Frontal Lobe Epilepsy Alters Functional Connections Within the Brain's Motor Network: A Resting-State fMRI Study

Kristine Elizabeth Woodward,¹⁻³ Ismael Gaxiola-Valdez,^{2,3}
Bradley Gordon Goodyear,²⁻⁵ and Paolo Federico^{1-4,6}

Abstract

Patients with frontal lobe epilepsy (FLE) often experience motor deficits, yet little is known of the impact of FLE on the activity of motor networks in the brain. Resting-state functional magnetic resonance imaging (rs-fMRI) has previously demonstrated an association between cognitive deficits in temporal lobe epilepsy patients and disruption of activity within pertinent brain networks. Hence, in the present study, rs-fMRI was used to determine whether FLE is associated with motor network disruption. Seven right-hemisphere FLE patients, six left-hemisphere FLE patients, and nine control subjects underwent rs-fMRI. Functional connectivity was computed between the sensorimotor cortex contralateral to the seizure focus and each voxel in the brain, and then compared voxel-by-voxel between patient groups and controls. A laterality index (LI) of connectivity between contralateral and ipsilateral sensorimotor cortices was calculated to investigate its association with epilepsy duration and seizure frequency. Positive laterality indices indicate reduced connectivity, and zero values indicate strong connectivity. Connectivity between the left and right sensorimotor cortices was significantly reduced in FLE patients compared with controls ($p < 0.05$), and LI was positively correlated with the number of lifetime seizures (left FLE: $r_s = 0.89$, right FLE: $r_s = 1.00$). Patients with FLE exhibit decreased connectivity within the motor network, in correlation with the number of lifetime seizures, thus demonstrating a potential relationship between seizure activity and changes in motor network organization. These findings suggest that motor network disturbances may in part be responsible for the motor deficits observed in FLE patients.

Key words: epilepsy; frontal; functional connectivity; motor system; resting-state

Introduction

FRONTAL LOBE EPILEPSY (FLE) is the second most common type of focal epilepsy (Manford et al., 1996). Patients with FLE commonly develop motor deficits including impaired coordination, decreased dexterity, and poor motor planning skills that can hinder the performance of daily activities (Exner et al., 2002; Helmstaedter et al., 1996; Upton and Thompson, 1996). Although the elimination of seizures may alleviate these deficits, only 20–30% of patients achieve seizure freedom with medication (Regesta and Tanganelli, 1999), and only 30–50% achieve seizure freedom with surgery (Bagla and Skidmore, 2011). Clearly, there is a need to better understand the underlying

mechanisms that give rise to FLE and its impact on brain function.

Previous studies have focused on understanding the physiological processes that occur at seizure foci during interictal and ictal periods. However, a gap remains in the understanding of potential interactions between the seizure focus and distant brain regions during these periods [for a review, see Bertram (2013)]. Indeed, epilepsy has been characterized as a network disorder (Kramer and Cash, 2012); therefore, studying interactions between brain regions is crucial to further understand focal epilepsy. One technique that can examine these interactions is resting-state functional magnetic resonance imaging (rs-fMRI), which measures the synchrony of activity between brain regions during periods of rest

¹Department of Neuroscience, University of Calgary, Calgary, Canada.

²Hotchkiss Brain Institute, University of Calgary, Calgary, Canada.

³Seaman Family MR Research Centre, University of Calgary, Calgary, Canada.

Departments of ⁴Radiology, ⁵Psychiatry, and ⁶Clinical Neuroscience, University of Calgary, Calgary, Canada.

(Biswal et al., 1995). The degree of synchrony is thought to indicate the strength of functional connections (i.e., functional connectivity) that are organized into distinct networks of functionally related brain regions (Zhang and Raichle, 2010). These networks are hypothesized to help develop, maintain, and increase the reliability of neural responses to external stimuli (Pizoli et al., 2011; Uddin et al., 2010).

