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THE IMPACT OF INTERICTAL EPILEPTIFORM DISCHARGES ON COGNITIVE PROCESSES IN THERAPY-RESISTANT EPILEPSY: AN INVASIVE STUDY USING INTRACRANIAL ELECTRODES

PhD thesis

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List of abbreviations

ASM – antiseizure medication

BDZ – benzodiazepine

BNT – Boston Naming Test

CBZ – carbamazepine

CLN – clonazepam

DGS-B – Digit Span – Digit backward test

DRE – drug-resistant epilepsy

EEG – electroencephalography

FCD – focal cortical dysplasia

FO – foramen ovale

GBP – gabapentin

GG – ganglioglioma

HFO – high-frequency oscillation

HS – hippocampal sclerosis

IED – interictal epileptiform discharges

LCM – lacosamide

LEV – levetiracetam

LGA – low-grade astrocytoma

LTG – lamotrigine

mtIED – medio-temporal interictal epileptiform discharges

NREM – non-rapid eye movement

nRT – nucleus reticularis thalami

ODG – oligodendroglioma

OXC – oxcarbazepine

PHB – phenytoin

RAVLT – Rey Auditory Verbal Learning Test

REM – rapid eye movement

ROCF – Rey–Osterrieth Complex Figure Test

RUF – rufinamide

SOZ – seizure-onset zone

SWR – sharp wave-ripple

TPM – topiramate

VLMT – Verbal Logical Memory Test

VPA – valproate

ZNS – zonisamide

1. Introduction

1.1. Introduction to Epilepsy, Refractory Epilepsy, Preoperative Investigation and Surgical Approaches, Foramen Ovale Electrode

Epilepsy is one of the most common chronic neurological disorder, with an estimated prevalence of 0.5 – 1%, affecting over 65 million people worldwide.¹ It is characterized by an enduring predisposition to generate epileptic seizures, as well as by the neurobiological, cognitive, psychological, and social consequences of the disorder.² Epilepsy poses substantial challenges for both patients and healthcare systems, not only because of the seizures themselves, but also due to the associated cognitive, psychological, and social impairments.

While many people with epilepsy achieve seizure control with antiseizure medications (ASMs), approximately 30%-40% develops refractory epilepsy,³ also known as drug-resistant epilepsy (DRE), in which seizures persist despite appropriate trials of two or more ASMs.⁴ Although more than 30 ASMs have been introduced over recent decades, the overall prevalence of DRE has remained largely unchanged.⁵ Persistent, uncontrolled epilepsy may lead to progressive dysfunction in specific brain regions, resulting in worsening cognitive and behavioral outcomes over time.⁶ In cases where pharmacological treatment fails, alternative therapeutic strategies, including epilepsy surgery, must be considered.

Epilepsy surgery represents a valuable treatment option for DRE patients,⁷ and has been shown to be significantly superior to continued medical therapy in terms of seizure control and quality of life in both pediatric and adult populations.^{6,9,9} The primary goal of surgery is to remove or disconnect the brain region responsible for seizure generation, thereby offering the potential for long-term seizure freedom. Seizure freedom is achieved in approximately 60–76% of patients within one year following surgery.^{10–12} Importantly, earlier surgical intervention has been associated with more favorable cognitive and psychosocial outcomes.¹³ Successful surgical treatment critically depends on the precise localization and complete resection of epileptogenic tissue.

Prior to surgery, patients undergo a comprehensive preoperative evaluation aimed at localizing the seizure onset zone and assessing the potential risks associated with intervention.^{14,15} This evaluation typically includes advanced neuroimaging, detailed

neuropsychological assessment, and prolonged electroencephalographic (EEG) monitoring. When non-invasive techniques fail to provide sufficient localization, invasive EEG recordings may be required. These include depth electrodes, subdural grid or strip electrodes, and foramen ovale electrodes, which allow direct recording from deep or cortical brain structures with high spatial and temporal resolution.

Beyond their clinical utility, preoperative invasive EEG investigations offer a unique opportunity to study the pathophysiological mechanisms of epilepsy and its impact on brain function. High-resolution intracranial recordings provide valuable insight into seizure propagation, epileptogenic network dynamics, and the effects of abnormal electrical activity on cognition, memory, and behavior—thereby serving as a powerful tool for both clinical decision-making and translational research.

1.2. Cognitive impairment in epilepsy

Cognitive impairment represents a major comorbidity of epilepsy,¹⁶ which is a leading cause of quality of life impairment.¹⁷ In chronic epilepsies, cognitive deficits are observed in about 70-80% of patients, while mood and behavioral disturbances occur in up to 60%.¹⁸ Specifically, impairments in memory, attention, language and executive functioning are well-documented across epilepsy syndromes,^{16,19} as are depression and anxiety disorders.²⁰ These deficits are present in more than half of patients at disease onset,²¹ and have been shown to be progressive in nature.²²

The etiology of cognitive deficits is usually considered multi-factorial, involving both irreversible factors—such as epilepsy syndrome and its underlying causes, including structural or morphological brain lesions, genetic, metabolic, or neurodegenerative disorders—and potentially modifiable contributors, such as active epilepsy (seizures and interictal discharges), antiepileptic treatments (antiseizure medications, epilepsy surgery, or neuromodulation), and psychiatric comorbidities.^{23,24} IEDs, seizures, epilepsy duration, age at onset, ASM treatment, psychiatric symptoms, and also brain pathology are usually associated with poor cognitive outcome,¹⁶ however the precise role and predictors of the different factors however remain mostly unknown.

1.3. Temporal lobe epilepsy

Temporal lobe epilepsy (TLE) represents the majority of adult focal epilepsy.²⁵ The temporal lobe, and particularly the hippocampus within the medial temporal structures, is also the most frequent site of seizure onset in adults. Importantly, it is the region most amenable to surgical cure, as anterior temporal lobectomy remains the most common and effective surgical treatment for TLE.

Medial temporal lobe has a well investigated and known cognitive function, with most prevalent impairments in hippocampal-dependent episodic memory functions.²⁶ The primary function of the medial temporal lobe (MTL) is forming and retrieving long-term memories, particularly episodic and spatial memories.²⁷

1.4. Memory consolidation

During memory consolidation, newly encoded memories, initially stored in hippocampal network, are transferred to neocortical networks for long-term storage. This exchange of information between the hippocampus and the cortex is coordinated by synchronized electrical activity.²⁸ This coordinated oscillatory activity enhances intracortical connectivity, promoting neuronal communication and supporting long-term plasticity.²⁹ The key electrophysiological markers of declarative memory network during non-rapid eye movement (NREM) sleep include hippocampal sharp wave-ripples (SWRs),³⁰ thalamocortical spindles,³¹ and the <1-Hz cortical slow oscillation.³² The hierarchical nesting of these three oscillations generates a synchrony over widespread regions in brain activity, which is hypothesized to facilitate information exchange between the hippocampus and the cortex.^{28,33,34} While this process predominantly occurs during NREM sleep, it also takes place during restful wakefulness.³¹

1.5. Interictal epileptiform discharges

Interictal epileptiform discharges (IEDs) are abnormal hypersynchronous patterns of brain activity associated with epilepsy. Hippocampal IEDs are considered to be the pathological exaggeration of SWRs - key markers of normal memory consolidation processes, the epileptic spike-pathological ripple complex.³⁰ SWRs' conversion to hippocampal IEDs and pathologic high-frequency ripples was evidenced in a rat kindling model.³⁵ Similarly, to SWRs, hippocampal IEDs exhibit a temporal relationship with

sleep spindles³⁶ and may induce spindle-like oscillations in the frontal brain regions, even during wakefulness, contributing to spatial memory impairments.³⁵

The role of IEDs in disrupting memory processes has been a major focus of study. Interictal activity is hypothesized to disrupt the physiological oscillatory patterns crucial for memory consolidation, they disturb the coupling between hippocampal ripples, thalamic spindles and cortical slow waves.³⁰ Evidence shows that IEDs can alter the activity and characteristics of sleep spindles,^{35,37–41} hippocampal sharp-wave ripples,⁴² slow waves,⁴³ and other related oscillations,^{44,45} thereby impairing this essential process.

IEDs arise from functional neural networks, and their interference with ongoing physiological processes⁴⁶ is increasingly seen as a significant factor in cognitive impairment.²³ They have been shown to interfere with transient cognitive functions, such as encoding and retrieval.^{35,47–49} Conversely, there is limited clinical data linking interictal spikes to more persistent, long-term cognitive impairment.^{48,50,51} Recent evidence from presurgical evaluations in patients with drug-resistant focal epilepsy has established a relationship between hippocampal IEDs during NREM sleep and impaired long-term memory consolidation.^{52,53} The properties of IEDs—such as their rate, location, and amplitude—are critical factors in determining their impact on cognitive functions.^{44,47,48}

Despite these findings, the exact mechanisms by which IEDs lead to cognitive impairment remain unclear. Understanding these interactions is crucial for elucidating how interictal discharges interfere with memory consolidation and cognitive function in epilepsy patients.

1.6. Sleep spindles

Sleep spindles are hallmarks of NREM sleep stage 2, and are characterized by waxing and waning oscillations with a 10–16-Hz frequency and with ≥ 0.5 -s duration.⁵⁴ They play a critical role in memory consolidation and brain plasticity.^{55,56}

Studies have shown that IEDs can significantly alter spindle activity. For instance, hippocampal IED density has been negatively correlated with hippocampal spindle density.⁴¹ Similarly, neocortical spindle rates are inversely related to IED spike rates.⁵⁷ IEDs are closely linked to the timing and frequency of spindles in various childhood epilepsy syndromes, which are often characterized by cognitive dysfunction.⁵⁸

Additionally, hippocampal IEDs can induce abnormal spindle-like activity in the frontal cortex during NREM sleep, REM sleep, and even wakefulness. This may disrupt hippocampal-frontal networks, further contributing to cognitive impairment.³⁵ The characteristics of individual IED-coupled spindles, such as their duration, amplitude, frequency, and spatial distribution, remain similar to those of normal, physiological spindles.

Spindle characteristics such as spindle duration, amplitude, and frequency are trait like individual features, however their modifications were reported in a variety of physiological and pathological conditions including learning,⁵⁹ aging,⁶⁰ developmental, neurodegenerative, and psychiatric diseases,^{61–64} and most notably, epilepsy.⁶⁵ These disruptions in spindle activity likely contribute to the cognitive deficits often observed in epilepsy patients.

1.7. Challenges of investigation medial temporal lobe and memory consolidation

Exploring interictal activity in the medial temporal regions presents significant challenges. Scalp EEG tends to substantially underestimate the occurrence of IEDs.⁶⁶ In contrast, intracranial EEG — including recordings with foramen ovale (FO) electrodes — provides more precise measurements.⁶⁷ Although FO electrodes do not directly contact the hippocampus, they capture signals from adjacent parahippocampal structures such as the entorhinal cortex and parahippocampal gyrus. While the detected medio-temporal IEDs (mtIED) may not originate exclusively from the hippocampus, they are generally assumed to predominantly reflect hippocampal–parahippocampal hypersynchronous activity relevant to hippocampal-dependent memory consolidation. Accordingly, conclusions from FO-based studies should be interpreted as reflecting broader mesial temporal lobe activity.

Interictal activity is also highly brain state–dependent. Non-rapid eye movement (NREM) sleep strongly enhances the occurrence of IEDs, especially in mesial temporal regions.^{46,68} At the same time, NREM sleep is crucial for memory consolidation, as it facilitates the coordination of physiological oscillatory activity supporting information exchange between the hippocampus and cortex for long-term memory storage.³¹ This overlap poses both a challenge and an opportunity: while NREM increases the burden of interictal activity, it also provides a critical window to study the mechanisms by which

IEDs interfere with physiological memory processes. Consequently, studies investigating the impact of IEDs on cognition and consolidation must include long-term sleep recordings to capture both the heightened occurrence of interictal activity and its interaction with sleep-dependent memory processes.

2. Objectives

Understanding the role and the mechanisms by which mtIEDs disrupt cognitive processes provides critical insights into the pathophysiology of epilepsy-related cognitive impairment. These findings have direct implications for developing targeted interventions aimed at mitigating interictal activity to preserve and improve cognitive function in epilepsy patients.

Key Goals:

Assess the Impact of IEDs on Cognitive Function

To quantify the relationship between medio-temporal interictal epileptiform discharge (mtIED) activity and episodic memory performance, and to compare this association with other potential markers of cognitive decline.

Examine the putative neurophysiological mechanisms by which medio-temporal IEDs alter memory consolidation

To investigate how mtIEDs potentially interfere with the physiological processes involved in memory consolidation, particularly focusing on their disruption of coordinated oscillatory activity crucial for hippocampal-cortical communication.

2.1. Study I: Quantitative investigation of potential factors causing cognitive impairment in temporal lobe epilepsy

The objective of this study was to identify, rank, and quantify the factors contributing to long-term cognitive dysfunction in focal epilepsy, with a particular focus on IEDs and other potentially reversible mechanisms. To achieve this, we examined the relationship between mesial temporal IED rates—recorded with foramen ovale (FO) electrodes—and offline cognitive performance in a heterogeneous cohort of 48 patients undergoing invasive presurgical evaluation.

A comprehensive battery of neuropsychological tests assessed episodic memory, while language, attention, and executive functions served as controls. Clinical variables such as seizure frequency and type, epileptogenic zone lateralization, mesial temporal lobe lesions, epilepsy duration, age at onset, and antiseizure medication use were included to control for potential confounding effects.

2.2. Study II: Investigation of the potential mechanisms by which interictal epileptiform discharges potentially alter oscillatory patterns of memory consolidation in temporal lobe epilepsy

The objective of this study was to explore how medio-temporal interictal epileptiform discharges (mtIEDs) might interfere with the physiological oscillatory events that support memory consolidation. Specifically, we examined the temporal coupling between mtIEDs and neocortical sleep spindles, and assessed whether this interaction leads to measurable alterations in spindle characteristics such as duration, amplitude, frequency, and spectral power.

To address this question, we analyzed NREM sleep recordings from refractory temporal lobe epilepsy patients implanted with parahippocampal foramen ovale (FO) electrodes, which allowed direct detection of medio-temporal discharges along with simultaneous cortical spindle activity. We distinguished between spindles that co-occurred with mtIEDs and those that were generated independently, enabling us to characterize the precise influence of epileptic activity on spindle morphology.

By examining how mtIEDs modify spindle properties, this study aimed to shed light on the neurophysiological mechanisms through which interictal activity may disrupt the coordinated hippocampal–cortical communication required for stable memory consolidation, and to determine whether such pathological spindle alterations could represent a mechanistic link to cognitive impairment in temporal lobe epilepsy.

3. Materials and methods

3.1. Materials and methods for Study I

3.1.1. Patient selection

We retrospectively included patients who underwent intracranial investigation with implanted FO electrodes as presurgical evaluation between 2004 and 2016 at the Clinic for Neurosurgery and Neurointervention, Semmelweis University (former National Institute of Clinical Neurosciences), Budapest, Hungary. Before FO implantation all patients underwent neuropsychological evaluation and structural brain magnetic resonance imaging (MRI). We only included patients with: (1) at least one whole day (24 hours) continuous recording; (2) clinical neuropsychological testing performed within 8 months (4 months before to 4 months after) of FO investigation; (3) unchanged antiseizure therapy between neuropsychological testing and the beginning FO monitoring; (4) with no active psychiatric comorbidities; and (5) no history of intellectual disability or major neurocognitive disorder. Forty-eight patients fulfilling these criteria were initially included. Informed consent for the video monitoring, scalp and FO recordings, and the use of the data for research purposes was obtained retrospectively from all patients. The study was approved by the ethics committee of the institute (IRB 8/2016).

3.1.2. EEG recordings and pre-processing

All recordings were acquired using the actually available version of the Brain Quick System (Micromed; with System 2, System Plus, and System Evolution software). The sampling rate was 256 Hz (2 patients), 512 Hz (4 patients), or 1024 Hz (42 patients). Scalp EEG electrodes were placed according to the International 10-20 system, with additional anterior temporal electrodes (T1, T2). EEG data were re-referenced using a common average reference and bandpass filtered between 0.53 and 70 Hz. Four- or six-contact FO electrodes were positioned adjacent to the bilateral mesial temporal lobes, with electrode localization confirmed by post-implantation CT scans and pre-implantation MRI fusion. FO signals were analyzed using a bipolar montage of adjacent contacts. EEG recordings were pre-processed offline using Matlab 2021a (MathWorks, Inc., Natick, MA), the EEGlab toolbox, and custom scripts.

