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Neural Network Applications in Understanding Neurodegenerative Disease Progression

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Abstract

Neurodegenerative diseases are a group of chronic progressive disorders characterized by the gradual degeneration of the structure and function of the affected nervous system. The two main components of the nervous system are the brain and spinal cord. Many neurodegenerative diseases, including Alzheimer's, Parkinson's, and spinocerebellar ataxia, can damage these areas and consequently affect memory, thought, and language. Moreover, there is no cure for these destructive diseases, and they are becoming more common due to population aging. Growing awareness of the risk factors and improving diagnostic technology have led to progress in the initiation and development of different investigational interventions. Artificial Neural Networks are a simplified model of the human brain's decision-making structure and have been extensively used in a wide range of medical applications.

Although the application of Artificial Neural Networks assists with various stages of research, its utility in the comprehension of neurodegenerative disease progression and management is largely untapped. This paper seeks to evaluate the existing applications of Artificial Neural Networks in Alzheimer's, Parkinson's, and spinocerebellar ataxia to determine the readiness of Artificial Neural Networks to support advanced progress in understanding neurodegenerative diseases and to help researchers know where to focus on preparing the application of Artificial Neural Networks in the management of different stages of neurodegenerative diseases. The results suggest that several prediction models have been developed from Artificial Neural Networks that can identify individuals at risk for Alzheimer's and Parkinson's, the progression of Alzheimer's, spinocerebellar ataxia, and Parkinson's. However, there is no model to identify the stages of the process of neurodegenerative diseases.

Keywords: Neural Network; Deep Learning; Multimodal Data; Alzheimer's Disease; Parkinson's Disease; Huntington's Disease; Amyloid-beta; Tau; Alpha-synuclein; In-vivo Imaging; Drug Discovery; Precision Medicine; Progression Modeling; Survival Modeling; Longitudinal Data

.1. Introduction

Almost 30 years ago, rumblings of a coming revolution in the endeavor to model healthy and pathological brain form and function using artificial neural networks started appearing in the scientific literature. Over this period, considerable progress in the development of these algorithms has been achieved. Today, highly sophisticated representations of brain structure and function can be developed using these models when provided with appropriate measurements of brain status. Nevertheless, a large gap exists between understanding how these models work and encoding this knowledge into the development of common sense algorithms that would enable them to develop an understanding of being sick in the manner that an experienced neurologist or geriatrician can for their patients. Now, as we move into a period where the

need for common sense artificial agent models to work on understanding normal and abnormal aging is urgent, this chapter takes stock of how near we are to the development of such models. It's easy to think of past milestones in achieving computer understanding and generation of fixed and dynamic structures in the world around us. Quite fundamental are Turing, LISP, and general expert systems architectures. An extension of the basic structure of such models to the overarching goal of building a model capable of understanding and generating the form and function of the parts of the central and peripheral nervous systems is notable. That is, the brain model sought could delve into the cellular, extracellular.

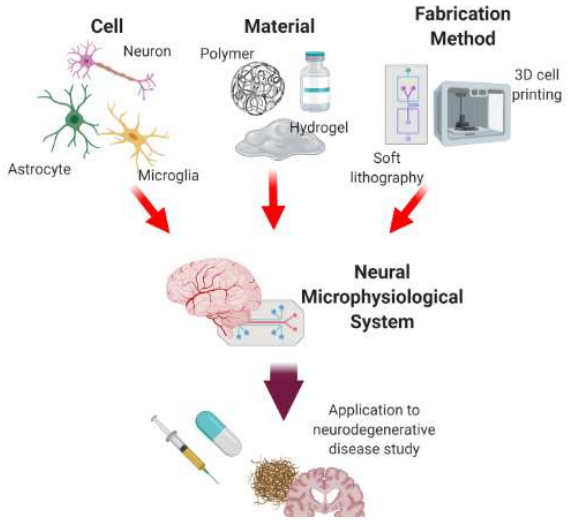

Fig 1: Neurodegenerative Diseases in Central Nervous System

1.1. Background on Neurodegenerative Diseases

Neurodegenerative diseases, such as Alzheimer's, Parkinson's, or Huntington's disease, result in a progressive loss of structure and function of neurons in the central nervous system. In particular, signs of neurodegeneration manifest in typical regions of the brain. The sparse and lengthy diagnostic process complicates the development and delivery of new therapeutic interventions. Currently, there is little understanding of the mechanisms of disease progression. In most cases, pathological material is required to confirm the final diagnosis.

