Influence of Correspondence on Local Shape Analysis and Structural Subdivision

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Abstract. Statistical shape analysis has become of increasing interest to the neuroimaging community due to its potential to precisely locate morphological changes. In this paper we compare 3 different common shape correspondence methods applied to a study of hippocampal shape in schizophrenic adolescents: correspondence via deformable fluid template registration, spherical harmonic (SPHARM) correspondence and Minimum Description Length (MDL) correspondence. These correspondence methods are evaluated in respect to our multivariate statistical shape analysis and a novel structural subdivision analysis. The results show the clearly non-negligible influence of the choice of correspondence in shape analysis studies. Surprisingly, the differences are especially striking in the structural subdivision analysis. Our results suggest that studying the validity of the correspondence in any shape based study using additional means such as presented in this paper gives insight necessary to judge the validity of the statistical results. In the hippocampus study in this paper the additional visualizations and tests showed that the MDL correspondence method produced the most sensible result.

1 Introduction

Quantitative morphologic assessment of individual brain structures is often based on volumetric measurements. Volume changes are intuitive features as they might explain atrophy or dilation due to illness. On the other hand, structural changes at specific locations are not sufficiently reflected in global volume measurements. Shape analysis has thus become of increasing interest to the neuroimaging community due to its potential to precisely locate morphological changess and potentially discriminate between healthy and pathological structures.

A key step in shape analysis involves establishing a correspondence between shape descriptions of different objects. The importance of a *correct* correspondence is evident as new knowledge and understanding related to diseases and normal development is extracted based on the established correspondence. Unfortunately there is no generally accepted definition for correspondence. It is thus difficult to evaluate different correspondence methods [1]. To our knowledge, no comparison studies of different correspondence methods in shape analysis have

been published so far. Most shape based studies in technical and medical literature simply assume a negligible influence of the choice of correspondence method.

One of the first and most influential research in shape analysis was presented by D'Arcy Thompson [2] in his ground-breaking book *On Growth and Form*. Bookstein and Dryden [3, 4] presented some of the first mathematical methods for 2D and 3D shape analysis based on sampled descriptions. These methods mainly relied on establishing correspondence via manually determined landmarks. This type of correspondence is time-consuming, error-prone and subjective. In practice, due to small sets of reliably identifiable landmarks, manual landmarking becomes often impractical.

The shape analysis of densely sampled Point Distribution Models (PDM) and their deformations was first investigated by Cootes and Taylor [5]. Inspired by their experiments, we [6] proposed shape analysis based on a parametric boundary description called SPHARM [7]. The SPHARM shape analysis approach was further extended to use the SPHARM implied PDM [8], a method also used by Shen [9]. Several correspondence establishing approaches have been proposed for PDMs based mainly on geometry [7, 10–13] and on population statistics [14, 15].

Pizer [16, 17] and Golland [18] proposed shape analysis on medial shape descriptions in 3D and 2D, respectively. They used a fixed topology sampled model with implicit correspondence that is fitted to the objects.

Several researchers also proposed shape analysis via warping a template to the space in which the individual shapes are embedded [19–21]. Inter-subject comparisons are made by analyzing the transformations or the implied deformation fields. This analysis has to cope with the high dimensionality of the transformation, the template selection problem and the sensitivity to the initial position. Nevertheless, several studies have shown stable shape analysis results. Correspondence mainly depends on the optimization criterion and the regularization in the deformation process.

In this paper we compare the effects of 3 selected correspondence methods on local shape analysis and on a novel shape based volumetric subdivision analysis. These methods and our shape analysis methods are presented in more detail in the next section. In the following sections, the influence of these methods in a shape study of the hippocampus structure in the setting of adolescent schizophrenia is presented and discussed.

2 Methods

This section describes the methods we applied to a hippocampus study in adolescents. MR images of the subjects were first segmented using a template based deformable fluid registration, which establishes the first type of correspondence. The segmented hippocampus surfaces are then converted into the SPHARM shape description, which leads to the second type of correspondence. Using the SPHARM correspondence as an initialization, a third type of correspondence is computed by optimizing the Minimum Description Length (MDL) across all ob-

jects. The local shape analysis is then applied to the surfaces established by each correspondence method. Our analysis continues with a novel template-based parcellation of the hippocampus into 5 sections for all surfaces. The final analysis studies the size of the bounding box for each surface.

