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Unifying the Analyses of Anatomical and Diffusion Tensor Images Using Volume-Preserved Warping

Dongrong Xu, PhD^{1,2,5,*}, Xuejun Hao, PhD^{1,2}, Ravi Bansal, PhD^{1,2}, Kerstin J. Plessen, MD, PhD^{1,2,3}, Weidong Geng, PhD⁵, Kenneth Hugdahl, PhD⁴, and Bradley S. Peterson, MD^{1,2}

¹MRI Unit, College of Physicians and Surgeons, Columbia University Medical Center, Columbia University, New York, New York, USA

²New York State Psychiatric Institute, New York, New York, USA

³Center for Child and Adolescent Mental Health, University of Bergen, Bergen, Norway

⁴Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway

⁵State Key Laboratory of CAD & CG, Zhejiang University, Zhejiang, P R China

Abstract

Purpose—To introduce a framework that automatically identifies regions of anatomical abnormality within anatomical MR images and uses those regions in hypothesis-driven selection of seed points for fiber tracking with diffusion tensor (DT) imaging (DTI).

Materials and Methods—Regions of interest (ROIs) are first extracted from MR images using an automated algorithm for volume-preserved warping (VPW) that identifies localized volumetric differences across groups. ROIs then serve as seed points for fiber tracking in coregistered DT images. Another algorithm automatically clusters and compares morphologies of detected fiber bundles. We tested our framework using datasets from a group of patients with Tourette's syndrome (TS) and normal controls.

Results—Our framework automatically identified regions of localized volumetric differences across groups and then used those regions as seed points for fiber tracking. In our applied example, a comparison of fiber tracts in the two diagnostic groups showed that most fiber tracts failed to correspond across groups, suggesting that anatomical connectivity was severely disrupted in fiber bundles leading from regions of known anatomical abnormality.

Conclusion—Our framework automatically detects volumetric abnormalities in anatomical MRIs to aid in generating a priori hypotheses concerning anatomical connectivity that then can be tested using DTI. Additionally, automation enhances the reliability of ROIs, fiber tracking, and fiber clustering.

Keywords

diffusion tensor imaging; anatomical imaging; multimodal imaging data analysis; volume-preserved warping; fiber tracking; fiber clustering and comparison

The general rubric of magnetic resonance imaging (MRI) subsumes various modalities of data acquisition (e.g., T1- and T2-weighted anatomical imaging, magnetic resonance spectroscopy, and diffusion tensor (DT) imaging (DTI)), each of which provides unique but complementary

*Address reprint requests to: D.X., 1051 Riverside Drive, NYSPI, Unit 74, New York, NY 10032. E-mail: dx2103@columbia.edu.

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information about brain structure and function. Combining data from multiple MRI modalities can provide a more comprehensive view of a subject or group of subjects than can any single MRI modality. For example, anatomical T1- or T2-weighted MR images can help to identify structural boundaries within the gray matter and white matter of the human cerebrum, whereas DTI and its derived measures (e.g., fractional anisotropy [FA], apparent diffusion coefficient [ADC]) provide information about the directional organization of brain tissue that can be used to track nerve-fiber pathways. Moreover, a map of the principal directions for the diffusion of water, generated using DTI, can help to more accurately parcellate the anatomy of the corpus callosum (CC) and other white matter structures (e.g., cingulum, external capsule, and anterior thalamic radiation) (1-4) that appear homogeneous in their contrast and signal intensities in T1- or T2-weighted images.

Researchers have long desired to integrate information from both modalities to provide a more comprehensive view of anatomical structure and connectivity in the human brain. The integration of T1-weighted and DT imaging data, however, faces at least two major obstacles: 1) the accurate coregistration of datasets from the two modalities, which differ profoundly in their contrast and possibly in the geometric distortion that they contain, and 2) the accurate selection of anatomically relevant regions of interest (ROIs) within the coregistered dataset that can serve as seed points for the identification and tracking of a relevant subset of nerve fibers within the brain. We will discuss each of these obstacles in turn in more detail.

The accurate coregistration of T1-weighted anatomical and DT images usually requires the implementation of nonlinear warping techniques, which is challenging for several reasons. First, because DT images are acquired using echo-planar imaging (EPI) pulse sequences, they are more prone than are anatomical T1- or T2-weighted images (which are usually not acquired using EPI) to spatial distortions arising from susceptibility artifacts at the interface of different media (e.g., at the interface of brain tissue and air in the sinuses), to eddy-current artifacts caused by the requisite switching of imaging gradients during the acquisition of DTI datasets, and to other distortions caused by inhomogeneities in the static magnetic field. Coregistering accurately images that contain differing kinds and degrees of geometric distortion is both difficult and complex. Second, image resolution and signal-to-noise ratios (SNRs) are higher in T1- or T2-weighted datasets than in DTI datasets, and these differences may introduce errors in the identification of corresponding structures across the images during their coregistration. Avoiding these errors requires additional imaging processing to make the resolution and SNR of the two types of images more comparable. Third, voxels in the two types of images contain data of differing dimensionality. Anatomical T1- or T2-weighted images contain one-dimensional, scalar data (i.e., only one intensity value per voxel), whereas DT images are multidimensional data-sets (i.e., they contain 3×3 symmetric, positive definite matrices at each voxel that represent the probability of the spatial diffusion of water molecules). Finally, these multidimensional DTI datasets represent tensors, which encode information about the spatial orientation of nerve fibers; thus any warping of DT images, either during coregistration with anatomical images or during spatial normalization of DTI datasets across individuals, requires careful preservation of the orientation and shape of tensors in order to maintain the integrity of that biologically relevant information.

