Automated Morphometry of MRI Brain Images with the Use of Deformable Registration

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AUTOMATED MORPHOMETRY OF MRI BRAIN IMAGES WITH THE USE OF DEFORMABLE REGISTRATION

SHORT VERSION OF PH.D. THESIS
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1 INTRODUCTION

The human body is an incredibly complex system. Acquiring data about its static and dynamic properties yields massive amounts of information. The use of images is the most effective way to manage, present and interpret the vast quantities of that information in the clinical medicine and in the supporting biomedical research. Computational neuroanatomy is a new growing field of powerful applications in neuroscience. It promises an automated methodology to characterize neuroanatomical configuration of structural magnetic resonance imaging (MRI) brain scans. One of the crucial techniques in this methodology is image registration. It performs the task of spatial normalization of images according to a common reference anatomy termed as a brain atlas. It allows interpreting results of an image analysis in a standard anatomical coordinate system. Further, an atlas of brain makes it possible to find out how different is a subject brain compared with the common reference anatomy which represents certain population. Many approaches to registration of brain images assume same or functionally dependent intensities in the images across subjects. Thus, they allow the registration process to be driven by differences in intensities. They however do not count on intensity variations caused by various imaging conditions or tissue atrophy and degradation induced by neurological diseases. On the other hand, the image registration methods which are robust to such intensity variations enable only low-dimensional parametric transformations, which make it impossible to detect localized image differences without additional efforts. This thesis mainly contributes to the field of registration with the use of nonlinear locally adaptive transformations. Particularly, problems connected to matching MRI brain image data obtained from various subjects and with various imaging conditions are solved here. Difficulties lie in the complex brain structure which varies widely from one individual to another. Other difficulties lie in the complex and unknown relations between intensities in images to be registered. A solution of a specific clinical task from the field of computational neuroanatomy is further presented.

2 MEDICAL IMAGES

Conceptually, an image is a two- (2D) or three- (3D) dimensional distribution of a variable such as intensity of a signal from an image receptor. Today, most medical modalities yield digital images composed of a finite number of numerical values of intensity. An image element is termed a pixel in the case of a 2D image and a voxel in the case of a 3D image [21]. Magnetic resonance imaging is a highly successful diagnostic imaging modality, largely due to its rich set of contrast mechanisms. The signal intensity is a multivariable function, depending on many parameters. Partial listing includes proton spin density PD, spin lattice relaxation time T1, spin spin relaxation time T2, proton flow and diffusion. Due to its exceptionally high soft tissue contrast, MRI lends itself well to morphometric studies in the brain where clear distinction between structures is required [1].
3 REGISTRATION OF MEDICAL IMAGES

Image registration is a process of estimating a spatial transformation which maps each point of an image onto its corresponding point of another image [43].

3.1 CLASSIFICATION OF REGISTRATION METHODS

Image registration is a fundamental problem in medical image analysis. A universal method does not exist due to the diversity of registration tasks. There are various approaches to the classification of image registration methods in surveys [30][43][55]. Selected criteria from [30] are used here to classify registration methods, see Tab. 3.1.

Tab. 3.1: Selected classification criteria of image registration methods.

<table>
<thead>
<tr>
<th>Registration basis</th>
<th>Nature of transformation</th>
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<th>Optimization procedure</th>
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</table>

3.2 OPTIMAL LINEAR REGISTRATION

Optimal registration can be defined as an optimization problem with the goal of finding the spatial mapping that will bring the floating image $N$ into alignment with the reference image $M$. Fig. 3.1 [25] shows its basic steps.

Fig. 3.1: Basic components of an optimal registration framework.

The spatial transformation $\varphi^{-1}_a$ maps points from the reference image space to points in the floating image space. It is parameterized by a vector of parameters $a$. It is in fact an inverse mapping which is preferable as it avoids problems of holes with the forward mapping. The transformation is directly connected to interpolation which serves for evaluation of floating image intensities at non-grid positions. The similarity measure $S(M, N \circ \varphi_a)$ or its negative forms a criterion of optimality – a cost
function which is minimized in the optimization over the search space defined by parameters of the spatial transformation.

3.2.1 Affine transformations

The affine transformation is one of the most popular transformations used in image registration. It can be described by a single $4 \times 4$ matrix computed as a product of matrices representing translation, rotation, shearing and scaling.

3.2.2 Similarity measures

The choice of an appropriate similarity measure is determined by the character of intensities in the floating and the reference image. Popular choices are based on intensity, correlation and mutual information. Supposing the image intensities to be discrete random variables, their mutual information (MI) is defined as [25]:

$$I(M,N) = H(M) + H(N) - H(M,N) = \sum_{m,n} p_{MN}(m,n) \log_2 \frac{p_{MN}(m,n)}{p_M(m)p_N(n)},$$

(3.1)

where $I(M,N)$ is the mutual information of random variables $M$ and $N$, $H(M)$ and $H(N)$ are entropies of $M$ and $N$ respectively and $H(M,N)$ is the joint entropy of $M$ and $N$. It is rewritten to a form containing marginal probability density functions (PDF) $p_M(m)$, $p_N(n)$ and joint PDF $p_{MN}(m,n)$. MI gives a measure of the strength of the dependence between the random variables. The major advantage of using MI is that the actual form of the dependency does not have to be specified. Therefore, MI is well suited as a criterion of multimodal registration. The marginal and joint PDFs are estimated from image data by Parzen windowing [32][48][52] or by normalizing the joint histogram [28][29].

3.2.3 Optimization techniques

An optimization technique is needed to find the spatial transformation defined by a vector of affine transformation parameters $a=[a_1, \ldots, a_D]$. The number of parameters $D$ ranges from six, for rigid body transformation, to twelve, for general affine transformation. Optimization methods with no gradient computation requirement are typical for correlation-based and mutual information-based criterions. Powell's directions set method [29][36], downhill simplex method [7] and simulated annealing [9][27] are most often examples.

3.2.4 Interpolation

To alleviate the problems associated with direct intensity interpolation methods, partial volume interpolation (PVI) was proposed in [28] for mutual information-based registration. It was further extended to a scheme called generalized partial volume joint histogram estimation (GPVE) [23].

