These studies suggest that in each stage of sleep the cerebral cortex undergoes synaptic reorganization to consolidate the memory of specific types of salient information. Conversely, this memory consolidation is lost when subjects are deprived of sleep or have fragmented sleep. A related theory, proposed by Giulio Tononi and Chiara Cirelli, is that rebalancing of synaptic strengths based on recent experience (synaptic homeostasis) occurs during sleep. The size of many excitatory synapses is increased during learning, requiring that some excitatory inputs be reduced to avoid overexciting the target neuron. Tononi and Cirelli found that the size of smaller synapses in motor and sensory cortex is reduced during sleep, resulting in strong inputs being strengthened while competing weaker ones are removed.

Diseases that cause sleep loss or that wake people from sleep can impair cognition. For example, *obstructive sleep apnea* can severely fragment sleep, resulting in daytime sleepiness, inattention, and other cognitive impairments. Fragmented sleep is also common in Alzheimer disease. Alzheimer patients tend to have fewer neurons in the ventrolateral preoptic nucleus, and the extent of neuronal loss correlates with their degree of sleep fragmentation. Whether treating sleep fragmentation can improve cognition in Alzheimer patients remains to be determined.

Sleep Changes With Age

Sleep changes with age in striking and characteristic ways. As every new parent quickly learns, the lengthy sleep time of a newborn is distributed almost randomly throughout the day. Although the EEG rhythms in newborns are not as well formed as those of older children or adults, more than 50% (8–9 hours per day) of that sleep is spent in a state much like REM sleep.

Sleep recordings from a premature infant exhibit an even higher percentage of REM-like sleep, indicating that in utero the fetus spends a large fraction of the day in a brain-activated but movement-inhibited state. As neuronal activity influences the development of functional circuits in the brain (Chapters 48 and 49), it is reasonable to think that the spontaneous activity of the immature brain during sleep facilitates the development of neural circuits.

By approximately 4 months of age, the average baby begins to show diurnal rhythms that are synchronized with day and night, much to the relief of weary parents. The total duration of sleep gradually declines, and by 5 years of age, the child may sleep 11 hours each night plus a nap, and 10 hours of sleep is typical around age 10. At these early ages, sleep is deep; stage N3 is prominent, with an abundance of delta waves in the EEG. As a result, children are not easily wakened by environmental stimuli.

With age, sleep becomes lighter and more fragmented. The percentage of time spent in stage N3 sleep drops across adulthood, and by the age of 50 to 60, it is not unusual for N3 to fade entirely, especially in men. This shift toward lighter stages of non-REM sleep results in two to three times as many spontaneous awakenings and more easily disrupted sleep. Many sleep disorders, including insomnia and sleep apnea, become more prevalent with age, and insomnia is common, often due to waking in response to neural signals to empty the bladder or due to discomfort from menopausal symptoms or from arthritis and other diseases. Why this change occurs with age is unclear; homeostatic sleep pressure appears normal, but the neural mechanisms for producing deep non-REM sleep may be less effective.

Disruptions in Sleep Circuitry Contribute to Many Sleep Disorders

Insomnia May Be Caused by Incomplete Inhibition of the Arousal System

Insomnia is one of the most common problems in all of medicine, yet the underlying neurobiology remains a mystery. Insomnia is defined as difficulty falling asleep or trouble staying asleep, so that function the next day is impaired. Positron emission tomography studies in patients with chronic insomnia demonstrate unusual activation of brain arousal systems during sleep, and the EEG often shows persistence of high-frequency activity (15–30 Hz) that is usually seen only during wake.

In addition, rats exposed to acute stress show high-frequency EEG activity during sleep, as well as simultaneous activity in neurons of the ventrolateral preoptic nucleus and components of the arousal system, such as the locus ceruleus and histamine neurons. This simultaneous activation can produce a unique state in which the EEG shows slow waves consistent with sleep along with high-frequency activity consistent with the awake state; this may explain why some patients appear asleep on the polysomnogram recording but they may feel awake.

