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A reliable MR measurement of medial temporal lobe width from the Sunnybrook Dementia Study

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Abstract

We studied the hippocampal angle and spatial relationships of medial temporal lobe (MTL) structures, using midbrain colliculi and inter-collicular sulcus (ICS) as landmarks, and measured MTL width on axial 3D-T1-weighted MRI at ICS level in 41 normal, aged participants. Mean hippocampal angle was 29° (range 17–42°) caudal to the anterior–posterior commissure (AC–PC) line. The slice at the ICS, parallel to the long axis of the hippocampus, best revealed a longitudinal view of hippocampus and parahippocampal gyrus in 76% of participants, compared to only 7% when slices were 20° caudal to orbitomeatal line (OML), an accepted technique used to examine MTL width in previous CT studies. The MTL width measured midway and at its thinnest between the anterior–posterior borders of the midbrain was highly reproducible (intraclass correlation coefficients >0.98) using these new methods. These simple decision rules, individualized orientation along the hippocampus and using a standardized landmark like the ICS, make these measures more comparable across subjects, and hence more useful in detecting and monitoring MTL atrophy in dementia.

Keywords: Magnetic resonance imaging; Hippocampus; Parahippocampal gyrus; Medial temporal lobe; Aging

1. Introduction

Medial temporal lobe (MTL) structures, specifically the hippocampus and parahippocampal gyrus (including entorhinal cortex), play an important role in memory [34]. Alzheimer's disease (AD) is the most common cause of the pathologic decline in memory in the elderly population [6]. Pathological evidence has proved that the MTL is the site of the neuropathology and volume loss in the early stage of AD [3,17]. Quantitative neuroimaging can detect MTL atrophy and has potential utility to aid in ante-mortem diagnosis of AD [12,18,19,26]. Most studies, however, have been based on time-consuming planimetric, slice-by-slice tracing protocols to obtain hippocampal volume. Reliable automatic volume measures are still in development as is the search for a simpler imaging marker of AD.

Several simpler approaches for estimating the MTL atrophy using linear measures have been investigated [7,10,11,13,14,22–25,27,30,31]. MTL width using computed tomography (CT) has been the most widely recognized linear measure [10,22–25,30,31]. This method uses temporal lobe-oriented CT scans, 20° caudal to the OML [22], which was presumed to be parallel to the plane through the hippocampus. This application of the MTL width assesses combined hippocampus and parahippocampal gyrus atrophy measured at its narrowest point [22,23]. In pathological correlations, this measure had good diagnostic accuracy for distinguishing AD from normal aging (sensitivity 92% and specificity 95%). Encouraged by the results, but aware of the limitations of CT, including bone artifact in the middle cranial fossa [20], and inaccuracies in measuring the edges between cerebrospinal fluid (CSF) and brain tissue [8], we set out to use high resolution three-dimensional magnetic resonance imaging (3D-MRI) to further explore or improve upon the CT method, as MRI significantly reduces bone artifact and improves image contrast at the interface of CSF and tissue.

Since this CT method was first reported in 1992 [22], only one published study has tried to apply it to MRI, and it failed to reproduce previous CT findings [13]. A simple method to quantify the MTL atrophy could be a welcome

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adjunct to clinical management of dementia. Further efforts to standardize this technique and to make it more reliable, as well as to translate it into a MRI protocol would be worthwhile. 3D-MRI permits manipulation of images to investigate if the angle 20° caudal to OML parallels the long axis of the hippocampus, as this has not been systematically verified in previous work. The effects of different angulation on MTL measurement need to be identified because a previous MRI study has shown remarkable individual variability in the angulation of the long axis of the hippocampus [16]. 3D-MRI also offers greater ability to explore anatomical landmarks and objectively identifies the best horizontal slice on which to measure the MTL width. The previous CT method gave only a subjective recommendation to find a level (not too high, not too low) on which to measure the MTL width without providing convincing reliability information [22].

Thus, to optimize linear measurement of the MTL width on 3D-MRI, our objectives were: (1) to define the best angle of orientation in which to view the MTL in each individual on axial MRI and to determine the effect of angulation on the axial appearance of the MTL, (2) to develop a reliable technique for identifying an optimal equivalent slice level across individuals in the axial plane using readily identifiable anatomic landmarks, and (3) to evaluate the resulting optimal linear measurement protocol in a sample of normal elderly subjects and compare this to the previous method developed for CT.

