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Differentiating ictal/subclinical spikes and waves in childhood absence epilepsy by spectral and network analyses: A pilot study

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HIGHLIGHTS

- Spectral and network analyses can be used to differentiate ictal and subclinical EEG discharges in childhood absence epilepsy, in a routine setting.
- Ictal transition periods (pre-during-post) have significantly higher spectral power compared to subclinical discharges.
- Ictal transition periods show significantly weaker connectivity between EEG channels as compared to subclinical discharges.

ABSTRACT

Objective: Childhood absence epilepsy (CAE) is a disease with distinct seizure semiology and electroencephalographic (EEG) features. Differentiating ictal and subclinical generalized spikes and waves discharges (GSWDs) in the EEG is challenging, since they appear to be identical upon visual inspection. Here, spectral and functional connectivity (FC) analyses were applied to routine EEG data of CAE patients, to differentiate ictal and subclinical GSWDs.
Methods: Twelve CAE patients with both ictal and subclinical GSWDs were retrospectively selected for this study. The selected EEG epochs were subjected to frequency analysis in the range of 1–30 Hz. Further, FC analysis based on the imaginary part of coherency was used to determine sensor level networks.
Results: Delta, alpha and beta band frequencies during ictal GSWDs showed significantly higher power compared to subclinical GSWDs. FC showed significant network differences for all frequency bands, demonstrating weaker connectivity between channels during ictal GSWDs.
Conclusion: Using spectral and FC analyses significant differences between ictal and subclinical GSWDs in CAE patients were detected, suggesting that these features could be used for machine learning classification purposes to improve EEG monitoring.
Significance: Identifying differences between ictal and subclinical GSWDs using routine EEG, may improve understanding of this syndrome and the management of patients with CAE.

1. Introduction

Childhood absence epilepsy (CAE) is one of the most common forms of idiopathic (genetic) generalized epilepsies in childhood (Engel Jr., 2001). Seizures in CAE are characterized by daily, multiple typical absences, i.e. short, abruptly starting and ending impairments of consciousness accompanied by electroencephalographic (EEG) 3 Hz generalized spikes and waves discharges (GSWDs). Their duration varies from 4–20s, most last around 10

Abbreviations: CAE, Childhood absence epilepsy; GSWDs, generalized spikes and waves discharges; EEG, electroencephalography; FC, functional connectivity; MEG, magnetoencephalography; EEG-fMRI, EEG combined with functional magnetic resonance imaging; DMN, default mode network; FFT, Fast Fourier Transform; ANOVA, analysis of variance.

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seconds (Panayiotopoulos CP. 2005). These discharges are bilateral, synchronous and symmetrical. Motor symptoms are not prominent in CAE. CAE accounts for 2–10% of all childhood epilepsies with an age of onset between 4–10 years with a peak at 5–7 years (Crunelli and Leresche, 2002; Matricardi et al., 2014).

Interictal EEGs of these patients often also show GSWDs without impairments of consciousness, behavioural alteration, or any objective symptoms. These GSWDs look identical to ictal EEG patterns seen during the absence seizures. Currently there are no objective tools to differentiate these two events based on EEG only. Only a thorough direct response testing of the patient during the occurrence of discharges can distinguish ictal vs. subclinical events. Direct testing, however, is challenging, since these discharges and/or absences are abrupt and can be short. Additional challenges may be posed by compliance problems of young children as it requires their active participation. A careful differentiation of these two events is however important in the clinical setting as it influences the management strategies.

We presume that investigating networks at sensor level can lead to the better understanding and differentiation of these GSWDs.

In previous studies, magnetoencephalography (MEG) and EEG combined with functional magnetic resonance imaging (EEG-fMRI) have been used to understand brain connectivity during absences (Moeller et al., 2008; Wu et al., 2017). The involvement of the thalamo-cortical network and the default mode network (DMN) is known to play an important role in the generation and propagation of absence seizures (Bai et al., 2010; Crunelli and Leresche, 2002; Danielson et al., 2011; Gotman et al., 2005; Miao et al., 2019). However, due to the low temporal resolution of fMRI it is difficult to investigate intricate temporal dynamics of neuronal networks during underlying absences. Further on, EEG-fMRI is an expensive and laborious tool, and is not easily available in many centres. Alternatively, network analyses techniques involving functional connectivity (FC) as well as spectral power analysis using specific frequency-based techniques such as wavelet and Fourier transforms on EEG data, have proven to give valuable information on the dynamics of a seizure (Kim et al., 2011; Sanchez Bornot et al., 2018). EEG has excellent temporal resolution; therefore, we have focused solely on EEG data for network analysis in this study.

FC is a measure to compute neuronal networks. It identifies brain regions that have synchronous activity in terms of similar frequency, phase or amplitude. The FC can be computed using coherence and phase synchrony methods in the frequency domain. Focusing on coherence analysis, this technique quantifies the frequency and amplitude dependent correlations of brain oscillations measured between sensors. This method has been widely used in various cognitive and clinical neurological studies in sensor space using EEG (Özerdem et al., 2011; Uhlhaas et al., 2010; Yeragani et al., 2006). It has also been used in the field of epileptology to study seizure onset zones (Brazier, 1972; Gotman, 1981; Song et al., 2013).

EEG is a non-invasive technique and poses a volume conduction problem, which can be described as a spatial spread of the electromagnetic fields, leading to the activity of a single brain source being observed by multiple sensors. This causes false connectivity to occur, leading to misinterpretations of interactions in the brain. A robust approach to sensor-level connectivity estimation is achieved by using the imaginary part of coherency, which is a technique that overcomes volume conduction effects of FC (Nolte et al., 2004). Therefore this technique was selected for FC analysis.

