User Manual:

Electrophysiological Biomarkers for Non-clinical Safety Evaluation of Neuro-interventional Devices

Tool Reference

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Introduction:

Brain electrophysiological signals can be acquired with invasive or non-invasive electrodes. These signals reflect the function of the brain, which can be used to detect changes induced by any intervention, including an unexpected accidental injury and intentional neurotherapy. The FDA research suggest that electrophysiological biomarkers can be more sensitive to brain functional changes than conventional postmortem histology, the current standard method used in the non-clinical safety evaluation, in detecting ultrasound induced brain injury [1]. Therefore, it can provide more insurance in the safety of neuro-interventional devices before they are used in human subject or marketing.

Through multiple animal studies, acute and sub-chronic electrophysiological biomarkers have been identified for brain injuries induced by high intensity focused ultrasound and mechanical impact, which can be used in the non-clinical evaluation of safety of neuro-interventional devices. **The biomarkers include: 1) within 1 hour after the perturbation of brain function, median-nerve stimulation induced somatosensory evoked potentials are significantly reduced and gradually recover in 30 mins to 1 hour depending on the severity of the injury [2-4]; 2) in the sub-chronic and chronic phase (1-12 weeks after the perturbation of the brain function), resting state low frequency brain oscillations, namely, delta waves increase, whereas, higher frequency oscillations (beta waves) decrease, resulting in an increase in delta/beta ratio on the ipsilateral side of the injury [1]**. The acute biomarker has been validated with different recording techniques and in different types of induced injuries [2- 4]. The translatability of the chronic electrophysiological biomarker has been verified by the analysis of electrophysiological data from human subjects acquired a brain injury [5].

The proposed Context of Use of this tool is for the non-clinical evaluation of safety of neuro-interventional devices, including implantable devices which directly cause a physical tissue damage and invasive or noninvasive devices that can change neuron activity, for example, transcranial current stimulation, transcranial magnetic stimulation, ultrasound neuromodulation, and so forth.

The detailed methods for data acquisition and analysis are provided below. It needs to be noted that the procedures described here were what the FDA lab used for data acquisition and analyses. However, the biomarkers, metrics themselves, are independent on the exact equipment, electrodes, and electrodes placement procedure used in the data acquisition and analysis. This is demonstrated in our publications as well in which multiple types of recording techniques provided same results. Also, to implement the biomarkers, please ensure that all animal use procedures are approved by the Institutional Animal Use and Care Committee.

Acute Biomarker: Reduction in the Median-Nerve Stimulation Induced Somatosensory Evoked Potential (SSEP)

Median nerve stimulation:

The median nerve was stimulated via a pair of 27-gauge stainless-steel needles inserted subcutaneously into the forelimb of the animal. Electrical stimuli consisted of biphasic pulse of current 0.2 ms in duration and 1-4 mA in amplitude generated by a current stimulator (DS7A, Digitimer; or Grass SD9 stimulator, Grass Technologies). The stimulating amplitude of current should be the minimum amplitude required to elicit visible limb movement in the forepaw. It is recommended 0.5 Hz frequency stimulation is used because it provides best responses (Figure 4 in [3]).

Somatosensory evoked potential (SSEP) recording:

Somatosensory evoked potential was recorded from the contralateral side of the somatosensory cortex over the centroid of the forelimb's representation area with either epidural (under the skull but above the dura) or epidermal (on the scalp) electrodes. For epidermal electrodes placement, hair was first removed by Nair. Either a home-made silver wire terminating in a ~ 1.5 mm loop or a self-sticky electrode was placed on the intact scalp. For epidural electrodes placement, the skull surface needs to be exposed after skin incision. A ~0.5 mm diameter of bur-hole is created by a dental drill. Then a platinum-iridium wire was inserted into the bur-hole setting on top of the dura as the recording electrode. Biocompatible tissue adhesive was used to secure the wire. A reference electrode was inserted on the posterior of the head in the same manner. Alternatively, self-tap stainless steel bone screws can be used as electrodes too. The FDA lab used RZ5D processor, PZ2 preamplifier and ZC16 headstage from Tucker-Davis Technologies to record electrophysiological signals from the electrodes at a sample rate of 3 kHz. However, any commercially available electrophysiological acquisition system which offers more than 512 Hz sampling rate can be used for data acquisition.

Somatosensory evoked potential (SSEP) data analysis:

For the analysis of somatosensory evoked potential, it is recommended that every 20 trials are averaged to provide a good signal to noise ratio. The averaged SSEP should be like the waveform in Figure 1, a positive peak at ~ 15 ms post median nerve (MN) stimulation and a negative peak ~ 22 ms post stimulation. Depending on the setup of the recording system, the polarity of the peaks can be opposite. Peak-to-peak amplitude is the metric to evaluate the injury to the brain. **If an injury is produced by the neuro-intervention process, the reduction in the peak-to-peak amplitude will be detected immediately. The degree of reduction is related to the severity of the damage.**

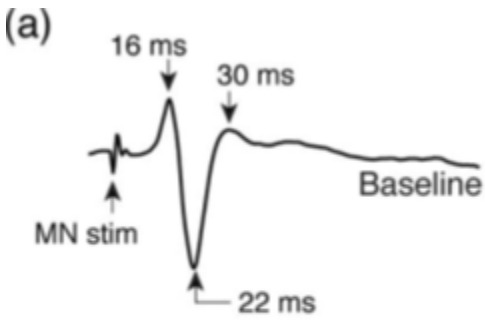

Figure 1. Median-nerve (MN) stimulation induced somatosensory evoked potential waveform. (Copied from [2])

