Chapter 21
Structural MRI: Morphometry

Christian Gaser

Abstract Human brains are characterised by considerable intersubject anatomical variability, which is of interest in both clinical practice and research. Computational morphometry of magnetic resonance images has emerged as the method of choice for studying macroscopic changes in brain structure. Magnetic resonance imaging not only allows the acquisition of images of the entire brain in vivo but also the tracking of changes over time using repeated measurements, while computational morphometry enables the automated analysis of subtle changes in brain structure. In this section, several voxel-based morphometric methods for the automated analysis of brain images are presented. In the first part, some basic principles and techniques are introduced, while deformation- and voxel-based morphometry are discussed in the second part.

21.1 Introduction

The Jena psychiatrist Hans Berger became famous for the discovery of electroencephalography. Less known, however, are Berger's imaginative studies of brain morphometry. He tried, for example, to estimate the cortical surface by gluing small metal plates onto a *post-mortem* brain. Since the area and weight of a single metal plate were known, the total weight of the plates was used in order to estimate the total area of the cortex. Nowadays, computer-based methods use the same idea with so-called triangulation. However, now the metal plates are replaced by small triangles forming a computerised mesh that renders the shape of the cortical surface and allows a reliable and accurate measurement. This new approach belongs to the recently developed methods for the automated analysis of brain structure that are referred to as 'computational morphometry' (Takao et al. 2010).

C. Gaser (✉)
Structural Brain Mapping Group, Departments of Neurology and Psychiatry, Jena University Hospital, Am Klinikum 1, 07747 Jena, Germany
e-mail: christian.gaser@uni-jena.de

M. Reuter and C. Montag (eds.), *Neuroeconomics*, Studies in Neuroscience, Psychology and Behavioral Economics, DOI 10.1007/978-3-642-35923-1_21

Besides the use of computer algorithms, the availability of new imaging methods played a seminal role in morphometry. These new imaging methods not only allow the acquisition of images of the entire brain in vivo but also the tracking of changes over time using repeated measurements. Thus, they represented a real advance because previously *post-mortem* examinations were the only way to examine brain structures.

The first imaging method that allowed mapping of cerebral structures in vivo was pneumoencephalography. This procedure involved drainage of most of the cerebrospinal fluid (CSF) from around the brain and replacement with air. The ventricular system of the brain could then be identified on an X-ray of the skull. However, this method proved to be very invasive and painful. It took until the70s of the last century before computed tomography provided images of the brain in three dimensions. The real breakthrough in imaging techniques, however, came with magnetic resonance imaging (MRI), which allowed a much higher spatial resolution without ionising radiation. This method has become the standard tool of macroscopic anatomy, both in clinical practice and in research. Another advantage of this imaging method is that variable image contrasts can be achieved by using different parameters for longitudinal (T_1) and transverse (T_2) relaxation times and proton density. The signal intensities on T_1, T_2 and proton density relate here to specific tissue contrasts. The most commonly used imaging sequence for MR-morphometry is T_1-weighted imaging because of its high contrast for brain parenchyma (see Fig. 21.1). Other imaging sequences can be used to evaluate CSF spaces, oedema or subacute stroke (T_2 weighted), to enhance parenchymal abnormalities, such as low-grade glioma (fluid-attenuated inversion recovery [FLAIR]), or to visualise acute ischaemia (diffusion weighted).

In addition to the various methodological developments, morphometry has gained increasing importance in the field of neuroscience because completely new