Added to the difficulty of coregistration is the problem of identifying and reliably segmenting ROIs that are morphometrically valid and anatomically relevant to the neural systems under investigation. This process is difficult because no two brains are exactly alike, and within many brain regions, including within the cerebral cortex, the contrast of both anatomical boundaries and internal structure can be insufficient for the reliable and valid delineation of anatomically discrete structures. Automated segmentation has been an elusive goal in the processing of medical images, leaving expert anatomical knowledge as the sole basis for the manual segmentation or definition of brain ROIs. The manual definition of ROIs, however, is

problematic because different experts usually produce different segmentations of the same image (5), and even the same expert will produce differing segmentations when segmenting the same image twice (6). The reliability and validity of segmentation can suffer even when subdividing highly discrete anatomical structures, such as the CC. Moreover, the manual definition of ROIs is usually time-consuming and financially costly.

Numerous attempts have been made to integrate information from T1- or T2-weighted images and DTI datasets (Refs. 7-12 are but a few examples), and several of these have also sought to address either the difficulty of cross-modal registration or the difficulty of accurate identification of ROIs used for the initiation of fiber tracking. To our knowledge, however, no method for multimodal imaging has yet been developed that simultaneously addresses the challenges of both coregistration and ROI delineation. Some groups, for example, have proposed elegant deformation algorithms that improve the quality of cross-modal coregistration (13-21), and others have used existing software packages for cross-modal coregistration, such as statistical parametric mapping (SPM) (18,19) and automated image registration (AIR) (20,21). These methods, however, have not been integrated with methods for the automated delineation of ROIs as a basis for fiber tracking. Other groups, in contrast, have attempted to reduce inaccuracies in the delineation of ROIs by generating an atlas of the brain through the averaging of manual segmentations from a group of experts (6), and then using that atlas as a template for automated ROI delineation in additional subjects. These methods for reducing inaccuracies in ROI delineation, however, do not address the problem of coregistering images across anatomical and DTI datasets. Thus, previously proposed methods for integrating information from T1-weighted and DTI datasets leave unsolved one or the other of the major difficulties in unifying the analyses of anatomical and DTI datasets.

To more comprehensively address these challenges in integrating the analysis of anatomical images and DTI datasets, we have developed an automated framework that identifies localized group differences in brain structure in spatially normalized, T1-weighted images, and that then uses those localized differences as seeding ROIs for the tracking of fiber pathways in the brain within DT images. Our framework employs volume-preserved warping (VPW) to automatically identify the morphometric differences between groups of subjects. We tested the performance of our framework on multimodal MRI data from a group of children with Tourette's syndrome (TS) and a group of age-matched normal controls (NC). After tracking fibers in the two diagnostic groups, we clustered the fibers tracts into bundles and then identified bundles with similar and differing 3D morphologies across the two groups of subjects.

IDENTIFICATION OF ROIS FOR FIBER TRACKING IN DT IMAGES

Our methods for coregistering T1-weighted and DT images (14) and for automatically selecting ROIs in DT images involve the following steps (Fig. 1):

1. Image coregistration (including spatial normalization within and across MRI modalities).
2. Automated selection of ROIs with VPW. Because it is automated, this algorithm minimizes the influence of human error in selecting ROIs in T1-weighted images for fiber tracking with DTI.
3. Use of the identified ROIs as seed regions for fiber tracking with DTI.
4. Clustering and morphological comparison of fiber tracts

Image Coregistration

We first acquire both T1-weighted and diffusion-weighted (DW) images for each subject, and then reconstruct the DT images from the DW data. Corresponding T1-weighted and DT images are typically treated as rigid bodies during their coregistration (often using AIR, SPM, etc.) (13,22,23). However, image distortion is inherent in the EPI image sequence used to acquire the DTI data. We therefore apply a nonlinear deformation procedure to correct this distortion during the coregistration process across T1-weighted and DT datasets (15,24,25). The deformation algorithm that we use is based on modeling the deformation of the T1-weighted image as a fluid (26), while maximizing the mutual information across scalar images (16), thus minimizing the difficulty of warping two images that have differing pixel intensities, differing contrast, and differing degrees of geometric distortion. This algorithm works well for images within the same MRI modality. However, in images from differing MRI modalities, structural details and boundaries between heterogeneous regions in white matter may vary in appearance, despite the fact that the images are of the same subject.

Therefore, to coregister the DT image of each subject to its corresponding T1-weighted image, we calculate the deformation fields (DFs) for this coregistration not directly by warping DT and T1-weighted images, but through warping the T1-weighted image of the maps of FA values that are derived from each DT image. We use the FA maps instead of the DT images because, unlike DT images, both FA maps and T1-weighted anatomical images are scalar images, and they are similar in image contrast. Therefore, their coregistration is far simpler and more accurate than is the coregistration of anatomical and DT images directly. Moreover, because the FA maps and their corresponding DT images are by definition already perfectly coregistered (because the FA maps are derived directly from the DT images), any geometric distortions found in the DT images will be present in the corresponding FA maps, and therefore any DF calculated from the coregistration of an FA map with the T1-weighted dataset can also be used to coregister the DT image reliably to its corresponding T1-weighted image.