One full post-implantation night, preferably the first, along with the following wake period was selected for analysis, provided there was no ASM reduction. For three patients, we analyzed the second post-implantation night due to technical issues or excessive artifacts in the FO electrodes during the first night. EEG epochs with artifacts were visually identified and excluded from the analysis. The seizure periods, defined as 30 minutes before and after the event, were also excluded from the analysis.

3.1.3. Sleep staging and characteristics

Sleep staging was performed on 30-second scalp EEG epochs and labeled as W, N1, N2, N3, or REM using an automated deep learning algorithm by Vallat and Walker.⁶⁹ This algorithm predicts the sleep stage for each epoch based on a single EEG channel and provides a corresponding confidence value for the prediction. We applied the algorithm iteratively, selecting the channel and corresponding sleep stage with the highest confidence value for each epoch. The age and gender of the subjects were also incorporated into the stage prediction process.

3.1.4. Detection of medio-temporal interictal epileptiform discharges

IED detection was performed on all bipolar FO channels. The channels with the highest IED frequency on each side were selected for further analysis. IED events were automatically detected using an amplitude threshold algorithm. FO channels were high-pass filtered (5 Hz, two-way least-squares finite impulse response filtering), a dynamic approach was employed channel-wise, whereas spikes were thresholded against the [75th percentile + 3 * Inter-Quartile Range] of the EEG signal. The IED detection approach was previously validated against visual analysis by an expert.

Two patients had FO EEG data available from only one side (1 left, 1 right).

In addition to (log-transformed) IED frequency, we also collected and analyzed data on IED amplitude and laterality. For amplitude, values were normalized to the patient-specific detection threshold to account for interindividual variability in baseline signal characteristics.

3.1.5. Neuropsychological evaluation

The neuropsychological measures analyzed in this study were extracted from the comprehensive examination routinely administered as part of the presurgical evaluation for epilepsy surgery. The neuropsychological assessments were conducted within an 8-month window surrounding the FO monitoring (from 4 months before to 4 months after), with no epilepsy-related surgical intervention occurring during this period. Episodic memory was assessed using the following tests: the Rey Auditory Verbal Learning Test (RAVLT; $n = 47$), Rey–Osterrieth Complex Figure test (ROCF; $n = 47$), Verbal Logical Memory Test (VLMT; $n = 47$), and the Location Learning test (LLT; $n = 47$). For language functions the Controlled Oral Word Association Test (COWAT; $n = 37$), Boston Naming Test (BNT; $n = 38$), and the Semantic Verbal Fluency test (SVF; $n = 37$) were administered. Attention and executive functions were evaluated using the Stroop Color-Word Test (SCWT; $n = 41$), the Digit Span – Digit forward test (DGS-F; $n = 42$) and the Digit Span – Digit backward test (DGS-B; $n = 42$). For memory, language, and attention-executive function assessments, the same patient pool participated in all function-specific tests. Summarized results are shown in **Table 1**.

Given the patient cohort with FO implants conveying important information about IEDs in the hippocampal-parahippocampal region, our primary focus was on investigating memory function, particularly consolidation. Therefore, from the available sub-scores, the 30-minute delayed recall scores from all memory tests were used for further analysis. As the neuropsychological evaluations were primarily conducted for clinical purposes, overnight delayed recall scores were not available.

Test scores were correlated with the IED rate on the side corresponding to the cognitive task being performed. Specifically, ROCF and LLT were correlated with the right-sided IED rate, while RAVLT, BNT, VLMT, COWAT and SVF scores were correlated with the left-sided IED rate. For tests where no laterality is expected and for non-hippocampal-dependent cognitive functions (DGS-B, DGS-F, SCWT, COWAT, and SVF) scores were correlated with combined left and right-sided IEDs.

We categorized the neuropsychological tests into two groups: hippocampal dependent and hippocampal independent. The hippocampal dependent group included tests that could potentially be influenced by hippocampal activity, such as the evident episodic

memory tests (RAVLT, ROCF, VLMT, and LLT) and based on previous findings we also included BNT. BNT performance has been associated with the function of the dominant left hippocampus,² and the raw BNT score is a significant predictor of left-sided TLE.⁷⁰ The control hippocampal independent group included tests such as DGS-B, DGS-F, SCWT, COWAT, and SVF.

3.1.6. Clinical characteristics

Self-reported seizure frequency and type were extracted from the patients' seizure diaries and averaged over the 6-month period preceding FO implantation. The high seizure frequency group was defined as outliers using the following formula: self-reported seizure frequency > 75th percentile + 1.5 * interquartile range (IQR) of the sample. Seizure onset laterality was categorized as either unilateral or bilateral.

ASMs were categorized in two ways. The first categorization was based on the number of medications taken (1 – 4), and the second on their known prevalence for cognitive and learning side effects (low- or high-risk group). The high-risk group included patients taking phenobarbital, topiramate, clonazepam, or clobazam.⁷¹

Medial temporal lesions were assessed based on pre-implantation MRI data. All patients underwent an epilepsy protocol MRI before implantation, with scans acquired using either a 1.5T or 3T scanner. These scans were reviewed by an experienced neuroradiologist and presented at the institutional interdisciplinary epilepsy surgery case discussion. MRI studies performed at other centers were re-evaluated. Imaging included T1-weighted and FLAIR whole-brain acquisitions, as well as angled coronal T2 images through the hippocampi. Patients were classified into two groups: those with a medial temporal lesion and those without any MRI-detectable lesions. Patients with isolated temporo-lateral or extratemporal lesions were excluded from this analysis (n = 2). Additionally, lesion laterality (unilateral or bilateral) was assessed.

Epilepsy onset and disease duration was extracted from previous medical records.

3.1.7. Statistical analysis

Descriptive statistics are reported as mean +/- standard deviation or median +/- interquartile range (IQR). IED characteristics were compared using the Wilcoxon rank sum test. Correlations of spike frequencies (separately in wake and NREM stages) with

cognitive test performance were analyzed by Pearson correlations. While spike frequency in wake and NREM deviated from the normal distribution (right-skewed distributions), the log-transformed (wake) and square-root transformed (NREM) versions were used in the correlational analyses. In a sensitivity analysis, all these associations were studied by Spearman correlations. The Wilcoxon Rank sum test was used for comparing spike frequencies across sleep stages. The 95% Confidence intervals for the Pearson and Spearman correlations are presented for all correlations. P values of < 0.05 were considered significant. Since correlational analyses were performed for several cognitive measures, we performed a correction for multiple testing separately for spike frequency in NREM and wake stages. The Benjamini-Hochberg method (B-H) was applied since cognitive measurements were not independent.

The association between clinical measures and cognitive functions is analyzed using linear mixed model analyses, separately for each cognitive test and sleep/wake status, and including the following predictors in each model: IED frequency, IED amplitude, lesion, number of ASMs, ASM risk for memory and learning dysfunction, disease duration, seizure laterality, self-reported seizure frequency, and GTCS. We employed this secondary approach to investigate the effects of the different predictors, including IED frequencies within the same model, to compare their impact directly. The Location Learning test was a special case, as the result of this cognitive measure was an ordinal value that strongly deviated from a normal distribution; therefore, only the Spearman correlation was employed.

Missing data were excluded, and no imputation techniques were used. All statistics were performed in R (version 4.3.2).

3.2. Materials and methods for Study II

3.2.1. Patient selection

The same patient population from Study I was evaluated in this study, with additional inclusion criteria. The criteria were as follows: (1) patients with a mesiotemporal IED rate of 10–50 per minute, ensuring a sufficient number of events in all spindle groups across patients and reducing the risk of random coincidence due to excessive IEDs; (2) patients with single-peaked IED waveforms to guarantee reproducible timing of IED peaks; (3) a minimum of 200 detected spindles during NREM sleep per night; and (4) patients with

no seizures or at most one seizure per night. The study was approved by the ethics committee of the National Institute of Clinical and Neurosciences, Budapest, Hungary (IRB 8/2016).

3.2.2. EEG recording and pre-processing

EEG recordings and preprocessing were conducted in the same manner as described in Study I.

One full night sleep was selected for analysis. The first postimplant night was excluded, and the one with the longest sleep period without epileptic seizure was selected.

Sleep stages and artifacts were scored visually for 30-s epochs according to standard criteria 32 by an expert trained in sleep research. We included all the artifact-free N2 epochs in the further analyses.

3.2.3. Detection of spindle and IED activity

3.2.3.1. Spindle detection and analysis

A previously established and validated method⁵⁹. EEG signals were offline rereferenced to averaged Tp9 and Tp10 to construct the mean mastoid reference. Sleep spindle detection was performed separately on scalp EEG channels F3, F4, P3, and P4. The raw EEG was band-pass filtered between 11 and 16 Hz using a zero-phase shift Hamming window-based filter. A spindle event was detected wherever the filtered signal exceeded an individually calculated amplitude and a fixed duration criterion. Amplitude threshold was set to three times the SD of the amplitude across N2 sleep epochs. Spindle onset was defined by the time point where the envelope signal (magnitude of the Hilbert transform) crossed the threshold, and offset when the signal fell under the threshold. Detections with duration < .5 s were rejected. We calculated the following parameters for all the patients and for all four scalp electrodes: (1) the mean spindle duration, (2) the mean maximal amplitude (defined by the mean maximum of the envelopes of filtered EEG signals over the detected spindles); and (3) the power spectral density. The peak frequency was defined as the frequency corresponding to the maximum spectral power. The spindle detection approach was validated against visual analysis by an expert. Visual detection was carried out blinded. Agreement between the two methods resulted in on average

89.3% ($\pm 7.1\%$) for true positive detections and 17.1% ($\pm 8.3\%$) for false positives during NREM sleep.

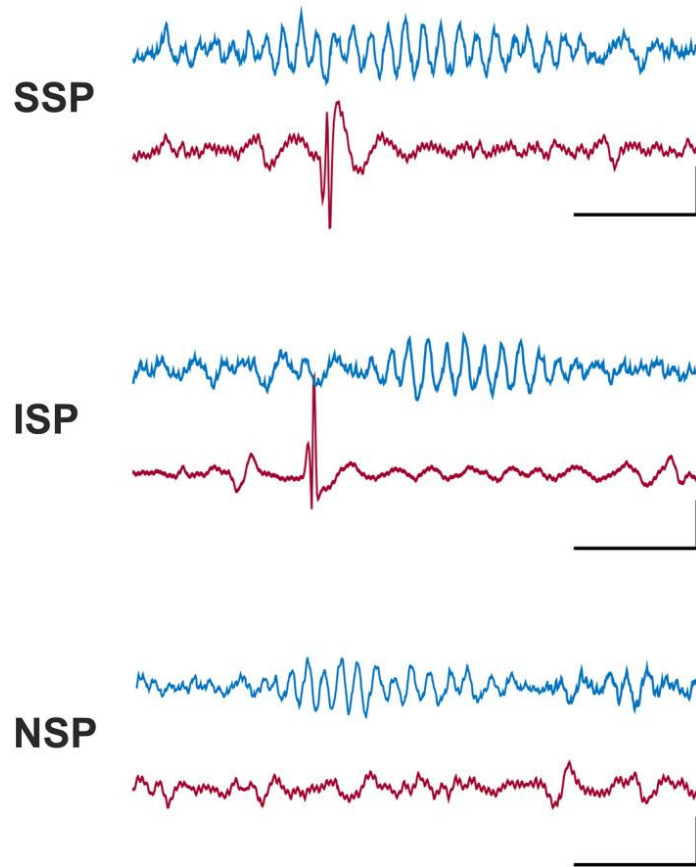
3.2.3.2. Detection of medio-temporal interictal epileptiform discharges

IED detection was conducted in the same manner as described in Study I.

3.2.4. Spindle categories

Spindles were categorized based on their temporal relationship to mtIEDs. Three groups were created: (1) spindles coinciding with mtIEDs (spike-spindle [SSP]), defined by an ipsilateral mtIED peak falling between the onset and offset of the spindle; (2) spindles induced by mtIEDs (induced spindle [ISP]), when an ipsilateral mtIED peak was detected within 1 s before spindle onset; and (3) no spike spindles (NSP), when no ipsilateral mtIED detection was in the time range between 1 s before onset and offset. See Figure 1 for illustration. If multiple criteria (1 and 2) were true, or a scalp detected IED coincided with the spindle, the event was rejected. **Figure 1.**

Figure 1 Experimental design.



Sleep spindles registered from scalp electrodes (F3, F4, P3, P4; blue; scale bar = 50 μ V, 500 ms) and medio-temporal interictal epileptic discharges simultaneously registered from foramen ovale electrode (red; scale bar = 100 μ V, 500 ms) in Patient 1 are shown. Examples of spindle types: SSP = scalp spindles (blue line) that co-occurred with medio-temporal interictal epileptiform discharges (IEDs; red line), ISP = scalp spindles that occurred within 1 s after a medio-temporal IED, NSP = scalp spindles with no temporal connection with medio-temporal IEDs

3.2.5. Antiseizure medications

Antiseizure medications (ASMs) were categorized based on their main pharmacodynamics into the following groups: (1) Na channel inhibitors (lamotrigine, carbamazepine, lacosamide, oxcarbazepine, rufinamide), (2) Ca channel inhibitors (gabapentin, zonisamide), (3) γ -aminobutyric acid type A (GABAA) receptor modulators (phenobarbital, clonazepam), (4) synaptic vesicle 2A modulator (levetiracetam), and (5) polypharmacological mechanism (valproate, topiramate). To investigate the possible pharmacological effects on spindle characteristics, we analyzed spindle duration and

spindle amplitude between patients who use a given type of ASM and those who do not. This comparison was performed for all the above-mentioned medication groups separately.

3.2.6. Cross-correlation

We computed cross- or autocorrelograms between mtIED peak and spindle onset times. IED times were taken as cross-correlogram references.

3.2.7. Neuropsychological assessment

Neuropsychological assessments were conducted in the same manner as described in Study I. According to memory investigation, the following tests were performed with the 19 patients: Rey Auditory Verbal Learning Test (RAVLT; $n = 15$), Rey–Osterrieth Complex Figure test (ROCF; $n = 17$), Location Learning Test ($n = 15$), and Verbal Reasoning Test ($n = 13$). Of these tests, we chose to assess the RAVLT and ROCF delayed recall, because they reflect memory consolidation, storing, and retrieval. Delayed recall scores were correlated with the ratio of SSPs (ratio of SSPs to all other spindles).

3.2.8. Statistical analysis

Statistical analysis was performed using custom MATLAB code. Differences between the spindle groups were analyzed by the nonparametric Wilcoxon signed rank test. Durations, amplitudes, and peak frequency for the spindle groups were extracted from each other, whereas in the null hypotheses, we assumed that these differences do not differ from zero. Significance level was set to $p = 0.05$, and the Bonferroni method was applied to correct for multiple comparisons; the corrected p value was $0.05/12 = 0.00416$ (rounded to the fifth decimal). Twelve statistical comparisons were performed: four electrode sites $\times$ three groups.

The power changes in the spindle spectra were assessed using a permutation test. Five thousand random samples were generated to test for statistically significant differences in each 0.5-Hz wide frequency bin between the two compared spindle groups.⁷² Two-sided paired t -tests were used in each frequency bin; t -values were set against the values of the randomly shuffled values from both spindle groups.

Benjamini–Hochberg procedure for false discovery rate (FDR) was applied to control for multiple comparisons by adjusting the p-values obtained for all frequency bins. Separate tests were performed at each derivation.

Due to small sample sizes, the Kruskal–Wallis test was used to compare ASM groups.

For cross-correlation statistics, we used the "xcorrvalue" MATLAB function that yields p-values of significance of the maximum cross-correlation vector using a permutation test with random vectors. If the random vector fraction was <0.0005 , then cross correlation was considered significant.⁷³

For group comparisons of spindle characteristics between patient groups of different epilepsy variables and cross-correlogram "types," we used Mann–Whitney or Kruskal–Wallis tests, depending on the nature of the data analyzed.

4. Results

4.1. Results for Study I.

4.1.1. Clinical and demographic characteristics

We investigated 48 patients with focal onset seizures using FO electrode implants. Of these, 27 were female (55%), with a mean age of 36.8 ± 10.02 years (range: 18–53), and an average epilepsy duration of 18.06 ± 12.96 years (range: 1–47). Temporal lobe pathology was present in 34 patients (71%), extratemporal in 2 patients (4%), while 12 patients (25%) were non-lesional. The most common etiology was hippocampal sclerosis (40% of all cases). Seizure onset was left temporal in 20 patients (42%), right temporal in 10 patients (21%), and bitemporal in 18 patients (37%). The mean seizure frequency was 4.08 per month ± 6.29 (range = 0.5–30) during the 6 months, and 61% of patients also experienced generalized tonic-clonic seizures (GTCS). The mean number of ASMs at the time of FO implantation was 2.44 ± 0.87 (range = 0–4). 5 patients (10%) were left handed. Detailed patient characteristics and neuropsychological test scores are shown in **Table 1**.

