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Review

On the relationships between epilepsy, sleep, and Alzheimer's disease: A narrative review

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ABSTRACT

Epilepsy, sleep, and Alzheimer's disease (AD) are tightly and potentially causally interconnected. The aim of our review was to investigate current research directions on these relationships. Our hope is that they may indicate preventive measures and new treatment options for early neurodegeneration. We included articles that assessed all three topics and were published during the last ten years. We found that this literature corroborates connections on various pathophysiological levels, including sleep-stage-related epileptiform activity in AD, the negative consequences of different sleep disorders on epilepsy and cognition, common biochemical pathways as well as network dysfunctions. Here we provide a detailed overview of these topics and we discuss promising diagnostic and therapeutic consequences.

1. Introduction

There is growing evidence of multidirectional and potentially causal relationships on different levels between sleep, epilepsy, and Alzheimer's disease (AD) (see Fig. 1). The co-occurrence of these pathologies has been documented in several studies within the last few years:

1.1. Epilepsy and sleep

Sleep and epilepsy are closely intertwined: Epileptic seizures and epileptiform neuronal activity as detected by the electroencephalogram (EEG) often show a circadian pattern: They tend to occur more often during sleep than during wakefulness, and are more likely in certain stages of sleep than in others [1–3]. The occurrence of epileptiform activity disrupts normal sleep architecture and fragments sleep, which in turn, increases the risk of seizures, closing a vicious circle [1,4]. Furthermore, sleep disturbances (for example, insomnia, hypersomnia, or circadian rhythm disorders) are more prevalent in patients with epilepsy than in the population without epilepsy [5].

1.2. Epilepsy and Alzheimer's disease

Epileptic seizures are more frequent in patients with AD, with a prevalence ranging from 9% to 21% in studies between 2016 and 2020 [6–9]. Epileptiform activity is generally found to be more prevalent in earlier stages of AD and in early-onset AD, as well as in patients with inherited forms of AD [10]. Importantly, epileptiform activity can precede the occurrence of cognitive deficits for years [11] and is associated with more rapid and earlier cognitive decline [3,12].

1.3. Sleep and Alzheimer's disease

Circadian disruption and sleep disturbances are common in patients with AD and often occur early in the disease [13]. Sleep disruption, in turn, impairs sleep-dependent memory formation [14] and accelerates cognitive decline [15].

1.4. Connecting epilepsy, sleep, and Alzheimer's disease

Though the existence of potentially causal connections between epilepsy, sleep, and AD is implied by their strong bilateral relationships, they are rarely assessed concurrently. The aim of our review was to inquire about these connections with a focus on the developments and research in the last ten years. Unraveling the mutual relationships between sleep, epilepsy, and AD is crucial, as it may identify modifiable risk factors, inform about and improve preventive measures, and offer possible treatment options.

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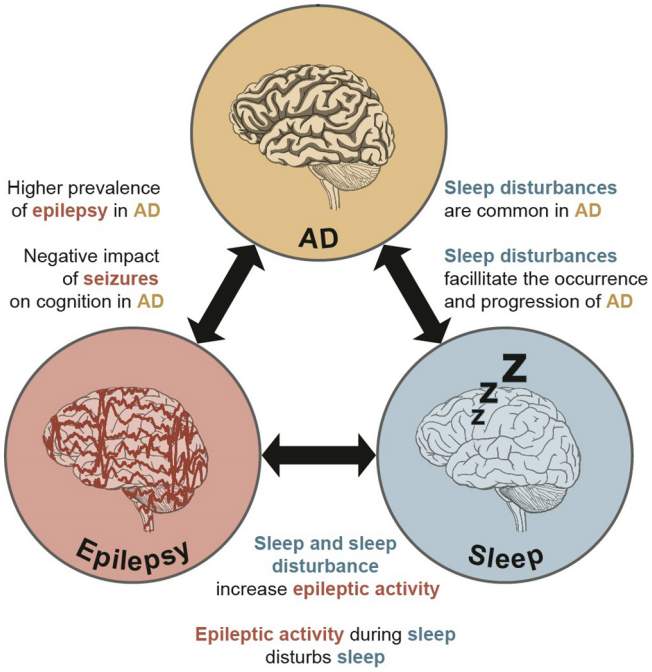

Fig. 1. Multidirectional relationships.

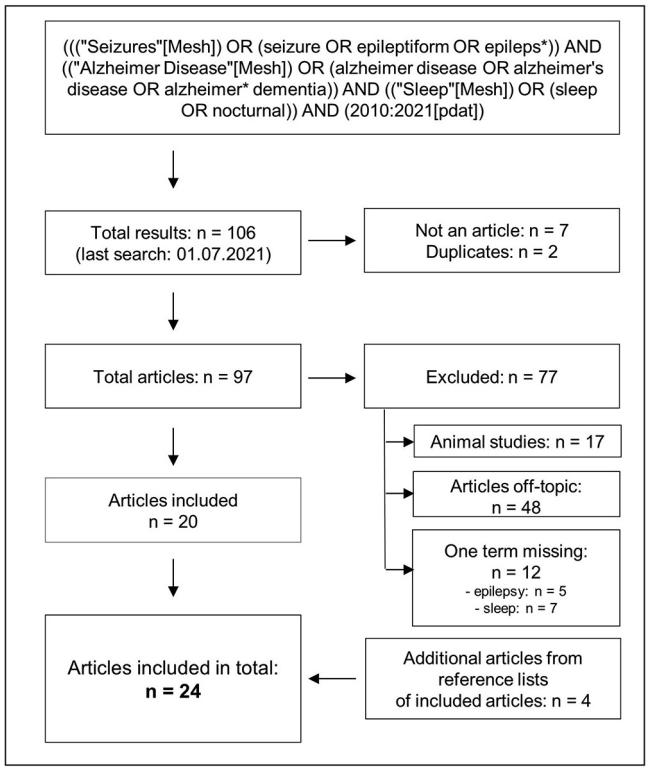

Fig. 2. Flow diagram of the selection process.

2. Methods

The Medline database was searched through PubMed using textword and subject headings (MeSH) with the following search strategy: "Epilepsy" OR "Seizures" AND "Alzheimer's disease" AND "Sleep" OR "Nocturnal" (see flow diagram below for complete search algorithm). We also screened the reference lists of included articles to find additional studies. The search was limited to studies published in the last 10 years (2010 to mid-2021). Only reviews and studies with a focus on humans were included. For more details about the exclusion criteria, see Table 1. In total, 19 articles and reviews responding to the research question were identified via the Medline database (for selection criteria, see Fig. 2). Four further articles and reviews were found through the reference lists of included articles. Finally, 24 articles were included for this review. For an overview of all included articles, see Table 2.

