron throughout the lifespan [21–24] suggests that iron content is related to kurtosis. Iron-sensitive MRI metrics (R_2^* , magnetic susceptibility) correlate with DTI metrics (mean diffusivity and fractional anisotropy) within iron-rich grey matter nuclei in aging and disease [25–27]. The relationship may be related to an interaction between diffusion encoding gradients and the magnetic fields generated by iron deposits [28, 29] or it may be due to physiological changes associated with iron deposition. However, the effect of iron on diffusion kurtosis remains unknown.

The purpose of the present study was to explore the relationship between iron deposition and mean kurtosis values in subcortical grey matter. In a discovery cohort of younger and older adults, we assessed age group differences in iron-sensitive MRI metrics and MK in subcortical grey matter structures as well as in white matter tracts and then examined relationships between measures of iron and MK in subcortical grey matter structures. Relationships between iron-sensitive MRI metrics and MK were then repeated in a replication cohort of healthy older adults from the Alzheimer's Disease Neuroimaging Initiative database.

Methods

Discovery cohort

Participants

A cohort consisting of 110 older adults (65 female/45 male; mean age = 69.3 years $\pm$ 6.3 years; age range 60 years–87 years) and 63 younger adults (42 female/21 male; mean age = 20.2 years $\pm$ 2.0 years; age range

18 years–28 years) participated in this study. Each participant gave written informed consent prior to enrolling in the study as approved by the local institutional review board.

Structural acquisition and processing

Imaging data were acquired using a 3 T Siemens Prisma (Prisma, Siemens Healthineers, Malvern, PA). Excitation was performed using the body coil on the scanner and signal was received using a 32-channel receive only coil. Images from a T_1 -weighted MP-RAGE sequence [echo time (TE)/repetition time (TR)/inversion time = 3.02/2600/800 ms, flip angle = 8°, voxel size = $0.8 \times 0.8 \times 0.8$ mm³] were used for registration from subject space to common space. T_1 -weighted images were analyzed with FMRIB Software Library (FSL). A transformation was derived between individual subject space to MNI152 T_1 -weighted space using FMRIB's Linear Image Registration Tool (FLIRT) and FMRIB's Nonlinear Image Registration Tool (FNIRT) in the FSL software package [30, 31].

Diffusion acquisition and processing

Diffusion-weighted data were acquired using a spin-echo EPI with twice-refocused (bipolar) diffusion encoding gradients using the following parameters: TE/TR = 102/3500 ms, FOV = 212×182 mm², voxel size = $1.7 \times 1.7 \times 1.7$ mm³, 64 axial slices, six $b = 0$ images, multiband acceleration factor = 4, and adaptive combine was used to combine signals from each channel in the 32-channel head coil. Diffusion-weighting was applied in 64 directions per b value with two b values ($b = 1500$ s/mm² and $b = 3000$ s/mm²). Six $b = 0$ images with reversed phase encoding were acquired to correct for susceptibility distortions.

Diffusion data were denoised using dwidenoise in mrtrix [32], and then corrected for motion, eddy current, and susceptibility distortions using eddy in FSL [33]. Next, skull stripping of the T_1 -weighted image and susceptibility corrected $b = 0$ image was performed using the brain extraction tool in the FSL software package [34]. Mean diffusivity (MD) was estimated using dtifit in FSL and MK was estimated in DIPY [35]. The brain mask was dilated and the area outside the dilated brain mask was used to calculate the noise term in the signal-to-noise ratio (SNR) calculation for the $b = 3000$ s/mm² shell using the noise estimate from dwidenoise [36]. Signal from the skull and extracranial regions were excluded from SNR estimation, and each mask and signal histogram was inspected to confirm that the ROI did not include any high signal regions. Denoised images from the $b = 1500$ s/mm² and $b = 3000$ s/mm² as well as the mean SNR map across all images in the $b = 3000$ s/mm² shell for a younger participant and an older participant are shown in Supplementary Fig. S1.

Iron acquisition and processing

Multi-echo data were collected with a 6-echo 3D gradient recalled echo sequence: $TE_1/\Delta TE/TR = 4/6/40$ ms, $FOV = 192 \times 224$ mm², matrix size = $192 \times 224 \times 96$, and slice thickness = 1.7 mm. R_2^* was calculated from the magnitude data assuming a monoexponential decay. Susceptibility ($\Delta\chi$) maps were constructed from the phase maps using the following procedure. A brain mask was derived from the first echo of the magnitude data. Background phase was removed using harmonic phase removal using the Laplacian operator (iHARPERELLA) [37]. Susceptibility maps were then derived using an improved least-squares (iLSQR) method and Laplace filtering with a threshold of 0.04 as a truncation value. Susceptibility values were normalized to median susceptibility in the lateral ventricles. All susceptibility and R_2^* maps were processed in MATLAB (The MathWorks, Inc., Natick, MA, USA). The R_2^* and susceptibility maps were aligned to each subject's T_1 -weighted image using a rigid body transform derived via the magnitude image from the first echo.

Regions of interest

Globus pallidus, putamen, caudate nucleus, thalamus, and hippocampus regions of interest (ROIs) were defined using the Harvard–Oxford subcortical atlas and the dentate nucleus was defined using a previously published atlas [38]. Each atlas was transformed from standard space to native space, thresholded at a level of 60%, and binarized. MK, SNR, mean susceptibility, and mean R_2^* were measured in each grey matter ROI. White matter ROIs for the superior longitudinal fasciculus, forceps major, and forceps minor were defined using the Johns-Hopkins white matter atlas, and mean MK was measured in each ROI. For each ROI, voxels with MK values that were negative or greater than 4 were excluded.

