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Network analysis of epileptic brain

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Abstract—We introduce a practical and computationally not demanding technique for inferring interactions at various microscopic levels between the units of a neuronal brain network from the measurements and the processing of macroscopic EEG signals. Our methodology is then applied for getting a glance to the microscopic interactions occurring in a neurophysiological system, namely, in the thalamo-cortical neural network of an epileptic brain of a rat, where the group electrical activity is registered by means of multichannel EEG. We demonstrate that it is possible to infer the degree of interaction between the interconnected regions of the brain during different types of brain activities, and to estimate the regions' participation in the generation of the different levels of consciousness.

1. Introduction

The current trends in neuroscience and neurophysiology are connected with the analysis of brain networks [1] which interact with each other to perform different types of cognitive tasks, as, e.g., the formation of a memory trace [2], the processing of a visual object [3], or the development (on a clinical level) of pathological rhythms like epileptic seizures [4]. These interactions are often quantified by means of the degree of synchrony, which can be measured both locally (i.e. within the same brain structure), or over a more global scale (i.e. in between brain structures) [5]. While neurophysiology aims at understanding the interplay of individual neurons [6], the majority of available data (especially those acquired from human subjects) comes from non invasive tests [7, 8, 9]. These tests are made, in daily practice, under the form of electro-encephalograms (EEG) or magneto-encephalograms (MEG), functional magnetic resonance imaging (fMRI), which actually measure the (electric or magnetic) group activity of large ensembles of cells. The focal riddle for physicists and neuroscientists consists, therefore, in disclosing the way microscopic scale neural interactions pilot the formation of the different activities revealed (at a macroscopic scale) by EEG and MEG signals.

We apply network approach cite24,16 for getting a glance to the microscopic interactions occurring in a neurophysiological system, namely, in the thalamo-cortical neural network of an epileptic brain of a rat, where the group electrical activity is registered via multichannel EEG. We demonstrate the possibility to determine the degree of interaction between the interconnected regions of the brain during different types of brain activities.

2. Experiments

At a physiological level, available recordings through EEG provide typical samples of brain dynamics at its macroscopic level. They reflect, indeed, integrated extracellular voltage changes of neural ensembles, located in the vicinity of the recording electrode. In parallel (and with the aid of intra- or extra-cellular single unit recordings), an operator is endowed with the opportunity of browsing on the activity of a single neuron, inspecting brain dynamics at its microscopic level.

In the current study the local field potential (LFP) and single unit recordings were obtained in 3 months-old Genetic Absence Epilepsy Rats (GAERS). A 1 MΩ Tungsten electrode was lowed in the deep layers of the somatosensory cortex, and another 1 MΩ Tungsten electrode was placed into the posterior thalamic nucleus. LFP and unit recordings of a given brain structure were gathered by the same electrode. All experimental procedures were performed in accordance with the guidelines of the council of the European Union of the 24th November 1986 (86/609/EEC), which were approved by local authorities (review board institution: LandesamtfürNatur, Umwelt und Verbraucherschutz Nordrhein-Westfalen; approval ID number: 87-51.04.2010.A322).

Fig. 1 illustrates the setup under which measurements are performed, the typical records of the EEG signal, as

