EPILEPTIC NETWORK ACTIVITY REVEALED BY DYNAMIC FUNCTIONAL CONNECTIVITY IN SIMULTANEOUS EEG-FMRI

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ABSTRACT

Recent findings highlighted the non-stationarity of brain functional connectivity (FC) during resting-state functional magnetic resonance imaging (fMRI), encouraging the development of methods allowing to explore brain network dynamics. This appears particularly relevant when dealing with brain diseases involving dynamic neuronal processes, like epilepsy. In this study, we introduce a new method to pinpoint connectivity changes related to epileptic activity by integrating EEG and dynamic FC information. To our knowledge, no previous work has attempted to integrate dFC with the epileptic activity from EEG. The detailed results obtained from the analysis of two patients successfully detected specific patterns of connections/disconnections related to the epileptic activity and highlighted the potential of a dynamic analysis for a better understanding of network organisation in epilepsy.

Index Terms— functional MRI, dynamic functional connectivity, epilepsy

1. INTRODUCTION

Functional connectivity (FC) based on functional magnetic resonance imaging (fMRI) during resting state is a powerful measure allowing for the observation of brain interactions. Typically, FC is estimated as the temporal correlation between the blood oxygenation level dependent (BOLD) signal of anatomically defined regions. By means of this technique, the existence of networks of regions characterised by coherent spontaneous BOLD activity in the resting brain has been shown and is nowadays considered a fundamental property of brain functional organisation [1, 2]. However, there is increasing evidence that the networks in the brain continuously reorganise during rest, which is missed by traditional, stationary analyses. To gain insight into brain network changes on shorter time scales, several groups have adopted a technique, which we here call dynamic FC (dFC): temporal correlations between the BOLD activity of distinct brain regions is computed using sliding time windows instead of across the full duration of the scan [3-7]. In this way, dFC allows to observe the dynamic fluctuations of brain connections, instead of yielding a static picture of brain networks. This can be particularly relevant in epilepsy, a disease characterised by temporary discharges of groups of neurons (seizures), specifically described as a pathology altering the normal brain network organisation [8-11]. The continuous switching of the diseased brain between epileptic and normal state, due to epileptic discharges that occurr in various moments in time, makes this pathology an ideal candidate for dynamic analysis, to be able to characterise at best the network mechanisms of seizure initiation, maintenance, and termination [9, 12]. In this context, simultaneous electroencephalography (EEG)-fMRI is a widely used technique to record epileptic activity and help in the detection of the epileptic focus (region generating discharges) and of the target for surgical resection [13]. Even in the context of dFC analysis, the information about epileptic activity given by the EEG appears fundamental in order to selectively observe the large-scale network changes related to the pathology and to characterise the different neuronal states of epilepsy, therefore, it should be integrated in the analysis. One previous study [9] explored FC dynamics in epilepsy and used the EEG information to separately analyze dFC before, during and after the seizure, but to our knowledge, no study has proposed yet to use the epileptic activity measured by EEG as a regressor to find how FC is modulated across the full scan. Here, we introduced a novel single-subject method of integration between dFC, that reveals time-varying network organisation, and simultaneous EEG-fMRI, that expresses the neuronal activity related to epilepsy. We applied this technique to two patients with focal epilepsy and identified for both of them the epileptic network, as a specific group of connections besides the epileptic focus, showing alterations in correspondence of the pathological neuronal activity. These connections included areas of the default mode network (DMN), that has already shown to be altered in epilepsy, appearing in line with previous findings, but offering a new dynamic perspective to study more accurately epileptic network dysfunctions.

2. METHODS

2.1. Subjects

Simultaneous EEG-fMRI and long-term EEG outside the scanner were performed on two patients with refractory focal epilepsy. Subject 1 was affected by tuberous sclerosis with two epileptogenic tubers. Subject 2, instead, was suffering of left hemispheric epilepsy symptomatic of a large abscess gliotic scar. The same subjects underwent surgical resection of the epileptogenic region and appeared seizure-free for more than one year after the operation.

