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RESEARCH ARTICLE

Widespread decoupling of spindles and slow waves in temporal lobe epilepsy

Katharina Schiller[1,2,3] | **Nicolás von Ellenrieder**[4] | **Daniel Mansilla**[1] | **Chifaou Abdallah**[1] | **Kassem Jaber**[5] | **Alfonso Garcia-Asensi**[5] | **John Thomas**[5] | **Erica Minato**[1] | **Jean Gotman**[4] | **Birgit Frauscher**[1,5,6]

[1]Analytical Neurophysiology Lab, Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, Canada

[2]Department of Pediatrics, Hospital Group Ostallgaeu-Kaufbeuren, Kaufbeuren, Germany

[3]Department of Pediatric Neurology, University Hospital Augsburg, Augsburg, Germany

[4]Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, Canada

[5]Analytical Neurophysiology Lab, Department of Neurology, Duke University, Durham, North Carolina, USA

[6]Department of Biomedical Engineering, Duke University, Durham, North Carolina, USA

Correspondence
Birgit Frauscher, Department of Neurology, Duke University Medical Center, 2424 Erwin Street, Ste. 1001, Durham, NC 27705, USA.
Email: birgit.frauscher@duke.eu

Katharina Schiller, Montreal Neurological Institute and Hospital, 3801 University Street, Montreal, H3A 2B4, QC, Canada.
Email: katharina.schiller@mcgill.ca

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Abstract

Objective: Memory impairment is common in people with temporal lobe epilepsy (TLE). Recent studies in healthy subjects showed a positive correlation between sleep spindles coupled to slow waves (SWs) and memory performance. We aimed to determine differences in spindle–SW coupling in TLE patients compared to healthy controls using combined high-density electroencephalography and polysomnography.

Methods: The study population consisted of 20 patients (12 female, 36.5 ± 9.9 years old) with unilateral drug-resistant TLE (10 left temporal) and 20 age- and sex-matched controls (12 female, 31.2 ± 6.3 years old). Spindles (10–16 Hz, .5–3 s) and SWs (.5–4 Hz) were automatically detected during all N2 and N3 epochs using validated detectors. Coupling of spindles with SWs was defined as overlap between both detected events.

Results: Coupled spindle–SW rates (per minute) were globally reduced in patients with TLE compared to healthy controls (median = .18 [interquartile range (IQR) = .08–.36] vs. .35 [IQR = .24–.46], $p = .014$, $d = -.46$). This reduction was also found for coupled fast spindle (12–16 Hz)–SW (.06 [IQR = .02–.13] vs. .18 [IQR = .07–.25], $p = .013$, $d = -.46$) and slow spindle (10–12 Hz)–SW rates (.11 [IQR = .04–.23] vs. .19 [IQR = .13–.27], $p = .034$, $d = -.40$). Within TLE patients, there was no local difference between the coupling rates in the lobe with the epileptic focus compared to the contralateral side (.09 [IQR = .02–.13] vs. .07 [IQR = .02–.13], $p = .18$). The effect size of the reduction was stronger in early than late sleep for both N2 and N3 sleep (early N2 $d = -.50$ vs. late N2 $d = -.39$; early N3 $d = -.53$ vs. late N3 $d = -.47$).

Significance: Despite a focal epileptic generator, patients with unilateral TLE showed a widespread decoupling between sleep spindles and SWs that was most prominent in early sleep. As coupling was shown to be associated with

Katharina Schiller and Nicolás von Ellenrieder contributed equally to this work.

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neuropsychological performance in healthy people, this global decoupling may constitute one potential mechanism of poor memory performance in people with TLE.

KEYWORDS
cognition, coupling, focal epilepsy, high-density EEG, sleep

1 | INTRODUCTION

Sleep plays an important role in memory consolidation.[1] Sleep spindles and slow waves (SWs) are characteristic physiological sleep oscillations of non-rapid eye movement (NREM) sleep stages N2 and N3.[2] Both correlate with cognitive function and are crucial for memory consolidation and brain maturation.[3,4] Epileptic activity can have a negative effect on sleep physiology; patients with epilepsy experience disturbances in both sleep macro- and microstructure.[5,6] Sleep spindles were found to be locally reduced in patients with focal epilepsy, and this reduction was associated with worse cognitive function.[7,8] High-amplitude SWs, which were shown to facilitate epileptic activity,[9,10] are increased in the area of the epileptic focus.[11] Patients with focal epilepsy may also show local slowing during wakefulness as an expression of cortical dysfunction, which was found to be related to cognitive impairment.[12] Distinguishing physiological sleep SW and pathological slowing during sleep remains a challenging task.

Recent findings in healthy adults showed that the coupling of spindles and SWs is associated with overnight memory consolidation and neurocognitive functions.[13–17] The coupling strength of spindles and SWs was positively correlated with declarative and procedural memory performance in healthy subjects.[13] Specifically, the coupling of fast spindles with SWs was associated with better memory consolidation in younger healthy adults.[16] Additionally in healthy children, increased spindle–SW coupling was found to coincide with better memory performance.[14] In patients with temporal lobe epilepsy (TLE), memory impairment is common.[18] One potential mechanism to explain cognitive dysfunction in people with epilepsy could be disturbed spindle–SW coupling. This, however, has not yet been investigated.

Therefore, the goal of this study is to compare spindle–SW coupling, defined here by the co-occurrence of spindles and SWs, between adult patients with unilateral TLE and healthy controls using full night high-density electroencephalographic (HD-EEG) recordings. In our primary hypothesis, we aimed to explore the global differences in coupled spindle–SW rates between patients and controls. As exploratory endpoints, we aimed to analyze (1) potential local alterations of coupled spindle–SW rates in the lobe of the epileptic focus, (2) sleep homeostatic influences across the night (early vs. late sleep), and (3) spindle–SW coupling dependence on sleep depth (N2 vs. N3 sleep). We hypothesized that coupled spindle–SW rates are reduced in patients with TLE compared to healthy controls, the reduction is present in N2 and N3 sleep, coupled spindle–SW rates are decreased in the brain region with the epileptic focus compared to the contralateral homologous brain region, and the reduction is stronger during early than late sleep.

