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A Multimodal Approach to Trace Motor Cortical-peripheral Pathways Based on Mixed Transcranial Magnetic Stimulation and Diffusion Tensor Imaging Technique

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Abstract. This paper shows how to exactly define the pathways involved in motor activities through the connection of data (registered by using a 3-Tesla Magnetic Resonance Image (MRI) system) as obtained from Transcranial Magnetic Stimulation (TMS) and Diffusion Tensor Imaging (DTI) technique. The pathways are identified by means of deterministic tractography algorithms applied to DTI images acquired with opportune diffusion sequences. In the same anatomical MRI, the DTI images are superimposed to the ones obtained when the TMS is applied to the cortical areas involved in the motor tasks. Our results indicate that by the superimposing of fiber bundles, it is possible to achieve an analysis of anatomical structures not based on the brain atlas obtained by normalization, as usually done from the medical staff. The main advantage is an analysis with no subjective parameters.

I. Introduction

The Diffusion Tensor Imaging (DTI) and the Transcranial Magnetic Stimulation (TMS) are two techniques that allow the study of the human brain with the main objective to verify morpho-functional theories. In most of the published works, these techniques have been used separately, [1],[2] or one technique was used to estimate the other, specifically, DTI was used to estimate the influence of the TMS stimulation in the human brain.[3]

Recently, it was proposed and demonstrated the validity to connect together the information of both studies. For example, interesting results have been achieved for the study of Wallerian degeneration of corticofugal tracts.[4] This paper introduces a procedure based on the combined utilize of TMS and DTI to improve the analysis of the brain pathway reconstructions. We test the approach on white matter fibers pathways, because this reconstruction is an important information during a presurgery plan.[5] In detail, the first step is the reconstructing of a specific white matter pathway by means of the DTI images, the second step is the use of TMS for the delimitation of brains used cortical areas. In the last step, we combine the two results for the final demonstration of our goal.
2. Concepts

2.1 Diffusion Tensor Imaging algorithm

The DTI is a non-invasive method based on Magnetic Resonance Image (MRI) technique to detect the diffusivity of water molecules in tissues. The diffusion is a 3-dimensional process and in most of the cases the molecular mobility in tissues is anisotropic. With the DTI, the diffusion anisotropy effects can be fully extracted, characterized, and exploited, providing details on the tissue microstructures. It is mainly used for the reconstruction of white matter fibers and for in vivo characterization of the microstructural organization of the tissues.[6]

The diffusion weighted images are acquired after the application of magnetic field gradients for a range of different non-collinear directions. For each field gradient, the echo attenuation values (i.e. "intensities") at each voxel can be used to calculate the apparent diffusion coefficient (ADC). The diffusion tensor is computed for each voxel with the set of ADCs, the result is an ellipsoid which models the diffusion profile of water for that voxel. This elaboration is followed by the identification of the directional pattern by means of a post-processing based on tractographic software. In this work, we follow the standards colour meaning for the images where green represents anterior-posterior direction, red represents left-right direction, and blue represents head-foot/dorsal-ventral direction[7].

The use of deterministic algorithm has been performed in order to achieve better result in tracks like the ones we are examining.[7] The DTI analysis, following this pipeline, allows non-invasive reconstruction of white matter fibers bundles in human brains[8].

2.2 Basal Ganglia system

The Basal Ganglia System is composed by four grey matter nuclei (Caudate Nucleus, Putamen, Globus Pallidus and Subthalamic Nucleus of Luys) situated in the deeper part of the brain. They perform very important functions in the activation of voluntary and involuntary movements, creating a lock/unlock system of the motor gesture. According to the current view, they are not fundamental in the conception and elaboration of the motor act, task assigned moreover to the frontal and prefrontal cortices, but the close connections with the surrounding structures make them important in its manifestation[9]. Different study techniques have demonstrated the existence of three different functional circuits (Direct, Indirect and Hyperdirect pathways). They vary according to interneural communication, and provide different effects (excitatory or inhibitory of the motor gesture). Specifically, direct pathway provides an inhibitory signal to the globus pallidus and consequently an excitatory signal to the Thalamus for the motor gesture. Indirect and Hyperdirect pathways both provide excitatory signals to the globus pallidus and consequently inhibitory signals to the Thalamus for the motor gestures.

