Multi-structure network shape analysis via normal surface momentum maps

Anqi Qiu, Michael I. Miller

Abstract

We present a shape analysis pipeline for the assessment of anatomical variations in subcortical networks in MR images. The shape analysis pipeline injects the global shape properties of the CFA subcortical template into the subcortical parcellations generated from FreeSurfer via large deformation diffeomorphic metric mapping (LDDMM). Examples are shown for this injection in several subcortical structures whose raw MR images were sampled from the database of Open Access Series of Imaging Studies (OASIS). The shape analysis is performed on random field representation of the template surface momentum maps that encode the shape variation of subcortical structure targets of each individual subject relative to the template. The momentum maps have the optimum property that they are supported only on the boundary of the subcortical structures with the direction normal to the subcortical nuclei boundary thereby reducing the dimension of shape variation significantly. A two-level statistical model was built on these momentum maps to assess anatomical connectivity among the subcortical structures on the basis of similar surface deformation (compression or expansion). Results in the study of healthy aging on the hippocampus–amygdala network indicate the anatomical connectivity between the basolateral complex of the amygdala and the subiculum of the hippocampus on the basis of shape compression in healthy elders relative to young adults.

Keywords: Diffeomorphisms, Surface momentum maps, Shape analysis, Random field

Introduction

MR-based volumetric assessment of the human brain has been widely employed in the brain development, normal aging, various neurodegenerative diseases, and neuropsychiatric disorders, including dementia, mild cognitive impairment, schizophrenia, temporal lobe epilepsy, and major depression. In the field of computational anatomy (Grenander and Miller, 1998; Toga, 1999), researchers have largely focused on studying and comparing anatomical configurations of the brain using brain mapping techniques. Compared to volumetric assessments of the brain, different patterns of anatomical shape changes provide richer information to distinguish diseases (e.g. (Yu et al., 2007; Gilmore et al., 2007; Terriberry et al., 2005; Christensen et al., 1997; Bookstein, 1997; Thompson et al., 1996; Chung, 2001; Ashburner and Friston, 2005; Apostolova et al., 2006a; Csernansky et al., 2004a)).

Characterizing the neuroanatomical shape abnormalities associated with neuropsychiatric illnesses is an area of growing importance. Most existing morphometric shape analysis has largely focused on characterizing the neuroanatomical shape abnormalities associated with a disease in the whole brain image volume, cortical hemisphere, or a particular brain region (Fischl et al., 1999; Ashburner, 2007; Csernansky et al., 2004b; Good et al., 2001; Gee et al., 2003; Thompson et al., 2003; Ballmaier et al., 2004). The analysis in the whole brain volumes using voxel-based morphometry (Ashburner et al., 2003) or in cortical hemispheres using spherical registration (van Essen, 2005; Yu et al., 2007; Fischl et al., 1999; Van Essen, 2004) has advantages of discovering brain regions that may be affected by diseases without the prior knowledge from pathological studies. Due to the complicated and convoluted nature of the cerebral cortex and its variability from one subject to another, the whole brain or cortical hemisphere approaches often encounter the problem of large misalignment. It leads to increasing variance of anatomical shape characteristics and thus the loss of statistical power for detecting group difference in shape. Region of interest analysis in particular brain regions, such as the hippocampus and thalamus, has been used to overcome the misregistration and has its own
interest in associating the structure change with disease stages (Apostolova et al., 2006a,b; Csermansky et al., 2004b, 1998). However, there is considerable variation in shape change across multiple structures across disease populations. The assessment of the degree and pattern of structural changes in the multiple structures in neuronal circuits is necessary to optimally distinguish subjects with early forms of various neuropsychiatric diseases. As the growth of large available databases emerges, such as in the study of Autism, Alzheimer’s disease, depression and others, there are tremendous demands on automatic, sensitive, and reliable methods for localizing group differences in multiple structures in neuronal circuits and identifying morphometric biomarkers associated with a specific neuropsychiatric or degenerative disease. In particular, one would expect to identify anatomical connectivity among multiple structures on the basis of similar shape alterations across clinical populations. Such anatomical connectivity may also be linked or shown in pathological studies. Nevertheless, region of interest analysis extended to multiple structures are not available yet. It may partly be due to the difficulties with the morphometric shape assessment in multiple structures, including structure delineation, structure mapping, and statistical testing.

