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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.

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Keywords

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

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 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), alpha (α) (8–12 Hz), α1 (8–10 Hz), α2 (10–12 Hz), beta (β) (12–25 Hz), β1 (12–15 Hz), β2 (15–18 Hz), β3 (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:

$$(coherence(f)) = \left(G_{XY}(f)^2\right)$$
$$(G_{XX}(f)G_{YY}(f))$$

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 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 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), 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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References

Aarts JH, Binnie CD, Smit AM, Wilkins AJ. Selective cognitive impairment during focal and generalized epileptiform EEG activity. Brain 1984; 107: 293–308. [PubMed: 6421454]

Barry JM, Holmes GL. Why are children with epileptic encephalopathies encephalopathic? J Child Neurol 2016; 31: 1495–504. [PubMed: 27515946]

Barry RJ, Clarke AR, Mccarthy R, Selikowitz M. EEG coherence in children with attention-deficit/ hyperactivity disorder and comorbid reading disabilities. Int J Psychophysiol 2009; 71: 205–10. [PubMed: 18848848]

Bender AC, Natola H, Ndong C, Holmes GL, Scott RC, Lenck-Santini PP. Focal Scn1a knockdown induces cognitive impairment without seizures. Neurobiol Dis 2013; 54: 297–307. [PubMed: 23318929]

Bender AC, Luikart BW, Lenck-Santini PP. Cognitive deficits associated with Nav1.1 alterations: involvement of neuronal firing dynamics and oscillations. PLoS ONE 2016; 11: e0151538. [PubMed: 26978272]

Besthorn C, Forstl H, Geiger-Kabisch C, Sattel H, Gasser T, Schreiter-Gasser U. EEG coherence in Alzheimer disease. Electroencephalogr Clin Neurophysiol 1994; 90: 242–5. [PubMed: 7511505]

Binnie CD, Kasteleijn-Nolst Trenite DG, Smit AM, Wilkins AJ. Interactions of epileptiform EEG discharges and cognition. Epilepsy Res 1987; 1: 239–45. [PubMed: 3504400]

Binnie CD, Channon S, Marston D. Learning disabilities in epilepsy: neurophysiological aspects. Epilepsia 1990; 31: S2–8. [PubMed: 2279478]

Binnie CD, Channon S, Marston DL. Behavioral correlates of interictal spikes. Adv Neurol 1991; 55: 113–26. [PubMed: 2003401]

Buckley AW, Scott R, Tyler A, et al. State-dependent differences in functional connectivity in young children with autism spectrum disorder. EBioMedicine 2015; 2: 1905–15. [PubMed: 26844269]

Burroughs SA, Morse RP, Mott SH, Holmes GL. Brain connectivity in West syndrome. Seizure 2014; 23: 576–9. [PubMed: 24794162]

Coben R, Clarke AR, Hudspeth W, Barry RJ. EEG power and coherence in autistic spectrum disorder. Clin Neurophysiol 2008; 119: 1002–9. [PubMed: 18331812]

Ebus SC, Overvliet GM, Arends JB, Aldenkamp AP. Reading performance in children with rolandic epilepsy correlates with nocturnal epileptiform activity, but not with epileptiform activity while awake. Epilepsy Behav 2011; 22: 518–22. [PubMed: 21940218]

French CC, Beaumont JG. A critical review of EEG coherence studies of hemisphere function. Int J Psychophysiol 1984; 1: 241–54. [PubMed: 6394561]

Galanopoulou AS, Bojko A, Lado F, Moshe SL. The spectrum of neuropsychiatric abnormalities associated with electrical status epilepticus in sleep. Brain Dev 2000; 22: 279–95. [PubMed: 10891635]

Gencpinar P, Dundar NO, Tekgul H. Electrical status epilepticus in sleep (ESES)/continuous spikes and waves during slow sleep (CSWS) syndrome in children: an electroclinical evaluation according to the EEG patterns. Epilepsy Behav 2016; 61: 107–11. [PubMed: 27337163]

Gmehlin D, Thomas C, Weisbrod M, Walther S, Resch F, Oelkers-Ax R. Development of brain synchronisation within school-age: individual analysis of resting (alpha) coherence in a longitudinal data set. Clin Neurophysiol 2011; 122: 1973–83. [PubMed: 21501970]

Holmes GL. What is more harmful, seizures or epileptic EEG abnormalities? Is there any clinical data? Epileptic Disord 2014; 16: 12–22.

