The Correlation of Hippocampal T$_2$-Mapping with Neuropsychology Test in Patients with Alzheimer’s Disease

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Abstract

**Objectives:** 1) To deduce T$_2$, the inverse of the transverse relaxation rate (R$_2$), in the hippocampus of healthy adults; 2) to investigate the brain iron deposition in Alzheimer’s disease (AD) patients and age-matched healthy controls using T$_2$-values.

**Methods:** T$_2$-weighted data from the bilateral-hippocampi of ten AD patients and sixty healthy controls were collected at six echo time points using multi-slice multi-echo turbo spin echo (MSME-TSE) imaging on a 3.0 T MR-scanner, followed by the neuropsychological testing. The correlations between T$_2$-values and Mini-Mental State Examination (MMSE) scores were investigated on group-wise basis (covariates in the group-wise analyses: gender, age, side and healthy/AD).

**Results:** There were no significant differences in hippocampal T$_2$-values on intra-gender and inter-gender basis (P > 0.05). Hippocampal T$_2$-values of both sides were similar (right: 85.2±2.4 milliseconds; left: 85.3±2.5 milliseconds). The bilateral hippocampal T$_2$ values correlated moderately with age (right: r = -0.59; left: -0.58; P < 0.001). The AD-group had significantly lower T$_2$-values in the hippocampus when compared to normal controls (P < 0.001) and such low T$_2$-values had a strong positive correlation with the MMSE score (R$^2$ = 0.97; P < 0.05).

**Conclusion:** Patients with AD showed significantly lower T$_2$ values, which can be attributed to the increased iron depositions in the hippocampus. A positive correlation between T$_2$-values and cognition scores suggests that quantitative T$_2$ can be used in the early diagnosis of AD and in the monitoring of the treatment response.

Introduction

Alzheimer’s disease (AD) is the most common cause of dementia for the elderly. It is pathologically characterized by the presence of senile plaques (SPs) and neurofibrillary degeneration (NFD) in cortical regions of the brain [1-3]. The redox-active biometals have been suggested to play considerable roles in the generation of the oxidative stress and in the modulation of amyloid-ß (Aß). Additionally, iron is recognized as a major cause of oxidative stress in AD. There is a close connection between the iron deposition and the AD on both regional and cellular levels. Postmortem biochemical studies have reported elevated iron concentrations in the hippocampus, cortical lobes, and basal ganglia regions of AD brains compared to controls [4-8]. Furthermore, the increased iron accumulation is shown in both SPs and NFD regions that are major sites for the catalytic redox activity [9,10]. Increasing evidences indicate that oxidative stress is one of the earliest events in the genesis of AD, and iron may play a crucial role [11]. Iron concentrations are elevated in cortex and basal ganglia in AD patients [4-6,12,13] indicating a disruption of iron homeostasis in the brain. Higher iron concentrations in AD...
brains may increase the possibility of free iron-catalyzed lipid peroxidation, which may cause cell membrane damages and subsequent cell deaths. Based on these findings, it is possible that iron chelators and inhibitors of the iron-dependent oxidative stress and lipid peroxidation (e.g., antioxidants or free radical scavengers) may have a therapeutic value [14-16]. Therefore, a quantitative measurement is required to assess and monitor the concentrations of iron deposited in the brain, which might provide a biomarker for early detection and design of therapeutic interventions.

Iron, in the form of ferritin, can reduce $T_2$ relaxation times or increase $R_2 (=1/T_2)$ values, and so we applied quantitative MR imaging proton transverse relaxation rate (R$_2$) which has the potential to measure brain iron content indirectly and manifest other features of AD pathology in vivo [17]. R$_2$ (=1/T$_2$), the transverse relaxation rate, describes the rate of dephasing of the hydrogen nuclei in specific structures [18] in the presence of external magnetic field. The R$_2$ value of proton depends on volume and surface interaction effects of confining structures/ compartments [19] and hence, the proton in different environments (chemical or magnetic) would have different R$_2$ values. Iron deposition causes local distortions of the effective magnetic field which enhances the relaxation rates of diffusing protons resulting in the increase of R$_2$ (or decrease of $T_2$) values. As a part of the middle temporal lobe composing the memory system, the hippocampus is one of the regions which is susceptible to damage from AD. Therefore, we chose hippocampus as the region of interest (ROI) for measurement of $T_2$ (and R$_2$) in this study.

