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Review

Neuropsychiatric Symptoms and Commonly Used Biomarkers of Alzheimer's Disease: A Literature Review from a Machine Learning Perspective

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Abstract. There is a growing interest in the application of machine learning (ML) in Alzheimer's disease (AD) research. However, neuropsychiatric symptoms (NPS), frequent in subjects with AD, mild cognitive impairment (MCI), and other related dementias have not been analyzed sufficiently using ML methods. To portray the landscape and potential of ML research in AD and NPS studies, we present a comprehensive literature review of existing ML approaches and commonly studied AD biomarkers. We conducted PubMed searches with keywords related to NPS, AD biomarkers, machine learning, and cognition. We included a total of 38 articles in this review after excluding some irrelevant studies from the search results and including 6 articles based on a snowball search from the bibliography of the relevant studies. We found a limited number of studies focused on NPS with or without AD biomarkers. In contrast, multiple statistical machine learning and deep learning methods have been used to build predictive diagnostic models using commonly known AD biomarkers. These mainly included multiple imaging biomarkers, cognitive scores, and various omics biomarkers. Deep learning approaches that combine these biomarkers or multi-modality datasets typically outperform single-modality datasets. We conclude ML may be leveraged to untangle the complex relationships of NPS and AD biomarkers with cognition. This may potentially help to predict the progression of MCI or dementia and develop more targeted early intervention approaches based on NPS.

Keywords: Alzheimer's disease, cognition, deep learning, machine learning, neuropsychiatric symptoms

INTRODUCTION

Research on machine learning (ML) techniques for dementia and Alzheimer's disease (AD) is expanding. Reviews and original studies have examined ML

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in the context of AD biomarkers derived from neuroimaging, cerebrospinal fluid (CSF), or plasma. For example, a meta-analysis reported that biomarker-based ML techniques might increase the sensitivity and specificity of the AD diagnosis [1]. In a study conducted in a community-based sample, ML models of plasma-derived AD biomarkers showed good predictive accuracy in identifying persons at high risk of dementia [2]. Multiple recent review articles examined the benefits of ML and various AD biomarkers [1, 3–9].

In addition to biomarkers of AD, researchers have examined potential risk factors for the development of cognitive impairment in old age. One of these factors are neuropsychiatric symptoms (NPS) such as depression, apathy, or anxiety, which are common in older adults regardless of cognitive status. Studies have shown that NPS are associated with an increased risk of mild cognitive impairment (MCI) and dementia [10]. We and others have shown that NPS are associated with AD biomarkers in brain aging [11, 12]. However, to date, less is known as to whether ML approaches are also useful in investigating the associations between NPS and AD biomarkers in brain aging.

ML algorithms, such as statistical ML and deep learning methods, are effective at detecting complex patterns in high-dimensional data. Deep learning has even surpassed human performances in pattern recognition in standard computer vision tasks such as object recognition [13], image classification [14], or complex strategic games [15, 16], just to name a few. These techniques have been explored in medical imaging research to process high dimensional data such as magnetic resonance imaging (MRI), positron emission tomography (PET), X-Ray, and computed tomography (CT). Considering a broad spectrum of medical research, ML techniques have shown promising results and new directions, such as in numerous medical imaging classification studies [17, 18], cross tracer harmonization [19], cross-modality translation [20], i.e., synthesizing artificial PET scans from CT scans and medical image segmentation tasks [21] which is otherwise laborious and time-consuming for human experts.

In light of the growing amount of research on ML in dementia and AD in recent years and considering the importance of understanding the pathways linking AD biomarkers and NPS with cognitive outcomes, ML approaches may have tremendous potential to interrogate NPS and AD biomarkers jointly in the context of brain aging. Therefore, we conducted a literature review to provide an overview of research on ML in NPS (e.g., depression, anxiety, apathy), commonly studied AD biomarkers (e.g., neuroimaging biomarkers such as PET or MRI), and cognitive outcomes (e.g., cognitive domains, cognitive status).

METHODS

To review existing literature on state-of-art ML techniques that examined NPS, cognition, and AD biomarkers, we conducted a PubMed search by May 31, 2022, using the following search terms that include relevant keywords related to NPS, AD biomarkers, and cognition: ("machine learning" [Title/Abstract] OR "deep learning"[Title/Abstract]) AND ("neuropsychiatric symptom*"[Title/Abstract] OR "depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms] OR "anxiety"[MeSH Terms] OR apathy[Title/Abstract/ OR agitation [Title/Abstract] OR sleep[Title/Abstract] OR irritability[Title/Abstract] OR delusion[Title/Abstract] OR hallucination[Title/Abstract] OR euphoria[Title/Abstract] OR disinhibition[Title/Abstract] OR aberrant motor behavior[Title/Abstract] OR eating[Title/Abstract]) AND ("Alzheimer's disease biomarker*[Title/Abstract] OR amyloid OR PiB-PET[Title/Abstract] OR amyloid PET OR Tau PET OR tau OR FDG-PET OR MRI OR amyloid beta OR amyloid β OR Aβ42 OR Aβ42/ Aβ40 OR phosphorylated tau OR p-tau OR total tau OR t-tau OR t-tau/Aβ42 OR p-tau/Aβ42 OR cerebrospinal fluid OR CSF OR neurofilament light chain OR NfL[Title/Abstract]) AND ("cognition OR cognitive impair* OR cognitive trajectories OR memory OR attention OR executive function OR language OR visuospatial OR subjective cognitive impairment OR SCI OR mild cognitive impairment OR MCI OR dementia OR Alzheimer's disease).

We opted to include both review articles as well as original research studies examining ML in the context of NPS, AD biomarkers, and/or cognition. To focus more on recent works, we excluded articles published before 2017. Two authors (JS and MMRS) independently screened the titles, abstracts, and full text of all articles retrieved by the PubMed search based on the pre-defined inclusion and exclusion criteria. We screened the references of the retrieved articles for further research that may be relevant to our review but was not retrieved in the PubMed search. Literature management and data extraction were performed using Excel Software (Microsoft).