3. Results

3.1. General characteristics of the selected articles

In total, 24 articles from 2010 until 01.07.2021 were included in this review. Of the 24 included articles, 17 were reviews and 7 experimental studies in humans. We classified them into four subtopics, which will be discussed in the following. For an overview of the included articles, see Table 2.

3.2. Sleep-stage-related epileptiform activity in Alzheimer's disease

Of the nine articles on this topic, seven articles concentrated on the occurrence of electrographic epileptiform activity in AD, while two articles focused on methods to detect these EEG signals.

Four of the seven articles were clinical studies about subclinical epileptiform activity in patients with AD.

In an important longitudinal study from 2016, Vossel et al. [3] investigated the occurrence of subclinical epileptiform activity (SEA) via overnight long-term scalp EEG and 1-h magnetoencephalography (MEG) with simultaneous EEG in patients with AD without known epilepsy compared to age-matched controls without dementia. They found significantly more SEA in the AD than in the control group (42% versus 10.5% detected by long-term EEG and/or MEG with EEG, and 21% versus 0%, respectively, detected by overnight EEG). In the follow-up cognitive testing over an average period of 3.3 years, a faster cognitive decline (objectified by the scores obtained in the Mini Mental Status Examination) was found in patients with AD with epileptiform activity than in those without. Epileptiform activity occurred significantly more often during sleep than wakefulness, especially in deeper sleep stages, and was most frequently detected over the temporal lobes.

Horváth et al. [16] examined the prevalence of epileptiform activity in patients with AD with 24--scalp EEG recordings in their experimental study from 2018. Patients with known epilepsy were

Table 1
Excluded articles classified by topics.

"off-topic"	Focus on a special therapy treating neurological disorders (e.g. ketogenic diet, caffeine, or cannabidiol) n = 19
	Focus on biochemical processes, search terms are only mentioned as possible therapeutic targets (e.g. 5'-nucleotidases) n = 8
	Articles on a specific illness presenting neurologic symptoms (e.g., bullosis pemphigoid or Down syndrome) or specific symptoms occurring in neurological disorders n = 18
	Other focus n = 3

Table 2
Included articles (in the order they are discussed in the text).

Topic	Authors Year	Title	Type of article	Topic (in reviews)/Results (in experimental studies) [Study design]
Sleep-stage-related epileptiform activity in Alzheimer's disease	Vossel et al. 2016	Incidence and impact of subclinical epileptiform activity in Alzheimer's disease	Experimental	[Overnight EEG and 1-hour MEG of 33 patients with AD without seizure history and 19 age-matched controls without dementia] - Epileptiform activity occurred more often in patients with AD than in controls and was associated with faster cognitive decline. - SEA occurred mainly during SWS and was detected mainly in the temporal lobes.
	Horváth et al. 2018	Prevalence, Semiology, and Risk Factors of Epilepsy in Alzheimer's Disease: An Ambulatory EEG Study	Experimental	[Ambulatory 24 hour-EEG in 42 patients with AD] - 28% of the patients with AD showed SEA in the EEG recordings but did not have any known seizure history. - 24% of the patients had electroclinical seizures during EEG recordings.
	Lam et al. 2017	Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease	Experimental	[Intracranial foramen ovale electrodes adjacent to the mesial temporal lobe in one patient with MCI and one patient with AD] - Intracranial electrodes detected SEA in the patient with AD and clinically silent seizures + IEA in the patient with MCI while scalp EEG detected less SEA and no seizures. - SEA occurred significantly more frequent during sleep than during wakefulness.
	Brunetti et al. 2020	Subclinical epileptiform activity during sleep in Alzheimer's disease and mild cognitive impairment	Experimental	[full-night video polysomnography in 50 patients with AD, 50 patients with MCI and 50 controls without dementia] - The occurrence of SEA was not different in patients with AD, MCI, or in healthy controls. - SEA did not differ through sleep stages.
	Vossel et al. 2017	Epileptic activity in Alzheimer's disease: causes and clinical relevance	Review	- Prevalence of EA is elevated in AD. - Patients with AD and EA are significantly younger than patients with AD without EA. - EA in AD appears mainly over the frontotemporal brain region and during deeper sleep stages.
	Horváth et al. 2020	Inhibiting Epileptiform Activity in Cognitive Disorders: Possibilities for a Novel Therapeutic Approach	Review	- Cortical excitability is a shared pathological trait between AD and epilepsy and a possible therapeutic target to slow down cognitive decline. - EA during sleep disrupts normal sleep architecture and thus likely impairs memory consolidation.
	Brown et al. 2018	Circadian and Brain State Modulation of Network Hyperexcitability in Alzheimer's Disease	Experimental	- Epileptiform activity is most prevalent in sleep stages 2 and 3, and least frequent in REM sleep. - SEA during sleep is likely to interfere with memory consolidation processes.
	Horváth et al. 2017	Sleep EEG Detects Epileptiform Activity in Alzheimer's Disease with High Sensitivity	Experimental	[24-h EEG of 5 patients with AD with known seizures] - Epileptiform activity occurred mainly in sleep stages 2 and 3. - Longer EEG recordings and particularly nighttime recordings are more sensitive for recording epileptiform activity.
	Lam et al. 2020	Night Watch on the Titanic: Detecting Early Signs of Epileptogenesis in Alzheimer Disease	Review	- Prior to cognitive decline in AD, there are years of clinically silent neurodegeneration with occurrence of network hyperexcitability. - Reinforces the need of techniques to detect network hyperexcitability.
Sleep disorders	Palma et al. 2013	Sleep loss as risk factor for neurologic disorders: a review	Review	- In AD, sleep disruption, sleep loss, and circadian rhythm disorders are a prominent feature and further contribute to cognitive decline. - NREM sleep, but also sleep deprivation have facilitating effects on the occurrence of IEA and of seizures.
	Benjamin et al. 2020	Sleep in Patients With Neurologic Disease	Review	- Pharmacological and behavioral interventions can help to normalize disturbed circadian rhythms in patients with AD. - Prevalence of sleep apnea in patients with epilepsy is elevated.
	Ju et al. 2017	Comorbid Sleep Disturbances in Neurologic Disorders	Review	- Insomnia and obstructive sleep apnea are typical sleep disturbances associated with epilepsy while circadian rhythm disturbances and sleep apnea are typically associated with AD. - Epileptiform activity leads to sleep fragmentation and disrupt normal sleep architecture. - ASM medication has various effects on sleep architecture.
	Smolensky et al. 2015	Diurnal and twenty-four hour patterning of human diseases: acute and chronic common and uncommon medical conditions	Review	- Circadian patterns are both found in AD (for example increased confusion and agitation at sunset) and in epilepsy (for example certain types of seizures occurring preferentially at a certain period of the day).

