



Resting-State fMRI and Machine Learning as Diagnostic Tools for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) presents a significant challenge in healthcare, necessitating accurate and timely diagnosis for effective management. Resting-state functional magnetic resonance imaging (Rs-fMRI) has emerged as a valuable tool for understanding neural correlates and the early detection of AD. This article reviews recent advancements in utilizing Rs-fMRI in combination with machine learning (ML) techniques for early AD diagnosis. First, we discuss the underlying principles of Rs-fMRI, highlighting its ability to detect alterations in brain functional connectivity (FC) patterns associated with AD. We then explore the potential of ML algorithms, particularly support vector machines (SVMs), in analyzing Rs-fMRI data and discriminating between AD patients and healthy controls. We indicate the challenges and opportunities in integrating Rs-fMRI and ML, such as in data preprocessing, feature selection, and model interpretation. We also address the importance of large-scale, multi-site studies to validate the robustness and generalizability of the proposed approaches. Overall, the integration of Rs-fMRI and ML holds great promise as a non-invasive, objective, and sensitive diagnostic tool for AD, potentially enabling early detection and personalized treatment strategies. However, further studies are warranted to optimize methodologies, enhance interpretability, and facilitate clinical translation.

Keywords: Rs-fMRI, Machine Learning, Support Vector Machines (SVMs), Alzheimer's Disease

1. Context

Alzheimer's disease (AD) is a progressive neurological disorder that is widely recognized as the leading cause (1) and the most common form of dementia, accounting for 60 - 80% of all dementia cases (2). Alzheimer's disease was first described in 1906 by German Alois Alzheimer as an abnormal accumulation of the amyloid-beta peptide, which leads to the formation of amyloid plaques, phosphorylation and aggregation of tau protein, and an inflammatory process that eventually leads to synapse loss and neuronal death. This aberrant amyloid-beta accumulation could be explained by a long-term increase in neuronal activity, specifically in the brain network's most active parts, leading to histological and imaging alterations. On the other hand, the symptoms

include gradual memory loss, learning disability, loss of capacity to conduct basic activities of daily life, confusion, and behavioral and personality changes (3). Indeed, dementia induced by AD can result in tissue loss throughout all brain regions, causing severe harm to the neural system and disrupting neural functioning, reducing the patient's cognitive ability. Tissue loss begins in the grey matter (GM) and subsequently spreads to the white matter (WM), corpus callosum (CC), and hippocampus (HC) (4). The HC, the brain region responsible for memory formation, is significantly affected by AD and tissue loss (5). Alzheimer's disease is a growing concern around the world, with 35 to 46.8 million people worldwide suffering from it recently. This figure will double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050, with an annual

incidence of 9.9 million persons. The primary cause of this increase is low and middle-income countries, which accounted for 58% of patients with dementia in 2015 and will increase to 68% by 2050, while high-income countries are expected to represent a 50% increase compared to today (6). Although prevalence studies of younger-onset dementia in the United States are sparse, researchers estimate that 110 out of every 100,000 patients aged 30 - 64 have younger-onset dementia (7). According to statistics, one Alzheimer's patient dies every three seconds around the world, and dementia-related costs continue to rise (8). However, due to a lack of awareness of AD, the majority of individuals are diagnosed in the intermediate to severe stages, missing the ideal time for early treatments (1). Alzheimer's disease is classified into three stages: Normal control (NC), mild cognitive impairment (MCI), and AD. Mild cognitive impairment, in particular, is an early stage of AD defined as an intermediate state between AD and normal function (9). While there is presently no treatment for dementia, new medications can halt the progression of individuals who have not yet reached the MCI stage. As a result, anticipating the proper time when cognitively normal patients would develop MCI is critical (10). Therefore, there is an urgent need to develop AD identification models to enable precise early detection of AD and MCI, allowing for prompt interventions and maximum cost-effectiveness in future treatments (2). Nonetheless, early detection necessitates utilizing complex algorithms, a time-consuming and arduous process. The primary goal is to improve the accuracy of AD prediction, although detection is also substantial. As a result, we require robust, cutting-edge, non-traditional technologies such as machine learning (ML) techniques (5).