Prediction of iron metrics from MK

To assess the relationship between MK and iron measures, support vector regression (SVR) was employed as a supervised learning approach. Prior to modeling, all variables were z -scored to ensure that each feature contributed equally to the prediction. SVR models were trained using a radial basis function kernel. Model training and hyperparameter optimization were performed using fivefold cross-validation, which partitions the data into five equally sized subsets: four folds were used to train the model, while the fifth served as the validation fold. This procedure was repeated five times, each time holding out a different fold, and the resulting coefficients of determination (R^2) scores were averaged to estimate model generalizability. Hyperparameters were tuned

using a grid search procedure. R^2 and the root-mean-squared error (RMSE) on a held-out test set (20% of the data) were reported to evaluate predictive performance. All SVR analyses were conducted using scikit-learn v1.6.1 in Python 3.7.

ADNI replication cohort

Database and participants

Data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) were used to replicate the observed relationship between iron metrics (R_2^* , magnetic susceptibility) and kurtosis. Up-to-date information can be found at www.adni-info.org. The ADNI study was approved by the local Institutional Review Boards of all participating sites. Study subjects and, if applicable, their legal representatives gave written informed consent at the time of enrollment for imaging data, genetic sample collection, and clinical questionnaires.

ADNI3 is a continuation of the ADNI project and the imaging protocol is updated for each ADNI substudy (ADNI1, ADNI2, and ADNI3). The ADNI3 MRI protocol contains multi-echo gradient echo and multi-shell diffusion acquisitions [39]. The ADNI3 database was queried for amyloid- β negative control participants scanned on a 3 T Siemens Prisma MRI scanner with T_1 -weighted, multi-shell diffusion MRI, and multi-echo gradient echo (2D-GRE) MRI images at the same scanning visit. From this cohort, we selected all individuals with a diagnostic status of control at the time of the visit, which included 72 control participants (48 female/24 male; mean age = 73.4 years $\pm$ 7.5 years; age range 56 years–90 years). Imaging data were downloaded between December 2019 and January 2024.

ADNI3 diffusion-weighted imaging (DWI) data were acquired with a multiband diffusion-weighted spin-echo EPI sequence ($TE/TR = 71/3400$ ms, field of view = 232×232 mm², voxel size = $2 \times 2 \times 2$ mm³, multiband acceleration factor = 3, and PA phase-encoding direction). Diffusion weighting was applied in 54 directions with b values of 1000 and 2000 s/mm². A two-echo 2D-GRE sequence ($TE_1/TE_2/TR = 4.92/7.38/571$ ms, flip angle = 60°, and voxel size = $3.0 \times 3.0 \times 3.0$ mm³) was used for correction of susceptibility distortion in the diffusion images. Iron-sensitive data were collected with a three-echo 2D-GRE sequence ($TE_1/\Delta TE/TR = 6/7/650$ ms, flip angle = 20°, field of view = 220×220 mm², matrix size of 256×256 , 44 slices, and slice thickness = 4.0 mm) and used for measurement of R_2 and magnetic susceptibility.

Image processing

Susceptibility images were processed as described in the previous sections. Diffusion data were first denoised [32]

and then corrected for motion and eddy currents using EDDY. Next, field maps were constructed and used to correct magnetic field inhomogeneities in the diffusion images using FUGUE as previously described [40]. Mean iron and kurtosis were extracted from each grey matter ROI as described above.

Statistics

All statistical analyses were performed using IBM SPSS Statistics software version 24 (IBM Corporation, Somers, NY, USA) and results are reported as mean $\pm$ standard deviation. A P value less than 0.05 was considered significant for all statistical tests. In the discovery cohort, age group differences were made using a 2 Group (younger, older) $\times$ 9 (subcortical grey matter and white matter) Region analysis of variance (ANOVA) for MK and separate 2 Group (younger, older) $\times$ 6 Region (subcortical grey matter) ANOVA for R_2^* and susceptibility. Significant interactions in the 2 Group (younger, older) $\times$ 9 (subcortical grey matter and white matter) Region ANOVAs were followed with post hoc between-group two-tailed t tests for each region.

Within older adult groups from both cohorts, relationships between age and both MK and iron (R_2^* and susceptibility) measures were assessed with separate Pearson correlations. These relationships were not assessed in younger adults due to their restricted age range. Within each age group from both cohorts, relationships between iron and MK, signal-to-noise ratio (SNR) and MK, as well as MK and MD in subcortical grey matter were assessed with separate Pearson correlations.

Results

Discovery cohort

Age group differences in MK

Maps of MK in each age group are shown in Fig. 1. Significant main effects of Group ($P < 10^{-3}$; $F = 90.4$) and region ($P < 10^{-3}$; $F = 790$) were seen in the 2 Group (younger, older) $\times$ 9 (subcortical grey matter and white matter) Region ANOVA. A significant interaction was observed between Group and Region ($P < 10^{-3}$; $F = 31.65$). Post hoc t tests revealed that the older adult group had higher MK than the younger group in the putamen ($P < 10^{-3}$), globus pallidus ($P = 0.002$), caudate nucleus ($P < 10^{-3}$), dentate nucleus ($P < 10^{-3}$), and hippocampus ($P < 10^{-3}$), but not in the thalamus ($P = 0.393$). In white matter ROIs, the older adult group had lower MK than the younger group in the superior longitudinal fasciculus ($P < 10^{-3}$), forceps major ($P = 0.011$), and forceps minor ($P < 10^{-3}$). These comparisons are shown in Figs. 2 and 3, and mean values for each group are summarized in Table 1.

