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Advanced Methods for Time-Varying Effective Connectivity Estimation in Memory Processes*

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***Abstract*— Memory processes are based on large cortical networks characterized by non-stationary properties and time scales which represent a limitation to the traditional connectivity estimation methods. The recent development of connectivity approaches able to consistently describe the temporal evolution of large dimension connectivity networks, in a fully multivariate way, represents a tool that can be used to extract novel information about the processes at the basis of memory functions. In this paper, we applied such advanced approach in combination with the use of state-of-the-art graph theory indexes, computed on the connectivity networks estimated from high density electroencephalographic (EEG) data recorded in a group of healthy adults during the Sternberg Task. The results show how this approach is able to return a characterization of the main phases of the investigated memory task which is also sensitive to the increased length of the numerical string to be memorized.**

I. INTRODUCTION

Several studies in the neuroscience field revealed that the processes at the basis of attentive or memory processes involve not isolate and specific cerebral areas but groups of brain areas strictly connected each other [1]. Moreover, the communication between such areas is characterized by a specific timing and is subjected to a temporal evolution strictly linked to the explicated cognitive function [2].

For this reason, the study of complex cerebral mechanisms such as those at the basis of cognitive processes required methodologies able to describe phenomena evolving in time and which globally involve the brain in terms of effective networks. The traditional methodologies do not allow to follow the temporal evolution of cerebral networks with sufficient accuracy, taking into account all the sources involved in the processes [3]. The first proposed approach in this sense was based on the estimation of time-varying connectivity patterns in short windows, in which the hypothesis of stationarity of signals was verified [4]. The second proposal consisting in a recursive algorithm involving a weighted influence of the past of the investigated signal [3] improved the estimates accuracy but didn't allow to include in the process all the cerebral sources due to its limitations related to the model dimension [5, 6]. The methodological advancements provided during the recent years led to the use of a generalized version of Kalman filter for the development of a consistent and reliable approach for the highly accurate estimation of time-varying connectivity patterns involving all the sources of the cerebral activity in the process [7, 8].

The new proposed approach for time-varying connectivity estimation, combined with advanced methodologies for the extraction of salient indexes describing the most important features of the investigated networks, were used for the study of cerebral mechanisms at the basis of short-term memory. In particular, we performed a study, conducted in normal healthy adult subjects (N=17) involved in the Sternberg memory task.

The cutting edge methodologies used in the study allowed to define and compute descriptors able to characterize with high accuracy the investigated cognitive function and to follow sample by sample its temporal evolution, providing consistent results among the involved population.

II. METHODS

A. *Adaptive Partial Directed Coherence*

The PDC [9] is a spectral measure, used to determine the directed influences between any given pair of signals in a multivariate data set.

The original formulation of such estimator is based on the hypothesis of stationarity of signals included in the estimation process. Unfortunately, such hypothesis leads to a complete loss of the information about the temporal evolution of estimated information flows. For overcoming this limitation, a time varying adaptation of squared PDC was introduced. The adaptation consisted in modifying the original formulation of PDC by including dependence from the time in the MVAR coefficients. Thus, the adaptive squared PDC estimator can be defined as follows:

$$\pi_{ij}(f,t) = \frac{\left|\Lambda_{ij}(f,t)\right|^2}{\sum_{k=1}^{N}\left|\Lambda_{kj}(f,t)\right|^2} \tag{1}$$

where t refers to a dependence of the MVAR coefficients from time and $\Lambda_{ij}(f,t)$ represents the ij entry of the matrix of MVAR model coefficients Λ at frequency f and time t.

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B. General Linear Kalman Filter

In the GLKF an adaptation of the Kalman Filter to the case of multi-trial time series is provided. In particular, the equations at the basis of the algorithm are:

$$\begin{aligned} Q_n &= G_{n-1} Q_{n-1} + V_n \\ O_n &= H_n Q_n + W_n \end{aligned} \tag{2}$$

where O_n represents the observation, Q_n is the state process, H_n and G_n are the transition matrices and V_n and W_n are the additive noises. To obtain the connection with the time-varying MVAR it is necessary to make the following associations:

$$Q_n = \begin{bmatrix} \Lambda_1(n)^T \\ \vdots \\ \Lambda_p(n)^T \end{bmatrix}, \quad O_n = \begin{pmatrix} x_1^{(1)}(n) & \cdots & x_d^{(1)}(n) \\ \vdots & \ddots & \vdots \\ x_1^{(K)}(n) & \cdots & x_d^{(K)}(n) \end{pmatrix} = Y_n \tag{3}$$

$$G_{n-1} = I_{dp} \quad , \quad H_n = \left(O_{n-1}, \quad \cdots, \quad O_{n-p}\right) \tag{4}$$

where K denotes the number of trials, whereas p is the model order, x is the vector of time series and d is the dimension of the measured process. The details of the algorithm are provided in [7].

