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Application of Machine Learning and Deep Learning Algorithms in the Detection of Parkinson's Diseases: a Review

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Abstract- Neuroimaging studies including functional, structural and molecular modalities that provide with underlying features and biomarkers for the detection of Parkinson's disease (PD). The usage of multimodality techniques in neuroimaging can help in diagnosing the disease from new perspective with better accuracy. This paper deals with the study of different Machine Learning (ML) and Deep Learning (DL) algorithms that had been applied on different modalities like Magnetic Resonance Imaging (MRI), it's various variants, Positron Emission Tomography (PET), Single Photon Emission Tomography (SPECT) and data like handwritten images, voice data, Gait data etc. Papers which implemented ML or DL techniques on these modalities have been reviewed and the method, cohorts along with results provided by each paper has been well illustrated.

Keywords- Parkinson's Disease, Magnetic Resonance Imaging, Positron Emission Tomography, Single Photon Emission Tomography, Machine Learning, Neural Networks.

I. INTRODUCTION

The Parkinson's disease is a disease related to brain that is neurodegenerative and characterized by various motors and non-motors symptoms. It can also be referred to as "Lessened Muscular Power" as the patient's body gets stiffened and there is a problem while walking, taking and in coordination. The situation gets worsened with the time. Thus, the proper diagnose of disease in early stages is necessary. There is no special test for its diagnosis and hence, doctors rely on the clinical features related to the diseases to differentiate it from Parkinsonism syndrome. There are four cardinal features associated with PD, Tremor while resting, Rigidity, Bradykinesia and Postural instability also abbreviated as TRAP [15].

The main cause of the disease is loss of dopamine, which is a special neurotransmitter released by the cells present in Substantia Nigra (SN) located in midbrain, at the top of spinal cord. This loss or cell damage can be because of multiple reasons like misfold proteins which are abnormally handled by the ubiquitin- proteasome and autophagy- lysosomal system, genetic mutation, mitochondrial dysfunction, increase in oxidative stress, pathogenic mechanism and inflammation. The one major characteristic of disease is the presence of clumps of Lewis bodies also referred to as alpha synuclein protein in SN. The dopamine is transported to the Basal Ganglia which is responsible for movement and its absence leads to resting tremor.

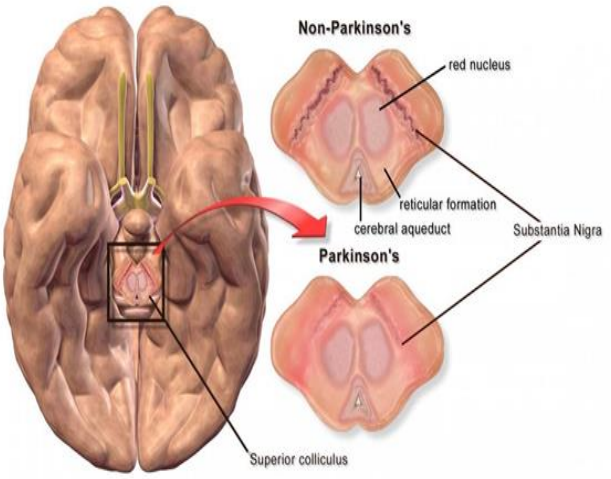

Fig 1. Illustration of a brain region, Substantia Nigra, where the loss of neurons occurs, involved in release of neurotransmitter, dopamine. Adopted from: wikipedia.org

But beyond this, there are many more regions involved. As the disease progresses, cerebral cortex and limbic system also get affected due to the presence of Lewy bodies that affect memory, thinking ability and results in mood swings and pain. Similar changes can be experienced in inferior temporal gyrus, an area responsible for the ability of our sight and this result in hallucination. There are several rating scales to assess the primary symptoms of disease. Unified Parkinson's disease Rating Scale (UPDRS) is widely accepted and has three sections to assess the

critical areas of disability, while the fourth section evaluates any complications of treatment [16]. Two other rating scales along with the above-mentioned scales are also used, namely: Hoehn and Yahr (H&Y), Schwab and England activities of Daily Living Scales. The H&Y scale provides with the gross assessment of progression in disease, ranging from no sign of disease (stage 0) to engage on wheelchair (stage 5). Various works had been accomplished using these scales which would be discussed in later section of the paper.