Table 1 Demographic, clinical and anatomical characterization of subjects.

Characteristics	
N	48
Sex n (%) female	26 (55)
Age in years, mean SD (range)	36.8 ± 10.02 (18 - 53)
Age at onset in years, mean SD (range)	18.39 ± 10.64 (0.3 - 44)
Disease duration in years, mean SD (range)	18.06 ± 12.96 (1 - 47)
MRI lesion n (%)	
Temporal	34 (71)
Hippocampal	30 (64)
Extratemporal	2 (4)
Non-lesional	12 (25)
Etiology n (%)	
HS	19 (40)
FCD	10 (20)
Seizures	
Laterality (%)	
left	20 (42)
right	10 (21)
bilateral	18 (37)
Frequency per month, mean SD (range)	4.1 ± 6.29 (0.5 - 30)
Patients with high seizure frequency n (%)	5 (10)
GTCS n (%)	29 (61)
ASMs	
Number, mean SD (range)	2.44 ± 0.87 (0 - 4)

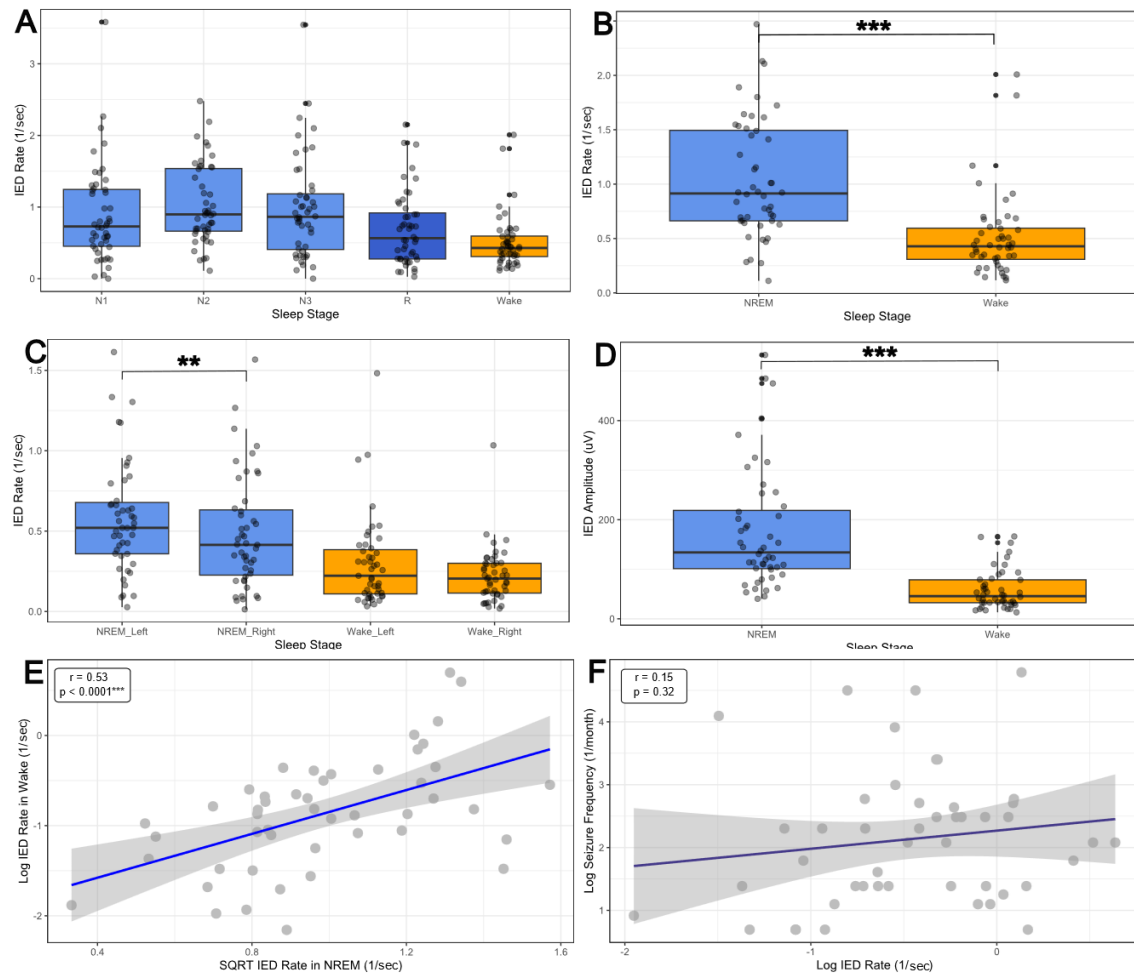
High risk ASM use n (%)	21 (45)
Neuropsychological test delayed recall score, mean SD	
RAVLT	9.45 ± 3.66
BNT	48.37 ± 8.62
VLMT	6.19 ± 3.08
ROCF	36.96 ± 13.41
LLT	1.23 ± 2.84
SCWT	48.93 ± 9.01
COWAT	31.95 ± 10.8
SVF	18.81 ± 4.72
DGS-B	4.07 ± 1.03
DGS-F	5.39 ± 1.02

HS = hippocampal sclerosis; FCD = focal cortical dysplasia; GTCS = generalized tonic-clonic seizure, ASM = antiseizure medication; RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey–Osterrieth Complex Figure test; BNT = Boston Naming Test; VLMT = Verbal Logical Memory Test; LLT = Location Learning test; COWAT = Controlled Oral Word Association Test, SVF = Semantic Verbal Fluency test; SCWT = Stroop color-word test; DGS-B = Digit Span – Digit backward test; DGS-F = Digit Span – Digit forward test

4.1.2. Characteristics of medio-temporal interictal epileptiform discharges

We computed the mtIED rate for both sides in each patient and across all sleep stages (**Figure 2A**). MtIEDs were significantly more frequent during NREM sleep (for left + right mtIED median = 55.4/min, IQR = 40.4–90.3) compared to wakefulness (median = 26.4/min, IQR = 19.6–36.1) (Wilcoxon rank sum, $p < 0.0001$) (**Figure 2B**). The median mtIED rate across all subjects on FO channels was 23.0/min (range = 3.3–72.4) on the left side and 18.7/min (range: 2.2–49.6) on the right side. A significant difference in mtIED rate between sides was detected during NREM sleep (Wilcoxon rank sum, $p < 0.01$), with a statistical trend observed during wakefulness (Wilcoxon rank sum, $p = 0.08$) (**Figure 2C**). MtIED amplitude was significantly higher during NREM sleep (median = 143.7 μ V, IQR = 104.2–226.9) compared to wakefulness (median = 45.8 μ V, IQR = 32.6–79.1) (Wilcoxon rank sum, $p < 0.0001$) (**Figure 2D**). Additionally, the mtIED rate during NREM sleep strongly correlated with the mtIED rate during wake ($r = 0.53$, 95% CI = 0.29–0.71, $p < 0.0001$) (**Figure 2E**). We also investigated the relationship between (log transformed) total (wake and sleep) mtIED rate and (log transformed) self-reported seizure frequency but found no significant correlation ($r = 0.15$, $p = 0.32$, 95% CI = -0.15 – 0.42) (**Figure 2F**).

Figure 2. Characteristics of medio-temporal interictal epileptiform discharges.



(A) The IED rate across sleep stages. (B) The IED rate across sleep stages. IED rates were higher in NREM sleep. (C) Lateralization of IEDs. IED rates were higher in the left side, significant in NREM sleep. (D) The IED amplitude across sleep stages. IED amplitudes were higher in NREM sleep. (E) Correlation between IED rate in NREM and wake. IED rate significantly correlated across sleep NREM and wake stages. (F) Correlation between IED rate and seizure rate. IED rate did not correlate with seizure rate. For (A-D) The central line indicates the median, the box indicates interquartile range. For (E-F), in the correlation plots colored lines indicate linear fits and shaded regions indicate 95% confidence intervals. Statistical significance is indicated by asterisk(s) (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). N1-3 = NREM1-3; R = REM

4.1.3. Correlation of medio-temporal interictal epileptiform discharge characteristics and clinical characteristics with cognition

Subsequently, we examined the cross-sectional relationships between mtIED characteristics and cognitive performance. Correlations were assessed with mtIED rates during both NREM sleep and wakefulness. The associations were analyzed using (1) Pearson/Spearman correlations and (2) a linear mixed model analysis, which included all IED and clinical variables in one model for each cognitive (memory) test and sleep/wake status.

Left mtIED rate in wakefulness is negatively associated with RAVLT, VLMT, and BNT. ROCF and LLT scores are also significantly related to right mtIED rate. The linear mixed model analyses confirmed all Pearson correlation results. See **Table 2** for the Pearson and Spearman correlations and **Table 3** for the results of the Linear Mixed Model analyses. Also, for correlations between mtIED rate and hippocampal-dependent cognitive functions, see **Figure 3**.

In contrast, cognitive measures of attention, executive function, and verbal function (COWAT, SVF, DGS-F, and SCWT scores) were not associated with mtIED rates (all p -values > 0.05). For details of correlations between mtIED rate and hippocampal-independent functions, see **Figure 4**.

Medio-temporal IED rate in NREM sleep is associated negatively with memory scores, including BNT (left mtIED), and also with DGS-B (bilateral mtIED), but not with other cognitive measures, such as verbal and attention function scores (COWAT, SVF, DGS-F, and SCWT scores; $|r \text{ values}| < 0.2$ and all p values > 0.3). Again, linear mixed model analysis confirmed the correlation between mtIED rates and BNT, but not with DGS-B.

After correction for multiple testing, the Pearson correlations of all hippocampus-dependent tests (memory test results in wake and BNT scores in NREM sleep) with mtIED rates remained significant (**Table 2** and **Figure 3**).

The linear mixed model analyses revealed that, among the clinical characteristics, only disease duration significantly affects performance on the RAVLT and VLMT tests. Other clinical factors, such as lesion, number of ASMs, ASM risk for memory and learning

dysfunction, disease duration, seizure laterality, self-reported seizure frequency, and GTCS, did not affect memory functions.

We also examined the possibility that mtIEDs affect cognitive functions differently in patients with lesions. Therefore, in separate linear models, we examined the effect of the lesion $\times$ mtIED interaction on hippocampal-dependent cognitive functions (RAVLT, BNT, VLMT, ROCF, LLT), but no significant interaction effect was found (all p-values > 0.1).

Table 2. Correlation of mtIED rate with cognitive test scores

Test	State	n	Pearson r	Pearson r 95%CI	p (Pearson)	Spearman r	Spearman r 95%CI	p (Spearman)
RAVLT	wake	46	-0.37	-0.60; - 0.09	0.01*	-0.38	-0.61; -0.10	0.009*
	NREM	46	-0.24	-0.50; 0.05	0.11	-0.27	-0.52; 0.02	0.07
VLMT	wake	46	-0.29	-0.54; 0.00	0.048*	-0.26	-0.51; 0.04	0.087
	NREM	46	-0.20	-0.46; 0.10	0.19	-0.16	-0.43; 0.14	0.29
BNT	wake	37	-0.43	-0.66; -0.13	0.007*	-0.37	-0.62; -0.06	0.023*
	NREM	37	-0.43	-0.66; -0.12	0.007*	-0.30	-0.57; 0.03	0.071
ROCF	wake	46	-0.35	-0.58; -0.06	0.018*	-0.35	-0.58; -0.07	0.016*
	NREM	46	-0.23	-0.49; 0.07	0.127	-0.25	-0.50; 0.05	0.1
LLT	wake	43	NA	NA	NA	0.40	0.11; 0.62	0.008*
	NREM	43	NA	NA	NA	0.04	-0.27; 0.33	0.807

RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey–Osterrieth Complex Figure test; BNT = Boston Naming Test; VLMT = Verbal Logical Memory Test; LLT = Location Learning test; DGS-B = Digit Span – Digit backward test

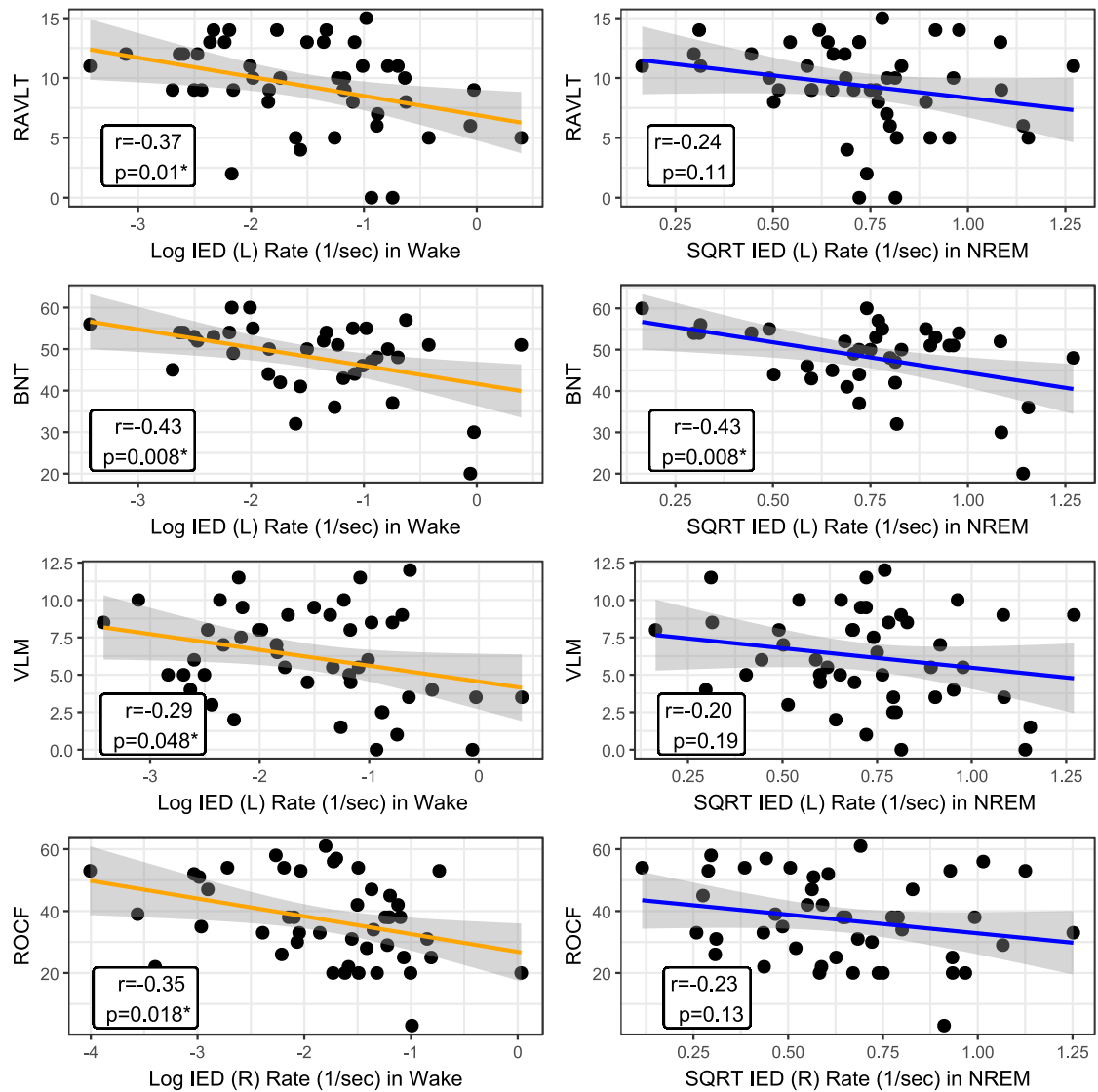
Table 3A. Association of wake IED frequency and clinical characteristics with cognition: results from linear mixed model analyses.

