



## Neuroscience Reviews: Sleep-Wake Cycles

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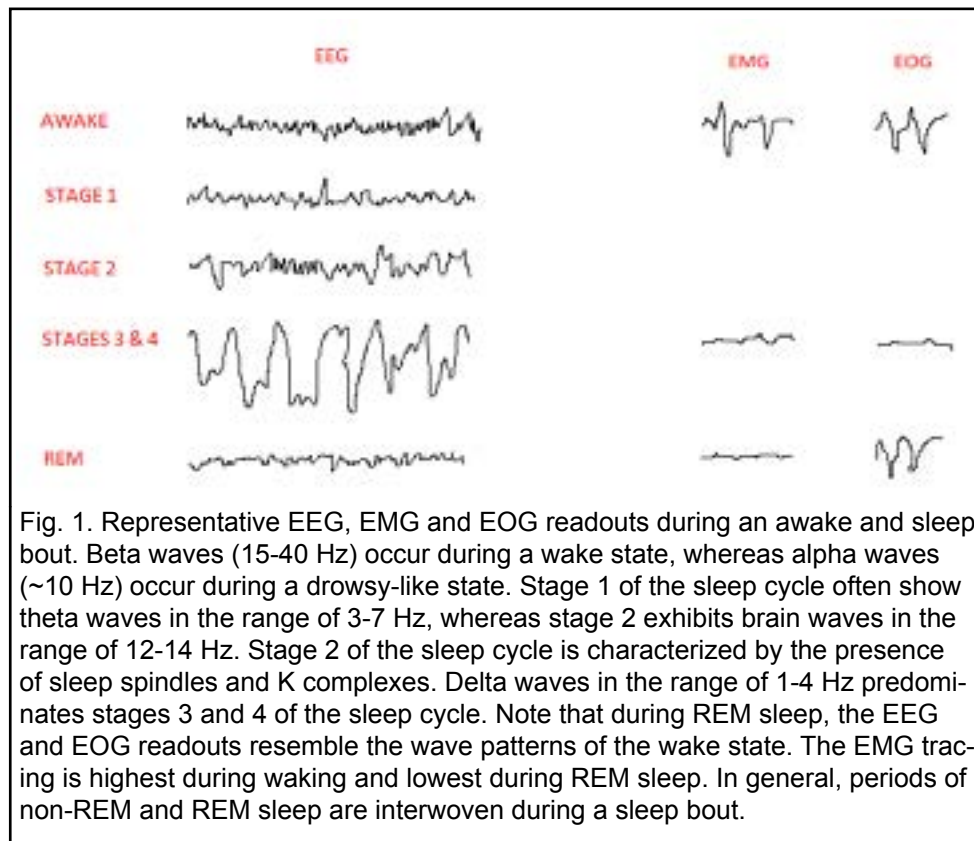
Sleep is a ubiquitous physiological process generated by the brain of vertebrate and invertebrate species. The widespread phenomenon of sleep suggests a dynamic process of brain activity that has evolved to have a functional relationship to metabolism, reproduction and/or survival; a phenomenon that is clearly species- and age-specific. In this brief review, we discussed the neurobiology of sleep with an emphasis on its mechanisms, its functions and its relevance to human health.

### Introduction

Sleep is studied by the use of brain imaging and quantitative electroencephalogram (EEG) readouts. From these imaging techniques, we know that sleep cycles between two states or phases: rapid-eye-movement (REM) and non-REM sleep that occur at regular 90-minute intervals. Non-REM sleep has three distinct EEG stages, whereas REM sleep is characterized by skeletal-muscle hypotonia (Brown et al., 2010). It should be noted that the brain is active during both sleep phases with different bouts of neuronal activity traced to each sleep phase. For example before a person goes to sleep (i.e., eyes closed and quietly resting), his/her brain shows prominent alpha waves (~10 Hz cycles per second), whereas during non-REM sleep, the brain exhibits EEG tracings of delta waves (~1 to 4 Hz cycles per second). Thus brain activity during a relaxed, awake state is quite

different from that of the non-REM phase of sleep where the EEG shows high-voltage, slow wave epochs (Hobson, 2012). The fact that switches of brain activity correspond to changes in behavioral states indicates that sleep-awake transitions are regulated by different populations of neurons that promote behavioral arousal or sleep (Steriade et al., 1993).

