Original article

Epileptic Disord 2019; 21 (6): 567-78

Benign Rolandic epilepsy: widespread increases in connectivity in a focal epilepsy syndrome

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Received June 24, 2019; Accepted November 04, 2019

ABSTRACT – *Aim.* Benign Rolandic epilepsy (benign epilepsy with centrotemporal spikes; recently renamed self-limited epilepsy with centrotemporal spikes) is associated with widespread deficits in cognition and behavior, suggesting abnormalities in networks that extend beyond the centrotemporal region. To assess functional connectivity in children with benign Rolandic epilepsy, we assessed EEG spectral power and coherence during awake and sleep records in 27 children with centrotemporal spikes. 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.

Methods. Epochs of EEG with and without centrotemporal spikes were compared during both waking and sleep.

Results. During the spike epochs, there was an increase in spectral power at all frequencies, although statistical significance was seen primarily in the delta, theta and alpha bandwidths. This increase in absolute power was seen at all electrode sites and was similar in left and right-sided electrodes. During centrotemporal spikes, there were significant changes in coherence compared to the EEG segments without spikes. In the theta, alpha and beta bandwidths, there were significant increases in coherence. The increases in coherences were widespread and bilateral, and involved electrode pairs outside the central and temporal regions. To determine if there was a relationship between location of the spikes and coherence values, right-sided, left-sided and bilateral centrotemporal spikes were compared. There was no relationship between location of the centrotemporal spikes and power or coherence values.

Conclusion. These findings indicate that benign Rolandic epilepsy results in generalized changes in spectral power and connectivity and raises the suggestion that from a functional standpoint, benign Rolandic epilepsy resembles a generalized rather than focal seizure disorder.

Key words: coherence, oscillations, power, BECTS, centrotemporal spikes, self-limited epilepsy with centrotemporal spikes

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doi:10.1684/epd.2019.1111

Benign Rolandic epilepsy (BRE), recently renamed self-limited epilepsy with centrotemporal spikes and also known as benign epilepsy with centro-temporal spikes (BECTS) is an idiopathic localization-related (*i.e.* focal) electroclinical syndrome that has an annual incidence of approximately 21 per 100,000 in children younger than 15 years of age and constitutes approximately 8-25% of all childhood epilepsies (Heijbel *et al.*, 1975). This common childhood epileptic syndrome is characterized by focal seizures with a seizure semiology consisting of unilateral facial sensorimotor symptoms, oropharyngolaryngeal symptoms, speech arrest, and hypersalivation (Beaussart, 1972; Loiseau and Beaussart, 1973; Beaussart and Faou, 1978; Holmes, 1992, 1993, 2000). During sleep, the seizures are often convulsive in type. From the published ictal recordings, it can be inferred that at least the majority of the generalized tonic-clonic seizures follow Rolandic activation and are therefore secondary generalized tonic-clonic seizures (Dalla Bernardina and Tassinari, 1975; Clemens, 2002; Panayiotopoulos *et al.*, 2008; Tedrus *et al.*, 2009).

The EEG features of BRE consist of centrotemporal spikes (CTS), focal, high-amplitude (usually > than 150 μV) central or mid-temporal surface negative spike or sharp waves of ~ 70-80 milliseconds with a following slow wave (*figure 1*) (Kellaway, 2000). CTS can be unilateral or bilateral and are exacerbated by drowsiness and sleep (Holmes, 1992, 1993) (*figure 2*). EEG and magnetoencephalography (MEG) studies show a tangential dipole in the Rolandic region with maximum negativity in the centrotemporal region and positivity in the frontal regions (Gregory and Wong, 1992; Yoshinaga *et al.*, 1992) (*figure 3*). Spikes may often exist in central, parietal, midline or even occipital regions which does not preclude a diagnosis of BRE. CTS may occur only in non-rapid eye movement (NREM) sleep and be absent during the awake and REM states (Kellaway, 1985, 2000). If spikes are present while awake, they are usually greatly increased in number and rate in drowsiness and stage N2 of sleep (Kellaway, 1985).

While the seizure semiology and interictal and ictal EEGs are indicative of a focal onset, there are many features of BRE that suggest the seizures are more akin to primary generalized epilepsy. During sleep, patients with BRE often have bilateral, often synchronous spike and wave discharges (Holmes, 1992). There is a strong correlation between CTS and sleep spindles, a generalized physiological paroxysmal pattern during N2 sleep (Nobili *et al.*, 1999). EEGs with CTS can be "converted" to generalized spike and wave activity when given medications such as carbamazepine (Genton, 2000; Dimova and Daskalov, 2002; Berroya *et al.*, 2004). In addition, generalized spike-wave discharges and CTS may occur in the same patients (Dimova and Daskalov, 2002; Datta *et al.*, 2019) (*figure 4*).

