A cortical network model for clinical EEG data analysis

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Abstract

We use computational models of neo-cortex to investigate how cortical neurodynamics may depend on network properties and on intrinsic and external signals and fluctuations. We have previously demonstrated plausible relations between structure, dynamics and function of a neural network model of paleo-cortex, and now use a similar paradigm for the neo-cortical case. We investigate the role of various network properties and external input on EEG dynamics, in particular relating to electroconvulsive therapy (ECT) of patients with major depression. Our results are suggestive for the neural mechanisms underlying EEG, as well as for the dynamical effects of ECT on human EEG.

Keywords: EEG, clinical data, neurodynamics, neo-cortical network, FitzHugh-Nagumo neurons.

1. Introduction

Electroencephalography (EEG) recordings from mental patients often show atypical behavior. Treatments and their effects on the patients are also monitored with EEG, as in the case of

electroconvulsive therapy (ECT), which today is the most effective method to treat severe depression. The EEG evoked by ECT stimulation generally exhibits a specific pattern of seizures in the central nervous system (CNS). Preliminary *ictal* EEG data show that the dynamical activity patterns shift between several different phases, and that there are differences between individuals, depending on seizure threshold, stimulus doses and sub-diagnosis of major depressed patients [8]. Thus, overall post-ECT EEG data shows similarities, but with variation in the dynamical activity patterns, as shown in Fig. 1 A and B.

[FIGURE 1 somewhere here]

Although it has been known since long that ECT can improve mental disorders, the anatomic and physiological mechanisms behind the dynamical patterns of the EEG evoked by ECT is poorly known. We have previously used cortical neural network models to investigate relations between structure, dynamics, and function in olfactory cortex and hippocampus [4,5,6]. Here we extend this approach and use neural network models of neo-cortical structures to describe possible mechanisms underlying the EEG-signal, and how ECT-like input might influence the system. We believe computational methods of this kind can be used as complementary tools to clinical and experimental methods in furthering our understanding of EEG and the underlying neurodynamics, as well as for improving ECT efficiency.

2. Modeling approaches

Using computational models based on neo-cortical circuitry, and with realistic parameter values, we analyzed EEG-like time series by varying the connection patterns between neurons and by using different types of input. Our models are based on a previous model by Giannakopoulos *et al* [3]. Pairs of excitatory and inhibitory neurons form the basis of that model, and the pairs are organized in a square lattice with lattice distance 0.2 mm. The excitatory and inhibitory neurons of each pair are mutually connected. In addition, the inhibitory neurons are connected through self-inhibition, while the excitatory neurons are connected to excitatory neurons in other pairs. Connections are modeled with

distance-dependent delays. We developed this model into three different models of varying complexity, aiming at more realistic structures (see below).

In all the three models, the network dynamics are described by Eq. (1). The neurons are modelled as continuous output units of a Fitzhugh-Nagumo type, described by Eq. (2) and Eq. (3), which are essentially the same as in Ref. [3]. Most values of the network parameters are also the same, but the term with inhibitory dendritic inputs in Eq. (1) is different. Here, we include the inputs from inhibitory neurons to other inhibitory and excitatory neurons.

$$t^{ex(in)}\dot{u}_i^{ex(in)}(t) = -u_i^{ex(in)}(t) + p^{+}\sum_{k=1}^{n} c_{ik}^{ex(in)/ex}\, g(v_k^{ex}(t - T_{ik}^{ex(in)/ex})) -$$
$$- p^{-}\sum_{k=1}^{n} c_{ik}^{ex(in)/in}\, g(v_k^{in}(t - T_{ik}^{ex(in)/in})) + e_i^{ex(in)}(t - T^{s}) \qquad (1)$$

$$\dot{v}_i(t) = c(w_i(t) + v_i(t) - \tfrac{1}{3}v_i(t)^3) + g_i u_i(t) \qquad (2)$$

