

Editorial overview: Physiology of sleep

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When the idea of this issue was conceived, the obvious questions were first, whether or not we really need any more reviews on sleep and second, if there had been enough advances in the past couple of years to merit a whole new issue on sleep. We thought that the answer to both questions was yes. While there have been a number of excellent reviews of various aspects of sleep physiology in the past few years, there were two groups of readers for whom we thought such an issue would be useful. First, there are established sleep researchers, for whom the opinions of colleagues are (almost) always of interest. There remain, however, many outstanding questions that need to be addressed in the field, and it is not always easy to insert opinions into a classical review. The second group is those who simply want to learn more about sleep. These may be researchers who are thinking about moving into the field, or people from other fields who have an interest in sleep. We thought that it would be invaluable for both groups to have a collection of opinion pieces that not only update the current state of play but also give insight into what might be of interest in the future.

We made the deliberate decision not to concentrate on abnormalities of sleep, or sleep dysfunction in clinical disorders. Although some articles include disorders, the main focus of the collection of articles in this issue was to provide an update on the mechanisms and functions of sleep with the core topic being the overarching question 'Why do we sleep?'. This question has two distinct aspects related to the ambiguity of the word 'why' that, depending on the context, can mean either 'how come' or 'what for'.

Addressing both sides of the 'why' of sleep is not a trivial task, and requires a broad range of interdisciplinary approaches to address a wide range of second-order questions that we grouped as follows. The first of these is 'how are sleep and wake states controlled, maintained and regulated by the brain?' To study this, a wide range of molecular, genetic and neurophysiological tools are used to dissect, characterise and manipulate candidate sleep- or wake- promoting neuronal populations in the brain. The second question is 'when and how do animals sleep?'. This is tackled using direct observations and manipulations of environmental variables, circadian assays and phylogenetic studies. The third question is 'What makes sleep different from wakefulness and other behavioural states?', or, in other words, 'How do we define sleep?'. To address this question, a variety of physiological measures (which includes everything from gene expression and hormonal levels, to sensory functions and direct measurement of brain activity) are typically collected and compared between states of vigilance. Finally, the key question that stirs lively debates and stimulates novel hypotheses is 'What is the biological purpose of sleep?'. Popular experimental paradigms used to study

this question include perturbation approaches, direct stimulation, and genetic tools. Using these techniques, much knowledge has been accumulated and a great deal of progress has been made over the last decades. Yet still the question of why sleep exists in the first place remains unanswered. Clearly, to address this question that challenges the field of sleep research, new knowledge, and, of course, novel conceptual advances are necessary. We hope that, by collecting together information and opinions from a diverse group of people in the field, these articles will help to consolidate knowledge and stimulate ideas.

In the current issue, the mechanistic question of how sleep is generated is addressed by several articles in which the state of the art in neuroanatomy and neurochemistry of sleep-wake states is summarised. These contributions do not merely provide a catalogue of relevant brain areas involved in sleep-wake switching, but also consider them in a wider context, such as the link with energy metabolism or motivation. Heinrich Gompf and Christelle Anaclet provide a comprehensive overview of brain structures involved in sleep-wake control. The key conclusion that they reach is that sleep-wake states are triggered and maintained through a dynamic interaction between many distributed circuits across the brain. This view opens novel opportunities for future studies and highlights important challenges for understanding how precisely sleep is controlled. There is increasing realisation that the brain areas involved in sleep-wake control are also responsible for other homeostatic functions. This brings with it new challenges. For example, Edward Harding, Nicholas Franks and William Wisden provide new insights into the neuroanatomical and functional links between sleep and body temperature regulation, which are thought to play an important role in sleep functions that include energy homeostasis or its restorative role. The relationship between sleep and metabolism is discussed further by Antoine Adamantidis and Denis Burdakov, who provide a focused overview of the hypothalamic circuitry, involved in nutrient sensing. As feeding is possible only during waking, during sleep animals are involuntarily fasting. Since hunger is a powerful wake-promoting factor, understanding neurophysiological substrates of how glucose levels regulate sleep-wake propensity is of great importance. Many factors at any given time point collectively contribute to whether the animal should be awake or asleep, as there are many competing biological drives that must be balanced. This point is discussed specifically with respect to neurobiological substrates of motivated behaviours by Maria Sotelo, Jean Tyan, James Dzera and Ada Eban-Rothschild. Of course, the time of day also matters greatly, as numerous aspects of physiology and behaviour are under a strict control – both from the endogenous circadian rhythmicity, as well as from predictable changes in the environment. One notable example is food availability and the need to align foraging behaviours and sleep to the 24-h rhythm. This is discussed by Rebecca Northeast, Vladyslav Vyazovskiy and David Bechtold. The circadian regulation of sleep is approached further in the contribution by Tom Deboer, who discusses the molecular and neuroanatomical substrates for the relationship

