Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1624-1639 | ISSN:2251-6727

Role of Computational Biology in the Diagnosis of Neurodegenerative Disorders.

Shubham singh[1]*, Priyanka Sinha[2], Sanjesh Rathi[3], Kumkum Chaturvedi[4], Veerendra Singh Nagoria[5], Dhillon Gagandeepkaur Kulwant[6].

[1]Assistant Professor, School of Pharmacy, Rai University, Ahmedabad-382260 Gujarat, India.

[2]Professor, Chettinad School of Pharmaceutical sciences, Chettinad Hospital & Research Institute and Chettinad Academy of Research & Education, Kelambakkam-603103, Tamilnadu, India.

[3]Professor & Principal, School of Pharmacy, Rai University, Ahmedabad-382260 Gujarat-382260 India

[4]Research Scholar, LNCT University, Kolar Road, Bhopal, MP, India.

[5]Assistant Professor, Rai School of Sciences, Rai University, Ahmedabad-382260 Gujarat, India.

[6]Assistant Professor, SMT. S. M. Shah Pharmacy, College, Ahmedabad-382260 Gujarat, India.

Correspondence author: Shubham Singh*

(Received: 04 February 2024 Revised: 11 March 2024 Accepted: 08 April 2024)

KEYWORDS
Neurodegenerative Disorders, Computational Biology, Technology.

ABSTRACT

Neurodegenerative disorders present a significant challenge in modern healthcare due to their complex and diverse manifestations. The beginning of computational intelligence has revolutionized the diagnostic landscape, offering promising ways for early and accurate detection of these debilitating conditions. Machine learning algorithms, a subset of computational intelligence, have emerged as powerful tools for analysing extensive datasets comprising genetic, imaging, and clinical information. Furthermore, computational intelligence facilitates the integration of multi-modal data, integrating information from genetic profiles, brain imaging (MRI, PET scans), and clinical assessments. This consolidative approach enables a comprehensive understanding of disease progression and aids in the development of predictive models for early medical assessment and prediction of the outcome. Moreover, the utilization of computational intelligence in neuroimaging analysis has shown remarkable potential. Advanced image processing techniques coupled with machine learning algorithms enable the detection of anatomical and useful abnormalities in the brain, often serving as precursors to neurodegenerative disorders. This chapter explores the vital involvement of computational intelligence within enhancing diagnosis of neurodegenerative disorders, like Parkinson, Alzheimer, etc. In conclusion, computational intelligence offers a transformative framework for advancing the diagnosis of neurodegenerative disorders. Embracing and refining these computational tools will undoubtedly overlay the way for more effective interventions and personalized medicine in the fight against these challenging conditions.

1. Introduction

1.1 Overview of Neurodegenerative Disorders

Neurological diseases include an extensive realm of ailments affecting the nervous system, which significantly impair the lives of countless persons worldwide. These disorders bring about the ongoing degeneration of neurons across the brain's central nervous system (CNS) or the peripheral nervous system (PNS). Declination of neuronal networks and their limited capacity of neurons to regenerate effectively, caused by their permanently specialized condition, result in the disruption of crucial communication pathways. This ultimately results in cognition, impaired memory, sensory perception, behaviour, and/or motivity (Wilson et al., 2023). Neurodegenerative disorders encompass certain situations

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1624-1639 | ISSN:2251-6727

such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Parkinson's disease, Huntington's disease, frontotemporal dementia, and the spino cerebellar ataxias. These disorders exhibit a wide range of pathophysiological characteristics, with some leading to recollect and reasonable problems, while alternatively impacting individuals motor skills, speech, and respiration (Abeliovich & Gitler, 2016) (Taylor, Brown Jr, & Cleveland,

2016) (Wyss-Coray, 2016) (Gitler, Dhillon, & Shorter, 2017). There are some common neurodegenerative disorders:

1.1.1 Alzheimer's Disease (AD)

Alzheimer's is the main result of dementia and is becoming increasingly costly, fatal, and burdensome and onerous diseases of today.(Bađun, 2019) (Georges, Miller, & Bintener, 2020). Alzheimer's disease, named after Alois Alzheimer, which is termed as dementia. It is a neurodegenerative illness that progresses slowly and is definitive development of neuritic plaques and neurofibrillary tangles. (**Fig.** 1). Amyloid-beta peptide (Aβ) within the brain's medial temporal lobe and neocortical areas causes the development of plaques and tangles. These parts of the brain are particularly susceptible to the disease's effects.(De-Paula, Radanovic, & Diniz, 2012). Currently, the approximate number is 50 million individuals diagnosed by means of Alzheimer's disease (AD) globally. Estimation from this figure will grow exponentially, doubling every quinquennially, and is expected to reach 152 million by the year 2050. Currently, there is none known remedy towards Alzheimer's illness, while there were therapies accessible so completely ameliorate the indication levels (Breijyeh & Karaman, 2020; Livingston et al., 2020; Yiannopoulou & Papageorgiou, 2020). Alzheimer's disease (AD) displays two separate types of neuropathological alterations that give facts of the progression and symptoms of the illness. The categories consist of constructive lesions, that are distinguished adjacent to building up of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil threads, and other throw down can be seen in the intellect of persons affected with Alzheimer's disease.

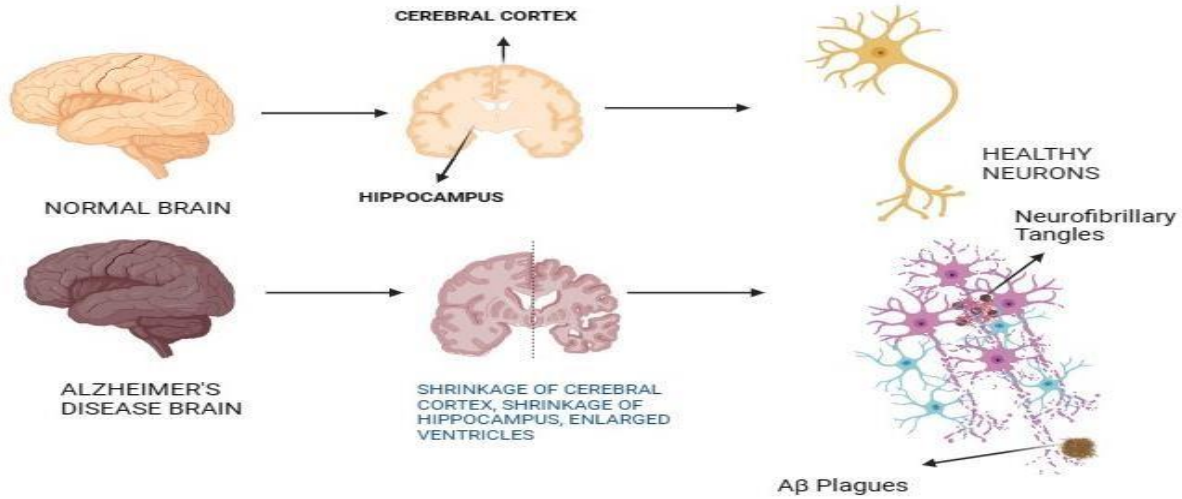

Fig. 1: Diagrammatic Representation of Healthy Brain and Alzheimer's Brain

In addition, there were doublet adverse lesions that have seen substantial reduction owing to synaptic, neural, and neuropil degeneration. Furthermore, neurodegeneration may arise from other factors, including oxidative stress ,neuroinflammation, and disfigurement to cholinergic neurons.(Serrano-Pozo, Frosch, Masliah, & Hyman, 2011) (Spires-Jones & Hyman, 2014) (Singh, Srivastav, Yadav, Srikrishna, & Perry, 2016).