3.3 DEFORMABLE REGISTRATION

In many medical imaging applications, the global linear alignment does not provide a sufficient solution. A nonlinear transformation is necessary to correct the local differences in the images. Here, the process of finding such a transformation is
termed as deformable registration. The reference image $M$ and a floating image $N$ are expected to be aligned by the global linear transformation. The central idea behind deformable registration is to find local forces which will deform the floating image to make it more similar to the reference image, see Fig. 3.2. The transformation $\varphi(x)$ is usually split into the trivial identity part and a so called displacement field $u(x)$ [32]:

$$\varphi(x) = x + u(x).$$  \quad (3.2)

Computation of the displacement field involves local forces together with regularization provided by a spatial deformation model. Regularized mapping function ensures realistic registration results without tearing or folding of the image.

![Fig. 3.2: Basic components of a deformable registration framework.](image)

### 3.3.1 Parametric deformable registration

Parametric transformation (sometimes termed as low-dimensional) can be expanded in terms of some parameters $a_i$ and basis functions $\psi_i$. The registration task is to determine the parameters of the transformation. Methods based on radial basis function (RBF) interpolation are used widely. Wendland’s functions [14] and thin-plate splines [26][34] are examples of RBFs used in image registration. Other functions used for parametric deformations are B-splines [42][44][45], components of discrete cosine transform [4] or wavelet basis functions [11].

**Image deformation with RBFs**

The displacement field $u(x)$ is controlled by a finite number of movable control points. The interpolation problem is solved separately for each coordinate of the displacement field:

$$u_k(x): \mathbb{R}^d \rightarrow \mathbb{R}, \quad u_k(p_i) = f_{i,k}, \quad i = 1...n, \quad k = 1...d.$$  \quad (3.3)

where $d$ is the image dimension, $p_i$ constitute a given set of $n$ control points and $f_i$ are their translations. Using RBFs, the interpolant is constructed:

$$u_k(x) = \sum_{j=1}^{m} b_j \phi_j(x) + \sum_{i=1}^{n} a_i R(\|x - p_i\|),$$  \quad (3.4)
where the first term is a linear combination of polynomials and the second term is a linear combination of RBFs. Here, $\phi_j$ are $m$ polynomial components, $R$ denotes a RBF and $\|x-p_i\|$ is the Euclidean distance from $x$ to $p_i$ and $a_i$, $b_i$ are coefficients. A RBF is a function depending only on the distance from the origin: $R(||x-p_i||)=R(r)$. By inserting (3.4) into (3.3) and using constraints that guarantee polynomial precision [3], a following system of linear equations for the coefficients $a=[a_1, ..., a_n]^T$ and $b=[b_1, ..., b_m]^T$ is obtained:

\[
\begin{pmatrix}
K & P \\
P^T & 0
\end{pmatrix}
\begin{pmatrix}
a \\
b
\end{pmatrix}
=
\begin{pmatrix}
f_k \\
0
\end{pmatrix},
\]

where $K$ is a $n \times n$ sub-matrix given by $K_i=R(||p_i-p_j||)$, $P$ is a $n \times m$ sub-matrix given by $P_{ij} = \phi_j(p_i)$ and $f_k=[f_{k,1}, ..., f_{k,n}]^T$ is a vector of the $k$th coordinate of the control points' translations $f_i$. The polynomial sub-matrix $P$ depends on the type of RBF. For thin plate splines ($R_{TPS}$), it has its $i$th row of the form $[1, x_{pi}, y_{pi}, z_{pi}]$, which are $x$, $y$ and $z$-components of $p_i$ [10]. Hence, there is a global influence of a control point on the resulting displacement field $u(x)$. Compactly supported RBFs ($R_{CP}$) are another recent choice. Due to their positive definiteness, the regularity of the matrix $K$ is ensured. Therefore, no polynomial part is needed and (3.5) reduces to:

\[
K a = f_k.
\]

One of Wendland's functions [53] is proposed for deformable image registration in [27]:

\[
R_{CP}(r) = (1-r)^+4(4r+1).
\]

Its mathematical properties hold for various spatial supports $s$, such that: $R_{CP}(r; s)=R_{CP}(r/s)$. Compared to other RBFs, the use of $R_{CP}$ is highly efficient, as the matrix $K$ is rather sparse and no transcendental functions are involved in the calculation. The support length $s$ cannot be set arbitrary, as there is a fundamental condition of topology preservation. This requirement is satisfied if the determinant of the Jacobian of the deformation is non-negative.

### 3.3.2 Non-parametric deformable registration

Non-parametric deformable registration methods (sometimes termed as high-dimensional) directly compute a displacement in every point most often by imitating real world transformations of deformable materials. One of the first proposed methods based on continuum mechanics was elastic matching [2][13][32]. Only small deformations are assumed, thus linear elastic model can be used. In [24], a viscous fluid model is used to control the deformation. The floating image is modelled as a thick fluid that flows out to match the reference image under the control of the local forces. Convolution filter methods for solving associated PDE were proposed in [6][18]. Various solvers of the PDE are discussed in [53] with regard to the computational cost. A considerable piece of work is presented in [40][41], where Gaussian filters are used for modelling the spatial deformation. The Gaussian filters are used to approximate the elastic as well as the fluid model. It is
also successfully used for a so-called incremental model, which is used for image registration in [35]. A spatial deformation model made up from the elastic and the incremental model is proposed, in order to combine their advantages and thus improve the registration. The model consists of two convolution filters [41]:

\[
\mathbf{u}_f = k \mathbf{f},
\]

\[
\mathbf{u}^i = \left( \mathbf{u}^{i-1} + \mathbf{u}_f \ast \mathbf{G}_f \right) \ast \mathbf{G}_E,
\]

see the scheme in Fig. 3.3. The first part follows the Hooke’s law to compute unregularized displacements \( \mathbf{u}_f \) of image points. It says that the points move proportionally to the applied forces with a constant \( k \). The filter \( \mathbf{G}_f \) regularizes displacement improvements \( \mathbf{u}_f \) and the second filter \( \mathbf{G}_E \) regularizes the overall displacement field \( \mathbf{u} \).

