

Early diagnosis of neurodegenerative disorders: a systematic review on multimodal artificial intelligence approaches

Leila Soleimanidou, Abdalhossein Rezai, Hamideh Barghamadi, and Iman Ahanian

Abstract—Neurodegenerative Disorders (NDDs), including Alzheimer's Disease (AD), Parkinson's Disease (PD), and Multiple Sclerosis (MS), affect the brain and spinal cord, causing motor, cognitive, and sensory impairments. Early detection and diagnosis using Artificial Intelligence (AI) methods, especially multimodal AI, are crucial for accurate treatment and disease management. This systematic review, following PRISMA guidelines, investigates and compares recent advancements in multimodal AI for improving diagnostic accuracy, addressing current trends, and identifying open research gaps. In this paper, total of 72 studies is selected based on inclusion criteria: studies involving adults diagnosed with NDDs and utilizing AI on multimodal data, such as MRI, cognitive tests, speech, and genetic information. Data are sourced from PubMed, Scopus, IEEE, and Web of Science, encompassing 1,646,152 individuals, including 31,981 with Alzheimer's, 65,321 with Parkinson's, 23,247 with MS, and 1,525,603 control group. Findings indicate that multimodal AI approaches, integrating data from various sources, significantly enhance diagnostic accuracy. Key modalities include MRI, cognitive tests, and speech analysis. However, challenges such as limited sample sizes, data heterogeneity, and the lack of standardized protocols persist, highlighting the need for robust validation and ethical frameworks. Despite substantial advancements, further research is needed to address data integration challenges and standardize multimodal approaches. Collaboration among researchers and clinicians will be vital for developing explainable AI models, ultimately improving diagnostic accuracy and treatment outcomes for NDDs.

Keywords—Neurodegenerative disorders; Prediction methods; Diagnosis; Early detection; Artificial Intelligence; Multimodal AI

I. INTRODUCTION

IN Neurodegenerative Diseases (NDD), when neurons degenerate, get damaged, or die, there can be gradual issues with cognitive and motor functions, depending on the affected brain area [1]. The most prevalent NDDs are Alzheimer's Disease (AD) [2] and Parkinson's Disease (PD) [3], which primarily affect cognition and movement, respectively. Another neurodegenerative condition is Multiple Sclerosis (MS), which affects the brain and spinal cord. MS can cause numerous symptoms, including issues with vision, mobility, sensation, and

balance [1]. In MS, the immune system attacks the central nervous system's protective myelin sheath, resulting in hampered nerve signals and the onset of symptoms [1].

New methods to support early detection of these disorders are urgently needed to provide improved care, facilitate quicker enrollment in drug trials, and foster the development of novel medications [4]. Diagnosing NDDs requires evaluating a variety of cognitive areas, including memory, language, functional abilities, constructive skills, problem-solving, attention, orientation, and perceptual skills [5]. Since all NDDs present with progressive motor and cognitive impairments, their diagnoses rely primarily on in-depth clinical evaluations. To improve treatment efficiency, increase access to clinical research, and support the creation of innovative pharmaceuticals, the need for available medical equipment for early detection is growing [4].

The use of Artificial Intelligence (AI) shows promising outcomes in supporting dementia early diagnosis [6]. AI has the capacity to enhance the discriminatory sensitivity of Magnetic Resonance Imaging (MRI) scans and extract more information from popular cognitive tests. A recent AI paradigm called "multimodal AI" aims to develop models for combining and analyzing data from several modalities [6-9]. This state-of-the-art technology creates new opportunities for the detection of neurodegenerative diseases by allowing the simultaneous analysis of various modal contents, including text, image, video, audio, and cognitive score data [7-10]. This advancement allows for the analysis of all the information gathered during standard clinical assessments, such as voice recordings, images from MRI scans, text data from medical histories, mathematical outcomes from cognitive evaluations, and image information from cognitive tests. This approach has the potential to develop far more accurate models [4].

Despite these advancements, there are existing limitations in the field. One significant challenge is the heterogeneity of data sources, which can lead to inconsistencies and difficulties in integrating multimodal data effectively [11]. Moreover, there is a lack of large, high-quality datasets that are essential for training robust AI models [12]. Ethical and privacy concerns regarding the use of patient data also pose significant barriers to the widespread adoption of AI in clinical practice [13].

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Additionally, there is a need for standardized protocols and guidelines for the implementation of AI-driven diagnostic tools to ensure their accuracy, reliability, and clinical utility [14].

To address these limitations, essential developments are needed in several areas. First, the creation of comprehensive, standardized datasets that encompass a wide range of NDD cases is crucial. Second, advancements in data integration techniques are necessary to effectively combine multimodal data and extract meaningful insights [15]. Third, the development of explainable AI models is essential to provide transparency and trust in AI-driven diagnostic decisions [13]. Finally, collaborations between researchers, clinicians, and policymakers are needed to establish ethical guidelines and regulatory frameworks that safeguard patient privacy while promoting the use of AI in healthcare [16].

