

# Application of Artificial Intelligence in the Prevention, Diagnosis and Treatment of Alzheimer's Disease: New Hope for Dealing with Aging in China

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**Abstract.** Alzheimer's disease (AD) has become a major issue around world, including China. The two major challenges for AD are the difficulty in early detection and poor treatment outcomes. Over the past decades, artificial intelligence (AI) was more and more widely used in the prevention, diagnosis and treatment of AD, which might be helpful to deal with the aging of population in China. Here, after a systematic literature searching on three English databases (MEDLINE, EMBASE, the Cochrane library), we briefly reviewed recent progress on the utilization of AI in the susceptibility analysis, diagnosis and management of AD. However, it is still in its infancy. More researches should be performed to improve the prognosis of patients with AD in the future.

**Keywords.** Dementia, Alzheimer's disease, artificial intelligence, aging

## 1. Introduction

With more than 176 million people aged  $\geq 65$  by the end of 2019, China has the largest elderly population in the world [1]. The incidence and prevalence of dementia is increasing with age. It was reported that Alzheimer's disease (AD) and other dementia were the 8th leading cause of mortality, years of life lost (YLLs) in China in 2017 [2]. Among the dementia patients, AD is the most common form, accounting for 60%-80% of cases [3]. The incidence of AD in China was calculated to be 0.04, and increased significantly from 404 per 100,000 people in 2007 to 624 per 10,000 people in 2014 [4]. In addition, the AD-related expenses were evaluated to be from about 91 billion RMB in 2010 to 332 billion in 2050 in China [5]. Thus, it is urgent to improve the method of predicting, diagnosis and treatment for AD patients.

Currently, the particular challenges for AD diagnosis and management were the lack of early diagnostic methods and effective therapy drugs. At the same time, the high proportion of failure in clinical trials for AD treatment had caused the decline in

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business investment by some drugs manufacture enterprise [6]. From 2002 to 2012, only one drug, memantine, was authorized in AD treatment, although more than 400 potential drugs for AD were conducted in clinic [7]. Fortunately, progress in genomics, proteomics and medical imaging examination, such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) and so on, holds promise for earlier diagnosis of AD and identifying candidate therapeutic targets in clinic [8]. However, processing such different kinds of massive data is very time consuming for doctors and researchers. Artificial intelligence (AI) technologies, including deep learning systems, might be promising approach for analyzing various kinds of data.

Here, we performed a systematic literature searching on three English databases (MEDLINE, EMBASE, the Cochrane library) about application of AI in the predicting, diagnosis and treatment of AD. Then, the recent progress in the field of AI-aided AD predicting, diagnosis and treatment was briefly reviewed.

## **2. AI-Aided AD Genetic Susceptibility Analysis**

One of the effective methods for early detection of AD patients is to identify population with high-risk. It was reported that risk factors for AD included age, metal exposure, traumatic brain injury, genetic risk factors, the immune system, mitochondrial function, air pollution, unhealthy life-style (e.g., smoking, alcohol drinking, lack of exercise, and exposure to greenery) and associated co-morbidities, including vascular disease and infection, etc. [9]. Among these factors for AD except for early-onset familial AD, genetic factors might account for about 70% of the causes [10, 11]. In addition, increasing evidence showed that most AD patients were caused by complicated interactions between a variety of genetic and environmental factors. However, analysis of large genetic data, including genetic variance, gene expression spectrum, gene-gene interactions, is time-consuming and laborious. Luckily, AI technologies, mainly machine learning, had been demonstrated to be convenient and powerful methods for such huge data processing. A critical review about the application of AI in the genetic analysis of AD was provided Mishra et al [12].

## **3. AI-Aided AD Diagnosis**

As mentioned above, one of the main challenges of AD was that it was difficult to detect in early stage before the appearance of significant memory loss and mental symptoms. At present, diagnosis of AD was mainly based on psychiatric and neurological symptoms, medical imaging examination, and the abnormal expression of biomarkers [13]. For example, up to now, the use of semi-quantitative approaches, including mini-mental state examination and Consortium to Establish a Registry for Alzheimer's Disease, had been the main criteria of clinical diagnosis. However, the investigation of these scales was complicated and time-consuming. In recent years, machine learning methods had generated quantitative scores for whole slide images (WSIs) that were highly consistent with previous scores [14].

Some studies have employed convolutional neural networks (CNNs), which might classify images by recognizing and mapping a lot of features, to diagnose AD from MRI and PET results [15-17]. For example, Ding et al. performed CNNs of

InceptionV3 architecture at fluorine 18 (18F) fluorodeoxyglucose (FDG) PET of the brain from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and got 82% specificity at 100% sensitivity, an average of 75.8 months prior to the final AD diagnosis [17]. Similarly, adopting automated segmentation of stained objects and a cloud-based interface, Tang et al found more than 70,000 plaque candidates from 43 whole slide images (WSIs) to train and test CNNs. They showed that networks obtained 0.993 areas under the receiver operating characteristic and 0.743 precision recall curves, respectively [18].

