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Hippocampal (Subfield) Volume and Shape in Relation to Cognitive Performance across the Adult Lifespan

Aristotle N. Voineskos,[1,2,3]* Julie L. Winterburn,[1,4,5] Daniel Felsky,[1,3] Jon Pipitone,[1] Tarek K. Rajji,[2,3] Benoit H. Mulsant,[2,3] and M. Mallar Chakravarty[4,5,6]*

[1]Kimel Family Translational Imaging Genetics Laboratory, Research Imaging Centre, Campbell Family Mental Health Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada
[2]Geriatric Mental Health Service, Campbell Family Mental Health Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada
[3]Department of Psychiatry and Institute of Medical Science, University of Toronto, Toronto, ON, Canada
[4]Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, ON, Canada
[5]Computational Brain Anatomy Laboratory, Cerebral Imaging Centre, Douglas Mental Health University Institute, Montreal, QC, Canada
[6]Departments of Psychiatry and Biomedical Engineering, McGill University, Montreal, QC, Canada

Abstract: Newer approaches to characterizing hippocampal morphology can provide novel insights regarding cognitive function across the lifespan. We comprehensively assessed the relationships among age, hippocampal morphology, and hippocampal-dependent cognitive function in 137 healthy individuals across the adult lifespan (18–86 years of age). They underwent MRI, cognitive assessments and genotyping for Apolipoprotein E status. We measured hippocampal subfield volumes using a new multiatlas segmentation tool (MAGeT-Brain) and assessed vertex-wise (inward and outward displacements) and global surface-based descriptions of hippocampus morphology. We examined the effects of

Additional Supporting Information may be found in the online version of this article.

Aristotle Voineskos and Julie Winterburn contributed equally to this work.

*Correspondence to: Dr. Aristotle Voineskos, Kimel Family Translational Imaging-Genetics Laboratory, Research Imaging Centre, Centre for Addiction and Mental Health, 250 College St, Room 105, M5T1R8, Toronto, Canada. E-mail: Aristotle.voineskos@camh.ca and Dr. Mallar Chakravarty, Computational Brain Anatomy Laboratory, Cerebral Imaging Centre, Douglas Mental Health University Institute, 6876 Boul. LaSalle, Montreal, QC, Canada. E-mail: mallar.chak@gmail.com

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age on hippocampal morphology, as well as the relationship among age, hippocampal morphology, and episodic and working memory performance. Age and volume were modestly correlated across hippocampal subfields. Significant patterns of inward and outward displacement in hippocampal head and tail were associated with age. The first principal shape component of the left hippocampus, characterized by a lengthening of the antero-posterior axis was prominently associated with working memory performance across the adult lifespan. In contrast, no significant relationships were found among subfield volumes and cognitive performance. Our findings demonstrate that hippocampal shape plays a unique and important role in hippocampal-dependent cognitive aging across the adult lifespan, meriting consideration as a biomarker in strategies targeting the delay of cognitive aging. *Hum Brain Mapp 36:3020–3037, 2015.*

Key words: aging; MRI; morphometry; cognition; memory; hippocampus

INTRODUCTION

Despite the predominant view of age-related structural susceptibility of the hippocampus and its role in episodic memory [Squire, 1992; Tulving, 2002; Van Petten, 2004] and working memory [Beauchamp et al., 2008; Yonelinas, 2013] performance, there are conflicting results in the literature on both accounts. While some studies have shown a relationship of volume with age, others have not [Head et al., 2005; Jack et al., 1997; Jernigan and Gamst, 2005; Jernigan et al., 2001; Lupien et al., 2007; Malykhin et al., 2008; Pruessner et al., 2001; Sullivan et al., 2005; Sullivan et al., 1995]. These inconsistent results may be due to the use of volumetric measurements focused on the whole hippocampus or anterior or posterior sections [Raz and Rodrigue, 2006; Shing et al., 2011; Van Petten, 2004]. In recent years, approaches indexing hippocampal subfield volume and shape have provided novel alternatives for characterization of hippocampal morphology in vivo [Winterburn et al., 2013; Yang et al., 2013; Yushkevich et al., 2009, 2010]. As the hippocampus is not a homogeneous structure, application of these new approaches may help to address the inconsistent findings from more conventional measurements of hippocampal structure [La Joie et al., 2010; Mueller and Weiner, 2009; Mueller et al., 2007; Yang et al., 2013]. They may also help to clarify whether age-related cognitive decline is associated with changes in hippocampal morphology.

Similar to studies of hippocampal volume and age, studies of the relationships of hippocampal volume with episodic and working memory performance, particularly in the context of aging, have not been consistent [Della-Maggiore et al., 2002; Raz and Rodrigue, 2006; Van Petten, 2004]. Higher-field scanners and novel segmentation approaches enable studies examining the relationship both of hippocampal subfield volume with age [La Joie et al., 2010; Mueller and Weiner, 2009; Mueller et al., 2007], and of subfield volume with cognitive performance [Engvig et al., 2012; Shing et al., 2011]. Hippocampal subfields seem susceptible to age-related effects, although not consistently across studies, with findings overlapping with changes observed in pathological aging, in particular in the CA1 subregion [Kerchner et al., 2012; Mueller and Weiner, 2009; Mueller et al., 2007, 2010]. Recent studies of hippocampal shape metrics have demonstrated differences between normal and pathological aging (particularly Alzheimer's disease) [Carmichael et al., 2012; Kerchner et al., 2012; Tondelli et al., 2012]. Shape metrics may offer classification or distinction among groups beyond conventional volumetric measures of the hippocampus [Achterberg et al., 2013], and predict conversion to disease [Shen et al., 2012]. Volume metrics are global measures of an entire structure or substructure (e.g., single number representation), whereas shape metrics provide more nuanced, multidimensional and local descriptions of difference (e.g., an entire mesh of displacements). This capacity for nuance may lead to better discrimination [Raznahan et al., 2014; Shaw et al., 2014b]. However, the relationship between hippocampal shape metrics and cognitive function across adult life is not known.

We have built a freely available (cobralab.ca/atlases/Hippocampus) high-resolution hippocampal atlas that reliably delineates subfields [Winterburn et al., 2013]. In combination with the **M**ultiple **A**utomatically **Ge**nerated **T**emplate (MAGeT-Brain; cobralab.ca/software/MAGeTBrain) segmentation approach, we have shown that this atlas can be successfully used to segment the hippocampus and its subfields in a population-based study [Pipitone et al., 2014]. The combination of these approaches permits high-throughput analysis of hippocampal morphology in a large sample. Within the present investigation, we also developed an approach that used our subfield atlases to assess both local and global hippocampal shape. Taken together, these approaches allow for a comprehensive investigation of hippocampal morphology. Therefore, we applied these approaches in a relatively large sample ($n = 137$) of healthy individuals across the adult lifespan (age range: 18–86) to determine relationships among age, hippocampal morphology, and episodic and working memory performance. We also analyzed the effects of Apolipoprotein E (APOE) genetic variation due to its effect on hippocampal volume reported by some [Mueller and Weiner, 2009] but not all studies [Morra et al., 2009]. We hypothesized that: (i) all subfields would decrease in volume with age; (ii) hippocampal shape would change with age; and (iii) hippocampal shape and subfield volumes would be associated with hippocampal-dependent cognitive function.

TABLE I. Demographic characteristics of subjects.

Demographic	Mean (SD)
Age	45.39 (19.02)
Education (years)	15.42 (1.95)
WTAR (IQ)	117.87 (7.83)+
MMSE	29.33 (0.92)++
	N
Gender	72M, 65F
Handedness	128R, 9L
APOE ϵ4	35C(4 homozygous), 98NC+++

WTAR = Wechsler Test of Adult Reading.
MMSE= Mini Mental State Examination.
C = carrier; NC = noncarrier.
NA = Test not administered.
+ 3 NA.
++ 2 NA.
+++ 4 NA.