In this study we have focused on exploring differences on the sensor level between ictal and subclinical GSWDs in CAE patients using routine EEG. Identification of relevant features would facilitate the diagnostic workout and improve the therapeutic management of these patients, since the clinical meaning of GSWDs is important for the clinical evaluation of CAE concerning planning of control examinations, treatment intensity and duration. Further it would help us characterize brain areas relevant for consciousness and could lead to the development of automatic or semi-automatic machine learning algorithms/classifiers to aid in epilepsy monitoring and diagnostics in the future.

2. Materials and methods

2.1. Subjects

All patients for this study were recruited from the North German Epilepsy Centre for Children and Adolescents, Schwentinental-Raisdorf, Germany. The patient data were retrospectively collected from a time frame of 2008–2018 and analyzed. The data was fully anonymized for this study. The study was approved (No. D 456/19) by the Ethics Committee of the Faculty of Medicine, University of Kiel, Germany.

EEG recordings from 26 CAE patients were analyzed. CAE diagnosis was made according to the clinical and electrographic criteria proposed by Panayiotopoulos CP., (2005). The inclusion criteria have been described in Fig. 1. Additional inclusion criteria for this study consisted of the following; 1) patients were tested during the GSWDs reliably and continuously for impairment of consciousness, 2) presence of both absence seizures and subclinical GSWDs in EEG (Fig. 1). We reviewed 205 EEG recordings. 12 patients, who met all the inclusion criteria for the study, were eventually selected for further analyses.

Discharges were classified as ictal (i.e. absences) or subclinical, based on direct questioning and testing of the level of consciousness during GSWDs. In order to check the level of consciousness short questions (e.g. what is your name? where are you? etc.) were asked during the first one to two seconds of GSWDs by qualified EEG technicians. The sudden and obvious discontinuation of commonly performed activities (i.e., speaking and moving), during GSWDs was used as an additional factor for the classification of EEG segments. The video EEG recordings were subsequently evaluated and categorized by experienced epileptologists. Only those segments were selected in which the level of consciousness was successfully and reliably evaluated.

In the cohort of 12 patients, there were 7 males and 5 females with a mean age of 7.3 ± 1.5 years. All patients had normal cognitive development, with the exception of patient P11, who had mild learning difficulties. P1 was the only patient with a family history of seizures. All patients were on medication at the time of EEG recordings with standard medications like ethosuximide, lamotrigine and valproic acid. The demographic data for all selected patients is given in Table 1.

2.2. EEG acquisition

Wakeful state EEGs were recorded in a clinical setting as part of routine examination of the subjects. The recordings were performed using the 10–20 international standard system for the positioning of 31 scalp electrodes (EEG recording system: Neurofile; IT-med, Bad Homburg, Germany). The standard electrodes: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2, plus additional electrodes: FT9, FC5, FC1, FC2, FC6, FT10, TP9, CP5, CP1, CP2, CP6, TP10 were used. The reference electrode was located between Fz and Cz. The sampling rate was 512 Hz and the impedance was kept below 10 kOhms. 111 EEG recordings from 12 patients were visually inspected and 33 EEG recordings were subsequently included for further analysis.

