# Cognitive care :Early Intervention for Alzheimer's disease

**A PROJECT REPORT**

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***In partial fulfilment for the award of the In partial degree***

***of***

**BACHELOR OF ENGINEER**

**IN**

**BIO MEDICAL ENGINNERING**

**DHANALAKSHMI SRINIVASAN COLLEGE OF ENGINEERING AND TECHNOLOGY, EAST COAST ROAD MAMALLAMPURAM**

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**MAY & 2024**

# Performance and Final Submission phase for Alzheimer's disease

Abstract

Decades of experimental and clinical research have contributed to unraveling many mechanisms in the pathogenesis of Alzheimer’s disease (AD), but the puzzle is still incomplete. Although we can suppose that there is no complete set of puzzle pieces, the recent growth of open data-sharing initiatives collecting lifestyle, clinical, and biological data from AD patients has provided a potentially unlimited amount of information about the disease, far exceeding the human ability to make sense of it. Moreover, integrating Big Data from multi-omics studies provides the potential to explore the pathophysiological mechanisms of the entire biological continuum of AD. In this context, Artificial Intelligence (AI) offers a wide variety of methods to analyze large and complex data in order to improve knowledge in the AD field. In this review, we focus on recent findings and future challenges for AI in AD research. In particular, we discuss the use of Computer-Aided Diagnosis tools for AD diagnosis and the use of AI to potentially support clinical practices for the prediction of indiindividual risk of AD conversion as well as patient stratification in order to finally develop effective and personalized therapies.

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Diagnostics (Basel). 2021 Aug; 11(8): 1473. Published online 2021 Aug 14. doi: 10.3390/diagnostics11081473

PMCID: PMC8391160PMID: 34441407

Artificial Intelligence for Alzheimer’s Disease: Promise or Challenge?

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Associated Data

Data Availability Statement

Abstract

Decades of experimental and clinical research have contributed to unraveling many mechanisms in the pathogenesis of Alzheimer’s disease (AD), but the puzzle is still incomplete. Although we can suppose that there is no complete set of puzzle pieces, the recent growth of open data-sharing initiatives collecting lifestyle, clinical, and biological data from AD patients has provided a potentially unlimited amount of information about the disease, far exceeding the human ability to make sense of it. Moreover, integrating Big Data from multi-omics studies provides the potential to explore the pathophysiological mechanisms of the entire biological continuum of AD. In this context, Artificial Intelligence (AI) offers a wide variety of methods to analyze large and complex data in order to improve knowledge in the AD field. In this review, we focus on recent findings and future challenges for AI in AD research. In particular, we discuss the use of Computer-Aided Diagnosis tools for AD diagnosis and the use of AI to potentially support clinical practices for the prediction of individual risk of AD conversion as well as patient stratification in order to finally develop effective and personalized therapies.

Keywords: Alzheimer’s disease, diagnosis, machine learning, artificial intelligence

1. Introduction

Alzheimer’s disease (AD) is an irreversible neurodegenerative disease that progressively destroys cognitive skills, up to the development of dementia. The clinical diagnosis of AD is based on the presence of objective cognitive deficits (which are, typically, prominent memory impairments). In some cases, AD may show atypical presentations, with impairments in non-amnesic domains (i.e., attention, executive functions, visuo-constructive practice and language) [1]. However, AD shares many common clinical features with other neurodegenerative dementia, including Lewy body dementia [2], frontotemporal disorders [3], and vascular dementia, making early and differential diagnosis difficult, especially in the first stage of the disease [4,5]. In atypical AD, clinical signs of fluent and non-fluent progressive aphasia, or dysexecutive/behavioral changes, may overlap with frontotemporal dementia syndromes [6]; posterior cortical atrophy (PCA) with underlying AD etiology may clinically overlap with dementia with Lewy bodies or corticobasal syndrome [7]. Finally, the occurrence of co-existing pathologies is a common feature in those cases of neurodegenerative diseases that share a common pathogenic mechanism, consisting of extracellular and/or intracellular insoluble fibril aggregates of abnormal misfolded proteins (e.g., the formation of amyloid plaques, tau tangles, or α-synuclein inclusions). In this context, the system biology approach, which aims at the integration of clinical and multi-omics data, can help to detect and recognize the pathophysiological and molecular changes characteristic of AD or other pathologies, as well as the associated clinical manifestations occurring, in particular, in the pre-clinical stages [8].

