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Study of the time-varying cortical connectivity changes during the attempt of foot movements by spinal cord injured and healthy subjects

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Abstract—**In this study we estimated time-varying cortical connectivity patterns from a group of Spinal Cord Injured (SCI) patients during the attempt to move a paralyzed limb. These data were compared with the time-varying connectivity patterns estimated in a control group during the real execution of the movement by using time-varying Partial Directed Coherence. Connectivity was estimated from high resolution EEG recordings with the use of realistic head modelling and the linear inverse estimation of the cortical activity in a series of Regions of Interest of the cortex (ROIs). The experimental evidences obtained support the conclusion that the SCI population involved a larger cortical network than those generated by the healthy subjects during the task performance. Such network differs for the involvement of the parietal cortices, which increases in strength near to the movement imagination onset for the SCI when compared to the normal population. Such details about the temporal evolution of the connectivity patterns cannot be obtained with the application of the standard estimators of connectivity.**

I. INTRODUCTION

IT has been suggested from previous studies that in stabilized Spinal Cord Injuried patients (SCIs) the motor cortical areas associated with the body movement below the damage level can be activated by a motor attempt involving the paralyzed limbs as well as a mental rehearsal of such attempt [1]. Recent results obtained with the use of EEG technology point to a consistent involvement of a number of fronto-parietal motor-related areas in tetraplegic SCI subjects during attempts to move their ‘‘disconnected” feet [2]. The same group has also found that in the SCI patients the recruitment temporal profile of the putative foot movement representation zone within the primary motor area (MI) was remarkably well-preserved in both the initial preparatory stage and the later stage of the self-generated movement attempts. The interest in the analysis of cortical patterns related to the imagination or the attempt to perform movements in the SCI patients relies on the possible use of significant “EEG descriptors” for the development of brain signal-controlled prosthetic devices. In this context, an interesting class of these “EEG descriptors” is composed by the estimation of functional connectivity between cortical areas, as derived from the application of the Directed Transfer Function (DTF) or Partial Directed Coherence (PDC) methods to the EEG signals [3-4]. It is worth of note that DTF and PDC for their nature return a “static” (or time-invariant) pattern of functional links between different cortical areas in the employed frequency bands when applied in their original formulation. In fact, the classical estimation of these methods requires the stationarity of the signals; moreover, with the estimation of a unique MVAR model on an entire time interval, transient pathways of information transfer remains hidden. However, the rapidly shifting nature of the cortical patterns sub-serving the imaginative tasks in SCI patients [2,5] requires a time-varying approach for the estimation of the functional connectivity links. Recently, a time-varying version of the PDC was derived and validated in a simulation study [6].

Here, we describe the time-varying cortical connectivity patterns estimated in a group of SCI patients and a group of control during the attempt of a combined foot and lips movement. Such time-varying cortical connectivity patterns were estimated in cortical Region of Interest (ROIs). The experimental hypothesis is that the time-varying approach could shed light on the occurrence of similar or different rapidly shifting cortical networks in the two populations during the analyzed task. In particular if, in a similar way to what is known for overt movement execution, covert movements of affected limbs in SCIs induce activation of either several “pre-motor” and more executive motor areas. Along this similarity, it is of utmost interest to assess if the functional relationships among the electrical activities in these areas differ between executed and attempted movements. Finally, the expected task-related differences in the functional network might address some aspects of the cortical reorganizational processes which do occur after SCIs.

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II. MATERIALS AND METHODS

A. *Time-varying multivariate connectivity estimation*

In this study, we used an adaptive formulation of PDC [6], based on an adaptive Multivariate Autoregressive (AMVAR) model. The time dependent parameter matrices were estimated by means of the recursive least squares (RLS) algorithm with forgetting factor, whose extension to multiple trials was previously introduced [7]. The fitting procedure of the AR parameters exploits the RLS technique with the use of a forgetting factor. It is based on the minimization of the sum of exponentially weighted prediction errors of the process past. Thereby, the weighting depends on an adaptation constant (forgetting factor) c, with 0<=c<<1, which controls the compromise between adaptation speed and the quality of the estimation. Values close to zero result in a slower adaptation with more stable estimations and vice versa. Effects of different weightings were shown in a simulation study [6]. A comprehensive description of this algorithm can be found in [7-8].

