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Predicting dementia development in Parkinson's disease using Bayesian network classifiers

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ABSTRACT

Parkinson's disease (PD) has broadly been associated with mild cognitive impairment (PDMCI) and dementia (PDD). Researchers have studied surrogate, neuroanatomic biomarkers provided by magnetic resonance imaging (MRI) that may help in the early diagnosis of this condition. In this article, four classification models (naïve Bayes, multivariate filter-based naïve Bayes, filter selective naïve Bayes and support vector machines, SVM) have been applied to evaluate their capacity to discriminate between cognitively intact patients with Parkinson's disease (PDCI), PDMCI and PDD. For this purpose, the MRI studies of 45 subjects (16 PDCI, 15 PDMCI and 14 PDD) were acquired and post-processed with Freesurfer, obtaining 112 variables (volumes of subcortical structures and thickness of cortical parcels) per subject. A multivariate filter-based naïve Bayes model was found to be the best classifier, having the highest cross-validated sensitivity, specificity and accuracy. Additionally, the most relevant variables related to dementia in PD, as predicted by our classifiers, were cerebral white matter, and volumes of the lateral ventricles and hippocampi.

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases, affecting about 1% of the population over 60 years old (Dodel, 2004). PD is mainly characterized by motor disorder (and other neuropsychiatric symptoms) and impairment in cognitive function even at early stages of the disease (Caviness et al., 2007; Aarsland et al., 2009). Dementia affects around 40% of PD patients. Its incidence is up to six times that of age-matched controls (Aarsland et al., 2009), rising to 83% after 20-year follow-up (Hely et al., 2008).

It is essential to distinguish between dementia and mild cognitive impairment (MCI) in order to enable earlier therapeutic intervention to prevent cognitive decline in PD. The Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR) (American Psychiatric Association, 1994) defines dementia as an acquired decline of mental functions as regards the patient's previous level of life functioning. Impairment in cognitive function may extend to areas such as abstract thinking, judgement, higher cortical functions, visual spatial skills, motor performance, emotional functions and personality change. The neuropsychological profile of cognitive dysfunction in PD has been broadened by recent clinical (Pagonabarraga et al., 2008), pathological (Galvin et al., 2006), and community-based (Williams-Gray et al., 2007) studies, which suggest that cognitive deterioration is characterized by a frontal-subcortical impairment progressing to dementia when posterior and cortical deficits are present during middle to late stages of PD. Apart from tests of memory alterations, other measures assessing relationships, work and social activities have been applied to assess the severity of cognitive perturbation in daily patient activities (Emre et al., 2007). Dalrymple-Alford et al. (2011) conducted one of the few studies that attempted to characterise MCI in PD patients. Caviness et al. (2007) suggested applying similar criteria as the ones used to characterize MCI in Alzheimer's disease.

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Neuroimaging studies in PD found different levels of cortical thinning when MCI or dementia was manifest (Lyoo et al., 2010). Neuroimaging methods can contribute to a better understanding of the natural course of dementia by identifying regions of the PD brain related to dementia and/or MCI. In turn, this has the potential to facilitate diagnosis of early stage dementia and cognitive impairment (MCI), which is important to ensure timely medical intervention and accurate evaluations of prognosis. Since MRI-based neuroimaging methods are sensitive to anatomical differences associated with cognitive decline in PD, our hypothesis is that the features identified automatically from structural MRI studies (such as cortical thickness and subcortical structures volume) could be applied to develop automated diagnostic support models for this condition. We study which regions of the brain degenerate during the three different phases of PD: cognitively intact (PDCI), with mild cognitive impairment (PDMCI), and with dementia (PDD). In addition to an effort to improve the clinical diagnosis of PDMCI and PDD by measuring cognitive and functional performance, our aim is to improve understanding of the neurodegenerative process in PD through neuroimaging techniques able to quantify morphological changes.

Voxel-Based Morphometry (VBM) (Ashburner and Friston, 2000) and Surface-Based Morphometry (SBM) are two of the most common MRI processing techniques applied to neurodegenerative diseases. VBM is implemented by SPM (Statistical Parametric Mapping) software and quantifies volumetric changes in white and grey matter, as well as cerebrospinal fluid. SBM's cortical topographic measurements quantify, for example, cortical thickness, area, volume and curvature. VBM and SBM together provide complementary variables (features), supplying more information than any classical manual method. Using Freesurfer[1], a software tool that applies SBM and VBM to quantify the volume of multiple subcortical structures, anatomical neurological information is extracted automatically (volume of subcortical structures and cortical thickness). This work analyses the relevance of these measurements for early PDMCI and PDD diagnosis generally.