(*continued on next page*)

Table 2 (*continued*)

Topic	Authors Year	Title	Type of article	Topic (in reviews)/Results (in experimental studies) [Study design]
	Baker et al. 2019	A Longitudinal Study of Epileptic Seizures in Alzheimer's Disease	Experimental	[Longitudinal study with patients with AD with and without epilepsy. Initial cognitive testing and 12-month follow-up] - Patients with epilepsy showed significantly more accelerated cognitive decline. Differences in sleep behavior between patients with AD with and without epilepsy were also found.
Biochemical processes	Liguori et al. 2021	Sleep disorders and late-onset epilepsy of unknown origin: Understanding new trajectories to brain amyloidopathy	Review	- Accumulation of Aß is not only linked to AD, but also to epilepsy and sleep disorders - Aß accumulation can increase neuronal excitability, which facilitates the occurrence of seizures. - Sleep deprivation was shown to induce Aß deposition and leads to reduced Aß clearance by the glymphatic system. On the other side, Aß deposition further disrupts NREM sleep.
	Bishir et al. 2020	Sleep Deprivation and Neurological Disorders	Review	- Sleep deprivation causes deficits in memory formation by attenuation of long-term potentiation in the hippocampus. - Sleep deprivation promotes Aß accumulation, leads to elevated cortisol and adenosine levels and increases hyperphosphorylation of tau proteins. - A possible mechanism by which sleep deprivation causes seizures is suspected in changes of membrane excitability, impacted synaptic plasticity, and changes in action potentials.
	Christensen et al. 2020	Is the glymphatic system the missing link between sleep impairments and neurological disorders? Examining the implications and uncertainties	Review	- The glymphatic system clears the brain from toxic metabolites such as Aß and tau. It is mainly active during sleep. - Sleep impairment in AD interferes with the functioning of the glymphatic system, leading to further accumulation of Aß and tau. - The strong interconnection between epilepsy and sleep indicates a probable role of malfunctioning of the glymphatic system in the pathogenesis of epilepsy although it has yet not been clearly linked.
	Berhe et al. 2020	Orexins role in neurodegenerative diseases: From pathogenesis to treatment.	Review	- Orexin induces and maintains wakefulness and is thus a potent regulator of sleep–wake cycle. It further plays an important role in learning and memory. - Low orexin levels have been correlated with cognitive deficits and sleep impairment in AD.
	Maciejewska et al. 2021	A review of the mechanisms underlying selected comorbidities in Alzheimer's disease	Review	- There is conflicting evidence as to the role of orexins in seizures, with more recent evidence pointing toward a pro-epileptogenic effect. - Melatonin is an important timer for the circadian rhythm. Reduced melatonin levels are associated with AD and lead to circadian rhythm disorders.
	Boison et al. 2015	Comorbidities in Neurology: Is adenosine the common link?	Review	- Adenosine pathways play an important role in facilitating sleep.
	Liu et al. 2019	Research progress on adenosine in central nervous system diseases	Review	- Imbalance of adenosine homeostasis by dominance of excitatory pathways disturbs memory consolidation, decreases cholinergic activity and can lead to epileptic seizures.
	Bak et al. 2018	Astrocytic glycogen metabolism in the healthy and diseased brain	Review	- Astrocytic glycogen metabolism has been connected with memory and learning. - Preponderance of excitatory transmitter glutamate (a product of glycolysis) has been linked to seizures.
Network dysfunction	Karageorgiou et al. 2017	Brain rhythm attractor breakdown in Alzheimer's disease: Functional and pathologic implications	Review	- Sleep and wake are promoted by mutually inhibitory, opposite states, the "brain rhythm attractors". - Breakdown of the brain rhythm attractor systems in AD → "twilight zone" in which neither sleep nor wake is fully reached and the cortex is always active → network hyperexcitability and seizures.
	Jargirdar et al. 2019	Corticothalamic network dysfunction and Alzheimer's disease	Review	- The corticothalamic network regulates sleep functions, attentional and cognitive processes → a dysfunction of this network in AD explains the joint occurrence of sleep impairment, cognitive deficits and seizures.

Abbreviations (in alphabetical order): Aß Amyloid-beta AD Alzheimer's Disease ASM antiseizure medication EA epileptiform activity EEG electroencephalogram IEA interictal eptileptiform activity MCI mild cognitive impairment MEG magnetoencephalography NREM non-rapid eye movement REM rapid eye movement SEA subclinical epileptiform activity SWS slow-wave sleep.

included in this cohort, which is an important difference from other studies. Epileptiform activity was detected in 48% of the patients, with more than half of them not having any seizure history. Twenty-four percent of all patients even had electroclinical seizures. The authors explained the high percentage of detection of epileptiform activity, compared to other studies, by the fact that they also conducted overnight recordings including deeper sleep stages, which are well known to promote epileptiform activity [17].

However, the results of the study of Brunetti et al. [18] did not corroborate the above findings. In their study with patients with AD, Mild cognitive impairment (MCI) and healthy controls, no significant differences in the occurrence of SEA on scalp EEG between the three groups were found – neither for the whole sleep period nor separately for the different sleep stages. SEA was found in approximately 7.5%, while none of it occurred in slow-wave sleep (SWS). The authors thoroughly discussed possible explanations for this discrepancy compared with the other studies mentioned above. For example, they named the use of magnetoencephalography (MEG) that detects epileptiform activity also in deeper parts of the brain. Furthermore they underlined the inclusion of patients taking potentially seizure-threshold-lowering medications such as certain antidepressants, which is another explanation for the increased detection of epileptiform activity in the other studies. Additionally, Brunetti et al. used different, narrower definition criteria for epileptiform activity. Finally, their study participants were significantly older, which decreases the risk of seizures, as epileptiform activity has been shown to occur more often in younger patients with AD or early-onset AD [10].

In order to detect epileptiform activity in deeper parts of the brain, Lam et al. [19] went further and assessed brain activity of one patient with MCI and one patient with AD by intracranial "semi-invasive" foramen ovale electrodes that are surgically positioned close to mesial temporal lobe structures [20]. Both patients had no seizure history but recurrent episodes of accentuated and transient symptom aggravation (confusion in one, anxiety in the other case), highly suspicious of non-convulsive seizures. Non-convulsive seizures, notably short episodes of confusion, have a higher prevalence in older adults than in younger patients [21].

In both patients, the foramen ovale electrodes showed significantly more epileptic spiking than the scalp EEG, with a frequency increase during sleep. Importantly, over 95% of the spiking was not apparent on scalp EEG. In the patient with MCI, the intracranial electrodes detected three "scalp EEG-silent" subclinical seizures, all of them occurring during sleep. The latter finding stresses once more the increased diagnostic yield of recording EEG not only during wakefulness, but also during sleep.