between circadian clock and sleep mechanisms. Mathematical modelling studies have always played a key role in explaining existing data and for formulating testable predictions, and a comprehensive overview of modelling studies used in sleep research is provided by John Abel, Kimaya Lecomte, Melissa St Hilaire and Elizabeth Klernan. The role of environmental factors is crucially important for understanding how sleep, wake and circadian rhythms are controlled, and Shu Tam, David Bannerman and Stuart Peirson present a novel and intriguing perspective of how and why light affects alertness and behavioural performance. The roles of ecological factors are discussed further in the contribution of Gianina Ungurean, Jacqueline van der Meij, Niels Rattenborg and John Lesku, which makes an important point that sleep-wake behaviour is much more plastic and flexible than it is typically thought. They consider why it is essential to consider sleep in a naturalistic setting, and why it is also important to study sleep in a broad variety of species. Then, Kathleen Reinhardt addresses one specific example of how novel insights into sleep evolution and function can be achieved, by studying primates in the wild. Remarkably little is known about sleep in natural environment, where the need to sleep must be balanced against environmental pressures. She posits that such studies are of crucial importance. Indeed, a phylogenetic approach has also been instrumental in the field of sleep research particularly as it opens up opportunities that arise as a result of establishing novel experimental animal models. To this end, Declan Lyons and Jason Rihel discuss the use of non-mammalian models in sleep research, focusing specifically on flies and zebrafish. They conclude that intriguing similarities exist with respect to fundamental aspect of sleep regulation between mammals and non-mammals and much can be learned from simple animals.

The question of how we define sleep is particularly important. The definition of sleep is classically based on a set of behavioural and electrophysiological criteria, most of which are neither strictly necessary nor sufficient. Even more importantly, the question remains as to whether (and to what extent) the phenomena that define sleep are functionally necessary. Maria Sanchez-Vives discusses the key electrophysiological signatures of sleep, focusing on the slow oscillation – the cellular and network counterpart of sleep slow waves. Eduarda Susin and Alain Destexhe then provide novel insights into cell specific dynamics during wake and sleep, and establish novel roles for excitation and inhibition in shaping brain oscillations during sleep. Next, Mojtaba Bandarabadi, Anne Vassalli and Mehdi Tafti provide an overview of the paradigm-shifting idea of sleep being a default state of neural networks. This influential concept provides not only an elegant explanation for a wide range of phenomena, such as local sleep control, but also offers a unique experimental model for addressing the origin and function of sleep oscillation. Of course, it is essential to combine *in vitro* models with observations made at the level of the whole brain and the whole organism, and Chen Song and Enzo Tagliazucchi give an overview of how using multimodal imaging approaches of the

human brain provide novel knowledge that links local and global sleep control, and how this helps to approach sleep functions. The meaning of brain activity patterns during sleep is hotly debated. One influential idea is that they reflect brain state which corresponds to a partial or complete disconnection from the outside world. This topic is addressed by Thomas Andrillon and Sid Kouider in their contribution, which provides an up-to-date account of neurophysiological substrates of sensory (de)coupling during sleep.

An intriguing conundrum remains that whilst the two sleep states – NREM and REM - are characteristically different with respect to brain activity and bodily functions they also share important similarities, such as their behavioural manifestations and diminished sensory responsiveness. Mitsuaki Kashiwagi and Yu Hayashi provide an overview of the development and phylogeny of REM sleep, and argue that further molecular and functional studies are necessary to provide better understanding of its origin and relationship to NREM sleep. Further to this, Paul-Antoine Libourel and Baptiste Barrillot provide a detailed and critical overview of the recent studies that suggest the existence of at least two sleep states in reptiles. Clearly, further work is needed in this area, and it is essential that the existing criteria for defining REM sleep are viewed in the context of phylogeny as well as pathology. The latter case is discussed in the contribution of Christelle Peyron, Sébastien Arthaud, Manon Villalba and Patrice Fort where the authors argue for the importance of recording and analysis of various measures for REM sleep, particularly in studies on animal models of human disease. What is often ignored is that NREM and REM sleep are not simply brain states as they are sometimes portrayed, but they have important peripheral manifestations. To this end, Giovanna Zoccoli and Roberto Amici remind us of the importance of the autonomic nervous system in maintaining bodily homeostasis, and provide an overview of sleep-state dependent autonomic regulation of the immune system, respiratory and cardiovascular functions as well as thermoregulation and energy homeostasis.

