MIGRAINE AND EPILEPSY: LOOKING FOR A COMMON PATHOPHYSIOLOGICAL MODEL

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1. ABSTRACT

This contribution reports about the results gathered from *in-silico* experiments testing the feasibility of a research program based upon a common pathophysiological mechanism for migraine and epilepsy. In a first set of experiments, the Electroencephalographic (EEG) signals from couples of corresponding electrodes in the two cerebral emispheres, as well as from couples of continguous electrodes in the left and right emisphere, were systematically correlated. In both cases, the existence of ordered distributions of activity patterns in the EEG signals from migranious and epileptic subjects was qualitatively assessed. In a subsequent and crucial set of experiments, we were able to obtain some spatially ordered and oscillating synchronization patterns of virtual neurons distributed over a bidimensional region, by means of a multi-agent simulation environment (Netlogo). On the basis of such results, a further development of our research program including the enrichment of the data set and the consideration of other powerful simulation approaches, e.g. Artificial Neural Network (ANN) or Genetic Algorithms (GA), seems in the good track of realizing a realistic simulation of the Cortical Spreading Depression Waves, potentially useful even for clinical purposes.

2. Introduction

Since a long time the existence of a common physiopathological frame for epilepsy and migraine represents a deeply discussed and still open question. Charcot and Dejerine were the first to try and associate the two pathologies and today we know that they were probably right. Among others, Hughling Jackson, considered migraine and epilepsy as closely related in mechanism as different in their clinical symptoms [23]. A first evidence of a possible connection comes from epidemiology: the two pathologies tend to appear together in the same individual or in the same family with a higher frequency than in the general population. In the global population the penetrance of epilepsy in 0.5-1%, while among migraine-affected people is much higher, about 5.9%. According to Pietrobon [19], in western countries prevalence of migraine is about 4% in males and more than double in females (Figure 1left). Among epileptic people, however, migraine is much more frequent: indication is from 8%–23%. In 1996, Ottman and Lipton [17] investigated the synchronous presence of migraine and epilepsy and their familial occurrence (Figure 1right). It is believed that the difficult diagnosis of migraine in epileptic patients is due to the fact that epileptic subjects don't care too much about migraine, and tend to consider it as accidental.

Figure 1. ***Left:*** *Statistics about migraine and epilepsy in the global population* While, for epilepsy, the prevalence among males and females is pretty similar, in the case of migraine the females/males ratio is more than 2. The reasons of that are not completely clarified, even if hormonal influence is obviously relevant, along the whole reproductive cycle. The age factor, however, is about the same in the two pathologies: both are typical of the juvenile or mature age, although epilepsy appears as slightly more precocious. (Data from Pietrobon [19]). ***Right:*** *Statistics about the combined, familiar occurrence of migraine and epilepsy.*The presence of epileptic and/or migranious symptoms in the closest (1405) relatives of 1957 adult epileptic subjects was checked through repeated thelephonic *phone* interview. Out of 87 subjects with epileptic symptoms, 23 (26 %) were also affected by migranious crisis (Data from [17])

The technique of election for quantitative measurements of electrical activity along the scalp produced by the firing of neurons within the brain is Electroencephalography (EEG) since its introduction by H. Berger in 1929 [24]. For a general introduction to EEG, including its theoretical and practical background, see for instance [16], as well as [1] . Here it will be enough to stress that the EEG signals have been up to now the most extensively used functional tests of brain

activity and, although their popularity decreased recently with the advent of anatomical imaging techniques such as Magnetic Resonance Imaging (MRI) and Computed Tomography (CT), they still remain a powerful diagnostic tool in the case of epilepsy. Epileptic activity, in fact, can create typical abnormalities on a standard EEG record [16], and very peculiar and clearly distinguishable abnormalities of the same type have been also observed in the case of migraine [4].

According to a more and more popular hypothesis [22] epilepsy and migraine are correlated, thus implying that a crucial role in both pathologies is played by an abnormal synchronization of the involved neuronal populations. In such a frame, we are designing a computational model able to simulate the qualitative features of EEG signals associated to migraine and epilepsy on the sole assumption of a similar synchronization process. Thus, in the first part of this contribution we justify our approach to the problem, and the choice of some computational tools derived from the technology of Multi-Agent Systems and, in perspective, from that of Artificial Neural Networks. Then, we show the preliminary results of some observations carried out on the EEG signals from migranious and epileptic individuals and, eventually, discuss the foreseeable development of our work.