The reviews of Vossel et al. and Horváth et al. [22,23] further discussed epileptiform activity in AD, its impact on cognition and possible therapeutic approaches.

Both reviews underlined the concept and role of cortical hyperexcitability, a common feature of epilepsy and AD. They invoked glutamate as an example for an excitatory neurotransmitter system that is likely to be overactivated in AD [24,25], and may be detrimental to cognitive functions [26] (also see 3.4.6). Increased glutamate release was also associated with SEA and interictal epileptiform activity (IEA) [27], and an increase in excitation plays an important role in ictogenesis [28].

Both research groups further promote the idea that epileptiform activity during sleep impairs memory consolidation during sleep. This is supported by the findings of reduced physiological hippocampal spindles [29], induction of spindles and delta waves during rapid eye movement (REM) sleep and wakefulness [30], reduced SWS, and increased time to REM sleep onset [31], as well as reduced REM sleep [32] in patients with epileptiform activity during sleep.

The review of Brown et al. [33] targeted circadian variations in network hyperexcitability in AD. Besides further analyzing the data acquired through intracranial electrodes in the two patients (see above) of the study of Lam et al. with regard to sleep-stage-dependent occurrence of interictal activity, the authors conducted a study with two mouse models of AD to investigate circadian effects of network hyperexcitability. Both, the data of Lam et al., and the mouse models, impressively demonstrated that epileptiform activity occurred mostly during sleep and thus had a strong circadian modulation.

Two of the nine articles centered further on detection methods of the often clinically silent epileptiform activity in patients with AD.

In their study from 2017, Horváth et al. [2] analyzed 24-h scalp EEG recordings of patients with AD and epilepsy that had manifested around the time of the onset of cognitive decline. Their aim was to determine the optimal setting for EEG recordings as to reliably detect epileptiform activity. They corroborated a strong association between epileptiform activity and sleep, with the majority (70%) occurring in NREM sleep, particularly in sleep stage 3, while only 18% of epileptiform activity was recorded during wakefulness. In summary, the sensitivity of detection of epileptiform activity was highest between 0:00 and 08:00 AM (where already 1-h long recordings reached a sensitivity of 0.8) and further improved with the duration of EEG recordings.

The review of Lam et al. [9] assessed methods – both already existing as well as still in development – that allow to detect as early as possible the often clinically "silent", or difficult to detect, epileptic activity in patients with AD. The authors motivated their study by the fact that prior to cognitive decline in AD there are years of "silent" neurodegeneration, possibly associated with the occurrence of aberrant activity in hyperexcitable neuronal networks. Once cognitive deficits become apparent, significant and probably already irreversible neurodegeneration has set in. "Hyperexcitability biomarkers" like subclinical epileptiform activity, could allow to detect AD in earlier and clinically silent stages. Modifying network hyperexcitability hence offers a therapeutic target in earlier stages of AD. Alternative electrophysiological technologies to detect epileptic activity that possibly evades scalp electrodes mentioned by the authors are magnetoencephalogram (MEG), intracranial electrodes (as used in their study from 2017 with two patients, see 3.2.1) and the application of machine learning to extract additional information from (non-)invasive EEG signals.

3.3. The role of sleep disorders in patients with Alzheimer's disease and epilepsy

Five articles discussed sleep disorders and their clinical consequences, including a focus on epilepsy and AD.

Palma et al. [34] and Benjamin et al. [35] assessed sleep loss (defined as an average sleep duration of less than 7–h) as a risk factor for different neurologic disorders. Ju et al. [36] and Smolensky et al. [37] underlined the occurrence of diurnal and circadian patterns in AD. Alzheimer's disease is, for example, associated with circadian phase delay that leads to sundowning (i.e., an increase of confusion and agitation at sunset) and (nighttime) insomnia as well as daytime sleepiness. As sleep plays an important role in memory consolidation, learning, and attention, its disturbance is known to have deleterious effects [15,38]. In AD, imaging studies revealed pathological changes in brain regions that regulate sleep [39], suggesting a common pathological pathway. Benjamin et al. further proposed the "normalization" of circadian rhythms (with pharmacological as well as with non-drug treatments such as exposure to bright light and physical exercise) as an important aspect of AD management.

As to the connection between epilepsy and sleep loss, Ju et al. and Palma et al. pointed out the pro-epilepto-/ictogenic effects of certain sleep stages and the rather protective effect of others. Palma et al. reported that sleep disruption has been found to increase the occurrence of IEA in patients with epilepsy, but not in controls without epilepsy [40,41]. Ju et al. pointed out that up to 2/3 of patients with epilepsy [42] have sleep disturbances that lead to sleep fragmentation and disruption of normal sleep architecture. Additionally, antiseizure medication (ASM) can further induce changes in sleep architecture or have a soporific effect, like, for example barbiturates and phenytoin [43]. Smolensky et al. further focused on circadian rhythms in epilepsy with a tendency of different epilepsy types to occur during a specific time of the day, for example temporal lobe seizures in the morning, parietal lobe seizures in the early evening, and frontal lobe seizures in the second part of the night [44].

Baker et al. [45] conducted a longitudinal study with patients with AD including initial cognitive testing and a 12-month follow-up. They clinically identified 28% of the included patients as probably or possibly having epilepsy (referred to as "patients with epilepsy" here). Via behavioral questionnaires, patients with AD and epilepsy indicated a significantly poorer sleep quality and sleep duration than controls without epilepsy. At follow-up cognitive testing, while cognitive performance had decreased in all patients with AD, the cognitive decline in patients with epilepsy was significantly more accelerated. Mostly affected were attention, fluency, and several memory domains.

Benjamin et al. discussed the elevated prevalence of sleep apnea in patients with epilepsy. Some ASMs – such as gabapentin or pregabaline – are associated with weight gain or with reduced tone of upper airway muscles, which increases the risk of sleep apnea [46]. The authors further described changes in sleep architecture with increased lighter and reduced deeper sleep stages caused by sleep apnea, which again, increase the risk of seizures [47].

3.4. Biochemical processes affecting sleep in Alzheimer's disease and epilepsy

Eight articles focused on different biochemical processes underlying normal brain function, with their dysfunction being the cause or consequence of sleep disturbances, epilepsy, or AD.

3.4.1. Accumulation of ß-Amyloid

Liguori et al. [48] linked epilepsy, sleep disorders, and AD in their review from 2021 with a common pathological feature: the accumulation of ß-amyloid. Importantly, deposition of Amyloid ß (Aß) plaques and hyperphosphorylated tau are the two major pathological features of AD [49]. Amyloid ß accumulation leads to dysfunction of synaptic circuits and neuronal transmission. This not only impairs synaptic plasticity and, consequently, learning and memory processes [10], but these aberrant neuronal patterns can also lead to network hyperexcitability [24,50]. Network hyperexcitability further impairs memory encoding [50–52] and can induce changes in network synchrony [53]. Changes in synchronization of neuronal activity occur during seizures, with desynchronization often occurring during early stages of the seizure and even preceding it, followed by synchronization at a larger scale, which increases until the end of the seizure and might even facilitate its termination [54].

