Clinical utility of sleep recordings during presurgical epilepsy evaluation with stereo-electroencephalography: a systematic review

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Abstract

Although the role of sleep in modulating epileptic activity is well established, many epileptologists overlook the significance of considering sleep during presurgical epilepsy evaluations in cases of drug-resistant epilepsy. Here, we conducted a comprehensive literature review from January 2000 to May 2023 using the PubMed electronic database and compiled evidence to highlight the need to revise the current clinical approach. All articles were assessed for eligibility by two independent reviewers. Our aim was to shed light on the clinical value of incorporating sleep monitoring into presurgical evaluations with stereo-electroencephalography (SEEG). We present the latest developments on the important bidirectional interactions between sleep and various forms of epileptic activity observed in SEEG recordings. Specifically, epileptic activity is modulated by different sleep stages, peaking in non-rapid eye movement sleep, while being suppressed in rapid eye movement sleep. However, this modulation can vary across different brain regions, underlining the need to account for sleep to accurately pinpoint the epileptogenic zone during presurgical assessments. Finally, we offer practical solutions, such as automated sleep scoring algorithms utilizing SEEG data alone, to seamlessly integrate sleep monitoring into routine clinical practice. It is hoped that this review will provide clinicians with a readily accessible roadmap to the latest evidence concerning the clinical utility of sleep monitoring in the context of SEEG and aid the development of therapeutic and diagnostic strategies to improve patient surgical outcomes.

Key words:

SEEG, epilepsy, sleep, seizure, interictal epileptiform discharges, high-frequency oscillations

Introduction

The complex and bidirectional interactions between sleep and epilepsy are widely acknowledged and there is growing evidence that sleep is an important modulating factor in epilepsy.[1,2] Despite this knowledge, a significant disparity persists between the scientific evidence concerning the interrelated associations between sleep and epilepsy and current clinical practice. This is partly attributed to the fact that epilepsy and sleep have traditionally been considered separate domains. For patients with drug-resistant epilepsy (DRE) who are eligible for surgery, many tertiary centers do not consider sleep during presurgical evaluations to localize the epileptogenic zone (EZ). Previous studies investigating the impact of sleep on epileptic phenomena have commonly employed scalp EEG recordings.[3] These studies have demonstrated that sleep can directly influence both ictal and interictal epileptic phenomena. In non-rapid eye movement (NREM) sleep, the rates of both seizures and interictal epileptiform discharges (IEDs) are increased compared to those in wakefulness.[3] This may be explained by neuronal hypersynchronization in thalamocortical circuits during NREM sleep, which are heavily involved in sleep regulation, through GABA-ergic mechanisms.[4] Conversely, rapid eye movement (REM) sleep suppresses the rates of seizures and IEDs.[3] This is often attributed to the desynchronization of neuronal rhythms in the cortical EEG during REM sleep, mediated primarily by cholinergic neurotransmission.[5-7]

While scalp EEG studies have enriched our understanding of the relationship between sleep and epilepsy, they are inherently limited by the fact that scalp EEG recordings are often blind to focal and deep-seated epileptic activity and susceptible to artefacts.[8] SEEG recordings offer the unique possibility to gain a detailed understanding of the precise intracranial correlates of different types of epileptic activity across the sleep-wake cycle. This enables sleep to be leveraged as a tool for delineating epileptogenic networks with greater precision to ultimately improve surgical outcomes. The aim of this systematic review is to provide a comprehensive overview of evidence for the importance of sleep in SEEG evaluations in DRE. We first discuss the role of sleep recordings as an adjunct to SEEG. Next, we substantiate this perspective by presenting recent findings on the modulatory effects of sleep states and sleep microstructure on the intracranial correlates of seizures and interictal epileptic activity. We then discuss the clinical implications of these modulatory effects on accurately localizing the EZ in presurgical assessments. Finally, we present practical

tools and considerations to effectively incorporate sleep into routine clinical SEEG practice for presurgical evaluations.

Methods

In May 2023, we conducted a systematic search of the PubMed electronic database, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Both reviewers (SH, AH) independently assessed articles for eligibility at each stage. Because our goal was to focus on emerging trends, we selected a cut-off of the year 2000. For any discrepancies in selections between the two reviewers, a consensus was established. The search strategy, detailed in Figure 1, was conducted using the following terms: ("SEEG" OR "stereoelectroencephalography" OR "stereo-EEG" OR "intracranial EEG" OR "intracerebral EEG" OR "iEEG") AND ("sleep" OR "polysomnography" OR "PSG") AND ("epilepsy" OR "seizure" OR "ictal" OR "interictal" OR "IED" OR "high-frequency oscillations" OR "HFO").

To find relevant articles that aligned with the scope of this review, the following inclusion criteria were applied: (i) original research involving human subjects from January 2000 to May 2023; (ii) assessment of epileptic activity using SEEG or comparable methods, such as chronic implants like responsive neurostimulation (RNS) or combined grid/strip and SEEG recordings.; (iii) consideration of sleep with respect to epileptic activity; (iv) and clinical relevance for the diagnostic evaluation and treatment of epilepsy. We excluded reviews and case studies ($n < 5$), as well as articles that were not written in the English language. We also excluded studies that solely examined the neurophysiological elements of sleep or those that lacked a comparative analysis between different sleep states. In other words, studies that only investigated brain activity during a single sleep stage without considering different stages or conditions were not included, as they did not provide insights into the influences of sleep on intracranial epileptic activity. We also excluded studies where the focus was not related to sleep. A total of 32 articles fulfilled the selection criteria and are discussed in this review.

Sleep recordings as an adjunct to SEEG

Sleep recordings with polysomnography (PSG) combined with SEEG provide a more comprehensive understanding of epilepsy and comorbid sleep disorders in the clinical evaluation of patients with DRE.[9] PSG involves scalp EEG, electrooculography (EOG) and electromyography

(EMG), as well as cardiorespiratory monitoring. The standard practice for sleep recordings, in line with American Academy of Sleep Medicine (AASM) recommendations, involves placing scalp EEG electrodes following the international 10-20 system (F3, F4, C3, C4, O1, O2, M1 and M2).[10] This setup offers coverage of the left and right frontal, central, and occipital regions, with the left and right mastoids serving as reference electrodes. In practice, however, many epilepsy centers choose not to employ the conventional mastoid referential montage and instead use a bipolar montage for the scoring of sleep (for example, F3–C3, C3–P3, Fz–Cz, Cz–Pz, F4–C4, C4–P4 or Fz/Cz and Cz/Pz).[11,12] This is because mastoid electrodes can often be contaminated by epileptic activity arising from the temporal lobe. Moreover, a mastoid referential montage may not be feasible for certain patients given the specific localization of implanted depth electrodes and the risk of infection. In such cases, it is advisable to consider utilizing a bipolar montage for sleep scoring as part of presurgical evaluations involving SEEG.

