

Estimation of the Cortical Connectivity by High-Resolution EEG and Structural Equation Modeling: Simulations and Application to Finger Tapping Data

Laura Astolfi, Febo Cincotti, Claudio Babiloni, Filippo Carducci, Alessandra Basilisco, Paolo M. Rossini, Serenella Salinari, Donatella Mattia, Sergio Cerutti, D. Ben Dayan, Lei Ding, *Student Member, IEEE*, Ying Ni, *Student Member, IEEE*, Bin He, *Fellow, IEEE*, and Fabio Babiloni*

Abstract—Today, the concept of brain connectivity plays a central role in the neuroscience. While functional connectivity is defined as the temporal coherence between the activities of different brain areas, the effective connectivity is defined as the simplest brain circuit that would produce the same temporal relationship as observed experimentally between cortical sites. The most used method to estimate effective connectivity in neuroscience is the structural equation modeling (SEM), typically used on data related to the brain hemodynamic behavior. However, the use of hemodynamic measures limits the temporal resolution on which the brain process can be followed. The present research proposes the use of the SEM approach on the cortical waveforms estimated from the high-resolution EEG data, which exhibits a good spatial resolution and a higher temporal resolution than hemodynamic measures. We performed a simulation study, in which different main factors were systematically manipulated in the generation of test signals, and the errors in the estimated connectivity were evaluated by the analysis

of variance (ANOVA). Such factors were the signal-to-noise ratio and the duration of the simulated cortical activity. Since SEM technique is based on the use of a model formulated on the basis of anatomical and physiological constraints, different experimental conditions were analyzed, in order to evaluate the effect of errors made in the *a priori* model formulation on its performances. The feasibility of the proposed approach has been shown in a human study using high-resolution EEG recordings related to finger tapping movements.

Index Terms—Finger tapping movement, high-resolution EEG, structural equation modeling.

I. INTRODUCTION

CHARACTERIZING brain activity in terms of the functional specialization of brain areas can provide only a limited account of the neuronal basis of the underlying processes. Thus, the necessity to describe how different brain areas communicate with each other is gaining more and more importance in neuroscience. The concept of brain connectivity plays a central role, made possible by the increase of noninvasive brain imaging methods [like functional magnetic resonance imaging (fMRI); high-resolution electroencephalography (EEG), or magnetoencephalography (MEG)] that return information about the brain activation during a motor or cognitive task. Two main definitions of brain connectivity have been proposed: the functional and the effective connectivity [1], [2]. While functional connectivity is defined as temporal correlation between spatially remote neurophysiological events [3], the effective connectivity is defined as the simplest brain circuit that would produce the same temporal relationship as observed experimentally between cortical sites [1]. Several computational methods have been proposed to estimate how different brain areas are working together during motor and cognitive tasks by using EEG and fMRI data [4]–[7]. Such methods typically involve the estimation of some covariance properties between the different time series measured from the different spatial sites during the tasks. The estimation returned information about the so-called *functional connectivity*. On the other hand, structural equation modeling (SEM) is a technique that has been used for a decade to assess *effective connectivity* between cortical areas in humans by using hemodynamic measurements [8]–[10]. The basic idea of SEM differs from the usual statistical approach of modeling individual observations, since

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L. Astolfi is with the Dipartimento di Fisiologia umana e Farmacologia (Department of Human Physiology and Pharmacology), University of Rome “La Sapienza,” P.le A. Moro 5, 00185 Rome, Italy (e-mail: laura.astolfi@uniroma1.it).

F. Cincotti and D. Mattia are with the IRCCS Fondazione Santa Lucia, 00179 Rome, Italy.

C. Babiloni is with the Dipartimento di Fisiologia umana e Farmacologia (Department of Human Physiology and Pharmacology), University of Rome “La Sapienza,” 00185 Rome, Italy, and also with the AFAR, Ospedale Isola Tiberina, 00186 Rome, Italy.

F. Carducci is with the Dipartimento di Fisiologia umana e Farmacologia (Department of Human Physiology and Pharmacology), University of Rome “La Sapienza,” 00185 Rome, Italy and also with the IRCCS FBF “San Giovanni di Dio,” 25124 Brescia, Italy.

A. Basilisco is with the Dipartimento di Fisiologia umana e Farmacologia (Department of Human Physiology and Pharmacology), University of Rome “La Sapienza,” 00185 Rome, Italy.

P. M. Rossini is with the AFAR, Ospedale Isola Tiberina, 00186 Rome, Italy, the IRCCS FBF “San Giovanni di Dio,” 25124 Brescia, Italy, and also with the Cattedra di Neurologia, Università Campus Bio-Medico, 00155 Rome, Italy.

S. Salinari is with the Dipartimento di Informatica e Sistemistica, Univ. “La Sapienza,” 00185 Rome, Italy.

S. Cerutti and D. Ben Dayan are with the Dipartimento di Bioingegneria, Politecnico di Milano, 20133 Milan, Italy.

L. Ding and B. He are with the University of Illinois, Chicago, IL 60607 USA, and also with the University of Minnesota, Twin Cities, MN 55455 USA.

Y. Ni is with the University of Illinois, Chicago, IL 60607 USA.

*F. Babiloni is with the Dipartimento di Fisiologia umana e Farmacologia (Department of Human Physiology and Pharmacology), University of Rome “La Sapienza,” 00185 Rome, Italy, and also with the IRCCS Fondazione Santa Lucia, 00179 Rome, Italy (e-mail: fabio.babiloni@uniroma1.it).

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SEM considers the covariance structure of the data [8]. So far, this technique has been applied to the estimation of connectivity based on functional imaging data, such as functional Magnetic Resonance Imaging [11], [12] or positron emission tomography [13]. However, the estimation of cortical effective connectivity obtained with the application of the SEM technique on fMRI data has a low temporal resolution (on the order of 10 s) which is far from the time scale at which the brain operates normally. Hence, it is of interest to understand if the SEM technique could be applied to the estimation of cortical activity, as obtained by the application of linear inverse techniques to the high-resolution EEG data [5], [14]–[16]. In this way, it would be possible to study time-varying patterns of brain connectivity, linked to the different parts of the experimental task studied. The importance of SEM technique in the modeling of brain connectivity with respect to the other available techniques of functional connectivity already available for EEG data lies in the possibility to use the *a priori* information provided by the physical connections furnished by the brain anatomy. The SEM technique merges the anatomical (constrained) model obtained by previous knowledge and the inter-regional covariances of measured brain activity data. The resulting functional model represents the influence of regions on each other through the putative anatomical connections.

Since, to our knowledge, this is the first attempt to apply this technique to the cortical data obtained by high-resolution EEG methods, we first explored the behavior of the SEM technique under different conditions that affects the EEG recordings, mainly the signal-to-noise ratio (factor SNR) and the length of the recordings (factor LENGTH). This was done by designing and implementing a simulation study. In particular, the questions being addressed in the present simulation study are as follows.

- 1) What is the influence of a variable SNR level imposed on the high-resolution EEG data on the accuracy of the pattern connectivity estimation obtained by SEM?
- 2) What is the amount of high-resolution EEG data necessary to get a usable accuracy of the estimation of connectivity between cortical areas?
- 3) How are SEM performances degraded by an imprecise anatomical model formulation? In other words, is this method able to perform a good estimation of connectivity pattern when connections between the cortical areas are not correctly assumed? Which kind of error should be possibly avoided?

In order to answer these questions, we used simulated models with built-in connectivity patterns involving four cortical areas. The estimation process retrieved the cortical connections between the areas under different experimental conditions (variable SNR and signal duration). The connectivity patterns estimated by the SEM technique were compared with those imposed on the simulated signals, and different error measures were then subjected to a statistical multivariate analysis.

Subsequently, we applied the SEM technique to the cortical estimates obtained from high-resolution EEG data related to a simple finger tapping experiment in humans, in order to underline the capability of the proposed methodology to draw patterns of cortical connectivity between brain areas during a simple motor task.

II. METHODS

A. Structural Equation Modeling (SEM)

In SEM, the parameters are estimated by minimizing the difference between the observed covariances and those implied by a structural or path model. In terms of neural systems, a measure of covariance represents the degree to which the activities of two or more regions are related.

