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Brain iron deposits are associated with general cognitive ability and cognitive aging

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Abstract

A novel analysis of magnetic resonance imaging (MRI) scans based on multispectral image fusion was used to quantify iron deposits in basal ganglia and microbleeds in 143 nondemented subjects of the generally healthy Lothian Birth Cohort, who were tested for general cognitive ability (intelligence) at mean ages of 11, 70, and 72 years. Possessing more iron deposits at age 72 was significantly associated with lower general cognitive ability at age 11, 70, and 72, explaining 4% to 9% of the variance. The relationships with old age general cognitive ability remained significant after controlling for childhood cognition, suggesting that iron deposits are related to lifetime cognitive decline. Most iron deposits were in the basal ganglia, with few microbleeds. While iron deposits in the general population have so far been dismissed in the literature, our results show substantial associations with cognitive functioning. The pattern of results suggests that iron deposits are not only a biomarker of general cognitive ability in old age and age-related cognitive decline, but that they are also related to the lifelong-stable trait of intelligence.

Keywords: Cognitive aging; Intelligence; General cognitive ability; Iron; Hemosiderin; Basal ganglia; Cognition; MRI

1. Introduction

Maintaining cognitive functions in old age is important in an aging society. Whereas some age-related cognitive decline is normative, there are large individual differences in its severity (Hedden and Gabrieli, 2004). At all ages, individuals who perform better on 1 type of cognitive ability test tend also to perform above average in a broad variety of other types of cognitive ability tests. Underlying this is a common factor of general cognitive ability (also called general intelligence or "*g*") that explains about 50% of the individual differences in the performance of diverse cognitive tests and is largely equivalent to the intelligence quotient (IQ) that broad cognitive batteries provide (Deary et al., 2010; Jensen, 1998; Jung and Haier, 2007). Normative (nonpathological) age-related cognitive decline tends to mostly affect this common factor and, to a lesser extent, the unique variance of some specific cognitive abilities (Salthouse and Czaja, 2000).

The biological factors underlying normal cognitive aging have been nominated as a priority for public health research

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(Deary et al., 2009), yet they remain largely unclear. Cerebral small vessel dysfunction may explain some age-related cognitive decline (Waldstein et al., 2001). Most studies of vascular dysfunction and cognition have focused on white matter lesions seen on brain imaging, but their effect appears to be modest (Frisoni et al., 2007). There are other important markers of small vessel impairment, such as brain microbleeds. These are increased in individuals with cerebral small vessel disease, but are also found in about 5% of otherwise healthy older adults (Cordonnier et al., 2007). Microbleeds are small focal microhemorrhages that leave residual iron deposits (IDs), mainly as the insoluble oxyhydroxide of hemosiderin, in lobar white matter, the basal ganglia, and internal capsule (Casanova and Araque, 2003; Cordo—nnier et al., 2007; Harder et al., 2008). Microbleeds appear as hypointense round dots on T2*-weighted magnetic resonance imaging (MRI) scans and are associated with hypertension, amyloid angiopathy, future risk of stroke and, when frequent, with cognitive impairment (Cordonnier et al., 2007). Other forms of IDs also appear in the basal ganglia where the lenticulostriate arteries enter the brain substance. These basal ganglia IDs increase in prevalence and extent with increasing age, correspond with increased attenuation on computed tomography (CT) scanning and hence were assumed to be calcium. Basal ganglia IDs are generally regarded as asymptomatic physiological consequences of aging, and consequently, unless present to a severe degree, have been ignored (Bartzokis et al., 2007; Casanova and Araque, 2003). However, detailed histopathology shows that these mineral deposits are closely related to small blood vessels and show staining properties predominantly of iron, although a small proportion of calcium may be present (Casanova and Araque, 2003; Slager and Wagner, 1956; Yao et al., 2009). Their association with aging differences in the normal range has rarely been studied (Bartzokis et al., 2007) and relationships with cognitive differences have so far only been tested for a few specific cognitive tasks in 2 rather exploratory samples (Pujol et al., 1992; Sullivan et al., 2009). Reports of relationships between IDs and differences in normal cognitive aging — a potential precursor of and contributor to pathological cognitive decline (Hedden and Gabrieli, 2004) — are absent from the literature. We tested the potential role of accumulated brain IDs as a biomarker of lower normal range general cognitive ability and age-related cognitive decline in a healthy elderly cohort on whom childhood general cognitive ability scores were available.

