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Applying tensor-based morphometry to parametric surfaces can improve MRI-based disease diagnosis

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ABSTRACT

Many methods have been proposed for computer-assisted diagnostic classification. Full tensor information and machine learning with 3D maps derived from brain images may help detect subtle differences or classify subjects into different groups. Here we develop a new approach to apply tensor-based morphometry to parametric surface models for diagnostic classification. We use this approach to identify cortical surface features for use in diagnostic classifiers. First, with holomorphic 1-forms, we compute an efficient and accurate conformal mapping from a multiply connected mesh to the so-called slit domain. Next, the surface parameterization approach provides a natural way to register anatomical surfaces across subjects using a constrained harmonic map. To analyze anatomical differences, we then analyze the full Riemannian surface metric tensors, which retain multivariate information on local surface geometry. As the number of voxels in a 3D image is large, sparse learning is a promising method to select a subset of imaging features and to improve classification accuracy. Focusing on vertices with greatest effect sizes, we train a diagnostic classifier using the surface features selected by an L1-norm based sparse learning method. Stability selection is applied to validate the selected feature sets. We tested the algorithm on MRI-derived cortical surfaces from 42 subjects with genetically confirmed Williams syndrome and 40 age-matched controls, multivariate statistics on the local tensors gave greater effect sizes for detecting group differences relative to other TBM-based statistics including analysis of the Jacobian determinant and the largest eigenvalue of the surface metric. Our method also gave reasonable classification results relative to the Jacobian determinant, the pair of eigenvalues of the Jacobian matrix and volume features. This analysis pipeline may boost the power of morphometry studies, and may assist with image-based classification.

Introduction

Computer-assisted diagnostic classification is becoming increasingly popular in neuroimaging, especially given the vast number of features available to assist diagnosis in a 3D brain image. Early diagnosis and treatment of degenerative brain diseases, such as Alzheimer's disease, depends on the ability to identify disease in its earliest stages, when brain changes may be subtle. In addition, there is interest in understanding which brain imaging features are best for diagnostic classification, as well as biomarkers to measure the severity of disease burden. Over the last decade, many methods have been proposed to study the problem of diagnostic classification based on structural magnetic resonance imaging (MRI) (Batmanghelich et al., 2012; Cuingnet et al., 2010, 2011; Fan et al., 2007; Golland et al., 2001; Gutman et al., 2009; Sabuncu and Van Leemput, 2011; Sun et al., 2009a; Vemuri et al., 2008; Xiang et al., 2009; Yushkevich et al., 2003), positron emission tomography (PET) (Chen et al., 2011; López et al., 2011), single photon emitting computer tomography (SPECT) (Fung and Stoeckel, 2007) or a combination of multi-source datasets (Calhoun and Adali, 2009; Chen et al., 2009; Correa et al., 2010; Groves et al., 2011; Jack et al., 2010; Kohannim et al., 2010; Sui et al., 2011; Yang et al., 2010; Yuan et al., 2012a). Surface-based modeling is useful in brain imaging to help analyze anatomical shapes, to detect abnormalities in cortical surface folding and thickness, and to statistically combine or compare 3D anatomical models across subjects (Drury et al., 1996; Fischl et al., 1999; Thompson and Toga, 1996; Vaillant et al., 2007; Wang et al., 2010c, 2011b; Yeo et al., 2008). Many surface-based morphometry studies describe structural differences at the group level, i.e., between different diagnostic groups. More recently, morphometric maps have also been used to classify individual subjects into diagnostic groups (Costafreda et al., 2011; Ferrarini et al., 2008; Kohannim et al., 2010;

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Sun et al., 2009a; Wang et al., 2010b). In one study (Sun et al., 2009a), maps of cortical gray matter density achieved 86.1% accuracy in discriminating psychotic patients from control subjects, in leave-one-out tests. In related work (Ferrarini et al., 2008), the notion of biomarker "nodes" was proposed, i.e. regions on surface meshes that contribute most to diagnostic classification; the authors tested their approach on ventricular surface models from Alzheimer's disease patients and matched controls. Overall, a set of surface-based morphometric features combined with a machine learning algorithm may offer a promising way to improve the performance of computer-assisted diagnostic systems.

An important question for diagnostic classification based on voxel-based or surface-based morphometric maps is which statistics are best to analyze. Statistics derived from anatomical surface models, such as gray matter thickness maps (Thompson et al., 2003, 2005), radial distances (distances from the medial core to each surface point) (Apostolova et al., 2010a, 2010b; Carmichael et al., 2006, 2007a, 2007b, 2007c; Chou et al., 2008, 2009; Morra et al., 2009, 2010; Styner et al., 2004; Thompson et al., 2004a, 2007), spherical harmonic analysis (Gutman et al., 2009; Styner et al., 2005), local area differences (related to the determinant of the Jacobian matrix) (Chung et al., 2008; Davatzikos et al., 1996; Woods, 2003), Gaussian random fields (Bansal et al., 2007), Reeb graphs (another way to compute radial distances) (Shi et al., 2009) have all been applied to analyze the shape and geometry of various brain structures. Surface tensor-based morphometry (TBM) (Chung et al., 2008; Davatzikos et al., 1996; Thompson et al., 2000a; Woods, 2003) is an intrinsic surface statistic that examines spatial derivatives of the deformation maps that register brains to common templates, and can help to detect subtle differences in local surface morphometry. In recent studies (Wang et al., 2008b, 2009a, 2010c, 2011b), surface multivariate TBM (mTBM) was found to be more sensitive for detecting group differences than other standard TBM-based statistics. As a result, here we decided to use mTBM statistics as the surface statistics to be included in a diagnostic classifier.