1.1.2 Parkinson's Disease (PD)

Parkinson's illness has significant impact on society. In 2016, roughly 6.1 million individuals globally were

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1624-1639 | ISSN:2251-6727

afflicted by this disease, indicating its widespread prevalence (V. Feigin et al., 2019; V. L. Feigin et al., 2019). Individuals with this condition often experience modest deterioration and impairment over time. The early diagnosis of Parkinson's illness might provide complications, with an average delay of 10 years between the beginning of symptoms and diagnosis (Gaenslen, Swid, Liepelt-Scarfone, Godau, & Berg, 2011). Early symptoms may include constipation, acting out dreams during REM sleep, hyposmia, asymmetric nonspecific shoulder ache, or sadness (Armstrong & Okun, 2020).

Parkinson's disease is a condition that becomes more common as people become older, with the number of cases increasing as people age. However, it should not be assumed that it just affects the elderly. Approximately 25% of those afflicted are under the age of 65, with 5-10% being under the age of 50 (Pringsheim, Jette, Frolkis, & Steeves, 2014). Parkinson's disease has three causes: genetics, environment, and the way they interact. Gene mutations like LRRK2, PRKN, SNCA, GBA and PINK1 were the ongoing area of investigation. SNCA mutations are characterised by earlier illness start, rapid advancement of motor symptoms, strong non-motor characteristics, such as rapid cognitive deterioration (Trinh et al., 2018). Seven specific LRRK2 mutations have been associated to Parkinson's disease. PRKN and PINK1 mutations have been identified as the primary etiological factors contributing to autosomal recessive and early-onset Parkinson's disease. PRKN mutations attributes 77% prior to the instances similar to juvenile Parkinson's disease (onset age < 20 years) as well as 10-20% of juvenile begining Parkinson's disease (Kasten et al., 2018) (Bloem, Okun, & Klein, 2021).

1.1.3 Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a condition of neuron degeneration a particular strikes both topmost and the bottommost motor neurons, causing motor and extra-motor symptoms. ALS patients may present with spinal-onset disease, which causes muscle atrophy in the extremities, or bulbar-onset disease, which causes speech and swallowing difficulties. The aetiology of ALS is mostly unclear. However, some patients from family history possesses this disease, which is linked to gene abnormalities that affect several activities, including non-motor cells. ALS is characterised by the build-up of ubiquitylated proteinaceous inclusions in motor neurons, while the underlying pathophysiology remains unclear. The corticospinal pathways show axonal loss, alterations in glial cells, and myelin pallor, whereas the motor cortex typically shows astrocytic gliosis and a varied diminution of higher motor neurons. Skeletal muscle exhibits both degenerative change and reinnervation, including clustering and clusters of angular atrophic fibres, fibre type (Kiernan et al., 2011).

1.1.4 Depression

Depression is a debilitating condition characterised by several symptoms, including poor selfesteem, lack of desire, anhedonia, low hunger, low energy, and pain, with no apparent explanation. Research suggests that depression may stem from maladaptive alterations in certain intellect loops. The lateral habenula (LHb) is now recognised by means of determining intellect responses in the etiology of depression. The lateral habenula (LHb) is a unspoiled brain structure that connects the prosencephalon (forebrain) to monoaminergic systems in the mesencephalon (midbrain) and rhombencephalon (hindbrain) (Aizawa, Amo, & Okamoto, 2011). Mesencephalon (midbrain) aminergic centres such as the dopaminergic (DA) substantia nigra pars compacta (SNc) and lateral habenula, serotonergic (5-HT) dorsal and median raphe (DRN, MRN), and GABAergic rostromedial tegmental nucleus (RMTg, alternatively referred to as tail-VTA) are generated by the lateral habenula. The "amine theory of depression" posits a particular insufficiency within monoamine neurotransmitters is the cause of depression (Yang, Wang, Hu, & Hu, 2018).

1.1.5 Dementia

Dementia is associated with the disability of the aged all over the world. Dementia negatively impact approximately fifty million individuals globally, with roughly ten million new cases are diagnosed each year. Dementia occurs when mental abilities such as memory, reasoning, and thinking decline to a level where they disrupt daily tasks. Dementia sufferers may experience emotional disturbances and personality changes. Dementia symptoms include memory loss, difficulties with tasks, disorientation, language issues, behavioural changes, and loss of initiative. Dementia symptoms were classified within three phases: early, medium, late. Early detection of 226 illnesses is challenging due to their gradual course. This condition causes loss of time, forgetfulness, and difficulty orienting in confidential situations. In the intermediate phase,

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1624-1639 | ISSN:2251-6727

changes in events and identities become more noticeable. Supplementary indicators consists of communication issues also a greater demand during personal hygiene. Persistent questioning and wandering might lead to behavioural changes. In the later stage, uncommon symptoms include near-total dependency and inactivity owing to memory issues. Symptoms and signs include difficulty walking, behavioural changes, difficulty recognising time and place, and difficulty identifying family and friends.

1.2 Need for Advanced Diagnostic Approaches

Traditional health technology assessment (HTA) uses a data modelling and evidence synthesis framework to reach findings regarding the clinical efficacy, safety, cost-effectiveness, and budget impact of therapies. The primary disadvantage or restriction of previously employed procedures was that they failed to figure out the exact gene responsible for a problem and could not always definitively confirm the existence of a specific ailment.

The mammalian brain is a remarkable example of evolution, with neat and tidy chemicals, cell morphology, and neural tracks for every subdivision. These properties were interconnected in every case anatomical and useful levels (Borrell & Calegari, 2014). This section introduces brain transcriptome atlases and discusses computational tools for understanding gene expression, brain function, and brain development/disease. The fast development of highthroughput technology has enabled the concurrent measurement regarding the reflection of million genes. Next-generation technologies have made it possible to examine the brain's transcriptome at many developmental stages. Brain transcriptome atlases provide vital insights into the brain's molecular architecture. High-dimensional transcriptome data require computational approaches for decoding. Using transcriptome data and proper methodologies, researchers may study the correlation between gene expression, brain features, and neurological illnesses. To address drawbacks like limited decision and insufficiency of non-coding genes, new computational tools are needed to find new chemical foundations of the brain(Li & Wang, 2019).

2. Basics of Computational Biology

Computational biology is a multidisciplinary field that uses computer science, mathematical applications, and analytics to resolve issues related to biology. It is likewise multidisciplinary, employing the same mathematical and computational disciplines but for decision-making challenges. Both focus on creating mathematical models and devising methods to solve them. Models in computational biology differ in their biological area, ranging from gene-protein interactions to organism-species linkages (Chicco, 2017). Computational biology contributes to drug development by characterising ligand-binding processes, identifying active sites, and refining the structure of ligand-target binding poses. Another major branch of computational biology is systems biology, which seeks to understand how biological systems function as a whole rather than as isolated components. Systems biology uses experimental and computational methods to create models of biological systems, ranging from signalling pathways to metabolic networks, and simulate their behaviour under various situations. Drug discovery, personalised medicine, and synthetic biology are all examples of systems biology applications.