Cognitive Test	Clinical Parameter	Estimate	Std. Error	t value	p value
RAVLT	(log) IED frequency	-1,61	0,63	-2,55	<u>0,02*</u>
	IED Amplitude	2,05	2,19	0,94	0,35
	Seizure onset laterality	0,06	1,04	0,06	0,95
	ASM high risk	-1,63	1,44	-1,13	0,26
	ASM number	-0,13	0,70	-0,18	0,86
	GTCS	-1,95	1,03	-1,89	0,07
	MTL lesion	-0,46	1,19	-0,38	0,70
	Disease duration	-0,08	0,04	-1,84	0,07
	Seizure frequency	0,01	0,02	0,59	0,56
BNT	(log) IED frequency	-4,39	1,78	-2,47	<u>0,02*</u>
	IED Amplitude	-1,65	5,42	-0,30	0,76
	Seizure onset laterality	-4,51	2,72	-1,66	0,11
	ASM high risk	-6,01	3,96	-1,52	0,14
	ASM number	4,07	2,19	1,86	0,07
	GTCS	-4,09	2,89	-1,41	0,17
	MTL lesion	1,81	3,19	0,57	0,57
	Disease duration	-0,21	0,13	-1,62	0,12
	Seizure frequency	-0,02	0,08	-0,30	0,77
VLMT	(log) IED frequency	-1,54	0,57	-2,71	<u>0,01*</u>
	IED Amplitude	2,53	2,03	1,24	0,22
	Seizure onset laterality	-1,17	0,96	-1,22	0,23
	ASM high risk	-0,58	1,40	-0,42	0,68
	ASM number	0,27	0,66	0,41	0,68
	GTCS	-0,17	0,92	-0,18	0,86
	MTL lesion	0,43	1,10	0,39	0,70
	Disease duration	-0,09	0,04	-2,30	<u>0,03*</u>
	Seizure frequency	0,00	0,02	-0,27	0,79
ROCF	(log) IED frequency	-5,97	2,56	-2,33	<u>0,03*</u>
	IED Amplitude	-6,72	8,52	-0,79	0,44
	Seizure onset laterality	-0,83	4,50	-0,19	0,85
	ASM high risk	-2,83	5,84	-0,48	0,63
	ASM number	4,40	2,81	1,57	0,13
	GTCS	-6,51	4,12	-1,58	0,12
	MTL lesion	-4,80	5,08	-0,94	0,35
	Disease duration	-0,11	0,18	-0,59	0,56
	Seizure frequency	0,06	0,08	0,68	0,50

Table 3B. Association of NREM IED frequency and clinical characteristics with cognition: results from a linear mixed model analysis.

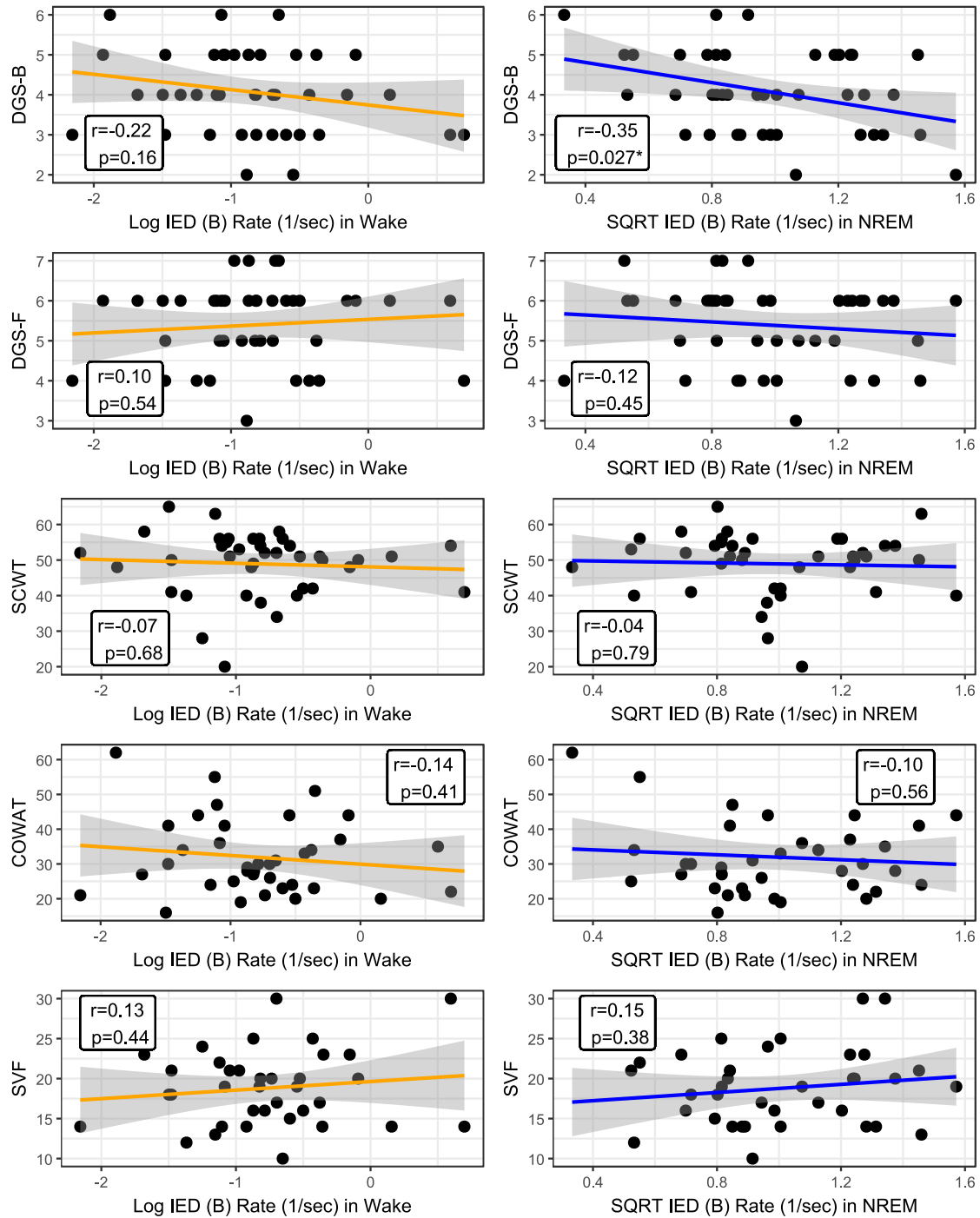
Cognitive Test	Clinical Parameter	Estimate	Std. Error	t value	p value
RAVLT	(sqrt) IED frequency	-3,95	2,41	-1,64	0,11
	IED Amplitude	-0,18	0,63	-0,28	0,78
	Seizure onset laterality	0,49	1,08	0,45	0,65
	ASM high risk	-2,23	1,50	-1,49	0,14
	ASM number	-0,14	0,72	-0,19	0,85
	GTCS	-1,98	1,07	-1,85	0,07
	MTL lesion	-1,04	1,20	-0,86	0,39
	Disease duration	-0,09	0,05	-2,06	<u>0,047*</u>
	Seizure frequency	0,00	0,02	0,10	0,92
BNT	(sqrt) IED frequency	-14,94	6,39	-2,34	<u>0,03*</u>
	IED Amplitude	-0,03	1,55	-0,02	0,99
	Seizure onset laterality	-2,70	2,82	-0,96	0,35
	ASM high risk	-6,91	4,18	-1,65	0,11
	ASM number	3,48	2,21	1,58	0,13
	GTCS	-3,79	2,99	-1,27	0,22
	MTL lesion	2,07	3,27	0,63	0,53
	Disease duration	-0,22	0,13	-1,61	0,12
	Seizure frequency	-0,06	0,09	-0,62	0,54
VLMT	(sqrt) IED frequency	-4,40	2,13	-2,07	<u>0,046*</u>
	IED Amplitude	0,75	0,59	1,28	0,21
	Seizure onset laterality	-0,73	0,99	-0,74	0,46
	ASM high risk	-0,78	1,47	-0,53	0,60
	ASM number	0,37	0,67	0,55	0,59
	GTCS	-0,44	0,95	-0,46	0,65
	MTL lesion	0,38	1,12	0,34	0,73
	Disease duration	-0,10	0,04	-2,41	<u>0,02*</u>
	Seizure frequency	-0,01	0,02	-0,66	0,51
ROCF	(sqrt) IED frequency	-10,24	8,67	-1,18	0,25
	IED Amplitude	-2,00	2,67	-0,75	0,46
	Seizure onset laterality	-2,98	4,55	-0,65	0,52
	ASM high risk	-5,27	6,14	-0,86	0,40
	ASM number	4,63	2,94	1,57	0,12
	GTCS	-6,12	4,39	-1,39	0,17
	MTL lesion	-5,97	5,30	-1,13	0,27
	Disease duration	-0,02	0,19	-0,10	0,92
	Seizure frequency	0,00	0,09	-0,01	0,99

Figure 3. Correlation between IED rate and medio-temporal dependent cognitive functions.



All subplots are scatter plots with best fit regression line and 95% confidence interval for the association between the measured cognitive test score and IED rate. For all subplots orange line indicate the IED rate in wake and blue line indicate IED rate in sleep. For all plots statistical significance is indicated by asterisk(s) (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). RAVLT = Rey Auditory Verbal Learning Test; BNT = Boston Naming Test; VLM = Verbal Logical Memory Test; ROCF = Rey–Osterrieth Complex Figure test

Figure 4. Correlation between mtIED rate and medio-temporal independent cognitive functions (language, executive functions and attention).



All subplots are scatter plots with best fit regression line and 95% confidence interval for the association between the measured cognitive test score and IED rate. For all subplots orange line indicate the IED rate in wake and blue line indicate IED rate in sleep. For all plots statistical significance is indicated by asterisk(s) (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). DGS-B = Digit Span – Digit backward test; DGS-F =

Digit Span – Digit forward test; SCWT = Stroop color-word test COWAT = Controlled Oral Word Association Test, SVF = Semantic Verbal Fluency test

4.2. Results for Study II

4.2.1. Clinical and demographic characteristics

The final sample consisted of 21 patients; nine were female, mean age was 35.7 ± 9.9 years (range = 18–60), the average duration of epilepsy was 12.7 ± 10.4 years (range = 1–42). Fourteen patients had temporal and seven patients extratemporal pathology. Detailed patient characteristics are summarized in **Table 4**.

Table 4. Demographic, clinical and anatomical characterization of subjects.

Patients	Age (y)	Sex	Structural neuroimaging	Handedness	Age at onset (y)	Epilepsy duration	SOZ laterality	ASM
1	37	male	HS L	R	32	5	L temp	LEV, LTG CBZ
2	31	male	parahipp. GG L	R	1	30	L temp	TOP, CBZ
3	27	female	insular LGG R	L	26	1	right insular	GAB, RUF
4	30	male	normal	R	21	9	bitemp	LEV, OXC ZON
5	60	female	viral encephalitis	L	33	27	bitemp	LTG, OXC LEV
6	41	male	HS L	R	22	19	L temp	TOP, LTG BZD
7	52	male	amygd. lesion L	R	33	19	L temp	CBZ, LAC LEV
8	29	male	HS L post encephalitis	R	0.1	28.9	bitemp	PHE, BZD
9	42	female	HS R	R	0.2	41.8	Rtemp	OXC
10	30	female	HS R	R	26	4	L temp	LEV, LTG
11	34	male	normal	L	17	17	bitemp	LTG, PHE
12	26	female	temp FCD L	R	3	23	L front	CBZ, LEV
13	35	female	mitochondrial encephalopathy	R	34	1	multifocal	OXC, BZD, LTG

14	40	female	parahipp. ODG L	R	32	8	left temp	TOP, ZON BDZ, CBZ
15	32	female	front FCD L	R	12	20	L front.	LEV, CBZ ZON, BZD
16	18	male	normal	R	13	5	bitemp.	CBZ, LTG BDZ
17	42	male	normal	R	22	20	bitemp.	LEV, VPA
18	41	male	HS R	R	10	31	bitemp.	CBZ, LTG BDZ
19	27	male	HS R	R	25	2	R temp	VPA, LTG BDZ
20	27	female	temp FCD R	R	9	18	bitemp.	VPA, LTG
21	49	male	HS R	L	12	37	bitemp.	VPA, CBZ, BZD

R = right; L = left; LGG: low-grade gliomas; GG: ganglioglioma, ODG: oligodendroglioma; FCD: focal cortical dysgenesis; HS: hippocampal sclerosis; LEV: levetiracetam; VPA: valproate; LTG: lamotrigine; CBZ: carbamazepine; TOP: topiramate; GAB: gabapentin; RUF: rufinamide; ZON: zonisamide; OXC: oxcarbazepine; LAC: lacosamide; PHE: phenytoin; BZD: benzodiazepine

4.2.2. Sleep spindle characteristics

A total of 3695.2 min of artifact-free N2 sleep was analyzed (range = 72.6–328.3 min per subject). For detailed characteristics, see **Table 5**. The duration, amplitude, and frequency of the spindles in all recording sites agreed with previous reports.⁷³

The median mtIED rate across all subjects on FO channels was $31.9 \pm 17.01/\text{min}$ (range = 14.2–48.9) for the left side and $21.89 \pm 5.81/\text{min}$ (range = 11.1–41.3) for the right side.

Spindles were assigned to three categories (NSP, ISP, SSP). All patients expressed all three spindle types, but with differing proportions.

Table 5. Sleep spindle characteristics at each electrode

Characteristics	F3, mean $\pm$ SD	F4, mean $\pm$ SD	P3, mean $\pm$ SD	P4, mean $\pm$ SD
Density, /min	6.76 $\pm$ 3.56	6.24 $\pm$ 3.91	7.08 $\pm$ 4.01	5.92 $\pm$ 4.52
Duration, ms	837 $\pm$ 291	832 $\pm$ 98	829 $\pm$ 224	817 $\pm$ 107
Maximal Amplitude, μ V	43.16 $\pm$ 9.813	42.91 $\pm$ 10.022	39.43 $\pm$ 11.813	38.76 $\pm$ 13.041
Frequency, Hz	12.276 $\pm$ 2.977	12.601 $\pm$ 0.924	13.240 $\pm$ 5.207	13.556 $\pm$ 1.039

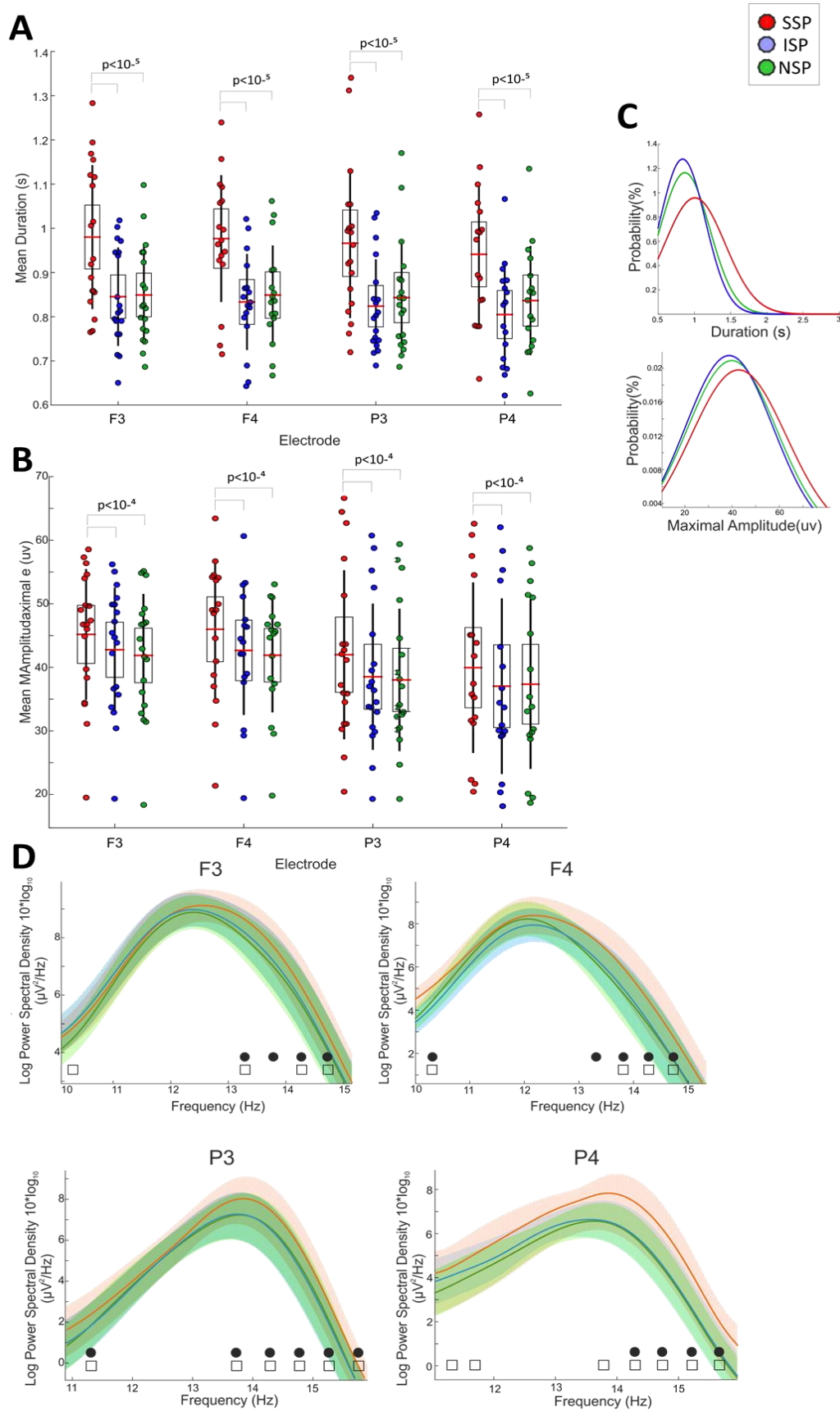
4.2.2.1. Sleep spindle duration

Spindles coupled with mtIEDs (SSP) had longer duration at all recording sites compared to spindles induced by IEDs (ISP vs. SSP; for all electrodes $p < 10^{-5}$) and spindles without IED connection (NSP vs. SSP; for all electrodes $p < 10^{-5}$), whereas duration of ISPs and NSPs did not differ (for all electrodes, $p > .1$). Mean duration differences between SSPs and NSPs were 134 ± 62 , 129 ± 46 , 139 ± 52 , and 104 ± 35 ms at F3, F4, P3, and P4 locations, respectively. Results are presented in **Figure 5A**.

