Neuronal networks in epileptic encephalopathies with CSWS

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Summary

Objective: The aim of our study was to investigate the neuronal networks underlying background oscillations of epileptic encephalopathy with continuous spikes and waves during slow sleep (CSWS).

Methods: Sleep electroencephalography (EEG) studies before and after the treatment were investigated in 15 patients with CSWS. To investigate functional and effective connectivity within the network generating the delta activity in the background sleep EEG, the methods of dynamic imaging of coherent sources (DICS) and renormalized partial directed coherence (RPDC) were applied.

Results: Independent of etiology and severity of epilepsy, background EEG pattern in patients with CSWS before treatment is associated with the complex network of coherent sources in medial prefrontal cortex, somatosensory association cortex/posterior cingulate cortex, medial prefrontal cortex, middle temporal gyrus/parahippocampal gyrus/insular cortex, thalamus, and cerebellum. The analysis of information flow within this network revealed that the medial parietal cortex, the precuneus, and the thalamus act as central hubs, driving the information flow to other areas, especially to the temporal and frontal cortex. The described CSWS-specific pattern was no longer observed in patients with normalized sleep EEG. In addition, frequency of spiking showed a strong linear correlations with absolute source power, source coherence strength, and source RPDC strength at both time points: (1) Spike and wave index (SWI) versus absolute source power at EEG1 ($r = 0.56$; $p = 0.008$) and at EEG2 ($r = 0.45$; $p = 0.009$); (2) SWI versus source coherence strength at EEG1 ($r = 0.71$; $p = 0.005$) and at EEG2 ($r = 0.52$; $p = 0.006$); and (3) SWI versus source RPDC strength at EEG1 ($r = 0.65$; $p = 0.003$) and at EEG2 ($r = 0.47$; $p = 0.009$).

Significance: The leading role of the precuneus and thalamus in the hierarchical organization of the network underlying the background EEG points toward the significance of fluctuations of vigilance in the generation of CSWS. This hierarchical network organization appears to be specific for CSWS as it is resolved after successful treatment.

KEY WORDS: Epileptic encephalopathy, CSWS, LKS, DICS, RDPC.

Key Points

- DICS and CSWS is a powerful tool for investigating dynamics in neuronal networks underlying epilepsy
- Delta frequency oscillation during CSWS was associated with sources in frontal, posteromedial, temporal cortex, as well as thalamus and cerebellum
- Thalamus, together with mesial temporal and parietal regions, constitute a central hub of the network underlying CSWS
- Posteromedial cortical region is precipitator, which acts on the thalamocortical network and facilitates the development of spike and wave discharges
- Coherence values between the described sources can be used as a marker of the severity of the CSWS pattern

Continuous spikes and waves during slow sleep (CSWS) is an epileptic encephalopathy with multiple clinical manifestations (various seizure types in association with cognitive, motor, and behavioral disturbances) related to a distinct electroencephalography (EEG) pattern characterized by a spike (sharp wave) and (slow) wave activity significantly activated during slow sleep.[1] This highly abnormal interictal epileptic EEG activity is considered to have a causal relation to the cognitive and motor impairments by interfering with sleep-related physiologic functions, and possibly neuroplasticity processes mediating higher cortical functions such as learning and memory consolidation.[1] CSWS is a typical EEG pattern characteristic of Landau-Kleffner syndrome (LKS) and atypical benign partial epilepsy of childhood (ABPE).[2]

Pathophysiologic mechanisms underlying CSWS are still not fully understood. Numerous studies have suggested that neurologic regression in children with CSWS could be attributed not only to neuronal impairment at the site of epileptic focus, but also to epilepsy-induced neurophysiologic changes in distant and connected brain areas, especially in areas of the default mode network.[3,4] These findings suggest a possible influence of epileptic activity on networks, which are involved in neuropsychological processes and consolidation of memory traces during sleep, and may explain neuropsychological deficits and developmental abnormalities in CSWS.

In summary, all previous functional neuroimaging studies investigating CSWS have identified complex networks, including brain areas with increased and decreased activity, as associated with CSWS. It is still unclear, however, how the networks underlying resting state activity during sleep of CSWS patients are hierarchically organized, which structures have a driving role, and how different components of the network interact. Highly frequent spike and wave discharges may disturb background EEG and hierarchical organization of underlying networks. Conversely, spontaneous fluctuations of background activity of the brain, for example, fluctuations of vigilance, may influence spike and wave activity. These questions—central questions of this study—are difficult to answer using traditional neuroimaging techniques such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) due to their poor temporal resolution. EEG, however, offers a better option for the analysis of functional and effective connectivity in networks because of its high temporal resolution.[4–7] In contrast, spatial resolution of EEG is poor due to the so-called inverse problem.[8] Nevertheless, modern advances in EEG inverse solutions have considerably enhanced the location power of EEG, which has allowed the use of EEG for studying activities even in deep structures in the brain.[9] Here we use a method of dynamic imaging of coherent sources (DICS), which operates in the frequency domain for EEG and magnetoencephalography (MEG) data and can characterize complex cortical and subcortical networks.[9–11] To analyze effective connectivity between sources, renormalized partial directed coherence (RPDC) can be used.[6]

Using these advanced analysis methods of functional and effective connectivity, we study networks underlying delta background EEG activity in children with CSWS and LKS.[12,13] In order to investigate specificity of hierarchical organization of networks associated with CSWS, in each patient EEG recordings obtained after a successful or poor treatment of CSWS were analyzed with the same methods as a control condition and compared with EEG recordings obtained before the treatment.