2. Methods

2.1. Participants

Forty-one (20 men and 21 women) healthy community dwelling elderly volunteers free of any history of neurological or psychiatric disease were included. The mean age (±S.D.) was 71 (±6) years; mean education was 15 (±2) years, and mean Mini-Mental State Examination score was 28.4 (±1.5) out of a possible 30. All participants were within normal limits on a detailed neuropsychological battery [28].

2.2. Imaging technique

Imaging was performed on a 1.5-Tesla MR unit (Signa, General Electric Medical Systems, Milwaukee, WI). All MR scans were conducted using a standardized T1-weighted 3D volumetric spoiled gradient recalled sequence with TR/TE/NEX-5/35/1, 35° flip angle, 22 × 16 cm field of view, 1.2–1.4 mm slice thickness (depending on the head-size of the subject), and a 256 × 192 matrix, generating 124 axial slices in 10.5 min. Any rotations of the subject's head were corrected in all axial and coronal planes following acquisition, and in the sagittal plane, images were realigned parallel to the anterior and posterior commissures (AC–PC) line [35]. Brain images were analyzed using ANALYZE AVW™ Software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN) on a Sun workstation (Sun Microsystems, Mountain View, CA).

2.3. Choosing the angle of orientation

Two angles of orientation were investigated. One angle was oriented parallel to the long axis of the hippocampus at the inferior border of the cornu ammonis and the subiculum (Fig. 1a) [4,15,16]. To determine the angulation of the long axis of the hippocampus, we measured the hippocampal angle, which was defined as the angle between the long axis of the hippocampus and the AC–PC plane. This was measured separately for the left and right hemispheres (which usually differed by <2°) and the average angle was used as the hippocampal angle to minimize the effect of left–right differences in angulation. The other orientation was at a fixed angle, 20° caudal to the OML, and was used for

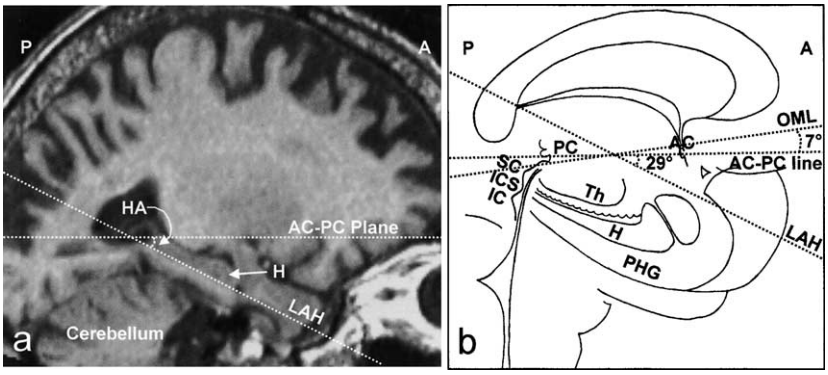

Fig. 1. (a) MR sagittal view through the body of the hippocampus (H) (A: anterior, P: posterior). Hippocampal angle (HA) is defined as the angle between the plane along the longitudinal axis of the hippocampus (LAH) at the inferior border of cornu ammonis and subiculum, and the plane along the line joining the anterior commissure (AC) and posterior commissure (PC) (AC–PC plane). (b) Diagram illustrating the anatomical relationship of midbrain structures including inferior colliculus (IS), inter-collicular sulcus (ICS) and superior colliculus (SC) with hippocampus and parahippocampal gyrus. Note the 7° difference between the OML and AC–PC line [29]. On average, the plane parallel to the LAH was 29° caudal to the AC–PC plane.

the purpose of comparison to previously published methods [22]. The OML is 7° rostral to the AC–PC plane [29] (Fig. 1b). Thus, the standard orientation of 20° caudal to the OML is actually equivalent to 13° caudal to the AC–PC plane.

