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# A Study Of Status Of Brain Morphometry Analysis In Neuroimaging

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**ABSTRACT**

Computational neuroanatomy is an emerging field of powerful applications in neuroscience which promises an automated methodology to characterize neuroanatomical configuration of structural magnetic resonance imaging (MRI) brain scans. This paper presents the current status of research in brain morphometric analysis. The primary objective of this paper is to help the researchers in understanding the current status of literature in brain morphometry analysis and to help in understanding different tools being currently used and different measures of performance for the classification tool.

**Keywords:** Neuro imaging, Brain Morphometry, Voxel-based Morphometry, support vector machines.

## 1 INTRODUCTION

The human body is an incredibly complex system. Acquiring data about its static and dynamic properties yields massive amounts of information. The use of images is the most effective way to manage, present and interpret the vast quantities of that information in the clinical medicine and in the supporting biomedical research. Magnetic resonance imaging (MRI) is an important diagnostic imaging technique for the early detection of abnormal changes in tissues and organs. It possesses good contrast resolution for different tissues and has advantages over computerized tomography (CT) for brain studies due to its superior contrast properties. Therefore, the majority of research in medical image segmentation concerns MR images. Anatomical segmentations of structural images of the human brain can be used for a plethora of purposes. A principal motivation is to understand the impact of neurodegeneration, trauma, epilepsy and other conditions on the brain's macroscopic

structure. Such understanding leads to morphometric descriptors with the potential to serve as biomarkers for the diagnosis and monitoring of brain disease. Beyond the realm of morphometric analysis, individual anatomical segmentation is frequently used in the analysis of functional imaging data, e.g. to precisely locate areas of hypo or hyper metabolism within the subject's own anatomical reference frame. Anatomical segmentation also enables studies of regional connectivity based on diffusion tensor imaging.

The morphometric methods relate to ways of statistically identifying and characterizing structural differences among populations for finding correlations between brain shape and, for example, disease severity. A large number of approaches for characterizing differences in the shape and neuroanatomical configuration of different brains have recently emerged due to improved resolution of anatomical human brain scans and the development of new sophisticated image processing techniques. The morphometric analysis of magnetic resonance images (MRI) of the brain has become a widely used approach to investigate neuroanatomical correlates of both normal brain development and neurological disorders. Studies of brain shape have been carried out by many researchers on a number of different populations, including patients with schizophrenia, autism, alzheimer, dyslexia and Turner's syndrome. In the analysis of medical images for computer-aided diagnosis and therapy, segmentation is often required as a preliminary stage. Medical image segmentation is a complex and challenging task due to the intrinsic nature of the images. The brain has a particularly complicated structure and its precise segmentation is very important. Many image processing techniques have been proposed for brain MRI segmentation, most notably thresholding, region-growing, and clustering. Since the distribution of tissue intensities in brain images is very complex, it leads to difficulties of threshold determination. Therefore, thresholding methods are generally restrictive and have to be combined with other methods. Region growing extends thresholding by combining it with connectivity conditions or region homogeneity criteria. Successful methods require precise anatomical information to locate single or multiple seed pixels for each region and together with their associated homogeneity Clustering is also a popular method for medical image segmentation, with fuzzy c-means (FCM) clustering and expectation–maximization (EM) algorithms being the typical methods.

Image segmentation is the most critical stage of data processing, because a good classification is dependent on the features extracted from the segmented images. It plays a crucial role in determining the sensitivity of the entire system. Today several different unsupervised classification algorithms are commonly used to cluster similar patterns in a data set based only on its statistical properties. Especially in image data applications, self-organizing methods for unsupervised classification have been successfully applied for clustering pixels or group of pixels in order to perform segmentation tasks. So in order to enhance the accuracy of any classification tool for automated analysis of better morphology it is imperative for us to design better algorithms and better algorithms invariably should have better segmentation techniques. Automated classification methods are commonly used for the analysis of neuroimaging studies. Several multiresolution approaches have been proposed to