Based upon EEG tracings, a desynchronized state (low voltage, fast EEG) is associated with behavioral arousal, whereas a synchronized state (high voltage, slow EEG) is linked to sleep. This pattern of brain activity is complemented by measuring muscle tone activity through the use of electromyography (EMG) recording. During non-REM sleep, skeletal muscle activity is reduced, whereas during REM sleep, there is complete loss of skeletal-muscle tone despite the EEG showing a desynchronized pattern of neural activity that is remarkably similar to the waking state



(Hobson, 2012; Lee and Dan, 2012). Another commonly used technique to map sleep bouts is the electro-oculogram (EOG) which records eye position and movement. When the brain enters a REM state of sleep, the EOG shows bilateral eye movements which dominate this particular phase of sleep, further allowing a clear-cut distinction from the wake state (Fig. 1). Other brain events observed during sleep cycles, include sleep spindles and K complexes which emerge during non-REM sleep, and theta waves which are also seen during non-REM sleep. Despite considerable knowledge about the mechanisms underlying the aforementioned brain patterns, their functional significance to sleep behavior remains poorly understood.

## Anatomy and Chemistry of Sleep

Observations from clinical work and basic science studies indicate that the brainstem and posterior hypothalamus are critical brain regions controlling sleep-wake transitions as

lesions to these structures cause excessive sleepiness (e.g., Von Economo's sleeping sickness or encephelitis lethargica), whereas lesions to the anterior hypothalamus and basal forebrain cause opposite symptoms of insomnia (Lavie, 1993). Further work by Moruzzi and Magoun implicate the ascending reticular activating system within the brainstem as a major neural circuit for maintaining wakefulness and behavioral arousal (Moruzzi and Magoun, 1949). More recent work indicates that the ventrolateral preoptic nucleus of the hypothalamus contains both sleep-promoting neurons and wake-promoting neurons that control daily transitions between a behavioral state and REM and non-REM sleep (Saper et al., 2005; Saper, 2013). It should be noted that if this hypothalamic nucleus is disturbed by biological "insults", a broad range of sleep disorders emerge in the form of insomnia, narcolepsy with cataplexy and REM sleep behavior disorder (Saper, 2013). Thus a clustering of hypothalamic neurons, in conjunction with axillary nerve cells in the brainstem, controls sleep and wake states (Fig. 2).

Given that the brainstem and hypothalamus are core components of the anatomy controlling sleep-awake transitions, a number of neurotransmitters are known to regulate these transition states. For example, acetylcholine, norepinephrine, serotonin, histamine and dopamine molecules from the ascending reticular activating system and hypothalamus promote wakefulness, whereas  $\gamma$  aminobutyric acid (GABA) and galanin from the ventrolateral preoptic nucleus of the hypothalamus promote sleep. In addition, orexin (hypocretin) molecules derived from the lateral hypothalamus maintain wakefulness as destruction of orexin-containing neurons leads to narcolepsy with cataplexy (Burgess and Scammell, 2012). With this evidence in hand, the aforementioned neurotransmitters have become appealing targets for the pharmacological treatment of several human sleep disorders.

## Human Sleep Disorders

A growing body of evidence shows that sleep loss or sleep fragmentation can have detrimental effects on a wide variety of physiological processes, including metabolism and cognition. Indeed, sleep deprivation, short sleep duration, sleep disturbances and circadian de-synchronization can lead to signs of obesity, particularly insulin resistance syndrome (Schmid et al., 2014). Furthermore,

sleep deprivation or sleep restriction can adversely affect cognitive processes, including the ability to learn and consolidate new memories (Diekelmann, 2014). There is also evidence that individuals who do not align with their endogenous circadian rhythms (e.g., shift workers or social jetlag travelers) often display signs of arterial hypertension and obesity which can lead to type 2 diabetes (Morrisette, 2013; Palagini et al., 2013). It is clear then that shortened sleep or misaligned sleep cycles can have potentially serious consequences to an individual's health.

Sleep disturbances are also linked with psychiatric and neurodegenerative disorders. For instance, disturbances in REM sleep and slow-wave sleep are associated with endogenous depression and bipolar disorder (Palagini et al., 2013), whereas chronic forms of REM sleep behavior disorder are associated with Parkinson's disease (PD) and dementia with Lewy body disease (Mahowald and Schenck, 2005; Maetzler et al., 2009; Peever et al., 2014). In this regard, sleep disturbances (e.g., REM sleep behavior disorder) are thought to be early manifestations of brain pathology (e.g., PD) which often precede the disease by at least a decade. Of potential interest, this information could be used for early diagnosis and to allow interventional therapies to begin before a severe state of disability is reached.

