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Vigilance and circadian function in daytime and nocturnal epilepsy compared to controls

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ABSTRACT

Background: People with epilepsy often experience daytime vigilance problems and fatigue. This may be related to disturbed sleep due to nocturnal seizures.
Aim: To compare subjective and objective markers of vigilance and circadian function in adults with epilepsy with nocturnal seizures to those with daytime seizures and healthy controls and to identify determinants of impaired daytime vigilance in epilepsy in an explorative study.
Methods: We included 30 adults with epilepsy (15 with daytime seizures and 15 with nocturnal seizures), and 15 healthy controls. All participants filled out the Epworth sleepiness scale (ESS), fatigue severity scale (FSS), Pittsburgh sleep quality index (PSQI) and the Munich chronotype questionnaire (MCTQ). Each participant performed two trials of the sustained attention to response task (SART) as a measure of vigilance, and had a post-illumination pupil response (PIPR) assessment as a marker for the circadian function.
Results: Both epilepsy groups reported more fatigue on the FSS than healthy controls ($p < .001$) and had higher SART error scores ($p = .026$). The poorer FSS and SART scores were most prominent among those with nocturnal seizures. The ESS, PSQI, MCTQ and the primary PIPR outcome did not differ between groups. Having nocturnal seizures ($p = .010$) and using more antiseizure medications ($p = .004$) were related to increased SART error scores.
Conclusions: Nocturnal epilepsy is associated with poorer vigilance, indicating lower quality of wake time. We could not relate this to circadian dysfunction. Further studies should focus on vigilance problems in people with nocturnal epilepsy and explore interventions to improve the quality of wake time.

1. Introduction

Daytime fatigue and vigilance problems are common but poorly understood, incapacitating, and multifaceted symptoms in epilepsy (Kwon et al., 2017; Englot et al., 2020; Lagogianni et al., 2021). These impairments may result from various factors, including poor sleep quality due to nocturnal seizures, comorbid sleep disorders, or related to antiseizure medications (Loring and Meador, 2001; Kwon and Park, 2016). Another mechanism may be the circadian modulation of vigilance, which may be altered in epilepsy (Hofstra and de Weerd, 2009; Kreitlow et al., 2022).

The circadian modulation of vigilance is driven by the suprachiasmatic nucleus (SCN) of the hypothalamus (Moore et al., 1995). The SCN receives information on environmental light levels from intrinsically photosensitive retinal ganglion cells expressing the photopigment melanopsin. These cells also modulate the pupillary light reflex (Lucas et al., 2001), and their function can be assessed by measuring the sustained pupil constriction after blue light, termed "Post-Illumination Pupil Response" (PIPR) (Gamlin et al., 2007). Individual differences in PIPRs are associated with individual differences in the circadian phase (van der Meijden et al., 2016). The relationship between epilepsy and circadian modulation of vigilance is unknown.

We compared daytime vigilance problems using a computer task among individuals with epilepsy with exclusively daytime seizures, those with exclusively nocturnal seizures, and healthy controls. We expected that those with nighttime seizures would have most vigilance problems. We also explored possible determinants of impaired vigilance in epilepsy, including seizure patterns, clinical characteristics and

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subjective and objective measures of circadian function.

2. Material and methods

2.1. Participants

Between March and December 2019, we screened people with focal epilepsy aged 18 years and older attending our outpatient clinic. Eligible individuals had to have at least one focal seizure per month and to use at least one antiseizure medication. Exclusion criteria were a recent (< 8 weeks) change in vigilance-influencing medications, any self-reported eye disease, colour vision deficiency as determined with the Richmond Hardy-Rand-Rittler 2002 test (Cole et al., 2006), use of any eye drops, a known comorbid sleep disorder, or an inability to sit. We recruited 30 subjects with epilepsy: 15 with only daytime seizures within the past year and 15 with only nocturnal seizures within the past year. We recruited a group of 15 age (± 5 years) and sex-matched healthy controls amongst peers of clinic attendees. Controls had no chronic medical condition and none of the exclusion criteria.

