Received: 24 August 2021 | Revised: 20 December 2021 | Accepted: 21 December 2021

DOI: 10.1111/epi.17161

Epilepsia®

CRITICAL REVIEW – INVITED COMMENTARY

The use of rodent models to better characterize the relationship among epilepsy, sleep, and memory

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Funding information
National Science Foundation, Grant/Award Number: OIA1632891

Abstract

Epilepsy, a neurological disorder characterized by recurrent seizures, is known to be associated with impaired sleep and memory. Although the specific mechanisms underlying these impairments are uncertain, the known role of sleep in memory consolidation suggests a potential relationship may exist between seizure activity, disrupted sleep, and memory impairment. A possible mediator in this relationship is the sleep spindle, the characteristic electroencephalographic (EEG) feature of non-rapid-eye-movement (NREM) sleep in humans and other mammals. Growing evidence supports the idea that sleep spindles, having thalamic origin, may mediate the process of long-term memory storage and plasticity by generating neuronal conditions that favor these processes. To study this potential relationship, a single model in which memory, sleep, and epilepsy can be simultaneously observed is of necessity. Rodent models of epilepsy appear to fulfill this requirement. Not only do rodents express both sleep spindles and seizure-induced sleep disruptions, but they also allow researchers to invasively study neurobiological processes both pre- and post- epileptic onset via the artificial induction of epilepsy (a practice that cannot be carried out in human subjects). However, the degree to which sleep architecture differs between rodents and humans makes direct comparisons between the two challenging. This review addresses these challenges and concludes that rodent sleep studies are useful in observing the functional roles of sleep and how they are affected by epilepsy.

KEYWORDS

epilepsy, memory, sleep, sleep spindles

1 | INTRODUCTION

Sleep is widely observed throughout the animal kingdom. Although its architecture is quite different across species, the vigilance state definitive of sleep is mostly preserved. The physiological processes that benefit from sleep are numerous, as are the detrimental consequences when sleep is neglected.[1] One of the most recognized benefits of sleep is its role in memory consolidation, the process by which transient events experienced during wake are

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transformed into long-term memories.[2] In individuals with epilepsy, disruptions are seen in both sleep and memory. While much is known about the consequences of these disruptions, less is known about the possible etiological mechanism affecting both processes.[3]

Electroencephalography is the standard tool used in sleep research to characterize the patterns of brain waves that occur during sleep. This technology has revealed that sleep comprises different stages, defined in part by characteristic patterns of EEG signals. Polysomnography is used to analyze brain activity during sleep. This method allows clinicians and researchers to evaluate sleep stages based on EEG features and to align those with physiological parameters such as muscle activity, respiration, and electrocardiography.

As much has been discovered about the functional benefits of sleep, there is advancing interest in characterizing specific sub-processes in the brain that generate the typical waveforms seen on EEG during sleep. One of these is the sleep spindle; a waxing and waning waveform that presents intermittently during non-rapid-eye-movement sleep.[4] Sleep spindles represent cortico-thalamic oscillations that are likely integral to sleep maintenance and memory consolidation – two domains known to be compromised among individuals with epilepsy.

Electroencephalographic is also used clinically in the diagnosis of epilepsy and in initial regional localization of the focus of abnormal brain rhythms. Certain epilepsies are classically associated with specific waveforms on EEG that are useful in predicting their prognoses. Similar patterns are seen in rodent models of epilepsy.[5–8] While abnormal brain rhythms are characteristic of epilepsy, well-known clinical implications of epilepsy include abnormalities in sleep architecture and poor memory function.

The use of rodent models is especially helpful in exploring neurological disorders, such as epilepsy. Studying the effects of epilepsy on sleep presents many challenges. In humans, the onset of epilepsy is often unexpected, and it is difficult to clearly define causal relationships between epileptic activity and changes in an individual's sleep architecture. Rodent models, however, can act as their own baseline controls, allowing research to be undertaken in the same animal pre- and post-induction of epilepsy. This review calls attention to the utility of rodent models in investigating the relationship between sleep, memory and epilepsy while highlighting the potential diagnostic role that sleep spindles could serve for characterizing epilepsy in humans.

Key Points

- Patients with epilepsy experience disrupted sleep and memory; however, the mechanism of this phenomenon has yet to be described
- Changes in sleep spindle density is associated with epilepsy
- Growing evidence supports the idea that the sleep spindle is a mediator between sleep and memory consolidation in animals
- Sleep spindle patterns may change during epileptogenesis
- Rodents provide a way to study pre- and post-epileptic interactions between sleep and memory which cannot be done in humans

2 | EPILEPSY

Epilepsy is a neurological disease diagnosed following the occurrence of at least two unprovoked seizures. An epileptic seizure is defined by Fisher et al. (2014)[9] as abnormal excessive or synchronous brain activity which may cause transient signs and/or symptoms such as temporary loss of consciousness or disturbances in cognitive function.

Over half of epilepsy patients suffer from focal seizures, while the remaining experience generalized seizures. Focal seizures originate from one region of the brain. Of these, the majority of cases in adults originate in the temporal lobes (temporal lobe epilepsy; TLE).[5,10] Pre-surgical evaluation methods include both scalp EEG (sEEG) and intracranial EEG (iEEG) recordings to define the primary site of seizure generation (epileptogenic zone).[5,6] Characteristic waveforms on EEG/iEEG have established associations with different types of epilepsy. For example, low-frequency, high-amplitude spikes are characteristic of TLE while low-voltage, fast activity is typical of neocortical epilepsy.[6,11] Generalized seizures include larger areas of the brain, with some of the most common types being absence and tonic-clonic seizures. An understanding of epileptic seizures, including their structure and anatomical origins, will be necessary to evaluate the relationships between seizure activity, sleep, and memory consolidation.

3 | EPILEPSY AND MEMORY IMPAIRMENTS

Patients with TLE commonly show signs of impaired cognition, especially in memory. While lesional etiology is most often associated with more severe cognitive dysfunction, most studies on cognition in TLE are generally obtained from patients with late-stage TLE or otherwise

severely affected patients. Using only these patients, however, makes it difficult to determine how memory naturally deteriorates as the disease progresses. Bjørke et al. (2021)[12] evaluated cognition in patients newly diagnosed with TLE and found that these patients often display cognitive deficits, despite the absence of structural brain abnormalities in some patients. These findings support the association of memory impairment to an underlying pathology. This pathology may also affect regions of the brain other than the temporal lobe as the disease progresses.

Unfortunately, even when studying newly diagnosed patients, investigations using only human patients severely limits knowledge on how the progression of memory impairment compares to an individual's memory capabilities before disease onset. Rodent models would allow the study of memory impairment, as well as other cognitive dysfunctions, pre- and post- onset of epilepsy. These studies would provide more detail to the underlying pathways associated with memory impairment and how epilepsy etiology affects memory formation and consolidation.

4 | SLEEP

In the awake state, the EEG is characterized by high-frequency, asynchronous oscillations. In the descent to sleep, the EEG gradually shifts to a more synchronized, slower rhythm that, in deep sleep, is dominated by low-frequency content. In each of the recognized stages of sleep, the EEG shows characteristic waveforms by which that stage can be identified.