In addition to CNNs, support vector machines (SVMs) had also been taken to analysis MRI images, sometimes combining MRI, and cognitive ability evaluation results to enhance the accuracy rate AD diagnosis [19-27]. For example, Klöppel et al. used SVMs to distinguish between structural MR scans from AD patients and elderly with normal cognitive function, in addition to distinguish between AD patients and frontotemporal lobar dementia suffers [20]. Moreover, in structural MRI images, SVMs successfully predicted progression from mild cognitive impairment (MCI), an early stage of AD, to AD, as well as separated healthy controls, patients with MCI and AD patients preferable to a combination of statistical methods and expert knowledge [21]. Moreover, combined use linear dynamic system and SVMs, Moradi et al integrated MRI images and cognitive assessment information to differentiate AD patients from healthy individuals [22]. Besides, Magnin et al. evaluated an automated method based on SVMs of whole-brain anatomical MRI from 16 AD patients and 22 healthy individuals, and got 96.6% mean specificity and 91.5% mean sensitivity, respectively [23]. Similarly to the work by Magnin et al, Gerardin et al. developed spherical harmonics (SPHARM) coefficients based on SVM, and showed that accuracy was superior to that of hippocampal volumetry [24].

A different approach, three-stage deep feature learning and fusion framework, was taken in another study, in which deep neural network was trained stage-wise and tested the proposed framework using ADNI data for AD diagnosis. They found that the method was superior to other state-of-the-art methods [28].

Meanwhile, several AI methods were used simultaneously in some investigations. Maj et al observed a combination of unsupervised and supervised machine learning methods to analyse correlation between AD and pattern of gene expression in different tissues and found that the Recurrent Neural Networks (RNN) was the most precise method for differentiating AD patients from healthy individuals [29]. Maroco et al performed a comparative analysis to compare seven non parametric classifiers, including Multilayer Perceptrons Neural Networks, Radial Basis Function Neural Networks, SVM, CART, CHAID and QUEST Classification Trees and Random Forests (RF) with three traditional classifiers, including Linear Discriminant Analysis (LDA), Quadratic Discriminant Analysis and Logistic Regression, in terms of overall classification accuracy, specificity, sensitivity, Area under the ROC curve and Press'Q, and found that RF and LDA were the best methods in AD diagnosis [30].

In addition to genomics and medical imaging data, AI technologies were also used to analyse other kind of data, such as proteomics. Using a classification method, called predictive analysis of microarrays, Ray et al. identified 18 signaling proteins, the serum concentration of which differentiated AD sufferers from healthy individuals with near 90% accuracy [31]. Similarly, a radial basis function (RBF) network for feature selection (FSRBF) for both feature selection and classification established a smaller set of 9 proteins that distinguished AD patients from healthy individuals [32].

#### 4. AI-Aided AD Management

It's well known that AD is a chronic progressive neurodegenerative disease characterized by memory and other cognitive functions loss, resulting in reduction or loss in daily life activities. So far, almost all clinical trials showed that no pharmacological therapy could alter progression of the disease, despite continuous advances in exploring aspects of AD pathophysiology [33]. The possible factors contributing to this limitation included heterogeneity of the AD patients and lack of objective efficacy methods or predictive biomarkers of treatment [34-36]. Therefore, the directions of AD treatment in the future are new drug development and individualized treatment, namely Precision medicine (PM).

##### 4.1. New Drug Development

Discovery and new understanding of disease pathogenesis is crucial for the novel treatment, as well as for diagnosis and prognosis. In oncology clinic, genomic materials were routinely sequenced to find and rank genomic biomarkers of cancer and therapeutic response [37, 38]. So, it's reasonable to speculate that a similar strategy in precision oncology could also be applied to identify candidate therapeutic targets and enhance therapeutic efficacy in AD. However, PM often relies on big data as well as on bioinformatic analysis of large datasets [39]. Zhang et al. used co-regulation, clustering and Bayesian inference together to cope with transcriptomic data and identified groups of immune-related and microglial-specific genes which abnormally expressed in brain tissue [40]. Among them, the microglial protein TYROBP was an important regulatory protein. Interestingly, it played neuroprotective role in animal AD model [41, 42]. Taken together, these results suggested TYROBP as a novel candidate treatment target.

##### 4.2. Patient Stratification

Diversity in symptoms and signs, disease progression, molecular mechanism and response to drug therapy usually existed among AD suffers. Thus, it is necessary to stratify patients in treatment. More recently, using unsupervised formal concept analysis (FCA), combined with the Knowledge Extraction and Management (KEM) environment, Hampel performed genome-wide analysis for biomarkers predicting treatment response in AD, and identified Blarcamesine (ANAVEX2-73), a selective sigma-1 receptor (SIGMAR1) agonist, as a predictor of treatment response [43].

Finally, AI, specifically natural language processing (NLP), may be employed to help fight AD stigma. For details, please refer to the review by Piloizzi et al. [44].

#### 5. Conclusion

In conclusion, AI technologies could more efficiently analysis large amounts of multidimensional data to provide further information into disease foundations, and to help with earlier screening, diagnosis, more accurate prognosis, patient stratification and development of new drugs, which is helpful to deal with the aging of population in Japan. However, it is still in the initial stage. More researches should be performed to

improve the diagnosis, treatment and prognosis of patients with AD in the future. First, most of the existing studies were retrospective or/ and small sample size. So, more clinic trials with larger sample sizes and well-designed, e.g., prospective, randomized, controlled, are required to improve the quality of the results. Second, with the new development of medical diagnosis and treatment technology, AI needs to combine with other new technologies or data, such as metabonomics, miRNA expression profile, and gut microbiota and so on. Last, considering the heterogeneity in AD patients, including different race in the world, it is important to further determine the role of the application of AI in the genetic susceptibility analysis, diagnosis and management of AD in Chinese population.

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