








Review

Sleep Paralysis: Pathogenesis, Clinical Manifestations, and Treatment Strategies

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Abstract

Sleep paralysis, colloquially known as “ghost pressing” is a state of momentary bodily immobilization occurring either at the onset of sleep or upon awakening. It is characterized by atonia during rapid eye movement (REM) sleep that continues into wakefulness, causing patients to become temporarily unable to talk or move but possessing full consciousness and awareness of their surroundings. Sleep paralysis is listed in the International Classification of Sleep Disorders, 3rd Edition (ICSD-3) as a parasomnia occurring during REM sleep that be classified as either isolated or narcolepsy-associated. Several brain areas, including the forebrain, hypothalamus, and brainstem, as well as several neurotransmitters and modulators, are involved in the control of REM sleep. The primary brain region responsible for inducing muscle paralysis during REM sleep is the subcoeruleus nucleus, also known as the sublateralodorsal (SLD) nucleus in rats. Sleep paralysis results from the inability to immediately restore muscle tone during the transition from sleep to wakefulness. In this article, we systematically review the neural circuit that controls REM sleep and the underlying mechanisms, predisposing factors, clinical characteristics, and treatments for sleep paralysis. We also compare isolated sleep paralysis (ISP) and narcolepsy-associated sleep paralysis and speculate upon the role of microsleep in sleep paralysis.

Keywords: sleep paralysis; narcolepsy; parasomnia; REM sleep; sleep disorder; sleep wake disorder; mechanism

1. Introduction

Sleep is one of the most important physiological phenomena in mammals. It can be categorized into rapid eye movement (REM) and non-rapid eye movement (NREM) sleep [1,2]. NREM sleep can be further divided into NREM stages 1, 2, and 3. Contrary to popular belief, sleep is not a passive state but one that involves dynamic cellular functions that are controlled and regulated by precise neural structures and networks.

REM sleep, also called active sleep, was first discovered in humans by sleep research pioneers Aserinsky and Kleitman in 1953 [3]. Alternating with NREM sleep (quiescent sleep periods), it is characterized by rapid eye movements, low-amplitude and high-frequency electroencephalography (EEG) waves, and muscle atonia, which was first described in cats by Jouvet *et al.* [4]. If muscle tone is not suppressed during REM sleep, REM sleep behavioral disorder can occur and cause injury to the patient and their sleep partners [5,6].

Although sleep paralysis can occur with narcolepsy (i.e., narcolepsy-associated sleep paralysis) [7], it more

commonly occurs without it (isolated sleep paralysis, ISP) [8,9], and many people experience it several times in their lives.

Narcolepsy is a chronic sleep disorder characterized by excessive daytime sleepiness, cataplexy (partial or complete collapse due to generalized muscle weakness), pre-sleep/first awakening hallucinations. Sleep paralysis and narcolepsy can occur in the same patients, and approximately 30–50% of patients with narcolepsy experience sleep paralysis [7]. Whether or not sleep paralysis occurs in narcolepsy patients might be related to the type of narcolepsy, lifestyle, and psychological factors (stress, anxiety, etc.). Sleep paralysis occurs more often with type 1 narcolepsy (NT1)—due to lack of orexin in the central nervous system—than NT2 [10].

Sleep paralysis itself is an innocuous condition, but it is frequently viewed with concern and even dread. If there are frequent episodes of sleep paralysis accompanied by excessive daytime sleepiness, cataplexy, or other symptoms, further investigation is necessary [10]. The state of physical immobility of sleep paralysis is often accompanied by “ghost-like” hallucinations and feelings of fear



Table 1. Comparison of isolated and narcolepsy-associated sleep paralysis.

| | Isolated sleep paralysis | Narcolepsy-associated sleep paralysis |
|------------------------|---|--|
| Definition | Occurring alone without narcolepsy | A common symptom of narcolepsy |
| Pathological mechanism | REM sleep abnormalities | Orexin deficiency and REM sleep abnormalities |
| Frequency | Low and episodic | High |
| Severity | Less severe | More severe |
| Concomitant symptom | Anxiety and fear Hallucinations | Excessive daytime sleepiness and cataplexy Pre-sleep/first awakening hallucinations |
| Treatment | Primarily non-pharmacological interventions | Primarily pharmacological interventions for narcolepsy |

REM, rapid eye movement.

[11]. These hallucinations typically fall into three categories: (1) a sense of an evil presence, fear, and hallucinations (intruder hallucinations); (2) chest pressure feeling and breathing difficulties (incubus hallucinations); and (3) vestibular–motor (VM) hallucinations, which are illusory sensations of movement and can include flying and out-of-body experiences [8,12]. The content of hallucinations during sleep paralysis is likely a continuation of dream content from REM sleep, as it occurs during the transition phase between REM sleep and wakefulness, where brain activity associated with REM sleep persists [13]. In many countries, sleep paralysis is intertwined with folklore and attributed to supernatural phenomena, such as witchcraft and demons, which can make it even more terrifying and distressing [8].

Although they share similar symptoms, isolated and narcolepsy-associated sleep paralysis differ in several aspects (Table 1).

In recent years, an increasing number of studies have explored the mechanisms underlying sleep paralysis and associated hallucinations [14,15]. In this article, we systematically review the epidemiology, predisposing factors, pathogenesis, and mechanisms of sleep paralysis, along with the brain circuit that regulates REM sleep.

2. Epidemiology

There is controversy regarding the reported prevalence of sleep paralysis, with estimates varying widely from 2% to 60%, which may be due to heterogeneity in terms of clinical presentation and/or the specific diagnostic tools used [13,16]. In a systematic review study involving 36,533 participants, the prevalence of lifelong sleep paralysis in the general population was reported as 7.6% [9] and varied in different populations, with higher prevalences in students (28%) and rural [17] and psychiatric patients (32%) [9]. However, a systematic review and meta-analysis involving a total of 167,133 participants from 25 countries in 2024 showed a global prevalence of sleep paralysis of 30%, with subgroup analyses similarly revealing a high prevalence in psychiatric patients (35%) and nonpsychiatric students (34%), while meta-regression showed no association with gender [16]. In addition, according to one previous report, roughly 75% of sleep paralysis episodes were reported to be accompanied by a wide variety of horrifying hallucinations [18].

However, a recent review and meta-analysis reported that 3.8% of patients with sleep paralysis experienced only visual hallucinations, 0.04% experienced only auditory hallucinations, and 24.25% reported both visual and auditory hallucinations; i.e., the vast majority (71.88%) of patients did not have hallucinations [16]. Furthermore, sleep paralysis was found to be accompanied by incubus experiences in 11% of cases in a meta-analysis study [19].

Sleep paralysis was reported to cause clinically significant distress in about 10% of patients and interfere with their lives in 7% of cases [20]. However, not all sleep paralysis attacks were reported to be fearful. One survey showed that up to 20% of sleep paralysis episodes were pleasant [21]. Cultural diversity and different lifestyles across regions greatly influence the incidence and experience of sleep paralysis.

3. Predisposing Factors Associated With Sleep Paralysis

Sleep paralysis can occur in both males and females, with onset usually during adolescence and without any obvious gender preference [22]. Many factors have been demonstrated to be associated with the intensity and/or frequency of sleep paralysis, and several medical conditions other than narcolepsy have also been implicated, including idiopathic hypersomnia, insufficient sleep syndrome, hypertension, Wilson’s disease, and obstructive sleep apnea [14,16,23–25]. The multifactorial nature of sleep paralysis demands a more detailed review of sleep-related predisposing factors, which are presented in the following sections.

3.1 Sleep Hygiene, Academic Stress and Gender Differences

Sleep hygiene, a determining factor of sleep quality, is closely related to the presence and onset of sleep paralysis [13]. Sleep deprivation, irregular sleep–wake schedules, jet lag, etc., can all lead to sleep paralysis, which might explain the relatively higher incidence of sleep paralysis in the young and student populations [26]. A study of predominantly Hispanic and female undergraduates at a large university in the southwestern United States showed that students with a history of sleep paralysis had poorer sleep quality and greater levels of mental stress than students without

a history of sleep paralysis [27]. Moreover, the incidence of most stress-related psychiatric disorders, such as anxiety and impulse control disorders, peaks during the school-age years, which in turn increases the risk of sleep paralysis [28,29]. The negative effects of academic burnout are another proven cause of the higher prevalence of sleep paralysis among medical students, especially females [30,31]. Besides, cross-sectional studies on engineering students in India have also shown a strong correlation between academic stress and poor sleep hygiene with sleep paralysis, which suggests that similar outcomes can also occur in other high-pressure academic fields [32,33]. Furthermore, the higher prevalence of sleep paralysis among female students may be partially explained by gender-specific stress responses since females are more likely to experience internalizing disorders (e.g., anxiety and depression), heightened emotional reactivity to stress, and increased rumination, all of which are known to disrupt sleep quality and increase vulnerability to parasomnias such as sleep paralysis [34,35]. Sociocultural expectations and gender-role stress may further exacerbate this risk among female students in competitive academic environments [34].

These psychological and behavioral responses may be rooted in sex-based neurobiological differences that shape how females perceive and physiologically respond to stress. Sex differences in the hypothalamic-pituitary-adrenal axis have been well-documented, with females exhibiting heightened activation, slower negative feedback, and prolonged cortisol exposure due to sex-specific patterns of corticotropin-releasing factor receptor signaling and trafficking [36,37]. These biological differences can lead to difficulty in downregulating the stress response in females, ultimately increasing the risk of stress-related sleep disturbances such as sleep paralysis. Additionally, sex differences in neurotransmitter systems, including serotonin, dopamine, and gamma-aminobutyric acid (GABA), contribute to gender-specific variations in the stress response and sleep regulation. These factors, along with the influence of gonadal hormones like estrogen, increase the vulnerability of females to sleep paralysis [38].

3.2 Circadian Disruption

Recent research increasingly suggests a complex reciprocal feedback loop among circadian misalignment, mood disorders, and sleep paralysis [39,40]. Understanding the interplay among the factors that contribute to circadian disruption is essential for elucidating the underlying mechanisms of sleep paralysis and developing effective intervention strategies.

3.2.1 Melatonin and Light Exposure

Melatonin secretion and light exposure are two principal factors linking the circadian clock with sleep regulation, particularly in modulating the timing of the sleep-wake cycle and the structure of REM sleep [41]. Under

typical conditions, melatonin is secreted during the night to promote sleep and maintain circadian rhythmicity. However, exposure to light (especially short-wavelength blue light) potently suppresses melatonin secretion and delays its onset in a dose-dependent manner, thereby shifting circadian phase and degrading sleep quality [42,43]. Irregular light exposure patterns, including excessive nocturnal screen media use or insufficient daytime light exposure, have been shown to impair melatonin excretion and circadian regulation, leading to an increased likelihood of sudden transitions from REM sleep to wakefulness without full restoration of motor control [44]. Furthermore, disrupted melatonin rhythms and circadian dysregulation have been implicated in mood disorders such as depression and anxiety, which are themselves established risk factors for sleep paralysis [45]. In short, disruption of melatonin secretion due to inappropriate light exposure destabilizes circadian rhythm regulation and sleep integrity during REM sleep, increasing the risk of sleep paralysis.

3.2.2 Seasonal (Photoperiodic) Factors

The season of birth determines the photoperiodic environment to which neonates are exposed, potentially influencing circadian preferences and susceptibility to sleep disorders such as sleep paralysis [46]. A study involving 1942 Chinese patients diagnosed with narcolepsy with cataplexy revealed a peak in births during November and a trough in April [46]. This suggests that individuals born during shorter photoperiods (typically winter) experience reduced natural light exposure in early life, which may disrupt melatonin secretion and delay circadian phase alignment, leading to long-term alterations in sleep-wake timing. These findings are supported by a systematic review and meta-analysis encompassing 3776 patients across eight regions, which identified consistent seasonal birth patterns associated with narcolepsy risk [47]. Although these studies focused on narcolepsy, the underlying mechanism involving early-life short photoperiods shaping the circadian system may similarly increase the risk of sleep paralysis.

3.2.3 Breakfast Regularity

Irregular breakfast consumption has been known to be associated with disruptions in circadian rhythms, potentially influencing sleep quality and increasing the risk of sleep paralysis [48]. One study found that skipping breakfast for six days induced a significant phase delay in the circadian rhythm of the body temperature in healthy young adults [49]. Additionally, analyses using big data have shown that unfavorable mealtime and meal skipping were associated with a higher risk of circadian syndrome, a condition characterized by concurrent metabolic, mood and sleep disturbances [50]. Given that both circadian misalignment and comorbid mood disorders are well-established risk factors for sleep paralysis, irregular breakfast habits can also contribute to sleep paralysis.

3.2.4 Chronotype

Chronotype refers to an individual's natural preference for specific activity periods throughout the day, categorized into morning, evening, and intermediate types [51]. In a study involving 432 Italian students, participants who reported experiencing sleep paralysis exhibited higher levels of anxiety and poorer sleep quality, and these individuals were more likely to have an evening chronotype (more active at night) [33]. In other words, individuals with an evening chronotype generally have poorer sleep quality, which is associated with an increased susceptibility to sleep paralysis. Moreover, evening-type individuals are more prone to circadian misalignment, especially in the context of modern lifestyles that often favor late-night schedules, which in turn disrupts the integrity of REM sleep [52]. Evening chronotype appears to negatively impact both sleep quality and circadian rhythm regulation, thereby increasing the risk of sleep paralysis. Further research is needed to explore the underlying mechanisms linking evening chronotype to sleep paralysis and to evaluate potential interventions targeting evening chronotype to mitigate the risk of sleep paralysis.

3.3 Psychiatric Disorders

Sleep paralysis has also been linked to psychiatric disorders, personality, intelligence, bizarre beliefs, sleep disorders, and post-traumatic stress disorder (PTSD) [29]. Patients with psychiatric disorders have the highest prevalence of sleep paralysis due to the vicious cycle that exists between psychiatric disorders and sleep disorders, and because they are at higher risk for sleep deprivation, substance abuse, and other factors that are positively correlated with sleep paralysis [16,29]. Interestingly, psychiatric patients may provide exaggerated accounts of their sleep behavior as an emotional response, subjectively considering themselves conscious yet unable to move their bodies. This may also explain the high prevalence of sleep paralysis in patients with depression and anxiety disorders, although this requires further verification. In addition, a higher prevalence has been demonstrated in people who have experienced stressful and traumatic events (childhood sexual abuse, disasters, death of loved ones, etc.) [53,54].

