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Current trends on the early diagnosis of Alzheimer's Disease by means of neural computation methods

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***Abstract*—The prevalence of dementia is expected to increment in the next decades as the elderly population grows and ages. Hence, Alzheimer's Disease (AD), as the most frequent dementia, will be more problematic from a socioeconomic point of view. Different diagnostic criteria have been proposed by clinicians for the early diagnosis of AD. After discarding the longitudinal and prognosis articles, a selection of articles from the last decade and based on Artificial Neural Networks (ANNs) was collated from the PubMed database, and complemented with researches extracted from others. The latest trends on this field were discovered in these selected articles, which were later discussed. Only articles based whether on shallow ANNs, Deep Learning (DL) or a mix of both were included. The total number of cross-sectional articles that complied with our selection criteria was 154. Convolutional Neural Networks (CNNs) combined with neuroimaging has been the most popular approach, yielding very good performance results. Approaches based on non-neuroimaging techniques, such as gait, genetics, speech and neuropsychological tests, were less common but have their own advantages. Multimodality solutions may become even more prevalent in the near future. Similarly, novel diagnostic criteria will appear and the popularity of currently not-so-common ones will expand. A new proposal emerged from these trends, which is based on ontogenetic ANNs.**

***Keywords*—Alzheimer's Disease; Mild Cognitive Impairment; Computer-Aided Diagnosis; Artificial Neural Network; Deep Learning**

I. Introduction

THE aging and increasing quantity of elderly population bring along an increment of patients with chronic diseases such as stroke and dementia. AD, as the most frequent type of the latter, is a neurodegenerative disease characterized by a rather slow development. Mild Cognitive Impairment (MCI) is a construct equivalent to the oligosymptomatic or prodromal stage of this disease [1]. It was proposed by clinicians for subjects characterized with cognition levels intermediate between those of Cognitively Normal (CN) and AD, and where no impact on their daily live activities has been observed [1].

AD has no cure yet so researchers have been working on finding good diagnostic and prognostic methods. The difficulty of both diagnosis and different diagnosis of AD and MCI is the main problem due to the unavailability of both standardized diagnostic criteria and specific biomarkers [2]. Thanks to the automatic characteristic of computation-based methods, their popularity has boosted. Initially, most of those that worked with Artificial Intelligence (AI) techniques were based on non-neural approaches, which are outside the scope of this work, such as Support Vector Machine (SVM), Decision Tree (DT) and Random Forest (RF) [3]–[5]. Neural approaches arrived later and have been obtaining very good performance results in different classification tasks. The main reason for such good behavior is that ANNs are able to work with multidimensional, noisy and complex data, and even with data where classes are highly overlapped [2]. Thus, as dementia diagnosis and prognosis are characterized with these troublesome properties, proposals based on Deep Neural Networks (DNNs) and shallow ANNs have become commonplace lately.

The main goals of this overview are two, each further explained in the next sections. On the one hand, finding trends on the selected ANN-based articles from the last decade but, unlike in [2], we will only focus on early AD diagnosis in cross-sectional studies. That is, prognosis and longitudinal studies will be excluded. On the other hand, a new proposal that emerged from the previous trends will be discussed. This high-potential ANN-based proposal will be able to face this classification challenge with efficiency, facilitating its incorporation in e-Health environments.

II. Trends on neural computation approaches for AD and MCI diagnosis

The last years have been very fruitful in the research of Computer-Aided Diagnosis (CAD) systems for AD, especially after the exceptionally good results of the solutions based on neuroimaging techniques and DL. A huge number of works have been published. Researchers have focused on the two main AD-related tasks: diagnosis and prognosis. Both cross-sectional and longitudinal studies have been posited by other researchers.

Articles were extracted from the PubMed database, which were complemented with other works from ScienceDirect and

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IEEE Xplore. In this work the selection criteria utilized to filter these articles were:

- Cross-sectional articles related to the diagnosis of AD or MCI.
- At least one of the classification methods or a module within it must be based on shallow ANNs, DNNs or a combination of both.
- Articles must have been written in English and published in peer-reviewed journals or conference papers between 2012 and 2022, both inclusive.
- Usage of some popular performance metric as to facilitate comparisons between different works. Examples of these metrics are Area Under the Curve (AUC), accuracy, sensitivity, specificity, F1 score and precision [6]–[9].