One of the main contributions of this article is to simultaneously consider different MR volume measurements of subcortical structures and cortical thickness to study PD-related cognitive decline and dementia. As far as we know, this has not been attempted previously. Due to the large number of variables, we aim to automatically identify the most discriminative cerebral regions by combining feature subset selection (FSS) methods with Bayesian network classifiers to study degeneration patterns in PD.

The first MRI study of PD applied regional approaches, selecting one or more regions manually or semi-automatically by tracing brain regions of interest (Apostolova et al., 2010). Selection is built on an a priori hypothesis on the selective involvement of certain brain regions leading to cognitive decline in PD. This hypothesis is based on pathophysiology, neuropsychology, and functional neuroimaging studies related to cognitive decline in PD where some predefined structures have been targeted for investigation. By contrast, this research uses FSS methods, which are robust statistical approaches that take into account all neuroanatomical measures (all brain regions as a whole) to identify the most predictive neuroanatomical markers that explain the course of PD. FSS is able to find those features that need to be analysed for diagnosis of dementia and of cognitive impairment in the early stages (MCI).

There is a growing interest in applying machine learning techniques to medical images, and in particular to brain MRI. Support Vector Machines (SVMs) have been applied to MCI in Alzheimer's disease (AD). Klöppel et al. (2008) and Davatzikos et al. (2008) applied SVMs to MCI diagnosis based on VBM analysis. Using volumetric analysis, Chen and Herskovits (2010) applied Bayesian machine learning algorithms (naïve Bayes, Bayesian-network classifier with inverse-tree structure, decision tree, multilayer perceptrons) and two statistical methods (discriminant analysis and logistic regression) to MCI diagnosis in AD. Duchesne et al. (2009) reported a study on the diagnosis of Parkinsonian syndromes (progressive supranuclear palsy and multiple systems atrophy) versus idiopathic PD with an SVM classifier. Recently, Jubault et al. (2011) performed a study of PD patients without dementia versus a control group, using a corticometric technique to obtain a measure of cortical thickness from VBM and the surface area of local folding. They applied random field theory and the general linear model to model the local cortical thickness or cortical area in combination with age and other variables as linear functions. Despite these studies, there works, there is no evidence of published studies applying classifiers to improve knowledge of MCI and dementia associated with PD based on SBM and VBM analysis. We propose to apply Bayesian classifiers as an accurate automatic decision support system for diagnosis of dementia and of cognitive impairment in the early stages in the following PD patient groups: PDMCI vs. PDCI, PDMCI vs. PDD, PDD vs. PDCI and among all three groups.

2. Methods

2.1. Subjects

The sample consisted of 45 patients (27 males and 18 females), split into the following three groups according to their degree of cognitive decline: 14 PDD (Parkinson's Disease with Dementia), 15 PDMCI (Parkinson's Disease with Mild Cognitive Impairment) and 16 PDCI (Parkinson's Disease Cognitively Intact). All dementia patients selected for this study fulfilled clinical criteria for PDD as defined in Emre et al. (2007).

Inclusion criteria were:

1) Idiopathic PD diagnosis using the London-based Parkinson's Disease Society Brain Bank criteria (Daniel and Lees, 1993). The severity of PD was assessed by subscale III of the motor subset of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987);
2) Cognitive decline diagnosis according to the Clinical Dementia Rating scale (CDR) (Morris, 1997), the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), (American Psychiatric Association, 1994) and the Mini-Mental State Examination (MMSE) (Folstein et al., (1975)). Subjects needed a Clinical Dementia Rating scale score of 1, a Mini-Mental State Examination score of less than 23, and both DSM-IV items to meet dementia criteria. Intact cognition was diagnosed when patients had a CDR score of 0 and MCI with a CDR score of 0.5;
3) Adherence to the Barcelona Hospital de Santa Creu i Sant Pau Parkinson's Disease and Movement Disorders Unit surveillance protocol with follow-up data of at least 2 years;
4) 3T MRI performed within a 4-week time interval after cognitive decline as determined by neuropsychological tests.

The exclusion criteria were: (1) dementia attributed to other systemic diseases/conditions, and (2) concurrent central nervous system malignancy or metastatic disease.

The study was approved by the local research ethics committee, and all subjects gave their informed consent to participate.

Table 1 reports clinical and demographic information, such as mean age, gender, years of education, MMSE and UPDRS-III. Groups were broadly matched for sex and age. There were statistically significant differences in the MMSE ($F(2, 42)=14.50$; $P=0.0001$) and UPDRS Part III: motor subscale ($F(2, 42)=7.50$; $P=0.002$) between PDMCI and PDD classes. After a Bonferroni post-hoc analysis of MMSE, significant differences were found between PDCI and PDD with $P<0.00004$ and between PDMCI and PDD with a $P<0.0001$. A Bonferroni post-hoc of UPDRS Part III was also performed and significant differences were found between PDCI and PDD with $P=0.012$ and between PDMCI and PDD with $P=0.002$.

