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Predicting memory performance in normal ageing using different measures of hippocampal size

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Abstract A number of different methods have been employed to correct hippocampal volumes for individual variation in head size. Researchers have previously used qualitative visual inspection to gauge hippocampal atrophy. The purpose of this study was to determine the best measure(s) of hippocampal size for predicting memory functioning in 102 community-dwelling individuals over 80 years of age. Hippocampal size was estimated using magnetic resonance imaging (MRI) volumetry and qualitative visual assessment. Right and left hippocampal volumes were adjusted by three different estimates of head size: total intracranial volume (TICV),

whole-brain volume including ventricles (WB+V) and a more refined measure of whole-brain volume with ventricles extracted (WB). We compared the relative efficacy of these three volumetric adjustment methods and visual ratings of hippocampal size in predicting memory performance using linear regression. All four measures of hippocampal size were significant predictors of memory performance. TICV-adjusted volumes performed most poorly in accounting for variance in memory scores. Hippocampal volumes adjusted by either measure of whole-brain volume performed equally well, although qualitative visual ratings of the hippocampus were at least as effective as the volumetric measures in predicting memory performance in community-dwelling individuals in the ninth or tenth decade of life.

Keywords Memory · Normal · Aging · Hippocampus · Magnetic resonance imaging

Introduction

Increased research effort has been directed toward investigating the relationship between the hippocampus and memory performance in recent decades. Support for this association has come from case reports [1–3], animal studies [4], neuroimaging investigations of young adults [5], normal ageing [6–8], mild cognitive impairment [9, 10], Alzheimer's disease (AD) [11, 12], organic amnesia [13], temporal lobe epilepsy [14], and head injury [15, 16].

There is appreciable variation in the size of brain structures in both normal individuals and those with underlying disease. For example, men tend to have larger absolute head size and brain size than women [17, 18] and, in absolute terms, the size of the hippocampus in males is generally larger than in females [19].

Various methods have been applied to correct for individual variation in absolute hippocampal size. Commonly employed methods of adjustment in imaging analyses include dividing hippocampal volume by total intracra-

nal volume (TICV) [12, 17, 20–23], whole-brain volume [19, 24, 25] or by a measure of cerebral area [26–28]. Researchers have also adjusted by TICV using a covariance approach [29–34]. As such, there is no universally accepted method for estimating head size. Furthermore, estimates have been derived from magnetic resonance imaging (MRI) sequences performed in the sagittal [20, 35, 36], axial [23, 37] and coronal planes [17, 21, 38, 39]. The number of slices used to estimate head size has also varied significantly [12, 39, 40], and the definition of TICV has been inconsistent across studies [35, 41].

Traditionally, studies investigating normal ageing and AD have used TICV-adjusted hippocampal volumes [6, 12, 21, 22, 33, 41]. In contrast, research efforts investigating temporal lobe epilepsy [25, 42], depression [40] or schizophrenia [43] have been more likely to use whole-brain adjustment. Given that TICV-adjusted volumes consider hippocampal size relative to “peak” brain size, use of TICV in older groups is potentially an effective means of correcting for premorbid brain size, which may provide a better indication of the degree of hippocampal shrinkage from premorbid levels.

Little research effort has been directed toward comparing different methods of correcting hippocampal volumes for head size. The available literature is complicated by definitional variations and inconsistent methodologies that preclude comparison of findings from different studies. Studies comparing visual and volumetric measures of the hippocampus have predominantly addressed the diagnostic accuracy of these measures without exploring the relative utility of these methods in predicting memory performance. Investigating the relationship between hippocampal size and memory is an important research pursuit because memory decline is a common cognitive complaint in normal ageing; therefore, it is crucial to consider whether changes in hippocampal volume might be the mechanism underlying this complaint.

As part of a broader project addressing the relationship between hippocampal size and memory in normal ageing [7], the purpose of this study was to identify the most effective measure of hippocampal size for predicting memory performance in older community dwellers: hippocampal volume relative to current brain volume, hippocampal volume relative to peak brain size (TICV) or visual estimation of hippocampal atrophy. Comparison of these quantitative and qualitative measurement techniques is of considerable clinical relevance as volumetric hippocampal measures have traditionally been accepted as the gold standard, but are difficult to apply in routine clinical examinations. If the simpler and less technically demanding visual estimation method proves to be as effective as volumetric measurement, this finding will support the utility of visual inspection as a more cost-efficient method of measuring hippocampal size in the clinical setting.