The ethical committee of Leiden University Medical Centre approved the study protocol. All participants provided informed consent.

2.2. Procedure

The one-hour test battery was assessed after a routine clinical appointment in the morning and consisted of the following measurements.

2.2.1. Questionnaires

The validated questionnaires included:

(1) Epworth Sleepiness Scale (ESS), measures daytime sleepiness with a score range 0–24, with a score ≥ 10 indicating clinically significant daytime sleepiness (Johns, 1991).
(2) Fatigue Severity Scale (FSS), determines daytime fatigue with nine questions with a mean total score of 1–7, with a higher total score indicating more fatigue (Krupp et al., 1989).
(3) Pittsburgh Sleep Quality Index (PSQI), assesses subjective sleep quality with a total score of 0–21, with higher scores indicating worse sleep quality (Buysse et al., 1989).
(4) The Munich Chronotype Questionnaire (MCTQ) assesses subjective circadian rhythm and preferences. It evaluates the mid-point of sleep on free days corrected for sleep debt on work days (MSFsc) (Roenneberg et al., 2003).

2.2.2. Sustained Attention to Response Task (SART)

The SART is an objective measure of vigilance, which was assessed twice. It is a computerized go/no go task of 4 min and 20 s (Robertson et al., 1997) and is administered in a quiet room with dimmed lights. During the task, numbers from 1 to 9 appear 225 times on the computer screen in random order and in different sizes. Each number is presented for 250 ms, followed by a black screen for 900 ms. Participants were instructed to respond to all numbers (targets) by pressing a key, except for the number 3 (non-target), and to value accuracy as crucial as response speed. Participants practiced once in advance. The total error score was the sum of commissions (response to non-target) and omissions (no response to a target).

2.2.3. Post-Illumination Pupil Response (PIPR)

We used a 15-minute PIPR protocol to objectively assess circadian function. As light exposure to one eye results in the dilatation of both eyes, the right eye was exposed to the light and the left pupil diameter was continuously recorded using an infrared LED light and a digital camera. We first exposed both eyes to mesopic (dimmed) lighting for three minutes. The right eye was then exposed to darkness for one minute, followed by red light (wavelength 660 nm) for 20 s and two minutes of darkness. After this, we illuminated both eyes for three minutes with mesopic lighting, followed by one minute of darkness. The right eye was then exposed to 20 s of blue light (wavelength 470 nm) and two minutes of darkness. The maximum intensities of the light sources were well below the American National Standard (ANSI-2007) recommendations for red, blue and infrared illumination. Details and background of the paradigm for PIPR assessments have been described elsewhere (van der Meijden et al., 2015).

We calculated the maximal pupil contraction, expressed as a proportion (%) from the baseline pupil diameter during red or blue light stimulation (Max CA% red/blue); and the sustained contraction in % from the baseline at the 20th second of red or blue light stimulation (Sustained% CA red/blue) (Herbst et al., 2012). We defined Max CA% blue as the primary PIPR outcome as it is most sensitive to circadian modulation (van der Meijden et al., 2016).

2.3. Analyses

We compared the three groups (epilepsy with daytime seizures, epilepsy with nocturnal seizures, healthy controls) for demographic and disease characteristics using Chi square, Mann-Whitney's U test, or ANOVA with Tukey's post-hoc analysis, depending on scale properties. Then, ANOVA with Tukey's post-hoc analysis were conducted for the PIPR and questionnaire outcomes. As the SART was assessed twice, we applied repeated measures random effects mixed model to analyze differences in SART outcomes between groups. We used backward elimination linear regression model to identify possible determinants, including age, gender, antiseizure medication use, all questionnaire outcomes, and all PIPR outcomes as independent variables. We used SPSS version 26.0 and an α-value of.05 for statistical significance.

