Multivariate methods for discrimination in the analysis of fMRI data

W. S. Rayens[1], Y. Liu[1], A. H. Andersen[2,3], and C. D. Smith[2,4]

[1]Statistics, University of Kentucky, Lexington, KY, United States, [2]Magnetic Resonance Imaging and Spectroscopy Center, University of Kentucky, Lexington, KY, United States, [3]Anatomy and Neurobiology, University of Kentucky, Lexington, KY, United States, [4]Neurology, University of Kentucky, Lexington, KY, United States

Introduction

Multivariate methods are likely to play an important role in the development of fMRI as an imaging biomarker or diagnostic tool to discriminate individuals with disease. Neuroimaging data, however, typically have more features than there are observations on individual subjects, causing problems with the use of linear discriminant analysis. The most common approach has been to use principal component analysis (PCA) as a first step to reduce the dimension of the data. Unfortunately, PCA only identifies gross variability and is not capable of distinguishing among-groups from within-groups variability. Partial least squares (PLS) for dimension reduction in discrimination was developed to circumvent this problem (1). PLS was first used for spatial pattern analysis of functional brain images by McIntosh et al. (2).

Methods

fMRI was used to observe cortical activation during a confrontation naming task in 13 women with high Alzheimer's disease (AD) risk and 11 with low risk, based on family history and apolipoprotein-E4 status (3). The identical scan protocol was repeated in the same subjects after 4 years (4). The EPI time series data were preprocessed using standard methods including slice timing correction, motion correction, spatial smoothing, masking, and image intensity normalization. Multiple linear regression analysis included motion parameter estimates in the baseline model. Fractional signal change values were calculated from each of three runs and collapsed to yield a single measure of activation per voxel per subject and session. Individual subject data were registered across sessions and normalized to Talairach coordinate space with AFNI software using an automated 12-parameter affine transformation. Region-of-interest data were subsequently extracted from 50 non-overlapping brain regions in each hemisphere based on the Talairach atlas of Lancaster & Fox (Fig. 1). ROI data in the left hemisphere were analyzed by linear discriminant analysis preceded by dimension reduction using either PCA, PLS, or oriented partial least squares (OrPLS) methods. OrPLS is a new technique developed by our group (5). When applied in the context of discrimination, within-class structure is accounted for thus enabling the analysis to orient away from within-class covariability.

Results

Figure 1

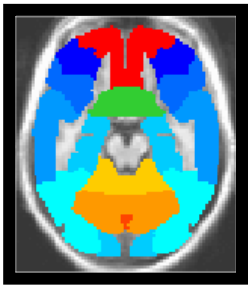

Table 1

Procedure	Preprocessing	Cross-Validated Misclassification Rates		Generalized Distance Baseline/Follow-up
		Baseline	Follow-up	
PCA	Standardized	0.5804	0.3811	0.00859 / 0.26335
PLS	Standardized	0.2902	0.2517	1.83146 / 3.72884
OrPLS	Standardized	0	0	1364360 / 4628538
SAS	Standardized	0.7098	0.2972	51155841 / 145226729

The results are summarized in Table 1. Cross-validated misclassification rates were computed by Lachenbruch's hold-one-out method. The generalized distance is the Mahalanobis distance between risk groups. Results from the PROC DISCRIM procedure in SAS are listed for comparison. All four approaches show the common trend of better separation of the groups at follow-up than at the baseline fMRI scan. This is consistent with our prior voxel-by-voxel analysis, which showed greater activation disparity between risk groups at follow-up (4). As anticipated, PLS performs better than PCA as indicated by lower misclassification rates. Finally, OrPLS is better tuned than ordinary PLS and yields perfect classification of the 24 subjects both at baseline and at follow-up.

Discussion

Our results support multivariate methods for discrimination and the potential of fMRI as a biomarker for diagnosis in individuals with high risk of future AD. In particular, we see the superior performance of OrPLS for dimension reduction in linear discriminant analysis. The OrPLS direction vector indicates which voxels or which linear combination of voxel responses best separates the two groups. In these data, the OrPLS vector implies a brain network which includes not only Brodmann areas 19 and 37 but also the parahippocampus, a region which did not by itself show an effect of risk group in the traditional voxel-based analysis. In the future, analysis of an independent sample will be used to validate this technique.

References

(**1**) M. Barker & W. Rayens, J Chemometrics 17:166-173 (2003). (**2**) A.R. McIntosh et al, NeuroImage 3:143-157 (1996). (**3**) C.D. Smith et al, Neurology 53:1391-1396 (1999). (**4**) C.D. Smith et al, J Neuroimaging 15:271-277 (2005). (**5**) W.S. Rayens & A.H. Andersen, Ital J Appl Statist 15:367-388 (2003).