The use of data that is already clinically readily available, the lack of additional costs or time commitments, and potential savings through early diagnosis and the selection of the most discriminated tests make it an enticing strategy for the healthcare business. No previous assessments have collected and compared available clinical records to aid in the early diagnosis of NDDs. Addressing this knowledge gap is crucial because it will reveal which data sets and methodologies are most worth developing into clinical tools. Our goal in this study is to conduct a systematic review and summarize the evidence on how multimodal analysis of clinically available data helps with the early diagnosis of NDDs.

The structure of this paper is as follows: The systematic review methodology is described in section 2. The results and characteristics of the evidence are presented in section 3. An in-depth discussion of the pertinent results is presented in section 4; its conclusions and open research issues are covered in section 5.

II. MATERIALS AND METHODS

A. Research question and study design

The primary objective of this systematic review is to provide a comprehensive summary of the research on the most prevalent forms of NDD including AD, PD, and MS to aid in diagnosis and identify areas for future study. To reduce publication bias, we reviewed all existing studies in the field of NDD using multiple databases, encompassing various biomarkers across different countries and datasets. This review emphasizes the significant role of AI in improving the diagnostic accuracy of NDDs. Moreover, a recent AI paradigm called "multimodal AI" is utilized to combine and analyze data from several modalities, including text, image, video, audio, and cognitive score data. This approach allows for the simultaneous analysis of multiple types of information collected during clinical assessments, leading to the development of more accurate diagnostic models. This systematic review highlights the potential of AI and multimodal AI in advancing the early detection and diagnosis of NDD. This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [17] guidelines to ensure transparent and complete.

B. Eligibility requirements

The inclusion criteria are as follows:

- Studies involving adults (18 years or older) with any type of neurodegenerative disorder.
- Studies focusing on detecting, diagnosing, or predicting AD, PD, or MS.
- Studies utilizing AI over available clinical data, such as speech, clinical text, video and audio data, MRI, imaging data, genetic information, blood tests, and movement-related data (drawing, video, sensor, and writing abnormalities).

Studies are excluded if they:

- Involve children or animals.
- are published in predatory journals or lacked peer-review.

Furthermore, Lack of control group and short follow-up period is accepted in our investigation

C. Sources of information and methods of searching

With the following two key terms: "neurodegenerative disorder," and "detection/diagnosis/prediction," we search four databases base on their characteristic for relevant studies; PubMed as it is a comprehensive, biomedical, authoritative, research-focused, and peer-reviewed; Scopus as it is multidisciplinary, extensive, abstract-indexed, high-impact, and global; IEEE as it is technical, engineering-centric, innovative, cutting-edge, and scholarly; and Web of science as it is multidisciplinary, citation-tracking, influential, scholarly, and bibliometric. In the research, terms such as "degenerative," "neurological," "Alzheimer", "Parkinson" and "Multiple Sclerosis" are employed for concept one as wild cards and free text words, and "detect", "diagnose" and "predict" for concept two. Additionally, there is TITLE-ABS-KEY (detect* OR diagnose* OR detect*) and Dementia, degenerative, neurological, Alzheimer's, Parkinson's or Multiple Sclerosis are also the TITLE-ABS-KEY acronym.

D. Selection and Data Visualization Process

- At the beginning, precise and criteria for selection and data extraction including the first author, the nation, the type of neurodegenerative disorder, the applied biomarkers, the number of participants, the publication year, and the journal are determined and shared with all reviewers.
- All authors are trained over the established criteria and in a practical example.
- Using the title and abstract, each paper is assessed separately based on the criteria for inclusion and exclusion. To minimize individual biases two of authors, select and extract the data to developed a data extraction table and gather information from each publication independently.
- In several meeting extracted data are compared and discussed and appropriate solutions proposed if there were any disagreements.
- Two other authors verified and approved the final data extraction table of the process for the final manuscript.

We follow above instruction to ensure that the selection and data extraction processes are conducted accurately and without bias and also to resolve disagreements among authors and reviewers.

E. Synthesis of findings

The findings from the selected articles are checked, gathered, and summarized by two authors and confirmed by two others. We use narrative synthesis to investigate and combine the findings and gaps in the existing data.