Subjects and Image Acquisition

This schizophrenia study examines the difference of hippocampal morphometry of an adolescent schizophrenic population to a normal control population. 15 schizophrenic subjects (age: 15.72y (2.47), gender ratio m/f: 80%/20%, duration of illness: 2.72y (2.75)) and 17 control subjects (age 15.88y (2.08), gender ratio: 42%/58%) were scanned on the same GE 1.5 Tesla Sigma Advantage MR system using a 3D IR Prepped SPGR acquisition protocol with a 256x256x124 image matrix at 0.9375x0.9375x1.5mm resolution.

Segmentation and Correspondence via Fluid Image Deformation

Our method for the hippocampal segmentation is based on a high-dimensional deformable registration of a template to each subject's MRI[20, 21]. The registration is performed in two separate steps: manual landmark selection and deformable registration. In the manual landmark selection step, the intensity of the subject MRI image is adjusted to match that of the template image. Then, global and hippocampus specific landmarks are manually determined on the MRI data set. The global landmarks roughly align the patient and template images on the basis of standard Talairach landmarks. The first two hippocampus specific landmarks identify the extremal positions on both the head and tail of the hippocampus, which specifies the long axis of the hippocampus. Then four landmarks (superior, lateral, inferior and medial) are placed on five equally spaced cross-sections along the head-tail axis. In the registration step, a single hippocampus template reference is initially placed using the landmarks and then deformed using a fluid image-based registration. The registration algorithm uses a coarse to fine procedure for computing the transformation field from the template MR image to the subject MR image. The reference template was built in-house based on the average MRI images of 3 healthy subjects. The output of this segmentation procedure is the volumes and surfaces of both left and right hippocampi. The segmentation results are evaluated by overlaying the resulting surfaces on the MR image. In case of segmentation errors, the whole procedure is repeated. Intra-rater reliability of the resulting volumes was at 0.90. All segmentations in this study were performed by a single, highly trained rater who was blinded to the diagnosis and treatment status. For reasons of brevity and clarity, we will focus for the remainder of this paper on the right hippocampus only, even though both left and right hippocampus were segmented.

The correspondence established by this procedure is mainly driven by the grayscale image intensities and normalization of the intensity distribution is thus an important step. The correspondence is further strongly biased by the hippocampus specific landmarks and the hippocampal shape of the template.
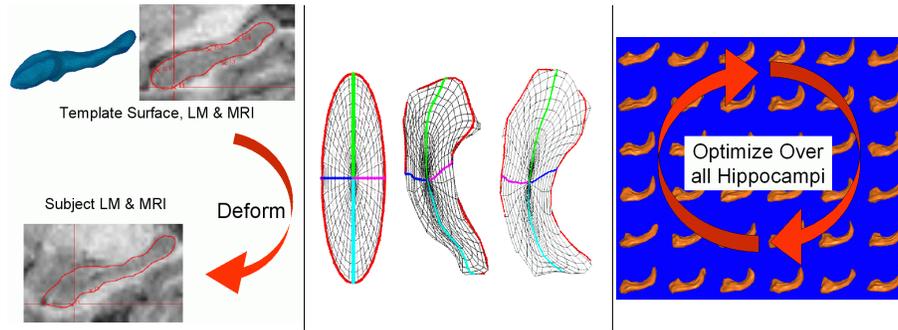
Fig. 1. Visualization of the 3 correspondence methods. Left: Correspondence is defined by deforming the same template into each hippocampus initialized with manually placed landmarks. Middle: SPHARM correspondence is defined by the equator and meridian of the first order ellipsoid. Right: MDL correspondence is defined by the optimal MDL value computed over all possible correspondences for the full population of hippocampi.

Correspondence via SPHARM: Uniform Area Parameterization Aligned to First Order Ellipsoid

The SPHARM description was introduced by Brechbühler[7] and is a parametric surface description that can only represent objects of spherical topology. The spherical parameterization is computed via optimizing an equal area mapping of the 3D quadrilateral voxel mesh onto the sphere and minimizing angular distortions [7]. The basis functions of the parameterized surface are spherical harmonics. SPHARM can be used to express shape deformations [22], and is a smooth, fine-scale shape representation, given a sufficiently small approximation error. Based on an uniform icosahedron-subdivision of the spherical parameterization, we obtain a Point Distribution Model (PDM) directly from the coefficients via linear mapping [22]. The correspondence of SPHARM is determined by aligning the parameterization so that the ridges (equator and meridian lines) of the first order ellipsoid coincide. It is evident that the correspondence of objects with rotational symmetry in the first order ellipsoid is ambiguously defined.