3. Results

The demographic and disease characteristics of the 45 participants are shown in Table 1. None of these characteristics differed significantly between groups.

Assessments outcomes are shown in Table 2. Fatigue (FSS) was significantly different between all groups (nocturnal seizures: 4.5 ± 1.3; daytime seizures: 3.9 ± 1.2; healthy controls: mean 2.6 ± 1.2, $p < .001$). Self-reported sleepiness (ESS), sleep quality (PSQI) and circadian preferences (MCTQ) did not differ between groups. Both epilepsy groups made more SART errors than the healthy controls. This difference was mainly due to the worse scores of the nocturnal seizure group (healthy controls 10.1 ± 5.6 vs. nocturnal seizures 15.9 ± 8.8, $p = .011$), see also Fig. 1. The maximum pupil contraction percentage after exposure to red light was near-significantly different between groups ($p = .059$). Post-hoc analysis showed significantly higher constriction in those with nocturnal seizures than those with daytime seizures (mean 46.8 ± 5.9 vs. 51.4 ± 4.0, $p = .046$). The main PIPR outcome (Max CA% blue) was also the highest in the group with nocturnal seizures but not significantly different between groups.

Two significant factors were related to worse SART scores using the regression model (model fit R^2 =.36): having nocturnal seizures ($\beta = 7.00$; SE=2.50; $p = .010$) and the number of antiseizure medications ($\beta = 3.57$; SE=1.12; $p = .004$).

4. Discussion

We confirmed the increased prevalence of fatigue among people with epilepsy (Kwon et al., 2017; Lagogianni et al., 2021). Interestingly, we found no association between self-reported fatigue and impaired vigilance, thus underscoring that these domains only partly overlap. We found that a higher ASM load predisposes to poorer vigilance, and postulate that vigilance impairments may partly explain the increased prevalence of fatigue in epilepsy. The majority of ASMs exhibit a clear dose response effect for the fatigue and cognitive side effects (Sarkis

Table 1
Demographics and clinical characteristics per group, N = 45.

	Healthy controls (HC), n = 15	Epilepsy – total group, n = 30	Epilepsy – Daytime seizures (DS), n = 15	Epilepsy – Nocturnal seizures (NS), n = 15	HC vs. Epilepsy total group	Epilepsy DS vs. NS
Gender: males, n (%)	7 (46.7)	17 (56.7)	8 (53.3)	9 (60.0)	χ^2 (1)= .40, p = .526	χ^2(1) = .14, p = .713
Age, mean (SD) range	48.2 (13.5) 28–67	40.4 (13.3) 21–74	39.8 (15.1) 21–74	40.9 (11.7) 22–64	F(1)= 3.45, p = .070	F(1)= .05, p = .820
Epilepsy type, n (%)					-	χ^2(3) = 5.42, p = .144
• Frontal	-	5 (16.6)	1 (6.7)	4 (26.7)		
• Temporal	-	5 (16.6)	4 (26.7)	1 (6.7)		
• Fronto-temporal	-	9 (30.0)	6 (40.0)	3 (20.0)		
• Other	-	11 (36.7)	4 (26.7)	7 (46.7)		
Epilepsy duration in years, median (IQR) range	-	17 (19) 2–42	15 (18) 2–29	18 (28) 2–42	-	U(1)= 134.5, p = .360
Seizure frequency per month, median (IQR) range	-	9.5 (28) 1–552	18.0 (52) 1–552	5.0 (12) 1–140	-	U(1)= 72.5, p = .098
Number of ASMs, median (IQR) range	-	2 (1) 1–5	2 (1) 1–5	2 (1) 1–5	-	U(1)= 74.5, p = .116
Self-reported hours of sleep night before assessments, mean (SD) range	6.4 (1.5) 3.0–9.0	7.2 (1.8) 2.0–12.0	6.8 (1.6) 2.0–8.5	7.6 (2.0) 3.0–12.0	F(1)= 1.92, p = .169	F(1)= 1.44, p = .240

ASM=anti-seizure medication; χ2 = Chi square testing; F=parametric testing using ANOVA; U=non-parametric testing using Mann-Whitney's.