Clinically, insomnia is often treated with cognitive behavioral therapy that is aimed at reducing the hyperarousal and improving sleep habits. Some patients may be treated with benzodiazepines and

related drugs that potentiate GABA transmission and, therefore, may help reduce activity in arousal-promoting brain regions. Other patients derive benefit from drugs that block the arousal system more directly, such as antihistamines.

Sleep Apnea Fragments Sleep and Impairs Cognition

Sleep apnea is one of the most common sleep disorders, affecting about 5% of adults and children. Patients with *obstructive sleep apnea* have repeated episodes of airway obstruction that force the individual to briefly awaken from sleep to resume breathing. During sleep, muscle tone falls, and in people with small airways, relaxation of airway dilator muscles such as the genioglossus (which normally acts to pull the tongue forward) results in collapse of the airway. This causes a brief period of no air flow, and consequently, blood levels of carbon dioxide rise while oxygen levels fall, activating chemosensory systems in the medulla that increase respiratory effort.

These chemosensory systems also activate neurons in the parabrachial nucleus that promote awakening, which results in a further increase in muscle tone that reopens the airway. These airway obstructions can occur hundreds of times per night, but the arousals are usually so brief that the individual may not remember them in the morning. Many people with obstructive sleep apnea do not feel rested in the morning; they feel sleepy all day and they have difficulty with a wide variety of cognitive tasks, especially those that require vigilance or learning.

Clinicians often treat sleep apnea with a *continuous positive airway pressure (CPAP) device* that delivers mildly pressurized air via the nose to inflate and open the airway during sleep. Sleep apnea can also be treated with upper airway surgery to remove obstructions such as large tonsils, a dental device to move the tongue forward, or weight loss to reduce adipose tissue in the neck. Treated patients often feel more alert and have better cognitive function, although there may be some residual cognitive impairment, possibly due to neuronal injury from repeated episodes of low oxygen saturation or hypoxia (Figure 44–8).

Narcolepsy Is Caused by a Loss of Orexinergic Neurons

Narcolepsy was first described in the late 1800s, but the underlying cause, a deficiency in a single

