# An Absolute Beginner's Guide to Surface- and Voxel-based Morphometric Analysis

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Morphometry is the study of the size and shape of the brain and its structures. The brain changes as it grows into adulthood, decays with age, and undergoes disease processes. The shape of the brain is highly dependent on genetic factors as well. All these properties have made brain morphometry one of the most studied modalities in brain imaging. There are several metrics that one can use to test a morphometry-related hypothesis such as gray matter volume, white matter volume, cortical thickness, or cortical curvature. This talk will describe two techniques for analyzing brain morphometry: voxel-based morphometry (VBM) and surface-based analysis (SBA).

**Voxel-based Morphometry (VBM)**.

VBM has been implemented in several different ways (e.g., (1-5); also see reviews by (6,7)). Here we describe generally how VBM is implemented. VBM starts by *spatially normalizing* the T1-weighted image of an individual to a *group template* (see Figure 1) in order to establish voxel-for-voxel correspondence across subjects. This is a *non-linear registration* which allows local areas to stretch and compress with respect to each other. This process creates a *deformation field* which is a map of how far each voxel in the input image must move to land at the matching point in the template image. This deformation is applied to the input image to create an image that is in voxel-for-voxel registration with the template. Note that in the example in Figure 1, the ventricles, which are quite large in the input image, have shrunk considerably after the deformation has been applied and so fit those in the group template much better. The deformed image is then *segmented* into tissue classes (gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF)) based upon the intensity in the image as well as tissue class priors which indicate the likelihood of finding a given tissue class at a given location. The segmented images have values that indicate the probability of a given class (i.e., they are not binary). At this point the value at each voxel is a *concentration*, the interpretation of which is discussed below. The segmented image is then *spatially smoothed*. The concentration images from different subjects are then combined in a voxel-wise statistical analysis. The statistical map shown in Figure 1 is that of an aging study in which the concentration is correlated with age. Blue indicates a negative correlation and red indicates a positive correlation.

*Modulated VBM*: "Modulation" in VBM is an operation where the voxel concentration is scaled based on the amount of stretching or compression that was applied to that voxel in the processes of applying the deformation field. This is done by computing the *jacobian* of the deformation field. The jacobian map in Figure 1 is red/yellow in places that needed to be compressed and blue in areas that needed to be stretched. The value at a voxel in the modulated image is interpreted as the *volume* of gray matter at that location. Studies like the aging study above can be conducted on volume instead of concentration.

