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COMMENTARY

Hippocampal Volume and Asymmetry in Mild Cognitive Impairment and Alzheimer's Disease: Meta-Analyses of MRI Studies

Feng Shi,[1] Bing Liu,[1] Yuan Zhou,[1] Chunshui Yu,[2] and Tianzi Jiang[1]*

ABSTRACT: Numerous studies have reported a smaller hippocampal volume in Alzheimer's disease (AD) patients than in aging controls. However, in mild cognitive impairment (MCI), the results are inconsistent. Moreover, the left-right asymmetry of the hippocampus receives less research attention. In this article, meta-analyses are designed to determine the extent of hippocampal atrophy in MCI and AD, and to evaluate the asymmetry pattern of the hippocampal volume in control, MCI, and AD groups. From 14 studies including 365 MCI patients and 382 controls, significant atrophy is found in both the left [Effect size (ES), 0.92; 95% confidence interval (CI), 0.72–1.11] and right (ES, 0.78; 95% CI, 0.57–0.98) hippocampus, which is lower than that in AD (ES, 1.60, 95% CI, 1.37–1.84, in left; ES, 1.52, 95% CI, 1.31–1.72, in right). Comparing with aging controls, the average volume reduction weighted by sample size is 12.9% and 11.1% in left and right hippocampus in MCI, and 24.2% and 23.1% in left and right hippocampus in AD, respectively. The findings show a bilateral hippocampal volume loss in MCI and the extent of atrophy is less than that in AD. By comparing the left and right hippocampal volume, a consistent left-less-than-right asymmetry pattern is found, but with different extents in control (ES, 0.39), MCI (ES, 0.56), and AD (ES, 0.30) group. © **2009 Wiley-Liss, Inc.**

KEY WORDS: magnetic resonance imaging; hippocampus; volumetric analysis; asymmetry; meta-analysis

INTRODUCTION

Alzheimer's disease (AD) is the most common progressive neurodegenerative disorder characterized by neurofibrillary tangles (NFTs) and amyloid deposition (Terry et al., 1991; Nestor et al., 2004). The spread of NFTs is hierarchized, starting from the medial temporal lobe structures including the hippocampus, followed by the association areas, and finally extending to the entire cortex (Delacourte et al., 1999). These microscopic changes will influence global structures, which can be assessed with volumetric magnetic resonance imaging (MRI) (Mortimer et al., 2004). In AD patients, numerous neuroimaging studies reported structural brain abnormalities, and hippocampal atrophy was taken as a consistent finding (Chetelat and Baron, 2003). Hippocampal volume and its change were proven to be effective in predicting disease progression and AD diagnosis (Mungas et al., 2002; Anstey and Maller, 2003; den Heijer et al., 2006).

As a better representation of the clinical manifestation of incipient AD, the criteria of mild cognitive impairment (MCI) was developed by Petersen in 1999 (Petersen et al., 1999). The rate of developing AD in MCI is ~10–15% per year, much higher than that in normal elderly subjects, which is about 1–2% per year (Pennanen et al., 2004). Consequently, investigating the hippocampal volume atrophy in MCI and the comparison of magnitude and extent of atrophy between MCI and AD attract great interest recently, because it has the potential to provide a measure for tracking the disease progression and understand the pathogenesis. In MCI, many studies reported bilateral hippocampal atrophy (Wolf et al., 2001; Hsu et al., 2002; Anstey and Maller, 2003; Wang et al., 2003; Pennanen et al., 2004; Wolf et al., 2004; Jessen et al., 2006). However, there were also some inconsistent results. Muller et al. (2005) found significant lower volume only existed in the left hippocampus, and Zhang et al. (2007) reported smaller hippocampal volume only on the right side. In several longitudinal studies, total hippocampal volume was reported as reduced in the following order: control > MCI > AD (Pennanen et al., 2004; Jessen et al., 2006), and the hippocampal volume in MCI converters to AD was significantly smaller than in MCI nonconverters (Devanand et al., 2007). In general, there are many previous studies that have investigated the hippocampal volume in MCI and AD patients, but studies on the statistical analysis of the magnitude and extent of hippocampal volumetric reduction are relatively rare, and the findings are also affected by limited sample size, especially in longitudinal studies.

To address this issue, we introduce the meta-analysis to determine the magnitude and extent of hippocampal volume in MCI and AD studies, by integrating the results of relevant cross-sectional studies and

[1] **National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing, China;** [2] **Department of Radiology, Xuanwu Hospital of Capital Medical University, Beijing, China**

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*Correspondence to: Tianzi Jiang, National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100080, China. E-mail: jiangtz@nlpr.ia.ac.cn

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overcoming the effect of small sample size in single study. Meta-analysis is a well established statistic method and widely used in brain and hippocampus volumetric studies on depression (Campbell et al., 2004b; Videbech and Ravnkilde, 2004), Schizophrenia (Boos et al., 2007), Posttraumatic Stress Disorder (PTSD) (Karl et al., 2006), etc. Instead of simply summarizing the previous studies' results, meta-analysis defines an effect size to represent the quantitative findings in each study and allow the comparisons across studies.

