Hippocampal-prefrontal coordination during sleep in physiological and pathological conditions

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Introduction and Hypothesis: Hippocampo-cortical oscillatory coupling occurs through the coordination of sharp-wave ripples (SPW-Rs, 100-250 Hz) in CA1, and cortical delta waves (2-5 Hz) followed by spindles (9-16 Hz) in prefrontal cortex (PFC). Recent studies showed artificially-induced delta-spindle oscillations in the PFC with electrical stimulation upon online SPW-Rs detection was sufficient to improve memory consolidation [1].
In animal models of Temporal Lobe Epilepsy (TLE), such as electrical kindling, SPW-Rs are gradually substituted by Interictal epileptiform discharges (IEDs), which also presents coupling between slow cortical oscillations in PFC [2]. This oscillatory coupling, however, correlates with memory impairment. Interestingly, IEDs evoke physiological responses similar to the ones involved in memory consolidation (for instance, Delta-Spindles in PFC). The underlying mechanisms of the cognitive impact of this pathological coupling triggered by IEDs is still poorly understood. Our hypothesis is that IEDs not only presents oscillatory coupling between CA1 and PFC, but also induce changes in synaptic plasticity in these areas.

Objective: We aimed to examine potential oscillatory and synaptic plasticity changes in PFC, CA1 and basolateral amygdala (BLA) circuits. First, we tested whether hippocampal-prefrontal oscillations are modified in urethane anesthetized animals by kindling-like electrical stimulation in BLA. Then, we performed fast-kindling (FK) [3] protocols applied in freely moving animals to access correlation between substitution of SPW-Rs by IEDs, slow oscillations in PFC, plasticity changes in BLA-PFC and BLA-CA1 pathways, sleep architecture and finally, memory impairment.

Materials and Methods: Wistar rats (300 g, n = 6) where anesthetized with Urethane (1.25 g/kg) and single tungsten electrodes were implanted in PFC and CA1 for Local Field Potential (LFP, 4 kHz sample frequency, 1-1kHz analog filter) recordings, and bipolar electrodes in BLA for Kindling-like electrical stimulation (monophasic square pulses, 6 trains of 10 s length, 20 min inter-train interval, 50 pps, 1 ms pulse length) and to evoke Field Post-Synaptic Potentials (fPSPs, monophasic square pulses, 0.5 Hz frequency and 0.2 ms pulse length) in CA1 and PFC. In freely moving animals, single tungsten wires were implanted in PFC and CA1 for LFP recordings and bipolar electrodes in BLA for electrical stimulation. Sleep recordings were performed before, during and after a 3 days FK protocol (biphasic square pulses, 10 trains of 10 s duration per day, 20 min inter-train interval, 50 pps, 1 ms pulse length).

Relevance: The present work provides information about plastic changes in an FK model. Amplitude of fPSPs were reduced during kindling-like stimulations in anesthetized animals ($F(2,2198) = 29,79$, $p < 0,000$ for CA1 and $F(2,2198) = 28,48$, $p < 0,000$ for mPFC), reducing synaptic efficacy both in BLA-PFC and BLA-CA1 pathways, which could relate to memory impairment previously described in the literature. To test this hypothesis, we designed a new set of experiments in freely moving animals. Our preliminary data showed that FK protocol can reproduce electrophysiological effects of classical kindling protocols, inducing SPW-Rs substitution for IEDs.
Ongoing experiments will bring information about memory impairment using spatial object recognition task and sleep architecture changes in control vs. kindled animals.

References: [1] doi:10.1038/nn.4304 [2] doi:10.1038/nm.4084 [3] doi: 10.3389/fncel.2014.00200