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Automated morphological analysis of magnetic resonance brain imaging using spectral analysis

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ABSTRACT

Analysis of structural neuroimaging studies often relies on volume or shape comparisons of labeled neuroanatomical structures in two or more clinical groups. Such studies have common elements involving segmentation, morphological feature extraction for comparison, and subject and group discrimination. We combine two state-of-the-art analysis approaches, namely automated segmentation using label fusion and classification via spectral analysis to explore the relationship between the morphology of neuroanatomical structures and clinical diagnosis in dementia. We apply this framework to a cohort of normal controls and patients with mild dementia where accurate diagnosis is notoriously difficult. We compare and contrast our ability to discriminate normal and abnormal groups on the basis of structural morphology with (supervised) and without (unsupervised) knowledge of each individual's diagnosis. We test the hypothesis that morphological features resulting from Alzheimer disease processes are the strongest discriminator between groups.

Introduction

Magnetic resonance imaging (MRI) of the brain has become an indispensable tool for diagnosis and research in neuroimaging. Segmentation of brain regions of structural or functional interest via labeling is a requirement for quantitative studies of morphology as it provides a neuroanatomical context to subsequent measurements or forms the basis of those measurements. The classic structural neuroimaging experiment seeks morphological measures which discriminate two sets of subjects grouped on the basis of other information (such as genetics, neuro-psychology, medication, etc). A related experiment first discovers such discriminators from training data and then applies them to classify new subjects. This can form the basis of a diagnostic system (e.g. Klöppel et al., 2008) Techniques employed range from simple manual volumetry (Jack et al., 1997) to sophisticated shape-based measurement and classification techniques (Wang et al., 2007). The alternative framework of "hypothesis-free" analysis exemplified by Voxel Based Morphometry (VBM) (Ashburner and Friston, 2000) is concerned with the detection and significance of local tissue density differences rather than an analysis of their morphological structure. More recent developments such as the incorporation of local measures of volume change into VBM as well as so-called DBM (Deformation-Based-Morphometry) (Ashburner et al., 1998) and TBM (Tensor-Based-Morphometry) (Studholme et al., 2004) have blurred the operational distinction between traditional morphological analysis and voxel-wise methods. While there is on-going debate about the reliability and interpretation of hypothesis-free techniques (Bookstein, 2001; Davatzikos, 2004), morphological analysis of individual structures, identified either manually or with computer-assistance, can be regarded as a practical gold-standard.

Manual segmentation methods requiring expert neuroanatomical knowledge or at least a protocol derived from expert knowledge, have been used for many years, and retain particular importance in the case of structures which are challenging for automatic segmentation techniques such as the hippocampus (Jack et al., 1997; Pruessner et al., 2000) and the entorhinal cortex (Du et al., 2001). Such methods are time-consuming and suffer from errors which are a function of a range of human factors (e.g. inter- and intra-observer variation, practice and temporal drift effects), segmentation protocol details and acquisition details (scan signal and contrast characteristics, patient motion and other artifacts, other scanner calibration and performance issues etc). In parallel there has been a huge amount of research effort devoted to automation, from techniques which simply separate brain from non-brain (Smith, 2002) to those which provide detailed gyral and sulcal labeling (Mangin et al., 2004). Automated techniques have improved immensely but can be computationally demanding, complex, and sensitive to image acquisition details and the presence of abnormal anatomy (Duncan and Ayache, 2000). Nevertheless, the identification of brain structures and/or tissue-classes is a necessary prerequisite to virtually all morphological analyses. The simplest and most common analysis which depends on neuroanatomical labeling is a cross-sectional (single time-point) volumetric comparison. Many authors have investigated higher order measures of shape (Csernansky et al.,

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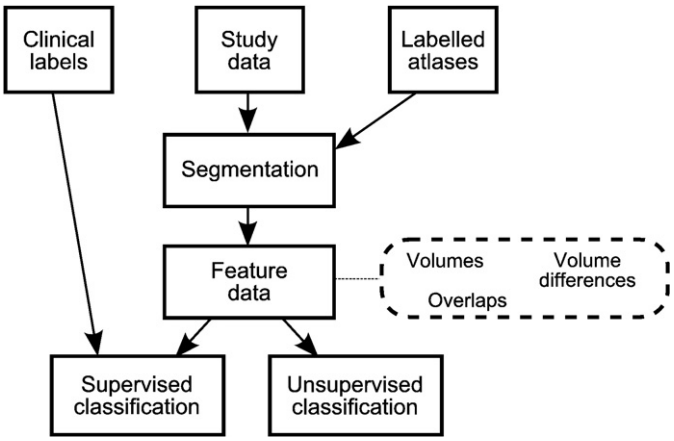

Fig. 1. A schematic illustration of the different components of the analysis pipeline.

1998; Kim et al., 2005; Wang et al., 2006) with varied success and interpretation of results and reproducibility on large cohorts remains difficult.

