Real-Time Spatial Localization System of Brain Regions for TMS Application by Co-registration with fMRI

A.S.C. Peres[1], V.H.O. Souza[1], E.M. Rodrigues[1], C.E.G. Salmon[1], D.B. de Araujo[1,2], and O. Baffa[1]

[1] Universidade de São Paulo, Departamento de Física e Matemática, Ribeirão Preto, Brazil
[2] Universidade Federal do Rio Grande do Norte/IINN, Natal, Brazil

Abstract— **Most TMS applications still use subjective parameters to establish the brain area that is to be stimulated. An obvious way to improve TMS applications is to combine them with neuroimaging techniques. In order to accomplish this it is necessary to use complex techniques, i.e. neuronavigation, to perform the co-registration. Although there are commercial neuronavigation systems available, in general they are expensive and proprietary. This work aims to improve the precision of TMS applications by measuring the magnetic field produced by the coil and by using neuronavigation software based in an open architecture and free software, allowing the use of different positioning systems for the co-registration with the neuroimage.**

Keywords— **TMS, fMRI, Neuronavigation, Magnetic Field Mapping.**

I. Introduction

Transcranial magnetic stimulation (TMS) [1,2] has been extensively investigated for use as a clinical and research tool in neurophysiology, as evidenced by a strong increase in published papers in recent years. Since the magnetic pulses are applied externally, the operator has no means to know exactly which cortical area is being stimulated. Thus, usually pre-established fiducial points are used to guide TMS application, even though are large anatomical variations among individuals.

To know the regions that are being actually stimulated in a given subject it is necessary to rely on the subject's own neuroimage [3]. In order to co-register the positions of the scalp with the internal structures, it is necessary to use a neuronavigator [4], which is a complex system that integrates spatial tracking software with graphical and mathematical tools. Neuronavigators are usually based on a closed platform, making it impossible to implement the user-specific tools, and they are expensive. However, this scenario is changing due to the development of open source implementations, allowing multiple users to change the code according to their needs.

In this way, one of our goals is to implement an open source software available to groups that have no possibility to acquire a commercial system. As a second objective, we combined TMS with functional Magnetic Resonance Imaging (fMRI), in order to access the functional brain site that one which to stimulate [5,6,7]. Moreover, this platform should be versatile, and operate with different TMS coil geometry, and respective field map.

Although the geometry of most of the coils used is known and the magnetic field can be calculated, it is important to know as precisely as possible the field being applied. In order to do so, it is necessary to perform a field map of the coil to be used. The measurements of magnetic fields can be obtained with small search coils, hall sensors, magnetoresistive sensors or MRI techniques [8]. The advantage of using MRI for magnetic field mapping is the possibility to map a large volume with high spatial resolution relatively fast.

II. Matrials, methods and results

A. TMS Coil Studies

Using a 3 mm diameter coil, with acrylic and PVC core, as a search coil, the magnetic field time variation was analyzed. The electromotive force (emf) was measured as a function of time (Fig. 1).

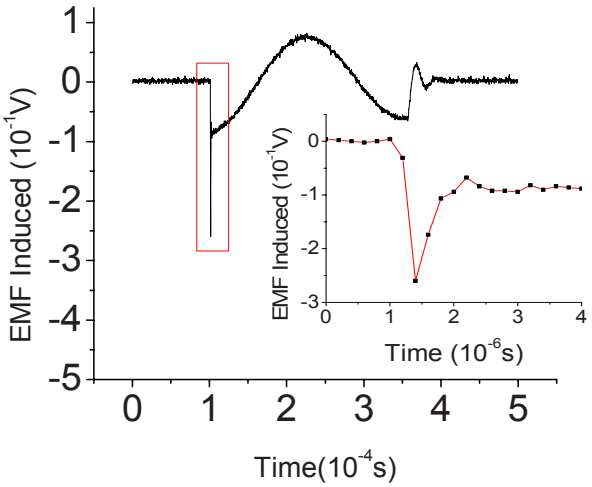

Fig. 1 Time variation of emf induced in the search coil to measure the magnetic flux produce by the TMS coil. The selected region in the box represents the initial ramp, detailed in the inset curve in the side

S. Supek and A. Sušac (Eds.): Advances in Biomagnetism – BIOMAG2010, IFMBE Proceedings 28, pp. 92–96, 2010.
www.springerlink.com

The signal starts with a large slope, of the order of 1μs, and then becomes biphasic. The average rise time of the initial slope was 1.4 ± 0.2 μs and the total pulse duration was 307 ± 7 μs, both results obtained after an average of six measurements.

