STUDY ON MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE CLASSIFICATION USING A NEW ONTOGENIC NEURAL ARCHITECTURE, THE SUPERVISED RECONFIGURABLE GROWING NEURAL GAS

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ABSTRACT

Alzheimer's Disease (AD) is one of the most prevalent aging-associated chronic diseases for the elderly population. Its prodromal stage is the Mild Cognitive Impairment (MCI). The detection of this stage versus AD is very difficult. We propose a new ontogenic neural architecture for dealing with the MCI-AD classification task. This is the Supervised Reconfigurable Growing Neural Gas (SupeRGNG), which is based on the Growing Neural Gas. We present a study on 495 Subjects from the Alzheimer's Disease Neuroimaging Initiative database, with 345 MCI and 150 AD. SupeRGNG yielded very good performance results just using six features related to neuropsychological tests: 0.98 accuracy, 0.98 specificity, 0.98 sensitivity, and 0.97 AUC. It outperformed many state-of-the-art proposals based on Deep Learning and neuroimaging. These findings suggest that our proposal may be an appropriate candidate for the early detection of AD in any clinical setting.

Keywords: Alzheimer's Disease, Mild Cognitive Impairment, Computer-Aided Diagnosis, Artificial Neural Network, Growing Neural Gas.

1 INTRODUCTION

High prevalence of chronic diseases associated with aging, such as dementia and stroke, together with the increasing number of population age 65 and older means substantial costs of health care, long-term care and hospice (Alzheimer's Association 2018). AD is currently an incurable and progressive neurodegenerative syndrome that causes dementia (Cabrera-León et al. 2023). Countries with high life expectancy are frequently more affected by dementia, totaling about 47 million people suffering it worldwide, of whom around 7 out of 10 have AD (Reitz and Mayeux 2014, Zhu and Sano 2006). As dementia is seen as a public

healthcare issue, protective and risk factors have been studied (Reitz and Mayeux 2014). Exact etiology and evolution of AD is not yet completely understood (Cabrera-León et al. 2023).

AD patients are characterized by increasing memory deficiencies and, in most cases, also with alterations in other cognitive functions. Such progressive deterioration negatively affects the subjects' behavior and emotional states and how well they cope with their daily life activities (Cabrera-León et al. 2023).

Conversely, MCI patients have cognitive performance between subjects with AD and Cognitively Normal (CN) (Petersen et al. 2014). The main difference is that performing daily life activities is not affected. MCI is sometimes an early sign of AD but not always a transitional stage between CN and AD (Petersen et al. 2014). Indeed, each year only 5-10% MCI patients convert to dementia, although between 10% and 15% from the amnestic form of MCI to AD (Janoutová et al. 2015, Mitchell and Shiri-Feshki 2009). Nowadays, no effective treatment against AD has been found. However, the intervention in the early and even prodromal stages of the disease will greatly improve the quality of life of both the AD patient and its caregiver (Reitz and Mayeux 2014, Zhu and Sano 2006).

Diagnosis and differential diagnosis of AD and MCI are complex problems due to the lack of both standardized diagnostic criteria and a specific biomarker (Petersen et al. 2014). The latter explains how common is the underdiagnosis of AD, especially in primary care. Looking for novel, preferably specific for AD, biomarkers is currently an active research area (Blennow and Zetterberg 2018, Leuzy et al. 2022, Mantzavinos and Alexiou 2017, Molinuevo et al. 2018).

Indeed, the high complexity of the aforementioned diagnosis and differential diagnosis induced researchers to search for innovative ways to facilitate and speed up both processes. Automatization via Machine Learning (ML) methodologies was then introduced, being neural computation techniques another approach. Artificial Neural Networks (ANNs) are their main information structure, which are inspired in the biological nervous systems. Artificial neurons connected to each other, as in their biological counterparts, are the principal processing element in ANNs (Hecht-Nielsen 1987). Many computational solutions for the diagnosis of AD have been studied, the majority dealing with diverse binary classification tasks (Basaia et al. 2019, Ebrahimi-Ghahnavieh et al. 2019, Hosseini-Asl et al. 2018). Deep Learning (DL) approaches have become predominant in the last decade (Basaia et al. 2019, Hosseini-Asl et al. 2018, Rashid et al. 2022, Song et al. 2021), albeit other neural (Sabbaghi et al. 2021, Suárez-Araujo et al. 2021, Urooj et al. 2021) and non-neural ones (Lahmiri and Shmuel 2019, Pellegrini et al. 2018) have been proposed too. Unfortunately, most recent researches can not be easily applied in primary care because they need invasive or expensive tests as, for example, Cerebrospinal Fluid (CSF) or neuroimaging, respectively (Manzak, Çetinel, and Manzak 2019).