B. *Experimental Design and EEG recordings*

We examined 5 subjects with spinal cord injury (SCI; 4 males, 1 female, mean age 22.4±2.8 years) and 5 healthy control subjects (CTRL; 4 males, 1 female, mean age 24.1± 1.5). Informed consent was obtained from all subjects. The task consisted of repetitive self-generated attempted (SCI subjects) or overt (control subjects) executions of the right foot dorsal flexion at the ankle. As to capture the EEG activity related to the attempted motor execution, SCI subjects were instructed to perform a brisk lip pursing (intact movements) whose electromyogram (EMG) functioned as a trigger for the subsequent EEG trial segmentation. As controlled condition, data were collected from controls during foot movements simultaneously executed with lip pursing. Each task was repeated every 6-7 s in a self-paced manner. Scalp potentials were collected with a 96 channel EEG system at a sampling frequency of 200 Hz. Bipolar EMG was recorded with surface electrodes in order to detect the onset of foot and lip movements. One hundred single EEG trials were recorded for each subject. The EEG signals for each task condition were averaged separately, time-locked to onsets of EMG. Structural MRIs of the subject's head were taken. The analysis period for the potentials time-locked to the movement execution was set from 1500 ms before to 0 time (EMG trigger).

C. *Estimation of the cortical activity and connectivity*

The cortical signals were estimated from high resolution EEG recordings, by using realistic head models and a cortical reconstruction with an average of 5,000 dipoles uniformly disposed along such cortical surface. The estimation of the cortical activity was obtained by the application of the linear inverse procedure as described in [6]. Cortical activity was then estimated in ROIs generated by the segmentation of the Brodmann areas on the accurate cortical model used. The average cortical signals obtained in each ROI were then subjected to the AMVAR modelling in order to compute the time-varying PDC.

The cortical regions of interest (ROIs) employed in the study were drawn on the computer-based cortical reconstruction of the individual head models of the 10 subjects. In details, we employed for both left and right hemispheres the supplementary motor area proper (SMAp); the caudal cingulate motor area (CMAc); the primary motor foot (M1-foot) representational area and the primary motor lip (M1-lip) representational area; the superior parietal cortex, SP and the pre-motor dorsal cortex, PMd.

III. RESULTS

By means of the linear inverse procedure, the estimation of the current density waveforms in the ROIs employed was performed for the 10 subjects. Time-frequency distribution of the instantaneous PDC was obtained for all the subjects from the set of cortical waveforms estimated in the 12 ROIs considered. The adaptation constant c was set to 0.02, according to the indications from a previous simulation study for the amount of data at disposal [6]. The optimum MVAR model order was 16 or 17 for the different subjects, as obtained by the Akaike Information Criterion (AIC). High values of connectivity could be noted in particular in the alpha [8-12 Hz] and beta2 [22-30 Hz] frequency bands, and involved mainly the PMd areas from the left and right hemispheres, the M1F left and right, the SMAp left and right and the CMAc left and right. Fig. 1 shows the time-varying connectivity patterns in the beta2 band, extracted at -500, -250 and 0 milliseconds before the lips movement onset, provided for a representative subject of the SCI group and for a representative one for the control group. Results are presented on the realistic reconstruction of the head and cortex of each subject, obtained from sequential MRIs. The different ROIs selected are depicted in different colors and

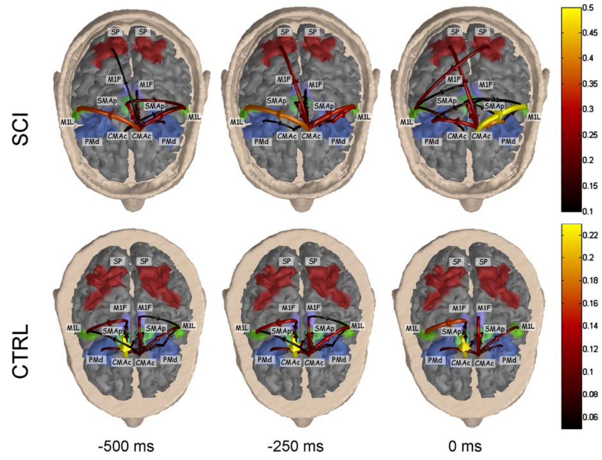

Fig.1. Different connectivity patterns before movement attempt in Spinal Cord Injury patients (first row: SCI) and controls (second row; CTRL).

