EEG resting state analysis of cortical sources in patients with benign epilepsy with centrotemporal spikes

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ABSTRACT
Benign epilepsy with centrotemporal spikes (BECTS) is the most common idiopathic childhood epilepsy, which is often associated with developmental disorders in children. In the present study, we analyzed resting state EEG spectral changes in the sensor and source spaces in eight BECTS patients compared with nine age-matched controls. Using high-resolution scalp EEG data, we assessed statistical differences in spatial distributions of EEG power spectra and cortical sources of resting state EEG rhythms in five frequency bands: δ (0.5–3.5 Hz), θ (4–8 Hz), α (8.5–13 Hz), β1 (13.5–20 Hz) and β2 (20.5–30 Hz) under the eyes-closed resting state condition. To further investigate the impact of centrotemporal spikes on EEG spectra, we split the EEG data of the patient group into EEG portions with and without spikes. Source localization demonstrated the homogeneity of our population of BECTS patients with a common epileptic zone over the right centrotemporal region. Significant differences in terms of both spectral power and cortical source densities were observed between controls and patients. Patients were characterized by significantly increased relative power in δ, α, β1 and β2 bands in the right centrotemporal areas over the spike zone and in the right temporal-parieto-occipital junction. Furthermore, the relative power in all bands significantly decreased in the bilateral frontal and parieto-occipital areas of patients regardless of the presence or absence of spikes in EEG segments. However, the spectral differences between patients and controls were more pronounced in the presence of spikes. This observation emphasized the impact of benign epilepsy on cortical source power, especially in the right centrotemporal regions. Spectral changes in bilateral frontal and parieto-occipital areas may also suggest alterations in the default mode network in BECTS patients.

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1. Introduction

Benign epilepsy, also known as Rolandic epilepsy, is the most common idiopathic childhood epilepsy with a prevalence of approximately 15% in children aged 1–15 years (Panayiotopoulos et al., 2008). Rolandic epilepsy is characterized by seizures that typically originate in the centrotemporal area with frequent sensory-motor symptoms and autonomic manifestations in the face, mouth and throat (Loiseau and Beaussart, 1973). The majority of Rolandic seizures occur during non-REM sleep, at sleep onset or rest (Camfield et al., 2014; Panayiotopoulos et al., 2008; Shields and Sneed, 2009). As the hallmark of benign childhood epilepsy, seizures are mostly associated with centrotemporal spikes (CTS) often followed by slow waves, which are typically activated by drowsiness and slow (non-REM) sleep (Blom and Brorson, 1966; Clemens and Majaros, 1987; Smith and Kellaway, 1964). Dipole source localization in patients with BECTS has demonstrated that CTS can be reliably modeled by single tangential dipole sources oriented from central to frontal lobes and localized in the high and low central regions (suprasylvian) (Gregory and Wong, 1992; Jung et al., 2003; Legarda et al., 1994; Panayiotopoulos, 1999b; Tsai and Hung, 1998). Despite the focality of CTS and Rolandic seizures in patients with benign epilepsy, there is growing evidence from neuroimaging studies reporting memory, language, attention, auditory and cognitive impairments in BECTS patients that BECTS may functionally and structurally affect a larger portion of the brain at rest (Bocquillon et al., 2009; Cataldi et al., 2013; Lopes et al., 2014; Northcott et al., 2007; Verrotti et al., 2014).

The present study attempted to investigate changes in the spectral power and spatial distribution of cortical sources of eyes-closed resting state EEG rhythms in patients with BECTS compared to healthy subjects under two conditions, in the presence and absence of CTS.

2. Methods

2.1. Subjects

Twenty-one children (9.84 ± 1.75 years) with BECTS and 12 healthy subjects (9.27 ± 1.70 years) used as controls were preselected for resting state analysis. The study was conducted at Amiens University...
the EEG recordings were then segmented into non-overlapping 2-s epochs. The EEG portions that exceeded a prede-
2.4. EEG source distribution analysis using eLORETA

EEG cortical source analysis was performed by the functional brain imaging method known as eLORETA (exact Low-Resolution Electromagnetic Tomography), which models 3D distributions of EEG cortical sources (Grech et al., 2008; Pascual-Marqui, 2002, 1999) in the frequency domain. This method does not require a priori knowledge of dipole positions and has been successfully used in recent studies on resting state EEG analysis (Babiloni et al., 2010; Li, 2010). eLORETA is a discrete, linear, weighted minimum norm inverse solution and provides better accurate localization of highly correlated point sources with low signal to noise ratio data (Pascual-Marqui, 2007; Pascual-Marqui et al., 2011). We first used eLORETA to localize interictal spike sources for each patient to investigate the spatial extent of spike sources.