detect significant changes in the brain volume using neighbourhood information. Various computer-aided techniques have been proposed in the past and include the study of texture changes in signal intensity, grey matter (GM) concentrations differences, atrophy of subcortical limbic structures, and general cortical atrophy. Brain image analyses have widely relied on univariate voxel-wise analyses, such as voxel-based morphometry (VBM) for structural MRI. In such analyses, brain images are first spatially registered to a common stereotaxic space, and then mass univariate statistical tests are performed in each voxel to detect significant group differences. However, the sensitivity of these approaches is limited when the differences are spatially complex and involve a combination of different voxels or brain structures. Recently, there has been a growing interest in support vector machines (SVM) methods to overcome the limits of these univariate analyses. These approaches allow capturing complex multivariate relationships in the data and have been successfully applied to the individual classification of a variety of neurological conditions.

Magnetic Resonance Images are examined by radiologists based on visual interpretation of the films to identify the presence of tumor abnormal tissue. The shortage of radiologists and the large volume of MRI to be analyzed make such readings labour intensive, cost expensive and often inaccurate. The sensitivity of the human eye in interpreting large numbers of images decreases with increasing number of cases, particularly when only a small number of slices are affected. Hence there is a need for automated systems for analysis and classification of such medical images. This paper presents a review of literature about how researchers have approached Brain morphometry analysis and some of the tools and measures that are currently being used for the said analysis. The papers also discusses in brief about kind of tools being presently used for brain morphometry analysis and presents an overview about how the performance of the classification should be analyzed.

## 2 REVIEW OF LITERATURE

The majority of structural MRI studies have employed Region of Interest (ROI) or Voxel-based Morphometry (VBM) methods for the analysis of neuroimaging data, to compare groups of patients and groups of controls, and reported deficits mainly in the temporal and prefrontal lobes (Lawrie and Abukmeil, 1998; Meisenzahl et al., 2008), particularly in the superior temporal gyrus (Honea et al., 2005), the medial temporal lobe (Honea et al., 2005; Wright et al., 2000), including the amygdala and hippocampal complex and the parahippocampal gyrus, as well as enlargement of the lateral ventricles (Shenton et al., 2001). Similar structural abnormalities have been detected in groups of patients in the early stages of schizophrenia (Kubicki et al., 2002; Steen et al., 2006). These are less pronounced compared to the established state, suggesting active disease processes around the time of onset, although genetic factors, substance misuse, antipsychotic drug treatment and other factors may be partly responsible (Meisenzahl et al., 2008; Olabi et al., 2011). There are, similarly, replicated gray matter density changes over time in high-risk individuals as they develop schizophrenia, again particularly in the prefrontal and temporal lobes (Job et al., 2005; Pantelis et al., 2003). Moreover, functional MRI studies have examined

