FRONTOPARIETAL CORTICAL NETWORKS REVEALED BY STRUCTURAL EQUATION MODELING AND HIGH RESOLUTION EEG DURING A SHORT TERM MEMORY TASK

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Abstract: **In this study we addressed questions related to the cortical sources involved in the spatial short term memory in humans. Such sources were estimated from non-invasive EEG recordings by using linear inverse procedure in a group of 9 normal healthy subjects. Analyzed neural activations from EEG recordings were obtained in regions of interest (ROIs) of few squared cm at the cortical level. Structural Equation Modeling (SEM) technique was then used to assess effective connectivity between cortical ROIs. Results showed an increase of connectivity of cortical prefrontal and premotor areas during the task phase in which an image have to be hold in the memory before an appropriate decision has to be made by the subjects.**

Keywords : **Spatial short term memory, Linear inverse problem, EEG, quasi/realistic head model, Structural Equation Modeling**

I. INTRODUCTION

Short time memory (STM) maintains information for use in on-line cognition. It combines a mental workspace with short-term buffers and executive processes for interpreting incoming stimuli, updating actively stored items accordingly, and maintaining the intermediate results of processing for further calculations. Animal studies and human neuroimaging studies indicate that tasks requiring STM activate a functional network linking regions of prefrontal cortex with posterior association cortices [1-3]. Haemodinamic and neurophysiological studies suggest that it may be possible to distinguish the contributions that these different areas make to STM. In some haemodynamic studies, the more ventral prefrontal areas have been engaged when the task required a higher level of executive control [4]. Other studies have found the location of prefrontal activation to depend upon the nature of the material to be retained, with the verbal material mapped to the dominant hemisphere, and the non verbal material mapped to the non dominant hemisphere[4]. Furthermore, it was suggested as spatial material in STM tasks was processed by dorsal cortical areas whereas non spatial material was processed by more ventral areas. Similarly, lesion studies suggested that the parietal cortex is specialized in spatial analysis in the areas near to the intraparietal sulcus. Hemodynamic evidences suggested also that the left perisylvian activation is associated with the maintenance of information in the articulatory loop [5]. All these studies support the hypothesis that although the parietal and prefrontal cortices make distinct contributions to complex processing of working memory, they are so interconnected that their activation patterns are nearly indistinguishable. Furthermore, the poor temporal resolution of the hemodynamic measurements (greater than 1 s) cannot return us information about the temporal structure of the sequential or parallel involvement of cortical frontoparietal network during the STM task. Instead, an adequate neural model of STM should specify not only which structures are involved but also the dynamics of their interactions. EEG recordings in humans during memory tasks could be useful in understanding the temporal dynamics of engagement of different cortical areas. Previous attempt to characterize STM activity with EEG recordings indicated a continuing interaction between the anterior and posterior cortex [6]. One drawback of the EEG analysis of STM tasks is the difficulty to related scalp recorded data with the activity of the underlying cortical areas. Recently, the use of realistic models of the head as volume conductor and hundreds of electrodes allows to reliably estimate the cortical current density from non invasive EEG measures (High Resolution EEG - HREEG;[7]). This is interesting since the remarkable time resolution that HREEG data and their relative cortical estimation can provide. Furthermore, the interactions between frontal and parietal brain regions of the cortical model adopted were analyzed with the use of the Structural Equation Modelling (SEM), a technique that was largely used in functional Magnetic Resonance Imaging (fMRI; [8-9]). With such technique, for the first time applied to the High Resolution EEG data of STM, we inferred effective cooperation between cortical areas by using specific anatomical constraints.

The cortical sources of spatial STM tasks were estimated from non-invasive EEG recordings by using linear inverse estimation in a group of normal healthy subjects. A quasi-realistic head model, obtained as an average of

152 head models built with the use of magnetic resonance images (MRIs) was used for the source estimation. With this model a easy identification of the principal Broadmann cortical areas was obtained. By using linear inverse estimation with quasi-realistic head model we were able to analyzed cortical activation at the level of region of interest (ROIs) of few squared centimeters.

