Parkinson's Disorder: Taking a Step towards Homogenizing Machine Learning and Medical Science

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Abstract--- *Machine learning is a scientific endeavor that has grown out of the need for analyzing and processing large scores of data. It aims towards inculcating the ability to learn within computer systems, thereby inciting a curiosity amongst science enthusiasts to explore the newly emerging field of technology. With machine learning being extensively used in everyday tasks, researchers are finding new ways of incorporating the technology in medical sciences, especially in neurodegenerative diseases like Parkinson's disease. Parkinson's is a major neurodegenerative disorder which is caused due to the dopamine deficit that occurs in the striatum part of the brain. It is the most sought-after disease in the field of neurological science due to its impact on a larger stratum of the world population. Therefore, the emergence of machine learning approaches to resolving the problems in the detection and treatment of this disease is a breakthrough in the field of clinical care. This review aims to analyze the less explored areas of treatment and diagnosis of PD. It addresses and evaluates the currently used computer-based modeling techniques and algorithms for the diagnosis of PD and emphasizes on specific aspects of treatment using machine learning. Hence, this review aims to unearth the gap between the recent works and the work that further needs to be done in the ambit of Parkinson's disease.*

Keywords--- *Parkinson's Disorder, Machine Learning, Neuro Degeneration, Dopamine.*

I. INTRODUCTION

Neurodegeneration is the phenomenon of slow and steady diminution in the cognitive and motor potencies of the brain. This degeneracy is a result of the continuous loss of neurons due to either structural or function failures or drastic reasons like complete death of neurons [1]. It is a characteristic of various eviscerating, incurable diseases and dementias, which are swiftly soaring to prevalence [2] and includes several common dementias like Alzheimer's disease, Parkinson's disease and Huntington's disease. There is a wide disparity between the pathophysiology of these diseases – with some leading to memory and cognitive impairment and others causing disability of motion, speech, and breath [2]. Parkinson's Disease (PD) is one such kind of persistent, progressive neurodegenerative disorder that impacts approximately seven to ten million people all around the world, with its likelihood increasing

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with age [3]. This multi-systemic condition arises due to the dysfunction in many neural networks of the brain [4-7], resulting in a myriad of impairments. The dysfunction caused due to PD is mainly characterized into two broad categories: motor symptoms and non-motor symptoms. Motor symptoms comprise of signs of tremors, muscle rigidity, bradykinesia (slow movement), postural instability (balance problems), walking or gait (walking style) difficulties, dystonia (twisting movements), and vocal impairments [8]. Whereas, the non-motor symptoms include an array of impaired abilities of brain like cognition, olfaction and some mental health disorders like depression [7, 9-10].

Though PD may be attributed to various phenomena, but its root cause remains uncharted. Most of the researchers adhere to the notion that PD is induced by the deterioration of nerve cells (neurons) in the Substantia Nigra which is a part of Basal Ganglia in the midbrain region and plays a major role in reward and movement (Fig. 1). As a result, the neurons cease to retain the potency to produce an important neurotransmitter called dopamine in brain.

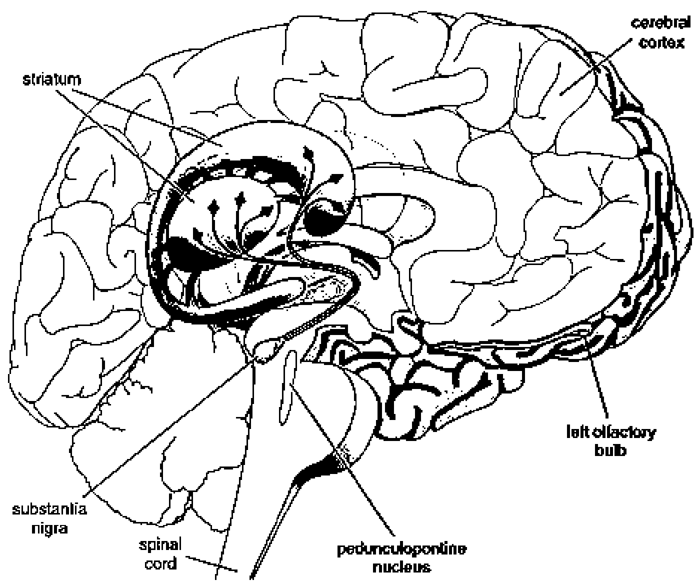

Fig. 1: A Diagrammatic Representation of the Various Regions of the Human Brain Including Striatum and Substantia Nigra

Source: An illustration by Tom Dunne, adapted from [40]

There is sufficient evidence in various studies related to PD, showing that 80% or more PD patients develop a significant loss in their dopamine levels due to degeneration of these dopaminergic nerve cells in the Substantia Nigra part of the brain [11]. This results in the hallmark motor triad of resulting tremors, muscle rigidity, bradykinesia, and other motor symptoms like gait [12, 32]. PD, as such, cannot be cured, but medication and deep brain stimulation can help assuage the motor symptoms, resulting in the improved life quality of those affected by this long-term ailment [13]. Sometimes surgery is also performed to alleviate the symptoms [14]. Among all the various treatments of PD, medications remain the most sought after and economical means of allaying the symptoms, with drugs like Levodopamine (L-Dopa) being ubiquitously used in treatment of PD. L-DOPA, also

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known as levodopa, is a precursor of dopamine used in the clinical treatment of PD and dopamine-responsive dystonia [11, 15]. It causes dopamine levels to increase and hence balances the levels of dopamine in the individual. L-Dopa is administered instead of dopamine itself as it crosses the defensive blood-brain barrier, which dopamine itself is unable to cross [15]. Although the response rate is moderately high relative to other psychiatric medications, it brings along various side effects like Hypotension, Arrhythmias, Mood Changes, and Depression.

