Hippocampal Atrophy in Persons With Age-Associated Memory Impairment: Volumetry Within a Common Space

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Objective: The objective of this study is to demonstrate the assessment of hippocampal atrophy within a standard brain atlas for persons with age-associated memory impairment (AAMI) compared with cognitively intact elderly. **Methods:** High-resolution three-dimensional (3D) brain magnetic resonance imaging (MRI) was performed on 20 nondemented persons: 10 had AAMI and 10 were normal elderly. Scans were aligned to a common atlas template to control for errors due to variable brain size and orientation as well as facilitating communication of results across centers. Manual outlining every 1 mm with volumes determined for both the hippocampal head and body was accomplished after coronal resampling perpendicular to the long axis of the hippocampus. **Results:** Subject groups were similar in age, sex ratios, and educational achievement. The AAMI group had significantly lower volumes for the right hippocampus and hippocampal head (p = .02) compared with controls. **Conclusion:** A growing body of work suggests the right hippocampal head as an early site of atrophy in early memory impairment. Subtle atrophic changes are detectable within a common atlas template allowing imaging assessment across centers. **Key words:** brain mapping, magnetic resonance imaging, hippocampus, Alzheimer's disease.

AAMI = age-associated memory impairment; AD = Alzheimer's disease; MCI = mild cognitive impairment; 3D = three dimensional; MRI = magnetic resonance imaging; MMSE = Mini Mental State Examination.

INTRODUCTION

In the absence of a blood or urine test for diagnosing preclinical Alzheimer's disease (AD), the best current biomarker is neuroimaging. Modern brain mapping now enables standardized detection of early brain abnormalities across centers (1). Hippocampal atrophy always occurs in AD, with a mean volume loss between 20% and 52% compared with age-matched controls (2–12). The challenge presented to neuroimaging in aging and dementia is centered on patients at risk for, or in the preclinical stage of, AD. A continuum of memory decline is being operationalized in the elderly from no subjective or objective complaints (normal aging) to complaints present with memory worse than young adults (age-associated memory impairment, AAMI) (13, 14) to memory worse than elderly norms (mild cognitive impairment, MCI) (15). Longitudinal studies suggest that 80% of patients with AAMI and hippocampal atrophy develop AD within 4 years (16, 17). Qualitative (16) and quantitative (5, 9, 17–20) studies of people with mild impairments, or those who eventually develop AD but did not meet criteria for the disease at the time of initial evaluation (21). have demonstrated significant hippocampal atrophy compared with normal age-related losses. Hippocampal volume loss due to normal aging may approach 46 mm³ per year over the age of 65 with a near linear decline (12). The hippocampus of the AD patient in the earliest stage of the disease is already 1.75 SD below the normal ageexpected loss (12). Sixty-seven of 80 MCI patients in a recent study (20) had hippocampal sizes less than half of that expected for normal elderly. No study has yetevaluated weather hippocampal atrophy, within a community-based population, predicts the AAMI/MCI continuum.

A normal right-greater-than-left asymmetry of medial temporal volumes has been confirmed in morphological studies based on in vivo imaging analysis (4, 6, 9, 10, 17, 18, 21–28). Longitudinal analysis reveals a reversal of this normal, ie, right-greater-than-left, hippocampal asymmetry as an early morphologic change in persons who later go on to develop AD (21). Although only one study explicitly tested this reversal of normal asymmetry in persons with AAMI (18), all studies of the AAMI/MCI continuum demonstrate a reversal of the normal hippocampal asymmetry when bilateral volumes were reported (9, 18, 21). Persons who are homozygous for the apolipoprotein E ϵ 4 (Apo-E4) allele may also have a greater reversal of the normal hippocampal asymmetry than those without the *ϵ*4 allele (29, 30).

Because high-resolution imaging is able to detect subtle early morphological changes, we used such imaging to test the hypothesis that patients with AAMI

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have a significant reversal of the normal right-greaterthan-left hippocampal asymmetry compared with elderly individuals with normal memory function. We also sought to determine which subregions of the hippocampus demonstrate significant atrophy in AAMI since a previous study has implicated the hippocampal head as being the most severely affected in AD (12). Identifying an early marker in patients destined to develop AD is important because treatments that delay symptom onset or slow disease progression could be initiated in this group to delay significant morbidity or nursing home placement.