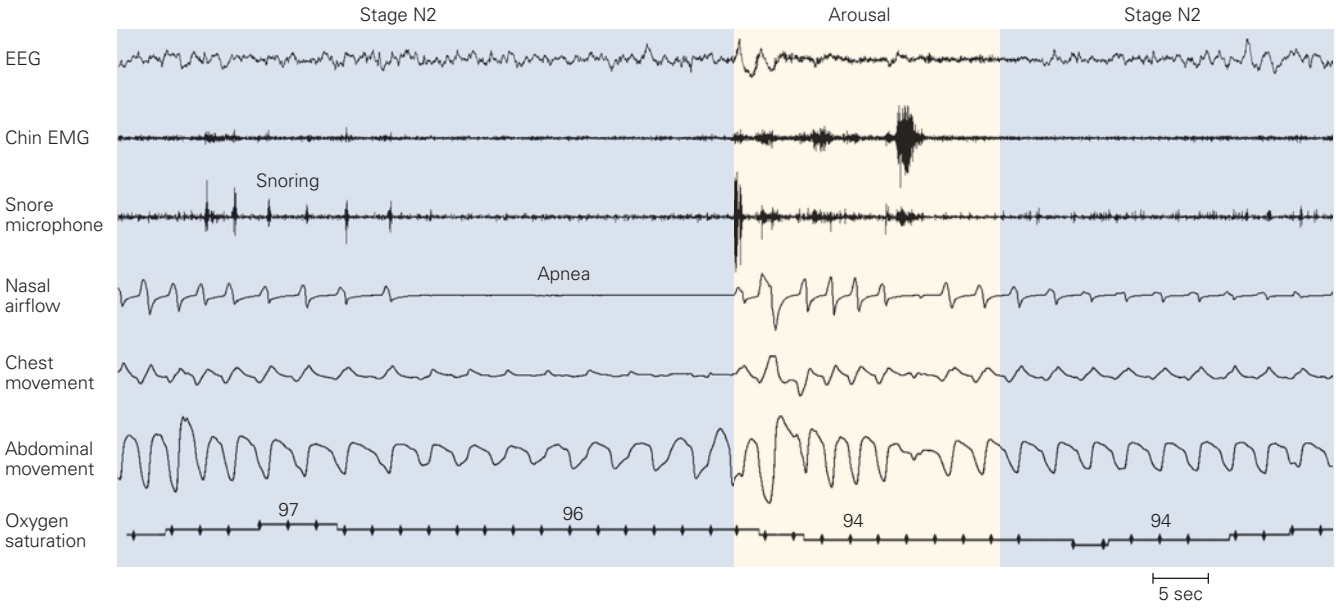

Figure 44–8 An episode of sleep apnea. At the start of this polysomnogram, an individual is in stage N2 sleep. Some snoring is detected, but nasal airflow is good and oxygen saturation is normal. The individual then experiences an obstructive apnea with no nasal airflow; nevertheless, respiratory effort persists (shown by the abdominal movement). The apnea is terminated by a brief awakening (low-voltage fast electroencephalogram [EEG]), accompanied by a loud snore, increased electromyographic activity, intensified respiratory effort, and opening of the airway. Oxygen saturation drops by about 3%, reaching its nadir about 15 seconds after the apnea finishes, as it takes time for blood to get from the lungs to the fingertip where oxygen saturation is measured.

neurotransmitter, has become clear only in the last two decades. Narcolepsy typically begins in the teen years as moderate to severe sleepiness every day, even with ample amounts of sleep at night. People with narcolepsy can easily fall asleep in class, while driving, or during other activities when sleep might be embarrassing or dangerous. Unlike sleep apnea, their sleep is restorative, and they often feel much more alert after a 15- to 20-minute nap.

In addition, in people with narcolepsy, elements of REM sleep often occur during wakefulness. For example, at night, while falling asleep or waking up, an individual with narcolepsy might find himself unable to move (*sleep paralysis*) or may have vivid dream-like hallucinations (*hypnagogic or hypnopompic hallucinations*) superimposed on wakefulness. Even more mysteriously, during the day, when surprised with a good joke or by unexpectedly seeing a friend, a person with narcolepsy can develop *cataplexy*, emotionally triggered muscle weakness that is similar to the paralysis of REM sleep. Mild cataplexy can cause weakness of the face and neck, but when severe, the individual can lose all muscle control, collapse to the ground, and be unable to move for 1 to 2 minutes.

Narcolepsy remained mysterious until the late 1990s when a new family of peptide neurotransmitters, orexins (also known as hypocretins), was discovered. There are two orexin peptides, derived from the same mRNA precursor, and they are found only in cells in the posterior lateral hypothalamus. It was soon found that loss of orexin signaling in animals or humans could reproduce the entire narcolepsy phenotype. People with narcolepsy show a highly selective loss of more than 90% of their orexin neurons, while other types of hypothalamic neurons are spared. This cell loss is probably due to an autoimmune attack as it is linked to genes that affect immune function and has been triggered by seasonal influenza epidemics and use of a certain influenza vaccine. Recently, researchers discovered that people with narcolepsy have immune cells (T lymphocytes) that target the orexin neuropeptides (Figure 44–9).

Orexinergic neurons promote wakefulness and suppress REM sleep, in part by activating monoaminergic neurons in the locus ceruleus and dorsal raphe as well as REM-off GABAergic neurons in the periaqueductal gray matter, all of which inhibit the REM sleep generating neurons in the pons. Thus, people and animals with loss of orexinergic neurons have great difficulty remaining awake for long periods, and REM sleep is disinhibited, such that REM sleep (or components of REM sleep, such as motor atonia during

