J Huazhong Univ Sci Technol［Med Sci］
DOI 10.1007/s11596-011-0493-1
31(4):578-585,2011

Investigation on Positive Correlation of Increased Brain Iron Deposition with Cognitive Impairment in Alzheimer Disease by Using Quantitative MR R2′ Mapping*

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Summary: Brain iron deposition has been proposed to play an important role in the pathophysiology of Alzheimer disease (AD). The aim of this study was to investigate the correlation of brain iron accumulation with the severity of cognitive impairment in patients with AD by using quantitative MR relaxation rate R2′ measurements. Fifteen patients with AD, 15 age- and sex-matched healthy controls, and 30 healthy volunteers underwent 1.5T MR multi-echo T2 mapping and $T2^*$ mapping for the measurement of transverse relaxation rate R2′ (R2′＝$R2^*$−R2). We statistically analyzed the R2′ and iron concentrations of bilateral hippocampus (HP), parietal cortex (PC), frontal white matter (FWM), putamen (PU), caudate nucleus (CN), thalamus (TH), red nucleus (RN), substantia nigra (SN), and dentate nucleus (DN) of the cerebellum for the correlation with the severity of dementia. Two-tailed *t*-test, Student-Newman-Keuls test (ANOVA) and linear correlation test were used for statistical analysis. In 30 healthy volunteers, the R2′ values of bilateral SN, RN, PU, CN, globus pallidus (GP), TH, and FWM were measured. The correlation with the postmortem iron concentration in normal adults was analyzed in order to establish a formula on the relationship between regional R2′ and brain iron concentration. The iron concentration of regions of interest (ROI) in AD patients and controls was calculated by this formula and its correlation with the severity of AD was analyzed. Regional R2′ was positively correlated with regional brain iron concentration in normal adults (r=0.977, P<0.01). Iron concentrations in bilateral HP, PC, PU, CN, and DN of patients with AD were significantly higher than those of the controls (P<0.05); Moreover, the brain iron concentrations, especially in parietal cortex and hippocampus at the early stage of AD, were positively correlated with the severity of patients' cognitive impairment (P<0.05). The higher the R2′ and iron concentrations were, the more severe the cognitive impairment was. Regional R2′ and iron concentration in parietal cortex and hippocampus were positively correlated with the severity of AD patients' cognitive impairment, indicating that it may be used as a biomarker to evaluate the progression of AD.

Key words: Alzheimer disease; iron deposition; quantitative magnetic resonance imaging; transverse relaxation rate R2′; imaging marker

Brain iron deposition has been proposed to play an important role in the pathophysiology of neurodegenerative disease[1-3]. Alzheimer disease (AD) is a neurodegenerative disease characterized by progressive dementia. Pathological studies of patients with AD reveal that plaques, neurofibrillary tangles and neurons contain considerable amounts of iron[4], indicating a disruption of iron homeostasis in the brain. Excessive iron can contribute to the formation of free radicals, leading to lipid peroxidation and neurotoxicity, which can result in cell membrane damage and cell death[5-7]. Estimating the amounts of iron deposition in the brain might be a new biomarker for evaluating the presence and progression of AD.

Iron in the brain can be detected and to varying degrees quantified using two quantitative MRI techniques. One method is the measurement of phase shift by using susceptibility-weighted imaging which uses local phase differences to map the iron[8, 9], but the phase shift is affected by the background field effects caused by air-tissue interfaces that lead to signal loss in tissues ad-

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*This project was supported by grants from the National Natural Science Foundation of China (No. 30870702 and No. 30570531) and 863 Project of China (No. 2006AA02Z4A1).

jacent to these areas. Another method is the measurement of transverse relaxation rates R2 and $R2^*$ ($R2=1/T2$, $R2^*=1/T2^*$) or transverse relaxation time T2 and $T2^*$[10-17]. Though they are strongly affected by iron concentration, pathologic water content because of neuronal damage also influences R2 and $R2^*$, which can cause signal loss unrelated to the internal iron content of the tissue[8, 12, 18]. This effect makes R2 and $R2^*$ less reliable indicators for estimating iron levels than more advanced methods such as $R2'$ relaxometry.

Special transverse relaxation rate $R2'$ is the difference between $R2^*$ and R2 ($R2'=R2^*-R2$, $R2=1/T2$, $R2^*=1/T2^*$, $R2'=1/T2'$)[10, 12, 18, 19], and arises from static field dephasing that reflects the reversible signal loss associated with local field inhomogeneity. Some studies have shown that $R2'$ strongly correlate to brain iron concentrations in normal volunteers, and has higher iron-related specificity and smaller iron-independent component; furthermore, $R2'$ has good correlation with iron in the substantia nigra of patients with Parkinson disease, and increased iron level of substantia nigra links to the severity of motor symptoms[10, 12, 20]. It is suggested that $R2'$ will be the stronger and more accurate means to map brain iron content.