The cyclic stages of sleep have been defined by the American Academy of Sleep Medicine as one stage of rapid eye movement (REM) sleep and three stages of NREM sleep (N1, N2, and N3). N3 sleep is also referred to as slow wave sleep (SWS). REM sleep is characterized by a wake-like EEG pattern displaying mixed frequency low-amplitude oscillatory activity, and is also classically associated with dreaming.[13] The stages of NREM sleep represent periods containing varying levels of wakefulness, with N1 representing the transition stage from wake to sleep and N2 being the first true sleep stage. SWS is synonymous with "deep sleep" and is made up of slow, high-amplitude oscillations.

Non-rapid-eye-movement sleep dominates the early hours of a typical 8-h sleep cycle, while the majority of REM sleep occurs in the later half.[14] Beginning with N2 sleep, the stage associated with spindles, the sleeper transitions into a deeper state of reduced arousal in which conscious awareness of external stimuli is lost, and muscle activity is greatly reduced.[15]

5 | SLEEP AND MEMORY

Of the potential functional benefits of sleep, assisting in the consolidation of memory is one of the most recognized.[2,16] In recent decades, sleep researchers have found compelling evidence pointing to NREM sleep as the main stage in which memory consolidation occurs.[17] Memories begin as transient events occurring during wake transduced by neuronal recruitment and changes in gene expression to form a "memory trace." For long-term storage, memory traces must be converted and transferred to neuronal circuits where they are stored via a process called "consolidation."[18,19] It is likely that sleep sets the parameters for this to occur. REM sleep may stabilize the consolidation process, and the redistribution of memories may serve as temporary storage for many different physiological systems, such as immunological memory. Sleeping after learning also reduces interference from outside stimuli, making it an optimal time for consolidation.[2]

6 | SLEEP CYCLES IN THE HUMAN AND THE RAT

Rodent sleep differs from human sleep in that it is polyphasic and there is not as discrete a transition between wake and sleep stages, as illustrated in Figure 1. Rats, for example, sleep primarily during the day and are awake more during the night. Traditionally, NREM sleep in rats has been characterized by a vigilance state consisting largely of EEG slow waves and has thus been used synonymously with "slow wave sleep" (SWS). Periods of SWS last less than 5 min and have been shown to decrease over the course of the light phase.[20,21] Further, Simasko and Mukherjee demonstrated that rats rapidly cycle through periods of brief wake, long duration wake, REM sleep, and SWS in characteristic patterns in both the light and dark phases.[22] Thus, the architecture of sleep is quite different between humans and rats; however, EEG recording reveals the presence of comparable sleep stages in both species.

7 | SLEEP SPINDLES

Sleep spindles are present in EEG recordings in 0.5–3 s bursts within the ~12–14 Hz frequency range.[23] The term "spindle" was first used by Alfred Lee Loomis to describe a waveform reminiscent of a wool-spinning device present in human sleep EEG recordings.[4]

The origins and electrophysiological processes that generate EEG spindles are well-defined. The thalamic reticular nucleus (TRN) has been identified as the origin of the spindle wave after discovery of its rhythmic firing in

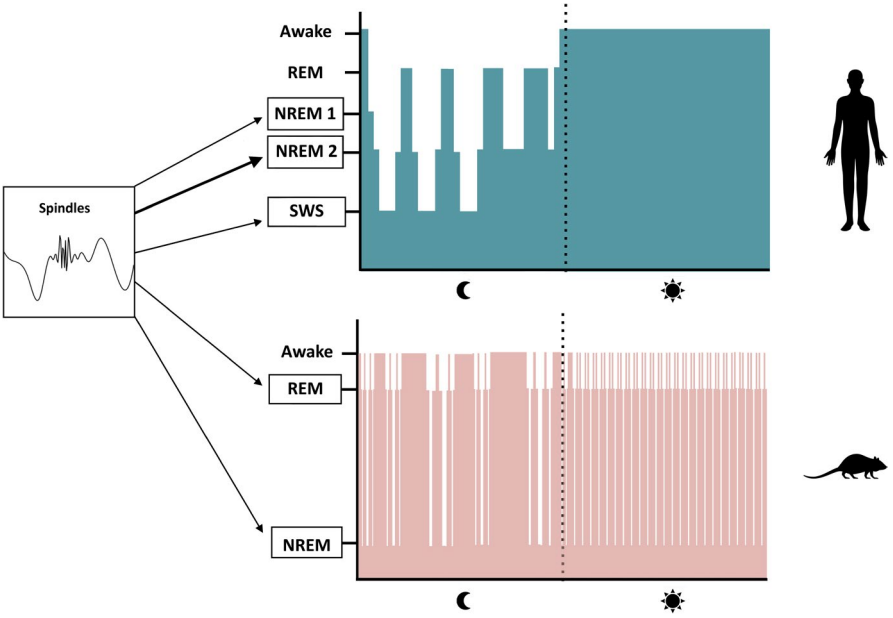

FIGURE 1 Sleep cycles in the human and the rat. Colored regions indicate the cycling vigilance states observed in the dark vs. light phase (abbreviations: REM, rapid eye movement sleep; NREM, non-rapid eye movement sleep, SWS, slow wave sleep). In humans, spindles first appear in NREM and are the characteristic feature of NREM (indicated by the thicker line). Note: spindle image is used solely as an icon and does not depict the different frequencies observed between humans and rodents

the absence of thalamic or cortical input.[24] In this sense, it is understood that the TRN acts as the "pacemaker" for spindle generation.[25] The TRN sets the pace by firing repetitive inhibitory GABAergic signals that are critical for relaying spindle-like rhythms in reciprocal projections between thalamus and cortex. This rhythmic sequence creates spike-bursts in glutamatergic thalamocortical pathways, ultimately causing postsynaptic excitation in the cortex.[23] These sequences generate the typical spindle pattern recognized on EEG.

Initiation and maintenance of spindles rests in reciprocal communication between the cortex and thalamus. Thalamic rhythms have been shown to phase couple with slow cortical oscillations, with the mechanism for spindle initiation thought to rest on depolarization of corticothalamic neurons via this slow oscillation. Spindle events are followed by a 5–10 s refractory period, likely triggered by an interplay between cortex, thalamus, and brainstem.[19]

The thalamus plays a critical role in modulating the flow of sensory information into the cortex.[26] During sleep, this may serve a protective function by 'gating' out conscious awareness of external stimuli.[27] In humans, sleep spindle density is greatest during N2 sleep (Figure 1).[28] The theory that spindles serve a "protective" sleep function was highlighted in work done by Kim et al.,[29] who showed that optogenetic stimulation of the TRN of mice resulted in an increase in spindle density that correlated with increased time spent in NREM sleep. It has been shown that persistence of cortical responses to auditory stimuli during NREM sleep was minimized whenever spindles were present.[30,31] Thus, it is hypothesized that spindles serve a functional role in the modulation of this particular state of consciousness. However, this idea has been challenged. Sela et al.[32] used Wistar Kyoto rats in a study involving cortical responses to noise during sleep spindle oscillations. This group found that auditory cortex responsiveness remained intact even while spindles were present and suggested that the gating of external auditory stimuli is influenced by other thalamic neuronal processes. Nonetheless, many in the field would agree that sleep spindles are likely associated with the gating of conscious awareness during NREM sleep, while the particular mechanism by which sleep spindles are involved remains unclear.