METHODS

Subjects

A total of 137 healthy volunteers [mean (SD) age: 45.4 (19.0); range: 18–86] were recruited at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada, as part of an ongoing neuroimaging, genetics, and cognition research program in neuropsychiatric disorders. Persons with previous head trauma and loss of consciousness, a neurological disorder, a history of primary psychotic disorder in a first-degree relative, current substance abuse (urine toxicology screens were obtained in all potential subjects), or a history of substance dependence were excluded from the study. All study procedures complied with the Declaration of Helsinki and were approved by the CAMH Research Ethics Board; all subjects provided written, informed consent. Subjects were assessed with the Edinburgh Handedness Inventory [Oldfield, 1971], the Hollingshead Four-Factor Index of Socioeconomic Status [Hollingshead, 1975], and the Wechsler Test of Adult Reading (WTAR) [Wechsler, 2001] for IQ. They completed the Structured Clinical Interview for DSM-IV-TR Axis I Disorders [First et al., 2001] to ensure they were free of neuropsychiatric disorders, and were screened for dementia using the Mini Mental State Examination (MMSE) [Folstein et al., 1975] (Table I).

Neurocognitive Assessment

Each subject underwent a comprehensive neurocognitive battery. The present analyses focus on verbal episodic memory, visuospatial episodic memory, and working memory: tests within the Repeatable Battery for the Assessment of Neuropsychological Status [Hobart et al., 1999] were used to assess verbal episodic memory ('list recall') and visuospatial episodic memory ('figure recall'). The Letter Number Sequence (LNS) test was used to assess verbal working memory performance. Complete cognitive data were available for 133 subjects (Table II).

APOE ε4 Genotyping

APOE ϵ4 carrier status was obtained by combining genotypes at rs7412 and rs429358. These SNPs were genotyped directly using standard ABI TaqMan Assay-on-Demand protocols and 10% of sample genotypes were duplicated for quality control with 100% reliability. Genetic information was available for 133 subjects (Table I).

Image Acquisition

T1-weighted magnetic resonance (MR) images were acquired for each subject using an 8-channel head coil on a 1.5 T GE Echospeed system (General Electric Medical Systems; Fairfield, Connecticut). Images were acquired using an axial inversion recovery-prepared spoiled gradient-recalled sequence with echo time 5.3 ms, repetition time 12.3 ms, time to inversion 300.0 ms, flip angle, 20°, and 1 excitation, for a total of 124 contiguous slices with 1.5 mm thickness and 0.78 mm × 0.78 mm in-plane voxel.

Image Segmentation

The first step in the analysis was to segment the hippocampus and hippocampal subfields on the T1-weighted images of all subjects. Segmentations were performed using the MAGeT-brain multiatlas segmentation tool, which leverages the neuroanatomical variability of a subject population to boost segmentation accuracy (Fig. 1) [Chakravarty et al., 2013; Park et al., 2014; Pipitone et al., 2014]. Five high-resolution (300 μm isotropic voxels) *in vivo* atlases of the hippocampus and hippocampal subfields were used for the automatic segmentation pipeline [Winterburn et al., 2013]. These atlases include definitions for the right and left CA1, CA2/CA3, CA4/dentate gyrus, strata radiatum/lacunosum/moleculare (SR/SL/SM), and subiculum. For further information on the MAGeT-Brain segmentation pipeline, see the Supporting Information. Segmented images were inspected by one of the authors (JLW), an expert in hippocampal subfield segmentation, to ensure high segmentation quality. Total brain volume (TBV) was estimated using mincBEAST [Eskildsen et al., 2013], an automated pipeline that is a part of the MINC toolkit (MNI, Montreal).

TABLE II. Mean Cognitive Scores and Effect of age on cognition based on a general linear model (with sex included in the model).

Cognitive task	Mean score (SD)	*P*	R^2
Letter Number Sequence (LNS)	16.17 (3.35)	0.021*	0.033
List Recall	7.20 (2.15)	<0.0001*	0.14
Figure Recall	11.87 (4.16)	<0.0001*	0.14

R^2 values are adjusted and apply to the effect of age only.
*Indicates $P < 0.05$.

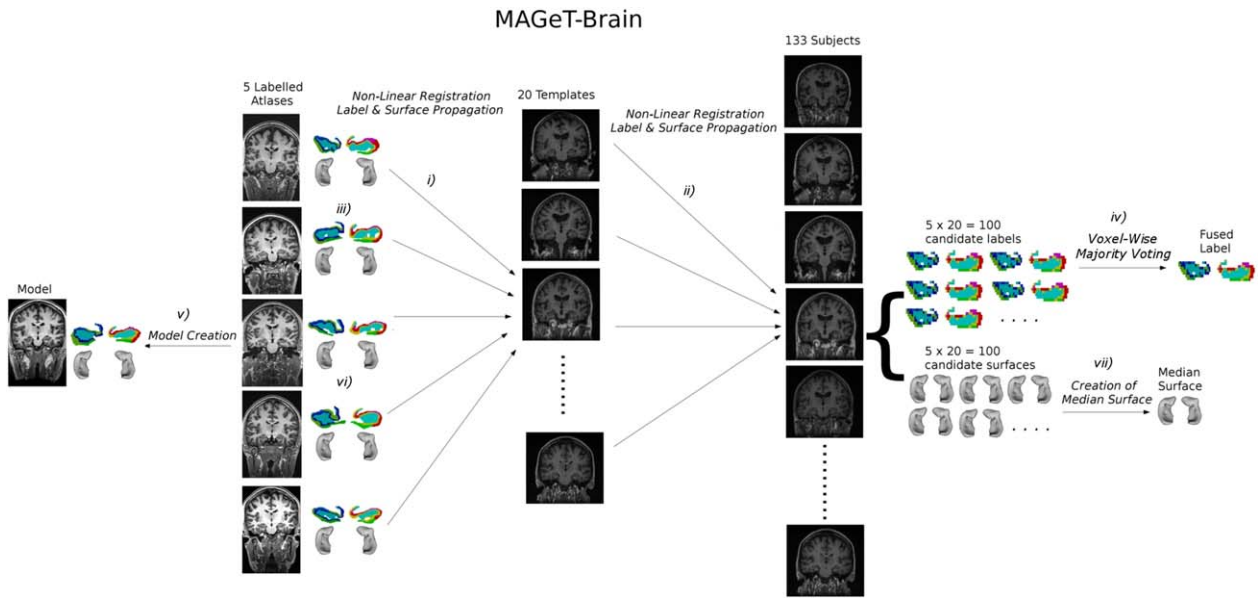

Figure 1.

MAGeT-Brain image registration and automatic segmentation pipeline: (i) 5 manually labeled atlases are registered nonlinearly to a subset of the subject population (*templates*, in this case 20). (ii) Each image from the template library is registered to every subject image. (iii) Labels are propagated along each possible registration pathway such that there are 100 (5 atlases x 20 templates) candidate segmentations for each subject. (iv) Creation of a single fused label for each subject via voxel-wise majority voting. (v) A single model image is created from the 5 atlas images, and a single surface-based representation of the hippocampus is created. (vi) The model surface is propagated along the MAGeT-Brain registration pathways. (vii) A single surface is created for each subject from the 100 candidate surfaces by determining the median position of each vertex.

