Late Onset Bipolar Disorder Versus Alzheimer Disease

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Abstract The aging of population is increasing the prevalence of some previously rare neuropathological condition, such as the Late Onset of Bipolar Disorder (LOBD). Bipolar Disorder appears at youth or even earlier in life, so that its appearance at sixty years or later is a rare event that can be confused with degenerative diseases such as Alzheimer's Disease (AD). A study designed inby the Hospital Universitario de Alava devoted to find diagnostic differences between these populations, in order to help improve diagnostic accuracy. In this paper we comment on some of the works that we have been carrying on this data.

1 Introduction

Bipolar disorder (BD) is a chronic mood disorder associated with cognitive, affective and functional impairment, often appearing at youth (around age 20 years), or even earlier [13], which has been considered as a risk factor for developing dementia [14, 15]. However, dementia syndrome arising as a result of a history of bipolarity does not correspond to the criteria of Alzheimer's disease (AD) [7]. On the other hand, late onset (i.e. age > 60 years) of BD [6] poses diagnostic quandaries in clinical practice, as it may be difficult to differentiate from behavioral impairment associated with Alzheimer's disease (AD), because both are progressive neuropsychiatric illnesses with overlapping symptoms and neuropathology, including cognitive impairment, emotional disturbances, neuroinflammation, excitotoxicity and upreg-

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ulated brain metabolism [17]. While the established viewpoint considers that AD and BD are distinct and unrelated clinical entities, there is a trend in recent years to question whether there is a link between both disorders based on the overlapping symptoms and the increased successful use of BD well-established treatments to treat dementia [3, 9]. Inflammation and oxidative stress have been found as common pathopshysiological processes underlying AD [1, 19] and BD [8, 10, 11], as well as many other neuropsychological illness, such as depression and mania [5]. These disorders seem to be epigenetically linked to decrease transcriptional activity. It has been observed that in BD and AD patients the frontal cortex exhibits an altered epigenetic regulation related to neuroinflammation, synaptic integrity and neuroprotection. Contributing oxidative stress to the pathogenesis of both diseases through similar mechanisms. New findings identifying the relative role of inflammation and the localization of effects could help in identifying new therapeutic routes for treatment and diagnosis. The study was designed to investigate the feasibility of identifying these effects differentiating LOBD from AD by means of machine learning approaches, either on the clinical variables or imaging data or both. The approach is closely related to predictive CAD systems, which have been proposed to improve the diagnostic accuracy complementing the neuropsychological assessments carried out by expert clinicians [18, 20, 21].

The paper structure is as follows: Sect. 2 contains a description of the materials of the study, including patient population, imaging performed and other variables gathered for the study. Section 3 contains a description of the kind of computational processes tested on these data, with some overall results. Section 4 gives our conclusions.

2 Materials

Patients with memory complaints included in the present study with AD and LOBD were referred to the psychiatric unit at Alava University Hospital, Vitoria from the hospital catchment area. All patients were living independently in the community. Healthy volunteers with an MMSE score of >26 were either recruited from the community through advertisements, or nonrelated members of the patient's families or caregiver's relatives. Selected subjects underwent a standard protocol including: clinical evaluation, a cognitive and a neuropsychological evaluation, and brain imaging (MRI). Cognitive status was screened in all groups with the Mini-mental State Examination (MMSE) and Cambridge cognitive examination (CAMCOG). All patients gave their written consent to participate in the study, which was conducted according to the provisions of the Helsinki declaration. After written informed consent was obtained, venous blood samples (10 mL) were collected from the volunteers, after which all the MRI imaging, mood scales and cognitive tests were performed.

Fifty-seven elderly subjects were included in the present study. The subjects were divided in three groups. The AD group included 20 subjects fulfilling the