Subjects and Methods

Subjects

Fifteen patients (eight male/seven female) were recruited from the Northern German Epilepsy Center for children and adolescents in Raisdorf and the Neuropediatric Department, Christian-Albrechts University of Kiel, Germany. All of the patients had a CSWS pattern in EEG during non–rapid eye movement (NREM) sleep (Fig. 1). Diagnoses were made

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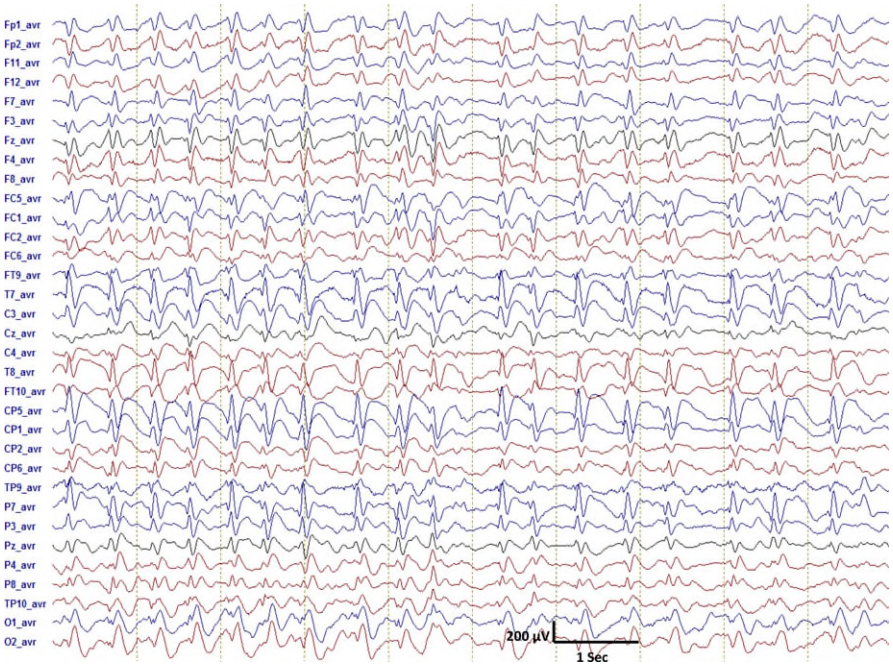

Figure 1.
CSWS EEG. Sleep EEG recording from a patient with CSWS showing continuous spike and wave activity significantly activated during slow sleep.

according to the International League Against Epilepsy (ILAE) 2001 classification scheme.[14] Patients who fulfilled the diagnostic criteria for ABPE (11 patients), LKS (3 patients), and CSWS (one patient) were included. Most of the patients exhibited various seizure types; only one patient with LKS did not present with epileptic seizures. Patients received 2–5 antiepileptic drugs (AEDs) during the time of observation. Ten patients received steroid therapy for the treatment of CSWS. All of the patients had developmental delay ranging from learning disabilities to global developmental delay. In addition, three patients with LKS syndrome had verbal auditory agnosia. Children with gross structural brain abnormalities or tetraparesis were excluded from the study. A thorough neurologic examination, neuropsychological testing, and structural MRI were performed in all cases. Routine sleep and wakefulness EEG studies (in accordance with the 10–20 system) were recorded in all cases at first admission to the epilepsy center and during routine follow-up investigations.

The study was conducted according to the Declaration of Helsinki (current version, 2013) on biomedical research involving human subjects (Tokyo amendment). Parents or legal guardians of participants gave their informed consent for using the data in an anonymous way for the research purposes.

EEG analysis

EEG recordings

Standard EEG recordings, according to the 10/20 system (EEG recording system: Neurofile; IT-med, Bad Homburg, Germany) taken during the routine admissions in the epilepsy center were used for the analyses. Sintered Ag/AgCl ring electrodes with built-in 5 kOhm resistors were attached using the "EasyCap" (Falk-Minow Services, Herrsching-Breitbrunn, Germany). Impedance was kept below 10 kΩ, sampling rate was 512 Hz. Reference was located between Fz and Cz. All assessed EEG studies were recorded during physiologic sleep for the period of the planned admission to the epilepsy center. Based on our previous studies we consider the number of electrodes to be sufficient for the correct detection of the sources.[14–17]

EEG recordings during physiologic sleep, at two different time points, were retrospectively taken for the DICS and RPDC analyses. EEG recordings from the time of the first admission to the epilepsy center and showing the maximum expression of the CSWS pattern (EEG1) were selected for the analyses. Further on, follow-up EEG studies (EEG2) recorded within the average of 3 years of follow-up period, showing the normalizations of the background activity or improvement of the CSWS pattern were taken for the follow-up analyses.

MRI recordings

Structural MRI recordings, including T1-weighted three-dimensional sequences, were done for each patient using a 3-Tesla Philips Achieva 3.0T TX MRI system (Philips, Best, The Netherlands).

Definition of CSWS pattern in EEG, assessment of paroxysms, and selection of EEG epochs

CSWS was defined according to the criteria proposed by previous authors: (1) activation or potentiation of epileptiform discharges in sleep[18]; (2) (near)-continuous, bilateral, or occasionally lateralized slow spikes and waves[18,19]; and

(3) occurrence "during a significant proportion" of the non-REM sleep with a threshold ranging from 25 to 85%.[18,20]

Two experienced neurophysiologists visually inspected the EEG segments independently. Spike and wave index (SWI) was calculated for each analyzed EEG. The SWI quantifies the frequency of spiking in the EEG tracing.[20] We defined the SWI as the percentage of 1-s bins with at least one spike and wave relative to the total 1-s bins in non-REM sleep[20] (Table 1). To achieve an acceptable signal-to-noise ratio for DICS analyses, EEG segments with adequate duration are required. Therefore, 3-min-long EEG segments were selected for the further DICS analyses.