Although strongly different in terms of their electroclinical characteristics and pathophysiology, BRE and primary generalized epilepsies, such as childhood absence seizures, have some common features such as a marked genetic predisposition, a similar age at onset, a normal neurodevelopmental profile, a normal EEG background activity, normal neuroimaging findings, and an overall good prognosis. Some authors have speculated about a possible clinical crossover between these childhood epilepsies (de Melo and Niedermeyer, 1991; Gambardella *et al.*, 1996; Ramelli *et al.*, 1998; Verrotti *et al.*, 2017a, 2017b).

In addition, children with BRE are at risk of several behavioral and neuropsychological co-morbidities that cannot be explained by focal pathology (Kavros *et al.*, 2008; Smith *et al.*, 2015). For example, about two

Figure 1. Example of typical CTS in the left central/temporal region.

Figure 2. Bilateral CTS during drowsiness.

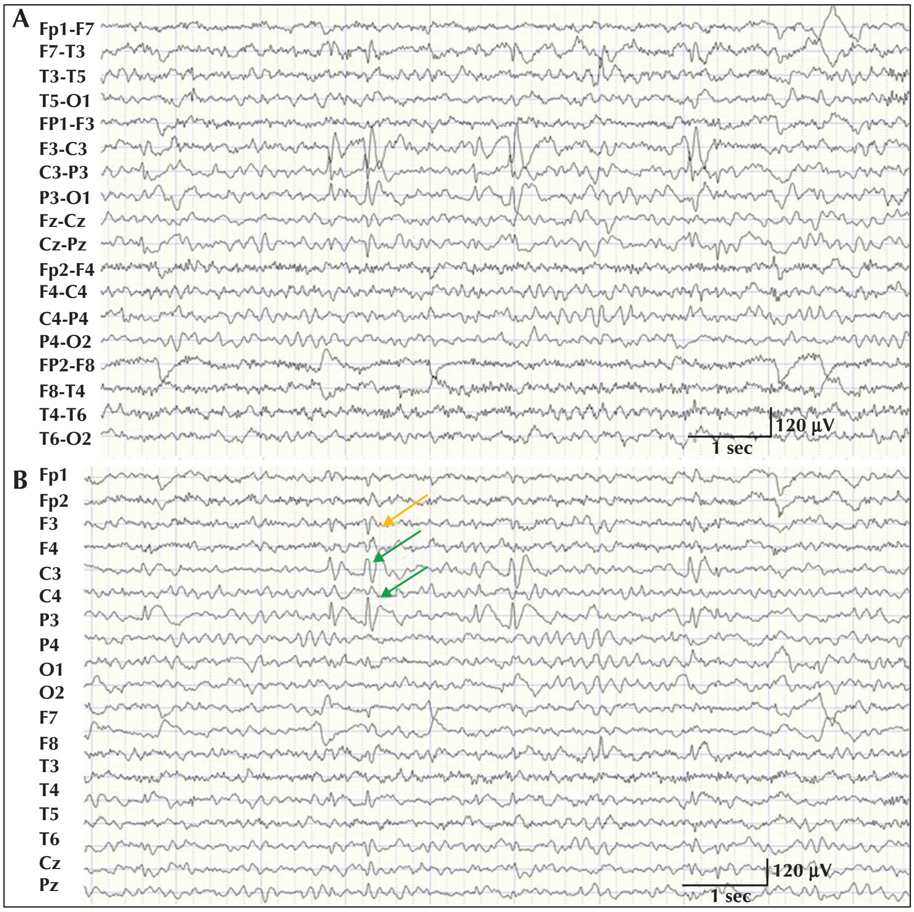

Figure 3. Example of tangential dipole in CTS. (A) Bipolar longitudinal montage showing phase reversal at C3. (B) The same EEG trace as in (A) using average reference montage. Note the surface negative spike at C3 and P3 (green arrows) and simultaneous surface positive spike at F3 (orange arrow). The negative field at C3/P3 and positive field at F3 constitutes a tangential dipole.

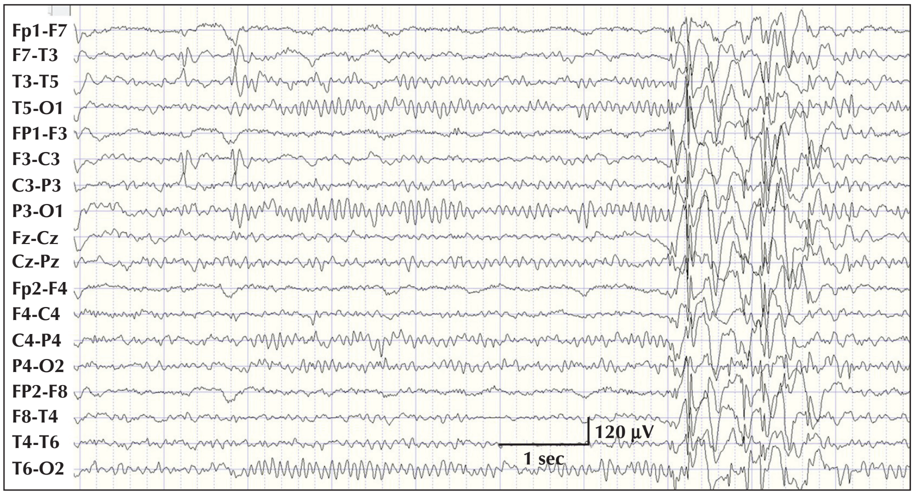

Figure 4. Example of EEG with left CTS and generalized discharges.

thirds of children with BRE have attention impairments and approximately a half have language impairments or reading disabilities, or both (Kavros *et al.*, 2008; Smith *et al.*, 2012, 2015; Vega *et al.*, 2015).