2.4. Choosing the vertical slice level best representing the MTL in the axial plane

The hippocampus and parahippocampal gyrus are located lateral to the midbrain. The vertical axis of the midbrain is roughly perpendicular to the long axes of hippocampus and parahippocampal gyrus. The superior colliculus (SC), inferior colliculus (IC) and inter-collicular sulcus (ICS) located between the superior and inferior colliculi in the dorsal portion of the midbrain, shown in Fig. 2iii, are readily identifiable in the sagittal plane, and were used as landmarks to define different vertical levels through the MTL. AC–PC aligned MR images were reconstructed along the long axis of the hippocampus (at the average angle between the left and right long axis of the hippocampus) and also in the plane 20° caudal to the OML. For each angle of orientation, six slices (1.8 mm thick) were generated using ANALYZE™ along these two planes, starting from the inferior border of the IC and ending at the superior border of the SC (Fig. 2iii). The slice passing through the ICS was used as the central location (i.e. zero level). Two ventral slices passed through the IC (IC-a, IC-b) and three dorsal slices passed through the SC (SC-a, SC-b, SC-c) (Fig. 2iii).

The ideal slice for measuring the MTL width in normal elderly individuals should show a longitudinal view of the hippocampus and parahippocampal gyrus [23], without being confounded by the lateral transverse fissure, inferior thalamus, or a poorly defined lateral border of the hippocampus. In order to identify this slice, a trained observer, blinded to angulation, evaluated all images with respect to the following features on the six slices defined above:

(a) The slices that best showed a longitudinal view of the hippocampus and parahippocampal gyrus between the anterior and posterior borders of the brainstem (Fig. 2i, IC-a and ICS).
(b) The slice on which the lateral border of the hippocampus was well defined by the temporal horn of the lateral ventricle (Fig. 2i, ICS).
(c) The slice that showed the inferior thalamus (Fig. 2i, SC-b).
(d) The slice that showed the lateral transverse fissure (Fig. 2i, SC-a).

2.5. Measuring MTL width

Based on the results of the visualization analysis, the slice at the level of the ICS was chosen as the best slice to use for