TABLE I
COMPARATIVE TABLE FOR NDD DETECTION

Author	Year	Country (First Author)	Disorder	Modalities / Indicators	Participants
Branco et al. [1]	2022	Italy	MS	EDDS	MS = 220
Abbas et al. [2]	2023	Australia	AD	MRI	AD = 84, HC = 154
Vásquez-Correa et al. [3]	2018	Spain	PD	Handwriting, Gait, Speech	HC= 40, PD= 44
Li et al. [4]	2023	USA	AD	Clinical Records	AD=23,835, CP=1,038,643
Thabtah et al. [5]	2020	New Zealand	AD	Cognitive score	AD = 1737
Zhou et al. [6]	2023	China	AD	Genetic data, Plasma biomarkers, Cognitive score	AD = 1116, MCI = 309, HC = 915
Rohanian et al. [7]	2021	UK	AD	Speech, Cognitive score	HC=78, AD=78
Ilias et al. [8]	2022	Greece	AD	Speech, Cognitive score	HC=78, AD=78
Moguilner et al. [9]	2022	USA	AD	Cognitive score, EEG, MRI	AD=76, HC=152
Pandey et al. [10]	2021	India	AD	Speech, Text	AD= 87, HC= 79
Safai et al. [11]	2022	India	PD	Multimodal MRI (DWI, fMRI, T1w)	PD = 75, HC=34
Dolci et al. [12]	2022	USA	AD	Genetic data, MRI (sMRI/fMRI)	AD=258, HC=530
Cagol et al. [13]	2023	Switzerland	MS	Cortical Lesions (CLs) MRI, Central Vein Sign (CVS) MRI, Brain Lesions MRI	MS=599, nonMS=452
Roca et al. [14]	2020	France	MS	Fluid Attenuated Inversion Recovery (FLAIR) MRI	MS = 1446 (train: 971, test: 475)
Arco et al. [15]	2021	Spain	AD	Cognitive score, MRI	AD=73, HC=61
Castellaro et al. [16]	2020	Italy	MS	CVS MRI	MS=791, CIS = 256
Bi X A et al. [18]	2021	China	PD	Genetic data, MRI	PD = 55, HC = 49
Zetterberg H. [19]	2019	Sweden	AD	Blood biomarkers (A β , tau, NfL) (Meta-analysis)	AD = 2000, HC = 4000 (27 Studies)
Marras et al. [20]	2018	Canada (Multinational)	PD	Clinical Records	PD = 44064
Pinto et al. [21]	2020	Portugal	MS	EDDS	MS = 187
Sakr et al. [22]	2024	Germany	MS	Clinical Record	MS = 9285 (train: 5517, test: 3768)
Montolió et al. [23]	2021	Spain	MS	RNFL (method Optical Coherence Tomography (OCT))	HC = 104, MS = 108
Storelli et al. [24]	2022	Italy	MS	MRI, Cognitive scores, EDSS	MS = 373
Zhang et al. [25]	2023	USA	MS	MRI, Clinical Records, EDDS	MS = 300
Walsh et al. [26]	2022	USA	MS	Clinical Records	MS = 2,532
Martynova et al. [27]	2019	Russia (Multinational)	MS	Pathobiological (Serum Cytokines)	G1:MS=833, HC=117, G2:MS=26, HC=11
Soman et al. [28]	2023	USA	PD	Knowledge Graph (Spoke), Clinical Records	PD=3,004, HC=457,197
Alalayah et al. [29]	2023	Saudi Arabia	PD	Audio Data	PD = 147, HC = 48
Govindu et al. [30]	2023	India	PD	Audio Data	PD = 23, HC = 8
Siderowf et al. [31]	2023	USA (Multinational)	PD	α -synuclein seed amplification assays	PD = 545, HC = 163
Nilashi et al. [32]	2023	Malaysia (Multinational)	PD	Clinical Records (UPDRS)	PD = 42
Alshammri et al. [33]	2023	Saudi Arabia	PD	Audio Data	PD = 23, HC = 8
Yu et al. [34]	2023	Canada	PD	Genetic data	PD = 14,828, HC = 13,283
Helmy et al. [35]	2022	Egypt	PD	Genetic data	N/A (computational study)
Sadaei et al. [36]	2022	USA	PD	Genetic data	PD = 879
Lilamand et al. [37]	2023	France	AD	Cognitive score, Plasma Leptin, CSF, A β , Biofluid (tau)	AD = 1036
Kavitha et al. [38]	2022	India	AD	MRI	AD = 64, non-demented = 72
Özge et al. [39]	2023	Turkey	AD	Cognitive scores, Clinical Records, Psychiatric disturbances, Neuroimaging	AD= 161
Bernardo et al. [40]	2021	Lithuania (Lithuania/ Brazil)	PD	Movement Disorders (writing)	PD=296, HC=218
Hansen et al. [41]	2022	Germany	AD	FDG-PET/CT, Cognitive tests	AD = 33, HC = 94
Rallabandi et al. [42]	2023	India	AD	PET, MRI	AD=493, HC=605,
Pahuja et al. [43]	2018	India	PD	Biochemical biomarkers, MRI	PD=637, HC=203
Martinc et al. [44]	2020	Slovenia	AD	Speech (audio + text), MMSE prediction	HC=78, AD=78
Pompili et al. [45]	2020	Portugal	AD	Speech, Text	HC= 78, AD= 78
Taleb et al. [46]	2020	Lebanon	PD	Eye Movement, Speech, Handwriting	HC= 21, PD= 21
Nasreen et al. [47]	2021	UK	AD	Speech (Interactional + Acoustic)	HC= 15, AD= 15
Ying et al. [48]	2022	China	AD	Speech, Text	AD= 87, HC= 79
Garcia et al. [49]	2018	Colombia (Multinational)	PD	Speech, Movement disorders (writing), Gait	HC= 41, PD= 49
Soleimanidou et al. [50]	2024	Iran	PD	Movement disorders (writing)	HC= 18, PD = 74
Zhang et al. [51]	2022	China	PD	EMG, Gait, EEG	PD = 12
Noella et al. [52]	2019	India	PD	Gait	HC= 73, PD=93
Jang et al. [53]	2021	Canada	AD	Eye-movement, Speech	AD/ MCI=79, HC=83
Nasreen et al. [54]	2021	UK	AD	Speech	HC= 15, AD = 15