2.3 Transcranial magnetic stimulation

The TMS is a method of brain stimulation through the intact scalp without causing pain at the surface. The stimulator produces a magnetic field pulse long few milliseconds of the same order of magnitude of the MRI scanner. The magnetic field pulse penetrates the scalp and the skull inducing electrical currents. In other words, the magnetic field 'carries' the electrical stimulus across the barrier of the skull and scalp into the brain. The induced current pulse (long 200 s) has an amplitude of the same order to that produced by a conventional stimulator which is applied to the surface of the brain directly. It is used to activate the axons of neurons in the cortex and subcortical white matter, rather than the cell bodies of cortical neurons (which have a much larger threshold).

The induced electrical stimulus activates a mixture of excitatory and inhibitory neurons beneath the coil, local to the area of cortex under the coil, project axons to or from the site of stimulation.[10] When the TMS is used in the primary motor cortex,[11] it produces muscle activity referred to motor evoked potential which can be recorded on electromyography. When used on the occipital cortex, 'phosphenes' (flashes of light) might be perceived by the subject. In most of the other areas of the cortex, the participant does not consciously experience any effects, but the behaviour should be
slightly altered (e.g. slower reaction time on a cognitive task), or changes in brain activity may be detected using Positron Emission Tomography, Electroencephalography or functional MRI.[12]

3. Procedures and methods

We used a protocol accepted by the ethical committee of research institution IRCCS Centro Neurolesi Lungodelgenti placed in Messina (Italy) to study with DTI-TMS mixed technique the motor skills disorders. The patients were submitted to a 3T Philips Achieve MRI acquisition system with the following sequences, T1 3D weighted sequence, T2 3D weighted sequence, DTI 32 directions echo planar imaging. The complete set of acquisition data has been repeated for three times in order to cover movements issues during the acquisitions and other related artefacts. After that, the patients were submitted to a TMS stimulus involving the motor areas by using an “eight coil” and neuronavigating the motor pathways.

For both MRI and TMS, the DICOM output files were elaborated and converted in order to obtain hdr/img format files where extracting the gradient information contained in the DTI sequences. The gradient vector is a 3D set of coordinates representing the direction along which a magnetic gradient has been applied. Each DTI pulse sequence has a set of gradient vectors associated with it, which is required for the consecutive analysis. Firstly, we clean the data by eliminating MRI noises related to the Eddy currents, after that we constructed Fractional Anisotropy maps by using DTI data and the region of interest on T1. The identification of the area of the study permits to trace the axons using a deterministic approach[13]. The last step of the post-processing is the superimposition of the fiber tractography with the TMS data by means of the support of 3D Slicer[14], this procedure is based on using the repere points obtained with TMS like guide executing task with a rigid registration method fixed on 6 degrees of freedom.

4. Results and discussions:

The procedures described in the previous section were applied to 10 patients. Fig. 1(left) displays the reconstruction of motor pathways, and in term of a global view it can be identified one principal pathway. The sagittal section has been used to better see pyramidal pathway.

The importance in the identification of the connections displayed in Fig. 1 is because corticospinal neurons make direct excitatory connections with alpha motor neurons in the spinal cords. A unique feature of the corticospinal synapse is that successive cortical stimuli produce progressively larger excitatory postsynaptic potentials in spinal motor neurons. This finding is the main mechanism that permits to perform individual movements of the digits, and to isolate movement of proximal joints.[15] The primary motor cortex also contains the representation of motor human homunculus, that is the result of the amount of cortical surface dedicated to a part of the body related to the degree of motor control exercised in that part. Thus, in humans much of the motor cortex is dedicated to moving the muscles of the fingers and the muscles of the face.[16]

To confirm the effective improvement of our technique, starting from a coronal rotated tridimensional image we demonstrated perfectly the direction of pyramidal pathway, during its route into the basal ganglia system, see Fig. 1(right).