A key issue for people affected by these diseases and the burden they place on local and international healthcare is the time from the first onset of symptoms to diagnosis and the ability to deliver early therapeutic intervention. In general, an incompleteness of understanding is a gatekeeper for the research process leading to the improvement of disease diagnosis and understanding of disease mechanisms. Diagnostic ability is determined by the extent of understanding, and future potential is limited by the insights of today. The proposed research attempts to remove this bottleneck by providing new insights into the relationship of imaging changes mapped spatially to measured connections in the network to biological changes also occurring in the same locations. With the help of recent advances in analytical machine learning and deep learning models, inspired by neural circuitry, neurodegenerative problems can be addressed in a new way. For example, challenges like disease severity prediction, summarizing a patient's spread of tau pathologies, disease conversion detection, disease monitoring, patient similarity, and disease progression representation with the help of machine learning and deep learning methods can be tackled in a new way. Importantly, the method developed and thoroughly tested will be generally applicable to all subtypes of neurodegenerative diseases and is expected to assist in mapping the estimated ten-year onset scale of disease severity to measurable phenotypic metrics, preferably captured by established imaging protocols.

Equ 1: Loss Function (Mean Squared Error)

$$L(\hat{y}, y) = \frac{1}{N} \sum_{i=1}^{N} (\hat{y}_i - y_i)^2$$

Where:

- N is the number of training samples,
- $\hat{y}_i$ is the predicted value for the i-th sample,
- y_i is the true value for the i-th sample.

1.2. Importance of Understanding Disease Progression

For any disease, but particularly neurodegenerative diseases, it is important to understand how the disease progresses. Is it the accumulation of the hallmark proteins that kill neurons that correlates with the progression of cognitive decline, or does neuronal cell death provide the clearest pathological measure of progression? Perhaps it is the progression of other host responses that drive the progression and killing of cells. It is likely that the answers will not be the same for all neurodegenerative diseases or that the importance of the different pathological processes will not be as clear at all stages of disease for all patients. Nevertheless, the answer will be important, in particular, in designing trials. If the progress of the disease is driven entirely by the accumulation of the hallmarks, then it is much easier to design a trial. The big question is whether any of these hallmarks contribute to the symptoms, and particularly the loss or execution of neurons that underlies these symptoms.

Key to developing new approaches, and in particular, to identifying new animal models and drug targets, is increasing our understanding of what is involved in the natural progression of disease. Then, if we succeed, we should and must run long-term studies of the animal models and perhaps patients to ensure that the translation of disease hallmark manipulation into amelioration of disease symptoms comes about. Clinical trials need to keep better track of what is happening throughout the bodies of those receiving the treatment, rather than assuming that any consequences arising are due to the introduced agent. There is enormous potential for a well-informed and developed patient advocacy group to help with this understanding. Knowledge of how a disease is progressing naturally will also facilitate the identification of appropriate models to study progression and to identify targets for manipulation for use in drug discovery.

2. Neural Networks in Healthcare

Neural networks have been used for purposes like disease classification and prediction, medical image analysis, automated extraction and interpretation of medical information, robotic surgery, and wearable remote beating heart identification. Predicting the presence of neurodegenerative diseases like Alzheimer's from the temporal lobe MRI scans and cerebrospinal fluid biomarkers, or the presence of schizophrenia from the gray and white matter brain images are all examples of neurodegenerative disease identification with the help of neural networks. Prediction of trends in neurodegenerative disease progression, personalized diagnostics in neuroimaging, and predicting magnetic resonance imaging from tissue parameters with the help of deep generative models are also examples of widely practiced neural network applications in health care. Recently, a research study demonstrated how by utilizing deep learning in combination with cognitive assessments, medical images, and electrophysiological data one can estimate where the disease pathology is located in Alzheimer's, assign a severity score, and have a rough time estimate in the order of a few years for clinically important disease milestones. They proposed models that can identify if the pathology is located in the medial temporal lobe accompanied by imagery and electrophysiological explanations of how the pathology is interacting with different imaging modalities and how these data points look to a trained deep learning model.