In this paper, we present an automated shape analysis pipeline for studying anatomical variation in subcortical networks, comprised of homogeneous subvolumes such as the amygdala–hippocampus circuit, basal ganglia circuit, thalamus, and ventricular systems. For investigating the shape of these subcortical nucleus structures, it is natural to study them via their segmentations. We use large deformation diffeomorphic metric mapping (LDDMM) to study their global shape by injecting the global properties of the predefined template subcortical structures (Computational Functional Anatomy (CFA) subcortical template) (Qiu et al., submitted for publication) into the segmentations. Even if the low-level voxel based segmentation is noisy, the integrated global properties of the template filters the noisy singularities of the voxel segmentation. The LDDMM generates a geodesic connection of the template to the population of shapes. The resultant template-based representation of the shape variations can be interpreted as a change of coordinates in a local chart centered around a template from which shape inference proceeds. The geodesic connection of subcortical template structures to the targets implies that the entire shape of the population is encoded via vector fields indexed over the template structures. This we term the momentum representation of the population. It becomes the parametric basis for our shape analysis pipeline, the random representation of the momentum maps supported on the template boundary. We model the momentum maps on each individual structure as random field via the orthonormal basis functions of the Laplace–Beltrami operator on the template surface and then identify anatomical connectivity among the subcortical structures on the basis of similar shape alternations (compression or expansion) between two clinical groups via principal component analysis.

Methods

Shape generation via the LDDMM image mapping

We model the space of anatomical shapes \( I \in \mathcal{I} \) to be an orbit of simple segmented subvolumes indexed over \( x \in \mathbb{R}^3 \). The shapes of the subcortical nuclei are represented via their smooth connected subregions \( \Omega^i \subset \mathbb{R}^3 \), \( i = 1, \ldots \) with associated smooth surface boundaries \( \partial \Omega^i \), where \( i \) indexes structures. As we shall see it is these smooth boundaries that carry the shape information in our setting. Of course the segmentations \( I \) are simple functions with value determined by the associated parcellations, for instance,

\[
I(x) = \text{amygdala}, x \in \Omega^{\text{amygdala}},
\]

\[
I(x) = \text{hippocampus}, x \in \Omega^{\text{hippocampus}}.
\]

For template analysis of the population we use the CFA subcortical template, including the lateral ventricles, amygdala, hippocampus, thalamus, caudate, putamen, and globus pallidus, generated by Qiu et al. (submitted for publication). Fig. 1 shows the CFA subcortical template used throughout generated from subcortical parcellations of 41 subjects using the diffeomorphic template estimation algorithm, which was detailed elsewhere (Qiu et al., submitted for publication). The template consists of a collection of homogeneous volumes and bounding smooth surfaces \( I, S \). The shapes and segmented imagery are assumed generated one from the other via a flow of diffeomorphisms, solutions of ordinary differential equations \( \phi_t = \nu_t(\phi_t), t \in [0, 1] \) starting from the identity map \( \phi_0 = \text{id} \), and associated vector fields \( \nu_t, t \in [0, 1] \). To study shape properties of the targets \( I \in \mathcal{I} \), the template is injected into the target coordinates via diffeomorphic metric mapping which computes the geodesic connection \( \phi_t \cdot h_{\text{temp}}, t \in [0, 1] \) connecting the template \( h_{\text{temp}} \) to the targets \( I \in \mathcal{I} \). To ensure the curves are flows of diffeomorphisms, \( \nu_t \in V \) a Hilbert space of smooth vector fields with kernel \( K \) and norm \( |||\nu|||_K \) (see Trouvè, in press; Dupuis, Grenander, and Miller 1998) for specific requirements. The integrated norm \( |||\nu|||_K, t \in [0, 1] \) of the vector field generating the transformation is the geodesic length of the curve. In these smooth Hilbert spaces, it is particularly convenient to define a linear transformation of the vector field, which we term the “generalized momentum”, determined via the kernel of the space \( K: \nu_t \to M_t = K^{-1} \nu_t, M_t \) is generalized momentum since \( \nu_t |||\nu|||_K = \langle M_t, \nu_t > \), the natural generalization of energy given by momentum acting against velocity. In interpreting these equations we point out that generally the momentum is not a smooth function and must be interpreted as a distribution acting against smooth vector fields (Miller et al., 2006).