Meanwhile, increasing evidence indicates that pathological factors may lead to asymmetry in brain (Toga and Thompson, 2003; Nardi and Bingman, 2007). Wolf et al. (2001) reported significant left-less-than-right hippocampal asymmetry in controls and MCI patients. Barnes et al. (2005) found a nonsignificant trend of left-less-than-right asymmetry in controls and the first scan of AD patients, but the asymmetry was not remained in the follow-up scan at 15 months later. These studies indicate the asymmetry in the left and right hippocampal volume exists and may varies with disease progression, and thus additional meta-analyses on hippocampal asymmetry were adopted to address this issue.

In this study, we conduct meta-analyses of the cross-sectional MRI studies which contain a volumetric analysis of the hippocampus in MCI or AD patients. Our aims are: (a) to summarize the previous hippocampal volume studies in MCI and AD patients and establish the extent of hippocampal atrophy; (b) to examine the moderating variables that might contribute to the discrepancies; and (c) to investigate the asymmetry patterns of the hippocampus in controls, MCI, and AD patients.

METHODS

Data Sources

The MEDLINE database was searched up to October 2007 using the following keywords: "Hippocampus" (as a Medical Subject Heading [MeSH] term) and "Alzheimer disease" (as a MeSH term) and "Volume." The term "Alzheimer disease" was then substituted with "Mild cognitive impairment" or "Dementia" (as a MeSH term), and the search was repeated. Titles and abstracts were examined to decide whether studies could be included, and the full article of candidates was checked to further determination. Additional studies were identified from the reference lists of key studies.

Study Selection

A total of 42 studies fulfilling the following criteria were included: (1) hippocampal volume counting was based on MRI volumetric data; (2) MCI or AD patients were involved; (3) a population of normal controls was reported concurrently; (4) they should be published in peer-review journal with English language; and (5) they were published not before 1998.

Considering the MRI techniques were developed rapidly and the value of earlier volumetric studies with older imaging paradigms might be largely diminished, studies published before the year 1998 were not included. Seventeen studies showed their hippocampal volume results with only figures or provided only the total hippocampal volume (left plus right). For these studies, we contacted the authors to request the detailed data via email. Five studies were remained in this manner (Head et al., 2005; de Leon et al., 2006; Ridha et al., 2006; Wang et al., 2006a; Zhang et al., 2007). If the same subjects were used in different studies, only one study with the largest sample was included (Laakso et al., 1998, 2000b). One study (Murphy et al., 2003) reporting excessive hippocampal atrophy was discarded for highly bias in the following sensitive test. In the remaining 28 studies, the minimum number of samples in patient and control group was 6. No studies were excluded based on the sample size but sample size correction was introduced by the following effect size definition.

If a study provided both raw volume (i.e., mm^3) and normalized volume of hippocampus (Laakso et al., 1998; Wolf et al., 2004; Muller et al., 2005; Yavuz et al., 2007), the latter would be chosen. When multiscan data was provided in a longitudinal study (Dixon et al., 2002; Barnes et al., 2005; Ridha et al., 2006), the first scan was chosen. If more than one control group were provided, for example, a younger and an older groups (Head et al., 2005), or nondemented cotwins and normal controls (Jarvenpaa et al., 2004), the one with better matched age and the nondemented cotwins were chosen.

Finally, 28 studies were included in our meta-analysis (Fig. 1), in which 23 studies included 700 AD patients and 751 controls (Laakso et al., 1998; de Toledo-Morrell et al., 2000; Laakso et al., 2000a,b; Wolf et al., 2001; Dixon et al., 2002; Hsu et al., 2002; Davies et al., 2004; Jarvenpaa et al., 2004;

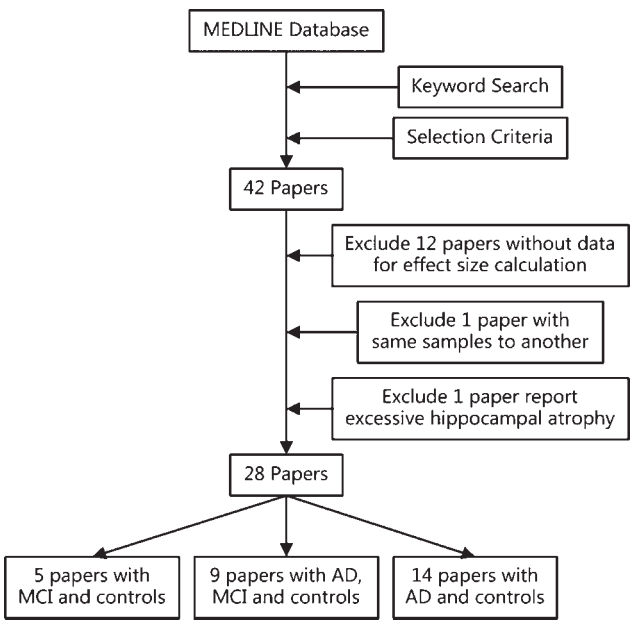

FIGURE 1. Cross-sectional studies selection.

