Chapter

Sleep Disorders and Epilepsy

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Abstract

Complex interplay and reciprocal interactions between sleep and epilepsy have been known for centuries. However, newer technologies and in-depth studies have provided us with better understanding of this relationship. Nocturnal seizures can interrupt sleep, while a number of factors, including antiepileptic drugs and sleep disorders, can aggravate seizures. Interestingly, different epileptic syndromes may trigger increase in seizure frequency at a certain phases of the sleep-wake cycle, while others may not show any correlation with these phases. We aim to provide an overview of the interactions between sleep and epilepsy, and provide better understanding how knowledge of the relationship between these two conditions can help more effective management of both disorders.

Keywords: sleep, epilepsy, seizures, antiepileptics, sleep deprivation

1. Introduction

For centuries, the intimate and reciprocal interaction between epilepsy and sleep was well recognized. In the late 1800s, Gowers investigated the relationship between grand mal epilepsy and the sleep-awake cycle [1]. In 1929, Langdon-Down and Brain found that nocturnal seizure occurrence had two peaks, approximately 2 h after bedtime and between 4 and 5 am, and daytime seizures occurred predominantly in the first 2 hours of awakening [2]. These conclusions were at first based solely on clinical observations. However, the advent of the electroencephalogram (EEG) revealed that sleep not only activated clinical seizures, but also interictal epileptiform discharges (IEDs), thus sleep and sleep deprivation becoming the standard laboratory activating techniques during the EEG recording. Epilepsy may also affect sleep architecture.

This chapter is an overview of the relationship between sleep and epilepsy.

2. Electrophysiology of sleep

The human states are divided into wakefulness, Non-REM (NREM) sleep, and REM sleep, REM being rapid eye movements. Sleep non-REM are subdivided in N1, N2, and N3. N1 and N2 are superficial sleep stages, where patient may be easily aroused and N3 is a deep sleep, where arousal is difficult. The characterization of each of those three stages is based on the EEG recording, in conjunction with eye and muscle activity recording. N2 is characterized by the presence of spindles and K-complexes and N3 - by the presence of high voltage slow delta waves.

The existence of two antagonistic systems promoting wakefulness and sleep was assumed in 1930 by von Economo [3]. In the 1940s, the "ascending arousal system" concept in the brainstem of animal and human brain, maintaining wakefulness, became clearer and more accepted. Now this system is called activating reticular arousal system (ARAS) [4]. The ARAS consist of neuronal network, containing several neurotransmitters, including acetylcholine, noradrenalin, serotonin, catecholamine, histamine, and orexin that play a role in the arousal system [5, 6]. Saper discovered that the ventrolateral preoptic area (VPLO) was involved in inducing NREM sleep [7]. It contains GABA-ergic and galanin-ergic neurons which inhibit the activating brainstem ARAS harboring and keep it from firing throughout the entire NREM sleep, providing the substrate of the "sleep system" with opposite function to the "wake system" When VLPO neurons fire during sleep, they inhibit the arousal system cell groups, thus disinhibiting and reinforcing their own firing. Similarly, when arousal neurons fire at high rate during wakefulness, they inhibit the VLPO, thereby disinhibiting their own firing [7]. This concept is nowadays accepted as the basics of the hypothalamic "sleep switch" module underlying alternations of sleep and awake cycle.

The brainstem cholinergic system provokes fast rhythms on the EEG, while abolishing thalamic spindle generation and delta oscillations [8]. Cortical neurons are depolarized by glutamate release, mainly from the thalamocortical fibers, but also by cortico-cortical axons once the activation has started and/or from reduction of K^+ conductance by acetylcholine, norepinephrine, and other neuromodulators [9].

3. Effect of sleep on epilepsy

Seizures and epilepsy syndromes are classified based on the time of occurrence of seizures regarding the sleep-wake cycle. Pure sleep epilepsies, arousal epilepsy, wakefulness epilepsy, and epilepsy occurring irrespective of time are the four main types of seizures [1, 2, 10]. Sleep accentuated epilepsy includes epilepsies with seizures occurring during both awake and asleep state, but epileptiform activity becomes accentuated during sleep.