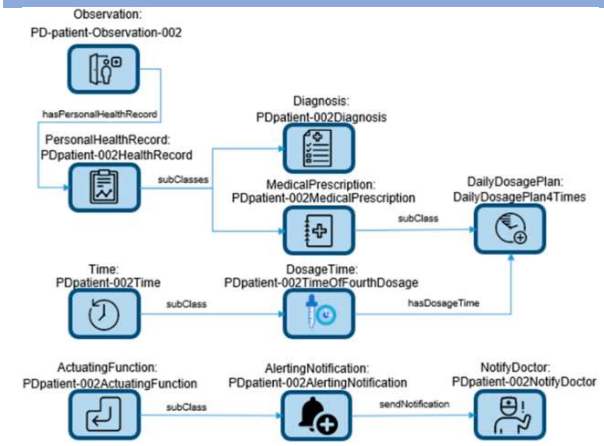

Fig 2: Neural Networks for Parkinson's Disease Monitoring and Alerting

2.1. Overview of Neural Networks

Neural networks, or artificial neural networks, refer to an interconnected set of nodes, each of which is a processing unit, much like that of a brain or a biological system in general. These nodes are also called neurons, and they operate on similar principles as biological neurons, with the concept of activation in response to inputs. Inputs to a neuron are modeled according to various schemes, such as simple summation used in generalized linear models or correlation weightings, and operate at near-infinity speeds. In the simplest form, these 'activations' are assumed to be binary; they are either active or not. They emulate the synaptic effects of a biological neuron. The weights assigned to these inputs or the correlation weightings between inputs are adjusted through learning strategies that allow the network to model complex patterns from complex data along many dimensions. The output from a given neuron is a scalar, either continuous in the case of regression or thresholded in the form of classes in the case of a classification model.

The neuron itself is part of a so-called layer—a perceptron with at least one input and one output and potentially many hidden layers that connect the input to the output. A full ANN consists of many such layers. If there is one such layer, it's called a perceptron, and if there are many of them, they are called multi-layer perceptrons. The first layer is called the input layer, and the last one is the output layer, with hidden layers in the middle. The connections between each layer are fully connected, with the resulting network known as connected neurons in an array fashion. In this sense, training a neural network involves adjusting the so-called weights in between the layers in order to optimize the performance and accuracy of the network once it has been trained.

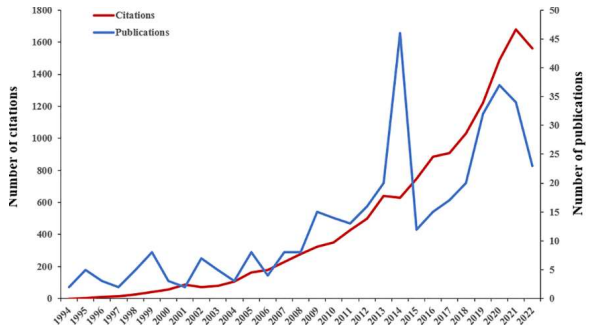

Fig : Research trends and hotspots of neuropathic pain in neurodegenerative diseases

2.2. Applications in Healthcare

In addition to imaging, the biological sciences are producing lots of data. At the forefront, genomics is empowering researchers to uncover the mechanisms of life in both normal and diseased cells. Clinical tests, next-generation

sequencing projects, and multi-omics studies are increasingly used to identify variations in genes responsible for disease. Due to the relentless pace of data production, the abilities to store, manage, and analyze the data have become a scientific discipline in its own right. Here too, deep learning can be applied.

For example, in the domain of personalized medicine, which is defined as the right treatment for the right patient at the right time, machine learning is used to correlate genomic data with the disease outcome of an individual patient. This is important because every patient is unique, and an average effective treatment may not work in every instance. Many methods can be applied to this task, which usually involve correlating the expression, splicing, or methylation data with model features. However, deep learning models have been demonstrated to be particularly well suited to rare cell type detection. Moreover, another major utility of deep learning in biology is drug discovery and drug target detection. In one of its applications, screening is used to genetically perturb each gene and answer how different genes influence a particular biological hypothesis. The data processed by machine learning algorithms includes information about the clustered regularly interspaced short palindromic repeats.

In conclusion, state-of-the-art machine learning models are pushing the boundaries of both the amount and type of data that can be used to answer questions across the whole domains of healthcare, including imaging, genomics, and clinical laboratory. They can be used in fundamental and translational research, wearable devices, and bioinformatics software. In addition to the automated derivation of new biological features, the artificial intelligence open-source libraries have contributed to accelerating biomedical discovery by creating a culture in which everyone can access innovative and open-source models. Hence, while given a situation where the references from the field of deep learning and biomedicine are extensive and still growing, we gathered those most relevant to the precise goals summarized.

