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Analysis of connectivity in NeuCube spiking neural network models trained on EEG data for the understanding of functional changes in the brain: A case study on opiate dependence treatment

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ABSTRACT

The paper presents a methodology for the analysis of functional changes in brain activity across different conditions and different groups of subjects. This analysis is based on the recently proposed NeuCube spiking neural network (SNN) framework and more specifically on the analysis of the connectivity of a NeuCube model trained with electroencephalography (EEG) data. The case study data used to illustrate this method is EEG data collected from three groups—subjects with opiate addiction, patients undertaking methadone maintenance treatment, and non-drug users/healthy control group. The proposed method classifies more accurately the EEG data than traditional statistical and artificial intelligence (AI) methods and can be used to predict response to treatment and dose-related drug effect. But more importantly, the method can be used to compare functional brain activities of different subjects and the changes of these activities as a result of treatment, which is a step towards a better understanding of both the EEG data and the brain processes that generated it. The method can also be used for a wide range of applications, such as a better understanding of disease progression or aging.

1. Introduction

Over the last four decades, EEG has been used extensively for the study of brain functional changes under different conditions, including neurological disease and treatment with drugs. In principle, EEG data can show changes of cortical activity that occur during milliseconds (Gevins et al., 2011; Smith et al., 2006), and it is recognised as a sensitive measure of drug effects on the brain and, in particular, of drug effects on the size and on the time course of post-synaptic potentials (Gevins et al., 2011; Smith et al., 2006). Nevertheless, localisation of changes in cognitive activity is limited in EEG in contrast to magnetic resonance imaging (MRI). Recently, a growing number of methods have been developed to localise the generators of EEG components, for example low resolution brain electro-magnetic tomography (LORETA) (Pascual-Marqui et al., 1999; Pascual-Marqui, Michel, & Lehmann, 1994) and statistical parametric mapping (SPM) (Penny, Friston, Ashburner, Kiebel, & Nichols, 2011).

Using standard statistical or machine learning techniques to classify EEG data from groups of patients under different treatment can suggest whether there is a functional improvement, as a result of treatment. For example, in already published studies (Wang, Wouldes, Kydd, Jensen, & Russell, 2014; Wang, Wouldes, Kydd, & Russell, 2012; Wang, Kydd, Wouldes, Jensen, & Russell, 2015), we demonstrated that improved cognitive functions in patients undertaking methadone maintenance treatment (MMT) in contrast to those dependent on illicit opiates. Additionally, we demonstrated that MMT cognitive functions are comparable to healthy subjects. Previously, we have investigated group difference on spectral power of EEG data using traditional statistical methods (*i.e.* analysis of covariance, independent sample t-test, etc.), and the results only reveal the fluctuation of neural activity within an individual channel. Traditional statistical and AI methods applied to study functional brain changes lack the ability to explain which functional areas of the brain are affected during treatment, how much they are affected and what are the changes of the dynamics of the brain as a chain of spiking activity over time. Time information is present in spatio-temporal brain data (STBD), such as EEG data, but when the data is processed (*e.g.* classified) this information is

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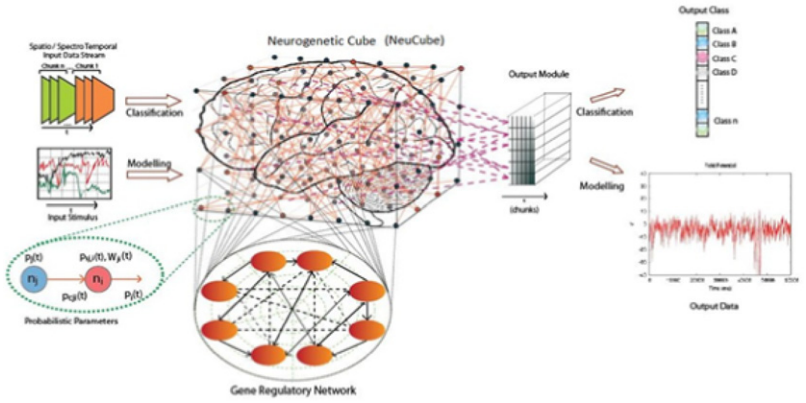

Fig. 1. The NeuCube architecture with its three main modules: input data encoding module; a 3D SNN cube module; an output evolving classification module (Kasabov, 2014). An optional Gene Regulatory Network (GRN) module can be incorporated if gene information is available. The spiking neurons can be implemented as a simple leaky integrate and fire model or probabilistic models (shown in the lower left section).

compressed and there is no explanation of the final results related to the time component. In this respect traditional methods can be considered "black boxes" in a sense (Kasabov, 2014). These are important questions that need to be addressed for a better understanding of functional changes in the brain under various conditions, including: neurological disease progression, disease treatment over time and ageing.

Recently, a new methodology, the "NeuCube framework", based on the connectivity analysis of evolving brain-inspired spiking neural networks (eSNN) models has been proposed (Kasabov, 2014). It has been demonstrated that the NeuCube provides significant accuracy of classification and interpretation of the brain data, suggesting its potential application to neurological clinical research. In this study, we introduce a new method for the connectivity analysis of NeuCube model trained on EEG data to reveal brain functional changes under different conditions and across different groups of subjects. As a case study, we take the problem of identifying differences between people with opiate addiction and those undertaking substitution treatment for opiate addiction.

The paper is constructed in the following way: Section 2 describes the functional characteristics of the NeuCube eSNN framework. Section 3 presents a methodology for connectivity analysis of a NeuCube model. Section 4 presents a case study of EEG data analysis of functional brain changes across groups of opiate addicts and those who have taken MMT in comparison with control subjects. This section presents results of the analysis and discussions based on a comparative analysis between NeuCube models and traditional statistical and machine learning techniques. The conclusion in Section 5 clearly identifies the NeuCube models as being superior to other methods, for the purpose of revealing functional brain changes and the prediction of response to treatment across applications.

2. The NeuCube spiking neural network framework

2.1. Spiking neural networks (SNN)

Some of the most valuable techniques used in *in silico* investigations are brain inspired machine-learning techniques, such as SNN. These techniques are potentially able to learn and reveal time, space and frequency information "hidden" in the STBD. In fact, the neural activity recorded can be represented as binary events, called spikes, which are then fed into a model. Each neuron of the network represents a computational unit, which is able to modify and evolve connections with the other neighbouring neurons to reflect the timing of the data from the sensory inputs (Kasabov, 2014). This is one of the main principles of SNN, considered the third generation of brain-inspired neural network techniques (Gerstner, 1995, 2001; Gerstner, Sprekeler, & Deco, 2012). Some of the main advantages that SNN techniques provide are: compact representation of space and time; fast information processing; time-based and frequency-based information representation; memory-based, so that they can be studied after training for data understanding.

2.2. The NeuCube SNN framework

The main principles of the NeuCube framework were first presented in Kasabov (2012, 2014) and further developed in Chen, Hu, Kasabov, Hou, and Cheng (2013), Scott, Kasabov, and Indiveri (2013) and Tu et al. (2015). A NeuCube model (Fig. 1) consists of: input data encoding module; a 3D SNN cube (SNNc); an eSNN classifier; and an optimisation module.

NeuCube has already been applied successfully for the classification and knowledge extraction of both EEG (Capecci et al., in press; Kasabov & Capecci, 2015) and functional MRI (fMRI) (Doborjeh, Capecci, & Kasabov, 2014) cognitive data, and to other type of spatio-temporal data for personalised disease prognosis (Kasabov et al., 2014; Othman et al., 2014) and neuro-rehabilitation (Chen et al., 2013; Taylor et al., 2014). This paper contributes to the set of methods related to the NeuCube with the introduction of a new methodology for connectivity analysis in relation to brain functions represented in the EEG STBD. The proposed method is applied on EEG data collected from people with drug addiction to reveal the possible changes of neural cognitive activity related to the treatment and the dose of drug administered. More specifically, we quantified the differences between groups on functional connectivity (*e.g.* positive/negative connection between neurons). Information processing in the brain involves multiple neurons and neural pathways distributed across different regions. To perform a particular task, there is a need to combine individual neuronal signals into a cognitive process. In this study, we did not examine the neural activity elicited by a cognitive task, however, the connection between neurons during resting state would implicate the potential difference between groups on cognitive function.

The NeuCube framework allows for the creation of different computational models for STBD based on the following information processing principles as listed in Kasabov (2014):

- The model has a 3D spatial structure that maps approximately the spatially located areas of the brain where STBD is collected.
- The same information paradigm—spiking information processing that ultimately generates STBD at a low level of brain information processing, is used in the model to represent and to process this STBD.

- Brain-like learning rules are used in the model to learn STBD, mapped into designated spatial areas of the model.
- A model is evolving in terms of new STBD patterns being learned, recognised and added incrementally, which is also a principle of brain cognitive development.
- A model always retains a spatio-temporal memory that can be mined and interpreted for a better understanding of the cognitive processes.
- A visualisation of the model evolution during learning can be used as a bio-feedback.

All the above principles make the NeuCube a suitable SNN architecture to learn and reveal complex spatio-temporal patterns, which justify its choice for the development of the new methodology to model EEG data and to extract knowledge from it in this paper.

Specific formulas used in the current version of NeuCube for the experiments in this paper are given in the Appendix.

