Time Varying Effective Connectivity for Describing Brain Network Changes Induced by a Memory Rehabilitation Treatment

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Abstract— **In clinical practice, cognitive impairment is often observed after stroke. The efficacy of rehabilitative interventions is routinely assessed by means of a neuropsychological test battery. Nowadays, more evidences indicate that the neuroplasticity which occurs after stroke can be better understood by investigating changes in brain networks. In this study we applied advanced methodologies for effective connectivity estimation in combination with graph theory approach, to define EEG derived descriptors of brain networks underlying memory tasks. In particular, we proposed such descriptors to identify substrates of efficacy of a Brain-Computer Interface (BCI) controlled neurofeedback intervention to improve cognitive function after stroke. Electroencephalographic (EEG) data were collected from two stroke patients before and after a neurofeedback-based training for memory deficits. We show that the estimated brain connectivity indices were sensitive to different training intervention outcomes, thus suggesting an effective support to the neuropsychological assessment in the evaluation of the changes induced by the BCI-based cognitive rehabilitative intervention.**

I. INTRODUCTION

A high percentage of patients surviving to a stroke event shows severe deficits in both motor and cognitive functions. Cognitive deficits are caused by the damage of information flows between different cerebral areas devoted to superior cortical functions such as language, memory and attention.

Currently, the diagnosis of cognitive impairments reported in a stroke patient, and the evaluation of their recovery due to a specific rehabilitation treatment, are based on a battery of neuropsychological tests able to investigate the residual functionality of each specific cognitive function.[1].

However, several neurophysiological studies in the last years demonstrated how all the phenomena of neuronal plasticity associated to specific cognitive rehabilitation interventions are based on modifications in the structure of cerebral networks elicited during such cognitive processes [2]. A detailed reconstruction of these connectivity patterns could thus improve the understanding of neurophysiological bases of such processes and lead to the development of new approaches for the evaluation of their modifies related to a rehabilitation intervention.

In this work we proposed the use of advanced methodologies for effective connectivity estimation [3], combined with a state of the art approach for the extraction of salient indexes describing the most important features of the investigated networks [4], for the study of cerebral mechanisms at the basis of plasticity phenomena induced by a new memory rehabilitation treatment based on the use of a neurofeedback training.

The aim was to seek for neurophysiological descriptors able to be sensitive to different training intervention outcomes and thus to support the neuropsychological assessment in evaluating the efficacy of a Brain-Computer Interface controlled neurofeedback training to promote an improvement in memory function deficits after stroke.

II. MATERIAL AND METHODS

A. Adaptive Partial Directed Coherence

The Partial Directed Coherence (PDC) [5] is a full multivariate spectral measure, used to determine the directed influences between any given pair of signals in a multivariate data set. An adaptive formulation of PDC, based on a time varying multivariate autoregressive (MVAR) model, is used in the study [3]. The original formulation of PDC was modified by including dependence from the time in the MVAR coefficients 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 *(i,j)* entry of the matrix of MVAR model coefficients Λ at frequency f and time t. The estimation of adaptive time-varying coefficients Λ is performed by means of the General Linear Kalman Filter whose details were reported in [3], [6].

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B. *Graph Theory Approach*

A graph is a mathematical object consisting in a set of vertices (or nodes) linked by means of edges (or connections) representing 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 whose entries are $G_{ij} = 1$ if the link exists, otherwise $G_{ij} = 0$ [7].

Degree. The degree of a node consists in the number of links connected directly to it [8]. Degree can be defined as follows

$$k_l = \sum_{\substack{i \in N \\ i \neq l}} G_{ij} + \sum_{\substack{j \in N \\ j \neq l}} G_{ij} \tag{2}$$

where G_{ij} represents the entry (i,j) of the adjacency matrix G.

Anterior Density. Number of connections exchanged between the electrodes located in the anterior part of the scalp. Before the computation of this index, it is necessary to arrange the adjacency matrix by disposing in the first N_1 rows and N_1 columns the connectivity values related to the nodes belonging to the anterior scalp area (all the anterior electrodes before the central line between the ears) and in the second N_2 rows and N_2 columns the connectivity values related to the nodes belonging to the posterior scalp area (all the posterior electrodes behind the central line between the ears). The formulation of such index is as follows

$$d_{Ant} = \frac{\sum_{i=1}^{N_1} \sum_{j=1}^{N_1} G_{ij}}{N(N-1)} \tag{3}$$

where N represents the number of nodes in the network.

