TEMPORAL LOBE EPILEPTOGENESIS IMPLIES LARGE-SCALE DYNAMICS IN A STATUS EPILEPTICUS-INDUCED MOUSE MODEL

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INTRODUCTION:

Temporal lobe epilepsy (TLE) is the most common type of focal epilepsies. While TLE is characterized by the presence of an epileptic focus (EF) that is held to be responsible for triggering seizures and driving interictal activities, recent studies show that epileptogenic networks (EN) and brain alterations are widely distributed. In this context, a fundamental question is yet to be answered: is the EN responsible for the emergence of epileptic activities, with the EF as one of its major outputs, or is the EF upstream in the cascade that leads to the formation of the EN? Using multisite chronic mSEEG recordings and chemogenetic tools in the status epilepticus (SE) induced intra hippocampal kainate mouse model of TLE, we propose to characterize in detail the emergence of epileptic activities in the EF and in remote regions and evaluate the role of the primary epileptogenic region for the development of the large-scale EN. We found that different epileptiform signatures, with ictal, ictal-like and interictal patterns, appear in the very early stage of the latent phase (LP) (as early as 72h after SE) in both the EF and distant regions and then evolve along the LP to become typical epileptic events characterizing the chronic phase. We investigate these network dynamics with high spatial and temporal precision using semi-surpervised detection of pathological activities. Our work aims at identifying key mechanisms involved in the development of epileptic neuronal networks and clarify the pathogenic stream of events at play between the EF and the EN.

METHODS:

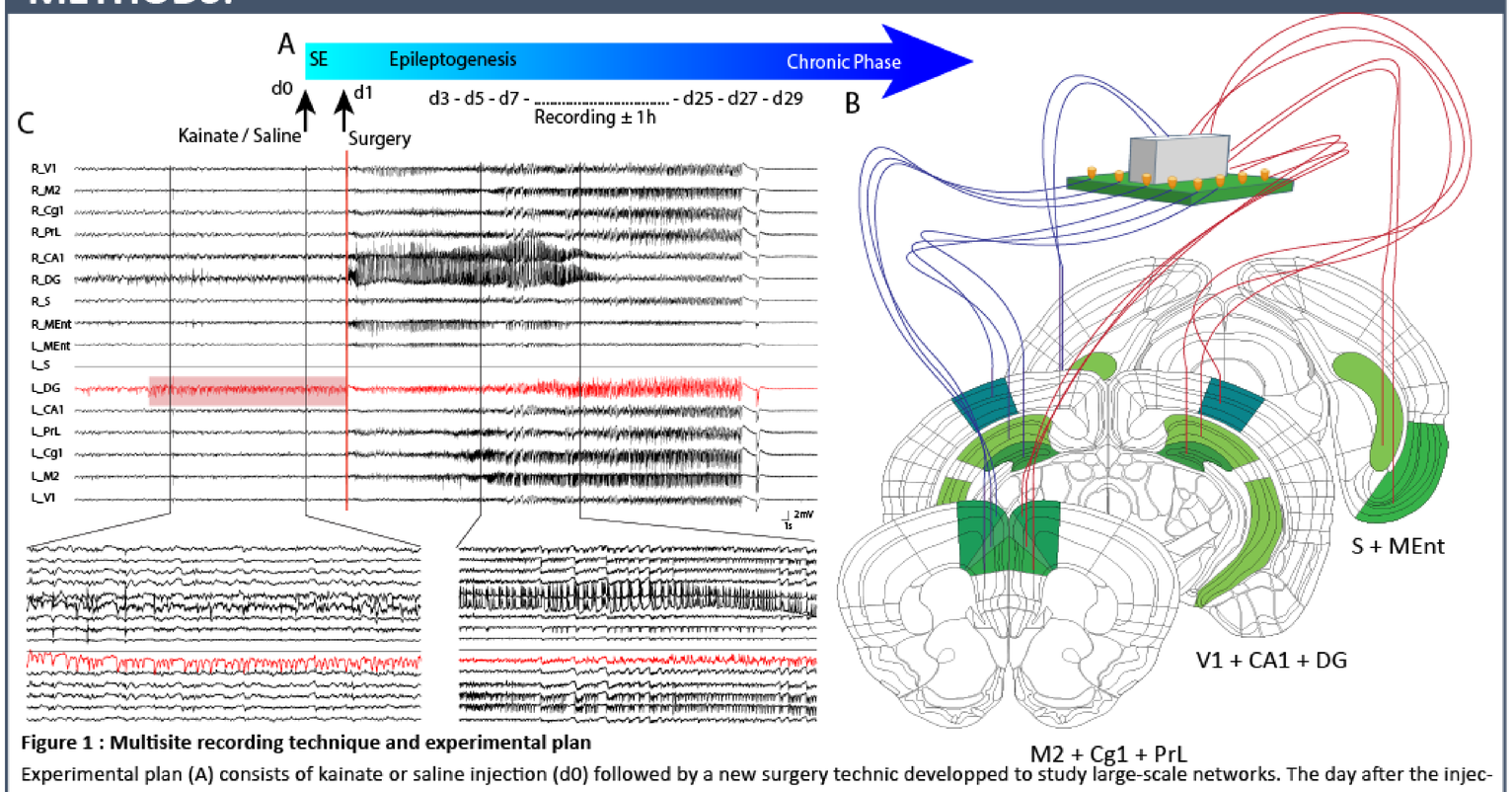

Figure 1 : Multisite recording technique and experimental plan

Experimental plan (A) consists of kainate or saline injection (d0) followed by a new surgery technic developped to study large-scale networks. The day after the injection (d1), an implantation surgery (B) is realised and 16 electrodes are implanted into targetted brain regions : secondary motor cortex (M2), cingulate cortex area 1 (Cg1), prelimbic cortex (PrL), primary visual cortex (V1), field CA2 of hippocampus (CA1), dentate gyrus (DG), subiculum (S), medial entorhinal cortex (MEnt). After a day of recovery, mice are recorded 1h every other day. This technique allows the recording of epileptic activities such as secondary generalized seizure (C) with an high temporal resolution.

RESULTS:

1. EF epileptogenesis: from epileptiform to typical ictal activities

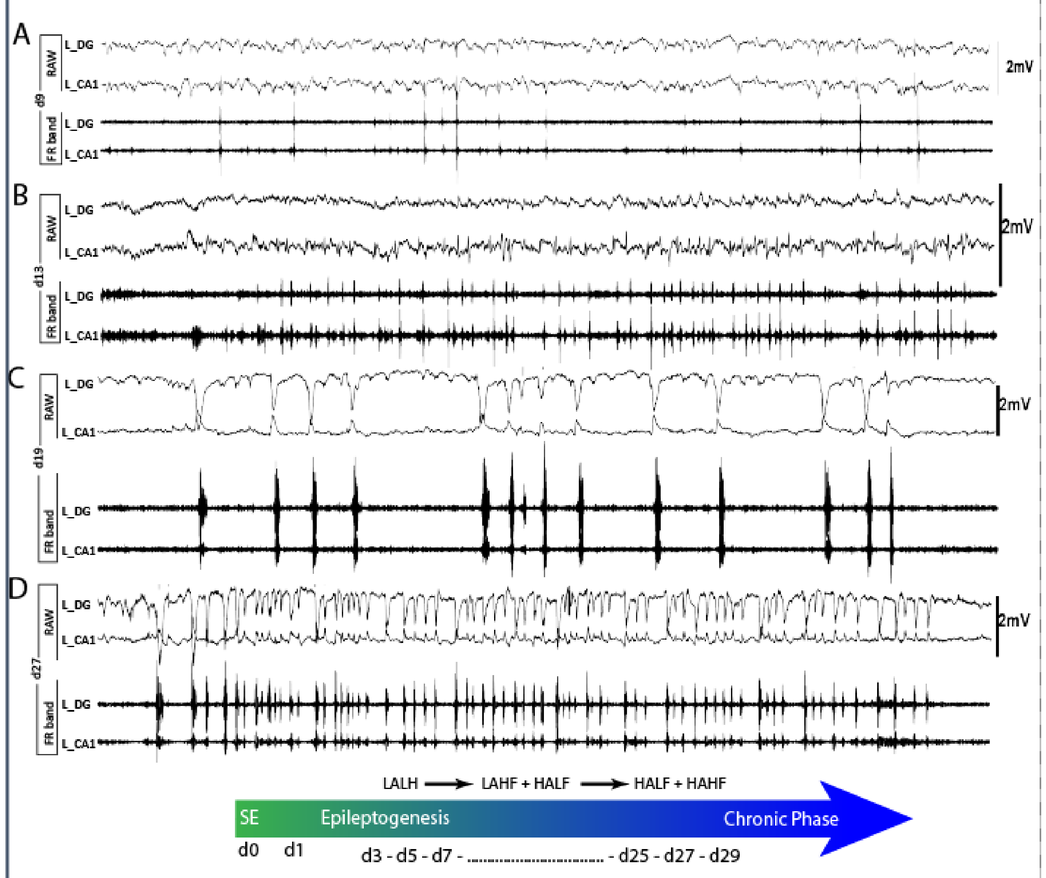

Figure 2: EEG traces of latent phase epileptic events on raw band and filtered in FRs band

Epileptic activities in the EF seem to appear gradually. Starting with low amplitude and low frequency activities with only few HFOs (LALF) (A). After few days post-K injection, low amplitude but rythmic activities with more present HFOs appear (LAHF) (B). The more the epileptic condition is setting into the network, the more intense the activities are, with high amplitude and low frequency patterns (HALF) (C) until becoming typical focal seizure that can be defined as high amplitude and high frequency periods (HAHF) (D).

