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Spatially Localized Hippocampal Shape Analysis in Late-Life Cognitive Decline

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Abstract

We present a method for generating data-driven, concise, and spatially localized parameterizations of hippocampal (HP) shape, and use the method to analyze HP atrophy in late-life cognitive decline. The method optimizes a set of shape basis vectors (shape components) that strike a balance between spatial locality and compact representation of population shape characteristics. The method can be used for exploratory analysis of localized shape deformations in any population of HP on which point-to-point correspondence mappings have been established via anatomical landmarking or high-dimensional warping. Experiments combine the method with an automated HP to HP mapping method to analyze tracings of 101 elderly subjects with normal cognition, mild cognitive impairment, and Alzheimer's Disease (AD) from an AD Center population. Results suggest that shape components corresponding to atrophy to the CA1 and subiculum HP fields—where early AD pathology is located—correlate strongly with robust measures of the cognitive dysfunction that is typical of early AD. Furthermore, the energy function minimized by the shape component optimization technique is shown to be smooth with few local minima, suggesting that the method may be relatively easy to apply in practice.

Keywords

Alzheimer's disease (AD); magnetic resonance imaging; CA1; Subiculum; shape analysis

INTRODUCTION

Parameterization of shape variability among a population of hippocampal (HP) is a key step in neuroimaging-based analyses of the HP degeneration associated with Alzheimer's disease (AD) (Chetelat and Baron, 2003). Shape parameterization—the conversion of the delineating HP boundary into a vector of numbers that captures its salient shape characteristics—can ease the comparison of HP structure across diagnostic groups, the analysis of relationships between HP structure and clinical variables, and the tracking of HP growth or atrophy over time. Our goal is to provide HP shape parameterizations that are intuitive, data-driven, and concise. Intuitive parameterizations allow medical end users with little computational knowledge to connect individual shape parameters to easy-to-understand aspects of HP anatomy. Data-driven methods generate the shape parameterization from a set of exemplar HP provided by the end user, rather than prior mathematical models of shape variability; they avoid forcing the end user to make strong prior assumptions about shape characteristics. Concise parameterizations

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summarize the population in a small number of salient parameters to avoid overwhelming the user with a sea of numbers.

We encourage intuitiveness by generating HP shape parameterizations that are spatially localized, i.e., each parameter accounts for the shape of a single HP region. Spatial locality is especially important in AD, because early in the disease course, the pathology that causes HP atrophy spreads sequentially from one HP region to another in a spatial pattern, which is largely distinct from HP atrophy associated with healthy aging (Braak and Braak, 1991). Therefore, HP shape parameters that account for atrophy to regions affected by early AD pathology, especially the CA1 and subiculum fields, have potential use as markers of early AD pathology that may be more sensitive and specific than overall HP volume.

Given a set of HP boundary tracings, we follow the pattern theory approach of establishing one-to-one transformations that map points on one HP surface to points on another, and examining the set of transformations *post facto* (Grenander and Miller, 2007). This article focuses on the second step: the analysis of mappings once they have been established. Given one-to-one HP correspondences, we take the linear subspace approach of expressing each HP as a linear combination of basis shapes. Each HP is represented as a vector $\mathbf{v}_j$ of the $3m$ coordinates of m points sampled from its boundary (i.e., $\mathbf{v}_j = [\mathbf{v}_{j,1}, \mathbf{v}_{j,2}, \dots, \mathbf{v}_{j,m}]$, $\mathbf{v}_{j,k} = [x_k, y_k, z_k]$) and $\mathbf{v}_j$ is approximated as a linear combination of k of the basis vectors— or shape components— $\mathbf{e}_1, \mathbf{e}_2, \dots, \mathbf{e}_k$:

$$\mathbf{v}_j^k = \mathbf{e}_0 + \sum_{i=1}^k \alpha_{j,i} * \mathbf{e}_i$$

The shape parameters are the coefficients $\alpha_{j,i}$. Linear subspace methods are attractive because they can be manipulated using robust, efficient tools from linear algebra, and because the shape component coefficients provide numerical summaries of HP modes of variation that can have intuitive anatomical meanings for end users. Each $\mathbf{e}_i = [\mathbf{e}_{i,1}, \mathbf{e}_{i,2}, \dots, \mathbf{e}_{i,m}]$ is interpretable as a deformation of a mean surface $\mathbf{e}_0$; for each surface point $\mathbf{v}_{j,k}$, $\mathbf{e}_i$ contains a subvector $\mathbf{e}_{i,k}$ that corresponds to a displacement of $\mathbf{v}_{j,k}$ away from its position on the mean surface (see Fig. 1).

