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APOE Related Hippocampal Shape Alteration in Geriatric Depression

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Abstract

Late-onset depression often precedes the onset of dementia associated with the hippocampal degeneration. Using large deformation diffeomorphic metric mapping (LDDMM), we evaluated apolipoprotein E epsilon-4 allele (apoE E4) effects on hippocampal volume and shape in 38 depressed patients without the apoE E4, 14 depressed patients with one apoE E4, and 31 healthy comparison subjects without the apoE E4. The hippocampal volumes were manually assessed. We applied a diffeomorphic template generation procedure for creating the hippocampal templates based on a subset of the population. The LDDMM mappings were used to generate hippocampal shapes for each subject and characterize the surface deformation of each hippocampus relative to the template. Such deformation was modeled as random field characterized by the Laplace-Beltrami basis functions in the template coordinates. Linear regression was used to examine group differences in the hippocampal volume and shape. We found that there were significant hippocampal shape alternations in both depressed groups while the groups of depressed patients and the group of healthy subjects did not differ in the hippocampal volume. The depressed patients with one apoE E4 show more pronounced shape inward-compression in the anterior CA1 than the depressed patients without the apoE E4 when compared with the healthy controls without the apoE E4. Thus, hippocampal shape abnormalities in late-onset depressed patients with one apoE E4 may indicate future conversion of this group to AD at higher risk than depressed patients without the apoE E4.

Keywords

hippocampal shape; geriatric depression; APOE; diffeomorphic mapping

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Introduction

Magnetic resonance (MR) based volumetric assessment of the hippocampus has been widely employed in normal aging, neurodegenerative diseases, and neuropsychiatric disorders, including mild cognitive impairment, Alzheimer's disease (AD), schizophrenia and major depression (Convit et al., 1997, Pantel et al., 1997, Jack et al., 1998, Steffens et al., 2000, Cardenas et al., 2003, Frisoni et al., 2006, Whitwell et al., 2007). In particular, hippocampal volume loss has been identified to be one of the hallmarks of AD. In advanced analysis using brain warping techniques, neuroimaging studies previously found different patterns of hippocampal shape changes associated with stages of AD (Csernansky et al., 2004, Apostolova et al., 2006, Wang et al., 2006).

The hippocampus formation connects frontal and limbic areas that are implicated in the development of depressive symptoms. MR based volumetric assessment of the hippocampus has been used to study the hippocampal volume in patients with geriatric depression (Krishnan et al., 1991, Pantel et al., 1997, Steffens et al., 2000), primarily pursuing the hypothesis that late-onset geriatric depression would be associated with smaller hippocampal volumes. These studies have yielded conflicting results, where some have found smaller hippocampal volumes in depressed elders, while others found no difference between depressed and comparison cohorts. These discrepancies may be due to methodological differences in hippocampal anatomical definitions or differences in the populations studied, which could reflect the underlying biological heterogeneity of Major Depressive Disorder. One potential source of this heterogeneity has been suggested in the observation that late-onset depression often precedes onset of dementia, particularly AD (Jorm et al., 1991, Kokmen et al., 1991, Speck et al., 1995, Steffens et al., 1997). Thus one would expect changes in hippocampus similar to that seen in AD, which has been discussed in recent hippocampal shape study in geriatric depression (Zhao et al., 2008).

Against this background, this study sought to determine the role of apolipoprotein E epsilon-4 allele (apoE E4), a risk allele for AD, in hippocampal shape abnormalities in late-onset depression. We hypothesized that the group of depressed patients with one apoE E4 may show more pronounced hippocampal shape abnormalities than the group of depressed patients without the apoE E4, especially in hippocampal subregions indicating the conversion of AD. To achieve this, we explored the hippocampal volume and shape in the populations of elderly depressed patients with or without the apoE E4 and a cohort of healthy elders without the apoE E4 using brain mapping technique, large deformation diffeomorphic metric mapping (LDDMM) whose sensitivity and robustness for characterizing structural variations across subjects have been demonstrated in several studies (Miller et al., 2005, Qiu et al., 2007, Vaillant et al., 2007, Qiu et al., 2008c).