To address the question of whether CTS are like generalized discharges regarding their pathological activation of neural structures, we assessed coherence of CTS in children with BRE. 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 is a measure of the functional association between two brain regions (Thatcher *et al.*, 1986; 2008). High coherence values are taken as a measure of strong connectivity between the brain regions that produce the EEG signals (Srinivasan *et al.*, 2007). Like many biological processes, there is likely a "sweet spot" for coherences in that both low and high coherences could be associated with cognitive dysfunction (Kleen *et al.*, 2011; Holmes *et al.*, 2015).

Here we report that coherences during CTS are quite high compared to non-CTS epochs. Remarkably, the increases in coherences were widespread and involved brain regions outside the area of the CTS, raising the idea that BRE from a functional standpoint is more like generalized than focal epilepsy.

Methods

Study design and participants

To assess functional connectivity in children with CTS, we reviewed the electronic medical record for EEG reports from the last five years using the key words "benign Rolandic epilepsy", "BRE", "centrotemporal spikes", "benign epilepsy with centrotemporal spikes" and "BECTS". The study was approved by the University of Vermont Institutional Review Board. A total of 46 records were reviewed and 27 showed CTS that were judged technically adequate for study. Of the 27 children (11 girls and 16 boys with a median age of eight years [range: 2-18 years]), 25 (92.6%) had an awake recording and 24 (88.9%) had recording of drowsiness/N2 sleep.

The 10-20 system of electrode placement was used and the Pz electrode served as the reference. All EEG analyses used the linked-ear montage. Epochs of CTS including the spike and following slow wave were marked and averaged over 60 seconds when possible (*figure 5*). In a few cases, the record was of insufficient duration to record 60-second epochs of CTS. In those cases, a minimum of 20 seconds of EEG with CTS was required. For each recording epoch, an identical duration of time without CTS was analyzed. This was done for both the awake state and during drowsiness/N2 sleep. Twenty seconds 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 used for split-half reliability but is 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.

Figure 5. Example of how CTS were quantified. Pink shaded areas included the spike and following slow wave. Equal duration events without spikes were randomly selected for comparison.

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. The sliding window of the 256-point FFT cross-spectral matrix was computed advancing in 64-point steps (75% overlap) the edited epochs. FFT absolute and relative power for each of the 19 electrodes comprised 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), high (↑) β (25-30 Hz), β1 (12-15 Hz), β2 (15-18 Hz), β3 (18-25 Hz), γ (30-40 Hz), high (↑) γ (40-50 Hz), γ1 (30-35 Hz), and γ2 (35-40 Hz). FFT coherences for each of the 171 electrode pairs was obtained with both intra-hemispheric and inter-hemispheric pair-wise combinations of electrodes evaluated.

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, where there is no consistency between phases of two EEG signals, to 1, where there is perfect alignment of phase.

Coherence was defined as:

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

Where $G_{xy}(f)$ is the cross-power spectral density (the power distribution of EEG series in the frequency domain) and G*xx*(f) and G*yy*(f) are the respective autopower spectral densities. FFT coherence for each electrode pair was obtained. Intra-hemispheric and inter-hemispheric pair-wise combinations of electrodes were evaluated. The method used to calculate coherence has been reported in other studies (Mott *et al*., 2019; Burroughs *et al*., 2014; Buckley *et al*., 2015).

Volume conduction contributes to coherence (Thatcher et al., 2008; Thatcher, 2008, 2012a). The cross-spectrum is the sum of the in-phase potentials (*i.e.* cospectrum) and out-of-phase potentials (*i.e.* quadspectrum). The in-phase component (instantaneous coherence) contains volume conduction and the synchronous activation of local neural generators. The out-of-phase component (lagged coherence) contains the network or connectivity contributions from locations distant to a given source. Since the same method was used for the epochs with and without CTS, volume conduction would have been factored in epochs with and without CTS.

Statistical analysis

The paired-t test was used to compare averaged EEG measures across epochs in EEGs with and without CTS. Changes in absolute spectral power and coherences were calculated across the awake and sleep states for each of the 27 children. A false detection rate was assessed using the Holm-Sidak test with an alpha of 0.05 and all *p* values reported were adjusted for false detection. Data are presented as mean ± standard error of the mean. 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;

Table 1. Location of CTS.

