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Investigating Sleep Disturbances and Cognitive Decline in Adults With Drug-Resistant Temporal Lobe Epilepsy

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ABSTRACT

Background: *Drug-resistant temporal lobe epilepsy (DR-TLE) is frequently accompanied by cognitive impairment and sleep disturbances, yet their interrelationship remains insufficiently characterized using objective sleep metrics. Disrupted slow-wave sleep, sleep fragmentation, interictal epileptiform discharges (IEDs), and obstructive sleep apnea (OSA) may mechanistically contribute to memory and executive dysfunction beyond seizure burden alone.* ***Objective:*** *To evaluate the association between polysomnographically measured sleep abnormalities and domain-specific cognitive impairment in adults with DR-TLE.* ***Methods:*** *In this cross-sectional observational study, 124 adults with confirmed DR-TLE underwent overnight polysomnography and comprehensive neuropsychological assessment. Primary exposures included slow-wave sleep (N3%), sleep efficiency, arousal index, NREM IED frequency, and OSA (AHI ≥15). Outcomes were standardized z-scores across memory, executive, processing speed, and working memory domains. Multivariable linear and logistic regression models adjusted for age, education, epilepsy duration, seizure frequency, depressive symptoms, and antiseizure medication burden.* ***Results:*** *Mean N3 sleep was reduced (12.6% ± 5.3), and 29.8% had moderate–severe OSA. Verbal memory (mean z −1.28) and executive function (−1.12) were most impaired. Reduced N3 independently predicted poorer verbal memory (β = 0.32, p = 0.001) and increased odds of multidomain impairment per 5% decrement (OR 1.67, 95% CI 1.21–2.31). Higher NREM IED frequency was associated with executive dysfunction (β = −0.29, p = 0.002), and OSA doubled odds of multidomain impairment (OR 2.41, 95% CI 1.08–5.39).* ***Conclusion:*** *Objective sleep abnormalities, particularly reduced slow-wave sleep, elevated nocturnal IEDs, and OSA, are independently associated with cognitive impairment in DR-TLE, underscoring the need for integrated sleep evaluation in comprehensive epilepsy care.*

Keywords: *Drug-resistant temporal lobe epilepsy; Slow-wave sleep; Cognitive impairment; Interictal epileptiform discharges; Obstructive sleep apnea; Polysomnography*

INTRODUCTION

Temporal lobe epilepsy (TLE) is the most prevalent form of focal epilepsy in adults and is frequently associated with structural and functional abnormalities of mesial temporal structures critical for memory processing (1). Despite advances in antiseizure pharmacotherapy, approximately 30–40% of individuals with epilepsy develop drug-resistant epilepsy (DRE), defined by the International League Against Epilepsy as failure of adequate trials of two appropriately chosen and tolerated antiseizure medications to achieve sustained seizure freedom (2). Within this subgroup, drug-resistant temporal lobe epilepsy (DR-TLE) represents a particularly vulnerable clinical phenotype characterized not only by persistent seizures but also by substantial neurocognitive morbidity. Memory impairment, especially in

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declarative domains, is consistently documented in mesial TLE, with lateralization effects influencing the predominance of verbal versus visuospatial deficits (3,7). However, converging evidence suggests that the cognitive phenotype extends beyond hippocampal dysfunction to involve executive processes, attention, and processing speed, implicating broader frontotemporal and network-level disruption (8). These cognitive impairments significantly compromise functional independence, psychosocial outcomes, and long-term quality of life, thereby positioning cognition as a co-primary outcome alongside seizure control in DR-TLE management.

Parallel to cognitive dysfunction, sleep disturbances are highly prevalent yet under-recognized comorbidities in epilepsy. Physiologically, sleep and epilepsy share bidirectional neurobiological mechanisms; non-rapid eye movement (NREM) sleep promotes neuronal synchronization that may facilitate interictal epileptiform discharges, whereas sleep deprivation lowers seizure threshold and increases cortical excitability (4,10). Objective polysomnographic studies demonstrate that patients with drug-resistant focal epilepsy, including DR-TLE, exhibit reduced sleep efficiency, increased wake after sleep onset, fragmentation of NREM sleep, and diminished slow-wave sleep (SWS) and rapid eye movement (REM) sleep proportions (9). Moreover, comorbid sleep-disordered breathing, particularly obstructive sleep apnea (OSA), appears more prevalent in refractory epilepsy populations compared with the general population, contributing to intermittent hypoxia and further sleep instability (11). These macro- and microarchitectural sleep abnormalities are not benign epiphenomena; they directly intersect with neural systems governing memory consolidation and executive control.