Amyloid ß was found to be pro-epileptogenic even prior to its plaque deposition, which goes in line with the observation that seizures often precede cognitive decline. In patients with late-onset epilepsy of unknown origin (LOEU), reduced levels of $Aß_{42}$ in CSF were found suggesting increased Aß deposition in the brain [55]. These patients show faster cognitive decline and generally a higher risk of progression to AD [12]. These findings further suggest a common pathogenesis of AD and epilepsy.

Sleep disruption is linked to Aß accumulation in a vicious circle: as the mainly sleep-dependent glymphatic clearance system is impaired due to sleep disruptions, (see 3.4.3), clearance of Aß is reduced. This reduction leads to its accumulation, thus promoting progression of AD and further sleep disruption. Insomnia and sleep deprivation induce Aß deposition [55,56] and impair sleep-dependent memory formation [13,57]. Cerebral Aß disrupts NREM sleep and Aß burden correlates positively with reduced SWA. As slow-wave oscillations in NREM sleep are essential for long-term memory consolidation, this is likely to have a negative impact on memory consolidation [58].

3.4.2. Biomolecular effects of sleep deprivation

Bishir et al. [59] focused on the biochemical mechanisms of sleep deprivation in neurological disorders. Sleep deprivation is known to cause deficits in attention, working memory, emotions, and hippocampal learning already in healthy subjects [60]. Hippocampal-dependent memory consolidation has been shown to be critically affected in sleep deprivation by attenuating long-term potentiation [61]. In AD, sleep deprivation impairs the clearance of Aß and tau via the glymphatic pathways (see 3.4.3), which leads to faster disease progression. In acute sleep deprivation, elevated tau levels in the interstitial fluid in rodents and elevated Aß levels in human CSF were found, while in chronic sleep deprivation, spreading of tau aggregates was accelerated [62]. Sleep deprivation has furthermore been shown to upregulate the expression of an enzyme that plays an important role in proteolysis (and thus, "production") of amyloid precursor protein (ß-site amyloid precursor protein-cleaving enzyme, BACE1) [63]. An impaired sleep–wake cycle has also been shown to increase tau hyperphosphorylation [64].

The authors formulated a possible explanation for the facilitation of epileptiform activity by sleep deprivation: McDermott et al. were able to link changes in ion channels and synaptic alterations leading to reduced membrane excitability in hippocampal neurons to sleep deprivation [61]. These changes in membrane excitability are further thought to have negative effects on long-term potentiation and consequently on memory formation [65,66].

3.4.3. Glymphatic clearance system

Christensen et al. [57] linked sleep impairment and the occurrence of different neurological disorders via the glymphatic system, which was first described in 2012 by Iliff et al. [67]. Because the brain does not have a lymphatic system, the clearance of metabolites, including Aß and tau, is realized by an intracellular trans-astrocytic, *glial* pathway ("glymphatic" = glial + lymphatic). The glymphatic system seems to be mainly active during sleep, above all in SWS, and suppressed during wakefulness [56,68,69]. The association between AD and sleep impairments such as reduced SWS, sleep fragmentation, and disruption of the sleep/wake cycle further points toward an important role of the glymphatic system in disease progression with accumulation of Aß and tau due to a reduced function caused by sleep loss [56,70].

Epilepsy has not yet been proven to be directly linked to the glymphatic system, but its strong interconnection with sleep indicates a probable role of malfunctioning of the glymphatic system in its pathogenesis, too. Abnormal neuronal activity and excitability in epilepsy is furthermore suspected to modify the flow of interstitial fluid [71], and, consequently, of the glymphatic system. Excitotoxic damage, caused both by impairment of interstitial fluid flow and by abnormal neuronal activity, may lead to further accumulation of potentially neurotoxic metabolites [72].

3.4.4. Pathways involved in sleep–wake-regulation

Two reviews described the dysfunction of biomolecular mechanism involved in sleep–wake regulation in AD.

Berhe et al. [73] and Maciejewska et al. [74] described the role of orexin in neurodegenerative diseases. Orexin, a neurotransmitter secreted from the lateral hypothalamus, is a potent regulator of the sleep–wake cycle as it initiates and maintains wakefulness [75]. Consequently, increased activity of orexin leading to sleep deprivation is thought to impair the sleep-dependent activity of the glymphatic clearance system (see 3.4.3), which can result in the accumulation of Aß, tau, and other waste metabolites. Orexin furthermore directly reduces clearance of Aß by suppressing phagocytosis [76]. Besides Aß, it also enhances the accumulation of tau [77].

Administration of orexin both increased wakefulness and Aß levels, while administration of an orexin antagonist decreased Aß levels [78].

In contrast, orexin plays an important role in memory processes by modulating long-term synaptic plasticity in the hippocampus [79]. Deletion of orexin neurons in mouse models resulted in impairment of learning and memory, while replacement of orexin led to an improvement in memory tasks [80].

Besides orexin, Maciejewska et al. [74], describe melatonin as an important timer for the circadian rhythm. The secretion of melatonin from the pineal gland occurs solely during the dark phase and is regulated by the Nucleus suprachiasmaticus, the "master clock" of the circadian rhythm [81,82]. Reduced CSF melatonin levels are already found in preclinical AD stages and further decrease with the progression of AD [83,84]. Decreased melatonin levels are associated with circadian rhythm disorders like night time insomnia and daytime sleepiness [85].

Regarding epilepsy, Berhe et al. reported conflicting evidence about whether orexin acts to suppress seizures, or, on the contrary, to enhance epilepto-/ictogenesis, with more recent evidence pointing toward the latter [86,87]. As orexin levels are highest during wakefulness and sleep–wake transitions, when the risk of seizures is also elevated [87,88], the authors propose a possible connection between orexin levels and the occurrence of seizures.

3.4.5. Astrocytic glycogen metabolism

Bak et al. [89] linked cerebral glycogen metabolism and the occurrence of neurological diseases. In the brain, glycogenolysis is mainly localized in astrocytes and has been connected with learning and memory consolidation processes [90,91]. In animal models, glycogen deficiency impaired memory performance. Furthermore, intracerebral injection of Aß caused memory loss, which could not be overcome by stimulating glycogenolysis, because Aß impairs glycogen synthesis. [92]. Glycogen metabolism has further been linked to epilepsy: The excitatory neurotransmitter glutamate is a product of glycogenolysis. A dysbalance between glutamate and the inhibitory neurotransmitter GABA with dominance of glutamate has been linked to seizures [93]. Concerning sleep, a connection between glycogen metabolism and sleep has been made for a long time as glycogen is used up during wakefulness and replenished during sleep – however, there is increasing evidence that glycogen levels might be related to reduced locomotion during sleep rather than to sleep itself [94].

