TSINGHUA SCIENCE AND TECHNOLOGY
ISSN 1007-0214 02/22 pp13–33
DOI: 10.26599/TST.2023.9010037
Volume 29, Number 1, February 2024

The Application of Artificial Intelligence in Alzheimer's Research

Qing Zhao, Hanrui Xu, Jianqiang Li*, Faheem Akhtar Rajput, and Liyan Qiao*

Abstract: Alzheimer's disease (AD) is an irreversible and neurodegenerative disease that slowly impairs memory and neurocognitive function, but the etiology of AD is still unclear. With the explosive growth of electronic health data, the application of artificial intelligence (AI) in the healthcare setting provides excellent potential for exploring etiology and personalized treatment approaches, and improving the disease's diagnostic and prognostic outcome. This paper first briefly introduces AI technologies and applications in medicine, and then presents a comprehensive review of AI in AD. In simple, it includes etiology discovery based on genetic data, computer-aided diagnosis (CAD), computer-aided prognosis (CAP) of AD using multi-modality data (genetic, neuroimaging and linguistic data), and pharmacological or non-pharmacological approaches for treating AD. Later, some popular publicly available AD datasets are introduced, which are important for advancing AI technologies in AD analysis. Finally, core research challenges and future research directions are discussed.

Key words: Alzheimer's disease; artificial intelligence; etiology discovery; computer-aided diagnosis; computer-aided prognosis; treatment

1 Introduction

Dementia is a clinical syndrome; it is manifested as a progressive deterioration of cognitive function, such as memory, the ability to pay attention and language skills, and a variety of neuropsychiatric symptoms and related behavioral disorders, resulting in impaired daily life and activities[1–3]. Alzheimer's disease (AD) is one of the primary causes of dementia in the world. It is estimated that a 95% incidence rate of AD occurs in individuals over 65 years old and will increase with age. For subjects aged between 65–69 years old and older than 85 years old, the incidence of AD is 0.6% and 8.4%[4], respectively.

The progression of AD is different for each individual. AD patients live approximately 4–8 years after diagnosis[5]. According to World Alzheimer Report, over 50 million peoples were living with this disease worldwide in 2019. The figure will increase to 152 million by 2050, which means that one person develops Alzheimer's every three seconds. Based on the risk of onset, AD is broadly classified into three stages:

(1) The preclinical stage describes a person with signs of pathology on brain images, such as cerebral amyloidosis. Still, it has no cognitive symptoms (in the impairment level of very mild cognitive decline).

(2) Individuals with mild cognitive impairment (MCI) have brain changes and subtle symptoms in this stage.

(3) Dementia, severe cognitive impairment, and noticeable brain changes appear in this stage.

The AD burden will escalate with an increased risk, and the treatment options will switch to limited. Usually, progress from MCI to dementia is needed over the years,

• Qing Zhao and Jianqiang Li are with the Faculty of Information Technology, Beijing University of Technology, Beijing 100124, China. E-mail: {zhaoqing, lijianqiang}@bjut.edu.cn.
• Hanrui Xu is with the School of Medicine, Tsinghua University, Beijing 100084, China. E-mail: 3420994613@qq.com.
• Faheem Akhtar Rajput is with the Department of Computer Science, Sukkur IBA University, Sukkur 65200, Pakistan. E-mail: fahim.akhtar@iba-suk.edu.pk.
• Liyan Qiao is with the Department of Neurology, Tsinghua University Yuquan Hospital, Beijing 100040, China. E-mail：qiaoliyan2000@aliyun.com.
∗To whom correspondence should be addressed.
Manuscript received: 2022-10-27; revised 2023-03-22; accepted: 2023-04-27

and not all patients with MCI will convert to dementia, even though there is currently no cure for this disease[6]. But the probability is higher for MCI patients to develop dementia than those without MCI. Therefore, improving the diagnosis rates is essential so individuals with high risk can be detected earlier to prevent or reduce future progression.

As a standard tool that used for brain pathology assessment and structural lesions exclusion (e.g., tumor and infarction), the neuroimaging can be mainly divided into two categories[7]. The first category is structural imaging, such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)[7, 8]. CT utilizes X-rays to reveal the two dimensional structure of brain, and MRI generates pictures of tissues inside the brain through radio waves and strong magnetic field. When the neurologic examination has no abnormal findings, CT is adequate for progressive cognitive decline detection. However, if a patient has motor dysfunction, the MRI might be adopted to recognize ischemic changes which cannot be identified by CT. The second category is functional imaging, such as functional MRI (fMRI) and Positron Emission Tomography (PET)[9, 10]. fMRI is a non-invasive technique, which uses MRI to measure hemodynamic changes caused by neuronal activity, and can show the neuronal active and functioning part of brain. PET is a nuclear medical imaging technique that utilizes radioactive substance to identity functional changes of brain and generates a three-dimensional image. Apart from neuroimaging, neuropsychological assessment can help to indicate the extent of deficits with higher precision for differential diagnosis. Recent researches show that language and memory impairment are crucial signs of AD, such as difficultly recalling names and finding suitable words to represent in spontaneous speech. The language of AD individuals is characterized by generating grammar errors and increased frequency of sound disruption and self-correction. Gene and cerebrospinal fluid (CSF) detection provides the reference for AD diagnosis; for example, mutations of the amyloid precursor protein (APP) gene and PS1 and PS2 genes account for 50% of familial early-onset AD. Therefore neuroimaging, neuropsychological examination, and genes play an essential role in AD detection.

The essential goals of AD research include discovering the factors that cause the disease, so that the disease's detection and prediction process can be established efficiently by exploring personalized treatment approaches[11, 12]. As shown in the Fig. 1. The workflow of traditional AD diagnosis includes three stages, i.e., doctor visits, body examination, and diagnosis. During the doctor visits stage, the basic information of each patient asked by doctors including symptoms, disease history, and family history etc. Then, the various items are checked according to the primary diagnosis of doctor, such as laboratory test, and imaging test, etc. Finally, the clinical diagnoses are produced according to produced test results. Traditional process rely on the clinician's knowledge and experience for test result analysis, and then for subsequent diagnosis. First, the various tests might produce high volume results, requiring a large amount of workload for clinicians to analyze, and the error-prone results might be generated since the physician's knowledge and experience are subjective and occasionally unreliable. Secondly, due

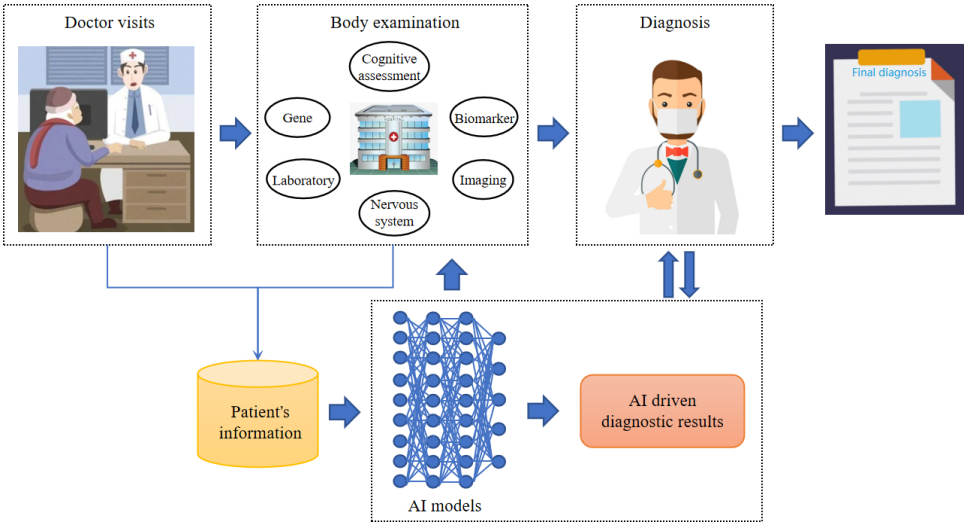

Fig. 1 AI empowered diagnosis workflow.

to the fact that the complicate interactions among many factors in neurobiological and immunological processes are involved, it is difficult to utilize a simplified model to understand the aetiology and then provide clues for researching solutions of reversible treatment as well as prevention of AD[13, 14].