Experimental and clinical neuroscience literature has established that sleep—particularly SWS—is critical for hippocampal–neocortical dialogue underlying systems-level memory consolidation (5,6). During physiological NREM sleep, coordinated slow oscillations, thalamocortical spindles, and hippocampal sharp-wave ripples facilitate the reactivation and redistribution of newly encoded information. In TLE, however, the epileptogenic hippocampus generates interictal epileptiform discharges (IEDs) that may disrupt this coordinated oscillatory coupling, thereby interfering with sleep-dependent memory consolidation processes (12). Although much of the mechanistic evidence derives from mixed epilepsy cohorts and experimental paradigms rather than exclusively DR-TLE populations, the biological plausibility of sleep-mediated cognitive impairment is compelling. Furthermore, emerging neuroimaging perspectives highlight the glymphatic system—a perivascular clearance pathway most active during deep NREM sleep—as a potential contributor to long-term neurobiological vulnerability when SWS is chronically reduced (5,22). While direct human evidence linking glymphatic dysfunction to cognitive trajectories in DR-TLE remains limited, impaired sleep-dependent clearance of metabolic byproducts represents a plausible pathway through which chronic sleep disruption may exacerbate neurodegenerative processes and executive dysfunction (14).

From a PICO-oriented framework, the population of interest comprises adults with drug-resistant temporal lobe epilepsy; the exposure is objectively and subjectively measured sleep disturbance, including macroarchitectural alterations, microstructural instability, and comorbid sleep disorders; the comparison, when applicable, includes individuals with controlled TLE or normative sleep parameters; and the outcomes encompass domain-specific cognitive impairment, particularly memory, executive function, attention, and processing speed. Although individual bodies of literature have independently documented cognitive deficits in TLE (3,7,8) and sleep abnormalities in refractory epilepsy (9,11), research explicitly integrating these domains in DR-TLE remains fragmented. A critical methodological limitation in the field is the predominance of cross-sectional designs, which

constrain inference regarding temporal precedence and causality (19). Additionally, heterogeneity in sleep measurement (polysomnography versus questionnaires), variability in neuropsychological batteries, and inadequate control for confounders such as polypharmacy, depression, and antiseizure medication effects complicate interpretation (20). Consequently, while associations between poor sleep and worse cognitive performance are consistently observed, it remains unclear whether sleep disruption independently predicts cognitive impairment, mediates seizure-related effects, or simply co-occurs due to shared neuropathology.

This gap is clinically significant. If sleep disturbance functions as a modifiable mediator of cognitive impairment in DR-TLE, then targeted sleep interventions—such as treatment of OSA, optimization of sleep hygiene, or chronotherapeutic medication strategies—could meaningfully alter cognitive outcomes beyond seizure reduction alone. Conversely, if sleep abnormalities primarily reflect underlying epileptogenic network dysfunction without independent contribution, therapeutic prioritization may differ. Clarifying this relationship therefore has direct implications for multidisciplinary epilepsy management and for the design of future longitudinal and interventional studies.

Accordingly, the objective of this narrative review is to synthesize and critically evaluate current evidence regarding the relationship between sleep disturbances and cognitive impairment in adults with drug-resistant temporal lobe epilepsy, with particular emphasis on mechanistic pathways, strength of evidence, and clinical implications. Specifically, this review addresses the following research question: In adults with drug-resistant temporal lobe epilepsy, to what extent are objectively measured sleep disturbances associated with domain-specific cognitive impairment, and what biological mechanisms plausibly mediate this relationship?

METHODS

This study was designed as a cross-sectional observational investigation to examine the association between objectively measured sleep disturbances and domain-specific cognitive impairment in adults with drug-resistant temporal lobe epilepsy (DR-TLE). A cross-sectional framework was selected to allow comprehensive phenotyping of sleep architecture and neuropsychological performance within a defined time window, while enabling evaluation of multivariable associations between sleep parameters and cognitive outcomes under real-world clinical conditions (23). The study was conducted at a tertiary epilepsy referral center with integrated neurophysiology and sleep laboratory facilities between January 2022 and December 2023. All assessments were performed in accordance with standardized clinical and research protocols to ensure methodological consistency across participants.

