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The influence of wakefulness fluctuations on brain networks involved in centrotemporal spike occurrence

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HIGHLIGHTS

- Wakefulness fluctuations and centro-temporal spikes (CTS) density are anticorrelated if drowsiness is followed by proper sleep.
- Wakefulness oscillations influence the fMRI-based connectivity between CTS generators and the left frontal operculum.
- Wakefulness fluctuations modulate the neuronal activity of key regions of the language circuitry in SeLECTS patients.

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ABSTRACT

Objective: Drowsiness has been implicated in the modulation of centro-temporal spikes (CTS) in Self-limited epilepsy with Centro-Temporal Spikes (SeLECTS). Here, we explore this relationship and whether fluctuations in wakefulness influence the brain networks involved in CTS generation.
Methods: Functional MRI (fMRI) and electroencephalography (EEG) was simultaneously acquired in 25 SeLECTS. A multispectral EEG index quantified drowsiness ('EWI': EEG Wakefulness Index). EEG (Pearson Correlation, Cross Correlation, Trend Estimation, Granger Causality) and fMRI (PPI: psychophysiological interactions) analytic approaches were adopted to explore respectively: (a) the relationship between EWI and changes in CTS frequency and (b) the functional connectivity of the networks involved in CTS generation and wakefulness oscillations. EEG analyses were repeated on a sample of routine EEG from the same patient's cohort.
Results: No correlation was found between EWI fluctuations and CTS density during the EEG-fMRI recordings, while they showed an anticorrelated trend when drowsiness was followed by proper sleep in routine EEG traces. According to PPI findings, EWI fluctuations modulate the connectivity between the brain networks engaged by CTS and the left frontal operculum.
Conclusions: While CTS frequency *per se* seems unrelated to drowsiness, wakefulness oscillations modulate the connectivity between CTS generators and key regions of the language circuitry, a cognitive function often impaired in SeLECTS.
Significance: This work advances our understanding of (a) interaction between CTS occurrence and vigilance fluctuations and (b) possible mechanisms responsible for language disruption in SeLECTS.

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1. Introduction

Self-limited epilepsy with centro-temporal spikes (SeLECTS), formerly known as Rolandic Epilepsy or Benign Epilepsy with Centrotemporal Spikes (BECTS), is the most common form of "self-limited focal epilepsies" (Scheffer et al., 2016; Specchio et al., 2022). The estimated incidence of SeLECTS is around 6 per 100,000 children per year, occurring four times more frequently than typical absence epilepsy (Miziara et al., 2012; Panayiotopoulos et al., 2008; Specchio et al., 2022). It is known to be age-dependent, to occur during crucial stages of development, with the typical age of onset between 3 and 10 years and a peak around 6–7 years. In SeLECTS, the most frequent seizure semiology is characterized by facial sensory, oropharyngolaryngeal motor symptoms, speech arrest, and salivation, suggesting the ictal involvement of the perisylvian network (PN) and particularly of the opercular-insular regions (Alving et al., 2017; Guerrini and Pellacani, 2012; Halász et al., 2019a). Functional imaging (Archer et al., 2003; Boor et al., 2007, 2003; Li et al., 2018; Xiao et al., 2016) and EEG/MEG (Alving et al., 2017) mapping studies provided evidence supporting this assumption.

Despite the good prognosis, with recovery usually occurring before age 15–16 year (Koutroumanidis et al., 2017; Panayiotopoulos et al., 2008), SeLECTS patients have been reported to present deficits in PN functions in elevated prevalence (Goldberg-Stern et al., 2010; Tovia et al., 2011; Verrotti et al., 2014; Wickens et al., 2017). Particularly, language disruption is the most prominent cognitive comorbidity (Besseling, Jansen, et al., 2013; Tovia et al., 2011; Ostrowski et al., 2023) and it may be present before seizure onset and persist after seizure remission (Deonna et al., 2000; Monjauze et al., 2011; Northcott et al., 2006). Cognitive abnormalities, including language dysfunction, have been associated with abundance (or frequency) of interictal epileptic discharges (mainly centrotemporal spikes (CTS)) both during wakefulness and sleep (Halász and Szűcs, 2023; Mirandola et al., 2013).

According to the AASM manual (Berry et al., 2013), sleep onset is defined by the first epoch scored as any stage other than stage wake (W) (generally corresponding to the first epoch of stage N1). This approach is helpful to characterize the macrostructure of 7–8 h of nocturnal EEG activity but appears unsatisfactory in revealing intrusions of sleep episodes into the wake state. Multispectral EEG indexes based on scalp EEG have been conceived to obtain a measurable quantification of drowsiness (Knaut et al., 2019; Olbrich et al., 2009). Drowsiness has been implicated in the modulation of CTS frequency, particularly during the first non-rapid eye movement (NREM) sleep cycle (Clemens and Majoros, 1987). Nevertheless, while the link between sleep and CTS occurrence have been widely investigated (Beelke et al., 2000; Nobili et al., 1999, 2001; Şanlıdağ et al., 2020), the relationship between drowsiness and increased spiking activity in SeLECTS has not been studied extensively. Whether fluctuations in wakefulness influence the cortico-subcortical networks involved in the CTS frequency generation remains unknown.

Functional MRI (fMRI), combined with careful characterisation of the level of vigilance based on concurrent EEG offers the possibility of exploring the relationship between CTS frequency and a multispectral EEG index of wakefulness by analysing both the EEG and fMRI data acquired simultaneously at rest. Herein, by means of an EEG-fMRI study we investigated the relationships between drowsiness and increased spiking activity in a homogenous population of SeLECTS patients. Specifically, we anticipate the involvement of brain regions either specifically linked to SeLECTS or to physiological sleep, or both, that act to facilitate the enhancement of CTS activity during drowsiness, with possible implications for other syndromes with similar epileptiform activity and onset in childhood (Specchio et al., 2022).

