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Accumulation of iron in the putamen predicts its shrinkage in healthy older adults: A multi-occasion longitudinal study

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ABSTRACT

Accumulation of non-heme iron is believed to play a major role in neurodegeneration of the basal ganglia. In healthy aging, however, the temporal relationship between change in brain iron content and age-related volume loss is unclear. Here, we present the first long-term longitudinal multi-occasion investigation of changes in iron content and volume in the neostriatum in a sample of healthy middle-aged and older adults (N = 32; ages 49–83 years at baseline). Iron content, estimated via R2* relaxometry, increased in the putamen, but not the caudate nucleus. In the former, the rate of accumulation was coupled with change in volume. Moreover, greater baseline iron content predicted faster shrinkage and smaller volumes seven years later. Older age partially accounted for individual differences in neostriatal iron content and volume, but vascular risk did not. Thus, brain iron content may be a promising biomarker of impending decline in normal aging.

1. Introduction

The brain changes with age but the mechanisms of change remain obscure (Raz and Kennedy, 2009). An influential hypothesis of brain aging postulates that age-related losses of brain parenchyma and reduction in functional capacity are driven by cumulative damage produced by build-up of reactive oxygen species (ROS) and ensuing oxidative stress (Harman, 1956; Dröge and Schipper, 2007; Sohal and Orr, 2012) and chronic neuroinflammation (Finch et al., 1969; Finch and Crimmins, 2004; Grammas, 2011). ROS originate in organelles, such as the mitochondria and peroxisomes (Murphy, 2009; Brown and Borutaite, 2012), and are part of normal metabolism (Görlach et al., 2015). However, excessive accumulation of ROS upsets the normal equilibrium and accelerates the rate of oxidative stress that degrades mitochondrial membranes, impedes energy production in the mitochondria, promotes DNA mutations, and hastens apoptosis (Sohal and Orr, 2012). Paradoxically, one of the major sources of intracellular ROS is iron, an essential participant in normal metabolic function, including synthesis of high-energy phosphate in the mitochondria (Halliwell, 1992; Mills et al., 2010; Ward et al., 2014). By producing highly reactive ROS via Fenton reaction, non-heme iron exerts detrimental effects on the cell (Zecca et al., 2004; Mills et al., 2010; Hare et al., 2013). Because of its major role in abetting ROS-related cellular damage, brain iron that can be estimated by noninvasive neuroimaging makes a plausible proxy of the processes that otherwise are very difficult to assess in vivo.

Since recent advances in magnetic resonance imaging (MRI) methods for iron estimation, studies of lifetime differences in brain iron content have proliferated (see Haacke et al., 2005; Daugherty and Raz, 2013, 2015 for reviews). The cumulative record thus far supports the proposition that brain iron accumulation may be a meaningful biomarker of impending structural and cognitive declines in aging and disease (Schenck and Zimmerman, 2004; Walsh et al., 2014; Ward et al., 2014; Daugherty and Raz, 2015). Nonetheless, the temporal relationship between iron accumulation and structural changes in the brain is unclear.

Postmortem studies show that subcortical regions vulnerable to age-related volume loss (e.g., the neostriatum) evidence greater iron content in older brains (Hallgren and Sourander, 1958; Thomas et al., 1993; Aquino et al., 2009) and cross-sectional MRI investigations largely replicate these findings (Antonini et al., 1993; Bartzokis et al., 1994; Xu et al., 2008; Cherubini et al., 2009; Peran et al., 2009; Sullivan et al., 2009; Haacke et al., 2010; Pfefferbaum et al., 2010; Penke et al., 2012). The cumulative evidence of age-related differences in iron content has been quantified in a recent meta-analysis of MRI studies, which identified the greatest age-related differences in the caudate nucleus and putamen (Daugherty and Raz, 2013). Cross-sectional studies, however, are not informative about the dynamics of continuous processes of change and individual variations in trajectories of aging (Raz and Lindenberger, 2011). Thus longitudinal studies are necessary to determine the potential contribution of iron accumulation to typical brain aging, and yet, when it comes to age-related iron accumulation, such studies are particularly scarce.