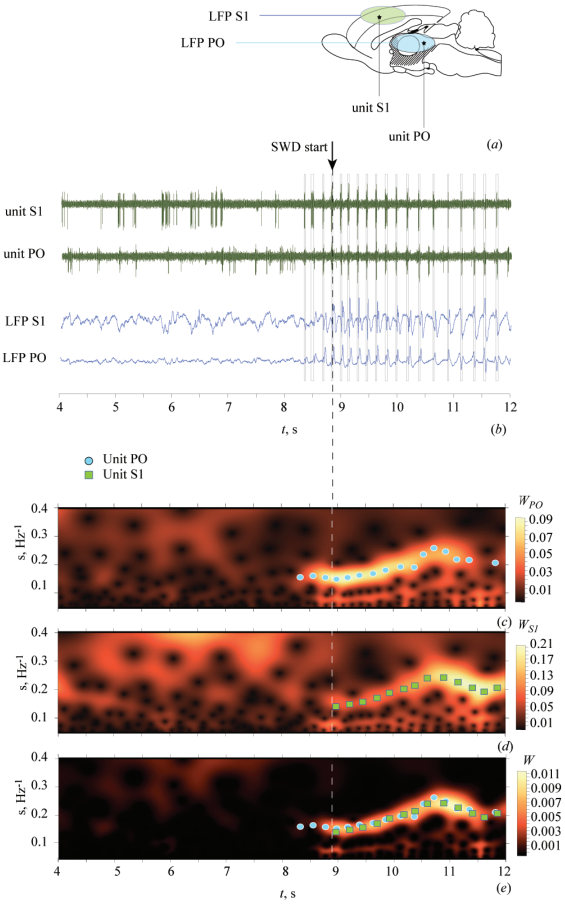

Figure 1: (*a*) Schematic illustration of the experimental setup. (*b*) The set of registered neurophysiological signals, reflecting the activity of single cells (unit S1 and unit PO) and the group activity in cortex and thalamus (LFP S1 and LFP PO). Panels (*c*- *e*) wavelet decompositions of the macroscopic signals. (c) $W_{\rm PO}(s,t)$ obtained from signal LFP PO, (d) $W_{\rm S1}(s,t)$ obtained from signal LFP S1, and (e) $W(s,t) = W_{\rm S1}(s,t) \times W_{\rm PO}(s,t)$. The solid circles and the solid squares shows the main spectral component of the signals, taken from the single cell in thalamus (unit PO) and cortex (unit S1), respectively.

well as that of one of its underlying microscopic components (the activity of a single neuron) measured by the same electrode as the EEG signal. Macroscopic and microscopic signals are acquired in two different brain structures: cortex (S1) and thalamus (PO), which enables us to give ground to the above discussion about interrelationships between local and global synchronization processes.

We analyze also the dynamics of the thalamo-cortical network by means of a multichannel set of EEG recordings taken from WAG/Rij rats [15] — a genetic animal model giving rise to absence epilepsy. In the experiment 6 month old WAG/Rij rats were chronically implanted electrodes in layer 4 to 6 of the somatosensory cortex, as well as in *i)* the posterior thalamic nucleus, *ii)* the ventral-posteromedial thalamic nucleus, *iii)* the anterior thalamic nucleus, and *iv)* the reticular thalamic nucleus. Experiments were carried out in accordance with the Ethical Committee on Animal Experimentation of Radboud University Nijmegen (RU-DEC).

3. Data Processing

To examine the dynamics of EEG signals $X(t)$ the wavelet power spectrum can be calculated as $W(f,t) = |M(f,t)|^2$, where $M(f,t)$ is the complex wavelet spectrum defined with the aid of continuous wavelet transform [12, 13]

$$M(f,t') = \sqrt{f} \int_{-\infty}^{+\infty} X(t)\psi^*\left((t-t')f\right)\,dt \qquad (1)$$

(the symbol "$*$" denotes the complex conjugation) with the Morlet mother wavelet

$$\psi(\zeta) = \frac{1}{\sqrt[4]{\pi}} \exp(j2\pi\zeta) \exp\left(-\frac{\zeta^2}{2}\right). \qquad (2)$$

In the recordings, a transition is observed from *normal, physiological* brain activity of the rat towards a *pathological, hyper-synchronous* behavior, corresponding to the occurrence of an epileptic seizure (the so-called spike-wave discharge [SWD] due to the specific waveform of the electroencephalographic signals with well-pronounced large amplitude sharp peaks and slow-waves), and involving an abiding change in local and global synchronization properties of the brain network.

Before seizure starts, the registered macroscopic activities of cortex and thalamus are complex signals with continuous power spectra (Fig. 1,*c,d,e* for $t < 8.4$ s). Such a behavior actually corresponds to cells firing spontaneously and in a uncorrelated manner. At the onset of the seizure, cells of cortex and thalamus start to exhibit a correlated bursting activity, which gives rise to the regularly repeated spike pattern that is seen in the macroscopic recordings (Fig. 1,*b* for $t > 8.4$ s).

The distributions of wavelet energy $W_{\rm S1}(s,t)$ and $W_{\rm PO}(s,t)$, $s = 1/f$ (obtained from the macroscopic signals S1 and PO) change from an almost homogeneous configuration ($t \le 8.4$ s) to a shape that is characterized by a local peak positioned in the frequency band corresponding to the epileptiform activity. This fact reveals that the onset of epileptic seizure establishes local synchronization *within* both cortex and thalamus, as well as global synchronization *between* these two regions of the brain. Indeed, by comparison of the surfaces $W_{\rm S1}(s,t)$ and $W_{\rm PO}(s,t)$, and by consideration of the surface

$$W(s,t) = W_{\rm S1}(s,t) \times W_{\rm PO}(s,t), \qquad (3)$$

one can see that the considered cells in the cortex and in the thalamus are synchronized at the frequency of the seizure and, moreover, they are synchronized with other cells belonging to the same part of the brain (see Fig. 1, *e* for $t > 8.4$ s).