Holmes GL, Lenck-Santini PP. Role of interictal epileptiform abnormalities in cognitive impairment. Epilepsy Behav 2006; 8: 504–15. [PubMed: 16540376]

Horak PC, Meisenhelter S, Song Y, et al. Interictal epileptiform discharges impair word recall in multiple brain areas. Epilepsia 2017; 58: 373–80. [PubMed: 27935031]

Jacinto LR, Reis JS, Dias NS, Cerqueira JJ, Correia JH, Sousa N. Stress affects theta activity in limbic networks and impairs novelty-induced exploration and familiarization. Front Behav Neurosci 2013; 7: 127. [PubMed: 24137113]

Khan S, Gramfort A, Shetty NR, et al. Local and long-range functional connectivity is reduced in concert in autism spectrum disorders. Proc Natl Acad Sci USA 2013; 110: 3107–12. [PubMed: 23319621]

Kleen JK, Scott RC, Holmes GL, Lenck-Santini PP. Hippocampal interictal spikes disrupt cognition in rats. Ann Neurol 2010; 67: 250–7. [PubMed: 20225290]

Koop JI, Fastenau PS, Dunn DW, Austin JK. Neuropsychological correlates of electroencephalograms in children with epilepsy. Epilepsy Res 2005; 64: 49–62. [PubMed: 15847849]

Krauss GL, Summerfield M, Brandt J, Breiter S, Ruchkin D. Mesial temporal spikes interfere with working memory. Neurology 1997; 49: 975–80. [PubMed: 9339676]

Mathewson KJ, Jetha MK, Drmic IE, Bryson SE, Goldberg JO, Schmidt LA. Regional EEG alpha power, coherence, and behavioral symptomatology in autism spectrum disorder. Clin Neurophysiol 2012; 123: 1798–809. [PubMed: 22405935]

Mocks J, Gasser T. How to select epochs of the EEG at rest for quantitative analysis. Electroencephalogr Clin Neurophysiol 1984; 58: 89–92. [PubMed: 6203708]

Nair A, Keown CL, Datko M, Shih P, Keehn B, Muller RA. Impact of methodological variables on functional connectivity findings in autism spectrum disorders. Hum Brain Mapp 2014; 35: 4035–48. [PubMed: 24452854]

Nickels K, Wirrell E. Electrical status epilepticus in sleep. Semin Pediatr Neurol 2008; 15: 50–60. [PubMed: 18555191]

Nielsen T, Abel A, Lorrain D, Montplaisir J. Interhemispheric EEG coherence during sleep and wakefulness in left- and right-handed subjects. Brain Cogn 1990; 14: 113–25. [PubMed: 2223041]

Oliveira JF, Dias NS, Correia M, et al. Chronic stress disrupts neural coherence between cortico-limbic structures. Front Neural Circuits 2013; 7: 10. [PubMed: 23390414]

Patry G, Lyagoubi S, Tassinari CA. Subclinical “electrical status epilepticus” induced by sleep in children. Arch Neurol 1971; 24: 242–52. [PubMed: 5101616]

Sanchez Fernandez I, Loddenkemper T, Peters JM, Kothare SV. Electrical status epilepticus in sleep: clinical presentation and pathophysiology. Pediatr Neurol 2012; 47: 390–410. [PubMed: 23127259]

Sanchez Fernandez I, Chapman KE, Peters JM, Harini C, Rotenberg A, Loddenkemper T. Continuous spikes and waves during sleep: electroclinical presentation and suggestions for management. Epilepsy Res Treat 2013; 2013: 583531. [PubMed: 23991336]

Sanchez Fernandez I, Chapman K, Peters JM, et al. Treatment for continuous spikes and waves during sleep (CSWS): survey on treatment choices in North America. Epilepsia 2014; 55: 1099–108. [PubMed: 24917485]

Scheltens-de Boer M Guidelines for EEG in encephalopathy related to ESES/CSWS in children. Epilepsia 2009; 50: 13–7. [PubMed: 19682043]

Shewmon DA, Erwin RJ. Transient impairment of visual perception induced by single interictal occipital spikes. J Clin Exp Neuropsychol 1989; 1: 675–91.

