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Age-related differences in iron content of subcortical nuclei observed in vivo: A meta-analysis

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ABSTRACT

Accumulation of non-heme iron in the brain has been proposed as a biomarker of the progressive neuroanatomical and cognitive declines in healthy adult aging. Postmortem studies indicate that iron content and lifespan differences therein are regionally specific, with a predilection for the basal ganglia. However, the reported in vivo estimates of adult age differences in iron content within subcortical nuclei are highly variable. We present a meta-analysis of 20 in vivo magnetic resonance imaging (MRI) studies that estimated iron content in the caudate nucleus, globus pallidus, putamen, red nucleus, and substantia nigra. The results of the analyses support a robust association between advanced age and high iron content in the substantia nigra and striatum, with a smaller effect noted in the globus pallidus. The magnitude of age differences in estimated iron content of the caudate nucleus and putamen partially depended on the method of estimation, but not on the type of design (continuous age vs. extreme age groups).

Introduction

Many aspects of the human brain, from molecular processes and gene expression to gross anatomy and systemic physiology, change profoundly with age. However, the magnitude and the pace of change differ among brain regions and vary in their impact on cognitive performance (Raz and Kennedy, 2009). The reasons for the lack of uniformity in the brain aging remain unclear. It may reflect differential sensitivity of brain components to age-related changes in key metabolic and neurochemical processes that affect cellular homeostasis and structural integrity. One such putative marker of age-related cellular vulnerability is iron. Although iron is an essential metabolite that is omnipresent in the neurons and neuritic processes, its excessive accumulation in specific regions of the brain may be a sensitive indicator of increased oxidative stress and thus a marker of age-related vulnerability (Bartzokis, 2011; Mills et al., 2010).

Within the brain, iron appears primarily in two forms: intracellular non-heme iron and heme iron that occupies the core of the hemoglobin molecule and is thus present in any location where blood flows or accumulates (Tingey, 1938). Whereas heme iron does not appear to play a significant role in oxidative stress and neurodegeneration (Halliwell, 1992; Mills et al., 2010), non-heme iron is an established promoter of reactive oxygen species (ROS) within brain tissue and is thus a potential contributor to cellular deterioration (Mills et al., 2010). As a rule, more than 90% of intracellular non-heme iron is sequestered in ferritin (Gomori, 1936; Hallgren and Sourander, 1958; Jara et al., 2006; Lauffer, 1992), until it is released to meet metabolic demands of neurotransmission, mitochondrial ATP generation, and DNA replication (Crichton and Ward, 1992; Fisher et al., 2006; Mills et al., 2010). Outside of ferritin, metabolically active (ferric) iron forms a labile pool bound to amino acids (Lauffer, 1992), other metabolites (Cabantchik et al., 2002), and possibly metallochaperones (Mills et al., 2010).

Non-heme iron is unevenly distributed across brain regions and structures, and the magnitude of age differences in iron content varies among the regions. Among the brain components, the basal ganglia have the highest concentrations of iron in early adulthood and show the most substantial age differences (Haacke et al., 2005; Hallgren and Sourander, 1958; Thomas et al., 1993). This pattern of non-heme iron distribution may reflect regional differences in need for iron that is proportional to metabolic demands of neurotransmission (see Mills et al., 2010 for a review). Indeed, dopaminergic transmission that is one of the main modes of neural activity in the iron-rich striatum depends on availability of iron (Zecca et al., 2004).

With iron being a necessary actor in neurotransmission and a potential promoter of apoptosis, intracellular stores of ferric iron must be strictly regulated. However, with advanced age, this fine balance gradually changes. As transport and storage mechanisms deteriorate (Bartzokis et al., 2011; Singh et al., 2009; Zhang et al., 2009), metabolically active iron accumulates outside of ferritin, increases oxidative stress, and notably degrades cellular integrity (Mills et al., 2010; Zecca et al., 2004). Although the causal relationship remains unclear, it is known that increased non-heme iron content is associated with atypical dopamine and serotonin metabolism (Berg et al., 2007), mutations in mitochondrial and nuclear DNA (Hamilton et al., 2001), and accelerated apoptosis (Zhang et al., 2009).

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Cellular degradation related to iron accumulation might explain the cumulative structural declines that accompany aging and neurodegenerative disease (Harman, 1956). For example, it is plausible that iron plays an important role in Alzheimer's disease (AD), as iron deposits co-localize with tangles (House et al., 2004), plaques (Quintana et al., 2006), and amyloid burden (Rival et al., 2009). According to a recent theory, iron-catalyzed oxidative stress is a primary cause of demyelination in normal aging and accelerated demyelination in AD (Bartzokis, 2011). Elevated iron concentration has been linked to the formation of Lewy bodies (Berg et al., 2007) and decline in the extra-pyramidal motor system (Spatz, 1922).

Iron content is relevant to cognitive performance. In older rodents, iron overload and oxidative stress produce declines in spatial navigation and motor control (Joseph et al., 2005; Maaroufi et al., 2009). In healthy adults, high iron content of the hippocampus contributes to age-related differences in memory (Rodrigue et al., 2012). Greater iron presence in the brain, primarily in the basal ganglia, is associated with general cognitive aptitude in septuagenarians (Penke et al., 2012). However, until recently, information about brain burden of non-heme iron in humans came almost exclusively from post-mortem studies, thereby hampering an understanding of its role in functional and cognitive changes that occur in healthy aging. Thus, the importance of obtaining correct in vivo estimates of brain iron content in healthy adults cannot be overstated, and the recent advent of MRI methods that derive contrast from the presence of iron is encouraging.