2. Methods

2.1. Study population

Twenty-five patients (20 males; mean age: 9.8 years; median age: 9 years (range: 6–17 years)) with SeLECTS were recruited; of those, 18 patients were included in a previously published article on the BOLD changes associated with interictal epileptiform discharges (Vaudano et al., 2019). The inclusion criteria for the present study were: (a) presence of CTS during the scan time (b) EEG recording during fMRI acquisition fulfilling the American Academy of Sleep Medicine (AASM) criteria for wakefulness, while exhibiting indications of drowsiness (at a time scale below 30 s): i.e., light sleep (N1) as defined by the AASM-based sleep classification; (c) good quality EEG and fMRI. For 9 patients out of the original population, we had access to the routine EEG acquired for clinical purposes outside the scanner (19 channels, Nihon Kohden Neurofax EEG-1200, Mod JE-120).

The following neuropsychological data were collected: general intelligence (IQ) consisting of verbal IQ (VIQ), performance IQ (PIQ), and full-scale total IQ (TIQ). All neuropsychological examinations were performed using the Italian version of the Wechsler Intelligence Scale for Children (WISCIII and WISCIV) and all scores were standardized for age and sex.

The human ethics committee of the University of Modena and Reggio Emilia approved this study (n. 80/10, Comitato Etico Area Vasta Emilia Nord), and written informed consent was obtained from parents and assent from patients.

2.2. EEG-fMRI protocol

The EEG-fMRI protocol is described extensively in Vaudano et al. (2019). Briefly, all recruited patients were scanned in the early afternoon, without sleep deprivation or sedation. Scalp EEG (1,024 Hz sampling rate, 10–20 electrode placement) was recorded by means of a 32-channel MRI-compatible system (22-bit digitization with a range of ±25.6 mV; Micromed, Mogliano Veneto, Italy). Foam pads were used to help secure the EEG leads, minimize motion, and improve patient comfort. The data were transmitted from the amplifier via an optic fibre cable to a computer located outside the scanner room.

Video of the subject's face was captured during the fMRI acquisition using a camcorder positioned on the head coil inside the scanner, resulting in a split-screen video-EEG recording (Ruggieri et al., 2015). The patients were asked to remain still during the scanning with eyes closed and remain awake. Functional MRI data were acquired using a 3 T Philips Intera System, consisting of gradient-echo-planar sequence from 30 axial contiguous slice (TR: 2 s or 3 s; in-plane matrix: 64 × 64; voxel size: 4 × 4 × 4 mm) over one session [total scan duration 8 min for TR = 2 s (240 volumes) and 10 min for TR = 3 s (200 volumes)] with continuous simultaneous EEG recording. A high-resolution T1-weighted anatomical image was acquired for anatomical visualization. The volume consisted of 170 sagittal slices (TR: 9.9 ms; TE: 4.6 ms; in-plane matrix: 256 × 256; voxel size: 1 × 1 × 1 mm).

2.2.1. EEG preprocessing and annotation

The BrainQuick System Plus software (Micromed) was used for offline correction of the MRI scanning gradient-switching artifacts and filtering of the EEG signal. In addition, the EEG data were exported in.edf format and reviewed and analysed by means of the BrainVision Analyzer 2.0 software (Brain Products GmbH,

Munich, Germany). Following the estimation and subtraction of the gradient-switching and heartbeat-related artifacts, an independent component analysis (ICA) was performed on EEG data to isolate CTS from physiological and artefactual activities (Avanzini et al., 2014; Vaudano et al., 2021). Two experienced electroencephalographers reviewed the preprocessed EEG recordings independently (AEV, SM) to identify interictal epileptiform abnormalities based on their spatial distribution and topography, resulting in CTS time markers.

Patients in which the recording showed only one CTS focus (without migration), intercital abnormalities were labelled as unilateral (right or left); otherwise, they were classified as bilateral. In this latter condition, left and right CTS were considered together in further analyses. In addition, the EEGs were reviewed (AEV) for the occurrence of sleep (Berry et al., 2013).

Before further EEG analysis (see below), ICA was applied to reject residual artifact- and CTS-laden components.

2.2.2. fMRI preprocessing and modeling

The Matlab (version 7.1) and SPM12 (Wellcome Centre for Human Neuroimaging, University College London, London, UK, https://www.fil.ion.ucl.ac.uk/spm/) software were used for fMRI data preprocessing and analysis. After discarding the first five scans (dummies), the fMRI volumes were slice timing-corrected and realigned to the first non-dummy volume. For the purpose of the group analysis, the thus-realigned fMRI data were spatially normalized to the standard EPI template. Finally, the normalized data were smoothed with an $8 \times 8 \times 8$ mm full width at half maximum Gaussian kernel. The six motion parameters derived from the fMRI preprocessing (translation and rotation in the X, Y, and Z direction, respectively) and a Volterra expansion of these (Friston et al., 1996) were used as covariates in the general linear model (GLM).

2.2.3. EEG analysis

2.2.3.1. EEG wakefulness index (EWI). We were interested in mapping the hemodynamic changes (modelled as blood oxygen level-dependent (BOLD) signal variations) in relation to fluctuations in the level of vigilance and CTS activity. To this end, we used the EEG Wakefulness Index (EWI) which was already applied in healthy subjects as a measure of vigilance fluctuations (Knaut et al., 2019). In essence, EWI is based on the power of EEG components with higher amplitude during wakefulness (wake > drowsiness) in relation to the power of EEG components with higher power during drowsiness in the denominator (drowsiness > wake) defined in terms of spectral and topographical instantaneous EEG information.

Specifically, EWI was calculated using the following equation:

$$r = \frac{p(\vartheta, F_{3,4}) + p(\alpha, O_{1,2}) + p(\sigma, O_{1,2}) + p(\beta, F_{3,4})}{p(\delta, F_{3,4}) + p(\vartheta, O_{1,2}) + p(\sigma, C_{3,4}) + p(\alpha, F_{3,4}) + p(\beta, F_{3,4})}$$

where p (ϑ, F3,4), for example, denotes the instantaneous power in the theta frequency band, averaged across the frontal EEG channels F3 and F4. The greater the EWI is, the higher the degree of wakefulness, and vice versa.