TABLE 1.

Cross-Sectional Volumetric Studies

			Patient				Control			
Study and year	Correction method	Study used	*N*	Male%	Age	MMSE	*N*	Male%	Age	MMSE
Barnes et al., 2005	Raw volume	AD	32	41	59	19.4	50	52	59.6	29.4
Basso et al., 2006		AD	56	50	71.2	18.3	42	52	73.2	29
Davies et al., 2004		AD	8	25	64.9	23	8	50	63.8	NS
Dixon et al., 2002		AD	9	56	70	21.5	14	43	74	30
Head et al., 2005a[a]		AD	25	32	77	23	25	28	77	29
Head et al., 2005b[a]		AD	25	44	78	25	25	28	76	29
Hsu et al., 2002		AD	20	50	74.5	22.7	20	50	74	29
		MCI	20	80	74.2	27.7				
Ridha et al., 2006		AD	7	43	49.8	23.9	25	36	46.5	NS
		MCI	6	50	49.4	27				
Scher et al., 2006		AD	24	NS	82.5	NS	102	NS	82.8	NS
Teipel et al., 2006		AD	34	47	69	23.1	22	50	61.5	29.4
van de Pol et al., 2006		AD	103	42	77	NS	73	47	78	NS
Wang L et al., 2003		MCI	18	61	74	NS	26	46	73	NS
Wang L et al., 2006		MCI	49	47	74.9	NS	86	34	73.4	NS
Chao et al., 2005	TIV correction	MCI	24	58	74.8	17.4	24	50	76	29
de Leon et al., 2006		MCI	7	71	69.4	28.7	9	44	61.4	29.4
Jessen et al., 2006		AD	13	31	68.8	23.1	14	43	66.5	29
		MCI	15	40	68.2	28				
Muller et al., 2005		MCI	18	61	67.3	25.2	18	61	66.9	28.7
Toledo-Morrell et al., 2000		AD	18	NS	68.6	24.1	30	NS	72.4	NS
Wolf et al., 2001		AD	10	40	78.2	22.4	17	26	78.5	28.3
		MCI	12	17	78.5	25.7				
Wolf et al., 2004		AD	32	38	77.8	20.5	35	40	78.7	28.9
		MCI	38	32	79.4	26.4				
Yavuz et al., 2007		AD	26	27	73.9	21.4	15	47	70.8	28.9
		MCI	22	32	71.3	26.6				
Zhang et al., 2007		AD	17	47	77.1	22.1	18	56	71.6	29.5
		MCI	17	47	73.1	27.9				
Jarvenpaa et al., 2003	ICA correction	AD	7	0	75	21.1	7	0	75	26
Laakso et al., 1998		AD	55	51	70	22	42	45	72	NS
Laakso et al., 2000a		AD	57	51	70	21.1	34	41	72	28.3
Laakso et al., 2000b		AD	30	23	73	20	30	33	69	29
Pennannen et al., 2004		AD	48	48	71.1	21.4	59	37	72.7	27.3
		MCI	65	49	72.8	24				
Sandstrom et al., 2006		MCI	20	60	75	26.7	20	45	71.2	28.4
Wang PN et al., 2006		AD	65	60	76.4	21.2	20	55	75.1	28.3
		MCI	58	74	76.3	25.9				

NS, not stated; TIV, total intracranial volume; ICA, coronal intracranial area at the level of the anterior commissure.
[a]Head et al. has two samples.

Pennanen et al., 2004; Wolf et al., 2004; Barnes et al., 2005; Chao et al., 2005; Head et al., 2005; Basso et al., 2006; Jessen et al., 2006; Ridha et al., 2006; Teipel et al., 2006; van de Pol et al., 2006b; Wang et al., 2006b; Scher et al., 2007; Yavuz et al., 2007; Zhang et al., 2007), and 14 studies included 365 MCI patients and 382 controls (Wolf et al., 2001, 2004; Hsu et al., 2002; Wang et al., 2003, 2006a,b; Pennanen et al., 2004; Muller et al., 2005; de Leon et al., 2006; Jessen et al., 2006; Ridha et al., 2006; Sandstrom et al., 2006; Yavuz et al., 2007; Zhang et al., 2007) (nine studies containing both AD and MCI) (Table 1).

Data Analysis

Data is analyzed using the RevMan 4.2.10 software supplied by Cochrane Collaboration (http://www.cc-ims.net/RevMan). For each study, effect size is calculated by Hedges g, which is similar to the metric Cohen d (Cohen, 1988) but includes an adjustment for small sample size bias (Hedges and Olkin, 1985). The formula is as follows:

$$g_i = \frac{\bar{x}_{1i} - \bar{x}_{2i}}{s_i}\left(1 - \frac{3}{4N_i - 9}\right)$$

$$s_i = \sqrt{\frac{(n_{1i}-1)sd_{1i}^2 + (n_{2i}-1)sd_{2i}^2}{N_i - 2}}$$

where in the ith study, $\bar{x}_{1i}$ and $\bar{x}_{2i}$ are the mean hippocampal volume in the control group and patient group, respectively; sd_{1i} and sd_{2i} are the standard derivation (SD); s_i is the pooled standard deviation; n_{1i} and n_{2i} are the number of subjects of two groups, respectively; and N_i is the number of total subjects in the ith study ($N_i = n_{1i} + n_{2i}$).