Methods

Participants

The participants were recruited from an established random population sample of older people living in central Sydney, Australia (Sydney Older Persons Study). The initial sample consisted of 630 participants aged between 75 and 96 years, with approximately equal numbers of males and females. The method of sample selection has been described in detail elsewhere [44, 45]. At 6-year follow-up, all surviving participants who were living independently in the community and capable of giving informed consent were invited to take part in an MRI study [7]. Individuals with either metallic inclusions or claustrophobia were excluded on technical grounds. Individuals were not excluded on the basis of pre-existing illnesses that commonly affect this age group, although the nature of any medical condition was documented. A particular strength of this study was that efforts were made to avoid applying strict exclusion criteria that would result in an artificially healthy sample of older persons which would not accurately reflect normal ageing. Rather, we hoped to gain insight into the relationship between hippocampal size and memory function in a population-based group of very old individuals who continue to live and function independently in the community setting.

Of 123 individuals recruited for the study, 5 did not undergo MRI scanning because of claustrophobia and 16 scans could not be analysed due to poor scan quality or missing sequences, resulting in a final sample of 102 participants (54 males and 48 females). All participants gave informed written consent to participate in the study. The relevant ethics review committees approved the study. The demographic characteristics of the participants are presented in Table 1.

Procedure

Participants were evaluated on a variety of clinical and experimental instruments, including a comprehensive neuropsychological test battery. All participants underwent neurological examination and cerebral MRI scanning. An extensive

Table 1 Demographic data on the study group (*CDR* Clinical Dementia Rating, *MMSE* Mini Mental State Examination)

Variable	Mean	SD	Range
Age	85.25	2.87	81–94
Education (years)	10.30	2.10	7–19
Estimated full scale IQ	108.98	9.94	83–128
MMSE total score	26.95	2.59	13–30
Informant CDR rating	0.36	0.64	0–3

medical history was obtained from informants to confirm details of each participant's functional ability.

Memory measure: logical memory percent retention

Logical Memory from the Wechsler Memory Scale–Revised [46] was chosen as the “gold standard” test of memory functioning and used as the dependent variable. Additional analyses were performed using other widely used memory measures: Visual Reproduction [46] percent retention, and total learning and percent retention scores on the California Verbal Learning Test (CVLT) [47]. An association between hippocampal atrophy and impaired delayed verbal retention has been reported previously [48–50]. More specifically, a robust positive correlation between percent retention on Logical Memory and (left) hippocampal volumes has been documented [25, 51]. Logical Memory percent retention scores have been shown to be very sensitive to memory impairment and discriminate between healthy older individuals and AD patients even when in the mild or preclinical stages of the disease [52, 53]. Retention scores on Logical Memory have been reported to be relatively impervious to the effects of education, IQ and advancing chronological age, especially after age 60 years [52, 54].

Magnetic resonance imaging

MRI scanning was performed on a 1.5-T scanner (Signa, General Electric Medical Systems, Milwaukee, Wis.). Volumetric measurements of the hippocampus and brain measures were derived from a T1-weighted three-dimensional fast spoiled gradient echo sequence performed in the coronal plane. This technique generated 124 contiguous 1.5-mm thick slices, using a repetition time of 12 ms, echo time of 3.5 ms, a 22-cm field of view, 30° flip angle and a matrix size of 256×256.

Volumetric estimation

The volumetric measurements were performed using the ANALYZE PC AVW version 3.0 software package (Bio-medical Imaging Resource, Mayo Foundation, Rochester, Minn.). Trained raters who were blind to all clinical data undertook image processing.

Three methods of adjusting hippocampal measures for variation in head size were employed in this study:

1. Hippocampal volume as a percentage of TICV
2. Hippocampal volume as a percentage of whole-brain volume including the ventricular system and brain stem (WB+V)
3. Hippocampal volume as a percentage of whole-brain volume with the ventricles extracted and the brain stem cut just below the medulla (WB)

The covariate approach was not the preferred method of adjustment to use in the current study on the grounds that it is limited in terms of generalizability. Hippocampal volume measures corrected via this method are not comparable across studies as the gradient of the regression line and the group mean for the relevant cerebral measure are specific to the particular group investigated and would not be consistent across studies. Given that a major impetus for this study was to address the fact that there is no universally accepted method of adjusting for head size, the techniques employed in the current study were chosen on the basis that they are unambiguous correction methods that could be consistently applied across studies. However, in view of the fact that the covariate method has been widely used in the literature, analyses were also conducted using the covariate technique for completeness.

