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Prediction of Parkinson's Disease A Machine Learning Approach

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1. INTRODUCTION

Although Parkinson's disease (PD) is mostly known for its motor symptoms, numerous non-motor symptoms have been reported to occur during the course of the disease. Impulse control disorders (ICDs) are psychiatric disorders characterized by the failure to resist an impulse, and unsuccessful attempts to control specific behaviors. ICDs and related disorders are frequent in PD with a prevalence ranging from 15-20% in cross-sectional studies, an incidence estimated to around 10% per year, and a cumulative incidence reaching almost 50% after 5 years of disease duration in longitudinal studies. PD patients with disease duration greater than 5 years are also subject to these disorders. The four most common ICDs in PD are pathological gambling, compulsive eating, hypersexuality, and compulsive shopping, but other frequent ICDs include punding and hobbyism, and the prevalence of each ICD, in particular pathological gambling, highly varies between different cultures. ICDs are associated with reduced quality of life, strained interpersonal relationships, increased caregiver burden, and require prompt addressing. Several case reports suggest that partial and total discontinuations of dopamine agonist (DA) treatment leads to a resolution of ICDs. Many factors have been associated with ICDs in PD, including socio-demographic, clinical and genetic biomarkers. In particular, men tend to develop more pathological gambling and hypersexuality disorders while women develop more compulsive buying and eating disorders. A younger age has been associated with ICDs in PD in numerous studies. Anxiety, depression, and rapid eye movement (REM) sleep behavior disorders have also been correlated to ICDs.

Dopamine replacement therapy has been shown to be the main risk factor for ICD.

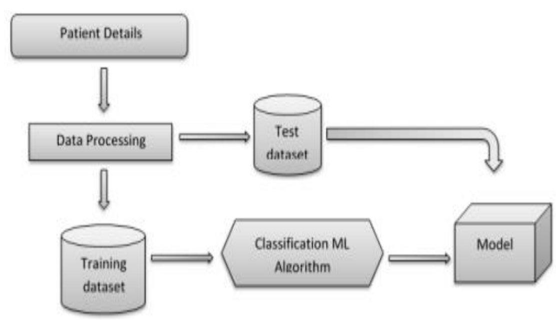

Fig.1: Example figure

Many factors have been associated with ICDs in PD, including socio-demographic, clinical and genetic biomarkers [14]. In particular, men tend to develop more pathological gambling and hypersexuality disorders while women develop more compulsive buying and eating disorders [15]. A younger age has been associated with ICDs in PD in numerous studies [4]. Anxiety, depression, and rapid eye movement (REM) sleep behavior disorders have also been correlated to ICDs. Dopamine replacement therapy has been shown to be the main risk factor for ICD. Both levodopa and dopamine agonists have been associated with ICDs, but with a stronger and higher association with dopamine agonists. Finally, associations between ICDs and several single-nucleotide polymorphisms (SNPs) in dopamine signaling pathway genes have been suggested.

2. LITERATURE REVIEW

Caregiver burden and the nonmotor symptoms of Parkinson's disease:

Parkinson's disease has traditionally been considered as primarily a motor disorder (Chaudhuri & Schapira, 2009). It is clear however that it is the burden of the nonmotor symptomatology which impacts significantly more highly on caregiver burden and quality of life (Benavides, Alberquerque, & Chana-Cuevas, 2013; Martinez-Martin, 2011). As Parkinson's disease advances there is an almost inevitable accrual of nonmotor symptoms alongside the motor aspects of the disease. Patients as their disease progresses require increasing support and this is not infrequently provided by an informal caregiver, most typically a spouse or family member (Martinez-Martin, Forjaz, Frades-Payo, et al., 2007). The role of the caregiver while being emotionally, physically, and psychosocially demanding is also costly and time intensive. The cost of care is typically borne by the family and one survey has estimated that the average caregiver spends an average of 22h per week fulfilling their role. The caregiver has a unique and privileged view of the patient's condition and often due to symptoms of apathy, cognitive impairment, and depression can provide a more accurate appraisal of symptoms and treatment effect. It is therefore imperative that the caregiver is involved, where possible in clinical appointments and treatment decisions. During this chapter the impact of nonmotor symptoms on the caregiver will be highlighted and the need for early and continued collaboration with the caregiver reiterated. The influence of certain key nonmotor symptoms on caregiver burden will be explored in more detail and the narrative will be punctuated with carer reflections as experienced by Jon Hiseman while caring for his wife Barbara, a world renowned saxophonist.