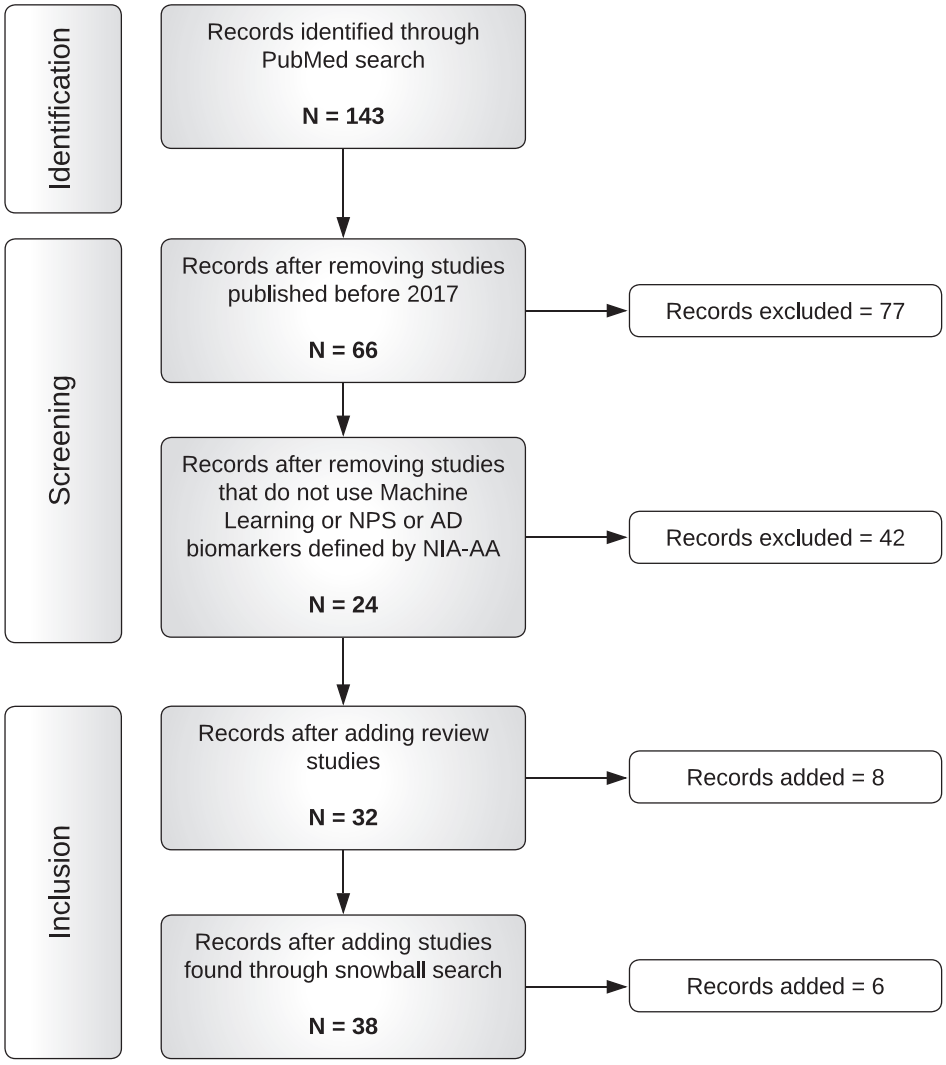

Fig. 1. Flowchart of literature search.

We extracted the article's title, variables/ measurements and ML models used, information about the dataset or study setting, study sample demographics, and a summary of main findings.

RESULTS

The PubMed search yielded a total of 143 articles. We excluded 77 articles published before 2017 and 42 that did not use any ML technique-based study analysis or did not include studies of NPS, or biomarkers related to AD or dementia as defined in the NIA-AA research framework [22]. We added 8 existing review articles that analyzed research studies applying ML methods to multiple AD biomarkers and added 6 articles through a snowball search from citations i.e., selecting relevant works from the article's related works retrieved from PubMed search. A total of 38 studies were finally included in this review. Figure 1 shows a flowchart of the literature search conducted for this review.

In the results section, we first describe one study that applied ML to examine NPS, AD biomarkers, and cognitive outcomes. Then, we present four studies that used ML in the context of NPS and cognitive impairment. Finally, the main part of the results section focuses on studies that used ML to examine AD

Table 1
Characteristics of reviewed literature on machine learning with NPS and AD biomarkers in context of brain aging

Author/s	Year	Dataset	Machine Learning Model	Participant Information	Key findings
Gill et al. [23]	2020	ADNI	Logistic Model Tree	Age: 55–90 y Cognitive status: NC and MCI at baseline	○ Study predicted future cognitive status using baseline clinical, neuropsychiatric, and structural MRI data. ○ The machine learning model found that MBI total scores had more prognostic utility than clinical or volumetric variables for diagnostic prediction. ○ The model identified 2–7 features that can optimally classify participants.

ADNI, Alzheimer's Disease Neuroimaging Initiative; NC, normal cognition; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; MBI, Mild behavioral impairment.

biomarkers in the context of brain aging. We first provide an overview of existing literature reviews, followed by a section on original studies. This section is further subdivided based on the biomarker and ML modalities used, i.e., MRI biomarkers, MRI biomarkers and statistical machine learning, MRI biomarkers and deep learning, PET biomarkers, fMRI biomarkers, and combination of imaging and other modalities.

