Experience-dependent changes to cortico-hippocampal networks during NREM sleep

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Abstract:

Memory reactivation during NonREM-ripples is thought to communicate new information to a systems-wide network. We now show a learning-specific increase in cortical ripple power associated with decreased hippocampal power across a hippocampal-prefrontal-parietal network, and increases in connectivity measured by Granger Causality. Disruption of either sleep or ripples impairs long-term memory consistent with a role for these ripples in memory consolidation.

Main Text:

We only retain memories of what is new and relevant to updating our model of the world. But what makes new information salient enough for triggering memory consolidation processes? We recently proposed that dopamine coming from LC and VTA to the hippocampus could determine the fate of memories [1]. Novel experiences sharing some commonalities with past ones ('common novelty') would activate the VTA and promote semantic memory formation via increased reactivation during sleep and ensuing systems consolidation[1,2]. By contrast, experiences that bear only a minimal relationship to past experiences ('distinct novelty') are thought to activate the LC to trigger strong sleep-independent, initial memory consolidation in the hippocampus, resulting in vivid and long-lasting episodic memories [1 2,3].

To test this, we compared different behaviors (Fig. 1A) to a non-learning Baseline condition: (1) Foraging, a mix of open-field foraging and track running with small chocolate rewards spread along a track. This controls for the effect of food rewards but contains no novelty. (2) Novelty, exploration of a new environment with novel cues/textures, a form of 'distinct novelty'. (3) Plusmaze, training to a new reward location, which tests abstractions across multiple events (16 trials) in a familiar environment (with updated cues). Based on our hypothesis the 'common novelty' of the plusmaze condition should specifically lead to changes in post-behavioral sleep[1,4].

We recorded 4h in rats after these four different conditions (Baseline, Foraging, Novelty, Plusmaze) and compared characteristics of NonREM-ripple events in the hippocampus. Surprisingly, after Plusmaze fewer ripples (across thresholds, Fig. S2) were detected than in the other conditions. Ripple count, rate of occurrence as well as duration showed a significant effect but the average frequency stayed the same (Fig. 1B). Next, we took the 300-500 largest ripple events (nr derived from maximum-count in Plusmaze for each animal, all ripples Fig.S3), and compared the corresponding oscillatory power in ECoCgs placed above the prefrontal and parietal cortex targeting the ripple-range (100-250 Hz) [5]. A rmANOVA across conditions and brain areas (±25ms of ripple peak) showed a significant interaction (Fig. 1C, D). After Plusmaze a decrease in hippocampal and increase in cortical ripple power was detected.

Next, parametric Granger Causality analysis (GC) on the same ripple events, including all causality flows between hippocampus (HPC), prefrontal (PFC) and parietal (PAR) cortices (Fig. 2A; non-parametric GC Fig. S4) showed learning-specific effects when comparing Plusmaze to the other conditions. In the slower frequency ranges (0-20Hz) PFC→HPC and PFC→PAR showed an increase and PAR→PFC a decrease in GC values. In the faster frequency ranges (20-300Hz) both HPC→PFC/PAR and PFC/PAR→HPC showed increases.

Fig.1 Behaviour and NREM Ripple/High Gamma power (n=3)