Originally, spindles were thought to exist as one type with greatest occurrence over central areas of the skull.[33,34] However, it was suggested by Gibbs and Gibbs decades ago that two discreet types of spindles existed based on characteristic frequency profiles.[23] Advances in topographical imaging and multi-electrode EEG technologies have led to the understanding that in both humans and rodents two distinct types of spindles exist. There are slow-spindles and fast-spindles that are topographically characterized as anterior and posterior, respectively.[35,36] Given these differences, it may be possible that subnetworks exist within the spindle circuit that generate spatially and temporally distinct spindles. Alternatively, the regional differences could derive from the state of the neurons and their intrinsic properties within these distinct regions. Either scenario could lead to subtle differences in function.

In humans, the two most common classifications for spindles are slow (11–13 Hz) and fast (13–15 Hz). Slow spindles are typically found in the frontal regions of the scalp while fast spindles are found over the parietal and central areas.[19,37] Fast spindles appear to peak earlier in sleep during N2 sleep, and slow spindles occur later and are more variable between N2 and N3 sleep stages.[30]

In rodents, there is less agreement on the frequency range in which spindles present. Frequency criteria have been variously reported to include 7–14 Hz, 8–12 Hz, and 10–18 Hz.[37–41] Additionally, there is variation in the understood duration of a spindling event in rodents, as some have suggested that spindling episodes typically last more than 2 s, while others find an average duration of 0.5 s.[42,43] This discrepancy was possibly due to differences in the range of frequency used to define spindles, different thalamocortical arrangements across rodent species, and the relative lack of a defined sleep stage characterized by high sigma power.[19]

Similar to humans, rodent spindles are topographically characterized as either anterior or posterior. Anterior spindles are described as having low frequency theta activity occurring at a mean frequency of 10.3 Hz and duration of 2.8 s in stages immediately before and after REM sleep. Posterior spindles, in turn, occur most commonly during SWS and are described as having a higher mean intrinsic frequency (12.4 Hz) and shorter mean duration (0.6 s) than anterior spindles.[35,36]

Unlike human sleep, where spindles are characteristic of one particular sleep stage, rodents do not generally have well-defined relationships between sleep stages and spindles. Most attempts at characterizing sleep in rodents are based on combined iEEG and electromyography (EMG) data, with the latter being used to characterize periods of wakefulness based on the degree of muscle tone. By analyzing EEG recordings in Sprague-Dawley rats, Mölle et al.[44] attempted to characterize sleep stages with respect to spindles by dividing sleep into one awake stage and just two sleep stages; SWS and REM sleep. In their classification system, both SWS and REM sleep contain spindles. Eschenko et al.[45] characterized SWS in rats by the presence of at least one spindle every 10 s, claiming this state of arousal as most reminiscent of N2 sleep in humans. There has also been an observed short-duration intermediate stage (IS) of sleep in rats that exists just before REM sleep, characterized by theta waves and high-amplitude anterior spindles.[35,42]

The general presence of spindles across various states of reduced arousal combined with poorly defined sleep stages makes direct comparisons between rodents and humans difficult. In a preliminary study, however, Lacroix et al.[46] observed distinct stages of electrophysiologic activity during NREM sleep in mice, allowing the researchers to characterize multiple stages of NREM sleep in rodents akin to what has been done in humans. It was concluded that humans and mice show strong similarities in sleep macro- and microarchitecture, legitimizing rodent models to study sleep physiology. Furthering this proposal is the observation that similarities in spindling behavior between humans and rodents do exist in the realm of sleep maintenance, memory, and response to insult.

8 | MEMORY CONSOLIDATION AND SLEEP SPINDLES

Hippocampal ripples, 100–200 Hz oscillations originating from CA1 pyramidal cells, are present during sleep and are understood to essentially "replay" information that was obtained while awake. Wilson and McNaughton studied this manifestation in rats by observing how the firing of place cells during spatial learning tasks was repeated during subsequent SWS episodes. Sleep spindles are also related to these firing sequences and are thought to promote plasticity due to their synchronous, rhythmic firing pattern. This activity is thought to promote the entry of calcium into cerebral pyramidal cells – a condition understood to promote adaptive changes in brain structure and function.[19,47] Cortical slow oscillations during NREM sleep associate hippocampal ripples with sleep spindles, allowing the neuronal networks to plastically remodel.[48,49] It has been suggested that activity from the hippocampus may prime the circuits of the neocortex to create more sleep spindles.[14]

Standard Consolidation Theory (SCT) was proposed in the 19th century to illustrate the memory consolidation process. SCT is centered around four key concepts: (1) The hippocampus is initially responsible for the retention and retrieval of long-term memories, (2) all declarative memories go through the same consolidative process, (3) pre-consolidated memories are identical to those in the neocortex, and (4) after long-term memories have been consolidated, they will no longer be affected by hippocampal lesions.[50] However, Winocur and colleagues found many flaws with the SCT and proposed an alternative, called the transformation model, which stipulates that: (1) context-specific memories may result in similar memories with differing details, (2) hippocampal memories are episodic and context-specific, while neocortical memories are schematic or semantic and context-independent, (3) as memories become independent from the hippocampus, the result is not necessarily loss of the hippocampus-dependent memories, and (4) memories are not reproduced but rather reconstructed from stored information.[50] While the transformation model adds clarification, the SCT still has features which provide insight to the way memories are transformed through plastic circuits to become stored as long-term memories, such as the idea that damage to the hippocampus will not necessarily remove long-term memories. In this way, these two models may provide complementary descriptions of the process of memory consolidation.

The active systems consolidation hypothesis combines aspects of these earlier models of memory consolidation, which were focused primarily on the hippocampus and neocortex, with spindles, and emphasizes the "active," rather than "passive," role that sleep plays in the process. This hypothesis posits that memory traces are temporarily stored in the hippocampus and repeated firing "pushes" the memory traces from the hippocampus to the neocortex for long-term storage. At this point, the memory is no longer referred to as a memory trace but rather a memory "engram."[2,18,19] This is thought to be a top-down process, governed by neocortical slow wave oscillations (SWO) that occur during NREM sleep at frequencies less than 1 Hz. This process is displayed in Figure 2. Further, it is thought that SWO are maintained by cortico-cortical circuits.[51,52] In addition, SWO have been reported to drive repeated firing of hippocampal sharp-wave ripples, while simultaneously triggering the thalamus to generate spindles.[2]

Ji and Wilson later showed that the re-firing of hippocampal neurons during SWS occurred alongside cortical neuronal firing, supporting the active systems consolidation hypothesis.[17] Because of the established role of NREM sleep in memory consolidation, the role that spindles (a characteristic feature of NREM sleep) have in this process has been widely studied.[53–60] Spindles are known to be phase related to ripples and cortical SWO in humans and rats.[61–63] Sirota et al.[62] suggested that hippocampal ripples influenced downstream spindling, igniting a positive feedback cycle between cortical slow oscillations, spindles, and ripples. It is not known whether spindles themselves are the physiological markers of specific processes by which information is encoded. Rather, the unique role that spindles play in memory consolidation may rest in the realm of plasticity, as mentioned earlier.[19]