Key points

- In healthy people, the coupling of sleep spindles and slow waves during NREM sleep is associated with memory performance.
- As memory dysfunction is common in people with temporal lobe epilepsy, we explored spindle–slow wave coupling in this patient group compared to healthy controls.
- Despite a focal epileptic generator in the temporal lobe, patients showed a widespread reduction in spindle–slow wave coupling.
- This reduction in spindle–slow wave coupling was stronger in early than late sleep.
- The global decrease may constitute one potential mechanism of poor memory performance in people with temporal lobe epilepsy.

2 | MATERIALS AND METHODS

2.1 | Study population and HD-EEG overnight recordings

For this prospective study, patients with unilateral drug-resistant TLE underwent combined polysomnography and HD-EEG recording during their hospitalization for presurgical evaluation in the epilepsy monitoring unit of the Montreal Neurological Institute and Hospital. HD-EEG was performed on average on day 3 of the hospitalization.

Day 1 was only chosen if the patient had a previous admission to our unit mitigating the potential influence of a first-night effect. HD-EEG was recorded for one to two nights. We systematically chose the first night for each patient. Patients did not undergo stereo-EEG during the same evaluation. The epileptic focus was defined based on phase 1 or 2 presurgical evaluation with long-term video-EEG monitoring, anatomical 3-T magnetic resonance imaging (MRI), positron emission tomography and neuropsychological evaluation, or stereo-EEG where applicable. The demographic characteristics of the patients are presented in Table 1. Patients with previous brain surgery were excluded from this study. Patients were age- and sex-matched with healthy controls who underwent combined polysomnography and HD-EEG recording at the sleep laboratory of the McGill University Health Centre. Healthy controls had neither sleep nor neurological disorders as assessed with a screening interview and questionnaires as well as no respiratory abnormalities as assessed in the polysomnography. The (Analytical Neurophysiology) ANPHY-sleep dataset is available open access.[19] Recordings were performed with the Nihon Koden system using 83 glued electrodes placed according to the 10–10 EEG system with a sampling rate of 1000 Hz and additional electrodes for electro-oculography (EOG) and chin electromyography (EMG). The study design is presented in Figure 1. All study participants provided written informed consent in agreement with the Research Ethics Board at the Montreal Neurological Institute (MP-37-2018-3886).

2.2 | Scoring of sleep macro- and microstructure and marking of interictal epileptiform discharges

Sleep was manually scored according to American Academy of Sleep Medicine criteria in 30-s epochs, displaying the EEG in a mastoid referential montage, EOG, and EMG.[20] According to Marzec and Malow,[21] seizures were scored as undefined and excluded from the sleep time. After a seizure, sleep was scored when the waveforms were comparable to preictal sleep. In patients with nocturnal seizures, 12 h of sleep recording after a focal to bilateral tonic–clonic seizure and 2 h after a focal impaired awareness as well as awareness unknown seizure were excluded for sleep microstructure analyses. We selected all N2 and N3 epochs available for each subject to perform detections of sleep spindles and SWs. In this article, NREM sleep will refer to N2 and N3 sleep combined. To study the effect of sleep homeostasis, we systematically chose the first and last 20 min of N2 and of N3 sleep. Because of a focal to bilateral tonic–clonic seizure in the first half of the night in Patient 11, this patient and the respective age- and sex-matched healthy control were excluded from the analysis of sleep homeostasis. Arousals and artifacts were manually marked and excluded from further analysis.

Sleep spindles (10–16 Hz, .5–3 s) and SWs (.5–4 Hz) were automatically detected in the common average montage in all 83 channels with a validated detector using a custom script written in MATLAB 2020a implemented in our lab.[22,23] According to Rosinvil et al.,[24] we adjusted SW thresholds by age and sex for each subject and created four groups: (1) female subjects aged <40 years (peak-to-peak SW amplitude = 77 μV, negative SW amplitude = 41 μV), (2) female subjects aged ≥40 years (peak-to-peak SW amplitude = 70 μV, negative SW amplitude = 37 μV), (3) male subjects aged <40 years (peak-to-peak SW amplitude = 74 μV, negative SW amplitude = 39.5 μV), and (4) male subjects aged ≥40 years (peak-to-peak SW amplitude = 60 μV, negative SW amplitude = 32 μV). The detections were visually checked for each subject. Spindles were further categorized into slow spindles (10–12 Hz) and fast spindles (12–16 Hz). Interictal epileptiform discharges (IEDs) were visually marked at their peak across all channels by an epileptologist in all N2 and N3 epochs.

2.3 | Coupling analyses

Coupling of spindle–SWs was defined as any overlap between both events in the same channel. In this article, coupling refers therefore to co-occurrence of spindles and SWs. Phase–amplitude coupling of spindles and SWs will be referred to as such. Detections of spindles and SWs at the time of an IED and SW detections starting up to 150 ms after the peak of an IED were excluded. This was chosen to exclude pathological SWs following the IED peak (total duration of IED = 200 ms). Rates of coupled spindle–SWs were calculated per minute during NREM epochs excluding the duration of artifacts. For the global comparison, all channels were considered for the analyses, whereas for the regional comparison of the temporal lobes, the electrodes FT7, FT9, Zyg1, T3, T9, TP7, TP9, TP11, T5, P9, P11 (left temporal) and FT8, FT10, Zyg2, T4, T10, TP8, TP10, TP12, T6, P10, P12 (right temporal) were used. To quantify the amount of co-occurrence (coupling) between spindles and SWs independent of their individual rates, we calculated the coupling strength. It should be higher when a larger proportion of spindles overlap with SWs. Thus, we defined the coupling strength for each channel as the increase in the probability of detecting a spindle at the same time as an SW relative to the probability to detecting a spindle at a random instant irrespective of the presence of SWs.

TABLE 1 Patient demographics.