3. Methods

3.1. **ElectroEncephalography records and patients selection.** The EEG signals analyzed in this work have been recorded in the Dept. of Neurological Sciences of La Sapienza - Rome University, according to the standard protocol [10] and using a 10–20 montage, except in the case of the migraine signals, which came from [12]. The exclusion criteria used to select the typical epileptic signals were the absence of any pharmacological, psychiatric or behavioral interference able to modify the expected EEG signal.

3.2. **Pearson Correlation Coefficient.** The Pearson correlation coefficient (denoted by R) was first introduced by Francis Galton in the 1880s and named after Karl Pearson. It is a common measure of the correlation between two variables X and Y and is widely used in all sciences as a measure of the strength of the linear dependence between such variables, giving a value between +1 and -1 inclusive:

$$R = \frac{\sum_{i=1}^{n}(Y_i - \bar{Y})(X_i - \bar{X})}{\sqrt{\sum_{i=1}^{n}(Y_i - \bar{Y})^2}\sqrt{\sum_{i=1}^{n}(X_i - \bar{X})^2}} \tag{1}$$

Positive and negative values indicate that the two variables show the same or, respectively, an opposite trend with respect to each other. Close to zero values indicate the absence of any significant linkage. For a complete survey of the Pearson Correlation Coefficient as a powerful data analysis tool, see [21].

Since at this stage of our work we wanted to minimize the use of any data transformation procedure, including those of the FFT type (shifting to the frequency domain), we made extensive use of the Pearson coefficient in order to assess differences/similarities between couples of signals. The couples were formed so that activity patterns (if any) synchronous in the two cerebral emispheres and moving in well defined directions could be evidentiated. Thus, the electrodes posited in the corresponding areas of the left and right emispheres (for instance, the P3/P4 or the O1/O2) were considered in a strict rostro-caudal order. The situation in which the hyperactivity focus is localized in the left or right emisphere only, was also considered, by taking couples of electrodes proximal to each other in the same emisphere (see figure 4 below).