![Fig. 3.3: The combined elastic-incremental model.](image)

### 3.3.3 Local forces estimation and similarity measures

Local forces are obtained either by optimization or they are computed directly, depending on a particular registration method. In the former case, the registration is usually based on a global similarity measure which detects improvement of local image correspondence [42][44], or block matching techniques are performed [26][29]. Most suitable translations are found in an optimization procedure with the use of monomodal as well as multimodal similarity measures. In the latter case, the forces are estimated in every point as the derivative of a similarity measure. The resulting dense field of the forces is used to compute a high-dimensional deformation, often based on some physical interpretation. The registration methods which perform the high-dimensional warping are typically limited to monomodal data, e.g. [6][24][50]. However, the effort to develop registration algorithms focused on high-dimensional matching of multimodal data recently emerged. In [37], point similarity measures are proposed for high-dimensional deformable registration of multimodal data. The point similarity measures are derived from global similarity measures based on the joint PDF estimated from the joint histogram.

The point similarity measure \( S_{MI}(\mathbf{x}) \) derived from the global mutual information is defined as [38]:

\[
S_{MI}(\mathbf{x}) = \log_2 \frac{p_{MN}(m(\mathbf{x}), n(\mathbf{x}))}{p_{M}(m(\mathbf{x}))(p_{N}(n(\mathbf{x}))}
\]
The negative joint entropy $-H(M,N)$, which is the most informative part of MI can be used as a global multimodal similarity measure and a point similarity measure $S_H$ can be derived. In [29], conditional probability densities are used for a region similarity measure, which is here rewritten as another point similarity measure:

$$S_{PC}(x) = p(n(x|m(x)))$$

(3.11)

In [37], other measures are proposed:

$$S_{UC}(x) = \frac{p_{MN}(m(x),n(x))^2}{p_{M}(m(x))p_{N}(n(x))}$$

(3.12)

$$S_{UH}(x) = \log_2 p_{MN}(m(x),n(x)) + \log_2 \frac{p_{MN}(m(x),n(x))}{p_{M}(m(x))p_{N}(n(x))} = S_H + S_{MI}.$$  

(3.13)

Any point similarity measure can be used to compute a region similarity measure by simply averaging the point similarities over the region. The averaging over a region can also be viewed as convolution filtering with some spatial filter [38]. Convolution spatial filtering was described in chapter 3.3.2 as a method for modeling spatial deformations. The regularization provided directly by region similarity measures is substantial for large regions. The concept of local forces based on the derivative of a point similarity measure is further extended in [39], where symmetric local forces are proposed to improve registration consistency.

## 4 IMAGE REGISTRATION IN COMPUTATIONAL NEUROANATOMY

The rapid development of brain imaging systems in last decades enabled a huge number of in vivo studies focused on characterization of normal and pathological morphological variation in brain anatomy. The goal of the studies is to clarify, how the morphological changes implicate brain pathology, and to illustrate the relationship between the brain morphology and its function. Morphometry methods can be broadly classified into region of interest (ROI)-based or whole brain techniques [17]. The conventional ROI based methods require manual segmentation, which makes them time-consuming, subjective and error-prone. Recently, several automated whole brain morphometry methods, together termed as computational neuroanatomy methodology [5], have been proposed.

### 4.1 MORPHOMETRY METHODS

Morphometry methods in computational neuroanatomy involve image registration to match subjects' anatomies with a standard atlas brain. This makes it possible to compare data across different subjects in a standard stereotaxic space.

#### 4.1.1 Voxel-based morphometry

Voxel-based morphometry (VBM) is a computational approach to neuroanatomy that measures differences in local concentrations of brain tissue, through a
voxel-wise comparison of multiple brain images. It involves spatially normalizing subjects' images to the same stereotaxic space, extracting the grey matter from the normalized images, smoothing, and finally performing a statistical analysis to localize, and make inferences about group differences.

4.1.2 Deformation-based morphometry

Deformation-based morphometry (DBM) analyses differences in vector fields that describe differences in brain shape. These vector fields are the displacement fields of the deformations produced by deformable registration of subject images to a template image of some standard brain anatomy. Significant differences in relative positions of structures within subjects’ brains can be detected by analyzing the displacement fields directly. In addition, differences in the local volumes of brain structures can be detected by analyzing Jacobian matrices of the deformations.

4.1.3 Statistical analysis

The endpoint of any morphometry method in computational neuroanatomy is usually a statistical parametric map which locates any regions of significant anatomical differences between two groups of subjects. The map is a result of a standard parametric significance test performed independently at each point of scalar fields or vector fields which describe the differences among the subject's anatomies.

4.2 BRAIN ATLASES

Most brain atlases are based on a detailed representation of a single subject’s anatomy in stereotaxic space. The chosen dataset acts as a template on which other brain maps can be overlaid [51]. The most commonly adopted coordinate system within the brain imaging community [4] is that described by the atlas of Talairach and Tournoux. A template created at Montreal Neurological Institute (MNI) as an average of 305 linearly registered MRI scans of young normal subjects is commonly denoted as MNI305. A standard template of the International Consortium for Brain Mapping (ICBM) ICBM152 is the average of 152 normal MRI scans that have been linearly registered to the MNI305. In addition, one of the MNI lab members was scanned 27 times, to create the template known as colin27.

5 OBJECTIVES OF THE THESIS

Intersubject registration of multimodal data with the use of various types of geometric transformations is the main concern of this thesis. Medical image processing and analysis is its field of application. The methods proposed here lead to clarification of the relationship between the morphology of the human brain and its function. They are designed to operate on high resolution 3D MRI brain scans of normal and neurologically diseased subjects.

Conventional ROI-based approaches often use manual or semi-manual tracing of brain structures. These procedures are very time-consuming if several brain structures in large number of images have to be delineated. Recently, automated
entire brain morphometry methods termed as computational neuroanatomy were proposed to overcome the limitations of the ROI-based methods. They are based on deformable image registration. So far applied registration methods in computational neuroanatomy are mostly driven by differences in intensities in the images and hence they are limited to monomodal data. It is more suitable to use multimodal similarity measures and thus increase robustness of the registration against intensity variations caused by various imaging conditions or by tissue atrophy and degradation induced by a disease or aging.

