Biomarkers Detection of Individual PD Symptoms and Therapeutic Effect Prediction with Machine Learning

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ABSTRACT

Symptoms of Parkinson's diseases are very complex with great individual differences. However, clinical diagnosis of PD now still depends on subjective observation limited to motor symptoms. Furthermore, screening of advantageous therapies to different indications is in short of an objective index. Can biomarkers help us predict individual PD symptoms and treatment effects? This review emphasized individual differences in PD symptoms and in therapeutic effects at first. Then we reviewed potential clinical biomarkers. Finally, machine learning as well as currently popular algorithms was reviewed as a practical tool in biomarkers screening. The review points out that the direction of future studies on biomarker screening is individual differences and robustness, which can be achieved with machine learning.

Abbreviations: PD: Parkinson's Disease; DBS: Deep Brain Stimulation; CFT: Complex Figure Test; LASSO: Least Absolute Shrinkage and Selection Operator; AD: Alzheimer's Disease

Introduction

Parkinson's disease (PD) is the second serious neurodegenerative disease only next to the Alzheimer's disease (AD). Almost 1.7% of the aged more than 65 years old are diagnosed with PD, and the number even reached 4% in groups older than 80 years [1-4]. Symptoms of PD are very complex with great individual differences. There are typical motor symptoms [5, 6] including the static tremor [7, 8], muscle rigidity [9, 10], bradykinesia and postural balance disorder. There are also non-motor symptoms [11-14] including various cognitive dysfunction [15] (including the verbal disorder, memory loss etc.), anxiety, depression, pain and widely existed sleep disorders, which finally lead to death. However, clinical diagnosis is very subjective and mainly depends on external motor symptoms observation, regardless of individual differences and objectivity. Several common treatments are available including drug therapy, ventrolateral nucleus of thalamus and posteroventral pallidotomy, and the deep brain stimulation (DBS). However, there

is no radical treatment of PD. These treatments relieved the PD symptoms with various shortcomings. For example, the effect of drug is limited in the middle and later period of PD, and there are contraindication and side effect of some surgeries [16].

Can biomarkers help us predict the individual PD symptoms and therapeutic effects? This is a big question in clinical diagnosis and individual treatment [17]. A lot of potential biomarkers of neurodegenerative disorders for early diagnose have been studied. For example, the Lewy body detection with PET could be applicable in early diagnose of dementia [18], but the Lewy body is limited in predicting the variabilities. A study on AD found that the PET imaging of tau was related patients' cognitive behavior. It suggests that the PET imaging of tau was the biomarker predicting various cognitive behaviors of AD patients [19]. Of course, this is a result of the "association", and the validation and generalization of the result requires further investigation. As far as we know, this kind of

study is rare. Most studies only found the effect of certain treatment on some cognitive function, and the effect is just the dichotomy (yes or no). For example, a study with DTI and dosage of l-Dopa could predict the effect of atomoxetine on PD [20]. Although the prediction accuracy reaches 80%~85%, the effect is only limited to the inhibition control and is just measured as all or nothing at all. Another study just investigated the tumble of PD patients but no cognitive function or the frequency of tumble [21]. Therefore, the question remains to be investigated.

To address these questions, machine learning is a practical tool [22-28]. Machine learning is an artificial intelligence in nature, and it is an interdisciplinary of probability theory, statistics, approximation theory, convex analysis. The arithmetic of machine learning induces a reliable rule from big data through cross validation and predict a new data. It could be used to make a dichotomy and diversification prediction. Through the cross validation, the core factor in prediction could be found out. For example, the sensitivity and specificity in distinguishing the AD and healthy control reached 87.1% and 93.3% [23]. Another study could even diagnose different stages of AD with convolutional neural network [29].