A notable feature of iron behavior in the healthy aging brain is significant regional variability in its content (Thomas et al., 1993). In their landmark study, Hallgren and Sourander (1958) quantified regional age-related differences in healthy brains from infancy to the age of 100 years. They found that in younger and middle-aged brains, advanced age was associated with greater iron concentrations in the basal ganglia than in subcortical white matter, but noted that the association between age and iron content was attenuated after middle age (Hallgren and Sourander, 1958). However, the reported estimates of adult lifespan differences in iron content could have been biased by several factors, such as inclusion of pre-adolescent participants and the exponential accumulation of iron in early life (Aquino et al., 2009; Thomas et al., 1993). These factors could have obscured a relatively small, but potentially meaningful, difference across the adult lifespan. The introduction of in vivo techniques has offered further insight into the potential role of iron in adult aging.

In principle, MRI is very well suited for in vivo assessment of regional iron content in the brain. Paramagnetic materials, such as iron, have very high magnetic susceptibility and, therefore, a short transverse relaxation time (T2) or long relaxation rate (R2). On T2-weighted images, iron-rich regions such as the basal ganglia, red nucleus and substantia nigra appear hypointense. Moreover, low intensity values of these regions are even lower in the brains of older adults (Siemonsen et al., 2008; Thomas et al., 1993). In spite of a strong correlation between T2 and iron content, T2-weighted imaging and T2 relaxometry are not the optimal methods of estimating iron content in vivo, as they are sensitive to other factors. For example, decreased water content also results in shortening of T2 and thus may be misinterpreted as increased iron content (Haacke et al., 2005).

To reduce the likelihood of such misinterpretations one can use the field-dependent R2 increase (FDRI) method, which relies on differences in spin–spin relaxation rates obtained from magnets of different field strengths. In FDRI, identical sequences with the same acquisition parameters are repeated back-to-back in two different magnets that differ in their field strengths (Bartzokis et al., 2011). In comparison to a single-magnet measure, FDRI yields a more precise estimate of local susceptibility related to iron content. However, the method calls for two different imaging systems. Thus, even with a great similarity of acquisition sequences and a minimal delay between the runs, FDRI introduces unwanted variability in subject orientation and scanner properties.

The validity of relaxometry as a method for in vivo estimation of brain iron content can be improved by using T2*, which is a sum of T2 and T2' (or R2*, a sum of their reciprocals). T2* and R2* are sensitive to the local field inhomogeneity and are less ambiguously related to the amount of iron in tissue than T2 is (Ordidge et al., 1994; see Haacke et al., 2005 for a review). The main disadvantage of the T2* method is that background field inhomogeneity that is unrelated to iron content may confound the estimates especially in the presence of other para- and diamagnetic elements(see Haacke et al., 2005 for a review). A component of T2*, T2', is potentially a more precise index of iron content than T2*, but its values are relatively small and difficult to measure with desirable precision.

To rule out the influence of potential confounds, phase information provided by susceptibility-weighted images (SWI; Haacke et al., 2005) has been recently proposed to deliver more precise and specific estimates of iron content than other methods. Regional differences in phase are proportional to iron content, as has been validated by correlation with published post-mortem values (Haacke et al., 2005; Ogg et al., 1999). Theoretically, phase can detect small regional differences in iron content better than T2* estimates and is easier to measure than T2' (Haacke et al., 2005). Further, phase is directional, and differences in phase direction can distinguish regions of calcification (diamagnetic) from those that contain non-heme iron (paramagnetic) based upon image intensity. However, phase-based estimates of iron content are not entirely problem-free. For example, unlike the T2* and T2', regional phase values are poorly localized and may be affected by signal from neighboring tissue. New post-acquisition processing methods have been developed to remove non-local effects and to improve regional estimates (Haacke et al., 2010a, 2010b; Langkammer et al., 2012), but at the time of this writing only one study (Bilgic et al., 2011) has used these methods to measure age differences in healthy adults.

Based on a histological study, ferritin and hemosedrin are the only paramagnetic materials of sufficient concentration to affect MR signal from brain tissue (Schenck, 1995). Concentrations of transferrin-bound iron, the labile pool, and soluble iron particles are probably insufficient to cause differences in MR signal (Haacke et al., 2005). Other endogenous paramagnetic materials (i.e., copper and manganese) are also at inadequate concentrations in healthy individuals to affect the signal (Haacke et al., 2005). However, the MRI methods cannot readily distinguish between heme (i.e., cerebral blood volume) and non-heme iron sources, which may correlate highly in subcortical regions (Anderson et al., 2005). Despite their limitations, the various MRI methods have been validated in several phantom studies and in comparison to post-mortem assays (Antonini et al., 1993; Bartzokis et al., 1994a, 1994b; Bizzi et al., 1990; Brass et al., 2006; Peran et al., 2009; Pujol et al., 1992; Thomas et al., 1993; Vymazal et al., 1995a). Like post-mortem observations, MRI studies of adult age differences in iron content have found regional discrepancies, albeit of various magnitudes (Bartzokis et al., 1997, 2007; Cherubini et al., 2009; Drayer, 1988; Peran et al., 2009; Pfefferbaum et al., 2009, 2010; Pujol et al., 1992; Xu et al., 2008). Haacke et al. (2005) recently commented on the variability among extant MRI studies and post-mortem methods, although the review only listed the results without a specific analysis of regional age differences.

Thus, the goal of this meta-analysis was to evaluate quantitatively the outcomes of studies reviewed in the last narrative review (Haacke et al., 2005) as well as those that appeared after that publication. In the meta-analysis, we focused on the brain regions in which age differences have been examined in a sufficient number of in vivo studies, i.e., globus pallidus (GP), putamen (Pt), caudate nucleus (Cd), red nucleus (RN), and substantia nigra (SN). Finally, our aim was to evaluate two potential sources of discrepancies among the studies in observed age differences: method of iron content estimation and the type of design vis a vis age (extreme groups or continuous).