Artificial intelligence (AI) is an emerging technology for various medical purposes, such as medical decision-making[15]. Comparing to traditional workflow of diagnosis that heavily relies on human labors, AI enable the automation of the diagnostic process. As shown in the Fig. 1. First, the basic information and test results are collected as the input data for AI models. Then, the discriminative features are identified by AI models from the input data to generate diagnostic results. Finally, doctors will produce the final diagnosis with potential reference to interaction with the suggestive decision that derived from the AI models, which have the potentials for enhancing the quality of the clinical decision-making. Based on the diagnostic results, we can design personalized treatment options for improving the cognitive ability of AD patients. Moreover, since AI techniques can learn the complexity or abstraction patterns from large-sample data resources, deeper investigation of molecular mechanisms using AI approaches can be led to large-scale and high-throughput analysis of transcriptome, genome, and gene-gene interactions. Based on the significance of AI in AD research, this paper aims to conduct an extensive and comprehensive review to explore and discuss the role of AI techniques in etiology discovery, diagnosis, prognosis, and treatment of AD that will inspire future evidence-based medicine research and practical applications. In the rest of the paper, we first introduce the AI techniques and their applications in the medical domain in Section 2. Then the machine learning approaches in etiology discovery, diagnosis, prognosis, and treatment are summarized in Section 3. In Section 4, we introduce some popular publicly available AD datasets. In Section 5, we discuss the challenges and try to provide an insight into solutions in the future research direction. Finally, the conclusion is given in Section 6.

2 Applications of Artificial Intelligence in Medicine

Machine learning is a branch of AI that focuses on designing a mathematical algorithm to improve learning through experience[15–17]. Existing machine learning methods mainly include supervised, semi-supervised, and unsupervised approaches[18, 19]. The supervised approaches rely on fully labeled data to construct a classifier, and the classical algorithms include Support Vector Machine (SVM)[20], Bayesian Network (BN)[21], and Artificial Neural Network (ANN)[22]. Considering the data labeling is a time-consuming and labor-intensive task, the semi-supervised approach is proposed, which utilizes iterative and bootstrap learning to build a classifier from a small set of annotated data. Although Semi-Supervised Learning (SSL) provides great potentials to reduce the workload of data annotation, the fact that the classifier is sensitive to the biased samples in the initial labeled data limits the application of SSL[23]. Unsupervised learning algorithms do not need labeled data, and they utilize statistical information from unlabeled data to learn inherent patterns for classifier construction. The typical unsupervised learning is data clustering which includes hierarchical clustering, distance clustering, and K-means, etc., which enable the large-scale data analysis, but the result has no standard form and is hard to interpret[24, 25]. Later, some researches integrated the advantages of supervised and unsupervised learning, and proposed reinforcement learning-based approaches[26–28]. These traditional machine learning methods need careful engineering and expert knowledge to build a feature extractor, which transforms raw data into a suitable internal feature vector used by the classifier to discover patterns from the input data. They are limited in their ability of raw data processing[29] since the feature engineering is a complicated task, which in many cases cannot find the appropriate feature set for the high quality classifier building. Recently, deep learning, a specific subset of machine learning, has becoming a hot topic, which allows a machine to automatically detect the multi-level feature representations for classification. A deep learning network composed of multiple non-linear modules that transform the raw input into higher and more abstract feature representations. The complex function can be learned by composition of enough transformations. In the medical domain, the broad adoption of healthcare information systems has caused an explosive growth of diverse biological data, such as medical images and text. Using AI tools to facilitate medical analysis and solutions is a promising and essential area.

Research on AI in the medical domain began after the naming of AI in 1956[30]. With the development

of information technology and the explosive growth of diverse clinical data in recent years, study on applications of AI in the medical domain has received increased attention from researchers. According to Refs. [31, 32], the automatic diagnosis and prediction of the disease are the main utilizes of AI. In recent years, AI has been widely used to diagnose various diseases. For instance, Yu et al.[33] developed a diagnostic model using an auxiliary preserve denoising autoencoders model to filter key features from image and blood test data. The selected features are inputted into the classifier for breast cancer classification, and it achieved 88% accuracy, 91% specificity and a 0.86 F1 score. Xu et al.[34] proposed a novel network that consists of a global-level attention network and a local-level attention network to classify cataracts using retinal fundus images. It obtains an accuracy of 90.65% on two class detection tasks. Zheng et al.[35] employed a 3D CNN model and chest CT images to classify COVID-19 and non-COVID-19; this model achieves an AUC of 0.959, a sensitivity of 90.7%, and a specificity of 91.1%.

For other medical applications, Fritz et al.[36] built a multipath CNN model for prediction of postoperative mortality by adopting preoperative lab values, patient characteristics, etc. By comparing multiple machine learning methods, including deep neural networks, logistic regression (LR), random forest (RF), and SVM, the results show that multipath CNN utilized LSTM better than other approaches. The above research has shown that using machine learning methods to analyze different medical data benefits healthcare. It demonstrates that adopting AI approaches in medical facilities can help improve the quality of medical applications in developing countries to help clinicians with insufficient experience.

3 Applications of AI in AD Analysis

AI technology, especially machine learning, has shown effectiveness for large-scale, high-dimensional, and complex data analysis. According to the clinical studies on AD[12], we provide an overview of recent research on AI-aid etiology discovery, diagnosis, prognosis, and treatment of AD. Around a hundred publications were retrieved from the google scholar website to find the relevant studies of AI-aid biomarker discovery, CAD, and CAP systems on AD published in English from January 2018 to date. As shown in Fig. 2, out of the researches considered in this review approximate 65% study CAD systems, 11% study prognosis, 19% study AI-aid biomarker discovery, and 5% adopt AI approaches for AD treatment. Among these, 4% of articles construct one model for diagnoses and prediction tasks. We found that the AD CAD system has received more research attentions than other AD applications. Two points could explain the reason. First, most of the existing public AD datasets involve diagnostic status, which can be used as the ground truth to train a diagnostic model. Second, difference from etiology discovery and treatment, the basis of diagnostic AD at a different stage has consensus.

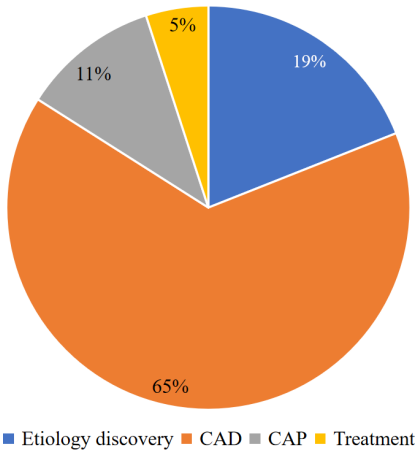

Fig. 2 Statistics of publications for AI-aid biomarker discovery, CAD, and CAP of AD.