EOG electrodes are placed on the outer corners of both eyes and are used to detect eye movements, important for identifying different sleep stages, particularly REM sleep.[10] EMG electrodes are typically placed on the mentalis and submental muscles in the chin area as well as the anterior tibialis muscle of both legs, in order to monitor muscle tone and activity during sleep.[10] Other physiological and respiratory parameters may also be recorded during PSG using various sensors, including heart rate, nasal airflow, oxygen levels, thoracal and abdominal movements, snoring sounds and body position.[10,13]

Simultaneous SEEG and PSG recordings serve several purposes in clinical settings. They may be used in the diagnosis and presurgical evaluation of sleep-related epilepsy and to provide guidance on appropriate treatment strategies.[9] In addition, combined SEEG-PSG can aid in the assessment of the complex, and often bidirectional, interaction between DRE and comorbid sleep disorders.[1,14] Moreover, the consideration of sleep in the presurgical evaluation of individuals with DRE can help to identify the precise location and extent of the EZ to ensure optimal surgical outcomes.[15]

Traditionally, epilepsy and sleep have been considered separate domains, and patients with DRE typically do not undergo PSG recordings during their presurgical evaluation with SEEG. This may be due to several factors such as: limited availability of specialized equipment, expertise and resources required for combined SEEG-PSG recordings; increased risk of infections from bandage changes; the technical challenges associated with integrating SEEG and PSG recording systems;

increased complexity and time due to additional equipment setup and data analysis which could extend the overall duration of the evaluation; and increased discomfort for patients due to the placement of additional electrodes alongside the already implanted SEEG depth electrodes. There is also no reimbursement from insurance companies for a combined SEEG-PSG study versus SEEG alone. To advance our understanding of the complex interactions between sleep and epileptic activity and improve clinical diagnosis, it is necessary to overcome these challenges and combine expertise from both fields.

In recent years, an increasing number of tertiary centers have enhanced their SEEG setup for epilepsy evaluations by incorporating additional PSG recordings.[12,15-18] This has yielded interesting and valuable findings regarding the modulatory effects of different sleep stages on various types of epileptic activity. A total of 32 original research articles from 15 centers globally fulfilled our selection criteria and are discussed in this review. Of these, five studies discussed the effects of sleep on intracranial ictal activity and 24 studies discussed the effects of sleep on intracranial interictal activity. Lastly, five studies describe tools and practical approaches that would enable sleep monitoring to be implemented in routine clinical practice for the presurgical evaluation of DRE. Note that two studies belong to more than one category (Figure 1). Figure 2 is a visual summary of the key findings extracted from the reviewed articles.

The bidirectional relationship between sleep and the ictal SEEG

A total of five studies utilized SEEG recordings or comparable methods to investigate the bidirectional relationship between sleep and ictal activity.[19-23] Given the diverse nature of these studies as highlighted in Table 1, they are discussed individually.

A study by Malow et al. (2000) used SEEG to examine the precise timing of temporal lobe seizures in 14 patients with DRE in relation to sleep arousals, to investigate whether seizure genesis is facilitated by or a cause of arousals.[23] Their findings revealed a pattern wherein sleep arousals consistently succeeded intracranial ictal onsets (60/67 seizures), with stage 2 of NREM sleep being the most frequent time for seizure occurrence (30/38 seizures).[23] Similarly, Dasheiff & Kofke (2003) showed that sleep-related seizures often involved patients awakening after the initial EEG onset of the seizure (304/308 seizures).[19] Likewise, Peter-Derex et al. (2020) showed that of 34

sleep-related seizures, both symptomatic and symptomatic, 70.6% (24/34) were followed by awakenings and 11.8% (4/34) were followed by an arousal [20].

A study by Dell et al. in 2021 revealed that seizure probability changes with day-to-day variations in sleep duration.[21] Logistic regression models showed that an increase in sleep duration by 1.66 ± 0.52 hours lowered the probability of a seizure occurring in the following 48 hours by 27%.[21] This suggests that a longer sleep duration may lower seizure risk for DRE patients. Following a seizure, patients slept for longer durations, potentially disrupting sleep patterns. Seizures occurring during sleep reduced sleep quality, with increased time spent aroused from sleep and reduced REM sleep.[21] These results highlight the correlation between day-to-day deviations from regular sleep duration and changes in seizure probability.

Finally, the study by Juan et al. (2023), demonstrated in 41 patients that, unlike focal impaired awareness seizures, the neural signatures of loss of consciousness during focal to bilateral tonic-clonic seizures consisted of paradoxical increases in cortical activation and neuronal firing.[22] These increases were observed most consistently in posterior brain regions, suggesting that loss of consciousness during focal to bilateral tonic-clonic seizures may occur through a different mechanism than during focal impaired awareness seizures, potentially accounting for the more negative prognostic consequences of the latter. Overall, given the evidence from these studies, clinicians are strongly recommended to actively manage both symptomatic and asymptomatic nocturnal seizures in order to address the associated sleep disturbances and cognitive symptoms.

The bidirectional relationship between sleep and the interictal SEEG

Among the 24 studies examining the impact of sleep on intracranial interictal activity, nine investigated IEDs, six assessed HFOs, eight evaluated both IEDs and HFOs with respect to sleep microstructure, and six were aimed at leveraging the modulatory effects of sleep on the interictal SEEG to optimize localization of the EZ and improve post-surgical seizure outcomes. Four studies belong to two or more of these categories. Due to differing methodologies, study designs, and heterogeneous epilepsy populations, direct comparisons between studies are limited. Nonetheless, studies are categorized below based on their objectives and conclusions to discern overarching patterns concerning the impact of different sleep stages on the interictal SEEG and its implications for surgical outcomes.

Effects of sleep on IED features

Several studies have expanded on the established effects of sleep on the rates of IEDs as observed in the scalp EEG by analyzing SEEG recordings of patients with DRE (Table 2). These studies consistently demonstrated that IED rates are highest in NREM sleep compared to wakefulness and REM sleep.[5,12,17,24,25] Specifically, Zubler et al. noted higher IED rates in the first half of the NREM cycle, corresponding to lower delta power, irrespective of the location of the seizure onset zone (SOZ).[24] Lambert et al. found increased IED rates during NREM sleep, particularly for mesiotemporal compared to neocortical regions, regardless of the location of the SOZ.[17] Conrad et al. showed that the sleep-related increase in IEDs was greater in patients with temporal lobe epilepsy compared to those with extra-temporal epilepsy.[25] Frauscher et al. (2016) demonstrated that phasic REM sleep, characterized by rapid eye movements, has an enhanced suppressive effect on IEDs compared to tonic REM sleep; this was suggested to be due to lower levels of local and global EEG synchronization.[5] This finding was consistent with that of another study by Campana et al, which revealed that IED rates were highest during NREM sleep, lower in tonic REM and lowest in phasic REM sleep, both within the SOZ and the region where the seizure first spreads.[12]

Five studies specifically assessed the influence of sleep on the spatiotemporal dynamics of IEDs as seen in the SEEG.[17,26-29] Conrad et al. studied the temporal dynamics of IEDs and showed that the spatial distribution of IEDs fluctuates significantly over time, which is attributed to enhanced IED propagation during sleep.[26] Fouad et al. also showed that the spatial distribution of IEDs varies across vigilance states, with IEDs in mesial areas peaking in NREM sleep, while those in lateral neocortical areas were highest in wakefulness.[28] Interestingly, Klimes et al. (2022) showed that while poor outcome patients had IEDs that fluctuated over time, good outcome patients had more dominant IED sources which were stable across vigilance states.[27] Lambert et al. analyzed simultaneous SEEG and sleep recordings from 20 patients with DRE and characterized the ‘spike co-occurrence’, a measure of the ability of a network to generate and propagate IEDs based on temporal concordance between IEDs in different brain regions.[17] They showed that spike co-occurrence was higher in all brain regions during NREM sleep compared to wakefulness, and that this increase was largest in mesiotemporal regions.[17] Finally, a study by Bower et al. demonstrated that both the relative synchrony and morphology of IEDs changed immediately before seizure onset, and that these changes were reactivated preferentially during post-seizure slow-wave

sleep.[29] These results support the view that physiological sleep processes create an environment that is conducive to the escalation and spread of epileptic activity.