The progression in the area of Artificial Intelligence (AI) had revolutionized this era with the forthcoming advancements in its subparts like Machine Learning, Deep Learning, Natural Language Processing, Computer Vision and many more. These branches of AI find their usage in diverse fields like Aerospace, Navigation, Biomedical, Manufacturing industries, Robotics, Digital platforms like IOT etc. This work focuses upon the Deep learning and Machine Learning applications in Biomedical Imaging considering Parkinson's disease.

Machine learning can be simply defined as making machines to learn from past experiences and indulging them performing a given task consistently which can be harder and tiresome for humans. In some cases, machines can act brilliantly by identifying certain patterns and regions which can be hard for humans to recognize in medical imaging, thus making diagnosis of diseases easy. This advantage of ML had led to its widespread usage in Biomedical Imaging. In supervised learning, machine knows the desired output and tries to classify the provided training data using the previous labeled data. In unsupervised learning, the data is not labeled, and the machine tries to identify the features by itself.

The reinforcement learning is quite different from the earlier two classification categories as it deals with the rewards and actions. The Machine Learning has currently witnessed a great usage in Biomedical Imaging like that of hemorrhage detection, Breast cancer detection, to diagnose various diseases like Alzheimer, Parkinson etc. Many authors have used various techniques like Linear Regression, Logistic Regression, Support Vectors Machines, Naive Baye's algorithm, Random Forest [1] etc. to detect the patterns and classify the patients from the healthy control.

Though NN was introduced in 1950's, they gained importance in late 1990's but still faced various issues like absence of sufficient data, vanishing gradient, over fitting problems, lack of computing power etc. These problems were readily handled by Deep learning models also called Deep Neural Networks (DNN). The term ANN and DNN often becomes confusing for some especially for the beginners in this field. ANN comprises of three layers namely input, hidden and output layer whereas, DNN can be considered as complex neural networks which comprises of input and output layer along with multiple hidden layers [2]. Fig II. Best illustrates the difference between ANN and DNN.

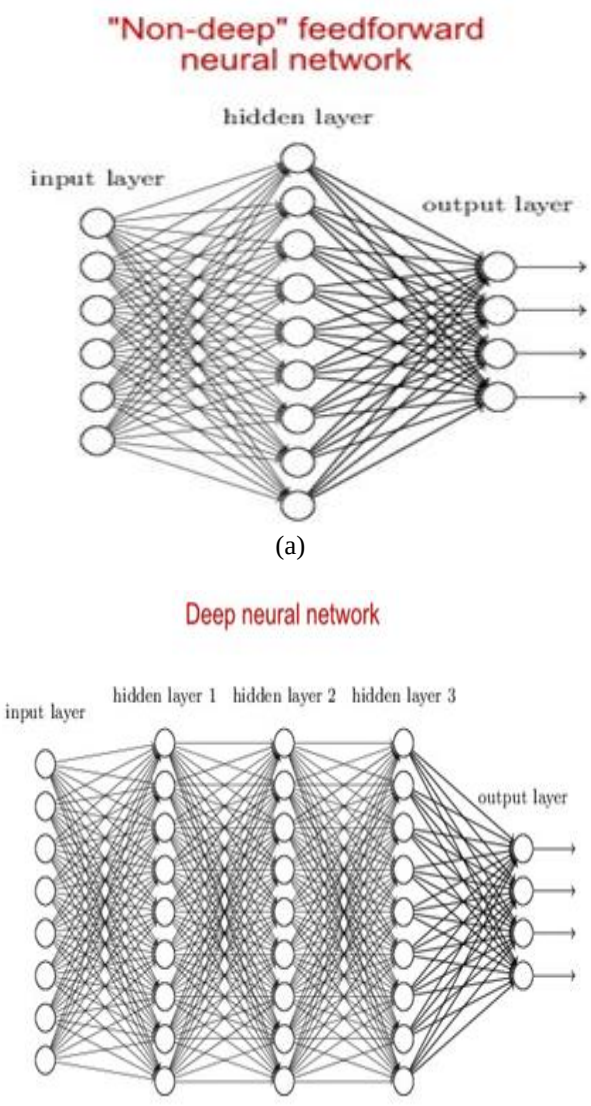

Fig 2. a) The ANN network with three layers b) The DNN network with multiple number of hidden layers. Adapted from [70]

The ANN accompanied by DNN has been excessively used in medical imaging as it eliminates the major step that needs to be performed in Machine Learning that is of feature selection. In ANN and DNN, the feature selection is performed along with the classification whereas, in ML models the features must be selected first and then they are given to the classifiers for the classification.