Table 2
Assessment outcomes per group, N = 45.

	Healthy controls (HC), n = 15	Epilepsy – total group, n = 30	Epilepsy – Day-time seizures (DS), n = 15	Epilepsy – Nocturnal seizures (NS), n = 15	HC vs. Epilepsy total group Statistic, p-value [95% CI]	HC vs. epilepsy DS vs. epilepsy NS Statistic, p-value [95% CI]
Subjective questionnaires						
Sleepiness: ESS score, mean (SD) range	6.0 (4.6) 0–14	8.2 (4.2) 2–21	7.1 (3.6) 2–12	9.3 (4.5) 2–21	F(1)= 2.52, p = .120 [.000 to.220]	F(2)= 2.29, p = .114 [.000 to.259]
Fatigue: FSS, mean (SD) range	2.6 (1.2) 1.6–6.2	4.2 (1.3) 1.2–6.6	3.9 (1.2) 1.9–5.8	4.5 (1.3) 1.2–6.6	F(1)= 18.41, p < .001 * [.090 to.479]	F(2)= 10.24, p < .001[a] [.093 to.492]
Sleep quality: PSQI, mean (SD) range	4.87 (2.72) 2–13	6.7 (3.0) 1–14	6.6 (3.3) 2–14	6.8 (2.8) 1–12	F(1)= 3.97, p = .053 [.000 to.261]	F(2)= 1.96, p = .154 [.000 to.242]
Circadian rhythm: MCTQ, mean MFSsc time (SD)	3:43 (0:35)	3:34 (1:08)	3:30 (1:07)	3:38 (1:10)	F(1)= 0.00, p = .974 [.000 to.002]	F(2)= 0.07, p = .930 [.000 to.045]
Objective assessments						
Vigilance: SART (repeated measures) total Errors, mean (SD) range	10.1 (5.6) 1–29	13.9 (8.3) 0–29	12.0 (7.3) 2–30	15.9 (8.8) 0–29	F(1)= 5.12, p = .026 * [.459 to 7.090]	F(2)= 4.71, p = .011[b] [.063 to 9.468]
Circadian modulation: PIPR in mm, mean (SD)						
– Max CA% red	49.0 (5.11)	49.1 (5.5)	46.8 (5.9)	51.4 (4.0)	F(1)= 0.01, p = .936 [.000 to.040]	F(2)= 3.04, p = .059[c] [.000 to.294]
– Sustained CA% red	38.4 (5.0)	38.0 (8.5)	37.1 (8.4)	38.9 (8.7)	F(1)= 0.03, p = .858 [.000 to.074]	F(2)= 0.22, p = .805 [.000 to.094]
– Max CA% blue (= main PIPR outcome)	54.9 (4.9)	57.1 (5.1)	56.2 (5.7)	58.2 (4.3)	F(1)= 1.95, p = .170 [.000 to.201]	F(2)= 1.68, p = .199 [.000 to.226]
– Sustained CA% blue	52.4 (7.7)	55.0 (6.4)	53.4 (7.1)	56.5 (5.5)	F(1)= 1.48, p = .231 [.000 to.187]	F(2)= 1.51, p = .234 [.000 to.220]

SART = Sustained Attention to Response Task; ESS= Epworth Sleepiness Scale; FSS= the Fatigue Severity Scale; PSQI= Pittsburgh Sleep Quality Index; MCTQ= Munich Chronotype Questionnaire; PIPR= Post-Illumination Pupil Response; Max CA% = Maximal pupil contraction % difference from the baseline pupil diameter; Sustained CA% = Sustained pupil contraction % difference from the baseline pupil diameter at the 20th second of light exposure; F= parametric testing using ANOVA; CI= confidence interval.
* Significant with p < .05. Tukey's HSD post-hoc test showed a significant difference between: [a] HC and both epilepsy groups; [b] HC and epilepsy NS; [c] epilepsy DS and epilepsy NS.

et al., 2018). Monitoring vigilance in ASM trials may be of interest by adding more specific biomarkers for this common adverse event. The SART is a useful and easy-to-perform tool to assess vigilance impairments (Van Schie et al., 2012).