Patient	Age, years/sex	Epileptic focus	MRI findings	Medication at admission	Medication on day of HD-EEG recording	Seizure during recording
1	26/F	L mesiotemporal	Normal	Lamotrigine 550 mg, lacosamide 500 mg, perampanel 8 mg	Lamotrigine 550 mg, lacosamide 500 mg, perampanel 8 mg	–
2	51/M	L mesiotemporal	L mesiotemporal FCD	Lacosamide 400 mg	Lacosamide 400 mg	–
3	41/F	R mesiotemporal	R MTS	Levetiracetam 2000 mg, lacosamide 200 mg	Lacosamide 200 mg	–
4	25/F	L mesiotemporal	L MTS	Lamotrigine 500 mg, phenytoin 100 mg	Lamotrigine 100 mg	
5	51/F	R mesiotemporal	R hippocampal atrophy	Levetiracetam 3000 mg, clobazam 10 mg	Levetiracetam 3000 mg	–
6	21/F	R mesiotemporal	Normal	Lamotrigine 400 mg, clobazam 10 mg, amitriptyline 75 mg	Lamotrigine 400 mg, clobazam 10 mg, amitriptyline 75 mg	–
7	24/M	L mesiotemporal	L mesiotemporal cystic area with possibly associated dysplastic cortex	Levetiracetam 3000 mg, lamotrigine 375 mg, lacosamide 400 mg	Levetiracetam 3000 mg, lamotrigine 375 mg, lacosamide 400 mg	–
8	43/M	R mesiotemporal	R MTS	Lamotrigine 250 mg, citalopram 20 mg	Lamotrigine 75 mg, Carbamazepine 400 mg, citalopram 20 mg	–
9	32/M	R posterior temporoinsular	R temporal neocortex atrophy & atrophy/agenesis of the R piriform	Lacosamide 250 mg, eslicarbazepine 800 mg, brivaracetam 200 mg, escitalopram 20 mg	Lacosamide 100 mg, eslicarbazepine 800 mg, brivaracetam 200 mg, escitalopram 20 mg	–
10	40/M	L mesial and basal temporal	Normal	Levetiracetam 2000 mg, carbamazepine 1200 mg	Levetiracetam 2000 mg, carbamazepine 800 mg	–
11	27/F	L mesiotemporal	Normal	Carbamazepine 800 mg	Eslicarbazapine 600 mg	4 seizures (00:53 a.m. focal to bilateral tonic–clonic seizure; 3:49 a.m.; 4:55 a.m.; 5:47 a.m. focal impaired awareness; all out of N2 or N3)
12	44/M	L mesiotemporal	L MTS	Levetiracetam 2000 mg, carbamazepine 600 mg, phenobarbital 120 mg, perampanel 12 mg, rufinamide 3200 mg	Levetiracetam 2000 mg, phenobarbital 120 mg, perampanel 12 mg	–
13	25/F	R mesiotemporal	R mesiotemporal FCD	Carbamazepine 1600 mg, Lamotrigine 300 mg, Clonazepam 50 mg	Carbamazepine 800 mg	–
14	37/F	L mesiotemporal	L MTS	Carbamazepine 1000 mg, Lamotrigine 400 mg	Carbamazepine 200 mg, lamotrigine 100 mg	1 seizure (7:59 a.m. focal to bilateral tonic–clonic seizure out of N2)
15	39/M	R mesiotemporal	R MTS	Phenytoin 600 mg, clobazam 10 mg	Eslicarbazepine 600 mg, clobazam 10 mg	–
16	39/F	R mesiotemporal	R MTS	Lamotrigine 400 mg, levetiracetam 2000 mg	Lamotrigine 100 mg, levetiracetam 500 mg	1 seizure (10:51 p.m., focal impaired awareness seizure out of wakefulness)
17	54/M	L mesiotemporal	L MTS	Carbamazepine 800 mg, lacosamide 300 mg, clobazam 30 mg, aripiprazole 5 mg, levomilnacipran 80 mg	Carbamazepine 200 mg, lacosamide 75 mg, clobazam 15 mg, aripiprazole 5 mg, levomilnacipran 80 mg	–
18	43/F	L mesiotemporal	Noncystic lesion in the hippocampus	Lamotrigine 450 mg	Lamotrigine 450 mg	–
19	29/F	R mesiotemporal	Normal	Levetiracetam 3000 mg, lamotrigine 300 mg, lacosamide 50 mg	Levetiracetam 2000 mg, lamotrigine 250 mg	–
20	40/F	R mesiotemporal	Normal	Levetiracetam 3000 mg, carbamazepine 800 mg, lacosamide 300 mg	Levetiracetam 3000 mg, carbamazepine 800 mg, lacosamide 300 mg	–

Abbreviations: F, female; FCD, focal cortical dysplasia; HD-EEG, high-density electroencephalography; L, left; M, male; MRI, magnetic resonance imaging; MTS, mesial temporal sclerosis; R, right.

