Correlation of Hippocampal Volume and Cognitive Performances in Patients with Either Mild Cognitive Impairment or Alzheimer's disease

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Keywords

Alzheimer's disease; Amnesic mild cognitive impairment; Auditory verbal learning test; Boston naming test; Daily living activities; Hippocampal volume.

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SUMMARY

Objective: To evaluate hippocampal volume changes and neuropsychological performances in patients with either amnesic mild cognitive impairment (aMCI) or Alzheimer's disease (AD). **Methods:** Thirty-eight AD dementia, 22 aMCI patients, and 20 healthy controls were enrolled. Bilateral hippocampal volume was measured concurrently with minimal state examination (MMSE), auditory verbal learning test (AVLT), Boston naming test (BNT), and activities of daily living (ADL) test. Baseline and two additional follow-up examinations were conducted. **Results:** Baseline hippocampal volumes were significantly smaller in AD group than that in aMCI and control groups. MMSE, AVLT, ADL, and BNT scores for the AD group were significantly different from that of both aMCI and control groups. Baseline hippocampal volumes were positively correlated with MMSE and AVLT scores in AD and aMCI patients. At follow-up, left hippocampal volume loss was positively correlated with decreased MMSE and AVLT scores both in AD and aMCI groups, while right hippocampal volume loss was positively associated with decreased AVLT performance only in AD group. Increased ADL and decreased BNT scores were positively associated with left hippocampal volume reduction only in the AD group. **Conclusions:** Current findings provide evidence of a close relationship between hippocampal volume and cognitive performances in patients with AD and aMCI, both at baseline and over follow-up.

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Introduction

Alzheimer's disease (AD) is the most common type of dementia in the elderly population. This progressive neurodegenerative disease is characterized by memory loss firstly and then a decline in global cognitive function, behavioral, and functional changes and has a great impact on daily living activities [1,2]. It has been shown that neuropathological lesions form in AD patients decades before the first clinical symptoms become apparent [3]. Recently, much effort has been invested in the development of biomarkers that allow for early diagnosis of AD, particularly at the prodromal stage termed amnesic mild cognitive impairment (aMCI). Apart from cerebrospinal fluid biomarkers, magnetic resonance imaging (MRI)-based volumetry has been proposed as a promising biomarker that permits detection of structural changes such as the loss of gray matter volume (GMV). In most studies, volumetry of medial temporal lobe (MTL) structures has been assessed for its diagnostic value in patients with AD or aMCI [4,5].

In patients with AD, the hippocampus, which is a central component of the MTL, is one of the most important networks underlying learning and memory acquisition [6]. In particular, the hippocampus shows a region-specific pattern of atrophy that

begins in the transentorhinal and entorhinal cortices then progresses through the entirety of the structure. Structural MR studies suggest that the progression of hippocampal atrophy in patients at the predementia MCI stage is a highly accurate predictive marker of progression to AD [7]. Early neuroimaging studies have also suggested that the most prominent diagnostic marker for AD is hippocampal atrophy and lateral ventricular enlargement [8,9]. In patients with aMCI and AD, MTL atrophy is correlated with a reduction in neuropsychological performance, especially related to memory tasks [10,11]. Some previous studies have shown that clinical symptoms cross-sectionally correlate with regional or whole brain atrophy as measured by only one single MR scan [12,13]. Several longitudinal studies have compared the progression of regional brain atrophy with varying levels of cognitive function [14,15], but the data were obtained from a small group size or a short time period. Other studies measured cognitive function using an MMSE test but did not correlate other cognitive performances with structural MR measurements [16].

The Boston naming test (BNT) is a valuable test for detecting impairments in language ability in patients with aMCI and AD [17]. A recent report suggested that GMV change in the left hippocampus was correlated with a decline in BNT and MMSE

performance [18]. Auditory verbal learning test (AVLT) is a 15-item word list of learning task, which is commonly used for memory evaluation. Structural MR studies have suggested that changes in hippocampus volumes are correlated with performance in delayed recall AVLT tests [19,20]. Additionally, changes in daily living activities as measured by the activities of daily living (ADL) test have also been shown to be accompanied by hippocampal volume loss in the elderly [21]. However, up-to-date, the association between the hippocampal volume loss and changes in AVLT, ADL, and BNT performance in patients with AD and aMCI in a longitudinal study has not been established.