This article combines an automated, dense HP mapping method with localized components analysis (LoCA), a linear subspace method that provides concise and spatially localized shape components, for assessment of relationships between HP atrophy patterns and cognitive decline in 101 elderly subjects from an academic dementia center. Previously, LoCA was shown to generate intuitive, succinct parameterizations of other human brain regions (corpora callosa and ventricles) and archaeological specimens (monkey skulls and arm bones), and it balanced spatial locality and conciseness more effectively than competing methods (Alcantara et al., 2007). In this article, we take the next step by showing that LoCA may provide useful quantitative measures for an important clinical problem, and that it may be relatively easy to apply to novel HP data sets. Specifically, we demonstrate that LoCA generates HP shape components that appear to quantify early-AD-associated HP atrophy, and that the shape component coefficients may be useful for predicting AD-associated cognitive decline. We also show that the energy function LoCA minimizes is relatively smooth and lacks significant numbers of local minima, suggesting that the LoCA computational problem may be solved in practice using fast and simple numerical methods.

Related Work

The problems of establishing dense correspondences between HP, and analyzing relationships between HP-to-HP mappings and clinical variables, have been addressed extensively. High-

dimensional warping methods use HP surface shape or anatomical imagery to find HP-to-HP correspondences by estimating a geometric transformation of the ambient 3D space that is one-to-one, onto, and smoothly invertible (Csernansky et al., 2005). Anatomical landmarking methods attempt to place surface points at roughly homologous anatomical locations across HP, based on local HP shape characteristics, contextual cues from anatomical imagery, and prior knowledge about HP anatomy (Styner et al., 2004; Thompson et al., 2004). In contrast, medial shape models that associate homologous networks of skeletal geometric primitives with each HP can provide intuitive, complementary shape information (Joshi et al., 2002). Once surface-to-surface mappings have been established between HP, each mapping may be reduced to a single measure that represents the magnitude of deformation required to warp one HP to match another; the measure can quantify HP shape differences between and within clinically relevant groups (Beg et al., 2005). For each point on the HP surface, the strength of association between per-subject surface point position and clinical variables of interest may be color-mapped onto a prototype HP surface, allowing visualization of the associations across the entire surface (Thompson et al., 2004). Finally, the transformation from a mean HP surface to each subject HP can be sampled at discrete surface points and represented as motion vectors, which are then projected onto a linear subspace for dimensionality reduction and exploration of modes of deformation from the mean (Wang et al., 2001).

We follow the linear subspace approach. Previous methods such as principal components analysis (PCA) generate shape components that are often difficult to interpret in anatomical terms because they represent complex patterns of shape change across an extended portion of the HP surface (Fig. 2). Other methods encourage shape components with large numbers of zero-magnitude entries or achieve this sparseness as a side-effect of optimizing a statistical independence criterion (e.g., Üzümcü et al., 2003; Chennubhotla and Jepson, 2001). LoCA, meanwhile, explicitly optimizes for spatial locality, and may have a superior ability to modulate the tradeoff between conciseness and spatial locality compared with the sparse methods (Alcantara et al., 2007).

METHODS

Subjects

One hundred and one subjects enrolled in the University of California, Davis Alzheimer's Disease Center (Table 1) received axial-oblique 3D Fast Spoiled Gradient Recalled Echo (FSPGR) MRI scans on a 1.5-tesla GE Signa scanner with the following parameters: TE: 2.9 ms (min), TR: 9 ms (min), flip angle: 15°, slice thickness: 1.5 mm, slice spacing: 0.0 mm, number of slices: 128, NEX: 2, FOV: 25 cm × 25 cm, matrix: 256 × 256, bandwidth: 15.63 KHz, phase FOV: 1.00, frequency direction: A/P. Each subject received an extensive clinical workup including a battery of neuropsychiatric tests sufficient for computing several composite measures of domain-specific cognitive function: semantic memory, episodic memory, executive function, and visuospatial function, respectively (Mungas et al., 2003). The measures were based on test scores of a development sample of 400 subjects from three academic AD centers; they have high reliability from roughly 2.0 σ below to 2.0 σ above the mean of the development sample. All measures are near-normally distributed, have linear measurement properties across a broad ability range, and lack significant floor and ceiling effects. The composite measures as well as the clinical dementia diagnosis from a Center consensus conference (normal, MCI, or AD) were our primary outcome measures.

