Asymmetry Analysis of Deformable Hippocampal Model Using the Principal Component in Schizophrenia

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Abstract: The hippocampus is thought to play an important role in learning and memory processing, and impairments in memory, attention, and decision making are found commonly in schizophrenia. Although many studies have reported decreases in hippocampal volume in the left hemisphere in schizophrenia, regionally specific hippocampal volume loss has not been revealed consistently using volume analysis. Recently, many studies have analyzed shape asymmetry using 3-D models; however, inconsistent results have been reported, mainly due to methodologic differences. We therefore used an active, flexible, deformable shape model for surface parameterization, and compared shape asymmetry based on principal component analysis (PCA) in the hippocampi of schizophrenic patients with those of the normal controls. Although the overall pattern of the statistical results did not change according to the number of principal components, the reconstructed results based on six major components were much more distinguishable. Although the left hemispheric hippocampal volume was larger than the right hemispheric was in this study, the difference was not significant. In shape asymmetry analysis, the right hemisphere hippocampus was bilaterally larger than the left hemisphere hippocampus was in the head of the superior CA1 and smaller in the tail and head of the inferior CA1. The asymmetry in the schizophrenia group was statistically smaller than that in the control group through reduction of the left hemisphere hippocampus volume. *Hum Brain Mapp* 25:361–369, 2005. © 2005 Wiley-Liss, Inc.

Key words: schizophrenia; hippocampal asymmetry; deformable model; alignment; PCA

INTRODUCTION

The hippocampus is thought to play an important role in learning and memory processing, and impairments in mem-

ory, attention, and decision making are found commonly in schizophrenia [Jessen et al., 2003; Weiss et al., 2003]. The lateralized specialization of the brain is well known and is thought to originate from evolutionary, developmental, hereditary, experiential, pathologic, and mental disorder-related factors [Geschwind and Galaburda, 1985; Toga and Thompson, 2003]. Many studies have reported decreases in the left hemisphere (LH) hippocampal volume in schizophrenia [Bogerts et al., 1993; Breier et al., 1992; Rossi et al., 1994; Shenton et al., 1992] and meta-analyses of such data suggest hippocampal volume reductions are bilateral in schizophrenia [Nelson et al., 1998]. As in previous studies, the left hippocampal volume in schizophrenia was associated with relatively more volumetric reduction than was the right hippocampus. Right hemisphere (RH) hippocampal

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volumes have been associated with age and illness duration in chronic schizophrenic patients [Velakoulis et al., 2001]. Furthermore, regionally specific hippocampal volume loss has been investigated in several studies based on the premise that hippocampal neuropathologic alterations may be more region specific [Becker et al., 1996; Bogerts et al., 1990, 1993; Csernansky et al., 1998; Hirayasu et al., 1998; Lieberman et al., 2001; Narr et al., 2001; Pegues et al., 2003; Rajarethinam et al., 2001; Shenton et al., 2002; Velakoulis et al., 2001].

Recently, 3-D models have been applied to the analysis of the shape asymmetry involved in changes of hippocampal volume. High-dimensional brain mapping to a triangulated model was used to determine bilateral deformations and asymmetry in the hippocampus head in schizophrenic patients [Csernansky et al., 2002; Wang et al., 2001]. Narr et al. [2001] obtained digitized points representing tissue boundaries, which were resampled and made spatially uniform by stretching a regular parametric grid over the surface. They found that significant asymmetries were present in the anterior hippocampal volumes in male subjects (RH > LH). Using an active, flexible, deformable shape model with spherical harmonic expansion, Shenton et al. [2002] reported that the major local regions responsible for the shape difference are in the tail of the hippocampus. Some previous studies have reported asymmetry of anterior hippocampal volumes, whereas others have reported asymmetry of posterior hippocampal volumes in schizophrenia groups. This discrepancy was due mainly to methodologic differences, i.e., different ways of generating models, describing measurements, carrying out statistical procedures, and eliminating unnecessary components from the analysis.