Correspondence via Minimum Description Length (MDL)

Kotcheff [14] and later Davies [15] proposed to use an optimization process that assigns the best correspondence across all objects of a training population. In contrast, both SPHARM and the registration based correspondence methods assign a correspondence to each individual object independent of other objects. Both Kotcheff's and Davies' methods are based on the assumption that the correct correspondences are, by definition, those that build an optimal statistical model given the training population. Kotcheff proposed to minimize the determinant of the covariance matrix and thus his method explicitly favors compact models. Davies built on this idea, but proposed a different objective function based on the Minimum Description Length (MDL) principle. The MDL princi-

ple is based on the idea of transmitting a dataset as an encoded message, where the code originates from some pre-arranged set of parametric statistical models. The full transmission then has to include not only the encoded data values, but also the coded model parameters. Thus MDL balances the model complexity, expressed in terms of the cost of transmitting the model parameters, against the quality of fit between the model and the data, expressed in terms of the coding length. MDL exhibits similarities to the determinant of the covariance matrix and the results are often similar.

Alignment and Scale
As a prerequisite for any shape analysis, objects have to be normalized with respect to a reference coordinate frame. A normalization is needed to eliminate differences across objects that are due to rotation and translation. This normalization is achieved in the presented study using the Procrustes[11] alignment method without scaling. We chose the average hippocampus aligned to its first order ellipsoid as the template of the Procrustes alignment. The hippocampi were both analyzed in their original scale, as well as normalized for individual total brain volume. Normalization with total brain volume is quite common in morphometric brain studies to accommodate for brain size differences due gender and age. In this hippocampus study the results were highly similar whether scaling normalization was employed or not, but due to reasons of brevity we present in this paper only the results based on the normalized hippocampi.

Both SPHARM based and the registration based correspondence is established without the need of a prior alignment for all objects, as each object's correspondence is computed independently from any other object's correspondence. In contrast, MDL based correspondence is computed across a population of objects and highly depends on a prior alignment and the choice of scale.

Local Shape Analysis
After alignment, the mean structure is computed by averaging the 3D coordinates of corresponding surface points across each group. The mean structure are visualized in a 3D overlay rendering. The difference between the 2 means is further visualized using the difference field that shows the difference vector between all corresponding points on the boundary. The variability across both population is then assessed using the covariance field visualization, which displays the local covariance ellipsoids.

The local shape analysis is then computed by testing the multivariate Hotelling T^2 difference at each location for significance using non-parametric permutation tests [23, 17]. This results in a raw significance map that represents the raw p-values of these local statistical tests and thus allows locating significant shape differences between the groups. We then correct these raw significance maps for the multiple comparison problem using a uniformly sensitive, non-parametric permutation test approach [23]. The raw significance map is an optimistic estimate of the real significance, whereas the corrected significance map is a pessimistic estimate that is guaranteed to control the rate of false positives at the given level α (commonly $\alpha = 0.05$) across the whole surface.
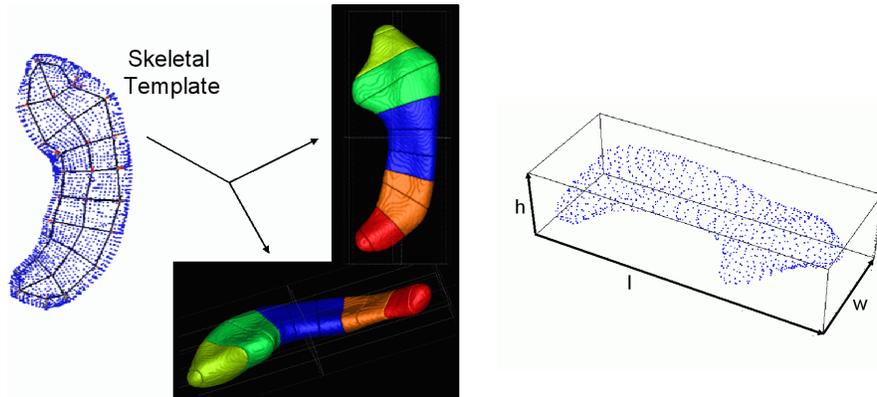
Fig. 2. Left: Hippocampal subdivision scheme, a uniformly spaced skeletal subdivision template is applied to each surface (2 head parts in green, body in blue: 2 tail parts in red). Right: The bounding box of a hippocampus after alignment. Analysis was performed on the length(l), width(w) and height(h) of the bounding box.

