

Functional brain connectivity in electrical status epilepticus in sleep

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ABSTRACT – *Aims.* Electrical status epilepticus in sleep (ESES) is an age-related, self-limited epileptic encephalopathy. The syndrome is characterized by cognitive and behavioral abnormalities and a specific EEG pattern of continuous spikes and waves during slow-wave sleep. While spikes and sharp waves are known to result in transient cognitive impairment during learning and memory tasks performed during the waking state, the effect of epileptiform discharges during sleep on cognition and behavior is unclear. There is increasing evidence that abnormalities of coherence, a measure of the consistency of the phase difference between two EEG signals when compared over time, is an important feature of brain oscillations and plays a role in cognition and behavior. The objective of this study was to determine whether coherence of EEG activity is altered during slow-wave sleep in children with ESES when compared to typically developing children.

Methods. We examined coherence during epochs of ESES versus epochs when ESES was not present. In addition, we compared coherence during slow-wave sleep between typically developing children and children with ESES.

Results. ESES was associated with remarkably high coherences at all bandwidths and most electrode pairs. While the high coherence was largely attributed to the spikes and spike-and-wave discharge, activity between spikes and spike-and-wave discharge also demonstrated high coherence.

Conclusions. This study indicates that EEG coherence during ESES is relatively high. Whether these increases in coherence correlate with the cognitive and behavioral abnormalities seen in children with this EEG pattern remains to be determined.

Key words: electrical status epilepticus in sleep (ESES), EEG, coherence, oscillations, phase lag, continuous spike and waves during slow wave sleep (CSWS)

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Electrical status epilepticus in sleep (ESES) is defined as an age-related, self-limited epileptic encephalopathy. The condition is characterized by cognitive and behavioral abnormalities and a specific electroencephalographic (EEG) pattern of continuous spike and waves during slow-wave sleep (CSWS) (Patry *et al.*, 1971; Galanopoulou *et al.*, 2000; Scheltens-de Boer, 2009; Sanchez Fernandez *et al.*, 2012, 2014; Singhal and Sullivan, 2014; Gencpinar *et al.*, 2016). While the clinical presentation of children with ESES is variable, the most severe clinical syndrome presents with global cognitive regression in addition to clinical seizures. The age at onset ranges from one to 14 years, with a peak between four and eight years (van den Munckhof *et al.*, 2015). Although seizures may be absent in up to 20% of cases, they are most often the presenting symptom, after which developmental delay, developmental arrest, or regression in cognitive performance or behavior becomes evident (Tassinari *et al.*, 2000). While CSWS and ESES are used interchangeably, ESES typically is used to describe the EEG pattern while CSWS is used to describe the clinical syndrome of cognitive and behavioral abnormalities associated with the ESES pattern (Gencpinar *et al.*, 2016). The hallmark EEG features of ESES are:

- a spike and wave occurring “during a significant proportion” of non-REM sleep with a threshold ranging from 25% to 85%;
- continuous or nearly-continuous, bilateral, or occasionally lateralized slow spikes and waves;
- and marked potentiation of epileptiform discharges during non-REM sleep (Sanchez Fernandez *et al.*, 2013).

Near-continuous epileptiform discharges have been causally related to neurocognitive regression in CSWS (Tassinari *et al.*, 2000; Holmes and Lenck-Santini, 2006). The pathophysiologic mechanisms underlying this condition are still incompletely understood. Recent data suggest that the abnormal epileptic EEG activity occurring during sleep might cause the typical clinical symptoms by interfering with sleep-related physiologic functions, and possible neuroplasticity processes mediating higher cortical functions such as learning and memory consolidation (Tassinari *et al.*, 2000; Holmes and Lenck-Santini, 2006). It is known that spikes and spike-and-wave discharges can lead to cognitive impairment in both animals (Kleen *et al.*, 2010) and humans (Aarts *et al.*, 1984; Binnie *et al.*, 1987, 1990, 1991; Shewmon and Erwin, 1989; Krauss *et al.*, 1997; Ung *et al.*, 2017). However, the cognitive impairment seen with interictal spikes is transient in nature in both humans (Aarts *et al.*, 1984; Nair *et al.*, 2014; Horak *et al.*, 2017) and rodents (Holmes and Lenck-Santini, 2006; Zhou *et al.*, 2007; Kleen *et al.*, 2010) and it has been difficult to link the neurocognitive regression in CSWS solely to nocturnal spikes (Ebus *et al.*, 2011).