Morphometric Analyses

Model creation

Analysis of the shape characteristics of a structure can provide information that is neuroanatomically unique in relation to volumetric assessment [Csernansky et al., 2005; Miller et al., 2009; Zhao et al., 2008]. Like most analyses in neuroimaging research, a common volumetric [Mazziotta et al., 1995] or surface-based [Raznahan et al., 2014] model is required to facilitate group analyses. For the analyses presented in this manuscript, we derived a model that is the average neuroanatomical representation of all five expertly segmented atlases used as input to the MAGeT-Brain pipeline (referred to henceforth as the *model*). This model has superior contrast, signal, and definition when compared to a single atlas and provides a common space for analysis of surface-based metrics (see below). From this model we were able to derive models of the hippocampus with ~10,000 vertices/hemisphere that we used as input to local (or vertex-based) and global (from a point distribution model) analyses. See the Supporting Information for further details.

Local (univariate) morphometric analysis

We used a surface-based metric proposed by Lerch et al. for analyzing hippocampal shape differences in a population [Lerch et al., 2008]. This method, along with local surface area metrics, has been used recently in morphometric analyses of the striatum, thalamus, and pallidum [Chakravarty et al., 2015; Magon et al., 2014; Raznahan et al., 2014; Shaw et al., 2014b]. In the present work, we have refined this technique and applied it to whole hippocampal morphology in a multiatlas framework. Briefly, this technique estimates the local shape differences of the hippocampus using surface displacements, and a univariate (vertex-wise) analysis is conducted using the surface-based representations of the left and right whole hippocampi created on the final model (described above). All possible combinations of nonlinear transformations for each subject were mapped and averaged to reduce noise and increase signal. Surface displacements at each vertex relative to the model were estimated between each deformation vector and the normal at each vertex on the surface using a dot product (Fig. 2). See the Supporting Information for further details.

Global (multivariate) morphometric analysis

While measuring local surface displacement is one descriptor of morphometry, it does not describe global shape patterns for a structure. We used a point-distribution model of the vertices across all subjects and

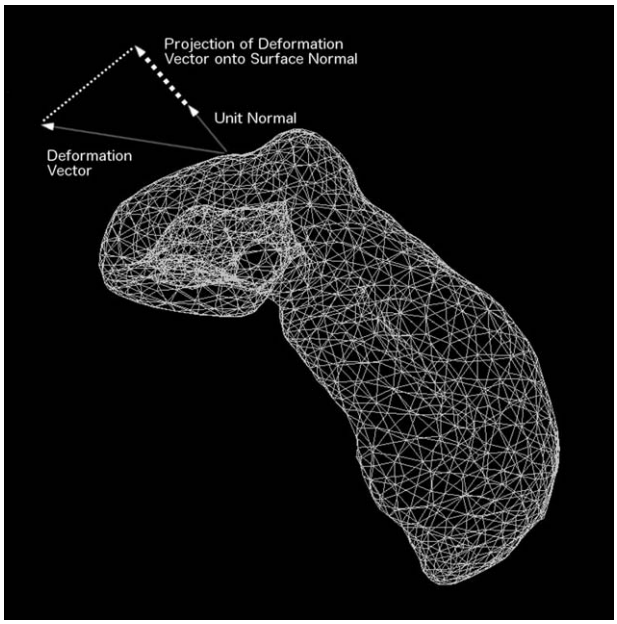

Figure 2.
Surface-based local morphometric analysis: Projection of the deformation vector at each vertex onto the unit vector of the surface normal at the same vertex (dot product) to determine the magnitude of displacement in the direction perpendicular to the surface at each vertex.

analyzed their variance using a principal component analysis (PCA) to explore global hippocampal shape [Chakravarty et al., 2011; Cootes et al., 1995]. Using each possible transformation mapping the model to each subject we were able to derive a median surface-based representation of each hippocampus (Fig. 1, vi & vii). All hippocampi were then normalized for 12-parameter linear dimensions (3 each of translations, rotations, scales, and shears) and were input into the PCA analysis. Each PC represents a dominant shape-mode in the data and the PC-score for each subject represents how much that subjects's hippocampus loads on that score.

Statistical Analysis

Volumetric analyses

A general linear model (GLM) was used to assess all relationships, and all tests were corrected for multiple comparisons using FDR [Benjamini and Hochberg, 1995]. Comparisons surviving 5% FDR were deemed to be significant. The relationship between hippocampal volumes and age was assessed first, with sex, years of education, APOE ϵ4 carrier status, and TBV included in the model. Next, the relationship between volume and cognitive scores (list recall, figure recall, and LNS scores) was assessed with age, sex, years of education, APOE ϵ4 carrier status, and TBV included in the model.

Local (univariate) morphometric analysis

First, a vertex-wise GLM was used to evaluate the relationship between age and local shape differences in the right and left whole hippocampus, while including age, sex, years of education, and APOE ϵ4 carrier status in the model. The shape metric is already normalized for TBV, so TBV was not included as a covariate. The effect of cognition was then evaluated in additional models including terms for cognitive test performance and covarying for age, sex, years of education, and APOE ϵ4 status. A 5% false discovery rate (FDR) correction was used to correct for multiple comparisons across the vertices [Genovese et al., 2002].

Global (multivariate) morphometric analysis

Global hippocampal shape was analyzed using a PCA. The relationship between PC score and cognitive performance was assessed using a GLM with age, sex, years of education, and APOE ϵ4 status included in the model. FDR was used to correct for multiple comparisons, and results that survived the 5% threshold were considered to be significant.

RESULTS

Relationship of TBV and Hippocampal Volume

Total brain volume (TBV) was colinear with total (right + left) hippocampal volume ($R^2 = 0.022$, $P < 0.05$), so was included in all volumetric statistical models.

Relationship of Volumetric Measures and Age

All right and left whole hippocampal and subfield volumes were inversely related to age after correction for multiple comparisons except for the right and left CA1 ($R^2 = 0.018$, $q = 0.069$ for both) (Fig. 3). Table III summarizes the results of all volumetric analyses involving age and cognitive tests. Quadratic effects of age were assessed, but found to be not significant ($R^2 < 0.02$, $q \gg 0.05$). Among the subfields studied, the right and left CA1 showed the least prominent relationship with age, with a 9.8×10^{-4}% and 1.0×10^{-3}% decrease in volume per year, respectively (based on the mean subfield volumes of the population, covarying for sex, education, APOE ϵ4 status, and TBV). The right and left CA2/CA3 showed the most prominent relationship with age, with a 2.6×10^{-3}% and 3.6×10^{-3}% decrease in volume per year, respectively. Age-by-sex interactions were also explored in all subfields, and were significant in the left CA2/CA3 ($R^2 = 0.025$, $P = 0.037$), but this interaction did not survive 5% FDR correction. No relationships between APOE ϵ4 status and subfield volume survived FDR correction. Given some investigations showing

