

CORTICAL RHYTHMS INDUCED BY TMS STIMULATION

Analysis with a Neural Mass Model

Filippo Cona, Melissa Zavaglia, Mauro Ursino

Department of Electronics, Computer Science and Systems, University of Bologna, Via Venezia 52, Cesena, Italy

Mario Rosanova

Department of Clinical Science, "Luigi Sacco", University of Milan, Milan, Italy

Keywords: Transcranial magnetic stimulation, Neural mass models, Cortical rhythms, Effective connectivity.

Abstract: Knowledge of cortical rhythms represents an important aspect of modern neuroscience, to understand how the brain realizes its functions. Recent data suggest that different regions in the brain may exhibit distinct rhythms when perturbed by Transcranial Magnetic Stimulation (TMS) (Rosanova et al., 2009) and that these rhythms can change due to the connectivity among regions. In this context, neural mass models can be very useful to simulate specific aspects of electrical brain activity and, above all, to analyze and identify the overall frequency content of EEG in a cortical region of interest (ROI). In this work we implemented a model of connectivity among cortical regions (Ursino, Cona and Zavaglia, 2010) to fit the impulse responses in three ROIs during an experiment of TMS stimulation. In particular we investigated Brodmann Area (BA) 19 (occipital lobe), BA 7 (parietal lobe) and BA 6 (frontal lobe). Results show that the model can reproduce the natural rhythms of the three regions quite well, acting on a few internal parameters. Moreover, model can explain most rhythm changes induced by stimulation of another region, by using just a few long-range connectivity parameters among ROIs.

1 INTRODUCTION

The study of brain rhythms represents an important aspect of modern neuroscience. The electrical activity of the brain is very complex, including different oscillatory patterns at different frequencies, which may change with the particular task. It is generally assumed that these rhythms are not merely epiphenomena, but play a relevant role in many perceptive, motor and cognitive functions.

An estimation of the intrinsic rhythms of brain regions, and of how these rhythms can be transmitted and modified as a consequence of brain connectivity, can be achieved using the TMS technique combined with EEG recordings. This technique allows the measurement of cortical reactivity and functional connectivity (Miniussi and Thut, 2010). TMS, in fact, can be used to elicit changes in the synchronization of the brain oscillatory activities, and thus in the rhythms power (Brignani, Manganotti, Rossini and Miniussi, 2008; Fuggetta, Pavone, Fiaschi and Manganotti, 2008).

Moreover, TMS has been used to perturb cortical regions in order to map the different cognitive and motor functions over the brain (Hallett, 2007) and to link these functions to characteristic oscillatory activities (Thut and Miniussi, 2009).

In a recent work, Rosanova et al. (2009) observed the oscillation rate in three brain regions (occipital, parietal, and frontal) following TMS stimulation of different intensities in a group of healthy volunteers. Results show that the natural frequency can be directly measured in virtually any area of the cerebral cortex. Moreover, these natural rhythms can be transmitted from one region to another (or the intrinsic rhythms can be modified) as a consequence of connectivity among ROIs.

The previous results are suitable to be analyzed using neurologically inspired computational models. Actually, the impulse response is a classical instrument in modeling literature to estimate parameters and validate model structure in a straightforward way. Computational models, in turn, are essential to reach a deeper understanding of the

neural mechanisms involved in rhythms generation and in their propagation .

In recent years, we developed a neural mass model to study rhythm generation and rhythm transmission among connected cortical regions. The model was built starting from equations proposed by Jansen and Rit (1995) and Wendling, Bartolomei, Bellanger and Chauvel (2002), with inclusion of a new loop to simulate the role of fast GABA-ergic interneurons in the genesis of gamma oscillations (Ursino et al., 2010). The model was able to simulate multiple rhythms within the same ROI and the transmission of rhythms from one region to another, by simply modulating a few parameters which represent short-range connections within a region and inter-area long-range connectivity (Ursino et al., 2010).

The experimental results by Rosanova et al. (2009) are particularly suitable to test our model. In particular, some model predictions (the presence of intrinsic rhythms in individual ROIs and the possibility to transmit rhythms via a few effective connections among ROI) agree at least qualitatively with these experimental data.