In the present longitudinal study, we have correlated normalized hippocampal bilateral volume measurements with MMSE, AVLT, ADL, and BNT performance tests in participants with AD, aMCI, and age-matched healthy controls. The purpose of this study was to determine whether AD or aMCI patients show a loss in hippocampal volume associated with cognitive impairment and changes in activities associated with normal function during daily living.

Material and Methods

Participants

Eighty participants were chosen for this study consisting of 22 aMCI individuals and 38 Alzheimer's disease with mild to

moderate dementia, and 20 healthy controls. Initial baseline parameters were recorded from all subjects followed by two additional assessments at 12 months involving 61 participants (aMCI = 17, AD = 29, control = 15) and at 24 months that included 49 participants (aMCI = 13, AD = 21, control = 15). All participants were newly admitted outpatients from the "Memory Clinic" of the Neurology Department, First Affiliated Hospital of Zhejiang University that were selected during the period from March, 2010 to January, 2012. AD participants receive no treatment during the initial baseline evaluation but were given cholinesterase inhibitors (a dose of 10 mg Donepezil daily) afterward. All other participants were free of medications known to affect cognition. A Clinical Dementia Rating (CDR) test was used to determine cognition levels during this study that included the following AD level options: 0 = none, 0.5 = questionable, 1 = mild, 2 = moderate, and 3 = severe. AD diagnosis was based on NINCDS/ADRDA criteria [22,23]. Participants with aMCI were diagnosed based on criteria described previously by Petersen et al. [24]. The same criteria were used during follow-up assessment for all participants. All participants were right-handed, aged 65 to 85 years with at least six years of education. Each participant received a medical history evaluation followed by a standard laboratory, physical and a neurological examination plus a neuropsychological assessment.

The exclusion criteria for subjects eliminated from the study were as follows: (1) insufficient command of the Chinese language or severe dementia, (2) living alone, (3) MRI evidence of

Table 1 Demographic characteristics and cognitive status, hippocampal volumes in aMCI and AD patients and control subjects at baseline and follow-up examinations

Features	Time point	Healthy controls		aMCI patients		AD patients		ANOVA <i>P</i> -value
		<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	
Gender (F/M)	Baseline	9/11		12/10		17/21		NS
Age, year	Baseline	20	73.7 (4.5)	22	74.2 (4.2)	38	75.5 (5.1)	NS
Education, year	Baseline	20	10.1 (1.7)	22	9.6 (2.3)	38	9.8 (2.2)	NS
MMSE	Baseline	20	28.9 (0.8)	22	27.7 (1.1)	38	21.5 (2.2)*	0.045
	1-year follow-up	15	28.7 (0.8)	17	26.9 (1.2)	29	19.7 (2.3)*	0.012
	2-year follow-up	15	28.5 (1.0)	13	26.3 (1.5)	21	17.8 (2.5)**	0.008
AVLT	Baseline	20	8.9 (1.5)	22	6.9 (1.3)*	38	5.1 (1.2)*	0.033
	1-year follow-up	15	8.6 (1.6)	17	6.2 (1.4)*	29	4.0 (1.1)**#	0.005
	2-year follow-up	15	8.1 (1.1)	13	5.9 (1.2)**	21	3.2 (1.7)**#	0.002
ADL	Baseline	20	14.9 (1.9)	22	18.0 (2.4)	38	27.5 (3.7)**#	0.01
	1-year follow-up	15	15.2 (1.8)	17	18.2 (2.8)	29	30.6 (4.2)**#	0.004
	2-year follow-up	15	15.0 (1.8)	13	20.8 (3.2)*	21	33.1 (4.3)**#	<0.001
BNT-30	Baseline	20	17.9 (1.4)	22	13.8 (1.9)*	38	10.5 (2.5)**#	0.019
	1-year follow-up	15	17.4 (0.9)	17	12.9 (2.5)*	29	9.4 (3.1)**#	0.007
	2-year follow-up	15	17.5 (0.8)	13	11.4 (2.1)**	21	7.9 (3.6)**#	<0.001
Raw hippocampal volume-L (mm ³)	Baseline	20	796 (70)	22	819 (71)	38	642 (59)*#	0.031
	1-year follow-up	15	788 (71)	17	794 (81)	29	610 (72)*#	0.023
	2-year follow-up	15	769 (80)	13	742 (73)	21	567 (63)*#	0.01
Raw hippocampal volume-R (mm ³)	Baseline	20	814 (91)	22	828 (83)	38	648 (80)*	0.039
	1-year follow-up	15	808 (81)	17	800 (92)	29	621 (63)*#	0.021
	2-year follow-up	15	795 (82)	13	773 (69)	21	583 (65)*#	0.009

aMCI, amnesic mild cognitive impairment; AD, Alzheimer's disease; MMSE, mini-mental state examination; AVLT, auditory verbal learning test; ADL, activity of daily living function; BNT-30, Boston naming test with 30 items; NS, not significant. Between-group differences were calculated using ANOVA analysis. The Scheffe' *post hoc* test was used for comparison between two groups. * $P \leq 0.05$, ** $P \leq 0.01$, compared with healthy controls, and # $P \leq 0.05$, ## $P \leq 0.01$, compared with aMCI group (*P*-values were derived from Scheffe' procedure).

