Deep Convolutional Neural Networks for Classification of Mild Cognitive Impaired and Alzheimer's Disease Patients from Scalp EEG Recordings

Francesco Carlo MORABITO, Maurizio CAMPOLO, Cosimo IERACITANO
DICEAM Department,
Mediterranean University of Reggio Calabria
Via Graziella Feo di Vito, 89060 Reggio Calabria, Italy
E-mail: morabito@unirc.it

Javad Mohammad EBADI
Chabahar Maritime University
Chabahar, Sistan and Baluchestan, Iran

Lilla BONANNO, Alessia BRAMANTI, Simona DE SALVO, Nadia MAMMONE, Placido BRAMANTI
IRCCS Centro Neurolesi Bonino-Pulejo
Via Palermo c/da Casazza, SS. 113, 98124 Messina, Italy

Abstract— In spite of the worldwide financial and research efforts made, the pathophysiological mechanism at the basis of Alzheimer's disease (AD) is still poorly understood. Previous studies using electroencephalography (EEG) have focused on the slowing of oscillatory brain rhythms, coupled with complexity reduction of the corresponding time-series and their enhanced compressibility. These analyses have been typically carried out on single channels. However, limited investigations have focused on the possibility yielded by computational intelligence methodologies and novel machine learning approaches applied to multichannel schemes. The study at screening level on EEG recordings of subjects at risk could be useful to highlight the emergence of underlying AD progression (or at least support any further clinical investigation). In this work, the representational power of Deep Learning on Convolutional Neural Networks (CNN) is exploited to generate suitable sets of features that are then able to classify EEG patterns of AD from a prodromal version of dementia (Mild Cognitive Impairment, MCI) and from age-matched Healthy Controls (HC). The processing system here used enforces a series of convolutional-subsampling layers in order to derive a multivariate assembly of latent, novel patterns, finally used to categorize sets of EEG from different classes of subjects. The final processor here proposed is able to reach an averaged 80% of correct classification with good performance on both sensitivity and specificity by using a Multilayered Feedforward Perceptron (MLP) of the standard type as a final block of the procedure.

Keywords—Alzheimer's disease, Mild Cognitive Impairment, Deep Learning, Convolutional Neural Networks, Scalp EEG

I. INTRODUCTION

Cognitive decline affects around the 20% of the elderly in EU. To early recognize the development of Alzheimer disease (AD) in subjects, a stage referred to as Mild Cognitive Impairment (MCI) has been considered as a prodromal syndrome of AD. At this stage, the related cognitive and behavioral impairment do not interferes with activities of daily living. AD accounts for 60% to 80% of all dementia diagnoses [1]. In AD, amyloid plaques and neurofibrillary tangles develop in the hippocampus, and in other cerebral cortex areas relevant for thinking and decisions making, thus limiting the connectivity of the brain or reducing its information processing efficiency. Currently, the clinical data available support the idea that the start-up of AD is associated with abnormal processing of β-amyloid (Aβ) peptide, that leads to the formation of Aβ plaques in the brain. This process occurs while individuals are still cognitively normal. However, it is largely unclear how Mild Cognitive Impairment (MCI) converts to AD [2-4]. In this work, by inspecting an experimental database of EEG recordings from both MCI and AD subjects, we aim to extract sets of features that can yield insights on the early electrophysiological manifestation of the disease. This can be useful to make coordinated actions on the disease management. The use of simple scalp EEG as a diagnostic tool can yield the opportunity to act at a screening level of large population at risk and to reduce the budgetary impact of their management. In the study, we propose a processing system based on computational intelligence methods and advanced machine learning to classify MCI subjects to both AD patients and Healthy Controls (HC).

In recent years, many studies considered a class comparison among healthy subjects, MCI and AD patients. They generally reported some inconsistent results, probably because of the heterogeneity and the different stages of the patients involved in the studies.