The EEG frequency bands were defined as follows:

- Delta (δ): 0.5/s–4/s.
- Theta (ϑ): 4/s–8/s.
- Alpha (α): 8/s–12/s.
- Sigma (σ): 12/s–15/s.
- Beta (β): 16/s–30/s.

At each time point, the power for each frequency band was computed using a zero-phase 6th order Butterworth band-pass filter and the amplitude of the filtered signal's Hilbert transform as implemented in the BrainVision Analyzer 2.0 software (Brain Products GmbH, Munich, Germany). EWI was downsampled to one value per TR, resulting in an EWI regressor for inclusion in the GLM analysis (see below).

2.2.3.2. CTS density regressor. The CTS marked on EEG were used to calculate a density vector as the number of CTS in each TR.

2.2.3.3. CTS-EWI relationship.

2.2.3.3.1. EEG inside the scanner. To explore the relationship between patient-specific spontaneous fluctuation in wakefulness (EWI) and the CTS frequency (number of CTS for TR), the following exploratory analyses were implemented in Python 3.9 and Matlab 2021b.

We calculated the Pearson correlation coefficient and the cross-correlation (Matlab *corrcoef* and *xcorr* functions) between each patient's EWI and CTS density time courses. To extract the long-term trend of the time series, otherwise hidden by noise, we performed a trend decomposition analysis of EWI and CTS density through the function "trenddecomp" in Matlab 2021b. In this work, the use of the word 'trend' specifically refers to the result of this analysis. In addition, we implemented a Granger Causality analysis between each patient's EWI and CTS density time courses.

In order to explore the correlation between EWI and CTS density at the group level, all the subject-specific EWI and CTS density time courses were normalized and concatenated and the Pearson correlation for the entire normalized dataset was calculated.

2.2.3.3.2. EEG outside the scanner. We repeated the CTS-EWI correlation analyses on EEG acquired outside the MRI scan as a standard clinical practice for diagnostic purpose. Clinical EEG data (available in 9 patients) were reviewed and analysed using BrainVision Analyzer 2.0 software (Brain Products, Munich, Germany). Interictal epileptiform abnormalities and sleep occurrence were identified and marked as previously described. Periods of proper sleep (N2-N3 NREM) were excluded from the analysis by limiting it to the period up to the last N1 epoch, before N2 appeared for the first time. Additionally, EEG sections with eyes open and major artefacts were excluded. The obtained segments were concatenated and the mean duration of the resulting datasets was on average 13.5 min (range 4–24). EWI and CTS density were extracted with the same procedure implemented for the EEG-fMRI data, the time bin was fixed equal to 2 s.

2.2.4. fMRI data modelling, event-related analysis (CTS density)

2.2.4.1. First-level analysis. We first mapped the BOLD changes related to spike density, taking into account putative EWI-related effects by building a GLM in which the CTS density and EWI vectors convolved with the standard canonical HRF constitute the effects of interest. The six scan realignment parameters and their Volterra expansion were included in the same GLM as regressors of no interest. The threshold for statistical significance of fMRI{T} maps was set at $p < 0.001$ (uncorrected) and cluster extent of 10 voxels or more.

2.2.4.2. Group-level analysis. Using the parameter estimates obtained by single-subject analyses, we performed a second-level (group) random-effect analyses for "CTS density" by means of a T test. The subjects' age, gender, age of epilepsy onset and epilepsy duration were included as covariates. The threshold of statistical significance was set at $p < 0{,}001$ (uncorrected) and cluster extent of 10 voxels or more. The resulted fMRI map was explored using a small volume correction (5 mm sphere) procedure and any BOLD activation/deactivation with a cluster-level threshold at $p < 0.05$, FWE corrected was considered, in line with previous studies (Coan et al., 2016; Poldrack, 2007; Sebastiano et al., 2020). The

MNI coordinates of the supra-threshold clusters were converted to Talairach space using the *mni2tal* Matlab routine.

2.2.5. Functional connectivity analysis using psychophysiological interaction

2.2.5.1. First-level analysis. We used a psychophysiological interaction [PPI; [(Friston et al., 1997; Kim and Horwitz, 2008; O'Reilly et al., 2012)] analysis to assess the EWI-dependent whole-brain functional connectivity of the CTS density-activated regions. To this end, from the CTS density-related group activation map, we chose a priori 6 seed locations: bilateral perisylvian structures (trasverse and superior temporal gyri), bilateral putamen, bilateral motor cortex, regions found to be key structures in the epileptogenic network of SeLECTS (Li et al., 2020; Vaudano et al., 2019; Xiao et al., 2016). The time series of a sphere of 8-mm radius around the group peak activity map (Table 2) was extracted for each seed from the normalized, smoothed echo planar imaging (EPI) images (Bonelli et al., 2012).

The single-subject PPI model included three regressors: (i) the time course of the seed region (as the physiological signal); (ii) the HRF convolved EWI regressor (as the psychological context) and (iii) the interaction between the two (representing an EWI-modulated change in functional connectivity, or PPI).

2.2.5.2. Group-level analysis. The contrast images obtained by each PPI analysis for each seed at single-subject level, were used to explore the group level connectivity with a one-sample *t*-test for each region-of-interest. The clinical variables epilepsy duration, age at onset, age, and sex were included as covariates. Each PPI seed region analysis can be considered to be an independent analysis, as we do not directly compare the PPI contrasts between seeds at the voxel or cluster level. The threshold of statistical significance was set at $p < 0{,}001$ (uncorrected) and cluster extent of 10 voxels or more. Similarly, to the CTS density second-level analysis, a small volume (5 mm sphere) and $p < 0.05$ cluster-level FWE correction was applied to the resulting fMRI map.