Effect size (ES) can be interpreted in terms of the percent of nonoverlap of score distributions of two groups. An ES of 0.0 indicate the distribution of volume for two groups are totally overlapped. ES of 0.2, 0.5, and 0.8 indicate a nonoverlap rate of 14.7, 33.0, and 47.4%, referring to small, medium, and large effects respectively (Cohen, 1988). The higher ES value is, the larger difference is found in two groups.

After computing the individual effect sizes, we use a random effects model to weigh the studies by an inverse variance method. In this way, we can obtain a combined effect size $\bar{g}$, which indicates the magnitude of the association across all studies. The formulas are as follows:

$$\bar{g} = \frac{\sum \omega_i g_i}{\sum \omega_i}$$

$$\omega_i = \frac{1}{\mathrm{SE}_i^2}$$

$$\mathrm{SE}_i = \sqrt{\frac{N_i}{n_{1i}n_{2i}} + \frac{g_i^2}{2(N_i - 3.94)}}$$

where g_i is the effect size of the ith study, ω_i is the inverse variance weight, and SE_i is the standard error.

Thus, the weighted combined effect size $\bar{g}$ and its 95% confidence interval (CI) can be obtained. A larger effect size means a greater difference in the hippocampal volume between the two groups. If a 95% CI contains 0, it means that no significant difference exists.

In addition, the homogeneity statistic, Q, is calculated to assess the variance of results across studies as follows:

$$Q = \sum \omega_i (g_i - \bar{g})^2$$

Q is distributed as $x^2(df = n_0 - 1$, n_0 is the number of studies). A significant Q statistic indicates that studies cannot share a common population effect size (i.e., they are heterogenous). In this case, further analysis is needed to investigate potential moderating factors.

In the following asymmetry analysis, the left and right hippocampal volumes are compared, which are dependent groups as called a correlated design (Rosnow and Rosenthal, 1996). Hedges g is employed to calculate the effect size. There are some arguments on how to compute the pooled SD (Mullen and Rosenthal, 1985; Rosenthal, 1991; Dunlop et al., 1996). In this study, we choose the original standard deviations instead of the paired t-test value, to avoid overestimating the actual effect size (Dunlop et al., 1996).

Sensitivity analysis is conducted to ensure that no single study will bias the combined results by removing one study each time and recalculating the combined effect size of the remaining studies. Usually, published studies tend to be biased toward positive findings, and a nonsignificant finding may not be published. This will cause the file drawer problem. Fail-safe number is introduced to assess this publication bias. The fail-safe number n_{fs} signifies the minimum number of unpublished studies with nonsignificant findings that needed to overturn the conclusion of the meta-analysis. A larger fail-safe number means the results are safer from publication bias. Orwin has provided a formula to calculate n_{fs} as follows (Orwin, 1983):

$$n_{\mathrm{fs}} = \frac{n_0(|\bar{g}| - g_c)}{g_c}$$

where n_0 is the number of studies, and g_c is the trivial value to which the obtained effect would be reduced, here we set 0.20 as the criterion effect size.

Moderator Variables

Two factors may largely influence heterogeneity in this study, namely head size correction methods and disease severities. In many studies, hippocampus volume is provided directly as raw volume. To account for variations in head size among subjects, some studies normalize hippocampus volume to total intracranial volume (TIV), also known as intracranial volume (ICV), defined as the sum of the whole brain volume (WBV) and the CSF volume. Some other studies also control hippocampus volume by coronal intracranial area (ICA) at the level of the anterior commissure. A subgroup analysis is performed to evaluate the effect of the heterogeneity of raw volume and two head size correction methods of the hippocampal volume in AD and MCI analysis.

MMSE (Mini Mental State Examination) score is always taken as indicator of disease severity and provided in MCI and AD studies. In MCI studies, mean MMSE score of each study ranged from 24 to 28.7 (Mean 26.7, SD 1.4), suggesting that subjects might have similar cognitive level. But in AD studies, it ranged from 17.4 to 25 (Mean 21.7, SD 1.9), suggesting that both mild and moderate Alzheimer's disease were included in these studies. The heterogeneity of disease severity may confound the findings in Alzheimer's disease. Thus, a subgroup analysis is designed to address the effect of the severity heterogeneity on the hippocampal volume by dividing AD into two groups. The studies whose mean MMSE score are larger than 22 were classified as mild AD group and others as moderate AD group.

