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Quantitative Susceptibility Mapping of Brain Iron in Healthy Aging and Cognition

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Abstract

Quantitative susceptibility mapping (QSM) is a magnetic resonance imaging (MRI) technique that can assess the magnetic properties of cerebral iron *in vivo*. Although brain iron is necessary for basic neurobiological functions, excess iron content disrupts homeostasis, leads to oxidative stress, and ultimately contributes to neurodegenerative disease. However, some degree of elevated brain iron is present even among healthy older adults. To better understand the topographical pattern of iron accumulation and its relation to cognitive aging, we conducted a systematic review of 47 QSM studies of healthy aging, with a focus on five distinct themes. The first two themes focused on age-related increases in iron accumulation in deep gray matter nuclei versus the cortex. The overall level of iron is higher in deep gray matter nuclei than in cortical regions. Deep gray matter nuclei vary with regard to age-related effects, which are most prominent in the putamen, and age-related deposition of iron is also observed in frontal, temporal, and parietal cortical regions during healthy aging. The third theme focused on the behavioral relevance of iron content and indicated that higher iron in both deep gray matter and cortical regions was related to decline in fluid (speed-dependent) cognition. A handful of multimodal studies, reviewed in the fourth theme, suggest that iron interacts with imaging measures of brain function, white matter degradation, and the accumulation of neuropathologies. The final theme concerning modifiers of brain iron pointed to potential roles of cardiovascular, dietary, and genetic factors. Although QSM is a relatively recent tool for assessing cerebral iron accumulation, it has significant promise for contributing new insights into healthy neurocognitive aging.

Keywords

Neuroimaging; Magnetic resonance imaging; Deep gray matter; Cortex; White matter

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1. Introduction

In vertebrates, iron exists in two distinct forms: heme iron, which is linked exclusively to circulating or accumulating blood, and non-heme iron, which is present in virtually all cells and is a contributor to essential biological processes in the brain such as oxygen transport, DNA synthesis, mitochondrial respiration, myelin synthesis, and neurotransmitter synthesis and metabolism (Gutteridge, 1992; Hentze et al., 2004; Koeppen, 1995 ; Rouault and Cooperman, 2006; Todorich et al., 2009). Early anatomical studies of post-mortem brain tissue reported that iron deposition was notable in deep gray matter regions related to motor control, particularly the globus pallidus, caudate, putamen, and substantia nigra, and that the amount of iron tended to increase from childhood to adolescence (Spatz, 1922). In a seminal study, Hallgren and Sourander (1958), conducted the first systematic analyses of age-related differences in iron across different regions of the brain. These authors conducted histological analyses of post-mortem tissue for 98 brains from individuals spanning infancy to 100 years of age. Hallgren and Sourander confirmed that non-heme iron concentration was particularly prominent in the deep gray matter regions, relative to cortical or white matter regions.

Elevated iron concentration in deep gray matter nuclei is associated with neurodegenerative disease, notably Parkinson's disease, in which movement disorder is prominent (Dexter et al., 1987; Gerlach et al., 1994; Ghassaban et al., 2019; Gotz et al., 2004; Ke and Qian, 2003; Sayre et al., 2000). Elevated brain iron may also have a role in dementia. As early as 1953, postmortem histochemical analyses suggested that a disturbance in the cerebral metabolism of iron was an aspect of Alzheimer's disease (AD) pathogenesis (Goodman, 1953). Connor et al. (1992), in a postmortem examination of regional tissue distribution of iron and iron-regulatory proteins, using immunoassay, concluded that alterations in iron-regulatory proteins are exacerbated in AD. In postmortem studies of AD patients, tissue histology has demonstrated that neuronal iron accumulation co-localizes with Aβ deposition and tau neurofibrillary tangles (Duce et al., 2010; Grundke-Iqbal et al., 1990; Lovell et al., 1998; Smith et al., 1997). Critically, however, the increased deposition of brain iron during later adulthood, observed by Hallgren and Sourander (1958), occurs in the absence of specific neurodegenerative disease and is one feature of the complex constellation of changes in central nervous system function typically associated with normal human aging (Martin et al., 1998; Sfera et al., 2018; Ward et al., 2014; Zecca et al., 2004).

The development and application of neuroimaging techniques, particularly magnetic resonance imaging (MRI), can provide a complementary perspective to the histological studies, by characterizing the properties of iron in the human brain *in vivo* as well as *ex vivo.* Thus, while a substantial literature exists, from both structural and functional MRI, regarding changes in the brain during later adulthood (Dennis and Cabeza, 2008; Fjell and Walhovd, 2010; Grady, 2012; Raz et al., 2010), relatively few studies have addressed the role iron deposition specifically. Our goal in this article is to review the contributions that different MRI methods, particularly quantitative susceptibility mapping (QSM), have made to understanding age-related differences in iron deposition and the relation of iron to cognitive aging, in healthy individuals. A central question that we are addressing is whether the age-related increase in brain iron, in otherwise healthy adults, contributes to the declines in some aspects of cognitive functioning that are observed during later adulthood.

Specialized structural MRI sequences, such as multiecho gradient echo sequences, are particularly informative regarding iron because variations in iron create local differences in magnetic susceptibility (Haacke et al., 2005; Liu et al., 2015a), and thus regions with increased iron also have higher susceptibility and a relatively fast transverse relaxation rate (R2) or short relaxation time constant (T2*). In these studies, the most frequently used quantitative MRI index of magnetic susceptibility is the relaxometry-based measure of R2*, which estimates iron content as a sum of relaxation due to spin-spin interaction (R2) and local susceptibility effects (R2') (Brass et al., 2006; Langkammer et al., 2010). Although relaxometry-based estimates of iron correlate highly with chemically determined iron concentration obtained postmortem (Brass et al., 2006; Langkammer et al., 2010), the R2* index and related relaxometry measures are potentially influenced by background field inhomogeneity unrelated to iron content (Haacke et al., 2015; Wang and Liu, 2015). Further, R2* can be affected by either paramagnetic (e.g., iron) or diamagnetic sources.

QSM is another quantitative MRI index of magnetic susceptibility that has several advantages over relaxometry-based measures (Langkammer et al., 2012; Li et al., 2011; Liu et al., 2011; Liu et al., 2015a). QSM is a more direct measurement of the intrinsic property of tissue and is independent of magnetic field strength. As compared to relaxometry, QSM has improved contrast of deep gray matter nuclei (Barbosa et al., 2015; Liu et al., 2013) and better sensitivity to the effects of age (Bilgic et al., 2016; Li et al., 2014) and neurodegenerative disease (He et al., 2015). For example, different regional patterns of iron deposition, as assessed by QSM, are expressed in AD (Acosta-Cabronero et al., 2013; Ayton et al., 2013) and cerebrovascular small vessel disease (Moon et al., 2016; Sun et al., 2017). Our primary goal here is to consider the degree to which QSM may shed light on age-related differences in cognition during healthy aging. In particular, does brain iron contribute to cognitive aging, or alternatively, are the effects of age and iron on cognition independent, until some threshold of neuropathology is crossed?

2. Methodological Considerations for QSM Studies of Aging

QSM is primarily sensitive to iron content in the case of gray matter and myelin content in the case of white matter, corresponding to positive (paramagnetic) and negative (diamagnetic) susceptibility values, respectively (Deh et al., 2018; Li et al., 2012; Li et al., 2011; Liu et al., 2015b). Thus, throughout the articles discussed here, we consider positive versus negative susceptibility values to correspond primarily to the relative contribution of iron versus myelin. The neurobiological source of magnetic susceptibility, however, is complex and not a one-to-one correspondence (Liu et al., 2015b). For example, whereas iron deposition is highest within deep gray matter nuclei, contributing to positive susceptibility values, these regions are also myelinated, though to a lesser degree than cortical neurons. Similarly, the susceptibility of white matter is determined primarily by myelin concentration, but iron is also present, in the oligodendrocytes forming the myelin and in the mitochondria in the axons (Meguro et al., 2008). As a result, average susceptibility values within a region of interest represent different signal sources. Although positive susceptibility is likely dominated by iron, the negative values are more difficult to interpret. Methods for addressing this difficulty are still in development. One approach is to use the absolute value (i.e., unsigned) combination of positive and negative values in separate maps of gray matter

and white matter (Betts et al., 2016). A second approach is to use biophysical modeling to separate the voxelwise distributions of paramagnetic (e.g., iron) and diamagnetic (e.g., myelin) susceptibility signals based on the frequency shift and transverse relaxation rates (Shin et al., 2021). A third algorithm, termed DECOMPOSE-QSM, uses the phase and magnitude from a gradient echo acquisition sequence to separately estimate paramagnetic susceptibility, diamagnetic susceptibility, and reference susceptibility within each voxel (Chen et al., 2021a), which has recently been applied to study neurodegeneration in AD (Ahmed et al., 2023).

QSM values, derived from the phase measured by gradient echo sequences, are influenced by the scan acquisition parameters, especially echo time (Sood et al., 2017). For example, the myelin water signal cannot be detected by later echo times (Liu et al., 2015b). For these reasons, it is preferable to use multiple echo times when acquiring a gradient echo sequence. Although it is possible to acquire single echo gradient echo sequences, they are much more prone to streaking artifacts (Liu et al., 2015b). After acquiring a gradient echo dataset, researchers also have several options for unwrapping the phase image, removing the background field, and ultimately constructing the susceptibility map (Ravanfar et al., 2021), such as the morphology enabled dipole inversion (Liu et al., 2012) or sparse linear equation and least-squares algorithm (Li et al., 2015b).

Researchers must also decide whether to use relative susceptibility values or to reference susceptibility values against a particular reference region. Although most researchers agree that susceptibility values should be referenced against a control region, there is considerable debate regarding the appropriate reference region (e.g., ventricles or white matter). This is a particularly important issue in aging, where the accuracy of tissue segmentation (e.g., avoiding iron-rich choroid plexus in the ventricles) and age-related differences in underlying tissue properties (e.g., degree of myelination, presence of lesions) can contribute to differences in susceptibility (Deistung et al., 2017; Ravanfar et al., 2021). However, prior studies have shown that the effect of referencing did not change the observed age-related differences in QSM values (Acosta-Cabronero et al., 2016; Li et al., 2014).

Variability among QSM studies in aging may also reflect differences in the analytical approach. Some studies use a region-of-interest approach, which can be conducted at the participant level, whereas others use a voxelwise approach, which can identify smaller clusters but requires group-level registration and some degree of spatial smoothing. Voxelwise analyses of cortical regions are particularly vulnerable to biased susceptibility measures in blood vessels, lesions, and regions near the air-tissue interface (Chen et al., 2021a; Liu et al., 2015b). One approach to address artifactual sources of susceptibility, especially around the edges of the brain and near the air-tissue interface, is to erode the edges of the susceptibility maps (Bhattarai et al., 2020; Howard et al., 2022). Another approach to reduce the number of artifactual susceptibility values is to threshold and remove the most extreme 15% of values (Garzón et al., 2017; Persson et al., 2020).

3. Scope of Review

We conducted an integrative literature review between March and April 2023 with PubMed searches using two search terms related to age (*ag*ing*; *older adults*) and three related to QSM (*QSM*; *Quantitative Susceptibility Mapping*; *magnetic susceptibility*). We conducted six searches, representing each combination of one age term combined via AND with one QSM term. These search queries identified a total of 114 unique publications. From these publications, we selected studies that met all of the following five criteria: 1) appeared in an English language journal, through 2023; 2) reported *in vivo* MRI scans of the human brain; 3) was an empirical research report (i.e., reviews were excluded); 4) included cognitively healthy human participants over 60 years of age; and 5) examined relations between a QSM measure of the brain and either age, cognitive performance, or other MRI measures (when limited to a sample of healthy older adults). Studies that examined relations between aging and R2*-based MRI measures were only included in the current review if these measures were examined in combination with QSM-based MRI measures.

