

Journal Club

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Sleep-Stage-Dependent Hippocampal Coordination with Cingulate and Retrosplenial Association Cortices

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Review of Koike et al.

A long line of research has examined the role of the hippocampus in learning, episodic spatial and nonspatial memory, and navigation. Although critically important in these processes, the hippocampus does not act in isolation. Effective hippocampal mnemonic and spatial processing requires cortical input, and the output of hippocampal network computations must be integrated with cortex to guide complex behavior. Much work on cortical-hippocampal interaction has focused on synchronization with the medial prefrontal cortex (mPFC) but recent data suggest that the anterior cingulate (ACC) and retrosplenial (RSC) association cortices may play significant roles in this coordination process, especially during sleep.

Recent observations indicate that increased rapid eye movement sleep [(REM; also known as paradoxical sleep (PS)] is positively correlated with increased expression of c-Fos, an immediate early gene that serves as a biomarker of neural activity (Renouard et al., 2015). Critically, increased c-Fos expression following REM hypersomnia is restricted to the ACC,

RSC, medial entorhinal cortex (MEC), and the dentate gyrus (DG). Accordingly, the observed pattern of c-Fos expression during REM reveals a cortico-hippocampal circuit with a potentially unique role in REM-sleep-dependent processing.

A recent study in *The Journal of Neuroscience* sought to identify the neurophysiological basis for increased c-Fos levels in RSC and ACC following REM hypersomnia and to investigate synchronization between these cortical structures and the hippocampus (Koike et al., 2017). The authors recorded single units and local field potentials (LFPs) simultaneously in the ACC, RSC, and hippocampus of rats across arousal states *in vivo*. They found that a majority of RSC neurons and nearly half of ACC units were more active during REM than during any other sleep–wake state. The increased firing activity during REM forms electrophysiological support for their conclusion that increased c-Fos expression in these areas results from REM-specific activation.

In addition to finding increased activity, Koike et al. (2017) detected a prominent theta rhythm in the LFP in all three structures during REM sleep. A similar rhythm was present in RSC and hippocampus, but substantially diminished in ACC, during the awake state. The theta rhythm is a 6–12 Hz oscillation measured in the LFP of the hippocampus (among numerous other areas) that entrains the spiking activity of neurons

within the region. Koike et al. (2017) performed cross-correlation analyses on pairs of raw LFPs between regions and observed significantly greater synchronization between the RSC and hippocampus during REM than during waking. Furthermore, Granger causality analysis indicated that coherence in the theta frequency range between the two regions was driven by the hippocampus rather than RSC. No such relationship between the ACC and either the hippocampus or RSC was observed.

Activation of neurons in several cortical and subcortical regions is entrained with the hippocampal theta rhythm across a wide range of behavioral states and tasks (Berke et al., 2004; Sirota et al., 2008). At the level of individual neurons, theta-phase coupling is manifested as spiking locked to particular phases of the theta rhythm. At the level of cortical ensembles, theta entrainment is often manifested as phase–amplitude coupling between theta phase and increased amplitude within the gamma frequency range (40–160 Hz) recorded in the LFP. The observed interaction between ACC, RSC, and hippocampal theta rhythms suggests that these cortical regions are similarly coordinated within theta frequency temporal windows and that interaction is increased specifically during REM. Consistent with this hypothesis, Koike et al. (2017) found evidence of single-unit and ensemble coupling to theta-frequency os-

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illatory activity. Neurons in both ACC and RSC exhibited theta phase-coupling to the theta rhythm recorded in the hippocampus during awake states, and RSC neurons exhibited significantly increased theta phase modulation during REM. The authors additionally observed phase–amplitude coupling between hippocampal theta phase and RSC gamma-frequency power during REM, but not during awake states. Like the preferred phase of single-unit theta entrainment, gamma oscillations in RSC occurred just after the peak of the theta wave.

Phasic entrainment of neurons with the theta rhythm has been proposed to underlie different cortico-hippocampal processing states (Hyman et al., 2005). For instance, activation of neurons during the peak or trough of the theta wave has been shown to yield long-term potentiation or long-term depression, respectively (Huerta and Lisman, 1995). Accordingly, hippocampal theta modulation of RSC ensembles during REM might indicate a mechanism by which the output of hippocampal computations is integrated with cortical circuits. The presence of theta–gamma coupling during REM but not waking is interesting considering that individual RSC neurons exhibit theta entrainment regardless of arousal state. This finding implies that larger populations of RSC neurons become coupled to the hippocampal theta rhythm during REM, which could produce greater gamma frequency power at the peak of the theta wave.