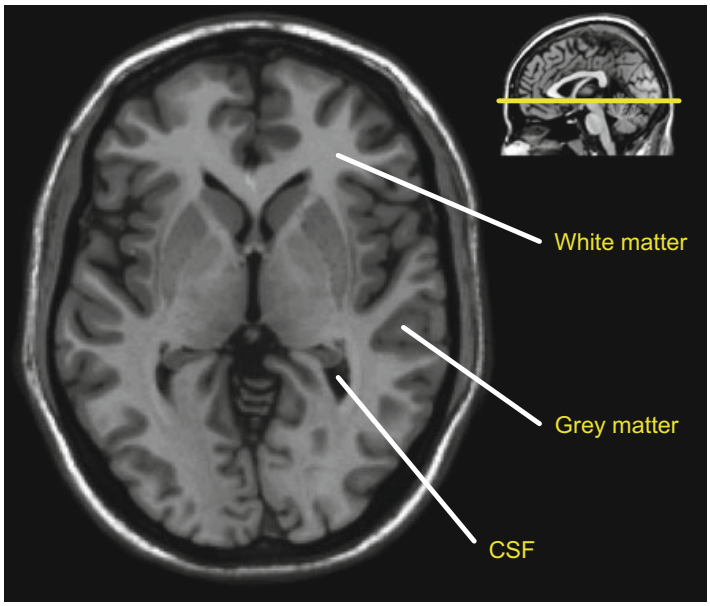

Fig. 21.1 T_1-weighted MRI scan. The small image (*top right*) shows the location of the axial slice (*main image*). This sequence reveals a high contrast for brain parenchyma and the different signal intensities relate to grey and white matter and cerebrospinal fluid (CSF) [modified from (Gaser 2005)]

applications have become possible. While in the early days the applications were limited to the quantification of global parameters such as brain weight or brain volume, nowadays a wide spectrum of applications is supported. This ranges from the investigation of local morphometric changes in certain diseases up to the detection of brain plasticity.

In this chapter, two different morphometric methods for the analysis of MR images of the brain are presented. In the first part, some basic principles and techniques are introduced, while two morphometric methods are discussed in the second part that both work on a voxel-wise level.

21.2 Basic Principles

21.2.1 Spatial Normalisation

Brains are characterised by considerable intersubject anatomical variability. In order to analyse brains across different subjects, an adjustment to a reference system using a stereotactic or spatial normalisation is required. This permits the analysis of brains in a standardised space or coordinate system. However, this procedure is also useful for brain morphometry and consequently a variety of methods based on this idea exists.

In order to spatially normalise brain images, it is first necessary to define a standardised coordinate system by using specific anatomical landmarks. The most widely used reference system is the Talairach atlas proposed by Talairach and Tournoux (1988). The basic idea is to define the anterior and posterior commissures and several points relative to them to align and scale a brain image. The anterior commissure is the origin of the coordinate system and all locations within the brain can now be defined with standardised coordinates in millimetres (Fig. 21.2). This allows the comparison of anatomical localisations between different brains and even different studies.

The adjustment due to spatial registration can be achieved in different ways (Fig. 21.3). The simplest procedure is to only correct the position of the images, for which displacements and rotations are applied. The image size (or brain size) remains unchanged, which is necessary, for example, for brain images of the same subject, in longitudinal (serial) measurements over time. Since image size is not changed, this special case is also referred to as ‘rigid body transformation’. In contrast, images of different subjects need to be additionally corrected for image size by scaling or resizing the image. Furthermore, for a full affine transformation, an additional shearing of the image can be applied (Fig. 21.3). Since the adjustment is done for the entire image in the same way (or linearly), the term ‘linear spatial normalisation’ is used.

In contrast to linear normalisation, nonlinear normalisation also corrects for local differences between two brains. For this, images are locally warped (deformed)

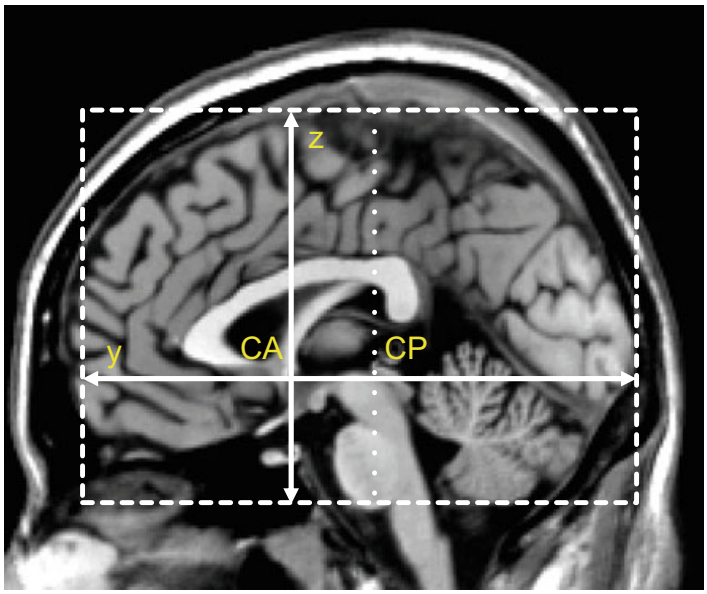

Fig. 21.2 Talairach coordinate system. The coordinate origin of the Talairach space is defined by the anterior commissure (CA). From here, all locations in the brain can be specified as coordinates in millimetres. The line through the anterior and posterior (CP) commissures is used for aligning the coordinate system. The image shows the extent in the y-direction (anterior-posterior) and z-direction (inferior-superior). The x-axis (not shown here) determines the left-right direction [modified from (Gaser 2005)]