The accuracy achieved by DNN models are higher than the ML models in most of the cases but the requirement of the large dataset for the implementation of DNN models sometimes restrict its usage in medical imaging. But still there is wide variety of work like detection of Alzheimer

disease [3-7], fetal biometry detection [8-10], prediction of survival time in patients with brain tumors [11-14] etc.

In this review the Parkinson's disease (PD) has been discussed and various Machine Learning and Deep Learning techniques applied till date for the successful diagnosis and classification of idiopathic PD patients from Normal control and the patients suffering from the diseases having symptoms similar to the Parkinson has been be considered.

The aims of this review are to 1) identify various techniques applied to classify Parkinson's patients from normal control; 2) The various modalities used till date for the detection and classification of disease and 3) differentiate between ML and DL techniques based on various parameters like sensitivity, specificity and accuracy. The works on different modalities like MRI, SPECT, PET etc. have been reviewed according to the cohort size, preprocessing, classification and results obtained.

II. IMAGING MODALITIES FOR PARKINSON'S DETECTION

This section is about the different approaches which have been used so far using the ML and NN techniques. There are varieties of modalities used for the detection of Parkinson's disease like PET scan, SPECT imaging, MRI images, DTI imaging and apart from these, some work had also been demonstrated using the handwriting, voice recording etc.

The main aim is to classify Parkinson's patient from Normal control (NC) and patients with other Parkinsonism syndromes called as atypical Parkinson like Corticol Basal, Multiple system Atrophy (MSA), Progressive Supranuclear Palsy (PSP) etc. Atypical Parkinson is those diseases in which patients have various symptoms similar to the Parkinson's symptoms but cannot be termed as Parkinson. As an example, MSA affects the autonomic nervous system accompanied by another Parkinson's syndrome. The autonomic nervous system is defined as a system that controls the automatic functions of the body.

The two automatic systems that are mostly affected are urinary and blood pressure control. This can also occur in Parkinson's patients but the severity in MSA patients are more as compared to PD patients. The patients with atypical Parkinson's become less responsive to medicines as compared to PD. Thus, the diagnoses of PD from atypical PD patients become critical [16].

1. Magnetic Resonance Imaging (MRI):
There is variety of MRI techniques used for the diagnostic purposes. These techniques and the main advantages related to them are discussed as follows [18][19]:

Table 1. Depicting the different MRI's techniques currently used for disease diagnosis.

Structural imaging • Widely used to gather information related to morphology of brain like shape, volume, surface, grey and white matter thickness. • Ultra-high-field MRI providing high spatial resolution and excellent contrast. • T1 weighted, T2 Weighted and IR techniques allow disintegration of various basal ganglia parts along with SN.	Quantitative Techniques: MT imaging depends on the energy transfer from free protons to the highly bound protons in free water Visualizations of the parts become easy as it increases the contrast with surrounding white matter. Relaxometry characteristics of tissue components like relaxation time and rates are calculated which and depends on its molecular structure. T1 weighted images depicts the interaction between surroundings and protons that depends on water mobility. T2 weighted images are widely utilized for iron content estimation.
Diffusion Imaging • With the usage of magnetic field gradient pulses, water diffusion is estimated by Diffusion Imaging. • The existence of high strength diffusion gradients in more than six directions is elaborated by Diffusion tensor.	Functional MRI • Revolve around the blood oxygenatedlevel-dependent signal. • Estimate the changes occurring in relative amount of deoxy /oxy-hemoglobin associated with activitiesin neurons. • Local field potential is reflected toindicate peri-synaptic events
Brain connectivity • Empower alteration of brain fiber bundles. • Helpful in calculating diffusion metrics in the tracts, quantity of tracts and possibility of connection between theregions.	Functional connectivity • Calculated, when in resting position or doing task. • Evaluated with fMRI to judge for the temporal correlation of low frequency. • Helpful in determining correlation coefficient, integration, network indices.

The MRI techniques have been extensively explored in various literatures for the purpose of both classification as well as segmentation.

2. ML and NN work implemented using MRI scan:

Numerous techniques have been implemented on MRI scans using Machine Learning and Neural Networks algorithms. This review paper focuses on the previous literatures dealing with the differentiating the PD patients with the NC and patients with the atypical Parkinsonism syndromes like SWEED, PSP, MSA etc. The Region of Interest (ROI) and Voxel based Morphometry (VBM) had been widely implemented.

