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fMRI comparison of optogenetic and electrical stimulation in the mouse hippocampus

Introduction

Optogenetic-fMRI has become a popular method to study induced activity and brain-wide networks in rodents. On the one hand, optogenetics may be applied to study basic neuroscience, e.g. which networks are recruited upon hippocampal stimulation[1], but also to study related disease mechanisms and possible treatments[2,3]. However, as optogenetics per se is not clinically feasible, possible findings based on optogenetics would have to be realized by electrical stimulation eventually. This implies the question how comparable the two modalities are. **In our study we are using fMRI to compare the brain-wide responses upon electrical and optogenetic stimulation of the mouse hippocampus, a brain area of high importance for diseases like temporal lobe epilepsy for example.**

Methods

Brain Stimulations

- Optogenetic/electrical stimulation in the right dorsal hippocampus (dHC) of Ai32-Rbp4Cre medetomidine-sedated mice (n=6).
- EEG recordings from the left dHC.
- The amplitude for electrical stimulation was ±200µA and ca. 90mW/mm^2 for the optogenetic pulses (blue light 460nm, Prizmatix, USA/Canada).
- Stimulation paradigms: 5 blocks of 1-2s duration (10Hz) and 60s rest periods. Single stimulation block of 10s (10Hz).

MR Scan

- 7T small animal system equipped with a CryoProbe (Bruker, Germany).
- GE-EPI sequence (TR=1.5s, TE=14, 23, 32 and 41ms, matrix 64x40, resolution 0.28x0.28mm^2, 12 slices, thickness 0.8mm). The four echo images were combined into a single multi-echo time-series[4].

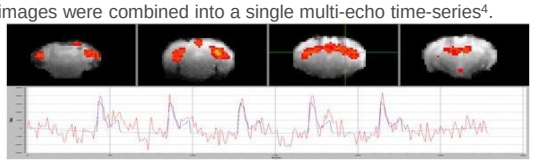

Figure 1: Fitting model using FIR model. Timeseries of a voxel (green cross) depict the model fit (blue) on pre-processed data (red).

Post-processing & Analysis

- Motion and slice-timing correction using FSL[5] (FMRIB, Oxford, UK).
- Spatial smoothing using 0.42mm FWHM Gaussian kernel and high-pass temporal filtering at 100s cutoff.
- EEG dataset was band-pass temporal filtered at 0-40Hz using EEGLAB[7].
- A GLM[6] analysis was conducted with Finite Impulse Response (FIR) basis functions of 7th-9th order[8] **(Fig. 1)**.
- Voxel-wise (Bonferroni) correction of the activation maps (p = 0.05).

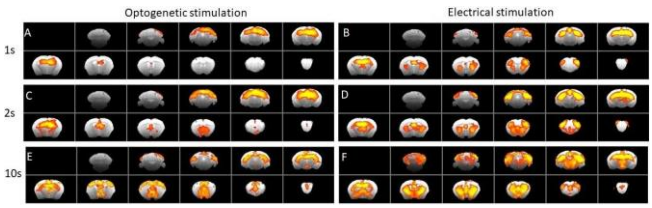

Figure 2: Group level FEAT analysis for stimulation paradigms. 1-2s block optogenetic (n=4) and electrical (n=6 and n=5) stimulation, respectively. 10s single pulse of optogenetic (n=3) and electrical stimulation (n=6).
Overlaid on a reference RARE image.

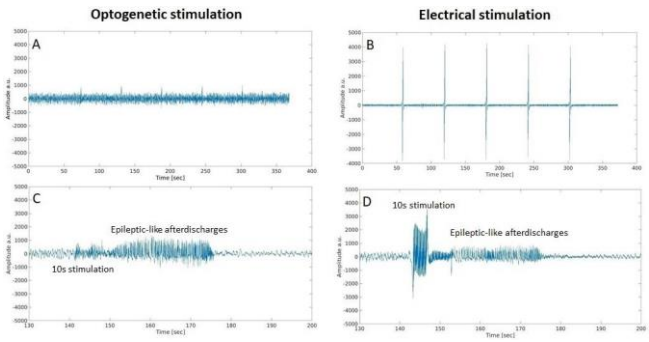

Figure 3: EEG recordings for stimulation paradigms. 1s block stimulation for optogenetic (A) and electrical (B) stimulations. Epileptic-like ADs after 10s single pulse in both paradigms (C-D).

Results

- Both stimulation paradigms yielded robust BOLD responses in the right and left HC and entorhinal cortex (EC), with a more bilateral recruitment of the EC with electrical as compared to the optogenetic stimulation **(Fig. 2A-B)**.
- Low duration electrical stimulation spread to more subcortical areas compared to optogenetic stimulation **(Fig. 2C-D)**.
- BOLD effect significantly increases after the single 10s excitation pulse, for both paradigms. During electrical stimulation activity has reached **more subcortical regions**, whereas a high activation in the **cortical regions** is observed during the optogenetic counterpart **(Fig. 2E-F)**.
- EEG recordings depict the block design stimuli for low duration **(Fig. 3A-B)** and the **induced epileptic-like afterdischarges (ADs) after the 10s pulse (Fig. 3C-D)**.

Conclusion

Besides showing similarities - the recruitment of the hippocampal network - we could highlight different activation patterns upon optogenetic or electrical stimulation. FMRI is an important tool to reveal these brain-wide differences.

References
[1] Weitz et al., 2015 [2] Krook-Magnuson et al., 2013 [3] Paschen et al., 2020 [4] Poser et al., 2006 [5] Jenkinson et al., 2002 [6] Woolrich et al., 2001 [7] Delorme and Makeig, 2004 [8] Liu et al., 2017

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