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# Update on the Study of Alzheimer's Disease Through Artificial Intelligence Techniques

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**Abstract:**
*Alzheimer's disease is the most common form of dementia that can cause a brain neurological disorder with progressive memory loss as a result of brain cell damage. Prevention and treatment of disease is a key challenge in today's aging society. Accurate diagnosis of Alzheimer's disease plays an important role in patient management, especially in the early stages of the disease, because awareness of risk allows patients to undergo preventive measures even before irreversible brain damage occurs. Over the years, techniques such as statistical modeling or machine learning algorithms have been used to improve understanding of this condition. The objective of the work is the study of the methods of detection and progression of Alzheimer's disease through artificial intelligence techniques that have been proposed in the last three years.*

*The methodology used was based on the search, selection, review, and analysis of the state of the art and the most current articles published on the subject. The most representative works were analyzed, which allowed proposing a taxonomic classification of the studied methods and on this basis a possible solution strategy was proposed within the framework of the project developed by the Cuban Center for Neurosciences based on the conditions more convenient in terms of cost and effectiveness and the most current trends based on the use of artificial intelligence techniques.*

**Keywords:** *Alzheimer disease, Detection, Progression, Artificial intelligence, Deep learning.*

## 1. Introduction

Alzheimer's disease (AD), as one of the most common forms of dementia, is a neurodegenerative disease that causes progressive cognitive decline and memory loss.

In terms of neuropathology, AD manifests with neuron loss and synaptic loss in the cerebral cortex and in specific subcortical regions in a progressive manner that ultimately leads to death [1].

The prevention and treatment of AD is a challenge within the problem of aging in today's society. It is estimated (2018 Alzheimer's disease facts and figures) that AD accounts for 60 to 70% of age-related dementia, affecting some 114 million people in 2050.

Due to its nature and long evolution, the care and treatment of patients with AD adds more economic burden to their family members. In addition, the psychological burden of caring for people with AD is very severe and, as a result, many families or caregivers experience high levels of emotional stress and depression.

For now, there is no cure for AD, the available treatments offer relatively little symptomatic benefit and are palliative in nature. Therefore, achieving effective and efficient intervention through early detection and diagnosis of AD is of great importance.

AD can be diagnosed but not predicted in its early stages, since the prediction is only applicable before the disease manifests itself.

Despite being a very recent area of research, a large number of advanced techniques are currently reported in the literature [2]. Cognitive function assessment techniques have been described as important indicators of dementia [3–5], such as the Mini Mental State Examination (MMSE), the cognitive subscale of the AD (ADAS) and the Rey Auditory Verbal Learning Test (RAVLT), which are used as preliminary screening tools in the detection of collaboration and vocabulary memory in patients with AD. The brain scan technique [6] is very popular, and is based on a magnetic resonance imaging (MRI) machine to obtain tomographic images with the aim of identifying structural and functional brain abnormalities, including dementia, and which allows estimating the volume and density of the brain components of the patient with AD. Structural imaging modalities of mild cognitive impairment (MCI), normal, and AD are illustrated in Figure 1 [7].

There are also a number of important biomarkers with significant characteristics throughout the progression of AD disease. Biomarker identification

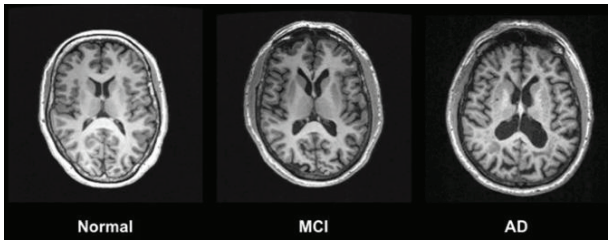


**Figure 1.** MRI images of MCI and AD compared to that of a healthy brain

approaches for monitoring disease progression have received increasing attention in the pathophysiology of AD. Finally, techniques based on IoT (Internet of Things) or generalized health techniques have emerged [8–12], which have been designed and developed to collect personal health data from patients with AD and further monitor the progression of this disease.

In [2] a study of the state of the art of modeling techniques for AD progression is carried out. The authors report that among the key techniques for the care of patients with AD, a fundamental aspect is to understand the progress of the disease and try to identify stable and sensitive biomarkers for accurate monitoring of AD progression. For example, atrophy of the temporal structures is considered a valid diagnostic marker in the stage of mild cognitive impairment. On the other hand, as the disease progresses in AD patients, changes in their cerebral cortex can be captured on magnetic resonance images.

Regression models [6, 13, 14] have previously been used in AD studies to explore correlations between cognitive measurement and magnetic resonance imaging changes. Therefore, the way to establish a model of AD progression based on cognitive scores has drawn attention due to its importance in the early diagnosis of AD.