described by labels. The connectivity links are represented by arrows, pointing from one cortical area ("the source") toward another one ("the target"). The color and size of the arrows code for the interaction strength, with the minimum strength coded in black and the maximum value coded in light yellow. Only statistically significant links are reported, with respect to a significance threshold computed as described in [6]. A common functional pattern involving the cingulate motor areas as a principal source of information directed towards the motor areas of the foot and the lips, as well as the premotor cortices, can be noted both in the SCI subject and in the control. The time evolution of the links revealed by time-varying PDC allows uncovering a different behavior in the two subjects which would have been invisible to conventional estimators. In particular, the connection between the CMAc of the left hemisphere and the MIL of the same hemisphere is stable for the control subjects while its strength increases significantly in the period preceding the movement for the SCI subject. The connection from the SMAp_R and the MIF_R which is weak and appears only in the last 250 ms before the movement attempt for the SCI subject shows, on the contrary, a different behavior for the control subject, increasing its strength during the movement preparation. Also the connection directed from the CMA of the left hemisphere and the MIF of the same hemisphere shows an opposite behavior for the two subjects. In fact, for the SCI (first row) it decreases in time and is absent at the EMG trigger (third figure of the first row). On the contrary, for the control subject this connection increases its strength during the movement preparation. The most interesting difference in the cortical network supporting the task is probably the one involving the parietal cortices in the SCI subject, which changes dramatically over time, by assuming more importance near to the EMG onset with respect to the half second before. This involvement of the parietal areas in the task is completely absent in the control population.

In order to compare results i) from different subjects in each group and ii) between the two groups, we focused to the connectivity time course of the 5 SCI patients and the 5 healthy controls. We normalized the waveforms to allow comparison despite different power spectra across subjects, and then we reported mean value and variance of such waveforms in each group (SCI and controls). To avoid spurious results, only results statistically significant for at least 3 out of 5 subjects from each group were used and reported.

Fig. 2 shows the mean time courses of interaction strength between selected regions of interest from each group of subjects analyzed. First row refers to the SCI patients group, second row refers to the control group. The thick line is the mean value of the time-varying connectivity strengths obtained across subjects of each group. The error bars describe the variance in each group. Time is expressed in msec from the EMG onset (0 time). The waveforms were normalized to allow comparison despite different power spectra, by subtracting their mean values and dividing by their standard deviations. The ROIs presented are the Brodmann area 6 of the right hemisphere (PMd_R), the primary motor area for the lips of the right hemisphere (M1L_R) and the supplementary motor area proper (SMAp) left and right. For these functional connections, it is possible to recognize a common trend for the two groups of subjects.

In particular, it is of interest the behavior of the pre-motor dorsal cortex of the right hemisphere (PMd_R) whose connectivity strengths towards the primary motor area of the lips (M1L) decreases during the 500 ms preceding the lips EMG onset. An increase of connectivity strengths is also observed during the period of time from 250 ms to the EMG onset between the supplementary motor area proper and the primary motor area of the lips.

IV. DISCUSSION

The application of the time varying cortical connectivity estimation techniques to the EEG data recorded from normal and SCI patients returned interesting information about the cortical networks sub-serving the analyzed tasks. In particular, the cortical network estimated in the control subjects highlight a substantially stable topology in the last 500 ms before the EMG onset, as observed by the second row of the Fig. 1, with light changes in the strength of the cortical connectivity between the primary and the supplementary motor cortices. Taken together, these evidences suggest a stable pattern of connectivity between the primary and premotor areas of the control subjects in the last 500 ms before the movement execution. Such pattern was in part replicated in the SCI group, for all concerns the involvement of the motor and premotor cortices in the 500 ms before the EMG onset (first row of Fig.1) but the analysis of time-varying connections showed differences in the evolution of these links during the movement preparation, in particular in the flows from the premotor to the primary motor areas. The time-varying PDC also showed similarities in the time courses between some areas in the two groups. The first row of Fig. 2 shows the substantial agreement of the strength evolution in time for the premotor, primary and supplementary motor areas for the SCI patients. The similarity with the time evolution of the cortical connectivity strength in the control population (second row of Fig. 2) can be appreciated. The experimental evidences of the present study are in accordance with previous studies [9] but add some important insights with respect to previous results, showing how some functional links in the SCI group change in time with respect to the control subjects. Moreover, such network differs for the involvement of the parietal cortices. A precise increment of the cortical connectivity between right and successively left superior parietal areas is observed in the group of SCI when compared to the Control group.