Pasha et al. [55]	2020	India	PD	Clinical data	PD=252
Dachena et al. [56]	2020	Italy	AD	Cognitive score, MRI, fMRI	AD = 33, HC= 36
Dixit et al. [57]	2023	India (Multinational)	PD	Movement, handwriting, Speech	N/A
Yang et al. [58]	2021	China	PD	Clinical data, MRI (T1WI, DTI)	PD=65, HC=36
Ilias et al. [59]	2023	Greece	AD	Speech, Text	AD=78, HC=78
Hegen et al. [60]	2023	Austria	MS	kFLC in CSF (Meta-analysis)	MS=3322, HC=5849 (32 studies)
Dwyer et al. [61]	2021	USA	MS	T2-FLAIR MRI	MS=1672
Güllmar et al. [62]	2023	Germany	MS	MRI (T1w GRE, DTI-ADC)	MS=327, HC=84
Kaya et al. [63]	2022	Turkey	MS	Static Plantar Pressure Distribution	MS=43, HC=62
Uzunköprü et al. [64]	2021	Turkey	MS	RNFL, Neurofilament Heavy chain (NfH) in CSF, Nitrotyrosine (NT)	MS=46, HC=21, CP=8
Hinsinger et al. [65]	2024	France	MS	CD138 (Specific CSF)	MS=158
Lommers et al. [66]	2022	Belgium	MS	Quantitative MRI (qMRI), Clinical Records (EDSS, cognitive tests)	MS = 35, HC = 36
Ahmadi et al. [67]	2019	Iran	MS	EEG	G1:MS=233, HC=333, G2:MS=187, HC=376
Vidal-Jordana et al. [68]	2024	Spain	MS	Optic Nerve MRI (ON-MRI), OCT, Visual Evoked Potentials (VEP)	MS=157
Svoboda et al. [69]	2022	Czech Republic	MS	Speech	MS=65, HC=66
Khodabandeh et al. [70]	2023	Iran	MS	OCT	G1: MS = 106, HC = 422 , G2:MS=45, HC=45
Balgetir et al. [71]	2021	Turkey	MS	Plantar Pressure Distribution	MS=43, HC=62
Montolió et al. [72]	2021	Spain	MS	OCT	MS=108, HC=104
Sarin et al. [73]	2023	Russia	PD	Movement Disorders (writing)	PD=25, HC=15, PD=37, HC=38, PD=31, HC=35

III. RESULTS

A. Selection of evidence

Number of total electronic records that are selected at the first step are 700. In the next step, 188 duplicate records are deleted. After screening the remaining 512 publications, 154 papers are disqualified because they didn't meet general requirements. At the end stage of the screening, 286 records have deleted as they didn't fit the eligibility requirements such as being recent, language restriction, being original research article, classification of NDD diagnostic. The review contained 72 items in all. Figure 1 depicts the entire search and selection procedure. This flowchart illustrates the steps in the scoping review process such as document identification, paper screening, and paper inclusion.

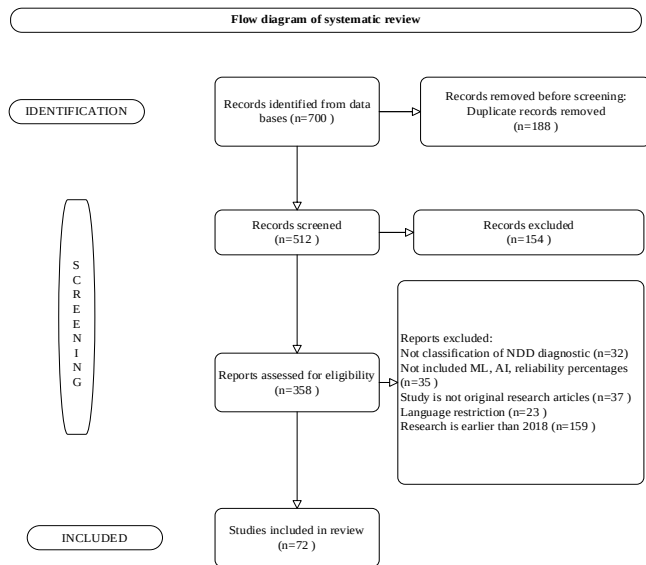


Fig. 1. Scope review flowchart in PRISMA

B. Specifications of the evidence

Table I gives a snapshot of 72 research studies [1-16, 18-73] focused on AD, PD, and MS, each examining different biomarkers and participant groups. Equally, 24 of the studies examine the AD, 24 look at the PD and 24 researches are focused on the MS. Here's a closer look at the key points:

- Number of participants; The studies collectively involve 1,646,152 participants, including 31,981 with AD, 65,321 with PD, 23,247 with MS, and 1,525,603 Control Groups.
- Geographic distribution; The studies span multiple countries, with significant contributions from the USA, India, and Spain.
- Year of publication; All studies are published after 2018, emphasizing the recent advances in this field.

The meta-data of the studies are shown in Figures 2 and 3. Figure 2 shows the number of papers by each country, highlighting the leading contributors to this research. Figure 3 illustrates the areas of interest by country, breaking down the number of studies focused on AD, PD, and MS. The majority of publications are from USA and India (n=9), Spain and China (n=5), Turkey and Italy (n=4), UK, Germany, Iran, France and Canada (n=3), Greece, Portugal, Russia, and Saudi Arabia (n=2) and other countries with one study.

Some of the studies containing more than 20,000 people whereas others are analyzing even less than 20 people. Most frequently used clinical data for diagnosing NDDs are illustrated in figures 4, 5 and 6, for AD, PD and MS, respectively. Based on the results, more applied modalities are cognition, speech, imaging and text for AD. More applied methods for PD are movement disorder, gait, speech, MRI, genetic and clinical records. More applied modalities for MS patients are MRI, OCT, clinical record and Cerebrospinal Fluid (CSF).

Furthermore, AD Diagnostic Methods in figure 4 shows that:

- Cognitive scores (22%) and speech data (22%) are the most frequently used modalities.

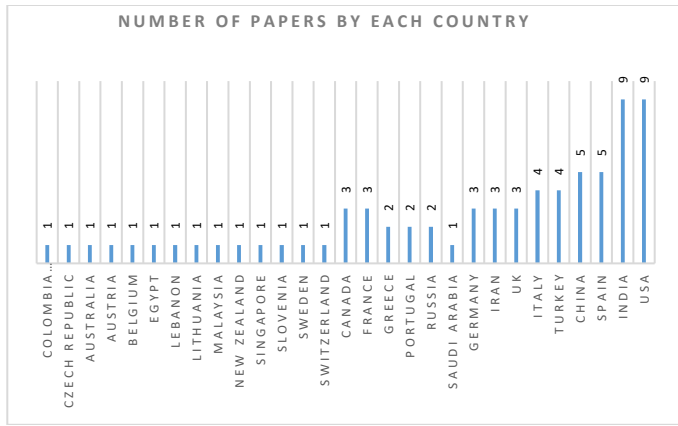


Fig. 2. Meta-data from the review process

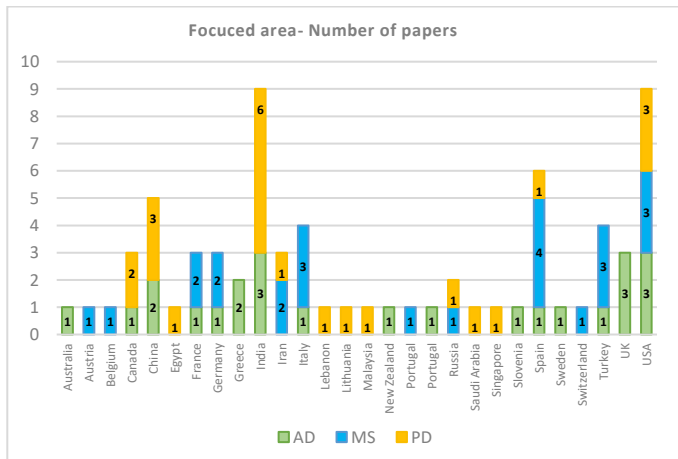


Fig. 3. The area of interest by the countries

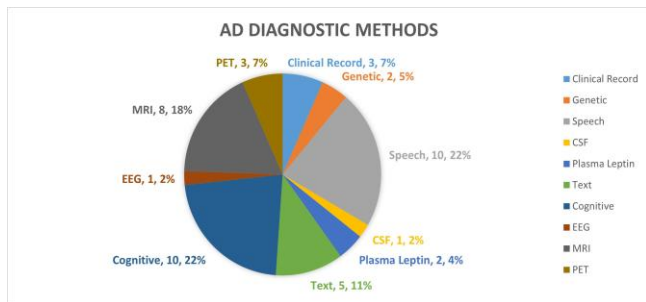


Fig. 4. The clinical data used most frequently in the diagnosis of AD.