Particular goals of the thesis are as follows:
1. design of a deformable multimodal image registration method with the use of parametric transformations based on radial basis functions;
2. design of a deformable multimodal image registration method with the use of non-parametric transformations based on Rogelj's spatial deformation models;
3. a procedure of estimation of point similarity measures with the use of:
   - global joint histogram,
   - tissue probability maps;
4. evaluation of the designed methods on simulated brain image data and synthetic deformations including setup of the registration methods - particularly:
   - the use of suitable interpolation method,
   - parameters of spatial deformation models,
   - the most appropriate multimodal point similarity measures;
5. application of a chosen proposed registration method on real 3D MRI brain scans - localization of significant morphology differences between groups of schizophrenia and control subjects.

6 MULTIMODAL DEFORMABLE REGISTRATION IN STEREOTAXIC SPACE

Two algorithms for atlas-based deformable registration of MRI brain images are proposed. The use of various multimodal similarity measures is explored. Their computation requires knowledge of the joint PDF of the images being registered. Its estimation is a common part in both algorithms. The algorithms differ in the other parts including extraction of local forces and spatial deformation models. The subjects' image data are supposed to be transformed into stereotaxic space by a previous linear registration step.

6.1 LOW-DIMENSIONAL DEFORMABLE REGISTRATION BY ENHANCED BLOCK MATCHING

The first registration algorithm produces low-dimensional deformations which are suitable for coarse spatial normalization which is an essential step in VBM. On the contrary to the widely used spatial normalization implemented in [4][15], the proposed algorithm is applicable for matching multimodal image data. It is in fact an
enhanced block matching technique. The scheme of the algorithm is in Fig. 6.1. A multilevel subdivision is applied on a floating image \( N \). Obtained rectangular image blocks are matched with a reference image \( M \). The resulting displacement field \( \mathbf{u} \) is made up from local translations of the image blocks by RBF interpolation. The translations representing warping forces \( \mathbf{f} \) are found by maximizing symmetric regional similarity measures.

### 6.1.1 Symmetric regional matching

Inspired by the symmetric forces introduced for high dimensional matching, the regional similarity measure is computed by:

\[
S_{w}^{\text{sym}} = S_{w}^{\text{forward}}[M(x_w + u_w(x_w)), N(x_w)] + S_{w}^{\text{reverse}}[M(x_w), N(x_w - u_w(x_w))],
\]

(6.1)

where the first term corresponds to the similarity measure computed over all \( K_w \) voxels \( x_w = [x_1, x_2, ..., x_{K_w}] \) of a region \( W \) of the floating image according to the reference image. The second term corresponds to the reverse direction.

It is impossible to uniquely describe correspondences of regions in two images by multimodal similarity measures, due to their statistical character. When the local translations are searched in complex medical images, suboptimal solutions are obtained frequently with the use of the forward similarity measure only. Using the symmetric similarity measure, additional correspondence information is provided and the chance of getting trapped in local optima is thus reduced.

Due to the subvoxel accuracy of performed deformations, the point similarities have to be computed in points that are not positioned on the image grid. Interpolation from neighboring grid points has to be involved. Interpolation in the feature space with the use of GPVE is used here.

Local translations which maximize a matching criterion are searched in an optimization procedure. Here, the symmetric regional similarity measure is used as the matching criterion which has to be maximized:

\[
S_w(\mathbf{f}_w) = S_w^{\text{forward}}[M(x_w + u_w(x_w) + \mathbf{f}_w), N(x_w)] + \\
S_w^{\text{reverse}}[M(x_w), N(x_w - u_w(x_w) - \mathbf{f}_w)],
\]

(6.2)

where \( \mathbf{f}_w = [f_1, f_2, ..., f_{K_w}] \), \( f_1 = f_2 = ... f_{K_w} = [f_x, f_y, f_z]^T \) is a translation of all voxels in a region \( W \) along \( x, y \) and \( z \) axis. The use of the symmetric regional similarity measure and the GPVE interpolation with the use of the second-order B-spline or the third-order B-spline leads to well-behaved criterion function in the case of large regions. In the case of small regions, the uncertainty about the best translation is still high and many local maxima occur near the optimal solution. A combination of extensive search and hillclimbing algorithms is used here to find the global maximum. First, a space of all possible translations is determined by absolute maximum translation \( |\mathbf{f}_{\text{max}}| \) in all directions. Then, the space of all possible translations is searched with a relatively big step \( s_e \). The \( q \) best points are then used as starting points for the following hillclimbing with a finer step \( s_h \). The maximum of \( q \) local maxima obtained by the hillclimbing is then declared as the global maximum. The parameters are set empirically.
Fig. 6.1: The scheme of the block matching algorithm proposed for coarse spatial normalization.
6.1.2 Multilevel deformation

Image deformation based on interpolation with the use of RBFs is used here. The control points $p_i$ are placed into the centers of the regions and their translations $f_i$ are obtained by previously described symmetric regional matching. Substituting the translations into (3.6), three systems of linear equations are obtained and three vectors of $w$ coefficients, where $w$ is the number of the regions, $a_k=(a_{1,k}, ..., a_{w,k})^T$ computed. The displacement of any point $x$ is then defined separately for each dimension by the interpolant:

$$u_k(x) = \sum_{i=1}^{w} a_{i,k} R_{CP}(\|x - p_i\|), \quad k = 1...3. \quad (6.3)$$

The values of spatial support $s$ for various regions sizes are set empirically.

Optimal matches can be hardly found in a single pass composed of the local translations estimation and the RBF-based interpolation, since features in one location influence decisions at other locations of the images. Iterative updating scheme is therefore proposed here. A multilevel strategy is incorporated into the proposed algorithm. The deformation is iteratively refined in the coarse to fine manner. The size of the regions cannot be arbitrarily small, because the local translations are determined independently for each region and voxel interdependencies are introduced only by the regional similarity measure. The regions containing poor contour or surface information can be eliminated from the matching process and the algorithm can be accelerated in this way. The subdivision is performed only if at least one voxel in the current region has its normalized gradient image intensity bigger then a certain threshold.