3D source localization in the frequency domain was then performed by computing the cross-spectra of EEG segments for each subject. The eLORETA algorithm was used to compute the current density (Intensity of the current/area, measured in A/m²) for each voxel within different frequency bands. The eLORETA solution space was restricted to the cortical gray matter of a realistic head model (MNI152) coregistered to the Talairach brain atlas and digitized at the Montreal Neurologic Institute (MNI) brain imaging center (Mazziotta et al., 2001). The brain compartment included 6239 voxels (5 mm spatial resolution). Before any statistical analysis, the eLORETA solutions were normalized for each voxel at each frequency band as implemented in the eLORETA software (Pascual-Marqui, 2002). The normalization was done by normalizing the eLORETA current density at each voxel to the eLORETA current density averaged across all frequencies (0.5–30 Hz) (Babiloni et al., 2010).

2.5. Statistical analysis of the eLORETA solutions

Statistical comparisons of cortical sources between the two groups were performed on the eLORETA current density of the voxels in all five frequency bands using the statistical nonparametric mapping approach (SnPM) via randomizations (Nichols and Holmes, 2002). The randomization determined the critical threshold values for the observed t-values with correction (p<0.05) for multiple comparisons across all voxels and all frequency bands. A total of 5000 permutations were used to determine the significance level for each test. The log of F-ratios were then color-coded and projected onto the MNI152 MRI and the cortical layer of the realistic head model. The color-coded Topographic Significance Maps (TSMs) represented statistical differences in estimated cortical sources between the groups.

3. Results

For illustrative purposes, we only present STP (sensor space) and TSM (source space) with statistically distinct spatial patterns. The remaining results can be found in Supplementary Materials. The absolute power for all the conditions is shown in Table 2.

3.1. Scalp topographic patterns (STP)

Fig. 3 shows the STPs for controls and patients in the δ, θ and α bands.

Compared to controls, the patient group presented significantly higher relative EEG power values in the θ band (Fig. 3, left STP map) in right centrotemporal and bilateral frontal and parieto-occipital areas under ECNS and ECWS conditions. The θ power increases in all cortical regions were more pronounced when spikes were included in the EEG segments analyzed (ECWS condition). In contrast, the relative α, β1, and β2 powers tended to decrease in homologous areas especially under the ECWS condition (Figs. 3 and S1). Furthermore, relative δ power significantly decreased in right centrotemporal and bilateral frontal areas, but only in the presence of CTS. The results obtained in the sensor space are summarized in Table 2. Table 3 lists the mean and standard deviation of absolute power values for each region, frequency band and condition. As shown, patients displayed increased absolute θ power and decreased absolute α power at the parietal and
Table 2
Observed patterns of changes in relative EEG spectral power in patients compared to controls in the five frequency bands.

| Frequency band | ECNS condition (eyes-closed without spike) | ECWS condition (eyes-closed with spike) |
|----------------|-------------------------------------------|----------------------------------------|
|                | Brain regions exhibiting significant changes in scalp EEG relative power | Brain regions exhibiting significant changes in scalp EEG relative power |
| δ (0-3.5Hz)    | -                                        | LF, RF ↓                               |
| θ (4-8Hz)      | C, RC, RT ↓                              | C, RC, RT ↓                            |
|                | LP, P, RP ↓                              | All cortical regions ↑                 |
| α (8.5-13Hz)   | PF, LF, RF ↓, LT, RC ↓                   | LP, P, RP, O↓                          |
| β₁ (13.5-20Hz) | PF↓                                      | C, RC↓                                 |
|                | LP, P, RP, O↓                            | All cortical regions ↑                 |
| β₂ (20.5-30Hz) | PF↓                                      | PF, LF, F↓, C, RC↓                     |
|                | LC, RP↓                                   | C, RC↓                                 |
|                | LP, P, RP, O↓                            | LP, P, RP, O↓                          |

The significant increase (↑) or decrease (↓) in EEG relative power was identified by statistical comparisons (p < 0.01) between controls and patients. See Fig. 1 for the abbreviations used for brain regions.occipital regions especially under the ECWS conditions in comparison to ECCT.