As seen, none are related to specific diagnostic criteria as the entire spectrum currently in use was of interest for this study. These 154 "selected articles", which met this selection criteria, were divided into neuroimaging-based and non-neuroimaging-based because important differences between the trends in both groups of criteria were found. There were 118 and 36 cross-sectional articles in these groups, respectively. If any of these works tackled one or more classification task, in the figures in this work they were counted independently as each task has different complexity (particularly between binary and multiclass problems). That is, there were 234 neuroimaging-related studies and 41 non-neuroimaging ones. On the other hand, databases were counted independently in the figures too because articles may use one or more databases for each classification task they worked in. In this case, 275 studies for neuroimaging; 41, for non-neuroimaging, which indicates that in the former it was far more common to use more than one database in each article, whereas in the latter, all works utilized only one.

A. Studies based on neuroimaging and brain signals techniques

Suárez-Araujo et al. [2] described neuroimaging techniques as "all imaging used to study the structure and function of the central nervous system, most frequently the brain". As no specific biomarker for AD has been discovered yet, neuroimaging techniques have been utilized as complementary diagnostic criteria for the diagnosis of AD, including for discarding other dementia and diseases.

In Table I a selection of cross-sectional works with the best performance results and based on neuroimaging techniques is shown.

Within the selected articles, several brain signals and neuroimaging techniques were used. Sorted in descending order of prevalence they were: Structural Magnetic Resonance Imaging (sMRI), Positron Emission Tomography (PET), Functional Magnetic Resonance Imaging (fMRI), Electroencephalography (EEG) and Functional Near-Infrared Spectroscopy (fNIRS). Indeed, Magnetic Resonance Imaging (MRI), in particular sMRI, outnumbered the other ones. PET was never utilized together with shallow ANNs. Multimodality takes advantage of favorably using synergies that usually happen when combining different modalities. Among the selected

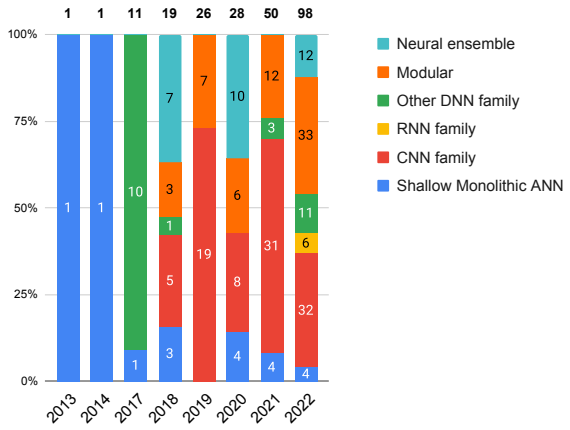

Figure 1. Number and percentage of neuroimaging-based studies per year, grouped by neural family

articles, multimodal studies where neuroimaging and non-neuroimaging data were combined were much more common than those where different modalities of neuroimaging were combined. The most popular one in the former was sMRI with scales or demographic data, whereas MRI with PET in the latter.

Neural computation methods found in articles in this group were heterogeneous. The majority of works made use of DNNs, Figure 1. Especially numerous were those based in the CNN family (almost 41% of the studies), with more complex versions of this network (in terms of number of layers, neurons and hyperparameters needed to tune) appearing in subsequent years. Modular approaches were used in more than 26% of the studies. On the other hand, the most common shallow ANNs was the Multilayer Perceptron (MLP) family (below 8% of the total).

Regarding databases, the Alzheimer's Disease Neuroimaging Initiative (ADNI) one was the most popular one in the neuroimaging-based articles, whether used alone or with others, followed by far by the varied group of private databases and the Open Access Series of Imaging Studies (OASIS) one, Figure 2. It was not rare that the selected articles in this group utilized more than one database.

Although the number of works in this group has increased yearly, the growth was dissimilar among the families of neural computation methods. The greatest positive increases took place with modular methods (particularly after 2020) and in CNN family (first works appearing in 2018 and in 2021 becoming the predominant, only surpassed in 2022 by the modular ones). It should be noted that many of these modular approaches have at least one of their modules based on DNNs, and of them, most on CNNs. On the other hand, the usage of neuroimaging with shallow ANNs stabilized.

