Characteristics and Determinants of Normal Sleep

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Although sleep appears to simply be a body and mind at rest, it is actually a dynamic and complex physiologic state that is necessary for survival. Normal sleep is characterized by behavioral and physiologic changes as well as 2 distinct sleep states, rapid eye movement (REM) and non-REM (NREM). Throughout the course of a night, people cycle between NREM and REM sleep via an ultradian rhythm, with most of sleep spent in NREM. Determinants involved in the regulation of sleep are the homeostatic and circadian processes. Despite being highly regulated, sleep is fragile, and its stages and duration may be affected by multiple factors, such as age, drugs, temperature, and medical and psychiatric disease. Variations in nighttime sleep impact subsequent sleep periods as well as daytime function.

Contrary to popular belief and behavioral observation, a sleeping brain is not a resting brain. Sleep is actually a dynamic and complex process, and although sleep is not yet fully understood, like food or water, it is known to be a physiologic drive required for survival.1 Herein, the characteristics and determinants of normal sleep are described.

CHARACTERISTICS OF NORMAL SLEEP

In humans, closed eyes, reclined position, decreased sensitivity to the external environment, and decreased activity are among the behaviors that characterize sleep. During sleep, a person’s response to or engagement in his or her surroundings is diminished but not completely absent. This reduced consciousness coupled with rapid reversibility distinguishes sleep from death, coma, and hibernation.

As the brain adjusts to sleep, so, too, do most physiologic functions. Activity in the parasympathetic nervous system is increased during most of sleep, while sympathetic nervous system activity is similar to that in wakefulness except for periods of rapid eye movement (REM). Breathing becomes irregular and even periodic in sleep. Control of body temperature is altered: during non-REM (NREM), body temperature is set and maintained at a lower temperature than during wakefulness, and temperature control ceases almost entirely during REM sleep.

Much of what happens during sleep is unobservable through behavior or subjective experience. Therefore, electrophysiologic measures, e.g., the electroencephalogram (EEG), electro-oculogram (EOG), and electromyogram (EMG), have been used to document the activity and organization of the processes that make up sleep. In this discussion, the characteristics of normal sleep are based on measures taken in normal young adults (i.e., aged 18 to 29 years).

NREM and REM Sleep

Two separate and distinct states have been found to occur during sleep: NREM and REM. During sleep, a person alternates between NREM and REM (Table 1).2 This NREM-REM cycle is hypothesized to be controlled by an ultradian process that lasts approximately 90 to 120 minutes. The NREM-REM cycle occurs 3 to 6 times per night in normal nocturnal sleep, with the biological sleep need being about 8 hours.

During NREM sleep, cognitive activity is typically fragmented, and body activity periodically occurs as a person moves through the 4 stages of NREM sleep, each of which is defined along EEG measures. The first stage 1 period lasts for 1 to 7 minutes, occurs primarily at the onset of sleep, and serves as a transitional stage throughout sleep. A sleeping person is easily awakened during stage 1, indicating that this stage has a low arousal threshold. However, in stage 1, about 90% of people, when awakened, report not having been asleep. After stage 1, a person enters stage 2, which lasts for 10 to 25 minutes. During stage 2, sleep spindles and k complexes occur periodically. As stage 2 progresses, high-voltage slow-wave activity, as measured by the EEG, increases to the point of becoming stage 3 of NREM sleep. In the first sleep cycle, the dur-
tion of stage 3 lasts only a few minutes, with the onset of stage 4 occurring as high-voltage slow-wave activity continues to increase. When high-voltage slow-wave activity accounts for more than 50% of the EEG, a person has entered stage 4 and stays there for about 20 to 40 minutes in the first sleep cycle. Stages 3 and 4 are sometimes referred to collectively as slow-wave, delta, or deep sleep and have a higher arousal threshold than stages 1 and 2.

Unlike NREM, during REM sleep, the brain exhibits fast (activated) EEG activity with the body almost paralyzed except for a few muscle twitches. Thus, EEG activation, skeletal muscle atonia, bursts of autonomic activity, and episodes of rapid eye movements characterize REM sleep. Although REM sleep is not segmented into stages like NREM, REM sleep is thought to consist of tonic and phasic periods, which are distinguished by short clusters of rapid eye movement activity (phasic) that are followed by periods of relative inactivity (tonic).

The first third of sleep is spent primarily in NREM stages 3 and 4, and the last third is spent primarily in REM. Although a sleeping person cycles between NREM and REM every 1.5 to 2 hours, the time spent in these different sleep states is not equal. Most (75% to 85%) of sleep is spent in NREM; the other 20% to 25% of sleep is REM. About 5% of nocturnal sleep is accounted for by wakefulness within sleep.

