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Current Opinion in Behavioral Sciences

Editorial overview: Sleep and cognition

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Current Opinion in Behavioral Sciences 2020, **33**: xx–yy

https://doi.org/10.1016/j.cobeha.2020.04.002

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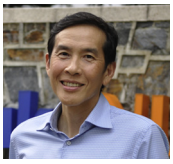

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Michael Chee is Professor and Director of the Centre for Sleep and Cognition at the Yong Loo Lin School of Medicine, National University of Singapore. He graduated with a MBBS from the National University of Singapore in 1983?and practiced as a neurologist for several years before turning to cognitive neuroscience. Following a short stint at the MGH-NMR Centre in Boston, he characterized the bilingual brain using fMRI before settling into the functional imaging of sleep deprived brain, specifically probing diminished working memory and capacity to process visual information, reduced distractor suppression and altered decision making. This was followed by work on altered static and dynamic functional connectivity in sleep deprivation and its relationship with sleepy eye-closures. More recently he probed the effects of different schedules of multi-night sleep restriction in adolescents and its ramifications including those on memory and learning. He is a multiple recipient of the National Medical Research Council of Singapore's top tier STaR award for clinician scientists, has received the National Outstanding Clinician Scientist Award and is an inaugural Fellow of the Organization for Human Brain Mapping. He serves as an Associate Editor for Sleep in addition to several other editorial boards.

Understanding how sleep influences cognition, which aspects of sleep are relevant to cognitive performance, and appreciating how disturbed, irregular or restricted sleep erodes cognitive performance are themes addressed in this collection of reviews and opinion pieces on sleep and cognition. We sincerely hope that these contributions will inspire scientists to consider sleep as a key component in their plans to conduct human and animal cognition studies.

Now that sleep is recognized as an important component in the dynamics of memory consolidation, how manipulating sleep can improve memory has become an enduring topic of interest. In this respect, Targeted Memory Reactivation (TMR) in which recent memories are triggered for further processing through presentation of learning-related stimuli during sleep, is a promising way to probe sleep-related memory consolidation mechanisms. Witkowski, Schechtman and Paller discuss how TMR can be used to examine two seemingly contrasting functions of memory: remembering specific experiences and generalizing across many experiences. Although it is hypothesized that the hippocampus allows for fast learning of unique episodic memories, while the cortex slowly extracts regularities from overlapping representations, it remains to be ascertained whether sleep is equally beneficial to both. In this context, the authors explain how TMR can help advance our understanding of the balance between specificity and generalization in memory consolidation. Besides reactivating recently encoded memoranda, re-exposure to previously consolidated memory traces renders memories labile again, and consequently vulnerable to disruption or alteration. Simon, Gomez and Nadel discuss how processing information during sleep may play an essential role in restabilizing the memories transformed across the phases of reactivation, modification and re-consolidation. In their view, TMR interventions have the potential to directly engineer reconsolidation during sleep, a prospect to be investigated further.

Although sleep plays an important role in systems memory consolidation, it should not be ignored that similar processes can take place during wakefulness. In this respect, evidence for rapid neocortical plasticity raises questions about the timescales at which systems consolidation occurs, and also the role played by sleep. These questions are brought forward and discussed by Pöhlchen and Schönauer who dwell on new ways to image and manipulate memory consolidation-related neural activity. They also question the strict distinction made between memory storage sites, and the timescale of involvement of the different neurophysiological systems. Altogether, this should lead us to think critically about the where and when of sleep-dependent memory processes.

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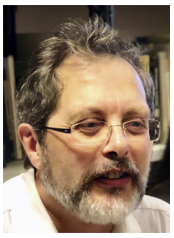

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Philippe Peigneux is Professor of Clinical Neuropsychology and Director of the Neuropsychology and Functional Neuroimaging Research Unit (UR2NF) at Université Libre de Bruxelles (ULB), Belgium. He is the former President (2012–2016) of the European Sleep Research Society (ESRS). His research is mainly focused on investigating the relationships between sleep and memory consolidation processes and their neurophysiological underpinnings, and in a wider perspective between cognitive processes and vigilance states, including sleep and biological rhythms, both in healthy and pathological conditions. His studies are conducted using a combination of cognitive approaches and advanced functional magnetic resonance (fMRI), electroencephalography (EEG), magnetoencephalography (MEG) and Near-InfraRed Spectroscopy (fNIRS).

On another note, emotions and sleep are closely intertwined; clinical studies show that sleep disturbances are core symptoms in many affective disorders. Conversely, healthy sleep helps regulate emotions and consolidate memories. It is therefore tempting to try manipulating sleep to improve symptoms in maladaptive pathologies. Talamini and Juan discuss the opportunities for direct applications in sleep considering our increasing understanding of the electrophysiological mechanisms underlying restorative sleep. In particular, they examine the potential of TMR phase-locked to slow oscillations dynamics to manipulate emotional processing and memories during sleep. Although still preliminary, such developments may pave the way to novel therapeutic applications in the field. Relatedly, stress at or around the time of memory encoding influences memory networks in a manner that modulates subsequent memory consolidation. Here, Kim and Payne focus their contribution on how sleep and stress interact to affect the tagging of salient memories, expanding on how the interleaving of SWS and REM impacts memory consolidation through effects on memory replay and selective consolidation of emotional content. They expound on the brain structures and neuromodulators involved and suggest that this mechanistic framework may also be relevant with other means of making memories more salient such as reward value and novelty.