overt brain pathology such as tumor, stroke, hydrocephalus, or significant trauma, a history of alcoholism, drug abuse, or psychiatric illness, or (4) MRI contraindications. All participants signed

an informed consent document prior to assessment. This study was approved by the ethics committee of the First Affiliated Hospital, Zhejiang University.

Figure 1 The images of hippocampus in sagittal and coronal plants, and the change of normalized hippocampal volumes in different groups over time. **A–C:** a female patient with amnesic MCI aged 69 years, and **d:** a female patient with moderate AD of the same age. **(A)** Coronal view of T1-MRI, **(B)** sagittal view of T1-MRI showing an obliquely oriented 3D-MRI overlaid in light yellow, **(C)** an enlarged view of the region around the right hippocampal formation in the coronal slice of the same aMCI subject (2 mm resolution), **(D)** an enlarged view of the region around the right hippocampal formation in the coronal slice of a patient with moderate AD. The changes in mean normalized left **(E)** and right hippocampus volumes **(F)** in AD patients, aMCI patients, and healthy controls during 2 years of follow-up. Average hippocampal volumes are shown in the bar graph with error bars denoting standard errors of the mean. * $P < 0.05$, ** $P < 0.01$, compared with healthy controls.

Neuropsychological Testing

The neuropsychological tests consisted of the MMSE, AVLT-delayed recall, ADL, and BNT-30. The abbreviated Boston naming test consists of 30 items (BNT-30) in which the participant attempts to name 30 objects depicted in drawings. The score is based on the number of correct responses [25]. All testing were performed by a trained neuropsychologist without knowledge of the patient's diagnosis or MRI results. Changes in hippocampal volume and neuropsychological parameters were calculated by subtracting the baseline score from the follow-up scores.

Image Acquisition and Postprocessing

MR scans were performed using a 3.0 Tesla MR Scanner (General Electric Medical System, Atlanta, GA, USA) with a three-dimensional (3D) T1-weighted magnetization prepared rapid gradient echo sequence (TR = 1820 ms, TE = 3.93 ms, TI = 1100 ms, a flip angle of 12 degree). Images were reoriented along the anterior–posterior commissure line with the anterior commissure set as the origin of the spatial coordinates. For each subject, the hippocampus was manually segmented and the raw

structural volume was obtained as previously reported [26]. Tracing of the hippocampus was performed on T1-weighted coronal images lying on a plane perpendicular to hippocampal major axis, with the corresponding sagittal and axial planes simultaneously presented for reference. The MRIcro software (www.mricro.com) was employed to delineate regions of interest (ROI). Hippocampal segmentation included the hippocampus proper, dentate gyrus, subiculum, alveus, and fimbria. Each hippocampus was segmented into approximately 30–40 consecutive slices with segmentation taking about 30 min. per subject. The volume of the entire hemisphere (intracranial volume) was also calculated using automatic procedure rather than manual segmentation methods. The normalized left side, right side, and total hippocampal volume (i.e., raw hippocampal/intracranial volume $\times$ 1000) were calculated for each subject, because there is an important correlation between the head size and the hippocampal volume. All measurements were performed by technicians without knowledge of the participants' clinical data using customized software for a standard GE work console. Intra- and inter-group variability among MRI technicians was tested using 10 subjects and showed correlation coefficients of 0.87 and 0.89, respectively.

Figure 2 Normalized total hippocampal volumes relative to MMSE scores (A), AVLT score (B) at baseline in mild and moderate AD patients (mAD) and amCI patients. The scatter plot represents the total normalized hippocampal volumes of all 60 participants (22 amCI and 38 AD) versus the respective MMSE, AVLT scores.