Eligible participants were adults aged 18–60 years with a diagnosis of unilateral or bilateral temporal lobe epilepsy confirmed by clinical semiology, prolonged video-electroencephalography (EEG), and structural neuroimaging, and meeting International League Against Epilepsy criteria for drug-resistant epilepsy, defined as failure of at least two appropriately chosen and tolerated antiseizure medication regimens (2). Only individuals with a minimum epilepsy duration of two years were included to reduce misclassification of early treatment resistance. Exclusion criteria comprised prior epilepsy surgery, progressive neurological disorders, intellectual disability (IQ <70), active substance use disorder, unstable psychiatric illness requiring hospitalization within the preceding six months, shift-work sleep schedules, and use of sedative-hypnotic medications initiated within three months before enrollment. Patients with previously diagnosed and adequately treated obstructive sleep apnea (OSA) were included, provided treatment adherence could be objectively verified.

Participants were consecutively screened from outpatient epilepsy clinics and inpatient monitoring units to minimize selection bias. All eligible individuals received detailed verbal and written information regarding study procedures, and written informed consent was obtained prior to participation.

Data collection was conducted over two structured visits within a four-week window to reduce temporal variability. Demographic and clinical variables were recorded using standardized case report forms, including age, sex, educational attainment (years of formal education), age at epilepsy onset, epilepsy duration, seizure frequency over the preceding six months (self-reported and corroborated by seizure diaries), lateralization of epileptogenic focus, magnetic resonance imaging findings, and current antiseizure medication regimen quantified as number of agents and defined daily dose equivalents. Depressive symptoms were assessed using the Beck Depression Inventory-II, and anxiety symptoms using the Generalized Anxiety Disorder-7 scale, given their established association with both sleep disturbance and cognitive complaints (20). Excessive daytime sleepiness was screened using the Epworth Sleepiness Scale (11).

Objective sleep assessment was performed using overnight in-laboratory polysomnography (PSG) conducted according to American Academy of Sleep Medicine scoring criteria (24). Recorded parameters included total sleep time, sleep efficiency, sleep latency, wake after sleep onset (WASO), percentage of NREM stage N1, N2, N3 (slow-wave sleep), REM sleep percentage, arousal index, apnea–hypopnea index (AHI), oxygen desaturation index, and periodic limb movement index. Sleep spindles and slow oscillation density were quantified using automated validated algorithms applied to central EEG derivations, with manual verification by a board-certified sleep specialist blinded to cognitive outcomes. Interictal epileptiform discharges (IEDs) during sleep were quantified from simultaneous EEG channels and expressed as IED frequency per hour of NREM sleep (12). Actigraphy was additionally performed for seven consecutive days to assess habitual sleep duration and circadian regularity.

Neuropsychological assessment was administered within seven days of PSG by trained neuropsychologists blinded to sleep results. The cognitive battery was selected to capture domains most frequently affected in TLE (3,7,8). Verbal memory was assessed using the Rey Auditory Verbal Learning Test (immediate recall, delayed recall, recognition), visuospatial memory using the Rey–Osterrieth Complex Figure Test (delayed recall), executive function using the Trail Making Test Part B, Stroop Color–Word Test, and Wisconsin Card Sorting Test, attention and processing speed using the Trail Making Test Part A and Digit Symbol Substitution Test and working memory using the Digit Span backward task. Raw scores were converted to age- and education-adjusted standardized z-scores based on normative data. Global cognitive impairment was operationally defined as performance $\geq$1.5 standard deviations below normative means in at least two cognitive domains, whereas domain-specific impairment was defined as a z-score ≤ -1.5 within that domain.

The primary independent variables were objective PSG-derived sleep parameters, particularly sleep efficiency, percentage of slow-wave sleep (N3), REM sleep percentage, arousal index, and IED frequency during NREM sleep. Secondary exposure variables included presence of OSA defined as AHI $\geq$15 events/hour and excessive daytime sleepiness defined as Epworth score >10 (11). The primary outcome variable was domain-specific cognitive performance (continuous z-scores), with secondary outcomes including categorical cognitive impairment status. Covariates included age, sex, education, epilepsy duration, seizure frequency, lateralization, depressive symptom score, number of antiseizure medications, and presence of OSA.

To address potential sources of bias and confounding, several strategies were implemented. Consecutive sampling minimized selection bias, and blinding of neuropsychological assessors to PSG findings reduced information bias. Standardized scoring criteria and validated instruments enhanced measurement reliability (24). Multivariable regression modeling was prespecified to adjust for demographic and clinical confounders known to influence cognition and sleep (20). Sensitivity analyses were conducted excluding participants with moderate-to-severe depressive symptoms to evaluate robustness of associations. Multicollinearity among predictors was assessed using variance inflation factors, and model assumptions were verified through residual diagnostics.