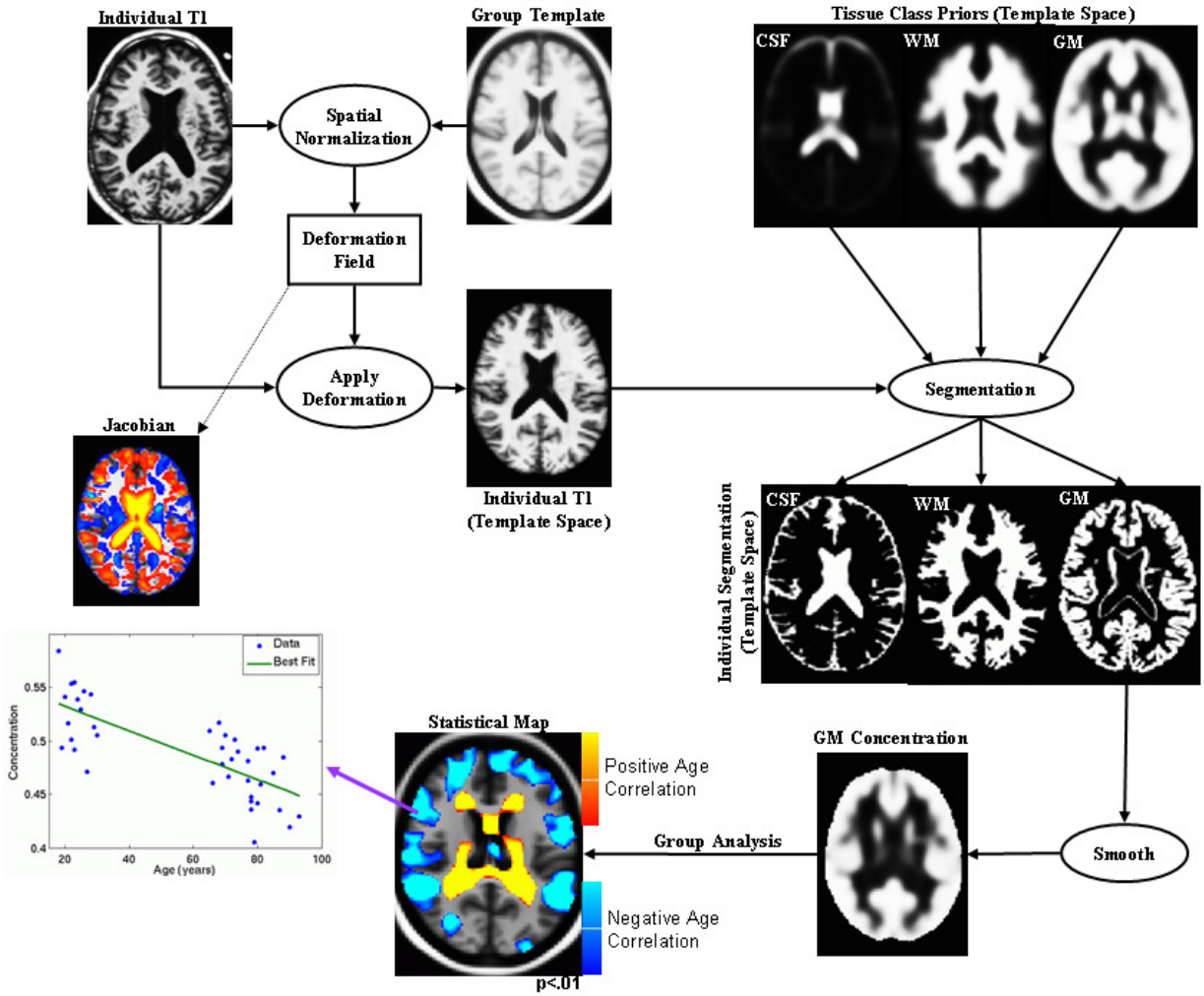


**Figure 1. VBM Processing Stream**

*VBM Interpretation*: In VBM, there are two quantities used to measure morphometric properties: volume and concentration. Volume is fairly intuitive, but concentration requires some explaining. To understand these two concepts, consider a simple study of the effects of gender on total gray matter volume in adults. One performs a volume study by collecting an MRI on males and females, counting the number of gray matter voxels in the brain, and then comparing the gray matter volume across the genders. However, people with bigger bodies tend to have bigger heads and so have bigger brains with more gray matter. This creates a confound in that men tend to have bigger bodies than women. Alternatively, one could divide the gray matter volume by the volume inside the cranium to account for head size. This can be thought of as a "concentration" in that it is the amount of gray matter per unit of intracranial volume. This would then be a concentration study.

This idea can be taken to a slightly smaller scale. Instead of whole brain gray matter, consider a study of the effects of aging on hippocampal volume in adults. Again one would collect MRIs on a population and segment hippocampus to compute its volume. Using the volume metric, one would

correlate the hippocampal volume with age. One could also perform a concentration study by dividing the hippocampal volume by intracranial volume. Alternatively, one could compute another concentration metric by segmenting the medial temporal lobe (MTL, the lobe where the hippocampus is located) and dividing by the MTL volume. This could be used, for example, in the case where one believed that the size of the hippocampus was changing relative to the size of the MTL. In VBM, this idea is extended to an even finer scale. The concentration *at a voxel* is the volume of the gray matter in a neighborhood around that voxel divided by the volume of the structures within a larger region around that voxel. The size of the neighborhood and region are dependent upon parameters set during the smoothing and spatial normalization processes.

Selected VBM Applications: aging (8), schizophrenia (9), Alzheimer's disease (10), multiple sclerosis (11), semantic dementia (12), autism (13), genetics (14), Huntington's disease (15), meditation (16).