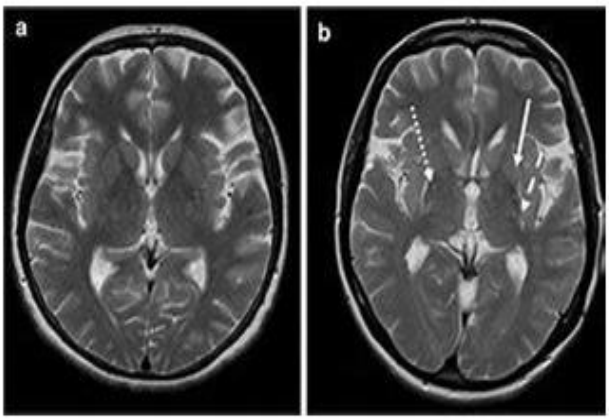

Fig 3. Striatal level, Axial T2 weighted MR images a) in a PD patient b) Putaminal Atrophy (arrow), Putaminal Hypointensity (dotted arrow) and Putaminal Hyperintense rim (dashed arrow) in a MSA-P patient. Adapted from [83].

Archer et al. [20] utilized the non-invasive diffusion weighted (DWI) MRI scans to distinguish between the Parkinsonism syndromes including PD, MSA and PSP patients. DWI scans are sensitive to detecting micro-structural differences between different forms of Parkinsonism. UPDRS rating scale part III as discussed previously was used along with scan to get accurate results. The study was based on ROI feature extraction technique and Receiver operating characteristic (ROC) analysis was performed using trained model and was statistically evaluated with Delong's test to compare area under curve (AUC's) between ROCs.

Numerous literatures demonstrate the effectiveness of utilization of different MRI techniques simultaneously to enhance the accuracy level of diagnosis. Corriea et al. [21] utilizes T1 weighted MPRAGE and diffusion weighted MRI scans to differentiate patients of PD, PSP and Corticobasal syndromes. The author compared two methods of feature selection, ROI and Principal Component Analysis (PCA) where SVM classifier was used. The accuracy level of PCA was greater than ROI, so PCA can be more effective in classifying the Parkinsonism syndrome diseases.

On the similar grounds, Salvatore et al. [23] assess the feasibility of employing the supervised learning to diagnose the PD and PSP patients using PCA as feature extraction and SVM as classifier.

The four critical brain regions were involved namely, Midbrain, Pons, Corpus Caltosum and Thalamus. Voxel based Morphometry was taken as biomarker and method was characterized by various parameters like accuracy, sensitivity and specificity. The literatures on Parkinson's disease classification using MRI scan have been described in Table II. Illustrating the technique, results and limitations.

3. SPECT Scan:

SPECT stands for Single Photon Emission Tomography. It illustrates the brain functionality as opposed to the MRI and CT scans which are basically used for brain structure. In this imaging ligands are used that belongs to group of compounds derived from cocaine that binds dopamine transporter. The variety of radiotracers are used for SPECT imaging that includes I-β-CIT, I-IPT, I-FP-β-CIT, TRODAT-1, I-Iodospiperone, I-Epidepride etc.

As the half-life of particles are more in SPECT as compared to the PET and hence, there is no need for an on-site cyclotron. The cost of radiotracer synthesis is low in SPECT imaging, and thus, larger number of patients can be investigated [23].

Prashanth et al. [24] had used the SPECT imaging with I-Isoflupane (DATSCAN) ligand to diagnose the PD patients even at early stages. The author had used SPECT scan to measure the striatal binding ration (SBR) to predict early stages PD. Basically SVM and Logistic Regression (LR) was utilized for classification purposes. While, SVM provides with high accuracy, Logistic Regression also proved to be a useful tool by producing high degree of fitting with statistical significance.

Towel et al. [25] successfully utilized the images of I-fluoropropyl-carbomethoxy- 3b-4-Iodophenyltropane (FP-CIT) along with the Singular Value Decomposition (SVD) to decrement the images of training set into D vector feature space. Naive Bayes (NB) and group prototype techniques were used for building classification model. The proposed technique was compared with the commercially available techniques, Brass software and QuantiSPECT software following the three embedded techniques namely two-box method, three-box method and crescent method. It was deduced that the proposed technique works better than the latter.