NINDS-ADRDA criteria for probable AD. The BD group included 12 subjects fulfilling DSM IV's criteria [14], all of them were bipolar I with a late onset of the disease. The healthy control group included 25 subjects without memory complaints. Subjects with psychiatric disorders (i.e. major depression) or other conditions (i.e. brain tumors) were not considered for this study. Demographic information for AD, BD, HC subjects, respectively: Age mean(SD) years is 78.65 (4.79), 69.55(7.58), 71.65 (8.55). Gender male/female 8/12, 7/5, 12/13. MMSE scores 19 (14–24), 25 (22–28), 29 (27–30). CAMCOG (mean, SD) 58.68 (19.50), 75.36 (11.40), 92.88 (8.14). Medications (n) Lithium (0, 0, 0), Risperidone (3, 3, 0), Quetiapine (1, 3, 0), Olanzapine (0,3,0). Patients were functionally assessed by the Functional Assessment Staging procedure (FAST). Patients with greater functional impairment show increments in cognitive loss. FAST ranks patients in 16 stages. Stage 1 marks subjects without difficulties, while Stage 7(f) marks patients unable to hold up his/her head. The last eleven stages are subdivisions of FAST between the late stages 6 and 7. FAST was administered by the study clinician.

Structural MRI and Diffusion-weighted imaging (DWI) data were obtained on a 1.5 T scanner (Magnetom Avanto, Siemens). Study protocol consists of 3D T1-weighted acquisition (isometric $1 \times 1 \times 1$ mm, 176 slices, TR = 1900 ms, TE = 337 ms and FOV = 256/76 %), a 3D Flair sequence (isometric $1 \times 1 \times 1$ mm, 176 slices, TR = 5000 ms, TE = 333 ms and FOV = 260/87.5%) and diffusion weighted sequence (slice thickness = 5 mm, 19 slices, TR = 2700 ms, TE = 88 ms, matrix 120/100, 3 averages, b = 1000 and 30 gradient directions) allowing fast acquisition minimizing the risk movement artifacts due to the agitated nature of the subjects [12].

Diffusion-weighted imaging (DWI) is an MRI method that produces in vivo MR images of biological tissues weighted with the local characteristics of water diffusion, allowing to study the integrity of the WM fibers [2, 16]. Diffusion is a real-valued second order tensor that can be estimated from the DWI signals obtained using six or more non-collinear gradient directions. The visualization of the diffusion tensor at each voxel site represented in its eigen-vector coordinate system with eigenvalues is called Diffusion tensor imaging (DTI). Scalar measures of water diffusion computed from DTI are the fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and others giving information about the magnitude of the diffusion process at each voxel, but losing directional information. Data preprocessing, except non-linear registration, have been performed using FSL software (http://www.fmrib.ox.ac.uk/fsl/), includes skull stripping, affine and non-linear registration, eddy current correction of DWI, and corregistration between structural and diffusion data for localization.

For each subject in the study, we have measured the following 3 categories of non-imaging variables. In order to reduce circularity effects, variable normalization (standardization) was carried out independently at each cross-validation folder. Neuropsychological variables (NEURO): Cognitive performance has been assessed with a battery of neuropsychological tests covering the following cognitive domains: executive function, learning and memory, and attention. The index for each cognitive domain is the mean of the standardized scores of the tests covering that domain. Biological markers (BIO): We selected biological markers for analysis based on the

relevant BD and AD literature, such as studies on inflammation. After extracting plasma from blood samples inflammatory cytokines Interleukins 1 and 6 (IL-1, IL-6) and Tumor Necrosis Factor (TNFα) were determined by enzyme immunoassay (EIA). Clinical observations (CLIN): The Neuropsychiatric Inventory (NPI) [34] was developed to provide a means of assessing neuropsychiatric symptoms and psychopathology of patients with Alzheimer's disease and other neurodegenerative disorders. The NPI assesses 10 (10-item NPI) or 12 (2-item NPI) behavioral domains common in dementia.

3 Summary Description of Methods

The analysis performed has been in general a process of feature extraction and classification, where we try to identify the most discriminant features as the most significative from the point of view of the biological understanding of the differences between LOBD and AD and providing insights into the mechanisms. The study of the ancillary variables, that is, the ones describing the clinical, neurological and blood biomarkers, has not been very conclusive. In fact, the best classification result is achieved when the clinical variables are used for classification with several state-of-the-art classifiers. Clinical achieves 85 % accuracy in a 10-fold cross-validation procedure, while adding other variables to the feature classification set does not improve results. The biological biomarkers are very poor discriminants (below 70 % accuracy in 10-fold cross-validation), which is consistent with the hypothesis that LOBD and AD share the inflammation as the biological process underlying the symptoms. However, the clinical classification results involve some degree of circularity, because they are directly correlated with the diagnostic decision. For instance, the importance of variables shown in Fig. 1 computed on a CART tree for the discrimination of controls versus LOBD patients, shows that FAST is the most important measure, which is not uncorrelated with the diagnostic decision. On the other hand, the inflammation biomarkers have surprisingly low discriminant power.