So far, there are no published studies on the use of $R2'$ to assess brain iron deposition in patients with AD. In this study, we quantified brain iron concentration of a group of normal volunteers by using $R2'$ measurement and compared with postmortem iron concentrations in normal adults[21] which provide reference iron concentrations for many of the brain regions analyzed, in order to establish the formula on the relationship between regional $R2'$ and regional brain iron concentration. The purpose of this study is to prospectively investigate the correlation of brain iron accumulation with the severity of cognitive impairment in AD patients.

1 MATERIALS AND METHODS

1.1 Subjects

This study was approved by the institutional review board of Tongji Hospital (Wuhan, China) and written informed consent was obtained from all participants. For patients with dementia, we obtained consent from their family members. Initially, 28 subjects with dementia were recruited from Tongji Hospital and a local hospital from February 2007 to June 2008. They received routine MRI examination to exclude prior neurologic diseases and multi-echo T2- and $T2^*$-weighted imaging to measure transverse relaxation rate $R2'$. In addition, they underwent extensive neurologic and neuropsychologic examinations clinically. Fifteen of these 28 were diagnosed as having AD according to the diagnostic criteria of the National Institute of Neurological and Communication Disorders, and Stroke/Alzheimer Disease and Related Disorders Association for probable AD[22]. The final AD population composed of 15 patients (8 women, 7 men; mean age, 69.8 years; range, 52-81 years) with Mini-Mental State Examination (MMSE) scores ranging from 0 to 24 (mean, 17.3); illness duration ranging from 2 to 8 years (mean, 5.4 years). These 15 AD patients were divided into the mild AD group (MMSE score >10, n=8) and severe AD group (MMSE score ≤10, n=7). Participants who had a history of neurologic or psychiatric disease and a history of traumatic brain injury resulting in neurologic sequelae were excluded, including 5 subjects that had imaging evidence of prior cerebral infarcts, and one with prior traumatic brain injury. In addition, the data for 7 other patients were excluded owing to obvious motion artifacts and susceptibility artifacts.

Fifteen age- and sex-matched healthy control subjects (8 women, 7 men; mean age 70.0 years; range 52—82 years; average MMSE score 30) and 30 healthy volunteers (15 women, 15 men; mean age 63.6 years; range 30—92 years; average MMSE score 30) with no history of neurologic disorder or head trauma and with normal neurologic examination findings were recruited from the hospital staff and local community. One expert neurologist performed the neurologic examinations for the patients with AD, control subjects, and normal volunteers, and generated the MMSE scores for each subject. Furthermore, in order to evaluate the severity of cognitive impairment of patients with AD, the relative ratio of MMSE (rrMMSE) was used as an index, which is the ratio of actual MMSE score of participates to their MMSE score based on the different education levels judged by NINCDS/ADRD criteria.

1.2 MR T2 Mapping and $T2^*$ Mapping

All the MR images were obtained using a 1.5-T system ((HDMR; GE Healthcare, Milwaukee, Wis) equipped with 8-channel phase-array head coil. Sagittal T1-weighted images were first acquired with a fast spin echo sequence to locate the prescribed positions of the anterior and posterior commissures. Conventional axial T1- and T2-weighted images were acquired for screening of cerebral disorders. T2 mapping and $T2^*$ mapping were taken parallel to the anterior-posterior commissural line. Axial T2 mapping images were obtained with a 2D multi-echo fast spin echo sequence, other parameters included: repeat time 3500 ms, echo time 30, 60, 90, 120 ms, echo number 4, slice thickness 6 mm, spacing 1 mm, field of view 24 cm×18 cm, number of excitation 1, matrix 288×256. Axial $T2^*$ mapping images were obtained with a 2D multi-echo fast gradient echo sequence, other parameters were: flip angle 40°, repeat time 250 ms, echo time of the first echo 3 ms, number of echoes 12, echo-train echo spacing 6 ms, number of interleaving echo trains 1, slice thickness 6 mm, spacing 1 mm, field of view 24 cm×18 cm, number of excitation 2, matrix 288×256. All source images of multi-echo T2 and $T2^*$-weighted imaging were sent to the workstation for image procession and analysis by using Functool Software.

1.3 Image Processing and Analysis

R2, $R2^*$, and $R2'$ maps were extracted on the MR workstation with an extended image reconstruction algorithm custom made within the manufacturer's image calculation environment. $R2'$ $(1/T2')=R2^*$ $(1/T2^*)$-R2 (1/T2), T2 and $T2^*$ values were calculated by fitting the signal intensity decay with TE to SI (TE) $=SI_0\, e^{-TE/T2}$ and SI (TE) $= SI_0\, e^{-TE/T2^*}$ for the T2 and $T2^*$ sequences, respectively[19]. $T2'$ is equivalent to $T2^*$ corrected for spin-spin (T2) effects. For each voxel, the quantitative T2 and $T2^*$ values were used to generate $T2'$ and $R2'$ values by applying this relationship.