Despite the similarities in contrast of FA maps and T1-weighted images, however, brain anatomy depicted in an FA map can still differ slightly in appearance from the corresponding T1-weighted image, especially at the boundaries between white and gray matter, where partial volume effects often alter contrast in the FA map. Thus, directly applying the deformation algorithm to FA maps and T1-weighted images may introduce a number of small-scale differences in the spatial registration of the two datasets. We therefore apply our nonlinear warping procedure (24) for calculation of the DF to registration of only the surfaces of the brain (i.e., to the boundary between gray matter and cortical cerebrospinal fluid [CSF]) that are identified separately in T1-weighted images and their corresponding FA maps, rather than to the entire volume of brain tissue. We then interpolate the calculated DF throughout the whole imaging volume (15,25). This interpolation of the DF is accomplished using the eigenfunctions of the linear operator in a partial differential equation (PDE) that models the fluid dynamics under an external force (15). We denote the DF from this first step of the coregistration process as DF_1 .

We then randomly select one T1-weighted image from the group of healthy subjects as a reference image and calculate for each subject a nonlinear DF, DF_2 , to normalize all T1-weighted images to this reference. However, we do not apply DF_2 directly to DT images to normalize them to the reference brain. Rather, to reduce the accumulation of errors across these two sequential steps for spatial normalization, we combine DF_1 (used to warp DT images to T1-weighted images) with DF_2 (used to warp T1-weighted images to the reference brain). This combined DF is subsequently applied to all DT images in their native spaces to bring them directly into the template, or reference, space. Diffusion tensors are then properly reoriented using an algorithm for DTI warping (14), so that their new orientations account for both the original orientation of the tensors and for the local deformation of brain tissue induced by the

warping procedure. This algorithm conserves the relative spatial orientations between tensors in the imaging volume, as described below.

Reorientation of Diffusion Tensors—Warping a DT image in a tensor space (containing at each voxel one 3×3 symmetric matrix that is positive definite) is not simply an extension of warping a scalar image (i.e., one scalar value at each voxel). Rather, it involves a strategy of extracting a rotation component from the spatial transformation in relation to the original orientation of the underlying fibers. This rotation component is then used to reorient tensors relative to the local underlying orientation of fibers, which itself is estimated from the tensors in a small neighborhood around the individual tensor being warped. For this tensor reorientation, we use a strategy based on Procrustean estimation that takes into account the effects of image noise on warping DT images by statistically estimating the rotation of tensors at each voxel (14). After spatial normalization, including tensor reorientation, fibers can be reconstructed validly from the deformed DT data, in that the 3D topology of the fibers in the original imaging space will be preserved in the template space, because the DF that warps the original imaging space to the template is itself topology-preserved (Fig. 2).

Identifying ROIs

Volume-Preserved Warping—Application of our VPW algorithm (Fig. 3) automates the selection of ROIs in anatomical images by detecting localized differences in anatomy between groups of subjects. VPW preserves during deformation the intensity-weighted volume V of each voxel, where $V = \text{intensity} \times \text{volume of the voxel}$ (see below the pseudocode for a detailed description of this procedure). The goal is to transform the original intensity-weighted volumes of brain masks (in which nonbrain tissue has been removed) into a normalized space and then compare the intensities of corresponding brain regions within this normalized space. Spatial normalization using VPW condenses relatively larger volumes so that they appear as voxels of relatively higher intensity values; smaller volumes are expanded, appearing as voxels of relatively lower intensities. To achieve these effects, we first mask the whole brain of each subject with a constant intensity value (say, 1.0) and then apply DF_2 to this mask. The resulting intensity values in the normalized brain masks identify clearly condensed and enlarged regions relative to the template brain (Fig. 3).

The concept of VPW originated with the Regional Analysis of Volumes Examined in Normalized Space (RAVENS) map (27-29) used for voxel-based morphometry, a procedure that distributes the intensity-weighted volume of each deformed voxel to its immediately neighboring voxels. However, by doing so, the RAVENS map generates unwanted seams, or gaps, in the data, in locations where the magnitude of the deformation has been extreme. Our VPW algorithm overcomes this problem by distributing the fixed intensity-weighted volume of the newly warped voxel to all of the voxels in the target space that this warped voxel overlaps, thereby producing a seamlessly warped image.

This strategy for spatially distributing the intensity-weighted imaging volume to the template space is based on a calculation of the percentage by which the deformed voxel from the original space overlaps voxels in the template imaging space (Fig. 4). Each voxel in an image can be represented by a regular hexahedron in the original space and a deformed hexahedron in the warped space. The intensity-weighted volume of the deformed voxel in the target space, however, should remain unchanged after deformation. We therefore must first calculate the exact deformation of each hexahedron. Once this calculation is complete, we can subsequently determine the percentage by which each deformed hexahedron overlaps each regular cell of the grid (i.e., each target voxel) in the template space. We can then use this percentage to distribute correctly the intensity-weighted volume from the deformed voxel to the appropriate neighboring voxels in the template space.

The shape of an irregular hexahedron, however, is relatively complex, thus increasing the difficulty of calculating the percentage overlap with other hexahedrons. A tetrahedron is the simplest 3D object, and no matter how it is deformed, a tetrahedron will remain a tetrahedron provided that it remains a 3D object (as is the case in VPW, in which the original topology of the brain is maintained). We therefore decompose each hexahedron into five tetrahedrons (Fig. 5). We can then calculate the distribution of intensities based on the percentage overlap of all five tetrahedrons with target voxels in the template imaging space.