3. Neural Network Applications in Neurodegenerative Diseases

The process of diagnosing neurodegenerative diseases can be complex and inconclusive, with many possible underlying factors. Given the relevance of neurodegenerative diseases, many works have approached the problem of predicting a particular outcome from a particular imaging analysis input for Alzheimer's disease and others, due to the increasing availability of data. While the performance of these works has consistently improved, they still present a diffuse capacity to return the conclusions reached by experts in research and clinical practice. Therefore, data analysis should not only take into account the existing data but also consider the expectations of specialists. In addition, the traditional methods used to interpret the results obtained from these methods are no longer sufficient, which makes diagnosis work more challenging than it seemed at the time.

The use of deep artificial neural networks is not inherently related to the diagnosis of neurodegenerative diseases. Due to their high complexity, these models have always been considered possible secondary tools that could be replaced in scenarios where human interpretation was limited. It is mentioned that these algorithms possibly do not allow the extraction of meaningful conclusions. However, in recent years, a large number of works have shown that it is possible to explain the predictions made by deep neural networks to fully understand the role of different features in decision-making. This exploration stage, capable of understanding a neural network, is a relatively new topic; it has undergone a significant change in recent years, showing a sharp increase in the number of papers that make this theme central to their work, demonstrating that models are already available that can provide diagnostic support based on experts and are able to reveal important information about the biological processes behind the results.

3.1. Current Approaches in Understanding Disease Progression

Disease progression in general can be explored through various approaches and from various scales, from systemic panels of markers of possible risk prediction, patient stratification, suggesting mechanisms with possible relevance to progression, modeling risks in the normal population for large trial designs, the tempo of onset and progression in clinical

manifestations, and molecular profiles of individual affected brains. Given these scales, neurodegenerative disease progression can be approached from the spatial, temporal (across individuals), injury (disease level progression), and population level completion or carried away by a more or less related episodic form of a new symptom or cognitive profile. To fully understand progression across these scales would necessitate either access to a large dataset with whole brain microscopic processing or advanced cell-resolution brain imaging. To date, there are not any long sparsely spaced longitudinal studies performed at any scales, limiting the insights into aging or injury experience.

Disease progression can be seen in at least a few interweaved aspects such as distinct cascades, precipitation of new symptoms or stage-specific imaging profiles, kinetically defined manifestations, sub-optimal overlaps in both time and anatomically precise mapping between samples in large cohorts, and shared trajectories of individuals in the at-risk state, including white matter or individual neural trajectories. Each of these is a window into how progression can be defined and studied using modern large-scale imaging-enhanced genomics characterizations that are only executable on sample allocation or associated pathology. Although it would be useful to measure a like-modeling quantified effect across each phenotype in appropriate patient samples. This will allow us to develop and recruit time-tellers for progressivist observations performed in a large enough population.

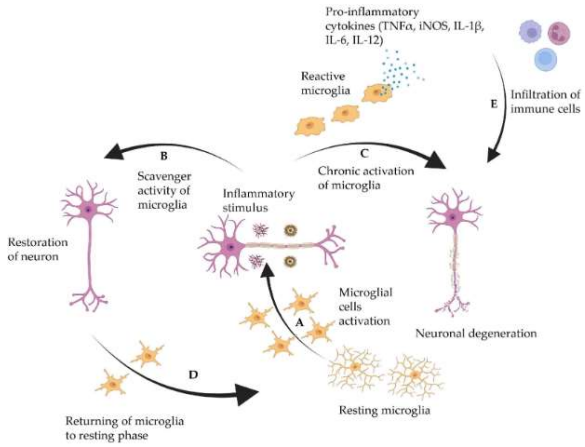

Fig 3: Neurodegenerative Disorders

3.2. Challenges in Traditional Methods

Over the years, neuroscience, and more specifically the field of neurodegenerative disorders, has made tremendous strides in understanding, identifying, and characterizing specific stages of the disease. The phenomenon of neurodegeneration is understood to be multifactorial and is a result of both extrinsic and intrinsic changes. While several manifestations have been used to observe the progression of the disease, including behavior, symptoms, and molecular biologic markers such as protein aggregates and cytokine levels, a significant challenge in the field has been to understand the heterogeneous changes that determine the progression of the disease and pinpoint the identity of these biomarkers. Once identified, these biomarkers could potentially play a significant role in a patient's diagnosis, prognosis, and treatment. Despite the advancements in knowledge, the lack of true therapeutic options for multiple neurodegenerative diseases remains a significant challenge.