2. HFOs detection characterize the dynamic development of the large-scale EN

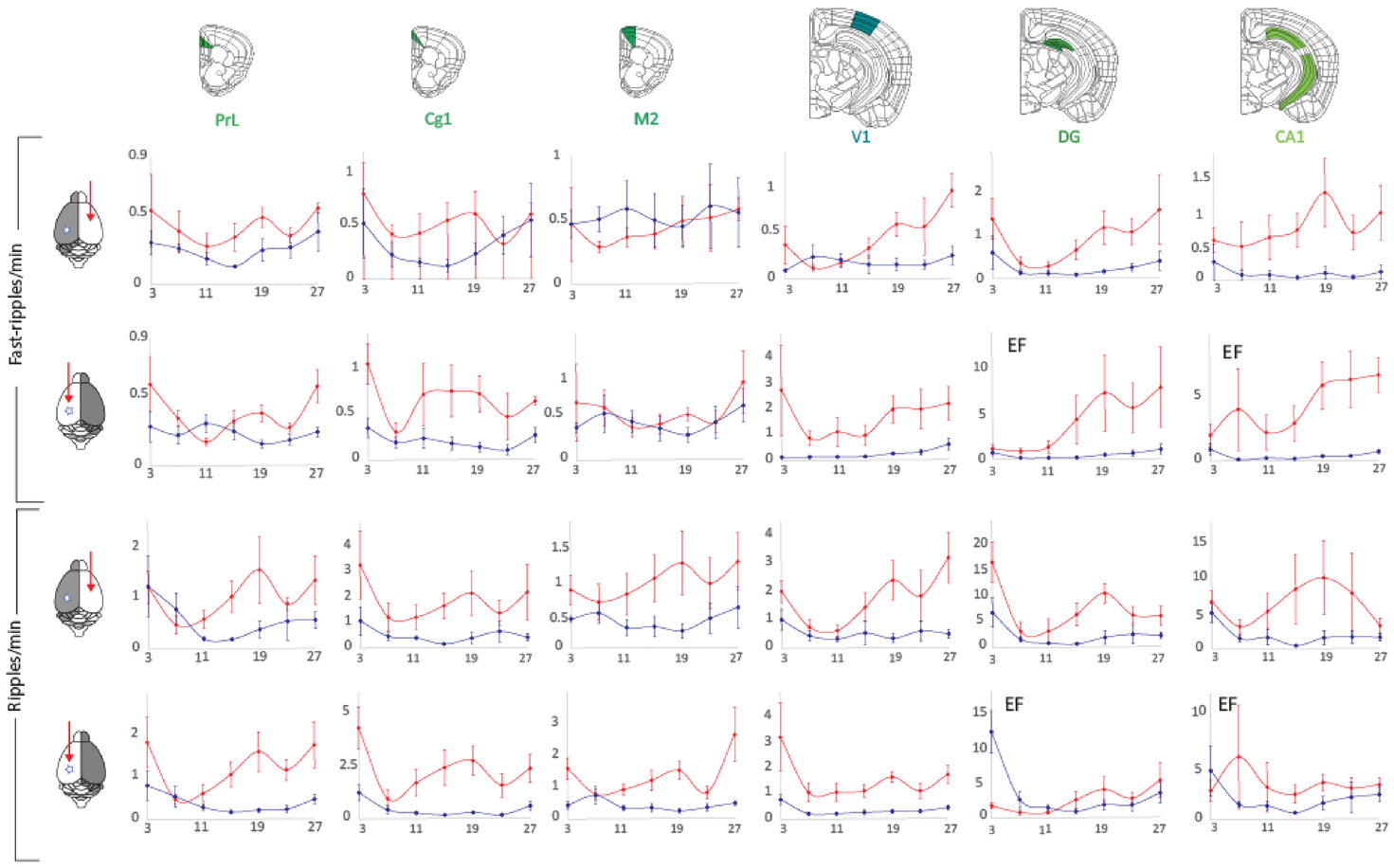

Figure 3: HFOs quantification during the latent phase until the chronic phase using multisite recording