Of the 114 originally identified publications, we excluded 20 for not including cognitively healthy adults older than 60 years of age, 13 for not being original research reports, six for not including human participants, one *ex vivo* study, and 27 that did not report some relation between a QSM measure of the brain and either age, cognitive performance, or another MRI measure within healthy older adults. Thus, a total of 47 published articles (identified with an asterisk in References) from the original search queries met the criteria for the current review. Eight of these involved a comparison of patients (e.g., Parkinson's disease, AD, multiple sclerosis) and healthy controls, and in these instances, we report only the findings of the healthy participants, as our focus here is on cognitive aging in healthy adults. We discuss the 47 included studies in terms of five themes: deep gray matter susceptibility; cortical susceptibility; the relation of susceptibility to neurocognitive function; multimodal imaging studies; and moderators of susceptibility in healthy aging. The studies associated with each theme, and the various forms of evidence supporting the themes, are presented in Tables 1–5. Note that findings from an individual study may contribute to more than one theme.

4. Deep Gray Matter Susceptibility Patterns in Healthy Aging

As noted previously (Section 1, Introduction), the histology data of Hallgren and Sourander (1958) demonstrated that the concentration of iron was higher for deep gray matter regions (4.76 – 21.30 mg/100 g tissue) than for cortical regions (2.92 – 5.03 mg/100 g tissue). These authors also observed, however, that within the deep gray matter regions, age-related differences in iron were independent of the overall level of iron. The globus pallidus (along with the substantia nigra and red nucleus) exhibited the highest concentration of iron overall, but iron in the globus pallidus did not increase markedly following 30 years of age. In contrast, iron content in the putamen and caudate nucleus, while lower overall, continued to increase beyond 50–60 years of age.

One theme of QSM studies (Table 1) is that susceptibility varies in relation to deep gray matter region, and age, in a manner consistent with the Hallgren and Sourander (1958)

histological data. For example, Gong et al. (2015) reported that susceptibility values were highest for the globus pallidus, substantia nigra, and red nucleus, consistent with Hallgren and Sourander. Similarly, Gong et al. reported that the magnitude of the age-related increase in susceptibility was greater for the putamen than for other deep gray matter regions. These authors also distinguished left and right hemisphere components of gray matter nuclei and found that susceptibility was relatively higher for the left side of the caudate and substantia nigra. This hemispheric asymmetry may reflect dopamine levels associated with lateralized motor function (Xu et al., 2008), although this hemispheric effect appeared to be independent of the age-related effects in susceptibility.

In their QSM study, Li et al. (2023) investigated six deep gray matter nuclei, for 220 individuals 10–70 years of age. In addition to susceptibility, these authors analyzed estimated iron content, for each deep gray matter region, from the multiplicative product of susceptibility and regional volume (adjusted for total intracranial volume). For both susceptibility and iron content, the putamen exhibited the most pronounced increase with age. Li et al. noted that whereas susceptibility increased with age for all deep gray matter regions, individual age-related trends could be either linear (substantia nigra), quadratic (putamen, caudate, and globus pallidus), or exponential (red nucleus, dentate nucleus). However, Li et al. did not directly compare the deep gray matter regions in terms of the absolute value of either susceptibility or iron content.

Whereas QSM studies reliably confirm the age-related increase in iron in the putamen, findings for other gray matter regions, particularly the thalamus, are mixed. Zhou et al. (2020) reported a statistically significant increase in thalamic susceptibility with age, consistent what they observed for other deep gray matter regions, but the effect size was small, $r = 0.164$. Gong et al. (2015) reported that the thalamus did not show any significant age-related effect, in contrast to the age-related increase in susceptibility for other deep gray matter regions. Taege et al. (2019) and Treit et al. (2021) reported significant age-related declines in susceptibility for the thalamus.

Several functional and structural properties of the thalamus may contribute to this variation in age-related effects. Deep gray matter nuclei are primarily associated with motor functioning, but the thalamus comprises heterogeneous sub-nuclei (e.g., pulvinar) implicated in sensory and cognitive functions, especially visual attention (LaBerge, 2000; LaBerge and Buchsbaum, 1990). The thalamus is relatively high in myelin, within the internal and external inter-medullary lamina, and the combination of these different sources of paramagnetic and diamagnetic signals may contribute to variability (Betts et al., 2016). Finally, it is important to note that the majority of the studies to date are cross-sectional, and thus age-related differences are necessarily confounded with individual differences. Although longitudinal studies have confirmed age-related increase in deep gray matter susceptibility (Gustavsson et al., 2022; Li et al., 2021), additional exploration of regional longitudinal trends is needed.

5. Cortical Susceptibility Patterns in Healthy Aging

The majority of the studies in Table 1 used a region of interest approach that focused exclusively on susceptibility values that are averaged across voxels from anatomically defined deep gray matter regions. Although some studies compared deep gray matter and selected supratentorial cortical regions (Gustavsson et al., 2022; Li et al., 2014), the majority focused on the deep gray matter regions. That is a logical and necessary first step, given the relatively lower levels of iron observed in cortex relative to deep gray matter nuclei in the absence of disease, as noted previously. However, in view of the anatomical connections between deep gray matter and cortical regions, and the role of deep gray matter regions in the coordination of sensorimotor functions (Alexander et al., 1986; Cummings, 1993; Graybiel and Saka, 2004; LaBerge, 2000), the effects of iron deposition in cortical regions other than deep gray matter are also important. The articles included in Table 2 illustrate a second theme in QSM research, the age-related variation in susceptibility across cortical regions, for healthy adults.

The application of voxelwise, whole-brain QSM measures has been a significant methodological advance in research on cortical susceptibility and aging. Two articles in 2016 reported whole-brain QSM patterns. Betts et al. (2016) conducted a voxelwise QSM analysis of 20 younger adults and 20 older adults at 7T, with the additional feature of constructing separate maps for positive and negative susceptibility. These authors observed that increased susceptibility for the older adult group was evident in deep gray matter regions, as expected, but also in supratentorial cortical regions, particularly superior frontal regions surrounding primary motor cortex. In addition, the clusters of negative susceptibility, primarily in white matter tracts, tended to be more negative (i.e., increasingly diamagnetic) for older adults relative to younger adults. Similarly, Acosta-Cabronero et al. (2016) conducted a voxelwise QSM analysis (at 3T) of 116 individuals 20–79 years of age, and because they sampled age as a continuous variable, they could define clusters of interest from the age-susceptibility correlation, rather than from a group contrast as in Betts et al. (2016).

In addition to confirming the strong age-related trends for increased susceptibility of deep gray matter, Acosta-Cabronero et al. (2016) observed significant age-related increases in susceptibility in sensorimotor cortex and prefrontal, insular, and dorsomedial frontal cortex, consistent with the Betts et al. (2016) findings. Acosta-Cabronero et al. found that age-related susceptibility effects in white matter tended to be positive, in contrast to Betts et al., though Acosta-Cabronero et al. did not separate positive and negative QSM maps as Betts et al. had done. Acosta-Cabronero et al. found that cortex rostral to the central sulcus (motor, premotor, dorsal prefrontal, dorsomedial surface, and insula) was more prone to iron accumulation with age than more posterior cortical regions, leading them to propose that the motor system, broadly defined, has a tendency to accumulate iron with age.

Thus, in contrast to region of interest analyses, voxelwise analyses provide a more comprehensive view of iron deposition across the whole brain and have yielded novel findings. The voxelwise approach, however, has several features that should be considered when interpreting these results. The threshold for cluster significance in a voxelwise analysis

is based on the contrast or correlation with an independent variable, for example, age, disease status, or a behavioral outcome, and thus the clusters of interest will vary in relation to threshold definition. In addition, unless gray and white matter tissue compartments are separated, the paramagnetic and diamagnetic components of the QSM outcome variable will combine in their contributions to cluster definition, which complicates interpretation. Finally, voxelwise analyses are inherently conservative by correcting for the multiple comparisons made across the population of voxels, and these analyses may miss more subtle effects of iron that are limited to particular cortical layers or depths (Deistung et al., 2013; Lee et al., 2023).

6. Relation of Susceptibility Measures to Neurocognitive Function

Whereas semantic knowledge and various forms of expertise (crystallized cognition) can remain constant or even improve with adult age, abilities that are dependent on perceptual-motor speed and working memory (fluid cognition) decline during adulthood (Craik and Bialystok, 2006; Horn, 1982; Park et al., 2002; Salthouse, 2004). A generalized, age-related slowing of central nervous system function appears to be a fundamental dimension of age-related decline in fluid cognitive abilities (Birren, 1965; Brinley, 1965; Madden, 2001; Salthouse, 1996, 2017; Salthouse and Madden, 2007). The vast majority of structural and functional neuroimaging studies of aging have focused on gray matter and white matter in the cerebral cortex, especially structural volume and functional activation in the case of gray matter, and the microstructural integrity of white matter as reflected in measures of the diffusivity of molecular water (Dennis and Cabeza, 2008; Fjell and Walhovd, 2010; Grady, 2012; Raz et al., 2010). As discussed in the previous sections of this article, excessive levels of brain iron contribute to neurodegenerative disease, and increases in brain iron occur during adulthood even in the absence of disease. A third theme, from recent QSM studies (Table 3), is that regional increases in brain iron contribute to age-related decline in neurocognitive function in healthy adults.

Initial studies of cognitive aging, based largely on neuropsychological assessment, proposed that decline in the structure and function of the frontal lobes was responsible for age-related decline in fluid cognitive abilities such as working memory and inhibitory function (Dempster, 1992; Moscovitch and Winocur, 1992; West, 2000; West, 1996). Subsequent research incorporating neuroimaging methods has led to a more nuanced view, in which age-related differences in behavioral measures reflect the connectivity of brain networks that vary in scale (Dennis and Cabeza, 2008; Madden et al., 2020a; Madden et al., 2017; Merenstein et al., 2023b; Monge et al., 2017). These networks, in turn, are comprised of deep gray matter and cerebral cortical regions that form anatomically and functionally distinct networks critical for behavior and cognition (Behrens et al., 2003; O'Muircheartaigh et al., 2015; Zhang et al., 2008; Zhang et al., 2010).

The deep gray matter nuclei are highly interconnected with virtually the entire cerebral cortex (Alexander et al., 1986; Fama and Sullivan, 2015; Haber and McFarland, 2001; Martin, 1996). Given the importance of deep gray matter regions to cortical network connections, it is likely that age-related increases in the deposition of iron in these regions would have consequences for cognitive function, especially the fluid abilities that are

most vulnerable to cognitive decline. In their 1970 review of aging and psychomotor slowing, Hicks and Birren (1970) proposed that the basal ganglia and their associated cortical targets comprised a neural mechanism of age-related psychomotor slowing. Rubin (1999) pointed out that evidence linking the frontal lobes to age-related decline in specific cognitive functions (e.g., inhibition) was no stronger than the evidence linking deep gray matter regions, especially the caudate, to the same form of age-related cognitive decline. Similarly, Grahn et al. (2008) surveyed evidence across basic neurobiological and clinical studies and concluded that the caudate has a significant cognitive dimension. These authors proposed that the caudate nucleus contributes to behavior through the excitation of correct action schemas and the selection of appropriate sub-goals based on an evaluation of action-outcomes, both processes fundamental to successful goal-directed action. The putamen, in contrast, appears to coordinate cognitive functions related more closely to stimulus-response, or habit, learning.

Previous reviews of imaging studies of brain iron suggest that age-related increase in deep gray matter iron, particularly in the caudate and putamen, contributes to deficits in neurocognitive function (Daugherty and Raz, 2013; Daugherty and Raz, 2015; Ghadery et al., 2015), perhaps by leading to a decrease in volume of cognitively relevant brain structures (Rodrigue et al., 2013). The majority of the studies included in these previous reviews, however, were based on MRI relaxometry rather than QSM as method of estimation for iron. In addition, previous research has not often compared different forms of neurocognitive outcome, focusing instead on a single outcome, such as working memory (Daugherty et al., 2015; Rodrigue et al., 2013) or motor performance (Adamo et al., 2014), and is limited by single age-group designs. However, the initial studies from MRI relaxometry have provided evidence for a relation between brain iron and age-related decline in neurocognitive function. For example, Ghadery et al. (2015) examined R2*-based estimates of iron in six deep gray matter regions and three cognitive domains (psychomotor speed, executive function, memory, and a composite global measure), in a sample of 336 individuals 55–72 years of age. These authors found that estimated iron load in the putamen accounted for 18–24% of the age-related variance in executive function, global cognitive function, and psychomotor speed, whereas iron in the globus pallidus accounted for only 7–9% of the age-related variance in these measures.

