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

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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.

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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...
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-Fernandez 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 (r = −1.159, P = 0.250, independent-samples t test).

MRI protocol

All the MR images were obtained using a 1.5-T system (Signa Excite II, GE Medical System, Milwaukee, USA) equipped with the standard head coil. The head was immobilized in the head coil with foam padding.
bilateral globus pallidus (GP), putamen (PU), caudate (CA), thalamus (TH), substantia nigra (SN), red nucleus (RN), and frontal white matter (FWM). Data for each structure were obtained from two contiguous slices. The third and fourth slices above the AC–PC line were used to obtain data from the GP, PU, CA, TH and FWM (Fig. 2), and the second and third slices inferior to the AC–PC line were used to obtain data from the SN and RN (Fig. 2). The ROIs of the subcortical nuclei were drawn according to the anatomical structures, while in the FWM the ROIs were circular (100 pixels).

A trained neuroradiologist, who was blinded as to the subjects’ exact age and gender, manually traced the ROIs. All the ROIs were re-measured one month later by the same person on the same images. The final values were the means of the two measurements.

Results

The means and standard deviations for the phase values of each brain structure are summarized in Table 1. As a check on the validity of the data, the phase values were correlated with published brain iron levels in normal adults (Fig. 3). Pearson correlation analysis showed a strongly negative correlation between the phase values measured from our subjects and the reference values of the brain concentrations ($r = -0.796, P = 0.032$), which indicated that the higher the iron deposition, the greater the negative phase value.

The effects of age, gender, and hemispheric location on the iron content were evaluated within a mixed linear model, in which the phase values for each hemisphere in each brain

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Fig. 2. ROIs depicted on the corrected phase images. (a) ROIs 1 and 2 correspond to bilateral FWM, 3 and 4 to CA, 5 and 6 to PU, 7 and 8 to GP, and 9 and 10 to TH. (b) ROIs 11 and 12 correspond to bilateral FWM, 13 and 14 to CA, 15 and 16 to PU, 17 and 18 to GP, and 19 and 20 to TH. (c) ROIs 21 and 22 correspond to bilateral SN, and 23 and 24 to RN. (d) ROIs 25 and 26 correspond to bilateral SN, and 27 and 28 to RN.
structure formed a vector of dependent variables; seven structures (GP, RN, SN, PU, CA, TH, and FWM) and hemisphere (left or right) were within-subject grouping factors; gender was a between-subject grouping factor; age was a covariate. The covariate was recentered at the sample means. Within the full model, in addition to the expected iron concentration difference among the structures [Wilks’ $\Lambda = 0.025$, $F(6,70) = 449.491, P < 0.001$], a significant Structure $\times$ Age interaction was present [Wilks’ $\Lambda = 0.580$, $F(6,70) = 8.465, P < 0.001$], indicating that the effects of age on iron concentration in brain components were not uniform. The overall effect of age on iron concentration was significant [$F(1,75) = 15.246, P < 0.001$]. The effect of hemisphere on iron concentration was also significant [Wilks’ $\Lambda = 0.659, F(1,75) = 38.868, P < 0.001$]. However, a significant Hemisphere $\times$ Structure interaction [Wilks’ $\Lambda = 0.620, F(6,70) = 7.144, P < 0.001$] indicated significant variation in the pattern of hemispheric differences across the brain. However, the effect of gender on iron concentration was not significant [$F(1,75) = 0.098, P = 0.755$].

The results of the mixed linear analysis indicated that the effect of the age and hemispheric location on iron content varied among different brain components. Thus, the data were fitted to seven separate linear models to determine the effects of age, gender, and hemispheric location on each brain structure. The results of these analyses are summarized below.

A significant effect of hemispheric location on iron content was detected in the PU [Wilks’ $\Lambda = 0.737, F(1,75) = 26.731, P < 0.001$], GP [Wilks’ $\Lambda = 0.903, F(1,75) = 8.907, P = 0.006$], SN [Wilks’ $\Lambda = 0.838, F(1,75) = 14.515, P < 0.001$], TH [Wilks’ $\Lambda = 0.817, F(1,75) = 16.761, P < 0.001$], and FWM [Wilks’ $\Lambda = 0.614, F(1,75) = 47.069, P < 0.001$]. Paired-samples $t$ tests further confirmed that the iron concentrations of the left PU, GP, SN, TH, and FWM were greater than those of the right ($t(75) = 5.082, P < 0.001$, for PU; $t(75) = 2.891, P = 0.005$, for GP; $t(75) = 3.865, P < 0.001$, for SN; $t(75) = 3.990, P < 0.001$, for TH; $t(75) = 6.244, P < 0.001$, for FWM). There were no hemispheric differences in the iron concentration of CA and RN ($P > 0.1$).

