Journal of Alzheimer's Disease 99 (2024) 1221–1223
DOI 10.3233/JAD-240231
IOS Press

Commentary

How to Cure Alzheimer's Disease

Andrzej W. Przybyszewski[a,b,*] and Artur Chudzik[a]
[a]*Faculty of Computer Science, Polish-Japanese Academy of Information Technology, Warsaw, Poland*
[b]*Department of Neurology, UMass Chan Medical School, Worcester, MA, USA*

Accepted 18 April 2024
Pre-press 18 May 2024

Abstract. There has been a lot of buzz surrounding new drug discoveries that claim to cure Alzheimer's disease (AD). However, it is crucial to keep in mind that the changes in the brain linked to AD start occurring 20–30 years before the first symptoms arise. By the time symptoms become apparent, many areas of the brain have already been affected. That's why experts are focusing on identifying the onset of the neurodegeneration processes to prevent or cure AD effectively. Scientists use biomarkers and machine learning methods to analyze AD progressions and estimate them "backward" in time to discover the beginning of the disease.

Keywords: Alzheimer's disease, Clinical Dementia Rating SUM of Boxes, cognitive tests, multi-granular computing, rough set theory

The potential impacts of these methods on early detection and treatment strategies are important for AD as the prevalence of this disease is increasing rapidly due to our aging population. By 2050, an estimated 152 million cases could exist worldwide [1]. The earliest biomarker for AD, total tau (t-tau) in the cerebrospinal fluid (CSF), appears 34 years before the onset of the first symptoms, which can be associated with clinical impairment several decades later [2].

Cognitive tests and CSF amyloid-β (Aβ) and phosphorylated tau (p-tau) also show changepoints 10–15 years before symptom onset. Cognitive changes were estimated by Cognitive Test Substitution, Logical Memory Delayed, Pair Associates Delayed, and Boston Naming Test [2]. Magnetic resonance imaging (MRI) visible changes in medial temporal lobes can be observed about 6 years before AD onset [2]. However, MRI changes were not the subject of [3].

*Correspondence to: Andrzej W. Przybyszewski, Faculty of Computer Science, Polish-Japanese Academy of Information Technology, 86 Koszykowa St., 02-008 Warsaw, Poland. Tel.: +48 608264992; E-mail: przy@pjwstk.edu.pl.

Regrettably, no cure for AD currently exists. By the time clinical symptoms and neurological diagnosis appear, many parts of the brain have already been affected inter alia by intercellular t-tau or Aβ, making recovery impossible. Since the neurodegenerative processes begin two to three decades before observed symptoms, the key to fighting AD is to estimate the beginning period of the AD-related brain changes.

In their review, Cabrera-León et al. (2024) focus on state-of-the-art studies on AD's automatic diagnosis, prognosis, and early stages, mainly mild cognitive impairment [3]. Classification methods were based on artificial neural networks, including deep learning, and data from modalities different from brain signals. By looking into different machine learning methods, databases, and measured parameters these examined studies shed some light on the complex mechanisms related to AD in the brain.

There has been a recent increase in cross-sectional studies that use neural computation methods, particularly in the last two years. These studies have utilized both artificial neural networks and deep neural networks-based studies, except in areas not involving neuroimaging where deep learning dominates.

ISSN 1387-2877/$35.00 © 2024 – IOS Press. All rights reserved.

Characterized by their deep layer structures and extensive computational requirements, deep learning methods present challenges in optimization and cost. Transfer learning has been highlighted as a solution to mitigate these issues; however, its application was limited in the studies reviewed. This could be because convolutional neural networks are not used as much when neuroimaging data are not involved.

The review observed a broad range of dataset sizes and highlighted the challenge of class imbalance in the datasets that can bias model predictions, with various tactics applied to overcome this issue. Importantly, binary classification tasks were more common than multiclass ones, with the most common being the differentiation between cognitively normal individuals and those with AD due to clearer distinctions in early research stages. Prediction of the severity stage of AD was rare. Authors noticed problems, particularly in the context of unbalanced datasets. Therefore, the review advocates the use of performance metrics, such as the area under the curve, sensitivity, specificity, precision, and balanced accuracy, to provide more meaningful comparisons of study outcomes, especially in the context of unbalanced data.