The recent years have seen a surge in the amount of work done in the field of medical sciences, especially in Parkinson's disease. Various researches have been conducted to help analyze the disease extensively and find markers that are deterministic of the disease. Apart from the medical techniques, non-invasive measures are also being used to improve the quality of life of PD patients. Predictive modeling techniques have become a trend in assessing the risk and diagnosing the disease effectively. Studies have shown an increase in interest in using machine learning algorithms in PD. Shetty and Rao [16] have demonstrated the use of machine learning for gait analysis in PD patients. Bo Peng et al. [17] have used a similar machine learning approach for the identification of morphometric biomarkers for PD. Zlotnik et al. [3] have also shown that machine learning algorithms can optimize the clinical assessments and help the clinicians in determining the disease progression in the patient using exclusive vocal inputs from the patient. Si-Chun et al. [18] have also tried to characterize the risk of developing side-effects like depression in individuals at an early stage of PD using analogous machine learning techniques. These examples are just the tip of the iceberg. There are numerous other researches where machine learning is exclusively used in dealing with different aspects of Parkinson's disease such as the estimation of the extent of the disease to monitor the disease progression, which is a significant aspect of PD. The progression of PD is usually monitored by an expert medical staff, which is costly and requires the patient to be physically present in the clinic, rendering the procedure taxing and burdensome [3]. It also requires several sessions to be conducted with the doctor, and the patient has to undergo a set of tasks that can be enervating for both the patient and the clinicians. These clinical sessions and assessments include highly specialized and expensive neuro-imaging techniques like MRI (Magnetic Resonance Imaging) images, DaT (Dopamine Transporter) scans and PET (Positron Emission Tomography) imaging, to name a few (Fig. 2). Moreover, preclinical diagnosis with low error rates can prove to be pivotal in improving clinical trials and studies concerning life-altering therapeutics [19]. It also paves the way for non-invasive techniques to be used effectively for the diagnosis and detection of complex diseases like PD.

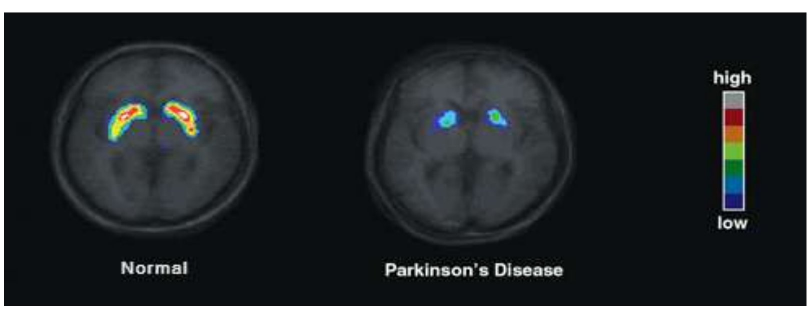

Fig. 2: A PET Scan Image Showing Difference between the Scans of a Normal Individual and a PD Patient

Source: PET images courtesy of Alain Dagher, Montreal Neurological Institute, McGill University, adapted from [40]

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Recent evidences are indicative of the fact that the use of machine learning classification techniques in psychiatry can prove a benign aid in predicting treatment response at an individual level [20]. These methods can prove to be very helpful in informing and assisting clinicians to make more efficient clinical decisions before the treatment, thereby leading to fewer unsuccessful trials and higher response rates [11]. More effective predictive analytics could be beneficial for PD, in particular, because of the clinical heterogeneity, high prevalence, and societal costs associated with the disease [11].

There are continuous efforts are being made to design and develop new and improved health care techniques, incorporating machine learning and giving an optimal treatment at the same time, therefore, with a similar approach, the current study aims to evaluate all the concerned areas of treatment related to PD and give an analysis of how the machine learning techniques are able to explicate these concerned areas using innovative and portable strategies. We also resort to finding the least explored areas concerning the integration of machine learning techniques in health care. Given the recent interest of clinicians and scientists in predictive and analytical modeling using machine learning to optimize health care, it becomes of utmost importance to sedulously analyze the currently available models and discover the less traversed areas with an urge to empower them with this study. By carefully analyzing and reviewing the various predictive and analytical approaches, we aim to give an unambiguous and equitable rationale. It will help prospective researches get a better understanding of what all models and techniques have been used to date and what all still needs to be focused upon—thereby helping the researchers to discern which areas have to be paid attention to for enhanced treatment of PD. The review is divided into various sections, with each section describing a particular aspect of PD. It also sheds light on the techniques that have been used to build these models to develop a clear intuition so as to which aspect needs more awareness in optimizing health care with respect to PD.