VBM Software: Statistical Parametric Mapping (SPM, www.fil.ion.ucl.ac.uk/spm) using the VBM toolbox (dbm.neuro.uni-jena.de/vbm). FMRIB Software Library (FSL, www.fmrib.ox.ac.uk/fsl).

**Surface-based Analysis (SBA)**: In SBA, one derives morphometric measures from geometric models of the cortical surface. There are several implementations of SBA. The one discussed here follows the FreeSurfer (surfer.nmr.mgh.harvard.edu) stream (17,18). Others include Brain Visa (brainvisa.info), CARET (brainvis.wustl.edu/wiki/index.php/Main_Page), and Brain Voyager (brainvoyager.com). Like VBM, the input to SBA is a high-resolution T1-weighted MRI (Figure 2A). The first step of SBA is the extraction of the cortical surface (see Figure 2). *Cortex* is the outer layer of the brain and has an inherent 2-dimensional structure. Figure 2B shows a coronal slice displaying two surfaces. The yellow line is the surface boundary between cortical white matter and cortical gray matter known as the *white surface*; this represents the inner boundary of cortex. The red line is the boundary between the gray matter and dura and/or CSF; this is referred to as the *pial surface*. The cortex is modeled as a *surface model* which is a mesh of triangles as shown in Figure 2D. Each triangle is known as a *face*. The place where the corners of the triangles meet is called a *vertex*. The parameters of the model are the coordinates (i.e., the X, Y, and Z) at each vertex. These coordinates are determined from the MRI during the extraction process. Once the coordinates of each vertex are known, the surface can be rendered as a surface embedded in 3D as is shown in Figure 2C. There are many manipulations that can be applied to the surface. For example, the surface can be *inflated* as shown in Figure 2E. Inflation is a process of unfolding the surface so there is no area hidden behind a fold; it is similar to unfolding a paper bag that had been wadded into a ball.

Knowledge of the coordinates also allows one to compute many morphometric measures. For example, the *surface area* of cortex can be computed by summing up the areas of the triangles. The distance between the white and pial surfaces gives a measure of the *cortical thickness* as shown in Figure 2G. Thickness is a direct measure of the amount of gray matter present at each point on the surface (Figure 2H). Like VBM's gray matter concentration, thickness can be used in a group analysis to track changes associated with age and disease process. Another metric is *curvature,* which is a measure of how sharply cortex is folded at each point as shown in Figure 2F. In this figure, gyri are green and sulci are red. Curvature is a direct measure of the folding pattern of cortex. The surface can be *morphed* into a sphere as shown in Figure 2I. This type of display clearly shows the 2D nature of the surface as each vertex can be localized with only two *spherical coordinates* (longitude and latitude). The curvature on the sphere is important for surface-based spatial normalization.