It is important to note that most the literature commonly report only the period of the biphasic wave, neglecting the initial slope. This can lead to an erroneous estimation of the intensity of the electric field induced, which causes depolarization of neurons.

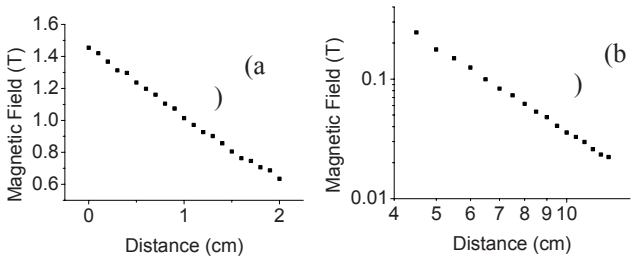

Fig. 2 a) Magnetic field decay at short distances to the TMS coil. b) Logarithmic representation to the intensity field decay, at 45 to 125 mm of distance to the TMS coil

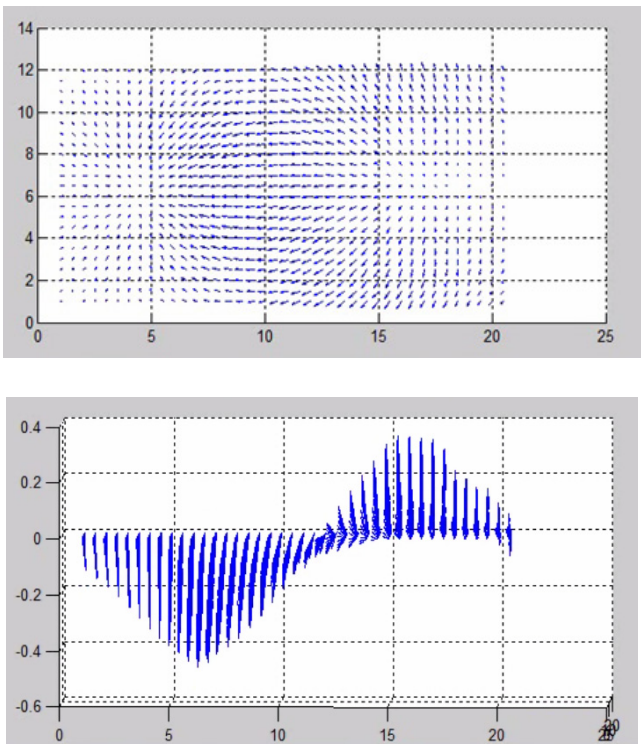

Fig. 3 Vector magnetic field distribution produced by butterfly coil shown in two perspectives

In order to know the magnetic field intensity dependence on a butterfly coil distance, we studied the field intensity at near points (20 mm) and at more distant points (45 to 125 mm). In the first case, a linear behavior was observed with slope -41.5 ± 0.5. This is expected, as the range of measurements is smaller than the outer radius of the coil. At distant points, it's possible to consider the butterfly coil as a point dipolar source, which equation is independent of coil size and falls with the third power of the distance.

A logarithmic plot of the measurements yielded the exponent of the distance dependence, which was equal to 2.34 ± 0.02. These results show that in this distance range the source size still influences the field intensity [9].

The results for the variation of magnetic field strength with distance from the source are shown in Figure 2.