Principal component analysis (PCA) is concerned with explaining variance-covariance structure through linear combinations of the original variables. This analysis can identify patterns in data and express the data in such a way as to highlight their similarities and differences [Johnson and Wichern, 1992]. By reducing the number of dimensions and ignoring the components of lesser significance, hippocampal models can be reconstructed with consideration of the important patterns in the model. Wang et al. [2001] applied PCA to quantify the vector fields of the asymmetries on the hippocampal surface. They hypothesized that certain subsets of the basic functions would characterize the symmetry pattern, and chose two-vector combinations according to the mean asymmetry measures.

In a previous study, we suggested a new parameterized surface model of the hippocampus, aligned to a single hippocampal template via a low-dimensional transformation with the principal axis and a high-dimensional transformation with the distance feature [Lee et al., 2004]. Our approach proved to give reliable correspondence within a group study. In this study, the magnitude of the difference of the distance feature was used as the asymmetry pattern. We believed that reconstructing this asymmetry pattern based on a few major principal components could make the results clearer.

The purpose of this study was to disclose the region-specific asymmetry of the hippocampal model between control and schizophrenia groups using PCA. In addition, we investigated the relationship between the number of principal components and the reconstructed asymmetry pattern.

SUBJECTS AND METHODS

Subjects

Twenty-two right-handed schizophrenic patients (15 males, 7 females; mean age, 26.6 ± 6.5 years) were recruited from Seoul National University Hospital, Seoul, Korea. The normal control group was recruited using Internet advertisements, and consisted of 22 healthy subjects matched with the patient group for age (mean age, 26.2 ± 6.1 years), gender (15 males; 7 females), handedness, and parental socioeconomic status. The mean period of education between the groups was statistically different (schizophrenic: 13.1, standard deviation [SD] 1.7; control: 15.0, SD 1.4 years; $P = 0.02$) and in post-hoc testing the educational periods of the schizophrenia group were ascertained to be shorter than were those of the control group. Mean parental socioeconomic status [Hollingshead and Redlich, 1958] was not significantly different (schizophrenic: 3.4, SD 0.7; control: 3.0, SD 0.7). All patients were interviewed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [1994] and met the criteria for schizophrenia. None of the patients or controls had a lifetime history of neurologic or significant medical illnesses, or substance abuse. None of the controls had a lifetime history of DSM-IV Axis I disorders. Symptom severity of the patients was rated on the Positive and Negative Syndrome Scale [Kay et al., 1987]. Thirteen patients with schizophrenia were drug naive, and nine patients had a history of neuroleptic medications; however, all patients had remained psychotropic drug free for at least 4 weeks before being recruited. The mean duration of illness in the schizophrenia group was 3.7 years (SD 4.7). This study was carried out under guidelines for the use of human subjects established by the institutional review board. All subjects gave written informed consent for the procedures before their participation in the study [Kim et al., 2003; Kwon et al., 2003].

Magnetic Resonance Imaging

Magnetic resonance (MR) scans of the entire brain were obtained using a 1.5-T General Electric SIGNA System (GE Medical Systems, Milwaukee, WI), with a 3D-SPGR T1-weighted spoiled gradient echo pulse sequence with the following parameters: 1.5 mm sagittal slices; echo time = 5.5 ms; repetition time = 14.4 ms; number of excitations = 1; rotation angle = 20 degrees; field of view = 21×21 cm; and matrix = 256×256 . Images were resampled to 1.0 mm^3 voxels.

MR images were processed using the image-processing software package Analyze v. 4.0 (Mayo Foundation, USA),

Figure 1.

Overview of data preprocessing. The hippocampal data were extracted using the Analyze v4.0 program, and clipped and smoothed for further processing. The extracted and smoothed hippocampus was rendered to a 3-D volume. The surface of the hippocampus was parameterized to consist of 2,562 points.

resampled to 1.0 mm^3 voxels, reoriented to the conventional position, and spatially normalized to align the anterior-posterior axis of the brain parallel to the intercommissural line, with the other two axes aligned along the interhemispheric fissure. The datasets were filtered using anisotropic diffusion methods with five iterations to improve the signal-to-noise ratio [Kim et al., 2003; Kwon et al., 2003].

