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Deformable model with surface registration for hippocampal shape deformity analysis in schizophrenia

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Changes to the hippocampal structure have been reported as consistent structural abnormalities in schizophrenic patients and have been related to the learning and memory deficits in such patients. Although many magnetic resonance (MR) imaging studies have focused on the hippocampal volume, local structural changes were difficult to discriminate from normal neuroanatomical variations. 3D shape deformation analysis of the brain structure may reflect localized schizophrenic abnormalities. A deformable model, evolved from the ellipsoid to hippocampal surface, with 2562 vertexes, was developed to analyze the left and right hippocampus shapes in 22 schizophrenic patients and 22 healthy age and gender matched controls. One of the most critical issues in the shape analysis is the determination of homologous points between two objects. To determine more accurate corresponding points, an alignment procedure, consisting of coarse and fine steps, following a deformation process, was applied. The performance of the alignment process was tested using artificial data, to get the alignment error to within 3° for each angle. A volume analysis indicated the hippocampal volume to be bilaterally reduced in schizophrenic patients compared to the normal controls, with a shape analysis showing a deformity pattern of the hippocampal surface. Bilateral inward deformities in the anterior and posterior hippocampus and a unilateral outward deformity in the right anterior hippocampus were observed, respectively.

Keywords: Schizophrenia; Hippocampus; MRI; Shape analysis; Deformable model; Alignment

Introduction

The midline structures of the brain, including the hippocampus and corpus callosum, are important regions used to investigate the brain abnormalities, as these areas can show shape deformations suggestive of neurodevelopmental anomalies (Csernansky et al., 1991; Innocenti et al., 2003). Therefore, neurodevelopmental aberrations in schizophrenia, which might alter the organization of hippocampal neurons, could also be expected to alter their shape and function. The hippocampus is though to play an important role in learning and memory processing, and impairments in memory, attention, and decision-making are commonly found with schizophrenia (Jessen et al., 2003; Weiss et al., 2003). Many quantitative MR imaging studies have found that a reduction in the hippocampal volume could be one of the most consistent structural abnormalities and related to deficits in learning and memory in schizophrenia (Altshuler et al., 2000; Gur et al., 2000; Heckers, 2001; McCarley et al., 1999; Narr et al., 2001; Wood et al., 2001), although others have not (Kegeles et al., 2000; Laakso et al., 2001; Rajarethinam et al., 2001; Stall et al., 2000). Recent meta-analyses of such data suggest that the degree of the reduction in the hippocampal volume to be approximately 5% in schizophrenics (Nelson et al., 1998; Wright et al., 2000). The power to detect the difference in the hippocampal structure may have been limited due to the exclusive reliance on the analysis of the hippocampal volume Posener et al., 2003; Velakoulis et al., 2001).

An analysis of the shape of the brain structure could, therefore, represents a more quantitative approach in the understanding of these abnormalities. There are two categories involved in a shape analysis: the quantitative description and the model based representation. The quantitative description includes use of the skeleton or medial axis, to extract shape features to obtain summary measures of all the structures (Golland et al., 1999; Kimia et al., 1995; Naf et al., 1997). The model based representation covers thin-plate-splines and fiducials, and elastically deformable contour and surface models, to measure regional differences in the shape (Bookstein, 1997; Christensen et al., 1997; Csernansky et al., 1998; Dale and Fischl, 1999; Davatzikos, 1997; Kelemen et al., 1999; MacDonald et al., 2000; Miller et al., 2002; Shenton et al., 2002). An active, flexible deformable shape model has been used to obtain a shape description of the amygdala–hippocampal complex using a spherical harmonic expansion (Shenton et al., 2002). From this model, the deformity of the hippocampus for schizophrenic patients was reported to be in the inferior aspect adjacent to the parahippocampal gyrus and the superior aspect adjacent to the

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lateral geniculate nucleus, but more anteriorly to the cerebral peduncles. High dimensional brain mapping, to a triangulated model, was used to obtain the bilateral deformations in the hippocampus head in schizophrenic patients (Csernansky et al., 1998; Wang et al., 2001). It was also reported that if the control subjects, on average, have a thinner subiculum on the left side, then this "thinning" effect was more pronounced in schizophrenia subjects (Csernansky et al., 2002).

One of the critical issues in the shape analysis is to define the homologous points between the template and target. One promising solution is to use a high-dimensional transformation, where the template surface is represented as a two-dimensional surface, which is transformed into each and every target (Csernansky et al., 1998; Wang et al., 2001, 2003). However, this approach assumes no transformation error, and needs manually placed landmarks, which may introduce intra- or inter-rater variability. Shenton et al. (2002) used a Fourier descriptor to align the entire hippocampus, by translation to the surface centroid and rotation to the three axes of the first-order approximation. As only a coarse alignment was applied, errors could be introduced when comparing the regional changes of the corresponding points.

Another important issue in the shape analysis is to normalize the size, since shape differences are sensitive to any size changes. It is important to derive a metric that measures the residual shape differences after correcting all the objects for the intracranial volume (ICV).

