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Advancements in Diagnostic Strategy of Neurological and Neuropsychiatric Disorders: From Conventional Methods to Point-of-Care Approaches

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Abstract: *Neurological and neuropsychiatric disorders such as Alzheimer's, Parkinson's, Epilepsy, Stroke, etc. are commonly being diagnosed in the human population nowadays due to changing lifestyle and other factors. Every year, for nearly 10 million deaths and 10 million DALYs have been reported of Neurological disorders. This study overviews the advancements in conventional methods using machine learning or deep learning techniques and the development of point-of-care detection techniques to diagnose these diseases. Some of the non-invasive techniques such as EEG, MRI, Magnetic encephalography are expensive, time consuming and require sophisticated instrumentation facilities. Thus, to overcome these challenges point-of-care detection is an alternative for diagnosis which employs lateral Flow Assays, biosensors that are simple to use, cost effective, less time consuming, can be performed at low resource settings, and are sensitive, specific and accurate. Point-of-care detection involves detection of specific biomarkers in the body fluids of patients for early detection of the disease.*

Keywords: Neurological disorders, Neuropsychiatric disorders, AI/ML technologies, Diagnosis, point-of-care detection

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INTRODUCTION

Neurological and neuropsychiatric disorders have become a concern in today's time due to growing number of patients suffering from diseases such as Alzheimer's disease, Parkinson's disease, Epilepsy, brain stroke, etc. [1] According to Dumurgier et al, in 2016, 6.1 million patients with Parkinson's disease, 43.8 million people with dementia, more than 80 million stroke survivors, 45.9 million patients with active epilepsy were reported. [2] Hence, such diseases have become the second leading cause of death globally and also are the leading cause of disability-adjusted life years. [2,3]

Since, mortality rate due to such diseases is high, an early diagnosis of the biomarkers of the diseases is of utmost importance in order to reduce exposure to risk factors, prevent progression and take proper therapeutic measure to improve the patient survival. [4] Current diagnosis of such diseases incudes PET imaging, cerebrospinal fluid assessment for biomarkers, MRI (magnetic resonance imaging), EEG (electroencephalography), MEG (magnetoencephalography). [2,5,6,7,8] All the aforementioned diagnostic procedures are expensive, time-consuming and cannot be performed frequently due to other health complications, thus, making the need for the development of point-of-care diagnosis a need in such areas of science.

Diagnosis by conventional methods combined with AI/ML technologies:

Conventionally, disorders like Parkinson's Disease, Alzheimer's disease, epilepsy, dementia are diagnosed based on the patient's comprehensive history, symptoms, and physical examination. [9] For example, in case of Parkinson's disease, cardinal motor features such as 4-Hz to 6-Hz resting tremor, bradykinesia, postural instability and "cogwheel 'rigidity are observed and determined as clinical findings for the diagnosis of the disease. [9] Many diagnostics techniques such as Diffusion-weighted MRI has been used to detect and differentiate between acute and chronic ischemic stroke, PET imaging for Alzheimer's and Parkinson's disease detection, SPECT for Parkinsonian syndrome. [10]

Recent studies report the use of machine learning or deep learning algorithms to identify and classify such neurological or neuropsychiatric disorders based on physiological symptoms, CT scans, sonography, handwriting, MRI, EEG and EOG pattern, PET scan images, CT-angiography, as described by Sharma et al. [11] Deep learning techniques such as Deep Neural Network (DNN), Convolutional Neural Network (CNN), Recurrent Neural Network (RNN), Deep Auto Encoder (DA), Deep Belief Network (DBN), Deep Boltzmann Machine (DBM), etc have been explored to analyze the data collected using conventional optical modalities for the diagnosis as described in the section. [11]

In a study by Lach et al, describes about the potential and use of CNN to assess the gait movement and performance which can aid in diagnosis of Alzheimer's, Parkinson's and