The anatomical parcellations \( I \in \mathcal{I} \) are generated using FreeSurfer (Dale et al., 1999; Fischl and, 1999; Fischl et al., 2002; Fischl et al., 2004a,b; Han and Fischl, 2007). The

![Figure 1](http://www.bioeng.nus.edu.sg/cfa/template/index.html)
topological and global shape properties of the CFA subcortical template regions are injected by solving the LDDMM image matching (Beg et al., 2005) projecting the template $I_{\text{temp}}$ into the target parcellations $I$. For this, we define a distance function $D(\phi_1 \circ I_{\text{temp}}, I) = \|I_{\text{temp}} \circ \phi_1^{-1} - I\|^2$ between the deformed template, $I_{\text{temp}} \circ \phi_1^{-1}$ and targets, $I$; the template shapes in
target coordinates are given by \( \phi_1 \cdot (I, S) \) where the optimizing \( \phi_1 = \int_0^1 \| v_t \| \gamma dt \) solves the inexact matching problem

\[
J(v) = \int_0^1 \| v_t \| \gamma dt + D(\phi_1 \cdot I_{\text{temp}}, I).
\]

where \( \phi_t = \phi_1 \cdot d_t^{-1} \). Shown in Fig. 2 are examples of the hippocampus generated from FreeSurfer and then examples of the CFA subcortical template injected into the target coordinates via the LDDMM image matching. The first panel of each row shows a sagittal slice with the boundary of the hippocampus delineated by FreeSurfer, while its surface representation is shown in the second panel of each row. The white arrows point to the place where the errors occur in the FreeSurfer labeling procedure (unsmoothness, topological error). Fig. 3 shows the examples of the caudate and the lateral ventricles. Panel (a) shows a sagittal slice with the contour of the caudate generated by FreeSurfer. The arrow points where the extra volume is included in the caudate, as illustrated in panel (b). Panels (e, f) show the volume and surface representations of the lateral ventricles. In the surface representation, the inferior lateral ventricle was clearly not labeled in the FreeSurfer process.

We quantitatively evaluated the shape denoising procedure by comparing the structure volumes after the shape denoising with those of FreeSurfer labeled volume using a volume overlap measurement defined in (Collins and Evans, 1997). Given two different labelings (before and after the segmentation denoising) of a structure, \( L_b \) and \( L_o \), then \( O(L_b, L_o) = \frac{\| L_b \| \cap \| L_o \|}{\| L_b \| + \| L_o \| - \| L_b \| \cap \| L_o \|} \) where \( V \) is a function that takes a label and returns its volume. When the labels, \( L_b \) and \( L_o \), are identical, \( O(L_b, L_o) \) achieves the maximum value of 1. Decreasing values of \( O(L_b, L_o) \) indicates less overlap. We computed \( O(L_b, L_o) \) for forty one subject with ten youths (4 males and 6 females, age: 21.3±1.57), ten adults (5 males and 5 females, age: 49.8±5.79), ten elders (5 males and 5 females, age: 73.6±7.05), and eleven patients with dementia (5 males and 6 females, age: 77.2±5.64) selected based on demographic information (gender, age, and diagnosis) whose raw MR images were chosen from the OASIS database. \( L_b \) is the labeling volume from FreeSurfer and \( L_o \) is the labeling volume after the shape denoising. Fig. 4 shows the average value of \( O(L_b, L_o) \) over the forty one subjects and the standard errors for each structure. Compared to the labeling volumes from FreeSurfer, the volume overlap for each individual structure is above 80%. The shape denoising gives roughly equivalent quality for each of the structures. The non-overlapped region between \( L_b \) and \( L_o \) most occurs where the FreeSurfer segmentation are not smooth or has topological errors as illustrated in Figs. 2 and 3. The discrepancy of \( L_b \) and \( L_o \) may also occur when thin structures are not able to identify in the MR images at the current MRI resolution.