There is increasing evidence that abnormalities in underlying oscillatory activity may play an important role in cognitive impairment in children with seizures (Holmes and Lenck-Santini, 2006; Holmes, 2014; Barry and Holmes, 2016). For example, in children with epilepsy, neither spikes nor spike-and-wave discharges correlate with the neuropsychological profile, whereas slow-wave activity on the EEG is related to memory impairment (Koop *et al.*, 2005). In a study of children with Dravet syndrome, it was found that cognitive outcome was related more to preserved alpha rhythm of the EEG than seizures or generalized spike-wave discharges on the EEG. Likewise, in an animal model of Dravet syndrome, cognitive impairment was related to altered theta rather than seizures or interictal spikes (Bender *et al.*, 2013, 2016). These studies raise the question of whether EEG background abnormalities are related more to cognitive impairment than interictal spikes.

Recent work in humans has demonstrated that coherence is a valuable marker of functional brain organization and connectivity. On a frequency by frequency basis, EEG spectral coherence represents the consistency of the phase difference between two EEG signals when compared over time. EEG coherence is interpreted as a measure of “coupling” and as a measure of the functional association between two brain regions (Thatcher *et al.*, 1987, 2012). High coherence values are taken as a measure of strong connectivity between the brain regions that produce the compared EEG signals (Srinivasan *et al.*, 2007). In both autistic spectrum disorder (Buckley *et al.*, 2015) and West syndrome (Burroughs *et al.*, 2014), EEG coherences are abnormally high. Remarkably, there have been no papers to date assessing coherence as a functional measure of brain connectivity in ESES.

We hypothesized that ESES during SWS has high coherence values. To address this hypothesis, we compared coherences across bandwidths and electrode pairs during SWS in children with ESES and normal children. In children with ESES, we also compared coherences during SWS during non-ESES and ESES epochs. Finally, to determine the “driver” of coherence during ESES, we examined epochs containing only spikes with epochs not containing spikes.

Methods

Study design and participants

Twenty-four-hour inpatient EEGs were documented from 29 neurotypically developing (TYP) children (mean±SD: 4.18±1.70 years) and 18 children (5.37±1.85 years) with ESES, as defined as an EEG with generalized spikes, sharp waves, spike and wave or polyspikes and



Figure 1. Example of ESES recording during slow-wave sleep. Note the high-amplitude (>150 microvolts) spike-and-wave discharges.

waves, occupying 85% of slow-wave sleep (*figure 1*). For every 10 seconds of SWS, the mean duration of epileptiform discharges had to be equal to 8.5 seconds or more. The TYP group comprised participants in an NIH natural history study of autism approved by the National Institutes of Health Institutional Review Board (NCT00298246). None of the children in the TYP group had autism or relatives with autism. Data from the TYP group have previously been published as part of a study on functional connectivity in children with autism (Buckley *et al.*, 2015). The EEGs from the children with ESES were from Dartmouth-Hitchcock Medical Center and the University of Vermont Medical Center with approval of both institutions' Institutional Review Board for analysis of de-identified EEG data. The 10-20 system of electrode placement was used and the Pz electrode served as the reference. The linked-ear montage was used for all EEG analyses. The EEGs were analyzed by SAB, ALK and GLH without any identifying information other than gender and age.

Epochs of artifact-free SWS were identified in each patient. For the ESES group, 60 seconds of non-continuous EEG demonstrating ESES (*figure 2A*) and 60 total seconds of SWS without ESES (*figure 2B*) were obtained. This 60-second epoch exceeds the 20-second time frame which is considered sufficient to assess quantitative EEG measures (Mocks and Gasser, 1984). Split-half reliability and the ratio of variance between the even and odd seconds of the time series of selected digital EEG (variance = sum of the square of the deviation of each time point from the mean of the time points) were calculated for each channel and a reliability of >0.95 was required before analysis. We also performed "test re-test" measures on all EEG data. Test re-test reliability uses the same equations as those