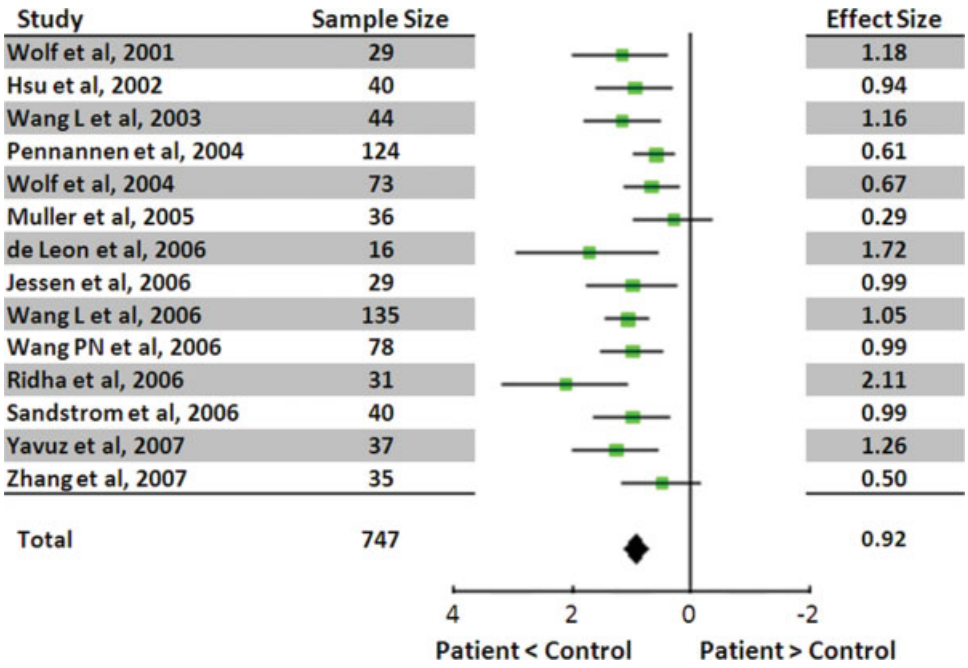

FIGURE 2. Standardized mean difference of left hippocampal volume in MCI patients with aging controls from a meta-analysis of 14 studies. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

RESULTS

Hippocampal Volume in MCI

Sensitivity analysis was first utilized and no outliers were found in this study. A total of 14 studies which met the inclusion criteria were entered into meta-analysis, including 365 MCI patients and 382 matched aging controls (Table 1). The Q test of heterogeneity was nonsignificant in both the left ($P = 0.16$) and right ($P = 0.08$) hippocampus. The combined effect size Hedges g revealed significant hippocampal volume loss: 0.92 (95% CI, 0.72–1.11) for the left hippocampus (Fig. 2) and 0.78 (95% CI, 0.57–0.98) for the right hippocampus (Fig. 3). The large effects of g indicated severe bilateral hippocampal atrophy in MCI, especially in left side.

Comparing with controls, the average volume reduction (AVR) weighted by sample size can be obtained as follows (Videbech and Ravnkilde, 2004):

$$\mathrm{AVR} = \frac{\sum((\bar{P}_i - \bar{C}_i)/\bar{C}_i \times N_i)}{\sum N_i}$$

where $\overline{P}_i$ and $\overline{C}_i$ are the hippocampal volume in patients and controls; N_i is the total sample size in ith study. The average volume reduction was 12.9% (SD 4.2%) in the left hippocampus and 11.1% (SD 5.6%) in the right hippocampus. The fail safe numbers in this case were 50.4 in the left and 40.6 in the right, which were large enough to provide convincing results.

Hippocampal Volume in AD

Sensitivity analysis was also performed and one study with excessive hippocampal atrophy, which largely influenced the combined results, was taken as an outlier (Murphy et al., 2003). Meta-analysis was performed in the remaining 23 studies comprising 700 AD patients and 751 matched aging controls (Table 1). The Q test of heterogeneity was significant in the left ($P < 0.001$) and right ($P < 0.001$) hippocampus. Random effect model was chosen in the meta-analysis to calculate the effect size to reduce the influence of heterogeneity. The statistical significances were revealed by combined Hedges g: 1.60 (95% CI, 1.37–1.84) for the left hippocampus and 1.52 (95% CI, 1.31–1.72) for the right hippocampus (Table 2). By conducting a two sample t-test for the effect size of each study in MCI and AD meta-analyses for each hippocampus, severe bilateral hippocampal atrophy pattern was found in AD than that in MCI (left, $P = 0.019$; right, $P = 0.004$). The average volume reduction was 24.2% (SD 7.8%) in the left hippocampus and 23.2% (SD 7.7%) in the right hippocampus. Fail-safe numbers in this case were 168 in the left and 158.4 in the right, which were large enough to provide convincing results.

