Longitudinal Study of Alzheimer's Disease Degeneration through EEG Data Analysis with a NeuCube Spiking Neural Network Model

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***Abstract*—Motivated by the dramatic rise of neurological disorders, we propose a SNN technique to model electroencephalography (EEG) data collected from people affected by Alzheimer's Disease (AD) and people diagnosed with mild cognitive impairment (MCI). An evolving spatio-temporal data machine (eSTDM), named the NeuCube architecture, is used to analyse changes of neural activity across different brain regions. The model developed allows for studying AD progression and for predicting whether a patient diagnosed with MCI is more likely to develop AD.**

I. Introduction

Over the last several decades, researchers have been trying to understand and model the human brain. The growing size of the elderly population and high incidences of neurological disorders, such as Alzheimer's Disease (AD), have made understanding the human brain a priority for the community to deal with. Since neurological disorders affect mechanisms involved in the formation of memory and synaptic plasticity, scientists from all over the word have focused their resources and efforts toward the understanding of these areas. As a consequence of the efforts made, there is a considerable amount of data now available. Most of the data collected possess both spatial and temporal information, which is difficult to process. Although, if we understand when and where abnormalities arise in the brain, we can also understand why and how they affect the other areas of the brain and how they evolve. Information scientists have developed computational techniques, such as spiking neural networks (SNN), that model the data available, emulating neural and learning functions of the human brain. However, many of the techniques used are not appropriate, as the data is heavily pre-processed, which comes at the cost of both time and information. Also several models lack biological plausibility and therefore they cannot represent the phenomena of study. This is why, we need to find a suitable modelling technique in order to model and understand the brain information available and make proper use of it. A type of spatio-temporal brain data (STBD) that has long been used to analyse mild cognitive impairment (MCI) and AD is electroencephalography (EEG) [1]. In this paper, we propose a SNN approach that models EEG data to achieve neural degeneration prognosis. The methodology is based on an evolving spatio-temporal data machine (eSTDM), named NeuCube [2]. As demonstrated in [3], the NeuCube allows for studying functional changes in brain activity across different conditions and different groups of subjects. The NeuCube has already been successfully applied to model and analyse AD EEG data, demonstrating its potential use as an indicator of the onset and/or the progression of a neurodegenerative process [4]. Now, we want to apply the NeuCube potential to a longitudinal study on patients affected by AD and people diagnosed with MCI. We want to study any cognitive fluctuation across time, paying special interest to finding evidence of neural degeneration across EEG rhythms. The relevance of oscillatory phenomena related to EEG functionality has been demonstrated in many studies such as [5]. These phenomena correspond to rhythms of type delta (δ: 0.5-3.5 Hz, generally related to sleep or rest); theta (θ: 3.5-7.5 Hz, generally related to learning, memory and sensory motor processing); alpha (α: 7.5-12.5 Hz, generally related to meditation); beta (β: 12.5-30 Hz, generally related to mental calculation, anticipation or tension); and gamma (γ: 30-60 Hz, generally related to attention and sensory perception). These rhythms are associated with different cognitive processes and communication between neuronal cells [6]. By extrapolating functional changes of brain activity from the EEG rhythms, we aim at developing a model that can be used by experts to diagnose the early onset of AD and to evaluate its progression. The paper is constructed in the following way: Section II describes the data and the

methodology used to analyse it; Section III reports the results and the conclusions; and in Section IV future work is also discussed.

II. EEG Data Modelling with the NeuCube Architecture

A. EEG Data Description

1) Study Population: The EEG data was collected by the Scientific Institute for Research, Hospitalization and Health Care (IRCCS) Bonino-Pulejo Neurolesi Centre of Messina, Italy. The data collection protocol was approved by the local ethical committee and consent forms were signed by the patients under study. Standard inclusion criteria were followed to select patients for the analysis. They underwent cognitive and clinical assessments, including mini-mental state examination (MMSE). Diagnosis of AD was made according to the criteria of the National Institute of Ageing-Alzheimer's Association. After diagnostic confirmation, patients were discriminated by gender, age, education, dementia onset, marital status and MMSE scores. All patients were under the influence of drug treatments such as cholinesterase inhibitors (ChEis), Memantine, anti-depressants, anti-psychotics and anti-epileptic drugs. The dosage of each drug administrated for the three-month period prior to the experiment was carefully monitored.