In this work we describe an innovative intelligent system based on SupeRGNG, the new non-deep neural architecture that we have developed. We demonstrate that the main goal of this paper, that is, to create an effective solution to help in the MCI-AD classification task, is fulfilled. Due to our system solely requiring neuropsychological scales to aid in the early and differential diagnosis of AD, it may be inferred that our system is helpful for practitioners in any clinical setting, especially in primary care.

2 METHODS

The proposed intelligent system for dealing with the MCI-AD classification problem is based on the SupeRGNG architecture.

The most important differences between our SupeRGNG and the Growing Neural Gas (GNG) (Fritzke 1995) in which it is based are related to their two main characteristics: using supervised learning and being reconfigurable. SupeRGNG uses the clustering provided by the GNG and, if necessary, reconfigures the network topology based on the labels in order to better represent the class distribution of the input data.

Two stages exist in our proposed intelligent system: a non-neural preprocessing one, and a neural processing stage after the previous one. In the preprocessing stage four steps are carried out in this order, which will be explained in subsection 2.2: imputation of missing data, scaling of the features, feature ranking or selection, and dimensionality reduction. On the other hand, the SupeRGNG architecture is the main component of the processing stage.

2.1 Data environment

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (University of Southern California 2004). Led by Principal Investigator Michael W. Weiner, MD, the ADNI was launched in 2003 as a public-private partnership. The main objective of ADNI has been to test whether serial Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

As in this work the MCI-AD classification task is dealt with, 345 MCI and 150 AD subjects (that is, a total number of 495 patients) were selected. This MCI class included subjects whose labels in ADNI were Early Mild Cognitive Impairment (EMCI), MCI and Late Mild Cognitive Impairment (LMCI). Only data from the baseline were extracted from the ADNI database. All the selected subjects were those initially recruited during the ADNI2 study. Patients with invalid values for any of the used attributes were discarded. In Table 1 several characteristics of these patients are presented, both grouped by class and as a whole. Mainly, the mean, the standard deviation and the interval (minimum and maximum values) of the patients' age, which is a relevant demographic data and AD risk factor, and the six features that were chosen by the feature selection method among the existing 202. These 202 features were multimodal as they included demographic data, neuropsychological tests, MRI and PET quantitative measurements, genetic-related variables, and blood biomarkers.

Table 1: Characteristics of the subjects included in our dataset: a demographic feature, and the six attributes, sorted by the FCBF feature ranking method, used by the model as input. Acronyms: SD (standard deviation).

	AD (n=150)		MCI (n=345)		AD + MCI (n=495)	
	Mean (SD)	Interval	Mean (SD)	Interval	Mean (SD)	Interval
Age	74.67 (8.18)	55.6 – 90.3	71.56 (7.38)	55.0 – 91.4	72.5 (7.77)	55.0 – 91.4
MMSCORE	23.07 (2.08)	19 – 26	27.98 (1.74)	24 – 30	26.49 (2.91)	19 – 30
MMDATE	1.6 (0.49)	1 – 2	1.08 (0.26)	1 – 2	1.23 (0.42)	1 – 2
MMBALLD	1.67 (0.47)	1 – 2	1.14 (0.35)	1 – 2	1.3 (0.46)	1 – 2
ADAS_Q7	2.4 (1.75)	0 – 7	0.43 (0.85)	0 – 8	1.03 (1.5)	0 – 8
MMYEAR	1.27 (0.44)	1 – 2	1.0 (0.05)	1 – 2	1.08 (0.28)	1 – 2
FAQSHOP	2.78 (1.82)	0 – 5	0.5 (1.14)	0 – 5	1.2 (1.73)	0 – 5

These six features, selected from the initial 202 by the feature ranking method described in subsection 2.2, constituted the final dataset. They consisted of several subtests and one total score of the following different neuropsychological tests:

- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) includes 11 subtests that assesses several cognitive functions such as praxis, memory, and language (Rosen, Mohs, and Davis 1984).
- Functional Activities Questionnaire (FAQ) measures, through ten questions, how well the subject is able to develop complex social activities, the so-called instrumental activities of daily life (Pfeffer et al. 1982).

- Mini-Mental State Examination (MMSE) is a popular 30-item neuropsychological test that evaluates different cognitive functions: orientation, memory, language, comprehension, reading, writing and constructional skills (Folstein, Folstein, and McHugh 1975).