Growing evidence supports the idea that oscillatory electromagnetic brain activity might be a hallmark of the disease. EEG allows noninvasive analysis of cortical neuronal synchronization, as revealed by resting state brain rhythms. Several studies support the idea that bio-markers derived from EEG rhythms, such as power density distribution, entropic complexity, and other quantitative features, differ among normal elderly, MCI, and AD subjects, at least at group level. Regarding the classification of these subjects previous studies have shown good results in the classification of HC to AD subjects through EEG markers. In particular, some of the authors have shown that the Permutation Entropy index, both in its univariate and multivariate version, can be an interesting biomarker for discriminating among the three above mentioned categories. In addition, through the use of a compressive sensing approach, the single traces of the EEG recordings of AD patients have been shown to be characterized by higher compressibility with respect to HC; this is because of the slowing effect and this property is gradually more evident already at the MCI stage [5-9]. It thus seems that resting state EEG makers are promising for large-scale, low-cost, noninvasive screening of elderly subjects at risk of AD [11, 12].

The use of novel processing techniques able to analyze big data can however improve the classification ability of bio-markers by using latent combinations of EEG multivariate data or their frequency and/or time-frequency representations.

This paper is organized as follows: the next Section will summarize the materials and methods used; Section III will give some information on database preparation and will present the multi-stage processing system based on deep architectures. Section IV reports the main results of the study. Finally, Section V concludes the paper.

II. MATERIALS AND METHODS

A. Study population (Subjects)

The study includes 119 dementia patients (63 AD subjects and 56 MCI subjects) at various stages of clinical evolution of the disease that have been recruited at the IRCCS Centro Neurolesi "Bonino-Pulejo" of Messina (Italy). Every patient has been enrolled within an ongoing cooperation agreement between DICEAM and IRCCS; they signed an informed consent form. The local Ethic Committee has approved the related clinical protocol. An examining committee carried out all the cognitive and clinical assessments. The diagnostic procedure was in accordance with the National Institute on Aging-Alzheimer's Association criteria. After diagnostic confirmation, the patients have been categorized by gender, age, schooling, estimated age of onset of dementia, marital status and the standard test Mini-Mental State Examination (MMSE).

Current use of any medications, but particularly cholinesterase inhibitors (ChEis), Memantine, anti-depressants, anti-psychotics and anti-epileptic drugs, has been quantified considering that patients had been receiving them for at least three months before the evaluation.

B. EEG recordings and preprocessing

The EEG have been recorded according to the golden standard, i.e. during a comfortable resting state. The electrodes have been located according to the standard 10–20 International System (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz). The sampling rate has been fixed to 1024 Hz, and a 50 Hz notch filter has been used. The reference electrode was A2, located on the right ear lobe.

Before the EEG recording, all the patients and their caregivers underwent a semi-structured interview including questions about: a) quality of the last night sleep; b) quantity of the night before the recording; c) meal timing and content.

The EEG recordings have been performed in the morning. During the EEG acquisition, the patients kept their eyes closed but remained awake: indeed, the technician prevented the drowsiness by calling the patient by name. The subjects did indeed not sleep during the recording, as confirmed by the EEG visual review, which consisted in looking for possible sleep patterns in the EEG traces. Each recording lasted approximately 5', although some parts of different length of the recordings have been manually discarded for the presence of heavy and small artifacts or unexpected behavior. Although this step outputs recordings of different duration, it is needed in order to process only artifact-free epochs and to avoid losing potentially useful information in any kind of automatic artifact rejection process.

In addition, the signals have been band-pass filtered between 0.1 and 30 Hz, aiming to include the bands considered relevant for AD diagnosis.

The EEG of 23 HC have also been made available by IRCCS for the classification study.

Table I reports a summary of the characteristics of the subjects/patients here analyzed.

III. DATABASE PREPARATION

One of the objectives of the present study is to take into account the multivariate (multi-channel) nature of the EEG. As a difference with many previous studies, we do not extract features from single channels, but we tried to consider the correlation and differences among the 19 channels, at both scalp level and per area.

Different patients do not necessarily have the same pathological state at the starting point of the investigation, as also highlighted by the MMSE score. In other words, the composition of both MCI and AD patient samples is not homogeneous. This will certainly reflect in some variability of the reported findings. The classification of AD might not be as directed as the standard descriptions suggest. Subtypes of AD are characterized by different atrophy patterns that have different impacts on memory loss. In order to have a balanced database, we extracted randomly from the resulting available database just 23 recordings from AD and MCI. The remaining EEG recordings are used as test cases.