3.4 Genetic Susceptibility

Based on recent findings that suggest a potential genetic basis for sleep paralysis susceptibility, ethnic differences in prevalence may provide additional clues to its underlying heritable components [9,55]. The systematic review encompassing over 36,000 participants revealed significant ethnic differences in the lifetime prevalence of sleep paralysis [9]. Specifically, Africans in the general population exhibited the highest prevalence of sleep paralysis (40.2%) among all ethnic groups, followed by Asians (31.0%). Among the student populations, Asians showed the highest prevalence (39.9%), whereas in psy-

chiatric samples, Hispanics had the highest prevalence (57.1%). Overall, the highest total prevalence was found in Asians (38.7%), followed by Caucasians (36.9%), Africans (34.1%), and Hispanics (18.5%). These findings suggest that variations in gene frequencies across ethnic groups may influence the expression of genes involved in sleep regulation, thereby contributing to the observed ethnic disparities in the prevalence of sleep paralysis. However, the underlying genetic mechanisms responsible for these differences remain underexplored. With the advancement of modern genetic technologies, it is now feasible to conduct large-scale investigations that could improve our understandings of the genetics involving sleep paralysis and its interaction with environmental factors.

In a study based on a community sample of twins from England and Wales, genetic factors were found to have a moderate influence (estimated at 53%) on sleep paralysis [56]. The study identified a significant association between the rs2304672 single-nucleotide polymorphism in the period circadian regulator 2 (*PER2*) circadian rhythm gene and sleep paralysis in both additive and dominant models of inheritance, suggesting that circadian rhythm disruptions mediated by *PER2* may cause individuals more susceptible to sleep paralysis. However, further work is needed to determine specific polymorphisms and their precise role in circadian rhythm regulation and sleep homeostasis.

Another prominent gene associated with sleep paralysis is the human leukocyte antigen (HLA) class II allele *DQB1*06:02*, which has been identified in approximately 90% of patients with NT1 [57]. This allele is widely regarded as a hall mark of NT1 and is believed to act via T-cell-mediated autoimmune mechanisms that target and destroy orexin-producing neurons in the lateral hypothalamus [10,58]. The resultant orexin deficiency leads to dysregulation of REM sleep, a core feature of both NT1 and sleep paralysis. The shared REM-related dysregulation underscores the potential utility of narcolepsy as a model for exploring the heritable components of sleep paralysis. Therefore, further investigation into the genetic basis of narcolepsy may provide critical insights into the etiology and inheritance patterns of sleep paralysis.

3.5 Physical Comorbidities and Nutritional Deficiency

While some physical health indicators have been examined in relation to sleep paralysis, there is no consensus in the current literature. An association of higher body mass index (BMI) with lifelong and recurrent episodes of fearful sleep paralysis has been observed, but no such link has been found in the majority of relevant studies [59,60]. Additionally, chronic pain and insomnia were also found to be associated with the experience of sleep paralysis [61]. A systematic review designed to assess the effects of vitamin D supplementation on the mental health of healthy adults suggests that while vitamin D is not directly linked to sleep paralysis, a severe deficiency may lead to poor

sleep quality, fatigue, and mood disorders, which can exacerbate the symptoms of sleep paralysis [62]. As vitamin D3 has been linked to neuromuscular function, sleep regulation, and mental health, its role in sleep paralysis warrants further study [63].

4. Brain Circuitry Controlling REM Sleep

Sleep paralysis occurs mainly in the transition between REM sleep and wakefulness. Therefore, it is imperative to understand the brain circuitry that controls REM sleep in order to elucidate the mechanism of sleep paralysis. REM sleep, which occurs in nearly all mammals and birds [64], arises in the brainstem and is facilitated by “REM-on” neurons and inhibited by “REM-off” neurons [65]. “REM-on” neurons are a class of neurons that are highly active during REM sleep but less active or even inactive during NREM sleep and wakefulness. They primarily function in triggering and maintaining REM sleep and coordinating REM sleep features such as rapid eye movements, muscle atonia, and desynchronized EEG activity [66]. In contrast, “REM-off” neurons are highly active during NREM sleep and wakefulness but almost completely inactive during the REM sleep, and they serve to prevent REM sleep from occurring [66]. Both types of neurons are widely distributed in brain regions such as the medulla oblongata, pons, midbrain, and hypothalamus. “REM-on” neurons inhibit “REM-off” neurons and vice versa, analogously to an electronic flip-flop switch. This serves as the foundation for a model of REM sleep generation [67], where mutual inhibition ensures there is rapid transition from one state to another [68].

The regulation of REM sleep directly or indirectly involves several anatomical nuclei primarily located in the lower brainstem, limbic system, thalamus, hypothalamus, and cortex. These are involved in the generation and maintenance of the sleep–wake cycle, of which REM sleep is a major component. In addition, neurotransmitters such as glutamate (Glu), GABA, glycine, histamine, acetylcholine, serotonin, and norepinephrine as well as neuropeptides such as orexin (OX) and melanin-concentrating hormone (MCH) are involved in the induction and regulation of REM sleep [69–71] (Fig. 1).

Understanding the mechanism of REM sleep is challenging not only because of its complexity and the ever-changing nature of the field but also variations in anatomical atlases and the terminology used to describe the same structures in different species [72–74]. For example, the subcoeruleus nucleus in humans is equivalent to the perilocus coeruleus alpha nucleus (peri-LCa) in cats and the sublateralodorsal (SLD) nucleus in rodents [70]. For clarity, only the term SLD is used in this review.

4.1 Modulation by “REM-On” Neurons

The brain circuitry responsible for regulating REM sleep was first investigated by Michel Jouvet, who discov-

ered an area in the dorsal pontine that is essential for muscle atonia during REM sleep [75]. With the advancement of experimental tools, decades of subsequent experimental work have further pinpointed the position of this “atonia generator” to the sublateralodorsal (SLD) nucleus of the pons [4,67,76–78]. In addition, caudal laterodorsal tegmental (cLDT) neurons, which are located dorsally adjacent to the SLD nucleus, are also thought to be associated with atonia production [67]. The SLD nucleus has now been shown to be the most active region in REM sleep [79], with many spinally projecting glutamatergic neurons in its ventral portion that function to produce muscle atonia in both direct and indirect ways. They directly synapse with inhibitory interneurons in the spinal ventral horn (SVH), which inhibit spinal motoneurons either directly via GABA or glycine or indirectly by projecting to GABAergic and glycinergic neurons in the ventromedial medulla [67,79–81]. In addition, many studies have highlighted the importance of the ventromedial medulla in developing muscle atonia, including the medially located ventral gigantocellular reticular nucleus (GiV) and a-gigantocellular reticular nuclei (GiA) [82–84]. The glutamatergic neurons in the ventromedial medulla are connected to interneurons in the spinal ventral horn, which in turn inhibit motoneurons in the spinal cord (Fig. 2) [85,86]. Furthermore, the pedunculopontine tegmentum (PPT) and the laterodorsal tegmentum (LDT) in the pontine reticular formation (PRF) release acetylcholine to activate glutamatergic neurons in the SLD nucleus to promote REM sleep.

Two functionally distinct types of glutamatergic neurons are found in the SLD nucleus: (1) corticohippocampal activation-promoting neurons, which act to increase consciousness through the parabrachial nucleus and medially adjacent precoeruleus region, and (2) reticulospinal REM sleep atonia-generating neurons, which cause atonia during REM sleep [4,67,87,88]. Glutamatergic projections from the parabrachial nucleus and precoeruleus, and cholinergic projections from the pedunculopontine tegmentum and the laterodorsal tegmentum, reach the intralaminar and reticular thalamic nuclei, lateral hypothalamus, and basal forebrain, which in turn reach the cortex and hippocampus to produce cortical activation [71,88,89]. Therefore, these two kinds of functionally separated glutamatergic SLD “REM-on” neurons might provide a pathological basis for separating changes in cortical activation and muscle tone associated with REM sleep observed in various REM sleep disorders, including sleep paralysis.

Another class of neurons, “inhibitory REM-on” neurons, is involved in REM sleep regulation. Although both “inhibitory REM-on” and “REM-on” neurons are closely related to the initiation and maintenance of REM sleep, they regulate REM sleep through different mechanisms. “REM-on” neurons are activated at the onset of REM sleep, and they activate the neural network primarily using glutamate as an excitatory neurotransmitter, whereas “inhibitory

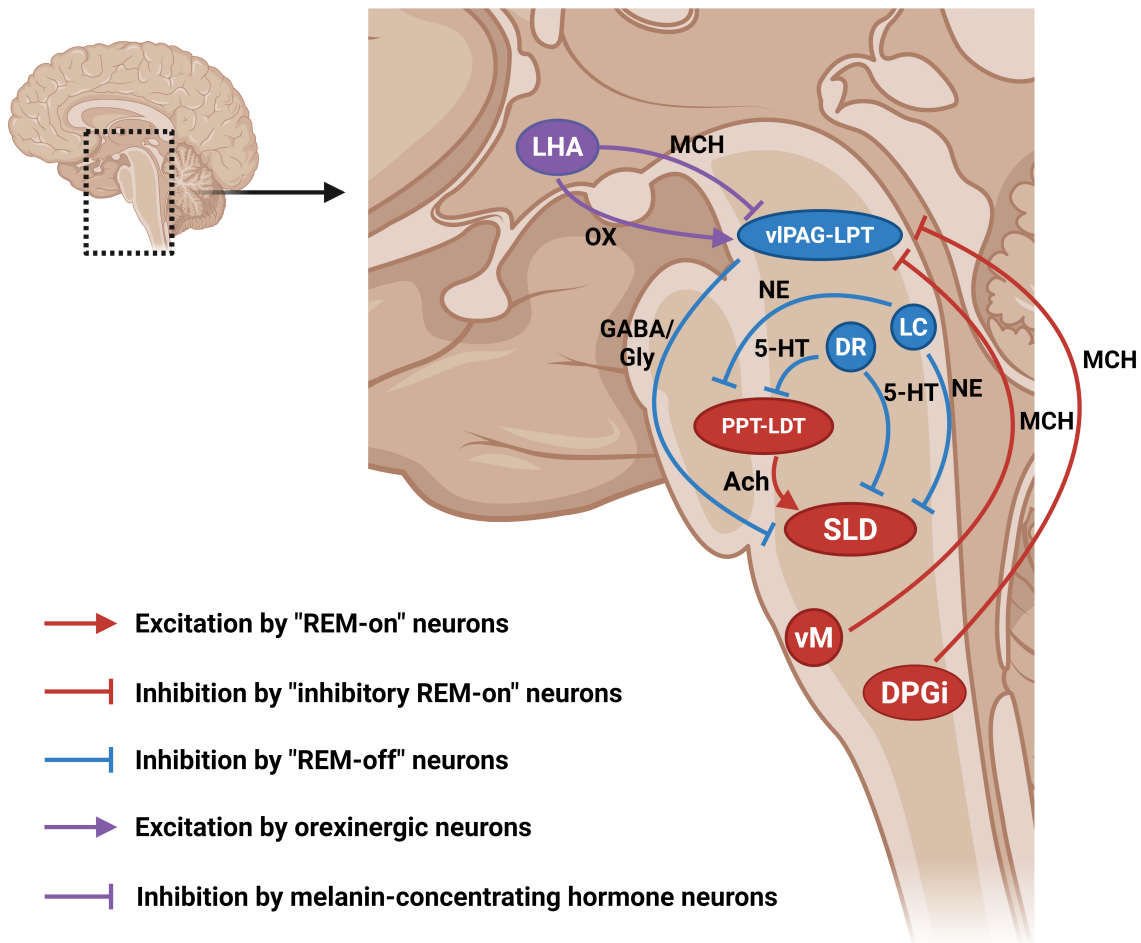


Fig. 1. Schematic diagram of the brain circuitry controlling REM sleep. Brain regions in red (i.e., “REM-on” structures) promote REM sleep, while brain regions in blue (i.e., “REM-off” structures) inhibit REM sleep. Brain regions in purple (i.e., neuropeptide-producing structures) regulate REM sleep by releasing different neuropeptides with different mechanisms. Arrows, excitation; “T” shaped line, inhibition; 5-HT, serotonin; Ach, acetylcholine; DPGi, dorsal paragigantocellular reticular nucleus; DR, dorsal raphe; GABA, gamma-aminobutyric acid; Gly, glycine; LC, locus coeruleus; LDT, laterodorsal tegmentum; LHA, lateral hypothalamus; LPT, lateral pontine tegmentum; MCH, melanin-concentrating hormone; NE, norepinephrine; OX, orexin; PPT, pedunculopontine tegmentum; SLD, sublateralodorsal nucleus; vIPAG, ventrolateral periaqueductal gray matter; vM, ventromedial medulla. Created with [BioRender.com](https://www.biorender.com) (Agreement Number: RM286L4OH2).

REM-on” neurons regulate the onset and termination of REM sleep by inhibiting the activity of other brain regions, particularly those associated with non-REM sleep and arousal. These neurons primarily use glycine and GABA to maintain stable REM sleep.

The “inhibitory REM-on” neurons can in turn inhibit the aforementioned brain region containing “REM-off” neurons (ventrolateral periaqueductal gray matter (vIPAG)/lateral pontine tegmentum (LPT)), resulting in the disinhibition of SLD neurons. Studies over the past few years have supported this framework, with neurons in those brain regions referred to as “inhibitory REM-on” neurons [90,91]. The locations of these neurons have been discovered, with MCH neurons found in the hypothalamus, SLD nucleus, ventromedial medulla (vM), and dorsal paragigantocellular reticular nucleus (DPGi) in the dorsal medulla

[92]. These “inhibitory REM-on” neurons inhibit “REM-off neurons” in the vIPAG/LPT, a common postsynaptic target, to facilitate the induction of REM sleep. As microinjection of MCH into the locus coeruleus nucleus has been shown to promote REM sleep [93], activation of the melanin-concentrating hormone system in the locus coeruleus nucleus is thought to be involved in the promotion of REM sleep. Similar neurons are also found in the preoptic area of the hypothalamus [94], with axons projecting to the ventrolateral periaqueductal gray matter, locus coeruleus, and dorsal raphe nuclei [95,96]. In addition, GABAergic REM sleep-promoting neurons can also be found in the vIPAG/LPT [90,92], but it remains unclear whether such neurons interact with local “REM-off” neurons.