The group IAF values are shown in Fig. 4. The IAF values of ECCT were significantly higher than those found for both the epileptic conditions in all regions excluding the right frontal region. ECWS showed lower IAF values in comparison to ECWS in almost all cortical regions.

### 3.1.1. Statistical comparisons of EEG cortical sources

To further investigate the impact of BECTS on the cortical sources of resting state EEG rhythms, we computed TSMs in the five frequency bands under the ECCT and ECWS conditions (Figs 5–7, S2–4). Fig. S5 shows the spatial extent of the distributed sources of interictal spikes localized using eLORETA and averaged across all patients. As shown, only the right centro-temporal regions are highly involved in the generation of the spikes.

Compared to controls, patients exhibited increased θ, α and β₂ activity under both conditions in the right centrotemporal regions, which are involved in the generation and propagation of the spikes. However, the spectral power increases of cortical sources were more pronounced in the presence of CTS, and were also observed in β₁ in the right centrotemporal region and its immediately surrounding regions.

In patients, the right temporo-parieto-occipital junction also showed increased θ and α activities under the ECNS condition (Fig. 5). However, the presence of CTS within EEG segments increased power in higher frequencies (β₁ and β₂) in the right temporo-parieto-occipital junction (Fig. S4). Furthermore, in patients, the bilateral temporal poles displayed increased cortical activities in all five-frequency bands under both conditions. To a lesser degree, the left centrotemporal area including the insula also exhibited increased power in all bands.

Compared to controls, patients were characterized by significantly decreased power in all bands in bilateral frontal and occipital lobes, especially in the presence of CTS. Other spurious increases/decreases in the power of various bands were also observed in deeper structures (see supplementary figures).

### 4. Discussion

This study was the first attempt to investigate differences in the topographic distribution of EEG relative and absolute spectral power and EEG cortical sources between healthy control subjects and patients with BECTS under the eyes-closed resting state condition in five frequency bands. Our findings demonstrated that BECTS has a profound effect on the spectral power of resting state EEG activities and cortical sources by activating/deactivating cortical regions.

In the sensor space, we found significant increases in relative and absolute θ power in all brain regions especially in the epileptogenic zone in the right centrotemporal region in comparison to healthy controls. Meanwhile, the θ power decreased in frontal and occipital regions in comparison to central region of epileptic patients. This observation is consistent with results from other studies conducted on Temporal Lobe Epileptic patients (TLE) (Quraan et al., 2013). Several studies (Clemens, 2004; Clemens et al., 2000; Douw et al., 2010; Schneebaum-Sender et al., 2012) have reported enhanced θ power in children with epilepsy with and without medication in comparison to controls (Clemens et al., 2010). However, it has been shown that the increased theta power in some cerebral regions is more pronounced in epileptic patients taking anti-epileptic drugs (Béla et al., 2007; Clemens, 2008; Clemens et al., 2006; Kikumoto et al., 2006). Nevertheless, in our study the drug effect can be ruled out to explain the spectral differences between the ECME (eyes-closed without spike) and ECWS (eyes-closed with spike) conditions.

Significant increases in θ, α, and β cortical sources were observed in the source space of the right centrotemporal area, the region of CTS generation, under the ECWS condition. Centrotemporal spikes are known to be highly reproducible sharp waves with similar morphological characteristics, high amplitudes and durations of more than 70 ms corresponding to frequencies above the θ band (Panayiotopoulos, 1999a,b. Therefore, in our analysis, the increased relative power in frequencies
The increase in relative power of higher frequencies especially several hundred milliseconds around CTS (Bourel-Ponchel, 2013; Gotman et al., 2005) resulted in a less significant increase in the power of low frequencies (θ band). Under both conditions, in most frequency bands, similar trends of spectral changes were observed in BECTS patients, which may reflect the modulatory effect of epileptic networks on the spectral power of cortical sources regardless of the presence of CTS in the scalp EEG segments analyzed. These findings indicate that, even in the absence of CTS in the scalp EEG, the activity of epileptic networks in BECTS has a profound impact on the EEG resting activity. This finding is consistent with those reported in other resting state studies (Ciucu et al., 2014; Kim et al., 2014; Pardoe et al., 2013). However, the presence of CTS clarified spectral differences between patients and controls with a wider spatial impact within the β1 band.