In the first QSM study of the relation between brain iron and neurocognitive function (Table 3), Li et al. (2015a) reported a significant correlation between increasing susceptibility in the globus pallidus and red nuclei, and decreasing manual dexterity, for 132 healthy adults 40–83 years of age. These authors, however, focused entirely on deep gray matter regions, and thus the potential role of cortical iron was not assessed. In addition, although composite measures of manual dexterity and executive function were obtained, the behavioral measures were weighted more towards motor function (Purdue pegboard), and age-related differences in the susceptibility-behavioral relation were not tested specifically.

As illustrated by the pattern in Table 3, QSM studies focusing on the age-cognition relation more directly have fairly consistently indicated an association between age-related increases in brain iron and decline in measures of fluid cognition. For example, in a voxelwise analysis of 67 healthy, community-dwelling individuals 18–78 years of age, Howard et

al. (2022) defined clusters from the correlation between susceptibility and fluid cognition. Consistent with the age-related effects reported by Acosta-Cabronero et al. (2016), Howard et al. found that susceptibility for pre- and post-central frontal gyri, among other regions, was related to fluid cognition and comparable in magnitude to those in the putamen (Figure 5 in Howard et al., 2022). In addition, increasing susceptibility in inferior temporal cortex, particularly in the right hemisphere, exhibited a mediating influence on the relation between age and fluid cognition. In a sample of 55 healthy older adults, Zachariou et al. (2020) found that high QSM-based iron concentration in the parietal lobe was associated with poorer working memory task performance. Thus, while motor and premotor cortical regions appear to be preferentially vulnerable to iron deposition, other cortical regions also appear to be involved when analyses focus on the age-cognition relation. However, some paradoxical effects have also been reported, in which higher levels of brain iron are associated with better neurocognitive performance in older adults (Kalpouzos et al., 2021; Persson et al., 2020; Treit et al., 2021). One potential explanation for these surprising results might be the use of net susceptibility measures, rather than separately analyzing the positive (paramagnetic) signal from the negative (diamagnetic) signal. Regardless, an important future direction for this line of work is to distinguish regions of age-related increase in iron deposition (both deep gray matter and cortical) from those regions contributing specifically to the age-related decline in fluid cognitive abilities.

7. Multimodal Imaging Studies of Susceptibility in Aging

As noted previously, variation in the level of brain iron can have either positive or negative consequences for overall brain functioning, because iron is a necessary nutrient for neural physiology and repair, and yet excessive iron also contributes to various forms of neurodegenerative disease. Several neuroimaging studies represent a fourth theme of QSM research, the combination of two or more imaging modalities to characterize age-related differences in susceptibility-based estimates of brain iron (Table 4). These multimodal studies are informative regarding both the underlying neurobiology and behavioral sequelae of increased brain iron. Although several multimodal QSM studies have focused specifically on AD, the biomarkers relevant for AD, primarily Aβ and tau, are not present exclusively in disease but occur in healthy adults as well, at sub-clinical levels. Our focus here is on susceptibility-estimated brain iron from QSM, as combined with information from other imaging modalities, to characterize neurocognitive function in healthy adults.

Combining QSM with positron emission tomography (PET) indicates that increased brain iron tends to co-localize with Aβ, even in healthy adults (Cogswell and Fan, 2023). Van Bergen et al. (2018b) provided clear evidence for the co-localization of iron and Aβ in a study of 116 healthy older adults, combining QSM with [18F]-flutemetamol PET, which can localize Aβ. In a voxelwise analysis, these authors found that positive correlations between iron load and Aβ plaques were present in a bilateral pattern of clusters in basal ganglia but also several regions in the frontal, temporal, and parietal lobes. When these clusters were thresholded for the level of Aβ, individuals with higher levels of Aβ in frontal and temporal clusters exhibited lower scores on a composite measure of fluid cognition. Van Bergen et al. (2018a) added analyses of fluid attenuated inversion recovery (FLAIR) images, as an estimate of small vessel cerebrovascular disease (from the

presence of white matter hyperintensities), to the Aβ PET and QSM imaging. Their findings indicated that in the oldest-old group (85–96 years), a relatively lower cortical iron load was associated with a lower vulnerability to loss of cognitive function, even when combined with other neuropathologies (e.g., decreased cortical volume and increased prevalence of cerebrovascular disease).

Only a handful of studies have combined diffusion-weighted imaging (DWI) with QSM. Two of these studies focused on diffusion properties of deep gray matter nuclei in relation to susceptibility in those nuclei, finding positive relations between diffusivity and susceptibility in the striatum (Gong et al., 2015; Yang et al., 2022). An additional study focused on diffusion properties of white matter found that lower neurite density in frontoparietal white matter was associated with higher susceptibility in adjacent frontoparietal gray matter regions (Zachariou et al., 2023). Higher susceptibility in deep gray matter nuclei has also been related to worse white matter microstructure, seen as higher diffusivity in association and projection tracts (Zhou et al., 2020). Together, these findings support the theoretical notion that the excessive accumulation of iron in gray matter regions should negatively interact with the function of oligodendrocytes (Todorich et al., 2009), seen as lower measures of white matter microstructure.

Relaxometry studies (e.g., Salami et al., 2018) suggest that deep gray matter iron may contribute to age-related disruption of resting-state functional connectivity in healthy aging, as assessed by functional magnetic resonance imaging (fMRI). Several QSM studies have also incorporated fMRI to similarly investigate the relation between susceptibility and measures of cortical activation or functional connectivity. Zachariou et al. (2020) combined QSM with task-related fMRI activation in an analysis of working memory performance, for 55 healthy older adults. These authors found that task performance was correlated positively with the strength of task-based functional connectivity between brain regions of a frontoparietal network associated with working memory. Higher cortical iron concentration in the parietal lobe, however, was associated with lower activation within this frontoparietal network and with poorer working memory performance, after controlling for both cerebral blood flow and brain volume. Zachariou et al. concluded that high cortical iron concentration disrupts communication within the frontoparietal networks supporting older adults' working memory performance.

The Zachariou et al. (2020) findings are consistent with the role of iron in age-related decline in fluid cognition, reviewed in Section 6 of this article. Other findings, however, do not fit this pattern. Persson et al. (2020), for example, found that striatal iron concentration, for a combined sample of younger and older adults, was related positively to both task-related fMRI activation and behavioral performance, within an implicit sequence learning task. Thus, exactly how brain iron deposition and fMRI activation interact with age-related declines in fluid cognition may depend on the nature of the behavioral task and the sampled brain regions. In addition, whereas Zachariou et al. (2020) limited analyses only to measures of positive susceptibility, Persson et al. (2020) instead used an average measure of susceptibility that is sensitive to iron, among several other neurobiological properties (e.g., the degree of myelination).

8. Moderators of Susceptibility Measures in Aging

A handful of studies illustrate our fifth theme, the role of other neurobiological variables as modifiers of brain iron in healthy aging (Table 5). The potential moderating effect of biological sex has been most frequently assessed, but these studies overwhelmingly report no significant differences between males and females in susceptibility for deep gray matter nuclei (Acosta-Cabronero et al., 2016; Gong et al., 2015; Li et al., 2023; Li et al., 2021; Persson et al., 2015; Treit et al., 2021; Xu et al., 2008). There is some minimal evidence that females may have lower susceptibility than males, but these effects vary anatomically (e.g., red nucleus vs. substantia nigra; Gong et al., 2015; Li et al., 2021) and are not consistent across studies. Only one study has assessed sex-related differences within cortical regions, and similarly observed no significant group differences (Acosta-Cabronero et al., 2016). Menstruation-related loss of iron in females has been posited as a likely mechanism of sex-related differences in brain iron accumulation (Tishler et al., 2012). However, most prior analyses have been conducted across women of all ages, including both early pre-menopausal (age 20–30 years) and late post-menopausal (ages 65–70 years) women, and the interaction of these lifespan differences may contribute to a net minimal effect of biological sex. Future investigations of these sex-related differences may therefore benefit from comparisons between pre- and post-menopausal women in midlife.

The effects of several health-related variables on iron accumulation in aging have also been examined in a few studies. There is some preliminary evidence that a diagnosis of type II diabetes is associated with higher susceptibility in the dorsal striatum and red nucleus, potentially through the damaging effects of hyperglycemia on neuronal metabolic functions (Li et al., 2021). Smoking tobacco products has also been linked to elevated susceptibility in the thalamus (Li et al., 2021), which could theoretically be attributed to hypertension. However, that same study observed that being hypertensive was paradoxically linked to lower susceptibility in the red nucleus (Li et al., 2021), and a separate study reported no significant effect of hypertension in cortical or deep gray matter regions across the adult lifespan (Acosta-Cabronero et al., 2016). But relative to the less modifiable effect of disease status, one particularly promising modifiable lifestyle variable is the consumption of a diet that is high in nuts, fish, and healthy oils, which has been linked to lower susceptibility in parietal cortex and the putamen among older adults (Zachariou et al., 2021).

Beyond biological sex and health-related variables, particular genetic combinations have been identified as a third moderating variable of susceptibility in aging, with some genotypes being associated with lower susceptibility values. For example, adults across the lifespan with less favorable combinations on genes involved in iron transport and storage, particularly C282Y and H63D mutations on the HFE gene (but also TF and SLC25A37; Elliott et al., 2018), have higher susceptibility in basal ganglia nuclei (Elliott et al., 2018; Kalpouzos et al., 2021). Studies of middle-aged and older adults similarly report that individuals with an ε4 allele on the APOE gene (involved in the transport of cholesterol and phospholipids in the brain) had higher susceptibility in the hippocampus, amygdala, caudate, and temporal and parietal cortices than those who do have not the ε4 allele (Ayton et al., 2017; Nir et al., 2022). Similarly, for the COMT gene (involved in endogenous dopamine synthesis), one study reported that older adults with the less favorable *Met* allele

combination had higher susceptibility values in the striatum and dorsolateral prefrontal cortex when compared to those with the more favorable *Val* combination (Gustavsson et al., 2022). Intriguingly, the difference in susceptibility values was not significant among younger adults in this study. Thus, the genetic influence on susceptibility patterns may become magnified as a function of increasing age, similar to previous reports between genotype combinations and diffusion-tensor based measures of white matter microstructure between younger-old (ages 65-80) and oldest-old (ages 80+ years) adults (Merenstein and Bennett, 2022).

9. Conclusions and Future Directions

QSM is a valuable tool for assessing the degree of cerebral iron accumulation *in vivo* and has shown great promise for contributing to our understanding of healthy neurocognitive aging. QSM has confirmed previous findings from *ex vivo* histology indicating that, across the adult lifespan, some deep gray matter nuclei (e.g., putamen) are more vulnerable to iron accumulation than others (e.g., thalamus, globus pallidus; Table 1). QSM has also confirmed and extended previous reports that, beyond deep gray matter nuclei, the frontal, temporal, and parietal cortical regions exhibit age-related increases in iron deposition (Table 2). Although the magnitude of cortical iron is lower than that of deep gray matter iron, both deep gray matter and cortical iron accumulation are associated with age-related decline in several domains of fluid cognition (Table 3).

The evidence to date, however, is not yet conclusive as to whether the relation of age to iron, and age to fluid cognition, are independent effects, or whether brain iron deposition influences the relation between adult age and cognition (but cf. Howard et al., 2022). This line of work therefore may benefit from more fine-grained analytical scales. For example, depth-wise analyses of cortical iron load can separately examine age-related differences in susceptibility at the most superficial (pial) depths versus deeper depths near the gray matter / white matter boundary (Lee et al., 2023), and these measures may, in turn, differentially explain age-related decline in cognitive performance. Multimodal neuroimaging studies can also provide a more detailed understanding about the interaction between brain iron and other neural substrates, with preliminary support for the notion that increased iron negatively interacts with neuroimaging measures of brain function, white matter microstructure, and AD-related pathologies, even in the absence of frank disease (Table 4).

Based on the methodological variability among QSM studies in aging, research in this field may benefit from the development of standardized toolboxes for QSM processing, such as IronSmith (Zachariou et al., 2022), and large-scale imaging consortia, to help guide the choice of acquisition parameters for QSM studies (e.g., the Human Connectome Project; Glasser et al., 2016). It is also imperative that future research determine the most appropriate reference region for studies of aging, by comparing susceptibility measured from samples of cerebrospinal fluid versus susceptibility in *ex vivo* white matter and gray matter tissue. Finally, we suggest that future research separately examine both positive and negative sources of susceptibility to help better characterize these distinct signals and how they vary in relation to age and neurodegenerative disease (Ahmed et al., 2023; Betts et al., 2016; Chen et al., 2021a; Shin et al., 2021).