Methods

Subjects

31 healthy elders without an apoE 4 allele, 38 depressed elders without an apoE 4 allele, and 14 depressed elders with one apoE 4 allele were included in this study. All subjects were recruited from individuals enrolled in the Conte Center for the Neuroscience of Depression at Duke University. Subjects were age 60 years or older; exclusion criteria included psychiatric diagnoses other than Major Depressive Disorder, substance abuse or dependence, primary neurological disease of dementia, and contraindications to MRI. The presence of comorbid generalized anxiety disorder symptoms did not prohibit enrollment if the evaluating clinician determined they were secondary to the depression diagnosis.

At time of enrollment into the Conte Center, depressed subjects met DSM-IV criteria for Major Depressive Disorder (MDD). This diagnosis and the absence of exclusionary diagnoses were evaluated with the NIMH Diagnostic Interview Schedule (DIS) (Robins et al., 1981), which assessed major depression and age of onset of first depressive episode, enriched with items assessing lifetime history of psychosis, mania, anxiety disorders, and substance abuse or dependence. Subjects were additionally assessed through a clinical interview with a geriatric psychiatrist to assure they did meet DSM-IV criteria for MDD and that other exclusionary psychiatric disorders including post-traumatic stress disorder were absent. Subjects had to meet DSM-IV criteria for MDD both through the DIS interview and the clinical interview to be participate in the Conte Center. This clinical interview also assessed for a history of dementia or cognitive and functional deficits supporting such a diagnosis. Individuals with a diagnosis of dementia or where it was suspected based on clinical history were not enrolled.

Nondepressed control subjects were community volunteers with a non-focal neurological examination and no evidence for depression or other neuropsychiatric disease on the DIS. The study was approved by the Duke University Health System Institutional Review Board, and all subjects provided written informed consent.

After enrollment in the Conte Center, depressed subjects received antidepressant treatment provided by a study geriatric psychiatrist. This algorithm-based treatment was personalized to the individual subject and followed the Duke STAGED approach (Steffens et al., 2002). In this treatment algorithm, all commercially available antidepressant medications were available. Typically treatment begins with a selective serotonin reuptake inhibitor, unless an individual's past history shows a history of lack of response or intolerance to that class of drug.

In addition to the use of the DIS for confirming the clinical diagnosis of Major Depression, demographic data were obtained through subject interview. Depression severity at time of MRI was assessed using the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) was used to assess global cognitive function; subjects who scored less than a 24 were excluded.

We have previously used these data in a shape analysis examining difference between healthy control subjects and remitted and nonremitted depressed subjects (Zhao et al., 2008). The current sample is smaller as 5 control subjects and 16 depressed subjects from the previous study did not provide a blood sample for genetic analyses.

Genotyping

Subjects underwent phlebotomy to obtain a blood sample for APOE genotyping. White blood cells were processed and APOE genotypes determined using previously described methods (Saunders et al., 1993).

Image Acquisition

All subjects were imaged using a 3.0Tesla whole-body Trio MRI scanner. A T1-weighted turbo-flash pulse sequence acquisition (TR/TE/Flip=22/7/25°, FOV=256mm, 160 slices, $1\times1\times1mm^3$) was obtained in a coronal oblique plane particularly designed for the segmentation of the amygdala-hippocampus complex.

Image Processing

Hippocampal Delineation—The hippocampus was delineated from MR images using the GRID program (MacFall et al., 1994). In the GRID interface, all MRI scans were manually aligned into the anterior commissure (AC) and posterior commissure (PC) space. The manual

tracing of the hippocampus was examined in the coronal sections. The most posterior coronal slice was determined when the pulvinar nucleus of the thalamus obscured the crura fornicis and the most anterior coronal slice was defined as one slice before the slice where the inferior lateral ventricles appeared horizontally. The anatomical definition of the hippocampus in the other coronal slices has been previously described (Steffens et al., 2000). The number of voxels scaled with the image resolution was computed as the *hippocampal volume* measurement. Notice that this method does not include the more posterior component of the body nor the tail. Reliability was established using data from ten subjects (six depressed and four control subjects) involving blinded repeated measurement of hippocampal volume separated by at least one week. This was done by a single analyst who also performed all hippocampal delineations for the study. Intraclass correlation coefficients attained were: left hippocampus = 0.99, right hippocampus = 0.98.