The role of the autonomic nervous system has been long neglected in the debate about sleep and cognition. For example, that sleep and interoception are tightly connected to our physical and mental well-being. This is a subject discussed by Wei and Van Someren who expound on how interoceptive afferents that are essential to physiological homeostatic control influence momentary affect, cognition, motivation, and conscious experience. Their review shows that sleep and sensory processes entail complex, dynamical relations within each modality of interoception, including thermoception, nociception, visceral sensations, and subjective feelings about these sensations. A better understanding of these complex relationships could benefit the management of functional somatic symptoms, chronic pain, and sleep disorders.

Along the line that there are significant non-cortical influences on sleep which affect cognition, Whitehurst, Chen, Naji and Mednick review how the behaviour of the autonomic nervous system during sleep impacts memory, extending prior work linking autonomic nervous system and cognition. For instance, increased heart rate variability during sleep appears to be positively associated with several memory measures. As well, short bursts in speeded heart rate are preceded by changes in EEG spectral power in delta and sigma bands. The latter correspond to SWA and spindles, which have clear positive associations with learning and memory. Differences in measures used to describe heart rate variability as well as the time scales used to determine these variations across publications indicates that there is room for more clarifying research, but this area certainly appears promising. Another way to explore autonomic system effects on brain physiology is fMRI, an approach with both advantages and pitfalls as discussed by Duyn, Ozbay, Chang, and Picchioni. Changes in CNS arousal that occur with sleep onset and are intertwined with changes in respiratory rate, depth and heart rate. Present approaches to analysing fMRI signals involve removing the latter signals but as the mechanistic basis for such signals is still unclear, it is uncertain how best to characterize fMRI BOLD signal changes during wake–sleep transitions. In addition to state-related cortical activity alterations that affect cerebral blood flow, other mechanisms such as circulating vasoactive agents and neurogenic control of blood vessel tone can affect the fMRI signal. For example, blood vessel resistance is influenced by state-

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related changes in autonomic nervous system function. In this context, the authors discuss how parasympathetic and sympathetic influences change in sleep, and how these various influences affect the interpretation of functional connectivity data obtained when a participant is not performing a task (and may be falling asleep). These are all facets that need to be taken into consideration for a proper interpretation of fMRI data.

Eventually, the outcomes most persons are concerned with relate to real world performance in humans. Hershner reviews how academic performance is influenced by sleep duration, quality, consistency, timing, and the presence of sleep disorders affects students' Grade Point Average. While the latter is a complex construct affected by multiple variables, including intelligence, motivation, personality, socio-economic status and health, it is a marker that parents and students care about. Modifying students' sleep behaviour may contribute to achieving better outcomes. Subjective sleep quality appears to be more predictive of GPA than sleep duration even though the latter is the focus of many efforts to improve sleep, for example starting school later. Besides time of day issues, consistency has emerged as a variable of interest, since those able to keep to a regular of sleep-wake pattern perform better. Fonseca and Genzel approach the topic of sleep and its effect on adolescent cognition by examining the same sleep factors but through a broader set of indicators, and through a different lens involving complementary studies. In an expanded section on chronotype, they review evidence that habitual early sleeping is a feature of higher achieving students from secondary to medical school. They also point out that variations in chronotype across the population suggest that an optimal school schedule should take into account the students' individual chronotype. This logically leads to the interesting concept of making school schedules more flexible and individually customized to a student's preferred sleep pattern.

Nowadays, a well-known problem with adolescents during school time is reduced sleep duration due to late time in bed. To provide an empirically supported basis for customizing sleep for different adolescents, Lo and Chee examine experimental studies of multi-night sleep restriction in adolescents under different levels of sleep restriction. These studies show a cumulative decline in vigilance following successive nights of sleep restriction, with incomplete recovery over a simulated weekend. The sleep dose effect appears non-linear, and naps may have outsized benefits when total sleep time over 24 hours is restricted. However, how to optimally deliver them remains an open question. Sleep restriction that precedes learning can impair the encoding of individual sets of stimuli as well as an organized body of facts. In contrast, consolidation appears less affected, perhaps as a result of the ability of young persons to recover SWS even in the setting of restricted sleep. To better customize sleep for diverse needs, systematically collected data from sleep wearables could be used to empower individuals to make their own judgements about how to obtain adequate sleep.