To compute in the template space the intersection of a tetrahedron with a regular hexahedron that represents a voxel in that space, we use the six sides of the regular hexahedron to subdivide the tetrahedron that has been warped to the template. After each successful division, the remaining part of a tetrahedron will contain either one or three new tetrahedrons (Fig. 6). By applying the same procedure recursively to these newly generated tetrahedrons, we can divide the original tetrahedron into a set of component tetrahedrons. Recursive subdivision of each component tetrahedron will terminate when each one of the component tetrahedrons falls entirely within one regular hexahedron in the template space. Consequently, we can determine the percentage by which each of the first set of five tetrahedrons overlaps any regular hexahedron in the template space. We can then use this percentage to determine the volume distribution of the deformed voxel from the original space. The following is the pseudocode of our procedure for deforming a voxel and distributing the volume seamlessly:

Loop1

For each voxel (a regular hexahedron) with nonzero intensity (*VoxIntensity*) in the original space:

Transform the coordinates of its eight corners by the DF

Decompose the deformed hexahedron in the warped space into 5 tetrahedrons (A_1, A_2, A_3, A_4, A_5)

Calculate the volume $V_1, \dots, V_5$ of each of the 5 tetrahedrons $A_1, \dots, A_5$, respectively

Sum the 5 volumes to be the volume of the warped hexahedron *VoxVolume*:

$$VoxVolume = V_1 + V_2 + V_3 + V_4 + V_5 \quad (1)$$

Compute the density of the warped hexahedron in the warped space:

$$VoxDensity = VoxIntensity / VoxVolume \quad (2)$$

Loop 2

For each tetrahedron (A_1, A_2, A_3, A_4, A_5) in the warped space:

Find in the neighborhood of each tetrahedron those potentially overlapping voxels (each of these voxels is a regular hexahedron): H_i ($i = 1, \dots, n$)

Loop3

For each of these regular hexahedrons H_i ($i = 1, \dots, n$):

Slice the tetrahedrons $A_1, \dots, A_5$ with each of the 6 sides of H_i

Compute the total volume V_{in} of the tetrahedrons that fall inside of H_i

Computer intensity I :

$$I = VoxDensity \times V_{in} \quad (3)$$

Distribute intensity I to H_i

EndLoop3

EndLoop2

EndLoop1

Automated Identification of ROIs—Once a DF is applied to a binary mask of the brain to normalize it to the template brain using the VPW algorithm, the resulting mask will display locally expanded regions in lower intensities and locally condensed regions in higher intensities relative to the intensity value in the image of the binary mask. With images from all subjects coregistered into the same template space, a voxel-wise statistical comparison of intensity values of the two groups of subjects will highlight differences in local anatomical structure across study groups. We first smooth the VPW-treated brain mask using a Gaussian filter to reduce noise, and then we use a Z-score to identify regions in one group of subjects where mask intensities differ statistically from the mask intensities in corresponding voxels within normalized images of a second group of subjects. Any location with a Z-score higher than a predetermined threshold will be preserved as a seed point for fiber tracking within the coregistered DTI data. The Z-score is calculated as:

$$z = \frac{\bar{V}_1 - \bar{V}_2}{\sqrt{\frac{\sigma_1^2}{N_1-1} + \frac{\sigma_2^2}{N_2-1}}}, \quad (4)$$

where, $\bar{V}_1$ and $\bar{V}_2$ are the average values of intensities of the corresponding voxels of the normalized brain masks in the first and second groups; and, σ_1 and σ_2 are the corresponding standard errors of those intensities. N_1 and N_2 are the numbers of subjects included in the two groups, respectively.

Fiber Tracking

Once we have used VPW to identify regions that differ anatomically across groups, we use these as ROI seed points for the tracking of fibers in the normalized DT images of both groups of subjects. We use a fiber tracking algorithm based on the streamline of the principal eigenvector of each tensor (3,13). This tracking procedure monitors the curvature of reconstructed fiber tracts from voxel to voxel. When the curvature becomes excessive, the tracking algorithm terminates. This tracking procedure also calculates the dot product of unit vectors representing the principal directions of the tensors in a given neighborhood. The dot product determines whether the fiber traversing a voxel continues to the next voxel or whether it terminates, thereby ensuring that the fibers will be reconstructed only within regions of well-oriented tissues. Instead of beginning from a single seed point, the tracking algorithm is initiated from every voxel in the imaging volume so that the bifurcation of fiber tracts can be reconstructed naturally (3,13). In fact, a Y-shaped fiber tract is represented by two single fiber tracts that merge at the point of bifurcation. All the reconstructed fiber tracts that pass through the identified ROIs are preserved and then further clustered into bundles.

Clustering and Comparison of Fiber Tracts

The procedure for identifying ROIs highlights group differences in local anatomical structure. Consequently, fibers that are tracked through these ROIs are excellent candidates for demonstrating group differences in the spatial organization and regional connectivity of fiber tracts. Individual fibers, however, will usually be too numerous and complex to analyze across all subjects of the study. Moreover, because fibers vary greatly in length, orientation, and shape, clustering individual fibers into specific “bundles” (i.e., distinct fiber pathways) and comparing bundles between groups of subjects remains a difficult task, one that no currently existing algorithm performs adequately. We therefore developed an algorithm specifically for comparing fiber bundles that appear in both groups of subjects within a given voxel. Our task was simplified somewhat by the fact that the tracking of fibers in groups of subjects was performed in brain that were already normalized to a common template space, with the corresponding ROIs identified across brains, thereby providing a common anatomical basis for comparing fiber trajectories.