There is indeed a need for more quantitative methods in the diagnosis and prognosis of mild cognitive impairment and AD. While qualitative measures such as cognitively normal, mild cognitive impairment, and dementia are commonly used, they can be subjective and not ideal for machine learning methods. By using more quantitative measures, we can better identify the onset of neurodegenerative processes and potentially develop more effective treatments and prevention strategies.

Furthermore, addressing the issue of homogeneity in binary classification studies within the field, we utilized the intelligent granular computing technique to evaluate AD progressions and potentially identify the beginning of neurodegeneration processes in a backward direction. Intelligent Granular Computing and Rough Set Theory are advanced computational approaches that offer promising avenues for understanding complex data patterns. Our granules are a set of attributes that determine different AD stages. We proposed to implement Intelligent Granular Computing as a Rough Set Theory that introduced rules determining the possibility of dementia in normal subjects observed for almost 30 years in the BIOCARD project [4].

In the BIOCARD study, neurologists evaluated subjects every year with the global score Clinical Dementia Rating (CDR) parameters to determine if a particular individual is normal, has mild cognitive impairment, or has dementia [4]. We used classification based on CDRSUM (sum of boxes) as a more precise and quantitative general index than the global score to provide more information on patients with mild dementia [5]. We were using the cognitive attributes described above with some combinations of additional attributes with the help of multi-granular computing to demonstrate that different sets of attributes were important for the classification of each patient [6]. Additionally, by using rules from patients classified by neurologists as AD and applying them to neurologically normal subjects (CDRSUM = 0), we found that some of them had CDRSUM > 0. Based on the study's rules, we predicted (in 21 normal subjects) that one subject might get mild dementia (CDRSUM > 4.5), one very mild dementia (CDRSUM > 2.25), and five others might get questionable impairment (CDRSUM > 0.75) [5].

Earlier detection and more personalized interventions are possible with artificial intelligence methods. They can uncover patterns invisible to neuropsychologists in the cognitive attributes of normal subjects. That might indicate their pre-dementia stage 5–10 years before symptoms onset [2].

AUTHOR CONTRIBUTIONS

Andrzej W. Przybyszewski (Conceptualization; Investigation; Writing – review & editing); Artur Chudzik (Writing – review & editing).

ACKNOWLEDGMENTS

The authors thank Anja Soldan from BIOCARD for informing us that patients, as we predicted, who might get mild or very mild dementia are still after 3 years, normal (CDR = 0). However, notice that in [2] states "all cognitive tests had changepoints 10–15 years before symptom onset".

FUNDING

The authors have no funding to report.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

REFERENCES

[1] GBD 2019 Dementia Forecasting Collaborators (2022) Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: An analysis for the Global Burden of Disease Study 2019. *Lancet Public Health* **7**, e105-e125.

[2] Younes L, Albert M, Moghekar A, Soldan A, Pettigrew C, Miller MI (2019) Identifying changepoints in biomarkers during the preclinical phase of Alzheimer's disease. *Front Aging Neurosci* **11**, 74.

[3] Cabrera-León Y, Báez PG, Fernández-López P, Suárez-Araujo CP (2024) Neural computation-based methods for the early diagnosis and prognosis of Alzheimer's disease not using neuroimaging biomarkers: A systematic review. *J Alzheimers Dis* **98**, 793-823.

[4] Albert M, Zhu Y, Moghekar A, Mori S, Miller MI, Soldan A, Pettigrew C, Selnes O, Li S, Wang MC (2018) Predicting progression from normal cognition to mild cognitive impairment for individuals at 5 years. *Brain* **141**, 877-887.

[5] O'Bryant SE, Waring SC, Cullum CM, Hall J, Lacritz L, Massman PJ, Lupo PJ, Reisch JS, Doody R; Texas Alzheimer's Research Consortium (2008) Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: A Texas Alzheimer's research consortium study. *Arch Neurol* **65**, 1091-1095.

[6] Digital and Analog Biomarkers in AD. https://nd.pja.edu.pl/ad-clinic.html