Brain Functional Localization: A Survey of Image Registration Techniques

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***Abstract*—Functional localization is a concept which involves the application of a sequence of geometrical and statistical image processing operations in order to define the location of brain activity or to produce functional/parametric maps with respect to the brain structure or anatomy. Considering that functional brain images do not normally convey detailed structural information and, thus, do not present an anatomically specific localization of functional activity, various image registration techniques are introduced in the literature for the purpose of mapping functional activity into an anatomical image or a brain atlas. The problems addressed by these techniques differ depending on the application and the type of analysis, i.e., single-subject versus group analysis. Functional to anatomical brain image registration is the core part of functional localization in most applications and is accompanied by intersubject and subject-to-atlas registration for group analysis studies. Cortical surface registration and automatic brain labeling are some of the other tools towards establishing a fully automatic functional localization procedure. While several previous survey papers have reviewed and classified general-purpose medical image registration techniques, this paper provides an overview of brain functional localization along with a survey and classification of the image registration techniques related to this problem.**

***Index Terms*—Brain functional localization, fMRI image processing, functional imaging, survey of image registration techniques.**

I. Introduction

FUNCTIONAL localization is a concept for defining the location of brain activity or functional maps with respect to the brain structure or anatomy [1], [2]. Previously, this problem was addressed in a more general framework called brain mapping [3]. Toga and Mazziotta have published a series of editorial books on the role of image registration techniques in brain mapping [4]–[6]. Many of the techniques that are discussed in these papers can be utilized to solve different aspects of the functional localization problem. Functional localization has important applications in neuroscience, in neurophathological studies of brain functional disorders, and also in neurosurgery in order to minimize postoperative functional deficits and neurological morbidity.

Functional brain images [e.g., functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT)] do not generally contain detailed structural information and, thus, do not provide an anatomically specific localization of functional information unless they are mapped to an anatomical image or brain atlas. The core part of a functional localization procedure is a sequence of image processing operations that involve resampling and registering functional images into an anatomical space. In single-subject studies, the anatomical space is simply defined by a high-resolution anatomical image, such as a T1-weighted MRI. The problem becomes more complicated when analyzing the functional information of a group of subjects. In group-analysis studies, the anatomical variability of the brains of different subjects is of concern, and requires performing an intersubject or subject-to-template nonrigid registration. This variability can be partially compensated via nonrigid registration techniques, ranging from affine registration to match the size and shape of different brains to high-dimensional brain warping techniques [6] to match the cortical surface and internal brain structures. These techniques are normally used to register the brains of different subjects into a custom or standard brain template or atlas.

Fig. 1 shows diagrams of the most commonly used functional localization procedures. Note that functional localization is only a part of functional image analysis. The other functional image preprocessing steps, including realignment via monomodal registration [7], [8], prospective and retrospective motion correction [9], and distortion correction [10], [11] are done prior to statistical analysis and functional localization procedures. The statistical analysis may be applied at different occasions during the process of functional localization. In a single-subject analysis [Fig. 1(a)], it is performed either before or after functional-to-anatomical registration. When it is done before the registration, the extracted activation maps have to be mapped to the anatomy with the same transformation that maps the functional image into the anatomical image. In most group analyses, the statistical analysis is done after intersubject registration; and intersubject registration is applied either to the functional images or to the anatomical images [Fig. 1(b) and (c)]. In the former, all the functional images are registered to a functional

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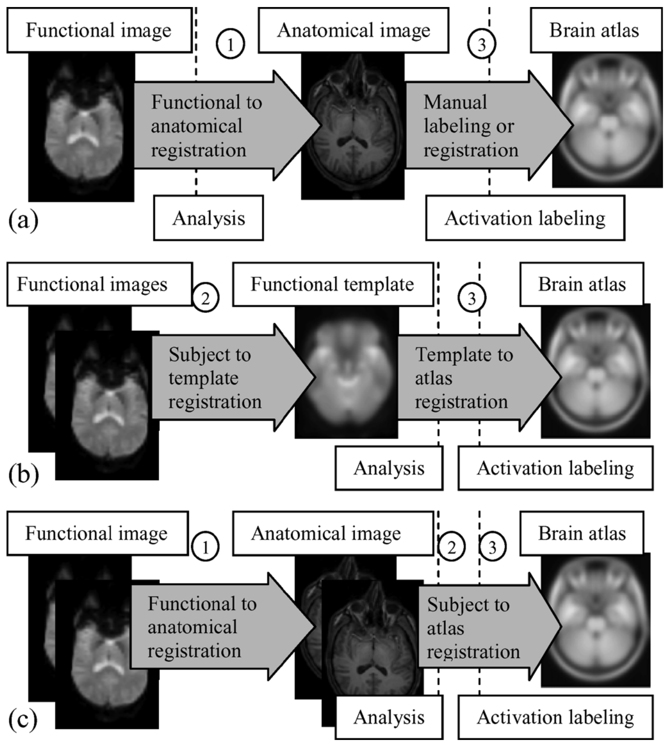

Fig. 1. Various functional localization procedures, (a) single-subject analysis, (b) and (c) group analysis: ① Functional-to-anatomical registration, ② intersubject or subject-to-atlas registration (spatial normalization), and ③ activation labeling (with respect to a standard brain atlas).

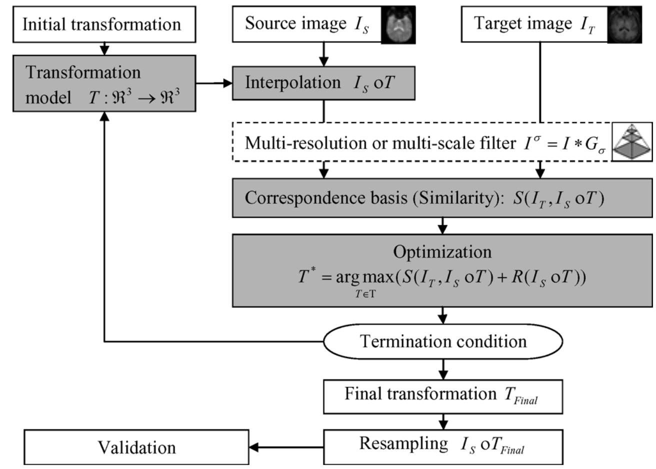

Fig. 2. A typical registration algorithm consists of four main components: a transformation model, a correspondence basis, an optimization technique, and an interpolation method. The optimization problem can be carried out in a multiresolution or multiscale framework.

template image and the functional template is further registered to a standard brain atlas. In the latter, the functional-to-anatomical registration is done in each subject's coordinate system and the intersubject or subject-to-atlas registration is done for the high-resolution anatomical images [Fig. 1(c)].

In almost all functional localization procedures, except in some of those applied to neurosurgery, a final step consisting of activation labeling is required. Usually, this step involves a nonrigid registration to a standard digital brain atlas. By reporting the results in a standard labeling framework, different studies can be compared. A digital brain atlas consists of a typical high-resolution brain structure with anatomical labels, coordinate labels, and sometimes functional labels [1], [3]. For group analyses, a brain template (e.g., the target brain) is registered to the brain atlas prior to functional localization, and a simple 3–D overlay to the atlas space is done for activation labeling. The accuracy and reliability of activation labeling is determined by the accuracy of registration between the different subjects and the template or the atlas, or between the template and the atlas.

A typical registration algorithm consists of four components: a correspondence basis, a transformation model, an optimization framework, and an interpolation method. Two images or two sets of images are involved in a registration algorithm; the source or moving image $I_S : \Re^3 \rightarrow \Re$ and the target or reference image $I_T : \Re^3 \rightarrow \Re$ are considered to be functions that assign scalar intensity values to the points in the 3–D physical coordinates. The optimization framework is set up to find the appropriate parameters of the transformation model $T : \Re^3 \rightarrow \Re^3$ to maximize a measure of similarity based on correspondences between the source and target images. This similarity term is denoted by $S(I_T, I_S \circ T)$. When the transformation is high-dimensional, a regularization term $R(I_S \circ T)$ is also added to the optimization function to preserve the topology and smoothness of the source image. The target image is fixed and the source image is transformed and resampled in each iteration of the registration algorithm by a fast and accurate interpolation method. These components are shown in Fig. 2. The registration algorithm may be solved in a multiresolution or multiscale framework with a Gaussian filter G_σ having a scale parameter σ. The termination condition is normally defined by a threshold on the variation of the optimization function.

The next three sections of this paper survey the state-of-the-art in brain atlases and brain templates, functional-to-anatomical registration, and intersubject registration. The four components (correspondence basis, transformation model, optimization framework, interpolation method) of a registration algorithm are considered in four subsections of Section III (functional-to-anatomical registration), followed by a subsection on the validation of functional to anatomical brain image registration. Except for the transformation model, the key developments in the components of a registration algorithm (correspondence basis, optimization framework, and interpolation method) have occurred for studies of multimodality functional-to-anatomical registration; thus, their main classification and discussion is presented in Section III. On the other hand, the main classification and discussion of transformation models is done in the section on intersubject registration (Section IV-B), since only a small portion of the papers on functional-to-anatomical registration have utilized transformations other than rigid or affine. The classification in Section IV is done from an application point of view; various intersubject registration techniques are listed in Section IV-A and are classified according to the transformation model and the correspondence basis in Section IV-B. Validation of intersubject registration techniques is different from validation of functional-to-anatomical registration techniques, and is discussed in Section IV-C. Cortical surface registration techniques are considered in Section IV-D. Finally, in the last section, all of the research topics are viewed from the perspective of the currently active research directions.

Several books contain tutorial articles on related topics [4]–[6], [12], [13]. The books on functional MRI by Jezzard *et al.* [14] and Huettel *et al.* [15], and a review article on fMRI preprocessing by Strother [16] provide general overviews of fMRI processing and analysis. Recent survey papers on image registration [17], [18] have presented extensive reviews on mutual-information-based medical image registration. This survey paper, however, is focused on those registration techniques which are related to the problem of brain functional localization, and hence the classification presented here is done from the application point of view. A few more general survey papers [19]–[21] may also be of interest to the reader.

II. Brain Atlases and Brain Templates

Due to large variations in the brain structure of human populations, the construction and use of standard brain atlases and brain templates pose a fundamental challenge in human brain mapping and in particular in brain functional localization [22]. As evident from Fig. 1, the use of brain atlases and brain templates in functional localization is twofold: first, they provide a standard basis for activation labeling, and second, in group analysis studies, the functional images of different subjects can only be compared and analyzed if the anatomical variations are compensated via appropriate mapping to a brain template or brain atlas. The words "brain atlas" and "brain template" are used interchangeably in the literature, while it is useful to discriminate them based on the difference in applications. A brain atlas provides a standard high-resolution structural brain [3] which normally contains coordinate, anatomic, cytoarchitectonic and functional labels and is basically used for activation labeling [1], [23]–[26]. Brain templates can be considered to be a subclass of brain atlases, which do not need to have labels or extra information about the anatomic or functional significance of locations, and are normally used as reference images for group analysis studies. For reporting the results in a standard coordinate system with a standard activation labeling, the brain template should be mapped to a standard brain atlas.

