DTI Analysis Methods: Voxel-Based Analysis

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Learning Points

- VBA is a technique that evaluates local voxel-wise differences across the whole brain based on a multistep pipeline, which includes spatial normalization (or image registration) to a template or atlas, smoothing, and statistical analysis.
- VBA is most useful for investigating group differences in DTI measures in an exploratory manner, without the need for specific a priori hypotheses about the location of potential alterations in DTI measures.
- VBA assumes that the spatial location of voxels is equivalent between subjects and is therefore fundamentally dependent on image registration to correct the inherent mismatch between individual images due to anatomical variation and pathology.
- Tract-based spatial statistics (TBSS) is a popular type of VBA that evaluates changes in a skeleton comprising a limited amount of white matter, in order to increase sensitivity by reducing registration error and partial volume effects.

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An Introduction to Voxel-Based Analysis

Voxel-based analysis (VBA) of diffusion tensor imaging (DTI) data is an exploratory technique to evaluate differences/changes of diffusion metrics in every voxel of a brain data set. In essence, VBA investigates DTI measures at the smallest scale possible, i.e., the voxel level, and as these measures are compared in every voxel, VBA also simultaneously evaluates the data at the largest scale, i.e., the whole brain. As a result, unlike with region-of-interest (ROI) analysis, VBA does not require an "a priori" hypothesis about precisely where in the brain differences may be found. This makes it an interesting analysis approach when there is a clear hypothesis that there are potential differences in DTI parameters somewhere in the brain, but the location of such differences is not known in advance. Although VBA indeed has many advantages compared to standard ROI or

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tractography-based approaches, it also has many limitations, which one should be aware of before embarking on any VBA study.

The aim of this chapter is to provide the reader with an overview of the different processing steps that need to be performed for a voxel-based analysis of DTI data, whilst emphasizing potential sources of error or specific challenges associated with each step. Along the way we will address common questions posed by those wishing to start their first DTI VBA, for example: When is VBA a good option for the analysis of your data? What assumptions underlie the method? What are the potential pitfalls in each processing step? Why is image registration and template selection so important? What is smoothing? What is multiple hypothesis testing?, and do I *really* need to worry about it? (yes you *really* do!) What is the difference between VBA and tract-based spatial statistics (TBSS)? And how do I interpret the resulting findings?

It is important to remember that the most optimal results will only by obtained by considering the many possible options that are inherent in conducting a VBA study of DTI data, *before you start the analysis*.

Summary Points

- VBA is a technique that evaluates local voxelwise differences across the whole brain.
- It is most useful for investigating group differences in DTI measures.
- It can be used in an exploratory manner, without the need for specific a priori hypotheses about the location of differences in DTI measures.

From Individual Data Sets to VBA Group Results: The Different Steps

As VBA compares diffusion metrics, such as fractional anisotropy (FA) or mean diffusivity (MD), between subjects at the voxel level, one of the main assumptions of VBA is that the DTI information located at a specific voxel is compared equivalently in each individual. In other words, the anatomical location of a particular voxel should be the same for each subject. In general, the gross anatomy of the brain is very similar across the (healthy) population, and all brain regions are present in more or less the same spatial position across individuals. Nevertheless, as a result of natural anatomical variation, there remain clear differences in the size and shape of different brain regions (e.g., due to age, gender, or pathology). Therefore, if we attempt to compare the same voxel in one person to the equivalent location in another person without accounting for this normal variation, we will fail. And if we fail, we also violate one of the main assumptions of the VBA method. Luckily, we can try and overcome this problem.

The image processing technique that aims to correct for differences in brain structure by changing the size and shape of the brain image as well as its local structure is called **image registration**. The end result of the image registration step is thus a brain image that has been *warped* to match another image, and in which voxels with the same spatial coordinates represent the same voxel of the same brain structure of both images. If images cannot be aligned to each other well, it makes no sense comparing quantitative DTI values on a voxel level.

Now one may pose the question: to which image will we align all our data sets? This image to which all data sets are registered is called the atlas or template, and many strategies and options exist for this **template selection**.

Once all data sets are located in the same atlas space, **smoothing** is typically applied, in order to increase the power of the statistical tests that are subsequently performed in each voxel. There are other reasons why you may wish to smooth the data and different choices have to be made regarding the type and extent of smoothing used. This will be discussed later in this section.

Statistical analysis is then performed on these warped, smoothed images. The results of these statistical tests, with or without correction for multiple comparisons, are then displayed with a color on the different slices of the atlas image, thus providing a global view of where in the brain the DTI measures are statistically different between groups of subjects.

In the following sections we will dive a bit deeper into these different steps of the VBA pipeline and highlight some options and limitations.

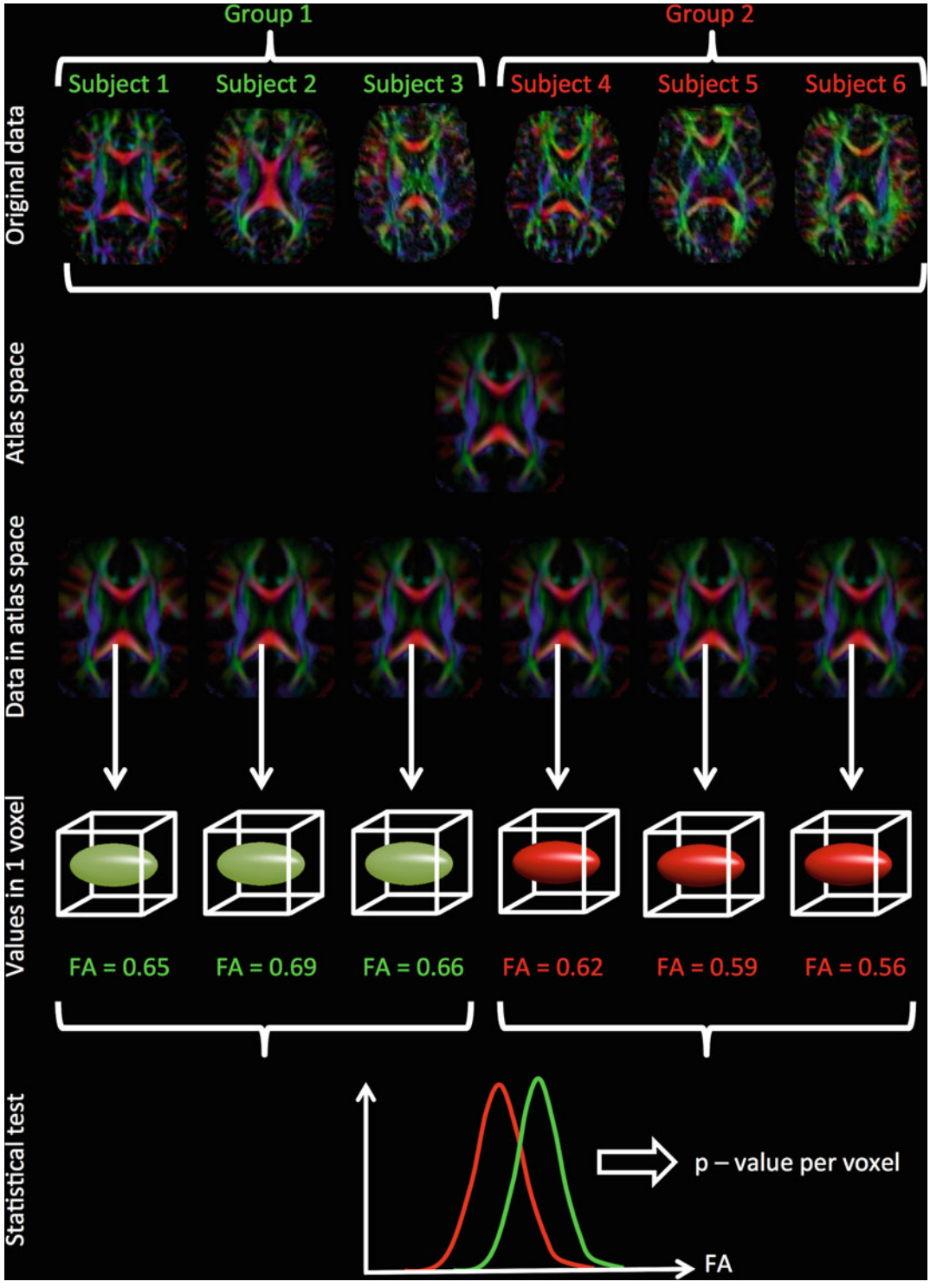

Fig. 10.1 Overview of different steps in the VBA pipeline of DTI data

A theoretical example of the VBA pipeline is displayed in Fig. 10.1. The DTI data of six subjects, three in each group, are registered to a DTI atlas. Once all data sets are located in the same space, FA values can be compared between both groups in each voxel. Note that in this example, all data sets are perfectly aligned to the atlas, which is an important assumption, but also an ideal situation that is not realistic.

