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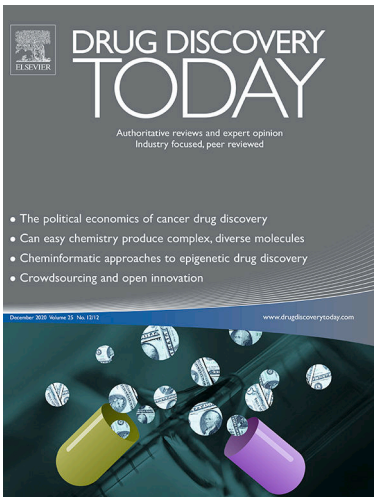

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Advancements and challenges in using AI for biomarker detection in early Alzheimer's disease

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Teaser: Machine learning is set to transform Alzheimer's disease research by analyzing vast amounts of clinical data. Potential impact includes a better understanding of the disease's etiology, early diagnosis, disease staging, biomarker discovery, pharmacological targets and drug development.

The rapid growth in Alzheimer's disease (AD) research has led to an unprecedented accumulation of biomedical and clinical data, including longitudinal patient datasets and comprehensive observational cohort databases comprising clinical, biomedical, neuroimaging and lifestyle data. Expert use of machine learning algorithms is indispensable in order to realize the full potential of the data for diagnosis and drug target discovery. Here, we provide an overview of the biomedical and neuroimaging measures for AD diagnosis and staging. We then critically review the application of machine learning (classification) methods to AD data and provide insight for future improvements and research directions. Future research should aim to improve interpretability, accessibility and thorough validation of the models, enabling translation into clinical applications.

Introduction

Alzheimer's disease (AD) remains one of the most expensive debilitating diseases today with a significant economic burden worldwide.[1] It is the most common cause of dementia characterized clinically by a gradual decline of cognitive functions, including memory, language and reasoning abilities, along with progressive physical and emotional deficits. AD pathology manifests through a complex interplay of biochemical, cellular, genetic and neuroanatomical factors, which can potentially be used as disease biomarkers to guide clinical diagnosis. Biologically, AD is a progressive neurodegenerative disorder with hallmark alterations in amyloid β (Aβ), the accumulation of Aβ plaques and tau neurofibrillary tangles in the brain. At a microscopic level, this proteinopathy, which starts with diffuse extracellular Aβ plaques, proceeds to dense Aβ plaques and the aggregation of phosphorylated tau; when plaques incorporate degenerating axons and dendrites (dystrophic neurites), they are referred to as a neuritic plaque,[2–4] which is a characteristic finding in postmortem AD brains. Hence, tauopathy is believed to be downstream of Aβ plaque formation [as evidenced by cerebrospinal fluid (CSF) and PET scans], and it precedes neurodegeneration measurable by structural MRI scans and subsequent clinical symptoms such as memory deficits.[5] Figure 1 shows the frontal cortex stained for amyloid plaque and p-tau, depicting normal brain (no-plaque), neuritic and non-neuritic plaques in the brain.[6] Of immense interest are the molecular mechanisms leading to these formations that can be viewed as early biomarkers of the disease.[4,6,7]

Although this simplified model of AD, known as the amyloid hypothesis, accounts for many major pathological and phenotypical aspects of the disease's development and progression, the hypothesis has been challenged in recent years[6,8–10] with emerging new findings from genetics, epigenetics, molecular biology and epidemiology. Importantly, targeting Aβ proteins so far has shown only modest therapeutic success in delaying the disease progression.[11–13] Moreover, an age-related accumulation of Aβ plaques can be seen in some non-symptomatic individuals.[14] When investigating the etiology of this disease, a major consideration is the heterogeneity of AD in patient populations[15] including the variability in clinical, neuroanatomical, pathophysiological and biochemical observations, where distinct variants of AD can be identified. It then follows that the underlying molecular mechanisms of AD and its progression can be variable, having huge implications for the diagnosis and treatment of patients, emphasizing the necessity of patient stratification.[16,17]

Several other cellular and molecular pathways associated with AD pathology are being investigated, which could contribute to biomarker discovery for earlier diagnosis, patient stratification and additional treatment options and drug discovery. Most notable are observations of microglial activation and its complex and contradictory effects on disease progression[18] with regard to the associated neuroinflammatory hypothesis of AD.[19,20] For example, patients with AD exhibit increased levels of inflammatory biomarkers in blood and CSF, such as proinflammatory cytokines and specific microglial-activated biomarkers.[19] Supporting this theory are genome-wide association studies (GWAS) reporting several AD risk genes that are related to immune system functions.[21] Also implicated in AD pathogenesis are mitochondrial dysfunction,[22,23] changes in neurotransmission (e.g., excitatory and inhibitory glutamate and GABA signaling, and the relevant transporters),[24,25] the impact of gut microbiota[26] and the presenilin (PSEN1) hypothesis.[10]

Diagnosis of AD has shifted from relying solely on autopsy data to the inclusion of clinical criteria, such as family history, clinical examination, neuropsychological testing and limited laboratory assessments,[27] and will now become increasingly more reliant on biomarkers from biofluids and advanced imaging technology.[9] This is inevitable considering the need for early diagnostic tools (before the onset of symptoms) and the need for objective criteria for a more accurate diagnosis. An accurate diagnosis is imperative not only for patient disease management but also for research, with precision in patient selection in observational studies, clinical trial enrollment, evaluation of new diagnostic tests and clinicopathologic correlations. In a radical move toward a purely biological definition of AD, the National Institute on Aging and the US Alzheimer's Association proposed a 'research framework' according to which AD is established by the underlying pathologic processes irrespective of the clinical consequences of the disease.[28] The framework proposed the use of three sets of biomarkers: Aβ deposition (A), pathologic tau (T) and neurodegeneration (N), collectively referred to as the ATN framework. Clinical use of this framework has been debated by the International Working Group[9] as potentially more useful in ruling out AD (in Aβ-negative individuals) than in diagnosing AD.[9]

Despite the limitations of these biomarkers and the debate around the clinicopathologic correlations of various neuropathological and neuroanatomical observations with AD symptomology, the need for more-accurate diagnostic tools persists. Above all, the onset of clinical symptoms, such as those identifiable by the clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) and Mini-Mental State Examination (MMSE) scores, is years behind pathological changes and might be too late for useful clinical interventions or preventative measures.[29–31] AD development and progression can be viewed as a continuum comprising an asymptomatic phase known as preclinical AD, through mild cognitive impairment (MCI) to AD dementia of varying severity. The preclinical phase is identifiable only through biomarkers, and it might or might not progress into MCI and AD, which indicates the limited specificity of the current biomarkers.[29–31] An additional challenge for biomarkers in MCI and AD is the accuracy in determining the cause of cognitive loss (i.e., eliminating false positives). Consequently, the accuracy and precision of biomarkers are crucial for patient outcomes and AD research, especially with clinical trials and cohort studies for accurately assigning the participants into AD and control groups.

The growing availability of patient-level longitudinal cohort data in recent years provides new research opportunities for AD. With the application of data science and machine learning (ML) algorithms, various aspects of AD can be investigated from a data modeling perspective that could offer new insights into the pathogenesis, clinical progression, biomarkers and therapeutics discovery. AD-specific databases such as Alzheimer's Disease Neuroimaging Initiative (ADNI)[32] and Open Access Series of Imaging Studies (OASIS)[33] are suitably designed to allow ML applications to various biomedical assays, neuroimaging data, lifestyle information, cognitive test results and genetic data. ML refers to computer algorithms that learn a model from data, often using statistical theories, to discover patterns (or rules) in data, such as correlations between variables (model features) and AD scales and categories (classes). Hence, they are data modeling methods. As depicted in Figure 2, supervised and unsupervised ML methods can contribute by discovering rules and patterns in data for future predictions, such as AD diagnosis and staging and response to therapeutics, as well as identifying the most relevant predictors to be used as disease biomarkers.