Volume measurement

The hippocampus was defined using an established tracing protocol [55]. The posterior boundary of the hippocampus was defined as the slice with the greatest length of fornix. Mesially, the open end of the hippocampal fissure was the limit of the hippocampus in the posterior and middle sections, while the uncus became the limit once the intralimbic gyrus became visible anteriorly. Lateral and inferior boundaries were defined by the grey matter/white matter interface. In the most anterior region, the alveus was used to define the boundary between the hippocampus and the amygdala. The uncus, alveus, fimbria and choroid plexus were included in measures of the hippocampal region, since exclusion can be difficult and may be a source of error. The fornix itself was excluded from the posterior slices when it could be identified as a discrete structure.

Thresholding was used to enhance the grey matter/white matter interface. The hippocampal boundaries were manually outlined on 35 to 40 sequential slices. All hippocampal volumetrics were performed by the same trained rater (T.C.L.). Intrarater reliability (intraclass correlation coefficient) for repeated tracing in 19 participants was 0.98 for the left and 0.96 for the right hippocampus.

TICV was calculated by tracing the inner table of the skull on every fifth slice of the 124 coronal slices using a semiautomated technique. A preliminary analysis indicated that this technique maintained accuracy and reliability. All intracranial volume measures were performed by a single rater (O.P.). An intrarater reliability coefficient of 0.99 was calculated by repeating five TICV measures. However, the low number of repeated measures used to calculate this reproducibility estimate is a potential limiting factor.

Table 2 Descriptive statistics for the visual and volumetric hippocampal measures (*LH* left hippocampus, *RH* right hippocampus, *TICV* total intracranial volume, *WBV* whole-brain volume, *WB+V* whole-brain volume including ventricles and brain stem)

Predictor ^a	Mean	SD	Range
LH unadjusted	3316.13	428.76	2102.59–4401.25
RH unadjusted	3402.06	456.80	2092.62–4363.54
LH/TICV	24.11	3.12	14.77–32.73
RH/TICV	24.70	3.08	12.99–33.40
LH/WB+V	29.18	3.69	18.94–37.06
RH/WB+V	29.90	3.67	16.79–37.14
LH/WB	30.12	3.86	19.94–39.19
RH/WB	30.87	3.83	17.34–38.77
LH visual rating	2.67	0.96	1.00–4.00
RH visual rating	2.69	1.00	1.00–4.00
Covariate method predictors ^b			
LH adjusted by TICV	3316.13	389.53	2154.84–4184.44
RH adjusted by TICV	3402.06	397.79	1767.79–4069.54
LH adjusted by WB+V	3316.13	394.02	2231.05–4298.39
RH adjusted by WB+V	3402.06	401.22	1883.80–4208.57
LH adjusted by WB	3316.13	395.20	2183.53–4333.01
RH adjusted by WB	3402.06	404.62	1887.96–4254.40

^aFor all measures, higher scores represent larger volumes

^bThe mean values for the left and right hippocampi using the covariate method of adjustment are identical to the unadjusted means because the covariate was mean-corrected

Whole-brain volumes were derived using a semiautomated technique that relied upon thresholding to enhance boundary definition. Tracings were performed by one of two trained raters, who each performed 50% of these ratings. A test–retest reliability coefficient of 0.97 was calculated by tracing 32 brains a second time. Because whole-brain size was considered to be more prone to variability than the smoother contours of the skull, every third coronal slice was traced for the two whole-brain measures. The gross measure of whole-brain volume (WB+V) was obtained by separating the cerebrum from the overlying dura, cerebrospinal fluid and skull, and included the ventricular system and brain stem. A more precise estimate of whole-brain volume (WB) was then obtained by extracting the lateral and third ventricles and excluding portions of the brain stem below the medulla.