One of the significant reasons behind the slow progress in the field has been the inability to define neurodegenerative disease progression through a common metric or a signature biomarker. For a long time, much of the research community has utilized traditional anatomic and metabolic information in the form of MRI, CT, ultrasound, positron emission tomography, and single-photon emission computerized tomography for understanding neurodegenerative disease. These measures are not indicative of early stages of the disease pathology, and it can also be challenging to obtain permission to collect pre-mortem and post-mortem information using these techniques. Moreover, autopsies of Parkinson's disease

patients have revealed abnormal aggregates in the later stages of the disease, and patients with dementia have shown a combination of tau, amyloid, and alpha-synuclein aggregation even when these were not observed during the initial stages. All these conundrums have led to more specialized techniques such as biomarker lumbar puncture and PET being slowly developed in clinical trials. These specialized techniques have made it challenging to understand large numbers of diverse patients who could potentially present mild or atypical symptoms. Even as this was taking place, fundamental concepts about neurodegenerative progression became more challenging to understand and simplify. For example, the Braak and Braak hypothesis suggested that aggregation in areas connected to the olfactory system next spreads to the brainstem. From the brainstem, the pathology progresses to the limbic system/amygdala, before ultimately spreading into the cerebrum. Due to the limitations of technology and the methods employed in clinical trials, much of the early literature studies have focused on quantifying the burden of these aggregates. Consequently, much of the earlier work on understanding disease progression provides information on end-stages of the disease, rather than capturing information on intermediary steps to understand the actual progression.

Equ 2: Backpropagation (Gradient Calculation)

$$\frac{\partial L}{\partial \mathbf{W}^{[l]}} = \frac{1}{N} \sum_{i=1}^{N} \delta_i^{[l]} (\mathbf{a}_i^{[l-1]})^T$$

Where:

- $\delta_i^{[l]}$ is the error term (or delta) for the i-th training sample at layer l,
- $\mathbf{a}_i^{[l-1]}$ is the activation of the previous layer for the i-th sample.

4. Case Studies and Research Findings

Case Study 1: Brain Iron Accumulation. Iron is primarily accumulated as its storage form, ferritin, in microglia and oligodendrocytes. Since an average brain iron burden of 11 mg is observed at birth, it was long assumed that increases in brain iron were due to increased myelination. Consequently, iron accumulation has clinical implications. The most common clinical manifestation in this population is developmental regression accompanying the accumulation of iron in the basal ganglia, withdrawal of hand skills, and a significant increase in irritability. Other common neurological issues include tremor, gait disturbance, dysphagia, dystonia, chorea, rigidity, dysarthria, and palilalia. Even though clinical similarities between the four disease entities sharing abnormal brain iron accumulation are common, variations prevent accurate differential diagnosis at an early disease state, which needs to be addressed.

Case Study 2: Amyotrophic Lateral Sclerosis-Frontotemporal Dementia. ALS demonstrates focal and patterned progression beginning in one or more body regions. In the case of bulbar onset ALS, localized to the tongue, pharynx, and upper extremities, this pattern offers the opportunity to investigate purely tract-based contractions from motor neurons and exclusively examine their correlating cognitive and behavioral changes. Thus, the characterization of FL with simultaneous testing of cortical, subcortical, white matter, and tract trajectories could provide insight into its anatomy and the effect of its strand on clinical behavior when researching such inclusive tracts using multimodal imaging. Related to the former point, all three populations of lesion-bearing motor neurons can provoke disinhibition through commonly overlapping circuits. Additionally, each motor neuron population can lead to cell death in their parent motor cortex projection neurons. With a complex interplay of suprathreshold activity and contractions involving directly retrogradely connected motor cortex neurons.