In this study, the regions of interest (ROIs) included

bilateral hippocampus (HP), parietal cortex (PC), frontal white matter (FWM), putamen (PU), caudate nucleus (CN), thalamus (TH), red nucleus (RN), substantia nigra (SN) and dentate nucleus (DN) of the cerebellum. All source images of T2 mapping and $T2^*$ mapping would be sent to the workstation for image analysis by using Functool Software. The R2, $R2^*$ and $R2'$ maps were obtained after images processing. Since $R2'$ maps were more sensitive to susceptibility artifact than R2 maps, for $R2'$ measurement all ROIs were traced manually first in $R2^*$ maps by using in-house software according to the anatomic structures (fig. 1), then transferred to corresponding $R2'$ maps for each patient individually. ROIs were chosen carefully to minimize partial volume effects and the influence of susceptibility artifact. $R2'$ values of ROIs in AD and control groups were measured in $R2'$ maps by an expert neuroradiologist who was blinded to the diagnosis of probable AD. To ensure consistency in measurement, all subjects were reviewed 1 month later and all ROIs on the same images were re-measured by the same person. The final $R2'$ value was the mean value of the two measurements.

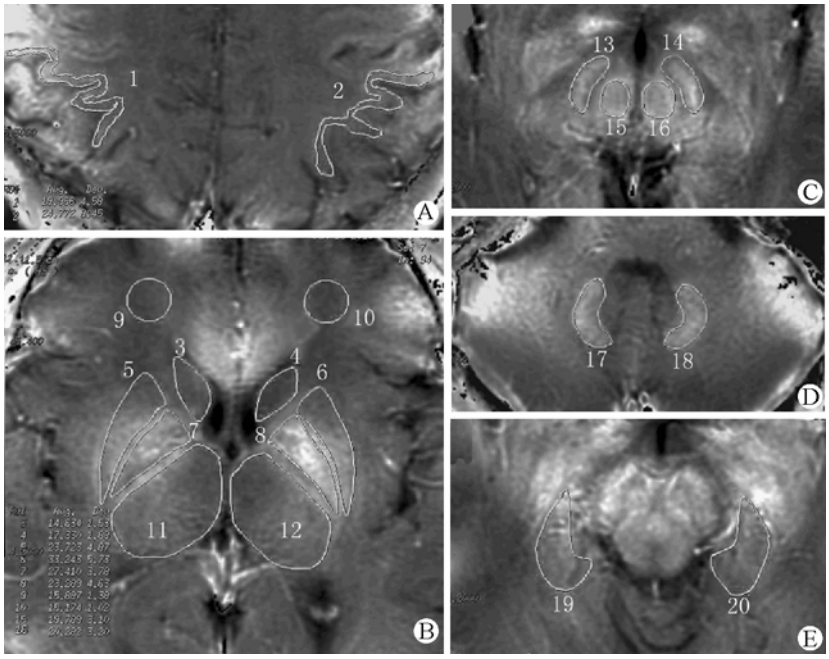

Fig. 1 $R2^*$ maps showing 20 gray and white matter regions as representative ROIs
1 and 2 refer to bilateral PC, 3 and 4 CN, 5 and 6 PU, 7 and 8 GP, 9 and 10 FWM, 11 and 12 TH, 13 and 14 SN, 15 and 16 RN, 17 and 18 DN, 19 and 20 HP

For the 30 normal volunteers, $R2'$ values of bilateral SN, RN, PU, CN, globus pallidus (GP), TH, and FWM were measured in $R2'$ maps using the above image analysis method. The correlation of regional $R2'$ with the postmortem iron concentration[21] of normal adults was analyzed in order to establish the formula on the relationship between regional $R2'$ and brain iron concentration. The postmortem iron concentration[21] provided reference iron concentrations for many of the brain regions analyzed in this study, thereby allowing us to validate our MR imaging protocol for assessing brain iron *in vivo*. The iron concentrations of ROIs in AD group and control group were calculated by above formula and their correlation with the severity of AD was analyzed.

1.4 Statistical Analysis

SPSS13.0 software for Windows (SPSS, version13.0; USA) was used for statistical analysis. Continuous variables were expressed as $\bar{x}\pm s$. To corroborate the validity of the $R2'$ technique for assessing brain iron concentrations, the average $R2'$ values for 7 brain regions from the normal volunteers were plotted against the postmortem iron concentrations of normal adults[21]. The correlation of $R2'$ and brain iron concentration of normal volunteers was performed with the linear regression. The comparison between the control and AD groups was performed with two-tailed *t*-test. The group comparison between the control and each AD group was performed with Student-Newman-Keuls test (ANOVA). The correlation of $R2'$ with the iron concentration in HP and PC of patients with AD was analyzed by linear correlation test. The *P* value less than 0.05 was considered to be statistically significant.

