

Management of Neurodegenerative Disease by Machine Learning: A Trending Approach

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Abstract—Machine learning and data mining techniques have been discovered to be critical for the investigation, retrieval, and analysis of any information created from any domain. Bioinformatics is a multi-dimensional strategy that incorporates the use of computer techniques for the collection of medicinal, healthcare or physiological evidence. These approaches are used to forecast patient prognosis in a variety of different medical domains, such as the risk for complications after already being hospitalized, cancer development, diabetic complications, sudden cardiac death, and so on. Furthermore, they may be utilized for breast cancer identification and treatment using mammography, brain tumor resection using magnetic resonance imaging, and brain cognitive state recognition utilizing functional MRI to identify neurodegenerative problems. As a result, the present investigation aims to exhibit the utilization of machine learning approach in management of neurodegenerative disorders.

Index Terms— Machine Learning, Neurodegenerative disorders, Alzheimer's disease, Parkinson's disease, Algorithms.

I. INTRODUCTION

Machine learning as well as data mining techniques [1] are found to be vital for the purpose of exploration, extraction, and interpretation of any data generated from any source. *Bioinformatics is a multifaceted approach that* includes the usage of computational means for medical, health, or biological data collected [2]. Over the last ten years, the total data has grown exponentially; moreover, the requirement to acquire modern knowledge with the aim of handling diseases makes bioinformatics a prominent research domain. Now, machine learning as well as big data methods has also been implemented for a better understanding of disease and fight against those diseases [3–6].

Machine learning techniques are found to be useful for the management of enormous amounts of data collected from the patient databases, which include medical records. These techniques are also capable of detecting the data patterns that cannot be defined by traditional statistical approaches [7–9]. These methods are employed to predict patient prognostication in several other medical areas, for example, the possibility of readmission after being discharged from the hospital [10], progression of cancer [11], complications in diabetes [12–13], cardiovascular mortality [14] etc.

Detection and diagnosis accomplished by the use of machine learning algorithms help a physician in the interpretation of medical imaging findings and also lead to a reduction in interpretation times [15]. These

predictive analytic encryptions are utilized for a variety of difficult jobs including dismemberment of pulmonary embolism with computed tomographic angiography [16-17] and detection of a polyp with virtual colonoscopy or computed tomographic in the colon cancer setting [18,19]. Further, they can be used for detection of breast cancer, and diagnosis by using mammography [20], segmentation of brain tumor by using MRI [21], and recognition of the brain's perceptive condition by using functional magnetic resonance imaging to detect neurological disorder [22–24]. Diagnosis of several neurodegenerative disorders is now upgraded by employing advanced neuroimaging techniques [25], so it is now contemplated as a valuable, initial, and dependable means for the detection of neurological disorders because every neurological disorder leads to impairment of definite brain regions [26]. The foremost concern, which arises from the health, as well as economic perspective, includes the effect of the aging society on the current healthcare system. Neurodegenerative diseases tend to affect a large population of the elderly and, till now no cure has been found for these diseases. Researchers usually look to discover new treatments to decelerate the progression of a certain disorder and aim for perfection in life of the patients. Heterogeneity in genetic, pathological as well as the pathological attributes of a certain neurologic disorder affects the rate of success in clinical trials [27].

II. NEURODEGENERATIVE DISEASES

Neurodegenerative diseases are considered a menace to mortal health. These disorders generally depend on age and are now turning gradually ubiquitous as an increase in the elderly populace has been observed in the last few years [28]. Some of the neurodegenerative disorders are Parkinson's disorder, Alzheimer's disease, ALS (Amyotrophic Lateral Sclerosis) spinocerebellar ataxias and frontotemporal dementia. These neurodegenerative disorders are found to be distinct in pathophysiology, for example, some of these cause memory or cognitive impairments whereas the rest are disturbing an individual's capability to act, speak or even breathe [29-32]. In such neurodegenerative diseases, the two major death pathways for neurons are apoptosis and necrosis [33-34]. The basic differences between these death pathways, necrosis and apoptosis recline in the discrepancy of cell structure as well as the leakage of cell components all through the concerned pathway [34-35]. Apoptosis is considered programmed cell death. There are some cytomorphological aspects of a cell undergoing apoptosis, such as shrinkage and DNA fragmentation, as well as chromosomal condensation [36-38]. When a cell undergoes apoptosis, apoptotic bodies are formed in several cases and there is no leakage of cellular contents [39]. Necrosis is indicated by cell swelling leading to the deprivation of cell membrane solidarity and leakage of the intracellular contents. The breaking of DNA is found to be associated with the process of degradation. However, chromosomal condensation is not included in the necrotic pathway [40].