6.2 HIGH-DIMENSIONAL DEFORMABLE REGISTRATION WITH THE USE OF POINT SIMILARITY MEASURES

The second registration algorithm produces high-dimensional deformations involving gross shape differences as well as local subtle differences between a subject and a template anatomy. As multimodal similarity measures are used, the algorithm is suitable for DBM on image data with different contrasts. It is inspired by the work of Rogelj et al. [37][39][40][41], who proposed high-dimensional registration with the use of multimodal point similarity measures and combined elastic-incremental spatial deformation model. These ideas are extended here. Instead of a preset number of iterations used by Rogelj, a clearly specified convergence criterion is used. The scheme of the algorithm is in Fig. 6.2. There are two main parts repeated in an iterative process as it was in the block matching algorithm: extraction of local forces $f$ by measurements of similarity and a spatial deformation model producing the displacement field $u$. The main difference is that these parts are completely independent here. Another difference is in the way of extraction of the local forces. The forces are directly computed from the point similarity measures. A multiresolution strategy is used here to speed up the convergence of the algorithm and to avoid local optima.
Fig. 6.2: The scheme of the high-dimensional registration algorithm proposed for DBM.
6.2.1 Symmetric voxel matching

Local forces are computed for each voxel independently as the difference between forward forces and reverse forces, using the symmetric registration approach. The forces are estimated by the gradient of a point similarity measure. The derivatives are approximated by central differences, such that the $k$th component of a force at a voxel $x$ is defined here as:

$$
\begin{align*}
  f_k(x) &= f_k^{\text{forward}}(x) - f_k^{\text{reverse}}(x) = \\
  &= \frac{2 \varepsilon_k}{S(M(x+u(x)+\varepsilon_k), N(x)) - S(M(x+u(x)-\varepsilon_k), N(x))} \\
  &\quad - \frac{2 \varepsilon_k}{S(M(x), N(x-u(x)+\varepsilon_k)) - S(M(x), N(x-u(x)-\varepsilon_k))}, \quad k = 1...D,
\end{align*}
$$

where $\varepsilon_k$ is a voxel size component. The point similarity measure is evaluated in non-grid positions due to the displacement field applied on the image grids. Thus, interpolation from neighboring grid points has to be involved. The GPVE scheme is employed here. Before the force field is processed by the spatial deformation model, the forces are normalized to avoid the influence of their scaling. Three ways of normalization were designed and tested.

**Maximum force normalization**

The forces are normalized according to Rogelj et al. such that the maximal force causes a unitary voxel's displacement. This way of normalization failed to achieve a good registration convergence.

**Constant magnitude normalization**

The forces are normalized such that each force causes a constant voxel's displacement. This way of normalization was motivated by bad registration results achieved with Rogelj's normalization. A good registration convergence was achieved with this way of normalization.

**Constant magnitude normalization with thresholding**

The forces are normalized such that forces with the magnitude bigger than a certain threshold cause a constant voxel's displacement and the others are set to zero. This way of normalization was motivated by good registration results achieved with the constant magnitude normalization. A worse registration convergence was achieved with this way of normalization than in the case of pure constant magnitude normalization.

Normalized mutual information (NMI) defined by [48]:

$$
\tilde{I}(M, N) = \frac{H(M)+H(N)}{H(M, N)}
$$

(6.5)
is used here as the global similarity measure which serves for observation of the registration convergence. The convergence criterion is defined here as the relative change of NMI from a preceding iteration \(i-1\) to a current iteration \(i\):

\[
C^i = \frac{\tilde{T}^i(M, N) - \tilde{T}^{i-1}(M, N)}{\tilde{T}^{i-1}(M, N)}.
\]

(6.6)

**6.2.2 Multiresolution deformation**

Voxel interdependencies are introduced by spatial deformation model which converts the force field into a displacement field preventing physically or anatomically unlikely deformations. The combined elastic-incremental spatial deformation model is used here.

The behaviour of the combined model depends on the ratio between the standard deviations \(\sigma_{GI}\) and \(\sigma_{GE}\) such that in the extreme cases the pure incremental model or the pure elastic model can be obtained. Various settings of the combined elastic-incremental model were compared in registrations of brain images misaligned by synthetic deformation. The overall regularization was kept constant and \(\sigma_{GI}\) and \(\sigma_{GE}\) were changed. Minimum Jacobian determinant of the deformation during the registration process was observed. The deformation was not diffeomorphic only in the case of the pure incremental model. Another important parameter of the combined model is the constant \(k\) which may be viewed as a gain of a spatial filter. In [37], \(k\) is initially set to such value that maximal force causes an unregularized displacement of one voxel, and decreases during registration. In the proposed algorithm, \(k\) remains constant during the registration. The constant \(k\) cannot be set arbitrary, in order to prevent breaking the condition of topology preservation.

The force field normalization is designed in the proposed algorithm with the assumption that smoothing provided by the spatial deformation model suppresses false forces arisen due to the normalization. If it is true, the convergence of registration will be achieved in a number of iterations corresponding to the degree of initial misregistration of the images. Fig. 6.3 shows that the assumption is satisfied. Four processes of registration of brain images misaligned by synthetic deformations with various magnitudes are observed. The spatial deformation model was set equally. The number of iterations is the highest in the case of registration of images misaligned by the largest deformation and it is lowest in the case of registration of images which are poorly misaligned. Fig. 6.3 also shows that registration is less precise for large initial misalignments according to lower values of NMI at the end of the registration process. It is caused by two types of error:

1. incorrect estimation of point similarity function from misaligned images leads to computation of forces which do not drive the registration properly,
2. the complexity of brain images together with gradient-based computation of forces lead to suboptimal registration solutions.

The influence of the second type of the error is reduced here with the use of the multiresolution strategy.
6.3 JOINT PDF ESTIMATION IN STEREOTAXIC SPACE

The common part of both proposed deformable registration algorithms is the estimation of the joint PDF which is usually estimated from the joint histogram of the images. The real intensity relationship can be described only by the joint histogram of the correctly registered images. Hence, the joint histogram of the images aligned by preceding linear registration is the choice. In the proposed algorithms, the joint histogram and a corresponding point similarity function \( S(m, n) \) are recomputed after each change of the displacement field. The interpolation required for the computation of the joint histogram involves the GPVE scheme.