2. Methods

2.1. Subjects

The sample of this study was composed of 147 members of the Lothian Birth Cohort (1936; Deary et al., 2007). Four participants were excluded from further analyses because they showed signs of dementia or minor cognitive impairment (self-reported medical history and/or Mini Mental State Examination [Folstein et al., 1975] scores below 24). Thus the size of the final sample was 143 (74 women, 69 men). Unique advantages of this sample are the availability of cognitive test scores over a period of more than 6 decades (see below) and a very narrow age range (71 to 72 years; mean, 71.9; SD, 0.3), which is desirable for studies of individual differences in cognitive aging (Hofer and Sliwinski, 2001). Their years of full-time education ranged between 9 and 20, with the average and median being 11.0 years (SD, 1.4 years). All were Caucasian and lived independently in the community. Written informed consent was obtained from all participants under protocols approved by the National Health Service ethic committees (MREC and LREC).

2.2. Neuroimaging

Brain images were obtained at age 72 from a GE Signa LX 1.5 T MRI clinical scanner using a self-shielding gradient set with maximum gradient strength of 33 mT/m, and an 8-channel head array coil in the SFC Brain Imaging Research Centre, University of Edinburgh (www.sbirc.ed.ac.uk). The relaxation and echo times (TR and TE) of the sequences scanned for each image modality were 9.8/4 ms for T1-weighted (T1W), 11,320/104.9 ms for T2-weighted (T2W), 940/15 ms for T2*-weighted (T2* W) and 9,002/147.38 ms for fluid-attenuated inversion recovery (FLAIR) images.

2.3. Cognitive testing

The participants underwent cognitive testing at 3 time points. General cognitive ability was assessed at all 3 time points using 2 different measures: First, the Moray House Test number 12 (MHT), a measure of general cognitive ability or IQ, had been administered when participants were 11 years old as part of the Scottish Mental Survey of 1947 (Scottish Council for Research in Education, 1949). The same test was readministered in this sample during a follow-up at a mean age of almost 70 years, using the same instructions and the same 45-minute time limit. The psychometric quality of the MHT has been established by Deary et al. (2004). Second, at a further follow-up at a mean age of 72 years, 6 subtests from the Wechsler Adult Intelligence Scale — Wais-III^{UK} — were administered: Symbol Search, Digit Symbol, Matrix Reasoning, Letter-Number Sequencing, Digit Span Backwards, and Block Design (Wechsler, 1998). Only the first unrotated principal component was extracted from these 6 subtests. It explained 48.9% of the variance, with all 6 subtests showing strong loadings between 0.63 and 0.76, and is interpreted as the general cognitive ability factor, which is well established in the psychometric literature (Deary et al., 2010; Jensen, 1998). In addition, the participants completed 2 reading recognition tests as measures of prior or premorbid general cognitive ability at age 72, the National Adult Reading Test

Table 1
Means, standard deviations, and test statistics for gender differences for the general cognitive ability measures

	Men		Women		Gender differences		
	Mean	SD	Mean	SD	$t(141)$	p	D
Age11 IQ (MHT)	100.23	16.65	103.33	11.30	1.26	0.21	0.22
Age 70 IQ (MHT)	101.11	13.10	101.15	10.75	0.02	0.99	0.00
WAIS-III^{UK} subtests							
Symbol search	24.70	6.36	26.09	6.48	1.30	0.20	0.22
Digit symbol coding	55.32	13.39	61.78	13.86	2.83	0.005	0.47
Matrix reasoning	14.61	4.78	12.74	4.96	2.29	0.024	0.38
Letter-number sequencing	11.14	3.05	10.81	2.56	0.71	0.48	0.12
Digit span backwards	7.70	2.30	8.14	2.23	1.16	0.25	0.19
Block design	36.61	10.00	33.26	9.03	2.11	0.037	0.35
NART	34.13	8.55	35.46	7.23	1.01	0.32	0.17
WTAR	41.57	6.10	41.92	5.63	0.35	0.72	0.06

Key: IQ, intelligence quotient; MHT, Moray House Test; NART, National Adult Reading Test; WAIS-III^{UK}, Wechsler Adult Intelligence Scale III, UK edition; WTAR, Wechsler Test of Adult Reading.

(NART; Nelson and Willison, 1991) and the Wechsler Test of Adult Reading (WTAR; Holdnack, 2001). For descriptive statistics of all cognitive measures, see Table 1.

2.4. Segmentation and quantification of iron deposits

There are qualitative rating scales for microbleeds (Cordonnier et al., 2009), but not for basal ganglia IDs, nor any reliable automated method to identify and quantify iron/mineral deposits on structural MRI. Therefore, we developed and validated an image analysis approach to quantify the volume of IDs using the different sensitivities of T2* W, FLAIR, and T1W imaging in combination to distinguish iron from calcium (Fig. 1). The technique developed is based on multispectral image fusion. It is applicable after selecting, by visual inspection, the magnetic resonance (MR) protocols that provide good separability for the pathology of interest, in this case IDs including brain microbleeds (BMBs). The first step was to select 2 MR sequences that reflect the different range of intensities for the tissue features to be segmented. Fig. 2 shows a section of axial T2* W and FLAIR images in a representative subject, with, from left to right: T2* W, T2* W fused with FLAIR mapped in the red/green color space, and the FLAIR image. A BMB is circled. Visual inspection of the different image contrasts available in this study revealed that the colored combination of T2* W/FLAIR is optimal for identifying IDs (where they appear green in color).