Sigurdsson T, Stark KL, Karayiorgou M, Gogos JA, Gordon JA. Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. Nature 2010; 464: 763–7. [PubMed: 20360742]

Singhal NS, Sullivan JE. Continuous spike-wave during slow wave sleep and related conditions. ISRN Neurol 2014; 2014: 619079. [PubMed: 24634784]

Srinivasan R, Winter WR, Ding J, Nunez PL. EEG and MEG coherence: measures of functional connectivity at distinct spatial scales of neocortical dynamics. J Neurosci Methods 2007; 166: 41–52. [PubMed: 17698205]

Supekar K, Uddin LQ, Khouzam A, et al. Brain hyperconnectivity in children with autism and its links to social deficits. Cell Rep 2013; 5: 738–47. [PubMed: 24210821]

Tassinari CA, Rubboli G, Volpi L, et al. Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. Clin Neurophysiol 2000; 111: S94–102. [PubMed: 10996561]

Thatcher RW. Coherence, phase differences, phase shift, and phase lock in EEG/ERP analyses. Dev Neuropsychol 2012; 37: 476–96. [PubMed: 22889341]

Thatcher RW, Walker RA, Giudice S. Human cerebral hemispheres develop at different rates and ages. Science 1987; 236: 1110–3. [PubMed: 3576224]

Thatcher RW, North D, Biver C. EEG and intelligence: relations between EEG coherence, EEG phase delay and power. Clin Neurophysiol 2005; 116: 2129–41. [PubMed: 16043403]

Thatcher RW, Krause PJ, Hrybyk M. Cortico-cortical associations and EEG coherence: a two-compartmental model. Electroencephalogr Clin Neurophysiol 2012; 64: 123–43.

Tucker DM, Roth DL, Bair TB. Functional connections among cortical regions: topography of EEG coherence. Electroencephalogr Clin Neurophysiol 1986; 63: 242–50. [PubMed: 2419082]

Ung H, Cazares C, Nanivadekar A, et al. Interictal epileptiform activity outside the seizure onset zone impacts cognition. Brain 2017; 140: 2157–68. [PubMed: 28666338]

Van den Munckhof B, Van D, Sagi L, et al. Treatment of electrical status epilepticus in sleep: a pooled analysis of 575 cases. Epilepsia 2015; 56: 1738–46. [PubMed: 26337159]

Varela F, Lachaux JP, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci 2001; 2: 229–39. [PubMed: 11283746]

Voytek B, Knight RT. Dynamic network communication as a unifying neural basis for cognition, development, aging, and disease. Biol Psychiatry 2015; 77: 1089–97. [PubMed: 26005114]

Whedon M, Perry NB, Calkins SD, Bell MA. Changes in frontal EEG coherence across infancy predict cognitive abilities at age 3: the mediating role of attentional control. Dev Psychol 2016; 52: 1341–52. [PubMed: 27441486]

Zhou JL, Lenck-Santini PP, Zhao Q, Holmes GL. Effect of interictal spikes on single-cell firing patterns in the hippocampus. Epilepsia 2007; 48: 720–31. [PubMed: 17284294]

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

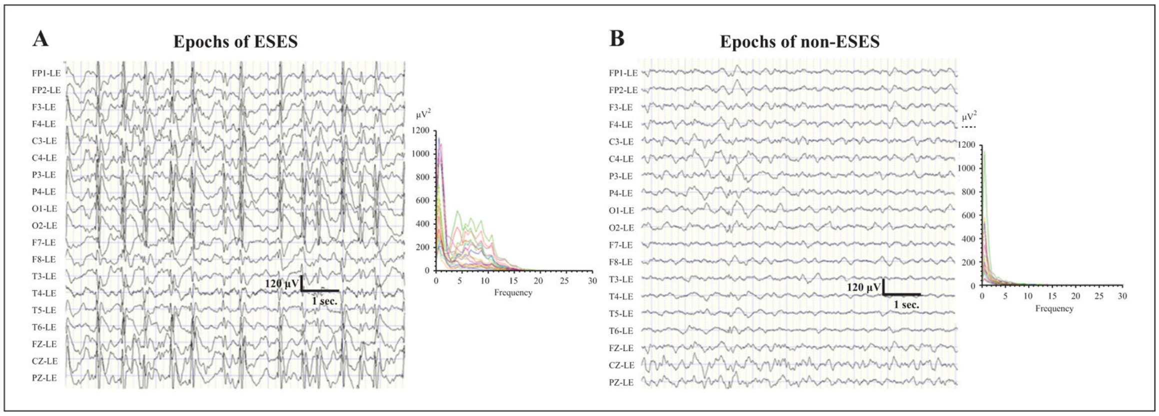

Figure 2.