used for split-half reliability but refers to the ratio of the variance of the first half of the EEG selections vs the variance of the second half of the EEG selections. A test re-test reliability of >0.90 was required before EEG data was statistically analyzed. In the TYP group, 10 minutes of continuous SWS EEG was analyzed. Since 85% of SWS consist of spikes and spike-and-wave discharges, shorter epochs were used in the children with ESES than the TYP group since it was often difficult to find 10 minutes of SWS without spike-and-wave complexes. In three patients with ESES, we compared 60-second epochs with 10-minute epochs of SWS with ESES and SWS without ESES using the paired-t test. No significant differences were noted in absolute power, relative power, power ratio, coherence or phase lag between 60-second and 10-minute epochs (data not shown). Thus, we concluded that it was appropriate to compare 60-second epochs between ESES patients and the TYP group.

To determine the electrical activity underlying coherence in ESES, epochs containing generalized spikes, sharp waves, spike and wave, or polyspikes and waves (*figure 3A*) were compared with epochs without spikes (*figure 3B*). The slow wave following the spike was considered as part of the epileptic discharge and was included in epochs of epileptiform activity.

EEGs were analyzed using NeuroGuide (Applied Neuroscience, Inc., Largo, FL). Frequencies from 0-30 Hz were analyzed using a Fast Fourier Transform (FTT) with the following parameters: epoch = 2 seconds at a sample rate of 128 samples/second = 256 digital time points and a frequency range from 0.5 to 30 Hz at a resolution of 0.5 Hz using a cosign taper window. FFT absolute and relative power was used for each of the 19 electrodes for delta (δ) (0-4 Hz), theta (θ) (4-8 Hz),

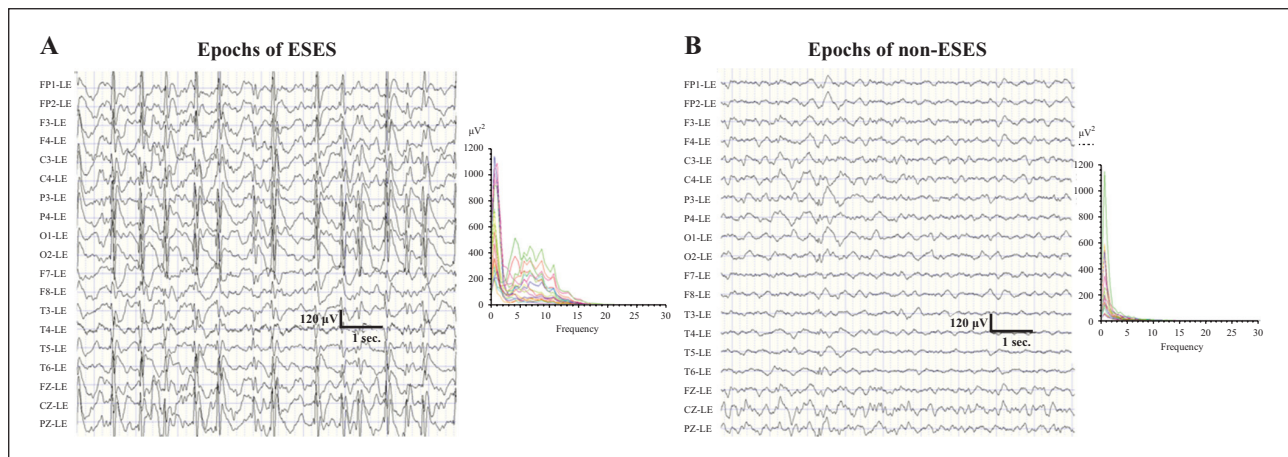


Figure 2. ESES during SWS. (A) Example of ESES during SWS. EEG absolute power is represented on the right. Colored lines represent different electrodes. Note the increased power in frequencies up to the β bandwidth. (B) Example of period during SWS without ESES. EEG absolute power is represented on the right. Compared to (A), the absolute power is primarily in the Δ bandwidth.