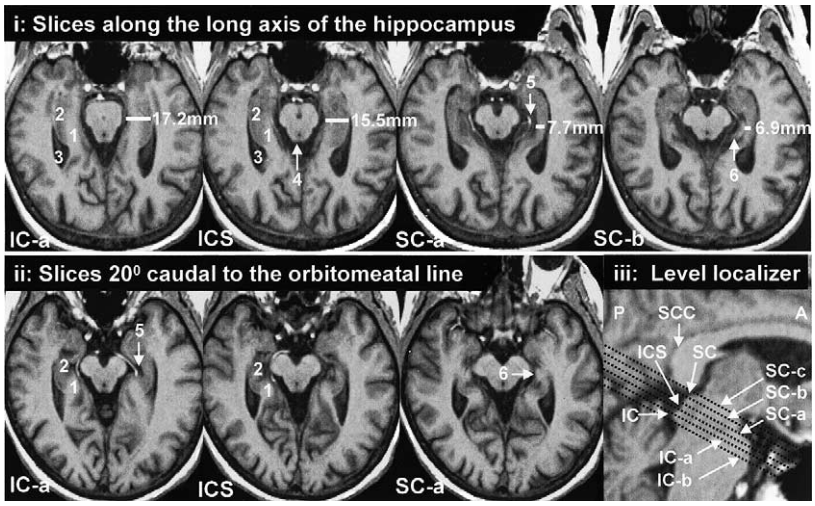

Fig. 2. (i) Axial view of the MTL structures along the LAH at the IC-a, ICS, SC-a and SC-b levels shown in Fig. 2iii Level localizer (A: anterior, P: posterior). IC-a shows the parahippocampal gyrus (1) and hippocampus (2) lateral to the midbrain. Note that the lateral border of the MTL is not well demarcated by the temporal horn of the lateral ventricle (3). ICS shows that the parahippocampal gyrus (1) and hippocampus (2) in the MTL region are now demarcated clearly by the temporal horn. A straight posterior border of the midbrain indicates the level of the ICS in the axial view (4). At the SC-a level, the lateral transverse fissure emerges (5), and at the SC-b level, a structure outside the MTL, the inferior thalamus (6) becomes apparent (also see Fig. 3b). The tMTL width was measured at each level and is represented by the white horizontal lines along with the width in millimeters. (ii) Demonstration of the effect of angulation on the appearance of the MTL structures in the axial MRI. Slices were oriented at 20° caudal to the OML from the same subject. The hippocampus (2) and parahippocampal gyrus (1) are seen as short segments and the lateral transverse fissure (5) is only half as long as the lateral transverse fissure in the images in the upper row-oriented along hippocampal axis. Number 6 indicates the inferior thalamus. (iii) Level localizer. A MR sagittal view (A: anterior, P: posterior) shows the lines through the inferior and superior colliculi depicted on axial view in Fig. 2i. AC–PC aligned MR images were reconstructed along the LAH from the inferior border of inferior colliculus (IC) to the superior border of superior colliculus (SC). Six slices (1.8 mm thick) were obtained from IC-b (the most inferior line) to SC-c (the most superior line). SCC: splenium of the corpus callosum.

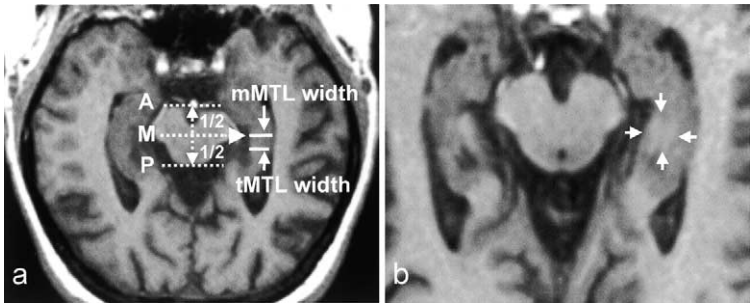

Fig. 3. (a) Methodology of linear measurements of the MTL width. All measurements were taken in the axial MR image at the level of the ICS between the anterior (A) and posterior (P) borders of the midbrain. mMTL width is the width at the point midway (M) between the anterior–posterior borders of the midbrain. tMTL width is the thinnest width at any point between the anterior–posterior borders of the midbrain. (b) An axial MRI slice at a level through the middle of the SC (SC-b level), parallel to the LAH shows that the left inferior thalamus, a structure outside the MTL (small arrows), becomes apparent and is hard to separate from the surrounding hippocampus. The inferior thalamus should not be included in the linear measurement.

linear measurements. Two linear measurements were taken on each side on this axial slice. One was the thinnest medial temporal lobe (tMTL) width, measured at its narrowest point between the anterior–posterior boundaries of the midbrain. The other was the midway medial temporal lobe (mMTL) width at the point midway between the anterior–posterior boundaries of the midbrain (Fig. 3a) (It was thought that this standard location might make future longitudinal studies more comparable). Special attention was made not to include the inferior thalamus in the measurements (Fig. 3b) as well as the tentorial edge and posterior cerebral artery. Additionally, for comparison to previous studies, the tMTL width was measured in order to replicate, as far as possible with MRI, the CT method used by Jobst et al. (jMTL width) [22].

All linear measurements were performed by a single trained investigator (FG), blinded to clinical information, using the ANALYZE region-of-interest module. To assess reliability, two raters (FG, NL) independently measured the hippocampal angle, the level of ICS and the widths of tMTL and mMTL from 20 scans. To investigate possible confounding effects of head-size on the linear measurements, each measure was also normalized by dividing by the total intracranial volume for the individual, derived from an in-house analysis program, and then multiplying by the mean total intracranial volume for the group to convert the number back into a linear value. Proton density and T2-weighted image were obtained in the same scanning session as the T1-weighted image used for linear measures. These images were segmented into gray matter, white matter and CSF voxels, including sulcal CSF, the sum of which reflects total intracranial volume, according to a standardized protocol [32].

To generate the correlation of the linear measures with volumetric measures of the MTL volumes, hippocampal volumes were obtained by tracing the body of the hippocampus in the sagittal plane and parahippocampal volume were derived by tracing the parahippocampal cortex in the coronal plane at 2.5 mm intervals, according to a recently published protocol [5].