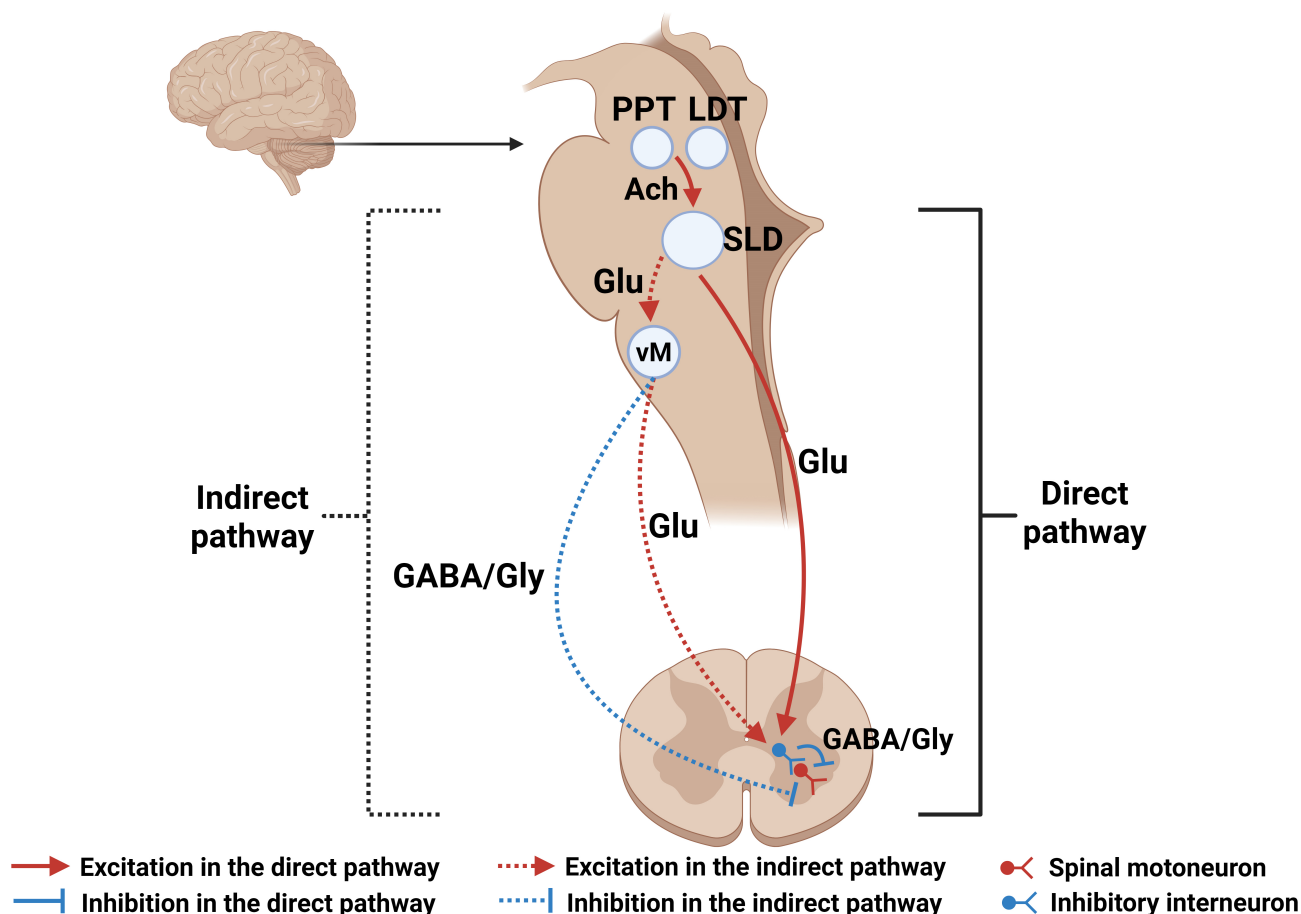


Fig. 2. Schematic diagram of structures in the central nervous system involved in the production of atonia during REM sleep. The SLD nucleus is the core region responsible for REM sleep. It induces muscle paralysis during REM sleep, either directly, by inhibiting spinal motoneurons through inhibition of interneurons in the spinal ventral horn, or indirectly, by inhibition of spinal motoneurons through the ventromedial medulla. Solid line, direct pathway; dashed line, indirect pathway; red color, excitation; blue color, inhibition; Glu, glutamate. Created with [BioRender.com](https://www.biorender.com) (Agreement Number: UF286L4YVE).

In summary, “inhibitory REM-on” neurons have been found in many brain regions and share a common mechanism for promoting REM sleep, that is, inhibiting “REM-off” neurons in inhibitory brain regions, thereby disinhibiting the SLD nucleus and initiating a series of reactions downstream.

4.2 Modulations by “REM-Off” Neurons

“REM-on” neurons receive input from a variety of neurons that suppress REM sleep (“REM-off” neurons). Of the various “REM-off” neurons, specific GABAergic neurons in brain regions that inhibit REM sleep are undoubtedly the most important.

REM-off GABAergic neurons in the vIPAG and adjacent (LPT; also called the deep mesencephalic nuclei, DpMe) project to the SLD nucleus and strongly inhibit REM sleep [92,97]. Before the discovery of “REM-off” neurons in the ventrolateral periaqueductal gray matter, it was proposed that monoaminergic neurons in the nearby dorsal raphe (DR) and locus coeruleus (LC) nucleus sup-

press REM sleep [98]. Serotonergic neurons in the dorsal raphe nucleus and noradrenergic neurons in the locus coeruleus nucleus are connected to both the SLD nucleus and pontine reticular formation (PRF), inhibiting the generation of REM sleep [65]. Interestingly, however, another subpopulation of GABAergic neurons in the ventrolateral periaqueductal gray matter projects to neurons of the dorsal raphe and locus coeruleus nuclei [92], inhibiting the release of monoamine neurotransmitters and thus promoting REM sleep, but it remains unclear whether such neurons interact with local “REM-off” neurons [90]. Under normal physiological conditions, the function of “REM-off” neuron-related circuits is to prevent inappropriate activation of neurons that produce atonia during the transition from REM sleep to wakefulness, while ensuring that muscle tone is rapidly restored upon awakening [66,99].

4.3 Involvement of Neuropeptides in Modulation of REM Sleep

Orexin (OX) and MCH, are two crucial peptides involved in the regulation of REM sleep. In general, orexin promotes wakefulness and suppresses REM sleep by activating neurons in the brain regions that inhibit REM sleep. In contrast, the melanin-concentrating hormone promotes REM sleep by inhibiting “REM-off” neurons in the brain regions that inhibit REM sleep [100].

Orexin-producing neurons are mainly found in the lateral hypothalamus (LHA) and regulate physiological processes, such as arousal and the sleep–wake cycle, to maintain wakefulness and inhibit REM sleep [101,102]. They also project to neurons that express orexin receptors in many nuclei with a role in regulating REM sleep, including in the ventrolateral periaqueductal gray matter, locus coeruleus nucleus [103], dorsal raphe nucleus [104], and basal forebrain [105], and activate these receptors in these brain regions, which enhances suppression of the SLD nucleus. Conversely, orexin-producing neurons also receive projections from nuclei containing neurons that express orexin receptors. For example, orexin-producing neurons in the lateral hypothalamus are inhibited by GABAergic neurons in the preoptic area [106], and by 5-HT neurons in the dorsal raphe nucleus and noradrenergic neurons in the locus coeruleus nucleus [107–109]. Conversely, cholinergic neurons in the basal forebrain also project to orexin-producing neurons in the lateral hypothalamus and have a positive effect on wakefulness [110].

MCH-producing neurons in the lateral hypothalamus with opposing functions to the orexin-producing neurons also project to neurons that express MCH receptors in many nuclei, including the ventrolateral periaqueductal gray matter, lateral pontine tegmentum, dorsal raphe nucleus, locus coeruleus nucleus, pontine reticular formation, and SLD nucleus, promoting REM sleep [111,112].

MCH activates MCH receptors on neurons in the ventrolateral periaqueductal gray matter/LPT to facilitate REM sleep by inhibiting the “REM-off” neurons in these nuclei. In addition, activation of the MCH receptors in the locus coeruleus nucleus is thought to be involved in promoting REM sleep, as microinjection of MCH into the locus coeruleus nucleus has been shown to evoke REM sleep [93].

However, the precise mechanisms underlying the regulation of REM sleep by these neuropeptides, as well as the downstream pathways through which MCH regulates REM sleep, are still unclear and require further investigation.

5. Pathogenesis of Sleep Paralysis

The pathogenesis of sleep paralysis involves complex neurophysiological processes and is related to abnormalities in the transition from the REM sleep stage to wakefulness. However, isolated and narcolepsy-associated sleep paralysis involve different pathogenic mechanisms

[57,113]. Isolated sleep paralysis results from disturbances in the physiological regulation of the sleep transition process, particularly imbalances in the SLD nucleus and related neurotransmitters [69]. In contrast, narcolepsy is primarily associated with the degeneration of orexinergic neurons, leading to deficiency in both orexin A and B neuropeptides [114,115]. Notably, these neuropeptides activate two distinct receptor subtypes, OX1R and OX2R, which mediate sleep-related symptoms differently. OX2R dysfunction leads to abnormal discharge of the SLD nucleus, resulting in impaired transition from REM sleep to wakefulness, and therefore its reduced activation is the primary mechanism for the development of sleep paralysis in narcolepsy [116,117]. In contrast, OX1R deficiency is more relevant to emotionally triggered cataplexy through limbic circuit dysregulation, while its role in sleep paralysis is limited [118]. The dual deficiency of orexin A and B results in abnormal REM sleep regulation and impaired transitions to wakefulness, thereby triggering various narcolepsy symptoms including sleep paralysis [7,66]. Overall, the mechanisms of narcolepsy are more complex, and the pathogenesis of isolated sleep paralysis may also be present in narcolepsy-associated sleep paralysis.

In narcolepsy patients, the lack of orexin A and B signaling in the circuit for REM sleep regulation can be caused by either a loss of orexin-producing neurons in the hypothalamus or a significant reduction or complete lack of orexin in patients [119–121]. This reduction results in orexin failing to activate orexin receptors (mainly OX2R) in the ventrolateral periaqueductal gray matter/LPT regions, leading to inappropriate disinhibition of the SLD nucleus during the transition from sleep to wakefulness, which in turn results in loss of muscle tone, i.e., sleep paralysis. In addition, some orexin-producing neurons are also found in the perifornical area, and their absence or hypofunction may further exacerbate the disruption of the sleep–wake cycle due to reduced levels of systemic orexin [122,123]. However, there is relatively little research on their specific role in and impact on narcolepsy, and more scientific evidence is needed to further validate this point.

Recent evidence suggests a strong link between the brain structures involved in emotional processing and muscle atonia during REM sleep. The amygdala, especially its central nucleus (CeA), has long been recognized as a core brain region for emotional processing and is now understood to exert a direct influence on REM sleep regulation and sleep paralysis [124,125]. GABAergic neurons in the CeA have been shown to send descending projections to key areas of the REM sleep regulating circuit, including the locus coeruleus nucleus, the lateral pontine tegmentum, and ventrolateral periaqueductal gray matter. Strong emotions, especially negative emotions such as fear and anxiety, activate GABAergic neurons in the central nucleus of the amygdala, which inhibits the locus coeruleus nucleus, the lateral pontine tegmentum, and ventrolateral periaqueductal

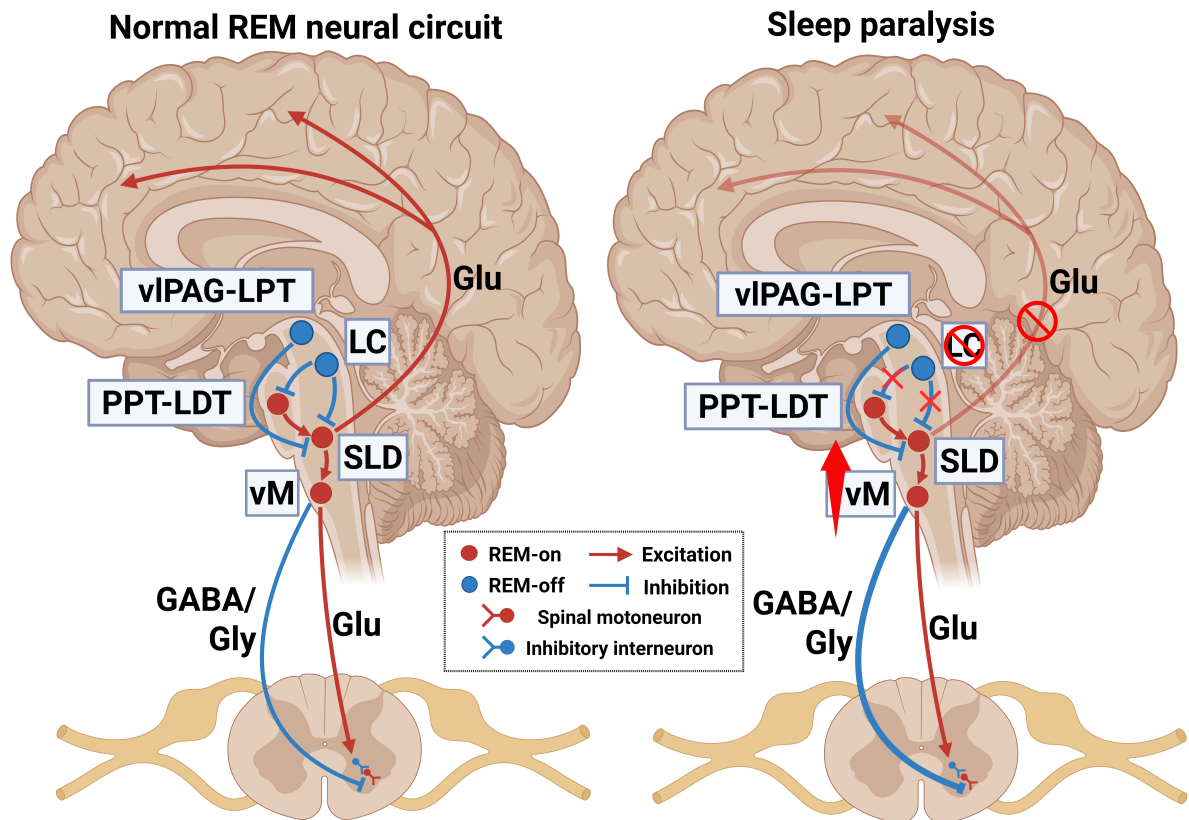


Fig. 3. Pathogenesis of sleep paralysis unrelated to orexin. Synergistic dysregulation of the two groups of glutamatergic neurons in the SLD, sudden cessation of locus coeruleus nucleus firing, and excitation of GABAergic and glycinergic neurons in the ventromedial medulla are responsible for sleep paralysis. Arrows, excitation; “T” shaped line, inhibition; brain regions in red, “REM-on” structures; brain regions in blue, “REM-off” structures; vPAG, ventrolateral periaqueductal gray matter. Created with [BioRender.com](https://www.biorender.com) (Agreement Number: IW286L53AE).

gray matter and in turn disinhibits the SLD nucleus [126–130]. However, this only occurs and results in sleep paralysis in the case of orexin deficiency, because CeA-mediated inhibition can be counteracted by inputs of excitatory orexin from the hypothalamus. Thus, in narcolepsy patients lacking orexin, this modulatory balance is disrupted. Emotions such as fear, laugh, surprise, or emotional stress leads to an excessive increase in GABAergic neuronal firing in the central nucleus of the amygdala, which may be an important mechanism underlying sleep paralysis. This abnormal discharge disrupts normal REM sleep regulation and muscle inhibitory mechanisms, leading to immobilization of the individual during the sleep–wake transition stage.