As the result, the recordings taken from three cortical and four thalamical electrodes are considered at different instants of time: *i)* at the beginning of a seizure, *ii)* at the end of a seizure, *iii)* at a time at which the rat is in a state of active wakefulness, and *iv)* at a time at which the rat is in a state of slow-wave sleep. Moreover (and according to the neurophysiological background of absence epilepsy [16]), the dynamics of the network is studied within three different frequency bands: *i)* Δ_{f_1} (the low-frequency, LF, oscillation range 1–5 Hz), *ii)* Δ_{f_2} (the range 5–10 Hz, SWD, of seizure activity), and *iii)* Δ_{f_3} (the range of high-frequency, HF, theta activity, 7–20 Hz). The wavelet energies W_{LF} , W_{SWD} and W_{HF} are calculated as

$$W_{LF,SWD,HF} = \int_{t-\tau}^{t} \left[\int_{f\in\Delta_{f_{1,2,3}}} W_i(f,\xi)df \right] d\xi \qquad (4)$$

where $\tau = 2.5$ s, and i is the number of the EEG channel.

The degree of the interactions $w_{i,j}$ between the different parts of the cortex and thalamus described by the i-th and j-th EEG channels in certain frequency band $[f_1, f_2]$ is defined as [14]

$$w_{i,j} = \left[\int_{f_1}^{f_2} |W_i(f) - W_j(f)|df \right]^{-1}. \qquad (5)$$

4. Brain structures interactions

We can analyze the degree of the interaction between the different parts of the cortico-thalamo-cortical network during the generation of the different forms of activity of epileptic brain [the SWD (at the onset and the end), active wakefulness, and deep slow-wave sleep, labeled as SWDO, SWDE, AW, and DSWS, respectively]. It can be assumed that in brain the neurons belonging to the different brain structures can be involved together in the generation of the certain rhythm. In this case the wavelet spectra of the EEG signals, taken from these areas of brain, are expected to demonstrate the increase of the similarity. According to this, the strength of the interaction between the corresponded areas of brain can be estimated by the calculation of the degree of similarity $w_{i,j}$ via Eq. (5), where the limits of integration are chosen accordingly to the frequency bands associated with the type of the rhythm (in our study the limits are defined by the bands $\Delta_{f_{1,2,3}}$).

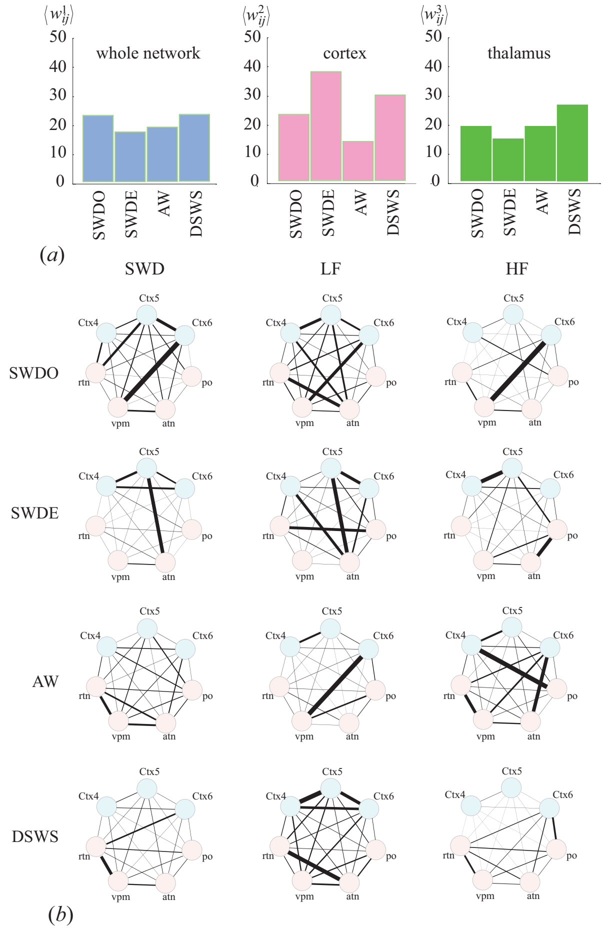

Figure 2: (*a*) The mean value of the strength of interaction between the different parts of the thalamo-cortical neuronal network.(*b*) The schematic illustration of the coefficients $w_{i,j}$, reflecting the degree of interaction between the different parts of the cortex and thalamus for the different frequency bands.