In Fig. 2 is shown the VOI corresponding to the Basal Ganglia placed with Caudate Nucleus (violet), Putamen (pink) and Globus Pallidus (fuchsia), the figure indicates the proof of a direct path exactly corresponding with the bundle of our reconstruction. The resolution of this approach gives rise to the possibility to study fiber bundles pathways passing through very small spaces (also few millimeters), such as between Caudate Nucleus and Putamen, minimizing any interferences. We can assert that the cortical area involved was Brodmann Area 4 by using a coregistrated Talairach Brain Atlas, after the normalization process of our image. It is known that every brain atlas, despite totally accepted by scientific community, introduces an error, that is the consequence of method used to obtain the atlas itself as a mathematical average of brains.
The use of TMS permits to identify and to delimit a specific cortical area, evaluating peripheral response induced by a magnetic brain stimulation, by peripheral sensors. Specifically, it is possible to identify: Primary Motor Area, Supplementary Motor Area, Visual Areas and Language Areas. Fig. 3 (left) shows the image resulting from TMS. By using the approach proposed on this paper, we are able to confirm the involvement of Primary Motor Area, previous delimited and also the accuracy of DTI reconstruction of Pyramidal Pathway (Fig. 3 (right)). In other words, with the tractographical algorithm we can offer a more accurate reconstruction, also of white matter bundles going through very small spaces, while with the simultaneous use of TMS we can exactly certify the cortical areas involved in specific morpho-functional connections.

Fig. 1: (Color online) Left: Sagittal section of DTI reconstruction of the Pyramidal Pathway. Right: Coronal rotated tri-dimensional section of the DTI reconstruction of the Pyramidal Pathway.

Fig. 2: (Color online) coronal rotated tridimensional section detail of the path followed by the cortico-spinal tract, with representation of Caudate Nucleus (violet), Putamen (pink) and Globus Pallidus (fuchsia)

5. Conclusions and future works

The approach presented here goes beyond the simple representation of fibers bundles. It provides the evidence of an improvement of the reconstruction method demonstrating that by tracing motor pathways, and in future other pathways like language, can be exactly seen which are the neural structures involved. In other words, this technique is able to remove other unrelated brain structures
from the reconstruction. In the near future, refining of the TMS technique will give rise to the possibility to obtain reconstructions of other brain areas. This DTI-TMS combined approach is promising to be used in the reconstruction of an atlas, being the calibration on a specific brain proving results with reduced implicit error. This will be the basis of an individual based analysis.

![Image](image_url)

**Fig. 3:** (Color online) (left) Axial, sagittal, coronal and tridimensional coronal rotated representation of the TMS reconstruction of Primary Motor Cortex (Brodmann Area 4), (right) demonstration of the integrative method of study for white matter fibers bundles (TMS+DTI)

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References


The aim of this book is to bring the interdisciplinary gap in biomedical engineering education. No single medical device has ever been developed without an extensive interdisciplinary collaboration but, nevertheless, a wide gap still exists between different themes like biomaterials, biomechanics, extracorporeal circulation research, nanotechnology, and safety and regulations.

We have to evitate that, due to the growing complexity, we only gather with and communicate in our own expert groups with their specific research topics. Therefore it is, in my opinion, extremely important that a high quality booking is available to cover these interdisciplinary islands by bringing representative research groups together. The aim of this book is a top review of current research advances in biomedical engineering but on an educational level, so it is also useful for teaching master's students, Ph. D. students, and professionals. The topics range from visualization technology and biosignal and imaging analysis over biomechanics and artificial organs to nanotechnology and biophotonics and cardiovascular medical devices. Meanwhile, each paper has been strictly peer-reviewed by global relevant meetings with internationally representative program committees.

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