$$\dot{w}_i(t) = (a - v_i(t) - bw_i(t))/c \qquad (3)$$

In Equations (1-3), u_i is the postsynaptic potential of neuron i, v_i is the membrane potential at the axon initial segment, and w_i is an auxiliary variable. a,b, and c are positive constants, which guarantee the existence of an oscillatory interval. $g(v) = \dfrac{M_g - m_g}{1 + \exp(-av)} + m_g$ is a monotonically increasing ($a > 0$), nonnegative ($0 \le m_g < M_g$) function that describes the relation between the pre- and postsynaptic potentials of the neurons. c_{ik} describes the topology of the network. p^+ and p^- stand for the excitatory and inhibitory connection strengths. The neurons have time-constants t^{ex} and t^{in}. The total time delay, T_{ik}, is due to a synaptic delay, T^s*=1 ms*, and the time a signal takes to travel through the axonal and dendritic trees between neuron k to neuron i with the propagation velocity *0.5 m/s*. g_i denotes the synaptic membrane conductance of neuron i. We take the mean membrane potential of all neurons, or alternatively, of all layer-5 neurons in the system as a model of the EEG readout.

Model I: The 1-Layer Pair Model

The 1-Layer Pair Model is a direct generalization of the model used by Giannakopoulos *et al* [3]. The network topology is shown in Fig. 2. This model includes excitatory-inhibitory, inhibitory-excitatory and inhibitory-inhibitory connections between neurons belonging to different pairs. The inhibitory-inhibitory connections replace the self-inhibition applied in the original model [3], thus mimicking a more realistic situation. In addition, we allow for some of the inhibitory neurons to be eliminated, so that our model can reflect the anatomical findings that about 80% of the neo-cortical neurons are excitatory (see for instance Ref. [7]). The pairs (i.e. the excitatory neurons with possible inhibitory partners) are organized in a 10 x 10 network, with periodic boundary conditions for the connections.

[FIGURE 2 somewhere here]

Model II: The Basic Circuit Model

In *The Basic Circuit Model* we incorporate the six-layer structure of neo-cortex, at the same time as we aim at restricting the network complexity. The network unit, a six-layer column, is a simplification of the basic neo-cortical circuit, suggested by Shepherd [7]. Fig. 3 shows that a "column" of this model consists of two inhibitory and three excitatory cell layers, as well as one fibre layer. The unit columns are organized in a square lattice, where each column connects to its nearest neighbours by lateral connections between layer 5 neurons only. Lateral connections in other layers are excluded for simplicity reasons, since primarily layer 5 pyramid cells form long-range connections. For our calculations, a 5 x 5 column network (125 neurons) was used, together with periodic boundary conditions. External input reaches neo-cortex through lateral connections. Our constant driving input is therefore given to layer 5 exclusively, while ECT is given directly to all the neurons in the network. The difference between neuron types is exclusively by a difference in their time-constants, here given as 12, 30, 20, 30 and 50 ms, for layers 2 to 5, respectively. The time constants in Eq. 1 should thus be written $t_i^{ex(in)}$ for this model.

[FIGURE 3 somewhere here]

Model III: The Detailed Circuit Model

The Detailed Circuit Model is our third model, with a circuitry inspired by Szentagothai [2]. In this model, we take the six-layer structure (whereof the first is a fibre layer) and some further connectivity topology of the neo-cortex into account. In the simulations, we use 100 neurons, whereof 80 are excitatory neurons of two types (pyramidal and spiny stellate neurons) and 20 are inhibitory neurons of two types (large basket neurons and short distant inhibitory interneurons). Each layer contains 4 x 4 excitatory neurons in a quadratic lattice with lattice distance 0.2 mm, and four randomly distributed inhibitory neurons. The distance between layers is 0.4 mm. Fig. 4A shows the network topology of excitatory neurons. Pyramidal neurons in layer 2, 3, 5 and 6 are reciprocally and horizontally connected with a limited connection radius. The stellate neurons in layer 4 distribute sensory information in the vertical direction only. Between each two neighbouring layers, there are forward and backward connections with a limited connection radius in the horizontal direction. We also take the top-down inputs from layers 2, 3 to layer 5, 6 into account. Each basket neuron in layers 3 and 5 has long distance horizontal connections to the neurons in the same layer, and vertical connections to other neurons in layers 3 and 5. Each inhibitory neuron in layer 2 and 6 has short distance connections to the neurons in the same and neighbouring layers. Each inhibitory neuron in layer 4 has short distance connections to the neurons in the same layer only. Fig. 4 B shows the horizontal and vertical connections of inhibitory neurons. Periodic boundary conditions are used for the connections of this model.