C. Graph Theory Approach

A graph is a mathematical object consisting in a set of vertices (or nodes) linked by means of edges (or connections) indicating the presence of some sort of interaction between the vertices. The structure of the investigated graph is described by means of an adjacency matrix G. When a directed edge exists from the node i to j, the corresponding entry of the adjacency matrix is $G_{ij} = 1$, otherwise $G_{ij} = 0$. Among all the indexes which can be defined for the characterization of investigated networks, we decided to consider three recently introduced indexes allowing to describe the existence of asymmetries and influences between different parts of the scalp [10].

Degree. The degree of a node is the number of links connected directly to it. In directed networks, the indegree is the number of inward links and the outdegree is the number of outward links. Connection weights are ignored in calculations. It can be defined as follows:

$$k_i = \sum_{j \in N} a_{ij} \tag{5}$$

where a_{ij} represents the entry ij of the Adjacency matrix A.

Symmetry. The symmetry index is the difference in the number of internal connections between two different spatial regions. It could assume values in the range [-1 ; 1] and it is defined as follows

$$S = \frac{\sum_{i=1}^{N_1} \sum_{j=1}^{N_1} A'_{ij}}{N_1 (N_1 - 1)} - \frac{\sum_{i=N_1+1}^{N_2} \sum_{j=N_1+1}^{N_2} A'_{ij}}{N_2 (N_2 - 1)} \tag{6}$$

where A' is the arranged version of A as reported in [10] and N_1 and N_2 are the number of connections in the two spatial regions, respectively.

Influence. The influence index represents the difference in the number of inter connections between two different spatial regions. It could assume values in the range [-1 ; 1] and it is defined as follows

$$I = \frac{\sum_{i=1}^{N_1} \sum_{j=N_1+1}^{N_2} A'_{ij} - \sum_{i=N_1+1}^{N_2} \sum_{j=1}^{N_1} A'_{ij}}{N_1 \cdot N_2} \tag{7}$$

The last two indices were used in the study for investigating the symmetries and influences between the two hemispheres and between frontal and parietal areas of the scalp.

D. High Density EEG Study

17 healthy adult subjects (ranging 40 to 60 years old; 8 males) were enrolled in the study. EEG signals were recorded by means of 60 electrodes positioned according to the extended 10–20 electrode placement system against a linked mastoid reference. EEG signals were digitized at 500 Hz and filtered with a 0.01 Hz high-pass and a 100 Hz low-pass. Subjects involved in the experiment were asked to perform a modified version of the Sternberg task [11], a paradigm built for eliciting cerebral processes at the basis of short-term memory. The subject is firstly given a short period for memorizing a series of numeric digits (encoding phase), secondly, he/she has to retain the memorized information for a certain period (storage phase) and then he/she has to retrieve it in a short time interval (retrieval phase). The subjects were instructed to answer, as quickly as possible, whether the probe was in the previous set of digits or not. The size of the initial set of digits determined two levels of difficulty for executing the task (4 digits → easy; 6 digits → difficult). Details about the timing of the experiment were reported in Fig.1.

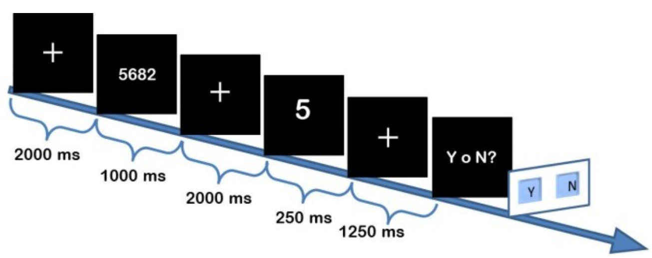

Figure 1. Timing of Sternberg paradigm. The crosses represent the fixation periods. The timing is as follows: 2000ms of fixation, 1000 ms to memorize the string of digits (Encoding phase), 2000 ms of Storage phase, 250 ms of presentation of the digit, 1250 ms of Retrieval of the information.