A total of seven patients were selected for the EEG data collection: three affected by AD and four diagnosed as suffering from MCI. They were all followed longitudinally for three months. During this period of time, the EEG data was recorded twice, at the beginning of the study and at the end of it, denoted as t_0 and t_1.

2) Data Collection: Before data collection, all patients and their caregivers went through a semi-structured interview, which included questions regarding the quality and duration of their sleep the night before the experiment along with the food consumed and the time it was consumed. Recordings were carried out using 19 EEG channel locations: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2 and the A2 electrode was used as reference. These were placed according to the sites defined by the standard $10-20$ international system. Data was recorded at a sampling rate of 1024 Hz for 5 minutes and a 50 Hz notch filter was applied during collection. Data was collected in the morning and under resting conditions, with subjects awake with their eyes closed and always under vigilant control.

3) EEG preprocessing: The EEG data was downsampled to 256 Hz and processed using a 5 seconds sliding temporal window (*i.e.* one window includes 1280 EEG samples). The EEG signal was divided into rhythms of type δ, θ, α and β by using a set of four band-pass filters implemented in Matlab that use inverse Fast Fourier Transform (FFT). The four EEG sub-bands were partitioned into m non-overlapping windows, where m depends of the length of the recording, which was 5 minutes on average.

B. The NeuCube for STBD Modelling and Understanding

The NeuCube architecture is an eSTDM based on neuromorphic, brain-like SNN information processing principles [2]. As explained in [7], a NeuCube development system consists of 10 different modules. To carry out the research presented in this paper, we used the basic configuration of NeuCube for STBD modelling and understanding [7] (or module M1) freely available online at: http://www.kedri.aut.ac.nz/neucube/.

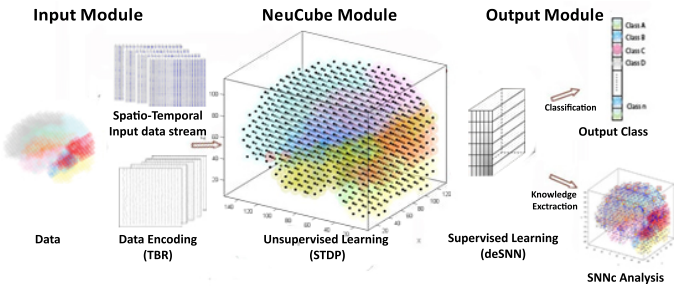


Fig. 1: The NeuCube for STBD modelling with its three main modules: input module for data encoding; a 3D SNN module; an output module for data classification and analysis.

In Fig. 1 the NeuCube for STBD modelling, classification and analysis is divided into three main modules:

- Input module, where input data are encoded into trains of spikes.
- 3D SNN cube (SNNc) module (the NeuCube module), where time and space characteristics of the STBD are captured and learned.
- Output module for data classification and new knowledge extraction from the SNNc analysis.

In the following paragraphs, these modules are used to describe the methodology applied to the study.

1) Input Module and EEG Data Encoding: The EEG data was first ordered as a sequence of real-value data vectors. Every data vector was transformed into a spike train using the threshold base representation TBR_{thr} algorithm [8]. This threshold was used to generate two types of spike sequences: a positive spike train corresponding to the signal increment, which is mapped to a specific input neuron in the SNNc; and a negative spike train, corresponding to the signal decline, which is mapped into another input neuron of the SNNc that is placed in the same position as the positive one. Algorithms that apply bi-directional threshold to transform vectors of consecutive values into trains of spikes, well suit EEG data as they identify only significant differences in the signal gradient (as demonstrated in Fig. 2). In the example shown in Fig. 2, 115 spikes were generated after applying the TBR_{thr} algorithm to the first 500 EEG data points recorded at t_1 from the central C_Z channel only of a patient affected by AD. As we can see from the figure, out of the total amount of spikes generated, 58 were positive spikes (identified as $+1$) and 57 were negative spikes (identified as -1).