Individual PD Symptoms and Therapeutic Effects

Individual PD Symptoms: Early in 1817, typical motor symptoms of PD were named by a general practitioner James Parkinson in London. He described 6 cases of shaking palsy and denominate these symptoms "Parkinson's Diseases". The motor symptoms are diagnostic criteria in traditional clinic. However, non-motor symptoms, including cognitive impairment [30], neuropsychiatric symptoms (e.g. depression [31], anxiety [32]),

autonomic nervous dysfunction (e.g. constipation [33], sleep disorders [34], sensory disturbance [35], pain) are symptoms prior to the motor symptoms. A multiple-sites study in Sydney conducted a 20-year follow-up on 52 PD patients, and the study found these non-motor symptoms were the main causes of disabilities [36]. Non-motor symptoms were not valued in such a long time because the non-motor symptoms in early period were relatively dormant and covered by motor symptoms in later period [37] and because the caregivers or the patients can not precisely report cognitive disabilities [38]. More and more researchers began to pay attention to the non-motor symptoms of PD in recent years.

Among these non-motor symptoms, cognitive disabilities attracted the most attentions for two reasons: first, cognitive functions are the core function, and the damage of non-motor symptoms is the cognitive disability; second, the cognitive disabilities are complex including cognitive control [39], working memory [40-43], language [16,44,45], visual and spatial attention [46]. Executive control means the ability of an individual solving problems and arrangement in limited time and stop-signal no-go task is the commonly used paradigm [47-49]. Working memory was tested with digit span forwards and backwards tasks [47]. Language fluency test was used to test the language fluency [50, 51]. Rey-Osterie complex figure test (CFT) is the usually used test of visual spatial and visual memory [52,53]. Alertness and Divided Attention Task and Trail Making test A and B are usually used paradigm for attention [47]. Non-motor symptoms are usually diagnosed with scales. Cognitive function of non-motor symptoms could be measured with paradigms of cognitive neuropsychology (Table 1).

Table 1.

PD symptoms			Measures
Motor			**Scales (UPDRS, PDQ-39)**
Nonmotor			scales (NMSquest)
	Cognitive		scales (MoCA、Wechsler Memory Scale、Wechsler adult intelligence scale、Mattis dementia rating scale)
		Executive Control	London Tower Test，Stop signal-Nogo task [53]
		Working Memory	digit span forwards and backwards task
		Language	language fluency test
		Visual Spatial and Visual Memory	*Rey-Osterrieth complex figure test*
		Attention	Alertness and Divided Attention Task and Trail Making test A and B
	Non-Cognitive		scales (MMSE, HAMD, PDQI, Constipation scale, PDSS-CV)

Note: UPDRS: United Pd Rating Scales; PDQ-39: Parkinson's Disease Questionnaire; NMSquest: Non-Motor Questionnaire; MoCA: Monte Carlo Cognitive Assessment; MMSE: Mini-Mental State Examination; HAMD: Hamilton Depression Scale; PDQI: Pittsburgh Sleep Quality Scale; PDSS-CV: PD Sleep Scales.

History of Available Therapies and Related Effects: Currently, PD is mainly treated with drugs and surgery. The drug is mainly levodopa, and the surgery is mainly the posterior section of the ventral nucleus or Globus pallidum of the thalamus and the deep brain stimulation developed in recent years. Surgery and

drugs have led alternately in the history of PD treatment and are now in a state of union. In 1817, James Parkinson noticed in a patient that the tremor disappeared dramatically after a cerebral hemorrhage in the contralateral side. This record may be the first conscious recognition of the science of the treatment of PD brain

disorientation. From the brain to the spinal cord, from the surface of the brain to the deep brain structure, in order to eliminate the symptoms of motor dysfunction, surgery involves almost all motion-related structures in recent 100 years. The early curative effect of surgery is often that the disappearance of tremor is often accompanied by the occurrence of hemiplegia and the recovery of hemiplegia accompanied by the recurrence of tremor. In 1941, Russel Meyers established the extrapyramidal surgery. He first excised the head of the caudate nucleus, and later switched to other structures in the basal ganglia, such as the forelimbs of the inner capsule. Meyers's pioneering work has demonstrated that tremor can be treated without paralysis.