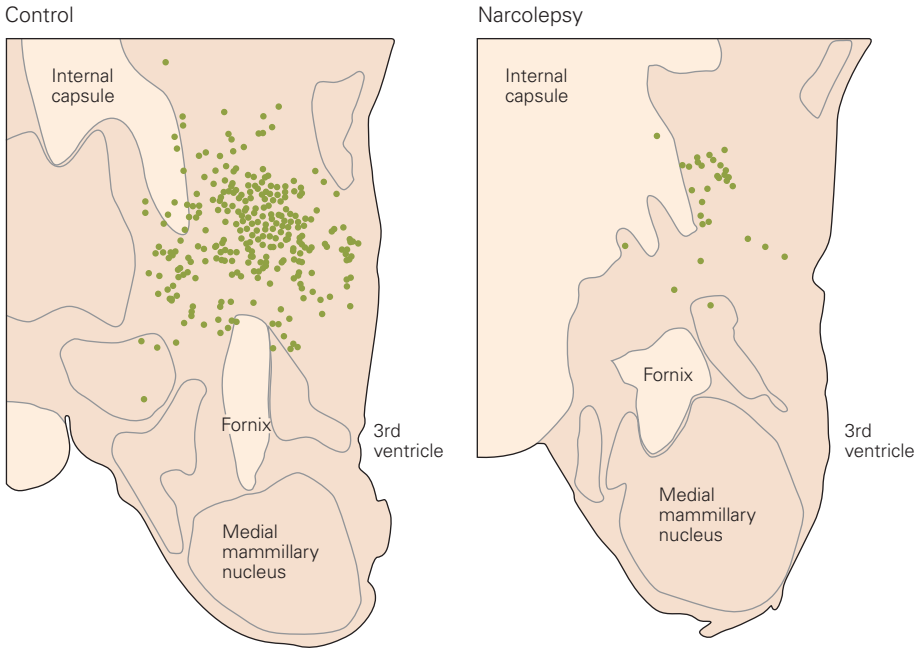

Figure 44–9 Narcolepsy is associated with a loss of hypothalamic neurons that produce the orexin neuropeptides. A dramatic loss of orexinergic neurons (**green dots**) is evident in these drawings of sections through the brain at the level of the mammillary bodies in an individual with narcolepsy (*right*) compared to a normal brain (*left*). (Reproduced, with permission, from Crocker et al. 2005. Copyright © 2005 American Academy of Neurology.)

wakefulness, or cataplexy) breaks through at inappropriate times during the day.

In terms of sleep circuitry, loss of orexinergic neurons can be considered to destabilize both the wake–sleep and the REM/non-REM switches in the brain. Thus, patients with narcolepsy can easily doze off during the day but also spontaneously wake from sleep more frequently at night. The dysregulation of REM sleep is also apparent on the Multiple Sleep Latency Test; healthy individuals almost never experience REM sleep during the day as it is under tight circadian control, but patients with narcolepsy often experience REM sleep during daytime naps.

The absence of orexin signaling also explains the mysterious symptom of cataplexy. Evidence from mice lacking orexins suggests that pleasant experiences turn on neurons in the prefrontal cortex and amygdala that can activate the brain stem pathways that trigger REM sleep paralysis. This influence is normally opposed by the orexin system, so that one may feel slightly "weak with laughter." When orexin signaling is absent, full-blown paralysis can occur.

Narcolepsy is treated with medications and behavioral approaches. Sleepiness can be substantially attenuated with wake-promoting medications such as amphetamine and modafinil. One to two strategically timed naps during the day are often helpful and can improve alertness for a couple of hours. Cataplexy often responds well to antidepressants such as serotonin or norepinephrine reuptake inhibitors, as these drugs strongly suppress REM sleep. Sodium oxybate taken during the night enhances deep sleep, and through an unknown mechanism, it helps consolidate wakefulness and reduce cataplexy during the day.

REM Sleep Behavior Disorder Is Caused by Failure of REM Sleep Paralysis Circuits

REM sleep behavior disorder—the loss of paralysis during REM sleep in some older adults—is the direct opposite of cataplexy. The lack of paralytic inhibition permits the patients to act out their dreams. The individual often calls out and may grab or violently punch or kick; injuries from hitting nearby furniture or the bed partner are not unusual. These dramatic movements typically awaken the patient, who can then recall a dream about fighting off an attacker in a way that closely matches the actual movements.