Although the scatterplot showed a trend that men had lower iron levels than women in the GP (Fig. 4c), the differences in the iron content between the genders were not significant ($P > 0.05$).

Finally, a significant effect of age on iron content was found in the PU [$F(75) = 61.300, P < 0.001$], RN [$F(1,75) = 4.437, P = 0.039$] and FWM [$F(1,75) = 4.191, P = 0.044$] (Figs. 4a, c, e). Linear regression analysis showed that the iron concentration in

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**Table 1**

<table>
<thead>
<tr>
<th>Phase Value</th>
<th>Men ($n=40$)</th>
<th>Women ($n=38$)</th>
<th>Total ($n=78$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen (PU)</td>
<td>Right</td>
<td>$-0.0340 \pm 0.0273$</td>
<td>$-0.0341 \pm 0.0278$</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>$-0.0395 \pm 0.0281$</td>
<td>$-0.0450 \pm 0.0337$</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>$-0.0367 \pm 0.0272$</td>
<td>$-0.0395 \pm 0.0298$</td>
</tr>
<tr>
<td>Caudate (CA)</td>
<td>Right</td>
<td>$-0.0984 \pm 0.0259$</td>
<td>$-0.1055 \pm 0.0332$</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>$-0.0999 \pm 0.0262$</td>
<td>$-0.1139 \pm 0.0418$</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>$-0.0992 \pm 0.0225$</td>
<td>$-0.1098 \pm 0.0354$</td>
</tr>
<tr>
<td>Globus Pallidus (GP)</td>
<td>Right</td>
<td>$-0.0955 \pm 0.0290$</td>
<td>$-0.1128 \pm 0.0538$</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>$-0.1028 \pm 0.0304$</td>
<td>$-0.1164 \pm 0.0370$</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>$-0.0991 \pm 0.0280$</td>
<td>$-0.1146 \pm 0.0435$</td>
</tr>
<tr>
<td>Substantia Nigra (SN)</td>
<td>Right</td>
<td>$-0.0818 \pm 0.0281$</td>
<td>$-0.0825 \pm 0.0262$</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>$-0.0971 \pm 0.0354$</td>
<td>$-0.0941 \pm 0.0299$</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>$-0.0895 \pm 0.0283$</td>
<td>$-0.0883 \pm 0.0230$</td>
</tr>
<tr>
<td>Red Nucleus (RN)</td>
<td>Right</td>
<td>$-0.0867 \pm 0.0601$</td>
<td>$-0.0822 \pm 0.0486$</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>$-0.0886 \pm 0.0697$</td>
<td>$-0.0777 \pm 0.0480$</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>$-0.0863 \pm 0.0627$</td>
<td>$-0.0799 \pm 0.0453$</td>
</tr>
<tr>
<td>Thalamus (TH)</td>
<td>Right</td>
<td>$-0.0096 \pm 0.0101$</td>
<td>$-0.0075 \pm 0.0105$</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>$-0.0114 \pm 0.0079$</td>
<td>$-0.0124 \pm 0.0100$</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>$-0.0105 \pm 0.0085$</td>
<td>$-0.0100 \pm 0.0097$</td>
</tr>
<tr>
<td>Frontal White Matter (FWM)</td>
<td>Right</td>
<td>$0.0057 \pm 0.0170$</td>
<td>$0.0089 \pm 0.0173$</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>$-0.0020 \pm 0.0158$</td>
<td>$-0.0137 \pm 0.0169$</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>$0.0018 \pm 0.0115$</td>
<td>$-0.0025 \pm 0.0151$</td>
</tr>
</tbody>
</table>

Fig. 3. Phase values vs. published iron concentration in normal adult brain. The phase values were measured from subjects more than 30 years old. The subgroup consisted of 32 men and 28 women, with a mean age of 48.3 years. The brain iron concentration was measured histologically from 55 to 59 normal adults aged 30–100 years. The mean age was 62 (Hallgren and Sourander, 1958).
these structures increased linearly with age ($R^2=0.45$, $P<0.001$, for PU; $R^2=0.051$, $P=0.047$, for RN; $R^2=0.061$, $P=0.029$, for FWM) (Table 2). No significant effect of age on iron content was found in the CA, GP, SN and TH ($P>0.1$).

Discussion

Hemispheric asymmetry of brain iron levels

The data reported here showed a hemispheric asymmetry of phase shifts in the human brain. The phase shifts were greater in the left hemisphere than in the right in the putamen, globus pallidus, substantia nigra, thalamus and frontal white matter, indicating that the left hemisphere had higher iron deposition than the right in those regions. The leftward pattern of iron asymmetry is consistent with our hypothesis.