Summary Points

- VBA assumes that the spatial location of voxels is equivalent between subjects,
- Natural variation in anatomy and pathology causes an inherent mismatch between individual images that can be corrected by registration to a template,
- The VBA pipeline contains three main steps: spatial normalization (or image registration), smoothing, and statistical analysis.

Image Registration

Introduction

One of the main assumptions of VBA is that the same voxels in different images are aligned to each other. Only in this case, can DTI measures, such as FA or MD, be compared between the same voxels of different subjects. Note that the process of spatially matching different images is frequently described using different terms, such as normalization, warping, aligning, registration, coregistration, etc. But in the end, although these terms may differ slightly in their technical definition, essentially they refer to the same concept.

A simplified example of the registration concept is shown in Fig. 10.2. The data set we want to register is shown on the top left of Fig. 10.2 and is also referred to as the *float image*, as this image will change during the registration process. On the top right of Fig. 10.2, the *reference image*, usually the atlas, is displayed. This is our target

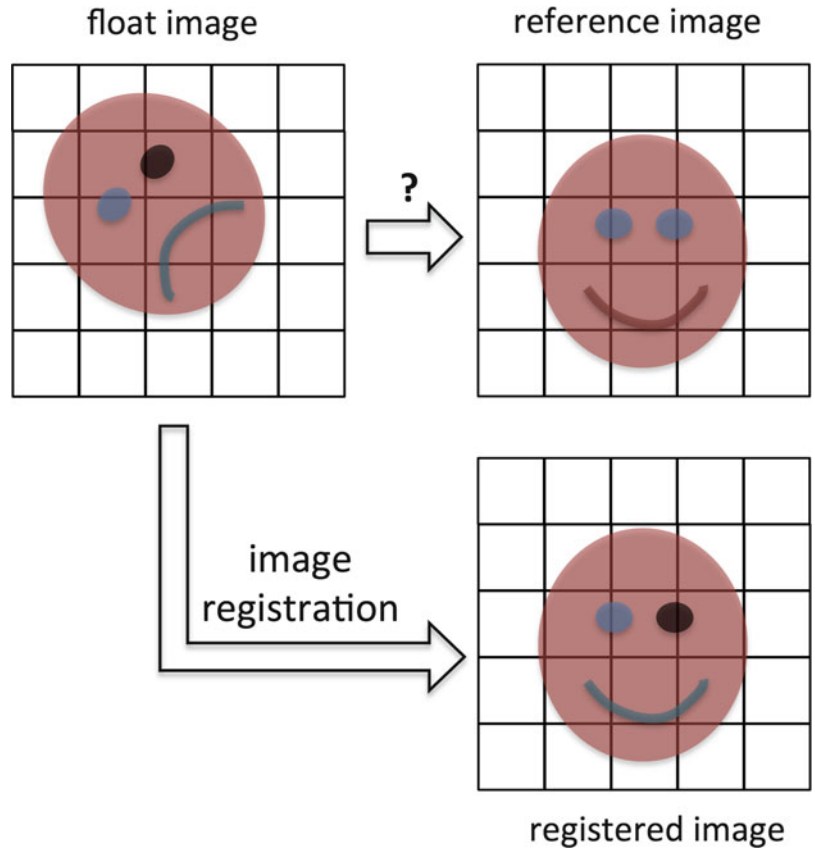

Fig. 10.2 The goal of image registration is to match a float image to the same coordinate space as the reference image. This can be done by applying global warping together with local alignment of structures

image for registration, i.e., we want to warp the float image so that it looks like the reference image. The result of the registration process is shown on the right bottom of Fig. 10.2. This registered image is the original float image, but warped into the space of the reference image. You can note two important characteristics of registration. First, you can see that the float image is translated (i.e., shifted in position along the cardinal axes, up/down, forward/back, and left/right) and rotated, but also that local structures of the float image, such as the mouth in this case, are deformed to match the reference image. Second, you can note from this example that the float image is spatially transformed, but that the colors—in DTI these are the values of the metrics, such as FA or MD—are not changed after registration. Thus, the goal of image registration is to spatially warp images in a way that corresponding voxels are in the same location, without changing the original image values of these voxels [1].

As the global as well as local morphology of the brain can significantly vary between different subjects, image registration is a challenging task. In addition to natural inter-subject brain variability, brain morphology can depend for example, on age, gender, and ethnicity. To make image registration even more challenging in the VBA setting, brain morphology can be significantly altered by the pathologies in patients that are studied.

Image Registration Techniques

The goal of this section is to provide some basic background knowledge of image registration. Image registration can be considered as an optimization problem, for which the similarity between two or more images needs to be maximized iteratively [2]. The image registration problem can thus be subdivided into:

- a method or algorithm used to find a maximal similarity
- an approach to measure similarity between images

Image registration algorithms can be subdivided into two broad categories: **global** and **local** registration techniques.

- **Global image registration techniques** apply the same deformation field (the matrix of numbers that defines how much a point is shifted), which transforms one data set to another, to all voxels of that data set. This can be done by rotating and translating the data set, referred to as a **rigid-body** transformation. In addition, global shearing ("stretching") and scaling parameters can be added, then resulting in an **affine** transformation.
- **Local registration techniques** determine a local deformation field for every voxel of the data set, in order to match every voxel with its corresponding voxel in the other data set.

A simplified example is given in Fig. 10.3, in which sagittal views of the brain, including the corpus callosum, are shown. In this example, the brain of subject X (shown in red) needs to be transformed to the template or atlas brain shown in blue. As a first step, the whole brain data set of subject X can be rotated and translated globally, in order to increase the similarity with the template brain. This registration technique, visualized in Fig. 10.3 by the purple box, is referred to as a **rigid-body transformation**. Subsequently, the resulting brain image can be scaled and skewed globally. The combination of the rigid-body transformation with additional global scaling and skewing is referred to as an **affine registration** (the purple and green boxes in Fig. 10.3). However, in order to obtain a better match of corresponding voxels in different data sets, local deformation fields need to be applied to the globally registered data set of subject X. This transformation is referred to as a **non-rigid or non-affine registration** and aims at aligning corresponding voxels of different data sets.