We classify two fiber tracts as belonging to the same bundle if:

1. The fibers occupy at least one common voxel within a single ROI in the template space
2. The similarity of the fiber tracts exceeds a predefined threshold, where “similarity” is a metric that is calculated as follows:
 - a. Reparameterize the two fiber tracts to be smooth curves and identify points of coincidence, if any, of the fiber tracts within the given ROI.
 - b. Resample the length of the fibers, using as the point of origin for tracking one of the voxels in which a point of coincidence of fiber tracts was detected within the ROI.
 - c. Align the two fibers at the voxel designated as the point of origin within the ROIs. Calculate the spatial distance between all pairs of corresponding, resampled locations along the entire length of the fibers, and then calculate the average of these distances.
 - d. Use knowledge of the errors inherent in a given algorithm for coregistration to calculate a Z-score of the average measured distance across the two fibers and associate to it a p -value.
 - e. Multiply this p -value by the percentage overlap of the two fiber tracts to yield the measure of similarity of the two fibers.

When calculating the p -value of the average measured distances across fibers, we assume a normal distribution of distances. Although the probability distribution may not in actuality be normal, calculating the p -value using a normal distribution still produces the information we desire—i.e., a value on a scale ranging from 0.0 to 1.0, with a higher value indicating a greater similarity across fiber tracts.

The percentage overlap is used to adjust the resulting similarity value so that the length beyond the overlapping portions of the two fibers will factor into the similarity measurement. In principle, similar fiber tracts across two spatially normalized brains should be of comparable length. However, the presence of noise in a DTI dataset and the corresponding tensor map may cause premature termination of fiber tracking in some cases—for example, in regions near the cortex, where FA values are low, the principal directions of the tensors are relatively uncertain, and noise levels are often comparatively high. In other cases, fibers may originate in the same region but branch off from one another, or they may originate in different structures but overlap for a portion of their length. To account for all these possibilities, we use the percentages by which two fibers may overlap with each other to prorate their similarity measure. If major

portions of two fibers overlap (i.e., if their percentage of overlap is high and therefore their final similarity measure is larger than a predetermined threshold), then we regard the two fibers as similar; otherwise, fibers of which only small portions overlap are classified as dissimilar (Fig. 7).

EXPERIMENT

Because T1-weighted anatomical images provide excellent contrast between gray matter, white matter, and CSF within the human brain, they have been widely used to study volumetric differences between groups of subjects (30-35). Our recent anatomical study of TS, for example, reported increased volumes of dorsal prefrontal and parietal cortices and reduced volumes of inferior occipital regions in subjects with TS compared with normal controls (8, 9). In addition, published reports indicate that children with TS have a smaller CC than do normal controls (36). These differences are thought primarily to represent the presence of adaptive responses that help to suppress tics, the defining symptom of this disorder. We hypothesized that coregistering anatomical and DTI datasets of subjects with TS, and using locations of anatomical group differences as seed points for fiber tracking, would help both to define the differences between fiber pathways in individuals with TS and those in normal controls. This would in turn help to clarify the pathophysiological significance of abnormalities in regional volume in individuals with TS.

We scanned 22 individuals with TS and 25 control subjects, 10 to 17 years of age. Patients and controls were age- and gender-matched, and written consent was obtained from parents or guardians. Exclusion criteria included an intelligence quotient (IQ) below 80 and a gestational age at birth <36 weeks. Images were acquired on a Siemens 1.5T scanner. Anatomical Magnetization-Prepared Rapid Acquisition of Gradient ECHO (MPRAGE) data were acquired at 176 sagittal slice locations of 1 mm thickness without gap, repetition time (TR) = 1910 msec, echo time (TE) = 3.93 msec, using a data matrix size = 256×192 , and field of view (FOV) = 256 mm, resulting in a voxel size = $1.0 \text{ mm} \times 1.0 \text{ mm} \times 1.33 \text{ mm}$. DW data were acquired along six directions using b-value at 1000 second/mm^2 plus one baseline image without DW gradient; TR = 4000 msec, TE = 96 msec, FOV = 240 mm, data matrix size = 128×128 , at 19 sagittal slice locations of thickness 4 mm with zero gap. The voxel dimensions of the DW data were $1.88 \times 1.88 \times 4.0 \text{ mm}^3$. The anatomical MPRAGE data covered the entire brain, whereas the DW dataset covered the parasagittal portions of the brain along the interhemispheric sulcus in the anterior-posterior direction, extending to the claustrum bilaterally, and including the entirety of the cerebellum to motor cortex in the inferior-superior direction.

Extracerebral tissues in the T1-weighted and DW baseline images were removed using an isointensity contour that thresholds cortical gray matter from overlying CSF. Connecting dura and fat were removed manually on each slice in sagittal, coronal, and axial views. The brainstem was transected at the pontomedullary junction. The isolated cerebrum in the DW baseline images was subsequently used as a mask to remove nonbrain tissues in all other DW images.

We examined the quality of the DW data and found that distortion induced by eddy currents was negligible, perhaps because those data were acquired on an MRI scanner with a low-strength magnetic field (1.5T) and at relatively low resolution ($128 \times 128 \times 19$). We therefore elected not to correct for eddy-current distortions. We then trilinearly resampled both the anatomical and DWI data to produce voxel dimensions of $1.0 \times 1.0 \times 1.0 \text{ mm}^3$. Anatomical data were cropped to the dimensions of $256 \times 256 \times 176$, which still covered the entire brain. DW data were zero-padded to $256 \times 256 \times 80$. The resampled DW data were then reconstructed into DT images. Subsequently, all the 47 DT images were coregistered to one randomly selected anatomical image from a healthy control that served as a template brain.

