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BCI-ASSISTED TRAINING FOR UPPER LIMB MOTOR REHABILITATION: ESTIMATION OF EFFECTS ON INDIVIDUAL BRAIN CONNECTIVITY AND MOTOR FUNCTIONS

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ABSTRACT: The aim of the study is to quantify individual changes in scalp connectivity patterns associated to the affected hand movement in stroke patients after a 1-month training based on BCI-supported motor imagery to improve upper limb motor recovery. To perform the statistical evaluation between pre- and post-training conditions at the single subject level, a resampling approach was applied to EEG datasets acquired from 12 stroke patients during the execution of a motor task with the stroke affected hand before and after the rehabilitative intervention. Significant patterns of the network reinforced after the training were extracted and a significant correlation was found between indices related to the reinforced pattern and the clinical outcome indicated by clinical scales.

INTRODUCTION

In neuroscience, the concept of brain connectivity is crucial to understand how communication between cortical regions is organized or re-organized in presence of a brain injury or brain disease [1], [2]. Group analysis studies are commonly performed when the aim is to evaluate the relevant differences between experimental conditions and/or the consistency of a treatment effect and how the differences or effects might affect the functional brain network configuration.

As such, this approach holds some limitations related to the unavoidable heterogeneity in the experimental group and further, specific effects that a given brain lesion has on neural networks (e.g. stroke) at the single patient level might be hidden. Thus, there is the need to provide measures that might account for individual pathological network configuration associated with different level of patient's impairment.

In this study, an approach based on the use of the resampling was applied to evaluate the brain network reorganization in each individual patient who underwent a rehabilitative training after stroke. Indeed typically a statistic comparison of two patient's conditions cannot be performed as the amount of data collected in an EEG recording session (multi-trial EEG dataset) are entirely used to obtain an unique connectivity estimation. To overcome this limitation, in the present work we applied jackknife approach [3] to multi-trials EEG data, thus generating a distribution of datasets out of a single observation (ie, single patient). These datasets can be then subjected to connectivity estimation to obtain a distribution of the connectivity estimator in each of the patient experimental condition as described below. We used motor task-related EEG data recorded on subacute stroke patients in two recording sessions: one preceding and one following a rehabilitative intervention based on motor imagery with the support of Brain Computer Interfaces (BCI) [2]. The BCI training in [2] lasted one month, with 3 weekly session in which patients were asked to perform motor imagery of the stroke affected hand to control a specifically designed BCI system. Control features for BCI were selected from a screening session among electrodes from sensorimotor strip on the affected hemisphere only, at frequencies relevant for sensorimotor activation (mainly beta). The patterns underlying the attempted movement of the paralyzed hand obtained before and after the intervention from each stroke patients were compared, in order to describe the individual significant connectivity changes induced by the BCI-assisted training. Connectivity matrices were also analyzed by means of a graph theory approach, and a correlation analysis was performed to test the existence of a relationship between the organization of brain networks (graph-theory derived indices) and the functional outcome measures specific for the upper limb motor function.

MATERALS AND METHODS

Partial Directed Coherence

As a frequency-domain version of Granger causality [4], PDC reveals the existence, the direction and the strength of a functional relationship between any given pair of signals in a multivariate data set.

In this study we used the squared formulation of PDC due to its higher accuracy and stability [5].

Resampling approach: Jackknife

To achieve a distribution of connectivity estimations allowing a comparison between conditions, in this study we exploited a resampling approach. Given an EEG dataset characterized by a certain number of trials, Jackknife performs leave-*N*-out on trials, where *N* is a percentage of trials to be randomly excluded from the

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estimation. Repeating the procedure for K replications, we can obtain K datasets to be subjected to connectivity estimation. Here, we set the parameters to the following values: K = 200 replications, percentage of excluded trials N = 50%.

Experimental design

EEG signals were acquired from 12 subacute stroke patients (mean age, 62.1 ± 9.9 years; time from the event: 1.75 ± 1.21 months; 6 left/6 right affected hemisphere). All the patients underwent standard motor rehabilitation and a newly proposed add-on intervention based on a BCI-assisted upper limb motor imagery training [2]. Immediately before and after the training intervention, the patients were subjected to two screening sessions (PRE and POST) including clinical assessment and EEG recordings during the attempt of a simple movement (grasping) by the hand affected by the motor deficit. The clinical assessment included the evaluation of the upper limb function by means of *Fugl-Meyer Assessment* (FMA, upper limb section).

Signal processing

After data preprocessing (down-sampling at 100 Hz with anti-aliasing filter, band pass filtering (1-45 Hz), and artifact rejection), we obtained for each patient and each condition (PRE and POST) an EEG dataset consisting of approximately 60 artifact-free trials related to the motor task. Then we applied the jackknife method. Brain connectivity was estimated from 29 channels by means of PDC. The achieved estimations were averaged within 5 frequency bands defined for each patient according to Individual Alpha Frequency [6]: theta [IAF-6;IAF-2], alpha [IAF-2;IAF+2], beta1 [IAF+2;IAF+11], beta2 [IAF-11;IAF+20] and gamma [IAF+20;IAF+35].