REM sleep behavior disorder was first identified in 1986 by Mahowald and Schenck. Ten years later, they reported that 40% of their original cohort of 19 patients had developed Parkinson disease or a related neurodegenerative disorder with deposition of alpha-synuclein, such as Lewy body dementia or multiple system atrophy. Subsequent studies have shown that about half of patients with REM sleep behavior disorder develop a synucleinopathy by 12 to 14 years after onset, and nearly all by 25 years. It is now thought that the synucleinopathy begins in the brain stem and early on damages the subceruleus neurons that normally drive REM sleep paralysis. If this relationship is confirmed, the diagnosis of REM sleep behavior disorder may identify individuals with nascent synucleinopathies who could be treated with drugs, not yet developed, that slow the neurodegeneration.

Restless Legs Syndrome and Periodic Limb Movement Disorder Disrupt Sleep

Restless legs syndrome occurs in about 10% of the population and is characterized by an irresistible urge to move the legs, usually accompanied by an annoying internal discomfort like "ants in the pants." This restless sensation typically occurs in the evening and first half of the night and often makes it hard to fall asleep. The sensation is much worse with rest and improves by moving the legs in bed or walking about.

Many people suffering from restless legs syndrome also experience *periodic limb movement disorder*, in which the legs and sometimes arms flex in a stereotyped way every 20 to 40 seconds during non-REM sleep. These leg movements fragment sleep and can produce daytime sleepiness. Iron deficiency is a common cause of restless legs, and treatment with iron can be very helpful. Genome-wide association studies have found genes common to both conditions, but the underlying pathophysiology is not yet understood. Patients with both disorders often improve with low doses of a D_2 dopamine agonist, the antiepileptic drug pregabalin, or an opiate drug.

Non-REM Parasomnias Include Sleepwalking, Sleep Talking, and Night Terrors

Parasomnias are unusual behaviors that occur during either REM or non-REM sleep. Non-REM parasomnias are common in children and include sleepwalking, sleep talking, confusional arousals, bed-wetting, and night terrors. About 15% of young adolescents have some sleepwalking, but this usually fades over time, so only about 1% of adults regularly sleepwalk.

The non-REM parasomnias typically begin with a sudden arousal from stage N3 sleep, which can occur spontaneously or be triggered by a noise or airway obstruction from sleep apnea. These are not full arousals, as for the first minute or two, the EEG still shows

the slow EEG delta waves typical of stage N3 sleep even as the child walks, dresses, or eats. Over time, the EEG changes to the pattern typical of wakefulness and eventually the individual wakes up. Sleepwalkers or talkers often have no memory of these events, so that reports from the family are necessary to make the diagnosis. Bed-wetting (enuresis) may also occur during deep non-REM sleep in some children.

Night terrors also occur in stage N3 sleep and are common in children age 2 to 5. The child often sits up and cries as if in great fear, sometimes with dilated pupils and a fast heart rate. During the episode, the child is inconsolable; attempts to calm or wake the child may only cause the screams and fearful behavior to worsen. Like sleep walking, but in contrast to ordinary nightmares, the child usually does not remember the night terror, and the events are typically much more difficult for the parent than the child.

The underlying cause of non-REM parasomnias is unknown. They are usually managed by ensuring adequate sleep to reduce pressure for deep non-REM sleep, reducing stress, and treating underlying sleep disorders such as sleep apnea that might trigger arousals from sleep. Fluid restriction in the evening may help with enuresis. Most children outgrow non-REM parasomnias as their N3 sleep decreases in late adolescence. Drugs that reduce the amount of N3 sleep, such as tricyclic antidepressants, are sometimes used as well. As with REM sleep behavior disorder, people can be seriously hurt sleepwalking if they fall down stairs or trip over furniture, and it is important to make the bedroom layout safe. The amount of time spent in stage N3 sleep is high in individuals with high homeostatic sleep pressure, so getting adequate sleep is also helpful.