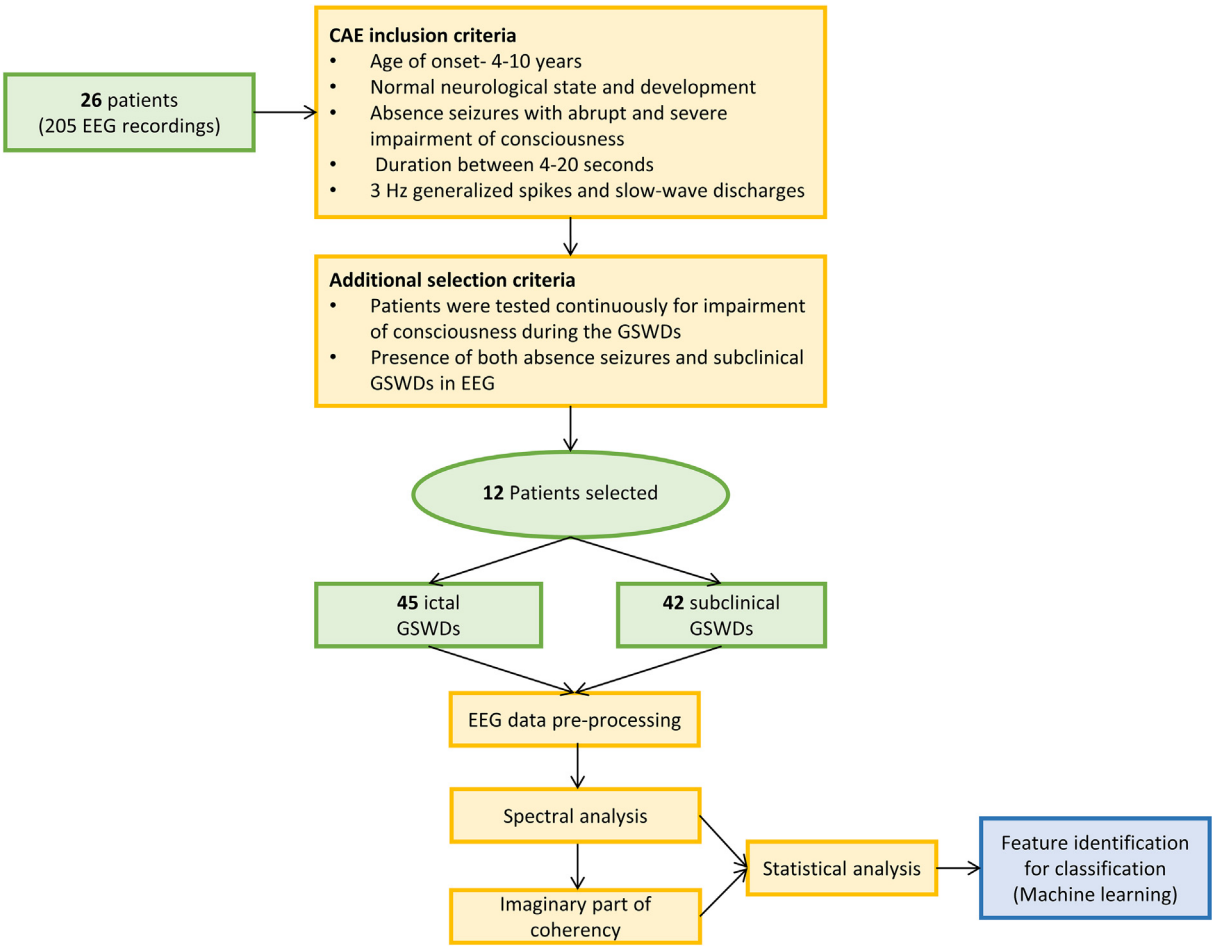

Fig. 1. Pipeline of the analysis procedure. Inclusion criteria and methodological procedure implemented in this study. CAE childhood absence epilepsy, GSWDs generalized spikes and waves discharges, EEG electroencephalography.

Table 1
Demographic data of patients.

Patients	Gender	Age at onset of epilepsy (years)	Age at EEG recordings (years)	Number of ictal GSWDs	Duration of ictal GSWDs (seconds)	Number of subclinical GSWDs	Duration of subclinical GSWDs (seconds)	Medication at the time of EEG recordings
P1	M	6	6	2	9–11.7	2	1–1.3	ESM
P2	M	9	9	2	12–13.8	6	1.2–3.3	LTG
P3	M	5	5	1	8.9	2	1.2–3.4	LTG
P4	M	7	12	2	9–12.8	1	1.3	LTG
P5	M	6	6	3	12–18.8	1	5	LTG, ESM, VPA
P6	F	4	6	1	3.5	4	2.2–8.8	LTG, ESM
P7	M	4	8	1	5.1	3	3.5–8.3	ESM, VPA
P8	F	6	7	6	5–15.7	1	1.2	ESM
P9	M	5	10	1	5.1	14	3–8.6	LTG
P10	F	10	13	4	6.5–9	5	2–12.6	LTG
P11	F	4	7	11	4–6.8	1	2.3	ESM, VPA
P12	F	7	9	11	4–10.9	2	2.9–3.4	LTG, ESM,VPA

EEG-Electroencephalography, GSWDs- Generalized spikes and waves discharges, M- Males, F-Females, ESM- Ethosuximide, LTG-Lamotrigine, VPA-Valproate.

2.3. EEG analysis

2.3.1. Selection of ictal GSWDs

The ictal segments i.e. absences were selected based on the following criteria: 1) A sudden interruption of on-going activities, a blank stare, possibly a brief upward deviation of the eyes, unresponsiveness when spoken to, (Fisher et al., 2017) 2) ictal GSWDs longer than 3 seconds and less than 30 seconds and 3) spontaneous absences as well as absences provoked via hyperventilation. Following these three criteria, 45 ictal GSWDs were selected from the 12 patients. All selected segments lasted between 3.1 and 18.8 seconds. The mean duration of ictal discharges was 8.4 seconds (SD 3.4).

2.3.2. Selection of subclinical GSWDs

The subclinical GSWDs were selected based on the following criteria: 1) patients were tested and did not show any signs of impairment of consciousness during GSWDs i.e. could promptly and correctly answer questions posed by the technicians, as validated by a supervising epileptologist. 2) Patients showed no objective clinical symptoms of a seizure and 3) duration of the discharge $\geq$ 1 second. Following this, 42 subclinical GSWDs were selected from the 12 patients. The duration of all selected segments ranged between 1 and 12.6 seconds long. The mean duration of subclinical discharges was 4.1 seconds (SD 2.4).

2.3.3. Time intervals of interest

In order to evaluate the dynamics of neuronal networks we chose to analyze ictal and subclinical GSWDs over a time course of pre- ictal/subclinical, during- ictal/subclinical and post- ictal/-subclinical. For pre and post segments a time period of 3 seconds was selected while for the ictal and subclinical GSWDs, the entire duration was taken. An example of ictal and subclinical discharges alongside the time intervals of interest can be viewed in Supplementary Figure A.1. Furthermore, the durations of ictal and subclinical discharges per subject have been plotted in Supplementary Figure A.4.

2.3.4. Pre-processing of EEG recordings

Data analysis was performed using the toolbox FieldTrip (Oostenveld et al., 2011) (http://fieldtrip.fcdonders.nl/). The EEG data was bandpass-filtered in the range between 0.1 Hz and 31 Hz. Subsequently, independent component analysis was used to suppress eye-blinks and eye-movement artifacts. After artifact removal, the EEG channels were re-referenced to the common average reference. Further, the dataset was normalized using a Z-score normalization and all selected intervals of interest were divided into 1 second long segments. For these segments furthermore, the mean and the trend were removed using general linear modelling.

2.3.5. Frequency analysis and imaginary part of coherency

For 1 second long segments, auto and cross-power spectral density matrices were estimated using a Fast Fourier Transform (FFT) with a Hanning-window (Popov et al., 2018). This was done for a frequency range of 1 to 30 Hz with steps of 1 Hz. The computed auto-power spectral density matrices were averaged through the segments for every subject and condition. Additionally, in order to clarify as to whether the duration of the discharges was influencing our results, rather than presence or lack of responsiveness, we also analysed the data after reducing the duration of the ictal discharges and adjusting it to the duration of the subclinical discharges. This analysis with matched durations has been described in detail in the Supplementary Information (Appendix A.2, Page 2–4).

Further, using the cross-spectral density matrix estimated for each segment, the absolute value of the imaginary part of coherency was calculated for every segment and each pair of EEG channels. An important point to note is that, since sensor data are composed of a mixture of brain source contributions due to volume conduction, it is difficult to interpret localization of networks in the brain. Therefore in this study we only describe the networks at the surface level.