After coregistration, we applied the VPW algorithm to the binary mask of the scalp-stripped, T1-weighted imaging data in their native spaces. The normalized masks displayed local deformations: brighter intensities represented condensed areas, and dimmer intensities represented expanded areas as a consequence of spatial normalization to the template brain (Fig. 8). Individual voxels from the normalized masks were then entered into an analysis of statistical significance using Eq. [1], with control and TS groups as the first and second groups, respectively. We retained all voxels having a Z-score value higher than 1.0. To group these remaining voxels into ROIs in which to initiate fiber tracking, we applied a morphological “OPENING” (erosion + dilation) operation to the map filtered using the Z-score threshold. Our results verified the previous reported finding (36) that TS compared with control children have a smaller CC (Fig. 9).

Because of the documented involvement of the CC in the pathophysiology of TS, we selected as ROIs the regions of significant local volumetric differences within the CC. To identify these ROIs, we used an “AND” logical operator applied to the regions of volumetric differences in combination with a mask of the CC in the template brain that had been outlined in advance (Fig. 9). Because the CC does not have a structural boundary along the axis perpendicular to the sagittal plane, we adopted ROIs from only the four sagittal slices surrounding the midline for subsequent fiber tracking.

We used these ROIs in the CC as seed points to track fibers and identified 362 fiber tracts in the averaged data of the TS group and 292 in the averaged data of the control groups (13) (Fig. 10). We applied a threshold of 0.2 to our similarity metric (this threshold value was found to be optimal during the development of our algorithm) to identify 12 major fiber bundles that appeared in both groups (including 107 of the 362 total fiber tracts in the TS group; and 105 of the 292 total fiber tracts in normal controls); the remaining majority of fiber tracts appeared in only one of the two groups (Fig. 11). The prefrontal cortex in the left hemisphere of both the TS and control groups contained a thick bundle of fibers (Fig. 10). However, after clustering and comparing the fiber tracts, we found that the fiber bundles in the two groups shared only a few fibers within this prefrontal region, indicating a little morphological similarity between these fiber bundles (Fig. 11). Indeed, these bundles differed in location, length, and curvature, as measured using our clustering and comparison algorithm. The localization of a distinct fiber bundle in the prefrontal region (dashed circle in Fig. 11) that was more prominent in the TS group in terms of both its thickness and tract density (i.e., the number of tracts divided by the diameter of the bundle) is consistent with prior reports of smaller CCs but larger prefrontal volumes in children with TS (8).

DISCUSSION

Our cross-modality framework for the unified analysis of anatomical and DT MRI datasets automatically identifies localized regions of anatomical group differences on T1-weighted images and then uses those regions as seed points for fiber tracking with DTI in order to make hypothesis-driven comparisons of fiber tracts across diagnostic groups. These ROIs are excellent candidates for seed points precisely because they lie in regions of anatomical group differences. Using these ROIs allows us to expand substantially our insight into between-group differences in anatomical connectivity using corresponding, known group differences in regional volume.

Because our framework is entirely automated, it minimizes human error in identifying ROIs for fiber tracking and hypothesis testing. Indeed, given the irregular shape and unusual location of the ROIs that we identified using VPW (for instance, the ROIs within the CC in our experiment; Fig. 9), a human expert would be unable to reproduce the results generated by our framework, even if the expert knew in advance of the presence of group differences in size of

the CC. Moreover, manually outlining ROIs based on knowledge obtained from previous populations or specimens may not be ideal for a given study because of the differences in brain morphology and volume between study samples or within individual subjects over time. Our proposed framework, in contrast, unifies anatomical and DTI data that are acquired from the same study population, thus ensuring an improved accuracy in identifying morphologically valid ROIs.

In addition, the integration of anatomical T1-weighted and DTI data can help to reduce errors in fiber tracking using DTI. DT and T1-weighted images usually differ in their noise levels and in the intensity of white matter, gray matter, and CSF. In DTI datasets, for example, CSF in some ventricular regions can appear similar to surrounding tissue, whereas these same regions are highly distinct in their appearance from gray and white matter in T1-weighted anatomical images. Certain fiber tracking algorithms based solely on DTI may erroneously detect fiber tracts in regions of CSF, where obviously none in fact exist. The clear distinction between tissue types in the anatomical MR images, however, and the coregistration of the DT and anatomical MR images, should help to prevent such errors in fiber tracking.

To calculate the DF needed to coregister a DTI dataset to T1-weighted images, one might consider using in place of FA maps the unweighted (b_0) baseline images that are acquired along with DWIs, because the contrast of the b_0 images can appear somewhat similar to that of anatomical MR images. The intensities and contrast of white matter, gray matter, and CSF do differ considerably across DT and T1-weighted images, and the DTI datasets in particular may contain susceptibility artifacts, not present in T1-weighted images, that alter structural information in the brain and that interfere with accurate coregistration. The contrast of FA-maps, however, is quite similar to that of T1-weighted images, which we found to be a distinct advantage for their accurate registration with the T1-weighted datasets. The b_0 images, in contrast, are heavily T2-weighted. We therefore employed the registration of FA maps to T1-weighted images in the calculation of the DFs needed to coregister the DT and T1-weighted images, which was possible only because the FA and DTI maps are themselves inherently perfectly coregistered, given that they are both constructed ultimately out of the same DW images.