Once the patterns distributions were obtained for each patient, condition and frequency band, we performed the statistical comparison between PRE and POST conditions. In particular, to evaluate the effects of the rehabilitative intervention, we focused on the pattern that was significantly reinforced for each patient in the POST with respect to the PRE session (POST vs PRE). To perform this comparison, we used a nonparametric test: the values in the POST pattern above the thresholds related to the percentile of 97.5% of the PRE distribution, were considered significantly reinforced. The PRE vs POST comparison (inverse condition) was also tested as control.

To summarize the properties of the reinforced networks we computed some binary graph indices able to evaluate the network organization [7].

- Characteristic Path Length

$$L = \frac{1}{n}\sum_{i \in N} L_i = \frac{1}{n}\sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}}{n-1} \qquad (1)$$

where L_i is the average distance between node i and all other nodes and d_{ij} is the distance between node i and node j.

- Clustering Coefficient

The binary directed version of Clustering Coefficient is defined as follows:

$$C = \frac{1}{n}\sum_{i \in N} C_i = \frac{1}{n}\sum_{i \in N} \frac{t_i}{(k_i^{out} + k_i^{in})(k_i^{out} + k_i^{in} - 1) - 2\sum_{j \in N} g_{ij} g_{ji}} \qquad (2)$$

where t_i represents the number of triangles involving node i, k_i^{in} and k_i^{out} are the number of incoming and outcoming edges of nodes i respectively and g_{ij} is the entry ij of adjacency matrix.

- Smallworldness

A network G is defined as small-world network if L_G > L_{rand} and C_G >> C_{rand} where L_G and C_G represent the characteristic path length and the clustering coefficient of a generic graph and L_{rand} and C_{rand} represent the correspondent quantities for a random graph. On the basis of this definition, small-worldness can be defined as follows:

$$S = \frac{C_G / C_{rand}}{L_G / L_{rand}} \qquad (3)$$

A network is said to be a small world network if S>1.

Correlation analysis

As a last step of the analysis, we performed Pearson's correlation (significance level 0.05) between the above defined neurophysiological indices extracted from the reinforced networks and the functional scale (FMA).

For the clinical measure, to account for the high inter-subject variability in terms of degree of the impairment, and for the consequent different level of recovery, we computed the parameter "effectiveness" [8], defined as follows:

$$Eff_{FMA} = \frac{FMA_{POST} - FMA_{PRE}}{Score_{\max} - FMA_{PRE}} * 100 \qquad (4)$$

where $Score_{max}$ is the maximum score that can be reached in FMA scale.

RESULTS

Fig. 1 shows the connectivity pattern reinforced at the end of the rehabilitative training obtained for a representative patient with a stroke in the left hemisphere: the pattern in the motor-related frequency band (beta1) shows a higher involvement of channels over the motor areas of the affected (left) hemisphere during the attempt to move the right hand.

Results of the Pearson correlation computed between graph measures extracted from the connectivity pattern and the clinical indices across the 12 stroke patients are reported in Table I and in Fig. 2. Such results show that the properties of the functional network reinforced after the training are significantly correlated with the clinical outcome selectively in beta1 band.

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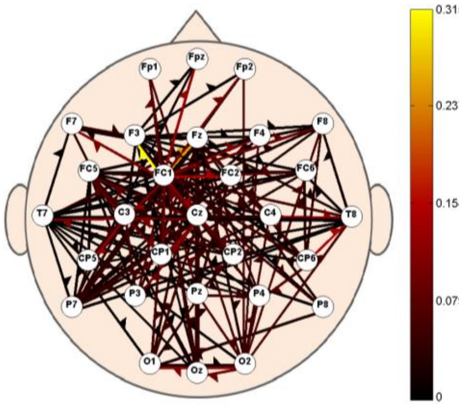

Figure 1: Reinforced connectivity pattern obtained in beta1 band (typical of sensory-motor rhythms) for a representative patient with lesion in the left hemisphere. The scalp is seen from the above, with the nose pointing to the upper part of the page. The effective connections between scalp electrodes (29 channels: Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, O1, Oz, O2) are represented by arrows whose color and diameter code for the corresponding PDC values.

Table 1: Results of the Pearson correlation computed between graph indices extracted from the reinforced pattern of motor task and the clinical recovery (effectiveness of Fugl-Meyer Assessment). Significances are highlighted in bold.

	THETA	ALPHA	BETA1	BETA2	GAMMA
			Smallworldness		
p	0.607	0.519	**0.001**	0.597	0.123
R	0.166	0.207	**0.822**	0.170	0.471
			Path Length		
p	0.468	0.653	**0.007**	0.764	0.151
R	-0.232	-0.145	**-0.735**	-0.097	-0.441
			Clustering		
p	0.390	0.368	**0.013**	0.350	0.093
R	0.274	0.286	**0.691**	0.296	0.507

In particular, the direct correlation between these neurophysiological measures and the clinical indices informs that the patients with higher clinical recovery show a better organization of the reinforced network related to the motor function (high clustering, low path length, high smallworldness). The PRE vs POST comparison performed as control returned no significant results.