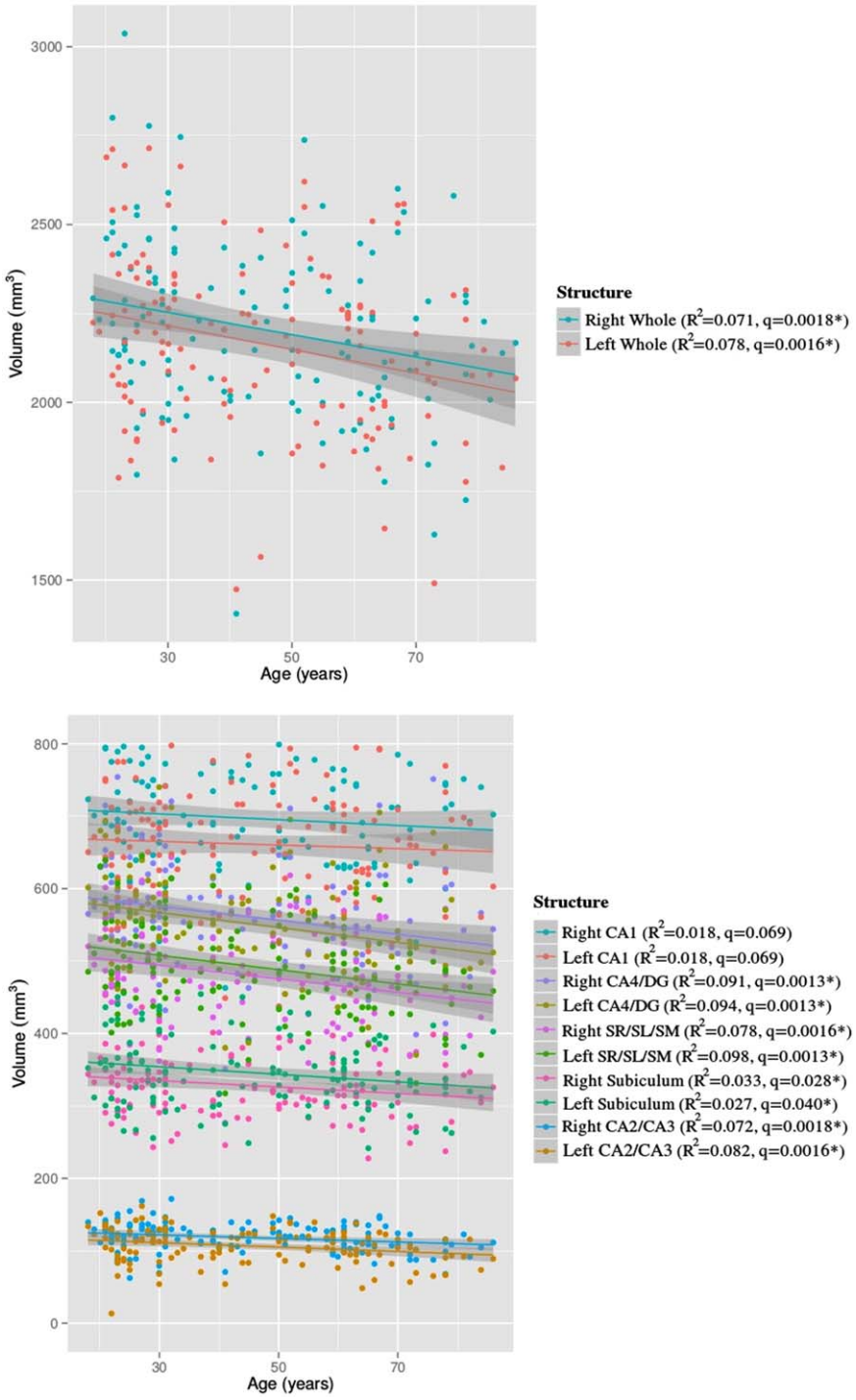

Figure 3.

Negative relationships of: (**a**) whole right and left hippocampus with age; and (**b**) all right and left hippocampal subfields (CA1, CA2/CA3, CA4/DG, SR/SL/SM, subiculum) with age. All analyses have 134 degrees of freedom. *Indicates significant negative relationship of volume with age (with sex, years of education, APOE ϵ4 carrier status, and total brain volume included in the model) after 5% FDR correction.

TABLE III. Summary of all volumetric statistical tests.

Variable of Interest	Covariates	Hemisphere	Structure	R^2	P	q
Age	Sex, education, APOE ϵ4 status, TBV	Right	CA1	0.018	0.066	0.069
			Subiculum	0.033	0.021*	0.028*
			CA4/DG	0.091	0.00031*	0.0013*
			CA2/CA3	0.072	0.0012*	0.0018*
			SR/SL/SM	0.078	0.00082*	0.0016*
			Whole	0.071	0.0012*	0.0018*
		Left	CA1	0.018	0.069	0.069
			Subiculum	0.027	0.033*	0.040*
			CA4/DG	0.094	0.00027*	0.0013*
			CA2/CA3	0.082	0.00073*	0.0016*
			SR/SL/SM	0.098	0.00020*	0.0013*
			Whole	0.078	0.00078*	0.0016*
List recall	Age, sex, education, APOE ϵ4 status, TBV	Right	CA1	0.0026	0.99	0.99
			Subiculum	0.0024	0.67	0.91
			CA4/DG	0.021	0.55	0.88
			CA2/CA3	0.00	0.88	0.96
			SR/SL/SM	0.00	0.78	0.93
			Whole	0.0065	0.73	0.93
		Left	CA1	0.015	0.28	0.66
			Subiculum	0.00	0.84	0.95
			CA4/DG	0.025	0.13	0.51
			CA2/CA3	0.0026	0.99	0.99
			SR/SL/SM	0.0040	0.31	0.66
			Whole	0.012	0.32	0.66
Figure recall	Age, sex, education, APOE ϵ4 status, TBV	Right	CA1	0.010	0.34	0.66
			Subiculum	0.027	0.063	0.44
			CA4/DG	0.066	0.054	0.44
			CA2/CA3	0.021	0.15	0.56
			SR/SL/SM	0.013	0.27	0.66
			Whole	0.033	0.12	0.47
		Left	CA1	0.017	0.23	0.66
			Subiculum	0.0053	0.29	0.66
			CA4/DG	0.060	0.027*	0.44
			CA2/CA3	0.0033	0.56	0.88
			SR/SL/SM	0.025	0.060	0.44
			Whole	0.032	0.077	0.44
LNS	Age, sex, education, APOE ϵ4 status, TBV	Right	CA1	0.0039	0.79	0.94
			Subiculum	0.0067	0.35	0.66
			CA4/DG	0.019	0.67	0.91
			CA2/CA3	0.037	0.019*	0.44
			SR/SL/SM	0.00	0.81	0.94
			Whole	0.0054	0.91	0.96
		Left	CA1	0.010	0.68	0.91
			Subiculum	0.0090	0.23	0.66
			CA4/DG	0.011	0.48	0.86
			CA2/CA3	0.026	0.086	0.44
			SR/SL/SM	0.00	0.56	0.88
			Whole	0.0063	0.68	0.91

R^2 values are adjusted and apply to the variable of interest only.
*Indicates significance before/after 5% FDR correction ($p/q < 0.05$). TBV = total brain volume

age-dependent effects of APOE ϵ4 [Felsky and Voineskos, 2013], analyses were repeated in a subset of the subjects older than 50 years of age, but results remained not significant in this subgroup.

Relationship of Local Morphometry and Age

Significant relationships between local shape of the whole hippocampus and age survived 5% FDR (right hippocampus: DOF = 124, $t = 2.47$; left hippocampus:

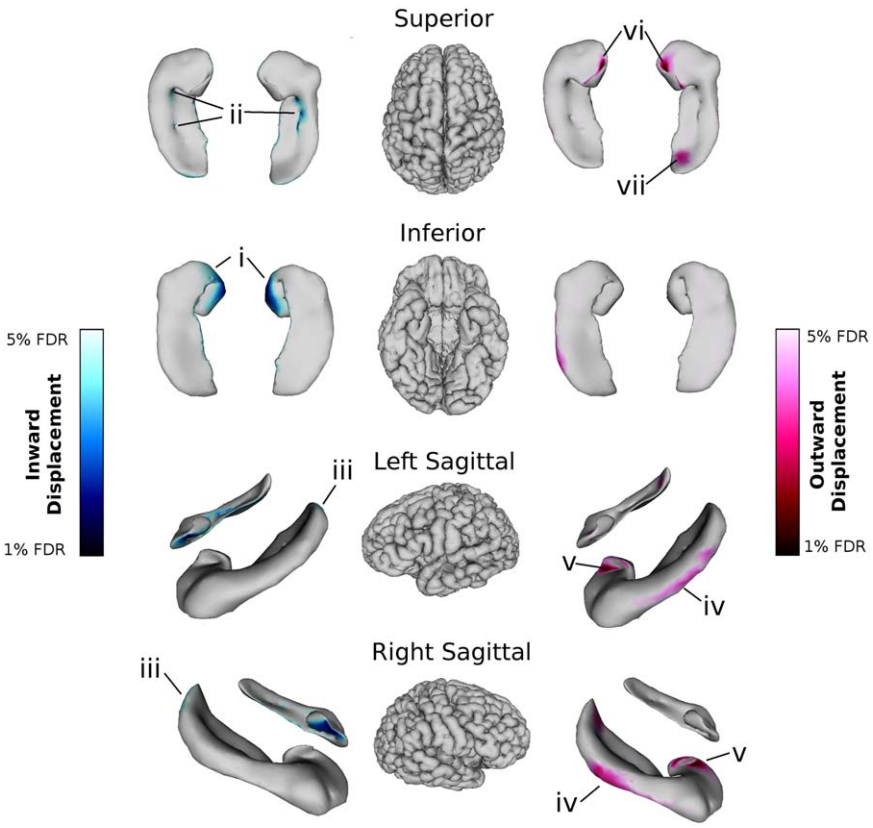

Figure 4.