The Structural Equation Model consists of a set of linear structural equations containing observed variables and parameters defining causal relationships among the variables. Variables in the equation system can be endogenous (i.e., dependent from the other variables in the model) or exogenous (independent from the model itself). The structural equation model specifies the causal relationship among the variables, describes the causal effects and assigns the explained and the unexplained variance.

Let us consider a set of variables (expressed as deviations from their means) with N observations. In this study, these variables represent the activity estimated in each cortical region, obtained with the procedures described in the following section.

The structural equation model for these variables is the following:

$$y = By + \Gamma x + \zeta \quad (2.1)$$

where

- y ($m \times 1$) vector of dependent (endogenous) variables;
- x ($n \times 1$) vector of independent (exogenous) variables;
- ζ ($m \times 1$) vector of equation errors (random disturbances);
- B ($m \times m$) matrix of coefficients of the endogenous variables;
- Γ ($m \times n$) matrix of coefficients of the exogenous variables.
- ζ assumed to be uncorrelated with the exogenous variables, and B is supposed to have zeros in its diagonal (i.e., an endogenous variable does not influence itself) and to satisfy the assumption that $(I - B)$ is nonsingular, where I is the identity matrix.

The covariance matrices of this model are the following:

$\Phi = E[x x^T]$ is the ($n \times n$) covariance matrix of the exogenous variables;

$\Psi = E[\zeta \zeta^T]$ is the ($m \times m$) covariance matrix of the errors.

If z is a vector containing all the $p = m + n$ variables, exogenous and endogenous, in the following order:

$$z^T = [x_1 \dots x_n y_1 \dots y_m] \quad (2.2)$$

the observed covariances can be expressed as

$$\Sigma_{\text{obs}} = (1/(N - 1)) \cdot Z \cdot Z^T \quad (2.3)$$

where Z is the $p \times N$ matrix of the p observed variables for N observations.

The covariance matrix implied by the model can be obtained as follows:

$$\Sigma_{\text{mod}} = E[zz^T] = \begin{bmatrix} E[xx^T] & E[xy^T] \\ E[yx^T] & E[yy^T] \end{bmatrix} \quad (2.4)$$

where

$$\begin{aligned} E[yy^T] &= E[(I - B)^{-1}(\Gamma x + \zeta)(\Gamma x + \zeta)^T((I - B)^{-1})^T] \\ &= (I - B)^{-1}(\Gamma \Phi \Gamma^T + \Psi)((I - B)^{-1})^T \end{aligned} \quad (2.5)$$

since the errors ζ are not correlated with the x

$$E[xx^T] = \Phi \quad (2.6)$$

$$E[xy^T] = ((I - B)^{-1}\Gamma\Phi)^T \quad (2.7)$$

$$E[yx^T] = (I - B)^{-1}\Gamma\Phi \quad (2.8)$$

since Σ_{mod} is symmetric.

The resulting covariance matrix, in terms of the model parameters, is the following:

$$\Sigma_{\text{mod}} = \begin{bmatrix} \Phi & ((I - B)^{-1}\Phi)^T \\ (I - B)^{-1}\Phi & (I - B)^{-1}(\Gamma\Phi\Gamma + \Psi)((I - B)^{-1})^T \end{bmatrix}. \quad (2.9)$$

Without other constraints, the problem of the minimization of the differences between the observed covariances and those implied by the model is underdetermined, because the number of variables (elements of matrices B , Γ , Ψ , and Φ) is greater than the number of equations $(m+n)(m+n+1)/2$. For this reason, the SEM technique is based on the *a priori* formulation of a model, on the basis of anatomical and physiological constraints. This model implies the existence of just some causal relationships among variables, represented by arcs in a “path” diagram; all the parameters related to arcs not present in the hypothesized model are forced to zero. For this reason, all the parameters to be estimated are called free parameters. If t is the number of free parameters, it must be $t \leq (m+n)(m+n+1)/2$.

These parameters are estimated by minimizing a function of the observed and implied covariance matrices. The most widely used objective function for SEM is the maximum-likelihood (ML) function

$$F_{\text{ML}} = \log |\Sigma_{\text{mod}}| + \text{tr}(\Sigma_{\text{obs}} \cdot \Sigma_{\text{mod}}^{-1}) - \log |\Sigma_{\text{obs}}| - p \quad (2.10)$$

where $\text{tr}(\cdot)$ is the trace of matrix. In the context of multivariate, normally distributed variables the minimum of the ML function, multiplied by $(N-1)$, follows a χ^2 distribution with $p(p+1)/2 - t$ degrees of freedom, where t is the number of parameters to be estimated and p is the total number of observed variables (endogenous + exogenous). The χ^2 statistic test can then be used to infer statistical significance of the structural equation model obtained. In the present study, the publically available software LISREL [17] was used for the implementation of the SEM technique.

B. Computer Simulation

We adopted an experimental design that analyzes the recovery of the connectivity of an estimated model with respect to an imposed one. This has been built under different levels of main factors SNR and LENGTH, as they have been imposed during the generation of a set of test signals, simulating cortical average activations and obtained starting from actual cortical data (estimated with the high-resolution EEG procedures already available at the High-Resolution EEG Laboratory at the University of Rome “La Sapienza”).

1) *Signal Generation*: Different sets of test signals have been generated in order to fit an imposed connectivity pattern [shown in Figs. 1(A), 2(A), 4(A)] and to respect imposed levels of temporal duration (LENGTH) and signal to noise ratio

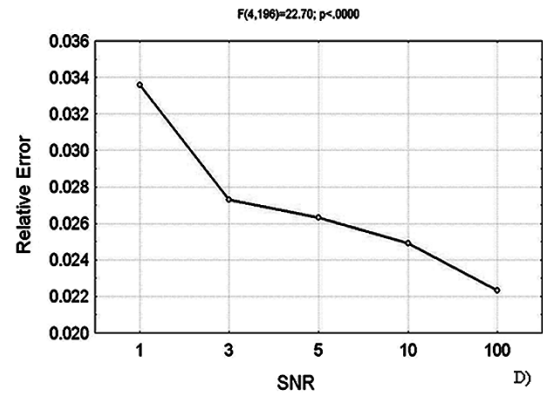
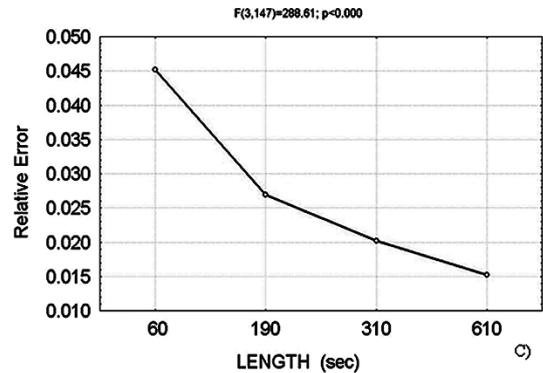
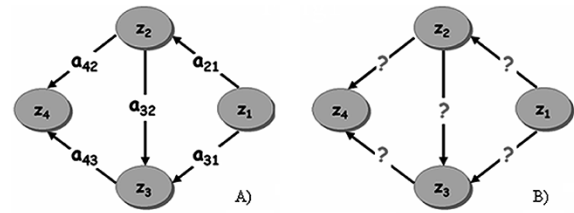


Fig. 1. (A) Connectivity pattern imposed in the generation of simulated signals. Values on the arcs represent the connections strength ($a_{21} = 1.4$; $a_{31} = 1.1$; $a_{32} = 0.5$; $a_{42} = 0.7$; $a_{43} = 1.2$). (B) Connectivity model used for the parameter estimation. (C) Results of ANOVA performed on the Relative Error: plot of means with respect to signal LENGTH as a function of time (seconds). ANOVA shows a high statistical significance for factor LENGTH ($F = 288.60$, $p < 0.0001$). Post-hoc test (Duncan performed at 5% level of significance) shows statistically significant differences between all levels. (D) Results of ANOVA performed on the Relative Error: plot of means with respect to SNR. Here, too, a high statistical influence of factor SNR on the error in the estimation is shown ($F = 22.70$, $p < 0.001$). Duncan post-hoc test (performed at 5%) points out that there is no statistically significant difference between levels 3, 5, and 10 of factor SNR.