[FIGURE 4 somewhere here]

3. Simulation results

In the clinical data, the ECT-stimulus had a frequency-range of 60-80 Hz and pulse width of 1 ms [8]. For practical reasons, the ECT input used in our simulations was applied with a shorter duration than in the clinical case, everything else being similar. The simulation results from our three models are presented separately. All figures in this section show the membrane potential (in symbolic units) of the neurons, which corresponds to v_i in Eq. (2).

Model I: For the *1-Layer Pair Model*, simulations were run with differences in connections, external input parameters, and the number of inhibitory neurons. The dynamics of the network were quite different in the different cases. The graphs in the figures below show how the mean membrane potential evolves over time. A network with 100 inhibitory and 100 excitatory neurons, driven by a constant input, produced a signal as shown in Fig. 5 A. Notice how the ECT pulse results in bursting activity and increased amplitude. In order to mimic the situation in the real neo-cortex, we created a new network structure by removing 75 of the inhibitory neurons from the one described above, so that 80% of the total number of neurons was excitatory. Fig. 5 B shows that this system responds to ECT in a completely different way than in the previous case. The dynamics in Fig. 5 B resembles the clinically measured response shown in Fig. 1 B. By increasing the inhibition strength of this system, we obtained the ECT response shown in Fig. 5 C, where the sudden extinction might remind us of the patient data in Fig. 1 A. The results we present suggest that the observed individual differences in the post-ECT EEG response could be reflected by the strength of the inhibitory connections.

[FIGURE 5 somewhere here]

Model II: The network of the *Basic Circuit Model* was tuned in the following way: Connection weights were made sufficiently weak, so that the system activity would die out, if not externally driven. An external constant driving input was then given to layer 5, strong enough to maintain oscillatory activity. When studied separately (laterally unconnected), the basic unit underwent stable oscillations, which responded to ECT by shifting into a different oscillatory activity, where various dominant frequencies occurred. A network of 5 x 5 units showed more complex dynamics, as shown in Fig. 6, where the clear periodicity of the single unit is absent. Notice how the ECT input between 400 and 500 ms alters the system dynamics, although the driving input is the same before and after the ECT pulse.

[FIGURE 6 somewhere here]

Fig. 6 shows that ECT is followed by a short high-amplitude period that decreases rather quickly in the beginning. Notice how the ECT “knocks out” the layer 5 neurons for almost 1s, and a lower dominant

frequency appears in the mean. When the layer 5 neurons start spiking again, they appear to dictate the system dynamics. The low frequency disappears, and the mean undergoes a phase shift.

Model III: Simulation results of the *Detailed Cirucuit Model* is shown in Fig. 7. The ECT input gave rise to spike-like activity of each pyramidal neuron in layer 2, 3, 5, and 6. Fig. 7 A and B show the activity of two pyramidal neurons in layer 5. Although the oscillatory amplitude of each pyramidal neuron keeps almost constant, the amplitudes of the mean activity of each layer and the mean activity of the entire network decrease gradually with time (see Fig. 7 C and D). The gradually decreasing amplitudes resemble the post-ictal patient data shown in Fig.1 B. This means that the ECT stimulus induced synchronized oscillations in the neuron population. After removing the ECT input, the neurons oscillate gradually out of phase. In Fig. 7 C and D we also see that the mean activities increase sometimes, as is usually seen in clinical EEG data. This dynamical pattern could be partly due to the increased connection complexity of this model, indicating that the collective activity of the neuron population undergoes complex dynamics phase shifts of alternating synchronization and desynchronization. This could possibly provide an explanation to the EEG dynamical pattern following ECT.

[FIGURE 7 somewhere here]

4. Discussion

The similarities we have pointed out between the model-generated activity and the clinically measured EEG are qualitative rather than quantitative. Although the network structures, especially in our Models I and II are oversimplified, we believe that they can function as a first abstraction. These models show that even simple network structures can generate different forms of complex activity patterns, such as altered dynamics due to ECT input and at least one subsequent post-ECT phase shift. More complex dynamics might be achieved by increasing the complexity of the network structure, which was done in Model III, resulting in phase shifts between synchronization and desynchronization, resembling *chaotic itinerancy*, which has been suggested to be relevant for the dynamical memory in the brain [9]. We have found similar dynamics in our mathematical analysis of post-ECT EEG data. Clinical data,

however, show more complex patterns such as phase shifts between epilectic recruiting, slow-wave, poly-spike etc. [1]. To simulate such patterns we are going to include in our models effects of neuromodulation, intra-cortical connectivity modifications, and connections to other cortical and sub-cortical structures. It is also worth noting that there are other ways of modeling EEG, which could be considered, as for instance taking the mean over only excitatory neurons in any particular, or all, layer(s).

