Identification of epileptic foci in refractory epilepsy through functional and structural connectivity based on MRI

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Abstract

Epilepsy is considered a disease in which ictal/interictal activity is generated and propagated through neuronal networks. Functional and structural connectivity, which can be implemented through magnetic resonance imaging (MRI), provide information about the network nature of epilepsy. With tractography and resting-state functional MRI (rs-fMRI), we aim to improve the identification of epileptic foci through connectivity analyses. This prospective study was approved by the Institutional Review Board. The study comprised 10 patients (3 women, 7 men; mean age: 31±10 years; range: 21-50 years). The selection criteria were adults with drug-resistant epilepsy, undergoing a clinically indicated standard MRI refractory epilepsy protocol, electrocorticography, video-EEG, F18-FDG PET or SPECT with possible treatment by surgery. In addition to the standard protocol, rs-fMRI, tractography and a 3D T1-weighted image (wT1-3D) were acquired and post-processed. A Crawford-Howell t-test was implemented to compare structural and functional connectivity matrices of each patient with healthy groups, obtaining contrast matrices. Maps were generated identifying clusters of 4 or more regions with significant differences (threshold of $p<0.05$), and they were compared with the patient's clinical diagnosis. The most statistically significant areas were identified in the contrast maps and compared with post-surgical results. Structural and functional connectivity maps were initially analysed separately, and then simultaneously. Tractography has a better sensibility and lower specificity than RS-fMRI; the simultaneous analysis increased the sensibility and precision values in more than 20%.

BACKGROUND AND AIM

Epilepsy is generally considered a disease of large neural networks, in which ictal and interictal activity is generated and propagated through neuronal networks involving one or both cerebral hemispheres [1,2]. There is evidence to suggest that epilepsy affects the functional and structural properties of brain networks, which can be investigated by analysis of brain connectivity [3,4,5]. Functional and structural connectivity analyses, which can be implemented through magnetic resonance imaging (MRI) techniques, provide information about the network nature of epilepsy [6].

Neuronal connectivity is defined as a set of physical connections, through axonal fibres, between the neuronal units of the gray matter (GM). This can be represented by a connectivity matrix, which is a mathematical representation of a network, given by a collection of nodes and links between pairs of nodes. To build these connectivity networks, the GM is segmented into several cortical and subcortical regions of interest (ROIs) that constitute the nodes, and the number of paths that connect two different regions is a weighting measure of the connection between them [7].

Resting-state functional MRI (rs-fMRI) can be used to noninvasively measure spontaneous neuronal activity and interregional activity correlations [8,9]. Connectivity analysis based on fMRI provides information about the physiopathogenesis of the epileptic network [10] and is currently used in presurgical evaluation of patients to identify patterns of functional connectivity that may be associated with an increased probability of seizure occurrence and to predict therapeutic outcomes [11]. However, the role of this technique in clinical applications is still limited, since further validation through invasive and follow-up studies is required to be considered reliable in the clinical setting [9,10].

On the other hand, there is currently growing evidence suggesting the importance of white matter (WM) in the pathogenesis of epilepsy [12, 13]. Ex vivo studies have shown that there are pathological changes in axonal integrity, cellular composition and myelination of WM in epileptic patients. Therefore, it is useful to analyse the connectivity of the WM in vivo through diffusion-weighted imaging (DWI). Tractography algorithms use the information given by DWI to identify microstructural alterations in tracts that are near or distant from the epileptogenic focus [14, 15]. This technique is also useful in predicting patient response to pharmacological or surgical treatments [16]. Because seizures spread rapidly in the brain, connectivity analyses are useful for the seizure initiation zone identification and the localization of hypo or hyperconnected areas of the brain that could affect the propagation of nerve impulses [3].
With tractography and resting-state functional MRI (rs-fMRI), we aim to improve the identification of epileptic foci through connectivity analyses.

METHODS

This prospective study was approved by the Institutional Review Board; patients undergoing clinically indicated standard MRI refractory epilepsy protocol, electrocorticography, video-EEG, F18-FDG PET or ictal/interictal SPECT with possible treatment by surgery. All patients signed a written informed consent (IC).

Participants

A total of 10 patients (3 women, 7 men; mean age: 31.5 years; range: 21-50 years) were retrospectively chosen from a cohort of refractory epilepsy patients. The selection criteria were adults (age≥18 years) with refractory childhood-onset epilepsy. The rs-fMRI data of the healthy group was obtained from the OpenfMRI database [17, 18, 19]. This included 70 healthy men or

women, ages 21-50. The exclusion criteria were patients cognitively unable to sign the IC.