2.4. Statistical analysis

A two-way repeated measurement analysis of variance (ANOVA) (Anderson and Braak, 2003; Suckling and Bullmore, 2004) based on a cluster permutation test, implemented in the FieldTrip toolbox (Oostenveld et al., 2011) was used to analyse the EEG data. This non-parametric approach via cluster-based Monte Carlo (Maris and Oostenveld, 2007) resampling was used to avoid the condition that the data should be normally distributed. Moreover, cluster correction here solves the problem of multiple comparisons. Alongside overcoming these issues, this statistical analysis gives additional information about the transition periods of ictal and subclinical discharges, i.e. the change from pre-interval to during-interval and from during-interval to the post-interval.

The ANOVA factors and their interaction were estimated by F-values. Prior to the calculation of the significance probability, a cluster-based test statistic needs to be computed. First a F-value is calculated for all sample points (channel, frequency). This F-value is combined in a cluster if its value exceeds a threshold defined as a critical value corresponding to the significane level of 0.05. After clusters are created, the within-cluster F-values are added to create cluster-level statistic for each cluster. Finally, the maximum of the cluster-level statistics is chosen as the cluster-based test-statistic. This process was repeated for 2000 permuted data. Following which, the significant probability was estimated between the number of permutations and the number of cases with a larger test statistic. A p-value below 0.05 was considered significant. This entire process was calculated for the time effect, group effect as well as interaction effect.

2.4.1. Statistical analysis for EEG band powers

Two-way repeated measurement ANOVA with two within-subjects factors (group $\times$ time) was performed for different frequency bands (delta 1–3 Hz, theta 4–7 Hz, alpha 8–12 Hz, beta 13–30 Hz) by averaging the respective power spectra in each frequency band. The "group" factor included two types of abnormal activity (ictal and subclinical GSWDs). The "time" factor was analysed for three different time intervals: pre- ictal/subclinical, during- ictal/subclinical and post- ictal/subclinical. A post-hoc test was performed for significant ($p < 0.05$) ANOVA results, which have more than one pair of comparisons (time or interaction effects).

2.4.2. Statistical analysis for functional connectivity via imaginary part of coherency

Similarly, to the analysis of band powers, two-way repeated measurement ANOVA with two within-subjects factors (*group* $\times$ *time*) was performed for the imaginary part of coherency in the delta, theta, alpha, and beta bands. Statistical tests were performed for each channel with all other channels, i.e. the number of statistical tests was equal to the number of channels.

3. Results

3.1. Comparison of power spectra

Two factors (*group* $\times$ *time*) ANOVA revealed significant main effect of *time* over all channels for all frequency bands (Appendix

A.1 in the Supplementary Information; Supplementary Figure A.2) and main effect of *group* for all frequency bands except the theta band (Fig. 2A). The interaction between *group* and *time* factors also revealed significance for delta, alpha and beta bands but not for theta band (Fig. 3A). The statistical *P* values obtained for spectral analysis have been given in Table 2.

Main effect of *group* for delta, alpha and beta bands, showed that ictal discharges have higher power compared to subclinical discharges (Fig. 2B). These significant differences were observed in fronto-central, centro-parietal and temporal regions for delta band (electrodes: FC2, Cz, C4, CP1, CP2, Pz, T4, TP10). For alpha band significant differences were widespread in frontal, fronto-central, centro-parietal and temporal regions (electrodes: Fp1, F3, Fz, FC5, FC1, FCz Cz, C4, CP2, Pz FT10, TP9, TP10). For beta band these significant differences were localized mostly in centro-parietal, temporal and occipital regions (electrodes: Cz, CP1, CP5, CPz, CP6, Pz, P4, FT10, T4, TP9, TP10, O2).

For interaction effect, post-hoc tests were performed for delta, alpha and beta bands (Fig. 3B). For delta band the transition periods from pre-ictal to during-ictal interval and during-ictal interval to post-ictal interval had higher power compared to the transition periods of subclinical discharges. These differences were localized primarily in the central region (electrodes: FC2, Cz, C4, CP2). For alpha and beta bands also ictal transition periods had higher power compared to subclinical transition periods. The power changes in alpha band were localized in the frontal,