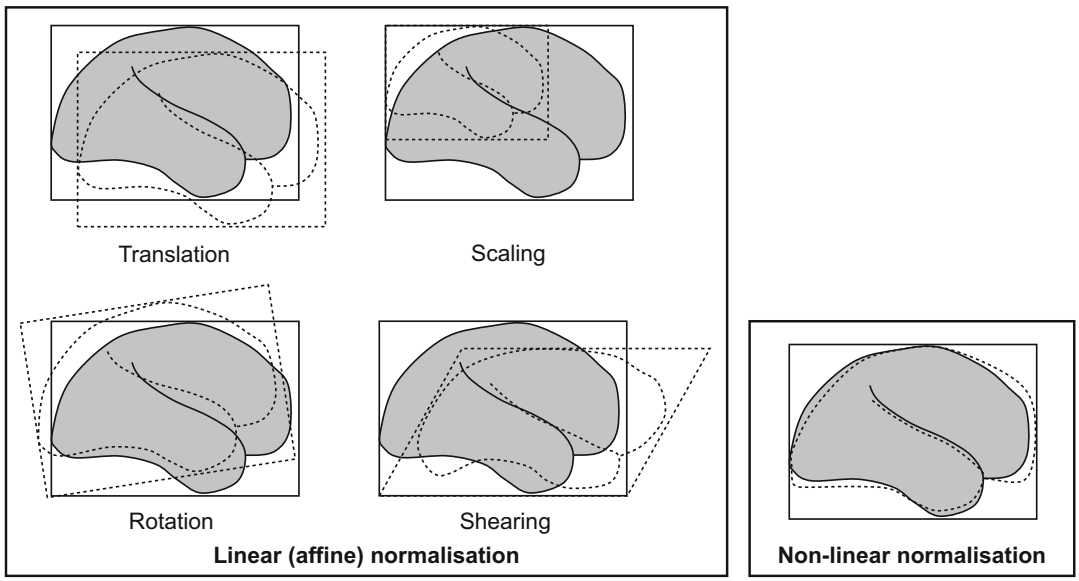

Fig. 21.3 Linear and nonlinear spatial registration. The *left side* of the figure shows the four possible linear transformations that are applied to the entire image. A special case is the so-called rigid body transformation. Here, the image is adjusted only by translations and rotations. An additional change in image size can be achieved by scaling and shearing the image. The aggregation of these linear transformations is known as 'affine normalisation'. In contrast to linear normalisation, nonlinear normalisation also corrects for local differences between two brains (*right side* of the figure). For this, images are locally warped (deformed) until the differences between them are minimised (modified from (Gaser 2005))

until the differences between them are minimised (Fig. 21.3). The cost of computing such local deformations is much higher and increases with the required spatial resolution of the deformations. The advantage of nonlinear normalisation, however, is the greater accurate adjustment of the brains to the reference brain.

Linear and nonlinear normalisation can be performed using different normalisation algorithms [a detailed overview is given in (Toga 1999)]. Landmark-based methods use manual label points (landmarks) in the brain. These corresponding points are defined in all brains and are then aligned. Contour-based methods use not just a few points or landmarks but the whole contour of a region, such as the outline of the corpus callosum in the sagittal plane or even the entire surface of the cortex as a three-dimensional contour (Thompson et al. 1997). Finally, intensity-based methods exist which use the local image intensity in order to achieve a spatial alignment between the images. Here, the squared sum of the signal intensity differences is used, for example, as an indicator of the similarity between two images. By minimising these intensity differences, an alignment of both images is achieved.

21.2.2 Segmentation

Segmentation algorithms are among the most commonly used methods in brain morphometry. The aim of these methods is to segment an image into separate anatomical tissue compartments, such as grey matter, white matter and CSF, after removing non-brain parts. With more sophisticated approaches, it is also possible to segment pathological changes, such as tumours, lesions or stroke-affected regions. However, in addition to the T_1 images, this usually requires MR sequences, such as T_2 weighting or FLAIR, where the pathological changes can be better differentiated.