Spectral analysis

For both EEG1 and EEG2, a multi-taper method was used to compute the power spectra for all recorded EEG channels.[21] The data epoch of 1-s length was tapered using a set of discrete prolate spheroidal sequences. The Fourier transformation was applied to the tapered data epochs, and auto-spectra were computed.[21] The dominant frequency band in the range 1–4 Hz was then defined accordingly for the subsequent individual source analysis. In a further analysis, all initial power estimates of the individual EEG electrodes were combined to get a pooled power estimate. This can be done by computing the individual second-order spectra using a weighting scheme and estimating the power to obtain the pooled estimate as described previously.[21]

Source analysis

DICS was used to identify sources in the brain responsible for the individual delta activity separately for EEG1 and EEG2.[22] In order to locate the origin of specific EEG activity observed on the scalp, forward, and inverse problems needed to be solved, the forward solution was estimated with specified models for the brain, and individual MRI studies were used to calculate individual lead-field matrixes[23]with specified models for the brain; a volume conduction model was calculated using a boundary-element method (BEM).[24] We have also used the individual EEG electrode locations for each patient separately while estimating the lead-field matrix. The DICS analysis was used to identify coherent brain regions underlying delta fluctuations in the EEG data.[22] For more detailed description of the DICS, see Data S1 and our previous publications.

Directionality analysis

To study the direction of informational flow between each of the sources described by DICS analyses the method of RPDC is applied.[6] RPDC is a causality analysis used to estimate the direction of information flow between two time series in the investigated frequency domain. The significant

Table 1. Demographic and clinical data

Patient no.	Gender/age at onset (y)	Diagnosis	Seizure type	1. SWI	2. SWI	Neuropsychology	AED during the observation period
1	M/5	ABPE	CPS	65%	46%	Global delay	ESM, VPA
2	M/9	ABPE	EM	65%	0	Learning disability	STM, VPA, LEV
3	M/7	ABPE	SGTC, GTCS, CPS, A	59%	5%	IQ 88	STM, CLB, PER, ESM, DXM
4	F/9	ABPE	AA, GTCS	86%	2%	Learning disability, IQ 60	ESM, DXM, CBZ
5	M/3	ABPE	AS	67%	0	Global developmental retardation	VPA, STM, LEV, DXM
6	F/7	ABPE	EM, CPS	89%	15%	Learning disability	ETX, LTG
7	F/6	CSWS	AA, SGTC	74%	37%	Learning disability	VPA, DXM, LTG, ESM
8	F/5	ABPE	A, AS, GTCS	68%	0	Learning disability	LTG, LEV
9	M/8	ABPE	PS, AA, TAS, GTCS	100%	0	Learning disability	DXM, ESM, STM, TPM, CLB
10	F/5	ABPE	CPS, SGTC, PSS, A	97%	15	Combined circumscribed developmental disorder	DXM, VPA, TPM, ESM
11	M/3	ABPE,	AA, AS, CPS, M	85%	99%	Severe delay	ESM, DXM, LEV
12	F/9	ABPE	GTCS, AS	53%	19%	Learning disability	VPA, ESM
13	F/5	LKS	AA, M, CPS, SGTC	96%	94%	Acute loss of expressive speech	ESM, STM, MET
14	M/6	LKS	No seizures	93%	0	Verbal auditory agnosia. behavioral disturbance, hyperactivity	LEV, DXM,
15	M/10	LKS	CPS, SGTC, AA, M	91%	51%	Auditory agnosia, hyperactivity, attention deficit	VPA, LTG, STM, MET

AED, antiepileptic drug; ABPE, atypical partial epilepsy; CBZ, carbamazepine; CSWS, continuous spike and wave during slow sleep; CLB, clobazam; DXM, dexamethasone; ESM, ethosuximide; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; PB, phenobarbital; PER, perampanel; STM, sulthiame; TPM, topiramate; VPA, valproate; MET, methylprednisolone; AA, atypical absence; A, absence; AS, atonic seizure; CPS, complex partial seizure; EM, eyelid myoclonus; M, myoclonia; GTCS, generalized tonic–clonic seizure; PS, partial seizure; PSS, perisylvian seizure; SGTC, secondary generalized tonic–clonic seizure; TAS, tonic–astatic seizure; LKS, Landau Kleffner syndrome.

RPDC values between each pair of brain regions in either direction are interpreted as one region transferring information to the other region. The RPDC is normalized over all existing connections in certain network connectivity between the described brain regions. For more detailed description of the method see Data S1.

Statistical analysis

The mean source absolute power, mean source coherence, and the mean RPDC values were tested with a Mann-Whitney test between the EEG1 and EEG2. The correlation between all the above-mentioned parameters with the spike and wave index was estimated separately for EEG1 and EEG2 using Spearman correlation test. In all the statistical analyses, the p-values for significance was set at 0.01.

Results

Spike and wave index

The range of spike and wave index at the first presentation (EEG1) varied between 53% and 100% (mean 79, 1%). At the follow-up investigation (EEG2), only one patient had worsened SWI (Pat N 11). Five patients had normalized sleep EEG2 recordings without any spike and wave activity, five patients had a substantially reduced SWI (<25%), whereas the remaining five patients had SWIs still ranging between 37% and 99%.