2) NeuCube Module and Unsupervised Learning: The spike sequences were presented to the SNNc, which was

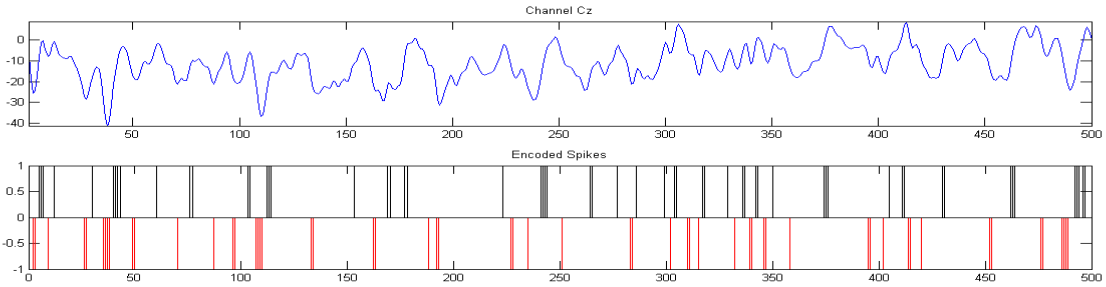


Fig. 2: Example of encoding spatio-temporal EEG data into trains of spikes using the TBR_{thr} algorithm [7]. The image shows the first 500 data points only of one EEG channel (the central C_Z channel). The EEG signal (0-64 Hz) recorded from a patient affected by AD at time t_1 of measurement is used for this example.

implemented using leaky integrate-and-fire (LIF) neurons [9]. The number of neurons in the cube was set as 1471 neurons, as each neuron represents 1 cm^3 of population of the human neural cells of the Talairach brain atlas [10]. The neurons were mapped in the cube following the standard mapping suggested in [11]. Thus, the spike sequences that represent the data from EEG channels are presented to the SNNc that reflects the number of input variables (*e.g.* the 19 EEG channels) and the functional brain areas associated with them. The SNNc was initialised according to the small-world (SW) connectivity [2] distance, which is based on the biological process that makes neighbouring neural cells to be highly and strongly interconnected Neurons' initial connection weights were calculated as the product of a random number $[-0.1, +0.1]$ and the multiplicative inverse of the Euclidean distance $d(i, j)$ between a pre-synaptic i and a post-synaptic neuron j (calculated according to their (x, y, z) coordinates). 20% of these weights were selected to be negative (inhibitory connection weights), as in the mammalian brain the number of GABAergic neurons is found to be about 20-30% [12], while 80% were positive (excitatory connection weights). The SNNc was trained in an unsupervised mode using the spike time dependent plasticity (STDP) [13] learning rule, as it allows spiking neurons to learn consecutive temporal associations from the EEG data within and across EEG channels. By using this unsupervised learning rule, a connection between two neurons become stronger as their temporal order of activation persists and repeats with the time. After learning, the final connectivity and spiking activity generated in the network was analysed and interpreted for a better understanding of the data and the brain processes that generate it (as demonstrated in Section III-B). This makes the NeuCube useful for learning spatio-temporal patterns from the STBD.

3) Output Module for Supervised Learning: The output classifier was trained *via* supervised learning method, using the dynamic evolving spiking neural network (deSNN) algorithm [14]. This algorithm combines the rank-order (RO) learning rule [15] with the STDP [13] temporal learning. In one pass data propagation, the same data used for the unsupervised training was propagated through the SNNc again to train the output classifier. Every training sample that represents a labelled EEG sequence of a patient was associated to an output neuron that is connected to every neuron in the SNNc. Initial connection weights between input and output neurons were all set to zero. Connection weights were initialised according to the RO rule and modified according to the spike driven synaptic plasticity (SDSP) learning rule [16]. Every generated output neuron was trained to recognize and classify spatio-temporal spiking patterns of the SNNc triggered by a corresponding labelled input data sample (as demonstrated in Section III-A).