2.6. Statistical analysis

Pearson's product moment correlation was used to compare the hippocampal angle between hemispheres and to examine any linear relationships of interest (e.g. tMTL width with age, MTL volumes, etc.). Mean hippocampal angle between hemispheres was compared with paired *t*-tests (two-tailed, alpha = 0.05). Inter- and intra-rater reliability was analyzed with the Shrout and Fleiss model three intraclass correlation coefficients [33]. Independent *t*-tests (two-tailed, alpha = 0.05) were utilized to examine group differences (e.g. men versus women).

3. Results

3.1. Hippocampal orientation

Hippocampal angle ranged from 17 to 42° caudal to the AC–PC line. Mean hippocampal angle (±S.D.) was 29° (±4°) caudal to the AC–PC line, which is equivalent to 36° caudal to the OML as illustrated in Fig. 1b. (Recall that the CT protocol using an angle 20° caudal to the OML is taking measurements 13° caudal to the AC–PC line.) The left hippocampal angle correlated with right hippocampal angle ($r = 0.7$, $P < 0.05$). Mean left hippocampal angle (±S.D.) was 29° (±4.2°), range 18–39° and mean right hippocampal angle was 30° (±4°), range 23–40°. On paired *t*-test, the left hippocampal angle was on average 1° (±3°) less caudal to the AC–PC line than the right ($t_{(1,40)} = 2.42$, $P < 0.05$). There was no significant difference between men and women in hippocampal angle ($t_{(2,39)} = -0.89$, $P > 0.05$). Inter- and intra-rater reliability of hippocampal angle measurement was high, with intraclass correlation coefficients = 0.98 for each.

3.2. MTL structures

The longitudinal view of the hippocampus and parahippocampal gyrus was best obtained when the angle of orientation was parallel to the long axis of the hippocampus through the ICS. Angle selection through the ICS between two observers was found to be reliable with an intraclass correlation coefficient of 0.94. The hippocampus and parahippocampal gyrus were both seen lateral to the anterior–posterior limit of the brainstem at this level and angle in 76% of cases (Fig. 2i, ICS), compared to only 7% of cases at an angle of 20° caudal to the OML. When a fixed angle of 20° was used, most cases showed the hippocampus and parahippocampal gyrus to be obliquely cut into segments, rather than exposed as a continuous longitudinal view as above (Fig. 2ii, IC-a and ICS). In the slices taken through the SC levels, the lateral transverse fissure and the inferior thalamus were frequently evident in the participants (Figs. 2 and 3b). At the IC levels, the lateral border of the hippocampus was difficult to define. The frequencies with which the MTL and neighboring structures appear at different vertical levels are shown for angles parallel to the long axis of the hippocampus and 20° caudal to the OML in Table 1.

3.3. MTL width measurements

Reliability was high with intraclass correlation coefficients of 0.98 for tMTL width and 0.99 for mMTL width in 20 scans between two observers and intraclass correlation coefficients were 0.99 for both tMTL width and mMTL width measured twice by the same rater. The results for the whole sample are presented in Table 2. Mean tMTL width was larger than jMTL width for the left ($t_{(2,39)} = 7.5$, $P < 0.001$), the right ($t_{(2,39)} = 7.1$, $P < 0.001$), and the thinnest width ($t_{(2,39)} = 7.5$, $P < 0.001$) (Fig. 4). Significant sex differences (men > women) were found on three MTL width measures: left tMTL width ($t_{(2,39)} = -3.3$, $P < 0.005$), left mMTL width ($t_{(2,39)} = -2.2$, $P < 0.05$) and overall tMTL width ($t_{(2,39)} = -2.6$, $P < 0.05$). Normalized values (with correction of the head-size) in all linear measurements for all participants did not reveal significant differences compared to unnormalized values in paired *t*-tests ($t_{(1,40)}$ value ranged from −0.15 to −0.51, $P > 0.05$). The sex differences were no longer significant on independent *t*-tests when normalized values were compared between men and women ($t_{(2,39)}$ values ranged from −0.06 to −0.62, $P > 0.05$).