ML methods, such as deep learning, are fundamental components of artificial intelligence (AI), particularly when analyzing images or text. The discovery of new biomarkers, along with their optimization, threshold selection and validation of their applicability, relies heavily on the effectiveness of the specific data modeling methods. Data modeling has become an integral part of research and scientific discovery today. In particular, biomedical disciplines routinely generate and employ large amounts of data. Examples of heavily data-reliant biomedical disciplines include genetics (e.g., GWAS studies), omics (e.g., proteomics and metabolomics), high-throughput drug screening, public health data, epidemiology and health economics.

This review evaluates the application of ML algorithms to AD and identifies gaps in methodology that can potentially limit the accuracy and use of these models. Whereas there are several reviews with 'machine learning' or 'AI' in the titles, their focus can range from natural language processing of patient speech[34] to the implementation of trustworthiness of AI systems.[35] Unlike these two examples, we are interested in identifying physical biomarkers relevant to the pathology of the disease, rather than tools for speech recognition or issues with clinical implementations. Moreover, several of the previous surveys focus exclusively on specific ML methods and deep learning architecture,[36,37] whereas others have focused on specific data types for AI (e.g., the MRI image,[38] multimodality imaging data,[39] sensor data analysis[40] or the genetic study of AD[41]). A recent review on biomarker discovery for AD assesses the suitability of datasets for ML.[42] Some reviews[43,44] have focused on the potential applications of AI and discussed the reported accuracy of the published ML models of AD. By contrast, this manuscript provides a deeper assessment of ML algorithms and available novel methodologies to overcome risks involving issues such as transparency, interpretability and applicability, using a clear language intelligible to biomedical and pharmaceutical scientists. We have also focused on identifying gaps in methodology for future improvements. First, we will discuss some of the AD biomarkers available within cohort databases, focusing on neuroimaging and fluid biomarkers. Next, we will briefly review the main types of AD-related data available for ML algorithms and the main types of ML algorithms for AD-related classification. Then, we discuss the central contribution that ML can offer to the discovery of biomarkers. We will detail some of the recent advancements and challenges of data modeling and ML in AD biomarker discovery. Finally, current challenges and obstacles to the use of biomarkers in clinical settings will be discussed.

Literature search methodology

This narrative review article was constructed by using a comprehensive and structured literature search to identify the relevant studies and reduce the risk of confirmation bias. Scientific databases including Web of Science and Google Scholar were systematically searched using a combination of keywords and Boolean operators structured as follows. First, the more general keywords of 'machine learning' or 'artificial intelligence' were used in combination with 'Alzheimer's disease' with or without the word 'biomarker'. The search was limited to peer-reviewed articles published in English within the past 10 years to ensure the inclusion of contemporary developments. This ensured identification of the most general important themes available in the current literature. Next, more-specific ML concepts were used as new keywords such as a combination of 'deep learning' or 'convolutional neural networks' with 'Alzheimer's disease'. Likewise, specific AD-related biomarkers such as 'structural MRI' were used in combination with 'machine learning' or 'artificial intelligence'. This allowed identification and inclusion of more-specialized research papers within the field. Additional references were identified by tracking the recent citations of the

select key articles. Selection criteria emphasized methodological diversity (for comprehensiveness) and rigor (for example by considering the size of the dataset or model accuracies), relevance to biomarker discovery and clarity in the application and evaluation of ML models. Priority was given to studies demonstrating novel ML approaches, clinical validation or translational potential. Review articles and meta-analyses were included to provide contextual background, whereas studies with insufficient methodological detail or lacking validation were excluded. This process ensured the inclusion of high-quality, representative literature about the current state of ML and AI applications to AD biomarker discovery.

AD biomarkers from neuroimaging

Because AD is associated with pathological changes in the brain structure and function, various neuroimaging techniques have historically been used as noninvasive, inexpensive and objective tools in the clinic and for research, to aid clinical diagnosis, monitor AD progression, determine AD subtypes[45,46] and predict clinical symptom onset.[47] These techniques can be used to explore Aβ and tau depositions, patterns of regional structural brain alterations (atrophy), metabolism alterations and deterioration of functional cortical networks due to neuronal destruction and loss of input from related cortical regions. The increasingly widespread availability of neuroimaging has led to its routine use in clinical practice and research, and large amounts of image data in health data repositories, longitudinal population databases and AD-specific cohort studies. Using the data, significant associations have been reported between the volumes of regional grey and white matter for many psychiatric conditions, aging and degenerative diseases such as AD.[48–50] The neuroimaging techniques used in AD are categorized into structural modalities, such as structural magnetic resonance imaging (sMRI) and diffusion tensor imaging (DTI), and also functional modalities, such as positron emission tomography (PET) imaging and functional MRI (fMRI) (Table 1).

sMRI

The sMRI sequences offer detailed images of the brain's structure to serve as a biomarker for determining the stage and severity of the neurodegenerative component of AD pathology.[51] Various sMRI methods include T1-weighted, T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI modalities. These methods differ in the sequence of applied radio frequency pulses to the tissue slice and the time of capturing the echo signals, with T1-weighted MRI being the shortest and FLAIR using the longest sequences to fine-tune and enhance the contrast between various tissue structures. T1-weighted MRI enhances fatty tissue signals while suppressing water signals (dark CSF) to allow a precise separation between the grey and white brain matter. T2-weighted MRI enhances water signals (bright CSF), emphasizing the contrast between CSF and brain tissue. This modality is proficient at detecting cerebrovascular changes like white matter hyperintensities and microbleeds, frequently seen in individuals with AD,[52] and the presence of cerebral infarctions.[53] FLAIR MRI can uncover white matter lesions, offering insights into CSF spaces and white matter integrity.[54,55] White matter hyperintensities (WMH) are closely associated with grey matter atrophy and cognitive decline, not only in AD but also in cognitively normal elderly individuals.[56]

AD-relevant information from sMRI can be visually assessed by a skilled neurologist; however, advanced quantitative analyses can reliably extract information about intricate morphometric brain changes from the voxel-level imaging data. A recent survey exploring the current neuroimaging practice in Europe found that MRI was the most used imaging technique for dementia (72%) with 90% of the responding neuroradiology centers using a combination of MRI protocols with T1 being the most common, and 75% performed visual analysis vs 23% performing volumetric analysis.[57] The quantitative analysis of sMRI data can be performed at the brain region level [volumetry or region of interest (ROI) analysis] or the voxel level (voxel-based analysis). ROI analysis involves segmenting the brain into different anatomical regions (ROIs) and measuring their structural features such as volume, surface area and thickness.[58–60] Figure 3 shows an example of ROI cortical depiction labeled per the DKT cortical labeling protocol.[61] By contrast, voxel-level analysis (tensor-based morphometry) enables the investigation of nuanced structural brain alterations at the voxel level.[60,62,63]

The success of quantitative analyses relies on the quality of the MRI scans, the quality of the automated brain segmentation algorithms and the ML algorithms that allow the identification of brain structure changes in healthy vs diseased states.[60] For example, volumetric T1-weighted MRI analysis has been used to quantitatively explore age-related structural brain changes in healthy adults,[64,65] to identify AD patients from healthy individuals,[66] to track the AD progression[60] and to distinguish AD from other types of dementia.[45] Standardization of MRI (and other neuroimaging methods) is an important consideration in the success of neuroimaging as a disease biomarker. Moreover, patient privacy is an important consideration owing to the possibility of facial recognition software to identify people from MRI scans.[67]

DTI

DTI is a type of structural MRI that uses anisotropic diffusion of water molecules to estimate axonal organization within white matter. It provides detailed information about the microstructural properties of white matter in the brain, including connectivity and integrity (damage and demyelination), and changes in these are associated with AD.[45,68] AD is associated with changes in specific measures from DTI including reduced fractional anisotropy and increased water diffusivities measured as mean diffusivity (of water molecules in all directions), radial diffusivity (perpendicular to axons) and axial diffusivity (parallel to axons).[69,70] In addition to early detection and diagnosis,[70] DTI is used for mapping white matter tracts (tractography),[71] for tracking disease progression over time and differentiating AD from other dementias.