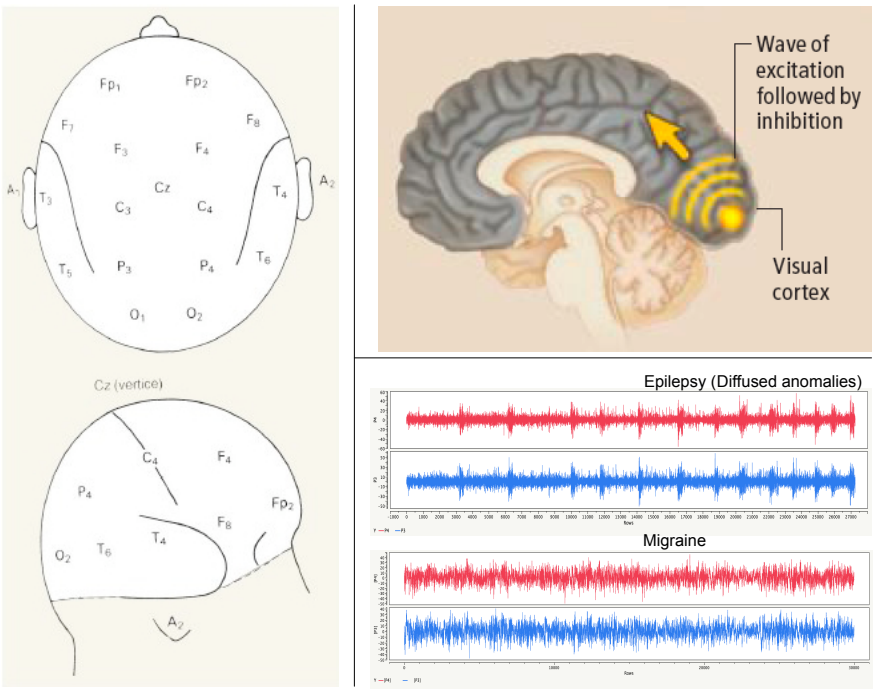

FIGURE 2. ***Left:*** *Electrode location on the human scalp in the "10-20 montage"* According to a standardized procedure 10 small electrodes (less than 1 cm diameter, wetted by a salt-past increasing the electrical conductivity) are symmetrically located on each emisphere according to the following nomenclature: Fp = frontal-pole; T = temporal, C = central, P = parietal, O = occipital] ***Upper Right:*** *Cortical Spreading Depression (CSD) wave originating in the visual cortex (Modified from* [8]*).* The average speed wave was estimated in 4-6mm/min [19] ***Lower Right:*** *Signals of corresponding electrodes from left and right emispheres.* The upper and bottom panels refer to EEG signals (about 32000 points at 270 Hz sampling) recorded from the P4 (blue) and P3 (red) electrodes of individuals with diagnosis of 'Diffused (epileptic) anomalies" and Migraine, respectively. The vertical axis (mV) goes from -50 to +50.

3.3. **Multi Agent System (MAS) and Artificial Neural Networks (ANN).** Multi agent systems (MAS) are useful for simulating the highly cooperative behaviour of individuals in social groups like human communities, insect colonies nests or multicellular organisms. Agents are able to carry out simple actions based upon instructions, memorization, and perception of external environment. The architecture of the agent system is such that each agent corresponds to a neuron or a neuron class and is able to send signals according to its neighbours, thus influencing their activation state. The time of the activation of the single agent may also change according to afferences of connected fibers, regulating the activation threshold as well as the firing frequency. The MAS system should be able to reproduce the EEG signal typical of migraine or epilepsy. The more or

less realistic conditions under which this may be achieved, could be taken as reinforcing/disproving the theory that the basis of both pathologies is a common synchronization mechanism.

Artificial Neural Networks (ANN) have been used in the last decades in modeling epilepsy because of their ability to represent complex, nonlinear system in their time-dependent changes. Very recently, they have been used to model the functions of the human Central Nervous System at the highest level [2]. In the general context of epilepsy studies, ANN were mainly directed toward the diagnosis of suspected epileptic events from EEG signals. The advantage consists in the shorter time (as compared to humans) needed to interpret very long signals like Holter EEGs, which last for 24 hours and more. ANN were also used for reliable predictions of an epileptic crisis long before its actual occurrence. To the latter aim, different types of ANN were used, mainly of the supervised feed–forward architecture [3][6][18], taking advantage of genetic algorithms in the learning phase. In the context of the present work, ANNs represent a precious source of inspiration for our MAS models and, in perspective, a promising tool to be used *per se* as well as in a combination with MAS.

4. Results

	Fp_1-Fp_2			T_3-T_4			C_3-C_4			P_3-P_4			O_1-O_2		
	P_{in}	P_{fin}	P_{tot}	P_{in}	P_{fin}	P_{tot}	P_{in}	P_{fin}	P_{tot}	P_{in}	P_{fin}	P_{tot}	P_{in}	P_{fin}	P_{tot}
Control	0.29	**0.66**	0.40	-0.32	-0.45	-0.06	0.12	0.07	-0.07	0.24	0.33	0.046	**0.66**	**0.77**	**0.80**
F. Epil.	**0.79**	**0.69**	**0.82**	0.11	0.02	0.04	0.13	0.12	0.15	-0.15	0.00	0.16	0.42	0.57	**0.64**
D. Epil.	0.58	**0.92**	0.54	-0.37	-0.33	-0.02	0.33	-0.02	0.25	0.19	**0.77**	0.49	**0.66**	**0.92**	**0.83**
Migr.	**0.97**	**0.96**	**0.93**	0.19	0.19	0.36	0.22	0.24	0.39	0.44	0.52	0.47	**0.86**	**0.91**	**0.83**

TABLE 1. *Time dependent Pearson correlations between left and right emisphere in different pathologies (F.Epil. = Focal Epilepsy; D. Epil. = Diffused Epilepsy.; Migr. = Migraine)* The correlations were calculated over the first (P_{in}) or last (P_{fin}) thousand points, besides than over the whole signals (P_{tot}), from the records of the following couples of electrodes: Fp = frontal-pole; T = temporal; P = parietal: O = occipital, C = central. Odd and even suffixes refer to right and left emispheres, respectively; values higher than 0.6 are in bold.

4.1. **Correlating signals from homo- and controlateral electrodes.**

An interesting trend is shown by correlating traces from symmetric couples of electrodes in the two emispheres within the same subject. Table I contains the Pearson coefficients obtained by coupling corresponding electrodes in the left and right emispheres and ordered in the rostro-caudal direction, from the fronto-parietal (F_{p1},F_{p2}) to the occipital (O_1,O_2) lobes.