The method of expressing hippocampal volumes as a percentage of the relevant head size estimate yielded very small values (e.g., the average participant’s left hippocampus was only 0.24% of TICV). Therefore, to simplify communication of results, adjusted hippocampal volumes were rescaled and expressed in such a manner that one unit would represent one-hundredth of 1% of the volume of the head size estimate. This was achieved by multiplying the numbers produced by 100 (i.e., 0.24% became 24 units).

Visual ratings

Visual ratings of hippocampal size were undertaken by a single radiologist (L.J.R.) who was not involved in the volumetric measurements, without consideration of the participants’ demographic and cognitive characteristics. In order to maximize the clinical relevance and applicability of our findings, the radiologist who performed the visual

ratings was a general service provider predominantly involved in a clinical, rather than a research, capacity.

Before performing the visual ratings of the hippocampus, the radiologist was given 2 to 3 h of training by an experienced neuropathologist (J.J.K.) to familiarize him with the anatomy of the hippocampus and the range of atrophy seen in normal ageing. He also reviewed a number

Table 3 Contributions of the hippocampal measures to performance on Logical Memory (*LH* left hippocampus, *RH* right hippocampus, *TICV* total intracranial volume, *WB* whole-brain volume, *WB+V* whole-brain volume including ventricles and brain stem)

Predictor	Logical Memory percent retention		
	<i>R</i> ²	Estimate ^a	<i>P</i> value ^b
LH unadjusted	0.077	0.015	0.005
RH unadjusted	0.050	0.011	0.024
LH/TICV	0.082	2.148	0.004
RH/TICV	0.068	1.981	0.008
LH/WB+V	0.138	2.357	0.000
RH/WB+V	0.116	2.173	0.001
LH/WB	0.143	2.293	0.000
RH/WB	0.121	2.126	0.000
LH visual rating	0.179	10.280	0.000
RH visual rating	0.149	9.035	0.000
Covariate method predictors			
LH adjusted by TICV	0.102	0.019	0.001
RH adjusted by TICV	0.075	0.016	0.005
LH adjusted by WB+V	0.126	0.021	0.000
RH adjusted by WB+V	0.103	0.019	0.001
LH adjusted by WB	0.129	0.021	0.000
RH adjusted by WB	0.106	0.019	0.001

^aEstimate refers to the estimate of the regression coefficient

^b*P* values of 0.000 indicate *P*<0.0005

Table 4 Contributions of the hippocampal measures to performance on other memory tasks (*CVLT* California Verbal Learning Test, *LH* left hippocampus, *RH* right hippocampus, *TICV* total intracranial volume, *WB* whole-brain volume, *WB+V* whole-brain volume including ventricles and brain stem)

Measure	R^2	Estimate ^a	P value ^b
Visual Reproduction percent retention			
LH adjusted by TICV	0.03	1.62	0.070
RH adjusted by TICV	0.01	0.87	0.338
LH adjusted by WB+V	0.05	1.71	0.023
RH adjusted by WB+V	0.02	1.04	0.174
LH adjusted by WB	0.06	1.76	0.014
RH adjusted by WB	0.02	1.13	0.121
LH visual rating	0.11	9.83	0.001
RH visual rating	0.11	9.21	0.001
CVLT total learning on trials 1 to 5			
LH adjusted by TICV	0.03	0.59	0.092
RH adjusted by TICV	0.02	0.48	0.180
LH adjusted by WB+V	0.05	0.64	0.029
RH adjusted by WB+V	0.03	0.55	0.066
LH adjusted by WB	0.04	0.58	0.039
RH adjusted by WB	0.03	0.49	0.086
LH visual rating	0.24	5.56	0.000
RH visual rating	0.21	5.00	0.000
CVLT percent retention			
LH adjusted by TICV	0.01	0.81	0.405
RH adjusted by TICV	0.00	0.66	0.502
LH adjusted by WB+V	0.02	1.25	0.124
RH adjusted by WB+V	0.02	1.11	0.178
LH adjusted by WB	0.03	1.35	0.083
RH adjusted by WB	0.02	1.22	0.120
LH visual rating	0.28	16.58	0.000
RH visual rating	0.22	14.24	0.000

^aEstimate refers to the estimate of the regression coefficient
^b P values of 0.000 indicate $P < 0.0005$

of study scans to assist in developing a rating scale. Only minimal training was undertaken to ensure that this technique could be widely applied in clinical settings that do not have access to specialist neuroradiologists with extensive training in this area. Intrarater reliability coefficients of 0.81 were calculated for visual ratings of both the left and right hippocampi by assessing seven scans on a second occasion, although these estimates were possibly limited by the small number of repeated measures performed.

