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Resting-State Oscillatory Dynamics in Sensorimotor Cortex in Benign Epilepsy With Centro-Temporal Spikes and Typical Brain Development

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Abstract: Benign Epilepsy with Centro-Temporal Spikes (BECTS) is a common childhood epilepsy associated with deficits in several neurocognitive domains. Neurophysiological studies in BECTS often focus on centro-temporal spikes, but these correlate poorly with morphology and cognitive impairments. To better understand the neural profile of BECTS, we studied background brain oscillations, thought to be integrally involved in neural network communication, in sensorimotor areas. We used independent component analysis of temporally correlated sources on magnetoencephalography recordings to assess sensorimotor resting-state network activity in BECTS patients and typically developing controls. We also investigated the variability of oscillatory characteristics within focal primary motor cortex (M1), localized with a separate finger abduction task. We hypothesized that background oscillations would differ between patients and controls in the sensorimotor network but not elsewhere, especially in the beta band (13–30 Hz) because of its role in network communication and motor processing. The results support our hypothesis: in the sensorimotor network, patients had a greater variability in oscillatory amplitude compared to controls, whereas there was no difference in the visual network. Network measures did not correlate with age. The coefficient of variation of resting M1 peak frequency correlated negatively with age in the beta band only, and was greater than average for a number of patients. Our results point toward a "disorganized" functional sensorimotor network in BECTS, supporting a neurodevelopmental delay in sensorimotor cortex. Our findings fur-

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ther suggest that investigating the variability of oscillatory peak frequency may be a useful tool to investigate deficits of disorganization in neurodevelopmental disorders. *Hum Brain Mapp 36:3935–3949, 2015.*

Key words: benign epilepsy with centro-temporal spikes; resting-state networks; magnetoencephalography; sensorimotor cortex; beta-band oscillations

INTRODUCTION

Benign Epilepsy with Centro-Temporal Spikes (BECTS) is a common childhood epilepsy characterized by sensorimotor seizures affecting mouth and face and high amplitude centro-temporal spikes [Gobbi et al., 2006; Panayiotopoulos et al., 2008]. Children with BECTS usually develop symptoms before the age of 11 and seizures tend to resolve at adolescence, regardless of medication [Hughes, 2010; Panayiotopoulos et al., 2008]. BECTS is associated with deficits in several neurocognitive domains, particularly language skills [Overvliet et al., 2010, 2011; Smith et al., 2012], but also motor skills [Overvliet et al., 2011], attention [Giordani et al., 2006; Smith et al., 2012], memory [Giordani et al., 2006; Pinton et al., 2006], and audition [Lundberg et al., 2005; Smith et al., 2012]. Some of these, such as motor development and language impairment, may correlate [Overvliet et al., 2011]. Recent evidence that neurocognitive deficits do not always fully recover by adolescence have challenged the benign nature of BECTS and sparked debate about the necessity for treatment [Hughes, 2010].

Centro-temporal spikes have received much attention in neurophysiological investigations of BECTS [Archer et al., 2003; Kamada et al., 1998; Lin et al., 2003; Pataraia et al., 2008; van der Meij et al., 2001], which have shown that the neural source of centro-temporal spikes is generally located in the primary sensorimotor cortices. However, BECTS is thought to be part of a spectrum of neurodevelopmental disorders, rather than having a distinct aetiology [Gobbi et al., 2006; Overvliet et al., 2010; Tsai et al., 2013]. Siblings of BECTS patients show similar neurocognitive impairments [Smith et al., 2012; Verrotti et al., 2013] and centro-temporal electroencephalography (EEG) spikes are also seen in other childhood developmental disorders [Holtmann et al., 2003] and in more complex epilepsy syndromes [Vears et al., 2012]. Nevertheless, sensorimotor cortex is thought to be the source of epileptiform activity. Ictal activity may spread from sensorimotor cortex to other areas, particularly the lateral sulcus [Overvliet et al., 2010, 2011]. The lateral sulcus hosts language processing areas, which display abnormal functional lateralization in BECTS [Lillywhite et al., 2009]. Downstream effects of ictal activity may thus eventually lead to disruption of functional neural systems, and neural adaptation or compensation may further disrupt normal brain function in children with BECTS.

The above evidence suggests that the neuropathology of BECTS cannot be solely characterized by spikes and, if we are to gain a better understanding of the disease, it is essential to study resting-state activity in the sensorimotor network. It has frequently been shown that resting-state networks can be studied using functional magnetic resonance imaging (fMRI), with the primary finding of several consistent networks involved in specific functional processing [Biswal et al., 1995; Damoiseaux et al., 2006; Greicius et al., 2003]. Using fMRI, a number of studies have found abnormalities in resting activity in language areas in BECTS, in connectivity between language and sensorimotor areas [Besseling et al., 2013a,b], and in local coherence of the blood oxygenation level dependent signal in several areas including sensorimotor cortex [Tang et al., 2014]. Unfortunately, the indirect nature of the fMRI measurement (which is related to blood flow) means that it cannot assess directly electrophysiological activity in the networks in question [Murphy et al., 2013]. In particular, neural oscillations (rhythmic activity in neural cell assemblies), which are thought to be crucial in mediating network activity [Donner and Siegel, 2011; Fries, 2005], cannot be studied using fMRI. Recent work [Brookes et al., 2011; Hall et al., 2013; Muthukumaraswamy et al., 2013a] has however begun to show that networks, with a similar structure to those in fMRI and including the sensorimotor network, can also be seen using magnetoencephalography (MEG). This opens up a unique opportunity to study, for the first time, resting-state electrophysiological activity in the sensorimotor network, in BECTS.

Here, we hypothesized that resting activity in patients would differ from controls in the sensorimotor network, but not in the visual network, which served as a control. We further expected differences to dominate in the beta band because of its hypothesized role in mediating long-range network integration [Donner and Siegel, 2011] and motor processing [Gaetz et al., 2010; Jurkiewicz et al., 2006], and because the sensorimotor network in fMRI correlates most strongly with beta-band EEG rhythm fluctuations [Mantini et al., 2007]. In addition to network activity, we investigated variability of amplitude and frequency of focal resting-state background oscillatory activity in primary motor cortex (the locations of which were obtained from a separate recording run using a motor response task), using a coefficient of variation analysis.