2 RESULTS

2.1 Correlation of Regional $R2'$ with Brain Iron Concentration in Normal Participants

$R2'$ in 7 brain subregions of 30 volunteers detected in this study is summarized in fig. 2. To test their validity, the correlation of $R2'$ with postmortem brain iron concentration in normal adults[21] was analyzed by Pearson Correlation Assay. It has been demonstrated in fig. 2 that $R2'$ in different brain subregions was positively correlated with iron concentration in corresponding regions (r=0.977, P<0.01). The formula of this linear correlation was: Y=0.671X+0.673, where Y is $R2'$, and X is brain iron concentration.

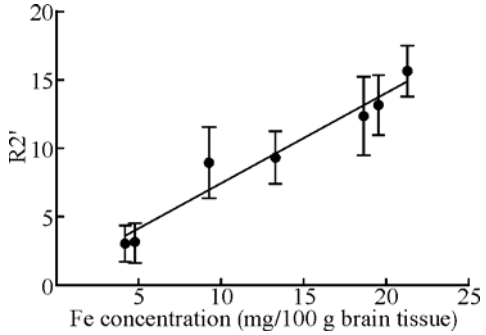

Fig. 2 Correlation of R2' in 7 brain subregions of 30 healthy volunteers with postmortem brain iron concentration of corresponding subregions[21] in normal adults

2.2 Comparison of R2' in Different Groups

The R2' in bilateral HP, PC, PU, CN, DN, SN, RN, TH and FWM of AD and control groups were measured respectively. It has been shown in fig. 3 that R2' values of bilateral HP, PC, PU, CN and DN in AD group were significantly higher than those in control group (P<0.05). However, there was no significant difference in bilateral SN, RN, TH and FWM between two groups (P>0.05). Furthermore, the pair comparison of R2' among the control, mild AD and severe AD groups in fig. 4 demonstrated that R2' values of bilateral PC, HP and left PU in mild AD group were significantly higher than that in control group (P<0.05), which indicates that bilateral PC, HP and left PU have higher sensitivity to the variation of R2' at the early stage of AD progression, particularly in bilateral PC and HP. R2' values of bilateral HP, PC, PU and DN in severe AD group were significantly higher than those in control and mild AD groups (fig. 5 and 6), indicating that the bigger the R2' was, the more severe the cognitive impairment in AD.

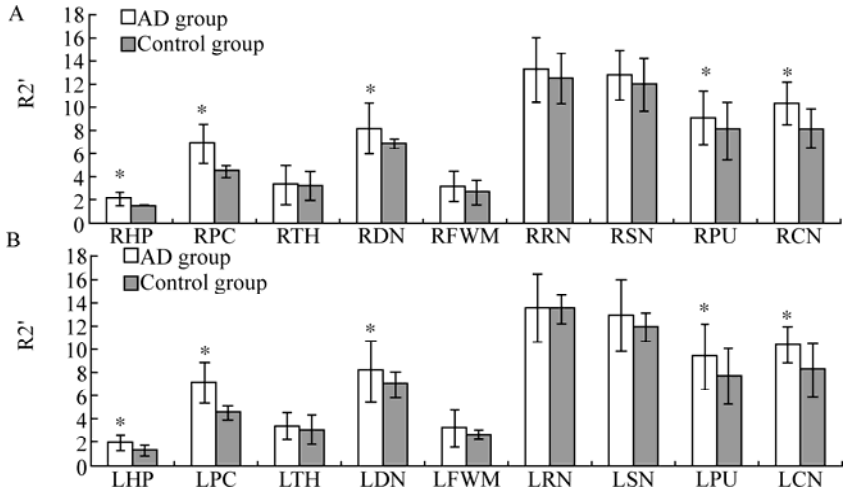

Fig. 3 Plot of R2' of each brain sub-regions between AD and control groups
A: Right hemisphere; B: Left hemisphere. $^{*}P$<0.05 AD group *vs.* control group (two-tailed test)