![Fig. 3. Caudate and ventricle examples of the template injection. Panel (a) shows a sagittal slice with the cyan contour at the boundary of the caudate automatically labeled in FreeSurfer. Its surface representation shows in panels (b). Similarly, panels (e, f) show the volume and surface representations of the ventricle segmented from FreeSurfer. The arrows point where the errors occur in the FreeSurfer labeling process. Panels (c, g) illustrate the same sagittal slice with the pink contour at the boundary of the caudate and ventricle after the template injection, while panels (d, h) give their surface representations. The raw MR images shown here were selected from the database of OASIS.](image)

![Fig. 4. Panel shows the validation of the segmentation denoising procedure using the volume overlap measurement when comparing with the FreeSurfer segmented volume. The error bars are the standard errors of the volume overlap. Black and white bars respectively denote the left and right structures. Key: Am – Amygdala, Hp – Hippocampus, Ca – Caudate, Pa – Globus Pallidus, Pu – Putamen, V – lateral and inferior lateral ventricles.](image)
Parametric shape encoding via normal surface momentum maps

The subcortical structures are homogeneous subvolumes with shape encoded via the mappings applied to the collection of template surfaces and subvolumes. As we now show, for homogeneous subvolumes the representation of shapes can be reduced to a representation of scalar fields which are concentrated on the boundary of the different homogeneous subvolumes. These scalar fields indexed over the bounding surfaces determine the “momen数” of the LDDMM mapped template shapes into the populations and become the variables for encoding the shape variation of the homogeneous subvolumes.

This parametric reduction follows from two key properties of the geodesic connection of the template to the target: (i) the conservation of momentum property, and (ii) the normality property. To see this, the geodesic connection from the template surface to the target shapes is the minimum length curve carrying $\phi_1(t)_{temp}$ exactly to $I$ satisfying

$$p(I) = \inf_{\phi} \int_0^1 \left( \| v_t \|^2 = \langle M_t, v_t \rangle \right) dt.$$  

The Euler equation associated to the geodesic shortest paths implies the geodesics completely encoded by the initial momentum field $M_0$ rooted at the template at time 0; along the geodesic path it is conserved (Miller et al., 2002, 2006) according to

$$M_t = |D\phi_t^{-1}| \left( D\phi_t^{-1} \right)^T M_0 \phi_t^{-1},$$

where $D$ is the Jacobian matrix and $^T$ is matrix transpose. The problem of studying shapes of a population in a nonlinear diffeomorphic metric space turns to a problem of studying the initial momentum attached to the template in a linear space (Vaillant et al., 2004). Secondly, the normality property of the geodesic follows from the fact that along the geodesic the momentum is normal to the level lines of the template, which is proven in (Miller et al., 2006) for the general case. As an example, the normality condition expressed by Eqn. (2) results in results in $M_I = \mu I_{temp}$ following the gradient of the template with $\mu = |D\phi_t| (1 - \phi_t - I_{temp})$. This is the essential basis for the parametric reduction we exploit for studying circuits of multiple structures which are homogeneous subvolumes. For homogeneous structures $\Omega$ such as the deep nuclei, the initial momentum is concentrated on the boundaries and normal to the bounding surfaces $S = \partial \Omega$. Parametrizing the momentum $M_0(x)$ at time 0 becomes our representation, exploiting the fact that it is concentrated on the boundaries of the substructures and generated from a collection of normal vector fields which are solely supported on the boundaries of each of the template structures. We can thus model it as

$$M_0(x) = \mu(x) N(x), x \in S,$$

with $N(x)$ the normal field to the template surfaces. Notice $M_0(x) = 0$ for $x \in S = \partial \Omega$. Population shape variation is represented by the signed-length of the scalar fields $\mu(x), x \in S$ with positive sign pointing outward motion and negative pointing inward motion relative to the template coordinates. We shall call $\mu(x)$ the “normal surface momentum map” encoding the shape change of subjects’ subcortical structures relative to the template, which will be considered as a random momentum map when interpreting it in statistical testing and empirical statistical model building.