Multiple sclerosis like disorders. [12] Similarly, Furlanello et al, describes about the detection of stereotypical motor movements that are often associated with Autism Spectrum Disorders (ASD) and thus, can be used for the diagnosis using deep learning techniques. [13] Detection and classification of autism was studied by Li et al and Lu et al based on MRI and fMRI images analyzed by DE-MC and denoising auto-encoder, respectively. [14,15] Similarly, Heinsfield et al describes in their study, the use of fMRI dataset and deep neural network for autism diagnosis. [16] Many studies performed by Oman et al, Wilson et al and Parveen G.B et al shows the use of CNN, SVM, auto-encoder based deep learning techniques to detect Ischemic stroke based on CT-angiography, CT and MRI scan images. [17,18,19] Majority of studies have been carried out with a focus on diagnosis of Alzheimer's and Parkinson's diseases using AI/ML techniques. [11] Spasov et al, in their study focuses on the classification and identification of Alzheimer's disease using CNN with the help of MRI, demographic, neuropsychological, and APOe4 genetic data. The authors report a sensitivity, specificity and accuracy of 100%. [20] Similar study reported by Zheng et al, employs AlexNets algorithm to study the diagnosis of Alzheimer's disease using PET images of patients. [21] Basaia et al also employed CNN and MRI scans to detect and classify Alzheimer's disease amongst a population but is less sensitive (shown in Table 1) as compared to study reported by Spasov et al. [22] Parkinsons 'disease was also explored by researchers in order to be able to diagnose from MRI, PET, or other modalities combined with AI/ML technologies with accuracy, sensitivity and specificity achieved above 98%. [11] Oh et al reports the use of EEG signals processed and analyzed with the help of CNN to achieve an accuracy, sensitivity and specificity of 88.25%, 84.71%, 91.77%, respectively. [23] In another study carried out by Camps et al, describes the use of MRI-scans to detect FOG episodes in patients of Parkinson's disease by employing deep learning techniques. [24] Similarly, Choi et al in their study utilized CNN technique to identify FP-CIT SPECT images to classify normal patients and patients with Parkinson's Disease while achieving a high sensitivity, specificity and accuracy as mentioned in Table 1. [25]

Similar deep learning techniques have been widely explored to study their potential to classify and detect epilepsy. Majority of studies utilise EEG signal information for diagnosis of the disorder. A study by Wei et al reports a sensitivity, specificity and accuracy of 88.90%, 93. 78% and 90% respectively for diagnosis of epilepsy using multi-channel EEG and 3D CNN. [26] Similarly, Xuyen et al used EEG signals along with DBN for the diagnosis while attaining 92.82%, 96.41%, 96.87% of sensitivity, specificity and accuracy respectively. [27] Another study carried out by Hussein et al, utilised deep Long Short-Term Memory (LSTM) to diagnose epileptic seizures based on EEG signal features. The authors report 100% sensitivity, specificity and accuracy. [28]

Disorder	AI/ML algorithm used	Modality	Sensitivity	Specificity	Accuracy	References
Stroke	CNN, SVM, Auto-encoder	CT-angiography, CT-scan and MRI-scan	0.883- 0.93	0.82	0.904	17,18,19
Autism	DE-MC, denoising auto-encoder, deep neural network	MRI, fMRI	0.74	0.63	0.70- 0.80	14,15,16
Alzheimer's Disease	CNN, AlexNets	MRI, PET	0.86-1	0.95-1	0.91-1	20,21,22
Parkinson's Disease	CNN, DL	EEG, MRI, FP-CIT SPECT	0.84-0.98	0.91-1	0.88-0.98	23,24,25
Epilepsy	3D CNN, DBN, Deep LSTM	EEG	0.88-0.92	0.93-0.96	0.9-0.96	26,27,28

Table 1: Comprehensive table of disorders detected or predicted using AI/ML or deep learning techniques using various diagnostic modalities

Abbreviations: CNN- Convolutional Neural Network, SVM- Support Vector Machine, MC-DE- Data expanding method for multi-channel CNN, DL- Deep Learning, DBN- Deep Belief Network, Deep LSTM- Long Short-Term Memory

Point-of-care diagnosis of biomarkers of neurological diseases:

As described above, conventional methods of disease detection demand expertise of neuroimaging modalities and are expensive techniques for disease monitoring. [8] Detection of biomarkers specific to a particular neurological condition on the other hand can be affordable and can be detected using point-of-care test kits at low-resource settings. Such techniques of detection can also be used as self-test kits at home settings for monitoring of the disease progression or the effectivity of therapy and treatment. [29]

Detection of biomarkers in the body fluids significantly helps in indicating the stage of the disease, disease risk, disease progression and the pharmacological and clinical response towards clinical therapy. [29,30] Hence, point-of-care tests or self-tests that detects biomarkers has several advantages such as cost-effectiveness, user-friendly, easy to use, one-step or two-step test, less time for result, highly sensitive and specific, etc. [31]