The sample size was calculated a priori using G*Power software based on detection of a moderate effect size ($f^2 = 0.15$) in multiple linear regression with up to ten predictors, $\alpha = 0.05$, and power $(1-\beta) = 0.80$, yielding a minimum required sample of 118 participants. To account for potential incomplete datasets, recruitment targeted at least 130 participants. Missing data were handled using multiple imputation by chained equations under the assumption of missing at random, incorporating all variables included in the analytic model. Imputed datasets were pooled according to Rubin's rules.

Statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY) and R version 4.2. Continuous variables were examined for normality using the Shapiro–Wilk test and visual inspection of histograms. Between-group comparisons (e.g., OSA vs non-OSA) were conducted using independent-samples t-tests or Mann–Whitney U tests as appropriate. Associations between sleep parameters and cognitive z-scores were initially explored using Pearson or Spearman correlation coefficients. Multivariable linear regression analyses were then conducted to estimate adjusted associations between sleep architecture variables and domain-specific cognitive performance. Logistic regression models were used for binary cognitive impairment outcomes. Interaction terms were introduced to explore potential effect modification by lateralization of seizure focus and OSA status. A two-tailed p-value <0.05 was considered statistically significant. False discovery rate correction was applied to account for multiple comparisons across cognitive domains.

The study protocol was approved by the Institutional Review Board of the hosting institution and conducted in accordance with the Declaration of Helsinki (25). All participants provided written informed consent prior to enrollment. Data were anonymized using unique study identifiers and stored on encrypted, password-protected servers accessible only to authorized study personnel. Double data entry procedures and periodic internal audits were implemented to ensure data accuracy and reproducibility. The full study protocol, statistical analysis plan, and de-identified dataset structure were archived to facilitate independent verification and replication of findings.

RESULTS

The final analytic cohort comprised 124 adults with confirmed drug-resistant temporal lobe epilepsy who completed both polysomnography and neuropsychological testing. Participants had a mean age of 34.8 ± 9.6 years (95% CI 33.1–36.5), and 72/124 were female (58.1%; 95% CI 49.3–66.5). Mean educational attainment was 13.6 ± 3.2 years (95% CI 13.0–14.2). Epilepsy duration averaged 13.2 ± 7.4 years (95% CI 11.9–14.5), with a median monthly seizure frequency of 3 (IQR 2–6). Polytherapy was common, with 88/124 (71.0%; 95% CI 62.5–78.3) receiving ≥2 antiseizure medications. Lateralization was slightly left-predominant (left TLE focus 67/124; 54.0%; 95% CI 45.2–62.6). Clinically relevant sleep-disordered breathing was frequent; moderate-to-severe obstructive sleep apnea (OSA; AHI ≥15 events/hour) was observed in 37/124 (29.8%; 95% CI 22.2–38.5). Depressive symptom burden was non-trivial

(BDI-II mean 16.4 ± 8.1; 95% CI 15.0–17.8), reinforcing the importance of confounding control in downstream models. Polysomnography demonstrated marked abnormalities in sleep continuity and architecture across the cohort. Mean total sleep time was 362.4 ± 54.8 minutes (95% CI 352.5–372.3), significantly lower than normative reference expectations (Cohen's d = −1.06; p < 0.001). Sleep efficiency averaged 78.3 ± 8.7% (95% CI 76.8–79.8), indicating clinically relevant sleep fragmentation (d = −0.85; p < 0.001), which was concordant with elevated wake after sleep onset (WASO) of 68.1 ± 28.5 minutes (95% CI 63.0–73.2; d = 0.98; p < 0.001). Critically, slow-wave sleep (N3) comprised only 12.6 ± 5.3% of total sleep time (95% CI 11.6–13.6), representing a substantial reduction relative to typical adult ranges (d = −0.92; p < 0.001). REM sleep was also reduced, with a mean of 17.9 ± 6.4% (95% CI 16.8–19.0; d = −0.48; p = 0.002). Microarousal burden was high, reflected by an arousal index of 19.4 ± 7.2 events/hour (95% CI 18.1–20.7; d = 1.31; p < 0.001). Interictal epileptiform discharge activity during NREM sleep showed substantial between-patient variability, with a mean IED frequency of 14.8 ± 9.5 events/hour NREM (95% CI 13.1–16.5), supporting the biological plausibility of sleep-stage-specific network disruption in this population.