A plethora of semi-automated and automated algorithms exists, such as intensity thresholding, region growing, classifiers, clustering, Markov random field models, artificial neural networks, deformable models or atlas-guided approaches (Pham et al. 2000). From all of these examples, one of the most commonly used methods will be presented here in detail: the Gaussian mixture model, which belongs to the group of classifiers (Ashburner and Friston 2005). First, an intensity histogram of the image is estimated that plots the frequencies of the image intensities on the y-axis (Fig. 21.4, bottom left). The simplified example in Fig. 21.4 shows only four different intensity distributions. Here, the smallest image intensities are assigned to the background (left part of the histogram), followed by CSF, grey and white matter with the highest image intensity in the right part of the histogram. Gaussian curves that can differ with regard to height and width are now fitted into this intensity distribution. The maximum of each of these four Gaussian curves represents the mean intensity value for the respective tissue compartment. For the example of grey matter, this means that at the peak maximum the probability that this image voxel belongs to grey matter is largest. The more the image intensity deviates from this

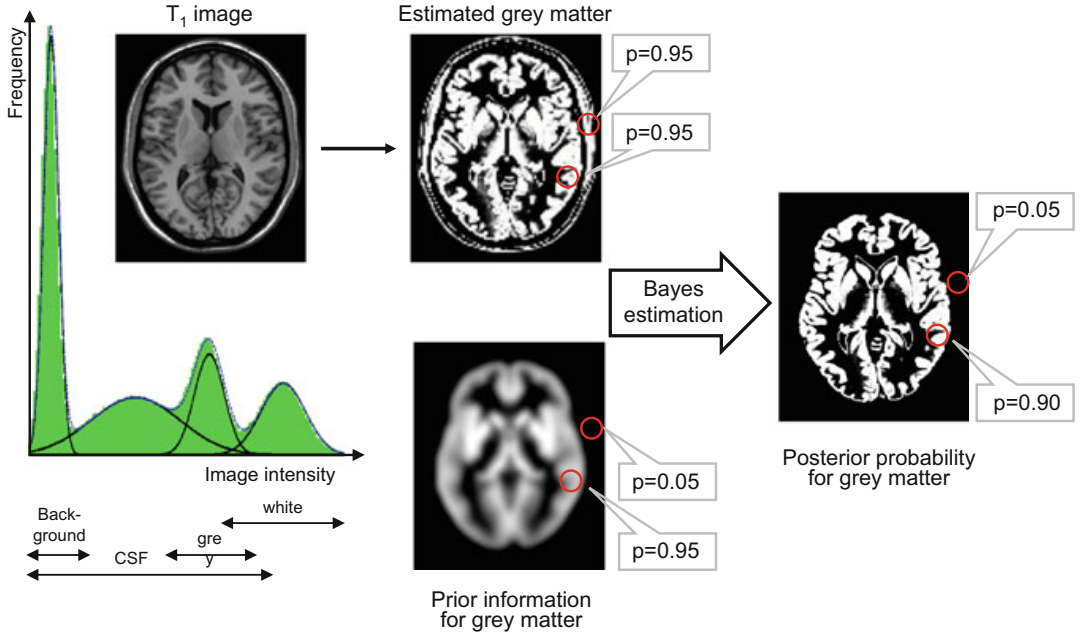

Fig. 21.4 Image segmentation using a priori information. First, the image intensities of the T_1 image (*upper left*) are used to plot their frequencies in a histogram. Several peaks—corresponding to different image intensities of the tissue compartments—can be differentiated. In the next step, Gaussian mixture curves for each tissue compartment are fitted into the histogram in order to estimate the probability that a voxel belongs to that tissue (*lower left*). A map for grey matter is shown (*upper right*) with the estimated probability for two selected locations (*red circles*). Based solely on a similar image intensity, the cerebral and extracranial circles exhibit a similar probability for belonging to grey matter. This can be adjusted by combining the image intensity-based information with prior information (*below*) using a Bayesian approach [modified from (Gaser 2005)]

value, the less likely it is grey matter and is rather CSF (at lower intensity) or white matter (with higher intensity).

