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NeuroImage

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NeuroImage 40 (2008) 35–42

Age, gender, and hemispheric differences in iron deposition in the human brain: An *in vivo* MRI study

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Received 22 April 2007; revised 14 November 2007; accepted 16 November 2007
Available online 24 November 2007

It is well known that iron accumulates in the brains of patients with various neurodegenerative diseases. To better understand disease-related iron changes, it is necessary to know the physiological distribution and accumulation of iron in the human brain. Studies have shown that brain iron levels increase with aging. However, the effects of gender and hemispheric laterality on iron accumulation and distribution are not well established. In this study, we estimated the brain iron levels *in vivo* in 78 healthy adults ranging in age 22 to 78 years using magnetic susceptibility-weighted phase imaging. The effects of age, gender, and hemispheric location on brain iron levels were evaluated within the framework of a general linear model. We found that the left hemisphere had higher iron levels than the right in the putamen, globus pallidus, substantia nigra, thalamus, and frontal white matter. We argue that the hemispheric asymmetry of iron content may underlie that of the dopaminergic system and may be related to motor lateralization in humans. In addition, significant age-related iron accumulation occurred in the putamen, red nucleus, and frontal white matter, but no gender-related differences in iron levels were detected. The results of this study extend our knowledge of the physiological distribution and accumulation of iron in the human brain.

Keywords: Magnetic susceptibility; Phase image; Brain iron; Hemispheric asymmetry; Gender difference

Introduction

There is accumulating evidence that iron is involved in the mechanisms underlying many neurodegenerative diseases (Pinero and Conner, 2000; Moos and Morgan, 2004; Thomas and Jankovic, 2004; Zecca et al., 2004). Abnormal iron deposition in the basal ganglia is seen not only in age-related neurodegenerative diseases such as Parkinson, Alzheimer and Huntington diseases but also in genetic neurodegenerative disorders with mutations in the iron metabolic pathways, such as neuroferritinopathy and Hallervorden–Spatz disease (Thomas and Jankovic, 2004). Estimating the amounts of iron deposits in the brain may be a new biomarker of the presence and progression of a variety of neurodegenerative diseases (Schenck and Zimmerman, 2004). To better understand the disease-related changes that involve iron deposition, it is necessary to know the physiological distribution of iron in the basal ganglia of normal subjects.

To date, postmortem and *in vivo* studies have demonstrated that in normal individuals, iron levels increase with age in subcortical and some cortical gray matter regions (Hallgren and Sourander, 1958; Loeffler et al., 1995; Bartzokis et al., 1994, 1997; Martin et al., 1998; Ogg et al., 1999). However, the rates of iron accumulation are different in various brain structures (Hallgren and Sourander, 1958). The globus pallidus has a rich supply of iron during the first two decades and no further increase seems to occur after 30 years of age. Although the iron values in the red nucleus and substantia nigra show considerable scattering, a rapid increase in iron content during the first two decades is also clearly demonstrated. In other structures, such as the putamen, iron deposits increase more slowly, and iron concentrations reach maximal values at about the sixth decade.

In addition to age, another important factor that should be taken into consideration is gender differences. Given the conspicuous gender-related differences in peripheral iron levels (Fleming et al., 2001), it is somewhat surprising that very little is known about such differences in the brain. Recently, Bartzokis et al. (2007) first reported that women had lower brain iron levels than men in the caudate, thalamus, and frontal white matter. Such gender-related differences in iron status may be responsible for the fact that women have a lower risk of developing neurodegenerative disease (Bartzokis et al., 2007). However, no further data have yet confirmed their findings.

The third source of differences in iron concentration in the human brain may be hemispheric localization, as distinct functions tend to be localized in the left or right hemispheres (Toga and Thompson, 2003; Sun and Walsh, 2006). Usually, language is localized predominantly in the left and spatial recognition in the

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Available online on ScienceDirect (www.sciencedirect.com).

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doi:10.1016/j.neuroimage.2007.11.017

right. Furthermore, more than 90% of people are naturally more skillful at using the right hand, which is controlled by the left hemisphere. The specialized functional roles of the hemispheres may be linked to neurochemical asymmetries. Tucker and Williamson (1984) proposed that the left hemisphere became organized around a dopamine activation system, which made the left hemisphere superior for complex motor programming (leading to a right hand preference) and speech. A leftward asymmetry of dopamine levels has been observed in the basal ganglia (Glick et al., 1982; Wagner et al., 1983; de la Fuente-Femandez et al., 2000). Considering that iron is an essential cofactor in the synthesis of dopamine (Wriggelsworth and Baum, 1988), we hypothesized that there may be a leftward bias of iron content in the human brain. Until now, no study has focused on hemispheric differences in brain iron levels.