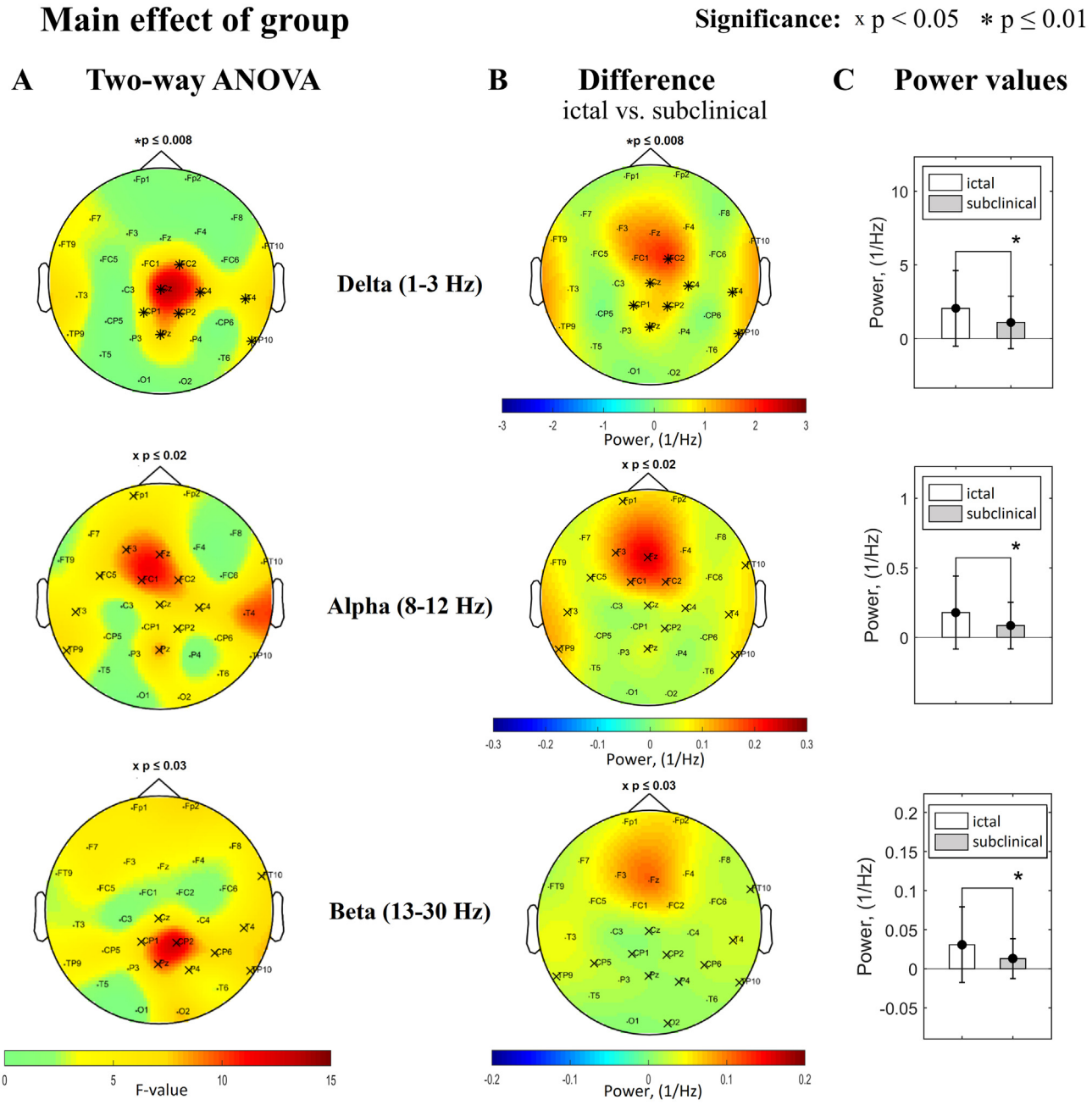

Fig. 2. Main effect of group for spectral power. A) Significant two-way ANOVA differences for group effect (ictal vs. subclinical) seen for delta, alpha and beta bands (cluster permutation, F-value masked by p < 0.05). B) Power differences for conditions ictal vs. subclinical. The significant frequency bands show that ictal discharges have higher power compared to subclinical discharges. C) Bar plots depict the average power values for conditions ictal vs. subclinical for all significant clusters. (Level of significance marked by × depicts p < 0.05 and * depicts p ≤ 0.01, ANOVA analysis of variance).