Fig. 2, *a* reports the mean degree of the interaction between the areas of brain belonging to the cortex, the thalamus, and the whole neuronal network, calculated by averaging the coefficients $w^k_{i,j}$ over the corresponding region of the brain network (with $k = 1$ for the whole cortico-thalamo-cortical network, $k = 2$ for cortex and $k = 3$ for thalamus). In Fig. 2, *b*, the values $w_{i,j}$ are shown by the increase (or decrease) of the line width, which connect the corresponding brain structures. From Fig. 2, *a* one easily sees that the cortico-thalamo-cortical network is characterized by a high degree of global interaction at the onset of the seizure (SWDO state) and during the DSWS state, while the minimal value of $w^1_{i,j}$ is achieved for the SWDE state. Looking at the $w^2_{i,j}$ and $w^3_{i,j}$ values (corresponding to cortex and thalamus, respectively), one finds that the thalamical network exhibits a high level of global interaction during the SWDO and DSWD states, while during the SWDE state the different regions of thalamus interact weakly with each other (the values of the coefficients $w^k_{i,j}$ become less than 20). On the contrary, the cortical regions interact more strongly at the end of the epileptic seizure (the values of the coefficients $w^k_{i,j}$ become greater than 40). From Fig. 2, *a* one can conclude that, along with the interaction within the differen parts of cortex and thalamus, the increase of the interaction *between* these parts manifests itself as a key feature of the epileptic seizure. Indeed, at the beginning of the SWD (i.e. when the seizure occurs spontaneously) there is an increase not only within the cortex and thalamus separately, but also between them.

From Fig. 2, *b* one can conclude that at seizure onset the different parts of neuronal network demonstrate a high level of interaction in the bands Δ_{f_1} and Δ_{f_2} (the low- and spike-wave frequency). The increase of the interaction in the Δ_{f_1} band is related to the presence of the low-frequency delta precursors, as shown in Ref. [17]. At the SWD end (the SWDE state), there are still strong interactions in the cortex, related to the SWD-frequency band. When the seizure is finished and the animal exhibits active wakefulness, the different parts of cortico-thalamo-cortical network start to interact stronger in the frequency band Δ_{f_3}, which corresponds to the generation of high-frequency brain rhythms. During the deep slow-wave sleep, such interactions can be observed in the band Δ_{f_1} of low-frequencies, while in the other bands the different parts of the brain interact more weakly. During the AW state, the parts of the cortex and thalamus interact almost equally with each other, but the high degree of the interaction here is revealed in the high-frequencies range. The conclusion is that, during the slow-wave sleep, the low-frequency oscillations (delta-waves) are generated by the neuron populations both in the cortex and in the thalamus, and this type of brain activity is characterized by a high degree of inter-layer interaction in these parts of the brain as well as over the whole neuronal network of cortex and thalamus.

5. Conclusion

We analyzed the synchronization in the cortico-thalamo-cortical network of brain of the rats with genetic predisposition to absence epilepsy [18], where the group electrical activity are registered by means of multichannel EEG. We demonstrated the possibility to determine the degree of interaction between the interconnected regions of the brain. Specifically, depending on the type of brain activity, we found that the neurons in cortex and thalamus interact in the different frequency bands with different degrees of intensity, which, in turn, leads to the formation of different synchronous patterns.

In addition, we detected strong synchronization of the cortical layers at the end of the epileptic seizures together with a decrease in their synchrony with thalamic nuclei. This is an indication of the attempt of the cortex, the location of the epileptic onset zone in this epilepsy model, to keep the seizure ongoing, which is corrupted by the thalamus.Interestingly, network analyzes of the multichannel EEG in the same epilepsy model showed a high coherence and phase consistency between cortex and thalamus and between cortical layers during the seizure in agreement to what is well known in absence epileptic patients.

Acknowledgments

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