(SNR). In the following, in order to use a more compact notation, signals have been represented with the z vector defined in (2.2), containing both the endogenous and the exogenous variables.

Channel z_1 is a reference source waveform, estimated from a high-resolution EEG (128 electrodes) recording in a healthy subject, during the execution of unaimed self-paced movements of the right finger.

Signals z_2 , z_3 , and z_4 were obtained by contribution of signals from all other channels, with an amplitude variation, plus zero mean uncorrelated white noise processes with appropriate variances, as shown in the following:

$$z = A * z + W \quad (2.11)$$

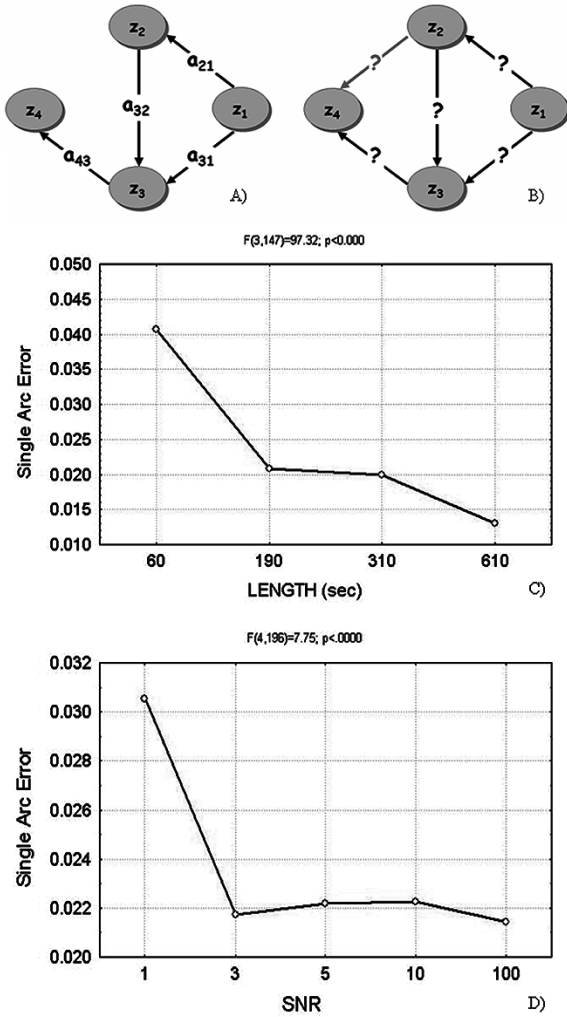


Fig. 2. (A) Connectivity pattern imposed in the generation of simulated signals. Values on the arcs represent the connections strength ($a_{21} = 1.4$; $a_{31} = 1.1$; $a_{32} = 0.5$; $a_{43} = 1.2$). (B). Connectivity model used for the parameter estimation. *Results of ANOVA performed on the error committed on the arc in excess a_{42} (Single Arc Error):* (C) plot of means with respect to signal LENGTH as a function of time (seconds). ANOVA shows a high statistical significance of factor LENGTH ($F = 97.32, p < 0.0001$). Post-hoc test (Duncan at 5%) shows statistically not significant differences between a signal length of 190 or 310 s (25 or 40 trials, 7.5 s per trial). (D) Plot of means with respect to SNR. A statistical influence of factor SNR on the error in the evaluation of the presence of arc a_{42} is shown ($F = 7.75, p < 0.0001$). Duncan *post-hoc* test (5%) points out that there is no statistically significant difference between levels 3, 5, 10, and 100 of factor SNR

where $\mathbf{z}[n]$ is the $[4 \times 1]$ vector of signals, $\mathbf{W}[n]$ is the $[4 \times 1]$ noise vector and \mathbf{A} is the $[4 \times 4]$ parameters matrix obtained from the Γ and \mathbf{B} matrices in the following way:

$$\mathbf{A} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ \gamma_1 & \beta_{11} & \beta_{12} & \beta_{13} \\ \gamma_2 & \beta_{21} & \beta_{22} & \beta_{23} \\ \gamma_3 & \beta_{31} & \beta_{32} & \beta_{33} \end{bmatrix} = \begin{bmatrix} a_{11} & \cdots & & a_{14} \\ \vdots & \ddots & & \vdots \\ & & \ddots & \\ a_{41} & \cdots & & a_{44} \end{bmatrix} \quad (2.12)$$

where β_{ij} stands for the generic (i, j) element of the \mathbf{B} matrix and γ_i is the i th element of the vector Γ .

All procedures of signal generation were repeated under the following conditions:

- SNR factor levels = $[1, 3, 5, 10, 100]$;

- LENGTH factor levels = $[60, 190, 310, 610]$ s. This corresponds, for instance, to $[120, 380, 620, 1220]$ EEG epochs, each of which is 500 ms long.

It is worth noticing that the levels chosen for both SNR and LENGTH factors cover the typical range for the cortical activity estimated with high-resolution EEG techniques.

2) *Parameter Estimation:* The set of simulated signals generated as described above has been given as input to the program LISREL for the estimation of SEM parameters. As mentioned in the methods section, SEM needs a model, based on previous information on the anatomical connections, on which the estimate is successively performed. For this reason, its performance has been observed in different situations, when connections between the four cortical areas are not always correctly assumed. The situations analyzed are as follows:

- an identical connectivity graph between the generated and the estimated model;
- a different number of connectivity arcs between the generated and the estimated model; in particular, we analyzed the case of an arc in excess and of an arc missing in the estimated model with respect to the generated one;
- the same number of connectivity arcs between generated and estimated models, but with an ambiguousness on its orientation.

3) *Performance Evaluation:* In order to evaluate the quality of the performed estimation, the following indexes were computed.

- The Frobenius norm of the matrix reporting the differences between the values of the estimated (via SEM) and the imposed connections (*Relative Error*)

$$E_{\text{relative}} = \frac{\sqrt{\sum_{i=1}^m \sum_{j=1}^m (a_{ij} - \hat{a}_{ij})^2}}{\sqrt{\sum_{i=1}^m \sum_{j=1}^m (a_{ij})^2}} \quad (2.13)$$

- The absolute value of the difference between the estimated parameter and the imposed value on a single particular arc (*single arc error*)

$$E_{\text{single}} = |a_{ij} - \hat{a}_{ij}| \quad (2.14)$$

Simulations were performed by repeating for 50 runs for each connectivity estimation obtained by SEM, in order to increase the robustness of the successive statistical analysis.

4) *Statistical Analysis:* The results obtained were subjected to separate analysis of variance (ANOVA). The main factors of the ANOVA were the SNR (with five levels: 1, 3, 5, 10, 100) and the LENGTH (with four levels: 60, 190, 310, 610 s). Separate ANOVAs were performed on the error indexes adopted (Relative Error, Single Arc Error). In all the evaluated ANOVAs, the correction of Greenhouse-Gasser for the violation of the spherical hypothesis was used. The post-hoc analysis with the Duncan test at the $p = 0.05$ statistical significance level was then performed.

C. High-Resolution EEG Recordings

The estimation of connectivity patterns by using SEM on high-resolution EEG recordings has been applied to the analysis of a simple movement task. In particular, we considered the right

hand finger tapping movement, externally paced by a visual stimulus. This task was chosen for it has been very well studied in literature with different brain imaging techniques like EEG or functional Magnetic Resonance Imaging [4], [7]. The anatomical model employed is based on the principal cortical areas recognized as active during this simple task in these studies. Namely, cortical areas used in this human study included the prefrontal areas (PF), including at large the Brodmann areas 8, 9, and 46; the premotor areas (PM), including the Brodmann area 6, the sensorimotor areas (SM) including the Brodmann areas 4, 3, 2, and 1, and the parietal areas (P), generated by the union of the Brodmann areas 5 and 7. The model employed the *a priori* knowledge about the flow of connections between these macro-areas, as derived from neuroanatomy and fMRI studies. In particular, information flow were hypothesized to exist from the parietal (P) areas toward the sensorimotor (SM), the premotor (PM), and the prefrontal (PF) ones [4], [6], [7].