HP Tracing

Two raters manually traced the left HP to include the CA1–CA4 fields, dentate gyrus, and the subicular complex using a graphical interface. The left HP was chosen because of its potentially asymmetric contribution to cognition in AD. First, each MRI was resliced perpendicular to the

long axis of the left HP. The boundary of the HP was then traced on contiguous coronal slices. A sagittal view was used to define the boundary between the amygdala and HP head at the rostral end. In anterior sections, the superior HP boundary was the amygdala. In sections in which the uncus lies ventral to caudal amygdala, the uncus was included in the HP. In posterior sections with no amygdala, the choroid fissure and the superior portion of the temporal horn of the lateral ventricle formed the superior boundary. The fimbria were excluded. The inferior boundary was the white matter of the parahippocampal gyrus. The lateral boundary was the temporal horn; in posterior sections, the tail of the caudate nucleus was excluded. The posterior boundary was the first slice in which the fornices were completely distinct from the thalamus. Inter-rater reliability in HP volume on a set of 10 HP not analyzed in this study exceeded 0.9 between our raters, and between each rater and additional expert raters in the Center.

HP Mapping

Dense one-to-one correspondences between subjects at homologous HP surface points were established using a radial surface mapping approach (Thompson et al., 2004). Briefly, medial curves were threaded down the center of each HP, and each HP was resampled to contain a fixed number of axis-aligned parallel traces. Within each trace, rays were cast outward from the medial curve point toward the surface every θ radians; the surface was resampled to contain only the points where the cast rays intersected with the manual trace. Across subjects, correspondences were established between points in analogous traces and analogous θ . In our experiments, each HP was resampled to have 15 traces and 20 surface points per trace (i.e. $\theta = 0.31$ radians).

LoCA

The resampled HP surface point positions were used as inputs to generalized procrustes alignment, which attempted to align corresponding points by globally by rotating, translating, and scaling subject HP (Fig. 3). The aligned subject HP were assembled into the vectors $\mathbf{v}_j$, and PCA was run to provide an initial set of $\mathbf{e}_i$. Then, the LoCA method iteratively went through all possible pairs $(\mathbf{e}_i, \mathbf{e}_j)$ of shape components and rotated $\mathbf{e}_i$ and $\mathbf{e}_j$ together in the plane they span by the same angle θ to minimize an energy function that depends on $\mathbf{e}_i$ and $\mathbf{e}_j$ (i.e., every $\mathbf{e}_i$ and $\mathbf{e}_j$ are orthogonal to each other at the beginning of LoCA optimization, and they are constrained to remain orthogonal throughout the procedure). The energy function, $E_{\text{tot}} = (1-\lambda) \times E_{\text{var}} + \lambda \times E_{\text{loc}}$, is a linear combination of a PCA criterion E_{var} that assigns lower energy to $(\mathbf{e}_i, \mathbf{e}_j)$ that maximize the projected variance of $\mathbf{v}_j$ onto $\mathbf{e}_i$ and $\mathbf{e}_j$, and a locality term E_{loc} that assigns lower energy to $\mathbf{e}_i$ for which entries $\mathbf{e}_{i,k}$ and $\mathbf{e}_{i,l}$ are both nonzero if and only if the geodesic distances between their corresponding surface points $\mathbf{v}_{i,k}$ and $\mathbf{v}_{i,l}$ are low (see Alcantara et al., 2007 for details). Because the leading k PCA shape components minimize the squared error between $\mathbf{v}_j$ and its k -th order approximation $\mathbf{v}_j^k$, E_{var} encourages conciseness, i.e., it tries to accurately represent the $\mathbf{v}_j$ using the smallest number of $\mathbf{e}_i$. Brent's method finds the θ that minimizes E_{tot} with respect to $\mathbf{e}_i$ and $\mathbf{e}_j$ (see Press et al., 1992 Chapter 10). Modifying all possible $(\mathbf{e}_i, \mathbf{e}_j)$ pairs in this manner constitutes one LoCA iteration; the iterations continue until the change in the $\mathbf{e}_i$ falls below a threshold. The parameter λ allows the user to modulate the relative importance of conciseness and spatial locality; in our experiments, it is set to 0.4.