Selection of the frequency band for the analysis

The pooled power spectrum estimated from all the scalp channels showed that the dominant frequencies in all EEG recordings were in the delta range. The pooled power spectrum for each patient separately for the EEG1 and EEG2 is included as a Figure S3. Moreover, the delta activity was chosen because this frequency is presumably not involved in epileptic activity in CSWS (spikes are in alpha and beta frequency bands and slow waves more in theta frequency band) and thus most likely less distorted through spikes and waves. Further on, previous studies have shown that delta activity represents a basis of long range functional connectivity in brain networks.[12,13,25]

DICS

Results of EEG1 recording

The grand average of the sources described by DICS analysis is shown in Figure 2 (results of DICS analyses for individual patients are shown in Figure S1A–C). All identified sources were statistically significant ($p = 0.003$) according to Monte Carlo random permutation across all the subjects. The source of the strongest power in all 15 patients was located in the dorsolateral prefrontal cortex. Defining this strongest source as the reference, five further coherent sources with a coherence value between 0.04 and 0.38 were identified. The second source in 10 patients was found in somatosensory association cortex (BA 7), whereas the other five patients, including two patients with LKS, showed sources at the posterior cingulate cortex (BA31). The next source was identified in the orbitofrontal prefrontal cortex and coincided in all 15 patients. The exact location of the fourth source varied somewhat across the patients (Figure S1A–C). The fourth source in 10 cases (including 3 patients with LKS) was found in the middle temporal gyrus (BA 21), in 4 cases in the parahippocampal gyrus (BA 34), and in one patient in the insular cortex (BA16). The fifth source was located in the medial thalamus (BA 23) in all cases. The last source is located bilaterally in the cerebellum in all cases.

Results of EEG2 recording

All the identified sources were statistically significant ($p = 0.005$) according to Monte Carlo random permutation across all the subjects. In the group of patients with completely normalized sleep EEG recording (four patients with APBE and one patient with LKS) the source with the strongest power in the frequency band 1–4 Hz was detected bilaterally in the somatosensory association cortex/precuneus (Fig. 3). The strongest source was used further as the reference region for coherence analysis between brain areas. In contrast to the network seen during EEG1, there were only two sources coherent with the first source in all patients with normalized EEG studies. The second strongest source was found bilaterally in the medial prefrontal cortex in all four patients. The last coherence was detected bilaterally in the dorsolateral prefrontal cortex. No subcortical or temporal sources were observed in normalized recordings. There was a minimal difference across the patients with respect to the local coherence maxima of the sources (Fig. 3).

In the group of patients with persistent EEG abnormalities (including two patients with LKS) the identified sources in the dominant frequency band of 1–4 Hz were identical to the sources described for EEG1 (Fig. 4).

RPDC

Results of EEG1 recording

RPDC analyses of EEG1 pattern showed the strongest direction of information from source 2 (precuneus/somatosensory association cortex) toward source 4 (temporal region) in all patients including LKS patients (Fig. 2). The second strongest information flow was identified from source 5 (thalamus) toward source 2 (temporal region) in all patients. Further on, a strong information flow was observed from source 2 (precuneus/somatosensory association cortex) toward the anterior regions: source 1 and then to the source 3. A significantly high bidirectional information flow was noted between the thalamus and source 2