Machine learning: NPS, AD biomarkers, and cognitive outcomes

From all the studies included in this review, only one study [23] utilized ML to combine NPS and AD biomarker information (please refer to Table 1). The study was derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database and demonstrated that NPS, in addition to neuroimaging-based measures of brain morphology, improved the prediction of MCI or dementia. The investigators combined mild behavioral impairment (MBI) scores with MRI and clinical features. A total of 235 features were used. In the study, the features were first ranked by evaluating the information gained from each feature in the context of target classes (AD, MCI, or healthy controls), and selected top features were used for the AD classification. Two-class (i.e., AD vs. healthy controls) and three-class (i.e., AD vs. MCI vs. healthy controls) decision tree based logistic model tree classifiers were developed. The models trained with MBI scores performed better than models trained on only clinical and MRI features. Among the seven features required for the three-class classification, four were neuroimaging markers (i.e., left hippocampus volume, cortical thickness and volume of the entorhinal cortex, and cortical thickness of the left middle temporal gyrus), and three were NPS markers (i.e., MBI total score, impulse dyscontrol score, and emotional dysregulation score).

Machine learning: NPS and cognitive impairment

We identified four studies that examined the effectiveness of ML techniques about NPS (see Table 2).

Two studies [24, 25] used random forest algorithms, a combination of multiple decision trees. In [24], the authors compared multiple ML models using demographics, electronic health record, and NPS data to predict conversion from MCI to dementia and concluded that random forest models outperformed other ML models. Subsequent analysis showed that global NPS measures are critical in assessing the risk of cognitive impairment and conversion to dementia. In [25], the authors used electronic health record data to predict the prevalence of NPS in dementia. It successfully detected the presence of psychotic and/or depressive symptoms in dementia patients.

Deep learning such as artificial neural networks used in [26] showed improved results in distinguishing AD dementia from MCI and AD dementia from MCI and unimpaired controls compared to statistical ML models (e.g., random forest). Study [27] used a Long Short-Term Memory (LSTM) model to detect agitation episodes in persons with dementia. The study used multiple modalities of data collected from sensors worn by participants, such as physical movement, heart and blood pressure rate, and other pertinent physiological data collected over time. LSTMs are techniques that can model long-term dependencies and find patterns from sequences of data points. While the evidence from this study was not strong, it provides a first approach to analyzing the risk of agitation in persons with dementia.

Table 2
Characteristics of reviewed literature on machine learning with NPS in context of brain aging

Author/s	Year	Dataset	Machine Learning Model	Participant Information	Key findings
Mallo et al. [24]	2019	Compostela Aging study	Random Forest	78 CU, 50 MCI	○ Prediction of conversion from MCI to dementia using socio-demographic, basic health status, and NPS proxies using machine learning model gave a 67% F1-score, and 88% accuracy. ○ Total 9 ML classifiers were explored by authors, random forest performed best. ○ NPS proxies such as NPI-Q total severity score, NPI-Q total stress score, and GDS-15 total score were found to be most predictive of conversion, consistent with NPS literature related to dementia.
Mar et al. [25]	2020	Basque Health Service's database	Random Forest	4,003 dementia patients	○ Machine learning models detected psychotic and depressive symptoms in dementia patients ○ Symptoms in psychotic cluster model had more discriminatory power.
Palermo et al. [27] .	2021	UK DRICR&T Centre	LSTM	46 dementia patients	○ Study used data collected from various sensors at multiple time points to detect agitation episodes. ○ LSTM models can model long range dependencies and were able to predict risk of agitation with 75% accuracy
Kang et al. [26]	2019	Clinical research center for dementia of South Korea	3-layer ANN, Logistic Regression	N = 14,926:3217 NC, 6002 MCI, 5707 ADD	○ Artificial Neural Network outperformed logistic regression model in 2-class and 3-class classification. ○ Neural net can predict NC, ADD, and MCI with 97% accuracy using neuropsychological data

UK DRICR&T Centre, UK Dementia Research Institute Care Research and Technology Centre; LSTM, Long Short-Term Memory model; ANN, Artificial Neural Network; CU, cognitively unimpaired; NC, normal cognition; MCI, mild cognitive impairment; ADD, Alzheimer's disease dementia; NPI-Q, Neuropsychiatric Inventory-Questionnaire; GDS-15, Geriatric Depression Scale-15 items; NPS, Neuropsychiatric Symptoms.

Machine learning: AD biomarkers in the context of brain aging

Overview of existing literature reviews on AD biomarkers and machine learning

Several review articles provide an overview of research studies involving ML techniques using AD biomarkers. The research all observed a strong potential for leveraging these methods for AD diagnosis, early prediction, drug development, and potential inclusion in clinical workflows. In addition, the importance of combining more than one modality data to improve performance was well-recognized.

Four reviews [1, 3, 6, 9] summarized original research works and architectures of deep learning techniques that used imaging biomarkers such as MRI and fluorodeoxyglucose (FDG)-PET in diagnostic classification studies, i.e., to identify persons with AD from cognitively unimpaired controls. Two reviews [6, 9] highlighted the importance of multi-modal neuroimaging to improve the prediction performance. Specifically, review [6] showed that the average accuracy of diagnostic classification increased from 86% to 96% as investigators shifted from single-modality to multi-modality data, i.e., MRI alone achieved 86%, FDG-PET alone showed 87% accuracy, MRI combined with FDG-PET reached 90%, MRI, FDG-PET and CSF together achieved 93%, and FDG-PET with AV45-PET achieved 96% accuracy. In [9], convolutional neural network, a deep learning model using multimodal PET images (FDG-PET and ^{18}F-florbetapir PET) showed better performance for AD vs. normal cognition classification and the prediction of MCI to AD conversion than using one modality alone.