Effects of age on MK in older adults

In subcortical grey matter structures of the older adult group, older age was correlated with lower MK in the globus pallidus ($r = -0.206$; $P = 0.033$), caudate nucleus ($r = -0.224$; $P = 0.020$), thalamus ($r = -0.264$; $P = 0.006$), and hippocampus ($r = -0.269$; $P = 0.005$). No significant correlations were observed in the putamen ($r = 0.082$;

Fig. 1 Group average images for mean diffusivity (first column) mean kurtosis (second column), R_2^* (third column), and susceptibility (fourth column) in younger (top row) and older (bottom row) participants. These images were created by transforming each participant's mean diffusivity, mean kurtosis, R_2^* map, or susceptibility map to Montreal Neurological Institute (MNI) common space and averaging within each group

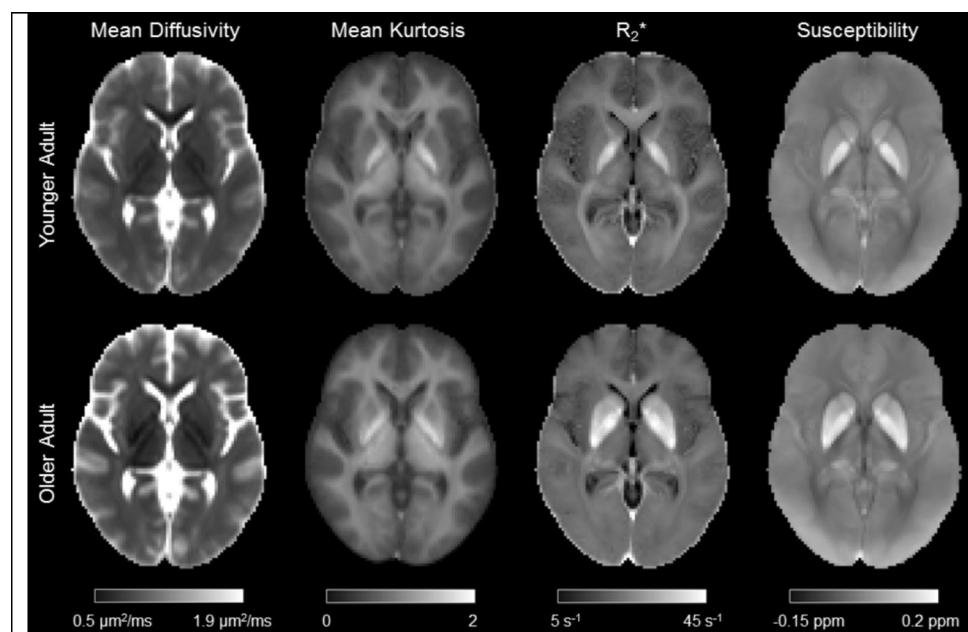


Fig. 2 Group comparisons of mean kurtosis (MK; shown in **A**), R_2^* (shown in **B**), and susceptibility (denoted $\Delta\chi$; shown in **C**) for all grey matter ROIs considered in this analysis

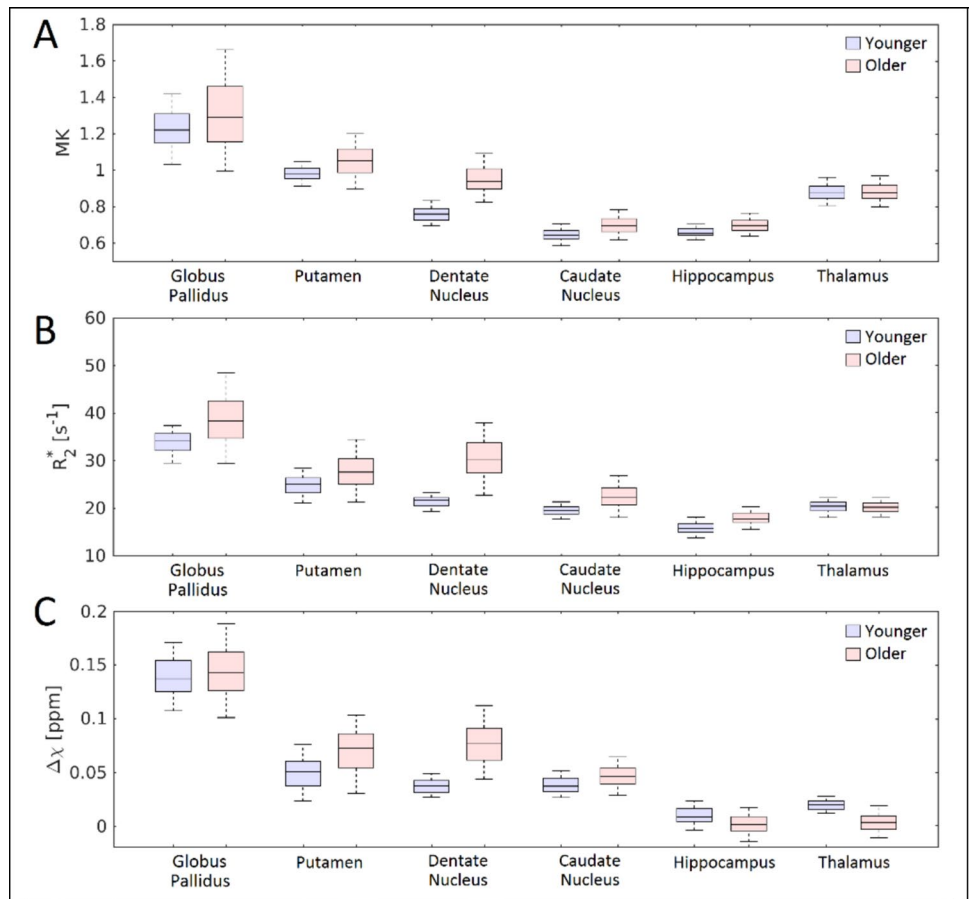
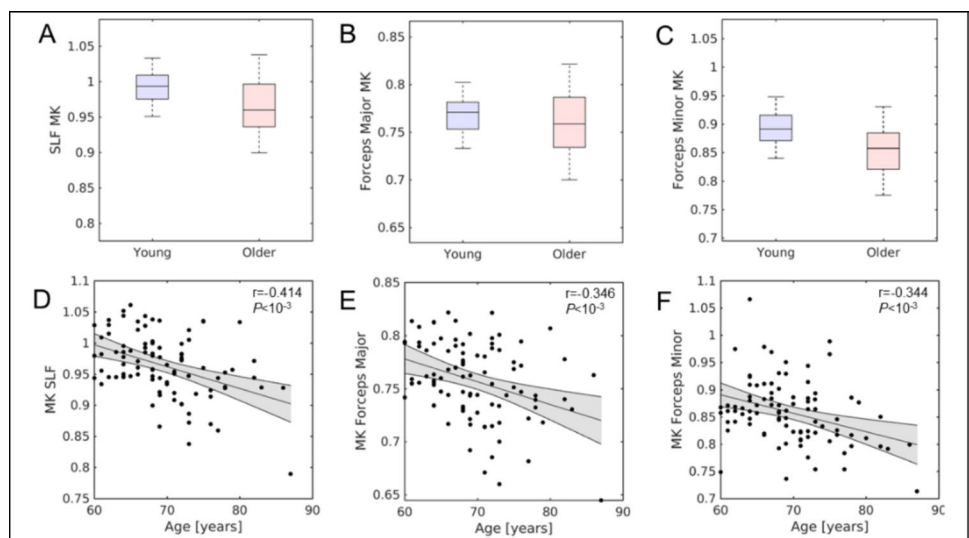