But rough technique led to a mortality rate of more than 15 percent. In 1947, in the United States, Spiegel and Wyss et al. applied the stereotactic neurophysiology to clinical treatment of motor disorders and psychosis, which established the independent clinical branch of stereotactic neurosurgery. Since the new method was first reported by academician Zhong cheng Wang in China in the 1960s, stereotactic surgery has been carried out in Beijing, Shanghai, Anhui and Shaanxi, and many Parkinson's patients have been treated. In 1961, Holnikiewicz and Walter bicker Meier, of the university of Vienna, gave patients the drug levodopa, a precursor to dopamine, after discovering that lower levels of dopamine are the pathology of PD. Within hours of taking the drug, patients who are unable to move can move again, and the effect lasts a day. Levodopa was approved in 1970. Since then, other dopamine-based treatments have emerged. In addition, since the target location is not accurate enough and the size of the lesion is difficult to control, there are many postoperative complications, which limits the in-depth development of stereotactic surgery.

At that time, few people are going to receive surgical treatment, which significantly reduces the source of disease requiring surgery, and the stereotactic surgery to treat Parkinson's disease is also in an ebb. In the late 1970s, the shortcomings of levodopa

gradually came to light, and its curative effect decreased with the development of the disease. Meanwhile, a series of side effects, such as "on-off" phenomenon, dysplasia, and end-agent phenomenon, made the surgical treatment of Parkinson's disease regain people's attention. Deep brain stimulation surgery was developed in the late 1970s and was first used to treat pain. In 1987, French Benabid applied DBS to stimulate the hypothalamus to treat the tremor of Parkinson's disease and achieved success, opening a new era for the treatment of PD by DBS. The advantage of DBS is non-destructive, reversible, with few side effects and complications, and DBS can be adjusted to achieve the best control of symptoms with long-term effective. No matter the DBS or other operations, the accuracy of target localization is the key to the success of the operation.

With the development of neuroimaging technology, neuro electrophysiological detection technology and microelectrode technology, under the guidance of MRI, the relationship between the position, size and the surrounding important structures of brain kernels as targets can be clearly observed. However, individual differences in the treatment process are significant, with each treatment regimen having its indication type (Table 2). Deep brain stimulation, which is clearly indicated in the NIH treatment guidelines, is not appropriate for patients with severe cognitive impairment because there are still some side effects with DBS. For example, several articles reported that patients with Parkinson's disease had faster decision-making speed when facing difficult problems after DBS, namely impulsive behavior [54]. Phillips et al. fount that 32% patients appeared dementia within 2 year-follow up after DBS, but only 16% patients appeared dementia in control group [55]. DBS can also cause a decline in executive or language functions [56,57]. The choice of electrode guided stereotactic disfigurement should satisfy at least three principles: the diagnosis of primary Parkinson's disease; levodopa is effective in treatment; good cognitive function and good cooperation. The selection of damage targets is mainly determined according to clinical symptoms.

Table 2.

Type of surgery	Tremble	Rigidity	Dilatory	Dyskinesia	Gait
pallidotomy	+/++	+/++	++	++	+
thalamotomy	++	+/++	-	+/++	-
DBS	++	+	-	+	-

The posterior and medial parts of the Globus pallidus were used as the routine therapeutic target. If the tremor symptoms did not improve significantly during the operation, the ventral nucleus of the thalamus was added. The ventral nucleus of the thalamus can be selected as the target for pure tremor type patients. There are many factors influencing the treatment effect, including the age of onset, the incidence side of movement disorder, drug dosage, and the location of electrode implantation [13]. Even different types of anesthesia may have different effects on postoperative cognitive function [58,59].

Potential Biomarkers: In 1912, German neurologists Frederick Louis and Alessandro Alzheimer stained the brains of dead Parkinson's patients. Among neurons under multiple subcortical nuclei, Louis found abnormal protein aggregation, and later generations gave his name to this protein aggregate the Lewy body [60-63]. Since then, discussion about the Lewy bodies and the Parkinson's disease continues to this day. Neurologist Konstantin Tretyakov found that the loss of neurons in the substantia nigra of the brain is a pathological marker of Parkinson's disease. Other researchers, however, believed that the pathology of Parkinson's disease originated in a part of the brain called the striatum [2,5,64-66].

In 1960, Oleg Hornikiewicz and Herbert Ellinger of the university of Vienna studied the levels of dopamine in the brains of two Parkinson's patients and four post-encephalitis Parkinson's patients. In all these samples, levels of dopamine in the brain were lower than in the normal brain. A few years later, researchers found that dopamine in the striatum came from neurons that the substantia nigra projected onto the striatum with the help of high-resolution PET [4,67, 68]. Therefore, biochemical including the dopamine could be considered as potential biomarkers.