Another topic of interest is the relation between sleep and trait-like cognitive abilities. Can we predict cognitive performance and intelligence from sleep measures? Ujima, Bódizs and Dresler suggest a small but consistent predictive power comes from considering chronotype and sleep spindles. They present the case in which 'morningness' corresponds to stronger academic performance but lower cognitive ability. Slow oscillations have been strongly linked to declarative memory in experimental studies and their decline in later life. However, in children and young adults, it appears that only sleep spindles have a consistent association with intelligence. Their profusion through the night calls for automated measurement methods but this is difficult to realize in practice as spindles exhibit heterogeneity at multiple levels and the validity of automatic detectors has yet to be conclusively demonstrated. The theme of sleep spindles and cognitive ability is further dealt with by Hoedlmoser who details developmental shifts in topography and frequency of sleep spindles in childhood and adolescents and describes how systematic changes in the evolution of this sleep feature relate to the maturation of cognitive ability in teens. Increased preponderance of fast spindles with maturation seems to account for changes in the efficiency of sleep-related declarative memory consolidation processes. The importance of longitudinal studies is emphasized as well as the importance of developing consensus in how 'fast' and 'slow' spindles are delineated. Finally, a third article addresses the association between sleep spindles and cognitive ability. Smith, Fang, Thompson and Fogel discuss how this component of non-rapid eye movement (NREM) sleep is associated with sleep-dependent brain processes related to trait-like fluid intelligence. They highlight that interindividual differences already arise during early childhood development, and that changes in spindle characteristics with age could be representative of developmental differences in thalamocortical networks, eventually resulting in measurable interindividual differences in behavioral performance.

Back to humans but now at the other extreme of life, there is increasing evidence for associations between typical age-related changes in sleep and brain structure. Baillet and Schmidt review studies exploring the association between neuroimaging markers of brain structure and sleep-wake parameters in healthy older adults. They cover associations between sleep questionnaire reports, PSG studies and actigraphically defined rest-activity rhythm disruptions with both local and diffuse changes in brain structure. Their review of the literature highlights large variations in associative strength across

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studies. They also discuss why the contribution of specific sleep-wake regulating mechanisms that affect human cognitive performance and 'brain fitness' need to be disentangled. Complementing the article on the modulatory influence of sleep on the brains of healthy old adults, Alfini, Tzuang, Owusi and Spira comment on the mixed findings regarding the associations between total sleep duration and insomnia on late life cognitive function across multiple domains. In contrast, objective evidence for nocturnal sleep disruption is emerging as a clear risk factor for cognitive decline. Sleep disordered breathing heralds a higher risk of cognitive decline in older persons, perhaps modulated by APoE4 status. Poorer quality, disrupted sleep as well as either extreme short or long sleep duration, are all associated with a diverse mix of adverse neuroimaging findings including cortical thinning, reduced microstructural integrity and altered functional connectivity. While associations have been established, the broader question of whether sleep mediates the severity of these changes remains to be clarified. It also remains to be seen if measures taken to improve sleep or sleep disordered breathing have long term benefits. Till then, the heterogeneity of present studies poses challenges in the broader interpretation and application of state-of-the-art findings to practice.

In a related manner, Chappel-Farley, Lui, Dave, Chen and Mander approach the narrower issue of insomnia in older persons and cognitive decline by taking a deep dive into the possible underlying mechanisms by which objective short sleep might contribute to the accumulation of beta-amyloid and tau in the brain. Their review posits that cortical arousal in cortical, physiological and emotive-cognitive forms serves to act to upregulate HPA axis activity, increase production and reduce clearance of molecules that enhance neurodegeneration as well as increase inflammation. Following their conclusions, much remains to be explored when seeking to link each aspect of hyperarousal to AD pathophysiology.

Finally, we have to realize that investigating the relationships between sleep and cognition is not an area restricted to human studies. Bo'dizs, Kis, Ga'csi and Topa'l discuss how sleep in dogs is a promising non-invasive translational model of human cognitive neuroscience. They review emerging studies on the relationships between sleep and cognition in dogs, and nicely provide insight into canine sleep and sleep-related physiological and cognitive and behavioural phenomena. It is fascinating to realize how dogs like humans have well-defined behavioural and polygraphic criteria of sleep. For example, they too exhibit sleep homeostasis, diurnal pattern of activity, circadian rhythms and environmentally shaped wake–sleep structure, sleep-related memory improvement, as well as specific sleep disorders and age-dependent changes in cognition and sleep. Along a similar vein, van der Meij, Ungurean, Rattenborg and Beckers offer a birds' brain view on the evolution of sleep in relation to memory. The approach is enlightening as most sleep-related memory consolidation theories are primarily based on studies in a few mammalian species. Here the authors show that recent evidence from research in birds who exhibit sleep states that are in most respects similar to those found in mammals (despite being distantly related) suggests that the way some types of memories are consolidated during sleep might be different in vertebrates other than mammals. Hence, this review shows how studying non-mammalian taxa can enhance and refine our understanding of sleep's role in memory, and their neurophysiological underpinnings.

In conclusion, the guest editors wish to thank our authors for an excellent collection of articles, that we hope will spur interested readers not only to gain knowledge but to also acquaint themselves with ongoing debates and crucial questions that remain to be addressed in the field. To paraphrase the pioneering sleep researcher Michel Jouvet: "Happy those who enter the field of sleep as so much remains to be discovered and understood"!

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