9 | LEARNING, MEMORY, AND PLASTICITY

The proposed relationship between spindles, learning, memory, and plasticity is supported by findings that spindle density increases in humans and rodents during sleep following acquisition of learned tasks.[14,45,58,64] Gais et al. found an increase in spindle density in humans during N2 sleep following acquisition of a declarative memory task compared to a non-learning group, suggesting that learned experiences may result in changes in spindle activity during NREM sleep following learning. The variance in spindle density across individuals appeared to be linked to the learning capabilities of each subject, with those who learned the task better displaying a higher sleep spindle density.[14] Similar findings have been reported in Sprague-Dawley rats: spindle density increased following learning of an odor-reward paradigm in the first hour of SWS, which is the stage in rats that is suggested as being most similar to human N2 sleep. This group proposed that network reorganization during memory consolidation is likely to continue to occur, supporting the idea that

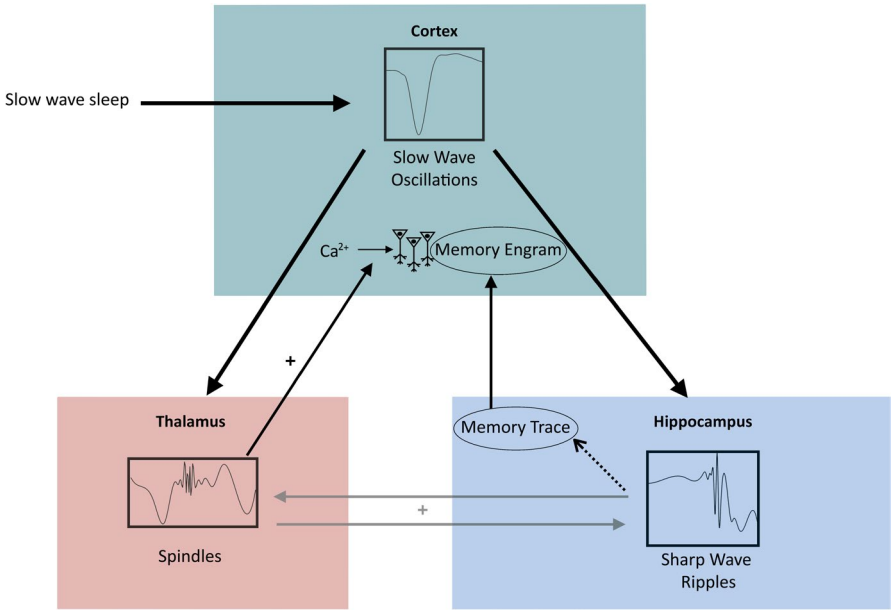

FIGURE 2 Active Systems Consolidation Hypothesis. The slow wave oscillations (SWO) that appear during slow wave sleep (NREM[3]) initiate the hippocampus and the thalamus to generate sharp wave ripples (SWR) and spindles, respectively. Spindles are more clearly seen during NREM[2] sleep; however, they also appear during SWS. SWR "push" temporary stored memory traces in the hippocampus into the cortex, forming long-term memory engrams. The rhythmic firing of thalamic spindles is thought to promote the entry of calcium into cerebral pyramidal cells, promoting plasticity. Sharp-wave ripples may also have a positive influence on spindling, and vice versa

spindles serve to promote plasticity.[45,64] Additionally, an increase in spindle density has been reported following reactivation of remote memory.[23,45] Mölle et al. observed increased spindling prior to ripples that had a longer duration during NREM sleep following learning.[49] Together, these findings support the idea that sleep spindles during NREM sleep in humans and SWS in rats are directly involved in the memory consolidation process.

10 | EPILEPSY, SLEEP, AND MEMORY

The dynamic relationship between sleep and epilepsy has been studied for decades, including both the effects that sleep has on epileptic activity and how sleep-related epilepsies affect an individual's sleep architecture. In humans, some of the known associations between epilepsy and sleep include increased sleep onset latency, decreased sleep stability, increased time spent in light NREM sleep, decreased time in REM sleep, and a decrease in sleep spindle density.[65] Chakravarty et al.[66] found patients with refractory focal epilepsy to have significantly decreased total sleep time, worse sleep efficiency, increased sleep latency, and increased REM latency when compared to patients with medically controlled epilepsy. Additionally, individuals with epilepsy may experience seizures during sleep, particularly NREM sleep. Further, Rossi et al. found that the typical spiking pattern seen in individuals with focal epilepsies tends to increase during NREM sleep. It is thought that the more global, harmonious pattern of brain activity seen on EEG during NREM sleep may lay the foundation for widespread seizure activity in numerous epilepsies that occur during sleep.[65] It has also been observed that sleep deprivation enhances seizure activity among individuals with epilepsy.[48] Thus, patients with epilepsy experience a detrimental cycle of recurrent seizures and continual sleep disruption, affecting memory consolidation in the process, as shown in Figure 3.

During sleep, physiological ripples, such as hippocampal ripples and interictal epileptiform discharges (IEDs), are most likely to occur during NREM sleep.[48,49,65] During this stage, the EEG shows synchronized patterns of delta waves and sleep spindles as opposed to REM sleep, which is more disorganized.[65] IED's occurring during periods of synchronous firing are akin to the synchronized firing of glutaminergic neurons, causing excitotoxicity and seizure activity. As previously discussed, communication between the hippocampus and the neocortex is critical for the formation of memories, and the slow waves of NREM sleep promote this communication by associating hippocampal ripples to sleep spindles. Gelinas et al.[49] found that in TLE, hippocampal IEDs actually induce spindling in the cortex,

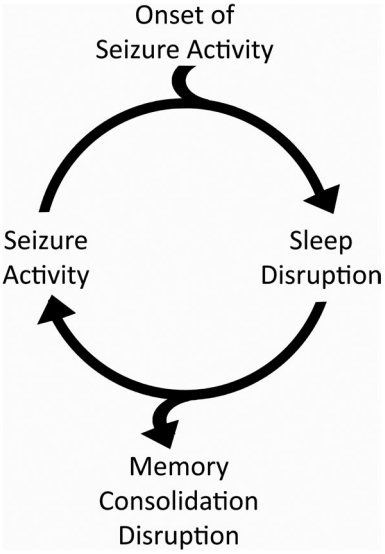

FIGURE 3 Cyclic effect of seizure activity and sleep disruption. Sleep disruption may occur with the onset of seizure activity, causing disruptions in memory consolidation and further seizure activity. This continued seizure activity may also contribute to further sleep disruption, creating an antagonizing cycle between sleep and seizures

disrupting the normal coupling relationship between spindles and ripples. It has been suggested that IEDs favor slow wave activity of NREM sleep in a similar fashion to other types of ripples.[48] This links IEDs to sleep spindles and plastic circuits. These connections, as well as the reduced sleep spindle density caused by epilepsy, may explain how seizure activity during sleep results in inhibited memory formation and consolidation.