Neuropsychological performance showed broad impairment with particular concentration in memory and executive domains. Mean verbal memory performance was −1.28 ± 0.88 z (95% CI −1.43 to −1.13), with 52/124 (41.9%) meeting the impairment threshold (≤−1.5 SD); the departure from normative expectation was large (Cohen's d = −1.28; p < 0.001). Visual memory was also reduced (−0.96 ± 0.74 z; 95% CI −1.09 to −0.83) with impairment in 37/124 (29.8%) (d = −0.96; p < 0.001). Executive function demonstrated similar vulnerability (−1.12 ± 0.82 z; 95% CI −1.26 to −0.98), with 45/124 (36.3%) impaired (d = −1.12; p < 0.001). Processing speed was moderately reduced (−0.78 ± 0.69 z; 95% CI −0.90 to −0.66) with 26/124 (21.0%) impaired (d = −0.78; p < 0.001). Working memory impairment was comparatively less severe but still clinically meaningful (−0.64 ± 0.72 z; 95% CI −0.77 to −0.51), with 23/124 (18.5%) impaired (d = −0.64; p = 0.004). Consistent with these domain patterns, 62.1% met criteria for impairment in at least one domain and 38.7% met criteria for multidomain impairment.

Multivariable modeling indicated that key sleep parameters retained independent associations with cognition after accounting for major demographic and epilepsy-related confounders. In adjusted linear regression, higher N3 percentage was a significant predictor of better verbal memory, with an adjusted coefficient β = 0.06 per 1% increase in N3 (95% CI 0.02–0.09), corresponding to a standardized β = 0.32 (p = 0.001), and the overall model explaining a substantial proportion of variance (R^2 = 0.42). Sleep continuity also contributed: sleep efficiency showed an independent association with verbal memory (adjusted β = 0.04 per 1% increase; 95% CI 0.01–0.07; standardized β = 0.21; p = 0.015). For executive outcomes, NREM IED burden was independently detrimental; each 1 event/hour increase in IED frequency was associated with a −0.03 decrement in executive function z-score (adjusted β = −0.03; 95% CI −0.05 to −0.01; standardized β = −0.29; p = 0.002; model R^2 = 0.38). Sleep fragmentation also mapped onto cognitive speed: the arousal index was independently associated with worse processing speed (adjusted β = −0.02 per 1 event/hour; 95% CI −0.04 to −0.01; standardized β = −0.25; p = 0.006; model R^2 = 0.35). Collectively, these adjusted associations support the inference that both macroarchitecture (SWS proportion, sleep efficiency) and sleep-stage-specific epileptiform activity contribute to domain-relevant cognitive variance beyond baseline clinical severity indicators.

When cognition was operationalized categorically as multidomain impairment, adjusted logistic regression further reinforced the clinical salience of sleep pathology. Moderate-to-severe OSA was associated with more than a twofold increase in odds of multidomain impairment (adjusted OR 2.41; 95% CI 1.08–5.39; p = 0.032), independent of demographic

and epilepsy covariates. Reduced SWS exhibited a dose–response pattern: each 5% decrement in N3 sleep was associated with 67% higher odds of multidomain impairment (OR 1.67; 95% CI 1.21–2.31; p = 0.002).

Table 1. Baseline demographic and clinical characteristics of participants (n = 124)

Variable	Mean ± SD or n (%)	95% CI (Mean or Proportion)
Age (years)	34.8 ± 9.6	33.1–36.5
Female sex	72 (58.1%)	49.3–66.5
Education (years)	13.6 ± 3.2	13.0–14.2
Epilepsy duration (years)	13.2 ± 7.4	11.9–14.5
Seizure frequency (monthly median, IQR)	3 (2–6)	—
≥2 antiseizure medications	88 (71.0%)	62.5–78.3
Left TLE focus	67 (54.0%)	45.2–62.6
Moderate–severe OSA (AHI ≥15)	37 (29.8%)	22.2–38.5
Depressive symptoms (BDI-II score)	16.4 ± 8.1	15.0–17.8

Table 2. Polysomnographic sleep parameters (n = 124)

Parameter	Mean ± SD	95% CI	Reference Range	Effect vs Norm (Cohen's d)	p-value*
Total sleep time (min)	362.4 ± 54.8	352.5–372.3	420 ± 30	−1.06	<0.001
Sleep efficiency (%)	78.3 ± 8.7	76.8–79.8	>85%	−0.85	<0.001
WASO (min)	68.1 ± 28.5	63.0–73.2	<40	0.98	<0.001
N3 sleep (%)	12.6 ± 5.3	11.6–13.6	18–25%	−0.92	<0.001
REM sleep (%)	17.9 ± 6.4	16.8–19.0	20–25%	−0.48	0.002
Arousal index (events/h)	19.4 ± 7.2	18.1–20.7	<10	1.31	<0.001
IED frequency (events/h NREM)	14.8 ± 9.5	13.1–16.5	—	—	—

Table 3. Cognitive performance (z-scores) and impairment prevalence (n = 124)