Template Generation—Template-based brain mapping techniques have been successful in describing anatomical variations between a collection of anatomies and a template. The template is often represented by a healthy control subject from the population being studied. The difficulties with this approach are that the template may not be truly representative of the population. Wide variation of the anatomy across subjects relative to the template may cause the failure of the mapping. Thus, one of the fundamental limitations of choosing the anatomy of a single subject as a template is the introduction of a statistical bias based on the arbitrary choice of the template anatomy. To avoid this issue, a representative structural shape created based on the shapes of a population is considered as a reasonable template for shape analysis.

In this study, we generated the left and right hippocampal template based on 10 healthy subjects without an apoE 4 allele (5 males and 5 females) and 10 depressed patients without an apoE 4 allele (2 males and 3 females) and with an apoE 4 allele (3 males and 2 females) using a diffeomorphic template generation algorithm (Qiu, 2008). The reason for not using the whole dataset to create a hippocampal template is partly because of the computational time. To ensure that the estimated template has a representative shape of the population, we sampled these 20 subjects in the way such that their hippocampal volumes are uniformly distributed between the minimal and maximal values of the hippocampal volumes in our population. During the template estimation process, the most anterior and posterior coronal slices of the hippocampus were considered as landmarks across all subjects to remove translation and scaling in the coronal axis. The hippocampal templates were generated via the diffeomorphic template generation procedure that statistically estimates the mean deformation among the population (Qiu, 2008). Figure 1 shows their surface representation in both inferior and superior views. The left and right template surfaces respectively have 2226 and 2574 vertices.

Shape Processing—The manual labeled hippocampal volumes were not eligible to directly examine shape comparison because the manual label procedure introduced random errors, including unsmoothness of the boundary and topological errors (e.g. holes). This may increase shape variation and thus reduce statistical power to detect group difference in shape. To avoid this issue, we generated the hippocampal shapes of each individual subject with properties of smoothness and topology by injecting the template shape into them using the LDDMM-image mapping algorithm(Qiu and Miller, 2008). Each hippocampal volume was approximated by the transformed template through the diffeomorphic map found in the LDDMM-image mapping. The smooth volume is highly overlapped with its manual segmentation (volume overlap ratio: 0.917 (±0.007) for the left; 0.919 (±0.006) for the right). Its surface representation was created by composing the diffeomorphic map on the template surface. The mathematical derivation of this template injection procedure and its evaluation on a variety of subcortical structures have been detailed elsewhere (Qiu and Miller, 2008).

We then applied the LDDMM-surface mapping algorithm(Vaillant and Glaunes, 2005, Vaillant et al., 2007) to map the template surface to each hippocampal surface. The Jacobian determinant of the deformation in the logarithmic scale was computed in the local coordinates of the template for statistical shape comparison across clinical populations. We shall call the logarithmic scale of the Jacobian determinant as *deformation map*. Its value represents the ratio of subject's hippocampal volume to the template volume in the logarithmic scale: i.e. positive values correspond to the expansion of subject's hippocampus relative to the template at a particular location, while negative values denote the compression of subject's hippocampus relative to the template.

Statistical Testing on Shapes—We assume the deformation map arises from a random process that is modeled as random field. It can be decomposed into a linear combination of a set of basis functions in the form of

$$F^{(j)}(x)=\sum_{i=1}^{N} F_i^{(j)}\psi_i(x),\ x \in S_{temp}, \tag{1}$$

where $F^{(j)}(x)$ is the deformation map of subject j. $\psi_i(x)$ is the i^{th} basis function of the Laplace-Beltrami (LB) operator on the template surface, S_{temp}. $\psi_i(x)$ is deterministic and only dependent on the geometry of S_{temp} (Qiu et al., 2006, Qiu et al., 2008b). We can thus use a finite number of random variables, F_i, $i = 1,2,\ldots, N$, to represent the deformation map and examine statistical testing on F_i, $i = 1,2,\ldots, N$. N is determined based on the goodness fit at a certain discrepancy level of 0.05 such that $\frac{|\mu^i(x) - \sum_{k=1}^{N_i} F_k^i \psi_k^i(x)|^2}{|\mu^i(x)|^2} = 0.05$.