MATERIALS AND METHODS

Subjects

Twenty-three patients aged 8–16 diagnosed with BECTS were recruited through local paediatric clinics. Seventeen age-matched typically developing controls were recruited

TABLE I. Patient group description

Patient	Age at MEG	Age at onset	Time since onset	Seizure freq/yr	Last seizure (days)	Medication	EEG spikes	MEG spikes
1	8.17	5	3.17	6.0	90	none	freq R	none
2	8.44	7	1.44	2.0	365	none	freq L	reg BL
3	9.04	6	3.04	0.5	540	none (1 wk off CBZ)	freq L	none
4	9.46	9	0.46	104.0	1	CBZ	freq BL	freq BL
5	9.46	7	2.46	12.0	120	CBZ	freq L	some L
6	9.69	8	1.69	3.0	90	CBZ	v freq R-BL	freq BL
7	9.82	9	0.82	12.0	60	CBZ	v freq L	some R
8	9.98	8	1.98	0.0	150	VPA	some L	none
9	10.26	8	2.26	104.0	7	CBZ	freq R-BL	some R-BL
10	11.36	10	1.36	2.9	540	none	freq L	freq R
11	11.80	9	2.80	5.0	120	none	v freq L	some L
12	11.88	6	5.88	0.5	60	LTG	v freq R	none
13	12.23	10	2.23	0.4	730	none	freq R	none
14	12.23	8	4.23	1.0	300	LTG	some R	none
15	12.26	5	7.26	52.0	2	CBZ	some R	reg L-BL
16	12.95	8	4.95	0.0	365	VPA	some R	none
17	14.98	9	5.98	0.5	912	VPA	some R	none

Medication: CBZ, carbamazepine; VPA, sodium valproate; LTG, lamotrigine. EEG and MEG spikes indicate frequency and dominant hemisphere. EEG spike information was obtained from the clinical letter and sleep-deprived EEG report. R, right, L, left, BL, bilateral. The number of observed spikes in the 3-min MEG recording is indicated as: some = 1–29, regular (reg) = 30–50, frequent (freq) > 50.

through approved advertisements on Cardiff University's noticeboard, in local primary schools, hospitals and other public locations. All patients and controls had normal or corrected-to-normal vision. Subjects and their parents or guardians gave age-appropriate informed consent according to the Declaration of Helsinki. Participating families received a small reimbursement for their participation. All procedures were approved by the local Ethics Committee.

A total of four patients were excluded: two patients were rediagnosed with symptomatic epilepsies after recruitment, one patient was unwilling to perform the brain scans on arrival, and one patient's data were of too poor quality to analyze.

Participation involved 2–3 h of neurocognitive testing and 2–3 h of neuroimaging scans on two separate days. Due to technical issues, subject willingness, and/or time limitations, we did not always obtain the full set of planned data acquisition. The current analysis required a completed eyes-open resting-state MEG dataset, finger abduction MEG datasets on both hands, and a structural MRI scan. Of the remaining 19 patients and 17 controls, we did not manage to obtain the finger-abduction dataset on one hand for one patient and one control, and the resting-state dataset for one further patient. The final analysis thus included 17 patients (aged 8.17–14.89, mean 10.82, 9M/8F, 1 left-handed) and 16 controls (aged 8.32–15.01, mean 11.11, 8M/8F, 3 left-handed). The two groups did not differ in age (independent samples t test, $t(31)=-0.44$, $P=0.66$) and performed their resting-state recording at a similar time of day ($t(31)=1.22$, $P=0.23$). Details of the patient group, including frequency of observed centro-temporal spikes, are given in Table I.

Neurocognitive Testing

All subjects were screened with questionnaires assessing their neurocognitive abilities by trained psychologists from the Dyscovery Centre. The testing session included the Kaufman Brief Intelligence Test (KBIT-2) [Kaufman and Kaufman, 2004], Movement Assessment Battery for Children (MABC) [Henderson et al., 2007], Test for Reception of Grammar (TROG-2) [Bischop, 2003], Detailed Assessment of Speed of Handwriting (DASH) [Barnett et al., 2007], Matching Familiar Figures Test [Moos and Moos, 1994], and Wechsler Individual Achievement Test (WIAT-II) [Wechsler, 2005].

Neuroimaging Data Acquisition and Preprocessing

Patients and controls underwent an MRI session in which a T1-weighted 1-mm anatomical scan was acquired, using an inversion recovery spoiled gradient echo acquisition.

In an MEG session, whole-head MEG recordings were made using a 275-channel CTF radial gradiometer system. An additional 29 reference channels were recorded for noise cancellation purposes and the primary sensors were analyzed as synthetic third-order gradiometers [Vrba and Robinson, 2001]. Two or three of the 275 channels were turned off due to excessive sensor noise (depending on time of acquisition). Subjects were seated upright in the magnetically shielded room. To achieve MRI/MEG coregistration, fiduciary markers were placed at fixed distances from three anatomical landmarks identifiable in the subject's anatomical MRI, and their locations were verified afterward using high-resolution digital photographs. For

two patients, we could not obtain an MRI scan of sufficient quality. These were replaced with a scan of a child of comparable age and head size for coregistration. Head localization was performed before and after each recording, yielding one measure of head motion per dataset by calculating the difference between the two localizations. A trigger was sent to the acquisition computer at relevant stimulus events.

In the MEG scanner, subjects were asked to perform a range of tasks. This included a 3-min acquisition where the subject sat still without a task instruction ("resting state") with their eyes open. Subjects further performed a task targeting motor cortex activity, in which they made brisk single abductions pushing a small lever sideways with their index finger in response to an auditory cue delivered through earphones. Subjects received visual feedback of how far they had pushed the lever, aiming to line a small vertical bar up to the center of a horizontal bar [Hamandi et al., 2011; Muthukumaraswamy, 2010, 2013b]. This task lasted 8 min, and subjects performed one for each hand. Electrodes were placed on the skin to measure the electromyography (EMG) of the first dorsal interosseus of each hand.

Eyes-open resting-state datasets were acquired at, or down-sampled to, 600 Hz, and filtered with a 1-Hz high-pass and a 150-Hz low-pass filter. The datasets were then segmented into 2-s epochs. The data were visually inspected and epochs with major artefacts such as head movements or large muscle contractions were excluded from subsequent analysis. Due to the generally infrequent and inconsistent occurrence of centro-temporal spikes in patients, we did not exclude epochs containing these from the data (Table I).

Resting-State Independent Component Network Analysis

We analyzed oscillatory resting networks using the methodology described by Brookes and coworkers [Brookes et al., 2011; Hall et al., 2013], similar to our previous work [Muthukumaraswamy et al., 2013a]. Using the preprocessed data, beamformer weights were computed on an 8-mm grid for each subject and frequency band, using the Synthetic Aperture Magnetometry (SAM) beamformer algorithm [Robinson and Vrba, 1999]. A multiple local-spheres volume conductor model [Huang et al., 1999] was derived by fitting spheres to the brain surface extracted by the FSL Brain Extraction Tool [Smith, 2002]. Beamformer time courses were then generated at every voxel and normalized by an estimate of the projected noise amplitude at that voxel [Hall et al., 2013]. The Hilbert transform was applied to each voxel time course, and the absolute value was computed to generate an amplitude envelope of the oscillatory signals in each frequency band. The data at each voxel were down-sampled to an effective sampling rate of 1 Hz [Luckhoo et al., 2012], and transformed to a paediatric template brain constructed of brain scans from 67 children, aged 9.6–12.9 (mean 11.09) [Wilke et al., 2003] using FLIRT in FSL. Data from all subjects were then concatenated in the time dimension across subjects.

