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Physiology of Normal Sleep: From Young to Old

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ABSTRACT

Human sleep, defined on the basis of electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG), is divided into rapid eye movement (REM) sleep and four stages of non–rapid eye movement (NREM) sleep. Collective monitoring and recording of physiological data during sleep is called polysomnography. Sleep which normally starts with a period of NREM alternates with REM, about 4-5 times, every night. Sleep pattern changes with increasing age. Newborns sleep for about 14-16 hours in a day of 24 hours. Although there is a wide variation among individuals, sleep of 7-8.5 hours is considered fully restorative in adults. Apart from restorative and recovery function, energy conservation could be one of the functions of sleep. The role of sleep in neurogenesis, memory consolidation and brain growth has been suggested. Though progress in medical science has vastly improved our understanding of sleep physiology, we still do not know all the functions of sleep.

Key words : electroencephalogram, electromyogram, electrooculogram, polysomnography, REM sleep, non–REM sleep, newborns, circadian rhythm, auto-regulation, sleep function

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Sleep is quantified and qualified on the basis of electrophysiological signals. There are definite changes in electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) during sleep (**Figure 1 and 2**). Modern definition and classification of sleep was suggested by Nathaniel Kleitman, in 1939 in his seminal book titled *Sleep and Wakefulness* (1). Unfortunately, Kleitman is remembered today by many only for his discovery of rapid eye movement sleep (REM sleep) in 1953 (2). Classification of sleep is described in detail in a manual written by Rechtschaffen and Kales (3). Normal human sleep, divided into non–rapid eye movement (NREM) and REM sleep, could be classified into five stages. They are stages 1, 2, 3 and 4 of NREM sleep and REM sleep (**Figure 2**). The American Academy of Sleep Medicine (AASM) modified the staging rules in 2007(4). The major change that they have introduced was combining stages 3 and 4 of NREM sleep.

Sleep starts with a period of NREM sleep. REM sleep takes place after a short period of NREM sleep. This alteration between NREM and REM occurs about 4-5 times during a normal night's sleep. The first REM period may be less than 10 minutes in duration, while the last one may exceed 60 minutes. Usually, REM sleep is the last phase of a full night's sleep, and one usually wakes up during this stage of sleep.

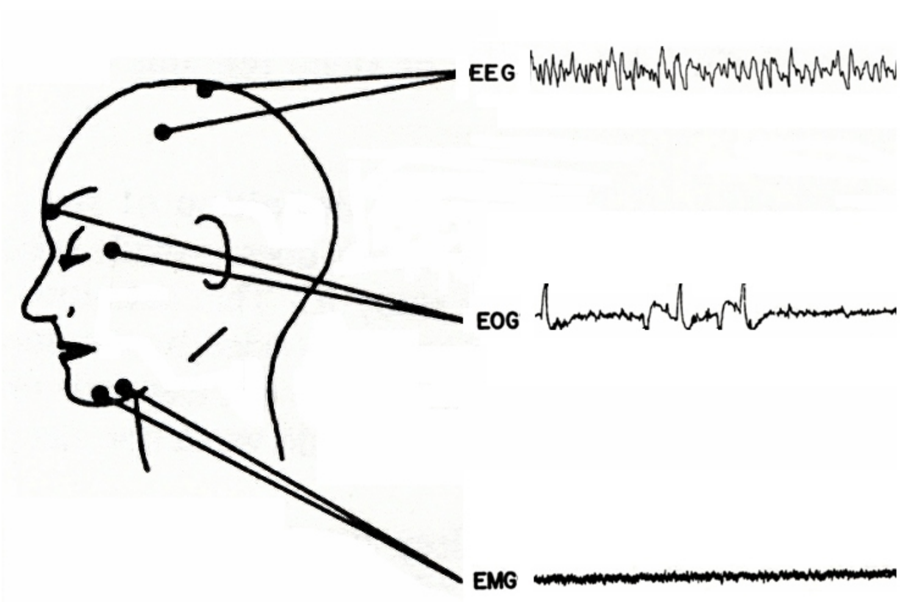

FIGURE 1 : Sleep-wakefulness, defined electrophysiologically, relies on changes in electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG). These signals are picked up from various sites using electrodes placed on the head.