Effects of sleep on HFO features

Six studies investigated the influence of sleep on the rates and spatial distribution of HFOs and are presented in Table 3.[5,30-34] The study by Sakuraba et al. showed that HFOs (80-200 Hz) occurred more frequently in slow-wave sleep compared to REM sleep.[32] They also found that HFOs recorded from electrode contacts near the EZ were less suppressed during REM sleep, and such contacts corresponded to the area of resection in patients with post-surgical seizure freedom.[32] This suggests that HFOs that are dominant in REM sleep are a valuable marker of epileptogenicity. Another study by Frauscher et al. from 2016 revealed that HFOs, like IEDs, were less frequent during phasic compared to tonic REM sleep.[5] The enhanced suppression of this interictal activity by phasic REM sleep was attributed to desynchronization of the EEG during phasic REM sleep.[5]

Bagshaw et al. investigated the effects of specific sleep states on two categories of HFOs – ripples (80-250 Hz) and fast ripples (>250 Hz) – in nine patients with lesional localized epilepsy.[30] Both ripple and fast ripple rates, like IEDs, were maximal in NREM sleep. Additionally, all sleep stages except for REM sleep showed a higher rate of ripples and fast ripples in the SOZ compared to non-SOZ regions.[30] Dumpelmann et al. similarly found that HFOs were increased in SOZ regions compared to non-SOZ regions. However, while HFOs increased with sleep stage in temporal and parietal regions, they remained stable in frontal regions.[31]

A study by von Ellenrieder et al. was aimed at investigating the rates and spatial spread of both physiological and pathological HFOs.[33] They also showed that the highest HFO rate and spatial spread was in NREM sleep and the lowest in REM sleep, and that HFO rates were closely linked to the accumulated amount of sleep. As the night progressed, physiological ripples increased with time spent in REM sleep, while pathological ripples and fast ripples decreased with time spent in NREM sleep, indicating distinct underlying mechanisms.[33] Finally, Klimes et al. reported increased local functional connectivity (~1 mm) and reduced widespread functional connectivity (~10 mm) of HFOs within the SOZ during slow-wave sleep, compared to wakefulness.[34] These findings demonstrate that slow-wave sleep accentuates the local synchrony underlying HFOs within the SOZ and reduces the functional connectivity between the SOZ and surrounding brain regions.

Association between sleep microstructure and interictal activity

Eight studies evaluated the association between physiological sleep events on IEDs or HFOs and are outlined in Table 4.[5,20,24,35-39] Such physiological sleep events include slow waves and sleep spindles as seen in NREM sleep, phasic REM sleep and sleep arousals.

Frauscher et al. (2015) examined eight DRE patients who had combined SEEG-PSG to identify specific components of NREM sleep that drive interictal activity.[37] They found that: (a) the increased IED and HFO rates observed in NREM sleep are specifically associated with the high-amplitude slow waves in this sleep state; (b) IED and HFO rates peaked during the transition from the 'up' (activation) state to the 'down' (deactivation) state of slow waves in NREM sleep, during a period of high synchronization.[37] von Ellenrieder et al. further validated this finding in a larger and more heterogeneous cohort of 45 patients.[38]

Song et al. analyzed SEEG recordings from 23 patients with DRE and examined the phase-event amplitude coupling between HFOs (80-150 Hz) and sleep oscillations.[36] They observed amplitude coupling between HFOs and sleep oscillatory phases for slow (0.1-2 Hz), delta (2-4 Hz), theta (4-10 Hz) and spindle (12-16 Hz) band activity, during either the peak-trough or trough-peak transition. Frontal and parietal lobes displayed a selective increase in HFO rates during the trough-peak transition within the SOZ, suggesting that this phase-event amplitude coupling may help to distinguish physiological and pathological HFOs and thereby delineate epileptogenic networks.[36]

Zubler et al. found in 10 patients with focal cortical dysplasia (FCD) type II that IED rates are positively correlated with sleep spindle density and negatively correlated with slow wave activity.[24] Another study in FCD type II patients explored thalamocortical influences on pathological SEEG activity by examining the distribution of three distinct FCD patterns of interictal activity in relation to sleep.[39] They reported that: (a) spikes/polyspikes >2 Hz were most frequent in wakefulness, N1, N2 and REM sleep and decreased with sleep depth; (b) spikes/polyspikes <2 Hz increased with sleep depth, particularly in N2 and N3 sleep; and (c) high-frequency rhythmic activity (>15 Hz) occurred only intermittently in N2 and N3 sleep.[39]

Frauscher et al. (2016) showed that, whereas IEDs and pathological HFOs are particularly suppressed during phasic REM sleep, physiological HFOs are increased in phasic compared to

tonic REM sleep.[5] This distinction may enable differentiation between physiological and pathological HFOs for more accurate EZ localization.[5]

Peter-Derex et al reported that IED rates significantly increased immediately before sleep arousals, compared to baseline and post-arousal periods, in N2 and REM sleep, particularly in the neocortex.[20] This increase showed a strong positive correlation with the slow wave component of NREM sleep arousals, highlighting the importance of sleep as a modulator of pathological interictal activity.

Chen et al. (2023) found that IEDs and ripples were clustered around the negative peaks of sleep slow waves, and that the increase in IED and ripple densities were associated with an increase in sleep slow wave amplitude.[35] Additionally, phase analysis showed that IEDs and ripples in the SOZ exhibited a similar facilitation by slow waves during the down state. These modulation patterns differed between the irritative and normal zones.

Optimizing selection of interictal epochs to improve EZ localization

Six studies were aimed at leveraging the modulatory effects of sleep on the interictal SEEG to optimize localization of the EZ and improve post-surgical seizure outcomes in patients with DRE. [16,26,27,40-42] These studies are highlighted in Table 5.

Klimes et al. (2019) explored the optimal sleep stage for precise EZ localization in the interictal SEEG.[16] They demonstrated that 10-min interictal SEEG recordings during NREM sleep stages N2 and N3 offer comparable EZ localization to outcomes obtained from the SOZ, which required an average of 12.7 days of recordings in the same sample.[16] Interestingly, combined vigilance state recordings did not surpass the accuracy of the NREM recordings. However, the studies by Conrad et al. (2020) and Klimes et al. (2022) showed that IED features fluctuate over time, thus advocating for at least 12-18 hours of continuous SEEG recordings to capture approximately 80% of this variance.[26,27] These findings relate to complex epileptic networks which might necessitate longer recording durations.[27]

A study by Weiss et al. assessed intraoperative SEEG recordings in anesthetized patients with DRE.[41] They reported that the rate, morphology and, in some cases, the spatial distribution of HFOs was modified under anesthesia, and that interictal high-frequency activity could be used to delineate the SOZ with greater accuracy in NREM sleep compared to intraoperative recordings.[41]

Therefore, intraoperative SEEG recordings cannot replace prolonged SEEG recordings during NREM sleep for identifying the EZ using interictal biomarkers. Minthe et al. reported that HFOs arising from a quiet background were strongly associated with the SOZ, whereas HFOs from a continuous oscillatory background were not, regardless of sleep stage.[40] This suggests that selecting epochs of HFOs and background EEG activity could help to distinguish epileptic brain regions from those that are healthy and physiologically active. Klimes et al. (2022) observed that patients with good surgical outcomes tended to have more dominant and stable IED sources in contrast to patients with poor surgical outcomes, and NREM sleep stage N3 was identified as the optimal sleep state for predicting outcome.[27] Finally, in a multicentre study, Thomas et al. demonstrated that the rate of IEDs with preceding gamma activity (30-100 Hz) during wakefulness is the optimal feature for predicting surgical outcome, and that this feature outperforms both the SOZ and the ripple rate.[42] Furthermore, this study presented evidence that surgical resection of brain regions with a high-spike-gamma rate in wakefulness increases the likelihood of achieving seizure freedom in patients with DRE.[42]

In light of the findings from these studies, there is promising evidence that shorter recordings of up to 24 hours could potentially replace the current standard of one to two weeks of inpatient SEEG recordings. It is worth emphasizing that specific biomarkers perform better in distinct sleep stages (for example, spike-gamma in wakefulness compared to IEDs in NREM sleep). Consequently, clinicians are advised to take sleep stages into account when evaluating EZ biomarkers, and to consider embracing multifeatured analyses, particularly in situations where recording durations are limited.