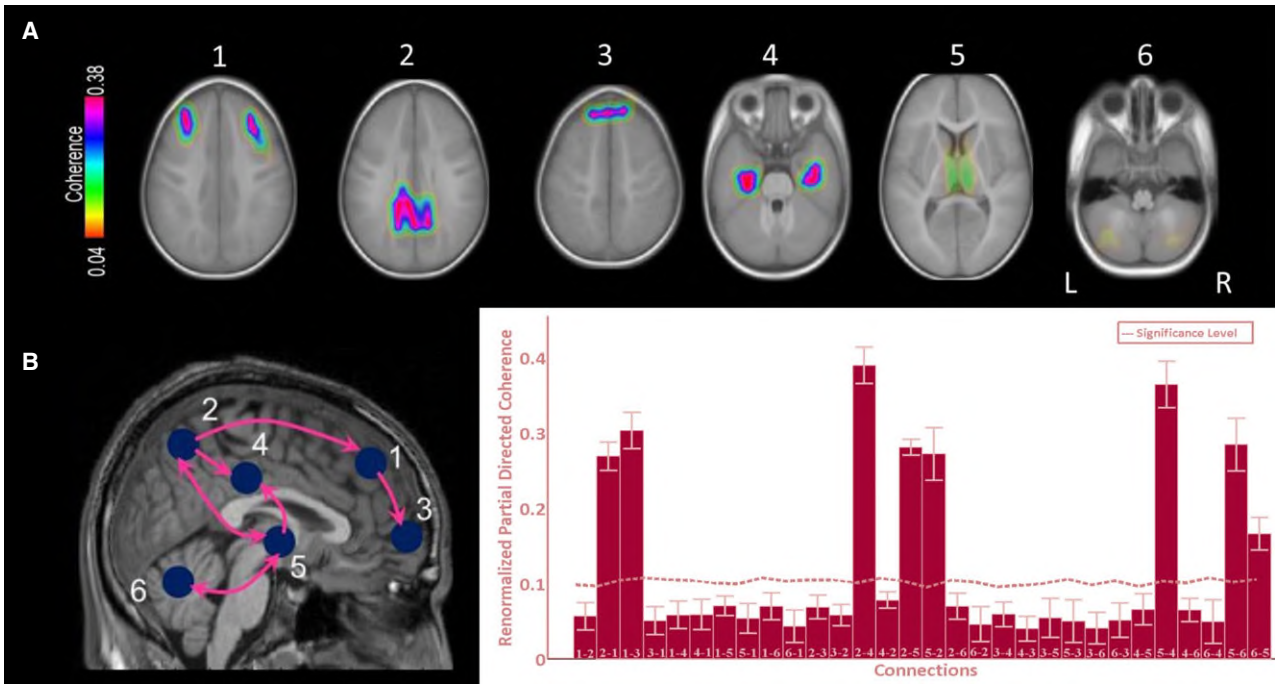

Figure 2.
Average of DICS and RPDC results of EEG1 recording. (**A**) The grand average of the strongest source (source 1) for all of the 15 patients was located in the dorsolateral prefrontal cortex. The second source (source 2) was found in posteromedial parietal cortex. The next source (source 3) was identified in the orbitofrontal prefrontal cortex. The fourth source was located the middle temporal gyrus. The grand average of the fifth source was found in the medial thalamus in all cases. The last source was identified in the cerebellum. (**B**) RPDC analyses of EEG1 pattern showed the strongest direction of information from the source 2 toward source 4 in all patients including LKS patients. The second strongest information flow was identified from the source 5 (thalamus) toward source 2 (temporal region) in all patients. Further on, a strong information flow was observed from the source 2 toward the anterior regions, source 1, and then to the source 3. A significantly high bidirectional information flow was noted between the thalamus and source 2 (temporal region) and the thalamus and cerebellum in all patients.

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RPDC results EEG2 recording

The group of patients with persistent spike and wave activity in EEG2, regardless of the severity of its expression, showed RPDC results identical to the results shown during the acute phase of the illness (see above), whereas patients with normalized EEG showed a clear trend of significant unidirectional information flow from posterior regions toward anterior regions predominantly (Fig. 3). The mean absolute source power, mean source coherence and the mean RPDC values showed significant differences ($p = 0.005$; $p = 0.008$; $p = 0.003$) between the first and follow-up EEG studies for all the patients.

Correlations

In addition, we have analyzed the correlations between spike and wave index and three different parameters: absolute source power, source coherence strength, and source RPDC strength. All three parameters showed a strong linear correlation with SWI at both time points: (1) SWI versus absolute source power at EEG1 ($r = 0.56$; $p = 0.008$) and at EEG2 ($r = 0.45$; $p = 0.009$); (2) SWI versus source coherence strength at EEG1 ($r = 0.71$; $p = 0.005$) and at EEG2 ($r = 0.52$; $p = 0.006$); and (3) SWI versus source RPDC strength at EEG1 ($r = 0.65$; $p = 0.003$) and at EEG2 ($r = 0.47$; $p = 0.009$; Fig. 5A–C).

Discussion

Neuronal networks during the acute phase of CSWS

Using EEG source analyses we describe the network and the hierarchy within the network underlying CSWS. Delta frequency oscillation during the acute phase of CSWS was associated with the coherent sources in dorsolateral prefrontal cortex, somatosensory association cortex/posterior cingulate cortex, medial prefrontal cortex, middle temporal gyrus/parahippocampal gyrus/insular cortex, thalamus, and cerebellum.

Our findings are in line with earlier functional brain imaging studies performed in children with CSWS showing