Finally we use the phase images of gradient recalled echo technique to describe the spatial distribution of the butterfly coil magnetic field. In this experiment a 3T Magnetic Resonance Scanner (Philips Achieva, The Netherlands) and a phantom filled with $CuSO_4 \cdot 5H_2O$ solution were used. The magnetic field of the TMS coil was generated by a direct current of 1.12A. This was necessary since TMS pulses are very short, not changing the phase of the proton spins [10]. The results are shown in figure 3, presenting the vector distribution of the magnetic field.

B. The Neuronavigation Software

The neuronavigation software was built using the graphical user interface development environment (GUIDE) of Matlab. First, an algorithm to load medical images (DICOM, Analyze, REC/PAR, Nift, and Minc) was implemented. For brain segmentation we use the freeware software MRIcro [11]. A three-dimensional reconstruction algorithm for brain volume preview was also developed in this project.

After that, we implement an algorithm to co-register the patient (real coordinate) with his/her digital images (virtual coordinate).

To do so, a tracking system based on electromagnetic waves (Polhemus Isotrak II) [12] was used to acquire the positions of the following fiducial points: right and left pre-auricular and nasal cavity. Then the neuroimaging points corresponding to these reference points were also acquired. With these reference points, a basis associated with the Polhemus and another, based on the coordinated image, were built. Thus to take a point from the scanner basis to the image basis (pixel position) just one coordinate transformation is needed.

The precision of the whole system was analyzed using a head phantom. A precision of 6 mm was obtained mainly due to the size of the pointing device presently used with

the Polhemus system. Use of the stylus pointing device will improve the precision. Software is under development, as well as the implementation of drivers that will allow the use of other tracking systems such as Claron (optical) [13] and Zebris (Ultra-sonic) [14].

C. fMRI Experiments

Ten healthy volunteers between 18 and 30 years, including 2 women and 8 men were used in the experiment. The project was approved by the Ethics Committee of *Hospital das Clínicas de Ribeirão Preto* (HCRP) according to HCRP No 6728/2007, and informed consent was obtained from all participants.

A 1.5 T scanner Siemens (Magneton Vision) with a quadrature coil transmitter/receiver head from HCRP was used in the experiment.

Echo Planar Images (EPI) of 66 blocks were acquired with 16 slices with 6 mm thickness, covering 9.6 cm, with the following parameters: ISI = 3540 ms, TE = 60 ms, flip angle = 90°, a matrix size = 128 x 128, FOV = 220 mm resulting in a voxel size = 1.72 x 1.72 x 6.00 mm.

As the region of interest in this study was the primary motor cortex, the slices were oriented approximately perpendicular to the axis of the central sulcus, thus covering a region beyond the lateral sulcus, ensuring the mapping of the entire pre- and post-central gyri.

For the high anatomical resolution images, a GRE, MPR, T1-weighed with 156 slices, TR of 9.7 ms, TE of 4 ms, flip angle of 12 degrees, matrix size of 256 x 256, FOV of 256 mm and a voxel size of 1 x 1 x 1 mm was used.

To verify that our neuronavigation system was viable, we decided to use a well-established block paradigm, known as finger tapping [15, 16], in which the volunteer alternates periods of rest and activity. Each period corresponds to 6 acquisitions in time. The volunteer started at rest and after a beep began the task until another signal was presented to end the task, thus totaling 6 periods of rest and 5 of activity.

The images were then processed with the software Brain Voyager QX, which performs statistical calculation algorithm using a General Linear Model (GLM) [17].

D. TMS and fMRI co-registration

Once the algorithm was tested with a phantom and the functional images were obtained, we set up a positioning system for co-registration with the fMRI images, consisting of a variable height chair and a table with a chin support.

To facilitate the positioning of the coil on the scalp, we developed a coordinate system for the skull of the volunteers. This system consists of a white nylon swim cap, on which we draw grid lines 1 cm apart horizontally and vertically.

An electromyography electrode was positioned on the thumb's abductor muscle to capture the MEP due to TMS in the motor cortex. This muscle was chosen due to the ease of positioning an electrode on it and also because of its large area of cortical representation.