We built four non-overlapping datasets to study the development of dementia in PD applying supervised classification: PDD-PDMCI, PDMCI-PDCI, PDD-PDCI and

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Table 1
Demographic table of the three groups of Parkinson's Disease of patients. Parkinson's Disease with Dementia (PDD); Parkinson's Disease with Mild Cognitive Impairment (PDMCI); Parkinson's Disease Cognitively Intact (PDCI); Male (m); Female (f); Mini-Mental State Examination (MMSE) and Unified Parkinson's Disease Rating Scale (UPDRS-III).

	PDCI ($n=16$)	PDMCI ($n=15$)	PDD ($n=14$)	ANOVA/χ^2test
Age	73.06 ± 3.82	74.20 ± 5.58	75.71 ± 4.39	$F(2, 42)=1.21$; $P=0.30$
Gender	10(m), 6 (f)	10(m), 5(f)	7(m),7(f)	$\chi^2(2, 42)=0.52$; $P=0.77$
Education (years)	8.50 ± 5.55	9.27 ± 4.13	6.14 ± 4.04	$F(2, 42)=1.76$; $P=0.18$
MMSE	27.50 ± 2.39	27.27 ± 2.31	22.07 ± 4.25	$F(2, 42)=14.50$; $P=0.0001$
UPDRS-III	24.63 ± 6.93	22.14 ± 9.57	35.36 ± 12.12	$F(2, 42)=7.50$; $P=0.002$

PDD-PDMCI-PDCI with 29, 31, 30 and 45 cases, respectively. All datasets contained 112 measurements of brain structures, obtained from a whole-brain Freesurfer analysis.

2.2. MRI acquisition and analysis

MRIs were obtained on a 3T Philips Achieva MR machine at Hospital Santa Creu i Sant Pau in Barcelona, Spain. Whole brain T1-weighted 3D images were acquired in the sagittal plane (TR (repetition time)=6.49 ms, TE (echo time)=3.08 ms, flip angle=8°, matrix of 288×288 mm and voxel size=$0.889 \times 0.889 \times 1.2$ mm) yielding 170 head slices. Images were inspected for artefacts by a dedicated neuroradiologist. Cortical parcellation and subcortical segmentation of images were performed using Freesurfer 4.3.1 running on a cluster (HP-Proliant 2 quad-core machines running Scientific Linux 5), outputting measurements of cortical thickness and volume of subcortical structures (Dale et al., 1999; Fischl and Dale, 2000). First, the image was corrected for intensity inhomogeneities, followed by an affine registration to the Talairach atlas. Afterwards, the skull was stripped (Segonne et al., 2004) and every voxel was classified as white matter (initial surface), grey matter or cerebrospinal fluid (CSF). The initial surface was refined to follow intensity gradients between the white and grey matter and between the grey and CSF surface, forming two division lines (the white matter surface and the pial surface). The distance between the white and the pial surfaces defines the thickness of the cortex at each location (Fischl and Dale, 2000).

The volumes of subcortical structures were quantified as in Fischl et al. (2002, 2004). First, the MRI was affine-registered to the Talairach space specifically designed to be insensitive to pathology and to maximize the accuracy of the final segmentation. Then, initial volumetric labelling and an inhomogeneity correction algorithm were applied to the image, followed by a high dimensional non-linear volumetric alignment to the Talairach atlas. The procedure finished with volume labelling using prior probabilities obtained from a training set (i.e., a set of subjects whose brain (surfaces and volumes) were labelled by hand).

Cortical parcellation was visually assessed and manually corrected according to guidelines by Freesurfer experts. The volume of the subcortical structures was normalized to each subject's Freesurfer eTIV (Total Intracranial Volume) according to Buckner et al. (2004).

Cortical parcellation was performed according to the Desikan–Kiliany Atlas (Desikan et al., 2006)[2].

2.3. Supervised classification

Supervised classification techniques require the definition of a class variable C, where each patient group (PDD, PDMCI, PDCI) has a different value of C. Here we compare classifiers to distinguish the three PD patient types, with the goal of identifying new neuroanatomical biomarkers that can be used to more effectively diagnose dementia and cognitive impairment in the early stages (MCI). Each patient case is defined as a pattern vector of predictive variables representing the brain structure measurements of volume or cortical thickness. We denote each of the n predictive variables as X_i, $i=1,\ldots,n$. We performed four studies, three using a binary variable C to distinguish between pairs of the following patient groups: PDMCI vs. PDCI, PDMCI vs. PDD and PDD vs. PDCI. A fourth study aimed to build a single classifier for diagnosis among the three groups altogether. Four machine learning classification models were examined: naïve Bayes (NB), filter selection naïve Bayes (FSNB), naïve Bayes correlation-based with feature subset selection method (CFS-NB) and support vector machines (SVMs).

