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Review Article

Sleep architecture in adults with epilepsy: a systematic review

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ABSTRACT

Objectives: To assess whether sleep architecture differs in subgroups of adults with epilepsy or in adults with epilepsy compared to control populations.
Methods: We completed a systematic review of papers published in two databases up to May 2018, with adults with epilepsy who have undergone either two consecutive nights of in-laboratory polysomnography (PSG) or one night of ambulatory PSG. Our review followed the PRISMA statements and guidelines and the protocol was registered in the PROSPERO platform prior to initiation of the review process (record CRD42018084009).
Results: Five studies out of 872 fulfilled our eligibility criteria. Only one study reported a significant difference in any sleep architecture parameter in group comparisons. Crespel et al., found that wake after sleep onset (WASO) time in minutes was higher in patients with refractory temporal lobe epilepsy when compared to refractory frontal lobe epilepsy (78.2 ± 5.3 vs. 28.1 ± 2.2; $p < 0.01$) and healthy controls (78.2 ± 5.3 vs. 27.9 ± 18.9; $p < 0.007$).
Conclusions: Only a few studies objectively assessed sleep in adults with epilepsy while controlling for key factors that influence sleep. However, even those reports are heterogeneous in regards to methodology and population characteristics. Further studies are required to access the extent of sleep architectural abnormalities in adults with epilepsy.

1. Introduction

Epilepsy is a neurological disorder with worldwide prevalence of around 1%, posing a major burden on society [1]. The presence of two unprovoked seizures at least 24 h apart or one seizure plus a 60% risk of recurrence operationally defines the disease [2]. Aside from presenting a high risk for recurrent seizures, adults with epilepsy experience significant comorbidities such as sleep disorders. In turn, sleep disorders such as obstructive sleep apnea may have consequences on seizure control as treatment with positive airway pressure therapy can reduce seizures, emphasizing the bidirectional relation between epilepsy and sleep [3]. Studies investigating sleep architecture have found differences between adults with epilepsy and healthy individuals. Studies of generalized epilepsies (GE), for instance, have reported reduction in the percentage of NREM sleep [4], reduction of REM sleep [5,6] and increased time awake after sleep onset (WASO) [4,5] in comparison to control populations. In focal epilepsies (FE), there are reports of decreased REM sleep [7,8], decreased [9] or increased N3 [8] and increased WASO [7,8]. However, studies include heterogeneous populations and methodological variations often precluding comparison. We performed a systematic review on sleep architecture in adults with epilepsy compared to healthy controls in order to address the knowledge gap in this area.

2. Methods

2.1. Research protocol and guideline

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements and guidelines [10–13] were used in protocol and development prior to the initiation of the review process (record CRD42018084009).

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2.2. Searches

Searches were performed on the MEDLINE and PsycINFO databases with search string "*epilep* AND sleep AND* (*polysomnogr* OR architecture OR macrostructure OR structure OR hypnogram OR organization*)", under titles and abstracts, up to 05/25/2018. There were no limits in the search.

2.3. Study selection

After identification and abstract appraisal, reports that met the following exclusion criteria were ruled out: studies focusing on diseases other than epilepsy; presence of other neurological diseases (eg, developmental delay); case reports, review articles, guidelines, opinion statements; age outside the range of 18–65 years; animal studies; and language other than English, Portuguese, Spanish, French and Italian; and duplicates. The remaining studies had their full texts retrieved and were further screened based on additional exclusion criteria: absence of minimal sleep architectural parameters (time spent in REM/NREM sleep, in minutes or percentage of total sleep time or total time in bed); sleep scored as a single stage; sleep structure data limited to a single sleep cycle or only graphically displayed; only individual data reported (group central tendency measures not available for architectural sleep variables); and unavailable full text article even after attempts to contact the author. The remaining reports were subsequently weighed for eligibility and those that met the following criteria were further ruled out: sleep staging methods not standard or not specified; presence of seizures in the 24 h prior to sleep recording; antiepileptic drugs (AEDs) not held stable for at least four weeks prior to sleep recording; and absence of habituation night prior to in-laboratory PSG (single ambulatory/home-PSG was allowed). The remaining studies entered the systematic review, as well as eligible reports identified in their reference sections.

All steps of the selection process were performed independently by two reviewers (PSO and LLN). In the event of discordance, consensus was achieved after discussion with a third more experienced author (MMG).

2.4. Data extraction

After the selection process, data extraction was performed independently by two reviewers (PSO and LLN) and then cross-checked in search for errors. Any corrections were made after agreement between the reviewers. Central tendency and dispersion measures for numerical variables were extracted as presented in the main report.