Analogous to combining multiple imaging modalities, four reviews [1, 3, 5, 8] focused on works that combine other modalities such as blood-based biomarkers, cognitive tests, diffusion tensor imaging, Tau-PET, cerebrospinal fluid biomarkers, and other clinical data. Overall, these reviews demonstrated that ML with novel biomarkers might increase the sensitivity and specificity of AD diagnosis. In particular, one review [1] reported studies that use neuroinflammation biomarkers, [5, 8] focused on biomarkers from language features analysis

using modern natural language processing techniques based on speech and electronic health record data, respectively. Language features are important indicators of cognitive state, as communication skills and interpersonal behavior deteriorate in many neurodegenerative diseases. Clinical notes often consist of rich clinical information to support the diagnosis. Another growing area of research interest is the application of ML to omics data, which contains genomics, transcriptomics, proteomics, and metabolomics that may reveal biomolecular markers associated with AD [4]. Insights from omics data help understand dynamic changes related to progression from an unimpaired to disease stage, which may be particularly interesting in the context of brain aging and AD [28]. Using genetic data of an individual, along with other clinical information and lifestyle factors, has been explored to develop targeted treatments and therapies with personalized biomarker assessment. The potential of ML lies in stratifying subjects based on these numerous factors, including with clustering algorithms [29]. ML algorithms can model high-dimensional data better compared to conventional statistical analyses, and this has enabled the AD diagnosis, prognosis, and early detection to be extended to other omics such as epigenomics, metagenomics, interactomics, and microbiomics [4].

A commonly known limitation of advanced ML approaches is the lack of transparency of its inner working, as highlighted in two reviews [5, 9]. Deep learning architectures such as convolutional neural networks contain non-linear convolutional layers which make it difficult to interpret the relative importance of features in the original data space. To address the issue, [7] attempted to study the interpretability of ML models. Specifically, the ML model - XGBoost (eXtreme Gradient Boosting) was developed using a combination of data modalities. The authors then used Shapley Values, an approach inspired by game theory principles, to explain the marginal contribution of features towards a prediction. The author concluded gender/ sex and Apolipoprotein E (*APOE*) ε4 features were the least decisive factors for having an AD diagnosis, whereas cognitive test scores showed the highest discriminative power.

Overview of original research on other AD biomarkers and machine learning

We first presented original studies focusing on developing ML using a single imaging modality for the classification of individuals or modeling the non-linear associations of imaging modality and cognitive status of individuals based on standardized neuropsychological testing such as Mini-Mental State Examination (MMSE) scores. The research on multimodality is then summarized. The most used imaging modalities were structural MRI (sMRI) and functional MRI (fMRI), with a few studies focusing on PET. The remaining ones used multiple imaging modalities at once or a combination of imaging and other modality information such as neuropsychological tests, demographic information such as age, gender/ sex, and education, behavioral measures, the mean reaction time of responses to target stimuli, clinical features related to cognitive outcomes, *APOE* ε4, Tau-PET, or speech features.

MRI biomarkers

MRI is one of the few non-invasive imaging modalities that have been explored most for AD biomarker analysis, mainly due to the availability of large-size datasets like ADNI, Open Access Series of Imaging Studies, Australian Imaging Biomarkers and Lifestyle Study of Ageing (AIBL), or National Alzheimer's Coordinating Center (NACC). In this review, we identified 11 original studies on ML and MRI biomarkers in the context of brain aging. For an overview of these studies, please refer to Table 3.

MRI biomarkers and statistical machine learning

Morphological changes in the brain related to neurodegenerative disorders have been well detected using sMRI and different ML techniques. Support vector machine (SVM) is an effective method that transforms data in high dimensional space and finds a hyperplane that best differentiates samples in data distributions to their class labels. Two studies [30, 31] used an SVM model trained on MRI features to distinguish between clinical groups. Precisely, the model developed by one study [30] differentiates early AD from old age depression, and the results highlight subtle structural changes in the latter. Similar to that, study [31] built an SVM model on features extracted using a PCA (Principal Component Analysis) and FDR (Fisher Discriminant Ratio) method on the voxel space from MRI features for identifying biomarkers in persons with MCI that convert to AD. AD patients have heterogeneous clinical characteristics. Training a single SVM model on a subset of these characteristics, manually selected as input, might produce biased results. Hence, as a successive effort [32] ensembles multiple SVM models by majority voting with different subsets of features, but always including MMSE for classifying persons with normal cognition, MCI,

Table 3
Characteristics of reviewed literature on machine learning and MRI biomarkers

Author/s	Year	Dataset	Machine Learning Model	Participant Information	Key findings
Klöppel et al. [30]	2018	Department of Geriatric Psychiatry, Mannheim, Germany, AIBL, ADNI	SVM	28 AD, 37 moderate or severe depression	○ SVM based predictive model was able to differentiate between clinically challenging scenarios such as subjects with depression and early dementia due to AD. ○ Although not useful for diagnostic decisions, authors suggest such analysis for individual analysis.
Salvatore et al. [31]	2015	ADNI	PCA, FDR, SVM	162 NC, 137 AD, 76 MCI who converted to AD within 18 months and 134 MCI who did not convert to AD within 18 months (MCInc)	○ Machine learning model highlighted similar atrophy patterns in AD and MCI patients converting to AD, suggesting MRI detectability of structural biomarkers at early stages.
Sørensen et al. [32]	2018	ADNI	Ensemble SVM	100 NC, 100 MCI, 100 MCI-converters, 100 AD	○ Ensemble classifiers are more robust and accurate than single classifiers and useful in multi-class classification.
Cao et al. [33]	2017	ADNI	Multiple kernel learning, k-NN, manifold learning	229 NC, 229 stable MCI, 168 progressive MCI, 192 AD	○ Nonlinear lower representation of data using multi kernel marginal fisher analysis. ○ Study shows using manifold learning can achieve better data representation for over sampling and dimensionality reduction. ○ Using a k-nearest neighbor classifier improves results compared to SVM approaches.
Pang et al. [35]	2019	ADNI	Semi-supervised deep Autoencoder	135 subjects	○ Deep learning approaches show effective hippocampus segmentation without the need for registration which is beneficial for AD diagnosis and assessment.
Chen et al. [36]	2021	Indira Gandhi Medical College	CNN	18 AD, 18 HC	○ CNN based methods outperform FCNN and SVM based techniques in terms of segmentation effects. ○ CNN had half the operation time in comparison to SVM and FCNN and better segmentation performance. ○ Important indicators in AD imaging such as reduction in gray matter volume and cerebral cortex were accurately segmented.
Qiao et al. [37]		ADNI, MIRIAD	CNN	368 NC, 298 AD, 446 MCI	○ The study uses contrastive loss layers in their CNN based on group categories comparative and subject MMSE ranking. ○ This help network learns better similarities of same group and subtle differences among AD, NC and MCI. ○ The CNN model takes pairs of MRIs as input.
Ambastha et al. [38]	2017	ADNI	Ensemble of CNNs, AdaBoost	100 HC, 100 AD	○ Deep learning to analyze neuroanatomical characterization of AD. ○ Developed a CNN that takes dual region inputs from MRIs that contribute towards AD. ○ The model found regional pairs that degenerate together and explain behavioral changes in AD.
Bhagwat et al. [39]	2019	ADNI	Anatomically partitioned artificial neural network	377 NC, late MCI 475, 75 significant memory concern, 149 late MCI, 278 AD	○ Study showed the effectiveness of neural network to predict cognitive scores at baseline and 1 year using high dimensional structural MRI data such as hippocampal segmentations and cortical parcellations.

