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Modeling spike-wave discharges by a complex network of neuronal oscillators

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HIGHLIGHTS

- Hierarchically organized networks of neuronal oscillators generate SWDs.
- Main characteristics (amplitude rise, main frequency, harmonics) were simulated.
- Stability of model to variation of structure and scaling was shown.
- Results of coupling analysis from experimental data were reproduced by the model.
- Specific pathological changes in brain architecture might be needed for SWDs.

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ABSTRACT

Purpose: The organization of neural networks and the mechanisms, which generate the highly stereotypical for absence epilepsy spike-wave discharges (SWDs) is heavily debated. Here we describe such a model which can both reproduce the characteristics of SWDs and dynamics of coupling between brain regions, relying mainly on properties of hierarchically organized networks of a large number of neuronal oscillators.

Model: We used a two level mesoscale model. The first level consists of three structures: the nervus trigeminus serving as an input, the thalamus and the somatosensory cortex; the second level of a group of nearby situated neurons belonging to one of three modeled structures.

Results: The model reproduces the main features of the transition from normal to epileptiformic activity and its spontaneous abortion: an increase in the oscillation amplitude, the emergence of the main frequency and its higher harmonics, and the ability to generate trains of seizures. The model was stable with respect to variations in the structure of couplings and to scaling. The analyzes of the interactions between model structures from their time series using Granger causality method showed that the model reproduced the preictal coupling increase detected previously from experimental data.

Conclusion: SWDs can be generated by changes in network organization. It is proposed that a specific pathological architecture of couplings in the brain is necessary to allow the transition from normal to epileptiformic activity, next to by others modeled and reported factors referring to complex, intrinsic, and synaptic mechanisms.

1. Introduction

Absence epilepsy is a generalized form of epilepsy which is characterized by a transient diminishment of the level of consciousness and responsiveness with only minimal, mainly facial movements. This form of epilepsy is mainly present in children and adolescents (Panayiotopoulos, 2001), and it may either remit (Berg, Levy, Testa, & Blumenfeld, 2014) or transform into

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other, convulsive forms with time (Sadleir, Farrell, Smith, et al., 2006). The study of the pathophysiology of absence epilepsy has revealed a variety of potential mechanisms of absence seizures occurrence (Crunelli & Leresche, 2002; Depaulis & Charpier, 2017; van Luijtelaar, Hramov, Sitnikova, & Koronovskii, 2011).

Electroencephalography is the main method to register manifestations of absence epilepsy, since EEG recordings show the typical spike-wave discharges (SWDs) during absence seizures. Traditional scalp EEGs are commonly used for diagnosis, however subcortical structures (primary different nuclei of thalamus) are considered to play a significant role in absence seizure spreading and maintenance, as was established in the genetic rodent models (Depaulis & Charpier, 2017; Inoue, Duysens, Vossen, & Coenen, 1993; Sitnikova & van Luijtelaar, 2007), in a single patient with depth electrodes (Williams, 1953), and more recently with fMRI, both in the genetic animal models (Tenney, Duong, King, & Ferris, 200) and in patients (Moeller et al., 2010). Patients suffering from absence epilepsy have no clinical indication for implantation of intracranial electrodes considering that the disease is relatively benign, therefore the main results regarding the role of the thalamus were obtained using genetic rat models such as WAG/Rij (Coenen & van Luijtelaar, 2003) and GAERS (Marescaux, Vergnes, & Depaulis, 1992).

In order to understand the mechanisms of absence epilepsy, it is important to build a mathematical model (here and further we use term "model" in sense of a mathematical model, not a biological, genetic or pharmacological one, except when it is explicitly mentioned) reproducing some of the main features: sudden onset and termination of SWDs, chemical processes in and between neurons and in extracellular media (concentrations of some substances like GABA and glutamate), and the involvement of specific brain regions. At present, there are several models partly reproducing certain features of the disease at different levels of detail.

A number of models were developed to test the hypotheses describing SWD initiation (onset of seizure) at the cellular level by simulation the dynamics of ion channels, the generation of action potentials under the influence of different concentration of various neurotransmitters. These models are described in detail in Destexhe (2014). Another class, so-called "lumped" models (Wendling, Benquet, Bartolomei, & Jirsa, 2016) approximate the activity of interacting cells populations, i.e. "lump" is an ensemble of a group of neurons which have a similar structure and function (Taylor & Baier, 2011). In such models, each population is modeled as a lumped oscillatory system described by several differential equations. For example, in Taylor et al. (2014) four ordinary differential equations (ODEs) were used: one for relay cells, one for interneurons, one for pyramidal cells and one for thalamo-cortical cells.