Temporal independent component analysis (ICA) was applied to the concatenated datasets using the fast ICA (research.ics.tkk.fi/ica/fastica) algorithm. We applied ICA separately for six bands identical to previous literature: 1–4 Hz (delta), 4–8 Hz (theta), 8–13 Hz (alpha), 13–30 Hz (beta), 30–50 Hz (gamma), and 50–90 Hz (high gamma) [Brookes et al., 2011; Muthukumaraswamy et al., 2013a]. We analyzed one additional band comprising 90–150 Hz, as High-Frequency Oscillations (HFOs) have been associated with epileptiform activity in BECTS [Kobayashi et al., 2011]. Prewhitening was applied to reduce the dimensionality of the source-space Hilbert envelope signals to 25 principal components before ICA [Brookes et al., 2011; Hall et al., 2013; Hyvärinen and Oja, 2000]. Fifteen independent components were derived for each frequency band. Although this ICA method does not require a priori selection of voxels, and is applied over the group-concatenated times series of all voxels in template space, we determined, a priori, to select only the sensorimotor and visual networks from the produced components for further analysis. For these two components, we computed the time-series standard deviation (SD) of the demeaned component amplitude for each subject (the individual's time series associated with the group-wide pattern of temporally correlated voxels relevant for the respective network), using a sliding window (20 1-s samples wide). The resulting SD time series were then subjected to a bootstrapping procedure (10,000 bootstrapped means) to obtain mean and confidence intervals. SDs can be interpreted as a measure of activity in a network [Muthukumaraswamy et al., 2013a], or variability thereof.

Beamformers normally suppress temporally correlated sources. There are a number of reasons why this problem is unlikely to greatly affect the currently applied ICA approach. First, correlation is calculated between the envelopes of temporally downsampled oscillatory sources rather than the raw oscillatory signal in the unfiltered time domain. This makes it possible to observe sources that are temporally correlated in their frequency envelopes but not in their raw signal and hence do not get suppressed [Brookes et al., 2011]. Furthermore, it is unrealistic that distant neural sources are perfectly correlated over the course of several minutes, which would be required to yield beamformer suppression [Hadjipapas et al., 2005]. Finally, even in scenarios where there may be pathologically strongly correlated sources, beamformers are still capable of revealing those sources and networks [Brookes et al., 2012; Gross et al., 2001; Schnitzler and Gross, 2005].

Coefficient of Variation in Amplitude and Frequency in Primary Motor Cortex

Localization of primary motor cortex

Analysis of finger-abduction data was time-locked to EMG onsets, marked as an increase in the rectified EMG

signal by 2.5 SDs above the noise floor between −0.5 s to +1 s around the auditory cue [Cheyne et al., 2008; Muthukumaraswamy, 2010]. The continuous recording was visually inspected to verify the EMG onset with readings from an optical displacement meter. All data were then epoched from −1.5 s to +2.5 s around the EMG markers. Epoched data were visually inspected and those with large artefacts (as above), movements in addition to the single finger abduction, or extraneous EMG activity were excluded from further analysis.

Motor cortex coordinates for focal resting-state analysis were obtained from the finger-abduction MEG data. The motor cortex response to finger abduction is well-characterized to have three components (Movement-Related Beta Desynchronization (MRBD), Movement-Related Gamma Synchronization (MRGS), and Post-Movement Beta Rebound (PMBR) [Jurkiewicz et al., 2006]). We chose the 60–90 Hz MRGS for localization of primary motor cortex, as it is strongly elicited during a finger movement [Cheyne et al., 2008], is predominantly contralateral [Cheyne et al., 2008; Crone et al., 1998; Jurkiewicz et al., 2006], is known to follow motortopical organization [Cheyne et al., 2008; Crone et al., 1998], is clearly present in children [Gaetz et al., 2010], and its localization does not differ with age [Gaetz et al., 2010].

For each hand, peak MRGS coordinates were obtained from the finger-abduction data using the SAM beamformer algorithm [Robinson and Vrba, 1999]. Finger-abduction datasets were first band-pass filtered at 60-90 Hz using a fourth-order bidirectional IIR Butterworth filter. For source localization, a multiple local-spheres forward model [Huang et al., 1999] was derived by fitting spheres for each sensor to the brain surface extracted by the FSL Brain Extraction Tool [Smith, 2002]. The SAM beamformer algorithm was then used to create a set of beamformer weights for the whole brain at 4-mm isotropic voxel resolution for each dataset. Virtual sensors were constructed at each voxel, and from these, paired t statistical images of source power (Student's t statistic) for a baseline window of −1.3 to −1.0 s premovement compared to an active window of 0–0.3 s postmovement were generated for each dataset. The individual paired t SAM images of each dataset were examined and the coordinates of peak activity of the contralateral MRGS response were obtained.

For illustration purposes, we generated group-level source images of the finger-abduction responses, using the MNI adult template brain. Previous research has shown that this approach is sufficiently accurate for localization of motor cortex activity, as it is an a priori, well-defined, area of interest [Gaetz et al., 2010].

Coefficient of variation in oscillatory amplitude

In this article, the finger-abduction data were only used to obtain coordinates of left and right contralateral primary motor cortex in each individual. The obtained coordinates were then applied to analyze oscillatory activity in the resting-state datasets. Thus, all results presented here are from analyses of the resting-state datasets.

For each resting-state dataset, virtual sensor waveforms were generated at each of the obtained finger-abduction peak voxel MRGS locations (L/R) using the SAM beamformer algorithm, optimized for each single obtained (virtual) sensor. For this analysis, resting-state virtual sensor data were band-pass filtered at 0–150 Hz. Time-frequency analysis of each single virtual sensor was conducted using the Hilbert transform from 1 to 150 Hz in 0.5-Hz steps with an 8-Hz wide band-pass, third-order Butterworth filter [Le Van Quyen et al., 2001]. Finally, the average amplitude-time series over epochs was obtained for each 1-Hz step within 6–150 Hz (due to the 8-Hz bandwidth, time-frequency data below 6 Hz could not be obtained). We subsequently calculated the mean and SD of oscillatory amplitude in each 1-Hz band over the 1200 averaged time samples. From these, we calculated the coefficient of variation (CV) by dividing the SD by the mean, which has the advantage of being scale-invariant and minimally affected by between-subject variance [Little et al., 2012]. We then averaged the obtained CV over the relevant 1-Hz bands per frequency band of interest. We used identical bands to those used in the network analysis (from 6 Hz, i.e., the theta band here was calculated from 6–8 Hz, the remaining bands are identical).

Coefficient of variation in oscillatory peak frequency

To obtain variability in peak frequency, the resting-state virtual sensor data were first filtered and transformed identical to amplitude analysis. We then calculated the amplitude-frequency representation for each 2-s epoch per dataset, averaging over all time samples per epoch. A single local maximum was then obtained per epoch amplitude-frequency curve to obtain peak frequency and amplitude per frequency band of interest (using identical bands to those used in the amplitude CV analysis). We then obtained the mean and SD of peak frequency, and amplitude at peak frequency, over epochs per subject. As a measure of peak frequency variability, we calculated the CV by dividing the SD of peak frequency over all epochs per dataset by the mean peak frequency.