Over the years, techniques such as statistical modeling or machine learning algorithms have been used to improve understanding of a wide range of health conditions. Common statistical models have been used in the simulation of AD disease progression [2]. The main difficulty of statistical models is their high dependence on too many assumptions, which means that the prediction method does not consider external factors for the time series. On the contrary, machine learning models have been good at dealing with the above problems. They do not require some strict assumptions. In addition, the factors in the real world are more complex and the machine learning model allows determining more decisive factors in the iterative training process. Prediction of AD disease progression can be applied to machine learning regression models using multitask learning, time series, and deep learning.

However, in the last two to three years, research in this line has continued to produce a large number of publications, most of which focus on the use of deep learning techniques. In this paper we will try to offer a general overview of the most recent results based on their classification and analysis. The work is structured as follows: in Section 2.1 we will analyze the most relevant studies of the state of the art that have been published on the subject in the last three years; in Section 2.2 we present a classification scheme of the methods studied, describing and analyzing the most representative works of each taxonomic unit. In Section 2.3, based on the analyses carried out, we discuss the results and outline an idea of facing the problem, taking into account the conditions and characteristics of the task; finally, we give the conclusions of this work.

## 2. Content

For the study, an in-depth investigation was carried out in the main databases such as IEEE Xplore, ACM Digital Library, and ScienceDirect, looking for works related to the detection and modeling of AD progression through deep learning. Some of the most popular articles were selected as representative, mainly those published in the last three years. Next, an evaluation and analysis of them was carried out, which allowed us to propose a classification that we present in Figure 2 of Section 2.2, but first we will stop at the analysis of the articles that refer to the most advanced states of the art recently published on the subject and that collect in a synthesized way the main advances achieved.

### 2.1. Recent Surveys in the Study of AD

In [2] the trends in the construction of prediction models for AD until 2019 are summarized, analyzing three main techniques: multitasking model, time series model, and deep learning. In particular, the basic structural elements of the most representative multitask learning algorithms are discussed and a multitask disease prediction model based on longitudinal time is analyzed.

The multitask learning approach belongs to statistical machine learning, which originates from the school of frequency statistics. The main strategy of this model is based on optimization through the construction of a loss function. The stepwise adjustment of the model parameters gradually reduces the prediction and the actual error of the cognitive score in the process of training the samples using gradient descent. Sparse learning methods select important features (biomarkers) in multiple iterations.

The authors focus the analyses referring to the time series model on the fact that if the progression of the disease is conditioned by its manifestations in different periods of time, it can be modeled based on these events based on the use of the Markov Random Fields (MRF) model. The main strategy of this model is to calculate the posterior probability and translate it into the problem of finding the integral. The authors review a paper [15] in which the hidden Markov model (HMM) is able to model disease progression more granularly than currently defined clinical stages and uncover more granular disease stages compared to corresponding stages in clinical diagnoses.

Regarding deep learning techniques, the authors focus on the analysis of the use of recurrent neural networks (RNN). Although RNNs have great advantages when dealing with time series data, they suggest that there are still many difficulties to overcome when performing disease prediction in the medical field. A typical drawback is that RNNs cannot handle sequential data with missing parts, since RNNs model a nonlinear relationship between consecutive data. Furthermore, RNNs require a fixed time interval. According to the authors, this assumption is not reasonable in the field of health care testing because the frequency of clinical testing varies with changes in the patient's condition. However, in the work the authors analyze

three strategies to solve this problem that focus on the completion of missing data, the establishment of fixed durations, and the optimization of the model.

Finally, the authors emphasize that the multitasking model plays an important role in terms of improving predictive performance, since relevance within similar tasks is exploited. They conclude that the problem of longitudinal data necessary for the progression of AD is a challenging task, whether for the time series model or for the deep learning model; each particular model has its own advantages in improving the quality of the data.

In [16], a systematic review of publications using deep learning approaches and neuroimaging data for the diagnostic classification of AD was carried out, taking as reference articles published between January 2013 and July 2018. Of 16 studies that met the full inclusion criteria, 4 used a mix of deep learning and traditional machine learning approaches, and 12 used only deep learning approaches. Combining traditional machine learning for classification and stacked autoencoder (SAE) for feature selection yielded accuracies of up to 98.8% for EA classification and 83.7% for the prediction of the stage of mild cognitive impairment (MCI), which is a prodromal stage of AD. Deep learning approaches, such as CNNs or RNNs, which use neuroimaging data without preprocessing for feature selection, have yielded accuracies of up to 96.0% for AD classification and 84.2% for MCI stage prediction.