As aforementioned, an accurate image registration result is of paramount importance for a reliable VBA result. For example, if a non-affine registration would not be performed, the final registration result of subject X to the template would include a mismatch around the corpus

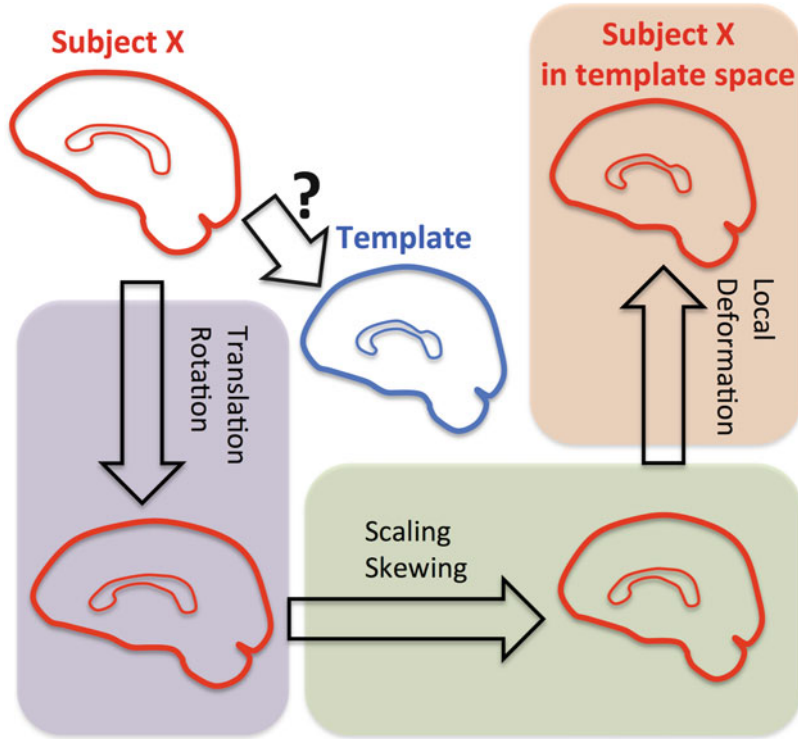

Fig. 10.3 Overview of the combination of global and local image registration techniques. To transform the brain of subject X to the template brain, both global and local image registration techniques are necessary. The *purple box* shows the rigid-body transformation, including global rotation and translation. In the *green box*, global scaling and skewing are added to the transformation, referred to as the affine transformation. The use of local deformations, as shown in the *orange box* and referred to as non-affine transformations, allows one to align both images on a local level

callosum in this example (see Fig. 10.4). Because similar registration errors would be present for the other subjects, it is clear that a voxel-wise comparison of DTI measures would lead to unreliable results. Indeed, the DTI measures in voxels of subject X are then compared with the same measures in non-corresponding voxels of subject Y, which might be more similar to the atlas or contain different registration errors.

In order to optimize the image registration algorithms, appropriate **image similarity measures** need to be defined. In the end, it will be this image similarity measure that will be optimized to obtain the most optimal image alignment. Examples of similarity measures are the sum of squared intensity differences (SSD), cross correlation, and mutual information (MI). In the SSD approach, the intensity in corresponding voxels of two images is subtracted and the absolute value of the result is squared. The SSD is then calculated as the sum of this squared difference over all voxels in the image. A schematic example is shown in Fig. 10.5. The sagittal views of the affine registration result, which was shown

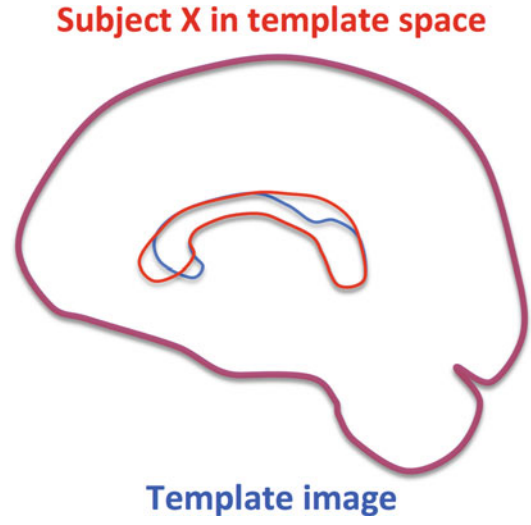

Fig. 10.4 Example of an affine registration result. Although both data sets are globally aligned, significant local image registration errors can be seen in the region of the corpus callosum

in Fig. 10.4, are visualized in grayscale intensities. On the top row, the image X that was registered to the template, the template image, and the overlay between both are displayed, showing

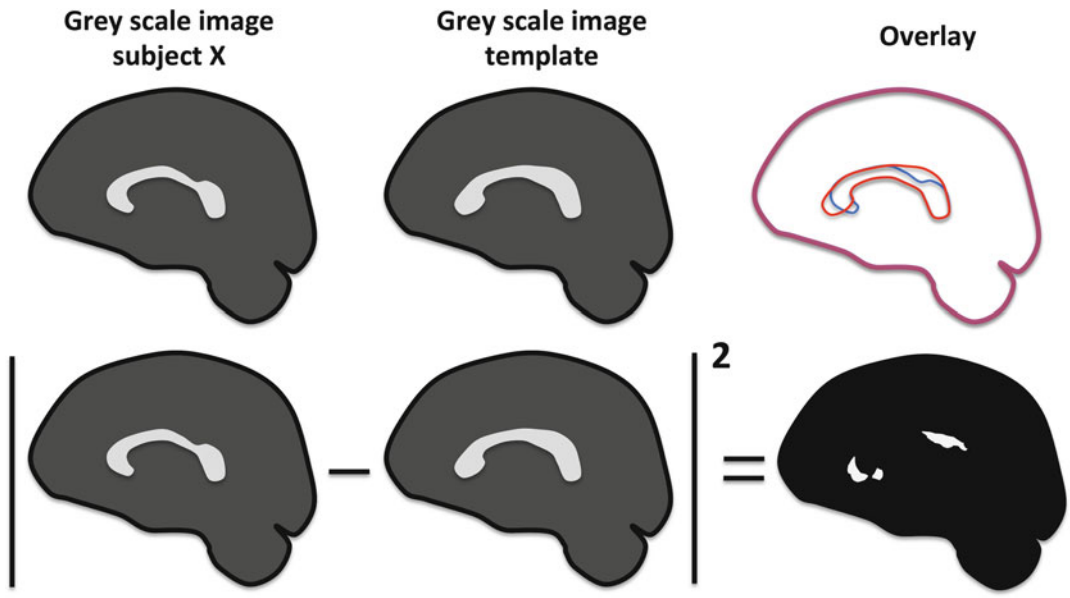

Fig. 10.5 An example of the sum of squared differences technique to measure image similarity. The intensities of the registered image and template are subtracted in every voxel and subsequently squared. Then, the total sum in every voxel is taken. When both images would be perfectly aligned, the sum of squared differences would be zero

some misregistration of the corpus callosum. In the second row, the calculation of the SSD is schematically depicted, highlighting the mismatch regions. If a perfect registration could be performed, the SSD measure would be zero, demonstrating optimal image similarity.

The SSD is a simple approach to evaluate similarity between images. More advanced methods that can take into account different intensity values of similar structures in different images, such as mutual information, generally produce better results. In addition, some specific image similarity methods have been developed for DTI data, using information on tensors, statistical relationships between measures, or anatomical information. In contrast to typical grayscale MRI images, DTI data contain more information in each voxel; therefore similarity measures can be optimized to make use of this additional information [3, 4].

Summary Points

- To register two images you need (a) a model (global and/or local) to warp the floating image to the reference image, and (b) a way to measure how well both images are aligned, in order to find an optimal registration.
- Rigid-body registration involves only translations and rotations, whilst affine registration also includes scaling and shearing.
- Examples of similarity measures include sum of squared intensity differences (SSD), cross correlation, and mutual information (MI).

Registration of DTI Data

The registration of DTI data is especially challenging. This is mainly caused by the fact that DTI data, unlike anatomical MRI or CT data, contain a tensor in each voxel, which also represents orientational information. Taking this tensor information into account can improve the registration result (an overview of DTI registration methods is provided in [5]). In the following paragraphs, we will describe several challenges in more detail.

DTI Registration Challenge 1: Reorientation

The tensor is directionally dependent and contains orientational information about the underlying

white matter microstructure. When transformations are applied to align data sets, a correction (i.e., a tensor reorientation strategy) needs to be applied to ensure that the directional DTI information is still accurate.