In this study, we applied quantitative MR imaging to measure the mean hippocampal $T_2$ relaxation times (and R$_2$ values) in 60 healthy adults, and then assess differences in $T_2$ values in the hippocampi between patients with AD and normal controls which can be attributed to different iron accumulation levels in both groups. The main objectives of this study were: 1) to provide baseline data for the early diagnosis and the longitudinal monitoring of AD with hippocampal $T_2$ relaxation times; 2) to prospectively investigate the abnormal iron deposition in the hippocampus of patients with AD using hippocampal $T_2$ relaxation times (and R$_2$ values) as a surrogate; and 3) to explore the relationship between the reduction in average $T_2$ values, likely due to the iron level, and the neuropsychological tests in these patients reporting memory loss.

Materials and Methods

Ethics statement

The study was approved by the Ethics Review Board of the First Affiliated Hospital of Xiamen University. The written informed consents were obtained from both groups: AD patients and healthy volunteers. In case the participants (AD patients) had impaired ability to consent, written consents were obtained from the next-of-kin or the care giver on their behalf.

Study population

Ten AD patients and 60 healthy adult volunteers of whom 10 controls were age-matched to the AD group were included in this prospective study (please refer to Table 1 for the demographic details and neuropsychological test scores of the participants). All the participants were right-handed. These patients underwent a series of neurological tests and a battery of neuropsychological assessments, which included the Mini-Mental State Examination (MMSE) and the Actiivity of Daily Living (ADL), to rule out other causes of cognitive impairment. We choose the MMSE score to indicate the cognitive level and not the ADL as the ADL test needs much more time than the MMSE and has less specificity with cognitive level. All cases meet the NINCDS/ADRDA [20] criteria for clinically probable AD. Sixty healthy adult volunteers were recruited, with age ranging from 18 to 70 years. They were further divided into three subgroups according to the latest principles of age group set by WHO: 1) youth group of 20 cases, mean age: 34 ± 6 years; 2) middle-aged group of 20 cases, mean age: 51 ± 3 years; and 3) elderly group of 20 cases, mean age: 65 ± 4 years.

Exclusion criteria included the following: patients with other brain diseases or with other causes of dementia supported by pathological brain scan and clinical findings, including significant cerebrovascular diseases (cortical infarctions, multiple lacunas lesions and chronic subdural hematoma); Parkinson’s disease; Huntington’s disease; Pick’s disease; Creutzfeldt-Jakob disease; Normal pressure hydrocephalus; Dementia with Lewy’s bodies; Corticobasal ganglionic degeneration; Progressive supranuclear palsy; Cancer (brain tumor or meningeal neoplasms); infection (AIDS, Neurosyphilis or Progressive multifocal leukoencephalopathy); Metabolic disorders (Hypothyroidism or Vitamin B$_{12}$ deficiency) and patients with depression or dysthymia according to the DSM-IV criteria. Control subjects underwent a structured interview to exclude patients with cognitive dysfunction, substance abuse, depression, and other cerebral pathology.

Image acquisition

All the MR images were obtained using a 3.0-T MR system (Achieva 3.0 T TX; Philips Healthcare, Netherlands) equipped with an eight-channel head coil. The head was immobilized in the head coil with foam padding. Conventional axial $T_1$- and $T_2$-
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weighted images were acquired for screening of space-occupying lesions and cerebrovascular diseases. A multi-slice multi-echo turbo spin echo sequence (MSME-TSE; sequence name on Philips scanner: sT₂-Cal_TSE) was used to get the T₂ map and was taken in parallel to the coronal-oblique images of hippocampus with the following parameters: A pulse repetition time (TR) of 2000 msec and 6 echo times (TE) of 20, 40, 60, 80, 100, and 120 msec were used. Flip angle = 90°, number of slice = 5 slices, slice thickness = 3 mm, slice gap = 0 mm, NSA = 1, FOV = 160 mm × 160 mm, and matrix size = 380 × 310.