RESULTS

Resting-State ICA Network Analysis

The sensorimotor and visual networks were both clearly present in the beta range (13–30 Hz) (Fig. 1A,B) [Brookes et al., 2011, 2012]. A t test confirmed our hypothesis that there was a difference in the resting sensorimotor but not visual network: the bootstrapped mean of the SD time series was significantly greater for patients than controls in the sensorimotor network ($t(31)=2.35$, $P=0.025$, effect size using the pooled SD=0.82, 95% CI using an inverted T distribution for small sample size=0.08–1.56), but there

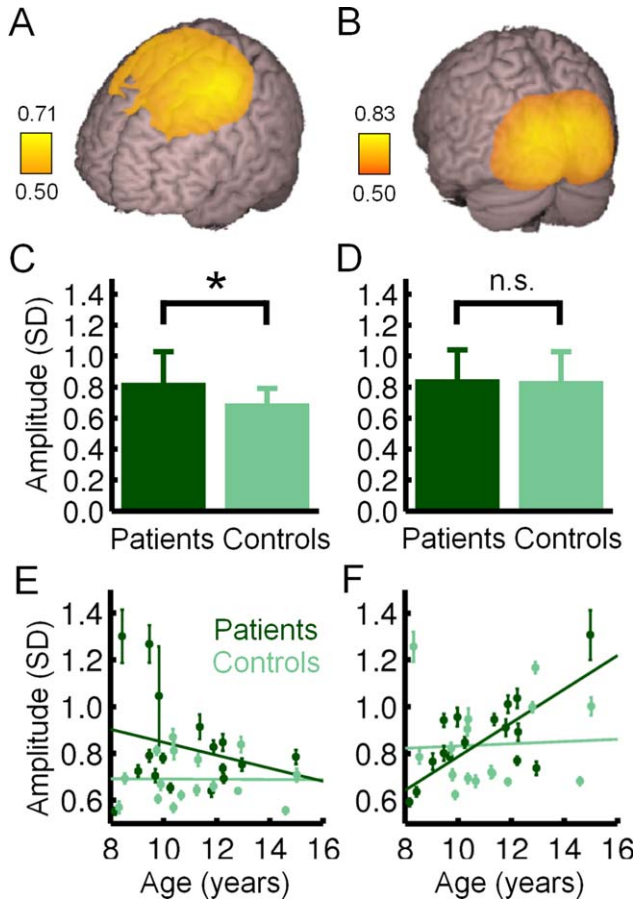

Figure 1.

Sensorimotor (**A, C, E**) and visual (**B, D, F**) network independent components of temporally correlated oscillatory activity in the beta band (13–30 Hz) generated for the whole group (N=33). (A, B) Component images transformed to MNI space. Images show absolute ICA weights (in A.U.) thresholded at 0.5. (C, D) Group average ICA resting network component amplitude SDs (in A.U.). Error bars represent SDs of group mean. *$P<0.05$; n.s. = $P>0.05$. (E, F) Correlations of individual SDs with age. Data points represent subject's bootstrapped SD means with 95% confidence interval. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

was no difference between groups in the visual network ($t(31)$=0.13, P=0.90, effect size=0.05, 95% CI=−0.66 to 0.76) (Fig. 1C,D).

If the difference in the sensorimotor network reflects the benign nature of a neurodevelopmental delay (a delay that recovers with age), we would expect negative correlations in both groups, and the difference between patients and controls to be most pronounced at the younger ages. The least-squares linear correlation fit displayed in Figure 1E,F shows that we indeed observed this pattern for patients, although the correlation was not significant (R=−0.25, P=0.34), nor for controls (R=−0.01, P=0.97). In the visual network, there was no trend for a negative correlation with age, with patients in fact showing a positive correlation (patients: R=0.67, P=0.003; controls: R=0.05, P=0.86).

The significantly greater SD in the sensorimotor network appears to be driven by the high values of three of the youngest patients (Fig. 1E). Two of these patients were >2 SD (but not >3 SD) from the group mean. However, several facts suggest that these values likely represent true patient variance. First, the three highest-SD patients did not have extreme values in the visual network (Fig. 1F), suggesting their values were not due to an artefact causing global spurious high temporal correlations in the beta band. Furthermore, there was no clear relationship, aside from age at time of testing, to these extreme values and clinical parameters, age of onset, seizure frequency or seizure recency (Table I).

In order of greatest sensorimotor network SD, the three patients with extreme values had head motion values of 1.10, 0.13, and 1.26 cm. However, head motion did not correlate with sensorimotor SD (R=0.22, P=0.21). In fact, the patient with the highest head motion value in the group (1.47 cm) had the lowest component SD (0.55). Moreover, head motion was not statistically different between groups ($t(31)$=1.51, P=0.14). Head motion also did not correlate with the visual network SD (R=−0.07, P=0.71).

We further assessed whether the extreme values were due to a tilted head position, by inspecting the measured head-to-dewar distances for each coordinate of each fiducial. Of the two most extreme patients, one patient had two coordinates (right pre-auricular X and left pre-auricular Z) that were >2 SD from the group mean of each respective coordinate. The most extreme case had no coordinates >2 SD. The third extreme case did not have any coordinates >2 SD either. Two other patients with coordinates >2 SD from the mean had sensorimotor SD values that were very central in the group. In conclusion, there was no relationship of SD to tilted head position in the dewar. Finally, the extreme cases were also not related to a low or high number of epochs analyzed, suggesting great values were not due to low or high amplitude.

The beamformer weights generated by the ICA network calculations were normalized by an estimate of weights × noise. Any systematic differences between the groups (e.g., age, head size, and motion) could potentially bias our ICA component results. To assess whether there was any such bias, we conducted a statistical comparison of the volumetric weights × noise images. The images were first spatially normalized to the paediatric template using FSL FLIRT with an affine transform. A non-parametric permutation two-sample t test was conducted with FSL Randomize using 5,000 permutations for each condition with 8 mm variance smoothing and the resulting P values were corrected for multiple comparisons using the omnibus test statistic [Nichols and Holmes, 2002; Singh et al., 2003a,b]. The resulting images, converted to MNI space for imaging purposes (Supporting Information Fig. 1), showed that

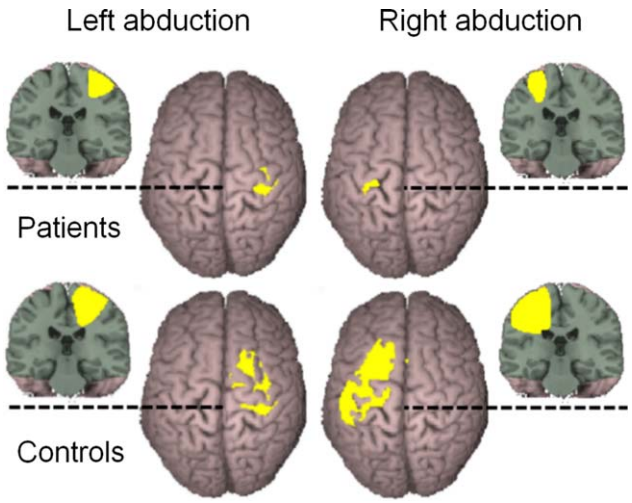

Figure 2.
Group average *t* statistic images of the 60–90 Hz Movement-Related Gamma Response paired *t* images obtained from the finger-abduction data. Each panel shows a superior view of a group and finger-abduction hand, as indicated. Insets are coronal sections at $y=-10$ mm. The images are normalized to the MNI template and thresholded at $P=0.001$ (voxel-based corrected).

there was no significant systematic bias for either patient to control group contrast. This analysis thus suggests that the component amplitude in the sensorimotor and visual networks were unlikely to be caused by a bias in beamformer weights.