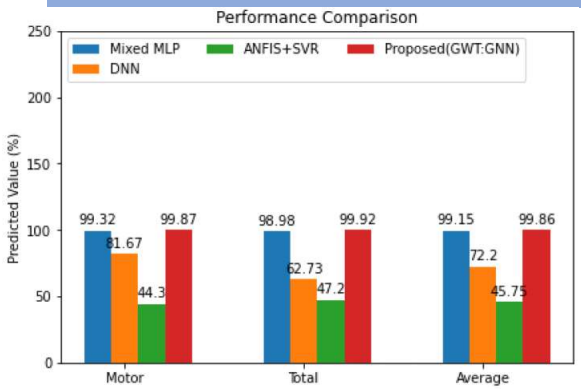

Fig : A Graph Neural Network (GNN) Based Classification Approach with Graph Wavelet Transform (GWT) Using Protein–Peptide Datasets

4.1. Key Studies Using Neural Networks

Modeling the dynamic shape of the cortical surface using temporally consistent structural connectivity by integrating temporal and spatial information in the form of reweighted spatiotemporal graph convolutional neural networks showed propagation of decreased surface volume. The study showed the presence of decreased volume aggregation regions for Alzheimer's and its progression through time, and a decrease in volume for Parkinson's and stroke-onset regions with a weak trend of propagation. Evaluation on a longitudinal mild cognitive impairment dataset allowed the investigation of how Alzheimer's disease progresses by color-coding regions with strong positive or negative propagation at different stages of conversion to reveal the increasing positivity of the propagation scores around the pericalcarine cortex through to the superior bank of the central sulcus. Using the time rankings of propagation, the surface region of interest in neuroimaging and the dataset could be pruned to develop content-based analysis pipelines for insight generation in a fraction of the time. High-ranking brain regions were validated in a separate study, demonstrating the capability for explainable AI and its extension towards uncovering correlations and creating hypotheses rather than only predicting future stages at a group level.

Gaussian gradient topographic independent component analysis applied to the multi-center Alzheimer's disease cohort found increased uptake as principal components within the salience, default mode network, and subcortical components, applied convolutional neural networks, and training data augmentation. Comparing results from those with no, rapid, and slow cognitive decline confirmed common aging signatures at the group level and stations that show change or cessation stratified by individuals. In contrast to traditional health levels, the individualization of stations may stress less focus on areas of existing apparent clinical diagnostic utility and focus on new areas that can facilitate early disease detection. Alzheimer's lead had relations to functional activity, suggesting commonalities to multiple timescales of uptake over the neurodegenerative timeline. In inter-region correlation, the entorhinal region was less related to the frontoparietal and default mode network. Discovery of dynamic vulnerable brain regions may help differentiate stages of progression. Brain functional states may be the mediating factors facilitating disease conversion but did not reduce to exact disease states. Dynamic output labels could help diagnose extending from a categorical distinction to risk estimates. Digital biomarkers of individual progression are informative for intervention start timing, raising possibilities towards personalized treatment.

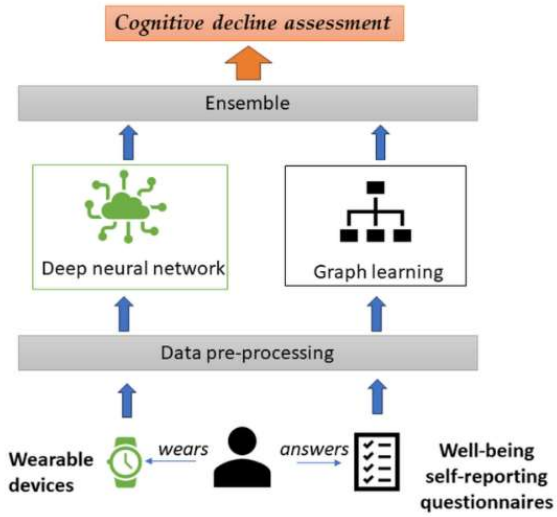

Fig 4: Deep Neural Network Ensemble

4.2. Insights and Discoveries

As the estimation of the rate of disease progression of patients with Alzheimer's disease, Parkinson's disease, and ALS is a valuable capability that can facilitate therapeutic development and treatment planning, the Triangle Learning Model and Goal-Based Balanced Tri-training model, well suited to simultaneously learn dynamic motion features from 3D skeleton data and estimate the ROP, are proposed. The Movement Disorder Society - Unified Parkinson's Disease Rating Scale, the Clinical Dementia Rating, and the Amyotrophic Lateral Sclerosis Functional Rating Scale scores are three commonly employed rating scales to assess the severity of Parkinson's disease, Alzheimer's disease, and Amyotrophic Lateral Sclerosis. The severity of a neurological disease relates to disturbances in characteristic motor control strategies quantifiable through the kinematics of upper limb movements. The characteristic motor control strategies are not limited to the following: the presence of freezing gait, bradykinesia, and dyskinesia.