Surface Subdivision using a Medial Subdivision Template

The computation of the regional volumes based on subdivision of anatomical brain structures is quite common. Often subdivision protocols are executed manually and are based on the structure's bounding box or on internal and external landmarks. Such subdivision schemes are often time-consuming, not fully reproducible and subjective. Further, subdivision schemes that are not based on a structure's shape are likely to mix different parts of the structure into the same subdivision due to the non-convex shape of most anatomical structures. Our novel surface subdivision is based on a prior subdivision template, which is propagated to each individual surface using the surface correspondence. In this paper, we analyze the volumetric measurements of the subvolumes using the above presented three correspondence methods.

The template subdivision is computed on the average surface of all Hippocampi. A single manifold Voronoi skeletal sheet of the average surface is computed and uniformly subdivided along the major skeletal axis[17]. The subdivision is then defined by the planes orthogonal to the skeletal sheet at the selected axis points. In this study, 10 subdividing planes resulted in 11 subvolumes. The 4 (2+2) most anterior subvolumes define the hippocampal head region, the 3 most interior subvolumes define the body, and the 4 (2+2) most posterior subvolumes define the tail region (see Fig. 2). The surface subdivision template is then propagated to each individual surface using the surface correspondence. This subdivision scheme is fully automatic and reproducible.

Bounding Box Analysis

In this shape analysis study, we also performed an analysis of the x,y and z extent of each surface's bounding box (see Fig. 2). Since all hippocampi are aligned to
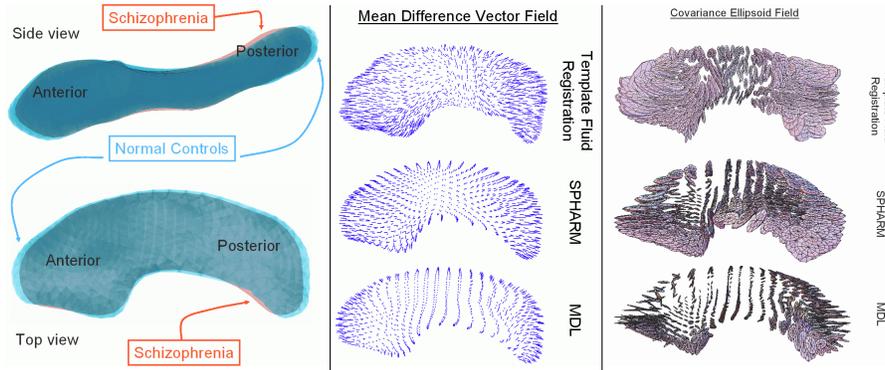
Fig. 3. Left: Overlay of the mean shape the schizophrenic (in red) and control population (in blue) from 2 different viewpoints. The control mean is enlarged compared to the schizophrenic mean, especially in the anterior head and poster tail region. Middle and Right: Difference vector field between the mean shapes and covariance ellipsoid field for the 3 different correspondence types. SPHARM and registration based correspondence seem to have many difference vectors running along the surface, as well as an enlarged variability compared to MDL.

the average hippocampus, the axis of the bounding box are coinciding with the axis of the first order ellipsoid of the average hippocampus.

3   Results

Volumetric differences
As a first step, we computed simply the full hipocampal volumetric differences between the groups using Student t-test. The test showed that the right hippocampus in control subjects is significantly larger than the ones in schizophrenia subjects (p-value: 0.037).