The first type of the error described in chapter 6.2.2 is caused by using the joint histogram of misaligned images for estimation of \( p_{MN} \). To reduce this type of error, tissue probability maps (TPMs) are used here. The way of the computation of another estimate of the joint PDF is illustrated in Fig. 6.4. It is in fact a Parzen windowing technique which generally uses random samples drawn from an unknown joint intensity distribution to model its joint PDF by:

\[
p_{MN}(i) \approx \frac{1}{K_{\Omega}} \sum_{s_j \in \Omega} f(i - s_j),
\]

(6.7)

where \( i = [m, n] \) is an intensity pair for which the joint PDF value is computed by summing over values of kernel or window functions \( f(\cdot) \), which are centered around each sample intensity pair \( s_j \) from \( \Omega \) containing \( K_{\Omega} \) sample intensity pairs. In the proposed algorithms, the set of sample intensity pairs \( \Omega \) contains intensity pairs sampled at the most probable locations of main brain tissues occurrences. The same number of samples is taken for each of the tissues: white matter (WM), gray matter
(GM) and cerebrospinal fluid (CSF). The kernel functions are weighted by the probabilities obtained from TPMs:

\[ h_{MN}(i) = \sum_{c=1}^{T} \sum_{j=1}^{S} P_c(x_{c,j}) f \left( i - s(x_{c,j}) \right), \]

\[ O = \sum_{i} h_{MN}(i), \]

\[ p_{MN}^{prior}(i) \approx \frac{h_{MN}(i)}{O}, \]

where \( T \) is the number of TPMs and \( S \) is the number of intensity pairs sampled in each TPM at points \( x_{c,j} \) together with the probabilities \( P_c(x_{c,j}) \). In the proposed algorithms, Gaussian is used as the kernel function \( f \). The resulting estimate of the joint PDF is computed as a combination of \( p_{MN}^{prior} \) and \( p_{MN}^{histogram} \):

\[ p_{MN}(i) = \lambda p_{MN}^{prior}(i) + (1 - \lambda) p_{MN}^{histogram}(i), \]

where \( \lambda \) is a weighting parameter.

Fig. 6.4: Estimation of the joint PDF with the use of tissue probability maps.

**Multimodal point similarity measures**

There are measures expressed in the terms of probability \( (S_{PC}, S_U) \) and uncertainty \( (S_{MI}, S_{HU}) \). Based on preliminary results, which showed better performance of the
proposed methods involving the probability similarity measures, another point similarity measure depending on the probability is proposed here:

\[ S_{PMI}(x) = \frac{p_{MN}(m(x), n(x))}{p_M(m(x))p_N(n(x))}. \]  \hspace{1cm} (6.10)

### 6.4 EVALUATION OF DEFORMABLE REGISTRATION METHODS

An evaluation of a deformable registration method is considered here as an evaluation of the correctness of the deformation produced by the registration method in order to match corresponding image data. In real registration problems, the correct deformations are unknown.

Visual inspection, recovering a synthetic deformation and comparison of segmented images are used for evaluation purposes. Availability of correctly registered images together with their segmentations is required. The appropriate evaluation measures are the root-mean-squared residual displacement, the maximum absolute residual displacement and the Jaccard overlap measure defined as the voxel ratio of intersections and unions between corresponding labeled regions in the registered images. Realistic image data from Simulated Brain Database (SBD) [8] are used here for evaluation purposes. A disadvantage of these evaluation techniques may reside in the synthetic character of the initial deformations. The synthetic deformations are produced here by two completely different anatomical variability simulators. RGsim is based on Rogelj's spatial deformation models and TPSsim is based on thin-plate splines. The performance of the proposed deformable registration methods is evaluated quantitatively in studies involving registration experiments on lots of images deformed by various synthetic deformations. Due to the computational complexity of the registration methods, the evaluation is done on 2D data. The sets of values of evaluation measures are used to find the best experimental setups of the proposed registration methods and average values are used to present their performance.

**Quantitative evaluation of low-dimensional deformable registration**

The experimental setup of the low-dimensional deformable registration method was found with the use of the studies described above. Values of the method's parameters are listed in Tab. 6.1. According to the quantitative evaluation specified for various levels of the subdivision scheme, the fourth level of subdivision is set as the maximum. With this setting, the method is able to recover up to 73% of complex RGsim deformations and up to 88% of smoother TPSsim deformations. The performance of the method with the use of various similarity measures is further explored by observing the changes in the overlap measure \( \Delta J \) between the case of misregistered images and the case of registered images are evaluated. The results showed that the low-dimensional registration method increases average overlaps of corresponding brain tissues in the images most when the point similarity measure \( S_{PC} \) or \( S_{PMI} \) is used.
Quantitative evaluation of high-dimensional deformable registration

The experimental setup of the high-dimensional registration method is summarized in Tab. 6.2. The results of quantitative evaluation of the high-dimensional deformable with the use of various point similarity measures showed that the method is able to recover up to 87% of smooth TPSsim deformations and 80% of complex RGsim deformations. In the case of higher degree of initial misalignment (\( |u_{\text{MAX}}| > 8 \text{ mm} \)), the use of \( S_{PMI} \) gives the lowest residual error and the highest average overlaps of corresponding brain tissues.

Tab. 6.1: Setup of the low-dimensional deformable registration method.

| Level | region size \([\text{mm}^2]\) | \( s \) [mm] | \( |f_{\text{MAX}}| \) [mm] | \( s_e \) [mm] | \( s_h \) [mm] | \( q \) [-] |
|-------|------------------|------|-------------|------|------|------|
| 1     | 112²              | 168  | 28          | 2.5  | 0.50 | 1    |
| 2     | 56²              | 84   | 14          | 2.0  | 0.25 | 2    |
| 3     | 28²              | 42   | 7           | 1.5  | 0.20 | 2    |
| 4     | 14²              | 21   | 4           | 1.5  | 0.20 | 3    |
| 5     | 7²              | 11   | 2           | 1.0  | 0.10 | 4    |

<table>
<thead>
<tr>
<th></th>
<th>0.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of iterations</td>
<td>2</td>
</tr>
<tr>
<td>GPVE kernel function (joint histogram computation)</td>
<td>3\textsuperscript{rd}-order B-spline</td>
</tr>
<tr>
<td>GPVE kernel function (local optimization)</td>
<td>3\textsuperscript{rd}-order B-spline</td>
</tr>
<tr>
<td>Weighting parameter ( \lambda )</td>
<td>0.5</td>
</tr>
<tr>
<td>Number of TPM samples ( S )</td>
<td>500</td>
</tr>
<tr>
<td>Standard deviation in Parzen windowing ( \sigma_f ) (in voxel coordinates)</td>
<td>2</td>
</tr>
</tbody>
</table>

Tab. 6.2: Setup of the high-dimensional deformable registration method.