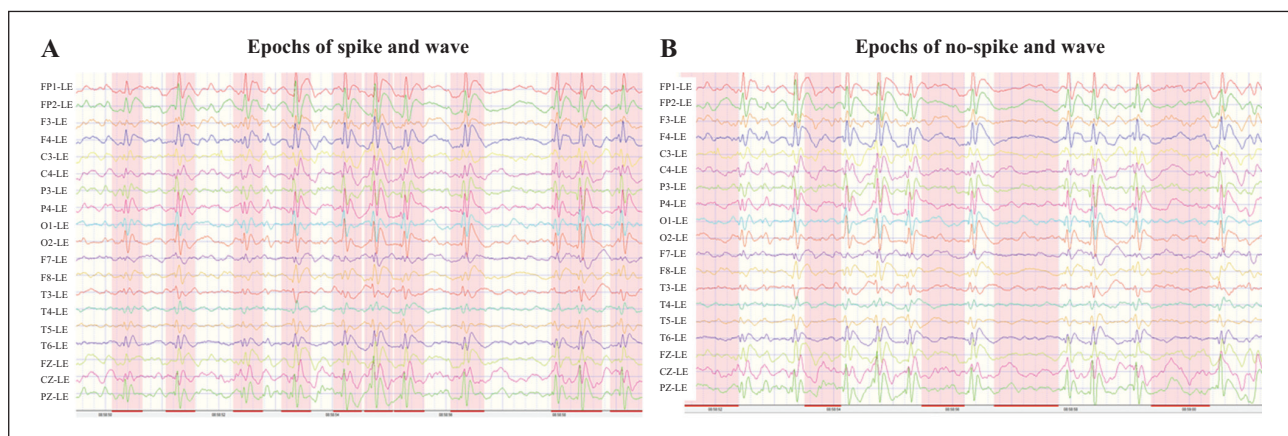


Figure 3. Epochs of EEG used for coherence measurement. (A) Calculation of coherence measure during spike and waves and polyspikes and waves. (B) Epochs of EEG without spikes measured for coherence. Shaded areas in pink are incorporated into the coherence measures.

alpha (α) (8-12 Hz), $\alpha 1$ (8-10 Hz), $\alpha 2$ (10-12 Hz), beta (β) (12-25 Hz), $\beta 1$ (12-15 Hz), $\beta 2$ (15-18 Hz), $\beta 3$ (18-25 Hz), and high β (25-30 Hz). FFT absolute power per Hz (1-30 Hz) and power ratios for each electrode (δ/θ , δ/α , δ/β , θ/α , θ/β , α/β) were measured. FFT coherence for each electrode pair and FFT phase lag (degrees) between electrode pairs were obtained. Intra-hemispheric and inter-hemispheric pair wise combinations of electrodes were evaluated (171 pairs of electrodes).

Coherence represents the consistency of the phase difference between two EEG signals when compared over time and serves as a measure of synchronization between two EEG signals based mainly on phase consistency. Two signals may have different phases but high coherence occurs when this phase difference tends to remain constant. Coherences vary from 0, with

no consistency between phases of two EEG signals, to 1, with perfect alignment of phase.

Coherence was defined as:

$$\text{Coherence}(f) = \frac{(G_{xy}(f))^2}{(G_{xx}(f) G_{yy}(f))}$$

Where $G_{xy}(f)$ is the cross-power spectral density and $G_{xx}(f)$ and $G_{yy}(f)$ are the respective autopower spectral densities. FFT coherence for each electrode pair and FFT phase lag (degrees) between electrode pairs were obtained. Intra-hemispheric and inter-hemispheric pair wise combinations of electrodes were evaluated (171 pairs of electrodes).

Statistical analysis

Hypotheses were proven or discarded based on unpaired *t* tests for comparisons between the TYP children and ESES children and paired *t* tests for comparisons within the same patient for SWS with ESES and SWS without ESES using Neurostat EEG statistical software. The *t* test was used since the data demonstrated a normal distribution. The *p* values are shown in two ways:

- electrode maps with color and thickness of the lines connecting electrodes, reflecting direction of the differences between groups and the degree of significance;
- *p* value heat maps with degree of significance in selected color-coded electrode pairs. Although data were reviewed from 171 electrode pairs, selected electrodes were chosen for illustration.