The construction of good representatives of human brain atlases involves specialized strategies for population-based averaging of anatomy that generates local encoding of anatomic variability and also cortical topography. This creates relatively crisp anatomical images with highly resolved structures in their mean spatial location and maps of cortical variability. These strategies may incorporate high-dimensional nonrigid registration to reconfigure the anatomy of a large number of subjects in an anatomic image database. Both the construction of brain atlases and their use are highly dependent upon advances in nonrigid intersubject registration [27]. An introduction to the construction and use of brain atlases and brain templates is presented in this section, while the details of intersubject registration techniques are discussed in Section IV. The goal in this section is neither to provide a tutorial on atlas construction nor a thorough review of the earlier studies, but to provide an overview of the role of brain atlases and brain templates in brain functional localization. The most prominent studies have been cited. More comprehensive tutorials can be found in the articles by Toga and Thompson [3], Thompson *et al.* [27], and Mazziotta [28].

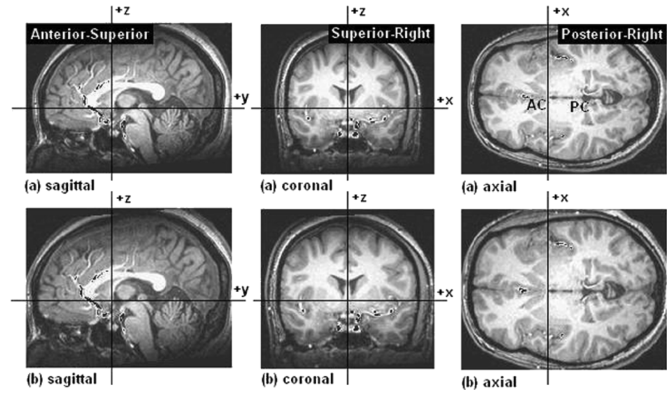

Fig. 3. A typical MRI brain scan in the Talairach coordinates, (a) the brain scan before the Talairach transformation (AC and PC are detected manually and the AC-PC line is aligned to the Talairach atlas), (b) after the Talairach transformation, the 12 different regions of the brain are linearly transformed to match the size and shape of the Talairach brain atlas.

A. *Atlas of Talairach and Tournoux*

In 1988, Talairach and Tournoux [29] introduced a stereotaxic atlas of the human brain based on post mortem sections of a 60-year-old female subject's brain. Although a single brain cannot be a good representative of the human brain, the Talairach atlas has become the de facto standard in brain mapping [1], [25]. The Talairach stereotaxic coordinate system is based on two relatively invariant subcortical point landmarks, the anterior commissure (AC) and the posterior commissure (PC). The AC is taken to be the origin of the coordinate system, the AC-PC line to be the y axis, the vertical line passing through the interhemispheric fissure to be the z-axis, and the line passing through the AC and being at right angles to the y and z axes to be the x-axis. The three axes, along with a line parallel to the x-axis passing through the PC, divide the brain into 12 cubic rectangular regions. Extremes of the cortical area are defined on each side and piecewise affine transformations are applied to these areas to map different brains to the Talairach standard coordinates [25], [30]. Fig. 3 shows a typical MRI brain scan registered to the Talairach coordinates using the AFNI software package [31].

B. *Digital Brain Atlases*

The large size of today's high-resolution brain datasets demands the use of automated computer algorithms, thus increasing the usefulness of computer-based brain atlases [22]. Computer-based digital representations of standard brain atlases are extensively used in brain mapping [3], functional and anatomical localization [30], [32]–[34], and automated activation labeling [23], [24]. Remarkable earlier investigations have appeared in [33] and [35]–[42]. Many of the digital brain atlas frameworks, such as the Harvard Brain Atlas [42], Talairach Daemon [23], Montreal Neurological Institute's (MNI's) single subject atlas [28], [43], and Cerefy Neuroradiology Atlas (CNA) [44], [45] have been developed based on an initial mapping to the Talairach standard coordinate system. A piecewise affine transformation of brain images to the Talairach coordinate system has constituted common practice for group analysis studies [25], [46]. Anatomic and functional labels including Brodmann areas are also well defined on digital representations of the Talairach atlas.

Nevertheless, not only is a single-subject brain such as the Talairach brain not sufficiently representative of the human brain structure, but also the piecewise Talairach transformation cannot compensate for the anatomic variability of different brains. More successful brain atlases can be obtained by averaging the anatomy of a population of brain images through high-dimensional nonrigid intersubject registration [47]. There have been many studies on the creation of more accurate high-resolution brain atlases based on state-of-the-art nonrigid registration techniques, for example [48]–[54]. Based on a database of high-resolution anatomical brain images, these techniques typically involve a first stage of registration to the Talairach stereotaxic space, a second stage of computing a geometric average brain, and a final stage of intensity averaging over the images registered to the computed geometric average brain. The second stage is the main part of this procedure, and involves the definition and computation of the geometric average brain. Intuitively, a minimum deformation from the database of brain images to the average brain is an appropriate measure. In [50], all the images are nonrigidly registered to every other image in the database, and all the registered images are averaged. In [48], the minimum deformation target brain is defined as the average brain that minimizes the deformation of all the brains in the database to the average target brain. As alternative approaches, a Bayesian approach to minimize the deformation energy of a set of multimodality images is utilized in [53]–[55] and a constrained optimization problem is solved in [51] to maximize the similarity of images to the average brain while constraining the sum of all required deformations to zero. All of these techniques utilize high-dimensional nonrigid intersubject registration techniques that are covered in Section IV of this survey article.

C. Probabilistic Atlases

A probabilistic brain atlas is a probability-encoded map of anatomic variability in the human brain, and can also be used to create an anatomical brain atlas with highly resolved structures in their mean geometric and intensity configuration. A statistical analysis along with a high-dimensional nonrigid registration algorithm is normally used in the creation of probabilistic brain atlases. Existing techniques can be classified into intensity-based and label-based techniques. The main problem of the techniques based on intensity averaging of the preregistered brains of a large group of homogeneous subjects is that the cortical and subcortical structures become blurred in the averaging process. Label-based techniques are based on brain segmentation, which is done either manually or by automatic or semi-automatic segmentation of landmarks. The atlas is normally described as a probability map of the segmented structures by determining the proportion of subjects assigned to the related anatomic label at each voxel position in the standard coordinate system. The success of a probabilistic brain atlas is reliant upon the generality and reliability of the statistical samples and methods that are used in its construction [56]. Such criteria have been included in the development of the atlas of the International Consortium of Brain Mapping (ICBM) [28], [39]. The maximum probability anatomical brain atlas in [57] and diffeomorphic probabilistic brain atlas in [58] constitute some of the new efforts in this field. A technique for probabilistic unbiased atlas generation based on a variational intersubject registration framework has also been developed in [59].

D. Deformable Atlases

A deformable brain atlas can be elastically transformed into the anatomy of individual brains using a nonrigid registration technique [27], [60], [61]. They can also be used in joint registration and segmentation [62], [63], thus providing an automatic basis for anatomical and functional localization and labeling. The level of accuracy of this brain mapping process and further use of the atlas in functional and anatomical labeling are extremely dependent on the registration technique or on how well the atlas structures can be matched to the individual anatomy. Methods comparing probabilistic information on brain structures from different groups of subjects reveal that most of the anatomical variability in a normal brain is in the cortical surface and in sulcal and gyral patterns rather than in deep brain structures [1], [64]. As a result, brain atlases and brain templates with identifiable cortical structures, including the important sulci and gyri, have proven helpful in neuroscience studies [27], [65]–[67]. Due to the important role of cortical surface structures in functional brain mapping, the development of surface-based brain atlases has also attracted much attention in recent years [68], [69]. The most comprehensive work on this topic has been done in [70] in the development of Population-Average Landmark and Surface-based (PALS) atlas of human cerebral cortex. The PALS-B12 is a surface-based population-average atlas of 12 normal young adults, which incorporates advanced hybrid intensity- and feature-based volume and surface nonrigid registration techniques. Intersubject volume registration and cortical surface registration are considered in Section IV.

It should be mentioned that in some diseases, such as Alzheimer's disease, remarkable differences are observed in deep brain structures between patients and normal subjects [27], [71]. In other dementias and in some psychiatric disorders, subtle abnormalities in the size and overall shape of the brain are discovered [72]. The statistics of deformation fields and gradient maps of the atlas transformations can be used to characterize the differences between diseased and normal brains for such cases. The use of deformable probabilistic brain atlases for anatomical abnormalities has been considered in [73] and [74]. High-dimensional volumetric nonrigid registration based on continuum mechanics and cortical surface registration has been utilized in the construction of these atlases. A similar study [75] has been conducted on anatomical changes in Parkinsonian patients. Analysis of functional information and comparison between the two groups is subtle and highly dependent on the accuracy of matching the brains to the deformable atlas. Disease-specific atlas construction is another approach for studying the differences between diseased and normal populations [27], [76]. Characterizing the structural and anatomical differences

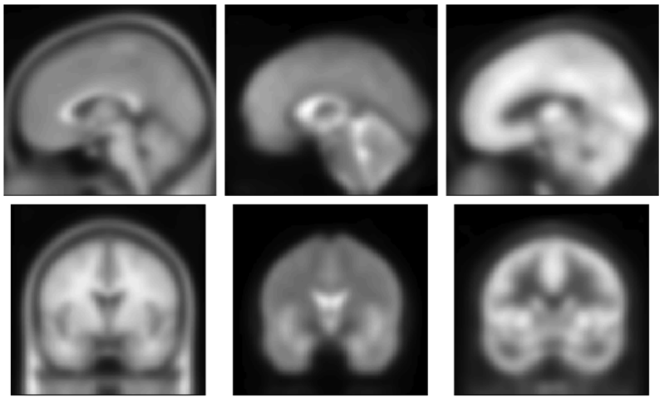

Fig. 4. MNI/ICBM152 standard average brain templates are obtained from the SPM2 template library, (a) T1-Weighted MRI, (b) EPI, and (c) PET templates.

is an ongoing research focus in clinical applications, although its effects on functional medical imaging have not been fully explored. Since functional information is usually mapped to the anatomy, the anatomical variability between groups of normal and diseased subjects may affect the accuracy of functional differentiation between the two groups.

E. MNI/ICBM Brain Templates

Brain templates can be regarded as a subclass of brain atlases which are normally used as references for mapping different brains in a group analysis study. The choice of a brain template in a group analysis study affects the outcome of statistical parametric mapping and consequently affects the localization of functional maps [77]. In some studies one of the brains is simply chosen to serve as the template. However, a template that statistically shows the average of the brains seems to be a better choice [78]. The simplest form of this kind of template, obtained via averaging the images that are premapped to a standard coordinate system, is called an average brain template. Normally the images used in constructing a brain template are spatially normalized to the Talairach standard coordinates, so most of the brain templates are originally in the standard coordinate system.