An aim of this and future studies is to get results that can be discussed in the more general framework of EEG analysis and treatment of mental disorders and brain function. The models, mimicking the experimental signals in terms of post-ECT stimulus EEG, open a possibility to determine optimal ECT stimulus doses for clinical effect.

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FIGURE CAPTIONS

Figure 1. Human EEG traces after ECT in patients with recurrent major depression using left prefrontal-to-ipsilateral electrodes. **A** The left EEG recording of the CNS seizure immediately after the first ECT-stimulus ended. **B** Data from another patient, but with a different CNS seizure pattern.

Figure 2. The circuitry of the 1-Layer Pair Model (Model I).

Figure 3. The Basic Circuit Model (Model II) is a simplification of the basic neo-cortical circuit, suggested by Shepherd [7]. The 6-layer column is the basic unit in this model. Only the pyramidal neurons in layer 5 make lateral connections to other columns.

Figure 4. The Detailed Circuit Model (Model III), following Szentagothai's circuitry. **A** shows the excitatory, and **B** the inhibitory connections.

Figure 5. A shows the mean activity before and after ECT, in a network containing 100 inhibitory and 100 excitatory neurons. **B** and **C** show the ECT-response of a network with 100 excitatory and 25 inhibitory neurons. In **C** the inhibition strength is increased with respect to **B**.

Figure 6 The figure shows the dynamics of a network of 5 x 5 basic units. The upper five figures show the activity of the 5 neurons in one column. An ECT-input is given between 400 and 500 ms, and alteres the dynamics of every single neuron. The lower figure shows the mean activity of the entire network.

Figure 7 The response of the Model III network to ECT input (the ECT input ended at 200 ms). **A** and **B** show that two arbitrary pyramidal neurons in layer 5 fire with spike-like activity. **C** shows the mean activity of the pyramidal neurons in layer 5. **D** shows the mean activity of the entire network.

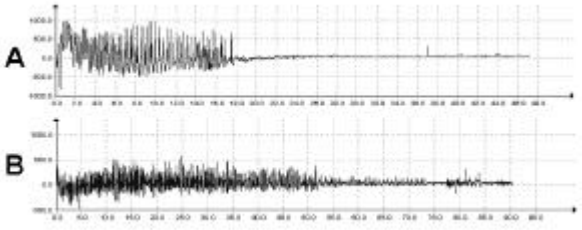


Figure 1

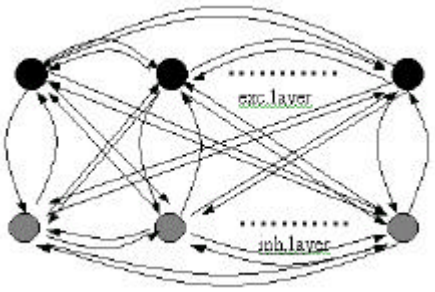
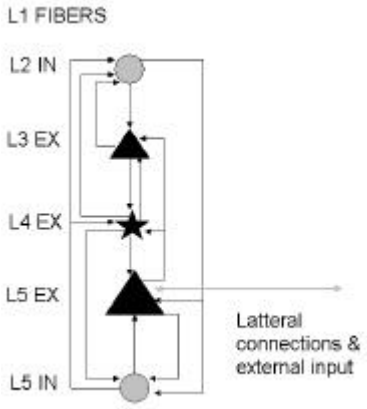


Figure 2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Latteral
connections &
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Figure 3