As indicated in Table 1, these features, which cover both functional and cognitive domains, were: the total score (MMSCORE) and three items (MMDATE, MMYEAR and MMBALLDL) of MMSE, one question of FAQ that assesses the dependence of the subject when purchasing (FAQSHOP), and one item of ADAS-Cog that evaluates the subject's long-short cognitive memory (ADAS_Q7).

2.2 Preprocessing of the data

Before inputting our data to the model, several preprocessing steps were deemed necessary: imputation of missing values, data scaling, feature ranking, and data projection. Thanks to these four processes, missing values were not found in the final dataset, the scales of the data were not too different, and the size of the dataset decreased from 202 to 6 features. This way, the quality of the original dataset improved which is useful for reducing both the complexity of the model and training time, and increasing the possibility of the model to yield better performance results.

Most ML algorithms dislike missing values in the data. Different imputation techniques were tested: leaving the data uncleaned, discarding patients with a missing value in any of the used features, substituting the missing value with the mean for that class, *idem* but with the mode of the class, and similarly but with the median value per class. Substituting a missing value with the median for that class provided better and more stable results.

Features with very different scales have a great impact as those with wider ones tend to artificially become more important for the model. Leaving the data as originally was, the popular "standard scaling" (removing the mean and scaling with the standard deviation) and "robust scaling" (similar but using the median and interquartile range instead, which is more robust to outliers) were the scaling methods analyzed. No improvements were found when using any of the tested scaling methods so none was finally applied.

The large number of features in the original dataset, 202, was the main reason for applying a feature ranking or selection method. Extreme Gradient Boosting (XGBoost) (Chen and Guestrin 2016) and FCBF (Yu and Liu 2003) were evaluated. The former builds a tree ensemble and, as a byproduct, also produces a ranking of features. The latter is a hybrid filter and wrap feature selection method where symmetric uncertainty is used not only to determine the correlation between features and categories but also to highlight redundancy between the features. Due to the latter characteristic, the feature ranking produced by FCBF was considered of higher quality and, hence, preferred. In Table 1, apart from the age, the vector of the most relevant and, at the same time, the least redundant features for the MCI-AD classification task sorted by FCBF is shown. Similarly, the ranking provided by FCBF for this classification task is displayed in Figure 1. From this figure, it can be seen that the features with the smallest FCBF scores were not included in our final dataset.

In order to test the statistical significance of each of the six features selected by FCBF, the non-parametric test Mann-Whitney U for two independent groups was used (Mann and Whitney 1947).

As the final step, our dataset was divided into a training set (396 subjects) and a test set (99 patients). Each of them preserved the percentage of subjects per class.

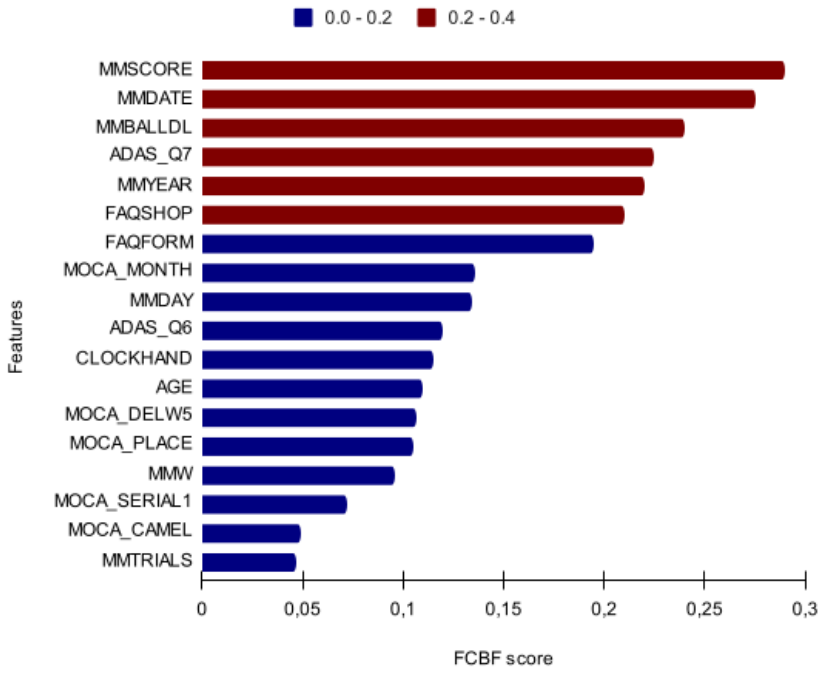

Figure 1: Ranking of features according to the FCBF method for MCI and AD subjects (ADNI2 study).