MRGS Localization

Figure 2 displays the group average one-sample *t* statistic images of the 60–90 Hz MRGS per group per finger-abduction hand, highlighting the strongly localized response in contralateral motor cortex. Figure 2 suggests that there may be spatial differences between the MRGS responses of patients and controls. However, for the CV analyses, we only used the coordinates at which the peak response occurred in each individual. A series of independent samples *t* tests on each of the three coordinates of the MRGS localization in each hemisphere did not reveal any significant differences in position between the two groups (6 *t* tests, all $P>0.20$). Figure 3 displays the CV results at individual peak MRGS locations.

Coefficient of Variation in Oscillatory Amplitude

To test whether ongoing resting-state oscillatory amplitude in any frequency band was more variable in patients or controls (Fig. 3A), we performed a repeated-measures ANOVA with within-subject factors Frequency Band (6 levels) and Hemisphere (L/R) and between-subject factor Group (patient/control) on the CV in oscillatory amplitude. This analysis revealed a main effect of Frequency Band ($F(5,155)=25.65$, $P<0.0005$), but not of Hemisphere ($F(1,31)=0.26$, $P=0.62$), or Group ($F(1,31)=0.46$, $P=0.50$). There was a trend for the interaction of Frequency Band × Group only ($F(5,155)=2.08$, $P=0.07$; Hemisphere × Group: $F(1,31)=1.26$, $P=0.27$; Frequency Band × Hemisphere: $F(5,155)=0.42$, $P=0.83$; Frequency Band × Hemisphere × Group: $F(5,155)=1.11$, $P=0.36$). Inspection of Figure 3A shows a trend for patients to have increased amplitude CV in the 50–90 and 90–150 Hz bands compared to controls, but as the interaction was not significant, we could not statistically compare these observations.

Coefficient of Variation in Oscillatory Peak Frequency

As peak frequency was obtained over a limited number of time samples, and subsequently averaged over a variable number of epochs, there is a potential risk of a difference in signal-to-noise confounding the result. However, the average number of epochs remaining in each dataset after excluding bad epochs was 89 in patients and 95 in controls, which was not significantly different ($t(31)=-1.17$, $P=0.25$).

A Frequency Band × Hemisphere × Group ANOVA revealed a main effect of Frequency Band ($F(5,155)=296.37$, $P<0.001$), and a Frequency Band × Group interaction ($F(5,155)=2.43$, $P=0.04$). There were no other significant main effects or interactions (all $P>0.2$). Simple main effects to identify the source of the Frequency Band × Group interaction showed that patients had a smaller CV than controls in the 6–8 Hz band ($P<0.05$), and showed a trend for a greater CV than controls in the 13–30 Hz band ($P=0.096$), which was driven by five patients that were >1 SD above the whole group mean. No other frequency bands showed a significant difference (all $P>0.05$) (Fig. 3B).

Our goal was to assess the variability in peak frequency, which we obtained by dividing SD by mean peak frequency. However, as we obtained our peak frequency over a limited number of time samples per epoch, we need to be cautious about one potentially confounding factor. A higher frequency has more cycles per time unit than a lower frequency, and can thus generate a larger variation as a by-product. Therefore, we assessed whether mean peak frequency differed between patients and controls. A Frequency Band × Hemisphere × Group ANOVA revealed that as expected, a main effect of Frequency Band was present ($F(5,155)=150840.47$, $P<0.0005$), but no other significant main effects or interactions (all $P>0.05$). Thus, mean peak frequency in primary motor cortex did not differ between patients and controls nor between hemispheres, in any frequency band.

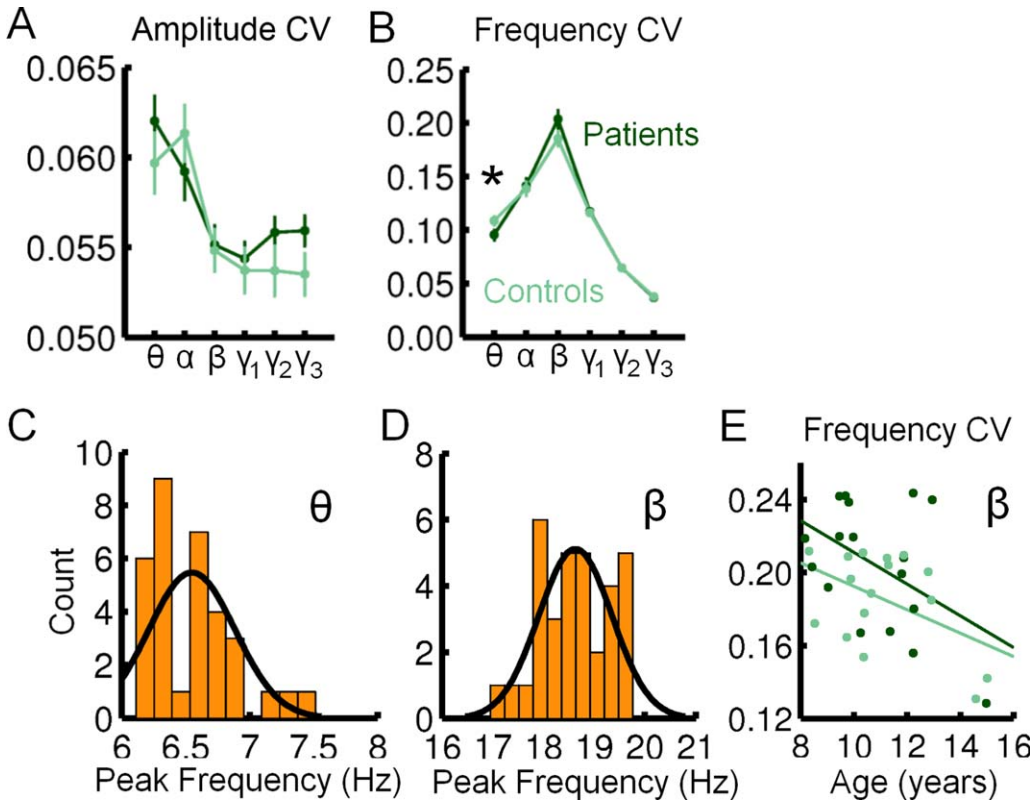

Figure 3.