Machine learning is becoming increasingly significant in computational biology. Machine learning algorithms may be taught on enormous biological datasets to spot patterns, forecast outcomes, and discover new insights. For example, machine learning algorithms has been exploited furthermore evaluating protein structure and function, detect disease-causing mutations, and categorise cancer subtypes based on gene expression patterns. Computational biology has also resulted in the creation of novel medications and cures. Virtual screening, which uses computer approaches to uncover possible drug candidates from enormous databases of substances, has become a common tool in drug development. Computer simulations may also be used to forecast therapeutic efficacy and safety, as well as to develop novel pharmaceuticals with superior qualities.

3. Applications of Computational Biology in Neurodegenerative Disorder Diagnosis

Neurodegenerative disorders (NDs) affect around 40 million individuals globally. Most of these illnesses do not have treatments that can effectively slow down or halt their course, mainly because it is difficult to unravel the simultaneous occurrence of complex and diverse pathophysiological processes. The current technology and computational skills indicate a positive outlook for unraveling these alterations in order to find new pathways that cause the beginning and progression of neurodegenerative diseases. Specifically, combining complex omic analytical tools such as microarray and mass

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1624-1639 | ISSN:2251-6727

spectrometry with computational systems biology approaches offers a systematic framework to uncover novel pathways that contribute to neurodegenerative diseases. Computational analysis for multivariate data is determined by elements such as prior biological knowledge, sample size, measurement number, and hypothesis/question. There has been minimal research on applying systems analysis techniques to NDs. Systems biology's structured computational approaches can help unravel the underlying processes of several elements of ND pathophysiology that occur concurrently. Integrating human tissue analysis with mice and culture models can highlight model limitations in accurately portraying human illness at the systems level. Integrating perturbation and time point analysis in models allows for the identification of disease-causing pathways and processes at the system level. Despite varying APs, NDs exhibit comparable pathophysiologic presentation.

3.1 Image and Computational Techniques

Examples of additional testing includes serum or urine tests as well as cerebrospinal fluid (CSF) analysis, and imaging or electro diagnosis, may be necessary to confirm or rule out a neurologic diagnosis. Imaging and electro diagnostic methods, including EEG and evoked potentials, are routinely employed to diagnose CNS diseases. In the last decade, technological advancements have enhanced examination of the neurological system. Advancements in magnetic resonance imaging (MRI) technology, such as functional MRI (fMRI) and high-resolution imaging, have enhanced the capacity to detect central nervous system diseases. emerging digital sensors and wearable technologies provide real-time diagnostic data for neurodegenerative illnesses (National Academies of Sciences & Medicine, 2023).

3.1.1 Neuroimaging Technologies

3.1.1.1 Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI), when combined with contemporary techniques, may provide detailed neuroimaging of cerebral anatomy and spinal cord, measure blood circulation, and identify mineral accumulations such as iron. The National Institute of Neurological Disorders and Stroke recommends the use of MRI for diagnosing stroke, traumatic brain injury, brain and spinal cord tumours, inflammation, infection, vascular irregularities, epilepsy-related brain damage, abnormally developed brain regions, and certain neurodegenerative disorders. Over the last 30 years, MRI technology and its combination with other diagnostic procedures have contributed significantly to the development of novel diagnostic methods. MRI is an important technique in the diagnosis of multiple sclerosis. To diagnose MS, doctors often do a medical history and physical before performing a lumbar puncture, evoked potential test, or MRI.

Table 1: Applications of Magnetic Resonance Imaging in Neurological Diagnostics

Techniques	Uses
Functional Magnetic Resonance Imaging	Evaluate the impact of strokes, injuries, and degenerative illnesses like Alzheimer's and Huntington's on cognitive performance.
Susceptibility-weighted Magnetic Resonance Imaging	These conditions include cerebral amyloid angiopathy, traumatic brain damage, vascular abnormalities of the central nervous system, arterial stroke, neurodegenerative disorders, and brain tumours.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1624-1639 | ISSN:2251-6727

FLAIR Magnetic Resonance Imaging	Possible diagnoses include multiple sclerosis, metastatic illness, tuberous sclerosis, and subarachnoid haemorrhage.
Diffusion tensor imaging Magnetic Resonance Imaging	Conditions such as brain tumours, neurodegenerative diseases (such as multiple sclerosis, epilepsy, and Alzheimer's disease), neuropsychiatric disorders (such as schizophrenia), Parkinson's disease, Huntington's disease, Williams syndrome, and fragile X syndrome.
Diffusion-weighted Magnetic Resonance Imaging	Causes of stroke include abrupt cerebral ischemia, brain tumours, white matter illnesses, peripheral nerve imaging, spinal cord damage, and multiple sclerosis.
Brain Volumetric analysis	Possible diagnoses include dementia, multiple sclerosis, epilepsy, and traumatic brain damage.
MR Spectroscopy	Possible causes include brain neoplasms, hereditary metabolic abnormalities, demyelinating illnesses, and infection-related localised lesions.
Double inversion recovery	Identification of demyelinating lesions in individuals with multiple sclerosis, cancer, epileptogenic foci, and cortical abnormalities.
MR Venography	Cerebral venous thrombosis

3.1.1.2 Positron Emission Tomography (PET)

PET scans can provide real-time insight into the brain's activity. It examines brain metabolism, regional blood flow, and neurotransmitter receptor binding. It has the capability to diagnose brain diseases such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, and many forms of dementia. The main obstacle to its widespread usage in clinical diagnostics is its present exorbitant cost, since it necessitates the use of a cyclotron to produce the beam of photons and radiochemicals for injection into the circulation (Politis and Piccini,
2012). Recent research has focused on early detection and diagnosis of Alzheimer's disease, with positron emission tomography (PET) being a popular method. PET can detect disease symptoms before a clinical diagnosis is made. PET using these tracers can detect Alzheimer's disease in the brain at an uncertain stage (Fantoni et al.,

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1624-1639 | ISSN:2251-6727

2018) (National Academies of Sciences & Medicine, 2023).

3.1.2 Image Analysis Algorithms

3.1.2.1 Computer-Aided Diagnosis

Neurological disorders include a wide variety of conditions, including degenerative illnesses such as Alzheimer's and Parkinson's, vascular disorders including stroke, intracerebral hemorrhage, and vascular malformations, as well as neoplastic diseases such as benign brain tumors and life-threatening malignancies. Inflammatory disorders can also occur. Computeraided diagnostic (CAD) tools have advanced significantly in recent years. The system uses wireless networks to monitor patients' health at all times and from any location. CAD is a computer system that interprets medical pictures, allowing radiologists and clinicians to give second views. Radiologists must equip CAD systems with the capacity to identify brain disorders. Using pattern recognition and machine learning algorithms is crucial for developing CAD systems (Gudigar et al., 2020).

In general, brain abnormalities is evaluated utilising two types of CAD systems:

- The approach categorises normal and abnormal brain problems into two or more classes.
- A technique for distinguishing the lesions.

CAD combines many image processing strategies, including pre-processing, segmentation, feature extraction, dimensionality reduction, and classification.