Although many of the causes and associated brain regions involved in the generation of epileptic activity have been identified (e.g., tumors, trauma, hippocampal sclerosis, abnormal vasculature, etc.), the origin and mechanistic maintenance of the aberrant neuronal firing is less established.[67] Since seizures have characteristic patterns on EEG, one mechanistic approach is to define the neuronal circuitry involved in the generation of such waveforms.[6,11] Spike and wave discharges (SWD), a characteristic EEG waveform associated with generalized absence seizures, are 3–4 Hz bilateral discharges.[19,68,69] The corticoreticular theory of epilepsy suggests that the thalamocortical framework that generates sleep spindles can be pathologically disrupted to produce SWD in response to a hyper-excitable cortex.[68] This theory is based on the recognition that sleep spindles and SWD share a common thalamocortical circuit.[70] Kostopolous (2000) further suggests that some physical alteration forces two or more spindles to merge into a spike, and the trailing spindles are replaced by a wave creating the classical spike-wave discharge seen on EEG during ictal events.[71] However,

this theory is challenged due to SWD and spindles having vastly different qualities (i.e., humans can be awoken during spindle activity but cannot be made conscious during SWD activity), and it does not account for SWD that occur during wakefulness.[71] Sitnikova shed doubt on the assumed tight-knit relationship between SWD and spindles because of observed differences in time-frequency characteristics and neuronal processes between the two firing patterns.[40] Nonetheless, the idea of a common anatomical network responsible for both sleep oscillations and seizure generation has remained prominent.[19] Further research utilizing rodent models of epilepsy into functional and mechanistic origins of these processes could provide insight into some of the most detrimental sequelae of epilepsy – sleep disturbance and memory impairment.

Due to the similar neuronal mechanisms between sleep spindles and epileptic activity, there is interest in identifying a relationship between seizures and sleep spindles. Tezer et al.[72] observed that spindle density significantly decreased in the moments preceding epileptic seizure activity, suggesting that the decrease in spindling during the preictal period may reflect the underlying pathology in the epileptic framework. Another study involving patients with TLE found decreases in spindle density, duration, and amplitude ipsilateral to the site of epileptic discharges.[73] A better understanding of the functional role of sleep spindles in epilepsy, or in specific types of epilepsy may lead to further understanding of the pathophysiology of epilepsy.[72] Additionally, due to alterations in normal spindling behavior observed in epilepsy and other diseases, it has been suggested that spindle activity could be a biomarker of neuropathology.[74] Sitnikova et al.[75] have used a genetic rat model of absence epilepsy to study anterior spindles and the suspected relationship with SWD. In these rats, the group observed spindles with higher frequency (20–25 Hz), and suggested that these fast spindles may be precursors to SWD. The group showed that lower duration and frequency of sleep spindles may be indicative of developing epilepsy in persons with a genetic disposition to the disorder. Furthermore, Myatchin and Lagae observed decreased spindle density in humans with absence epilepsy.[76] Feng et al.[39] measured spindle characteristics using surgically implanted microelectrodes in different nuclei of the thalamus. Interestingly, they found an increased occurrence of spindles during focal limbic seizures in the ventral posteromedial nuclei of the thalamus, which is a relay nucleus thought to contribute to spindle generation. Additionally, the researchers observed increased burst firing of centrolateral nuclei during seizures. It is hypothesized that these two mechanisms, both associated with sleep, may account for the loss of consciousness that occurs during seizure activity.[39]

The role of sleep in memory plays a critical part in evaluating the effects of epilepsy on memory. While there are many sleep disorders that do cause problems with memory consolidation, not all disorders do. Memory consolidation becomes vulnerable when the time spent asleep or the structure of the sleep cycle is altered, such as in insomnia or narcolepsy.[77] This also applies to epilepsy. About half of patients with epilepsy experience some form of sleep related seizures, and many patients will only experience seizures while they sleep. The experience of seizures during the day may also be linked to the decrease of REM sleep and sleep efficiency.[65] These altered epilepsy-related sleep patterns can result in problems in the consolidation of memories (Figure 4).

The relationships between sleep, epilepsy, and memory may be attributed to the role of NREM sleep in each realm. As discussed earlier, it is understood that memory consolidation occurs during NREM sleep, and it is reliant on the synchronous firing of cortical SWO, hippocampal ripples, and thalamocortical spindles. Since NREM sleep is associated with frequent seizure activity in patients with epilepsy, IEDs that occur during NREM sleep are thought to disturb this harmonious

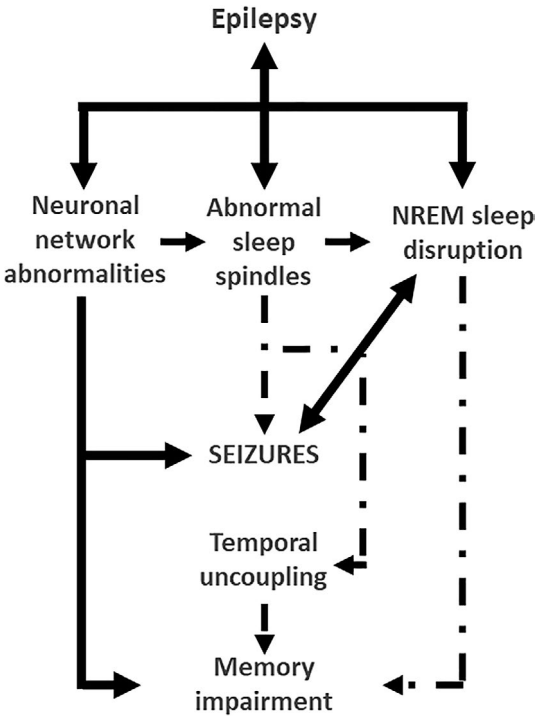

FIGURE 4 Proposed role of spindles in epilepsy, sleep, and memory. The bold arrows show the known associations with epilepsy, including neuronal network abnormalities, abnormal sleep spindles, and disruptions in NREM sleep. Epileptic seizures commonly occur during NREM sleep, impairing sleep quality, which further promotes seizure activity. The dotted arrows show hypothesized roles that spindles may play in these processes that can be further explored using rodent models

communication. Thus, it is likely that this interference affects sleep maintenance and the consolidation of memories and may be causal in the impaired memory seen in individuals with epilepsy.[48] In the study involving patients with refractory focal epilepsy mentioned earlier, the reported detriments of sleep were associated with worse cognitive function, particularly features of memory.[66] Figure 4 illustrates where relationships between sleep disruptions and epilepsy are known, as well as where relationships with sleep spindles are suspected but require further research.

Overall, significant alterations in sleep spindles have been associated with epilepsy in both humans and rodents. Consistently, a reduction in the density of spindles during NREM sleep appears to be a hallmark of the disease. A better understanding of what spindle parameters reflect functionally, and further refinement of the associations between sleep spindles and epilepsy may one day allow for sleep spindles to serve as a useful marker for epileptic processes.