In the presence of neurological disorders or disease, it is generally believed that reduced connectivity relative to healthy brain regions indicates network disruption, whereas increased connectivity implies compensatory recruitment of additional brain regions (Wang et al., 2011). Altered connectivity has been reported in patients with neurological disorders, such as amyotrophic lateral sclerosis (Mohammadi et al., 2009), stroke (Park et al., 2011), Parkinson's disease (Wu et al., 2009), and multiple sclerosis (Dogonowski et al., 2013). In patients with left-hemisphere temporal lobe epilepsy, decreased connectivity has been demonstrated within language (Waites et al., 2006) and memory networks (Doucet et al., 2012), in association with language and memory deficits, respectively. This suggests that behavioral deficits in epilepsy may be the result of disrupted activity within associated resting-state networks, due to repeated seizure activity. A previous fMRI study reported that children with FLE had an increased number of functional connections within the frontal lobe, but a decreased number of functional connections between the frontal lobe and the rest of the brain (Vaessen et al., 2012). Furthermore, the extent of this frontal lobe isolation was positively correlated with the degree of cognitive impairment. Sensorimotor network connectivity has also been studied in children with FLE, revealing disruptions compared to control participants in association with poor motor function (Widjaja et al., 2013).

A possible pathophysiological explanation for network disruption in epilepsy is the increase in inhibitory synaptic activity necessary to suppress seizure activity. As seizures accumulate over a patient's lifetime, the chronic increase in inhibitory activity near the seizure focus may disrupt the resting-state synchrony between brain regions in close proximity (e.g., language and memory networks in temporal lobe epilepsy and motor networks in FLE) (Juhász et al., 1999; Waites et al., 2006). Indeed, previous studies have demonstrated that the number of years since seizure onset was directly related to a decrease in functional connectivity in patients with absence epilepsy (Luo et al., 2011) and primary generalized tonic-clonic seizures (Wang et al., 2011). Functional connectivity changes in attention and auditory resting-state networks of the frontal lobe were also associated with age at seizure onset in children with FLE. Specifically, weaker connectivity was seen in auditory networks, and stronger connectivity in attention networks, in children who had seizures beginning at an earlier age (Widjaja et al., 2013). However, no associations were found between connectivity in the sensorimotor network and age at seizure onset, or duration of epilepsy (Widjaja et al., 2013).

While resting-state motor networks have been examined in children with FLE (Widjaja et al., 2013), to our knowledge, no studies have examined motor network connectivity in adult patients with FLE. Brain connectivity continues to change throughout childhood and into adulthood (Casey et al., 2005; Fair et al., 2009); therefore, we believed it was important to study adult subjects. As such, we hypothesized that patients with FLE would exhibit decreased connectivity between the sensorimotor cortices of the healthy and epileptic hemispheres,

as measured by rs-fMRI. We also hypothesized that the extent of decreased connectivity would be directly related to seizure frequency and the number of years since onset of seizures.

Materials and Methods

Participants

This study was approved by the Conjoint Health Research Ethics Board of our institution. Written informed consent was obtained from all participants prior to their participation. Patients with FLE were identified through the Alberta Health Services—Calgary Zone Epilepsy Clinic, the Seizure Monitoring Unit of the Foothills Medical Center, and the Comprehensive Epilepsy Program, in Calgary, AB. Seven right-hemisphere FLE patients (5M, 2F; age = 32.9 ± 11.8 years) and six left-hemisphere FLE patients (4M, 2F; age = 39.3 ± 17.5 years) were recruited. A diagnosis of FLE was confirmed by history, examination, routine electroencephalography (EEG), video-EEG monitoring, and/or anatomical magnetic resonance (MR) imaging. Nine nonepileptic controls (4M, 5F; age = 29.9 ± 12.8 years) were recruited through word of mouth, and they had no known reported neurological or psychiatric disorders. Other exclusion criteria included previous neurosurgery and contraindications to MR imaging (pregnancy, severe claustrophobia, metallic foreign bodies in the eye, and certain implanted medical devices [e.g., cardiac pacemaker, aneurysm clip]). All participants were right-handed. Patient details are given in Table 1.

Behavioral motor testing

Participants were assessed for motor impairments as part of a separate, concurrent, motor task-based fMRI study. The task was similar to Luria's motor sequences (Luria and Haigh, 1973). Participants performed a series of bimanual movements for a total of 5 min, in blocks of 24 sec of rest alternating with 24 sec of task. Movements were cued by a visual stimulus at 2-sec intervals (circle = hand held in fist, vertical line = hand held vertically, horizontal line = hand held horizontally). A different movement was performed with each hand simultaneously (e.g., holding the left hand in a fist and holding the right hand vertically). Performance was video recorded and later scored blindly on a scale of 1 to 4, where 1 represented no deficit (Table 2) (Helmstaedter et al., 1996). This task permitted the assessment of a participant's ability to form correct hand posture, accurately time movements, and coordinate and plan movement. Participant performance was compared between patients and control subjects using the Mann–Whitney U test.

fMRI data collection

While in the MR scanner, participants were asked to remain awake and move as little as possible while focusing attention on a central fixation cross displayed on a projector screen. Each participant's head was immobilized using foam cushioning, and participants had the option to terminate the study at any time during the scan using a squeeze ball placed by their side.