To get a parameterized surface model of the hippocampus, a multiple surface deformation algorithm, originally developed to generate a cortical triangular mesh, was used in this study and had the topology of a sphere and showed very promising results (MacDonald et al., 2000). The strength of our model is that the vertices, indexed identically on each model, will lie within a very close proximity (Chung et al., 2003). The volume of the model was corrected for ICV to remove whole brain size effect. The shape models of all the data were aligned with the template via a low-dimensional transformation, based on the principal axis, and a high-dimensional transformation, based on the distance feature represented in the ellipsoid.

We hypothesized both shape differences and local shape deformities could be detected because the volume of each hippocampal shape model was corrected for its ICV and aligned to the target data based on surface matching algorithm. Finally, the deformity patterns of the right and left hippocampus were compared, respectively, to discriminate the two groups of subjects.

The purpose of this study is to obtain a parameterized surface model of the hippocampus of each subject based on a multiple surface algorithm to align all the hippocampal surface data into the target one using surface pattern matching algorithm, and to compare shape deformities based on the distance map in the hippocampus of the schizophrenic patients with those of the normal controls.

Method and materials

Subjects

Twenty-two right-handed schizophrenic patients (male: 15, female: 7; mean age 26.6 ± 6.5 years) were recruited from Seoul National University Hospital, Seoul, Korea. The normal control group had been recruited from internet advertisements and consisted of 22 healthy subjects matched for age (mean age 26.2 ± 6.1 years), sex (male: 15, female: 7), handedness, and parental socioeconomic status with patients group. Mean period of education (SZ, 13.1 (SD = 1.7) and Control, 15.0 (SD = 1.4) years, respectively) was statistically different among the groups; educational periods of the schizophrenia group were ascertained to be shorter than those of the control comparison group in the post hoc test. However, mean parental socioeconomic status (Hollingshead and Redlich, 1958) was not significantly different (SZ, 3.4 (SD = 0.7), Control, 3.0 (SD = 0.7)). All the patients were interviewed with the Structured Clinical Interview for DSM-IV and met those criteria for schizophrenia (American Psychiatric Association, 1994). None of the patients and controls had a lifetime history of neurological or significant medical illnesses and 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, 1987). Thirteen patients with schizophrenia were drug naive and nine patients had a history of neuroleptic medications. However, all of them had remained psychotropic drug-free during a period of at least 4 weeks at the time of being recruited, and their mean duration of illness was 3.7 (SD = 4.7) years in the schizophrenia group. 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).

Image acquisition and processing

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°; field of view = 21 × 21 cm; and matrix = 256 × 256. Images were resampled to 1.0 mm^3 voxels.

The MR images were processed using an image-processing software package, ANALYZE (version 4.0, Mayo Foundation, USA), 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 inter-commissural line, with the other two axes aligned along the inter-hemispheric fissure. The data sets were filtered, using anisotropic diffusion methods, with five iterations, to improve the signal-to-noise.

Building parameterized 3D shape models and segmentation

Hippocampal boundary definitions and manual delineation

The neuroanatomical regions of interest (ROIs) were manually traces onto all the coronal slices, with the references of the sagittal or axial planes, using the ANALYZE ROI module. Boundaries of the hippocampus were defined using a minor modification of the method previously report (Pantel et al., 2000). Tracing was performed initially on the sagittal slices for a reliable separation, and preceded to the coronal plane applying different boundaries according to the positions of the head, body, or tail hippocampus.

To assess inter-rater reliability, a tracing was performed independently on a set of 10 MR scans by two raters and volumes of the traced regions were measured automatically. The intra-class correlation coefficients (ICC) were calculated and found to be high: 0.89/0.90 for the left/right side of the hippocampus (Kwon et al., 2003).