On the behavioral side, additional analyses are needed that can separate different components of fluid cognition. Diffusion decision modeling of reaction time, for example, can distinguish nondecision time (sensory encoding and response initiation) from the rate of information extraction and evidence thresholds (Ratcliff et al., 2016; Voss et al., 2013). Application of this modeling to date suggests that the age-related decline in fluid cognition is dominated by increased nondecision time and cautiousness (Madden et al., 2020b; Merenstein et al., 2023a; Ratcliff, 2008). Because nondecision time relies on sensorimotor circuits comprising deep gray matter-cortical connections, the age-related increase in brain iron may have a specific relation to this component of reaction time. Future studies incorporating these new directions, and adopting longitudinal assessments where possible, should seek to determine how the detrimental effects of iron accumulation can be modified, and potentially mitigated, through neural and lifestyle interventions (Table 5).

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References

*Acosta-Cabronero J, Betts MJ, Cardenas-Blanco A, Yang S, Nestor PJ, 2016. In vivo MRI mapping of brain iron deposition across the adult lifespan. Journal of Neuroscience 36, 364–374. doi: 10.1523/JNEUROSCI.1907-15.2016 [PubMed: 26758829]

Acosta-Cabronero J, Williams GB, Cardenas-Blanco A, Arnold RJ, Lupson V, Nestor PJ, 2013. In vivo quantitative susceptibility mapping (QSM) in Alzheimer's disease. PLoS One 8, e81093. doi: 10.1371/journal.pone.0081093 [PubMed: 24278382]

Adamo DE, Daugherty AM, Raz N, 2014. Grasp force matching and brain iron content estimated in vivo in older women. Brain Imaging and Behavior 8, 579–587. doi: 10.1007/s11682-013-9284-6 [PubMed: 24363212]

Ahmed M, Chen J, Arani A, Senjem ML, Cogswell PM, Jack CR, Liu C, 2023. The diamagnetic component map from quantitative susceptibility mapping (QSM) source separation reveals pathological alteration in Alzheimer's disease-driven neurodegeneration. NeuroImage 280, 120357. doi: 10.1016/j.neuroimage.2023.120357 [PubMed: 37661080]

Alexander GE, DeLong MR, Strick PL, 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annual Review of Neuroscience 9, 357–381. doi: 10.1146/annurev.ne.09.030186.002041

Ayton S, Fazlollahi A, Bourgeat P, Raniga P, Ng A, Lim YY, Diouf I, Farquharson S, Fripp J, Ames D, Doecke J, Desmond P, Ordidge R, Masters CL, Rowe CC, Maruff P, Villemagne VL, Australian Imaging B, Lifestyle Research G, Salvado O, Bush AI, 2017. Cerebral quantitative susceptibility mapping predicts amyloid-beta-related cognitive decline. Brain 140, 2112–2119. doi: 10.1093/brain/awx137 [PubMed: 28899019]

Ayton S, Lei P, Bush AI, 2013. Metallostasis in Alzheimer's disease. Free Radical Biology & Medicine 62, 76–89. doi: 10.1016/j.freeradbiomed.2012.10.558 [PubMed: 23142767]

Barbosa JH, Santos AC, Tumas V, Liu M, Zheng W, Haacke EM, Salmon CE, 2015. Quantifying brain iron deposition in patients with Parkinson's disease using quantitative susceptibility mapping, R2 and R2*. Magnetic Resonance Imaging 33, 559–565. doi: 10.1016/j.mri.2015.02.021 [PubMed: 25721997]

*Bauer CE, Zachariou V, Seago E, Gold BT, 2021. White matter hyperintensity volume and location: Associations with WM microstructure, brain iron, and cerebral perfusion. Frontiers in Aging Neuroscience 13. doi: 10.3389/fnagi.2021.617947

Behrens TE, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott CA, Boulby PA, Barker GJ, Sillery EL, Sheehan K, Ciccarelli O, Thompson AJ, Brady JM, Matthews PM, 2003. Non-

invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nature Neuroscience 6, 750–757. doi: 10.1038/nn1075 [PubMed: 12808459]

*Berman S, Drori E, Mezer AA, 2022. Spatial profiles provide sensitive MRI measures of the midbrain micro- and macrostructure. NeuroImage 264, 119660. doi: 10.1016/j.neuroimage.2022.119660 [PubMed: 36220534]

Betts MJ, Acosta-Cabronero J, Cardenas-Blanco A, Nestor PJ, Düzel E, 2016. High-resolution characterisation of the aging brain using simultaneous quantitative susceptibility mapping (QSM) and R2 measurements at 7T. NeuroImage 138, 43–63. doi: 10.1016/j.neuroimage.2016.05.024 [PubMed: 27181761]

Bhattarai A, Chen Z, Ward PGD, Talman P, Mathers S, Phan TG, Chapman C, Howe J, Lee S, Lie Y, Egan GF, Chua P, 2020. Serial assessment of iron in the motor cortex in limb-onset amyotrophic lateral sclerosis using quantitative susceptibility mapping. Quantitative Imaging in Medicine and Surgery 10, 1465–1476. doi: 10.21037/qims-20-187 [PubMed: 32676365]

*Bilgic B, Pfefferbaum A, Rohlfing T, Sullivan EV, Adalsteinsson E, 2012. MRI estimates of brain iron concentration in normal aging using quantitative susceptibility mapping. NeuroImage 59, 2625–2635. doi: 10.1016/j.neuroimage.2011.08.077 [PubMed: 21925274]

Bilgic B, Xie L, Dibb R, Langkammer C, Mutluay A, Ye H, Polimeni JR, Augustinack J, Liu C, Wald LL, Setsompop K, 2016. Rapid multi-orientation quantitative susceptibility mapping. NeuroImage 125, 1131–1141. doi: 10.1016/j.neuroimage.2015.08.015 [PubMed: 26277773]

Birren JE, 1965. Age changes in speed of behavior: Its central nature and physiological correlates. In: Welford AT, Birren JE (Eds.), Behavior, aging, and the nervous system. Thomas, Springfield, IL, pp. 191–216.

Brass SD, Chen NK, Mulkern RV, Bakshi R, 2006. Magnetic resonance imaging of iron deposition in neurological disorders. Topics in Magnetic Resonance Imaging 17, 31–40. doi: 10.1097/01.rmr.0000245459.82782.e4 [PubMed: 17179895]

Brinley JF, 1965. Cognitive sets, speed and accuracy of performance in the elderly. In: Welford AT, Birren JE (Eds.), Behavior, aging, and the nervous system. Thomas, Springfield, IL, pp. 114–149.

*Chen BT, Ghassaban K, Jin T, Patel SK, Ye N, Sun CL, Kim H, Rockne RC, Mark Haacke E, Root JC, Saykin AJ, Ahles TA, Holodny AI, Prakash N, Mortimer J, Waisman J, Yuan Y, Somlo G, Li D, Yang R, Tan H, Katheria V, Morrison R, Hurria A, 2018. Subcortical brain iron deposition and cognitive performance in older women with breast cancer receiving adjuvant chemotherapy: A pilot MRI study. Magnetic Resonance Imaging 54, 218–224. doi: 10.1016/j.mri.2018.07.016 [PubMed: 30076946]

Chen J, Gong N-J, Chaim KT, Otaduy MCG, Liu C, 2021a. Decompose quantitative susceptibility mapping (QSM) to sub-voxel diamagnetic and paramagnetic components based on gradient-echo MRI data. NeuroImage 242, 118477. doi: 10.1016/j.neuroimage.2021.118477 [PubMed: 34403742]

*Chen L, Soldan A, Oishi K, Faria A, Zhu Y, Albert M, van Zijl PCM, Li X, 2021b. Quantitative susceptibility mapping of brain iron and β-Amyloid in MRI and PET relating to cognitive performance in cognitively normal older adults. Radiology 298, 353–362. doi: 10.1148/radiol.2020201603 [PubMed: 33231528]

Chen NK, Guidon A, Chang HC, Song AW, 2013. A robust multi-shot scan strategy for high-resolution diffusion weighted MRI enabled by multiplexed sensitivity-encoding (MUSE). NeuroImage 72, 41–47. doi: 10.1016/j.neuroimage.2013.01.038 [PubMed: 23370063]

*Chiang GC, Cho J, Dyke J, Zhang H, Zhang Q, Tokov M, Nguyen T, Kovanlikaya I, Amoashiy M, de Leon M, Wang Y, 2022. Brain oxygen extraction and neural tissue susceptibility are associated with cognitive impairment in older individuals. Journal of Neuroimaging 32, 697–709. doi: 10.1111/jon.12990 [PubMed: 35294075]

Cogswell PM, Fan AP, 2023. Multimodal comparisons of QSM and PET in neurodegeneration and aging. NeuroImage 273, 120068. doi: 10.1016/j.neuroimage.2023.120068 [PubMed: 37003447]

Connor JR, Snyder BS, Beard JL, Fine RE, Mufson EJ, 1992. Regional distribution of iron and iron-regulatory proteins in the brain in aging and Alzheimer's disease. Journal of Neuroscience Research 31, 327–335. doi: 10.1002/jnr.490310214 [PubMed: 1573683]

Craik FI, Bialystok E, 2006. Cognition through the lifespan: Mechanisms of change. Trends in Cognitive Sciences 10, 131–138. doi: 10.1016/j.tics.2006.01.007 [PubMed: 16460992]

Cummings JL, 1993. Frontal-subcortical circuits and human behavior. Archives of Neurology 50, 873–880. doi: 10.1001/archneur.1993.00540080076020 [PubMed: 8352676]

Daugherty A, Raz N, 2013. Age-related differences in iron content of subcortical nuclei observed in vivo: A meta-analysis. NeuroImage 70, 113–121. doi: 10.1016/j.neuroimage.2012.12.040 [PubMed: 23277110]

Daugherty AM, Haacke EM, Raz N, 2015. Striatal iron content predicts its shrinkage and changes in verbal working memory after two years in healthy adults. Journal of Neuroscience 35, 6731–6743. doi: 10.1523/JNEUROSCI.4717-14.2015 [PubMed: 25926451]

Daugherty AM, Raz N, 2015. Appraising the role of iron in brain aging and cognition: Promises and limitations of MRI methods. Neuropsychology Review 25, 272–287. doi: 10.1007/s11065-015-9292-y [PubMed: 26248580]

Deh K, Ponath GD, Molvi Z, Parel GT, Gillen KM, Zhang S, Nguyen TD, Spincemaille P, Ma Y, Gupta A, Gauthier SA, Pitt D, Wang Y, 2018. Magnetic susceptibility increases as diamagnetic molecules breakdown: Myelin digestion during multiple sclerosis lesion formation contributes to increase on QSM. Journal of Magnetic Resonance Imaging 48, 1281–1287. doi: 10.1002/jmri.25997 [PubMed: 29517817]

Deistung A, Schafer A, Schweser F, Biedermann U, Turner R, Reichenbach JR, 2013. Toward in vivo histology: A comparison of quantitative susceptibility mapping (QSM) with magnitude-, phase-, and R2*-imaging at ultra-high magnetic field strength. NeuroImage 65, 299–314. doi: 10.1016/j.neuroimage.2012.09.055 [PubMed: 23036448]

Deistung A, Schweser F, Reichenbach JR, 2017. Overview of quantitative susceptibility mapping. NMR in Biomedicine 30, e3569. doi: 10.1002/nbm.3569

Dempster FN, 1992. The rise and fall of the inhibitory mechanism: Toward a unified theory of cognitive development and aging. Developmental Review 12, 45–75. doi: 10.1016/0273-2297(92)90003-K

Dennis NA, Cabeza R, 2008. Neuroimaging of healthy cognitive aging. In: Craik FIM, Salthouse TA (Eds.), The handbook of aging and cognition. Psychology Press, New York, pp. 1–54.