In a series of studies, the MNI created a brain template called MNI305 that was based on averaging a relatively large number of normal MRI brain images [37]. This template was created in a two-stage process. First, 241 brain images were registered to the Talairach coordinates and their average was calculated as the first-pass image. Then, 305 normal MRI scans were linearly normalized to the first-pass image and their average was computed to obtain the MNI305 template. The ICBM adopted a standard MNI template named ICBM152 by registering 152 normal brain scans to the MNI305 template [39] using a nine-parameter affine transformation. This template has been incorporated into several commonly used functional image analysis software packages such as AFNI, SPM and FSL. Fig. 4 shows the templates of three different modalities, T1-weighted anatomical MRI, fast fMRI EPI, and PET.

Although in many studies the group analysis is done through the registration of brain images to MNI templates, the results are usually reported in the Talairach coordinate system. The MNI template is designed on the basis of the Talairach standard coordinates, but due to the limited power of the Talairach piecewise transformation in compensating the anatomical variability in different brains and the template construction procedure, the corresponding points in the template and atlas spaces do not exactly appear at the same location [1], [79]. The extremes of misalignments when overlaying the two standard spaces are in the temporal lobes of the MNI template, which extend about 10 mm below the temporal lobes of the Talairach brain [1]. A simple translation formula has been suggested in [1] to map the MNI coordinates into the Talairach space. In a more recent study, an affine transformation has been used to improve the agreement of the two coordinate systems for deep brain structures [80]. The mis-localizations that may occur due to the differences between the MNI and Talairach spaces, their related transformations, and the interpretation of the results have been discussed in [81].

III. Functional-to-Anatomical Registration

The registration of functional-to-anatomical brain images is the main part of the functional localization procedure. The early registration techniques were developed for functional PET/SPECT to anatomical CT/MRI registration and are referred to as multimodality registration techniques. Due to the different sources of contrast and intensity values, fMRI to anatomical MRI registration poses similar challenges, and many of the prior multimodality registration techniques have been utilized on this relatively newer problem. T1-weighted, T2*-weighted, and Proton Density (PD) MR images have been the benchmarks in many of the recent investigations on multimodality image registration.

A. Correspondence Basis

Finding correspondences between the functional and anatomical images is the most important and challenging part of a multimodality registration procedure. Although an exact one-to-one correspondence exists between the functional and anatomical images of a subject, usually these correspondences are not visible in both modalities. Typically, the spatial resolution, signal-to-noise ratio, and contrast in functional images are less than those in anatomic images; hence the brain structures are quite vague in fMRI and even more so in PET and SPECT images. Fig. 5 shows typical slices of anatomical and functional MR images of a subject obtained in one scanning session.

At the highest level of classification, the correspondences can be established either extrinsically or intrinsically. Extrinsic methods are based on artificial fiduciary markers that are attached to the skull and are visible in both functional and anatomical imaging modalities. Image registration using extrinsic markers is usually fast and straightforward, but has major drawbacks such as the preparation needed before the acquisition and the limited applicability to low-dimensional registration problems. Some extrinsic methods, such as the stereotaxic frame screwed rigidly into the patient's head table in neurosurgery planning, also produce additional artifacts and image distortions in the types of scans commonly used for fMRI. Nonetheless, these methods have provided a useful benchmark for the evaluation and validation of multimodality registration techniques, which is discussed in Section III-E.

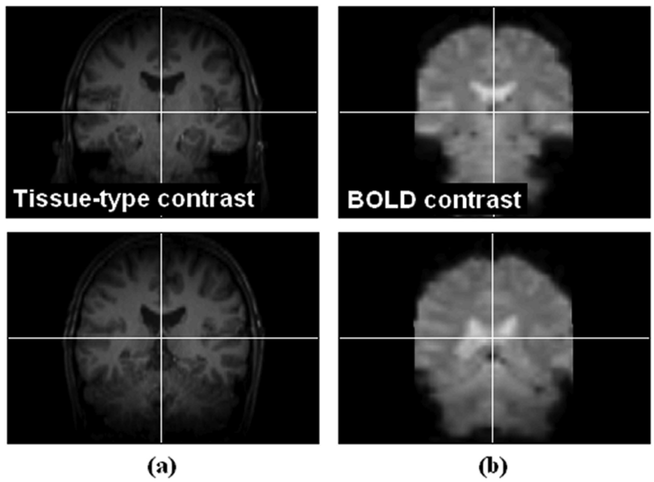

Fig. 5. Two coronal view slices of typical (a) anatomical and (b) functional MRI brain scans of a subject taken in one scanning session. Contrast in anatomical MRI reflects tissue type while in fMRI Blood Oxygenation Level Dependent (BOLD) level.

The intrinsic methods of finding correspondences between functional and anatomical images can be classified as feature-based methods and intensity-based methods. Feature-based methods rely on automatic feature extraction or segmentation, or manual or semi-automatic landmark detection, in the source and target images. The registration problem is formulated as matching these features or landmarks or minimizing a distance measure between them. Many of the early registration techniques were developed based on feature-based correspondences between multimodality images. Among the most popular feature-based registration techniques, the "head-and-hat" technique [82], [83], the "Chamfer matching" technique [84], and the iterative closest point (ICP) algorithm [85] are noteworthy. The "head-and-hat" technique is based on the segmentation of the skin surface from CT, MRI, and PET images and because of its simplicity and relatively low computational complexity it has been considered quite practical in PET to MRI registration. The chamfer matching technique uses a distance transform based on structural segmentations in the images. An extension of these registration techniques is the surface-based registration technique presented in [86]. The major drawback of the segmentation-based techniques is that the registration accuracy is limited by the segmentation accuracy.

The ICP algorithm, on the other hand, relies on the detection of surface and point landmarks and an iterative minimization of landmark distances. A major drawback with the landmark-based registration techniques is that normally the landmark detection step has to be done via user interaction. In essence, the extraction of anatomical feature correspondences, landmarks or segmentation-based features from functional brain images is very difficult and inaccurate. Therefore, only a few of the early feature-based registration techniques have been applied to the registration of functional-to-anatomical brain images. For example, the performance of feature-based registration techniques based on edge and ridge detection using Derivative of Gaussian (DoG) filters and scale space has been considered in several articles [87]–[89]. Another technique for the registration of functional PET to anatomical MR images using point, line and plane features has appeared in [90]. For a complete review and classification of the earlier feature-based registration techniques, the reader is referred to the survey paper by Maintz and Viergever [21]. There are very few recent papers on the utilization of landmark or feature detection techniques for multimodality brain image registration [91], [92]. Typically, these techniques have been tested on anatomical images and have not been used for functional-to-anatomical registration. In a hybrid intensity- and feature-based approach, the use of morphological tools has been proposed in [93] to extract surface and edge features and incorporate them into a cross-correlation intensity-based registration.

Intensity-based methods are based on intensity similarity measures between two images [94]. The basic methods utilize absolute or sum-of-square intensity differences [7], cross-correlation of intensity values [95], or variance of intensity ratios [96]. In contrast to the feature-based registration methods that use a relatively sparse set of processed and extracted information from the images, the intensity-based techniques can typically use all the available image information. Joint histograms of the source and target images have been considered as a basis for measuring intensity correspondences. The joint histogram of two images is more dispersed when the images are not in alignment. Research on quantifying the joint histogram of two brain images [96], [97] was redirected to use similarity measures based upon information theory, i.e., the concept of entropy and joint entropy of images [98], which resulted in the introduction of mutual information (MI) as a generally applicable similarity measure. Image registration via maximization of MI was introduced by two independent groups: Collignon and Maes *et al.* [99], [100] and Viola and Wells [101], [102].

MI is a measure of statistical dependence between two random variables or the amount of information one variable contains about the other. The MI of two images describes the amount of information in the joint histogram of the images; hence its maximization results in the best match of intensity correspondences between the images for registration. In the early follow-up studies, normalized formulations of MI were introduced in [100] and [103]. These two normalized measures are referred to as normalized mutual information (NMI) and entropy correlation coefficient (ECC). Many studies carried out on the use of MI and NMI in different medical image registration applications indicate that MI is regarded as the *de-facto* standard in multimodality image registration. For a more complete review of the broad range of the articles on MI-based medical image registration, the reader is referred to the review papers by Pluim *et al.* [17] and Maes *et al.* [18].

Despite the wide use of MI in medical image registration, there have been a few cases in which other similarity measures have shown to be more robust. These cases typically occur in applications with images of lower signal-to-noise ratio, such as ultrasound images. Correlation Ratio (CR) was introduced as another multimodality similarity measure in [104], and its performance was compared to MI for registration of ultrasound to MRI images [105], [106]. General formulas for the use of local and global correlation coefficient of intensity values (CC), CR, and MI similarity measures in multimodality nonrigid registration have been developed in a variational framework in [107].

In [108], it has been shown that all of the intensity similarity measures perform satisfactorily in the rigid registration of simulated SPECT to real MRI images. A protocol for the evaluation of nine similarity measures for rigid registration of SPECT, PET and MR images has shown the superiority of the measures based on information theory, e.g., MI and NMI [109]. The effect of implementation parameters on the accuracy of registration using different similarity measures has also been considered in this study.

Using simulated images, the deficiencies of MI in capturing some obvious image features has been shown in [110], and local phase information measure has been introduced to address those deficiencies. Phase information measure is inherently a feature-based correspondence measure based on frequency filtering, and has shown to be more robust than MI in extremely noisy cases such as the registration of ultrasound to MRI [111]. However, a practical case more relevant to the topic of this survey, i.e., functional-to-anatomical brain image registration, is the problem of image outliers. Image outliers may be present between the multimodality images due to incomplete data acquisition, different Fields Of View (FOV), lesion evolution, or neurosurgery; and can potentially affect the accuracy of registration techniques. This problem was addressed in an early comparison of intensity-based similarity measures [112]. In a more recent track of work, local frequency maps have been proposed to overcome the problems that may occur due to the different FOV or image outliers [113], [114]. The robustness of this technique has been compared with that of MI-based registration technique in [115]. Local frequency maps are obtained in the frequency domain based on Gabor filtering and phase gradient.

In [116] a more general concept of similarity has been introduced based on point similarity measures. Point similarity measures provide a general basis for relative comparison of local image correspondences. Information-theory-based similarity measures including MI can also be regarded as point similarity measures, and it is also possible to incorporate segmentation information and feature correspondences as part of these measures.

The majority of recent publications on correspondence basis are within the class of multimodality intensity-based similarity measures and specifically rely on information theory. These techniques can be classified into three groups: 1) methods that improve the computational accuracy and efficiency of joint histogram and joint entropy estimation; 2) methods that incorporate spatial information into MI; 3) methods that utilize more generalized measures from information theory.