Fig. 3 Group comparisons of mean kurtosis in the superior longitudinal fasciculus, forceps major, and forceps minor are shown in the top row (**A–C**). Within older adults, associations between age and MK in these white matter tracts are shown in the bottom row (**D–F**). Significant correlations were seen between MK and age in each white matter tract ($P < 10^{-3}$)



$P = 0.401$) or dentate nucleus ($r = -0.145$; $P = 0.135$). In white matter tracts of the older adult group, older age was significantly associated with lower MK in the superior longitudinal fasciculus ($r = -0.442$; $P < 10^{-3}$), forceps major ($r = -0.339$; $P < 10^{-3}$), and forceps minor ($r = -0.370$; $P < 10^{-3}$).

Age group differences in iron

Maps of mean R_2^* and susceptibility in each age group are shown in Fig. 1. Significant main effects of Group ($P < 10^{-3}$; $F = 293.350$) and region ($P < 10^{-3}$; $F = 620.713$) were seen in the 2 Group (younger, older) $\times$ 6 (subcortical grey matter)

Table 1 Age group differences in mean kurtosis

	Younger adult	Older adult	<i>t</i> -statistic
Putamen MK	0.75 ± 0.05	0.95 ± 0.12	173
Globus pallidus MK	1.22 ± 0.12	1.31 ± 0.22	10.4
Caudate nucleus MK	0.64 ± 0.04	0.70 ± 0.06	44.3
Dentate nucleus MK	0.99 ± 0.06	1.06 ± 0.10	28.0
Thalamus MK	0.88 ± 0.05	0.89 ± 0.06	0.794
Hippocampus MK	0.66 ± 0.03	0.70 ± 0.04	33.9
Superior longitudinal fasciculus MK	0.99 ± 0.03	0.96 ± 0.05	-22.8
Forceps major MK	0.77 ± 0.03	0.75 ± 0.04	-6.5
Forceps minor MK	0.89 ± 0.04	0.85 ± 0.06	-20.5

Mean kurtosis values in subcortical grey matter regions of interest and white matter tracts

Data are presented as mean ± standard deviation

Post hoc *t* tests were used for group comparisons of MK in each ROI from which the *t*-statistics are shown

Bolded *t*-statistics denote statistically significant age group differences

Region ANOVA of R_2^* . A significant interaction between Group and Region was observed ($P < 10^{-3}$; $F = 36.437$). Post hoc *t* tests revealed that the older adult group had higher mean R_2^* than the younger group in the putamen ($P < 10^{-3}$), globus pallidus ($P < 10^{-3}$), caudate nucleus ($P < 10^{-3}$), dentate nucleus ($P < 10^{-3}$), and hippocampus ($P < 10^{-3}$), but not in the thalamus ($P = 0.568$).

Significant main effects of Group ($P < 10^{-3}$; $F = 80.2$) and region ($P < 10^{-3}$; $F = 11,123$) were seen in the 2 Group (younger, older) × 6 (subcortical grey matter) Region ANOVA of susceptibility. A significant interaction between Group and Region was observed ($P < 10^{-3}$; $F = 49.0$). Post hoc *t* tests revealed that the older adult group had higher mean susceptibility than the younger group in the putamen ($P < 10^{-3}$), globus pallidus ($P = 0.030$), caudate nucleus ($P < 10^{-3}$), and dentate nucleus ($P < 10^{-3}$). Lower susceptibility was observed in the thalamus ($P < 10^{-3}$) and hippocampus ($P < 10^{-3}$) of older adults relative to younger adults. These comparisons are shown in Fig. 2 and are summarized in Table 2.

Effects of age on iron in older adults

Older age was correlated with lower R_2^* in the caudate nucleus ($r = -0.292$; $P = 0.001$) and hippocampus ($r = -0.194$; $P = 0.044$). No significant correlations between age and R_2^* were observed in the putamen ($r = 0.064$; $P = 0.517$), globus pallidus ($r = 0.086$; $P = 0.383$), dentate nucleus ($r = -0.118$; $P = 0.230$), and thalamus ($r = -0.183$; $P = 0.061$). No significant correlations were seen between age and susceptibility in any grey matter ROI ($P_s > 0.061$).

Table 2 Age group differences in grey matter iron metrics

	Younger adult	Older adult	<i>t</i> -statistic
Putamen R_2^*	21.0 ± 1.4	30.7 ± 5.1	206
Globus pallidus R_2^*	33.9 ± 3.3	39.1 ± 5.7	41.5
Caudate nucleus R_2^*	19.2 ± 1.5	22.4 ± 3.6	43.6
Dentate nucleus R_2^*	24.4 ± 2.7	28.0 ± 4.2	34.3
Thalamus R_2^*	20.2 ± 1.2	20.1 ± 1.8	0.33
Hippocampus R_2^*	15.9 ± 1.5	17.8 ± 1.9	44.0
Putamen $\Delta\chi$	0.036 ± 0.009	0.080 ± 0.024	175.8
Globus pallidus $\Delta\chi$	0.138 ± 0.018	0.147 ± 0.028	4.82
Caudate nucleus $\Delta\chi$	0.037 ± 0.009	0.048 ± 0.015	25.7
Dentate nucleus $\Delta\chi$	0.048 ± 0.021	0.071 ± 0.024	37.3
Thalamus $\Delta\chi$	0.018 ± 0.006	0.004 ± 0.011	-78.5
Hippocampus $\Delta\chi$	0.009 ± 0.010	0.002 ± 0.011	-16.0