3. Connectivity analysis of a NeuCube spiking neural network model trained on EEG STBD

3.1. Modelling EEG data in the NeuCube

The EEG data modelling procedure used here is shown graphically on Fig. 2 and it consists of the following procedures:

1. The time series data obtained from the EEG device is first ordered as a sequence of real-value data vectors. One of the main advantages of the NeuCube is that there is no need of additional pre-processing of the EEG data, such as normalisation, scaling, and smoothing. The model can also deal with noisy data, which is significantly time-saving.
2. In order to obtain an input compatible with the SNNc, each real-value input time series (*e.g.* the measured EEG data in one electrode) is transformed into a spike train (*i.e.* sequence of binary events) using a spike encoding method, and more specifically, the Threshold-Based representation method (TBR). This algorithm well suits EEG STBD, since it identifies just differences in consecutive values, as demonstrated and implemented in the artificial silicon retina chip (Delbruck, 2007; Dhoble, Nuntalid, Indiveri, & Kasabov, 2012) and the artificial cochlea chip (Chan, Liu, & Van Schaik, 2007).
3. The input spike sequences are presented to an evolving brain-mapped SNNc that reflects the number of input variables (*e.g.* the 26 EEG channels in the case study from Section 4), the functional brain areas associated with them and the size of the data available.
4. The SNNc is implemented using leaky integrate and fire (LIF) model (Gerstner, 2001) neurons and is initialised as "small-world" (SW) connected networks. The SW connectivity principle has been chosen here as it is based on the biological process that makes neighbouring neural cells to be highly and strongly interconnected to each other, therefore, the initialisation is fundamental for the learning process of this model.
5. The SNNc is trained in an unsupervised mode using spike timing dependent plasticity (STDP) (Song, Miller, & Abbott, 2000) learning rule. This algorithm allows spiking neurons to learn consecutive temporal associations from the EEG data within- and across-EEG channels. The neurons become able to form new connections in the architecture, which can then be analysed and interpreted. This makes the NeuCube architecture useful for learning spatio-temporal patterns from EEG data, forming associative type of memory that can be further explored.

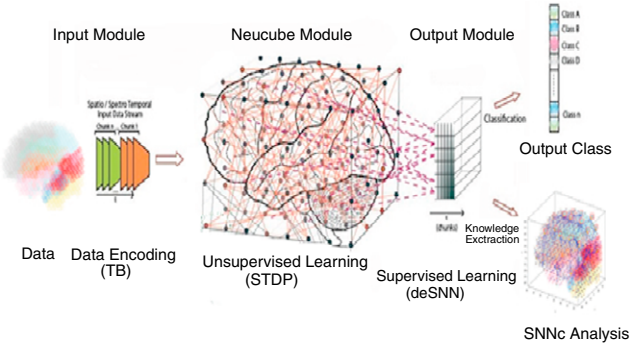

Fig. 2. A graphical representation of the NeuCube-based methodology used for EEG data modelling and connectivity analysis.

6. The output classifier is trained in a supervised mode (*i.e.* method based on classification of data with a known pattern) using dynamic evolving SNN (deSNN) (Kasabov, Dhoble, Nuntalid, & Indiveri, 2013) algorithm to classify the EEG STBD into the respective classes. This classification method combines the rank-order (RO) learning rule (Thorpe & Gautrais, 1998) and the STDP (Song et al., 2000) temporal learning for each output neuron to learn a spatio-temporal pattern using only one pass of data propagation.
7. The classification results are evaluated using repeated random sub-sampling validation (RRSV) or leave one out cross validation (LOOCV).
8. Steps (4)–(7) are repeated using different parameter values in order to optimise the classification output. The best performing model can then be recorded for further uses.
9. The trained SNNc is visualised, its connectivity and the dynamic spiking activity are analysed for a better understanding of the data and the brain processes that generated it including changes of brain functionality across different conditions and groups of subjects.

It is important to highlight that the NeuCube model is a stochastic model (*i.e.* initial connection between the neurons of the network are randomly generated) and therefore the output classification accuracy depends on the parameters settings. Based on previous studies that we have conducted, we have identified some critical variables requiring careful optimisation. These parameters are:

- The TBR which is applied to the input EEG data streams transforming them into spike trains. The rates of the spikes depend on the TBR threshold, which can be determined either as a particular value for every input variable or as a global threshold to be applied to all of them (Eq. (A.1) described in Appendix A).
- Connectivity between neurons of the network. Depending on the SW connectivity rule, each neuron of the SNNc is initially connected to its neighbouring neurons within a distance that depends of a SW connectivity parameter (Eq. (A.2) described in Appendix A).
- The threshold of firing, the refractory time and the potential leak rate of the LIF neurons (Eqs. (A.3)–(A.4) described in Appendix A). When a LIF neuron of the SNNc receives a spike, its post synaptic potential (PSP) increases gradually with every input spike according to the time of the spike arrival, until it reaches an established threshold of firing. An output spike is then emitted and the membrane potential is reset to an initial state (refractory time). Between input spikes, the membrane potential also leaks. In our experiments, the three parameters were set to 0.5, 6 ms and 0.002 respectively after optimisation.

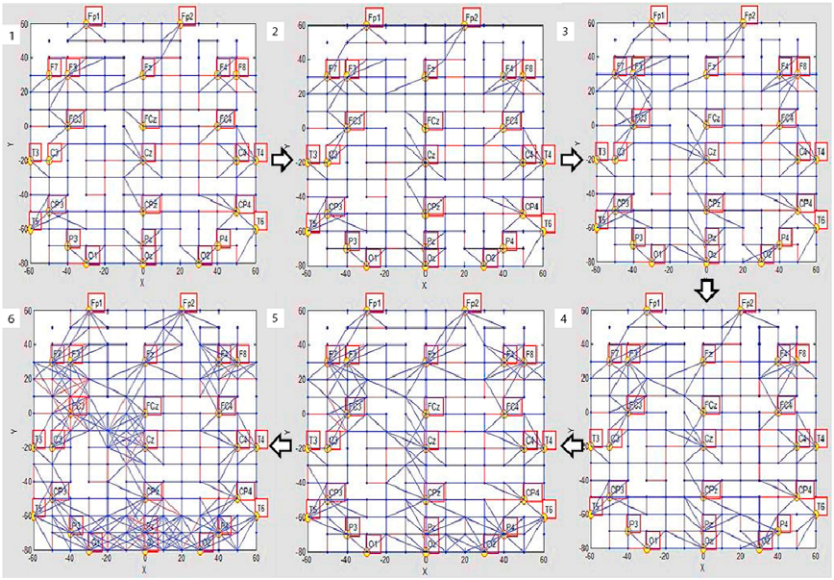

Fig. 3a. Example of a step-wise connectivity evolution in a SNNc activity during STDP learning on EEG data recorded from all subjects who belonged to all three groups – H, O and M – during an EO state (for interpretation—see next section). The figure shows the (x, y) projection only of the 3D SNNc. The six pictures visualise the cube connectivity during STDP learning from the initial randomly generated connections (1) until unsupervised training is finished—(6). Blue lines are positive connections (excitatory synapses) generated, while red lines are the evolved negative connections (inhibitory synapses). In yellow are the input neurons with their labels corresponding to the 26 EEG channels. A video of the step-wise connectivity evolution is included with the supplementary data available online (see Appendix C).

- The STDP learning rate parameter. According to the STDP learning rule (see Song et al., 2000 for more details), the firing activity of two connected neurons causes their connection weight to increase or decrease depending on the order of firing, so that the connection weight will reflect on the temporal relationship between the activities of these neurons (Eq. (A.5) described in Appendix A).
- The number of times that the NeuCube is trained in an unsupervised mode. This is set by default as 1 which is suitable for incremental, on-line adaptive learning.
- The parameters *mod* and *drift* of the deSNN classifier (Kasabov et al., 2013) (Eqs. (A.6)–(A.7) described in Appendix A). The values of these parameters depend on the data and problem in hand and need to be optimised for an optimal performance.

Optimisation of these parameters can be achieved *via* grid search method, genetic algorithm, or quantum-inspired evolutionary algorithm (Platel, Schliebs, & Kasabov, 2009). Taking into account that every parameter tuned also involves a considerable amount of processing time, we need to select the proper number of variables to be optimised. In this study, a grid search method was applied, mainly to find the best value associated to the TBR parameter, as this threshold is applied to the entire signal gradient according to the time and therefore the rate of generated spike trains depends on it. Moreover, since the NeuCube is a stochastic model, altering this value means also modifying the initial model configuration each time.

Default parameters were not set up prior to the experiment, but they were chosen as considered the ones leading to the optimal results and in consistence with information reported in previous neuroscience reports. For instance, the refractory time suggested by our model was 6 ms. In general, the refractory time interval for neural spiking reported by previous study is about 5 ms, however, it might require more time in response to certain events (Berry & Meister, 1998).

3.2. Connectivity analysis of a NeuCube model trained on EEG STBD for the study of brain functional changes

A NeuCube model can accommodate data in one pass learning to dynamically evolve an output classifier. A new output neuron can be generated in the output classifier for every new input pattern learned in the SNNc and trained in one pass learning mode (Kasabov et al., 2013). This ability of the NeuCube models enables the brain processes to be traced over time and to extract new information and knowledge about them. First, a NeuCube model is trained until satisfactory performance (*e.g.* classification) of the EEG data. Then, the SNNc connectivity structure is analysed for a better understanding of the dynamics of the data across different subjects and different groups of subjects. In fact, the connectivity of the SNNc represents dynamic spatio-temporal associations of the brain activities measured by the input variables (the EEG channels). Through the analysis of NeuCube evolved connectivity, the following research questions can be addressed and studied in general:

(a) How the connectivity evolves in a SNNc trained with data of all subjects from groups (Fig. 3a) versus training a model on data of an individual subject or a group of subjects performing a task, when compared to another individual or another group? Fig. 3a represents an example of a step-wise SNNc connectivity evolution during unsupervised training on EEG data recorded from all subjects who belonged to all three groups – healthy (H), opiate addicted (O) and people using methadone (M) as treatment – during an eyes open (EO) resting state.
(b) What is the functional change of brain activities when a subject with history of drug use is compared with a control (healthy) subject? Fig. 3b (left) illustrates the different SNNc connectivity generated after a SNNc model which was trained with EEG data recorded from all subjects who belonged to the M group *versus* the same initial SNNc trained with EEG data recorded from all subjects who belonged to the H group during an EO resting state.
(c) What are the differences in the activities of brain regions between subjects undertaking treatment for drug addictions and those without treatment. In our case study, these are opiate addicts *versus* those undertaking treatment for addiction. Fig. 3b (right) shows different SNNc connectivity resulted after a SNNc was trained with EEG data recorded from all subjects who belonged to the M group *versus* the connectivity generated with data recorded from all subjects of O group during the EO state.