Heterogeneity Analysis

The results of subgroup analysis for head size correction methods were shown in Table 2. In MCI studies, a heterogeneity trend was found in overall studies ($P = 0.16$ in the left, $P = 0.08$ in the right). In subgroup analysis, mild heterogeneity was only found in right hippocampus of the TIV correction

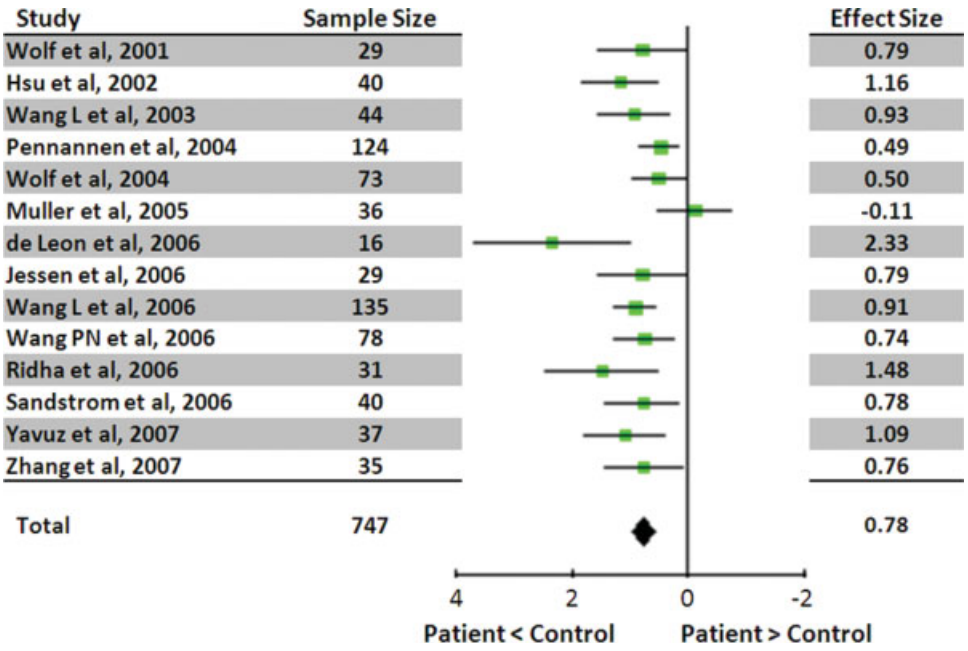

FIGURE 3. Standardized mean difference of right hippocampal volume in MCI patients with aging controls from a meta-analysis of 14 studies. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

group ($P = 0.04$). But when one study (de Leon et al., 2006) was excluded in sensitivity analysis, heterogeneity was reduced to nonsignificant ($P = 0.21$). In AD studies, significant heterogeneity observed in overall studies was largely reduced in these subgroups, and only remained in the raw volume group ($P = 0.04$ in left, $P = 0.01$ in right).

To investigate the influence of disease severity, subgroup analysis of MMSE score was performed in AD studies (Table 3). Significant bilateral hippocampal heterogeneity was reduced in mild AD (MMSE > 22) group ($P = 0.16$ in left, $P = 0.08$ in right), but remained in moderate AD (MMSE $< = 22$) group ($P < 0.001$ in left, $P < 0.001$ in right). The effect size which showed the atrophy was smaller in mild AD group (1.33 in left, 1.32 in right) than in moderate AD group (1.78 in left, 1.67 in right), as usually expected.

Hippocampal Asymmetry in Controls, MCI and AD

To compare the asymmetry of the left and right hippocampi, meta-analyses were performed in the controls, MCI, and AD patients, respectively.

In the controls, 29 studies were involved, including 915 subjects. Combined effect size was achieved as 0.39 (95% CI, 0.26–0.52; Left < Right). In MCI patients, 14 studies were selected, including 365 subjects. Combined effect size was

TABLE 2.

Subgroup Meta-Analyses of Head Size Correction Methods

			Left hippocampus			Right hippocampus		
Subgroup	Correction methods	*N*	Effect size	95% CI	*P*(Q)	Effect size	95% CI	*P*(Q)
MCI	Absolute	4	1.15	0.81–1.49	0.28	1.00	0.72–1.28	0.70
	TIV correction	7	0.83	0.51–1.14	0.22	0.73	0.33–1.13	0.04*
	ICA correction	3	0.77	0.50–1.04	0.39	0.61	0.34–0.88	0.63
	All studies	14	0.92	0.72–1.11	0.16	0.78	0.57–0.98	0.08
AD	Absolute	11	1.33	1.08–1.58	0.04*	1.36	1.09–1.63	0.01**
	TIV correction	7	1.49	1.12–1.87	0.08	1.33	1.03–1.62	0.26
	ICA correction	6	2.15	1.78–2.53	0.07	2.00	1.75–2.25	0.37
	All studies	24	1.60	1.37–1.84	0.001***	1.52	1.31-1.72	0.001***

N, the number of studies; TIV, total intracranial volume; ICA, coronal intracranial area at the level of the anterior commissure; *P*(*Q*), Q statistic test to assess heterogeneity.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

TABLE 3.