1) The joint and marginal histograms of multimodality images have nonuniform and fuzzy shapes and a uniform histogram binning cannot adequately represent their characteristics and, thus, the computational accuracy of intensity similarity measures such as MI are adversely affected. Improvements have been realized through adaptive histogram binning [117], K-means clustering histogram binning [118], [119], and robust Maximum *A Posteriori* (MAP) estimation of joint histograms [120].
2) In practice, a major drawback of MI, based on the Shannon entropy, is that it ignores the spatial information and dependence of the gray values of the neighboring voxels in an image. Several methods have been proposed to incorporate such spatial information into the MI similarity measure, for example Jumarie entropy [121]. A combination of gradient information and MI has been examined in [122]. The concept of second-order MI has been developed [123] based on the co-occurrence matrices of the neighboring voxel intensities. Most of the more recent studies, such as the use of spatial feature vectors [124], multifeature MI [125], and regional MI [126], are based on higher dimensional histograms. In another extension, the multidimensional MI has been proposed for the simultaneous registration of multiple multimodality images [127]. The maximum distance gradient magnitude (MDGM) method [128] utilizes a two-element attribute vector of MI and spatial feature information in computing a multidimensional MI similarity measure. In contrast to the techniques which rely on derivatives for incorporating spatial feature information, to improve the noise robustness, the so called quantitative-qualitative measure of MI (Q-MI) has been developed in [129] utilizing the regional saliency values computed from the scale space maps of the images.
3) f-information measures are a general class of measures in information theory that can be used in quantifying the divergence of probability density functions (PDFs) as models of joint histogram of images. A comprehensive study, statistical analysis and comparison of the performance of various f-information measures in registering PET, CT and MR brain images has been carried out in [130], concluding that several measures can potentially provide significantly more accurate results than MI. Kullback-Leibler distance (KLD) is one of the measures based on information theory that has been used in some of the recent multimodality registration studies [131]–[135]. KLD provides learning capability and incorporation of prior information in multimodality image registration.

B. Transformation Model

Since the brain is constrained in the skull and the functional and anatomical brain images are normally acquired at a minimal time interval, thus limiting the possible long-term brain changes, the assumption that a rigid transformation is sufficient to register the images is in general fairly accurate. As a result, the majority of the multimodality registration studies simply assign a rigid transformation to the registration framework [87], [88], [90]–[93], [96], [100]–[103], [106], [108], [109], [111], [112], [114], [117]–[119], [123], [124], [126], [129], [131]–[133], [135]–[148]. A rigid transformation consists of three translation and three rotation parameters in the 3-D space providing a six degree of freedom model that is estimated through the registration algorithm. Sometimes three scale parameters are also added to the rigid transformation. Such a nine-parameter transformation is in fact an affine transformation and seems to serve as an appropriate practical model for the registration of most functional-to-anatomical brain images

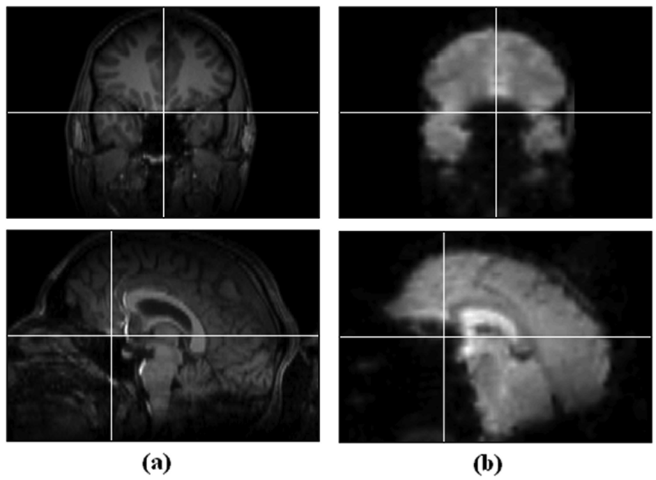

Fig. 6. Coronal and sagittal slices of typical (a) anatomical and (b) functional MRI brain scans of a subject taken in one scanning session. The effect of nonrigid distortions and signal loss artifacts near the bony tissues of sinuses is marked by crosshairs.

[114], [127], [149]. In its complete form, an affine transformation can also contain three shearing parameters, yielding a transformation with 12 degrees of freedom. The rigid and affine transformations can be fully modeled as 4×4 matrices of translation, rotation, scale, and shear. A tutorial on rigid and affine transformations has been provided in [150].

In practice, the most realistic reason for using transformations with high degrees of freedom for functional-to-anatomical brain image registration is the presence of local nonrigid geometric distortions in fast functional imaging. The fMRI echo planar images (EPIs) are typically distorted by severe geometric distortions due to eddy current effects, field inhomogeneity and susceptibility artifacts, as well as dephasing effects leading to signal loss and misplacement of intensities [151], [152]. Fig. 6 exemplifies the signal loss and distortion artifacts in a typical EPI scan.

There has been a considerable amount of research on the prospective or retrospective physical correction and compensation of these distortion and signal misplacement artifacts. Discussion of these techniques is beyond the scope of this survey paper, while it is noted that these techniques cannot completely correct the effect of nonlinear distortion artifacts and nonrigid registration can be effective in reducing the local mis-registrations caused between functional and anatomical images. A few studies have relied on affine transformation for distortion correction via registration of EPI to an anatomical image [153], [154], while most of the others have utilized high-dimensional nonrigid transformations [155]–[162]. The transformation models that have been used in these studies include unidirectional B-spline basis functions [156], Optical flow (OF) model [107], [155], [159], [160], and free form deformation (FFD) with regular grid of control points [157], [158], [161], [162]. Nonrigid transformation models have also been used in more general multimodality brain image registration studies, e.g., [116] and [163]–[168]. A detailed description and classification of the nonrigid transformation models is presented in Section IV-B.

One of the most important challenges in the development of nonrigid registration techniques for functional-to-anatomical brain image registration is the definition of appropriate constraints to avoid excessive deformations. Regularization methods, smoothness and diffeomorphic constraints have been widely studied in the development of intersubject nonrigid registration techniques [6] and are discussed in detail in Section IV-B. These methods have also been used in the above-mentioned studies on registration of functional EPI to anatomical MRI; e.g., [155]–[158]. Other researchers have investigated geometric constraints utilizing physical analysis of distortion effects in EPI [157], [162]. Based on the analysis of Spin Echo (SE) EPI, a logarithmic Jacobian correction term has been incorporated into the optimization procedure in [157]. A similar analysis has been performed in [162] for gradient echo EPI, where a Jacobian correction term along with a dephasing factor was incorporated into the optimization framework. It should be noted that elastic regularization does not necessarily need to comply with physical elastic properties of the imaging material, especially pertinent in cases such as EPI sequences used in fMRI, where the localized distortions arise from artifacts in the imaging methods rather than changes or differences in anatomy.

C. *Optimization*

The core of a registration algorithm is an optimization framework involving a search of those parameters of the transformation model that minimizes a cost function. The cost function is normally defined as a function of correspondences or similarity between the source and target images, and may also contain explicit regularization terms for smoothness and diffeomorphic constraints to preserve topology. In some feature-based registration algorithms, for example point matching on a set of point correspondences, a direct optimization technique such as the minimum norm solution can be used. In more complex situations, iterative optimization techniques are used, for example Powell's method, downhill simplex, gradient descent, conjugate gradient, quasi-Newton, Levenberg-Marquardt, genetic (evolutionary) algorithm, or simulated annealing.

Due to the nonoptimality of feature and intensity similarity measures and the corresponding cost functions, the solution of the registration problem is frequently not considered to be the global optimum. Additionally, global optimization techniques such as evolutionary algorithms and simulated annealing are characterized by quite slow convergence rates and have been used only rarely in medical image registration. On the other hand, multiresolution and multiscale optimization frameworks have shown to be effective in obtaining a faster and more robust convergence toward the solution [136]–[138]. Maes *et al.* [136] compared various multiresolution gradient and nongradient based optimization techniques such as Powell, simplex, steepest descent, conjugate gradient, quasi-Newton, and Levenberg-Marquardt methods, and obtained a speed-up by a factor of 3 in a two-level multiresolution formulation of conjugate gradient and Levenberg-Marquardt methods for affine registration of CT and MRI images.

Most of the widely used optimization algorithms, including gradient descent, quasi-Newton and Levenberg-Marquardt, require derivative calculation. While it is possible to numerically estimate the derivative of a cost function with respect to the transformation parameters via computing local variations, analytical expressions for the gradient of similarity measures have shown to be effective in speeding-up the calculation and achieving a smoother and more robust optimization. The gradient expressions for CR, CC, and MI similarity measures have been computed based on a variational formulation in [107]. Several groups have investigated analytical methods for the computation of the gradient of MI. Viola and Wells [101], [102] used a mixture of Gaussian distributions and Parzen window estimation to model the PDF distributions and derived analytical expressions for stochastic approximation of MI and its derivative. Maes *et al.* [136] computed exact expressions for the gradient of joint entropy and MI based on partial volume interpolation; and Thevenaz and Unser [138] introduced a rather fast optimization algorithm based on the computation of the gradient of MI using smooth Parzen window modeling of PDF distributions by cubic B-spline functions.

D. Interpolation

Interpolation is used within each iteration of the registration algorithm to resample the transformed source image to the physical space of the target image. As a general concept of image resampling, interpolation reconstructs a continuous image from its discrete samples. When the Nyquist criterion is satisfied as per the sampling theory [169], the continuous image can be perfectly reconstructed by the ideal interpolation kernel which is the sinc function corresponding to a low-pass rectangular filter in the Fourier domain. Nevertheless, sinc interpolation is impractical due to the infinite kernel width and signal band-limitedness assumption. In practice, windowed sinc functions can be used but there are also many other kernels with appropriate characteristics for interpolation.

The common interpolation kernels are symmetric and fulfill the separability property; thus, a 1-D kernel can be applied sequentially in the three dimensions of the image. While the nearest-neighbor interpolation is the simplest technique, the trilinear, quadratic and cubic B-spline kernels seem to be the most popular in registration applications. In essence, the choice of an interpolation kernel between linear interpolation and higher order spline interpolation kernels involves a tradeoff between speed and accuracy. Interpolation methods and their impact on medical image processing have been discussed in several tutorial articles by Meijering [170], Meijering *et al.* [171], Lehman *et al.* [172], and Thevenaz *et al.* [173].

In a series of investigations of the specific effects of interpolation on multimodality registration, it has been observed that linear interpolation or higher order interpolation techniques may introduce new intensity values leading to unpredictable changes in the marginal PDF estimation [99], [174]. Partial Volume (PV) interpolation has been introduced [99] to solve this problem. PV interpolation results in a continuous and differentiable registration criterion. The effect of interpolation artifacts on the accuracy of MI estimation has been addressed in [174], and has been further considered through the introduction of generalized partial volume interpolation in [175], [176] and sinc approximating kernels in [177].

E. Validation

Validation is necessary to guarantee the fidelity and usefulness of registration techniques, and includes considerations such as accuracy, robustness, consistency, reliability, resource requirements, computational complexity, and impact [178], [179]. Accuracy and robustness are the first issues that need to be verified in any investigation. Reliability is the correct performance of the algorithms for a reasonable range of data, and highly depends on the accuracy, robustness, and consistency of the techniques for real datasets. Validation of functional-to-anatomical image registration suffers from the problems associated with finding appropriate correspondences between images of different modalities. The most promising similarity measures that are currently used in multimodality image registration operate in the intensity domain and not in the spatial domain, thus, they do not provide useful information about the correctness of registration, the magnitude of registration errors, and the spatial distribution of errors [180]. Therefore, independent quantitative and qualitative assessments of registration fidelity are essential to prove the usefulness of any multimodality image registration algorithm.