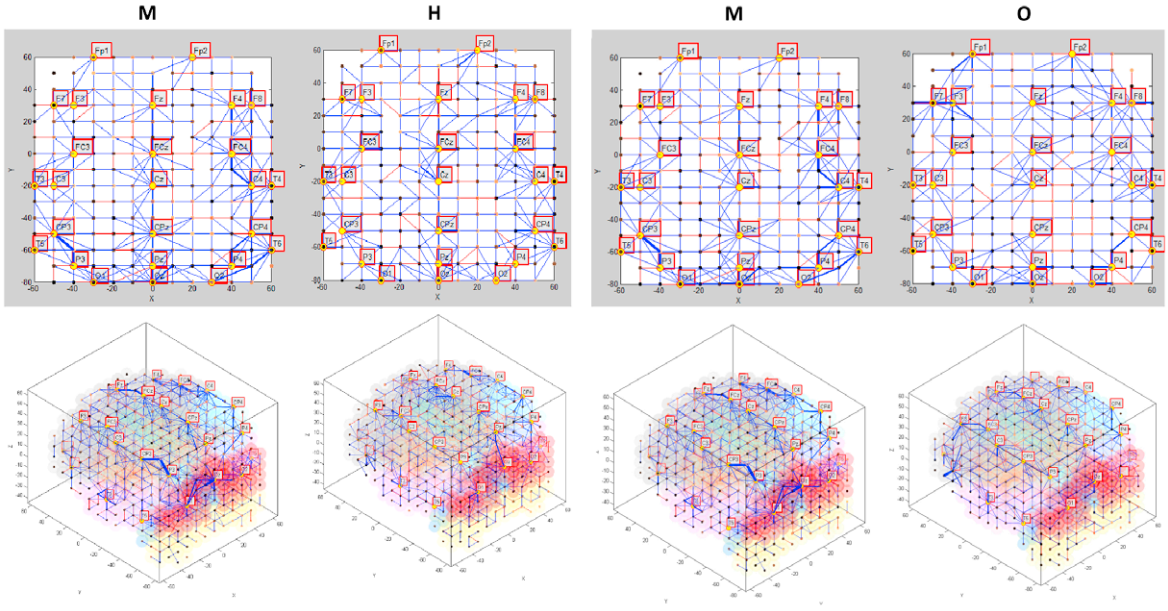

Fig. 3b. Examples of the SNNc connectivity after unsupervised training is finished. A SNNc was trained using EEG data recorded from all subjects who belonged to the M group and from all subjects who belonged to either the control H group (left) or the O group (right) during an EO state (for interpretation—see next section). The top figures show the (x, y) projection only of the 3D SNNc, while the bottom figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe). Blue lines represent positive connections (excitatory synapses), while red lines represent the evolved negative connections (inhibitory synapses). In yellow are the input neurons with their labels corresponding to the 26 EEG channels.

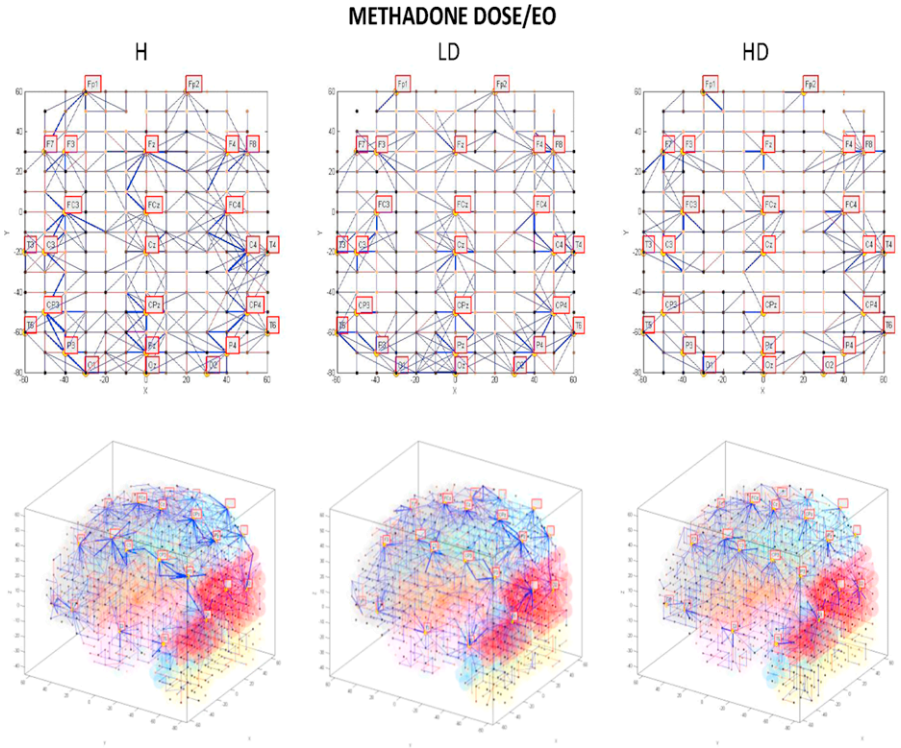

Fig. 3c. Examples of the SNNc after unsupervised training is finished. The SNNc was trained using EEG data recorded during the EO state, from 12 subjects who belonged to the control group (H), from patients taking below 60 mg of methadone (LD) and from M patients taking 60 mg or above of methadone (HD) (for interpretation—see next section). The top figures show the (x, y) projection only of the 3D SNNc, while the bottom figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe). Blue lines represent positive connections (excitatory synapses), while red lines represent negative connections (inhibitory synapses). In yellow are the input neurons with their labels corresponding to the 26 EEG channels.

(d) What is the functional change of brain activities when a different dose of drug is administered? Fig. 3c represents the connectivity of a SNNc after training it with EEG data recorded from patients who have been treated with a different dose of methadone before completing the same trial.

These research questions are illustrated here on EEG data related to the case study problem and explained in more detail in the following section. The above research questions are generic and can be studied in relation to other brain disorders and patients response to respective treatments.

4. Connectivity analysis of NeuCube models trained on EEG data for the understanding of functional brain changes related to opiate substitution treatment (methadone) and predicting patients response to treatment

4.1. Case study problem definition

Methadone has been used as a pharmacological substitute for the treatment of opiate dependence since the mid-1960s. As a substitute for illicitly used opiates, the purpose of MMT is not to achieve a drug-free state but to reduce the harm associated with illicit drug use and to improve life quality and psychosocial functioning for the individual (Lobmaier, Gossop, Waal, & Bramness, 2010). The benefits of MMT have been demonstrated by many studies. For example, MMT has been shown to effectively reduce the use of other drugs, injection-related risky behaviour, criminal activity, mortality, and the transmission of HIV and other blood-borne pathogens, such as hepatitis-B (Ball, Lange, Myers, & Friedman, 1988; Bell, Hall, & Byth, 1992; Gibson, Flynn, & McCarthy, 1999; Marsch, 1998). Consequently, MMT is now the most common treatment for opiate dependence in many countries, including the United States of America, Australia, the United Kingdom and New Zealand (Adamson et al., 2012; Joseph, Stancliff, & Langrod, 1999).

Despite methadone's effective clinical use, it remains uncertain whether MMT has negative effects on cognitive function, given that methadone has clinically similar actions and analgesic effects to morphine (Dole, 1988), for a review (Wang, Wouldes, & Russell, 2013). Methadone primarily binds to receptors that are found throughout the brain and are densely concentrated in the periaqueductal gray, amygdale, hippocampus, thalamus and striatum (Martin, Hurley, & Taber, 2007; McBride, Chernet, McKinzie, Lumeng, & Li, 1998). In humans, these areas are critical for pain perception, visual and sensory processing, memory and attention. Therefore, there is particular concern whether long-term use of a sedative opiate antagonist, such as methadone, has effects on cognitive function. To address this question, a more detailed analysis of EEG data collected from different groups of patients and healthy subjects is performed in this study, using the NeuCube modelling framework and its connectivity and activity analysis.

4.2. EEG data collection

Prior to commencing this research, ethical approval was granted by the Northern Regional X Ethics Committee of New Zealand and informed consent was given by all participants. All EEG recordings were conducted between 12 pm and 4 pm, apart from three participants (one was from the opiate user group and two were from the healthy control group) who completed EEG recording at 6 pm, due to their availability. All EEG recordings were conducted on a one-to-one basis in a sound and light attenuated laboratory. A QuickCap (Neuroscan 4.3) 40 sensor shielded cap was used to acquire EEG data from the cephalic sites. The 26 cephalic sites included Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, Cpz, C3, C4, CP3, CP4, FC3, FCz, FC4, T3, T4, T5, T6, Pz, P3, P4, O1, O2, and Oz electrode sites (10–20 International System). A further 14 channels recorded other data, *e.g.* VPVA and VPVB vertical electro-oculogram (EOG), HPHL and HNHR horizontal EOG, heart rate (HR), muscle movements and events, etc. HR is considered as one of the most sensitive measures of withdrawal, which has been shown to be positively correlated with severity of opiate withdrawal (Zilm & Sellers, 1978). EEG was recorded relative to the average of A1 and A2 (mastoid) electrode sites. Horizontal eye movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eye-lid. Skin resistance was kept at <5 kΩ. Scalp and EOG potentials were amplified and digitised continuously by a system (NuAmps, SCAN 4.3) having a frequency response from DC to 100 Hz (above which attenuating by 40 dB per decade), and a sampling rate of 500 Hz. Electrical impedance was always <5 kΩ.