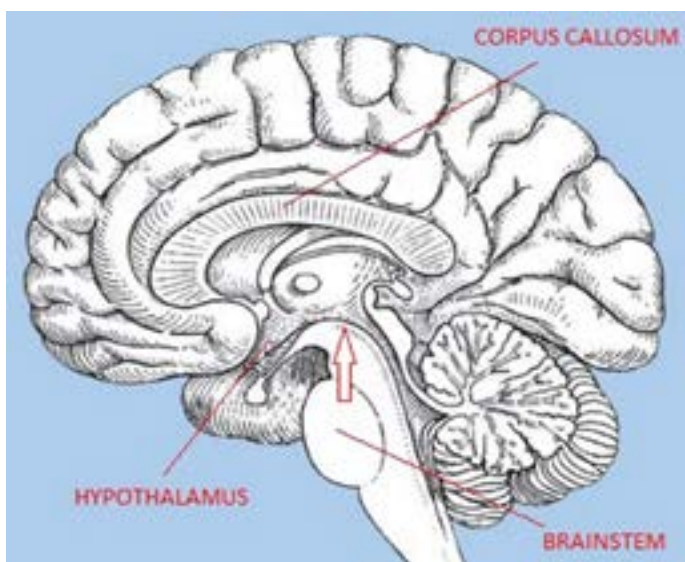


Fig. 2. A schematic diagram of the human brain illustrates key neuronal pathways governing daily sleep-wake cycles. In brief, brainstem neurons project (red arrow) to the thalamus which relays chemical signals to the cortex, the site of consciousness. Neurotransmitters such as acetylcholine, serotonin, norepinephrine and other wake-promoting molecules are produced in the brainstem. The hypothalamus receives signals from the ascending reticular activating system; it produces both sleep- and wake-promoting neurotransmitters such as galanin and orexin (hypocretin), respectively. The circadian regulation of sleep-wake cycles is controlled by the suprachiasmatic nucleus (SCN) of the anterior hypothalamus; the SCN is the biological clock. In general, the daily flow of specific neurotransmitters switches the brain between sleep and wake bouts. The corpus callosum is labeled for orientation reference. Schematic illustration adapted and modified from NIH NINDS.

In general, there is ample evidence showing that changes in sleep physiology contribute to, and are linked to, the development of psychiatric and neurodegenerative disorders.

There are nearly 100 identified sleep and wake disorders, some of which are treated with a combination of stimulant drugs for excessive daytime sleepiness or sedative hypnotics for individuals experiencing difficulty falling asleep at night (Mahowald and Schenck, 2005). For instance, stimulant drugs such as modafinil are prescribed for narcolepsy, whereas non-benzodiazepines (zolpidem; the so-called Z-drugs) are used for insomnia. Another drug used to promote sleep

is lunesta which improves sleep maintenance and provides rapid sleep onset (Greenblatt and Zammit, 2012). Modafinil acts as a selective reuptake blocker for the neurotransmitter dopamine, whereas zolpidem and lunesta act through the activation of GABA receptors likely in the ventrolateral preoptic nucleus of the hypothalamus (Burgess and Scammell, 2012; Greenblatt and Zammit, 2012). Manipulation of chemical circuits in the brain is, therefore, the basis through which diagnostic and therapeutic interventions are formulated for the management of sleep and wake disorders (Table 1).

Sleep Disorders	Common Symptoms	Pharmacological and Therapeutic Treatments
Obstructive Sleep Apnea	Snoring and inability to breath	Continuous positive airway pressure, adjustable airway pressure devices
Narcolepsy	Falling asleep spontaneously	Modafinil, sodium oxybate
Insomnia	Inability to fall asleep	Zolpidem, ramelton, melatonin
Restless Legs Syndrome	Unpleasant sensation in the legs	Ropinirole, benzodiazepines, opioids, anticonvulsants
Circadian Rhythm Disorders	Disturbances of the biological clock	Behavior therapy, light therapy, chrono-therapy, melatonin
Parasomnias	Abnormal behavioral activity	Clonazepam, amitriptyline, melatonin
REM Sleep Behavior Disorder	Acting out dream mentations	Clonazepam, zopiclone, triazolam

**Table 1.** A brief list of sleep disorders in modern societies. Most of the 100 identified sleep/wake disorders carry considerable metabolic and cognitive risk. For example, obstructive sleep apnea is associated with hypertension, inflammation and increased cardiovascular risk. Along similar lines, insomnia and circadian rhythm disorders are highly co-morbid with psychiatric diseases. Adverse health outcomes of sleep disturbances often required medical attention. For example, symptoms associated with parasomnias (i.e., somnambulism) and REM sleep behavior disorder can be treated with benzodiazepine anxiolytics such as clonazepam and antidepressant drugs (e.g., amitriptyline). The hormone melatonin is often used for treatment of insomnias and parasomnias. Dopamine agonists such as ropinirole are used for the treatment of restless legs syndrome. Non-pharmacological treatments for sleep disturbances include light therapy and adjustable airway pressure devices.