Examinations involved two phases: model building (construction of a model capable of assigning each patient case to one of the classes of C (PD, PDMCI or PDD), and the actual classification (where the learned model assigns a class label to unlabelled cases).

[2] The atlases used for the subcortical segmentation are RB_all_with-skull_2008-03-26.gca and RB_all_2008-03-26.gca.

2.3.1. Feature subset selection

Feature subset selection (FSS) methods address redundant or irrelevant features in the database, i.e., features that do not improve the prediction accuracy of classification models (Kohavi and John, 1997). FSS techniques analyse the hidden relationships among features, and identify the most relevant and highly correlated features. This improves the search performance for the best possible classifier. In this article, we apply an FSS method based on a filter approach (Guyon and Elisseef, 2003; Saeys et al., 2007), which focuses on evaluating features by analysing general data characteristics (not taking into account the classifier learning algorithm). We use a univariate filter naïve Bayes (FSNB) classifier and a multivariate filter naïve Bayes (CFS-NB) classifier, which are different from the naïve Bayes classifier.

2.3.2. Classification models

The following is a brief explanation of the Bayesian classifiers and support vector machines (SVMs) applied:

- Naïve Bayes classifier (Minsky, 1961) is a classical classifier based on the assumption that all predictor variables are conditionally independent given the class C. This paradigm always has the same structure: all the predictor variables $X_1, \ldots, X_n$ are included in the model.
- The filter approach to selective naïve Bayes (FSNB) (Blanco et al., 2005) is learned by testing the independence between X_i and C by means of the statistic $2NI(X_i, C)$, where N denotes the dataset size and $I(X_i, C)$ the mutual information between X_i and C variables, which asymptotically follows a chi-squared distribution. Predictive variables that pass the test are used to learn a naïve Bayes classifier. FSNB is able to detect relevant cerebral structures removing irrelevant variables, but it cannot encode dependencies between predictive variables.
- CFS-NB is a naïve Bayes classifier learned with the predictive variables selected by multivariate filter correlation-based feature selection (CFS) (Hall, 1998). CFS-NB is able to detect relevant cerebral structures evaluating the value of a subset of features and taking into account the level of intercorrelation among individual features and the class variable. It assigns higher scores to subsets containing attributes that are highly correlated with the class and have a low correlation with each other (degree of redundancy). In this article we applied the forward selection rank search.
- SVM (Vapnik, 1995) selects a hyperplane with the maximum margin between the predictive variables. Unlike the previous three, SVM is not a Bayesian classifier. In view of its widespread use in neuroimaging reports, however, it is included here for comparison purposes. Here, we apply the sequential minimal optimization algorithm (SMO) (Platt, 1999) to train the SVM classifier with a linear kernel.

Naïve Bayes and SVM perform the classification taking into account all the features (cortical thickness and volume measures). On the other hand, FSNB and CFS-NB apply filter feature selection techniques (FSS) to discard variables that are considered to be irrelevant (also redundant for CFS) without constructing the classification model (Kohavi and John, 1997). In general, naïve Bayes classifiers are straightforward to build and perform relatively well in real problems, but FSNB and CFS-NB models are better for parsimonious and interpretable models.

We used the probabilistic graphical model software ELVIRA (Elvira Consortium, 2002) to generate naïve Bayes and FSNB models. The Waikato environment for knowledge analysis (WEKA) (Witten et al., 2011) was used to generate the CFS-NB model and SVMs with a linear kernel. Bayesian classifiers are usually based on categorical variables. On this ground, we used the method proposed by Fayyad and Irani (1993) to discretise the continuous data. As the SVM model is able to deal with continuous data, however, we standardized the original database before applying the algorithm.

2.3.3. Performance validation and statistical comparison

We applied stratified k-fold cross-validation for all machine learning classifiers, with $k=5$ (Stone, 1974), in order to honestly estimate their classification performance measures.

The k-fold cross-validation is a procedure providing a random partition of examples into k folds. In stratified k-fold cross-validation the original dataset is split into k folds with approximately the same proportions of class values and size per fold. One partition per fold is used as a test data set and the remaining partitions as the training data set. The training data set is used to construct the classification model. This procedure is repeated k times leaving out a different fold for testing each time. The mean of five different accuracies obtained from $k=5$ different classification models is used as the estimation of the accuracy of the model induced from the whole dataset. This model will then be used to classify new patients.