Figure 2 illustrates the 1st, 6th, 12th, 19th LB basis functions of the left hippocampal template. The 1st LB basis function (ψ_1) is constant and thus its associated coefficient (F_1) encodes the global hippocampal volume change. As moving to the higher order of the LB basis, regions with positive (warm color) or negative (cool color) values alternate. Therefore, the LB basis functions can be used to characterize uniform or nonuniform shape change over the hippocampus whose variation across subjects is encoded in the LB coefficients (F_i, $i = 1,2,\ldots, N$). Advantages for using the LB basis function to represent functions defined in the cortical surface were detailed in (Qiu et al., 2008a).

To compare the shape between any two groups, we modeled each individual F_i, $i = 1,2,\ldots, N$, using linear regression with diagnosis as main factor covarying with the total brain volume and age. Permutation testing was used to provide correct statistical results to evaluate the significance of the LB-coefficients for group comparisons of interest (Nichols and Holmes, 2002). In 10,000 randomized analyses, all subjects were mixed and randomly assigned into three groups. In each randomized analysis, the linear regression model analysis was performed on each LB-coefficient, and the t-value for the pairwise group contrast of interest was obtained. Then the highest *t*-value across the LB-coefficients was used to construct the empirical distribution of *t*-statistics, so that the resulting permutation-based threshold controlled for false positives across the entire set of the LB-coefficients. This threshold was set at a significance level of 0.05. The LB-coefficients with t-statistics above the threshold were selected to characterize the pattern of shape differences between groups.

Results

For the sake of simplicity, we shall denote the group of the healthy comparison controls without an apoE E4 as “CON”, the group of the depressed patients without an apoE E4 as “DEP”, and the group of the depressed patients with one apoE E4 as “E4 DEP”.

Sample Demographics

Table 1 lists demographic information of the subjects within the three groups. Demographic variables and clinical measures were compared using ANOVA for continuous variables and logistic regression for categorical variables. The subjects in CON and E4 DEP were older but there was no difference in sex or MMSE score between the groups. There was no difference in current depression severity between the two depressed groups. Forty-seven out of the 52 depressed subjects were on antidepressant medications at time of MRI, including selective serotonin reuptake inhibitors, venlafaxine, bupropion, and nortriptyline. There was no significant difference in concurrent antidepressant use between the two depressed groups.

Hippocampal Volume

Figure 3 illustrates the hippocampal volume measurements. Asterisks, circles, and diamonds represent the volumes of the left and right hippocampi in the groups of CON, DEP, and E4 DEP, respectively. Horizontal bars denote the locations of the hippocampal mean value in each group. The mean (standard deviation) values of the left hippocampal volumes in CON, DEP, E4 DEP are respectively 3520.2mm^3 (481.1), 3381.6mm^3 (414.9), and 3375.7mm^3 (662.9); the mean values of the right hippocampal volumes in CON, DEP, E4 DEP are respectively 3607.9mm^3 (542.0), 3620.4mm^3 (451.1), and 3533.1mm^3 (634.1).

To statistically explore effects of the depression and apoE E4 on the hippocampal volumes, we separately examined the volume comparisons between CON and DEP and between CON and E4 DEP using linear regression to model the hippocampal volumes with the diagnosis as main factor after covarying with the total brain volume and age. Our statistical results revealed no statistically significant difference in both left and right hippocampal volumes between CON and any group of depressed patients (left: DEP: p=0.1404; E4 DEP: p=0.5244; right: DEP: p=0.9118; E4 DEP: p=0.8930). No volume differences found in the comparison of DEP and E4 DEP (left: p=0.7310; right: p=0.7529).

Hippocampal Shape

We statistically investigated shape differences between CON and DEP or E4 DEP via the surface deformation maps.