R_2^* and susceptibility, denoted $\Delta\chi$, values in subcortical grey matter regions of interest. Data are presented as mean ± standard deviation and units for R_2^* and $\Delta\chi$ are s^{-1} and ppm, respectively

Post hoc *t* tests were used for group comparisons of R_2^* in each ROI from which the *t*-statistics are shown

Bolded *t*-statistics denote statistically significant age group differences

Relationships between MK and diffusivity

In the older adult cohort, significant negative correlations were seen between MK and MD in the superior longitudinal fasciculus ($r = -0.834$; $P < 10^{-3}$), forceps major ($r = -0.713$; $P < 10^{-3}$), and forceps minor ($r = -0.712$; $P < 10^{-3}$) with higher MK related to lower MD. MK and MD were negatively correlated in the putamen ($r = -0.329$; $P < 10^{-3}$), globus pallidus ($r = -0.781$; $P < 10^{-3}$), and caudate nucleus ($r = -0.490$; $P < 10^{-3}$), dentate nucleus ($r = -0.580$; $P < 10^{-3}$), thalamus ($r = -0.314$; $P < 10^{-3}$), and hippocampus ($r = -0.412$; $P < 10^{-3}$). These correlations are shown in Fig. S2. Similar correlations were observed in each ROI in the younger adult cohort ($P_s < 10^{-3}$).

Relationships between MK and iron

In the older adult group, MK and R_2^* showed significant positive associations in all grey matter ROIs, including the putamen ($r = 0.702$; $P < 10^{-3}$), globus pallidus ($r = 0.475$; $P < 10^{-3}$), caudate nucleus ($r = 0.602$; $P < 10^{-3}$), dentate nucleus ($r = 0.667$; $P < 10^{-3}$), thalamus ($r = 0.202$; $P = 0.038$), and hippocampus ($r = 0.327$; $P = 0.001$). The MK- R_2^* correlations in the older adult group remained significant after controlling for age ($P_s < 0.027$). In the younger group, significant positive correlations were seen between MK and R_2^* in the putamen ($r = 0.366$; $P = 0.004$), globus pallidus ($r = 0.702$; $P < 10^{-3}$), caudate nucleus ($r = 0.289$; $P = 0.037$), dentate nucleus ($r = 0.654$; $P < 10^{-3}$),

thalamus ($r=0.265$; $P=0.043$), and hippocampus ($r=0.283$; $P=0.030$). These associations are plotted in Fig. 4.

In the older adult group, MK and susceptibility were significantly associated in the putamen ($r=0.606$; $P<10^{-3}$), globus pallidus ($r=0.473$; $P<10^{-3}$), caudate nucleus ($r=0.293$; $P=0.003$), dentate nucleus ($r=0.546$; $P<10^{-3}$), and thalamus ($r=0.276$; $P=0.004$). Controlling for age did not alter the significance of these correlations ($P_s>0.014$). No association was seen between susceptibility and MK in the hippocampus ($r=-0.327$; $P=0.001$). In the younger adult group, significant positive associations were seen between MK and susceptibility in the putamen ($r=0.366$; $P=-0.004$), globus pallidus ($r=0.827$; $P<10^{-3}$),

caudate nucleus ($r=0.292$; $P=0.025$), and dentate nucleus ($r=0.567$; $P<10^{-3}$) but no significant relationships between MK and susceptibility were seen in the thalamus ($r=0.208$; $P=0.115$) or hippocampus ($r=0.071$; $P=0.594$). These associations are plotted in Fig. 5.

Relationships between MK and SNR

In the older adult group, no significant associations were seen between SNR and MK in the putamen ($r=-0.176$; $P=0.075$), globus pallidus ($r=-0.057$; $P=0.567$), caudate nucleus ($r=-0.132$; $P=0.183$), dentate nucleus ($r=-0.181$; $P=0.067$), thalamus ($r=-0.121$; $P=0.222$),

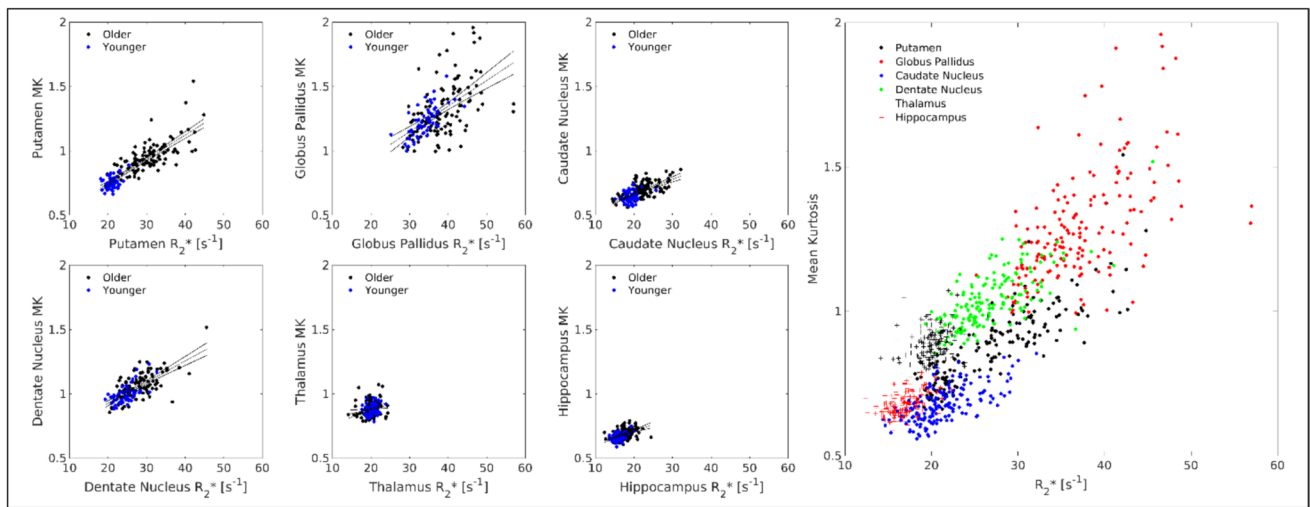


Fig. 4 Correlations between MK and R_2^* in the putamen (A), globus pallidus (B), caudate nucleus (C), dentate nucleus (D), thalamus (E), and hippocampus (F). The association between MK and R_2^* in all subcortical ROIs is shown in G