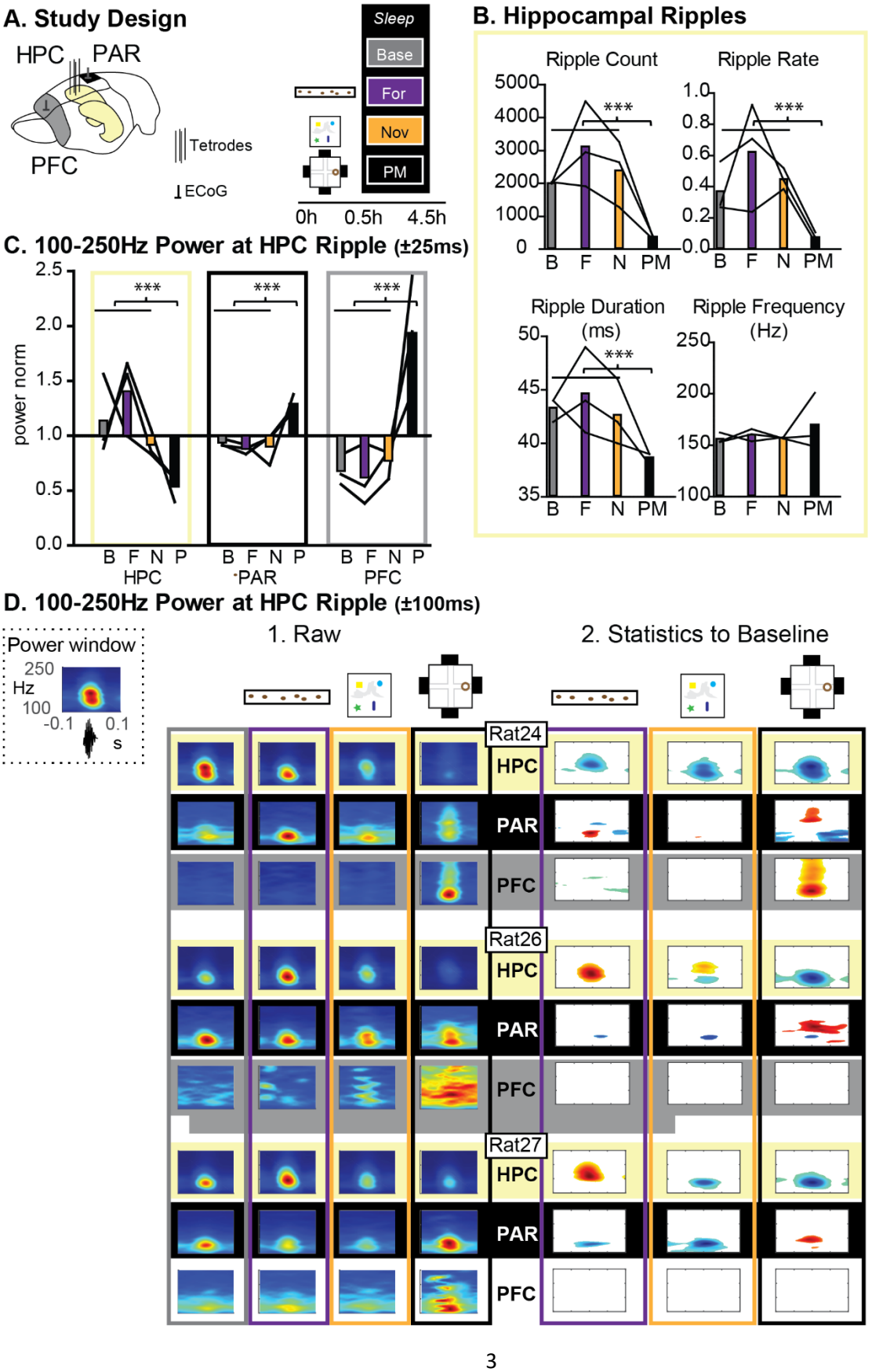

Fig.1 Behavior and NREM Ripples A. Study design. Three animals were allowed a 4h sleep-period (average ± SEM NREM 93.34min ±3.45, Transitional 2.6min ±0.78, REM 7.9min ±1.38Fig. S2) in four conditions: Baseline, after Foraging on a linear track with coco crumbs (1.5m), after Novelty (1.5mX1.5m open-field with novel objects/textures), and after Plusmaze (1.5mX1.5m, 10min free exploration, then 16 trials to goal with wheetos). During sleep the right hippocampus (AP-3.5, ML 2, tetrodes, yellow, **HPC**), the right parietal cortex (AP -6, ML 5, ECoG, black, **PAR**) and above the right prefrontal cortex was recorded (AP 3.5, ML 0.5, ECoG, grey, **PFC**). **B. Hippocampal ripples** across conditions. **Cond Effect** Count p=0.013 F=8.75, Rate of occurrence per sec p=0.041 F=5.27, duration p=0.053 F=4.62, frequency (Hz) p=0.68 F=0.53, **Orthogonal comparisons**: *p<0.05, **p<0.01,***P<0.001 **C.** N**ormalized power** (for each animal and brain area) for **100-250Hz ±25ms around the hippocampal ripple** of the largest 300-500 ripples in each condition. **Full Model (BA, Cond)**: BA X Cond p= 0.001 F=8.81 (all other p>0.09) **Orthogonal comparisons**:***P<0.001. **D. 1. raw power for 100-250Hz ±100ms around the hippocampal ripple** of the top 300-500 ripples in each condition and **2. the statistics** against baseline for each animal separately. Significant increases are shown in warm colors and decreases in cold colors.