(*Continued*)

Table 3
(*Continued*)

Author/s	Year	Dataset	Machine Learning Model	Participant Information	Key findings
Qiao et al. [40]	2022	ADNI	3D CNN	AD, MCI and NC subjects at 4 time points	○ Since MMSE values have ordinal relationship, authors transformed regression of MMSE into multi-class classification with multiple subnetworks. ○ Model better predicts MMSE scores at various time points compared to baseline and better highlight subtle changes in subjects.
Cui et al. [41]	2019	ADNI	CNN, RNN	198 AD, 167 progressive MCI, 236 stable MCI, 229 NC	○ A combination of 2 deep learning models; CNNs that can learn spatial features, as input to RNN which can model longitudinal features; outperforms existing methods for AD diagnosis. ○ The framework also handles for missing data. ○ Overall focus on longitudinal analysis of AD using deep learning.

AIBL, Australian Imaging Biomarkers and Lifestyle Study of Ageing; ADNI, Alzheimer's Disease Neuroimaging Initiative; SVM, support vector machine; AD, Alzheimer's disease; PCA, principal component analysis; FDR, Fisher Discriminant Ratio; NC, normal cognition; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; k-NN, k-nearest neighbor; (F)CNN, (fully) convolutional neural networks; HC, healthy controls; MIRIAD, Minimal Interval Resonance Imaging in Alzheimer's Disease; MMSE, Mini Mental Status exam; RNN, recurrent neural network.

AD, and MCI that converted to AD at follow-up. Study [33] showed that SVM results could be outperformed by using manifold learning as dimensionality reduction for AD vs. MCI and multi-class classification datasets. The study applied a multi-kernel learning framework that allows learning an optimal combination of base kernels and used a k-nearest neighbor model for classification. It also investigated kernel weights for regions of interest (ROI) identification and external validation.

MRI biomarkers and deep learning

[34] demonstrated the superior performance of convolutional neural networks (CNNs) compared to statistical ML methods for AD diagnosis. Deep neural networks are particularly effective at image classification and segmentation of relevant objects in images or regions of interest (ROI) in medical scans, e.g., [35, 36]. One research [37] used a 3-dimensional convolutional neural network consisting of 4 convolutional layers and two dense layers along with a contrastive loss function for a diagnosis classification, i.e., persons with AD versus normal controls versus MCI. Study [38] developed an ensemble of convolutional neural networks that take in dual region inputs to find cliques of brain regions that degenerate with AD progression for atrophy-based neuroanatomical characterization.

About longitudinal analyses, tracking patterns in structural brain changes related to AD progression are crucial to understanding the pathophysiology of AD. To identify relationships between morphological patterns in imaging scans and cognitive scores such as MMSE, two studies [39, 40] used convolutional neural network-based models. Study [39] adopted a unique approach of anatomically partitioned artificial neural network which combines two high-dimensional structural MRI measures, i.e., hippocampal segmentations and cortical thickness, as input to the model. Study [40] used whole MRI scans at baseline and future time points by transforming regression of MMSE into multi-classification with discrete MMSE values. In contrast, study [41] constructed a combination of 3-dimensional CNN and recurrent neural network (RNN) architectures using T1-MRI scans at multiple time points. The features extracted from each MRI scan are then input to cascaded bi-directional gated recurrent (a type of RNN) units to perform classification between persons with AD, MCI, and healthy controls. Since the deep learning architecture used in this study can track AD progression across longitudinal MRI scans, it performs better than single time point MRI scan-based models.

PET biomarkers

PET based imaging measurements have been used to define AD in its preclinical stage and allow investigation of progression of AD [22]. Here we included three studies on ML and PET biomarkers in the

Table 4
Characteristics of reviewed literature on machine learning and PET biomarkers

Author/s	Year	Dataset	Machine Learning Model	Participant Information	Key findings
Son et al. [42]	2019	Florbetaben Imaging in Alzheimer's and Related Neurological Conditions (FLORIAN)	2D and 3D CNNs	85 NC, 233 MCI, and 112 AD	○ Deep learning models make diagnostic predictions differently from human expert readers of PET scans which is complementary in nature. ○ Study showed deep models outperforming humans in case of equivocal (visually ambiguous) scans and 2D CNNs performing better than 3D CNNs.
Choi et al. [45]	2020	ADNI, UK PD Brain Bank	3D CNN	243 AD, 393 NC, 666 MCI, and 62 PD subjects with dementia	○ Developed a deep neural network that can capture cognitive signatures of multiple neurodegenerative diseases; here AD, MCI and PD and analyze their variations. ○ Also showed benefits of transfer learning in case of small datasets.
Whittington et al. [43]	2021	ADNI	Linear regression	NC, MCI, and subjects with dementia for various studies	○ Fitting a linear regression at the voxel space on a chronological dataset, authors propose a new algorithm for local and global longitudinal tau quantification. ○ Method accounts for more complex deposition of tau than of amyloid.