Hence, the present study was designed with the following two main purposes:

i) to analyze whether the response of individual ROIs to direct TMS stimulation can be simulated with sufficient accuracy with the model by modifying just a few internal parameters of that region. This aspect is the same as to fit the natural rhythm of a ROI with a parsimonious biologically inspired model;

ii) to analyze whether a model of interconnected ROIs can at least approximately explain how natural rhythms can be transmitted or modified as a consequence of inter-region connections. In this case too, we are looking for a parsimonious description.

In this work, we simulated the behavior of Brodmann Area (BA) 19 (occipital lobe), BA 7 (parietal lobe) and BA 6 (frontal lobe) with a network of three interconnected regions. Parameters are given to reproduce the effect of TMS stimulation of medium intensity in one representative subject.

2 METHODS

2.1 Experimental Data Recording (TMS and EEG)

During the experiment, subjects were lying on an ergonomic chair, relaxed, and with eyes open

looking at a fixation point on a screen. A focal bipulse, figure-of-eight coil with 60mm wing diameter driven by a biphasic stimulator (eXimia TMS Stimulator; Nexstim) was used to stimulate the subjects' cortex. Three cortical sites (middle or superior occipital gyrus, superior parietal gyrus, and middle or caudal portion of the superior frontal gyrus) were selected based on an atlas of brain regional anatomy (Tamraz and Comair, 2000), anatomically identified on a T1-weighted individual MRI (resolution 1 mm) acquired with a 1 T Philips scanner and were targeted by means of a Navigated Brain Stimulation (NBS) system (Nexstim). We recorded high-density EEG using a TMS-compatible 60-channel amplifier (Nexstim) which gates the TMS artifact and prevents saturation by means of a proprietary sample-and-hold circuit (Virtanen, Ruohonen, Naatanen and Ilmoniemi, 1999). The EEG signals, referenced to an additional electrode on the forehead, were filtered (0.1–500 Hz) and sampled at 1450 Hz with 16-bit resolution. Two extra sensors were used to record the electrooculogram. In most cases, no TMS-induced magnetic artefacts were detected, and in all cases, the EEG signals were artefact-free after the stimulus. TMS trials containing noise, muscle activity, or eye movements were automatically detected and rejected. The event related potentials were obtained by averaging across all the trials of each session (100–200 per session). More technical details on the procedure can be found in Rosanova et al. (2009).

In this work, only data from one subject have been examined, obtained with a TMS intensity as high as 120 V/m.

2.2 Cortical Sources Reconstruction

Source modelling was performed following a multiple step procedure: the free licence package SPM (<http://www.fil.ion.ucl.ac.uk/spm>) was used to create the cortical mesh by adapting an average Montreal Neurological Institute (MNI) cortex to the subject's MRI data; skull and scalp meshes were also co-registered with EEG sensors positions into the subject's MRI space; a 3-spheres BERG method was obtained to calculate the Lead Field Matrix by using the free access Brainstorm software package (<http://neuroimage.usc.edu/brainstorm>); the inverse solution was calculated on a single trial basis by applying an empirical Bayesian approach with estimation of covariance components using Restricted Maximum Likelihood (Friston, Henson, Phillips and Mattout, 2006). In order to compute the overall current evoked by TMS in different cortical

areas, cortical sources were attributed to different Brodmann areas using an automatic tool of anatomical classification (<http://www.ansir.wfubmc.edu>). Currents recorded within each area were cumulated in order to produce a new time series.

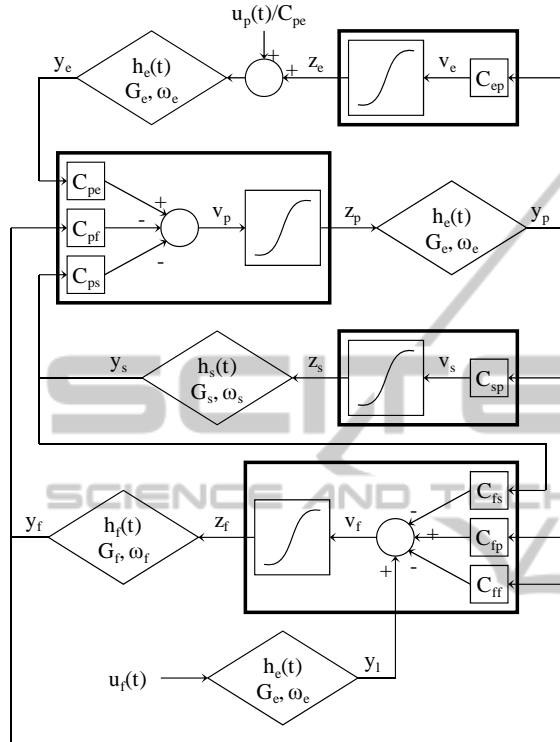


Figure 1: Model layout of a single cortical region.