The processing system we used here to make the classification among categories is based on a deep learning framework for multivariate time-series classification: multi-channels deep convolutional neural networks (MC-DCNN) which has been proposed in [14]. Traditional convolutional neural networks (CNN) usually include two parts [13-15]. One is a feature extractor module, which is able to learn features from raw data automatically. The second module is a trainable fully connected MLP, which performs classification based on the learned features from the previous part. Eventually, a fine-tuning supervised step of the whole processing structure can be executed. Generally, the feature extractor is composed of multiple similar stages, and each stage includes three cascading layers: filter (convolutional) layer, activation layer and pooling layer. The input and output vectors of each layer are referred to as feature maps. In previous works on CNN [13-15], the feature extractor usually contains one, two or three such three-layer stages. There are two popular pooling layer, referred to as "average" and "max" pooling; we decided to use the max pooling approach since it is considered to improve the performance.

In this work, the CNN input is generated by a pre-processing step of the EEG time recordings. Each EEG channel time-series is subdivided in non-overlapping windows of 5 s; a time-frequency representation (TFR) is thus generated for each epoch, and the average TFR on all of the epochs is computed. Figure 1 illustrates the procedure of moving window on the original 19-channels EEG, and the corresponding generation of the TFR per each channel. At this level, the channels are considered separately, i.e., the features are generated independently on each channel. However, the subsequent processing schemes allows to combine the features, and, thus, to mix the channels generating, in practice, a multi-channel representation. Then, the TFR is decomposed in three parts, roughly corresponding to the rhythms of interest (sub-bands), and some statistical quantities are computed (i.e., average value, standard deviation, and skewness of the energy distributions). We thus have 3 parameters for the whole TFR, and 3 parameters for each sub-band, for a grand-total of 12 parameters (time-frequency features) for each channel. The input vector of the CNN is comprised of 12x19=228 entries.

The CNN we propose here has two hidden convolutional layers. The input vector convolves with 19 masks of 12 elements (one per channel) generating 3 features for channel. The activation layer with logistic sigmoid activation functions has length 57. Figure 2 details the transformation of 12 inputs to the 3 nonlinear outputs of the convolutional scheme. The nonlinearity used at this level is a logistic sigmoid. Then, the pooling layer generates a sub-sampled representation of 19 elements (each one is generated taking the maximum over 3 entries). The second convolutional layer is generate through the first (compressing) layer of an auto-encoder MLP. In particular, the auto-encoder MLP compresses the 19 outputs of the previous layer in 10 elements that form the input of the final classification NN (10-7-2). The classification NN is trained by supervised learning (backpropagation). The output of the network is a couple of bits (actually, a soft-max nonlinearities is used, thus the sum of the two outputs is constrained to unity), that correspond to MCI or AD label.

Figure 3 illustrates the scheme of CNN here used. The 228 inputs are passed through a convolutional layer that reduces in the ratio ¼ the vector elements. Each triple of entries is thus subsampled to just one elements, simply taking the maximum over the three numbers. This step allows to introduce an additional design variable, thus reducing the size of the feature vectors. The resulting 19 elements are then further reduced to just 10 through the auto-encoding scheme (at this level, the corresponding labels are not used, namely, the training is unsupervised). Finally, the 10 latent variables are used as the input of the classification NN.

IV. RESULTS

The database of 23*3 EEG recordings (AD-MCI-HC) has been used to train the CNN model to extract set of features and to classify the patterns. The technique of k-fold validation (k=4) has been used to measure the performance on test set, as usual in machine learning literature.

The EEG recordings have been preprocessed through a time-frequency transformation in order to extract 228 parameters from the generated maps corresponding to all of the 19 traces (channels). These 228 parameters form the input of the processing system. The TFR here selected is the Continuous Wavelet Transform (CWT) with the Mexican Hat function selected as mother wavelet. Other possible TFR schemes can be used, for example the Adaptive Optimal Kernel (AOK) procedure. Then, the CNN scheme based on one layer of filtering+subsampling step and an auto-encoder MLP will reduce the dimensionality of the input patterns to 10 latent features that form the input of the MLP used as a classification NN.