Classifier performance is evaluated using five metrics: accuracy, sensitivity, specificity, true positive predictive value and true negative predictive value. True positives (TP) and true negatives (TN) are defined as the positive and negative cases, respectively, correctly identified by the classifier. The false positives (FP) and false negatives (FN) are defined as the number of cases incorrectly identified as positive and negative, respectively, by the classifier.

Accuracy: percentage of cases correctly identified by the classifier in the study, defined as $(TP+TN)/(TP+TN+FP+FN)$.
Sensitivity: proportion of all the real positive cases correctly classified as positive, defined as $TP/(TP+FN)$.
Specificity: proportion of all the real negative cases correctly classified as negative, calculated as $TN/(TN+FP)$.

The Kruskal–Wallis non-parametric test with $\alpha=0.05$ was applied to compare the performance of the different classifiers, i.e., their accuracies, sensitivities and specificities.

3. Results

Table 2 shows the result of the first three studies analysing pairs of classes (PDD vs. PDCI, PDD vs. PDMCI, PDMCI vs. PDCI), and a fourth three-label classification problem (PDD vs. PDMCI vs. PDCI), illustrating the feasibility of applying four machine learning classifiers (naïve Bayes, FSNB, CFS-NB and SVM). Classifier performance is expressed in terms of mean stratified five-fold cross-validation accuracies, sensitivities, and specificities.

3.1. Classification of PD with and without dementia in PD (PDD vs. PDCI)

The highest accuracy (97%,) was obtained by the CFS-NB classifier, which takes into account only seven predictive variables. These predictive neuroanatomical biomarkers are left white matter, left and right inferior lateral ventricles, left hippocampus, right lateral ventricle, left cerebellum white matter, and right entorhinal (listed in Table 3). According to the non-parametric Kruskal–Wallis test, there was no significant difference between the accuracies of the four classifiers ($\chi^2(3,16)=1.12$; $P=0.77$). No significant differences were found either between sensitivities and specificities ($\chi^2(3,16)=1.27$; $P=0.73$ and $\chi^2(3,16)=0.00$; $P=1.00$, respectively).

3.2. Classification of PD with dementia and mild cognitive impairment (PDD vs. PDMCI)

In this study, the naïve Bayes, FSNB and CFS-NB classifiers obtained the same mean accuracy of 96%, a sensitivity of 92% and a specificity of 100%. Even though the parameters of each classification model did not match, the FSNB and CFS-NB classifiers did signal the same four predictive variables as highly predictive neuroanatomical biomarkers: left cerebral cortex, left caudate, right inferior lateral ventricle and left entorhinal (illustrated in Table 3). The Kruskal–Wallis non-parametric test did not detect any significant differences for accuracies ($\chi^2(3,16)=3.35$; $P=0.34$), sensitivities ($\chi^2(3,16)=2.83$; $P=0.41$) and specificities ($\chi^2(3,16)=6.33$; $P=0.09$).

Table 2
Results of five-fold cross-validated classification model accuracy, sensitivity and specificity for the three pairwise studies (PDD vs. PDCI, PDD vs. PDMCI, and PDMCI vs. PDCI) and for three groups of PD patients (PDD vs. PDMCI vs. PDCI). The Kruskal–Wallis test with 3 degrees of freedom and a significance level $\alpha=0.05$ was applied to detect differences between the accuracies, sensitivities and specificities of the four classifiers.