Data acquisition

For the acquisition of MR images, a 3.0 T Signa PET/MRI system (General Electric Healthcare) was used, with an 8-channel high resolution brain coil. A standard brain imaging protocol for epilepsy was performed, which included the acquisition of sagittal T1 weighted images, and axial FLAIR, Fast Field Echo and T2 weighted images. It also comprised diffusion weighted imaging (DWI), with b value=1000 s/mm2, using an Echo-Planar (EPI) Spin-Echo (SE) sequence in contiguous axial slices. In the coronal axis, a hippocampal FLAIR, a T1 weighted image (Inversion Recovery sequence) and a T2 weighted image (SE) were obtained.

In addition to the standard protocol, resting-state functional MRI (closed eyes), a tractography and a three-dimensional T1-weighted image (wT1-3D) were acquired (Table 1). All images were acquired while patients were awake, no sedation was used.

	wT1	DWI	fMRI
Scanning sequence	GRE	EPI_SE	EPI_GRE
Slice Thickness [mm]	1	3	4
GAP [mm]	0	0	0
Matrix	256x256	80x80	96x96
Echo Time [ms]	3.276	92.7	23
Repetition Time [ms]	7.812	12000	2800
Flip Angle [º]	12	90	90

Table 1: Summary of sequences design.

Data processing

Functional Connectivity

Functional connectivity between different areas of the brain was quantified using the CONN toolbox [20]. This involved the application of several preprocessing steps to the rs-fMRI, including functional realignment, slice-timing correction, outlier identification, direct segmentation-normalization, and smoothing [21]. In addition, the rs-fMRI were also denoised to remove subject motion, outliers from the BOLD signal and residual physiological effects [22]. Finally, seed-based connectivity measures were obtained to identify connectivity patterns between pre-defined ROIs and the rest of the brain [23].

Structural Connectivity

To obtain the structural connectivity matrices, DWI were first preprocessed to correct subject motion and eddy current distortions, and non-brain tissue was deleted. Next, Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques (BEDPOSTX) was carried out. The number of fibres modelled per voxel was 2 and the chosen deconvolution model was with sticks with a range of diffusivities. Finally, after registration was run, the probabilistic tracking with crossing fibers was done to obtain the connectivity matrices, based on seeds given by the aal2 atlas and applying the ball-and-stick model [24]. All the aforementioned steps were executed with FMRIB's software FSL [25, 26, 27].

Statistical analysis

For each pair of ROIs, statistical analysis of functional and structural connectivity was conducted, contrasting each patient and the control groups. To test the existence of a significant difference ($p<0.05$) across all the connections between the single patient and the group of control, a Crawford-Howell modified t-test was used to generate a new contrast matrix (CM) [28]. A case-control comparison was made due to the fact that there was significant variability in the location of the patients' epileptic foci. SPM 12, CAT 12, and CONN toolboxes were run using version R2019a of MatLab.

Maps were generated identifying clusters of 4 or more regions with significant differences (threshold of $p<0.05$), and they were compared with the patient's clinical diagnosis.

RESULTS

Based on the comparison with post-surgical outcomes, the tractography has a sensibility of 40% compared to the 86.7% associated to RS-fMRI. On the other hand, the functional protocol presented lower specificity than structural connectivity analysis (Table 2). Both techniques showed low precision values and high Negative Predictive Value (NPV). In the fourth column of Table 2, the results of the simultaneous analysis are shown.

	Tractography	RS-fMRI	Tractography + RS-fMRI
n	4	10	4
Sensibility	40	86.67	100
Specificity	88.27	73.07	93.45
Precision	17.39	18.84	45
NPV	95.97	98.7	100

Table 2: Performance to locate epileptic foci.

CONCLUSIONS AND DISCUSSION

The analysis of contrast matrices obtained from Crawford-Howell t-test is a possible clinical method to implement in the assessment of individual patients. The simultaneous analysis of structural and functional connectivity improves the tractography sensibility and the specificity of rs-fMRI. Precision can be improved by increasing the sample of patients and healthy subjects.

Precision can be improved by increasing the sample of patients and healthy controls. Other metrics are being studied to improve the performance of the diagnostic algorithm.

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