We have two goals in this work: The first is to move beyond simple volumetry but avoid some of the drawbacks, including computational cost and interpretability, of traditional higher order shape analysis without resorting to intensive manual techniques. The second goal is to partition a group of subjects purely on the basis of observed morphology, i.e. an unsupervised classification approach without prior knowledge of clinical status, and compare the associated discriminators with those derived from a supervised approach. We focus on achieving high-quality structural segmentation using state-of-the-art automated label fusion based segmentation techniques (Aljabar et al, 2007). These techniques select candidate segmentation atlases from a pre-existing database and, by appropriate combination of candidate labels at the voxel level, become robust to many sources of random error including unavoidable anatomical variation, registration error and random labeling errors in the atlas population. The subsequent analysis step uses the overlap of labeled structures as the simplest possible generic indicator of shape similarity beyond volumetric measures. We summarise group morphology by constructing a complete graph where each subject is represented by a node and pairs of nodes are connected with edge-weights that are a function of the morphological similarity (e.g. label overlap) of one or more structures. We apply spectral analysis techniques (von Luxburg, 2007) to the graph to generate indicator vectors which can be used to partition the graph, and therefore the subjects, on the basis of morphological similarity. The resulting unsupervised morphological classification is compared with a supervised linear discriminant analysis which seeks the morphological measure which best separates groups when the clinical status of each subject is known. The analysis framework is generic in that we are at liberty to choose both the methods for generating morphological features and the manner in which we compare those features between subjects.

In this paper we focus on an exemplar application in dementia where departures from normal anatomy are gradual and progressive and where previous studies suggest that label fusion and volumetric and overlap-based similarity measures should be able to describe the morphology present in the cohort. There has been an immense amount of work on characterising the appearance of dementia in structural MRI (Chetelat and Baron, 2003) and thereby measuring disease progression (Fox et al., 2001), detecting early disease (Jack et al., 1997) and distinguishing disease processes from normal ageing (Laakso et al., 1998). There is evidence of subtle pre-clinical global changes in brain morphology exemplified by the work in Fox et al. (1996,1999). The reliable automated morphological analysis of structural changes associated with Alzheimer's disease will add to our understanding of the structural consequences of pathology in this group of diseases. With the advent of treatments which provide symptomatic relief and the prospect of disease-modifying agents, it is increasingly important to characterise and detect Alzheimer's disease by its effect on brain morphology.

Methods

The analysis pipeline has several stages: First, label fusion of registered atlases is used to obtain high-quality segmentations of neuroanatomical structures for each subject. After this, all subjects in the analysis cohort are spatially normalised to a standard reference space for group analysis. Feature data are then extracted from the spatially normalised segmentations for use in either a supervised or an unsupervised classification step. The data extracted are either raw

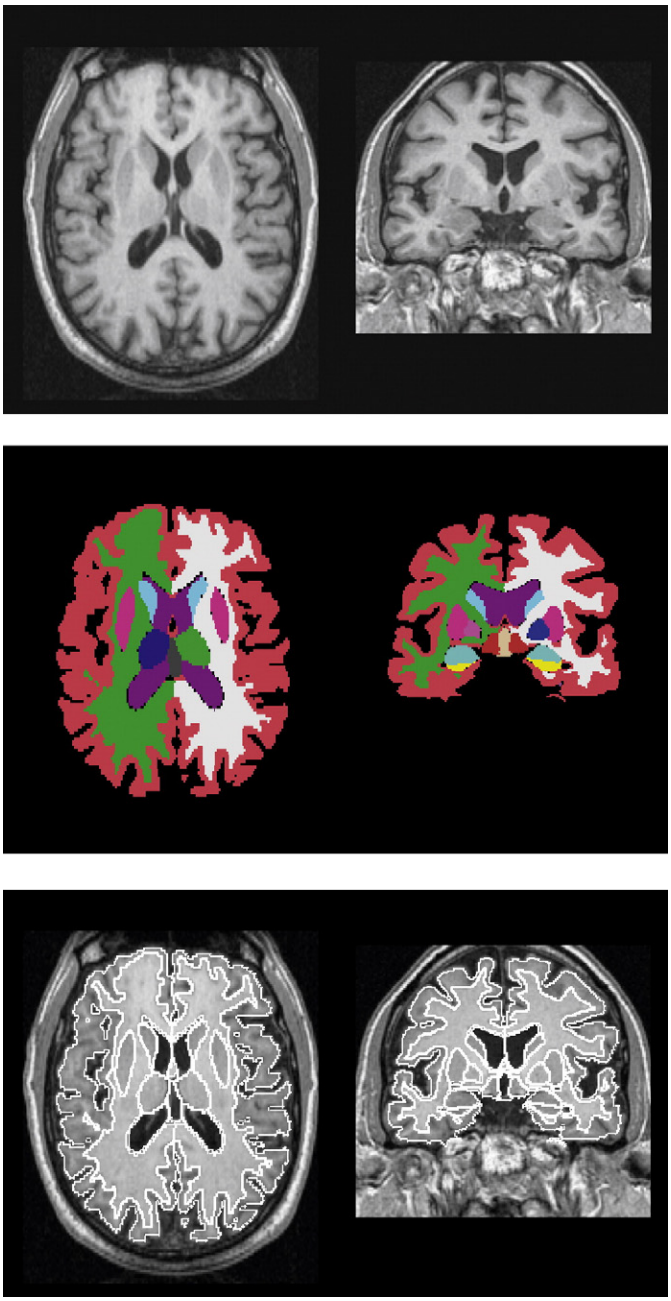

Fig. 2. An example of a label fusion segmentation of a control subject. Top: original scan; Middle: label fusion result; Bottom: label fusion overlay on the original scan.