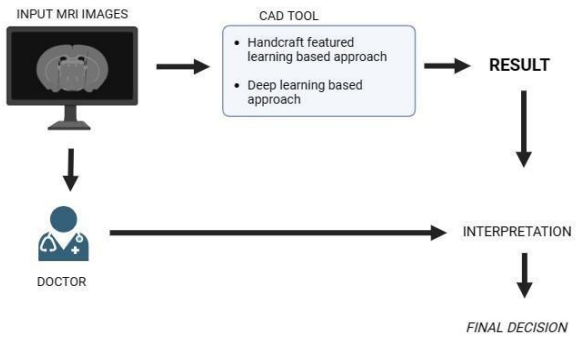

Fig. 2: Diagrammatic representation of CAD

3.1.2.2 Deep Learning Approaches

Deep learning involves training and testing multi-layered neural networks to understand complicated structures and attain high degrees of abstraction. There are 2 distinct categories of deep learning models, each using a distinct methodology for transmitting information over networks. Deep learning (DL) is a collection of machine learning techniques that has generated significant enthusiasm in the scientific community by surpassing established performance standards in areas such as speech and picture recognition. Deep learning surpasses conventional machine learning methods by acquiring the optimal representation from unprocessed data via nonlinear transformations, leading to increased levels of abstraction and intricacy. DL has been used in neuroimaging research on mental and neurological illnesses because to its capacity to identify nuanced and complicated patterns. These disorders are characterized by subtle and widespread alterations. Despite being in its primary stages, the use of deep learning in neuroimaging has shown encouraging outcomes. This might potentially result in substantial advancements in the search for imaging-based biomarkers of mental and neurologic disorders. However, further advances are needed to fully realise the promise of deep learning in neuroimaging (Vieira, Pinaya, & Mechelli, 2017).

3.2 Role of Genomics, Proteomics, and Metabolomics in Diagnosis

3.2.1 Genomics

Genomic studies of neurological illnesses examine the genome, transcriptome, and epigenome. There are two technologies accessible for genomic studies: sequencing and array platforms. Genomic variation studies typically employ peripheral blood samples, however saliva can also be used. Brain tissue is the primary focus of transcriptome research due of its relevance to disease mechanisms. Research on peripheral blood and cerebrospinal fluid (CSF) has focused on identifying new biomarkers. These three tissues have also been used to study epigenetic changes. Skin fibroblasts are widely exploited in iPSC technologies. To better understand neurological illnesses, it's important to investigate them from a systems viewpoint, as the disease process is sometimes unclear. Brain transcriptome studies may extract gene expression information at the full genome level and identify dysregulation in disease conditions by comparing it to healthy controls. Microarray systems are the primary tool for brain transcriptome investigations because to their established technology and inexpensive cost. Sequencing

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1624-1639 | ISSN:2251-6727

technique has been widely employed since 2008, but is often confined to small sample sizes due to its expensive cost.

3.2.1.1 Genetic Markers

Biomarker research and validation remain a priority in the study of neurodegenerative disorders. Numerous research have been undertaken to identify biomarkers that can aid in preclinical illness diagnosis, predictive prognosis, and subtyping. Searching for these circumstances might be challenging due to their ambiguous nature. These genetic markers can lead to harmful mutations that cause monogenic diseases. The link between genetic biomarkers and disease development is complicated due to variations in penetrance and the interaction of genetic risk factors with the environment. Over the last several decades, significant advancements have been made in the development of biomarkers that provide valuable insights to clinicians and medicine manufacturers into crucial biochemical processes involved in neurodegenerative illnesses. Biomarker research involves significant scientific collaboration, which will be accelerated by working in an open science environment. Genetic testing in individuals with early-onset neurodegenerative disorders can confirm and refine diagnosis, as well as forecast illness in very specific cases. Most genomes and transcriptomics biomarkers cannot function independently. There is a growing need to generate harmonised data across locations in order to develop powerful biomarker studies that incorporate many types of indicators, including neuroimaging, employing deep learning and artificial intelligence.

3.2.1.2 Next-Generation Sequencing (NGS)

The medical determination of a neurological condition may be devastating for sufferers and their families. Most illnesses do not have a cure and can only be treated to slow their course. Advancements in next-generation sequencing (NGS) technology in genomic medicine offer new prospects for early detection and treatment of neurological illnesses, which is a pressing aim. Advances in NGS technology have reduced the time and cost of clinical sequencing, allowing for more study and assessment of genetic variations. Whole genome sequencing is now more inexpensive than many clinical diagnostic procedures. Next-generation sequencing technologies can aid in diagnosing neurological diseases with high genetic and phenotypic heterogeneity, as well as identifying new disease-associated variants and genes for previously undiagnosed conditions(Foo, Liu, & Tan, 2013).

Table 2: Subtypes of neurological diseases and applications of NGS

Classes of Neurological Diseases	Examples	Applications of NGS
Neurodevelopmental diseases in childhood	Infantile epilepsy Brain malformation Infantile syndromic seizures	Quick diagnosis with the use of whole genome or exome sequencing Gene discovery Carrier testing Diagnostic screening
Heterogenous monegenic disorders	Parkinsonism Cerebral palsy Mitochondrial diseases	Gene discovery Carrier testing Diagnostic screening

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1624-1639 | ISSN:2251-6727

Neuropsychiatric diseases	Autism Schizophrenia Intellectual disability	Performing whole exome or genome-wide sequencing in order to find genes that possess de novo mutations. Risk predictions

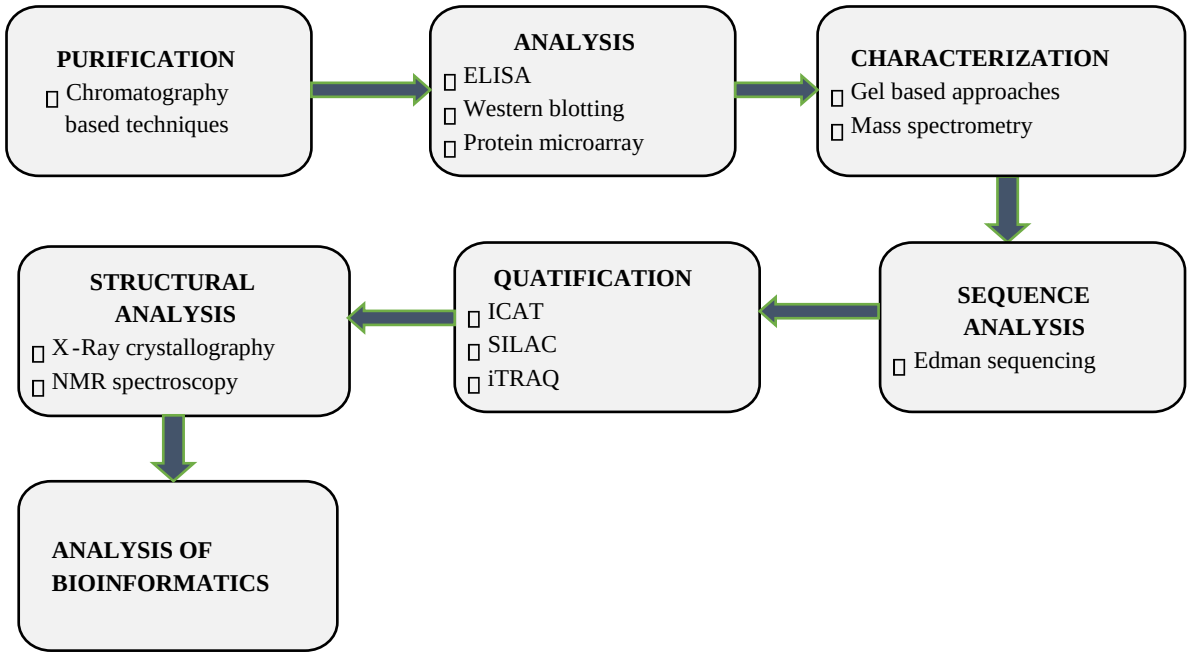

Fig. 3: Applications of proteomics techniques

3.2.2 Proteomics

Proteomics plays a key role in illness diagnosis, prognosis, and monitoring. Moreover, it assumes a significant function in the process of drug development as target molecules. Proteomics identifies the expression, structure, functions, interactions, and changes of proteins throughout their life cycle. Proteomics is a powerful tool for understanding gene function, although it is more difficult than genomics. Analysis of the transcriptome or proteome can distinguish between two cell biological states based on fluctuations in gene expression levels.