Table 2
Mean, standard deviation and 95% confidence interval of tMTL, mMTL, and jMTL widths (mm) from 41 normal subjects

	Mean	S.D.	95% Confidence interval	
			Lower limit	Upper limit
tMTL width[a]				
Left	14.11	2.10	13.45	14.78
Right	14.33	1.60	13.83	14.84
Smallest[b]	13.53	1.77	12.97	14.09
mMTL width				
Left	14.97	2.01	14.34	15.61
Right	15.02	1.64	14.50	15.54
Smallest	14.25	1.63	13.73	14.77
jMTL width				
Left	11.05	2.62	10.22	11.87
Right	11.19	2.59	10.37	12.01
Smallest	10.26	2.48	9.48	11.04

tMTL width: the tMTL width between the anterior and posterior borders of the midbrain; mMTL width: the MTL width at the midway of the midbrain; jMTL width: the tMTL width according to Jobst et al. [22].

[a] Paired *t*-tests show significant differences ($P < 0.0001$) between all three corresponding measures of tMTL and jMTL widths.

[b] The smallest value of either left or right side.

3.4. Correlation analyses

The tMTL and mMTL widths were significantly correlated with each other (r ranged from 0.50 to 0.91, $P < 0.01$). A significant correlation was also found between the left tMTL and left jMTL widths ($r = 0.4$, $P < 0.01$).

Table 1
The percentages of subjects showing the MTL structures or features viewed with scan angulation parallel to the LAH and a fixed −20° to the OML at different levels ($n = 41$)

Slice level[a]	Hippocampus and parahippocampal gyrus		Clear lateral border of hippocampus		Lateral transverse fissure		Inferior thalamus	
	LAH (%)	−20° OML (%)	LAH (%)	−20° OML (%)	LAH (%)	−20° OML (%)	LAH (%)	−20° OML (%)
SC-c	0	0	48	29	7	0	100	100
SC-b	0	0	100	59	30	8	77	100
SC-a	20	0	100	82	50	23	30	70
ICS	*76*	7	*93*	71	*3*	35	*0*	31
IC-a	73	0	40	41	0	35	0	0
IC-b	20	0	3	24	0	10	0	0

Italicized numbers highlights that ICS level is the most reliable slice for consistently viewing the longitudinal extent of the hippocampus and parahippocampal gyrus without the confounding presence of the inferior thalamus and lateral transverse fissure in LAH plane.

[a] Slice levels correspond to those in Fig. 2iii Level localizer; SC: SC-a 1.8 mm above ICS, SC-b 3.6 mm above ICS, and SC-c 5.4 mm above ICS; IC: inferior colliculus, IC-a 1.8 mm below ICS, IC-b 3.6 mm below ICS; ICS: inter-collicular sulcus.

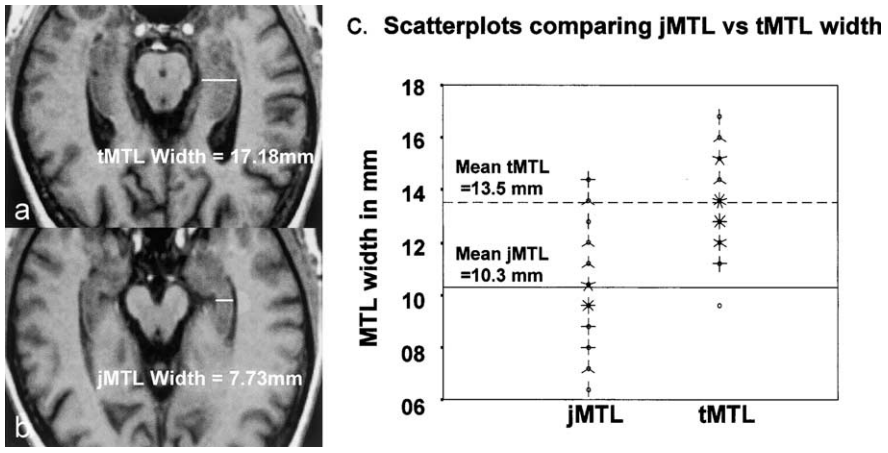

Fig. 4. Examples demonstrating the difference in the MTL width related to angulation using our technique (a) and the Jobst method (b). (a) tMTL width: the tMTL width using our technique at the level of the ICS parallel to the LAH. (b) jMTL width: the tMTL width replicating the Jobst technique from the same subject at the level of the middle height of the MTL in the plane 20° caudal to the OML. (c) A graph demonstrates that jMTL width is systematically smaller than tMTL width ($t_{2,39} = 7.5$, $P < 0.001$). The solid line is the mean of the jMTL width, and the dotted line is the average of the tMTL width. Each circle represents one subject and the lines indicate additional subjects.