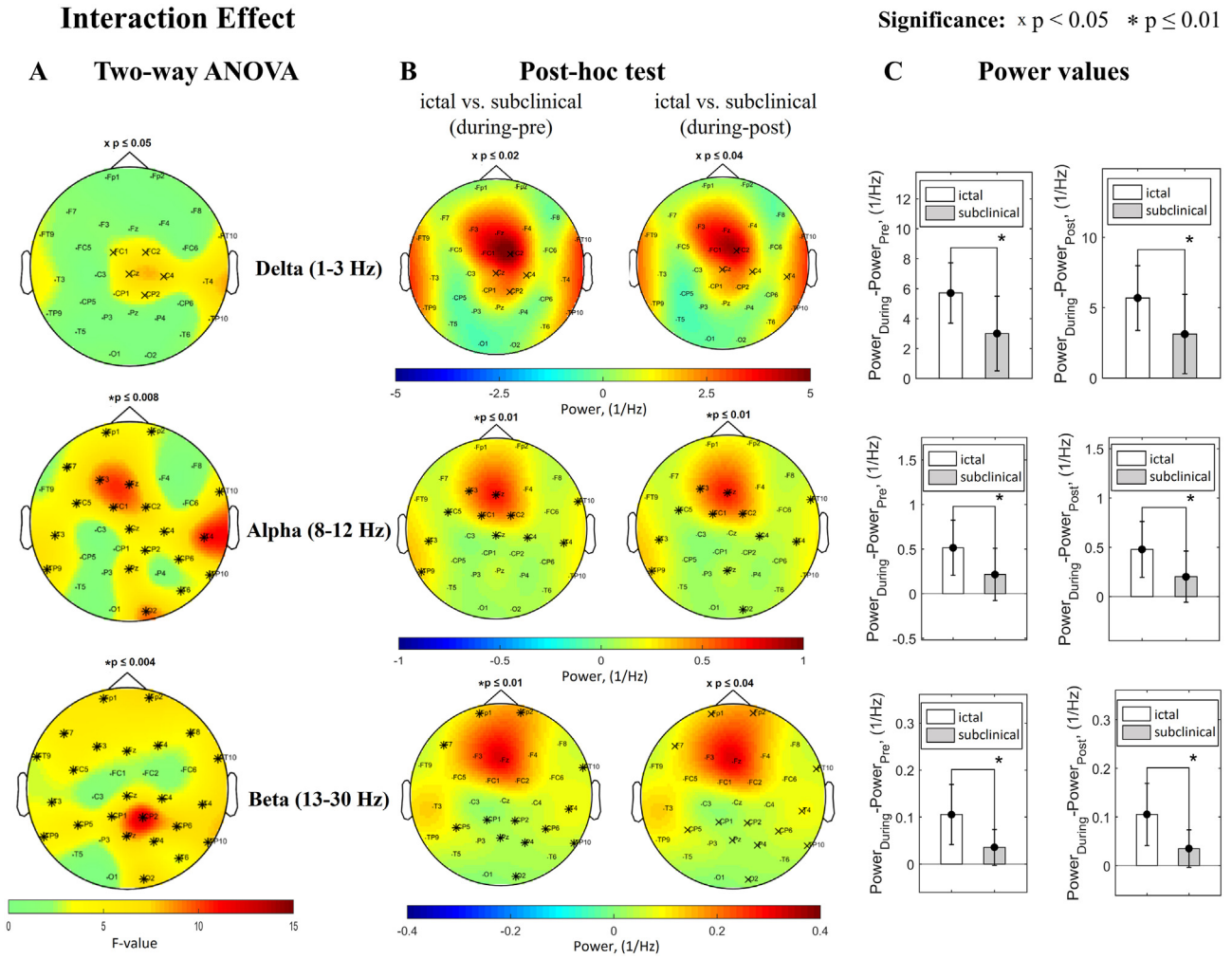

Fig. 3. Interaction effect for spectral power. A) Two way repeated measure ANOVA, cluster permutation differences for delta, alpha and beta frequency bands. B) Post hoc comparisons for conditions ictal vs. subclinical (during minus pre interval, during minus post interval). These comparisons show that the transition periods of ictal discharges through all time points have higher power compared to the transition periods of subclinical discharges C) Average power values of significant clusters for interaction effect. (Level of significance marked by × depicts $p < 0.05$ and * depicts $p \leq 0.01$, ANOVA analysis of variance).

fronto-central, temporal and occipital regions (electrodes: F3, Fz, FC5, FC1, FC2, FT10, T3, T4, Cz, C4, TP9, Pz, O2) and for beta band in the frontal, centro-parietal, temporal and occipital regions (electrodes: Fp1, Fp2, F7, FT10, CP1, CP2, CP5, CP6, T4, Pz, P4, O2).

3.2. Comparison of imaginary part of coherency

Two factor (*group* × *time*) ANOVA revealed significant main effect of *time* over all channels for all frequency bands (Appendix A.1 in the Supplementary Information; Supplementary Figure A.3) and no main effect of *group* for all frequency bands. For interaction effect, a significant difference was observed for all frequency bands (Fig. 4A). The statistical *P* values optained for FC have been given in Table 3.

Post-hoc test for interaction effect revealed, that the transition of connectivity from pre-ictal to during-ictal and from during-ictal to post-ictal was significantly weaker in all bands, compared to the subclinical transition periods (Fig. 4B). For delta band connectivity differences were observed in fronto-temporal, fronto-central, and centro-parietal regions, while differences in connectivity in theta, alpha and beta band were long range, linking the right and left hemispheres of the brain.

4. Discussion

In the current study, differences between ictal and subclinical GSWDs in children with CAE were investigated. To the best of our knowledge, this study is the first to conduct spectral analysis and FC on low-density surface-EEG data to find the significant differences between ictal and subclinical GSWDs.

Using spectral power analysis, our study revealed statistically significant differences between ictal and subclinical GSWDs at frequencies 1–3 Hz (Delta), 8–13 Hz (Alpha) and 14–30 Hz (Beta). However, no significant differences were found for the transition periods of frequencies 4–7 Hz (theta band).

It has been reported in previous EEG, EEG-fMRI and MEG studies that the frontal cortex plays an important role in the propagation of ictal GSWDs (Amor et al., 2009; Guo et al., 2016; Gupta et al., 2011; Holmes et al., 2004; Szaflarski et al., 2010). In a particular study, spectral power of 1–4 Hz frequency was analysed during absences in CAE using computational EEG (Kim et al., 2011). Their findings strongly suggest that absences may have focal features, even though ictal discharges on visual review by epileptologists appear to be broadly distributed. Furthermore, in a study done on MEG data, source analysis revealed localizations in frontal cortex and parieto-occipito-temporal junction (POT) in frequency

Table 2
Statistical results for Spectral analysis.

A) Two way ANOVA

Frequency bands	Factor	*P* value
Delta	time	**<0.001**
(1–3 Hz)	group	**0.008**
	time × group	**0.05**
Theta	time	**<0.001**
(4–7 Hz)	group	no clusters
	time × group	no clusters
Alpha	time	**<0.001**
(8–12 Hz)	group	**0.02**
	time × group	**0.008**
Beta	time	**<0.001**
(13–30 Hz)	group	**0.03**
	time × group	**0.004**

B) Post hoc comparisons

Conditions	Delta *P* values	Theta *P* values	Alpha *P* values	Beta *P* values
Effect of Time				
during vs. pre	**<0.001**	**<0.001**	**<0.001**	**<0.001**
during vs. post	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Effect of Group				
ictal vs. subclinical	**0.008**	**-**	**0.02**	**0.03**
Interaction effect				
ictal vs. subclinical (during-pre)	**0.02**	**-**	**0.01**	**0.01**
ictal vs subclinical (during-post)	**0.04**	**-**	**0.01**	**0.04**

Factor group- ictal, subclinical, **Factor time**- pre-, during-, post- time intervals, **'-'** insignificant *P* values, ANOVA-Analysis of variance.

bands 1–4 Hz, 4–8 Hz, 8–12 Hz, 12–30 Hz and 30–80 Hz (Wu et al., 2017). Similarly, another study showed significant ictal sources obtained from MEG data, in the frontal and parietal cortex at frequency bands 1–7 Hz and 8–30 Hz (Miao et al., 2019). For delta band our study revealed significant activity of electrodes localized in the frontal-central region, while for alpha band and beta band frontal, frontal-central, central-parietal, and temporal clusters of activity were observed. Our findings are thus in line with the above mentioned studies. Based on this we can hypothesize that the significant electrodes may correlate with the cortical and subcortical regions involved in the pathogenesis of ictal and subclinical GSWDs.