Group average CV oscillatory activity in motor cortex. Results are shown for six frequency bands of (**A**) amplitude and (**B**) peak frequency. Frequency bands are indicated by their Greek symbols (gamma 1/2/3 = 30–50 Hz, 50–90 Hz, 90–150 Hz). (**C, D**) Histograms of oscillatory peak frequency in motor cortex collapsed over groups. (**C**) The theta band (6–8 Hz) shows a non-normal distribution skewed toward the lower frequencies. (**D**) The beta band (13–30 Hz) follows a normal distribution. (**E**) Negative correlation of motor cortex beta-band peak frequency CV with age. All results are collapsed over hemispheres. Error bars represent SEM. *$P<0.05$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Post Hoc Analysis of Beta-Band Frequency Variability: Age and Hemispheres

Age is a strong determining factor in BECTS symptomatology. We assessed whether age predicted frequency variability by performing a regression analysis. As there was no significant effect of hemisphere in either amplitude or frequency analysis, values were averaged over hemispheres.

There is a potential caveat of spurious local maxima in the amplitude-frequency curves due to low amplitude causing artificially high variability. We took two measures to address this issue. First, we assessed the distribution of peak frequency in the two frequency bands that showed a difference in variability between patients and controls (theta), or was our hypothesis (beta). If true frequency peaks were obtained, and the frequency band chosen was appropriate, the distribution of peak frequency should be relatively normal. Figure 3C shows that for the 6–8 Hz band, the distribution of peak frequency was skewed toward 6 Hz, suggesting either an absence of frequency peaks, or that peaks occurred at a lower frequency than included in this band. In contrast, peak frequency within 13–30 Hz appeared normally distributed around 18.5 Hz, with no values at the extremes of the range (Fig. 3D). The Shapiro–Wilk test for normality confirmed a significantly non-normal distribution of peak frequency within the 6–8 Hz band ($P=0.007$), but not for the 13–30 Hz band ($P=0.75$). Thus, peak frequency variability may suffer from an edge effect in our 6–8 Hz theta band. For this reason, caution is needed in interpreting the theta-band group difference. Because our main hypothesis regards the beta-band, we will further focus on the beta band only.

A second precaution to exclude effects due to low amplitude at peak frequency was to include amplitude as a covariate in the regression with age. For patients, as expected, frequency CV correlated negatively with age ($R=-0.46$, $P=0.03$) (Fig. 3E). Also, amplitude correlated positively with age ($R=0.58$, $P=0.007$), but frequency CV did not correlate with amplitude ($R=-0.06$, $P=0.42$). A regression model with only age as a predictor of frequency

CV showed there was a trend for age to predict lower frequency CV (R^2=0.21, F(1,15)=4.00, P=0.06; age: β=−0.46). Adding amplitude at peak frequency as an additional predictor to age increased the predictive power of age, but the model was not significant (R^2=0.28, F(2,14)=2.68, P=0.10; age: β=−0.64, P=0.04; amplitude: β=0.32, P=0.28).

For controls, the same trends were present as for patients, with a negative correlation between frequency CV and age (R=−0.48, P=0.03), and a trend for a positive correlation of power with age (R=0.38, P=0.07). Similar to patients, there was no significant correlation between frequency CV and power (R=−0.11, P=0.34). A regression model with only age as a predictor of frequency CV showed a trend for a significant prediction (R^2=0.22, F(1,14)=4.02, P=0.07; age: β=−0.47), and a model adding power at peak frequency as an additional predictor to age was not significant (R^2=0.23, F(2,13)=1.93, P=0.18; age: β=−0.50, P=0.08; power: β=0.08, P=0.76). These regression analyses suggest that the correlation between power and age did not drive the correlation of frequency CV and age in either group.

It can be imagined that any age-driven correlation can be confounded by head motion, as the youngest children are the smallest and have most room to "move around" in the scanner. Indeed, there was a trend for head motion to positively correlate with M1 beta-band frequency CV (R=0.31, P=0.08, whole group). However, when controlling for head motion, beta-band frequency CV and age still showed a significant negative partial correlation (R=−0.41, P=0.02). Therefore, head motion did not fully explain the strong correlation of M1 beta-band peak frequency variability with age.

To investigate whether a correlation of peak frequency with age was unique to the beta band, we also calculated the correlation of age with all other frequency bands over the whole group. In contrast to the beta band, a correlation with age was absent for the theta and alpha bands (R=0.16, P=0.36; R=0.26, P=0.15, respectively), as well as the highest gamma band (90–150 Hz: R=−0.09, P=0.63). It was significant, but positive, for the 30–50 Hz and 50–90 Hz gamma bands (R=0.40, P=0.02; R=0.51, P=0.002, respectively). Thus, our results suggest that the negative correlation of M1 peak frequency variability with age in the beta-band is unique, and may be an informative marker of child motor cortex development.

BECTS patients often have a predominance of spikes in one hemisphere. We therefore additionally tested whether left and right motor cortex beta-band peak frequency correlated in individuals. Trial-to-trial peak frequency per individual did not correlate between hemispheres (all $-0.15<R<0.16$ (mean 0.005), all $P>0.11$). However, peak frequency of the left and right motor cortex correlated positively in patients (R=0.50, P=0.04), and controls (R=0.51, P=0.04), and frequency CV correlated positively in patients (R=0.54, P=0.03), with a trend for a similar correlation in controls (R=0.46, P=0.08). This suggests that beta-band peak frequency variability is a trait of an individual, rather than a lateralization index or an indication of spike side. We did not observe sufficient numbers of centro-temporal spikes in the resting-state data of BECTS patients to investigate the role of spikes here (Table I).

In summary, beta-band peak frequency in primary motor cortex correlated negatively with age in both patients and controls. There was a trend for greater peak frequency variability in BECTS patients than in typically developing controls, whereas the average peak frequency did not differ. In the patient group, frequency variability correlated between the left and right motor cortex, with a similar trend for the control group. Thus, age and hemisphere effects on peak frequency variability were similar in patients and controls, and an abnormally high beta-band frequency variability may be tied to some of the neurological abnormalities present in BECTS.

Comparison of Global Network and Local Motor Cortex Measures

Over the whole group, there was a trend for a positive correlation between sensorimotor component amplitude SD and beta-band peak frequency CV (R=0.30, P=0.09). Furthermore, of the three patients with very high sensorimotor network SD values, two were among the five patients with abnormally high peak frequency CV values. However, the patient with the highest network SD did not have an abnormally high peak frequency CV. This, together with the fact that network measures did not correlate with age, whereas local frequency variability did, suggests that the two measures are independent markers that are more closely tied to disease-related disruption and brain maturation, respectively.

Correlations with Neurocognitive Scores

We performed a cross-correlation on all standard (age-corrected) subscores to determine which tests best reflected motor skills and language skills, respectively (Supporting Information Table I). For motor skills, we chose the MABC_B (Balance), as it correlated with some of the other MABC subcomponents and nonverbal IQ, but not with verbal IQ (KBIT-2). For language skills, we chose the WIAT_WR (Word Reading), as it correlated with all other subscores of the WIAT, verbal IQ, DASH, and TROG, but not the MABC or nonverbal IQ. Two patients did not perform the neurocognitive tests. Therefore, all correlations were based on 15 patients and 16 controls. Patients scored significantly lower than controls on both tests (MABC_B: t(29)=−3.06, P=0.005; WIAT_WR: t(29)=−3.18, P=0.004).