Variables extracted were:

1. Study variables
   a. First author
   b. Year
   c. Country
   d. Design
   e. Objectives
   f. Inclusion/exclusion criteria
   g. Population and groups studied
   h. Number and category of PSGs performed
   i. Effect sizes and statistical significance of group comparisons, if available
   j. Main findings
2. Epidemiologic and disease variables
   a. Age
   b. Sex
   c. Epilepsy type (focal vs. generalized)
   d. Drug regimen (drug naïve, mono or polytherapy)
   e. EEG findings during the PSG
   f. Comorbidities
3. Sleep variables
   a. Total sleep time (TST)
   b. Wake after sleep onset (WASO) in minutes
   c. Wake after sleep onset (WASO) as a percentage of TST
   d. Total time spent in sleep stages (N1, N2, N3, NREM, R), in minutes
   e. Total time spent in sleep stages, as a percentage of TST
   f. Stage shifts

2.5. Risk of bias

The risk of bias of selected studies was assessed by simple yes/no answers to the following questions based on the Critical Appraisal Skills Program [14] for Case Control studies:

1. Was the research question stated clearly?
2. Were the patients with epilepsy recruited in an acceptable way?
3. Is the control population a non-clinical population?
4. Is the control group adequately described?
5. Was sleep assessed and reported comprehensively?

A positive answer for all questions means that the objectives were clearly stated, patients were consecutively selected, control group comprised of age-matched healthy individuals with no exposure to drugs with CNS action and stage duration (minutes or percentage of TST) were reported in regards to all four sleep stages (N1, N2, N3 and R sleep).

3. Results

A total of 827 reports were identified. Of these, 632 studies were excluded after abstract review. The main reasons for exclusion were type of publication (eg, review articles, opinion statements), population out of the specified age range, animal studies and duplicates. In the screening phase, another 172 studies were excluded after full text review, the main reason being the absence of minimal data on sleep architecture. Twenty-three studies were identified in the screening phase and one additional study identified in reference sections were assessed for eligibility. Ultimately, only five studies met criteria [15–19]. The flowchart with each step of the selection process is presented in Fig. 1.

Overall, a total of 108 patients with epilepsy and 73 healthy controls were evaluated with in-laboratory PSG (two studies) [16,17] or ambulatory/home PSG (three studies) [15,18,19]. Sleep staging was performed according to the American Academy of Sleep Medicine (AASM) criteria [20] in one study [19] and the prior gold standard Rechtschaffen and Kales [21] in the remainder. Four studies aimed to access daytime sleepiness as a primary objective, either in relation to acute effects of a newly introduced AED (two studies) [16,18], chronic AED regimen (one study) [15] or in untreated newly diagnosed patients (one study) [19]. One study aimed to compare sleep architecture and seizure timing during video-EEG (v-EEG) in subgroups of patients with refractory focal epilepsy who were surgical candidates [17]. Data on sleep architecture was retrieved from baseline PSGs prior to new AED initiation in the two studies that assessed acute effects of newly introduced drugs [16,18]. General characteristics of included studies are detailed in Table 1 in order of publication.

3.1. Epidemiologic variables, type of epilepsy and comorbidities

Mean age of subjects ranged from 21.2 ± 1.7 to 38.2 ± 11.4 years in epilepsy patients and 25 ± 1.3 to 30.1 ± 5.7 years in controls. Female