Resting EEG data was collected with patients undertaking MMT (M group), people currently using illicit opiates (O group) and healthy volunteers (H group) in two states: eyes open (EO) and eyes closed (EC). In the EO condition, participants were asked to fixate on a red dot in the centre of the computer screen for two minutes. In the EC condition, participants were asked to sit still with their eyes closed for two minutes.

The M group consisted of 18 males and 14 females, with a mean age of 39.36 (SD $=$ 5.14) years. Their mean duration of education was 12.06 (SD $=$ 2.00) years; mean duration of opiate use was 10.03 (SD $=$ 6.08) years; mean duration of MMT 7.29 (SD $=$ 6.39) years; and current methadone dose 70.86 (SD $=$ 40.61; range 8–180) mg/day.

All the participants recruited were between 18 and 45 years of age, had basic English literacy skills and were able to provide written informed consent. Inclusion criteria for the M group was undertaking methadone for a minimum of six months and stabilised on their current dose for at least 2 weeks. Participants in the opiate user group were required to meet the DSM-IV criteria for opiate dependence and were not allowed to be currently undertaking MMT. The inclusion criteria for healthy control subjects was no current or lifetime history of drug or alcohol abuse other than nicotine dependence.

4.3. A NeuCube model to analyse EEG data from H, O and M groups

For our study, we resized the raw EEG data to 26 ordered vectors of real value data, as 26 were the EEG channels used during the EEG recording. Data from 20 healthy subjects, 15 subjects addicted to opiates and 22 subjects under MMT was available for the EC state. On the other hand, data from 20 healthy subjects, 17 subjects addicted to opiates and 25 subjects under MMT was available for the EO state. Every EEG STBD sample fed into the NeuCube was labelled to represent one of the subjects. We averaged every subjects neural activity per channel every 2048 data points, which means every 4 s of recordings. We considered this information enough for our analysis. We obtained a total of 37 and 33 data points per channel and per sample for the two resting state EC and EO respectively (as this was the lowest number of data points after averaging the signal).

For the experiments, we generated a SNNc of 1471 brain mapped spiking neurons. We used the 3D Talairach Atlas (Koessler et al., 2009; Lancaster et al., 2000; Talairach & Tournoux, 1988) to map 1471 brain areas of 1 cm^3 each into single spiking neurons of the SNNc and then entered the data from the EEG channels into the corresponding input neurons of the SNNc (see Kasabov, 2014).

Results can be affected by subjects' poly-drug use, a common complication in a population with drug dependence and it is unlikely that patients or opiate users have no history of use of other types of drugs. The question is, while this is true, what more can we learn from the SNNc about the brain functional differences (changes) between these groups?

For a better understanding of the data and to address the research questions raised in the previous section, different analysis of the connectivity of the SNNc have been performed and reported below.

Table 1
Parameters settings of the SNNc models used for training the data of all groups during EC and EO state.

SNNc parameters settings	
EC	
Threshold of firing: 0.5	Potential leak rate: 0.02
STDP: 0.1	TBR: 7.94
Long Dist. possibility: 0.01	Weight threshold 0.15
EO	
Threshold of firing: 0.4	Potential leak rate: 0.02
STDP: 0.1	TBR: 52.62
Long Dist. possibility: 0.01	Weight threshold 0.07

Table 2
Parameters settings of the NeuCube models used for connectivity and spiking activity analysis for class M versus class H and class O subjects (EO states only).

Network analysis parameters settings	
Threshold of firing: 0.4	Potential leak rate: 0.02
STDP rate: 0.1	Long Dist. possibility: 0.01
Connection distance: 0.15	Times to train: 1
TBR threshold: 52.62	Weight threshold 0.07
Max. spike gradient	Spreading level
10 inputs	2

4.4. Analysis of spiking neuronal activity and connectivity generated in EC versus EO resting state across the studied subject groups

To analyse and visualise the SNNc activity generated by the resting EEG data recorded when subjects are with EC or EO, Fig. 4a shows the initial connections and the connectivity evolved after STDP learning rule was applied to either H, O or M group. The cube connectivity can be analysed and interpreted for a better understanding of the EEG data to identify differences between brain states during the execution of either the EC or the EO state. Table 1 reports the parameters settings used to obtain these results. According to Fig. 4a, the neural activity generated during the two scenarios was different. Both states manifested high activity around the input neurons – which were allocated so that they spatially mapped the brain-location of the 26 EEG electrodes – and along the central area (Fz, Cz, Pz, etc.). The neural activity generated during the EO was significantly different from the EC, having a greater connectivity on the left frontal, central and occipital–parietal regions. This was also confirmed by the step-wise analysis of the SNNc (shown in Fig. 3a). We can observe that the initial connections in the cube are firstly generated around the input neurons represented by the 26 EEG channels. Then, as the unsupervised learning precede, more connections evolved in the frontal lobe of the left hemisphere (T3, C3, FC3, F2 and F3), the central areas (FCz, Cz) and the occipital–parietal regions (O1, O2, Oz, Pz, P3, P4). As a result of the activity observed during the EO state, we decided to focus our subsequent analysis on the data collected during this state only.

4.5. Analysis of NeuCube connectivity with the aim of discovering functional changes of brain activities in subjects under treatment (M) compared with control subjects (H)

Fig. 4b illustrates the neural activity obtained after the SNNc was trained with EEG data corresponding to the M and the H group separately (EO only). The parameters settings used to obtain this results were set in accordance with the ones reported in Table 1.

Analysing the figure, we can observe that there are differences in the SNNc connectivity between the M and H groups, indicating alternations of neural activity induced by history of opiate exposure.

Table 3
Classification accuracy percentage obtained using a NeuCube classification model *versus* traditional machine learning methods (MLR, SVM, MLP, and ECM).

Samples/classes-EC	MLR	SVM	MLP	ECM	NC
15 samples Opiate (% accuracy)	53	40	60	40	**67**
22 samples Methadone (% accuracy)	50	64	59	73	**100**
Overall accuracy (%)	51	54	59	59	**86**
Samples/classes-EO	MLR	SVM	MLP	ECM	NC
17 samples Opiate (% accuracy)	59	29	53	53	**75**
25 samples Methadone (% accuracy)	48	68	56	68	**82**
Overall accuracy	52	52	55	62	**79**

The NeuCube network analysis per class is illustrated in Fig. 4c. Table 2 reports the parameters settings used for the network analysis. The networks connectivity identifies higher spiking activity in the 10 EEG channels allocated in the visual cortex. Both spike spreading level and maximum spike gradient are reported. As shown in Fig. 4c, the pathway of spiking activity of the M group is similar to the H group, despite their greater level of intensity.

4.6. Analysis of NeuCube connectivity with the aim of discovering functional changes of brain activities in subjects under treatment (M) compared with subjects without treatment (O)

Fig. 4d shows the neural activity obtained after the SNNc was trained with the data corresponding to the M and the O group separately (EO only). The parameters were set in accordance with the ones reported in Table 1.

As shown in Fig. 4d the neural activity of the M group was different from the O group, in particular, greater excitation in the parietal and occipital regions was observed in the M group. According to these results, we focused on these regions analysing the maximum spike gradient of the input channels and their information spreading level (Fig. 4e). The parameter settings used are reported in Table 2. Consistent with the previous studies (Wang et al., 2014, 2012, 2015), our findings implicate that there are different cognitive-related effects between methadone and illicit opiates. To further test this hypothesis, we have classified the O group *versus* M group (Table 3) for both resting states (EC and EO). The high classification accuracy obtained *via* the NeuCube methodology proved the model ability to manifest this difference and also that the two classes were in fact two distinguishable groups. We compared the results obtained using the proposed NeuCube model with traditional machine learning methods, such as multiple linear regression (MLR), support vector machine (SVM), multilayer perceptron (MLP) and evolving clustering method for classification (ECM). We used the NeuCom software environment for the experiments (http://www.theneucom.com). Tables B.1 and B.2 in Appendix B report the parameters settings used to obtain these results for either EC and EO state.

When training a NeuCube model on the EEG data, we used 26 input features/variables (the EEG channels) and entered the times series of each input variable to train the SNNc. In contrast, the other methods could not take time series data without transforming it into a static and fixed length data vectors, used to train a model one after another. The results in Table 3 were obtained using LOOCV method when the best top 20 features were selected for every traditional machine learning method tested (MLR, SVM, MLP, ECM) and for every sample in the LOOCV procedure. Selecting features in time series processing is not recommended though as once a model is trained these features will be fixed and any change in the dynamics of the EEG data in future experiments would not be tolerated for incremental learning and model adaptation. In this respect NeuCube offers a certain advantages from the point of view of adaptive and incremental learning of STBD. But the most important difference between a NeuCube model and the