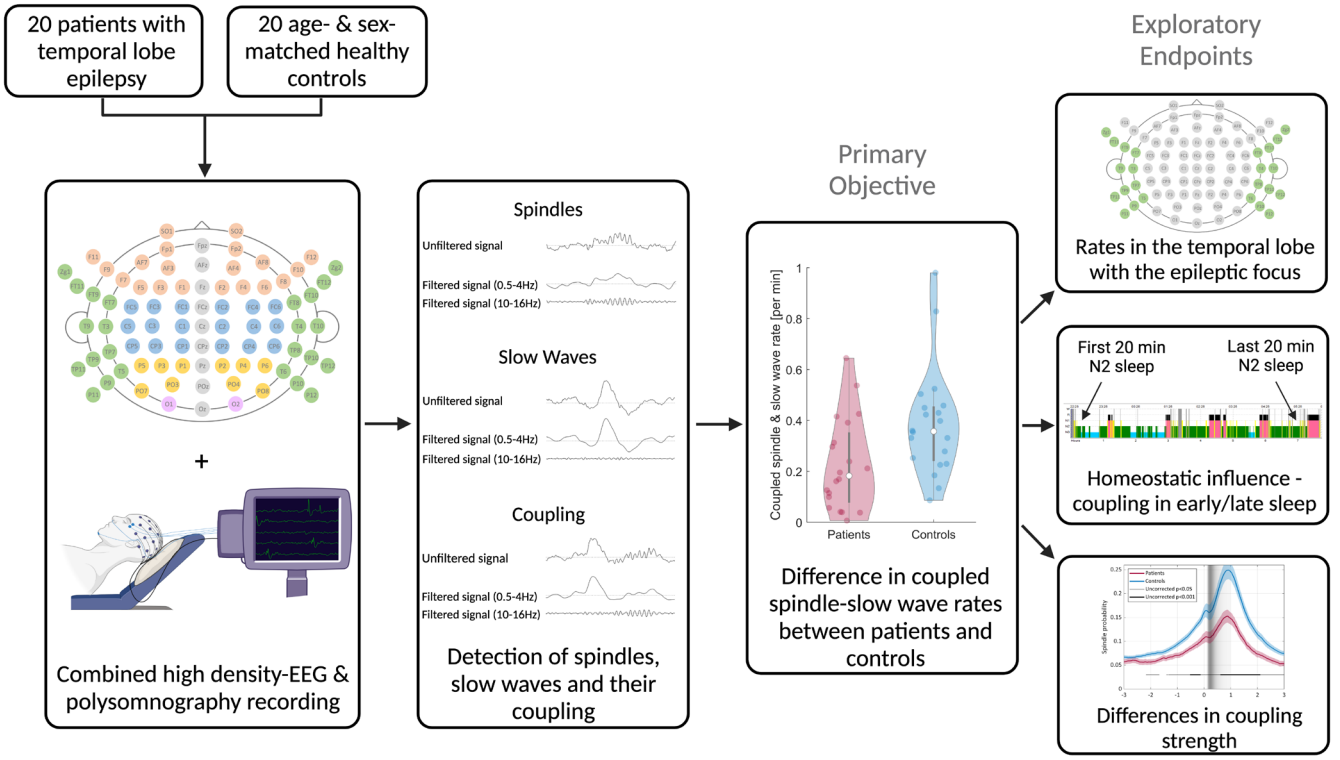

FIGURE 1 Study design (created with BioRender.com). EEG, electroencephalography.

Note that with this definition, the coupling strength is independent of the rate of both SWs and spindles. Finally, global phase–amplitude coupling of spindles and SWs was determined using a Hilbert transform to compute the instantaneous phase angles of the detected SW. SW phases corresponding to the times of spindle events at the spindle center were extracted. Preferred coupling phase and phase coupling strength were computed for patients and controls.[25]

2.4 | Statistics

Data were tested for normal distribution with the Kolmogorov–Smirnov test and reported as mean ± SD in the case of normally distributed data or median (interquartile range [IQR]) otherwise. Group comparisons between patients and controls were performed with the *t*-test in the case of normally and Mann–Whitney *U*-test in case of nonnormally distributed data. Effect sizes for group comparisons were calculated using Cohen delta for normally distributed data and Cliff delta for nonnormally distributed data. Within-patient or within-control comparisons such as regional analyses (ipsilateral temporal vs. contralateral temporal or left temporal vs. right temporal) were performed using a paired *t*-test or Wilcoxon signed-rank test. The effect size for paired nonparametric tests was calculated using the matched-pairs rank biserial correlation (RC), a recommended estimate of the effect size for paired nonparametric tests such as the Wilcoxon signed-rank test. Its value ranges from −1 to +1.[26] IED rate (per minute) and coupled spindle–SW rates (per minute) were correlated using a Spearman correlation. Statistical analyses were performed using MATLAB 2020a.

3 | RESULTS

3.1 | Study population and sleep macrostructure

The final study population consisted of 20 patients with unilateral drug-resistant TLE (12 females, mean age = 36.5 ± 9.9 years, 10 left temporal and 10 right temporal) and 20 healthy controls (12 females, mean age = 31.2 ± 6.3 years). Eighteen of the 20 patients had mesiotemporal TLE (Table 1).

The parameters of sleep macrostructure did not differ between patients with TLE and healthy controls (Table 2). In particular, there were no differences in the percentage of N2 and N3 sleep in regard to total sleep time (TST) between patients and controls (%N2 [TST] patients vs. controls: 46.7 ± 9.9 vs. 51.7 ± 5.6, $p = .06$; %N3 [TST] patients vs. controls: 22.3 ± 8.0 vs. 22.2 ± 3.9, $p = .95$).

TABLE 2 Parameters of sleep macrostructure.

Parameter	Patients with TLE, $n = 20$	Healthy controls, $n = 20$	Patients vs. controls, p
TST, h (IQR)	6.4 (5.6–7.8)	6.1 (5.4–6.7)	.21
Sleep latency onset, min (IQR)	9.0 (5.6–10.9)	7.8 (3.8–19.4)	.67
REM onset latency, min (IQR)	92.0 (68.5–153.0)	70.0 (54.0–112.0)	.14
Sleep efficiency, % (IQR)	89.8 (79.9–93.9)	89.5 (83.0–93.5)	.82
WASO, min (IQR)	38.0 (18.4–74.0)	28.7 (17.1–48.5)	.34
%N1, TST (IQR)	12.5 (9.3–16.7)	10.3 (7.9–12.7)	.08
%N2, TST	46.7 ± 9.9	51.7 ± 5.6	.06
%N3, TST	22.3 ± 8.0	22.2 ± 3.9	.95
%REM, TST	17.6 ± 6.6	15.8 ± 4.7	.31

Abbreviations: IQR, interquartile range; REM, rapid eye movement; TLE, temporal lobe epilepsy; TST, total sleep time; WASO, wake after sleep onset.