In this study with the body of techniques roughly described above we address questions related to the cortical sources involved in the spatial STM in humans. In particular, we were interested in which cortical sources are activated during a spatial STM tasks. Furthermore, the sequences of activation of such cortical sources were also of interest for us. Results showed an active partecipation of cortical prefrontal and parietal areas during the task phase in which an image have to be hold in the memory before an appropriate decision has to be made by the subjects.

II. METHODOLOGY

A. Head model, subjects, task and EEG recordings

Head model : The quasi realistic head model used in this study was obtained by using the average head model available from the Montreal Neurological Institute. Such model was based on the MRIs head images of 152 normal subjects. The scalp, skull, dura mater and the cortical surfaces were then obtained with a countouring algorithm. Such surfaces were then used to build the Boundary Element Model of the head as volume conductor employed in the present study. It is worth of note that the quasi-realistic cortical reconstruction can be used to precisely determine the region of interest (ROI) belonging to each Broadmann areas. In total, we were able to reconstruct cortical activity in each one of the 44 ROIs corresponding to the known Broadmann areas of the cortex.

Tasks: After a warning stimulus, subjects were exposed to the vision of a cue on the computer screen. Cue visual stimulus consist of a couple of vertical bar that were first presented (trigger time) and then hidden for few seconds (delay time). During this time subjects were asked to hold the images in memory and after a go stimulus appear on the computer screen produce a motor performance in accordance to the image. The motor performance was represented by the clicking of mouse buttons after a go signal. In particular, the subjects have to push left bottom of mouse if higher left than right vertical bar, or viceversa. A brief on-line feed-back on the performance was automatically provided. Time course of the task was as follows: *STM condition* (STM) : Pre-trigger time: duration 1 sec; warning visual stimulus (trigger time): duration 1 sec; cue stimulus: duration 5.5-7.5 sec; visual go stimulus: duration 1 sec; inter-trial interval: duration 5 sec. The control condition in which the spatial bar remains on the screen for all the task duration will be also developed and this was called in the following no STM condition (NSTM).

Subjects and EEG recordings: Nine healthy subjects were considered in this study. Each EEG recording was made by using forty scalp electrodes, that were positioned according to an extension of the international 10-20 system. EEG data were recorded with 0.3-70 Hz bandpass and linked-earlobes reference. Electrooculogram (0.3-70 Hz bandpass) and surface rectified electromyographic activity of bilateral extensor digitorum muscles (1-70 Hz bandpass) were also collected. For each subject, recorded EEG data were related to about 100 trials. The EEG band of interest analyzed in this study was the alpha (9-11 Hz).

Deblurring analysis: Artifact-free EEG activity from 4 s before to 4 s after the onset of electromyographic response (zerotime) was then considered for the EEG linear inverse procedures. EEG segments contaminated by blinking, eye movements, mirror movements, and/or other artifacts were rejected off-line. Amplitude gray scale maps of the alpha and beta ERD/ERS peaks were calculated on a 3-D "quasi-realistic" head model by a spline interpolating function.

B. Estimation of cortical source current density.

Cortical current density were estimated by using depth weighted minimum norm solution of the linear inverse problem formulated as follows:

$$\mathbf{Ax} + \mathbf{n} = \mathbf{b} \qquad (1)$$

where **A** is the lead field matrix, in which each j-th column describes the potential distribution generated on the scalp electrodes by the j-th unitary dipole, **b** is the vector of the recorded potential values, and **n** is the measurement noise, supposed to be normally distributed. The electrical lead field matrix **A** and the data vector **b** must be referenced consistently. The solution of the linear system with L2-norm was generally obtained by solving the following equation:

$$x = \mathrm{argmin}\,\mathbf{(\|\, D(Ax\text{-}b)\|^2 + 1^2 \,\|\, Cx\|^2\,)} \qquad (2)$$

where the matrices **D** and **C** are associated with the matrices representing the metrics of the data and source space, respectively, and λ is the Lagragian parameter. The source estimate **x** was the source distribution that, among infinite possible solutions to the linear system (2), explains the EEG data with a minimum amount of energy (weighted minimum norm solution). The standard weighted minimum norm estimate was obtained by setting the matrix **D** to the identity and the matrix **C** equal to a diagonal weight matrix **W**. In the latter matrix, the i-th element was equal to the L2 norm of the i-th column of the lead field matrix **A**. An optimal regularization of this linear system was obtained by the L-curve approach. This curve, which plots the residual norm versus the solution norm at different λ values, was used to choose the optimal amount of regularization in the solution of the linear inverse problem.

