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A multivariate statistical analysis of the developing human brain in preterm infants

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Abstract

Preterm delivery accounts for 5% of all deliveries and its consequences contribute to significant individual, medical, and social problems. The neuroanatomical substrates of these disorders are not known, but are essential for understanding mechanisms of causation, and developing strategies for intervention. In the recent years, multivariate pattern recognition methods that analyse all voxels simultaneously have been proposed to characterise the neuroanatomical differences between a reference group of magnetic resonance (MR) images and the population under investigation. Most of these techniques have overcome the difficulty of dealing with the inherent high dimensionality of 3D MR brain image data by using pre-processed segmented images or a small number of specific features. However, an intuitive way of mapping the classification results back into the original image domain for further interpretation remains challenging. In this paper, we propose the idea of using Principal Components Analysis (PCA) plus the maximum uncertainty Linear Discriminant Analysis (MLDA) approach to classify and analyse MR brain images that have been aligned with either affine or non-rigid registration techniques. This approach avoids the computation costs intrinsic to commonly used covariance-based optimisation processes for solving small sample size problems, resulting in a simple and efficient implementation for the maximisation and interpretation of the Fisher's classification results. In order to demonstrate the effectiveness of the approach, we have used a neonatal MR brain data set that contains images of 93 preterm infants at term equivalent age and 20 term controls. Our results indicate that the two-stage linear framework makes clear the statistical differences between the control and preterm samples, showing a classification accuracy of 95.0% and 97.8% for the controls and preterms samples, respectively, using the leave-one-out method. Moreover, it provides a simple and intuitive method of visually analysing the differences between preterm infants at term equivalent age and the control group, such as differences in cerebrospinal fluid spaces, structure of the corpus callosum, and subtle differences in myelination.

Keywords: Multivariate statistics; Small sample size; Brain images; Preterm infants

1. Introduction

Preterm delivery accounts for 5% of all deliveries and its consequences contribute to significant individual, medical, and social problems. The principle cause of morbidity among survivors is neurological, resulting from the profound effect of preterm birth on the developing brain: half of all infants born at less than 25 weeks have neurodevelopmental impairment at 30 months of age [46] and in less immature infants neuropsychiatric impairments such as Attention Deficit Hyperactivity Disorder, learning difficulties and behavioural problems, are common in the teenage

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years [31,6,4]. The neuroanatomical substrates of these disorders are not known, but are essential for understanding mechanisms of causation, and developing strategies for intervention.

In the last years, the development of computational methods for morphological analysis of the human brain has enabled the automatic characterisation and quantification of neuroanatomical differences between a reference group of images and the population under investigation. Traditionally, such morphological analysis of brain images has been based either on the definition of regions of interest given some a priori hypothesis or on voxel-wise measurements with little prior knowledge [15,2,17,38,1]. However, as pointed out recently by Lao et al. [27], these methodologies have shown practical limitations in their ability to identify new (or subtle) previously unexplored relationships between control and patient populations.

In the recent years, multivariate pattern recognition methods that analyse all voxels simultaneously have been proposed to classify and analyse morphological and anatomical structures of magnetic resonance (MR) brain images [21,24,20,14,16,48,27]. Most of these techniques work in high-dimensional spaces of particular features such as shape or statistical parametric maps and have overcome the difficulty of dealing with the inherent high dimensionality of 3D MR brain image data by using pre-processed segmented images or a small number of features pre-selected from specific image decomposition approaches. However, an intuitive way of mapping the classification results of the whole brain images, which is not tuned to a particular set of variables or features, back into the original image domain for further interpretation remains challenging.

In this paper, we use the general multivariate statistical methodology (PCA + LDA) to identify the most discriminating hyper-plane separating two populations. We describe a novel approach to overcome the well-known instability of the LDA within-class scatter matrix and to increase the computational efficiency of the approach. The approach is not restricted to any particular set of features. The MR brain images are firstly aligned in a common coordinate system. The resulting images are then projected from the original vector space to a lower dimensional space using the well-known PCA. A maximum uncertainty LDA-based (MLDA) approach is applied next to find the best linear discriminant features on that PCA subspace. The MLDA method is based on the maximum entropy covariance selection method developed to improve quadratic classification performance on limited sample size problems [43,45].

In order to demonstrate the effectiveness of the methodology, we have used a neonatal MR brain data set that contains images of 93 preterm infants at term equivalent age and 20 term controls. The results indicate that the two-stage linear statistical framework not only makes clear the statistical differences between the control and preterm samples, showing a leave-one-out classification accuracy of 95.0% and 97.8% for the controls and preterms samples, respectively, but also provides a simple and intuitive method of analysing and visualising the results for further medical interpretation.

2. Spatial normalisation

The spatial normalisation or pre-processing of the data is an important step for any pattern recognition analysis. The purpose of the spatial normalisation stage is to remove any confounding effects from the data that are not relevant for the analysis. In the context of the classification of medical images this means that all images need to be mapped to a common coordinate system so that the voxel-wise features extracted from the images correspond ideally to the same anatomical location across all subjects.

The registration or spatial normalisation step is normally achieved by warping each image to a common reference or template using a variety of registration techniques [23,29,10,9,32,11,41,5,17,44,25,35,47,8,36]. It has essentially two goals: (a) to reduce variability due to size, position and orientation of the brain and (b) to reduce variability due to differences in the brain shape. A classification technique can then be categorized into techniques that deal with differences in brain shape (deformation-based morphometry, [2]) and those that deal with differences in the local composition of brain tissue after removing global shape differences (voxel-based morphometry, [1]). While both approaches require warping of images into a standard reference space using either elastic or fluid registration techniques, they differ fundamentally in the way the features are extracted from the aligned images. In deformation-based morpho-metry the deformation fields themselves are used to study similarities and differences, whereas in voxel-based morphometry these fields are used principally for normalisation. We have used in this work the voxel-based morphometry features.

In our multivariate statistical analysis, we have randomly chosen the image of one term-born infant as reference or atlas. This procedure of choosing one individual brain as atlas is based on our previous results [3] which have demonstrated that the morphometric changes of preterm brain injury are largely independent of the choice of the reference space. In order to map the anatomy of each subject into the anatomy of the atlas we have first applied an affine registration [37] followed by non-rigid registration based on free-form deformations [35]. Both algorithms are based on the maximisation of normalised mutual information as a voxel-based similarity measure.

Each registered image then forms a pattern of interest consisting of n attributes or voxels which is then converted to an n-dimensional feature vector. The goal is to analyse all the data simultaneously rather than feature-by-feature as in the pure deformation- or voxel-based morphometry approaches. For this n-dimensional feature representation to make sense in classification problems, we are making implicitly the assumption that two images that look like one another correspond to two close points in the high