2.3 Supervised Reconfigurable Growing Neural Gas

In this work we present a novel intelligent supervised system, based on SupeRGNG, which is the main component of our system's processing stage. SupeRGNG, whose structure is shown in Figure 2, can be included in the ontogenic ANNs family. Ontogenic neural architectures are ANNs able not only to change their connections during learning, as other ANNs do, but also to automatically adapt their topology to the problem (Fiesler 1994, Fritzke 1997). These characteristics made them quite suitable for clustering, data visualization and vector quantization.

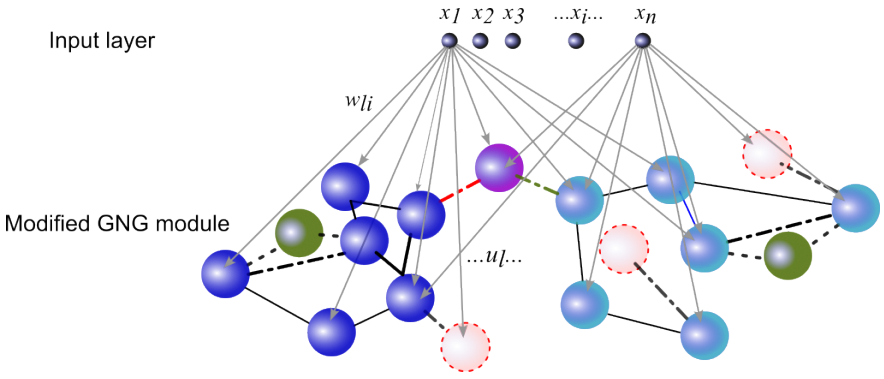

Figure 2: Structure of the Supervised Reconfigurable Growing Neural Gas, where x_i is the i-th component of the input vector; $w_l i$, the weight of neuron li; and u_l, a neuron/unit of the GNG module.

Although SupeRGNG is the main model in this work, the "originalGNG" architecture was also developed, both for comparisons purposes and as the basis of SupeRGNG. Unlike SupeRGNG, it lacks the "tuning of

the inter-class boundaries" procedure, which will be described later. Both "originalGNG" and SupeRGNG are based on the GNG, another ontogenic neural architecture (Fritzke 1995, Fritzke 1997), which also lacks any labeling procedure.

Compared to similar unsupervised ANNs, such as the Self-Organizing Map (SOM) (Kohonen 2001) and the combination of Neural Gas (NG) (Martinetz and Schulten 1991) and Competitive Hebbian Learning (CHL) (Martinetz 1993), the topology of the GNG is much more dynamic thanks to its ability to create new neurons and delete the least useful ones (although this happens as a side effect of deleting connections). These processes are called neurogenesis and neural apoptosis, respectively, and will be explained later. In contrast to the GNG, the combination of NG and CHL (Martinetz 1993) has several disadvantages (Fritzke 1997): the total number of adaptation steps and the network size must be predefined, and its hyperparameters are not constant. The GNG is also able to stop growing if a user-defined performance criterion has been met (Fritzke 1997).

As the already mentioned self-organizing maps, a GNG can be seen as a graph of connected neurons that dynamically changes (Cabrera-León et al. 2023). A GNG starts with a reduced number of connected neurons (usually 2) and, while the learning process takes place, it grows, adapts and shrinks according to the topological learning induced by the input space. A competitive learning algorithm generates the graph and keeps it updated (Fritzke 1997).

For a certain input vector $\xi = (x_1, \ldots, x_n)$, the Best Matching Unit (BMU) or winner neuron s_1 is characterized by having the minimal, usually Euclidean, distance between the neuron's weight (w) and the input vector. In (1) the adaptation process is exposed, where the weight of only the BMU and its neighbors are modified. Unlike in other ANNs, in the GNG neighbors of a certain neuron are neurons that have an edge connecting them. However, these adjustments are different (highly recommended) and given by the values of the learning rates for the winner and neighbors, respectively called e_b and e_n (Fritzke 1995).

$$\begin{aligned} \Delta w_{s_1} &= \varepsilon_b(\xi - w_{s_1}) \\ \Delta w_n &= \varepsilon_n(\xi - w_n) \text{ for all direct neighbors } n \text{ of } s_1 \end{aligned} \tag{1}$$