The best classification performance was obtained when multimodal neuroimaging and fluid biomarkers were combined. Additionally, the authors reflect and conclude that not all problems can be solved with deep learning. This is because deep learning that extracts attributes directly from the input data without preprocessing for feature selection has difficulty integrating different data formats as input. Because weighting for input data is done automatically within a closed network, adding additional input data to the network causes confusion and ambiguity. However, a hybrid approach places the additional information in parts of the process that develops with classical machine learning methods and the neuroimaging in parts of the process that develops with deep learning methods before combining the two results.

The authors propose that deep learning will be advanced by overcoming these problems and presenting specific solutions for each problem. As more and more data is acquired, research using deep learning will have a greater impact. The expansion of 2D CNN-like networks into 3D CNN-like networks is important, especially in the study of AD, which deals with multimodal neuroimaging.

Furthermore, Generative Adversarial Networks (GANs) [17] can be applied to generate synthetic medical images for data augmentation. Furthermore, reinforcement learning [18], a form of learning that adapts to changes in data as it makes its own decisions based on the environment, may also demonstrate applicability in the field of medicine. EA research using deep learning is still evolving for better performance and transparency. As multimodal neuroimaging data and computational resources grow rapidly, research on diagnostic classification of AD using deep learning is shifting toward a model that uses only deep learning algorithms rather than hybrid methods, although it is necessary to develop methods to integrate completely different data formats.

In [19], an analysis of the most relevant studies examining AD using MRI data, machine learning, and deep learning techniques is performed with various AD datasets. The article takes a tour of the history of the discovery of AD and the techniques that have been used for its detection through magnetic resonance imaging and its different modalities. It is a very instructive article for specialists who are beginning to study the subject.

In general, based on a literature review carried out, the authors found that published articles tend to focus on two main areas of research, namely biomarkers and neuroimaging, but with a growing interest in the analysis of images. This study reviewed some of the important data sets related to AD.

In [20], the authors carry out a fairly detailed analysis of how Alzheimer's disease affects different parts of the brain, the stages of Alzheimer's disease, the neuroimaging techniques that are being used to visualize the effects, the resources of relevant data sets and how the different Artificial Intelligence-based methods developed over the years are able to identify changes in the brain and then formulate the defining characteristics. Finally, they perform a comparison of all the methods discussed with a relevant performance metric.

In [21], some of the recent approaches that use machine learning and deep learning algorithms to predict AD early and contribute to its therapeutic development are explored. These approaches were categorized in terms of learning technique and data modality used. In addition, they were discussed from different aspects and their strengths, limitations and results were compared.

### 2.2. Classification of Artificial Intelligence Methods for the Study of AD Published in the Last Three Years

Figure 2 shows the scheme that includes the classification proposed in this study.

Deep Learning (DL) has been described as "a new area of research in Machine Learning (ML), which has been introduced with the aim of bringing ML closer to one of its original objectives: artificial intelligence."

The DL structure generally comprises more than two levels of abstraction and representation to help understand texts, images, and sounds [22]. On the other hand, one way to see the classification of DL methods in the detection and progression of AD is from the nature of the data it processes. In general they can be divided into three classes: Methods that use images, methods that use clinical data and biomarkers, and methods that use mixed data from images and clinical data.

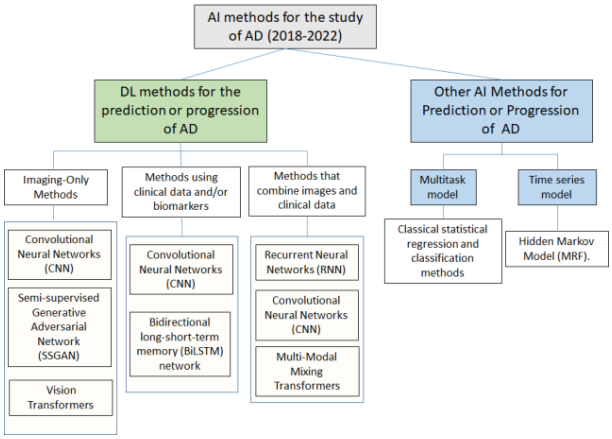


**Figure 2.** Classification of Artificial Intelligence methods for the study of AD published in the last three years

### Methods using only image data

In [23] the authors present the first automatic end-to-end deep learning framework for prediction of future patient disability progression based on multimodal brain magnetic resonance imaging of patients with multiple sclerosis (MS).

The model uses parallel convolutional pathways, an idea introduced by the popular Inception network, and was trained and tested on two large clinical test datasets. As a result, they obtained a 3D CNN network model with parallel convolutional layers to predict future progression in MS patients using magnetic resonance imaging. The results also indicate that supplementing the model with enhancer lesion labels, if available, further improves prediction accuracy. Finally, the proposed model includes an estimation of the uncertainty.