Moreover, the insula acts synergistically with the amygdala to exacerbate the episodes of sleep paralysis by integrating interoceptive and emotional information [131]. It forms a broader regulatory circuit with the anterior cingulate cortex and the parabrachial nucleus [132]. Within this circuit, glutamatergic neurons in the anterior cingulate cortex send excitatory projections to the parabrachial nucleus, where GABAergic neurons are subsequently activated, enhancing GABAergic inhibition of brainstem “REM-off”

nuclei [133,134]. This mechanism further destabilizes REM sleep regulation and contributes to pathological muscle atonia during the sleep–wake transition.

All of the above are mechanisms by which sleep paralysis occurs in the presence of orexin deficiency; pathogenesis unrelated to orexin will be discussed below (i.e., occurring in both isolated and narcolepsy-associated sleep paralysis) (Fig. 3).

There are two groups of glutamatergic neurons in the SLD nucleus, with one promoting cortical activity during REM sleep and contributing to REM sleep maintenance and the other enabling muscle atonia. During wakefulness, the two groups of glutamatergic neurons in the SLD nucleus are inhibited, and consciousness is restored along with muscle tone. However, when these two groups of neurons are dysfunctional, “REM-on” neurons that promote cortical activity during REM sleep are inhibited, while neurons that promote muscle atonia continue to be activated, resulting in the loss of muscle tone while conscious [70,99,135].

During wakefulness, noradrenergic neurons in the locus coeruleus nucleus are highly active. However, when cataplexy occurs, noradrenergic neurons in the lo-

cus coeruleus nucleus suddenly stop firing and cause a loss of muscle tone [136]. Evidence suggests that the mechanisms of cataplexy and sleep paralysis overlap in some aspects, particularly in those involving noradrenergic neuron inactivation and muscle atonia [137,138]. Thus, neuronal inactivation in the locus coeruleus nucleus may also lead to sleep paralysis when consciousness is normally restored during REM sleep–wake transitions. However, unlike locus coeruleus neurons, dorsal raphe neurons do not cease firing during sleep paralysis. At the same time, the ventromedial medulla is a key area for generating muscle atonia, and it has been confirmed that the activity of the GABAergic and glycinergic neurons in the ventromedial medulla increases during cataplexy [139]. Thus, inhibition of spinal motor neurons due to increased ventromedial medulla activity may be another mechanism promoting sleep paralysis.

The mechanism underlying sleep paralysis has been established. However, relatively little is known about the pathological causes of its complications (hallucinations). One reason that patients feel very scared during sleep paralysis is incubus hallucination, i.e., the feeling of a heavy weight on their ribs or that someone is pressing on their chest. This is because when sleep paralysis occurs, the diaphragm (the primary respiratory muscle) continues to function normally, while the activity of striated muscles, including some of the auxiliary respiratory muscles, is inhibited [140]. However, recent studies have shown that the state of skeletal muscle paralysis leads to significant decreases in alveolar ventilation and tidal volume, which can lead to hypercapnia during REM sleep. When patients with sleep paralysis suddenly become aware of these physiological changes, they experience dyspnea and suffocation [8,16,23]. In addition, decreased excitability due to the hyperpolarization of motor neurons in the respiratory muscles affects the sensation of respiration, resulting in the patient's perception of chest pressure and dyspnea.

Hallucinations can be classified as serotonergic or dopaminergic depending on the neuronal transmitters involved. Serotonergic hallucinations (e.g., those caused by lysergic acid diethylamide), also known as nonpsychotic hallucinations, are similar in nature to dreams, and the experiencer is able to clearly perceive that they are not reality [141,142]. In contrast, dopaminergic hallucinations are psychotic hallucinations (common in schizophrenia) that the experiencer cannot distinguish them from real life [143].

Hallucinations during sleep paralysis often resemble dreams to the extent that the event itself is sometimes interpreted as a dream, and the patient is able to fully recognize it as a hallucination [140]. Therefore, hallucinations accompanying sleep paralysis are often considered to be serotonergic. Serotonin is functionally involved in the production of hallucinations and fear during sleep paralysis, mainly through its action on serotonin 2A receptors (5-HT_{2A}), which are widely distributed in the visual cortex and limbic system [11,144,145]. Activation of the serotonergic arousal

system during the transition between REM sleep and wakefulness can facilitate the wakefulness process, which leads to serotonin overactivity in the visual cortex and limbic system of sleep paralysis patients and ultimately to hallucinatory experiences via 5-HT_{2A} activation [146]. 5-HT_{2A} receptor activation in the visual cortex elicits visual hallucinations by increasing cortical excitability and altering visually evoked cortical responses, yet 5-HT_{2A} receptors in the limbic system play a very important role in the regulation of fearful emotions [147,148]. Their joint action profoundly modulates circuits in which hallucinatory experiences and fear are intertwined. This also provides treatment for hallucinations and fear symptoms of sleep paralysis, as detailed in the Treatment section below.

Current research suggests that an increasing number of road traffic accidents are related to microsleep in drivers [149] including professional drivers such as long-haul truck drivers and those working in logistics, who are required to drive vehicles for extended periods of time with irregular schedules [150]. Despite regulatory mandated rest periods, these drivers often sleep in their vehicles under suboptimal conditions such as noise, lack of space, poor ventilation, and temperature fluctuations [151]. In addition, modern behavioral factors such as excessive smartphone use at night also exacerbate poor sleep quality [152,153]. These environmental and behavioral stressors severely impact sleep quality and sleep continuity, leading to increased daytime sleepiness and microsleep. Because microsleep also occurs during the sleep–wake transition and shares some similarities with the occurrence of sleep paralysis, we propose that microsleep may arise during the transition between REM sleep and wakefulness, leading to sleep paralysis. Microsleep is a sleep-like condition of short duration that occurs when people are overtired or lack sleep [154–156]. Typically, this phenomenon involves a brief shutdown of the brain's activation system with parallel activation of the sleep-promoting centers [157]. In one study, these microsleeps were found to be associated with decreased neural activity in arousal-related brain regions, including the thalamus, midbrain, and posterior cingulate cortex, but with increased activity in the frontoparietal, insula, parahippocampal, and temporo-occipital cortices [158]. Severe sleep deprivation, poor sleep quality, and excessive fatigue are all causes of microsleep, which greatly overlap with the predisposing factors of sleep paralysis. Therefore, we speculate that sleep paralysis may be produced when microsleep occurs in the transition between sleep and wakefulness. Its occurrence is more likely when people are in a microsleep state, resulting in the recovery of people's consciousness and inability to move. Although microsleeps are common and pose significant risks in daily life [159,160], a comprehensive, systematic understanding of the underlying brain mechanisms is still lacking [158], and this speculation needs to be further verified by scientific research.

In conclusion, disruptions of REM sleep regulation (premature activation of either motor inhibitory pathways or the brain's arousal system) resulting in a state of muscular paralysis misaligned with conscious arousal is central to the pathogenesis of sleep paralysis.

6. Treatment

There is no specific treatment for sleep paralysis, and the main principles of treatment are to improve sleep, optimize mood, and manage related psychiatric disorders [16,113,161]. Due to the specific characteristics of ISP, therapeutic interventions are unnecessary in most cases, as patients usually return to normal for some time after several episodes. The management of ISP focuses on prevention, and medications are used only in patients who have frequent attacks and exhibit severe symptoms for which non-pharmacological interventions have been unsatisfactory [14]. Narcolepsy-associated sleep paralysis patients usually have more severe symptoms than ISP, and treatments are directly focused on narcolepsy.

6.1 Non-Pharmacologic Management

Examples of non-pharmacologic management include sleep hygiene improvement, lifestyle modification, cognitive-behavioral therapy (CBT), and the induction of out-of-body experiences (OBEs).

A recent online cross-sectional study reported on three of the most common preventive interventions for sleep paralysis, namely adjustments to the sleep environment, sleep patterns, and sleep position [113]. It also found that the overall effectiveness of disruptive interventions is low, with contextualization (e.g., focusing on an object in the room or telling oneself that one is now sleeping) and breathing (e.g., rapid breathing) being more effective, but that most patients attempted to move limbs or smaller body parts as well as make noise as counteractive measures [20,113]. Since sleep hygiene is a crucial cause of sleep paralysis [162], improving sleep hygiene such as through a suitably adjusted bedroom temperature, a stable sleep-wake routine, adequate sleep, and so on, can promote sleep initiation and maintenance [29]. Moreover, sleep paralysis has been reported to occur mostly during sleep in a supine [163] rather than sitting [140] position, and maintaining a lateral or prone sleeping position is also an effective preventive measure [113,164].

In 2024, Sawant and Kamble [63] reported a case of an ISP patient with osteoporosis, finding that lifestyle changes such as practicing yoga, meditation, and chanting may have an important role in the recovery of sleep paralysis by reducing stress, enhancing sleep quality, and promoting psychological well-being. Meditation is particularly effective and has been shown to stabilize REM sleep patterns and reduce the frequency of sleep paralysis [63,165,166].

CBT is also recommended [25,167]. This psychotherapeutic approach improves the mood and psychological

well-being of patients by optimizing their negative thinking and behavioral patterns associated with sleep paralysis, thereby effectively reducing the impact of hallucinations and fears during episodes of sleep paralysis and reducing the incidence [168,169]. As such, it may be the best strategy for patients with depression, anxiety, and other psychiatric disorders.

In a recent study, it was observed that individuals with isolated sleep paralysis who experienced OBEs (a type of vestibular-motor hallucination) had more positive emotions (e.g., happiness, excitement, etc.) and fewer negative emotions (e.g., fear, anxiety) than people with isolated sleep paralysis who did not experience OBEs and those with other types of hallucinations. It was also found that subjects experienced auditory, visual, and tactile sensations prior to sleep paralysis episodes, which are known as "aura". As a result of this insight, a clinical approach was proposed for the treatment of recurrent sleep paralysis by which OBEs are induced in patients by training them to recognize "aura", combined with psychoeducation to reduce the negative emotions associated with sleep paralysis [21,170].

6.2 Pharmacologic Managements

Since sleep paralysis often co-occurs with narcolepsy, the medications used for treating sleep paralysis are also used for narcolepsy.

(1) Serotonin and noradrenaline reuptake inhibitors (e.g., venlafaxine), tricyclics, selective serotonin reuptake inhibitors (SSRIs), and other antidepressants are known to reduce the number of sleep paralysis episodes [14,25,171,172]. They can enhance the activity of serotonin and norepinephrine, which in turn increases the effects of two REM sleep-inhibitory brain regions, locus coeruleus and dorsal raphe nuclei. Therefore, they have a pharmacological role in suppressing sleep paralysis. However, while most patients experience improved sleep with SSRIs, a recent case report found that sertraline (a type of SSRIs) may cause isolated sleep paralysis as a potential side effect [173,174]. Therefore, further research is necessary to elucidate the effects of SSRIs on sleep, and practice guidelines should clarify their role. Moreover, when prescribing depressants to patients, doctors must remain alert to the possibility of sleep paralysis and consider substituting medications, such as trazodone, if necessary [174,175].

(2) The selective 5-HT_{2A}R inverse agonist pimavanserin [11] is a drug that selectively targets hallucination and fear responses in sleep paralysis. It was first proposed to use for the treatment of sleep paralysis because of its ability to inhibit 5-HT_{2A} receptors in the visual cortex and limbic system, which effectively relieves hallucination and fear responses in sleep paralysis.

(3) Pitolisant, an N-piperidinyll derivative [176], is an inverse agonist of the histamine H₃ receptor with wake-promoting effects [177]. Pitolisant blocks the self-inhibitory effect of histamine on its release, leading to in-

creased histamine release [178]. Additionally, Pitolisant affects other neurotransmitter systems, enhancing the release of acetylcholine and dopamine in the cerebral cortex [178]. Therefore, it is used in the European Union for the treatment of narcolepsy in adults with or without cataplexy, and it has recently been shown to be effective for the treatment of sleep paralysis [179]. Solriamfetol, a phenylalanine derivative, is a dopamine and norepinephrine reuptake inhibitor, so it should theoretically have an effect on sleep paralysis [180,181] and has undeniable advantages over Pitolisant in terms of withdrawal symptoms and drug abuse [179,182].

(4) At present, FT218 (a controlled-release sodium oxybate) and JZP-258 (a novel low-sodium oxybate) [179, 183], AXS-12 (reboxetine, a selective norepinephrine reuptake inhibitor) [179], and THN102 (the combination of modafinil and flecainide) [184] are being developed and tested. Both FT218 and JZP-258 are in Phase III clinical trials; the former is being tested for the treatment of excessive daytime sleepiness associated with narcolepsy and sudden collapse and has been designated an orphan drug by the FDA, whereas the latter is being tested for the treatment of narcolepsy. AXS-12 was first developed for the treatment of depression and is now being developed for the treatment of sudden collapse and excessive daytime sleepiness associated with narcolepsy. It has been designated an orphan drug by the FDA. THN102 is in Phase II clinical trials for the treatment of excessive daytime sleepiness associated with narcolepsy [179]. All have demonstrated some anti-narcolepsy effects and can be used as potential drugs for sleep paralysis [182].

(5) Supplementation of orexin could be a potential treatment for narcolepsy-associated sleep paralysis caused by orexin deficiency [113,185]. However, there is a lack of sufficient data to demonstrate its therapeutic efficacy [16].

(6) In the case report of the ISP patient with osteoporosis mentioned above, it was also suggested that oral or injectable vitamin D can be used to correct severe vitamin D deficiency and thereby help improve mood and energy levels, which indirectly aids in the recovery from sleep paralysis while addressing bone problems [63]. In addition, a systematic review found that vitamin D supplementation significantly improves sleep quality and thus mitigates sleep paralysis [186].

Most current pharmacologic managements for sleep paralysis have primarily been studied and implemented in adults, and their applicability to younger individuals remains unclear [187]. One study indicates that only sodium oxybate has data supporting its use in pediatric patients and has received approval from the European Medicines Agency, whereas other medications are used off-label based on expert opinion and clinical practice [188]. Additionally, Pitolisant has been approved by the European Medicines Agency for the treatment of narcolepsy with or without cataplexy in children and adolescents aged 6 years and older [188,189]. Therefore, currently available research on medi-

cations approved for use in minors is limited to the management of narcolepsy, and future research is essential to evaluate the safety and efficacy of these medications for minors with sleep paralysis.

7. Conclusions and Future Directions

Sleep is a crucial restorative state that is dependent on precise coordination of the production of numerous biological and chemical structures and their proper function. Knowledge of the multiple interactions between neuromodulators, brain regions, and the whole organism provides insights into REM sleep mechanisms and the pathogenesis of many sleep disorders.