III. ALZHEIMER'S DEMENTIA

Alzheimer's syndrome, the most prevalent dementia is specified as a gradually progressive neurodegenerative disorder having characterized features such as neuritic plaques and neurofibrillary tangles owing to the accretion of amyloid- β peptide in the brain, the medial temporal lobe as well as neocortical arrangements [41]. The German Psychiatrist, Alois Alzheimer observed the existence of amyloid plaques as well as an enormous neuronal loss when he examined the brain of an individual who suffered from loss of memory as well as a change in personality before his death, Alois then characterized that condition as a severe disorder related to the cerebral cortex [42-43].

Memory loss in the individuals suffering from Alzheimer's disorder is linked with the loss of neurons occurring in the hippocampal region. The persistence of this massive loss of neurons is associated with the advancement of the disorder [44-47]. Initially, the motor function was considered to be spared until and unless Alzheimer's disorder reaches its later stages, but in recent studies, it has been concluded that motor deficiency is also present during preclinical AD [48].

Neuronal loss preceding the clinical signs of Alzheimer's disease takes place in the entorhinal cortex layer II, the locus coeruleus moreover in the nucleus basalis of Meynert [44]. When the disease progresses, neuronal losses occur in the frontal cortex as well as other cortical/subcortical regions that can come out to be very severe in some cases [46,47]. Apoptosis pathways or Necroptosis pathways are considered to be involved. In the case of apoptosis, it is proposed that the initiator or the executor caspases get activated in the disorder [49-53]. The amount of extrinsic apoptotic pathway protein i.e., Fas as well as its ligands are also raised in the brains of patients suffering from AD [54]. A recently concluded study suggests that necroptosis signaling is also increased dramatically in the case of AD as the RIP1-RIP3-MLKL axis protein levels are augmented and the interactions among them are also increased [55].

Structural MRI conducted for patients suffering from AD reflected uneven atrophy of the lateral temporoparietal, precuneus cortices, mesial temporal, as well as the hippocampus [56-58], out of these, the most peculiar discovery was atrophy of mesial temporal [59-61]. The extent of atrophy observed on the MRI contemplates the severity of the disorder as well as the aggregation of neurofibrillary tangles [62-63].

A. Models of Deep Learning Algorithms in Alzheimer's Disease

The technique of machine learning is related to artificial intelligence which is generally employed for classification, reversion, clustering as well as normative modelling. Algorithms in machine learning are classified as supervised models in which the generated data is labelled and unsupervised algorithms in which the main goal is to distinguish untagged information in the clusters of interrelated cases, the third class being semi-supervised algorithms that include both labelled as well as unlabeled data [65]. The algorithm in machine learning is considered to be an operation used to select the best model amongst a certain group of options available that suits a particular group of findings. These algorithms possess numerous advantages, which may include their nonlinearity, fault tolerance, as well as real-time operations, which make them appropriate for composite applications [66]. Many machine learning algorithm such as K-Nearest Neighbours, Naive Bayes, Decision Trees/ Random Forests, Support Vector Machines, Neural Networks etc. have been developed until now. Significant research on biomarkers like CSF [t-tau/A β 1-42] [67], p53[68], amyloid [69], tau [70], amyloid- β 42 [71], D-glutamate [72] and Metabolites biomarkers [73] along with their prediction models of Alzheimer's disease have been performed.

B. Tau Protein, p-tau (Hyperphosphorylated Tau) and A β 42 (Amyloid- β 1-42) Amid Machine Learning

Numerous biomarkers for AD have already been considered till now comprising the accretion of tau and amyloid (A β) in the CSF [74], the metabolic changes in the brain developed from FDG-PET (fluoro-deoxyglucose positron emission tomography) [75], and MRI is exercised to measure the morphological changes in brain [76].