Integrating sleep monitoring into routine SEEG recordings

The preceding sections of this review emphasize the need for physicians to consider sleep states and microstructure when examining ictal and interictal markers in presurgical SEEG assessments in patients with DRE. However, integrating sleep recordings with PSG into routine clinical practice is challenging, both from technical and labor-related perspectives and also because of increased patient discomfort due to the placement of additional electrodes. This typically includes water-resistant, adhesive collodion-based scalp electrodes,[43,44] which, while effective, raises concerns regarding electrode artifacts when attempting to record for several days without changing the bandage as well as increased skin irritability.[45] Subdermal electrode wires (SWE) provide an

alternative, maintaining reliable recording characteristics and stable impedances for the complete duration of the implantation.[45,46] To overcome these challenges, emerging automatic scoring techniques based solely on intracranial EEG are gaining traction, eliminating the need for auxiliary measures like EOG and EMG. This section provides insights into various available tools and approaches to facilitate this objective. The relevant studies are outlined in Table 6.

A promising contribution comes from the work by von Ellenrieder et al. (2022), who developed an algorithm for automated sleep scoring from whole night SEEG recordings based on oscillatory and non-oscillatory spectral features, thus eliminating the need for scalp EEG, EOG, and EMG.[47] The features that were examined included the total power, and the relative and absolute power across various frequency bands, as well as their variability within an epoch. This algorithm also stands out notably for its minimal prerequisites, as it does not require recording specific brain regions or patient-specific data. The algorithm demonstrated proficiency in scoring long-term recordings of patients with intracranial electrodes undergoing presurgical evaluation, achieving an overall agreement of 78% in the test set (11 patients) when compared with expert scoring from board-certified neurophysiologists based on conventional measures.[47] This algorithm could be easily implemented by tertiary centers for analyzing sleep in SEEG recordings and is openly available (https://doi-org.proxy3.library.mcgill.ca/10.5281/zenodo.6412063).

Several additional studies have also contributed to the development of tools for sleep scoring using SEEG.[25,48-50] Conrad et al. (2023) utilized the normalized alpha-delta ratio to classify 10-min segments representing sleep or wakefulness.[25] This classification was validated using manual sleep scoring in a subset of their cohort who had a complete scalp EEG setup and offers a valuable alternative for monitoring NREM sleep stages in situations where scalp EEG or PSG are not practical or feasible. Reed et al. (2017) introduced a reliable automated method for detecting slow wave sleep based on spectral power and spindle frequencies in intracranial SEEG electrodes.[49] Kremen et al. (2017) employed spectral power features across multiple frequency bands in a single SEEG electrode from epilepsy surgery patients and achieved impressive classification accuracy in distinguishing awake and slow wave sleep states.[50] The method was further refined by Kremen et al. in 2019, where the authors developed an automated framework to differentiate between the sleep states N2, N3 and wakefulness with high accuracy.[48]

Conclusion

In this comprehensive review, we have explored the clinical significance of incorporating sleep monitoring into SEEG presurgical evaluations for individuals with DRE. This approach would enable clinicians to account for the modulatory effects of different sleep states and sleep microstructure on epileptic activity, which may have further implications for delineating the EZ and predicting surgical outcomes. Clinicians are strongly advised to address even asymptomatic nocturnal seizures to actively manage the associated sleep disturbances and cognitive symptoms in epilepsy. In addition, the selection of 12-18 h interictal epochs is recommended for optimal EZ localization. We have also highlighted practical alternatives, including automated sleep scoring algorithms derived solely from SEEG, eliminating the need for extra electrodes. This can be used to integrate sleep monitoring into routine SEEG assessments without disrupting established workflows.

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Figure legends

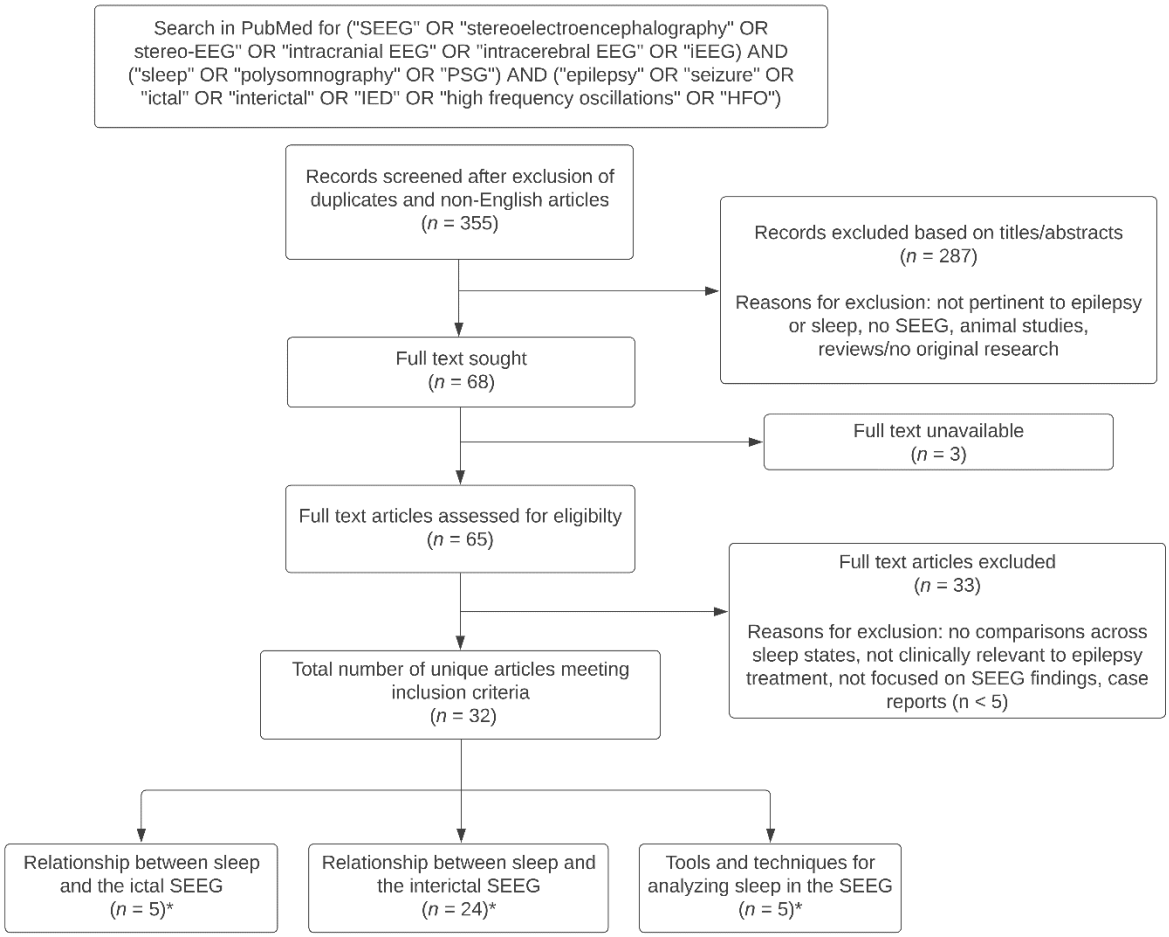

**Figure 1. Literature search flowchart following PRISMA guidelines. ***Some studies belong to multiple categories; one study investigated the effects of sleep on both ictal and interictal SEEG, and one study investigated the effects of sleep on the interictal SEEG and also described tools/techniques for analyzing sleep in the SEEG.