Gowers noted that seizures happening during daytime cluster at certain times of the day, specifically upon awakening and late afternoon; and seizures occurring at night tend to occur mainly at bedtime and early morning hours before awakening [2] Janz observed that up to 45% of patients with primarily generalized tonic–clonic seizures had nocturnal seizures [10].

In general, NREM sleep facilitates interictal epileptiform activity (IEA) and REM inhibits IEA and is protective against seizures. NREM sleep is a synchronized state that allows better conduction of electrical impulses rather than REM sleep that is an asynchronous state [11–14]. The hypothesis is that during NREM sleep more neurons are in a resting state making them more recruitable into discharges. Whereas during REM sleep there is more neuronal firing that makes neurons less available to generate IEA. Despite the fact that the generators of different sleep and arousal states exert some common effects on seizure disorders, the distinct pathways, seizure manifestations, and mechanisms involved also depend on the pathophysiology of the specific epileptic syndrome. This section will briefly discuss the effect of sleep on specific epilepsy syndromes.

4. Adult epilepsies, associated with sleep

Seizures are divided in generalized and focal. In generalized seizures, the epileptic activity starts in multiple brain regions simultaneously, while in focal

seizures, the epileptic discharges originate in one area of brain that may or may not spread to other regions of the brain. Seizures occurring with loss of consciousness are known as focal dyscognitive seizure or focal seizure with loss of consciousness, formerly known as complex partial seizures. Seizures occurring without change in awareness are called focal simple seizures where there is no loss of consciousness.

4.1 Generalized seizures

4.1.1 Primary generalized tonic-clonic seizures

Gowers first noted that patients with primary generalized tonic-clonic seizures have their seizures in two peaks during sleep: the first - two hours after sleep onset and at the end of the sleep cycle [1]. There are two peaks of sleep-related seizures occurred between 9-11 pm and 3-5 am respectively [10]. Further studies showed that generalized tonic-clonic epilepsy occurs mainly during NREM sleep [15, 16]. Generalized interictal epileptiform activity (IEA) increases in NREM sleep [17]. In arousal epilepsies or epilepsies occurring during awake and sleep states, IEA can occur at any time. Meanwhile, in pure sleep epilepsy, IEA have been described during REM sleep and/or on awakening in 9% of the patients and restricted to NREM sleep in 41% [10].

4.1.2 Juvenile myoclonic epilepsy

Juvenile myoclonic epilepsy [JME] is a syndrome characterized by the combination of myoclonic, absence, and generalized tonic-clonic seizures that especially occur in the morning in the first one to two hours after awakening, that is a hallmark of this syndrome. Seizures are often triggered by externally provoked arousals in the morning after a sleepless night associated with alcohol consumption. JME is an age-related, genetic, and generalized epilepsy syndrome that typically begins in early adolescence [10, 18]. Seizures can also occur on awakening from a nap, but rarely at other times during the day [18]. The classic EEG shows generalized spike-wave complexes at 4-6 Hz as well as polypiles. The discharges increase markedly at sleep onset and awakening, but are less frequent in NREM sleep, REM sleep, and wakefulness. The arousal period is apparently a hyper-synchronous state that makes more permissible the conduction of epileptic discharges.

Valproic acid or other newer broad-spectrum antiepileptics [AEDs] such as levetiracetam, lamotrigine, topiramate, zonisamide and perampanel may lead to excellent seizure control in patients who adhere to rigid compliance and avoid seizure precipitant such as sleep deprivation and alcohol binges. Medication requirement typically endures throughout life, with seldom patients being successfully weaned from therapy long-term in later adulthood.

A closely related primary generalized epilepsy syndrome called generalized tonic-clonic seizures upon awakening (GTCOA) has a similar pattern of occurrence of convulsions, but without myoclonic seizures.

4.2 Focal seizures

4.2.1 Temporal lobe epilepsy

Sleep related complex partial seizures originating in the temporal lobe are frequent and represent around 33% of all temporal lobe seizures [19]. Nocturnal temporal lobe epilepsy (NTLE) is a subtype of medically refractory temporal lobe epilepsy, usually presenting during adolescence with seizures nearly exclusively

confined to nighttime sleep [18]. In most cases, seizures are characterized by sudden awakening from sleep with a sensory aura, which then progresses to a focal seizure with impaired awareness. The latter is often associated with amnestic automatisms that mimic a NREM parasomnia called confusional arousal. Most patients (around 70%) also have secondary generalized tonic-clonic seizures [18].