MR data were acquired using a 3.0 T GE Discovery MR750 whole body scanner (GE Healthcare, Waukesha, WI) with a receive-only 8-channel phased-array head coil (8 Channel High Resolution Brain Array, distributed by GE Medical Systems). Resting-state MR images providing blood oxygen level

TABLE 1. FRONTAL LOBE EPILEPSY PATIENT CHARACTERISTICS

<i>Gender</i>	<i>Age at scan (years)</i>	<i>Age at seizure onset (years)</i>	<i>Seizure burden</i>	<i>Months since last seizure</i>	<i>Seizure focus</i>	<i>Seizure types</i>
Patients with right FLE						
M	16	7	Low	7	Supplementary sensorimotor	FDC, GTC
F	20	12	Moderate	0	Primary motor	FDC, FNDC, GTC
M	32	26	Moderate	14	Anterior frontopolar	FNDC
M	33	28	Low	20	Anterior frontopolar	FDC
F	36	0	Low	10	Supplementary sensorimotor	FDC, GTC
M	46	39	Low	13	Anterior frontopolar	FDC, GTC
M	47	28	Low	112	Supplementary sensorimotor	GTC
Mean $\pm$ SD	32.9 $\pm$ 11.8	20 $\pm$ 13.9				
Patients with left FLE						
M	19	4	Low	6	Supplementary sensorimotor	FDC, FNDC, GTC
M	28	2	Very high	2	Primary motor	FDC, FNDC, GTC
M	30	8	High	0	Primary motor	FNDC, GTC
M	39	2	Very high	1	Dorsolateral	FDC, GTC
F	55	12	Low	18	Primary motor	FNDC, GTC
F	65	41	Low	30	Primary motor	FDC, FNDC
Mean $\pm$ SD	39.3 $\pm$ 17.5	11.5 $\pm$ 15.0				
Control subjects						
M	16, 23, 23, 33	n/a	n/a	n/a	n/a	n/a
F	19, 24, 31, 43, 57	n/a	n/a	n/a	n/a	n/a
Mean $\pm$ SD	29.9 $\pm$ 13.0	n/a				

Seizure types are listed as focal without dyscognitive features (FNDC), focal with dyscognitive features (FDC), generalized tonic-clonic (GTC). Seizure burden was evaluated at the time of study as low (seizures every 6 months or longer), moderate (every 1–6 months), high (every 2–4 weeks), or very high (every 2 weeks or less).

FLE, frontal lobe epilepsy; n/a, not applicable.

dependent (BOLD) contrast were collected for 5 min using a gradient-recalled echo, echo planar imaging sequence (voxel dimensions $3.75 \times 3.75 \times 4$ mm, 28 slices, 4-mm slice thickness, 64×64 matrix, TE = 30 msec, TR = 1.5 sec, flip angle = 65 degrees). Participants also underwent T₁-weighted multi-slice spoiled gradient echo (28 slices, 4-mm thickness, 128×128 matrix, minimum TE, TR = 150 msec, flip angle = 18 degrees) and 3D magnetization-prepared gradient-echo sequences (2-mm slices, $384 \times 256 \times 112$ matrix, preparation time = 500 msec, minimum TE, TR = 8.9 msec, flip angle = 20 degrees) for anatomical registration of the fMRI data.

Preprocessing

Preprocessing of MR data was performed using fMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl/) (Jenkinson et al., 2012). These steps included brain extraction using the Brain Extraction Tool (Smith, 2002), correction for interleaved slice timing using Fourier-space time-series phase-shifting, motion correction using Motion Correction:

FMRIB's Linear Image Registration Tool [MCFLIRT (Jenkinson et al., 2002)], spatial smoothing with a 6-mm full width half-maximum Gaussian kernel, high pass temporal filtering (Gaussian-weighted least-squares straight line fitting with sigma = 100.0 sec), grand-mean intensity normalization of the entire 4D dataset using a single multiplicative factor, and registration to the common brain template of the Montreal Neurological Institute (MNI).