Relationships between right and left whole hippocampal shape and age (with sex, years of education, and APOE ϵ4 carrier status included in the model). Blue colour maps on the hippocampal surfaces indicate inward displacement after 1–5% FDR correction; red colour maps indicate outward displacement after 1–5% FDR correction. In both hemispheres, inward displacement was localized in (i) the inferior and medial hippocampal head (anterior subiculum and inferior SR/SL/SM of the hippocampal uncus); (ii) the medial hippocampal body (along the CA1-CA4/DG border); and (iii) the tip of the hippocampal tail (posterior CA1). Outward displacement in both hemispheres was localized to (iv) the lateral hippocampal body (CA1); (v) the lateral edge of the uncus in the hippocampal head (SR/SL/SM); and (vi) the base of the uncus (CA1). (vii) In the right hemisphere only, outward displacements were also observed on the superior tail (a region including parts of the CA4/dentate gyrus, SR/SL/SM, and CA1).

DOF = 124, $t = 2.56$) (Fig. 4). Table IV summarizes all results of local morphometry analyses. Patterns of inward and outward displacement were mainly symmetric along both hippocampi. In both hemispheres, inward displacement was localized in the inferior and medial hippocampal head (anterior subiculum and inferior SR/SL/SM of the hippocampal uncus; Fig. 4 i), the medial hippocampal body (along the CA1-CA4/DG border; Fig. 4 ii), and the tip of the hippocampal tail (posterior CA1; Fig. 4 iii). Outward displacement in both hemispheres was localized to the lateral hippocampal body (CA1; Fig. 4 iv), the lateral edge of the uncus in the hippocampal head (SR/SL/SM; Fig. 4 v), and the base of the uncus (CA1; Fig. 4 vi). In the right hemisphere only, outward displacements were also observed on the superior tail (a region including parts of the CA4/dentate gyrus, SR/SL/SM, and CA1; Fig. 4 vii).

Relationship of Local Morphometry with APOE ε4 Status

Local morphological relationships based on APOE ϵ4 status were analyzed (Table IV). At the 5% FDR level, no relationships were significant; however relationships were found at a more liberal correction of 10% FDR (Fig. 5). Inward surface displacements were observed in both the right (DOF = 124, $t = 2.43$) and left hippocampi (DOF = 124, $t = 2.58$) in ϵ4 carriers relative to noncarriers along the medial hippocampal head, especially the base of the hippocampal uncus (CA1; Fig. 5 i), the anteromedial portion of the hippocampal body (CA2/CA3; Fig. 5 ii), and the medial side of the hippocampal uncus (SR/SL/SM; Fig. 5 iii). The area of significant inward displacement in the hippocampal head was larger in the right hemisphere than the left. Outward surface

TABLE IV. Summary of all local morphometry statistical tests.

Variable of Interest	Covariates	Structure	FDR	*t*-stat
Age	Sex, education, APOE ϵ4 status	Right whole	5%	2.47
Age	Sex, education, APOE ϵ4 status	Left whole	5%	2.56
APOE ϵ4 status	Age, sex, education	Right whole	10%	2.43
APOE ϵ4 status	Age, sex, education	Left whole	10%	2.58
List Recall/Figure Recall/LNS	Age, sex, education, APOE ϵ4 status	Right/left whole	10%	-

All tests had 124 degrees of freedom. Note: Although 5% FDR was set as the threshold for significance throughout this manuscript, 10% FDR is presented for the APOE ϵ4 and cognition results, as only trend-level results survive correction for multiple comparisons in these tests

displacements were also observed in both hemispheres in the hippocampal head, particularly on the anterior portion of the inferior surface (subiculum; Fig. 5 iv) and the inferior surface of the uncus (SR/SL/SM; Fig. 5 v). Some outward displacements were also observed on the lateral surface of the uncus in both hemispheres (SR/SL/SM; Fig. 5 vi).

Relationship of Volumetric Measures with Episodic and Working Memory Performance

A greater left CA4/DG volume was associated with a higher figure recall score ($R^2 = 0.060$, $P = 0.027$) (Table III), but this relationship did not survive FDR correction at the 5% level. Similarly, a greater right CA2/CA3 volume was associated with a higher LNS score ($R^2 = 0.037$, $P = 0.019$), but not after correcting for multiple comparisons. Direct correlations between cognitive scores and hippocampal volumes (no covariates) are reported in Supporting Information Table S1.

Relationship of Local Morphometry with Episodic and Working Memory Performance

No significant local shape differences were found that explained LNS, list recall, or figure recall performance after correction at 5% FDR (or at a more liberal 10% FDR threshold) (Table IV).

Relationship of Global Morphometry to Age and Memory Performance

The first PC of the whole left hippocampus (eigenvalue = 4.92), which identifies an elongation along the anterior–posterior axis, explained 65% of the variance in the data and showed a significant linear relationship with LNS test performance ($R^2 = 0.066$, $q = 0.021$) (Table V), even after FDR correction at the 5% level. The patterns of the shape distribution for the top three right and left PCs are shown in Figure 6. The first PC of the whole right hippocampus (eigenvalue = 5.40) has a significant relationship with age ($R^2 = 0.045$, $P = 0.0094$), and the third right PC (eigenvalue = 3.05) has a significant relationship with figure recall performance ($R^2 = 0.041$, $P = 0.015$); however neither of these associations survives FDR correction. The GLM was repeated for the first left PC with only right-handed subjects, and the results remained significant ($R^2 = 0.073$, $q = 0.029$).

DISCUSSION

We conducted a comprehensive examination of hippocampal morphology across the adult lifespan, and then assessed relationships among age, shape, and episodic and working memory performance. Relationships between age and hippocampal volumes were found, but not between cognitive scores and hippocampal volumes. Relationships were also found between age and hippocampal shape, both using local (univariate, vertex-wise), and global (multivariate, principal component analysis) indices of hippocampal shape. In addition, relationships were found between global hippocampal shape and cognition. These results suggest that hippocampal shape may be a more informative biomarker of age- and cognition-related effects on the hippocampus than subfield volume. After 5% FDR correction, none of the subfield volumes predicted episodic or working memory performance. In contrast, hippocampus shape analysis provided a significant relationship with working memory performance, consistent with prominent age-related effects on shape. The first principal component characterizing left hippocampal shape, an elongation along the antero-posterior axis of the hippocampus, significantly predicted working memory performance across the adult lifespan.

Overall, our findings suggest that people with healthy ("normal") cognitive aging have relatively preserved hippocampal subfield volumes. However, hippocampal shape appears to provide unique information regarding age and cognition effects on hippocampal morphometry. Specific shape changes may serve as a novel biomarker of working memory performance in a normal aging population. Shape analysis using local vertex-wise metrics also provided substantive findings in relation to age. We found considerable age-related bilateral inward and outward displacement.