Unsupervised quantification of HFOs (ripples + fast-ripples) have been done from the latent phase (d3) to the chronic phase (d27). Graphs represent the numbers of total events / min along the progression of the disease (3 = d3 post-K injection) until the chronic phase (27 = d27 post-K injection). Parameters of detection were: Ripples (min. osc.:4, filters 80-250Hz, std_thrsld:3), Fast-Ripples (min. osc.: 8, filters: 250-500Hz, std_thrsld:3). n_epileptic = 5, n_saline = 5. Grey rectangles indicate the EF HFOs quantification. Blue stars represent kainate injected hippocampus, and red arrows represent the line graphs corresponding hemisphere.

3. Controlateral epileptiform spike-trains with ripples are observed early in the latent phase while focal spikes-train in the chronic phase are charaterized by fast-ripples

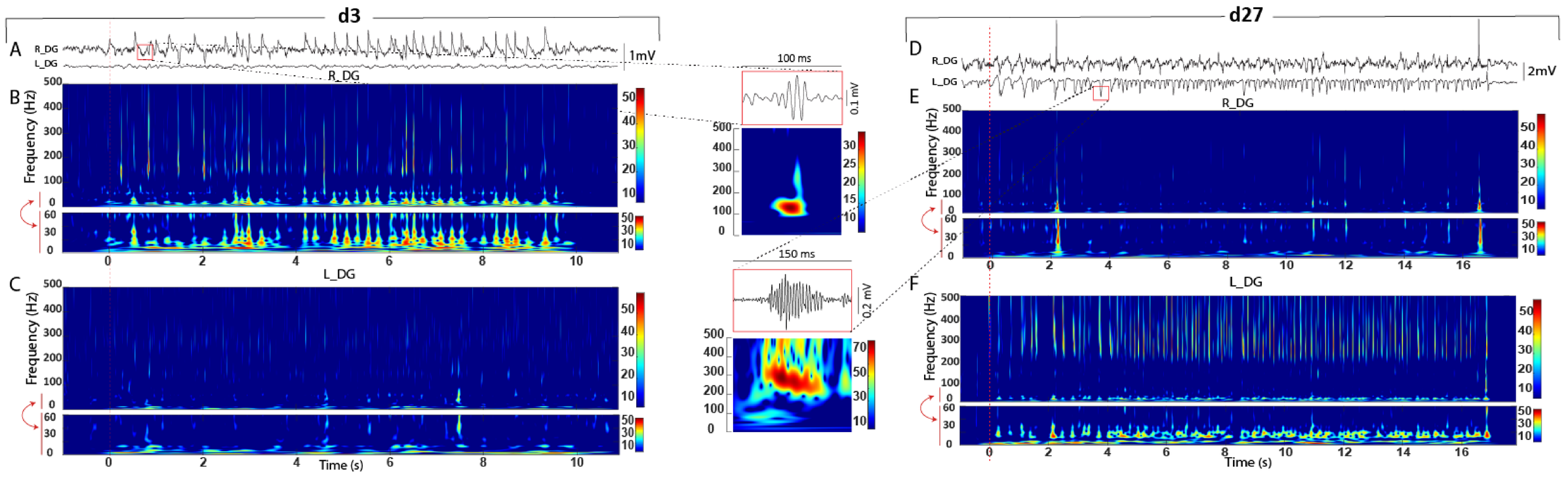

Figure 4: Raw data and time frequency plots in the same mouse during epileptic events at d3 and d27 post-K injection

First pathological activities seem to appear in the very early latent phase (d3, left column). They can be recorded in the controlateral hippocampus (RH, R_CA1, R_DG) with spiky activities in the raw band data (A). Time frequency plot of the RH (B) confirms the presence of high frequency oscillations (HFOs) belonging to the ripples band (80-250Hz). Surprisingly, the epileptic focus (LH, L_CA1, L_DG) do not have such activties, and the corresponding time frequency plot (C) confirms the absence of HFOs. Secondly, in the chronic phase (d27, right column), pathological activties seem to concern only the EF. HFOs decreased in the RH (E), but can now be recorded in the EF (F). Those HFOs appers to be in the fast-ripples band, which is consistent with previous studies of our lab (Sheybani et al., 2018).

Reference: Sheybani L, Birot G, Contestabile A, Seeck M, Zoltan Kiss J, Schaller K, Michel CM, Quairiaux C (2018) Electrophysiological evidence for the development of a self-sustained large-scale epileptic network in the kainate mouse-model of temporal lobe epilepsy. J Neurosci 38:3776–3791.

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