The cortical activity estimate of each dipole belonging to a particular cortical ROI was then averaged together with the other belonging to the same ROI. From these current density waveforms the cortical spectral power synchronization, (Event Related Synchronization; ERD) and desynchronization (Event Related Desynchronization; ERS [10]) indexes were computed for the alpha band. In this way 44 values of ERD and ERS in each frequency band analyzed was then produced.

C. Structural Equation Modeling.

In neuroimaging effective connectivity is defined as the influence one neural system exerts over another [11]. Effective connectivity provides direct insights into how the observed correlations are mediated. One method used to estimate effective connectivity is structural equation modeling (SEM). This technique combines an anatomical (constraining) model and the inter-regional covariances of activity. The ensuing functional model represents the influence of regions on each other through the putative anatomical connections. Structural equation modelling or path analysis is a technique developed in economics, psychology and the social sciences. The basic idea differs from the usual statistical approach of modelling individual observations. SEM considers the covariance structure. Parameters are estimated by minimizing the difference between the observed covariances S_{obs} and these implied by a structural or path model S_{mod}. In terms of neural systems a measure of covariance represents the degree to which the activities of two or more regions are related.

$$S_{obs} = (1/(N\text{-}1))\cdot\mathbf{x}\cdot\mathbf{x}^T, \qquad (3)$$

where $\mathbf{x}$ is the a $p\times N$ matrix of deviation (from the mean) scores of the p observed variables with N observations. Let us consider a model where the variables $\mathbf{x}$ are direct causal implication of a set of independent variables $\mathbf{z}$. Algebraically, this can be written as a set of variables $\mathbf{x}$, which may cause one another**,** with residuals $\mathbf{z}$:

$$\mathbf{x}\cdot\mathbf{I} = \mathbf{x}\cdot\mathbf{C}+\mathbf{z}, \qquad (4)$$

where $\mathbf{C}$ is a unidirectional matrix of path coefficients and $\mathbf{I}$ is the identity matrix. The path coefficients are the parameters of the model (connection strengths) and correspond to an estimate of effective connectivity. A path coefficient represents the response of a dependent variable to a unit change in an explanatory variable, whilst the other variables in the model are held constant [12]. Because $\mathbf{x} = \mathbf{z}\cdot(\mathbf{I}\text{-}\mathbf{C})^{-1}$ we can write the covariance structure implied by the model like:

$$\mathbf{x}\cdot\mathbf{x}^T = S_{mod} = (\mathbf{z}\cdot(\mathbf{I}\text{-}\mathbf{C})^{-1})^T\cdot(\mathbf{z}\cdot(\mathbf{I}\text{-}\mathbf{C})^{-1})$$

$$\mathbf{x}\cdot\mathbf{x}^T = (\cdot(\mathbf{I}\text{-}\mathbf{C})^{-1})^T\cdot\mathbf{S}\cdot(\mathbf{I}\text{-}\mathbf{C})^{-1} \qquad (5)$$

where $\mathbf{S} = \mathbf{z}\cdot\mathbf{z}^T$ is the covariance matrix of the residuals $\mathbf{z}$. The parameters in $\mathbf{C}$ and in $\mathbf{S}$, called *free parameters*, are estimated by minimizing a function of the observed S_{obs} and implied covariance S_{mod} matrices. The most widely used objective function for SEM is the maximal likelihood (ML) function:

$$F_{ML}(\mathbf{C}) = \log|S_{mod}| + \mathrm{tr}(S_{obs}\cdot S_{mod}^{-1}) - \log|S_{mod}| - n \qquad (6)$$

where tr(.) is the trace of the matrix. In the context of multivariate, normally distributed variables the minimum of the maximum likelihood function (used to estimate the free parameters) times the number of observations minus one, follows a χ^2 distribution with $(p/2)(p + 1) - n$ degrees of freedom [12], n is the number of free parameters and p is the number of observed variables. The χ^2 statistic test can be used to infer statistical significance to the implied model in the context of SEM. The connection strengths between each cortical area depicted in the model can be tested among the STM and NSTM task by using the Analysis of Variance (ANOVA).