Sub-Chronic and Chronic Biomarker: Increase in Delta/Beta Ratio on the Ipsilateral Side of the Injury

Resting state brain electrophysiological signal acquisition:

To acquire brain resting state electrophysiological signals, µECoG arrays (Neuronexus) with 16 small recording electrodes (surface area ~0.03 mm2) arranged in a 4 × 4 grid were implanted at the epidural space in anesthetized animals. In short, after removing the hair with Nair, a skin incision is made in the midline. Scalp is retracted to expose the skull. A 2.5 mm by 2.5 mm craniotomy is created with a high-speed dental drill. µECoG is placed on the surface of the cortex above the dura and secured by dental cement for chronic recording. NeuraLynx Digital Data Acquisition System, including a DL 4SX-M 32ch Base, a headstage pre-amplifier HS-18- CNR-MDR50, a HS-18-N2T-16 adaptor and Cheetah data acquisition software was used to record brain signals at a sampling frequency of 16 kHz from freely moving animals in their home cages. However, as mentioned in the introduction, other types of surface electrodes, for example, stainless steel bone screw, or commercially available probes like NeuroNexus EEG surface grids, and any electrophysiological system with capability of acquiring signals at above 10 kHz sampling rate can be used for data acquisition.

Resting state electrophysiology data analysis:

Electrophysiological signals band-passed between 0.5 and 300 Hz were imported into Matlab (Mathworks) for manual removal of segments with myoelectric and movement artifacts with FieldTrip Toolbox [6]. Electrophysiological signals were downsampled to 2 kHz, then scored for the presence of artifacts based on the animal's movement state. Only recording snippets with ≥ 4 s artifact-free data, and recording sessions with ≥ 10 clean snippets, were used for quantitative analysis. Power spectral density was computed with a multitaper Fast Fourier Transform (FFT) (NW = 3, k = 5) estimate using Matlab functions from the Chronux Toolkit [7].

Absolute power was obtained for the δ (1–4 Hz), ɵ (4–8 Hz), α (8–13 Hz), β (13–30 Hz) and γ (30–100 Hz) frequency bands. Delta/beta ratio was calculated by dividing the total power between 1 and 4 Hz by the total power between 13 and 30 Hz. Figure 2 shows example electrophysiological traces recorded and analyzed. **When a brain injury is produced, an increase in the delta/beta ratio will be observed between 1-12 weeks post intervention.**

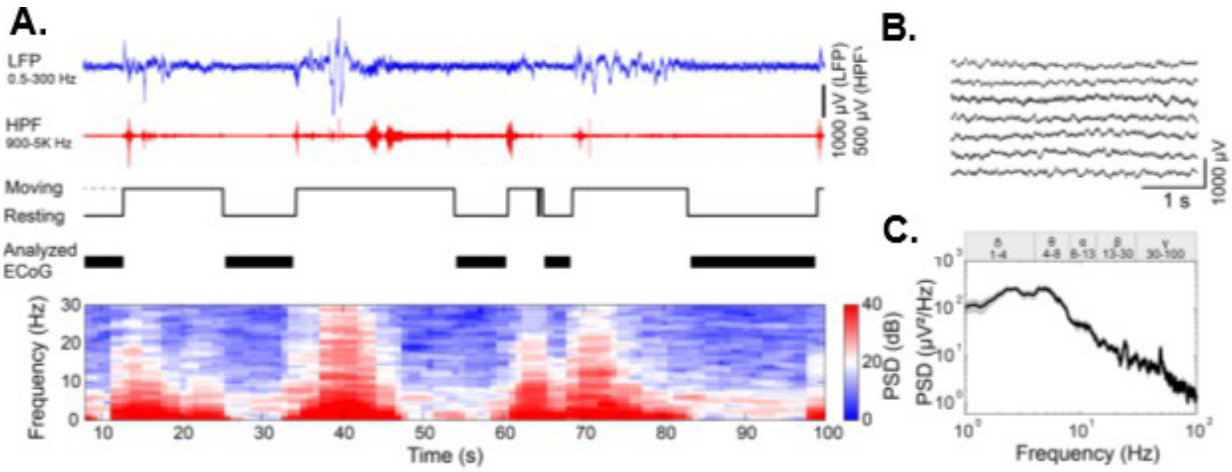

Figure 2. Resting state electrophysiological signals and analysis. A. Example raw electrophysiological data and movement activities acquired from freely moving mice in their home cages. The presence of myoelectric and movement artifacts correlated with animal moving. Analyzed electrophysiological signals were representative of resting state signals, as indicated by black bars on the fourth row of the figure. The bottom heatmap shows the time-frequency analysis of raw signals. Myoelectric and movement artifacts produced contamination in power spectral density (PSD) across the full frequency range, with 0–30 Hz shown in the figure. **B.** Extracted 4 s clean snippets from data shown in (**A**). **C.** Averaged power spectral density of electrophysiological signals in (B). Gray area indicates the standard error. (Copied from [1])

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