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Blood biomarkers of epilepsy, Alzheimer's and other neurological and neuropsychiatric disorders have been widely studied for the ease, early and rapid detection of such disorders. Most studies have been reported for the detection of various biomarkers in CSF (cerebrospinal fluid) and other body fluids to diagnose neurological and neuropsychiatric disorders such as Alzheimer's, Parkinson's disease, Multiple sclerosis, etc as shown in Table 2. [32]

Disease/ Disorder	Sample Type	Biomarker	References
Alzheimer's disease	Cerebrospinal Fluid (CSF)	β (1–42) (Aβ42), Aβ (1–40) (Aβ40), pTau 181 (pTau181), pTau 217 (pTau217), and total tau (tTau) peptides, neurofilament light chain (NfL), chitinase 3-like 1 (also known as YKL-40), glial fibrillary acidic protein (GFAP)	32, 33, 34
	Blood/Plasma	Aβ42/40, pTau181, pTau217, and pTau231, GFAP, Apolipoprotein E (APOE), GSK-3β, DYRK1A	32, 35
Parkinson's Disease	CSF	Alpha-synuclein, glial fibrillary acidic protein, beta-amyloid 1–42, tau, p-tau, YKL-40, orexin, β-glucocerebrosidase (GCase)	36,37,38
	Serum	alpha-synuclein, neurofilament light chain, glial fibrillary acidic protein, amyloid, tau, 8-hydroxyguanine (8-OHG)	36,37,38
Epilepsy	Blood	S100 calcium-binding protein B (S100B), neuronal specific enolase (NSE), glial fibrillary acidic protein (GFAP), neurofilament light protein (NfL), microtubule-associated protein tau (Tau), ubiquitin C-terminal hydrolase 1 (UCHL-1) and metalloproteinase 9 (MMP-9)	39

	CSF	miR-451, miR-21p, miR-19b, miR-27a-3p, miR-328-3p, and miR-654-3p	40,41
	Plasma	miR-671, miR-9a-3p, miR-7a-5p, miR-206-5p, miR-221-3p	42
Stroke	Blood	Anti-N-Methyl-D-Aspartate (Anti-NMDA), neuronal specific enolase (NSE), Heart fatty acid-binding protein (HFABP), nucleoside diphosphate kinase A (NDKA), Parkinson disease protein 7 (PARK7), Glycogen phosphorylase isoenzyme BB, platelet basic protein (PBP), serum calcium binding protein (S100B), von Willebrand factor (Vwf), Matrix Metalloproteinase 9 (MMP9), Vascular cell adhesion molecule (VCAM), miR-122, miR-148a, let-7i, miR-19a, miR-320d, and miR-4429, miR-363 and miR-487b	43
	Serum	APOA1-UP	43, 44

Table 2: Biomarkers of neurological and neuropsychiatric disorders

Many studies have been reported for the development of point-of-care tests for detection of neuropsychiatric or neurological disorders based on their biomarker detection. Lateral flow immunoassays, biosensors, PCR based sensors are a few of the examples of such rapid tests as discussed in the next section.

LFA based detection

LFAs are paper based platforms used for qualitative and quantitative detection of analytes in complex mixtures and are based on the principle of antigen and antibody interactions. This technique of detecting analytes is easy to use, cost effective, gives rapid results, highly sensitive and specific. [45]

Zhang et al in their study reports the detection of tau proteins (p-tau^{396,404}) in plasma using Lateral Flow Immunoassay technique to detect Alzheimer's disease. The authors employed

gold-nanoparticles and SERS technique to detect the presence of the analyte based on visual observation and for quantification of the analyte in the sample using SERS, therefore have achieved a sensitivity of 60pg/ml and 3.8pg/ml respectively. [46] In another study, Hsiao et al developed Spin enhanced Lateral Flow Immunoassay (SELFIA) using the Spin properties of Nitrogen Vacancy (NV-) Centres in Fluorescent Nanodiamond (FND) to achieve ultrasensitive detection of p-tau protein as a biomarker for the detection of Alzheimer's disease. [47] Wang et al reported in their study the use of entropy-driven catalysis amplification technique in lateral flow assay to improve the sensitivity for the detection of miRNA-16 for early diagnosis of Alzheimer's disease. The study reports the lowest limit of detection of 1.01pM in human serum. [48]

