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Reviews

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Local sleep and wakefulness—the concept and its potential for the understanding and treatment of insomnia disorder

Introduction

The aim of this article is to review the shift from global to local concepts of sleep–wake regulation and to further contribute to the translation of this concept to the understanding of the clinical problem of insomnia and, potentially, to the development of new treatment approaches.

Sleep–wake regulation: from global to local

As the mythic brotherhood of Hypnos (god of sleep) and Thanatos (god of death) in ancient Greek mythology suggests, sleep has, over centuries, been regarded as an inactive state, close to death. Yet from an evolutionary perspective, mere inactivity would have had substantial disadvantages as sleeping animals or humans face the prospect of dangers and perpetrators and cannot obtain food or reproduce genes. This perspective suggests that sleep is more than just a passive state, but serves critical functions.

The discovery of sleep stages

The assumption of sleep as a unitary and inactive state was challenged when the cyclic alteration of rapid eye movement (REM) and non-rapid eye movement (NREM) sleep was discovered in the 1950s and 1960s based on electroencephalographic recordings [3]. Particularly, the description of REM sleep and its correlation with vivid dreaming suggested that the brain is far more active during sleep than expected [12].

Regional activity patterns of sleep stages

Functional brain imaging studies using positron emission tomography (PET; e.g. [2, 7, 20, 25–28, 37, 38]) and functional magnetic resonance imaging (fMRI; e.g. [9, 13, 21, 46]) contributed to the understanding of alterations in brain activity underlying the emergence of NREM and REM sleep. In brief, global mean levels of brain metabolic activity decrease from waking to NREM sleep [2, 7, 20, 25–27] and then increase again during REM sleep [7, 27, 28, 38]. With regard to regional activity patterns, relative metabolism in the thalamus and in broad areas of the cortex is lower in NREM sleep than during wakefulness in healthy humans [2, 7, 20, 25, 26, 37]. REM sleep is associated with increased relative metabolism in the pontine reticular formation and in limbic and paralimbic areas as well as a decrease of metabolic activity in frontocortical areas [7, 28, 29, 35, 38]. These activity patterns are believed to underlie the reduced level of consciousness during both sleep stages (frontal deactivation) and the emergence of vivid emotions during REM sleep (limbic activation). Interestingly, a coexistence of features of NREM and REM sleep was observed in different regions of the neuroaxis in avians and monotreme mammals [40]. Also in humans, local features of NREM sleep were observed during REM sleep [5, 6, 19], suggesting the possibility of a co-occurrence of different sleep activity patterns in distinct areas of the brain.

Evidence for highly localized aspects of sleep and wakefulness

Recent work indicates that even sleep and wake processes can co-occur simultaneously in distinct brain areas, from entire hemispheres to very localized areas at the single cortical column level.

For instance, EEG recordings of aquatic mammals, such as the bottlenose dolphin, demonstrate that, while one hemisphere is awake, the other hemisphere can show sleep. This unihemispheric sleep allows the dolphin to still regularly swim to the surface for breathing in an aquatic environment [43]. Other observations indicate that,