C. PET - Based Tau Biomarker with Machine Learning

Deep learning algorithms are employed in various operations in the quickly mounting massive and complex quantity of imaging data [77]. The prognosis of AD generally depends on deep learning techniques, which use neuroimaging data, which can be MRI or amyloid PET. The MRI scans are unable to anticipate molecular pathological indications of AD whereas amyloid PET is unable to anticipate the development of AD because of the deposition of amyloid- β earlier in the disorder development moving to plateau during advanced stages [78]. The existence and location of accumulation of tau in the brain have also been well-recognized [79]. Several researchers which examined neuropathology related to AD were able to generate a staging algorithm that describes tau's anatomical distribution [80]. Successive research has discovered that the tau's topography coincides with the accumulation of neurofibrillary tangle. The data obtained from the Cross-sectional autopsy shows that tau pathology concerned with AD initiates with accumulation of tau in the medial temporal lobe, which further expands to lateral temporal cortex as well as some parts in medial parietal lobe, moreover ultimately expands to the wider neocortical regions [81]. Choi et al. were successful in developing a deep CNN-based automatic image analysis strategy to correctly foresee prospective cognitive deterioration in individuals with MCI by means of FDG and florbetapir PET [68]. Jo and his colleagues were successful in developing a novel framework based on deep learning. They employed tau PET for detection of morphological phenotypes of tau accumulation [69].

D. NMDAR (N-Methyl-D-Aspartate Receptor) Intervened Biomarkers with Machine Learning

NMDA receptors are found to be vital in cognitive functioning [82]. Glutamate mediated by the NMDA receptor is a chief excitative neurotransmitter present in the CNS of mammals [83]. NMDA receptors and glutamate tend to have a significant role in synaptic plasticity along with molecular mechanisms of memory as well as learning [84]. Their critical involvement in excitative neurotransmission shows that there is an interruption in normal signalling via iGluRs in Alzheimer's disease [85-86]. L-Amino acids were found to be predominant in Nature. But it has been noted that D-amino acids influence protein folding, and the neuronal proliferation, as well as functional laterality of the brain. D- amino acids are also considered to be responsible for cognitive functions as well as the psychiatric disorders [87]. A study also brought to light that cognitive functions are affected by the levels of D-glutamate in patients suffering from AD or MCI [88]. Some previously conducted research also indicated that a decline in plasma levels of D-glutamate is responsible for the cognitive deterioration in the case of AD [88-89].

In some pilot studies, some machine learning models having NMDA receptor-mediated biomarkers such as D-amino acid oxidase activator, which is also identified as G72 protein echelon for detection of schizophrenia are used. They enlisted 149 participants, out of which 60 were healthy controls whereas 89 patients were suffering from schizophrenia. The G72 rs1421292 and G72 protein are used in the naive Bayes model, which presented the finest model for susceptibility of disorder (sensitivity was found to be 0.7969, and the specificity was found to be 0.9372, whereas the total integrated area beneath the receiver functioning distinctive curvature was found to be 0.9356) [90]. The use of biomarkers in the NMDAR and tryptophan catabolic pathways is also helpful in the prognosis of schizophrenia [91].

E. Algorithms for Metabolic by product Biomarkers

Lately concluded preliminary researches were able to examine blood metabolic intermediates and products as possible AD biomarkers [92]. Stamate along with his colleagues [72] made use of the facts obtained from the EMIF (European Medical Information Framework) for the invention of the AD Multimodal Biomarker that is abbreviated as EMIF-AD [93]. They discovered 800 metabolites by employing algorithms from machine learning to detect those suffering from AD from a certain set of data. Stamate and his colleagues also correlated the efficiency of metabolites based on blood for the prediction of AD along with the cerebrospinal fluid markers. Deep learning and other artificial intelligence techniques; XGBoost, as well as random forest algorithms to distinguish AD from the CN were employed. The internal validation of these models was carried out by utilizing nested cross-validation. While working with the assessment records, Deep learning exhibited an AUC of 0.85 whereas XGBoost exhibited 0.88 and Random Forest exhibited 0.85.