A study is presented in [24] in which the authors discuss that accumulation of abnormal tau in neurofibrillary tangles (NFTs) occurs in AD and in a spectrum of tauopathies. These tauopathies have diverse and overlapping morphologic phenotypes that obscure classification and quantitative assessments.

The authors propose the application of deep learning in the neuropathological evaluation of NFT in postmortem human brain tissue to develop a classifier capable of recognizing and quantifying tau content.

The histopathological material used in the study was obtained from 22 autopsy brains of patients with tauopathies. They used a custom web-based computing platform integrated with an internal information management system to manage the images they called whole slide images (WSI) and expert annotations as ground truth. They used fully annotated regions to train a fully convolutional neural network (FCN) against expert annotations. As a result, they found that the network was able to identify and quantify NFTs with a variety of intensities and diverse morphologies.

In [25], the authors implemented a CNN for early diagnosis and classification of AD using magnetic resonance imaging, using ADNI 3 imaging class with a total number of samples for network training of 1512 patients mild, 2633 normal and 2480 with AD. A significant accuracy of 99% was achieved. The model performed well compared to many other related works. In addition, they also compared the result with their previous finding in which classical machine learning algorithms were applied using the OASIS dataset, showing that when dealing with a large amount of medical data, deep learning approaches may be a better option than traditional machine learning.

In [26], the authors conducted the research with the aim of building a classifier for diagnosis of AD based on brain imaging through transfer learning using a large and diverse data set. MRI data from more than 217 imaging sites were collected to constitute the largest brain MRI sample reported to date, according to the authors (85,721 images from 50,876 participants). They then used an Inception-ResNet-V2 network to build a highly generalizable gender classifier. The gender classifier achieved 94.9% accuracy and served as the base model in transfer learning for the objective diagnosis of AD. After transfer learning, the fitted model for EA classification achieved 91.3% cross-validation accuracy for excluded sites (not used in network training) in the dataset Alzheimer's Disease Neuroimaging Initiative (ADNI) and 94.2%/87.9% accuracy for direct tests on two independent data sets not used in training (AIBL/OASIS).

When this AD classifier was tested on brain images of patients with mild cognitive impairment (MCI) who had not been used in training, MCI patients who eventually progressed to AD were 3 times more likely to be classified as AD than patients with MCI who did not reach AD (65.2% vs. 20.6%). Predicted AD classifier scores showed significant correlations with disease severity. In summary, the proposed AD classifier could offer a biomarker that could be integrated into AD diagnostic practice. The trained model, code, and preprocessed data are freely available to the research community. The code to train and test the model is available at https://github.com/Chaogan-Yan/BrainImageNet.

In [27], the authors implement a CNN for AD detection and classification of MRI images. The methodology starts with basic preprocessing techniques, such as image resizing and pixel normalization, and then the extracted features are integrated into a one-dimensional vector that is sent to the CNN with the corresponding labels. Four labels (classes) are used according to the four stages of AD considered, which are (Not demented, Very mildly demented, Mildly demented, and Moderately demented).

The evaluation of the prediction model showed an efficient result of the model for only ten epochs; the accuracy of the model was 97%.

In [28], the authors discuss the problem that while several experiments have recently used machine learning approaches for computer-aided diagnosis of AD, a bottleneck in diagnostic performance has been found in most of the previous studies, mainly due to the inborn defects of the selected learning models.

To solve this bottleneck, the authors propose a deep learning architecture. Compared to previous workflows, the proposed approach is capable of assessing a variety of groups in a single environment involving fewer labeled learning samples and limited prior domain knowledge. A substantial improvement in efficiency was achieved in the description of all diagnostic classes.

Recently in [34] an optimized vision transformer called OViTAD is introduced to predict healthy brains, MCI, and AD using data from rs-fMRI and structural MRI (sigma = 3.4 mm). The prediction pipeline included two separate pre-processing steps for the two modalities, cutting-level vision transformer training and evaluation, and a post-processing step based on voting for the majority concept. Experimental results showed that the optimized vision transformer proposal outperformed and was on par with vision transformer-based methods, and the number of trainable parameters was reduced by 30% compared to the standard vision transformer. The mean performance of OViTAD over three replicates was 97% $\pm$ 0.0 and 99.55% $\pm$ 0.39 for both modalities of multiclass classification experiments, which outperformed most CNN-based models and the existing deep learning. This study showed that vision transformers could outperform and compete with state-of-the-art algorithms to predict various stages of Alzheimer's disease with less complex architectures.