In June 1997, at the national institutes of health in Bethesda, Maryland, a team led by geneticist Michael polyamorous discovered a gene mutation that could cause a type of inherited Parkinson's disease. This gene is responsible for the synthesis of synuclein. Since then, its diploid and triploid genes have been found to cause Parkinson's disease, and other genetic mutations have been linked to rare genetic cases. By now, dozens of pd-related genes have been identified [69-71], including the LRRK2 [72-74], SNCA [75-77], GBA [78-81], PARK [82,83], COMT [84-86], APOE [87,88], MAPT [89-91]. LRRK2 is one of most studied PD-related genes. Interestingly, its most common mutation, G2019S (common in Ashkenazi and north African populations and extremely rare in Asian populations) will not worsen the overall cognitive decline of patients, but reduce the risk of dementia; PD patients with SNCA gene mutation have cortical spongiform changes in addition to Louie in vitro, early onset, rapid progression and high incidence of dementia. A follow-up study with a sample size of 4 million over 11 years showed that the severity of mutations in the GBA gene varied, as did the symptoms of PD [79].

The relationship between this genetic diversity and the diversity of cognitive dysfunction predicts important potential biological markers. And therefore, blood samples and saliva samples for PD-related gene or protein analyses should be considered as potential biomarkers. With the development of neuroimaging, such as PET and MRI, some scholars have pointed out that MRI structure images are more likely to become reliable biological markers [17]. Cerebrospinal fluid (e.g., A aspir42), gray matter, white matter [50,92] and metabolic levels of many metabolites (e.g., 18f-fdg) all indicate the occurrence and development of PD. Studies have shown that the gray matter volume of the hippocampal and thalamus of preoperative MRI is correlated with the changes of language memory performance before and after surgery [16]. A five-year tracking MRI study with sample size of 168 Parkinson's cases, divided the patients into serious atrophy and not serious atrophy according to the size of cholinergic basal forebrain, and found the degree of atrophy was significantly associated with the decrease of memory and language fluency of the patients 5 years after the surgery [3]. It prompts that the multiple-modal biological indicators should consider cholinergic biological basis.

Another similar MRI study found that the decline of gray matter volume and the increase of white matter diffusion in basal nuclei was correlated with the cognitive disabilities, and this result was not found in other brain areas such as the entorhinal cortex, amygdala, insula, hippocampus and thalamus [93]. A study based on PD without cognitive impairment found that these patients had no significant atrophy of gray matter compared to normal people, but extensive changes in white matter had occurred, suggesting that white matter may be a biological indicator prior to both gray matter and cognitive changes [50]. A method of whole-brain voxel analysis using multimodality MRI data (white and gray matter) and supervising/non-supervising classification algorithm can accurately distinguish PD from other diseases [94]. An MRI study suggests that the structural density of different subregions of the substantia nigra is related to the development of PD. Other studies have suggested a correlation between the level of brain functional connectivity in PD symptoms and progression [1, 95, 96]. These results suggest that the structural features of conventional MRI, including white and gray matter, and brain functional connectivity, may be useful predictors of biology [30].

Machine Learning – A Practical Tool: Machine learning is another name of pattern recognition, including unsupervised learning, supervised learning and reinforcement learning. Classification is one of the most important goal of machine learning (especially supervised learning). Here we briefly reviewed supervised learning as well as algorithms, including linear and non-linear classifiers. Logistic regression and K-Nearest Neighbors Algorithm are frequently used linear classifiers. In a recent study, multivariate regression analyses were applied to the resting-state functional MRI data, and it reported that pretreatment functional connectivity patterns within the default mode network and visual network significantly predicted posttreatment obsessive–compulsive disorder severity, explaining up to 67% of the variance [97]. Non-linear classifier mainly includes support vector machines (SVM) and neural network (especially recently developed deep learning). SVM is usually used for dichotomy and requires controlled features. But deep learning supports multi-classification and screens features automatically. Convolutional neural network is the most popular deep learning algorithm [29,98-100]. Several tools are available for algorithm optimization, including the TensorFlow, torch, Theano, caffe etc..