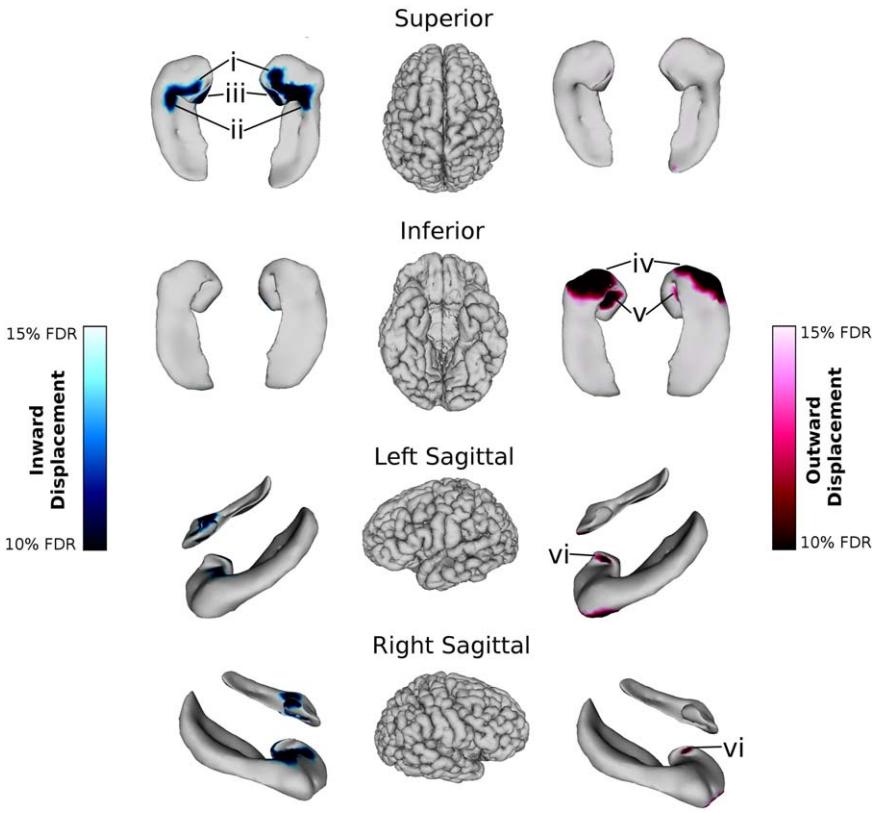

Figure 5.

Relationships between right and left whole hippocampal shape and APOE4 ϵ4 status (with age, sex, and years of education included in the model) in ϵ4 carriers relative to noncarriers. Blue colour maps on the hippocampal surfaces indicate inward displacement after 10–15% FDR correction; red colour maps indicate outward displacement after 10–15% FDR correction. Inward surface displacements were observed in ϵ4 carriers relative to noncarriers along the medial hippocampal head, especially (i) the base of the hippocampal uncus (CA1); (ii) the anterior medial portion of the hippocampal body (CA2/CA3); and (iii) the medial side of the hippocampal uncus (SR/SL/SM). Outward surface displacements were also observed in both hemispheres in the hippocampal head, particularly on (iv) the anterior portion of the inferior surface (subiculum); and (v) the inferior surface of the uncus (SR/SL/SM). (vi) Some outward displacements were also observed on the lateral surface of the uncus in the left hemisphere (SR/SL/SM).

These results are consistent with the only other adult lifespan study of hippocampal shape [Yang et al., 2013]. However, that study did not include cognitive data or APOE ϵ4 genotype data. With respect to cognitive data, we found that the first principal component explained most of the variance of left hippocampal shape (which

TABLE V. Summary of principal components on the right and left whole hippocampus from the global shape analysis.

Principal component	Eigenvalue	Variance explained	Linear variables	$R^{2\ (\text{Estimate})}$	*t-stat (p)*	*q*
Right PC1	5.40	74.19%	Age	0.045 (-2.01×10^{-4})	−2.64 (0.0094)	0.056
Right PC2	3.24	9.59%	—	—	—	—
Right PC3	3.05	7.51%	Figure Recall	0.041 (9.08×10^{-4})	2.47 (0.015)	0.13
Left PC1	4.92	65.23%	LNS	0.066 (1.60×10^{-3})	3.33 (0.0012)	0.021*
Left PC2	3.23	12.10%	—	—	—	—
Left PC3	3.02	9.33%	—	—	—	—

*Indicates significance after 5% FDR correction ($q < 0.05$)

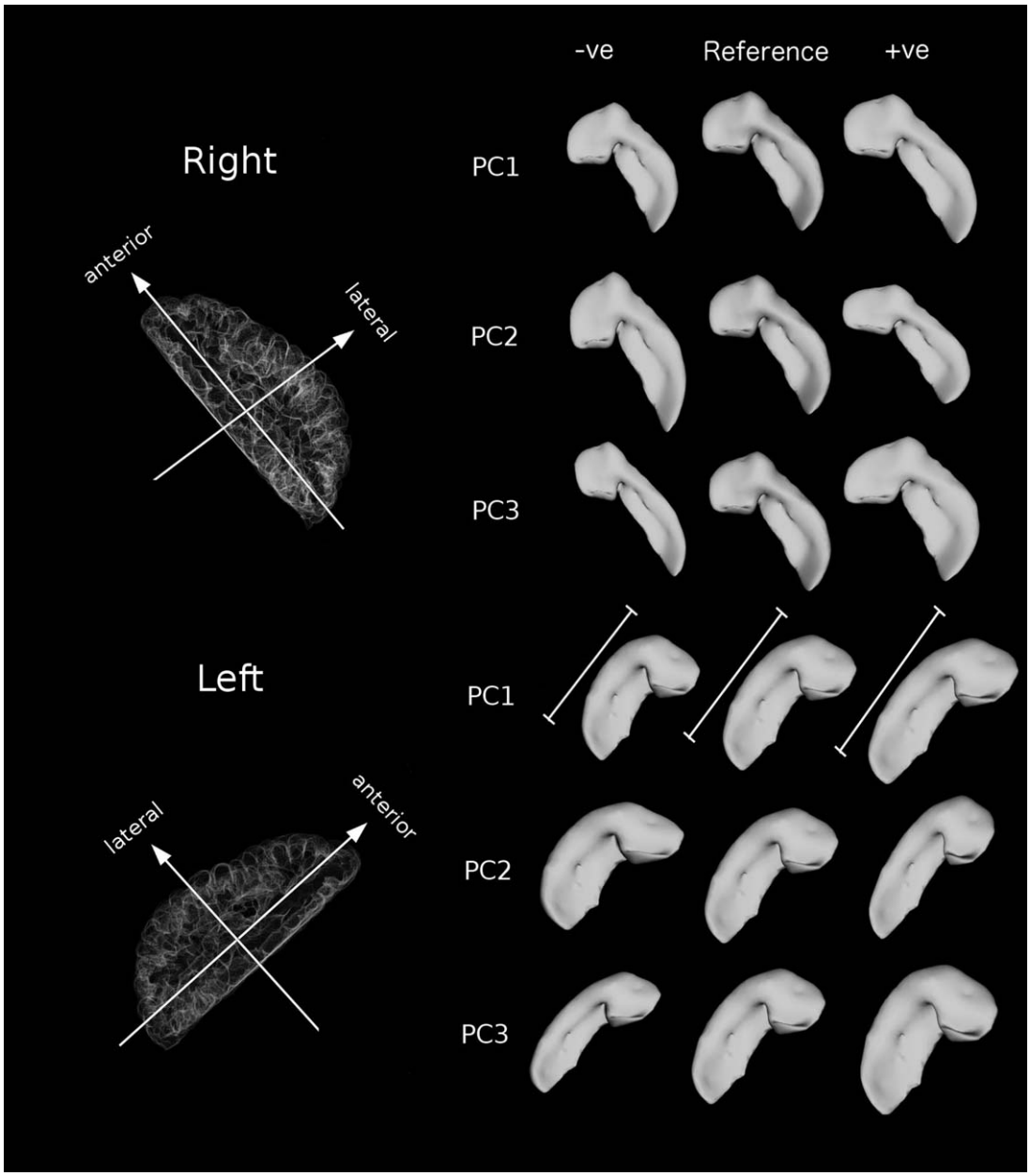

Figure 6.

