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Noradrenaline: Sleep on it

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Sleep involves infra-slow ~50-second fluctuations between disengagement and sensory reactivity. New findings reveal that the brain's noradrenaline system controls these dynamics by acting in the thalamus to affect sleep spindles, and by modulating coordinated heart rate variations.

Everything is in flux, changing constantly. Why would sleep be any different? The concept of impermanence is central to many philosophies and religions, ranging from Heraclitus in ancient Greece ("No man ever steps in the same river twice") to *Anicca* in Buddhism ("everything is in a constant state of change"). Considering that all animals sleep for hours every day[1], it should perhaps not be a surprise that sleep would constantly change during such long periods. Indeed, mammals continuously alternate between different sleep 'stages', each with its unique fingerprint of electrical brain activity, brain biochemistry, autonomic physiology, dreaming, and reactivity to the external environment. Even within the same stage of non-rapid eye movement (NREM) sleep, several important dynamics have long been recognized. Slow wave activity declines over hours as the need for sleep gradually dissipates[2]; a cyclic alternating pattern at the scale of tens of seconds affects EEG, motor, and autonomic aspects of arousal[3]; and resting-state electrophysiological and hemodynamic fluctuations of similar time-scale (less than 0.1 Hz) correlate between homologous sites across the two hemispheres[4].

More recently, an infraslow oscillation of 0.02 Hz (period = 50 s) was revealed during NREM sleep, representing alternations between phases of consolidated and vigilant sleep[5]. Phases of consolidated sleep are rich with sleep spindles, 11–15 Hz oscillations of electrical brain activity associated with synaptic plasticity and with a lower probability to wake up in response to external stimuli[6]. Thus, spindle-rich NREM periods could be optimal for memory consolidation and recovery functions. Conversely, during phases of vigilant sleep, sensory reactivity is elevated while heart rate and autonomic activities are increased[5].

What could be the mechanism driving oscillations in arousal during NREM sleep? A new study by Osorio-Forero *et al.*[7] reported in this issue of *Current Biology* tested the hypothesis that locus coeruleus-noradrenaline (LC-NA) activity plays a key role. NREM sleep entails withdrawal of wake-promoting neuromodulatory signaling including acetylcholine, histamine, noradrenaline (NA), dopamine, and hypocretin. Several reasons point specifically to the LC-NA system as a prime suspect for modulating arousal during sleep: LC activity rises just before sleep-to-wake transitions[8], it is inversely correlated with sleep spindle activity[9,10], and activating the LC leads to immediate awakening from sleep[11]. Indeed, a recent study combining sensory stimulation during sleep with LC-NA recordings and manipulations showed that low LC-NA activity during sleep mediates unresponsiveness, whereas high LC-NA activity promotes sensory-evoked awakenings[12].

Through a tour-de-force set of experiments in freely behaving mice, Osorio-Forero and colleagues combined electrophysiology, recordings of free extracellular NA, causal manipulations of LC-NA activity, and autonomic heart rate measurements to establish a number of exciting novel results[7].

First, the authors showed that LC-NA activity is essential for generating the 0.02 Hz fluctuations in arousal during NREM sleep, as evident by the clustering of sleep spindles. Using pharmacology, they showed that NA signaling via α1- and β-receptors in the thalamus is necessary for the generation of 0.02 Hz fluctuations between spindle-rich and spindle-poor periods. Next, they employed optogenetics, a cell-type-specific and temporally precise method to manipulate activity in LC neurons secreting NA. By boosting or silencing LC activity during specific phases of the 0.02 Hz oscillation, they established that this activity is both necessary and sufficient for the infraslow oscillations in spindle clustering.

Second, they established that NA acting in the *thalamus*, rather than in the somatosensory cortex, is associated with sleep spindle dynamics. Optogenetically activating LC output in the thalamus, but not in cortex, suppressed sleep spindles and their 0.02 Hz fluctuations. Moreover, the authors recorded NA levels in the thalamus with fiber photometry using $GRAB_{NE}$ — a genetically encoded fluorescent sensor. They found that thalamic NA levels fluctuate on infraslow time intervals and inversely correlate with sleep spindle power. *In vitro* patch-clamp thalamic recordings in combination with optogenetics revealed that LC activity drives cellular depolarization that renders thalamocortical cells 'immune' to burst discharges necessary for spindles. The central role of the thalamus in mediating LC-NA effects on forebrain arousal echoes classical work showing that some of the densest LC ascending projections target thalamic sites[13].