Hemispheric asymmetry of MR tissue properties has been reported. Supprian et al. (1997) reported a lateral asymmetry of transverse relaxation time (T2) in the frontal lobe white matter, with T2 longer on the right than on the left. Steen et al. (2000) reported a significant right–left difference in longitudinal relaxation time (T1) in the gray matter. They found that T1 was significantly longer in the right subcortical gray nuclei and the left cortical gray matter of the frontal lobe (Steen et al., 2000).

Proton relaxation times (T1 and T2) are inherent properties of a tissue. A growing body of evidence suggests that iron has an important role in determining the relaxation properties of brain tissue. The major effect of iron in the brain is to shorten T2 and, to a lesser extent, T1 (Vymazal et al., 1999). Many studies show that transverse relaxation rate ($R_1$, $R_1=1/T_1$) and longitudinal relaxation rate ($R_2$, $R_2=1/T_2$) are strongly correlated with, and may be partially dependent upon, iron concentration (Haacke et al., 2005). Therefore, interhemispheric differences in iron concentration may contribute to hemispheric asymmetry of T1 and T2. Shorter T1 in the left subcortical gray nuclei and shorter T2 in the left frontal white matter suggest higher brain iron concentrations in these regions. Their results are consistent with our conclusion that the left hemisphere had higher iron deposition than the right in most of the subcortical gray nuclei and the frontal white matter.

In the brain, iron is co-localized with dopaminergic neurons (Bread, 2003). In addition, iron deficiency in the brain can impair dopamine production and cause motor problems (Levenson et al., 2004). These observations revealed a tight connection between iron and dopamine metabolism. Postmortem and in vivo studies demonstrated a leftward bias of dopamine levels in the globus pallidus and putamen (Glick et al., 1982; Wagner et al., 1983; de la Fuente-Fernandez et al., 2000). This finding indicated that the left substantia nigra synthesizes more dopamine than the right. Due to the fact that tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, is an iron enzyme (Wrigglesworth and Baum, 1988), we speculated that more iron was needed to facilitate dopamine synthesis in the left substantia nigra. Thus, the hemispheric asymmetry of iron content in the substantia nigra may reflect the underlying hemispheric difference in the iron requirements for dopamine metabolism. Past studies have suggested that iron can be transported neurally, particularly within dopaminergic neurons (Faucheux et al., 1995). So, a leftward bias of iron content in regions receiving dopaminergic projections from the substantia nigra, such as the globus pallidus and putamen, might be expected to result from, or even induce, a leftward bias of iron content in the substantia nigra.

Dopamine plays an essential role in regulating voluntary movement (Chinta and Andersen, 2005). Some investigators ascribe the right-hand preference in people to the leftward bias of dopamine (Toga and Thompson, 2003). Therefore, the leftward bias of iron content in the dopaminergic system, which underlies the leftward asymmetry of dopamine, may also be related to motor lateralization in humans.

An interesting finding of this study was a leftward asymmetry of iron levels in the putamen and no difference in the caudate. The putamen is the more overtly motor part of the striatum, whereas the caudate is mainly connected with more associative cortical regions, not directly involved in motor control (Yelnik, 2002). This finding also suggested that the iron level asymmetry in the dopaminergic system may be related to motor control.

Gender differences in brain iron levels

Considering the established fact of lower peripheral iron levels in women (Fleming et al., 2001), it seems reasonable to assume that women have lower iron levels than men in the brain. Recent data reported by Bartzokis et al. (2007) seemed to confirm this speculation. However, our data showed that there were no gender-related differences in iron levels in any of the regions studied.

Iron comes mainly from the diet, but the blood–brain barrier prevents the brain from having direct access to iron in the plasma pool. Iron is transported to the brain by plasma transferrin through an interaction between circulatory transferrin and transferrin receptors in the brain microvasculature (Bradbury, 1997). Most of the iron entering the brain finally leaves with the bulk outflow of cerebrospinal fluid through arachnoid villi and other channels (Bradbury, 1997). Thus, the blood–brain barrier and the blood–cerebrospinal fluid barrier play a regulatory role in the homeostasis of brain iron. In normal conditions, the peripheral iron level may not readily affect the iron. Therefore, we proposed that there may be no systematic differences in the iron content of human brain between the genders.

The discrepancy between our data and that reported by Bartzokis and coworkers may be ascribed to the use of a different MRI technique. The method adopted by Bartzokis’ group was the field-dependent R2 increase (FDRI) technique. Briefly, FDRI is based on the measures of brain R2 obtained with two different field-strength MR instruments. FDRI proved to be a specific measure of tissue ferritin (Bartzokis et al., 1993). Although ferritin accounts for the majority of nonheme iron in the brain, it is not the only form in which iron is found. In the substantia nigra, 10–20% of the iron is combined with neuromelanin (Zecca et al., 2001). Iron is also found in hemosiderin, the insoluble, degraded form of ferritin (Haacke et al., 2005). Thus, the FDRI technique may not detect all the iron in the brain. However, there are no reports to clarify the extent to which the phase shift can predict the total iron concentration. In addition, differences in the characteristics of the populations studied may also account for the discrepancy. Therefore, we suggest that more data are needed to elucidate the effect of gender on brain iron levels.

