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Unveiling relevant non-motor Parkinson's disease severity symptoms using a machine learning approach

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ABSTRACT

Objective: Is it possible to predict the severity staging of a Parkinson's disease (PD) patient using scores of non-motor symptoms? This is the kickoff question for a machine learning approach to classify two widely known PD severity indexes using individual tests from a broad set of non-motor PD clinical scales only.
Methods: The Hoehn & Yahr index and clinical impression of severity index are global measures of PD severity. They constitute the labels to be assigned in two supervised classification problems using only non-motor symptom tests as predictor variables. Such predictors come from a wide range of PD symptoms, such as cognitive impairment, psychiatric complications, autonomic dysfunction or sleep disturbance. The classification was coupled with a feature subset selection task using an advanced evolutionary algorithm, namely an estimation of distribution algorithm.
Results: Results show how five different classification paradigms using a wrapper feature selection scheme are capable of predicting each of the class variables with estimated accuracy in the range of 72–92%. In addition, classification into the main three severity categories (mild, moderate and severe) was split into dichotomic problems where binary classifiers perform better and select different subsets of non-motor symptoms. The number of jointly selected symptoms throughout the whole process was low, suggesting a link between the selected non-motor symptoms and the general severity of the disease.
Conclusion: Quantitative results are discussed from a medical point of view, reflecting a clear translation to the clinical manifestations of PD. Moreover, results include a brief panel of non-motor symptoms that could help clinical practitioners to identify patients who are at different stages of the disease from a limited set of symptoms, such as hallucinations, fainting, inability to control body sphincters or believing in unlikely facts.

1. Introduction

Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons mainly in the pars compacta of the substantia nigra [1]. The exact cause of this neuronal death is still unknown. The direct consequence is that the levels of dopamine in the striatal region of the brain drop sharply. This neurotransmitter shortage is the main cause of the disease's classical motor symptoms, such as tremor or hypokinesia [2,3]. In addition to these classical motor symptoms, a number of non-motor symptoms also occur in PD patients, e.g. cognitive impairment, mood disorders, sleep disturbances, gastrointestinal and urinary dysfunction. They are probably related to serotonergic and noradrenergic denervation, as well as dopamine.

The objective of this study is to quantitatively analyze the inner relationships between both motor and non-motor symptoms. To do this, we propose a supervised classification task in which two clinical indexes used for assessing global PD severity are predicted from a combination of non-motor clinical symptoms only. By checking the symptoms most often selected for classification, we will be able to relate different non-motor symptoms to disease progression. The two severity indexes are well established in PD clinical practice. Hoehn & Yahr (HY) staging [4] is a severity index based purely on motor aspects [5], and clinical impression of severity index for PD

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(CISI-PD) staging [6] is based on the assessment of four different domains.

A dataset including information on 410 PD patients has been used. Information on HY and CISI-PD staging and from a battery of tests on non-motor symptoms was measured *a priori* and available for each patient. Clinical severity indexes employ a test for each individual symptom. After all tests have been completed, the whole stage is computed by applying a simple arithmetic operation, usually an addition. To explore beyond this linear constraint, all the individual symptom tests within each non-motor criterion were put together. A selection process was then performed to find which subset best classifies either HY or CISI-PD stages.

We discuss not only the numeric performance but also the relationship of the non-motor symptoms to the neurodegenerative progression of the disease. The discovery of key relationships between changes in non-motor symptoms and the advance of PD could potentially help to identify disease subtypes and make the clinical evaluation faster and more accurate.

The content of the paper is divided as follows. Section 2 extends the rationale behind this study and surveys the state of the art of this new approach to non-motor symptoms in PD. Section 3 details the dataset, PD severity indexes and methodological approaches used throughout the study. Section 4 reports the quantitative and qualitative results. The results are discussed in Section 5, and conclusions and future lines are outlined in Section 6.

2. Rationale and background

The most common PD manifestations are motor symptoms, such as bradykinesia, rigidity, rest tremor, and disorders of gait or posture [2,3]. It is now universally accepted, however, that a wide range of non-motor symptoms are also clear manifestations of PD. Some of these non-motor symptoms may even precede the classical motor manifestations [7] and are related to the degeneration of olfactory and lower medulla structures [8,9].