fMRI

fMRI measures brain activity by detecting small changes to the blood flow in response to stimuli or actions (paradigms) and using oxygen-level-dependent (BOLD) signals. The application of fMRI in AD monitors the associations between brain regional hemodynamics and the clinical symptoms.[72] In addition, resting-state (rs)-fMRI is conducted when no specific task is being executed and it captures the BOLD signal fluctuations in various brain regions over time to identify

patterns of functional activities in each voxel or region; and functional connectivity between brain regions.[73] The rs-fMRI could potentially be more efficient compared with structural imaging in detecting brain (function) alterations in preclinical AD.[74] Some rs-fMRI methods that have been employed in studies of AD include temporal BOLD signal variability,[72] the (regional) amplitude of low-frequency fluctuations,[75,76] regional homogeneity (similarity of the BOLD signals in a cluster of nearby voxels)[77,78] and the functional connectivity measured as the temporal correlation between various brain regions.

PET

PET scans evaluate various functions in the brain by using specific radioactive tracers, including radiotracers for cerebral glucose utilization, neuroinflammation, different neurotransmitter systems and the AD protein aggregates, specifically the amyloid deposits.[79,80] For example, PET imaging with the ^{18}F-fluorodeoxyglucose radiotracer (FDG-PET) is commonly used to detect glucose uptake in various brain regions, where a reduction in glucose metabolism in brain regions of interest (e.g., the hippocampus and the posterior cingulate cortex) is indicative of AD. The reduced glucose utilization in AD could be due to neuronal loss or loss of activity, bioenergetic changes, accumulation of amyloid plaques and neurofibrillary tangles that disrupt typical neuronal functioning, and/or neuroinflammation and oxidative stress. FDG-PET has been found, through meta-analytic evidence, to have the ability to provide high sensitivity (>90%) and specificity (>89%) in differentiating AD from cognitively normal subjects.[81]

Other radiotracer examples include Aβ radiotracers (e.g., ^{11}C-labeled Pittsburgh compound B and ^{18}F-labeled florbetapir), tau radiotracers (e.g., [^{18}F]-flortaucipir) and tracers for microglial activation [translocator protein (TSPO) radiotracers].[80,82] These biomarkers have shown potential as diagnostic tools in AD using visual inspection and quantitative analysis.[79,83] In particular, FDG-PET and amyloid-PET have found clinical applications in differential diagnostic algorithms of dementia from neurodegenerative diseases.[84] In addition, radiotracers are being developed to investigate various other aspects of AD pathophysiology, including cholinergic depletion[85] and synaptic density indicators such as synaptic vesicle glycoprotein 2 (SV2).[86]

Single photon emission computed tomography (SPECT)

SPECT is an imaging technique using gamma rays that creates a 3D image of a radioactive tracer distributed in tissues after being injected into the bloodstream. This enables visualization and quantification of changes in blood flow patterns in the brain regions as an indicator of brain metabolism and function. SPECT is widely used in AD to identify functional changes in the brain. In longitudinal studies, subgroups of AD patients have shown posterior cerebral hypoperfusion on SPECT images.[87] Quantitative studies have shown high sensitivity and specificity of SPECT images in differentiating AD from vascular dementias and detecting the shift from asymptomatic to symptomatic stages of AD.[88]

Fluid biomarkers of AD

A substantial amount of work in AD research has focused on discovering and validating biomarkers for improving diagnostic criteria and for applications in clinical research.[89,90] Apart

from the biomarkers derived from neuroimaging discussed in the previous section, CSF measures of Aβ and total or phosphorylated tau, as well as plasma or blood biomarkers, have been commonly used in clinical practice and research.[91] Lesser-known biomarkers include brain-derived exosomes in serum and CSF,[92] plasma glial fibrillary acidic protein (GFAP),[93] the axonal cytoskeleton protein neurofilament light chain (NfL),[94] inflammatory proteins,[95] the biomarker of blood–brain barrier integrity, shedded form of platelet-derived growth factor receptor-β (sPDGFRβ)[96,97] and mitochondrial markers such as CoQ10.[98]

Although many AD fluid biomarkers are CSF-based, the field of studying plasma or blood-based biomarkers has increased dramatically.[99] This is because Aβ is tenfold more concentrated in CSF than in the blood.[100] It is important to also note that levels of fluid biomarkers vary greatly and progress at different rates over the course of the disease.[90,91,101] For example, most charts depicting biomarker timelines show Aβ appearing first, tau second and neuronal loss much later. Some investigators would argue that abnormal Aβ and tau in the brain, as measured with PET, and Aβ42 and tau phosphorylated at threonine 181 (p-tau181) levels in the CSF are the current core biomarkers of AD. However, a direct comparison of these and various plasma biomarkers at different stages of AD (longitudinal studies) and across AD studies must be delineated to enable accurate estimation and staging of AD in clinical practice.[102] In a recent cross-sectional and longitudinal study[93] using the AIBL cohort, it was found that plasma p-tau181 biomarkers performed equivalent to or better than some other plasma biomarkers in predicting an Aβ−/+ status from amyloid-PET. However, a panel of biomarkers including the ratio of plasma Aβ1-42 to Aβ1-40, p-tau181 and GFAP had a superior predictive capability for Aβ−/+ status across AD. Plasma p-tau181 has been shown to correlate with CSF p-tau and to increase in preclinical AD and further increase in MCI and dementia AD.[103] It must be noted, however, that the prediction of Aβ−/+ status serves only as a surrogate for the more sought-after clinical AD phenotype (i.e., the cognitive decline).

Biomarkers can be assessed in terms of how they correlate with neurodegeneration. Several neurodegeneration biomarkers (e.g., NfL and total tau) are common across several diseases and lack specificity to AD. Interestingly, a recent study[104] showed that brain-derived tau (BD-tau) in blood is an AD-specific neurodegeneration biomarker; it can differentiate AD from non-AD dementia, and its levels correlate with longitudinal loss of cognition and atrophy rates across preclinical, MCI and dementia stages of AD. BD-tau levels increase according to concomitant Aβ and neurodegeneration abnormalities. In other words, plasma brain-derived tau was shown to be an amyloid-associated neurodegenerative biomarker capable of identifying Aβ+ individuals at risk of short-term cognitive decline in AD.

Still, other markers associated with synaptic pathology have recently been studied in AD. Some investigators would in fact propose that synaptic loss might develop before tau alterations and in response to elevations in soluble oligomeric forms of Aβ associated with early AD. To this end, a range of fluid biomarkers such as neurogranin, α- and β-synuclein, visinin-like protein 1 (VILIP-1) and neuronal pentraxin 2 have been developed.[91] Most of these fluid biomarkers of neurodegeneration are CSF measures and their time courses have been suggested to lapse behind Aβ and tau biomarkers.[91] In terms of the blood biomarkers, the combined use of the axonal injury biomarker (NfL) and neuroinflammation biomarker (GFAP) has been suggested to enhance the accuracy of AD diagnosis and prediction of AD onset.[105]

ML for the classification of AD-related data

ML algorithms have been extensively used to investigate AD and explore associations between various clinical and physical measures of AD. These methods can identify patterns in data that could be associated with AD diagnosis cross-sectionally or predict future diagnosis and progression rates. These methods can therefore achieve two main outcomes: (i) prediction of an AD outcome (e.g., AD diagnosis, stratification of AD patients, prediction of progression from healthy to AD, prediction of Aβ status or the rate of neurodegeneration); (ii) identification of main predictors of AD from the pool of all the collected data (e.g., biomarkers, clinical manifestations, possible risk factors). From a drug discovery perspective, these so-called AD predictors that are measurable indicators of AD can be used to identify potential drug targets, assign patients to the correct AD class, select patient populations for clinical trials, monitor treatment response during clinical studies, predict potential side effects and guide the development of new drugs by providing insights into disease mechanisms. With the application of advanced ML methods and the larger sets of available data, it is expected that more can be learned from the available databases than from single hypothesis-driven clinical trials within the field.