METHODS

Subjects

The AAMI group included 10 right-handed persons selected on the basis of having 1) a subjective memory complaint; 2) a clinical dementia rating (CDR) score (31, 32) of 0.5; 3) neuropsychological performance on two of four formal memory tests greater than 1 SD below the norms for young adults; and 4) no evidence of dementia (13, 14). All persons were either enrolled in a longitudinal aging study or presented to our clinics at the University of California, Los Angeles, and agreed to participate. Consecutive sampling of individuals who had a cognitive evaluation that included clinical, neuropsychological, and imaging studies was done. The comparison group consisted of 10 right-handed older persons without subjective or objective cognitive impairment recruited from the community. Most of these persons have been included in previous work (33, 34). Exclusion criteria for all subjects were the presence of a focal lesion on brain MRI, history of severe head trauma, current major psychiatric illness, or an active medical problem that could cause memory impairment. After complete description of the study to the subjects, written informed consent was obtained.

Neuropsychological Testing

Evaluation of subjects' neuropsychological performance included Mini Mental State Exam (MMSE) (35); the Wechsler Adult Intelligence Scale (36); logical memory, immediate and delayed, (Wechsler memory scale—WMS) (37); controlled oral word fluency (38); Boston Naming Test (39); Benton Visual Retention Test (40); Rey–Osterrieth Complex figure (41, 42); and the Buschke–Fuld selective reminding test (43).

Imaging

Scanning was done on a General Electric 1.5T Signa scanner (Milwaukee, WI). Scanning parameters were FAST-3D-SPGR TR = 14.6 ms; TE = 3.3 msec; slice thickness = 1.5 mm; flip angle = 35 degrees; NEX = 1; FOV = 25 cm; matrix 256×256 ; pixel size = 0.97656; scan time = 8 minutes. A fast scan was chosen to reduce movement artifact in elderly patients. Sagittal acquisitions were used to take advantage of the superior in-plain resolution (determined by pixel size), compared with the out-of-plane resolution (determined by the slice thickness), when measuring objects, such as the hippocampus, with a greater anterioposterior than mediolateral dimension. Each MRI dataset was aligned via a nine-parameter linear registration (44) to the Talairach coordinate system (45). Aligning neuroimaging data in a common atlas allow for control over variability due to head size differences and orientation during scan acquisition; furthermore, using a common space for imaging assessments insures that results can be compared with other studies across centers.

After spatial normalization within the Talairach atlas target, in which the long axis of the left hippocampus was identified, each study was identically resliced using sync interpolation perpendicular to this line in 1-mm oblique coronal slices (Figure 1*A*). These datasets were then randomly mirrored along left and right to blind the outliner to their true left-right orientation as well as to the diagnostic group. The two hippocampi were then manually outlined on each 1-mm slice, and volumes were determined. To determine the intrarater reliability of the sole outliner (M.L.X.) who contoured all the subjects in this study, five random hippocampi were recontoured once for a reliability assessment.

Beginning rostrally, at the posterior uncus, the hippocampus was outlined with the superior border defined by the alveus, demarcating the amygdala superiorly from the underlying hippocampus, excluding the parahippocampal gyrus medially and its white matter inferiorly (Figure 1B). Progressing posteriorly, the head of the hippocampus exhibits its characteristic digitations with its superior and medial border defined by the temporal horn of the lateral ventricle, the lateral border by the transverse (choroid) fissure, and the inferior border by the hippocampal sulcus. When the hippocampal sulcus was not open, a line was drawn from its indentation to the temporal horn. Ammonic horn takes on its typical appearance at the level of the lateral geniculate through the body of the hippocampus. Measurements at this level included the dentate gyrus, cornu ammonis fields 4 through 1, the subiculum, and the alveus and fimbria. The limit between the subiculum and the transentorhinal cortex of the parahippocampal gyrus was defined by a line from the inferior border of the subiculum to the medial edge of the dentate gyrus as it curves into the hippocampal sulcus. The first section that contained a complete view of the cerebral peduncles was defined as the posterior limit of the hippocampal head (Figure 1C). The posterior limit



Fig. 1. Sagittal MRI within the Talairach atlas (45) demonstrating the long axis of the hippocampus (A). The alveus demarcates the superior boarder of the hippocampus rostrally with the amygdala above (B). The posterior limit of the hippocampal head is defined as the first oblique coronal slice in which both cerebral peduncles are present (C). The posterior limit of the hippocampal body is defined as the first oblique coronal slice in which all four colliculi are present (D). Outlines shown in gray dots. of the hippocampal body was defined as the first slice in which all four colliculi were visualized (Figure 1*D*). The hippocampal tail was not contoured.