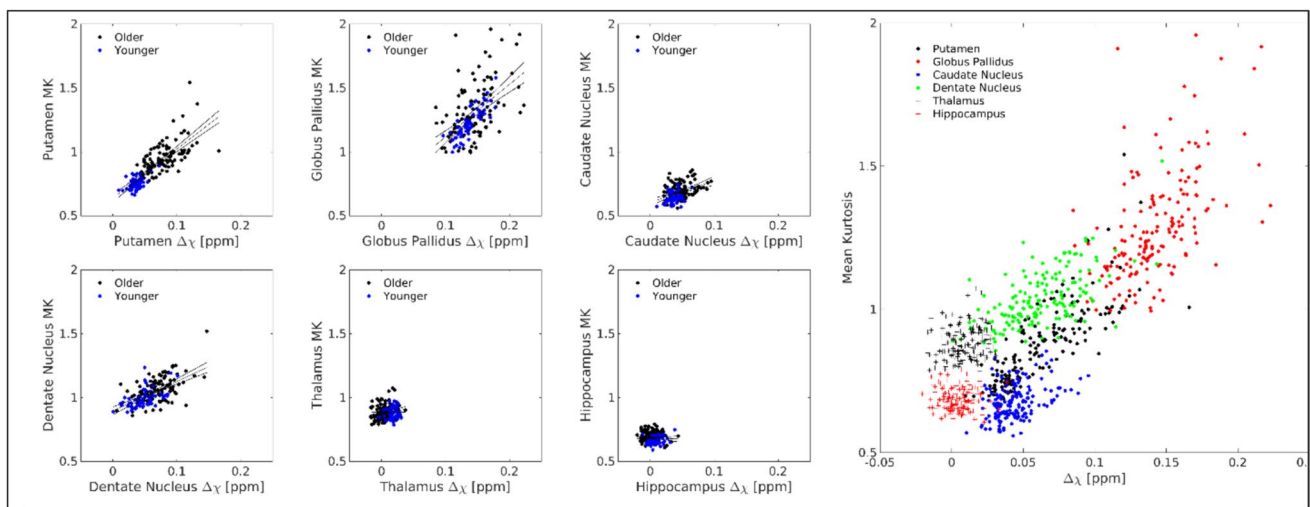


Fig. 5 Correlations between MK and susceptibility (denoted $\Delta\chi$) in the putamen (A), globus pallidus (B), caudate nucleus (C), dentate nucleus (D), thalamus (E), and hippocampus (F). The association between MK and susceptibility in all subcortical ROIs is shown in G

or hippocampus ($r = -0.109$; $P = 0.275$). Similarly, no significant associations were observed between SNR and MK in any ROI in the younger adult group ($P_s > 0.124$). These associations are plotted in Fig. 6.

Influence of denoising on MK

To assess whether the observed relationships between kurtosis and iron-sensitive measures (R_2^* , magnetic susceptibility) could be introduced or amplified by the denoising procedure, we repeated the analysis without applying denoising in the preprocessing pipeline. For each participant, diffusion data were spatially smoothed using a Gaussian kernel with a full width half maximum of 3.4 mm to improve SNR prior to the kurtosis calculation. The resulting correlations between kurtosis and iron measures were qualitatively similar to those reported in the main text. Significant correlations were seen between iron-sensitive measures and kurtosis in the putamen (R_2^* : $r = 0.720$, $P < 10^{-3}$; $\Delta\chi$: $r = 0.607$, $P < 10^{-3}$), globus pallidus (R_2^* : $r = 0.457$, $P < 10^{-3}$; $\Delta\chi$: $r = 0.484$, $P < 10^{-3}$), caudate nucleus (R_2^* : $r = 0.620$, $P < 10^{-3}$; $\Delta\chi$: $r = 0.243$, $P = 0.012$), dentate nucleus (R_2^* : $r = 0.542$, $P < 10^{-3}$; $\Delta\chi$: $r = 0.437$, $P < 10^{-3}$), and thalamus (R_2^* : $r = 0.229$, $P = 0.018$; $\Delta\chi$: $r = 0.243$, $P = 0.012$). In the hippocampus, MK was positively related to R_2^* ($r = 0.356$, $P < 10^{-3}$) but not magnetic susceptibility ($r = -0.059$, $P = 0.555$).

Prediction of iron metrics from MK

SVR models were developed to predict iron measures (R_2^* and $\Delta\chi$) from MK. Model predictions were compared across training and held-out test sets to assess performance. The R^2 and RMSE were computed for both iron measures. For

R_2^* , comparable performance across training ($R^2 = 0.809$; RMSE = 12.06) and test sets ($R^2 = 0.760$; RMSE = 11.20) was found, indicating that the SVR model generalized well and was not overfitting the training data. Similarly, for $\Delta\chi$, comparable performance across training ($R^2 = 0.782$; RMSE = 0.001) and test sets ($R^2 = 0.718$; RMSE = 0.001) was seen. Figure 7 depicts the relationship between predicted and actual target iron metrics on the test set.