2.2.5.3. Correlation between PPI analysis and neuropsychological variables. We explored the relationships between the PPI findings and neuropsychological scores. A whole-brain correlation analysis was used to test for a linear relation between the connectivity findings with the neuropsychological scores: verbal IQ, performance IQ, and full-scale total IQ. For this latter correlation, we limited the analysis to the 18 SeLECTS cases with complete neuropsychological evaluation data. The statistical significance level was set at $p < 0.001$ (uncorrected), with a cluster extent of 10 voxels.

Fig. 1 summarizes graphically the methodological approach adopted for EEG and fMRI analysis.

3. Results

3.1. Behavioural and clinical data.

The clinical, EEG and neuropsychological data are summarized in Table 1. 23 patients were right-handed (Oldfield, 1971). Disease duration ranged between 0 and 64 months (mean: 24 months; median: 18 months). Structural MRI scan was reported negative for lesions in all patients recruited. History of ESES (Encephalopathy related to Status Epilepticus during slow Sleep) was reported in 1 patient (#23), according to the definition by Rubboli and colleagues (Rubboli et al., 2023). Total IQ was available in 24/25 patients, and VIQ and PIQ in 18/24 patients. The mean total IQ was equal to 95.8 (range: 66–124), mean VIQ = 97.4 (range: 66–124), and mean PIQ = 98.7 (range: 71–128). Head motion was below 3 mm of translation or 3° of rotation in all cases. Thirty fMRI runs were acquired with a TR = 3 s and 4 runs with TR = 2 s.

No spindles or K complexes were observed on the EEGs recorded during fMRI scanning.

No significant correlation was observed between the total IQ, VIQ and PIQ and the total number of CTS recorded during fMRI CTS density, duration of epilepsy and age at seizure onset.

3.2. CTS-EWI correlation

There was no correlation between CTS density and EWI over the entire time recording ($r = 0.03$, $p = 0.004$) or sliding windows, irrespective of their length. Directionality and causality were not significant. As far as the EEG data acquired outside the scanner for clinical purposes, in all the clinical EEG selected, signs of proper sleep were observed, reaching N2 NREM in 8 patients, N3 in the remaining subject. For 8/9 patients we observed a negative correlation between EWI and CTS density; A positive correlation was found for one patient (#8). See Supplementary Table 1 for a complete summary of the characteristics of routine EEG datasets and correlation. Fig. 2 illustrates a representative case.

3.3. Group analyses

3.3.1. BOLD signal changes related to CTS density

Significant CTS density-related BOLD changes were found in the following regions: Bilateral putamen, bilateral sensory-motor cortex (B4), left transverse temporal gyrus (BA42), right superior temporal gyrus (BA22), right insula (BA13), left supplementary motor area (BA6), right middle and inferior frontal gyrus (BA8 and BA47) and left cingulate gyrus (BA23) (Table 2 and Supplementary Fig. 2).

3.3.2. Functional connectivity analysis using PPI

Significant functional connectivity was observed between the left perisylvian and motor area seeds and left frontal operculum (Fig. 3; Table 3), particularly BA47 (Fig. 4). For the left motor area, we found EWI-modulated functional connectivity also with the temporal pole, lateralized to the left side (Fig. 3). We did not detect any significant whole-brain functional connectivity for the other seeds.

3.3.3. Correlation analyses

We did not find any significant correlation between the PPI results and the neuropsychological variables.

4. Discussion

The present report is, to our knowledge, the first study that explores the relationship between CTS generated networks and drowsiness in a well-characterized population of SeLECTS using concurrently recorded EEG and fMRI data. We parameterized the fluctuations of wakefulness by adopting a multispectral EEG index (i.e. EWI) already applied with similar purposes in healthy controls who exhibit signs of drowsiness (N1 NREM) but not deep sleep during EEG recordings (Knaut et al., 2019).

Our analyses provide two main results: (a) EWI fluctuations and CTS density appear to be independent from each other in awake or drowsy subjects. When considering periods of drowsiness preceding proper sleep (N2/N3 NREM) EWI fluctuations and CTS density exhibited an anti-correlated trend; (b) in contrast with the EEG analysis, fMRI connectivity approaches have shown that fluctuation of vigilance can affect the relationship between the regions directly involved in the epileptogenic network and the activity of the left frontal operculum, particularly the "pars orbitalis", a region

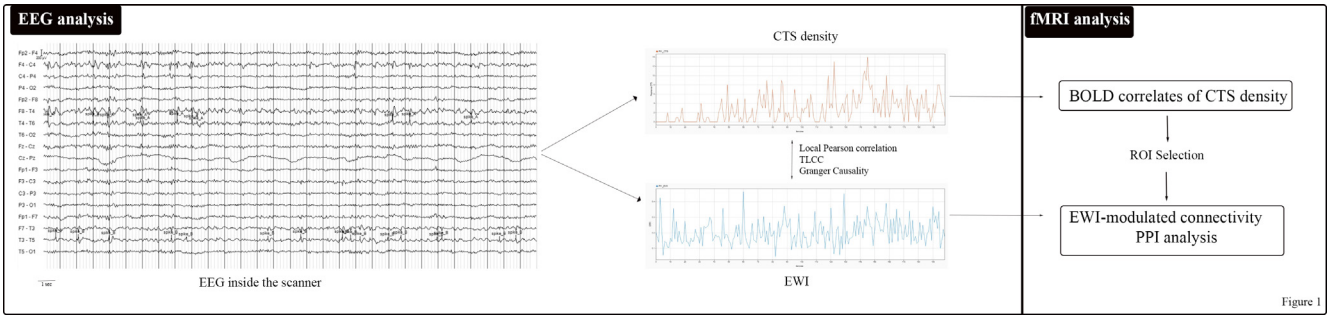

Fig. 1. Workflow of the methodological approach to explore the relationships between CTS density and EWI. Spike A: right spikes, Spike B: left spikes. TLCC: Time-Lagged Cross Correlation.