Results

During ESES, there was a marked increase in coherence compared to the SWS segments without ESES (*figures 4, 5*). This increase in coherence occurred across all bandwidths and many electrode pairs. Of the 62 electrode pairs demonstrated in the heat map in *figure 5*, 12 (19.3%) in the Δ range, 36 (58%) in the Θ range, 49 (79%) in the α range, and 49 (79%) in the β range showed statistically increased coherences. In no electrode pairs did the ESES epochs show lower coherences than the non-ESES epochs. Likewise, there were significant increases in coherence in the EEGs with ESES

compared to the TYP group (*figures 6, 7*). Coherences were significantly increased in the ESES group across all bandwidths. Of the 62 electrode pairs demonstrated in the heat map in *figure 8*, 16 (25.8) in the Δ range, 31 (50%) in the Θ range, 54 (87%) in the α range, and 52 (83.8%) in the β range showed statistically increased coherences, other than a few electrode pairs in the high β (25-30-Hz) bandwidth where coherences were lower in the TYP group than the ESES group. While all bandwidths demonstrated increases in coherence, the Δ frequencies were less likely to be significantly increased than the other major bandwidths (Θ , α and β). In the Δ bandwidth, some asymmetries in coherence were seen, with higher coherences noted over the left hemisphere, when compared with the TYP group. The composite coherence score showed that during ESES, coherence was substantially increased compared to non-ESES periods and with slow wave sleep (SWS) in the TYP group (*table 1*). In addition to the mean differences between groups shown in *table 1*, for each individual child, the mean coherences were higher in the ESES patient than the mean score for the TYP group.

To determine the component of the ESES that was contributing to the increased coherences, periods of ESES with and without spikes were compared. As demonstrated in *figure 8*, coherences were significantly higher during the spike component of the ESES than the non-spike component. Likewise, the composite coherence score during spikes was higher during spikes versus no-spike epochs (*table 1*). This was also true for each individual patient. Also, coherence

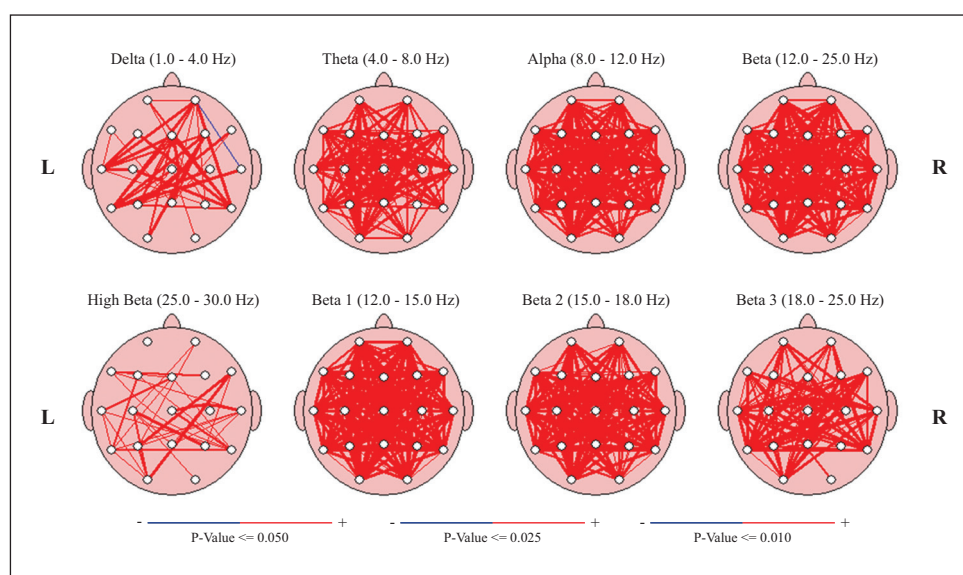


Figure 4. Coherence during ESES. Marked increases in coherence were seen at most electrode pairs during ESES compared to non-ESES periods. Red lines indicate that the ESES segments had higher coherences than during the non-ESES segments during SWS. The significance values are illustrated by weight of the lines. L/R refer to the left and right side of the head.