The intensity distributions for each tissue compartment overlap because at a common voxel size of $1 \times 1 \times 1$ mm^3 any given voxel might contain more than one tissue. This is referred to as 'partial volume effect' and most often occurs at the border between brain parenchyma and CSF, at boundaries between grey and white matter, and in structures where white matter fibres cross the grey matter. These partial volume effects can be modelled explicitly in order to estimate a more accurate segmentation (Tohka et al. 2004).

To guide tissue segmentation, additional tissue probability maps can be used to consider prior anatomical knowledge about the spatial distribution of different tissues (Ashburner and Friston 2005). Image intensity and prior knowledge can then be combined via a Bayes estimator. In fact, prior anatomical knowledge is used to drive and restrict the tissue segmentation algorithm (Fig. 21.4, right). While this may be valuable as long as the prior probability maps match the subject's tissue distribution, it might lower segmentation accuracy in all populations that deviate from these maps (e.g. children, Alzheimer's disease patients) (Wilke et al. 2008).

21.3 Voxel-Based Methods

Voxel-based methods allow the analysis of each voxel in the MR data. This voxel-wise analysis is possible because all brains are adjusted by means of a spatial normalisation to a standard anatomical space. Thus, each voxel relates to the same corresponding anatomical structure across all brains, which can be assumed if a high-dimensional nonlinear spatial normalisation is applied.

While different voxel-wise measures can be used for that approach, the most common approach is to segment brains into different tissue compartments and analyse the local distribution for a specific tissue. This method is referred to as 'voxel-based morphometry.' Another approach is to analyse the deformations that are necessary in order to non-rigid deform a brain to adapt it to another brain. Because this approach is based on deformations, it is known as 'deformation-based morphometry.'

Prior to statistical analysis, the images have to be spatially smoothed (filtered) with a Gaussian kernel. The reason for this is threefold. First, parametric tests assume that the data follow a Gaussian distribution and after smoothing with a Gaussian kernel the data are more normally distributed according to the central limit theorem (Nichols and Hayasaka 2003). Second, smoothing accounts for small interindividual differences in local brain anatomy that remain after spatial normalisation. Finally, smoothing enables greater sensitivity for effects that approximately match the size of the smoothing kernel according to the matched filter theorem (Ashburner and Friston 2000).

In the next step, smoothed images can then be compared in each voxel (Fig. 21.5). For statistical analysis, usually a general linear model is used. This model—the equivalent of a multiple regression—incorporates a number of different statistical models ranging from simple correlation to repeated measures ANOVA in longitudinal designs. The result is a statistical parametric map, which allows a statistical statement about the initial hypothesis in each voxel. However, due to the mass-univariate approach, a correction for multiple comparisons has to be applied. The most frequently used correction is based on the Gaussian random field theory (Worsley et al. 1996) that enables a correction on the voxel or cluster level (although a correction on the more theoretical set level is also possible) (Friston et al. 1996). Another option for the consideration of the issue of multiple comparisons has become very popular in recent years. This method is based on the adaptive control of the false discovery rate (FDR) and was originally proposed for microarray data to identify genetic effects (Benjamini and Hochberg 1995). Finally, permutation tests do not assume normally distributed data and enable a correction for multiple comparisons particularly for small sample sizes. They use random shuffles of the data to attain a correct distribution of a test under a null hypothesis (Nichols and Holmes 2002). Again, a correction on the voxel or cluster level is possible. Another possibility is to use a correction based on threshold-free cluster enhancement (TFCE) that combines both levels by accumulating cluster-like local spatial support at a range of cluster-forming thresholds (Smith and Nichols 2009).