3.2.2.1 Protein Biomarkers

Protein microarrays, often called protein chips, are a new proteomics technology that can identify large amounts of data from tiny samples. Protein microarrays can be categorized as analytical, functional, or reverse-phase.

Functional protein microarray

Purified protein microarrays can explore interactions with DNA, RNA, protein, drugs, lipids, enzymes, and substrates. The primary objective of using functional protein microarray was to investigate the substrate specificity of protein kinases in yeast. The functional protein microarray evaluated the functional properties of many proteins. A study on protein-protein interactions in

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1624-1639 | ISSN:2251-6727

A. thaliana discovered Calmodulin-like proteins (CML) and their interactions with CaM substrates.

Reverse-phase protein microarray

The different cellular conditions bring these cell lysates which are set in an order on nitrocellulose slides and then examined using antibodies specific to the proteins of interest. Subsequently, antibodies were identified using fluorescent, chemiluminescent, and colorimetric methodologies. Slides are printed with reference peptides to facilitate protein quantification. Microarrays are used to detect and analyse proteins that have been changed or are not functioning properly, and these proteins are linked to certain illnesses.

3.2.3 Transcriptomics

To better understand neurological illnesses, it's important to look at them from a systems viewpoint, as the underlying causes are sometimes unclear. Brain transcriptome research may collect gene expression information throughout the whole genome and uncover dysregulation in disease conditions by comparing it to healthy controls. Cortical structure and function changes with age are linked to normal cognitive growth (Knickmeyer et al., 2008, Gilmore, Knickmeyer, & Gao, 2018,Giedd & Rapoport, 2010), due to cortical thinning considered a morphological marker as an alternative to cortical maturity (Tamnes et al., 2017)(Amlien et al., 2016). Cortical thickness alterations inside the brain, particularly cortical thinning, have been linked to a variety of mental diseases (Khundrakpam, Lewis, Kostopoulos, Carbonell, & Evans, 2017). Cortical thickness disparities found in several neurodevelopmental diseases, including schizophrenia, are frequently assumed to result from aberrant brain maturation trajectories (Gogtay, Vyas, Testa, Wood, Häfner et al., 1994 & Pantelis, 2011). Cortical thickness variations may be caused by modifications in synaptic size and/or neuronal, or density, as well as the myelination of fibers that penetrate the cortical mantle. Imaging transcriptomic investigations have employed the expression patterns of certain cell-type marker genes to discover cellular co-relators of these Imaging Derived Phenotypes, shedding information on the molecular underpinnings of brain alterations that came about in both normal and abnormal neurodevelopment (Arnatkeviciute, Fulcher, Bellgrove, & Fornito, 2022).

3.2.3.1 RNA Expression Profiles

Long non-coding RNAs (lncRNAs) are transcripts that consist of over 200 nucleotides and do not code for proteins or code for proteins in low amounts. These elements contribute significantly to the cell's transcriptional output and display functional traits such as expression specific to certain tissues, determination of cell fate, regulated expression, processing and editing of RNA, compensation for differences in gene dosage, genomic imprinting, and conserved evolutionary properties. Long non-coding variations have been linked to neurological illnesses such as Alzheimer's, schizophrenia, Huntington's, and Parkinson's disease. Neurological problems are ubiquitous, thus understanding the underlying causes is critical. lncRNAs have a role in pathogenesis through several methods, including decoy, scaffolding, miRNA sequestration, histone modification, and transcriptional interference. Understanding the role of lncRNAs can inform their potential as therapeutic biomarkers (Bhattacharyya, Pandey, Bhattacharyya, & Dey, 2021).

3.2.3.2 Microarray Analysis

The basic premise behind microarray technology is the complementary hybridization of nucleic acids (Schena, Shalon, Davis, & Brown, 1995) (Lockhart et al., 1996). Gene expression microarrays are high-throughput 'dot-blot' technologies that tie known DNA to a solid platform. The targets are amplified RNA or complementary DNA (cDNA) species taken from samples and are tagged with fluorescent markers. During the process of hybridization between a labeled sample and a DNA microarray, each probe specifically attaches to its associated target. Highresolution fluorescence scanners are used to analyse microarrays and measure the intensity of fluorescent signals from probe-bound targets. The signal is thought to be proportional to the amount of RNA species in the samples. Microarrays include probes for hundreds of identified genes in the human genome, enabling for 'transcriptome profiling' of each sample. There are many microarray platforms that use oligonucleotides or cDNAs. Platform selection is influenced by array size, cost, and availability of genes. Microarray study of gene expression in postmortem brains can reveal molecular alterations associated with disease states. Postmortem brain research provide particular constraints, such as restricted sample numbers and fluctuating clinical phenotypes common to complicated illnesses. Recent research using microarrays have linked brain illnesses to dysregulated genes and

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1624-1639 | ISSN:2251-6727

aberrant gene expression patterns (Mirnics & Pevsner, 2004).

3.3 Biomarker Discovery and Validation

A biological marker (biomarker) is “a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions” (Cagney et al., 2018). Biomarkers can be used for risk assessment, illness screening, diagnosis, prognosis, therapeutic benefit prediction, and disease monitoring. Early in the development phase, it's important to specify the intended application of a biomarker, such as risk stratification or screening, as well as the target population.

When conducting discovery studies with archived specimens, it's important to consider the patient population, study power (number of samples and events), disease prevalence, biomarker test validity, and analysis plan. Randomization is necessary in biomarker development to account for non-biological influences such as modifications to the chemical substances used in a reaction, personnel, and machine drift, which can cause batch effects (Leek et al., 2010). Randomly allocate illustrations deriving out of controls and cases to arrays, testing plates, or batches to ensure an equal distribution of cases, controls, and specimen age (Ransohoff, 2005).

Blinding avoids bias from uneven appraisal of biomarker results by excluding the personnel who create the information from identifying the scientific results (Ransohoff, 2005). To generate accurate biomarker data, it is recommended to apply randomization and blinding at all stages of the study.

The term "validation" refers to "a process to establish that the performance of a test, tool, or instrument is acceptable for its intended purpose". Intrinsic updation evaluates a molecular marker's performance using resampling approaches like bootstrapping or cross-validation to ensure reasonable expectations. Extrinsic updation evaluates molecular marker's production in an individualistic dataset that was rarely utilized throughout the time of creation. This requires data from various times, institutions, or geographic locations, as discussed in the following paragraphs. There are two types of biomarker validation: analytical and clinical.

