

Brain Facts

SLEEP

SLEEP REMAINS ONE OF THE GREAT

mysteries of modern neuroscience. We spend nearly one-third of our lives asleep, but the function of sleep still is not known. Fortunately, over the past few years, researchers have made great headway in understanding some of the brain circuitry that controls wake-sleep states.

Scientists now recognize that sleep consists of several different stages; that the choreography of a night's sleep involves the interplay of these stages, a process that depends upon a complex switching mechanism; and that the sleep stages are accompanied by daily rhythms in hormones, body temperature, and other functions.

Sleep is crucial for concentration, memory, and coordination. Without enough sleep, people have trouble focusing and responding quickly — in fact, sleep loss can have as big an effect on performance as drinking alcohol. It is also important for our emotional health. And growing evidence suggests that a lack of sleep increases the risk of a variety of health problems, including diabetes, cardiovascular disease and heart attacks, stroke, depression, high blood pressure, obesity, and infections.

Disorders of sleep are among the nation's most common health problems, affecting up to 70 million people, most of whom are undiagnosed and untreated. These disorders are one of the least recognized

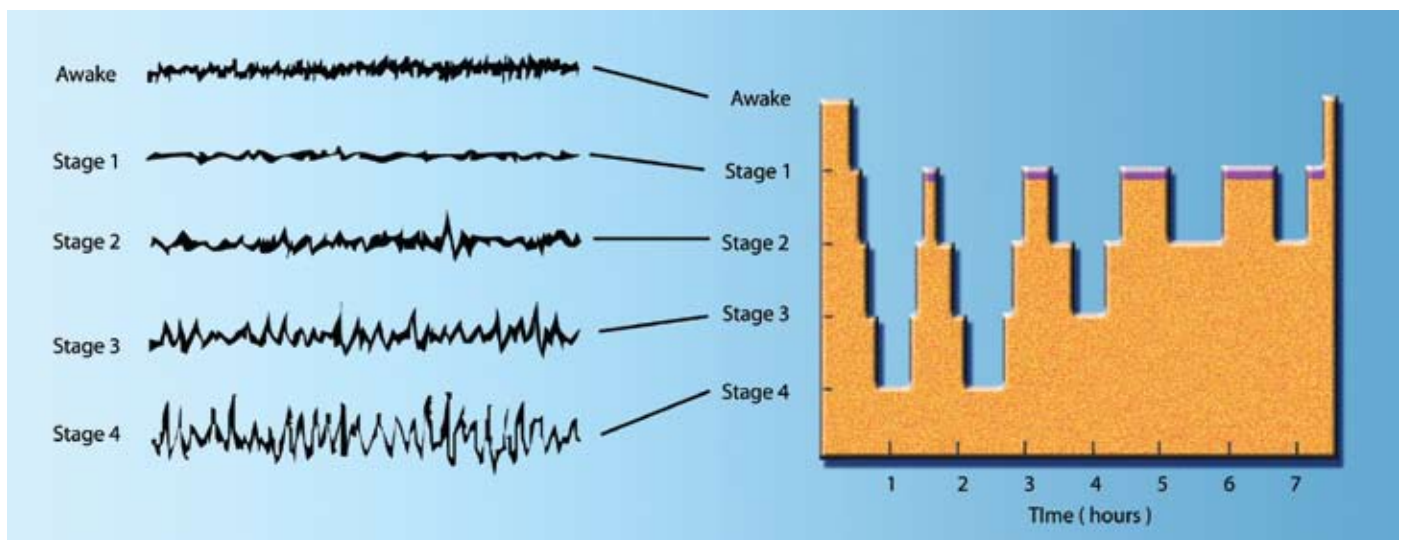
sources of disease, disability, and even death, costing an estimated \$100 billion annually in lost productivity, medical bills, and industrial accidents. Research holds promise for devising new treatments to allow millions of people to get a good night's sleep.

Brain activity during sleep

Although sleep appears to be a passive and restful time, it actually involves a highly active and well-scripted interplay of brain circuits to produce its various stages.

The stages of sleep were discovered in the 1950s in experiments using electroencephalography (EEG) to examine human brain waves during sleep. Researchers also measured movements of the eyes and the limbs. They found that over the course of the first hour or so of sleep each night, the brain progresses through a series of stages during which the brain waves slow down. This period of *slow wave sleep* is accompanied by relaxation of the muscles and the eyes. Heart rate, blood pressure, and body temperature all fall. If awakened at this time, most people recall only fragmented thoughts, not an active dream.

Over the next half hour or so, brain activity alters drastically from deep slow wave sleep to generate neocortical EEG waves that



SLEEP PATTERNS. During a night of sleep, the brain waves of a young adult recorded by the electroencephalogram (EEG) gradually slow down and become larger as the individual passes into deeper stages of slow wave sleep. After about an hour, the brain re-emerges through the same series of stages, and there is usually a brief period of REM sleep (on dark areas of graph), during which the EEG is similar to wakefulness. The body is completely relaxed; the person is deeply unresponsive and usually is dreaming. The cycle repeats over the course of the night, with more REM sleep, and less time spent in the deeper stages of slow wave sleep as the night progresses.

are similar to those observed during waking. Paradoxically, the fast, waking-like EEG activity is accompanied by *atonia*, or paralysis of the body's muscles (only the muscles that allow breathing and control eye movements remain active). This state is often called *rapid eye movement* (REM) sleep. During REM sleep, there is active dreaming. Heart rate, blood pressure, and body temperature become much more variable. Men often have erections during this stage of sleep. The first REM period usually lasts 10 to 15 minutes.