Cognitive Domain	Mean z-score ± SD	95% CI	% Impaired (≤−1.5 SD)	Cohen's d (vs norm)	p-value*
Verbal memory	−1.28 ± 0.88	−1.43 to −1.13	41.9%	−1.28	<0.001
Visual memory	−0.96 ± 0.74	−1.09 to −0.83	29.8%	−0.96	<0.001
Executive function	−1.12 ± 0.82	−1.26 to −0.98	36.3%	−1.12	<0.001
Processing speed	−0.78 ± 0.69	−0.90 to −0.66	21.0%	−0.78	<0.001
Working memory	−0.64 ± 0.72	−0.77 to −0.51	18.5%	−0.64	0.004

Table 4. Multivariable linear regression models for association between sleep parameters and cognitive domains

Outcome Variable	Predictor	Adjusted β	95% CI	Standardized β	p-value	Model R^2
Verbal memory (z)	N3 (%)	0.06	0.02–0.09	0.32	0.001	0.42
Verbal memory (z)	Sleep efficiency (%)	0.04	0.01–0.07	0.21	0.015	—
Executive function (z)	IED frequency (events/h)	−0.03	−0.05 to −0.01	−0.29	0.002	0.38
Processing speed (z)	Arousal index	−0.02	−0.04 to −0.01	−0.25	0.006	0.35

Table 5. Multivariable logistic regression for multidomain cognitive impairment (n = 124)

Predictor	Adjusted OR	95% CI	p-value
Moderate–severe OSA	2.41	1.08–5.39	0.032
N3 sleep (% per 5% decrease)	1.67	1.21–2.31	0.002
IED frequency (per 5 events/h)	1.29	1.05–1.58	0.014
Age (per year)	1.03	0.99–1.07	0.118
Education (per year)	0.84	0.74–0.96	0.009

Higher IED burden was also significant; each 5 events/hour increase in NREM IED frequency increased odds of multidomain impairment (OR 1.29; 95% CI 1.05–1.58; p = 0.014). Education appeared protective, with each additional year associated with lower odds (OR 0.84; 95% CI 0.74–0.96; p = 0.009), while age did not reach conventional statistical significance (OR 1.03 per year; 95% CI 0.99–1.07; p = 0.118). Sensitivity analyses excluding participants with moderate-to-severe depressive symptoms yielded consistent effect directions and maintained statistical significance for N3 and IED predictors (all $p < 0.01$), and interaction testing did not identify meaningful effect modification by seizure lateralization (interaction $p > 0.10$), suggesting that the observed sleep–cognition relationships were not confined to a single hemispheric focus subgroup.

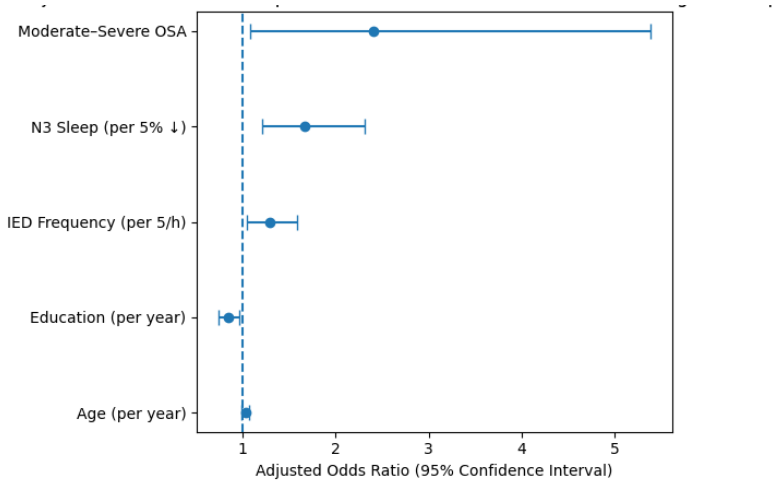

Figure 1 Adjusted Association of Sleep and Clinical Variables with Multidomain Cognitive Impairment