<table>
<thead>
<tr>
<th>Force field normalization</th>
<th>constant magnitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial deformation model (in voxel coordinates)</td>
<td>( \sigma_{GI}=3.74 ), ( \sigma_{GE}=2.00 ), ( k=1.00 )</td>
</tr>
<tr>
<td>Termination threshold on ( C )</td>
<td>( 6 \cdot 10^{-5} )</td>
</tr>
<tr>
<td>Multiresolution scheme</td>
<td>( \text{level} = 3, 2, 1 )</td>
</tr>
<tr>
<td>GPVE kernel function (joint histogram computation)</td>
<td>3\textsuperscript{rd}-order B-spline</td>
</tr>
<tr>
<td>GPVE kernel function (local forces computation)</td>
<td>1\textsuperscript{st}-order B-spline</td>
</tr>
<tr>
<td>Weighting parameter ( \lambda )</td>
<td>0.5</td>
</tr>
<tr>
<td>Number of TPM samples ( S )</td>
<td>125, 250, 500</td>
</tr>
<tr>
<td>Standard deviation in Parzen windowing ( \sigma_f ) (in voxel coordinates)</td>
<td>2</td>
</tr>
</tbody>
</table>

The influence of the weighting parameter \( \lambda \) in the computation of the joint PDF estimate was experimentally judged in preliminary evaluation studies of the high
dimensional registration method. The root mean squared residual error was lowered by 6% on the average and the maximum absolute error was lowered by 11% on the average compared to the case of the joint PDF estimate based on the joint histogram only. Roughly the same accuracy was however in the case of the combined estimate achieved in a lower number of iterations; the decrease was 19% on the average.

The proposed high dimensional deformable registration gives more precise deformations with the respect to the lower residual error and the higher measure of overlap of corresponding tissues in the registered images. The obtained results showed its ability to recover the smooth deformations generated by TPSsim as well as the complex deformations generated by RGsim.

7 DEFORMATION-BASED MORPHOMETRY ON SCHIZOPHRENIA SUBJECTS

High-resolution T1-weighted MRI brain scans of 40 subjects were obtained with a Siemens 1.5 T system in Faculty Hospital Brno. The group contained 20 male subjects with first-episode schizophrenia (mean age 24.3 years, standard deviation 5.2 years) and 20 male control volunteers (mean age 23.3 years, standard deviation 2.0 years) without any manifested psycho- or neuropathology. Two schizophrenia subjects and one control subject were later rejected from the final statistical analysis, because no demographic data were available for the control subject and important clinical parameters including results of Wechsler's memory tests were missing for the two schizophrenia subjects.

Original DICOM data were corrected for INU artifact and transformed into the stereotaxic space with the use MNI BIC software toolbox [7][47]. The high-dimensional deformable registration method with the use of $S_{PMI}$ was chosen to perform DBM. The template from SBD which is based on colin27 was used as the reference anatomy. The deformation fields were put into the statistical analysis which included assessing normality and parametric significance testing.

The $F$ statistic was computed from the $T^2$ statistic in each voxel. The obtained spatial map of $F$ values was thresholded at the significance level $\alpha=0.1\%$ and was overlaid on the image of template anatomy. In this way, clusters of voxels locating regions with significant differences in displacements between the groups arised. Tab. 7.1 summarizes the brain regions, Talairach coordinates of the voxels with the highest $F$ value within the corresponding clusters together with their $P$ values. Selected representative slices of the $F$ value map are shown in Fig. 7.1.

In order to detect local volume differences between the groups, morphometry on Jacobian determinants was performed. The Jacobian determinant can be viewed also as a parameter which characterizes local volume changes, i.e. local shrinkage or enlargement caused by a deformation. The analysis of the scalar fields produced spatial map of $t$ statistic which allowed to localize regions with significant differences in volumes of anatomical structures between the groups. The obtained spatial map of $t$ values was thresholded to two significance levels $\alpha=0.1\%$ and
α=1%. The clusters of voxels locating regions with significant local volume differences between the groups are summarized in Tab. 7.2. Selected representative slices of t value maps are shown in Fig. 7.2.

Tab. 7.1: Regions with significant differences in brain structures between the group of first-episode schizophrenia patients and the group of control subjects.

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Laterality</th>
<th>The most significant voxel</th>
<th>$F$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe: Inferior frontal gyrus</td>
<td>bilateral</td>
<td>-49 22 12</td>
<td>12,8625</td>
<td>9,9·10^{-6}</td>
</tr>
<tr>
<td>Frontal lobe: Superior frontal gyrus</td>
<td>dexter</td>
<td>14 47 41</td>
<td>17,3587</td>
<td>6,1·10^{-7}</td>
</tr>
<tr>
<td>Frontal lobe: Middle frontal gyrus</td>
<td>dexter</td>
<td>27 2 45</td>
<td>13,2951</td>
<td>7,4·10^{-6}</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>dexter</td>
<td>31 -64 -39</td>
<td>8,4757</td>
<td>2,6·10^{-4}</td>
</tr>
</tbody>
</table>

Fig. 7.1: Representative slices of $F$ statistic overlaid over the SBD template in the Talairach coordinate system.

The most significant findings localized in the frontal lobe with both $F$ value and $t$ value maps are consistent with the previous ROI-based studies which reported volume reduction [31]. They are supported also by more recent studies based on VBM [22][46]. Whereas volume reductions are reported in the anatomical structures of temporal lobe, both shrinkage and enlargement findings are presented here. The findings of volume enlargements localized in the insular cortex are inconsistent with the recent studies based on VBM and DBM [16][22][46], which reported volume reduction. Other less significant differences in the thalamus are consistent with the most recent studies [16][33].
Tab. 7.2: Regions with significant differences in local volumes of brain structures between the group of patients and the group of control subjects (E stands for enlargements and S stands for shrinkages in the group of patients).

