Partial least squares regression of dynamic functional connectivity and EEG reveals the epileptic network activity

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Aim - Focal epilepsy is characterized by a complex and not yet fully understood organization of brain networks involved in the generation, propagation, and modulation of seizures, besides the regions of epileptic focus. Simultaneous electroencephalography (EEG) - functional magnetic resonance imaging (fMRI) recordings can capture hemodynamic changes related to epileptic activity. Combining this information with the recently introduced technique of dynamic functional connectivity (dFC), capable of revealing the temporal fluctuations of brain connections during resting state fMRI[1], appears promising to identify large-scale network changes related to epilepsy. Different studies have attempted to integrate EEG and dFC information, mostly manually defining periods of epileptic/non-epileptic events on the EEG and analyzing them separately[2]. In this work, we aim to propose a new method to integrate dFC and EEG by applying partial least squares (PLS) with the goal of defining the epileptic network. PLS is a multivariate statistical analysis that has been applied to functional neuroimaging[3] to associate brain activity and behavior/experimental design, but, to the best of our knowledge, not to dFC analysis. Here, PLS seems the ideal candidate method to directly extract networks from dFC maximizing their relationship with EEG.

Methods - The processing pipeline is detailed in Fig. 1. Simultaneous EEG-fMRI and T1-weighted MRI were performed on one patient with focal left hemispheric epilepsy. An "epilepsy regressor" was constructed as follows[4]: interictal epileptiform discharges were identified on a long-term EEG recorded outside the scanner and averaged to obtain an "epileptic voltage map. The correlation of this map with the successive instantaneous spontaneous EEG maps acquired inside the scanner was calculated to yield the EEG-derived signal $\boldsymbol{m}_{EEG}$ in the fMRI scale. To allow the correlation with the dFC data (which cannot be done directly as $\boldsymbol{m}_{EEG}$ is a "first-order" timecourse, while dFC, usually computed as sliding window correlation of two timecourses, is of "second-order"), we assessed the sliding-window variance of $\boldsymbol{m}_{EEG}$ deriving the vector $\boldsymbol{c}_{EEG}[t] = cov(\boldsymbol{m}_{EEG}[t, t+\Delta t], \boldsymbol{m}_{EEG}[t, t+\Delta t])$. Then, we parcellated the cortex into $N = 90$ regions (AAL90) and computed dFC with the technique described in,[5] , but using sliding-window covariance as well, instead of correlation, for homogeneity of the two measures. The dFC between the fMRI time courses $\boldsymbol{xi}$ and $\boldsymbol{xj}$ of regions $r = i$ and $r = j$ was therefore given by $\boldsymbol{\sigma ij}\ [t] = cov(\boldsymbol{x_i}[t, t+\Delta t], \boldsymbol{x_j}[t, t+\Delta t])$ for every window of length Δt. The computation of $\boldsymbol{\sigma ij}$ for all windows and all pairs of brain regions yielded $T\ N \times N$ symmetric FC matrices (T = number of windows). Due to symmetry, we selected the upper triangular part of each matrix and inserted it (after vectorization) as a row of the $T \times (N^2 - N)/2$ matrix $\boldsymbol{C}$, describing along its columns the dynamic time course $\boldsymbol{\sigma ij}\ [t]$. Then, we applied PLS regression to normalized $\boldsymbol{C}$ and $\boldsymbol{c}_{EEG}$ data to detect the set of connections that optimally explains the epileptic activity. In particular, having only a one-dimensional variable to predict ($\boldsymbol{c}_{EEG}$), PLS resulted in a linear regression model seeking for subsets of dFC data (PLS components) that give the best prediction. The vector $\boldsymbol{w}$ containing the coefficients of the linear combination of FC time courses yielding the first PLS component was selected. By reshaping $\boldsymbol{w}$ into a 90×90 symmetric matrix $\boldsymbol{W}$, we obtained a picture of the contribution of every functional connection to the epileptic activity: i.e., the epileptic network. To detect the regions whose global connectivity significantly correlates with epileptic activity, we computed the positive and negative node strengths of $\boldsymbol{W}$ as $s_i^+ = \sum_{j=0}^{N} r_{ij}\ (r_{ij} > 0)$ and $s_i^- = \sum_{j=0}^{N} r_{ij}\ (r_{ij} < 0)$. The significance of the nodal strength values was assessed with a non-parametric randomization test corrected for multiple comparisons, using 999 surrogates obtained by phase randomization of the columns of the matrix $\boldsymbol{C}$, and testing the null-hypothesis of zero node correlation.

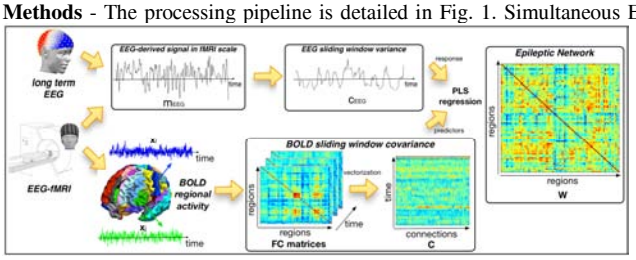

Fig. 1 – Flowchart of the method to integrate dFC and EEG.

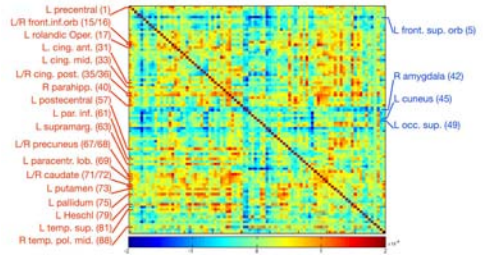

Fig. 2 – Epileptic network and regions with positive (red) / negative (blue) significant nodal strength.

Results – We detected a brain network, identified as epileptic network (fig. 2), showing altered dynamics related to the epileptic activity, even outside the epileptic focus. Higher global connectivity in correspondence with the epileptic spikes ($pcorr < 0.05$) was found for different regions of the the default mode network (ant./post. cingulate cortex, precuneus, parahippocampal/supramarginal gyrus, inf. parietal lobule, temporal pole), for which abnormal functionality related to epilepsy was already hypothesized[1,2].

Discussion – The introduction of PLS in this analysis has different advantages: first, the use of a multivariate approach to assess the correlations takes into account all brain connections at a time allowing to catch the hidden dependence between the large number of variables that we have to deal with. Second, PLS technique is conceptually similar to principal component analysis (PCA), which was previously applied to dFC[5] in order to find the network components maximizing the variance in the data. However, PLS directly seeks for linear combinations of data that optimize a specific criterion, and appears therefore convenient when the objective of the analysis is well defined (i.e. highlight the associations between two data sets). Here, PLS allows looking directly for networks that maximize the correlation with the epileptic activity, taking in consideration the entire dataset.

Conclusions - We proposed a novel approach to identify patterns of abnormal functional connectivity related to epileptic activity. The additional information about network dysfunction that this approach provides goes beyond the epileptic focus identification and can be of clinical relevance, yielding a more detailed picture of the pathology and the still unclear abnormal connectivity pattern that underlies focal epilepsy. The main novelty of the method is given by the use of a multivariate statistical technique (i.e., PLS) to integrate dFC and EEG, with the goal of identifying the epileptic network. Experimental results for one subjects with focal epilepsy appeared promising and consistent with previous knowledge, encouraging further extensive analyses.

References

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