In all cases, besides correlating the overall traces (P_{tot}), sampled at 270 Hz for a total of about 64,000 points, the first and the last 1000 points have been also correlated (P_{in}, P_{fin}, respectively). The aim was to check whether in the time window spanned by the analyzed signal, namely within the about 138 sec of its total duration, some significant change occurred. An even more ambitious goal was to enlight a space-dependent trend, linked to the rostro–caudal direction.

Although the data in Table I did not substantiate clearly none of the above expectations, it seems fair drawing, on their basis, the following minimal conclusions: a) all the analyzed signals show a quite synchronous behaviour, between the left and right emispheres, in the fronto-parietal and the occipital lobes; b) the signal associated to the migraine diagnosis shows the highest correlation as compared to both the epileptic cases.

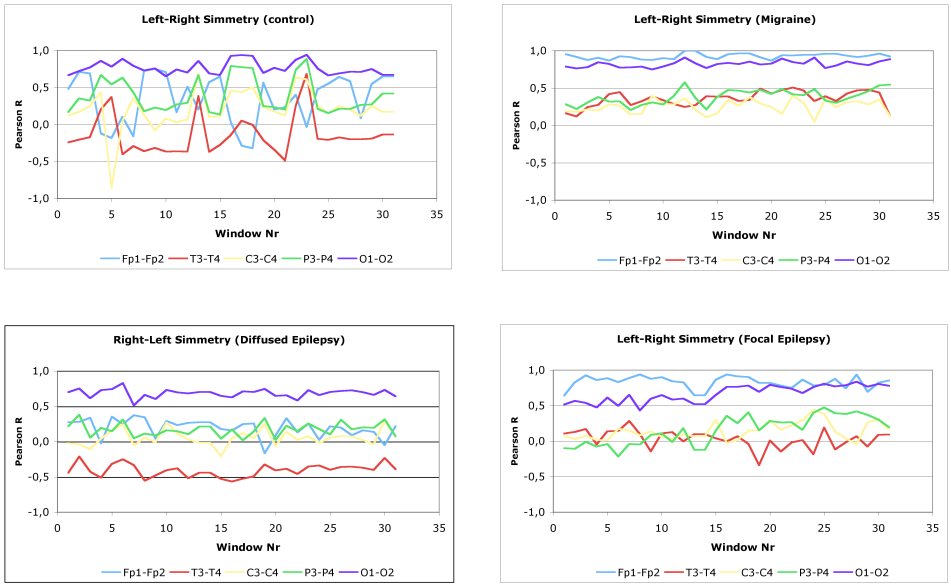

FIGURE 3. *Time and space dependent simmetry of the emispheric activity in migraine and epilepsy.* EEG signals digitized at 270 Hz for a total of 32,000 points were considered as contiguous, non overlapping windows of 2000 points each. Corresponding windows from corresponding electrodes in the two emispheres, were correlated by the Pearson R as indicated in each panel. For the electrodes nomenclature and location, see Figure 2

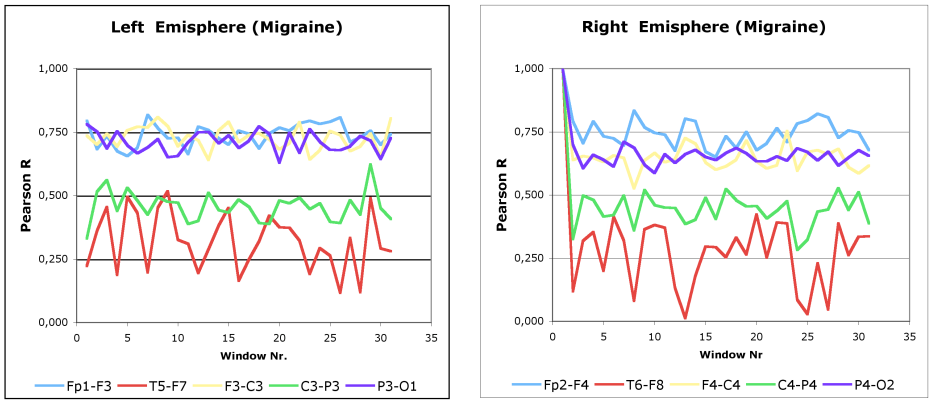

FIGURE 4. *Time and space dependent simmetry of the intraemispheric activity in migraine.* The couples of electrodes considered for correlations are indicated in each panel. All other conditions as in figure 2 and 3.