The visual ratings were completed over a 2-day period. After brief review of the full data set, every third slice through the length of the hippocampus from the coronal sequence was displayed on a 21-inch monitor in a manner resembling a typical radiological film with 12 images. The hippocampus was rated on a four-point scale in a manner consistent with the volumetric measures, with a higher number indicating a larger hippocampus (1 severe atrophy, 2 moderate atrophy, 3 mild atrophy, and 4 normal hippocampus).

Statistical methods

The independent effect of the predictors on memory performance was explored using linear regression. Each model

was fitted with a single predictor. This was performed for each of the predictor variables (i.e., hippocampal volumes adjusted by TICV, WB+V and WB, and the visual ratings) and results were compared to identify the best predictor of memory performance. The dependent variable was Logical Memory percent retention scores, although the analyses were later repeated using Visual Reproduction percent retention and total learning and percent retention scores on CVLT as the dependent variable. A statistical significance level of 0.05 was used for all analyses.

Results

The descriptive statistics for unadjusted hippocampal volumes and primary predictor variables are presented in the top panel of Table 2. While not central to this study, the descriptive statistics for the various measures using the covariate method are presented in the lower panel of Table 2. The table shows the broad ranges for unadjusted hippocampal volumes, with the largest hippocampal size being more than twice that of the smallest. On average, the right hippocampus was larger than the left hippocampus in the study group.

The mean Logical Memory percent retention score was 69.9 (SD 23.4). This falls within the published mean range of performance (i.e., 65–77% retention) for Americans aged 80–90 years [56]. A score of 100% was fixed as the maximum obtainable score, even when a participant recalled more information after a delay than on immediate recall. This was done to avoid high percentages influencing any association that may exist between memory performance and hippocampal size, as a score greater than 100% is not really meaningful in this context. Five participants attained a score of 100%, while three individuals were unable to recall any elements of the stories after a delay.

The results of the regression analyses are presented in Table 3. The upper panel of Table 3 includes the partial regression coefficients for each primary predictor (i.e., each measure of hippocampal size) as well as the variance (R^2) in memory performance on Logical Memory percent retention explained independently by each predictor. For example, a one-unit increase in TICV-adjusted left hippocampal volume (i.e., in this case, an increase in hippocampal size equal to one-hundredth of 1% of TICV) increased Logical Memory percent retention score by 2.15% and accounted for 8% of the variance in memory performance. For the visual ratings of the left hippocampus, a one-unit increase (as reflected by a shift to a category suggestive of less hippocampal atrophy) was reflected by a 10.28% improvement in Logical Memory percent retention score and explained 18% of the variance in memory performance. The results of the regression analyses using the covariate method are presented in the lower panel of Table 3.

All adjusted volumes and visual measures reached significance. The unadjusted hippocampal volumes were less effective predictors than the adjusted volumes. All predictors were oriented in the same direction (i.e., higher value represented a larger hippocampus). These results reveal that visual ratings were the best predictors of memory performance.

Analyses were also performed on other commonly used memory measures: Visual Reproduction percent retention, and total learning score and percent retention scores on the CVLT (Table 4).

There were fewer significant associations identified with these memory measures than with Logical Memory percent retention. The left hippocampal volumes adjusted by WB+V and WB were significant predictors of both Visual Reproduction percent retention and CVLT total learning scores. The visual ratings significantly predicted memory performance on all three tasks. The large regression coefficients reflect the robustness of the associations (e.g., shifting to a category suggestive of less hippocampal atrophy is associated with a 16.58% improvement in CVLT percent retention). TICV-adjusted hippocampal volumes did not significantly affect performance on any of these memory measures.

Discussion

The mean volume of the right hippocampus was found to exceed that of the left hippocampus. This finding is in line with published results in healthy adults of all ages [21, 25, 26, 33, 51, 57, 58]. The mean hippocampal volumes were comparable in size to other reported estimates for healthy older adults [26, 28]; however, other studies have reported smaller volumes [33]. This discrepancy may reflect differences in tracing protocols, scanner specifications or the marked variation in hippocampal size seen in healthy 80- and 90-year-olds.