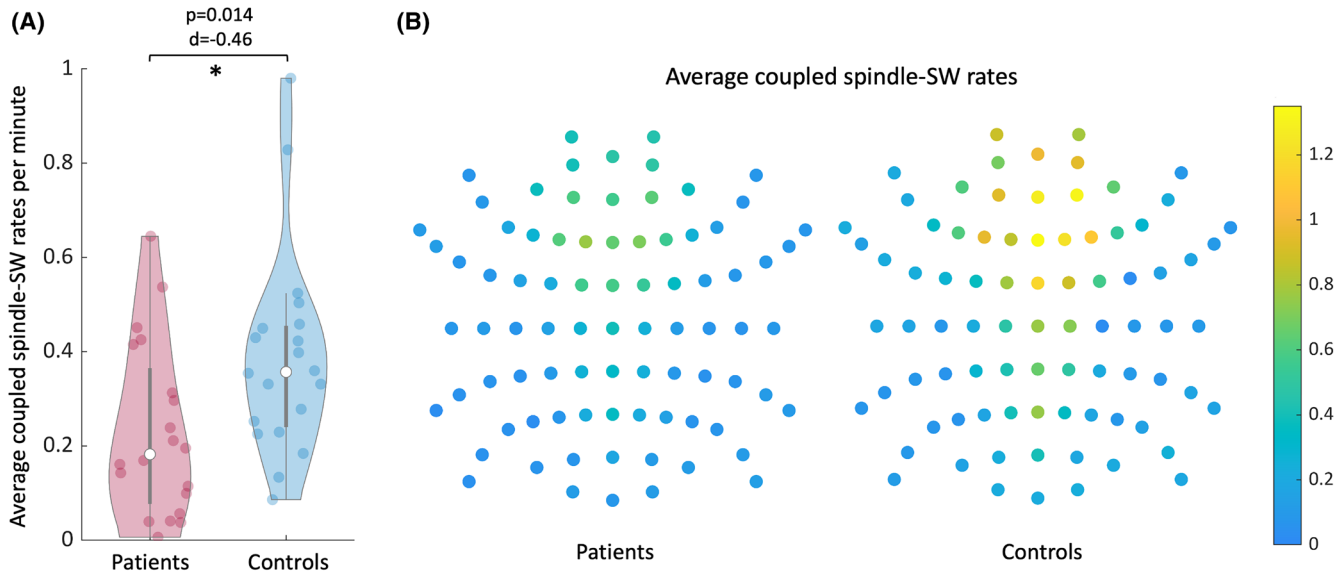

FIGURE 2 (A) Coupled spindle–slow wave (SW) rates during non-rapid eye movement (NREM) sleep are reduced in patients with temporal lobe epilepsy compared to healthy controls. (B) The spatial distribution of average coupled spindle–SW rates during NREM sleep in patients and controls. Rates are similarly distributed in both groups with a frontal maximum. *Statistically significant.

3.2 | Sleep spindles and SWs

The global spindle rate during NREM sleep was significantly reduced in patients with TLE compared to controls (3.6 ± 1.1/min vs. 4.8 ± .8/min, $p = .0005$, $d = 1.2$). The reduction was driven by fast spindles (1.8 ± 1.0 vs. 2.9 ± 1.0, $p = .0001$, $d = 1.1$), whereas there was no difference in slow spindles (1.8 ± .7 vs. 1.8 ± .6, $p = .80$, $d = .08$). Within patients, in the lobe with the epileptic focus compared to the contralateral side, global and fast spindle rates were significantly reduced compared to the contralateral side, whereas there was no difference in slow spindles (all spindles: 2.7 ± 1.1 vs. 2.8 ± 1.2, $p = .045$, RC = −.5; fast spindles: .9 [IQR = .7–1.3] vs. 1.0 [IQR = .8–1.3], $p = .048$, RC = −.5; slow spindles: 1.4 ± .7 vs. 1.4 ± .7, $p = .52$, $d = .1$). Spindle rates separated for N2 and N3 are presented in Table S1.

Global SW rates during NREM sleep did not differ between patients and controls (1.0 [IQR = .5–1.6] vs. 1.5 [IQR = .9–2.5], $p = .07$, $d = -.34$). Within patients, in the lobe with the epileptic focus compared to the contralateral side, SW rates were significantly increased during NREM sleep (ipsitemporal vs. contralateral: .5 [IQR = .2–1.6] vs. .5 [IQR = .2–1.0], $p = .03$, RC = .56). Table S1 shows SW rates separated for N2 and N3.

3.3 | Coupling of sleep spindles and SWs

3.3.1 | Epilepsy patients versus healthy controls

Coupled spindle–SW rates during NREM sleep were globally reduced in patients with TLE compared to healthy

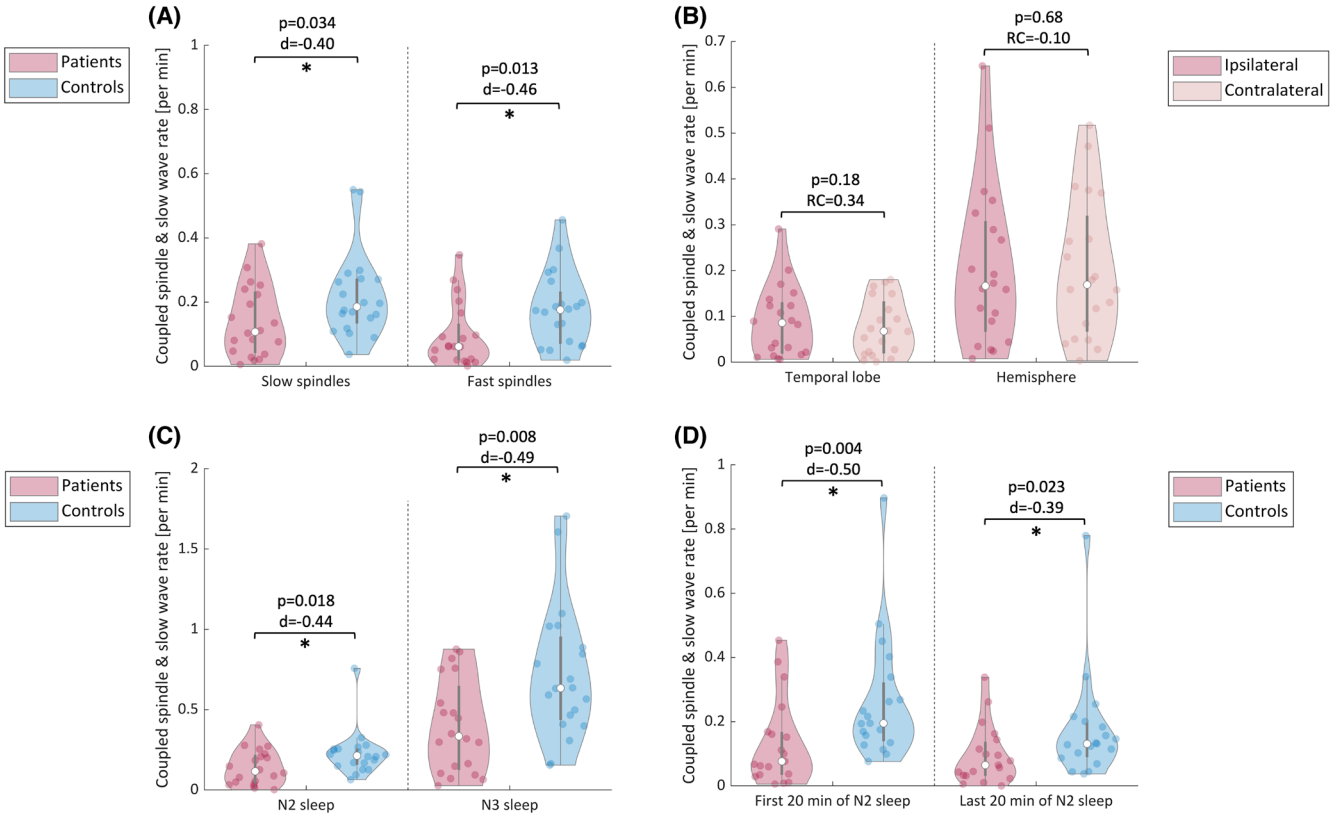

FIGURE 3 (A) Coupled slow spindle–slow wave (SW) and fast spindle–SW rates during non-rapid eye movement sleep are reduced in patients versus controls. (B) Within patients with temporal lobe epilepsy, there was no difference in coupled spindle–SW rates in the hemisphere with the epileptic focus compared to the contralateral hemisphere and the temporal lobe with the epileptic focus compared to the contralateral side. (C) Coupled spindle–SW rates are reduced in patients compared to controls during N2 epochs and N3 epochs. (D) There was a stronger effect in reduction of coupled spindle–SW rates in early compared to late sleep. *Statistically significant. RC, rank biserial correlation.