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2.2. MRI acquisition and preprocessing

MRI was acquired using a 3T Siemens TIM Trio MR scanner with a gradient echo EPI sequence (TR/TE/FA = 1.5s/35ms/85°, voxel size= 3.75x3.75x5.5mm^3, 25 slices and 1100 scans) during resting (eyes closed). T1-weighted and T2-weighted images pre- and post-operation were also acquired. An initial realignment to the first fMRI volume was performed to correct for head motion, and then spatial smoothing with Gaussian filter (FWHM=5mm) was applied using SPM8 (FIL,UCL,UK). The anatomical AAL atlas [14] (N=90 regions without the cerebellum) was mapped onto the subjects functional space using the IBASPM toolbox [15]. The first 10 volumes were discarded so that the fMRI signal achieves steady-state magnetization. Voxels time series labelled within the atlas were detrended for slow oscillations using a first-degree polynomial and DCT basis function up to cut-off frequency of 1/125 Hz. The time series of all voxels belonging to each atlas region were averaged together, leading to N time courses $\mathbf{x}_r$, $r = 1, \ldots, N$, describing the regional activity temporal pattern.

2.3. EEG acquisition and preprocessing

Long-term EEG outside the MRI was recorded with 29 scalp electrodes (10-10 position convention) using EEG sampling rates of 512 Hz. Simultaneous EEG-fMRI recordings were acquired with a 64 MR-compatible EEG cap (EasyCaps, FalkMinnow Services, Herrsching, Germany) according to the 10-10 system. Electrodes were equipped with an additional 5k resistance and impedances were kept as low as possible. EEG was acquired at 5kHz using two BrainAmp MR compatible amplifiers (Brain Products, Munich, Germany) and recordings were synchronized with the MR clock. MR gradient and cardioballistic artefacts were removed from the EEG using Vision Analyzer (Brain Products, Munich, Germany) with average artefact subtraction methods and EEG data was subsequently downsampled to 250Hz. The EEG topography-based analysis proposed in [13] was performed, allowing for the evaluation of the epileptic activity even in absence of spikes inside the MR scanner. First, interictal epileptic discharges were visually marked on the long-term EEG by an experienced neurophysiologist and averaged. Then, the EEG topography map at the maximum of the global field power was selected as the epileptic map. The absolute value of the spatial correlation between the epileptic map and the intra-MR EEG was computed and yielded a fitting vector quantifying the presence of the epileptic map in the intra-MRI EEG. The convolution of this vector with the haemodynamic response and its down-sampling to the fMRI temporal resolution, provided finally an EEG-derived signal $\mathbf{m}_{\text{EEG}}$ in the fMRI scale, containing the information about the resemblance of the instantaneous EEG with the epileptic topography.

2.4. Localizing the epileptic focus

To localise the epileptic focus, we computed the Spearman correlation coefficient ρ_r between the N fMRI regional time courses $\mathbf{x}_r$ and the vector $\mathbf{m}_{\text{EEG}}$, reflecting the epileptic activity (1):

$$\rho_r = \text{corr}(\mathbf{m}_{\text{EEG}}, \mathbf{x}_r) \quad r = 1, \ldots, N. \tag{1}$$

The significance of the obtained correlation values was assessed with a non-parametric randomization test, using 999 surrogates of $\mathbf{m}_{\text{EEG}}$ and testing the null-hypothesis of no correlation between the two signals. The regions whose correlation survived the test ($p_{\text{corr}} < 0.05$ corrected for multiple comparisons) were identified as the epileptogenic regions.

2.5. Revealing epileptic network dynamics

We illustrated the proposed processing pipeline in fig. 1. The main contribution of our method is the computation of sliding-window covariance for both dFC and EEG, that made possible the integration between the two measures. In fact, the assessment of the temporal correlation between the EEG time-dependent signal $\mathbf{m}_{\text{EEG}}$ and the connections' dynamics (usually obtained in dFC analysis by the sliding-window correlation of two fMRI time series) is not possible due to the different nature of the two ($\mathbf{m}_{\text{EEG}}$ is a "first-order" statistics, while the FC time courses, computed as correlations, are "second-order" ones). To overcome this problem, we introduced an additional step, i.e., the assessment of the sliding-window covariance of the EEG-derived signal, that was then correlated with the FC time courses, computed also in terms of covariance instead of correlation, for homogeneity of the two measures. The whole procedure is detailed in the following. First, the dFC was estimated by computing the covariance between the time courses of all N=90 brain regions, using a sliding-window technique [3] with a window length Δt=20 TR (30s) and a step size s=1 TR (1.5s). The connectivity between the time courses $\mathbf{x}_i$ and $\mathbf{x}_j$ of regions $r = i$ and $r = j$ was therefore given for every window of length Δt by (2):