Shape principal components (PCs) of the right and left whole hippocampus viewed from above (axial). The "reference" shape is from the hippocampal model (created from 5 manually segmented atlases), and "–ve" and "+ve" indicate negative and positive PC contributions to the hippocampal model, respectively. The first PC on the left side explained 65% of the variance in the data, and showed a significant linear relationship with LNS test performance ($R^2 = 0.066$, $q < 0.021$). This PC represents a lengthening along the anterior–posterior axis (results have been normalized for volume). The first right PC explained 74% of the variance in the data, and showed a significant relationship with age ($R^2 = 0.045$, $P = 0.0094$), but this did not survive correction for multiple comparisons. This PC also represents a lengthening along the anterior–posterior axis of the hippocampus. The third right PC explained 7.5% of the variance in the data, and showed a significant relationship with figure recall performance ($R^2 = 0.041$, $P = 0.015$), but this relationship did not survive correction for multiple comparisons. This PC represents a thickening along the medial-lateral axis of the hippocampus.

shows a longer longitudinal axis), and significantly predicted working memory performance. Although working memory performance (a composite of executive function, attention, and memory) is classically considered a frontally based task, considerable evidence supports a prefrontal-hippocampal circuit, or a prefrontal-parietal-hippocampal circuit [Oztekin et al., 2009b] as one of the main neural mechanisms underlying working memory performance. Verbal working memory is also supported by a medial temporal lobe—prefrontal circuit [Oztekin et al., 2009a]. Therefore, a longer or wider hippocampal axis may provide more surface area for projections to cortical regions, which can support working memory performance. The hippocampus has rich connectivity within the medial temporal lobe [Yassa et al., 2010], among subfields, and to the anterior thalamus (as part of the so-called Papez circuit) [Bezaire and Soltesz, 2013; Bennett et al., 2014], and may be under influences of many of the similar mechanisms that shape the geometry of the neocortex. The surface area and the complexity of the human cerebral cortex have been postulated to be a result of, in part, the rate of neuronal proliferation and programmed cell death of neurons through the neurodevelopemental period. These neurons migrate from the ventricular zone, across the intermediate zone on a scaffold of radial glia, and then go on to differentiate into neuronal subtypes that allow for the laminar organization of the cerebral cortex [Rakic, 1988]. Increased surface area has been hypothesized to be one of the substrates for increased short- and long-range cortical connectivity [Rakic, 1988; Van Essen, 1997]. Since the hippocampus is one of the best-preserved structures throughout vertebrates in nature, it is likely to be partly governed by many processes similar to the ones described above [Eckenhoff and Rakic, 1984]. Therefore, although purely speculative, the lengthening of the long axis of the hippocampus (which is likely to correspond to an increase in surface area) may also be indicative of enhanced intrastructural and/or extrastructural connectivity. The hippocampal head shows connections to the white matter in the amygdala and uncinate fasciculus and in other regions including the prefrontal cortex [Travis et al., 2014]. Furthermore, posterior hippocampal activity has been correlated with cingulate, precuneus, and inferior parietal cortical activity [Travis et al., 2014]. Future work investigating anatomical relationships between hippocampal shape and cortical regions may help further improve our understanding of network-based 'connectivity' mechanisms underlying working memory performance.

Only modest relationships of hippocampal subfield volumes with age were found. In particular, there was an absence of a relationship between the CA1 subfield and age after correction for multiple comparisons. In contrast, others have reported a decreased CA1 subfield volume in people with Alzheimer's disease [Mueller et al., 2010; Kerchner et al., 2012] and mild cognitive impairment [Mueller et al., 2010; Pluta et al., 2012] compared to healthy controls. Such a decrease has also been reported in older healthy individuals compared to younger healthy individuals [Mueller et al., 2007]. Others have shown that age-related changes in CA1 may be dependent on the presence of hypertension [Shing et al., 2011], rather than being directly due to age itself. However, studies of older apparently healthy individuals typically include a heterogeneous group, with some subjects in a preclinical pathological aging stage: in these subjects, neuroimaging can detect preclinical disease change, or predict onset of Alzheimer's disease using CA1 subfield volume [Apostolova et al., 2010; Devanand et al., 2012]. CA1 volume data from our sample of healthy, carefully screened subjects provides support for preserved CA1 volume as a marker of healthy aging. In contrast, all other subfields had significant, although modest, negative relationships with age. This includes the CA4/DG subfield which is typically considered as a subfield spared from the effects of pathological aging, at least in early phases, yet one that is consistently shown to decrease in volume in healthy aging [Mueller and Weiner, 2009; Small et al., 2011]. Furthermore, unlike the CA1 volume, DG volume does not appear to be a predictive marker of conversion to Alzheimer's disease. One could view the similar rates of decrease across these subfield regions in our sample as supporting potentially shared mechanisms of age-related change in these subfields. However, modest, rather than strong, relationships with age are not surprising given that cell numbers are preserved in normal aging in humans, nonhuman primates and rodents in the principal cell types of the hippocampus (granule cells, CA1 and CA3 pyramidal cells) [Samson and Barnes, 2013].

We were surprised to find only a weakly significant correlation between total brain volume (TBV) and hippocampal volumes. While this may be a somewhat unexpected finding, it is difficult to compare this result to other results in the field due to methodological differences in brain volume correction, the use of total intracranial volumes (rather than TBV) in many cases, and the infrequent explicit examination of the correlation of total brain and hippocampal volumes [Fjell et al., 2013]. Many studies use the intracranial volume (ICV) measure similar to the total intracranial volume (TIV) measure developed by Buckner et al., which is well-correlated with manually segmented volumes that account, in part, for TBV using an automated estimate [Buckner et al., 2004]. In Buckner's work, hippocampal volume is shown to be directly correlated with the TIV [Buckner et al., 2004]. However, other more recent publications that use this measure do not explicitly report correlations among ICV, brain volume, and hippocampal volumes [Fjell et al., 2013; Krogsrud et al., 2014]. In publications where these correlations are not directly reported, it is possible to infer the presence or absence of a relationship among these variables based on whether volumetric relationships of the hippocampus with age do or do not change following normalization for TBV. For instance, in a recent paper by Li et al., normalization by TBV did not

change the direction of the slopes of the hippocampal volume vs. age relationship in a lifespan analysis [Li et al., 2014]. However in other studies, the inclusion of brain volume in the analysis completely changes the direction of the effect, suggesting correlation between the measures [Maller et al., 2006].

With respect to APOE genotype, we were somewhat surprised that we did not find any significant effect of ϵ4 carrier status on hippocampal and subfield volume and only trend-level relationships (10% FDR) with respect to shape. Our findings align with some groups [Morra et al., 2009], but not with others [Mueller and Weiner, 2009]. In addition, some studies have shown age-dependent effects of ϵ4 status across the adult lifespan [Felsky and Voineskos, 2013; Nichols et al., 2012].