Three-dimensional statistical maps can detect consistent local differences in anatomical surfaces. But, when they are applied to classification, the feature dimension is usually much larger than the number of subjects in the sample being analyzed — the "high dimension/small sample size problem". When a vast number of variables are measured from a small number of subjects, it is often possible to divide the subjects into groups based on the observed features, but the resulting classification rules may generalize poorly to new observations. To select the most useful features, feature reduction can be beneficial. Feature selection approaches are widely used in machine learning, (e.g. Fan et al., 2005; Guyon et al., 2002; Kuncheva and Rodríguez, 2010; Stearns, 1976). Even so, most methods still generate very large numbers of features, making it difficult to state intuitively why features are being used to make biological inferences. To address this, *sparse learning* methods have been proposed to select the most biologically germane features (Friedman et al., 2008; Tibshirani, 1996). Sparse learning methods enjoy strong theoretical properties (Candès and Wakin, 2008; Donoho, 2006) and are receiving increased attention in many application areas (Beck and Teboulle, 2009; Candès et al., 2006; Figueiredo et al., 2007; Wu et al., 2009). Sparse learning has also been applied in neuroimaging to study genetic influences on the brain (Hibar et al., 2011; Kohannim et al., 2011; Le Floch et al., 2011; Vounou et al., 2010, 2012; Wang et al., 2012a), functional connectivity (Huang et al., 2010; Ryali et al., 2012), and for outcome predictions (Shen et al., 2010; Stonnington et al., 2010; Sun et al., 2009a; Wang et al., 2010a, 2010b, 2011a). In many computer vision, medical imaging and bioinformatics applications, using sparsity as a prior leads to state-of-the-art results (Liu and Ye, 2010; Liu et al., 2010b; Sun et al., 2009a; Wright et al., 2009).

Here we developed a new approach, based on conformal slit mapping (Wang et al., 2009a), multivariate tensor-based morphometry (mTBM), and sparse learning, to identify cortical biomarkers for classification problems. We hypothesized that mTBM might improve the accuracy for analyzing group differences in neuroimaging data, and for helping individual classification, when used with a sparse learning classifier. We tested our hypothesis on a dataset used in a prior work (Thompson et al., 2005): it consists of 42 subjects with genetically confirmed William syndrome and 40 age-matched controls. The point of using Williams syndrome data as a test is that the diagnosis can be verified using a genetic test. Despite many years of research on brain differences in Williams syndrome – finding differences widely distributed in the brain – no one known trait offers powerful group classification on its own. As such, we chose this dataset as an interesting test case, as it may also identify distinctive cortical features for further study.

Fig. 1 summarizes the steps we used to analyze cortical surface morphometry. The cortical surface data was from our prior study (Thompson et al., 2005). With 10 selected landmarks on each cortical hemispheric surface, we computed a conformal mapping from a multiply connected mesh to the so-called *slit domain*, which consists of a canonical rectangle or disk in which 3D curved landmarks on the original surfaces are mapped to parallel lines or concentric slits in the slit domain (Wang et al., 2008a). In this canonical parametric domain, cortical surfaces were matched by a constrained harmonic map (Wang et al., 2007). Multivariate surface statistics were computed from the registered surfaces (Wang et al., 2010c). In one experiment, they were applied to identify regions with significant differences between the two groups. In another experiment, cortical features were fed to a sparse learning method to classify each subject into one of two groups by a leave-one-out test. We also tested other possible surface morphometry statistics to compare them with our multivariate surface statistics. Although the method is illustrated on Williams syndrome data, it is intended to be useful for other disorders as well. Tests on more diverse datasets are reserved for further work.

Subjects and methods

Subjects

We tested our algorithm on data from a prior study by Thompson et al. (2005). Subjects and brain-scanning protocols were used exactly as in the study by (Reiss et al., 2004; Thompson et al., 2005). Exclusion criteria included a history of medical conditions not typically associated with WS, such as epilepsy or other neurological conditions. All WS participants were evaluated at the Salk Institute (La Jolla, CA) as part of a program project on genetics, neuroanatomy, neurophysiology, and cognition. WS diagnosis was genetically confirmed in all cases by fluorescent in situ hybridization, which tested for deletion of one copy of the elastin gene on chromosome 7. A total of 42 subjects with genetically confirmed Williams syndrome and 40 age-matched healthy controls were included in the study. The studying subject age and sex information is listed in Table 1. Wechsler Full-Scale intelligence quotient (IQ) scores were available for 41 of the 42 WS subjects (mean, 68 ± 9; range, 46–83); the untested subject exhibited similar levels of cognitive function on other measures. As in the earlier studies (Reiss et al., 2004; Thompson et al., 2005), healthy control subjects (with no history of major psychiatric, neurological, or cognitive impairment) were recruited at both the Salk Institute and Stanford University. Control subjects were further screened to rule out any history of learning, language, or behavioral disorder. The majority of controls in the study did not have IQ testing performed. Those that did ($n = 16$) had a mean full-scale IQ of 104 with an SD of 12 (range, 86–126). All procedures were approved by the Institutional Review Boards of both institutions, and all participants provided informed consent (and parents or guardians provided written consent where appropriate).

3D MRI brain images were collected using a GE-Signa 1.5 T scanner (General Electric, Milwaukee, MI). The same 3D spoiled gradient