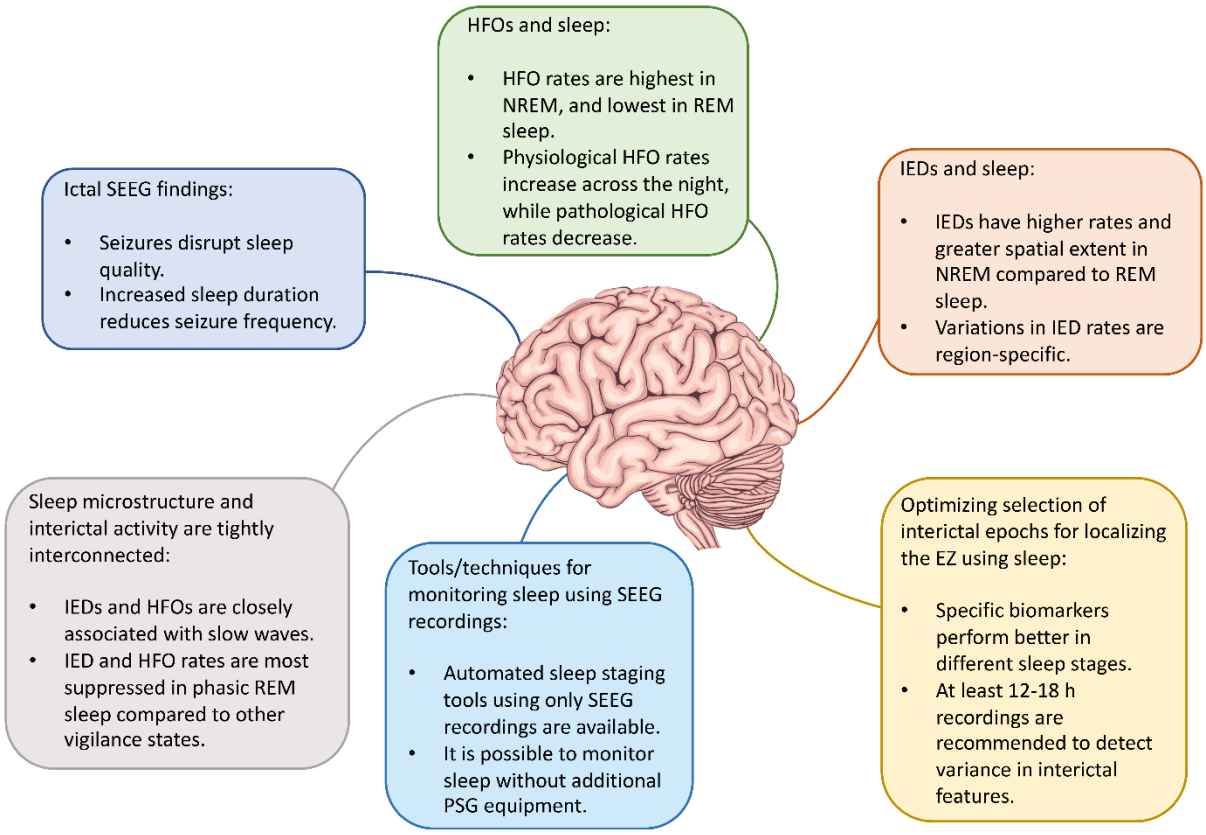

Figure 2. Visual summary of key findings regarding the clinical utility of sleep recordings in the presurgical SEEG evaluation of patients with epilepsy.

Table 1. Overview of studies investigating the bidirectional relationship between sleep and the ictal SEEG.

Study	Cohort	Measurements	Main findings
Juan et al. 2023[22]	DRE, n = 41 (19 female) Median age = 33y (range 14-63)	a) SEEG or subdural grids and depth electrodes: 179 seizures (50 FBTC and 129 FIA) b) Power spectrum measurements: slow wave activity (1-4 Hz) as sleep marker, beta (15-25 Hz), beta/delta ratio (beta/SWA) as cortical activation marker c) Neuronal firing from macro- and microelectrode recordings	a) FBTC seizures consisted of deeper loss of consciousness compared to FIA seizures, even before generalization occurred b) Early loss of consciousness in FBTC seizures was paired with a paradoxical decrease in slow wave activity, while showing a widespread increase in cortical activation and neuronal firing
Dell et al. 2021[21]	Focal epilepsy, n = 10 M_{age} = 46.3y (range 26-62)	a) Ambulatory intracranial EEG seizure advisory device: 4340 days analyzed, 2527 seizures b) Intracranial EEG sleep scoring based on algorithm by Kremen et al. (2019) to determine sleep onset, offset and transitions (N1 excluded) c) Spectral, entropy-based, and wavelet transform features	a) Seizure likelihood varies based on day-to-day differences in sleep duration (1.66 ± 0.52 h increase in sleep duration decreased seizure odds by 27% in the following 48 h) b) Increase in sleep duration following a seizure c) Decrease in sleep quality following a sleep-onset seizure (increase in arousal time, decrease in REM sleep duration)
Peter-Derex et al. 2020[20]	DRE, n = 36 (17 female) M_{age} = 35.7 ± 11.3y	a) Combined SEEG + PSG: 54 symptomatic/asymptomatic seizures b) Analysis of seizures, epileptic bursts, and isolated spikes (< 1 s bursts) c) Time windows (3 s): arousal, pre-arousal, post-arousal, baseline d) Modulating factors: sleep stage, anatomic location	a) 75.6% (34/45) of seizures occurred during sleep, 82.4% of which occurred during N2 b) The majority of sleep-related seizures were followed by awakenings (70.6%) or arousals (11.8%) c) Wake after sleep onset was increased in patient with nocturnal seizure compared to those without (p=0.02, d=0.67)
Dasheiff & Kofke 2003[19]	Patients with sleep-onset seizures, n = 22	a) SEEG + video recordings: 308 hippocampal sleep-onset seizures b) Arousals determined from extended behavioral change leading to wakefulness	a) Predominant pattern of sleep seizures had patient waking up after the initial EEG onset of the seizure (304/308)

	M_{age} = 31.04y (range 19-45) TLE = 16 FLE = 3 Generalized = 3		b) Only 4 seizures where the patient woke up as first behavioral sign immediately before the seizure
Malow et al. 2000[23]	DRE, n = 14	a) Bilateral temporal depth electrodes targeting the hippocampus and amygdala + bilateral temporal four-contact strip electrodes over the anterior lateral and inferior temporal neocortex (additional placed if necessary) + scalp electrodes: 4.8 ± 3.6 seizures recorded from each subject b) 7 subjects with EOG + chin EMG for sleep staging	a) EEG seizure onset preceded an arousal in 13/14 patients (60/67 seizures) b) In EOG + EMG subjects, all seizures occurred during NREM sleep and none in REM sleep

Abbreviations: DRE = drug resistant epilepsy, FBTC = focal to bilateral tonic-clonic, FIA = focal impaired awareness, FLE = frontal lobe epilepsy, M_{age} = mean age, POLE = parieto-occipital lobe epilepsy, TLE = temporal lobe epilepsy

Table 2. Overview of studies investigating the effects of sleep on IED features.