II. Parkinson’s As A Heterogenous Disease

Technology, as it is today, is largely dependent on intelligent systems and artificial intelligence. Applications of these approaches in the medical sciences have always brought novel solutions to critical medical problems. Such is the case with Parkinson’s disease, which uses these approaches in various areas of treatment of PD. Around 1% of the world’s total population is affected by Parkinson’s disease, and the numbers are likely to double by 2030 [22-23]. Parkinson’s disease, as discussed in various studies, is highly heterogeneous and progressive [14]. It is known to be a multi-systemic disease as it has at least a combination of three symptoms and affects more than one system of bodily organs due to the dysfunction of several neural networks [4-7]. Hence, it is an area of keen interest in the array of neurodegenerative disorders. With the current unavailability of any associated biomarkers, Parkinson’s is paid a great deal of attention for an early diagnosis and detection along with an accurate prediction of the progression of the disease and its treatment methodology. Therefore, in the further section, we analyze the several areas related to PD, which have been of keen interest to the researchers.

III. Diagnosis And Detection: Treading On Parkinson’s

The accurate diagnosis and early detection have always been the first approach in understanding and treatment of complex diseases such as Parkinson’s [19]. There have been several large-scale cross-sectional cohort studies that have been conducted for a better diagnosis, analysis, and prediction of PD [14]. All these aspects of understanding and treating PD have had several different approaches throughout the discovery of PD. From initial detection approaches like analysis of the primary symptoms to using as advanced clinical approaches as DaT scans (Dopamine Transporter Scan) to detect PD, clinicians have come a long way. However, all this while, technology was a clear companion to the science of medicine. The integration of these two in today's time has been repeatedly validated through various innovative researches. One such study by Nalls et al. discusses the use of classification modeling and statistical analysis to diagnose PD [19]. The study further reveals a much portable technique for diagnosis rather than the conventional imaging, which usually turns out to be both expensive and cumbersome for the patient. The study results in a highly accurate and easy to implement machine learning model which takes several inputs from the patients including the results of various clinical tests and offers a prospective new approach distinguishing the participants with PD from the controls. These inputs were then selected based on stepwise logistic regression, and the data from later conducted non-invasive lab tests which were then classified using resampling and other techniques. The proposed model turned out to be highly accurate (AUC 0.9 or higher) and hence showed how beneficial the amalgam of machine learning and clinical assessments could be in diagnosis and detection [19]. Another study with a similar aim of distinguishing PD cases from controls was given by Zhang et al. [14]. This was a more recent study conducted on the neuroimaging data, which used a deep learning model to predict the relationship between brain images. This study considered the neuroimaging data from the PPMI cohort and developed a Graph Convolution Network (GCN) for effectively modeling the non-linearity in the images, unlike previous studies. This study, hence, is an exceptional approach to view and explore the neuroimaging data as a non-linear sample rather than the basis for a linear model [14].

The overall accuracy of the model was high (AUC 0.93) and, therefore, validates the need for machine learning to model the traditional ways of diagnosis. Similar to this study, using a deep learning framework, there was another novel approach put forth by Wingate et al. for the prediction of PD [24]. This approach used medical imaging data and devised a framework for analyzing and further utilizing the information obtained from Deep Convolutional and Recurrent Neural Networks (DNNs). The input of the model was the MRI images and DaT scans, which used DNN training combined with transfer learning and domain adaptation methodology for accurate prediction of PD status in the subjects. The model showed an overall accuracy of 98% on an input of both DaT scans and MRI image data, 94% on an input of DaT scan, and an optimized accuracy of 81.1% for an input field of MRI images [24]. All of these studies are successful implementations of various machine learning approaches in the diagnosis and detection of PD. This shows the enthusiasm of researchers in exploring the primary facets of PD, like diagnosis and detection of the disease by implementing the contemporary machine learning approaches.

IV. TRACING PARKINSON'S ALONG THE STRIDES OF MACHINE LEARNING

Another challenge that comes with an accurate diagnosis of a disease is a continuous attempt to determine the degree of its severity and disease progression. In Parkinson's disease, this task becomes a little easy as the disease shows at least one or more motor symptoms, which can be easily tracked using motion and other advanced sensor technologies. The task, however, remains equally demanding due to the arduous need to quantify the results. This is, however, made easy using the concomitant techniques of machine learning. There are various studies in the recent