Dexter DT, Wells FR, Agid F, Agid Y, Lees AJ, Jenner P, Marsden CD, 1987. Increased nigral iron content in postmortem parkinsonian brain. Lancet 2, 1219–1220. doi: 10.1016/s0140-6736(87)91361-4 [PubMed: 2890848]

Duce JA, Tsatsanis A, Cater MA, James SA, Robb E, Wikhe K, Leong SL, Perez K, Johanssen T, Greenough MA, Cho HH, Galatis D, Moir RD, Masters CL, McLean C, Tanzi RE, Cappai R, Barnham KJ, Ciccotosto GD, Rogers JT, Bush AI, 2010. Iron-export ferroxidase activity of beta-amyloid precursor protein is inhibited by zinc in Alzheimer's disease. Cell 142, 857–867. doi: 10.1016/j.cell.2010.08.014 [PubMed: 20817278]

*Elliott LT, Sharp K, Alfaro-Almagro F, Shi S, Miller KL, Douaud G, Marchini J, Smith SM, 2018. Genome-wide association studies of brain imaging phenotypes in UK Biobank. Nature 562, 210–216. doi: 10.1038/s41586-018-0571-7 [PubMed: 30305740]

Fama R, Sullivan EV, 2015. Thalamic structures and associated cognitive functions: Relations with age and aging. Neuroscience & Biobehavioral Reviews 54, 29–37. doi: 10.1016/j.neubiorev.2015.03.008 [PubMed: 25862940]

Fjell AM, Walhovd KB, 2010. Structural brain changes in aging: Courses, causes and cognitive consequences. Reviews in the Neurosciences 21, 187–221. doi: 10.1515/revneuro.2010.21.3.187 [PubMed: 20879692]

*Garzón B, Sitnikov R, Bäckman L, Kalpouzos G, 2017. Can transverse relaxation rates in deep gray matter be approximated from functional and T(2)-weighted FLAIR scans for relative brain iron quantification? Magnetic Resonance Imaging 40, 75–82. doi: 10.1016/j.mri.2017.04.005 [PubMed: 28438711]

*Garzón B, Sitnikov R, Bäckman L, Kalpouzos G, 2018. Automated segmentation of midbrain structures with high iron content. NeuroImage 170, 199–209. doi: 10.1016/j.neuroimage.2017.06.016 [PubMed: 28602813]

Gerlach M, Ben-Shachar D, Riederer P, Youdim MB, 1994. Altered brain metabolism of iron as a cause of neurodegenerative diseases? Journal of Neurochemistry 63, 793–807. doi: 10.1046/j.1471-4159.1994.63030793.x [PubMed: 7519659]

Ghadery C, Pirpamer L, Hofer E, Langkammer C, Petrovic K, Loitfelder M, Schwingenschuh P, Seiler S, Duering M, Jouvent E, Schmidt H, Fazekas F, Mangin JF, Chabriat H, Dichgans M, Ropele S, Schmidt R, 2015. R2* mapping for brain iron: Associations with cognition in normal aging. Neurobiology of Aging 36, 925–932. doi: 10.1016/j.neurobiolaging.2014.09.013 [PubMed: 25443291]

*Ghassaban K, He N, Sethi SK, Huang P, Chen S, Yan F, Haacke EM, 2019. Regional high iron in the substantia nigra differentiates Parkinson's disease patients from healthy controls. Frontiers in Aging Neuroscience 11, 1–10. doi: 10.3389/fnagi.2019.00106 [PubMed: 30740048]

Glasser MF, Smith SM, Marcus DS, Andersson JLR, Auerbach EJ, Behrens TEJ, Coalson TS, Harms MP, Jenkinson M, Moeller S, Robinson EC, Sotiropoulos SN, Xu J, Yacoub E, Ugurbil K, Van Essen DC, 2016. The Human Connectome Project's neuroimaging approach. Nature Neuroscience 19, 1175–1187. doi: 10.1038/nn.4361 [PubMed: 27571196]

*Gong N-J, Wong C-S, Hui ES, Chan C-C, Leung L-M, 2015. Hemisphere, gender and age-related effects on iron deposition in deep gray matter revealed by quantitative susceptibility mapping. NMR in Biomedicine 28, 1267–1274. doi: 10.1002/nbm.3366 [PubMed: 26313542]

Goodman L, 1953. Alzheimer's disease: A clinico-pathologic analysis of twenty-three cases with a theory on pathogenesis. Journal of Nervous & Mental Disease 118, 97–130. [PubMed: 13109530]

Gotz ME, Double K, Gerlach M, Youdim MB, Riederer P, 2004. The relevance of iron in the pathogenesis of Parkinson's disease. Annals of the New York Academy of Sciences 1012, 193–208. doi: 10.1196/annals.1306.017 [PubMed: 15105267]

Grady C, 2012. The cognitive neuroscience of ageing. Nature Reviews Neuroscience 13, 491–505. doi: 10.1038/nrn3256 [PubMed: 22714020]

Grahn JA, Parkinson JA, Owen AM, 2008. The cognitive functions of the caudate nucleus. Progress in Neurobiology 86, 141–155. doi: 10.1016/j.pneurobio.2008.09.004 [PubMed: 18824075]

Graybiel AM, Saka E, 2004. The basal ganglia and the control of action. In: Gazzaniga MS (Ed.), The cognitive neurosciences III. The MIT Press, Cambridge, MA, pp. 495–510.

Grundke-Iqbal I, Fleming J, Tung YC, Lassmann H, Iqbal K, Joshi JG, 1990. Ferritin is a component of the neuritic (senile) plaque in Alzheimer dementia. Acta Neuropathologica 81, 105–110 doi: 10.1007/BF00334497 [PubMed: 2082650]

*Guan X, Guo T, Zhou C, Wu J, Zeng Q, Li K, Luo X, Bai X, Wu H, Gao T, Gu L, Liu X, Cao Z, Wen J, Chen J, Wei H, Zhang Y, Liu C, Song Z, Yan Y, Pu J, Zhang B, Xu X, Zhang M, 2022. Altered brain iron depositions from aging to Parkinson's disease and Alzheimer's disease: A quantitative susceptibility mapping study. NeuroImage 264, 119683. doi: 10.1016/j.neuroimage.2022.119683 [PubMed: 36243270]

*Guan X, Zhang Y, Wei H, Guo T, Zeng Q, Zhou C, Wang J, Gao T, Xuan M, Gu Q, Xu X, Huang P, Pu J, Zhang B, Liu C, Zhang M, 2019. Iron-related nigral degeneration influences functional topology mediated by striatal dysfunction in Parkinson's disease. Neurobiology of Aging 75, 83–97. doi: 10.1016/j.neurobiolaging.2018.11.013 [PubMed: 30554085]

*Gustavsson J, Papenberg G, Falahati F, Laukka EJ, Kalpouzos G, 2022. Contributions of the catechol-o-methyltransferase Val158Met polymorphism to changes in brain iron across adulthood and their relationships to working memory. Frontiers in Human Neuroscience 16, 1–14. doi: 10.3389/fnhum.2022.838228

Gutteridge JMC, 1992. Iron and oxygen radicals in brain. Annals of Neurology 32, S16–S21. doi: 10.1002/ana.410320705 [PubMed: 1510375]

Haacke EM, Cheng NY, House MJ, Liu Q, Neelavalli J, Ogg RJ, Khan A, Ayaz M, Kirsch W, Obenaus A, 2005. Imaging iron stores in the brain using magnetic resonance imaging. Magnetic Resonance Imaging 23, 1–25. doi: 10.1016/j.mri.2004.10.001 [PubMed: 15733784]

Haacke EM, Liu S, Buch S, Zheng W, Wu D, Ye Y, 2015. Quantitative susceptibility mapping: Current status and future directions. Magnetic Resonance Imaging 33, 1–25. doi: 10.1016/j.mri.2014.09.004 [PubMed: 25267705]

Haber S, McFarland NR, 2001. The place of the thalamus in frontal cortical-basal ganglia circuits. Neuroscientist 7, 315–324. doi: 10.1177/107385840100700408 [PubMed: 11488397]

Hallgren B, Sourander P, 1958. The effect of age on the non-haemin iron in the human brain. Journal of Neurochemistry 3, 41–51. doi: 10.1111/j.1471-4159.1958.tb12607.x [PubMed: 13611557]

He N, Ling H, Ding B, Huang J, Zhang Y, Zhang Z, Liu C, Chen K, Yan F, 2015. Region-specific disturbed iron distribution in early idiopathic Parkinson's disease measured by quantitative susceptibility mapping. Human Brain Mapping 36, 4407–4420. doi: 10.1002/hbm.22928 [PubMed: 26249218]

Hentze MW, Muckenthaler MU, Andrews NC, 2004. Balancing acts: Molecular control of mammalian iron metabolism. Cell 117, 285–297. doi: 10.1016/S0092-8674(04)00343-5 [PubMed: 15109490]

Hicks LH, Birren JE, 1970. Aging, brain damage, and psychomotor slowing. Psychological Bulletin 74, 377–396. doi: 10.1037/h0033064 [PubMed: 4322220]

Horn JL, 1982. The theory of fluid and crystallized intelligence in relation to concepts of cognitive psychology and aging in adulthood. In: Craik FIM, Trehub S (Eds.), Aging and cognitive processes. Plenum Press, New York, pp. 237–278.

*Howard CM, Jain S, Cook AD, Packard LE, Mullin HA, Chen NK, Liu C, Song AW, Madden DJ, 2022. Cortical iron mediates age-related decline in fluid cognition. Human Brain Mapping 43, 1047–1060. doi: 10.1002/hbm.25706 [PubMed: 34854172]

*Jäschke D, Steiner KM, Chang DI, Claaßen J, Uslar E, Thieme A, Gerwig M, Pfaffenrot V, Hulst T, Gussew A, Maderwald S, Göricke SL, Minnerop M, Ladd ME, Reichenbach JR, Timmann D, Deistung A, 2023. Age-related differences of cerebellar cortex and nuclei: MRI findings in healthy controls and its application to spinocerebellar ataxia (SCA6) patients. NeuroImage 270, 119950. doi: 10.1016/j.neuroimage.2023.119950 [PubMed: 36822250]

*Kalpouzos G, Mangialasche F, Falahati F, Laukka EJ, Papenberg G, 2021. Contributions of HFE polymorphisms to brain and blood iron load, and their links to cognitive and motor function in healthy adults. Neuropsychopharmacology Reports 41, 393–404. doi: 10.1002/npr2.12197 [PubMed: 34291615]

*Kan H, Uchida Y, Arai N, Ueki Y, Aoki T, Kasai H, Kunitomo H, Hirose Y, Matsukawa N, Shibamoto Y, 2020. Simultaneous voxel-based magnetic susceptibility and morphometry analysis using magnetization-prepared spoiled turbo multiple gradient echo. NMR in Biomedicine 33, e4272. doi: 10.1002/nbm.4272 [PubMed: 32043682]

Ke Y, Qian ZM, 2003. Iron misregulation in the brain: A primary cause of neurodegenerative disorders. The Lancet Neurology 2, 246–253. doi: 10.1016/S1474-4422(03)00353-3 [PubMed: 12849213]

Keuken MC, Bazin PL, Backhouse K, Beekhuizen S, Himmer L, Kandola A, Lafeber JJ, Prochazkova L, Trutti A, Schäfer A, Turner R, Forstmann BU, 2017. Effects of aging on T_1, T_2, and QSM MRI values in the subcortex. Brain Structure and Function 222, 2487–2505. doi: 10.1007/s00429-016-1352-4 [PubMed: 28168364]

Koeppen AH, 1995. The history of iron in the brain. Journal of the Neurological Sciences 134 Suppl, 1–9. doi: 10.1016/0022-510x(95)00202-d [PubMed: 8847538]

*Koskimäki J, Polster SP, Li Y, Romanos S, Srinath A, Zhang D, Carrión-Penagos J, Lightle R, Moore T, Lyne SB, Stadnik A, Piedad K, Cao Y, Shenkar R, Dimov AV, Hobson N, Christoforidis GA, Carroll T, Girard R, Awad IA, 2020. Common transcriptome, plasma molecules, and imaging signatures in the aging brain and a Mendelian neurovascular disease, cerebral cavernous malformation. GeroScience 42, 1351–1363. doi: 10.1007/s11357-020-00201-4 [PubMed: 32556941]

LaBerge D, 2000. Networks of attention. In: Gazzaniga MS (Ed.), The new cognitive neurosciences, 2nd ed. MIT Press, Cambridge, MA, pp. 711–723.