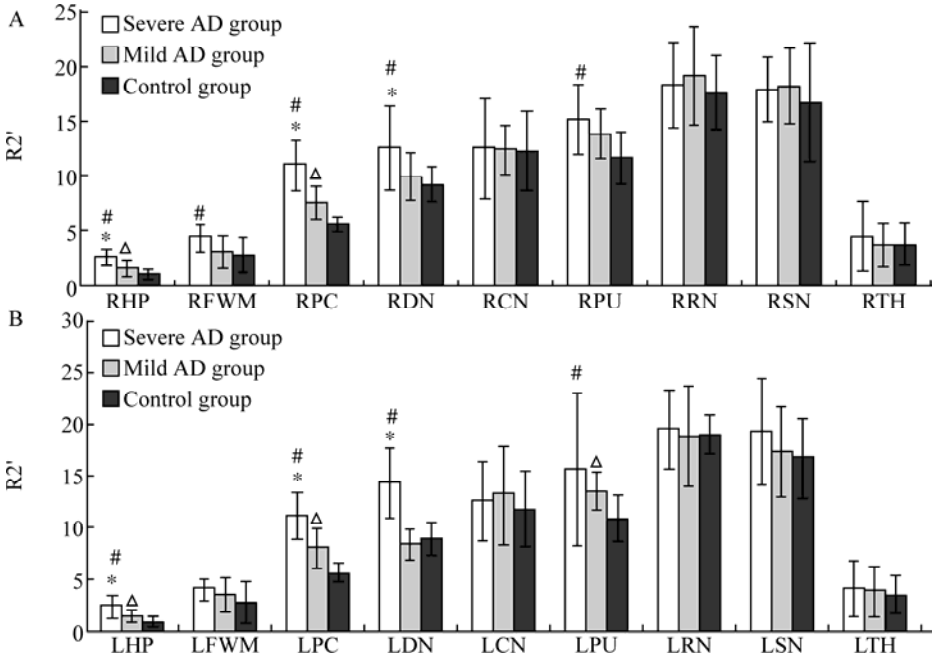

Fig. 4 Plot of R2' of each brain subregions in mild AD, severe AD, and control groups. All data were analyzed by the test of normality and met the requirement of analysis of variance.
A: Right hemisphere; B: Left hemisphere $^{*}P$<0.05 severe AD group *vs.* mild AD group, $^{\triangle}P$<0.05 mild AD group *vs.* control group, $^{\#}P$<0.05 severe AD group *vs.* control group [Student-Newman-Keuls test (ANOVA)]

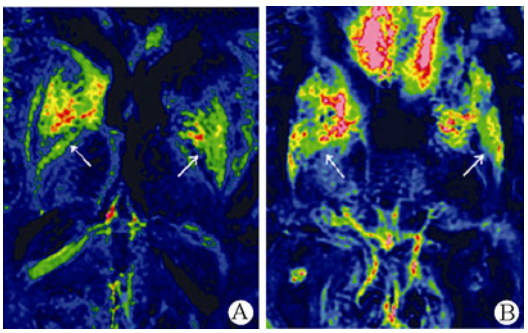

Fig. 5 R2' map of bilateral putamen in control subject (A) and a severe AD patient (B). R2' values of bilateral PU and CN of AD patient are increased and large and bright colorful regions are observed when compared with those of control subject.

2.3 Correlation of R2' and Brain Iron Concentration with Severity of Cognitive Impairment

According to NINCDS-ADRDA diagnostic criteria for AD[22], the rrMMSE is negatively correlated with the severity of cognitive impairment of patients. Fig. 7, and 8 have shown the correlation of R2' and iron concentrations in bilateral PC and HP with the severity of cognitive impairment, respectively. The brain iron concentration of the subregions was calculated according to the formula of the Result 2.1: Y=0.671X+0.673, where Y is R2', and X is brain iron concentration. Fig. 7, and 8 have demonstrated that rrMMSE is negatively correlated with R2' and iron concentration measured in the bilateral PC and HP in AD group (r ranging from 0.783-0.929; P<0.01), indicating that R2' and iron concentration in brain subregions are both positively correlated with the severity of cognitive impairment of patients with AD. In particular, the sensitivities of those factors in bilateral PC were higher. The bigger the R2' and brain iron concentration are, the smaller the rrMMSE, which means significantly severe cognitive impairment.

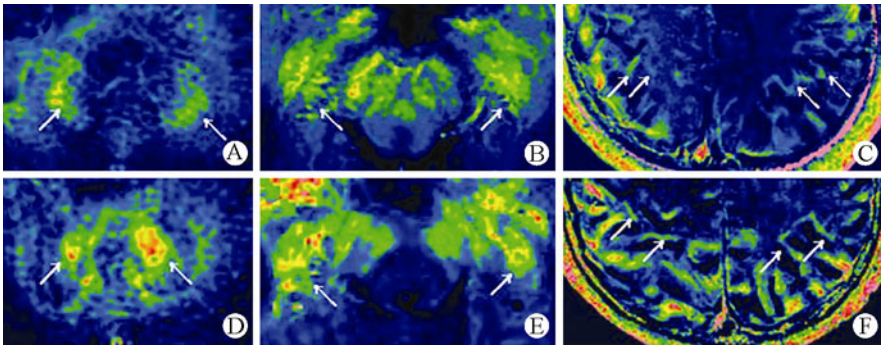

Fig. 6 R2' map of bilateral DN, HP and PC in control group (A, B and C respectively) and the same patient with severe AD (D, E and F respectively) as in fig. 5. R2' values of bilateral DN, HP and PC of AD patient are increased and large and bright colorful regions are observed when compared with those of control subject respectively.