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past, which demonstrate the use of different technologies in monitoring the patient status and prediction of disease progression of PD. A study by Zlotnik et al. interprets the challenge of automatically determining the degree of PD as a regression task [3]. The study exclusively utilizes the patient's voice as an input parameter to monitor his condition and proposes and ensemble learning method using a supervised machine learning algorithm. This study is a portable and innovative means to estimate the extent of the disease rather than the widely used expensive and troublesome clinical assessments. The study is based on the fact that during the course of the disease, approximately 70-90% develop vocal impairment and the quantification of which can directly predict the progress of the disease. This is achieved by employing Random Forest, a supervised machine learning algorithm, wherein several features distorted due to vocal impairment are taken as inputs, and the machine learning algorithms are employed to measure the degree of the condition. The resultant accuracy was best achieved at 0.609 (in terms of spearman coefficient) using a two-fold cross-validation set [3]. This shows the extent of accuracy and ease, the unification of machine learning and clinical assessments can cover. In due agreement of the same, a review by Ramdhani et al. reveals how clinical assessments are optimized using wearable sensors and data-driven modeling [25]. The study clearly justifies how the expansion of machine learning algorithms is beneficial in devising unique classification and probabilistic clinical models in the sphere of health care. The review further elucidates that the contemporary learning techniques do not only transmute the traditional paradigms for treatment but also enhance the use of modern therapeutics [25]. Facilitating the review, a recent study by Tsoulos et al. provides a precursory evidence that different features within a large group of PD subjects can be determined with the help of artificial systems [23]. This study employs a Neural Network Construction (NNC) technology in discriminating PD patients from healthy individuals and determining the motor status with respect to each patient within the cohort of PD subjects. The overall accuracy of the model using several hybrid algorithms within the NNC came out to be 93% for distinguishing between PD and healthy patients and 76.5% for discerning the patient motor status as “ON” or “OFF” [23]. With advancements in machine learning techniques, there are various attempts being made for an accurate measurement of the patient motor status, similar to research conducted by Memedi and Somayeh in [26]. Comparable to the study by Tsoulos et al. in [23], the findings by Memedi and Somayeh in [26] are based on Partial Least Square (PLS) regression for predicting the motor status and aims towards optimizing the proposed models in the past. The study employs a data-driven modeling technique of PLS for precise selection of features and reducing the dimensionality of the input smartphone data. The derived accuracy of the model was considerably greater than that of the models using Support Vector Machines (SVM) or Principal Component Analysis (PCA) methodologies [26]. These findings are proof of significant research being done in supervising and monitoring the course and progression of the disease using machine learning techniques. This further motivates researchers to establish more accurate and efficient models for such purposes.

V. THE CONQUEST OF PREDICTION IN PARKINSON'S

The modern and contemporary technologies are gaining more attention with respect to prediction and predictive analysis approaches. The ability to forecast the disease, its severity, or its side effects, also gives a hope to the patients as well as the clinicians to be able to triage the disease(s) or its ill effect(s) at significantly early stages to avoid or control the degeneration caused in the quality of life in the patients and to enhance the treatment and clinical trials. Hence, the predictive techniques are being favored in the recent times due to their immense scope to control the further impairments caused, at earlier stages. In Parkinson's disease, predictive diagnosis and detection have always been well attended to. The previous sections of this study also provide insights into machine learning techniques used for predicting the disease. Therefore, giving significant evidence for machine learning and artificial intelligence-based techniques being most-suited for any sort of predictive analysis. There has been a surge in the number of prediction algorithms in recent years.

One such study by Li et al. strives to predict the severity level of PD in the patients after drug therapy [7]. The study proposed an exhaustive cross-validated prediction framework using feature selection and regression techniques for prediction. It evaluated the disease severity of each patient based on UPDRS-III scores and developed a prediction model using dynamic connectivity efficiency (dnE) of fMRI images. Using the acquired knowledge to predict the UPDRS-III scoring in other patients, the model successfully predicted the severity level of the disease after drug therapy, accurately [7]. Along with monitoring the effect of the drug, predicting side effects of a disease are also equally beneficial. In a recent study by Wilson et al., the cognitive decline was predicted in patients with PD using clinical markers in combination with machine learning techniques [27]. As the disease progresses, approximately 80% of the PD patients are likely to develop cognitive impairment [28]. Therefore, it is highly significant to identify the patients with a high risk of developing cognitive impairment at earlier stages of PD for improved monitoring and treatment of the patients. The findings from the study deduced that age is a crucial factor in the risk analysis and put forth a range of clinically available measures encompassing the capability for identifying drug-naïve patients with a higher risk of developing a cognitive impairment [27]. The study used a grouping model that was implemented through machine learning techniques and hence coalesced the clinical approaches and machine learning technology. This study was a novel attempt in the prediction of side-effects that are developed by patients during the course of treatment as well. Side-effects of treatment in PD patients are common and are not limited to, affecting only the physical health of the patient but can cause severe disturbances in their mental health as well. Various studies on PD have shown that depression is a major side-effect in the patients developing at the time of diagnosis or during the course of treatment [29-30]. A potential cohort study by Gu et al. identified the risk of an individual to develop depression at the earliest stage of PD. The study utilized the available markers for distinguishing high risk of developing depression in the patients and concatenated it with a logistic regression model and a highly efficient algorithm called XGBoost. This longitudinal study provided personalized estimates of depression in early PD using machine learning algorithms [18]. Hence, giving a new recognition and hope to maneuver machine learning algorithms with an aspiration of accurate and in time predictive analysis of diseases in an attempt to refine the clinical care and treatment conventions.