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.

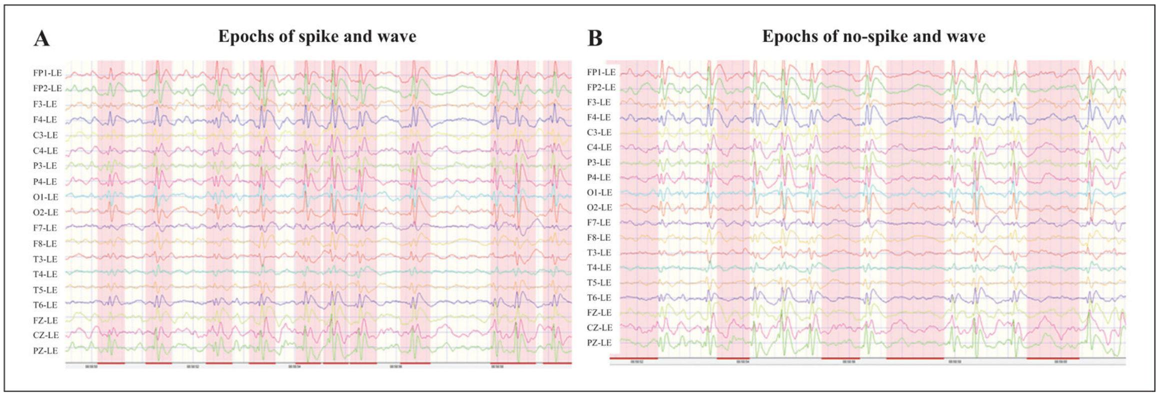

Figure 3.
Epochs of EEG used for coherence measurement. (A) Calculation of coherence measure during spike and waves and polyspikes and waves. (B) Epochs of EEG without spikes measured for coherence. Shaded areas in pink are incorporated into the coherence measures.