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Impulsive and compulsive behaviors in Parkinson's disease:

Background: Impulsive and compulsive behaviors (ICBs) are a heterogeneous group of conditions that may be caused by long-term dopaminergic replacement therapy (DRT) of Parkinson's disease (PD). The spectrum of ICBs includes dopamine dysregulation syndrome (DDS), punding, and impulse control disorders (ICDs). Contents: We made a detailed review regarding the epidemiology, pathology, clinical characteristics, risk factors, diagnosis as well as treatment of ICBs. Results: The prevalence of ICBs in PD patients is approximately 3–4% for DDS, 0.34–4.2% for punding, and 6–14% for ICDs, with higher prevalence in Western populations than in Asian. Those who take high dose of levodopa are more prone to have DDS, whereas, ICDs are markedly associated with dopamine agonists. Different subtypes of ICBs share many risk factors such as male gender, higher levodopa equivalent daily dose, younger age at PD onset, history of alcoholism, impulsive, or novelty-seeking personality. The Questionnaire for Impulsive–Compulsive Disorder in Parkinson's Disease-Rating Scale seems to be a rather efficacious instrument to obtain relevant information from patients and caregivers. Treatment of ICBs is still a great challenge for clinicians. Readjustment of DRT remains the primary method. Atypical antipsychotics, antidepressants, amantadine, and psychosocial interventions are also prescribed in controlling episodes of psychosis caused by compulsive DRT, but attention should be drawn to balance ICBs symptoms and motor disorders. Moreover, deep brain stimulation of the subthalamic nucleus might be a potential method in controlling ICBs. Conclusion: The exact pathophysiological mechanisms of ICBs in PD remains poorly understood. Further researches are needed not only to study the pathogenesis, prevalence, features, and risk factors of ICBs, but to find efficacious therapy for patients with these devastating consequences.

Prevalence of repetitive and reward-seeking behaviors in Parkinson disease:

We surveyed 297 patients with Parkinson disease (PD) with systematic screens and rigorous definitional criteria. Pathologic hypersexuality lifetime prevalence was 2.4%. Compulsive shopping was 0.7%. Combined with our pathologic gambling data, the lifetime prevalence of these behaviors was 6.1% and increases to 13.7% in patients on dopamine agonists.

Impulse control disorders in Parkinson disease: A cross-sectional study of 3090 patients:

An association between dopamine-replacement therapies and impulse control disorders (ICDs) in Parkinson disease (PD) has been suggested in preliminary studies. Objectives: To ascertain point prevalence estimates of 4 ICDs in PD and examine their associations with dopamine-replacement therapies and other clinical characteristics. Design: Cross-sectional study using an a priori established sampling procedure for subject recruitment and raters blinded to PD medication status. Patients: Three thousand ninety patients with treated idiopathic PD receiving routine clinical care at 46 movement disorder centers in the United States and Canada. Main outcome measures: The Massachusetts

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Gambling Screen score for current problem/pathological gambling, the Minnesota Impulsive Disorders Interview score for compulsive sexual behavior and buying, and Diagnostic and Statistical Manual of Mental Disorders research criteria for binge-eating disorder. Results: An ICD was identified in 13.6% of patients (gambling in 5.0%, compulsive sexual behavior in 3.5%, compulsive buying in 5.7%, and binge-eating disorder in 4.3%), and 3.9% had 2 or more ICDs. Impulse control disorders were more common in patients treated with a dopamine agonist than in patients not taking a dopamine agonist (17.1% vs 6.9%; odds ratio [OR], 2.72; 95% confidence interval [CI], 2.08-3.54; P < .001). Impulse control disorder frequency was similar for pramipexole and ropinirole (17.7% vs 15.5%; OR, 1.22; 95% CI, 0.94-1.57; P = .14). Additional variables independently associated with ICDs were levodopa use, living in the United States, younger age, being unmarried, current cigarette smoking, and a family history of gambling problems. Conclusions: Dopamine agonist treatment in PD is associated with 2- to 3.5-fold increased odds of having an ICD. This association represents a drug class relationship across ICDs. The association of other demographic and clinical variables with ICDs suggests a complex relationship that requires additional investigation to optimize prevention and treatment strategies.

Longitudinal analysis of impulse control disorders in Parkinson disease:

To investigate the longitudinal dose-effect relationship between dopamine replacement therapy and impulse control disorders (ICDs) in Parkinson disease (PD). Methods: We used data from a multicenter longitudinal cohort of consecutive patients with PD with ≤5 years' disease duration at baseline followed up annually up to 5 years. ICDs were evaluated during face-to-face semistructured interviews with movement disorder specialists. Generalized estimating equations and Poisson models with robust variance were used to study the association between several time-dependent definitions of dopamine agonist (DA) use, taking dose and duration of treatment into account, and ICDs at each visit. Other antiparkinsonian drugs were also examined. Results: Among 411 patients (40.6% women, mean age 62.3 years, average follow-up 3.3 years, SD 1.7 years), 356 (86.6%) took a DA at least once since disease onset. In 306 patients without ICDs at baseline, the 5-year cumulative incidence of ICDs was 46.1% (95% confidence interval [CI] 37.4-55.7, DA ever users 51.5% [95% CI 41.8-62.1], DA never users 12.4% [95% CI 4.8-30.0]). ICD prevalence increased from 19.7% at baseline to 32.8% after 5 years. ICDs were associated with ever DA use (prevalence ratio 4.23, 95% CI 1.78-10.09). Lifetime average daily dose and duration of treatment were independently associated with ICDs with significant dose-effect relationships. Similar analyses for levodopa were not in favor of a strong association. ICDs progressively resolved after DA discontinuation. Conclusion: In this longitudinal study of patients with PD characterized by a high prevalence of DA treatment, the 5-year cumulative incidence of ICDs was ≈46%. ICDs were strongly associated with DA use with a dose-effect relationship; both increasing duration and dose were associated with ICDs. ICDs progressively resolved after DA discontinuation.

3.METHODOLOGY

Many factors have been associated with ICDs in PD, including socio-demographic, clinical and genetic biomarkers. In particular, men tend to develop more pathological gambling and hypersexuality disorders while women develop more compulsive buying and eating disorders. A younger age has been associated with ICDs in PD in numerous studies. Anxiety, depression, and rapid eye movement (REM) sleep behavior disorders have also been correlated to ICDs. Dopamine replacement therapy has been shown to be the main risk factor for ICD. Both levodopa and dopamine agonists have been associated with ICDs, but with a stronger and higher association with dopamine agonists. Finally, associations between ICDs and several single-nucleotide polymorphisms (SNPs) in dopamine signaling pathway genes have been suggested. The predictive performance of these factors altogether has been underexplored. Only three studies reported predictions at the patient level. In all three studies, authors trained a logistic regression using clinical and genetic data, and measured its predictive performance using the area under receiver operating characteristic (ROC) curve (ROC AUC). None of these studies had cross-validation or a replication cohort, altering the confidence in the reported performance.

Disadvantages:

1. None of these studies had cross-validation or a replication cohort, altering the confidence in the reported performance.
2. Impulse control disorders (ICDs) are psychiatric disorders characterized by the failure to resist an impulse, and unsuccessful attempts to control specific behaviors.

Our main objective was to predict ICDs from clinical and genetic data using machine learning approaches. We utilized two longitudinal cohorts to train and cross-validate the models on one cohort, but also assess the generalization capability of these models on the other cohort. The objective was to predict the risk of ICDs at the next visit, knowing the clinical history of the patient and their genotyping data.

Advantages:

1. machine learning methods are potentially useful for predicting ICDs
2. Predict the risk of ICDs at the next visit, knowing the clinical history of the patient and their genotyping data.

Fig.2: System architecture

MODULES:

To implement aforementioned project we have designed following modules

- Data exploration: using this module we will load data into system

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- Processing: Using the module we will read data for processing
- Splitting data into train & test: using this module data will be divided into train & test
- Model generation: Model building - SVM, RF, DT, LR, XGBoost, Voting classifier, RNN and GRU. Accuracy calculated
- User signup & login: Using this module will get registration and login
- User input: Using this module will give input for prediction
- Prediction: final predicted displayed

4. IMPLEMENTATION

ALGORITHMS:

SVM: Support Vector Machine(SVM) is a supervised machine learning algorithm used for both classification and regression. Though we say regression problems as well its best suited for classification. The objective of SVM algorithm is to find a hyperplane in an N-dimensional space that distinctly classifies the data points.

RF: A Random Forest Algorithm is a supervised machine learning algorithm which is extremely popular and is used for Classification and Regression problems in Machine Learning. We know that a forest comprises numerous trees, and the more trees more it will be robust.

DT: A decision tree is a non-parametric supervised learning algorithm, which is utilized for both classification and regression tasks. It has a hierarchical, tree structure, which consists of a root node, branches, internal nodes and leaf nodes.

LR: Logistic regression is a Machine Learning classification algorithm that is used to predict the probability of certain classes based on some dependent variables. In short, the logistic regression model computes a sum of the input features (in most cases, there is a bias term), and calculates the logistic of the result.

XGBoost: XGBoost is a popular and efficient open-source implementation of the gradient boosted trees algorithm. Gradient boosting is a supervised learning algorithm, which attempts to accurately predict a target variable by combining the estimates of a set of simpler, weaker models.

Voting classifier: A voting classifier is a machine learning estimator that trains various base models or estimators and predicts on the basis of aggregating the findings of each base estimator. The aggregating criteria can be combined decision of voting for each estimator output.

RNN: Recurrent Neural Networks(RNN) are a type of Neural Network where the output from the previous step is fed as input to the current step. RNN's are mainly used for, Sequence Classification — Sentiment Classification & Video Classification. Sequence Labelling — Part of speech tagging & Named entity recognition.