Machine learning has grown in importance in disease identification and treatment over the last few years (11). It is a type of artificial intelligence (AI) technology used for classification, regression, clustering, and normative modeling classified as supervised models labeled by data, unsupervised algorithms, in which the goal is to segregate unlabeled data into groups of related cases, and semi-supervised algorithms, which include both labeled and unlabeled data. A ML algorithm is a method for picking the best model from a set of alternatives that fit a set of observations and has various advantages, such as nonlinearity, fault tolerance, and real-time operation, making it appropriate for complicated applications. Support Vector machine (SVM), K-Nearest neighbors (K-NN), logistic regression classification (LRC), random forest (RF), and artificial neural networks (ANN) are some of the most common ML classifiers. In contrast,

deep learning (DL) technology can automatically extract valuable features from complicated image data, avoiding complex human feature extraction stages and saving a lot of workforce and material resources. However, there are several limitations to DL technology. It necessitates a substantial amount of labeled data for training, which may result in costly data collection, annotation, and scarcity in certain regions. Furthermore, DL training and reasoning typically require significant computational resources, which can result in high computing expenses and energy usage. In addition, DL models are frequently referred to as "black boxes" since their inner workings are difficult to comprehend and can limit applications in fields that demand interpretability, such as healthcare and finance. Moreover, they may not generalize to new, unexplored data, resulting in over-fitting issues via shifting tasks between domains (8). Despite significant advances in DL algorithms, traditional ML techniques are still preferred in developing AI diagnostic models due to their distinct advantages. They require fewer data points and have better interpretability (12). Machine learning methods, such as SVM, have shown promise in distinguishing AD patients from healthy controls (HC) using brain imaging data. Support vector machine works by identifying a hyperplane that divides the data points into different classes to maximize the margin between the hyperplane and the closest data points. It can also handle high-dimensional data, such as brain imaging data in AD research (2). The naive Bayes and RF models were found to be optimal for predicting MCI and AD susceptibility, respectively (13). The extreme gradient boosting (XGB) model, which used a combination of clinical and imaging characteristics, showed promise for predicting the likelihood of MCI in those with normal cognitive function (14). Following this, Franke et al. (15) employed a recommended relevance vector machine (RVM) model to predict brain age by combining GM and WM images. Wang et al. also improved age prediction performance by integrating partial least squares regression with a stacking algorithm to merge two imaging models: Structural MRI (sMRI) and functional MRI (fMRI) (16). The outstanding performance of these models in brain tumor diagnosis represents a significant step forward in this field, with the promise of providing more precise and reliable tools for radiologists and healthcare professionals in their critical role of identifying and classifying brain tumors using MRI imaging techniques (17).

Magnetic resonance imaging (MRI) is used in medical diagnosis to visualize the structure and function of the brain. Physicians examine AD symptoms and administer numerous tests to diagnose dementia. Magnetic

resonance imaging scans can detect anomalies in the brain linked with MCI and predict which MCI patients are more likely to develop AD in the future (6). Magnetic resonance imaging, including sMRI and fMRI, is the prominent medical imaging method for understanding and evaluating the anatomical alterations in sensitive regions associated with AD (4). The fMRI produced encouraging results based on sensitivity measures from several ML approaches. Observation of fMRI techniques will aid in dementia detection and changes in neuron connections, which will determine changes in brain function. Functional magnetic resonance imaging is classified as a non-invasive technology since it focuses on measuring and mapping brain processes without injecting any tracer into patients' bodies (18). The sMRI technique is more convenient than other neuroimaging techniques for detecting structural changes. Indeed, sMRI demonstrates brain tissue shrinkage, particularly in the HC, confirming the structural change in the brain (9). However, structural characteristics were retrieved inadequately throughout the sMRI scan. In that circumstance, resting-state fMRI can provide more valuable and complementary information in identifying early-stage dementia and AD in each patient (18). Resting-state fMRI is an imaging technique that alters the nuclear magnetic signal by adjusting the blood oxygen level. It has been widely used in research on various neuropsychiatric diseases such as stroke, Parkinson's disease (PD), AD, and depression. Numerous resting-state functional magnetic resonance imaging (Rs-fMRI) studies have shown brain functional reorganization in MCI patients. As a result, Rs-fMRI is practical for investigating brain function in MCI patients (19). It also assesses functional connectivity (FC) to precisely and efficiently detect biomarkers for AD (2), as well as objective neuroimaging indicators for the research of affective disorders by examining the activities of live brains (20). Therefore, researchers can predict brain age using Rs-fMRI data, allowing us to study neuronal activation in the human brain by integrating ML algorithms.

