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A new algorithm for spatiotemporal analysis of brain functional connectivity

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ABSTRACT

Specific networks of interacting neuronal assemblies distributed within and across distinct brain regions underlie brain functions. In most cognitive tasks, these interactions are dynamic and take place at the millisecond time scale. Among neuroimaging techniques, magneto/electroencephalography – M/EEG – allows for detection of very short-duration events and offers the single opportunity to follow, in time, the dynamic properties of cognitive processes (sub-millisecond temporal resolution).

In this paper, we propose a new algorithm to track the functional brain connectivity dynamics. During a picture naming task, this algorithm aims at segmenting high-resolution EEG signals (hr-EEG) into functional connectivity microstates. The proposed algorithm is based on the *K*-means clustering of the connectivity graphs obtained from the phase locking value (PLV) method applied on hr-EEG. Results show that the analyzed evoked responses can be divided into six clusters representing distinct networks sequentially involved during the cognitive task, from the picture presentation and recognition to the motor response.

1. Introduction

There is increasing evidence that cognitive functions arise from the activation of networks distributed over distinct and possibly distant brain regions as opposed to isolated focal areas (Sporns, 2010). Hence, efforts focused on the analysis of brain connectivity as a key concept to understand brain cognitive functions. Due to its excellent spatial resolution, fMRI has become one of the most commonly used noninvasive methods to study cerebral functions (Allen et al., 2012).

However, in many cases, the short duration of most cognitive processes (∼500 ms for picture naming, for example) would greatly benefit from the use of techniques that have a much higher time resolution (on the order of ms), which is not the case of fMRI (∼1 s). Along this line, several studies indicated that the use of electroencephalography (EEG, 1 ms time resolution for signals classically sampled at 1 kHz) combined with appropriate signal processing techniques can bring relevant information about normal networks during cognitive activity (Rodriguez et al., 1999) or about altered networks associated with tumors (Bartolomei et al., 2006) for instance.

This excellent temporal resolution of the EEG signals allowed us to analyze the dynamic properties of cognitive processes, an issue so far addressed in a few studies only. In Murray et al. (2008), authors proposed an algorithm based on the amplitude of event related potentials (ERPs) to follow time-varying voltage topographic maps. However, these algorithms do not account for brain connectivity quantified directly from scalp signals (electrode space) or indirectly from reconstructed brain sources (source space).

Regarding the approaches based on the connectivity analysis, most of reported methods make use of a constant time window to track the dynamics of functional connectivity, as estimated from EEG recordings. This window is typically chosen either empirically or based on a priori information about the analyzed task (Rodriguez et al., 1999). A few attempts have been recently reported to avoid this constraint (De Vico Fallani et al., 2008; Dimitriadis et al., 2010; Allen et al., 2012). However, most of proposed algorithms are not adapted to tracking changes over very short durations (in

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the order of 500 ms, as in the case of responses evoked by visual stimuli).

In this paper, we propose a novel algorithm to track the dynamics of brain functional connectivity at millisecond scale. The proposed algorithm is based on the K-means clustering of the connectivity networks obtained by the phase locking value (PLV) method. Performance evaluation was assessed on high-resolution electroencephalographic (hr-EEG) signals recorded in subjects during a picture naming task.

2. Materials and methods

2.1. Functional connectivity measure

Functional connectivity is classically defined as the temporal correlation (wide sense) among electrophysiological signals generated by distinct neuronal assemblies (Friston, 1994). Several methods have been proposed to quantify brain functional connectivity. In this study, we used a method, which belongs to the so-called "phase synchronization" (PS) family.

It is well known that the respective phases of two oscillators may synchronize even if their amplitudes stay uncorrelated. The general principle of PS methods is to detect the existence of a phase locking between two systems defined as:

$$\varphi_{xy}(t) = |\Phi_x(t) - \Phi_y(t)| \le C$$

where $\Phi_x(t)$ and $\Phi_y(t)$ are the unwrapped phases of the signals (x and y) representative of the two systems at time t and C a constant. The first step for estimating the phase synchronization is to extract the instantaneous phase of each signal. In this study, we used the method based on Hilbert transform. The second step is the definition of an appropriate index to measure the degree of synchronization between estimated instantaneous phases. To proceed, we used the phase locking value (PLV) (Lachaux et al., 1999), as illustrated in Fig. 1B. For each channel pair, x and y, at time t ($t = t_1, \ldots, t_T$ where $T = D * f_s$; D and f_s denote the signal length relative to the onset and the sampling frequency, respectively) for the N trials and for subject j ($j = 1, \ldots, M$, where M denotes the number of subjects), PLV is defined as:

$$\mathrm{PLV}^j_{xy}(t) = \frac{1}{N}\left|\sum_{n=1}^{N}\varphi_x(t) - \varphi_y(t)\right| \tag{1}$$