2.3 Model of a Single Cortical Area

The model of a cortical region consists of four neural populations, which represent pyramidal neurons, excitatory interneurons, and inhibitory interneurons with slow and fast synaptic kinetics ($GABA_{A,slow}$ and $GABA_{A,fast}$ respectively). Each population represents a group of neurons of the same type, which approximately share the same membrane potential and so can be lumped together. All populations are described with a similar mathematical formalism. Briefly, each population receives an average postsynaptic membrane potential (say v) from other neural populations, and converts this membrane potential into an average density of spikes fired by the neurons. In order to account for the presence of inhibition (when potential is below a given threshold) and saturation (when potential is high) this conversion is simulated with a static sigmoidal relationship. Moreover, each population sends synapses to other populations (or, in case of pyramidal neurons, to other regions too).

Each synaptic kinetics is described with a second order system, but with different parameter values.

In the following, a quantity which belongs to a neural population will be denoted with the subscript p (pyramidal), e (excitatory interneuron), s (slow inhibitory interneuron) and f (fast inhibitory interneuron). To model a whole cortical region, the four populations are connected via excitatory and inhibitory synapses, with impulse response $h_e(t)$, $h_s(t)$ or $h_f(t)$, assuming that pyramidal neurons and excitatory interneurons have similar dynamics. The average numbers of synaptic contacts among neural populations are represented by eight parameters, C_{ij} (see Fig. 1), where the first subscript represents the target (post-synaptic) population and the second subscript refers to the pre-synaptic population. These connections agree with those proposed by Wendling et al. (2002) but with the addition of the new self-loop C_{ff} . The model is displayed in Fig. 1. For more details see Ursino et al. (2010).

2.4 Model of Connectivity Among Areas

To simulate cortical connectivity between two regions (the pre-synaptic and post-synaptic regions will be denoted with the superscript k and h , respectively), we assumed that the average spike density of pyramidal neurons of the pre-synaptic area (z^k) affects the target region via a weight factor, W_j^{hk} (where $j = p$ or f , depending on whether the synapse targets pyramidal neurons or $GABA_{A,fast}$ interneurons) and a time delay of 1 ms. This is achieved by modifying the membrane potential v_p^h and/or v_f^h of the target region, with the time dynamics of an excitatory synapse. Long range synapses which target to slow inhibitory interneurons or to excitatory interneurons have not been considered since they have a minor role in model dynamics (Ursino et al., 2010). The generalization to more than two regions is trivial.

2.5 Simulation of TMS Experiments and Parameter Fitting

In order to simulate the TMS experiment described above, we implemented a model of connectivity among three cortical regions. These regions wish to simulate the Brodmann Area (BA) 19 (occipital lobe), BA 7 (parietal lobe) and BA 6 (frontal lobe). A manual fitting between simulated EEG and real data has been achieved both in the time and frequency domains. In particular, we focused

attention on the 400 ms following the TMS impulse, and on the frequency range 10–50 Hz. In order to eliminate possible differences in amplification, all experimental time series have been preliminarily multiplied by a constant gain so that their amplitudes would be comparable to those of the simulated signals. It is worth noting that we didn't consider the first oscillations in the experimental signals because they are mostly artefactual. The time frequency maps were obtained using the Morlet wavelet transform.

Manual fitting has been subdivided into two steps:

Step i) In the first step, we tried to investigate the impulse response of a single region, when the same region receives the TMS stimulus. In this phase, connectivities among regions were put to zero. The TMS stimulus in the single cortical area was simulated by instantly modifying the four state variables representing the outputs of the synapses blocks (y_p, y_e, y_s, y_f) by the same amount (say Δy).

Table 1: Model parameters.