From an ML perspective, AD outcomes that we aim to predict are either a category (e.g., patients categorized as AD or MCI) or a continuous quantity (e.g., levels of neurodegeneration on a continuous scale). ML methods for the prediction of categorized data – known as 'class label' in ML terminology – are called classification techniques, whereas ML methods for the prediction of continuous quantities are regression techniques. From our experience, classification techniques seem to be more common in published AD-related ML literature. For example, classification algorithms can identify the best set of biomarkers to accurately classify individuals into healthy, clinical AD or MCI classes.[106–109] In this example classification task, the clinical status of the individuals is the 'class label' and each individual's attributes (including some potential biomarkers) are known as the 'features'.

This section focuses on the classification task, an ML task where each subject is described by a set of predictive features and is associated with a class label. The goal of a classification algorithm is to learn a model that predicts the class label (e.g., whether or not a subject has AD or whether the subject's condition will progress from MCI to AD), based on the values of the features (e.g., biomarker results of each individual). Studies applying classification algorithms to AD data can be characterized by the type of data being analyzed and the type of ML algorithm applied to the data. Hence, the remainder of this section is divided into two parts. The first part discusses the main types of data that have been used for AD-related classification, including different types of predictive features and different types of class labels (to be predicted). The second part discusses the main types of classification (supervised ML) algorithms that have been used for AD-related classification, as well as two important related issues: the need for adjusting the hyperparameter settings of those algorithms, to maximize predictive performance; and the need for interpreting the 'black box' models usually produced by supervised ML algorithms, which can be used for biomarker discovery by identifying the most important features in very accurate predictive models.

Types of AD data available for ML

When using classification algorithms to analyze AD-related data, the choice of the data to be analyzed is more fundamental than the choice of the algorithm because, in practice, we need to first define the data and then choose a good algorithm suitable for that kind of data. It is particularly important to consider the cross-sectional or longitudinal nature of datasets.[108–110] Longitudinal datasets contain repeated measures of variables across time (e.g., blood cholesterol levels or cognitive test results across different time points). Longitudinal datasets have become more widely available in recent years, with national-level initiatives and investments worldwide for the creation of standardized clinical databases. These include data from AD-focused research initiatives such as ADNI and data from versatile national and international longitudinal databases such as the All of Us database in the USA and the UK Biobank. It must be noted that a comprehensive list of the available databases is outside the focus of this current paper, hence we just briefly mention some major databases. In the USA, the NIH-funded National Alzheimer's Coordinating Center (NACC) has coordinated the development and maintenance of the Uniform Data Set (UDS) with clinical and neuropathological data collected from various AD Research Centers (ADRCs) using a standardized protocol. Other data-focused research initiatives in the USA include the database generated by the ADNI and that developed by the Knight ADRC (OASIS), which are both longitudinal, multicenter, observational, prospective studies of normal cognitive aging, MCI and early AD. Similar initiatives and many databases can be found in Europe and the UK. For example, the European Medical Information Framework for AD Multimodal Biomarker Discovery (EMIF-AD) collated data from 11 European cohorts.[111] Another example is the Australian Imaging, Biomarkers and Lifestyle (AIBL) study, which has preclinical, prodromal and clinical stages of AD defined from biological and cognitive perspectives.[112]

Regarding sources of data, reviews of the literature have noted that the most used dataset has been ADNI,[42,107,113,114] followed by the OASIS dataset[113]; with other sources of data being used less often (e.g., Kaggle datasets). The temporal nature of longitudinal data provides the opportunity for analyzing disease progression across time, as well as the opportunity for detecting the influence of early pathological changes and earlier lifestyle choices on later diagnoses of AD-related conditions.[106,109] In addition, longitudinal research can allude to causal mechanisms that cannot be captured by cross-sectional studies. However, a proper sophisticated analysis of longitudinal data should in principle involve classification algorithms designed specifically to cope with the temporal nature of longitudinal data[110] – some examples of such algorithms will be briefly discussed later. Applications of ML to AD have mostly utilized neuroimaging data, particularly MRI, as predictive features for models,[108,109] with fluid biomarkers,[109] cognitive scores[109,113] and genetic data being less frequent. The latter was found to be the least used type of feature in a specific review,[109] possibly owing to the larger cost and ethical issues associated with their data collection and use. In any case, genetic data are analyzed, for example focusing on ML applied to single nucleotide polymorphism (SNP) data.[114] Sometimes the predictive performances obtained by classification algorithms trained with less expensive features (e.g., certain fluid biomarkers) are competitive with the results obtained by more-expensive features (e.g., functional MRI/PET imaging).[115] Furthermore, the relevance (predictive power) of a feature for AD-related classification also tends to be dependent on the current stage of the disease or medical condition. For example, it was noted that plasma analytes have more predictive power around the inception of the disease, whereas MRI tends to have more predictive power in a later stage of the disease.[115]

Several reviews of the literature have noted that combining different types of features (multiple modalities of data e.g., neuroimages and fluid markers) usually increases the predictive performance, compared with using a single data modality.[113,116–118] However, as more modalities are considered, it becomes more difficult to find sizable numbers of subjects (AD patients or controls) with data for all considered modalities. Despite this, subjects with missing data for a subset of the modalities can still be used for ML, as long as the ML algorithm or some data pre-processing method effectively copes with missing values.[119,120]

In general, classifying subjects into 'normal vs AD' is relatively easier (tending to obtain higher predictive accuracies) than classifying subjects into 'normal vs MCI' or 'MCI vs AD'.[118,121] This is expected, because intuitively the clinical differences in the two groups of subjects in the former case tend to be significantly greater than the differences in the two groups of subjects in the latter two cases. Although binary classification is more common, there are also many studies classifying subjects into three or four classes representing different levels of AD severity or AD stages.[109,113]

Types of ML algorithms for AD-related classification

Many studies have used deep learning, more precisely various types of deep neural networks (DNNs), for analyzing AD-related data.[106,113,116,118] This is partly due to the fact that neuroimages are overall the most used type of data in this area and that DNNs are, in general, the state-of-the-art type of method for image classification.[122,123]

Convolutional neural networks (CNNs)[124] have been one of the most popular and most successful types of DNN for AD-related classification,[106,113,116] particularly when analyzing neuroimages. This is not surprising, considering that CNNs were designed to work with grid-structured inputs where there are strong spatial dependencies between neighboring local regions of the grid[124]; and this is naturally the case in images, where neighboring locations in an image tend to have the same color. CNNs exploit the similarities between neighboring local regions of images to create features representing local patterns that help to improve predictive performance. In addition, the CNN algorithm learns increasingly more complex and more abstract representations of the input data along the sequence of hidden layers of the network, automatically performing 'feature construction' in a way optimized for the classification task, which is a major characteristic of deep learning.

The longitudinal nature of a time series of neuroimages can be explored by recursive neural networks (RNNs) and long-short-term-memory (LSTM) neural networks,[124] which are DNNs tailored to process temporal (or sequential) data. However, although RNNs and LSTMs have been used for AD classification,[106,113,116] their use in this field has not been as popular as their wider use in other fields.[106,108] In any case, the application of DNNs to AD-related data faces the problem that the datasets in this field are usually relatively small by comparison with datasets in other fields, and DNN algorithms usually require large datasets to achieve high predictive accuracy. For example, a recent review of ML for AD-related classification[109] noted that, in 62% (18/29) of the analyzed studies, the sample size was <100 instances (cases).