Jacobian matrices, like VPW, could be used to measure the local expansion and contraction induced during the warping and coregistration of images. Jacobian matrices, however, are associated only with the spatial transformation, or DF, that maps the coordinates of one space to those of a template space, and therefore Jacobian matrices reflect only the transformation of shape, without capturing the anatomical differences induced by pathology or by individual variance within the brain. Thus the determinant, J , of a Jacobian matrix for local deformation remains the same over any arbitrary brain tissue, regardless of the values contained within the voxels that compose that tissue. VPW, in contrast, combines a local measure of either contraction or expansion of volumes (which alone is similar to the determinant of the Jacobian matrices) together with a measure of the difference between the values contained within the voxels of a spatially normalized image and the template image (i.e., $VPW = \text{Jacobian} + \text{“residual” image}$) (37). Therefore, VPW is far more suitable than is the Jacobian for our purpose, which is to identify individual or group differences in regional volume, because it contains information beyond that provided by spatial transformation alone.

Moreover, the determinant J of a Jacobian matrix is a nonlinear measure of local deformation, and therefore the J -values for equivalent degrees of expansion and compression will not be directly comparable. In the topology-preserved deformation used when warping brain images, a value of $J = 1$ indicates no local expansion or compression, $J \in (1, +\infty)$ indicates local expansion, and $J \in (0, 1)$ indicates local compression. Values of $J = 1.5$ and $J = 0.5$, however, do not indicate an equivalent degree of local expansion or compression, respectively, and

therefore the degree of expansion in a brain region of one group cannot be compared directly with the degree of compression in the corresponding brain region of another group, at least not without considerably more computational effort and expense. In addition, J-values are difficult to translate directly into measures of change in volume within a brain structure. Thus J values cannot be easily incorporated into our calculation of a Z-score for the statistical estimation of changes in local volume across multiple subjects in different groups. VPW, in contrast, can easily be used to estimate changes in volume, because it provides a linear measure of those changes that is compatible with the formula for calculating Z-scores. VPW is therefore the simplest approach to identifying regions of statistically significant expansion or contraction in volume across individuals or groups, regions that can then be used as seed points to study anatomical connectivity with fiber tracking and DTI.

Comparing fiber tracts in 3D space is generally difficult because of the presence of complex spatial curvatures and changing directionalities of reconstructed fiber tracts. Our algorithm specifically permits this type of comparison, however, because the fibers that are tracked are restricted to those passing through the anatomical ROIs identified automatically within a normalized template space, where the underlying tissues, including axons that compose fiber tracts, are assumed to correspond across individuals. This algorithm, however, cannot be applied to unwieldy fiber structures, such as those that are locally tangled, that loop upon themselves, or that contain sharp turns in their local trajectories. The algorithm that we used for fiber-tracking guarantees the absence of such unwieldy local features.

Abnormal fiber architecture may undoubtedly appear in any region of the brain, not only in regions where volumetric abnormalities have been identified. Abnormal connectivity, however, is likely present in fibers connected to regions where volumetric abnormalities are identified. Certainly, this is a reasonable basis for formulating a priori hypotheses in neuroimaging data-sets. However, one of our goals was to develop a tool that would allow investigators specifically to build on findings from anatomical MRI studies and to formulate reasonable, data-driven, a priori hypotheses concerning disturbances in anatomical connectivity across diagnostic groups. Because the findings from anatomical and DT MRI are mutually informative, combining such findings facilitates a more detailed, more efficient, and more hypothesis-driven assessment of abnormalities in anatomical structure and connectivity in the brains of patients with neuropsychiatric illness than does either of these modalities alone. By focusing fiber tracking on ROIs in specific areas of volumetric abnormality, our framework excludes the many hundreds of thousands of fiber pathways in the brain that may be irrelevant to the investigative goals of specific studies and that would ultimately entail a vastly greater number of statistical comparisons across groups. Future research should focus on extending the advantages of multimodal MRI to functional and spectroscopic imaging data.

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Figure 1.

Overview of our framework for unifying image analyses of anatomical and DTI datasets. Diffusion tensor (DT) images are first coregistered to their corresponding T1-weighted images. T1-weighted images are then normalized to a single T1-weighted image that has been selected as a template. All DT and T1-weighted images are thus coregistered to the template. We subsequently apply the VPW algorithm to normalize to the template brain the binary-masked version of the T1-weighted image from each subject. We then statistically analyze the results from VPW to identify ROIs that represent brain regions containing localized volumetric differences across groups. These ROIs are used as seed points in the coregistered DTI data to track fibers leading to or from those abnormal brain regions. Those fibers can then be compared in a subsequent analysis of differing connectivity across groups.

Figure 2.

The valid spatial normalization of fiber tracts in DT images. We first randomly selected from our database a healthy T1-weighted image as a template brain, in which we simulated two fiber bundles passing through the CC. We then randomly selected another five T1-weighted images of healthy brains and transferred the curves representing the fiber bundles in the template brain to these five images by applying the DFs for warping the template brain to the five images generated by STAR (38). Following the anatomy of these five T1-weighted images and the warped curves, we subsequently simulated five DTI datasets with fiber tracts grouped into two bundles and with noise superimposed. We then normalized all five DTI datasets back to the template space, using our Procrustean DTI warping algorithm (14) and the DFs for each individual to the template space generated by HAMMER (39). The five normalized DTI datasets were then averaged in the template space. (Note that we intentionally used STAR for data preparation and HAMMER for final normalization, so that registration errors would not be concealed by use of the same algorithm.) **a:** Two fiber bundles simulated in the template brain. **b:** A coronal slice of one of the five simulated DTI datasets, displayed in a color map of its primary direction (red for left–right orientation, green for perpendicular to the view and blue for bottom–top, as these were axial datasets). The bluish traces at the tip of the yellow arrows (buried in noise) indicate the locations of one of the two simulated fiber bundles. **c:** The ground truth of the simulated fiber tracts displayed in the T1-weighted image of template brain, with landmarks on all the bifurcations and end points. **d:** The reconstructed fiber tracts in the averaged DTI datasets within the template brain, with the landmarks from (c) superimposed. Matches between the reconstructed fibers and the ground truth are obvious.