Parameters	Common		
G_e	5.17		
G_s	4.45		
G_f	57.1		
ω_e	75		
ω_s	30		
ω_f	75		
C_{ep}	5		
C_{pe}	25		
C_{sp}	60		
Parameters	BA 19	BA 7	BA 6
C_{ps}	65	15	70
C_{fp}	52	70	50
C_{fs}	12	12	12
C_{pf}	35	7.5	35
C_{ff}	35	9.5	22.5
Δy_i	-0.04	0.012	-0.01

Table 2: Inter regions connections toward pyramidal neurons.

to \ from	BA 19	BA 7	BA 6
BA 19	-	0	0
BA 7	34	-	0
BA6	0	0	-

Table 3: Inter regions connections toward GABA_{A,fast} neurons.

to \ from	BA 19	BA 7	BA 6
BA 19	-	20	15
BA 7	0	-	40
BA6	10	15	-

This operation simulates a sudden change in the membrane potentials of the four neural groups, which agree with other TMS implementations in neural models (Esser, Hill and Tononi, 2005).

In order to reproduce the intrinsic frequency content of each region, we acted on the numbers of synaptic contacts among the neural populations of each ROI (C_{ij}). The list of parameters is shown in Table 1. In particular, we focused only on those internal parameters ($C_{ps}, C_{fp}, C_{pf}, C_{ff}, C_{fs}$) that most influenced the frequency content of the model output (Ursino et al., 2010). The intensity of the stimulus Δy was positive when the deflection in the time response was negative (see BA 7 in Table 1) and negative otherwise (BA 19 and BA 6 in Table 1).

Step ii) By maintaining the same internal parameters of the three regions obtained in step i, we acted on inter-regions connectivity, to simulate the changes in the frequency rhythms that each region exhibit as a consequence of stimulation in another region, still trying to preserve the fitting results achieved in step i. To have a parsimonious description, we assumed that the connectivity from one region to another may target either to pyramidal neurons or to fast inhibitory interneurons (i.e., we never used both simultaneously). This reduces the number of connectivity parameters to six. As it is reported in Tables 2 and 3, only a connectivity is toward pyramidal cells, while all the remaining ones are toward GABA_{A,fast} interneurons, underlying the importance of this neural group in the generation of different rhythms (Ursino et al., 2010).

3 RESULTS

Real and simulated signals were compared both in time and frequency domains. In particular, Figs. 2-4 display the time patterns and the spectrograms of the simulated and real signals in response to TMS stimulation on BA19 (Fig. 2), on BA7 (Fig. 3) and on BA 6 (Fig. 4). Results show that the model can reproduce the main experimental patterns of cortical activity quite satisfactorily.

The main result is that each region exhibits a different intrinsic rhythm, and this rhythm exhibits evident changes as a consequence of the stimulation of another region. The model can explain both these aspects, ascribing the first to the internal parameters of the region, and the second to the mutual long-range connections among regions. Focusing on BA 19, one can observe that this region exhibits an activity mainly in the alpha range when it is directly stimulated by TMS, although with components also

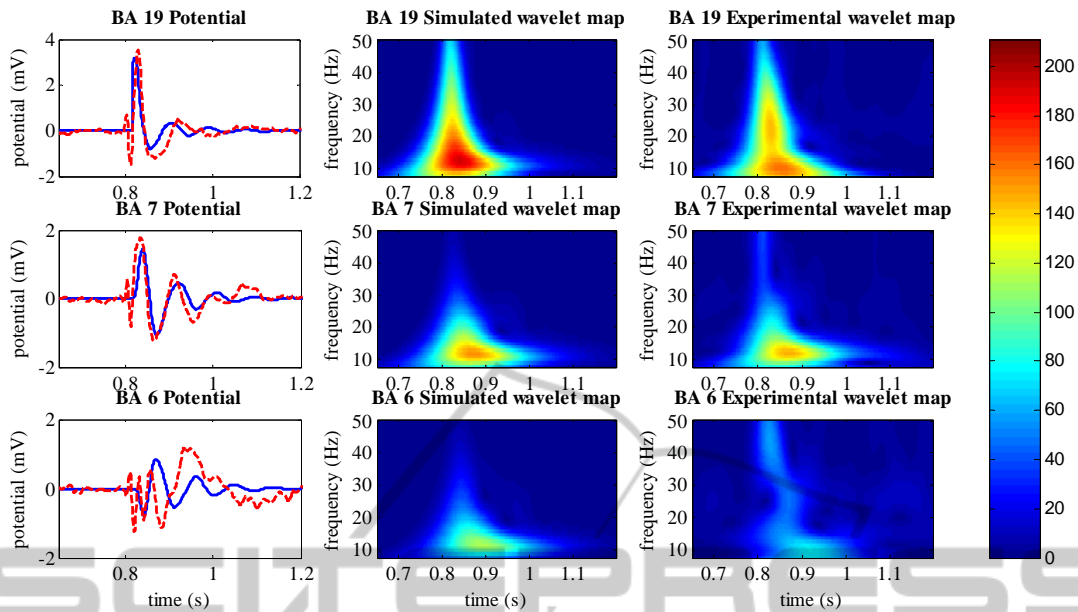


Figure 2: Cortical activations due to TMS stimulus on BA 19. In the first column are shown the experimental (red dashed line) and simulated (blue line) time responses, while in the second and third columns are shown the respective time frequency maps.