C. *Experimental Design*

Two stroke patients (Patient A, female, 70 years old; right hemisphere stroke lesion and Patient B, male, 20 years old, left hemisphere stroke) were enrolled in a neurofeedback-based intervention protocol implemented in BCI close loop, to target post-stroke memory disorders. The protocol consisted of 10 training sessions in which the patients were instructed to voluntarily increase their sensorymotor rhythm (SMRs; 12-15 Hz) amplitude over an established threshold. Each time the SMR amplitude exceeded the threshold for ≥ 250 ms, the participant was rewarded by gaining points. The threshold was automatically adapted after each run on the basis of all previous runs. Cz was used as feedback electrode; each training session lasted 25' (3 min baseline; 6 feedback runs, 3-min each).

Before (PRE) and after (POST) the entire rehabilitation treatment, EEG scalp signals were recorded (64 channels; Brain products, 200Hz sampling frequency) while patients were performing the Sternberg memory task [9]. Patients declarative memory and the visuo-spatial short-term memory deficits were assessed before and after the training by means of the Rey Auditory Verbal Learning Test (RAVLT) and the Corsi Block Tapping Test (CBTT), respectively [1].

In the Sternberg task, each trial starts with the presentation of a fixation cross in the middle of the screen, for 2 seconds. Afterwards, a "memory set" of 4 or 6 digits is presented for 1 second to allow memorization (encoding phase). The presentation of the digits series is followed by another fixation cross window presented for 2 seconds (storage period). Then a single probe digit is presented for 250 ms (retrieval phase) followed by a fixation cross presented for 1250 ms. Afterwards, the question "yes or no?" appears at the screen for a maximum duration of 1500 ms, and the participant is required to give an answer about the presence (target) or not (no target) of the probe in the memory set. The conditions 4/6 digits and target/notarget are randomized within the recording session. 36 trials for each condition were administered. A detailed description of the timing of the experiment for the four different conditions is reported in Fig.1.

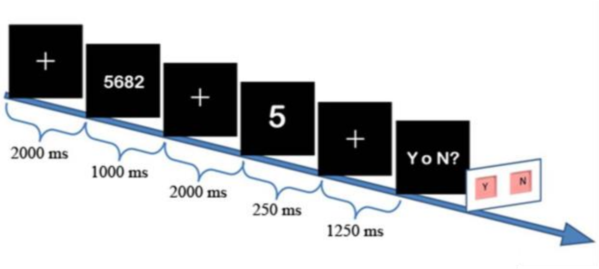

Figure 1 – Timing of Sternberg task (4 digits, target case)

D. *Effective Connectivity Analysis*

PRE and POST EEG data were band-pass filtered in the range [1-45]Hz, depurated from ocular artefacts by means of Independent Component Analysis and subjected to a time-varying connectivity estimation approach [3]. Time-varying connectivity patterns were then averaged in the three memory phases (encoding, storage and retrieval) and in the four frequency bands defined according to the Individual Alpha Frequency [10]. A graph theory approach was then applied to the achieved networks with the aim to characterize their salient properties [8].

In order to describe modifies in memory processes induced by the rehabilitative treatment, statistical comparisons, at single subject level, between PRE and POST measurements (neuropsychological tests, behavioural data, connectivity networks, graph theory indexes) were performed. In particular, a dependent samples t-test was applied for a significance level of 5% corrected by means of False Discovery Rate for preventing type I errors due to multiple comparisons.

III. RESULTS

A. Results for Patient A: Positive Outcome

The Patient A was able to learn the modulation of her SMR as indicated by the increase of SMR amplitude from 7.7 μV^2 to 8.4 μV^2 across the 10 training sessions.