The need for tensor reorientation after image alignment of DTI data or during iterative registration processes is explained in Fig 10.6. To simplify things, the concept of reorientation is explained for only one white matter fiber bundle, containing three voxels. Consider that in the original DTI data set of subject X, this bundle runs vertically. The DWI image intensities of the three voxels in that bundle are high for the DWI that was acquired with a diffusion sensitized gradient perpendicular to the bundle, and low for the DWI acquired with a diffusion sensitized gradient parallel to the bundle. For simplicity, only two DWIs are considered here. The corresponding white matter bundle of the template image, however,

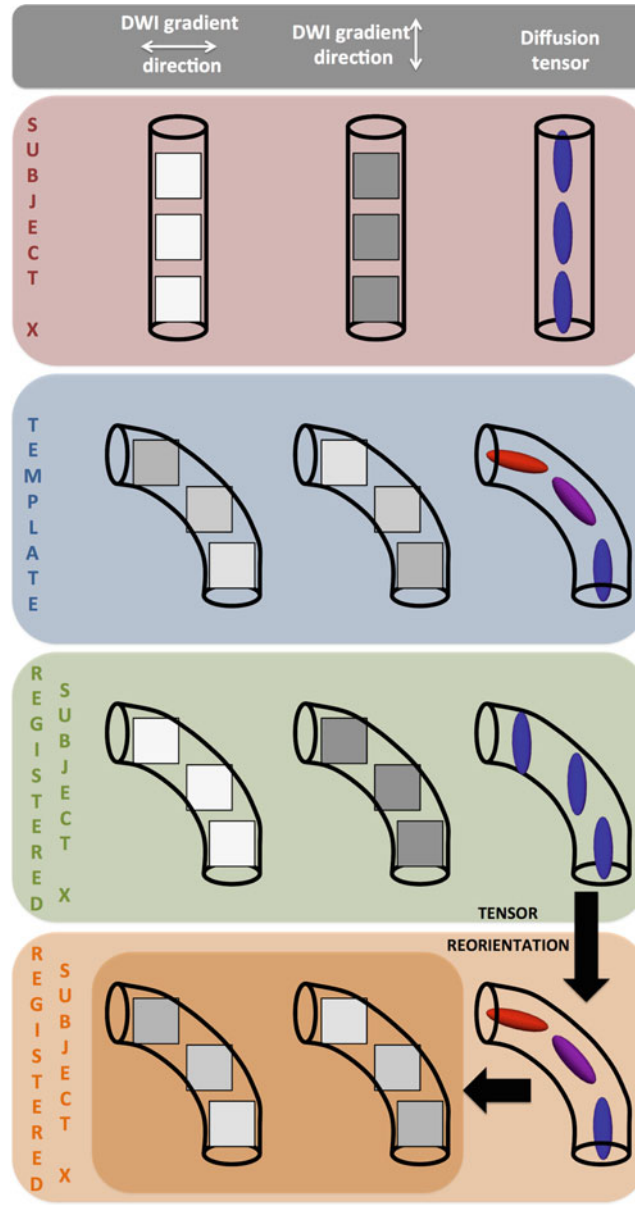

Fig. 10.6 Simplified overview of the tensor reorientation problem in DTI. Tensors indeed need to be reoriented after image registration in order to be aligned with the underlying microstructure

contains some curvature. As a result, the DWI intensities for the different gradients are different in these voxels.

It is now assumed that we can align both white matter bundles perfectly, i.e., the corresponding voxels of the white matter bundle are perfectly registered. The resulting deformation field is then applied to the DWIs and the tensor is recalculated. Now, if we refer to Fig. 10.6 again, we see that the registration process changes the spatial location of voxels in order for them to match, but not their values or image intensity. However, if only the spatial location of the voxels is changed, and not their image intensities, the directional diffusion information, and therefore the tensor, are not changed compared to the information in native space. Indeed, as explained in Chaps. 4 and 6, the image intensities of the different DWIs and the values of the tensor are related to the orientation of the white matter bundle.

As a result, the tensor information of the registered data set of subject X to template space thus no longer reflects the underlying microstructural white matter information, as can be observed in Fig 10.6. In order to correct for this, Alexander and Gee [4] proposed different methods, referred to as the "finite strain" and the "preservation of principle directions" approach. The finite strain method decomposes the transformation matrix in a deformation and a rotation component, whereafter only the latter is used to reorient the tensors. However, shearing, nonuniform scaling, and stretching factors affect the orientation as well. Together with the rotational component, they are taken into account in the preservation of principal direction strategy.

When a global, i.e., rigid-body or affine, registration method is applied, the same reorientation is applied to all voxels. However, in the case of non-rigid registrations, the local transformation matrix, which can be different for each voxel, is used to calculate local tensor reorientation.

It is important to note that tensor reorientation approaches do not affect the rotationally invariant quantitative DTI measures, such as the eigenvalues, the FA, or MD. As they are rotationally invariant, reorienting the tensor does not change their values. In a VBA analysis, it is therefore not necessary to reorient the tensors if only the rotationally invariant, quantitative DTI information is used in the subsequent analysis.

DTI Registration Challenge 2: The Tensor Information

DTI image registration can be optimized by using information from other modalities, such as anatomical MRI, or by incorporating scalar and tensor information. Park et al. [6] compared the use of different input images on the overall registration result of DTI data. They evaluated registration results after using T2-weighted images, FA images, the difference of the first and second tensor eigenvalues, FA and the tensor trace, all three tensor eigenvalues, and finally the six independent tensor components [6]. In this study, it was demonstrated that the use of the six independent tensor components as input channels performed most optimal in aligning the tract morphology and tensor orientation. This was further confirmed by other studies [7].

Scalar Anatomical MRI Information, Such as 3D T1-Weighted Images

Using scalar anatomical MRI information to determine the deformation field between DTI data sets is similar to the approach used in functional MRI analysis. First, the DTI data set is transformed to the 3D T1-weighted image of the same subject, using a rigid-body or affine transformation. The DTI information used for this registration is normally the b0 or non-diffusion weighted image, as this image mostly resembles the anatomical image. Thereafter, the 3D T1-weighted image is aligned to a T1-weighted atlas, such as the Montreal Neurological Institute (MNI) template. The resulting deformation field is then applied to the DWIs, which were transformed into the space of the T1, or to the transformed quantitative DTI maps directly.

The advantages of this approach are:

- T1-weighted atlases can be used.
- Many open-source software packages support this type of algorithms, such as SPM (www.fil.ion.ucl.ac.uk/spm), FSL (www.fmrib.ox.ac.uk/fsl), AFNI (afni.nimh.nih.gov/afni).

However, using this approach is not optimal for DTI data, for several reasons:

- The unique white matter DTI information is not used to guide the registration. The image intensity of white matter is uniform on T1-weighted images, which can result in mismatching of different fiber bundles [6, 8].
- As DTI data sets are usually acquired using an EPI sequence, different artifacts are present compared to the T1 image. For example, geometric distortions due to eddy currents and susceptibility. This results in misregistration between the b0 image and T1-weighted image.

Scalar DTI Information, Such as FA or MD Maps

In this approach, the scalar DTI information, such as contained in FA or MD maps, is used as input information to guide the registration. As a result, no anatomical data sets are involved, and registration is directly performed based the DTI information. Compared to using anatomical information, this method has several advantages:

- Some white matter information (as present in FA or MD maps) is used to increase the registration accuracy.
- The DTI information is directly aligned to an atlas and no anatomical MRI image is needed.

Although this will increase registration accuracy, this approach has some drawbacks:

- FA and MD values do not always discriminate fiber bundles that are located close to one another, potentially resulting in misregistration of these bundles.
- There needs to be an FA template to align the subject data to.

Diffusion Tensor Information

Many approaches have been proposed that incorporate the specific DTI information into the registration process in order to increase registration quality. For example:

- By including several channels of scalar image information. Guimond et al. [9] and Park et al. [6] have used different channels of input information, such as the T2-weighted image intensity, fractional anisotropy, trace of tensor, and eigenvalues.
- By using the scalar information from the whole tensor to align two DTI data sets and detect correspondences between them [6, 7, 10–13]. In addition to using the tensor elements, DTI feature vectors can be derived and used to drive the registration ([14–16]).
- By using DTI tractography or other connectivity information to guide image alignment [17–20].