VI. DRUG RESPONSIVENESS IN PD: A LESS TRAVERSED PATH

Parkinson's disease is a persistent, progressive neurodegenerative disorder that, as such, cannot be cured, but the symptoms can be alleviated using deep brain stimulation and medication [3, 13]. It is known to affect multiple systems in the brain, which leads to considerable depletion in the number of dopamine producing neurons in the substantia nigra, further giving rise to a substantial reduction in the amount of dopamine in the striatum [12, 31].

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This depletion in the levels of dopamine, results in the debilitation of the “motor” circuit within the basal ganglia-thalamocortical region of the brain [12, 32].

Dopamine deficiency further results in the disruption of a structural and functional segregation between basal ganglia and cortex, advancing to the development of harmonized oscillations between basal ganglia regions and the cortex [12, 33-36].

The observations from several studies evidence the presence of a correlation between motor deficiency in PD and these anomalous coordinated oscillations, which can be subdued by dopaminergic therapies [12, 37-39]. These dopaminergic therapies involve the administration of levo-dopamine, commonly known as L-Dopa, which is a precursor of dopamine. In addition to the treatment, patients can respond to L-dopa therapy to varying extents in advanced PD involving major complications like L-dopa induced dyskinesias (LID) and motor fluctuations.

Hence, it is an essential aspect of treatment, to be able to determine the patient’s responsiveness to these L-dopa therapies. There have been various studies conducted to understand the L-dopa responsiveness of PD patients, such as the one conducted by Akram et al. [12]. The study is an attempt to assess the variations in the functional connectivity of the basal ganglia with cortical and sub-cortical areas with respect to responsiveness to Levodopamine. The study employs a seed-based approach in analyzing the resting-state functional connectivity MRIs (fc-MRI) for comprehending the responsiveness of the drug.

The study maps the differences in functional connectivity patterns of the basal ganglia using fcMRI and reveals its association with different degrees of response to L-dopa therapy [12]. However, there are not many studies conducted aiming to amalgamate the machine learning approaches in apprehending the L-dopa responsiveness in patients.

Hence, this aspect of Parkinson’s disease has been left less explored and can be incorporated in future research work, giving a direction to enhanced clinical treatment and assessment of PD. Henceforth, the accurate prediction of L-dopa response in advanced PD can prove to be a revolutionary approach for improved diagnosis and treatment of the disease.

VII. THE ANATOMIZATION: COLLATING THE DISCUSSION SO FAR

The immense efforts made in subsuming the machine learning techniques in studying PD are evident in the reviewed studies.

This takes us to further acknowledging the constant struggle in agglutinating the science of logic and the science of medicine and in resolving the conflicts between the two sciences. Also, the efforts do not seem to be bounded to explore the territories of machine learning technologies and hence are not only maneuvering the distinct algorithms available rather are also drawing on to different machine learning approaches like supervised, unsupervised and reinforced learning techniques. The evidence of the popularity of machine learning techniques in dealing with the various aspects of PD can be distinctly seen in Table 1.

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Table 1: The Various Discussed Studies in the Review

Year	Author	Objective	Models used	Accuracy achieved
2015	Nalls et al.	Diagnosis and detection of PD patients from healthy patients	Stepwise Logistic Regression	0.923 AUC
2015	Zlotnik et al.	Determination of degree of Parkinson's condition using patient's voice	Random forest	0.609 (Spearman's correlation)
2018	Zhang et al.	Development of a computational framework for analyzing the neuroimages in PPMI data	Graph Convolution Networks (GCN)	0.93 AUC
2019	Li et al.	Prediction of the drug therapy effect of levodopa treatment	Dynamic nodal efficiency (dnE)	0.54 and 0.65 (Pearson's correlation) for on and off states
2019	Wingate et al.	Prediction of Parkinson's disease	Deep neural network (DNN)	96-97%
2019	Tsoulos et al.	Discrimination of PD patients from healthy patients	Neural Network Construction (NNC)	93.11%
2020	Si-Chun et al.	Prediction of depression in patients with newly diagnosed PD	XGBoost and Logistic Regression	0.94 and 0.83 AUC

There are several illustrations that have been frequently made to compare the different machine learning algorithms which have been employed in resolving the various aspects of PD. A similar attempt has been made in the current study to visualize these different algorithms with an objective to seek the most commonly used technique.

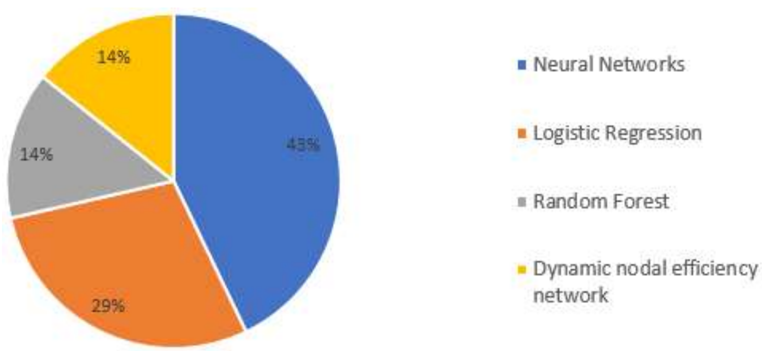

Fig. 3: A Pie Chart Representing the Various Machine Learning Algorithms which have been Used in the Discussed Studies

Figure 3 distinctly shows that the most popular machine learning techniques used for modeling are the Neural Networks which are regarded as an unsupervised machine learning approach. This elucidates the fact that there has been sufficient research work done with respect to encountering various aspects of PD, for a comparative analysis to be done.