The absence of low signal on T1W images appears to differentiate pure calcium deposits from IDs (Brass et al., 2006, Fig. 3). T1W images appear to be insensitive to calcium and thus help differentiate iron mineral deposits with and without calcium (Brass et al., 2006). Thus, when IDs are not associated with calcification, fusions based on T1W images do not provide sufficient contrast to segment the IDs. Compare Fig. 3 (without) and Fig. 4 (with calcification). Fig. 4 shows 1 slice including a mineralized basal ganglia. The presence of calcium does not change the color in which the ID areas are identified in the colored combination of T2* W and FLAIR because both iron and calcium appear as low intensity signals in T2* W and low contrast areas of medium intensity in FLAIR images. But the presence of calcium has an opposing effect on T1W signal intensity to that of iron, and therefore alters the darkness of the areas that contain both minerals in these sequences (Brass et al., 2006).

After selecting either set of 2 sequences, we registered the axial volumes using the affine linear registration tool FLIRT (Jenkinson et al., 2002). In order to transform the registered volumes into a color space, we selected the hue, saturation, and value color space to represent the modulation in red and green colors — in an angle of 120° — and fused them to obtain a volume in the red/green color subspace. To guarantee that both images have good contrast, we equalized the contrast of the images prior to their fusion using Analyze 8.1 (Analyzedirect.com, Rochester, Minnesota).

The next step was to remove the skull and extract the brain. For this, we used the Object Extraction Tool in Analyze 8.1, which applies thresholding, morphological erosion, dilation, and region growing steps. T2* W images were used to obtain the brain mask and extract the brain of the fused volume, because they offer the best contrast between brain and background, and display better integrity of the brain tissue with the cerebrospinal fluid (CSF).

To segment and quantify ID volumes, a minimum variance quantization (MVQ) algorithm using Floyd-Steinberg's error diffusion dither (Floyd and Steinberg, 1976) was applied. It converted the fused red/green sequence into a clustered sequence with 32 levels in the same red/green color space. During the clinical validation of this method, the effect of changing the number of clusters in the MVQ algorithm was tested, and it was demonstrated that, for this technique, the segmentation achieves very high levels of reliability and repeatability with 32 clusters (Valdés Hernández et al., 2010). The clusters that correspond to each tissue type were selected by mapping them in a normalized graph of the red/green space and visually determining the range of green that best identifies the iron areas.

Fig. 1. Three cases (a, b, c) illustrating different types of iron deposits (IDs). First column: axial slice of a volume obtained from modulating T2*-weighted (T2* W) and fluid-attenuated inversion recovery (FLAIR) to the red and green frequency bands of the visible spectrum, respectively, and then their fusion after spatial registration. Second column: ID masked in blue on a section of the first column image after extracting cerebrospinal fluid. Third column: corresponding sections in T2* W (above) and T1-weighted (T1W; below) for each case. Case (a) shows basal ganglia IDs with calcium. Case (b) shows basal ganglia IDs without calcium. Case (c) shows small basal ganglia IDs with calcium and a microbleed in the left thalamus. Note that areas containing calcium appear hypointense on T1W, while areas with only hemosiderin deposits are undetected; all areas that contain calcium deposits (note the left choroid plexus in case [a]) or iron are hypointense on T2* W.

We named this technique MCMxxxVI (see supplementary Fig. 1). This stands for Multispectral Coloring Modulation and Variance Identification, and incorporates the number "1936" represented in roman numerals, reflecting our study sample, the Lothian Birth Cohort (1936; Deary et al., 2007). A detailed derivation of this technique, clinical validation results, and its comparison with the commonly used thresholding technique can be found in Valdés Hernández et al. (2010).

This technique does not discriminate between different types of iron content. As a result, some vessels may appear selected in the automatic segmentation process. For this reason, a postprocessing manual step to remove the areas not considered to contain IDs and BMBs was required.

In the absence of an established and validated visual method for quantifying brain IDs in addition to BMBs, we developed a simple visual rating scale to categorize the putaminal IDs, from none (0) to medium-high (4), based on comparison with 4 standard cases (Fig. 5). This provided a simple method for describing the population that could be used to relate our population to those in other studies, in the absence of any previous standardization of brain iron volume.

