A JOURNEY INTO ANATOMICAL AND PHYSIOLOGICAL DEPTH THROUGH SLEEP

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1. INTRODUCTION

Sleep and wakefulness constitute a cyclical state that is intrinsically involuntary and must be continuous throughout the life of living organisms (Zhuang et al., 2005). Sleep, characterized by the relative absence of sustained wakefulness but indispensable for the health and well-being of the individual, functions as the primary activity of infancy and represents a metabolically active body state (Motamedi- Fakhr et al., 2014; Carley & Farabi, 2016).

Following a period of prolonged sleep deprivation, symptoms such as paranoid hallucinations, personality disorders, apprehension, and a state of delirium may manifest. During the Ancient Greek period, sleep was equated with death, and it was believed that Hypnos (the god of sleep) and Thanatos (the god of death) were twin brothers. Both were identified as the sons of Nyx, who was revered as the deity of the night (McNab, 2005). Sleep, a state that has historically sparked curiosity and remains enveloped in mysteries, involves bodily changes whose mechanisms have been the subject of research for years, yet its full complexity remains elusive to date. The need for sleep is an irrefutable biological necessity. Driven by this fundamental requirement, research efforts continue to focus on understanding the sleep and wakefulness states, revealing the underlying patterns, causes, and mechanisms, often centered on specific brain activations (Carley & Farabi 2016; Schneider, 2017,).

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Although often traditionally conceptualized as a passive body state, sleep is, in reality, an active physiological process involving significant energy expenditure (Blumberg et al., 2020). Physiologically, the brain is characterized by three distinct states: wakefulness, rapid eye movement (REM), and non-rapid eye movement sleep (NREM) (Schneider, 2017). REM sleep was first identified by Aserinsky and Kleitman in 1953 (Aserinsky & Kleitman, 1953; Siegel, 2005). REM is characterized by dreams and repetitive rapid eye movements, whereas NREM is a lighter stage that constitutes the majority of sleep and lacks rapid eye movements (Siegel, 2005; McNamara et al., 2010). REM sleep is alternatively termed active sleep, while NREM sleep is referred to as quiet sleep. Just as changes occur in various physiological functions, disorders can also be observed in sleep (Carskadon & Dement, 2005).

In individuals exhibiting a sound sleep pattern, sleep initiates with NREM—one of the two sleep phases characterized by a reciprocal relationship. Deep NREM sleep (NREM III) is typically observed within 80–100 minutes after sleep onset, just prior to the commencement of the first REM episode. NREM and REM phases subsequently alternate in a cycle recurring approximately every ninety minutes (Carskadon & Dement, 2005; Algın et al., 2016). During sleep, NREM occurs when the REM drive is attenuated, and conversely, REM occurs when the NREM drive is reduced. NREM sleep, which follows the state of wakefulness, comprises three distinct stages: Period I, Period II, and Period III. NREM Period III is predominantly observed in geriatric and newborn individuals. NREM Periods I and II collectively account for approximately half of total sleep, though the functions of these stages remain an area of no consensus. NREM III, conversely, is alternatively referred to as the deep sleep period associated with the alleviation of physical fatigue. NREM I is characterized by high-frequency, low-amplitude EEG

activity, while NREM III exhibits high-amplitude, low-frequency EEG activity. NREM II, however, is distinguished by the observation of EEG sleep spindles (Pagel & Parnes, 2001; Algın et al., 2016). REM sleep is often likened to wakefulness because its EEG activity is characterized by low amplitude and high frequency (Purves et al., 2001). On average, the first REM sleep episode commences approximately 90 minutes after sleep onset. Since this cyclical pattern is conserved across every night of sleep, the process typically repeats 4–6 times. On average, the overall sleep process consists of these cyclical stages with approximate percentage distributions of: REM (30%), NREM I (2.5%), NREM II (45%), and NREM III (20–25%). The initial REM period is the shortest sleep segment of the night, lasting an average of 5–15 minutes. Primarily, NREM sleep dominates the first half of the night, while REM sleep becomes more prevalent in the subsequent half. If the sleeping individual wakes up at the conclusion of one of these cycles, aligned with the day's accumulated fatigue, the probability of waking in a fully restored and rested manner is significantly high (Pagel & Parnes, 2001; Algın et al., 2016). For an individual maintaining a healthy lifestyle, the continuous maintenance of this sleep cycle, which is contingent upon numerous factors, constitutes an essential fundamental principle. Accordingly, this chapter has narrated and elucidated the physiological changes occurring in the human body and the anatomical structures functional for the sleep-wakefulness state, which continues to be the subject of ongoing research.

2. WHAT IS ELECTROENCEPHALOGRAM (EEG)?

The impetus provided by the psychiatrist Hans Berger, who lived in the 19th–20th centuries, to understand the complex mechanisms of brain function led directly to the development of the electroencephalogram (EEG) (Gloor, 1969; Read & Innis, 2017). The Electroencephalogram (EEG) is based on the principle

of quantitatively recording the complex functional electrical activity generated in the brain using electrodes placed on the scalp (Dhivya & Nithya, 2018; Chen et al., 2019). Viewed differently, the EEG method records the electrical signals generated by neurosynaptic connections—signals corresponding to physical, cognitive, and instinctive activities and events (Dement & Kleitman, 1957; Platt & Riedel, 2011; Michel & He, 2019). This process utilizes a standardized set of EEG electrodes, typically ranging from 10 to 20 in number. The EEG method is internationally recognized and plays a major role in revealing findings often undetected by modern imaging methods, particularly when clinicians face diagnostic difficulties. Furthermore, for detailed data processing, clinicians can customize the number of electrodes as needed (Dhivya & Nithya, 2018; Chen et al., 2019). The results obtained from EEG, which is frequently employed in neurological sleep units to measure brain activations during sleep, yield vital information regarding bodily function while simultaneously holding significant promise for the field of neuroscience (Motamedi-Fakhr et al., 2014). Activation within a single nerve cell can be recorded using microelectrodes placed in its vicinity. However, recording data from an individual neuron at a site relatively distant from structures like the scalp presents a considerable challenge. EEG data are generated when the summation of electrical activity, originating from synchronously active neuron clusters involved in the same duty and function, is perceived by scalp electrodes. The synchronous activity occurring across these neurons is crucial for elucidating the physiology and underlying mechanisms of the nervous system (Binnie & Prior, 1994).