Analytical validation

Analytical validation involves establishing a molecular marker production characteristic, like reactiveness, particularity, trueness, correctness, and multi-lab repeatability, using a predetermined technique. Systemic and scientific corroboration aims towards biomarker's verification and accomplishment (constant measurement of unknown real values), rather than it’s utility.

Clinical validation

Scientific affirmation strives to creates a link within biosignature and their desired outcome, as well as demonstrate its utility. External validation for clinical studies can be done retrospectively or prospectively. Retrospective utilization of clinical trial data is an external validation method that involves evaluating biomarkers outside of the original research design (Ou, Michiels, Shyr, Adjei, & Oberg, 2021).

3.4 Predictive Modelling for Early Detection

For many neurological illnesses, predicting the disease state is a significant clinical goal. Neuroimaging gives precise information on brain anatomy and function, enabling statistical predictions. To examine the comparative, detailed clarification of distinctive picture, techniques and regions of the brain while predicting disease state using whole-brain neuroimaging data, a multinomial logit model with Gaussian process priors is proposed. To achieve posterior inference on the Advanced Markov Chain model, Monte Carlo methods are implemented. The proposed model is descriptive and adaptable, making it suitable for analyzing the value of various data techniques or brain areas in each requisition. Additionally, it enables precise measurement of uncertainty in forecasts, which is essential for forecasting disease states in clinical settings (Filippone et al., 2012).

4. Challenges and Opportunities

4.1 Ethical considerations in using computational biology for diagnosis

Many of the above-mentioned early detection

strategies for digital biomarkers use machine learning or artificial intelligence. Their ethical and responsible implementation provides obstacles in terms of data source and analysis technique, as well as application field. Several prominent organizations, including the World Health

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1624-1639 | ISSN:2251-6727

Organization and the European Commission, have issued guidelines for contemplating "AI ethics" in the context of therapy. The techniques often depend on widely accepted notions that include fundamental values of medical ethics, such as kindness, nonmaleficence, fairness, respect for autonomy, and a particular focus on clearance, explicable, definability, openness, management, and liabilities (Ford, Milne, & Curlewis, 2023).

Precision health leverages data from numerous origins especially omics, routine, atmosphere, online communities, healthcare records, and health insurance declares via provide individualized safe keeping, prevention and foresee illness, and deliver correct treatment, remedies. This creates substantial benefit of sensing technologies (such as electronic health monitoring devices), computations (such as machine learning), along with transmission (similar to interactions across health data centres). Because health data contain sensitive private information, such as the patient's and caregiver's identities as well as the patient's medical conditions, careful care is always necessary. Leaking this sensitive information has a negative impact on one's individual life, especially tormenting, upper level security premiums, as well as job less because of medical history (Thapa & Camtepe, 2021).

4.2 Future directions and potential advancements in the field

4.2.1 CRISPR/Cas9 and gene-editing in neurodegenerative disorders

Genetic defects have a role in a variety of degenerative conditions that afflict millions of individuals globally. Some genetic abnormalities can be recognized during the early stages of infancy, although many shall not exhibit either symptom till maturity. In consequence of instance, the abnormal involuntary movement disorder that distinguish (an exceptional inherent neurodegenerative disease that bring nerve cells in the intellect to break down and die) Huntington's disease (HD) frequently appear until since maturity. The therapeutic options for most hereditary disorders are limited, if not nonexistent. Gene-editing methods such as nucleases with zinc fingers (ZFNs), mega nucleases, effector nucleases that resemble transcription activators (TALENs), and CRISPR-

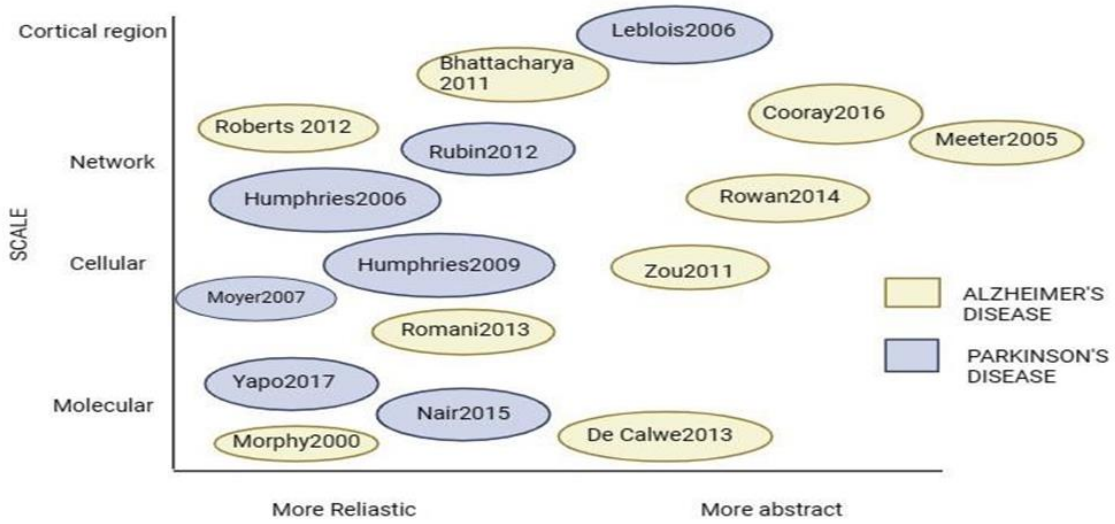

Fig.3: Computational models

Cas9 are used for modifying genes, have generated significant interest as potential treatments for specific neurodegenerative diseases. These tools have the ability to edit, replace, and modify faulty regions of the genome.

CRISPR is a bacterial adaptive immunological system capable of targeting particular foreign nucleic acid sequences (Jansen, Embden, Gaastra, & Schouls, 2002). CRISPR is made up of distinct spacer sequences separated through miniature, recurrent, self-complementary sequences, as well as other chronologies that encode Cas proteins (Makarova, Koonin,Grishin, & Wolf, 2006). The CRISPR-Cas9 system, which was

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1624-1639 | ISSN:2251-6727

originally developed from S. pyogenes, has proved to be effective for gene editing in eukaryotes (Barrangou et al., 2007). Following extensive exploration on the CRISPR-Cas 9 system, it is now possible to use it for gene editing purposes, such as introducing desired genetic changes and fixing mutated areas of the genome. (Sander & Joung, 2014).

Other gene editing methods, such as TALENs and ZFNs, need particular planning to mark the DNA for clear-cut DSBs (Mao et al., 2013), which is already time-consuming and costly operation. Additional

issues include cleavage, size, off-target and cytotoxicity (Carlson, Fahrenkrug, & Hackett, 2012). ZFNs cause off-target effects as well as shows cytotoxicity, and their efficacy is limited (Kim & Kim, 2014). In contrast, TALENs are more efficient than ZNFs but need several neurological illnesses are hereditary in nature, and for most of them, varied therapies remain unavailable. The management of neurological issues is presently limited due to misinterpretation of complex workings made from the brain, including the unknown etiology and genetic factors involved in many neurodegenerative illnesses. These characteristics impede the progress of creating new pharmacological targets. Identification of the pathogenic microorganisms (Kolli, Lu, Maiti, Rossignol, & Dunbar, 2018).