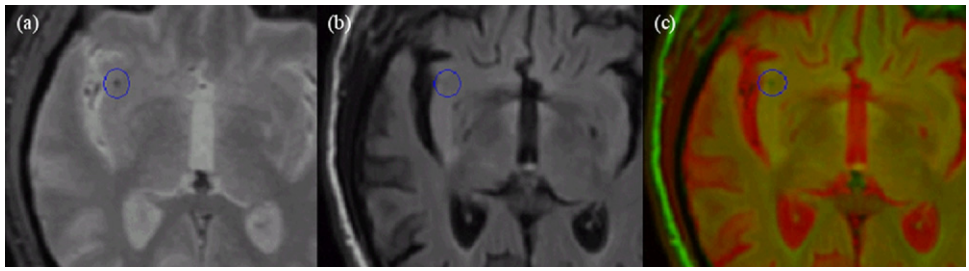

Fig. 2. Section of an axial slice of a subject displaying the registration and color fusion (c) of (a) T2*-weighted (T2* W) and (b) fluid-attenuated inversion recovery (FLAIR) images, with a brain microbleed circled in the subcortical white matter located in the right insula.

2.5. Extraction of brain tissue and intracranial volume

The same technique described above was used to extract the brain tissue volume, using a combination of T1W and T2W image sequences to extract CSF (appearing red in the fused image). Once the CSF was segmented, subtracting the CSF volume mask from the mask of the whole intracranial cavity yielded the brain tissue volume mask, which quantitatively constitutes the brain tissue volume. The boundary for the intracranial volume was considered in the foramen magnum, below the edge of the cerebellum tonsils.

2.6. Statistical analyses

Age in days was statistically controlled in all analyses. The effective sample size varied slightly across analyses (between 130 and 143) due to missing cognitive data.

For all reported analyses, the total iron volume for each subject was standardized to the brain volume to derive the percentage of IDs in brain tissue. Iron volumes standardized to intracranial volume yielded virtually identical results, presumably because atrophy did not play a major role in this healthy, community-dwelling sample. Because the percentage of IDs was half-normal distributed in our sample (see below), we used Tobit regressions (Baba, 1990; Tobin, 1958) with IDs as the dependent variable to calculate censored correlations with the cognitive measures.

3. Results

About half (50.30%) of our healthy, elderly sample showed detectable IDs, spreading over a wide range and forming up to 0.55% of the total brain tissue, mostly as basal ganglia IDs associated with the perforating arteries; being a largely healthy older cohort, few subjects had microbleeds. In line with a previous report (Bartzokis et al., 2007), men showed a higher incidence (55.07% vs. 45.95%) and degree (percentage in brain tissue) of IDs than women, though neither gender difference was statistically significant (both, $p > 0.27$). Also, all associations of IDs with cognitive variables did not differ significantly between the genders, which is why we report them for both genders combined, controlling for gender. Gender differences for all cognitive ability measures are shown in Table 1.

Compared with the group without detectable IDs ($n = 71$), those with IDs at age 72 ($n = 72$) had significantly lower general cognitive ability at age 70 ($t[138] = 2.04$ [2-tailed]; $p = 0.043$; D = 0.35), and age 72 ($t[141] = 3.63$ [2-tailed], $p = 0.0004$; D = 0.61), but not at age 11 ($t[133] = 1.31$ [2-tailed]; $p = 0.19$; D = 0.23). Censored correlations, including the entire sample and treating IDs as a continuous variable, revealed that higher IQ measured at age 11 was significantly associated with having fewer IDs at age 72 ($r = -0.19$; $p = 0.0324$; 95% confidence interval [CI], −0.36 to −0.02). Two reading recognition tests that are considered valid estimates of prior or premorbid general cognitive ability (Crawford et al., 2001; Holdnack, 2001; Nelson and Willison, 1991) showed significant negative associations with IDs, with similar effect sizes as the one found for childhood IQ (NART: $r = -0.18$; $p = 0.0253$; 95% CI, −0.34 to −0.02; WTAR: $r = -0.18$; $p = 0.0273$; 95% CI, −0.33 to −0.02), thus supporting this finding.

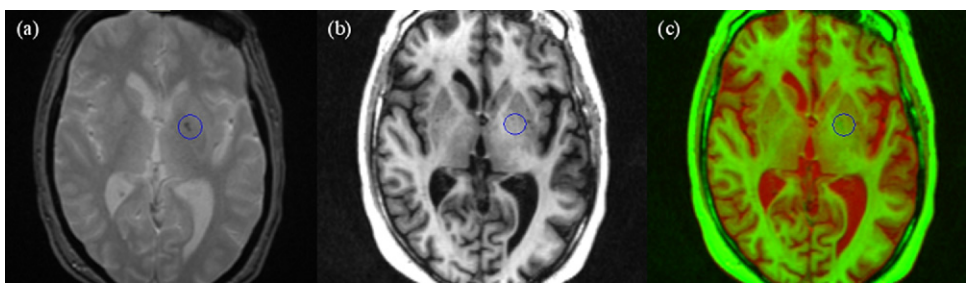

Fig. 3. Example case with iron deposition but without calcium (circle). Axial slice showing the registration and color fusion results of (a) T2*-weighted (T2* W) and (b) T1-weighted (T1W) images. (c) The fused T2* W and T1W map does not show any color change to indicate mineral deposition (cf. Fig. 4).