Using the drawing tool of FSL, white matter and cerebrospinal fluid regions were segmented by manually creating masks. Manual segmentation was used because it is as accurate and no more time consuming than autosegmentation (unpublished observations). The average BOLD signal time course was obtained for each of the white matter and cerebral spinal fluid masks. These time courses plus the six directional estimates of head displacement (i.e., translation and rotation in the x, y, and z directions) were entered into a first-level General Linear Model (GLM) using FSL's fMRI Expert Analysis Tool (FEAT), and the resulting residual data were used for remaining analyses.

TABLE 2. PERFORMANCE SCALE USED TO RATE PARTICIPANT HAND MOVEMENTS DURING THE COORDINATION TASKS

<i>Score</i>	<i>Description</i>
1 (no impairment)	Participant performs the sequences correctly and fluently
2 (mild impairment)	Participant performs the sequences too slowly and/or with interruptions
3 (impairment)	Participant displays significant interference or inadequate strength while performing the sequences; movements cannot be separated and appear to be mixed, both hands perform same hand movement during bimanual task
4 (severe impairment)	Participant is unable to execute either the unimanual or bimanual sequence, or coordination breaks down after a few repetitions

First-level analysis

The left and right sensorimotor cortices served as regions of interest (ROIs). These ROIs were identified using the MNI template and consisted of the primary motor cortex (precentral gyrus—Brodmann's Area 4) and the primary sensory area (postcentral gyrus—Brodmann's Areas 3, 2, and 1), defined as extending from the lateral surface to the midline, and from the vertex of the brain to the level of the superior aspect of the lateral ventricles caudally (Tjandra et al., 2005). ROIs were subsequently registered to each individual's native fMRI data using FSL's FMRIB's Linear Image Registration Tool [FLIRT (Jenkinson et al., 2002)] and trimmed to the 400 most temporally correlated voxels using inter-voxel cross-correlation (Golestani and Goodyear, 2011). This corresponded to 84–91% of the initial ROI voxels, as shown in Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/brain). This trimming method allowed us to objectively determine the most contiguous group of voxels to use as a mask, allowing greater consistency of the masks between participants.

For patients with right FLE, the time course of the average resting-state BOLD signal of the left (healthy) hemisphere ROI was extracted and used in a GLM analysis to determine the degree to which the time course of BOLD signal for every voxel in the brain was correlated with the ROI in the left hemisphere. Similarly, for patients with left FLE, the right (healthy) hemisphere ROI was used. For controls subjects, each of the left- and right-hemisphere ROIs were used in separate analyses, to permit comparisons with the appropriate patient group. The healthy hemisphere ROI, rather than the epileptic hemisphere ROI, was selected because it more likely represents an unaffected region of the motor network, thereby allowing us to determine the degree to which the sensorimotor cortex of the epileptic hemisphere was functionally disconnected from the remaining motor network.

Higher-level analysis

Group analyses were conducted using a General Linear Mixed Model within FSL (Jenkinson et al., 2012), to create average connectivity maps for each group (controls $\times$ 2, right FLE, and left FLE), and the difference between right FLE patients and controls, and between left FLE patients and controls. Maps were generated using a corrected cluster significance of $p=0.05$, using *AlphaSim*, which uses Monte Carlo simulations of null distribution image data to estimate family-wise error rates (Ward, 2000).

Laterality index

For each participant, a laterality index (LI) of average Z-scores was computed for the healthy hemisphere and epileptic sensorimotor ROIs as follows, using a method similar to that of Langan et al. (2010):

$$LI = \frac{(\text{avg } Z_{\text{healthy}} - \text{avg } Z_{\text{epileptic}})}{(\text{avg } Z_{\text{healthy}} + \text{avg } Z_{\text{epileptic}})}$$

where “healthy” is the sensorimotor ROI of the hemisphere contralateral to the seizure focus, and “epileptic” is the sensorimotor ROI of the hemisphere ipsilateral to the seizure focus (i.e., right ROI map for patients with left FLE, and left ROI map for patients with right FLE; see Supplementary

Figs. S1 and S2). The average Z-score for the healthy sensorimotor ROI indicates how strongly this region is connected to itself. We would expect the healthy sensorimotor ROI to be strongly connected to itself within this functionally homogeneous region, and therefore the average Z-score serves as a “control” value of expected connectivity of the ROI in the healthy hemisphere. The average Z-score for the epileptic sensorimotor ROI indicates how strongly this region is connected to the healthy sensorimotor ROI. Thus, an LI of zero indicates that the connectivity of the epileptic sensorimotor ROI to the healthy sensorimotor ROI is the same as the healthy sensorimotor ROI connectivity relative to itself. Positive LI values indicate reduced connectivity between the healthy sensorimotor ROI and epileptic sensorimotor ROI, relative to connectivity within the healthy sensorimotor ROI itself. Negative LI values indicate increased connectivity between the healthy sensorimotor ROI and epileptic sensorimotor ROI, relative to connectivity within the healthy sensorimotor ROI itself.