Abbreviations: BS 95% CI, bootstrapped 95% confidence intervals; CES-D, Center for Epidemiological Study depression scale; CFI, comparative fit index; FIML, full information maximum likelihood; ICV, intracranial volume; MMSE, mini-mental state exam; RMSEA, root mean square error of approximation; ROS, reactive oxygen species; SRMR, square root mean residual; SWI, susceptibility-weighted imaging; WRMR, weighted root mean residual.

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A single longitudinal study of healthy adults found an increase in iron content in the caudate nucleus and putamen after two years (Daugherty et al., 2015). A study of neurodegenerative disease that followed a control group of younger and middle-aged adults over two years showed increase in iron content in the putamen and globus pallidus, but not the caudate nucleus (Walsh et al., 2014), whereas a small control group of middle-aged and older adults evidenced no change in striatal iron content (Ulla et al., 2013). The mixed evidence with regards to regional vulnerability notwithstanding, an increase in iron content in the basal ganglia appears to occur in normal aging and further longitudinal study is warranted.

Moreover, because all extant longitudinal in vivo studies of brain iron involved only two measurement occasions, the temporal order of regional iron accumulation and loss of volume in the brain could not be assessed (see Daugherty and Raz, 2015 for a review). The variance partitioning approach in cross-sectional mediation analyses (e.g., Rodrigue et al., 2013) cannot reveal the temporal order of events and the relationship between them (Lindenberger et al., 2011). A sole longitudinal study of healthy adults showed that iron accumulation in the neostriatum can explain its shrinkage (Daugherty et al., 2015), but as a two-occasion study it could not examine the lead–lag relations between the variables. Thus, multiple occasions of measurement are required to test the hypothesis of iron accumulation as a driver of shrinkage.

A plausible alternative hypothesis is that the age-related increase in iron content is not an independent phenomenon that precedes regional shrinkage, but instead is a relative shift in concentration due to shrinkage. Although we found no support for this hypothesis in our previous study (Daugherty et al., 2015), the two measurement occasions design limited testing of change–change associations.

Thus, the present study was designed to expand upon our previous longitudinal study (Daugherty et al., 2015) by testing these hypotheses in a new sample of middle-aged and older healthy adults who were assessed up to four times over seven years. Iron content was estimated via R2* relaxometry in the neostriatum, a technique that has demonstrated reliability and validity (Daugherty and Raz, 2015; Daugherty et al., 2015). These measures of iron content were combined with regional volumes in models evaluated with a latent-variable longitudinal modeling technique—simple and parallel change latent growth curve analyses. This statistical approach produces error-free estimates of change in iron content and volume, individual differences therein, and allows testing the precedence of change in one factor predicting change in the other. We hypothesized that longitudinal increase in iron in the caudate nucleus and putamen would precede and predict shrinkage of both regions.

2. Materials and methods

2.1. Participants

Middle-aged and older adults (N = 32; 58% female) were recruited from the Metro Detroit area as part of a long-term longitudinal study. Participants (age 49–83 years at baseline) were assessed two to four times over 7 years (average delay between baseline and the first follow-up = 15.69 months, *SD* = 1.28; between the first and second follow-up = 15.40 months, *SD* = 2.79; and between the second and third follow-ups = 58.05 months, *SD* = 5.28), see Table 1 for a demographic profile of the sample and Fig. 1 for a graphic display of the assessment schedule. The participants were screened for neurological and cardiovascular pathology, thyroid disorder, endocrine disease, psychiatric disease, drug and alcohol abuse, and head injury. Participants reported right-hand dominance (Edinburgh Handedness Questionnaire; Oldfield, 1971) and were screened for vision and hearing problems at each assessment. For inclusion, participants scored less than 16 on the Center for Epidemiologic Study depression scale (CES-D; Radloff, 1977) and at least 26 on the mini-mental state examination (MMSE; Folstein et al. 1975) at enrollment and each follow-up. Q5

The sample used in this study consisted of cases with complete data at baseline and the first follow-up assessment (i.e., at least two assessments). In addition to the selected sample of N = 32, 23 persons were enrolled in the study at baseline and follow-up but were excluded from analyses. Seven cases were dropped because upon retrospective evaluation they were found to violate the health criteria set at enrollment. The remaining 16 cases had incomplete MRI data at the first two assessments due to either incorrect acquisition or excessive artifacts.