#### Methods using clinical data and/or biomarkers

In [29], the results obtained in tests performed to verify the performance of metabolites in blood to classify AD in comparison with CSF biomarkers are reported. This study analyzed samples from 242 cognitively normal (CN) and 115 people with dementia type AD using plasma metabolites (n 5,883). DL, Extreme Gradient Boosting (XGBoost), and Random Forest (RF) methods were used to differentiate AD from NC. These models were internally validated using nested cross-validation. This study showed that plasma metabolites have the potential to match the AUC of well-established AD CSF biomarkers in a relatively small cohort. Further studies in independent cohorts are needed to validate whether this specific panel of blood metabolites can separate AD from controls, and how specific it is for AD compared to other neurodegenerative disorders.

In [30], the authors assume that multitask modeling improves the performance, robustness, and stability of AD progression detection. However, they state that multimodal multitasking modeling has not been evaluated using time series and the deep learning paradigm, especially for the detection of AD progression. To this end, in this work, they propose a robust deep learning assembly model based on a CNN and a bidirectional long-short-term memory (BiLSTM) network. This multitask multimodal model jointly predicts multiple variables based on the fusion of five types of multimodal time series data plus a basic knowledge set (BG). Predicted variables include the AD multiclass progression task and four critical cognitive scores regression tasks. The proposed model extracts local and longitudinal features of each modality using a stacked CNN and BiLSTM network. At the same time, local features are extracted from the BG data using a feedback neural network. The resulting features are merged into a deep network to detect common patterns that are used together to predict classification and regression tasks. To validate the proposed model, the authors performed six experiments in five ADNI Initiative modalities with data from 1536 subjects. The results of the proposed approach achieve state-of-the-art performance for multiclass progression and regression tasks.

#### Methods that combine images and clinical data

In [31], the authors propose the use of a multimodal recurrent network to predict the probability of conversion from MCI to AD. They developed an integrative framework that combines not only cross-sectional neuroimaging biomarkers at baseline, but also longitudinal biomarkers of cerebrospinal fluid (CSF) and cognitive performance obtained from ADNI. The results showed that 1) the prediction model for MCI to AE conversion yielded up to 75% accuracy (area under the curve (AUC) = 0.83) when a single data modality was used separately; and 2) the prediction model achieved the best performance with 81% accuracy (AUC = 0.86) when incorporating longitudinal data from multiple domains.

In [32], the authors discuss that with the advent of the DL paradigm, it has been possible to extract high-level abstract features directly from magnetic resonance images that internally describe the data distribution in low-dimensional manifolds. The authors propose a new exploratory analysis of AD data based on deep convolutional autoencoders. The aim was to find links between cognitive symptoms and the underlying neurodegenerative process by merging information from neuropsychological test results, diagnoses, and other clinical data with image features extracted solely through a decomposition based on MRI data. In the work, the distribution of the characteristics extracted in different combinations is analyzed and visualized through regression and classification analysis, and the influence of each coordinate of the autocoding variety on the brain is estimated. Image-derived markers can then predict clinical variables with correlations greater than 0.6 in the case of neuropsychological assessment variables such as MMSE or ADAS11 scores, achieving a classification accuracy greater than 80% for the diagnosis of EA.

In [33], they discuss that the fusion of multiple data modalities can provide a holistic view of the analysis of AD status. Therefore, on this basis, they use DL to comprehensively analyze images (MRI), and genetic data (single nucleotide polymorphisms (SNP)) and clinical test data to classify patients into AD, MCI, and controls (CN). The authors use stacked automatic denoising encoders to extract features from clinical and genetic data, and 3D convolutional neural networks (CNN) for image-type data. They also developed a

new data interpretation method to identify high-performance features learned by deep models with clustering and perturbation analysis. Using the ADNI dataset, they showed that deep models outperform classical models. They further demonstrated that multi-modality data integration outperforms single-modality models in terms of accuracy, recall, and mean F1 scores. The developed models identified the hippocampus, the amygdala brain areas, and the Rey Auditory Verbal Learning Test (RAVLT) as salient features, which are consistent with the known AD literature.

An articulated and deep learning framework for predicting clinical scores in AD is presented in [34]. Specifically, the feature selection method combining cluster LASSO and correntropy is used to downsize and detect features of AD-related brain regions. The authors explore multilayer recurrent neural network regression independently to study the internal connection between different brain regions and the time correlation between longitudinal data. The proposed joint deep learning network studies the relationship between MRI and clinical score, and predicts clinical score. Predicted clinical score values allow clinicians to make early diagnosis and timely treatment of disease.

In [35] the Multimodal Mixing Transformer (3MT) was presented, for classification based on multimodal data. The authors use it in their work to classify patients with Alzheimer's disease (AD) or who are cognitively normal (CN) using neuroimaging data, gender, age, and Mini-Mental State Examination (MMSE) scores. The model uses a cross-attention cascade mode transformer architecture. Auxiliary outputs and a mode drop mechanism were incorporated to ensure a level of mode independence and robustness. The result is a network that allows the combination of an unlimited number of modalities with different formats and the full utilization of the data: it handles all missing data combinations while maintaining classification performance. 3MT was tested on the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset and achieved a testing precision of 0:987, 0:0006. To test its generalizability, 3MT was applied directly to the flagship Australia Imaging and Lifestyle Biomarker Aging (AIBL) study after training on the ADNI dataset, and achieved a test precision of 0:925, 0:0004 without fine tuning.