$$\boldsymbol{\sigma}_{ij}[t] = \text{cov}(\mathbf{x}_i[t, t + \Delta t], \mathbf{x}_j[t, t + \Delta t]). \tag{2}$$

The computation of σ_{ij} for every window and for all pairs of brain regions yielded T_s $N \times N$ symmetric FC matrices (T_s= number of windows). Due to symmetry, we selected only the upper triangular part of each FC matrix, we vectorized it and inserted it as a column of the $(N^2 - N)/2 \times T_s$ matrix $\mathbf{C}$, describing along its rows the dynamic time course $\boldsymbol{\sigma}_{i,j}[t]$ ($t = 1, \ldots, T_s$). Applying to $\mathbf{m}_{\text{EEG}}$ the same sliding window technique adopted for dFC computation, we derived the vector $\mathbf{m}'_{\text{EEG}}[t]$, whose values were obtained for every window of length Δt as follows (3):

$$\mathbf{m}'_{\text{EEG}}[t] = \text{cov}(\mathbf{m}_{\text{EEG}}[t, t + \Delta t], \mathbf{m}_{\text{EEG}}[t, t + \Delta t]). \tag{3}$$

We assessed then their temporal correlation, computed through Spearman correlation coefficient for all connections $i - j$ (4):

$$r_{ij} = \text{corr}(\mathbf{m}'_{\text{EEG}}, \boldsymbol{\sigma}_{i,j}), \tag{4}$$

which yielded $(N^2 - N)/2$ correlation values that we reshaped in the $N \times N$ symmetric matrix $\mathbf{R}$. The matrix $\mathbf{R}$ highlighted the pattern of increase (positive correlation) or decrease (negative correlation) of brain connections, related to the epileptic activity, and can be seen, therefore, as the epileptic network. Despite its appearance, this matrix differs substantially from a usual FC matrix for the incorporation of the information given by the EEG, allowing specifically to highlight the connections/disconnections related to epileptic activity. Significant correlations were assessed with a non-parametric randomisation test, using 999 surrogates obtained by phase randomisation of the rows of the matrix $\mathbf{C}$, and testing the null-hypothesis of no correlation between $\mathbf{m}'_{\text{EEG}}$ and $\boldsymbol{\sigma}_{i,j}$. Aiming at detecting the regions whose global connectivity to the rest of the brain showed a positive or negative correlation with the epileptic activity, we then computed the N positive and negative node strengths from the matrix $\mathbf{R}$ ($\mathbf{s}^+$ and $\mathbf{s}^-$, respectively):