3.5. Network dysfunction in Alzheimer's disease linking to sleep disorders and epilepsy

Two research groups presented network models to understand AD and its comorbidities.

3.5.1. Brain rhythms attractor breakdown in Alzheimer's disease

In their excellent review from 2017, Karageorgiou and Vossel [95] presented the brain rhythms attractor model as a possible explanation for the strong bidirectional relationship between AD and sleep disorders. This model describes two mutually inhibitory attractor systems, each of them consisting of specific neuronal networks in the hypothalamus and brainstem. Each attractor sets the brain to a specific state – sleep or wake. By activation of one system, the other system is inhibited.

The cause of the rhythm attractor breakdown in AD is supposed to be the deposition of hyperphosphorylated tau in the brainstem and basal forebrain, where nuclei involved in sleep/wake regulation are located. The consequence of a breakdown in AD is a state the authors refer to as "the twilight zone", in which none of the two opposite states of consciousness is any longer fully reached. According to the authors, this model presents an explanation for the elevated number of patients with AD with circadian rhythm disorders such as daytime sleeping and nighttime awakenings as well as disturbances of their sleep architecture.

The authors as well associated the sleep–wake attractor breakdown with the increased occurrence of seizures in AD with Aß deposition leading to neuronal hyperexcitability that then promotes epileptiform activity. Permanent neuronal activation in turn promotes Aß aggregation, closing a vicious circle.

3.5.2. Corticothalamic network dysfunction

Jagirdar and Chin proposed a connection between the corticothalamic network and AD in their review from 2019 [96]. As the corticothalamic network regulates, among others, sleep and arousal as well as attentional and cognitive processes, its dysfunction could explain the joint occurrence of symptoms from these domains in AD. The corticothalamic network consists of reciprocal connections between the cerebral cortex and thalamus. It is regulated by the GABAergic thalamic reticular nucleus (TRN) [97]. During sleep, TRN is active and inhibits the transmitting of sensory information from the thalamus to the cortex [98], which is important for sleep maintenance. TRN activity furthermore induces slow-wave activity (SWA), which is thought to be essential for regeneration and homeostatic maintenance of neurons after wakefulness and thus for memory consolidation [99].

Furthermore, abnormal synchronization in the corticothalamic circuitry is associated with certain non-convulsive seizures with cessation of movement and a temporary loss of consciousness in patients without AD. Based on the similar semiology of seizures in patients with AD, the authors hypothesized a similar pathological pathway, involving a dysfunction of the corticothalamic network, for certain nonconvulsive seizures in AD. As Aß deposition in patients with AD has been found in subcortical areas such as the thalamus [100], the authors postulated that this might be a pathological correlate of thalamocortical circuit disruption in AD.

4. Discussion

The number of results found in the PubMed database for any combination of two of our three search terms since 2010 until mid of July 2021 (nearly 2000 for AD AND epilepsy, largely over 2000 for sleep AND AD, and even over 4000 for sleep AND epilepsy) reflects the broad interest in these topics (for the exact numbers, see Fig. 3). The comparison with the only 99 results for a combination of all three terms however underlines the urgent need for liberation from silos of academic departments and from the constraints of established paradigms to strive for a more integrative perspective of neurodegeneration [101].

Sleep, AD, and epilepsy were linked in different ways throughout the articles we have selected for this review (see Fig. 1). We found a "tridirectional" connection linking epilepsy, AD, and sleep. Remarkably, the articles that dealt with this were no older than from 2016, which indicates that this is an emerging topic. The main link between epilepsy, AD, and sleep concerns epileptiform activity, which is more common in patients with AD than in patients

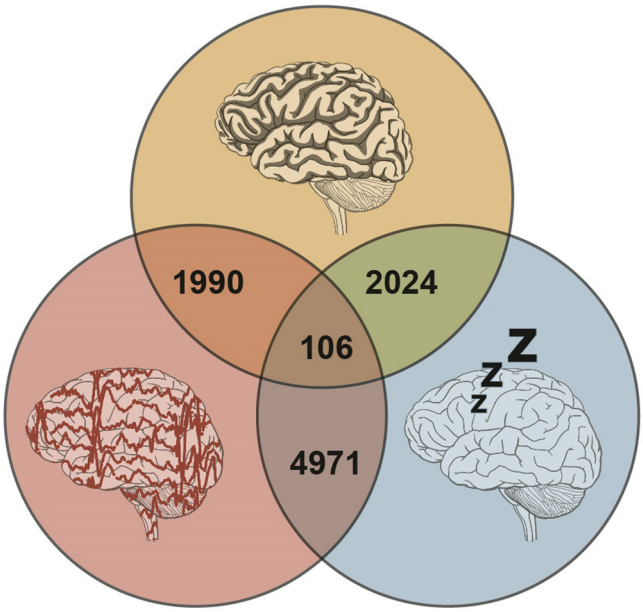

Fig. 3. Pubmed search result numbers (last search: 01.07.2021). It is striking, how relatively few studies assessed the trilateral interactions between epilepsy, sleep, and Alzheimer's disease.

without AD, and occurs preferentially during sleep. This leads to the following questions that should be addressed in future studies:

4.1. Epileptiform activity and sleep disruption – consequences or causes of neurodegeneration?

Throughout our collected articles, the "chicken or egg problem" has repeatedly been put forward: Palma et al. [34] inquired whether sleep pathologies occurred as results of neurodegeneration or if they could also increase the risk of the occurrence of AD. Similarly, Vossel et al. [22] raised the question whether epilepsy increased the risk of the occurrence of AD or whether it was the consequence of the pathological changes occurring in AD. Generalizing, one may ask: Are sleep disturbances and epilepsy mainly symptoms of progressing neurodegeneration – or are they also contributing to the progression of AD, maybe even to its very development? Palma et al. raised this question already in 2012, but a comprehensive answer is still lacking. Though recent research suggests that both questions have to be affirmed and thus implies several vicious loops, important aspects remain unclear.

As to sleep disturbance and epilepsy being a consequence of AD, a common pathological denominator can be found in Aß and tau aggregation. Seizures in AD are often originating from the temporal lobes, a brain region strongly affected by early Aß and tau deposition [11]. Seizures could in this case be the consequence of the pro-epileptogenic effect of Aß deposition [7,22], and sleep loss the consequence of Aß deposition in brain areas that are involved in sleep regulation, such as the nucleus basalis of Meynert in the basal forebrain, the thalamus, and several nuclei in the brainstem [81]. As to why the appearance of sleep disturbances and seizures can precede cognitive decline [11,13], Aß and tau have been found to be accumulating years before cognitive symptoms appear, already leading to cell damage, disruption of neuronal circuits, and appearance of aberrant networks before the occurrence of the first cognitive symptoms [102].