Left—The first 21 LB basis functions were used to characterize the deformation maps of the left hippocampus based on the goodness fit at a discrepancy level of 0.05. The linear regression and subsequent permutation testing revealed the 19^{th} LB basis function with significant group difference in surface deformation between CON and DEP (corrected p=0.0136) after controlling the total brain volume and age. For the visualization purpose, we constructed the shape difference pattern between these two groups based on the 19^{th} LB basis function, which is illustrated in the inferior and superior views in Figure 4(a,b). The surface deformation pattern denotes the shape difference between the two groups indexed over the template surface in terms of ratio of the local hippocampal volume in CON to one in DEP. Visually, the surface patterns in Figure 4(a,b) are effects of the 19^{th} LB basis function (see the last panel of Figure 2), which best discriminates the two groups. Figure 4(a,b) suggest that the shape alteration of the left hippocampus in DEP is not uniformly distributed on the left hippocampal surface. On these maps, the subiculum accounts for a small region in the medial part of the head and body of the hippocampus, which is best seen in the inferior view in panel (a). The medial part of the head

and body in the left inferior hippocampus show the compression in DEP relative to CON while the rest was expanded in DEP. Subfield CA1 accounts for much of the hippocampal head and for lateral edges of the hippocampal body. Much of this region can be seen in panel (b) to be relatively the expansion except the medial aspect of the left hippocampal head. The dentate gyrus and subfields CA2, 3, 4 in the superior view of panel (b) were shrunk in DEP relative to CON.

The linear regression and subsequent permutation testing revealed the 12^{th} and 13^{th} LB basis functions with significant group difference in surface deformation between CON and E4 DEP (corrected p=0.0408, 0.0220). Figure 4(c,d) illustrate the shape difference between these two groups. The shape abnormalities in E4 DEP are relatively in the same pattern as shown in DEP (Figure 4(a,b)) except that the head of the left hippocampus shows the expansion in E4 DEP. Large volume reduction occurs in the anterior lateral aspect of the left hippocampus (CA1) and the medial body (subiculum, CA2,3,4) in the group of E4 DEP.

The linear regression revealed the 13^{th} LB basis function with near significant group difference in surface deformation between DEP and E4 DEP (uncorrected p=0.0645). But it was not shown as statistical significance after the correction for multiple comparisons.

Right—The first 24 LB basis functions were extracted to characterize the deformation maps of the right hippocampus based on the goodness fit at a discrepancy level of 0.05. Only the 16^{th} and 24^{th} LB basis functions (corrected p=0.0486, 0.0148) show the shape difference between CON and DEP in the linear regression testing after controlling the total brain volume and age. Figure 4(e,f) show this shape difference constructed based on these two LB basis functions. Relatively very mild shape alterations in DEP nonuniformly occur in the right hippocampus. The 19^{th} and 22^{th} LB basis functions (corrected p=0.0196, 0.0190) show the shape difference between CON and E4 DEP in the linear regression testing after controlling the total brain volume and age. Figure 4(g,h) illustrate the shape difference between these two groups constructed based on these two LB basis functions. Similar to the left hippocampus, large volume reduction occurs in the anterior lateral aspect of the right hippocampus (CA1) (panel (g)) and the body (panel (h)) in the group of E4 DEP. The rest region in cool color shows the shape expansion in E4 DEP relative to CON.

The linear regression revealed the 22^{th} LB basis function with significant group difference in surface deformation between DEP and E4 DEP (uncorrected p=0.0428). Similar to the left side, it was not shown as statistical significance after the correction for multiple comparisons.

Discussion

In this study, elderly depressed patients with or without an apoE E4 do not differ from healthy comparison subjects without an apoE E4 in the hippocampal volume but did differ markedly from them in the hippocampal shape. As there were no volume differences, the shape abnormalities in the groups of DEP and E4 DEP have the alteration pattern of compression and expansion distributed over the hippocampal templates when compared with the CON group. Relative to the hippocampal shape in CON, the hippocampal shape changes in E4 DEP are in close agreement with those in DEP. But, more pronounced shape abnormalities, including shape compression and expansion, occur in E4 DEP than in DEP. Especially, E4 DEP shows the shape compression in the anterior lateral aspect of the left and right hippocampi, most corresponding to CA1 (pointed by arrows in Figure 4(c,g). This shape alteration pattern may be useful in identifying patients with depression who will have future conversion to AD since both CA1 shape compression and presence of the apoE 4 allele have been identified as high risk factors of early AD.