Image Preparation and Hippocampal Modeling

Hippocampi were manually traced onto all of the coronal slices, with the references of the sagittal or axial planes, using the Analyze region-of-interest (ROI) module. The boundaries of the hippocampus were defined using a minor modification of the method reported previously [Pantel et al., 2000]. To assess interrater reliability, tracing was carried out independently on a set of 10 MR scans by two raters and the volumes of the traced regions were measured automatically. The intraclass correlation coefficients (ICCs) were cal-

culated and found to be high: 0.89/0.90 for the left/right side of the hippocampus [Kwon et al., 2003]. The following overall preprocessing flow is displayed in Figure 1. After pruning all except the hippocampal volume from the entire brain volume, the smoothed and clipped volume was converted into binary to discriminate the boundary. An active, flexible, deformable shape model, developed originally by MacDonald et al. [2000], was used for cortical surface parameterization. The deformation process was carried out based on an objective function, which was a weighted sum of several different terms, such as Image, Stretch, Self-proximity, and Inter-surface proximity terms. The optimal parameterized model was obtained by minimizing this objective function, with the hippocampal surface consisting of 2,562 points per object. All parameterized shape models were obtained for each hippocampal dataset by the same algorithm. This procedure is described in detail in our previous study [Lee et al., 2004].

Figure 2.

The left hemisphere (LH) hippocampi were aligned to a single target of an LH hippocampus that was selected arbitrarily from the control group to find homologous points. The mirrored right hemisphere (RH) hippocampi were then aligned to the contralateral LH-aligned hippocampi.

Alignment

First, the target model of the left hippocampus with a normal distribution was obtained from a normal control subject but not included in the test dataset. To find homologous points, the left hippocampi were aligned to a single left hippocampus (Fig. 2). The mirrored right hippocampi were then aligned to the contralateral left-aligned hippocampus. For each group g , the asymmetry vector field $u_i^k(g, x)$ was obtained from

$$u_i^k(g, x) = u_i^R - u_i^L \quad (i = 1, 2, 3, \dots, n) \quad (1)$$

where n is a vertex number, k is a subject number, and u_i^R, u_i^L the mean distance fields, which are calculated from the center of the hippocampal model to the boundary, in the right and left models, respectively. The asymmetry measurement M , calculated by subtracting the right hippocampal distance field from the left, is $\|u_i^k(g, x)\|$. The alignment process consisted of two steps, the coarse and fine alignments. The coarse alignment was based on the main axis and the fine alignment was based on the mean squared difference. The vertex of the source had the same index as the target did through reindexing. Each subject had the same single template domain and homologous points. The details of the alignment process have been described in our previous study [Lee et al., 2004].

Asymmetry Measures via PCA

To quantify the asymmetries of the hippocampus described by the magnitude of the vector fields for all subjects,

we carried out PCA on the hippocampal data to reduce the dimensionality of the parameter space from the number of surface vertices, n , to the number of subjects, N . We then defined asymmetry measurement matrix $M^g = [M_1^g, \dots, M_N^g]$ where M_k^g is 1-by- n column vector $\{\|u_1^k(g, x)\|, \dots, \|u_n^k(g, x)\|\}$. The covariance structure for the measurement matrix can be defined as follows:

$$\bar{M}_k^g = \frac{1}{N} \sum_{k=1}^N M_k^g \quad \{g = NC, SZ\}$$

$$\Sigma = \frac{1}{N-1} \sum_{k=1}^N (M_k^g - \bar{M}_k^g)(M_k^g - \bar{M}_k^g)^T \quad (2)$$

We numerically estimated the eigenvector matrix E of dimension N -by- N and the eigenvalue vector $\{\lambda_1, \dots, \lambda_N\}$ corresponding to each eigenvector by using singular value decomposition on the measurement matrix M^g .