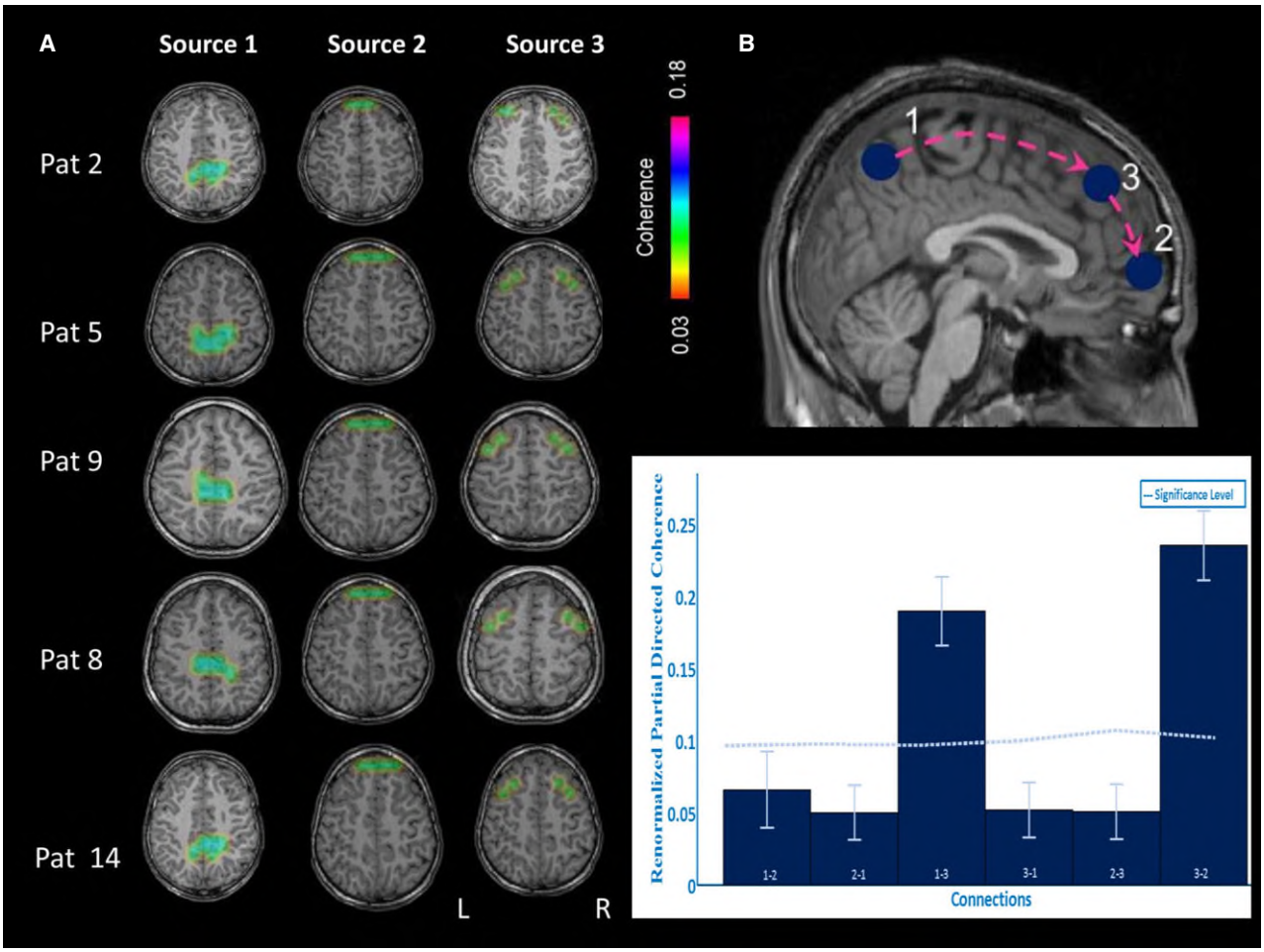

Figure 3.
DICS and RPDC results of EEG2 in patients with normalized EEGs. (**A**) Results of RPDC analyses in patients with normalized EEG showing the source with the strongest power bilaterally in the somatosensory association cortex/precuneus. The second strongest source was found bilaterally in the medial prefrontal in all four patients. The last coherence was detected bilaterally in the dorsolateral prefrontal cortex. (**B**) Results of RPDC analyses in patients with normalized EEG showing a clear trend of significant unidirectional information flow from posterior regions toward anterior regions predominantly.

disorders of metabolism and perfusion not only at the site of the epileptic focus, but also in distant and connected brain areas.[3] In our previous EEG-fMRI study on patients with CSWS, we found activations bilaterally in the perisylvian region and involvement of the motor/premotor cortex, cingulate gyrus, and thalamus.[4] Consistent with our findings, various noteworthy functional neuroimaging studies have demonstrated changes in the key nodes of default mode network (DMN) areas associated with CSWS.[3,4] These findings suggest that spikes during CSWS have the potential to interfere with the activity in the DMN, and cause a disruption to neuropsychological processes during sleep.

The complex network seen during CSWS may explain the diversity of neuropsychological deficits characteristic for this condition.[26] The insular cortex and cingulate gyrus are important parts of neuronal networks for working memory, self-control, emotional processing, and social cognition.[4,27] Temporal regions, including the perisylvian region, are involved in acoustic perception and language development.[4,28] Functional abnormalities in these regions may explain the frequent association of CSWS with auditory agnosia, acquired aphasia, aggressiveness, attention-deficit/hyperactivity disorder, and autistic features.[29,30] Consolidation of memory traces during sleep involves similar cortical structures.[31] Urbain and colleagues found decreased memory retention after a night of sleep in children with idiopathic focal epilepsies, suggesting disruption of cognitive networks in the sensitive phase of development possibly related to the occurrence of interictal epileptiform discharges during slow-wave sleep.[32]

To date, the structure and hierarchy of this network has not been investigated. Using RPDC analyses we were able to describe an effective connectivity within the network. We found that the strongest information flow in all patients

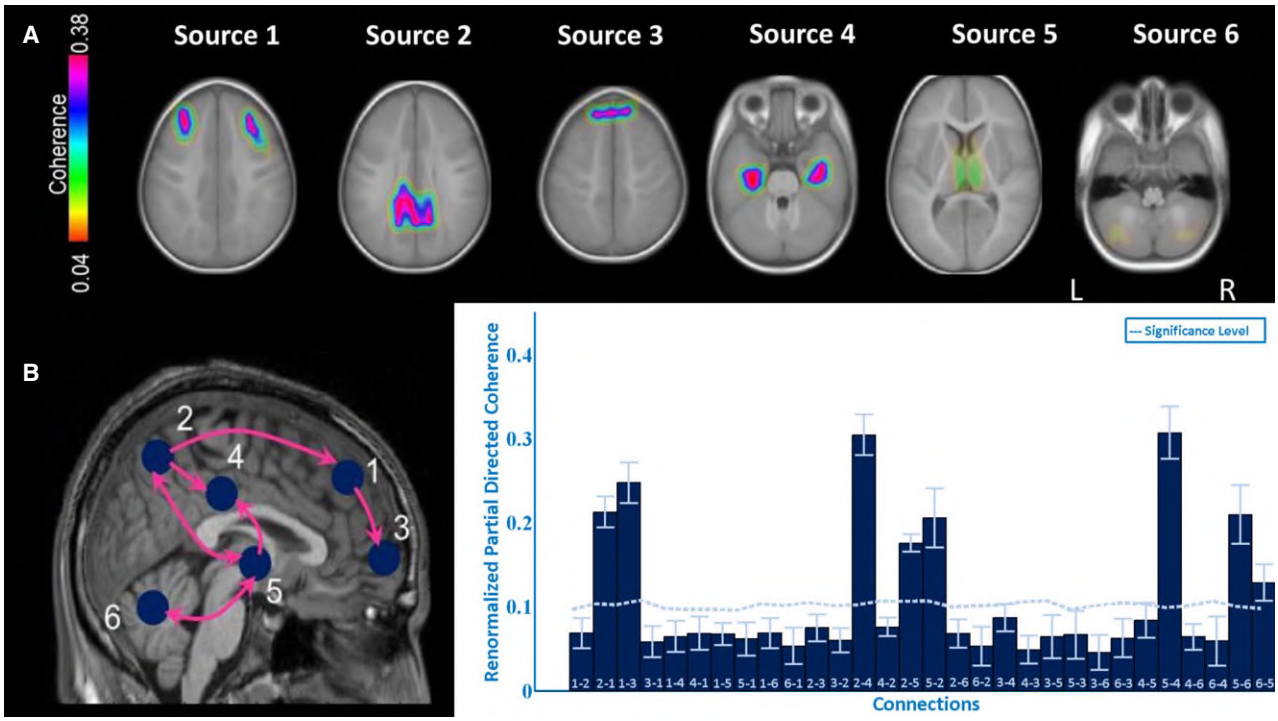

Figure 4.