The previous study (Zhao et al., 2008) using a slightly larger sample found depression-related contraction in the lateral aspect of the hippocampus that could parallel findings in AD (Scher et al., 2007). However, the apoE E4 status was not considered in this previous analysis (Zhao et al., 2008). Based on these findings, this present study focused on determining the role of the apoE E4 on hippocampal shape abnormalities in depression and explored whether depressed patients with one apoE E4 have more similar shape abnormal pattern as AD patients. In the comparison with AD, geriatric depression shows no hippocampal volume reduction in the groups of with or without an apoE E4 while there is a strong evidence of hippocampal volume reduction in patients with AD (Jack et al., 1998). Compared with healthy comparison subjects, both geriatric depression and early AD patients share the common structural abnormality in the subiculum and CA1, CA2,3,4 in the middle body of the hippocampus while middle aged depressed patients only share the abnormality in the subiculum not in CA1 (Posener et al., 2003). Several longitudinal imaging studies on AD (Wang et al., 2003, Apostolova et al., 2006) have identified the structural abnormality in CA1 as the onset of AD, which is strongly shown in the group of E4 DEP but not in the group of DEP. This may implicate the future conversion of elderly depressed patients to AD, especially those with one apoE E4. A longitudinal imaging study following up with our elderly patients is still needed to be conducted for confirming this relationship of hippocampal shape abnormalities in AD and depressed patients with apoE E4.

The study has limitations that should be noted, specifically our definition of the hippocampus. Our measure does not include the more posterior component of the body nor the tail. Thus our findings are only applicable to the head and anterior body. Additionally, the samples were not matched for potential differences such as handedness, and even slightly differed in age which itself has an effect on brain structure, although we covaried for age in our analyses. Finally, a more complete analysis could have been performed if some of the control subjects had been apoE E4 carriers.

In this study, we first reported the hippocampal shape template generated based on a group of healthy elders and elderly depressed patients. This available template will be valuable to the neuroimaging researchers, especially to those interested in depression studies.

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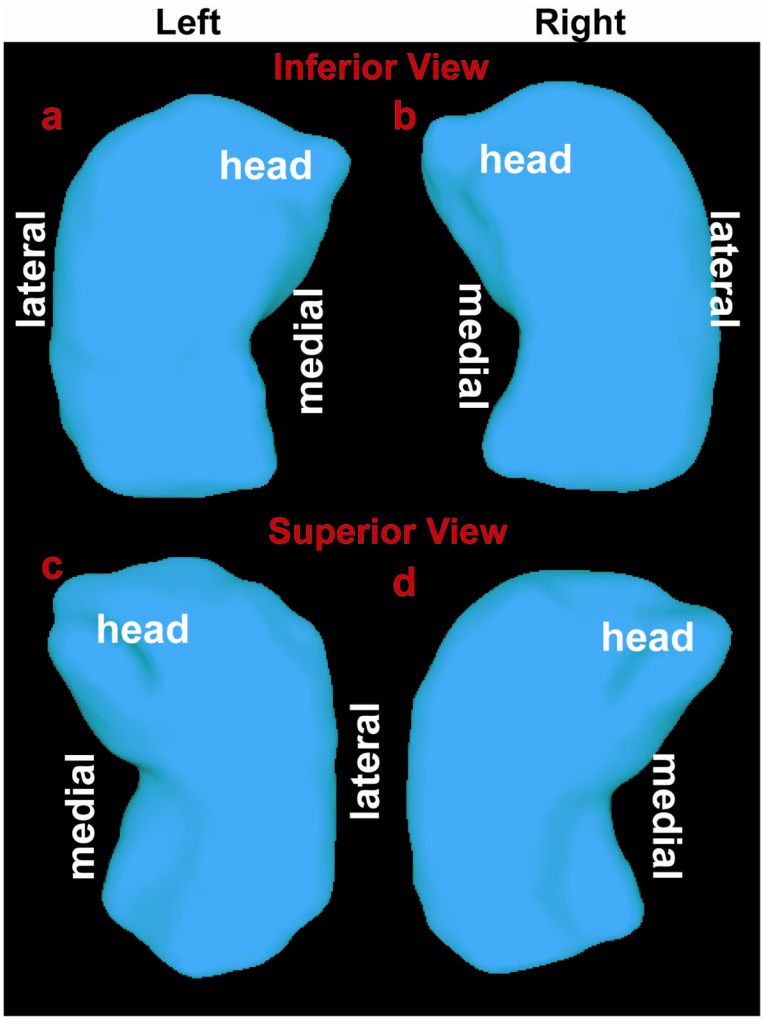

Figure 1.
Panels (a, c) illustrate the template of the left hippocampus created based on 20 subjects using a diffeomorphic template generation algorithm. Similarly, panels (b, d) show the template of the right hippocampus.