	Naïve Bayes	FSNB	CFS-NB	SVM	P-value
PDD vs. PDCI					
Accuracy	93.33 ± 9.12	93.33 ± 10.66	97.00 ± 6.74	96.67 ± 10.82	$\chi^2(3,16)=1.12$; $P=0.77$
Sensitivity	92.33 ± 13.57	86.00 ± 14.91	93.33 ± 14.91	93.33 ± 14.91	$\chi^2(3,16)=1.27$; $P=0.73$
Specificity	100.00 ± 0.00	100.00 ± 0.00	100.00 ± 0.00	100.00 ± 0.00	$\chi^2(3,16)=0.00$; $P=1.00$
PDD vs. PDMCI					
Accuracy	96.55 ± 7.85	96.66 ± 10.33	96.55 ± 7.85	79.31 ± 13.84	$\chi^2(3,16)=3.35$; $P=0.34$
Sensitivity	92.33 ± 14.91	92.00 ± 14.91	92.00 ± 14.91	71.00 ± 18.26	$\chi^2(3,16)=2.83$; $P=0.41$
Specificity	100.00 ± 0.00	100.00 ± 0.00	100.00 ± 0.00	87.00 ± 18.26	$\chi^2(3,16)=6.33$; $P=0.09$
PDMCI vs. PDCI					
Accuracy	86.66 ± 13.40	89.00 ± 14.48	90.09 ± 8.40	84.10 ± 15.94	$\chi^2(3,16)=1.44$; $P=0.69$
Sensitivity	86.33 ± 18.24	92.33 ± 15.00	93.00 ± 14.91	81.67 ± 17.00	$\chi^2(3,16)=1.12$; $P=0.77$
Specificity	88.33 ± 16.24	88.33 ± 17.00	88.33 ± 16.24	88.33 ± 16.00	$\chi^2(3,16)=0.31$; $P=0.94$
PDD vs. PDMCI vs. PDCI					
Accuracy	64.44 ± 14.49	70.00 ± 26.66	68.88 ± 16.48	62.22 ± 18.59	$\chi^2(3,16)=1.10$; $P=0.77$
Sensitivity	64.44 ± 14.49	70.00 ± 26.66	68.88 ± 16.48	62.22 ± 18.59	$\chi^2(3,16)=1.10$; $P=0.77$
Specificity	82.22 ± 7.24	85.56 ± 8.42	84.44 ± 8.24	81.11 ± 9.29	$\chi^2(3,16)=1.10$; $P=0.77$

Table 3
Neuroanatomical biomarkers selected by CFS-NB and FSNB classifiers. Shown in parentheses are the labels corresponding to the Freesurfer atlases.

PDD vs. PDCI	PDD vs. PDMCI	PDMCI vs. PDCI	PDD vs. PDMCI vs. PDCI
Left cerebral white matter (2)	Left cerebral cortex (3)	Brain stem (16)	Left thalamus proper (10)
Left hippocampus (17)	Left caudate (11)	Left hippocampus (17)	Left inferior lateral ventricle (5)
Left cerebellum white matter (7)	Right inferior lateral ventricle (44)		Left entorhinal (1006)
Left inferior lateral ventricle (5)	Left entorhinal (1006)		Left fusiform (1007)
Right inferior lateral ventricle (44)			Left caudal anterior cingulate (1002)
Right lateral ventricle (43)			
Right entorhinal (2006)			

3.3. Classification of PD with mild cognitive impairment and without dementia (PDMCI vs. PDCI)

Table 2 shows that the highest accuracy was for CFS-NB with 90% (sensitivity=93%, specificity=88%). The most predictive neuroanatomical biomarkers to distinguish between PDMCI and PDCI groups (as selected by the CFS-NB and FSNB classifiers) were the brain stem and left hippocampus (as illustrated in Table 3). The Kruskal–Wallis non-parametric test reported no significant difference among accuracies ($\chi^2(3,16)=1.44$; $P=0.69$), sensitivities ($\chi^2(3,16)=1.12$; $P=0.77$) and specificities ($\chi^2(3,16)=0.31$; $P=0.94$).

3.4. Classification of PD with dementia, mild cognitive impairment and without dementia (PDD vs. PDMCI vs. PDCI)

We present the results of building general classifiers for three groups of PD patients (PDD, PDMCI and PDCI), where each group is a possible value of a class variable. The FSNB classifier achieved the highest performance (accuracy=70%, sensitivity=71%, specificity=85%). Table 2 shows that the results of these classifiers were not more accurate than the results of classifiers previously applied to pairs of groups.

Table 3 illustrates the neuroanatomical biomarkers selected by FSNB: two volume measures of the left thalamus proper, the right inferior lateral ventricle, and three average thickness measurements that are the left caudal anterior cingulate, the left entorhinal and the left fusiform.

4. Discussion

Our novel automatic procedure for predicting dementia development in PD is based on neuroanatomical biomarkers extracted from whole brain Freesurfer analysis, identifying the most relevant structural brain changes to discriminate between the different PD phases (PDCI, PDMCI and PDD). These changes reflect progressive medial temporal and cortical involvement, which relates to the described pattern of cognitive domain impairment in PD (Pagonabarraga et al., 2008).

One of the main contributions of this study is to simultaneously use different MR volume measurements of subcortical structures and cortical thickness output by a Freesurfer analysis in order to automatically select features from a whole brain MRI without requiring an a priori selection of regions of interest. This was possible by applying FSS techniques on CFS-NB and FSNB classification models.