VIII. CONCLUSIONS

There is an underlying attempt in unifying computer intelligence, which is mostly based on fundamental logic

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and medical science, beyond the research works discussed in this review. There is an inherent parallelism in the paradigm of these approaches, which can be coalesced into a single stratagem for exploring the undiscovered wavelengths of medicine and logic. Through our review, we aimed to embed this coherent approach in solving crucial real-life problems and hence make revolutionary and life-altering advances in the field of science. The above discussions, make it clear that there are extensive researches where machine learning has been significantly used to deal with several aspects of complex disorders like Parkinson's. There are algorithms not only being employed but also being formulated for a precise and efficacious implementation of the devised models which are results of extensive researches being held with respect to the different aspects of PD.

A contrast between the various explored studies, revealed the high accuracy in the substantial deployment of the Artificial Neural Networks in the variegated areas of PD concerning an improved treatment and diagnosis. However, little work is done in assimilating the drug information related to Parkinson's and predicting drug responsiveness, especially L-Dopa response. Albeit, there are several instances where machine learning has found its way to predicting the drug responsiveness in various diseases and dementias, it is interesting to know that there is no practical case where machine learning techniques are used to predict drug responses in PD. Since L-dopa is widely used to combat the symptoms of PD, therefore it is of great importance to create a machine learning model that can predict the response of PD patients to L-Dopa drugs. Since prolonged administration of L-Dopa can have several side effects like hallucinations, delusions, psychosis, agitation, etc., there is an urgent need to have an idea about how a patient who has Parkinson's disease will respond to the drug to safeguard the patient from the ill effects of the drug. The use of machine learning in predicting L-Dopa response in patients will pave the way for copious developments in the field of drug responsiveness in Parkinson's. It will be an initial step towards saving the lives of people struggling with Parkinson's' from the precarious side-effects of the drugs used to mitigate the symptoms of the disease, thereby improving the quality of life of PD patients. This review, therefore, indicates the urgency of doing intensive research in the field of drug response prediction in Parkinson's disease so as to leverage the work of doctors and save the precious lives of the patients.

REFERENCES

[1] Kunwar, A. and K. I. Priyadarsini, "Curcumin and its role in chronic diseases", 'Anti-inflammatory Nutraceuticals and Chronic Diseases', *'Advances in Experimental Medicine and Biology',* Springer, Cham, vol. 928, pp. 1-25, 2016.

[2] Gitler, Aaron D., Paraminder Dhillon and James Shorter, "Neurodegenerative disease: models, mechanisms, and a new hope", *'Disease Models & Mechanisms',* vol. 10, pp. 499-502, 2017.

[3] Zlotnik, Alexander, Juan M. Montero, Rubén San-Segundo and Ascensión Gallardo-Antolín, "Random forest-based prediction of Parkinson's disease progression using acoustic, ASR and intelligibility features" *In the proceedings of 'Sixteenth Annual Conference of the International Speech Communication Association', Interspeech, Dresden, Germany,* pp. 503-507, 2015.

[4] Brooks, David J. and Nicola Pavese, "Imaging biomarkers in Parkinson's disease", *'Progress in neurobiology'*, vol. 95, no. 4, pp. 614-628, 2011.

[5] Luo ChunYan, Wei Song, Qin Chen, ZhenZhen Zheng, Ke Chen, Bei Cao, Jing Yang, JianPeng Li, XiaoQi Huang, QiYong Gong, Hui-Fang Shang, "Reduced functional connectivity in early-stage drug-naive Parkinson's disease: a resting-state fMRI study", *'Neurobiology of aging',* vol. 35, no. 2, pp. 431-441, 2014.

[6] Ziegler, Erik, Maud Rouillard, Elodie André, Tim Coolen, Johan Stender, Evelyne Balteau, Christophe Phillips and Gaëtan Garraux, "Mapping track density changes in nigrostriatal and extranigral pathways in Parkinson's disease", *'Neuroimage'*, vol. 99, pp. 498-508, 2014.

[7] Li, Xuesong, Yuhui Xiong, Simin Liu, Rongsong Zhou, Zhangxuan Hu, Yan Tong, Le He, Zhendong Niu, Yu Ma, and Hua Guo, "Predicting the Post-therapy Severity Level (UPDRS-III) of Patients With Parkinson's Disease After Drug Therapy by Using the Dynamic Connectivity Efficiency of fMRI", *'Frontiers in neurology',* vol. 10, pp. 668, 2019.

[8] APDA, 2020, "23 Parkinson's Symptoms To Look For", *APDA.* [online] Available at: <https://www.apdaparkinson.org/what-is-parkinsons/symptoms/#motor> [Accessed 11 April 2020].

[9] Jankovic, Joseph, "Parkinson's disease: clinical features and diagnosis", *'Journal of Neurology, Neurosurgery & Psychiatry',* vol. 79, no. 4, pp. 368-376, 2008.