Replication cohort

Effects of age on MK and iron

Significant correlations were seen between age and MK in the globus pallidus ($r = -0.352$; $P = 0.003$), caudate nucleus ($r = -0.380$; $P = 0.001$), dentate nucleus ($r = -0.234$; $P = 0.049$), thalamus ($r = -0.472$; $P < 10^{-3}$), and hippocampus ($r = -0.318$; $P = 0.008$) with higher age associated with

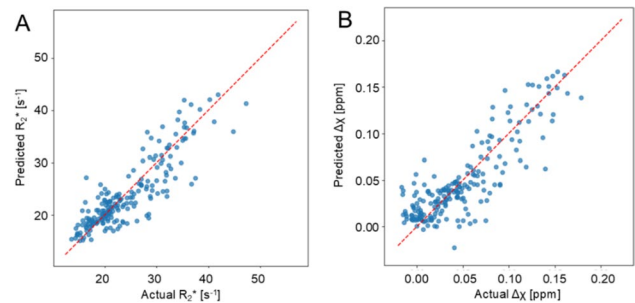


Fig. 7 The relationship between the actual and predicted R_2^* (shown in **A**) and $\Delta\chi$ (shown in **B**). A strong linear correspondence is seen between actual values and values predicted from MK for both R_2^* and $\Delta\chi$

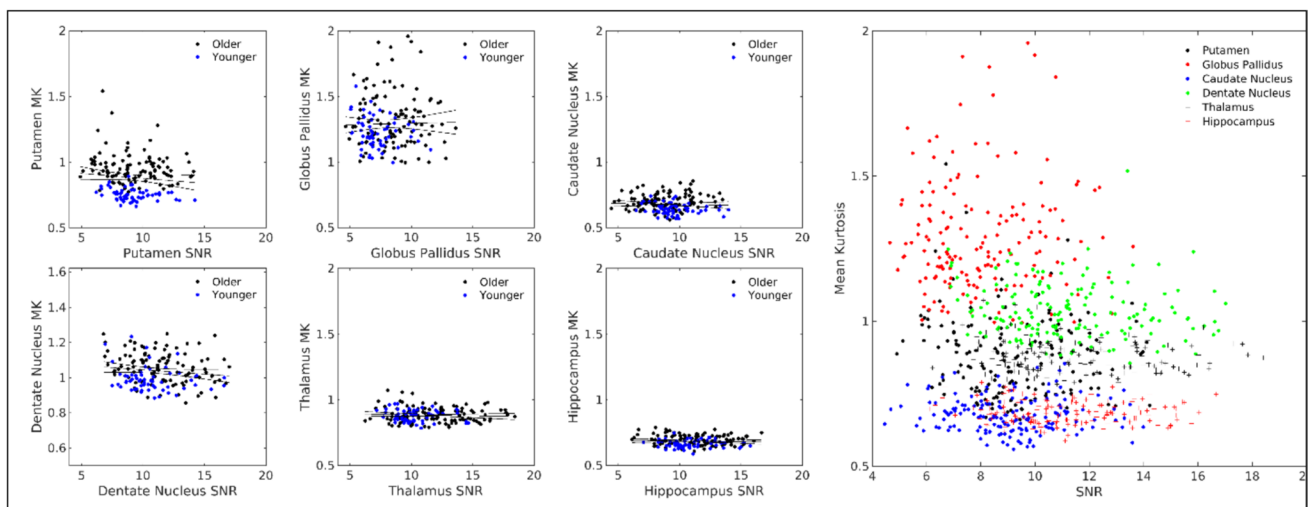


Fig. 6 Correlations between MK and SNR from the $b = 3000$ s/mm² shell in the putamen (**A**), globus pallidus (**B**), caudate nucleus (**C**), dentate nucleus (**D**), thalamus (**E**), and hippocampus (**F**). The association between MK and SNR in all subcortical ROIs is shown in **G**

lower MK. No association was observed between MK and age in the putamen ($r=0.135$; $P=0.266$). Older age was correlated with lower R_2^* ($r=-0.275$; $P=0.021$) and susceptibility ($r=-0.248$; $P=0.035$) in the caudate nucleus. Iron measures were not correlated with age in other grey matter ROIs ($P_s > 0.088$).

Relationships between MK and iron

MK and R_2^* were significantly positively associated in iron-rich grey matter ROIs, including the putamen ($r=0.504$; $P=0.007$), globus pallidus ($r=0.244$; $P=0.043$), caudate nucleus ($r=0.685$; $P < 10^{-3}$), and dentate nucleus ($r=0.331$; $P=0.005$). The MK- R_2^* correlations remained significant after controlling for age ($P_s < 0.042$). No association between MK and R_2^* was seen in the thalamus ($r=0.231$; $P=0.056$) or hippocampus ($r=-0.102$; $P=0.406$). Significant correlations were seen between MK and susceptibility in the putamen ($r=0.565$; $P < 10^{-3}$), globus pallidus ($r=0.309$; $P=0.010$), caudate nucleus ($r=0.480$; $P < 10^{-3}$), and dentate nucleus ($r=0.627$; $P < 10^{-3}$). No association was seen between MK and susceptibility in the thalamus ($r=0.120$; $P=0.330$) and hippocampus ($r=0.200$; $P=0.105$).

Discussion

This study examined how age affects MK in subcortical grey matter structures and in white matter tracts as well as investigated the relationship between MK and iron-sensitive MRI measures (R_2^* , magnetic susceptibility) in subcortical grey matter. In a discovery cohort, we found that age differentially affects MK in white matter and subcortical grey matter structures with lower white matter MK and higher grey matter MK in older relative to younger participants. Further, MK was significantly correlated with age in white matter tracts with lower MK associated with higher age. In subcortical iron-rich grey matter of older adults, both a discovery and replication cohort revealed that higher MK was significantly correlated to higher iron measures (R_2^* and magnetic susceptibility). Finally, denoising was not found to substantially change the observed correlations between MK and iron measures.

Postmortem studies in humans have found age-related reductions in white matter volume and fibers in older adults [16, 17]. These reductions should manifest as decreased MK [8, 18]. In agreement with this, we observed that older adults had, on average, lower MK in white matter tracts as compared to the younger adult group and a negative correlation between white matter tract MK and age in older adults. Prior imaging studies using DKI to examine age-related differences within white matter tracts found negative correlations

between MK and age [10–14], and our correlations between MK and age in the older adult group replicate these findings.