Although motor symptoms are more psychologically debilitating for PD patients due to public embarrassment, current drugs significantly improve and alleviate these manifestations throughout the disease's course. By contrast, non-motor symptoms are very prevalent [10] and tend to accumulate and increase in severity with disease progression [11]. In the long run, non-motor symptoms become the most important problem for the quality of life of long-term survivors [12,13]. Nevertheless, these non-motor aspects have been kept separate from the motor disorder and have only recently received the attention of clinicians and researchers. Furthermore, even patients have overlooked [14] and failed to declare symptoms to doctors and health professionals [15], thereby compromising treatment.

As discussed in Section 3.2, motor impairment and disability in PD are divided into stages by the HY scale, and this scale is used universally to describe patients and select participants for PD studies, including clinical trials. There is no similar alternative for describing and classifying PD patients taking into account non-motor symptoms. This would be very helpful considering the importance of this aspect of the disease. Following this rationale, the objective of this study is to explore whether such a system would be possible using scores and cutoffs from already valid and established non-motor symptom scales (see Section 3.3 for a detailed description).

State-of-the-art literature in regard to this issue is limited. One of the first papers using computerized models to relate external symptoms and neurogenesis and internal central nervous system flows in PD was [16]. Moving onto classification, Refs. [17–19] predicted general PD prognosis using speech analysis features and a battery of classifiers. All these studies are limited by the number of patients, usually just a few dozen. Regarding other features, Ref. [20] used neuropsychological features in order to find personality markers of early PD diagnosis, i.e. comparing patients and control individuals. This is the classical approach when trying to predict disease from healthy samples. However, as far as we know, our research is the first attempt to analyze and relate motor and non-motor manifestations in PD using machine learning as the research tool.

3. Materials and methods

3.1. Patients

The sample consists of consecutive patients diagnosed as having PD by neurologists with competence in movement disorders, who applied international criteria [21]. Patients that were unable to understand or answer questionnaires or had any comorbidity or disorder interfering with or impeding assessment of PD manifestations were excluded. The database for this study, sourced from an international collaboration [11], was prepared by one of the authors (PMM). The study included 410 patients (males, 61.3%). Age (mean $\pm$ sd) was 64.48 ± 9.91 years and duration of disease, 8.07 ± 5.75 years. Treatment was 81.02% levodopa; 61.36% dopamine agonists (49.5% in combination); 6.44% selegiline; 5.42% rasagiline; and 38.64% other antiparkinsonian drugs. Detailed information is presented in Table 1 listed by patient severity stage.

3.2. Severity indexes

Here we briefly introduce each of the indexes used as class variables in the supervised classification problems. The results reported in Sections 4.3 and 4.4 include outputs considering all three possible stages, or analyzing only the closest two.

- The HY scale is a classical instrument used to categorize patients according to PD stages [4]. HY is based on motor impairment only and recognizes five stages. Despite the original formulation, the HY index is usually reconfigured in three stages, namely `mild`, `moderate` and `severe`. This is a classical adaptation in the PD state of the art [5,22,23], and the translation is straightforward.[1]
- CISI-PD [6]. Known as clinical impression of severity index for PD, CISI-PD extends the evaluated motor symptoms criteria to more complex aspects like the patients' cognitive state. It records the clinician's global impression of severity, and it is composed of four different items that cover the motor signs, disability issue, possible motor complications and decline in cognitive state. These four criteria are scored on a scale from 0, none, to 6, in the worst cases. The range of values for a patient is thus from 0 to 24. This continuous formulation was categorized into HY-like `mild`, `moderate` and `severe` stages to assure equivalent severity across indexes.

3.3. Non-motor symptom scales

A total of 87 individual tests collected from the following five non-motor scales form the predictor variables of the classification problem. All patients completed all tests, although not all values for all tests could be collected (see Section 3.4). Further details on each individual test are available as *supplementary content*. An introduction to the five non-motor scales follows.

- Scales for outcomes in Parkinson's disease-cognition or SCOPA-COG [22]. This rating scale is the result of the sum of 10 cognitive tests, covering symptoms from various domains, such as

[1] `mild` $\Rightarrow$ HY$\equiv$1 or 2; `moderate` $\Rightarrow$ HY$\equiv$3; `severe` $\Rightarrow$ HY$\equiv$4 or 5.