Amyloid plaques and neurofibrillary tangles are the neuropathological hallmarks of the disease [9,10], which can be evaluated in vivo by neuroimaging investigation and cerebrospinal fluid (CSF) biomarker assessment; namely, considering amyloidβ1-42 (Aβ42), its ratio with amyloid β1-40 (Aβ42/Aβ40), total tau protein (t-tau), and hyperphosphorylated tau (p-tau181).

As AD is multi-factorial, many conditions can influence the individual risk and age of onset, particularly metabolic impairments (diabetes mellitus, hypertension, obesity, and low HDL cholesterol), depression, hearing loss, traumatic brain injury, and alcohol abuse [11]. Lifestyle factors such as smoking, low physical activity, and social isolation are potentially modifiable, while several of these may have bi-directional relationships and may be early manifestations, other than risk factors, in the prodromal phase of dementia [12]. All of these clinical, biological, socio-demographic, and lifestyle factors contribute to defining the development of the disease and, therefore, are useful in trying to understand the still-misunderstood etiology of AD.

Decades of experimental and clinical research have contributed to unraveling many mechanisms in the pathogenesis of the disease, such as the β-amyloid hypothesis, but the puzzle remains incomplete. Clinical and biological data from electronic health records and multi-omics sciences represent a potentially unlimited amount of information about biological processes, such as genomes, transcriptomes, and proteomes, which can be explored through Big Data exploitation [8,13]. The rapid collection of data from tens of thousands of AD patients far exceeds the human ability to make sense of the disease.

Complex AI-based models can be successful in extracting meaningful information from Big Data; however, as their complexity increases, it becomes more and more difficult to interpret how they produce their output. Thus, they have been called black-box models. Making AI explainable is a key problem of AI technological development in recent years, and is of pivotal importance in healthcare applications, where both patients and clinicians need to trust research methods to make decisions about people’s health [14]. The AD pathology is characterized by high complexity and heterogeneity, and many authors have demonstrated the absence of etiological uniformity and diverse treatment suitability for each patient, supporting the need for an accurate individual diagnosis [15,16]. In order to make the most of biological experiments and refine their findings, they have to be supported and followed by complex biological modeling, based on mathematical and statistical tools such as Artificial Neural Networks [17]. Formalized domain expertise from psychology, neuroscience, neurology, psychiatry, geriatric medicine, biology, and genetics can be integrated with novel analytic approaches from bioinformatics and statistics to be applied on Big Data in AD research projects, with the aim of answering detailed questions through the use of predictive models. These can succeed in answering key questions about promising biomarker combinations, patient sub-groups, and disease progression, finally leading to the development of effective treatment strategies, helping patients with tailored medical approaches [18].

In this context, AI technology represents a promising approach to investigate the pathological mechanisms of AD by analyzing such complex data. In this review, we focus on recent findings using AI for AD research and future challenges awaiting its application: Will it be possible to make an early diagnosis of AD with AI? Will AI be able to predict conversion from Mild Cognitive Impairment (MCI) to AD dementia, stratify patients, and identify “malignant” forms with worse disease progression? Finally, will AI be able to predict the course and progression of the disease and help in finding a cure for AD?

1.1. AI and the Biomedical Research

AI has recently significantly revolutionized the way that digital data is analyzed and used. Currently, in some applications, AI is used to perform simple tasks, such as face or speech recognition, and often outperforms human abilities in those tasks [19]. This is definitely a great opportunity to be transferred to medical care, due to the potential for fast, low-cost, and accurate automation; for example, in the processing of digital images by AI algorithms [20]. Several studies have been performed with the attempt to ameliorate the knowledge of complex multifactorial diseases such as AD: AI exploits the features of Machine Learning (ML) and Deep Learning (DL) to develop algorithms that can be used in the clinical and biomedical fields for the classification and stratification of patients, based on the integration and processing of a large variety of available data sources, including neuroimaging, biochemical markers, clinical, and neuropsychological (NPS) data from patients and controls. An extensive application of AI in the biomedical field is for Computer-Aided Diagnosis (CAD). This kind of application aims to automate the diagnostic process upon data analysis, potentially contributing to reaching an early and differential diagnosis of AD or dementia of different etiology (Figure 1).