Location of CTS	Number (Percentage)
L Central	10/27 (37%)
R Central	7/27 (25.9%)
L Mid-temporal	3/27 (11/1%)
R Mid-temporal	1/27 (3.7%)
Bi-central	6/27 (18.5%)
Bi-mid-temporal	0

– and p value heat maps with degree of significance in selected electrode pairs, color-coded from all 171 electrode pairs. Although data was reviewed from 171 electrode pairs, selected electrodes were chosen for illustration.

Results

All of the records had a sufficient number of CTS to record a minimum of 20 seconds of CTS and non-CTS epochs. The location of the spikes is shown in *table 1*. A tangential dipole was found in 25/27 (92.6%). Two children had CTS and generalized spike-wave activity. During the CTS, there was an increase in spectral power at all frequencies (*figure 6*) although statistical significance was seen primarily in the Δ, Φ, and α bandwidths (*figure 7*). This increase in absolute power was seen at all electrode sites and was similar in left and right-sided electrodes. When relative power was assessed, there was a decrease in Δ and γ frequencies while increases were seen in the Θ and α bandwidths (*figure 8*).

During CTS, there were significant changes in coherence compared to the EEG segments without spikes (*figures 9-11*). *Figure 9* shows p values for selected electrode pairs and *figures 10 and 11* shows a heatmap of p values for all 171 electrode pairs in both hemispheres.

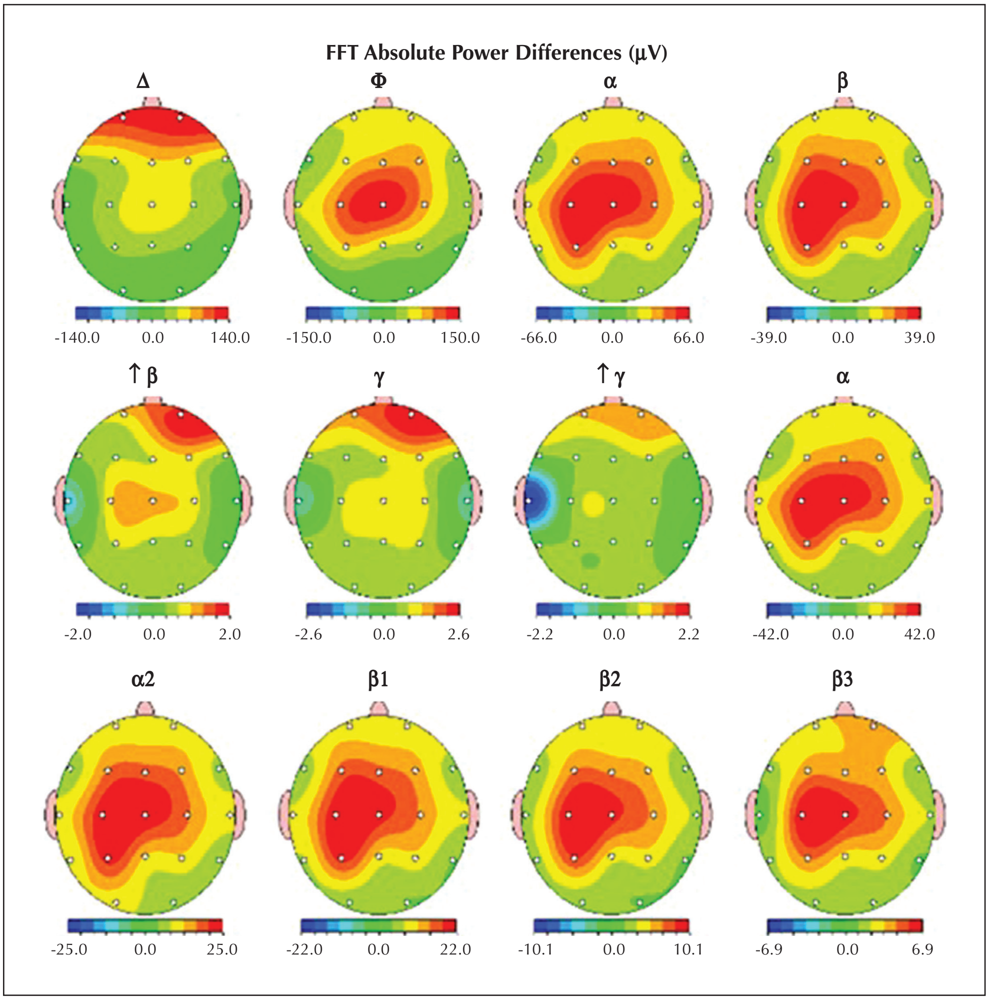

Figure 6. FFT absolute power differences in μV at various bandwidths during epochs of CTS versus non-CTS epochs.