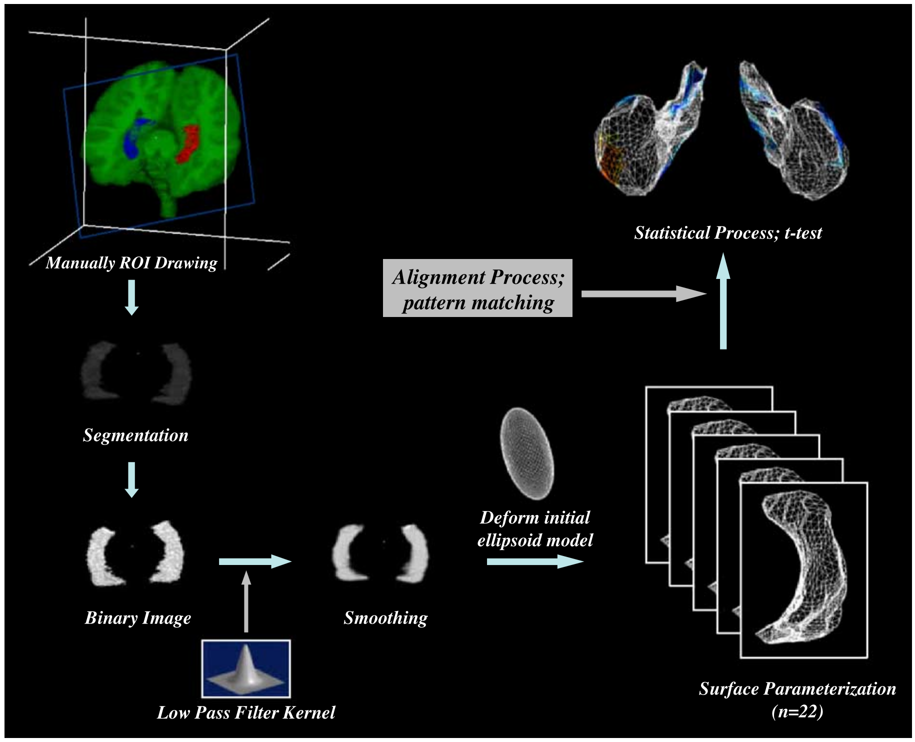

Fig. 1. Overview of the data processing. The hippocampal data were extracted using the ANALYE 4.0 program and clipped and smoothed for further processing. The extracted and smoothed hippocampus was rendered to a 3D volume. The surface of the hippocampus was parameterized and consisted of 2562 points.

Preprocessing

The minimum hexahedrons covering the hippocampus were obtained for all data. The ROI were defined as the largest hexahedron from all the data. All the other parts were set to zero, except the ROI, which was clipped to reduce the memory and time required for the following processing. The surface of the object was very rough because of the slice based manual drawing. Therefore, a low pass filter, with a size of 3 × 3 × 3 mm^3, was used to smooth the surface of the object. While the intensity feature usually gives important information for the deformable model approach, that in the hippocampus has relatively low contrast, 70–100 in 8-bit data, and no distinguishable boundaries along significant portions of its surface. Therefore, the clipped volume was converted into binary to discriminate the boundary. The overall preprocessing flow is displayed in Fig. 1. We corrected the volume of hippocampus for its ICV to remove the effect of whole volume before further statistic process.

$$D_{\mathrm{Individual}(i)}{}' = D_{\mathrm{Individual}(i)} \times \frac{V_{\mathrm{std}}}{V_{\mathrm{src}(i)}} \qquad (1)$$

V_{std} and $V_{\mathrm{src}(i)}$ are ICVs of the single standard and each ith subjects each.

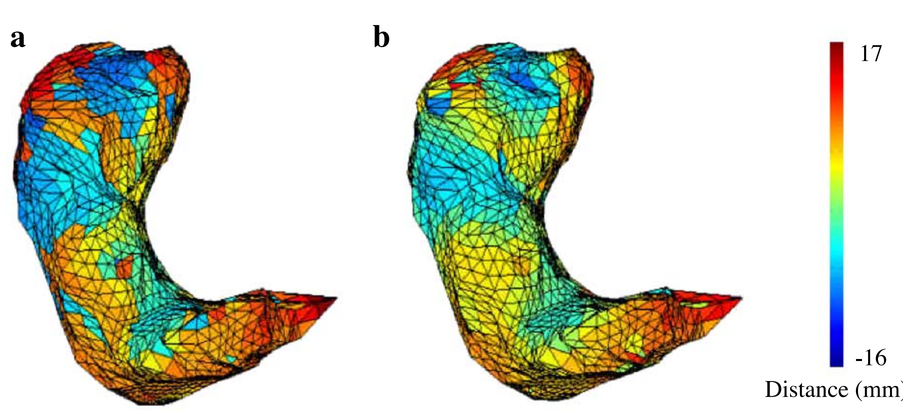

Fig. 2. Diffusion smoothing of the distance distribution on the triangulated mesh of hippocampus. The initial distance distribution (a) was obtained between the vertex of target and source model. After 1000 iterations with 6 mm FWHM diffusion Gaussian kernel, the finite distance distribution becomes smooth and stable (b).