11 | RODENT MODELS

Rodent models provide a tool for studying epilepsy in ways that are otherwise not feasible to carry out in human participants. When using rodents, neural processes can be recorded before, during, and after ictal episodes in a controlled setting. The most common conditions used to study epilepsy in rats include using chemo-convulsants, administration of electrical stimulation, or studying genetic epilepsy model systems. Different models confer different types of seizure, reflecting various manifestations of epilepsy in humans. Thus, studying rodent models of epilepsy can provide findings that generalize toward epilepsy as a whole, as well as more specific subsets of the disease.[10]

Some of the methods for investigating the effects of sleep and epilepsy on memory with rodent models include in vivo and ex vivo studies, behavioral tasks, and optogenetic stimulation. Each of these strategies provide unique perspectives on epilepsy and sleep that cannot be fully studied in humans. Utilization of in vivo and ex vivo studies facilitate the evaluation of neurochemical changes following induction of epilepsy, chronicity of epileptiform activity, and neural network activity in wake and sleep. Behavioral studies may be performed before and after induction and following the establishment of chronic seizure activity to evaluate various changes in cognitive function, including memory, problem-solving, and attention. Such studies in rodents may provide a better understanding of the development of epilepsy and how it affects the quality of life in human patients, advancing existing studies such as those performed by Bjørke et al. (2021). Network responses, such as those related to spindles, NREM sleep, and memory consolidation, may be examined using optogenetic stimulation. While most studies have identified strong correlations between spindles and memory consolidation, the emergence of optogenetics, which is able to manipulate specific cell types and circuits without the effects of drugs, is beginning to reveal mechanisms underpinning these phenomena.[78]

12 | CONCLUSION

Epilepsy is associated with impaired sleep and poor memory, but how these are mechanistically linked is poorly understood. However, the known role of sleep in memory consolidation suggests that an important component is the interactions between seizure activity, sleep disruption and memory impairment. Current evidence suggests that the cortico-thalamic oscillatory components that generate sleep spindles may play an important role in sleep maintenance and memory consolidation. Although not well established, multiple studies have found associations between spindles, quality of NREM sleep, and memory consolidation. Additionally, there is emerging evidence of an association between altered spindle characteristics and epilepsy in both humans and rodent models.

Sleep maintenance and memory consolidation – two modalities that are reflected by sleep spindles neurophysiologically – are compromised in epilepsy. Underlying pathways may also be involved in the progression of epilepsy and associated memory impairments; however, human studies are severely limited in their ability to study this progression. It is possible that spindles may serve as a tool to further understand the neurophysiological mechanisms underpinning the disease. However, there is still much to learn about what observed alterations in typical spindle behavior reflects functionally. Fortunately, rodents have served as useful models to study spindle characteristics and epilepsy. Accordingly, such studies are likely to play a crucial role in further elucidating the functional role of sleep spindles in relation to the observed deficits of sleep maintenance and memory consolidation among patients with epilepsy, and could, therefore, eventually lead to the identification of candidate biomarkers for such disruptions.[19]

Human studies are unable to examine the development of interactions between sleep, spindles of sleep, epileptiform activity, and memory impairment from initiation of epileptic neural behaviors through the development of chronicity. Despite differences in sleep architecture, the functional role of sleep is consistent across species, and the deleterious effects of epileptic activity on sleep are also preserved. Rodent models of

epilepsy permit the manipulation of neuronal circuits to study the mechanisms that lead to alterations in sleep spindles and their effect on memory consolidation. The ability to use the same rodent from a naïve baseline state, through epileptogenesis, and into full development of epilepsy enables access to these processes that are unavailable in human studies. Thus, rodent models enable a fuller understanding of the mechanistic linkages between sleep, epilepsy, and memory dysfunction in mammalian systems as a whole.

ACKNOWLEDGEMENTS

The authors thank Morgan Roque for the creation of Figure 3. She is a student in the Visual Integration of Science Through Art (VISTA) Center at Louisiana Tech University. This work was supported by a grant from the NSF (EPSCoR RII-2 FEC OIA1632891) to TAM and LLP.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Orzeł-Gryglewska J. Consequences of sleep deprivation. Int J Occup Med Environ Health. 2010;23(1):95–114. https://doi.org/10.2478/v10001-010-0004-9
2. Rasch B, Born J. About sleep's role in memory. Physiol Rev. 2013;93(2):681–766. https://doi.org/10.1152/physrev.00032.2012
3. Bazil CW. Epilepsy and sleep disturbance. Epilepsy Behav. 2003;4 (Suppl 2):39–45. https://doi.org/10.1016/j.yebeh.2003.07.005
4. Loomis AL, Harvey EN, Hobart GA. Distribution of disturbance-patterns in the human electroencephalogram, with special reference to sleep. J Neurophysiol. 1938;1(5):413–30. https://doi.org/10.1152/jn.1938.1.5.413
5. Siegel AM. Presurgical evaluation and surgical treatment of medically refractory epilepsy. Neurosurg Rev. 2004;27(1):1–18. https://doi.org/10.1007/s10143-003-0305-6
6. Tanaka H, Khoo HM, Dubeau F, Gotman J. Association between scalp and intracerebral electroencephalographic seizure-onset patterns: a study in different lesional pathological substrates. Epilepsia. 2018;59(2):420–30. https://doi.org/10.1111/epi.13979
7. Singh S, Sandy S, Wiebe S. Ictal onset on intracranial EEG: do we know it when we see it? State of the evidence. Epilepsia. 2015;56(10):1629–38. https://doi.org/10.1111/epi.13120
8. Worrell GA, So EL, Kazemi J, O'Brien TJ, Mosewich RK, Cascino GD, et al. Focal ictal β discharge on scalp EEG predicts excellent outcome of frontal lobe epilepsy surgery. Epilepsia. 2002;43(3):277–82. https://doi.org/10.1046/j.1528-1157.2002.37501.x
9. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475–82. https://doi.org/10.1111/epi.12550
10. Kandratavicius L, Balista P, Lopes-Aguiar C, Ruggiero R, Umeoka E, Garcia-Cairasco N, et al. Animal models of epilepsy: use and limitations. Neuropsychiatr Dis Treat. 2014;10:1693. https://doi.org/10.2147/ndt.s50371
11. Velasco AL, Wilson CL, Babb TL, Engel J. Functional and anatomic correlates of two frequently observed temporal lobe seizure-onset patterns. Neural Plast. 2000;7(1–2):49–63. https://doi.org/10.1155/np.2000.49
12. Bjørke AB, Østby Y, Grahl SG, Larsson PG, Olsen KB, Johansen Nævra MC, et al. Cognition in adult patients with newly diagnosed non-lesional temporal lobe epilepsy. Epilepsy Behav. 2021;116:107771. https://doi.org/10.1016/j.yebeh.2021.107771
13. Dement W, Kleitman N. The relation of eye movements during sleep to dream. J Exp Psychol. 1957;53(5):339–46. http://mrgregoryonline.com/Studies/Dement.pdf
14. Gais S, Mölle M, Helms K, Born J. Learning-dependent increases in sleep spindle density. J Neurosci. 2002;22(15):6830–4. https://doi.org/10.1523/jneurosci.22-15-06830.2002
15. Fuller PM, Gooley JJ, Saper CB. Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. J Biol Rhythms. 2006;21(6):482–93. https://doi.org/10.1177/0748730406294627
16. Jenkins J, Dallenbach K. Obliviscence during sleep and waking. Am J Psychol. 1924;35(4):605–93. www.jstor.org/stable/1414040
17. Ji D, Wilson MA. Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat Neurosci. 2007;10(1):100–7. https://doi.org/10.1038/nn1825
18. Tonegawa S, Liu X, Ramirez S, Redondo R. Memory engram cells have come of age. Neuron. 2015;87(5):918–31. https://doi.org/10.1016/j.neuron.2015.08.002
19. Fernandez LJ, Lüthi A. Sleep spindles: mechanisms and functions. Physiol Rev. 2020;100:805–68. https://doi.org/10.1152/physrev.00042.2018.-Sleep
20. Borbély AA, Sleep-deprivation NHU. Effects on sleep and EEG in the rat. J Comp Physiol A. 1979;133(1):71–87. https://doi.org/10.1007/BF00663111
21. Trachsel L, Tobler I, Borbely AA. Electroencephalogram analysis of non-rapid eye movement sleep in rats. Am J Physiol Regul Integr Comp Physiol. 1988;255(1):R27–37. https://doi.org/10.1152/ajpregu.1988.255.1.r27
22. Simasko SM, Mukherjee S. Novel analysis of sleep patterns in rats separates periods of vigilance cycling from long-duration wake events. Behav Brain Res. 2009;196(2):228–36. https://doi.org/10.1016/j.bbr.2008.09.003
23. de Gennaro L, Ferrara M. Sleep spindles: an overview. Sleep Med. De Políticas Públicas. 2003;7(800):422–40. https://doi.org/10.1016/S1087-0792(02)00116-8
24. Steriade M, Deschenes M, Domich L, Mulle C. Abolition of spindle oscillations in thalamic neurons disconnected from nucleus reticularis thalami. J Neurophysiol. 1985;54(6):1473–97. https://doi.org/10.1152/jn.1985.54.6.1473