[10] Khoo, Tien K., Alison J. Yarnall, Gordon W. Duncan, Shirley Coleman, John T. O'Brien, David J. Brooks, Roger A. Barker and David J. Burn, "The spectrum of nonmotor symptoms in early Parkinson disease", *'Neurology',* vol. 80, no. 3, pp. 276-281, 2013.

[11] Lang, Anthony E. and Andres M. Lozano, "Parkinson's disease", *'New England Journal of Medicine',* vol. 339, no. 16, pp. 1130-1143, 1998.

[12] Akram, Harith, Chengyuan Wu, Jonathan Hyam, Thomas Foltynie, Patricia Limousin, Enrico De Vita, Tarek Yousry, Marjan Jahanshahi, Marwan Hariz, Timothy Behrens, John Ashburner and Ludvic Zrinzo, "L-Dopa responsiveness is associated with distinctive connectivity patterns in advanced Parkinson's disease", *'Movement Disorders',* vol. 32, no. 6, pp. 874-883, 2017.

[13] Ruonala, Verneri, Mika P. Tarvainen, Pasi A. Karjalainen, Eero Pekkonen and Saara M. Rissanen, "Autonomic nervous system response to L-dopa in patients with advanced Parkinson's disease", *In the proceedings of '2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)', IEEE*, Milan, Italy, pp. 6162-6165, 2015.

[14] Zhang, Xi, Lifang He, Kun Chen, Yuan Luo, Jiayu Zhou and Fei Wang, "Multi-view graph convolutional network and its applications on neuroimage analysis for parkinson's disease", In the proceedings of 'AMIA Annual Symposium Proceedings', *American Medical Informatics Association,* vol. 2018, pp. 1147-1156, 2018.

[15] Cools, Roshan, "Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease", *'Neuroscience & Biobehavioral Reviews',* vol. 30, no. 1, pp. 1-23, 2006.

[16] Shetty, Sachin and Y. S. Rao, "SVM based machine learning approach to identify Parkinson's disease using gait analysis", *In the proceedings of '2016 International Conference on Inventive Computation Technologies (ICICT)', IEEE,* Coimbatore, India, pp. 1-5, 2016.

[17] Peng, Bo, Suhong Wang, Zhiyong Zhou, Yan Liu, Baotong Tong, Tao Zhang and Yakang Dai, "A multilevel-ROI-features-based machine learning method for detection of morphometric biomarkers in Parkinson's disease", *'Neuroscience letters',* vol. 651, pp. 88-94, 2017.

[18] Gu, Si-Chun, Jie Zhou, Qing Ye and Can-Xing Yuan, "Personalized prediction of depression in patients with newly diagnosed Parkinson's disease: A prospective cohort study", *'Journal of Affective Disorders',* vol. 268, pp. 118-126, 2020.

[19] Nalls, Mike A., Cory Y McLean, Jacqueline Rick, Shirley Eberly, Samantha J Hutten, Katrina Gwinn, Margaret Sutherland, Maria Martinez, Peter Heutink, Nigel M Williams, John Hardy, Thomas Gasser, Alexis Brice, T Ryan Price, Aude Nicolas, Margaux F Keller, Cliona Molony, J Raphael Gibbs, Alice Chen-Plotkin, Eunran Suh, Christopher Letson, Massimo S Fiandaca, Mark Mapstone, Howard J Federoff, Alastair J Noyce, Huw Morris, Vivianna M Van Deerlin, Daniel Weintraub, Cyrus Zabetian, Dena G Hernandez, Suzanne Lesage, Meghan Mullins, Emily Drabant Conley, Carrie A M Northover, Mark Frasier, Ken Marek, Aaron G Day-Williams, David J Stone, John P A Ioannidis and Andrew B Singleton, "Diagnosis of Parkinson's disease on the basis of clinical and genetic classification: a population-based modelling study", *'The Lancet Neurology',* vol. 14, no. 10, pp.1002-1009, 2015.

[20] McGuire, Lynne I., Alexander H. Peden, Christina D. Orrú, Jason M. Wilham, Nigel E. Appleford, Gary Mallinson, Mary Andrews, Mark W. Head, Byron Caughey, Robert G. Will, Richard S. G. Knight and Alison J. E. Green, "Real time quaking-induced conversion analysis of cerebrospinal fluid in sporadic Creutzfeldt-Jakob disease", *'Annals of neurology',* vol. 72, no. 2, pp. 278-285, 2012.

[21] Dosenbach, Nico UF, Binyam Nardos, Alexander L. Cohen, Damien A. Fair, Jonathan D. Power, Jessica A. Church, Steven M. Nelson, Gagan S. Wig, Alecia C. Vogel, Christina N. Lessov-Schlaggar, Kelly Anne Barnes, Joseph W. Dubis, Eric Feczko, Rebecca S. Coalson, John R. Pruett, Jr., Deanna M. Barch, Steven E. Petersen and Bradley L. Schlaggar, *"Prediction of individual brain maturity using fMRI", 'Science',* vol. 329, no. 5997, pp. 1358-1361, 2010.