Study	Cohort	Measurements	Main findings
Conrad et al. 2023[25]	DRE, n = 101 (54 female) Median age = 36y (range 16-69)	a) SEEG (83/101) or grids/strips/depths (18/101): split complete recordings into 10-min segments, and randomly selected 1-min per segment for analysis b) Temporal analysis of IEDs across vigilance states	a) IED rates follow a circadian rhythm b) IEDs increase during sleep compared to wakefulness ($p<0.001$, effect size $r = .81$), and post-ictally compared to pre-ictally ($p<0.001$, $r=.59$) c) These increases were elevated in TLE compared to extra-TLE patients ($p=0.044$, $r=.20$ for sleep states; $p=0.004$, $r=.29$ for pre/post-ictal)
Klimes et al. 2022[27]	DRE, n = 30 M_{age} = 32.57y (range 14-56) TLE = 13 Engel IA = 14	a) SEEG + scalp EEG/EOG/EMG: first 2-3 days of continuous SEEG + 1 h segments before and after seizures b) Spatio-temporal features: spike rate spatial variance, line-length variance, skewness variance c) Logistic regression model to demonstrate use of proposed features	a) Patients with good surgical outcomes had more dominant IED sources which were stable across vigilance states compared to patients with poor surgical outcomes. b) This was expressed by a higher variance of IED rates, a lower variance of line length, a lower variance of positive skewness (all $p<0.05$). c) ≥18 h of continuous SEEG recordings are required to capture 80% of the variance in IED features and correctly predict surgical outcomes
Fouad et al. 2022[28]	DRE, n = 11 (6 females) M_{age} = 33.63 ± 14.69y Mesial seizure onset zones = 8	a) SEEG or subdural grids/strips + scalp EEG: mean 9.7 ± 2.3 h recordings per patient b) IED rates and morphology compared across brain regions and vigilance states	a) IED rates are influenced by vigilance states and anatomical brain regions ($p<0.0001$) b) IED rates in mesial areas were highest during NREM sleep compared to W and REM (both $p<0.0001$), while IEDs in lateral neocortical areas were highest in W compared to NREM sleep ($p=0.04$) and REM sleep ($p=0.01$)

Conrad et al. 2020[26]	DRE, n = 20 (12 females) M_{age} = 34.5y (range 5-58)	a) SEEG and/or cortical grids/strips: interictal segments 12 h before and after a seizure b) Spatiotemporal IED features	a) Change in spatial distribution of IED clusters over time (combined p-value<0.001) b) Significant relationship between primary IED clusters and alpha/delta ratio (p<0.001 in 8/20 patients) – implies that spatial distribution of IEDs is associated with sleep-wake patterns in these patients
Lambert et al. 2018[17]	DRE, n = 20 (10 female) M_{age} = 34.3 ± 11.7y MTLE = 12	a) SEEG + video-EEG: 1 h W and 1 h NREM segments b) Analyzed IED rate in W and NREM based on brain regions and epileptogenicity	a) Higher IED rate in NREM compared to W (p<0.001, d = 0.39) b) This increase was largest in mesiotemporal regions (p<0.001), regardless of SOZ involvement
Bower et al. 2017[29]	Drug resistant MTLE, n = 6	a) Hybrid macro- and micro SEEG electrodes + scalp EEG: ≥ 3 min epochs in various conditions b) IEDs from 5 conditions: slow-wave sleep and W 2-h before seizure (pre-epochs), slow-wave sleep and W 6-h after seizure (post-epochs), 5-min prior to seizure onset (near-onset)	a) Near-onset IED shapes were most similar to those in post-epochs b) Post-seizure changes in IED shape and synchrony were more pronounced in slow-wave sleep (p=0.0486) compared to wakefulness (p=0.559)
Campana et al. 2017[12]	DRE, n = 9 (5 female) FCDII = 5 Hippocampal sclerosis = 4	a) Combined SEEG + PSG: overnight recordings b) NREM (combined N1, N2, N3), tonic REM (no rapid eye movements), phasic REM (≥3 s rapid eye movement bursts) c) Quantitative analysis: global, local and functional synchronization	a) NREM sleep contained the most IEDs, followed by tonic REM sleep, then phasic REM sleep (p=0.016 in the seizure onset zone, p=0.002 in the diffusion zone) b) Most patients showed global and local synchronization in tonic REM sleep compared to phasic REM sleep
Zubler et al. 2017[24]	DRE and FCDII, n = 10 (5 female) M_{age} = 21.05y (range 4-40)	a) Combined SEEG + PSG: first seizure-free NREM-cycle reaching N3 b) Computed power spectrum between 0.5-180 Hz in independent 5-s bins: sigma power (sum of 12-16 Hz power, proxy for sleep-spindle density), delta power (sum	a) Increased IED rate in the first half compared to the second half of the NREM cycle, corresponding to increased sleep-spindle density, and decreased slow-wave activity b) Similar both within and outside the SOZ

		of 0.5-4 Hz power, proxy for slow-wave activity)	
Frauscher et al. 2016[5]	DRE, n = 12	a) Combined SEEG + PSG: phasic and tonic REM segments of equal duration (total of 189.2 min) b) Tonic REM (no rapid eye movements) vs phasic REM (≥5 s rapid eye movement bursts) c) Compared the following: frequency powers, IED rates, HFO rates (ripples and fast ripples)	a) Frequency power was decreased in phasic REM compared to tonic REM ($p<0.001$), indicating reduced synchronization b) Phasic REM sleep contained less IEDs compared to tonic REM sleep ($p<0.001$)

Abbreviations: DRE = drug resistant epilepsy, FCDII = focal cortical dysplasia type II, MTLE = mesiotemporal lobe epilepsy, M_{age} = mean age

Table 3. Overview of studies investigating the effects of sleep on HFO features.

Study	Cohort	Measurements	Main findings
von Ellenrieder et al. 2017[33]	DRE, n = 15	a) Combined SEEG + PSG: whole night recording b) Analyzed the rate and propagation of HFOs across vigilance states	a) HFO rates are influenced by the amount of accumulated sleep – across the night, physiological ripples increase (7.8% per hour in REM, 4.8% in N2, 2.7% in N3) b) While the rate of pathological ripples and fast ripples increase in REM (0.1% per hour for ripples, 7.7% for fast ripples), they decreased in N2 (-2.3% for ripples, -4.5% for fast ripples) and N3 (-7.9% for ripples, -16.7% for fast ripples) c) Spatial spread of HFOs is influenced by sleep stage, but not sleep cycle
Frauscher et al. 2016[5]	DRE, n = 12	a) Combined SEEG + PSG: phasic and tonic REM segments of equal duration (total of 189.2 min) b) Tonic REM (no rapid eye movements) vs phasic REM (≥5 s rapid eye movement bursts) c) Compared the following: frequency powers, IED rates, HFO rates (ripples and fast ripples)	a) Phasic REM sleep contained less ripples, and fast ripples compared to tonic REM sleep (both $p<0.001$) b) Physiological ripples (those in normal channels) were increased in phasic REM compared to tonic REM, while pathological ripples (those in the irritative zone and seizure onset zone) were increased in tonic REM compared to phasic REM (both $p<0.001$)
Klimes et al. 2016[34]	MTLE, n = 7 M_{age} = 32y (range 21-47)	a) Combined SEEG + scalp EEG: 10-min interictal segments, 1-3 W and 1-3 sleep, selected for each patient b) Spectral power analysis in 8 frequency bands (between 1-600 Hz): for unipolar signals, increased power implies increased local synchrony, while for bipolar signals, increased power implies decreased widespread synchrony	a) Local synchrony is increased across all frequency bands in both W and sleep (all $p<0.05$) b) In contrast, the synchrony between adjacent electrodes is decreased in the SOZ compared to the non-SOZ, especially at higher frequencies and during sleep
Sakuraba et al. 2016[32]	DRE, n = 13 (8 females)	a) SEEG + subdural grids/strips + scalp EEG/EOG/EMG: 5-min	a) Increased HFO rates in slow-wave sleep compared to REM ($p<0.0001$)