The acceleration data are labeled into the three typical states: Freezing of Gait, Non-FoG, and Fasciculations, and are classified offline. The deep learning-based method in detecting and classifying fasciculation behavior, which is one of the important early symptoms of amyotrophic lateral sclerosis, should be noninvasively and automatically detected. A Recurrent Neural Network takes time-domain signals such as gyroscope and accelerometer data as input and achieves state-of-the-art performance in detecting fasciculation events in amyotrophic lateral sclerosis patients. The machine learning method for decoding achieves state-of-the-art performance in distinguishing sporadic amyotrophic lateral sclerosis patients' electromyography from those of healthy controls and from patients with mimicking disorders.

5. Future Directions and Implications

Given the advances in neuroimaging measures of the brain from a variety of sources, these data can be easily modeled in this framework. USNMs are developed based on biological hypotheses. The identification of USNMs using a data-driven approach through a specific disease cohort would provide a novel means by which biomarkers could be discovered. The progression pattern estimated by the USNM will capture unique changes in the network of causal relationships in the assessment for changes of deterioration. The networks offer new insights into the field of neuroscience as well, as they capture the underlying associations that define the progression rate of the disorder.

In the field of neurodegenerative diseases, this direction of research will change the way by which therapeutic interventions are gauged and neurodegenerative diseases are understood. Current research trials observe a particular

pattern of disease progression change and interpret this slowdown as an indication of success. The use of USNMs as a gauging instrument will make it possible to determine whether this disease slowdown is actually due to treatment. Furthermore, by having stability along the rapid transition as a gauge, researchers will be able to better identify the true effect of the intervention being applied. This will not only result in an increase in detection power but will also reduce the amount of time, cost, and subjects required to detect this effect. Once different disease patterns have been observed over time, they can be studied to understand the causes of the progression actions. In order for neurodegenerative diseases to be fully treated, it is important to understand the mechanism that converts healthy subjects into cases.

5.1. Potential for Precision Medicine

Progress towards precision medicine depends on early detection and treatment of disease, tailored to an individual's symptoms, genetics, environment, or lifestyle attributes. In dementia diagnosis, this objective is only partially being met by employing neuroimaging, fluid biomarkers, and clinical examination data, which is integrated with information on a patient's cognitive status, medical history, and family conditions. In the context of chronic diseases such as Alzheimer's and prion diseases, every piece of information about the patients matters. To access patient data, cutting-edge technology such as machine learning will play an increasingly crucial role, particularly in the early disease detection phase when showing the least amount of clinical symptoms, in contrast to the substantially advanced neuropathological, genetic, and epigenetic disease profiles.

Detection rates are current, albeit distressing, data about the number of patients that have been excluded from a majority of clinical drug trials for Alzheimer's disease, which advance understanding in the brain's pathophysiology and can allow medications to identify the minimal existence of neuropathological symptoms. Although this can represent one of the biggest changes of success, numerous but impractically large undertakings are reliant on big data analyses to discover and verify the link between a patient's clinical profile and various other exogenous and endogenous data, which often relate genetic, proteomic, and transcriptomic levels to global phenotypic disease development, as well as to measure outcomes such as brain atrophy from multiple structural imaging data provided by computational models.

Fig 5: The Future of Precision Medicine

5.2. Ethical Considerations

As explained above, care should be taken when applying cutting-edge computational methods to studying neurodegenerative diseases due to the relevance and sensitivity of the possible results, the almost infinite capacity for deconvoluting and analyzing human data, the lack of objective validation and evaluation metrics for predicting progression, and the subtle and serious ethical questions involved, such as fairness, uncertainty, interference, and privacy. There are some key considerations regarding the ethical challenges in AI research, such as the duty of care, public interest, data governance and management, accountability and transparency, equality, non-discrimination, and fair treatment.

In the context of healthcare, some open questions and pitfalls arise, such as who is ethically responsible for regulating the use of AI in healthcare? Given the complex nature of the health sector, how do we ensure that AI serves the collective good rather than private interests? How do we avoid the reinforcement of existing biases and inequalities in AI-designed tools? What are the hidden costs of continuing down our current AI-driven path? From a general AI ethics perspective,

other questions arise, such as who is ethically responsible for regulating the use of AI in healthcare? Given the complex nature of the health sector, how do we ensure that AI serves the collective good rather than private interests? How do we avoid the reinforcement of existing biases and inequalities in AI-designed tools?