To extract the normal scalar momentum maps for each subvolume $\mu(x), i = 1, \ldots, n$ of the template onto the population of brains, we model the template and target surfaces as two-dimensional smooth manifolds with the neighborhood of every point on the surface equivalent to a two-dimensional plane in the Euclidean space. Each plane can be uniquely defined by a point and a vector originated at this point and normal to the plane, thus representing the surfaces as triangulated meshes. After rigidly (rotation and translation) aligning the template and target surfaces, LDDMM surface mapping (Vaillant and Glaunès, 2005; Vaillant et al., 2007) is applied to extract the momentum fields indexed over the template surface $S_{temp}$ which carries them onto the target surfaces $S$. The LDDMM surface mapping directly compares
the normal vectors of the deformed template surface and the target surface in the matching functional given by

\[ D(\phi_1 \cdot S_{\text{temp}}, S) = \sum_{f \in g} \eta_{b_1(c(f))} \cdot W(\phi_1(c(f)), \phi_1(c(g)))\eta_{b_1(c(g))} - 2 \sum_{f \neq g} \eta_{b_1(c(f))} \cdot W(\phi_1(c(f)), (c(g)))\eta_{b_1(c(g))} + \sum_{g \neq r} \eta_{(c(g))} \cdot W(c(q), c(r))\eta_{(c(r))}, \]

where the deformed template and target surfaces are represented by the center of face \( i, c(i) \), and the normal vector of face \( i, \eta_{k(i)} \). \( f, g \) are indexes of the faces on the deformed template surface and \( q, r \) are indexes of the faces on the target surfaces. \( W \), a radial positive definite \( 3 \times 3 \) diagonal matrix function, serves as smoothing kernel. The terms in Eqn. (6) integrate local geometry for each face via inner products of its normal with normals of neighboring faces. The choice of kernel function \( W \) controls the local neighborhoods used in the calculations. The first and last terms measure the local geometry within the deformed template surface and the target surfaces, and the second term measures the mismatch in local geometry between the deformed template surface and the target surface via the correlation of the normal vector on the deformed surface with the smoothed normal vector in the neighborhood on the target surface. The LDDMM surface mapping is used because it directly provides the surface representation of the momentum maps that encode the shape variations of targets relative to the template and facilitate statistical testing on shape differences described in the next section.

The pipeline for the reduction of the target brains to the normal surface momentum maps encoding each shape is depicted in Fig. 5 below. The template segmentation is injected onto the target segmentations generated from Freesurfer via diffeomorphic mapping \( \phi_1 \): \( S_{\text{temp}} \to I \) for the population of segmentation parcellations. Each target shape is generated according to \( S' = \phi_1 \cdot S_{\text{temp}} \), \( i = 1, 2, ..., n \). The momentum maps indexed over the template coordinates \( M_{\phi_1} = \mu'N \) are extracted by surface mapping \( S_{\text{temp}}' \) to \( S' \). Shown in Fig. 5 is a depiction of one momentum map encoding of the target shape via the template with the associated normal momentum field.

**Random field modeling of the momentum maps**

When trying to characterize shape variations, perhaps most importantly, one is asked to detect group differences when shape variations of adjacent structures are considered. This can be quite challenging when the deformation data are geometric objects and of very high dimensionality and the number of individuals in each group is small. In this section, we examined a two-level hierarchical statistical analysis model by first building random fields within each subcortical structure based on its geometry and then reducing the data dimensionality via principal component analysis (PCA) for expressing the correlation pattern of shape variations in the multiple subcortical structures in order to identify anatomical connectivity between regions on the basis of similar shape change pattern (e.g., compression or expansion).