IV. PARKINSON'S DISEASE

Parkinson's syndrome is known to be a progressive neurodegenerative disorder in which the loss of midbrain dopaminergic neurons occurs. Various evidences indicate that in most cases, the combination as well as the interaction of genetic risk variants, aging, along with environment results in the development of PD [94-95]. In Parkinson's syndrome, phosphorylated synuclein accumulates in the Lewy neurites and Lewy bodies. The pathology of the Lewy body is responsible for the neuronal loss in the pars compacta region of substantia nigra, it also spreads to subcortical as well as the cortical regions, thus leading to the motor as well as nonmotor manifestation of PD [96]. In the case of PD, up to 90% of individuals gradually develop a voice as well as speech disorders, generally termed hypokinetic dysarthria (HD) [97]. 15% of patients who were suffering from Parkinson's disease have ancestral record of this disorder, found to be induced due to genetic changes in the *PARK2*, *ARK7*, *LRRK2*, *PINK1*, or the *SNCA* genes [98]. *LRRK2* mutation is more prevalent in familial Parkinson's but has a late time of onset. Various autosomal dominant types of gene mutations comprise mitochondrial dysfunction as well as dysfunctional sort of gene products. The genetic changes occurring in the case of transmembrane protein 230 commonly known as the *TREM230* gene are associated with the Parkinson's familial form [99], whereas genetic changes in *PARK7* are found to be linked with familial forms of Parkinson's thus various studies aim to measure *PARK7* in the CNS and plasma samples [100].

MRI is mainly employed for the evaluation of structural causes including vascular diseases, tumors, etc., and the neurodegenerative diseases. PD is also found to be comorbidity with any other diseased state, and hence physicians are recommended to be tremendously cautious not to decipher positive results found by structural neuroimaging as proof against the Parkinson's diagnosis if the clinical syndrome is indicative. SPECT imaging which involves the use of tracers that are radioactively labelled and bind with the presynaptic striatal dopamine transporter is found to be useful for the assessment of the dopaminergic nigrostriatal pathway integrity, which is initiated to be flawed in PD. A decline in SPECT signal inside the striatum indicates a flaw in the dopaminergic nigrostriatal pathway because DaT is declined in the presynaptic terminals due to neuronal degeneration [101]. Following are the studies based on machine learning for Parkinson's Early Detection

A. Dopaminergic Imaging

Machine learning is found to be helpful in dopaminergic imaging analysis for Parkinson's early detection. Prashanth et al. [102] examined the use of various support vector machine methods in categorizing SPECT images to detect PD. By the use of striatal-binding ratios in the striatal regions obtained from PPMI dataset, it was concluded that the support vector machine was effective in Parkinson's early detection, and the support vector machine with a non-linear kernel was found to attain higher detection rate that was found to be $96.14 \pm 1.89\%$ than the support vector machine with linear kernel. In a research, Oliveira et al. [103], adopted a support vector machine and some other classifiers for categorization of binding potential at every voxel in the

striatum of SPECT images meant for the Parkinson's premature recognition and stated that the support vector machine was able to achieve the highest detection rate that was found to be 97.86%. Thereafter, Prashanth et al. [104] also included the non-motor PD features comprising the measurement of cerebrospinal fluid for improving the early PD detection rate. Then, Prashanth et al. [105] also observed that the features based on shape and surface fitting were found to be more effective than striatal-binding ratios for Parkinson's premature recognition and feature classification with a support vector machine produced a classification accuracy of about $97.29 \pm 0.11\%$ when n was 427 [105]. As per observations made by Oliveira et al. [106], the extent of the striatal area uptake at 96.5% rate of detection, was able to surpass the feature based on the uptake ratio for Parkinson's early detection when n was 443. These outcomes were sufficient to establish the role of the approach based on machine learning in investigation of dopaminergic image for the premature recognition of PD.

B. Structural MRI

The machine-learning-based approach was helpful in improving the diagnosis from an MRI. The categorization of combined MRI measurements which includes gray matter volume, and white matter volume along with the volume of cerebrospinal fluid with a support vector machine was useful in the early detection of PD accurately where the average accuracy was found to be about 80% ($n=19$)[107]. The use of a classifier of linear discriminant analysis along with imaging features that was applied to the MRI images of early Parkinson's patients where 99% are in early stages and n was 374, produced a classification accuracy of approximately 81.9% that was found to be greater than that produced by support vector machine i.e. 69.1% [108]. In a study, Singh and Samavedham [109] established that in the case of early PD, structural changes can be identified by employing MRI along with a map approach that is unsupervised as well as self-organizing($n=518$), which produced a classification accuracy of greater than 95%. This approach was then used for a larger database ($n=1316$) from PPMI and ADNI and produced a classification performance of $95.37 \pm 0.02\%$ to differentiate patients with PD from the healthy individuals [110], which established the role of the approach based on machine learning in the detection of Parkinson's disease.