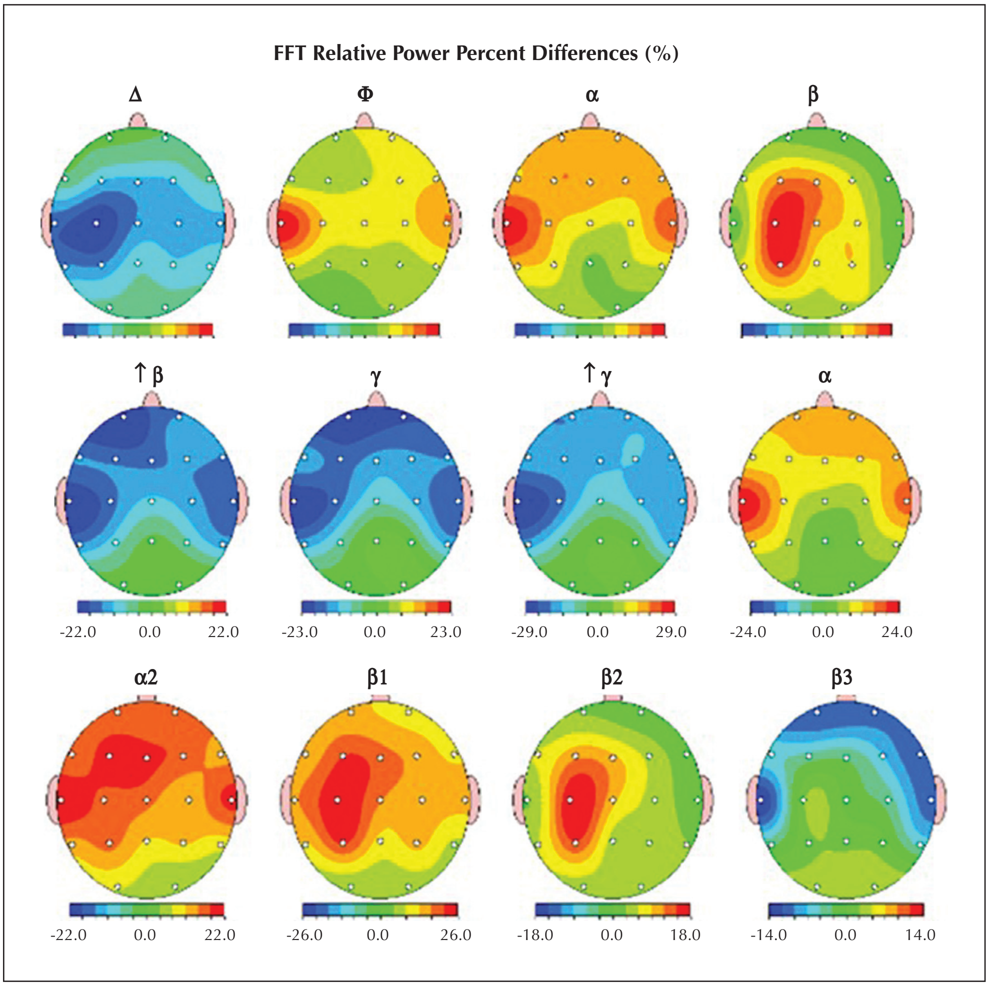

Figure 7. FFT relative power percent differences (%) during epochs of CTS versus non-CTS epochs.

In the Δ bandwidth, coherences were decreased during the CTS (*figure 9*), although with the corrected *p* values for false detection, few electrode pairs differed significantly. In the Θ, α and β bandwidths, significant increases in coherence were noted. The increases in coherences were widespread and bilateral, and involved electrode pairs outside the central and temporal regions. To determine if there was a relationship between location of the spikes and coherence values, right-sided, left-sided and bilateral CTS were compared. There was no relationship between location of the CTS and coherence values (data not shown).

Discussion

The major finding in this analysis is that EEGs from children with CTS have marked increases in coherence during spikes compared to periods without CTS both during the awake and sleep states. These marked increases in coherences involved multiple frequencies and extended beyond the centrotemporal region. In addition, widespread changes in power were also seen during the CTS.

CTS are transitory events of a synchronous discharge of neurons, producing high power and wideband frequencies with a succession of action potentials (*figure 1*) (Prince and Connors, 1986; de Curtis and Avanzini, 2001). The hallmark of this synchronous discharge of neurons in the epileptic focus is the paroxysmal depolarization shift (PDS) which is a large and sustained depolarization of the neuron (Matsumoto and Ajmone-Marsan, 1964; Ayala *et al.*, 1973). During a PDS, the cell membrane near the soma undergoes a high-voltage (approximately 10 to 15 mV) and long (100 to 200 mseconds) depolarization and has the effect of generating a train of action potentials that are conducted away from the soma along the axon of the neuron. The PDS is followed by a large hyperpolarization which serves to limit the duration of interictal paroxysms. Time-frequency analysis reveals large high-frequency (80-500 Hz) power changes associated with