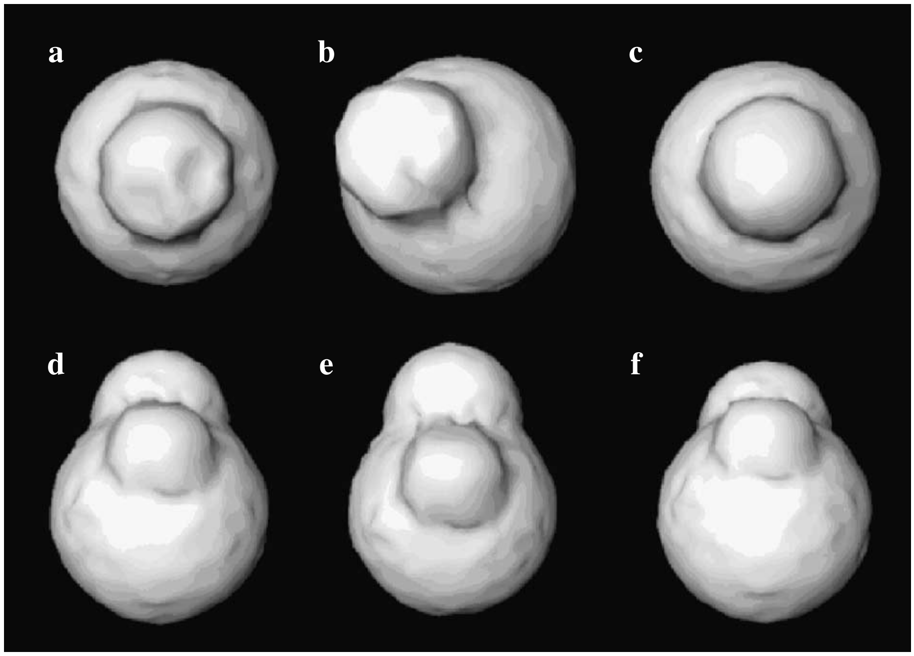

Fig. 3. Evaluation of the alignment using the artificial data. Two kinds of artificial data were used, which contained random noise. The left columns (a and d) are the target data, the middle columns (b and e) are the source data. The results are represented in the right columns (c and f). Each data source was made by rotating the target data by 15° (b) and 10° (e).

Parameterized shape model

An active, flexible, deformable shape model, originally developed by MacDonald et al. (2000), was used for the cortical surface parameterization. The deformation process was performed from 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 2562 points per object. All the parameterized shape models were obtained for each hippocampal data by the same algorithm, respectively.

Alignment by distance map

The hippocampus template was selected as target for the alignment process. The target data in this study was not included in either group to avoid bias of the deformity. Starting with a single template, which was not included in the control group, the 3D displacement vectors, $\boldsymbol{u}$, are given by

$$\boldsymbol{u}_{\mathrm{s}} : x \mid\!\rightarrow \boldsymbol{u}(x) \in \Omega_{\mathrm{s}} \qquad \boldsymbol{u}_i : x \mid\!\rightarrow \boldsymbol{u}(x) \in \Omega_i \qquad (i = 1, \ldots\ldots, M) \tag{2}$$

Where Ω_{s} is a single template domain, Ω_i is each subject data domain, and M is the subject number.

The alignment process consisted of two steps, the coarse and fine alignments. First, the principal axis was searched, as this was the main one, roughly representing the shape pattern. The principal axis, $\boldsymbol{u}_{\mathrm{p}}$, is defined as:

$$\boldsymbol{u}_{\mathrm{p}} = \frac{1}{N} \sum_{i=0}^{N} (\boldsymbol{u}_i - \boldsymbol{c}_i) \qquad \{u_i \mid \boldsymbol{u}_i \subseteq | l - k | \& \boldsymbol{u}_i \subseteq h_i\} \tag{3}$$

Here, l is the long axis of the object, k is the size of the empirically defined kernel, according to the size of the hippocampus, N is the number of the vector in the kernel. $\boldsymbol{c}_i$ represents each centroid vector of the object.

$$\boldsymbol{u}_i' = \mathrm{R}(\boldsymbol{u}_{\mathrm{i}}(\mathrm{x})) + \mathrm{T} \tag{4}$$

Each centroid of the object was translated by the translation matrix, T. The rotation matrix, **R**, consisted of the angle between $\boldsymbol{u}_{\mathrm{s}}$ and $\boldsymbol{u}_i$. The hippocampus was coarsely aligned by rotating the angle between the axes of the objects.

Since the distance values indicated the shape pattern, they were used as feature information. The fine alignment was then performed by minimizing the mean squared difference between

Fig. 4. The deformable 3D models of two hippocampal data. Target data are depicted as a shaded surface display, and the source as a wire-flame. The left columns (a and d) represent the CA1 region of the hippocampus. The middle columns (b and e) are the head of the subiculum and the right columns (c and f) are the whole hippocampus. Before the alignment (a, b, and c), there was an ambiguous match of both surfaces. After the alignment, using principal axes and the distance map (d, e, and f), the fit of both surfaces were very close.

Fig. 6. Extracted features from the vertex of hippocampus surface were mapped to the target subject. The distance feature implied the surface differences and the local deformities (top low). The magnitude of distance (a) and the distance between two example samples (b) are suitable for analysis the hippocampus. The feature of the mean curvature (c) and the average curvature (d) could not represent the surface characteristics of hippocampus.