Image Analysis

The raw data acquired using the sequence sT₂-Cal_TSE were transferred to a separate workstation (Philips Extended WorkSpace version 2.6.3.1), where the data were processed by a self-coded program to obtain the T₂ map. After that, the T₂ relaxation times [21] were calculated on the T₂ map (Figure 1). R₂ is defined as the reciprocal of the proton transverse relaxation time, T₂ (i.e., R₂ = 1/T₂×1000). The units for T₂ and R₂ are millisecond (msec) and second⁻¹ (sec⁻¹), respectively. Regions of interest (ROIs) were first delineated on the intermediate echo time images (60 msec or 80 msec, Figure 1). ROIs were set to include the maximum contours of the hippocampus and exclude the hippocampal boundaries. Furthermore, the alveus and fimbria of hippocampus, and the cerebrospinal fluid (CSF) in the gyri uncinatus of the hippocampal head should be ruled out to reduce CSF partial volume effects. Manual tracing a ROI in a sample subject was illustrated on the representative long axial images of hippocampus in Figure 1. A trained neuroradiologist with more than 15 years of experience, who was blinded as to the subjects’ exact group, manually traced the ROIs. All the ROIs were remeasured two months later by the same reader on the same images. The final values were the means of the two measurements.

Statistical analysis

Group differences in age, education, and MMSE or ADL score were analyzed using one-way analysis of variance (ANOVA) with least significant differences post hoc analysis. Sex differences between groups were assessed by a χ² test. The paired-sample t test was used to analyze the differences between the left and the right side of the hippocampus, and Student’s t test was employed to figure out if there were gender wise differences and ANOVA was adopted to identify the differences of T₂ values among these subgroups in the healthy volunteers. Furthermore, the relationship between the T₂ values and the age of subjects was analyzed using the Pearson’s Correlation test. Group differences in T₂ (and R₂) values were tested for significance by using one-tailed t test. Iron levels tend to increase with age, but typically reach a plateau in the elderly population [22]. Therefore, to eliminate the effect of age itself on iron levels between groups, an analysis of covariance (ANCOVA) (with age as the covariate) was also used to assess T₂ (and R₂) differences. To investigate the relationship between T₂ (and R₂) values in the hippocampus and MMSE scores for the participants with AD, a Pearson’s correlation coefficient, adjusted for age, was used to assess the direction, strength, and significance of the correlations. All statistical computations and analyses were carried out using the SPSS statistical package (SPSS for Windows, version 13.0; SPSS Inc., Chicago, IL), and the results were declared statistically significant when associated with a two-sided P < 0.05.

Results

Demographics, Clinical Data

There were no significant differences in age, sex and education levels (P > 0.05) between the age-matched elderly controls (N = 10) and the AD group (N = 10) (Table 1). The AD group had significantly lower MMSE score (P < 0.05, Table 1) in comparison to the control group.

Hippocampal T₂ of normal adults and its relationship with age, gender and side

The hippocampal T₂ values of both sides were (85.2±2.4) milliseconds (right hippocampus) and (85.3±2.5) milliseconds (left hippocampus), respectively, and there were no significant differences in hippocampal T₂ values on the left and the right side of the same sex group of healthy volunteers (t = 0.62, P = 0.5383). There were no further significant gender-wise differences (P > 0.05). The bilateral hippocampal T₂ values correlated moderately with age (r = -0.59 for right side and -0.58 for left side, respectively; P < 0.001) (Figure 2).
**Discussion**