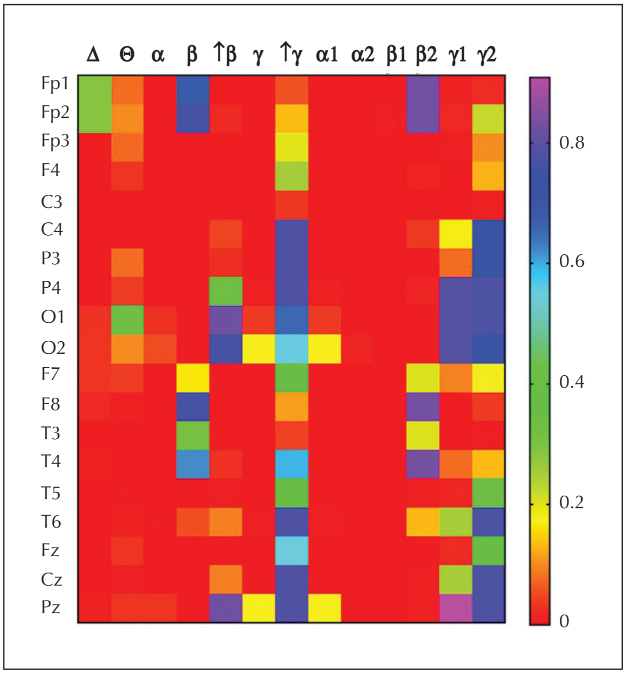

Figure 8. Heat map of *p* value significance corrected for false detection rate for power at each electrode during CTS and during comparable periods without CTS.

IIS (Kobayashi *et al.*, 2009; Jacobs *et al.*, 2016). During the slow wave of the spike and wave complex, there is a decrease in high frequency oscillations (>100 Hz) (Urrestarazu *et al.*, 2006; Kobayashi *et al.*, 2009).

CTS were associated with widespread increases in power in all brain regions compared to comparable periods without spikes (Adebimpe *et al.*, 2015).

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, 2012b) and high coherence values indicative of strong connectivity between brain regions that generative the EEG activity (Srinivasan *et al.*, 2007). Decreased coherences in neural circuits have been associated with cognitive and behavioral abnormalities, including rodent models of stress (Jacinto *et al.*, 2013; Oliveira *et al.*, 2013) and schizophrenia (Sigurdsson *et al.*, 2010) and human 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).

There is now considerable evidence that the CTS, independent of seizures, plays a role in cognitive comorbidities in BRE. Patients with incidental CTS may experience epilepsy comorbidities, despite not having seizures (Danielsson and Petermann, 2009). There is a correlation between number of CTS and cognitive function. Yan *et al.* (2017) found that children

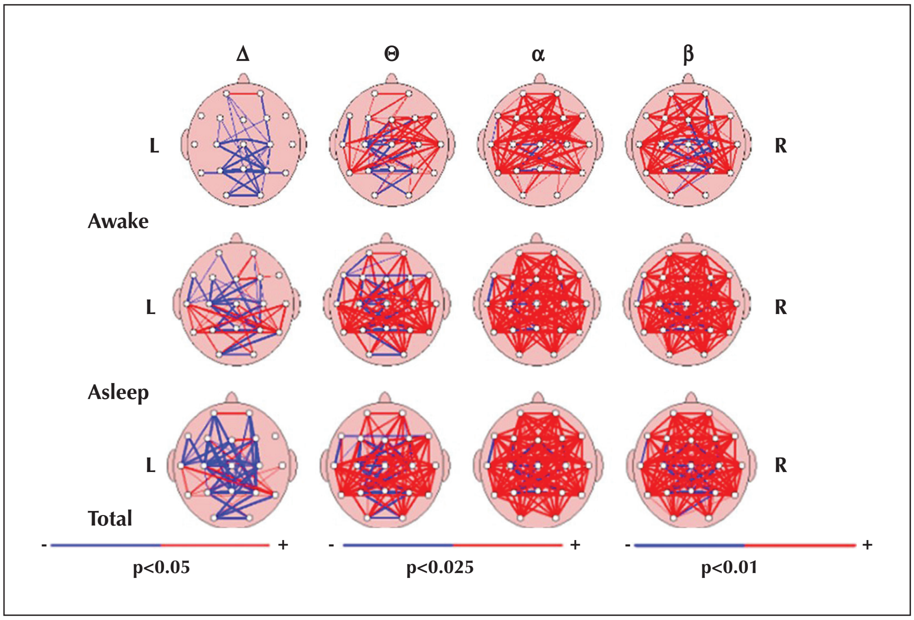

Figure 9. Coherences between selected electrode pairs during and between CTS during the awake and sleep states along with the combined data. Blue lines indicate *p* values that show significantly reduced coherence during CTS than between CTS while red lines indicate increased coherences. The significance of the *p* value is reflected by the thickness of the lines.

