



## In Focus

## All You Need Is Sleep

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## 1. Introduction

In 21st century, the century when the humanity hopes to embark on interplanetary travel, we are yet to fully reach an understanding of our very own idiosyncratic *terra incognita* – the human sleep. Sleep is a highly conserved evolutionary process that constitutes approximately one third of our life, and the lack or inadequate sleep may lead to impairment across multiple cognitive domains (Tononi and Cirelli, 2014; Lim and Dinges, 2010). Sleep deprivation also leads to aberrant brain functioning, immunological and metabolic collapse, and if it is sufficiently prolonged it will ultimately lead to death (Tononi and Cirelli, 2014). Moreover, many sleep disorders are associated with major neuropsychiatric and neurodegenerative disorders (Emamian et al., 2016; Rosenzweig et al., 2015), and the duality of this link is further evident from interrelated improvements, or refractoriness of both, during the treatment. In a landmark study by Kuhn et al. (2016) an increase in homeostatic plasticity (overall synaptic strength) and a partial occlusion of associative plasticity (transmission across single synapses) after sleep deprivation compared with sleep is demonstrated (Kuhn et al., 2016). This study adds another small but important step towards evidence for the synaptic homeostasis hypothesis of sleep–wake regulation (Tononi and Cirelli, 2014). Combined, its results indicate that sleep may act to recalibrate synaptic plasticity in the human cortex and hence, to enable further plasticity during ensuing wakefulness (Kuhn et al., 2016). *Dormio ergo sum* (Latin), or perhaps, I exist/think/feel because I sleep.

## 2. Sleep and Structural Brain Plasticity

Study by Kuhn et al. (2016) also adds to a growing body of evidence from animal and human studies that support a close relationship be-

tween structural brain plasticity, and hence its functioning, and the sleep–wake cycle (Tononi and Cirelli, 2014). In addition to possible alterations in synaptic volume and number, significant changes in the interstitial brain space during sleep have also been shown (Xie et al., 2013). For example, a recently discovered glymphatic system appears to act during sleep as a waste clearance system for neurotoxic waste products, including  $\beta$ -amyloid (Jessen et al., 2015). However, whilst functional neuroimaging techniques have accelerated progress in various fields of neuroscience, their usefulness in the field of sleep has been somewhat marred by technical difficulties, such as noisy scanner environment and uncomfortable coils, all preventing imaging of habitual sleep in subjects. Nonetheless, with further engineering advances in the field, and with the use of modern functional neuroimaging (e.g. resting state functional neuroimaging) combined with neurophysiological methods (e.g. electroencephalography (EEG) and magnetoencephalography (MEG)) with their advantages in spatial and timely resolution, biomarker availability, and patient comfort, should help to accelerate our understanding of the very building units of sleep, and its links to other debilitating brain disorders.

## 3. Nuclear Medicine Asleep in Sleep Research?

Nuclear medicine neuroimaging methods, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), have become regular part of clinical routine in many bigger neuroimaging centers. They are by large considered safe, and as such they might have strong potential for future sleep research (Dang-Vu et al., 2014). However, a lack of studies at the interface of nuclear medicine and sleep research is even more profound and beguiling by comparison to that of other types of neuroimaging (Otte et al., 2002). For example, at date of submission of this in focus article, MEDLINE yielded 20,183 results on “sleep AND EEG”, but only 315 on “sleep AND SPECT” and 480 on “sleep AND PET”. By contrast, “sleep AND fMRI” yielded 2,642 results, although the loud fMRI environment continues to present a serious obstacle for investigations during sleep. To date several PET and SPECT tracers show an interesting potential for use in sleep research. For example, the SPECT brain perfusion tracer, <sup>99m</sup>Tc-labelled tracer N,N'-1,2-ethylene-diylbis-L-cysteine diethyl ester dihydrochloride (ECD) could be one good candidate, with a physical half-life of 6.0 h. This tracer is known to get trapped in the neurons, and it is not further metabolized in the brain. This means that its distribution indicates the status of brain perfusion shortly after injection, i.e., the perfusion state is “frozen”, whereas the scan can be performed after

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the patient is awake again some hours later. This tracer also allows for multiple scans per night by increasing the doses from scan A to scan B. A more favorable approach with better image quality is the split-dose approach; in this, repeated scans are performed with an interval between two injections of the tracer of at least 1 h and with half of the recommended activity injected for each of the two scans (Audenaert et al., 2000). This approach could also be used to assess intra-individual changes in brain perfusion during and after sleep. Similarly, the PET brain metabolism tracer  $^{18}\text{F}$ -FDG is another interesting candidate for future sleep research, with further advantage of high spatial resolution. This tracer is known to be transported via glucose carrier into the cell and then phosphorylated into  $^{18}\text{F}$ -FDG-phosphate, with no further metabolic changes. Apart from  $^{18}\text{F}$ -FDG and  $^{99\text{mTc}}$ -ECD tracers, a variety of additional radioligands that specifically target neurotransmitters that are highly implicated in sleep, or sleep control and cognition (e.g. acetylcholine, serotonin, and dopamine) are increasingly available on the market, for in detail review see Dang-Vu et al. (2014).

#### 4. Conclusion

Sleep serves a crucial restorative function for the brain, and clarifying the neurobiological effects of sleep is an important goal in the basic and clinical neurosciences. The onus is now on the wider neuroimaging and bioengineering society to undertake bolder and more demanding multimodal approaches in order to contribute to highly needed advances in the field of sleep research.

#### Disclosure

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