Statistical Analysis

After the $\mathbf{e}_i$ are estimated, they are rank ordered so that for each k , the sum of $\|\mathbf{v}_j - \mathbf{v}_j^k\|_{L2}$ over all $\mathbf{v}_j$ is minimized. Each $\mathbf{v}_j$ is represented by its shape component coefficients $\alpha_{j,i}$ for the top 20 ranking $\mathbf{e}_i$ to capture its salient shape characteristics. The distributions of these shape component coefficients across subjects appeared approximately Gaussian by visual inspection. The coefficients were rescaled so that a unit change in $\alpha_{j,i}$ corresponded to a 1-mm change in the position of the HP surface point that was moved maximally by $\mathbf{e}_i$. The signs of the $\alpha_{j,i}$ were

then flipped, when necessary, so that a negative change in any $\alpha_{j,i}$ corresponded to localized atrophy—a local inward motion of the HP surface. These transformations allowed us to interpret coefficients of regression (i.e., line slopes) between the $\alpha_{j,i}$ and cognitive scores as the number of millimeters of local HP contraction that correspond to a one-point decrease in cognitive score according to the regression model. However, we emphasize that the transformations do not affect the nature of the underlying relationships between the $\alpha_{j,i}$ and clinical variables.

Relationships between the coefficients and the composite cognitive measures were assessed across all subjects in linear regression models that controlled for age, number of years of education, gender, and ethnicity. F tests assessed the significance of relationships, and shape components and regression coefficients were used to assess the relationships in anatomical terms. Specifically, each shape component was classified according to which HP cytoarchitectonic fields its HP atrophy appeared to take place in, based on a prior parcellation of the HP into approximate regions corresponding to the CA1, subiculum, and the combined CA2-4 and dentate gyrus fields (see Csernansky et al., 2005 Fig. 1). Similar linear models with the same covariates analyzed clinical diagnosis as a categorical outcome measure. To compare these results with a more traditional, less anatomically informative HP morphometric measure, similar linear regression models evaluated relationships between the cognitive outcomes and total HP volume.

Optimization Analysis

As described earlier, the shape components are obtained by iteratively rotating pairs of shape components ($\mathbf{e}_i, \mathbf{e}_j$) in the plane they span by an angle θ , such that the rotated $\mathbf{e}_i$ and $\mathbf{e}_j$ minimize an energy function E_{tot} . A key practical issue in the application of LoCA for novel HP data sets is the ease with which the method is able to find low-energy rotations of ($\mathbf{e}_i, \mathbf{e}_j$). In particular, if E_{tot} has noisy, high-frequency fluctuations, many local minima, or flat plateaus, it is likely that simple methods for optimizing θ , such as gradient descent, will become trapped at a suboptimal θ . In this scenario, using LoCA in practice would require a complex, nonlinear optimizer, regularization of E_{tot} , or another preconditioning scheme to avoid the local minima. Each of these additional steps could reduce the robustness and ease of use of LoCA for novel HP analyses, so we used a brute-force method to investigate the landscape of E_{tot} with respect to θ . At each LoCA iteration, for each pair ($\mathbf{e}_i, \mathbf{e}_j$), we compute E_{tot} for all θ at 0.017-radian increments between 0 and $\pi/2$. Because rotating ($\mathbf{e}_i, \mathbf{e}_j$) by $\pi/2$ amounts to swapping $\mathbf{e}_i$ and $\mathbf{e}_j$ and negating $\mathbf{e}_i$, the cost function is repeating with a period of $\pi/2$. Visualizing plots of E_{tot} as a function of θ allow us to qualitatively judge the difficulty of obtaining the θ that provides the global minimum of E_{tot} . Ideally, E_{tot} would be smooth with a single well-defined minimum for each ($\mathbf{e}_i, \mathbf{e}_j$). To decrease computational burden, the calculations were run on a subset of 45 HP from this data set.