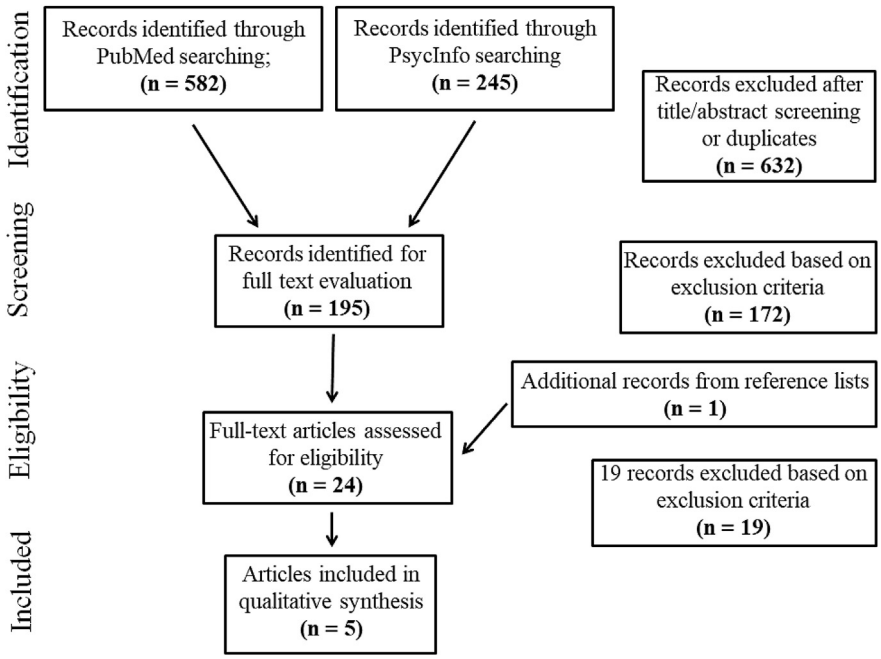

Fig. 1. Paper selection process.

subjects composed epilepsy groups in 55.8% and controls in 28.6%. Only one study did not specify gender composition of subjects [17].

Two studies included patients with refractory focal epilepsies, the majority treated with AED polytherapy. Crespel et al., specified AED regimens in temporal lobe epilepsy (TLE) and frontal lobe epilepsy (TLE) subgroups: valproate (VPA) plus lamotrigine (LMT); carbamazepine (CBZ) plus LMT; CBZ plus vigabatrin (VGB) and LMT [17]. Romigi et al., studied the effects of pregabalin (PGB) on patients with refractory focal epilepsies without reporting localization of the epileptogenic focus. The drug was added to AED regimens that included CBZ, topiramate (TPM), phenobarbital (PB), LMT, VPA and levetiracetam (LVT) [18]. Manni et al., assessed patients with generalized epilepsies on monotherapy with either PB or VPA [15]. Gigli and Maestri studied drug naïve patients with TLE [16] or both focal and generalized epilepsy [19], respectively.

The majority of studies employed exclusion criteria to control for comorbidities that might influence sleep architecture, such as the presence of sleep or mood disorders. However, formal screening instruments were seldom used. Manni's exclusion criteria specified absence of sleep disorders, history of drug abuse and mood disorders, but only the later were formally assessed by the State Trait Anxiety Inventory (STAI)-X2 and IPAT Clinical Depression Questionnaire (CDQ) instruments [15]. Maestri's exclusion criteria included relevant medical or psychiatric disorders or concurrent therapy with drugs that affect sleep or sleepiness and sleep disorders were assessed by sleep history and the Berlin Questionnaire for sleep apnea [19]. Romigi excluded patients with sleep disordered breathing by means of ambulatory sleep monitoring prior to the PSG [18]. The studies of Gigli and Crespel did not report comorbidities [16,17]. No study reported results of EEG during the PSG.

3.2. Sleep architecture

Mean total sleep time (TST) was reported in all studies and ranged from 406.2 ± 28.9 to 493 ± 62 min in epilepsy and 414.4 ± 28.9 to 443 ± 20 in controls. In generalized epilepsies, it ranged from 413.5 ± to 452 ± 19, whereas in focal epilepsies it ranged from 406.2 ± 28.9 to 493 ± 62 min. No study found significant differences between epilepsy and controls or epilepsy subtypes.

Time awake after sleep onset (WASO) was reported in four studies, either as percentage of total sleep time (two studies) [16,18] or absolute time in minutes (two studies) [17,19]. It ranged from 13.6 ± 9.8 to 78.2 ± 5.3 min in epilepsy and 12.3 ± 8.4 to 27.9 ± 18.9 min in controls. Crespel et al., found a higher WASO time in refractory TLE vs. FLE (78.2 ± 5.3 vs. 28.1 ± 2.2; $p < 0.01$) and controls (78.2 ± 5.3 vs. 27.9 ± 18.9; $p < 0.007$) [17].

All studies reported NREM and REM sleep stages as percentage of TST. One study reported only total NREM time without reporting individual stages [17]. The proportion of N1 ranged from 3.1 ± 2.3 to 8.5 ± 4.1 in epilepsy and 7.3 ± 2.9 to 8.5 ± 0.9 in controls. In generalized epilepsies, it ranged from 3.8 ± 0.6 to 7.8 ± 2.4, whereas in focal epilepsies it ranged from 3.1 ± 2.3 to 8.5 ± 4.1, as percentage of TST. Duration of N2 ranged from 38.2 ± 7.1 to 60.4 ± 7.3 in epilepsy and 41.1 ± 6.5 to 50.4 ± 3.1 in controls. In generalized epilepsies, it ranged from 38.7 ± 2.1 to 49.8 ± 2.4, whereas in focal epilepsies it ranged from 38.2 ± 7.1 to 60.4 ± 7.3. Duration of N3 ranged from 22.2 ± 11 to 35 ± 4.3 in epilepsy and 22.4 ± 1.8 to 26 ± 7.1 in controls. In generalized epilepsies, it ranged from 23.8 ± 2.4 to 35 ± 4.3, whereas in focal epilepsies it ranged from 22.2 ± 11 to 33.5 ± 6.9.