To determine whether timing of mtIEDs within the spindle span has implications on spindle duration, we divided the duration of SSPs into three equal parts and compared spindle durations when mtIED coincided in the first or the last third. No differences were found (for all electrodes, $p > .1$).

We also aimed to assess whether the prolongation of spindles varied between the frontal and the parietal electrodes. Duration differences of SSP and NSP spindles were compared between the ipsilateral frontal and parietal electrodes (F3-P3, F4-P4). No significant differences were revealed (F3 vs. P3, $p = .121$; F4 vs. P4, $p = .601$).

Figure 5. Characteristics of the spindle types.



SSP = scalp spindles that co-occurred with medio-temporal interictal epileptiform discharges (IEDs; red), ISP = scalp spindles that occurred within 1 s after a medio-temporal IED (blue), NSP = scalp spindles with no temporal connection with medio-temporal IEDs (green). **(A)** Spindle duration (horizontal lines = mean, boxes = 95% confidence interval, vertical bold lines = SD). Note that SSP had a longer duration at each recording site, whereas ISP had a duration similar to NSP. Numbers of events included in the analysis: SSP (F3) = 6453, (F4) = 5312, (P3) = 6678, (P4) = 5453; ISP (F3) = 7589, (F4) = 6134, (P3) = 7312, (P4) = 6478; NSP (F3) = 10 865, (F4) = 9876, (P3) = 11 567, (P4) = 9893. For detailed statistics, see Table S2. **(B)** Spindle maximum amplitudes. Note that SSP had the highest maximum amplitude. Numbers of events: SSP (F3) = 6453, (F4) = 5312, (P3) = 6678, (P4) = 5453; ISP (F3) = 7589, (F4) = 6134, (P3) = 7312, (P4) = 6478; NSP (F3) = 10 865, (F4) = 9876, (P3) = 11 567, (P4) = 9893. For detailed statistics, see Table S3. **(C)** Probability distribution of durations (upper panel) and maximum amplitudes (lower panel) across spindle groups at all electrodes. **(D)** Differences in power spectra (mean $\pm$ SEM). SSP exhibited a relative increase in spectral power within the higher sigma frequency ranges. Dots indicate significant frequency bins corresponding to corrected $p < .05$ between SSP and ISP; squares indicate significant frequency bins corresponding to corrected $p < .05$ between SSP and NSP

4.2.2.2. Sleep spindle amplitude

SSPs had higher maximal amplitude over the other groups (SSP vs. ISP for all electrodes, $p < 10^{-4}$; SSP vs. NSP for all electrodes, $p < 10^{-4}$). There was no amplitude difference between ISP and NSP (for all electrodes, $p > .1$). Results are presented in Figure 5B. Also, amplitude difference did not vary between the frontal and parietal electrodes (F3 vs. P3, $p = .629$; F4 vs. P4, $p = .795$).

4.2.2.3. Sleep spindle frequency

The peak frequency was not different among the spindle groups; however, the maximal power of the peak frequency was higher in SSP (SSP vs. ISP, all corrected $p < .001$; SSP vs. NSP, all corrected $p < .001$) at all electrodes.

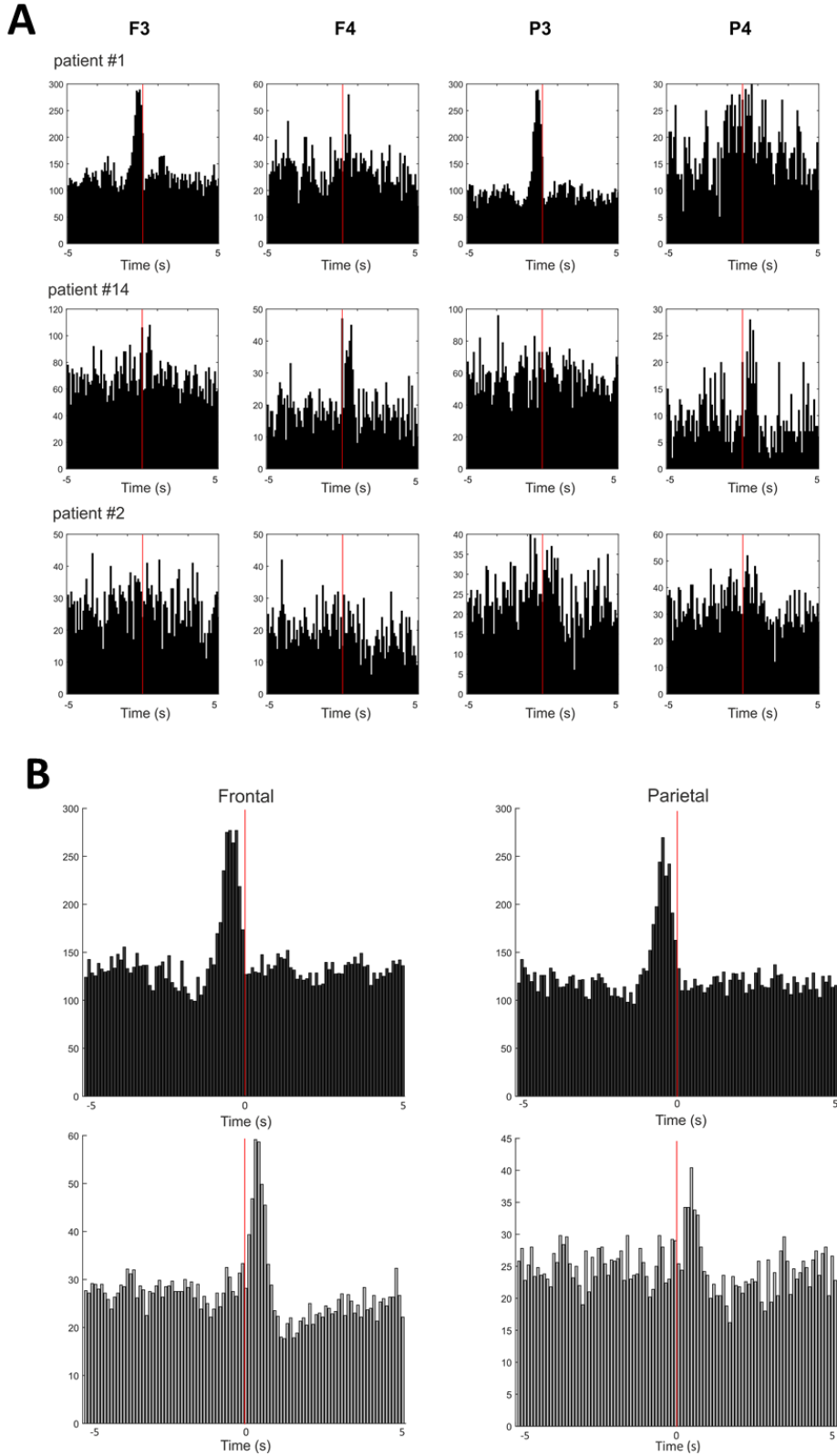
We aimed to further specify the difference, so we investigated the power spectrum at all frequency bins in all spindle groups. The SSP group exhibited a relative increase in spectral power within the higher sigma frequency ranges compared to other spindle groups; frequency bins remaining significant after FDR correction were 12.5–15.5 Hz in the frontal electrode sites and 13.5–15.5 Hz in the parietal electrode sites (SSP vs. NSP for all electrodes, $p < 10^{-5}$; SSP vs. ISP for all electrodes, $p < 10^{-5}$; presented in **Figure 5C**.

4.3. Temporal relationship between sleep spindles and mtIEDs

To study the temporal relationship between spindles and mtIEDs, we computed cross-correlations between mtIED peak occurrences and spindle onsets. In 11 patients (52%), we found significant cross-correlation, but the direction of this coherence was of two kinds. In eight (39%) patients, the mtIEDs tended to precede the spindles, with an average time offset of 450 ± 92 ms for the frontal electrodes and 378 ± 99 ms for the parietal ones. In contrast, in three patients (14%), mtIEDs tended to follow the spindles with similar timing; the average time offset was 462 ± 268 ms for the frontal and 400 ± 100 ms for the parietal electrodes. (For examples of individual cross-correlograms and also for averaged cross-correlograms of each group, see **Figure 6**.)

Next, we investigated the effect of temporal correlation differences on spindle characteristics. We found no duration or amplitude difference among spindle groups when patients were allocated into three groups based on the temporal coherence (patients with no significant correlation between mtIEDs and spindles; patients with significant coherence, where spindles tended to precede mtIEDs; and patients with significant coherence, where spindles tended to follow mtIEDs). For detailed data, see **Table 6**.

Figure 6. Cross-correlation of medio-temporal interictal epileptiform discharges and scalp spindle onsets



Red lines indicate peak of medio-temporal IEDs. **(A)** Examples from patients with high and low correlations. In Patient 1, spindles preceded IEDs. Numbers of events: IEDs: right = 6939, left = 1717; spindles: F3 = 1514, F4 = 1233, P3 = 1135, P4 = 818. In Patient 14, IEDs preceded spindles. Numbers of events: IEDs: right = 1571, left = 6503; spindles: F3 = 785, F4 = 854, P3 = 691, P4 = 449. In Patient 2, we found no correlation. Numbers of events: IEDs: right = 1253, left = 4280; spindles: F3 = 765, F4 = 1869, P3 = 744, P4 = 929. **(B)** Averaged cross-correlogram of patients with significant correlations. Upper panel shows patients with significant correlation where spindles preceded IEDs (n = 3; numbers of events: IED = 31 463; spindle frontal = 9651, parietal = 9804; p frontal = 6.345×10^{-5} , lag = -430 ms; p parietal = 1.567×10^{-5} , lag = -410 ms). Lower panel shows patients with significant correlation where IEDs preceded spindles (n = 8; numbers of events: IED = 57 484; spindle: frontal = 20 013, parietal = 16 347; p frontal = 7.934×10^{-8} , lag = 410 ms; p parietal = 2.676×10^{-6} , lag = 430 ms)

Table 6. Effect of cross-correlogram “types” and epilepsy variables on spindle characteristics

			SSP (Mean±SD)	ISP (Mean±SD)	NSP (Mean±SD)
Temporal relationship					
Mean Duration	No temporal connection	n=9	0.968 ± 0.172	0.851 ± 0.127	0.830 ± 0.114
	Temporal connection with spindles preceding mtIEDs	n=3	0.953 ± 0.186	0.857 ± 0.149	0.857 ± 0.128
	Temporal connection with spindles following mtIEDs	n=8	0.996 ± 0.118	0.861 ± 0.067	0.866 ± 0.086
	Kruskal-Wallis, P		0.113	0.451	0.378
Mean Maximal Amplitude	No temporal connection	n=9	43.107 ± 13.533	39.750 ± 12.594	40.585 ± 13.022
	Temporal connection with spindles preceding mtIEDs	n=3	44.405 ± 8.656	41.386 ± 7.533	42.397 ± 7.323
	Temporal connection with spindles following mtIEDs	n=8	45.49 ± 3.718	41.132 ± 2.795	42.926 ± 3.167
	Kruskal-Wallis, P		0.287	0.734	0.685
Epilepsy variables					
Mean Duration	Hippocampal lesions	n=12	0.952 ± 0.134	0.830 ± 0.091	0.833 ± 0.106
	No Hippocampal lesions	n=9	1.017 ± 0.195	0.875 ± 0.134	0.862 ± 0.119
	Mann–Whitney P, U		0.395, 91	0.600, 87	0.600, 87
	Epilepsy duration <10 years	n=8	0.972 ± 0.206	0.865 ± 0.159	0.841 ± 0.134

Mean Maximal Amplitude	Epilepsy duration >10 years	n=13	1.007 ± 0.187	0.866 ± 0.123	0.853 ± 0.113
	Mann–Whitney P, U		0.866, 101	0.942, 100	0.642, 104
	Hippocampal lesions	n=12	44.694 ± 8.652	41.491 ± 7.992	42.838 ± 8.715
	No Hippocampal lesions	n=9	45.853 ± 12.543	42.393 ± 11.925	43.342 ± 11.431
	Mann–Whitney P, U		0.778, 84	0.657, 86	0.840, 83
	Epilepsy duration <10 years	n=8	41.415 ± 12.606	38.185 ± 11.083	39.533 ± 11.254
	Epilepsy duration > 10 years	n=13	45.695 ± 12.047	42.124 ± 11.352	42.831 ± 11.321
	Mann–Whitney P, U		0.447, 107	0.575, 105	0.575, 105

Abbreviations: mtIED, medio-temporal interictal epileptiform discharge; ISP, induced spindles; NSP, no spike spindles; SSP, spike-spindles.

4.4. Epilepsy variables

Differences in spindle characteristics were considered when patients were divided into groups based on epilepsy variables. The mean duration and mean maximal amplitude among spindle groups did not vary when patients were divided into groups based on epilepsy duration and hippocampal lesion. For detailed data, see **Table 6**.

4.4.1.1. Antiseizure medications

Spindle duration and maximal amplitude in patients taking Na channel inhibitors (n = 18), Ca channel inhibitors (n = 4), GABAA modulators (n = 10), levetiracetam (n = 7), and drugs with polypharmacological mechanisms (n = 7), did not differ significantly (all p values > .1) from other patients.

4.4.1.2. Neuropsychological assessment

Correlations between the ratio of SSPs and the delayed recall score on the RAVLT and ROCF were analyzed separately for all four electrodes: F3, F4, P3, and P4. Because the distribution of SSP ratio values deviated significantly from normal distribution, Spearman correlations were used with statistical control of years of intractable seizures. The correlation between SSP ratio and ROCF delayed recall score reached a statistical tendency level (Spearman $r = -.49$, $n = 15$, $p = .076$) at P3 electrode. Correlations between SSR and RAVLT scores did not reach statistical significance ($p < .05$) or tendency level ($p < .1$) at any electrodes.

5. Discussion

In this dissertation, we set out to examine both the clinical impact and the neurophysiological mechanisms by which medio-temporal interictal epileptiform discharges (mtIEDs) potentially disrupt memory in temporal lobe epilepsy (TLE). Study I addressed the clinical associations between IEDs and cognition, while Study II investigated the physiological substrate of these effects by focusing on the interaction between IEDs and sleep spindles. The integration of these two studies provides converging evidence that interictal activity is a clinically relevant and non-negligible contributor to memory impairment in drug-resistant epilepsy, with possible mechanistic links to altered oscillatory patterns of memory consolidation.

In Study I, we aimed to identify the potential causative factors contributing to sustained hippocampal-dependent memory deficits in adult TLE patients with implanted foramen ovale (FO) electrodes. Our study was the first to systematically quantify and directly compare the relative contribution of mesial temporal interictal epileptiform activity to memory impairment against multiple established clinical factors within a single analytical framework. We found a strong negative correlation between all measured hippocampal-dependent cognitive scores and the rate of mesial temporal IEDs. While longer disease durations were associated with worse verbal memory performance, other clinical characteristics, including self-reported seizure frequency, did not significantly impact memory outcomes. Thus, more frequent mesial temporal interictal epileptiform activity emerged as the strongest and most prominent determinant of long-term episodic memory deficits in patients with TLE.