Event related potential (ERP) data were recorded with 96 electrodes on a group of three healthy subjects at the University of Illinois at Chicago. ERP data were recorded with a left ear reference and submitted to the artifact removal processing. Six hundred trials of 600 ms of duration were acquired. The Magnetic Resonance Images of each subject's head were also acquired at the University of Illinois at Chicago. Such images were used for the construction of the realistic head model for each analyzed subject. Such realistic models are necessary for the estimation of the cortical activity in the appropriate region of interest (ROI) by using the linear inverse procedure algorithms from the scalp recorded ERP data [18]–[20]. The time varying power spectral values of the estimated cortical activity in the theta (4–7 Hz), alpha (8–12 Hz), and beta (13–30 Hz) frequency bands were also computed in each ROI employed. The cortical waveforms were then used for the estimation of the connectivity pattern by using the SEM. We divided the analysis period of the analyzed ERP recordings into two phases. The first one, labeled as “PRE”, considers the 300 ms before the onset of the electromyographic (EMG) trigger of the finger extension before the tap, and it is intended as a generic preparation period. The second phase includes the 300 ms after the EMG trigger up to the end of ERP recording of a single trial and it is intended to give results about the arrival of the somatosensory feedback, and it will be labeled “POST” in the following.

D. Estimation of Cortical Source Current Density

The solution of the following linear system:

$$Lz = d + n \quad (2.15)$$

provides an estimate of the dipole source configuration z that generates the measured EEG potential distribution d . The system includes also the measurement noise n , supposed normally distributed.

In (2.15), L is the lead field or the forward transmission matrix, in which each j th column describes the potential distribution generated on the scalp electrodes by the j th unitary dipole. The current density solution vector ξ was obtained as follows [21]:

$$\xi = \arg \min_z (\|Lz - d\|_M^2 + \lambda^2 \|z\|_N^2) \quad (2.16)$$

where M, N are the matrices associated to the metrics of the data and of the source space, respectively, λ is the regularization parameter, and $\|z\|_M$ represents the M norm of the vector z . The solution of (2.16) is given by the inverse operator G as follows:

$$\xi = Gd, \quad G = N^{-1}L'(LN^{-1}L' + \lambda M^{-1})^{-1}. \quad (2.17)$$

An optimal regularization of this linear system was obtained by the L-curve approach [22], [23]. As a metric in the data space we used the identity matrix, while as a norm in the source space we use the following metric:

$$(N^{-1})_{ii} = \|L_{\cdot i}\|^{-2} \quad (2.18)$$

where $(N^{-1})_{ii}$ is the i th element of the inverse of the diagonal matrix N and all the other matrix elements N_{ij} , for each $i \neq j$, are set to 0. The L_2 norm of the i th column of the lead field matrix L is denoted by $\|L_{\cdot i}\|$.

By using the relations described above, at each time point of the gathered ERP data an estimate of the signed magnitude of the dipolar moment for each of the 5 000 cortical dipoles was obtained. In fact, since the orientation of the dipole was already defined to be perpendicular to the local cortical surface of the model, the estimation process returned a scalar rather than a vector field. In order to obtain the cortical current waveforms for all the time points of the recorded EEG time series, we used a unique “quasioptimal” regularization λ value for all the analyzed EEG potential distributions. Such quasi-optimal regularization value was computed as an average of the several λ values obtained by solving the linear inverse problem for a series of EEG potential distributions. These distributions are characterized by an average Global Field Power (GFP) with respect to the higher and lower GFP values obtained during all the recorded waveforms. The instantaneous average of the dipole's signed magnitude belonging to a particular ROI generates the representative time value of the cortical activity in that given ROI. By iterating this procedure on all the time instants of the gathered ERP, the cortical ROI current density waveforms were obtained and they could be taken as representative of the average activity of the ROI, during the task performed by the experimental subjects. These waveforms could then be subjected to the SEM processing in order to estimate the connectivity pattern between ROIs, by taking into account the time-varying increase or decrease of the power spectra in the frequency bands of interest. Here, we present the results obtained for the connectivity pattern in the alpha band (8–12 Hz), since the ERP data related to the movement preparation and execution are particularly responsive in such frequency interval (for review, see [24]).

III. RESULTS

A. Computer Simulation Results

1) *Correct Formulation of the Connectivity Model*: The first situation analyzed is shown in Fig. 1. A set of signals was generated as described in the previous section, in order to fit the connectivity pattern shown in Fig. 1(A). Parameters were estimated on the model shown in Fig. 1(B), which has exactly the same structure of Fig. 1(A). We are thus testing the goodness of the estimation of model parameters via SEM when no errors are made in the model assumption phase. The appropriate index for

this analysis is the Relative Error, as defined in Section II (2.13). It was computed for each of the 50 runs of the generation-estimation procedure performed for each level of factors SNR and signal LENGTH and then subjected to ANOVA. ANOVA has pointed out a rather strong statistical significance of both factors employed on the performance of SEM. In fact, the factors SNR and LENGTH were both highly significant ($p < 0.0001$). Fig. 1(C) shows the plot of means of the Relative Error with respect to the signal length levels, which reveals a decrease of the connectivity estimation error with the increase of the length of the available data. Fig. 1(D) shows the plot of means with respect to different SNR levels employed in the simulation. Since the main factors were found highly statistically significant, post-hoc tests (Duncan at 5%) were then applied. Such tests showed statistically significant differences between all levels of the factor LENGTH, while there is no statistically significant difference between levels 3, 5, and 10 of the factor SNR.

2) *Hypothesis of a Model With an Arc in Excess or a Missing Arc*: Since a perfect formulation of the connectivity model is not always a realistic option, we analyzed several situations in which the connections between the four cortical areas were not correctly assumed in the estimated model.

Arc in Excess: The first one is described in Fig. 2. The SEM parameter estimation was performed on the model shown in Fig. 2(B), containing an arc which is absent in the imposed pattern [Fig. 2(A)]. The aim was to test if the SEM procedure can reject the error made in the model assumption. The appropriate index for this analysis is the Single Arc Error (2.14) on arc a_{42} , i.e., the one which is not present in the correct model. The ANOVA performed on the simulation results showed that both the main factors signal LENGTH and SNR have a statistical influence on the ability of SEM to reveal the modeling error. Fig. 2(C) and (D) shows the plot of means with respect to the different levels of the main factors LENGTH and SNR. As before, they are both significant with $p < 0.001$ as well as their interaction (SNR \times LENGTH) with $p < 0.0001$. Post-hoc test (performed with the Duncan procedure at 5% level of significance) shows not statistically significant differences between the LENGTH levels of 190 s or 310 s as well as between levels 3, 5, 10, and 100 of the main factor SNR. In order to evaluate the influence of the exceeding arc in the model on the global parameter estimation, the Relative Error (2.6) was also computed. Fig. 3(A) and (B) shows the plot of mean of this index with respect to the two main factors, with a level of statistical significance lower than 0.001.

Missing Arc: In this case the χ^2 statistic test returns no statistical significance of the estimated model. Hence, the corresponding error values were not computed and no statistical analysis was performed.

3) *Ambiguity on an Arc Direction*: A situation that can occur is when the existence of a connection between two structures is well known, and there is the need to investigate its direction. Parameters were estimated on a model representing this situation [Fig. 4(B)]. The signals had been generated according to the pattern of Fig. 4(A) and the Single Arc Error made on the arc representing the wrong direction (a_{24} in this example) was considered. The statistical analysis performed on the simulation results with the ANOVA reported no statistical significance of the main factor SNR, while the factor LENGTH (EEG-