The local error variable that allows identifying regions with neurons suboptimally adapted to the input data is given by (2). Neurogenesis, which happens after a fixed number λ of adaptation steps, depends on this error to find where to create a new neuron. As indicated in (3), the new neuron is placed between q, the neuron with the highest error, and f, the neighbor of q with the highest error. New neurons are colored green in Figure 2, where the two new edges connecting it to q and f are indicated with a dashed-dotted line; and the edge between q and f that gets deleted, with a dashed-dotted line. Parameter β is used to decrease the error variables of the neurons q and f.

$$\Delta error(s_1) = ||w_{s_1} - \xi||^2 \tag{2}$$

$$w_r = 0.5(w_q + w_f) \tag{3}$$

The topology of a GNG changes with the creation and deletion of edges. A new edge is created between the first and second BMUs on each adaptation step (or its age reset to 0 if it already existed). An edge is removed when its age surpasses the maximum allowed age (a_{max} parameter). Neural apoptosis occurs when it gets disconnected from others. In Figure 2 dead neurons are shown in red, and different styles of dashed lines are used to indicate whether edges are going to be created (dashed) or eliminated (dashed-dotted).

The GNG will gradually approximate the structure of the input data manifold (Fiesler and Beale 1997), after repeating this learning algorithm enough times with all the available training data (the so-called "epochs").

Our "originalGNG" is a simple neural model where a GNG is used for clustering the input data whereas, in the labeling phase, labels of the clusters are assigned by the simple majority voting of the labels in the neurons within each cluster.

Our SupeRGNG is built based on the topology produced by the clustering phase of the "originalGNG". An initial labeling process akin to that in the "originalGNG" occurs after the clustering, and it is followed by the "tuning of the inter-class boundaries" procedure, whose steps are:

a) Find the inter-class boundaries in the network.
b) Cluster disconnection: if labels are different, delete the edge even if neurons become solitary (as later they will be correctly reconnected). In Figure 2, the neuron in red-blue color, which belonged to the light blue class, was erroneously connected to the cluster of dark blue neurons, so its edge (red and dashed line) is eliminated. Inadequate values of certain GNG parameters may have this outcome.
c) Cluster reconnection: connect all clusters whose label is the same and were erroneously separated, usually due to suboptimal GNG hyperparameters values. The closest neurons of each of the clusters to be connected are selected and a new edge is created between them. In Figure 2, the neuron in red-blue color in the previous step gets connected (green and dotted line) to the cluster of light blue neurons.

Our models and experiments were implemented with the Python 3.6 language programming. Part of the data preprocessing was performed with "scikit-learn", a well-known Python library for ML (Pedregosa et al. 2011). Our "originalGNG" model was built based on the GNG implementation found on "Neupy", a Tensorflow-based Python library for prototyping and building shallow ANNs and Deep Neural Networks (DNNs) (Shevchuk 2015). Our SupeRGNG model was implemented based on our "originalGNG".

3 RESULTS

Performance results and training times for both models were analyzed. Several commonly used performance metrics were utilized, such as accuracy, specificity, sensitivity and Area Under the Curve (AUC) (Suárez-Araujo et al. 2021). We consider the AUC as the main performance metric as, unlike others such as accuracy, it is not affected by class unbalanced datasets, as is the case (Fawcett 2006). The training time includes both the time for the initialization of the network and the time it spent for the training phase.

An initial analysis of the hyperparameters of both the "originalGNG" and the SupeRGNG was carried out with some straightforward synthetic datasets. This analysis eased the posterior selection of more optimal combinations of hyperparameters when dealing with the real dataset. From this analysis it was concluded that several hyperparameters have more impact than others on both the performance and the training times of our proposed shallow ANNs:

- The greater the number of epochs, the greater the training time was, and the more stable the models and performance results could be considered. This hyperparameter has the greatest impact on training time, followed by the number of neurons.
- The greater the number of neurons, the slower the training process was, the better the problem space was modeled by the network, and, apparently, the more difficult for the "originalGNG" the clusters separation was. This hyperparameter has the greatest impact on both hard disk and memory consumptions.
- Inadequate combinations of the values given to some of the hyperparameters (especially, the number of iterations before a neuron is added and the maximum age of an edge) may have two unpleasant outcomes: networks to not grow enough, even not above the initial number of neurons, so they

do not properly represent the input space, and the creation of multiple small-sized clusters, which hardly represent the input space.
- SupeRGNG is way more robust to inappropriate combinations of hyperparameters' values than "originalGNG", although up to a point.