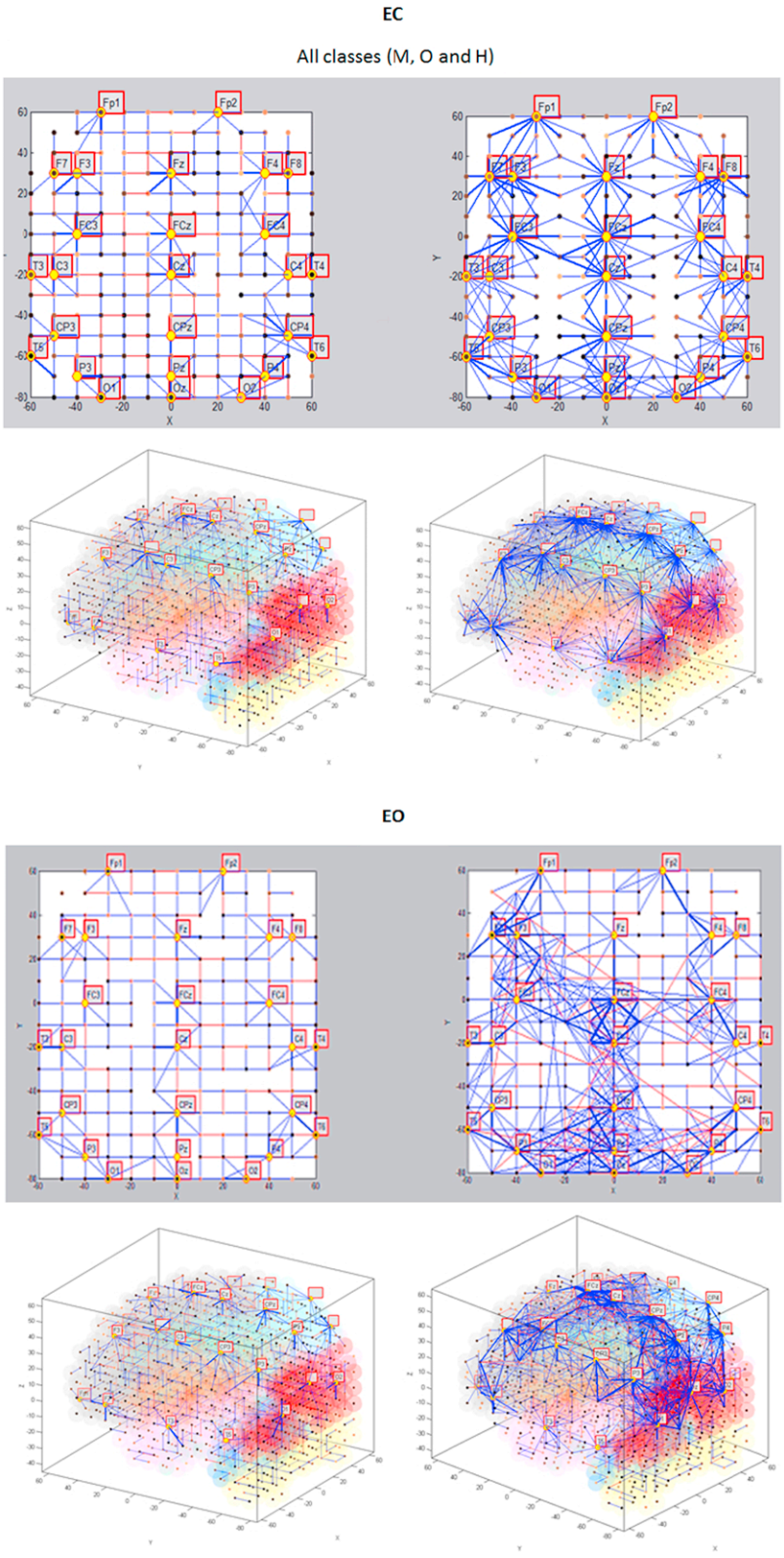

Fig. 4a. NeuCube connectivity before (left) and after training (right) the SNNc with the EEG data recorded from all subjects who belonged to all three groups – H, O and M – during either the EC (top) or the EO state (bottom). For both resting states, the top figures show the (x, y) projection only of the 3D SNNc, while the bottom figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe). In yellow are the input neurons with their labels corresponding to the 26 EEG channels. Blue lines are positive connections (excitatory synapse), while red lines are negative connections (inhibitory synapse). The brighter the colour of a neuron, the stronger its activity with a neighbour neuron. Thickness of the lines also identifies the neurons enhanced connectivity.

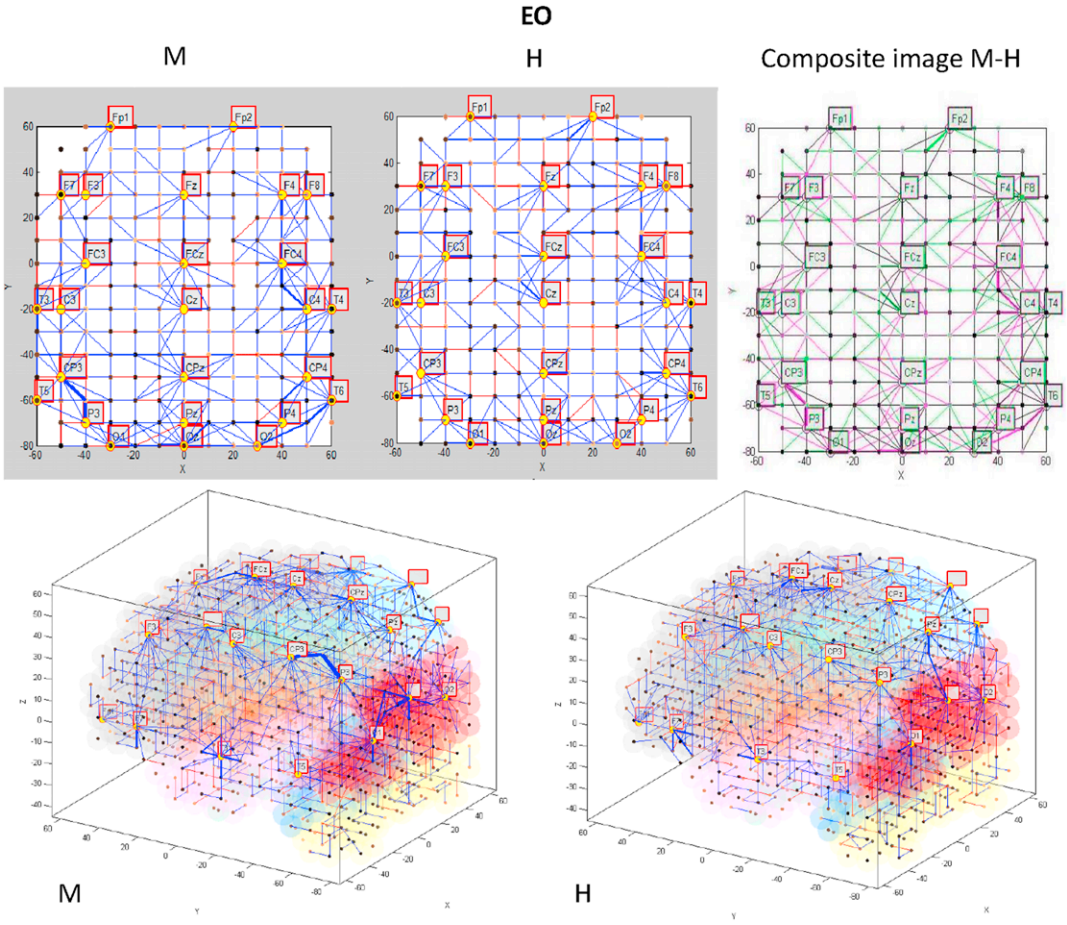

Fig. 4b. NeuCube connectivity obtained after training the SNNc with the EEG data recorded during the EO state from all subjects who belonged to either the M group or the control H group. The top figures show the (x, y) projection only of the 3D SNNc, while the bottom figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe). Blue lines are positive connections (excitatory synapses), while red lines are negative connections (inhibitory synapses). The brighter the colour of a neuron, the stronger its activity with a neighbouring neurons. Thickness of the lines also identifies the neurons enhanced connectivity. In yellow are the input neurons with their labels corresponding to the 26 EEG channels. The composite image (top right-hand side figure) identify differences between connectivity of two groups of subjects overlaid in different colour bands. Grey regions in the composite image show where the two models have the same intensities. Magenta (for M group) and green regions (for H group) show where the intensities are different.

traditional machine learning methods is that a NeuCube model has a brainlike structure and uses brain-like learning methods to learn STBD, so that the model can be interpreted for new discoveries related to the source of the EEG data the brain. In contrast, the traditional machine learning methods, being successfully applied on many problems so far, cannot be of much use for STBD modelling, analysis, model interpretation and knowledge discovery.

4.7. Connectivity analysis of the NeuCube model aiming at discovering functional changes in brain activities related to different doses of the drug administered

Since every EEG sample was an identifiably-labelled subject and there are potential dose-related effects suggested by the literature, we further analysed the methadone dose-related effect on spiking activity in our M group through the analysis of the connectivity of the NeuCube trained model with these EEG data. Data corresponding to the M group were divided into two subgroups, low dose (LD) and high dose (HD) of methadone, according to their daily dose of drug administered (high − dose $\leq$ 60 mg $<$ low − dose). For the EO task, we obtained 14 samples for the low dose class and 11 samples for the high dose class. We also compared these two groups with 13 subjects of the healthy control groups. Thirteen subjects were randomly chosen from the healthy control group to minimise the possible confounding effects associated with sample size.

Table 4
Parameters settings of the SNNc models used for training the data who belonged to one of three groups – H, LD, HD – during EO state. The parameter optimised was TBR while the other parameters were set as default value.

SNNc analysis parameters settings	
Methadone dose EO	
Thr. of firing: 0.5	Pot. leak rate: 0.002
STDP: 0.5	TBR: 32.44
Long Dist. possibility: 0.01	Weight Thr.: 0.07

In order to study these effects, we analysed the SNNc activity and connectivity obtained after training the SNNc with the EEG data corresponding to the H, LD and HD group separately. Fig. 4f reports the SNNc activity generated per class after setting the parameters according to Table 4.

As shown in Fig. 4f, there are similarities and differences between groups (H *versus* HD or H *versus* LD). It appears that there is a greater reduction of connectivity in the HD group when compared to either the H or the LD group. Our findings suggest that the dose administered may play a role in treatment response and it needs to be addressed in treatment planning.