E. Effective Connectivity Analysis

EEG signals were down sampled to 100 Hz and band-pass filtered in the range [1-45] Hz. Independent Component Analysis (ICA) was used for removing ocular artifacts. EEG traces were segmented in relation with the specific timing of the paradigm, [0 6000] ms according to the onset of the first window containing the digits series and classified according to different conditions (Target_4digits, No Target_4digits, Target_6digits, No Target_6digits). Residual artifacts were then removed by means of a semi-automatic procedure based on a threshold criterion. Only the artifacts-free trials were subjected to the subsequent effective connectivity analysis performed by means of GLKF approach. The connectivity patterns estimated for each time sample were averaged in three time intervals: [0:1000] ms (encoding phase); [1000:3000] ms (storage phase) and [3000:6000] ms (retrieval phase) and in four frequency bands, defined according to the Individual Alpha Frequency (IAF) [12]. To discard all the effects due to the environment or to the stimulation used for administering the paradigm, a statistical comparison between each condition and the corresponding baseline was computed for a significance level of 5% False Discovery Rate (FDR) corrected for multiple comparisons. The baseline period was the time interval [-1000:0] ms defined according to the onset of the screen containing the digits series. During this interval, the subject had to look at the fixation cross.

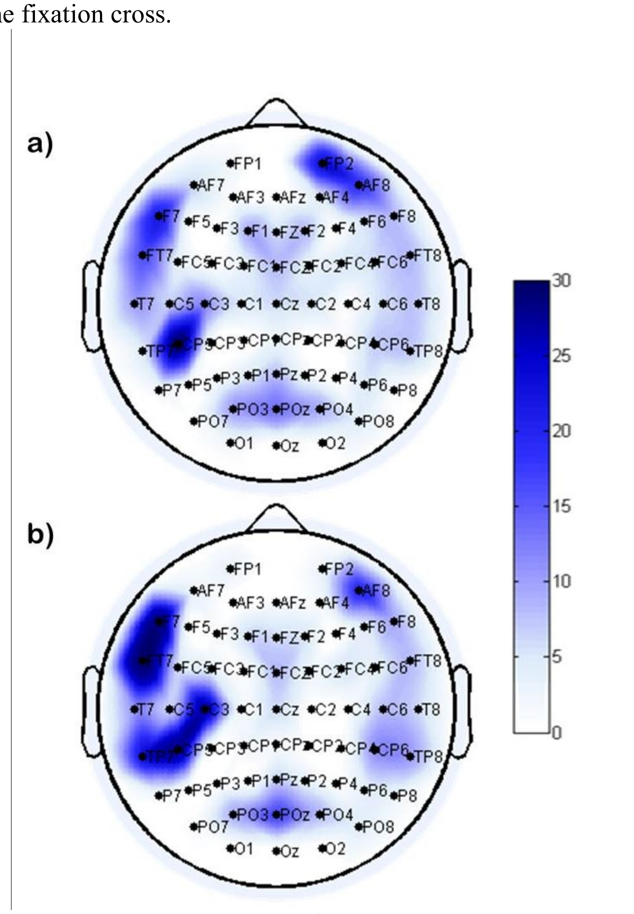

Figure 2. Outdegree maps computed from connectivity patterns in alpha band, for a representative subject during the Storage phase of Sternberg paradigm. Target condition, 4 digits (panel a) and 6 digits (panel b).

III. RESULTS

In Fig.2 we reported the outdegree maps (representing the total number of significant connections spreading from each electrode in the connectivity network) obtained for a representative subject during the Storage phase of Sternberg paradigm, in alpha band. Outdegree maps are referred to the Target condition, for the 4 digits (panel a) and 6 digits (panel b) cases, and are represented on a 2D scalp model, seen from above with the nose pointing to the top of the page. The hue of blue code for the degree of information spreading from the corresponding electrodes. Similar degree maps resulted from the No Target condition.

Outdegree maps reported in Fig.2 show some common features for the two considered conditions. The main difference between the two cases consists in a stronger involvement of FT7 electrode as source of information during the 6 digits case with respect to the 4 digits one. The results reported here for a representative subject were consistent among the investigated population.

Once we have qualitatively described the main properties of the investigated networks, asymmetry and influence graph indexes can help us to describe the features of the achieved patterns from a quantitative point of view, and to verify their consistence among the population included in the study. In Fig.3 we reported an average among the population of time-varying asymmetry and influence indexes computed on connectivity patterns elicited during the Sternberg task, in alpha band, for the two conditions 4 (in blue) and 6 (in red) digits. In particular, the influence index was computed between the two hemispheres, while the asymmetry was computed between the anterior and posterior parts of the scalp. In order to validate the achieved values for graph indexes and to distinguish them from chance, we generated 50 random graphs for each real network, each time maintaining the same edges density. Statistical differences between the considered index and the one achieved from the average across 50 random graphs were indicated sample by sample by means of the symbol (*) in green in Fig.3.