III. Preliminary Results

A. Classification

To investigate whether data collected during the two different sessions (t_0 and t_1) discriminates four different stages of neural degeneration (from early MCI to advanced AD), we classified the data samples by using the entire EEG signal from 0-64 Hz. Data was divided into four classes: data collected at t_0 from subjects diagnosed as having MCI was labelled as class 1 (MCI t_0), while the data collected at t_1 from the same subjects was labelled as class 2 (MCI t_1); and data collected at t_0 from AD patients was labelled as class 3 (AD t_0), while the data collected as t_1 from the same patients was labelled as class 4 (AD t_1). In total we obtained 14 samples, two for each of the seven subjects, one at t_0 and one at t_1. Even though, every subject underwent several minutes of data recording, we resized each samples to 42240 data points for 19 EEG channels, as this was the size of the smallest sample available.

A crucial step in obtaining desirable results from the NeuCube model is the optimisation of its numerous parameters. This can be achieved *via* grid search method, genetic algorithm, or quantum-inspired evolutionary algorithm [17], [18]. Therefore, unsupervised and supervised training, and validation are repeated changing the values of the parameters until the desired classification output is achieved. In this study, this was obtained *via* grid search method that evaluated the best combination of parameters that resulted in the highest classification accuracy. The optimised parameter values are:

- The TBR_{Thr} for encoding algorithm was set at 0.5;
- The SW connectivity radius was set at 2.5;

- The threshold of firing Θ, the refractory time r and the potential leak rate l of the LIF neuron model were set at 0.5, 6 and 0.002 respectively;
- The STDP rate parameter α of the unsupervised learning algorithm was set at 0.01; rate was set at 0.001;
- The variables mod and $drift$ of the deSNN classifier were set at 0.8 and 0.005 respectively [14].

In Table I, we report the classification accuracy obtained with this combination of parameters. The results, obtained after testing, are expressed in the confusion table as the number of correctly classified samples *versus* the number of misclassified samples.

TABLE I: The NeuCube confusion table obtained by classifying EEG data from 7 patients as a test subset into the four classes: MCI t_0, MCI t_1, AD t_0 and AD t_1. The correctly predicted classes are located in the diagonal of the table.

Confusion Table				
	MCI t_0	MCI t_1	AD t_0	AD t_1
MCI t_0	**2**	1	0	0
MCI t_1	0	**1**	0	0
AD t_0	0	0	**1**	0
AD t_1	0	0	0	**1**

As a result of training a NeuCube model to classify data from the four classes: MCI t_0, MCI t_1, AD t_0 and AD t_1, the testing results showed a perfect classification of three classes, but not MCI t_1. These results demonstrated the capability of the NeuCube to achieve high classification accuracy for the classes MCI t_0, AD t_0 and AD t_1, but also to indicate if some of the patients data from the MCI t_1 class is closer to the data from the MCI t_0 class or to the AD t_0 class, pointing to a possible development of the disease in the future. As reported in Table I, one of the two subjects from the MCI t_1 class showed similar EEG patterns at t_1 as in t_0, indicating that this subject is not likely to develop AD in the near future. The four classes were in effect identifying four different stages of neural degeneration (from early MCI to advanced AD). This is a good indication that a NeuCube model can be used in the future for predicting if MCI patients will develop AD.

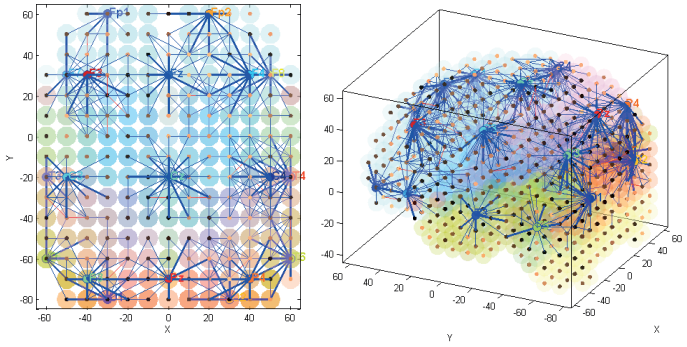
B. Analysis of Functional Changes in Brain Activity of AD

As a case study, we selected EEG data collected from a patient affected by AD (a woman of 83 years of age). This patient scored 16, at t_0, and 13, at t_1, in the MMSE cognitive test, which indicates decline in cognitive ability. However, more information can be obtained from the EEG data by discriminating relevant EEG sub-bands. Our goal is to better understand the advancement of the disease and to localize specific areas of the brain that are more seriously affected by neural degeneration, this may well lead to a better personalised treatment.