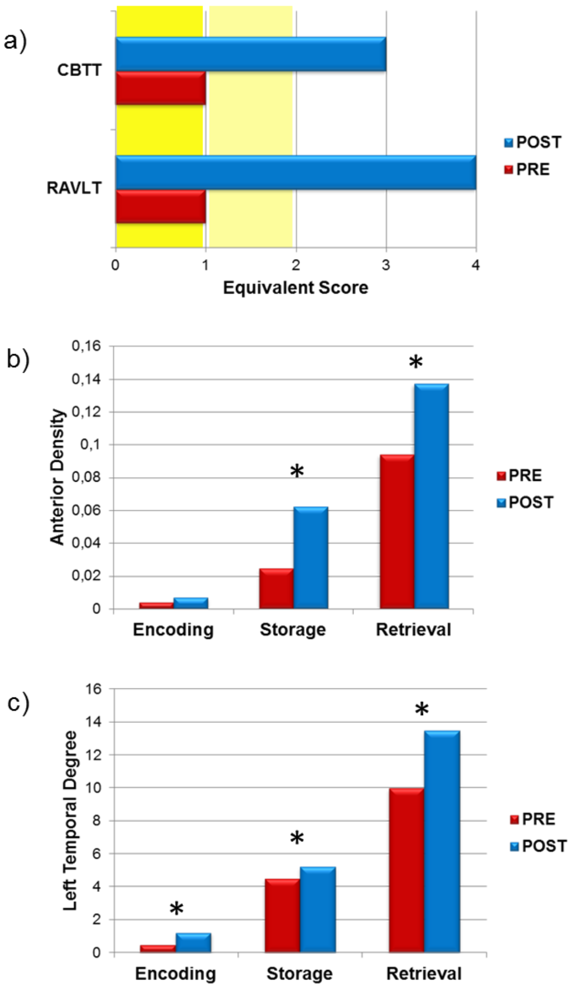

Figure 1. a) Bar diagrams reporting the equivalent scores achieved for RAVLT and CBTT neuropsychological tests administered to patient A before (PRE, red bars) and after (POST, blue bars) the rehabilitation period. Equivalent scores below 2 (in yellow) highlight a pathological condition for the specific cognitive function investigated by the test. b,c) Anterior Density and Left Temporal Degree indexes achieved in Alpha band during Sternberg task in PRE (red bars) and POST (blue bars) sessions for the representative stroke patient A. The symbol (*) reported above the bars highlights a statistical significance between PRE and POST sessions (paired t-test; p<0.05).

Memory Assessment. As reported in Fig.1a, the neuropsychological tests revealed a significant improvement of the tested memory function after the neurofeedback-based training (PRE-POST comparison, paired t-test, $p<0.05$). Equivalent scores for both CBTT and RAVLT tests increased from 1 to 3 and 4 respectively, thus indicating a transition from a pathological (PRE) to a physiological (POST) condition.