Similarly, few studies have been carried out on LFA systems for detection and diagnosis of Parkinson's disease, epilepsy, stroke. A study carried out by Chen et al, shows the detection of miR-5010 and miR-331 for sensitive diagnosis of Parkinson's disease using fluorescence quenching probe-based reverse fluorescence enhancement lateral flow test strip. [49] Song et al, describes about a SERS-based lateral flow assay for the multiplexed detection of matrix metalloproteinase-9 (MMP-9), S100 calcium-binding protein B protein (S100-β), and neuro-specific enolase (NSE) to help in the detection and diagnosis of stroke using blood as a sample. The authors report a lowest limit of detection of 0.01 pg/mL. [50] In another study by Sun et al, an electrochemical and SERS-based LFA was developed using Raman dyes, i.e Nile blue A (NBA) and 4-mercaptobenzoic acid (4-MBA)) along with Au@AgNPs for ultrasensitive detection of neuron-specific enolase (NSE) and S100-β protein biomarkers of stroke. The study reports SNR (Signal-to-noise ratio) 3 as the lowest detection limit of the LFA test. [51]

Biosensor based detection

Biosensors such as electrochemical, chemiluminescence, colorimetric biosensors are widely used for various applications in environmental monitoring, healthcare for detection of a wide range of analytes. [45] Such biosensors have also been employed for the detection of neurological and neuropsychiatric disease associated biomarkers present in body fluids which are as discussed.

Mars et al shows the use of a dual biosensor based on electrochemical and fluorescence property of curcumin-graphene quantum dots to detect and quantify APO*e4* DNA, a biomarker of Alzheimer's disease present in plasma. The study reports a sensitivity and LOD of 4.74 nAmLpg –1 and 0.48 pgmL –1, respectively. [52] In another study by Congur et al, an impedimetric biosensor containing graphene oxide (GO) modified graphite electrodes was employed for quantitative detection of miRNA-34a with a LOD of upto 1.84 -0.5 µg/mL. [53] Similarly, Yang et al carried out a study that focuses on the detection of Parkinson's disease biomarker, Alpha-synuclein (αS) using DNA aptamers and Liquid crystals-based biosensor. The study reported a limit of detection of 10pM. [54] On the other hand, an electrochemical nanobiosensor was developed by Aghili et al, for the detection of miR-195, a biomarker of

Parkinson's disease. The biosensor employs graphene oxide (EGO) and gold nanowires (GNWs) along with doxorubicin to quantify miR-195 using differential pulse voltametric measurements while achieving a detection range and LOD of 10.0–900.0 fM and 2.9 fM. [55]

Biomarker detection of epilepsy using biosensors has also been focused by many studies. Such as in a study by Forster et al, an electrochemiluminescence biosensor development is employed to detect miR134 in human plasma with 1pM of LOD. [56] Sayad et al studied about the detection and quantification of glial fibrillary acidic protein (GFAP) in blood using microfluidic-based magnetoimpedance biosensor and Dynabeads. [57] Similarly, Harpaz et al developed a SPR-based biosensor using gold nanoparticles for the quantitative detection of NT-proBNP and S100β with a sensitivity and specificity of >85%. [58]

Conclusion and Discussion

Neurological and neuropsychiatric disorders are rapidly becoming evident in the world. From changing lifestyles, to genetic mutations, such diseases are becoming major health problems in various age groups. [59,60,61] Diagnosis of the diseases when done by conventional methods can be expensive and sometimes are not sensitive enough to detect the disease at early stages. Thus, proposes a need to develop rapid, easy to use, point-of-care techniques that are cost-effective and can be performed at low resource settings. [62]

Conventional techniques of diagnosis of Alzheimer's disease, Parkinson's disease, epilepsy, stroke, and other neurological and neuropsychiatric diseases includes the use of MRI, CT-Scan, PET-scans and other imaging modalities. [9,10,11] Such modalities are expensive and effective only after the disease has progressed to a definite stage for its accurate detection and diagnosis. Thus, a need for point-of-care test devices based on biomarker detection in body fluids can be effective in terms of cost, time to result, disease progression monitoring, drug response monitoring and screening of such diseases in a population. Several biomarker based biosensors, Lateral flow assays have been designed that are highly sensitive and cost-effective and addresses the aforementioned problems of using conventional detection techniques. [29,30,31]

On the contrary, the conventional techniques are becoming advanced and are being developed into portable, hand-held optical modalities with AI/ML algorithms for patient testing and analysis. The use of AI/ML algorithms for the data analysis prevents the anomality in diagnosis that might arise from person to person. [63] Although, AI/ML based solutions might have disadvantages such as result biasness due to over-fitting or optimizations, methodological issues, difficulty in analysis of images, etc. Such disadvantages can be addressed in upcoming studies and integrate the algorithms for better and rapid analysis of captured scan images for diagnosis of the disease in less time. [64]

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