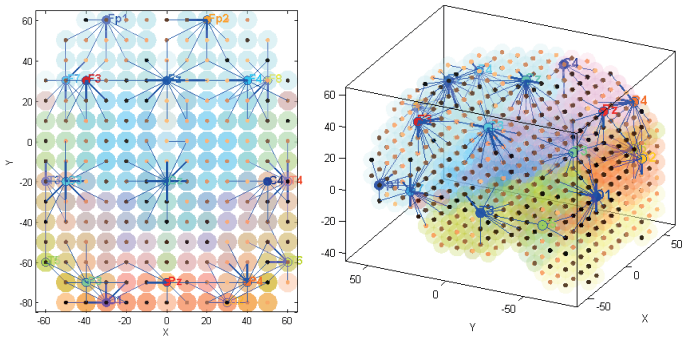
Data was visualised after STDP learning by applying a threshold of 0.2 to the total amount of connection weights generated.

Fig. 3 and Fig. 4 show the trained SNNc along with the corresponding 12 brain functional areas. Yellow-green denotes the temporal lobe; pink denotes the parietal lobe; light-blue denotes the frontal lobe; red denotes the fronto-temporal space; light-yellow denotes the posterior lobe; orange denotes the occipital lobe; green denotes the anterior lobe; blue denotes the sub-lobar region; grey denotes the limbic lobe; purple denotes the pons; blue-green denotes the midbrain; and brown denotes the medulla. Also, the 19 input neurons are labelled according to their corresponding EEG channels. In the figures, blue lines indicate excitatory synapses and red lines inhibitory synapses; the thickness of these lines indicates the strength of activity between neurons.

Fig. 3 shows the SNNc connectivity generated after unsupervised learning of the EEG signal (0-64 Hz) at t_0 and t_1.



(a) EEG signal collected at t_0.

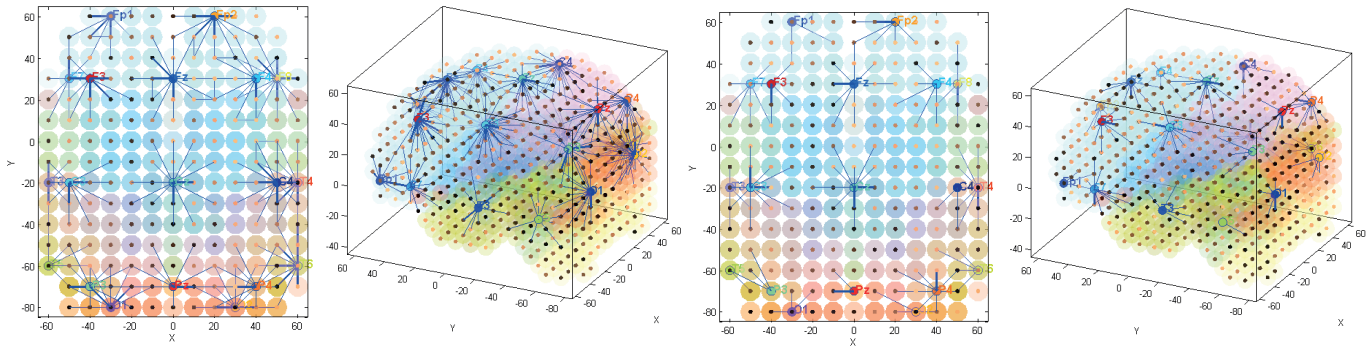


(b) EEG signal collected at t_1.

Fig. 3: Connectivity generated after unsupervised learning of the SNNc was performed on the encoded EEG signal (0-64 Hz). The figure shows a xy-plane projection and the 3D SNNc.