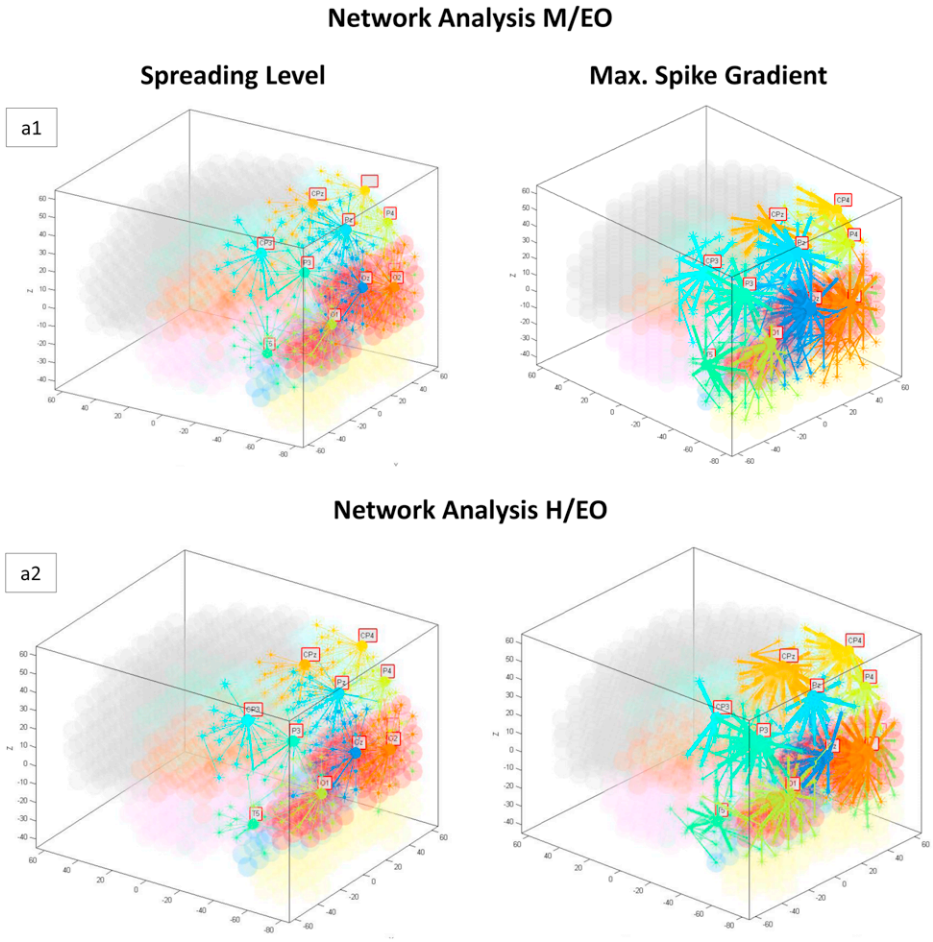

Fig. 4c. NeuCube connectivity and spiking activity analysis per class – M group (a1) and H group (a2) – obtained for the EO state. The figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe), the spike spreading level (left) and the maximum spike gradient (right) of the 10 EEG channels allocated in the visual cortex (CP3, CPz, CP4, T5, T6, P3, Pz, P4, O1, Oz, O2) highlighted by different colours. Thickness of the lines identify a stronger activity between neurons.

To further study the network connectivity, we focused on the occipital–parietal regions to extract new knowledge from the trained SNNc (for visualisation and analysis, as opposed to training purposes). Fig. 4g illustrates the network's connectivity by means of its spike spreading level and its maximum spike gradient emitted by class over the 10 EEG channels allocated in the particular brain area of interest.

The parameters settings used to plot these figures are the same as per Table 2. The results consistently support our argument showing a greater difference between the HD and the H groups compared to the difference between LD and the H groups.

5. Discussions, conclusion and further directions

The NeuCube constitutes a brain-inspired three-dimensional structure of SNN for on-line learning and recognition of spatio-temporal brain data (STBD) (Kasabov, 2014). It takes into account the spatial coordinates of the sources of the STDB using a standard brain-template, offering a better understanding of the information and the phenomena of study. The goal of the proposed study was to develop a method for the analysis of the connectivity and the dynamic activity of a NeuCube model trained on EEG STBD in order to understand changes in brain activities across subjects and groups. Traditional data mining/machine learning algorithms are not able to properly deal with this kind of data. Our results demonstrated that a NeuCube model not only achieves a better sensitivity and specificity in classifying EEG data compared to traditional AI methods, but it is also interpretable for a better understanding of the EEG data and the processes that generated it. This makes the NeuCube modelling approach widely applicable for neuroscience research across data and problems. In particular, the paper demonstrated:

1. The NeuCube ability to classify EEG data collected from different groups of patients and healthy subjects.
2. Connectivity analysis of a SNNc after training with EEG STBD from different groups of subjects (different classes) to extract new knowledge and to study the brain regions involved.
3. Connectivity analysis aiming at the understanding the correlation between a dose of treatment and results of treatment.
4. Connectivity analysis aiming at the understanding the impact of different dose of treatment on brain activities and at predicting response to treatment.

A further development and research are planned including:

- Further development of the methods of the NeuCube framework, including: analysis of the ability of a NeuCube model in terms of how "deep in time" spatio-temporal patterns, "buried" in STBD, can be efficiently learned; how different "time lags" can be represented in the NeuCube; spatio-temporal rule extraction from a trained NeuCube model; analysis and interpretation of the output connectivity along with the SNNc connectivity in relation to a better understanding of brain differences across groups of subjects.

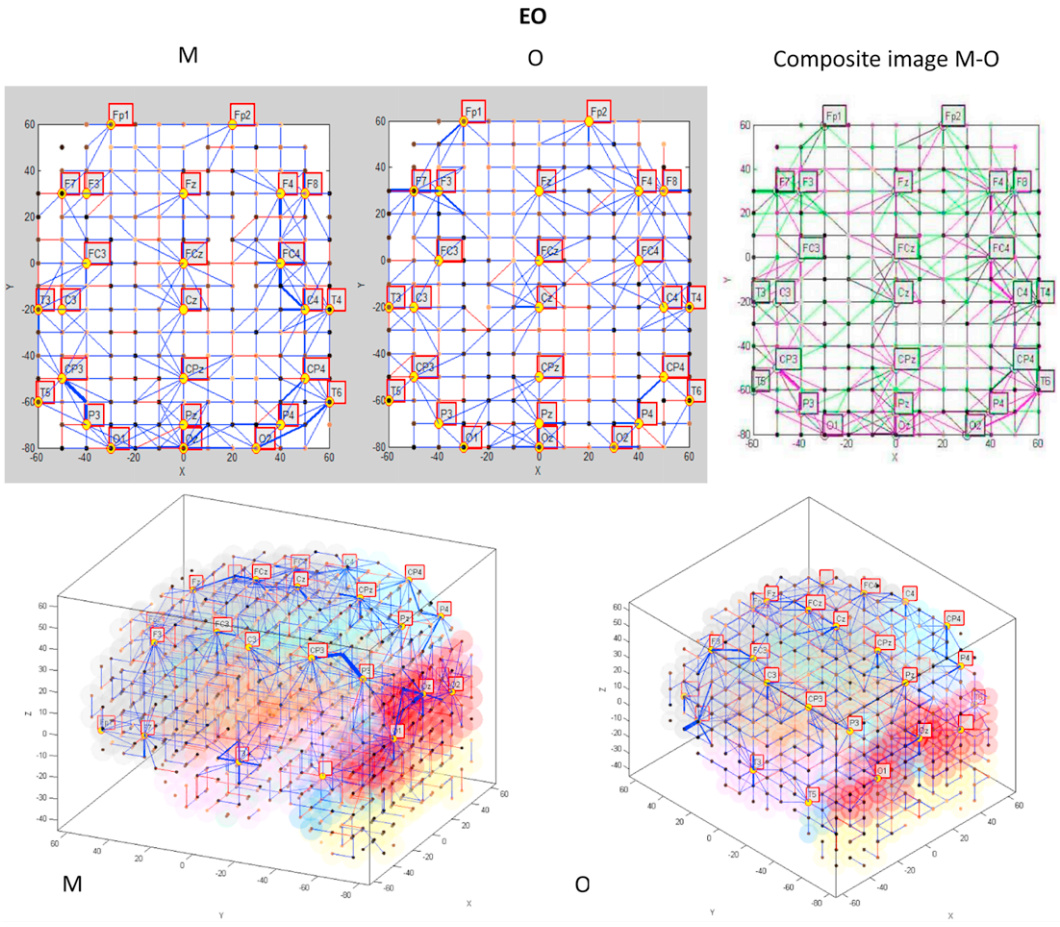

Fig. 4d. NeuCube connectivity obtained after training the SNNc with the EEG data recorded during the EO state from all subjects who belonged to either the M group or the O group. The top figures show the (x, y) projection only of the 3D SNNc, while the bottom figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe). Blue lines are positive connections (excitatory synapses), while red lines are negative connections (inhibitory synapses). The brighter the colour of a neuron, the stronger its activity with a neighbouring neurons. Thickness of the lines also identifies the neurons enhanced connectivity. In yellow are the input neurons with their labels corresponding to the 26 EEG channels. The composite image (top right-hand side figure) identify differences between connectivity of two groups of subjects overlaid in different colour bands. Grey regions in the composite image show where the two models have the same intensities. Magenta (for M group) and green regions (for O group) show where the intensities are different.

- Further application for the study of EEG STBD in relation to understanding brain functionality, *e.g.* longitudinal study on patients undertaking methadone treatment in terms of defining any cognitive fluctuation across time; development of a gene regulatory network (GRN) optimisation module as part of the SNNc to improve the results and to study how certain genes may influence treatment; analysis of EEG data collected from people taking a single oral dose of "party pill" using NeuCube; analysis of EEG data collected from people with depression; analysis of brain data collected from people with schizophrenia.

Acknowledgements

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Appendix A. Some equations detailing the functionality of NeuCube (Kasabov, 2014)

The following equations describe the implementation of the main algorithms of the NeuCube-based model used in this study. The spike encoding method used in this study is the TBR encoding algorithm. A self-adaptive bi-directional threshold (TBR_{thr}), which is applied to the EEG signal $x(t)$ as follows:

$$TBR_{thr} = \mu + s\,\sigma \tag{A.1}$$

where μ is the mean of the differential signal with respect to time, $x(t) = \{x_{t_2} - x_{t_1},\ x_{t_3} - x_{t_2}, \ldots, x_{t_n} - x_{t_{n-1}}\}$, calculated by using all samples; σ is its standard deviation; s is a scale parameter of σ.