Quantitative validation of registration accuracy is only possible if a ground truth is available. Extrinsic markers also referred to as fiducial markers, have been regarded as the earliest tools in providing the ground truth [96], [143], [144]. Extrinsic markers are either invasively placed by neurosurgery, or are attached to the skin surface, scalp or skull frames, and are typically far from the internal brain structures; but provide quite accurate gold standards for the evaluation and validation of rigid and affine registration. Fitzpatrick *et al.* [145] conducted a project called "Retrospective Registration Evaluation Project" (RREP) and provided a common evaluation framework based on gold standard PET, CT, and MR images of nine patients undergoing neurosurgery. Fiducial markers visible in all modalities were attached to the stereotaxic frames on each patient and were manually removed from the images to ensure the blindness of the evaluation and validation studies. Results of the first comparison of the registration results submitted by 12 participant groups were published by West *et al.* in 1997 [181]. The results were compared according to the median and maximum of the Fiducial Registration Error (FRE) for each technique, computed on 10 volumes of interest on the images of all nine patients. The interslice distance in the RREP database of this study was 4 mm for the MR images and 8 mm for the PET images. Considering both median and maximum FRE measures, the intensity-based registration techniques of Collignon and Maes *et al.* [98], Hill *et al.* [97], and Woods *et al.* [96] provided subvoxel accuracy in the registration of PET to MR images. Considering maximum FRE measure, the chamfer matching method of Jiang *et al.* [182] and considering median FRE measure, the head-and-hat technique of Pelizzari *et al.* [82], [83] provided comparable results.

Based on FRE measures in the RREP framework, West *et al.* [140] compared the performance of eight surface-based (feature-based) and six volume-based (intensity-based) registration techniques and concluded that the volume-based techniques were significantly more accurate than surface-based techniques in CT to anatomic MRI registration and were also slightly more accurate in PET to anatomic MRI registration. In the same study, they also performed a statistical hypothesis test on the differences between the results obtained from MR images corrected and uncorrected for field inhomogeneity, and did not find the difference significant for PET to anatomic MRI registration. A comparison of these results along with some of newer studies has also been presented in [21]. While the slice thickness was rather high in the original RREP study, a second series of nine patient datasets with PET, CT, T1-weighted, $T2^*$-weighted, and PD MR images have later been added to the project, and the database has been used as a gold-standard in the evaluation and validation of many multimodality brain image registration studies, for example [91]–[93], [103], [117]–[119], [125], [130], [136], [137], [139], [145], [146], and [149]. The major drawback of validation strategies based upon extrinsic markers is that the markers are spatially sparse, and far from the interior brain structures and, thus, do not provide the local resolution and accuracy that is needed in the validation of nonrigid registration techniques. Only rigid registration techniques have been validated using the RREP database.

An alternative to validation of registration based on extrinsic markers is validation with brain phantoms that are considered to serve as gold standards. Physical phantoms have been used in [157] and [160] to validate nonrigid registration of EPI to T1-weighted anatomical MRI, and in [106] to validate ultrasound to MRI registration. Physical phantoms can provide multimodality contrast and realistic motion, distortion and imaging issues [157]; however, similar to in-vivo human brain images, they normally suffer from the lack of quantitative registration validity measures [183]. Moreover, they cannot be easily deformed in a controlled manner. Digital brain phantoms, on the other hand, are more flexible and have been widely used in recent studies. However, the construction of accurate and realistic digital brain phantoms is a complicated task. An accurate digital brain phantom called *BrainWeb* has been developed at the McConnell Brain Imaging Center of the MNI at McGill University [184], [185] and has been widely used in validation. An MRI simulator in *BrainWeb* uses the Bloch equations to implement a discrete event simulation of NMR signal for more than 10 parameterized tissue classes and realistically models the MRI noise and partial volume effects. The simulator provides gold standard T1-weighted, $T2^*$-weighted, and PD-MRI synthetic images with different parameters, for normal and Multiple Sclerosis (MS) lesion brains. The *BrainWeb* database has been used in the validation of various rigid (e.g., [111], [114], [119], [127]–[129], [131], [135], and [147]) and nonrigid (e.g., [105], [110], [115], [134], [155], [158], [164], [166], and [168]) multimodality registration techniques. By applying simulated and synthetic motion and distortion to the gold standard images in these studies, ground truth measures have been defined and the accuracy of registration techniques has been quantified. PET and SPECT simulations have also been used in several studies, e.g., [141], [142], [108], and [186].

Some researchers have used images that were manually aligned by clinical experts as gold standards [113], [132]. Cross-validation and comparison of two techniques has been done in a few studies [87], [112], [148]. In many of these cases, the computational complexity of the algorithms has also been addressed through the validation procedure. Consistency tests using Monte Carlo simulations have been done in [147] on the images obtained from *BrainWeb* database, and in [108] on three registrations between interictal and ictal SPECT images and MRI. Consistency tests have also been done on the registration of a time series of functional images to an anatomical image in [154]. Robustness to different implementation issues such as the interpolation and optimization methods has also been considered as part of validation in the development of registration techniques, for example in [100] such an analysis has been done using the RREP database.

It should be noted that either most of the quantitative validation measures are not directly applicable to real images for local precision evaluation, or the assessments are not readily transferable from in-vitro to in-vivo data. Hence, qualitative assessment of registration fidelity through visual inspection is also useful. Qualitative assessment of registration accuracy has been done mostly through simple visualization techniques incorporating segmented edges and contours or checkerboard alignment of images through visual inspection [87], [88], [90], [96], [102], [107], [112], [131], [132], [134], [141], [149], [153], [155], [156], [160], [165], [166], [168]. It is often useful for registration results for real data to be cross-validated by comparing the accuracy of registration judged by expert observers with other evaluation criteria. For example, in [145] the fidelity of expert evaluation of registration accuracy was statistically validated by comparison with an external fiduciary marker method for gold standard CT and MR images. The images were obtained from five patients undergoing neurosurgery with four extrinsic markers implanted in the skull frame. The experts' visual assessments were accurate within 2 mm, whereas 0.5 mm accuracy of gold standard registration was estimated by the fiducial marker. Although qualitative validation has been used also as part of in-vivo validation of nonrigid registration techniques, it cannot be considered as an appropriate technique unless supported by additional validation strategies.

From a more practical viewpoint, the validation of nonrigid registration of functional EPI to anatomical MRI images has been much more challenging due to the need for local performance measures. Attachment of extrinsic markers and detection of intrinsic landmarks are difficult and, more importantly, they do not provide the desired local resolution for validation. Quantitative evaluation measures for images obtained from physical phantoms often suffer from the difficulty of providing adequately realistic details to properly simulate the appearance of the brain in real images. For currently available digital brain phantoms, there is not yet an appropriate simulation of EPI intensity, contrast, noise, signal loss, and distortion artifacts. The practical papers that have addressed the problem of fMRI EPI-to-anatomical MRI registration have typically relied on additional validation strategies. The technique in [153] has shown to be able to correct the effect of intentionally mis-adjusted shimming in EPI. Comparison of the transformation deformation fields to real field map acquisitions has been used in [157] and [162]. Qualitative validation based on the ultimate goal of registration, the postanalysis of the location of activation maps, has been presented in several studies, such as [157], [158], and [187].

IV. Intersubject Registration

Oftentimes, normal or pathological aspects of brain function can only be identified through the analysis of functional imaging data from a group of normal and/or diseased subjects [188]–[190]. The variability of brain anatomy between different subjects is a major problem in analyzing a group of functional images, and is arguably the most important challenge in functional localization [1], [3]. This variability not only affects the accuracy and reliability of statistical analysis but also creates serious problems in activation labeling and in reporting and comparing the results of different studies.

Because the anatomical variability is highly nonlinear, an accurate mapping between different brains and between different brains and brain atlases or templates is only possible through nonrigid transformations. The nonrigid brain warping techniques [6] have flexibility beyond the simple rigid and affine registrations. In practice, to perform intersubject registration, all of the brain images are registered to a standard brain atlas or brain template. This procedure is called spatial normalization [7], [191]. From an algorithmic viewpoint, brain warping techniques can be categorized as either volume registration techniques or surface registration techniques. Volume registration attempts to match the size and shape of different brains with each other or to warp them into a standard brain template, usually based upon voxel intensity values or anatomical features, utilizing internal landmarks as well as surface boundaries. Surface registration utilizes the layered structure of the sulcal and gyral structures on the cortical surface, which divides the brain into separate cytoarchitectural and anatomical regions, to guide the registration process. The spatial normalization techniques are listed in Section IV-A, detailed classification of transformation models and registration techniques are discussed in Section IV-B followed by a discussion on validation of intersubject registration in Section IV-C. Cortical surface registration techniques are discussed in Section IV-D.

A. Spatial Normalization

The simplest practical form of spatial normalization is the piecewise linear Talairach transformation which has been discussed in Section II-A. Because the Talairach coordinate system has been widely used and is generally accepted as the standard stereotaxic reference, it is normally used for postanalysis activation labeling, and the Talairach transformation has been used in many group-analysis studies. Nevertheless, after Talairach registration, differences on the order of centimeters may be observed between the anatomical landmarks detected in the spatially normalized brains [192]. The fact that the low-dimensional Talairach transformation cannot adequately deal with the anatomical variability in different brains has been the motivation for developing higher dimensional spatial normalization techniques. Even other low-dimensional warping techniques, such as polynomial warping [193], have been shown to be more accurate than the Talairach transformation for intersubject anatomical landmark matching [194]. The other drawback of the Talairach transformation is that it is based on manual selection of landmark anatomic reference points.

The accuracy of spatial normalization along with the resolution and signal-to-noise ratio (SNR) of the original functional images define the accuracy of the functional analysis and functional localization. Spatial normalization techniques can significantly affect the results of statistical functional image analyses such as statistical parametric mapping [190], [195]. As an example, in a recent study on somatosensory and auditory activation in the parasylvian cortex [189], it has been observed that activation maps may be detected on the wrong side of the sylvian fissure due to the possible inaccuracies in spatial normalization. Although brain templates of all functional imaging modalities, such as PET, SPECT and fMRI, are available and also can be created specific to a study, the advanced spatial normalization techniques are more accurate if applied to high-resolution anatomical MRI scans. These techniques typically rely on both intensity and feature correspondences that are better defined on high-resolution anatomical images. In some suggested procedures, accurate functional-to-anatomical registration is applied to the images of each subject. Then, the high-resolution anatomical images of all subjects are spatially normalized to a high-resolution brain atlas or brain template, and finally the transformations used in the spatial normalization of anatomical images are applied to the functional images [77]. Most of the newer developments are towards the use of spatial normalization in the high-resolution anatomical space of brain images.