Subgroup Meta-Analysis of Disease Severity in AD Studies

		Left hippocampus			Right hippocampus		
MMSE	*N*	Effect size	95% CI	*P*(Q)	Effect size	95% CI	*P*(Q)
>22	11	1.33	1.07–1.59	0.06	1.32	1.05–1.60	0.03
≤22	11	1.78	1.43–2.14	0.001***	1.67	1.37–1.97	0.001***
All studies[a]	22	1.59	1.35–1.84	0.001***	1.52	1.30–1.74	0.001***

N, the number of studies; *P*(*Q*), Q statistic test to assess heterogeneity.
[a]Two studies not provided MMSE score.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

obtained as 0.56 (95% CI, 0.36–0.76; Left < Right). In AD patients, 23 studies were involved including 700 subjects. Combined effect size was 0.30 (95% CI, 0.19–0.40; left < right) (Fig. 4). A consistent left-less-than-right asymmetry was found in all three groups. Meanwhile, by conducting a two sample *t*-test for the asymmetry degree among three groups, only a trend toward significance was found ($P = 0.605$) between MCI and control group. Taking right hippocampus as baseline, the relative left hippocampus average volume reduction weighted by sample size could be obtained as 6.3% (SD 4.9%) in AD, 9.1% (SD 6.5%) in MCI, and 5.8% (SD 4.6%) in controls.

DISCUSSION

Through these meta-analyses, significant bilateral hippocampal atrophy is validated in both MCI and AD patients (Fig. 5). The extent of hippocampal volume loss in MCI is smaller than that in AD, which partially supports the fact that MCI is a transitional stage of AD. In the asymmetry analysis, a left-less-than-right pattern is found consistently but with different extents in all three groups, namely, MCI, AD, and controls. The disturbance of hippocampus asymmetry may be a characteristic that suggests the onset of illness.

The heterogeneity of studies may come from the following aspects: (1) Variations in MRI acquisition protocols. In this article, the included studies used 1.5–4T MR machine and the obtained slice thickness exceeded 3 mm in 3 of 28 studies (de Toledo-Morrell et al., 2000; Dixon et al., 2002; Sandstrom et al., 2006). (2) Variations in hippocampal boundary delineation methods (Anstey and Maller, 2003; Campbell et al., 2004a). In most studies, hippocampus was manually traced by 1–2 neuroanatomists or trained operators in coronal oblique images acquired perpendicular to the long axis of the body of the hippocampus according to anatomical guidelines. The raters were claimed blind to the diagnoses and neuropsychological performance of all subjects but not blinded to hemisphere (left or right). The intra- or inter-rater reliability was reported higher than 0.90. (3) Variations in the characteristics of AD patients in different studies, such as disease severity, cognitive profile, family history, and genetic variations like ApoE allele

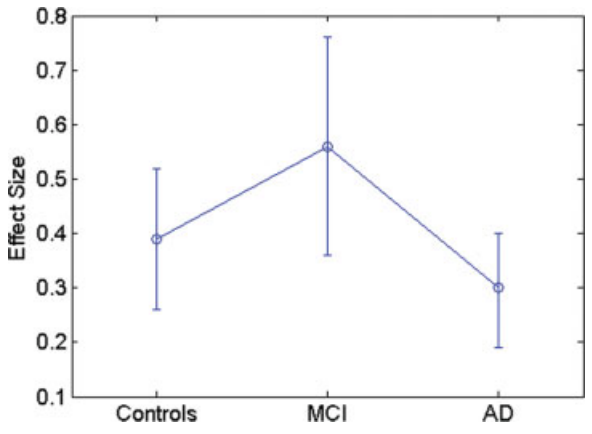

FIGURE 4. Asymmetry of hippocampal volume in the controls, MCI, and AD. Positive effect size means the left-less-than-right pattern of hippocampus volume. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

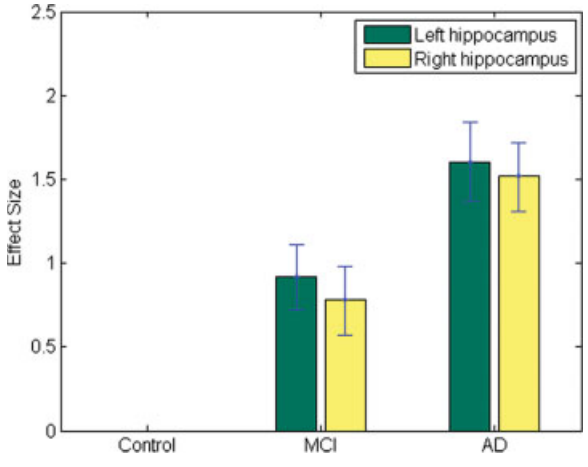

FIGURE 5. An illustration of hippocampal volume reduction in MCI and AD patients in comparison with controls. Note that control group is taken as baseline, and the effect size is set as zero. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

distribution. For example, the study of Ridha et al. (2006) was based on autosomal dominant AD patients; while no dominant inheritance AD patients were included in Basso et al. (2006). Only four studies provided the Apo E allele distribution in their subjects as around 50%. (4) Variations in head size correction methods. A total of 12 studies directly provided the raw volume of hippocampus (Table 1). However, it would be reasonable to consider the influence of whole brain volume to hippocampus volume. A total of 9 studies corrected hippocampus volume with total intracranial volume (TIV), which was independent with brain atrophy and was proved to be a good measurement for premorbid brain size and, therefore, a better measure for adjusting individual differences in brain size. Other 7 studies corrected their volume with the area of specific slice, as coronal intracranial area at the level of the anterior commissure (ICA), for which the accuracy was affected by the slice chosen. So, TIV correction method is recommended to use in future hippocampus volumetric studies, because it takes the intracranial volume into account and more reasonable than area correction method.