Statistical Analysis

Because the hippocampal volume data did not generate a normal distribution, a bootstrap analysis (46) was used to test the significance of mean differences. The program Resampling Stats was used to evaluate significance. Briefly, bootstrap analysis combines both groups' mean values and randomly selects two new groups from the combined dataset. The mean difference of these two random groups is then calculated and recorded. This procedure is repeated 1000 times, producing a distribution of possible mean differences from the observed dataset. The observed mean difference between the cognitively intact and hippocampal volumes can then be compared with the distribution of the possible mean differences. The probability of finding the observed difference based on the distribution of possible differences generated from the same dataset by resampling is then recorded. This process was repeated 10 times for the four comparisons reported (left and right hippocampal head and body) to arrive at an average probability value for each comparison. If the observed difference was greater than 95% of the differences expected from 10,000 random resamplings in the bootstrap method, the observed difference was judged to be statistically significant at the .05 level.

RESULTS

Demographic data and results from the cognitive evaluation for the two groups are shown in Table 1. The only significant difference between the AAMI and cognitively intact elderly groups was the performance on the WMS logical memory test, immediate and de-

TABLE 1.	Demographic Data and Mean (SD) Raw Scores on
Cogn	itive Tests for the Normal and AAMI Groups

	Normal	AAMI
Sex	5 males/5 females	6 males/4 females
Age	73.0 (7.42)	71.0 (5.16)
Education, y	15.9 (2.38)	14.5 (2.01)
MMSE	29.2 (0.98)	28.9 (1.30)
BNT	57.9 (2.51)	55.0 (5.27)
CFL	43.0 (9.43)	38.9 (11.32)
WMS-R LMI ^a	28.1 (5.6)	19.6* (6.7)
WMS-R LMII ^a	22.6 (6.4)	12.8* (8.4)
Buschke-Fuld recall	97.0 (21.0)	93.6 (23.8)
Buschke–Fuld store	81.9 (24.4)	73.0 (34.4)
Buschke–Fuld retrieve	46.7 (25.5)	39.8 (27.5)
Rey-O copy	34.6 (2.1)	34.2 (1.7)
Rey-O delay	18.4 (7.3)	17.1 (7.5)
WAIS Block Design	34.7 (4.8)	31.6 (6.6)
BVRT correct	6.7 (1.5)	6.0 (1.1)
BVRT error	5.7 (3.3)	5.4 (2.5)

^a Three subjects in each group did not receive this test.

BNT, Boston Naming Test; WMS LM, Wechsler Memory Scale Logical Memory (I, immediate; II, delay) from the WAISR; ReyO, Rey– Osterrieth Complex Figure; BVRT, Benton Visual Retention Test. layed. This difference is consistent with the criteria used to separate the two groups and is similar to the recent operational definition of MCI put forth by the Alzheimer's Disease Cooperative Study, which requires abnormal performance on the logical memory portion of the WMS (these recent criteria were proposed after the execution of the present study).

The outliner (M.L.X.) had an intrarater reliability of 97% on five randomly selected studies that were recontoured (average of the percent difference between the first and second volume measures). All hippocampal volumes were lower in the AAMI group compared with the cognitively intact elderly, with the right hippocampal head and total volume showing a significant volume loss (p = .02). The mean hippocampal volumes and standard deviations (SDs) for the two groups are shown in Table 2.

DISCUSSION

The present study demonstrates the sensitivity of hippocampal volumetry in a comparison of AAMI and normal elderly within a standard atlas space. Although both hippocampi were reduced, we found a significant (p = .02) volume loss in the right hippocampal head in patients with age-associated memory impairment. Although the present study subjects have not been followed long enough to determine if they have AD, our finding agrees with the right-greater-than-left location of hippocampal atrophy seen in early AD patients (12) and those at risk for AD (30) and supports the view that the pathologic process responsible for hippocampal atrophy may predate the clinical manifestation of severe memory loss or AD by several years.

Nearly all hippocampal imaging studies reveal that, when bilateral control data are presented, the right hippocampus is larger than the left (Table 3); this normal asymmetry averages to 6.7% across studies. Patients with MCI or AAMI may have a reversal of this normal right-greater-than-left hippocampal asymmetry. Although only explicitly tested once (18), all imaging studies of the hippocampus in MCI or AAMI have demonstrated a reversal of this normal asymmetry when bilateral data are presented (9, 18, 21).