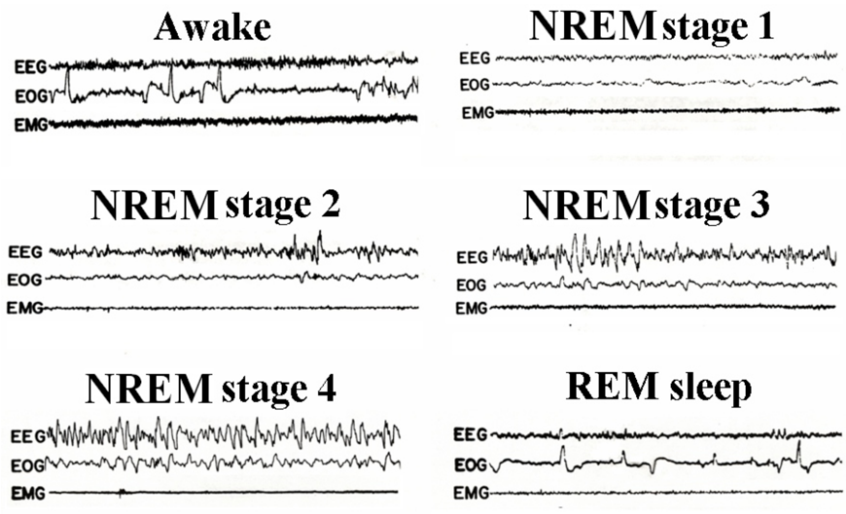

FIGURE 2 : There are distinct changes in electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) as the subject goes from wakefulness to stages I, II, III and IV of NREM sleep and REM sleep.

Polysomnography:

Collective monitoring and recording of physiologic data during sleep is called polysomnography. Traditionally three primary measures, namely EEG, EMG and EOG are used to assess different stages of sleep-wakefulness (**Figure 2**). Six electrodes (labeled C3, C4, A1, A2, O1, and O2) and one ground electrode are placed around the cranium to record EEG, using the 10-20 system of electrode placement. Some people think that it is sufficient to record from only four EEG electrodes (C3, C4, A1, A2) and one ground electrode. On the other hand, others use eight EEG electrodes (labeled C3, C4, F3, F4, O1, O2 , A1, and A2) and one ground electrode. Ear or mastoid process (A1, and A2) electrodes are used as reference electrodes. EOG is recorded by placing one electrode above and to the outside of the right eye, and another electrode below and to the outside of the left eye. EMG is actually recorded from two sites. In the classical recording for classification of sleep-wakefulness three EMG leads are placed on the chin (one in the front and center and the other two underneath and on the jawbone).

In the modern polysomnography many variables other than EEG, EMG and EOG are recorded. They include electrocardiogram (ECG), respiratory effort, nasal and/or oral airflow, oxygen saturation (SpO_2), body position, and limb movements. ECG is recorded with the help of two electrodes placed on the upper chest near the right and left arms. These are recorded merely to note the heart rate and rhythm, and for alerting the technician to a possible emergency situation. They also demonstrate whether desaturation during apnea leads to arrhythmias or not. Airflow is monitored with the help of a thermistor or thermocouple sensor. This device looks similar to a nasal cannula and is secured just under the patient's nose. It senses the amount of air moving into and out of the airways and sends signals to the physiological recorder. This tracing is used to determine the presence and extent of apneic episodes. Respiratory effort is assessed using a piezo crystal. Two Velcro bands, one placed around the chest under the breasts and one around the abdomen, serve to determine chest wall and abdominal movements during breathing. Each band has a piezo crystal transducer. The force of chest or abdominal expansion on the bands stretches the transducer and alters the signals to the physiological recorder. These leads, combined with the airflow sensor, help to detect apnea. Limb movements are assessed by recording EMG. For that purpose two EMG leads are placed on the inside of each calf muscle, about 2-4cm apart. Oxygen saturation of blood is measured by a pulse oximeter probe placed on the finger, or earlobe of the patient.