D. The connectivity model used

Anatomical Model: The determination of the underlying anatomical model include regions and connections between those regions. Different methods can be combined to identify important regions: categorical comparisons between different conditions and eigenimages highlighting structures of functional connectivity, in conjunction with results from primate electrophysiology and with f-MRI studies on activated areas involved in specialized tasks. The connectivity between the identified regions is mostly based on neuroanatomical studies in primates and humans. Since a model is always a simplification of reality, a compromise between complexity, anatomical accuracy and interpretability has to be reached.

We built a plausible model that should account for the delay period of the depicted task in both the two conditions of STM and no-STM. We seek for an interesting temporal window inside the delay period that is free from interfering processes of the latest condition of *visual cue*, and free from the next condition of preparation to the movement or the *go signal*. The chosen temporal window lasts 2 seconds, one second after the beginning of the delay period. We tested many different variations of a plausible model (cite) that included both the right (R) and left (L) hemisphere interactions. The areas involved were the right and left prefrontal areas overlapping with the B.A. 9/46, the supplementary motor area (B.A. 6) and the parietal B.A. 7 and the areas overlapping with the associative visual cortices B.A. 18-19. All these cortical areas are linked together in the model examined as depicted in Fig. 1.

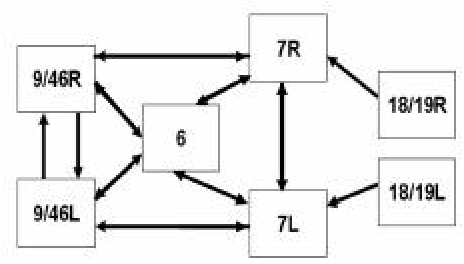

Figure 1. The connectivity model used to depict the links between cortical areas during the STM and NSTM tasks. The arrows depict the direction of the effective connectivity among different cortical areas.

III. Results

In all but one of the nine subjects analyzed, the connection model presented in Fig. 1 was correctly estimated for both STM and NSTM tasks. This means that the covariance structure of the model proposed is supported by the ERD data computed over the cortical ROIs. Successively, to answer to the question if the effective connectivity between the cortical ROIs considered in the model changed from STM to NSTM tasks, we inserted the path coefficients estimated for both conditions in a two-way ANOVA. The main effects of the ANOVA were TASK (two levels, STM and NSTM) and ARCVALUE (as much levels as the path coefficients estimated). The ANOVA returned a significant interaction between the TASK and ARCVALUE ($p < 0.001$)). The post-hoc tests performed with the Duncan procedure return statistical significant differences between the path coefficients from area 6 toward the areas 9-46L ($p<0.013$), from the area V2R toward the area 9-46L ($p<0.03$) and from the area 9-46R to the 9-46L ($p<0.019$).

IV. Discussion

In this study we estimated the effective connectivity between particular cortical ROIs in a group of healthy subjects during a STM task, by using the NSTM task as baseline for the statistical comparisons. The SEM estimates an increase of connectivity between the left and right B.A. 9/46 and between the B.A. 6 and the 9/46L during the STM task with respect to the NSTM task. Furthermore, the level of effective connectivity between the frontal B.A. 9/46 and parietal area 7 was not modulated by the STM and NSTM task.

A possible interpretation of these results is that the visual short term memory modulate the effective connectivity between the frontal cortical areas of both hemispheres (described by the 9/46 B.A). Moreover, the generic attention and the preparation to the subsequent manual action requested by both tasks can be described by the link between the B.A. areas 9/46 and 7. This last conclusion was suggested by the fact that the link between these B.A is statistically significant in the proposed model but were not changed in amplitude by the two tasks. In conclusion, this study opens the avenue for the use of SEM technique in conjunction with high resolution- EEG methodology, to estimate effective connectivity between cortical areas.

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