Application of a fussed lasso logistic regression classifier to the study of corpus callosum thickness in early Alzheimer's disease

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TARGET AUDIENCE: Researchers interested in machine learning or neuroimaging biomarkers of Alzheimer's disease (AD).

PURPOSE: There is great interest in finding neuroimaging biomarkers of AD pathology. We describe a fused Lasso (least absolute shrinkage and selection operator) logistic regression (FLLR) classifier that is able to differentiate patients with very mild/mild AD from normal controls (NC) using their corpus callosum (CC) thickness profile. FLLR associates a cost with the logistic model coefficients' absolute values ($|\beta_j|$) and absolute differences between adjacent coefficients ($|\beta_j - \beta_{j-1}|$). As a result, FLLR produces a classifier with only a small number of non-zero locally constant coefficients.

METHODS:

Subjects: The OASIS cross-sectional dataset[1] contains MRI brain scans from 416 right-handed subjects. Of these, we used 98 healthy NCs aged 60 or above without dementia (CDR=0) and all 98 subjects aged 60 or above with very mild/mild AD (CDR=0.5 or 1). MRI volumes: Scans are 3D sagittal MPRAGE volumes of matrix size: 256×256×128, voxel size: 1×1×1.25 mm^3, TR=9.7 ms, TE=4.0 ms, TI=20 ms, TD=200 ms, flip angle=10°, using a 1.5 T Siemens Vision scanner (Erlangen, Germany). CC Segmentation: A multi-atlas segmentation method using the Automatic Registration Toolbox (ART) module 'yuki' (www.nitrc.org/projects/art) was used to segment the CC. 'yuki' produces 99 non-zero thickness values spaced at equal intervals along a medial axis of the CC (Fig. 1). Statistical analysis: After removing possible confounding effects such as age, sex and intra-cranial volume, we applied the FLLR to the callosal thickness profile. FLLR found locally homogeneous and spatially contiguous regions rather than isolated points since it links neighboring values of a sequence of thicknesses so as to take their correlations into account. FLLR minimizes penalized log-likelihood function of (γ, β) from $\log\frac{p_i}{1-p_i} = d_i\gamma + x_i\beta$ and $log\prod_{i=1}^{n} p_i^{y_i}(1-p_i)^{1-y_i}$,

$$\sum_{i=1}^{n}\{-y_i(d_i\gamma + x_i\beta) + \log(1 + e^{d_i\gamma + x_i\beta})\} + \Omega(\beta;\lambda_1,\lambda_2),$$

where $p_i = \Pr(y_i = 1)$, $y_i = 1$ if the i-th subject is in the AD group, γ's are covariates such as MMSE, x's are callosal thicknesses and $\Omega(\beta;\lambda_1,\lambda_2) = \lambda_1\sum_{j=1}^{t}|\beta_j| + \lambda_2\sum_{j=1}^{t}|\beta_j - \beta_{j-1}|$. Tuning parameters (λ_1, λ_2) were chosen by a five-fold cross-validation method minimizing prediction error.

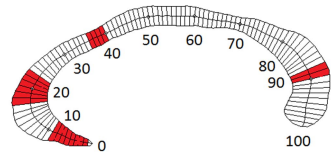

Fig. 1. 99 thicknesses superimposed on a CC. Regions of red are thinner in AD than NC.

RESULTS:

We found sparse but contiguous regions that indicate possible callosal atrophy in AD. FLLR found sections of the genu, rostrum, and splenium in AD (red in Fig. 1) to be proportionally thinner than those in NC. Callosal thickness in these regions combined with the Mini Mental Status Examination scores (MMSE) differentiated AD from NC with 84% accuracy (Table 1).

Est. \ True	NC	AD
NC	89 (87)	22 (27)
AD	9 (11)	76 (71)
total	98	98

Table 1. Classification error rate by 5-fold cross-validation: accuracy=0.84 with 78% sensitivity, 91% specificity. In parenthesis are the numbers of subjects classified based on MMSE only.

DISCUSSION:

The regions identified by this method include parts of the genu and rostrum that are connected to the frontal lobes structures, and a region in the splenium that seems to contain fibers that run to the medial temporal lobes. Both are regions that are implicated in AD[2]. 9 NCs were misclassified as AD. In clinical practice, such subjects would be candidates for further evaluation. 22 ADs were misclassified as normal. Of the 22 false negatives, 20 subjects with CDR=0.5 and 2 subjects with CDR=1 were misclassified as normal. A possibility of misdiagnosis should be considered further in these cases since thinning of the CC appears in the normal range incongruent with these clinical symptoms. Also, subjects with very mild AD (CDR=0.5) may include those with non-AD pathologies or with AD pathology but not yet sufficiently advanced neurodegenration.

CONCLUSION:

FLLR does not require subdividing the CC yet is more specific than analyses based on subdivisions. In addition, it simultaneously provides a predictive model. The classifier in this study is based on two commonly used diagnostic procedures, the MMSE and a structural MRI. The accuracy of a classification using only MMSE was 81% (numbers in parentheses in Table. 1). Our study showed that structural MRI of the CC could be complementary to cognitive measures for the diagnosis of AD. The FLLR model can be easily extended to include other imaging or chemical biomarkers of AD.

REFERENCES:

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