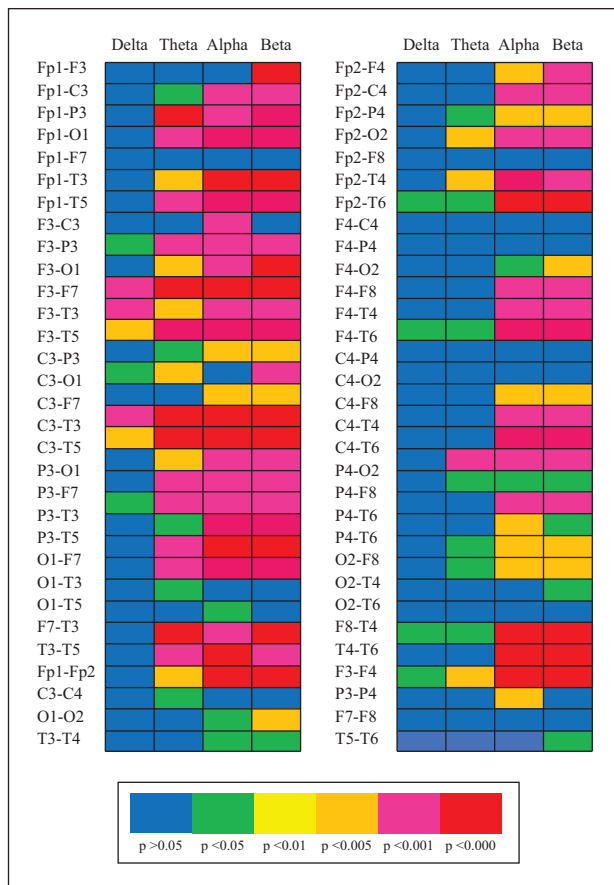


Figure 5. Heat map of p values for coherence between selected electrode pairs. Marked increases in coherence were seen during ESES compared to non-ESES periods.

values during no-spike epochs of ESES were significantly higher than those during non-ESES periods in the same patient ($t[15]=4.038, p = 0.0011$).

During ESES, there were also large increases in absolute power across the four major bandwidths (Δ , Θ , α and β) and relative power in the δ/θ , δ/α , δ/β , δ/γ , θ/α and θ/β compared to epochs without ESES (data not shown).

Discussion

The major finding in this analysis is that EEGs from children with ESES have marked abnormalities in coherence compared to periods of SWS without ESES and SWS in TYP children. While high coherence seems implicit in a recording with generalized spikes, it should be noted that the coherence values are increased at all bandwidths during spike-free epochs. It also should be noted that coherence cannot be assessed solely by examining the raw EEG signal. For example, in hypsarrhythmia, an abnormal interictal pattern consisting of high-amplitude and irregular waves and spikes in a background of chaotic and disorganized activity, coherence values are high (Burroughs *et al.*, 2014).

The children with ESES were older than those in the TYP group and it is known that coherence increases with age (Gmehlin *et al.*, 2011). In our previous study examining coherence in autism in children, using a series of general linear models controlling for age, we found little difference in coherence between four and

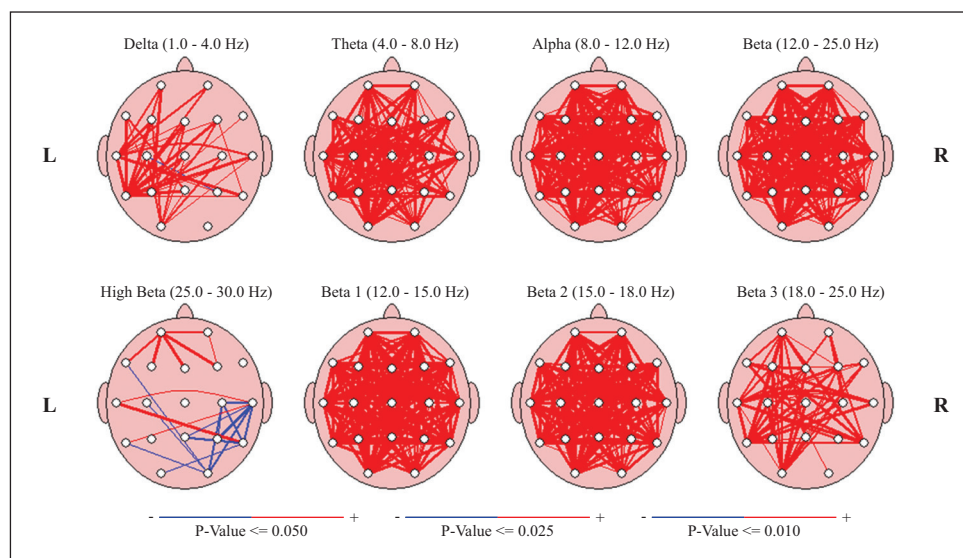


Figure 6. Coherence during SWS in children with ESES and TYP. Marked increases in coherence was seen at most electrode pairs during ESES segments in SWS compared to TYP controls. Red lines indicate that the ESES segments had higher coherences than during the SWS in the TYP controls while blue lines indicate lower coherences in the ESES segments in SWS compared to TYP controls. The significance values are illustrated by weight of the lines. L/R refer to the left and right side of the head.