Grand average of DICS and RPDC results of EEG2 in patients with persistent CSWS. (**A**) The grand average of sources of the strongest power in patients with persistent CSWS was located in the dorsolateral prefrontal cortex. The second source was found in posteromedial parietal cortical region. The next source was identified in the orbitofrontal prefrontal cortex and coincided in all patients. The fourth source was found the middle temporal gyrus and parahippocampal gyrus. The fifth source was located in the medial thalamus in all cases. The last source is located bilaterally in the cerebellum in all cases. (**B**) RPDC analyses of EEGs in patients with persistent CSWS showed the strongest direction of information from the source 2 toward the source 4. The second strongest information flow was identified from the source 5 toward source 2. Further on, a strong information flow was observed from the source 2 toward the anterior regions, source 1, and then to the source 3. A significantly high bidirectional information flow was noted between the thalamus and source 2 (temporal region) and the thalamus and cerebellum in all patients.

was directed toward temporal regions (including insula, parahippocampal gyrus, and middle temporal gyrus) from the posteromedial cortical region (precuneus/posterior cingulate) and the thalamus. A significantly high, bidirectional projection was found between the thalamus and the posteromedial cortical region. Previous studies have demonstrated that the precuneus/posterior cingulate has the most active interactions with the rest of the DMN areas,[33] and shows the highest metabolic rate, consuming more glucose than any other area of the brain.[34] These findings suggest that the precuneus/posterior cingulate might play a key role within the DMN and hence in the level of awareness and vigilance.[35] We have found that the posteromedial parietal cortical region is an important part of the network underlying CSWS, with a strong casual relation with the thalamus and temporal regions, which is considered as a generator of the bilateral spike and wave activity during CSWS and LKS.[4,36,37] We presume, however, that the posteromedial cortical region is not part of the ictal process itself, but rather a precipitator, which allows susceptible regions to generate epileptic discharge. Speculations regarding the role of posteromedial cortex as a precipitator of the network are based on numerous findings. Previous authors discussed links between the physiologic processes, such as fluctuations of vigilance and epilepsy.[35] Our findings are in line with those of the previous EEG-fMRI study, suggesting that during reduced level of vigilance, decreased activity in the precuneus may increase the likelihood of an epileptogenic cortical state to arise and generalized spike-wave to be generated within the thalamocortical network.[35] We have found that the posteromedial parietal cortical region is an important part of the network underlying CSWS, with the strongest casual relation with the thalamus and temporal regions, which is considered as a generator of the bilateral spike and wave activity during CSWS and LKS.[4,36,37] These connections were no longer found on the normalized EEG studies. Based on the findings of previous authors[26,33,35] and our results, we can speculate regarding the associations between sleep and CSWS pattern. In addition, our findings are in line with those of previous studies, suggesting that the thalamus together with the temporal and posteromedial cortical region may be seen as a central hub of the underlying