CNN, convolutional neural networks; NC, normal cognition; MCI, mild cognitive impairment; AD, Alzheimer's disease; PD, Parkinson's disease; PET, Positron emission tomography; ADNI, Alzheimer's Disease Neuroimaging Initiative.

context of brain aging (please refer to Table 4 for an overview). Study [42] developed a convolutional neural network model to predict disease progression in cases of visually ambiguous PET scans and provided reassurance in clinical diagnosis and prognosis assessment. In contrast, research [43] used a simple linear regression method to quantify tau in Tau-PET scans, unlike standardized uptake value ratio (SUVR) approaches. The proposed algorithm TauIQ accounts for global and local deposition of tau and uses the existing method AmyloidIQ to derive the time of accumulation from the Tau-PET scan. It uses linear regression to generate canonical images, which are input to the TauIQ algorithm with MRI scan to create local and global tau depositions.

Neuroimaging based studies often face the challenge of scarcity of labeled data to train supervised ML algorithms [22]. This is particularly true for PET studies due to the high cost and accessibility of PET imaging. Hence some researchers have explored transfer learning, a common technique in the ML field to transfer knowledge from one learning task to another learning tasks [44]. Study [45] built a custom 4-layer 3-dimensional convolutional neural network trained on FDG-PET images of persons with AD and normal cognition, and then tested this model for AD versus MCI classification, and also MCI versus Parkinson's disease classification. Such transfer learning techniques are effective in diagnosis tasks when the available dataset has limited image samples but can be fine-tuned or extended to other tasks.

fMRI biomarkers

In our review, we included three studies on ML and fMRI biomarkers in the context of brain aging (please refer to Table 5 for an overview). Studies that used ML on fMRI data either focused on classifying persons based on their functional connectivity patterns or on differentiating between brain states using functional networks of the brain. Much similar to regressing MMSE scores on sMRI scans of individuals, study [34] investigated the relationship between fMRI and MMSE scores using different non-linear models.

Since ML based approaches can help in analyzing morphological patterns in the brain to understand the phenomenon under inspection, researchers have explored resting state fMRI (rs-fMRI). In two studies [46, 47], the authors combined rs-fMRIs with MMSE scores for AD classification. Study [46] used rs-fMRIs to calculate group-level independent component analysis (ICA) maps, and to extract subject specific time courses and spatial ICA maps. 3D ICA maps were fed to a convolutional neural network model for classification, whereas time course functional connectivity maps were used for MMSE regression. The overall framework performed the

Table 5
Characteristics of reviewed literature on machine learning and fMRI biomarkers

Author/s	Year	Dataset	Machine Learning Model	Participant Information	Key findings
Amini et al. [34]	2021	ADNI	KNN, SVM, DT, LDA, RF, and CNN	fMRI of 675 patients	○ Deep learning approaches such as CNN significantly outperform traditional methods. ○ Study uses a multi-task feature extraction method that will adjust weights in input layers as per similarities and differences of tasks.
Duc et al. [46]	2020	Chosun University National Dementia Research Center, South Korea	3D CNN, SVR, linear regression, ensemble regression	198 NC and 133 AD	○ A framework that can jointly perform AD diagnosis with a deep learning model and predict MMSE scores using pre-processed features. ○ Results show use case of functional brain features with machine learning models for both tasks.
Jin et al. [47]	2020	From 6 different scanners of hospitals in China, and ADNI	SVM, elastic regression models	215 HC, 221 MCI, and 252 AD	○ Using a machine learning framework, authors confirmed that AD is associated with hypoconnectivity and aberrant brain activity in DMN. ○ Machine learning models can identify patterns of functional dysconnectivity aiding in diagnostic status and clinical score prediction.

ADNI, Alzheimer's Disease Neuroimaging Initiative; KNN, k-nearest neighbors; SVM, support vector machine; SVR, support vector regression; DT, decision tree; LDA, Linear discriminant analysis; RF, random forest; CNN, convolutional neural networks; fMRI, functional magnetic resonance imaging; NC, normal cognition; AD, Alzheimer's disease; MMSE, Mini Mental Status exam; HC, healthy controls; DMN, default-mode network.

classification of AD versus healthy controls and predicted MMSE scores using rs-fMRI data. In [47], the researchers focused on learning about aberrant brain activity and dysfunction of the whole-brain networks in AD. The study used SVM and ElasticNet regression model, which is a regularized linear regression model combining multiple penalties as loss functions, to identify the key fMRI features and predict cognitive status, and cognitive test scores based on connectivity data.

Combination of imaging and other modalities

In addition to individual imaging modalities discussed above, researchers used various other features such as clinical information, demographic variables, CSF biomarkers, behavioral measures, or MMSE scores for diagnosing AD. Few studies utilized features from resting state EEG and audio. We detected 8 studies on ML and multiple biomarkers in the context of brain aging that we included in this review (please refer to Table 6).