In the first level, we assume each scalar momentum map \( \mu'(\cdot) \) on subvolume structure \( i \) is a random field according to

\[ \mu'(x) = \sum_{k} F_{\phi_k}(x), x \in S_{\text{temp}}, \]

where the \( F_{\phi_k} \) are random variables and \( \phi_k(\cdot) \) are chosen as the \( k \)-th basis function of a complete set of orthonormal bases generated by the Laplace–Beltrami (LB) operator on template structure \( S_{\text{temp}} \) (Qiu et al., 2006, 2008). The finite number of random variables, \( F_k, k = 1, ..., n \), characterizing the random momentum map \( \mu'(\cdot) \) of structure \( i \) is determined by a goodness-of-fit at a certain discrepancy level.

Shown in Fig. 6 are illustrations of the several Laplace–Beltrami basis functions defined on the amygdala and hippocampus templates which are used for the reduction of the momentum maps to discrete random variables. Each row shows the second, fifth, and seventh LB basis functions generated for the amygdala and hippocampus structures. The top row shows the LB basis functions for the amygdala; the bottom row shows the LB basis functions the hippocampus. Positive and negative regions rapidly alternate once moving to the high order basis, which can characterize high frequency shape variations.

In the second level, we express the correlation pattern of the deformation, represented by \( \mu'(\cdot) \), across the subcortical structures through the correlation of \( F_k \) using principal components (PCs) to identify anatomical connectivity between the subcortical regions on the basis of similar shape changes (compression or expansion) between two groups. Ones with high absolute principal component values clearly covary together and are therefore correlated. To do so we assume \( F_k \) from all structures, \( i = 1, 2, ..., n \), are Gaussian distributed with fixed mean and covariance. \( n \) denotes the number of the structures involved in the study. Denote \( F \) to be a feature vector in the form of

\[ F = [F_1, F_2, ..., F_1, F_2, ..., F_n, F_2, ...,]. \]

PCA is used to linearly project \( F \) to the orthogonal directions, \( U_j, j = 1, 2, ..., m \), that carry the greatest variance according to \( F = \sum_{j=1}^{m} \alpha_j U_j \). The lower order PC-scores, \( \alpha_j, j = 1, 2, ..., m \), retain those characteristics of the shape variation in the subcortical structures. The PC-scores are linearly independent variables. We can thus test each of the PC-scores using a linear regression model with diagnosis as independent variable after covarying for total intracranial volume, age, gender, or other factors.

**Momentum shape analysis on hippocampus–amygdala network in healthy aging**

We applied this shape analysis pipeline to a study of healthy aging influence in the hippocampus–amygdala circuit. These two structures were assessed in 10 young adults and in 10
healthy elders using magnetic resonance (MR) imaging. The MR scans used in this study were selected from the database of OASIS (Marcus et al., 2007). The group of young adults included 5 males and 5 females with mean age of 22.9 (SD: 2.8) years; the group of elders included 5 males and 5 females with mean age of 71.0 (SD: 2.8) years.

We processed the raw MRI images by following the steps illustrated in Fig. 5. FreeSurfer was used to prelabel the hippocampus and amygdala from the MR image volumes as automated subvolume segmentation step. We injected the CFA subcortical template volume with labels of the hippocampus and amygdala into the prelabeled images to generate hippocampal and amygdala shapes. The LDDMM-surface mapping algorithm was then applied to extract the normal surface momentum maps encoding the shape of the targets in the template coordinates, denoted as $\mu_{\text{hippo}}$, $\mu_{\text{amyg}}$. Using a computer with 4G memory and dual core CPU, the shape denoising process via LDDMM image mapping takes about 30 min per subject; the extraction of the surface momentum maps via LDDMM-surface mapping takes around 30 min per subject.