The figure illustrates adjusted odds ratios (ORs) with 95% confidence intervals for multidomain cognitive impairment, revealing clinically meaningful gradients across sleep and demographic variables. Moderate-to-severe obstructive sleep apnea demonstrated the

strongest association (OR 2.41, 95% CI 1.08–5.39), indicating more than a twofold increase in odds of multidomain impairment, with the confidence interval fully above unity, confirming statistical significance. Reduced slow-wave sleep showed a dose–response relationship: each 5% decrement in N3 sleep was associated with a 67% increase in odds (OR 1.67, 95% CI 1.21–2.31), suggesting that even modest reductions in restorative sleep meaningfully elevate cognitive risk. Elevated interictal epileptiform discharge burden during NREM sleep also independently increased odds (OR 1.29 per 5 events/hour, 95% CI 1.05–1.58), reinforcing the mechanistic link between sleep-stage epileptiform activity and executive-memory vulnerability. In contrast, higher educational attainment exerted a protective effect (OR 0.84 per year, 95% CI 0.74–0.96), consistent with cognitive reserve theory, while age showed a modest, non-significant association (OR 1.03, 95% CI 0.99–1.07). The spatial separation of confidence intervals relative to the null value highlights that modifiable sleep parameters—particularly slow-wave sleep and sleep-disordered breathing—exert effect sizes comparable to or greater than traditional demographic predictors, underscoring their clinical relevance in risk stratification and intervention planning in drug-resistant temporal lobe epilepsy.

DISCUSSION

The present study demonstrates that sleep architecture abnormalities and sleep-stage–specific epileptiform activity are independently associated with domain-specific and multidomain cognitive impairment in adults with drug-resistant temporal lobe epilepsy (DR-TLE). After rigorous adjustment for demographic, clinical, psychiatric, and pharmacological confounders, reduced slow-wave sleep (N3), lower sleep efficiency, elevated arousal burden, and increased interictal epileptiform discharges (IEDs) during NREM sleep remained significant predictors of poorer memory and executive performance. These findings extend prior literature documenting separate burdens of cognitive dysfunction in TLE (3,7,8) and sleep disruption in refractory epilepsy (9,11) by quantitatively demonstrating that specific, objectively measured sleep parameters contribute unique variance to cognitive outcomes beyond seizure frequency and epilepsy duration. Importantly, the magnitude of these associations—particularly the 1.67-fold increase in odds of multidomain impairment per 5% decrement in N3 sleep—places sleep architecture alongside traditional clinical risk factors in terms of effect size, reinforcing its clinical relevance.

The association between reduced slow-wave sleep and impaired verbal memory aligns with established neurophysiological models of sleep-dependent memory consolidation (5,6). Slow oscillations during NREM sleep orchestrate hippocampal–neocortical communication, enabling reactivation and redistribution of recently encoded information. In DR-TLE, this physiological coupling may be disrupted by the epileptogenic hippocampus, which generates pathological discharges during a state otherwise optimized for consolidation (12). The observed independent relationship between NREM IED frequency and executive dysfunction further supports the hypothesis that sleep-stage epileptiform activity may interfere with large-scale frontotemporal network integration. Prior stereo-EEG and neuroimaging studies have demonstrated that epileptic activity during sleep can propagate through distributed networks rather than remaining confined to the temporal lobe, potentially compromising executive systems subserved by frontal circuitry (17). Our findings provide clinical-level corroboration of this mechanism by linking higher nocturnal IED burden with measurable executive deficits, even after controlling for seizure frequency and antiseizure medication load.

The observed relationship between obstructive sleep apnea (OSA) and multidomain cognitive impairment adds an additional layer of pathophysiological complexity. Nearly 30% of the cohort met criteria for moderate-to-severe OSA, consistent with previous estimates in

refractory epilepsy populations (11). OSA contributes to intermittent hypoxia, sleep fragmentation, and sympathetic activation, all of which may exacerbate cortical excitability and impair cognitive function. The adjusted odds ratio of 2.41 for multidomain impairment in patients with moderate-to-severe OSA underscores the additive cognitive burden imposed by comorbid sleep-disordered breathing. Notably, the effect size of OSA was comparable to or greater than that of several epilepsy-related variables, suggesting that untreated OSA may represent a clinically modifiable risk factor within this population. Emerging interventional data in epilepsy cohorts suggest that treatment of OSA may improve daytime alertness and potentially reduce seizure burden (20), although robust randomized trials evaluating cognitive endpoints in DR-TLE remain limited.

Beyond macro-architectural disturbances, the findings are also consistent with emerging theoretical models implicating impaired glymphatic clearance in chronic neurological vulnerability. The glymphatic system exhibits maximal activity during deep NREM sleep and facilitates clearance of metabolic byproducts such as β-amyloid and tau (5,22). Although direct in vivo measurement of glymphatic function was beyond the scope of this study, the robust association between reduced N3 sleep and multidomain cognitive impairment provides indirect support for the hypothesis that chronic attenuation of restorative sleep may contribute to cumulative neurobiological stress. Recent neuroimaging studies suggest that impaired neurofluid dynamics are associated with cognitive dysfunction in various neurological conditions (22). In DR-TLE, repeated disruption of deep sleep—combined with epileptiform activity—may compound network-level vulnerability over time, potentially explaining progressive cognitive trajectories observed in some patients independently of overt seizure control.