4.1. Feature selection algorithms

In terms of accuracy no statistically significant differences were found between filter and non-filter classification models. However, the advantages of filtered (FSS) versus unfiltered classification models are first that the FSS models are robust statistical approaches that consider all neuroanatomical measures (all brain regions as a whole) and select the most predictive neuroanatomical markers that explain the course of cognitive decline in PD. At the same time, they maximally differentiate between the groups under consideration. Second, using FSS, we can obtain an accurate and simpler model easily interpretable by clinicians. Finally, FSS methods proved to be a viable way of identifying new neuroanatomical biomarkers and also structural changes in the development of dementia in PD.

Table 3 illustrates that the predictive variables selected by FSS in the three-label class classifier case and in the pairwise studies are different. The neuroanatomical biomarkers selected uniquely by the FSNB three-class classifier are the fusiform gyrus and the anterior cingulate gyrus. However, both study types signalled entorhinal cortex and the inferior lateral ventricle variables. We discuss these brain structures on predictive variables in this section.

In terms of classifier performance for dementia diagnosis in PD (PDD vs. PDCI study), no statistically significant difference was found between Bayesian classifiers and SVM. The CFS-NB obtained the highest accuracy of 97%. These results are not comparable because of the lack of other comparable results in the literature. However, as referenced in Duchesne et al. (2009), their SVM classifier managed to distinguish between Parkinsonian syndromes and idiopathic Parkinson's disease with an accuracy of 91%. CFS-NB, FSNB and naïve Bayes models, which have the highest cross-validated classification performance at 96%, proved useful to discriminate between PDD and PDMCI. Finally, for the diagnosis of PDMCI vs. PDCI, the CFS-NB achieved an accuracy of 90%. Potentially, the results demonstrate that these Bayesian classifiers are a feasible option for building a decision support system for diagnosis of cognitive impairment in the early stages as well as in manifest dementia in PD.

4.2. Predictive variables

According to our filter Bayesian classifier study, the predictive variables involved in the evolution of dementia in PD patients are: left cerebral cortex, left caudate, left entorhinal cortical thickness and right inferior lateral ventricle for PDD vs. PDMCI and left hippocampus and brain stem for PDMCI vs. PDCI. The predictive variables for detecting dementia in PD were: left cerebral white matter, left cerebellum white matter, right entorhinal cortical thickness, left hippocampus, right lateral ventricle, and left and right inferior lateral ventricles from PDD vs. PDCI. All structures lose volume in the PDD vs. PDMCI, PDMCI vs. PDCI, and PDD vs. PDCI discrimination stages, except the inferior lateral ventricles, which gained volume across the spectrum of cognitive impairment in PD. Most likely this reflects the loss of periventricular white matter. These classifier results are consistent with the evidence found in the literature on atrophy in the brain regions of the predictive variables.

Burton et al. (2004) compared PDCI and PDD with Alzheimer's disease, and dementia with Lewy bodies and controls, which is beyond the scope of our study. In their comparison between PD and PDD, they found significant grey matter losses in the fusiform and lingual gyri of the left occipital lobe (Brodmann areas 18 and 19) and less significantly in the same areas on the right hemisphere. They did not study white matter or cerebrospinal fluid (CSF). In our study, the most predictive variables are white matter (left cerebral white matter and left cerebellum white matter) and CSF (right lateral ventricle, right inferior lateral ventricle and left inferior lateral ventricle). In terms of grey matter, only the volume of the left hippocampus and the right entorhinal thickness are significant. These findings are not consistent with Burton et al.'s results. However, these differences are possibly attributable to the fact that their PDD group included only subjects who met DLB (dementia with Lewy bodies) criteria (i.e., patients had additional symptoms of fluctuation and/or hallucinations) and did not include subjects with a progressive steady cognitive decline in the absence of these features. Therefore, as Burton et al. note in the discussion section of their article, their sample was possibly biased against the inclusion of PD subjects who might also have hippocampal changes. They also state that the differences they found in the occipital lobe in PDD were contrary to previous findings.

Few studies about dementia associated with PD included mild cognitive impairment in PD (Apostolova et al., 2010, 2012;