Almost 53% of the selected articles tackled the CN-AD or CN-MCI classification tasks. The CNN family has been the predominant in all the studied classification tasks but nonAD-AD. The second most common neural family in all of them was the modular approaches group.

The main findings from works that utilized neuroimaging were the prevalence of the CNN family, the usefulness of

Table I
SUMMARY OF THE SELECTED CROSS-SECTIONAL STUDIES THAT YIELDED THE BEST PERFORMANCE RESULTS, WHOSE METHOD WAS BASED ON SHALLOW OR DEEP ANNS AND USED NEUROIMAGING DATA (MONOMODALITY OR MULTIMODALITY). MODULAR METHODS ARE INDICATED WITH "+" SYMBOLS BETWEEN THEIR MODULES IN THE "METHODS" COLUMN. IN BOLD THE BEST METHOD WHEN SEVERAL WHERE COMPARED.

Reference	Dataset	Features	Methods	Results
Sabbaghi et al. [10]	Neuronetrix: 95 CN, 75 AD	EEG	**RBFN**; MLP	0.98 ac, 1 se, 0.96 sp
Lu et al. [11]	ADNI-2: 100 CN, 100 AD	fMRI	KFS-ELM	0.99 ac
Rashid et al. [12]	ADNI; OASIS-1, OASIS-2; IXI: 1365 CN, 1365 MCI, 1365 AD	3D-MRI	CNN	CN-AD 1 ac
Wu et al. [13]	OASIS: 80 CN, 80 AD	MRI	**WS-AMN**; WSDAN; ResNet, VGG; Inception	1 ac, 1 se, 1 sp, 1 F1, 1 pr
Sheng et al. [14]	ADNI-2: 43 CN, 53 EMCI, 34 LMCI, 30 AD	sMRI, fMRI	GoogLeNet	CN-EMCI-LMCI-AD 0.97 ac
Sun et al. [15]	ADNI: 316 CN, 365 MCI, 288 AD	MRI, 5 demographic, APOE, CSF, 4 scales	ResNet	0.9 ac, 0.9 se, 0.89 sp, 0.95 AUC
Jiang et al. [16]	ADNI: 243 CN, 307 AD	3D-MRI, 2 demogaphic, 1 scale	fully CNN+MLP	0.99 ac, 0.99 se, 0.98 sp, 0.99 F1
Wang et al. [17]	ADNI: 205 CN, 174 AD	MRI, SNP	3D-CNN+MLP	0.84 ac, 0.92 AUC
Zhao et al. [18]	ADNI: 209 CN, 191 MCI, 113 AD	PET, 3 demographic, 3 scales	AlexNet+SVM; ZF-Net+SVM; **ResNet+SVM**; InceptionV3+SVM	CN-AD 1 ac, 1 se, 1 sp, 1 AUC
Bhasin et al. [19]	ADNI: 112 sMCI, 75 pMCI	3D-MRI	TGA+CNN+SVM	0.98 ac
Ashtari-Majlan et al. [20]	ADNI-1: 231 CN, 100 sMCI, 164 pMCI, 200 AD	MRI, 1 demographic, 5 scales	**CNN**; SVM; MLP	CN-AD 0.98 ac, 0.99 AUC; sMCI-pMCI 0.79 ac, 0.94 AUC

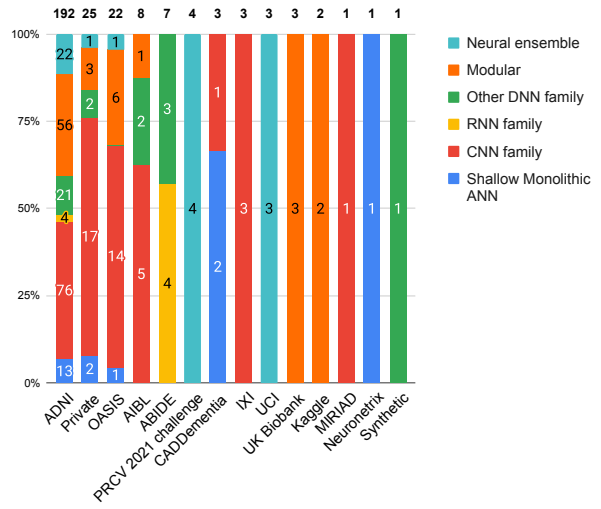

Figure 2. Number and percentage of neuroimaging-based studies where each database was used, grouped by neural family

transfer learning (using a network pretrained with a different dataset than the final one, which will be used for fine-tuning the final network with the final dataset), and the advantage given by image augmentation techniques (including those based on Generative Adversarial Networks (GANs)) as they provide more training samples. It can be concluded that they have become mandatory for studies combining neuroimaging and CNNs in order to yield the most optimal performance values, reduce training times, and require less number of training samples.