It is common to derive labels for imaging scans of individuals based on their cognitive scores, such as MMSE, and use them for classification or regression tasks. While many investigators used a combination of MMSE and MRI or fMRI in their models [32, 34, 39, 40, 46, 47], others have utilized [32, 48, 49] MRI, age, sex, and MMSE scores from the ADNI dataset for diagnosing AD. In addition, study [48] used additional datasets such as AIBL, Framingham Heart Study (FHS), and NACC for testing. The authors trained a fully connected neural network to generate disease probability maps for AD versus healthy controls classification. These maps from 200 specific locations augmented with age, sex, and MMSE scores were used to classify AD versus healthy controls using MLP. The model-predicted regions of high AD risk overlapped with the segmented areas that indicated high localized deposition of amyloid-β and tau. Frölich [50] showed that a particular combination of modalities could help increase the predictive power of ML models compared to single predictor models. Specifically, hippocampal volume and total tau were most significant in identifying MCI patients progressing to AD dementia and adding biomarkers to the SVM model improved statistical measures that could be of clinical utility, such as selecting patients for trials. Instead of using MMSE scores in cognitive status classification, study [49] segregated training groups based on cognitive profiles and trained three different classifiers including decision trees, random forest and SVM with improved accuracy comparing to benchmark approaches. The authors claimed to be independent of MMSE scores, but class segregations were performed based on MMSE scores. Study [51] constructed the analysis of brain atrophy

Table 6
Characteristics of reviewed literature on machine learning and multiple biomarkers

Author/s	Year	Dataset	Machine Learning Model	Participant Information	Key findings
Qiu et al. [48]	2020	ADNI, AIBL, FHS, NACC	FCN + MLP	229 NC and 188 AD from ADNI, 320 NC and 62 AD from AIBL, 73 NC and 29 AD from FHS, and 356 NC and 209 AD from NACC	○ Adding age, gender and MMSE information to deep learning model greatly increased performance (acc: $0.968 \pm$ pared to MRI data alone (acc: 0.834 ± 0.020)
Donnelly-Kehoe et al. [49]	2018	ADNI	Decision trees + (random forests, SVM, AdaBoost)	400 (100 each HC, MCI, converters MCI, AD)	○ Random forest performs best compared to other machine learning models. ○ Morphological features did not allow machine learning model to reach good accuracy compared to MMSE alone. ○ And hence study performs a cognitive profile dependent analysis.
Liu et al. [51]	2020	ADNI	Group Guided Fused Laplacian Sparse Group Lasso	AD, MCI, and NC at various time points	○ Study proposed a group guided fused Laplacian that can calculate overall graphs among tasks and ROIs and a graph Laplacian to capture dependent structure at time points. ○ A framework that benefits from multi-modality, multitask and longitudinal analysis shows significance.
Bhagwat et al. [52]	2018	ADNI1, ADNI2, ADNIGO, AIBL	Siamese Neural Network	LMCI, EMCI, MCI, SMC, NC, and AD	○ Follow up clinical information helps improve multi-modal performance at baseline. ○ However, 2-timepoint input offers best performance. ○ Overall approach can help identify stable and declining trajectories without strong thresholds (4-point change, time window, etc.)
Beltrán et al. [53]	2020	ADNI	Random forests, gradient boosting	NC, early MCI, stable MCI, and AD	○ Comparison of expensive vs inexpensive biomarkers with machine learning models shows a cost-effective way to screen patients that might need additional testing.
Delmotte et al. [54]	2021	Neurology Memory Clinic UZ/KU Leuven	Linear Mixed effects model	228 subjects into various ATN classes	○ A linear mixed effects model to explore effects of continuous CSF biomarkers on time course cognitive scores (MMSE). ○ Certain classes such as A–/T–/N+ shows a pronounced deterioration of MMSE over the 3-year follow-up period.
Frölich et al. [50]	2017	Dementia Competence Network	SVM	115 MCI (28 converted to AD, 87 remained stable, and 17 converted to non-AD dementia)	○ Using an SVM model with linear kernel and different combinations of 9 predictor variables authors analyze if adding multi-modality helps in prediction of MCI to AD progression. ○ Hippocampal volume and total tau had best single predictor performance. ○ Adding other variables helped improve specificity of model at a fixed sensitivity value.

ADNI, Alzheimer's Disease Neuroimaging Initiative; AIBL, Australian Imaging Biomarkers and Lifestyle Study of Ageing; FHS, Framingham Heart Study; NACC, National Alzheimer's Coordinating Center; FCN, fully convolution network; MLP, Multilayer Perceptron; NC, normal cognition; AD, Alzheimer's disease; MCI, mild cognitive impairment; SMC, significant memory concern; LMCI, late MCI; EMCI, early MCI; MMSE, Mini Mental Status exam; MRI, magnetic resonance imaging; HC, healthy controls; ROI, regions of interest; CNN, convolutional neural networks; VGG, Visual Geometry Group; XGBoost, (eXtreme Gradient Boosting); ATN; amyloid/tau/neurodegeneration; SVM, support vector machine.

and AD progression as a multi-task learning problem, where cognitive scores were regressed on MRI features extracted at various time points using group-based regularization and hence exploited correlations between different ROIs and their relative importance. This study performed experiments on MRI and PET as a single modality and also using a combination of MRI, PET, CSF, and demographic information where each modality is considered as a group in group guided fused Laplacian regularization.

Similarly, study [52] proposed to model long-term symptom trajectories using multi-modal data. Their framework used a hierarchical clustering algorithm to cluster symptom trajectories using clinical assessments. They grouped subjects that have similar clinical progression by assigning them trajectory labels and used them as classification labels. They used a longitudinal Siamese neural network for predictive modeling symptom trajectories using longitudinal data with multiple modalities such as clinical scores, MMSE, *APOE* ε4 status, Alzheimer's Disease Assessment Scale-Cognitive Subscale, age, and specific MR measures. Study [53] showed that using ML approaches such as random forests and gradient boosting in combination with relatively inexpensive and non-invasive biomarkers such as those available from blood samples is promising, i.e., predictive models can perform almost as well as models built using rather expensive biomarkers such as MRI and PET or combination of all. Moreover, using a model built on blood tests can provide initial risk estimation of MCI patients converting to AD and thus identify patients that may benefit from additional testing. For example, [54] used a simple linear mixed effects model adjusted for age and sex trained on CSF biomarkers for amyloid/tau/neurodegeneration (ATN) classification. Cognitive performance (MMSE) scores were collected over three years, and patients were stratified into ATN classes based on CSF measures, PET, and MRI measurements, along with neuropsychological tests. The classification model showed prognostic value in predicting the course of cognitive decline.