Building on these clinical associations, Study II provided the first evidence of systematic differences in human spindle characteristics due to mtIEDs. Specifically, spindles co-occurring with mtIEDs lasted longer, had higher amplitude, and displayed a frequency shift toward the higher sigma range. We propose that these altered “spike-spindles” reflect aberrant thalamocortical synchronization imposed by interictal activity, thereby compromising hippocampal–cortical communication during consolidation. Previous human and animal studies had suggested that mtIEDs can induce spindle-like activity, even during wakefulness.³⁵ To investigate this, we analyzed spindles preceded by mtIEDs within a 1-second time window; however, these induced spindles showed no significant

alterations and were statistically indistinguishable from spindles without temporal correlation to mtIEDs. This dissociation suggests that the most disruptive influence arises when mtIEDs and spindles coincide in time, directly distorting ongoing oscillatory events rather than merely triggering them. In addition, we showed that delayed recall tended to worsen with the ratio of spike-spindles (SSPs), indicating that not only the overall spike rate but specifically the spike–spindle rate contributes to cognitive impairment.

5.1. Interictal activity and cognition

We analyzed mtIEDs throughout 24 hours and investigated their relationship with cognitive performance. Our findings revealed a negative correlation between mtIED rate and hippocampal dependent long-term memory performance, with stronger correlations observed during wakefulness than NREM sleep. As expected, hippocampal independent cognitive functions, language and executive performance, remained unaffected by mtIEDs. We also found DGS-B to be affected by mesial temporal spiking. DGS-B may partially rely on hippocampal function, while TLE patients have shown significantly worse performance on the Digit Span test.⁷⁴ Neuropsychological evaluations were conducted outside of the video-EEG monitoring period and were not time-locked to IED activity. This ensured that test scores were not influenced by ASM tapering or acute changes in seizure frequency. As a result, the observed associations reflect general, sustained cognitive deficits rather than transient effects of momentary hippocampal dysfunction. However, the maximum interval between IED detection and cognitive testing was four months, during which epilepsy therapy remained unchanged. Therefore, we may reasonably also assume that both IED burden and cognitive performance remained stable.

During memory consolidation, the information exchange between the hippocampus and cortex is coordinated via synchronized electrical activity of these regions.²⁸ The coordinated oscillatory activity enhances intracortical connectivity, promoting neuronal communication and supporting long-term plasticity.²⁹ While this process predominantly occurs during NREM sleep, it also takes place during restful wakefulness.³¹ Interictal activity is hypothesized to disrupt the physiological oscillatory patterns crucial for this process. Evidence shows that IEDs can alter the activity and characteristics of sleep

spindles,^{35,37–41} hippocampal sharp-wave ripples,⁴² slow waves,⁴³ and other related oscillations,^{44,45} thereby impairing this essential process.

In our study, we found a negative correlation between memory performance at a 30-minute delay and mtIED rate during waking, with a lesser extent in NREM sleep. This suggests that interictal spikes during waking may impair the initial steps of memory consolidation. Such disruptions could compromise the stabilization and integration of newly acquired information. The observed memory deficits may reflect a combination of impairments across multiple stages of memory consolidation process, including encoding, storage, and retrieval.^{75–77} These disruptions could potentially impact long-term memory storage.

Previous research has established a strong association between IEDs and transient cognitive impairment.^{47–49} Most studies have focused on the waking state, using tasks that allow time-locking IEDs to different memory processes (e.g., encoding and recall). There are fewer studies that explore longer-term cognitive disturbances and interictal activity using invasive methods across both sleep and wake periods. Bender *et al.*⁷⁸ also identified a negative correlation between hippocampal spiking and cognitive performance in a cohort of FO-implanted patients. However, their findings were linked to executive function scores rather than memory. Executive deficits can also reflect medial temporal dysfunction.^{24,79} Also, they measured only interictal activity during sleep and generated composite scores for memory and executive function from all available tests, whereas we analyzed the tests independently, and we only had one test measuring executive function. Similarly, Lambert *et al.*⁵² found a negative direct effect of mtIEDs on memory retention in patients with hippocampal stereo-EEG implants. Aligning with our findings, they observed correlations between wake spike rate and 30-minute delayed recall, and also between NREM spike rate and 1-week delayed recall. Although, longer delayed recall scores were not available for our investigation, but we also found correlations of 30 min delayed scores of BNT and NREM mtIED frequency.

While interictal activity is known to be brain state-dependent, with higher activity during NREM sleep, particularly in medial temporal lobe epilepsy,²³ the correlation between wake and sleep IED rates is less frequently discussed. As expected, we found IED rates to be higher during NREM sleep, but we also observed a strong correlation between wake

and sleep rates. This correlation may help explain the relationship between sleep IED rate and 30-minute delayed recall scores. In addition to mtIED rate, mtIED amplitude was also assessed potential influencing factor. In contrast with Quon et al.⁴⁴ we found no correlation between mtIED amplitude and cognitive performance.

5.2. Clinical characteristics and cognition

We also investigated the potential effect of seizure characteristics, disease duration, MRI lesion, ASM treatment. The linear mixed model analyses revealed that, among all those variables, only disease duration had a significant effect on cognitive scores.

Regarding the impact of seizures on cognition, we discovered no clear correlations. Seizures documented in the past 6 months, as reported in seizure diaries, and the presence of GTCSs were unrelated to memory performance. Only bilateral seizure onset zone was correlated with one memory measure (DGS-B), which did not remain significant after correction. In light of previous investigations where seizure frequency was the primary factor impairing verbal memory retention in frequently seizing subgroups,⁵² we also analyzed the subgroup with high seizure frequency. No correlation was found between seizure number and cognition in this subgroup either. These findings are limited by the reliance on self-reported seizure diaries, which may under or overestimate true seizure frequency, and by the small sample size in the high-frequency group (n = 5). Previous findings have also yielded inconsistent results regarding the relationship between seizure number and cognition. Studies demonstrating the impact of seizures on cognitive disturbances usually emphasize seizure frequency as a primary factor,^{80–84} often without accounting for other variables, particularly interictal activity. Additionally, several studies have failed to find a significant association.^{85–87} According to Holmes et al., frequent recurrent seizures and those occurring in the immature brain may correlate with potentially permanent deficits, but there is no clear evidence suggesting that weekly seizures in adults independently contribute to cognitive dysfunction.⁸⁸ Instead, lifetime seizure load has been identified as a more reliable predictor of cognitive disturbances.⁸⁹

Seizures and IEDs are the electrographic hallmarks of epilepsy, typically co-occurring and both contributing to transient cognitive dysfunction. However, the exact relationship between interictal activity and seizures remains unclear.³¹ In our cohort, we found no correlations between mtIED rate and seizure frequency. Ictal and interictal activity exhibit

similar multidien and sleep-wake cyclic probability distributions,⁹⁰ they generally show higher activity during NREM sleep than during REM sleep or wakefulness. However, their distribution across NREM stages differs: IEDs occur most frequently during NREM 3 sleep, whereas focal seizures are most common during NREM 1 sleep.⁹¹ Nonetheless, the co-occurrence patterns of spikes and seizures appear to be highly subject-specific.⁹² IEDs, whether bilateral or contralateral to the seizure focus, were associated with impaired memory performance.⁴⁷ Moreover, epileptiform activity outside the seizure onset zone disrupted memory processes, whereas spikes within the seizure onset zone did not negatively impact memory.⁴⁸ These findings suggest that interictal activities in epilepsy may independently contribute to the development of cognitive disturbances, separate from the effects of seizures. We hypothesize, that seizures account for only a small portion of all abnormal electrical activity observed in epileptic patients. In contrast to sporadic seizures, ongoing interictal activity may have a greater influence on disrupting physiological networks.

5.2.1. Disease duration, onset

We also assessed the relationship between cognitive scores and both age at disease onset and disease duration. Disease duration was negatively affected verbal memory measures. The association between poor cognitive outcomes and early onset or prolonged disease duration has long been debated.^{16,93} Compromised cognitive function has been reported as early as the disease onset or even before it manifests.^{21,94} However, in adults, cognitive decline generally progresses gradually, resembling the age-related cognitive decline observed in individuals without epilepsy.²² While age at onset is considered an important predictor, particularly since epilepsy can hinder cognitive maturation in children,⁸⁹ the exact nature of these cognitive comorbidities remains unclear. It is still debated whether they are primary consequences of epilepsy itself or secondary attributes associated with the disease.

5.2.2. MRI lesion

We examined the relationship between medial temporal lobe lesions and memory dysfunction, as well as whether these lesions influenced the association between mtIEDs and cognitive performance, but found no significant correlations. A limitation of this result is that temporal lobe lesions were identified only through structural MRI, without

performing hippocampal volumetry or connectivity analysis. Medial temporal lobe lesions alone have not consistently been associated with memory disturbances.⁸² Although, hippocampal sclerosis has been linked to poorer cognitive performance compared to other pathologies.²² TLE is increasingly recognized as a neuronal network disorder rather than solely the result of a preexisting lesion.^{95,96} Cognitive disturbances may therefore stem from disrupted neural circuits involved in cognition, rather than from localized structural abnormalities.⁹⁷ As such, hippocampal atrophy or changes in connectivity may offer a more reliable basis for assessing the prevalence of cognitive dysfunction.²⁴

5.2.3. ASM treatment

We also evaluated the impact of ASMs on cognition. High-risk ASM treatment showed a trend level correlation with verbal memory. This aligns with earlier studies indicating that certain AEDs can have pronounced cognitive effects.⁷¹ As opposed to high-risk ASM usage, we found no significant correlations between the number of ASMs and cognitive scores. This finding contrasts with previous studies that predominantly found a greater number of AEDs to be negatively associated with both subjective and objective cognition in people with epilepsy.^{35,36} However, other research has shown that no ASM was independently linked to cognitive dysfunction⁹⁸. This contrast may be explained by the limitation that we only assessed the ASM regimen at the time of admission and did not account for the patients' full ASM history. Given the highly refractory nature of the study population, where patients had already been exposed to prolonged and varied ASM treatments, the cumulative effects of these medications could have influenced cognitive outcomes.

5.3. Interictal activity and sleep spindle characteristics

5.3.1. Sleep spindles co-occurring with IED

When investigating the effect of IEDs on the electrophysiological hallmarks of sleep and memory processes — the sleep spindles — we found robust alterations in the characteristics of spindles that co-occurred with IEDs. Specifically, spindles temporally overlapping with mtIEDs exhibited changes across all measured parameters: they lasted longer, had higher amplitudes, and showed a frequency shift toward the higher sigma range.

Spindles temporally coupled with mtIEDs lasted approximately 140 ms longer than those without such coupling. Spindles are generated within the thalamus through alternating excitation between thalamocortical and nucleus reticularis thalami (nRT) neurons. Studies on spindle termination in rodents have shown that, although nRT firing declines sharply before spindle cessation, spindle duration itself depends on the magnitude of nRT cell activation at spindle onset.¹⁰⁰ The authors proposed that an unspecified ongoing network activation may underlie this effect.

Regarding the influence of IEDs on spindle length, two potential mechanisms may be considered. The first posits that an ongoing network activation could simultaneously promote the emergence of longer spindles and facilitate IED generation. The second hypothesis suggests that the occasional co-occurrence of IEDs and spindles transiently alters the network state that determines nRT activation levels, thereby producing pathologically prolonged spindles. In the aforementioned investigations, it was not tested whether modifying the network state during an ongoing spindle could influence its duration. Since we observed variable interactions between IED and spindle timing without a consistent effect on spindle length, we hypothesize that distinct network mechanisms independently govern spindle timing and duration, with IED generation interacting separately with these processes.

In addition to their longer duration, sleep spindles occurring in association with medio-temporal-recorded IEDs exhibited, on average, approximately 9% higher amplitudes compared to those occurring in isolation. Previous studies have reported higher spindle amplitudes in the epileptic hemisphere of patients with focal epilepsy,⁶⁵ whereas no lateralization effect was observed in individuals with idiopathic generalized epilepsy. Our findings may help to explain this observation. Furthermore, larger-amplitude sleep spindles have been shown to recruit more widespread cortical areas, reflecting a more global network engagement.^{73,101} Therefore, alterations in spindle amplitude may contribute to functional disruptions in memory consolidation and cortical communication.

We also observed enhanced spectral power in the higher frequency bins corresponding to the upper sigma range, whereas the peak frequency itself remained unchanged. Increased spectral power between 12.5 and 15.5 Hz was detected in both frontal and parietal electrodes; however, IED co-occurred spindles recorded at P3/P4 showed a more

prominent increase than those at F3/F4. Although changes in spindle duration and amplitude were similar across frontal and parietal regions, the observed frequency differences may suggest preferential regional coupling, even if not statistically significant.

Physiological spindles can be classified into slow (11.0–12.75 Hz) and fast (12.5–14.5 Hz) types,^{73,102} with slow spindles typically biased toward frontal regions, while fast spindles predominate in centroparietal areas and are thought to play a greater role in memory consolidation.^{103,104} Our findings suggest that parietal fast spindles interact more strongly with mtIEDs than the slower frontal spindles. Previous studies³⁴ have reported that posterior hippocampal spindle–ripples are linked to temporoparietal sleep spindle activity, indicating strong coupling between these regions. The relatively posterior positioning of FO electrodes along the hippocampal axis supports our observation that posterior mtIEDs preferentially interact with parietal fast spindles.

The question arises as to whether such relatively subtle changes in spindle characteristics correspond to functional differences. Because spindle parameters are known to exhibit strong intraindividual stability,^{105,106} and are among the most heritable EEG traits,¹⁰⁷ even minor alterations in their features have frequently been associated with decreases in cognitive abilities and the presence of neuropsychiatric disorders.^{61,62,64,108,109} Based on these findings, we propose that the observed alterations are pathological in nature and likely represent consequences of epileptic network dysfunction.

5.3.2. Sleep spindles “induced” by IEDs

Beyond co-occurrence, other temporal relationships between mtIEDs and spindles were also observed, which we refer to as induced spindles. Analysis of spindle onset timing revealed variable patterns across patients. In more than half of the subjects, clear temporal coherence was identified between mtIEDs and cortical spindles, although this relationship was patient-specific. In 52% of patients, mtIEDs tended to precede spindle onset by approximately 0.4 seconds, whereas in another 14%, the opposite relationship was observed within the same time window.

The characteristic alterations in spindle properties were not seen in the induced spindles. Gelinas et al. have also reported that mtIEDs can induce frontal lobe spindling within a

similar ~0.4-second time frame, and consistent with our findings, these induced spindles displayed oscillatory properties comparable to those of physiological frontal spindles, including waveform morphology, duration, and peak frequency.³⁵

According to the proposed mechanism, IEDs may trigger a brief suppression of neuronal activity — a so-called DOWN-state — in the mesial prefrontal cortex. This inhibition is followed by a rebound increase in neuronal firing that could give rise to the subsequent sleep spindle. Similar IED–spindle coupling has been observed in humans,³⁹ and studies in children have shown that stronger coupling correlates with lower intellectual quotient scores.⁴⁰ Together, these findings imply that IED-triggered spindles may not facilitate normal cognitive functions and instead represent a functionally altered, pathological variant of physiological spindles.

Our findings align with previous studies reporting correlations between temporal IEDs and frontal spindles,²⁷ although, in contrast, we also identified cases where spindles preceded IEDs — a relationship not described before. We found no preferential regional coupling, as these interactions could occur at both frontal and parietal sites. This differs from earlier reports that localized significant correlations primarily to the frontal lobe. Distinct anatomical relationships between epileptic foci and spindle-generating networks,^{39,110} may account for such variability. Furthermore, the proportion of patients showing each type of correlation may be influenced by additional epileptic activity undetected by the present recording methods.

Further investigations are required to better characterize the temporal dynamics between hippocampal spikes and cortical spindles. Importantly, regardless of the existence or direction of temporal coupling, only the spindles co-occurring with mtIEDs exhibited altered characteristics. It should be emphasized, however, that in prior studies, the interpretation of IEDs as spindle-inducing events was based on increased spindle probability following IEDs. In our work, spindles were classified as “mtIED-induced” when preceded by mtIEDs within a defined temporal window; nevertheless, we do not have direct evidence that these spindles were causally induced by medio-temporal epileptic discharges.

