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