3.1 AI-aid etiology discovery of Alzheimer's disease

One of the significant goals of AD research is etiology studies, which discover risk factors that cause AD. The etiology discovery results can provide clues for studying AD's diagnosis, prognosis, and treatment. A previous study reported that the cause of AD is related to several factors, such as increasing age, environmental factors, genetic factors, etc[37, 38]. Aging is a significant risk factor for AD cases, and most AD patients have a late onset after 65 years old. AD can be classified into two types based on age. First, early-onset AD (EOAD), which accounts for 1%–6% of all AD cases, the age ranges from 30 to 60 or 65. The second type is late-onset AD (LOAD), which commonly appears with age above 65 years old. Both these two types may occur in a person with a family with a positive history of AD[39]. AD onset occurs in women and men, but about two-thirds of AD patients are women. Several types of research reported that neurodegeneration and clinical symptoms appear more rapidly in women than men once diagnosed[40]. Some of the work found that

environmental is an additional AD risk factor that possibly includes air pollution, inorganic and organic hazards, brain trauma, industrial chemicals (flame retardants), low education levels, lifestyle (exercise, smoking, alcohol consumption), and exposure to heavy metal (manganese, aluminum)[41–44]; where metals, pesticides, and nanoparticles have been shown to increase the risk of developing AD by alternating on tau phosphorylation and (or) aggregation[45]. Among these risk factors, it is estimated that approximately 60%–70% of the risk is contributed by genetic factors for AD cases[46–48]. Most EOAD is inherited in an autosomal dominant pattern, and research showed that the development of AD is strongly associated with mutations of dominant genes, such as apolipoprotein E gene (APOE), Presenilin-1 (PSEN-1), Presenilin-2 (PSEN-2), and Amyloid precursor protein (APP)[49, 50]. In other AD-related genes, several single nucleotide polymorphisms (SNPs) in estrogen receptor (ER) and ER have been shown to increase the risk of AD in women because they may influence exogenous estrogen in older women and affect cognitive aging. STX5 may increase the risk of AD by investigating AD and other types of dementias[51]. VCP has a positive relationship with AD risk[52]. Researching the proteomics in the AD brain found that the ALDOC is related to AD[53]. HLA-B is regarded as a signal of patients with hypersensitivity syndrome and has high specificity as well as sensitivity assessment values; one research found that the frequency of HLA-B significantly differs between normal and AD[54, 55]. IL10RB is one of the cell signaling molecules for an aging disease in young people. It is demonstrated as one of the best discriminators to distinguish between normal and AD individuals[56]. DDX19A has been proved to be an AD-related gene by transcriptome-wide association study (TWAS) and imaging-wide association study (IWAS)[57]. The miR-335-5p is one of the miRAN which is regarded as an upregulated biomarker of AD[58]. In recent decades, deep investigation of a molecular mechanism using AI approaches has become more popular to find etiology and risk factors for complex disease understanding, such as cancer and AD. Most AI-based etiology discovery methods detect disease risk factors by evaluating the effectiveness of different factors in the automatic diagnosis model. Sharma et al.[59] utilized an ensemble of RF. They regularized regression to build a diagnostic model to discover new genetic factors of AD from different brain regions, including the hippocampus, entorhinal cortex, prefrontal cortex, and middle temporal gyrus. The new detected gene factors containing PDYN, ANKIB1, CORO1C, CRLF3, SLC25A46, RAE1 and non-encoding RNA genes BC037880, and AK057435. Zakeri et al.[54] discovered gene factors of AD by building co-expression networks using gene expression data from three stages of AD (normal, MCI and AD). This research discovered eight genes and five miRNAs as AD biomarkers. Wang et al.[60] incorporate statistical and machine learning methods to identify diagnostic biomarkers of AD by combining gene expression data from six brain regions. A total of 44 genes, such as CEL, TNNI3, APOH, FABP2 et al., are discovered as essential biomarkers of AD, and the blood biomarkers are also significant for AD diagnosis. Gene-gene interactions have essential roles in the pathogenesis of AD. Chen et al.[61] used a machine learning framework named joint density-based non-parametric differential interaction network analysis and classification to analyze gene expression data, which not only focuses on the genetic variations associated with AD but also on relationships between gene products. For example, the research found that CALML3 affects the onset of AD because CALML3 is contained in the transport of Ca^{2+}, and Ca^{2+} can affect AD. From the above research, it can be demonstrated that machine learning algorithm has essential advantages in analyzing molecular mechanisms and complex networks of genetic interactions. Huang et al.[62] discovered the full genome spectrum of AD utilizing a machine learning model based on AD-associated gene data set (AlzGene) and gene-gene interaction dataset (GIANT). Table 1 shows the gene factors discovered by AI model.

3.2 CAD systems of Alzheimer's disease

In recent years, machine learning methods have been widely used in studies of differential diagnosis of AD based on neuroimaging, linguistic and genetic data. The learning process of the AI-aid differential diagnosis system mainly consists of three steps, as shown in Fig. 3: (1) Input data; a CAD system for AD usually uses speech, image, text or multi-modality. (2) Kim et al.[63] defined feature extraction as commonly adopted to mean the construction of linear combinations of continuous features with good discriminatory ability between categories. For example, the gray level co-occurrence matrix features are generally utilized for image classification. (3) Classification includes two stages of training and test. The collected data is used to

Table 1 Etiologies for AD revealed by AI-aid methods.

Literature	Model	Gene factor discovery
Zakeri et al.[54]	Gene co-expression network	MBOAT1, LCOR, ARMC7, CREBRF, HNRNPUL1, PLAFL2, MRI1, LAMTOR1, miR-4722-5p, miR-4768-3p, miR-1872, miR-940, miR30b-3p
Sharma et al.[59]	Co-expression network	BACE1, LRP1, CASP7, MME, GAPDH, GSK3B, PSEN1, PSEN2, MAPT, CASP3, APP, SNCA, TNF, LPL, APBB1, APOE
Wang et al.[60]	RF, regularized regression	CORO1C, PDYN, SLC25A46, CRLF3, RAE1 ANKIBI
Chen et al.[61]	Non-parametric kernel approach	UQCRB-NDUFV2, NDUFV3-ATP5PB, NDUFB8-PSENEN, NDUFC2-NDUFA5, NDUFV2-NDUFA10, NDUFS8-IL1B, CAPN2-NDUFAB1, ATP5MC2-NDUFB5, PSEN1-NDUFAB1, PPP3CC-NDUFB5
Huang et al.[62]	SVM	Whole-genome spectrum

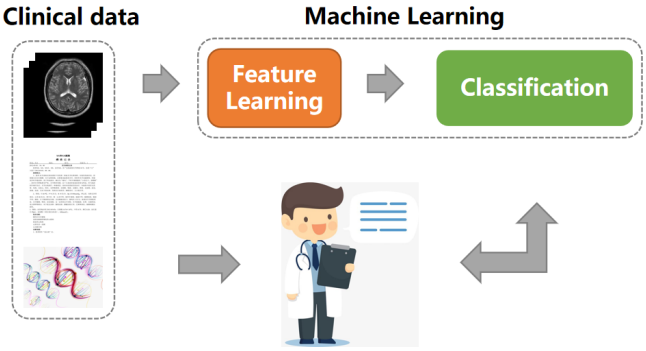

Fig. 3 Learning process of AI-aid differential diagnosis system.

train a machine learning model, and then the model is used to classify new cases. The widely used classifiers contain SVM, RF, and softmax.

We investigated 100 publications on CAD systems for AD, and 66% of articles adopted neuroimaging data, 10% adopted linguistic data, 5% adopted gene data, and 19% adopted multi-modality data for diagnostic model construction, as shown in Fig. 4.

3.2.1 Neuroimaging-based CAD systems

According to the recommendations from the National Institute of Aging (NIA), the Alzheimer's Association (AA) and the International Working Group (IWG), the

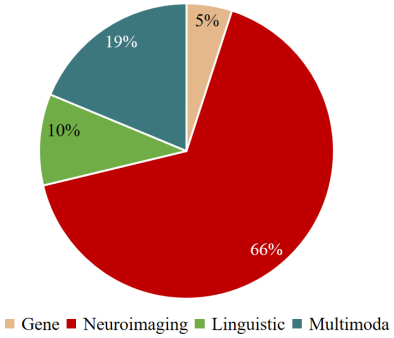

Fig. 4 Proportion of different modal data in CAD systems of AD.