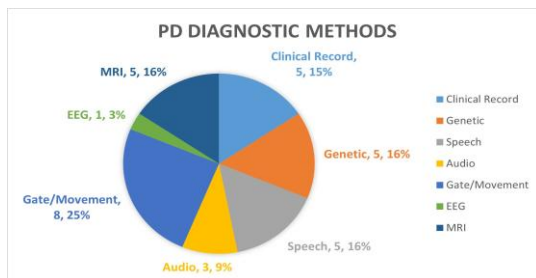


Fig. 5. The clinical data used most frequently in the diagnosis of PD

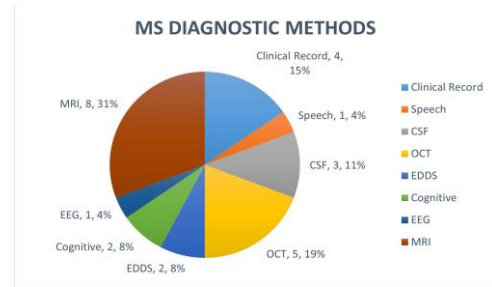


Fig. 6. The clinical data used most frequently in the diagnosis of MS

- MRI (18%) and Text Data (11%) are also commonly employed.

PD diagnostic methods in figure 5 illustrates which:

- Gait/movement disorders (25%) is the leading modality.
- Speech data and MRI each account for 16%, while genetic data and clinical records also play significant roles.

MS Diagnostic Methods in Figure 6 demonstrates that:

- MRI (31%) is the most prevalent method.
- OCT (19%) and clinical records (15%) follow closely.

The systematic review reveals that while imaging techniques like MRI and Positron Emission Tomography (PET) scans are critical across all NDDs, other modalities such as cognitive scores, speech data, and genetic data also play crucial roles. The emphasis on multimodal data integration highlights the need for comprehensive diagnostic approaches to enhance accuracy and early detection.

C. Narrative synthesis of relevant findings from the evidence

According to all papers that have been studied, the most often analyzed modalities are imaging, cognition, speech, genetic, gate, CSF and movement disorders.

1) medical imaging

Imaging is one of the most popular, but expensive method, which has been using in all kind of NDDs [2, 9, 11-16, 18, 24, 25, 38, 42, 43, 52, 56, 58, 61, 62, 68]. The combination of non-imaging data with biomedical imaging data from brain scans such as MRI, PET, and CT makes the automated diagnosis of the NDD perform better [9, 12, 15, 18, 24, 25, 42, 43, 56, 58].

According to several researches, the performance of multiple imaging modalities is higher than single modal analysis [15, 42]. The accuracy of multimodal investigations using MRI and PET data to distinguish between HCs and AD patients is from 74.3% to 98.0%.

Using paired MRI and PET scan data has been just in classification of the AD [42]. Most research employed a latent picture of features space to combine their multiple modalities across the feature fusion stage [9, 15, 42]. Depth polynomial network is additionally employed by some authors to apply linear restrictions to multimodal data for the feature fusion [42]. While some studies employ further methods such as guide discriminative feature for diagnosis [15] and encoded features [2, 15, 42]. others increase the efficacy of the discriminative features within several modalities during the classification stage by using encoded features and hierarchical representation of features. Regarding the AI techniques, a study found that the self-adaptive resource allocation network is able to classify both HC and PD with 98.78% accuracy [43]. As Mild Cognitive Impairment (MCI) represents early-stage of Alzheimer's

disease, precision of the prediction made by Rallabandi et al. [42] on the MCI-to-AD crossover is 95.9%.

2) Cognitive score

There are 12 investigations, pertaining to different kind of the NDD, use the cognitive data [5-9, 15, 24, 37, 39, 56, 66]. The most common multimodal data combinations are the cognitive assessments combined with MRI, genetic information and voice analysis. For the multimodal research, the data of cognitive scores have been collected in numeric rang, from the cognitive exams. To accomplish these objectives, standardized cognitive tests that evaluate a person's executive functioning, language, retention, concentration, and visual and spatial abilities are frequently utilized. A modified version of the mini-mental state examination is used in conjunction with longer neuropsychological evaluations to assess people cognitive functioning. To distinguish among AD dementia and MCI, Rohanian et al. [7] have employed the cognitive score in addition to the MMSE scores matched with speech data, with accuracy of 79.2%.

3) Speech and audio data

It is known that delays in speech and language are consistent markers for nonverbal dementia [3, 7, 8, 10, 28, 44-49, 53, 54, 57, 59, 69]. The majority of the multimodal studies concentrated on AI approaches linked to natural language processing. The long short-term memory frameworks have been widely used throughout speech multimodal investigations to extract audio and text properties [7, 8, 44, 45]. This entails timing the synchronization of text and audio data to ensure the model used for AI can analyze the relationship amongst spoken and written terms.