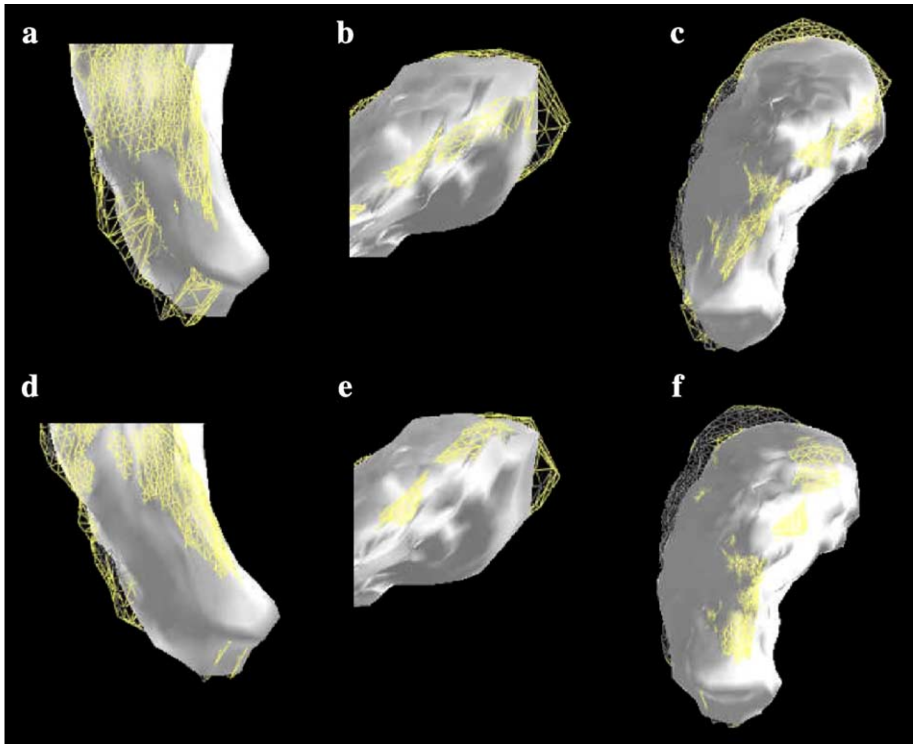

Fig. 4.

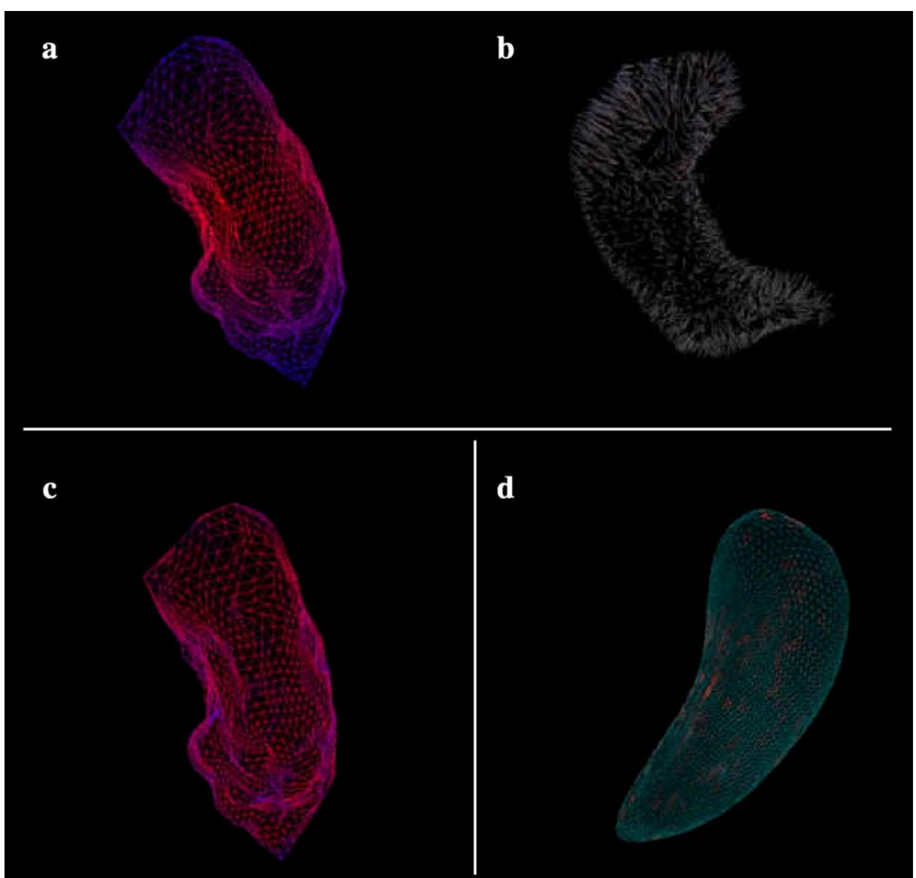

Fig. 6.

Table 1
Data are given as the mean ± SD. Statistically significance levels are based on paired sample t tests ($P < 0.01$)

Hippocampus	Age (year)	Volume (mean ± SD)	
		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

The hippocampal volume was bilaterally reduced in the schizophrenic patients compared to the normal controls.

the distances of template and the subject. The distance was mapped as a feature on the sphere of the same spatial domain. Each vertex of the sphere contained the distance from the hippocampus. The objective function for alignment is represented by:

$$J = \sum_{i=0}^{n} (D_s(\boldsymbol{u}_i(x,\ y,\ z)) - (D_t(u_i(x,\ y,\ z)))^2 \tag{5}$$

D_s and D_t are the distances on the source and target, n the vertex number, and x, y, z is the position of the vertex on the sphere.