2.1. ALTERATION IN ELECTROENCEPHALOGRAM (EEG) DATA AND THEIR CLINICAL INTERPRETATIONS

A neuron communicates with another neuron via electrical impulses. Pertaining to EEG generation, pyramidal cells located in the cortex receive synaptic input onto their dendrites via corticocortical and thalamocortical nerve pathways. Synaptic transmission is mediated by the interaction between neurotransmitters released from the presynaptic terminal and the receptors located in the postsynaptic membrane. These neurotransmitters and their corresponding receptors can modulate activity in either an excitatory (stimulating) or inhibitory (stimulus-reducing) direction. Depending on the intensity of the incoming stimuli, if the membrane potential reaches a supra-threshold depolarized state, an action potential is generated, which then propagates toward the axon terminal (Kirschstein & Köhling, 2009).

The EEG quantifies the temporal variations in the brain's electrical activity. This measurement is rendered in terms of key parameters such as frequency, amplitude, and latency (delay). The recorded electrical potential typically ranges between -100 and +100 μV. The brain's recorded electrical activity is derived from the summation of postsynaptic potentials (PSPs) generated by cortical neurons. The postsynaptic potential (PSP) is the voltage resulting from the action potential (AP) that is generated by the alteration of ion channel conductance in the cell membrane, following the release of neurotransmitters involved in synaptic connection and binding to the postsynaptic cell. These voltage changes, originating from the synchronous activities of nearby neurons proximal to the scalp electrodes, can persist for a few milliseconds up to hundreds of milliseconds (Read & Innis, 2017).

The recorded data, reflecting the temporal dynamics of the brain's complex functional activity, are classified into distinct categories based on their frequencies. These categories, ordered

from the fastest waveform to the slowest, are the beta, alpha, theta, and delta waves (Baykan et al., 2019).

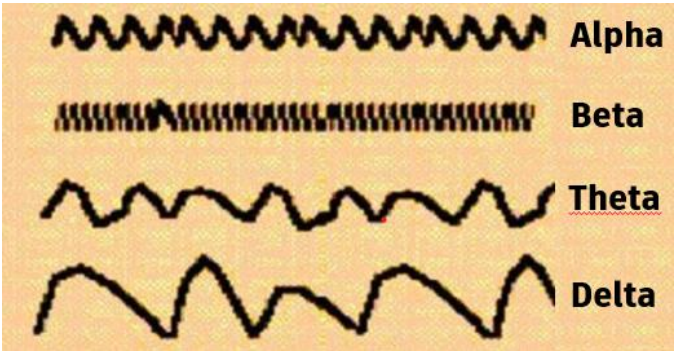
Beta; is the EEG wave activity at frequencies that are above 13 Hz.

Alpha; is the EEG wave activity at frequencies that are between 8 - 13 Hz. At the same time, it is the wave activity that is reactive with eye activities.

Theta; is the EEG wave activity at frequencies that are between 4 – 8 Hz.

Delta; is the EEG wave activity at frequencies that are below 4 Hz. They are normal wave activities in adult individuals in sleep (Figure 1)(Baykan et al., 2019).

Figure 1. EEG wave activities alpha, beta, delta and theta (Baykan et al., 2019)



3. ELECTROENCEPHALOGRAPHİC (EEG) WAVEFORMS AND SLEEP STAGE ARCHİTECTURE

The elucidation of the relationships among the metabolic, physiological, and anatomical changes occurring during sleep and the underlying neural structures began with the utilization of the electroencephalogram (EEG) toward the end of the 1950s and persists to the present day (Webb & Cartwright, 1978). Many studies focusing on the quantification of human brain changes

commonly incorporated metrics such as the electrocardiogram (ECG), electrooculogram (EOG), cardiovascular beat count, and heart rate variability. The use of the electroencephalogram (EEG) has become increasingly widespread in recent years to achieve detailed and precise results in assessing neural activations and in clinical diagnosis (Rabbi et al., 2009). The underlying mechanisms are the subject of ongoing investigation by numerous researchers who consider the physiological changes that occur during sleep. The EEG enables the recording of neuronal changes across the brain, both regionally and topographically, by placing electrodes on the scalp, thereby circumventing the need for an invasive intervention (Dement & Kleitman 1957; Platt & Riedel, 2011; Michel & He, 2019). Based on the electroencephalogram data obtained during sleep, four distinct EEG activity stages have been established for sleep (Kirschstein & Köhling, 2009). These are;

Stage I: Non-periodic activity characterized by low voltage accompanied by the absence of sleep spindles and rarely bursting alpha waves.

Stage II: Activity where low voltage sleep spindles are observed in the background.

Stage III: Appears as non-rapid activities possessing high voltage and sleep spindles are observed.

Stage IV: Appears as non-rapid activities possessing high voltage and sleep spindles are not observed.

Concurrently with sleep onset, EEG activities exhibit dynamic, temporal variations. Within this cyclical process, Stage III and Stage IV are defined as the deepest stages of sleep, while Stage I represents the lightest stage. Following sleep onset, the stages rapidly transition from I to IV. After Stage IV has occurred (for varying durations within the cycle), the sequence subsequently reverses, progressing through Stage III, II, and then

I, respectively. Consistent rapid eye movements accompanied by REM bursts are observed specifically during Stage I. Following the cessation of REM, the cyclical process reinitiates, with sleep progressing back to Stage I, III, or IV (Kirschstein & Köhling, 2009).