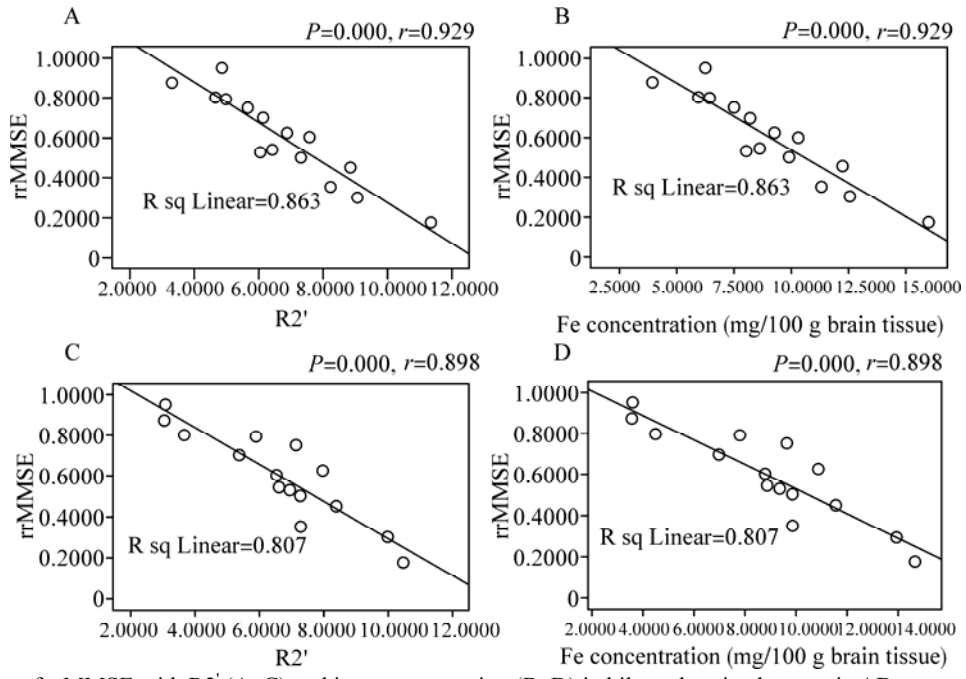

Fig. 7 Correlation of rrMMSE with R2' (A, C) and iron concentration (B, D) in bilateral parietal cortex in AD groups. A, B: Right hemisphere; C, D: Left hemisphere

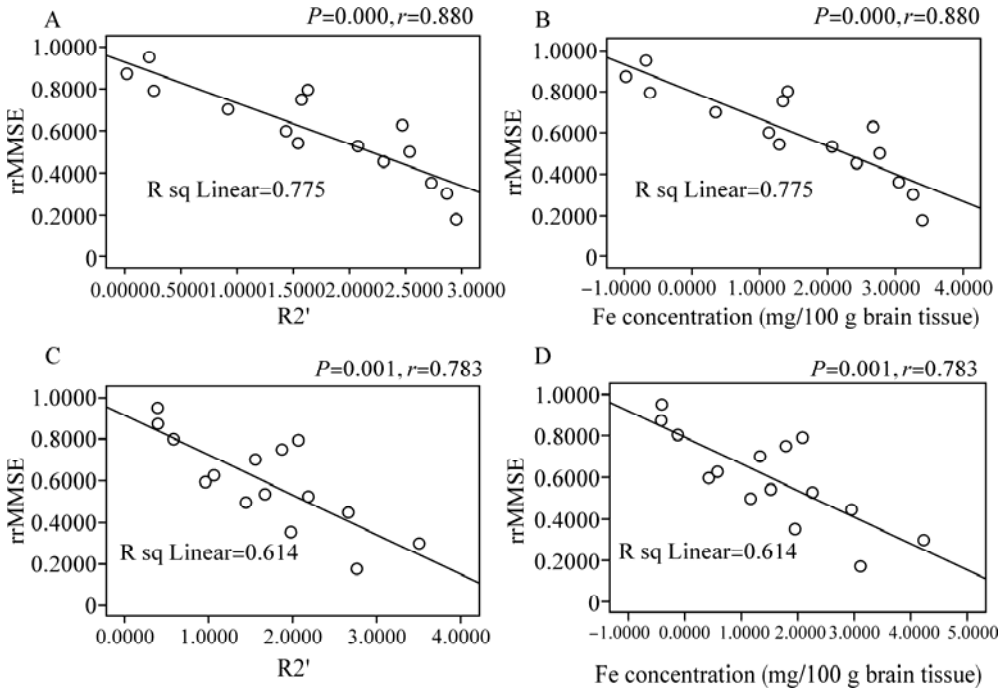

Fig. 8 Correlation of rrMMSE with R2' (A, C) and iron concentration (B, D) in bilateral hippocampus in AD groups
A, B: Right hemisphere; C, D: Left hemisphere