The optimized angles of each direction were obtained when the objective function was minimized. Finally, the 3D model was aligned by rotating in relation to these optimized angles. The vertex of the source, through re-indexing, had the same index as the target. In this process, the vertex index of source was defined by the shortest distance to the vertex index of target, as the vertex index of the source was not exactly matched to that of the target. Therefore, each subject has the same single template domain and homologous points.

Analysis of group differences

The surfaces of the single objects were parameterized, providing a point-to-point correspondence between the homologous surface points. To increase the signal-to-noise ratio (SNR) as defined in Dougherty (1999) and Worsley et al. (1996), Gaussian kernel smoothing is desirable in many statistical analyses. By smoothing the data on the cortical surface, the SNR will increase if the signal itself is smooth and in turn, it will be easier to localize the morphological changes. However, due to the discrete nature of the vertex whose geometry is non-Euclidean, we cannot directly apply Gaussian kernel smoothing on the hippocampal surface. However, by reformulating Gaussian kernel smoothing as a solution of a diffusion equation on a Riemannian manifold, the Gaussian kernel smoothing approach can be generalized to an arbitrary curved surface. This generalization is called diffusion smoothing (Chung et al., 2003). Fig. 2 illustrates the results of the diffusion smoothing with 6 mm FWHM Diffusion Gaussian kernel for 1000 iterations. If the iteration step size is large, the distance became instable and the singularity (the white spot) began to appear.

The hippocampal surfaces are distributed as a Gaussian random variable and hence a statistical inference on surface distance change will be based on a simple t test without any correction for multiple comparisons.

Results

Alignment

The homologous points of the surface were obtained through two steps. The principal axes were used for the coarse alignment to a single subject template. The precise homologous points of the surface were then obtained using the distance map calculated from the surface point to the center of the object.

Our suggested alignment process was evaluated using artificial data, which was added to by the random noise. The source data were arbitrarily translated and rotated, and then applied the alignment process (Fig. 3). The data were tested 10 times to find all the final differences, to within 3°, for each axis. For the real hippocampal data, the target was also precisely aligned with the template in the anterior and posterior hippocampus (Fig. 4).

Volume and shape analysis

The hippocampal volumes were estimated by calculating the volume enclosed by the parameterized surface and compared using the t test. Significant differences were found in the left and right hippocampal data similar with previous studies (Altshuler et al., 2000; Gur et al., 2000; Heckers, 2001; Narr et al., 2001; Wood et al., 2001) (Table 1). The shape differences between groups were estimated using the mean square difference (MSD) between the homologous points of the surface pairs, following alignment of all the shapes to a single subject template. The correlation between the volume and shape deformity was tested, but none was found (Table 2). The significant differences in each side of the hippocampus were obtained using t tests ($P < 0.05$) and mapped on the individual hippocampal data (Fig. 5).

The volume analysis indicated the hippocampal volume was bilaterally reduced in schizophrenic patients compared to the normal controls, and the shape analysis showed a deformity pattern of the hippocampal surface. Bilateral inward deformities in the anterior and posterior hippocampus and a unilateral outward deformity in the right anterior hippocampus were observed, respectively. More precisely speaking, as shown in Fig. 5, the right hippocampus revealed inward deformity in the superior medial portion of the head and in the superior lateral portion of the body and outward deformity in the inferior lateral portion of the head. The left hippocampus revealed inward deformity in the head in the same subregion as in the right side and in the lateral portion of the body. Bilateral inward deformities in the posterior

Table 2
The correlation coefficients between the volume and the shape deformity. The shape deformity was represented by the number of vertices whose distance was greater than the given threshold (t = 5 mm)

	Left	Right
Control	−0.226 (P = 0.324)	0.438 (P = 0.047)
Schizophrenia	0.283 (P = 0.202)	0.419 (P = 0.053)

Since there was no correlation within the groups, the shape deformity could be regarded as an independent measure from the volume. Note that the numbers in the blankets are the P values.

