Mapping Image Data to Stereotaxic Spaces: Applications to Brain Mapping

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Abstract: A methodology for spatial normalization of image data is presented. This methodology is based on a map between homologous features of an individual brain and the target brain, which is used to drive a three-dimensional elastic warping transformation. Functional or structural information present in the original, nonnormalized images is preserved during this transformation. In particular, information such as the volume or the total amount of a radioactive agent in any brain region can be calculated directly from the normalized images. Moreover, subtle morphological characteristics of an individual brain are captured by the properties of the spatial transformation applied to that brain. Intersubject or interpopulation comparisons are performed by comparing the corresponding transformations. *Hum. Brain Mapping* 6:334–338, 1998. © 1998 Wiley-Liss, Inc.

Key words: spatial normalization; registration; stereotaxy; computational neuroanatomy; brain mapping

INTRODUCTION

The widespread use of modern tomographic imaging techniques has led to the collection of large numbers of three-dimensional (3D) images of the structure and function of the human brain, allowing large-scale studies whose goal is to characterize the structural and functional organization of populations rather than of isolated individuals. A major obstacle in studies including multiple subjects, however, has been variability across individuals. One way to account for such variability is to spatially normalize image data to a common stereotaxic space. This requires the development of spatial transformation methods that morph

one brain to another, in a way that anatomical homologies are preserved. If this morphing is perfect, then a particular location in the stereotaxic space corresponds to the same anatomical brain region in all subjects of a population. Therefore, functional, anatomical, or other data of different subjects can be directly compared pointwise in the stereotaxic space.

Several methodologies for spatial normalization have been developed during the past 10 years, ranging from Fourier or algebraic polynomial transformations [Friston et al., 1995], to transformations using image similarity criteria [Bajcsy and Kovacic, 1989; Miller et al., 1993; Collins et al., 1994; Thirion, 1996], to landmark-based transformations [Bookstein, 1989].

In our previous work we developed a methodology that determines a spatial transformation of brain images based on prominent features, such as boundaries of brain structures and prominent cortical sulci [Davatzikos, 1997]. Feature-based techniques have also been developed by other investigators in the field [Thompson and Toga, 1996; Joshi et al., 1995]. In this

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paper we summarize this work, and we present recent results, as well as current and future directions of research.

THE STAR ALGORITHM

The general framework of our spatial transformation algorithm for registration (STAR) is the following:

1. Parametric representations of a number of anatomical features, typically closed or open surfaces, are determined from MR images. Examples of such features are the outer cortical surface, the ventricular surface, and the sulci; the latter are modeled as thin convoluted ribbons that are “sandwiched” between opposite sides of the cortical folds.
2. A map is established from these features to their corresponding features in the template brain, which is associated with a stereotaxic reference system (usually the Talairach space). This map between a subject’s features and the template’s features is such that it maps regions of similar geometric structures to each other.
3. The feature-to-feature map is then used to drive a 3D elastic transformation, which interpolates the spatial normalization transformation in the regions where features are not available. Other interpolants could also be used. However, elastic transformations are suitable to this application, since they tend to preserve the relative positions of anatomical structures while they allow for considerable interindividual variability.

These three steps will be described in more detail.

Feature extraction

A deformable surface algorithm (DFSA) [Davatzikos and Bryan, 1996] is first used to extract a parametric representation of the outer boundary of the brain. This is accomplished by first extracting the brain tissue and removing the dura, skull, fat, and skin [Goldszal et al., 1998]. An elastic surface is then initialized at a spherical configuration surrounding the brain, and shrink-wraps around it. To speed up convergence, a multiresolution scheme is applied, according to which the elastic surface is comprised of progressively larger numbers of polygons.