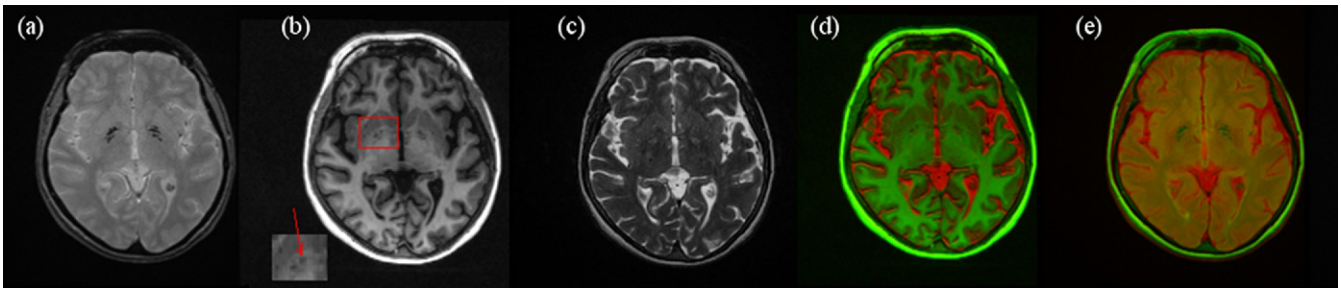

Fig. 4. Example case with iron deposition with calcium. Central axial slice of a subject displaying from left to right: (a) T2*-weighted (T2* W), (b) T1-weighted (T1W), (c) T2-weighted (T2W), and (d) the registration and fusion results of T2W and T1W, and (e) T2* W and fluid-attenuated inversion recovery (FLAIR) images. The low signal on the T1W image (b) indicates that calcium is present as well as iron (inset).

Furthermore, more IDs were significantly associated with lower general cognitive ability at ages 70 ($r = -0.27$; $p = 0.0015$; 95% CI, −0.44 to −0.10) and 72 ($r = -0.31$; $p < 0.0001$; 95% CI, −0.46 to −0.15). These continuous associations indicate a dose-response relationship between IDs and general cognitive ability. The effect of the relationships between IDs and general cognitive ability measured in old age remained substantial in size and significant after adjusting for age 11 IQ in the analyses (Table 2). This key result effectively means that more IDs are associated with greater relative cognitive decline between age 11 and old age. The associations were largely unchanged (data not shown) after excluding any potentially undetected cases of early dementia by rerunning all analyses excluding participants with scores 1 SD below the mean on the Wechsler Memory Scale-III logical memory test, which is a more sensitive criterion than the Mini Mental State Examination (MMSE). Further analyses (supplementary results) showed that the relationship with IDs was significant for 5 of the 6 cognitive subtests that constitute the general cognitive ability factor before age 11 IQ was controlled, and for 4 of the 6 tests after it was controlled. No significant relationships were found for more specific cognitive measures of information processing speed, memory, or verbal fluency, as assessed by additional cognitive measures described in the Supplements.

To illustrate the nature of the central findings, Fig. 6 depicts the scatter plots of IDs with general cognitive ability at ages 11, 70, and 72 (panel a), as well as general cognitive ability at ages 70 and 72 after adjusting for general cognitive ability at age 11, indicating age-related cognitive decline (panel b). The lines are derived from linear regression analyses, and they show that, even though many subjects had low amounts of IDs and thus clustering on the extreme left side of each scatter plot (i.e., reflecting the censored nature of the ID data), there was a clear linear trend of decreasing general cognitive ability and accelerated cognitive decline with more IDs in every analysis.

4. Discussion

Our results showed a negative association of IDs with both general cognitive ability and successful cognitive aging in a healthy elderly cohort, accounting for 4%–9% of the variance. IDs in individuals with normal cognitive functions have so far been dismissed in the literature, but our results showed substantial associations with cognitive functioning in early as well as late life, especially compared with other existing biomarkers of cognitive aging (Cordonnier et al., 2007; Deary et al., 2009; Frisoni et al., 2007; Hedden and Gabrieli, 2004). Because histopathological studies suggest that increased basal ganglia attenuation on computed to-