Although not essential for the procedure here considered, that aims to extract good latent features, the performance of the auto-encoder are quite good (reconstruction accuracy >90%, p=0.01) both on the training and the test database.

The performance of the final classification model on the available database has been measured with different metrics. With regard to the accuracy of the classification system, it is able to achieve an 82% accuracy for the three-way scheme (AD-MCI-HC). In this case, the output of the classification NN includes three nodes with soft-max nonlinearities, and the class is assigned to the one corresponding to the maximum of the three numbers. The corresponding sensitivity and specificity are of 83% and 75%. The performance achieved are certainly better for two-way classifiers, reaching 85%, in particular, for discriminating AD and MCI from HC. The discrimination ability of the AD vs. MCI processor was 78% (sensitivity 78%, specificity 75%). The full set of results is reported in Table II. The results reported refer to the performance measure in the validation phase. The performance on the training database are always better with an average accuracy of more than 95%.

The good performance achieved implies the conclusion that the system is able to extract from the original database a subset of latent features that are capable to represent the differences among the three sub-classes. This can be useful to support more elaborated diagnoses, based on various clinical supports.

V. CONCLUSIONS

In this paper, we proposed a deep machine learning approach based on the convolutional neural networks (CNN) concept and on the autoencoder MLP to classify AD patients from MCI and HC subjects. The objective is to gain insight on the differences among the three categories just using scalp EEG recordings, that are easy to generate, cheap, noninvasive, and well accepted by subjects, as a difference with Magnetic Resonance. The number of patients considered in this study is originally relevant; however, we decided to use a limited subset, in order to work on a balanced database. An ongoing effort is carried out within our research groups to generate a large database for both MCI and AD patients, also adding a similar number of HC. One aspect not considered here is the stage of the AD; however, most severe cases are excluded from the analysis, in favor of early stage patients.

The results achieved show that although just scalp EEG recordings have been considered, it seems possible, in the limits of the available database here analyzed, to clearly discriminate with quite good classification performance AD subjects from both MCI and HC.

In the future, a detailed study on the latent features extracted by the CNN model will be carried out, aiming to substantiate the approach and better justify the system's performance in view of any translational study.

TABLE I.

Category	Number of subjects	Age	MMSE
AD	63	78.1±3.8	16.6±5.4
MCI	56	76±6.6	23.4±6.68
HC	23	75±5.7	-

TABLE II.

Category	%Accuracy	%Sensitivity	%Specificity
AD-MCI-HC	82	83	75
MCI-HC	85	84	81
AD-HC	85	85	82
MCI-AD	78	78	75

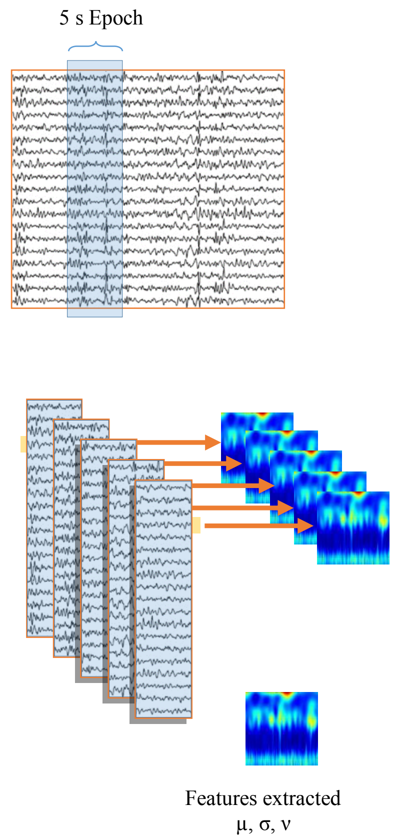

Figure 1 – The EEG Pre-processing Scheme: The recording is decomposed in Epochs of 5 s; for each epoch, the TFR is computed for each channel; the final TFR is obtained by averaging the sub-TFR obtained per epoch.

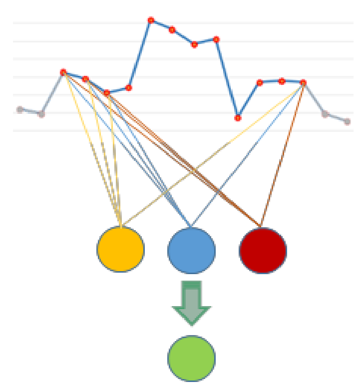

Figure 2 – A detail of the convolutional scheme on a set of 12 input features (corresponding to one channel).