In addition to classification using neuroimaging data, many studies use 'tabular data' (where each row represents a subject and each column represents a predictive feature, plus a final column representing the class label of each subject). The state-of-the-art for tabular data can be considered

in general ensembles of decision trees, rather than DNNs.[125,126] Support vector machines (SVMs) also tend to achieve very competitive predictive performance in tabular data.[36,127] Hence, SVMs and decision-tree-based ensembles have also been frequently used in AD-related classification studies. In fact, SVMs have been the most popular classification algorithm for AD-related data according to several literature reviews[107,108,114,128]; and decision-tree-based ensembles (e.g., random forest) have also been reasonably popular.[109] Note that, although standard SVMs and decision-tree-based ensembles are not designed for longitudinal data, there are specialized versions of these algorithms developed for coping with the temporal nature of longitudinal data (e.g., a longitudinal version of SVM[129] and longitudinal versions of random forests[130,131]).

Adjusting the hyperparameter settings of classification algorithms

Most ML algorithms for classification have many hyperparameters that need to be set before they are trained on the input data, and usually the predictive performance of the learned models is sensitive to variations in the settings of those hyperparameters. This is the case particularly for DNNs and SVMs. In principle, hyperparameter settings can be optimized in a 'semi-automated' way, with users trying a few combinations of hyperparameter settings and selecting the one with the best predictive performance in a validation set – separated from the test set to be used later for measuring generalization performance of the optimized model. However, this usually requires good knowledge of the ML algorithm. For example, experiments have shown a strong positive correlation between a user's experience with deep learning and the predictive performance of the trained DNNs.[132]

In principle, more-effective optimization of the hyperparameter settings can be achieved with more systematic and automated approaches, developed in the area of automated ML (Auto-ML)[133,134] – or, more specifically, the neural architecture search (NAS) in the case of DNNs.[135] However, advanced Auto-ML methods tend to be computationally expensive, because they must iteratively generate and evaluate many hyperparameter settings of classification algorithms across many iterations.

The Auto-ML methods used in AD-related DNNs have been mainly relatively simple and fast, like cross-validation or grid search[114] or a combination of random and grid search,[136] rather than the more sophisticated Bayesian optimization or evolutionary algorithms.[134] Hence, the use of Bayesian optimization or evolutionary algorithms could lead to some improvements in predictive performance in future AD-related classification studies using DNNs or other types of classification algorithms whose performance is sensitive to the algorithm's hyperparameter settings.

Risk of overfitting and information leakage

When applying classification algorithms to AD-related data (or any other type of data) one should be careful to mitigate the risk of overfitting and to avoid data leakage. Overfitting occurs when a classification model is too adapted to specific details of the training data and, as a result, the model does not generalize well to the test data (which is independent from the training data and is used for measuring generalization performance). For example, overfitting can occur when the data are very noisy, so that a complex model can be fitted to noisy patterns in the data, rather than true patterns in the data, or when the number of predictive features is much larger than the number of instances.[114] The risk of overfitting can be mitigated, for example, by using some regularization

technique that reduces the number of parameters being learned during a model's construction (e.g., using dropout in DNNs[137] or by ensemble learning, which averages the predictions of many base models in the ensemble[122]).

Data leakage occurs when information in the test set is used in any part of the training process of a classification model.[36] The test set must be used only to evaluate the generalization ability (predictive accuracy) of the final classification model, after all the training process has been completed, to avoid data leakage, because data leakage leads to overoptimistic and misleading measures of predictive accuracy. Note that procedures such as feature selection, feature construction and tuning of classification algorithm hyperparameters to maximize their predictive performance are all part of the training process and must be carried out using the training set only, with no access to the test set. Unfortunately, this crucial principle in the evaluation of classification algorithms is often not followed. In particular, in a review of 32 studies using the CNN algorithm and anatomical MRI data for AD classification,[36] it was noted that in six cases there was a clear data leakage and in another ten studies it was unclear whether or not there was data leakage, based on the incomplete description of the experiments in the study. In other words, between 19% and 50% of those 32 reviewed studies have reported overoptimistic values of predictive accuracy owing to data leakage.

Interpreting 'black box' models for AD-related classification and biomarker discovery

Algorithms such as DNNs, SVMs and ensembles of decision trees learn black box models that provide predictions that cannot be directly understood or interpreted by users[106,117,118] owing to the complexity of those models (usually with a large number of features). For example,[138] when predicting the probability of death for patients with pneumonia, a substantially more accurate neural network model was dismissed in favor of an interpretable but less accurate logistic regression model, because the black box neural network model was 'too risky'; it could make predictions based on misleading patterns in the original data (which might not apply to new patients). Here, a misleading pattern learned by a rule-discovery algorithm was: 'IF (patient has asthma) THEN (patient has a lower risk of death)'.[138] This pattern was true in the original data because the asthmatic patients with pneumonia were usually directly admitted to the intensive care unit (ICU) and received more-thorough treatment in the ICU, which decreased their risk of death. In this example, the neural network could have potentially learned several other misleading patterns in the data that were not explicitly identifiable; hence, the neural network model was considered too risky for real patients.[138]

A number of techniques have been developed by the ML community for improving the interpretation of black box models or explaining their predictions,[139] including techniques specifically for neural networks.[140] These techniques are often referred to as explainable AI (XAI) techniques. A common type of XAI technique for providing at least some interpretation of a black box model consists of using a feature importance measure to identify the most important features in the model; and, then, if the model at hand is very accurate, such top features could be considered as candidate biomarkers, to be validated by clinical tests later. For example, a feature importance measure was used to identify the most important features in a random forest model[115] (a type of decision tree ensemble), which involved the results of some cognitive tests, followed by several lipoprotein levels in the plasma and other features like BMI and testosterone level. Likewise, Ludwig *et al*.[141] used a feature importance measure to identify the most important miRNAs

involved in AD used in a gradient-boosted trees model (another type of decision-tree-based ensemble). Note that feature importance provides a 'global' measure of the importance of a feature (considering the entire model), which does not tell us the importance of a specific feature value in the classification of a specific patient. There are also 'local' interpretability methods that provide a fine-grained explanation for the classification of each specific patient in the test dataset. A comprehensive review of global and local interpretability methods is available.[139]

In the past few years, there has been increasing interest in applying XAI techniques in AD research.[142–145] In a recent review of XAI techniques for AD classifications,[145] a feature-importance technique called SHAP was found to be the most prevalent XAI technique used in 33 out of 77 reviewed papers. It should be noted, although SHAP and other XAI techniques are designed to explain the predictions of a black box classification model, ironically, in cases where users do not have expertise on XAI's technical details, it becomes a type of 'black box XAI technique'. In this case, users would not understand how an XAI technique computed the importance of the features, a situation analogous to a user not understanding how a black box model computed its predictions.

The need for expertise in the interpretation of SHAP's results has been discussed,[146] where it was noted that "SHAP may require additional expertise to interpret". It has also been noted that SHAP and related techniques might not provide a good explanation for the complex interactions between features in complex black box models.[143] It is also important to note that, regardless of the XAI technique being used, model interpretability requires that the features used in modeling are also interpretable. For example, when using neuroimages as model features, the voxel-level features are inherently noninterpretable, whereas mapping these into ROI will result in more meaningful models. In addition, the evaluation of XAI techniques faces the challenge that there is no 'ground truth' for what a correct explanation for a classification is; and so the evaluation of a XAI technique is often based on *ad hoc* intuitions of XAI researchers.[143,145] Therefore, it seems particularly important to have the results of XAI methods evaluated by medical experts. However, several recent reviews of XAI techniques noted that, among their reviewed papers, they did not find any paper where a medical expert interpreted the results produced by an XAI method.[142,143,145] Hence, this is an important research direction for the field of AD-related classification with ML methods.