Sleep Has Many Functions

Although there has been remarkable progress in our understanding of the brain circuitry that regulates sleep and wakefulness, we still understand relatively little about the actual functions of sleep. For an activity that occupies one-third of the life of humans, and much more in some other species, we have very little understanding of sleep's purposes. Allan Rechtschaffen, who first systematized the stages of sleep (and was an author of this chapter in earlier editions of this book), once said that if sleep did not have a vital function it would be the biggest mistake that evolution ever made. He found that rats would die of overwhelming infection and hypothermia if chronically deprived of sleep. However, the methods for keeping animals continuously awake were stressful, and it is unclear whether the consequences observed were due to loss of sleep or continuous stress. Indeed, it is not clear if prolonged sleep loss and stress can be dissociated.

One proposed function of sleep suggests that a period of brain inactivity is needed to permit metabolic recovery of the brain. The role of adenosine as a sleep-promoting humoral factor is based on the rundown of adenosine triphosphate (ATP) stores to adenosine during the awake period. Another idea is that sleep may permit the body to reconstitute injured tissue and replenish energy stores, but there is little evidence that sleep deprivation impairs any of these processes.

A recent hypothesis has been raised by the observation that during sleep the extracellular space in the brain expands, thus permitting the cerebrospinal fluid to "clean out" undesirable molecules that should not be allowed to build up extracellularly. The waking brain has very little extracellular space, largely due to ion fluxes to and from neurons during synaptic communication. These fluxes establish an osmotic gradient that drives most fluid in the brain into cells. During sleep, neurons and glia may shrink as that fluid moves back into the extracellular space. Among the molecules that may be washed out from the extracellular space during sleep are beta-amyloid peptides. In mice engineered to produce high levels of human beta-amyloid, sleep deprivation reduces the clearance of beta-amyloid from the extracellular space in the brain, thus accelerating its deposition in the plaques that are characteristic of Alzheimer disease (Chapter 64). Because buildup of beta-amyloid peptide in the brain is thought to be an early step in Alzheimer disease, work is now underway to determine whether poor sleep may predispose people to this disease.

In addition to these biochemical functions, sleep also promotes memory formation. As described earlier, the synaptic homeostasis model suggests that synapses are rebalanced during sleep, although it is not clear why this process would require sleep. A more basic need may be to provide a time for synapses to consolidate new memory traces. During the waking state, experience can modify synaptic strength on the fly by such processes as protein phosphorylation, insertion of premade receptors into the postsynaptic membrane, or translation of mRNA in the dendrites into new protein. But some portion of the synaptic remodeling that underlies memory formation requires nuclear-dependent transcription of new mRNA. Because synaptic sites on dendrites may be a millimeter from the nucleus or even more in some neurons, time is required for messenger molecules that are produced at the synapse to reach the nucleus and alter transcription and then for

the resulting mRNA to be transported back to the dendrite where it can result in new protein synthesis. This process may require a time when these messengers are not competing with new incoming signals to complete their work in stabilizing memories.

One thing about sleep is certain: It is required for normal brain function, and inadequate sleep, as defined by an increased tendency to fall asleep during the day, is associated with impaired cognitive function. Medical training programs are now being redesigned to reduce the risk of interns and residents making critical medical decisions while sleep deprived. Similar approaches to school start times, drowsy driving, and other aspects of our society could potentially improve productivity and save many lives.

