Neural Networks 46 (2013) 109–115

Contents lists available at ScienceDirect

Neural Networks

journal homepage: www.elsevier.com/locate/neunet

Characterization of seizure-like events recorded *in vivo* in a mouse model of Rett syndrome

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HIGHLIGHTS

- Detection of seizure-like events (SLEs) from 24 h LFP recordings.
- Investigate SLE and inter-SLE states in MeCP2-deficient model of Rett syndrome.
- Seizure initiation associated with random mechanisms.
- Seizure termination associated with deterministic mechanisms.
- Rett-related seizures share similarities with absence seizures.

ARTICLE INFO

Article history:
Received 23 February 2013
Received in revised form 1 May 2013
Accepted 5 May 2013

Keywords:
Epilepsy
Seizure
Automated seizure detection
Rett syndrome
Gamma distribution

ABSTRACT

Rett syndrome is a neurodevelopmental disorder caused by mutations in the X-linked gene encoding methyl-CpG-binding protein 2 (MECP2). Spontaneous recurrent discharge episodes are displayed in Rett-related seizures as in other types of epilepsies. The aim of this paper is to investigate the seizure-like event (SLE) and inter-SLE states in a female MeCP2-deficient mouse model of Rett syndrome and compare them to those found in other spontaneous recurrent epilepsy models. The study was performed on a small population of female MeCP2-deficient mice using telemetric local field potential (LFP) recordings over a 24 h period. Durations of SLEs and inter-SLEs were extracted using a rule-based automated SLE detection system for both daytime and nighttime, as well as high and low power levels of the delta frequency range (0.5–4 Hz) of the recorded LFPs. The results suggest SLE occurrences are not influenced by circadian rhythms, but had a significantly greater association with delta power. Investigating inter-SLE and SLE states by fitting duration histograms to the gamma distribution showed that SLE initiation and termination were associated with random and deterministic mechanisms, respectively. These findings when compared to reported studies on epilepsy suggest that Rett-related seizures share many similarities with absence epilepsy.

1. Introduction

Rett syndrome is a neurodevelopment disorder manifesting from mutations in the X-linked gene encoding methyl-CPG-binding protein 2 (MECP2) (Amir et al., 1999). Predominantly found in girls, the syndrome causes impairment of cognitive and motor abilities, communication dysfunction, breathing irregularities and intractable seizures (Hagberg, Aicardi, Dias, & Ramos, 1983). Although MECP2 is expressed throughout the body, the brain appears to be the organ most affected by the loss of MECP2 function. The effects on the brain can be seen with electroencephalography (EEG), where studies on girls with Rett syndrome reveal the presence of severe intractable seizures. These observations indicate that neural network activity is altered in the Rett syndrome brain; however,

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0893-6080/$ – see front matter
http://dx.doi.org/10.1016/j.neunet.2013.05.002

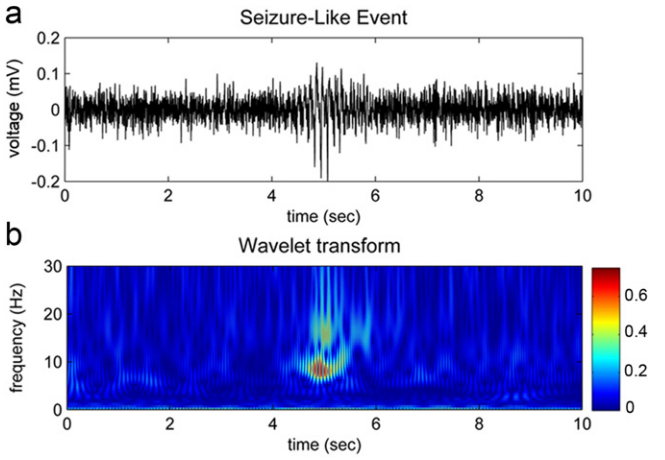

Fig. 1. A sample *in vivo* LFP recording with the corresponding wavelet plot. (a) A 10 s time-series recording centered on a single SLE of approximately one second duration. The SLE is characterized by high amplitude spikes appearing at regular intervals. (b) The wavelet plot of the SLE shows the presence of a strong theta rhythm that persists for the duration of the SLE.

the underlying mechanisms responsible for the alterations in network activity remain to be determined.

Understanding the mechanisms behind seizure state initiation and termination may elucidate ways to counteract them. For example, if the system is of a deterministic nature, then it is feasible to control the system, and in doing so treat the disorder (Suffczynski et al., 2006). Suffczynski et al. examined the mechanisms of seizures from various epilepsy models (focusing primarily on absence seizures) and found that in most cases the occurrence of seizures was dictated by a random process, and the duration was controlled by a deterministic process (Suffczynski et al., 2006). Resulting from this finding they suggest that it is very unlikely to predict in advance when a seizure will occur, but it may be possible to apply a controlled stimulation to stop a seizure when or just before it has been initiated (Suffczynski et al., 2006).