Regarding IEA, most studies have found an increase in interictal epileptiform activity during NREM sleep with decrement during REM sleep. The spike frequency was 85% in NREM and 12.5% in REM sleep [20]. Sammaritano found that the extent of the electrical field increased in more than 75% of the spikes in NREM compared with the wake state. Meanwhile, there was a restriction of the electrical field of the epileptiform activity during REM sleep. Desynchronization of EEG pattern during REM sleep reduces the likelihood of spatial and temporal summation of aberrant depolarizations [21]. One third of patients have bilateral IEDs that occur independently on both sides, especially during NREM. However, localization of the primary epileptogenic area is more reliable in REM sleep than in wakefulness, and in wakefulness more than in slow-wave sleep. Therefore, REM sleep provides an opportunity to better localized the epileptic focus. When seizures occur during daytime they are common in the afternoon or are bimodal, and peak in the morning and afternoon [22].

5. Pediatric epilepsy associated with sleep

5.1 Generalized epilepsies

5.1.1 Absence epilepsy

Absence seizures clinically present as a brief transitory behavioral arrest lasting a few seconds that is detectable while patient is awake and typically triggered by hyperventilation, and less often by photic stimulation [23]. Typical EEG shows a generalized 3-Hz spike-wave complexes. The activation of the IEA is most marked in the first sleep cycle [24]. Absence seizures are often inhibited by full wakefulness and REM sleep. During NREM slow-wave sleep the cell activity is more synchronous and allows the activation of spike-wave responses, whereas during REM, a traditional desynchronization state, spike and wave are uncommon [25]. The spike and waves present during NREM state differ also from wakefulness IEDs because they are briefer, more fragmented, more irregular, and slower than during wakefulness [20].

5.1.2 West syndrome

West Syndrome is characterized by the triad of infantile spasms, psychomotor retardation, and hypsarrhythmia in the EEG. Hypsarrhythmia is characterized by chaotic and disorganized background of high voltage, asynchronous spike and slow-wave activity [26]. Only 2-5% of the spams occurred during sleep despite increase in EEG abnormalities during NREM sleep [27]. The hypsarrhythmia pattern may become more apparent during sleep. During REM sleep, a marked attenuation or disappearance of the hypsarrhythmia pattern is noted [28]. Treatment of Infantile spasms includes ACTH, prednisone, and vigabatrin. Vigabatrin [gamma vinyl, gamma-aminobutyric acid (GABA)] is a specific, irreversible inhibitor of GABA-transaminase. Other treatment includes Zonisamide, Topiramate, Valproic acid, Nitrazepam, Pyridoxine, and Ketogenic diet. Surgery

should be considered in cases with asymmetric spasm, focal neurologic abnormalities on examination, EEG with focal or lateralizing features, and radiologic evidence of structural abnormality.

5.1.3 Lennox – Gastaut syndrome

Lennox-Gastaut's syndrome [LGS] usually begins in the first decade of life and is characterized by multiple types of primary generalized seizures, including prominent nocturnal tonic, astatic/atonic, atypical absence, myoclonic, and generalized tonic-clonic seizures with associated psychomotor and cognitive delay. It is often preceded by a history of infantile spasms with hypsarrhythmia in the EEG. Typical EEG shows slow spike-wave [SSW] complexes at 1.5-2.5 Hz, multifocal epileptiform abnormalities, paroxysmal fast activity, and diffuse background slowing. The quantity of the bursts of SSW complexes increases during NREM sleep [29]. Paroxysmal fast activity is a typical pattern of LGS characterized by diffuse bursts activity with a frequency of 15-20 Hz, mainly during NREM with an occurrence up to hundred times per night, but absent during REM sleep [23].

5.2 Focal epilepsies

5.2.1 Frontal lobe epilepsy

Frontal lobe epilepsy [FLE] is the second most common focal epilepsy. Seizures with origin in the frontal lobe tend to occur preferentially during sleep and have prominent motor features, often recognized by family members or friends, **Table 1**. There are two very distinct epileptic syndromes that characterized frontal lobe seizure. They are known as nocturnal frontal lobe epilepsy and supplementary sensorimotor area epilepsy.