RESULTS

Relationships Between Shape Components and Cognitive Measures

The top 20 LoCA shape components are shown in Figure 4. Significant shape variability was seen across the structure, especially in the HP head region (see components 1, 4, 5, 6, 7, 13, 18). Statistically significant relationships between shape component coefficients and cognitive outcome variables are shown in Table 2. The shape components that covered the approximate regions of the CA1 and subiculum fields were strongly associated with cognitive outcomes, whereas the shape components that covered some combination of these fields and the approximate regions of CA2-4 and dentate gyrus (see components 2, 4, 5, 6, 7, 9, 11, 13, 15, 18) were not significantly associated with cognitive outcomes. As expected, all regression coefficients indicated that local contraction of the HP surface is associated with lower cognitive

performance. Also as expected, overall HP volume was strongly associated with the cognitive outcomes.

Optimization

Plots of E_{tot} as a function of θ during the first and third iterations of LoCA for all pairings of the top 10 ranked shape components are shown in Figure 5. Most plots show a smooth, slowly varying energy function with one or two well-defined minima. The number of curves with multiple local minima reduced nearly to zero by the third iteration. For almost all energy curves, including those that did have multiple local minima, Brent's method, a relatively simple minimizer, found the global minimum. Each of these observations suggests that the optimization problem presented by LoCA may be relatively straightforward to solve in practice without a great deal of optimizer parameter tuning or complex optimization methods.

DISCUSSION

The CA1 and subiculum are the first HP fields to experience atrophy due to AD pathology, and several of the cognitive outcome scores (especially episodic memory) reflect what may be the earliest detectable cognitive symptoms of incipient AD (Backman et al., 2001). The specificity of our HP-cognition relationships to CA1 and subiculum suggests that our localized HP shape measures may be detecting early-AD-related atrophy, which manifests itself in decline on AD-associated cognitive outcome measures. Also, this specificity agrees with results from similar studies that were based on a manual HP parcellation (Csernansky et al., 2005). Therefore, future work should determine the degree to which these measures may be useful as neuroimaging markers in a clinical setting for detecting the presence of early AD pathology, predicting the rate of future AD-associated cognitive decline, or predicting the cognitive effects of HP-modifying treatments in clinical trials.

The LoCA optimization involves iterative minimization of a complex energy function that is not theoretically guaranteed to be well behaved. Empirically, however, the LoCA optimization landscape is mostly smooth and gradual, with a single well-defined minimum per pair of shape components. This is a promising indication that simple optimization methods might be successful in finding low-energy shape components, and that LoCA may be easy to deploy with a minimum of delicate optimizer parameter tuning. Future work should investigate why a few of the energy curves do have multiple local minima, and determine whether the energy landscape is as well behaved for other shape data sets.

One limitation of our work is that we only analyzed the left hippocampus. Considering that the time course of AD-associated pathological effects may differ between left and right hippocampi, with the left side damaged more severely in earlier disease stages, we felt it prudent to analyze the two sides separately, beginning with the left (Fox et al., 1996). Future work will focus on extending LoCA so that spatial patterns of atrophy to the left and right hippocampi are quantified in a unified framework in which atrophy patterns that occur equally across both sides of the brain is dissociated from atrophy that is specific to one side or the other.

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FIGURE 1.

Left: A typical LoCA shape component representing a smooth deformation of the medial portion of the HP head. Arrows represent the direction and magnitude of deformation applied to the prototype HP. Magnitude is also mapped to blue color. Right: A range of HPs corresponding to the mean shape component coefficient ± 2 SD.

FIGURE 2.

Comparison of a typical PCA shape component with a typical LoCA shape component, rendered as in Figure 1 left. The PCA shape component represents a spatially complex deformation that covers portions of the entire surface; the LoCA shape component is spatially localized. The locality eases the interpretation of the surface deformation in anatomical terms. A, P, M, and L refer to anterior, posterior, medial, and lateral directions.

FIGURE 3.

Point-to-point correspondences between HP were established by a radial mapping approach (see text and Thompson et al., 2004). HP were then globally aligned by generalized procrustes alignment (GPA). Left: The average positions of corresponding HP surface points after GPA are shown as a wireframe mesh. Right: The positions of corresponding surface points across all subjects after GPA are shown for a selected HP slice, along with the mean surface (blue). All points rendered with the same color and character are in correspondence. Corresponding points are in similar positions and are displaced approximately normally from the mean surface, suggesting that the correspondence method induces minimal shape distortion into the shape parameterization process.

FIGURE 4.

The top 20 LoCA shape components, ranked by reconstruction error, shown from top-down and bottom-up viewpoints (A, P, L, M indicate the anterior, posterior, lateral, and medial directions, respectively). The magnitude of motion of each HP surface point is mapped to blue color as in Figure 1 left. Alternate views of four shape components are shown below.