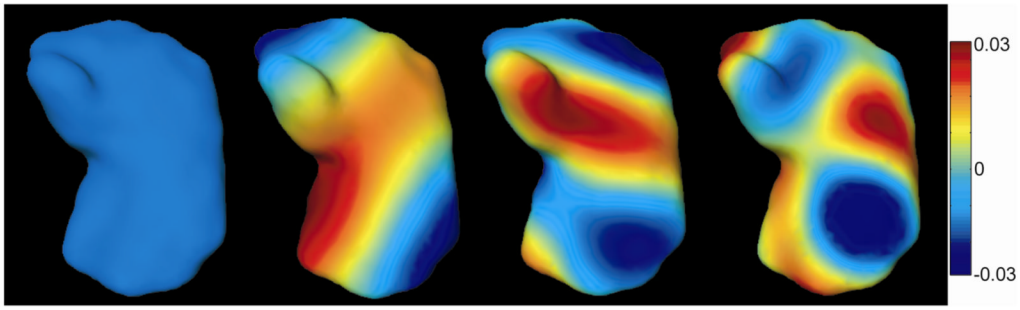

Figure 2.
Examples of the Laplace-Beltrami (LB) basis functions on the left hippocampal template. From left to right, panels respectively illustrate the 1^{st}, 6^{th}, 12^{th}, 19^{th} LB basis functions in the superior view of the left hippocampal template.

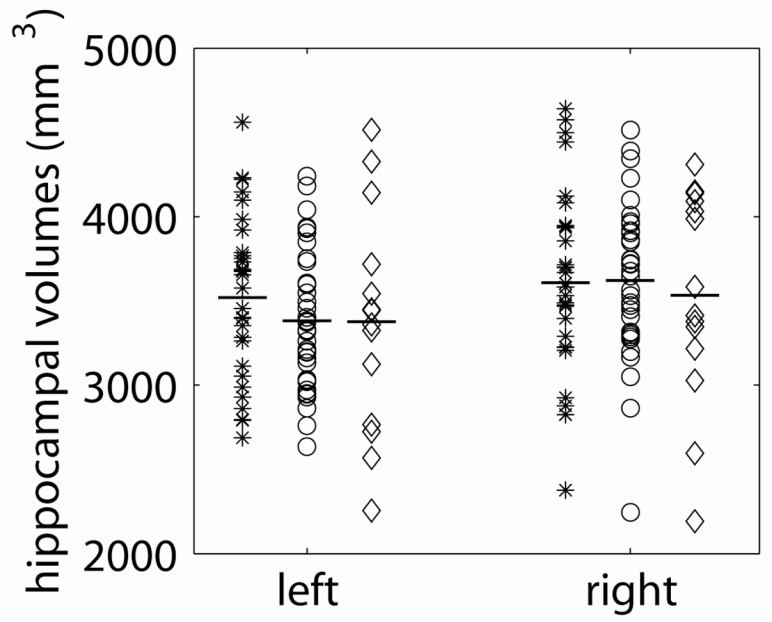

Figure 3.
Figure shows hippocampal volume measurements within the groups of healthy controls without an apoE E4 (asterisk), depressed elders without an apoE E4 (circle), and depressed elders with one apoE E4 (diamond). Each mark corresponds to one subject. Horizontal bars denote the locations of the mean values in each group.