Table 1
Demographic and electroclinical data of SeLECTS.

ID/ Sex	Age at fMRI (yo)	Handedness*	Epilepsy Onset (yo)	Epilepsy duration (mo)	ESES Hystory	EEG Scoring	CTS during fMRI (n)	ASM	IQ	VIQ	PIQ
1/F	7	R	7	1	N	Wake	P4 (348)	Naive	120	124	110
2/M	6	R	4	32	N	Wake	T4 (562) C3 (785)	VPA	66	N/A	N/A
3/M	9	R	7	25.18	N	Wake/N1	T4 (307)	Naive	115	N/A	N/A
4/M	9	R	5	44.9	N	Wake	CP5 (131)	LEV + VPA	101	110	128
5/M	9	R	8	9	N	Wake	AF4 (77)	LEV + CLB	79	78	85
6/F	13	R	10	30.8	N	Wake	T4 (158)	Naive	106	103	107
7/M	8	R	8	24	N	Wake/N1	C4 (125)	Naive	100	102	104
8/M	11	R	11	3.9	N	Wake	C4 (51)	OXC	104	101	106
9/M	12	R	10	24.28	N	Wake	T4 (701) C3 (899)	Naive	93	N/A	N/A
10/M	11	L	11	2	N	Wake	F4 (295)	Naive	97	97	97
11/M	17	R	13	36	N	Wake	C3 (251)	VPA	73	69	85
12/M	15	R	8	77	N	Wake	F8 (810) C3 (406)	VPA	95	N/A	N/A
13/M	7	R	6	0.15	N	Wake	T4 (222) T3 (200)	Naive	81	89	77
14/M	7	R	5	19.3	N	Wake	Pz (497)	LEV	109	123	93
15/M	9	R	7	24	N	Wake/N1	C3 (530)	OXC	N/A	N/A	N/A
16/M	8	R	6	15.14	N	Wake	T4 (1633)	CBZ	89	75	106
17/M	10	R	7	27.22	N	Wake	CP5 (540)	LEV	110	91	109
18/F	8	R	7	12	N	Wake/N1	T3 (84)	Naive	95	N/A	N/A
19/M	6	R	6	0.16	N	Wake	T4 (641) F7 (525)	Naive	124	115	128
20/M	13	R	13	1	N	Wake	T3 (83)	OXC	95	95	91
21/F	10	R	10	1	N	Wake/N1	C3 (185)	Naive	106	N/A	N/A
22/M	13	L	13	1	N	Wake	C4 (47)	Naive	84	77	93
23/M	6	R	2	45.9	Y	Wake/N1	P4 (477)	Hydr + VPA + CBZ	84	102	71
24/M	10	R	8	9.22	N	Wake	C4 (83)	Naive	100	108	92
25/F	10	R	–	64	N	Wake	C3 (22)	VPA + LEV	75	66	95

R, right; L, left; M, male; F, female; yo, years; mo, months; ASM: antiseizure medications; VPA, valproic acid; LEV, levetiracetam; OXC, oxcarbazepine; ESM, ethosuximide; Hydr, hydrocortisone; CBZ, carbamazepine; CLB, Clobazam.
Spikes during fMRI sessions are described based on their topography and total number.
* Oldfield (1971). Spikes during fMRI sessions are described based on their topography and total number.

mainly associated with language-related functions, including semantic and phonological processing, grammatical processing, and selective attention to speech (Ardila et al., 2016; Unger et al., 2023).

4.1. EWI fluctuation and CTS density: Insight from the EEG analysis

The exploration of the relationship between EWI and CTS density over the intra-MRI recordings did not reveal any significant correlation, cross-correlation, or Granger causality. However, when the correlation analysis was performed over periods of drowsiness and N1 NREM sleep recorded during routinary clinical EEG recordings, EWI and CTS density were found to be anti-correlated. This may be explained by the fact that, in all the clinical EEG selected, patients reached deeper sleep stages (N2, N3) than in the MRI scanner, yielding a significant direct effect on CTS. Therefore, the covariation of EWI and CTS density seems to reflect a net effect of a gross state change (wakefulness versus sleep) while brief sleep intrusions into the wakefulness are not sufficient to detect this interaction with EEG analyses. This can be seen in analogy to the described tonic firing mode of thalamic neurons during wakefulness versus the more burst-like activity during deeper sleep (Weyand et al., 2001). Thalamic activity varies with early changes of wakefulness as a result of a net change in state of vigilance and not a continuous gradual shifting (Knaut et al., 2019). In SeLECTS, CTS are related to spindles rate, thereby supporting observations that spikes and spindles generation may involve the same thalamocortical circuitry (Kramer et al., 2021; Spencer et al., 2022) and indicating the thalamus and thalamo-cortical pathways as necessary facilitators of spikes during NREM sleep. At the cellular level,