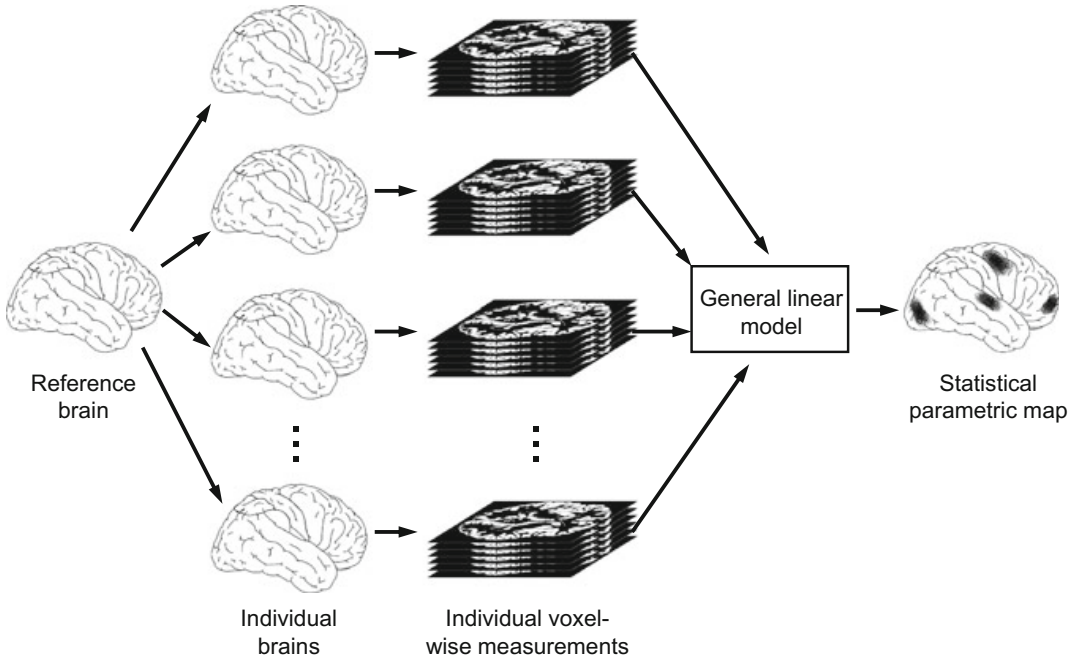

Fig. 21.5 Principle of a voxel-based analysis. For a voxel-wise analysis, it is first necessary to spatially register all brains to a reference brain. Now, in each voxel a morphometric parameter (e.g. grey matter volume) is estimated that can be statistically analysed using a general linear model. The result is a statistical parametric map which allows a statistical statement about the initial hypothesis in each voxel [modified from (Gaser 2005)]

Since the analysis is made on a voxel-wise level, this approach offers several advantages over conventional morphometry. One such advantage is the reduction of partial volume effects, since a structural change can be detected in each voxel of the brain and not only in the entire structure. Thus, structures that are only partially altered can be detected with higher sensitivity compared to region-based methods. Furthermore, an analysis can not only be carried out in predefined regions but also throughout the brain. Large sample numbers can be examined with high reliability due to the automated measurement. These advantages might explain the great popularity of these methods in recent times.

21.3.1 Deformation-Based Morphometry (DBM)

DBM is based on the application of nonlinear registration procedures to spatially normalise one brain to another one. The simplest case of spatial normalisation is to correct the orientation and size of the brains. In addition to these global changes, a nonlinear normalisation is necessary to minimise the remaining regional differences by means of local deformations. If this local adaptation is possible, the deformations now reveal information about the type and localisation of the structural differences between the brains and can undergo subsequent analysis (Fig. 21.6).