The most common multimodal combinations of data are voice coupled hand movement data, text coupled speech, and cognitive scores coupled speech. When using AI to distinguish between both NDD and HC by examining speech and language features, most research have produced encouraging results, such as accuracy of 97.6% in [3]. With clinical and handwriting data, only four researchers looked at speech to distinguish PD from HC; they found classification accuracy of 97.6%, 97.62% and 97.03% in [3],[46] and [57], respectively.

The Active Data Representation model for speech processing is utilized by Martinc et al. [44] to integrate textual and auditory data at both sentence and word levels. To determine whether someone has AD, Nasreen et al. [47] have looked at the function and significance of the interactional components in discourse. They found that utilizing dysfluency features, interactional features, and a combination of both feature datasets, they can predict the AD with an accuracy of 90%. A multimodal fusion-based paradigm for detecting the AD is proposed by Pandey et al. [10] and incorporates both voice and text transcripts. They are able to attain accuracy of 81% amongst people with HC and AD using a less complex design, less processing work, and less complexity. The Support Vector Machine (SVM) classifier is used by Ying et al. [48] to classify AD patients. Using a modified Wav2Vec2.0 framework and deep linguistic features acquire by a modified Bidirectional Encoder Representations from Transformers; it is possible to classify AD from HC with an accuracy of 89.1%. To diagnose dementia via the speech and language modality, Ilias et al. [8] have devised a novel approach that uses a visual transformers and cross-modal attention layers. The classification accuracy for the AD using the suggested method in [8] is 90%.

4) Genetic data

A variety of genetic variations can suggest a higher risk of the AD or PD development [6, 12, 18, 34-36]. It has been demonstrated that genetic data integrated with a multimodal approach improves classification performance when joined together with speech or single brain imaging data.

The MRI and genetic data are the most common multimodal combinations. Bi et al. [18] have presented the Clustering Evolutionary Random Neural Network Ensemble (CERNNE), model for the PD prediction. A structure for multifunctional evaluation is created that can predict the brain regions and genes associated with PD and use the CERNNE to differentiate between the patients. The CERNNE is able to identify altered fusion characteristics in the PD patients thanks to the utilization of genetic data, and this helped to distinguish PD from HC with an AUC of 0.88.

5) Gait

The gait (walking) movement data are employed in PD-related studies [3, 52]. Generally, respondents are asked to walk over nine meters at their average pace while a marker-based motion detection equipment collect gait data. These data are then used to filter additional numerical movement characteristics such as gait velocity, step/stride dimension, rhythm, variation, left-right asymmetry, and controlling posture, e.g., maximum toe clearance [51].

The gait information has been frequently integrated with information from the speech, MRI, and EEG techniques to classify the PD patients against HC. This results in classification accuracy ranging from 85.0% to 97.3% [3, 51]. Furthermore, multimodal fusion strategies combining handwriting, speech, and gait data via i-vector representation have demonstrated promising performance, with AUC values reaching 0.85 using score-level and super-i-vector fusion approaches. According to the investigation, independent studies using each modality produced inferior classification results than the super-i-vector merging strategy. To verify the language independence of the technique, Vasquez et al. [3] have offered performing additional testing using different problems. Additionally, they use CNNs that had been created using Time-Frequency Representations, and this enable the neural network to comprehend hidden representations. The recommended method correctly classified the PD people and HC, with accuracy of 97.3%.

6) Brain electrical activity

EEG data, which provide details on the neuronal activity of the brain, can help in the identification of neurodegenerative illnesses [9, 51, 67]. In this regard, a non-invasive screening approach based on quantitative EEG analysis and handwriting kinetics has been proposed for MCI, achieving 96.3% classification accuracy using a dual fusion model with an SVM-RBF kernel classifier.

7) Cerebrospinal fluid

The liquid called cerebrospinal fluid, which surrounds the brain and spinal cord and contains a number of chemicals that can help with the diagnosis of the brain illnesses, is clear and colorless. One way for finding someone with AD is to check if specific proteins, including amyloid beta and tau, are found in the CSF [37, 60, 64, 65].

For a considerable amount of time, neurologists have used CSF testing to look into a range of brain issues. These tests are invasive, needing the inserting of a spinal needle entering the lower spine whilst under local anesthesia. Advanced machine

learning techniques utilizing CSF biomarkers have also been explored, with classification accuracies reaching over 94% for distinguishing MCI from HC, though such methods often come with increased computational costs.

8) Other methods

In addition to the mentioned biomedical information, other numerical information pertaining to sleep and olfactory function, movement, eye movement and hand movement has also been demonstrated to be useful in aiding the classification of the NDD from controls.

According to studies, both AD and PD have altered sleep-wake cycle. Loss of olfactory perception, or smell, is another common symptom in PD and AD patients. In this regard, olfactory and non-motor data, along with other biomarkers, have been utilized to classify early PD subjects from HCs using AI, with an SVM classifier achieving an AUC of 0.964.