4. NEURAL CORRELATES SLEEP AND DREAMING

The dream state is defined in research as a phenomenon during REM sleep where cognitive activities acquired during wakefulness are functionally weakened in inter-neuronal synaptic connections, thereby promoting forgetting rather than consolidation (Crick & Mitchison, 1983).

Research demonstrates that EEG data during REM sleep exhibit similarities to EEG data in the awake state, and individuals awakened from REM sleep report highly realistic (veridical) dream experiences. The resemblance of REM sleep to wakefulness is differentiated by the concomitant loss of muscle motor activity (atonia); based on this physiological distinction, REM sleep is alternatively termed paradoxical sleep or active sleep (Siegel, 2005).

Dream recall is predominantly reported during awakenings from REM sleep. This recall often involves the dreamer's interactions with others, set in abnormal, bizarre or familiar spatial contexts, described through the dreamer's own narration. When the content of the dream is elicited, disturbing, unrealistic, and occasionally even impossible narratives are reported. While some researchers assert that the dream state is exclusively integrated with REM sleep, the occurrence of interesting, impossible, or bizarre events and settings reported by dreamers in NREM Stage 2 is very rare. The setting and narrative structure of NREM dreams tend to be more familiar (McNamara et al., 2010). The sleep process, often colloquially understood as a passive state, is an active process during which emotional

reflections (mood) are either intensely experienced or actively modulated. REM sleep, which is integrally associated with dreaming, was incorporated into the formal sleep scoring system following its initial definition via EEG (Dement & Kleitman, 1957).

Biologically, REM sleep involves three distinct processes: neuroanatomical, neurophysiological, and neurochemical. Firstly, the heightened activation observed in limbic and paralimbic brain regions facilitates the reprocessing of previously learned emotional inputs. The second process is the neurophysiological correlate of REM sleep, characterized by theta oscillations across subcortical and cortical nodes. This involves an enhancement of the perceptual and contextual connections between emotional inputs and various anatomical structures. These structural connections enable further anatomical regions to contribute to the REM state. Consequently, the experienced emotional input undergoes advanced consolidation and integration into the memory of the event. The third process, conversely, occurs in brain regions where aminergic neurochemical concentration is lower. However, in cases of excessive stress and anxiety, there is a noradrenergic input state originating from the locus coeruleus (Sullivan et al., 1999; Pace-Schott & Hobson, 2002; Ramos & Arnstein, 2007; Valentino & Bockstaele, 2008; Itoi & Sugimoto, 2010; Goldstein & Walker, 2014). The enhancement of emotionally-sourced inputs in memory and their consolidation during REM sleep contribute to psychological recovery by facilitating depotentiation through interaction with the autonomic nervous system. This process is further supported by the strengthened connections with the brain cortex, aiding in the integration and assimilation of emotional inputs. These acquired emotional data are initially preserved over a long period. In the subsequent processing phase, emotions that have critically transferred into feelings are extinguished. Crucially, the brain

retains the emotionally acquired information, but the resulting response to these inputs loses its initial intensity and no longer elicits a strong affective reaction (Goldstein & Walker, 2014).

Conversely, during NREM sleep, depotentiation occurs for emotional stimuli. Compared with wakefulness, a significant reduction is observed in the amygdala's response to prior emotional stimuli, coupled with an increase in connectivity with the medial prefrontal cortex (mPFC). Significant emotional extinction is observed, proportional to the intensity of the emotional experience and the duration of preceding wakefulness. The emotional extinction observed in brain regions and the amygdala can be associated with gamma adrenergic activity throughout the night. Therefore, the attenuation of emotional response observed in individuals with low nocturnal gamma measurement shows a correlation with this finding (Keane et al., 1976; Berridge & Foote, 1991; Cape & Jones, 1998; Pare et al., 2002; Nishida et al., 2009; Goldstein & Walker, 2014).

5. SLEEP AND RESPIRATORY DYNAMICS

The regulation of the day-night cycle, hormones, neurotransmitters, and the circadian rhythm are among the factors physiologically effective in sleep. Anatomically, the respiratory system and the nervous system also exhibit activity during sleep (Izac, 2006). During sleep, atmospheric air is predominantly inspired via the nose. It is predicted that inspiration not occurring through the nose during the waking state is 7%, whereas this figure decreases to 4% at the onset of sleep. While nasal and mouth resistance are equal during wakefulness, nasal resistance becomes lower compared with mouth resistance during sleep. However, this resistance increases in the supine lying position. It is known that in sleep, which holds a significant relationship with the respiratory system, nasal congestion can be effective in the

determination of the apnea-hypopnea index, will delay REM sleep, and can increase NREM sleep (Chebbo et al., 2013).

The respiratory mechanism, which functions to meet the oxygen requirements of tissues, facilitate the excretion of metabolic carbon dioxide, and support cellular oxidation, is a complex process mediated by the central nervous system, the motor neurons associated with respiration, and the respiratory muscles. During sustained wakefulness, both voluntary and metabolic pathways are activated to maintain the balance of oxygen and carbon dioxide levels in the blood, which is essential for pH regulation. However, upon the initiation of the sleep state, the activity within the active centers responsible for stimulation during wakefulness declines. Consequently, metabolic stimuli become the primary determinants of the required ventilation. In this context, patients with respiratory system disorders who require ventilation may rely on stimulations present during the state of wakefulness, and changes can often be observed in their sleep-wakefulness patterns. Given that the onset of sleep disables certain compensatory mechanisms, it can precipitate the development of hypoventilation or other respiratory system disorders. Therefore, the transition to sleep actually constitutes a more vulnerable physiological state (Sowho et al., 2014).