Fig.2 Behaviour and Granger Analysis during Ripple windows (n=3)

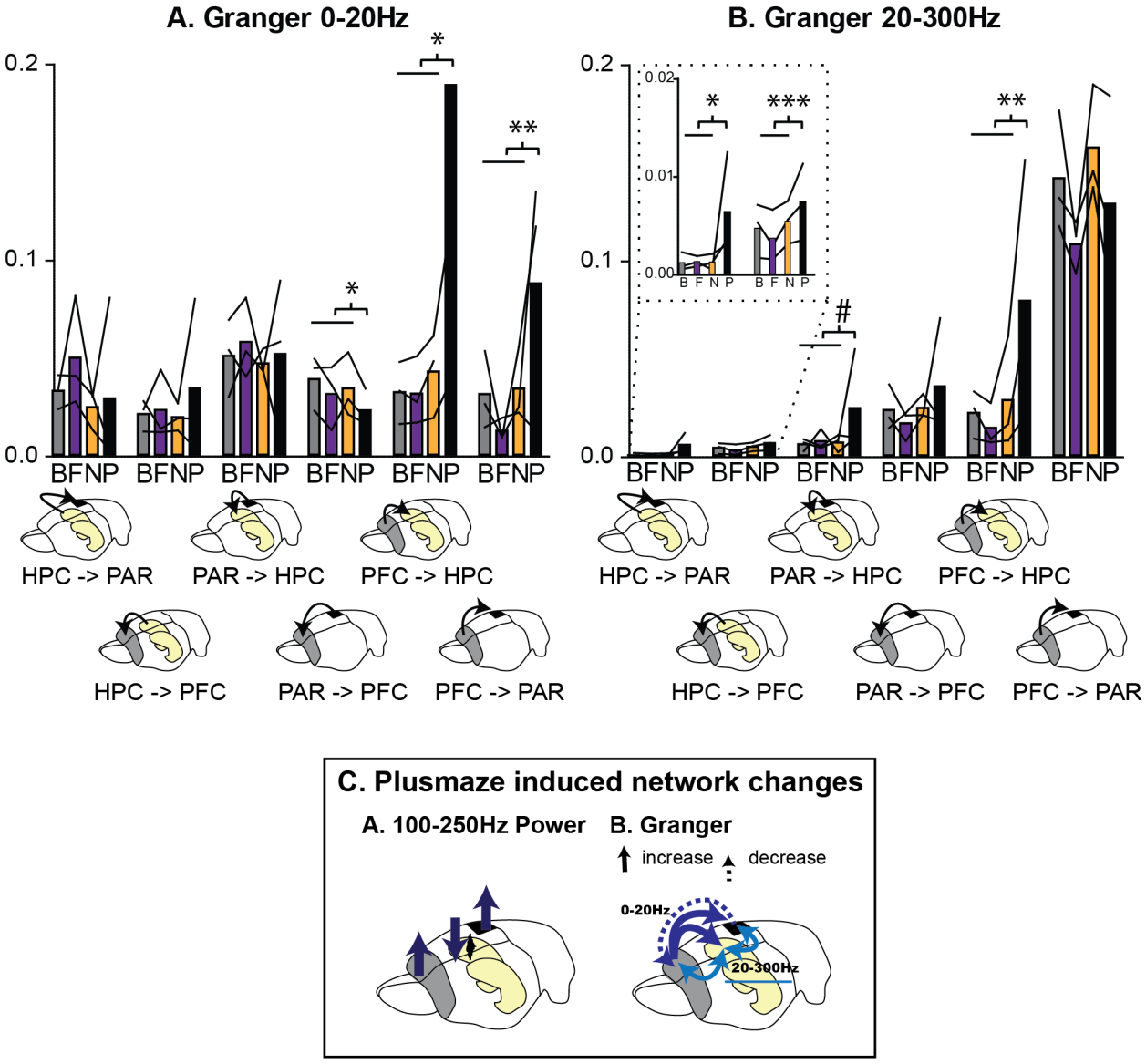

Fig. 2 **Granger Causality Analysis** (parametric) is shown for both 0-20Hz and 20-300Hz of the top 300-500 ripple events with the six possible directionalities. **A.** In the **slower frequencies** Plusmaze induced an increase in prefrontal cortex to hippocampal and to parietal cortex and a corresponding decrease for parietal to prefrontal cortex. **B.** In contrast in the **faster frequency** band Plusmaze induced and increase in hippocampal to cortical and cortical to hippocampal values (parietal cortex to hippocampus p=0.053). **Full Model (BA, Cond, Osc)**: BA X Osc X Cond p= 0.055 F=1.98, Osc X BA p< 0.001 F=25.43, Cond X BA p= 0.011 F=2.66, BA p= 0.005 F=6.84. For each oscillatory band separately: **0-20Hz** BA X Cond p= 0.021 F=2.39, **20-300Hz** BA X Cond p= 0.008 F=2.81, BA p< 0.001 F=23.07 (all other p>0.1).**Orthogonal comparisons**: #p=0.053, *p<0.05, **p<0.01,***P<0.001, **C**. Summary