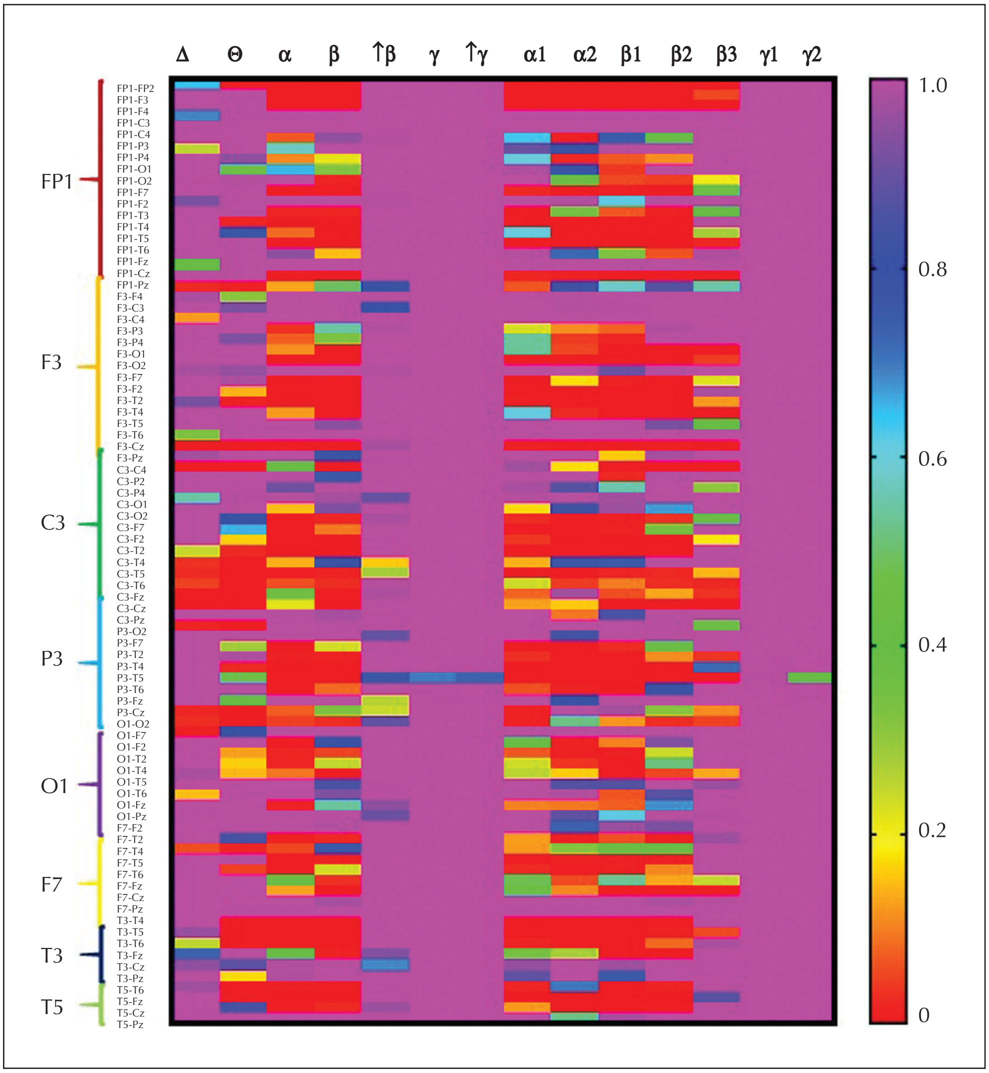

Figure 10. Heat map of coherence values across frequencies and electrode pairs after false detection rate for left hemisphere.

with a high spike-wave index had lower full intelligence quotient (FIQ), verbal intelligence quotient (VIQ), and performance intelligence quotient (PIQ) than children with a lower spike-wave index and there was a negative correlation between the FIQ, VIQ, PIQ, and spike-wave index that was not related to age, age at onset, disease course, years of education, and total number of seizures. Finally, supporting this idea is a distinct relationship between CTS and neuropsychological performance, with children having better neuropsychological performance following CTS remission (Baglietto *et al.*, 2001).

It is tempting to speculate that tangential dipole frequently seen in CTS in children with BRE may have a role in the excessive connectivity between disperse neuronal ensembles. In this study, most children had a tangential dipole identified and we therefore could not compare power spectra and coherence data in children with and without dipoles. Future studies will need to incorporate similar quantitative measures of other types of interictal spikes in children.