The TBR_{thr} is 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; 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. Both kinds of input neurons are further connected with other neurons through connectivity initialisation and STDP learning.

The small world (SW) connectivity rule is applied to the NeuCube initialisation. In the SNNc, let i and j be a pre-synaptic and post-synaptic neuron respectively. Then, the distance

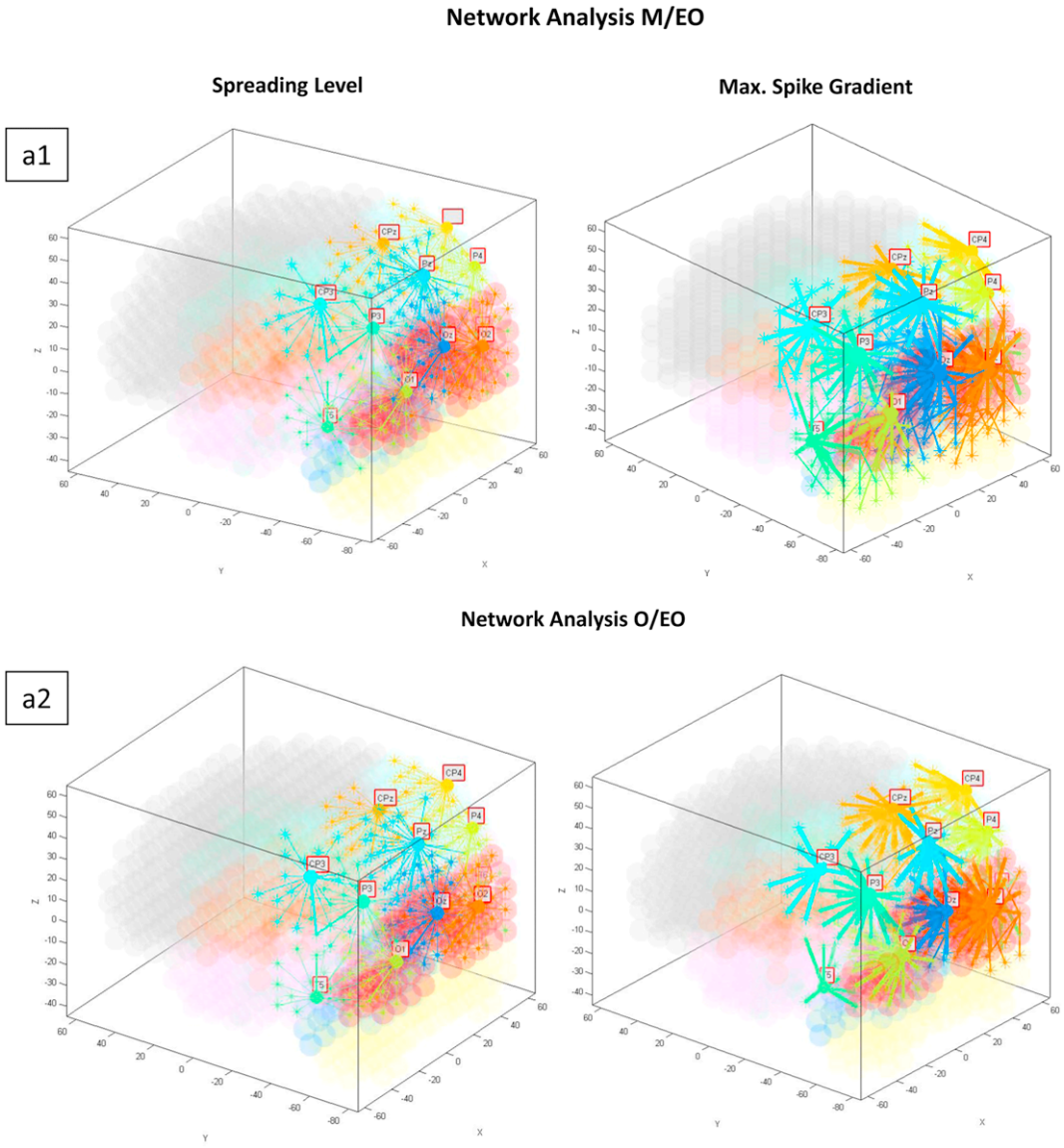

Fig. 4e. NeuCube network connectivity and spiking activity analysis per class – M group (a1) and O group (a2) – obtained for the EO state. The figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe), the spike spreading level (left) and the maximum spike gradient (right) of the 10 EEG channels allocated in the visual cortex (CP3, CPz, CP4, T5, T6, P3, Pz, P4, O1, Oz, O2) highlighted by different colours. Thickness of the lines identify a stronger activity between neurons.

between these two neurons is calculated as the Euclidean distance $d(i, j)$, based on their (x, y, z) coordinates. Initial connections are randomly generated, however, each neuron of the cube can connect only to its neighbouring neurons within a distance threshold D_{thr}, which is a proportion of the maximum Euclidean distance between two neurons. This is compute in Eq. (A.2):

$$D_{thr} = \max(d(i, j))\, p \tag{A.2}$$

where p is the SW connectivity parameter. The initial connections weights are calculated as the product of a random number $[-1, 1]$ and the multiplicative inverse of $d(i, j)$. 20% of these weights are randomly selected to be negative, which represents the inhibitory connections weights, while 80% of them are positive, which represents the excitatory connections weights. To emphasise the significance of the input neurons in the SNNc, their connection weights are doubled with respect to the other neurons.

The neurons of the cube are modelled as LIF neurons. The action potential v_j of a neuron j increases with every input spike S_i from neuron i according to its connection $(c_{i,j})$ and depending on the frequency/time of the incoming spikes. When the v_j reaches the firing threshold Θ, then an output spike S_j is emitted and the neuron potential is reset to zero.

$$S_i = \begin{cases} 1 & v_j \geq \Theta \\ 0 & \text{otherwise.} \end{cases} \tag{A.3}$$

The membrane potential will keep to zero for the length of its refractory time (r). Between spikes, the membrane potential leaks according to the potential leak rate (l).

$$v_j(t) = \begin{cases} v_j(t-1) + w_j & r = 0 \\ v_j(t-1) - l & \text{otherwise.} \end{cases} \tag{A.4}$$

The STDP learning rule is applied in an unsupervised mode of learning for the SNNc to capture spatio-temporal relationships from the encoded data. The STDP follows the Hebbian learning rule, which describes the connection established between two neurons as stronger as their activation persists and repeats. In

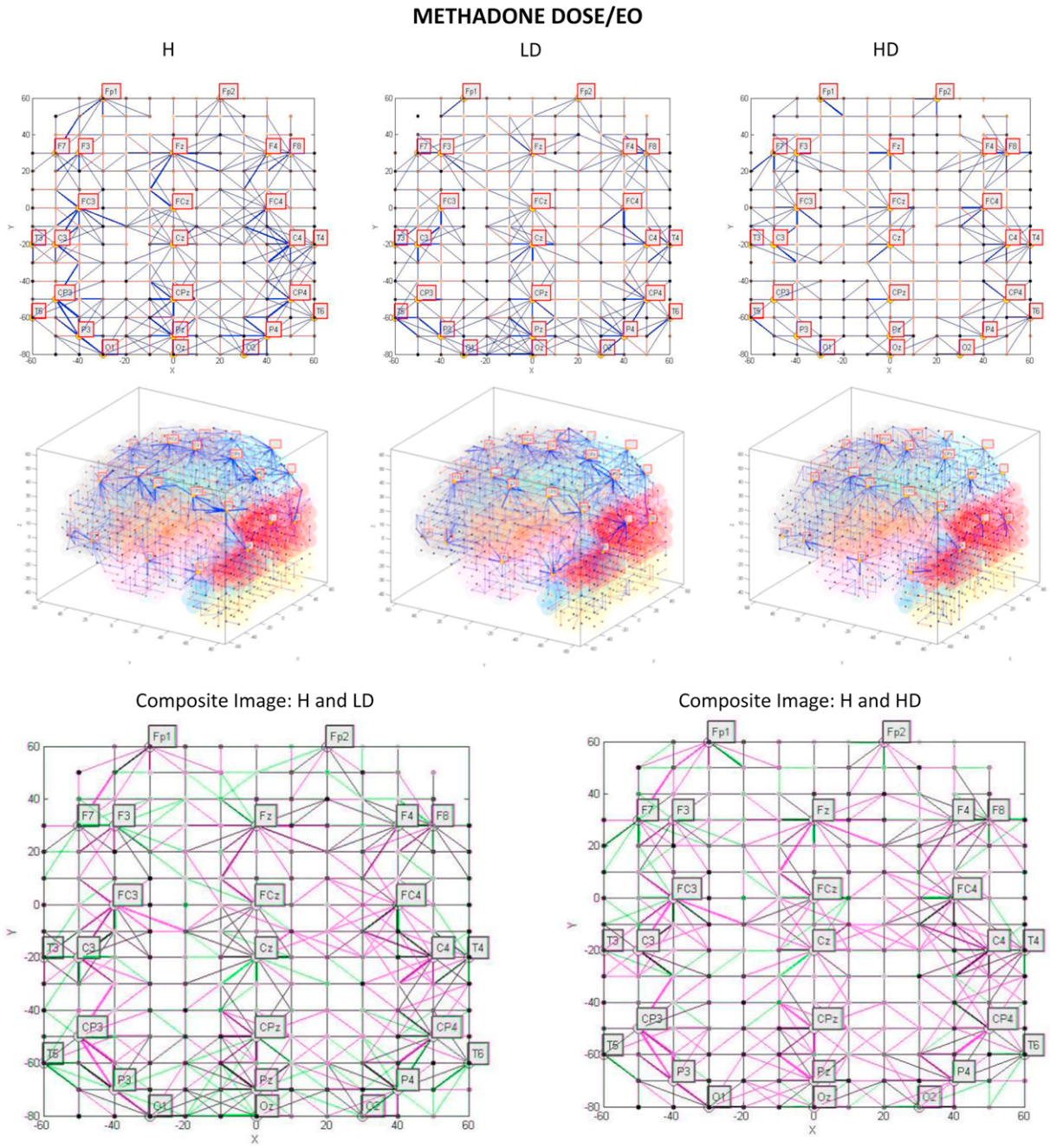

Fig. 4f. The SNNc connectivity after training it with EEG data corresponding to the EO task for the three classes—H, LD and HD of methadone. The top figures show the (x, y) projection only of the 3D SNNc, while the middle figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe). Blue lines are positive connections (excitatory synapses), while red lines are negative connections (inhibitory synapses). The brighter the colour of a neuron, the stronger its activity with a neighbouring neurons. Thickness of the lines also identifies the neurons enhanced connectivity. In yellow are the input neurons with their labels corresponding to the 26 EEG channels. The composite images (lowest figures) identify differences between connectivity of two groups of subjects overlaid in different colour bands. Grey regions in the composite image show where the two models have the same intensities. Magenta (for H group) and green regions (for either LD or HD group) show where the intensities are different.