5.3.3. Spindle characteristics alteration and cognition

We examined whether alterations in spindle characteristics associated with mtIED co-occurrence had any impact on memory consolidation. A trend-level correlation was observed between delayed recall performance and the ratio of IED co-occurring spindles in the parietal region. This finding may suggest that an increased number of spike-spindles could reduce the efficiency of memory consolidation and, consequently, impair memory performance. However, this result is limited by the relatively small sample size. Further studies involving larger cohorts will be required to confirm this relationship and to control for additional clinical factors. It should also be noted that this correlation does not reflect an immediate effect of altered spindle activity on memory, as the memory testing sessions and electrophysiological recordings were conducted several days or weeks apart.

When analyzing differences in spindle characteristics across medication groups, no significant effects of antiepileptic medication were observed. Although this analysis was limited by the small sample size, the within-subject comparison of spindle subtypes in our study makes it unlikely that the main findings were substantially biased by medication effects.

6. Conclusions

In conclusion, our study provides novel insights into the mechanisms and predictors of epilepsy-related cognitive dysfunction. Understanding these mechanisms is essential for improving both patient management and quality of life. In this dissertation, we explored potential biomarkers underlying sustained cognitive impairment in focal epilepsy, prioritizing them according to their potential impact and reversibility, and examined the neurophysiological mechanisms by which interictal epileptiform discharges (IED) activity alters cognitive functions.

First, we demonstrated that mesial temporal IEDs represent a robust biomarker associated with hippocampal-dependent cognitive deficits. This study was the first to evaluate the contribution of mesial temporal interictal activity to memory impairment in relation to multiple established clinical variables within a unified analytical framework. While longer epilepsy duration was related to poorer verbal memory performance, other clinical characteristics—including seizure frequency, seizure-related variables, and antiseizure medication use—showed limited or no association with cognitive outcomes. We employed an offline approach, in which cognitive performance was assessed independently of immediate electrophysiological recordings, thereby providing insight into the sustained cognitive effects of habitual interictal activity rather than transient, task-related disruptions. Together, these findings indicate that habitual interictal activity, as quantified by 24-hour recordings, may serve as a practical and clinically accessible biomarker for predicting long-term cognitive decline, and raise the possibility that interictal activity is not merely an epiphenomenon but a major contributor to chronic cognitive impairment in temporal lobe epilepsy.

Second, we investigated the interaction between medio-temporal IEDs and neocortical sleep spindles to elucidate potential neurophysiological mechanisms through which interictal activity interferes with memory consolidation. This study provides the first description in humans of how medio-temporal IED–spindle co-occurrence alters spindle properties. We found significant changes in spindle characteristics—including increased duration, higher amplitude, and a frequency shift toward the higher sigma range—specifically when spindles co-occurred with mtIEDs. Our results further suggest that an

increased number of co-occurring spike–spindles may reduce the efficiency of memory consolidation and, consequently, impair memory performance.

In addition, we replicated previous findings demonstrating that IEDs can induce sleep spindles; however, no morphological alterations were observed in these induced spindles. In contrast, our results indicate that direct temporal co-occurrence between interictal discharges and sleep spindles is associated with altered spindle properties, suggesting that interictal activity may disrupt thalamocortical oscillations essential for physiological memory consolidation. This mechanism provides a plausible neurophysiological explanation for the link between interictal activity and cognitive impairment and highlights a potential therapeutic target.

Collectively, our results underscore that the treatment of epilepsy should address not only seizures but also interictal EEG abnormalities. Reducing interictal epileptiform activity may represent a viable strategy to mitigate cognitive decline and enhance quality of life in patients with epilepsy.

7. Summary

This dissertation provides novel insights into the mechanisms and predictors of epilepsy-related cognitive dysfunction. It identifies interictal epileptiform discharges (IEDs) as a key marker of cognitive decline in epilepsy and proposes that their pathological effects operate through disruption of physiological oscillatory mechanisms underlying cognition. The work is based on intracranial invasive EEG recordings, enabling high temporal and spatial resolution assessment of mesiotemporal activity and its interactions with neocortical networks.

In Study I, we demonstrated for the first time that mesiotemporal interictal epileptiform activity shows a stronger and more consistent association with hippocampal-dependent memory impairment than other commonly considered clinical factors within a unified analytical framework. Using an offline analytical approach, we showed that habitual interictal activity exerts a sustained influence on cognitive performance in temporal lobe epilepsy, independent of immediate task-related effects. Interictal discharge frequency quantified over continuous 24-hour recordings emerged as a reliable indicator of long-term cognitive decline, whereas seizure frequency, seizure laterality, and antiseizure medication use showed only negligible effects.

In Study II, we provided the first human evidence that temporal co-occurrence of mesiotemporal interictal discharges and neocortical sleep spindles is associated with systematic alterations in spindle characteristics. Spindles overlapping with mtIEDs exhibited increased duration, higher amplitude, and a shift toward higher sigma frequencies. A higher proportion of IED–spindle co-occurrences showed a trend-level association with reduced memory consolidation efficiency, suggesting disruption of thalamocortical oscillatory mechanisms essential for memory consolidation.

Together, these results establish interictal activity as a major and previously underappreciated determinant of cognitive dysfunction in epilepsy, highlighting the importance of targeting interictal EEG abnormalities alongside seizures to preserve cognitive function and improve quality of life.

References

1. Ak N, C B, I K, Jw S, Cr N. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. *Epilepsia*. 2010;51(5). doi:10.1111/j.1528-1167.2009.02481.x
2. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475-482. doi:10.1111/epi.12550
3. Kalilani L, Sun X, Pelgrims B, Noack-Rink M, Villanueva V. The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis. *Epilepsia*. 2018;59(12):2179-2193. doi:10.1111/epi.14596
4. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010;51(6):1069-1077. doi:10.1111/j.1528-1167.2009.02397.x
5. Perucca E, Perucca P, White HS, Wirrell EC. Drug resistance in epilepsy. *Lancet Neurol*. 2023;22(8):723-734. doi:10.1016/S1474-4422(23)00151-5
6. M M, Hr C. More than seizures: improving the lives of people with refractory epilepsy. *Eur J Neurol*. 2015;22(1). doi:10.1111/ene.12603
7. Engel J. THE CURRENT PLACE OF EPILEPSY SURGERY. *Curr Opin Neurol*. 2018;31(2):192-197. doi:10.1097/WCO.0000000000000528
8. Wiebe S, Blume WT, Girvin JP, Eliasziw M, Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med*. 2001;345(5):311-318. doi:10.1056/NEJM200108023450501
9. Dwivedi R, Ramanujam B, Chandra PS, et al. Surgery for Drug-Resistant Epilepsy in Children. *N Engl J Med*. 2017;377(17):1639-1647. doi:10.1056/NEJMoa1615335
10. Lamberink HJ, Otte WM, Blümcke I, et al. Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study. *Lancet Neurol*. 2020;19(9):748-757. doi:10.1016/S1474-4422(20)30220-9
11. Wu Y, Zhang Z, Liang P, Zou B, Wang D, Zhai X. Quality of life of children with residual seizures after epileptic resection surgery. *Front Neurol*. 2022;13:1066953. doi:10.3389/fneur.2022.1066953
12. Widjaja E, Jain P, Demoe L, Guttmann A, Tomlinson G, Sander B. Seizure outcome of pediatric epilepsy surgery. *Neurology*. 2020;94(7):311-321. doi:10.1212/WNL.00000000000008966
13. Bjellvi J, Olsson I, Malmgren K, Wilbe Ramsay K. Epilepsy duration and seizure outcome in epilepsy surgery. *Neurology*. 2019;93(2):e159-e166. doi:10.1212/WNL.00000000000007753
14. Jobst BC, Cascino GD. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. *JAMA*. 2015;313(3):285-293. doi:10.1001/jama.2014.17426

15. Vakharia VN, Duncan JS, Witt J, Elger CE, Staba R, Engel J. Getting the best outcomes from epilepsy surgery. *Ann Neurol*. 2018;83(4):676-690. doi:10.1002/ana.25205
16. Elger CE, Helmstaedter C, Kurthen M. Chronic epilepsy and cognition. *Lancet Neurol*. 2004;3(11):663-672. doi:10.1016/S1474-4422(04)00906-8
17. de la Loge C, Dimova S, Mueller K, et al. PatientsLikeMe® Online Epilepsy Community: Patient characteristics and predictors of poor health-related quality of life. *Epilepsy Behav*. 2016;63:20-28. doi:10.1016/j.yebeh.2016.07.035
18. Helmstaedter C, Witt JA. Epilepsy and cognition – A bidirectional relationship? *Seizure - Eur J Epilepsy*. 2017;49:83-89. doi:10.1016/j.seizure.2017.02.017
19. Novak A, Vizjak K, Rakusa M. Cognitive Impairment in People with Epilepsy. *J Clin Med*. 2022;11(1):267. doi:10.3390/jcm11010267
20. Scott AJ, Sharpe L, Hunt C, Gandy M. Anxiety and depressive disorders in people with epilepsy: A meta-analysis. *Epilepsia*. 2017;58(6):973-982. doi:10.1111/epi.13769
21. Pugh R, Vaughan DN, Jackson GD, Ponsford J, Tailby C. Cognitive and psychological dysfunction is present after a first seizure, prior to epilepsy diagnosis and treatment at a First Seizure Clinic. *Epilepsia Open*. 2024;9(2):717-726. doi:10.1002/epi4.12909
22. Helmstaedter C, Elger CE. Chronic temporal lobe epilepsy: a neurodevelopmental or progressively dementing disease? *Brain*. 2009;132(10):2822-2830. doi:10.1093/brain/awp182
23. Holmes GL. Interictal Spikes as an EEG Biomarker of Cognitive Impairment. *J Clin Neurophysiol*. 2022;39(2):101. doi:10.1097/WNP.0000000000000728
24. Hermann BP, Struck AF, Busch RM, Reyes A, Kaestner E, McDonald CR. Neurobehavioural comorbidities of epilepsy: towards a network-based precision taxonomy. *Nat Rev Neurol*. 2021;17(12):731-746. doi:10.1038/s41582-021-00555-z
25. Téllez-Zenteno JF, Hernández-Ronquillo L. A review of the epidemiology of temporal lobe epilepsy. *Epilepsy Res Treat*. 2012;2012:630853. doi:10.1155/2012/630853
26. Zhao F, Kang H, You Li, Rastogi P, Venkatesh D, Chandra M. Neuropsychological deficits in temporal lobe epilepsy: A comprehensive review. *Ann Indian Acad Neurol*. 2014;17(4):374-382. doi:10.4103/0972-2327.144003
27. Hermann B, Seidenberg M, Jones J. The neurobehavioural comorbidities of epilepsy: can a natural history be developed? *Lancet Neurol*. 2008;7(2):151-160. doi:10.1016/S1474-4422(08)70018-8
28. Dudai Y, Karni A, Born J. The Consolidation and Transformation of Memory. *Neuron*. 2015;88(1):20-32. doi:10.1016/j.neuron.2015.09.004
29. Igarashi KM, Lu L, Colgin LL, Moser MB, Moser EI. Coordination of entorhinal-hippocampal ensemble activity during associative learning. *Nature*. 2014;510(7503):143-147. doi:10.1038/nature13162

30. Buzsáki G. Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. *Hippocampus*. 2015;25(10):1073-1188. doi:10.1002/hipo.22488
31. Diekelmann S, Born J. The memory function of sleep. *Nat Rev Neurosci*. 2010;11(2):114-126. doi:10.1038/nrn2762
32. Niknazar M, Krishnan GP, Bazhenov M, Mednick SC. Coupling of Thalamocortical Sleep Oscillations Are Important for Memory Consolidation in Humans. *PLoS One*. 2015;10(12):e0144720. doi:10.1371/journal.pone.0144720
33. Klinzing JG, Niethard N, Born J. Mechanisms of systems memory consolidation during sleep. *Nat Neurosci*. 2019;22(10):1598-1610. doi:10.1038/s41593-019-0467-3
34. Jiang X, Gonzalez-Martinez J, Halgren E. Coordination of Human Hippocampal Sharpwave Ripples during NREM Sleep with Cortical Theta Bursts, Spindles, Downstates, and Upstates. *J Neurosci Off J Soc Neurosci*. 2019;39(44):8744-8761. doi:10.1523/JNEUROSCI.2857-18.2019
35. Gelinas JN, Khodagholy D, Thesen T, Devinsky O, Buzsáki G. Interictal epileptiform discharges induce hippocampal-cortical coupling in temporal lobe epilepsy. *Nat Med*. 2016;22(6):641-648. doi:10.1038/nm.4084
36. Ferrillo F, Beelke M, Nobili L. Sleep EEG synchronization mechanisms and activation of interictal epileptic spikes. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol*. 2000;111 Suppl 2:S65-73. doi:10.1016/s1388-2457(00)00404-1
37. Sákovics A, Csukly G, Borbély C, et al. Prolongation of cortical sleep spindles during hippocampal interictal epileptiform discharges in epilepsy patients. *Epilepsia*. 2022;63(9):2256-2268. doi:10.1111/epi.17337
38. Lagarde S, Roehri N, Lambert I, et al. Interictal stereotactic-EEG functional connectivity in refractory focal epilepsies. *Brain J Neurol*. 2018;141(10):2966-2980. doi:10.1093/brain/awy214
39. Dahal P, Ghani N, Flinker A, et al. Interictal epileptiform discharges shape large-scale intercortical communication. *Brain*. 2019;142(11):3502-3513. doi:10.1093/brain/awz269
40. Yu H, Kim W, Park DK, et al. Interaction of interictal epileptiform activity with sleep spindles is associated with cognitive deficits and adverse surgical outcome in pediatric focal epilepsy. *Epilepsia*. 2024;65(1):190-203. doi:10.1111/epi.17810
41. Frauscher B, Bernasconi N, Caldarrou B, et al. Interictal Hippocampal Spiking Influences the Occurrence of Hippocampal Sleep Spindles. *Sleep*. 2015;38(12):1927-1933. doi:10.5665/sleep.5242
42. Henin S, Shankar A, Borges H, et al. Spatiotemporal dynamics between interictal epileptiform discharges and ripples during associative memory processing. *Brain*. 2021;144(5):1590-1602. doi:10.1093/brain/awab044

43. Sheybani L, Vivekananda U, Rodionov R, et al. Wake slow waves in focal human epilepsy impact network activity and cognition. *Nat Commun.* 2023;14:7397. doi:10.1038/s41467-023-42971-3
44. Quon RJ, Camp EJ, Meisenhelter S, et al. Features of intracranial interictal epileptiform discharges associated with memory encoding. *Epilepsia.* 2021;62(11):2615-2626. doi:10.1111/epi.17060
45. Meisenhelter S, Quon RJ, Steimel SA, et al. Interictal Epileptiform Discharges are Task Dependent and are Associated with Lasting Electrographic Changes. *Cereb Cortex Commun.* 2021;2(2):tgab019. doi:10.1093/texcom/tgab019
46. Lambert I, Roehri N, Giusiano B, et al. Brain regions and epileptogenicity influence epileptic interictal spike production and propagation during NREM sleep in comparison with wakefulness. *Epilepsia.* 2018;59(1):235-243. doi:10.1111/epi.13958
47. Kleen JK, Scott RC, Holmes GL, et al. Hippocampal interictal epileptiform activity disrupts cognition in humans. *Neurology.* 2013;81(1):18-24. doi:10.1212/WNL.0b013e318297ee50
48. Ung H, Cazares C, Nanivadekar A, et al. Interictal epileptiform activity outside the seizure onset zone impacts cognition. *Brain.* 2017;140(8):2157-2168. doi:10.1093/brain/awx143
49. Horak PC, Meisenhelter S, Song Y, et al. Interictal Epileptiform Discharges Impair Word Recall in Multiple Brain Areas. *Epilepsia.* 2017;58(3):373-380. doi:10.1111/epi.13633
50. Wang L, Song YL, Sun P, Li ZC, Zhao N. Analysis of EEG abnormalities of cognitive impairment and epileptic seizures in patients with epilepsy. *Eur Rev Med Pharmacol Sci.* 2019;23(24):10964-10969. doi:10.26355/eurrev_201912_19800
51. Lv Y, Wang Z, Cui L, Ma D, Meng H. Cognitive correlates of interictal epileptiform discharges in adult patients with epilepsy in China. *Epilepsy Behav EB.* 2013;29(1):205-210. doi:10.1016/j.yebeh.2013.07.014
52. Lambert I, Tramonni-Negre E, Lagarde S, et al. Hippocampal Interictal Spikes during Sleep Impact Long-Term Memory Consolidation. *Ann Neurol.* 2020;87(6):976-987. doi:10.1002/ana.25744
53. Lambert I, Tramonni-Negre E, Lagarde S, et al. Accelerated long-term forgetting in focal epilepsy: Do interictal spikes during sleep matter? *Epilepsia.* 2021;62(3):563-569. doi:10.1111/epi.16823
54. Lmj F, A L. Sleep Spindles: Mechanisms and Functions. *Physiol Rev.* 2020;100(2). doi:10.1152/physrev.00042.2018
55. G T, C C. Sleep function and synaptic homeostasis. *Sleep Med Rev.* 2006;10(1). doi:10.1016/j.smrv.2005.05.002
56. Beenhakker MP, Huguenard JR. Neurons that fire together also conspire together: is normal sleep circuitry hijacked to generate epilepsy? *Neuron.* 2009;62(5):612-632. doi:10.1016/j.neuron.2009.05.015