In looking for some more conclusive indication of any symmetrical and/or synchronized activity in the EEG records, we decided to improve the time resolution of our analysis and carried out the correlation analysis in subsequent, non overlapping windows of 2000 points each. The results, shown in figure 3, confirm that the highest synchronous activity is concentrated in the occipital lobe under all conditions. Moreover, particularly in the Migraineous and in the Focal Epileptic conditions, the concomitant lower and higher synchronization in the temporal/central and frontoparietal areas, respectively, are consistent with an oscillating behaviour, namely a clustering in well defined areas of the maximal and minimal activity occurring in a given time span. It is worth mentioning that a similar (although less clear) trend is also observed by correlating EEG records from proximal electrodes within the same emisphere, as reported in figure 4 in the prominent case of Migraine.

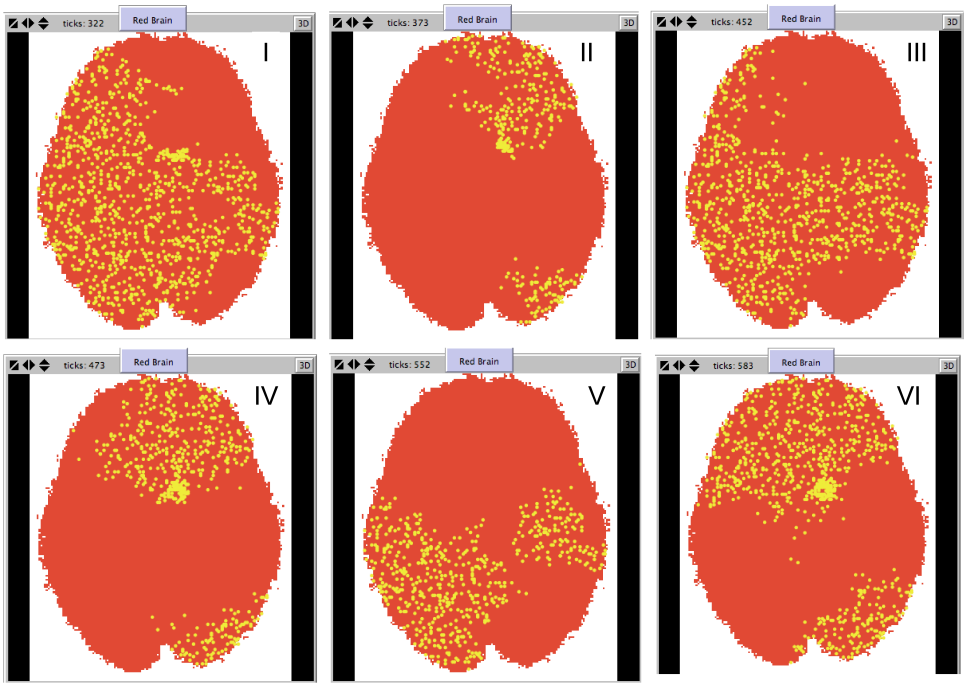

FIGURE 5. *Oscillating activity waves of brain neurons simulated by independent agents.* Panels from I to VI have been recorded in sequence at about the same time interval (10±5 sec) from each other. The algorithm used in the simulation is described in [7]

4.2. **Simulating Cortical Spreading Depression.** Even if neither migraine nor epilepsy are actually fully understood in their deep causes and detailed mechanisms, a most probable connection between them concerns the specific abilitiy of neural cells to get synchronized under various circumstances. The first conjecture about the causal relationships linking synchronization and epilepsy dates back to Matsumoto (1964), showing that hyperactivity of a limited number of cells unable to recruit a larger network was also unable to originate an epileptic event. The somehow paradoxical discovery of the extensive synchronization occurring in migraine is due to Leao [14], while studying an epileptic model in rabbits. Leao observed a depolarizing wave moving at a 3 mm/min speed in

the rabbits cortex. He named the wave Cortical Spreading Depression (CSD), since after its passage the cortex remained inactive for some time. Only in 1994, however, Lauritzen [13] hypothesized that CSD could have been at the origin of the visual aura in human migraine. He showed that associated with the visual aura was a high-activity wave moving in the anterior direction from the occipital region at speed from 2 to 6 mm/min. Such a wave was followed by a temporary suppression of the cortical electrical activity. The frequent absence of the visual aura in many subjects has been explained by assuming that CSD may also originate in visually silent regions [19]. CSD, in fact is not limited to the occipital area: its starting point may be observed most frequently in the CA1 hyppocampal area, followed by the neo-cortex, and it remains a most interesting phenomenon of neural synchronization.