Statistical Analysis

Between-group comparisons for continuous variables were analyzed using univariate analysis of variance. The Levene test was performed to assess the equality of variances. A Scheffe' *post hoc* test was used to determine differences between the three equal variance groups. Chi-square test was utilized for analysis of dichotomous variables. Correlations between the MRI volumetry and neuropsychological test scores were determined using Pearson's correlation coefficient analysis. Data analysis was performed using SPSS 16.0 software package. Values were considered significantly different at $P \leq 0.05$.

Results

Group Baseline and Follow-Up Demographic Data

The demographic information for each group over time is summarized in Table 1. Gender and age distribution did not differ significantly although the control group had the lowest mean age. There was also no significant difference between the mean education levels of each group. A number of subjects dropped out during the 2 years of follow-up periods due to either refusal by the subjects to continue with the study (5 controls and 9 patients without known reasons, 4 aMCI patients transfer to AD status, 6 mild or moderate AD patients transfer to severe AD status) or the appearance of other medical conditions such as acute stroke that resulted

in elimination from the study (2 patients with aMCI and 5 patients with AD).

Group Cognitive and ADL Results

The results of neuropsychological tests for each group over time are also summarized in Table 1. Performance in memory, naming ability, and daily activity functions was significantly impaired in AD patients compared with healthy controls. The AD group had significantly lower MMSE and AVLT scores compared with the aMCI and the control groups both at baseline and follow-ups ($P \leq 0.05$). No significant MMSE score differences were found between aMCI patients and controls; however, AVLT and BNT-30 performance in aMCI patients was significantly lower than controls ($P \leq 0.05$) either at baseline or at follow-ups. Moreover, both AD and aMCI individuals exhibited significant differences in ADL and BNT-30 scores compared with healthy controls ($P \leq 0.05$) at the 2-year follow-up. There was a significant reduction in AVLT, BNT-30, and ADL scores in the participants with AD during the follow-up periods. By contrast, in either aMCI or control groups, AVLT, ADL, BNT-30 scores were not significantly different at the follow-up appointments.

Hippocampal Volume Comparisons between Groups Over Time

Coronal and sagittal view of hippocampus in an aMCI patient are shown in Figure 1A–B, and the coronal 3D views of two

Figure 3 Relationship between the change in left and right hippocampal volume versus the decline of AVLT score in patients with Alzheimer's disease (A) and amnesic MCI patients (B).

participants (aMCI and AD) with enlarged right hippocampus contours are shown in Figure 1C–D. Baseline values and those at follow-ups showed that the raw left and right hippocampal volume in participants with AD were significantly smaller than that of participants with aMCI and healthy controls (Table 1). Similarly, the normalized baseline hippocampal volume in participants with AD was smaller than that of participants with aMCI and healthy controls (Figure 1E,F). Moreover, participants with AD had a significantly smaller volume in both the left and right hippocampi compared to that of participants with aMCI or controls at the follow-up examinations ($P \leq 0.05$). However, no significant difference in hippocampal volume was seen on either side when aMCI patients were compared with healthy controls despite an overall smaller mean hippocampal volume seen in the aMCI patients (Figure 1E,F).

Correlation Analysis of Hippocampal Volume Changes With MMSE and AVLT Scores Over Time

A positive association was noted between normalized total hippocampal volumes and corresponding MMSE and AVLT scores both in AD and aMCI groups at baseline (Figure 2A,B). At the 2 years of follow-up examination, decreased AVLT scores were positively correlated with a loss of hippocampal volume, particularly in the left hippocampus seen in the AD group ($r = 0.72$, $P \leq 0.05$; Figure 3A). However, in the aMCI group, a positive correlation was found between decreased AVLT scores and loss of left hippocampal volume only ($r = 0.55$, $P \leq 0.05$; Figure 3B). Similar correlations were also seen between the changes in MMSE scores and hippocampal volume loss in AD and aMCI patients (data not shown). However, no correlation was observed between left or right hippocampal volume change and cognitive function in healthy controls at the 2 years of follow-up period (data not shown).

Correlation of Changes in Hippocampal Volume With ADL and BNT-30 Scores Over Time

In the AD group, a positive correlation was observed only between the loss of left hippocampal volume and an increase in ADL scores ($r = 0.43$, $P \leq 0.05$; Figure 4A). In addition, a positive correlation was also seen between reduced BNT-30 scores and the loss of either left or right hippocampal volume ($r = 0.35$, $P \leq 0.05$; $r = 0.51$, $P \leq 0.05$, Figure 4B). However, there was no significant correlation between the loss of hippocampal volume and changes in ADL or BNT-30 scores in the aMCI or control group at the 2 years of follow-up period (data not shown).