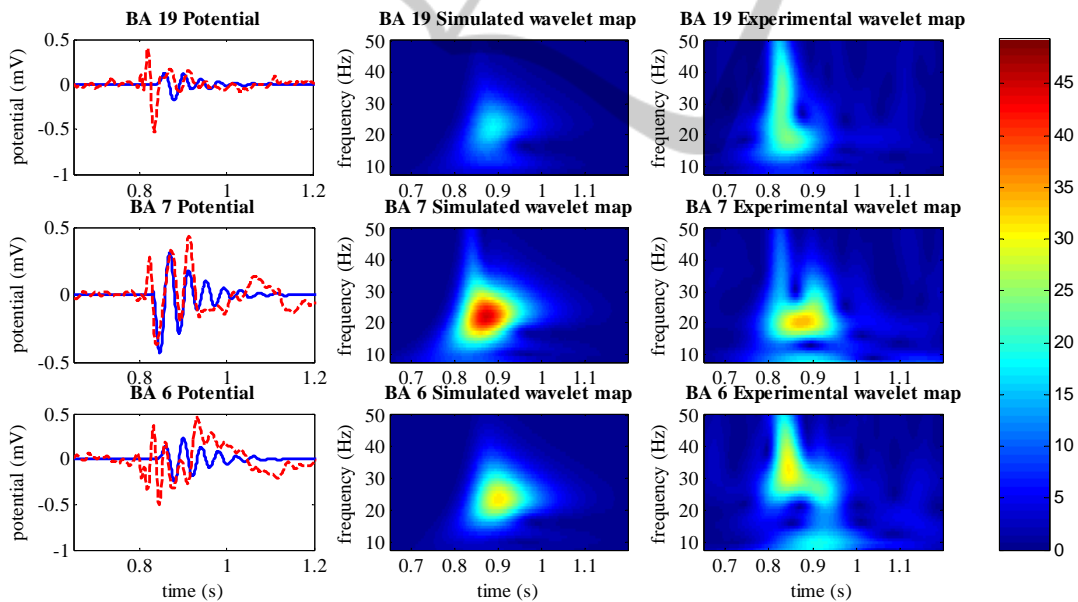


Figure 3: Cortical activations due to TMS stimulus on BA 7.

in the beta and gamma ranges (Fig. 2), while it oscillates in the beta range when BA 7 is stimulated (Fig. 3).

BA 7 exhibits an activity in high-beta range when directed stimulated (Fig. 3), while it oscillates mostly in alpha range when the BA 19 is stimulated (Fig. 2). BA 6 oscillates mostly in gamma and alpha range when it is stimulated by the TMS (Fig. 4), and it oscillates in beta range and in alpha range

respectively when BA 7 (Fig. 3) and BA 19 (Fig. 2) are stimulated. It is worth noting that the activity of BA 19 and BA 7 is not statistically significant with respect to the baseline activity following stimulation of BA 6 (Rosanova et al., 2009). Hence, we did not try to carefully simulate these signals with the model (Fig. 4).

As it is reported in Tables 2 and 3, the strongest connectivities are those toward BA 7, which is the