25. Steriade M, Domich L, Oakson G, Deschenes M. The deafferented reticular thalamic nucleas generates spindle rhythmicity. J Neurophysiol. 1987;57(1):260–73. https://doi.org/10.1152/jn.1987.57.1.260
26. Sherman SM, Guillery RW. The role of the thalamus in the flow of information to the cortex. Philos Trans R Soci London B Biol Sci. 2002;357(1428):1695–708. https://doi.org/10.1098/rstb.2002.1161
27. Steriade M, Llinas RR. The functional states of the thalamus and the associated neuronal interplay. Physiol Rev. 1988;68(3):649–742.
28. Purcell SM, Manoach DS, Demanuele C, Cade BE, Mariani S, Cox R, et al. Characterizing sleep spindles in 11,630 individuals from the National Sleep Research Resource. Nat Commun. 2017;8(1):15930. https://doi.org/10.1038/ncomms15930
29. Kim A, Latchoumane C, Lee S, Kim GB, Cheong E, Augustine GJ, et al. Optogenetically induced sleep spindle rhythms alter sleep architectures in mice. Proc Natl Acad Sci USA. 2012;109(50):20673–8. https://doi.org/10.1073/pnas.1217897109
30. Dang-Vu TT, Bonjean M, Schabus M, Boly M, Darsaud A, Desseilles M, et al. Interplay between spontaneous and induced brain activity during human non-rapid eye movement sleep. Proc Natl Acad Sci USA. 2011;108(37):15438–43. https://doi.org/10.1073/pnas.1112503108
31. Schabus M, Dang-Vu TT, Heib DPJ, Boly M, Desseilles M, Vandewalle G, et al. The fate of incoming stimuli during NREM sleep is determined by spindles and the phase of the slow oscillation. Front Neurol. 2012;3:40. https://doi.org/10.3389/fneur.2012.00040
32. Sela Y, Vyazovskiy VV, Cirelli C, Tononi G, Nir Y. Responses in rat core auditory cortex are preserved during sleep spindle oscillations. Sleep. 2016;39(5):1069–82. https://doi.org/10.5665/sleep.5758
33. Mccormick L, Nielsen T, Nicolas A, Ptito M, Montplaisir J. Topographical distribution of spindles and K-complexes in normal subjects. Sleep. 1997;20(11):939–41. https://doi.org/10.1093/sleep/20.11.939
34. de Gennaro L. Effect of slow-wave sleep deprivation on topographical distribution of spindles. Behav Brain Res. 2000;116(1):55–9. https://doi.org/10.1016/s0166-4328(00)00247-3
35. Gandolfo G, Glin L, Gottesmann C. Study of sleep spindles in the rat: a new improvement. Acta Neurobiol Exp. 1985;45(5–6):151–62.
36. van Luijtelaar ELJM. Spike-wave discharges and sleep spindles in rats. Acta Neurobiol Exp. 1997;57(2):113–21.
37. Averkin RG, Szemenyei V, Bordé S, Tamás G. Identified cellular correlates of neocortical ripple and high-gamma oscillations during spindles of natural sleep. Neuron. 2016;92(4):916–28. https://doi.org/10.1016/j.neuron.2016.09.032
38. Huguenard JR, Prince DA. A novel T-type current underlies prolonged Ca2+-dependent burst firing in GABAergic neurons of rat thalamic reticular nucleus. J Neurosci. 1992;12(10):3804–17. https://doi.org/10.1523/jneurosci.12-10-03804.1992
39. Feng L, Motelow JE, Ma C, Biche W, McCafferty C, Smith N, et al. Seizures and sleep in the thalamus: focal limbic seizures show divergent activity patterns in different thalamic nuclei. J Neurosci. 2017;37(47):11441–54. https://doi.org/10.1523/JNEUROSCI.1011-17.2017
40. Sitnikova E. Thalamo-cortical mechanisms of sleep spindles and spike-wave discharges in rat model of absence epilepsy (a review). Epilepsy Res. 2010;89(1):17–26. https://doi.org/10.1016/j.eplepsyres.2009.09.005
41. Uygun DS, Katsuki F, Bolortuya Y, Aguilar DD, McKenna JT, Thankachan S, et al. Validation of an automated sleep spindle detection method for mouse electroencephalography. Sleep. 2019;42(2):1–13. https://doi.org/10.1093/sleep/zsy218
42. Benington JH, Kodali SK, Heller HC. Scoring transitions to REM sleep in rats based on the EEG phenomena of pre-REM sleep: an improved analysis of sleep structure. Sleep. 1994;17(1):28–36. https://doi.org/10.1093/sleep/17.1.28
43. Sitnikova E, Hramov AE, Koronovsky AA, van Luijtelaar G. Sleep spindles and spike–wave discharges in EEG: their generic features, similarities and distinctions disclosed with Fourier transform and continuous wavelet analysis. J Neurosci Methods. 2009;180(2):304–16. https://doi.org/10.1016/j.jneumeth.2009.04.006
44. Mölle M, Eschenko O, Gais S, Sara SJ, Born J. The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. Eur J Neurosci. 2009;29(5):1071–81. https://doi.org/10.1111/j.1460-9568.2009.06654.x
45. Eschenko O, Molle M, Born J, Sara SJ. Elevated sleep spindle density after learning or after retrieval in rats. J Neurosci. 2006;26(50):12914–20. https://doi.org/10.1523/jneurosci.3175-06.2006
46. Lacroix MM, de Lavilléon G, Lefort J, Kanbi KE, Bagur S, Laventure S, et al. Improved sleep scoring in mice reveals human-like stages. bioRxiv. Published online 2018:489005. https://doi.org/10.1101/489005
47. Sejnowski TJ, Destexhe A. Why do we sleep? Brain Res. 2000;886(1–2):208–23. https://doi.org/10.1016/s0006-8993(00)03007-9
48. Halász P, Bódizs R, Ujma PP, Fabó D, Szűcs A. Strong relationship between NREM sleep, epilepsy and plastic functions — a conceptual review on the neurophysiology background. Epilepsy Res. 2019;150:95–105. https://doi.org/10.1016/j.eplepsyres.2018.11.008
49. Gelinas JN, Khodagholy D, Thesen T, Devinsky O, Buzsáki G. Interictal epileptiform discharges induce hippocampal–cortical coupling in temporal lobe epilepsy. Nat Med. 2016;22(6):641–8. https://doi.org/10.1038/nm.4084
50. Winocur G, Moscovitch M, Bontempi B. Neuropsychologia memory formation and long-term retention in humans and animals: convergence towards a transformation account of hippocampal – neocortical interactions. Neuropsychologia. 2010;48(8):2339–56. https://doi.org/10.1016/j.neuropsychologia.2010.04.016
51. Contreras D, Steriade M. Spindle oscillation in cats: the role of corticothalamic feedback in a thalamically generated rhythm. J Physiol. 1996;490(1):159–79. https://doi.org/10.1113/jphysiol.1996.sp021133
52. Mölle M, Bergmann TO, Marshall L, Born J. Fast and slow spindles during the sleep slow oscillation: disparate coalescence and engagement in memory processing. Sleep. 2011;34(10):1411–21. https://doi.org/10.5665/SLEEP.1290
53. Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R. Practice with sleep makes perfect. Neuron. 2002;35(1):205–11. https://doi.org/10.1016/s0896-6273(02)00746-8