In order to obtain a better registration of deeper cortical regions, the sulci can be used as additional features. We model the sulci as thin convoluted ribbons that are “sandwiched” between two juxtaposed

sides of their adjacent cortical folds. For the extraction of the sulcal ribbons, we developed an active contour algorithm [Vaillant and Davatzikos, 1997], which will be referred to as SPA. In SPA, an active contour, i.e., an elastic parametric curve, is initially placed on a sulcus on the outer cortical surface. The active contour is then “pushed” inwards, and slides along the medial surface of the sulcus until it reaches the root of the sulcus. This procedure results in a parametric representation of the sulcal ribbon, in which one family of isoparametric curves is comprised of consecutive deformed configurations of the active contour, while the orthogonal family of isoparametric curves is comprised of trajectories of individual points of the active contour.

Feature matching

Based on the parametric surface representations determined as described above, a surface-to-surface map is established. Specifically, the parametric grids determined through DFSA or SPA are elastically stretched so that regions of similar geometric structures (e.g., regions of high curvatures) are in registration, i.e., they have the same parametric coordinates. Global characteristics of the shape of the brain, including features such as the interhemispheric and Sylvian fissures, are matched automatically. However, because of the convoluted nature of the cortex, more detailed characteristics, such as individual sulci or gyri, cannot be automatically identified and matched in the current implementation of the algorithm. Such features are outlined manually on the outer cortical surface and are subsequently used in the elastic stretching of the parametric grid, which results in a more accurate match of individual cortical regions.

Elastic warping

The feature-to-feature map established as described above drives a 3D elastic warping transformation, the details of which can be found in Davatzikos [7]. In particular, the surface features described above are warped to their homologues in the target brain (e.g., the atlas); the transformation is then interpolated in the rest of the brain via the elastic equations. In order to account for abnormalities, such as large ventricular atrophy often present in elderly or diseased subjects, we use the framework of pretrained elasticity. In this framework, a uniform strain is applied within the ventricular region, and results in the contraction of the ventricles. The magnitude of the ventricular strain is determined from the volume of the ventricles in the brain image to be spatially normalized, relative to the

Figure 1.

A: Overlays of an MR image on the outline of the target MR image before spatial transformation (**a**), at an intermediate stage (**b**), and at the final stage (**c**). **d:** The target. **B:** Representative cross sections from 2 individuals with different degrees of atrophy (**a** and **d**). **b** and **c:** The respective volumetric density functions of CSF after spatial normalization. Note that the shapes of the ventricles are very similar after normalization; they are similar to the shape of the Talairach atlas ventricles. However, the CSF density of the

individual with the larger ventricles is higher, reflecting the fact that more CSF was mapped into the same target region for that individual. **e:** Average distribution of white matter obtained from 20 elderly subjects. Only in the left hemisphere (seen as right image) were three sulci used as additional features, resulting in a better registration (reduced fuzziness) of the precentral and postcentral gyri (arrows), compared to the right hemisphere.

ventricular volume of the target brain; higher levels of strain result in a higher contraction of the ventricles. An example of the spatial transformation mapping one MR image to another is shown in Figure 1A.

The STAR algorithm can be applied in two different ways. First, the source image can be transformed to the target image, as in Figure 1A. Second, any information associated with the source image can be mapped to the target image. For example, information about the volume of a particular structure in the source image can be mapped to a stereotaxic space for subsequent regional volumetric analysis, as explained in more detail below. Similarly, a registered functional image can be spatially normalized via the same spatial transformation.

APPLICATIONS IN BRAIN MAPPING

Regional volumetric analysis

One of the applications of spatial normalization is to facilitate volumetric measurements of structures or partitions of them. For this reason, our spatial transformation warrants that the volume of any region in an individual's image is preserved after spatial normalization. This is a very important issue; for example, interhemispheric volumetric differences would disappear after spatial normalization to a symmetric template, such as the Talairach atlas. In our transformation, the preservation of regional volumes is achieved as follows. Each location in the stereotaxic space is

associated with a counter which sums up the volume of a particular tissue (e.g., gray matter) mapped to that location. Each voxel in the image to be transformed is mapped to some location in the stereotaxic space, through the elastic transformation. If this location does not coincide with the location of the center of a voxel, then the counters of the voxels adjacent to that location are then incremented according to their distance from that location; the total increment of the adjacent counters is equal to the volume of the voxel that was transformed. This procedure is repeated for every voxel of the image that is transformed. Figure 1B shows representative cross sections of the distributions of ventricular cerebrospinal fluid (CSF) after spatial normalization, for 2 subjects with different degrees of ventricular atrophy. Note that the shapes of the ventricles are very similar in Figure 1Bb and 1Bc, since they both match the shape of the ventricles of the Talairach atlas, which was the target. However, the brightness of the images differs, since brightness is proportional to the original ventricular CSF volumes.