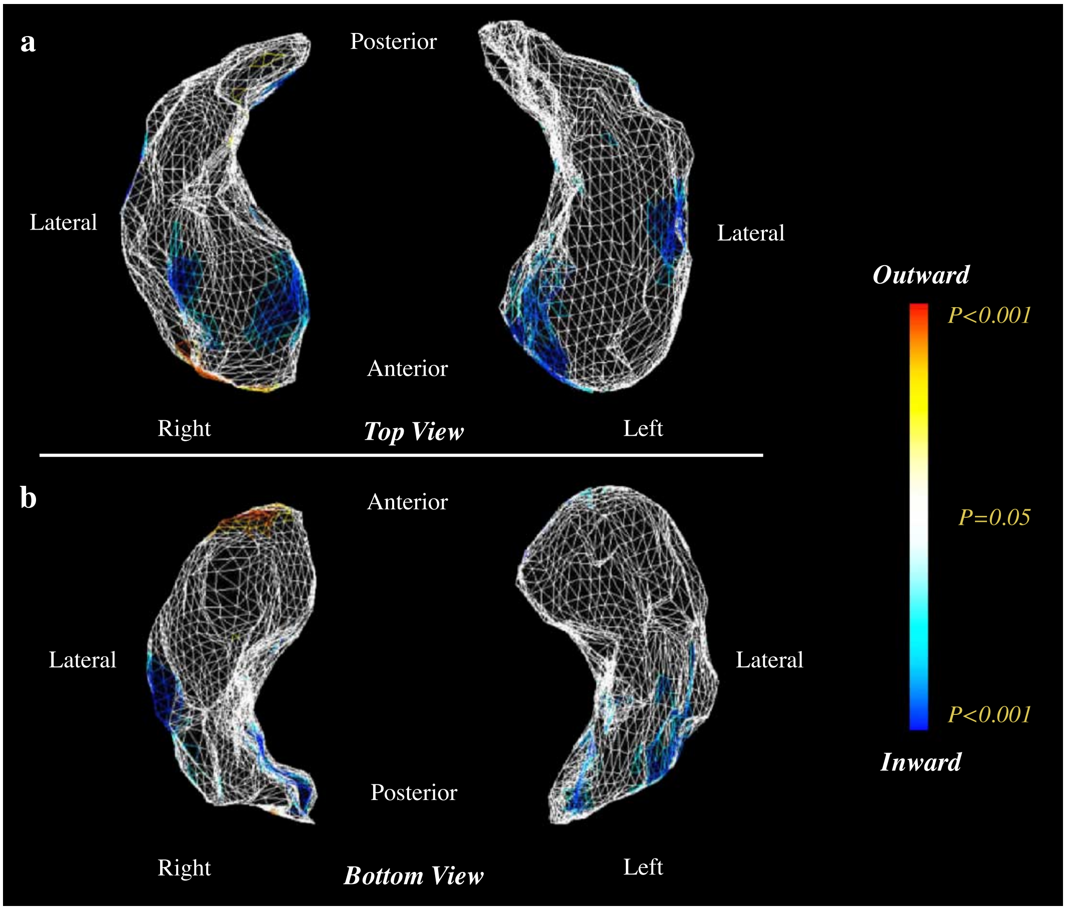

Fig. 5. Difference in the hippocampal surface shape patterns between the control and schizophrenia groups, visualized as the significant levels (P values < 0.05), were computed using the t test. (a) and (b) row represent the right and left hippocampus in the top and the bottom views. A bilateral inward and a unilateral outward deformity were observed to appear in the right anterior hippocampus, respectively.

portion of the hippocampus were distributed in the inferior subregions of the posterior body and in the medial subregions of the tail.

Discussion

The number of subjects

Both schizophrenic group and normal control group have 22 subjects consisting of males, 15 and females, 7. All the patients were interviewed with the Structured Clinical Interview for DSM-IV and met those criteria for schizophrenia. The normal control subjects were carefully selected to be matched for age, sex, handedness, and parental socioeconomic status with patients group. While this study could not reveal gender effect because of small data size, this study was controlled for gender, which was done by matching the numbers of male and female. Our previous studies showed good results with the same data set we used (Kim et al., 2003; Kwon et al., 2003).

Shape model and alignment

A global shape difference, caused by an overall volume difference, should be removed to represent the local deformity. Even after removing the global difference, determining the corresponding points between the two parameterized models should still be treated very carefully. For this purpose, the raw segmented hippocampus data was smoothed using a low pass filter and a two-step alignment procedure applied.

Landmark based morphometrics have been the first attempt during the past decade to obtain representation of shape (Bookstein, 1996). The Landmark feature was suitable for having the distinct point such as anterior–posterior commissure and the major sulci. Csernansky et al. (1998, 2002) modeled the surface of the template hippocampus and determined the corresponding target points using a higher-dimensional transformation. Since the performance of this approach depends on the accuracy of the transformation and manually placed landmarks, there may be intra- and inter-rater variabilities. Shenton et al. (2002) used a 3D ellipsoid, which was the first-order approximation of the structures for alignment.

The mean curvature has been used for the global shape pattern of the brain subsystem such as corpus callosum (Davatzikos, 2001). The average curvature was applied to the whole brain consisted of lots of sulci and gyri (Fischl et al., 1999). As shown in Fig. 6, mean and average curvature were not suitable parameter for the shape of hippocampus. The distance feature represented the characteristics of the hippocampal surface more clearly, which is similar to Gerig's work that used distances from the medial line (Styner and Gerig, 2001).