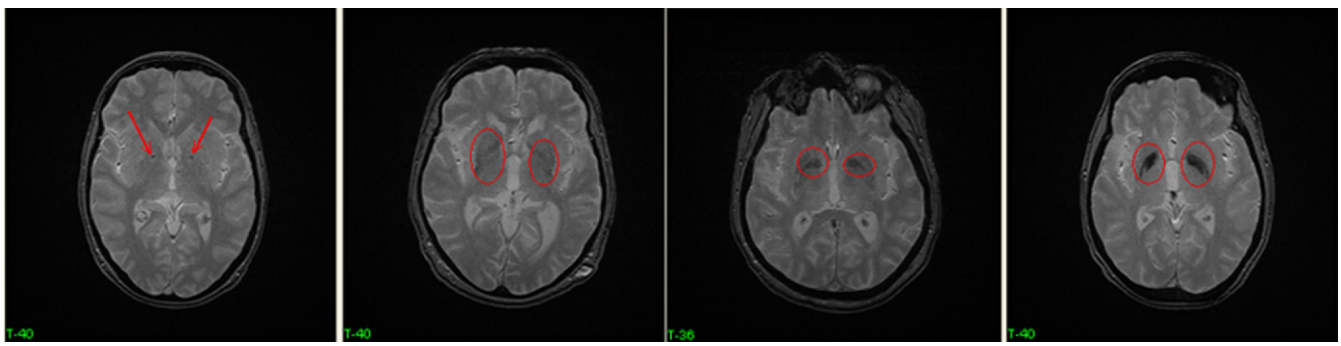

Fig. 5. Examples to illustrate the 4 groups of iron deposits in the basal ganglia in T2*-weighted (T2* W) images. From left to right: 1 (none) to 4 (medium-high), denoting increasing putaminal iron deposits.

Table 2
Censored (tobit) correlations between brain iron deposits and indicators of general cognitive ability and cognitive aging

	Percentage of iron deposits in brain tissue	Percentage of iron deposits in brain tissue, with age 11 IQ controlled[a]
Age 11 IQ	−0.19 (−0.36 to −0.02)	—
Age 70 IQ	−0.27 (−0.44 to −0.10)	−0.18 (−0.36 to 0.00)
Age 72 general cognitive ability factor	−0.31 (−0.46 to −0.15)	−0.25 (−0.41 to −0.09)

95% confidence intervals shown in parentheses. All coefficients are fully standardized. Age in days at cognitive testing and gender are controlled in all analyses.

Key: IDs, iron deposits; IQ, intelligence quotient.

[a] By adjusting for IQ at age 11, this means the coefficients in this column effectively represent the association between IDs and relative cognitive change between childhood and old age.

mography scan is mostly due to IDs rather than to calcification (Brass et al., 2006; Casanova and Araque, 2003; Slager and Wagner, 1956; Yao et al., 2009), these attenuations might also be a marker for cognitive decline. The association of IDs late in life with age 11 general cognitive ability indicates that IDs are not simply related to general cognitive ability in old age, but are at least partly related to the lifelong-stable trait of general cognitive ability (Deary et al., 2004). This means that either early life general cognitive ability leads to lifestyle differences that influence the amount of iron deposited in the brain between childhood and old age, and/or that both are indicators of vascular frailty that is already present early in life and increases in old age. That the relationships with old age general cognitive ability remained significant after controlling for childhood general cognitive ability as measured by the same validated test (Deary et al., 2007) (which can be understood as the individual baseline for eventual cognitive decline), and after excluding subjects who might have early dementia not detected by the Mini Mental State Examination, suggests that IDs are a biomarker of age-related cognitive decline in people without signs of dementia, beyond any association of IDs with lifelong-stable general cognitive ability differences. These associations with cognitive aging might be due to the link between IDs and microangiopathy, or alternatively perhaps due to a frequent co-occurence of IDs in astroglia, oxidative stress, and mitrochondrial insufficiency (Schipper, 2004). However, all these mechanistic interpretations must be regarded as speculative at this stage and further studies are clearly warranted.

Our study is in agreement with the few earlier reports of associations of specific cognitive tasks with IDs in the basal ganglia (Pujol et al., 1992; Sullivan et al., 2009) and BMBs (Cordonnier et al., 2007). Compared with these studies, the current 1 stands out in that we carefully assessed general cognitive ability — the variable that has been shown to be most important for differences in normal cognition and cognitive aging in the psychometric literature (Deary et al., 2009, 2010; Jensen, 1998; Salthouse and Czaja, 2000) — in a longitudinal design spanning over 6 decades and based on a large cohort with narrow age range, which is the preferable design for differential aging studies (Hofer and Sliwinski, 2001). While the availability of childhood general cognitive ability data in an elderly sample might be rather unique to our study, our results suggest that reading recognition tests are a valid substitute in this context. Gender differences in IDs that have been found in 1 study (Bartzokis et al., 2007) received only weak support in our sample and do not appear to affect relations with cognitive differences.

We applied a novel, semiautomated procedure that can provide a detailed picture of brain IDs. Initial validations for its accuracy of brain volume measurement, of white matter lesion volume measurement, and of IDs has been undertaken and show it can accurately segment white matter lesions (Valdés Hernández et al., 2010). However, more testing in different patient cohorts with focal lesions as well as more diffuse abnormalities will be required for the full evaluation of the method.

