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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