The volunteer's head was positioned in the chin support, and the three points (real and virtual) for the co-registration were collected. Once co-registered, scans on the volunteers' scalp with the Polhemus's probe were made, until it was on the most probable of activity center found by the fMRI (hot spot). Besides the stimulation of this position, a set of points distant 1cm and 2cm from the left and right (longitudinal mapping), from the top and below (transversal mapping) and a distant point, totaling 10 points.

For the application of TMS, we first determined the motor threshold for each volunteer, that was found when at least 5 MEPs were elicited out of 10 pulses applied at the hot spot [18].

Once the motor threshold was determined, the intensity was adjusted to 120% of the threshold and for each point 8 stimulations separated by 5s were performed.

The data were then interpolated and plots of the MEP intensity versus position were made, summing 4 curves per volunteer, 2 for right hand and another 2 for left hand. Then the distance along the direction between the positions of the maximum activations obtained by fMRI and by TMS were determined, as shown in figures 4.

We analyzed first the behavior of all curves, computing the average and its deviation to the displacement of the peak for all curves, and obtained 7 ± 6 mm.

Thus we proceeded to a second analysis, which separated the values obtained in the stimulation of the right and left hand. The results show no significant variations for the two hemispheres, where we found 7 ± 6 mm for the stimulation on the right hand and 8 ± 7 mm for the stimulation of the left hand.

Finally a comparison between the sample into transversal curves and longitudinal curves was made. This result showed a significant difference in the orientation of the mapping, with the value (11±6) mm for the longitudinal curves and (4±3) mm for the transversal curves.

This discrepancy between distances obtained in the transverse and longitudinal direction is probably due to the fact that the longitudinal curve includes the motor and pre-motor cortex. Since both cortices can induce MEP in the thumb brevis, two peaks were found in the longitudinal curves in many volunteers, as can be seen in Figure 5d.

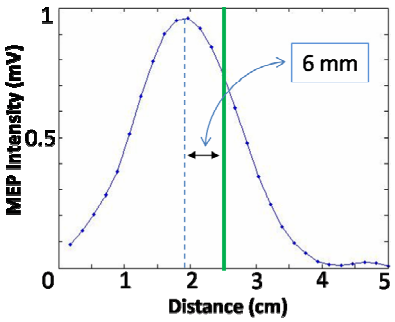

Fig. 4 MEP curve by the position of stimulation. The curve is represented by blue dots while the black line segment corresponds to the center of activity found by neuronavigator

As the value of maximum activity in fMRI was chosen visually by the experimenter, as explained above, when there were two points with high statistical significance, as shown in Figures 5a, b and c, the midpoint between them was chosen as the hot spot. The result can be seen in figure 5d, where the greatest fMRI activity was between 2 peaks of MEP, thus inducing an error in the measurement of distances. Therefore, only transverse curves must be used. The results obtained with the fMRI are very close to the precision of the neuronavigator, which are sufficient for the purpose for which it was designed, as in all volunteers we obtained the region of maximum activity defined by the neuronavigator. These results are similar to the ones obtained by Lotze, 2003 [19].

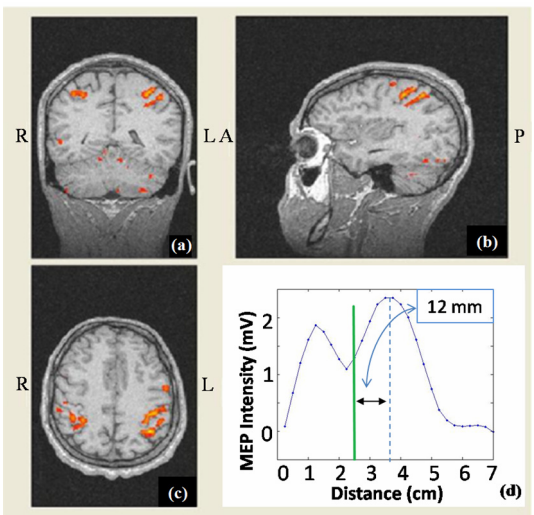

Fig. 5 fMRIs of a volunteer showing the motor area activated by the proposed protocol. (a) Coronal image; (b) Sagital image; (c) Axial image; (d) MEP intensity curve induced by TMS

III. Conclusion

We observed that 100% of the applications of TMS were in the center of activity found by neuronavigator were followed by MEP. Thus we may say that the neuronavigator is a good alternative to assist the localization of brain regions, not only reducing the application time of TMS, but also improving the accuracy of the test.