Other limitations include that we were unable to separate BMBs from IDs and that we have not examined other factors potentially coassociated with cognitive aging (e.g., white matter lesions), because a larger sample will be required to adjust for these factors. However, in this healthy sample few subjects had many white matter lesions. The results found in this generally healthy sample might also not extend to patients with conditions like stroke or dementia.

The current study suggests that, rather than being unimportant physiological features of no pathological consequence, IDs (including microbleeds) might in fact be markers of small vessel dysfunction and thus provide further evidence of the importance of the vascular-brain interface in maintaining normal brain function. Other lifetime associations remain to be tested, but the association of IDs with early life general cognitive ability suggests that early life vascular status is important for lifelong wellbeing. Further studies in different populations are required to confirm these findings and examine the correlations between IDs and cognition in patients with small vessel stroke, or dementia, and at different ages.

Disclosure statement

The authors have no actual or potential conflicts of interest to report.

Written informed consent was obtained from all participants under protocols approved by the National Health Service ethic committees (MREC and LREC).

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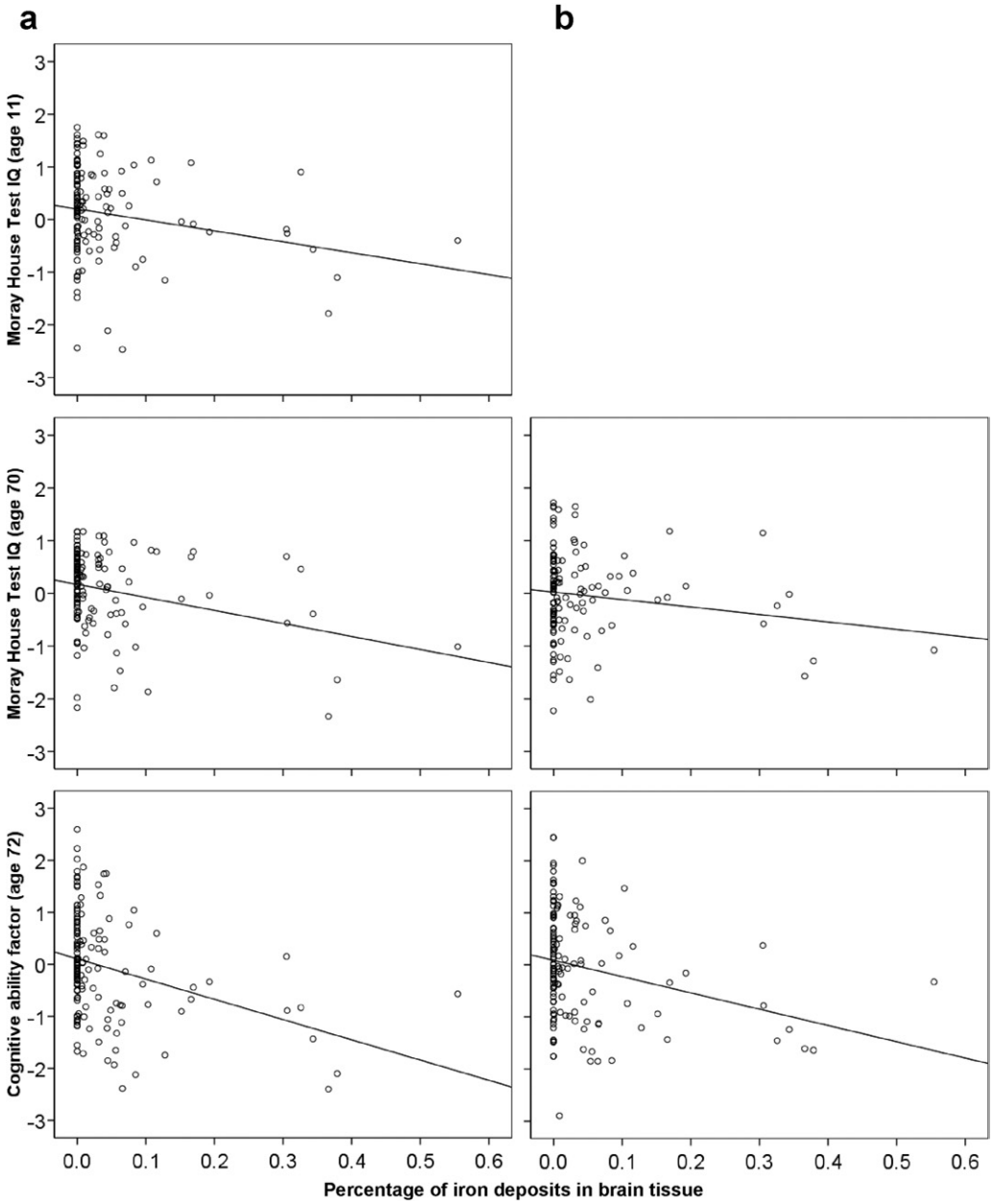

Fig. 6. Scatter plots of the percentage of iron deposits on general cognitive ability. Panel (a) shows the relationship of iron deposits (IDs) with intelligence quotient (IQ) at age 11 and 70 as well as the general cognitive ability factor at age 72. Panel (b) shows the same relationships for old age general cognitive ability after controlling for childhood (age 11) IQ. Lines are derived from linear regressions.