DISCUSSION

In this review, we provide an overview of research on ML utilizing NPS and AD biomarkers information in the context of brain aging. To the best of our knowledge, only one study examined ML using both NPS and AD biomarkers [22], and only four studies examined ML using NPS in the context of brain aging [24–27]. Most ML studies included in this review focused on AD biomarkers, particularly neuroimaging biomarkers such as MRI, PET, and fMRI.

In general, the studies included in this review provide convincing evidence for the potential application of ML in the context of brain aging. Statistical ML models such as SVM, Random Forests, Linear Regression, and Boosting techniques [24, 30, 38, 43] have shown promising results with existing AD biomarkers regarding a wide range of clinical utilities and observations, e.g., to correctly classify individuals into having MCI or AD or being cognitively unimpaired. Since these methods allow for better introspection into model predictions and working compared to complex deep learning models, they are more commonly used in research. Unfortunately, research on ML utilizing both NPS and AD biomarkers in the context of brain aging is minimal at this point but will likely increase in the near future. Based on the results of this review, we believe that ML methods will prove to help examine the complex and non-linear associations between NPS and AD biomarkers in predicting the cognitive status and trajectories of older adults. Thus, ML techniques may ultimately be used to identify persons at risk for progression to MCI or dementia at an early stage, i.e., when they are still cognitively unimpaired, based on information about the neuropsychiatric and AD biomarker status of a person. This may significantly impact the potential delay of slowing cognitive impairment, for example, through early initiation of individually targeted therapeutic approaches. We also hypothesize that ML considering both NPS and AD biomarker information will be more efficient and successful in correctly classifying individuals as compared to ML based on either NPS or AD biomarkers alone, as also implicated by the promising preliminary results of one study included in this review [23]. However, it must be noted that ML methods rely on pre-processed features from domain experts, which limits the discovery of novel biomarkers and may not be effective in the case of very high-dimensional datasets such as raw neuroimaging modalities. Besides, given sufficient data, ML methods robustly model nonlinearities, but it is difficult to examine the complexities such nonlinear mappings. Shapley values [7] are helpful in seeing the "overall" effects and can aide in interpretation of model predictions.

Similarly, deep learning-based studies included in this review showed improved results in diagnostic classification, segmentation, and biomarker discovery in specific scenarios [26, 35, 50]. With more datasets being collected and made publicly available, it is possible to train these deep neural networks, investigate raw imaging and other modality datasets, and potentially discover new biomarkers that were previously unknown. Nevertheless, deep learning also comes with an additional overhead of limited interpretability of its working, computation cost, and huge dataset requirement to train on. Therefore, tech-

niques such as transfer learning as shown in [45], few-shot learning [55], and knowledge distillation [56] remain active areas of research to mitigate these limitations. Our review should be interpreted by considering its strengths and limitations. The strengths of the review are that we applied a rigorous search strategy and that our team has expertise in machine learning, mathematical statistics, and NPS and AD biomarkers from a clinical and research perspective. Two authors did the literature search and screening process independently, thus ensuring higher methodological quality. Furthermore, to the best of our knowledge, no current review provides an overview of research on ML considering NPS and AD biomarkers in the context of brain aging. Limitations of our review pertain to the high heterogeneity of studies included, particularly those focusing on ML and AD biomarkers, which makes it challenging to summarize and comprehensively interpret the findings. Furthermore, only one study could be included in this review that examined ML in the context of brain aging by considering both NPS and AD biomarker information. More research is thus needed that utilizes the strengths of ML to untangle the relationships between NPS and AD biomarkers in predicting cognitive trajectories in older adults. In the past, our group has proposed four possible mechanisms linking NPS and AD pathology in predicting cognitive outcomes: etiologic, shared risk factor/ confounding, reverse causality, or interaction pathways [57]. ML may help better explore these hypothetical mechanisms in the future and clarify which mechanisms are empirically valid. Another limitation is that we did not systematically examine the quality of included studies or compare them based on quality rating. However, this was not feasible due to the significant heterogeneity of included studies regarding methodology.

In our review, we only focused on ML, NPS, and commonly used AD neuroimaging biomarkers, i.e., MRI biomarkers, PET biomarkers, fMRI biomarkers, and combination of imaging and other modalities. However, there are also several studies that examine ML and retinal imaging biomarkers in AD. For example, investigators of one study [58] proposed a bilateral deep learning network that fuses features from four retinal photographs along with demographic information to detect patients with AD dementia. Whereas another study [59] developed a ML framework to classify healthy individuals from patients with AD using retinal vasculature features. The proposed framework has a modular pipeline that performs image quality control, segmenting vessel maps from fundus images using a deep learning model and using a *t*-test feature selection process from those maps to train a binary SVM classifier. Authors also generated saliency maps to investigate the contributions of relevant parts of vascular system for machine learning prediction. A ML based model found that retinal thickness was affected by AD severity [60]. Optical coherence tomography measurements are inexpensive and non-invasive compared to MRI, CSF, and PET. An XGBoost algorithm was used to build high accuracy diagnostic model for AD using eight optical coherence tomography features. Furthermore, ML has also been successfully used to investigate depression and other NPS in diseases other than AD, such as hypertension [61], major depressive disorder [62], cancer [63], cardiovascular disease [64], and general life [65].

In conclusion, this review shows that studies on ML in the context of brain aging have mainly focused on AD biomarkers. To date, only a little research is available on ML NPS and AD biomarkers. However, given the clinical significance of NPS in the context of brain aging, we argue that more studies on ML, NPS, and AD biomarkers need to be conducted. ML is a promising tool to identify persons at risk for progression to MCI or dementia. NPS is also an independent risk factor of MCI or dementia. Therefore, the prediction model of MCI or dementia can be substantially improved by using ML in samples enriched by NPS. This may have implication for future AD prevention trials that target samples enriched with NPS.

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