It has been demonstrated that the use of DTI-specific information with multiple channels results in more accurate registration of DTI data. As an accurate image alignment is one of the most important assumptions in VBA, including DTI information during the registration will increase the reliability of the VBA results [6, 7]. However, some drawbacks of this approach should be mentioned:

- As this approach is more complex compared to the scalar registration methods, computation time is increased.
- There is a need for tensor information in atlas space, as this tensor information is needed to drive the registration.

Summary Points

- In order to achieve successful DTI registration, the orientational dependence of the diffusion data needs to be accounted for, i.e., any rotation of the DWIs should be corrected for, e.g., by using tensor reorientation during affine registration.
- Registration can be improved by incorporating diffusion information, such as scalar DTI measures (e.g., FA/MD), tensor information, or a combination of different data types.

Atlas or Template

The atlas or template is the reference frame to which all data are registered and which is used to report the results. It has been demonstrated that the choice of this atlas or template can affect the VBA results [21–23]. As a result, the atlas selection is an important step in the VBA processing pipeline for DTI data. An overview of possible DTI atlas selection approaches is provided in Zhang and Arfanakis [23].

DTI templates can be subdivided into two broad categories:

- a standard template,
- a population-/study-specific template

A population- or study-specific template is usually constructed based on the data sets that are analyzed. As a result, in theory, this atlas is the best representation of these data sets, and should thus result in minimizing the registration errors. A standard template, on the other hand, is an atlas that was created from a group of healthy subjects and is independent from the subject data sets that need analyzing. However, these atlases usually contain anatomical labels and predefined region of interests, which might be of interest for the study. So, again, there is no single correct approach of selecting an optimal template for your study. The optimal choice will depend on your study and data (i.e., goals, hypothesis, patient population, data quality). In the following paragraphs, a more detailed description of the template selection choice is provided, including some advantages and limitations of the different approaches.

Standard Template

Standard templates are typically constructed by averaging data from a group of healthy subjects that have been registered to a stereotaxic atlas. For example, anatomical T1-weighted templates were constructed by the Montreal Neurological Institute (MNI) and the International Consortium of Brain Mapping (ICBM) [24–26], and are widely used in functional MRI research. Mori et al. created the first standard DTI atlas in the ICBM space, containing fiber orientation maps and white matter parcellation maps [27]. Peng et al. [28] and Zhang et al. [21] created a DTI atlas in the ICBM-152 space by registering high quality DTI data sets of 67 healthy subjects using a non-affine registration procedure.

One of the main **advantages** of using standard templates is that they provide the possibility to make use of predefined anatomical regions for subsequent region-of-interest analysis in atlas space. Furthermore, as the standard templates are widely used, results, and coordinates of significant findings in particular, can be easily compared across studies.

However, there are some **drawbacks** when using a standard template. First, as most standard templates are created from healthy subject data, they do not necessarily represent an average brain of the subjects of your study, especially when pathology is present in some subjects. A simplified example is given in Fig. 10.7. Assume again that DTI measures are compared between healthy subjects and patients with Alzheimer's disease. Although some atrophy can be present in the healthy control group, it will be more severe in the Alzheimer's group. As a result, when all data is transformed to a standard atlas of a healthy brain, the registration result will be much better for the healthy subject data compared to the Alzheimer subject data. This is especially notable at borders with CSF (shown in black in Fig. 10.7), where the groups will not be matched correctly. Not only will there be registration errors (something we don't want in VBA), there is also a bias towards a certain subject group. As a result, this will create false positive findings, caused by more significant misregistration in one of the subject groups in specific brain regions.

Another limitation of some standard templates is that the diffusion tensor information is not always present, hence limiting the information that can be used to drive the registration process to this atlas.

Population-Specific Atlas

The general idea of population- or study-specific atlases is to use the data sets that are studied to determine an atlas space, to which all data sub-

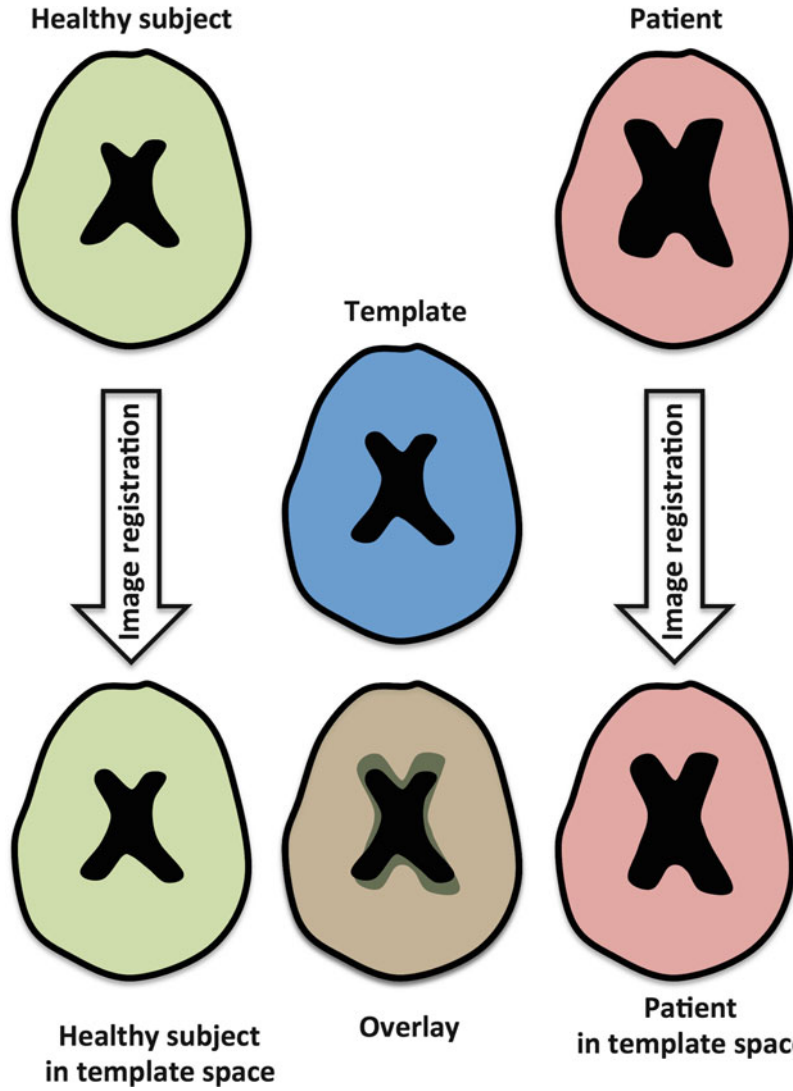

Fig. 10.7 A simplified example of image registration of healthy subjects and subjects with enlarged ventricles to a healthy subject atlas. Registration errors can occur in the group with enlarged ventricles, thereby introducing a potential bias in the VBA results

sequently are registered. The simplest way to construct a study-specific atlas is to select **one DTI data set** from the study population as the template. This subject can be chosen randomly, based on visual inspection of all data or based on calculations that determine which subject is most representative for the population. In the latter case, all data sets are registered to each other and the deformation fields from one subject to all others are averaged. The subject with the smallest average deformation field to all other subjects can then be regarded as the most representative subject of the population under study.

The **advantage** of selecting an individual subject of the study as the template is that the data quality of the template image is similar to the data quality of all other subjects. In addition, tensor information is present in this atlas and can therefore be used during the registration of all data sets to this atlas. However, this approach also has some **limitations**. As discussed, selecting the most representative subject is not trivial. In addition, in the case of an individual subject atlas, there is information on predefined anatomical regions, as is the case in standard template spaces. Similar as with the standard templates, a

bias can be introduced as the selected subject can be a patient or a control subject.