54. Robertson EM, Pascual-Leone A, Press DZ. Awareness modifies the skill-learning benefits of sleep. Curr Biol. 2004;14(3):208–12. https://doi.org/10.1016/j.cub.2004.01.027
55. Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. Nature. 2004;430(6995):78–81. https://doi.org/10.1038/nature02663
56. Schabus M, Gruber G, Parapatics S, Sauter C, Klösch G, Anderer P, et al. Sleep spindles and their significance for declarative memory consolidation. Sleep. 2004;27(8):1479–85. https://doi.org/10.1093/sleep/27.7.1479
57. Tucker MA, Hirota Y, Wamsley EJ, Lau H, Chaklader A, Fishbein W. A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. Neurobiol Learn Mem. 2006;86(2):241–7. https://doi.org/10.1016/j.nlm.2006.03.005
58. Clemens Z, Fabó D, Halász P. Overnight verbal memory retention correlates with the number of sleep spindles. Neuroscience. 2005;132(2):529–35. https://doi.org/10.1016/j.neuroscience.2005.01.011
59. Walker MP, Stickgold R. Sleep, memory, and plasticity. Annu Rev Psychol. 2006;57(1):139–66. https://doi.org/10.1146/annurev.psych.56.091103.070307
60. Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci. 2010;11(2):114–26. https://doi.org/10.1038/nrn2762
61. Siapas AG, Wilson MA. Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. Neuron. 1998;21(5):1123–8. https://doi.org/10.1016/s0896-6273(00)80629-7
62. Sirota A, Csicsvari J, Buhl D, Rgy BG. Communication between Neocortex and Hippocampus during Sleep in Rodents. www.pnas.orgcgidoi10.1073pnas.0437938100
63. Jiang X, Gonzalez-Martinez J, Halgren E. Posterior hippocampal spindle ripples co-occur with neocortical theta bursts and downstates-upstates, and phase-lock with parietal spindles during NREM sleep in humans. J Neurosci. 2019;39(45):8949–68. https://doi.org/10.1523/jneurosci.2858-18.2019
64. Fogel SM, Smith CT. The function of the sleep spindle: a physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. Neurosci Biobehav Rev. 2011;35(5):1154–65. https://doi.org/10.1016/j.neubiorev.2010.12.003
65. Lanigar S, Bandyopadhyay S. Sleep and epilepsy: a complex relationship. J Sleep Disord Ther. 2014;03(03):453–7. https://doi.org/10.4172/2167-0277.1000165
66. Chakravarty K, Shukla G, Poornima S, Agarwal P, Gupta A, Mohammed A, et al. Effect of sleep quality on memory, executive function, and language performance in patients with refractory focal epilepsy and controlled epilepsy versus healthy controls – a prospective study. Epilepsy Behav. 2019;92:176–83. https://doi.org/10.1016/j.yebeh.2018.12.028
67. Bertram EH. Temporal lobe epilepsy: where do the seizures really begin? Epilepsy Behav. 2009;14(1):32–7. https://doi.org/10.1016/j.yebeh.2008.09.017
68. Aghakhani Y, Bagshaw AP, Bénar CG, Hawco C, Andermann F, Dubeau F, et al. fMRI activation during spike and wave discharges in idiopathic generalized epilepsy. Brain. 2004;127(5):1127–44. https://doi.org/10.1093/brain/awh136
69. Fogerson PM, Huguenard JR. Tapping the brakes: cellular and synaptic mechanisms that regulate thalamic oscillations. Neuron. 2016;92(4):687–704. https://doi.org/10.1016/j.neuron.2016.10.024
70. Sitnikova E. Sleep spindles in rats with absence epilepsy. Sleep Spindles Cortical Up States. 2017;2(1):18–27. https://doi.org/10.1556/2053.01.2017.004
71. Kostopoulos GK. Spike-and-wave discharges of absence seizures as a transformation of sleep spindles: the continuing development of a hypothesis. Clin Neurophysiol. 2000;111:S27–38. https://doi.org/10.1016/S1388-2457(00)00399-0
72. Tezer FI, Rémi J, Erbil N, Noachtar S, Saygi S. A reduction of sleep spindles heralds seizures in focal epilepsy. Clin Neurophysiol. 2014;125(11):2207–11. https://doi.org/10.1016/j.clinph.2014.03.001
73. Yu Y, Yan Y, Tian S, Feng Z, Shi M. Circadian rhythm of interictal epileptiform discharges and changes of spindles in patients with temporal lobe epilepsy. Biomed Res. 2018;29(6):1263–7.
74. Urakami Y, Ioannides AA, Kostopoulos GK. Sleep spindles – as a biomarker of brain function and plasticity. In: Ajeena IM, editor. Advances in clinical neurophysiology. Rijeka, Croatia: InTech; 2012. p. 73–108. doi:https://doi.org/10.5772/48427
75. Sitnikova E, Hramov AE, Grubov VV, Ovchinnkov AA, Koronovsky AA. On–off intermittency of thalamo-cortical oscillations in the electroencephalogram of rats with genetic predisposition to absence epilepsy. Brain Res. 2012;1436:147–56. https://doi.org/10.1016/j.brainres.2011.12.006
76. Myatchin I, Lagae L. Sleep spindle abnormalities in children with generalized spike-wave discharges. Pediatr Neurol. 2007;36(2):106–11. https://doi.org/10.1016/j.pediatrneurol.2006.09.014
77. Cellini N. Memory consolidation in sleep disorders. Sleep Med Rev. 2017;35:101–12. https://doi.org/10.1016/j.smrv.2016.09.003
78. Binder S, Mölle M, Lippert M, Bruder R, Aksamaz S, Ohl F, et al. Monosynaptic hippocampal-prefrontal projections contribute to spatial memory consolidation in mice. J Neurosci. 2019;39(35):6978–91. https://doi.org/10.1523/JNEUROSCI.2158-18.2019

How to cite this article: Merten JE, Villarrubia SA, Holly KS, Kemp AS, Kumler AC, Larson-Prior LJ, et al. The use of rodent models to better characterize the relationship among epilepsy, sleep, and memory. Epilepsia. 2022;00:1–12. doi:10.1111/epi.17161