Table I lists some of the widely used spatial normalization techniques. These techniques include: 1) the Talairach transformation [25]; 2) the polynomial warps (PW) method of Woods *et al.* [193]; 3) the harmonic basis function technique of the SPM software package by Ashburner and Friston [196]; 4) the demons algorithm by Thirion [197]; 5) Automatic Nonlinear Image Matching and Anatomical Labeling (ANIMAL) by Collins and Evans [198], [199]; 6) Large deformation fluid diffeomorphisms (LDFD) by Miller, Joshi and Christensen [200]; 7) elastic techniques based on Navier-Stokes continuum mechanics by Gee and Bajcy (NSCM) [201]; 8) the inverse consistent elastic registration (ICER) by Christensen and Johnson [202]; 9) the B-spline FFD model nonrigid registration by Rueckert *et al.* [203]; 10) the robust optical flow (ROF) technique of Hellier *et al.* [204]; 11) Octree Spatial Normalization (OSN) by Kochunov *et al.* [205], [206]; 12) HAMMER (Hierarchical Attribute Matching Mechanism for Elastic Registration) by Shen and Davatzikos [207]; 13) RPM (Robust Point Matching) by Chui *et al.* [208], [209]; 14) the iconic feature-based nonrigid registration (PASHA algorithm) by Cachier *et al.* [210]. Detailed descriptions of the characteristics of these techniques are covered in the following section, along with classification of volume registration techniques according to the transformation model, correspondence basis, and regularization methods.

B. Volume Registration

In intrasubject multimodality registration, rigid transformation and intensity similarity measures based on information theory have been widely used in most of the applications. In contrast, the choice of appropriate transformation models and correspondence bases has been more controversial in volume registration techniques for spatial normalization. The use of various nonrigid transformation models and hybrid intensity- and feature-based correspondences has been explored in many

TABLE I
SOME OF THE WIDELY USED SPATIAL NORMALIZATION TECHNIQUES AND THEIR MAIN CHARACTERISTICS

	Technique	Transformation model	Correspondence basis
1	Talairach [25]	13-parameter piecewise linear transformation	8 manually detected points
2	PW [193]	polynomial warps	intensity-based: MSD
3	SPM [196]	low-frequency cosine harmonic basis functions	intensity-based: weighted MSD
4	Demons [197]	diffusion model: demons points	diffusing attraction forces
5	ANIMAL [198],[199]	locally affine	correlation of image gradients
6	LDFD [200]	Euler-Lagrange PDE	hybrid landmark and intensity
7	NSCM [201]	Navier-Stokes PDE	intensity-based: likelihood
8	ICER [202]	harmonic basis functions	intensity-based: SSD
9	FFD [203]	regular grid of control points FFD	intensity-based: MI
10	ROF [204]	optical flow model	intensity-based: Displaced Frame Difference (DFD)
11	OSN [205],[206]	locally affine octant regions with Gaussian filtering	intensity-based: CC and geometrical centroids
12	HAMMER [207]	sub-volume regions with Gaussian filtering	Geometric Moment Invariant (GMI) attribute vectors
13	RPM [208],[209]	Thin Plate Spline (TPS) warps	anatomical feature point sets: cortical surface and sulci
14	PASHA [210]	diffusion model normalized optical flow model	hybrid intensity and feature IFB (Iconic Feature-Based)

studies. Constraining the deformation fields to be smooth and physically correct with regularization techniques has also been a subject of active research.

The simplest transformation that has been used for spatial normalization in the literature is the affine transformation [149], [211], [212]. Compared to a rigid transformation with 6 degrees of freedom, which is quite useless in spatial normalization, an affine transformation can approximately match the size of different brains. A 13-parameter piecewise linear Talairach transformation [25] has been used in many group analysis studies as a fundamental part of the functional image analysis software packages such as AFNI [31]. The drawbacks of the Talairach transformation as mentioned in Section IV-A are its limited accuracy in matching the brain structures and its semi-manual characteristic. Online and offline procedures for Talairach registration have been presented in [46], and an automatic Talairach registration technique has been developed in [213]. The technique developed in [213] uses mid-sagittal plane extraction and shape matching for corpus callosum to automatically detect seven of the eight (AC, PC, plus front and back, top and bottom, and left and right extents) Talairach landmark points (all except the most Inferior Point (IP)). Among the other low-dimensional nonrigid transformations, the polynomial warping method by Woods *et al.* [193] and the harmonic basis functions by Ashburner and Friston [196] have

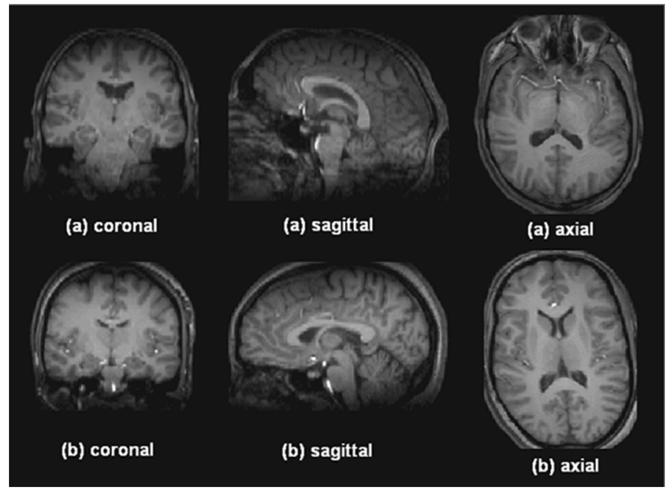

Fig. 7. MRI scans of two different subjects: position, orientation and field of view are different between the images. Spatial normalization is needed to bring different brain anatomies into alignment.

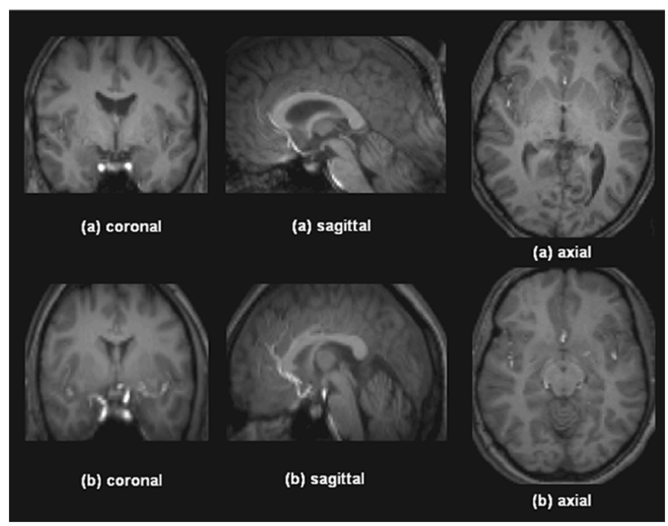

Fig. 8. MRI scans of the subjects in Fig. 7 are spatially normalized to the MNI/ICBM152 template using the low frequency cosine harmonic basis function spatial normalization technique in SPM2.

been widely used. Figs. 7 and 8 show T1-weighted MRI scans of two different subjects before and after spatial normalization using the volumetric registration method of the SPM software package [196].

Higher dimensional transformation models can be divided into two main groups: parametric models and nonparametric models. Some of the most important high-dimensional parametric models include: 1) FFD models with regular grid of control points, typically based on B-spline basis functions [51], [203], [214]–[222] or radial basis functions [57], [60], [77], [223]–[225]; 2) elastic-body spline warping models [226] such as thin plate spline (TPS) warping models [227]–[229] mainly used as interpolators for point set matching; 3) local affine transformations [166], [205], [206], [230]–[232]; 4) wavelet-mediated deformations [233]. A parametric particle method based on vector field formulation has also been developed [234]. On the other hand, the nonparametric models are based on partial differential equations (PDEs) describing the deformation of elastic material under external forces driving the deformation and internal forces imposing smoothness constraints. The external forces are computed through the similarity measures, and the internal forces are normally formulated as cost functions penalizing excessive deformations. The deformation field models are normally described by Navier-Stokes equations in continuum mechanics [54], [235]–[241] or by Euler-Lagrange equations in a variational framework [107]. The registration problem is solved numerically using Finite Element Methods (FEM) [242] or through the calculus of variations [107]. OF models [204] and the dense deformation fields of grid points in the Demons algorithm [197] are also classified as nonparametric models. The Demons algorithm has also been considered as an approximation of viscous fluid registration as investigated in [237]. In order to decrease the computational cost and to improve the local resolution of nonrigid transformations, several researchers have proposed adaptive techniques for the selection of control points in FFD [214], [243], [244] and also in NSCM [245] transformation models. Adaptation is typically done through the identification of the mis-registration areas with lower local similarity measures and/or higher contrast.

Analogous to the correspondence basis classification of functional-to-anatomical registration techniques in Section III-A, the intersubject volume registration techniques are classified into intensity-based, feature-based, and hybrid intensity- and feature-based techniques. Intensity-based correspondences are based on voxel intensity similarity measures which are either information-theory-based measures such as MI [50], [52], [59], [212], [223], [240], [246]; NMI [51], [216], [220], [221]; and KLD [55], [239], [247]; or based on likelihood functions of voxel intensities [215], [248] or voxel intensity differences computed as local or global sum of square differences (SSD) [58], [77], [149], [197], [233], [249]; mean square differences (MSD), or weighted MSD [49], [196], [202], [204], [225], [234], [250].

Feature-based registration techniques rely on geometrical or structural image features extracted by preprocessing voxel intensity values. Pointset landmark matching has been one of the most practical techniques, utilized for affine registration [211], Talairach transformation [213], elastic body spline and TPS warping [226], [227], and [229], and RPM [208]. Except in two cases, all of these techniques are based on manually detected point landmarks. A semi-automatic technique has been investigated in [227], and automatic detection of Talairach points has been introduced in [213]. Based on detectable substructures in MRI, a point set matching technique has been developed in [45] using finite element methods. Another group of feature-based registration techniques relies on level set motion and shape models; for example [251] and [238]. The geometric moment invariant (GMI) attribute vectors introduced in HAMMER [207] has provided a flexible framework for follow-up studies [252]–[254]. The attribute vectors include a set of image features at each voxel and are considered as morphological signatures of voxels. The incorporation of surface registration in HAMMER has also been considered in [255] and [256]. Wavelet-based attribute vectors [257], [258] rely upon the extraction of correspondence features from wavelet subimages. A more robust registration technique has been achieved via constraining the deformation field by 3-D statistical model of deformations (SMD+HAMMER) [259].

The relatively newer spatial normalization techniques based on OSN and HAMMER have utilized tissue classification and voxel intensity values, hence they are considered as hybrid feature- and intensity-based registration techniques. In [241] segmentation and tissue classification has been used to incorporate voxel class probabilities via MI and KLD formulations in an information theory framework. Several voxel intensity similarity measures have been tested in combination with feature correspondences in the OSN and PASHA algorithms. The PASHA algorithm [210] has been formulated based on the concept of iconic feature-based registration, which is regarded as a general form of a few older registration techniques, inspired by the Demons algorithm [197], the block matching technique [139], and the nonlinear ICP [260]. The use of other geometric features extracted from sulci models has appeared in a few articles, e.g., [261] and [262]. There are also a few studies that rely on hybrid intensity and point set landmark features in registration [217], [219]. In a more comprehensive framework called the landmark-initialized inverse consistent linear elastic registration [263] a hybrid registration technique based on ICER has been developed. Several correspondence bases have been used in this registration technique, including manually detected landmarks, semi-automatic structural segmentation by artificial neural networks, tissue classification, and normalized intensity similarity measures.