4.2.2 Advancements in computational models and algorithms

Advances in scientific and computerized neuroscience, along with high-performance computers, have led to a rapid surge in the creation of computational models to research neural disease causes.(refer to Figure 3). In the foreseeable future, researchers and scientists will focus on developing computational models to deliver effective therapeutic and pharmaceutical solutions (Gandolfi, Boiani, Bigiani, & Mapelli, 2021).

5. Conclusion

Computational biology's significance in the diagnosis of neurodegenerative illnesses has grown in importance as technology and our understanding of disease processes. It combines several forms of data, such as genomic, transcriptomic, proteomic, and clinical data, to obtain insight into the complicated processes that underpin neurodegenerative illnesses.

Collaboration between computational biologists and clinicians is critical for improving our understanding of neurodegenerative illnesses and using research findings in clinical practice. Overall, computational biology has significant potential for enhancing our understanding of neurodegenerative illnesses and developing diagnostic and therapeutic methods for these debilitating conditions. In summary, the future of neurodegenerative disorder diagnosis will be defined by early detection, precision medicine, and the integration of multi-omics data, advanced technologies, and collaborative research efforts, all of which will make things better for patients suffering from these debilitating conditions.

References

[1] Abeliovich, A., & Gitler, A. D. (2016). Defects in trafficking bridge Parkinson's disease pathology and genetics. *Nature, 539*(7628), 207-216.

[2] Aizawa, H., Amo, R., & Okamoto, H. (2011). Phylogeny and ontogeny of the habenular structure. *Frontiers in neuroscience, 5*, 138.

[3] Amlien, I. K., Fjell, A. M., Tamnes, C. K., Grydeland, H., Krogsrud, S. K., Chaplin, T. A., . . . Walhovd, K. B. (2016). Organizing principles of human cortical development— thickness and area from 4 to 30 years: insights from comparative primate neuroanatomy. *Cerebral cortex, 26*(1), 257-267.

[4] Armstrong, M. J., & Okun, M. S. (2020). Diagnosis and treatment of Parkinson disease: a review. *Jama, 323*(6), 548-560.

[5] Arnatkeviciute, A., Fulcher, B. D., Bellgrove, M. A., & Fornito, A. (2022). Imaging transcriptomics of brain disorders. *Biological Psychiatry Global Open Science, 2*(4), 319331.

[6] Bađun, M. (2019). Alzheimer Europe. In *Encyclopedia of Gerontology and Population Aging* (pp. 1-5): Springer International Publishing.

[7] Barrangou, R., Fremaux, C., Deveau, H., Richards, M., Boyaval, P., Moineau, S.,Horvath, P. (2007). CRISPR provides acquired resistance against viruses in prokaryotes.*Science, 315*(5819), 1709-1712.

[8] Bhattacharyya, N., Pandey, V., Bhattacharyya, M., & Dey, A. (2021). Regulatory role of long non coding RNAs (lncRNAs) in neurological disorders: From novel biomarkers to promising therapeutic

strategies. *Asian journal of pharmaceutical sciences, 16*(5), 533-550. Bloem, B. R., Okun, M. S., & Klein, C. (2021). Parkinson's disease. *The Lancet, 397*(10291), 2284-2303.

[9] Borrell, V., & Calegari, F. (2014). Mechanisms of brain evolution: regulation of neural progenitor cell diversity and cell cycle length. *Neuroscience research, 86*, 14-24.

[10] Breijyeh, Z., & Karaman, R. (2020). Comprehensive review on Alzheimer's disease: Causes and treatment. *Molecules, 25*(24), 5789.

[11] Cagney, D. N., Sul, J., Huang, R. Y., Ligon, K. L., Wen, P. Y., & Alexander, B. M. (2018). The FDA NIH Biomarkers, EndpointS, and other Tools (BEST) resource in neuro-oncology. *Neuro-oncology, 20*(9), 1162-1172.

[12] Carlson, D. F., Fahrenkrug, S. C., & Hackett, P. B. (2012). Targeting DNA with fingers and TALENs. *Molecular therapy-Nucleic acids, 1*.

[13] Chicco, D. (2017). Ten quick tips for machine learning in computational biology. *BioData mining, 10*(1), 35.

[14] De-Paula, V. J., Radanovic, M., & Diniz, B. S. (2012). and Orestes V. Forlenza. *Protein Aggregation and Fibrillogenesis in Cerebral and Systemic Amyloid Disease, 65*, 329.

[15] Feigin, V., Nichols, E., Alam, T., Bannick, M., Beghi, E., Blake, N., . . . Ellenbogen, R. (2019). GBD 2016 Neurology Collaborators: Global, regional, and national burden of neurological disorders, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol, 18*(5), 459-480.

[16] Feigin, V. L., Nichols, E., Alam, T., Bannick, M. S., Beghi, E., Blake, N., . . . Ellenbogen, R. G. (2019). Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology, 18*(5), 459-480.

[17] Filippone, M., Marquand, A. F., Blain, C. R., Williams, S. C., Mourão-Miranda, J., & Girolami, M. (2012). Probabilistic prediction of neurological disorders with a statistical assessment of neuroimaging data modalities. *The annals of applied statistics, 6*(4), 1883.

[18] Foo, J. N., Liu, J., & Tan, E.-K. (2013). Next-generation sequencing diagnostics for neurological diseases/disorders: from a clinical perspective. *Human genetics, 132*, 721-734.

[19] Ford, E., Milne, R., & Curlewis, K. (2023). Ethical issues when using digital biomarkers and artificial intelligence for the early detection of dementia. *Wiley Interdisciplinary Reviews: Data Mining and Knowledge Discovery*, e1492.

[20] Gaenslen, A., Swid, I., Liepelt-Scarfone, I., Godau, J., & Berg, D. (2011). The patients' perception of prodromal symptoms before the initial diagnosis of Parkinson's disease. *Movement Disorders, 26*(4), 653-658.

[21] Gandolfi, D., Boiani, G. M., Bigiani, A., & Mapelli, J. (2021). Modeling neurotransmission: Computational tools to investigate neurological disorders. *International Journal of Molecular Sciences, 22*(9), 4565.

[22] Georges, J., Miller, O., & Bintener, C. (2020). Estimating the prevalence of dementia in Europe. *Report N*.

[23] Giedd, J. N., & Rapoport, J. L. (2010). Structural MRI of pediatric brain development: what have we learned and where are we going? *Neuron, 67*(5), 728-734.

[24] Gilmore, J. H., Knickmeyer, R. C., & Gao, W. (2018). Imaging structural and functional brain development in early childhood. *Nature Reviews Neuroscience, 19*(3), 123-137.

[25] Gitler, A. D., Dhillon, P., & Shorter, J. (2017). Neurodegenerative disease: models, mechanisms, and a new hope. *Disease models & mechanisms, 10*(5), 499-502.

[26] Gogtay, N., Vyas, N. S., Testa, R., Wood, S. J., & Pantelis, C. (2011). Age of onset of schizophrenia: perspectives from structural neuroimaging studies. *Schizophrenia bulletin, 37*(3), 504-513.

[27] Gudigar, A., Raghavendra, U., Hegde, A., Kalyani, M., Ciaccio, E. J., & Acharya, U. R. (2020). Brain pathology identification using computer aided diagnostic tool: A systematic review. *Computer Methods and Programs in Biomedicine, 187*, 105205.