In order to show the performance of the STAR algorithm on a representative sample of 20 subjects, in Figure 1Be we show a representative crosssection of the average distribution of white matter obtained from 20 elderly subjects of widely varying degrees of atrophy. (All subjects were participants to the Baltimore Longitudinal Study of Aging [Shock et al., 1984]; MR images were segmented as described in Goldszal et al. [1998].) Relatively fuzzy areas correspond to regions of relatively poorer registration. In order to demonstrate the improvement obtained by using certain sulci as features, we used three sulci of only the left hemisphere (right in the images) as features, in addition to the outer cortical and ventricular boundaries: the central, precentral, and postcentral sulci. The improvement of the registration at the precentral and postcentral gyri, reflected by the reduced fuzziness, is apparent in the left hemisphere, as indicated by the arrows on the right in Figure 1B.e. We note that, using these images, atrophy that is localized around specific sulci or gyri can be detected, because the images shown in Figure 1Be will have relatively lower intensity in such regions. Therefore, techniques that have been developed for the analysis of functional images, such as statistical parametric mapping, can also be used to detect regions of localized atrophy in our framework.

Spatial normalization of functional images

The spatial normalization transformation determined from the relatively higher-resolution anatomic images can be applied to the lower-resolution func-

tional images. In our laboratory, we first register anatomic and functional images using the AIR package developed by Roger Woods et al. at University of California at Los Angeles. We then apply STAR to the anatomic images, and determine the spatial normalization transformation. Finally, the functional images are spatially normalized using the exact same transformation determined from the anatomic images.

Computational neuroanatomy using shape deformations

The spatial transformation that maps an anatomical template to a target brain carries all the shape characteristics of the target brain with respect to the template brain. Therefore, shape comparisons between two different brains can be performed by comparing the corresponding shape transformations. Similarly, population comparisons can be performed by statistically comparing the corresponding shape transformations, indicating where in the brain and how two populations differ. Since the template plays the role of a measurement unit, it must be the same for all brains. In previous studies [Davatzikos et al., 1996; Davatzikos and Resnick, 1998], we used shape transformations to characterize sex differences in the corpus callosum, and to correlate such differences with neurocognitive performance. Specifically, we determined that the female splenium is significantly more bulbous than the male splenium, and that bulbosity correlates with performance in women but not in men; this is in agreement with the hypothesis that women process verbal and visuospatial tasks more bilaterally.

CONCLUSIONS

We have described an approach for spatial normalization as well as some of its applications in the analysis of structural and functional brain images. Our approach is feature-based, so it does not depend on signal properties, which can vary across modalities and individuals. Moreover, it can utilize structures such as the cortical sulci, which are often associated with boundaries of functionally and cytoarchitectonically different regions. Therefore, it can potentially improve the registration of activation foci in a stereotaxic space, thereby improving the sensitivity of statistical parametric mapping methods in detecting such foci.

An important element in our approach is that the information that is present in the original, nonnormalized images is preserved after spatial normalization. Therefore, localized volumetric characteristics can be

examined after spatial normalization. Similarly, in the spatial normalization of PET images, the total radioactivity measured within any region can be preserved after normalization.

Current directions of research in our laboratory include the automated identification of the sulci, which currently requires human intervention, using hierarchically defined prior spatial probability distributions. Moreover, we are applying our morphometric methods to studies on normal and diseased aging, head injury, and stroke subjects.

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