Unlike the cardiac system, the respiratory system lacks a dedicated regulatory unit analogous to the heart's pacemaker that can intrinsically control its own rhythm. Instead, the fundamental parameters of respiration—the inspiration-expiration rhythm, respiratory depth, and respiratory rate—are centrally governed by the brainstem (specifically the Medulla oblongata and pons). The Medulla oblongata houses two primary clusters of respiratory neurons: the dorsal respiratory group (DRG) and the ventral respiratory group (VRG). The DRG, which comprises the neuron group within the ventrolateral subdivision of the nucleus tractus solitarii (nuc. tractus solitarii), is active during inspiration. This

group is responsible for integrating afferent input from the pulmonary branches of the vagus nerve (n. vagus), baroreceptors and chemoreceptors of the aorta and common carotid artery (a. carotis communis), and central receptors. The VRG, conversely, is composed of premotor neurons involved in inspiration and includes a separate subdivision containing premotor neurons that drive expiration. Beyond inspiratory and expiratory neurons, the VRG also incorporates the nucleus ambiguus (nuc. ambiguus), the Bötzinger complex, the pre-Bötzinger complex, and the caudal and rostral retroambigual neurons. In this medullary region, bulbospinal neurons originating from both the VRG and DRG project their axons to synapse with spinal nerves, thereby facilitating the stimulation of the accessory muscles of respiration. The cranial nerve nuclei that innervate the muscles of the larynx and pharynx (the nuc. ambiguus contributes to the n. glossopharyngeus) are situated in close proximity to the VRG. The key rhythm-generating component within the VRG is the pre-Bötzinger complex. This complex is characterized by the presence of mu-opioid and neurokinin receptors. Specifically, mu-opioid signaling acts to depress (slow down) the pre-Bötzinger complex activity, whereas neurokinin exerts an accelerating effect. The control of respiratory activity is further modulated by receiving input from respiratory neurons located in the pons (Buchanan, 2013; Sowho et al., 2014).

The respiratory rhythm relies on the phrenic nerve (n. phrenicus), which originates from the cervical spinal nerves, and the intercostal and subcostal nerves (nn. intercostales and n. subcostalis), which arise from the thoracic spinal nerves. These nerves contribute to thoracic movements, initiating the entry of atmospheric air into the lungs and its subsequent release.During inspiration, propriobulbar neurons of the respiratory system, premotor neurons, and their synaptic connections interact with the ventral and dorsal respiratory neuron groups to generate phasic

respiratory activity. Following the synaptic connection between the expiratory neurons in the Bötzinger complex and the brainstem-spinal cord, inspiratory activity is terminated concurrently with the onset of expiratory activity. In contrast to the n. phrenicus and nn. intercostales/n. subcostalis, which innervate the diaphragm and the anterolateral chest wall muscles, the nerve fibers directed to the pharyngeal muscle motor neurons cannot actively ensure inhibition during expiration within the respiratory control mechanism. The tonic activity in these pharyngeal nerves is achieved not via projections from the ventral and dorsal respiratory neurons to the motor neurons, but rather through inputs originating from the reticular formation (formatio reticularis). Crucially, when transitioning from wakefulness to sleep, the activity of the reticular formation is suppressed. This suppression leads to a decrease in the tonic activity of the nerve fibers supplying the muscles of the upper respiratory tract (pharynx and above), thereby creating a state of collapse in the airways (Buchanan, 2013; Sowho et al., 2014).

6. ANATOMY AND PHYSIOLOGY OF SLEEP

Stimulation occurs in distinct regions of the brain during the states of sleep and wakefulness. In the waking state, the human prefrontal cortex exhibits activation, which is necessary for cognitively demanding functions such as memory, reasoning, planning, and goal-directed actions (Landolt & Borbély, 2001). During a normal sleep state, integrated with the experience of dreaming and characterized by a functional loss of consciousness, the active behaviors observed during wakefulness are absent. Sleep is evaluated as a complex process contingent upon both physical and mental health. The body undergoes cyclically alternating and distinct physiological states during REM (Rapid Eye Movement) and NREM (Non-Rapid Eye Movement) sleep (Berteotti et al., 2014).

The state of sleep (REM, NREM) and wakefulness is characterized by changes in various body systems within the homeostatic process. During REM sleep, structures located in the brainstem (pons) and the anterior-inferior part of the brain are active, whereas the medulla oblongata and the anterior-inferior part of the brain are engaged during NREM sleep. The continuity of the waking state is maintained by neural connections established by the brainstem reticular formation (formatio reticularis) with the brain's thalamocortical system via dorsal nerve fibers, and with the posterior hypothalamus and the anterior-inferior part of the brain via ventral nerve fibers (Jones et al., 2005).

Among the subcortical structures, the hippocampus, amygdala, and striatum correlate with REM sleep, while the insular lobe (lobus insularis) and the medial section of the prefrontal cortex in the frontal lobe (lobus frontalis) show activation associated with emotions. The endocrine system, which functions jointly with the nervous system as the neuroendocrine system, also regulates these physiological processes in the brain through hormonal balance (Goldstein & Walker, 2014). Serotonin and acetylcholine play an active role in REM sleep, while GABA and serotonin are prominent in NREM sleep (Algın et al., 2016).

REM sleep is anatomically correlated with increased activation in the limbic system, the dorsal prefrontal brain section, and the amygdala. The second of the NREM stages, however, is associated with greater cortical activation when compared directly with REM sleep (McNamara et al., 2010).

The most significant endocrine change occurring during REM sleep is the profound decrease in the noradrenaline level. This reduction falls well below the levels observed during NREM sleep and the wakefulness state across the 24-hour day-night

cycle. Noradrenaline plays crucial roles in general neural stimulation and in the determination of emotional processes within the body. The neuroanatomical and neurophysiological changes occurring at these levels are functionally key to maintaining bodily homeostasis (Kametani & Kawamura 1990; Marrosu et al., 1995; Shouse et al., 2000; Park, 2002; Ouyang et al., 2004; Goldstein & Walker, 2014).