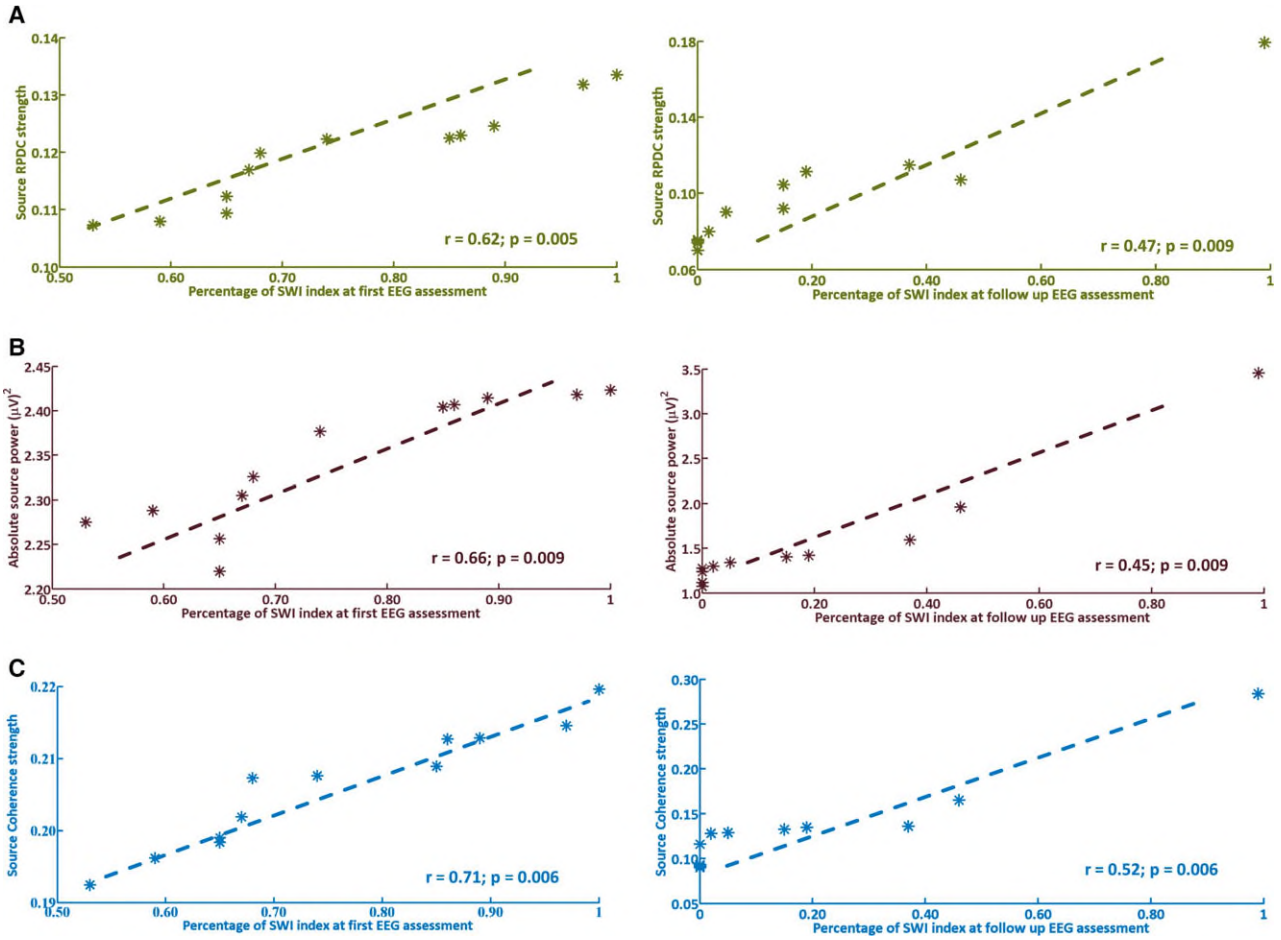

Figure 5.

(**A**–**C**) Correlations. Figure shows correlations between spike and wave indexes and three different parameters: (**A**) SWI versus absolute source power; (**B**) SWI versus source coherence strength; and (**C**) SWI versus source RPDC strength. All three parameters showed a strong linear correlation with the SWI at both time points EEG1 and EEG2.

network.[38] An activation of spike and wave activity during slow sleep provides a clear argument for involvement of the thalamocortical network.[26] Synchronization of epileptiform spikes and slow oscillation during slow sleep may involve mechanism similar to one described by Steriade and colleagues.[38] Their theory suggests the existence of a synchronous bursting mode of the thalamocortical system, proposing that during slow sleep, the cortex is more prone to abnormal synchronizing processes.[38]

Furthermore, on RPDC was able to identify a significant informational flow from parietal regions (source two) toward frontal regions (source one and three). This complex pattern of propagation may disrupt the maturation of the complex sensory and cognitive networks in the perisylvian, prefrontal, and cingulate cortices and cause neuropsychological deficits.[4,26]

We identified the cerebellum as involved in the network underlying the CSWS EEG pattern, and found it to have a significantly high bidirectional exchange of information with the thalamus. Our findings are aligned with the hypothesis that cerebellar neurons can control the balance of excitation and inhibition in the thalamus, thereby exhibiting a modulatory effect on occurrence of generalized spike-wave discharges (GSWDs).[39] The role of cerebellum within the epileptic networks has been extensively studied.[39] In the previous EEG-fMRI study of patients with CSWS we found a deactivation in the cerebellum.[4] Recent studies have shown that direct stimulation of the cerebral cortex can be effective in disrupting thalamocortical oscillations and thereby stopping generalized oscillations in thalamocortical networks, such as GSWDs.[39]

Neuronal networks after the cessations of CSWS

The above described CSWS-related network was no longer observed in follow-up EEG studies of patients with normalized sleep EEG recordings, suggesting that the described network can be seen as a specific network for the CSWS pattern. We found that delta activity in children with

normalized background EEG activity after the treatment was associated with the sources in posteromedial parietal regions, medial prefrontal, and the dorsolateral prefrontal cortex. Results of the network analyses of patients with normalized EEG were in line with the previous results with the resting state DICS analyses of healthy children.[40] Michels and colleagues found that delta activity was associated with sources in the posterior cingulate cortex and frontal regions showing an age-specific pattern of the source coherence during the resting state. We did not observe subcortical or temporal sources in normalized EEG, whereas children with the persistent CSWS EEG pattern still exhibited the network seen during the acute phase of CSWS. We found that, in children with reduced, but persistent, spiking, source power and strength of coherence between the described sources was directly proportional to the SWI, suggesting that the coherence values can be used as a marker of the severity of the CSWS pattern. Furthermore, analyses of delta waves in follow-up EEGs of patients with relatively rare spiking (Table 1) showed the same network as seen during the acute phase, but with reduced coherence values (Figure S2). In these patients, >85% of background activity was free of spikes; thus analyzed frequency was mostly part of the normal background activity and not only of spike and wave discharges. This leads us to the conclusion that the described network can be attributed not only to the spike and wave discharges per se but rather to general background oscillations in the EEG of patients.

Conclusion

Using EEG recordings we were able to describe the neuronal networks underlying CSWS that have been described previously only via functional neuroimaging techniques. The high temporal resolution of EEG has enabled us to investigate the hierarchy within the described network using RPDC analyses. This showed that the thalamus, together with mesial temporal and parietal regions, constitutes a central hub of the underlying network. We presume that the posteromedial cortical region is not part of the ictal process itself but rather a precipitator, which acts on the thalamocortical network and facilitates the development of spike and wave discharges. The involvement of this thalamocortical network and a further propagation toward the frontal region may interfere with restructuring of cognitive networks in a sensitive phase of cognitive development.

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Disclosure

None of the authors have 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.

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Supporting Information

Figure S1. (**A, B**) DICS and RPDC results for EEG1 recording.

Figure S2. (**A, B**) DICS and RPDC results for EEG2 recording in patients with persistent CSWS.

Figure S3. Pooled power spectra of all patients for EEG1 and EEG2.

Figure S4. Results of the source analyses of the spikes using the Linearly Constrained Minimum Variance method.

Data S1. Methods.