We find significant hippocampal atrophy in MCI and AD groups, which may be the result of neuron loss, because strong correlations have been found between neuron number and total hippocampal volume in both AD patients and aging subjects (Scheff and Price, 2003; Kril et al., 2004). Neurons in human hippocampus CA1 subfield are significantly reduced in AD patients (Zarow et al., 2005). Moreover, postmortem studies have shown that such a reduction was in the following order: controls $>$ MCI patients $>$ mild AD patients (Scheff et al., 2006, 2007).

The measure of hippocampal volume has been used for predicting MCI (DeCarLi et al., 2004; Jack et al., 2005; Apostolova et al., 2006; den Heijer et al., 2006) and AD (Growdon, 1999; Mungas et al., 2002; de Toledo-Morrell et al., 2004). Recently, the role of hippocampus in the MCI translation has attracted more attention. One study (Devanand et al., 2007) found that the hippocampal volume was significantly smaller in MCI converters to AD than in MCI nonconverters. Moreover, MCI patients with smaller hippocampi (especially the CA1 and subicular subregion) had an increased risk of converting into AD patients (Apostolova et al., 2006). However, other studies reported that the volume of the amygdala or entorhinal may be more predictive than that of the hippocampus (Dickerson et al., 2001; Silbert et al., 2003; de Toledo-Morrell et al., 2004; Stoub et al., 2005; Basso et al., 2006; Wang et al., 2006b). In general, hippocampal volume may be a nonindependent predictor of the conversion, and other features, such as age (Hampel et al., 2002; van de Pol et al., 2006a), the volume of amygdala (Horinek et al., 2006; Horinek et al., 2007) and entorhinal cortex (EC) (de Toledo-Morrell et al., 2004; Jessen et al., 2006), and hippocampal shape features (Narr et al., 2004; Wang et al., 2006a; Li et al., 2007; Scher et al., 2007), need to be integrated to improve the prediction.

In this study, a left-less-than-right pattern is found in all three groups, which is consistent with previous studies. In some studies (Jessen et al., 2006; Ridha et al., 2006; Wolf et al., 2001), the right hippocampus was found to be significantly larger than the left in the controls and MCI, but not in AD, which indicates the asymmetry was the least in AD group. In a longitudinal study (Barnes et al., 2005), a left-less-than-right pattern was found in the baseline of AD patients, but this result was not repeated at a follow-up scan conducted 15 months later, which suggested the asymmetry in AD was reduced with disease progression. A neonatal study found the preterm infants tended to have less asymmetrical hippocampus than full-term infants (Thompson et al., 2008). And males with schizophrenia established nonsignificant hippocampus volume asymmetry whereas the control subjects did (Fukuzako et al., 1997). The abnormal disturbance found in MCI and AD patients in this study may be a state characteristic, and this feature may have the potential to be used in tracing the progression of this disease.

There are several limitations in our meta-analyses. One limitation is the publication bias. Because some relevant studies may not be included in the MEDLINE database and inevitably missed in this study. Fail-safe number is employed to assess this bias. Second, MCI has many subtypes. In which, amnestic MCI was recognized as the closest to Alzheimer's disease. In cross-sectional MCI analyses in this article, only 3 of 14 studies declare their patient subtype as amnestic MCI, which is not sufficient to conduct a meta-analysis. Third, in hippocampus delineation, many studies report that their raters are blind to clinical neuropsychological data, but most of them are not blind to hemisphere (left or right). The left-right hippocampus asymmetry found in this study may be affected by rater's handedness. But considering the asymmetry is obtained by integrating many relevant studies and a significant trend is also got when comparing asymmetry degree in MCI and AD, the asymmetry found is still meaningful. Fourth, the combined effect sizes are obtained by putting together all relevant studies in AD and MCI analyses. Note that the subgroup analyses are also provided and that effect sizes has similar magnitude with the overall results, it is appropriate to get this combined effect size for an overview of the degree of hippocampus atrophy in AD and MCI analyses.

In summary, from the aspect of the extent of hippocampal volume loss, our results partly support the hypothesis that MCI is a transitional stage between normal people and AD. Our study also shows the consistent left-less-than-right asymmetry in the aging control, MCI, and AD groups, but their different extents suggest the asymmetry may change dynamically according to disease progression. These findings obtained in this study may be helpful in tracing hippocampus change from normal people to severe AD patients longitudinally and providing more candidate markers for predicting MCI and AD.

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