Following a night of total sleep deprivation, a 60% increase in amygdala activation is typically observed in the brain. In the continuing process, regulatory and supervisory centers in the upper brain (specifically, the medial aspect of the prefrontal cortex) show decreases in their functional connections with the amygdala. Furthermore, the locus coeruleus, the major noradrenergic nucleus located in the brainstem, exhibits increased coupling in its amygdala connections with the adrenergic activating center, resembling a fight-or-flight state. As a consequence of sleep disorders, this pattern results in excessively increased amygdala reactivity coupled with a drop in connectivity between the amygdala and the medial prefrontal cortex. A decrease in sleep quality can similarly correlate with heightened amygdala reactivity in the brain. The variability in changes occurring in the connections between the cortical centers (prefrontal cortex) and the amygdala can differ among individuals, often varying according to their ability to cope with stress (Motomura et al., 2013; Prather et al. 2013; Goldstein & Walker, 2014).

The eye is a sensory organ whose functionality changes according to the state of sleep (Algın et al., 2016). Eyelid closure, occurring voluntarily or involuntarily following prolonged, physically taxing activities, is an inevitable action at the onset of sleep. This mechanism ensures the initiation and maintenance of sleep by reducing the stimuli transmitted to the cortex for evaluation. Simultaneously, the eye and its associated structures

are protected from potential involuntary trauma during sleep. Within the orbit, not only is relaxation observed in the levator palpebrae superioris muscle (m. levator palpebrae superioris), which controls eyelid movement, but contraction is also seen in the orbicularis oculi muscle (m. orbicularis oculi), which contributes to keeping the eyes closed among other ocular muscles. In a study concerning the position of the eye beneath the closed eyelid, it was reported to be in the straight gaze position (44%), in an upward-rotating position (42%), and to a lesser extent, in a lateral or downward gaze position (McNab, 2005).

Beyond the central nervous system, changes occur in the peripheral nervous system. Following a sleepless night, the reactivity of the peripheral nervous system and autonomic nervous system affects the eye as the visual organ. Pupil diameter and the activation state of eye muscles are influenced by the state of sleep or sleeplessness (Franzen & Buysse, 2008). Images and light entering the visual field are transferred either directly or indirectly from the retina to the suprachiasmatic nucleus (nuc. suprachiasmaticus), which acts as a photosensitive regulator. During wakefulness, nerve fibers carrying impulses originating from the rostral part of the pons and the caudal part of the brain bifurcate upon reaching the reticular formation (formatio reticularis) in the diencephalon. One branch projects to the thalamus and the other to the hypothalamus. Impulses are then carried to the cortex via thalamocortical, basocortical, and hypothalamocortical nerve fibers. Glutamate is the primary neurotransmitter utilized in the transmission of these impulses. Glutamate, which is accepted as the main neurotransmitter of wakefulness, can produce excitatory discharges through the function of specific glutamate receptors that enable its activation, even during slow-wave sleep (Algın et al., 2016).

The aftermath of a sleepless night, which heightens autonomic nervous system impulses, is evident in altered heart

rate within the cardiovascular system (Zhong et al., 2005; Sauvet et al., 2010). Neurons located in the brainstem, upon the commencement of the sleep state, act to reduce energy consumption while ensuring the provision of necessary oxygen and nutrients to the brain—a structure vital for continued function—and other structures essential for the maintenance of vitality. During NREM sleep, a decrease occurs in blood pressure and cardiac output, and vagal bradycardia is observed. Despite this overall reduction, cerebral blood flow increases. In REM sleep, a tonic decrease in blood pressure and heart rate is also present. Impulses directed to the heart, kidneys, and pelvic cavity decrease, whereas impulses directed to the skeletal muscles and those reaching the brain occur at a higher rate. Sympathetic system activation during REM sleep can induce phasic increases in blood pressure and heart rate. In NREM sleep, the reduction in respiration is accompanied by a resultant increase in blood acidity (carbon dioxide accumulation). This state triggers vasodilation in the blood vessels supplying the brain. Homeostatic mechanisms then promote an increase in respiration, which becomes slightly irregular. Critically, the oxygen-carbon dioxide balance in the blood remains unchanged compared to wakefulness. During sleep, the circulatory system, respiratory system, and nervous system function collaboratively to maintain homeostasis (Coote, 1982).

In terms of emotional neurosynaptic activities within the brain, sleep deprivation reveals a difference in preventive neural expectation in both the amygdala and the insular lobe (lobus insularis). In individuals who frequently experience stress and anxiety in their normal lives, the inclusion of sleep deprivation leads to an outwardly noticeable increase in their expectations. When these individuals psychologically anticipate the continuation of this state, the anxiety level further escalates,

potentially resulting in unusual responses to sleeplessness (Goldstein et al., 2013).

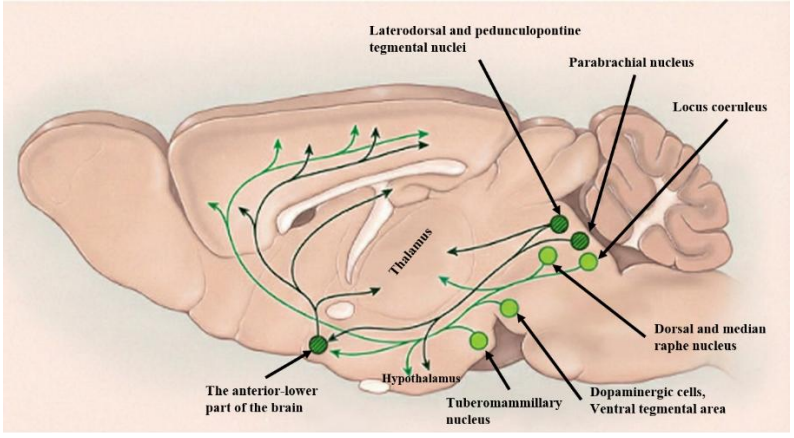
It is known that insufficient sleep or total sleep deprivation results in an exaggerated subcortical limbic or striatal response—either positive or negative—in connection with prefrontal cortex activity in the frontal lobe. This condition, which manifests as emotional instability, is characteristically observed following sleeplessness or insufficient sleep (Dahl, 1996).