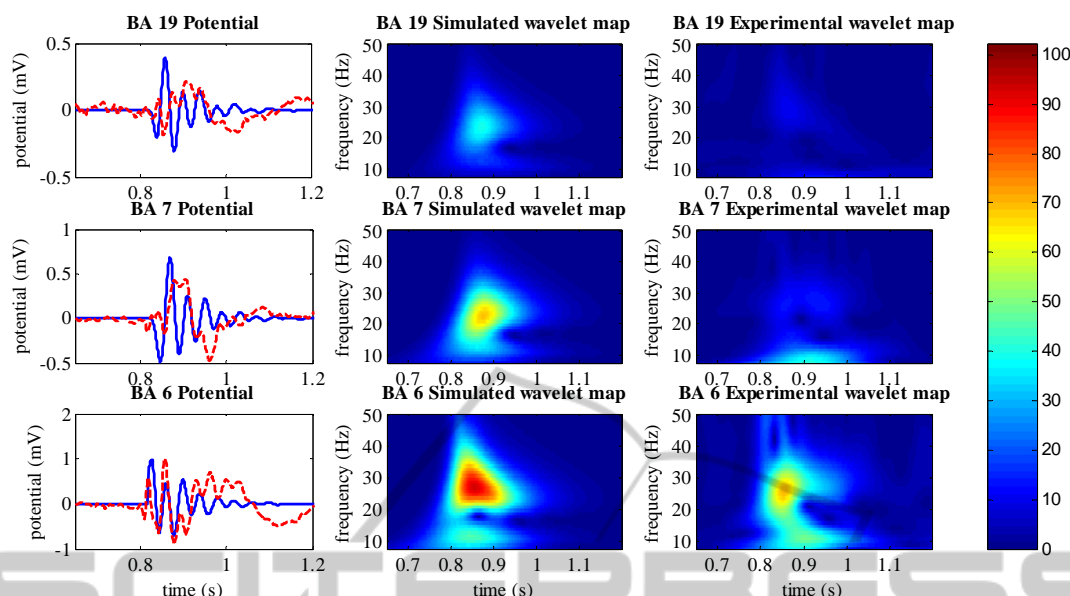


Figure 4: Cortical activations due to TMS stimulus on BA 6.

only region receiving a connectivity toward pyramidal cells. The other two regions receive a connectivity only toward GABA_{A,fast} interneurons.

4 CONCLUSIONS

The main objective of the present work was to investigate whether a recent neural mass model of interconnected regions (Ursino et al., 2010), can explain the patterns of neural rhythms evoked by TMS stimulation, in three different cortical regions (occipital, parietal and frontal). Results are reliable and underline the following fundamental aspects:

i) The impulsive response evoked in a cortical region via a TMS stimulus of medium intensity can be fitted quite well acting just on a few parameters internal to the region, which represent the number of synaptic connections between the neural populations involved.

ii) Different regions exhibit different natural rhythms when directly stimulated by TMS (roughly in the alpha band for the BA19, in the beta band for the BA7 and in the gamma band for the BA6). This result, which was well evident in the former work by Rosanova et al. (2009), is now explained in terms of differences in the internal connections between the neural populations, without the need to hypothesize changes in synaptic dynamics (i.e., all synapses which refer to a given class of neurons have the same dynamics in the model, independently of the cortical region).

iii) The natural rhythms in a ROI are modified if another region is stimulated. Model can simulate these rhythm changes fairly well, ascribing them to effective connectivity among ROIs. Substantially, the main new result of this study is that a simple and parsimonious pattern of connectivity (with only six weights) can explain how a natural frequency can be modified and/or a new rhythm can be received following stimulation of another ROI. In general, the simple connectivity pattern shown in Tables 2 and 3 can mimic many of the rhythm changes observed during the experiment in the three regions (occipital, parietal and frontal). In perspective, this result may have important implications for neuroscience. On one hand, the way a natural rhythm is transmitted from one region to another may play an important role in many perceptive, motor or cognitive brain functions (Fries, Nikolic and Singer, 2007; Kaiser and Lutzenberger, 2005; Steriade, 2006). Furthermore, the observation of rhythm changes in different brain regions may provide important clues to assess brain connectivity from high resolution scalp EEG, a problem of large relevance in contemporary cognitive neuroscience.

iv) Most interregional connections in this study are directed from pyramidal toward fast GABAergic interneurons. We do not think that this result signifies that excitatory pyramidal-pyramidal connections are unimportant in brain connectivity. Rather, this result underlines that fast inhibitory interneurons play an essential role in rhythm transmission, especially at high EEG frequencies

(high beta and gamma). This is probably a consequence of their fast dynamics. A similar conclusion was achieved, via a sensitivity analysis, in another modeling paper (Ursino et al., 2010).

Although the results attained in the present work are quite satisfactory, the study also exhibits several limitations, which may become the target of future improvements or extensions. First, there is no warranty that the parameter values obtained in this study are unique. Probably, different combinations of parameters do exist which provide similar results. The problem of the uniqueness of parameter estimates is very complex in all non-linear fitting procedures. The solution will require the inclusion of additional knowledge, to constrain parameter estimates (for instance, the use of additional anatomical or neurophysiological knowledge, and the use of Bayesian estimation techniques).