The model proposed in Suffczynski, Kalitzin, and Lopes da Silva F. (2004) is an advanced version of an much older model (Lopes da Silva, Hoeks, Smits, & Zetterberg, 1974), and is intermediate between the distributed neuronal network and lumped models, and it models the populations of interacting neurons integrating neuronal and network properties. The model consists of ODEs for transmembrane potentials and includes four cell types: two for the cortex and two for the thalamus (each type is modeled as a lumped system). In addition, specific properties of GABA were taken into account and sigmoid transfer functions were used. The transitions between the oscillatory and non-oscillatory regimes occur spontaneously, without changing the parameters of the system, due to its bistability.

Some authors have modeled in detail the role of GABA, one of the main neurotransmitters responsible for the occurrence of SWDs. In Destexhe and Sejnowski (1995) and Marten, Rodrigues, Benjamin, Richardson, and Terry (2009) the action of GABA is modeled by reaction–diffusion equations, and equations for the transmembrane potential. The model proposed in Chen et al. (2014) includes neurons of basal ganglia in addition to neurons of cortex and thalamus and demonstrates their bidirectional functional role in the onset and termination of absence seizures. In the Taylor et al. (2015), model the efficiency of SWD abatement by applying an external stimulus was studied. Liu, Wang, and Fan (2016) extended the Taylor model by introducing cortical inhibitory neurons. Finally, a phenomenological model of connected phase oscillators was proposed in Schmidt, Petkov, Richardson, and Terry (2014); it demonstrates transitions between different EEG-states such as transitions from the normal EEG to pathological SWDs.

The importance of the structure of a neural network for generation of SWDs is only at the beginning of being explored, although many authors assume that an intact cortico-thalamo-cortical network is imperative for SWD occurrence (Meeren, Veening, Möderscheim, Coenen, & van Luijtelaar, 2009). An important problem of the existing models is that all neurons of each structure generate an integrated signal that is transmitted to other structures, thereby simplifying connectivity between brain structures. However, actual neurons have individual projections to neurons of other structures, with being connected to some of them but not to all. At the same time, they may be not connected with nearby situated neurons of the same structure; an exception to the latter are neurons of the reticular thalamic nucleus, which are heavily interconnected. Therefore, the resulting network has a complex topology (see e.g. review Bullmore & Sporns, 2009), in which some neurons or small groups of them are important for the generation of SWDs due to the presence of effective feedback loops. The existence of such microcircuits was shown in Silberberg, Grillner, LeBeau, Maex, and Markram (2005). At the same time, there is the possibility that other neurons are not involved in the generation of SWDs or they are involved only passively. A large number of elements of a detailed network may lead to the emergence of fundamentally new effects which are not available in the "lumped" models, including effects important for the occurrence of SWDs. It is generally accepted that the generalized SWD are the result of synchronized firing of large number of neurons within and between brain structures (Snead, 1995). In addition, indeed, as has been shown in the relatively simple models, network topology can be essential to the synchronization of neurons (Belykh, de Lange, & Hasler, 2005). Differences in the structure of connections between neurons under normal and pathological conditions have not been studied largely, and have not been taken into account in existing approaches to generate SWDs using the same "lumped" model, which simulate a normal EEG, but with specifically selected parameters (Wendling, Bellanger, Bartolomei, & Chauvel, 2000). Similarly, in Breakspear et al. (2006) the bifurcation in the model of normal brain considered as an excitatory medium is studied for epilepsy modeling by choosing a special regime in which stationary wave exists.

Information about network structures in genetic rat models can be obtained from studies on coupling analysis from EEG or LFP (local field potentials) time series. In Meeren, Pijn, van Luijtelaar, Coenen, and Lopes da Silva (2002) the focal role of somatosensory cortex was established in WAG/Rij rats, one of the genetic absence models. In Lüttjohann and van Luijtelaar (2012) and Sysoeva, Lüttjohann, van Luijtelaar, and Sysoev (2016) the dynamics of involvement of different thalamic structures in the genesis (preictal to ictal to postictal) of SWDs was revealed. Propagation of SWDs over the cortex was studied in humans using MEG data in Westmijse, Ossenblock, Gunning, and van Luijtelaar (2009).

The aim of the present work is to describe a model which will reproduce the experimentally observed characteristics of SWDs and coupling, relying mainly on properties of hierarchically organized (oscillators are collected into groups corresponding to for absence epilepsy relevant brain structures) network of a large number of oscillators.