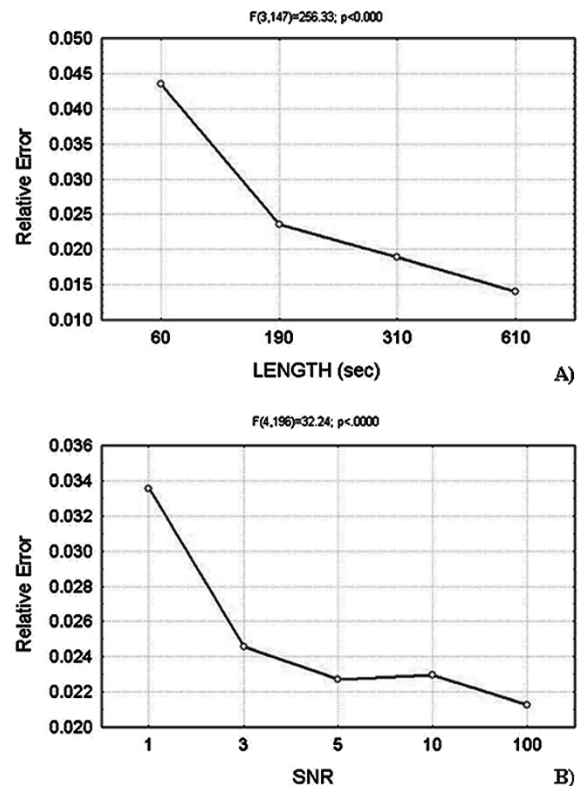


Fig. 3. Results of ANOVA performed on the Relative Error for the same situation of Fig. 2: (A) plot of means with respect to signal LENGTH as a function of time (seconds). ANOVA shows a high statistical significance for factor LENGTH ($F = 256.33$, $p < 0.0001$). Post-hoc test (Duncan performed at 5% level of significance) shows statistically significant differences between all levels. (B) Results of ANOVA performed on the Relative Error: plot of means with respect to SNR. Here, too, a high statistical influence of factor SNR on the error in the estimation is shown ($F = 32.24$, $p < 0.001$). Duncan post-hoc test (performed at 5%) points out that there is no statistically significant difference between levels 5 and 10 of factor SNR.

TRIAL) is still statistically significant (with $p < 0.0001$). The plot of means in function of the levels of LENGTH is reported in Fig. 4(C). Fig. 5(A) and (B) shows the plot of means of the Relative Error with respect to the signal LENGTH levels and to different SNR levels employed in the simulation.

B. Human Study

Fig. 6 shows the cortical connectivity patterns obtained for the period preceding the movement onset in the subject #1, in the alpha frequency band. Each pattern is represented with arrows, that connect one cortical area to another one. The colors and sizes of arrows code the level of strength of the functional connectivity observed between ROIs. The labels indicate the names of the ROIs employed. Note that the connectivity pattern during the period preceding the movement in the alpha band involves mainly the parietal left ROI (PI) coincident with the Brodmann areas 5 and 7, functionally connected with the left and right premotor cortical ROIs (PMI and PMr), the left sensorimotor area (SMI), and both the prefrontal ROIs (PFI and PFr). The stronger functional connections are relative to the link between the left parietal and the premotor areas of both cerebral hemispheres. After the preparation and the beginning of the finger movement, in the POST period changes in the connectivity pattern can be noted. In particular, the origin of the functional connectivity links is posi-

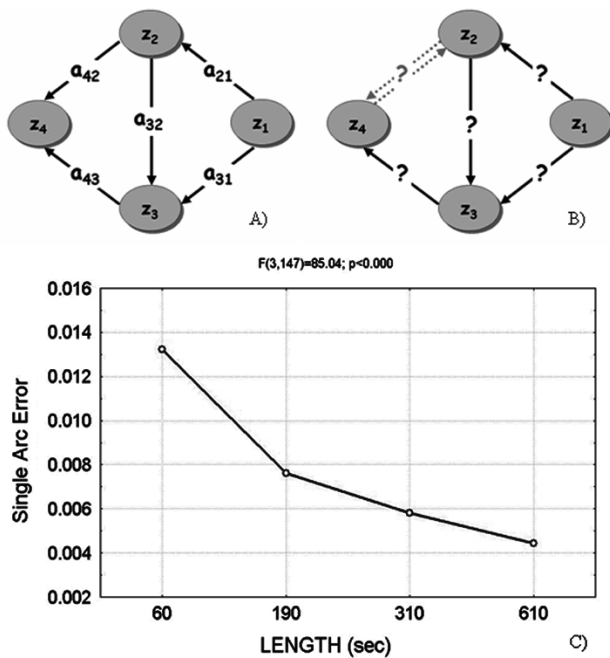


Fig. 4. (A) Connectivity pattern imposed in the generation of simulated signals. Values on the arcs represent the connections strength ($a_{21} = 1.4$; $a_{31} = 1.1$; $a_{32} = 0.5$; $a_{42} = 0.7$; $a_{43} = 1.2$). (B) Connectivity model used for the parameter estimation. No assumption has been made on the direction of arc a_{42} (both directions are present in the model). (C) Results of ANOVA performed on the error committed on the wrong direction arc a_{24} , not present in the imposed model (Single Arc Error): plot of means with respect to signal LENGTH as a function of time (seconds). ANOVA shows a high statistical significance of factor LENGTH ($F = 85.04, p < 0.0001$). Post-hoc test (Duncan at 5%) shows statistically significant differences between all levels of length.

tioned in the sensorimotor left cortical areas (SMI). From there, functional links are established with prefrontal left (PFI), both the premotor areas (PMI, PMr). A functional link emerged in this condition connecting the right parietal area (Pr) with the right sensorimotor area (SMr). The left parietal area (PI) so active in the previous condition was instead linked with the left sensorimotor (SMI) and right premotor (PMr) cortical areas.

IV. DISCUSSION

A. Methodological Considerations

The application of the SEM to the cortical estimated waveforms from high-resolution EEG recordings poses several methodological questions.

The first question is how the SEM estimates of the cortical connectivity could be affected by errors in the amplitude estimates of the cortical waveforms, generated by the application of the linear inverse operator \mathbf{G} to the gathered high-resolution EEG data. From the definition of the resolution matrix [21], [25] derives that current density estimates depend upon the linear inverse \mathbf{G} (time invariant) but also upon the actual current distribution (time varying). This implies that amplitudes estimated at a given cortical site will depend upon the actual sources activated everywhere else and which change indeed over time. Consequently errors in the amplitude estimation are not necessarily systematic along time. There are however some simulation results and experimental data analysis using linear inverse solutions that suggest that is the analysis procedure is independent of

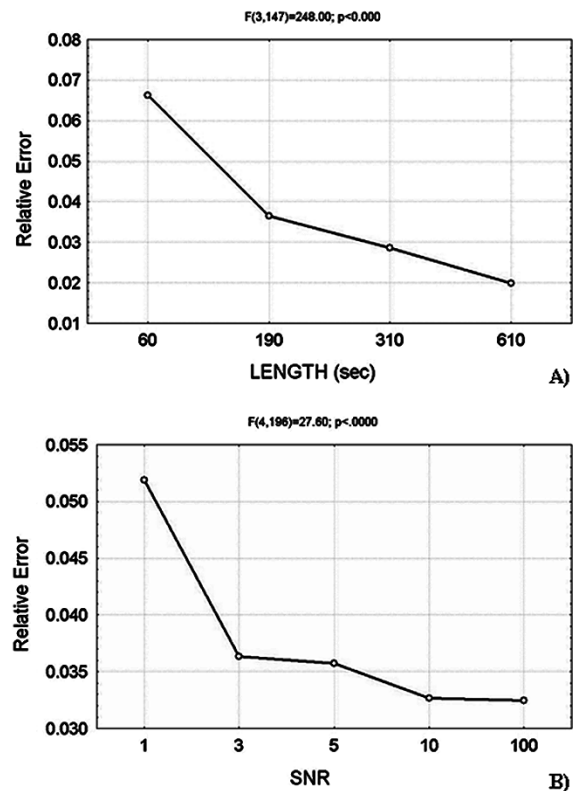


Fig. 5. Results of ANOVA performed on the Relative Error for the same situation of Fig. 4: (A) plot of means with respect to signal LENGTH as a function of time (seconds). ANOVA shows a high statistical significance for factor LENGTH ($F = 248.00, p < 0.0001$). Post-hoc test (Duncan performed at 5% level of significance) shows statistically significant differences between all levels. (B) Results of ANOVA performed on the Relative Error: plot of means with respect to SNR. Here, too, a high statistical influence of factor SNR on the error in the estimation is shown ($F = 27.60, p < 0.001$). Duncan post-hoc test (performed at 5%) points out that there is no statistically significant difference between levels 3, 5, and 10 of factor SNR.

a global effect factor (temporal variance), then results are rather stable and reasonable [25]. Connectivity estimates are generally independent of amplitude factors and might produce reasonable results for this particular reason.