C. Functional MRI (fMRI)

In various studies, rs-fMRI has been found useful for Parkinson's early detection. Wu et al.[111] adopted efficient connectivity obtained by using rs-fMRI to inspect individuals with an indication of early Parkinsonism ($n=16$) and then observed decreased connectivity of substantia nigra pars compacta with the striatum, and thalamus, as well as the cerebellum region, which was found to be negatively associated to the Unified PD Rating Scale scores. The rate of detection for early Parkinsonism by employing only the rs-fMRI imaging features is generally not found to be high i.e., about 74%[107] and improvement is required. The results obtained from two rs-fMRI studies conducted in asymptomatic LRRK2 mutation carriers indicated that disruption in functional connectedness precedes the existence of motor symptoms [112,113]. Rolinski et al. [114] used rs-fMRI to scrutinize patients who enter the rapid eye movement stage while sleeping ($n=26$), as well as patients suffering from PD ($n=10$) and observed that measures of functional connectedness of basal ganglia network dysfunction distinguished REM behaviour disorder and Parkinson's disease from healthy controls with high sensitivity of about 96% and specificity of about 74% for a REM behaviour disorder, 78% for Parkinson's disease which indicates that rs-fMRI can be used as a biomarker for identification of early changes in functional connectedness in the basal ganglia network in individuals who are at higher risk of Parkinson's syndrome and persons suffering from Parkinson's syndrome.

D. Multi-Modal Data

Multi-modal imaging when combined with clinical data is able to improve Parkinson's early detection. Long et al. [107] observed that combining the multi-modal features has brought significant improvement in Parkinson's early detection and multi-modal imaging (both MRI as well as rs-fMRI) along with combined multi-modal features (volume of gray matter, white matter as well as cerebrospinal fluid, along with the Regional homogeneity, the amplitude of low-frequency fluctuation and the Functional connectivity) produced higher classification accuracy of 87% in comparison to single-modal features where accuracy in case of MRI is 80% and in the case of rs-fMRI, accuracy is 74%. In a study, Oliveira et al. [106] studied the SPECT images of individuals with early indications of PD and observed that various data features were having greater classification accuracy i.e., 96.5%, 95.4%, and 93.9% for the length of the striatal region, the putaminal binding potential, as well as the striatal-binding potential respectively, whereas the classification accuracy obtained from the combined imaging features was about 97.9%. Afterward, Prashanth et al. [104] categorized non-motor clinical data features including the REM sleep behaviour disorder, and the olfactory loss, as well as

measurements of cerebrospinal fluid along with SPECT imaging markers by using classifiers like the support vector machine and random forests, thus observed that by combining the data features and the support vector machine classification produced the finest performance in the early detection of PD, the rate of detection was found to be $96.40 \pm 1.08\%$ ($n = 401$).

V. CONCLUSION

Machine learning processing is a artificial intelligence technique that allow for the rigorous probing of various datasets in order to detect previously unknown patterns and correlations in the data. ML algorithms have been used to research neurological diseases, and they possess the potential in earlier detection, prediction, and the creation of novel therapeutics. There are several deep - learning strategies, and selecting the optimal approach to deploy to data from different sources is critical for obtaining accurate outcomes.

The very first region of neuroscience to profit from the implementation of computer approaches to perk up prognosis was neuroimaging; more lately, the development of computational methodologies to motor control and language specification assessment has shown commitment in reducing the time required to conduct clinical evaluation. Deep learning applications in longitudinal patient information gathering and digital medical records have the ability to improve prognostic forecasting and client classification. To fully integrate deep learning into predictive and therapeutic neurology practise, as well as the creation of prospective therapies, substantial quantities of controlled information and thorough evaluation of neural network models will be required.

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