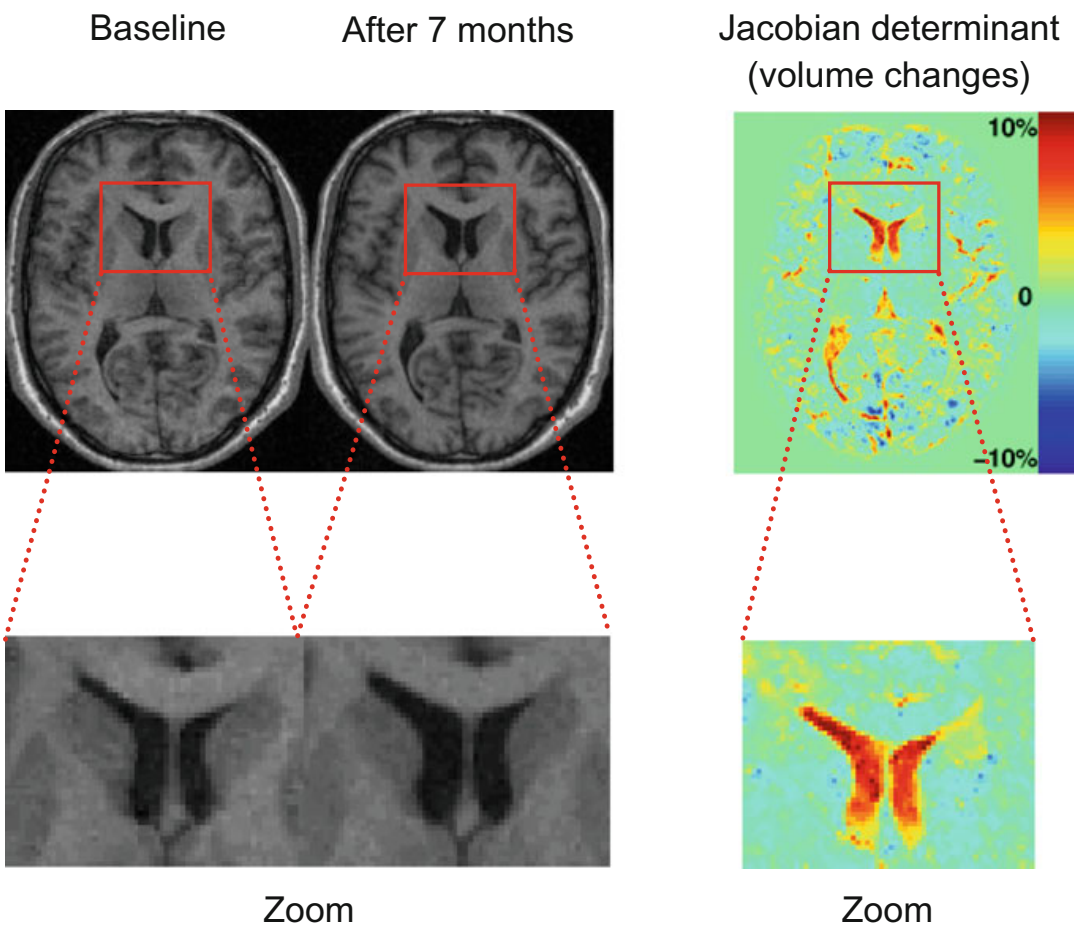

Fig. 21.6 Principle of DBM. *Left* This example shows two T_1 images of a male patient with schizophrenia at his first episode and a subsequent scan after 7 months. In the enlarged views shown underneath, the larger lateral ventricles at the second time point can be clearly seen. The principle of DBM is to warp the second scan to the baseline scan by introducing high-dimensional deformations. Once this is achieved, the differences between both images are encoded in the deformations applied for the warp. These deformations can then be used to calculate volume changes by using the Jacobian determinant (*right images*) [modified from (Mietchen and Gaser 2009)]

Figure 21.6 shows an example for a single patient with schizophrenia. A first baseline scan was acquired at the beginning of his first psychotic episode and a subsequent scan was acquired after 7 months where the enlarged ventricles are visible with the naked eye. The second image is warped to the baseline scan by introducing high-dimensional deformations. Differences between both images are minimised and are now coded in the deformations. Finally, a map of local volume changes can be quantified by a mathematical property of these deformations–the Jacobian determinant. This parameter is well known from continuum mechanics and is usually used for the analysis of volume changes in flowing liquids or gases. The Jacobian determinant allows a direct estimation of the percentage change in volume in each voxel and can be statistically analysed (Gaser et al. 2001). This

approach is also known as 'tensor-based morphometry' because the Jacobian determinant represents such a tensor.

A deformation-based analysis can be carried out not only on the local changes in volume but also on the entire information of the deformations, which also includes the direction and strength of the local deformations (Gaser et al. 1999). Since each voxel contains three-dimensional information, a multivariate statistical test is necessary for analysis. A multivariate general linear model or Hotelling's T_2 test is commonly used for this type of analysis (Gaser et al. 1999; Thompson et al. 1997).

The principle of DBM can be applied to both cross-sectional and longitudinal data. In a cross-sectional design, typically brain images of two groups are warped to a reference image. Thereafter, the different deformations to the reference image between the two groups can be compared. On the other hand, longitudinal data comprise measurements of the same subject at different time points. Here, the idea of DBM is slightly modified. Now, the baseline image at the first time point serves as a reference image. All subsequent images of a subject are warped to this baseline image and the individual changes over time can be obtained. This allows the tracking of subtle changes over time, which cannot be detected by conventional morphometry.