3 DISCUSSION

3.1 Main Forms of Brain Iron in Patients with AD

Abnormal brain iron deposition has been proposed to play an important role in the pathophysiology of AD; However, accurate visualization of brain iron deposition in patients with AD by using R2' is not established in the literature currently. Normally, there are two categories of iron in the brain: heme iron and non-heme iron. Non-heme iron, more than 90% of which is stored in ferritin, is the main type of brain iron[8]. Ferritin has a large spherical protein coat, about 12 nm in diameter, that surrounds a crystalline core of hydrous ferric oxide [$5Fe_2O_3.9H_20$][55]. There can be up to 4500 iron atoms stored in the 8-nm-diameter internal cavity of one ferritin protein. Iron(II) passes into the core through six channels in the protein coat and is oxidized to iron(Ⅲ) for storage. Transferrin concentrations in brain tissue are at least 10 times lower than ferritin and can only bind two iron atoms compared to thousands of iron atoms within each ferritin molecule. The concentrations of other iron species are also considered to be too low to affect MR contrast[8]. The human brain also contains other paramagnetic ions, like copper and manganese. It is suggested that non-pathological concentrations of copper and manganese are too small to produce detectable MR contrast[23]. In AD, brain iron level was increased in HP, basal ganglia, and neocortex. Increased iron levels in AD patients was proved as magnetic iron compounds, biogenic magnetite (Fe_3O_4), the Fe^{2+}-ion-containing iron oxide, and their genesis within the 8 nm diameter cores of the iron storage protein ferritin[24].

In fact, Fe_2O_3 and Fe_3O_4 are superparamagnetic because of nano-scale of the crystal grains. Therefore, ferritin and magnetite are considered to be the main forms of iron deposition to produce MR contrast in the AD brains.

3.2 R2' is Reliable in Measuring Brain Iron Deposition in Patients with AD

Paramagnetic iron deposition in the brain can increase proton transverse relaxation rates and lead to the signal changes on T2- and T2*-weighted images. R2' is the difference between R2* and R2, whose susceptibility effect associates with iron and is independent of other parameters which affect R2 and R2*, such as pathologic tissue water concentrations. A number of researchers suggest that the key information for quantifying brain iron lies in R2', which is strongly correlated to brain iron concentrations, and has higher iron-related specificity and smaller iron-independent component[8, 10, 12, 18]. we quantified the brain iron concentration of a group of normal volunteers using R2' by comparing with postmortem iron concentrations in the literature[21] and found that there was a positive correlation between regional R2' in CN, PU, GP, TH, SN, RN and FWM and brain iron concentration in normal adults, indicating the effectivity and reliability of this method to qualify brain iron concentration of patients with AD. Gelman found that R2' is strongly correlated to brain iron concentrations in normal adults[12]. Ordidge demonstrated that R2' has the best correlation with iron in the substantia nigra of Parkinson disease patients. Significant increases in R2', but not R2, in the substantia nigra of PD patients, are consistent with several postmortem studies on PD that have measured elevated levels of iron in the substantia nigra region[10], furthermore, increased iron level of substantia nigra links to the severity of motor symptoms[20].

These results demonstrated that R2' is a reliable parameter in measuring brain iron deposition in patients

with AD.

3.3 Close Relationship between Brain Iron Deposition and AD

3.3.1 Selective Increase of Brain Iron Deposition Reflects Neuropathological Progression of AD Our data showed conspicuous increase of $R2'$ and iron concentration in bilateral HP, PC, PU, CN and DN of patients with AD, which is consistent with the postmortem biochemical studies that have measured excessive brain iron in cortical and basal ganglia regions of the AD brain[25-29]. However, iron levels had no distinct changes in FWM, TH, SN and RN of AD subjects, which suggests that $R2'$ reflects difference in iron-induced susceptibility of brain tissue and that the increased iron levels in HP, PC, PU, CN and DN is not a generalized phenomenon, but reflecting the neuropathological progression of AD. Increased iron deposition in the brain has been demonstrated to be associated with AD for some reasons as following: (a) [Fe^{2+}] iron accumulation is a source of redox-generated free radicals[30]. The oxidative chemistry is proposed to play a major role in deleterious free radical-mediated brain injury in neurodegenerative disease; (b) The lack of iron-regulatory protein 2 (IRP2) is associated with neuronal apoptosis in mice with fully ablated IRP2, and abnormal distribution of IRP2 has an association with neurofibrillary tangles and other pathology in postmortem study of AD[30, 31]; (c) Brain iron accumulation has been associated with both amyloid plaques and neurofibrillary tangles[4]; (d) Iron also increases the aggregation of β-amyloid proteins[6]; (e) Some ultra-high-field MR microimaging studies found senile-plaques-like lesions and iron deposition associated with amyloid deposits in the hippocampus and cortex of AD patients and transgenic mouse models[28, 29, 32].