This technique, when allied with magnetic field maps, can predict with good precision what areas are being stimulated, and more than that, the intensity and direction of the magnetic field applied in a certain region.

Acknowledgments

The authors wish to thank the Brazilian agencies CAPES, CNPq, and FAPESP for partial financial support. Moreover, we are grateful to Mr. Lourenço Rocha for technical support. This work is part of the CINAPCE project.

References

1. Barker AT, Jalinous R, Freeston IL (1985) Non-invasive magnetic stimulation of human motor cortex. The Lancet 325:1106-1107.
2. Hallett M (2000) Transcranial magnetic stimulation and the human brain. Nature 406:147-150.
3. Siebner HR, Bergmann TO, Bestmann S, et al (2009). Consensuspaper: Combining transcranial stimulation with neuroimaging. Brain Stimulation 2:58-80.
4. Herwig U, Schönfeldt-Lecuona C, Wunderlich AP, et al. (2001). The navigation of transcranial magnetic stimulation. Psychiatry Research: Neuroimaging 108(2):123-131.
5. Kwong KK, Beliveau JW, Chesler DA, et al. (1992) Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proccedings of the National Academy of Science 89:5675-5679.
6. Ogawa S, Tank DW, Menon R, et al. (1992) Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging, Proccedings of the National Academy of Science 89(13):5951-5955.
7. Huettel SA, Song AW, MacCarthy G. Functional magnetic resonance imaging. Sinauer Associates, Inc., 1st ed. Cap 7, pp 159-184.
8. Tomasi D, Panepucci H (1999) Magnetic field mapping with the phase reference method. Mag Reson Imaging 17:157–160.
9. Wikswo JP Jr (1989). Biomagnetic Sources and Their Models. Advances in Biomagnetism. Proceedings of Seventh International Conference on Biomagnestism pp.1-18.
10. Peres ASC, Souza VHO, Maziero M, et al. (2009) Vector magnetic field mapping of a Transcranial Magnetic Stimulation coil using Magnetic Resonance Imaging: in vitro and in vivo experiments. Ifmbe Proceedings 25/9:571–574.
11. MRIcro at http://www.sph.sc.edu/comd/rorden/mricro.html
12. Polhemus at http://www.polhemus.com
13. Claron at http://www.clarontech.com/measurement.php
14. Zebris at http://www.zebris.de/english/medizin/medizin-3dmesssysteme.php?navanchor=1010025

15. de Araujo, DB, Araujo D, Rosset S, Wichert-Ana L, Baffa O, et al. (2004) FMRI in epilepsy. Medical Physics, 724, 3-7
16. Stewart H, Mostofsky SL, Rimrodt JGB, et al (2006). A typical Motor and Sensory Cortex Activation in Attention-Deficit/ Hyperactivity Disorder: A Functional Magnetic Resonance Imaging Study of Simple Sequential Finger Tapping. Biological Psychiatry 59:48-56.
17. Brain Voyager at (http://www.brainvoyager.com/)
18. Khol A, et all An integrative transcranial magnetic stimulation mapping, 2006.
19. Lotze M, Kaethner RJ, Erb M, et al. (2003). Comparison of representational maps using functional magnetic resonance imaging and transcranial magnetic stimulation. *Clinical Neurophysiology 114(2):306-312.*

Author: André Salles Cunha Peres
Institute: Dep. Física e Matemática – USP
Street: Av. Bandeirantes 3900
City: Ribeirão Preto
Country: Brazil
Email: andre@biomag.usp.br