In a previous study, it has been reported that the mean fractional EEG power for seizures with impaired behavioural responses is higher compared to seizures with spared behavioural responses, and it was seen for frequency ranges of 2.5–4 Hz and 10–125 Hz (Guo et al., 2016). The group effect for our study revealed similarly that ictal discharges have higher power compared to subclinical discharges (Fig. 2B). Also, we observed that the transition of spectral power from pre-ictal to during-ictal and from during-ictal to post-ictal was higher, compared to the transition periods of subclinical GSWDs (Fig. 3B). This was seen for all the significant frequency bands: delta, alpha, and beta. As, EEG amplitude is related to the intensity and the synchrony of neuronal electrical activity, we speculate that during seizures a more intensive and larger neuronal activity is present, which may cause larger and longer-lasting EEG changes. This is then further reflected in the transition periods from pre- to during- and during- to -post interval for ictal as well as subclinical EEG discharges. These transition period differences, could play an important role in the development of seizure detection algorithms.

In our study we could also confirm, that ictal discharges have a longer mean duration compared to subclinical discharges. This is in line with a former study (Guo et al., 2016), showing that the mean seizure duration is longer for seizures with impaired behaviour as compared to seizures with spared behaviour. In order to clarify as to whether the significant differences were solely due to the duration of the discharges, we carried out an additional analysis. We matched the total durations of ictal/subclinical discharges and then conducted spectral analysis for all frequency bands. The results for this were compatible with the original results and show significant power differences between ictal and subclinical discharges (Supplementary Figures A.5, A.6, A.7, A.8). We thus have a strong reason to presume that the differences that we found in the original data cannot be purely due to the duration of ictal and subclinical EEG discharges.

To get a deeper understanding of the brain regions that are coherent with each other, network analysis is essential. When dealing with interpreting brain connectivity using EEG data, overcoming the volume conduction problem is necessary. Volume conduction causes multiple channels to observe the activity of a single brain source. Here, FC based on imaginary part of coherency was used to avoid this problem, since it is insensitive to volume conduction. This methodology has been described in detail by Nolte et al. (2004). FC based on imaginary part of coherency revealed significant differences for delta, theta, alpha and beta frequency bands for this study. It was observed that ictal transition periods, from pre-ictal to during-ictal and from during-ictal to post-ictal had a significantly weaker surface connectivity compared to subclinical transition periods for all frequency bands.

Previous studies have demonstrated the involvement of cortical regions and thalamus in the generation and propagation GSWDs present in absences (Amor et al., 2009; Bai et al., 2010; Holmes et al., 2004; Moeller et al., 2010). In another resting state fMRI study, CAE patients had marked differences compared to controls in whole brain FC and had decreased connectivity in the thalamus and basal ganglia alongside increased connectivity in the medial occipital cortex (Masterton et al., 2012). Various studies have reported a decrease in activity in certain brain regions during absences, several of which coincide with the DMN (Berman et al., 2010; Moeller et al., 2008). Also, thalamo-cortical activation and suspension of the default state have been shown in generalized epileptic discharges in an EEG-fMRI study (Gotman et al., 2005). Furthermore, resting state functional network analysis studies have shown abnormalities in the dorsal attention network, salience network and DMN, suggesting that it might contribute to impair-