Nocturnal frontal lobe epilepsy (NFLE) predominates in male, typically with onset in infancy through adolescence, and is familial in 6-40% of the cases [30–32]. It is characterized by paroxysmal arousals with brief hypermotor features, motor attacks with complex dystonic and dyskinetic movements, and/or episodic nocturnal wandering that mimics the NREM parasomnia called sleepwalking. NFLE usually presents with multiple attacks per night. Video-EEG polysomnography is necessary for definitive diagnosis. Approximately 50% of the cases have normal ictal or interictal EEGs. NFLE usually respond to carbamazepine, but cases of medically intractable NFLE have been well established [30–33].

Supplementary sensorimotor area (SSMA) epilepsy is another unique subtype of frontal lobe epilepsy. Seizures characteristically begin with somatosensory auras progressing to a "fencing" posture with the arm contralateral to seizure

Early hyper-motor activity
Short duration
Minimal or no post-ictal period
Presence in clusters
Often secondarily generalized
Occurrence at night

Table 1.
General features of frontal lobe seizures.

focus relatively extended and ipsilateral arm abducted and flexed; speech arrest or vocalization and flailing or trashing limb movements.

5.2.2 Autosomal dominant nocturnal frontal lobe epilepsy

The autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) shares the same characteristics as NFLE described above, but is associated with genetically heterogenous mutations in the nicotinic acetylcholine receptor complex, which is inherited in an autosomal dominant pattern [33]. There are four known loci for ADNFLE, three with known causative agents. These genes, CHRNA4, CHRNB2, and CHRNA2, encode various nicotinic acetylcholine receptor α and β subunits [34].

ADNFLE is often misdiagnosed as nightmares. Attacks often occur in clusters and typically first manifest in childhood.

5.2.3 Benign focal epilepsy of childhood

This is the most common type of epilepsy within the pediatric sleep-related epilepsy spectrum and accounts for 15-25% of all childhood epilepsies [35]. Benign Rolandic' s epilepsy or benign focal epilepsy of childhood with centrotemporal spikes is a simple partial seizure disorder with hypersalivation, hemifacial and/or hand focal motor-clonic activity that might secondarily spread with generalized tonic-clonic seizures. Seizures often occur exclusively during sleep in three-quarters of patients [36, 37]. The mean age of onset is 7 (3 to 13 years), with recovery by mid-adolescence. Normally, the children affected have normal development with infrequent seizure, but occasionally treatment is necessary. EEG shows high voltage spike and wave discharges over the ipsilateral centrotemporal regions but may occur bilaterally. The discharges increase in frequency, voltage, field, and complexity during sleep. Sleep usually enhances central-midtemporal epileptic discharges, especially in first third of the night, during N3, but also during REM sleep [38]. Treatment is usually successful with AEDs that are effective in partial epilepsy such as carbamazepine, oxcarbazepine, or levetiracetam.

5.2.4 Laundau – Kleffner syndrome electrical status epilepticus of sleep

Laundau-Kleffner syndrome (LKS) is a rare childhood disorder characterized by loss of language comprehension and verbal expression in association with electro-encephalographic finding of status epilepticus during sleep [ESES]. This syndrome is associated with subacute progressive language regression. At some point during this syndrome, there is a dramatic activation of IEA during sleep called ESES that consist of generalized spike-wave complexes at 2-2.5 Hz occurring for >85% of slow wave-sleep with or without clinical seizures. There is marked attenuation of the spikes during REM sleep and wakefulness EEG. With the onset of ESES, there is usually an associated cognitive decline with a speech disorder [39]. Seizures may manifest as nocturnal focal motor or generalized tonic-clonic seizures. LKS most commonly presents in children 2-10 years of age. There is usually remission of the seizures and epileptiform discharges by age of 15, however some patients can develop an autistic regression [40]. Corticosteroid and IVIG are effective and can be considered for treatment of both clinical and EEG changes [41–43]. AEDs including valproate, ethosuximide, clonazepam, clobazam, vigabatrin and felbamate are also effective. In refractory cases, epilepsy surgery including temporal lobectomy in lesional and non-lesional cases have been associated with improvement in language and refractory seizures [44, 45].