To reduce the effect of correlations between near electrodes, we apply a normalization procedure (z-score) so that the PLV values were compared with the 200 ms baseline preceding the presentation of the image. Let μ_{xy} and σ_{xy} are the mean and standard deviation computed from a 200 ms pre-stimulus baseline. The normalized PLVs are then defined as $\bar{\mathrm{PLV}}^j_{xy}(t) = (\mathrm{PLV}^j_{xy}(t) - \mu^j_{xy})/\sigma^j_{xy}$. A thresholding procedure is then applied on the functional connectivity values in order to retain the strongest functional connections. The connectivity measure was computed in the low gamma frequency band (30–45 Hz). More precisely, the phases were estimated for each frequency and the average phase at 30–45 Hz was used. Indeed, this frequency band was shown to be highly relevant in the context of the cognitive task performed by subjects, as reported in Rodriguez et al. (1999).

The PLVs were then averaged over subjects:

$$\bar{\mathrm{PLV}}_{xy}(t) = \frac{1}{M}\sum_{j=1}^{M}\mathrm{PLV}^j_{xy}(t) \tag{2}$$

where $\bar{\mathrm{PLV}}_{xy}(t)$ represents the general term of the average adjacency matrix $\bar{\mathrm{PLV}}(t)$ which defines a functional connectivity graph G at each time t, $G = \{G(t), t = 1, \ldots, T\}$, computed for the V pairs of x and y channels, where V is equal to $(Nc \cdot (Nc - 1)/2)$ and Nc is the number of channels in the hr-EEG montage. According to Eqs. (1) and (2), T adjacency matrices are obtained.

2.2. Segmentation algorithm

The objective of this algorithm is to identify clusters among the T graphs $G(t)$. As illustrated in Fig. 1C, the proposed algorithm is based on three main steps:

Step 1 (Initialization). To start with, K graphs G^k, $G^k = \{\bar{G}^k, k = t_1, \ldots, t_K\}$, are selected where $k = t_l$ and l is randomly chosen in (K varies from 3 to 12 and k varies from 1 to K) with the restriction of rejecting the K graphs if the time interval between two t_l is less than 30 ms.

Step 2 (Assignment). The spatial correlation $sC^k(t)$ between $G(t)$ and $\bar{G}^k$ is then computed as follows:

$$sC^k(t) = \frac{\sum_{i=1}^{V}\bar{G}^k_i \cdot G_i(t)}{\sqrt{\sum_{i=1}^{V}\bar{G}^{k\,2}_i} \cdot \sqrt{\sum_{i=1}^{V}G_i^2(t)}} \tag{3}$$

where i denotes the ith edge in $G(t)$ and $\bar{G}^k$. As depicted in Eq. (3), sC is normalized by the variance of graphs G and G^k. Thus, sC ranges from 0 to 1 high values denote graph with high similarity. Conversely, low values are indicative of low similarity between graphs.

Each graph $G(t)$ is then assigned to the cluster for which the spatial correlation was the highest. The assigned clusters are defined as $\hat{G}^k$:

$$\hat{G}^k = \{G(t) : sC^k_{G(t),\bar{G}^k} \ge sC^{k'}_{G(t),\bar{G}^{k'}} \forall \;\; 1 \le k' \le K\} \tag{4}$$

From these spatial correlation values, the global explained variance (GEV) is calculated as defined in Murray et al. (2008):

$$\mathrm{GEV} = \sum_{k=1}^{K}\mathrm{GEV}^k \tag{5}$$

$$GEV^k = \sum_{t=1}^{T}(sC_{G(t),\bar{G}^k})^2 . \gamma_{G(t),\hat{G}^k} \quad \text{where} \quad \gamma_{G(t),\hat{G}^k} = \begin{cases} 1 & \text{if}\, G(t) \in \hat{G}^k \\ 0 & \text{if}\, G(t) \notin \hat{G}^k \end{cases} \tag{6}$$

Step 3 (Update). At each iteration, the new centroids $\bar{G}^k$ are updated by averaging all the graphs yielding to the same cluster

$$\bar{G}^k = \frac{1}{|\hat{G}^k|}\sum_{G' \in \hat{G}^k} G' \tag{7}$$

For each K, Steps 2 and 3 were repeated 500 times. The set of centroids leading to the highest GEV was retained. When the algorithm converges (reaching the highest GEV), $K+1$ graphs $\bar{G}$ are then selected randomly and the entire above procedure (from Step 2 to Step 3) is repeated until $K = 12$.

To choose the optimal number of clusters, we used a method based on the cross validation (CV) criterion (Murray et al., 2008) which is a ratio between the GEV and the degrees of freedom for a given set of graphs. As reported, the global minimum of this criterion gives the optimal number of segments. Note that in the same segment, the graphs can have different SC values with the same cluster and therefore two consecutive graphs (in time) can be classified in two distinct clusters. To overcome this, the decision