IAF differences between the groups may reflect decreased cognitive performances in patients as suggested in several studies (Angelakis et al., 2004; Khader et al., 2010; Klimesch et al., 1993). The lower IAF was correlated with lower power at parietal and occipital region especially under the ECWS condition. This finding might explain cognitive and attention impairment in BECTS patients (Holmes and Lenck-Santini, 2006; Metz-Lutz et al., 1999).

Another major finding of this study was the increased relative θ and α power under the ECWS condition, and the increased relative α1 and β2 power under the ECCT condition consistently in the right temporoparieto-occipital (TPO) junction. This finding may suggest that the epileptic zone in BECTS impairs the right temporoparieto-occipital region. The temporoparieto-occipital region is believed to be involved in high level neurological functions (De Benedictis et al., 2014), especially auditory, visual, somatosensory and memory processes. Impairment of the TPO in children with epilepsy has been shown to be associated with higher activity in this region (Barba et al., 2007; Besseling et al., 2013; Santini, 2006; Metz-Lutz et al., 1999).
The bilateral increases in all bands under both conditions in the poles of the temporal lobes, known to be the regions responsible for language and speech processing, suggest possible interhemispheric synchronization in temporal regions due to CTS. Several studies (Ay et al., 2009; Baglietto et al., 2001; Kossoff et al., 2007; Liasis et al., 2006; Metz-Lutz et al., 1999; Northcott et al., 2007) have discussed the impaired visual and auditory networks and alternation of source activities at the bilateral poles of the temporal lobes in BECTS patients. 

A compelling finding of the present study was the decreased activities of cortical sources in the frontal and occipital lobes in BECTS patients compared to healthy subjects in all frequency bands and conditions, notably under the ECWS condition. The frontal and occipital cortical depression in BECTS patients is likely to be associated with decreased activity of the default mode network (Archer et al., 2003; Blumenfeld et al., 2004; Fahoum et al., 2013; Gotman et al., 2005; Ibrahim et al., 2014; Laufs et al., 2007; Ligot et al., 2014; Yang et al., 2014). This finding is also in line with the frontal decrease in the relative power of lower frequencies observed in the time–frequency domain several hundred milliseconds before and after centrotemporal spikes in BECTS patients (Bourel-Ponchel, 2013). The reduced activity of the prefrontal and frontal lobes might also explain some of the cognitive impairments and other brain malfunctions related to benign epilepsy (Holmes and Lenck-Santini, 2006; Weglage et al., 1997), as it has been shown that any dysfunction in this region in childhood is likely to affect cognitive development (Badre et al., 2009; Stuss and Alexander, 2000).

Certain discrepancies between the topographic distribution of scalp EEG relative spectral power (in the sensor space) and the spatial distribution of cortical sources (in the source space) in different frequency bands were observed in this study. In our study, the increased or decreased cortical activities in various frequency bands estimated by means of the eLORETA approach were not expected to exactly follow the same spatial pattern of the spectral changes obtained using power spectrum analysis in the sensor space. The discrepancies can be explained by methodological differences between the approaches. Our STP maps were obtained by averaging the relative power values over groups of electrodes in each of 13 regions, while eLORETA maps were t-maps generated from statistical analysis of all 6234 voxels, whose source activities were estimated using all electrodes. Frequency-domain eLORETA generally provides better results for EEG resting analysis because the estimated neuronal generator distribution, when using this approach, does not depend on the polarity of the scalp EEG maps (Pascual-Marqui, 2014).

A potential limitation of our study is the sample size. For the thirteen cerebral regions, we computed the minimum sample size (Freedman et al., 2001) with the statistical power of 80%. The average sample size required for performing statistical comparisons between the groups was about 7 which was less than the sample sizes (eleven patients and twelve controls) set in our study.

Our overall findings indicate that, in addition to the dysfunction of the right centrotemporal region, which is the epileptic focus, cortical depression of frontal and occipital regions may show resting network
disruption in benign childhood epilepsy with centrencephalomalacic spikes. These findings encourage further investigation into the impact of BECTS on the resting state networks.

Appendix A. Supplementary data

Supplementary data associated with this article can be found online at http://dx.doi.org/10.1016/j.nicl.2015.08.014.

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