Instead of selecting an individual subject as the atlas space, population-specific atlases can be constructed based on the whole population that is studied [29, 30]. The resulting atlas should then be the best average representation of all the data that is being analyzed. Van Hecke et al. [22] demonstrated that the accuracy of VBA results can be improved when using a population-specific atlas compared to the use of a standard template.

As mentioned, the main **advantage** of the population- or study-specific atlas is that it is the best representation possible of the data sets that are studied (when the appropriate approach and registration techniques are used). As a result, image registration accuracy will be maximized and unbiased to the subject group. By constructing a study-specific atlas, registration errors to the atlas can still be present, but they will be unbiased towards the subject groups. Another advantage of a study-specific data set is that it can be made with all tensor information present. This provides the opportunity to use the tensor-based information during registration, again improving registration accuracy; or to perform tractography in the atlas space.

As with the individual subject atlas, an important **limitation** of the population-specific atlas is that it does not contain anatomical labels and delineated regions, in contrast to the standard templates. In addition, as it is made from the data of a specific study, it is usually (though not necessarily) constructed from fewer data sets compared to the standard templates.

Summary Points

- In order to compare DTI values between groups, individual datasets need to be registered to a common template space or atlas
- Standard atlases are created from large numbers of subjects and are useful for reporting results in a commonly used and well-defined space. Standard atlases are less suitable for subjects with gross morphological differences to the standard template.
- A population-specific atlas is created only from subjects under investigation and is less subject to misregistration bias.

Smoothing

What Is Smoothing?

Smoothing involves blurring the data using a filter, typically a Gaussian kernel. As a result, the image value in each voxel is recalculated, based on the weighted values of neighborhood voxels, as determined by the kernel. Typically, the size of this kernel is defined by the full width at half maximum (FWHM). The FWHM is an indication of the distribution of the kernel values, meaning that when the FWHM is 4 mm, the kernel is 4 mm wide at 50 % of its peak value. Consider the example given in Fig. 10.8.

In Fig. 10.8a, an axial FA slice is shown that will be smoothed by a Gaussian kernel. As an example, we focus on a row of voxels, as shown in Fig. 10.8b. Note that in this example, we explain Gaussian smoothing in a single row of voxels in the x direction, whereas in practice the voxels in the y and z direction will also be taken into account. In Fig. 10.8b, the FA values of the 9 voxels of interest are displayed. The FA value of the middle voxel is depicted in red, as the value of this voxel will be changed during the smoothing in this example. Of course, in practice this process is repeated for all voxels. The Gaussian kernel that will be used for smoothing is shown in Fig. 10.8b. Note that the FWHM of this kernel is 6 mm, as we assume a voxel to have a width of 2 mm. The FA values of the different voxels will be weighted, whereby the weighting factor is determined by the Gaussian kernel. The total sum of the weighting factors thereby equals 1. The resulting weighting factors for the different voxels for this Gaussian kernel are shown in Fig. 10.8c. Next, the FA value of every voxel is multiplied by the corresponding weighting factor (see Fig. 10.8d), and the resulting sum of these values will be the FA value middle voxel in the smoothed image, in this case an FA of 0.664. As mentioned, this process is repeated for all voxels, thereby taking all neighboring voxels (in all dimensions)

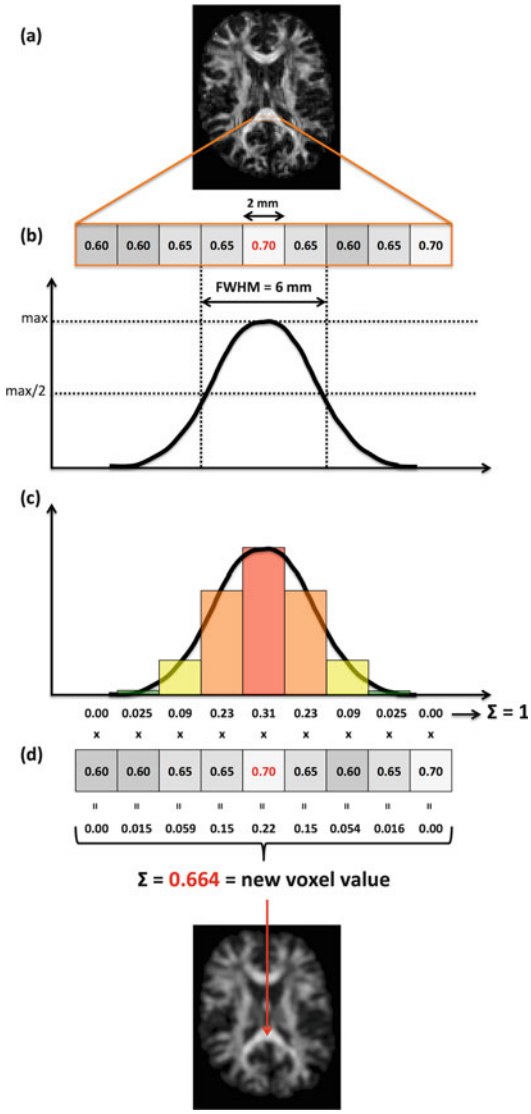

Fig. 10.8 A simplified example of the process of image smoothing in one dimension. An FA map (**a**) is smoothed by a Gaussian kernel with an FWHM of 6 mm (**b**). In (**c**) the different weighting factors are shown. Finally, the resulting FA value after smoothing is calculated (**d**) and the smoothed FA map is displayed

into account. The resulting smoothed FA map is also shown in Fig. 10.8d.

Why Should You Smooth (and Why Not)?

In Fig. 10.8, the process of smoothing was explained. In this simplified example, an isotropic Gaussian smoothing kernel was used. But why would you smooth your data? Why would you bother blurring images when you pushed your scanner and patients to the limits to acquire high resolution data sets? There are several reasons why DTI data sets are smoothed before statistical testing in VBA:

- It helps to accommodate for imperfect registration.
- It reduces the noise and increases SNR.
- It makes the data more normally distributed.

However, an obvious limitation of smoothing is that the resulting data is blurred. In addition, by smoothing the data, information of different white matter structures and tissue types (white matter vs. gray matter vs. CSF) will be averaged. Although it does make sense to integrate information from different neighboring voxels of the same white matter structure, averaging information from other structures or tissue types can introduce false positive as well as false negative results.

Determining the Smoothing Kernel Size

An important parameter related to smoothing is the smoothing kernel size. However, it is not straightforward to determine the optimal size of the smoothing kernel for a specific study. To complicate matters further, it has been demonstrated that the choice of the kernel size can significantly affect the VBA results [31, 32]. This stresses the importance of selecting the optimal kernel size, or at least having a clear argument for using a specific smoothing kernel width.

So, is there a way of determining an optimal smoothing kernel size? According to the matched filter theorem, the optimum smoothing kernel width should be similar to the expected extent of the signal difference, as the SNR then reaches its maximum [33]. In other words, for DTI, an "a priori" hypothesis is needed on the extent of change in the diffusion metrics that are expected. But this shifts the problem from not knowing how to choose the optimal kernel size to the problem of predicting the size of the hypothesized differences. After all, one of the strengths of VBA is

that it is an exploratory approach to search in the whole brain for unknown group differences.

Although similar problems exist with functional MRI analysis, they may be more straightforward to address, as the expected differences relate to the extent of GM brain activity in fMRI and the size of anatomical structures in VBM.

Smoothing in DTI

The problems related to smoothing DTI data are similar to problems in ROI analysis, as for both methods, the size of the expected differences should be known for an optimal result. However, in ROI analysis the location of the differences should also be known, which is not necessary for VBA, as all the voxels of the whole brain are evaluated simultaneously. On the other hand, smoothing of DTI data in VBA has some specific issues. These are related to the specific nature of DTI information, i.e., white matter tract information. These white matter tracts are aligned along a specific orientation and can significantly vary in size and width. Smoothing with isotropic Gaussian kernels will therefore introduce widespread averaging of information across different white matter bundles and tissue types. This is not desirable, as we know for example that white matter degeneration is not present in CSF. An example of how different kernel sizes would average information from different structures is shown in Fig. 10.9.