Correlations of neural measures with neurocognitive scores are displayed in Figure 4. Neither test correlated significantly with the ICA sensorimotor network SDs in either group (MABC_B: patients: R=−0.12, P=0.68; controls: R=−0.08, P=0.77; WIAT_WR: patients: R=−0.16,

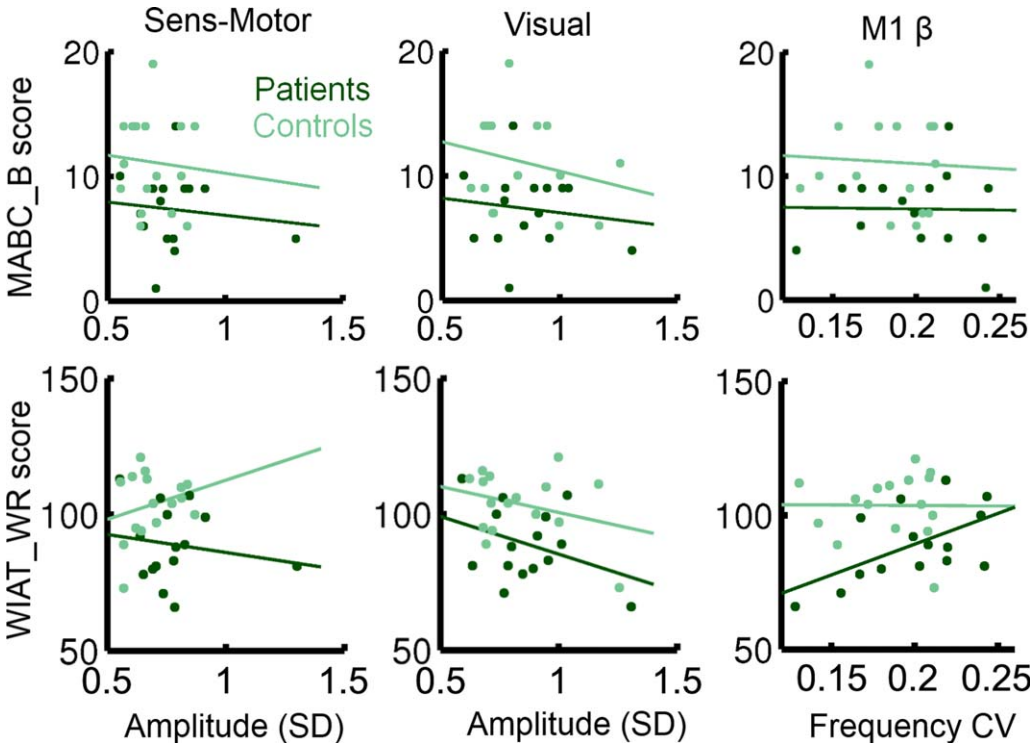

Figure 4.

Correlations of neural measures with neurocognitive tests for motor skills (MABC balance, top panels) and language skills (WIAT word reading, bottom panels). Correlations are displayed for sensorimotor network SD, visual network SD, and motor cortex (M1) beta-band peak frequency CV. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

P=0.56; controls: R=0.25, P=0.37). There were also no significant correlations of either neurocognitive test with the visual network SDs (MABC_B: patients: R=−0.13, P=0.64; controls: R=−0.24, P=0.37; WIAT_WR: patients: R=−0.36, P=0.19; controls: R=−0.30, P=0.26). MABC_B scores did also not correlate with the motor cortex beta-band CV in peak frequency in either group (patients: R=−0.02, P=0.95; controls: R=−0.06, P=0.84). The WIAT_WR showed a significant positive correlation in patients (R=0.57, P=0.03), but not in controls (R=−0.01, P=0.97). The correlation was in the opposite direction to our expectations, suggesting that better language performance correlated with a greater frequency CV. However, when correcting for multiple comparisons for 12 correlations at α=0.05, no correlation survived the adjusted significance threshold (Bonferroni correction, adjusted α=0.0042). In summary, increased variability in resting-state sensorimotor beta-band activity was not directly related to impaired motor and language skills.

DISCUSSION

Using ICA of correlated temporal sources of ongoing oscillatory neural activity in resting MEG, we found greater SDs of sensorimotor resting-state network activity in patients with BECTS than in age-matched typically developing control children. Consistent with an interpretation of greater variability in sensorimotor cortex activity, we further found that a number of BECTS patients had a more variable peak frequency of spontaneous background beta-band oscillatory activity in bilateral motor cortex than average, with greatest variability for the youngest children. These converging findings were in contrast to activity within the visual network, chosen as a control network, and to variability of frequencies higher and lower than beta, which did not differ between patients and controls, and did not decline with age. These findings suggest that children with BECTS have a "less stable" network of areas involved in sensorimotor functioning. In addition, our study suggests investigating the variability of oscillatory peak frequency may be a useful tool to investigate deficits in neurodevelopmental disorders. Oscillatory amplitude and frequency are commonly studied, but peak-frequency variability is not usually reported.

The present findings support the hypothesis that BECTS is associated with a delay in the development of stable functioning of the bilateral sensorimotor areas [Koutroumanidis, 2007]. Moreover, the pattern of correlations with age in our results proposes beta-band peak frequency variability as a neural correlate of this delay. The concept of

neural "disorganisation" has previously been proposed to relate to epilepsy [Overvliet et al., 2010], as well as other neurocognitive disorders such as autism [Kennedy and Courchesne, 2008], and may also be applicable to brain immaturity. An exaggerated age-related developmental instability in patients with BECTS may explain the delay in their development of motor cortex function, and the impaired motor control that is generally observed in BECTS [Overvliet et al., 2011]. Our findings are consistent with a recent fMRI study by [Besseling et al. 2014] who showed that the consistency between structural and functional connectivity was reduced for BECTS patients in medial parietal and centro-temporal clusters, especially at younger ages, supporting a developmental delay in these areas. The capability of MEG to study neural oscillations, thought to be crucial for long-range neural communication [Donner and Siegel, 2011; Fries, 2005], allowed the present study to further show that the stability in synchronization, and the frequency of background beta-band oscillations appear to be an important determinant of this neurodevelopmental delay in sensorimotor cortex.

Similar to most previous fMRI studies [Besseling et al., 2013a,b; Tang et al., 2014], a small number of EEG studies examining resting background rhythms in BECTS found either global abnormalities, or local abnormalities outside of sensorimotor cortex. Braga et al. [2000] reported global increases in oscillatory power in a group of children with rolandic spikes, particularly in lower-frequency ranges in older patients. In contrast, using LORETA source localization, Besenyei et al. [2012] found increased low-frequency oscillatory resting-state activity localized to a parietotemporal area for patients versus controls. This was found only in 4–6 Hz out of a range of 1–25 Hz in 1-Hz bands. In a pilot study of four patients, Clemens et al. [2013] did not replicate this area, but reported that some patients had inconsistent "abnormal" connectivity patterns at an early stage of BECTS, which reverted back to a "normal" pattern at remission. However, our findings, as well as those of others [Besseling et al., 2013a,b; Lillywhite et al., 2009], suggest that there exist clear specific patterns of neural activity in relevant functional areas that characterize the abnormalities in BECTS. Understanding these deficits may be crucial in driving progress in assessing the merits of treatment and improving the core cognitive deficits associated with BECTS.