brain image is significant for Alzheimer's diagnosis at all impairment levels. The different modalities of images focus on different examinations[64–67]. fMRI and PET are functional molecular imaging modalities, and they are used to evaluate functional changes in brain function. On the other hand, MRI and Diffusion Tensor Imaging (DTI) are adopted to assess brain morphometry and the sensitivity of neuron degeneration. Tripoliti et al.[68] proposed a conventional machine learning-based model, which consists of six steps for automatic diagnosis and monitoring of the progression of Alzheimer's disease using fMRI imaging. The experiments were conducted on the fMRI data from Dartmouth College. The results show that the proposed model achieved 94% accuracy for two class problems (classification between healthy elderly subjects and demented elderly subjects), 97% accuracy for three class problems (classification among healthy elderly subjects, demented elderly subjects with very mild AD, and demented elderly subjects with mild AD), and 98.78% for four class problems (classification among healthy young subjects, healthy elderly subjects, demented elderly subjects with very mild AD, and demented elderly subjects with mild AD). To address a single classifier is hard to obtain a high classification performance on the 11C-PIB PET imaging (the accuracy usually ranges from 60%–88%) because the size of functional brain image PET is relatively small and the amount of noise contained in it. The work[69] combines three different classifiers (K-Nearest Neighbors, Random Forests, and Neural Nets) by weighted and unweighted schemes to discriminate AD, MCI, and Control Normals (CN) on the PET dataset. The unweighted method achieved results with an accuracy of 84.3%, 75.2%, and 88.6% for AD, MCI and CN, respectively. The weighted method gets 89%, 75%, and 84% in terms of accuracy for AD, MCI and CN, respectively. In recent years, deep learning

approaches demonstrated promising prediction results in AD[70]. A CAD system differentiates two non-invasive structural MRIs with different periods. The work produces a jacobian volume to recognize the regions of interest between MCI subjects and AD subjects by voxel-based morphometric analysis. Then the CNN-SVM classifier is used to extract features of their regions for AD prognosis prediction[71]. Experimental results show an accuracy of 87.2%, sensitivity of 92.4%, and specificity of 80.4%. Similarly, Lei et al.[72] proposed a multi-scale CNN model which introduces channel attention to learn the dependency relation between two channels and assign corresponding weight value for each channel to extract multi-scale features for AD diagnosis. The results show an accuracy of 97.91% for AD/NC, 94.44% for AD/MCI, and 90.74% for MCI/NC. Hong et al.[73] employ multimodality images, longitudinal MRI, PET and DTI, to develop an LSTM-based network for AD progression prediction. In another work, the proposed model achieves an AUC of 93.5% for AD vs. NC, 79.8% for AD vs. MCI, and 77.7% for AD vs. NC vs. MCI. The tau deposition in the human brain is an essential biomarker for AD diagnosis[74, 75]. Jo et al.[76] utilized tau deposition in tau PET images and developed a 3D CNN-based network to separate AD from CN; the experiments conducted on Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset, the result shows an accuracy of 90.4% based on 5-fold cross-validation. To obtain complementary information from different measures, a deep ensemble learning model (DELearning) is proposed to predict AD using multi-modality data (including neuropathology, clinical evaluations, and brain MRI imaging) from National Alzheimer's Coordinating Center (NACC) database. This work focuses on the two outcomes prediction: AD and NC, Through comparing DELearning and six ensemble learning models (LogitBoost, AdaBoostM1, Vote, RF, Bagging, Staking), the DELearning outperforms baselines in terms of precision, recall, F1 score, and accuracy[77]. Lei et al.[78] incorporated MRI data and various clinical scores at multiple time points to build longitudinal scores prediction framework. The Alzheimer's disease Neuroimaging Initiative (ADNI) experiments show that the proposed method outperforms baselines and effectively reveals the relationship between MRI data and clinical scores.

Neuroimaging data have been utilized to recognize structural and functional biomarkers of AD, as shown in the Table 2. The surface area, volume, and cortical thickness[73] are extracted through Freesurfer to detect the region of interest (ROI), such as cortical thickness, volume, and surface area, of MRI. The work[78] generates 93 ROIs by computing the total intracranial volume for each subject. The energy, entropy and gray level co-occurrence matrix features (GLCM) are most commonly adopted for image analysis. The work[68] extracts entropy, energy, and 13 Haralick texture features by texture analysis, where the first two features are computed from multiwavelet transformation, and the Haralick texture features are computed utilizing 64 GLCM in 8 directions. Some studies combine patient information, such as gender, age, and medical history, to enhance the performance of CAD systems[67, 71, 77]. The temporal dependencies among features play an essential role in AD prediction. A 3D Jacobian determinant volume of longitudinal changes of each subject is calculated to recognize the differences between the baseline and the 12-month follow-up[71]. Considering all features for AD classification might cause noise because most features are redundant. Selecting compelling features is vital to generate an optimum classification performance. Lei et al.[78] utilized a joint learning model for feature selection where the high dimension of MRI features are reduced by the regularization method

Table 2 Related studies with different imaging features for AI-aid diagnosis of AD.

Literature	Feature name
Tripoliti et al.[68]	Demographics, head motion, behavioral, volumetric measures, activation patterns, and hemodynamics
Wu et al.[69]	Volume, voxel intensities, and texture
Er and Goularas[71]	Longitudinal time sequence features, gender, age, and total intracranial volume
Lei et al.[72]	Global and local ROI features
Hong et al.[73]	Longitudinal sequence features, thickness standard deviation, cortical thickness average, volume of WM parcellation, surface area, and the volume of cortical
Jo et al.[76]	Parcellation and ROI features five heatmaps, the top ten regions
An et al.[77]	medical history, hachinski ischemic score, cerebrovascular disease, unified Parkinson's disease rating scale, neuropsychiatric inventory questionnaire, geriatric depression scale, and functional activities questionnaire
Lei et al.[78]	Intensity homogeneity, brain segmentation, and ROI features

LASSO, and the non-Gaussian noise and impulsive noise are removed through correntropy. The experimental results show that it is the most influential parameter among selected features. Lei et al.[72] introduced a channel attention mechanism to learn global and local ROI features and assign a higher weight coefficient for essential features. Finally, the features are fed into a classifier for classification or prediction. The widely used classifier includes SVM, RF, KNN, etc.

3.2.2 Linguistics based CAD systems

Several studies attempted to utilize linguistic data to distinguish AD patients with different impairment levels from non-AD subjects—the modalities of linguistic data including audio, text or both. Alkenani Ahmed et al.[79] took advantage of several based learning methods. They developed multiple heterogeneous stacked fusion models using written and spoken languages to enhance the robustness and generalizability of the AD diagnostic model. The feature space uses two linguistic patterns, character *n*-gram and lexico syntactic sare. These stacked fusion models obtain an AUC of 98.1% and an F1 score of around 95% on the spoken-based dataset. The AUC of 99.47% and the F1 score of 97% on the written-based datasets. By taking fully connected positive features (diagnosis, procedures and lab values) in electronic health records as the input graph, the Graph Attention Network (GAT) serves as the attention-based feature aggregator for generating the representative node embeddings to be used for predicting AD[16]. The deep-deep neural networks language models (D2NNLM) are explored[80], utilizing higher order *n*-grams to learn the linguistic changes to recognize MCI and AD-type dementia from NC. The results show D2NNLM statistically significant AUC on the clinical Pitt Corpus. Fraser et al.[81] adopted topic models trained on word embeddings to extract information units in monolingual and multilingual spaces and combined supervised and unsupervised learning methods to recognize MCI from healthy older adults in English and Swedish. Results show that the multilingual method improves classification accuracy over the one-language approach. Besides utilizing text data, some works combine audio files and related automatic speech recognition (ASR) transcriptions to improve language comprehension. Fraser et al.[82] extracted 370 features from text and audio data to derive a wide range of linguistic phenomena and adopt a multilinear logistic regression model to classify AD and NC. The results achieve the best accuracy, 81.92% when using the top-35 features-motivated by the success of deep neural networks language models on medical neural language tasks. Luz et al.[83] classified AD and non-AD through extracting a set of acoustic features and using a classifier of linear discriminant analysis (LDA), decision trees (DT), nearest neighbor (1NN), RF, and SVM on spontaneous speech data from ADReSS challenge, the best result is obtained from RF model with an accuracy of 62.5%. To better understand semantic information, Edwards et al.[84] extracted features in the text at both the phoneme and word level, and combine them with the acoustic features to train a new multi-modal and multi-scale model for AD identification. The best result is obtained by the combination of word and phoneme representations. Sadeghian et al.[85] extracted features using a deep learning model to reduce the complexity of feature engineering of conventional machine learning methods. Specifically, it combines linguistic features from an automatically determined transcription of the speech (including punctuation) and acoustic features of speech to train a multi-layer perceptron (MLP) classifier to discriminate between AD and NC. In the experiments, the accuracy is 94%. The lack of large data set poses a challenge for the deep learning model. Thus, they proposed the transfer learning base approach for AD prediction from targeted speech[86]. The models are pre-trained on a large dataset to learn word representations and fine-tuned on the target dataset for the classification task, which means the features in this work are learned in an unsupervised way, and the best result is obtained by the combination of pre-trained deep transformer-based models and LR classifier. This paper mainly investigates studies for linguistic-based AD prediction in the English domain. Besides English, there are a lot of researches adopting data in a variety of language domains, such as Swedish[81, 87], French[88, 89], and Spanish[90, 91], but a little in Chinese, the reason could be lack of public text and speech dataset. Developing the AD diagnosis systems for early screening in Chinese is essential.