1.1. Utilizing Multimodal Neuroimaging Data

Neurologists are increasingly interested in using multimodal neuroimaging data such as fMRI and sMRI in conjunction with powerful ML algorithms to identify AD and MCI (21). A classification framework using information from sMRI and fMRI can successfully predict the conversion of MCI, and distinct brain regions obtained in this framework from inter-subject and intra-subject design are most likely diagnostic indicators for AD (22). Most research has concentrated

on structural MRI, which detects structural alterations in the brain. However, studies have revealed that fMRI alterations begin before structural changes, and resting-state FC may be a more sensitive technique to detect brain changes in preclinical AD patients (23). Zhang et al. found aberrant FC in resting-state networks when MCI progressed to AD (24). Reduced FC in the Malaysian population is caused by accelerated neurodegeneration, which can be detected early using fMRI with improved diagnostic accuracy of approximately 82.6% sensitivity and 79.1% specificity in distinguishing AD from HC (25). As a result, fMRI provides insights into cerebral activity, which helps detect functional changes before conspicuous anatomical changes appear (26). Hence, the potential of ML-based fMRI applications for automated diagnostic procedures to identify MCI patients has recently been highlighted (27).

1.2. Resting-State Functional Magnetic Resonance Imaging for Early Detection of Alzheimer's Disease

Resting-state functional magnetic resonance imaging is a promising method for detecting functional damage in the early stages of AD, bridging the gap between molecular-level pathogenic alterations, physiological functional loss, macro-level tissue loss, and neurodegeneration. Compared to other functional imaging approaches, it has several advantages. It does not require research participants to perform any action, making it helpful in imaging uncooperative patients by requiring merely their immobility while obtaining images. Several Rs-fMRI studies have demonstrated changes in the default mode network (DMN), a core network among resting state networks (RSNs), and a decline in brain function caused by various illness states such as AD. Abnormal DMN functioning according to Rs-fMRI is a significant pathogenic characteristic of AD patients, as evidenced by decreased FC in the DMN compared to MCI and HC (28). Resting-state functional magnetic resonance imaging can be utilized to detect remodeling of large-scale network (LSN) brain FC in dementia patients, which has the potential to help physicians in illness assessment and serve as a biomarker in the prediction of AD progression risk (29). Cortical and subcortical brain regions have been thought to exhibit a prime pattern of ongoing connectome across the human brain at rest, indicating that Rs-fMRI is a reliable measure of FC research (30). The resting-state FC is mainly stable amid cognitive decline and AD pathology, implying that it could be a possible hallmark for determining underlying cognitive status and predicting the likelihood of future AD conversion (31). Fundamentally, one of the most

essential properties of Rs-fMRI is its capacity to measure longitudinal FC changes, which are more profound in the early stages of the disease than in the late stages (32). The inter-synchronization of neuron clusters that leads to FC is recognized by spontaneous low-frequency fluctuations in the blood oxygen level dependent (BOLD) signal, and these clusters are known as RSN or intrinsic connectivity networks (ICN). Resting state network FC patterns yield more valid inferences about cortico-cerebellar and cortico-subcortical connectivity estimates than structural connectivity studies (30). As a result, the analysis of Rs-fMRI signals has expanded our understanding of the brain mechanisms underlying cognitive and sensory functions (33). In fact, it has the potential to be a tool for evaluating macroscale connectomics and characterizing intrinsic brain activity (IBA). Since the first study on Rs-fMRI, in which the left and right hemisphere regions exhibited a strong association with the BOLD signal, various researchers have been drawn to this technique to assess spontaneous brain activity (34). Resting-state functional magnetic resonance imaging is a frequently used technology for studying IBA in AD, and IBA analysis can aid in the early detection of disorders before brain shrinkage develops and in understanding the pathophysiological mechanism of AD by examining the relationship between changes in brain activity and cognitive behavior (35). Static regional homogeneity (ReHo) has been utilized to explore IBA in AD using Rs-fMRI to investigate the modifications in dynamic IBA to find dynamic imaging indicators of AD (28). A unique neural activity (NA) metric based on Rs-fMRI signal oscillations demonstrated considerably reduced NA, indicating that the significant decrease in NA identified in MCI patients is particularly sensitive to early alterations in neuronal function (36). Moreover, A β deposition reduces NA in AD and MCI, as evaluated by Rs-fMRI (37). These findings support the concept that Rs-fMRI can detect changes in spontaneous brain activity and FC in response to A β retention. As a result, multiple investigations have found that Rs-fMRI performs well in identifying AD (38).