Figure 5 shows the activity patterns observed in the area representing a coronal section of the human brain, by means of a simulation device described elsewhere [7]. The six panels in the figure refer to the neurons activity distribution at various times (proportional to the ticks number in each panel) from an initial fully randomic distribution (see the inset) to the synchronous firing of neurons clustering in different and alternating regions of the "brain".

5. Discussion

The hypothesis of a fundamental similarity in the pathophysiological mechanisms of migraine and epilepsy assigns a crucial role to the synchronized electrical hyperactivity of neurons.

Recruiting a larger and larger number of phase-coupled neurons, in fact, should allow to account for: i) the peculiar activity bursts appearing in EEG signals; ii) the close temporal correlation of the activity bursts with macroscopic clinical symptoms like epileptic seizures or individual perceptions like visual aura; iii) the typical rythmic occurrence and spatial patterns of the activity waves. Such apparently simple phenomena appear amenable to simulation, taking advantage of the continuous increase in hardware power and flexibility/sophystication of simulation environments [5].

The complexity of the underlying neurological mechanisms, however, inspired our choice of a 'weak' modelistic strategy, based upon the modulation of the collective behaviour emerging from small changes in the individual properties of a large number of autonomous agents sharing the same environment and nonlinearly interacting among each other. It is worth reminding that, in general, the first aim of a 'weak' modeling approach, as opposed to a 'strong' one, is to reproduce the functional behaviour of a complex system, even by computational methods only approximately matching the physical structure of the system.

All in all, the most interesting outcome of our study may be summarized as follows:

- Concerning the analysis of EEG signals, a necessary prerequisite to any modelistic effort, a simple and flexible tool like the Pearson correlation coefficient showed a somewhat unexpected euristic power: as a matter of fact Figures 3,4 and Table I indicate that by just dissecting the time series into a number of subsequent windows in order to increase the resolution of the method, allowed us to identify the presence of time and space ordered activity patterns of neurons from both homo- and contralateral signals.

- Concerning the multi-agent simulation environment, Netlogo appeared more flexible as compared to other programmable tools specialized for neuronal systems, like Neuron [11], although probably less powerful at increasing models size. As an example, by the very same tool (Netlogo) it was relatively straightforward to work out simulations based upon completely different mechanisms, as those shown in figure 5 and 6. The latter one, in particular, concerns the results generated in terms of recordable signals (lower half) by the periodic oscillations changing the relative position of two 'foci' which synchronize the activiy of the neuronal population in which they are embedded.