Furthermore, there is accumulating evidence that sleep and epilepsy play a pathophysiological role in disease progression. Neuronal hyperactivity has been associated with increased release of tau and amyloid, leading to their accumulation, which suggests a facilitating role of epileptiform activity in AD progression [9,103]. Remarkably, not every patient with epilepsy develops AD. The risk of developing AD for individuals with long-term epilepsy was only found to be significantly elevated for seizures beginning 10 years prior to the diagnosis of AD, suggesting an already existing common pathological pathway for those patients [104]. As to sleep disturbance: SWS restriction has been found to lead to Aß aggregation, while its enhancement reduces it [105]. Insomnia and sleep apnea have been found to increase the risk of developing AD [106] and sleep deprivation has been found to increase Aß levels.

4.2. Are there further reasons to treat epileptiform activity and sleep disturbances?

There is strong evidence pointing toward sleep's essential role for memory consolidation. A hallmark rodent study in 1994 found a reactivation of the same visuo-spatial patterns during sleep that had occurred in wakefulness while exploring new environments. Furthermore, the patterns appeared in the same order as they did during wakefulness [107]. In human studies, significant memory improvement can be observed already after short periods of sleep [108]. Slow oscillations are generated in the prefrontal cortex during SWS and are especially associated with hippocampus-dependent memory consolidation. The underlying process of long-term memory-consolidation is thought to be the synchronization of neuronal activity by the reactivation of newly acquired, still labile, memory patterns (like the ones observed in the rodents) in the hippocampus in order to consolidate them and enable cortical long-term storage [109–111]. Reduction of SWS has therefore been shown to lead to further cognitive decline [112,113], which speaks in favor of a treatment of sleep disturbances in AD.

Furthermore, as epileptiform activity has been shown to occur more frequently in SWS compared to other sleep stages or wakefulness [3,4,16,111] they are likely to interfere with the then occurring memory consolidation processes (see Fig. 4).

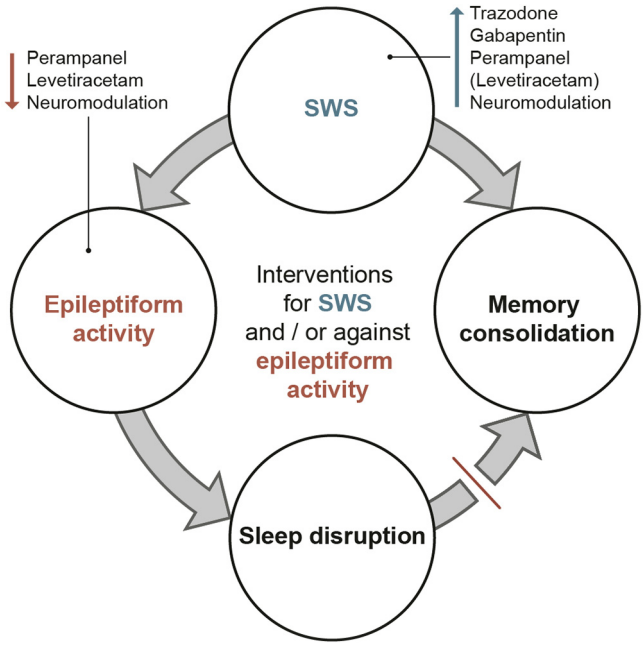

Fig. 4. Consequences of SWS enhancement. A crucial point is that when slow-wave sleep is therapeutically enhanced, the potential increase in epileptiform activity should be monitored and probably also treated, for example by long-acting and sleep stabilizing anti-seizure medication such as perampanel or a combination of levetiracetam and trazodone or gabapentin.

An argument that SWS is disturbed by epileptiform activity is also found in patients with accelerated long-term forgetting (ALF). Accelerated long-term forgetting is a common symptom of patients with transient epileptic amnesia (TEA), a form of temporal lobe epilepsy manifestating as episodes of transient amnesia. Patients with ALF forget new memory contents at an accelerated rate, while learning and short-term memory retrieval are intact [114]. Atherton et al. found that patients with ALF did not profit from SWS regarding memory consolidation, as did healthy controls. Crucially, the negative correlation between SWS duration and memory retention after sleep for the ALF patients even points toward a detrimental effect of SWS due to a possible increase of epileptiform activity during SWS and a consecutive disruption of memory consolidation processes [111].

Besides this possible disruption of sleep and SWS, epileptiform activity itself is furthermore suspected to cause worsening of cognitive functions. While the deteriorating effect of epileptic seizures on cognitive functions has been a subject of extensive research [115,116] and has also been found for patients with AD [11,117,118], less is known about a potentially harmful effect of SEA on cognition, and further research is therefore urgently needed. Recent findings however point toward a similarly detrimental effect for SEA [3,23,119]. For example, interictal epileptiform activity in wakefulness has been found to disrupt short-memory retrieval and impede neuronal plasticity [120,121].

The symptoms that are most noticeable and often have the most impact on everyday life for patients with AD are memory loss and other cognitive deficits. Consequently, if SEA presents a further, but treatable "threat" to cognitive functions by itself and by impairing sleep, this clearly favors to suppress epileptic activity.

4.3. How can subclinical epileptiform activity and sleep disturbances reliably be detected?

As SEA and overt seizures often precede other recognizable features of AD [13], detecting them could allow for an early diagnosis of AD and – hopefully in the future – for the prevention or at least a slowing of further neurodegeneration. Accordingly, mesial temporal epileptiform activity, hyper- and also hypoactivity of hippocampal neurons, as well as disruptions of SWA, have been discussed as diagnostic "biomarkers" of AD [9,58,103,122].

In AD, epileptic seizures can be very challenging to detect clinically (as they are mostly non-convulsive) or to be recognized as epileptic (as fluctuations in behavior, temporary worsening of memory, or short episodes of absence are also common non-epileptic features of AD) [7,11]. In addition, subclinical epileptiform activity can by definition not be directly observed [123]. The classical, almost a century old, method of detecting epileptiform activity is EEG. However, "standard" scalp EEG is mostly performed for a duration of under an hour during wakefulness, with limited capability to register epileptiform activity in deeper brain regions. Sensitivity for the detection of SEA in the first 30 min of EEG recordings has been shown to be around only 15% [16]. Consequently, detection sensitivity can be increased by extending EEG duration, and, importantly, with recordings during sleep [2]. Besides standard EEG, there are various other detection methods, some already established and others still being developed: For example, the combination of EEG and MEG allowed Vossel et al. 2016 to detect SEA in deeper brain regions [3]. Another method was used by Lam et al.: They detected significantly more SEA and even seizures with intracranial foramen ovale electrodes in patients with AD without epilepsy, while scalp EEG conducted at the same time showed significantly less SEA and did not detect any seizures [19]. Of course, foramen ovale electrodes are an invasive method, and thus their use is likely to remain restricted.