	M_{age} = 25.4y (range 12-41) Engel 1 = 6	interictal segments from each sleep stage b) HFO rates between REM and slow-wave sleep c) Relate surgical resection areas to dominant HFO areas	b) Electrodes with REM dominant HFOs were correlated with the resected area in seizure-free patients ($p<0.001$), but not in non-seizure free patients
Dumpelmann et al. 2015[31]	DRE, n = 15 (5 females) M_{age} = 30y (range 8-52) Engel 1 = 8	a) SEEG and/or subdural grids/strips + scalp EEG/EOG/EMG: first 2 days and nights following implantation b) Ratio between HFO rates in resected and non-resected contacts	a) SOZ channels have higher HFO rates than non-SOZ channels in all vigilance states ($p<0.001$) b) Increased HFO rates during sleep compared to W and REM in temporal regions ($p<0.01$) c) HFO rates remain stable in frontal regions across sleep stages ($p>0.05$)
Bagshaw et al. 2009[30]	Lesional focal epilepsy, n = 9 M_{age} = 38.7y (range 24-54)	a) SEEG + scalp EEG/EOG/EMG: 10-min segments in each vigilance state (W, N1/N2, N3, REM) b) Compared the following rates and durations: IED, ripples, fast ripples	a) Maximal HFO rates found in the same stage as IEDs (mostly NREM) b) HFO duration remains stable across vigilance states c) Higher HFO and IED rates in the SOZ compared to non-SOZ across all vigilance states

Abbreviations: DRE = drug resistant epilepsy, MTLE = mesiotemporal lobe epilepsy, M_{age} = mean age

Table 4. Overview of studies investigating the relationship between sleep microstructure and interictal activity.

Study	Cohort	Measurements	Main findings
Chen et al. 2023[35]	DRE, n = 30 (14 female) M_{age} = 22.8 ± 9.7y TLE = 16	a) Combined SEEG + PSG: 20-50 min artifact-free N2/N3 sleep from the first sleep cycle b) Type I ripples (co-occurring with IEDs) and type II ripples (not co-occurring with IEDs) c) Distribution of IEDs and ripples based on sleep slow wave phases	a) IEDs and ripples clustered around the negative peak of sleep slow waves b) There was a positive association between the sleep slow wave amplitude and IED and ripple densities c) Within the SOZ, IEDs and both ripple subtypes were similarly modulated by the slow wave phase. In the irritative zone, ripple subtypes experienced different modulation patterns in response to slow wave phases.
Peter-Derex et al. 2020[20]	DRE, n = 36 (17 female) M_{age} = 35.7 ± 11.3y	a) Combined SEEG + PSG: 54 symptomatic/asymptomatic seizures b) Analysis of seizures, epileptic bursts, and isolated spikes (< 1 s bursts) c) Time windows (3 s): arousal, pre-arousal, post-arousal, baseline d) Modulating factors: sleep stage, anatomic location	a) Epileptic bursts differ across time windows ($p < 0.0001$) and sleep stages ($p = 0.0014$), without interaction b) Increased epileptic bursts before arousals compared to baseline and post-arousal windows, regardless of sleep stage or anatomic location. c) Similar pre-arousal increase in isolated spikes, but only for N2 and REM sleep d) Increase in neocortical isolated spike rates during the arousal associated with the slow-wave component of NREM arousals ($r = 0.99$, $p < 0.0001$)
Song et al. 2017[36]	Patients with epilepsy, n = 23 (11 female) M_{age} = 37.57y	a) Video SEEG: 40-90 min mixed-stage sleep (confirmed by eyes closed) b) Ripples on spikes differentiated from ripples on oscillations using a custom algorithm c) Ripples classified into subtypes based on frequency bands (slow, delta, theta, and spindle)	a) Ripples on spikes (AUC=0.78) performed better than ripples on oscillations (AUC=0.63 to 0.65) for recognizing frontal neocortical epileptogenic areas (all p=0.001) b) Ripple event amplitude was coupled with the sleep oscillatory phase

	(range 18-69) MTLE = 9	d) Ripple events transformed into ripple phasors, allowing for measurement of phase-amplitude coupling	c) Preferred phase angles of ripple coupling differed between SOZ and non-SOZ for all oscillatory types (strongest for ripples on delta, p=0.001) d) Ripples occurring during the trough-peak transition of slow oscillations were higher in the parietal and frontal lobe SOZ (all p<0.05)
Zubler et al. 2017[24]	DRE and FCDII, n = 10 (5 female) M_{age} = 21.05y (range 4-40)	a) Combined SEEG + PSG: first seizure-free NREM-cycle reaching N3 b) Computed power spectrum between 0.5-180 Hz in independent 5-s bins: sigma power (sum of 12-16 Hz power, proxy for sleep-spindle density), delta power (sum of 0.5-4 Hz power, proxy for slow-wave activity)	a) Increased IED rate in the first half compared to the second half of the NREM cycle, corresponding to increased sleep-spindle density, and decreased slow-wave activity b) Similar both within and outside the SOZ
Frauscher et al. 2016[5]	DRE, n = 12	a) Combined SEEG + PSG: phasic and tonic REM segments of equal duration (total of 189.2 min) b) Tonic REM (no rapid eye movements) vs phasic REM (≥5 s rapid eye movement bursts) c) Compared the following: frequency powers, IED rates, HFO rates (ripples and fast ripples)	a) Frequency power was decreased in phasic REM compared to tonic REM (p<0.001), indicating reduced synchronization b) Phasic REM sleep contained less IEDs, ripples, and fast ripples compared to tonic REM sleep (all p<0.001) c) Physiological ripples (those in normal channels) were increased in phasic REM compared to tonic REM, while pathological ripples (those in the irritative zone and seizure onset zone) were increased in tonic REM compared to phasic REM (both p<0.001)
von Ellenrieder et al. 2016[38]	DRE, n = 45	a) Combined SEEG + scalp EEG: first cycle of N2 and N3 b) Interaction between HFOs and slow waves	a) Difference in coupling of HFOs with slow waves in normal and epileptic brain regions – HFOs tend to occur before the slow wave peak in epileptic channels, but after the in normal channels b) This effect was seen across different brain regions

Frauscher et al. 2015[37]	DRE, n = 8 (3 female) M_{age} = 34.63y (range 21-45)	a) Combined SEEG + scalp EEG: first cycle of N2 and N3 b) Analyzed IEDs and HFOs during high amplitude widespread slow waves, low amplitude widespread slow waves (control), isolated slow waves, and no slow wave epochs	a) Increase in IEDs and HFOs rates during high amplitude widespread slow waves compared to controls ($p<0.001$) b) IED and HFO rates were highest during the 'up' to the 'down' state transition of slow waves
Menezes Cordeiro et al. 2015[39]	FCDII, n = 5 (3 female) M_{age} = 27y (range 21-38)	a) Combined SEEG + scalp EEG: first sleep cycle b) Defined 3 interictal patters in SEEG: spike/polyspike followed/not by slow wave (>2 Hz) (pattern 1); pattern 2, spike/polyspike followed/not by high amplitude slow waves disrupted by baseline <2 Hz (pattern 2); >15 Hz discharges, rhythmic activity with regular morphology (pattern 3)	a) Pattern 1 most common amongst all vigilance states (58-100%) b) Increase in pattern 2 in NREM c) Pattern 3 was uncommon, and only sometimes observed in NREM

Abbreviations: DRE = drug resistant epilepsy, FCDII = focal cortical dysplasia type II, MTLE = mesiotemporal lobe epilepsy, M_{age} = mean age

Table 5. Overview of studies aimed at optimizing the selection of interictal epochs for EZ localization.