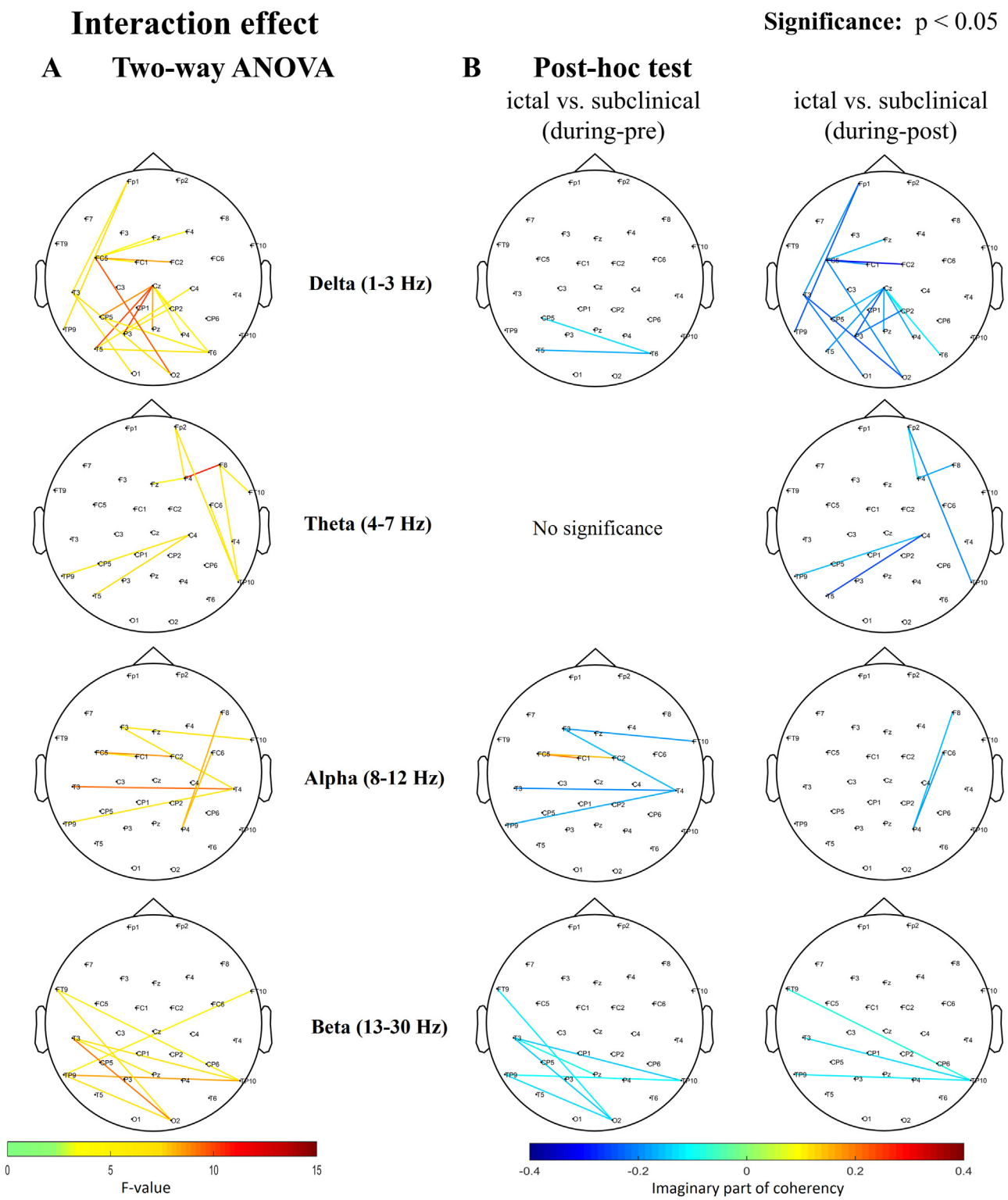

Fig. 4. Interaction effect for functional connectivity based on imaginary part of coherency.A) Significant two-way repeated measure ANOVA (F-value masked by $p < 0.05$) interaction effect, with two within subject factors (group × time) seen for all frequency bands. B) Post hoc comparisons for conditions ictal vs. subclinical (during minus pre interval, and during minus post interval) depicting significant channel connections. These comparisons show that ictal discharges have a weaker connectivity between channels compared to subclinical discharges. (ANOVA analysis of variance).

ment of consciousness and cognitive deficits in CAE patients (Li et al., 2015; Luo et al., 2014). In a study done regarding the cortico-thalamic connectivity in CAE using MEG, it was seen that at 1–7 Hz inhibitory connections were seen in patients with the thalamo-parietal/occipital (F-T-P/O) network (Miao et al., 2019). In this study, for delta band (1–3 Hz), FC showed a weaker synchronization of channels taking place during ictal GSWDs in fronto-temporal, fronto-central, centro-parietal channels, suggesting the involvement of the thalamo-cortical network as well as areas of the DMN (Fig. 4B). As for theta band (4–7 Hz), there was no

Table 3
Statistical results for Functional connectivity.

Functional Connectivity **Two way ANOVA**				
Frequency bands		**Factor**		***P* values**
Delta		time		**0.04**
(1–3 Hz)		group		**-**
		time × group		**0.04**
Theta		time		**0.03**
(4–7 Hz)		group		**-**
		time × group		**0.05**
Alpha		time		**0.02**
(8–12 Hz)		group		**-**
		time × group		**0.04**
Beta		time		**<0.001**
(13–30 Hz)		group		**-**
		time × group		**0.04**
Conditions	**Delta** ***P* values**	**Theta** ***P* values**	**Alpha** ***P* values**	**Beta** ***P* values**
A) **Post hoc comparisons**				
Effect of Time				
during vs. pre	**0.02**	**0.02**	**0.02**	**0.004**
during vs. post	**0.02**	**0.02**	**0.02**	**0.003**
Effect of Group				
ictal vs. subclinical	**-**	**-**	**-**	**-**
Interaction effect				
ictal vs. subclinical(during-pre)	**0.01**	**-**	**0.02**	**0.02**
ictal vs. subclinical(during-post)	**0.02**	**0.02**	**0.02**	**0.01**

Factor group- ictal, subclinical, **Factor time**- Pre-, during-, post- time intervals, **'-'** insignificant P values, ANOVA-Analysis of variance.

significant connection found for the transition period pre-during, though a small number of weaker connections were seen between the central-temporal and frontal-temporal electrodes for the transition period during-post. Our results suggest similar observations as the above mentioned studies, keeping in mind that we're only interpreting networks at the sensor level. For differences in connectivity in alpha (8–12 Hz) and beta bands (13–30 Hz), long range weak connections were observed for both transition periods linking the right and left hemispheres of the brain, suggesting widespread network propagation. The imaginary part of coherency depicted significant differences for interaction effect reflecting most probably wider, more intensive and complex network activations during absence seizures, with simultaneous deactivation of other networks. We presume that weaker connectivity linked to network deactivation between regions may be leading to severe impairment of consciousness during ictal GSWDs. However, in subclinical GSWDs the connectivity between regions is more pronounced, and there is no impairment of consciousness.

Several limitations of the present study should be considered. First, in this study, the number of subjects as well as the number ictal and subclinical GSWDs analysed were small. In order to validate our findings it would be important to analyse a larger group of patients with the methods presented here. Secondly, further studies would be required using more precise and objective tools for the assessment of reaction time and other behavioural markers during GSWDs, in correlation with alterations in spectral components and connectivity patterns. Additionally, analysis including the comparisons of ictal discharges with subclinical discharges of durations 3 seconds or more could be investigated as well. Thirdly, certain muscle artifacts might have been included in the results even though considerable efforts were made to minimize them. Also, it is important to note that other techniques such as directionality analysis are required in order to improve FC at the sensor space level.

Finally, this important pilot study lays the foundation for future diagnostic research, and has several applications. Since routine EEG data were used, this approach brings the analysis closer to a clinical setting. Simple existing methods were used so that this pipeline could be easily integrated into clinical practice. These methods may be applicable to other clinical situations as well as to advance future studies. The findings of this research represent a step forward in quantifying features of ictal and subclinical discharges in absence epilepsy, which could further be used for classification purposes, e.g. using machine learning in monitoring using clinical computers, tablets, smartphones and smart watches.

5. Conclusion

In conclusion, our findings suggest that using spectral analysis and FC at sensor level, EEG data alone can provide useful information regarding differences between ictal and subclinical GSWDs in CAE. Furthermore, this analysis provides an insight into the network dynamics involved in the transition periods of ictal and subclinical GSWDs. In this study, ictal discharges depicted a higher spectral power as compared to subclinical discharges, for frequency bands delta, alpha and beta. FC showed that ictal discharges have weaker channel connectivity compared to subclinical discharges for all frequency bands. These identified features could be used as a next step to develop a classifier or machine learning algorithms, for facilitating EEG monitoring and EEG diagnostics of CAE patients.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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