The analyses revealed robust, significant associations between all predictors and Logical Memory percent retention scores. In keeping with previous reports, all associations were in the expected direction such that increasing hippocampal size was reflected as improved memory performance [25]. While one study failed to find a significant relationship between Logical Memory and visual ratings of temporal lobe atrophy [59], the use of patients with AD and Logical Memory free recall rather than percent retention may account for the variations in findings.

The associations between the hippocampal measures and the other memory measures (Visual Reproduction percent retention, and total learning and percent retention on CVLT) provided further support for the conclusions drawn from the initial analyses using Logical Memory percent retention. While there were fewer significant associations with these memory measures, the pattern of results was similar. These findings reinforce the notion that Logical Memory percent retention is a sensitive measure of the integrity of the hippocampal region [25, 51, 52], and provide further justification for the selection of this task as the gold standard for measuring the aspects of memory that are subserved by the hippocampus.

Comparison of the R^2 values enabled identification of the best method for explaining variance in memory performance on Logical Memory. These results indicated that the TICV-adjusted volumes performed most poorly in this regard. Hippocampal volumes adjusted by both WB+V and WB performed equally well, but the visual ratings were at least as effective as volumetry in predicting memory performance. The analyses using hippocampal volumes adjusted by TICV, WB+V and WB by way of the covariate method revealed the same pattern of results. On the basis of these findings, visual ratings appeared to be the best measure of hippocampal size for predicting memory functioning in this group of community-dwelling older individuals.

Few studies have systematically compared methods of adjusting hippocampal volumes for variation in head size. Free et al. [17] examined six different structures as possible correction factors in young adults including four area measures (corpus callosum, cranial, parenchymal excluding corpus callosum and brain stem) and two volumes (cranial

and cerebral). Hippocampal volumes were most strongly related to cerebral volume. However, covariance correction via cranial volume resulted in the most consistent reduction in variance for the hippocampal volumes.

Laakso and colleagues [60] compared three methods of volume normalization in distinguishing between AD patients and patients without dementia: dividing hippocampal volumes by one of two estimates of TICV or multiplying hippocampal volumes by brain area divided by cranial area. They concluded that the latter method resulted in the highest sensitivity and correct classification rate, although all normalized volumes resulted in high sensitivity and specificity and discriminated well between groups.

The current findings suggest that hippocampal volume adjustment by TICV may not be the most appropriate technique to apply in very old individuals. Although Free et al. [17] found that correction via TICV best reduced variance in hippocampal volumes, they did not compare the efficacy of such methods in predicting memory performance. In our study, TICV-adjusted volumes were the least-effective predictors of current memory function and were only marginally better than the unadjusted volumes in accounting for variance in memory performance. Based on these results, it appears that the relationship between hippocampal volume and current brain size (as indexed by either measure of whole-brain volume) is more crucial in predicting memory function than the association between hippocampal volume and peak brain size. This implies that a hippocampus that is disproportionately atrophic relative to whole-brain volume exerts a deleterious impact on memory performance, regardless of whether the brain itself has undergone appreciable atrophy from its peak or optimal size.

Qualitative visual ratings of hippocampal atrophy have been compared to volumetric measures in several studies, particularly with respect to lesion localization and lateralization in temporal lobe epilepsy [61]. The diagnostic accuracy of visual inspection has been reported to be equivalent to, or slightly better than, volumetric assessment in identifying hippocampal sclerosis [62]. Visual ratings provide some advantage over volume measures in terms of simplicity and cost-effectiveness, but this method may fail to detect hippocampal atrophy that is mild or equivalent bilaterally. Volumetric measures permit quantitative assessment of volume loss, enabling more effective comparison of hippocampal size across different individuals [42] and greater sensitivity to subtle volume loss. This is particularly pertinent in non-epilepsy research when the investigation focuses on hippocampal volumes in absolute rather than relative terms.