Regarding image data, our general procedure has consisted in selecting significant voxels from the volumes which are then used as features for classification. The classification results are some kind of post-hoc analysis providing the value of the selected pixels. We have found that DTI data is most discriminant than anatomical information. In the first works, [3] the selection process was performed on the FA and MD voxel representation, achieving surprisingly high classification, i.e. 100 % accuracy with SVM classifiers in a leave-one-out process. The feature selection process consisted in computing the Pearson's correlation between the categorical variable and the voxel value across subjects. The distribution of the absolute values is used to select the voxels having values above some percentile of the distribution. Changing the percentile provides feature vectors of different sizes. In this regard some circularity of the analysis leads to the high classification results shown in Fig. 2, because we are selecting pixels which are either correlated or anticorrelated with the classification of the volume.

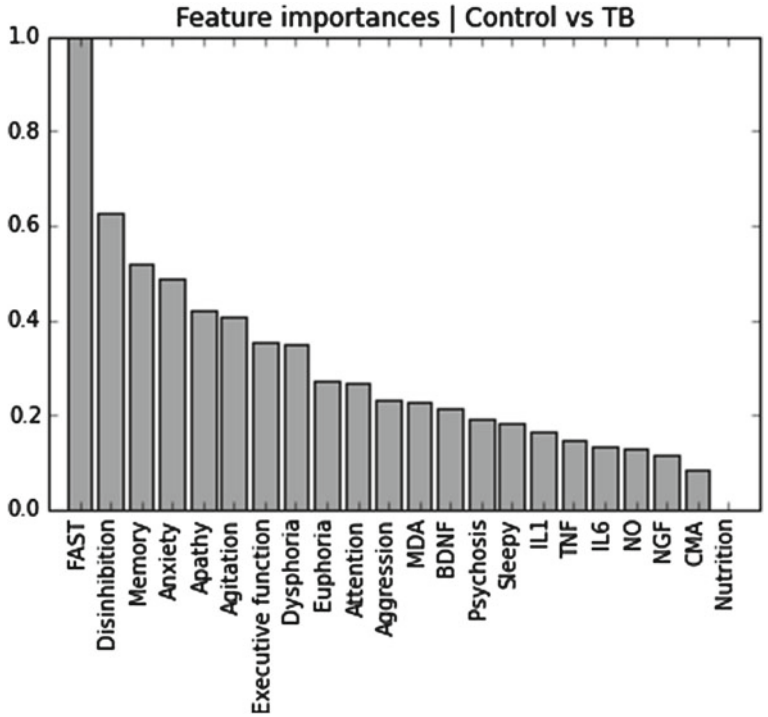

Fig. 1 Importance of ancillary variables in the discrimination of HC versus LOBD

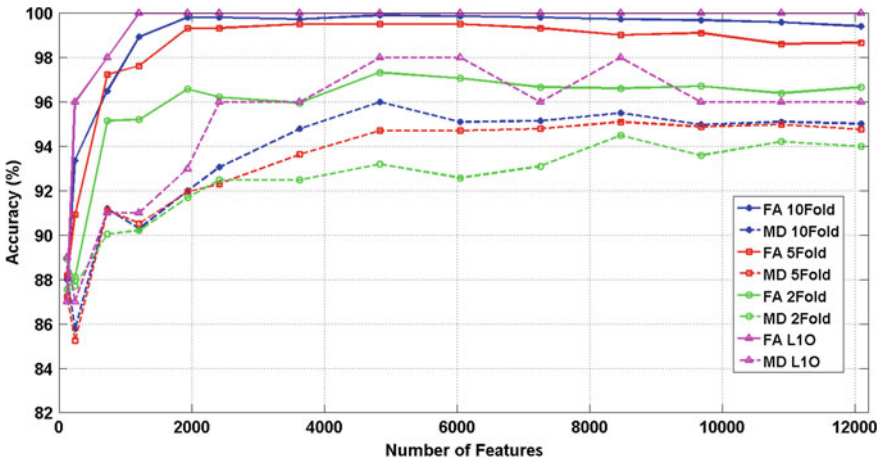

Fig. 2 Average accuracy on FA and MD data in the discrimination of LOBD versus AD reported in [3] for increasing feature vector size and cross-validation number of folders. L1O means Leave-one-out cross-validation