It is also known that patients who contracted encephalitis lethargica (sleeping sickness), which causes psychoneurological symptoms, could sleep for an average of 20 hours per day along with disruptions in the night-day cycle. Constantin Alexander von Economo, a psychiatrist and neurologist, discovered that lesions were frequently present in the posterior cranial fossa and the hypothalamus in the brains of individuals afflicted by the disease. These regions within the central nervous system are known to be associated with waking. Subsequent experimental studies, such as electrographic stimulation of the reticular formation in cats, demonstrated EEG results similar to the body's reaction when awake. The inferences drawn suggest that the reticular formation assists in integrating information related to mood control and shapes general innervation and somatomotor responses. With technological advancement, recent contributions to the literature emphasize that systems exerting a key effect on arousal are predominantly regulated neurochemically (Economo, 1930; Scammell et al., 2017).

Regarding the pathways involved in the increase of wakefulness, a portion of these tracts, originating from the paramedian region in the midbrain, continues as the dorsal pathway from the diencephalon toward the thalamus, and as the ventral pathway toward the anterior and lower parts of the brain, the hypothalamus, and the cortex. In the dorsal pathway, which

carries sensory impulses, somatomotor responses and signals related to consciousness are processed in the thalamus. Patients with damage to the ventral pathway experience difficulty maintaining wakefulness. It has been reported that individuals with destruction in the paramedian thalamus exhibit a decrease in the duration of time spent awake. In cases of thalamic damage, the neighboring neuroanatomical structures, the hypothalamus and midbrain, may also be affected. Since both the ventral and dorsal pathways actively participate in the general state of wakefulness, clinical problems can arise. It is necessary for the dorsal pathway to provide the signal transmission connecting the thalamus and the cortex, and for the ventral pathway to remain functional for maintaining appropriate wakefulness behaviors (Ranson, 1939; Moruzzi & Magoun, 1949; Bassetti et al., 1996; Posner, 2007; Fuller et al., 2011; Giber et al., 2015; Lewis et al., 2015; Scammell et al., 2017).

Figure 2. Neuroanatomical structures that play a role in maintaining wakefulness (Scammel et al., 2017)



The thalamus contributes to the generation of rhythmic activities observed during sleep. Sleep spindles, which are bursts of activity between 7−15 Hz occurring in NREM sleep, are produced by the reticular nuclei and thalamocortical nerve cells.

Conversely, NREM slow waves primarily originate from the cortex in the brain, although the thalamus is also reported to have a contributory role (Huguenard & McCormick, 2007; Crunelli et al., 2015; Lewis et al., 2015; Scammell et al., 2017).

The monoamines responsible for promoting arousal in the brain are serotonin, dopamine, histamine, and norepinephrine. The locus coeruleus (LC) is the principal source of norepinephrine. These monoaminergic systems innervate the anterior-lower part of the brain, the cortex, and the lateral hypothalamus. These components, which also serve a firing role in the brain, exhibit high firing during the wakefulness state, slow firing during NREM sleep, and cease firing during REM sleep. The locus coeruleus is responsible for general arousal and mediates rapid awakening from sleep via photoactivation. It also drives arousal in response to situations involving anxiety, stress, novel stimuli, reward, and threat (Luppi et al., 1995; Aston-Jones & Cohen, 2005; Carter et al., 2010; Gompf et al., 2010; Schwarz et al., 2015; Scammell et al., 2017).

Serotonin, located in the anterior-lower part of the brain, originates from the dorsal raphe and median raphe nuclei. These nuclei stimulate the amygdala, insular lobe (lobus insularis), and the medial prefrontal cortex, independent of the sleep-wakefulness state. Serotonin plays a critical role in heat production. It has been reported that sleep disorder resulting from decreased or depleted environmental serotonin manifests as a consequence of hypothermia in a cool environment, and this sleeplessness state does not occur in a hot environment. Furthermore, serotonin directly stimulates neurons in brain sections responsible for increasing wakefulness (Ito et al., 2013; Weissbourd et al., 2014; Murray et al., 2015). The increased concentration of dopamine, produced from numerous parts of the brain, also encourages the maintenance of the wakefulness state (Wisor et al., 2001; Ferris et al., 2014). The nucleus

tuberomammillaris is the sole neuronal source of histamine in the brain, and it is responsible for stimulating wakefulness-related neurons in the cortex, thalamus, and brain (Parmentier et al., 2016). Cholinergic neurons, which facilitate the production of both neurally inhibitory (such as GABA) and excitatory (such as glutamate) neurotransmitters, are situated in the anterior-lower part of the brain. These cholinergic neurons are responsible for enhancing perceptions functional during wakefulness, promoting rapid cortical activity, and supporting sensory processing and neuroplasticity in the cortex. Since the anterior-lower part of the brain is directly responsible for arousal, damage to this section has been reported to cause a slowing of EEG waves. Cholinergic neurons fire in rapid cortical rhythms during wakefulness and REM sleep but exhibit lower firing rates during NREM sleep (Boucetta et al., 2014; Xu et al., 2015; Scammell et al., 2017).

Neurons situated around the nucleus accumbens in the preoptic area (area preoptica) are connected with brain regions that promote wakefulness. They facilitate these connections via vertically projecting nerve fibers, thereby contributing to the arousing effects of substances like caffeine (Lazarus et al., 2011).