Spearman's rank correlation analysis was performed between LI and the following seizure factors: age at epilepsy diagnosis, years since diagnosis, lifetime seizures (total or generalized tonic-clonic seizures alone), seizures within the past year (total or generalized tonic-clonic seizures alone), and the number of months since the last seizure. Seizure factors were identified and quantified by reviewing each patient's history in clinic and hospital charts. Most patients met with their physician once per year, and more if they were having difficulty controlling their seizures. By reviewing the number of seizures between each clinic/hospital visit, the seizure frequency was determined. The total number of lifetime seizures was determined by summing the number of seizures as documented in each patient's complete medical record since onset of their epilepsy.

Results

Behavioral motor testing

All control subjects performed the task well and received a score of 1. Patients with FLE performed significantly worse, with an average score of 1.5 ± 0.7 ($p=0.04$), confirming a motor deficit in this group. A detailed breakdown of the performance for the three groups is shown in Table 3. In contrast, both FLE groups had subjects with scores of 2 or 3, particularly in the left FLE group, where 4 out of 6 subjects had a score greater than 1. Patients with foci in the sensorimotor cortex did not perform significantly worse than those with seizure foci in other locations in the frontal lobes. Specifically, two patients with right FLE had foci in the sensorimotor cortex and received scores of 1 and 2 (average = 1.5 ± 0.7), which

TABLE 3. PERFORMANCE SCORES DURING BEHAVIORAL MOTOR TESTING FOR EACH PARTICIPANT GROUP, RATED ON A SCALE OF 1 TO 4 (SEE TABLE 2)

Group	Number of participants that received the corresponding score:				Mean $\pm$ SD
	1	2	3	4	
Controls	9	0	0	0	1.0 ± 0.0
Right FLE	5	2	0	0	1.3 ± 0.5
Left FLE	2	3	1	0	1.8 ± 0.8

was not significantly different from the average score of 1.3 ± 0.5 that right FLE patients with seizure foci in other locations received ($p=0.20$). Four patients with left FLE had foci in the sensorimotor cortex: two received scores of 1, and two received scores of 2 (average = 1.5 ± 0.6). This was not significantly different from the average score of 2.0 ± 0.8 that left FLE patients with seizure foci in other locations received ($p=0.36$). When pooling together the data from patients with seizure foci within either the left or right sensorimotor cortex (three with a score of 1 and three with a score of 2, average = 1.5 ± 0.6), no significant differences were seen for patients with seizure foci in other frontal lobe regions (1.6 ± 0.8 , $p=0.86$).

fMRI findings

Brain regions demonstrating significant connectivity for all three participant groups (controls, right FLE, and left FLE) included the contralateral sensorimotor cortex, supplementary motor area, and premotor cortex (see Supplementary Figs. S1 and S2 for average group maps). This is consistent with previous studies examining resting-state connectivity within motor networks (Biswal et al., 1995; Damoiseaux et al., 2006). Figure 1 shows that relative to control subjects, both left and right FLE patients exhibited decreased inter-hemispheric connectivity between the sensorimotor cortices. Right FLE patients also exhibited reduced connectivity within the sensorimotor cortex of the healthy hemisphere, and with the left superior temporal gyrus, left occipital pole, and right fusiform gyrus (all regions are summarized in Table 4).

For control subjects, LI was not significantly different from zero, with an average LI of 0.00 ± 0.03 (range: -0.06 to 0.05) when using the left sensorimotor cortex ROI as the seed region for connectivity analysis, and an average LI of 0.06 ± 0.05 (range: -0.01 to 0.14) when using the right sensorimotor cortex ROI as the seed region for connectivity analysis. LI was

equal to 0.08 ± 0.04 (range: 0.01 to 0.14 ; six out of seven beyond the control range) for right FLE patients, and 0.19 ± 0.11 (range: 0.07 to 0.35 ; four out of six beyond the control range) for left FLE patients. However, LI did not significantly differ between each patient group and control subjects.