Ericsson et al. [26] had designed a rigid model, visualizing FP-CIT ligand by SPECT scan. The Basal Ganglia was segmented then using the designed automatic computer aided detection model, Decision Support System. The features were extracted based on the image intensity

distribution and SVM was explored for the classification of PD from Normal control. Segmentation of basal ganglia was performed by considering optimizing the fit of 3D model of the region. The intensity was higher in the specified region than the nearby region and thus, intensity distribution can differentiate between the brain regions. SVM provides with the decision value of each sample and classification is done by setting a threshold.

The literatures on Neural Networks techniques had also provided with the promising results as Acton et al. [27] studied the PD patients with the help of dopamine-based transport tracer, TRODAT-1 and SPECT. The images were co-registered to the template of TRODAT-1 and corresponding three slices to striatum were extracted using a mask and to use them, they were converted to manageable size by down -sampling them by factor of 3.

The final images were then inputted to ANN architecture. The best result came by using the 80 hidden nodes and learning parameter 0.355.

The illustration of usage of iso-surfaces to reduce the redundant data by conserving the important information is best presented in the paper Ortiz et al.[28]. The result of these iso-surfaces was then given to CNN architectures like LeNet and AlexNet to classify the images of DATSCAN. The extraction of features using iso-surfaces proposes the connection of voxels that had specified intensities. Basically, a threshold was set and the surface that envelopes the remaining voxels above the threshold.

The thresholds levels of 0.4, 0.5, 0.6, 0.7 and 0.8 were set. Then forward selection and backward selection were applied on that. Through the series of experiment, it was deduced that best accuracy was achieved for the iso-surfaces with threshold between 0.6-0.7. The result of classifications of two architectures was presented in Fig. IV and Fig. V.

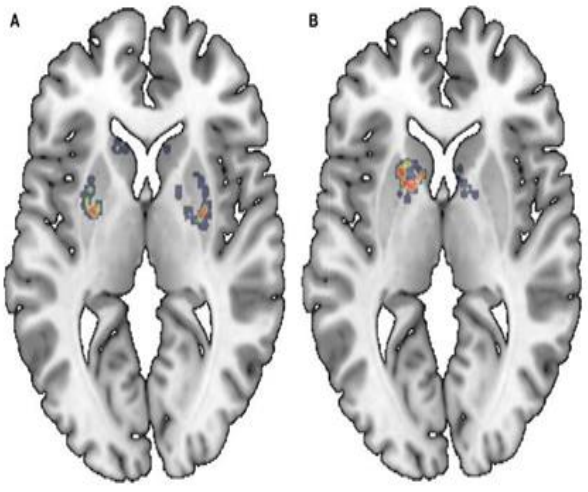

Fig 4. Salency map of LeNet architecture superimposed on MRI A) Normal Control B) PD. [28]

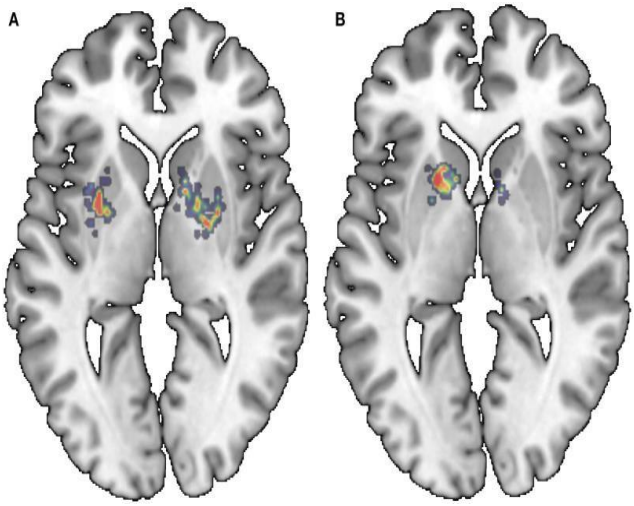

Fig 5. Salency map of AlexNet architecture superimposed on MRI A) Normal Control B) PD. [28]

The variants of SPECT Scan have been widely utilized for classification and prediction along with MRI and the literatures related to it are covered in Table III.

4. PET Scan

Positron Emission Tomography (PET) helps in estimating neuro-receptor binding and glucose metabolism enabling the understanding of Parkinson's disease. The functional behavior of the various brain regions involved in movement are also analyzed through PET scans. The PET scan normally focuses on glucose metabolism rather than the dopamine transporter as involved in SPECT imaging.

