Possible Mechanisms Contributing to Memory Consolidation During Sleep

20

Neocortical synaptic changes induced by sleep spindles-related firing patterns

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Sleep spindles are highly synchronous oscillations (7–14 Hz) occurring during slow wave sleep as sporadic events or triggered by the sleep slow oscillation (0.6–0.8 Hz). Although recent works have shown a functional link between spindles and learning or memory consolidation processes, their impact on synaptic transmission is largely unexplored. We studied the ability of a neuronal firing pattern underlying spindles recorded *in vivo* to induce activity-dependent synaptic plasticity in layer V pyramidal cells in vitro. A spindle stimulation pattern (SSP) was extracted from the intracellular trace of a neuron during a slow oscillation upstate that was recorded within the primary somatosensory cortex of a cat anesthetized with ketamine-xylazine, which is known to induce a sleep-like state. Since the cortical sleep slow oscillation works as a sleep spindles pacemaker, in order to mimic their recurrence the SSP was repeated every 1.5 s (0.6 Hz). Whole-cell patch-clamp recordings were obtained from layer V pyramidal cells of rat primary somatosensory cortex visualized by infrared microscopy, and composite EPSPs were evoked within layers II-III. Simultaneous trains of EPSPs and action potentials (AP) triggered by the SSP induced an NMDAr-dependent short-term potentiation (STP) and a L-type Ca++ channel-dependent long-term potentiation (LTP). The magnitude of both the STP and the LTP depended on the number of applied spindle trains. In contrast, spindle trains of EPSPs alone induced long-term depression (LTD). A homogeneous firing pattern with the same frequency as the mean of the original spindle train left synapses unaltered as well as a mirror SSP and a shuffled SSP. On the contrary a synthetic spindle pattern consisting of repetitive spike bursts at 10 Hz induced both STP and LTP. We conclude that sleep spindles can change strength at excitatory neocortical synapses on different time-scales and in different directions according to a Hebbian rule. This may account for the proposed role of sleep spindle for learning and memory consolidation.

21

The contribution of the noradrenergic system to memory consolidation during sleep in humans

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The locus coeruleus (LC) of the brainstem is the major noradrenergic nucleus in the central nervous system. Its connections extend to the thalamus, hippocampus and the entire neocortex. One main function of the LC is the modulation of the arousal state, with it being in a state of high tonic activity during wakefulness and shut off during REM sleep. LC activity can increase the signal-to-noise ratio of neurons and thus promote information processing. Through its hippocampal connections, it may also modulate memory function or synaptic potentiation. Interestingly, during SWS, which is a state of low arousal, the LC is still active, although at a lower rate than during wakefulness. In a series of experiments, we investigated whether this activity is related to the consolidation of memories during sleep. Subjects (healthy, young males) had to perform an odour recognition task, which required them to learn six different unfamiliar odours and, 24–h later, to recognize them among twelve odours. In a placebo-controlled design, they received the alpha2–adrenergic agonist clonidine (0.1125 mg i.v.), which activates autoreceptors in the LC and thus prevents further noradrenalin release. The substance was administered either during sleep or during a period of night-time wakefulness after the learning task. These experiments showed a significant increase in performance when subjects slept as compared to those that stayed awake. However, this sleep-related increase could be eliminated by clonidine. In subjects that remained awake, clonidine did not have any effect on memory. Thus, apart from reducing arousal, the incomplete suppression of noradrenergic activity during SWS might have a functional role in memory consolidation.

22

Slow-wave activity as an electrophysiological marker of synaptic plasticity: human high-density EEG recordings

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A recent hypothesis suggests that changes in slow wave activity (SWA, EEG power 1–4 Hz) during sleep reflect plastic changes of cortical synapses (Tononi and Cirelli 2005). Thus, inducing local synaptic changes should result in local SWA changes. To examine this possibility, we used high-density EEG analysis to investigate local changes in SWA homeostasis. Electrode and MRI co-registration allowed an anatomical localization of these changes. In a first experiment sleep was recorded after subjects ($n = 11$) performed a visuo-motor learning task (Huber et al., 2004). In NREM sleep following this task, we found (i) increased SWA of up to 25% in a cluster of electrodes overlying right parietal cortex (BA 40 and 7) and (ii) a strong positive correlation between this local increase of SWA and post sleep performance improvement. In a second experiment we asked whether arm immobilization would also lead to local SWA changes in the cortex, and whether these changes are related to synaptic depression and performance alterations. 12–h left arm immobilization resulted in (i) a significant decrease of interjoint coordination of arm movements, (ii) an amplitude reduction of somatosensory evoked potentials over right sensorimotor cortex (−67.3 ± 9.1%, $P < 0.05$, $n = 7$) which indicates depression of relevant synapses, and iii) a decrease of SWA over right sensorimotor cortex during subsequent sleep (−22.1 ± 5.9%, $P < 0.001$, $n = 14$). In a third experiment we took advantage of recent work showing that repetitive transcranial magnetic stimulation (rTMS) applied to motor cortex can produce localized potentiation of TMS-evoked cortical responses (Esser et al., 2005). During sleep after such an rTMS potentiation protocol we found an increase of SWA (26.6 ± 15.3%, $P < 0.05$, $n = 9$) in a cluster of left central electrodes (BA 6). Together these results provide compelling evidence that paradigms

involving plastic changes in circumscribed brain regions can give rise to local changes in SWA and support a role for sleep at the cellular level.
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23

Locus coeruleus firing during SWS is time locked to slow oscillations: possible contribution of the noradrenergic system to off-line information processing in rats

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Spindle activity has been suggested to provide a physiological substrate for off-line information processing (Gais, et al, 2002). The grouping of spindle activity by slow oscillations during slow-wave sleep (SWS) has been shown in humans and rats (Molle, et al, 2002; 2005) supporting the concept that phases of cortical depolarization during slow oscillations drive the thalamocortical spindle activity. Our previous investigations indicated that the noradrenergic system is involved in a late phase of memory consolidation (Roullet and Sara, 1998; Tronel and Sara, 2004). Recently we showed a surge of activity of noradrenergic neurons of the Locus Coereleus (LC) during SWS occurring exclusively after learning (Yeshenko and Sara, 2005). In the present study we aimed to characterize LC activity in relation to dominant oscillations during SWS. Rats were implanted with movable micro-drives into LC and medial prefrontal cortex (mPFC) for unit and local field potential (LFP) recordings, and epidural electrodes for monitoring EEG. Recordings were made in freely moving animals during their rest period. The peaks of cortical hyperpolarization or down-state and depolarization or up-state were detected on both EEG and LFP signals. LC and mPFC unit activity was triggered on peaks of cortical up-and down-states and spindle onset. LC neuronal activity was highly synchronized during SWS. Firing of LC neurons mostly occurred during the transition from down to up state, in a time window of 50–300 ms after the peak of cortical hyperpolarization. The LC activity was systematically elevated immediately after the spindle onset. These findings further suggest functional inter-relationships between the noradrenergic nucleus in the brain stem with cortical plasticity mechanisms during SWS. Given the reciprocal connections between LC and frontal cortex and noradrenergic involvement in memory consolidation, the neuromodulatory influence on off-line information processing merits further investigation.