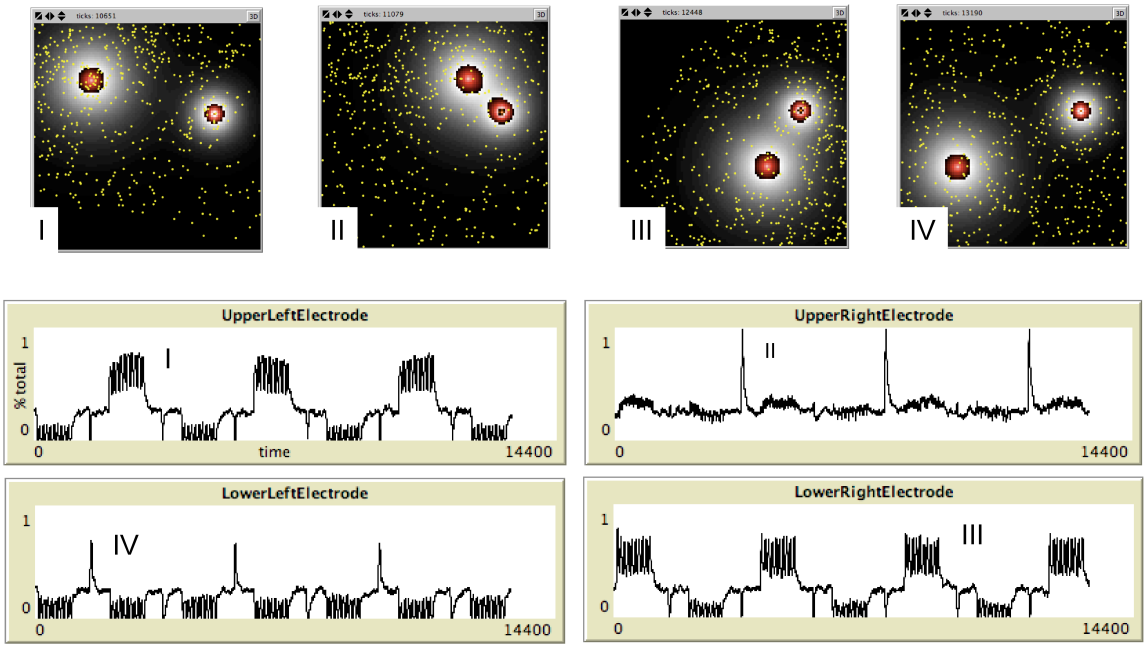

FIGURE 6. ***A multiple-agent based oscillating field model for simulating hypersynchronized neuron waves*** *The four upper panels show one cycle of the periodical, relative location changes which neuron undergo in the migraneous or epileptic syndromes. The fraction of the total neurons active in each quadrant of the neurons field is reported in the four bottom panels. The prominent peaks are labelled I - IV according to their association with the corresponding condition depicted in the upper panels.*

The similarity of the signals in the lower paner of figure 6 with the alternating bursts of activities and 'interictal' phases, observed *in vitro* but also *in vivo* is very encouraging.

Even more promising appears the possible synergic combination of a multi-agent environment with other general-purpose programmable simulation algorithms (like AAN or genetic algorithms) which showed extremely powerful to underpin the basic mechanisms at the root of highly complex functions in the human SNC [2].

One limit of our study is, at present, the analysis of single EEG signals, in spite of the fact that the complexity of the phenomena at hand would require a solid statistical basis for any model/conjecture. Another limit could appear the analysis of EEG signals restricted to the time domain, with no attempted extension to the frequency domain. However, it should be reminded that our purpose at this stage is just to check: i) the feasibility of working out a common mechanism for migraine and epilepsy based upon the synchronization of specific neuronal regions; ii) the phenomenological similarity between natural EEG signals and signals simulated by a multi-agents programming environment. Thus, shifting towards relatively simpler methods and a few, exemplary data-sets, appears compatible with such a minimal and intermediate task, which, in all cases, paves the way leading to further, more ambitious extensions.

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6. APPENDIX

6.1. **EEG records of parietal electrodes in migraine and epilepsy.** Figure 7 shows EEG signals from the right parietal (P4) electrode recorded under identical conditions from individuals with diagnosis of epilepsy (2) and migraine (1) and normalized for the different intensities (see the legend for details). The parietal lobe is frequently the area where epileptic foci are localized, but the signals in the figure do not show any significant difference from the control as well as between each other, as confirmed by the R value very close to zero in any of the 6 couples tested. A number of reasons could account for that, the most relevant being the unfavourable signal/noise ratio, as indicated by the high (and similar) standard deviation shown by all traces.

6.2. **The epilepsy-migraine connections.**

6.2.1. *Genetical aspects.* Specific interest has been dedicated to looking for a genetical explanation of the statistical association between the two pathologies since both migraine and epilepsy may be defined as multifactorial genetical diseases. Most of the genetical investigations considered up to now the familiar hemiplegic migraine (FHM), which is a monogenic disease including both migraine and epileptic symptoms.

An FHM diagnosis is generally based upon the presence of the *aura motoria*, accompanied by usually monolateral and sometimes bilateral emiplegy. However, the *aura motoria* is not the only one to appear, since it often follows the appearence of the *aura visiva* and *aura sensitiva*, as symptoms of the involvement of the corresponding cortical areas. Moreover, also the neurovegetaive symptoms, like *nausea e fotofobia* quite often do appear.