Video cameras are used to monitor the patient. If the patient's activity is tape recorded while sleeping, the technician can review the tape at any time during the analysis. It helps to verify whether strange-looking waveforms were caused by the patient's movement, or due to any other reason. Though visual assessment of polysomnogram, and EEG in particular, is essential for any sleep-wake analysis, scoring of about 1400 pages (i.e. a patient's one night record) is time consuming. So, people often resort to computer scoring to come to a conclusion, which is not a healthy practice. But automation is superior to manual scoring in some ways, as the computer can use a lot of parameters, such as alpha rhythm, sleep spindles, delta waves, rapid eye movements or tonic chin EMG levels to make a hypnogram (**Figure 3**).

Sleep stages :

The most important parameter required for sleep analysis is EEG. The different EEG waves found during sleep and wakefulness could be classified as delta (4Hz, 150-250V), theta (4 - 8 Hz, 100-200V), alpha (8-13 Hz, 50 -100V), beta (13Hz, 50V) on the basis of their frequencies and amplitudes. During the wakeful stage, the EEG alternates between beta and alpha activity. Alpha activity is observed when the subject is relaxed and the eyes are closed. Beta activity appears when the subject is alert with eyes open and scanning the visual environment. The amount of visual scanning would be reflected in the EOG, either as abundant or as scarce activity. The EMG may be high or moderate, depending on the degree of muscle tension.

The alpha activity decreases during stage 1 of NREM sleep (**Figure 2**). The EEG consists mostly of low voltage, mixed frequency activity, with much of it in 3-7 Hz range. The EOG activity is

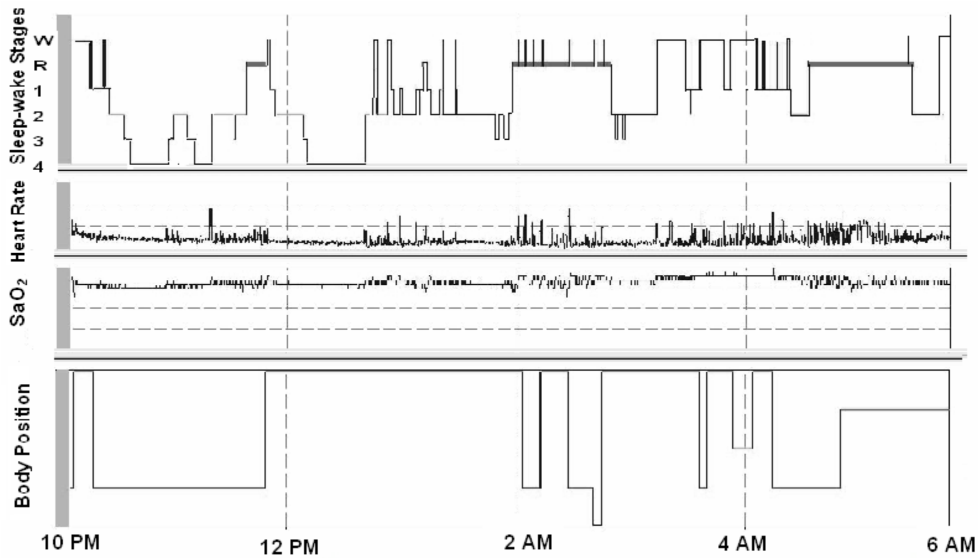

FIGURE 3 : Computer assisted scoring of sleep-wakefulness is shown in the upper graph. Simultaneous recording of heart rate, SaO_2 and body position are shown below that. W- wake stage; R- REM sleep; 1, 2, 3 and 4 are NREM sleep stages 1, 2, 3 and 4

mostly absent, but slow rolling eye movements would be present. The EMG is moderate to low during this period. Against the background of low voltage, mixed frequency EEG (of stage 1), sleep spindles (12-14 Hz sinusoidal waves) appear as the person enters stage 2 of NREM sleep. Eye movements (EOG) are rare, and EMG is low to moderate during stage 2. During stage 3, delta waves appear in the EEG, but the EOG and EMG continue to remain as before. There is a quantitative increase in delta waves during stage 4, so that they come to dominate the EEG tracing. The EOG continues as before, and EMG shows slight reduction. In a nutshell, as the sleep progresses to deeper stages, i.e. from stage 1 to 4, the EEG shows increasing voltage and decreasing frequency. Muscles are progressively relaxed during the deeper stages of sleep. Though muscle activity is reduced, the sleeper makes postural adjustments after about every 20 minutes. During NREM sleep, the heart rate and BP decline, but the gastrointestinal motility and parasympathetic activity increase.