### 2.3. Discussion

After analyzing the described literature, we can conclude that the task of estimating the progression of AD continues to be an open problem today, where the use of the time series model and the deep learning model have their own advantages in improving the quality of the data that are used as input but still have limitations. Future work in this direction is moving towards a model that uses only deep learning algorithms instead of hybrid methods. In this sense, the open problems to be solved focus on the development of methods that allow the integration of different data formats in deep learning networks.

Regarding the diagnostic task, there is a great diversity of approaches proposed in the last three years based on DL. Almost all of them have striven to offer the best model that could efficiently employ the medical data set and diagnose disease success accurately, especially in its early stages. The data that are generally used are biomarkers and neuroimaging, but with a growing interest in image analysis without discarding biomarkers.

The type of data determines the type of DL algorithm to be used and the level of complexity of the proposed model.

Most of the DL-based approaches that use biomarker data tend to merge them with other modalities to improve prediction accuracy, so this combination increases their complexity.

Although CNNs have shown promising results, they have a very strong suitable inductive bias. Several authors have attempted to incorporate multimodal data by combining a CNN feature extractor with some form of modality information injections. However, these methods assume no missing data, which means that retraining is required for each missing data scenario. For example, a model trained on image, MMSE, and age data is not capable of making predictions with MMSE alone. Therefore, the most common solution has been to discard samples with missing modalities, with the risk of underusing data. This problem requires an approach that can automatically handle various missing data situations.

Apparently, due to the latest works posted in the arXiv repository [34, 35], the trend in this sense is towards the use of transformer-type networks that have shown high performance in other areas of knowledge.

#### Proposal of a research framework oriented to the development of AD diagnosis and progression model based on artificial intelligence

The first problem to face in our research would be the task of diagnosing AD, taking into account the availability of MRI images both in international databases and in own databases. In this case, we think that an approach based on the use of images could give good results in the short term, giving the possibility of classifying the images into classes such as AD and mild cognitive impairment and normal cognition. For this, training could be carried out based on the transfer of a CNN network in one of the variants that have reported the best results in the literature.

In Figure 3 we present the general scheme of the projected model oriented to the development of the AD progression estimation

In the case of the disease progression task, the approach that has the most prospects for development and that is in the state of the art are the combined methods of image analysis and clinical data based on transformers network type. These methods have the advantage of dealing with time series data by applying some of the strategies recommended in the literature to solve the problem of filling in missing data, establishing fixed durations, and optimizing the model.

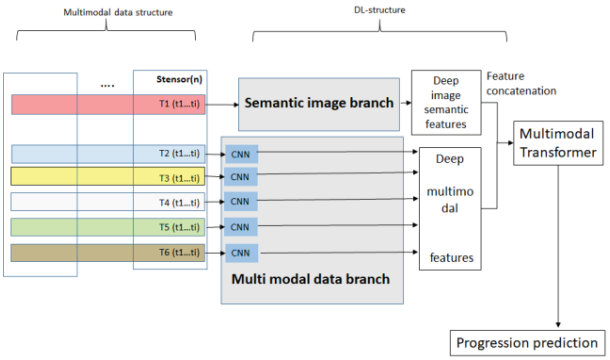


**Figure 3.** Preliminary scheme of the progression prediction model

**Table 1.** Structure of a STensor

| STensor $(n = 1, t_1 \dots t_i)$ |
|---|
| 1. T1 $(t_1 \dots t_i)$. MRI images of the hippocampi; |
| 2. T2 $(t_1 \dots t_i)$. Attributes of the hippocampi on MRI images; |
| 3. T3 $(t_1 \dots t_i)$. Cognitive score; |
| 4. T4 $(t_1 \dots t_i)$. Neuropathological data; |
| 5. T5 $(t_1 \dots t_i)$. Evaluation data; |
| 6. T6 $(t_1 \dots t_i)$. Demographics |

The proposal could be framed in the multimodal modality with a single task (detection of the degree of progression in classes (Normal, DCI and EA).

### Multimodal data structure

In mathematics, a tensor is an algebraic object that describes a multilinear relationship between sets of algebraic objects related to a vector space. Objects that tensors can map between include vectors and scalars, and even other tensors.

In the Tensorflow framework (https://www.tensorflow.org), all calculations involve tensors. A tensor is an n-dimensional vector or matrix that represents all data types. All values of a tensor contain an identical data type with a known (or partially known) form.