**DETERMINANTS OF SLEEP**

Sleep is regulated by several processes. A 90-minute ultradian rhythm controls the NREM-REM cycle, while homeostasis and circadian rhythmicity determine the amount and timing of sleep. In the brain, sleep and wakefulness are controlled via the hypothalamus through the ventrolateral preoptic nucleus (VLPO) and the posterior lateral hypothalamus, respectively. Although sleep is highly regulated, it is fragile and may be affected by multiple factors. Among these factors, age is perhaps the most influential, and many are environmental variables.

**Homeostasis**

Reduced sleep alters the homeostatic control of sleep, so, for example, a person who does not get the required amount of sleep at night experiences sleepiness the next day. This sleepiness can be reversed by extending sleep times on subsequent nights. The presence of the homeostatic process in sleep has been verified through the Multiple Sleep Latency Test (MSLT), in which participants spend the night in a sleep laboratory and are then given 5 nap opportunities the following day or over successive days. Subjects whose sleep was reduced by 2 to 8 hours the night before, or whose sleep was reduced by 1 to 2 hours over successive nights, showed increased daytime sleepiness the next day or days as evidenced by the MSLT and performance testing.1

<table>
<thead>
<tr>
<th>Table 1. Distribution of Sleep States in Normal Nocturnal Sleep</th>
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</thead>
<tbody>
<tr>
<td>Sleep is entered through NREM</td>
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<tr>
<td>The NREM-REM cycle occurs 3 to 6 times per night or about</td>
</tr>
<tr>
<td>every 90 to 120 minutes</td>
</tr>
<tr>
<td>Time spent in sleep states are as follows:</td>
</tr>
<tr>
<td>75% to 80% in NREM sleep</td>
</tr>
<tr>
<td>2% to 5% in stage 1</td>
</tr>
<tr>
<td>45% to 55% in stage 2</td>
</tr>
<tr>
<td>3% to 8% in stage 3</td>
</tr>
<tr>
<td>10% to 15% in stage 4</td>
</tr>
<tr>
<td>20% to 25% in REM sleep</td>
</tr>
<tr>
<td>&lt; 5% in wakefulness within sleep</td>
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<tr>
<td></td>
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</tbody>
</table>

*Based on Carskadon and Dement.2*

Reduced sleep time not only decreases sleep latency, but it also may lead to a different sleep pattern during subsequent opportunities for sleep. Slow-wave sleep is increased on recovery nights following partial and total sleep deprivation. Further, the sleep characterized by slow-wave activity dominates during the first few hours of sleep and then decreases in the final sleep hours. REM is recouped only after slow-wave sleep has been recovered, suggesting that this NREM sleep is favored during recovery sleep.

**Circadian Rhythm**

The circadian process regulates the timing of sleep and wakefulness. The circadian rhythm is evidenced by body temperature: people tend to sleep when their body temperature is low (e.g., middle of night) and tend to be alert when their body temperature is high (e.g., early evening.) If sleep is delayed until early morning, an individual may not sleep as long as he or she would have at night because body temperature rises as the day progresses, thereby making when a person sleeps a determinant of how long he or she sleeps. In normal nocturnal sleep, REM sleep occurs in early morning hours. However, when sleep is delayed until early morning, REM sleep is the more prevalent sleep state, occurring as the early part of the sleep period.

**Ventrolateral Preoptic Nucleus**

Within the hypothalamus, the VLPO has been identified as containing γ-aminobutyric acid (GABA) and galanin neurons that are necessary for normal sleep.2 During sleep, the VLPO neurons have been found to fire twice as much as during waking, and in animals with lesions in the VLPO cluster, duration of sleep was diminished by about 50%.

Wakefulness appears to be mediated by orexin/hypocretin neurons contained in the posterior lateral hypothalamus. These neurons are hypothesized to inhibit the VLPO neurons, thereby establishing a feedback loop that offers 2 stable patterns, wakefulness and sleep. If either set of neurons fails to fire at its normal rate, then instability occurs in the form of state instability (insomnia and/or daytime sleepiness).
Age

Age may be the most influential factor affecting sleep as is evidenced by its influence on sleep continuity and stages. At birth, sleep occupies much of the 24-hour day, with newborns and infants ultimately sleeping at least twice as much as adults. During this period, about 50% of sleep is REM sleep compared with the approximate 25% of REM sleep in adults, but by age 3 years, the amount of time spent in REM sleep has decreased to that of adults and then stays steady well into old age. The ultradian process that controls the NREM-REM cycle exists from birth, but the cycle is shortened to about 50 to 60 minutes in newborns. The NREM sleep stages emerge at 2 to 6 months, and once the brain is developed enough to accommodate slow-wave activity, stages 3 and 4 become prominent.