Another important aspect of nonrigid registration is regularization. In the most general form of nonrigid registration, each image voxel has 3 degrees of freedom and can be displaced in the 3-D space independent of its neighbors. Therefore, the maximum number of parameters of a high-dimensional transformation is three times the number of image voxels. Nevertheless, independent displacement of all voxels is undesirable since it may result in physically unrealistic deformations. Regularization aims at constraining the solution of nonrigid registration to achieve physically acceptable and topologically correct smooth deformation fields. Regularization is inherent in parametric nonrigid transformation models based on basis function interpolators such as TPS [226], and also B-splines in FFD models [203], [216]. The elasticity degree of the deformation field is determined and can be controlled by the number and distribution of the basis functions which are placed at the position of regular or irregular control points. In a multiresolution framework, the number of control points increases from the initial coarse resolution level to finer resolutions, thus increasing the elasticity and accuracy of the transformation model. The elasticity and resolution of the transformation can also be locally determined by adaptive selection of control point locations or by adaptive grid point refinement [223], [244]. Gaussian smoothing of deformation field has also been a straightforward regularization technique for subvolumes, locally affine transformations and block matching registration techniques [197], [205], [207]. A few techniques have utilized Gaussian smoothing of deformation fields, e.g., OSN and HAMMER. Nonstationary diffusion filter Gaussian smoothing has been used in [249] in the development of a locally adaptive regularization scheme. In addition to this kind of elasticity inherent in parametric models, other smoothness and physics-based constraints have also been applied in different applications. Smoothness constraints based on the derivatives of the deformation field formulated as the bending energy have been used for a regular grid of control points in the FFD model [203]. Jacobian of transformation has also been incorporated as constraints for topology preservation via interval analysis optimization in a nonrigid registration algorithm [222].

The PDE-based elastic models are generally more flexible than the parametric basis function models. Elasticity in these models is formulated through the constraints applied to the original Euler-Lagrange equation in the continuum mechanical elastic material and viscous fluid models. Elasticity based on the Navier-Stokes equation is suitable for small deformations while for larger deformations, the viscous fluid model is appropriate [200], [201], [237], [241], [262]. The degree of elasticity is determined by the elastic Lamé constants and is formulated as a competitive cost function between external energy in similarity maximization and the internal strain, bending or membrane energy for smoothness. Smoothness constraints have been formulated based on derivative, Laplacian, or Jacobian transforms of the deformation field in different studies. The competitive regularization algorithms have been integrated in most of the widely used spatial normalization techniques, namely SPM [196], Demons [197], ANIMAL [199], LDFD [200], NSCM [201], ICER [202], ROF [204], FFD [203], HAMMER [207], and PASHA [210] (Table I). In addition to linear elastic constraints, which guarantee the nonnegativity of the Jacobian of the deformation field in ICER, the effect of inverse consistency constraints has been considered in [202]. In [264] the asymmetric property of most registration algorithms has been discussed and a symmetric registration technique has been developed based on the so-called inversion invariant energy minimization. Symmetric image registration has also been considered in [265]. In an overview [210], various regularization techniques have been classified and the so-called pair-and-smooth techniques have been shown to provide a better behavior compared to the other competitive regularization techniques. The regularization terms are not exclusive and hybrid cost functions based on several constraints may provide better results, an example being the combination of locally weighted fluid regularization and elastic regularization [266].

C. Validation

Compared to the validation of multimodality registration techniques, which depend highly on the use of preapproved or simulated gold standards, there are several quantitative methods for the validation of intersubject registration techniques for real data. Nevertheless, due to the highly complex brain anatomic variability in different subjects, validation of intersubject registration techniques is quite challenging. Although the simulated and synthetic deformations, specifically based on the *Brainweb* digital brain phantom, have been used in many articles, e.g., [204], [239], [240], and [265], due to the fact that there is no appropriate model of intersubject brain anatomical variability, this sort of validation has not been considered as an appropriate indicator of the performance of intersubject registration techniques. Instead, various quantitative measures have been used in individual studies. Cross-validation through the use of similarity measures other than those utilized in each registration technique is one of the basic evaluation methods [215], [219], [220], [223], [233], [251]. Other measures based on average brain [197], [196], [246], [252], [267]–[269], tissue overlap [204], [206], [225], [235], [240], [241], [256], [263], [270], and sulcus distance [208], [217], [225], [255], [262], [267] have been used in the literature. Consistency tests have also been employed as a part of validation in several studies [77], [202], [212], [228].

Validation through manual expert segmentations has been presented in several articles [63], [251], [258]. In some articles the performance of automatic techniques has been compared to manual and semi-automatic registration techniques. For example, the automatic Talairach registration technique developed in [213] has been compared with the registration based on Talairach points detected by a skilled technician. In determining correspondences between MRI images, the feature detection algorithm in [258] has shown to perform similarly to experts even for complex cortical structures. Qualitative validation of the registration results has also been carried out through visual inspection [45], [62], [197], [205], [207], [208], [210], [219], [227], [229], [230], [234], [236], [246], [249], [250], [252], [261], [266], matching of detected landmarks and segmentations, and more practically through the postanalysis and interpretation of the loci of activation maps [77], [188]–[190], [195], [233], [248], [268]. In some articles such observations and analysis have been quantified using empirical measures. For example in [195], the impact of four spatial normalization techniques on activation detection has been quantified through the overlap of activation maps. In another study [268], the t and p values of statistical parametric mapping have been compared across the results obtained from three different spatial normalization techniques. The sensitivity of detected activation maps has been analyzed in [233]. The precision of functional localization has been analyzed through the use of the volumetric Talairach transformation and two surface-based registration techniques [188]. More practical consideration of the effect of spatial normalization on activation maps has appeared in some fMRI analysis studies [189] and [190].

A few articles have been solely dedicated to the evaluation, comparison and validation of intersubject registration techniques. Some of these articles have relied on human expertise for detailed identification of features; for example in [194] a statistical analysis was carried out on the accuracy of matching 128 carefully defined and expert manually detected landmarks per hemisphere. The Talairach transformation and the PW technique [193] were compared, showing that PW provides more accurate results in spatial normalization. In [271], several ranking measures were utilized, based on frequency-adaptive wavelet-space thresholding, to compare the PW technique to the low-frequency cosine basis function technique of SPM. In [270], a comparison of three registration techniques was carried out based on labeled structures overlap measures, relying on the highly detailed manually labeled MRI brain images of the Brain Segmentation Repository (BSR) at the Center of Morphometric Analysis at Massachusetts General Hospital, Boston. In [269], several validation criteria, including segmentations based on the BSR database, expert detected landmarks, atlas-based segmentation, and average brain construction were used to compare the accuracy of a B-spline based topology preserving registration technique [222] with Demons algorithm. In another study, Crivello *et al.* [195] compared the average brain image statistics and several measures of tissue overlap. They also performed a statistical analysis on the effect of spatial normalization on the overlap of activation maps detected for PET functional data of 18 subjects. Based on their analysis, they concluded that the current spatial normalization techniques had limited effects on those activation maps that were detected through low-resolution functional analysis [with a full-width at half-maximum (FWHM) of 8 mm in low-pass filtering of functional images]. The activation maps in such cases overlapped in 42.8% of the total activation volumes of four different spatial normalization techniques. However, the overlap was shown to fail dramatically (only 6.2% overlap) when a high-resolution functional analysis (FWHM of 4 mm) was applied.

In a more comprehensive comparison of six intersubject registration techniques, Hellier *et al.* [267] utilized four different classes of performance measures: 1) quantitative similarity measures (MSE, CC, and MI) between the registered brains and the average brain volume as well as visual inspection of the sharpness of the average brain volume; 2) tissue overlap measures; 3) correlation of differential characteristics; 4) sulcal shape and distance measures. For the fourth item, they utilized the active ribbon modeling technique described in [272] for 12 major sulci and computed two measures showing the global positioning distance and the similarity of sulci shapes. Based on the results obtained, they concluded that compared to an affine transformation, the higher dimensional registration techniques performed much better according to the first three performance criteria, but they did not perform better at matching cortical sulci structures. This conclusion has been confirmed in [270], indicating that intersubject cortical variability remains a severe challenge for volume registration techniques. It, thus, appears to be necessary to incorporate the new track of studies on cortical surface registration into the spatial normalization procedure.

D. Cortical Surface Registration

There are several reasons why cortical surface registration is needed for functional localization. First, most of the normal anatomical variability in the brain is in the cortical layered structure, and functional localization is extremely sensitive to the accuracy of registration in this area [192], [273], [274]. Second, the cortical surface structures, sulci and gyri, subdivide the brain into anatomically separate areas needed for activation labeling [275]–[277]. Third, due to the highly folded nature of the cortical surface, a small inaccuracy in volume registration may result in large inaccuracies in structural localization, for example for points located at two sides of a sulcus [189].

The cortical surface registration techniques have originated from some of the earlier feature-based registration techniques, such as the crest lines [278] and convex hulls [279] algorithms. These techniques are based on geometrical landmarks characterizing the cortical surface structure. A few methods are based on manually identified surface landmarks, such as the viscoelastic fluid sheet registration in [192]. Surface features have also been utilized in combination with volume registration techniques. Examples of hybrid volume and surface registration techniques include ANIMAL+sulci [199] and HAMMER+surface [255], [256], [280]. The evolution of cortical surface registration techniques involves a sequence of geometrical image processing algorithms including surface reconstruction, segmentation and structural modeling, inflation, flattening, and mapping to a surface-based coordinate system.

Surface reconstruction is an unfolding procedure to represent or visualize the folded geometry of the cortical surface. In its simplest form, it is achieved by segmentation of gray and white matter interfaces, a connecting procedure, and finally a triangular tessellation [281]–[285]. Davatzikos and Prince [286] and Davatzikos and Bryan [287] had a leading role in utilizing deformable active shape models for the cortical surface. The reconstruction process was improved in [282] by evolving the fuzzy segmentation and isosurface algorithm to a deformable surface model. Three other groups, Van Essen *et al.* [288], Dale and Fischl *et al.* [281] and Joshi *et al.* [289] investigated cortical surface reconstruction procedures based on tissue classification and triangular tessellation. A tutorial on surface reconstruction, surface-based atlases, surface-based spatial normalization, and functional mapping to the cortical surface has been written by Drury *et al.* [290]. Surface mapping has also been considered in a more general tutorial on brain mapping by Thompson and Toga [291]. A few of the surface reconstruction algorithms have been implemented as software tools for surface visualization and mapping. The tools listed in Table II are Surefit, based on the technique of Van Essen *et al.* [288], Freesurfer by Fischl *et al.* [281], [292], [293], BrainSuite by Shattuck and Leahy [294], and Cortical reconstruction using implicit surface evolution (CRUISE) by the Image Analysis and Communications group at Johns Hopkins University (Baltimore, MD) [283], [295]. Most of these techniques are based on initial segmentations for white matter, gray matter, and cerbrosplinal fluid tissue classification, triangular tessellation for reconstruction, and a topology correction method to provide geometrical smoothness and topology preservation [296]. A common approach for topology correction has been the use of deformable surface models [297]–[299]. Graph-based topology correction algorithms have been used in CRUISE and BrainSuite [283], [294], [297], [300].