Third, the authors tested whether LC-NA activity may also modulate autonomic changes in arousal during sleep, such as changes in heart rate, blood pressure, and pupil dilation. Using simultaneous monitoring of heart rate and sleep spindles, peripheral cardiac pharmacology, and LC optogenetics, they established that LC-NA also coordinates heart rate variations, by suppressing parasympathetically driven heart rate variability (Figure 1).

The Osorio-Forero study highlights several important general themes and opens new questions. One intriguing observation is that, on average, thalamic NA levels are higher in NREM sleep than in

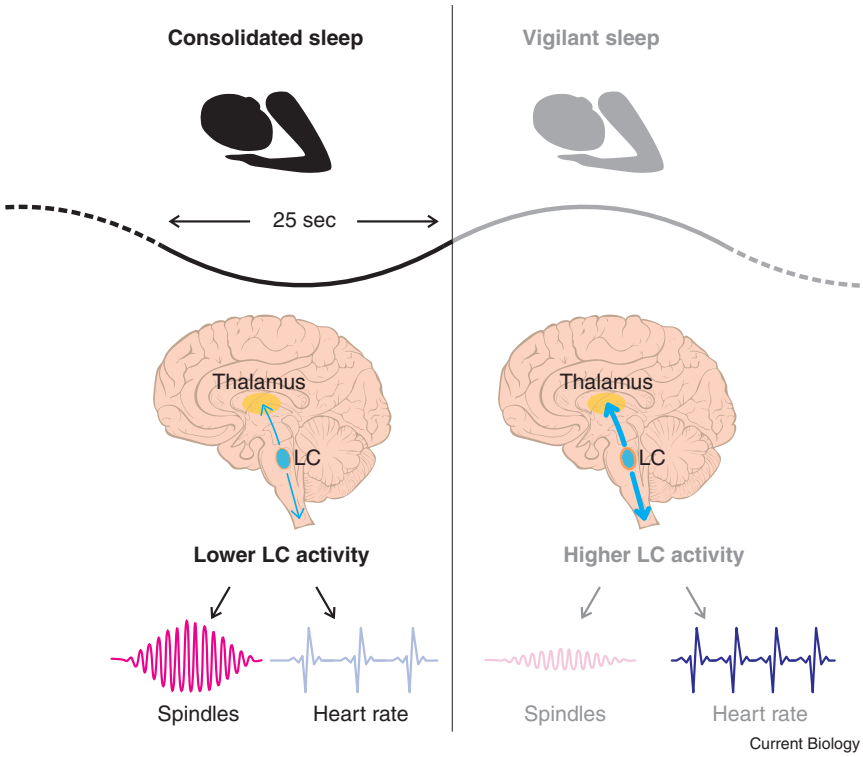

Figure 1. Locus coeruleus-noradrenaline controls infraslow 0.02 Hz fluctuations in arousal during NREM sleep.
During NREM sleep, infraslow fluctuations with a period of ~50 seconds alternate between periods of consolidated sleep (left column, ideal for memory consolidation and recovery functions) versus periods of vigilant sleep (right column, with greater sensory reactivity). During consolidated sleep, lower locus coeruleus-noradrenaline (LC-NA) activity in the thalamus drives higher sleep spindle density while descending projections reduce autonomic arousal and reduce heart rate. Conversely, during vigilant sleep, higher LC-NA activity in the thalamus suppresses sleep spindle density while descending projections enhance autonomic arousal and elevate heart rate.

quiet wakefulness. At first, this result seems at odds with the classical view that LC is considerably less active during sleep than in wakefulness[8]. However, it is important to recognize that the level of extracellular NA is not the same as the mean firing rate of individual LC neurons. Rather, NA levels also depend on the precise properties of LC firing, on synaptic release probability, and on clearance in the extracellular space — all of which are regulated by brain states such as sleep, and modulated locally in target regions. Accordingly, slightly different profiles of extracellular NA could exist during sleep in the thalamus versus the cortex[9], and synchronous burst firing of LC neurons during sleep[14] could boost NA release despite the low average firing rate in individual LC neurons. In addition, differences between quiet and active wakefulness may play a role: LC firing in *quiet* wakefulness (as examined here) is lower and closer to sleep levels[15], while the classical view (NA in wake > NA in sleep) mainly stems from comparing sleep with *active* wakefulness. Thus, future studies should further clarify the relation between LC firing, NA release, and its clearance across diverse regions during clearly defined states of wakefulness and sleep.