The following parameters' values were tested with the real dataset (other parameters with default values): 1000 epochs, [25, 50, 75, 200] maximum number of neurons, and from 5 to 1295 with step 15 for both maximum edge age and number of iterations before a new neuron is added. Although all configurations of SupeRGNG achieved good values of AUC, the optimal combinations for SupeRGNG were two: both used 1000 epochs and 50 neurons, and whether 155 and 650 or 860 and 1085 for the other two parameters.

Stability of the performance results with the real dataset was further checked by using a larger value (that is, 3000) for the number of epochs. Results confirmed stability, especially with smaller numbers of neurons.

In Table 2 a brief qualitative comparison with previous works and the most optimal and stable results for both "originalGNG" and SupeRGNG are shown. It shows that our SupeRGNG yielded good and stable performance results, sometimes even outperforming other proposals that mostly not only made use of difficult to apply, invasive, expensive, or ionizing diagnostic criteria, but also were based on DNNs, which most authors deemed superior. Our SupeRGNG outperformed Modular Hybrid Growing Neural Gas (MyGNG), a modular hybrid ANN that combined a GNG for clustering and a perceptron for labeling (Cabrera-León et al. 2023). With exactly the same dataset their MyGNG obtained up to 0.956 AUC.

Table 2: Comparison with other works that used ADNI data and dealt with the MCI-AD classification task. Acronyms: Accu (accuracy), AUC (Area Under the ROC Curve), DSA (Deeply Supervised Adaptable), NT (Neuropsychological Tests), SaDE-WNN (Self-adaptive Differential Evolution Wavelet Neural Network), Sens (sensitivity), Spec (specificity).

Works	Neural method	Features	Subjects	Accu	Spec	Sens	AUC
Hosseini-Asl et al. (2018)	3D-DSA-CNN	MRI	70 MCI, 70 AD	1.0	1.0	1.0	
Basaia et al. (2019)	3D-CNN	MRI	253 EMCI, 510 LMCI, 294 AD	0.86	0.84	0.88	
Song et al. (2021)	3D-CNN	MRI, PET	160 MCI, 95 AD	0.85	0.95	0.68	
Urooj et al. (2021)	SaDE-WNN	MRI	304 MCI, 258 AD	0.94	0.98	0.86	0.97
Rashid et al. (2022)	Biceph-net (CNN-based)	MRI	N/A	0.98			
Cabrera-León et al. (2023)	MyGNG (GNG+perceptron)	NT	345 MCI, 150 AD	0.85	0.82	0.91	0.96
Current work	"originalGNG" (GNG-based)	NT	345 MCI, 150 AD	0.89	0.89	0.89	0.9
	SupeRGNG (GNG-based)			0.98	0.98	0.98	0.97

4 CONCLUSIONS AND FUTURE WORKS

We have developed a novel ontogenetic neural architecture, the Supervised Reconfigurable Growing Neural Gas, which has allowed us to develop a lightweight intelligent computing system for aiding in the early and differential diagnosis of the considered rather difficult MCI-AD classification task.

The proposed system has a great discrimination power allowing the early detection of AD in any medical setting, and even in sociosanitary institutions. This is necessary in order to improve the quality of treatment which can control the evolution of subjects with AD or MCI and, most importantly, to reach the improvement of the quality of life for both patients and caregivers.

Our system is an adequate computing solution for early AD diagnosis as it only needs a few common and non-invasive diagnosis criteria, as neuropsychological tests are, in order to reach a quick and reliable diagnosis. Furthermore, we found out that, in some cases, it is unnecessary to apply the whole tests to the patient, even only one item of the test is enough. Therefore, it can be applied on primary care as well as on specialized care.

The importance of the preprocessing stage has been demonstrated by the better performance achieved when using FCBF for feature selection, which allowed a drastic data dimensionality reduction. The reconfigurable characteristic of SupeRGNG is responsible for the performance increase compared to the "originalGNG" on which it is based.

Good performance results demonstrates the capacity of our system, yielding similar or even better results than those of other researchers' proposals, despite the fact that they frequently used more powerful methods, like DL architectures, and more invasive and expensive clinical criteria.

Several future works can be proposed. Further testing of the parameters of our SupeRGNG and comparisons with other methodologies might be carried out. Final validation of the proposed system through comparisons with human experts would be of interest. Studies on data preprocessing and feature selection techniques will be useful and necessary in order to achieve better performance results. This is particularly important for other classification tasks, including multiclass ones, that clinicians find interesting to study.

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