$$\mathbf{s}_i{}^+ = \sum_j^N r_{ij} \quad r_{ij} > 0, \tag{5}$$

$$\mathbf{s}_i{}^- = \sum_j^N r_{ij} \quad r_{ij} < 0. \tag{6}$$

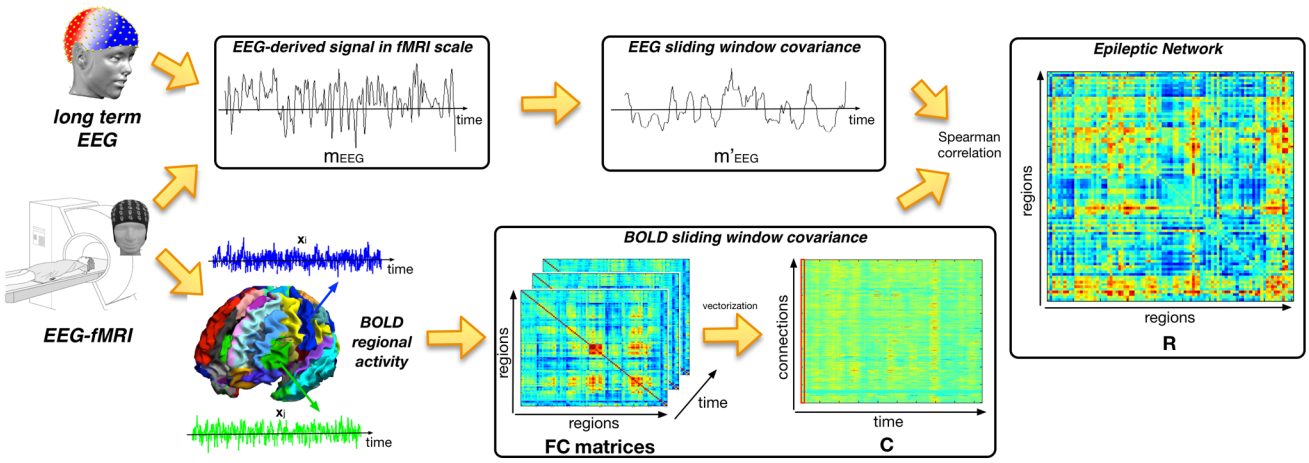

Fig. 1. Flowchart of the pipeline to integrate dFC derived from fMRI with epileptic activity as measured by EEG.

3. RESULTS

3.1. Localization of the epileptic focus

The epileptic focus was located in the left orbito-frontal medial cortex and left insula for subject 1 (positive correlation, $p_{\text{corr}} < 0.05$ corrected for multiple comparisons) and in the bilateral posterior cingulate cortices, right inferior occipital cortex and left thalamus for subject 2 (negative correlation, $p_{\text{corr}} < 0.05$ corrected for multiple comparisons). The focus localisation was consistent with previous analysis on these patients [13], performed using simultaneous EEG-fMRI and general linear model to localise the focus.

3.2. Epilepsy-related network dynamics

The epileptic networks as characterised by the matrices $\mathbf{R}$ for the two subjects are displayed in fig. 2, where the regions showing a significantly higher/lower ($p_{\text{corr}} < 0.05$ corr. for multiple comparisons) global connectivity in correspondence of the epileptic spikes (positive/negative correlation) are highlighted. Between those, the following regions belonging to the DMN were observable: supramarginal gyrus and temporal pole for subject 1, posterior cingulate cortex and temporal pole for subject 2. Fig. 3 shows a 3-D representation of these regions, together with the identified epileptic focus, for the two subjects.

4. DISCUSSION

In this work, we proposed a novel method to integrate information between dFC from fMRI and epileptic activity from EEG, aiming at highlighting patterns of brain connections / disconnections specifically related to epilepsy. Exploiting the knowledge provided by dFC concerning the dynamics of brain networks, we were able to selectively observe the neuronal changes related to the epileptic states, by means of correlation with the time-varying electrical activity supplied by the EEG. One previous study on epilepsy proposed dFC methods to explore the fluctuations in network organisation [9] in the different intervals of seizures, but, to our knowledge, ours is the first work directly linking the EEG-derived information with the dFC data, by the use of the EEG as regressor in the estimation of the dFC. As detailed in the methods section, the key contribution of our procedure is the use of sliding-window covariance for the computation of both dFC and EEG-derived epileptic activity, allowing for the integration between the two measures, that now appear statistics of the same order. As a result of the integration, not only the matrix $\mathbf{R}$ contains information about the brain networks characterising resting state in epileptic patients, but also it innerly includes the information concerning the times of spike occurrence, identifying connections whose strength changes with epileptic activity. In the analysis of two subjects with focal epilepsy, this technique allowed for the detection of specific brain networks with altered dynamics related to the epileptic activity, even if outside the epileptic focus (fig. 3). The identified epileptic network included for both patients, even if showing different epileptic foci, regions belonging to the DMN (supramarginal gyrus, temporal regions, posterior cingulate cortex) for which a potential dysfunction related to epilepsy was already hypothesised in literature [9, 11, 12, 17]. These interesting findings open a new spectrum of analyses looking at epilepsy in dynamic perspective, and proposing a new point of view that appears particularly relevant for this disease, characterised by continuously changing neuronal organization. In the future, the enlargement of the study sample and the additional observation of the specific connections of these regions will allow for a more precise clinical interpretation of the results. Moreover, the rather new approach of dFC leaves space to further improvements, that could concern a finer parcellation of the brain, especially useful in epilepsy considering the high focalisation of epileptic activity, as well as the testing of the effect of different lengths for the sliding windows.