Brain iron stores can be imaged *in vivo* using magnetic resonance imaging (MRI). Iron deposition produces MR signal changes in both magnitude and phase images by creating subvoxel magnetic inhomogeneities, which dephase water protons passing nearby (Haacke et al., 2005). As a paramagnetic substance, iron deposited in the brain leads to a negative phase shift relative to the surrounding parenchyma. In general, the higher the iron content, the greater are the magnetic field inhomogeneities and the resultant negative phase shifts (Abduljalil et al., 2003). Ogg et al. (1999) demonstrated that phase shifts reflect iron-induced differences in brain tissue susceptibility in gray matter.

In this study, we estimated the brain iron stores in a life-span sample of healthy adults using susceptibility-weighted MR imaging through the effect of iron on the brain tissue susceptibility. The goals were to detect possible hemispheric differences in brain iron levels, to assess the effect of gender on brain iron concentrations, and to confirm the findings on age-related iron deposition *in vivo*.

Material and methods

Subjects

The adult volunteers who participated in this study were recruited from the community and hospital staff. The participants signed an informed consent form approved by the hospital's research ethics committee. Subjects were excluded if they had a history of neurological or psychiatric disease, including head trauma. An experienced neuroradiologist examined all the MR images for signs of space-occupying lesions and cerebrovascular diseases. The subjects with evidence of infarct, focal parenchymal loss that may have resulted from infarct, or patchy areas of hyperintensity on T2-weighted images were excluded from further analysis.

The final sample consisted of 78 healthy adults ranging in age 22 to 78 years (mean=43.3, SD=14.1). The subjects included 40 men (mean=41.5 years, SD=11.9) and 38 women (mean=45.2 years, SD=15.9), with no differences in age between the genders ($t=-1.159$, $P=0.250$, independent-samples t test).

MRI protocol

All the MR images were obtained using a 1.5-T system (Signa Exite II, GE Medical System, Milwaukee, USA) equipped with the standard head coil. The head was immobilized in the head coil with foam padding.

Sagittal T2-weighted images were first acquired with a fast spin-echo sequence to locate the precise positions of the anterior and posterior commissures. The susceptibility-weighted MR images were taken parallel to the anterior–posterior commissural line (AC–PC line) using a three-dimensional gradient-echo sequence with the following parameters: TR=51 ms, TE=38 ms, FA=20°, Nz=28 slices, slice thickness=2 mm, FOV=24 cm and matrix size (Nx×Ny)=256×256. Both phase and magnitude images were acquired, but only phase data were used in further analysis. Finally, conventional axial T1- and T2-weighted images were acquired for screening of space-occupying lesions and cerebrovascular diseases.

Image processing

The susceptibility-weighted MR phase image was filtered with a high-pass filter, to create a new phase map termed the corrected phase image. The purpose of applying a high-pass filter was to remove slowly varying phase shifts, which arise predominantly from air–tissue interfaces and background field inhomogeneities. In this study, the high-pass filter was performed by using a low-pass filter with a central matrix size of 32×32 to divide the original phase image. The detailed methods of image processing can be found in the papers of Haacke et al. (2004) and Sehagl et al. (2005).

In the corrected phase image, phase values range from $-\pi$ to $+\pi$. Due to the dipolar field induced by iron deposition, regions of high negative phase (dark) were typically surrounded by rims of high positive phase (light) (Fig. 1). Therefore, in the phase images, the contours of brain structures, especially those with high iron concentrations, were more distinct than those in the T1- and T2-weighted images.

Data acquisition

The phase values of the regions of interest (ROIs) were measured on the corrected phase images. The ROIs included the

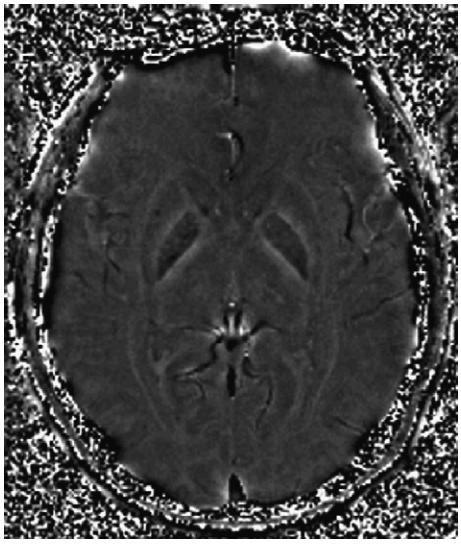

Fig. 1. An example of the corrected phase image. In the corrected phase images, the brain structures, especially those with high iron concentrations, were surrounded by a light rim, which reflects the dipolar nature of the iron-induced paramagnetic susceptibility differences.