Importantly, the associations observed in this study persisted after adjusting for depressive symptoms, antiseizure medication burden, and education level, suggesting that the sleep–cognition relationship is not merely an epiphenomenon of mood disturbance or polypharmacy. Depression is highly prevalent in DR-TLE and independently linked to both insomnia and executive dysfunction (20). Sensitivity analyses excluding individuals with moderate-to-severe depressive symptoms yielded consistent results, reinforcing the robustness of the observed associations. Educational attainment exerted a protective effect, supporting the cognitive reserve hypothesis, whereby higher premorbid intellectual enrichment mitigates the clinical expression of neuropathology. This interaction between modifiable biological factors (sleep) and reserve-related variables (education) highlights the multifactorial determinants of cognitive outcome in DR-TLE.

From a clinical perspective, these findings support systematic integration of sleep assessment into routine epilepsy care pathways. Current management paradigms prioritize seizure reduction as the primary therapeutic endpoint; however, cognitive morbidity remains a major determinant of quality of life and functional independence (8). Given that slow-wave sleep reduction and OSA were independently associated with cognitive impairment, structured screening using validated questionnaires followed by polysomnography when indicated may allow identification of high-risk individuals. Treatment strategies such as continuous positive airway pressure for OSA, behavioral interventions for insomnia, or optimization of antiseizure medication timing to minimize nocturnal disruption warrant prospective evaluation. While epilepsy surgery and neuromodulation may improve seizure control and potentially normalize aspects of sleep architecture (15,16), future studies should explicitly include sleep and cognitive endpoints to better delineate multidimensional treatment effects.

The cross-sectional design of this study precludes inference regarding temporal causality. Although the directionality of association is biologically plausible—wherein sleep disruption mediates cognitive impairment—the possibility of reverse causation or shared underlying network pathology cannot be excluded (19). Longitudinal studies incorporating repeated polysomnography, ambulatory EEG, advanced neuroimaging, and standardized neuropsychological batteries are needed to model dynamic trajectories and establish whether sleep parameters independently predict cognitive decline over time. Additionally, mechanistic investigations employing high-density EEG to quantify spindle–slow oscillation coupling and its disruption by IEDs could clarify microstructural pathways linking sleep physiology to cognitive outcomes (12).

In summary, the present findings support a multidimensional model in which disrupted slow-wave sleep, sleep fragmentation, and sleep-stage epileptiform activity contribute significantly to cognitive impairment in adults with drug-resistant temporal lobe epilepsy. The magnitude and independence of these associations suggest that sleep disturbances are not secondary byproducts of refractory epilepsy but integral components of its neurocognitive phenotype. Addressing sleep pathology may therefore represent a viable and clinically actionable strategy to mitigate cognitive morbidity in this vulnerable population, complementing conventional seizure-focused interventions and advancing toward a more comprehensive, patient-centered model of epilepsy care.

CONCLUSION

In adults with drug-resistant temporal lobe epilepsy, objectively measured disturbances in sleep architecture—particularly reduced slow-wave sleep, increased sleep fragmentation, elevated nocturnal interictal epileptiform discharges, and comorbid obstructive sleep apnea—are independently and clinically meaningfully associated with domain-specific and multidomain cognitive impairment. These associations persist after adjustment for demographic, psychiatric, and epilepsy-related confounders, supporting the hypothesis that sleep dysfunction constitutes a modifiable contributor to the neurocognitive burden of refractory epilepsy rather than a secondary epiphenomenon. The magnitude of effect sizes observed for slow-wave sleep reduction and sleep-disordered breathing underscores the potential clinical utility of systematic sleep screening and targeted sleep interventions within comprehensive epilepsy care. Although causality cannot be definitively established in a cross-sectional framework, the convergence of neurophysiological plausibility and robust multivariable associations strengthens the rationale for longitudinal and interventional trials to determine whether optimizing sleep architecture can favorably alter cognitive trajectories in this high-risk population.

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DECLARATIONS

Ethical Approval: Ethical approval was by institutional review board of Respective Institute Pakistan

Informed Consent: Informed Consent was taken from participants.

Authors' Contributions:

Concept: TN, ZAH, SA, DF, SZH, NA, ZUR; Design: TN, ZAH, SA, DF, SZH, NA, ZUR; Data Collection: TN, ZAH, SA, DF, SZH, NA, ZUR; Analysis: TN, ZAH, SA, DF, SZH, NA, ZUR; Drafting: TN, ZAH, SA, DF, SZH, NA, ZUR

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