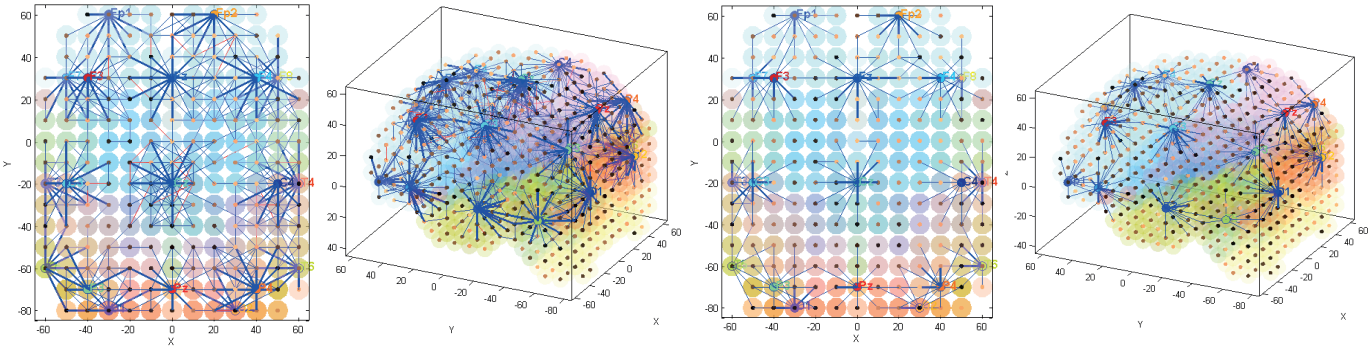
The figures show significant decrease in neural activity from t_0 to t_1. The observed reduction in the model neural connectivity is compatible with neuronal changes associated with the advance of the disease. AD is a degenerative brain disorder that eventually destroys brain cells causing decline in cognitive activity and memory loss [19]. Using the NeuCube SNN-based visualization, we can obtain a better understanding and interpretation of the physiological brain ageing of AD patients.

More information can be extracted from the data by identifying relevant EEG sub-bands for AD to study the patient



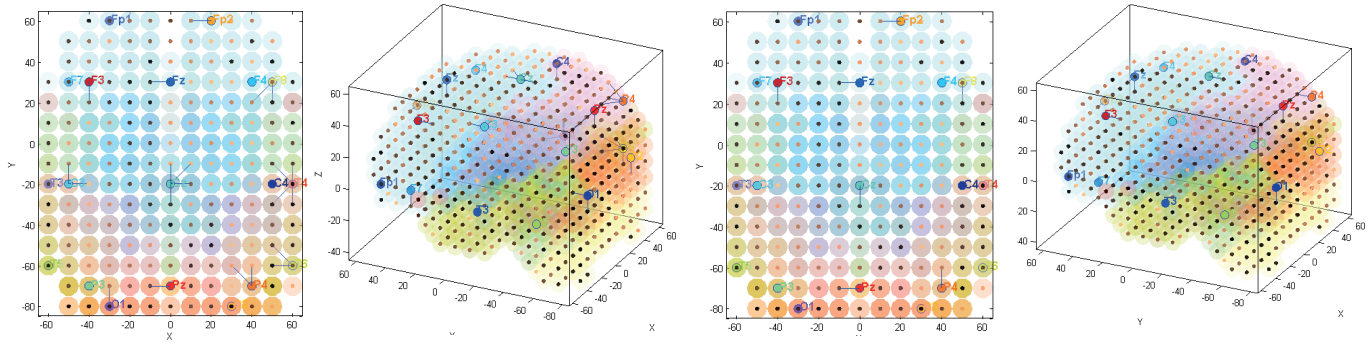
(a) α band of EEG collected at t_0.

(b) α sub-band of EEG collected at t_1.



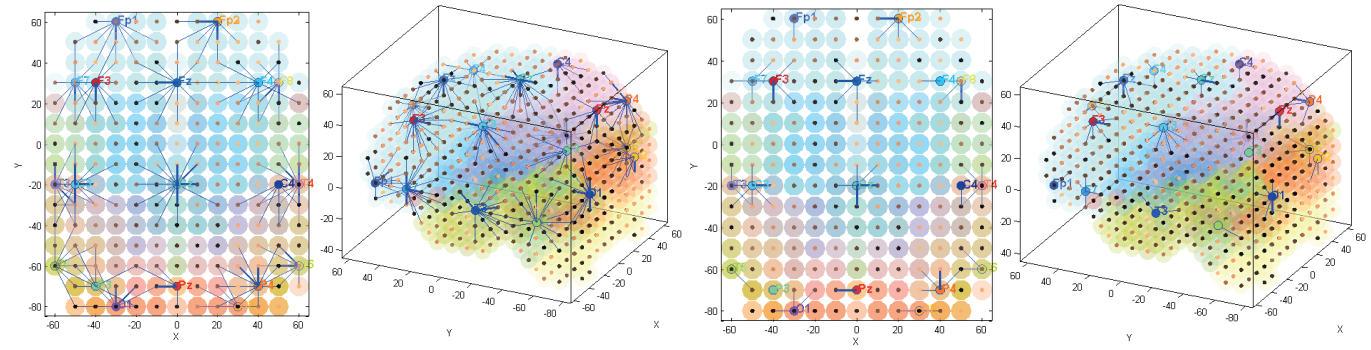
(c) β sub-band of EEG collected at t_0.