To model Rett syndrome, several mutant *in vivo* mouse models have been developed that either lack MeCP2 or express a clinically relevant mutant form of MeCP2. Studies in these mice have confirmed that MeCP2 deficiency recapitulates many of the features found in clinical Rett syndrome, such as alteration of brain development, impaired synaptic communication, and neural network activities (Asaka, Jugloff, Zhang, Eubanks, & Fitzsimonds, 2006; Chao, Zoghbi, & Rosenmund, 2007; Dani et al., 2005; Taneja et al., 2009).

Recently, local field potential (LFP) recordings were used to examine the hippocampal and cortical network activity of female *Mecp2*$^{-/+}$ mice (Guy, Hendrich, Holmes, Martin, & Bird, 2001), and the results from this study revealed the presence of spontaneous epileptiform discharges (Fig. 1(a)) and abnormal neural network oscillatory activity. The mechanism through which the lack of MeCP2 leads to these electrophysiological anomalies remains largely uninvestigated.

To address the question of the underlying mechanisms of seizure generation in the MeCP2-deficient brain, a way to quantitatively detect seizure-like events (SLEs) was required. There have been many documented seizure detection schemes ranging from wavelets and support vector machines to independent component analyses (De Lucia, Fritschy, Dayan, & Holder, 2008; Guerrero-Mosquera, Trigueros, Franco, & Navia-Vazquez, 2010; Logesparan, Casson, & Rodriguez-Villegas, 2012; Nandan et al., 2010). In this study we applied an automated seizure-like event (SLE) detection method based on Colic, Wither, Eubanks, Zhang, and Bardakjian (2011), Suffczynski et al. (2006) and Wither et al. (2012). The automated rule-based SLE detection algorithm was applied on 24 h recordings of $n = 7$ mice to localize and determine the durations of the SLEs and inter-SLEs. SLEs counts were compared for daytime and nighttime to assess the influence of the circadian rhythm, as well as for high and low delta frequency range (0.5–4 Hz). Due to its goodness of fit to neurological data (Misic, Vakorin, Kovacevic, Paus, & McIntosh, 2011) and prevalence in literature (Suffczynski et al., 2006), the gamma distribution was fitted to the SLE and inter-SLE duration distributions. Fitting to the gamma distribution we intended to determine if Rett-related seizure initiation and termination mechanisms are defined by a deterministic or random process. This paper will provide an account of our findings and describe the implications for possible treatment options.

2. Methods

2.1. Ethics statement

All animal experimentation strictly followed the guidelines of the Canadian Council of Animal Care, and was thoroughly reviewed and approved by the Toronto General and Western animal care committee (Protocol 1321.7). Surgeries were performed under general anesthesia, and all precautions were taken to minimize animal discomfort.

2.2. Electrophysiological data

Female *Mecp2*$^{tm1.1Bird}$ (Guy et al., 2001) and *Mecp2*^{tm2Bird} (Guy, Gan, Selfridge, Cobb, & Bird, 2007) mice between the ages of 300–400 days were implanted with a mouse-specific wireless telemetry probe (TA11ETA-F10; Data Sciences International (DSI), St. Paul, MN) for recording of general activity and local field potential (LFP). The surgical implantation procedure is described in El-Hayek et al. (2011) and Wither et al. (2012). Mice were anesthetized with 2% isoflurane and the wireless transmitter was placed into their peritoneal cavity. Silicone elastomer insulated sensing and reference wires connecting the transmitter were orientated rostrally toward the head via a subcutaneous route. The sensing wire was soldered to a polyimide-insulated stainless steel electrode with an outside diameter of 125 μm, and placed in the somatosensory cortex region (bregma −0.6 mm, lateral 1.5 mm, and depth 1.5 mm) with the reference wire placed at bregma −5 mm, lateral 1 mm, and depth 1.5 mm. The somatosensory cortex was chosen as the site for recording as it has been shown to exhibit large amplitude potentials that reflect cortical hyper-excitability in Rett girls (Glaze, 2005). The implantation surgery caused no apparent abnormalities in the mice, and average body weights of *Mecp2*$^{-/+}$ mice returned to pre-operative values within two weeks post-surgery (32.3 g versus 32.4 g for *Mecp2*$^{-/+}$ ($n = 7$)).

Single channel local field potential (LFP) waveforms were collected from ($n = 7$) implanted female MeCP2-deficient mice for continuous 24 h periods. Waveform data were transmitted from the TA11ETA-F10 telemetry probes to a wireless receiver (RPC-1, DSI), which passes the data through a data exchange matrix serving as a multiplexer (DSI), and was analyzed using DataQuest A.R.T. (DSI). All LFP waveforms were transmitted at 200 Hz and were sampled at 1 kHz.

2.3. Automated SLE detection

LFP traces of 24 h duration were visually inspected by condition blinded investigator to confirm and quantify the presence of discharge activity as previously described (D'Cruz et al., 2010; Wither et al., 2012; Yang, Chen, & Fredholm, 2009). A discharge event was