Equ 3: Regularization (L2 Norm)

$$L_{\text{reg}} = \lambda \sum_{l=1}^{L} \|\mathbf{W}^{[l]}\|_2^2$$

Where:

- λ is a regularization hyperparameter,
- $\|\mathbf{W}^{[l]}\|_2^2$ is the squared Frobenius norm of the weight matrix at layer l.

6. Conclusion

The development and application of neural network algorithms for the characterization of neurodegenerative disease progression have resulted in a greatly expanded wealth of knowledge of underlying disease pathology. In particular, they have led to the development of models that can help disentangle the causal mechanisms at play and can be implemented to identify potential targets for novel treatments. Despite their power, there are challenges in developing these models related to insufficient data, noisy measurements, errors in measurement, and interpretability. These must be addressed for neural networks to move forward for use as biomarkers in trials and ultimately in the clinical setting. Great strides have been made, especially for Alzheimer's disease and Parkinson's disease, toward goals of understanding and using these models. These models are made possible because of advances in hardware, the development of new neural network algorithms, careful data processing, and a critical look at the data to account for calibration. Insights from these models would be completely unattainable from traditional regression analyses and have already made a significant impact in the fields of Alzheimer's disease and Parkinson's disease by providing incremental discoveries that have deepened the understanding of Alzheimer's disease and Parkinson's disease pathobiology. Their important insights into the structure of related trials should ultimately help to inform the development of drugs and other treatments, significantly speeding up the drug approval process and making new treatments more readily available.

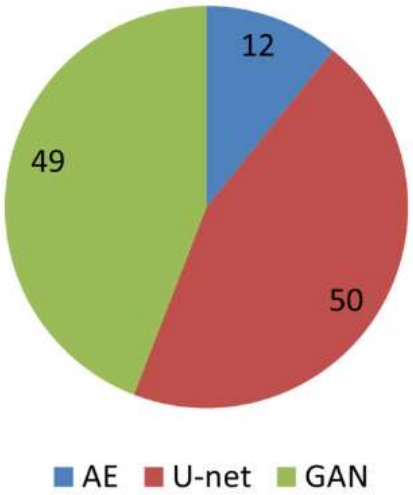

Fig : Pie chart of numbers of articles in different categories of neural networks

6.1. Future Trends

In this review of the application of neural networks to brain imaging of neurodegenerative disorders, we have identified strategies for the management of neurodegeneration data and the potential value of the application of neural networks. Future advances and research should consider several aspects of neural network technology. Future models could evaluate the quality of the input dataset using brain scans as an option, similar to the way in which autoencoders are used to determine the distribution of elements within datasets. These are unsupervised models that are usually used for dimensionality reduction in machine learning and feature extraction in deep learning. Unsupervised learning as an element in the learning process will likely become more common because of data variability, data scarcity, and reinterpretation of types of data input for neurodegeneration.

Models should also take into consideration varying assessment quality and incorporate additional broad data from accessible routine functional abilities to stratify patients and properly support clinical decisions. Additional demographic information from imaging studies and other relevant biomarkers from electronic health records, at either single or multiple time points, should also be evaluated. Furthermore, covariance information between assessment scores and biological indicators from brain imaging could be estimated more explicitly as part of a statistical inference model. Currently, the reported methods primarily aggregate assessment scores only. The evaluation of combinations for test composition and parameter setting should be considered in neural network model development. Due to the sheer number of tests and growing concern among neuroscientists, establishing the integration of clinical and study-applied assessments requires numerous evaluations of testing. To this end, random test samples and clinical evaluation data generation represent the significant bulk of a study design; some other studies provide a bottom-up assessment of unlimited natural domain encoding.

The model updating process and techniques for neurodegenerative rerun prediction, with particular attention to statistical assessment and reproducibility, should also be highlighted; currently, they are related to the literature data obtained and training states. For example, the deep learning time series prediction models are currently applied in an end-to-end neural network approach, where the neural network is used in the prediction task. However, these methods do not clearly identify and investigate neural network settings and designs for underlying data shuffle, last time steps adjustment, or device drift correction. Furthermore, potential research using convolutional neural networks and cellular automaton models should focus more on the neural mechanisms of brain reuniting. The different types of models used in the convolutional networks include most of the neural network models, with certain settings required for post-processing and control processes that show promise in task probe applications. Finally, based on the current situation of data-related large annual variability, the network should be trained using additional data, including low-dose CT, ultrasound, and other unknown radiology settings.

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