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Figure 1

The framework of AI in AD research. Single-modality or integrated data can be processed by several algorithms and tasks, leading to useful outcomes for early and accurate diagnosis, prediction of the course and progression of disease, patient stratification, and discovery of novel therapeutic targets and disease-modifying therapies.

ML is a fundamental branch of AI, consisting of a collection of data analysis techniques that aim to generate predictive models by learning from data, progressively improving the ability to make predictions through experience (see glossary; Table 1) [21]. DL is a sub-field of ML and uses methods that are able to learn relationships between inputs and outputs by modeling highly non-linear interactions into higher representations, at a more abstract level (see glossary) [22]. Moreover, there are two main categories of predictive models based on ML or DL techniques: Supervised and unsupervised. In supervised learning, the algorithms learn from labeled data to associate an input (e.g., cortical thicknesses data) with a specific output (e.g., presence/absence of a disease or neuropsychological test performance), leading to models that are able to predict the output variable. In unsupervised learning, the algorithms learn from unlabeled data with the purpose of identifying clusters among the observations, based on similar features (see glossary); unlike in supervised learning, there are no correct answers and the aim of the algorithm is to discover structures within variables.Bottom of Form

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AI techniques have found a wide range of applications in the clinical and biomedical fields, in an effort to automate, standardize, and improve the accuracy of early prediction (regression task), classification of patients (classification task), or the stratification of subjects, based on the processing of specific data (see glossary). In a classification task, the algorithm is trained to associate a label (e.g., “AD diagnosis”) to a given set of features (e.g., clinical parameters, cognitive status, genotypes, biochemical markers, imaging, and so on), in order to be able to generate predictions. Once the model is ready, it is able to predict a class, defined by a label (e.g., “AD” or “control”), by analyzing the set of features of a new given example. The regression task instead involves predicting the value of a variable (e.g., “hippocampus volume” or “biomarker level”) mea

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a continuous scale.

Despite ample research effort, we still do not have a cure capable of modifying and/or halting the course of the disease. Some clinical trials are ongoing, especially with the use of monoclonal antibodies targeting Aβ peptides, modified Aβ species, and monomeric as well as aggregated oligomers, which have shown to be safe and have clinical efficacy in AD patients [23]. However, AI pipelines can be applied in automatic compound synthesis in order to analyze the literature and high-throughput compound screening data, to perform an initial molecular screening and automated chemical synthesis [24]. By updating the AI model after cell- or organoid-based experiments, AI can be used to propose a new molecular optimization plan and new bioassays can be conducted to evaluate the biological effects of the compound, thus enabling an automated drug development cycle based on AI design and high-throughput bioassay, greatly accelerating the development of new drugs [25]. AI technology can be used to repurpose known drugs for treatment of Alzheimer’s disease [24,26,27,28]. This is a fast, low-cost drug development pathway, in which AI is used to predict drug repurposing by analyzing large-scale transcriptomics, molecular structure data, and clinical databases. Finally, AI can be exploited to simplify clinical trials too, both in the design and implementation phase [24]. Participant selection can be optimized by using AI algorithms on genetic and clinical data, thus predicting which subset of the population may be sensitive to new drugs [29]. Notably, coupling AI with data from wearables enables almost real-time non-invasive diagnostics, potentially preventing drop-out at subject level [30]. Although promising and rapidly growing, only few of these AI applications have made it to the clinical application stage; nonetheless, AI represents a promising technology to support research and, finally, to develop novel effective therapies [24,31].

1.2. Public Databases and Biobanks

The application of AI-based techniques for AD and other diseases research requires extensive data sets, composed of hundreds to thousands of entries describing subjects over many clinical and biological variables, which can be employed to develop novel algorithms by analyzing the features of the disease. In the last 20 years, many open data-sharing initiatives have grown in the field of neurodegenerative disease research [32]; and, in particular, in AD research. Some important data-sharing resources are the Alzheimer’s Disease Genetics Consortium (ADGC, www.adgenetics.org, accessed on 30 May 2021 Date Month Year), Alzheimer’s Disease Sequencing Project (ADSP,

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