The momentum is a random field essentially defined on the continuum of the surface representations. For statistical testing we represent $\mu_{\text{amyg}}$, $\mu_{\text{hippo}}$ by a linear combination of a spatially localizing LB basis functions defined on the amygdala and hippocampus in the form of

$$\mu_{\text{amyg}}(x) = \sum_{i=1}^{31} f_{i}^{\text{amyg}} \psi_{i}^{\text{amyg}}(x), x \in S_{\text{temp}}^{\text{amyg}},$$

$$\mu_{\text{hippo}}(x) = \sum_{i=1}^{53} f_{i}^{\text{hippo}} \psi_{i}^{\text{hippo}}(x), x \in S_{\text{temp}}^{\text{hippo}},$$

based on a goodness fit at a discrepancy level of 0.2 such that $\mu_{\text{amyg}}(x) = \sum_{i=1}^{31} f_{i}^{\text{amyg}} \psi_{i}^{\text{amyg}}(x), x \in S_{\text{temp}}^{\text{amyg}} = 0.2$. A total of 84 LB coefficients over the two structures were selected and were used to construct feature vectors $F^{(j)}$ for each subject for $j = 1, 2, ..., 20$ according to

$$F^{(j)} = [f_{1}^{\text{amyg}}, f_{2}^{\text{amyg}}, ..., f_{31}^{\text{amyg}}, f_{1}^{\text{hippo}}, f_{2}^{\text{hippo}}, ..., f_{53}^{\text{hippo}}].$$

PCA was then performed on $F^{(j)}$ to extract the first ten principal components, $U_k$, that characterize 85% of the shape variations of the hippocampus and amygdala. We thus can approximate $F^{(j)} = \sum_{k=1}^{10} \alpha_{k}^{(j)} U_k$ for the $j$th subject. We tested each PC-score, $\alpha_{k}^{(j)}$, using a linear regression model when the grouping is considered as independent variable after covarying with estimated total intracranial volume (Buckner et al., 2004). The normality of these PC scores were assessed by computing the coefficient of correlation between the residuals and their expected values under normality. A high value of the correlation coefficient is indicative of normality. For the ten PC-scores, all correlation coefficients are above 0.92, which suggests the PC-scores follow Gaussian distribution. Thus, we reported the p-values for each PC-score derived from the linear regression models here: 0.5661, 0.1950, 0.2111, 0.2257, 0.0404, 0.0844, 0.6536, 0.9853, 0.7947, 0.7932, respectively. The fifth principal component shows statistically significant group difference at a significance level of 0.05. To visualize this result, we back projected the group difference in the fifth PC-score, $\alpha_{5}^{(\text{young})} - \alpha_{5}^{(\text{elder})}$, to the coordinate system of the LB coefficients based on $F_{i}^{(\text{young}-\text{elder})} = (\alpha_{i}^{(\text{young})} - \alpha_{i}^{(\text{elder})}) U_5$.

Then, we projected $F_{i}^{(\text{young}-\text{elder})}$ to the coordinate systems of the template, $(S_{\text{temp}}^{\text{amyg}}, S_{\text{temp}}^{\text{hippo}})$, based on

$$\mu_{\text{amyg}}(x) = \sum_{i=1}^{31} f_{i}^{(\text{young}-\text{elder})} \psi_{i}^{\text{amyg}}(x), x \in S_{\text{temp}}^{\text{amyg}},$$

$$\mu_{\text{hippo}}(x) = \sum_{i=1}^{53} f_{i}^{(\text{young}-\text{elder})} \psi_{i}^{\text{hippo}}(x), x \in S_{\text{temp}}^{\text{hippo}},$$

which shows the group difference in the momentum maps as illustrated in Fig. 7(a).

We now emphasize the contribution of the LB bases of each structure to the statistical significant principal components representing the mixture of the information from the different structures. To illustrate this, selectively shown in Fig. 8 are the LB coefficients which contributed to the fifth principal component as signalled by the 2nd, 5th, 7th LB basis functions localized to the amygdala and hippocampus. This figure indicates distinct contribution of the LB basis functions of the two structures to the change shown in Fig. 7(a).

To interpret the momentum maps in terms of how the two structures change in the group of elders relative to the group of young adults, Fig. 7(b) shows the geodesic flow (Miller et al., 2002; Miller et al., 2006) generated based on the momentum map of Fig. 7(a) demonstrating the displacement map between the young adults and elders. Compared to the group of young adults, blue denotes the region where the structure is compressed in the group of elders, while red indicates the region where the structure is expanded in the group of elders. The
figure suggests that the regions in the subiculum subfield of the hippocampus are compressed in the group of healthy elders compared to the group of young adults. Moreover, the basolateral complex nuclei of the amygdala also show the shrinkage in the group of elders. Thus, the subiculum subfield of the hippocampus and basolateral complex nuclei of the amygdala are anatomically connected on the basis of the compression deformation in the elders relative to the young adults.