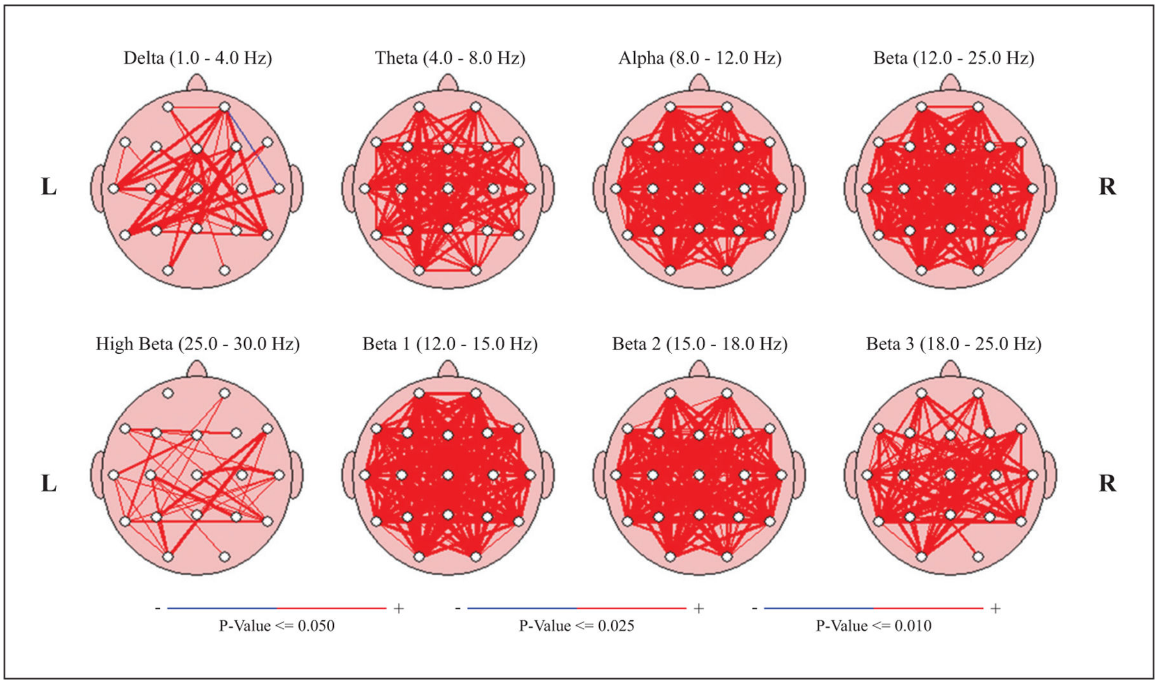

Figure 4.

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.

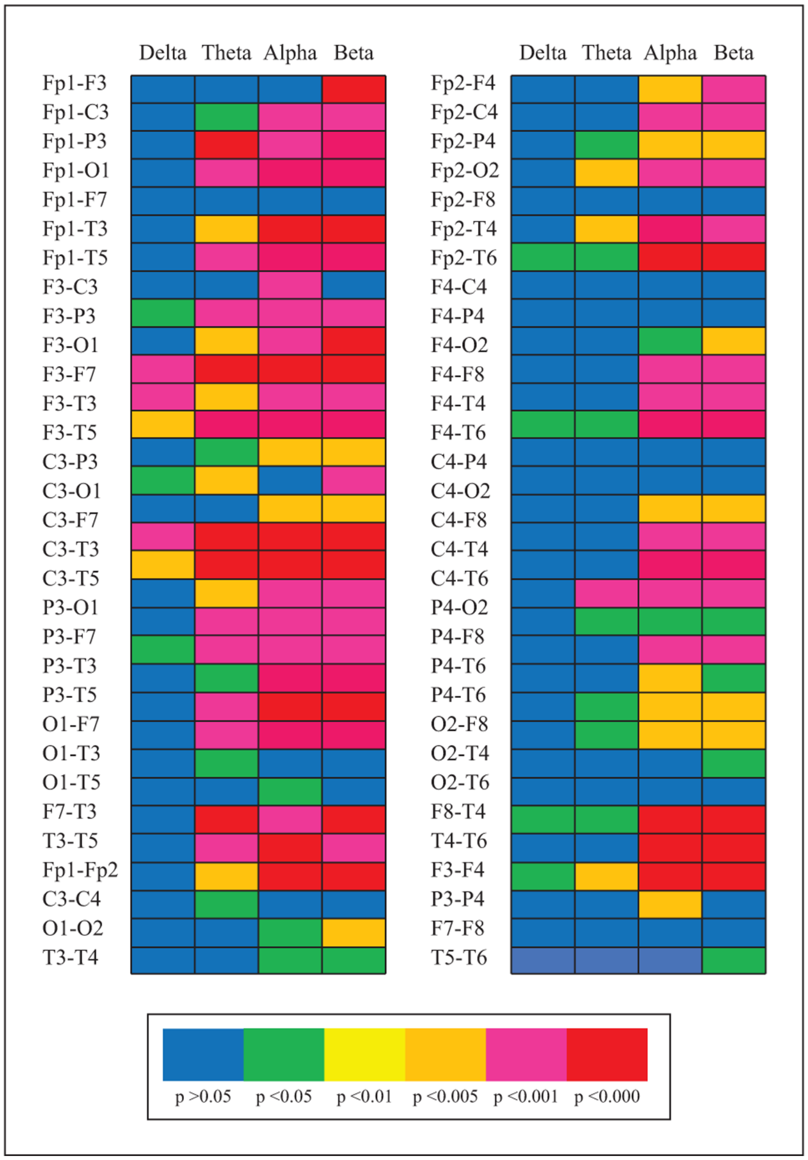

Figure 5.