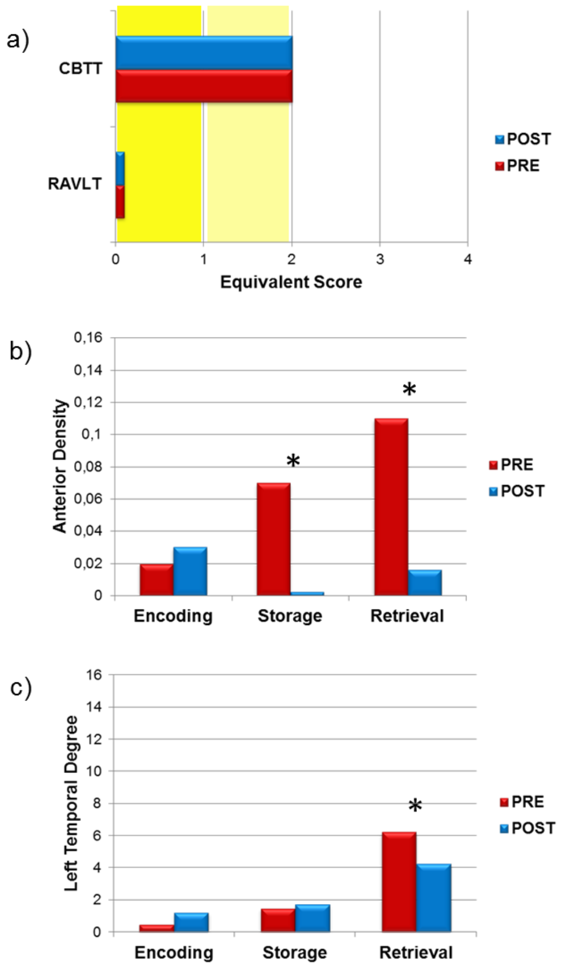

Figure 2. a) Bar diagrams reporting the equivalent scores achieved for RAVLT and CBTT neuropsychological tests administered to patient B before (PRE, red bars) and after (POST, blue bars) the rehabilitation period. Equivalent scores below 2 (in yellow) highlight a pathological condition for the specific cognitive function investigated by the test. b,c) Anterior Density and Left Temporal Degree indexes achieved in Alpha band during Sternberg task in PRE (red bars) and POST (blue bars) sessions for the representative stroke patient A. The symbol (*) reported above the bars highlights a statistical significance between PRE and POST sessions (paired t-test; p<0.05).

Behavioral Data. Analysis of the behavioral performance obtained at the Sternberg task revealed a significant increase of correct answers and a significant decrease of the reaction time after training (PRE-POST comparison, paired t-test, $p<0.05$).

EEG derived Brain Network. Analysis of the connectivity patterns revealed a significant POST training increase of Anterior Density index (Fig.1b) estimated in the alpha band only for Storage and Retrieval phases of the Sternberg task associated with an increase of Left Temporal Degree index (Fig.1c) in alpha band for all the three memory phases (Encoding, Storage and Retrieval).

B. Results for Patient B: Negative Outcome

The Patient B did not show changes in the amplitude of his SMR across the 10 training sessions. The amplitude value remained stable around 2.3 μV^2.

Memory Assessment. In this Patient (Fig.2a) we did not find significant changes in the memory functions as evaluated by means of neuropsychological assessment (PRE-POST comparison, paired t-test, p>0.05). Equivalent scores for both RAVLT and CBTT tests remained around 1 and 2 respectively, indicating a persistency of the pathological profile.

Behavioral Data. Similar negative outcome was found for the behavioral assessment. Data analysis revealed a decrease of the percentage of correct answers and no significant difference in reaction time between PRE and POST sessions of Sternberg task (paired t-test, p<0.05).

EEG derived Brain Network. Connectivity pattern analysis revealed in Patient B an opposite profile of changes in the POST training analysis with respect to what observed in Patient A. In fact, a significant decrease in the Anterior Density index (Fig.2b) for Storage and Retrieval phases and of Left Temporal Degree index (Fig.2c) for the Retrieval memory phase both estimated in the alpha band, were observed.

IV. DISCUSSION

In the present paper we proposed a new approach based on the use of advanced methodologies for effective connectivity estimation and graph theory for defining a set of neurophysiological indexes able to describe the modifies related to the plasticity induced by the rehabilitative intervention. In particular, we selected as descriptors of memory processes at the basis of Sternberg task, the anterior density and left temporal degree indexes in alpha band. In fact, the importance of fronto-central and left fronto-temporal areas in Sternberg task has been already demonstrated in a preliminary study conducted on healthy subjects performing the task [11]. The central executive, located in frontal areas of the brain, is in fact responsible for coordinating the other working memory subsystems, for recruiting and allocating attentive resources to inhibit the irrelevant processes and for decoding the information associated with the material to keep in memory [12]. The left temporal areas are instead responsible for the strategy planning, the recoding of the visual material into phonological code, the rehearsal of the stimuli by inner speech and the provisional storage of the material [13].

The results showed in this paper confirmed the role of such indexes as valid descriptors of modifies in networks elicited during Sternberg task. In particular for both representative subjects the variations of such indexes between PRE and POST sessions were in agreement with behavioral results and above all with the outcome of neuropsychological tests on memory functions.

V. CONCLUSION

The results showed in the present study demonstrated the possibility to use the combination of advanced methodologies for effective connectivity estimation and graph theory indexes for describing the neurophysiological changes in cerebral networks induced by a memory rehabilitation treatment.

The neurophysiological descriptors were sensitive to different training intervention outcomes, thus suggesting an effective support to the neuropsychological assessment in the evaluation of the changes induced by the BCI-based cognitive rehabilitative intervention.

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