3.3.2 Positive Correlation between Iron Concentration of Bilateral PC and HP with Severity of Dementia Our results illustrate that $R2'$ in mild AD group was significantly increased in bilateral parietal cortex and hippocampus as compared with that in control group ($P<0.05$), so does iron concentration since there is a positive line correlation between regional $R2'$ and brain iron concentration in normal adults, suggesting that parietal cortex and hippocampus are more sensitive than basal ganglia and DN for detecting increased iron deposition during the early stage of AD procession. Pathological study revealed that plaques, neurofibrillary tangles, and neurons contain considerable amounts of iron, and iron deposition is markedly increased in bilateral HP and parietal cortex of AD patients[4, 26, 29], which are consistent with our findings. Brain iron concentration measured in this study was significantly different between mild and severe AD subjects in the bilateral HP, PC, PU, CN, and DN, and iron levels were markedly increased in severe AD subjects as compared with those in mild AD subjects, indicating that more iron deposition may reflect the much more severity of dementia. We also demonstrated in fig. 7 and 8 that there was a significantly negative line correlation between rrMMSE and iron concentration of bilateral PC and HP in AD group, especially PC, which has the bigger negative correlation coefficient. Therefore, iron concentrations of bilateral PC and HP may be used as a biomarker to evaluate the severity of dementia in patients with AD.

Some previous studies attempted to investigate whether the increased iron concentration was a marker for disease-related cell loss or whether the iron contributes to the pathogenesis of AD. The length of illness seems to have no impact on basal ganglia iron levels[33], suggesting that iron increases in AD are not caused by the illness itself and may be interpreted as a risk factor for AD. AD patients with memory complaints show higher R2 value in the temporal gray matter notably the HP[34] than healthy controls. Furthermore, increased FDRI-based iron levels in the caudate and PU are especially prominent in patients with young-onset AD[33]. All these data support the hypothesis that brain iron is a risk factor for early age of onset. Our study demonstrated that there was a strongly negative correlation of rrMMSE with iron concentration measured in the bilateral PC and HP in AD group. Taken together, these studies indicate a role for iron deposition as a marker of early neurodegeneration related to cognitive disorders.

3.3.3 $R2'$ is Superior to Phase Shift Measurement to Map Brain Iron Our previous research had proved a new susceptibility weighted imaging method, referred to as phase-corrected imaging which used local phase shift to map the iron, was also sensitive to increased brain iron deposition[9]. The results showed that regional phase shifts were negatively correlated with regional brain iron concentration in normal adults (r=-0.926, P=0.003), but $R2'$ was positively correlated with iron concentration in corresponding subregions (r=0.977, P=0.000) with bigger correlation coefficient, which showed that $R2'$ has a closer relationship with brain iron levels in normal adults. Phase shift values in bilateral HP, PC, PU, CN and DN of AD patients were significantly higher than those of the controls ($P<0.05$), which is similar as the result of $R2'$ in this study. Furthermore, phase shift in bilateral HP had no significant difference between mild AD and control group ($P>0.05$), but $R2'$ in bilateral HP had significant difference between these two groups ($P<0.05$), indicating that $R2'$ is more sensitive than phase shift in detecting brain iron change at the early stage of AD regression. Although iron concentration of PC calculated by the methods of $R2'$ and phase shift are positively correlated with the severity of patients' cognitive impairment ($P<0.05$), the correlation of $R2'$ with the severity of dementia is stronger than that of phase shift since correlation coefficient of $R2'$ to rrMMSE (r=0.929) is bigger than that of phase shift (r=0.873). These results demonstrate that $R2'$ is more sensitive in measuring brain iron deposition than phase shift, although both $R2'$ and phase shift are affected by susceptibility artifact related to field inhomogeneity.

We believe that $R2'$ based on T2 and $T2^*$ mapping, is a reliable parameter in measuring brain iron deposition. In patients with AD, the regional $R2'$ and brain iron concentration, particularly in PC and HP, was significantly positively correlated with the severity of patients' cognitive impairment, indicating that $R2'$ might be used as an imaging marker to evaluate the progression of dementia in patients with AD. The potential role of iron deposition and its assessment by $R2'$ technique might provide exciting potential applications to the diagnosis, longitudinal monitoring, and therapeutic development for AD.

Acknowledgments

We thank Prof. Yin Pin for his assistance in statistical analysis. We thank our patients and families for their contributions to AD research.

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(Received Apr. 7, 2010)