In early childhood, slow-wave sleep occurs more frequently than at any other time in life. Slow-wave sleep changes across the life span, declining as people age to the point of being almost nonexistent in the elderly. In older adults, it is the ability to sleep continuously in a 7- to 8-hour period that is often diminished, not as is commonly believed, the need to sleep. The amount of time spent in nocturnal sleep does decline beginning in the sixth decade, but the decreased nocturnal sleep may be in part offset by an increase in daytime naps—daytime sleepiness is higher in older adults compared with young and middle-aged adults.

There remains a dearth of data describing the sleep norms and needs across the life span. However, 2 studies conducted with polysomnograms both in a sleep laboratory and in participants’ homes had similar findings for middle-aged adults on several measures (Table 2). The largest discrepancies between the studies were the time spent in NREM sleep stage 1 and stages 3 and 4.

Drugs

Most drugs, be they prescription, over-the-counter, or recreational, that cross the blood-brain barrier affect sleep. For example, stimulants may delay or sedatives may promote sleep and sleep consolidation. Additionally, drugs can impact sleep by suppressing or increasing certain stages. For example, slow-wave sleep is increased by low-dose sedatives, alcohol, and some GABAergic drugs. Conversely, alcohol, along with the stimulants cocaine and amphetamines, suppress REM sleep. Antidepressants, such as tricyclics, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors, have the greatest REM suppressant effect. Finally, benzodiazepines appear to have no effect on REM sleep, although this class of agents does suppress slow-wave activity.

When drugs that affect a sleep state are withdrawn or discontinued, that sleep effect typically rebounds. For example, REM rebound occurs upon discontinuation of antidepressants, barbiturates, cocaine, and amphetamines. In the case of alcohol, once it has been metabolized, REM rebound can occur within the night.

Drugs may also have the opposite clinical effect of their intended effect when withdrawn. Sedative withdrawal has been known to result in rebound insomnia and stimulant withdrawal in rebound sleepiness. Duration of action is critical. Long-acting depressants taken for sleep may cause daytime sleepiness, while stimulants taken for wakefulness may cause insomnia. Dose and duration of action are most often related to these effects.

External Temperature

Environmental temperature can disrupt sleep, although individuals vary in their sensitivity to temperature extremes and to optimal sleep temperature. Often it is not sleep onset that is disturbed by temperatures above or below thermoneutrality but rather sleep continuity. In extreme heat or cold, wakefulness and light sleep increase, with REM sleep more sensitive to temperature than NREM sleep. During REM sleep, people have little to no ability to thermoregulate their bodies, so control of body temperature is poikilothermic in this sleep state.

Medical and Psychiatric Disease

The stages and duration of sleep can be affected by primary sleep disorders as well as non–sleep-related medical and psychiatric disorders. For example, short REM latency is common in narcolepsy, circadian rhythm sleep disorder (jet lag and shift work types), and depression. In people with a breathing-related sleep disorder due to sleep apnea, slow-wave sleep and REM sleep are suppressed. Conditions characterized by pain or other physical discomfort, such as Parkinson’s disease and rheumatoid

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**Table 2. Sleep Norms for Middle-Aged Adults**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Sleep Latency, min</th>
<th>REM Latency, min</th>
<th>Sleep Time, h</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3/4</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–39</td>
<td>17.0</td>
<td>99</td>
<td>7.2</td>
<td>16.0</td>
<td>54.0</td>
<td>10.0</td>
<td>20.0</td>
</tr>
<tr>
<td>40–49</td>
<td>17.0</td>
<td>86</td>
<td>7.2</td>
<td>14.0</td>
<td>56.0</td>
<td>8.0</td>
<td>22.0</td>
</tr>
<tr>
<td>50–59</td>
<td>18.0</td>
<td>87</td>
<td>6.7</td>
<td>20.0</td>
<td>57.0</td>
<td>6.0</td>
<td>17.0</td>
</tr>
</tbody>
</table>

Abbreviation: REM = rapid eye movement.
arthritis, are often associated with frequent arousals that impede sleep continuity.

CONCLUSION

Impediments to sleep, be they reduced sleep time and/or ability to maintain sleep, affect both wakefulness and sleep. The consequences of diminished sleep, specifically effects on NREM and REM sleep, have been described here. At this time, the clinical significance of NREM and REM is uncertain. However, the consequences of diminished sleep include excessive sleepiness and decreased alertness, and the clinical significance of these effects is known to be cognitive implications, such as lapses in attention and memory. Thus, normal sleep is required for individuals to be able to successfully navigate their time spent awake.

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

REFERENCES