Other studies found that alterations in circadian function are a vital driver in explaining seizure patterns (Kreitlow et al., 2022). Our main markers for circadian function did not differ significantly between groups. The main PIPR outcome showed a trend, with suboptimal

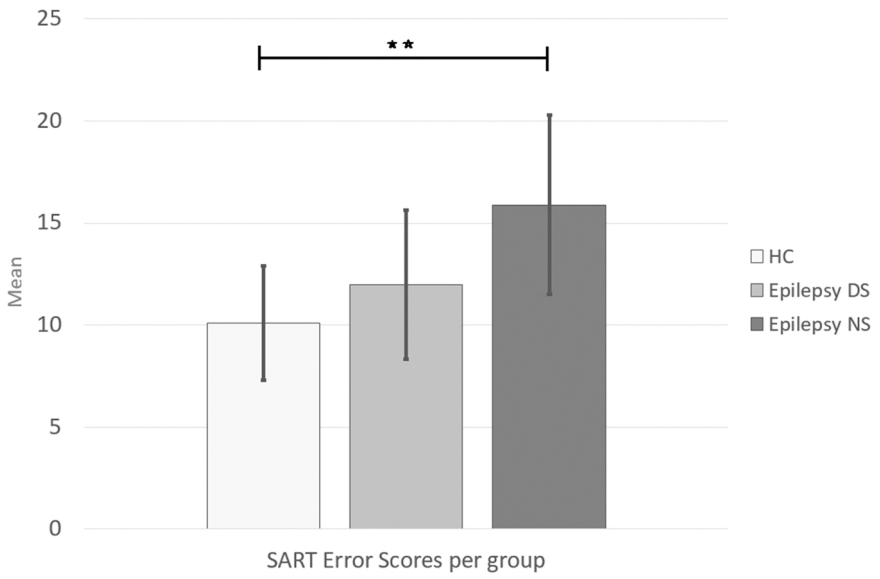

Fig. 1. Vigilance problems across groups, including 30 adults with epilepsy (15 with daytime seizures and 15 with nocturnal seizures), and 15 healthy controls. Vertical lines represent standard deviations. SART = Sustained Attention to Response Task; HC= healthy controls; DS= day-time seizures; NS= night-time seizures. * * $p < .001$.

outcome in those with nocturnal seizures but given the small sample size, we cannot exclude a relevant difference. The maximum contraction after *red* light was different between the epilepsy groups, yet the relevance of this finding is unknown.

The sample size limits our explorative study. Also, seizure diaries highly underestimate the seizure burden and frequency, hence we cannot confirm the exclusive nocturnal or diurnal seizure patterns with certainty (Hoppe et al., 2007). Lastly, the self-reported sleep duration seemed shorter in the healthy controls, however non-significantly. The impact of sleep duration on vigilance has not been taken into account in this study. Extensive studies including objective measurements of sleep and circadian rhythm are needed to improve the clinical profiling and to understand how vigilance impairments impact daily life in individuals with epilepsy.

5. Conclusion

People with epilepsy reported more fatigue and had more daytime vigilance problems. Despite the small sample size, nocturnal seizures and ASMs were both related to impaired vigilance. We did not find contrasts in our subjective and objective markers for circadian function. Further studies should pay more attention to the marked vigilance problems in people with nocturnal epilepsy and explore interventions to improve the quality of wake time.

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Declaration of Competing Interest

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