[28] Häfner, H., Maurer, K., Löffler, W., Fätkenheuer, B., Der Heiden, W. A., Riecher-Rössler, A., . . . Gattaz, W. (1994). The epidemiology of early schizophrenia: influence of age and gender on onset

and early course. *The British journal of psychiatry, 164*(S23), 29-38.

[29] Jansen, R., Embden, J. D. v., Gaastra, W., & Schouls, L. M. (2002). Identification of genes that are associated with DNA repeats in prokaryotes. *Molecular microbiology, 43*(6), 15651575.

[30] Kasten, M., Hartmann, C., Hampf, J., Schaake, S., Westenberger, A., Vollstedt, E. J., . . .

[31] Dulovic, M. (2018). Genotype-phenotype relations for the Parkinson's disease genes Parkin, PINK1, DJ1: MDSGene systematic review. *Movement Disorders, 33*(5), 730-741.

[32] Khundrakpam, B. S., Lewis, J. D., Kostopoulos, P., Carbonell, F., & Evans, A. C. (2017).

[33] Cortical thickness abnormalities in autism spectrum disorders through late childhood, adolescence, and adulthood: a large-scale MRI study. *Cerebral Cortex, 27*(3), 1721-1731.

[34] Kiernan, M. C., Vucic, S., Cheah, B. C., Turner, M. R., Eisen, A., Hardiman, O., . . . Zoing, M. C. (2011). Amyotrophic lateral sclerosis. *The Lancet, 377*(9769), 942-955.

[35] Kim, H., & Kim, J.-S. (2014). A guide to genome engineering with programmable nucleases.

[36] *Nature Reviews Genetics, 15*(5), 321-334.

[37] Knickmeyer, R. C., Gouttard, S., Kang, C., Evans, D., Wilber, K., Smith, J. K., . . . Gilmore, J. H. (2008). A structural MRI study of human brain development from birth to 2 years. *Journal of neuroscience, 28*(47), 12176-12182.

[38] Kolli, N., Lu, M., Maiti, P., Rossignol, J., & Dunbar, G. L. (2018). Application of the gene editing tool, CRISPR-Cas9, for treating neurodegenerative diseases. *Neurochemistry international, 112*, 187-196.

[39] Koonin, E. V., Makarova, K., Grishin, N., & Wolf, Y. I. (2006). *A putative RNAinterference-based immune system in prokaryotes: the epitome of prokaryotic genomic diversity*. Paper presented at the SYMPOSIA-SOCIETY FOR GENERAL MICROBIOLOGY.

[40] Leek, J. T., Scharpf, R. B., Bravo, H. C., Simcha, D., Langmead, B., Johnson, W. E., . . . Irizarry, R. A. (2010). Tackling the widespread and critical impact of batch effects in highthroughput data. *Nature Reviews Genetics, 11*(10), 733-739.

[41] Li, J., & Wang, G.-Z. (2019). Application of computational biology to decode brain Transcriptomes. *Genomics, Proteomics & Bioinformatics, 17*(4), 367-380.

[42] Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., . . . Cooper, C. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet, 396*(10248), 413-446.

[43] Lockhart, D. J., Dong, H., Byrne, M. C., Follettie, M. T., Gallo, M. V., Chee, M. S., . . . Norton, H. (1996). Expression monitoring by hybridization to high-density oligonucleotide arrays. *Nature biotechnology, 14*(13), 1675-1680.

[44] Mao, Y., Zhang, H., Xu, N., Zhang, B., Gou, F., & Zhu, J.-K. (2013). Application of the CRISPR–Cas system for efficient genome engineering in plants. *Molecular plant, 6*(6), 2008-2011.

[45] Mirnics, K., & Pevsner, J. (2004). Progress in the use of microarray technology to study the neurobiology of disease. *Nature neuroscience, 7*(5), 434-439. Ou, F.-S., Michiels, S., Shyr, Y., Adjei, A. A., & Oberg, A. L. (2021). Biomarker discovery and validation: statistical considerations. *Journal of Thoracic Oncology, 16*(4), 537-545.

[46] Pringsheim, T., Jette, N., Frolkis, A., & Steeves, T. D. (2014). The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Movement Disorders, 29*(13), 1583-1590.

[47] Ransohoff, D. F. (2005). Bias as a threat to the validity of cancer molecular-marker research. *Nature Reviews Cancer, 5*(2), 142-149.

[48] Sander, J. D., & Joung, J. K. (2014). CRISPR-Cas systems for editing, regulating and targeting genomes. *Nature biotechnology, 32*(4), 347-355.

[49] Schena, M., Shalon, D., Davis, R. W., & Brown, P. O. (1995). Quantitative monitoring of gene expression patterns with a complementary DNA microarray. *Science, 270*(5235), 467470.

[50] Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. *Cold Spring Harbor perspectives in medicine, 1*(1), a006189.

[51] Singh, S. K., Srivastav, S., Yadav, A. K., Srikrishna, S., & Perry, G. (2016). Overview of

[52] Alzheimer's disease and some therapeutic approaches targeting Aβ by using several synthetic

and herbal compounds. *Oxidative medicine and cellular longevity, 2016*.

[53] Spires-Jones, T. L., & Hyman, B. T. (2014). The intersection of amyloid beta and tau at synapses in Alzheimer's disease. *Neuron, 82*(4), 756-771.

[54] Tamnes, C. K., Herting, M. M., Goddings, A.-L., Meuwese, R., Blakemore, S.-J., Dahl, R. E., . . . Crone, E. A. (2017). Development of the cerebral cortex across adolescence: a multisample study of inter-related longitudinal changes in cortical volume, surface area, and thickness. *Journal of neuroscience, 37*(12), 3402-3412.

[55] Taylor, J. P., Brown Jr, R. H., & Cleveland, D. W. (2016). Decoding ALS: from genes to mechanism. *Nature, 539*(7628), 197-206.

[56] Thapa, C., & Camtepe, S. (2021). Precision health data: Requirements, challenges and existing techniques for data security and privacy. *Computers in biology and medicine, 129*, 104130.

[57] Trinh, J., Zeldenrust, F. M., Huang, J., Kasten, M., Schaake, S., Petkovic, S., . . . König, I.

[58] R. (2018). Genotype-phenotype relations for the Parkinson's disease genes SNCA, LRRK2, VPS35: MDSGene systematic review. *Movement Disorders, 33*(12), 1857-1870.

[59] Vieira, S., Pinaya, W. H., & Mechelli, A. (2017). Using deep learning to investigate the neuroimaging correlates of psychiatric and neurological disorders: Methods and applications. *Neuroscience & Biobehavioral Reviews, 74*, 58-75.

[60] Wilson, D. M., Cookson, M. R., Van Den Bosch, L., Zetterberg, H., Holtzman, D. M., & Dewachter, I. (2023). Hallmarks of neurodegenerative diseases. *Cell, 186*(4), 693-714.

[61] Wyss-Coray, T. (2016). Ageing, neurodegeneration and brain rejuvenation. *Nature, 539*(7628), 180-186.

[62] Yang, Y., Wang, H., Hu, J., & Hu, H. (2018). Lateral habenula in the pathophysiology of depression. *Current opinion in neurobiology, 48*, 90-96.

[63] Yiannopoulou, K. G., & Papageorgiou, S. G. (2020). Current and future treatments in Alzheimer disease: an update. *Journal of central nervous system disease, 12*, 11795735209073