During the night, these cycles of slow wave and REM sleep alternate, with the slow wave sleep becoming less deep and the REM periods more prolonged until waking occurs. Over the course of a lifetime, the pattern of sleep cycles changes. Infants sleep up to 18 hours per day, and they spend much more time in deep slow wave sleep. As children mature, they spend less time asleep and less time in deep slow wave sleep. Older adults may sleep only six to seven hours per night, often complain of early waking that they cannot avoid, and spend very little time in slow wave sleep.

Sleep disorders

The most common sleep disorder, and the one most people are familiar with, is *insomnia*. Some people have difficulty falling asleep initially, but other people fall asleep and then awaken partway through the night and cannot fall asleep again. Although a variety of short-acting sedatives and sedating antidepressant drugs are available to help, none produces a truly natural and restful sleep state because they tend to suppress the deeper stages of slow wave sleep.

Excessive daytime sleepiness may have many causes. The most common are disorders that disrupt sleep and result in inadequate amounts of sleep, particularly of the deeper stages.

In *obstructive sleep apnea*, as sleep deepens, the airway muscles in the throat relax to the point of collapse, closing the airway. This prevents breathing, which causes arousal from sleep and prevents the sufferer from entering the deeper stages of slow wave sleep. This condition also can cause high blood pressure and may increase the risk of heart attack. Increased daytime sleepiness leads to an increased risk of daytime accidents, especially automobile accidents. Treatment may include a variety of attempts to reduce airway collapse during sleep. Whereas simple things like losing weight, avoiding alcohol and sedating drugs prior to sleep, and avoiding sleeping on one's back can sometimes help, most people with sleep apnea require devices that induce continuous positive airway pressure to keep the airway open. This can be accomplished by fitting a small mask over the nose that provides an airstream under pressure during sleep. In some cases, surgery is needed to correct the airway anatomy.

Periodic limb movements of sleep are intermittent jerks of the legs or arms that occur as the individual enters slow wave sleep and can

cause arousal from sleep. Other people have episodes in which their muscles fail to become paralyzed during REM sleep, and they act out their dreams. This *REM behavior disorder* also can be very disruptive to a normal night's sleep. Both disorders are more common in people with Parkinson's disease, and both can be treated with drugs for Parkinson's or with a benzodiazepine called clonazepam.

Narcolepsy is a relatively uncommon condition — only one case per 2,500 people — in which the switching mechanisms controlling the transitions into sleep, particularly REM sleep, do not work properly. This problem is due to the loss of nerve cells in the lateral hypothalamus containing the neurotransmitter orexin (also known as hypocretin). Narcoleptics have sleep attacks during the day, in which they suddenly fall asleep. This is socially disruptive, as well as dangerous — for example, if it strikes while they are driving. They tend to enter REM sleep very quickly as well and may even enter a dreaming state while still partially awake, a condition known as *hypnagogic hallucination*. They also have attacks during which they lose muscle tone — similar to what occurs during REM sleep but while they are awake. These attacks of paralysis, known as *cataplexy*, can be triggered by emotional experiences, even by hearing a funny joke.

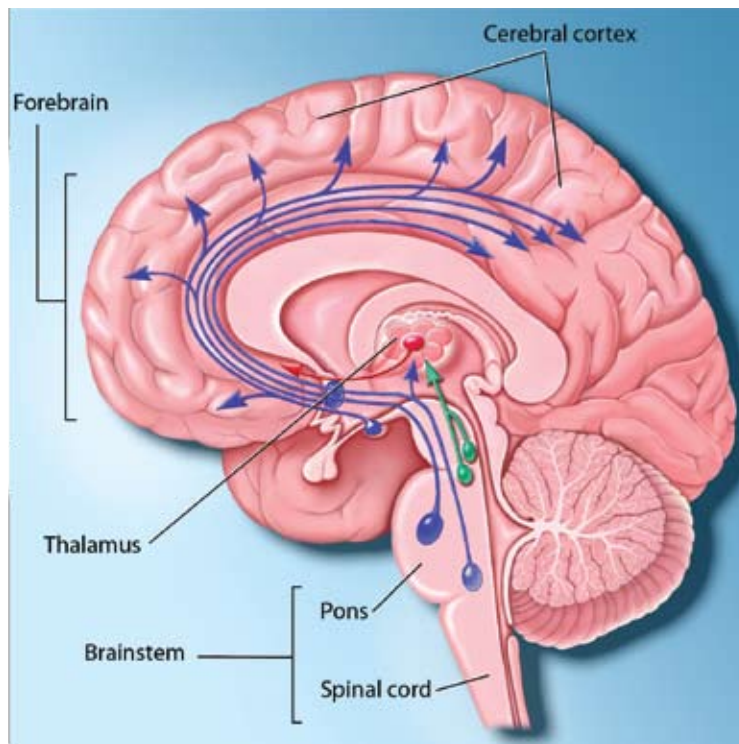
Recently, studies into the mechanism of narcolepsy have given researchers major insight into the processes that control these mysterious transitions between waking, slow wave sleep, and REM sleep states.