For the between-group comparison of hippocampal asymmetry, the q eigenvectors were selected according to the following equation and predefined pwr ratio:

$$pwr \geq \sum_{i=1}^q \lambda_i / \left(\sum_{i=1}^N \lambda_i \right) \quad (3)$$

The projection and reconstruction of the asymmetry matrix in the newly found eigenvector dimension can then be defined as:

$$T = M^g E$$

$$M^{g*} = T E^* \quad (4)$$

where T is projected data, E^* is a subset of E whose unwanted eigenvectors were zero-padded, and M^{g*} was reconstructed data with the contribution by unwanted eigenvectors removed. The surfaces of the single objects were parameterized, providing a point-to-point correspondence between the homologous surface points. The statistic on shape asymmetry, then, was based on a simple t -test.

Statistical Analysis of Group Differences

To carry out the t -test on the values of the discrete vertex, the values must have a Gaussian distribution. If the distribution of values were not Gaussian, this would be a case of multiple comparisons, which would necessitate a correction such as a Bonferroni correction or the use of a nonparametric test.

We overcame the limitation of not being able to apply a simple t -test directly to the values of the discrete vertex using diffusion Gaussian smoothing [Chung et al., 2003]. The values for the measures of asymmetry were distributed

TABLE I. Hippocampal volume in schizophrenic patients and normal controls

Hippocampus	Age (yr)	Volume cm ³	
		Left	Right
Schizophrenia (n = 22)	26.6 ± 6.5	2.836 ± 0.515	2.849 ± 0.552
Control (n = 22)	26.2 ± 6.1	3.338 ± 0.489	3.192 ± 0.514

Data are given as the mean ± SD. Statistical significance levels are based on paired sample *t*-tests ($P < 0.01$). The hippocampal volume was bilaterally reduced in the schizophrenic patients compared to that in normal controls.

as a Gaussian random variable on the hippocampal surfaces. We carried out diffusion smoothing with a 3-mm full-width half-maximum (FWHM) diffusion Gaussian kernel for 100 iterations. If the iteration step size was large, the distance became unstable and a singularity (white spot) began to appear. Statistical inferences could then be based on simple *t*-tests with no correction for multiple comparisons.

RESULTS

Asymmetry of Volume

As reported in our previous study, the hippocampal volume was reduced bilaterally in schizophrenic patients com-

pared to that in normal controls (Table I) [Lee et al., 2004]. Although the right volume is larger than the left in schizophrenia and the left volume of healthy controls is larger than that in the right, as shown in Table I, it is difficult to interpret the hippocampal asymmetry nonstatistically. We can presume that, in general, the asymmetry of volume was decreased in schizophrenia compared to asymmetry of volume in the healthy controls. The smaller areas in schizophrenia mean that the degree of asymmetry in schizophrenia was smaller than in the healthy controls. In other words, where generally there must have an asymmetry, it was not apparent.

Asymmetry of Shape Using PCA

The shape asymmetry analysis using the mean square difference (MSD) showed that the RH hippocampus was bilaterally larger than the LH hippocampus was in the head of the superior CA1, and smaller in the tail and head of the inferior CA1. In both the control and the schizophrenia groups, we observed larger LH hippocampi overall (Fig. 3); however, only a very small region was detected as statistically significant (Fig. 3c,f). The eigenvalue distributions were obtained in control and schizophrenia groups (Fig. 4). The low components, regarded as noise elements, were eliminated using the PCA. We selected the six dominant components, and the eigenvalue sums were more than 60% (control, 66.2%; schizophrenia, 68.2%). The subtle regions of L

Figure 3.

The mean square difference (MSD) results are illustrated in the control (a, d) and the schizophrenia (b, e) groups. The group differences of shape asymmetry are presented in c and f. In both cases, the shape asymmetry is mapping onto the right hemisphere (RH) average hippocampal model. The regions in which the RH hippocampus is larger than is the left hemisphere (LH) hippocam-

pus are noted in red. In particular, the RH hippocampus was bilaterally larger than the LH hippocampus was in the head of the superior CA1 (a, b); however, we showed that the superior aspect of the LH hippocampi was large in both control and schizophrenia groups (d, e), but was not statistically significant (c, f).