Dalaker et al., 2011). Apostolova et al. (2010) hypothesized that cognitive decline would be associated with hippocampal and caudate atrophy and ventricular enlargement. They found no differences in any of these three variables in the comparison between PDMCI vs. PDCI, but they identified ventricular changes in PDD vs. PDMCI and ventricular and caudate changes in PDD vs. PDCI. They attributed the lack of hippocampal changes to the small size of their sample (their PDMCI group is slightly smaller than ours). Our study suggests that the left hippocampus is one of the most predictive variables for distinguishing between PDMCI vs. PDCI and PDD vs. PDCI, which corresponds to the hippocampal atrophy found in previously published studies (Summerfield et al., 2005; Junqué et al., 2005; Camicioli et al., 2011). We also found evidence of lateral ventricular reduction in PDD vs. PDMCI (right inferior lateral ventricle) and in PDD vs. PDCI (right and left inferior lateral ventricle and right lateral ventricle), where left caudate is a discriminative variable for the classification PDD vs. PDMCI. This conforms to Dalaker et al. (2011), who also identified an enlargement of the left inferior lateral ventricle between PDMCI vs. PDCI. Bilateral enlargement of the lateral ventricles, in combination with hippocampal and entorhinal cortex atrophy, points to a progressive neurodegeneration of medial temporal structures involving both the anterior and posterior aspects of temporo-occipital association cortices. These structures, accounting for the highest discrimination performance between demented and non-demented patients, reinforce the idea that the degeneration of temporal and posterior cortical structures plays a predominant role in the progression to dementia in PD (Pagonabarraga et al., 2008; Galvin et al., 2006; Williams-Gray et al., 2007).

Our PDMCI vs. PDCI study also pointed to the brain stem as a discriminative variable. As part of the brain stem, the substantia nigra is clearly involved in the neurodegenerative process in PD. Jubault et al. (2009) found evidence of brain stem reductions in idiopathic PD, and Behring et al. (1998) found atrophy of the cerebral cortex, caudate nucleus, and substantia nigra. Also eosinophilic intracytoplasmic neuronal inclusions were found in brain stem and cerebellar nuclei in a post-mortem study of a case with a 5-year course of progressive presenile dementia and Parkinsonism.

In PDD vs. PDMCI and PDD vs. PDCI comparisons, Kenny et al. (2008) found reduced entorhinal cortex volumes in patients with PDD compared to controls and PDCI patients.

Finally, our study suggests that white matter is a significant variable in PDD vs. PDCI. Several studies report periventricular white matter lesions in dementia (Román, 2004), as well as white matter volume reduction in PDMCI (Wang et al., 2010).

The differences of discriminating variables found between these two groups are possibly due to the fact that the changes in some regions are predominant in the first phase of the dementia (PDMCI vs. PDCI) while other regions are more affected in a second phase (PDD vs. PDMCI). It is also possible that the lack of a characteristic pattern observed when comparing the changes seen in these two groups is related to the heterogeneity of PDMCI patients and inherent to its definition (Mufson et al., 2012).

Regarding three-label classifiers, no statistically significant difference was found. The FSNB classifier achieved the highest accuracy with 70% and provides highly predictive neuroanatomical biomarkers to describe a pattern across sectional stages of cognitive decline in PD. The neuroanatomical regions selected by this classifier are in temporal lobe areas, entorhinal cortex, thalamus and fusiform gyrus, as well as the anterior cingulate gyrus related to the limbic/paralimbic system. The inferior lateral ventricle and entorhinal cortex are consistent with PDD vs. PDMCI and PDD vs. PDCI studies. The loss of grey matter in the anterior cingulate gyrus may be related to the impairment associated with cognitive strategies in PD (Taylor et al., 1986). Nagano-Saito et al. (2005) found that the thalamus and caudate nucleus are neuroanatomical biomarkers for dementia in PD.

4.3. Differences between two- and three-class classifiers

Our results show three-class classifiers perform no better than classifiers considering just pairs of classes. Additional preliminary tests using classification schemes for PDCI+PDMCI vs. PDD and PDMCI+PDD vs. PDCI did not obtain better results than two-label class classifiers, confirming thus the approach for pairwise classifiers.

Some of the structures selected by the two- and three-label class classifiers are different. The three-label class classifiers select features that are better at simultaneously discriminating the three class labels, whereas the two-label class classifiers are more accurate and determine the most discriminative features at the early (PDMCI vs. PDCI) and later (PDD vs. PDMCI) stages of dementia. For example, the left hippocampus (selected by the PDMCI vs. PDCI classifier) may degenerate mostly at an early stage of dementia in Parkinson's disease, whereas other regions such as the entorhinal cortical thickness play a most important role at a later stage.

5. Conclusions

To the best of our knowledge, this research is the first application of classification models proposed for diagnosing dementia and cognitive decline impairment in the early stages of PD using automatically selected features of cortical thickness and cortical and subcortical region volumes from a whole brain MRI without requiring an a priori selection of regions of interest. This was possible thanks to FSS techniques applying the CFS-NB and FSNB classification models to study PD-related cognitive decline and dementia. This prevents relevant structures for neurological studies from being discarded.

Our results show that the most discriminative neuroanatomical biomarkers for predicting dementia in PD are the ones based on volumetric measures, particularly the enlargement of the lateral inferior ventricles combined with hippocampus and white matter reduction. Of the cortical thickness variables, entorhinal cortex is the most predictive of dementia in PD.

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