5. CONCLUSIONS

In conclusion, we proposed a novel approach exploiting dynamic functional connectivity to identify the patterns of dysfunction related to epileptic activity. The main novelty of the method is given by the integration between dFC and EEG-derived knowledge about epileptic spikes, aiming at describing the different neuronal states characterising epilepsy. Experimental results for two subjects with focal epilepsy appeared promising, encouraging further extensive analyses.

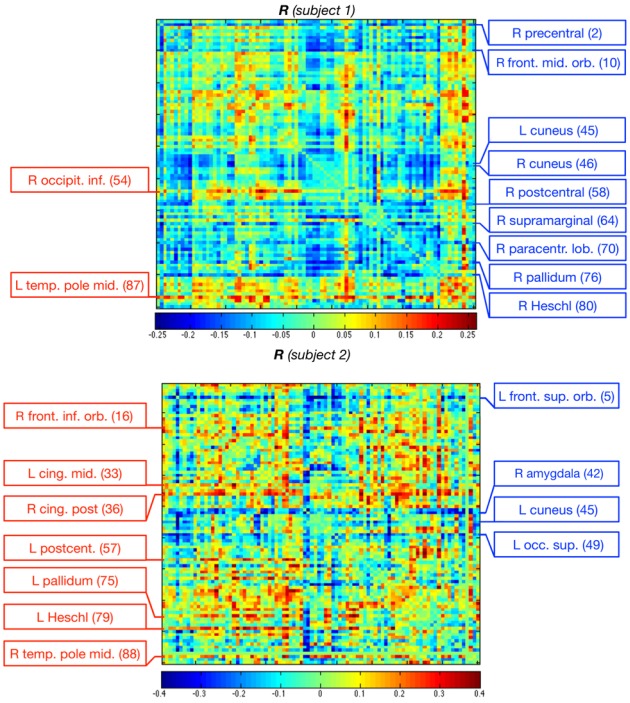

Fig. 2. Epileptic networks of the two subjects (top: subj. 1, bottom: subj. 2), showing the Spearman correlations between the connectivity time courses $\sigma_{i,j}[T]$ and the EEG-derived signal $\mathbf{m}'_{\text{EEG}}[t]$. Despite its appearance, this matrix differs substantially from a FC matrix for the incorporation of the information given by the EEG, allowing to highlight network organisation changes related to the epileptic spikes. The regions whose node strength showed a significant positive (red on the left) and negative (blue on the right) correlation ($p_{\text{corr}} < 0.05$) are reported, showing the patter of connections/disconnections related to epilepsy. The region numbers correspond to AAL90 parcellation [14].

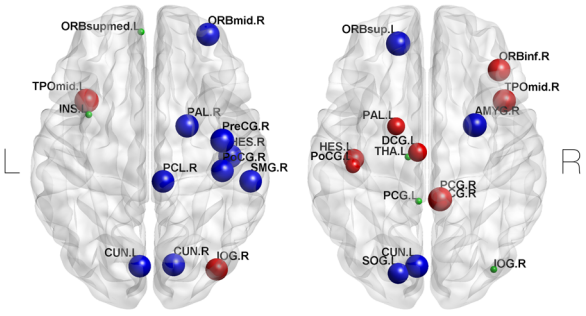

Fig. 3. Graphic representation where the nodes represent positive (red) and negative (blue) node strengths $\mathbf{s}_i^+$ and $\mathbf{s}_i^-$ with significant correlation values ($p_{\text{corr}} < 0.05$ corrected for multiple comparisons) with the epileptic activity, for the two subjects (left: subj. 1, right: subj. 2). The size of the nodes is weighted by the absolute value of s_i^+/s_i^-. In green, the epileptic focus is reported. BrainNet Viewer software and acronyms [16] were used for graph visualisation.

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