Finally, it should be noted that interpreting black box models is not the only approach to achieving interpretable models or discovering biomarkers. Despite the current popularity of black box models like DNNs, SVMs and decision-tree-based ensembles, traditional classification algorithms that directly produce 'white box' (interpretable) models can also be effective, and sometimes they are competitive with more complex black box classifiers. For example, decision tree models (consisting of a single tree, not an ensemble) are usually considered interpretable,[147] as long as the tree is not too large; and a traditional decision tree algorithm, J48, achieved the best predictive performance among six classification algorithms (including SVM).[148] When using white box models, candidate biomarkers can, in principle, be identified by directly examining the effect of each feature in the model,[147] without necessarily using a separate feature importance measure as in the case of black box models.

ML-driven discoveries and the applications in the AD field

Data-driven research on AD has contributed enormously to the knowledge about pathology, genetic etiology, biomarkers and target discovery for future drugs, depending on the type of the data features investigated. For example, a study published in 2021 reviewed 1442 research publications that used ADNI data[149] to obtain data-driven models of disease progression, progression of Aβ and tau, biological classification, prediction of an individual's risk of progression and automated diagnosis and prognosis, among others. The overall assessment of findings from these data-driven investigations[149] not only supported the Aβ and tau biomarker profiles and validated the previously proposed hypothetical temporal model of the AD biomarkers[150] but also offered evidence for heterogeneity of the disease.[151] The temporal model of biomarkers proposes a sigmoidal increase in abnormality of each biomarker, where different biomarker abnormalities start at different times during the disease progression, starting with CSF Aβ42, followed by the PET amyloid imaging, the CSF tau and neurodegeneration measured by FDG PET or structural MRI, all occurring before clinical symptom manifestations.[150] Beyond Aβ and tau models, ML applied to various sources of AD data has helped characterize the impacts of cardiovascular disease,[152] metabolic syndrome,[153] immune response,[154,155] cognitive reserve[156] and sex effects.[157] For example, it has been shown through the analysis of fluid biomarkers and genetics that a microglial transmembrane receptor TREM2 can attenuate the detrimental impact of APOE ε4.[149,154]

Additionally, data-driven investigations using various neuroimaging have been used to identify brain regions of early metabolic,[158] structural[47,158,159] and functional change in AD,[70,160] and regions of tau and Aβ depositions.[161,162] ML algorithms using these neuroimaging data have been developed for a noninvasive AD diagnosis and prognosis,[116,118,144,163,164] conversion from MCI to AD,[66,119,165] classification of stages of AD[107] and patient stratification.[166] One promising application is brain age estimation, which uses structural MRI to predict biological brain age, where the discrepancy between predicted and chronological age could serve as a biomarker for neurodegeneration.[157,167] This biomarker shows strong correlations with established AD pathology markers such as Aβ and tau.[157] Another key advancement lies in ML-based detection of WMHs, which are associated with accelerated brain aging and structural abnormalities in AD.[168,169] Omics studies have been particularly useful in providing large amounts of data for patient cohorts. For example, ML applied to proteomic studies validated the temporal profiles of the amyloid and tau pathways.[170] A recent meta-analysis of seven datasets of AD brain proteome identified 2698 differentially expressed proteins out of 12 017 proteins and genes, including 35 previously reported AD genes and risk loci. The identified proteins are those enriched in multiple cell types, indicating the involvement of neurons, microglia, astrocytes, oligodendrocytes and epithelial cells in AD pathology.[170]

In one recent study,[171] specific genetic variants and Aβ parameters were identified for two different subtypes of late-onset AD (i.e., the inflammatory and noninflammatory subtypes). The study was aimed at developing improved mouse models of late-onset AD by using the AMP-AD database (the NIH Accelerating Medicines Partnership Program for Alzheimer's Disease study) along with transcriptome data from existing mouse strains. By applying several linear and nonlinear ML methods, including SVM, random forest and neural network, followed by an analysis of variable

importance, the polygenic combinations that were most influential in modeling the disease were identified and prioritized.

An example contribution of ML to the discovery of novel drug targets for AD is an ML framework that identified candidates for drug repurposing for AD using the AMD-AD cohort data.[172] The ML framework identified associations between the stage of AD (mRNA profiles occurring in early, mid or late AD) and differential gene expression in neuronal cells perturbed by these drugs. Drugs whose gene expression profiles correlated best with the AD stage were found to target proteins involved in regulating innate immunity, autophagy and microtubule dynamics.

Concluding remarks and future perspectives

AD is a debilitating long-term disease and a major unmet medical need from a drug discovery standpoint. The past couple of decades have seen a surge in research investments resulting in AD-related scientific discoveries and unprecedented accumulation of biomedical and clinical data. Expert use of ML algorithms is indispensable to realize the full potential of the data. In particular, the landscape of longitudinal patient data offers new opportunities for data-driven research approaches for knowledge discovery around AD pathophysiology, as well as the identification and validation of disease biomarkers for prediction and early diagnosis of AD, and patient stratification. With the help of ML, the longitudinal clinical, biomedical and lifestyle attributes of patients and controls can be analyzed more efficiently to develop all-encompassing models of the AD time course that incorporate emerging pathophysiological aspects such as neuroinflammation pathways and the complement system,[173,174] roles of glial cells[18,175] and astrocytes, gene regulation pathways,[176] mitochondrial dysfunction,[177] gut microbiome,[178] and co-morbidities such as infections[179] and diabetes.[180] Despite the abundance of research on ML applied to AD (as evident from numerous research publications), in general these models have not been translated into real-life clinical applications. The real-life implementation of these AD models requires further developments in the interpretation and validation of ML models to ascertain their reliability.

In view of the points discussed within this manuscript and the examples provided above, more effort should be focused on analyzing and interpreting the workings of the ML models and deciphering the impact of different features in the model, to identify the most important features in the model. Model interpretability not only serves as a reliability test but also leads to better accessibility of models to scientists and clinicians outside the ML community. During model interpretation, comparisons are made between the model's use of features (e.g., biomarkers) and the existing scientific knowledge or working hypothesis, and the plausibility of the model's findings (i.e., its scientific validity) is assessed. This requires biomedical and clinical knowledge of AD and an understanding of the predictive features used by the model. AD models should be comprehensible by humans and provide useful information about associations and patterns in data. Also, local interpretability methods, which explain a model's specific prediction for each individual patient (as opposed to a global interpretation of the model as a whole) are important to provide explanations that take into account the particular characteristics (feature values) of each patient. In addition, other forms of model interpretation include providing information regarding the uncertainty of each prediction (e.g., the AD status prediction) and interpretation of the model's predictions by examples.[181]

As discussed in the previous section, in the past few years, there has been an increasing interest on using XAI techniques to interpret black box models (like DNNs and ensembles) for AD-related classification, and the results of applying these techniques are now discussed in many papers, as summarized in recent reviews of this area.[142,143,145] Despite the progress in this area, the use of XAI techniques for analyzing AD-related black box models still has some important limitations, and requires more research. In particular, there is a lack of 'ground truth' for evaluating the results of an XAI technique (i.e., there is no completely objective, formal way to show that the result of an XAI technique is better than the result of another, because model interpretability has a strongly subjective nature).

One approach to cope with the subjective nature of model interpretability consists of asking medical experts to evaluate the results of XAI techniques,[182,183] preferably a number of experts (not just one), to get a more robust evaluation. This approach is particularly important in AD-related classification (and other biomedical problems), where human lives are at stake. However, the three aforementioned recent reviews of XAI techniques applied to AD-related classification have consistently identified a lack of studies where a medical expert interpreted the results produced by an XAI method.

Moreover, it is recommended to test the validity of ML models using data from multiple sources (different clinics, neuroimaging settings and biomedical laboratories). This is in addition to the usual model validation methods, such as internal and external validation tests, and is especially important with the less interpretable black box models. A real estimate of the model's performance, when applied to new patients, can only be achieved by evaluating its prediction accuracy using a test dataset from an independent database. There are few AD models in the literature that have used multiple sources of patient data for in-depth analysis of model accuracy.