This article focuses on the neural network of REM sleep and the mechanisms involved in the pathogenesis of sleep paralysis. The REM arousal transition and REM muscle atonia are regulated due to the actions of “REM-on” and “REM-off” neurons throughout the brain. It is generally recognized that the SLD nucleus is the core region for generating REM sleep muscle atonia. Neuropeptides (i.e., orexin and MSH) are also widely distributed in the brain and are responsible for regulating many physiological functions, including sleep. Their presence facilitates the coupling of the aforementioned sleep behaviors to neurotransmitter regulatory systems. Sleep paralysis is a dissociative state, with REM sleep muscle atonia continuing into the waking state. It is important to note that although sleep paralysis typically causes fear and interferes with the daily lives of those affected, the vast majority of sleep paralysis episodes are benign and not associated with serious pathology. Therefore, sleep paralysis does not require treatment in most cases, only when there is repetition and fear.

The current studies have some clear limitations. A large number of variables related to sleep paralysis have been proposed. However, it is worth noting that there is a great deal of variation in the methods used to assess sleep paralysis across studies, which is a limitation. An important area for future research is the use of methods that more accurately assess predisposing factors for sleep paralysis and the development of more standardized and uniform diagnostic criteria to allow differentiation from other sleep disorders (nightmares, night terrors, etc.). Although there has been some research in recent years into the role of the various components that control REM sleep, how these components work together through different brain regions in regulating sleep remains unclear. For example, melanin-concentrating hormone is a substance that acts on the REM sleep network and regulates REM sleep. It has only recently been discovered, and its mechanism of action is still far from clear. Further studies on neuropeptides can reveal more details of the complete sleep network in all its complexity, which can help to explain the pathogenesis of various sleep disorders. Therefore, future efforts should be directed toward understanding the regulatory mechanisms of different neuropeptides. It is only in recent years that our

understanding of REM sleep control circuits has expanded to include numerous brain regions, and it is important to further investigate the relationship between sleep paralysis and different regions of the brain, particularly how the conflict arises between muscle atonia and consciousness during the transition between REM sleep and wakefulness. A deeper understanding of this circuit will certainly help us to further explore the mysteries of REM sleep and sleep disorders. In addition, it is important to further clarify the differences between REM sleep, isolated sleep paralysis, and narcolepsy-associated sleep paralysis, such as the subtle differences in eye movements and EEG and electromyography (EMG) data. Moreover, there is some evidence demonstrating that although ISP does not always progress to narcolepsy, its frequent early occurrence during the course of narcolepsy suggests that it may be a precursor. This has important clinical implications, i.e., in the early identification and intervention of ISP in patients to potentially prevent progression to more severe narcolepsy, but validation is required through future studies with large sample sizes.

Arguably, the most pressing issue in understanding the REM sleep network is to study and treat the associated human diseases. Currently, there are no specific medications for sleep paralysis. Future research should continue to focus on why REM sleep-controlling circuits are susceptible to pathological recruitment, as well as more subtle neurological action mechanisms. In addition, more in-depth exploration of the interactions between other sleep disorders and sleep paralysis, as well as continued probing of the effects of genetic polymorphisms on the prevalence of sleep paralysis, would be of great help in developing additional therapeutic strategies targeting the pathogenesis of sleep paralysis. Whether various hormones have an effect on the pathogenesis of sleep paralysis is also a question for further research. Therefore, in the future, we recommend establishing a multidisciplinary collaborative treatment model—integrating expertise from sleep medicine, neurology, psychiatry, genetics, endocrinology, and other fields—to develop and formulate more effective and targeted individualized treatment plans for normalizing activity of the disrupted neural pathways mediating sleep paralysis.

Abbreviations

5-HT, Serotonin; 5-HT_{2A}R, Serotonin 2A receptor; Ach, Acetylcholine; BMI, Body mass index; CBT, Cognitive-behavioral therapy; CeA, Central nucleus of the amygdala; cLDT, Caudal lateral dorsal tegmentum; DPGi, Dorsal paragigantocellular reticular nucleus; DpMe, Deep mesencephalic nuclei; DR, Dorsal raphe; EEG, Electroencephalography; EMG, Electromyography; GABA, Gamma-aminobutyric acid; GiA, α -gigantocellular reticular nuclei; GiV, Ventral gigantocellular reticular nucleus; Glu, Glutamate; Gly, Glycine; ICSD-3, International Classification of Sleep Disorders, 3rd Edition; ISP, Isolated sleep paralysis; LC, Locus coeruleus; LDT, Laterodor-

sal tegmentum; LHA, Lateral hypothalamus; LPT, Lateral pontine tegmentum; MCH, Melanin-concentrating hormone; NE, Norepinephrine; NREM, Non-rapid eye movement; NT1, Type 1 narcolepsy; OBEs, Out-of-body experiences; OX, Orexin; peri-LCa, Peri-locus coeruleus alpha nucleus; PPT, Pedunclopontine tegmentum; PRF, Pontine reticular formation; PTSD, Post-traumatic stress disorder; REM, Rapid eye movement; SLD, Sublaterodorsal; SSRIs, Selective serotonin reuptake inhibitors; SVH, Spinal ventral horn; vPAG, Ventrolateral periaqueductal gray matter; vM, Ventromedial medulla.

Author Contributions

YW and DY conceptualized the review and revised the manuscript. YW, QL, ZZ, QO and XZ conducted the literature research and wrote the first draft of the manuscript. YW and KY created figures. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

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References

- [1] Shen YC, Sun X, Li L, Zhang HY, Huang ZL, Wang YQ. Roles of Neuropeptides in Sleep-Wake Regulation. *International Journal of Molecular Sciences*. 2022; 23: 4599. <https://doi.org/10.3390/ijms23094599>.
- [2] Falup-Pecurariu C, Diaconu Ş, Țiņţ D, Falup-Pecurariu O. Neurobiology of sleep (Review). *Experimental and Therapeutic Medicine*. 2021; 21: 272. <https://doi.org/10.3892/etm.2021.9703>.
- [3] Aserinsky E, Kleitman N. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science (New York, N.Y.)*. 1953; 118: 273–274. <https://doi.org/10.1126/science.118.3062.273>.
- [4] Jouvet M, Michel F, Courjon J. Sur un stade d'activité électrique cérébrale rapide au cours du sommeil physiologique. *Comptes Rendus des Séances de la Société de Biologie et de ses Filiales* 1959; 153: 1024–1028.
- [5] Schenck CH, Lee SA, Bornemann MAC, Mahowald MW. Potentially lethal behaviors associated with rapid eye movement sleep behavior disorder: review of the literature and forensic implications. *Journal of Forensic Sciences*. 2009; 54: 1475–1484. <https://doi.org/10.1111/j.1556-4029.2009.01163.x>.

- [6] Mutz J, Javadi AH. Exploring the neural correlates of dream phenomenology and altered states of consciousness during sleep. *Neuroscience of Consciousness*. 2017; 2017: nix009. <https://doi.org/10.1093/nc/nix009>.
- [7] Bassetti CLA, Adamantidis A, Burdakov D, Han F, Gay S, Kallweit U, *et al*. Narcolepsy - clinical spectrum, aetiopathophysiology, diagnosis and treatment. *Nature Reviews. Neurology*. 2019; 15: 519–539. <https://doi.org/10.1038/s41582-019-0226-9>.
- [8] Cheyne JA, Rueffer SD, Newby-Clark IR. Hypnagogic and hypnopompic hallucinations during sleep paralysis: neurological and cultural construction of the night-mare. *Consciousness and Cognition*. 1999; 8: 319–337. <https://doi.org/10.1006/ccog.1999.0404>.
- [9] Sharpless BA, Barber JP. Lifetime prevalence rates of sleep paralysis: a systematic review. *Sleep Medicine Reviews*. 2011; 15: 311–315. <https://doi.org/10.1016/j.smrv.2011.01.007>.
- [10] Scammell TE. Narcolepsy. *The New England Journal of Medicine*. 2015; 373: 2654–2662. <https://doi.org/10.1056/NEJMra1500587>.
- [11] Jalal B. The neuropharmacology of sleep paralysis hallucinations: serotonin 2A activation and a novel therapeutic drug. *Psychopharmacology*. 2018; 235: 3083–3091. <https://doi.org/10.1007/s00213-018-5042-1>.
- [12] Campillo-Ferrer T, Alcaraz-Sánchez A, Demšar E, Wu HP, Dresler M, Windt J, *et al*. Out-of-body experiences in relation to lucid dreaming and sleep paralysis: A theoretical review and conceptual model. *Neuroscience and Biobehavioral Reviews*. 2024; 163: 105770. <https://doi.org/10.1016/j.neubiorev.2024.105770>.
- [13] Denis D. Relationships between sleep paralysis and sleep quality: current insights. *Nature and Science of Sleep*. 2018; 10: 355–367. <https://doi.org/10.2147/NSS.S158600>.
- [14] Bhalerao V, Gotarkar S, Vishwakarma D, Kanchan S. Recent Insights Into Sleep Paralysis: Mechanisms and Management. *Cureus*. 2024; 16: e65413. <https://doi.org/10.7759/cureus.65413>.
- [15] Ableidinger S, Holzinger B. Sleep Paralysis and Lucid Dreaming-Between Waking and Dreaming: A Review about Two Extraordinary States. *Journal of Clinical Medicine*. 2023; 12: 3437. <https://doi.org/10.3390/jcm12103437>.
- [16] Hefnawy MT, Amer BE, Amer SA, Moghib K, Khlidj Y, Elfakharany B, *et al*. Prevalence and Clinical Characteristics of Sleeping Paralysis: A Systematic Review and Meta-Analysis. *Cureus*. 2024; 16: e53212. <https://doi.org/10.7759/cureus.53212>.
- [17] Olunu E, Kimo R, Onigbinde EO, Akpanobong MAU, Enang IE, Osanakpo M, *et al*. Sleep Paralysis, a Medical Condition with a Diverse Cultural Interpretation. *International Journal of Applied & Basic Medical Research*. 2018; 8: 137–142. https://doi.org/10.4103/ijabmr.IJABMR_19_18.
- [18] Cheyne JA, Newby-Clark IR, Rueffer SD. Relations among hypnagogic and hypnopompic experiences associated with sleep paralysis. *Journal of Sleep Research*. 1999; 8: 313–317. <https://doi.org/10.1046/j.1365-2869.1999.00165.x>.
- [19] Molendijk ML, Montagne H, Bouachmir O, Alper Z, Bervoets JP, Blom JD. Prevalence Rates of the Incubus Phenomenon: A Systematic Review and Meta-Analysis. *Frontiers in Psychiatry*. 2017; 8: 253. <https://doi.org/10.3389/fpsy.2017.00253>.
- [20] Sharpless BA, Grom JL. Isolated Sleep Paralysis: Fear, Prevention, and Disruption. *Behavioral Sleep Medicine*. 2016; 14: 134–139. <https://doi.org/10.1080/15402002.2014.963583>.
- [21] Kliková M, Sharpless BA, Bušková J. Could sleep paralysis be pleasant? *Journal of Sleep Research*. 2021; 30: e13154. <https://doi.org/10.1111/jsr.13154>.
- [22] Iranzo A. Parasomnias and Sleep-Related Movement Disorders in Older Adults. *Sleep Medicine Clinics*. 2018; 13: 51–61. <https://doi.org/10.1016/j.jsmc.2017.09.005>.
- [23] Farooq M, Anjum F. Sleep Paralysis. *StatPearls: Treasure Island (FL)*. 2025.
- [24] Mainieri G, Maranci JB, Champetier P, Leu-Semenescu S, Gales A, Dodet P, *et al*. Are sleep paralysis and false awakenings different from REM sleep and from lucid REM sleep? A spectral EEG analysis. *Journal of Clinical Sleep Medicine: JCSM: Official Publication of the American Academy of Sleep Medicine*. 2021; 17: 719–727. <https://doi.org/10.5664/jcs.9056>.
- [25] Sharpless BA. A clinician's guide to recurrent isolated sleep paralysis. *Neuropsychiatric Disease and Treatment*. 2016; 12: 1761–1767. <https://doi.org/10.2147/NDT.S100307>.
- [26] Duarte JM, Lisi GR, Carroll BT, Garro MF, Appiani FJ. The prevalence of sleep paralysis in medical students in Buenos Aires, Argentina. *Journal of Neurosciences in Rural Practice*. 2023; 14: 272–275. https://doi.org/10.25259/JNRP_16_2022.
- [27] Benham G. Sleep paralysis in college students. *Journal of American College Health: J of ACH*. 2022; 70: 1286–1291. <https://doi.org/10.1080/07448481.2020.1799807>.
- [28] Wróbel-Knybel P, Flis M, Rog J, Jalal B, Karakuła-Juchnowicz H. Risk factors of sleep paralysis in a population of Polish students. *BMC Psychiatry*. 2022; 22: 383. <https://doi.org/10.1186/s12888-022-04003-0>.
- [29] Denis D, French CC, Gregory AM. A systematic review of variables associated with sleep paralysis. *Sleep Medicine Reviews*. 2018; 38: 141–157. <https://doi.org/10.1016/j.smrv.2017.05.005>.
- [30] Muzammil MA, Syed AR, Farooq MH, Ahmed S, Qazi MH, Patel T, *et al*. Frequency and Factors of Sleep Paralysis Among Medical Students of Karachi. *Cureus*. 2023; 15: e41722. <https://doi.org/10.7759/cureus.41722>.
- [31] Pagnin D, de Queiroz V, Carvalho YTMS, Dutra ASS, Amaral MB, Queiroz TT. The relation between burnout and sleep disorders in medical students. *Academic Psychiatry: the Journal of the American Association of Directors of Psychiatric Residency Training and the Association for Academic Psychiatry*. 2014; 38: 438–444. <https://doi.org/10.1007/s40596-014-0093-z>.
- [32] Yadav R, Khanna A, Singh D. Exploration of Relationship Between Stress and Spirituality Characteristics of Male and Female Engineering Students: A Comprehensive Study. *Journal of Religion and Health*. 2017; 56: 388–399. <https://doi.org/10.1007/s10943-015-0174-7>.
- [33] Colombo C, Cellini N. Lifetime prevalence and characteristics of sleep paralysis in Italian university students population. *Sleep Medicine*. 2024; 122: 106–112. <https://doi.org/10.1016/j.sleep.2024.08.013>.
- [34] Lee SY, Wuertz C, Rogers R, Chen YP. Stress and sleep disturbances in female college students. *American Journal of Health Behavior*. 2013; 37: 851–858. <https://doi.org/10.5993/AJHB.37.6.14>.
- [35] Marta OFD, Kuo SY, Bloomfield J, Lee HC, Ruhyanudin F, Poynor MY, *et al*. Gender differences in the relationships between sleep disturbances and academic performance among nursing students: A cross-sectional study. *Nurse Education Today*. 2020; 85: 104270. <https://doi.org/10.1016/j.nedt.2019.104270>.
- [36] Uhart M, Chong RY, Oswald L, Lin PI, Wand GS. Gender differences in hypothalamic-pituitary-adrenal (HPA) axis reactivity. *Psychoneuroendocrinology*. 2006; 31: 642–652. <https://doi.org/10.1016/j.psyneuen.2006.02.003>.
- [37] Bangasser DA, Curtis A, Reyes BAS, Bethea TT, Parastatidis I, Ischiropoulos H, *et al*. Sex differences in corticotropin-releasing factor receptor signaling and trafficking: potential role in female vulnerability to stress-related psychopathology. *Molecular Psychiatry*. 2010; 15: 877, 896–904. <https://doi.org/10.1038/mp.2010.66>.