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

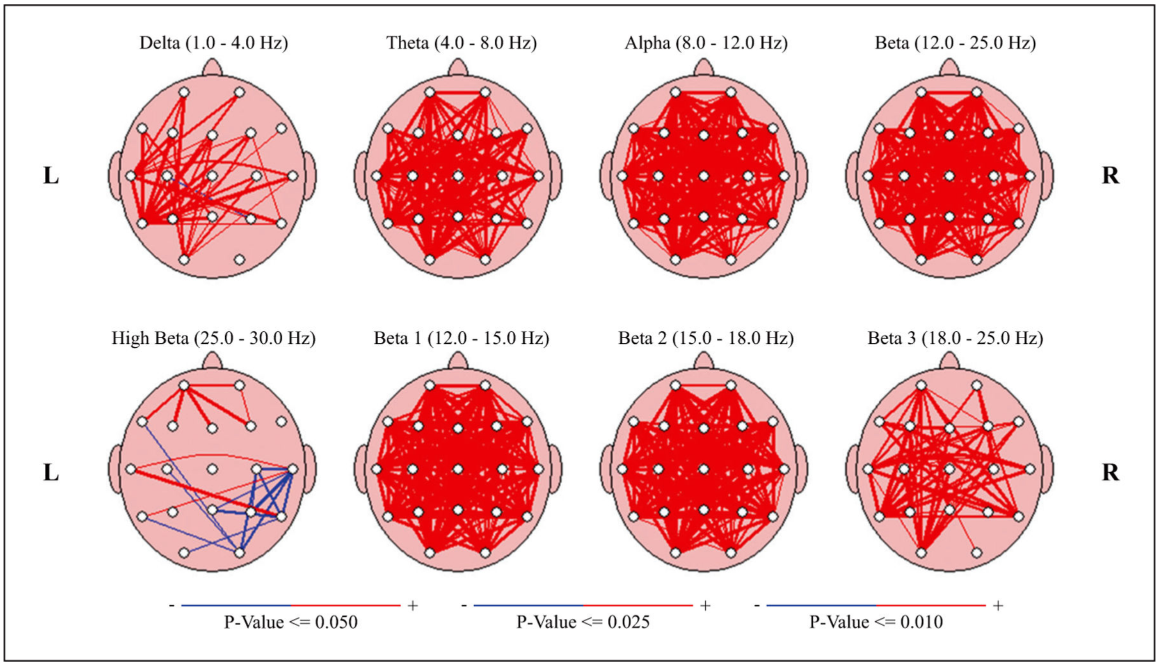

Figure 6.

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.