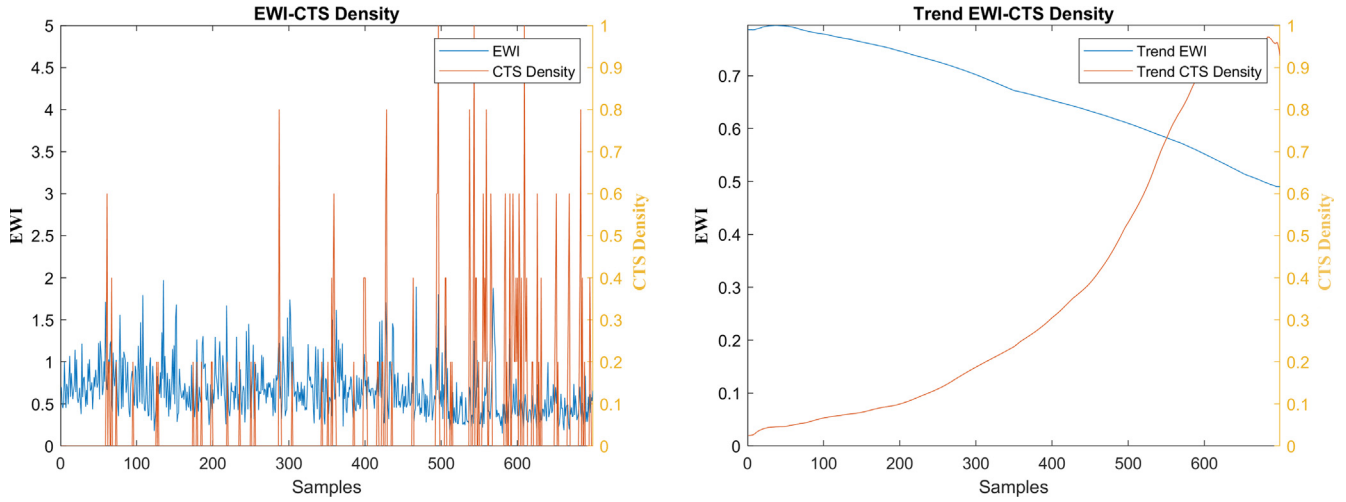

Fig. 2. Trend estimation of EWI and CTS density in one representative example. Clinical EEG of patient #1 showed an anti-correlated trend between CTS density and EWI (r = -0.9687; $p < 0.0000$). Ordinate = time (1 value every 2 s); Abscissa = EWI and CTS density values.

Table 2
Peak coordinates of CTS density group analysis ($p < 0.05$, small volume and family-wise error correction).

Cluster				Voxel level	MNI Coordinates		
K	Brain areas	R/L	BA	Z	x	y	z
420	Transverse Temporal Gyrus	L	42	4.72	−64	−14	14
	Frontal Lobe, Precentral Gyrus	L	6/4	3.69	−60	0	16
63	Superior Temporal Gyrus	R	22	3.79	62	4	−4
228	Middle Frontal Gyrus	R	8	3.67	56	10	40
	Precentral Gyrus	R	4	3.63	50	−4	42
155	Middle Temporal Gyrus	R	21	3.66	62	−48	−4
130	Putamen	R	–	3.56	26	−8	10
41	Superior Frontal Gyrus	L	6	3.53	−6	24	58
57	Insula	R	13	3.51	38	−18	6
51	Putamen	L	–	3.44	−30	−10	8
12	Middle Temporal Gyrus	L	20	3.41	−56	−38	−8
75	Cingulate Gyrus	L	23	3.38	0	−14	28
12	Inferior Frontal Gyrus	R	47	3.35	48	34	−6
61	Precentral Gyrus	L	4	3.33	−42	−2	56

BA, Brodmann area; L, left; R, right.

spindles result from phasic firing of thalamic reticular nucleus neurons and thalamo-cortical relay cells which generate the typical spindles activity (Bandarabadi et al., 2020). If a similar thalamic behaviour is needed to facilitate CTS occurrence, we might speculate that the analysis of the slight fluctuations between wakefulness and light sleep by means of EEG power bands in 10/8 min EEG dataset, may not be sensitive enough for the detection of thalamic mode switches (tonic versus phasic) as none of the patients reach deeper sleep stages (N2/N3). While further studies are warranted to validate this hypothesis, our data seems to support the need for the involvement of the thalamic mechanisms of synchronization in order to appreciate a measurable relationship between CTS density and EWI (Nobili et al., 1999, 2001).

4.2. EWI fluctuation and CTS density: Insight from the fMRI connectivity analysis

While the EEG analysis did not reveal any dependency or correlation between CTS density and EWI, group-level PPI suggest that CTS density generating networks, particularly perisylvian and motor seeds regions, are coupled with the left inferior frontal gyrus and this connectivity is modulated by wakefulness-dependent brain states. Two possible explanations for this result are: (a) the connectivity between the regions involved in the CTS generation and the left frontal operculum is influenced by wakefulness oscillations and (b) the neuronal engagement of the left inferior frontal gyrus by changes in the wakefulness state is modulated by the activity of the CTS generating circuitry. Either way, the activity of the left inferior frontal gyrus seems to be disrupted by the interaction of the CTS occurrence and the vigilance state. In SeLECTS, a number of studies investigated the global and local brain connectivity changes in wakefulness and sleep (Besseling et al., 2013; Goad et al., 2022; Zeng et al., 2015). The interest relies in the well-known relationship between SeLECTS features, such as spike occurrence and cognitive measures, and sleep macro and microstructural characteristics. While some of the results of those studies are ambiguous, all support a disrupted connectivity during sleep compared to wakefulness, extended beyond the epileptic rolandic cortices and influenced by CTS occurrence and timing of disease (Goad et al., 2022; Kramer et al., 2021). This evidence comes mainly from high-density EEG studies and focuses on proper sleep stages (N2/N3 NREM), while no previous data have been published focusing on brain connectivity during drowsiness states. Our findings might fill this gap and highlight the importance to extend EEG connectivity studies even at the first sleep stages and at the grey zone between wakefulness and sleep. The relationship between CTS network and inferior frontal gyrus is strongly supported by functional and structural neuroimaging studies