For the linguistic data-based AD diagnostic model, the features are mainly divided into acoustic and text-based features[92], as shown in the Table 3. The prosodic temporal features of the Acoustic feature are most commonly used in the research, followed by the pause pattern, which is an ASP-related feature. The text-based feature consists of word embeddings and lexical and syntactical features (i.e., *n*-gram, TTR, TTC, syntactic complexity). The *n*-gram is the sequence of characters or words with length *n*, which can be

Table 3 Related studies with different linguistic features for AI-aid diagnosis of AD.

Literature	Category	Feature name
Zhu and Razavian[16]	Text-based	Word embedding
Alkenani Ahmed et al.[79]	Text-based	Character *n*-gram, Type-Token Ratio (TTR), Type-token count (TTC), content density (CD), idea density, word, character, stop word, and sentence count
Orimaye et al.[80]	Text-based	Lexical features
Fraser et al.[81]	Text-based	Part-of-speech, word, and character *n*-gram
Fraser et al.[82]	Text-based, acoustic features	Part-of-speech, syntactic complexity, grammatical constituents, psycholinguistics, TTR, information content, repetitiveness, MFCCs
Luz et al.[83]	Acoustic features	ComParE, emobase, eGeMAPS, MRCG, minimal
Edwards et al.[84]	Text-based, acoustic features	Word and sentence embedding, phonetic representation, GeMPAS, eGEMAPS, emobase, emobase2010, emolarge, ComParE2016, MRCG
Sadeghian et al.[85]	Text-based, acoustic features	Race, speech rate, content density, the Linguistic Inquiry Word Counts (LIWC), total number of pause, idea density, fraction of pause less than 0.5 s or 1 s
Alireza et al.[86]	Text-based	Word embedding

consecutive or overlapping. The Type-Token Ratio (TTR) and Type-token count (TTC) is adopted to measure lexical complexity. TTR is the total number of unique words (i.e., tokens) to the total number of words in a given instance, and TTC is the total number of unique words[79]. In addition, the idea density and word, character, stop word and sentences account are extracted as features for AD recognition in Ref. [79], where idea density is used to calculate the number of ideas described in a given sentence. The idea means full use of complex propositions and new information. The work[82] computes syntactic complexity by the clauses, the mean length of sentences and T-units. In addition, some works[80, 81, 84, 86] use deep learning models, i.e., CBOW, Glove, Sen2vec, and pre-trained language model, i.e., BERT, to automatically learn features (i.e., word and sentence embeddings) from text and showed that they are beneficial for the AD prediction task. The prosodic temporal features, ASR-related, and spectral features are widely used acoustic features, specifically pause patterns. The spectral features are the frequency domain representation of the speech signal derived by Fourier transform, such as mel-frequency cepstral coefficients (MFCC). Some works[83, 84] adopted the standardized acoustic feature set, such as emobase, ComParE, MRCG, and eGeMAPS. The detail of these feature sets is introduced in the following. The emobase[93] feature set includes voice quality features, MFCC, line spectral pairs (LSP), intensity features, fundamental frequency F0, and F0 envelopes.

ComParE[94] feature set contains MFCC, energy, voicing related low-level descriptors (LLDs), and spectrum. The LLDs consist of psychoacoustic spectral sharpness, voice quality, logarithmic harmonic-to-noise ratio, spectral harmonicity, and Viterbi smoothing for F0. The total number of features is 6373.

eGeMAPS[95] feature set includes the alpha ratio, F0 semitone, F1, F2, F3, MFCC, shimmer loudness, slope V0 features, jitter, spectral flux, and Hammarberg index. Note that the research in Ref. [50] reported the gender difference could be reduced by using semitones to express F0.

MRCG[96] utilizes time-frequency representation to encode the audio signal's multi-resolution power distribution. The multi-resolution contains one high-resolution level and three low-resolution levels. The local information is encoded through a high-resolution level, and the remaining three low resolutions extract the spectro-temporal information. The total number of 6912 features is generated using the statistical function on the 768 MRCG features. Besides the above acoustic feature set, the minimal feature set used in Ref. [83], consists of the basic statistics of pause, a vocalization count, the duration of vocalizations and the speech rate. This standardized feature set is effective in increasing the reliability of the speech-based diagnosis model. Still, the results in the studies[97–99] corroborated that a combination of text and acoustic features can further improve the performance of AD classification.

3.2.3 Gene based CAD systems

The development of high-throughput omics has helped us understand disease mechanisms at a detailed molecular level. Thus far, a lot of work uses omics data and AI algorithms to develop various diagnosis models to identify the risk factors of complex diseases[7]. Wei et al.[100] proposed a model-averaged NB model to predict LOAD individuals with 312 to 318 SNPs from 1411

patients, which achieved a 0.72 AUC value. Xu et al.[101] developed an SVM model for analyzing gene-encoded protein sequence data that reached an accuracy of 85.7% by testing 279 AD-associated protein sequence data and 1463 non-AD-associated protein sequence data in the UniProt database.

Javier et al.[102] conducted comparisons of classical machine learning approaches, including Bootstrap Stage-Wise Model Selection (BSWiMS), Least Absolute Shrinkage and Selection Operator (LASSO), RF, Recursive Partitioning and Regression Trees (RPART), KNN, mRMR, and ensemble of above approaches to predict late-onset AD by using genetic variation data from ADNI cohort. The result shows that the ensemble of all machine learning methods achieved the best performance with an ROC AUC of 71.9%. Park et al.[103] developed a deep-learning approach for AD prediction using multiple heterogeneous omics datasets. The result obtained an accuracy of 82.3% by integrating gene expression and DNA methylation data. Some studies adopted blood-based expression data to predict AD, early AD or uncover key genes associated with AD because it is hard to obtain an omics dataset from brain issues of AD subjects. Lee et al.[30] adopted five feature selection approaches and five classifiers, including LR, L1-GLM, RF, SVM and DNN, to discriminate against AD individuals; the results obtain 65.7%, 87.4%, and 80.4% AUC values for ADNI, ANM1 and ANM2 datasets in internal validation.

The above studies show that using machine learning approaches to predict and diagnose AD by analysis of genetic data. But if incorporated with other modal data, such as text, audio, and image, the accuracy of the predicted model can be significantly improved.

3.2.4 Multimodal data based CAD systems

Recently, most works integrate molecular and phenotypic data, such as MRI and neuropsychological tests, for AD prediction. Compared to individual modal data, the medical data from different modalities can provide more complementary medical information to each other about the disease condition of patients[104–106]. Therefore, the effective adoption of multi-modality data is crucial for reliable clinical disease diagnosis. Qiu et al.[107] employed multi-modality data of MRI, clinical information, as well as functional and neuropsychological assessments to develop a deep learning-based model for AD, NC, MCI, and nADD (non-AD dementias) classification. By comparing the MRI-only CNN model, non-imaging traditional machine learning model, along with fusion model on NACC and OASIS datasets, the results show that the MRI-only model yielded AUC of 84.4% (NACC) and 84.6% (OASIS) for COGNC (NC/MCI and DE) task, AUC of 86.9% (NACC) and 85.8% (OASIS) for COGDE (DE/NC and MCI) task, AUC value of 73.4% (NACC) and 69.4% (OASIS) for ADD (AD/nADD) task. Non-imaging model obtained an AUC of 93.6% (NACC) and 95.9% (OASIS) for the COGNC task, AUC of 96.2% (NACC) and 97.1% (OASIS) for COGDE task, AUC of 74.9% (NACC) and 68.9% (OASIS) for ADD task. The fusion model yielded an AUC of 94.5% (NACC) and 95.9% (OASIS) for the COGNC task, AUC of 97.1% (NACC) and 97.1% (OASIS) for COGDE task, AUC of 77.3% and 77.3% for ADD task. From the comparing results, we can find that fusion of modalities performs better than both MRI-only and non-imaging models.