Highlights

1. Sleep involves distinct changes in the electroencephalogram (EEG), electromyogram (EMG), and electro-oculogram (EOG) that are recorded on a polysomnogram. These changes can be used to divide sleep into rapid eye movement (REM) sleep—during which the EEG is similar to wake, but the body has such low muscle tone that it is essentially paralyzed—and three stages of non-REM sleep (N1–N3), with low to high amounts of slow waves in the EEG.
2. During the night, sleep alternates between periods of non-REM sleep followed by bouts of REM sleep, with the entire cycle taking about 90 minutes. Over the course of a night, non-REM sleep becomes progressively lighter, while REM sleep bouts become longer.
3. The waking state is actively produced by an ascending arousal network. The key neurons required to drive wakefulness are glutamatergic neurons in the parabrachial and pedunculopontine tegmental nuclei, dopaminergic neurons in the midbrain, glutamatergic neurons in the supramammillary nucleus, and GABAergic and cholinergic neurons in the basal forebrain that directly innervate the cerebral cortex. Modulatory cell groups, using mainly monoamines such as norepinephrine, serotonin, and histamine as neurotransmitters, can drive arousal under appropriate conditions, but unlike the main pathways, lesions of these cell groups do not impair baseline wakefulness.
4. During sleep, the ascending arousal system is inhibited by GABAergic neurons in the ventrolateral preoptic nuclei and the parafacial zone. Conversely, during wake, the ventrolateral preoptic neurons are inhibited by neurons in the ascending arousal system. These mutually antagonistic pathways produce a neural circuit resembling an electrical flip-flop switch, which favors rapid and complete transitions between sleep and wakefulness. Similarly, populations of mutually inhibitory neurons in the caudal midbrain and pons govern transitions between REM and non-REM sleep. Monoamine neurotransmitters, such as serotonin and norepinephrine, also act on these switching neurons and prevent transitions into REM sleep during wakefulness. Orexin neurons in the lateral hypothalamus activate REM sleep-suppressing neurons, preventing transitions from wake into REM sleep.
5. Sleep is regulated by a homeostatic drive to sleep, so that the longer one is awake, the more intense the drive, and the more sleep is required to satisfy the need to sleep. There is also a circadian influence on sleep that inhibits sleep during the day but promotes it at night, especially during the latter part of the night, when homeostatic sleep drive wanes. The circadian cycle is synchronized with the outside world by light signals from the retina to the brain's master circadian clock in the suprachiasmatic nucleus. The suprachiasmatic nucleus then activates hypothalamic pathways that regulate wake–sleep states, as well as many other behaviors, hormonal cycles, and physiological adjustments.
6. Sleep needs change throughout development, from about 16 hours per day in a newborn to about 8 hours per day in a healthy young adult. However, sleep-promoting mechanisms weaken with aging, and so individuals over 70 years old have more fragmented sleep and sleep about an hour less per day.
7. Sleep apnea is a condition in which the airway collapses due to reduced muscle tone during sleep. This impaired breathing causes frequent awakenings and can impair cognition. Restoring airway patency with continuous positive airway pressure (CPAP) can overcome this problem.
8. Insomnia may be caused by hyperactivation of the arousal system, and it is best treated with cognitive behavioral therapy.
9. Narcolepsy is caused by selective loss of the orexin (also called hypocretin) neurons in the hypothalamus. The orexin neuropeptides normally promote wake and regulate REM sleep, and loss of orexin signaling results in chronic daytime sleepiness and poor control of REM sleep.

Specifically, people with narcolepsy may quickly transition into REM sleep after dozing off, and they can have fragments of REM sleep, such as cataplexy and hypnogogic hallucinations, during wake. Narcolepsy is usually treated with medications that promote wake and suppress REM sleep.

10. REM sleep behavior disorder is due to loss of atonia during REM sleep, causing patients to act out their dreams. REM sleep behavior disorder is usually an early manifestation of either Parkinson disease or Lewy body dementia.
11. Restless legs syndrome is a genetically influenced disorder in which people feel that they have to move their legs. This makes them very uncomfortable when awake, and they can have periodic leg movements during sleep that disrupt sleep.
12. Sleepwalking and related parasomnias usually occur in young children during deep (stage N3) non-REM sleep. They are best managed by ensuring adequate, good-quality sleep.
13. Sleep loss impairs the ability to maintain sustained attention and clouds judgment. The reasons for this are not understood. Theories about the brain requiring down time to recharge its metabolic status or to allow it to flush out unwanted products from the extracellular space have received attention, but it is unclear whether this accounts for the penalty paid due to lack of sleep. One attractive theory for the function of sleep is that it may be required for synaptic remodeling that is necessary for certain types of learning.