The above analysis suggests that learning a new goal location in a Plusmaze changes cortico-hippocampal networks during NonREM-ripples. But is this activity necessary for long-term memory performance? To test this, we implanted animals with additional stimulating electrodes to the ventral hippocampal commissure (AP-1.3, ML 1, DV 3.8). Using similar methods others[6,7] have shown that disrupting ripple activity daily (1h/d) slowed down learning in tasks trained over many days. Our one-session Plusmaze task allowed us to target a longer sleep period (4h) and compare this to a separate sleep deprivation group. Specifically, we compared 4h of sleep and sleep deprivation in unimplanted animals (within-subject, n=16, Fig. 3A) as well as sharp-wave-ripple-disruption (SWR-D), control-disruption (200ms after SWR, Con-D) and baseline (no stimulation) in implanted animals (within-subject, n=6, Fig. 3C). Animals performed above chance at 24h test (no food present) but performance fell to chance if sleep deprived after learning (Fig. 3B). SWR-D could mimic the sleep-deprivation effect, while both Baseline and Con-D showed above chance performance (Fig. 3D). Thus sleep and more specifically NonREM-ripples are necessary for long-term memory performance in this task.

Fig.3 Sleep Deprivation and Ripple Disruption

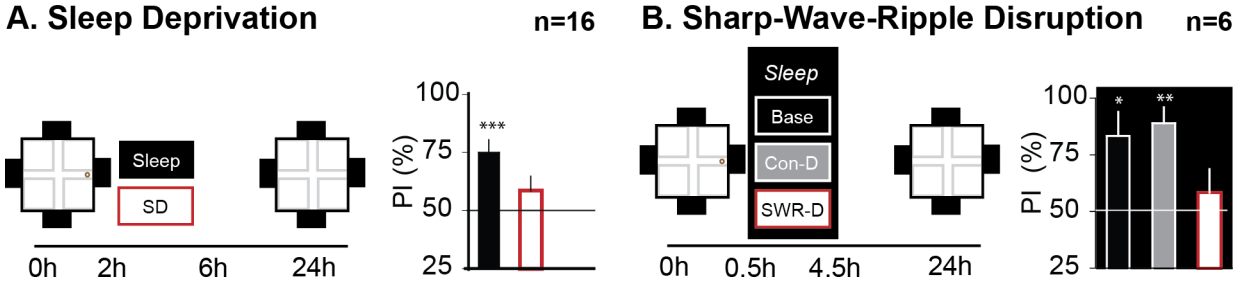

Fig.3 Sleep Deprivation and Ripple Disruption A. Animals were trained in the Plusmaze and were either sleep deprived (gentle handling) or allowed to sleep for 4h and then retested 24h later (no food present). Only after sleep and not sleep deprivation (SD) could the animals remember the previous day's goal location. cond p=0.052 $F_{1,15}$=4.45, ***sleep to chance p<0.001, T_{15}=4.56 **B.** As above but now implanted animals were trained in the Plusmaze and then received sharp-wave-ripple disruption (SWR-D), control-disruption (200ms delay, Con-D) or no-disruption (Base) for 4h. Only with intact ripples could the animals remember the previous day's goal location. cond p=0.025 $F_{2,10}$=5.42, to chance *p=0.025 ** p=0.003

In sum, we could show that 'common novelty' – extracting a new goal location in a familiar maze across multiple trials – induces changes across the hippocampal-prefrontal-parietal network during NonREM ripples in contrast to 'distinct novelty' or very familiar behaviors (Baseline, Foraging). Analysis revealed that 'common novelty' decreased the amount and power of ripples in the hippocampus, but increased the cortical response. Granger analysis of these ripple events showed increased prefrontal connectivity to both hippocampus and parietal cortex in the slower frequency ranges. In the faster frequencies both hippocampus to cortex and cortex to hippocampus was increased (Fig. 2C). Finally, ripple activity and sleep after learning in the Plusmaze is necessary for long-term memory performance in this task.

Interestingly, the observed network reconfiguration takes the shape of a bi-directional increase in LFP predictability, between the hippocampus and the neocortex, this may correspond to not only increased flow of replayed information from hippocampus to neocortex, but also in greater control exerted by the neocortex on the timing – and potentially the information content – of hippocampal ripples [8-10]. The cortico-hippocampal interplay involve ripple-frequency LFP in neocortex as well as in the hippocampus. This may reflect variability in neocortical population activity, or the hippocampal ability to trigger local neocortical modes giving rise to neocortical ripples [5] and conversely the power of neocortical ripple to "broadcast" and influence hippocampal activity.

These results are the first direct experimental support for the hypothesis that different types of novelty affect sleep related consolidation differently[1,2,11]. Reactivations during sleep-ripples are thought to allow memory abstraction across multiple events, such as multiple trials or sessions in a learning task, and thus the consolidation from initial hippocampal to long-term cortical memory storage when we encounter something new that fits into what we know [12].

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