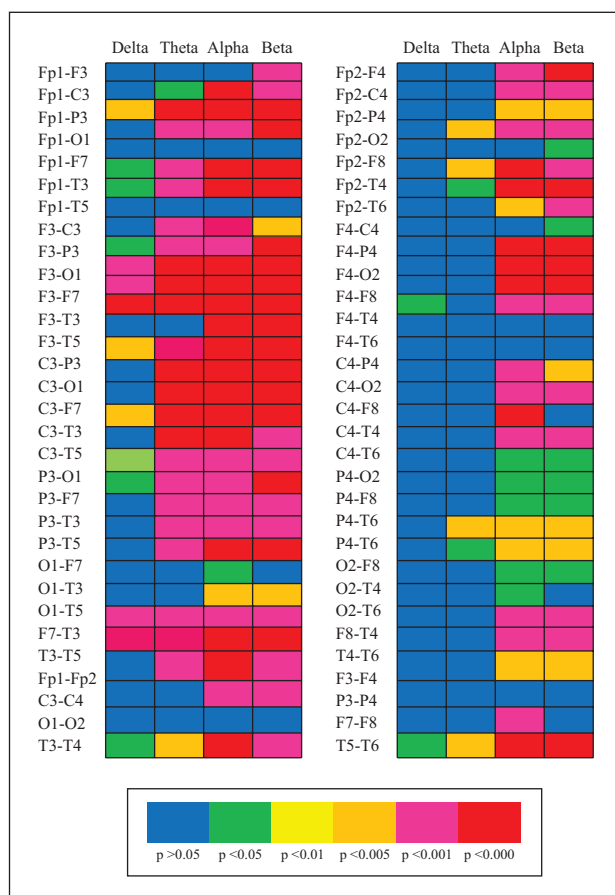


Figure 7. Heat map of p values for coherence between selected electrode pairs. Marked increases in coherence were seen during ESES compared to SWS in TYP controls.

five years (Buckley *et al.*, 2015), thus making it highly unlikely the differences seen here were due to different ages. In addition, with such a large effect size, it is highly unlikely the increased coherence in the children with ESES was simply due to the ESES population being older. In addition, using paired comparisons, coherences were much higher during ESES periods than during non-ESES periods in SWS within the same patient.

Of interest, in the Δ bandwidths, the ESES group had higher coherences than the TYP group over the left hemisphere relative to the right. Asymmetries of coherence have been reported in other studies (French and Beaumont, 1984; Tucker *et al.*, 1986; Nielsen *et al.*, 1990; Whedon *et al.*, 2016). It is known that many children with ESES have language abnormalities (Nickels and Wirrell, 2008). Whether these aberrant coherences in the dominant hemisphere are correlated with language impairment in our cohort of patients is not known.

As a measure of “coupling” oscillations, coherence provides a dynamic link between brain areas required for the integration of distributed information (Varela *et al.*, 2001; Thatcher, 2012). Since high coherence values are an indication of strong connectivity between the brain regions that produce the EEG signals (Srinivasan *et al.*, 2007), it is difficult to understand why high coherences would be detrimental. Decreased coherences have been associated with cognitive and behavioral abnormalities. Indeed, in rodent models of stress (Jacinto *et al.*, 2013; Oliveira *et al.*, 2013) and schizophrenia (Sigurdsson *et al.*, 2010),