Difference between Mean Object
In Figure 3 the difference between the mean shapes of schizophrenic and control subjects is visualized. The 3D overlay renderings suggest that the main differences are located in the anterior head and the posterior tail region. This assessment is also clearly visible in the mean difference field using MDL correspondence and to lesser degree in the SPHARM difference field. The registration based correspondence seems to produce many areas of enlarged difference between the mean shape. In most areas that show large differences between the different methods the difference vectors for SPHARM and registration based correspondence run along the surface. The variability for MDL is also markedly reduced compared to the other methods as shown in the covariance ellipsoid fields. The
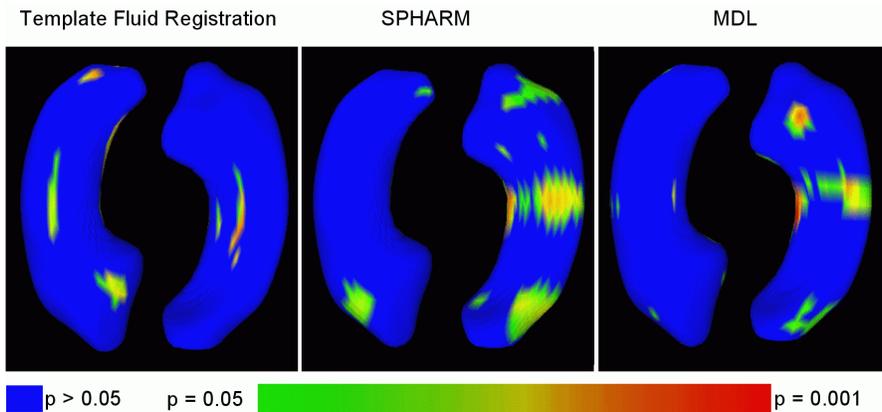
Fig. 4. Local shape analysis: Raw p-value significance maps from bottom (left) and top (right) view points computed from local non-parametric permutation tests (blue: no significant differences, green-red: differences of increasing significance). After correction for multiple comparison no regions are significantly different between controls and schizophrenics. While the raw significance maps for SPHARM and MDL show moderate agreement, this is less the case for the registration based correspondence.

registration based correspondence seems less regularized than SPHARM and MDL.

3D Local Shape Analysis

The raw significance maps shown in Figure 4 visualize the difference between the different correspondence methods. While the raw significance maps for SPHARM and MDL show moderate agreement, this is less the case for the registration based correspondence. Only SPHARM and MDL show a significantly different tail region in the raw maps. Both methods also surprisingly show the strongest significant difference in the body region, where the mean differences are quite small, but so is the variability. The head region, which shows large mean differences, is not significant due to the large variability in that region. The significance for any of the methods is low across the whole surface and after correction for multiple comparisons, there are no significant regions anymore. The low number of subjects is probably the main reasons for the low significance in all methods.

Subdivision and Bounding Box Analysis

Due to the cumulative nature of volumetric measurements, we expected more stable results across the correspondence methods in the subdivision analysis than in the local shape analysis. As shown in Figure 5, this is not the case. The different correspondence methods result in different patterns of significantly different regions. The registration based correspondence shows the full head region to be moderately significance and a minor trend in the body region. SPHARM cor-

Subdivision Volume Analysis – p-values

	P Tail	A Tail	Body	P Head	A Head
Registration	0.74	0.68	0.11	0.048	0.049
SPHARM	0.17	0.27	0.004	0.043	0.067
MDL	0.01	0.51	0.17	0.11	0.014

Template Fluid Registration   SPHARM   MDL

p > 0.2   p > 0.05   p = 0.05   p = 0.001
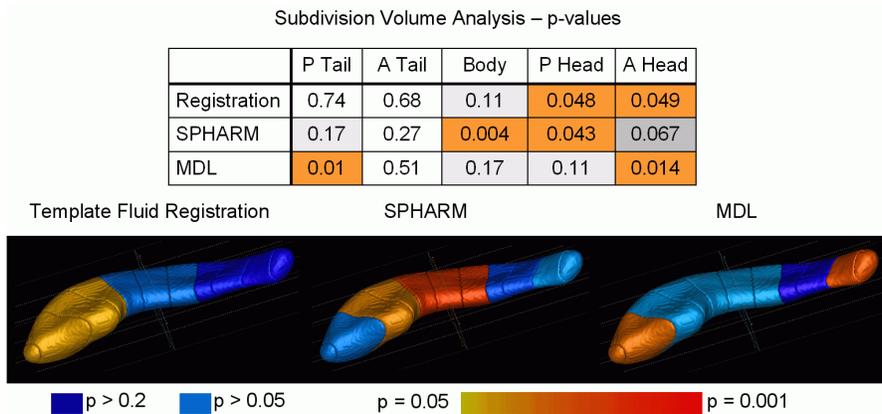
Fig. 5. Statistical analysis results from the volumetric subdivision measurements: p-value table (top) and corresponding statistical maps(bottom, blue: no significant differences, cyan: moderate trend, yellow-red: differences of increasing significance). The three correspondence methods show remarkably different results. Registration based correspondence results in differences mainly in the head region, whereas SPHARM results in differences mainly in the body region and MDL in most anterior and most posterior regions.

respondence shows the highest significance in the body region and a moderate significance in the posterior head region, as well as trends in the anterior head and posterior tail region. MDL correspondence shows good significance in both the anterior head and posterior tail region, as well as trends in the posterior head and body region. In summary, the main agreement between the methods is that the anterior tail region shows no significant difference. They all suggest differences between the groups in the other regions albeit with surprisingly dissimilar patterns.