Three diferent types of FHM have been defined as FHM1, FHM2 and FHM3. FHM1 is caused by a mutation of the CACNA1A gene, which codes for the Cav 2.1 subunit forming the pore in the type P/Q Calcium channel. FHM2 is associated to a mutation of the ATP1A2 gene, coding for the α 2 subunit of the NA/K pump. Finally, FHM3 has been attributed to mutations in the SCN1A gene, coding for the protein forming the pore of the voltage-dependent Na channel named Nay 1.1. [19].[22]

6.2.2. *Pharmacological data.* A further connection between migraine and epilepsy, deals with the increasing number of antiepileptic drugs (AED) nowadays used in the profilactic therapies against migraine, with considerable success. Such therapies, in fact, are able to decrease both the frequency and the pain intensity of the migraine crisis. Among such drugs it is worth to mention the Na *valproate* (VPA), the *topiramate* (TPM) and the *gabapentine* (GPT).

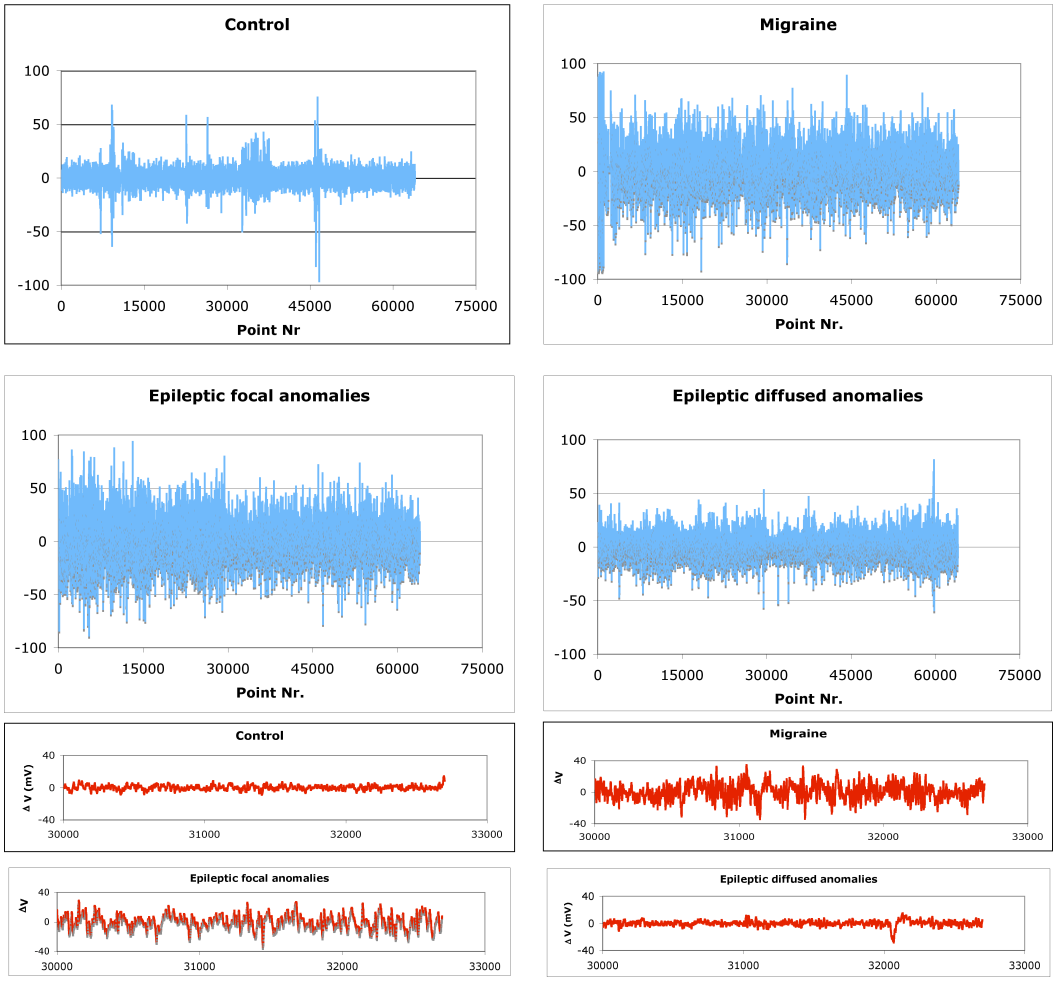

FIGURE 7. *EEG records of parietal (P4) electrodes from migrainous and epileptic subjects* The EEG signals, digitized at 270 Hz, span about 235 sec and have been normalized to make easier the comparison. The lower panels (red) contain 10 sec windows of the corresponding signals, starting at point Nr 30000.