Duration of REM sleep ranged from 10.5 ± 6.4 to 21.8 ± 2.1 in epilepsy and 17 ± 4.7 to 20.4 ± 3.7 in controls. In generalized epilepsies, it ranged from 20 ± 2.1 to 21.8 ± 2.1, whereas in focal epilepsies it ranged from 10.5 ± 6.4 to 18.7 ± 7.7. No study found significant differences between epilepsy and controls or between epilepsy types in NREM or REM sleep duration or percentage.

Two studies reported the number of sleep stage shifts. Gigli et al., found a mean number of stage shifts of 201.1 ± 39.9 in drug naïve TLE compared to 176.9 ± 56.4 shifts in controls [16]. Romigi et al., reported mean number of stage shifts of 78.3 ± 40.5 in refractory focal epilepsies [18]. Data are summarized in Table 2.

3.3. Risk of bias

Selected studies included clear statements about research questions and objectives. However, only the paper by Maestri

Table 1
Summary of included studies.

Study (first author, year, design)	Objective	*n*	Population	PSG	Sleep variables	Main findings
Manni, 1993, cross-sectional	Assess daytime sleepiness and psychomotor performance in subjects on chronic PB or VPA	10 PB, 10 VPA, 10 controls	Controlled GE	1 ambulatory	TST, stage %	Not statistically significant trend towards increased daytime sleepiness and impaired psychomotor functions with PB. Sleep parameters comparable between groups.
Gigli, 1997, interventional	Study effects of controlled-release CBZ on nocturnal sleep and daytime somnolence in TLE	7 patients, 9 controls	Drug naïve TLE	1 acclimation, 2 in-lab PSGs	TST, WASO, stage %	Acute CBZ increased daytime sleepiness and sleep stage shifts in controls and increased R stage entries and reduced R % in TLE. Baseline sleep comparable between groups.
Crespel, 1998, retrospective	Compare seizure rate and distribution across sleep stages in TLE and FLE surgical candidates	12 TLE, 10 FLE, 10 controls	Refractory TLE, FLE	1 acclimation, 1 in-lab PSG	TST, WASO, % NREM and R	Seizures more frequent during sleep in FLE and during wake in TLE. TLE had increased WASO and decreased sleep efficiency vs. FE and controls.
Romigi, 2009, interventional	Evaluate add-on PGB on sleep-wake cycle and daytime somnolence in FE	12 patients	Refractory FE	1 acclimation, 1 ambulatory	TST, WASO, stage %	Increased daytime sleepiness and R%, decreased seizures and N2% at 3 mo follow-up.
Maestri, 2013, retrospective	Evaluate daytime sleepiness in newly diagnosed epilepsy	30 FE, 17 GE, 44 controls	Drug naïve GE, FE	1 ambulatory	TST, WASO, stage %	Daytime sleepiness and sleep parameters comparable between groups.

PB: phenobarbital; VPA: valproic acid; CBZ: carbamazepine; PGB: pregabalin; TLE: temporal lobe epilepsy; FLE: frontal lobe epilepsy; GE: generalized epilepsy; FE: focal epilepsy; PSG: polysomnography; TST: total sleep time; WASO: wake after sleep onset; NREM: non-REM sleep; R: REM sleep.

and colleagues [19] reported that the patients were consecutively selected, which was our criteria for acceptable recruitment. The third and fourth questions were related to control group quality and all of the studies had positive evaluations, except for one which did not have a control group [18]. One study [17] had a negative evaluation in the last question because it reported time spent in total NREM sleep without distinction of each NREM stage, which makes difficult a comparison with the remaining studies (see Table 3).

4. Discussion

We performed the first systematic review of sleep architecture in epilepsy. Only five out of over 800 studies referencing sleep architecture were included from the two databases. Strict inclusion criteria were adopted because sleep architecture has great individual variability that is influenced by age, medication, comorbidities and sleep recording and polysomnography staging methodology [22]. Controlling for many of these factors would

Table 2
Sleep architecture in generalized and focal epilepsies.