We observed age-related increases in MK of all subcortical grey matter nuclei except the thalamus when comparing younger and older adults in the discovery cohort, but age-related decreases in MK of all regions except the putamen within the older adult groups in both the discovery (globus pallidus, caudate nucleus, thalamus, and hippocampus) and ADNI (globus pallidus, caudate nucleus, thalamus, hippocampus, and dentate nucleus) cohorts. Few studies have used kurtosis to examine how aging affects subcortical grey matter. Our age group comparisons are in partial agreement with at least one earlier imaging study examining age effects in MK in subcortical grey matter nuclei over the adult lifespan (25 years–84 years), which found that age positively correlated with MK in the putamen [11]. However, whereas Gong, et al. [11] found that age negatively correlated with MK in the caudate nucleus, globus pallidus, and thalamus in their lifespan cohort, we only observed these age-related reductions in MK within our older samples. Taken together, our findings indicate that age effects in MK vary across nuclei and may change nonlinearly across the adult lifespan. Of note, MK values in white matter were comparable to those in iron-rich subcortical grey matter nuclei. This similarity may be due the small white matter bundles that permeate striatal nuclei [41–43] and this observation is consistent with an earlier study [41].

Histological and imaging studies have found that iron accrues in subcortical grey matter nuclei throughout life [21–24]. Consistent with these results, iron-sensitive MRI metrics were found to be elevated in older adults for all grey matter nuclei except for the thalamus ROI. Iron metrics were highly correlated in all iron-rich grey matter structures (Fig. S5). Iron deposition has been found to alter DTI metrics (mean diffusivity and fractional anisotropy) within iron-rich grey matter nuclei in aging and disease [25–27]. Consistent with these observations, we found negative correlations between iron metrics (R_2^* , magnetic susceptibility) and mean diffusivity in all iron-rich grey matter structures (relationships shown in Figs. S3, S4). Interestingly, MK was found to be correlated with iron measures in all subcortical grey matter nuclei in the older adult discovery cohort as well as in all iron-rich grey matter nuclei in the ADNI replication cohort. In the younger adult discovery cohort, MK was correlated with iron measures in all grey matter structures except the thalamus.

One interpretation of the observed elevated MK values in subcortical grey matter nuclei of older adults relative to younger adults is that age-related neuronal loss and expansion of the extracellular space may increase the relative contribution of anisotropic components from these fiber bundles. These changes may lead to greater microstructural heterogeneity and increase kurtosis in grey matter nuclei of

the older adult group. Alternatively, the elevated MK values in iron-rich subcortical grey matter may be due to the influence of iron. In both younger and older cohorts, structures with higher tissue R_2^* or susceptibility values had, on average, higher MK. Iron in subcortical grey matter is not uniformly distributed in tissue but is predominantly stored intracellularly within ferritin complexes [44]. Ferritin is the primary iron storage protein in the brain and contains several thousand ferric iron atoms per molecule [45], giving rise to nanoscale paramagnetic inclusions within cells and tissue microenvironments. While ferritin does not constitute a physical diffusion barrier, its spatially heterogeneous distribution generates local magnetic field perturbations [46, 47]. As water molecules diffuse through these fields, their phase accumulation becomes coupled to molecular motion, leading to deviations from a monoexponential signal decay. This coupling between diffusion and susceptibility can produce apparent non-Gaussian diffusion behavior, reflected in elevated kurtosis, even when the underlying molecular diffusion remains only weakly restricted.

The results presented here suggest that iron content is related to MK. This relationship may be problematic in interpreting MK differences in neurological conditions where iron is deposited. For example, in Parkinson's disease, iron deposition occurs alongside neuronal loss in the basal ganglia [48–51] and studies have found that MK is increased in the basal ganglia of populations with Parkinson's disease [19, 20]. The mechanism for these increases is unknown [19], since higher kurtosis values are thought to indicate more complex tissue microstructure [8, 18]. Given the relationship between R_2 , magnetic susceptibility, and MK presented here, the increases in MK may be related to iron deposition from pathology. However, additional studies are needed to confirm that the relationship holds in pathological populations.

This study is not without caveats. Older adults tend to have elevated iron levels as compared to younger adults [21–24] and this iron deposition will increase tissue R_2 , thereby reducing the SNR. One limitation in the calculation of MK is SNR and low SNR may positively bias MK [52, 53]. Here, we employed a denoising strategy to increase SNR [32] and mitigate the positive bias on MK. While no significant associations were observed between MK and SNR in any grey matter nuclei, we cannot rule out that noise biased MK values in the subcortical grey matter ROIs. Susceptibility values were normalized to median susceptibility in the lateral ventricles and ventricular enlargement may introduce bias.

We examined age-related differences in MK in two older adult cohorts using gradient strengths identical to those used in the HCP Lifespan ($b = 1500 \text{ s/mm}^2$ and $b = 3000 \text{ s/mm}^2$) and ADNI3 ($b = 1000 \text{ s/mm}^2$ and $b = 2000 \text{ s/mm}^2$) studies, and these results may aid in the

interpretation of MK differences due to age or pathology [39, 54]. We observed age-related increases in MK and iron measures (R_2^* and susceptibility) in iron-rich grey matter structures, but age-related reductions in MK in white matter. Significant correlations were seen between MK and iron measures (R_2^* and susceptibility) in iron-rich grey matter structures of a discovery cohort consisting of younger adults and older adults as well as in a replication cohort of older adult controls from the ADNI database. These findings indicate that higher MK may be related to iron content in iron-rich grey matter structures.

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Author contributions J.L. designed the study concept, analyzed data, and wrote the draft of the manuscript. K.S. collected data and contributed to the revisions of the manuscript. V.M. collected data and contributed to the revisions of the manuscript. M.S. performed analyses and contributed to revisions of the manuscript. I.B. designed the study concept and contributed to the revisions of the manuscript. X.H. designed the study concept and contributed to the revisions of the manuscript.

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Data availability The data in the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors report no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were performed in accordance with the ethical standards of the local Institutional Review Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent and Ethical Approval All participants in the study gave written informed consent in accordance with local institutional review board (IRB) regulations.

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