Golovanevsky et al.[37] combined neural networks and attention to present a multimodal AD diagnosis framework (MADDi) to classify NC, AD, and MCI using imaging, genetic, and clinical data. By evaluating the contributions of each modality on overlap patient set, the results show that the model achieved an accuracy of 82.29%, 77.78%, 71.66%, 92.5%, 78.33%, 85.83%, and 96.88% for the adoption of clinical data, genetic data, imaging data, clinical and genetic data, genetic and imaging data, imaging and clinical data, all above modalities, respectively. It demonstrated that a combination of three modalities could further improve the AD diagnosis model. Lin et al.[108] utilized a linear discriminant analysis (LDA) scoring approach to fusing multi-modality data, including MRI, PET, CSF, and genetic features, to classify AD, MCI, and NC. To evaluate the contribution of each modality, the model obtained an accuracy of 61.5% for only MRI, 56.3% for only PET, 55% for only CSF, 62.5% for without MRI, 65.5% for without PET, 63.9% for without CSF, 66.3% for without gene, and 66.7% for the fusion of different modalities on the three-way diagnosis. The results show that the MRI has the most significant effect on the model performance, followed by CSF and PET. The performance increased by 0.5% when considering genetic features because the genetic feature is the minor data.

Chen et al.[109] developed a deep learning-based model to classify NC, MCI, and AD by fusing multi-modality data, such as MRI, MRI text reports, mental and psychological test results, and few-shot learning.

In the comparative experiments conducted on a dataset from a third-class hospital in Shanghai, the model obtained an accuracy of 59.2% for only structured reports, 52.8% for only text reports, 47.6 for only MRI, 66.8% for the fusion of multi-modalities, as well as 79.6% for the combination of multi-modalities and few-shot learning. It has been proved that multi-modality data fusion can improve classification accuracy. The details can be seen in Table 4. For multi-modal feature selection, Spooner et al.[110] developed a model to recognize AD-relevant biomarkers by feature selector automatically. In the experiments conducted on the Sydney Memory and Aging Study and ADNI datasets, the identified AD biomarker included that the APOE gene, abnormal gait, tau, phosphorylated tau and amyloid-(A42). In addition, inflammation, depression and low-level education are thought to play an essential role in the pathophysiology of AD. Using the SVM model, Kate et al.[111] discovered AD multi-modal biomarkers from 810 subjects, including normal, MCI, and AD. The results show that APOE genotype, age, neuropsychological memory score, hippocampus and amygdala are significant biomarkers to distinguish between normal and MCI. Comparing amyloid-positive CN individuals and amyloid-positive MCI individuals, the latter had lower bilateral hippocampal and amygdala volumes, along with lower whole brain average cortical thickness. The study[112] highlighted the longitudinal multi-modal structure MRI as a prognostic and diagnostic biomarker that has potential value for presymptomatic to early symptomatic familial frontotemporal dementia.

3.3 CAP system of Alzheimer's disease

A prognosis that concerns quantification of disease progressions is equally significant to diagnosis, such as prediction of the disease progression in a time frame or assessment of the time to dementia onset. Existing AD prognostic studies mainly focus on predicting MCI to AD. We summarize some representative studies in Table 5. In earlier times, Ritter et al.[113] used SVM, classification tree, and RF to extract features from neuropsychological testing, MRI, FDG-PET, CSF, medical history, demographic information, and neurological and physical examinations into a combined feature set for the prediction of sMCI (stable MCI) and pMCI (progressive MCI) within three years. The best performance is with maximal accuracy of 73% by using SVM and 10-fold cross-validation. To better preserve the integrity of intra-modality, Zhang et al.[114] utilized multiple kernel learning (MKL) to encapsulate features of each modality by themselves for the prediction of sMCI and pMCI in 18 months. This model achieved an accuracy of 76.4% on the ADNI dataset. Cheng et al.[115] predicted MCI conversion to leverage MCI subjects' information with NC and AD as auxiliary domains, and developed a domain transfer learning model on the ADNI dataset, containing 51 AD subjects, 99 MCI subjects, and 52 NC subjects. This model obtained an accuracy of 79.4%, outperforming the methods without utilizing information from the auxiliary domain.

In machine learning-based AD diagnosis, adequate label data for prediction tasks is hard to obtain since manual labeling is time-consuming and labor-intensive. Yuan et al.[116] proposed a semi-supervised model to classify sMCI and pMCI in 3 years. It first extracted quantitative trail (QT) from 228 labeled structural MRI and SNP features from genotype data to construct two initial classifiers. Then, the 136 unlabeled structural MRI samples are automatically annotated through a co-learning strategy; finally, the RF is used to train a combined classifier to classify MCI patients from the ADNI-2 dataset. Results show an accuracy of 85.5%. In a recent study, deep learning gained popularity in predicting disease progression. Lin et al.[117] designed a deep learning method based on CNN to predict MCI to AD conversions using MRI data within three years. This study gets an accuracy of 79.9%. Tabarestani et al.[118] utilized Cerebrospinal fluid (CSF), MRI, PET cognitive test scores demographic with genetic, and two variations of the RNN model, i.e., long short-term memory (LSTM) and gated recurrent units for prediction of the patient status of following three-time points by the previous three historical time points. The results show that the predictive performance of LSTM and GRU are significantly improved by incorporating the L1 feature, and the accuracy of LSTM based model is higher than GRU based model. Some works built a model for both classification and prognosis tasks. Beheshti et al.[119] developed a new model that utilizes a genetic approach and feature ranking to analyze sMRI data to classify NC with AD and predict the conversion of pMCI with sMCI three years before clinical diagnosis. The results researchedan accuracy of 93.01% for classification and 75% for pMCI as well as sMCI prediction. Zheng et

Table 4 Summary of CAD system for AD detection using neuroimaging, linguistic, and gene data.

Literature	Modality	Dataset	Task	Result
Tripoliti et al.[68]	fMRI	Private	Classification: NC (young and elderly), AD (mild and very mild)	94% for NC (elderly)/AD, 97% for NC (elderly)/AD (mild and very mild), 98.78% for NC (young and elderly)/AD (mild and very mild) ((ACC)
Wu et al.[69]	PET	ADNI	Classification: NC, MCI, AD,	84.3% for AD, 75.2% for MCI, 88.6% for CN (ACC)
Er and Goularas[71]	MRI	ADNI	Classification: MCI, AD	87.2% (ACC)
Lei et al.[72]	MRI	ADNI	Classification: AD, MCI, NC	97.91% for AD/NC, 94% for AD/MCI, 90.74% for MCI/NC (ACC)
Hong et al.[73]	MRI, PET, DTI	ADNI	Classification: NC, MCI, AD,	77.7% (AUC)
Jo et al.[76]	Tau-PET	ADNI	Classification: AD, NC, MCI	90.4% (ACC)
An et al.[77]	MRI	NACC	Classification: AD, NC	76.4% (ACC)
Lei et al.[78]	MRI	ADNI	AD score prediction	4.781 for M06, 5.099 for M12, 4.521 for M18, 5.736 for M24, 4.981 for M36 (MAE)
Alkenani Ahmed et al.[79]	Spoken, text	DementiaBank, AD Blog corpus	Classification: AD, NC	98.1% for DementiaBank, 99.47% for AD blog corpus (ACC)
Orimaye et al.[80]	Text	Pitt Corpus	Classification: MCI, Ad	80% for MCI dataset, 83% for AD dataset (AUC)
Zhu and Razavian[16]	Text	Private	Classification: AD, NC	80.2% (AUROC)
Fraser et al.[81]	Text	Gothenburg (private), Karolinska, DementiaBank	Classification: MCI, NC	63% in English, 51% in Swedish (ACC)
Fraser et al.[82]	Audio, text	DementiaBank	Classification: AD, NC	81.92% (ACC)
Luz et al.[83]	Audio, text	ADreSS Challenge	Classification: AD, NC	62.5% (ACC)
Edwards et al.[84]	Audio, text	ADreSS Challenge	Classification: AD, NC	79.17% (ACC)
Sadeghian et al.[85]	Audio, text	Private	Classification, AD, NC	94% (ACC)
Alireza et al.[86]	Text	DementiaBank	Classification: AD, NC	88.08% (ACC)
Wei et al.[100]	Gene	NACC	Classification: LOAD, NC	72% (AUC)
Xu et al.[101]	Gene	ADNI	Classification: AD, NC	85.7% (ACC)
Javier et al.[102]	Gene	ADNI	Classification: LOAD, NC	71.9% (AUC)
Golovanevsky et al.[37]	MRI, clinical data, gene	ADNI	Classification: AD, NC, MCI	96.88% (ACC)
Qiu et al.[107]	MRI, clinical information, functional and neuropsychological assessments	LBDSU, NACC, ADNI, OASIS, AIBL, FHS, PPMI, NIFD	Classification: AD, NC, MCI, nADD	94.5% for COG_{GN}, 97.1% for COG_{DE}, 73.3% for ADD on NACC (AUC)
Lin et al.[108]	MRI, PET, CSF, gene	ADNI	Classification: AD, NC, MCI	66.7% (ACC)
Chen et al.[109]	MRI, text report, structured report	Private	Classification: AD, MCI, NC	79.6% (ACC)