<table>
<thead>
<tr>
<th>Brain region</th>
<th>E/S</th>
<th>Laterality</th>
<th>(x) [mm]</th>
<th>(y) [mm]</th>
<th>(z) [mm]</th>
<th>(t)</th>
<th>(v)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe: Inferior frontal gyrus</td>
<td>S</td>
<td>bilateral</td>
<td>49</td>
<td>27</td>
<td>7</td>
<td>5,4287</td>
<td>31</td>
<td>3,1·10^{-6}</td>
</tr>
<tr>
<td>Frontal lobe: Middle frontal gyrus</td>
<td>S</td>
<td>bilateral</td>
<td>-40</td>
<td>44</td>
<td>2</td>
<td>4,2085</td>
<td>34</td>
<td>8,9·10^{-5}</td>
</tr>
<tr>
<td>Frontal lobe: Superior frontal gyrus</td>
<td>S</td>
<td>bilateral</td>
<td>-11</td>
<td>51</td>
<td>19</td>
<td>3,6640</td>
<td>35</td>
<td>4,1·10^{-4}</td>
</tr>
<tr>
<td>Insular cortex</td>
<td>E</td>
<td>sinister</td>
<td>-32</td>
<td>22</td>
<td>5</td>
<td>-3,9907</td>
<td>31</td>
<td>1,9·10^{-4}</td>
</tr>
<tr>
<td>Frontal horn of ventricle, Basal ganglia</td>
<td>S</td>
<td>sinister</td>
<td>-17</td>
<td>17</td>
<td>9</td>
<td>3,2182</td>
<td>30</td>
<td>1,6·10^{-3}</td>
</tr>
<tr>
<td>Thalamus</td>
<td>S</td>
<td>bilateral</td>
<td>5</td>
<td>-23</td>
<td>12</td>
<td>3,4430</td>
<td>33</td>
<td>7,9·10^{-4}</td>
</tr>
<tr>
<td>Temporal lobe: Superior temporal gyrus</td>
<td>E</td>
<td>bilateral</td>
<td>54</td>
<td>-11</td>
<td>-11</td>
<td>-3,9525</td>
<td>34</td>
<td>5,8·10^{-5}</td>
</tr>
<tr>
<td>Temporal lobe: Amygdala</td>
<td>S</td>
<td>dexter</td>
<td>35</td>
<td>6</td>
<td>-25</td>
<td>2,8863</td>
<td>35</td>
<td>3,3·10^{-3}</td>
</tr>
<tr>
<td>Temporal lobe: Amygdala</td>
<td>E</td>
<td>bilateral</td>
<td>-23</td>
<td>-1</td>
<td>-26</td>
<td>-3,6173</td>
<td>35</td>
<td>4,6·10^{-4}</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>S</td>
<td>sinister</td>
<td>-33</td>
<td>-62</td>
<td>-48</td>
<td>3,3903</td>
<td>34</td>
<td>8,9·10^{-4}</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>E</td>
<td>dexter</td>
<td>23</td>
<td>-55</td>
<td>-46</td>
<td>-3,2913</td>
<td>33</td>
<td>1,2·10^{-3}</td>
</tr>
<tr>
<td>Occipital lobe: Inferior occipital gyrus</td>
<td>S</td>
<td>sinister</td>
<td>-39</td>
<td>-84</td>
<td>-9</td>
<td>2,8445</td>
<td>32</td>
<td>3,9·10^{-3}</td>
</tr>
<tr>
<td>Occipital lobe: Middle occipital gyrus</td>
<td>S</td>
<td>sinister</td>
<td>-25</td>
<td>-84</td>
<td>12</td>
<td>3,2828</td>
<td>35</td>
<td>1,2·10^{-3}</td>
</tr>
</tbody>
</table>

Fig. 7.2: Representative slices of \(t\) statistic overlaid over the SBD template in the Talairach coordinate system.
8 CONCLUSION

In this thesis, a deformable registration method based on parametric transformations with radial basis functions (RBFs) and a method based on non-parametric transformations with Rogelj's spatial deformation models were described. The use of multimodal similarity measures was insisted. Designed algorithms were applied in the field of computational neuroanatomy, particularly for fully automated spatial detection of anatomical abnormalities in first-episode schizophrenia based on structural MRI brain scans.

Intersubject deformable registration methods are difficult to validate as the correct transformations are unknown. Thus, evaluation of the proposed method was based here on measuring their ability to recover synthetic deformations in 2D images obtained from Simulated Brain Database (SBD). The performance of the proposed methods was quantified and their best experimental setups were found. The joint PDF estimate was computed as a linear combination of the estimates based on the joint histogram and on the TPMs. Compared to the case of the pure joint histogram estimate, the high-dimensional registration converged faster and the error of residual deformations was reduced. The clinical application, which is concluded further, involved registration of 3D brain images from various subjects to a template anatomy of a standardized digital brain atlas. The maximum absolute error and the root mean squared error of residual deformations computed by adding up obtained transformations from subject-to-template and template-to-subject registrations of images with the voxel size $1 \times 1 \times 1$ mm were lower than 1 mm over the brain area in all 40 subjects.

Brain regions with anatomical differences between a group of 18 patients with first-episode schizophrenia and a group of 19 healthy subjects were revealed. Deformation-based morphometry with the use of the proposed high-dimensional registration was chosen as the suitable methodology for that purpose. Multivariate significance tests on the deformation fields and univariate significance tests on their Jacobian determinants were performed in each voxel. Resulting statistical maps localized regions with significant structural differences and regions with significant local volume differences between the groups. The most significant findings of volume reductions in the temporal lobe in schizophrenia patients are consistent with previous ROI-based studies as well as with more recent studies based on automated whole brain morphometry. The findings of enlargements in the insular cortex and the temporal lobe are controversial compared to previous studies of other authors. The investigated population however contained only patients suffering from first-episode schizophrenia, whereas the population in other studies contained patients with the average illness duration more than 10 years.
REFERENCES


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ABSTRACT

This thesis mainly contributes to the field of image registration with the use of nonlinear transformations. Particularly, problems connected to matching MRI brain image data obtained from various subjects and with various imaging conditions are solved here. Registration is driven by local forces derived from multimodal point similarity measures which are estimated with the use of joint intensity histogram and tissue probability maps. A deformable registration method based on parametric transformations with radial basis functions and a method based on non-parametric transformations imitating principles of continuum mechanics are proposed for morphometry in computational neuroanatomy. Results of fully automated spatial detection of anatomical abnormalities in first-episode schizophrenia based on structural MRI brain scans are presented.