differences in function and cognitive ability between schizophrenia and healthy controls, reporting abnormal activation in a network of brain regions, particularly implicating the prefrontal cortex (Meyer-Lindenberg, 2010) and connectivity from it to the rest of the brain (Lawrie et al., 2002).Despite the fact that the univariate methods used in these analyses have delivered quite consistent and interesting results, they suffer, however, from certain limitations. ROI methods are confined to predefined brain regions and cannot capture distributed patterns of neuroanatomical and neurophysiological abnormality across the brain. VBM and other approaches to computational morphometry, on the other hand, require brain averaging and cannot capture individual deviations from the norm. To this end, the scientific community has turned to machine learning in an effort to detect the MRI correlates of clinical relevance and utility. Machine learning methods have already been applied in the analysis and interpretation of functional and structural MRI data (LaConte et al., 2005; Lemm et al., 2011; Pereira et al., 2009), in 'mind reading' paradigms (Cox and Savoy, 2002; Haynes and Rees, 2006), in the classification of cognitive states (Mitchell et al., 2004; Mourão-Miranda et al., 2005), and in lie detection approaches (Davatzikos et al., 2005a). More recently, classification algorithms have been applied to diagnose neurological and psychiatric disorders (Bray et al., 2009; Klöppel et al., 2011; Orru et al., 2012), such as dementia (Davatzikos et al., 2011; Klöppel et al., 2008a; Klöppel et al., 2008b), depression (Fu et al., 2008; Mourão-Miranda et al., 2011) and schizophrenia (Davatzikos et al., 2005b; Fan et al., 2008b; Koutsouleris et al., 2009; Koutsouleris et al., 2011). Multivariate pattern recognition techniques provide the possibility of making inferences about a subject's health status at an individual level and, thus, are well suited for clinical decision making purposes. Over the past years, schizophrenia has been intensively studied using neuroimaging techniques, such as structural and functional magnetic resonance imaging (sMRI and fMRI respectively) in order to identify the neurobiological processes underlying the disorder, with the ultimate scope of developing new diagnostic and therapeutic initiatives. There are now many sMRI and fMRI studies in schizophrenia which implicate a range of structural and functional brain abnormalities (Dauvermann et al., 2013; Lawrie and Abukmeil, 1998; Olabi et al., 2011; Wright et al., 2000), some of which are evident even before disease onset and are predictive of illness (Lawrie et al., 2008; Moorhead et al., 2013).

Brain morphometry methods ultimately aim to extract imaging biomarker information that characterizes structural patterns of changes across groups of subjects, e.g. healthy and diseased. Methods vary in the type of imaging biomarkers they use. In voxel-based morphometry (VBM) from high resolution T1-weighted brain magnetic resonance imaging (MRI) data, imaging biomarkers are derived from processed images such as gray matter concentration maps, that are registered to a reference space in order to enable voxel-by-voxel comparisons across subjects (Ashburner and Friston, 2000). Several thousand voxel biomarkers need to be evaluated if the analysis is performed throughout the whole brain, as is common practice. Voxel-based brain morphometry has proven a valuable exploratory tool to characterize structural changes in various diseases as well as in several aspects of normal development (Mietchen and Gaser, 2009).Several groups have shown that

VBM combined with high-dimensional classification techniques can accurately distinguish AD patients, MCI patients and elderly controls (Liu et al., 2004; Klöppel et al., 2008; Duchesne et al., 2008; Cuingnet et al., 2011; Liu et al., 2012). Automatic voxel-based classification of AD patients vs frontotemporal demented patients has also been shown feasible (Klöppel et al., 2008; Davatzikos et al., 2008). As a natural alternative and complementary approach to voxel based morphometry, however, imaging biomarker information may also be obtained from volumes of specific brain structures of interest (Huppertz et al., 2010; Giorgio and De Stefano, 2013). There is now widespread agreement that medial temporal atrophy, in particular hippocampal atrophy, is a sensitive AD biomarker (Frisoni et al., 2009, 2010; Jack et al., 2011). Note that other biomarkers than voxels and volumes include cortical thickness measurements (Fischl and Dale, 2000; Jones et al., 2000), cortical folding patterns (Mangin et al., 2004), and longitudinal metrics of volume changes (Freeborough and Fox, 1997),, not to mention potential disease biomarkers available from other modalities than T1-weighted imaging. It is not yet clear how accurate fully automated volume-based morphometry (VolBM) can be at predicting disease compared to VBM. Cuingnet et al. (2011) reported hippocampus volume estimation methods that are competitive with whole-brain VBM to detect AD at an early stage. Other studies showed that volumes of medial temporal lobe regions computed using NeuroQuant exhibit statistically significant differences between early AD patients and controls (Brewer et al., 2008) and correlate with clinical scores (Kovacevic et al., 2009). It is sometimes argued that whole-brain voxel-level information is ideal for classification in that it captures the whole pattern of disease induced anatomical changes. In practice, however, high-dimensional classifiers suffer from the so-called curse of dimensionality, which inherently limits their accuracy unless trained from unrealistically large datasets. Moreover, high-dimensional classifiers tend to appear as "black boxes" to clinicians as opposed to rather simple volumetric measures of brain tissue or structure that are well known to be affected by age or disease. The interpretation of voxel-based classifiers in terms of spatial patterns of changes is an open methodological issue (Gaonkar and Davatzikos, 2012).