[22] Nussbaum, Robert L. and Christopher E. Ellis. "Alzheimer's disease and Parkinson's disease", 'Genomic Medicine, *The New England Journal of Medicine',* vol. 348, pp. 1356-1364, 2003.

[23] Tsoulos, Ioannis, Georgia Mitsi, Athanassios Stavrakoudis and M. D. Papapetropoulos, "Application of Machine Learning in a Parkinson's Disease Digital Biomarker Dataset Using Neural Network Construction (NNC) Methodology Discriminates Patient Motor Status", *'Frontiers in ICT',* vol. 6, no. 10, 2019.

[24] Wingate, James, Ilianna Kollia, Luc Bidaut and Stefanos Kollias, "A Unified Deep Learning Approach for Prediction of Parkinson's Disease", 'arXiv preprint arXiv:1911.10653', 2019.

[25] Ramdhani, Ritesh A., Anahita Khojandi, Oleg Shylo and Brian H. Kopell, "Optimizing clinical assessments in Parkinson's disease through the use of wearable sensors and data driven modeling", *'Frontiers in computational neuroscience',* vol. 12, no. 72, 2018.

[26] Memedi, Mevludin and Somayeh Aghanavesi, "A partial least-squares regression model to measure Parkinson's disease motor states using smartphone data", *In the proceedings of 'The 53rd Hawaii International Conference on System Sciences',* 2020.

[27] Wilson, Heather, Gennaro Pagano, Tayyabah Yousaf, Sotirios Polychronis, Rosa De Micco, Beniamino Giordano, Flavia Niccolini and Marios Politis, "Predict cognitive decline with clinical markers in Parkinson's disease (PRECODE-1)", *'Journal of Neural Transmission',* vol. 127, pp. 51-59, 2020.

[28] Aarsland, Dag, Kjeld Andersen, Jan P. Larsen and Anette Lolk, "Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study", *'Archives of neurology',* vol. 60, no. 3, pp. 387-392, 2003.

[29] Marsh, Laura, William M. McDonald, Jeffrey Cummings, Bernard Ravina and NINDS/NIMH Work Group on Depression and Parkinson's Disease, "Provisional diagnostic criteria for depression in Parkinson's disease: report of an NINDS/NIMH Work Group", *'Movement Disorders',* vol. 21, no. 2, pp. 148-158, 2006.

[30] Goetz, Christopher G, "New developments in depression, anxiety, compulsiveness, and hallucinations in Parkinson's disease", *'Movement disorders',* vol. 25, no. S1, pp. S104-S109, 2010.

[31] Braak, Heiko, Kelly Del Tredici, Udo Rüb, Rob AI De Vos, Ernst NH Jansen Steur and Eva Braak, "Staging of brain pathology related to sporadic Parkinson's disease", *'Neurobiology of aging',* vol. 24, no. 2, pp. 197-211, 2003.

[32] Hoehn, Margaret M. and Melvin D. Yahr, "Parkinsonism: onset, progression, and mortality", *'Neurology',* vol. 17, no. 5, pp. 427-442, 1967.

[33] Alexander, Garrett E., Mahlon R. DeLong and Peter L. Strick, "Parallel organization of functionally segregated circuits linking basal ganglia and cortex*", 'Annual review of neuroscience',* vol. 9, pp. 357-381, 1986.

[34] Albin, Roger L., Anne B. Young and John B. Penney, "The functional anatomy of basal ganglia disorders", 'Perspectives on Disease*, Trends in neuroscience',* vol. 12, no. 10, pp. 366-375, 1989.

[35] Alexander, Garrett E. and Michael D. Crutcher, "Functional architecture of basal ganglia circuits: neural substrates of parallel processing", *'Trends in neurosciences',* vol. 13, no. 7, pp. 266-271, 1990.

[36] Bergman, Hagai, Ariela Feingold, Asaph Nini, Aeyal Raz, Hamutal Slovin, Moshe Abeles and Eilon Vaadia, "Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates", *'Trends in neurosciences',* vol. 21, no. 1, pp. 32-38, 1998.

[37] Hammond, Constance, Hagai Bergman and Peter Brown, "Pathological synchronization in Parkinson's disease: networks, models and treatments", *'Trends in neurosciences',* vol. 30, no. 7, pp. 357-364, 2007.

[38] Lalo, Elodie, Stéphane Thobois, Andrew Sharott, Gustavo Polo, Patrick Mertens, Alek Pogosyan and Peter Brown, "Patterns of bidirectional communication between cortex and basal ganglia during movement in patients with Parkinson disease", *'Journal of Neuroscience',* vol. 28, no. 12, pp. 3008-3016, 2008.

[39] Shimamoto, Shoichi A., Elena S. Ryapolova-Webb, Jill L. Ostrem, Nicholas B. Galifianakis, Kai J. Miller and Philip A. Starr, "Subthalamic nucleus neurons are synchronized to primary motor cortex local field potentials in Parkinson's disease", *'Journal of Neuroscience',* vol. 33, no. 17, pp. 7220-7233, 2013.

[40] Ted L. Rothstein and C. Warren olanow, "The neglected side of Parkinson's disease", *'American Scientist',* vol. 96, no.3, pp. 218-225, 2020.