FIGURE 5.

The LoCA energy function, plotted as a function of the rotation angle by which each pair (e_i, e_j) of shape components is rotated during the first and third optimization iterations, is shown in cell (i, j) of the matrix, with (e_1, e_2) at bottom left. The optimal rotation angle found by Brent's method is also shown. Because the energy function repeats with a period of $\pi/2$, the plots were translated so that the maximum is at the lefthand boundary; each curve is scaled to a range between 0 and 1. Analogous curves for the second iteration are similar to these but are not shown to reduce clutter.

TABLE 1

Subject characteristics

Variable	All (N = 101)	Normal (N = 44)	MCI (N = 43)	AD (N = 14)
Age ^{bc}	73.79 ± 7.47	71.34 ± 7.31	74.21 ± 6.83	80.21 ± 6
Years of education	10.64 ± 6	10.75 ± 5.79	11.02 ± 6.65	9.14 ± 4.47
Gender (M, F)	37, 64	13, 31	21, 22	3, 11
Ethnicity (Afr. Am., Hisp., White, other)	7, 48, 40, 6	2, 24, 15, 3	3, 16, 22, 2	2, 8, 3, 1
Left HP volume ^{a,b,c}	1.68 ± 0.36	1.86 ± 0.31	1.61 ± 0.28	1.28 ± 0.37
Brain volume ^{b,c}	900.44 ± 96.95	916.57 ± 91.59	912.55 ± 87.74	815.18 ± 100.62
W.M. Lesion volume ^a	9.42 ± 14.67	5.34 ± 6.1	12.44 ± 19.71	13.59 ± 14.63
CDR sum ^{a,b,c}	1.7 ± 2.55	0.53 ± 1.45	1.63 ± 2.05s	4.96 ± 3.39
MMSE ^{a,b,c}	25.57 ± 4.96	27.81 ± 2.82	25.1 ± 5.14	19.85 ± 5.05
Semantic memory ^{b,c}	-0.24 ± 0.98	0.01 ± 0.9	-0.26 ± 0.96	-1.09 ± 0.9
Episodic memory ^{a,b,c}	-0.53 ± 1.02	0.12 ± 1	-0.83 ± 0.64	-1.65 ± 0.55
Executive function ^{a,b,c}	-0.31 ± 0.76	0.01 ± 0.76	-0.41 ± 0.63	-1.01 ± 0.61
Visuospatial function ^{a,b,c}	-0.22 ± 1	0.11 ± 0.9	-0.33 ± 1.06	-1.06 ± 0.54

Numerical are show shown as mean ± SD (minimum, maximum).

^aSignificant difference between normal and MCI.

^bSignificant difference differences between normal and AD.

^cSignificant differences between MCI and AD.

TABLE 2

Results of regressing LoCA coefficients against cognitive outcome measures in linear models controlling for age, ethnicity, gender, and education

Shape component	HP field(s)	Cognitive outcome	β	F	P
1	CA1 Subiculum	Semantic	0.92	4.35	0.04
		Executive	1.25	5.27	0.024
2	CA1	Episodic	0.48	8.01	0.006
		Executive	0.87	9.87	0.002
4	CA1 Subiculum	Semantic	0.44	6.60	0.012
		Episodic	0.33	6.82	0.011
		Diagnosis	–	5.58	0.005
9	CA1 subiculum	Semantic	0.37	4.07	0.05
		Spatial	0.42	6.15	0.02
11	Subiculum	Diagnosis	–	4.28	0.02
18	CA1 subiculum	Episodic	0.16	5.04	0.03
		Diagnosis	–	4.65	0.012
20	CA1	Semantic	0.21	6.16	0.015
		Episodic	0.20	9.82	0.002
		Executive	0.28	6.67	0.011
		Spatial	0.2	6.1	0.016
		Diagnosis	–	6.61	0.002
HP volume	–	Semantic	0.13	6.94	0.01
		Episodic	0.12	10.21	0.002
		Executive	0.15	5.28	0.024
		Diagnosis	–	12.0	3e–5

The regression coefficient, β , represents millimeters of local HP contraction per unit decrease in cognitive measures. All statistically significant regression ($P < 0.05$) among the top 20 shape components are listed.