As shown in Figure 2, LI for FLE patients was positively correlated with the total number of lifetime seizures, suggesting that cumulative seizure activity is associated with decreased inter-hemispheric connectivity between the sensorimotor cortices (left FLE, $r_s=0.89$; right FLE, $r_s=1.00$). No significant correlation was observed between LI and other seizure burden factors.

Discussion

This is the first known study to examine resting-state motor networks in adult patients with FLE. Relative to control subjects, we observed decreased inter-hemispheric connectivity between the sensorimotor cortices of the healthy and epileptic hemispheres. We also observed a significant relationship between the reduction in connectivity (expressed as a LI) and the total number of lifetime seizures.

Motor impairments and resting-state connectivity

Decreased connectivity between motor regions in the brain has been observed in other patient populations who experience motor deficits, including brain tumors (Otten et al., 2012), stroke (Park et al., 2011), amyotrophic lateral sclerosis (Mohammadi et al., 2009), and Parkinson's disease (Wu et al., 2009). Our findings of reduced connectivity and impaired motor function in patients with FLE provide further support that an altered resting-state motor network may be associated with motor deficits. This is supported by a previous study of children with FLE, which found reduced functional connectivity in sensorimotor networks that decreased in

FIG. 1. Brain regions exhibiting significantly reduced connectivity with the healthy hemisphere sensorimotor cortex in FLE patients, relative to control subjects. Color scale indicates statistical significance of the difference from control subjects (expressed as a Z-score), and blue colors indicate regions of reduced connectivity in FLE patients compared to controls. Images are oriented so that the epileptic hemisphere (E) is on the left and the healthy hemisphere (H) is on the right. Slice locations are given in mm of the Montreal Neurological Institute template brain. The approximate region of interest location used for the connectivity analysis is indicated by the green circle. FLE, frontal lobe epilepsy.

TABLE 4. BRAIN REGIONS EXHIBITING SIGNIFICANTLY LESS CONNECTIVITY WITH THE HEALTHY HEMISPHERE SENSORIMOTOR CORTEX IN FRONTAL LOBE EPILEPSY PATIENTS, RELATIVE TO CONTROL SUBJECTS

Cortical region	# of voxels	Z-max	x	y	z
Patients with left FLE (right seed)					
Left (epileptic) postcentral gyrus	163	3.06	-54	-12	32
Left (epileptic) precentral gyrus	80	2.52	-18	-28	54
Patients with right FLE (left seed)					
Right (epileptic) superior temporal gyrus	157	3.01	58	-28	14
Right (epileptic) postcentral gyrus	136	2.83	64	-24	50
Left (healthy) postcentral gyrus	110	2.78	-58	-28	54
Left (healthy) occipital pole	101	2.97	-38	-98	2
Left (healthy) superior temporal gyrus	90	2.93	-42	-42	24
Right (epileptic) fusiform gyrus	80	2.72	34	-50	-10

Coordinates are given in mm of the Montreal Neurological Institute template brain, and are of the local maxima Z-score of each brain region.

association with impaired motor function (Widjaja et al., 2013). Our findings also extend upon previous studies of temporal lobe epilepsy patients, where reduced connectivity within memory networks was correlated with poorer memory test scores (Doucet et al., 2012), and decreased connectivity within language networks provided a possible explanation for patients' language impairments (Waites et al., 2006).

In our study, reduced functional connectivity was also observed in brain regions outside of the frontal lobes, providing supportive evidence for greater isolation of the frontal lobes from the rest of the brain. These findings are consistent with a previous study of pediatric FLE patients that demonstrated a decreased overall connectivity between the entire frontal lobe and other brain regions that was consistent with their cognitive and motor impairments (Braakman et al., 2013). Decreased connectivity with regions outside the frontal lobe, which was observed in our study, may also explain patients' poorer performance on the coordination task, which requires input from other brain lobes.

Relationship between LI and total lifetime seizures

In healthy adults there is generally a strong structural connection between the left and right sensorimotor cortices, and

therefore a high degree of correlation between these regions in the resting state. Therefore, LI in healthy controls should be near zero, as we observed in our control subjects. The average LIs in the right and left FLE groups were not significantly different from the control group. However, six patients with right FLE and four patients with left FLE exhibited LI values outside of the control range. Furthermore, there was a direct correlation between the LI and the total number of lifetime seizures in both of these patient groups (Fig. 2). This is consistent with the possibility that with increased seizure activity, the epileptic sensorimotor cortex becomes progressively more isolated. To rule out the possibility that this trend may be related to an intrinsic difference in LI between the right and left ROIs, we conducted a paired *t*-test between the LIs of control subjects when using the left sensorimotor cortex ROI and the right sensorimotor cortex ROI. This comparison did not reveal any significant differences; therefore, we believe that the difference between right and left FLE patients and controls was due to seizure burden and not a confounding factor of the ROI used for each patient group.