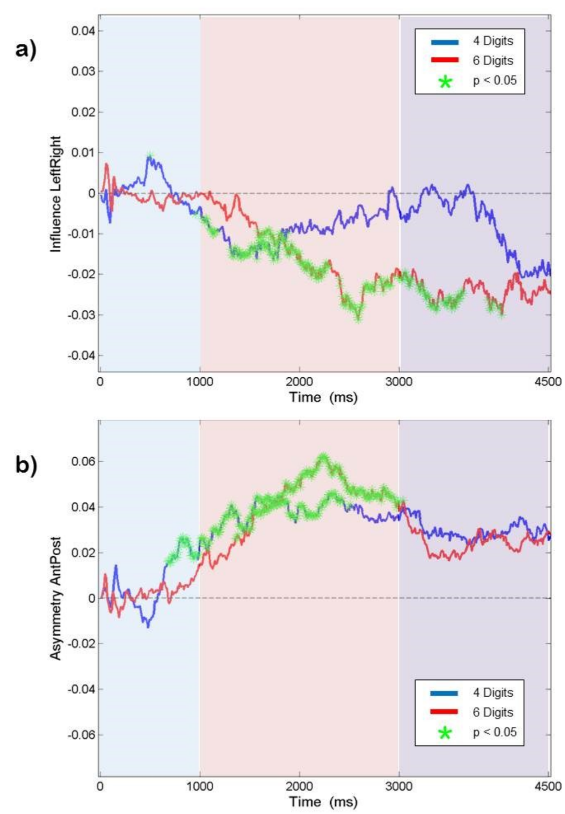

Figure 3. Average value among population of time-varying asymmetry

and influence indexes computed on connectivity patterns elicited during the Sternberg task in alpha band, for the two conditions 4 (in blue) and 6 (in red) digits. The influence was computed between the two hemispheres, while the asymmetry was computed between anterior and posterior part of the scalp. Statistical differences between the index and the chance level were indicated sample by sample by means of the symbol (*) in green. The three memory phases were highlighted by means of different colors (blue→ encoding, red → storage, violet → retrieval)

Results reported in panel a) revealed differences between the two cases 4 and 6 digits. In the 4 digits case the influence between the two hemispheres remained around zero without differing from the chance level for any of the time samples included in the estimation, except for the initial phase of the encoding phase, showing an influence directed from the right to the left hemisphere. In the 6 digits condition, the results showed significant values of the influence index during the storage and retrieval phases, meaning a significant influence of the right hemisphere to the left one.

Panel b) revealed similar behavior for the two conditions 4 and 6 digits. In particular, we found significant positive values for asymmetry index between anterior and posterior parts of the scalp at the end of encoding phase and for all the entire storage phase in both conditions. The result, thus, confirmed a higher involvement of the anterior region of the scalp in respect to the posterior one during the first two memory phases.

IV. Discussion

A body of techniques at the state of the art in the estimation of effective connectivity in the time-frequency domain, together with well-established indices for the interpretation of the connectivity networks were applied for the study of cerebral processes at the basis of short-term memory.

The results show that the methodological advancements in effective connectivity allowed to extract time-varying patterns consistent and reliable among the population without any a priori selection of a subset of electrodes related to the task under investigation. In fact, the inclusion of all the electrodes used for the high resolution EEG recording into the multivariate analysis allowed to avoid the presence of spurious links due to the "hidden source problem". The consequent application of advanced approaches for the extraction of graph indexes from the time-varying networks led to a complete characterization of the temporal evolution of the network with a high resolution in time. The use of such approaches allowed for the first time to describe changes in the network behaviour across the different investigated memory phases.

Moreover, the results obtained are in agreement with previous works in literature describing the neurophysiology at the basis of the investigated cognitive function. In particular, the high involvement of frontal cortex and the high influence of the right parietal cortex on the left fronto-temporal part of the brain have been demonstrated to be at the basis of short term memory processes [13, 14]. The novelty introduced by the results presented in this paper consisted in the high temporal resolution by which the phenomena were described and in the possibility to use the graph indexes to quantify the task difficulty (differences between the 4 digits and 6 digits conditions).

V. Conclusion

In conclusion, advanced methodologies for time-varying effective connectivity estimation combined with accurate approaches for the extraction of graph indexes allowed to describe the most important features of the networks at the basis of short term-memory processes and to follow their temporal dynamics with a high temporal resolution.

The methodological approach described in this paper could open the way to the use of time-varying effective connectivity for the comprehension of phenomena at the basis of complex tasks not completely investigated so far.

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