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Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2010.04.032.

Table S1
Censored (tobit) correlations of brain iron deposits with the individual tests that constitute the general cognitive ability factor as well as measures of information processing speed, memory, and estimated early-life cognitive ability

	Percentage of iron deposits in brain tissue	Percentage of iron deposits in brain tissue, with age 11 IQ controlled[a]
WAIS-III^{UK} subtests that define the general cognitive ability factor		
Symbol search	−.23 (−.39 to −.08)	−.18 (−.34 to −.03)
Digit symbol	−.23 (−.38 to −.08)	−.19 (−.34 to −.04)
Matrix reasoning	−.28 (−.45 to −.12)	−.25 (−.42 to −.09)
Letter-number sequencing	−.20 (−.38 to −.02)	−.14 (−.32 to .04)
Digit span backwards	−.12 (−.28 to .05)	−.06 (−.22 to .10)
Block design	−.30 (−.47 to −.13)	−.26 (−.44 to −.08)
General information processing speed factor	.04 (−.11 to .20)	−.01 (−.17 to .16)
Simple reaction time (mean)	.09 (−.05 to .24)	.07 (−.09 to .22)
Choice reaction time (mean)	.00 (−.18 to .18)	−.04 (−.22 to .14)
Inspection time	.00 (−.18 to .17)	.02 (−.16 to .20)
General memory factor (WMS)	−.07 (−.24 to .11)	.04 (−.15 to .22)
Logical memory (initial recall)	.05 (−.12 to .23)	.13 (−.05 to .31)
Logical memory (delayed recall)	−.01 (−.18 to .16)	.05 (−.12 to .23)
Spatial span (forward)	−.04 (−.21 to .13)	−.06 (−.23 to .12)
Spatial span (backward)	−.06 (−.24 to .12)	−.03 (−.22 to .15)
Verbal Paired Associates I (first recall)	−.01 (−.19 to .17)	.00 (−.18 to .18)
Verbal Paired Associates II	.03 (−.13 to .19)	.06 (−.10 to .22)

95% confidence intervals are shown in parentheses. All coefficients are fully standardized. Age in days at cognitive testing and gender are controlled in all analyses.

Key: IDs to iron deposits; IQ, intelligence quotient; WAIS, Wechsler Adult Intelligence Scale; WAIS-III^{UK}, Wechsler Adult Intelligence Scale III, UK edition; WMS, Wechsler Memory Scale.

[a] By adjusting for cognitive ability at age 11, this means the coefficients in this column effectively represent the association between IDs and relative cognitive change between childhood and old age.

Supplementary material

Supplementary results

The relationships of iron deposits (IDs) with the 6 individual subtests of the Wechsler Adult Intelligence Scale III, UK edition (WAIS-III^{UK}; Wechsler, 1998) that constitute the general cognitive ability factor are shown in the upper part of supplementary Table S1. Except for Digit Span Backwards, all subtests showed a significant negative association with IDs. For 4 of the 6 tests (Symbol Search, Digit Symbol, Matrix Reasoning, and Block Design), the association survived controlling for Moray House Test intelligence quotient (IQ) at age 11 (i.e., prior general cognitive ability) (Deary et al., 2007; Scottish Council for Research in Education, 1949), indicating unique effects of IDs on age-related cognitive decline.

In addition to the WAIS-III^{UK}, a series of other cognitive tests were administered at the same testing session at age 72 (for details, see reference 11). These included 3 so-called elementary cognitive tasks (simple reaction time, 4-choice reaction time, and inspection time), which were submitted to a principal components analysis to derive a general speed of information processing factor (explained variance of the first unrotated component: 55.39%) as well as 6 subtests of the Wechsler Memory Scale III^{UK} (Logical Memory initial recall, Logical Memory delayed recall, Spatial Span forward, Spatial Span backward, Verbal Paired Associates I (first recall), and Verbal Paired Associates II) (Wechsler, 1998), from which a general memory factor was extracted (explained variance of the first unrotated component: 36.82%). As the middle part of Supplementary Table S1 shows, none of these tests and factors was significantly related to IDs, neither before nor after controlling for childhood IQ. Thus, IDs seem to affect general cognitive ability, but not information processing speed or memory.

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