NREM sleep alternates with REM sleep. Human REM sleep is marked by the EEG reverting to a low voltage, mixed frequency pattern, similar to that of NREM stage 1 sleep. The eyeballs show rolling movement, with superimposed bursts of rapid eye movements during this phase of sleep. So bursts of prominent REMs appear in EOG.The REM sleep is also called “paradoxical sleep”, as the

EEG (recorded from animals) during this phase becomes desynchronised (i.e. low voltage fast activity), similar to the wake stage. REM sleep, which appears after 30-90 minutes of NREM sleep, is characterised by a profound loss of muscle tone (except eye, middle ear and respiratory muscles). Muscle twitches, respiratory changes, increased heart rate and coronary blood flow are the other features of this stage. The subject recalls dreaming, when woken from REM sleep. Though REM sleep is associated with dream, some mental activity is associated with NREM sleep also. But it is less vivid and not accompanied by full dream narrative. Dreams are usually visual, but the congenitally blind have auditory dreams. REM sleep is associated with penile erection and testosterone release.

It is a common assumption that mammalian sleep and wake states are distinctly different. Though modern science identifies waking, NREM sleep and REM sleep, very objectively, by using physiological signs and behavioural correlates, studies have shown that each of these states can intrude into the other. Some components of REM sleep can, at times, appear in awake states in some clinical conditions. Similarly, wakeful behaviour can intrude into sleep, in some clinical conditions, resulting in striking consequences (5).

Sleep-wake cycle consists of inherent rhythmic changes with 24 hour (circadian) periodicity in physiological, biochemical, and psychological processes in the body. Circadian sleep rhythm is one of the several intrinsic body rhythms modulated by the suprachiasmatic nucleus of the hypothalamus, and the pineal gland. They set the body clock to approximately 25 hours, with clues such as environmental variables (like light exposure) and activity schedule entraining it to a 24-hour cycle. Light, which entrains the circadian clock to a 24-hour rhythm, is called a "zeitgeber," a German word meaning "time-giver". Thus, the inherent circadian rhythm continuously interacts with the external environments. Sleep-wake cycle can continue even without external clues, but then the cycle length assumes a periodicity of around 25 hours.

Sleep changes with age:

The amount of sleep needed by each person is usually constant, although there is a wide variation among individuals and cultures. In adults, sleep of 7-8.5 hours is considered fully restorative. In some cultures, total sleep often is divided into an overnight sleep period of 6-7.5 hours and a mid afternoon nap of about one hour. Sleep pattern changes with increasing age. Newborns show several sleep-wake cycles in a day of 24 hours. This polycyclic rhythm passes through a biphasic pattern before a monocyclic pattern is established in young adults. In newborns, the total duration of sleep in a day can be 14-16 hours. Most of it is REM sleep. During old age, total sleep is not only reduced, it is often divided into an overnight sleep period of less than 6-7.5 hours and a mid afternoon nap of about one hour.

Neural regulation of sleep:

According to traditional belief, prolonged activity of the brain during the day is followed by rest, at night, in the form of sleep. Sleep was considered as a passive process till the 1950s (6). This passive theory of sleep was replaced by the active sleep genesis concept, mainly after the realization that brain activity is only slightly reduced during sleep. Findings during the next 50 years emphasized that sleep is an active process of the brain. Employing various modern techniques, discrete areas were demarked by various scientists who assigned them the roles in the regulation of NREM and REM sleep (**Figure 4**). This led to the assertions about the roles of the preoptic and other basal forebrain areas in the generation of NREM sleep, and the interactions of the pedenculo-pontine and lateral dorsal tegmental areas with the dorsal raphae nucleus and locus coeruleus, for the generation of REM sleep (7). Unfortunately, overemphasis of localization of sleep regulating areas had led to a misunderstanding of sleep regulation itself. The emphasis on the active regulation of sleep cannot overlook the basic fact that the passive withdrawal of wakefulness plays a role in the initiation of sleep. There is now growing evidence to suggest that sleep is auto-regulatory and that it is not necessary to attribute sleep genesis to either an active or a passive mechanism (8,9).