Not only can an isotropic Gaussian smoothing kernel average out signals from different structures and/or tissue types, this effect will also depend on their location, as white matter tracts and brain structures vary in size, shape, and width across the brain.

To address these problems, anisotropic smoothing kernels were introduced in DTI-based VBA [32, 34]. In these methods, the smoothing kernel shape is not isotropic and can vary across the brain. For example, the kernel shape can be determined based on an FA map. At edges of the FA image, for example between the white matter structure and CSF, the smoothing kernel will stop, as shown in Fig. 10.10. As a result, the chance of averaging signal in the white matter structure alone is increased. In addition, this approach can cope with the variations between shape, size and width of white matter tracts across the brain, as the shape of the smoothing kernel is locally adapted.

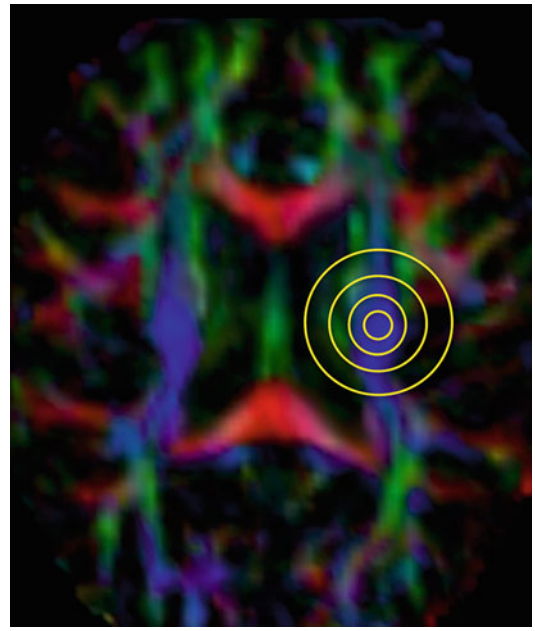

Fig. 10.9 An example of how voxel values from different structures and tissue types are taken into account during smoothing with an isotropic Gaussian smoothing kernel with different widths. In this example, the diameter of the *yellow circles* reflects the FWHM of the Gaussian smoothing kernels. As can be observed, different information is included during smoothing for different FWHM of the smoothing kernels

However, signal can still be averaged between adjacent white matter structures. In addition, this still relies on a prior hypothesis of the size and shape of the expected differences in diffusion metrics between groups of subjects.

Summary Points

- Smoothing is typically performed after image registration to accommodate for imperfect registration, to reduce the noise and increase SNR, and to obtain more normally distributed data.

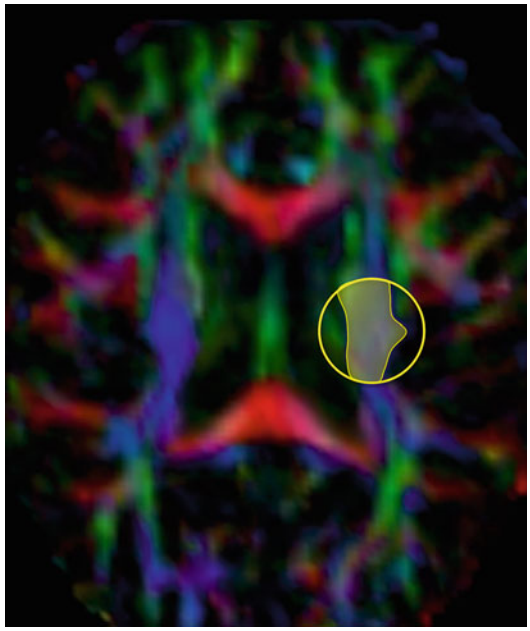

Fig. 10.10 Example of an anisotropic smoothing kernel. As can be seen, the information that is included during smoothing is limited to the white matter structure that is delineated in *yellow*. The FWHM of the smoothing kernel will affect the information included during smoothing, and thus the results, less

- The FWHM reflects the smoothing kernel size of the Gaussian kernel.
- VBA results can be affected by the smoothing that is performed and the FWHM of the smoothing kernel.
- Anisotropic smoothing methods were introduced to average out information within white matter structures during smoothing.

Statistical Analysis

As with all VBA approaches, such as VBM and functional MRI, statistical comparison of DTI metrics is performed in every voxel. Although this is one of the strengths of the technique, i.e., an exploratory whole brain analysis at the smallest scale, it also introduces a "multiple comparisons" problem.

The "Multiple Comparisons" Problem

When a statistical test is performed, a threshold—for example $p<0.05$—is used to assess whether the result is statistically significant or not. However, for a threshold of 0.05, there is still 5 % chance that a type I error—i.e., a false positive result—occurs. Although this is reasonable for a single statistical test, it becomes problematic when thousands of statistical tests are performed, all with a 5 % chance of a type I error. This is known as the multiple comparisons problem. In order to reduce the type I error in VBA, some correction for multiple comparisons should be performed. When very strict corrections, such as the Bonferroni correction (dividing the statistical threshold by the number of statistical tests that are performed), are applied, typically no statistically significant differences are found. However, there is a whole range of other less strict methods to correct for multiple comparisons, the most popular being the theory of Gaussian Random Fields [35], false discovery rate [36], and permutation-based approaches [37]. Unfortunately, there is no consensus on the most optimal technique to correct for multiple comparisons. Different techniques are used in literature, which makes it difficult to compare results, and in many studies no significant findings are reported after correction for multiple comparisons. For the latter reason, many studies report uncorrected values. It is therefore important to interpret the results of studies in the context of the statistical analysis and correction for multiple comparisons that was used.

There are several options to reduce the number of statistical tests that need to be performed in a VBA setting. For example, one can apply a white matter mask and only evaluate the voxels within this mask. In many studies this would make sense, as the quantitative DTI measures are best characterized in white matter and researchers are typically only interested in white matter when DTI is used. Other approaches can be even more limiting in the amount of voxels analyzed, by deriving masks in atlas space from:

- Predefined anatomical labels
- Manually drawn regions of interest
- Tractography results in atlas space

Parametric or Nonparametric Statistics?

Parametric statistical tests, such as the typically used *t*-test or regression tests, require the residuals of the model to be normally distributed. However, Jones et al. demonstrated that this assumption only holds in around 60 % of the voxels [31]. Most of the voxels in which the residuals were not normally distributed were situated in the gray matter. When DTI metrics of smaller groups of subjects are compared, nonparametric statistics, such as permutation or bootstrap based testing, should be strongly considered. Jones et al. [31] also demonstrated that Gaussian smoothing reduces the amount of voxels with non-normally distributed residuals, but the number of voxels with non-normally distributed residuals remained high.

Summary Points

- As statistical tests are performed in all voxels, false positive results can be reported. A correction for multiple comparisons should be performed to reduce the number of false positive findings.
- Nonparametric statistical analysis should be considered, especially when the subjects groups that are studied are small.

To VBA or Not to VBA?

Pros and Cons

So, given all the aforementioned limitations, should we use VBA at all? The answer is not straightforward. VBA has many **advantages**:

- It is an exploratory technique.
- DTI metrics are evaluated in the whole brain and at the same time at the smallest scale with which one can obtain diffusion measures, i.e., the voxel level.
- It doesn't need a lot of manual interaction, making it less observer dependent.

However, VBA also has some significant **limitations**:

- Results are only relevant when perfect image registration is achieved.
- Results are less observer dependent, but are significantly parameter dependent.