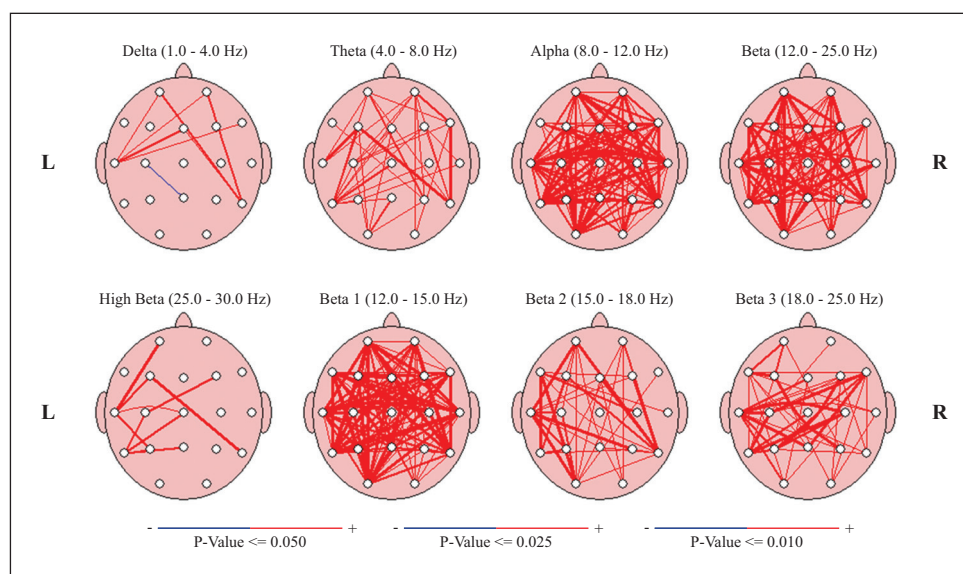


Figure 8. Coherence during spikes and inter-spoke intervals in children with ESES. Increases in coherence were seen at most electrode pairs during ESES segments with spikes compared to the inter-spoke interval. Red lines indicate that the spike segments had higher coherences than during the inter-spoke interval. The significance values are illustrated by weight of the lines. L/R refer to the left and right side of the head.

Table 1. Composite coherence scores (mean of all electrode pairs at all bandwidths) during SWS in the TYP group, periods of ESES and non-ESES and ESES with spikes and ESES without spikes. (**p* value of comparison with periods of ESES, ***p* value comparing ESES-spikes and ESES-no spikes).

	TYP	ESES	Non-ESES	ESES-Spikes	ESES-No Spikes
Minimum	13.29	17.06	9.948	31.42	16.54
Medium	19.93	33.85	18.10	41.42	26.07
Maximum	29.04	45.05	29.27	41.73	27.56
Mean	20.95	33.72	17.81	35.08	24.65
S.D.	4.266	1.758	1.033	4.894	3.805
P	<0.0001*		<0.0001*		0.0054**

coherences in the hippocampus and prefrontal cortex are decreased. Likewise, decreases in coherence occur in conditions such as Alzheimer's disease (Besthorn *et al.*, 1994), intellectual impairment (Thatcher *et al.*, 2005), attention-deficit disorder and reading difficulties (Barry *et al.*, 2009), and autism (Coben *et al.*, 2008; Mathewson *et al.*, 2012; Khan *et al.*, 2013). However, neuronal synchrony in the brain is finely tuned and it is likely that functional "over connectivity" may be as detrimental as "under-connectivity" as a network that is over-connected may not be able to adapt to increased cognitive demand (Supekar *et al.*, 2013). High phase locking of neurons in multiple brain regions likely results in neurons in both structures firing with excessive synchrony with a diminished ability to develop localized functional ensembles (Voytek and Knight, 2015). We suggest that, as with other electrophysiological processes, there is an ideal "sweet spot" for coherence and that deviations in either a positive or negative direction can alter behavior and cognition. The findings must be interpreted cautiously. This is an EEG study that examined the relationship of coherence with ESES and we provide no data indicating that increased coherence during ESES in SWS is responsible for the behavioral and cognitive issues in children with CSWS. Rather, we wish to raise the possibility that an overly coherent brain during SWS during childhood may play a role in the behavioral and cognitive problems seen in these children. In one of the other epileptic encephalopathies, West syndrome, it has been shown that children have marked abnormalities in coherence and that improvement in seizures and development are seen only in children in whom the coherences improved (Burroughs *et al.*, 2014). In future studies, it will be valuable to examine the relationship of coherences during SWS with clinical symptoms in children with CSWS and whether changes in coherence are a predictor of treatment success. □

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