Study	Cohort	Measurements	Main findings
Thomas et al. 2023[42]	DRE, n = 83 TLE = 34 Engel IA = 37	a) SEEG + 512Hz sleep recording (scalp EEG/EOG/EMG) + complete neuroimaging datasets: 10-min interictal SEEG segments in W, NREM, REM b) Detection of IEDs, ripples, and gamma activity c) Extracted 135 features categorized from following categories: rate, ratio, morphology, spike propagation, teager energy, vigilance states, suppression	a) Spike-gamma rate in W (AUC = 0.755 ± 0.07) is the best single feature indicative of a favorable surgical outcome, outperforming the SOZ (AUC = 0.563 ± 0.05) and the ripple rate (AUC = 0.537 ± 0.07) b) Channels with spike-gamma rate > 1.9/min had a high probability of being within the EZ (80%), thus resection of these regions can provide a high likelihood of achieving seizure-freedom
Klimes et al. 2022[27]	DRE, n = 30 M_{age} = 32.57y (range 14-56) TLE = 13 Engel IA = 14	a) SEEG + scalp EEG/EOG/EMG: first 2-3 days of continuous SEEG + 1 h segments before and after seizures b) Spatio-temporal features: spike rate spatial variance, line-length variance, skewness variance c) Logistic regression model to demonstrate use of proposed features	a) N3 sleep stage performed the best in predicting outcome when running the model in 3-h segments of isolated states of vigilance (0.67 median accuracy vs 0.58 in W and 0.61 in REM) b) ≥ 18 h of continuous SEEG recordings required to capture 80% of the variance in spike features and correctly predict surgical outcomes
Weiss et al. 2021[41]	DRE, n = 16 (5 female) M_{age} = 36.94y (range 20-56) MTLE = 6 Engel IA = 6	a) SEEG: 10-min segment from subset of electrodes (3-7/patient) while anesthetized + 10-60 min NREM sleep segment from all electrodes 1-2 days after implantation b) Analysis of HFO features: rates, frequency, power	a) HFOs amplitude was higher in sleep than in anesthetized condition ($p<0.01$) b) HFOs and sharp-spikes were higher in the SOZ ($p<0.01$) for both sleep and anesthetized conditions, but the increase was greater during sleep ($p<0.05$) c) Ripples on oscillations (80-250 Hz) during sleep were the best predictors of good outcomes (AUROC = 0.80)
Conrad et al. 2020[26]	DRE, n = 20 (12 females) M_{age} = 34.5y	a) SEEG and/or cortical grids/strips: interictal segments 12 h before and after a seizure b) Spatiotemporal IED features	a) Change in spatial distribution of IED clusters over time (combined $p<0.001$) b) Median of 12 continuous hours (range 6-86 h) needed for capturing

	(range 5-58)		80% of the total variability in the spatial distribution of IEDs
Minthe et al. 2020[40]	DRE, n = 23 (15 female) M_{age} = 33.70y (range 12-60)	a) SEEG (all) + additional subdural grids (6 patients): 2 min segments (3 night + 3 day) per patient b) Entropy measurement of HFO patterns (oscillatory vs quiet background): low values indicative of stability	a) HFOs originating from quiet background activity displayed a robust correlation with SOZ channels ($p<0.001$) – no such correlation was observed for HFOs from continuous oscillatory activity ($p=0.563$) b) Background activity type was consistent within the same brain region over consecutive days, regardless of sleep stage
Klimes et al. 2019[16]	DRE, n = 30 (14 female) M_{age} = 34.2 ± 10.1y Engel I = 13	a) SEEG + scalp EEG/EOG/EMG: 10-min segments of W, N2, N3, REM (mostly from 1st sleep cycle) b) Analyzed interictal SEEG markers of the EZ across multiple frequency bands and vigilance states c) Features used to train a support vector machine model for classifying SEEG contacts in the EZ	a) The model performed the best in NREM (N2 and N3) compared to W and REM ($p<0.01$), but there was no improvement when using combination of all vigilance states ($p>0.05$) b) Multifeature approach used by the model performed better than IEDs and HFOs ($p<0.01$)

Abbreviations: DRE = drug resistant epilepsy, MTLE = mesiotemporal lobe epilepsy, M_{age} = mean age

Table 6. Overview of tools and techniques for monitoring sleep in SEEG recordings.

Study	Cohort	Measurements	Main findings
Conrad et al. 2023[25]	DRE, n = 101 (54 female) Median age = 36y (range 16-69)	a) SEEG (83/101) or grids/strips/depths (18/101): split complete recordings into 10-min segments, and randomly selected 1-min per segment for analysis b) Alpha-delta ratio averaged across all electrodes (highest in W, lowest in N3)	a) Validated the use of normalized alpha-delta ratio for differentiating W and sleep (AUC = .90) b) Normalized alpha-dela ratio agreed with classification by SleegSEEG algorithm (AUC = .91)
von Ellenrieder et al. 2022[47]	DRE, n = 44 (33 training set, 11 testing set)	a) Combined SEEG + scalp EEG, EOG, EMG: median 9 h 55 min recording duration per patient b) Analyzed 65 features: oscillatory and non-oscillatory	a) Development of automatic sleep scoring algorithm (SleepSEEG) with good performance for W, N2, N3, REM b) Metrics: 78% overall agreement in test set between algorithm and manual sleep staging by experts c) Poor performance for N1
Kremen et al. 2019[48]	MTLE, n = 8 (3 female) M_{age} = 40 ± 11y	a) SEEG, subdural grids or strips + scalp EEG: total of 420 min analyzed across patients b) Spectral power features from 8 frequency bands (between 0.1-235 Hz) in one electrode	a) Automated unsupervised method to distinguish between W, N2, N3 with only SEEG recordings from a single electrode b) Metrics: 94% sensitivity, 93% specificity, classification of N3 (95% sensitivity, 93% specificity) significantly better than classification of N2 (78% sensitivity, 96% specificity)
Kremen et al. 2017[50]	MTLE, n = 7 (4 female) M_{age} = 34 ± 12y	a) Combined SEEG + scalp EEG: 10-min slow wave sleep and 10 min W for training and testing datasets b) Spectral power features from 9 frequency bands (between 0.1-600 Hz) in one electrode	a) Classifier for differentiating W and slow-wave sleep using multiple spectral power features in a single SEEG electrode b) Classification accuracy: 97.8 ± 0.3% in healthy tissue and 89.4 ± 0.8% in epileptic tissue
Reed et al. 2017[49]	Patients with epilepsy, n = 9	a) Combined SEEG + scalp EEG/EOG/EMG: 10 h continuous overnight recordings	a) Automated method for identifying slow-wave sleep with only SEEG recordings

		b) Analyzed power spectra (1-250 Hz) in 10 most lateral SEEG contacts across vigilance states	b) Method based on analysis of spectral power and spindle frequencies c) Metrics: mean positive predictive value of 64% across all nights, mean kappa score of 0.72 compared to manual sleep staging by experts

Abbreviations: DRE = drug resistant epilepsy, MTLE = mesiotemporal lobe epilepsy, M_{age} = mean age