However, the sensorimotor characteristics we found did not significantly correlate with behavioral measures. Absence of a correlation between neural findings and cognitive tasks is not uncommon in BECTS research, especially in sensorimotor cortex [Besseling et al., 2013a; Tang et al., 2014]. This may be due to the generally small group size, variability in cognitive impairments [Ewen et al., 2011], and correlations that may not be linear. However, correlations with behavioral performance have been found for language areas or connectivity between language and sensorimotor areas [Besseling et al., 2013b; Lillywhite et al., 2009]. In BECTS, language deficits are more commonly reported than motor deficits. It is possible that the combination of weaker deficits in motor than language skills and greater variability of the former obscure clear correlations with sensorimotor resting activity. Other factors such as socioeconomic status and intelligence may further contribute to what extent neurocognitive disabilities develop, and children may develop coping strategies that ameliorate behavioral deficits.

It is unclear whether and how motor deficits in BECTS relate to the commonly reported linguistic difficulties. The deficits in the language domain may be a downstream effect of altered motor cortex functioning, either due to spread of activity to areas involved in language processing [Ibrahim et al., 2012; Overvliet et al., 2011; Overvliet et al., 2010], and/or as a result of motor execution difficulties such as tongue immobility [Lundberg et al., 2005]. We may speculate that the presence of epileptiform activity in sensorimotor areas initially causes a local disruption in sensorimotor functioning, which may then affect the development of functional networks. This, in turn, may cause the difficulties in motor and language skills. Perhaps epileptiform activity causes a disruption in neural activity that creates variability in the frequency of rhythmic neural firing that we observed in the present study, resulting in "unstable" local and network activity.

Both our network and individual motor cortex findings suggest bilateral occurrence of abnormalities in sensorimotor cortex, which raises the question of how our findings relate to centro-temporal spikes. Although spikes generally have a unilateral predominance, the side of predominance can change over time [Ewen et al., 2011], and they often appear bilaterally. One study found that even if spikes occur unilaterally, patterns of oscillatory disruption occur in both hemispheres [Lin et al., 2006]. Note however that this was based on only 10 epochs, all oscillatory ranges tested increased to some degree, and there was no control region included in this study, precluding exclusion of a global increase in oscillatory power. Furthermore, both contra- and ipsilateral motor cortex are thought to play a role in unilateral motor movements [Jurkiewicz et al., 2006]. Thus, it is also possible that predominantly unilateral epileptiform activity is related to the bilateral and network-level neural variability that we found here. We did not observe sufficient centro-temporal spikes to statistically investigate their relationship with the present neural findings in our 3-min MEG recording. However, observed MEG spike frequency did not appear to show a clear relationship to beta-band sensorimotor network values (Table I, Fig. 1E), nor frequency CV (Fig. 3E). Perhaps future MEG studies recording sleep-deprived and sleep resting-state activity may observe higher spike rates, or a relationship to overnight spikes from ambulatory EEG may allow investigation of how spikes link to these neural findings.

In contrast to the negative correlation of age with frequency variability in the beta band, age was positively correlated with frequency variability of 30–90 Hz gamma

oscillations. This measure was not tied to BECTS, but could serve as an additionally interesting marker of neural development. Oscillations in this frequency band have been related to neck-jaw muscle artefacts, but these are generally localized to bilateral extrastriate areas which are remote from sensorimotor cortex [Muthukumaraswamy, 2013]. HFOs in the gamma range are associated with the location of seizure-onset zone [Guggisberg et al., 2008; Jacobs et al., 2011; Kobayashi et al., 2009, 2011; Rampp et al., 2010]. Although HFOs are usually of higher frequency than those assessed in the current study (>80 Hz up to as much as 600 Hz), Ibrahim et al. [2012] found that ictal oscillatory desynchronization in childhood epilepsy was greatest in the highest sub-HFO gamma band (81–150 Hz) in the motor cortex of patients that had motor deficits. Moreover, both beta and gamma oscillations have been linked to GABAergic inhibition [Gaetz et al., 2011; Kubota et al., 2004]. Our findings of (opposite) age-related beta and gamma-band frequency variability in M1 may therefore reflect GABAergic brain maturation [Gaetz et al., 2010].

Our study has a number of limitations. First, the patient group was heterogeneous with respect to a number of factors (Table I), potentially confounding interpretation of neural changes as a group. Patients varied in state and type of medication, which may have an unknown influence both on our neural measures and cognition [Ebus et al., 2011]. There was also variability in the group in time since disease onset, seizure recency, and seizure frequency. There were no apparent relationships between the neural measures we report here with any of these patient characteristics. Estimates of seizure recency and frequency were based on verbal report by patients and their parents or guardians at the time of data acquisition, and may contain potential inaccuracies, but are generally reflective of the clinical scenarios. Given that there is partial covariation of most of these factors with age, this further complicated interpretation of the role of these factors with respect to the present neural findings. We have therefore not conducted formal statistical tests on these relationships. Although several patients at the time of recording reported little or no recent seizures, some of these patients showed spikes in their MEG recording, and vice versa. Thus, seizure recency was not the only measure of disease status, as some patients who were seizure free for a year or more still had indications of "active" disease with typical sensorimotor cortex spikes. Most importantly, all patients were in the known age range of active disease in BECTS prior to the expected remission. We feel this allowed valid gross-group conclusions of disease marker effects and correlations with age as compared to typically developing age-matched controls.

Second, we did not control for head size, which is directly related to age. Smaller head size is known to correlate with lower amplitude of beta-band oscillations [Gaetz et al., 2008, 2010], but it is not known whether head size correlates with peak frequency. Peak frequency within a characteristic oscillatory response is known to decrease with age, though this may be specific to adults [Gaetz et al., 2010]. Third, our frequency filtering precluded investigation of frequencies in the HFO range and below 6 Hz. A recent study suggested that low-frequency oscillations may be related to the abnormal development of functional networks [Michels et al., 2011], which should be investigated in future studies. Fourth, we could not assess the influence of spikes on network and local motor cortex activity. Finally, both our groups had a relatively small sample size that may have impacted on statistical power.

CONCLUSION

Two separate analyses converged to show greater variability in resting-state beta-band sensorimotor oscillatory activity in BECTS compared to age-matched typically developing controls. This was in contrast to the visual network, and variability in other frequency bands, where there was no difference between groups. This convergence supports the relevance of our findings for the characterization of neural abnormalities in BECTS. The present findings support a neurodevelopmental delay of brain activity related to sensorimotor areas, and suggest that the frequency at which beta-band oscillations are expressed is less stable in patients with BECTS than in typically developing controls. Network measures and local frequency variability may be independent neural markers that are more closely tied to disease-related disruption and brain maturation, respectively. This study suggests that, in addition to the language domain, a focus on sensorimotor functioning in BECTS may contribute toward defining the most appropriate intervention strategies. In addition, our study suggests that investigating the variability of oscillatory peak frequency may be a useful tool to investigate deficits of neural disorganization in neurodevelopmental disorders.

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