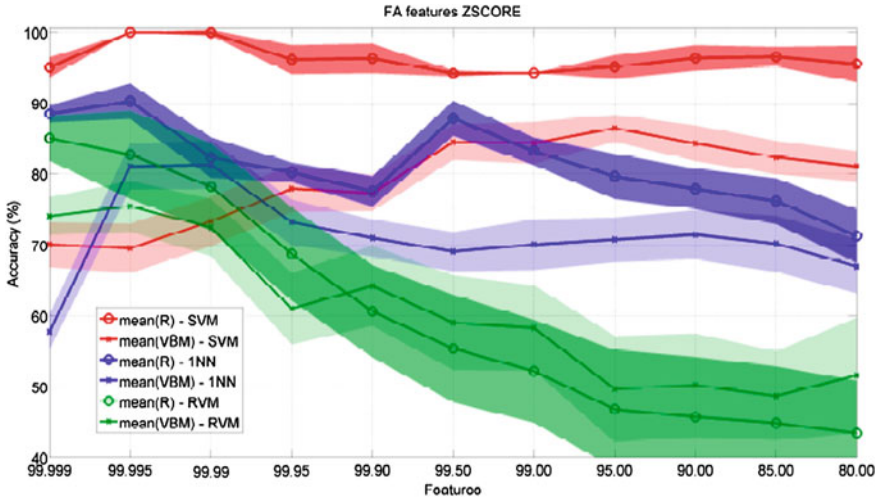

Fig. 3 Comparison of features obtained by VBM and the residuals of lattice autoassociative memories

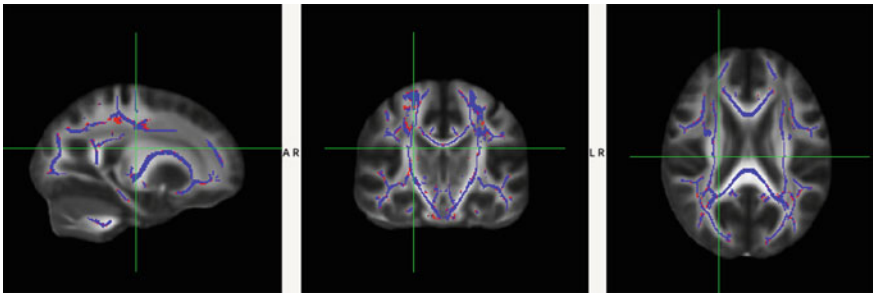

Fig. 4 TBSS preliminary results on the discrimination of LOBD and AD on FA data

Another process consisted in the computation of a lattice associative memory recall residuals as the features for classification [22], the lattice associative memory is built to store complete volumes, so that they can be recalled from the memory, serving also as content addressable storage. The selection of the residuals for classification is performed by Pearson's correlation and compared with other feature extraction. The comparison with feature selection based on a Voxel Based Morphometry (VBM) shows enhanced results, as can be appreciated in Fig. 3. Therefore, diffusion information which is relevant to the integrity of the white matter seems to provide strong clues to the discrimination of LOBD and AD.

Further analysis [4] has been then carried by performing the selection of voxels highly correlated with biomarker variables, by means of the eigenanatomy approach which performs canonical correlation analysis to find sparse eigendecomposition of the data, where the selected voxels can be used as features for classification. That

way we test the feasibility of finding which brain white matter locations are more discriminant. Moreover, blood biomarker can be giving some clue as to what it is happening in the brain at the molecular level. Results find that regions of the brain highly correlated with the oxidative biomarker MDA are the most discriminant, however results are far from the 100 % accuracy.

4 Conclusions and Further Work

The discrimination of LOBD and AD is an interesting problem, because they share many cognitive traits, and biological causes, such as inflammation. In fact, our results on the ancillary variables, i.e. clinical, neurological tests and biological markers are rather disappointing, suggesting the difficulty of the problem at hand. The imaging data seems to be more fruitful, giving good results in some cases and pointing to localization that may give clues for medical research. We are still processing and working on the data. For instance, new results applying track based statistics (TBSS) illustrated in Fig. 4 are on the way, and may give further clues to the understanding of the subtle differences between LOBD and AD.

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