REFERENCES

[1] McKhann G.M., D.S. Knopman, H. Chertkow, B.T. Hyman, C.R. Jack Jr., C.H. Kawas *et al.*, The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association workgroup Alzheimer’s Dement, 7 (2011), pp. 263–269.

[2] Braak H., Braak E., Neuropathological stageing of Alzheimer’s-related changes, Acta Neuropathol, (1991), Vol.82, pp.239-259.

[3] Y. He, Z. Chen, G. Gong, A. Evans, Neuronal Networks in Alzheimer's Disease, The Neuroscientist, 1 (2009), 15(4), pp.333-350.

[4] M. A. Kramer, F.L. Chang, M.E. Cohen, D. Hudson A.J. Szeri, Synchronization measures of the scalp electroencephalogram can discriminate healthy from Alzheimer’s subjects, International Journal of Neural Systems, Vol. 17, No. 02, pp. 61-69.

[5] D. Labate, F. La Foresta, G. Morabito, I. Palamara, F.C. Morabito, Entropic measures of EEG complexity in Alzheimer's disease through a multivariate multiscale approach, IEEE Sensors Journal, Vol. 13 (9), pp. 3284-3292, 2013.

[6] Morabito F. C., Labate D., La Foresta F., Bramanti A., Morabito G. and Palamara I., Multivariate multiscale permutation entropy for complexity analysis of Alzheimer’s disease EEG, Entropy 14 (2012) 1186-1202.

[7] F.C. Morabito, D. Labate, A. Bramanti, F. La Foresta, G. Morabito, I. Palamara, and H.H. Szu, Enhanced Compressibility of EEG Signal in Alzheimer's Disease Patients, IEEE Sensors Journal, 13(9), pp. 3255-3262, 2013.

[8] Labate D., La Foresta F., Palamara I., Morabito G., Bramanti A., Zhang Z., Morabito F.C., EEG complexity modifications and altered compressibility in mild cognitive impairment and Alzheimer's Disease, Smart Innovation, Systems and Technologies, Vol. 26, pp. 163-173, 2014.

[9] Morabito F.C., Labate D., Morabito G., Palamara I., Szu H.H., Monitoring and diagnosis of Alzheimer’s disease using a noninvasive compressive sensing EEG, Proc. SPIE 8750, Independent Component Analyses, Compressive Sampling, Wavelets, Neural Net, Biosystems, and Nanoengineering XI, 87500Y (May 29, 2013).

[10] Jeong, J. EEG Dynamics in Patients with Alzheimer’s Disease. *Clinical Neurophysiology* (2004), 115, pp.1490-1505.

[11] Dauwels, J.; Srinivasan, K.; et al. Slowing and Loss of Complexity in Alzheimer’s EEG: Two sides of the Same Coin? *International Journal of Alzheimer’s Disease*, 2011, 539621.

[12] Adeli H., Ghosh-Dastidar S., Dadmehr N., Alzheimer's disease: models of computation and analysis of EEGs, Clin EEG Neurosci. 2005 July; 36(3):131-40.

[13] Y. Zheng, Q. Liu, E. Chen, Y Ge, J. L. Zhao, Time series classification using multi-channels deep convolutional neural networks. In: Li F, Li G, Hwang S W, Yao B, Zhang Z, eds, Web-Age Information Management, volume 8485 of Lecture Notes in Computer Science, 298–310. Springer International Publishing, 2014.

[14] Y. Zheng, Q. Liu, E. Chen, Y Ge, J. L. Zhao**,** Exploiting multi-channels deep convolutional neural networks for multivariate time series classification. Frontiers of Computer Science. 10(1), 96-112, 2016.

[15] C. A. Lima , A. L. Coelho, M. Eisencraft, Tackling EEG signal classification with least squares support vector machines: a sensitivity analysis study. Comput Biol Med. 40(8), 705–714, 2010.

