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Age and sex related differences in subcortical brain iron concentrations among healthy adults

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ABSTRACT

Age and sex can influence brain iron levels. We studied the influence of these variables on deep gray matter magnetic susceptibilities. In 183 healthy volunteers (44.7 ± 14.2 years, range 20–69, ♀ 49%), in vivo quantitative susceptibility mapping (QSM) at 1.5 T was performed to estimate brain iron accumulation in the following regions of interest (ROIs): caudate nucleus (Cd), putamen (Pt), globus pallidus (Gp), thalamus (Th), pulvinar (Pul), red nucleus (Rn), substantia nigra (Sn) and the cerebellar dentate nuclei (Dn). We gauged the influence of age and sex on magnetic susceptibility by specifying a series of structural equation models. The distributions of susceptibility varied in degree across the structures, conforming to histologic findings (Hallgren and Sourander, 1958), with the highest degree of susceptibility in the Gp and the lowest in the Th. Iron increase correlated across several ROIs, which may reflect an underlying age-related process. Advanced age was associated with a particularly strong linear rise of susceptibility in the striatum. Nonlinear age trends were found in the Rn, where they were the most pronounced, followed by the Pul and Sn, while minimal nonlinear trends were observed for the Pt, Th, and Dn. Moreover, sex related variations were observed, so that women showed lower levels of susceptibility in the Sn after accounting for age. Regional susceptibility of the Pul increased linearly with age in men but exhibited a nonlinear association with age in women with a leveling off starting from midlife. Women expected to be post menopause (+51 years) showed lower total magnetic susceptibility in the subcortical gray matter. The current report not only is consistent with previous reports of age related variations of brain iron, but also adds to the current knowledge by reporting age-related changes in less studied, smaller subcortical nuclei. This is the first in-vivo report to show lower total subcortical brain iron levels selectively in women from midlife, compared to men and younger women. These results encourage further assessment of sex differences in brain iron. We anticipate that age and sex are important co-factors to take into account when establishing a baseline level for differentiating pathologic neurodegeneration from healthy aging. The variations in regional susceptibility reported herein should be evaluated further using a longitudinal study design to determine within-person age related changes.

1. Introduction

1.1. Aging of the brain parenchyma

Brain aging is characterized by a regional shrinkage across multiple gray and white matter regions of the brain parenchyma (Persson et al., 2014; Fjell and Walhovd, 2010), as well as a decline in the dopamine synthesis of subcortical nuclei (Seeman et al., 1987; Severson et al., 1982; Wang et al., 1998; Volkow et al., 1998). As the brain ages, non-heme iron accumulates across brain structures (Hallgren and Sourander, 1958).

Iron serves as a cofactor in several neuronal specific functions such as the synthesis of myelin and neurotransmitters (Piñero and Connor, 2000). In particular, iron is required for efficient dopaminergic neurotransmission (Berg and Youdim, 2006; Mills et al., 2010), supported by pathways connecting deep subcortical nuclei. The latter are of vital importance for motor- and cognitive functions (Volkow et al., 1998), which are subject to decline with increasing age. A balanced iron level

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promotes normal cell function of the nervous system, but excessive levels of non-heme iron can cause age related cellular vulnerability (Dixon and Stockwell, 2014). In both aging and neurodegenerative diseases, excessive accumulation of intracellular ferrous iron ($Fe^{2}+$) gets catalyzed to ferric iron ($Fe^{3}+$), which may cause reactive oxygen species (ROS), oxidative stress, and cell death (Andersen et al., 2014; Dixon and Stockwell, 2014).

Non-heme iron can only be studied directly postmortem (Hallgren and Sourander, 1958; Morris et al., 1992; Ramos et al., 2014; Ward et al., 2014), while in-vivo magnetic resonance imaging (MRI) can estimate iron deposits based on the interplay between its paramagnetic properties and the proton relaxation resonance behavior of tissue water (Schenck, 2003). Most of the non-heme iron in the brain affecting the MRI signal is believed to be consisting of ferritin and hemosiderin (Schenck, 2003; Schenck and Zimmerman, 2004).

1.2. Brain Iron in the aging parenchyma

Pioneering post mortem findings, discovered half a century ago, indicate aging related brain iron accumulation with varying degree across brain structures. Iron deposits showed a rapid increase until young adulthood, followed by a smaller rise and, and for some structures even a plateau after midlife (Hallgren and Sourander, 1958). With the progress of MRI techniques, researchers have followed in the footsteps of this landmark work, and both linear and nonlinear age trends of iron distribution were observed (Bilgic et al., 2012; Haacke et al., 2005, 2010; Li et al., 2014; Xu et al., 2008). Iron concentrations are greater in the subcortical nuclei relative to the cerebral white matter and cortex among healthy adults (Gelman, 1995; Haacke et al., 2005; Li et al., 2014). The nuclei studied the most by far with in-vivo MRI are the striatum and the globus pallidus (Bartzokis et al., 1997, 2011; Bilgic et al., 2012; Cherubini et al., 2009; Haacke et al., 2005, 2010; Hagemeier et al., 2013; Pfefferbaum et al., 2009; Xu et al., 2008). The age dependency in MR based iron estimates of the substantia nigra, red nucleus, thalamus, the pulvinar complex and the cerebellar dentate nucleus is studied to a lesser extent, and with greater variability of results (Bilgic et al., 2012; Haacke et al., 2010; Li et al., 2014; Pfefferbaum et al., 2009).