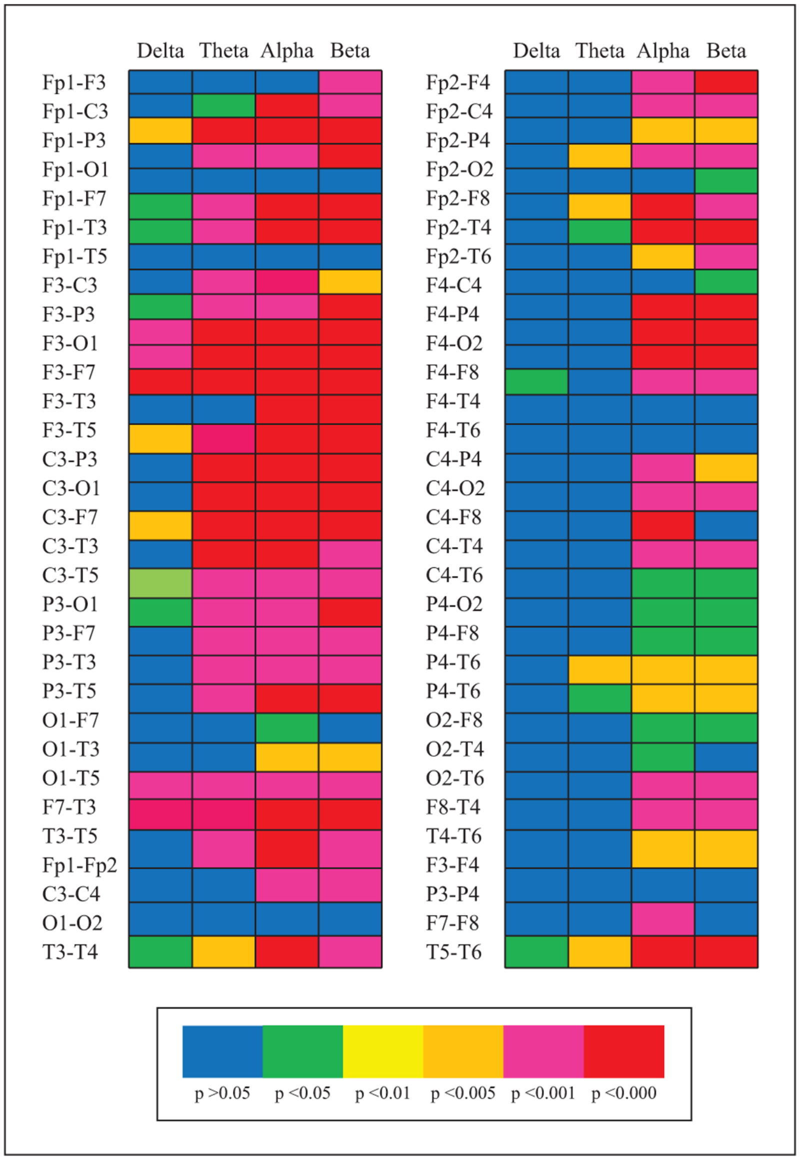

Figure 7.

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.

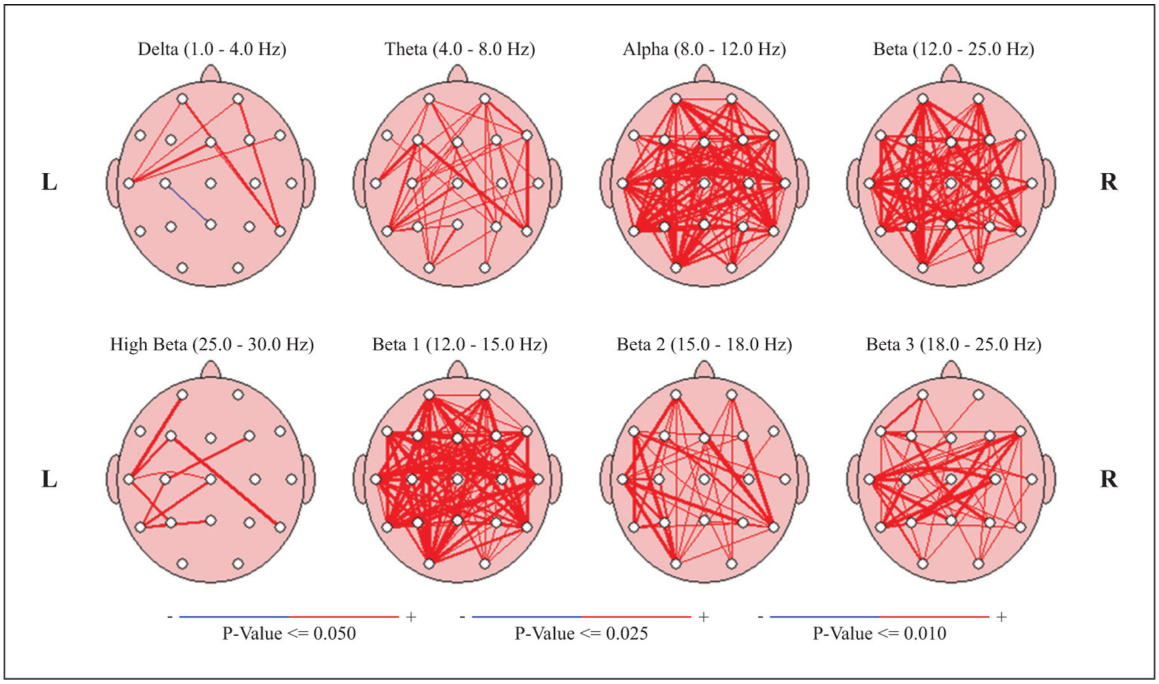

Figure 8.

Coherence during spikes and inter-spike intervals in children with ESES. Increases in coherence were seen at most electrode pairs during ESES segments with spikes compared to the inter-spike interval. Red lines indicate that the spike segments had higher coherences than during the inter-spike 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.

	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 **

* *p* value of comparison with periods of ESES,

** *p* value comparing ESES-spikes and ESES-no spikes.