Table 5 Summary of CAP system for AD detection using neuroimaging, linguistic, and gene data.

Literature	Modality	Dataset	Task	Conversion period (months)	Result
Ritter et al.[113]	MRI, FDG-PET, CSF	ADNI	Prediction: sMCI, pMCI	0–36	73% (ACC)
Zhang et al.[114]	FDG-PET, MRI, CSF	ADNI	Prediction: sMCI, pMCI	0–18	76.4% (ACC)
Cheng et al.[115]	MRI, PET, CSF	ADNI	Prediction: sMCI, pMCI	0–36	79.4% (ACC)
Yuan et al.[116]	MRI, SNP	ADNI	Prediction: sMCI, pMCI	0–36	85.5% (ACC)
Lin et al.[117]	MRI	ADNI	Prediction: sMCI, pMCI	0–36	79.9% (ACC)
Tabarestani et al.[118]	CSF, MRI, PET	ADNI	Prediction: AD, MCI, NC	0–12, 0–24, 0–36	88% for 0–12 months, 87% for 0–24 months, 88% for 0–36 months (ACC)
Beheshti et al.[119]	MRI	ADNI	Classification: NC, AD Prediction: sMCI, pMCI	0–36	93.01% for NC/AD 75% for sMCI/pMCI (ACC)
Zheng et al.[120]	fMRI, MRI, PET, CSF	ADNI, ABIDE	Prediction: sMCI, pMCI Classification: AD, ASD, sMCI, NC	0–36	92.31% for AD/sMCI/NV, 92.3% for sMCI/pMCI, 89.77% for NC/ASD (ACC)
Yubraj et al.[121]	sMRI, CSF, FDG-PET, gene	ADNI	Classification: AD, NC, sMCI, pMCI Prediction: sMCI, pMCI	0–24	98.33% for AD/NC, 93.59% for sMCI/pMCI, 96.83% for AD/sMCI, 94.64% for AD/pMCI, 96.43% for NC/pMCI, 95.24% for NC/sMCI (ACC)

al.[120] proposed an end-to-end graph network to classify and predict AD using multi-modality data (fMRI, MRI, PET, demographic information, cognitive tests, cerebrospinal fluid biomarkers, and risk factor). The model obtained an accuracy of 92.31% for AD/sMCI/NC, 92.3% for sMCI/pMCI on the ADNI dataset, and 89.77% for NC/ASD (Autism Spectrum Disorder) on ABIDE dataset. Yubraj et al.[121] developed a machine learning-based model to classify and predict AD by combining four biomarkers, such as FDG-PET, sMRI, CFS, and AOPE. The results reached an accuracy of 98.33% for AD/NC, 93.59% for sMCI/pMCI, 96.83% for AD/sMCI, 94.64% for AD/pMCI, 96.43% for NC/pMCI, and 95.24% for NC/sMCI.

3.4 AI-aid treatment of Alzheimer's disease

Treatment in AD subjects aims to alleviate and possibly improve cognition loss along with maintain autonomous function. The treatment of AD mainly includes pharmacological and non-pharmacological approaches. Currently, AD drugs can only alleviate symptoms rather than reverse the progress of the disease[122, 123]. It is essential to keep searching for therapeutic drugs, moreover, machine learning provides a promising way for drug discovery. Fang et al.[124] applied recursive partitioning and a naive Bayesian algorithm to build a classifier for predicting chemical-protein interactions of AD using the multitarget-quantitative structure-activity relationships (mt-QSAR) approach. They utilize validated models to systematically predict the potential targets from 25 key AD targets for six approved anti-AD drugs and 19 known active compounds associated with AD. Repurposing drugs for AD has recently received much attentions[125]. Rodriguez et al.[126] developed a Drug Repurposing In AD (DRIAD) framework using machine learning algorithms, including LR, SVM, RF, and two-layer fully connected NN, to quantify potential relationships between the pathology of AD severity and molecular mechanisms. DRIAD tested 80 compounds, where 33 were FDA-approved and might be directly used for repurposing; the remaining 33 preclinical compounds and 14 investigational compounds, which DRIAD highly scored, can provide a reference for FDA-approved compounds selection. Adverse drug reactions (ADRs) are one of the significant reasons for the failure of drugs. Thus, an effective predictive model of ADRs is essential. Jamal et al.[127] used a relief-based feature selection method to recognize relevant properties and employed a machine learning model to predict neurological ADRs before preclinical testing. They predicted ADRs for existing anti-AD drugs and uncharacterized drugs on the side effect resource (SIDER) dataset. The model obtains an accuracy of 93.2% for chemical, 92.41% for phenotypic, 94.18% for integration of three properties, and 82.11% for biological properties.

Besides pharmacological approaches, more scientists

have integrated personalized and adaptive elements to design a cognitive training game. Some studies design adaptive games by dynamically changing the parameters of games and generating new content[17, 128–130]. Relevant studies showed that adaptive electronic science games could match the different levels of players with the different difficulties of games so that games can improve cognitive ability[12, 131–133], which provides an important reference for AD treatment. As mentioned above, there are still no drugs that can cure or effectively reverse AD. Thus, AI-based AD treatment research mainly focuses on mining the relations between chemicals and proteins.