Current neuroimaging techniques allow the identification of subtle structural abnormalities. Modern brain mapping can now control much of the measurement error that previously confounded the sensitivity of past studies. Comparing hippocampal assessments with varying methodologies is difficult. Confounding variables such as differing head sizes, slice thickness, scanning parameters, and misalignment during image acquisition all add to the variance in results across studies. The present study, which suffers from a small

^{*} p < .01.

TABLE 2. Mean Hippocampal Volumes (SD) for Normal Cognitively Intact Elderly and Subjects With AAMI Within the Talairach
Coordinate Space (45)

	Total Hip	ppocampus	Hippoca	mpal Head	Hippocar	npal Body
	(volum	ne mm ³)	(volum	ne mm³)	(volum	e mm ³)
	Left	Right	Left	Right	Left	Right
Normal	2087 (361)	2239 (533)	756 (234)	918 (305)	1331 (260)	1320 (351)
AAMI	1887 (303)	1814* (264)	599 (194)	658* (167)	1287 (234)	1156 (208)

* p = .02.

TADLE 5. CONTROL INPOCAMPALASYMMETICS FIOM NORMALIVE DATASE	TABLE 3.	Control Hippocampal	Asymmetries Fron	n Normative Dataset
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Reference	Slice Spacing (mm)	% A/P extent ^a	Ν	Age Mean (range)	Asymmetry % R > L
Jack et al. (22)	4	56	52	30 (20–40)	11
Pearlson et al. (26)	(NA plani	metric)	16	69 (±4.5)	3
Watson et al. (23)	3	95	11	32.6 (20-59)	7
Bhatia et al. (24)	2	95	29	34.2 (22-47)	0.1
Scheltens et al. (25)	(NA lin	ear)	21	70.9 (±10.6)	5
Killiany et al. (4)	1.5	90	7	70 (63-80)	3
de Leon et al. (17)	4	NA ^b	38	70 (±8.5) ^c	18
Lehéricy et al. (6)	5	90	8	69.2 (±2.7)	4
Soininen et al. (18)	2	90	16	70.2 (±4.7)	10
Sullivan et al. (27)	3	53	72	43.9 (21-70)	9
Parnetti et al. (9)	4	1-mm gap	6	? (63-80)	3
Lehtovirta et al. (10)	2	90	34	72 (±4)	7
Kaye et al. (21)	4	38	18	86.8 (±1.9)	3
Kidron et al. (28)	2.6	90?	20	73.5 (67-88)	11
Schuff et al. (47)	1.4	95	17	72.2 (61-85)	0
Krasuski et al. (48)	5.0	90	21	69.3 (±6.8)	5

^a Percentage based on a hippocampal length of 40 mm.

^b Volume of parahippocampal fissure.

^c Ages for study 2 results are extrapolated from the main study.

sample size and thus, is prone to Type I errors, sought to demonstrate how control for such variance is accomplished by registering imaging data to a standard atlas. With the increase in neuroimaging studies and with multicenter collaboration, the interpretation and extrapolation of results is assisted by a common coordinate system within which morphologic and functional changes can be compared.

The cause for the right hippocampal volume loss in preclinical AD or in the AAMI/MCI continuum is unclear. An early reversal of the normal medial temporal asymmetry may reflect asymmetry in the pathophysiology of early AD. There may be greater synaptic pruning or neuronal loss in the right hippocampus in patients with mild cognitive impairment or incipient AD that could contribute to volume loss in this region first. Conversely, individuals with developmental or acquired reductions in the neuronal reserve of the right hippocampus, reflected by smaller volumes, may simply be at an increased risk for mild cognitive decline. All of our patients were right handed; thus, the influence of handedness could not be assessed. The reversal of the normal hippocampal asymmetry has been documented to occur in normal elderly subjects nearly 4 years before their development of AD (21), with ensuing equal rates of change for both hippocampi $(-14 \text{ to } -46 \text{ mm}^3/\text{year})$ (12, 21). These prior data suggest that the right-greater-than-left atrophic process may predate the development of AD by more than 4 vears. Long-term, community-based prospective studies that use high-resolution imaging will be needed to determine at what point before dementia onset the normal hippocampal asymmetry first reverses. Future studies also should determine sensitive automated measures, validated with manual high-resolution volumetry, that accurately reflect changes in the hippocampus so that larger samples can be more quickly assessed.

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