1.3. Sex differences

A far less studied determinant of variability of brain iron levels is sex. Sex differences in the incidence and symptomatology of neurodegenerative diseases have been reported (de Rijk et al., 2000; Taylor et al., 2007). Younger male AD and PD patients show greater ferritin iron concentrations, as measured by an increase in the field-dependent relaxation rate, compared to healthy controls (Bartzokis et al., 2004, 2007). Compared to women, men showed a steeper decline over time in cognitive abilities tapping basal ganglia functions in adults free of dementia (Persson et al., 2013). Females exhibit lower levels of peripheral iron levels (e.g. Bartzokis et al., 2007; Fleming et al., 2001; Whitfield et al., 2003), and men have shown higher iron concentrations according to changes in MRI contrast in the cortical white matter and subcortical nuclei (Bartzokis et al., 2007, 2011; Hagemeier et al., 2013; Tishler et al., 2012). However, a lack of sex related differences in iron levels has also been reported (Xu et al., 2008). Early histologic findings suggest that lower peripheral iron levels may influence brain iron levels, since anemia was found to reduce brain iron postmortem (Hallgren and Sourander, 1958). Pre-menstrual blood loss reduces peripheral iron levels in women and may contribute to sex differences in brain iron accumulation (Tishler et al., 2012; Whitfield et al., 2003). Women had lower levels of brain iron compared to men from midlife to old age according to a recent histologic report (Ramos et al., 2014). Sex steroids, whose levels change post menopause (Al-Azzawi and Palacios, 2009), may also influence sex related variations of brain iron levels (Gu et al., 2010).

1.4. In-vivo mapping of susceptibility

Q4

Although iron can only be measured directly by histology, it can be estimated in vivo using MRI based on proton relaxation rates or by the effect of the magnetic susceptibility of iron on the MRI signal phase.

The field-dependent relaxation rate increase (FDRI) is defined by the degree by which the MRI field strength affects the measured transverse relaxation rate (R_2). The method requires imaging at two field strengths, making it time consuming (e.g. Bartzokis et al., 2004; Bartzokis et al., 1993) and susceptible to between scan variability and differences of orientation, thereby affecting precision.

Both the magnitude signal (R_2^*) (Gorell et al., 1995; Haacke et al., 2005) and the phase signal (Haacke et al., 2007) derived from MRI gradient echo (GRE) data have been used to estimate iron content. GRE phase reflects the magnetic field, which is a weighted sum of all surrounding iron. R_2^*/T_2^* reflects the phase variance in a voxel and depends on echo time (TE), voxel size, field strength, object orientation and other imaging parameters (Brown et al., 2014). These measures have limitations. Both R_2^* and phase suffer from non-local field effects. It is also possible to generate a magnetic field correlation (MFC) map to quantify iron, but MFC also depends on imaging parameters such as voxel size and echo time (Jensen et al., 2009).

To address the non-local field effects in the phase information while retaining the quantitative information in the magnetic field, a deconvolution of the magnetic field from the phase data is needed to obtain tissue magnetic susceptibility (see Wang and Liu, 2014 for a review). This method is referred to as quantitative susceptibility mapping (QSM). A recently developed QSM algorithm, morphology enabled dipole inversion (MEDI), calculates the magnetic susceptibility tissue distribution from complex GRE data, incorporating both phase and magnitude information (de Rochefort et al., 2010; Wang and Liu, 2014). QSM has recently been validated by postmortem imaging showing that iron is the dominant source of magnetic susceptibility in the subcortical gray matter (Langkammer et al., 2012).

1.5. Research questions

We aimed at filling the current gaps of knowledge considering age and sex related variations of susceptibility of the deep gray matter nuclei, as outlined above. In particular, we studied age-related susceptibility differences in the smaller nuclei, such as the pulvinar complex, midbrain nuclei, and the cerebellar dentate nucleus, which were studied to a lesser extent in the literature. We have chosen to estimate brain iron using QSM. Previous studies using QSM have applied mixed protocols (Li et al., 2014; Bilgic et al., 2012), and we applied MEDI QSM (Wang and Liu, 2014), using the same rigorous scan protocol over a large study cohort ($n = 183$) of healthy adults with a wide age range (20–69 years). We expected, based on the literature, to observe both linear and nonlinear age effects in susceptibility. We also gauged if the level of susceptibility was inter-correlated across the ROIs. Additionally, the influence of sex and the interaction of sex and age as they influenced regional susceptibility were assessed. Differences in total subcortical brain iron from expected menopause onset (51 years) (Al-Azzawi and Palacios, 2009; Cheung et al., 2011; Gold et al., 2001) were also examined. Our regions of interest (ROIs) were: caudate nucleus (Cd), putamen (Pt), globus pallidus (Gp), red nucleus (Rn) and substantia nigra (Sn), thalamus (Th), pulvinar (Pul), and the dentate nucleus (Dn).

2. Methods

2.1. Participants

This study was approved by the First Affiliated Hospital of Dalian Medical University Research Ethics Committee. Written consent was

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