Discussion

In this study, mean hippocampal atrophy rates (annual rate of 3–6%) for participants with AD were similar to those reported in other studies [27,28]. And a previous study has shown that 1.6–1.7% hippocampal atrophy occurs normally in the elderly population caused by aging. These rates are higher in individuals with stable MCI (2.8%), MCI patients that transition to AD (3.7%), and AD patients (3.5–4%) [29]. In the studies using the ADNI database of patients with AD and MCI and healthy elderly

Figure 4 Relationship between the change in left and right hippocampal volume versus increased ADL scores (A) and decreased BNT scores (B) in patients with Alzheimer's disease. Left or right hippocampus for each subject is indicated by marker type.

controls, hippocampal volumes were reported in AD varying between 1600 mm³ [30] and 3000 mm³ [10]. The hippocampal volume of AD patients in our study was about 1600 mm³. The remarkable difference among studies might derive from the segmentation of the template hippocampus used to extract the structure in each individual.

In the present study, we found smaller volume in the left side compared with the right, and left-to-right hippocampal asymmetry was also found to increase in conjunction with a decline cognitive function. These results are similar to those described in an earlier study [31]. Recently, Dawe et al., using postmortem MR measurements, found that hippocampal volume is smaller in subjects with clinically diagnosed AD compared to subjects with mild or no cognitive impairment [32]. As seen in the present study, a strong association was also found between changes in hippocampal volume and global cognition, episodic memory function in their study [32]. Linkage has been reported between the hippocampal volume and the performance in the California verbal learning test in elders [33]. Similarly, we found, at the initial baseline examination, a strong association between total normalized

hippocampal volume and MMSE and AVLT scores in both AD and aMCI patients.

In addition, previous studies have shown a positive correlation between constructional recall scores and the right CA1 and subiculum areas [34]. Spatial memory has been shown to be heavily dependent on brain structure that changes during normal aging and in AD patients [35]. In the present study, we did not define precise areas of anatomical deformation within the hippocampal subfields; however, our study does reveal a stronger positive correlation between changes in hippocampal volume loss and neuropsychological tests performance in the participants with AD than that in aMCI patients. We also did observe, as has been seen previously in AD patients [36], a stronger correlation between performance in memory tasks and left, rather than right, hippocampal volume changes in aMCI patients. Sabuncu *et al.* found a close association between hippocampal volume loss and MMSE scores in a follow-up study at 12 months [37]. Similarly, we found that the change in left hippocampal volume loss was correlated with a decline in AVLT and MMSE scores in AD patients at approximately the 24-month period. In contrast to the results observed in the AD group, no significant correlation was found in the control group between the changes in hippocampal volume and overall cognitive performance (as assessed by the MMSE) or the specific memory test of AVLT. Moreover, medial, frontal, and temporoparietal atrophy has been shown to be associated with basic ADL impairment in mild AD dementia [38]. Arlt *et al.* recently found that the rate of GMV change in the left hippocampus correlated with reduced performance in the MMSE, BNT, and trail making test B [18]. Our present findings agree with these studies, showing a strong correlation between left hippocampal volume and ADL or BNT-30 performance in AD patients, but not in aMCI patients or healthy controls. These results indicate that the relationship between impaired cognitive performances, daily living functions, and hippocampal volume is much more specific to individuals suffering from AD.

This study has correlated high-resolution MRI hippocampal scan results in a well-defined cohort of aMCI, AD, and normal controls with neuropsychological test data. However, our results can be considered preliminary based on the experimental design

(observational and longitudinal) and the fact that the proportion of patients completing the follow-up visits was relatively low. Clearly, future studies are needed that employ a larger samples size. In addition, we cannot rule out the existence of early AD pathology in the aMCI group that may have affected the hippocampus even if dementia was excluded based on medical history and neuropsychological exams. Finally, although most studies of this type utilize manual or semi-automated hippocampal volume calculations, a fully automated MR-based volumetry system may be more suitable for studies involving a larger longitudinal cohort.

Conclusions

This study indicates that there exists a close relationship between the loss of hippocampal volume and changes in cognitive performances in patients with AD and aMCI, while the correlation between the hippocampal volume and daily living functions only exist in patients with AD. Furthermore, left hippocampal volume loss may serve as a unique predictor of memory decline in both aMCI and AD patients. Our findings give further motivation for future longitudinal studies on cognitive tests performances and atrophy rates of different hippocampal subfields in stable aMCI patients, progressive aMCI patients, and all courses of AD patients.

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Conflict of Interest

The authors declare no conflict of interest.

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