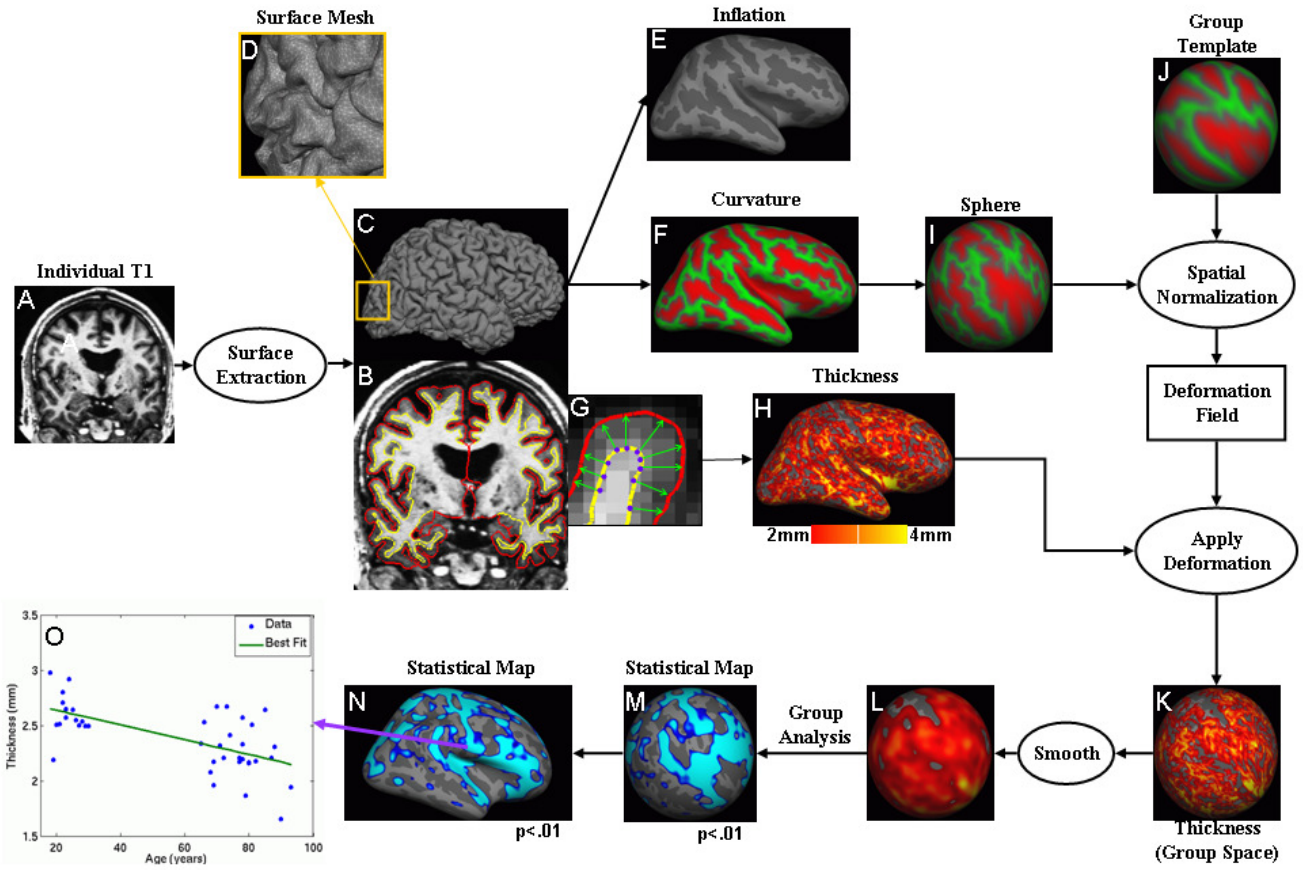


Figure 2: Surface-based analysis processing stream.

*Surface-based Spatial Normalization and Group Analysis*: as with volume-based analysis, surface-based measures need to be aligned across subjects to perform a group analysis. For VBM, this was performed by adjusting the 3D volume coordinate of a voxel so as to best match MRI intensity across subjects. For SBA, the process is similar except that the 2D spherical coordinate of a vertex is adjusted so as to best match the curvature across subjects. Aligning the curvature aligns the *folding patterns* (i.e., gyri and sulci). The motivation for this is that cortical function often follows the folding patterns (19). As with VBM, the SBA spatial normalization is non-linear, meaning that parts of the surface may be compressed or stretched in order to match the curvature better. Once the spatial normalization has been computed, it is applied to the thickness data of each subject to map it into a common group space (something like Talairach or MNI space but on the surface) as in Figure 2K. This allows the thickness to be compared across subjects at homologous points on cortex. The thickness is then smoothed and fed into a group analysis along with the thicknesses from other subjects. Figures 2M, 2N, and 2O show the results of an aging analysis using the same data from the VBM study in Figure 1.

Selected SBA Applications: Huntington's disease (20), schizophrenia (21), multiple sclerosis (22), animal phobia (23), meditation (24), genetic influences (25), ADHD (26), Polymicrogyria (27), autism (28), aging (29), Alzheimer's disease (30).

Software: FreeSurfer (surfer.nmr.mgh.harvard.edu), Brain Visa (brainvisa.info), CARET (brainvis.wustl.edu/wiki/index.php/Main_Page), Brain Voyager (brainvoyager.com).

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