Correlations between the linear and volumetric measurements were not significant (r ranged from –0.06 to 0.33).

4. Discussion

To establish a reliable and easy-to-implement method for evaluating the MTL atrophy on MRI, two major modifications were made to previous CT techniques. These included new rules for selecting the angle of orientation that best exposed the MTL structures in the axial plane and a new method for reliably choosing the best slice level on which to make linear measurements.

Instead of using a fixed scan angulation for all persons [22,23], the angle along the long axis of the hippocampus was defined in each subject and used to maximally expose a true horizontal view of the MTL. Previous studies have proposed a temporal lobe-oriented angle, 20° caudal to the OML on axial CT [22,23] because this orientation approximates a horizontal view of the hippocampus, thereby optimizing visualization of the lateral and medial borders, which is obviously important for measuring the MTL width. However, the limitations of CT for choosing individualized angulation at the time of acquisition make it difficult to obtain images truly parallel to the long axis of the hippocampus in every individual. Two interesting findings emerged when we evaluated the hippocampal angle individually in our 3D-MRI study. The first was that the hippocampal angle varied greatly from 17 to 42° between subjects. A previous study of young healthy volunteers showed that the hippocampal angle could vary 28° between individuals [4]. However, this study utilized the angle at which scans were acquired, which could vary with head position, and measured the angle between the long axis of the hippocampus and the plane of acquisition. As far as we are aware ours is the first study to reliably document the variability in hippocampal angle relative to the AC–PC line, that is using a standard approach in normal subjects. The second observation of note was that our mean hippocampal angle was 36° (±10°) negative to the OML, which is about 16° more caudal than the angulation used in the previous CT studies [10,22–25,30,31].

The effect angulation had on the appearance of the MTL and the MTL width measurements was considerable in our study. Not surprisingly, the plane 20° caudal to the OML [22] cut the MTL structures of the hippocampus, parahippocampal gyrus and the lateral transverse fissure obliquely to a different extent depending on the individual (Fig. 2ii). The resulting variability in angulation, which could be 10–15°, markedly changed the appearance of these structures in axial section. Orientation along the long axis of the hippocampus takes into account individual variability and reliably exposes the equivalent horizontal views of the MTL across subjects. Reconstruction along the long axis of the hippocampus can be reliably achieved with high inter- and intra-rater agreement. The angulation effect on the linear measurement of the MTL width is illustrated in Table 2 and Fig. 4. For example, tMTL width measured in the plane parallel to the long axis of the hippocampus is about 3 mm larger on average than the tMTL width using the Jobst technique [22,23].

The second novel feature of our protocol was that a method was devised that allowed objective and consistent selection of the axial section to be measured. A key problem for applying the CT rules for the MTL width measurement to MRI relates to reproducibility. Our preliminary MR study replicating the original Jobst method [22,23] yielded intraclass correlation coefficients <0.80 between the different raters only after many training sessions and implementation of ad hoc rules. The good agreement reported for the Jobst et al. study [22] was not based on the preferred statistical method for testing reliability. They used the difference

between the measures taken by the different raters, instead of using the more widely accepted intraclass correlation coefficient to test agreement. In fact, the standard deviation of the difference was larger than the mean difference in that study, indicating the reproducibility of the measure may be not as good as originally suggested [22]. As demonstrated in Fig. 2i, the MTL width is wider in the inferior sections and gradually becomes thinner at the superior levels. It is essential with MRI to objectively define a slice level not only for reproducibility, but also for the reliable comparison of different disease states and also within individuals over time. Using the prominent brainstem colliculi and ICS as the landmarks (Fig. 2iii), we were able to determine that the most representative plane showing a major part of the hippocampal body laterally and a portion of the parahippocampal gyrus medially was at the level of the ICS. The ICS can be easily and reliably defined in the mid-sagittal plane (see Fig. 2iii). Linear measurements made at this level were highly reproducible and required minimal training to reach high agreement.