controls (.18 [IQR = .08–.36] vs. .35 [IQR = .24–.46], $p = .014$, $d = -.46$; Figure 2A). The spatial distribution of the coupled spindle–SW rates was similar in patients and controls with a frontal maximum (Figure 2B). A similar reduction was also found in coupled slow spindle–SW and fast spindle–SW rates (slow spindle–SW: .11 [IQR = .04–.23] vs. .19 [IQR = .13–.27], $p = .034$, $d = -.40$; fast spindle–SW: .06 [IQR = .02–.13] vs. .18 [IQR = .07–.25], $p = .013$, $d = -.46$; Figure 3A). We performed a subanalysis excluding all patients who experienced seizures during the recording ($n = 3$) and the respective age- and sex-matched healthy controls ($n = 3$). There was a similar effect in reduced coupled spindle–SW rates between patients and controls (.19 [IQR = .08–.34] vs. .39 [IQR = .28–.48], $p = .009$, $d = -52$).

3.3.2 | Regional analysis in the temporal lobe

There was no difference in coupled spindle–SW rates during NREM sleep between the hemisphere with the epileptic focus compared to the contralateral hemisphere (.17 [IQR = .07–.31] vs. .17 [IQR = .07–.32], $p = .68$, RC = −.10; Figure 3B). Additionally, coupled spindle–SW rates did not differ between the temporal lobe with the epileptic focus (ipsitemporal) and the homologous contralateral side (.09 [IQR = .02–.13] vs. .07 [IQR = .02–.13], $p = .18$, RC = .34; Figure 3B). In healthy controls, coupled spindle–SW rates did not differ between the left and right hemisphere as well as between the right and left temporal lobe (all $p > .05$).

3.3.3 | Sleep homeostatic properties: Early versus late sleep

Coupled spindle–SW rates were decreased in patients compared to healthy controls in both N2 only and N3 alone (Figure 3C, Table S2). To study the influence of homeostatic properties, the first 20 min of N2 (early N2) and N3 (early N3) were compared to the last 20 min of N2 (late N2) and N3 (late N3). The reduction of coupled spindle–SW rates in patients compared to controls was present in early and late N2 (Figure 3D) and N3, with a stronger effect size in