1.3. Machine Learning in Neuroimaging Analysis

The SVM is one of the most used ML algorithms and has surpassed practical neuroimaging analysis over the last 20 years. Because of its relative simplicity and flexibility, SVM has been employed in various fields to solve various categorization challenges. Hundreds of researchers have used ML to classify individuals with diverse mental and neurological illnesses, improving early diagnosis. Due to its relative simplicity, SVMs are

used in brain disorder research via multivoxel pattern analysis (MVPA) to tackle various clinical problems. Even when dealing with high-dimensional data, SVMs have a decreased risk of over-fitting. SVM analysis can predict diagnosis and prognosis, especially in individuals with brain illnesses such as AD, schizophrenia, and depression. It can characterize non-linear choice limitations in a high-dimensional variable space by addressing a quadratic improvement issue (39). As a matter of fact, SVM is an ML-based pattern classification strategy that has distinct advantages in addressing small-scale sample learning issues and has been widely used in biological data analysis (40).

The SVM classifier is developed to classify AD using higher-order dynamic functional brain networks at various frequency ranges. Khazaei et al. (41) used linear SVM classifiers to diagnose AD with 100% accuracy. Syaifullah et al. achieved 90.5% accuracy in AD diagnosis using SVM on a restricted dataset (38). According to typical brain connection analysis techniques, brain connectivity remains consistent during the fMRI imaging technique. However, current data suggests that the brain connectivity connection exhibits dynamic changes during the resting state using an SVM classifier in higher-order dynamic functional networks with significant potential for diagnosing AD (42). The efficacy of Rs-fMRI for multi-class AD classification using SVM was demonstrated with an accuracy of 86.86% (43). Yan et al. used a multimodal SVM-based ML algorithm to combine Rs-fMRI and diffusion tensor imaging (DTI) data, achieving an accuracy of 98.58% in the AD group, 97.76% in the amnesic MCI group, and 80.24% in the subjective cognitive decline (SCD) group (35). XGB + Decision Tree + SVM with optimized parameters surpassed all other models, with 95.75% efficiency. The implication of the proposed ensemble-based learning approach outperforms previous ML models. Costafreda et al. employed SVM to detect MCI with 80% and 77% sensitivity, respectively (44). K-nearest neighbor KNN and SVM classification algorithm models are utilized to investigate and classify AD, demonstrating that Rs-fMRI multi-band characteristics have more potential as AD biomarkers than single-band features (45). Furthermore, the decreased ReHo of the right caudate was identified as a possible biomarker for MCI diagnosis using SVM. The SVM results indicated a diagnosis accuracy of 68.6%, and this is the first study to use fMRI data to illustrate the relationship between the right cerebrum and MCI using ML (39). Furthermore, the findings of the SVM and ANN-based methods suggested the best accuracies of 80.36% and 74.40%, respectively, and the optimal accuracies for AD and MCI were 79.55% and 78.79% in the SVM-based method. As a result, the

SVM-based technique with multimodal measurements could provide practical diagnostic information for detecting AD and MCI (21).

2. Conclusions

Resting-state functional magnetic resonance imaging and ML hold significant promise as diagnostic tools for AD. Through the analysis of brain FC patterns and the application of advanced ML algorithms, these technologies offer non-invasive, early detection capabilities, allowing for timely intervention and personalized treatment strategies. However, further research and validation studies are necessary to optimize their clinical utility, address challenges such as data standardization and replication, and ensure their integration into routine clinical practice for the effective management of AD. Despite these challenges, the convergence of Rs-fMRI and ML represents a pivotal advancement in AD diagnosis, offering hope for improved patient outcomes and enhanced understanding of this complex neurodegenerative condition.

Footnotes

Authors' Contribution: Study concept and design, S. I., and A. N.; analysis and interpretation of data, S. I., and H. D.; drafting of the manuscript, S. I., and H. D.; critical revision of the manuscript for important intellectual content, H. B., F. D., and M. F.; study supervision, A. N. Moreover, all authors have read and approved the final version submitted.

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