In our strategy we propose to use the concept of SuperTensor (STensor) and Tensor for the structuring of the multimodal data that the model will use to perform the EA prediction task.

The *STensor* of patient $n$: Contains the data derived from the processing of MRI images and the clinical data of patient $n$ under study at all evaluated time points $(t_1, t_2, \dots, t_i)$.

Tensor $Tk(t_1 \dots t_i)$. It contains the data of each one of the modalities within the Stensor of the patient n under study at all the evaluated moments of time $(t_1, t_2, \dots, t_i)$. $k = \{1, 2, 3, 4, 5, 6\}$.

A Tensor n will then be made up of 6 tensors that are constituted as follows (Table 1).

As an example, Figure 4 shows the scheme for obtaining Tensors 1 and 2. These two tensors will be responsible for containing the segmented images of the patient's hippocampi (tensor 1) and the data extracted from them (tensor 2) at each of the moments of time. The rest of the tensors will be made up of the longitudinal data of each measurement made to the patient.

### Semantic image branch

Medical images are naturally associated with rich semantics about human anatomy, reflected in a large number of recurring anatomical patterns, offering unique potential to foster the learning of deep semantic representations and produce semantically more powerful models for different medical applications.

In [36] the Semantic Genesis model was introduced. Based on the fact that medical images are naturally associated with rich semantics about human anatomy, which is reflected in a large number of recurring anatomical patterns, the authors offer unique potential to foster the learning of deep semantic representation. and produce semantically more powerful models for different medical applications.

In this sense, the authors propose a self-supervised learning framework that allows models to directly learn the common visual representation of the image data, and take advantage of the semantic-enriched representation of consistent and recurring anatomical patterns, taking into account the wide set of unique properties that medical imaging offers.

The results presented by these authors demonstrate that Semantic Genesis is superior to publicly available 3D models, pre-trained by self-monitoring or even fully-monitored, as well as 2D ImageNet-based transfer learning.

For our research we propose an adaptation of this model. The model is conceptually simple: an encoder-decoder structure with jump connections in the middle and a classification head at the end of the encoder. Figure 4 shows the general outline of our proposal.

***1) Self-discovery of anatomical patterns*:** The models begins building a set of anatomical patterns from the MRI hippocampus images, as is shown in Figure 4. To extract deep features of each image of a patient, an auto encoder network is trained with training data which self-learns a mapping of each patient.

As shown in Figure 4, due to the consistent and recurring anatomies in these patients, that is, each coordinate contains a unique anatomical pattern, it is

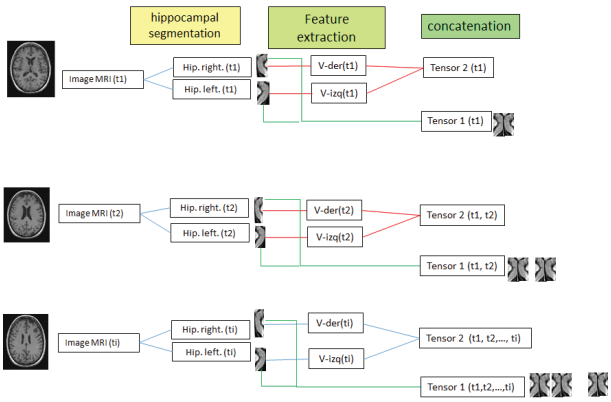


**Figure 4.** Conformation process of tensors 1 and 2 from the image of the hippocampi and the features extracted from them

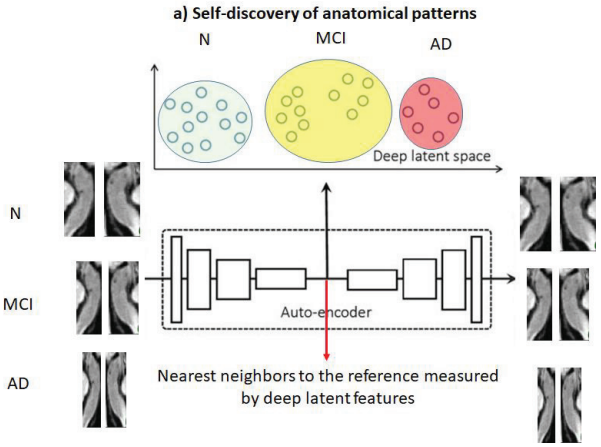


**Figure 5.** Proposal of model for the extraction of deep features from the hippocampus images based on Semantic Genesis approach [36]