The fact that the average LIs were not significantly different between groups was likely due to the small number of participants, some of whom had low seizure burdens,

FIG. 2. Correlation between laterality index (LI) of inter-hemispheric connectivity and the total lifetime number of seizures for left and right FLE patients. Greater LI values indicate reduced connectivity between the healthy hemisphere sensorimotor cortex and the epileptic hemisphere sensorimotor cortex (left FLE patients: $r_s = 0.89$; and right FLE patients: $r_s = 1.00$).

therefore resulting in LIs within the normal range. With more patients, particularly those with a greater number of lifetime seizures, we expect that the average LIs would differ between groups, especially between control subjects and patients with FLE.

In support of our observations, previous human studies have shown that the number of years since seizure onset is directly related to decreased functional connectivity in absence epilepsy (Luo et al., 2011) and primary generalized tonic-clonic seizures (Wang et al., 2011). Reduced functional connectivity of the auditory and attention networks was also associated with age at seizure onset in children with FLE, with stronger attention network connectivity, and weaker auditory network connectivity being found in children with an earlier age of seizure onset (Widjaja et al., 2013). Contrarily, in this same study no significant relationships were found between connectivity in the sensorimotor network and age at seizure onset, or duration of epilepsy (Widjaja et al., 2013). On the other hand, *increased* resting-state motor network connectivity that was positively correlated with the number of years since seizure onset was observed in another study of idiopathic generalized epilepsy (Maneshi et al., 2012). The disparity between studies may reflect the unique presentation of each epilepsy type and the differing impacts that different seizure types may have on functional networks.

Pathophysiology of reduced resting-state connectivity

Increased synaptic inhibition has been observed in regions surrounding the seizure focus, possibly as a means to suppress oncoming seizure activity (Zhao et al., 2011). In FLE, if the sensorimotor cortex ipsilateral to the seizure focus was part of the inhibitory surround region, activity may not fluctuate synchronously with the contralateral homologous region, thus decreasing functional connectivity. However, one might expect this phenomenon to occur just prior to seizure onset, and not during interictal periods. With increasing number of seizures over a patient's lifetime, it is possible that more permanent inhibitory synaptic connections form that persist into interictal periods. As a result, increased seizure frequency would be directly related to reduced synchrony (and therefore connectivity) between the sensorimotor cortices of the epileptic and healthy hemispheres, as observed in the present study. In support of this interpretation, it is well known that patients with temporal lobe epilepsy often have reduced interictal metabolism and blood flow in the hemisphere ipsilateral to the seizure focus, the extent of which directly correlates with the number of years since seizure onset (Breier et al., 1997).

While there are regions of increased inhibition surrounding the seizure focus, there are also regions of hyper-excitability and hyper-synchrony within the seizure focus, and in other brain regions that are targets of seizure propagation (Spencer, 2002). If these regions located outside of the seizure focus were to repeatedly fire together due to increased seizure frequency, they would likely form stronger functional connections during interictal periods. The formation of these new networks could therefore cause disruptions and decreases in connection strength within typical motor networks, as observed in the present study. Indeed, an EEG-fMRI study of idiopathic generalized epilepsy showed that decreases in functional connectivity between motor regions were directly

correlated to the number of interictal discharges recorded during the fMRI acquisition (Luo et al., 2012). Since interictal discharges may follow pathways of seizure propagation, it could be reasoned that more frequent interictal discharges might establish and maintain atypical motor networks and thus alter connectivity.

It has also been demonstrated that patients with FLE have frontal lobe atrophy, both ipsilateral and contralateral to the seizure focus (Cascino et al., 1992; Ferrier et al., 1999), and decreased volume and increased diffusivity across the entire corpus callosum (O'Dwyer et al., 2010). These observations were in correlation with the number of years since FLE onset (O'Dwyer et al., 2010). Another study of patients with temporal lobe epilepsy demonstrated a direct relationship between hippocampal atrophy and disrupted functional connectivity (Pereira et al., 2010). Thus, frontal lobe atrophy may, in part, account for the decreased motor network connectivity observed in the present study.