- [38] Hodes GE, Bangasser D, Sotiropoulos I, Kokras N, Dalla C. Sex Differences in Stress Response: Classical Mechanisms and Beyond. *Current Neuropharmacology*. 2024; 22: 475–494. <https://doi.org/10.2174/1570159X22666231005090134>.
- [39] Khan S, Malik BH, Gupta D, Rutkofsky I. The Role of Circadian Misalignment due to Insomnia, Lack of Sleep, and Shift Work in Increasing the Risk of Cardiac Diseases: A Systematic Review. *Cureus*. 2020; 12: e6616. <https://doi.org/10.7759/cureus.6616>.
- [40] Siemann JK, Grueter BA, McMahon DG. Rhythms, Reward, and Blues: Consequences of Circadian Photoperiod on Affective and Reward Circuit Function. *Neuroscience*. 2021; 457: 220–234. <https://doi.org/10.1016/j.neuroscience.2020.12.010>.
- [41] Brown GM. Light, melatonin and the sleep-wake cycle. *Journal of Psychiatry & Neuroscience: JPN*. 1994; 19: 345–353.
- [42] Tähkämö L, Partonen T, Pesonen AK. Systematic review of light exposure impact on human circadian rhythm. *Chronobiology International*. 2019; 36: 151–170. <https://doi.org/10.1080/07420528.2018.1527773>.
- [43] LeGates TA, Fernandez DC, Hattar S. Light as a central modulator of circadian rhythms, sleep and affect. *Nature Reviews. Neuroscience*. 2014; 15: 443–454. <https://doi.org/10.1038/nrn3743>.
- [44] Pandi-Perumal SR, Srinivasan V, Spence DW, Cardinali DP. Role of the melatonin system in the control of sleep: therapeutic implications. *CNS Drugs*. 2007; 21: 995–1018. <https://doi.org/10.2165/00023210-200721120-00004>.
- [45] Quera Salva MA, Hartley S. Mood disorders, circadian rhythms, melatonin and melatonin agonists. *Journal of Central Nervous System Disease*. 2012; 4: 15–26. <https://doi.org/10.4137/JCNS.D.S4103>.
- [46] Guo J, Xu L, Wang J, Li C, Zhang C, Dong X, *et al.* The month of birth has a seasonal effect in Chinese patients with narcolepsy and cataplexy. *Journal of Clinical Sleep Medicine: JCSM: Official Publication of the American Academy of Sleep Medicine*. 2022; 18: 461–467. <https://doi.org/10.5664/jcsm.9626>.
- [47] Hsu CW, Tseng PT, Tu YK, Lin PY, Wang LJ, Hung CF, *et al.* Month of birth and the risk of narcolepsy: a systematic review and meta-analysis. *Journal of Clinical Sleep Medicine: JCSM: Official Publication of the American Academy of Sleep Medicine*. 2022; 18: 1113–1120. <https://doi.org/10.5664/jcsm.9816>.
- [48] Wehrens SMT, Christou S, Isherwood C, Middleton B, Gibbs MA, Archer SN, *et al.* Meal Timing Regulates the Human Circadian System. *Current Biology: CB*. 2017; 27: 1768–1775.e3. <https://doi.org/10.1016/j.cub.2017.04.059>.
- [49] Ogata H, Horie M, Kayaba M, Tanaka Y, Ando A, Park I, *et al.* Skipping Breakfast for 6 Days Delayed the Circadian Rhythm of the Body Temperature without Altering Clock Gene Expression in Human Leukocytes. *Nutrients*. 2020; 12: 2797. <https://doi.org/10.3390/nu12092797>.
- [50] Akbar Z, Shi Z. Unfavorable Mealtime, Meal Skipping, and Shiftwork Are Associated with Circadian Syndrome in Adults Participating in NHANES 2005–2016. *Nutrients*. 2024; 16: 1581. <https://doi.org/10.3390/nu16111581>.
- [51] Kivelä L, Papadopoulou MR, Antypa N. Chronotype and Psychiatric Disorders. *Current Sleep Medicine Reports*. 2018; 4: 94–103. <https://doi.org/10.1007/s40675-018-0113-8>.
- [52] Zou H, Zhou H, Yan R, Yao Z, Lu Q. Chronotype, circadian rhythm, and psychiatric disorders: Recent evidence and potential mechanisms. *Frontiers in Neuroscience*. 2022; 16: 811771. <https://doi.org/10.3389/fnins.2022.811771>.
- [53] Daffre C, Oliver KI, Nazareno JRS, Mäder T, Seo J, Dominguez JP, *et al.* Rapid eye movement sleep parasympathetic activity predicts wake hyperarousal symptoms following a traumatic event. *Journal of Sleep Research*. 2023; 32: e13685. <https://doi.org/10.1111/jsr.13685>.
- [54] Tomacsek V, Blaskovich B, Király A, Reichardt R, Simor P. Altered parasympathetic activity during sleep and emotionally arousing wakefulness in frequent nightmare recallers. *European Archives of Psychiatry and Clinical Neuroscience*. 2024; 274: 265–277. <https://doi.org/10.1007/s00406-023-01573-2>.
- [55] Jalal B, Hinton DE. Lifetime presence and rates of sleep paralysis in Denmark of ethnic Danes and non-ethnic Danes. *Psychiatry and Clinical Neurosciences*. 2016; 70: 253. <https://doi.org/10.1111/pcn.12385>.
- [56] Denis D, French CC, Rowe R, Zavos HMS, Nolan PM, Parsons MJ, *et al.* A twin and molecular genetics study of sleep paralysis and associated factors. *Journal of Sleep Research*. 2015; 24: 438–446. <https://doi.org/10.1111/jsr.12282>.
- [57] Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. *Lancet (London, England)*. 2007; 369: 499–511. [https://doi.org/10.1016/S0140-6736\(07\)60237-2](https://doi.org/10.1016/S0140-6736(07)60237-2).
- [58] Mahoney CE, Cogswell A, Korálnik IJ, Scammell TE. The neurobiological basis of narcolepsy. *Nature Reviews. Neuroscience*. 2019; 20: 83–93. <https://doi.org/10.1038/s41583-018-0097-x>.
- [59] Sharpless BA, McCarthy KS, Chambless DL, Milrod BL, Khalsa SR, Barber JP. Isolated sleep paralysis and fearful isolated sleep paralysis in outpatients with panic attacks. *Journal of Clinical Psychology*. 2010; 66: 1292–1306. <https://doi.org/10.1002/jclp.20724>.
- [60] Wróbel-Knybel P, Flis M, Rog J, Jalal B, Wołkowski L, Karakuła-Juchnowicz H. Characteristics of Sleep Paralysis and Its Association with Anxiety Symptoms, Perceived Stress, PTSD, and Other Variables Related to Lifestyle in Selected High Stress Exposed Professions. *International Journal of Environmental Research and Public Health*. 2022; 19: 7821. <https://doi.org/10.3390/ijerph19137821>.
- [61] Young E, Xiong S, Finn L, Young T. Unique sleep disorders profile of a population-based sample of 747 Hmong immigrants in Wisconsin. *Social Science & Medicine (1982)*. 2013; 79: 57–65. <https://doi.org/10.1016/j.socscimed.2012.06.009>.
- [62] Guzek D, Kołota A, Lachowicz K, Skolmowska D, Stachoń M, Głowska D. Association between Vitamin D Supplementation and Mental Health in Healthy Adults: A Systematic Review. *Journal of Clinical Medicine*. 2021; 10: 5156. <https://doi.org/10.3390/jcm10215156>.
- [63] Sawant D, Kamble N. Overcoming Recurrent Isolated Sleep Paralysis: A Case Report of Integrative Management With Yoga, Meditation, and Vitamin D3 Supplementation. *Cureus*. 2024; 16: e76626. <https://doi.org/10.7759/cureus.76626>.
- [64] Arrigoni E, Chen MC, Fuller PM. The anatomical, cellular and synaptic basis of motor atonia during rapid eye movement sleep. *The Journal of Physiology*. 2016; 594: 5391–5414. <https://doi.org/10.1113/JP271324>.
- [65] Vetrivelan R, Bandaru SS. Neural Control of REM Sleep and Motor Atonia: Current Perspectives. *Current Neurology and Neuroscience Reports*. 2023; 23: 907–923. <https://doi.org/10.1007/s11910-023-01322-x>.
- [66] Scammell TE, Arrigoni E, Lipton JO. Neural Circuitry of Wakefulness and Sleep. *Neuron*. 2017; 93: 747–765. <https://doi.org/10.1016/j.neuron.2017.01.014>.
- [67] Lu J, Sherman D, Devor M, Saper CB. A putative flip-flop switch for control of REM sleep. *Nature*. 2006; 441: 589–594. <https://doi.org/10.1038/nature04767>.
- [68] Iranzo A. The REM sleep circuit and how its impairment leads to REM sleep behavior disorder. *Cell and Tissue Research*. 2018; 373: 245–266. <https://doi.org/10.1007/s00441-018-2852-8>.
- [69] Fraigne JJ, Torontali ZA, Snow MB, Peever JH. REM Sleep at its Core - Circuits, Neurotransmitters, and Pathophysiology. *Frontiers in Neurology*. 2015; 6: 123. <https://doi.org/10.3389/fneur.2015.00123>.
- [70] Fuller PM, Saper CB, Lu J. The pontine REM switch: past and present. *The Journal of Physiology*. 2007; 584: 735–741. <https://doi.org/10.1111/j.1365-2214.2007.01573.x>.

[//doi.org/10.1113/jphysiol.2007.140160](https://doi.org/10.1113/jphysiol.2007.140160).

- [71] Luppi PH, Clément O, Sapin E, Gervasoni D, Peyron C, Léger L, *et al.* The neuronal network responsible for paradoxical sleep and its dysfunctions causing narcolepsy and rapid eye movement (REM) behavior disorder. *Sleep Medicine Reviews*. 2011; 15: 153–163. <https://doi.org/10.1016/j.smrv.2010.08.002>.
- [72] Fung SJ, Xi M, Zhang J, Torterolo P, Sampogna S, Morales FR, *et al.* Projection neurons from the central nucleus of the amygdala to the nucleus pontis oralis. *Journal of Neuroscience Research*. 2011; 89: 429–436. <https://doi.org/10.1002/jnr.22554>.
- [73] Reinoso-Suárez F, de Andrés I, Rodrigo-Angulo ML, Garzón M. Brain structures and mechanisms involved in the generation of REM sleep. *Sleep Medicine Reviews*. 2001; 5: 63–77. <https://doi.org/10.1053/smrv.2000.0136>.
- [74] Hefnawy MT, Amer BE, Amer SA, Khlidj Y, Elfakharany B, Alazzeq ZJ, *et al.* Recommendations for future research on sleep paralysis. *Sleep & Breathing*. 2024; 28: 1437–1438. <https://doi.org/10.1007/s11325-024-03000-9>.
- [75] JOUVET M, MICHEL F. Release of the “paradoxal phase” of sleep by stimulation of the brain stem in the intact and chronic mesencephalic cat. *Comptes Rendus des Seances De La Societe De Biologie et De Ses Filiales*. 1960; 154: 636–641. (In French)
- [76] Henley K, Morrison AR. A re-evaluation of the effects of lesions of the pontine tegmentum and locus coeruleus on phenomena of paradoxical sleep in the cat. *Acta Neurobiologiae Experimentalis*. 1974; 34: 215–232.
- [77] Mouret J, Delorme F, Jouvét M. Lesions of the pontine tegmentum and sleep in rats. *Comptes Rendus des Seances De La Societe De Biologie et De Ses Filiales*. 1967; 161: 1603–1606. (In French)
- [78] Valencia Garcia S, Libourel PA, Lazarus M, Grassi D, Luppi PH, Fort P. Genetic inactivation of glutamate neurons in the rat sublaterodorsal tegmental nucleus recapitulates REM sleep behaviour disorder. *Brain: a Journal of Neurology*. 2017; 140: 414–428. <https://doi.org/10.1093/brain/aww310>.
- [79] Karlsson KAE, Gall AJ, Mohs EJ, Seelke AMH, Blumberg MS. The neural substrates of infant sleep in rats. *PLoS Biology*. 2005; 3: e143. <https://doi.org/10.1371/journal.pbio.0030143>.
- [80] Lai YY, Siegel JM. Pontomedullary glutamate receptors mediating locomotion and muscle tone suppression. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 1991; 11: 2931–2937. <https://doi.org/10.1523/JNEUROSCI.11-09-02931.1991>.
- [81] Onoe H, Sakai K. Kainate receptors: a novel mechanism in paradoxical (REM) sleep generation. *Neuroreport*. 1995; 6: 353–356.
- [82] Siegel JM, Wheeler RL, McGinty DJ. Activity of medullary reticular formation neurons in the unrestrained cat during waking and sleep. *Brain Research*. 1979; 179: 49–60. [https://doi.org/10.1016/0006-8993\(79\)90488-8](https://doi.org/10.1016/0006-8993(79)90488-8).
- [83] Kanamori N, Sakai K, Jouvét M. Neuronal activity specific to paradoxical sleep in the ventromedial medullary reticular formation of unresdrained cats. *Brain Research*. 1980; 189: 251–255. [https://doi.org/10.1016/0006-8993\(80\)90024-4](https://doi.org/10.1016/0006-8993(80)90024-4).
- [84] Chen MC, Vetrivelan R, Guo CN, Chang C, Fuller PM, Lu J. Ventral medullary control of rapid eye movement sleep and atonia. *Experimental Neurology*. 2017; 290: 53–62. <https://doi.org/10.1016/j.expneurol.2017.01.002>.
- [85] Brooks PL, Peever JH. Glycinergic and GABA(A)-mediated inhibition of somatic motoneurons does not mediate rapid eye movement sleep motor atonia. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2008; 28: 3535–3545. <https://doi.org/10.1523/JNEUROSCI.5023-07.2008>.
- [86] Vetrivelan R, Fuller PM, Tong Q, Lu J. Medullary circuitry regulating rapid eye movement sleep and motor atonia. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2009; 29: 9361–9369. <https://doi.org/10.1523/JNEUROSCI.0737-09.2009>.
- [87] Krenzler M, Anaclet C, Vetrivelan R, Wang N, Vong L, Lowell BB, *et al.* Brainstem and spinal cord circuitry regulating REM sleep and muscle atonia. *PloS One*. 2011; 6: e24998. <https://doi.org/10.1371/journal.pone.0024998>.
- [88] Fuller PM, Sherman D, Pedersen NP, Saper CB, Lu J. Reassessment of the structural basis of the ascending arousal system. *The Journal of Comparative Neurology*. 2011; 519: 933–956. <https://doi.org/10.1002/cne.22559>.
- [89] Peever J, Fuller PM. The Biology of REM Sleep. *Current Biology: CB*. 2017; 27: R1237–R1248. <https://doi.org/10.1016/j.cub.2017.10.026>.
- [90] Weber F, Hoang Do JP, Chung S, Beier KT, Bikov M, Saffari Doost M, *et al.* Regulation of REM and Non-REM Sleep by Periaqueductal GABAergic Neurons. *Nature Communications*. 2018; 9: 354. <https://doi.org/10.1038/s41467-017-02765-w>.
- [91] Park SH, Weber F. Neural and Homeostatic Regulation of REM Sleep. *Frontiers in Psychology*. 2020; 11: 1662. <https://doi.org/10.3389/fpsyg.2020.01662>.
- [92] Sapin E, Lapray D, BéroD A, Goutagny R, Léger L, Ravassard P, *et al.* Localization of the brainstem GABAergic neurons controlling paradoxical (REM) sleep. *PloS One*. 2009; 4: e4272. <https://doi.org/10.1371/journal.pone.0004272>.
- [93] Monti JM, Lagos P, Jantos H, Torterolo P. Increased REM sleep after intra-locus coeruleus nucleus microinjection of melanin-concentrating hormone (MCH) in the rat. *Progress in Neuro-psychopharmacology & Biological Psychiatry*. 2015; 56: 185–188. <https://doi.org/10.1016/j.pnpbp.2014.09.003>.
- [94] Lu J, Greco MA, Shiromani P, Saper CB. Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2000; 20: 3830–3842. <https://doi.org/10.1523/JNEUROSCI.20-10-03830.2000>.
- [95] Lu J, Bjorkum AA, Xu M, Gaus SE, Shiromani PJ, Saper CB. Selective activation of the extended ventrolateral preoptic nucleus during rapid eye movement sleep. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2002; 22: 4568–4576. <https://doi.org/10.1523/JNEUROSCI.22-11-04568.2002>.
- [96] Hsieh KC, Gvilia I, Kumar S, Uschakov A, McGinty D, Alam MN, *et al.* c-Fos expression in neurons projecting from the preoptic and lateral hypothalamic areas to the ventrolateral periaqueductal gray in relation to sleep states. *Neuroscience*. 2011; 188: 55–67. <https://doi.org/10.1016/j.neuroscience.2011.05.016>.
- [97] Boissard R, Fort P, Gervasoni D, Barbagli B, Luppi PH. Localization of the GABAergic and non-GABAergic neurons projecting to the sublaterodorsal nucleus and potentially gating paradoxical sleep onset. *The European Journal of Neuroscience*. 2003; 18: 1627–1639. <https://doi.org/10.1046/j.1460-9568.2003.02861.x>.
- [98] Monti JM. The role of dorsal raphe nucleus serotonergic and non-serotonergic neurons, and of their receptors, in regulating waking and rapid eye movement (REM) sleep. *Sleep Medicine Reviews*. 2010; 14: 319–327. <https://doi.org/10.1016/j.smrv.2009.10.003>.
- [99] Dauvilliers Y, Siegel JM, Lopez R, Torontali ZA, Peever JH. Cataplexy—clinical aspects, pathophysiology and management strategy. *Nature Reviews. Neurology*. 2014; 10: 386–395. <https://doi.org/10.1038/nrneuro.2014.97>.
- [100] Sabetghadam A, Grabowiecka-Nowak A, Kania A, Gugula A, Blasiak E, Blasiak T, *et al.* Melanin-concentrating hormone and orexin systems in rat nucleus incertus: Dual innervation, bidirectional effects on neuron activity, and differential influences