LaBerge D, Buchsbaum MS, 1990. Positron emission tomographic measurements of pulvinar acitivity during an attention task. The Journal of Neuroscience 10, 613–619. doi: 10.1523/JNEUROSCI.10-02-00613.1990 [PubMed: 2303863]

Langkammer C, Krebs N, Goessler W, Scheurer E, Ebner F, Yen K, Fazekas F, Ropele S, 2010. Quantitative MR imaging of brain iron: A postmortem validation study. Radiology 257, 455–462. doi: 10.1148/radiol.10100495 [PubMed: 20843991]

Langkammer C, Schweser F, Krebs N, Deistung A, Goessler W, Scheurer E, Sommer K, Reishofer G, Yen K, Fazekas F, Ropele S, Reichenbach JR, 2012. Quantitative susceptibility mapping (QSM) as a means to measure brain iron? A post mortem validation study. NeuroImage 62, 1593–1599. doi: 10.1016/j.neuroimage.2012.05.049 [PubMed: 22634862]

Lee S, Shin HG, Kim M, Lee J, 2023. Depth-wise profiles of iron and myelin in the cortex and white matter using χ-separation: A preliminary study. NeuroImage 273, 120058. doi: 10.1016/j.neuroimage.2023.120058 [PubMed: 36997135]

*Li G, Tong R, Zhang M, Gillen KM, Jiang W, Du Y, Wang Y, Li J, 2023. Age-dependent changes in brain iron deposition and volume in deep gray matter nuclei using quantitative susceptibility mapping. NeuroImage 269, 119923. doi: 10.1016/j.neuroimage.2023.119923 [PubMed: 36739101]

*Li J, Zhang Q, Che Y, Zhang N, Guo L, 2021. Iron deposition characteristics of deep gray matter in elderly individuals in the community revealed by quantitative susceptibility mapping and multiple factor analysis. Frontiers in Aging Neuroscience 13, 1–13. doi: 10.3389/fnagi.2021.611891

*Li W, Langkammer C, Chou YH, Petrovic K, Schmidt R, Song AW, Madden DJ, Ropele S, Liu C, 2015a. Association between increased magnetic susceptibility of deep gray matter nuclei and decreased motor function in healthy adults. NeuroImage 105, 45–52. doi: 10.1016/j.neuroimage.2014.10.009 [PubMed: 25315786]

Li W, Wang N, Yu F, Han H, Cao W, Romero R, Tantiwongkosi B, Duong TQ, Liu C, 2015b. A method for estimating and removing streaking artifacts in quantitative susceptibility mapping. NeuroImage 108, 111–122. doi: 10.1016/j.neuroimage.2014.12.043 [PubMed: 25536496]

Li W, Wu B, Avram AV, Liu C, 2012. Magnetic susceptibility anisotropy of human brain in vivo and its molecular underpinnings. NeuroImage 59, 2088–2097. doi: 10.1016/j.neuroimage.2011.10.038 [PubMed: 22036681]

*Li W, Wu B, Batrachenko A, Bancroft-Wu V, Morey RA, Shashi V, Langkammer C, De Bellis MD, Ropele S, Song AW, Liu C, 2014. Differential developmental trajectories of magnetic susceptibility in human brain gray and white matter over the lifespan. Human Brain Mapping 35, 2698–2713. doi: 10.1002/hbm.22360 [PubMed: 24038837]

Li W, Wu B, Liu C, 2011. Quantitative susceptibility mapping of human brain reflects spatial variation in tissue composition. NeuroImage 55, 1645–1656. doi: 10.1016/j.neuroimage.2010.11.088 [PubMed: 21224002]

Liu C, Li W, Johnson GA, Wu B, 2011. High-field (9.4T) MRI of brain dysmyelination by quantitative mapping of magnetic susceptibility. NeuroImage 56, 930–938. doi: 10.1016/j.neuroimage.2011.02.024 [PubMed: 21320606]

Liu C, Li W, Tong KA, Yeom KW, Kuzminski S, 2015a. Susceptibility-weighted imaging and quantitative susceptibility mapping in the brain. Journal of Magnetic Resonance Imaging 42, 23–41. doi: 10.1002/jmri.24768 [PubMed: 25270052]

Liu C, Wei H, Gong NJ, Cronin M, Dibb R, Decker K, 2015b. Quantitative susceptibility mapping: Contrast mechanisms and clinical applications. Tomography 1, 3–17. doi: 10.18383/j.tom.2015.00136 [PubMed: 26844301]

*Liu M, Liu S, Ghassaban K, Zheng W, Dicicco D, Miao Y, Habib C, Jazmati T, Haacke EM, 2016. Assessing global and regional iron content in deep gray matter as a function of age using susceptibility mapping. Journal of Magnetic Resonance Imaging 44, 59–71. doi: 10.1002/jmri.25130 [PubMed: 26695834]

*Liu MQ, Chen ZY, Bian XB, Liu MY, Yu SY, Ma L, 2015c. MRI evaluation of lateral geniculate body in normal aging brain using quantitative susceptibility mapping. Chinese Medical Sciences Journal 30, 34–36. doi: 10.1016/s1001-9294(15)30006-7 [PubMed: 25837358]

Liu T, Eskreis-Winkler S, Schweitzer AD, Chen W, Kaplitt MG, Tsiouris AJ, Wang Y, 2013. Improved subthalamic nucleus depiction with quantitative susceptibility mapping. Radiology 269, 216–223. doi: 10.1148/radiol.13121991 [PubMed: 23674786]

Liu T, Xu W, Spincemaille P, Avestimehr AS, Wang Y, 2012. Accuracy of the morphology enabled dipole inversion (MEDI) algorithm for quantitative susceptibility mapping in MRI. IEEE Trans Med Imaging 31, 816–824. doi: 10.1109/tmi.2011.2182523 [PubMed: 22231170]

Lovell MA, Robertson JD, Teesdale WJ, Campbell JL, Markesbery WR, 1998. Copper, iron and zinc in Alzheimer's disease senile plaques. Journal of the Neurological Sciences 158, 47–52. doi: 10.1016/S0022-510X(98)00092-6 [PubMed: 9667777]

Madden DJ, 2001. Speed and timing of behavioral processes. In: Birren JE, Schaie KW (Eds.), Handbook of the psychology of aging. Academic Press, San Diego, CA, pp. 288–312.

Madden DJ, Jain S, Monge ZA, Cook AD, Lee A, Huang H, Howard CM, Cohen JR, 2020a. Influence of structural and functional brain connectivity on age-related differences in fluid cognition. Neurobiology of Aging 96, 205–222. doi: 10.1016/j.neurobiolaging.2020.09.010 [PubMed: 33038808]

Madden DJ, Parks EL, Tallman CW, Boylan MA, Hoagey DA, Cocjin SB, Packard LE, Johnson MA, Chou Y. h., Potter GG, Chen N. k., Siciliano RE, Monge ZA, Honig JA, Diaz MT, 2017. Sources of disconnection in neurocognitive aging: Cerebral white-matter integrity, resting-state functional connectivity, and white-matter hyperintensity volume. Neurobiology of Aging 54, 199–213. doi: 10.1016/j.neurobiolaging.2017.01.027 [PubMed: 28389085]

Madden DJ, Siciliano RE, Tallman CW, Monge ZA, Voss A, Cohen JR, 2020b. Response-level processing during visual feature search: Effects of frontoparietal activation and adult age. Attention, Perception, & Psychophysics 82, 330–349. doi: 10.3758/s13414-019-01823-3

Martin JH, 1996. Neuroanatomy text and atlas, 2nd edition. Appleton & Lange, Stamford, CT.

Martin WR, Ye FQ, Allen PS, 1998. Increasing striatal iron content associated with normal aging. Movement Disorders 13, 281–286. doi: 10.1002/mds.870130214 [PubMed: 9539342]

Meguro R, Asano Y, Odagiri S, Li C, Shoumura K, 2008. Cellular and subcellular localizations of nonheme ferric and ferrous iron in the rat brain: A light and electron microscopic study by the perfusion-Perls and -Turnbull methods. Archives of Histology and Cytology 71, 205–222. doi: 10.1679/aohc.71.205 [PubMed: 19359804]

Merenstein JL, Bennett IJ, 2022. Bridging patterns of neurocognitive aging across the older adult lifespan. Neuroscience & Biobehavioral Reviews 135, 104594. doi: 10.1016/j.neubiorev.2022.104594 [PubMed: 35227712]

Merenstein JL, Mullin HA, Madden DJ, 2023a. Age-related differences in frontoparietal activation for target and distractor singletons during visual search. Attention, Perception, & Psychophysics 85, 749–768. doi: 10.3758/s13414-022-02640-x

Merenstein JL, Zhao J, Mullin HA, Rudolph MD, Song AW, Madden DJ, 2023b. High-resolution multi-shot diffusion imaging of structural networks in healthy neurocognitive aging. NeuroImage 275, 120191. doi: 10.1016/j.neuroimage.2023.120191 [PubMed: 37244322]

Monge ZA, Geib BR, Siciliano RE, Packard LE, Tallman CW, Madden DJ, 2017. Functional modular architecture underlying attentional control in aging. NeuroImage 155, 257–270. doi: 10.1016/j.neuroimage.2017.05.002 [PubMed: 28476664]

*Moon Y, Han SH, Moon WJ, 2016. Patterns of brain iron accumulation in vascular dementia and Alzheimer's dementia using quantitative susceptibility mapping imaging. Journal of Alzheimer's disease, 737–745. doi: 10.3233/JAD-151037

Moscovitch M, Winocur G, 1992. The neuropsychology of memory and aging. In: Craik FIM, Salthouse TA (Eds.), The handbook of aging and cognition. Erlbaum, Hillsdale, NJ, pp. 315–372.

*Nir TM, Zhu AH, Gari IB, Dixon D, Islam T, Villalon-Reina JE, Medland SE, Thompson PM, Jahanshad N, 2022. Effects of ApoE4 and ApoE2 genotypes on subcortical magnetic susceptibility and microstructure in 27,535 participants from the UK Biobank. Pacific Symposium on Biocomputing 27, 121–132. [PubMed: 34890142]

O'Muircheartaigh J, Keller SS, Barker GJ, Richardson MP, 2015. White matter connectivity of the thalamus delineates the functional architecture of competing thalamocortical systems. Cerebral Cortex 25, 4477–4489. doi: 10.1093/cercor/bhv063 [PubMed: 25899706]

Park DC, Lautenschlager G, Hedden T, Davidson NS, Smith AD, Smith PK, 2002. Models of visuospatial and verbal memory across the adult life span. Psychology and Aging 17, 299–320. doi: 10.1037/0882-7974.17.2.299 [PubMed: 12061414]

*Persson J, Garzón B, Sitnikov R, Bäckman L, Kalpouzos G, 2020. A positive influence of basal ganglia iron concentration on implicit sequence learning. Brain Structure and Function 225, 735–749. doi: 10.1007/s00429-020-02032-7 [PubMed: 32055981]

*Persson N, Wu J, Zhang Q, Liu T, Shen J, Bao R, Ni M, Liu T, Wang Y, Spincemaille P, 2015. Age and sex related differences in subcortical brain iron concentrations among healthy adults. NeuroImage 122, 385–398. doi: 10.1016/j.neuroimage.2015.07.050 [PubMed: 26216277]

*Poynton CB, Jenkinson M, Adalsteinsson E, Sullivan EV, Pfefferbaum A, Wells W, 2015. Quantitative susceptibility mapping by inversion of a perturbation field model: Correlation with brain iron in normal aging. IEEE Transactions on Medical Imaging 34, 339–353. doi: 10.1109/TMI.2014.2358552 [PubMed: 25248179]

*Quevenco FC, Preti MG, van Bergen JMG, Hua J, Wyss M, Li X, Schreiner SJ, Steininger SC, Meyer R, Meier IB, Brickman AM, Leh SE, Gietl AF, Buck A, Nitsch RM, Pruessmann KP, van Zijl PCM, Hock C, Van De Ville D, Unschuld PG, 2017. Memory performance-related dynamic brain connectivity indicates pathological burden and genetic risk for Alzheimer's disease. Alzheimer's Research & Therapy 9, 24. doi: 10.1186/s13195-017-0249-7

Ratcliff R, 2008. Modeling aging effects on two-choice tasks: Response signal and response time data. Psychology and Aging 23, 900–916. doi: 10.1037/a0013930 [PubMed: 19140659]