B. *Studies based on non-neuroimaging techniques*

Many non-neuroimaging techniques have been being used way before the first neuroimaging ones have, mainly because of their lower technical complexity and costs.

The variety of modalities in the selected articles belonging to the non-neuroimaging techniques group was wider [2], and included: blood, demographic data, gait and movements of body parts (such as eyes and limbs), retinal Optical Coherence Tomography Angiography (OCTA), genes, neuropsychological tests, and speech. Speech-related works have used transcripts based on the speech, the oral speech itself or a combination of both. Capture of gait and movements of body parts is nowadays easier thanks to the low cost and complexity of webcams, smartphones and wearable devices. Such equipment has been utilized in the gait-related selected articles.

The cross-sectional researches in this group that obtained the best performance results with each modality have been summarized in Table II.

In the last decade the number of articles in this group also grew, even increased by a factor of 5, stabilizing after 2020, Figure 3. A similar proportion of shallow and deep ANN-based

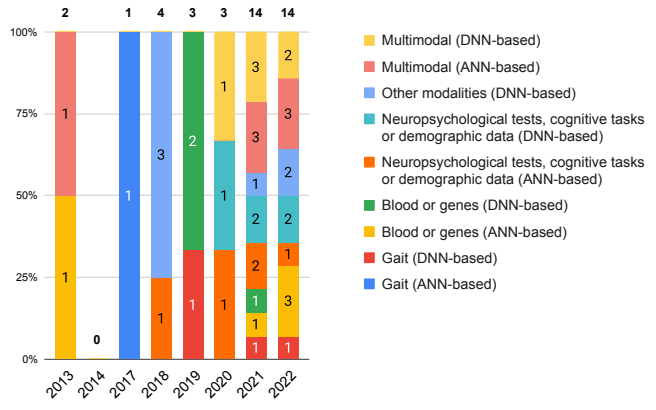

Figure 3. Number and percentage of non-neuroimaging-based studies per year, grouped by modality and neural family

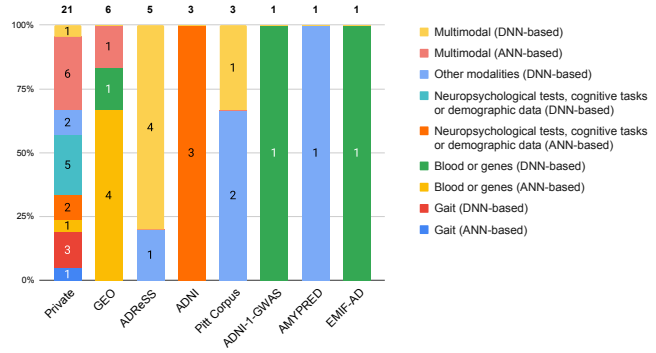

Figure 4. Number and percentage of non-neuroimaging-based studies where each database was used, grouped by modality and neural family

works were found each year, but when speech, transcript or eye movement was used, where only DNN-based works were found. Shallow ones were mostly utilized with blood and genes data. Novel modalities began being used in the last years, such as gait. Almost 32% of the studies made use of multimodal data, so it was the most used one, and it was more frequent in binary classification tasks and with shallow ANNs. About the classification tasks being tackled, near 54% were CN-AD and CN-MCI. Only works based on shallow ANNs worked in the MCI-AD problem.

Regarding databases, the popularity of private datasets was much higher than in the neuroimaging case, ranking the first position (above 52%), followed from a distance by Gene Expression Omnibus (GEO) and ADReSS databases (both sum 27%), Figure 4. Unlike with neuroimaging, the ADNI one was fourth with a mere 7%. A reason that may explain this is the lack of big, multisite databases with some types of non-neuroimaging data. Also, databases in this group are almost always limited to a family of non-neuroimaging diagnostic criteria, especially significant with non-private databases such as GEO, for blood and genes, and ADReSS and DementiaBank (which includes Pitt Corpus), for speech and transcripts. None of the selected articles in this group used more than one database, unlike in the neuroimaging case.