A multiple surface deformation algorithm was used to obtain the parameterized surface of each hippocampus. This algorithm generated a cortical triangular mesh, with the topology of a sphere, and showed very promising results in analysis of the brain structure (Chung et al., 2003; MacDonald et al., 2000; Thompson et al., 2001; 2003). In this study, all the data were parameterized with the same number of points, 2562, making the correspondence problem easier than with other approaches. The vertices, indexed identically on each models, will lie within a very close proximity. To determine the corresponding points more correctly, linear surface registration was used, employing a distance map measured from the surface centroid to the surface of the sphere. There are several features, such as the average and mean curvatures, which require mapping on the sphere for pattern matching. While the curvature was usually used as the feature for the cortical surface parameterization, the distance map was more suitable for the hippocampus surface, as its structure is relatively smooth and simple. The surface pattern matching algorithm was evaluated using an artificial object, which was added to by random noise to get good results.

The hippocampus template used in this study was not included in either group to avoid bias of the deformity. In our previous study, a standard brain was chosen from the data of 180 normal Korean brain MR images. The hippocampus template is of this standard brain. The middle region of the subiculum was difficult to model using the sphere model, as it was very narrow and thin. This introduced modeling error, and consequently, to the deformity error in the statistical test. Instead, the ellipsoid was used as an initial model, which was more similar to the hippocampal data, and resulted in a satisfactory result.

Shape deformity in schizophrenia

In the present study, bilateral inward deformities were observed in the anterior and posterior regions and a unilateral outward deformity in the right anterior region of the hippocampus in patients with schizophrenia. The inward deformity in the head of the hippocampus was greatly similar to those found in previous studies (Csernansky et al., 2002; Tepest et al., 2003).

Because 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), it has been hypothesized that the neuropathological alterations may be more region-specific (Csernansky et al., 1998; Narr et al., 2001; Pegues et al., 2003; Rajarethinam et al., 2001; Shenton et al., 1992). MR volumetric studies, however, have failed to yield consistent findings on compartmental volume changes in the hippocampus. The volume reduction of the anterior hippocampus or amygdala–hippocampal complex has been reported only in a few studies (Pegues et al., 2003; Shenton et al., 1992), while others have reported posterior volume reduction (Becker et al., 1996; Narr et al., 2001; Velakoulis et al., 2001). Therefore, it is still unclear whether the anterior or posterior region of the hippocampus is involved in schizophrenia. Interestingly, Rajarethinam et al. (2001), despite no volume difference in the sub-regions of the amygdala-hippocampus complex, found significant correlations between the left hippocampus and negative symptoms, and the left anterior and posterior hippocampus volumes and positive and negative symptoms, respectively. These findings suggest that different regions of the hippocampus may be uniquely related to different dimensions of psychopathology. In other words, no region of hippocampus may be specific to schizophrenia. Compared with findings from volumetric studies, shape analyses including the present study consistently revealed inward deformities in the hippocampal head. Csernansky et al. (2002) interpreted these findings as supporting for hypothesis that schizophrenia involved a disturbance of the connections between the hippocampus and prefrontal structures. Notably, findings in the current study showed that the anterior inward deformities were distributed on the superior and medial portions of the bilateral heads. Among hippocampal subfields, CA4/CA3 and the subiculum are especially suggested to be involved in schizophrenia (Harrison and Eastwood, 2001). Thus, our results may support the involvement of those subfields in the hippocampal head in the pathophysiology of schizophrenia. However, discussing the possible involvement of a sub-region in the head may be too premature, and our findings should remain as preliminary waiting for replications.

The outward deformity in the inferior lateral portion of the right hippocampal head found in the current study is a new finding. Deformities may implicate either volume changes or a displacement of the structure surface. Given no evidence of increased hippocampal volume, it is hard to infer that this outward deformity reflects volume increases. Combined with the superior medial inward deformity, the outward deformity in the present study may reflect an outward and downward displacement of the right hippocampal head. Though it is also premature to interpret the mechanism of the displacement, the finding reminds of volume increases of the right amygdala in a recent study (Narr et al., 2001). Whether the displacement of the hippocampal head reflects developmental abnormalities or secondary changes by adjacent tissues remains elusive. Posterior inward deformities were found in several small regions including bilateral inferior boarders of the hippocampus. These are consistent with volume reductions of the posterior regions in previous studies (Becker et al., 1996; Narr et al., 2001; Velakoulis et al., 2001). However, the spatial relations of these regions to adjacent parahippocampal structures and possible shape changes sparing volume should also be considered for further investigation.

In summary, we obtained a parameterized surface model of the hippocampus of each subject based on a multiple surface algorithm, aligned all the hippocampal surface data into the target one using surface pattern matching algorithm, and compared shape deformities based on the distance map in the hippocampus of the schizophrenic patients with those of the normal controls.

We found that our findings were similar to the previous studies, that is, head deformities in previous shape analyses and posterior volume reductions in previous volumetric studies. Furthermore, we also showed new finding of the rightward outward deformity, which could be related with the displacement of the right head.

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