The required steps to go from the cortical surface reconstruction to the surface registration and visualization for functional localization include cortical surface inflation, flattening and probably more advanced structural segmentation [292], [295], [301]. Inflation is useful for visualization, and flattening to planar, spherical or ellipsoidal maps is a simplification to permit registration of the cortical surface to surface-based standard coordinates [288], [302]–[304]. Detection of structural surface features, i.e., sulci and gyri, has a direct impact on surface registration techniques. Most of the research on sulcus morphology, modeling, detection, and labeling has been inspired by the properties of the sulcus homology and variability in Ono's Atlas of the Cerebral Sulci [305]. Fundamental work has been done in [306] on active contour models, and in [272] on active ribbon models. Alternatives and extensions to these techniques

TABLE II
CHARACTERISTICS OF CORTICAL SURFACE RECONSTRUCTION TECHNIQUES

Technique	Ref.	Segmentation	Topology correction	Reconstruction
Freesurfer	[292] [293]	Intensity-based tissue (WM, GM) segmentation and connected components algorithm	Minimization of smoothness energy functional	Triangular tessellation
Surefit	[288]	Bayesian segmentation of white matter	Local parametric quadratic charts	Triangular tessellation and isosurface generation
BrainSuite	[294]	Intensity-based tissue (WM, GM, CSF) segmentation	Graph-based topology correction	Triangular tessellation (Marching Cubes algorithm)
CRUISE	[283] [295]	Adaptive Fuzzy C-means clustering-based segmentation of WM, GM and CSF	GTCA (Graph-based Topology Correction Algorithm)	Triangular tessellation (Nested cortical surface reconstruction)

have been made in modeling the cortical sulci through statistical shape models and active shape models [307]–[314]. In other work, a method based on filling a cortical mesh with gyral labels has been developed [315], and a surface feature extraction algorithm based on Laplacian maps has been developed [285]. On the basis of differential geometry, a conformal mapping approach to brain surface mapping has also been presented in [316]. An object-based morphometric approach to compare cerebral cortex structures have been used in [317].

Surface reconstruction and sulcal models have been used in surface mapping and registration techniques, for example [318]. The importance of surface registration for functional and anatomical brain mapping has been discussed in [192]. An overview of the earlier techniques has been presented in [319]; but the necessity of using cortical surface registration in spatial normalization and functional localization has only been considered recently. In [188], it has been shown that the surface-based registration techniques perform better than the Talairach volume registration technique in the localization of auditory cortex activations. In [320], an evaluation method has been developed for quantitative assessment of accuracy and comparison of a few cortical surface registration techniques using known synthetic deformations and their effect on group activation analysis. The newer cortical surface registration techniques are based on geometrical features [288], [303], [321] or sulcus models and maps [322]–[324], [262]. In [284], a technique has been developed based on spherical mapping of hemispheres and has been validated according to sulcus alignment and automatic labeling, and in [325], a hybrid technique has been formulated based on the level set method and geometrical features. These new techniques have been evaluated separately and there has been no comparison of their performance.

The final stage of functional localization, activation labeling, is highly affected by the topics covered in this section. Cortical surface reconstruction is useful primarily for visualizing the 3-D location of activation maps as well as for high-level manual neuroanatomic labeling [326], [327]. On the other hand, automatic neuroanatomic labeling has been possible using accurate surface registration and sulcus matching techniques. These are the most comprehensive algorithms discussed in this section, utilizing segmentation, reconstruction, and structural mapping procedures to produce reliable labels. The purpose of these algorithms is to decrease the burden of tedious subjective manual labeling in common applications. The validation of the automatic labeling techniques includes statistical analysis of consistency, accuracy and efficiency with respect to experts' manual labeling [276], [328], [329]. Nevertheless, due to the difficulties in sulcus matching, most of the algorithms have been used to produce assisted labeling rather than fully automated labeling. Some of the most important structural brain labeling algorithms, listed in Table III, are anatomical automatic labeling by Tzourio-Mazoyer *et al.* [43], sulcus extraction and assisted labeling by Le Gualher *et al.* [272], program for assisted labeling of sulcus regions (PALS) by Rettman *et al.* [330], and Mindboggle by Klein and Hirsch [328].

V. DISCUSSION

A. Brain Atlases and Brain Templates

The success of a brain atlas depends upon how well the brains of different anatomies can be matched to the representation of anatomy in the atlas. Although the atlas of Talairach and Tournoux has become a universal standard framework for reporting neuroscientific studies, it does not provide a complete representation of the human brain anatomy. The ICBM population-based atlases are constructed by averaging a relatively large number of brain MRI scans that are transformed into the Talairach coordinates. Since the low-dimensional Talairach transformation cannot capture the high-dimensional variability of the brain anatomy, the standard MNI and ICBM atlases are representatives of the average brain size and shape, and the cortical structures are quite vague and blurred in these atlases due to the effect of low-pass filtering in the averaging process. In practice, the MNI and ICBM templates and the Talairach brain atlas are being used as standard frameworks in many functional neuroimage analysis studies. However, when researchers try to achieve an accurate functional localization, even through a tedious manual anatomical labeling and interpretation, by overlaying functional data onto the Talairach atlas, the inaccuracy of the registration steps and even the slight differences between standard templates and the Talairach atlas pose serious limiting factors.

Newer automatic labeling algorithms and advanced brain warping and nonrigid registration techniques are based on matching internal brain and cortical surface structures and, thus, require more accurate representations of the anatomy in the atlas. Deformable and probabilistic brain atlases have been proposed to address these requirements. Cortical surface registration, sulcus matching techniques, and advanced nonrigid

TABLE III
CHARACTERISTICS OF AUTOMATIC STRUCTURAL BRAIN LABELING TECHNIQUES

Technique	Ref.	Preprocessing/Registration	Structure/Sulcus matching	Atlas and automatic labeling
SEAL	[272]	Talairach transformation and Neural network based tissue classification	Cortical surface extraction and parametric shape modeling of sulcus using active ribbon method	Matching sulcus probability maps on a labeled probabilistic brain atlas
AAL	[43]	SPM cosine harmonic basis function spatial normalization	Coordinate matching after spatial normalization	MNI152 single subject atlas with 45 anatomical volumes of interest in each hemisphere
Mindboggle	[328]	Linear registration to MNI152 atlas, and segmentation to gray matter	An algorithm for detection and matching 3D sulcus pieces	MNI152 and Talairach labeled atlases
PALS	[330]	Cortical surface reconstruction and mapping	Automatic segmentation of sulcal regions using a watershed transform	Sulcus labeling based on Ono's atlas of the cerebral sulci

registration techniques can be utilized as tools in the construction of more realistic and accurate deformable brain atlases. Nevertheless, structural variability in the cortical morphology is a real challenge for developing a standard cortical map of the brain. Brain variability becomes more severe and its effects become more profound when comparing the function and structure of different groups of subjects, e.g., in studying the functional and anatomical differences of diseased and healthy groups. Considerable variations of brain anatomy in psychiatric and mental diseases such as dementia, schizophrenia, and Alzheimer's disease have been the motivation for developing disease-specific brain atlases. The choice of an atlas or template, in standard coordinates or based on deformable subpopulation atlases, depends on the type of clinical and scientific studies and may greatly affect the interpretation and comparison of the results.

B. *Functional-to-Anatomical Registration*

Functional-to-anatomical brain image registration has gone through several decades of active research, and still remains an important research area. In single-subject analysis and specifically in neurosurgical applications, the accuracy and reliability of functional-to-anatomical image registration is the limiting factor. In group analysis, however, spatial normalization is the most prominent source of inaccuracy. In practice, the current functional-to-anatomical registration techniques involve the optimization of an affine transformation model in a multiresolution framework to maximize a similarity measure. MI or normalized MI has shown to be the most robust and accurate similarity measure in many studies.

Research on the improvement of functional-to-anatomical image registration is now focused on finding appropriate correspondences through more general and reliable similarity measures based upon information theory. A direction of research is towards extending MI to incorporate spatial information. Rigid and affine transformations provide practical bases for robust and reliable functional-to-anatomical registration. However, nonrigid registration has been proposed to deal with the effect of nonlinear local distortions in functional images, specifically in EPI sequences used for fMRI. Different techniques can be used in the validation of rigid and affine registration techniques, while in-vivo validation of nonrigid multimodality registration techniques is extremely difficult due to the lack of reliable and accurate local correspondences between images. Several aspects of in-vivo validation are being actively investigated, including the effect of registration on functional localization and activation labeling, and the accuracy of registration in the presence of motion and distortion, different fields of view, limited resolution, and signal voids in functional images.

C. *Intersubject Registration*

Current spatial normalization techniques, such as the low-frequency cosine basis functions in SPM, the Demons algorithm, ANIMAL, OSN, HAMMER, and PASHA, seem to perform satisfactorily in common neuroscience applications. However, more accurate functional localization is often desired, especially as images of higher resolution become available, for more demanding applications. The direction of future research is, thus, anticipated to be toward utilizing more complicated hybrid intensity- and feature-based techniques. Due to the complex variability of the brain anatomy, a fair amount of computational effort is required to achieve this. The development of accurate spatial normalization techniques and high-resolution anatomical brain atlases/templates should be done in parallel. More work is needed to further develop spatial normalization and intersubject registration techniques, in various aspects such as the transformation model, correspondence bases, regularization and optimization; and especially in-vivo validation.

One of the main challenges that researchers have pointed out and developers have proposed for future research is the effect of spatial normalization on functional maps. Noting that the resolution of functional imaging and the accuracy of functional analysis techniques are being improved, the accuracy and reliability of spatial normalization are expected to play a critical role. Analysis of functional maps in studies of diseases such as dementia, in which severe anatomical differences exist between healthy and diseased brains, may lead to spurious results or invalid interpretations and conclusions, in which anatomical differences are mischaracterized as functional differences. One approach to overcome this problem is the use of subpopulation or disease-specific atlases. Cortical surface registration techniques are being incorporated for routine use in spatial normalization techniques for functional analysis. The convoluted structure of the cortical surface and the level of variability versus homology in sulcal and gyral patterns in the brain is a real challenge for cortical surface registration. Development of methods such as cortical reconstruction, segmentation, tissue classification, and flattening and mapping to planar, ellipsoidal or spherical surfaces, utilizes powerful tools from differential geometry, image processing and computer vision, including deformable active and statistical shape models. Topology correction in cortical reconstruction, finding appropriate correspondences in reconstructed and mapped structures, sulcus modeling, and descriptions and subsequent mapping to standard cortical structural maps are required. These techniques are expected to be used both for volumetric spatial normalization in group analysis studies, and for making automatic activation labeling tools for the last stage of functional localization.

In conclusion, technical advances in functional brain imaging and automatic functional localization are leading to clinical and scientific applications with higher spatial and temporal resolutions. The construction of standard and subpopulation brain atlases and brain templates, functional-to-anatomical registration, and spatial normalization through volumetric registration and cortical surface registration are deemed important fields of study in this burgeoning area of research.

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