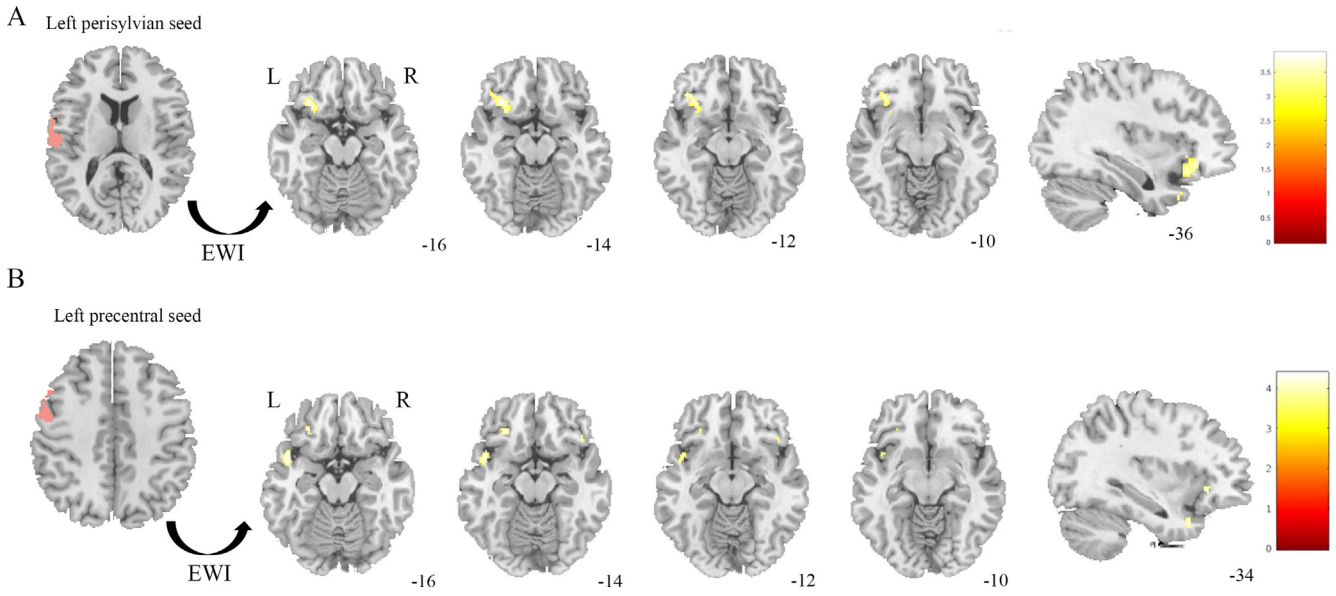

Fig. 3. PPI group analysis. EWI modulated changes in functional connectivity in SeLECTS seeding from (pink) the left perisylvian (transverse temporal gyrus, Panel A) and motor seed (Panel B). All images (axial and sagittal slices) represent T-value maps generated in Statistical Parametric Mapping that are overlaid onto a structural image (in Montreal Neurological Institute space) for visual localization purposes. Only significant psychophysiological interaction activations at the specified threshold are displayed. No deactivations were observed. All clusters survived a correction for multiple comparison [FWE] within a 5-mm sphere ($p < .05$). L, left; R, right. See text for details. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Peak coordinates of PPI group analysis ($p < 0.05$, small volume and family-wise error correction).

ROI	Cluster				Voxel level	MNI Coordinates		
	K	Brain areas	R/L	BA	Z	x	y	z
L Perisylvian	34	Inferior Frontal Lobe	L	47/11	3.39	−34	24	−14
L Precentral gyrus	56	Temporal Pole	L	38	3.36	−45	10	−16
	10	Inferior Frontal Lobe	L	47	3.45	−26	32	−14

BA, Brodmann area; L, left; R, right.

(Besseling et al., 2013, 2014; Li et al., 2018, 2020; Lillywhite et al., 2009; Overvliet et al., 2013; Smith et al., 2021; Zeng et al., 2015). Specifically, an altered functional connectivity between the sensorimotor network and the left inferior frontal gyrus in children with SeLECTS might link epileptiform activity to the identified neuropsychological profile of anterior language dysfunction in these patients (Halász et al., 2019b). However, this is the first time that such an association has been related to wakefulness-dependent brain states. Previous clinical studies shown that language performances significantly correlated with CTS frequency during drowsiness and early sleep, but not with CTS frequency in wakefulness (Kramer et al., 2021; Northcott et al., 2006). Intriguingly, in a recent study, spindles rate rather than CTS rate has been correlated with neuropsychological deficits in SeLECTS, thus supporting the key role of the sleep physiology and its disruption to determinate the cognitive profile of these patients (Kramer et al., 2021). By contrast, the same authors point out that language challenges appear to be independent on spindles rate arguing for different mechanisms behind these alterations. Based on our PPI findings, it can be hypothesized that fluctuations of wakefulness are implicated in the appearance of these disturbances by modulating the interference between the CTS occurrence and key nodes of language network activity. Of note, and apparently in contrast with this speculative conclusion, we did not observe any correlation between PPI and neuropsychological metrics in our data. Interestingly, the same finding was observed in previous EEG-fMRI studies in SeLECTS by our (Vaudano et al., 2019) and other groups (Li et al., 2018). It has been proposed that IQ may not be the most sensitive measure of cognition (Li et al., 2018) and multidimensional cognitive tests, individually tailored to specific deficits, are needed for appropriate neuropsychological evaluation (Filippini et al., 2016; Northcott et al., 2005). Notably, children with SeLECTS have been shown to have range of specific cognitive deficits, despite IQ within normal ranges (Northcott et al., 2005; Tristano et al., 2018).

4.3. Clinical implications

The possible impairment of cognitive abilities is an essential feature of the spectrum of Self-limited Focal Epilepsies of Childhood (SELFE) (Baggio et al., 2022) with localization in the PN, such as SeLECTS. It has been shown that the amount, localisation, and persistence of interictal epileptiform discharges, including CTS, over time, particularly during sleep, correlate with the degree of cognitive deficits, rather than frequent seizures (Miano and Datta, 2019). Furthermore, patients affected by SELFE are at risk of developing ESES, a condition that should be timely identified and treated to minimize cognitive and behavioural consequences (Rubboli et al., 2023). However, currently, there are no accepted EEG parameters that allow to foresee this complicated evolution (Cantalupo et al., 2019). In this context, our finding of a possible link between the fluctuation of wakefulness and the neuronal activity of the left frontal operculum, suggests that monitoring the CTS occurrence and frequency during drowsiness and first sleep stages might be included among parameters that will help