Data on fixations, saccades, and pursuit movement parameters can be gathered in clinics because it is known that eye movements alter in both AD and PD [46, 53]. Fixations and saccades are terms used to describe when a person's gaze remains fixed for 60 MS or more, whereas pursuit is used to characterize tracking movements [53]. Jang et al. [53] have combined deep learning methodology with the integration of language and eye movement modalities for AD-relevant research. The classification of the AD and MCI yielded a global AUC of 0.83.

Studies have shown that hand movements can change in patients with PD and AD, and this can be used as a technique for early identification [40, 49, 50, 57, 73].

A number of studies combined data from handwriting and/or drawing with speech and movement modalities. Hand gestures are used as component in a comprehensive feature evaluation for the classification of NDD among HCs. Taleb et al. [46] have utilized voice as well as handwriting modalities to classify the PD. They obtain accuracy of 97.62% in differentiating between controls and early PD. They recommend utilizing jittering-trained models and Convolutional Neural Network-Bidirectional Long Short-Term Memory systems in conjunction with artificial data augmentation strategies [46].

To summarize, different methods are used in the NDD diagnosis. For an accurate diagnosis and prediction, these methods should be utilized in concern with other diagnostic instruments and clinical evaluations.

IV. DISCUSSION AND LIMITATION

The cognitive scores, MRI, and PET scans worked together to reach classification accuracy for the AD vs. MCI of 86%. With claimed accuracies of 90% to 98%, gait, handwriting/drawing, and speech data are the most reliable data combinations for distinguishing NDD from the HCs. Overall, the brain scan images results boosted the results of automated NDD detection. Most multimodal trials focused on natural language processing, computer vision, and associated AI techniques. Furthermore, it has been shown that information on hand, eye, and gait movements can aid in the diagnosis of the NDD. The majority of models' workflows comprised feature extraction, selection, fusion, plus the use of multisource distinguishing features in the classification in terms of the AI methods applied to multisensory sets of data for the initial detection of the NDD. The amount of the dataset, the difficulties

in creating the model, and the specific goals such as being noninvasive or affordable to detect the NDDs are some of the variables that impact how accurate the AI is in identifying the NDD. A comprehensive examination of records over the previous seven years, a hybrid approach of clinical expertise and medical engineering scientists' knowledge, applying reliable PRISMA-compliant methodologies, and summarizing NDD detection findings and AI approaches are some of the study's strong points.

It's crucial to recognize the restrictions, though. We highlight that there are variances in sample sizes, as the Table I illustrated some rather small (number of patients ≤ 255 people in 44 (61%) studies), and disparities in study designs, making it difficult to compare the findings of these studies. Therefore, developing standard protocols for data collection and analysis in NDD research to ensure consistency and comparability across studies and also increasing the overall sample size to enhance the statistical power of the findings is recommended for future research. Apart from data size, improving data quality and addressing potential biases in the datasets used for NDD research need to be considered. Additionally, the majority of applications are restricted to gathering data on biomarkers using various networks, followed by the use of a statistical model to categorize cases of the AD, PD, and MS. The lack of association analysis between biomarkers and the inability to integrate distinguishing traits limit this type of research. For this systematic investigation, we analyze 72 studies, and none of them had integrated all the categories of multimodal data into a single classification method. So, combining different modalities and the integration of additional data modalities (e.g., genetic data, proteomics) to provide a more comprehensive understanding of NDDs would be strong need for future studies. Also, to improve interpretability and accuracy of multimodal data integration, leveraging advanced AI techniques, such as explainable AI and deep learning is recommended.

Because NDD is difficult to diagnose, most tests are performed in a clinical setting. So, assembling a sizable multimodal dataset for the purpose of early diagnosis of various illnesses is very challenging. Therefore, validating of AI-based diagnostic methods in real-world clinical settings to assess their practicality and reliability is essential for clinical application. The last matter that should be highlighted is the need for research on the cost-effectiveness of AI-based diagnostic tools to ensure their accessibility and affordability for widespread clinical use.

V. CONCLUSIONS AND OPEN RESEARCH ISSUES

This systematic review investigates the multidisciplinary assessment of clinically accessible information for the early diagnosis of neurodegenerative disorders. The majority of the studies (87.5%) have been published in the past five years, highlighting the recency and relevance of multimodal analysis. This method integrates data from medical imaging, cognitive assessments, gait, eye and hand movement tests, speech, language, EEG, and genetic assessments. Emerging biomarkers such as blood-based biomarkers, cerebrospinal fluid tests, plantar pressure, PET scans, and others have also been used to assist in the detection of NDDs.

Despite these advancements, several challenges remain. Variations in study designs, dataset limitations, and sample

sizes make it difficult to compare research findings. Additionally, there is a critical need to integrate all data sets into a single classification model. Advanced methods such as implicit representation learning and high-order Laplacian normalized low-rank representation are necessary to address issues related to missing or noisy data.

VI. REFERENCES

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