The use of computerized methods to detect epileptiform activity is a subject of ongoing research: Through pattern recognition and machine learning, artificial intelligence becomes able to detect epileptiform activity that the human expert is not able to see. Artificial neural networks have been trained to identify scalp-EEG-negative seizures by associating the scalp EEGs with corresponding recordings obtained by intracranial electrodes and have identified correctly 40% of scalp-EEG negative seizures, while clinicians could not detect any of them [124].

To allow EEG monitoring over longer periods of time and thereby significantly improve detection of SEA and sleep disorders, detection devices will have to be as small and unobtrusive as possible, which requires novel ultra-low energy algorithms and hardware as, for example enabled by hyperdimensional computing [125,126]. Long-term monitoring would permit to detect intermittent epileptiform activity as well as changes in sleep architecture over longer periods of time. This would allow to also monitor the effects of treatment on both epileptiform activity and sleep disturbances. Additionally, more comprehensive scientific information about the effect of subclinical epileptiform activity and sleep changes, for example on cognition or the progression of neurodegeneration, could be obtained in a more objective way. As a supplement to sleep diagnostics by means of EEG, polysomnography should be mentioned above all, which ideally should also be used at home and can be supplemented by video recording [101].

4.4. What are therapeutic options to reduce epileptiform activity and treat sleep disturbances in AD?

Only a few studies have so far investigated the effect of ASM in IEA [127–129] and even fewer in SEA. Both positive and neutral effects concerning the improvement of cognitive functions in AD have been reported. The finding that an improvement of cognition only appeared in patients with AD who also had a reduction of epileptiform activity strongly suggests a contribution of the epileptiform activity to cognitive decline [130,131]. Levetiracetam and lamotrigine have been shown to be effective regarding seizure reduction in AD [132]. Additionally, studies indicate a neutral to even possibly positive effect of levetiracetam on cognition [133,134]. It further seems to have little effect on sleep or might even increase sleep efficiency and SWS [42,132,135]. However, relevant side effects of levetiracetam are tiredness as well as worsening of depression, irritability, and anxiety, which in turn can lead to insomnia [136,137]. Lamotrigine showed stabilizing effects on sleep and may as well have positive effects on cognition [1,138].

Regarding the goal of improving sleep, it is important to note that the objective to increase the amount of SWS might collide with the objective to reduce the occurrence of epileptiform activity, as the latter is elevated during SWS [4] (see Fig. 4). This dilemma of improving SWS but at the same time preventing the occurrence of epileptiform activity has not been solved using a single drug yet, though recent studies imply that perampanel might be a good candidate to evaluate [139]. Alternatively, a combination of two drugs could be conceivable [125]. Studies have, for example, shown a positive effect of trazodone, an antidepressant, in patients with AD with significant SWS enhancement [140,141]. La et al. further found a significant increase in cognitive performance in patients with AD treated with trazodone for sleep impairment in a longitudinal study over 3–4 years [141]. To prevent the potentially increased occurrence of epileptiform activity and its associated negative effects, trazodone could then be combined with an ASM, for example levetiracetam (see above). Furthermore, gabapentin has been shown to increase SWS as well as sleep efficiency, and to decrease arousals [4,142]. Seizure frequency in patients with epilepsy has also been reduced [143], but not interictal epileptiform activity [144]. In addition, gabapentin often induces weight

gain, which may promote or enhance obstructive sleep apnea [43]. Again, a careful combination with another ASM could be appropriate. When considering polytherapy, the monitoring of side effects is key, as the majority of ASMs may have – dose- or non-dose-dependent – cognitive and neuropsychiatric adverse effects, and this can be compounded by polytherapy. Consequently, polytherapy should only be continued when there is an increase of efficiency outweighing side effects. In doing so, it is important to avoid some ASMs: Phenytoin and valproate for example have been shown to worsen cognitive functions and to impair sleep by disturbing sleep architecture [74,145], and they furthermore affect liver enzymes, which increases the risk of drug–drug interactions.

A non-pharmacological treatment option could be neuromodulation. It is already being used in different modalities for patients with drug-resistant epilepsies, and several studies have applied transcranial current stimulation in elderlies during sleep to enhance memory, though with mixed results. There is also a study applying transcranial current stimulation during a nap in patients with mild cognitive impairment, which showed an increase in sleep oscillations as well as a memory improvement [146].

5. Conclusions

In this review, we presented relationships between sleep, epilepsy, and AD on different pathophysiological levels, many of them still being a subject of extensive ongoing research. Due to their tight connections, their mutual influence has to be taken into consideration in the therapy regimen: For example, enhancing NREM sleep might improve cognitive functions, however, it might also increase epileptiform activity, thereby negatively affecting cognition.

These connections further open up to different promising research directions:

First, to be able to treat, one has to improve diagnostics. Research has come a long way in understanding the advantages but also the limits of classical electrophysiological detection methods, and in developing new ones. Not only do novel devices allow long-term monitoring of epileptiform activity and sleep, but they also unravel the (side) effects of different personalized treatments, their interactions, and their influence on other clinical aspects [125].

In addition, as new AD biomarkers emerge, there is a large potential for new treatment targets. A timely example is cortical hyperexcitability [9]: While it might allow to detect neurodegeneration at a relatively early stage and therefore presents a potential screening target, its treatment might additionally slow the occurrence of cognitive deficits. Additionally, the search for new treatments for AD still presents a vast field for research. A few examples are the inhibition of proteins involved in the process of tau hyperphosphorylation (GSK3-inhibitors) [74,147] or of Aß aggregation (BACE-1-inhibitors) [147,148] or monoclonal antibodies targeting Aß aggregates [148,149].

Concerning the "chicken or the egg" problem: Epileptiform activity and sleep disorders are increasingly understood not only as consequences of neurodegeneration, but also as contributing, potentially modifiable factors. This allows deeper insights into a biomolecular level into the underlying – and potentially shared – pathogenesis, which could open up to potential new treatments. For example, besides network hyperexcitability, neuroinflammation is more and more revealed as playing an important role in the pathogenesis of AD [150] and also of epilepsy [151].

To conclude, detecting neurodegeneration at an earlier stage could not only allow the implementation of personalized preventive measures, but also – bearing in mind possible interactions and side effects – to begin treatment as early as possible, thus slowing disease progression and maintaining cognitive functions and independence for a longer time.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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