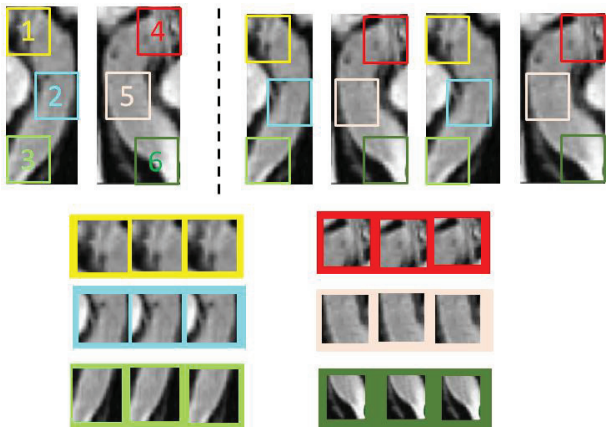


**Figure 6.** Extraction of patches (anatomical patterns) based on their coordinates

feasible to extract similar anatomical patterns based on the coordinates. Therefore, patches of a number C of random but fixed coordinates are cut out in this small set of discovered patients, sharing similar semantics. Similarity calculation is performed at the patient level rather than at the pattern level to ensure balance between diversity and consistency of anatomical patterns. Finally, pseudo-labels are assigned to these patches based on their coordinates, resulting in a new dataset, where each patch is associated with one of the C classes (Figure 5).

***2) Self-classification of anatomical patterns***: After self-discovery of a set of anatomical patterns, representation learning is formulated as a C-way multiclass classification task. The goal is to encourage models to learn from the anatomical patterns that recur in patient images, fostering a deeply semantically enriched representation. As illustrated in Figure 6, the classification branch encodes the input anatomical pattern into a latent space, followed by a sequence of fully connected (fc) layers, and predicts the pseudolabel associated with the pattern.

***3) Self-restoration of anatomical patterns***: The goal of self-restoration is for the model to learn different sets of visual representation by recovering original

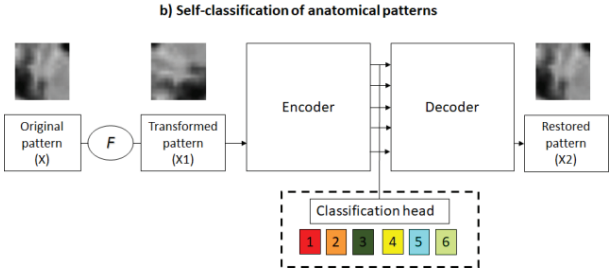


**Figure 7.** Self-classification and self-restoration of anatomical patterns

anatomical patterns from the transformed ones. As shown in Figure 7, the restore branch encodes the input transformed anatomical pattern into a latent space and decodes it to the original resolution, with the goal of recovering the original anatomical pattern of the transform. This makes it possible to obtain very robust characteristics for each class of patient.

### Multimodal data branch

As a second stage, we propose a scheme where a separate CNN subnet would be used to learn each modality. CNN for time series introduces 1D convolution (Conv1D), which can learn univariate time series data. The convolution is performed separately along the time dimension for each input tensor. Depending on the number of filters, the CNN expands each univariate time series into more abstract and informative features, called feature maps, that are more suitable for Transformer prediction. The CNN sub-network is applied to extract local features in each time series function.

Furthermore, the reference data contained in tensor 6 plays the background role to improve the accuracy and confidence of the learning process. These reference data are the static characteristics of the patient, such as demographics and some statistical characteristics extracted from their longitudinal time series data. The results of this deep feature extraction step are merged together with the results of semantic feature extraction from the hippocampi images.

Finally, the merged deep features of each time series are passed to the transformer network to obtain the prediction of the degree of progression.

## 3. Conclusion

In this work we present an update on the methods for the study of Alzheimer's disease using artificial intelligence techniques; we refer to the most recent works published in the last three years; and we present a taxonomic classification of the methods studied according to the type of data with which they work. We carried out the analysis of the articles that contain the methods of the state of the art based on the taxonomic classification, reaching the conclusions that allowed us to make a proposal on how to face the problem based on the analysis of the advantages and disadvantages of the methods studied, which focuses on several solution variants based on deep learning

techniques, and which can be implemented in the short and medium term. Each variant then requires a process of evaluation, implementation, and adaptation to the characteristics of our research.

As part of the discussion of this work, we proposed a strategy for predicting the progression of AD based on the use of DL techniques with the aim of developing future research by our team. The scheme will combine hippocampal MRI data to extract informative imaging features and five time-series modalities under a CNN-Transformer design.

State-of-the-art results have shown that advanced network design can lead to significant improvement in the monitoring of AD patients. The proposed preliminary design might be able to optimize multiclass classification by simultaneously learning and merging discriminant features from images, time series, and BG data. The resulting model can provide promising performance. Systematized experiments in the state of the art suggest that no single modality can be sufficient to assess AD progression on its own. In addition, they pointed out the importance of merging the characteristics learned from these modalities.

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