The pedunculopontine tegmental nucleus (nuc. tegmentalis pedunculopontinus) and the dorsolateral tegmental nucleus (nuc. tegmentalis dorsolateralis) are the locations where communities of cholinergic neurons are found in the midbrain and pons. These nuclei also contain GABAergic and glutamatergic neuron populations. They are the fastest firing, active neurons during both wakefulness and REM sleep. The innervation of these nuclei, which connect with many subcortical regions, to the cortex is relatively sparse. Electrical stimulation in the nuc. tegmentalis pedunculopontinus region triggers the stimulation of thalamocortical pathways, which consequently leads to rapid EEG activity (Steriade et al., 1991; Wang & Morales, 2009;

Boucetta et al., 2014; Furman et al., 2015; Kroeger et al., 2016; Cox et al., 2016; Scammell et al., 2017).

The parabrachial nucleus (nuc. parabrachialis) is a neuronal cluster whose fundamental function is to transmit sensory signals to the brain and regulate the duration of arousal. Destruction of this nucleus results in a lack of reaction, sensitivity, and awareness (Parvizi & Damasio, 2003; Fuller et al., 2011; Fischer et al., 2016; Scammell et al., 2017). Orexin, also termed hypocretin, is a neuropeptide responsible for regulating wakefulness and REM sleep (Sakurai et al., 1998; de Lecea et al., 1998). Orexin is necessary for the sustained continuity of wakefulness (Adamantidis et al., 2007). Orexin is produced by neurons situated in the lateral hypothalamus and plays an active role in brain regions ensuring the maintenance of the wakefulness state (Scammell et al., 2017). Damage that may occur in orexin neurons causes an increase in the sleepy state without affecting the total sleep quantity (Herrera et al., 2016). Destruction occurring in the lateral and posterior hypothalamus, where orexins are found, results in a heavy sleep state. Furthermore, since orexin cannot stimulate the wakefulness state following this damage, an individual may experience a desire to sleep for 15−20 hours a day. Even upon waking, the desire to return to sleep persists (Herrera et al., 2016).

Regarding somnogens, which increase during wakefulness and promote sleep, the NREM sleep process follows a prolonged wakefulness state, driven by the active role of cytokines such as adenosine, prostaglandin D2, interleukin-1, and tumor necrosis factor-alpha (Krueger et al., 2011). Another characteristic of somnogens is their effect on increasing slow-wave activity on one side of the cortex. In this process, increased EEG delta waves emerge in the corresponding brain section causing a focal activity increase belonging to that side (Huber et al., 2004). After focal seizures, a decrease is usually observed in

focal EEG data. A new motor skill or motor activity, even if it does not significantly strain the individual's overall performance, elicits a response characterized by increased EEG delta waves in the corresponding motor stimulation region of the cortex during NREM sleep. Moreover, an experimental study conducted on rats that were permitted only a few hours of sleep (without adherence to a night-day cycle) recorded frequently observed, focal slow waves, which correlated with poor performance in motor capabilities. It remains unknown whether the physiological mechanism of local sleep (local increase in slow waves) follows a top-down or bottom-up (ascending from the subcortical circuit) direction (Vyazovskiy et al., 2011; Scammell et al., 2017).

Another brain section highlighted by experiments conducted by Constantin von Economo is the preoptic area (area preoptica) and the anterior-lower part of the brain in individuals experiencing sleeplessness problems. Lesions occurring in these regions are reported to result in persistent sleeplessness. The reason for this is emphasized to be the location of sleep-promoting neurons within the anterior-lower part of the brain and the preoptic area (von Economo, 1930; Scammell et al., 2017). Although the majority of neurons located in the anterior-lower part of the brain contribute to wakefulness, a fraction of neurons also play an active role in NREM sleep. These neurons, which are few in number, activate and begin firing a few seconds before the onset of NREM sleep and continue to fire throughout this stage (Kim et al., 2015; Xu et al., 2015; Scammell et al., 2017).

The parafacial region located in the medulla oblongata of the brainstem is known to contain neurons that promote NREM sleep. Conversely, damage occurring in this region, which disrupts its connection with GABAergic and glycinergic neurons, results in an increase in wakefulness (Batini et al., 1958; Anaclet et al., 2014). Structures crucial for the formation of paradoxical sleep (REM sleep), which is characterized by slow waves (often

mislabeled in older literature, as REM is characterized by fast, low-voltage EEG), are situated in the brainstem, with GABAergic and glutamatergic neurons playing a key role (Luppi et al., 2012). Although its precise mechanism is not fully elucidated, the transition to NREM sleep is thought to be associated with neurons in the preoptic area (area preoptica) and the anterior-lower part of the brain (Saper et al., 2010). Regarding REM sleep, connections within the pons of the brainstem are critical. It has been reported that a lesion occurring in the distal pons leads to an EEG activity characterized by rapid and low amplitude, but muscle atonia is absent. Conversely, a transection occurring in the rostral pons region preserves muscle atonia during REM sleep, but rapid EEG activity is not observed (Jouvert, 1962; Hobson et al., 1975; Siegel et al., 1984; Scammell et al., 2017). Furthermore, the sublaterodorsal nucleus region in the pons has been defined as the area thought to mediate muscle atonia during REM sleep (Scammell et al., 2017).

Another endocrine gland involved in the sleep-wakefulness cycle is the pineal gland (gl. pinealis), which secretes melatonin from its pinealocyte cells. During the day, light entering the eye stimulates the retinohypothalamic tract (tr. retinohypothalamicus). Ganglion neurons located in the retina stimulate the suprachiasmatic nucleus (nuc. suprachiasmaticus). Nerve fibers emerging from here inhibit the superior cervical ganglion (ganglion cervicale superius). Consequently, this sympathetic system inhibition prevents melatonin from entering the circulation. At night, light deprivation causes the sympathetic system to be stimulated. The pineal gland then releases melatonin, which contributes to the initiation of the sleep state. Disruption of this cycle, such as in the case of jetlag, negatively impacts the melatonin release mechanism, consequently causing changes in the sleep-wakefulness state (Ilahi et al., 2018).