Figure 4.

Distribution of the eigenvalues in the control and schizophrenia groups through principal component analysis. The hippocampal model was reconstructed with six eigenvalues and the eigenvectors of the 22 principal components.

> R and R > L were more prominent in the reconstructed hippocampal data (Fig. 5). As shown in the statistically significant region (Fig. 5c,f), the shape asymmetry of the

schizophrenia group was smaller in the head and middle of the superior subiculum, CA3/CA4, and the tail of the inferior CA1.

DISCUSSION

Number of Subjects

Each of the schizophrenic and normal control groups had 22 subjects consisting of 15 males and 7 females. All patients were interviewed with the Structured Clinical Interview for DSM-IV and met those criteria for schizophrenia. We carefully selected normal control subjects to match the patient group for age, gender, handedness, and parental socioeconomic status. Although this study could not reveal a gender effect because of the small dataset, it was controlled for gender by matching the numbers of male and female subjects. Our previous studies showed good results with the same dataset [Kwon et al., 2003; Lee et al., 2004].

Volume and Shape Asymmetry Comparison of Schizophrenia Subjects and Normal Controls

The RH hippocampal volume has been shown to be larger than the LH in both control and schizophrenia groups in many previous studies [Csernansky et al., 1998, 2002; Narr et al., 2001; Pegues et al., 2003]. Pruessner et al. [2000] pointed out that the vast majority had either normative R > L asymmetry or no left-right differences. Although the LH hippocampal volume was larger than that of the RH in our

Figure 5.

Shape asymmetry of the hippocampus for control (a, d) and schizophrenia groups (b, e) through principal component analysis. The subtle regions of L > R and R > L are prominent. As shown in c and f, the shape asymmetry of the schizophrenia group was smaller in the head and middle of the superior subiculum, CA3/CA4, and in the tail of the inferior CA1.

study, there was no significant difference in terms of volume. A global shape difference caused by an overall volume difference should be removed to represent the local asymmetry. Shenton et al. [2002] reported that the major local regions responsible for the shape difference between the healthy controls and the schizophrenia groups are in the tail. Another interesting study reported that the LH hippocampus was larger than the RH was in the head of the CA1/CA2. The area in which the LH hippocampus is smaller than the RH was revealed overall [Csernansky et al., 2002; Wang et al., 2001].

As we have only the imaging data, it is difficult to interpret precisely the subfields of the hippocampus. We followed the definition of the areas from the illustration in the study by Posener et al. [2003], which showed global areas such as CA1–2 and the tail of the subiculum. On the control map, the subfield CA1 accounted for much of the hippocampal head and for the lateral and posterior edges of the hippocampal body and tail. The subiculum accounts for a smaller region in the medial part of the head and body of the hippocampus. This is best seen in the inferior view, because the subiculum is covered partially by the dentate gyrus and subfields CA3 and CA4 in the superior view. In this study, we found that the RH hippocampus was unilaterally smaller than the LH hippocampus was in the tail of the superior CA1, and that the RH hippocampus was larger in the region of the superior head in both control and schizophrenia groups (Fig. 5a,b,d,e). Although the findings are similar to the results of Shenton et al. [2002], the significant regions were revealed at the head and middle of the superior subiculum, CA3/CA4, and the tail of the inferior CA1. In Figure 5 (c,f), the blue color indicates that the shape asymmetry in the schizophrenia group was smaller than it was in the control group. This region shows that the hippocampal volume is less in the LH than in the RH in schizophrenia [Bogerts et al., 1993; Breier et al., 1992; Rossi et al., 1994]. Harrison and Eastwood [2001] suggested that there was greater cellular volume loss and disorganization within CA3/CA4 and the subiculum. The anterior and posterior compartments of the hippocampus have distinct neural connections [Cavada et al., 2000; Goldman-Rakic et al., 1984] and seem to be functionally dissociated [Lepage et al., 1998; Strange et al., 1999]. Hippocampal CA1 neurons that project to the medial prefrontal cortex are found predominantly in the head of the hippocampus [Barbas and Blatt, 1995; Carmichael and Price, 1995]. The abnormality in this area therefore provides support for hypotheses that schizophrenia involves a disturbance of the connections between the hippocampus and the prefrontal structures [Narr et al., 2001; Pegues et al., 2003; Weinberger et al., 1992].