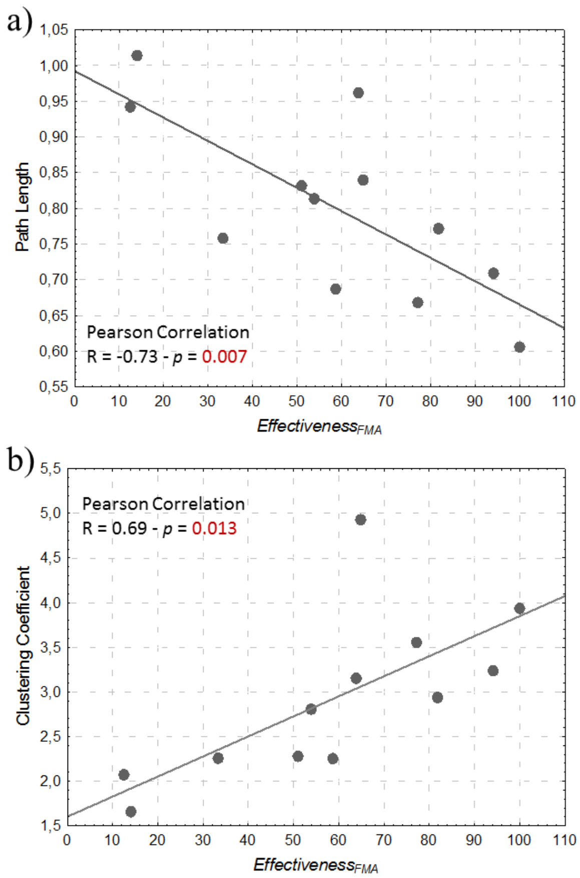

Figure 2: a) Scatter plot obtained between Path Length and the clinical recovery (effectiveness of Fugl-Meyer Assessment) in beta1 band; b) scatter plot obtained between Clustering and the clinical recovery measure in beta1 band.

DISCUSSION

In the present work, we performed a statistical evaluation of the individual brain network reorganization following a rehabilitative training in a population of subacute stroke patients. To perform the single-patient statistical comparison between the two conditions (pre- and post- intervention), jackknife was applied to multi-trial EEG datasets. The comparison between the 2 distribution of data set relative to PRE and POST sessions (POST vs PRE) revealed that the properties of the brain networks associated to attempted movements were reinforced as a function of the functional improvement (FMA effectiveness) observed after the BCI-assisted rehabilitation training.
The correlation between normalized indices of the network properties (clustering, path length, smallworldness) and the normalized index of the functional recovery (FMA effectiveness) suggests that patients with higher level of functional motor recovery show a better organization of the reinforced network such as high clustering, low path length, high smallworldness. Consistently, such correlation was specific for motor-related frequency band (beta 1) while

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no similar results were achieved for any other frequency band (Table I).

To assess the clinical recovery, we computed the effectiveness parameter, one of the most used rehabilitation impact indices [8]. One limit in applying such effectiveness parameter resides in the possible underestimation of clinical improvement in moderate versus severe stroke.

Although these are encouraging findings, the small patients sample (n=12) and the high variability within the group limits their interpretation. Future studies including a larger patient sample subjected to a stratification according to the clinical impairment at baseline, are thus needed.

In a previous study, [2], we showed that BCI-supported motor imagery training can significantly improve the upper limb motor outcome in a population of subacute stroke patients.

The current study represents a first step forward as it addressed i) the need of single patient estimation of connectivity networks to better isolate efficacy of treatment with respect to the high inter-individual variability in stroke population and ii) the estimation of task –related reorganizational scalp connectivity patterns changes (with respect to the resting state network), thus targeting the main outcome of the rehabilitative intervention described in [2], i.e. upper limb motor recovery.

An important aspect to discuss is related to the connectivity estimation performed with EEG sensor time series. It is known that this procedure can lead to the detection of spurious connections due to the mixing effects caused by volume conduction [9]. In this study we performed a statistical comparison between two experimental conditions that represents a way to mitigate these effects. Furthermore, in view of clinical application scalp EEG analysis can represent a more suitable procedure with respect to the use of method for solving the inverse problem that needs to take into account the presence of brain lesions. Altogether, the presented results show the feasibility of the procedure in a study aimed at capturing intervention-related variations in patients' physiological activity, in challenging conditions characterized by high individual variability.

CONCLUSION

In conclusion, the proposed procedure provided quantifiable measures of brain networks changes after a BCI-based training at the single subject level; such measures correlate significantly with the variations captured behaviourally by functional scales commonly used in the clinical practice

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