Given these observations, one might ask what neural processes are supported via increased hippocampal communication with these structures, and especially RSC, during REM. Multiple lines of evidence indicate that sleep-related synchronization between cortex and the hippocampus might play a special role for memory processing. At the most basic level, the construction of an episodic memory requires sequentially linking spatially and temporally discrete events in time, a process that the hippocampal architecture and subsequent neurophysiological dynamics seem especially suited for. It is well known that initial episodic processing requires the hippocampus, but following encoding, episodic memory becomes hippocampus independent and likely consolidated into distributed cortical populations (Frankland and Bontempi, 2005). It is thought that sleep is important for this consolidation process, and several studies have reported that sleep disruption produces impairments in memory encod-

ing, whereas sleep-dependent memory improvement is observed across species in a variety of tasks. Increased hippocampal communication with cortical areas might reflect the consolidation of episodic memories across cortical populations.

There is some indication that different sleep stages play different roles in memory consolidation. Perhaps most relevant to the current work, Boyce et al. (2016) recently demonstrated a link between the occurrence of REM theta oscillations and consolidation of context-dependent memories. Accordingly, hippocampus–RSC synchronization during REM might be important for the integration of unique sensory or behavioral contextual information with episodic memories before cortical consolidation. RSC is reciprocally connected to multiple cortical sensory processing regions, and neurons within the region exhibit activation patterns that can be sensitive to sensory context and spatial location (Wyss and Van Groen, 1992; Jacob et al., 2017). In support of this hypothesis, optogenetic activation of RSC ensembles initially active during contextual fear conditioning is sufficient to reinstate learned behavior (Cowansage et al., 2014), suggesting that a contextual memory can be consolidated for future recall within RSC.

The limited interaction between hippocampus and ACC reported by Koike et al. (2017) is surprising given the pattern of c-Fos expression levels. Although the magnitude of ACC–hippocampal theta coherence reported by Koike et al. (2017) is consistent with previous reports describing both theta coherence generally and task-dependent theta frequency coherence shifts, the authors find little other evidence of ACC–hippocampal interaction across arousal states (Young and McNaughton, 2009; Remondes and Wilson, 2013). However, it is possible that ACC communicates with hippocampus during more discrete time windows of interaction such as hippocampal sharp-wave-ripple events (SWRs). SWRs are short duration (100–200 ms), high-frequency (150–250 Hz), hippocampal LFP events that occur during slow-wave sleep (SWS) or immobile waking. SWRs are coincident with the simultaneous activation of large populations of hippocampus neurons in addition to cortical ensembles (Siapas and Wilson, 1998; Csicsvari et al., 1999). During SWS and SWR-related activity bursts, neurons often exhibit sequential activation that mimics activity patterning during previous experience (Wilson and McNaughton, 1994; Rothschild et al., 2017). Thus, cortical and hippocampal activation during SWRs potentially reflects an offline

processing state, wherein populations of neurons that were coactive during prior events strengthen their connections via spike timing-dependent plasticity mechanisms. Indeed, recent work has shown increased activation of ACC units and increased ACC–hippocampus gamma-coherence locked to SWRs during waking and SWS (Remondes and Wilson, 2015; Wang and Ikemoto, 2016).

The lack of theta–gamma phase–amplitude coupling between hippocampus and ACC is somewhat at odds with the presence of ACC units whose firing activity is locked to hippocampal theta, and suggests that only a small percentage of ACC units exhibit this tendency. This observation could be explained by relatively sparse direct projections from the hippocampus to ACC compared with hippocampus–RSC interconnectivity (Wyss and Van Groen, 1992). On the other hand, the absence of theta–gamma coupling in ACC during all arousal states and in RSC during waking could be explained by diminished active navigation during waking states, given that most sessions were dominated by sleep with relatively short bouts of waking interspersed. Neurons in both the ACC and RSC are sensitive to action execution, and RSC neurons exhibit spatially modulated firing only recognizable during active navigation (Alexander and Nitz, 2017). Accordingly, a lack of significant movement during awake states may decrease firing activity in both regions which could possibly explain the significantly greater mean firing rate observed in REM. Furthermore, the power and frequency of the hippocampal theta rhythm is positively correlated with running speed. In combination, decreased firing activity and potentially weak theta rhythms may explain the reduction in theta–gamma phase–amplitude coupling during waking states.

Along these lines and as Koike et al. (2017) point out, it would be useful to examine interaction within this circuitry following more complex behavior including different spatial and nonspatial learning paradigms. Engagement of RSC and ACC neurons is correlated with learning and memory, choice, action, various spatial variables, and much more (Cowen et al., 2012; Jacob et al., 2017; Alexander and Nitz, 2017). Although Koike et al. (2017) do an excellent job characterizing the neurophysiological dynamics within this circuit, it is possible that the profile of interaction between these association cortices and the hippocampus would shift if the animal were engaged in more cogni-

tively demanding behaviors during the awake state.

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