A second question is how reliable are the spectral features of the time series estimated by the inverse solution. In this respect, we note that the several studies in literature reported that the cortical activity in ROIs from EEG or MEG measurements could be estimated with moderate errors by using accurate realistic head models [15], [16], [26]–[28]. In particular, computer simulations demonstrated that cortical modeling of the source space performed with at least 3000 equivalent current dipoles allowed the estimation of the cortical waveforms with few percent errors with respect to the reference waveforms [15], [16]. From the correct estimation of the cortical waveforms the computation of their spectral properties are straightforward by using standard analysis tools.

A third question is related to the possible use of different objective function for the minimization process. In fact, it might be argued that with SEM and some searching techniques, it is also possible to generate a complete network reconstruction (including both network structure and connectivity strengths) by the so-called overall model fit (e.g., using Akaike information criterion as the minimized object function). However, in the case

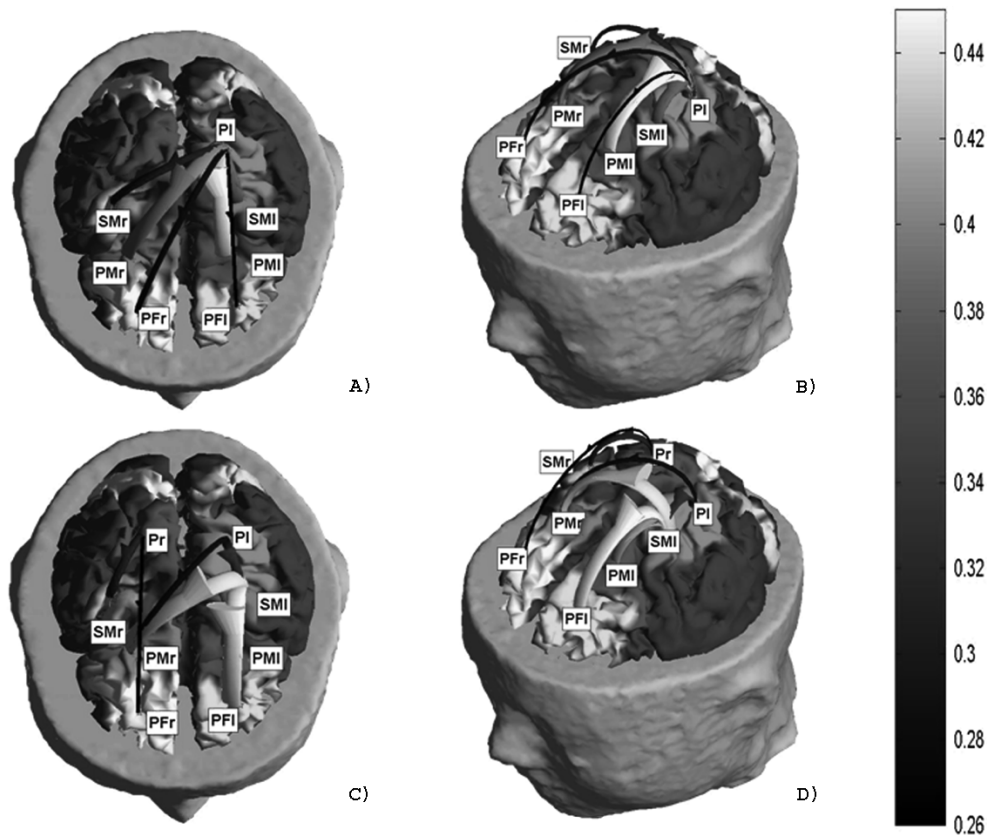


Fig. 6. (A)–(D). Figure shows the cortical connectivity pattern obtained for the period preceding and following the movement onset in the subject, in the alpha (8–12 Hz) frequency band. The realistic head model and cortical envelope of the subject analyzed obtained from sequential MRIs is used to display the connectivity pattern. Such pattern is represented with arrows, that move from one cortical area toward another one. The colors and sizes of arrows code the level of strengths of the functional connectivity observed between ROIs. The labels are relative to the name of the ROIs employed. (A)–(B). Connectivity patterns obtained from ERP data before the onset of the right finger movement (electromyographic onset; EMG), from above (left) and from the left of the head (right). (C)–(D). Connectivity patterns obtained after the EMG onset. Same conventions as above.

of application of that particular overall model fit technique to the EEG or cortical data related to more complex experimental paradigm, like for instance those related to the working memory or attentive process, a larger number of ROIs is required. In this case, the application of such modified procedure could be difficult due to the high number of ROIs, or node, in the model.

A fourth question is related to the possible benefit of the SEM technique to assess cortical connectivity from EEG measurements with respect to the other methodologies often employed to analyzed scalp recorded data. In fact, many approaches to analysis of scalp connectivity have been implemented during the past years, involving the use of different methodologies such as the linear techniques including the cross-correlation or coherence [5], [6], [14] or the non linear ones, like mutual information, mutual dimension, generalized synchronization, and neural complexity [29]–[31]. All these techniques are able to reveal direct flow of information between scalp electrodes in the time domain, although non linear techniques were reported to be more sensitive with respect to the others, and more computationally demanding [32]. However, all these procedures relying on the concept of functional connectivity estimates, that is based on the computation of the correlation structure among the data. In fact, the functional connectivity is defined as the temporal coherence among the activity of different neurons, and measured by cross-correlating the EEG or the recorded spike trains. Functional connectivity is usually inferred by statistical dependen-

cies among signals in coupled neuronal systems. Effective connectivity, a more abstract notion, could be defined as the simplest neuronal-like circuit that would produce the same temporal relationship as observed experimentally between two neurons in a cell assembly. This definition, generated from the spike recordings in primates, can be generalized to the activity of larger patches of the cortical tissue, as obtained from hemodynamic or cortical current density estimates. SEM is a technique that relying on the concept of effective connectivity with respect to the concept of functional one. In this context, effective connectivity is defined as “the influence that one neural system exerts over another either directly or indirectly” [33]. Functional connectivity reduces to testing the null hypothesis that activity in two regions shares no mutual information. Mutual information is a statistical description of the degree to which two regions demonstrate similar behavior or statistical interdependence [34]. In other words, the characterization of brain activity in terms of functional connectivity is “model free.” In contrast, characterizing brain activity in terms of effective connectivity requires a causal model, in which regions and connections of interest are specified by the researcher, often constrained by a combination of neuroanatomical, neuropsychological, and functional neuroimaging data. This is a crucial point when considering the distinction between functional and effective connectivity because it emphasizes the shift between a description of what the brain does to a theory of how it does it.

B. Experimental Results

The experimental design adopted for the simulation study aimed to analyze the most common situations in which the proposed application of SEM technique to high-resolution EEG data may take place. The levels chosen for main factor levels SNR and LENGTH, as well as the simple errors in the model formulation that have been examined, cover the most typical situations that can occur in such analysis. The results obtained has shown a significant statistical influence of the factors considered on SEM performances.

On the basis of the simulations performed, we are now able to answer the questions raised in Section I.

- 1) There is statistical influence of a variable SNR level imposed on the high-resolution EEG data on the accuracy of the connectivity pattern estimation. In particular, an $\text{SNR} = 3$ seems to be satisfactory in order to obtain a good accuracy, since there are not significant differences in the performance for higher values.
- 2) The minimum amount of EEG data necessary to get a usable accuracy of the estimation of connectivity between cortical areas is 190 s of registration (equivalent, for instance, to 380 trials of 500 ms each). However, in this case, an increase of the length of the available EEG data is always related to a decrease of the connectivity estimation error.
- 3) Different situations, in which the connections between the four cortical areas were not correctly assumed in the estimated model, were evaluated in order to analyze their influence on SEM performances. In the first situation, there was a deliberate error in the hypothesized model, consisting of the presence of an arc not corresponding to an actual influence between areas. The aim was to test if the SEM procedure can reject the error made in the model assumption and to evaluate the influence of the introduction of such modeling error on the goodness of parameter estimation. The analysis of the Single Arc Error on the arc in excess, revealed that a $\text{SNR} = 3$ and an amount of EEG data of 190 s of registration seems to be satisfactory in order to obtain good accuracy. The effect on the global performance of parameter estimation can be inferred by comparing the Relative Error obtained in this situation to the correct one. From Fig. 1(C) and (D), compared to Fig. 3(A) and (B), it can be seen that the error values remain on the same level in both cases, and the general performance is not decreased by this kind of error. In the second situation analyzed, the voluntary error in the hypothesized model consists in the lack of an arc corresponding to an influence between areas. The performed analysis has not reported statistical significance, as indicated by the χ^2 to degrees of freedom ratio: $\chi^2/\text{df} > 1$. This suggests that, in case of results of this kind, an arc can be added to the putative model in order to decrease the χ^2 to degrees of freedom ratio. In the third situation analyzed, the estimated model contained arcs in both directions between two areas, corresponding to a single arc in the model imposed in the signal generation. The Single Arc Error computed on the “wrong direction” arc

shows that the error is rather smaller (less than 1.5% for all factors and levels considered) than in the case of an arc in excess in a single direction in the first situation analyzed. On the other hand, it is worth of notice that the general performance, as indicated by the Relative Error [Fig. 5(A) and (B)], is significantly worse in this case than in the case of correct modeling, especially for low values of factor LENGTH [cf. Fig. 1(C) and (D)]. This means that a simple error like the attribution of both directions to a couple of channels causes a significant increase of the error made in the parameter estimation.