It should be noted that other groups that perform manual and automated segmentation of the hippocampal subfields have done so using T2-weighted [Kerchner et al., 2010, 2013; Mueller et al., 2007, 2009, 2010; Pluta et al., 2012; Winterburn et al., 2013; Wisse et al., 2013] or proton density images [De Flores et al., 2015; La Joie et al., 2010, 2013; Raz et al., 2014; Shing et al., 2011]. While this has been an extremely useful addition to the field, many of these techniques only segment a small subset of the hippocampus along the anterior–posterior axis [Kerchner et al., 2010, 2013; Mueller et al., 2007, 2009, 2010; Raz et al., 2014]. In addition, many of these acquisitions are high resolution in the coronal plane but are acquired with a slice thickness of 2–3 mm. While we previously demonstrated the feasibility of automated segmentation of the subfields on standard T1-weighted segmentations through a simulation [Pipitone et al., 2014], we further note that these experiments in the original validation used images with 0.9 mm isotropic voxels measured at 3T. Nonetheless, previous studies from our group [Pipitone et al., 2014; Treadway et al., 2015] and by others who have adopted the Winterburn protocol demonstrate the feasibility of its implementation in a wide range of applications [Iglesias et al., 2015; Winterburn et al., 2013].

Our study was the first, to our knowledge, to assess the relationship of either hippocampal subfield volumes or hippocampal shape metrics with cognitive performance across the adult lifespan. The different aspects of cognitive performance that we assessed were susceptible to the effects of age to varying degrees. However, we did not find significant age-specific effects of whole hippocampal or subfield volumes on these cognitive functions. Only modest variance in visuospatial memory performance (figure recall) was explained by the CA4/DG subfield (e.g., the left CA4/DG explained 6% of the variance) and this finding did not survive corrections for multiple comparisons. Likewise, the right CA2/CA3 subfield explained 3.7% of the variance in working memory, but the relationship did not survive correction for multiple comparisons. Both animal studies and more recent human neuroimaging studies have attempted to clarify the function of individual subfields in relation to memory performance. For instance, pattern separation and completion (functions that support visuospatial memory) by DG and CA3 has been shown [Bakker et al., 2008; Leutgeb et al., 2007; Yassa et al., 2010]. This demonstrated function of these subfields aligns with our finding of DG subfield volume providing modest explanation of the variance in visuospatial memory performance. Subjects were asked to draw the Rey–Osterrieth figure from memory, which is a complicated diagram requiring pattern separation and completion ability. Conversely, novelty detection and allocentric encoding is considered a function of the CA1 subfield [Suthana et al., 2009]. We did not, however, find a relationship with CA1 volume and any type of memory performance. It is worth noting that much of our knowledge of specific subfield function emerges from mouse and rat studies [Brun et al., 2002, 2008; Mizumori et al., 1989]. The standard paper and pencil neurocognitive tests in humans that we used may not be adequately designed to reflect functions such as allocentric encoding.

The relationships between hippocampal shape and cognitive performance were consistent in both younger and older adults. Others have shown that compensatory neural mechanisms help ensure normal cognitive performance in healthy aging populations [Raz and Rodrigue, 2006; Raz et al., 2005; Sullivan and Pfefferbaum, 2006; Voineskos et al., 2012], rather than preservation of regions important for cognitive performance in young adult life. It is possible that our subjects who were in their seventh, eighth, or ninth decade of life, without experiencing mild cognitive impairment or a dementia, may exhibit compensatory brain change in other regions. There is considerable evidence for such changes in the cortex of healthy older individuals [Raz et al., 1997, 2005]. Other compensatory changes can also occur in white matter fiber connections [Voineskos et al., 2012], which can help ensure normal cognitive performance in aging, particularly in the executive function/working memory domain [Sullivan and Pfefferbaum, 2006; Voineskos et al., 2012].

Some limitations of our study deserve consideration. Hippocampal subfield definition and measurement remain ongoing sources of disagreement and technical challenge respectively [Winterburn et al., 2013; Yushkevich et al., 2009, 2010, 2015]. We used a CA2/CA3 subfield and a CA4/DG subfield among our subfield classifications, and challenges in differentiating CA3 from the DG have been described, with CA2/CA3 and DG often considered together [Carr et al., 2010; Chakeres et al., 2005]. Given the role of CA3 in pattern completion and rapid and flexible acquisition of spatial memories [Lavenex and Banta Lavenex, 2013], it is possible that the CA3 subfield may in part contribute to our finding that the CA4/DG subfield explained 6% of the variance in visuospatial memory performance. However, we have previously demonstrated that the CA4/DG subfield can be segmented with excellent reliability [Winterburn et al., 2013]. Also, the very existence of a CA4 as defined by *Duvernoy* [Duvernoy, 2005] is widely debated within the field, and is often included as

the dentate hilus [Adler et al., 2014]. Although we have previously demonstrated good reliability of subfield segmentations, some regions such as the CA2/CA3 region are less well-reliably segmented [Winterburn et al., 2013]; this is not surprising due to its overall size and thickness in comparison to the resolution of standard T1-weighted MR imaging data. For those subfields, use of a higher field scanner might have further improved resolution, and thus subfield segmentation accuracy. In turn, discovery of relationships among subfield volume and cognitive performance may have been facilitated. Although the relationships of hippocampal subfield volume and shape with memory performance that we did find were consistent across the adult lifespan, our study was cross-sectional and not longitudinal. While our older individuals were no different from our younger individuals in sex and education, cross-sectional studies may be subject to a cohort effect. Furthermore, it remains an open question of whether variability of brain morphometry and cognitive measures is greater in late adult life compared to early adult life [Raz and Lindenberger, 2011; Salthouse, 2011]. These factors might limit the capability of a study such as ours to determine associations between brain morphometry and cognitive performance.

Other studies have found more pronounced differences in subfield volume or shape in older vs. younger individuals, or relationships with age of greater negative magnitude [Mueller and Weiner, 2009; Mueller et al., 2007; Yang et al., 2013]. One possible explanation for our findings of a more limited relationship between age and hippocampal subfield volumes may be the preserved health and cognition of our older subjects, as documented by a detailed assessment. Therefore, one interpretation is that preserved hippocampal subfield volumes may be important for successful cognitive aging. Our finding that the brain–behavior relationships in the hippocampus in our sample are similar in our younger and older subjects further supports this interpretation.

The interpretation of results based on local and global shape measures may not be as intuitive as those based on volumetric measures. Volume measures are sometimes thought of as a proxy for total neuronal or overall cell counts; however, there is little evidence for this in the human MR literature and limited supporting evidence in the murine MR literature [Lerch et al., 2008, 2011]. There has been support in recent reports that the shape of subcortical structures represents a neurodevelopmental phenotype [Chakravarty et al., 2015; Raznahan et al., 2014; Shaw et al., 2014a, 2014b]. However, given the variability of brain anatomy in the late stages of life and the potential influence of genetic, lifestyle, and environmental factors, it is unclear whether the shape descriptions in our manuscript can truly be considered neurodevelopmental.

In summary, our study is the first examination of the relationship among hippocampal subfield volumes, hippocampal shape, and memory performance across the adult lifespan. We observed modest relationships between subfield volumes and age, as well as episodic and working memory performance. In contrast, characteristics of hippocampal shape emerged as the most powerful predictors of hippocampal-dependent cognitive performance. Several interventions have been shown to change hippocampal structure and function [Engvig et al., 2012; Erickson et al., 2011; Kuhn et al., 2013; Pajonk et al., 2010]. Thus, our findings may help to select the interventions that specifically preserve aspects of hippocampal shape important for working memory performance. Such a strategy to attempt to prolong healthy aging and delay the onset of dementia would not be an exclusive one, but rather complementary to other strategies that currently target compensatory structures or networks that are involved in successful cognitive aging.

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