Another central open question is the degree to which LC-NA control of arousal is global or modular. Classically, LC-NA activity is regarded as global: given that NA is secreted from varicosities along unmyelinated widely distributed axons of highly interconnected cells, NA has been viewed much like a 'brain hormone' that is released uniformly across wide brain areas. In support of this global view, the current study reports that during natural NREM sleep, changes in sleep spindles mediated by forebrain projections are coordinated with changes in heart rate mediated by hindbrain projections. However, recent studies argue for a complex and heterogenous profile of LC-NA neuromodulation, involving distinct cell-types, specific input/output wiring of cellular subpopulations, and regional variability in release and receptor distribution[16]. The present results show that regional pharmacological NA manipulations affect local spindles but do not affect spindles in distant brain regions, showing that LC-NA neuromodulation can, in principle, regulate arousal in a modular manner. Therefore, it is possible that under some circumstances, different aspects of arousal could be mediated by regionally specific neuromodulation in a manner that is not necessarily always coordinated. An exciting area for future research is to investigate the degree of modular LC-NA control of arousal in atypical vigilance states where forebrain/EEG, motor, and autonomic aspects may be dissociated, such as during sleepwalking and other parasomnias, cataplexy, and sleep paralysis. Local LC-NA neuromodulation could also play interesting, yet to be understood roles in physiological non-uniform brain states such as sleep deprivation or unihemispheric sleep in marine mammals and migrating birds.

Now that some key mechanisms mediating the 0.02 Hz infraslow oscillation have been revealed and can be experimentally manipulated, future studies should also address its functional significance. Would loss of this 0.02 Hz rhythm be harmful, or associated with specific pathologies? Conversely, would boosting it enhance the functional benefits of sleep? It could be that the infraslow oscillation, beyond providing 'sentinel'-like periods of vigilance, supports hitherto unknown restorative functions at the molecular/cellular/circuit level that are promoted by sleep.

The current study supports the notion that low LC-NA signaling is essential for consolidated sleep, when we are disconnected from external stimuli. Conversely, elevated LC-NA activity in sleep could contribute to hyper-arousal in clinical conditions such as insomnia and PTSD[17]. Indeed, a recent study directly established that LC-NA activity determines the probability of a sound waking a sleeping animal[12]. In fact, this likely reflects a more general principle that goes beyond sleep: that NA is a key factor necessary for external sensory events to affect

perception and behavior. Even in wakefulness, pharmacological down- and up-regulation of NA signaling in healthy humans affects perception and late sensory responses[18].

Finally, the current results join other lines of sleep research stressing that low LC-NA signaling is at the core of deep restorative sleep. Indeed, monoamines and their relation to sleep and arousal are highly conserved across species[19]. Diverse research — ranging from genetics, through plasticity and memory consolidation[20], to glymphatic waste clearance[21] — all implicate low LC-NA activity in the functional benefits of restorative sleep. While other neuromodulators remain to be investigated with similar detail, "a journey of a thousand miles begins with a single step". Osorio-Forero *et al.* did a remarkable job in taking that step by showing how LC-NA activity controls arousal dynamics, reminding us that everything, including sleep, is ever-changing.

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Decision making: An analogue implementation of a drift-diffusion computation in the *Drosophila* mushroom body

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A new study combines electrophysiology, optogenetics, and behavior to investigate a decision-making circuit in the fly brain, revealing all the major features predicted by drift-diffusion models. Strikingly, much of this computation takes place subthreshold, independent of action potentials.

Animals live in complex environments where surviving and thriving require making fast and accurate decisions. These can be recreated in the laboratory using two-alternative forced-choice tasks with experimentally controlled