## 3 BRAIN MORPHOMETRY TOOLS

This section reviews some of the brain morphometry tools being widely used in neuro imaging and analysis.

SPM (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm) is popular neuro imaging analysis software that implements a VBM pipeline. In brief, the pipeline first converts an incoming MR scan into several tissue probability maps, including a GM probability map, using a Bayesian image segmentation algorithm called New Segment. The GM probability map is then spatially smoothed and warped to a reference space to enable voxel-by-voxel comparisons of different subjects. This normalization step involves rescaling the smoothed GM probability values, considered as voxel wise GM concentrations, by the Jacobian determinants of the deformations in order to compensate for spurious volume variations introduced by the warping. In addition, the reference space itself is iteratively optimized from the GM

and WM probability maps of different subjects using the DARTEL algorithm.

FreeSurfer (surfer.nmr.mgh.harvard.edu) is today probably the most widely used software for VolBM. It implements a complex image processing pipeline described which segments an incoming scan in a large number of anatomical structures and subsequently computes corresponding volumes. A current limitation of FreeSurfer is its computational complexity compared to SPM, which may restrict its use in clinical routine. On an up-to-date single-processor PC, the FreeSurfer pipeline typically takes several hours to run for a single scan while SPM takes minutes. Other highly accurate volume extraction methods such as multi-template segmentation methods also require heavy computationals.

The algorithm called MorphoBox is freely available as a web application. One key algorithmic difference with FreeSurfer that enables reduced computation time is that MorphoBox splits the segmentation of anatomical structures into two sequential steps: 1) labeling of total intracranial volume (TIV) voxels in brain tissue (CSF, GM, CSF) similarly to SPM's New Segment except that no atlas-based prior is used at this stage; and 2) brain structure segmentation by combining tissue maps obtained in step 1 with anatomical masks derived from a single subject template via non rigid registration. In FreeSurfer, both steps are collapsed into one step that directly infers structure-wise labels using a local image intensity model.

## 4 EVALUATION OF CLASSIFICATION PERFORMANCE

Diagnostic or predictive accuracy concerns are common in all phases of a Disease Management (DM) program, and ultimately play an influential role in the assessment of program effectiveness. Areas such as the identification of diseased patients, predictive modeling of future health status and costs, and risk stratification, are just a few of the domains in which assessment of accuracy is beneficial, if not critical. Evaluation of diagnostic tests is a matter of concern in modern medicine not only for confirming the presence of disease but also to rule out the disease in healthy subjects. Conventionally, a standard way of describing the accuracy of a diagnostic test is the two-by-two table. This is performed when the test results are recorded as dichotomous outcomes (positive/negative results). Diagnostic tests , with two outcome categories such as a positive test (+) and negative test (–) are known as dichotomous. Two popular indicators of inherent statistical validity of a medical test are the probabilities of detecting correct diagnosis by test among the true diseased subjects (D+) and true non-diseased subjects (D-). For dichotomous response, the results in terms of test positive (T+) or test negative (T-) can be summarized in a 2×2 contingency table (Figure 1). The columns represent the dichotomous categories of true diseased status and rows represent the test results.