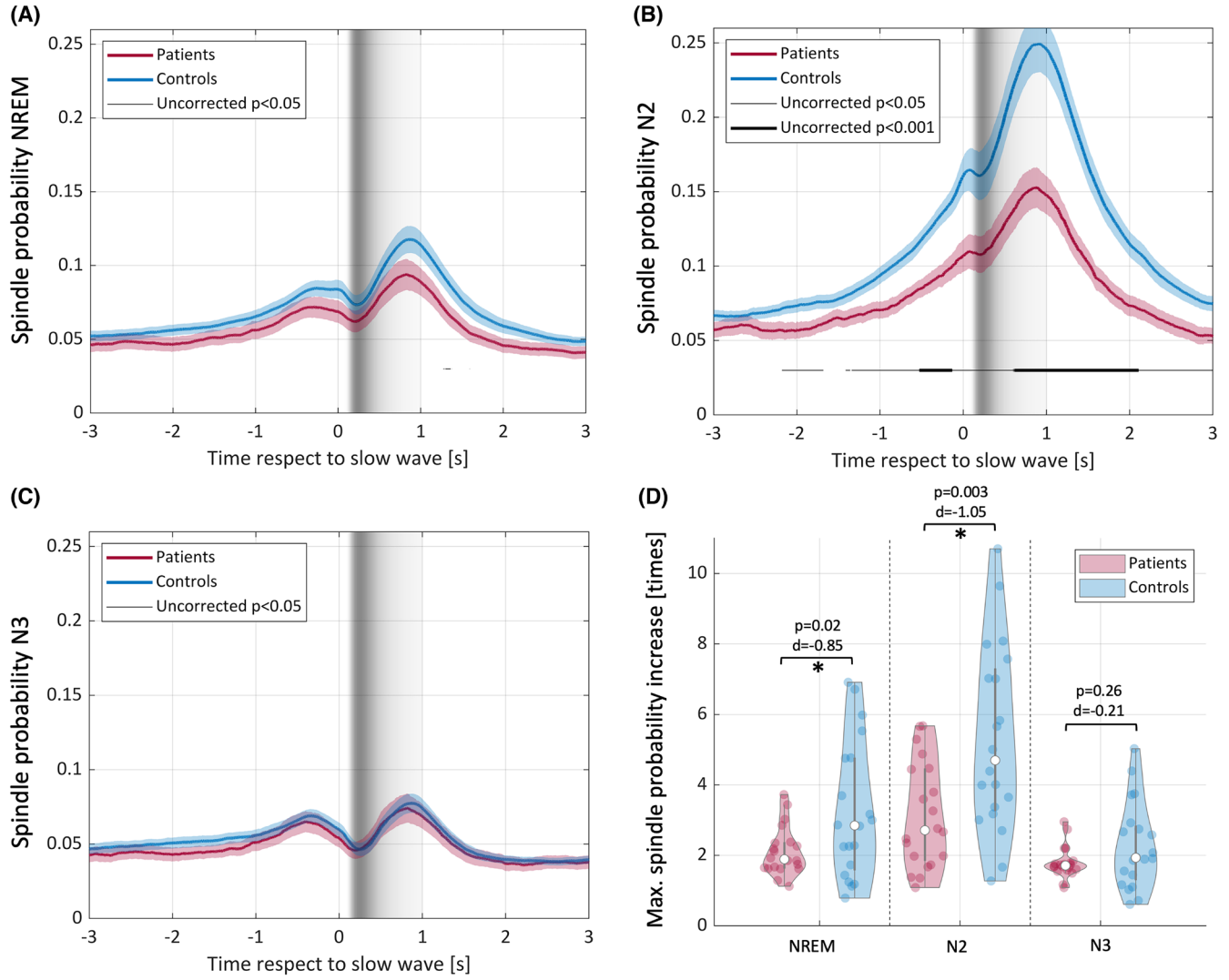

FIGURE 4 (A) Spindle probability at the time of slow wave (SW) detection during non-rapid eye movement (NREM) sleep (mean ± SE). The gray gradation shows the distribution of the peak of the SW over all participants. There was a significant difference between patients and controls in coupling of spindles and SWs after the peak of the SW. (B) Spindle probability at the time of SW detection during N2. There was a significant difference between patients and controls in coupling of spindles and SWs before and after the peak of the SW. (C) Spindle probability at the time of SW detection during N3. There was no significant difference between patients and controls in spindle probability before and after the peak of the SW. (D) The coupling strength is significantly reduced in patients compared to controls during NREM sleep and N2 but did not differ during N3. *Statistically significant.

early compared to late sleep (early N2 $d = -.50$ vs. late N2 $d = -.39$; early N3 $d = -.53$ vs. late N3 $d = -.47$; Table S2).

3.3.4 | Differences in spindle–SW coupling strength between sleep stages N2 and N3

The coupling strength was reduced in patients compared to controls during NREM sleep (2.11 ± .69 vs. 3.23 ± 1.93, $p = .020$, $d = -.85$; Figure 4D). This was mainly driven by the decrease of coupling strength during N2 (3.12 ± 1.51 vs. 5.29 ± 2.63, $p = .003$, $d = -1.05$), with no difference during N3 sleep (1.71 [IQR = 1.59–1.81] vs. 1.93 [IQR = 1.30–2.83], $p = .26$, $d = -.21$). The timing of coupling is presented in Figure 4A–C. The coupling between spindles and SWs differed between patients and controls after the peak of the SW during NREM sleep and before and after the peak of the SW during N2, whereas there was no significant difference during N3. Similarly, the amount of coupling (percentage of all SWs coupled with a spindle) was reduced in patients compared to controls in N2 (29.1 ± 9.8% vs. 44.4 ± 10.9%, $p < .0001$, $d = -1.48$) but not in N3 and NREM (N3: 16.4 ± 8.0% vs. 17.3 ± 5.4%, $p = .68$, $d = -.13$; NREM: 19.8 ± 8.6% vs. 23.7 ± 6.8%, $p = .13$, $d = -.50$).

3.3.5 | Phase–amplitude coupling between spindles and SWs

The preferred coupling phase angle did not differ between patients and controls (209° [IQR = 196–233] vs. 223° [IQR = 213–231], $p = .46$). Phase coupling strength (phase locking value) was also not significantly different between patients and controls (.21 ± .07 vs. .22 ± .05, $p = .67$).

3.3.6 | Correlation with IED rate

Sixteen patients showed IEDs during NREM sleep, and four were IED negative. The median IED rate per patient was .26/min (IQR = .05–.79). The IED rate was not significantly correlated with coupled spindle–SW rates (NREM: $r = -.18$, $p = .44$; N2: $r = -.31$, $p = .19$; N3: $r = -.09$, $p = .70$).

4 | DISCUSSION

Using combined HD-EEG and polysomnography, we explored the coupling of spindles and SWs as sleep oscillations, which play an important role in memory consolidation and cognition, in patients with drug-resistant TLE and a healthy control group. Our main findings were that (1) there was global decoupling between sleep spindles and SWs in people with TLE compared to healthy controls, (2) there was no difference in coupling rates between the lobe with the epileptic focus and the homologous contralateral side, (3) the effect of reduced coupling was stronger in early than late sleep, and (4) the reduction in coupling strength was driven by N2 sleep.

4.1 | Coupled spindle–SW rates are reduced in patients with TLE

This is the first work to show a decrease of coupled spindle–SW rates in patients with epilepsy in comparison to a healthy control group. Patients showed a widespread reduction of coupling activity compared to controls. Recent studies in healthy participants pointed toward a correlation of coupled spindle–SWs with overnight memory consolidation and neurocognitive functions.[13–17] In young healthy adults in particular, the coupling of fast spindles–SWs promoted memory consolidation.[16] Other studies also suggested that fast spindles are generally a better predictor for cognitive functions compared to slow spindles.[27] Memory complaints and dysfunction are frequently encountered in patients with TLE and especially mesial TLE.[28,29] The decrease in coupled spindle–SW rates and especially the reduction of coupled fast spindles–SWs found in our cohort may be one mechanism explaining poor memory performance in patients with TLE.[30] In patients with Alzheimer disease, transcranial stimulation applied during a daytime nap enhanced the coupling of spindles with SWs and ultimately improved memory performance.[31] In patients with TLE, slow oscillatory transcranial stimulation increased the amount of sleep spindles, which improved declarative memory performance,[32] but changes in coupling of spindles with SWs were not directly examined. Despite a focal epileptic focus, our cohort showed a global decrease of coupled spindle–SW rates. This is notable, as alterations of sleep oscillations in focal epilepsy were previously found to be locally disturbed.[7,8] It would be interesting to explore coupling of spindles and SWs in various focal epilepsies outside TLE.

Regarding the global phase–amplitude coupling, we did not find a difference in the preferred phase angle and phase coupling strength between TLE patients and controls. This is in contrast to previous findings reporting a reduced phase–amplitude coupling strength in TLE patients, which was further negatively correlated with executive functions.[25] However, in the study of Bender et al.,[25] only one channel (Fz) was used for calculating phase–amplitude coupling between spindles and SWs, whereas in our study, all channels of the 83-channel HD- EEG were used for analyses. Furthermore, a large proportion in Bender et al.[25] were bilateral TLE patients, whereas in our study, only patients with unilateral TLE were included.

Furthermore, interictal epileptic activity may disrupt memory processes during NREM sleep.[28] However, we did not find a correlation between coupled spindle–SW rates and IED rates. This might be because the majority of our cohort (18/20) were patients with mesial TLE, and IEDs originating from a deep generator were therefore not visible on the scalp EEG.[33] Alternatively, it may be that it is not epileptic activity itself but the underlying neuropathology of epilepsy that could be responsible for the alteration of physiological sleep oscillations and their coupling.