Hippocampal Modeling and Alignment Methods

Several different methods have been suggested for modeling hippocampal shape. Shenton et al. [2002] used a spherical harmonic function for modeling and a 3-D ellipsoid as the first-order approximation of the structures for alignment. Thompson et al. [1996, 2004] made the manually derived contours spatially uniform by modeling them as a 3-D

parametric surface mesh. Csernansky et al. [2002] modeled the surface of the template hippocampus and determined the corresponding target points using a higher dimensional transformation. Although the performance of these approaches depends mainly on the accuracy of the transformation and manually placed landmarks, our approach, which obtains each surface model from manually delineated data and is aligned in two steps, depends predominantly on the manual delineation procedure. As the manual delineation procedure was examined carefully, the modeling and the correspondence were more reliable [Lee et al., 2004]. The study region of our previous study, the anterior and mid-body CA1 and CA2 hippocampal region, was similar to the results of Narr et al. [2004].

We have the limitation that the isolating locations of asymmetries using root MSD did not accord with the true anatomy of the hippocampus. It is, nevertheless, too small a mismatched location error to affect the result. We therefore did not only obtain good result in our previous study [Lee et al., 2004] but also in many subsequent studies [Shenton et al., 2002; Wang et al., 2001, 2003].

Reconstruction With the Selected Principal Components

The most general methodology in the analysis of raw data is in itself shape analysis. The raw hippocampal data comprised not only a shape pattern, but also a modeling error and the noise originating from the partial volume effect. It is difficult to confirm the veracity of raw data without “ground truth.” Recently, many researchers have used component analysis to overcome this limitation and to find ground truth [Joshi et al., 2002; Shen et al., 2001; Wang et al., 2003]. Independent component analysis (ICA) is a statistical and computational technique for revealing hidden factors that underlie sets of random variables, measurements, or signals. The method of ICA did not define the prior knowledge for selecting the independent component in the shape analysis. We therefore used PCA to eliminate the unnecessary components such as errors and noises using the eigenvalue. The principal components were selected through the ratio of accumulation about the total summation of eigenvalues as shown in Figure 4.

The statistical results were evaluated according to the number of principal components (Fig. 6). As expected, the overall pattern of the statistical results did not change according to the number of principal components. As the information from the asymmetry pattern should be preserved, we selected the six dominant components; the sum of the eigenvalues was more than 60% (control, 66.2%; schizophrenia, 68.2%). As shown in Figure 4, the distribution of eigenvalues diminished rapidly after the sixth component. The eigenvalues of the low components below 60% revealed smaller values and gradients of variance than did the total sum values of the eigenvalues. Although we selected the number of components arbitrarily, there was reasonable rationale to select the principal components through the histogram of eigenvalue distribution (Fig. 4) and observ-

Figure 6.

Changes in the results according to the number of the principal components. N is the number of principal components used in the reconstruction. There was more localization of regions until the sixth principal component, but there were no differences after the sixth component.

ing the changes of the results according to the changes in the numbers of eigenvectors (Fig. 6). The unnecessary components such as noise and modeling errors could be reduced effectively by removing the lower components.

In summary, we obtained a parameterized surface model of the hippocampus using a multiple-surface algorithm, aligned all the hippocampal surface data into the target hippocampus using a surface pattern-matching algorithm, and compared the shape asymmetry in the hippocampus of the schizophrenic patients with those of the controls, based on the distance map, using PCA. Our findings were similar to previous studies, i.e., the smaller LH hippocampus in the tail of the superior CA1. The asymmetry of the schizophrenia group was smaller than that of the control group because of the LH hippocampus volume reduction. We believe that our PCA study offered criteria for reconstructing hippocampal models with selected principal components.

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