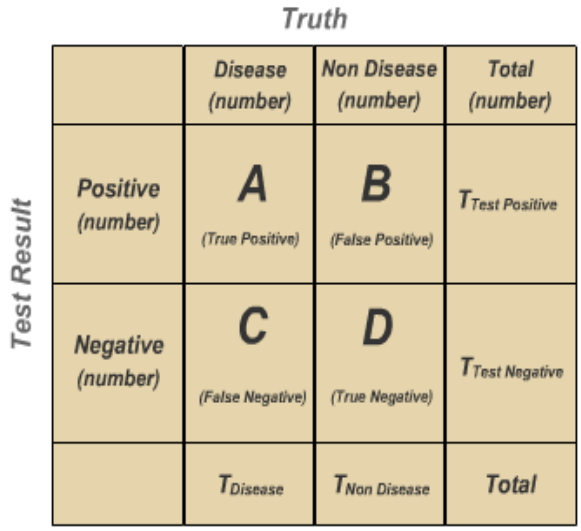


**Figure (1): Diagnostic Test Results in Relation to True Disease Status in a 2×2 contingency Table**

A diagnostic test result has four possible outcomes. They are:

*True Positive (Hit)*: If the test is positive and it is classified as positive, it is counted as True Positive (TP).

- *False Positive (false alarms)*: If the test is positive and it is classified as negative, it is counted as False Positive (FP).
- *False Negative (Misses):* If the test is negative and it is classified as positive, it is counted as False Negative (FN).
- *True Negative (correct rejections)*: If the test is negative and it is classified as negative, it is counted as True Negative (TN).

Any assessments of diagnostic performance require some comparisons of diagnostic decisions with 'truth'.

A convenient global way to quantify the diagnostic accuracy is to express the performance by a single number. The most common global measure is the area under the ROC plot (AUROC/ AUC). AUROC is an effective and combined measure of sensitivity and specificity for assessing inherent validity of a diagnostic test. Maximum AUROC = 1 means that the diagnostic test is perfect in differentiating diseased with non-diseased subjects. The area under ROC is obtained by adding the successive areas of trapezoids instead of collecting ROC points. Trapezoids are used rather than rectangles in order to average the effect between points.

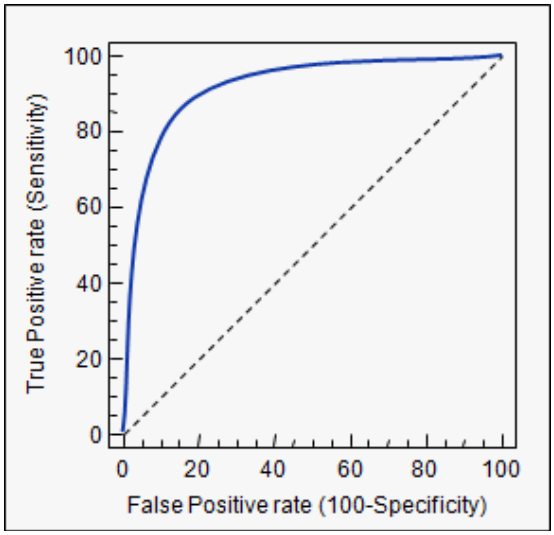


**Figure (2) : ROC curve.**

Deciding a good value for AUC depends on the context of individual problem. A rough guideline is to examine the likelihood ratios. The interpretation of the AUC range is given

**Table 1. Interpretation of AUC range**

| **AUC Range** | **Interpretation** |
|---|---|
| 0.9-1.0 | Excellent |
| 0.80-0.90 | Good |
| 0.70-0.80 | Fair |
| 0.60-0.70 | Poor |
| <0.60 | Fail |

## 5 CONCLUSION

This paper explains the importance of brain morphometry analysis and the need to have an automated analysis tools. The paper presents a detailed review of literature stating current status of research and various approaches being employed by different researchers for analyzing neural images. The overview about current tools being used helps the researchers in identifying the methods, limitations and advantages of tools being currently used for brain morphometry. An insight in to performance measures helps to understand how the results for the analysis tool can be categorized and analyzed.

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