Of the retained sample (N = 32), 13 persons (46% female) had missing longitudinal data (n = 2 at the second follow-up, n = 11 at the third follow-up). These participants did not differ from the 19 with complete four measurement occasions with respect to age (t = 0.20, p = 0.85), MMSE (t = 0.27, p = 0.79), CES-D (t = −0.42, p = 0.68), or years of

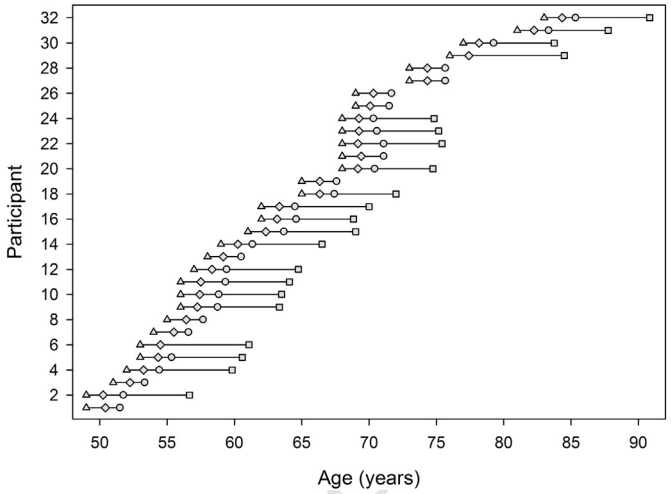

Fig. 1. Distribution of ages-at-measurement and intervals between measurement occasions for the 32 participants. The symbols represent each measurement occasion: triangle = 1st occasion; diamond = 2nd occasion; circle = 3rd occasion; square = 4th occasion. The mean interval duration between baseline and first follow-up measurement was 15.69 months (*SD* = 1.28). The mean interval between the second and third visits was 15.40 months (*SD* = 2.79), and between the third and the fourth occasions was 58.05 months (*SD* = 5.28).

t1.1 **Table 1**
t1.2 Demographic profile of the sample measured four times.

t1.3		Baseline	Follow-up 1	Follow-up 2	Follow-up 3
t1.4	N	32	32	30	21
t1.5	Age (years)	62.94 ± 9.38	64.34 ± 9.33	65.37 ± 9.09	70.85 ± 9.91
t1.6	Education (years)	16.28 ± 2.37	16.84 ± 2.67	16.90 ± 2.83	16.86 ± 2.69
t1.7	MMSE	28.69 ± 1.23	28.44 ± 1.16	28.73 ± 1.02	28.52 ± 1.33
t1.8	CES-D	4.16 ± 4.22	3.84 ± 4.14	3.53 ± 3.19	3.29 ± 3.90
t1.9	Hypertension freq.	11	10	11	10
t1.10	Systolic (mm Hg)	130.76 ± 12.67	128.16 ± 11.17	128.65 ± 12.50	127.05 ± 10.63
t1.11	Diastolic (mm Hg)	80.01 ± 6.42	77.64 ± 7.27	76.33 ± 6.21	77.12 ± 6.62

t1.12 *Note*: Sample averages and standard deviations are reported. MMSE—mini-mental state exam (cut-off > 25); CES-D—center for epidemiologic study-depression scale (cut-off < 16); Hy-
t1.13 pertension was determined by clinical diagnosis or observed blood pressure > 140 mm Hg systolic or 90 mm Hg diastolic.

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