Recently, there have been many different new algorithms that support our classification. A study with 92 features including MRI, PET and cerebrospinal fluid used multiple modal extremely sparse layer algorithm (multimodal sparse hierarchical extreme SVM) and dissociated AD from normal controls with 96.1% accuracy [22]. A study using the convolution neural network algorithm could diagnose and predict the different stages of AD [29]. Another study used convolutional neural networks to diagnose subcortical underdevelopment, and the code for the related algorithms is open source [98]. The overall process and algorithm architecture of this study are shown in (Figure 1).
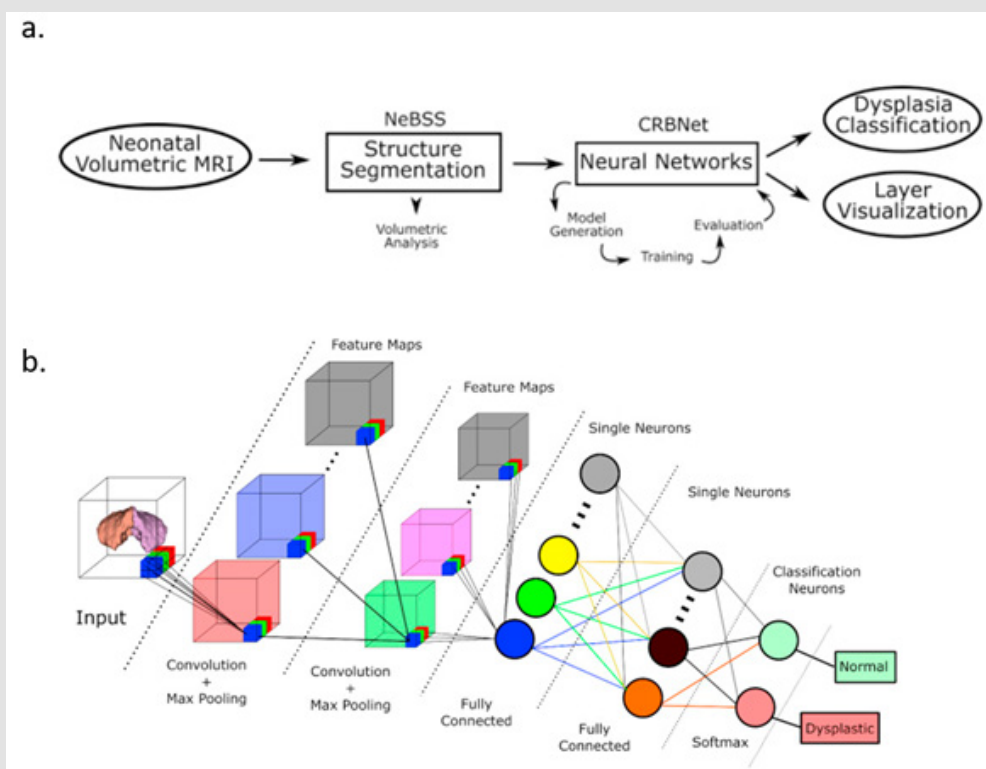
Figure 1: The study of convolution neural network was used to diagnose subcortical immature structures.
a)   the overall process of the study.
b)   algorithm architecture. The evolution of PD therapeutic methods and effect evaluation.

Feature selection is a core question in supervised learning. To minimize the generalization error, in other word, to minimize the underfitting and overfitting, is the guide of feature selection. The correlation between the features and the predicted results is usually used but not enough and limited because the relationship may be mediated by other factors or may be non-linear. Ergodic combination of features or greedy feature selection are usually used. However, the best choice is regularization with a least absolute shrinkage and selection operator [LASSO] regression model [97] or Ridge Regression model.

Conclusion

This review provides an overview of PD-related studies and proposes individual symptoms of PD should be appreciated in biomarker screening, especially increasingly attention-getting non-motor symptoms. Some potential biomarkers as well as the advantage of the machine learning in biomarker screening is reviewed. The review points out that the direction of future studies on biomarker screening is individual differences and robustness, which can be achieved with machine learning.

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