GRU: The Gated Recurrent Unit (GRU) is a type of Recurrent Neural Network (RNN) that, in certain cases, has advantages over long short term memory

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(LSTM). GRU uses less memory and is faster than LSTM, however, LSTM is more accurate when using datasets with longer sequences.

5. EXPERIMENTAL RESULTS

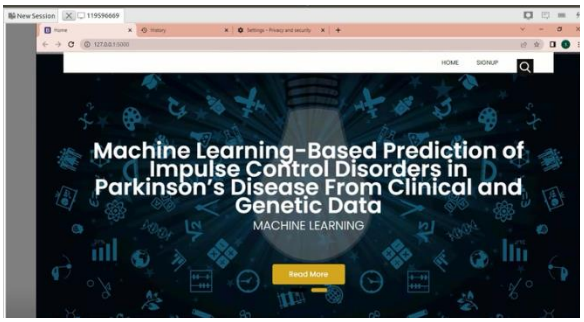

Fig.3: Home screen

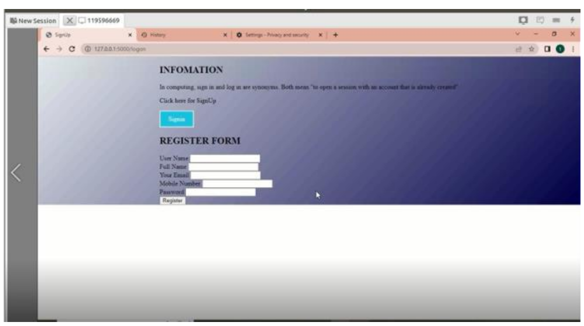

Fig.4: User registration

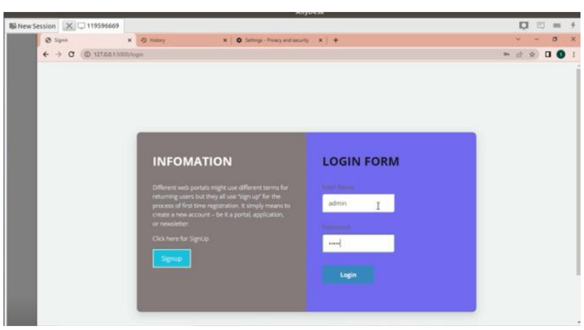

Fig.5: User login

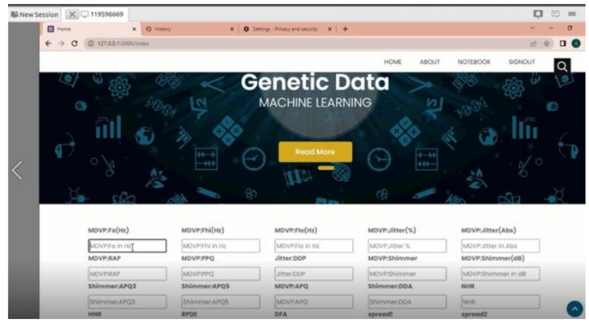

Fig.6: Main page

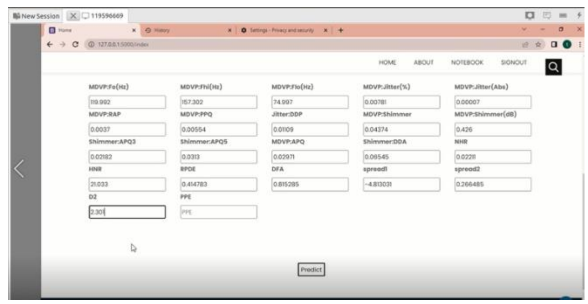

Fig.7: User input

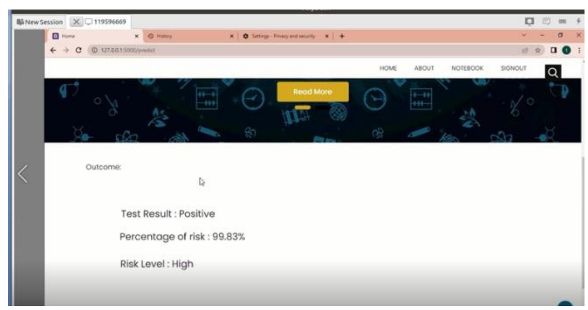

Fig.8: Prediction result

6. CONCLUSION

Our study shows the feasibility of prediction of impulse control disorders in Parkinson's disease. Nevertheless, the improvements obtained compared to a trivial model are not sufficient to support clinical utility at this stage of research. Nonetheless, our study highlights a sound methodology and sets a baseline that future studies can compare to. Further studies including other risk factors and investigating the first onset of ICDs are required to obtain clinically relevant models.

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