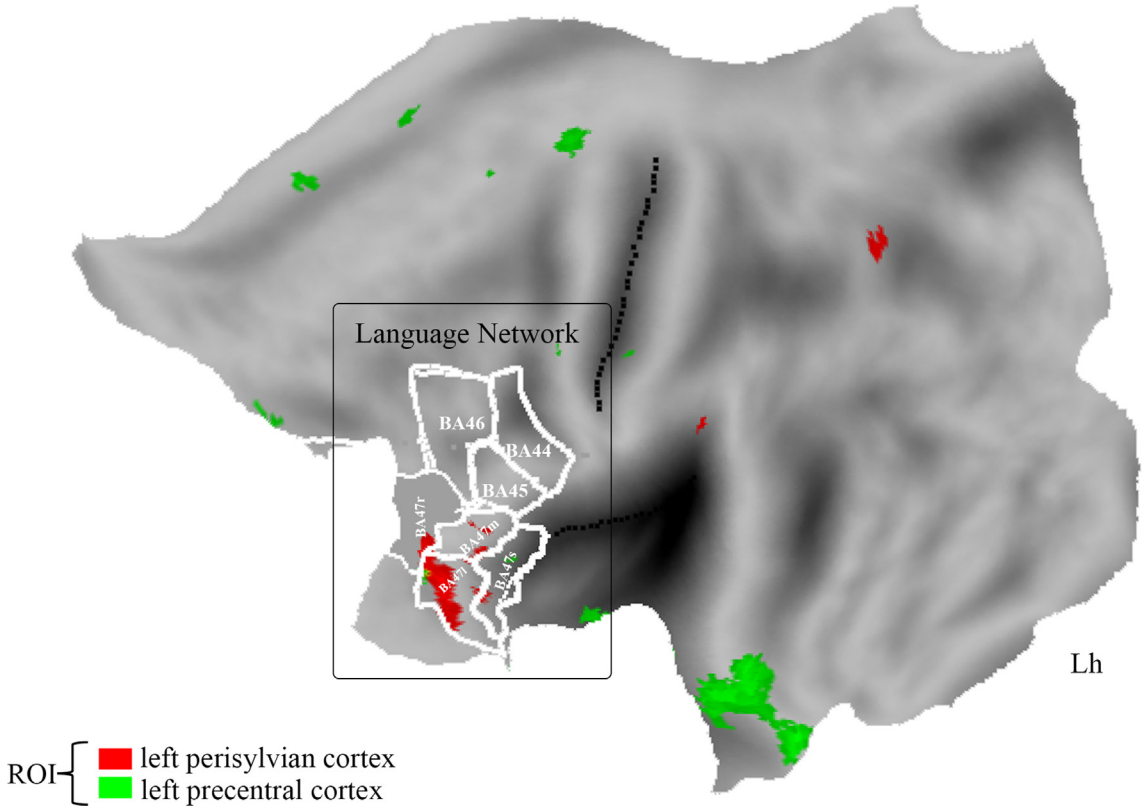

Fig. 4. PPI group analysis and language network. The PPI analysis results are overlaid onto flat left hemisphere (Lh) template as implemented in Caret [Caret, http://brainvis.wustl.edu/wiki/index.php/Caret:About (Van Essen, 2005) $p < 0.001$, 10 voxels extent]. EWI modulated functional connectivity from left perisylvian seed are displayed in red colour, from the left precentral ROI in green colour. For localization purposes, functional results were plotted and compared against Brodmann areas of anterior language areas (BA44, BA45, and BA47) indicated by the white numbers. The black lines on the flat template show the central and sylvian fissure surface landmarks as implemented in Caret. See text for details. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

clinicians to predict neurocognitive sequelae and to choose a treatment strategy.

4.4. Methodological considerations

The present results are a good example of how EEG-fMRI can theoretically enhance our understanding of brain function, as a new effect became detectable in the fMRI, even in the absence of correlation between the electrophysiological events of interest. We were nonetheless able to test whether the regression slope between the seeds in CTS density network and the rest of the brain was modulated by the strength of EWI oscillations. It goes without saying that this exploration was possible only by characterizing EEG events changes spatially using fMRI.

4.5. Limitations

A limitation of the present work is the lack of EEG-fMRI data in SeLECTS patients during sleep. Such data would allow to verify our hypothesis on the anticorrelated relationship between CTS density and EWI in those EEG where N1 NREM declines to proper sleep and on parallel to verify the PPI analysis findings in relation to deeper sleep stages. However, such data are quite difficult to obtain considering the ages of patients with SeLECTS and the setting of EEG-fMRI. Previous studies in children with EEG-fMRI while sleeping were performed under sedation (Siniatchkin et al., 2010) the effect of which on epileptic activity and related-hemodynamic changes remain poorly understood (Centeno et al., 2016). Furthermore, we studied our patients without applying any activation procedure (sleep deprivation) nor sedation. The relatively low number of SeLECTS investigated and the fact that patients were mostly at different stages of their disease in term of seizures frequency and neuropsychological measures at the moment of fMRI and on different medications are common limitations that apply to this work, with important implication for the sensitivity and specificity of our findings.

5. Conclusion

Our findings suggest that while CTS frequency *per se* seems unrelated to drowsiness unless proper sleep is reached, wakefulness level fluctuations modulate the connectivity between the brain networks hemodynamically engaged by the CTS occurrence and the left inferior frontal gyrus, a region associated with language, a cognitive function often impaired in SeLECTS patients. This observation supports and expands previous knowledge on the interactions between CTS, cognition and sleep and speculates on wakefulness fluctuations beyond proper sleep as modulator of the relationship between epileptiform discharges occurrence and activity of key regions of the language circuitry.

Conflict of interest statement

S. Meletti received research grant support from the Ministry of Health (MOH), the non-profit organization Foundation "Fondazione Cassa di Risparmio di Modena – FCRM"; he has received personal compensation as scientific advisory board member for UCB and EISAI. A.E. Vaudano received personal compensation as scientific advisory board member for Angelini Pharma. None of the authors has any conflict of interest to disclose.

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Appendix B. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.clinph.2024.05.005.

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