6. Comorbid sleep disorders in epilepsy

Many patients with epilepsy complain of excessive daytime sleepiness (EDS), with reported prevalence as high as 16.9%–28% [46–48]. In fact, EDS is the most common complaint of subjects referred to sleep disorder centers. EDS in epileptic patients may result from nocturnal seizures, sedative effects of antiepileptic drugs, poor sleep hygiene, and co-morbid primary sleep disorders [49]. EDS in these patients is often mistakenly attributed to AED adverse effect rather than to an underlying primary sleep disorder.

More than 50% of the epileptics suffer from insomnia up to certain extent, as a result of adverse effects of AEDs, substance abuse, nocturnal seizures, and comorbid anxiety and depression. and out of these 43% has poor seizure control and significant impact on quality of life [50].

Co-morbid primary sleep disorder should be sought and treated, but the exact incidence of primary sleep disorders in patients with epilepsy remains uncertain.

Obstructive sleep apnea (OSA) is the most common cause of sleep-disordered breathing and may exacerbate seizure burden in as many as 33% of patients with medically intractable epilepsy undergoing pre-surgical planning [51, 52]. Predisposing factors for OSA are older age, male, obesity, dental mal-occlusion and Crowded upper airways [53].

Polytherapy AEDs in patients with drug-resistant epilepsy are at increased risk of obesity as compared to monotherapy. Anti-seizure drugs including valproic acid, pregabalin, perampanel, gabapentin and vigabatrin are associated with weight gain, therefore, can potentially worsen or increase the risk of OSA [54]. Adults who developed epilepsy later in life or had worsening seizure control, had a higher apnea–hypopnea index (AHI) and Epworth Sleepiness Scale (ESS) score compared with those who were seizure-free or had an improvement in seizure control [52]. Nasal continuous positive airway pressure (CPAP) therapy demonstrated seizure reduction in patients with OSA and refractory epilepsy in several observational studies [55–59].

Restless legs syndrome (RLS), which is defined as the urge to move the legs that improve or partially relieves with activity, worsen with inactivity and is worse at night, is common feature in epileptics with a prevalence of 10.2%–28.2% [48, 60].

7. Sleep deprivation

Sleep deprivation is one of the most potent triggers of epileptic seizures and epileptiform discharges in patients with generalized epilepsy, triggering seizures in up to 25% of patients suffering from epilepsy [61].

Back in the 1960s and 1970s a series of articles suggested that sleep deprivation was a facilitator of interictal epileptiform discharges, and therefore a promoter of seizures. Lack of adequate sleep causes dysregulation of the hypothalamic pituitary function with release of stress hormones such a cortisol and noradrenaline, which leads to worsening of seizure control [62]. In a recent study, more than 97% of patients with epilepsy reported at least one factor that provokes seizures, and the top three were sleep deprivation, stress, and fatigue [61]. In many cases alcohol consumption was also a common trigger.

Sleep deprivation is often used in epilepsy monitoring units to increase the frequency of seizures. In addition, interictal epileptiform discharges are also more apparent after sleep deprivation.

Environmental factors and sleep hygiene are also crucial in the control of seizures. Appropriate noise level, light intensity, surrounding temperature, humidity, and type of bed are needed for a comfortable sleep. Another important issue is sleep hygiene. Certain behaviors and practices interfere with normal nocturnal sleep. They include time of going to sleep, consumption of food and drinks before sleep, watching TV, working on the computer, using the phone, reading, or physical activity before sleep.

Sleep deprivation is the most common trigger for awakening seizures seen in juvenile myoclonic epilepsy.

8. Effect of epilepsy on sleep

The effect of epilepsy on sleep was first described in 1890 by Fere, based on clinical findings of difficulty falling asleep and impairing sleep efficiency. About two-third of patients suffering from epilepsy have sleep dysfunction [63]. Three main mechanisms that need to be considered regarding this topic are: 1. the epilepsy itself may be associated with sleep disturbance due to mechanisms intrinsic to the syndrome; 2. the effect of seizures on sleep architecture; and 3. the effect of AEDs on sleep.

Experimental amygdala kindling, an animal epilepsy model involving temporal structures, showed disturbed sleep patterns with sleep fragmentation and a shift toward lighter sleep [64]. In humans, patients with epilepsy have reduced NREM N2 and N3 sleep and REM sleep [65]. Sleep abnormalities seem to be more marked in patients with temporal lobe epilepsy compared to generalized epilepsies [15]. The limbic system participates in the neural networks underlying sleep organization, sleep induction, and arousal. **Table 2** shows the effects of epilepsy on seizures.