A further challenge for clinical applications of ML models is their generalizability issue.[184] It could be envisaged that generalizability requires that the training dataset (i.e., the population of patients and controls used for model development) is a good representative sample of the clinical populations for which the models are intended. This potentially includes the similarity of distribution of ethnicities, genetic variability, age range and environmental and/or lifestyle factors between the dataset and the future patient populations. Notably, the designed AD datasets from clinical trials usually incorporate a similar number of AD and control subjects (i.e., a dataset with a balanced class distribution that helps ML algorithms to achieve a high predictive accuracy). However, the situation is very different in real-life screening scenarios where the large majority of patients or clients are expected to be non-AD, leading to a dataset with a very imbalanced class distribution. This highlights the necessity of implementing rigorous model validation strategies such as methods to estimate the posterior distribution of the accuracy,[185] providing a reliability measure for each prediction based on the similarity of the individual's features (clinical, genetics, environmental) to the model's training set population.

The above scenario involves the concept of 'dataset shift' in the ML literature. That scenario involves a shift of the class distribution between the training dataset and the real-world application dataset; but dataset shift can also involve a shift in the distribution of the features' values. There are ML methods to detect dataset shift and try to correct the model to cope with the detected shift[186,187]; but such dataset shift methods are understudied in the context of AD classification.

Besides providing a prediction for AD, ML algorithms can help with knowledge discovery by detecting associations and patterns within the data that are otherwise unidentifiable without these ML algorithms. These patterns and associations can direct researchers to new disease hypotheses or biomarkers. However, the credibility of such extrapolations is heavily reliant on the validity of these computer models as explained above. This necessitates a comprehensive critical analysis of these findings and triangulation strategies (e.g., multiple data sources and multiple ML techniques).

The heterogeneity of AD is an additional complication in the ML modeling of this disease, compromising the model accuracy and the effectiveness of biomarker discovery. The heterogeneity of AD means that there could be some rarer variants of the disease within the patient populations in the training or test datasets with a potentially different pathological and/or clinical disease course. This necessitates patient stratification studies, which is another understudied subject within this disease area. The heterogeneity of AD also complicates the statistical identification of specific biomarkers for potential AD variants, especially in the case of low frequency of these within patient populations. Using the analogy from GWAS studies, which detect phenotype (e.g., disease) associations with common genetic variants, specific algorithms might need to be designed to cope with phenotype associations with low-frequency variants.[188]

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Author contributions

The authors contributed equally to all aspects of the article.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Figure legends

Figure 1. Frontal cortex stained for amyloid plaque (green) and p-tau (red), depicting normal brain (no-plaque), neuritic and non-neuritic plaques in the brain. Amyloid plaque with 7F2 positivity is considered neuritic and without 7F2 positivity is considered non-neuritic. Adapted, with permission, from Ref[6].

Figure 2. Supervised and unsupervised machine learning methods applied to AD. Unlike unsupervised methods, supervised methods incorporate the known AD status of patients (labels) in the learning process.

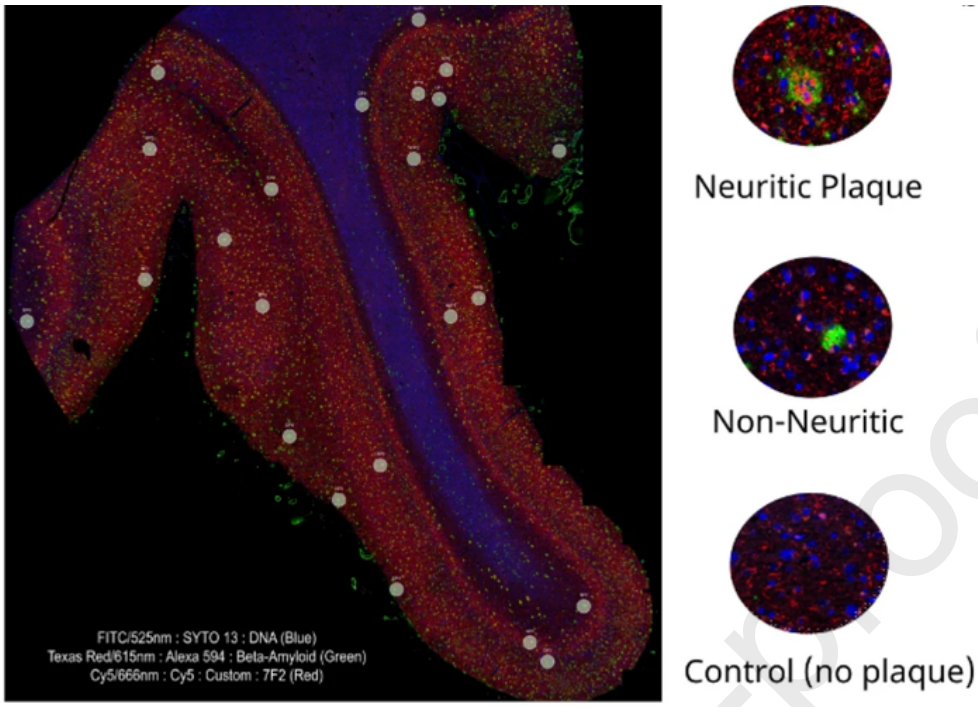
Figure 3. Cortical ROI depiction with labels based on the DKT cortical labeling protocol displayed in the ROYGBIV interactive online brain image viewer used to label the Mindboggle-101 data are displayed on a left cortical surface. Adapted, with permission, from Ref[58].

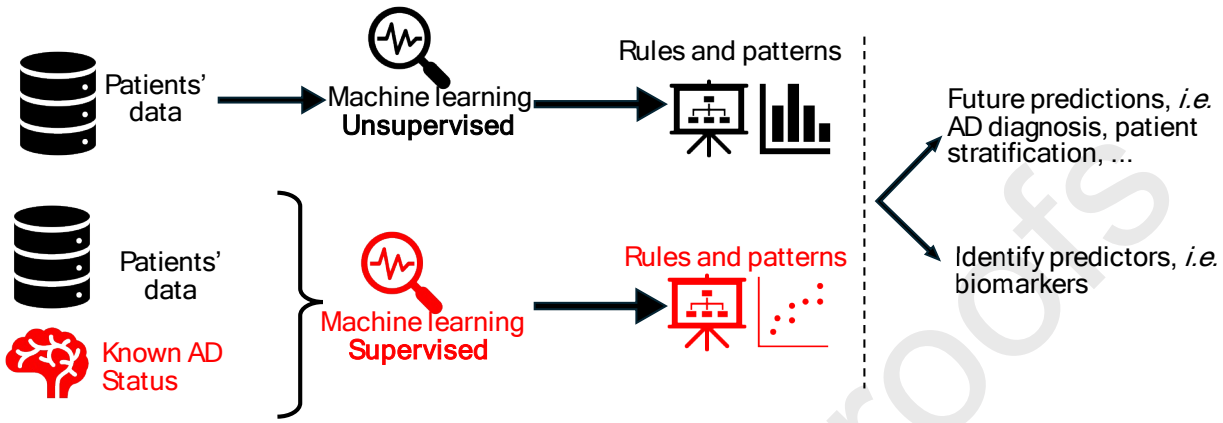
Table 1. Summary of neuroimaging techniques used in AD