In addition, we reliably obtained two different linear measures: (1) tMTL width, which may be most useful for cross-sectional analyses as it reflects the extremes of the MTL width range, and (2) mMTL width, which may be more useful for monitoring progression of atrophy over time, given that the anatomical location for this measurement is unlikely to change between the original and follow-up scans of the same individual.

Our results show how much the methodology (e.g. slice level and angulation) can affect the measurement of a target structure in the case of the MTL. The CT technique of Jobst et al. [22] in our hands yielded a significant correlation ($r = 0.4$, $P < 0.01$) in the left tMTL width, but the MTL width was systematically smaller than with our approach, which takes individual variation into better account (Fig. 4).

Linear measures of the MTL did not correlate well with volumetric measures in this study. The lack of correlation may be attributable to the small variability of the MTL atrophy in our normal subjects. Other possible explanations could be related to the fact that the MTL is a complex, three-dimensional structure. Our linear measures included both the hippocampus (major part) and parahippocampal gyrus (minor part), but we were only measuring width at one level and at one point in the anterior–posterior extent. Furthermore, the hippocampal and parahippocampal volumes we used in this study were not total volumes as described in our published protocol from a study of AD and aging [5]. In particular, our volumetric measure of the parahippocampal gyrus comprised cortex only and excluded subcortical white matter, which was included in our linear protocol for measuring the MTL.

Our subgroup analysis showed that the tMTL and mMTL widths on the left as well as overall tMTL width in men were significantly larger than in women when not corrected for head-size. These differences disappeared when head-size was taken into account. Sex differences in the MTL associated with the brain-size have also been investigated in other studies [2,21]. One study [2] obtained the same result as we did; in the other, the size of the MTL was larger in elderly men than in elderly women when not corrected for the head-size; the opposite was obtained after correcting for the head-size [21]. These conflicting results suggest that head-size needs to be considered in future studies of the MTL in order to properly understand potential sex differences in normal aging and disease states.

Our cohort of 41 neuropsychologically normal, community dwelling volunteers, who ranged in age from 56 to 82 years, revealed no correlation of the MTL width with age. This contrasts with the study of Jobst et al. [22], which had more controls ($n = 75$) and a greater range of age from 47 to 88 years. In that study, the MTL width did correlate with age ($r = -0.62$, $P < 0.0001$), possibly because a greater number of younger participants were in the sample. Older neurologically normal subjects may have more brain atrophy due to the aging process as well as common medical conditions such as hypertension, atherosclerosis, etc., whose prevalence increase with age [21]. In “super” healthy adults, age-related differences in the MTL were not detected [9]. The criteria of ‘normal’ adopted in the different studies may explain the different effects of aging found in these studies.

An important question is whether this simple linear measure could have clinical utility. Our technique is only suitable for MRI at the present. The protocol would have greater routine applicability if it could be adapted for CT. Previous studies suggest this may be the case [10,22–25,30,31]. The problem has been reproducibility and generalizability across different sites [1]. The advantage of the linear measures is that they only take 15 min to do, compared to approximately 2 h for tracing volumes. Even semi-automatic volumetric methods still require considerable expertise and training in identifying key landmarks. The utility of our particular technique needs to be tested in a patient sample in our imaging laboratory. Also of note is that our method of measuring the MTL width was based on elderly normal subjects. We have not applied this technique to a younger group. We expect that the relationship between midbrain landmarks and corresponding anatomy in axial sections should be similar between younger and elderly participants, but this needs to be verified.

In summary, we have developed a protocol for measuring the MTL width along the long axis of the hippocampus at the level of the ICS. We showed in our sample of 41 elderly volunteers that we could reliably and optimally measure the MTL width using this protocol. The simple decision rules developed in this study make the MTL width more comparable across subjects. This is likely to increase the utility and reliability of linear measurements derived from MRI for diagnosis of diseases that target the MTL structures, such as AD. For longitudinal comparisons, this technique may also be helpful in reliably monitoring disease progression within subjects over time. Investigations on the sensitivity and specificity of this measure in aging and dementia and

in longitudinal monitoring are currently in progress in our laboratory.

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