In conclusion, the ANOVA results (integrated with the Duncan post-hoc tests performed at $p < 0.05$) indicated a clear influence of different levels of the main factors SNR and LENGTH on the efficacy of the estimation of cortical connectivity via SEM. In particular, it has been noted that at least a SNR equals to 3 and a LENGTH of the measured cortical data of 190 s are necessary to decrease significantly the errors related to the indexes of quality adopted.

It might be argued how these results, obtained by using several levels of cortical SNR, could be directly extended to the SNR related to the scalp recorded EEG data. In general, a difference exists between the imposed SNR at the cortical level and those observed at the scalp level. This difference is due to the errors in the estimation procedure of the cortical activity. Such errors, already described in simulation studies in literature [26]–[28], could be treated as additional source of noise in the propagation from the cortex to the scalp. Such simulations indicated that for high-resolution EEG studies with a realistic head modeling tessellation ranging from 3000 to 5000 dipoles, the Relative Errors in the cortical estimation are less than 10%. Hence, we could insert this 10% error in the cortical estimate due to the inversion process as an additional noise source error. In this hypothesis, the cortical SNR can hardly be higher than 10, even if the scalp SNR is very high, due to the inversion error introduced by the use of the (2.17). On the other hand, when the scalp SNR is much lower than 10, the contribution of the inversion error vanishes. In the intermediate cases, the cortical SNR is only slightly lower than scalp SNR; a scalp SNR equal to 3, for instance, would yield a cortical SNR equal to 2.3. It is worth noticing that these SNR conditions are generally obtained in many standard EEG recordings of event-related activity in humans, usually characterized by values of SNR ranging from 3 (movement related potentials) to 10 (sensory evoked potentials) and a total length of the recordings starting from 50 s [35].

The simulation study has shown that the ability of SEM to perform a good estimate of connectivity pattern, when connections between the four cortical areas are not correctly assumed, depends on the kind of error made in the model formulation. It seems that the error consisting in the lack of a connection arc is the worst, with respect to the parameter estimate, though it can be easily detected by a χ^2 statistical test. Putting in the model an arc not corresponding to an actual influence between areas, on the contrary, does not particularly influence the goodness of general parameter estimate and the exceeding arc is attributed a value near to zero. Putting arcs in both directions between two areas, while the influence is directed only from one to the other, causes larger errors in the parameter estimation, though it allows

to discriminate the right direction with a precision which does not depend on the signal SNR and which is very high for most levels of signal LENGTH.

Although the performance seems to be rather good for a correct assumption of the hypothesized model, it decreases when even a simple error is made, depending on the error type. This degradation of the performance seems to indicate the opportunity to use connectivity models not too detailed, in terms of cortical areas involved, as a first step of the network modeling. By using a coarse model of the cortical network to be fitted on the EEG data, there is an increase of the statistical power and a decrease of the possibility to generate an error in a single arc link [1]. In the present human study, such observation was taken into account by selecting a coarse model for the brain areas subserving the task being analyzed. This simplified model does not take complete account all the possible regions engaged in the task, and all the possible connections between them. Elaborate models, permitting also cyclical connections between regions can become computationally unstable [13].

Our model of interactions between cortical areas is based on previous results on similar tasks obtained with different brain imaging methods. It is sufficient to address some key questions regarding the influence of the premotor and motor areas toward the prefrontal cortical areas during the task analyzed. The finger tapping data analyzed here present a high SNR and a large number of trials, resulting in an extended record of ERP data. Hence, the present simulation results suggest the optimal performance of the SEM method as applied to the human ERP potentials. The connectivity pattern estimated via SEM (Fig. 6) illustrates the potentiality of the methodology employed, that includes the use of high-resolution EEG recordings, the generation of a realistic head model by using sequential MRIs, and the estimation of the cortical activity with the solution of linear inverse problem. With this methodology, it will be possible not only to detect where the cortical areas are activated by a particular task in the brain but also how such areas are effectively connected together subserving the analyzed task. In particular, influence of the parietal area has been observed toward the premotor cortical areas during the task preparation, consistent with the role that the parietal areas have in the engage of attentive resources as well as temporization, as assigned by several electrophysiological studies on primate or hemodynamical studies on humans [36]. It is of interest noticing the shift of the cortical areas behaving as the most relevant origin of functional links, occurring when the somatosensory reafferences arrive from the periphery to the cortex. In fact, the left sensorimotor area becomes very active with respect to the left parietal one, which, in turn, used to be mainly engaged in the time period preceding the finger movement. Connections between the sensorimotor area and the premotor and left prefrontal areas are appropriate to distribute the information related to the movement of the finger to the higher functional regions (prefrontal and premotor).

Taken together, our results return the information that quite accurate estimation of the cortical connectivity patterns can be achieved by using realistic models for the head and cortical surfaces, high-resolution EEG recordings, and the SEM technique.

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Laura Astolfi received the degree in electronic engineering *magna cum laude* from the University of Rome "La Sapienza" in 2003. She is currently enrolled in the Ph.D. degree course in bioengineering at the University of Bologna, Bologna, Italy.

She is with the Department of Human Physiology and Pharmacology of the University of Rome "La Sapienza" and the Neurophysiopathology Unit of the Fondazione Santa Lucia, Rome. Her research interests involve the study of the cortical connectivity, the neuroelectrical inverse problem and the multimodal

integration of fMRI and HR EEG data.

Dr. Astolfi is a member of the International Society for the Bioelectromagnetism (ISBEM).



Febo Cincotti received the Laurea degree *cum laude* in electronic engineering in 1998, and the Ph.D. degree in biophysics in 2003, from the University of Rome "La Sapienza," Rome, Italy.

He is a Research Scientist at the Neurophysiopathology Unit of the Fondazione Santa Lucia—IRCCS, Rome. His research interests include neuroelectrical inverse problem, brain-computer interfaces, and development of algorithms for high-resolution EEG processing.



Claudio Babiloni received Laurea degree *cum laude* in psychology at University of Rome "La Sapienza," Rome, Italy, in 1987 and the Ph.D. degree in medical sciences and engineering at International Doctoral School of Aalborg, Aalborg, Denmark, in 2001.

He is a Senior Research Scientist of Division of High Resolution EEG at the Department of Human Physiology, University of Rome "La Sapienza." His research interests include the role of brain rhythms in human cognition.



Filippo Carducci received the Degree in electronic engineering from the University of Rome "La Sapienza," Rome, Italy, in 1992, and the Ph.D. degree from the University "G. D'Annunzio" of Chieti, Chieti, Italy, in 2002.

He is with the Human Physiology and Pharmacology Department, University "La Sapienza," where he is a Lecturer of Human Physiology with the II Faculty of Medicine. His research interests include realistic and standardized modeling of the human head applied to high-resolution EEG, multimodal

brain data integration, and neuronavigation techniques.



Alessandra Basilisco received the Laurea degree in electronic engineering from University of Rome "La Sapienza," in 2002. She is a Ph.D. degree student in biophysics at the Dipartimento di Fisiologia Umana e Farmacologia—HR-EEG Division, University of Rome "La Sapienza," Rome, Italy, and a Technical Consultant with the Istituto Superiore di Sanità, Rome. Her research interests include neuroelectrical inverse problem, multimodal integration of high-resolution EEG and fMRI, and cortical functional connectivity.