4.2 | Coupled spindle–SW rates are globally but not focally reduced in patients with epilepsy

Whereas coupled spindle–SW rates on a global level were reduced in patients with TLE compared to healthy controls, there were no local differences in coupling in the region with the epileptic focus compared to the homologous contralateral side. In our previous work, we found a local decrease of sleep spindles determined by localization of the epileptic focus in patients with various focal

epilepsies[7] which we could replicate in our cohort of patients with TLE. Despite the local reduction of spindles and increase of SWs probably due to pathological slowing in the epileptic focus, we could not find a difference in the spindle–SW coupling in the lobe with the focus. This might be because the rates of coupling were low in the temporal area in general. As in healthy controls, the maximum of coupled spindle–SW rates in patients was found in the frontal areas. Therefore, a reduction of coupling in the lobe with the epileptic focus may be more visible in patients with unilateral frontal lobe epilepsy.

4.3 | Reduction of spindle–SW coupling is stronger in early than in late NREM sleep

The decrease of spindle–SW coupling in patients was stronger in early compared to late sleep. A reduction of physiological sleep oscillations was previously found to be more pronounced in the beginning than at the end of the night in patients with epilepsy.[7,34] In contrast, IED rates were found to be higher in the first than the last sleep cycle and in particular in the beginning of the night to be related to higher amplitude SWs.[7,9,35] IED rates were further found to be negatively correlated with spindle rates.[36] However, we could not find a direct correlation between IED rates and coupled spindle–SW rates potentially due to a deep generator in the majority of patients, which could affect the visibility of IEDs in the scalp EEG.[33] However, a higher amount of pathological high-frequency oscillations was previously found in the beginning than at the end of the night.[37] This might thus explain a higher disturbance in the coupling of spindles with SWs in early NREM sleep.

4.4 | Coupling strength is reduced during NREM sleep and driven by N2 sleep

The coupling strength was used to determine the likelihood of coupling between spindles and SWs independently from their individual rates. By doing so, we can rule out that decreased coupled spindle–SW rates in patients are based on the global reduction of spindle rates that was present during NREM sleep. The reduction of the coupling strength in patients with epilepsy was driven by a strong decrease during N2 epochs, whereas there was no difference in N3 sleep. The effect size of the reduction of coupled spindle–SW rates was high during N2, where sleep spindles are more frequent than in N3 sleep. Next to sleep spindles, K-complexes defined by high-voltage biphasic SWs are the hallmark of N2 sleep.[38] They can be followed by sleep- or arousal-promoting responses.[39] Previous studies in healthy adults found that spindles are most often observed at the positive phase following the peak of a spontaneous K-complex and that there is a spindle-refractory period for about 1–3 s after the peak.[40] This was also observed in our data, and we found the majority of spindles coupled to SWs after the peak during N2 sleep. For N3 sleep, there was no significant difference in coupling strength between patients and controls. An explanation might be that there are per definition many more SWs during N3 sleep in contrast to N2 sleep, where SWs, mainly K-complexes, are less frequent, and therefore a reduction of coupling would be better visible.

4.5 | Strengths and limitations

A systematic approach was performed to analyze the coupling of spindles and SWs in a homogenous group of patients with TLE using HD-EEG, which covers large parts of the brain and allowed a regional investigation of these sleep oscillations. By matching epilepsy patients with healthy controls, a potential confounding effect of age and sex could be controlled. Sleep of epilepsy patients was recorded in the epilepsy monitoring unit, whereas healthy controls slept in the sleep laboratory. However, the research sleep laboratory is also based in a hospital setting, with very limited environmental differences compared to the epilepsy monitoring unit, thereby minimizing the differences. Additionally, detections were performed automatically and are therefore objective and reproducible. However, our study has some limitations. Although we found the reduction of coupled spindle–SW rates in patients with TLE, a correlation of coupling activity and memory performance could not be explored, because memory performance was not assessed before and after the sleep recording. Therefore, the association between reduced spindle–SW coupling and memory impairment remains speculative. Future studies are needed to evaluate the association of decreased coupling and neuropsychological performance. Furthermore, the patients were on different antiseizure medication. Previous findings showed that there was only a very minor effect of antiseizure medication on coupling strength.[41] The strong effect of the reduction in coupling of spindles and SW that was present in our patients on various medication increases the generalizability to adult patients with TLE.

5 | CONCLUSIONS

The coupling of sleep spindles and SWs was previously found to be correlated with memory performance in healthy people. Here, we could demonstrate that the coupling between spindles and SWs was disturbed in our cohort of patients with TLE, who commonly experience memory

dysfunction. Patients showed, in comparison to a healthy control group, a widespread reduction of coupling despite their focal epileptic generator; this decrease was more pronounced in early sleep. The disruption in coupling may explain, among other influencing factors, one mechanism for poor memory performance in patients with TLE.

AUTHOR CONTRIBUTIONS

Conception and design of the study: Katharina Schiller, Nicolás von Ellenrieder, and Birgit Frauscher. *Acquisition and annotation of data:* Katharina Schiller, Daniel Mansilla, Chifaou Abdallah, Kassem Jaber, Alfonso Garcia-Asensi, John Thomas, Erica Minato, Jean Gotman, and Birgit Frauscher. *Statistical analysis and interpretation of results:* Katharina Schiller, Nicolás von Ellenrieder, and Birgit Frauscher. *Manuscript preparation:* Katharina Schiller, Nicolás von Ellenrieder, and Birgit Frauscher. *Manuscript revision and approval:* all authors.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data of the healthy control group are available open access in the ANPHY high-density EEG sleep database (doi: 10.1038/s41597-024-03722-1). The data of patients that support the findings of this study are not publicly available, as the current research ethics board approval does not allow open data sharing. However, the data are available from the corresponding authors upon reasonable request and if in line with the local research ethics board requirements.

ETHICS APPROVAL AND PATIENT CONSENT STATEMENT

This study was approved by the research ethics board at the Montreal Neurological Institute (MP-37-2018-3886). All study participants provided written informed consent.

ORCID

Nicolás von Ellenrieder https://orcid.org/0000-0003-0845-347X
Daniel Mansilla https://orcid.org/0000-0002-5445-2526
Birgit Frauscher https://orcid.org/0000-0001-6064-1529

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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