In the present study we used a manual fitting procedure. An improved fitting may be achieved, in future works, using an automatic algorithm. This, however, must deal with the problem of multiple solutions and with a smart choice of an initial guess.

The experiment was performed on 7 subjects, but in this pilot study we used data recorded just from one of them. Fitting to all available data will be attempted in future works, once an automated estimation algorithm is available. Comparison between the connectivity patterns obtained on different subjects will be of the greatest value to check the repeatability of the obtained results, and to understand which connectivity parameters are more subject dependent.

In the present study, we did not consider connections between cortical regions and the thalamus. Conversely, cortico-thalamic connections are known to play a pivotal role in generating brain oscillations (Steriade, 2006) as well as in the transmission of information among cortical regions. The choice of not including thalamic regions in the model was motivated by a parsimony reason: we wished to realize a parsimonious model of a TMS stimulation experiment, with a reduced number of regions and of connectivity parameters. Consequently, a single ROI in the model can be considered representative not only of cortical dynamics, but more generally of an entire cortico-thalamic circuit. Inclusion of an explicit description of the thalamus may represent a possible model extension. However, we expect that this enlarged model would require more data to fit individual parameters in both cortical and thalamic regions altogether.

REFERENCES

- Brignani, D., Manganotti, P., Rossini, P. M. and Miniussi, C., (2008). Modulation of cortical oscillatory activity during transcranial magnetic stimulation. *Human Brain Mapping*, 29(5), 603-612.
- Esser, S. K., Hill, S. L. and Tononi, G., (2005). Modeling the effects of transcranial magnetic stimulation on cortical circuits. *Journal of Neurophysiology*, 94(1), 622-639.
- Fries, P., Nikolic, D. and Singer, W., (2007). The gamma cycle. *Trends in Neurosciences*, 30(7), 309-316.
- Friston, K., Henson, R., Phillips, C. and Mattout, J., (2006). Bayesian estimation of evoked and induced responses. *Human Brain Mapping*, 27(9), 722-735.
- Fuggetta, G., Pavone, E. F., Fiaschi, A. and Manganotti, P., (2008). Acute modulation of cortical oscillatory activities during short trains of high-frequency repetitive transcranial magnetic stimulation of the human motor cortex: a combined EEG and TMS study. *Human Brain Mapping*, 29(1), 1-13.
- Hallett, M., (2007). Transcranial magnetic stimulation: a primer. *Neuron*, 55(2), 187-199.
- Jansen, B.H. and Rit, V.G., (1995). Electroencephalogram and visual evoked potential generation in a mathematical model of coupled cortical columns. *Biological Cybernetics*, 73(4), 357-366.
- Kaiser, J. and Lutzenberger, W., (2005). Human gamma-band activity: a window to cognitive processing. *Neuroreport*, 16(3), 207-211.
- Miniussi, C. and Thut, G., (2010). Combining TMS and EEG offers new prospects in cognitive neuroscience. *Brain Topography*, 22(4), 249-256.
- Rosanova, M., Casali A., Bellina V., Resta F., Mariotti M. and Massimini M., (2009). Natural frequencies of human corticothalamic circuits. *Journal of Neuroscience*, 29(24), 7679-7685.
- Steriade, M., (2006). Grouping of brain rhythms in corticothalamic systems. *Neuroscience*, 137(4), 1087-1106.
- Tamraz, J. and Comair, Y. (2000). *Atlas of regional anatomy of the brain using MRI*. Berlin: Springer.
- Thut, G. and Miniussi, C., (2009). New insights into rhythmic brain activity from TMS-EEG studies. *Trends in cognitive sciences*, 13(4), 182-189.
- Ursino, M., Cona, F. and Zavaglia, M., (2010). The generation of rhythms within a cortical region: Analysis of a neural mass model. *Neuroimage*, 52(3), 1080-1094.
- Virtanen, J., Ruohonen, J., Naatanen, R. and Ilmoniemi, R.J., (1999). Instrumentation for the measurement of electric brain responses to transcranial magnetic stimulation. *Med.Biol.Eng Comput.*, 37(3), 322-326.
- Wendling, F., Bartolomei, F., Bellanger, J. J. and Chauvel, P., (2002). Epileptic fast activity can be explained by a model of impaired GABAergic dendritic inhibition. *European Journal of Neuroscience*, 15(9), 1499-1508.