Discussion

In this paper, we present an automatic shape analysis pipeline for anatomical shape comparison across clinical populations in a subcortical network. This shape analysis pipeline contains several key components, including template shape injection, the construction of the normal surface momentum maps, as well as random field statistical testing on the normal surface momentum maps. This pipeline allows us to identify anatomical connectivity among the subcortical regions on the basis of similar shape alterations between two clinical groups.

In the template shape injection, we inject the CFA subcortical template with nice properties of smoothness and topology to FreeSurfer segmented subcortical volumes to smooth out unfavorable features using the LDDMM image mapping. We quantified the volume overlap between the structure volumes after the template shape injection and FreeSurfer labeled volumes. Among 41 subjects, the volume overlap measurement is above 80% for each individual structure. Even though we only discussed the shape analysis when FreeSurfer segmented subcortical volumes were used throughout this paper, the procedure for the shape comparison can also deal with subcortical parcellations generated using other approaches, for instance, manual labeling. The introduction of topological and smoothness properties via the integration of the template based LDDMM algorithms has been previously examined in the manual segmented medial temporal lobe (Miller et al., 2005; Kirwan et al., 2007).

Our main focus of this work here is to reduce the study of parametric shape of homogeneous subvolumes to statistical inference on the normal surface momentum maps in the structural template surfaces. In the segmented volumes the subcortical structures are considered as homogeneous subvolumes. Their shape variation relative to the template thus concentrates on the boundary of the structures. We apply the LDDMM surface mapping algorithms to construct the normal surface momentum maps indexed over the boundaries of the subcortical structures for encoding the shape variation.

In our two-level statistical model, the momentum maps of each structure are first assumed to arise from random processes that are modeled as an expansion of the LB basis functions indexed over the surface boundaries. There are other orthonormal bases that can be used for this purpose (e.g. spherical harmonics, spherical wavelets) (Yu et al., 2007; Chung et al., 2008). Both spherical harmonics and spherical wavelets are built on a sphere. They thus need the correspondence information between the structural surface and a sphere, which introduces distortion non-uniformly distributed over the structure. This may directly increase shape variations across subjects and decrease statistical power. Thus, we prefer using the LB bases that are computed based on the surface geometry in each individual structure. They are intrinsic to the template structure and not dependent on the deformation data. The size (local surface area) of the structures has been automatically taken into account when we first decompose the normal momentum maps in a linear combination of the LB bases. The correlation of the normal momentum maps within each structure is only locally measured. In the second level of our statistical model, the multiple structures are studied through the correlation of the LB coefficients representing each structure shape variation via PCA to identify anatomical connectivity among the subcortical regions on the basis of similar shape deformation. This is similar to the idea in defining functional connectivity between brain regions on the basis of similar functional response in functional MRI studies (Worsley et al., 2005). For the purpose of seeking anatomical connectivity among the subcortical regions, one may suggest directly applying PCA on the momentum maps from all structures at once. This approach considers each structure equally contributed to the shape variations in the multiple subcortical structures without the size (surface area) information of each individual structure. Every point on all structures also equally contributes to the statistical analysis, which is often not true because of unequal sampling on the template surface and geometry differences. Furthermore, PCA considers that every point on the template structure is correlated with all other points including ones on the other structure even though they are far apart. We thus prefer our two-level statistical model on the momentum maps of the multiple subcortical structures.

In this paper, we applied this shape analysis pipeline to the study of healthy aging in the hippocampus–amygdala circuit and demonstrated the sensitivity of the method in a small sample size of MR images. This automated shape analysis pipeline will be used to assess shape abnormalities in the subcortical regions in mild cognitive impairment and Alzheimer’s disease using the dataset publicly available through Alzheimer’s Disease Neuroimaging Initiative (ADNI).

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