Additionally we computed also a novel probabilistic extension of our subdivision scheme (methods omitted due to reasons of brevity). The probabilistic subdivision method associates each subdivision plane with an uncertainty computed from the standard deviation of the plane location across the whole population. The results of the probabilistic subdivision are highly similar to the results of the non-probabilistic subdivision. Thus, the differences between the correspondence methods can be quite stably reproduced.

The results of the final analysis based on the bounding box around each hippocampus are shown in figure 6. There is a significant difference in the bounding box length, while there is a minor trend in the bounding box width and no significance in the bounding box height. This suggests that the control hippocampi are more elongated than the schizophrenic hippocampi.
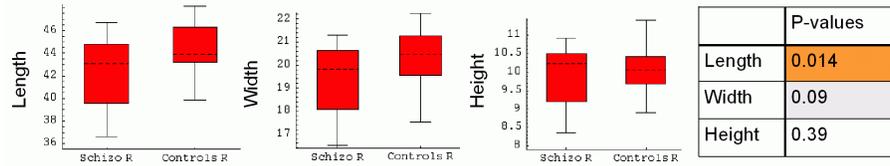
Fig. 6. Results of Bounding Box (BB) analysis. Left: Percentile plots of BB length, width and height (upper and lower lines: 0%,100%; box: 25% to 75%; middle line: Median, 50%). There is only a significant difference in the BB length, which shows that the control hippocampi are more elongated than the schizophrenic hippocampi.

4   Discussion

The visualization of the mean difference and covariance maps showed quite clearly that the initial correspondence established upon segmentation by the deformable registration can be considered less suited for a statistical shape analysis than the SPHARM and MDL correspondence. Due to its higher variance a larger number of subjects would be necessary to attain the same level of significance as SPHARM and MDL. Furthermore, the correspondence appears noisier and less stable.

The result of the bounding box analysis hints at a partial explanation for the differences between the correspondence methods in the subdivision analysis. It shows that the hippocampus in the control population are more elongated in the A-P direction. SPHARM correspondence is based upon equal area proportions on the surface. Due to this approximative non-uniform scaling difference SPHARM surface points in controls are placed in average further away from the center than the corresponding points in schizophrenics. This leads to an significantly enlarged body region for the SPHARM correspondence. MDL has no equal area constraints and does not 'move' corresponding points along the surface unless the overall variability of the point distributions is reduced.

In the presented study, MDL seems to show the most sensible results. Davies et al [24] had already discussed the possible advantages of MDL in shape analysis and we favorably compared MDL to other correspondence methods in model building [1]. However, in all current MDL based shape analysis studies, MDL is optimized over the same populations of objects that are later statistically compared. This application practice introduces a significant statistical bias that needs to be corrected before results based on MDL correspondence can be regarded statistically sound. As a next step we will implement an unbiased computation of the MDL criterion based on a separate healthy control population.

One of the main reasons for the clear differences between the different correspondence methods could be the relatively low number of samples coupled with the large shape variability due to the high age and gender range in this study of adolescents. We are currently performing the same analysis in a second study of adult schizophrenia with a much larger sample size. Preliminary results are

quite stable across different correspondence methods, which suggests that the sample size indeed could be a major factor regarding a stable shape analysis.

5 Conclusions

In this paper, we show that the choice of correspondence method has a non-negligible influence on both the analysis of local shape and on the analysis of regional subvolumes. This influence is likely especially high in studies with a low number of subjects. We suggest that studying the influence of the correspondence method in any shape based study using additional means such as mean overlays, mean difference vector maps and covariance maps gives additional insight necessary to judge the validity of the statistical results. In the hippocampus study in this paper the additional visualizations and tests show that the MDL correspondence method produced the most sensible result.

The results in the hippocampus study suggest that the right hippocampi of adolescent schizophrenic subjects is overall smaller than those in adolescent healthy controls with a main difference observed in the anterior-posterior elongation. After correction for multiple comparisons, the local shape analysis does not show any differences, but the raw significance maps suggest a small deformation difference in the tail as well as in the body region. The subdivision analysis mainly shows significantly smaller right hippocampal regions in schizophrenics in the anterior head and posterior tail region.

Acknowledgment

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