## Functions of Sleep

Despite the ubiquity of sleep across phylogeny, the function of sleep is not clear due in part to the wide variation in sleep times within and between species (Siegel, 2012). Regardless, sleep in mammals appears to enhance the consolidation of newly formed declarative and procedural memories by promoting the growth of new connections (i.e., synapses) between neurons (Ackermann and Rasch,

2014). Another function of sleep may be related to neuron metabolite clearance from the brain. More specifically, this hypothesis states that during bouts of sleep, the brain clears itself from cellular waste material that accumulates during the subjective day (Xie et al., 2013). As such, this intercellular clearance pathway would be similar to that of the peripheral lymphatic system which plays an important role in the removal of excess fluid and proteins from the body. All in all, the above

findings suggest that the architecture of sleep is generated by neurons whose firing patterns encode signals for metabolic and cognitive functioning. A better understanding of sleep

and its relationship to coma and anesthesia, for instance, may lead to new insights on the neural mechanisms of consciousness.

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## Bibliographies

Dr. German Torres (torresg@nyit.edu) received a Ph.D. in Neuroscience from the University of California at Santa Barbara and is currently an Associate Professor in the Department of Biomedical Sciences at the New York Institute of Technology, College of Osteopathic Medicine. His specific research interests are centered on the biological basis of brain disorders.

Dr. Judith M. Horowitz (Judith.Horowitz@fredonia.edu) is an accomplished researcher in the fields of psychology and neuroscience. Dr. Horowitz has held an appointment as visiting scientist at Roswell Park Cancer Institute and has written articles published in

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## Editor's Column

Summer is upon us. I hope all Carrier readers are having a good and relaxing summer. As I write this column, it is one day before Bonus Registration Day for the Society for Neuroscience annual meeting. This year, the meeting in November will be held in Washington DC where we can hope it will not be too cold. As you probably know, the International Neuroethics Society also holds its annual meeting in the same city as SNS but a couple days before. This year the INS meeting will occur on November 13 and 14, with the SFN meetings formally beginning on November 15. I hope many of you are planning to attend the SFN meeting and that you think about attending the INS as well. Find out more about the INS at [www.neuroethicsociety.org](http://www.neuroethicsociety.org). In addition, we urge you to attend the David Kopf Lecture on Neuroethics on Sunday, November 16 at 11:30 am. The speaker this year is Mahzarin Banaji, Ph.D. of Harvard University who will talk on "Mind, Brain, and the Ethics of Intergroup Behavior". It will be a very interesting talk.

This 81st issue of the *Carrier* is another in our series of Neuroscience Reviews by German Torres and his colleagues. It is a quite interesting overview of the origins, brain mechanisms and functions of sleep. We are all aware of the need for sleep, but it is surprising to realize that we know little about why sleep is needed or what it does. Yet, as German and Judith rightly point out, disorders of sleep cause a myriad of both physical and mental problems. Thus, sleep seems related to many body and brain functions and also seems to be instrumental in long-term memory formation.

As I write this column, my wife and I are staying in our condo in Dublin, OH, having left

our Florida home for a couple months. Just before we left, a fairly rare weather phenomenon occurred. Very early in the hurricane season, a hurricane formed off the eastern Florida coast and gradually drifted north, finally hitting the Outer Banks of North Carolina pretty hard over the July 4th holiday. Hurricane Arthur was the earliest hurricane of any hurricane season to make landfall in North Carolina. It continued up the coast bringing flooding to many areas of the east coast and New England and even up into Canada. As we watched reports of its formation in Florida, we did hope it would not decide to go west (young hurricane) over us, but did feel for those it impacted.

David Kopf Instruments has been publishing the Kopf Carrier since December 1993. It is the oldest company newsletter certainly in the Neuroscience community and most likely one of the oldest in the scientific company community. We have published a wide variety of articles, ranging from technique articles, to neuroethics articles. All prior issues are archived on the Kopf web page at [www.kopf-instruments.com](http://www.kopf-instruments.com) and can be downloaded. We invite you to browse the collection, It has many useful articles that often can be of help in the lab or in training situations.

I invite any interested reader to submit an article for publication in the *Carrier*. The article can be on almost any topic of interest to the greater Neuroscience and scientific community. Kopf Instruments does not hold copyrights to the article; that remains in the hands of the author. There is a \$500 stipend for a published article. If you are interested in submitting an article, please send it to me at the email address below.

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