(d) β sub-band of EEG collected at t_1.



(e) δ sub-band of EEG collected at t_0.

(f) δ sub-band of EEG collected at t_1.



(g) θ sub-band of EEG collected at t_0.

(h) θ sub-band of EEG collected at t_1.

Fig. 4: Connectivity generated in the SNNc after unsupervised learning of the EEG data in α, β, δ and θ sub-bands at t_0 and t_1. The figure shows the 2D (xy) plane and the 3D (x, y, z) SNNc. Significant reduction of connectivity is observed in the created NeuCube models from time t_0 to t_1 in the β sub-band and less in the α and θ sub-bands, across the cortical areas.

neural activity. Fig. 4(a)-(h) show the SNNc connectivity generated after unsupervised learning of the EEG data in α, β, δ and θ sub-bands at t_0 and t_1. As we can study from the figures, functional connectivity decreases as the disorder advances (from t_0 to t_1). The disease affects both α and θ sub-bands, decreasing the connectivity across the brain regions. For the δ sub-band almost no connectivity is generated over the brain regions. Researchers reported that older AD patients have relatively more power in the α sub-band compared to the δ sub-band [20]. These findings are consistent with the ones reported in Fig. 4. Therefore, these brain frequency bands can be considered significant EEG markers for this AD patient. Higher frequency bands, such as β, show higher activity at t_0 and t_1 when compared with the other brain waves. Still, neural connectivity generated in β frequency decreases from t_0 to t_1 (Fig. 4(c) and (d) respectively). Reduction of β wave activity over time is correlated with severe cognitive dysfunction [21]. This finding suggests that a decrease in β power is not only due to ageing, but may reflect an alteration of AD especially in the early stages. The analysis of the SNNc models at t_0 and t_1 confirms neurological studies that have found a significant decrease of EEG power at 14-18 Hz and 18-22 Hz (β sub-band) in AD patients. Fig. 4(g) and (h) show a reduction in the neuronal connectivity, particularly in the temporal regions, from t_0 to t_1. This is produced by memory impairments in old AD patients over time that is most pronounced in the θ band frequency. This analysis provides new evidences that can be used to improve our understanding of AD. Thus, the NeuCube can provide a powerful decision making tool that can support clinicians to target efficient drug treatments.

IV. Conclusion and Future Work

The goal of the study has been to analyse how the proposed NeuCube SNN system can be used for the classification and analysis of AD EEG data during longitudinal studies. This is important for the creation of new decision-support systems for neuronal degeneration prognosis and neurodegenerative pathologies understanding. By means of the proposed model, we were able to investigate patterns of neurons' electrical activity elicited from patients diagnosed with MCI and/or AD during a longitudinal study. We demonstrated the potential of using SNNs for the analysis of complex dynamic brain activity generated by progressive disorders. Particularly, the used NeuCube SNN system enables us to predict whether a MCI patient is likely to develop AD. If we were using traditional statistical analysis methods, such as EEGLAB [22] or Neuroguide [23], we would be able to differentiate the EEG band frequencies in the longitudinal study only. However, the NeuCube visualisation module is also able to reveal the areas of the brain involved with the variation of neural activity. Significantly, the NeuCube models revealed new findings, such as tracing the neural brain activities, which we would not have obtained if we were using traditional statistical methods instead. Also, our findings prove the NeuCube potential for dealing with both spatio and temporal components of EEG data without losing any meaningful information. The proposed methodology could be further developed in a computational neurogenetic model for processing STBD and genetic data related to AD.

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