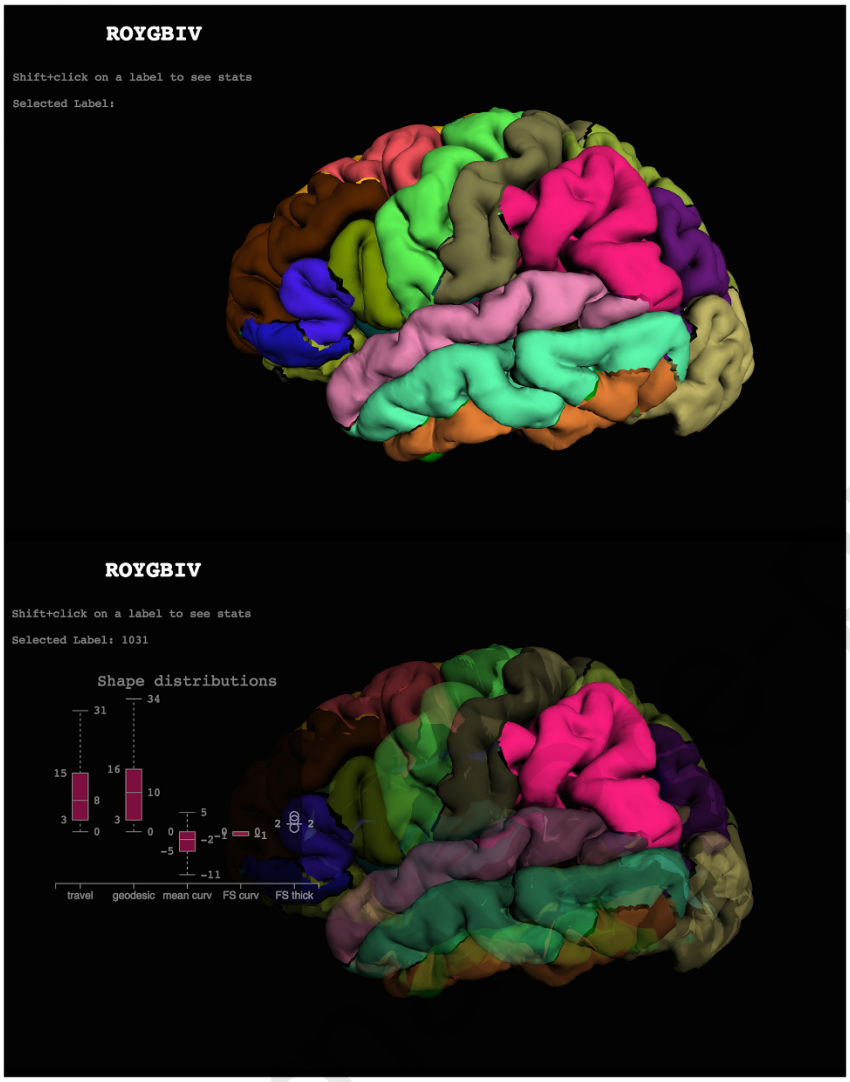
Modality	Biomarker(s)	Contribution to AD diagnosis
Structural imaging		
T1-w MRI	GM and WM volumetric, cortical thickness, brain surface	Measures brain volume or cortical thickness; visualizes anatomical structural changes and brain atrophy
T2-w MRI	Tissue characteristics	Detects cerebral microbleeds due to increased fluid or water content in AD progression; detects brain inflammation
FLAIR	FLAIR signals	Visualizes brain lesions, such as white matter hyperintensities
DTI	Fractional anisotropy, mean diffusivity, radial diffusivity, axial diffusivity	Visualizes white matter integrity and microstructural changes
Functional imaging		
fMRI	Changes in blood oxygenation levels to infer neural activity	Assesses functional connectivity, activity and activation patterns associated with specific tasks or stimuli
rs-fMRI	Spontaneous fluctuations in the BOLD signal to map functional networks and connectivity via ALFF, ReHo, functional connectivity	Assesses functional connectivity and activity patterns in the brain

PET (FDG-PET and amyloid PET)	A nuclear imaging technique that measures functional activities, visualizes biological processes such as protein aggregation and glucose metabolism	Visualizes and quantifies amyloid and tau pathology, as well as changes in glucose metabolism
SPECT	A nuclear imaging technique that measures blood flow in the brain to distinguish active regions from non-active ones	Provides information on cerebral perfusion and allows visualization and quantification of amyloid and tau pathology

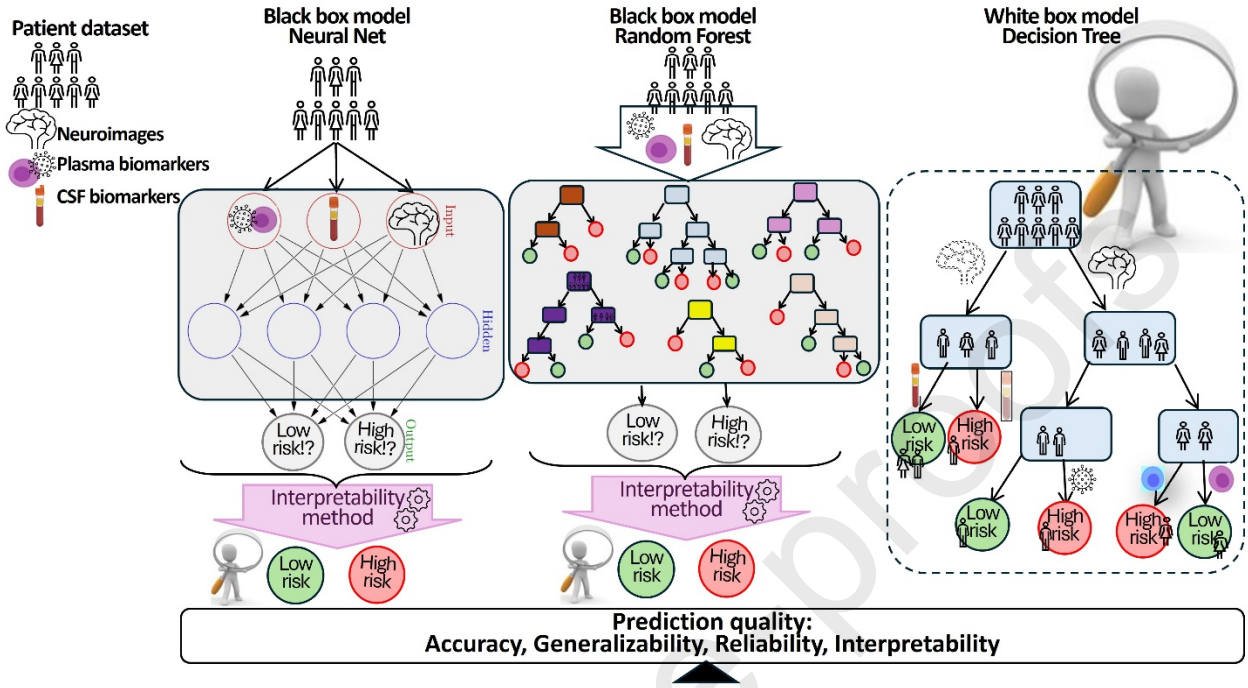
Abbreviations: AD, Alzheimer's disease; amyloid PET, amyloid positron emission tomography; BOLD, blood-oxygen-level-dependent; DTI, diffusion tensor imaging; FDG-PET, fluorodeoxyglucose positron emission tomography; FLAIR, fluid-attenuated inversion recovery; fMRI, functional magnetic resonance imaging; GM, grey matter; rs-fMRI, resting-state functional magnetic resonance imaging; SPECT, single photon emission computed tomography; T1-w MRI, T1-weighted magnetic resonance imaging; T2-w MRI, T2-weighted magnetic resonance imaging; WM, white matter.







Graphical Abstract



Highlights:

- The rise of longitudinal patient data and AI techniques enables knowledge discovery in Alzheimer's disease
- Machine learning offers improved diagnosis, progression tracking and therapeutics outcome assessment
- Understanding AI 'black box' models is crucial for trustworthy predictions and biomarker discovery
- Clinical adoption of AI requires better accuracy, validation, generalizability, accessibility and interpretability

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Conflict of interest:

The authors have disclosed that they have no conflicts of interest.