Age-related iron deposition in the brain

The results of this study confirmed significant effects of age on brain iron levels. Age-related iron deposition was found in the putamen, red nucleus and frontal white matter. We found that from 22 years to over 70 years, the iron concentration in the putamen
and frontal white matter increased linearly with age. Despite the fact that brain iron values showed considerable scattering, an age-associated increase of the iron level was also observed in the red nucleus.

The results of our study also demonstrated that the rates of iron deposition varied among various brain structures. We found that the iron concentration in the globus pallidus, substantia nigra, and caudate did not change with age. These findings suggest that iron accumulation in these structures is non-linear: rapid in the first two decades and gradually slowing as the individual enters adulthood. In these regions, the iron levels approached a distinct plateau in the middle age. The patterns of iron accumulation with age in various structures reported here are consistent with the results derived from postmortem studies (Hallgren and Sourander, 1958).

**Methodological limitations**

The findings reported here should be viewed in the context of several methodological limitations. One drawback is that the phase values were obtained from portions of the structures of interest. Owing to the restriction of slab thickness in the susceptibility-weighted MR sequence, the basal ganglia could not be entirely covered. Somewhat different findings may have been obtained if the structures were evaluated in their entirety.

The brain normally contains several essential metals. Of these, iron, manganese and copper are magnetic and have the potential to affect the MR signal (Schenck and Zimmerman, 2004). In normal conditions, the concentrations of manganese and copper are too small to produce detectable MR contrast (Schenck, 2003). Therefore, local phase changes are mainly induced by the iron. However, we cannot rule out the possibility that in some small regions, brain manganese or copper concentration might be sufficient to induce detectable phase shifts unrelated to iron.

The high-pass filter used in this study could affect the phase measurements based on the size and shape of the anatomic structure (Ogg et al., 1999). The filter would reduce the apparent phase shift in large uniform structures (such as caudate and putamen), but have little effect on small structures (such as cortical gray matter). Thus, spatial filtering could alter the true phase shifts of various brain structures. However, the spatial filtering was

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**Fig. 4. Regional phase value vs. age.** The line is the linear regression. Sample of 78 healthy individuals: 40 men (open triangles, dashed line) and 38 women (solid circles, solid line): (a) Putamen, (b) Caudate, (c) Globus pallidus, (d) Substantia nigra, (e) Red nucleus, (f) Thalamus, (g) Frontal white matter.
unlikely to have a major affect on the apparent phase shifts in this study, since the inter-regional phase shifts were highly correlated with the iron concentration among various structures and the age-related changes in phase shifts were generally consistent with the widely referenced postmortem data of Hallgren and Sourander (1958).

Because of the paramagnetism of deoxyhemoglobin, blood volume is a potential confounding influence on iron content determined by magnetic susceptibility measurements. However, there is no evidence that regional blood volume or oxygen utilization in the brain varies in the pattern observed in this study. Furthermore, cerebral blood volume decreases with age (Meyer et al., 1978), which would lead to a decrease in tissue paramagnetism instead of the increase that we observed. Therefore, blood volume and hemoglobin saturation probably had little effect on the major results of this study.

Finally, the estimates of age-related changes in brain iron levels relied on a cross-sectional design, which is sensitive to individual differences and cohort effects of the population studied (Raz et al., 2003). This may result in underestimating or exaggerating the exact age-related changes of brain iron levels.

**Conclusion**

The results of this study provided evidence of hemispheric asymmetry of brain iron deposition. We speculated that this asymmetry may reflect underlying hemispheric differences in the iron requirements for dopamine metabolism and may be related to motor lateralization in humans. The data also demonstrated that there were no gender-related differences in brain iron concentration. Finally, age-related iron deposition was detected, consistent with the result of postmortem studies reported previously. The results of this study extend our knowledge of the physiological distribution and accumulation of iron in the human brain.

**Table 2**

Regression analysis for regional phase values versus age

<table>
<thead>
<tr>
<th>Region</th>
<th>Slope</th>
<th>Intercept</th>
<th>$R^2$</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen (PU)</td>
<td>-0.0010</td>
<td>0.020</td>
<td>0.449</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Red Nucleus (RN)</td>
<td>-0.0010</td>
<td>-0.045</td>
<td>0.051</td>
<td>0.047</td>
</tr>
<tr>
<td>Frontal White Matter (FWM)</td>
<td>-0.0002</td>
<td>0.010</td>
<td>0.061</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Fig. 4 (continued).
Acknowledgments

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References