7. IMPACT OF PAİN ON SLEEP

It is rarely observed that pain sensation up to moderate severity, occurring anywhere in the body, acutely disrupts an individual's sleep state. However, in cases of acute pain, somatomotor and neurological responses that disrupt sleep can occur. In chronic pain conditions, pain stimuli that might be ignored or responded to minimally in normal situations are known to exert a cumulative, detrimental effect on both sleep duration and quality (Foo & Mason, 2003).

Physiologically, the sleep onset latency (transition phases to sleep) of individuals with chronic pain is explained as being longer compared to normal individuals. Furthermore, their slow-wave sleep (SWS) can be fragmented by the intrusion of alpha wave activity (Moldofsky et al., 1975; Witting et al., 1982; Moldofsky et al., 1983; Mahowald et al., 1989; Lavie et al., 1992; Drewes et al., 1998; Schneider et al., 2001).

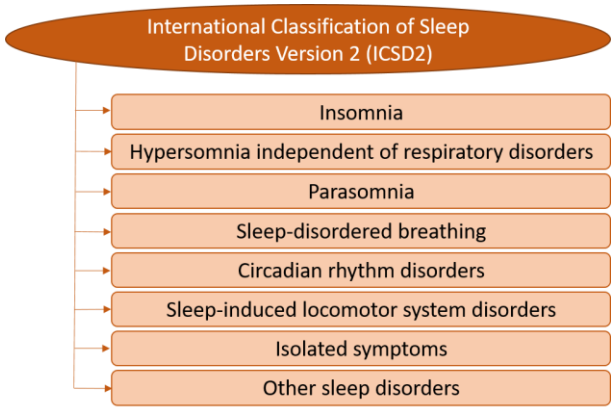
Just as pain causes sleep disorders, insufficient sleep duration and quality (sleep disorders) can also trigger pain problems. Individuals with pain complaints commonly report to clinicians that their pain becomes even more severe the following day when accompanied by sleep disorders (Moldofsky et al., 1975; Drewes et al., 1994; Jamieson et al., 1995; Affleck et al., 1996; Moldofsky, 2001; Raymond et al., 2001). Beyond this reciprocal relationship, additional factors such as underlying depressive episodes, mood-disrupting elements like anxiety, careless or excessive drug use, and hormonal imbalances can also independently trigger or exacerbate both pain and sleep disorders in individuals with chronic pain complaints (Foo & Mason, 2003).

8. THE STATE OF SLEEPLESSNESS

The state of sleeplessness (insomnia) can originate from numerous events that occur both before and during sleep. According to the globally accepted International Classification of

Sleep Disorders Version 2 (ICSD-2), a total of 85 defined sleep disorders are recognized. These disorders are grouped under eight main headings (Karadağ, 2007).

Figure 3. International Classification of Sleep Disorders



An individual's psychosocial attitude and behavior are determined by the combination of their emotional behaviors regarding emotion and state with the social environment in which they live. Circadian sleep disorders, depression, and anxiety, which correlate with psychosocial status disorders (an important contemporary issue), can negatively affect sleep (Baglioni et al., 2016). There is a consensus in the literature that disrupted sleep pattern and duration increase the incidence of illnesses, burnout, and the need for health services (Âkerstedt, 2006).

The transformation of psychophysiological sleeplessness into a persistent state is considered the stress-related primary reason for sleeplessness. It is known that major depressive episodes, anxiety disorders, and psychological traumas experienced by the individual also trigger a noradrenaline imbalance, which plays a critical role in the neuroendocrine system, and consequently lead to sleeplessness pathologies (Goldstein & Walker, 2014).

Sleeplessness brings forth numerous physiological and metabolic problems. Health issues such as cardiovascular problems, diabetes, and obesity are cited in the literature as some of these consequences. In severe cases where the body cannot maintain homeostasis, the intolerable state of sleeplessness can result in mortality. In one study, mortality was reported in rats whose sleep was prevented over a 5-week period. It was also conveyed that sepsis in the rats had an effect on this process. The most critical aspect of this widely discussed issue is that sleep deprivation disrupts the thermoregulation mechanism and affects the level of immune defense, leaving the body vulnerable. It is predicted that fatal familial insomnia syndrome, which is assumed to be genotypic in origin, can also indirectly lead to mortality if no solution is found (Rechtschaffen & Bergmann, 1989; Everson & Toth, 2000; Kripke et al., 2002; Âkerstedt, 2006).

It is known that a decrease in comprehension ability may occur in an individual who cannot get sufficient sleep, and this situation can lead to occupational accidents by causing loss of attention in working life. These occupational accidents can sometimes result in mortality. Furthermore, the significant physiological effect of sleeplessness on the anatomical structures of the brain should not be disregarded (Âkerstedt, 2006).

9. RESULT

Sleep, which constitutes an indispensable component of life, has consistently been a subject of interest and curiosity for numerous researchers. Sleep that is insufficient in both quantity and quality can precipitate various pathologies across an individual's physiological, metabolic, neurological, and psychological functions. To properly understand the processes of sleep and wakefulness, numerous studies, spanning from the past to the present, have generated hypotheses aimed at elucidating the

anatomical structures within the central nervous system connected with sleep and their underlying physiological mechanisms.

Although the increasing volume of recent studies appears to have created a saturation in the literature, the entire mechanism and all functions of sleep have not yet been fully elucidated or explained. While a portion of the formation, types, and pathologies associated with wakefulness and sleep is currently understood, there remain many topics on which a complete consensus has not yet been formed. The existing unknowns regarding sleep and wakefulness currently maintain their enigmatic position in the field of neuroscience. The critical contribution expected from daily advancing technology and the integration of new methods indicates that the existing questions concerning sleep will eventually be answered by researchers in the future.

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