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Methods of automated absence seizure detection, interference by stimulation, and possibilities for prediction in genetic absence models

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HIGHLIGHTS

- The detection of spike-wave discharges in the rodents ECoG can be automated with high sensitivity and specificity.
- The real-time early detection of spike-wave discharges with continuous wavelet transform of rodents ECoG is feasible.
- Spike-wave discharges can be aborted with various forms of stimulation.
- Spike-wave discharges are preceded by precursor activity, allowing SWD prediction, and control.

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ABSTRACT

Background: Genetic rat models for childhood absence epilepsy have become instrumental in developing theories on the origin of absence epilepsy, the evaluation of new and experimental treatments, as well as in developing new methods for automatic seizure detection, prediction, and/or interference of seizures.
Method: Various methods for automated off and on-line analyses of ECoG in rodent models are reviewed, as well as data on how to interfere with the spike-wave discharges by different types of invasive and non-invasive electrical, magnetic, and optical brain stimulation. Also a new method for seizure prediction is proposed.
Results: Many selective and specific methods for off- and on-line spike-wave discharge detection seem excellent, with possibilities to overcome the issue of individual differences. Moreover, electrical deep brain stimulation is rather effective in interrupting ongoing spike-wave discharges with low stimulation intensity. A network based method is proposed for absence seizures prediction with a high sensitivity but a low selectivity. Solutions that prevent false alarms, integrated in a closed loop brain stimulation system open the ways for experimental seizure control.
Conclusions: The presence of preictal cursor activity detected with state of the art time frequency and network analyses shows that spike-wave discharges are not caused by sudden and abrupt transitions but that there are detectable dynamic events. Their changes in time-space-frequency characteristics might yield new options for seizure prediction and seizure control.

Contents

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1. Introduction

The possibility to record the electroencephalographic activity over a prolonged period in chronically implanted well accepted genetic models such as WAG/Rij and GAERS (Depaulis and van Luijtelaar, 2006), but also in other rats such as some Wistars, Fischer 344, Brown Norway, and their F1 and intercrosses, and transgenic mice endowed with spontaneous occurring spike-wave discharges (SWDs) (Willoughby and Mackenzie, 1992; Burgess, 2006; Noebels, 2006) have yielded large data sets, e.g., for genetic analyses of absence epilepsy (Jandó et al., 1993; Vadász et al., 1995; Gauguier et al., 2004). These long lasting recordings are also necessary for the study of long term drug effects and epileptogenesis (van Luijtelaar et al., 2013), for chronic drug studies (D'Amore et al., 2014), for the study of circadian rhythms of SWDs and the consequences of their shifts (Smyk et al., 2012). The analyses of these large data sets have led to new insights on the characteristics of absence epilepsy, but also to refinement of the experiments by having larger and more solid data sets. These large data sets prompted the need for reliable and automated methods to detect and describe these pathological phenomena and their difference with sleep spindles (Sitnikova et al., 2009). Thanks to the availability of new signal analytical methods it is now possible to analyse in larger details first off line but now also on-line SWDs in the genetic rodent models. The new methods describe seizures in the time and frequency domain without violating assumptions on stationarity, but also across space as done in network analyses (Meeren et al., 2002; Lüttjohann and van Luijtelaar, 2012). They offer new possibilities for understanding the (absence) epileptic brain and their typical SWDs but the methods might have also some value for describing other seizure types, the consequences of seizures, and whether new and different interventions, dependent on real-time seizure detection might be putative effective treatment options. Examples are neuro feedback training in WAG/Rij rats (Osterhagen et al., 2010), deep brain stimulation (Lüttjohann and van Luijtelaar, 2013; Blik, 2015), or stimulation with laser light; these SWD aborting stimuli can be given contingent upon the real-time detection of SWDs (Paz et al., 2013). The application of new signal analytical tools have demonstrated the presence of preictal activity in cortex and thalamus, while different types of network analyses have, in principle, paved the way for SWD prediction. In the following paragraph the different systems and principles used for the reliable detection of SWD in the ECoG of rat/mice strains endowed with mainly spontaneous SWDs are reviewed. This is followed by a short review of the various DBS techniques in order to interrupt ongoing seizure activity (Vercueil et al., 1998; Feddersen et al., 2007; Lüttjohann and van Luijtelaar, 2013) and other stimulation techniques. In the third paragraph activity preceding the onset of SWDs (precursor activity) based on time frequency analyses and on networks will be discussed (van Luijtelaar et al., 2011; Li et al., 2007; Lüttjohann et al., 2013), followed by a paragraph on possibilities for seizure prediction in genetic models based on network precursor activity.

2. Detection of SWDs

2.1. Off line methods

An overview of the different methods that have been described is presented in Table 1. The first modern approach to develop a reliable off line SWD detection system for the analyses of previously obtained data sets was in fact a High Voltage Spindle (HVS) detection system (Jandó et al., 1993). HVS, large amplitude sharp spindles, mimic SWDs, although not all included HVS would unambiguously classify as SWDs, since the spikes of the HVS might be less sharp and the waves were sometimes missing. 16 6–8 month old rats (Fischer 344 and Brown Norway strains) were used to develop and train the system, as well as their F1 and F2 descendents, and back-crosses with the parental strains for its evaluation and subsequent quantitative genetic analyses of the HVS (Vadász et al., 1995). An artificial neural network was used, which should be properly trained first before the desired output of the test data set is generated. The input of this three layer (input, hidden, and output) back propagation neural network was either a raw single channel frontal ECoG with visually marked HVS and ECoG's from 16 animals from the same strains but without HVS, or Fast Fourier Transformed (FFT) ECoG's from the same rats. A sliding window of 10 ms was used. It was found that feeding the network with the outcomes of the FFT significantly shortened the training time compared to having the raw ECoG as input and that the network performed better if it was fed by data of several animals. It was mentioned also that search for the most optimal effective neural network configuration, given the variable number of cells within each of the three layers of the neural network, is rather time consuming; if done, than the network could be used for large data sets. The performance of the network was evaluated in a test data set of 137 animals against visual scoring: the number of HVS which were detected properly by the network reached 93–99% of the manually marked HVS. HVS with small spike components or small amplitude were sometimes missed, while falsely detected events (non-HVS, body scratching, grooming, typical sleep spindles, artifacts) varied between 18% and 40%. The authors discussed extensively that there is always a trade-off between number of correct detections, number of missed detections, and number of false positives. Despite its good sensitivity this back propagation neural network was not used by others, its number of false positives, the low learning speed and the time consuming procedure to optimize the network configuration might have been a major bottleneck for its broad and widespread application.

A second automated off line detection system was developed by Westerhuis et al. (1996) and it was used in many subsequent ECoG studies in WAG/Rij rats. WAG/Rij and GAERS are currently the most used and best characterized and established genetic rat models of absence epilepsy. The cortical frontal–parietal differential ECoG of adult male WAG/Rij rats was used, it was filtered between 1 and 100 Hz, sample rate 200 Hz. It was based on a moving window and it subsequently calculated the absolute difference of two consecutive