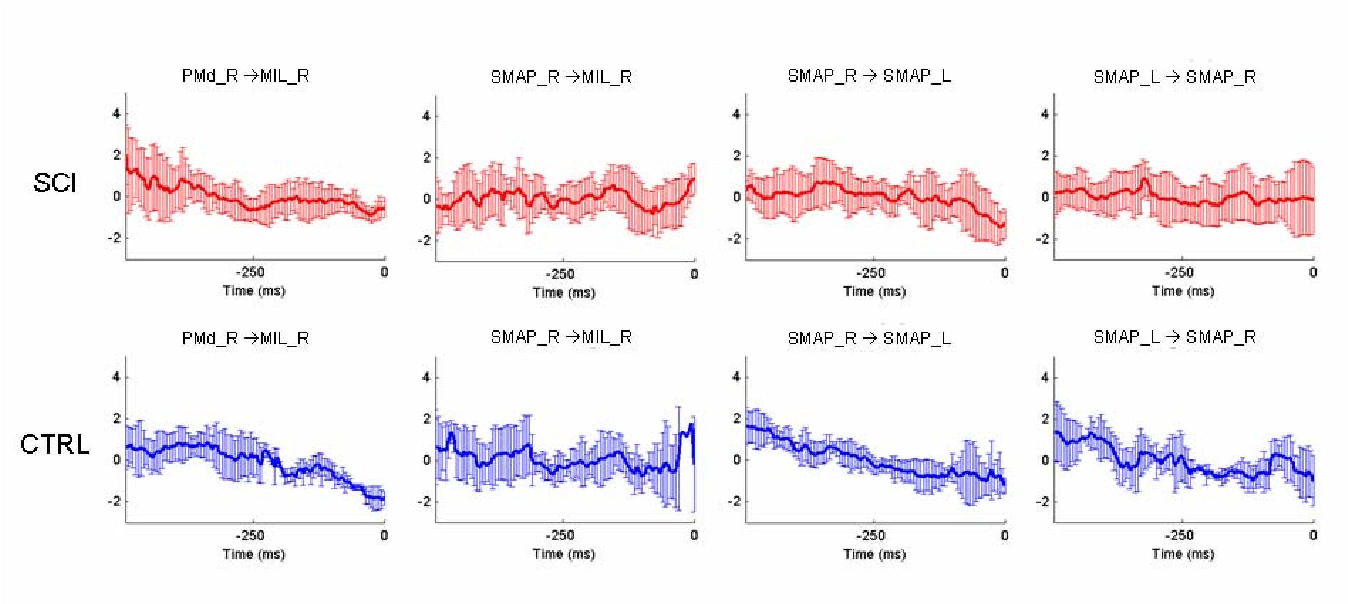

Figure 2. Time varying connectivity patterns in a group of SCI patients (first row) and normal subjects (CTRL, second row). The label above each graph indicates the direction of connectivity between cortical areas. The thick line is the mean value of the time-varying connectivity strengths obtained across subjects of each group. The error bars describe the variance in each group. Time is expressed in msec from the EMG onset (0 time). The waveforms were normalized to allow comparison despite different power spectra, by subtracting their mean values and dividing by their standard deviations.

Such control increases with time and is generated by both parietal cortices around the EMG onset, while was almost absent at about half a second before.

These important changes in the strengths of functional cortical connectivity sub-serve a more general control of “superior” cortices in the organization of the imagined movement. The possible interpretation relies on the fact that the attempt to move a paralyzed limb for the SCI patients needed more cortical resources than in the control population, this being due to the necessity to restore the sensation and the relative position of the lost limb within the body structure. In fact, it is already known that the imagination of the spatial relationships between the limbs and the body structure are usually performed by the parietal cortices [10]. In the case of the control group probably this lack of connectivity between such cortical areas subtends an increase of the functional independence in the organization of the movement generated by the motor cortices, due to the fact that the rather simple movements of the right foot may not be sufficient to elicit significant functional links from and to this area in normals. A stationary analysis of connectivity applied on the same data set, also suggested that functional connectivity in SCI group showed a preferential interaction between the ‘‘non-primary” motor areas and the putative MI foot site, as estimated for both motor execution and attempt. Under this latter condition however, it could be observed an ‘‘enlargement” of the functional network by including the superior parietal cortex [2] in the SCI group when compared to the controls. However, the application of the methodology here presented allows inferring the precise time-course of similar cortical connectivity patterns between subjects and between groups, in terms of time course of the information flow during the task execution, as well as differences in their time-dependent functional organization.

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