Limitations

The resting-state data for this study were collected following performance of a motor task for a separate task-based fMRI study. The period of time that elapsed between task performance and data collection for the resting-state scan was greater than 6 min, which has been shown to be sufficient to allow brain activity and connectivity to return to baseline (Barnes et al., 2009). Therefore, it is unlikely that residual processing accounted for the differences observed in functional connectivity between patient and control groups.

The number of participants in the present study was low due to the limited number of FLE patients presenting at our referral center. Due to low patient numbers, patient heterogeneity is a concern; neuropsychological and task-based fMRI results have been shown to exhibit a dependence on seizure focus location within the frontal lobe (Koudijs et al., 2010), and seizure frequency, severity, and duration (Upton and Thompson, 1996). We accounted for the effects of heterogeneous seizure burden factors by considering and investigating correlations between LI and seizure factors. It was more difficult to account for the location of the seizure focus as there were not enough participants to further separate them into subgroups, however, none of the patients had visible lesions on MR imaging. Of note, four out of six patients with left FLE had seizure foci within the primary motor cortex, whereas only one out of seven patients with right FLE had seizure foci within the primary motor cortex. This discrepancy may have influenced our results. To further investigate this possibility, it would be ideal to recruit more subjects and either separate patients into subgroups based on seizure foci within more specific frontal lobe regions, or incorporate seizure focus location in data analysis.

One limitation of our study is the relatively small sample size and a difference in the age range of participants studied (right FLE: 32.9 ± 11.8 [range: 16 to 47], left FLE: 39.3 ± 17.5 [range: 19 to 65], controls: 29.9 ± 13.0 [range 16 to 57]). This reflects the difficulty in recruiting FLE patients for such a study. Despite this, there was no statistically significant difference in the mean ages between groups. In support of this observation, another study found no significant difference in functional connectivity between regions in the motor network between a younger group of patients

(age 22.8 ± 2.3) and an older group (age 70.7 ± 6.0) (Damoiseaux et al., 2008). In contrast, another study found significant differences, with older patients (age 61.8 ± 3.6) having significantly reduced connectivity in the motor network compared with younger patients (age 26.6 ± 2.3) (Wu et al., 2007). One important difference between these studies and ours is that the age gap between groups was much larger than the maximum gap of 10 years in our study. Thus, it is unlikely that the small age difference between our study groups affected our results.

There were small differences in the proportion of males and females in each of our study groups, where both FLE groups had more male than female subjects compared with the control group (right FLE 5M, 2F; left FLE 4M, 2F; control 4M, 5F; Table 1). However, these differences likely did not influence the results of the present study. Indeed, a previous study of major resting-state networks (executive control, salience, and default mode) in males and females found no gender-based differences (Weissman-Fogel et al., 2010). The authors also further argued that resting-state fMRI studies do not need to be controlled for gender (Weissman-Fogel et al., 2010). Alternatively, another study found small magnitude gender differences in the sensorimotor networks, with males having marginally stronger functional connectivity within the sensorimotor network (Allen et al. 2011). If these effects were to be present in our dataset, then one would have expected that both patient groups (which have proportionally more males) would have greater sensorimotor network connectivity than control subjects. Instead, the opposite result was found. This suggests that, if anything, the results of the present study may have been weakened somewhat, and not a product of, any potential gender-based differences in sensorimotor resting-state networks.

The patients in the present study were taking one or more antiepileptic drugs in a variety of combinations. Previous investigations of the effect of antiepileptic drugs on fMRI data have provided variable results. Some studies demonstrated dose-dependent reductions of task-related BOLD signals (Jansen et al., 2006; Szaflarski and Allendorfer, 2012), whereas others observed no significant drug effect (Braakman et al., 2013; Yasuda et al., 2013). Whether antiepileptic drugs have an effect on resting-state connectivity, which is based on signal synchrony rather than signal amplitude, warrants further investigation.

Conclusions

Patients with FLE exhibit significantly reduced connectivity between the sensorimotor cortices of the epileptic and healthy hemispheres, which may be dependent on the number of lifetime seizures. This result suggests that repeated seizure activity generates motor network disturbances, which in turn may be responsible for the motor deficits experienced by patients with FLE.

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Address correspondence to:

Paolo Federico
Departments of Clinical Neurosciences and Radiology
University of Calgary
Room C1214a
Foothills Medical Centre
1403 29th Street NW
Calgary
Alberta T2N 2T9
Canada

E-mail: pfederic@ucalgary.ca