this study, this algorithm has not been implemented as a standard exponential model, but described as follows:

$$w_j(t) = \begin{cases} w_j(t-1) \pm \alpha/\Delta t & t_j \neq t_i \\ w_j(t-1) & t_j = t_i. \end{cases} \tag{A.5}$$

Depending on the order of the first incoming spike, if a neuron i fires before a neuron j then, its weight w_j increase otherwise it decreases, with respect to the STDP learning rate (α). This parameter linearly decays with respect to time variation: $\Delta t = t_j - t_i + 1$, the time elapsed between a spike was received from neuron i and a spike was emitted by the neuron j.

The deSNN classification algorithm (Kasabov et al., 2013) is applied here in a supervised mode of learning. According to this classifier, every training sample is associated to an output neuron, which is connected to each and every other neuron of the SNNc. The connection weights of these output neurons are all set to zero initially. Then, according to the rank-order (RO) learning rule, a connection weight between neuron i to neuron j, ($w_{i,j}$), is

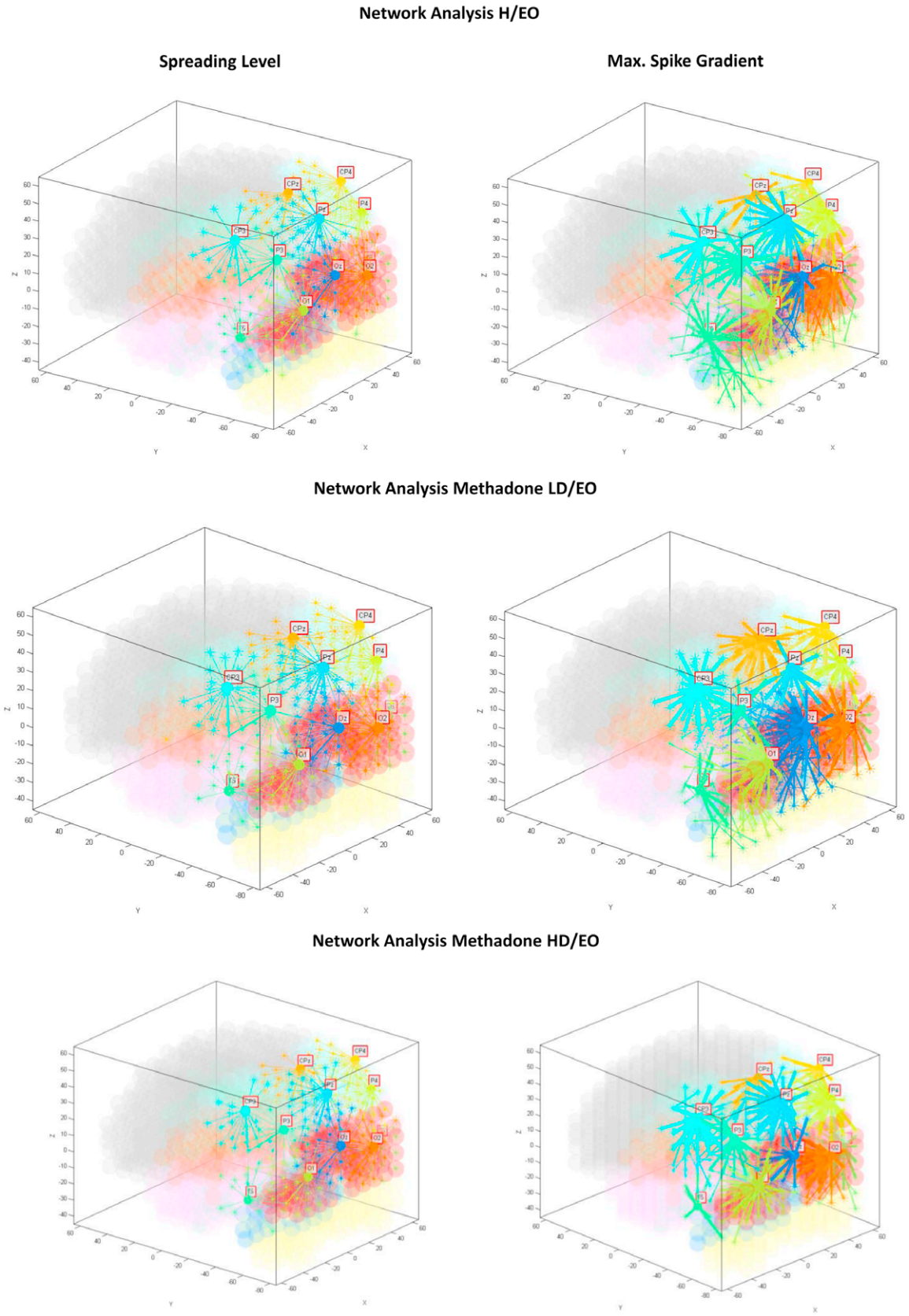

Fig. 4g. NeuCube model connectivity and spiking activity analysis per class – H, LD and HD groups – obtained for the EO task. The figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe), the spike spreading level (left) and the maximum spike gradient (right) of the 10 EEG channels allocated in the visual cortex (CP3, CPz, CP4, T5, T6, P3, Pz, P4, O1, Oz, O2) highlighted by different colours. Thickness of the lines identify a stronger activity between neurons.

Table B.1
Parameters settings used to classify O group *versus* M group (EC state) in a NeuCube classifier using RSSV method and in traditional machine learning classification methods (MLR, SVM, MLP and ECM). The parameters that influence traditional machine learning models are: class performance variance (CPV); the use of signal noise ratio (SNR) for feature selection method; normalised minimum radius of influence field cluster (MIF); normalised maximum radius of a cluster (MxIF); SVM kernel (Kernel); MLP training cycles (Tr. Cycles), hidden units (HU) output value precision (OVP), output function precision (OFP) and output activation function (OAF).

EC			
MLR		SVM	
CPV	0.05	Method	Inductive
		CPV	0.32
		Kernel	Polynomial
		Degree γ	1
MLP		ECM	
CPV	0.01	CPV	0.41
HU	5	MxIF	1
Tr. Cycles	500	MIF	0.01
OVP	0.0001	M of N	3
OFP	0.0001		
OAF	Linear		
NeuCube			
TBR	145.3	Con. Dist.	0.15
Refr. time	6	P. leak rate	0.002
STDP	0.01	Thr. of firing	0.5
Mod	0.4	Drift	0.25

Table B.2
Parameters settings used to classify O group *versus* M group (EO state) in a NeuCube classifier using RSSV method and in traditional machine learning classification methods (MLR, SVM, MLP and ECM). The parameters that influence traditional machine learning models are: class performance variance (CPV); the use of signal noise ratio (SNR) for feature selection method; normalised minimum radius of influence field cluster (MIF); normalised maximum radius of a cluster (MxIF); SVM kernel (Kernel); MLP training cycles (Tr. Cycles), hidden units (HU) output value precision (OVP), output function precision (OFP) and output activation function (OAF).

EO			
MLR		SVM	
CPV	0.14	Method	Inductive
		CPV	0.56
		Kernel	Polynomial
		Degree γ	1
MLP		ECM	
CPV	0.04	CPV	0.18
HU	5	MIF	1
Tr. Cycles	500	MIF	0.01
OVP	0.0001	M of N	3
OFP	0.0001		
OAF	Linear		
NeuCube			
TBR	33.16	Con. Dist.	0.15
Refr. time	6	P. leak rate	0.002
STDP	0.01	Thr. of firing	0.5
Mod	0.4	Drift	0.25

computed depending on a modulation factor mod and the order of the first incoming spike, $order(i, j)$, as follows:

$$w_{i,j} = mod^{order(i,j)}. \tag{A.6}$$

Then, the new connection weights will change according to the spike driven synaptic plasticity (SDSP) learning rule using a drift parameter, which is used to modify the connection weights to take into account the occurrence of following spikes with respect to time $S_i(t)$; *i.e.* if there is a spike arriving from neuron i at time t after the first one was emitted the weight increases otherwise it decreases.

$$w_{i,j}(t) = \begin{cases} w_{i,j}(t-1) + drift & S_j(t) = 1 \\ w_{i,j}(t-1) - drift & S_j(t) = 0. \end{cases} \tag{A.7}$$

Appendix B

See Tables B.1 and B.2.

Appendix C. Supplementary data

Supplementary material related to this article can be found online at http://dx.doi.org/10.1016/j.neunet.2015.03.009.

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