Although this study dealt solely with CTS in BRE, there is evidence from both functional MRI and EEG studies that other types of interictal spikes result in changes in connectivity that are not spatially restricted to the epileptogenic focus. For example, interictal spikes in patients with temporal lobe epilepsy involve other brain regions, most notably the contralateral temporal lobe, frontal lobe and other extratemporal regions (Mankinen *et al.*, 2012; Coito *et al.*, 2015; Burianova *et al.*, 2017; Tong *et al.*, 2019). However, compared to CTS, temporal lobe spikes predominately effect function ipsilateral to the spikes. Likewise, the neuropsychological profile of patients with temporal lobe epilepsy

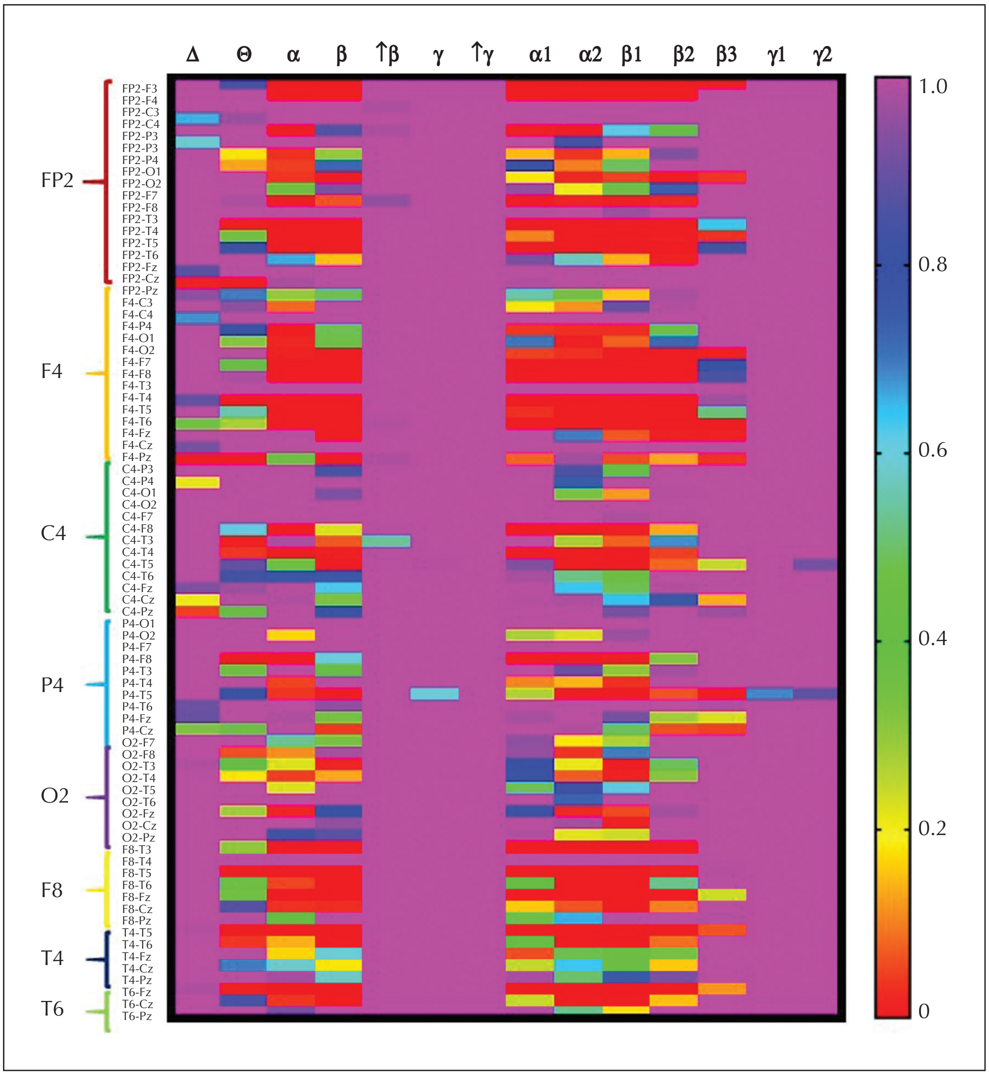

Figure 11. Heat map of coherence values across frequencies and electrode pairs after false detection rate for right hemisphere.

is usually specific to the function of the region from which the interictal spikes are generated. Patients with interictal spikes in the language-dominant temporal lobe often have difficulties with language and verbal memory deficits, whereas interictal spikes in the non-dominant hemisphere are associated with impaired spatial memory (Bell *et al.*, 2011; Allone *et al.*, 2017). The cognitive deficits in temporal lobe epilepsy appear to be more modality-specific and limited compared to the widespread deficits seen in children with BRE.

Extrapolating information from interictal EEG abnormalities in BRE to behavior and cognitive difficulties is clearly speculative. However, it is plausible that the highly coherent network activity during CTS may have a causative role in the widespread behavior and cognitive deficits seen in this disorder. An intermittent diffuse hyper-excitable network in BRE would be consistent with the broad nature of the cognitive and behavioral abnormalities seen in children with this syndrome. While it is difficult to see how brief periods of increased coherence during CTS could lead to behavioral and cognitive disorders, the finding that these deficits resolve following the resolution of CTS suggests that momentary disruption can have pronounced effects on brain function. ☐

Disclosures.

None of the authors have any conflict of interest to declare.

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