**R₂ versus R₃ or R₄**

Many investigators [23-26] have proposed R₃, the free induction decay rate due to the presence of magnetic field gradient irregularities and minor differences in chemical environment, and even R₄, the difference between R₂ and postmortem iron concentrations. Those researchers [23-26], however, suggest R₂ or R₃ may be a more specific measure of iron in the brain as cortical white and gray matter regions with similar iron concentrations have similar R₂ or R₃ values, but significantly different R₄ values. Other factors, such as the increased water content, may also contribute to changes in R₃ values besides tissue iron concentrations. However, in the case of gray matter (e.g., hippocampus as ROIs in our study), where water concentrations are similar, iron appears to be the dominant factor in determining R₂, and the iron-related specificity of R₃ would, therefore, be enhanced. Hence, increase in R₂ values of the gray matter are thought to reflect increase in the iron contents of this brain tissue type.

The inferred R₂ values from the measured data also vary depending on the inter-echo spacing and the field strength of MRI scanner being used in the experiment [27], which would account for slightly different results reported in the literature.

**Comparison of T₂ (and R₂) values between AD patients and age-matched controls**

T₂ (and R₂) differences between the AD group and the healthy control group suggest iron concentration has increased in the hippocampal region and a disruption of iron homeostasis in the brain has happened in those with memory complaints, consistent with incipient AD pathogenesis and biochemical data. Excessive brain iron deposition would promote the aggregation of β-amyloid peptide and increase β-amyloid toxicity [11], and its neurotoxicity can, therefore, lead to nerve cell death. Previous histochemical stains reveal iron in amorphous amyloid plaques, in neurofibrillary tangles, and in cortical neurons in AD brains [28,29]. This may account for the severe encephalatrophy, especially in the hippocampus located in the temporal lobe of brain, observed from MR imaging in patients with AD. Haley et al [30] conducted a study of 10 patients with AD and 40 healthy participants, and found T₂ values in the right hippocampus of AD patients to be significantly reduced compared to normal aged participants, thereby, affecting the sensitivity of estimating iron level in the hippocampus by T₂ values.

The preliminary study of House et al [32] and the work of Campeau et al [33] indicated that hippocampal R₂ values in the
AD group were essentially unchanged compared to the controls. However, our results contradicted their findings. A 7 T MR imaging study by Huesgen et al [34] has also reported a non-significant reduction in $T_2$ relaxation times ($R_2$ increase) of AD hippocampus. They explained that AD progression accelerates the neuronal degeneration and the hippocampal atrophy. Atrophy of brain tissue may increase the amount of CSF, thus reducing $R_2$ and counteracting any iron increases. The final $R_2$ values, therefore, remain unchanged. It is interesting to note that some researchers [35-37] have reported $R_2$ reductions in the hippocampus of AD patients. Nevertheless, the reported absence of an association between hippocampal volumes and $T_2$ relaxation times in AD [34,38] suggests that the atrophy, resulting in increased water contents, is not the dominant mechanism driving $R_2$ reduction in this brain region. The hippocampus is rich in myelin relative to other gray matter regions. A loss of myelin in AD hippocampi has been inferred from a decrease in 2',3'-cyclic nucleotide-3'-phosphodiesterase (CNPase) activity [39], which suggests a possible mechanism for reducing hippocampal $R_2$ values in AD, and is analogous to the pathologic processes reducing $R_2$ in white matter. Hence, demyelination and atrophy cause the hippocampal $R_2$ values to decline.

Wang et al [40] studied the animal model of AD in mice using histochemical staining for senile plaques and $T_2$ mapping. They found that senile plaques were deposited as early as 4 months in transgenic model of AD. Iron depositions in the hippocampus and the cortex were detected by Perl's-DAB (stain for iron) as early as 6 months of age, and there was an overall increase in number and load of plaques and iron with age. They further found that $T_2$ values decreased in the cortical and the hippocampal regions of adult mice group, and it tended to shorten with age. They [40] believed that shortening of $T_2$ values in AD transgenic mouse may be associated with the interaction between Aβ peptide and iron. In the early days iron deposition was not as obvious as senile plaques. As a result, it reduced $T_2$ values in AD transgenic mouse which may be related to a deposition of Aβ peptide. However, in the elder mice group, both Aβ and iron contributed, with iron taking a leading role, resulting in reduced $T_2$ values. Their preclinical study established iron accumulation to be the dominant factor in the reduction of $T_2$ value in AD.