Functions of sleep :

The importance of sleep is evident from the health problems resulting from

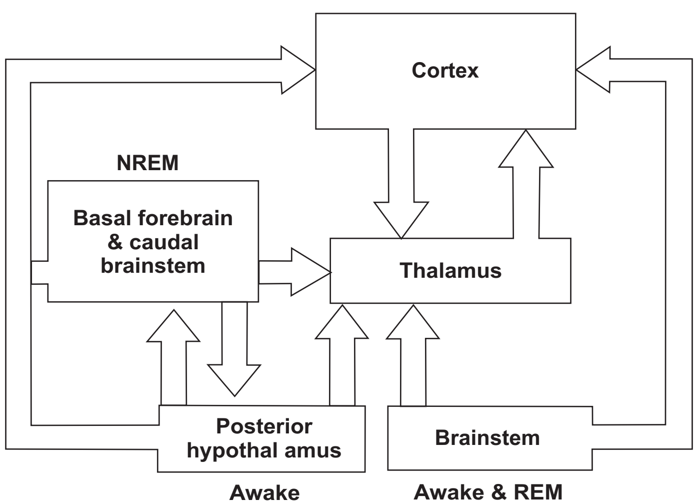

FIGURE 4 : The diagram shows the areas of the brain which are primarily implicated in the regulation of NREM and REM sleep and wakefulness. It also shows the major neural connections involved in the regulation of sleep-wakefulness.

sleep disorders. Some sleep disturbances can be described as temporary mild inconveniences, while others are far more serious with disastrous consequences. Persistent and repeated interruption of sleep affects the physical and mental health of the individual. Inadequate sleep causes not only misery to the sufferer, but it also has far reaching socioeconomic consequences. Sleep is considered essential for life as it is preserved through evolution. Moreover, both REM and NREM sleep show rebound after sleep restriction or deprivation. Sleep pressure after sleep deprivation is so strong that one falls asleep, even at the cost of one's own life. Sleep-deprived rodents die earlier than the food-deprived animals. Rats deprived of sleep die in 2-3 weeks, while food-deprived rats may survive for 4-5 weeks. Almost all mammals show NREM–REM cyclic alternation. Sleep must be having a universal functional significance, though it is still difficult to enumerate its functions. Some of the possible functions of sleep are listed below (10).

- Sleep may be having a restorative and recovery function, especially for the brain. Sleep is said to prevent metabolic brain injury. Sleep time may be related to defense against oxidative stress. Normal metabolism produces high levels of reactive oxygen species (ROS) by mitochondria. ROS levels are reduced during sleep. Sleep facilitates the synthesis of molecules that protect brain cells from oxidative stress.

- Energy conservation could be one function of sleep. Energy consumption during sleep is less by 15%. Energy intake (food intake) is increased on sleep deprivation. Sleep is more in newborns, infants and in small mammals with high surface to mass ratio. Energy cost of thermoregulation is high in small animals. Carnivores and omnivores, which are generally safe when asleep, may be using the energy-conservation aspects of sleep. Carnivores that eat meals with high calorific density can afford to have long periods of sleep.

- Sleep may have a thermoregulatory function. Mild heating of hypothalamic sleep regulatory area & warm atmospheric temperature induce sleep in animals. Body heating prior to sleep increases slow wave sleep in man. Many sleep - active neurons in the brain are thermosensitive. Cooling of brainstem (REM generating areas) in experimental animals produces an increase in REM sleep. Brain temperature increases during REM sleep, even though thermoregulation is suppressed during this stage of sleep. REM sleep is maximum during early morning, when the body temperature is at the lowest level. This prevents the fall in brain temperature.

