Wireless telemetry as an ideal tool for continuous intrahippocampal EEG recording in chronic epilepsy mouse models

Yana Van Den Herrewegen**, An Buckinx**, Gino De Smet†, Ise J. Smolders† and Dimitri De Bundel†

**Experimental Pharmacology (EFAR), cluster Neurosciences, Vrije Universiteit Brussel, Belgium

Introduction

Tethered recording systems are until date routinely used as a method for long-term continuous EEG monitoring in animal models of epilepsy. Nevertheless, tethered systems display some shortcomings when chronically used in mice, in some cases even compromising experiments and animal welfare as restraining is inevitable. Therefore, together with the miniaturization of transmitters, wireless telemetry systems are increasingly being used as an alternative method to precisely measure biopotentials in the rodent brain. As EEG recordings are the most powerful read-outs in animal models of epilepsy, we evaluated the use of wireless radio-telemetry in the intrahippocampal post-status epilepticus kainic acid (IHKA) model, an established mouse model for studying temporal lobe epilepsy and epileptogenesis.

The IHKA model

This chronic mouse model for temporal lobe epilepsy is obtained by unilateral kainic acid injection in the dorsal hippocampus, leading to status epilepticus (Fig. 3a). As seen in patients with temporal lobe epilepsy, this induces typical cellular changes in the hippocampus, such as loss of inhibitory and excitatory neurons, dispersion of the dentate gyrus and extensive astrogliosis (Fig. 1). Additionally, mice develop spontaneous limbic seizures after a latent period of 1 to 2 weeks. From the 4th week onwards, the mice display a stable amount of spontaneous hippocampal seizures with an average 31 ± 3 (mean ± SEM) seizures per hour (Fig. 3b). As these spontaneous seizures are not observable behaviorally, continuous electroencephalography monitoring is inevitable.

Surgery: implantation of the i.p. transmitter with deep electrodes

We optimized the surgical procedure for implantation of an i.p. transmitter and placement of intracerebral electrodes to increase the survival rate of the mice. Under isoflurane anesthesia, a wireless radiofrequency transmitter (ETA-F10, DSI) was implanted intraperitoneally. An incision on the head was made, to which the leads of transmitter were subcutaneously tunneled. After closing the abdominal wall, three holes were drilled in the skull: one above the cerebellum for the reference electrode, one above the right hippocampus for the recording electrode and one above the left hippocampus for the anchor screw. The intrahippocampal recording electrode was implanted at stereotaxic coordinates AP: -2 mm, ML: -1.5 mm and DV: 2.1 mm relative to bregma. Subsequently the electrodes were fixed with white glass ionomer cement. Afterwards no severe inflammatory reactions could be observed either at the abdomen or near the head stage.

EEG signals

Increasing the signal-to-noise ratio

To increase the signal-to-noise ratio of the acquired EEG signal, we applied three types of filters. Removal of power line interferences (50 Hz, 100 Hz, 150 Hz and its harmonics) was obtained by application of a notch filter and a 60 Hz low-pass filter. A high-pass filter of 0.008 Hz removed a drifting baseline. As shown in Fig. 4, application of these filters did not disguise the desired electrophysiological signatures.

Table 1: Commonly used filters

<table>
<thead>
<tr>
<th>Filter type</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Notch</td>
<td>50 Hz</td>
</tr>
<tr>
<td>High-pass</td>
<td>0.008 Hz</td>
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<tr>
<td>Low-pass</td>
<td>60 Hz</td>
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Artefacts in wireless telemetry

1. Physiological artefacts

**EEG contamination**

The occurrence of ECG in the EEG signal, corresponded to damaged lead insulation. To reduce ECG artefacts, the leads were carefully inspected for insulation damage before and after surgery.

**Movement artefacts**

EMG artefacts, extensively present in tethered telemetry, were rather limited in our wireless recordings. They mostly occurred in case of damaged lead insulation, as seen with ECG artefacts. To properly recognize movement artefacts, simultaneous EMG- or video-monitoring is necessary.

2. Non-physiological artefacts

**Electrical noise**

EEG contamination arising from electrical devices, such as computers, light sources, etc. are hard to identify and eliminate. Powerline contamination (50Hz and its harmonics) on the other hand can easily be identified after Fast Fourier transformation. This decomposes the EEG signal into its constituting frequencies and reveals the dominating frequencies. In our case, electrical cables were the largest noise contributor and could efficiently be removed.

Conclusion and future perspectives

In our research we successfully implemented wireless telemetry as a tool for long-term continuous EEG monitoring in mice. We first optimized the surgical procedure to reduce the risk of inflammation and to increase survival rates. Besides the complete abolishment of inflammation, we also managed to maintain the mice up to 5 months in the recording setting. Finally we accomplished to reduce both physiological and non-physiological artefacts, by optimizing the surgical procedure and by applying filters during analysis. All together, this enabled us to more objectively recognize and score electrophysiological seizures. We will therefore continue to use wireless telemetry to study both epileptogenesis and chronic seizures, while focusing on astrocytes and glialin.