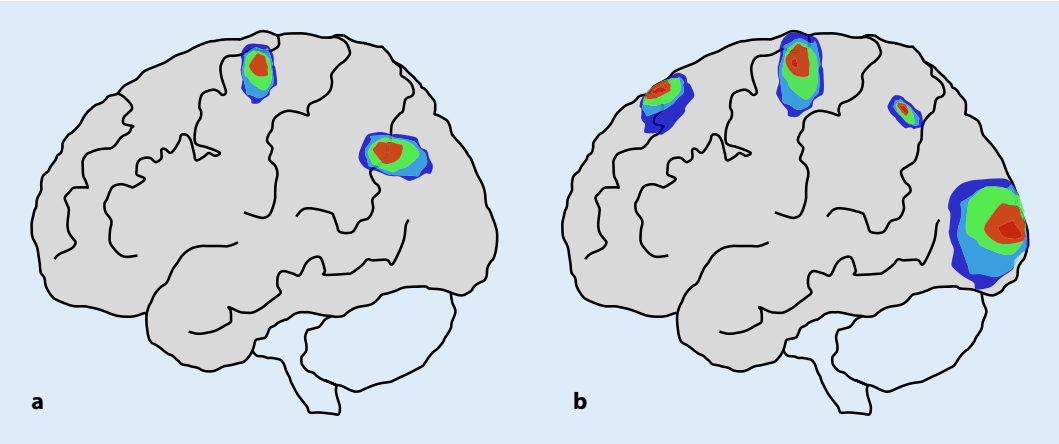

Fig. 1 ▲ Schematic conceptualization of local 'islands of wakefulness' during sleep in healthy individuals (**a**) and individuals suffering from insomnia (**b**). These local wake-like activity patterns, not captured in standard polysomnographic recordings, may be considerably increased in individuals suffering from insomnia (**b**) and responsible for the perception of disrupted and non-restorative sleep. Please note that figure only represents a hypothetical and not a data driven depiction of the concept

if a bottlenose dolphin is deprived of slow wave sleep in one hemisphere, an increase in sleep pressure is only observed in this hemisphere [39]. In turn, following bi-hemispheric sleep deprivation, the animal exhibits an increase in slow wave sleep in both hemispheres.

A pivotal study, beyond the level of entire hemispheres, demonstrated 'local sleep' during wakefulness in rats. More specifically, rats had microwire arrays implanted in deep layers of the motor cortex, which recorded both the local field potentials and local multiunit activity across spontaneous sleep and wake states [45]. During extended wakefulness, cortical neurons briefly went 'offline' as in sleep, accompanied by slow waves in the local EEG. The main difference was that, during sleep, virtually all cortical neurons showed on–off oscillations in the slow wave range, whereas during a prolonged wake state, only locally distributed subsets of neurons entered off-periods, usually for shorter durations. Moreover, the increasing occurrence of local off-periods during prolonged wakefulness was associated with attention deficits and worse performance in a sugar pellet reaching task. This observation suggests that local 'islands of sleep' during wakefulness may be responsible for cognitive impairments due to sleep deprivation.

As in rats, local 'sleep' and 'wake' periods have also been observed in humans. For instance, Nobili and colleagues (2011) analyzed intracerebral recordings of five patients with therapy-resistant epilepsy, which were recorded as part of standard diagnostics prior to surgery [34]. This analysis demonstrated that also human sleep can be characterized by the coexistence of wake- and sleep-like activity patterns in different cortical areas. Particularly, a high number of local wake-like activations in the motor cortex were accompanied by patterns of deep NREM sleep in the prefrontal cortex and on the scalp. The local wake-like activations in the motor cortex during polysomnography mostly had a duration of 5–10 s, but could last up to 120 s. Together, this study demonstrates that during NREM sleep, parts of the cortex can be electrophysiologically activated while others are strongly deactivated. Interestingly, also during 'phasic' REM sleep (that is, REM sleep with a high density of rapid eye movements) wake-like EEG activation patterns similar to those observed when performing a voluntary movement were documented in intracranial recordings in humans [11]. Recent reviews provide a detailed overview of observed local aspects of sleep and wakefulness in the animal and human brain (e.g. [10, 23, 44]). Strikingly, during sleep onset, EEG activity synchronization patterns were observed to emerge locally, implying a transient coexistence of wake-like and sleep-like activity in different cortical areas [31]. This finding supports early ideas of a link between local impairments of brain synchronization and disturbances of sleep initiation in sleep disorders, like primary insomnia [30].

Sleep in insomnia disorder

Insomnia disorder is characterized by difficulties initiating or maintaining sleep being accompanied by distress and perceived negative daytime consequences. Individuals suffering from insomnia can encounter problems such as diminished productivity, fatigue, low mood and irritability [47]. Despite a complaint of substantially disturbed sleep continuity and reduced total sleep time, studies demonstrate that in many patients, overnight polysomnography shows no or only minor sleep changes [4]. Could local wakefulness during sleep be an explanation of what happens in the brain of individuals suffering from insomnia (**Fig. 1**)?