Although much remains to be learned about bodily functions of sleep, the majority of current theories focus on brain mechanisms. Sleep disruptions are typical for a wide range of brain disorders and also manifest during healthy ageing. Laura McKillop and Vladyslav Vyazovskiy provide a critical comparison of human and rodent studies on the relationship between sleep and ageing, and conclude that caution is warranted when making direct inferences without taking into account methodological differences and the role of the environment. Having said that, animal studies clearly have been instrumental for making important advances in understanding sleep physiology during ontogeny. In their fascinating review on sleep development, Mark Blumberg, James Dooley and Greta Sokoloff discuss recent findings which suggest an importance of sleep during early ontogeny in the formation of sensorimotor maps. Arguably, sleep disruption in early age, and especially during adolescence, which is associated with massive synaptic remodelling in the brain, can lead to

negative consequences later in the adulthood. To address this, Chiara Fontanellaz-Castiglione, Andjela Markovic and Leila Tarokh discuss the role of sleep during adolescence in brain maturation, while Rachel Sharman and Gaby Illingworth urge taking school time into consideration, given an important role of sleep and circadian rhythms in learning and performance.

Although the specific neurophysiological mechanisms underpinning the role of sleep in brain plasticity remains unclear, one possibility is that slow waves are of particular importance. Igor Timofeev, Sarah Schoch, Monique LeBourgeois, Reto Huber, Brady Riedner and Salome Kurth provide an overview of spatio-temporal dynamics of sleep slow waves and discuss how topographical changes in brain oscillations mirror brain development. There is considerable evidence that sleep plays a role in neural plasticity not only during development, but also in adulthood. Michele Bellesi and Luisa de Vivo provide an overview of recent findings across species and ages which suggest that sleep and wake are associated with ultrastructural synaptic changes. While the biological significance of these findings remains to be determined, substantial evidence points to an important role of sleep in various aspects of learning and memory. In their contribution, Anumita Samanta, Alejandra Alonso and Lisa Genzel discuss the role of neuromodulators in reactivation of memory traces during sleep. The role of state-dependent changes in neurotransmitter milieu is important in this context, as especially highlighted by different roles of NREM and REM sleep in the slow development of motor skills and schema-related learning, as discussed in the contribution by Sofia Isabel Ribeiro Pereira and Penny Lewis, and in emotional memory, overviewed by Stéphanie Trouche, Marco Pompili and Gabrielle Girardeau. The circadian rhythms should not be forgotten in this context, and Marcos Frank presents an updated overview of a State-Clock Model, which attempts to account for the role of endogenous circadian rhythmicity into sleep-wake dependent modulation of synaptic plasticity.

While there is no doubt that sleep plays an important role in neural function and especially synaptic plasticity and learning, its contribution to fundamental cellular functions remains an important area of study. Natalie Hauglund, Chiara Pavan and Maiken Nedergaard provide an up-to-date account on the influential hypothesis that sleep provides an opportunity for clearing the brain from the potential neurotoxic products of metabolism that accumulate during waking. An overview of the glymphatic system is provided, and an important emphasis is made on its role in the amyloid beta removal. Impaired protein homeostasis is a hallmark of neurodegenerative disorders, and Julie Williams and Nirinjini Naidoo then write specifically about the intriguing bidirectional link between sleep regulation and endoplasmic reticulum stress, drawing evidence from both rodent and fly literature. Expounding on this topic, Tarja Porkka-Heiskanen and Henna-Kaisa Wigren discuss the molecular underpinnings of sleep

regulation, focusing specifically on fly models and on the recently proposed roles of sleep in redox homeostasis and immune function.

Sleep research is a relatively new field, and it is perhaps not surprising that increased knowledge and novel insights generate more questions that will need to be addressed in the future. The field has been always driven by the opportunities that arise with the advent of novel technologies and methodological tools, and has advanced by considering new concepts and models (no matter how wrong they are or turned out to be). It is becoming increasingly clear that a holistic approach will be necessary to make a substantial progress, and the view that sleep can be understood using laboratory studies in only a few model organisms is now clearly outdated. First and foremost, sleep is a behavioural state. We argue that it is impossible to understand the biological meaning of any behaviour when it is taken out of a naturalistic context and studied under conditions radically different from those in which it evolved. Sleep is a physiological phenomenon, and bodily functions associated with sleep should be considered as important as investigating changes in the brain. The existing theories and hypotheses, and the efforts put by many of our colleagues in answering the questions of ‘how come?’ and ‘what for?’ of sleep over the last decades have taken us far, but there is still a long way to go before sleep ceases to be a mystery.