- on arousal and feeding. *Neuropharmacology*. 2018; 139: 238–256. <https://doi.org/10.1016/j.neuropharm.2018.07.004>.
- [101] de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, *et al*. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proceedings of the National Academy of Sciences of the United States of America*. 1998; 95: 322–327. <https://doi.org/10.1073/pnas.95.1.322>.
- [102] Inutsuka A, Yamanaka A. The physiological role of orexin/hypocretin neurons in the regulation of sleep/wakefulness and neuroendocrine functions. *Frontiers in Endocrinology*. 2013; 4: 18. <https://doi.org/10.3389/fendo.2013.00018>.
- [103] Soya S, Takahashi TM, McHugh TJ, Maejima T, Herlitze S, Abe M, *et al*. Orexin modulates behavioral fear expression through the locus coeruleus. *Nature Communications*. 2017; 8: 1606. <https://doi.org/10.1038/s41467-017-01782-z>.
- [104] Yang C, Zhang L, Hao H, Ran M, Li J, Dong H. Serotonergic neurons in the dorsal raphe nucleus mediate the arousal-promoting effect of orexin during isoflurane anesthesia in male rats. *Neuropeptides*. 2019; 75: 25–33. <https://doi.org/10.1016/j.npep.2019.03.004>.
- [105] Zhang LN, Yang C, Ouyang PR, Zhang ZC, Ran MZ, Tong L, *et al*. Orexin-A facilitates emergence of the rat from isoflurane anesthesia via mediation of the basal forebrain. *Neuropeptides*. 2016; 58: 7–14. <https://doi.org/10.1016/j.npep.2016.02.003>.
- [106] Sakurai T, Nagata R, Yamanaka A, Kawamura H, Tsujino N, Muraki Y, *et al*. Input of orexin/hypocretin neurons revealed by a genetically encoded tracer in mice. *Neuron*. 2005; 46: 297–308. <https://doi.org/10.1016/j.neuron.2005.03.010>.
- [107] Li Y, Gao XB, Sakurai T, van den Pol AN. Hypocretin/Orexin excites hypocretin neurons via a local glutamate neuron-A potential mechanism for orchestrating the hypothalamic arousal system. *Neuron*. 2002; 36: 1169–1181. [https://doi.org/10.1016/s0896-6273\(02\)01132-7](https://doi.org/10.1016/s0896-6273(02)01132-7).
- [108] Muraki Y, Yamanaka A, Tsujino N, Kilduff TS, Goto K, Sakurai T. Serotonergic regulation of the orexin/hypocretin neurons through the 5-HT1A receptor. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2004; 24: 7159–7166. <https://doi.org/10.1523/JNEUROSCI.1027-04.2004>.
- [109] Yamanaka A, Muraki Y, Tsujino N, Goto K, Sakurai T. Regulation of orexin neurons by the monoaminergic and cholinergic systems. *Biochemical and Biophysical Research Communications*. 2003; 303: 120–129. [https://doi.org/10.1016/s0006-291x\(03\)00299-7](https://doi.org/10.1016/s0006-291x(03)00299-7).
- [110] Xie X, Crowder TL, Yamanaka A, Morairty SR, Lewinter RD, Sakurai T, *et al*. GABA(B) receptor-mediated modulation of hypocretin/orexin neurons in mouse hypothalamus. *The Journal of Physiology*. 2006; 574: 399–414. <https://doi.org/10.1113/jphysiol.2006.108266>.
- [111] Torterolo P, Lagos P, Monti JM. Melanin-concentrating hormone: a new sleep factor? *Frontiers in Neurology*. 2011; 2: 14. <https://doi.org/10.3389/fneur.2011.00014>.
- [112] Monti JM, Torterolo P, Lagos P. Melanin-concentrating hormone control of sleep-wake behavior. *Sleep Medicine Reviews*. 2013; 17: 293–298. <https://doi.org/10.1016/j.smrv.2012.10.002>.
- [113] Rauf B, Sharpless BA, Denis D, Perach R, Madrid-Valero JJ, French CC, *et al*. Isolated sleep paralysis: Clinical features, perception of aetiology, prevention and disruption strategies in a large international sample. *Sleep Medicine*. 2023; 104: 105–112. <https://doi.org/10.1016/j.sleep.2023.02.023>.
- [114] Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charnay Y, *et al*. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nature Medicine*. 2000; 6: 991–997. <https://doi.org/10.1038/79690>.
- [115] Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M, *et al*. Reduced number of hypocretin neurons in human narcolepsy. *Neuron*. 2000; 27: 469–474. [https://doi.org/10.1016/s0896-6273\(00\)00058-1](https://doi.org/10.1016/s0896-6273(00)00058-1).
- [116] Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, *et al*. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell*. 1999; 98: 437–451. [https://doi.org/10.1016/s0092-8674\(00\)81973-x](https://doi.org/10.1016/s0092-8674(00)81973-x).
- [117] Dauvilliers Y, Mignot E, Del Rio Villegas R, Du Y, Hanson E, Inoue Y, *et al*. Oral Orexin Receptor 2 Agonist in Narcolepsy Type 1. *The New England Journal of Medicine*. 2023; 389: 309–321. <https://doi.org/10.1056/NEJMoa2301940>.
- [118] Mieda M, Hasegawa E, Kisanuki YY, Sinton CM, Yanagisawa M, Sakurai T. Differential roles of orexin receptor-1 and -2 in the regulation of non-REM and REM sleep. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2011; 31: 6518–6526. <https://doi.org/10.1523/JNEUROSCI.6506-10.2011>.
- [119] Sasaki K, Suzuki M, Mieda M, Tsujino N, Roth B, Sakurai T. Pharmacogenetic modulation of orexin neurons alters sleep/wakefulness states in mice. *PloS One*. 2011; 6: e20360. <https://doi.org/10.1371/journal.pone.0020360>.
- [120] Mochizuki T, Arrigoni E, Marcus JN, Clark EL, Yamamoto M, Honer M, *et al*. Orexin receptor 2 expression in the posterior hypothalamus rescues sleepiness in narcoleptic mice. *Proceedings of the National Academy of Sciences of the United States of America*. 2011; 108: 4471–4476. <https://doi.org/10.1073/pnas.1012456108>.
- [121] Mignot E, Lammers GJ, Ripley B, Okun M, Nevsimalova S, Overeem S, *et al*. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Archives of Neurology*. 2002; 59: 1553–1562. <https://doi.org/10.1001/archneur.59.10.1553>.
- [122] Thannickal TC, Nienhuis R, Siegel JM. Localized loss of hypocretin (orexin) cells in narcolepsy without cataplexy. *Sleep*. 2009; 32: 993–998. <https://doi.org/10.1093/sleep/32.8.993>.
- [123] Berteotti C, Liguori C, Pace M. Dysregulation of the orexin/hypocretin system is not limited to narcolepsy but has far-reaching implications for neurological disorders. *The European Journal of Neuroscience*. 2021; 53: 1136–1154. <https://doi.org/10.1111/ejn.15077>.
- [124] Hong SB, Tae WS, Joo EY. Cerebral perfusion changes during cataplexy in narcolepsy patients. *Neurology*. 2006; 66: 1747–1749. <https://doi.org/10.1212/01.wnl.0000218205.72668.ab>.
- [125] Sardar H, Goldstein-Piekarski AN, Giardino WJ. Amygdala neurocircuitry at the interface between emotional regulation and narcolepsy with cataplexy. *Frontiers in Neuroscience*. 2023; 17: 1152594. <https://doi.org/10.3389/fnins.2023.1152594>.
- [126] Snow MB, Fraigne JJ, Thibault-Messier G, Chuen VL, Thomasian A, Horner RL, *et al*. GABA Cells in the Central Nucleus of the Amygdala Promote Cataplexy. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2017; 37: 4007–4022. <https://doi.org/10.1523/JNEUROSCI.4070-15.2017>.
- [127] Mahoney CE, Agostinelli LJ, Brooks JNK, Lowell BB, Scammell TE. GABAergic Neurons of the Central Amygdala Promote Cataplexy. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2017; 37: 3995–4006. <https://doi.org/10.1523/JNEUROSCI.4065-15.2017>.
- [128] Hasegawa E, Maejima T, Yoshida T, Masseck OA, Herlitze S, Yoshioka M, *et al*. Serotonin neurons in the dorsal raphe mediate the anticataplectic action of orexin neurons by reducing amygdala activity. *Proceedings of the National Academy of Sciences of the United States of America*. 2017; 114: E3526–E3535. <https://doi.org/10.1073/pnas.1614552114>.