Correlations of $T_2$ (and $R_2$) values with MMSE score

One of the most important findings in our measurement was a strongly positive correlation between the $T_2$ relaxation times in the hippocampus and the MMSE score ($R^2=0.97, P < 0.05$) or a strongly negative correlation between the $R_2$ and the MMSE score ($R^2=0.95, P < 0.05$) for the patients with AD. The results establish a connection between the iron deposition in the hippocampus and the severity of AD patients, and suggest that iron deposition relates to the pathology and the progression in AD. Such information may assist in the diagnosis of AD, as well as in yielding a clinical biomarker that would be valuable in the monitoring of AD. House et al [32] reported negative correlations in the gray matter and positive correlations in the white matter between $R_2$ and cognition/ memory scores, that is, in participants with memory problems, $R_2$ tends to increase in gray matter and decrease in white matter. There are, however, some exceptions to these general trends. $R_2$ in the internal capsule showed mainly weak negative correlations with MMSE score, perhaps reflecting the influence of interdigitating gray-matter bridges between the caudate and the putamen. $R_2$ values in the left hippocampus were positively correlated weakly with some memory scores and the MMSE results. As discussed above, the high myelin content of the hippocampus relative to other gray matter regions could make this structure vulnerable to $R_2$-reducing processes that are more pronounced in white matter, and which ultimately obscure correlations with memory scores. Laasko et al [35] found there was no correlation between $T_2$ values and memory test scores in their AD patients, but found a significant negative correlation between the hippocampal $T_2$ values and MMSE scores. This observation is equivalent to a positive correlation between $R_2$-values and MMSE scores, which is contrary to our own findings. The work of Wang et al [37] mentioned that the right hippocampal $T_2$ was correlated with cognitive performance in AD, whereas the amygdaloid $T_2$ was not. They [37] argued that this might be partly explained by their study sample and the fact that most of the patients in their study had moderate dementia. They further argued these results could not conclude whether the measurement of amygdaloid $T_2$ helps in monitoring the cognitive deterioration of AD. Their work motivated us to focus on the measurement in one specific region-hippocampus.

Limitations

There are two main limitations of our study. First of all, our study included limited number of AD patients. Further evaluation in larger samples is required, especially, more patients with mild cognitive impairment recruited in the following studies. Another limitation of this study is that only $R_2$ values in the hippocampus were measured. Although AD is traditionally characterized as a gray matter disease, white matter changes were considered only a secondary phenomenon related to the neuronal degeneration. However, histopathological, biochemical, and MR imaging changes in AD white matter have been observed in several studies [41-44]. Some early research [42] indicated that white matter changes in AD were not purely a secondary phenomenon related to neuronal degeneration, while reports from the past few years [45,46] suggest that demyelination may have closer links to AD pathogenesis than previously thought. House et al [32,47] showed that $R_2$-values and iron concentrations in various brain regions of AD patients were correlated, though hippocampal analysis was not included. Higher water content, associated with decreasing protein and lipid levels, can also contribute to $R_2$ reduction in white matter of AD patient if iron concentration is fixed. This would explain that in normal cortical brain tissue, where gray and adjacent white matter have similar iron concentrations, the $R_2$ of the gray matter is smaller than $R_2$ of the white matter [48,49], and would account for variance in $R_2$-values reported in various AD research studies.
Conclusions

Patients with AD showed significantly lower T2 values suggesting increased iron depositions in the hippocampus. In addition, R2 values from hippocampus in AD showed opposite correlation with cognition scores. Therefore, quantitative R2 measurements in the hippocampus might offer useful means for the early diagnosis and the monitoring of AD, and provide an indication of the treatment response.

Author Contributions

Conceived and designed the experiments: ZL XZ. Performed the experiments: ZL CY CH JL. Analyzed the data: XW ZL CH  DK. Wrote the manuscript: ZL XZ DK.

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