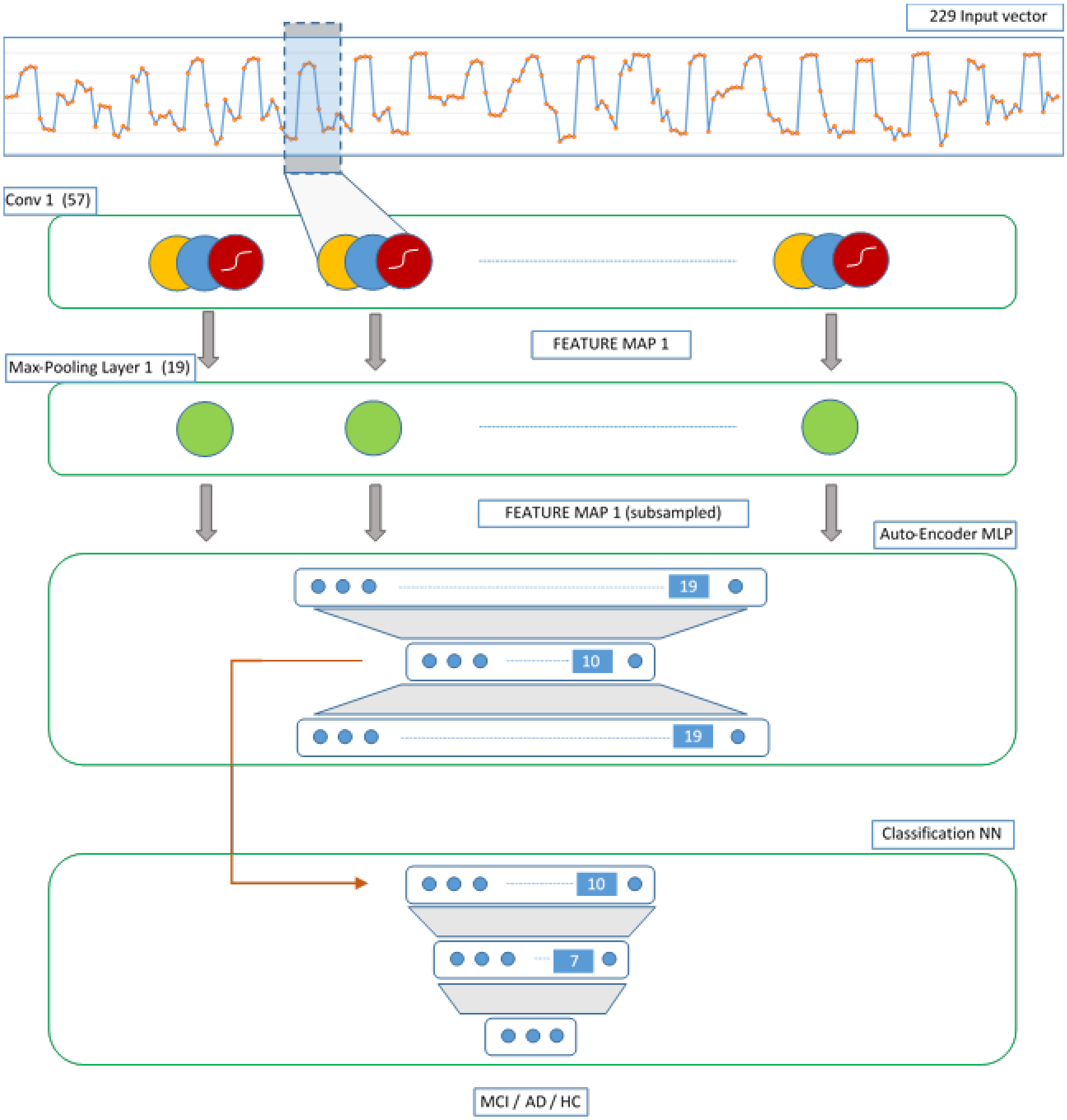

Figure 3 – The Proposed Convolutional Neural Network Scheme. The vector of features obtained from the TFR are convolved with suitable masks in order to obtain high-level feature representation. Then, an auto-encoding NN generates a further compressed latent representation of 10 features. Finally, the classification NN is trained to discriminate among AD, MCI and HC subjects.