- The role of REM sleep in brain growth has been suggested for long. Sleep, especially REM sleep, is more in new-borns. Premature babies have higher REM sleep. REM sleep amount is strongly correlated with brain maturity at birth, in the animal kingdom. Guinea pigs have very little REM sleep at birth. New-born guinea pigs are born with teeth, claws, fur and open eyes. They thermoregulate and make locomotor movements within an hour of birth. They eat solid food within a day of birth. As their brain is relatively mature at birth the new-born guinea pigs have very little REM sleep. Similarly, sheep and giraffe are relatively mature at birth, and have very little REM sleep.

- Sleep may also facilitate neurogenesis. Protein synthesis in the brain is increased during slow-wave sleep. Short-term (2–3-days) total sleep deprivation, blocks proliferation of cells in the dentate gyrus. Experimentally reducing light input in neonates reduced cells in the visual system. When neonates were also REM sleep-deprived, this shrinkage in the visual system was accelerated. It is suggested that the neuronal development proceeds according to genetic programmes, only when NREM sleep of neonates is interrupted by REM sleep.

- Memory consolidation during sleep has been proposed by many investigators. There has been a manifold increase in publications on this topic during the last few years. Non-declarative memory (motor skill) is enhanced during sleep, probably during specific sleep stages. The role of sleep in declarative memory consolidation remains largely unproven. Sleep deprivation and disturbed sleep certainly reduce concentration and learning. Motor training and improved performance produce increased slow waves in the parietal cortex, during sleep. So slow-wave sleep may facilitate memory consolidation. Regions active during task performance in PET imaging, are more reactivated during REM sleep. Several genes that are believed to contribute to memory consolidation are up regulated during sleep.

- Sleep is proposed to have many other functions. Discharge of emotions through dreaming is an age-old function ascribed to sleep. Those animals which are immature at birth benefit from the sleep-induced reduction in activity. Reduced activity would also lead to reduced exposure to danger. According to some studies man shows disturbed behaviour after REM deprivation. But, depressed persons show marked improvement on REM sleep deprivation.

Unanswered questions about sleep :

Sleep patterns of some animals make us doubt the validity of above mentioned statements regarding functions of sleep. There is near absence of sleep in postpartum marine mammals (whales, dolphins) and also their neonates do not sleep for several days. When on land, fur seals show both NREM and REM sleep. But when they are in water, they show no REM sleep. When they move back onto land, after spending weeks in the water, they show no REM rebound. Cetacean mothers show no rebound increase in sleep after the postpartum period. Migratory birds also do not sleep during their long migration. This sleep reduction during the migration is not followed by sleep rebound. Moreover, it is not possible to assert that all animals sleep, though lower forms of animals show rest-activity cycles. Length of sleep also varies in different mammals. Giraffes and elephants sleep for 4-5 hrs, whereas opossum, bats and giant armadillos sleep for 18 hrs. Amount of NREM and REM sleep also varies in different animals. Platypus has more REM sleep than any other animal (about 10 hrs). Guinea pig has only 1 hour of REM sleep per day. Length of REM-NREM cycle varies from less than 12 min in rats to 90 min or more in man. Variation in sleep and its duration and pattern is not restricted to animals.

Mild body heating increases sleep, with no rebound insomnia, not only in animals but also in man. Heating the body, prior to sleep increases slow-wave sleep in man. Extending sleep time can slightly increase REM sleep in humans, with no rebound reduction during the subsequent night. Administration of monoamine oxidase inhibitors or brain lesions can suppress REM sleep for months or years (with no detectable cognitive or physiological symptoms). Sleep reduction in mania is also not followed by rebound sleep.

Conclusion :

It can be concluded that sleep is important for health and survival. Modern technology had made great advances in recording and analyzing sleep-wakefulness, and also the progress in medical science have vastly improved our understanding of the physiology of sleep. But, we still do not know all the functions of sleep. Though some sleep disturbances are temporary mild inconveniences, physical and mental health of the individual are grossly affected when there is persistent repeated interruption of sleep. Inadequate sleep causes not only misery to the sufferer, but it also has far reaching socioeconomic consequences.

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