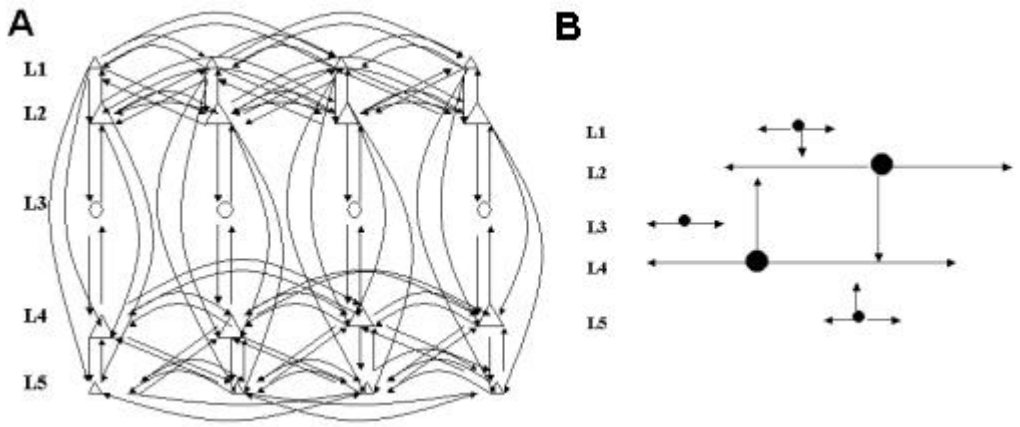


Figure 4

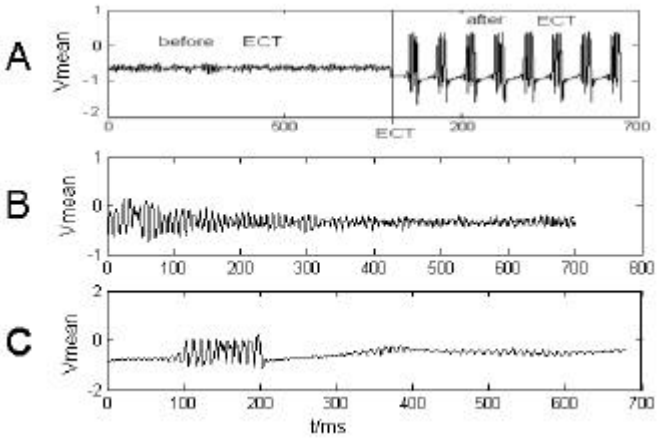
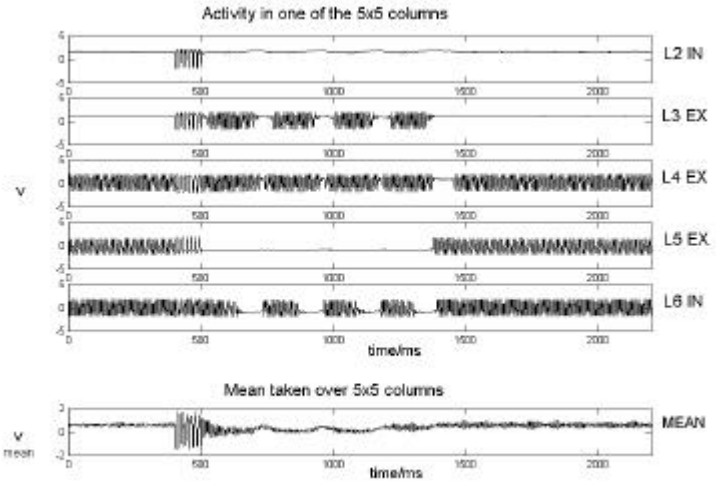


Figure 5


Activity in one of the 5x5 columns
L2 IN
L3 EX
L4 EX
L5 EX
L6 IN
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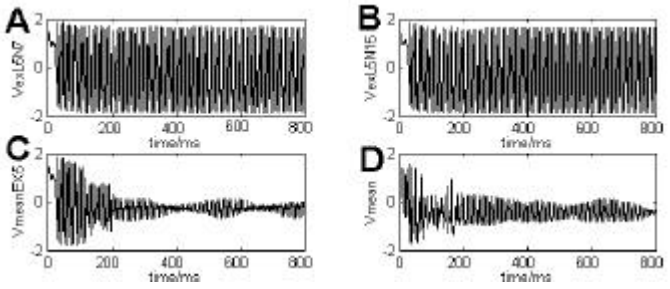
time/ms
Mean taken over 5x5 columns
MEAN
V
mean
time/ms

Figure 6


A
B
C
D
VexL6N7
VexL5N15
VmeanEK5
Vmean
time/ms
2
0
-2
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200
400
600
800

Figure 7