Figure 3.

A schematic example of VPW. The value in each cell of the grid indicates the voxel's intensity. When an image is normalized to a template space using VPW, relatively larger areas will be condensed, and relatively smaller areas will be expanded. In the template space, a higher average intensity within a voxel indicates a condensed area; a lower average intensity indicates expansion.

Figure 4.

VPW algorithm illustrated in 2D space. A regular voxel with volume V from the native space of a single subject is deformed using the DF to an irregular quadrilateral in the template space. This irregular quadrilateral intersects voxels A, B, C, D, E, and F in that template space, with a percentage of a , b , c , d , e , and f ($a + b + c + d + e + f = 1.0$) of the whole volume V , respectively. Instead of distributing the volume V to the voxels immediately adjacent to the center of the quadrilateral, voxels A~F each will receive a portion of the volume V , according to the percentage of their intersection with (a~f) with the deformed quadrilateral, respectively.

Figure 5.
A cube (hexahedron) decomposed into five tetrahedrons.

Figure 6.

Three cases of a tetrahedron sliced by a single plane. **a:** The most common case: a tetrahedron $V_0V_1V_2V_3$ is sliced by one side of a voxel. If the top portion of the voxel is cut, then the remaining portion will consist of three new tetrahedrons ($V_1V_2V_3V_5$, $V_1V_3V_4V_5$, and $V_3V_5V_6V_4$). If, on the other hand, the bottom portion is cut, then only one new tetrahedron ($V_4V_5V_6V_0$) will remain. **b:** A special case is when a tetrahedron is cut into two tetrahedrons ($V_0V_1V_4V_3$ and $V_3V_4V_2V_0$). No matter which is cut, only one tetrahedron remains. **c:** Other special cases include when the cutting plane coincides with one side of the tetrahedron or passes one edge of the tetrahedron. In these instances, the tetrahedron remains undivided.

Figure 7.

Simulated tracts for comparing fibers and measuring their similarity. For clarity of visualization, the overlapping portions of the two fibers were detached from one another, and the fibers were colored according to their direction: red for horizontal and green for vertical. The white oval denotes the aligning voxel (the point of origin) within the ROI. **a:** Two fiber tracts having a similarity measure of 1.0. **b:** Two fiber tracts branch into differing directions near their ends; these tracts share 76.4% of their length, with a similarity of 0.988 within this overlapping segment, resulting in an overall similarity of 0.756 ($0.988 \times 76.4\%$) across the entire lengths of the fibers. **c:** Two fiber tracts overlap partially but run in differing directions. These tracts have a similarity measure of 0.572.

Figure 8.
VPW. **a:** Anatomical images of one subject's brain. **b:** Binary mask of this brain. **c:** The deformed version of the same brain generated with the VPW algorithm. Condensed regions become brighter and expanded regions become darker. **d:** The template brain.

Figure 9.

ROIs identified by the VPW algorithm. Regions where statistically significant differences in localized volume were identified are displayed on midsagittal slices in the template brain space following the application of the VPW algorithm. The ROIs in the CC are the regions in which the CC in the TS group is smaller than those of controls. Upper row: the outline of the brain is displayed in white. Red indicates areas in which volumes are higher in the control group compared with the TS group. Bottom row: the extracted ROIs, displayed in red within the CC, were used for fiber tracking in the DTI dataset.

Figure 10.

Fiber tracts associated with the ROIs that were identified using the VPW algorithm. Fiber tracts are viewed from above the right forehead and are superimposed on a single axial slice of the template brain. Fibers are painted according to direction: red for anterior–posterior; green for superior–inferior; blue for left–right. The purple arrows indicate the locations where the fibers in both groups pass through the axial plane of the image. Although these fibers appear here to project similarly downward, Fig. 11 shows that they actually do not resemble one another spatially; rather, they share only a few fiber tracts in common. (TS) = the TS group, (NC) = normal controls, A = Anterior; P = Posterior; L = Left; R = Right.

Figure 11.

Fiber bundles compared and clustered across TS and control groups. We identified 12 fiber bundles that appeared in both groups (viewed from above the right forehead). Corresponding fiber bundles are color-coded identically across groups. **a:** TS group. **b:** Normal controls. Yellow arrows: the thin fiber tracts indicate that the corresponding fiber bundles of the two diagnostic groups in Fig. 10 (purple arrows) share only a small number of fiber tracts. The fiber bundle within the dashed circle, which connects with frontal cortices, is more prominent in the TS group than in the controls; this finding is consistent with prior reports of larger prefrontal volumes in children with TS. **c:** TS group. **d:** Normal controls. Panels (c) and (d) are counterparts to (a) and (b), respectively; fibers that differ across groups are displayed in blue and are superimposed on fibers that were judged as similar across groups. Fibers that are shown in all other colors, as in (a) and (b), except for blue in both images, were identified as similar across groups. A = Anterior; P = Posterior; L = Left; R = Right.