Paolo M. Rossini received the M.D. degree from the Università Cattolica of Rome, Rome, Italy, in 1974.

He is Chair of Neurology University CBM-Rome, Chair Department of Neuroscience, Hospital Fatebenefratelli, Rome, Scientific Director Scientific Institute on Psychiatry and Dementias in Brescia.

Dr. Rossini was Editor-in-Chief of *EEG Journal* and *Clinical Neurophysiology* from 1995–2003. He has authored more than 300 scientific papers on clinical neurophysiology, neurology, and functional brain imaging for peer-reviewed international journals. He has been an ad hoc reviewer for *Brain*, *Stroke*, *Neurology*, *Annals of Neurology*, *Brain Research*, *Journal of Neuroscience*, *European Journal of Neuroscience*, *Neuroscience Letters*, *Experimental Brain Research*.

He has been an ad hoc reviewer for *Brain*, *Stroke*, *Neurology*, *Annals of Neurology*, *Brain Research*, *Journal of Neuroscience*, *European Journal of Neuroscience*, *Neuroscience Letters*, *Experimental Brain Research*.



Serenella Salinari received the doctoral degree in engineering in 1970 from the University of Rome "La Sapienza," Rome, Italy.

Since 1970, she has been with the Department of Systems and Informatics of the University of Rome "La Sapienza," Faculty of Engineering, where she is a Professor of Modeling of Biomedical Systems. Her scientific activity, has been in the field of the mathematical modeling and analysis of biological data. In particular, in the past, this activity was concerned with the analysis of the movements of internal organs

such as the study of the biomechanics and control of the intestinal peristalsis, of the uterine contractility and of the motility of the gallbladder. More recently, her main research interests were focused on mathematical models applied to metabolic systems and on the modeling and signal analysis of scalp recorded potentials.



Donatella Mattia received the M.D. degree from the University of Rome "La Sapienza," Rome, Italy in 1987. In 1991, she completed her training as resident in Neurology and became neurologist at the same University. She also received the Ph.D. degree in "physiopathology of movement disorders" in 1996, from the Department of Neuroscience, "La Sapienza" University of Rome.

From 1992–1995, she was a Research Fellow at the Montreal Neurological Institute and Department of Neurology and Neurosurgery, McGill University, Montréal QC, Canada. Currently, she is an Assistant Researcher in the Department of Clinical Neurophysiology, high-resolution EEG Laboratory, Fondazione Santa Lucia, IRCCS, Rome, Italy. Her research interests include cortical excitability and plasticity processes in different neurological disorders as evaluated by neuroelectric imaging techniques.



Sergio Cerutti is Professor of Biomedical Signal and Data Processing at the Department of Biomedical Engineering of the Polytechnic University, Milan, Italy. Since November 2000, he is the Chairman of the department.

His research interests are mainly in the following topics: biomedical signal processing (ECG, blood pressure signal and respiration, cardiovascular variability signals, EEG, and evoked potentials), cardiovascular modeling, neurosciences, medical informatics, and regulation and standards in medical

equipments and devices. Since March 1983 he has also taught a course at a graduate level on Biomedical Signal Processing at Engineering Faculties (Milan and Roma) and at Specialization Schools of Medical Faculties (Milan and Roma).

Prof. Cerutti was an elected member of IEEE-EMBS AdCom (Region 8) in the period 1993–1996. He is actually Fellow Member of IEEE and Associate Editor of IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING. He is a member of the Steering Committee of the IEEE-EMBS Summer School on Biomedical Signal Processing; he was the local organizer of three IEEE-EMBS Summer Schools held in Siena on 1995/1999/2003.



D. Ben Dayan received the Laurea Degree in electronics engineering from Politecnico di Milano, Milano, Italy, in 2000.

Since 2000 to 2002 he was a researcher in theoretical Physics in the field of neuroscience at the Hebrew University of Jerusalem, Jerusalem, Israel. Currently, he is studying toward the Ph.D. degree at the Politecnico di Milano and at the Institute for Neuroinformatics UNI|ETH Zurich, Switzerland on the effects of noise in neural networks.



Lei Ding (S'01) was born in China in 1976. From 1995 to 2001, he was a student in biomedical engineering at Zhejiang University, Hangzhou, China. He received the Bachelor degree in engineering in 2000 and majored in biomedical signal and image processing as a graduate student from 2001. He began studying toward the Ph.D. degree at the University of Illinois at Chicago in August 2002, and he is presently in the Biomedical Engineering Program at the University of Minnesota, Minneapolis. His thesis concerns three-dimensional source localization and

estimation in electrical functional imaging of the brain.



Ying Ni (S'01) received the B.S. degree in electrical engineering from Communication University of China, Beijing, P.R. China, in 2000, and M.S. degree in electrical engineering from the University of Illinois at Chicago, Chicago, IL, in 2003.

After graduation, she was a Visiting Research Specialist in Bioengineering Department, University of Illinois at Chicago. Since 2003, she is a Research Specialist with the University of Illinois at Urbana-Champaign, IL.



Bin He (S'87–M'88–SM'97–F'04) received the Ph.D. degree in biomedical engineering with the highest honors from the Tokyo Institute of Technology, Tokyo, Japan, and completed his postdoctoral fellowship in biomedical engineering at Harvard University—Massachusetts Institute of Technology (M.I.T.), Cambridge.

After working as a Research Scientist at M.I.T., he joined the faculty of the University of Illinois at Chicago (UIC) and became a Professor of bioengineering, electrical and computer engineering, and computer science at in 2003. Since 2004, he has been a Professor of biomedical engineering, electrical engineering, and neuroscience at the University of Minnesota at Twin Cities. His major research interests include biomedical functional imaging and source imaging, neural engineering, cardiovascular engineering, and bioelectromagnetism.

Dr. He is the recipient of NSF CAREER Award, American Heart Association Established Investigator Award, the University of Illinois University Scholar Award, and the University of Illinois at Chicago College of Engineering Faculty Research Award, and is listed in *Who's Who in Science and Engineering*, *Who's Who in America*, and *Who's Who in the World*. He has been active in professional activities in the field of biomedical engineering and bioelectromagnetism. He currently serves as the President of International Society of Bioelectromagnetism, and VP for Publications and Technical Activities (2005–2006) of the IEEE Engineering in Medicine and Biology Society. He serves as the General Chair of the 5th International Conference on Bioelectromagnetism and the 5th International Symposium on Noninvasive Functional Source Imaging within the Human Brain and Heart. He serves as Associate Editor for IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, IEEE TRANSACTIONS ON INFORMATION TECHNOLOGY IN BIOMEDICINE, and the *International Journal of Bioelectromagnetism*. Dr. He also serves as the Editor of the Book Series on Bioelectric Engineering, being published by Kluwer Academic (Norwell MA), and is on the editorial board of *Clinical Neurophysiology* and the *Journal of Neural Engineering*. He served as the sole Guest Editor for special issues at *IEEE Engineering in Medicine and Biology Magazine*, IEEE TRANSACTIONS ON INFORMATION TECHNOLOGY IN BIOMEDICINE, *Electromagnetics*, *Critical Reviews in Biomedical Engineering*, and *Methods of Information in Medicine*.



Fabio Babiloni was born in Rome, Italy in 1961. He got the master degree in electronic engineering at the University of Rome "La Sapienza" *summa cum laude* in 1986, and the Ph.D. in computational engineering at the Helsinki University of Technology, Helsinki, Finland, in 2000 with a dissertation on the multimodal integration of EEG and fMRI.

He is currently Associate Professor of Human Physiology with the Faculty of Medicine at the University of Rome "La Sapienza." He is author of more than 65 papers on bioengineering and neurophysiological topics on international peer-reviewed scientific journals. His current interests are in the field of multimodal integration of EEG, MEG, and fMRI data, cortical connectivity estimation, and brain computer interface.

Prof. Babiloni is member of the International Society of Bioelectromagnetism, the Italian Society of Physiology and the Italian Society of Clinical Neurophysiology. He is an Associate Editor of the scientific Journals *Clinical Neurophysiology* and the *International Journal of Bioelectromagnetism*.