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Selected Reading

Buhr ED, Takahashi JS. 2013. Molecular components of the mammalian circadian clock. Handb Exp Pharmacol 217:3–27.

Kryger MH, Roth T, Dement WC. 2017. *Principles and Practice of Sleep Medicine*, 6th ed. Philadelphia: Elsevier.

Saper CB. 2013. The central circadian timing system. Curr Opin Neurobiol 23:747–751.

Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. 2010. Sleep state switches. Neuron 68:1023–1042.

Scammell TE, Arrigoni E, Lipton JO. 2017. Neural circuitry of wakefulness and sleep. Neuron 93:747–765.

References

Achermann P, Borbely AA. 2003. Mathematical models of sleep regulation. Front Biosci 8:683–693.

Anaclet C, Pedersen NP, Ferrari LL, et al. 2015. Basal forebrain control of wakefulness and cortical rhythms. Nat Commun 6:8744.

Aschoff J. 1965. Circadian rhythms in man. Science 148: 1427–1432.

Aserinsky E, Kleitman N. 1953. Regularly occurring periods of eye motility and concomitant phenomena during sleep. Science 118:273–274.

Bal T, von Krosigk M, McCormick DA. 1995. Synaptic and membrane mechanisms underlying synchronized oscillations in the ferret lateral geniculate nucleus *in vitro*. J Physiol 483:641–663.

Boeve BF. 2013. Idiopathic REM sleep behaviour disorder in the development of Parkinson's disease. Lancet Neurol 12:469–482.

Buyssee DJ, Germain A, Hall M, Monk TH, Nofzinger EA. 2011. A neurobiological model of insomnia. Drug Discov Today Dis Models 8:124–137.

Chemelli RM, Willie JT, Sinton CM, et al. 1999. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell 98:437–451.

Crocker A, Espana RA, Papadopoulou M, et al. 2005. Concomitant loss of dynorphin, NARP, and orexin in narcolepsy. Neurology 65:1184–1188.

Dement W, Kleitman N. 1957. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. Electroencephalogr Clin Neurophysiol Suppl 9:673–690.

de Vivo L, Bellesi M, Marshall W, et al. 2017. Ultrastructural evidence for synaptic scaling across the wake/sleep cycle. Science 355:507–510.

Dijk DJ, Czeisler CA. 1995. Contribution of circadian pacemaker and sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci 15:3526–3538.

Fuller PM, Sherman D, Pedersen NP, Saper CB, Lu J. 2011. Reassessment of the structural basis of the ascending arousal system. J Comp Neurol 519:933–956.

Lim AS, Ellison BA, Wang JL, et al. 2014. Sleep is related to neuron numbers in the ventrolateral preoptic/intermediate nucleus in older adults with and without Alzheimer's disease. Brain 137:2847–2861.

Lin L, Faraco J, Li R, et al. 1999. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 98:365–376.

Lu J, Sherman D, Devor M, Saper CB. 2006. A putative flip-flop switch for control of REM sleep. Nature 41:589–594.

Mahowald MW, Schenck CH. 2005. Insights from studying human sleep disorders. Nature 437:1279–1285.

McCormick DA, Bal T. 1997. Sleep and arousal: thalamocortical mechanisms. Annu Rev Neurosci 20:185–215.

Moruzzi G, Magoun HW. 1949. Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol Suppl 1:455–473.

Peyron C, Faraco J, Rogers W, et al. 2000. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nat Med 6:991–997.

Saper CB, Scammell TE, Lu J. 2005. Hypothalamic regulation of sleep and circadian rhythms. Nature 437:1257–1263.

Stickgold R. 2005. Sleep-dependent memory consolidation. Nature 437:1272–1278.

Tononi G, Cirelli C. 2014. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 81:12–34.

Xie L, Kang H, Xu Q, et al. 2013. Sleep drives metabolite clearance from the adult brain. Science 342:373–377.

Xu M, Chung S, Zhang S, et al. 2015 Basal forebrain circuit for sleep-wake control. Nat Neurosci 18:1641–1647.

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