57. Kramer MA, Stoyell SM, Chinappen D, et al. Focal Sleep Spindle Deficits Reveal Focal Thalamocortical Dysfunction and Predict Cognitive Deficits in Sleep Activated Developmental Epilepsy. *J Neurosci Off J Soc Neurosci*. 2021;41(8):1816-1829. doi:10.1523/JNEUROSCI.2009-20.2020
58. Gibbs SA, Nobili L, Halász P. Interictal epileptiform discharges in sleep and the role of the thalamus in Encephalopathy related to Status Epilepticus during slow Sleep. *Epileptic Disord Int Epilepsy J Videotape*. 2019;21(S1):54-61. doi:10.1684/epd.2019.1058
59. Z C, D F, P H. Overnight verbal memory retention correlates with the number of sleep spindles. *Neuroscience*. 2005;132(2). doi:10.1016/j.neuroscience.2005.01.011
60. Muehlroth BE, Rasch B, Werkle-Bergner M. Episodic memory consolidation during sleep in healthy aging. *Sleep Med Rev*. 2020;52:101304. doi:10.1016/j.smr.2020.101304
61. Gibbs EL, Gibbs FA. Extreme spindles: correlation of electroencephalographic sleep pattern with mental retardation. *Science*. 1962;138(3545):1106-1107. doi:10.1126/science.138.3545.1106
62. Shibagaki M, Kiyono S, Watanabe K. Spindle evolution in normal and mentally retarded children: a review. *Sleep*. 1982;5(1):47-57. doi:10.1093/sleep/5.1.47
63. F F, R H, Mj P, et al. Reduced sleep spindle activity in schizophrenia patients. *Am J Psychiatry*. 2007;164(3). doi:10.1176/ajp.2007.164.3.483
64. Astori S, Wimmer RD, Lüthi A. Manipulating sleep spindles--expanding views on sleep, memory, and disease. *Trends Neurosci*. 2013;36(12):738-748. doi:10.1016/j.tins.2013.10.001
65. Clemens B, Ménes A. Sleep spindle asymmetry in epileptic patients. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol*. 2000;111(12):2155-2159. doi:10.1016/s1388-2457(00)00482-x
66. Clemens Z, Janszky J, Szűcs A, Békésy M, Clemens B, Halász P. Interictal Epileptic Spiking during Sleep and Wakefulness in Mesial Temporal Lobe Epilepsy: A Comparative Study of Scalp and Foramen Ovale Electrodes. *Epilepsia*. 2003;44(2):186-192. doi:10.1046/j.1528-1157.2003.27302.x
67. Fernández Torre JL, Alarcón G, Binnie CD, Polkey CE. Comparison of sphenoidal, foramen ovale and anterior temporal placements for detecting interictal epileptiform discharges in presurgical assessment for temporal lobe epilepsy. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol*. 1999;110(5):895-904. doi:10.1016/s1388-2457(99)00039-5
68. Frauscher B, Gotman J. Sleep, oscillations, interictal discharges, and seizures in human focal epilepsy. *Neurobiol Dis*. 2019;127:545-553. doi:10.1016/j.nbd.2019.04.007
69. Vallat R, Walker MP. An open-source, high-performance tool for automated sleep staging. Peyrache A, Büchel C, Bagur S, eds. *eLife*. 2021;10:e70092. doi:10.7554/eLife.70092
70. Busch RM, Frazier TW, Haggerty KA, Kubu CS. Utility of the Boston Naming Test in Predicting Ultimate Side of Surgery in Patients with Medically Intractable Temporal Lobe Epilepsy. *Epilepsia*. 2005;46(11):1773-1779. doi:10.1111/j.1528-1167.2005.00300.x

71. Hermann B, Meador KJ, Gaillard WD, Cramer JA. Cognition across the lifespan: antiepileptic drugs, epilepsy, or both? *Epilepsy Behav EB*. 2010;17(1):1-5. doi:10.1016/j.yebeh.2009.10.019
72. Simor P, Szalárdy O, Gombos F, et al. REM Sleep Microstates in the Human Anterior Thalamus. *J Neurosci*. 2021;41(26):5677. doi:10.1523/JNEUROSCI.1899-20.2021
73. Andrillon T, Nir Y, Staba RJ, et al. Sleep spindles in humans: insights from intracranial EEG and unit recordings. *J Neurosci Off J Soc Neurosci*. 2011;31(49):17821-17834. doi:10.1523/JNEUROSCI.2604-11.2011
74. Zhu G, Wang J, Xiao L, et al. Memory Deficit in Patients With Temporal Lobe Epilepsy: Evidence From Eye Tracking Technology. *Front Neurosci*. 2021;15. doi:10.3389/fnins.2021.716476
75. Craig M, Dewar M. Rest-related consolidation protects the fine detail of new memories. *Sci Rep*. 2018;8. doi:10.1038/s41598-018-25313-y
76. Dewar M, Alber J, Butler C, Cowan N, Della Sala S. Brief wakeful resting boosts new memories over the long term. *Psychol Sci*. 2012;23(9):955-960. doi:10.1177/0956797612441220
77. Wamsley EJ. Memory Consolidation during Waking Rest. *Trends Cogn Sci*. 2019;23(3):171-173. doi:10.1016/j.tics.2018.12.007
78. Bender AC, Jaleel A, Pellerin KR, et al. Altered Sleep Microarchitecture and Cognitive Impairment in Patients With Temporal Lobe Epilepsy. *Neurology*. 2023;101(23):e2376-e2387. doi:10.1212/WNL.0000000000207942
79. Sawrie SM, Martin RC, Gilliam FG, et al. Visual confrontation naming and hippocampal function: A neural network study using quantitative 1H magnetic resonance spectroscopy. *Brain*. 2000;123(4):770-780. doi:10.1093/brain/123.4.770
80. Helmstaedter C, Elger CE, Vogt VL. Cognitive outcomes more than 5 years after temporal lobe epilepsy surgery: Remarkable functional recovery when seizures are controlled. *Seizure*. 2018;62:116-123. doi:10.1016/j.seizure.2018.09.023
81. van Schalkwijk FJ, Gruber WR, Miller LA, Trinka E, Höller Y. Investigating the Effects of Seizures on Procedural Memory Performance in Patients with Epilepsy. *Brain Sci*. 2021;11(2):261. doi:10.3390/brainsci11020261
82. Wilkinson H, Holdstock JS, Baker G, Herbert A, Clague F, Downes JJ. Long-term accelerated forgetting of verbal and non-verbal information in temporal lobe epilepsy. *Cortex*. 2012;48(3):317-332. doi:10.1016/j.cortex.2011.01.002
83. Helmstaedter C. Effects of chronic epilepsy on declarative memory systems. *Prog Brain Res*. 2002;135:439-453. doi:10.1016/S0079-6123(02)35041-6
84. Jokeit H, Daamen M, Zang H, Janszky J, Ebner A. Seizures accelerate forgetting in patients with left-sided temporal lobe epilepsy. *Neurology*. 2001;57(1):125-126. doi:10.1212/wnl.57.1.125

85. Visser M, Forn C, Gómez-Ibáñez A, Rosell-Negre P, Villanueva V, Ávila C. Accelerated long-term forgetting in resected and seizure-free temporal lobe epilepsy patients. *Cortex J Devoted Study Nerv Syst Behav*. 2019;110:80-91. doi:10.1016/j.cortex.2018.02.017
86. Jarčušková D, Palušná M, Gazda J, Feketeová E, Gdovinová Z. Which clinical and neuropsychological factors are responsible for cognitive impairment in patients with epilepsy? *Int J Public Health*. 2020;65(6):947-956. doi:10.1007/s00038-020-01401-7
87. Gauffin H, Landtblom AM, Vigren P, et al. Similar Profile and Magnitude of Cognitive Impairments in Focal and Generalized Epilepsy: A Pilot Study. *Front Neurol*. 2021;12:746381. doi:10.3389/fneur.2021.746381
88. Holmes GL. What is More Harmful, Seizures or Epileptic EEG Abnormalities: Is There any Clinical Data? *Epileptic Disord Int Epilepsy J Videotape*. 2014;16(Spec No 1):S12-S22. doi:10.1684/epd.2014.0686
89. Black LC, Schefft BK, Howe SR, Szaflarski JP, Yeh H shain, Privitera MD. The effect of seizures on working memory and executive functioning performance. *Epilepsy Behav*. 2010;17(3):412-419. doi:10.1016/j.yebeh.2010.01.006
90. Leguia MG, Andrzejak RG, Rummel C, et al. Seizure Cycles in Focal Epilepsy. *JAMA Neurol*. 2021;78(4):1-10. doi:10.1001/jamaneurol.2020.5370
91. Sheybani L, Frauscher B, Bernard C, Walker MC. Mechanistic insights into the interaction between epilepsy and sleep. *Nat Rev Neurol*. Published online March 10, 2025:1-16. doi:10.1038/s41582-025-01064-z
92. Karoly PJ, Freestone DR, Boston R, et al. Interictal spikes and epileptic seizures: their relationship and underlying rhythmicity. *Brain*. 2016;139(4):1066-1078. doi:10.1093/brain/aww019
93. Oyegbile TO, Dow C, Jones J, et al. The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. *Neurology*. 2004;62(10):1736-1742. doi:10.1212/01.wnl.0000125186.04867.34
94. Witt JA, Helmstaedter C. Cognition in the early stages of adult epilepsy. *Seizure - Eur J Epilepsy*. 2015;26:65-68. doi:10.1016/j.seizure.2015.01.018
95. Whelan CD, Altmann A, Botía JA, et al. Structural brain abnormalities in the common epilepsies assessed in a worldwide ENIGMA study. *Brain J Neurol*. 2018;141(2):391-408. doi:10.1093/brain/awx341
96. Tailby C, Kowalczyk MA, Jackson GD. Cognitive impairment in epilepsy: the role of reduced network flexibility. *Ann Clin Transl Neurol*. 2017;5(1):29-40. doi:10.1002/acn3.503
97. Kaaden S, Quesada CM, Urbach H, et al. Neurodevelopmental disruption in early-onset temporal lobe epilepsy: Evidence from a voxel-based morphometry study. *Epilepsy Behav*. 2011;20(4):694-699. doi:10.1016/j.yebeh.2011.02.020

98. Foster E, Malpas CB, Ye K, et al. Antiepileptic drugs are not independently associated with cognitive dysfunction. *Neurology*. 2020;94(10):e1051-e1061. doi:10.1212/WNL.00000000000009061
99. Witt JA, Elger CE, Helmstaedter C. Adverse cognitive effects of antiepileptic pharmacotherapy: Each additional drug matters. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol*. 2015;25(11):1954-1959. doi:10.1016/j.euroneuro.2015.07.027
100. Barthó P, Slézia A, Mátyás F, et al. Ongoing network state controls the length of sleep spindles via inhibitory activity. *Neuron*. 2014;82(6):1367-1379. doi:10.1016/j.neuron.2014.04.046
101. Dempsey EW, Morison RS. The production of rhythmically recurrent cortical potentials after localized thalamic stimulation. *Am J Physiol-Leg Content*. 1941;135(2):293-300. doi:10.1152/ajplegacy.1941.135.2.293
102. De Gennaro L, Ferrara M. Sleep spindles: an overview. *Sleep Med Rev*. 2003;7(5):423-440. doi:10.1053/smr.2002.0252
103. Schabus M, Dang-Vu TT, Albouy G, et al. Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. *Proc Natl Acad Sci U S A*. 2007;104(32):13164-13169. doi:10.1073/pnas.0703084104
104. Mölle M, Bergmann TO, Marshall L, Born J. Fast and slow spindles during the sleep slow oscillation: disparate coalescence and engagement in memory processing. *Sleep*. 2011;34(10):1411-1421. doi:10.5665/SLEEP.1290
105. Buckelmüller J, Landolt HP, Stassen HH, Achermann P. Trait-like individual differences in the human sleep electroencephalogram. *Neuroscience*. 2006;138(1):351-356. doi:10.1016/j.neuroscience.2005.11.005
106. De Gennaro L, Ferrara M, Vecchio F, Curcio G, Bertini M. An electroencephalographic fingerprint of human sleep. *NeuroImage*. 2005;26(1):114-122. doi:10.1016/j.neuroimage.2005.01.020
107. Ambrosius U, Lietzenmaier S, Wehrle R, et al. Heritability of sleep electroencephalogram. *Biol Psychiatry*. 2008;64(4):344-348. doi:10.1016/j.biopsych.2008.03.002
108. Ferrarelli F, Huber R, Peterson MJ, et al. Reduced sleep spindle activity in schizophrenia patients. *Am J Psychiatry*. 2007;164(3):483-492. doi:10.1176/ajp.2007.164.3.483
109. Papp A, Horváth A, Gombos F, Bódizs R, Kamondi A, Szűcs A. Analysis of slow and fast sleep spindle properties in Parkinson's disease - A comparative EEG study. *Int J Psychophysiol Off J Int Organ Psychophysiol*. 2022;182:220-230. doi:10.1016/j.ijpsycho.2022.11.001
110. Nir Y, Staba RJ, Andrillon T, et al. Regional slow waves and spindles in human sleep. *Neuron*. 2011;70(1):153-169. doi:10.1016/j.neuron.2011.02.043

8. Bibliography of the candidate's publications

8.1. Publications related to the thesis

1. **Sákovics A**, Csukly G, Borbély C, Virág M, Kelemen A, Bódizs R, Erőss L, Fabó D. Prolongation of cortical sleep spindles during hippocampal interictal epileptiform discharges in epilepsy patients. *Epilepsia*. 2022 Sep;63(9):2256-2268. **(IF: 6.740)**
2. **Sákovics A**, Csukly G, Borbély C, Kelemen A, Jordán Z, Hajnal B, Szabó JP, Erőss L, Fabó D. Interictal epileptiform discharges as the most significant confounding factor underlying memory impairment in focal epilepsy. *Epilepsy Res*. 2025 Jul 30; 218:107636. **(IF:2.0)**

Cumulated impact factor of publications related to the thesis: **8.740**

8.2. Publications not related to the thesis

1. Jordán Z, Szabó JP, **Sákovics A**, Kelemen A, Halász L, Erőss L, Fabó D. Epileptiform discharges in the anterior thalamus of epilepsy patients. *iScience*. 2024 Mar 27;27(5):109582. **(IF: 4.10)**
2. Szabó JP, Fabó D, Pető N, **Sákovics A**, Bódizs R. Role of anterior thalamic circuitry during sleep. *Epilepsy Res*. 2022 Oct; 186:106999. **(IF: 2.20)**
3. Gyebnár G, Szabó Á, Sirály E, Fodor Z, **Sákovics A**, Salacz P, Hidasi Z, Csibri É, Rudas G, Kozák LR, Csukly G. What can DTI tell about early cognitive impairment? - Differentiation between MCI subtypes and healthy controls by diffusion tensor imaging. *Psychiatry Res Neuroimaging*. 2018 Feb 28; 272:46-57. **(IF: 2.270)**
4. Horvath A, Szucs A, Csukly G, **Sakovics A**, Stefanics G, Kamondi A. EEG and ERP biomarkers of Alzheimer's disease: a critical review. *Front Biosci (Landmark Ed)*. 2018 Jan 1;23(2):183-220. **(IF: 2.214)**
5. Szűcs A, Horváth A, Rásonyi G, Fabó D, Szabó G, **Sákovics A**, Kamondi A. Ictal analgesia in temporal lobe epilepsy - The mechanism of seizure-related burns. *Med Hypotheses*. 2015 Aug;85(2):173-7. **(IF: 1.136)**

Cumulated impact factor of publications not related to the thesis: **11,92**

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