How is sleep regulated?

During wakefulness, the brain is kept in an active or aroused state by the actions of two major systems of nerve cells that use either acetylcholine or monoamines, such as norepinephrine, serotonin, dopamine, and histamine, as their neurotransmitters. Nerve cells in the upper part of the pons and in the midbrain that mainly contain acetylcholine send inputs to activate the thalamus. When the thalamus is activated, it in turn provides information from the sensory systems about the world around us to the cerebral cortex. Other nerve cells in the upper brainstem, largely containing norepinephrine, serotonin, and dopamine, send their outputs directly to the hypothalamus, the basal forebrain, and the cerebral cortex. They are joined by nerve cells in the hypothalamus containing the neurotransmitter orexin and another group containing histamine, and neurons in the basal forebrain containing acetylcholine or GABA, all of which also send outputs directly to the cortex. This activates the cerebral cortex so that input from the thalamus is interpreted accurately during wakefulness.

During REM sleep, the cholinergic nerve cells activate the thalamus, producing an EEG pattern that is similar to wakefulness,

THE WAKING AND SLEEPING BRAIN. Wakefulness is maintained by activity in two systems of neurons. Neurons that make the neurotransmitter acetylcholine are located in two main arousal centers, one in the brainstem (green pathways) and one in the forebrain (red pathway). The brainstem arousal center supplies the acetylcholine for the thalamus and brainstem, and the forebrain arousal center supplies that for the cerebral cortex. Activation of these centers alone can create rapid eye movement sleep. Activation of other neurons that make monoamine neurotransmitters such as norepinephrine, serotonin, and histamine (blue pathways) is needed for waking.



but the monoamine pathway from the upper brainstem directly to the cerebral cortex is quiet. As a result, the input from the thalamus to the cerebral cortex is perceived as dreams. When the nerve cells containing the monoamine neurotransmitters are active, they suppress the occurrence of REM sleep.

The brainstem cell groups that control arousal from sleep are, in turn, influenced by two groups of nerve cells in the hypothalamus, the part of the brain that controls basic body cycles. One group of nerve cells, in the ventrolateral preoptic nucleus, contains the inhibitory neurotransmitters galanin and GABA. When the ventrolateral preoptic neurons fire, they are thought to turn off the arousal systems, causing sleep. Damage to the ventrolateral preoptic nucleus produces irreversible insomnia.

A second group of nerve cells in the lateral hypothalamus promotes wakefulness and suppresses REM sleep. They contain the neurotransmitter orexin, which provides an excitatory signal to the arousal system, particularly to the monoamine neurons. In experiments in which the gene for the neurotransmitter orexin was experimentally removed in mice, the animals became narcoleptic. Similarly, in two dog species with naturally occurring narcolepsy, an abnormality was discovered in the gene for the type 2 orexin receptor. Although humans with narcolepsy rarely have genetic defects in orexin signaling, most develop the disorder in their teens or 20s because of the loss of orexin nerve cells. Recent studies show that in humans with narcolepsy, the orexin levels in the brain and spinal fluid are abnormally low. Thus, orexin appears to play a critical role in activating the monoamine system and in preventing abnormal transitions, particularly into REM sleep.

Two main signals control our need for sleep and its circuitry. First is homeostasis, or the body's need to seek a natural equilibrium

of wakefulness followed by rest and sleep. Several mechanisms for the signal of accumulating sleep have been suggested. Evidence suggests that levels of a chemical called adenosine, which is linked to brain energy and activity homeostasis, increase in the brain during prolonged wakefulness and that these levels modulate sleep homeostasis. Interestingly, the drug caffeine, which is widely used to prevent sleepiness, acts as an adenosine blocker.

If an individual does not get enough sleep, the sleep debt progressively accumulates and leads to a degradation of mental function. When the opportunity to sleep comes again, the individual will sleep much more, to “repay” the debt. The slow wave sleep debt is usually “paid off” first.

The other major influence on sleep cycles is the brain's circadian timing system. The suprachiasmatic nucleus is a small group of nerve cells in the hypothalamus that acts as a master clock. These cells express clock proteins, which go through a biochemical cycle of about 24 hours, setting the pace for daily cycles of activity, sleep, hormone release, and other bodily functions. The suprachiasmatic nucleus also receives input directly from the retina, and the clock can be reset by light so that it remains linked to the outside world's day-night cycle. The suprachiasmatic nucleus provides signals to an adjacent brain area, called the subparaventricular nucleus, which in turn contacts the dorsomedial nucleus of the hypothalamus. The dorsomedial nucleus in turn contacts the ventrolateral preoptic nucleus and the orexin neurons that directly regulate sleep and arousal.