4 Public AD Dataset

Data collection is fundamental to building a machine learning model for AD applications. The open established datasets are selected in most studies to add research value. The Alzheimer's Disease Neuroimaging Initiative (ADNI) database[134, 135] is one of the most popular datasets for AD prediction, and was established in 2003. The study of ADNI takes about 17 years and consists of 4 phases: ADNI-1 (5 years), ADNI-GO (2 years), ADNI-2 (5 years), and ADNI-3 (5 years). It contains multiple data types, including brain imaging data, such as MRI, PET, clinical data, biospecimen, and genetic data. The category of AD stages in ADNI includes AD, MCI, NC, etc. In addition, ADNI will continue to track and update the database of the pre-diagnosed population. The National Alzheime's Coordinating Center (NACC) database[136, 137] maintained a cumulative database and was founded in 1999. It includes more than 45 000 participants and different types of clinical data, such as neuropathology, clinical evaluations, and brain MRI imaging. In the linguistic domain, DementiaBank is a primary public dataset to evaluate the spoken language of the AD patient. It collected 45–90 years old English-speaking participants from 1983 to 1988. The OASIS (Open Access Series of Imaging Studies) database[138, 139] consists of four versions of data sets. OASIS-1 and OASIS-2 are cross-sectional and longitudinal MRI data. OASIS-3 is a longitudinal multimodal neuroimaging, clinical biomarker, and cognitive dataset collected from 1378 normally aging with AD members. OASIS-4 included clinical, biomarker, MRI, and cognitive data from patients presenting with memory complaints. The UK Biobank (UKB)[140, 141] is a large-scale prospective study designed to promote research into key factors of health and disease, mainly in middle-aged and older adults[142]. The participants have generously provided a wealth of information on the environment, lifestyle, socio-demographic, health and well-being, as well as a range of cognitive and physical tests since 2006. To date, the UKB has approved projects studying dementia and cognitive impairment, such as high risk factors for dementia, whole-neuroimaging and genome-wide association studies, along with diagnostic models[143]. Pitt corpus consists of picture descriptions derived by Cookie Theft Picture collected by the University of Pittsburgh[144] and distributed by DementiaBank[145, 146]. The Cookie Theft Picture is produced through AD patients and healthy participants and related to their neuropsychological data. It is worth noting that the existing public AD-related linguistic datasets are still limited in the Chinese domain. The Alzheime's Disease Sequencing Project (ADSP)[147] is part of the NIA Alzheimer's Disease Genetics Portfolio and contains more than 350 investigators worldwide. ADSP contains multiple genes and accompanying phenotypic information, such as age, gender, and cognitive measures.

5 Perspective for the Future

With the development of data sharing sources and adoption of AI technologies for etiology discovery, diagnosis, prognosis as well as treatment of disease, the novel technologies and medical service system will be introduced to address the public healthcare demand for high quality human-centered operation of emergency care, as shown in Fig. 5.

(1) Boosting early detection and prevention of dementia

As mentioned above, most existing diagnostic models

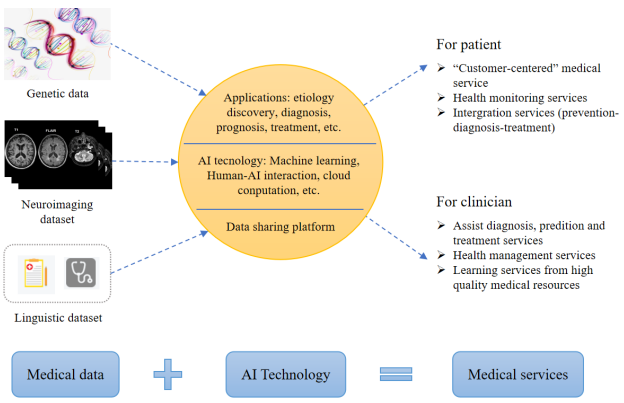

Fig. 5 Tendency of medical services system in the future.

recognize AD patients, mainly focusing on MCI and the dementia stage. To reduce the substantial burden on patients, carers, and society and increase the quality of healthcare, it is essential to shift focus to recognizing individuals in the preclinical stage. By early intervention, lifestyle changes can be delayed, reducing healthcare costs and preventing further progression. With the treatment option for AD being limited, the key transformation of AD is focused on prevention rather than treatment. The United States Congressional Budget Office has noticed that preventive care is a key innovation for healthcare[148]. However, previous research showed that AD prevention is hard to implement, because of lacking healthcare resources. The new solutions facilitate practical preventive care by engaging patients in preventing disease, utilizing interactive, patient-oriented techniques based on health information systems.

(2) High-quality data sharing resource

The quality of the health data resources is fundamental for obtaining correct results. Large-scale and diversified data resources can reflect the real distribution of data and improve the ability of researchers to spot important and weak factors. However, as mentioned above, most of the real-world AD datasets are private, so it cannot conduct a comparative study of these researches with future work. Moreover, the widely used public dataset, such as ADNI, comes from developed countries and does not contain significant populations in developing countries. For linguistic-based AD research, current CAD systems are mainly based on English, rarely in Chinese. The promising solution is to develop and improve the data-sharing resource by promoting cooperation between national and international medical institutions.

(3) "Customer-centered" medical service system

A critical characteristic of the transformation driven by AI technology in healthcare is replacing the "patient-centered" medical service system with a "customer-centered" medical service system. It aims to improve patient satisfaction by boosting the quality of healthcare services and encouraging individuals to assume responsibility for their health. On the other hand, with the development of information technology, it is believed that intelligent and partially autonomous local implementations can support end-user self-determination; at the same time, telemonitoring and telecare are supported by the development of wearable devices as well as smartphone applications. These devices will also collect the data resources.

(4) Constructing a reliable and high quality CAD or CAP system

Although a lot of powerful ML based models have been presented to solve real-world medical problems and have obtained the remarkable performance when many samples existed, their clinical application is limited without the trust of human experts[149]. Understanding the reasons of a decision made by ML model is a prerequisite of next medical decision. For the future ML applications, the human-in-the-loop is a solution to enhance ML performance and receive reliable results in medical applications by collaboration of humans and ML approaches. First, in the building time, medical experts can provide prior knowledge in the different stages of model building, i.e. data producing, pre-processing, feature selection and training stages, to help for producing high quality training samples and improving the performance of the ML prediction. Second, in the running time, providing an interface of Human-AI interaction enable medical experts as the users of ML models to validate and refine models and obtain the acceptable outputs. It provides great potentials to improve not only the performance of ML models but also the interpretability of the clinical decision.

6 Conclusion

This article reviews recent research on AI (machine learning) based solutions on etiology discovery, automatic diagnosis, prognosis and treatment for AD using different modalities. The multi-modality data includes neuroimaging, linguistic, genetic and multi-modality data to help new researchers to build a comprehensive understanding of AI technology applied in AD research. Emerging AI technologies offer possibilities in the medical domain but also bring challenges. AI-based models can assist radiologists, neurosurgeons and other medical staff with better clinical decision-making and analyze the relationship between complex factors for etiology discovery and aid treatment of AD. Although certain limitations exist, we believe that with the continuous improvement of data sharing resources and computational creativity, a comprehensive and integral analysis system can be established soon to help AD research.

Acknowledgment

This work was partially supported by the National Key R&D Program of China (No. 2020YFB2104402)

and Beijing Postdoctoral Research Foundation (No. 2022ZZ075).

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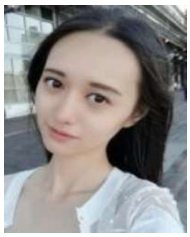

Qing Zhao received the MS degree in software engineering from Beijing University of Technology in 2016, and PhD degree in computer science and technology from Beijing University of Technology in 2021. She is currently a lecturer at Faculty of Information Technology, Beijing University of Technology, China. Her current research interests include natural language processing, semantic analysis, and medical data analysis.

Hanrui Xu is an MS candidate at the School of Medicine, Tsinghua University, China. Her main research interests include Alzheimer's disease and cognitive disorders.

Jianqiang Li received the BS degree in mechatronics from Beijing Institute of Technology in 1996, the MS and PhD degrees in control science and engineering from Tsinghua University in 2001 and 2004, respectively. He is currently a Beijing Distinguished Professor in Beijing University of Technology. His current research interests include Petri nets, enterprise information system, social computing, predicative data mining, Internet of things, privacy protection, and big data.

Faheem Akhtar Rajput received the PhD degree from Beijing University of Technology in 2020 and MS degree in computer science from National University of Computing and Emerging Science NUCES FAST Karachi in 2011. He is currently an assistant professor at the Department of Computer Science, Sukkur IBA University, Pakistan. His current research interests include data mining, machine learning, deep learning, information retrieval, privacy protection, internet security, Internet of Things, and big data.

Liyan Qiao received the bachelor and master degrees from Inner Mongolia Medical College in 1993 and 1996, respectively. She received the PhD degree at Peking Union University in 2002. She worked as a resident in the affiliated hospital of Inner Mongolia Medical from 1996–1999. She is currently the director of the Department of Neurology in Tsinghua University Yuquan Hospital, as well as a professor at the School of Medicine, Tsinghua University, China. Her current research interests include neurodegenerative disease and Neuroimmunology disease.