Interestingly, patients with insomnia often report a subjective perception of having been awake when being awoken out of polysomnographically determined REM sleep [16]. Earlier work demonstrated that frequently observed spontaneous arousals (that is, a transient abrupt change of frequency in the EEG) are more frequently experienced as changes into the wake state when occurring during REM sleep compared to arousals during NREM sleep [1, 8, 24]. This corresponds to the finding of increased (micro-)arousals during REM sleep and a positive correlation between sleep mis-

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Local sleep and wakefulness—the concept and its potential for the understanding and treatment of insomnia disorder

Abstract

In ancient mythology, sleep was often regarded as an inactive state, close to death. Research in the past century has, however, demonstrated that the brain is highly active and oscillates through well-defined stages during sleep. Yet it is only over the past decade that accumulating evidence has shown that sleep and wake processes can occur simultaneously, localized in distinct areas of the brain. The aim of this article is to review relevant aspects of the shift from global to local concepts of sleep–wake regulation and to further translate this perspective to the clinical problem of insomnia. Animal and human studies show that local wake-like activations ('islands of wakefulness') can occur during both major sleep stages, i.e. non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Preliminary evidence suggests that higher levels of local wake-like activity, not captured in standard polysomnographic recordings, might underlie the perception of disrupted sleep or even wakefulness during polysomnographic epochs of sleep in patients with chronic insomnia. To further decipher the neural mechanisms, advanced techniques of high-density electroencephalography (hdEEG) and non-invasive brain stimulation techniques can be applied. Furthermore translating the concept of local sleep and wakefulness to the prevalent health problem of chronic insomnia might help to reduce the current mismatch between subjective sleep–wake perception and standard recordings, and might inform the development of new treatments.

Keywords

Local sleep · High-density electroencephalography · Non-invasive brain stimulation · Insomnia disorder

Lokaler Schlaf- und Wachzustand – das Konzept und sein Potenzial für Verständnis und Therapie von Insomnien

Zusammenfassung

Im antiken Griechenland und über nachfolgende Jahrhunderte wurde Schlaf oftmals als ein inaktiver Zustand mit einer Nähe zum Tod angesehen. Arbeiten im letzten Jahrhundert zeigen hingegen, dass das Gehirn im Schlaf sehr aktiv ist und durch verschiedene, gut charakterisierte Schlafstadien oszilliert. Erst in den letzten Jahren wird zunehmend deutlich, dass Schlaf- und Wachprozesse zeitgleich nebeneinander in umschriebenen Arealen des Gehirns auftreten können. Das Ziel der vorliegenden Arbeit ist es, relevante Aspekte dieses Wechsels von globalen zu lokalen Konzepten der Schlaf-Wach-Regulation weiter herauszuarbeiten und diese Perspektive weiter für den Bereich der klinisch relevanten Insomnie zu erschließen. Studien an Tieren und Menschen zeigen, dass wachähnliche Aktivierungsmuster („lokale Inseln von Wachheit") in beiden Hauptschlafstadien auftreten können, dem Non-Rapid-Eye-Movement(NREM)- und dem Rapid-Eye-Movement(REM)-Schlaf. Erste, jedoch nicht ausreichend replizierte Befunde weisen darauf hin, dass höhere Level von lokaler wachähnlicher Aktivität, die in Standardableitungen der Polysomnographie nicht erfasst werden, der oft berichteten Wahrnehmung von gestörtem Schlaf oder sogar dem Erleben von Wachheit während polysomnographischer Schlafphasen bei Patienten mit chronischer Insomnie zugrunde liegen könnten. Um die neuronalen Mechanismen lokaler Schlaf- und Wachaktivität näher zu verstehen, sind neuere Untersuchungsmethoden wie die High-Density-Elektroenzephalographie (hdEEG) oder nichtinvasive Gehirnstimulationsverfahren notwendig. Die weitere Übertragung des Konzepts lokaler Schlaf-Wach-Regulation auf das häufige Gesundheitsproblem Insomnie könnte die aktuell unzureichende Passung zwischen subjektiver Schlaf-Wach-Wahrnehmung und Standarduntersuchungsmethoden verbessern und eventuell zur Entwicklung neuer Therapieverfahren beitragen.