	Generalized			Focal				
Study, year	Manni et al., 1993[a]	Manni et al., 1993[a]	Maestri et al., 2013	Gigli et al., 1997	Crespel et al., 1998	Crespel et al., 1998	Romigi et al., 2009	Maestri et al., 2013
n, population	10 PHB	10 VPA	17 drug naïve	7 drug naïve	12 TLE	10 FLE	12 FE	30 drug naïve
TST, min	420 ± 17	452 ± 19	413.5 ± 30.3	407.6 ± 18.6	484 ± 79	493 ± 62	433.2 ± 46	406.2 ± 28.9
WASO, min	–	–	13.6 ± 9.8	–	78.2 ± 5.3[b]	28.1 ± 2.2	–	17.9 ± 13.8
WASO, %	–	–	–	5.3 ± 2.4	–	–	3.5 ± 3.9	–
N1, %	3.8 ± 0.6	4 ± 0.6	7.8 ± 2.4	5.5 ± 2.2	–	–	3.1 ± 2.3	8.5 ± 4.1
N2, %	49.8 ± 2.4	38.7 ± 2.1	48.1 ± 3.4	38.2 ± 7.1	–	–	60.4 ± 7.3	49.4 ± 4.7
N3, %	25.7 ± 2.7	35 ± 4.3	23.8 ± 2.4	33.5 ± 6.9	–	–	22.2 ± 11	23.7 ± 3.5
NREM, %	–	–	–	–	81.2 ± 23.4	81.9 ± 19.2	–	–
R, %	20 ± 2.1	21.8 ± 2.1	20.2 ± 3.3	17.6 ± 4.8	18.7 ± 7.7	18.1 ± 6.7	10.5 ± 6.4	18.3 ± 5.2

FE: focal epilepsy; TLE: temporal lobe epilepsy; FLE: frontal lobe epilepsy; PHB: phenobarbital; VPA: valproic acid; TST: total sleep time; WASO: Wake after sleep onset; NREM: non-REM sleep; N1: NREM stage 1; N2: NREM stage 2; N3: NREM stage 3; R: REM.
[a] Mean ± SEM; all other studies reported as mean ± SD.
[b] Significantly higher in TLE vs. FLE, $p < 0.01$.

Table 3
Risk of bias assessment.

Study (first author, year)	Was research question stated clearly?	Were epilepsy patients recruited in acceptable way?	Is control population non-clinical?	Is control group adequately described?	Was sleep assessed and reported comprehensively?
Manni, 1993	Yes	No	Yes	Yes	Yes
Gigli, 1997	Yes	No	Yes	Yes	Yes
Crespel, 1998	Yes	No	Yes	Yes	No
Romigi, 2009	Yes	No	–	–	Yes
Maestri, 2013	Yes	Yes	Yes	Yes	Yes

support that significant group differences are related to epilepsy variables such as epilepsy type or status of disease control.

The only sleep parameter with a significant group difference was reported by Crespel et al., who showed increased WASO in refractory TLE compared to FLE and controls [17]. While they did not report prior seizure burden or other measures of disease status, subsequent video-EEG monitoring with AED reduction showed that the TLE group had a lower seizure frequency compared to FLE. The authors hypothesized this difference may relate to varying pathophysiology in TLE and FLE, and that chronic disruption of sleep in TLE may lead to increased seizures. Notably, they did not assess sleep comorbidities [23]. Given the possibility that the impairment of sleep in TLE relates more to disease mechanisms than to the status of seizure control, AED choices for this group might take into consideration specific pharmacological effects on sleep architecture until further evidence is available. The similarities of sleep architecture between different epilepsy subgroups as well as in comparison to healthy controls (which were found in four out of five studies in this review) highlight the limitation of standard PSG metrics to mirror complaints frequently seen in clinical practice. These traditional measures may not fully capture the complexity of sleep regulation [24].

The first night effect has been described in epilepsy when sleep was assessed by in-lab PSG [25,26]. In this systematic review, three out of five selected studies assessed sleep by ambulatory PSG and two of those did not register a prior acclimation night. Although it is possible that first night effect played a role in those cases, there is some evidence indicating that ambulatory PSG is not associated with first night effect in healthy individuals [27]. As this effect is expected to be a consequence of environment unfamiliarity and is not present in healthy subjects, it is fair to assume that epilepsy patients would not experience it either.

Despite the fact that studies were highly selected, they are still heterogeneous in regard to objectives and hypothesis, which precluded a meta-analysis. Although the association between sleep and epilepsy has long been recognized and the standards of PSG established half a century ago [21], there are still knowledge gaps in how epileptic networks and therapies impact sleep. Further investigation is required given the emerging role of sleep therapies as beneficial on epilepsy outcomes. The assessment of sleep stage dynamics in epilepsy might bring new insights on this topic, as has recently been the case in other conditions [28,29].

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Conflict of interest

The authors have no conflicts of interest to declare.

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