Considerably less research effort has been directed toward comparing visual and volumetric measures in non-epileptic populations. A recent study compared the diagnostic value of visual inspection and volumetry in identifying medial temporal lobe atrophy in dementia [38]. Both visual and volumetric techniques successfully discriminated between AD patients and patients without dementia. When com-

bined with Mini Mental State Examination (MMSE) [63] scores, visual inspection effectively discriminated between AD patients and controls (sensitivity 95%), while volumetric methods demonstrated no significant diagnostic gain over and above the use of the MMSE score alone. Wahlund et al. [38] suggested that visual examination may have afforded a higher rate of correct classification by allowing more lateral portions of the structure to be considered. Similar findings were reported by Desmond et al. [24]. Volumetry correctly identified AD patients and controls with 85% accuracy, but visual assessment marginally out-performed volumetrics in predicting the diagnosis of AD or control. A notable limitation of both studies is that the participants were relatively young (in their 60s, on average) and, therefore, these findings may not be generalized to older individuals, particularly considering that discriminating between AD patients and controls becomes more difficult in individuals of advanced age [59, 64].

The results of the current study support the sensitivity of visual inspection in gauging the extent of hippocampal atrophy [62, 64, 65] and are in broad agreement with studies reporting the superiority of visual hippocampal ratings over quantitative volumetric methods in distinguishing between individuals with and without dementia [24, 38]. In keeping with the theories of Wahlund et al. [38], visual assessment may be the best predictor of memory performance because it allows for consideration of peripheral structures in addition to the hippocampus itself. In spite of attempts to consider specifically the nominated hippocampal area in the current study, visual inspection inadvertently provides information about both hippocampal size and perihippocampal space. The latter will reflect atrophy of both the hippocampus and surrounding structures. Therefore, additional information relating to the integrity of the medial temporal lobe may be gained from inspecting adjacent brain structures that also have a role in memory processing. In contrast, the hippocampal volumes involved quantifying the size of the hippocampus itself, irrespective of the size of surrounding structures.

These findings raise the question of the importance of medial temporal areas surrounding the hippocampus to memory processing. In view of accumulating evidence indicating that the perirhinal and parahippocampal cortices play a role in human memory function [66–69], the relationship between Logical Memory and these extrahippocampal medial temporal subregions should be explored in future research in order to clarify whether any such relationships might also contribute to the superior performance of the visual ratings in predicting memory performance on Logical Memory in the current study.

There are a number of ways to define “normal”, and the current sample was defined as normal on the grounds that the participants were living independently in the community. This definition was employed in a deliberate effort to provide an accurate reflection of “normal ageing” in elderly community dwellers, as opposed to applying strict exclu-

sion criteria (e.g., MMSE cut-off score) that might result in an artificially healthy sample of older persons. However, as a result, the current participants ranged in terms of their level of cognitive functioning (MMSE range 13–30) and, therefore, we appreciate that some of these individuals may have fulfilled other criteria for dementia which could have impacted our findings. Hence, another avenue for future research would be to investigate whether these findings in normal ageing can be generalized to clinical populations such as patients with AD.

In addition, the ongoing study of these participants in the Sydney Older Persons Study will help to clarify whether volumetric and visual measures of hippocampal size can be utilized to predict memory decline in a longitudinal context, which would have important implications for the transition between normal ageing and neurodegenerative disease.

Conclusion

Visual ratings of the hippocampus appeared to have the largest impact on memory performance in the group under study. In terms of the volumetric measures, the TICV-adjusted volumes were the poorest independent predictors of memory function. The WB+V-adjusted and WB-adjusted volumes explained similar degrees of variance in memory performance, which is likely attributed to the fact

that volumes yielded from these adjustment methods were very highly correlated ($r=0.96$). The current study expands previous findings by documenting that the size of the hippocampus relative to current brain size is a more crucial determinant of memory function in this group than the size of the hippocampus relative to peak brain size. Furthermore, this study demonstrates that visual inspection of the hippocampus is at least as effective as volumetric assessment in predicting memory function in community dwellers over 80 years of age. This is a particularly valuable finding given that visual assessment is faster, more cost-effective and more readily available in a clinical setting than volumetric techniques. Importantly, the clinical utility of this finding also extends to diagnostic decision-making in geriatrics, as the current results suggest that visual assessment of the hippocampus potentially offers an effective and accessible adjunct to existing neurological and neuropsychological assessment techniques in the diagnosis of neurodegenerative diseases such as AD.

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