Ratcliff R, Smith PL, Brown SD, McKoon G, 2016. Diffusion decision model: Current issues and history. Trends in Cognitive Sciences 20, 260–281. doi: 10.1016/j.tics.2016.01.007 [PubMed: 26952739]

Ravanfar P, Loi SM, Syeda WT, Van Rheenen TE, Bush AI, Desmond P, Cropley VL, Lane DJR, Opazo CM, Moffat BA, Velakoulis D, Pantelis C, 2021. Systematic Review: Quantitative Susceptibility Mapping (QSM) of Brain Iron Profile in Neurodegenerative Diseases. Frontiers in Neuroscience 15. doi: 10.3389/fnins.2021.618435

Raz N, Ghisletta P, Rodrigue KM, Kennedy KM, Lindenberger U, 2010. Trajectories of brain aging in middle-aged and older adults: Regional and individual differences. NeuroImage 51, 501–511. doi: 10.1016/j.neuroimage.2010.03.020 [PubMed: 20298790]

*Reeves JA, Bergsland N, Dwyer MG, Wilding GE, Jakimovski D, Salman F, Sule B, Meineke N, Weinstock-Guttman B, Zivadinov R, Schweser F, 2022. Susceptibility networks reveal independent patterns of brain iron abnormalities in multiple sclerosis. NeuroImage 261, 119503. doi: 10.1016/j.neuroimage.2022.119503 [PubMed: 35878723]

Rodrigue KM, Daugherty AM, Haacke EM, Raz N, 2013. The role of hippocampal iron concentration and hippocampal volume in age-related differences in memory. Cerebral Cortex 23, 1533–1541. doi: 10.1093/cercor/bhs139 [PubMed: 22645251]

Rouault TA, Cooperman S, 2006. Brain iron metabolism. Seminar in Pediatric Neurology 13, 142–148. doi: 10.1016/j.spen.2006.08.002

Rubin DC, 1999. Frontal-striatal circuits in cognitive aging: Evidence for caudate involvement. Aging, Neuropsychology, and Cognition 6, 241–259. doi: 10.1076/1382-5585(199912)06:04;1-B;FT241

Salami A, Avelar-Pereira B, Garzón B, Sitnikov R, Kalpouzos G, 2018. Functional coherence of striatal resting-state networks is modulated by striatal iron content. NeuroImage 183, 495–503. doi: 10.1016/j.neuroimage.2018.08.036 [PubMed: 30125714]

Salthouse TA, 1996. The processing-speed theory of adult age differences in cognition. Psychological Review 103, 403–428. doi: 10.1037/0033-295x.103.3.403 [PubMed: 8759042]

Salthouse TA, 2004. What and when of cognitive aging. Current Directions in Psychological Science 13, 140–144. doi: 10.1111/j.0963-7214.2004.00293.x

Salthouse TA, 2017. Neural correlates of age-related slowing. In: Cabeza R, Nyberg L, Park DC (Eds.), Cognitive neuroscience of aging: Linking cognitive and cerebral aging (2nd ed.). Oxford, New York, pp. 259–272.

Salthouse TA, Madden DJ, 2007. Information processing speed and aging. In: Deluca J, Kalmar J (Eds.), Information processing speed in clinical populations. Psychology Press, New York, pp. 221–241.

Sayre LM, Perry G, Atwood CS, Smith MA, 2000. The role of metals in neurodegenerative diseases. Cellular and Molecular Biology 46, 731–741. [PubMed: 10875436]

Sfera A, Bullock K, Price A, Inderias L, Osorio C, 2018. Ferrosenescence: The iron age of neurodegeneration? Mechanisms of Ageing and Development 174, 63–75. doi: 10.1016/j.mad.2017.11.012 [PubMed: 29180225]

Shin H-G, Lee J, Yun YH, Yoo SH, Jang J, Oh S-H, Nam Y, Jung S, Kim S, Fukunaga M, Kim W, Choi HJ, Lee J, 2021. χ-separation: Magnetic susceptibility source separation toward iron and myelin mapping in the brain. NeuroImage 240, 118371. doi: 10.1016/j.neuroimage.2021.118371 [PubMed: 34242783]

Smith MA, Harris PL, Sayre LM, Perry G, 1997. Iron accumulation in Alzheimer disease is a source of redox-generated free radicals. Proceedings of the National Academy of Science 94, 9866–9868. doi: 10.1073/pnas.94.18.9866

Sood S, Urriola J, Reutens D, O'Brien K, Bollmann S, Barth M, Vegh V, 2017. Echo time-dependent quantitative susceptibility mapping contains information on tissue properties. Magnetic Resonance in Medicine 77, 1946–1958. doi: 10.1002/mrm.26281 [PubMed: 27221590]

Spatz H, 1922. Über den Eisennachweis im Gehirn, besonders in Zentren des extrapyramidal-motorischen Systems. I. Teil [On the detection of iron in the brain, especially in centers of the extrapyramidal motor system. I part.]. Zeitschrift für die gesamte Neurologie und Psychiatrie 77, 261–390.

Sun Y, Ge X, Han X, Cao W, Wang Y, Ding W, Cao M, Zhang Y, Xu Q, Zhou Y, Xu J, 2017. Characterizing brain iron deposition in patients with subcortical vascular mild cognitive impairment using quantitative susceptibility mapping: A potential biomarker. Frontiers in Aging Neuroscience 9, 1–10. doi: 10.3389/fnagi.2017.00081 [PubMed: 28174533]

Taege Y, Hagemeier J, Bergsland N, Dwyer MG, Weinstock-Guttman B, Zivadinov R, Schweser F, 2019. Assessment of mesoscopic properties of deep gray matter iron through a model-based simultaneous analysis of magnetic susceptibility and R(2) - A pilot study in patients with multiple sclerosis and normal controls. NeuroImage 186, 308–320. doi: 10.1016/j.neuroimage.2018.11.011 [PubMed: 30445148]

Tishler TA, Raven EP, Lu PH, Altshuler LL, Bartzokis G, 2012. Premenopausal hysterectomy is associated with increased brain ferritin iron. Neurobiology of Aging 33, 1950–1958. doi: 10.1016/j.neurobiolaging.2011.08.002 [PubMed: 21925770]

Todorich B, Pasquini JM, Garcia CI, Paez PM, Connor JR, 2009. Oligodendrocytes and myelination: The role of iron. Glia 57, 467–478. doi: 10.1002/glia.20784 [PubMed: 18837051]

Treit S, Naji N, Seres P, Rickard J, Stolz E, Wilman AH, Beaulieu C, 2021. R2 and quantitative susceptibility mapping in deep gray matter of 498 healthy controls from 5 to 90 years. Human Brain Mapping 42, 4597–4610. doi: 10.1002/hbm.25569 [PubMed: 34184808]

*van Bergen JMG, Li X, Quevenco FC, Gietl AF, Treyer V, Leh SE, Meyer R, Buck A, Kaufmann PA, Nitsch RM, van Zijl PCM, Hock C, Unschuld PG, 2018a. Low cortical iron and high entorhinal cortex volume promote cognitive functioning in the oldest-old. Neurobiology of Aging 64, 68–75. doi: 10.1016/j.neurobiolaging.2017.12.014 [PubMed: 29351872]

*van Bergen JMG, Li X, Quevenco FC, Gietl AF, Treyer V, Meyer R, Buck A, Kaufmann P, Nitsch RM, van Zijl PCM, 2018b. Simultaneous quantitative susceptibility mapping and Flutemetamol-PET suggests local correlation of iron and β-amyloid as an indicator of cognitive performance at high age. NeuroImage 174, 308–316. doi: 10.1016/j.neuroimage.2018.03.021 [PubMed: 29548847]

Voss A, Nagler M, Lerche V, 2013. Diffusion models in experimental psychology: A practical introduction. Experimental Psychology 60, 385–402. doi: 10.1027/1618-3169/a000218 [PubMed: 23895923]

Wang Y, Liu T, 2015. Quantitative susceptibility mapping (QSM): Decoding MRI data for a tissue magnetic biomarker. Magnetic Resonance in Medicine 73, 82–101. doi: 10.1002/mrm.25358 [PubMed: 25044035]

Ward RJ, Zucca FA, Duyn JH, Crichton RR, Zecca L, 2014. The role of iron in brain ageing and neurodegenerative disorders. Lancet Neurology 13, 1045–1060. doi: 10.1016/S1474-4422(14)70117-6 [PubMed: 25231526]

West R, 2000. In defense of the frontal lobe hypothesis of cognitive aging. Journal of the International Neuropsychological Society 6, 727–729; discussion 730. doi: 10.1017/s1355617700666109 [PubMed: 11011518]

West RL, 1996. An application of prefrontal cortex function theory to cognitive aging. Psychological Bulletin 120, 272–292. doi: 10.1037/0033-2909.120.2.272 [PubMed: 8831298]

*Xu X, Wang Q, Zhang M, 2008. Age, gender, and hemispheric differences in iron deposition in the human brain: An in vivo MRI study. NeuroImage 40, 35–42. doi: 10.1016/j.neuroimage.2007.11.017 [PubMed: 18180169]

*Yang L, Cheng Y, Sun Y, Xuan Y, Niu J, Guan J, Rong Y, Jia Y, Zhuang Z, Yan G, Wu R, 2022. Combined application of quantitative susceptibility mapping and diffusion kurtosis imaging techniques to investigate the effect of iron deposition on microstructural changes in the brain in Parkinson's disease. Frontiers in Aging Neuroscience 14, 1–12. doi: 10.3389/fnagi.2022.792778

*Zachariou V, Bauer CE, Pappas C, Gold BT, 2023. High cortical iron is associated with the disruption of white matter tracts supporting cognitive function in healthy older adults. Cerebral Cortex 33, 4815–4828. doi: 10.1093/cercor/bhac382 [PubMed: 36182267]

*Zachariou V, Bauer CE, Powell DK, Gold BT, 2022. Ironsmith: An automated pipeline for QSM-based data analyses. NeuroImage 249, 118835. doi: 10.1016/j.neuroimage.2021.118835 [PubMed: 34936923]

*Zachariou V, Bauer CE, Seago ER, Panayiotou G, Hall ED, Butterfield DA, Gold BT, 2021. Healthy dietary intake moderates the effects of age on brain iron concentration and working memory performance. Neurobiology of Aging 106, 183–196. doi: 10.1016/j.neurobiolaging.2021.06.016 [PubMed: 34284261]

*Zachariou V, Bauer CE, Seago ER, Raslau FD, Powell DK, Gold BT, 2020. Cortical iron disrupts functional connectivity networks supporting working memory performance in older adults. NeuroImage 223, 117309. doi: 10.1016/j.neuroimage.2020.117309 [PubMed: 32861788]

Zecca L, Youdim MB, Riederer P, Connor JR, Crichton RR, 2004. Iron, brain ageing and neurodegenerative disorders. Nature Reviews Neuroscience 5, 863–873. doi: 10.1038/nrn1537 [PubMed: 15496864]

Zhang D, Snyder AZ, Fox MD, Sansbury MW, Shimony JS, Raichle ME, 2008. Intrinsic functional relations between human cerebral cortex and thalamus. Journal of Neurophysiology 100, 1740–1748. doi: 10.1152/jn.90463.2008 [PubMed: 18701759]

Zhang D, Snyder AZ, Shimony JS, Fox MD, Raichle ME, 2010. Noninvasive functional and structural connectivity mapping of the human thalamocortical system. Cerebral Cortex 20, 1187–1194. doi: 10.1093/cercor/bhp182 [PubMed: 19729393]

*Zhang Y, Wei H, Cronin MJ, He N, Yan F, Liu C, 2018. Longitudinal atlas for normative human brain development and aging over the lifespan using quantitative susceptibility mapping. NeuroImage 171, 176–189. doi: 10.1016/j.neuroimage.2018.01.008 [PubMed: 29325780]

*Zhou W, Shen B, Shen W. q., Chen H, Zheng Y. f., Fei J. j., 2020. Dysfunction of the glymphatic system might be related to iron deposition in the normal aging brain. Frontiers in Aging Neuroscience 12, 1–6. doi: 10.3389/fnagi.2020.559603 [PubMed: 32116644]

Table 1:

Age-Related Differences in QSM for Deep Gray Matter Regions

First author (year)	N	Age	CN	PT	SN	GP	RN	TH	DN	STN
Li et al. (2023)	220	10-70	+	++	+	+	+		+	
Gong et al. (2015)	42	25-78	+	++	+	+	+	0		
Zhou et al. (2020)	213	43-80	+	+	+	+	+	+	+	
Acosta-Cabronero et al. (2016)	116	20-79	+	+	+	0	+	0	+	
Betts et al. (2016)	20	22-28								
	20	64-75	+	+	+	0	+	+	+	+
Guan et al. (2022)	100	*M* = 24								
	189	*M* = 61	+	+	+	+	+	+		
Li et al. (2014)	191	1-83	+	+	+	+	+		+	
Ghassaban et al. (2019)	24	*M* = 63	+	+	+	0	+	0	0	
Liu et al. (2016	174	20-69	+	+	+	0	+	+		
Chen et al. (2013)	27	60-82	+	+		+		+		
Kan et al. (2020)	17	*M* = 28								
	19	*M* = 71	+	+	+	+	+		+	
Keuken et al. (2017)	64	19-75	+	+	+	0	+			0
Persson et al. (2015)	183	21-69	+	+		+	0	+	0	0
Reeves et al. (2022)	170	9-81	+		+		+			
Taege et al. (2019)	33	*M* = 52	+	+			+	+	−	
Treit et al. (2021)	498	5-90	+	+			+		−	
Zachariou et al. (2022)	35	66-86	+	+			+		+	
Kalpouzos et al. (2021)	208	20-79	+	+			+			
Persson et al. (2020)	21	*M* = 36								
	15	*M* = 70	+	+			+			
Moon et al. (2016)	18	*M* = 47	+	+			0		0	
Zachariou et al. (2021)	73	61-86	+	+			0			
Xu et al. (2008)	78	22-78	0	+	0		0	+	0	
Li et al. (2015a)	132	43-80	0	+	0		0	0		0
Poynton et al. (2015)	11	21-29								

First author (year)	N	Age	CN	PT	SN	GP	RN	TH	DN	STN
	12	64-86	0	+		+	+	+	−	0
van Bergen et al. (2018a)	80	55-96	0	+			0		0	
Bilgic et al. (2012)	11	21-29								
	12	64-86	0		+	+	+	+	0	0
Howard et al. (2022)	67	18-78	0	+	0	0	+	+	0	0
Chiang et al. (2022)	32	50-87	0	0	0					
Li et al. (2021)	44	*M* = 59	Δ	Δ	Δ	Δ	Δ	0	Δ	
Gustavsson et al. (2022)	208	20-79	Δ	Δ						
Garzon et al. (2018)	22	26-42								
	18	65-77			+		+			+
Berman et al. (2022)	42	18-30								
	25	61-70			0		0			
Liu et al. (2015c)	30	< 45								
	17	45-59								
	20	60+						+		
Zhang et al. (2018)	166	1-83						−		
Jäschke et al. (2023)	154	17-78							+	

Note. QSM = quantitative susceptibility mapping. Age = range or mean years of age of sample.

For studies with two or more age groups, age group differences are presented in the cells for the oldest group. For each region, symbols indicate observations of increases (+), decreases (−), or non-significant differences (0) in susceptibility as a function of increasing age. Duplicate symbols (++) indicate that the magnitude of the age effect was larger for that region relative to other regions examined. Blank cells indicate that the region was not examined in the corresponding study. Studies are sorted by age effects in the caudate and putamen.

CN = caudate nucleus; PT = putamen; SN = substantia nigra; GP = globus pallidus (combining internal and external limbs); RN = red nucleus; TH = thalamus; DN = dentate nucleus of the cerebellum; STN = subthalamic nucleus; Δ = longitudinal change.

Table 2:

Age-Related Differences in QSM for Cortical, Limbic, and White Matter Regions

			QSM Region						
First author (year)	***N***	**Age**	**FC**	**TC**	**PC**	**OC**	**HC**	**AM**	**WM**
Acosta-Cabronero et al. (2016)	116	20-79	++	+	++	0	0	0	0
Betts et al. (2016)	42	18-30							
	25	61-70	++	+	+	+	+	+	+
Howard et al. (2022)	67	18-78	+	+	+		0	0	
Kalpouzos et al. (2021)	208	20-79	+	+	+	+			
Zachariou et al. (2023)	95	60-86	+	+	+	+			
Zachariou et al. (2021)	73	61-86	+	0	+	0			
Li et al. (2014)	191	1-83	+		+		+		
Chiang et al. (2022)	32	50-87	0	0	0		0	0	
van Bergen et al. (2018a)	80	55-96	−	−	−		0	0	
Gustavsson et al. (2022)	208	20-79	Δ						
Bilgic et al. (2012)	11	21-29							
	12	64-86					0		
Xu et al. (2008)	78	22-78					+		
Koskimäki et al. (2020)	7	18-49							
	11	50-79							+

Note. QSM = quantitative susceptibility mapping. Age = range or mean years of age of sample.

For studies with two or more age groups, age group differences are presented in the cells for the oldest group. For each region, symbols indicate observations of increases (+), decreases (−), or non-significant differences (0) in susceptibility as a function of increasing age. Duplicate symbols (++) indicate that the magnitude of the age effect was larger for that region relative to other regions examined. Blank cells indicate that the region was not examined in the corresponding study. Studies are sorted by age effects in the frontal lobe.

FC = frontal cortex; TC = temporal cortex; PC = parietal cortex; OC = occipital cortex; HC = hippocampus; AM = amygdala; WM = white matter; Δ = longitudinal change.

Table 3

Relations between QSM and Cognitive Aging

First author (year)	*N*	Age	QSM region	Cognitive domain	Relation
Chen et al. (2018)	27	60-82	Putamen	A Language	−
			Globus pallidus	Fluid cognition	−
Chen et al. (2021b)	150	*M* = 69	Hippocampus	Episodic memory	−
			Hippocampus	Executive function	−
			Globus pallidus	Executive function	−
			Temporal cortex	Episodic memory	−
			Frontal cortex	Episodic memory	−
Gustavsson et al. (2022)	208	20-79	A Prefrontal cortex	A Working memory	+
Howard et al. (2022)	67	18-78	Temporal cortex	Fluid cognition	−
			Posterior cingulate	Fluid cognition	−
			Motor cortex	Fluid cognition	−
			Putamen	Fluid cognition	−
Kalpouzos et al. (2021)	208	20-79	Putamen	Working memory	−
			Putamen	Executive function	+
Li et al. (2015a)	132	43-80	Globus pallidum	Manual dexterity	−
			Red nucleus	Manual dexterity	−
Persson et al. (2020) *	21	M = 36			
	15	M = 70	Striatum	Implicit learning	+
Treit et al. (2021)	498	5-90	Caudate	Episodic memory	+
				Executive function	+
van Bergen et al. (2018b)	116	50-95	Hippocampus	Global cognition	0
			Cortex	Global cognition	0
			Deep gray matter	Global cognition	0
Zachariou et al. (2020)	55	61-86	Parietal cortex	Working memory	−
Zachariou et al. (2023)	95	60-86	Precentral gyrus	Executive function	−

Note. Age = range or mean years of age of sample. For each study, symbols indicate positive (+), negative (−), or nonsignificant (0) associations between susceptibility in the listed region and performance on the listed cognitive domain. Studies are sorted alphabetically by first author name.

Δ = longitudinal change.

* Data presented are averaged across all participants.

Table 4

Relations between QSM and Other Imaging Measures

				QSM region											
First author (year)	**N**	**Age**	**Other measure**	**FC**	**TC**	**PC**	**OC**	**CN**	**PT**	**GP**	**RN**	**SN**	**TH**	**HC**	**AM**
van Bergen et al. (2018b)	116	50-95	AP	+	+	+	+	+	+	+				+	+
Chen et al. (2021b)	150	*M* = 69	AP	+	+	+	+	−	0	0				+	+
Bauer et al. (2021)	80	60-86	Deep WMH	+	+	+	+	+	+						
			PV WMH	0	0	0	0	0	0						
van Bergen et al. (2018a)	80	55-96	Global WMH	0	−	−	0							0	0
Chiang et al. (2022)	32	50-87	Global WMH	0	0	0		0	0	0				0	0
Li et al. (2021)	44	*M* = 59	Global WMH					0	0	0	0	0	0		
Gong et al. (2015)	42	25-78	FA/*M* Kurtosis					0	+	0	0	0	0		
Yang et al. (2022)	25	*M* = 67	Axial kurtosis					+	0	0	0	0			
Zhou et al. (2020)	213	43-80	Diffusivity index					+	+	+	+	+	+		
Zachariou et al. (2023)	95	60-86	Neurite density	−		−									
Garzon et al. (2017)*	22	*M* = 36	R2*					+	+	+	+	+		+	
	18	*M* = 70													
Taege et al. (2019)	33	*M* = 52	R2*					+	+	+	+		−		
Li et al. (2014)	191	1-83	R2*	+		+		+	+	+	+	+			
Quevenco et al. (2017)	37	62-89	Nodal strength	+	0	+	+	+	0	0				0	0
Persson et al. (2020)*	21	*M* = 36	BOLD signal	+	+										
	15	M = 70													
Zachariou et al. (2020)	55	61-86	Functional conn	−											
Guan et al. (2019)	35	*M* = 58	Functional conn	−	−										

Note. Age = range or mean years of age of sample.

For each study, symbols indicate positive (+), negative (−), or nonsignificant (0) associations between susceptibility and another MRI measure. Studies are sorted by the secondary MRI measure that was examined.

FC = frontal cortex; TC = temporal cortex; PC = parietal cortex; OC = occipital cortex; CN = caudate nucleus; PT = putamen; GP = globus pallidus; RN = red nucleus; SN = substantia nigra; TH = thalamus; HC = hippocampus; AM = amygdala; Aβ = amyloid beta; WMH = white matter hyperintensities; FA = fractional anisotropy; BOLD = blood oxygen level dependent; PV = periventricular; conn = connectivity.

*Data presented are averaged across all participants.

Table 5

Moderators of QSM in Aging

				QSM region											
First author (year)	***N***	**Age**	**Moderator**	**FC**	**TC**	**PC**	**OC**	**CN**	**PT**	**GP**	**RN**	**SN**	**TH**	**HC**	**AM**
Li et al. (2023)	220	10-70	**Female sex**						+		0				
Acosta-Cabronero et al. (2016)	116	2O-79	Female sex	0	0	0	0	0	0	0	0	0	0	0	0
Persson et al. (2015)	183	21-69	Female sex					0	0	0	0	−	0		
Treit et al. (2021)	498	5-90	Female sex					0	0	0			0		
Gong et al. (2015)	42	25-78	Female sex					0	0	0	−	0	−		
Xu et al. (2008)	78	22-78	Female sex					0	0	0	0	0	0		
Li et al. (2021)	44	*M* = 59	Female sex					0	0	0	0	0	0		
			Smoking					0	0	0	0	0	+		
			Diabetes					+	+	0	+	0	0		
			Hypertension					0	0	0	−	0	0		
Zachariou et al. (2021)	73	61-86	Healthy diet			−			−						
Acosta-Cabronero et al. (2016)	116	20-79	Hypertension	0	0	0	0	0	0	0	0	0	0	0	0
Nir et al. (2022)	27,535	44-80	APOE ε4											+	+
Kalpouzos et al. (2021)	208	20-79	HFE	0	0	0	0	0	+	0					
Elliott et al. (2018)	8,428	40-69	HFE					+	+	+					
			TF					+	+	+					
			SLC25A37					+	+	+					
Gustavsson et al. (2022)	208	20-79	COMT	+				+	+						

Note. Age = range or mean years of age of sample.

For each study, symbols indicate positive (+), negative (−), or nonsignificant (0) effects of the moderating variable on susceptibility values for a given region. Studies are sorted by the moderator that was examined (sex, lifestyle or health-related factor, genotype). Blank cells indicate that the region was not examined in the corresponding study.

FC = frontal cortex, TC = temporal cortex, PC = parietal cortex, OC = occipital cortex, CN = caudate nucleus, PT = putamen, GP = globus pallidus, RN = red nucleus, SN = substantia nigra, TH = thalamus, HC = hippocampus, AM = amygdala. APOE ε4, HFE, TF, SLC25A37, COMT = individual genes.