When the diagnoses are uncertain and the neurologist cannot determine whether the disease is Parkinson or Parkinsonism syndrome DATSCAN and PET scans are recommended.

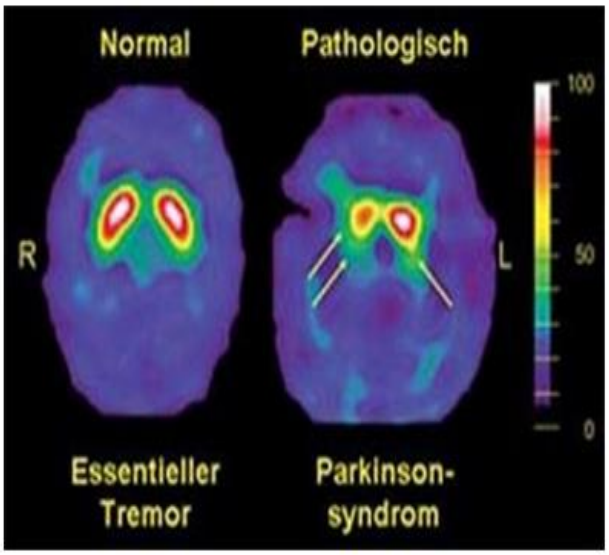

Fig 6. DATSCAN image demonstrating essential tremor on the left and Parkinsonism syndrome on right.[71]

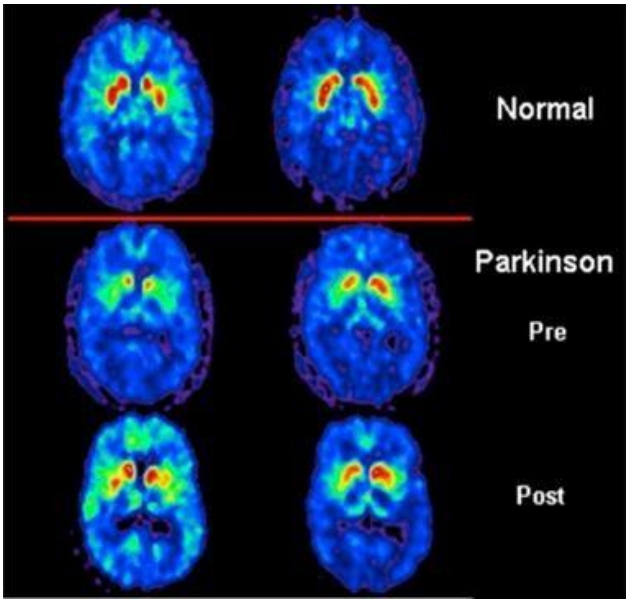

Fig 7. PET scan with upper scan of normal control, middle scan illustrating abnormalities in putamen of Parkinson's patient and last scan showing return to normal scan after introducing levadopa.[71]

Several of the literatures relies on the usage of FDG PET scan in which a small amount of fluoro-deoxy-glucose (FDG) is injected into the patient which produces color coded images of the body showing different tissues.

5. Miscellaneous:

Apart from the literatures on the popular scans described above, many others also demonstrated the detection and classification of PD patients using handwritten characters, foot sensor and voice data. It had been reported in various research that almost 90% of PD patients exhibit vocal impairments often regarded as dysphonia. The voice disorder can be due to various factors like polyps development, contact ulcers on vocal cords or paralysis due to stroke.

Multiple classification models like Decision tree, SVM, Naive Bayes etc. have been applied on the voice dataset to effectively diagnose and distinguish between PD and normal control. Apart from the Machine learning techniques, many Neural Networks models have also provided with better results which are best illustrated in the Table III.

Table 2. Summary of the various work on MRI data for Parkinson disease illustrating the ML and NN techniques applied till date.

III. CONCLUSION

The literatures described in Table II and Table III illustrates the various Machine Learning and Deep learning techniques applied till date and scope of different architectures that can be applied further to improve the accuracy of prediction for categorizing PD patients. There are various limitations majorly that of unbalanced dataset which generally produces false accuracy. Also, in certain work the amount of dataset used is less which does not provide with the appropriate results especially when applying deep learning architectures. It can be best inferred that deep learning models provide us with the much better results and accuracy than the machine learning models and can be explored more in the near future. There is much scope in application of DL techniques on PD disease detection.

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