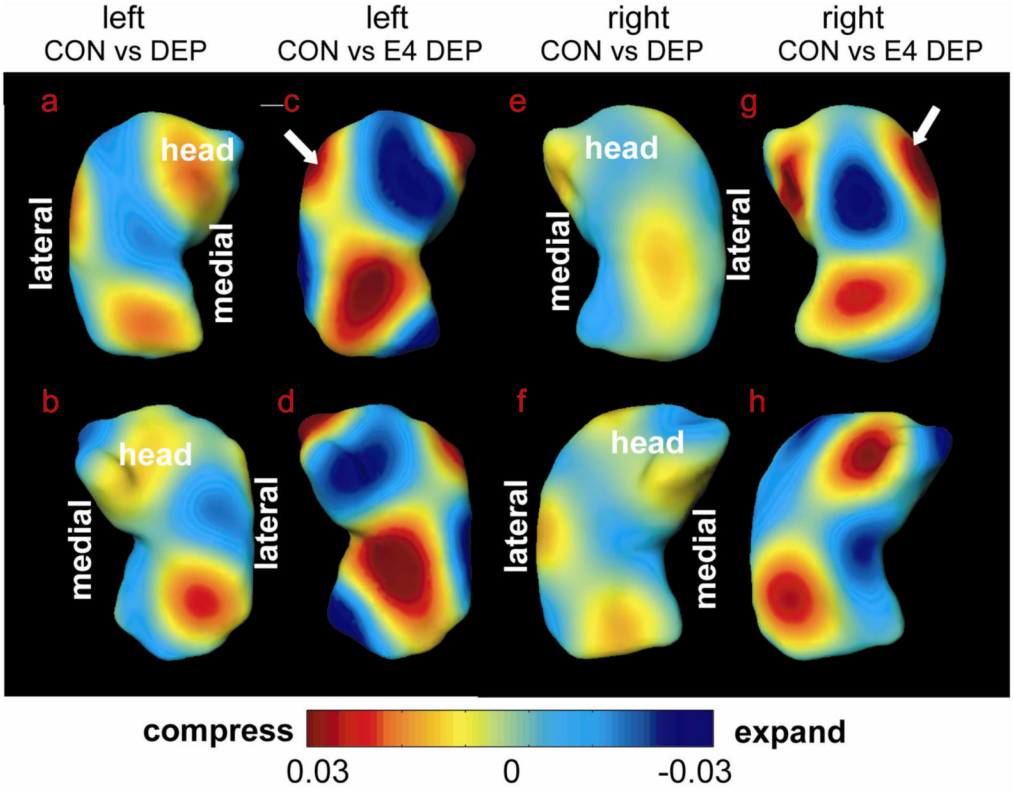

Figure 4.

Panels (a, b) illustrate the shape difference of the left hippocampus between the groups of the healthy controls (CON) and depressed patients without an apoE E4 (DEP). Panels (c, d) illustrate the shape difference of the left hippocampus between the groups of the healthy controls and depressed patients with one apoE E4 (E4 DEP). Similarly, panels (e, f) show the shape difference of the right hippocampus between the groups of the healthy controls and depressed patients without an apoE E4. Panels (g, h) show the shape difference of the right hippocampus between the groups of the healthy controls and depressed patients with one apoE E4. The top row illustrates the inferior view of the hippocampus, whereas the bottom row shows the superior view of the hippocampus. Compared with the healthy control group, regions (warm color) are where the hippocampus is compressed in the group of the patients; regions (cool color) are where the hippocampus is expanded in the group of the patients. Arrows points the anterior lateral aspect of the hippocampus where the depressed patients with one apoE E4 have pronounced compression.

Table 1

Demographic information in this study. Key: CON --- healthy controls without an apoE E4, DEP ---depressed patients without an apoE E4, E4 DEP ---depressed patients with one apoE E4.

	CON N = 31	DEP N = 38	E4 DEP N = 14	Test Statistic	p value
Age	68.9 (5.9)	64.7 (4.5)	68.8 (6.5)	$F = 6.16$	0.0032
Sex (% Female)	67.8% (21/31)	71.1 % (27/38)	50.0% (7/14)	$\chi^2 = 1.99$	0.3690
MMSE	28.7 (1.7)	28.9 (1.6)	27.9 (1.9)	$F = 1.56$	0.2163
MADRS	-	14.9 (11.1)	16.9 (10.7)	$t = 0.56$	0.5759
Antidepressant Use	-	92.1% (35/38)	85.7% (12/14)	Fisher's exact test	0.6024
Brain volume (cm^3)	1547.7 (161.7)	1548.5 (161.2)	1520.7 (162.9)	$F = 0.17$	0.8462