In contrast to neuroimaging, usage of data augmentation techniques was never reported by researchers. Similarly happened with both transfer learning and methodologies to deal with missing input data.

The CNN family was less popular than in the neuroimaging case, and it was mostly found with gait or neuropsychological data and forming part of modular methods. Other types of DNNs different to CNNs, such as the transformer [29] and the Recurrent Neural Networks (RNNs) [30], [31] families, got more common, especially with textual and speech data, respectively. MLPs and Backpropagation Networks (BPNs) were the predominant shallow ANNs, although non-neural Machine Learning methods occasionally yielded better performance.

The main findings from works that utilized non-neuroimaging were the specialization of the datasets for each modality, the prevalence of private datasets and multimodality, the increased popularity of transformers and the opposite with CNNs, and the little or no use of data augmentation techniques, imputation methods and transfer learning.

III. Ontogenic Neural Networks for AD and MCI Diagnosis: Our Proposal

The current trends on neural computation-based works and how difficult it is to solve the problem of early diagnosis of AD were the main findings of the previous analysis. Considering the above, we propose the use of ontogenetic neural architectures as they are characterized by some properties common to what we consider that the optimal neural solutions should have: high capability to solve complex and dynamical problems efficiently, good feasibility, low cost, and the need to use diagnostic criteria that are less invasive, better cost-effectiveness and low likelihood of impairing the patients' quality of life. The first of these properties is brought along by the added plasticity that such ANNs have, which can be explained by its definition. Fiesler and Beale [32] defined an "ontogenic neural network" as an ANN whose interconnection strengths change according to a predetermined learning rule, and, additionally and unlike other ANNs, the ANN also automatically adapts its topology (*i.e.* the number of layers and number of neurons per layer) to the problem. Indeed, topology modification has demonstrated to be a good candidate to successfully solve the stability-plasticity dilemma, one of the main problems that all neural networks need to face.

In the POE model explained in [33] to describe bio-inspired systems, the ontogenic neural architectures that will be described in the next paragraphs - Hybrid Unsupervised Modular Adaptive Neural Network (HUMANN), Modular Hybrid Growing Neural Gas (MyGNG) and Supervised Reconfigurable Growing Neural Gas (SupeRGNG) - lay in the Ontogeny-Epigeny plane due to their neural growth (in these cases referred as neurogenesis) and network topology modification processes.

HUMANN implements the general approach of the classification process, which has three stages [34]: feature extraction, template generation and discrimination. It uses a multilayer neural structure with three modules, each with different neurodynamics, connectivity topologies and learning laws [34].

Table II
SUMMARY OF THE SELECTED CROSS-SECTIONAL STUDIES THAT YIELDED THE BEST PERFORMANCE RESULTS, WHOSE METHOD WAS BASED ON SHALLOW OR DEEP ANNS AND DID NOT USE NEUROIMAGING DATA (MONOMODALITY OR MULTIMODALITY). MODULAR METHODS ARE INDICATED WITH "+" SYMBOLS BETWEEN THEIR MODULES IN THE "METHODS" COLUMN. IN BOLD THE BEST METHOD WHEN SEVERAL WHERE COMPARED.

Table II – *Continued from previous page*

Reference	Dataset	Features	Methods	Results
Tang et al. [21]	Private: 60 CN, 60 AD	Blood, 1 scale, 1 demographic	BPN	0.93 ac, 0.90 se, 0.95 sp, 0.93 AUC
Ma et al. [22]	ROSE: 13 CN, 26 AD	Retinal OCTA	OCTA-Net	0.99 ac, 0.97 AUC
Mahendran et al. [23]	GEO: 74 CN, 87 AD	Gene expressions	AE+IDBN	0.97 ac, 0.95 se, 0.96 sp, 0.95 F1
Sosa-Marrero et al. [24]	ADNI-2: 150 AD, 345 MCI	6 scales	MyGNG	0.85 ac, 0.82 sp, 0.91 se, 0.96 AUC
Suárez-Araujo et al. [25]	ADNI: 203 CN, 128 MCI	3 scales, 2 demographic	CPN	0.87 ac, 0.9 se, 0.85 sp, 0.95 AUC
Cheah et al. [26]	Private: 59 CN, 59 MCI, 30 AD	1 scale	CNN	CN-MCI 0.88 ac, 0.85 se, 0.91 sp, 0.91 AUC; CN-AD 0.89 ac, 0.82 se, 0.95 sp, 0.94 AUC
Chiricosta et al. [27]	GEO: 90 AD, 90 non-AD	Blood	MLP; LR; LDA; DT; NB; kNN; RF; **SVM**	0.89 ac, 0.95 se, 0.93 AUC, 0.90 F1, 0.86 pr
Ilias and Askounis [28]	ADReSS: 78 AD, 78 non-AD	Speech, Transcripts	BERT+ViT+Co-attention	0.9 ac, 0.89 se, 0.91 sp, 0.9 F1, 0.91 pr