21.3.2 Voxel-Based Morphometry (VBM)

VBM provides the voxel-wise estimation of the local amount or volume of a specific tissue compartment (Ashburner and Friston 2000). VBM is most often applied to investigate the local distribution of grey matter, but can also be used to examine white matter. However, the sensitivity for detecting effects in white matter is limited due to the low intensity contrast in large homogeneous white matter regions with only small changes in intensity. The concept of VBM incorporates different preprocessing steps: (1) spatial normalisation to a reference brain (template), (2) tissue classification (segmentation) into grey and white matter and CSF and (3) bias correction of intensity non-uniformities. Ashburner and Friston (2005) proposed an approach whereby all three steps are combined within the same generative model. This model is based on a mixture of Gaussians and additionally considers smooth intensity variations and nonlinear registration using tissue segmentations. This approach allows for more accurate and reliable results than simple serial applications of each single step.

Further improvement can be achieved if high-dimensional spatial registration techniques such as diffeomorphic registration approaches are used. Diffeomorphic registrations are based on a large-deformation framework and not only provide a number of elegant mathematical properties but generally allow for a better accuracy of the spatial registration (Ashburner 2007).

Local deformations are now used in order to reduce structural differences between original and template images. This facilitates a precise comparison within brain regions between different subjects. However, existing structural differences between

the brains are now largely reduced and the sensitivity for detecting these effects in the statistical analysis is therefore minimised. Thus, the volume of a particular tissue within a voxel has to be preserved. This is attained by multiplying (or modulating) voxel values in the segmented images by the Jacobian determinants that are derived from the spatial registrations. This process is referred to as 'modulation.'

References

Ashburner J (2007) A fast diffeomorphic image registration algorithm. Neuroimage 38(1):95–113
Ashburner J, Friston KJ (2000) Voxel-based morphometry–the methods. Neuroimage 11(6 Pt 1):805–821
Ashburner J, Friston KJ (2005) Unified segmentation. Neuroimage 26(3):839–851
Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate—a practical and powerful approach to multiple testing. J Roy Stat Soc B Met 57(1):289–300
Friston KJ, Holmes A, Poline JB, Price CJ, Frith CD (1996) Detecting activations in PET and fMRI: levels of inference and power. Neuroimage 4(3 Pt 1):223–235
Gaser C (2005) Morphometrie. In: Walter H (ed) Funktionelle Bildgebung in Psychiatrie und Psychotherapie. Schattauer Verlag, Stuttgart, pp 89–104
Gaser C, Volz HP, Kiebel S, Riehemann S, Sauer H (1999) Detecting structural changes in whole brain based on nonlinear deformations-application to schizophrenia research. Neuroimage 10 (2):107–113
Gaser C, Nenadic I, Buchsbaum BR, Hazlett EA, Buchsbaum MS (2001) Deformation-based morphometry and its relation to conventional volumetry of brain lateral ventricles in MRI. Neuroimage 13(6 Pt 1):1140–1145
Mietchen D, Gaser C (2009) Computational morphometry for detecting changes in brain structure due to development, aging, learning, disease and evolution. Front Neuroinform 3:25. doi:10.3389/neuro.11.025.2009
Nichols T, Hayasaka S (2003) Controlling the familywise error rate in functional neuroimaging: a comparative review. Stat Methods Med Res 12(5):419–446
Nichols TE, Holmes AP (2002) Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 15(1):1–25
Pham DL, Xu C, Prince JL (2000) Current methods in medical image segmentation. Annu Rev Biomed Eng 2:315–337
Smith SM, Nichols TE (2009) Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 44(1):83–98
Takao H, Abe O, Ohtomo K (2010) Computational analysis of cerebral cortex. Neuroradiology 52 (8):691–698
Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system—an approach to cerebral imaging. Thieme, New York
Thompson PM, MacDonald D, Mega MS, Holmes CJ, Evans AC, Toga AW (1997) Detection and mapping of abnormal brain structure with a probabilistic atlas of cortical surfaces. J Comput Assist Tomogr 21(4):567–581
Toga AW (ed) (1999) Brain warping. Academic Press, San Diego
Tohka J, Zijdenbos A, Evans A (2004) Fast and robust parameter estimation for statistical partial volume models in brain MRI. Neuroimage 23(1):84–97
Wilke M, Holland SK, Altaye M, Gaser C (2008) Template-O-matic: a toolbox for creating customized pediatric templates. Neuroimage 41(3):903–913
Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, Evans AC (1996) A unified statistical approach for determining significant signals in images of cerebral activation. Hum Brain Mapp 4(1):58–73