Patients suffering from nocturnal seizures show reduced sleep efficiency, increased time into REM period, and increased drowsiness [65]. The effects of AEDs on sleep will be discussed separately in the next section.

Increased sleep onset latency
Increased awakening after sleep onset
Increased NREM N1 and N2
Decreased frequency of spindles during N2
REM sleep suppression
Increased sleep fragmentation

Table 2.
Common effect of epilepsy on sleep.

9. Effect of antiepileptic drugs on sleep

Anti-epileptic drugs [AEDs] may reduce sleep fragmentation, while improving nocturnal seizures control. However, AEDs have differential effects on sleep architecture [66]. Several studies identified that gabapentin, tiagabine, pregabalin, clobazam, and carbamazepine reduce sleep latency and/or improve sleep efficiency. Phenobarbital, carbamazepine, phenytoin, valproic acid, and higher doses of levetiracetam may have an effect or aggravate daytime sleepiness. Felbamate, zonisamide, and lamotrigine at high doses may causes insomnia. Some AEDs

Drug	Sleep effect
Phenobarbital	Decreases SOL, decreases WASO, decreases REM, increases EDS
Gabapentin	Decreases SOL, decreases WASO, increases NREM N3, increases REM, improve insomnia
Carbamazepine	Increases NREM N3, increases sleep fragmentation
Phenytoin	Decreases SOL, decreases REM, increases sleep fragmentation
Pregabalin	Increases NREM N3, improve insomnia
Levetiracetam	Decreases NREM N3 increases EDS
Ethoxizimide	Decreases NREM N3, increases REM
Valproic acid	Increases sleep fragmentation, increases WASO, increased daytime sleepiness
Benzodiazepines	Decreases NREM N3 and SOL

SOL: sleep onset latency, WASO: wake after sleep onset, EDS: excessive daytime sleepiness.

Table 3.
Common antiepileptic drug effect on sleep architecture.

have no effect or have minimal effect on sleep architecture such as topiramate, zonisamide, lamotrigine, vagabatril, lacosamide, and low doses of levetiracetam [66]. Dose-dependent sleep effects of antiepileptic drugs and nondrug treatments independent of the improvement of epilepsy have not been studies and may help to identify if these changes are clinically significant.

Table 3 shows the most common antiepileptic drugs effect on sleep architecture.

10. Effect of ketogenic diet

Ketogenic diet improves total sleep time and NREM slow-wave sleep [67].

11. Effect of vagal nerve stimulator on sleep

Vagus nerve stimulation [VNS] is used in some form of refractory epilepsy. VNS increases NREM N3 stage and reduces daytime sleepiness. VNS may worsen or increase risk for sleep-disordered breathing [67].

12. Effect of epilepsy surgery on sleep

Epilepsy surgery has a positive effect on sleep. It improves total sleep time, decreases wake after sleep onset, increases REM sleep, and improves the subjective sleep quality. No changes were seen in the subjects who continued to have frequent seizures after surgery [67].

13. Seizures and parasomnia

Parasomnias are disorders with undesirable physical and mental events that occur mainly or exclusively during NREM and REM sleep, often accompanied by skeletal muscle activity and autonomic arousal. Mental phenomena may also occur, including emotions, thoughts, and images.

The NREM parasomnias are associated with central nervous system activation, skeletal muscle activity, and signs of autonomic arousal. Common examples of NREM parasomnias in children are confusion arousals, sleepwalking, and nocturnal terrors that present with different degree of motor and autonomic activation. The distinction between NREM parasomnias and seizures might requires the need for polysomnography with video recording and extended EEG leads.

REM sleep involves a highly energized state of brain activity with increased motor activation during REM where patients can enact the dreams. Patient scream, throw punches and kicks, show exploratory behaviors, involving staring, head rising, head turning, grasping, and searching; stalking imaginary prey, as well as episodic attack behavior; and locomotion. The mechanisms responsible for the oneiric behaviors are postulated to result from the disruption of brain neuronal organization during REM sleep. There is presumably disinhibition of motor pattern generators in the mesencephalic locomotor region, which results in phasic motor over-activation with behavioral release during REM sleep.

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