HUMANN-S is its supervised version. The first neural module of HUMANN-S is a Self-Organizing Map [35]; the second one, the Tolerance layer; and the last one, a Perceptron type net, which performs the last stage of a classification process, the discrimination task. In [36] some schemes of HUMANN-S ensembles, combined via Simple Majority Voting or Weighted Majority Voting, were compared to tackle a multiclass Differential Diagnosis of Dementia task. The selected HUMANN-S modules were those with low validation errors and with a high diversity between pairs. With only 5 neuropsychological tests from 30 patients extracted from a private dataset, both schemes of HUMANN-S ensemble outperformed the physician. Values of sensitivity of 0.96, 0.22 and 0.85 and specificity of 0.9, 0.67 and 0.88 were obtained when classifying AD, Vascular dementia and other types of dementia, respectively. Both schemes yielded values of accuracy of 0.89.

A MyGNG is a novel supervised method that combines the ontogenetic ANN called Growing Neural Gas (GNG) [37] with a perceptron [24]. This perceptron, whose input is the GNG output, uses a backpropagation-like learning algorithm. The GNG is used for clustering the input data, whereas the perceptron, for labeling them. In [24], features were ranked with Fast Correlation-Based Filter (FCBF) [38], which is able to select the most relevant features while discarding those that provide similar outcomes. Just 6 items from 3 neuropsychological tests were the selected features. From the ADNI database 345 MCI and 150 AD patients were extracted. MyGNG yielded 0.96 AUC, 0.85 accuracy, 0.82 specificity and 0.91 sensitivity.

A SupeRGNG is another novel ontogenetic neural architecture derived from the aforementioned GNG [37] but appending the new "tuning of the inter-class boundaries" procedure [39]. In it, the topology produced by the GNG is modified in a supervised manner, by means of the cluster disconnection and reconnection steps. Using the same dataset as in [24], the SupeRGNG outperformed the MyGNG presented there according to all the performance metrics used: 0.97 AUC, 0.98 accuracy, 0.98 specificity and 0.98 sensitivity. Additionally, in [39] the SupeRGNG was further compared with several DL-based solutions that also dealt with the MCI-AD classification problem and that also were trained with datasets built with ADNI subjects (albeit with neuroimaging data). The SupeRGNG outperformed some of those solutions too, providing good and stable performance results.

IV. CONCLUSIONS

In this work, current and good performing ANN-based proposals for the early diagnosis of AD have been collated and analyzed, and the trends in this field have been shown and discussed. Differences between the trends with neuroimaging-based articles and non-neuroimaging-based ones were found, hence they were analyzed separately.

Based on these trends, it was concluded that new proposals based on ontogenetic neural architectures as the ones presented may set a trend for future researches due to their good capabilities in complex classification tasks and requiring input data derived from cost-effective and low invasive diagnostic criteria.

Neural computation-based CAD systems for AD diagnosis have yielded superb performance results, both with neuroimaging and non-neuroimaging data. The high costs of neuroimag-

ing techniques have not deterred their usage. Similarly happened with DNNs, which need expensive hardware and long training times. Strategies to mitigate both impacts, such as data augmentation techniques and transfer learning, respectively, were popular and are highly recommended. Although DL-approaches that used neuroimaging are almost always at the top of the list in terms of performance metrics, several solutions have outperformed them, such as those based on multimodality and ontogenic architectures.

Many proposals for both the diagnosis and prediction of AD will arise, especially while it remains incurable. Novel modalities and techniques will be published in the next decades for diagnosis and prediction of AD. Works that make use of multimodality or are based on ensembles of ANNs, even deep ones, might become the best candidates and, probably, will be developed shortly.

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