Schlüsselwörter

Lokaler Schlaf · High-Density-Elektroenzephalographie · Nichtinvasive Gehirnstimulation · Insomnie

perception and the duration of REM sleep in patients with insomnia [14, 15]. Along these lines, functional neuroimaging research has detected also NREM sleep abnormalities in patients with insomnia. Compared to healthy controls, patients with insomnia showed an increase in global cerebral glucose metabolism during NREM sleep as well as wakefulness and a reduced decline in the activity of wake-promoting brain regions in the transition phase from waking to NREM sleep [36]. Furthermore, regional glucose metabolism was associated with the discrepancy between subjective and polysomnographic parameters of sleep duration in healthy sleepers and patients with insomnia [22]. These findings are consistent with the hyperarousal model of insomnia positing that insomnia is characterized by a persistent (24 h) hyperarousal, including increased cognitive activity (e.g. rumination), increased emotional reactions and decreased sleepiness during the day [42].

More specifically, Riedner and colleagues [41] used topographic high density EEG (hdEEG) analyses of NREM sleep and showed that patients with insomnia had more high-frequency (high beta/low gamma) EEG activity compared to good sleeping controls [41]. The difference between the groups was widespread across the scalp, comprising frontotemporal and occipital regions. More specifically, insomnia patients showed higher local alpha activity in the sensory, premotor and primary motor areas during deep NREM sleep than controls. This suggests that during deep sleep distinct cortical areas can be relatively active in insom-

nia patients compared to controls. This locally observed overactivity may reflect local states of wakefulness contributing to the reported perception of sleep as light, wake-like and non-restorative.

Of future interest are non-invasive brain stimulation techniques that can be used to alter cortical activity in specific regions. For example, in transcranial direct current stimulation (tDCS), a weak electrical current is applied through electrodes placed on the scalp. Anodal stimulation can be used to increase activity, whereas cathodal stimulation is used to decrease activity [33]. This approach is promising for insomnia research because it could be used to decrease activity in hyperactive brain regions during sleep. However, a recent study did not demonstrate any sleep–wake effects in patients with insomnia [18], using a tDCS protocol previously shown to induce effects in healthy controls [17]. This indicates that tDCS effects are brain state specific and that future research is needed to investigate whether tDCS might have any therapeutic potential. Of particular interest, other studies have begun to investigate the effects of auditory stimulation during sleep [32]. These and other stimulation techniques can be used to further explore concepts of altered arousal during sleep from global to local levels of activity and may be used to synchronize a desynchronized sleeping brain with local 'islands of wakefulness' in patients with primary insomnia.

Implications and conclusions

Recent work suggests that sleep could be perceived as non-restorative due to local 'islands of wakefulness' during sleep. Particularly, patients with insomnia, who have the subjective perception of being awake during polysomnographic sleep, may therefore report what is going on in their brain: namely locally occurring wake-like activity during sleep. Future studies are needed to further explore the neural mechanisms of non-restorative sleep beyond the level of standard polysomnography. These studies might include hdEEG and brain imaging studies across sleep–wake states. Furthermore, interventional studies using non-invasive brain stimulation techniques, such as direct current or acoustic stimulation, might be used to test these concepts and, potentially, develop new treatments by orchestrating the sleeping brain and suppressing local wake-like phenomenons for the reinstatement of a restorative sleep.

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Compliance with ethical guidelines

Conflict of interest. L. Stålesen Ramfjord, E. Hertenstein, K. Fehér, C. Mikutta, C. Schneider, C. Nissen and J.G. Maier declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

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