The latter point is very important. In every step of the VBA pipeline, choices have to be made, for example, regarding:

- the registration technique and its parameter settings
  - which affine technique?
  - which non-affine technique?
  - which information to drive the registration?
  - which similarity measure for registration?
- the atlas to use
  - standard vs. population specific?
- the smoothing method and the kernel width
  - anisotropic vs. isotropic smoothing?
  - kernel width?
- the statistical test and method to correct for multiple comparisons
  - parametric vs. nonparametric tests?
  - correction for multiple comparison? Which method?

Note that this is a non-exhaustive list of examples, and at each level there are even more parameter settings to consider!

Why Parameter Settings Are Important?

The importance of the choices made at different steps of the VBA pipeline has been demonstrated by Jones et al. [38]. In this study, the same DTI data sets were sent to nine different research groups. Each of these groups performed a voxel-based analysis of the same DTI data set, using their own selected set of methods and parameters. The nine research groups reported different clusters in various anatomical locations despite analyzing identical DTI datasets. This demonstrates the sensitivity of VBA to choices in the pipeline.

Although most VBA studies follow the prototypical pipeline, i.e., image registration, smoothing, and voxel-based statistical analysis, there is currently no standardization with regard to the methods and parameters that should be used. As a result, different VBA approaches and parameter settings are used in different studies. In light of the Jones et al. [38] study, comparison of results across studies is very difficult.

Tract-Based Spatial Statistics, an Alternative to VBA

With the goal of optimizing VBA for DTI data sets, tract-based spatial statistics (TBSS) was introduced by Smith et al. [39]. Although this approach can also be regarded as a voxel-based analysis, some modifications from the standard VBA pipeline were introduced in TBSS. The main difference between TBSS and standard VBA is the construction of "a skeleton." First, all FA images are aligned to a template by using a non-affine transformation and are subsequently averaged to result in a group mean FA map. From this image, a skeleton is created by selecting the locally maximal FA values, which are assumed to form the center of the white matter tracts. TBSS then projects the FA values of each registered data set onto the skeleton. More specifically, the locally highest FA value perpendicular to the skeleton in each registered FA map is then projected onto the skeleton. The projection on the FA skeleton can, to a certain extent, compensate for potential registration errors. In addition, as statistical tests are performed on the skeleton, there is no need for smoothing and less statistical tests are performed compared to a standard VBA.

Although the skeleton projection step in TBSS can indeed correct for some local misregistration, it cannot compensate for larger registration errors that might occur. As the projection procedure must search locally for the highest FA value, in order to avoid finding spurious correspondences, it will not be able to correct for larger misregistrations [40]. Indeed, the study of Zalesky and colleagues [40] used synthetic deformations of ground truth images to demonstrate that the skeleton projection only recovers less than 10 % of the registration errors. As an accurate image registration is as important in TBSS as in classical VBA, similar care must be taken with respect to the use of a non-affine registration method, tensor information during registration, and population-specific atlases in case subjects are studied with significant pathology or atrophy. It was indeed demonstrated by Keihaninejad et al. [41] that the use of a population-specific atlas outperformed the standard template or individual subject template in the study of Alzheimer's disease.

Although TBSS is an elegant way of trying to overcome some of the drawbacks of VBA, as for all methods, there are some limitations, which should be taken into account when performing a TBSS analysis. For example, as only the local maximal FA values are projected on to the skeleton and therefore evaluated, an inherent assumption is made that pathology will mainly affect the local maximal FA values, which is not necessarily the case. TBSS is also more sensitive to changes in DTI measures in diagonally oriented tracts, as their skeleton contains more voxels than horizontal or vertical ones [42]. In addition, the presence of white matter lesions that reduce FA values will affect the results, as it is possible that some voxels that do not belong to the core of the tract have larger FA than those in the core because of the presence of the lesion [43]. Furthermore, by limiting the analysis to local FA maxima on the skeleton, which comprises a relatively small percentage of the total image, a lot of potentially valuable information is not used in the analysis. Sometimes this may not be apparent as some authors choose to display their findings on an artificially thickened skeleton which appears to encompass more white matter voxels than were actually analyzed. This is typically done to emphasize findings, but as with tractography visualizations, it can be misleading to those unfamiliar with the techniques (see Chap. 8). Finally, in regions of crossing fibers, the FA skeleton cannot be determined reliably as the FA in these regions is typically very low. With 60–90 % of white matter voxels containing multiple fiber populations, this may complicate the interpretation of TBSS findings significantly [44].

How Do TBSS and Classical VBA Approaches Compare?

Given the fact that TBSS and classical VBA approaches differ with regard to core aspects of voxel-based analysis, i.e., registration and smoothing, and given we know that parameter selection significantly affects VBA results, it is worth exploring how TBSS results compare with those from classical VBA. Although most studies choose to apply one method or the other, a few studies have directly compared results of the typical VBA approach with those of TBSS when analyzing the same dataset. Sage et al. [8], for example, reported very similar results to TBSS when an optimized VBA (in terms of registration method and atlas building) was performed. It was also demonstrated that the VBA results were more reliable compared to the results of a non-optimized VBA. Preti et al. [45] compared TBSS results with an atlas-based approach to obtain DTI measures in specific tracts of healthy subjects and subjects with mild cognitive impairment and Alzheimer's disease. They concluded that the comparison of the healthy subjects with the patients was similar for the atlas-based approach and TBSS, but that the atlas-based approach was more sensitive to detecting changes between patients with mild cognitive impairment and Alzheimer's disease.

Schwarz et al. [46] evaluated the use of more advanced group-wise registration methods on the accuracy of VBA and TBSS. Using synthetic data sets as well as comparing healthy subject data with data from Alzheimer's patients, they showed that the TBSS skeleton projection step *lowered* the overall accuracy of the results when the image registration was optimized.

In summary, both classical VBA and TBSS can be successfully applied to study voxel-wise differences in DTI parameters at a group level. Despite the widespread adoption of TBSS as a gold standard VBA approach, it is not without significant shortcomings. There have been insufficient studies that have compared the accuracy of TBSS results with classical VBA results on the same datasets to determine if one approach should be used in preference to the other. Regardless of which technique is applied however, the quality of the inter-subject registration is central to determining the sensitivity and accuracy of VBA results.

VBA in Clinical Practice?

When applied responsibly, with due consideration for its limitations, VBA can be a powerful tool to analyze DTI data from patient populations with neurological and psychiatric disorders. However, is it the most appropriate tool to use in clinical practice, when a DTI data set from an individual patient needs to be analyzed and interpreted? Although the most appropriate use of VBA is for group analysis, some authors have applied the technique to analyze individual patient data. For example, in traumatic brain injury patients, Lipton et al. [47] used the enhanced Z-score microstructural assessment of pathology (EZ-MAP) approach to evaluate regional FA abnormalities. In this VBA approach, a patient's FA value is compared to the FA values of a normal reference group in every voxel. However, this requires a large reference group and the results can depend on this reference group. Kim et al. [48] suggested some improvements to overcome these problems. Patel et al. [49] used VBA to detect FA changes in lesions and normal appearing white matter in individual MS patients. Although FA reductions were observed in many regions, the authors also reported abnormal FA values due to misregistration. Given its underlying assumptions and limitations, we would not advocate the use of standard VBA (or TBSS) to analyze individual patient data at the present time.

Conclusion

The aim of this chapter was to introduce the VBA approach for DTI data, to elaborate on the different steps involved, and to outline its advantages and limitations. Compared to a standard ROI or even tractography-based analysis, VBA is a more automated approach and therefore less observer

dependent. However, many choices have to be made in the VBA pipeline with regard to image registration, template selection, smoothing, and statistical analysis, which the final VBA results will ultimately depend on. VBA should not be viewed as a generic DTI analysis technique that can be applied without any hypothesis. Whether or not VBA is a suitable way to analyze your data will depend on your specific study, the questions you hope to answer, on the number and type of patients that are studied, the type of DTI data acquisition and data quality, etc. Although VBA has been applied in many DTI studies, the lack of a standard approach means that it remains primarily a research tool, rather than a technique that can be used clinically to assess individual patients.

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