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Identifying EEG Features Specific to Pain-induced Awakenings

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***Abstract*— There is currently no objective biomarker for pain. In this study, we used an optogenetic approach to activate nociceptors in mice and trigger awakenings within milliseconds while recording their electroencephalogram (EEG). We performed spectral analyses to test if these pain-induced awakenings have a specific EEG marker compared to spontaneous awakenings. In contrast to natural awakenings, we found that they have lower beta, gamma, and high gamma relative power during an awakening, but that the relative power in gamma and high gamma bands remain elevated for longer when transitioning back to sleep. The increased time to return to baseline power may help explain why chronic pain patients suffer from poor sleep quality and daytime fatigue.**

***Clinical Relevance*— Identifying an EEG marker of pain-induced awakenings will allow objective quantification of pain in rodents, which will facilitate mechanistic studies and preclinical research to develop new analgesics.**

I. INTRODUCTION

Lack of objective biomarkers for pain has severely hampered the development of efficacious and safe analgesics [1]. Neuroimaging and electrophysiology have identified physiological measurements modulated by noxious stimuli, but these were not specific to pain. While sleeping, the activity within the brain is less likely to be 'contaminated' with processing of external stimuli or cognitive processes. In this study, we used an optogenetic strategy to trigger a single action potential-activation of peripheral nociceptors that caused awakenings and contrasted the resulting EEG spectral features against those from natural awakenings to characterize EEG markers of a pain-induced awakening.

II. METHODS

We used a transgenic mouse line where the light-sensitive channelrhodopsin (ChR2) is expressed specifically in peripheral sensory neurons positive for Na(v)1.8 channel [2]. One Na(v)1.8::ChR2 mouse and two WT mice were instrumented with EEG/EMG electrodes for fronto-parietal recordings. To trigger a pain-induced awakening, we delivered a transdermal single pulse (10 ms at 50 mW/mm2) light stimulation using a TTL-activated laser [3]. For spontaneous awakenings, EEG/EMG-implanted mice were left undisturbed until they woke up. EEG/EMG data were amplified, recorded with Sirenia Acquisition Software (Pinnacle Technology Inc.), sampled at 400 Hz using an EEG low-pass filter at 100 Hz, manually labelled, and stored into Matlab® R2020b files. We created absolute and relative power spectral plots from the EEG of 10 seconds prior to and 25 seconds after the onset of each awakening. The frequency ranges of interest were delta (1-4.5 Hz), theta (5-9 Hz), alpha (15-30 Hz), beta (15-30 Hz), gamma (30-70 Hz), and high gamma (70-100 Hz). Relative power is the proportion of the power in the frequency band of interest out of the total power.

III. RESULTS

Our preliminary results indicate that the primary differences between the relative power over time of natural awakenings and pain-induced awakenings are that 1) in beta, gamma, and high gamma frequency bands, the pain-induced awakenings show lower increase in relative power transitioning into wake and 2) in gamma and high gamma frequency bands, the pain-induced awakenings fail to return to pre-awakening relative power levels (Fig. 1).

IV. DISCUSSION & CONCLUSION

We will extend the study and determine whether these features are specific to pain or if they are also triggered by innocuous sensory modalities such as auditory stimuli.

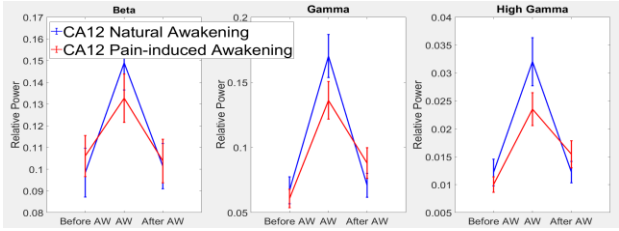

Fig 1. Comparison of relative power before, during, and after awakenings by frequency band between natural (n=22) and pain induced awakenings (n=21). Bars are standard errors.

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