- [129] Pintwala S, Peever J. Circuit mechanisms of sleepiness and cataplexy in narcolepsy. *Current Opinion in Neurobiology*. 2017; 44: 50–58. <https://doi.org/10.1016/j.conb.2017.02.010>.
- [130] Shackman AJ, Fox AS. Contributions of the Central Extended Amygdala to Fear and Anxiety. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2016; 36: 8050–8063. <https://doi.org/10.1523/JNEUROSCI.0982-16.2016>.
- [131] Namkung H, Kim SH, Sawa A. The Insula: An Underestimated Brain Area in Clinical Neuroscience, Psychiatry, and Neurology. *Trends in Neurosciences*. 2017; 40: 200–207. <https://doi.org/10.1016/j.tins.2017.02.002>.
- [132] Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep state switching. *Neuron*. 2010; 68: 1023–1042. <https://doi.org/10.1016/j.neuron.2010.11.032>.
- [133] Peter-Derex L, von Ellenrieder N, van Rosmalen F, Hall J, Dubeau F, Gotman J, *et al.* Regional variability in intracerebral properties of NREM to REM sleep transitions in humans. *Proceedings of the National Academy of Sciences of the United States of America*. 2023; 120: e2300387120. <https://doi.org/10.1073/pnas.2300387120>.
- [134] Maciel R, Yamazaki R, Wang D, De Laet A, Cabrera S, Agnorelli C, *et al.* Is REM sleep a paradoxical state?: Different neurons are activated in the cingulate cortices and the claustrum during wakefulness and paradoxical sleep hypersomnia. *Biochemical Pharmacology*. 2021; 191: 114514. <https://doi.org/10.1016/j.bcp.2021.114514>.
- [135] Peever J, Luppi PH, Montplaisir J. Breakdown in REM sleep circuitry underlies REM sleep behavior disorder. *Trends in Neurosciences*. 2014; 37: 279–288. <https://doi.org/10.1016/j.tins.2014.02.009>.
- [136] Wu MF, Gulyani SA, Yau E, Mignot E, Phan B, Siegel JM. Locus coeruleus neurons: cessation of activity during cataplexy. *Neuroscience*. 1999; 91: 1389–1399. [https://doi.org/10.1016/s0306-4522\(98\)00600-9](https://doi.org/10.1016/s0306-4522(98)00600-9).
- [137] Kornum BR, Knudsen S, Ollila HM, Pizza F, Jennum PJ, Dauvilliers Y, *et al.* Narcolepsy. *Nature Reviews. Disease Primers*. 2017; 3: 16100. <https://doi.org/10.1038/nrdp.2016.100>.
- [138] Szabo ST, Thorpy MJ, Mayer G, Peever JH, Kilduff TS. Neurobiological and immunogenetic aspects of narcolepsy: Implications for pharmacotherapy. *Sleep Medicine Reviews*. 2019; 43: 23–36. <https://doi.org/10.1016/j.smrv.2018.09.006>.
- [139] Siegel JM, Nienhuis R, Fahringer HM, Paul R, Shiromani P, Dement WC, *et al.* Neuronal activity in narcolepsy: identification of cataplexy-related cells in the medial medulla. *Science (New York, N.Y.)*. 1991; 252: 1315–1318. <https://doi.org/10.1126/science.1925546>.
- [140] Stefani A, Högl B. Nightmare Disorder and Isolated Sleep Paralysis. *Neurotherapeutics: the Journal of the American Society for Experimental NeuroTherapeutics*. 2021; 18: 100–106. <https://doi.org/10.1007/s13311-020-00966-8>.
- [141] Studerus E, Kometer M, Hasler F, Vollenweider FX. Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. *Journal of Psychopharmacology (Oxford, England)*. 2011; 25: 1434–1452. <https://doi.org/10.1177/0269881110382466>.
- [142] van der Zwaard R, Polak MA. Pseudohallucinations: a pseudo-concept? A review of the validity of the concept, related to associate symptomatology. *Comprehensive Psychiatry*. 2001; 42: 42–50. <https://doi.org/10.1053/comp.2001.19752>.
- [143] Gaebel W, Zielasek J. Future classification of psychotic disorders. *European Archives of Psychiatry and Clinical Neuroscience*. 2009; 259 Suppl 2: S213–8. <https://doi.org/10.1007/s00406-009-0049-6>.
- [144] Riva G. Neurobiology of Anorexia Nervosa: Serotonin Dysfunction Link Self-Starvation with Body Image Disturbances through an Impaired Body Memory. *Frontiers in Human Neuroscience*. 2016; 10: 600. <https://doi.org/10.3389/fnhum.2016.00600>.
- [145] Saulin A, Savli M, Lanzenberger R. Serotonin and molecular neuroimaging in humans using PET. *Amino Acids*. 2012; 42: 2039–2057. <https://doi.org/10.1007/s00726-011-1078-9>.
- [146] Aghajanian GK, Marek GJ. Serotonin and hallucinogens. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*. 1999; 21: 16S–23S. [https://doi.org/10.1016/S0893-133X\(98\)00135-3](https://doi.org/10.1016/S0893-133X(98)00135-3).
- [147] Vollenweider FX, Kometer M. The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. *Nature Reviews. Neuroscience*. 2010; 11: 642–651. <https://doi.org/10.1038/nrn2884>.
- [148] Frokjaer VG, Mortensen EL, Nielsen FA, Haugbol S, Pinborg LH, Adams KH, *et al.* Frontolimbic serotonin 2A receptor binding in healthy subjects is associated with personality risk factors for affective disorder. *Biological Psychiatry*. 2008; 63: 569–576. <https://doi.org/10.1016/j.biopsych.2007.07.009>.
- [149] Kumagai H, Kawaguchi K, Sawatari H, Kiyohara Y, Hayashi M, Shiomi T. Dashcam video footage-based analysis of microsleep-related behaviors in truck collisions attributed to falling asleep at the wheel. *Accident; Analysis and Prevention*. 2023; 187: 107070. <https://doi.org/10.1016/j.aap.2023.107070>.
- [150] Philip P, Akerstedt T. Transport and industrial safety, how are they affected by sleepiness and sleep restriction? *Sleep Medicine Reviews*. 2006; 10: 347–356. <https://doi.org/10.1016/j.smrv.2006.04.002>.
- [151] Garbarino S, Guglielmi O, Sanna A, Mancardi GL, Magnavita N. Risk of Occupational Accidents in Workers with Obstructive Sleep Apnea: Systematic Review and Meta-analysis. *Sleep*. 2016; 39: 1211–1218. <https://doi.org/10.5665/sleep.5834>.
- [152] Exelmans L, Van den Bulck J. Bedtime mobile phone use and sleep in adults. *Social Science & Medicine (1982)*. 2016; 148: 93–101. <https://doi.org/10.1016/j.socscimed.2015.11.037>.
- [153] Carter B, Rees P, Hale L, Bhattacharjee D, Paradkar MS. Association Between Portable Screen-Based Media Device Access or Use and Sleep Outcomes: A Systematic Review and Meta-analysis. *JAMA Pediatrics*. 2016; 170: 1202–1208. <https://doi.org/10.1001/jamapediatrics.2016.2341>.
- [154] Priest B, Brichard C, Aubert G, Liistro G, Rodenstein DO. Microsleep during a simplified maintenance of wakefulness test. A validation study of the OSLER test. *American Journal of Respiratory and Critical Care Medicine*. 2001; 163: 1619–1625. <https://doi.org/10.1164/ajrccm.163.7.2007028>.
- [155] Blaivas AJ, Patel R, Hom D, Antigua K, Ashtyani H. Quantifying microsleep to help assess subjective sleepiness. *Sleep Medicine*. 2007; 8: 156–159. <https://doi.org/10.1016/j.sleep.2006.06.011>.
- [156] Hertig-Godeschalk A, Skorucak J, Malafeev A, Achermann P, Mathis J, Schreier DR. Microsleep episodes in the borderland between wakefulness and sleep. *Sleep*. 2020; 43: zsz163. <https://doi.org/10.1093/sleep/zsz163>.
- [157] Sil'kis IG. Generation of Ponto-Geniculo-Occipital (PGO) waves as a possible reason of disturbances in visual perception in microsleep. *Rossiiskii Fiziologicheskii Zhurnal Imeni I.M. Sechenova*. 2011; 97: 472–482.
- [158] Poudel GR, Innes CRH, Bones PJ, Watts R, Jones RD. Losing the struggle to stay awake: divergent thalamic and cortical activity during microsleeps. *Human Brain Mapping*. 2014; 35: 257–269. <https://doi.org/10.1002/hbm.22178>.
- [159] Horne J, Reyner L. Vehicle accidents related to sleep: a review. *Occupational and Environmental Medicine*. 1999; 56: 289–294. <https://doi.org/10.1136/oem.56.5.289>.
- [160] Akerstedt T. Consensus statement: fatigue and accidents in

- transport operations. *Journal of Sleep Research*. 2000; 9: 395. <https://doi.org/10.1046/j.1365-2869.2000.00228.x>.
- [161] Ramos DF, Magalhães J, Santos P, Vale J, Santos MI. RECURRENT SLEEP PARALYSIS - FEAR OF SLEEPING. *Revista Paulista De Pediatria: Orgao Oficial Da Sociedade De Pediatria De Sao Paulo*. 2019; 38: e2018226. <https://doi.org/10.1590/1984-0462/2020/38/2018226>.
- [162] Attarian H. Treatment options for parasomnias. *Neurologic Clinics*. 2010; 28: 1089–1106. <https://doi.org/10.1016/j.ncl.2010.03.025>.
- [163] Cheyne JA. Situational factors affecting sleep paralysis and associated hallucinations: position and timing effects. *Journal of Sleep Research*. 2002; 11: 169–177. <https://doi.org/10.1046/j.1365-2869.2002.00297.x>.
- [164] Cui N, van Looij MA, Kasius KM. Successful treatment of sleep paralysis with the Sleep Position Trainer: a case report. *Journal of Clinical Sleep Medicine: JCSM: Official Publication of the American Academy of Sleep Medicine*. 2022; 18: 2317–2319. <https://doi.org/10.5664/jcsm.9996>.
- [165] Solomonova E, Dubé S, Blanchette-Carrière C, Sandra DA, Samson-Richer A, Carr M, *et al*. Different Patterns of Sleep-Dependent Procedural Memory Consolidation in Vipassana Meditation Practitioners and Non-meditating Controls. *Frontiers in Psychology*. 2020; 10: 3014. <https://doi.org/10.3389/fpsyg.2019.03014>.
- [166] Turmel D, Carlier S, Bruyneel AV, Bruyneel M. Tailored individual Yoga practice improves sleep quality, fatigue, anxiety, and depression in chronic insomnia disorder. *BMC Psychiatry*. 2022; 22: 267. <https://doi.org/10.1186/s12888-022-03936-w>.
- [167] Mundt JM, Pruiksmá KE, Konkoly KR, Casiello-Robbins C, Nadorff MR, Franklin RC, *et al*. Treating narcolepsy-related nightmares with cognitive behavioural therapy and targeted lucidity reactivation: A pilot study. *Journal of Sleep Research*. 2025; 34: e14384. <https://doi.org/10.1111/jsr.14384>.
- [168] Trauer JM, Qian MY, Doyle JS, Rajaratnam SMW, Cunnington D. Cognitive Behavioral Therapy for Chronic Insomnia: A Systematic Review and Meta-analysis. *Annals of Internal Medicine*. 2015; 163: 191–204. <https://doi.org/10.7326/M14-2841>.
- [169] Espie CA, Kyle SD, Williams C, Ong JC, Douglas NJ, Hames P, *et al*. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep*. 2012; 35: 769–781. <https://doi.org/10.5665/sleep.1872>.
- [170] Herrero NL, Gallo FT, Gasca-Rolín M, Gleiser PM, Forcato C. Spontaneous and induced out-of-body experiences during sleep paralysis: Emotions, “AURA” recognition, and clinical implications. *Journal of Sleep Research*. 2023; 32: e13703. <https://doi.org/10.1111/jsr.13703>.
- [171] Guilleminault C, Raynal D, Takahashi S, Carskadon M, Dement W. Evaluation of short-term and long-term treatment of the narcolepsy syndrome with clomipramine hydrochloride. *Acta Neurologica Scandinavica*. 1976; 54: 71–87. <https://doi.org/10.1111/j.1600-0404.1976.tb07621.x>.
- [172] Ristanovic RK, Liang H, Hornfeldt CS, Lai C. Exacerbation of cataplexy following gradual withdrawal of antidepressants: manifestation of probable protracted rebound cataplexy. *Sleep Medicine*. 2009; 10: 416–421. <https://doi.org/10.1016/j.sleep.2008.04.004>.
- [173] Palagini L, Baglioni C, Ciapparelli A, Gemignani A, Riemann D. REM sleep dysregulation in depression: state of the art. *Sleep Medicine Reviews*. 2013; 17: 377–390. <https://doi.org/10.1016/j.smrv.2012.11.001>.
- [174] Sohi M, Jain L, Ang-Rabanes M, Mogallapu R. Sertraline-Induced Sleep Paralysis: A Case Report. *Cureus*. 2023; 15: e49014. <https://doi.org/10.7759/cureus.49014>.
- [175] Kierlin L, Littner MR. Parasomnias and antidepressant therapy: a review of the literature. *Frontiers in Psychiatry*. 2011; 2: 71. <https://doi.org/10.3389/fpsyg.2011.00071>.
- [176] Schwartz JC. The histamine H3 receptor: from discovery to clinical trials with pitolisant. *British Journal of Pharmacology*. 2011; 163: 713–721. <https://doi.org/10.1111/j.1476-5381.2011.01286.x>.
- [177] Romigi A, Vitrani G, Lo Giudice T, Centonze D, Franco V. Profile of pitolisant in the management of narcolepsy: design, development, and place in therapy. *Drug Design, Development and Therapy*. 2018; 12: 2665–2675. <https://doi.org/10.2147/DDDT.S101145>.
- [178] Ligneau X, Perrin D, Landais L, Camelin JC, Calmels TPG, Berrebi-Bertrand I, *et al*. BF2.649 [1-piperidine, hydrochloride], a nonimidazole inverse agonist/antagonist at the human histamine H3 receptor: Preclinical pharmacology. *The Journal of Pharmacology and Experimental Therapeutics*. 2007; 320: 365–375. <https://doi.org/10.1124/jpet.106.111039>.
- [179] Thorpy MJ. Recently Approved and Upcoming Treatments for Narcolepsy. *CNS Drugs*. 2020; 34: 9–27. <https://doi.org/10.1007/s40263-019-00689-1>.
- [180] Bogan RK, Feldman N, Emsellem HA, Rosenberg R, Lu Y, Bream G, *et al*. Effect of oral JZP-110 (ADX-N05) treatment on wakefulness and sleepiness in adults with narcolepsy. *Sleep Medicine*. 2015; 16: 1102–1108. <https://doi.org/10.1016/j.sleep.2015.05.013>.
- [181] Schweitzer PK, Rosenberg R, Zammit GK, Gotfried M, Chen D, Carter LP, *et al*. Solriamfetol for Excessive Sleepiness in Obstructive Sleep Apnea (TONES 3). A Randomized Controlled Trial. *American Journal of Respiratory and Critical Care Medicine*. 2019; 199: 1421–1431. <https://doi.org/10.1164/rccm.201806-1100OC>.
- [182] Barker EC, Flygare J, Paruthi S, Sharkey KM. Living with Narcolepsy: Current Management Strategies, Future Prospects, and Overlooked Real-Life Concerns. *Nature and Science of Sleep*. 2020; 12: 453–466. <https://doi.org/10.2147/NSS.S162762>.
- [183] Barateau L, Dauvilliers Y. Recent advances in treatment for narcolepsy. *Therapeutic Advances in Neurological Disorders*. 2019; 12: 1756286419875622. <https://doi.org/10.1177/1756286419875622>.
- [184] Vodovar D, Duchêne A, Wimberley C, Leroy C, Pottier G, Dauvilliers Y, *et al*. Cortico-Amygdala-Striatal Activation by Modafinil/Flecainide Combination. *The International Journal of Neuropsychopharmacology*. 2018; 21: 687–696. <https://doi.org/10.1093/ijnp/pyy027>.
- [185] Nepovimova E, Janockova J, Misik J, Kubik S, Stuchlik A, Vales K, *et al*. Orexin supplementation in narcolepsy treatment: A review. *Medicinal Research Reviews*. 2019; 39: 961–975. <https://doi.org/10.1002/med.21550>.
- [186] Abboud M. Vitamin D Supplementation and Sleep: A Systematic Review and Meta-Analysis of Intervention Studies. *Nutrients*. 2022; 14: 1076. <https://doi.org/10.3390/nu14051076>.
- [187] Dye TJ. Clinical Evaluation and Management of Narcolepsy in Children and Adolescents. *Seminars in Pediatric Neurology*. 2023; 48: 101089. <https://doi.org/10.1016/j.spen.2023.101089>.
- [188] Blackwell JE, Kingshott RN, Weighall A, Elphick HE, Nash H. Paediatric narcolepsy: a review of diagnosis and management. *Archives of Disease in Childhood*. 2022; 107: 7–11. <https://doi.org/10.1136/archdischild-2020-320671>.
- [189] Plazzi G, Pizza F, Lecendreux M, Gringras P, Barateau L, Bruni O, *et al*. Pharmacological management of narcolepsy in children and adolescents. *Journal of Sleep Research*. 2024; 33: e14055. <https://doi.org/10.1111/jsr.14055>.