UNIVERSITÀ DEGLI STUDI DI VERONA

Dottorato di Ricerca XXVI ciclo – anno 2011
Borsa di Internazionalizzazione
- Scheda progetto –

Scuola di Dottorato di	**Scienze, Ingegneria e Medicina**
Corso di Dottorato in	**Informatica**
Coordinatore	**Prof. Luca Viganò**
Titolo del progetto	Characterization of the cortico-subcortical motor connections plasticity after stroke

Partner straniero:

La lettera di intenti o eventuale strumento convenzionale già esistente dovrà essere prodotta entro e non oltre la fine del mese di marzo 2011.

N.	Denominazione	Eventuale iniziative previste	Sede attività didattica	Periodo di permanenza previsto per il Dottorando*
1.	Signal Processing Institute (LTS5)	☐ attivazione co-tutela di tesi X rilascio certificazione di "Doctor Europaeus"	X SI ☐ NO	6 mesi
2.		☐ attivazione co-tutela di tesi ☐ rilascio certificazione di "Doctor Europaeus"	☐ SI ☐ NO	.... mesi
3.		☐ attivazione co-tutela di tesi ☐ rilascio certificazione di "Doctor Europaeus"	☐ SI ☐ NO	.... mesi
4.		☐ attivazione co-tutela di tesi ☐ rilascio certificazione di "Doctor Europaeus"	☐ SI ☐ NO	.... mesi

* Periodo di permanenza complessivo previsto: minimo 6 mesi, massimo 18 mesi.

Docenti referenti presso gli Atenei partner

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1.	Thiran	Jean-Philippe	Swiss Federal Institute of Technology	JP.Thiran@epfl.ch	+41 21 693 4623
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3.					
4.					

Il Coordinatore del Corso di Dottorato

Data _____

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DESCRIZIONE del progetto (min. 2500 – max 5000 caratteri)

(si richiede di specificare il ruolo dell'Ateneo partner nel progetto di ricerca, al fine di giustificarne il carattere internazionale e l'eventuale compartecipazione finanziaria del partner).

Characterization of the cortico-subcortical motor connections plasticity after stroke

Introduction

Stroke is a major public health issue with high incidence, mortality and morbidity. It represents the third cause of death in the over-65 years population and the first cause of disability. Most patients with brain attack do not achieve complete recovery and the significant disability among survivors has a great impact on healthcare and society (Dombovy, 2004). There is mounting evidence that function recovery after brain injury is largely attributable to adaptative plasticity in the remaining cortical and sub-cortical apparatus (Frost et al., 2003). The term "brain plasticity" encompasses all possible mechanisms of neuronal reorganization: recruitment of pathways that are functionally homologous to, but anatomically distinct from, the damaged ones; synaptogenesis; dendritic arborisation; reinforcement of existing but functionally silent synaptic connections, especially at the periphery of the damaged core (Wall et al., 2002). The proposed project aims at applying advanced MRI techniques to study motor connections plasticity and their structural properties after stroke at the cortical and sub-cortical level.

Rationale

To date, human brain plasticity has been studied using many different techniques including positron emission tomography (PET), electroencephalography (EEG), functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS) and (MEG). Compared to EEG, the other techniques are more accurate tools to create a spatial map of the cortex and to examine changes in structural organization of sensory and motor areas (Landers, 2004). TMS and MEG allow the detection of sensorimotor areas reshaping, as a result of either neuronal reorganization or recovery of the previously damaged neural network. PET and fMRI are both based on the phenomenon that an increase in a brain region's neuronal activity (induced by movement or task execution) is accompanied by concomitant increase in local blood flow and blood oxygenation. However, better insights into stroke recovery are provided by techniques that non-invasively measure brain-network changes after stroke. In this context, Diffusion Tensor Imaging (DTI), has provided with a precious tool to investigate the structural basis of brain network remodeling after stroke. However, DTI, suffering from the limitations of the applied gaussian model performs well in regions where there is only one fibre population but fails in regions with several fibre populations. This aspect could be a fundamental drawback when studying complex phenomena as axonal spouting and/or degeneration after brain lesions like stroke. For the above mentioned reason, a variant of DTI, called Diffusion Spectrum Imaging (DSI), was developed by Wedeen et al. (Wedeen et al., 2005). DSI is a high b-values multidirectional DTI technique, which measures directly the probability density function of displacement of water molecules in the tissue, without needing a superimposed a priori model. Therefore, it can resolve multiple axon directions within a single voxel and thus detect intravoxel white matter fibers crossing as well as white matter insertions into cortex (Tuch et al., 2002), (Tuch et al., 2003) . In addition, DSI can be combined with other imaging techniques like magnetization transfer imaging (MT) in order to characterize both the axonal properties of the studied networks and to define their myelin content. This is particularly important, if considered that new fiber connections originating from axonal sprouting processes are supposed to be surrounded by a thinner myelin layer than fibers pre-existing the stroke insult. MT is a noninvasive quantitative MR imaging strategy that is able to detect subtle or occult alterations in normal-appearing brain tissue in neurologic disorders. The MT effect results from macromolecular proteins and lipids in myelin membranes, which are undetectable on conventional T1- and T2-weighted brain images because their signal intensity decays rapidly. MT selectively saturates the macromolecular bound protons to strategically probe tissue integrity at the microstructural level. The MT ratio (MTR) is computed on the basis of 2 serially acquired images; 1 with MT saturation and 1 without. The images without MT saturation represent PD-weighted images and in combination with the T1 weighted images the opportunity arises to synthesize images with further improved structural details (Filippi and Rocca, 2006).

Methodology

The proposed project aims at applying advanced MRI techniques to study motor connections plasticity and their structural properties after stroke at the cortical and sub-cortical level. Our hypothesis is that diffusion imaging will show brain network changes over time that correlate with the degree of the recovery. Understanding the modifications of connectivity between functional brain areas after stroke will allow a precise reconstruction of cerebral plasticity mechanisms and tissue architecture changes after a focal injury, opening new perspectives for future virtual reality rehabilitation programs and robot-assisted movement therapy. The proposed approach consists in analyzing the DSI data in both a pathological and a control group of subjects to derive the fiber network (white matter). To this end, novel algorithms will be developed for both deriving the ODF functions from the raw data and to reconstruct the fibers in the region of interest. An automatic segmentation method will be designed to this end. Then, the validation of the proposed system will be performed by assessing the reproducibility of the results as well as its dependency on contextual factors like signal to noise ratio, number of gradients, etc.

Overall goal

The overall goal of the project is to analyze the existing DSI data from a longitudinal study in 12 patients and 12 controls to study the connections between motor cortical areas and the subcortical nuclei, in order to obtain a reproducible measure of plasticity of the cortico-subcortical network after stroke.
Aim 1: To set up a method to evaluate the connectivity matrix between cortical motor areas and cortical motor areas and subcortical nuclei involved in motor control.
Aim 2: To correlate cortico-cortical and cortico-subcortical motor network changes over time with the degree of rehabilitation-induced functional recovery evaluated with the NIHSS (National Institute of Health Stroke Scale), FIM (functional independence measure) and modified Rankin scores.
Aim 3: To combine the data about the remodeling of the connections between the motor cortical areas with the data obtained from the analysis of the cortico-subcortical motor network.

Objectives

1. **Cortical motor area and sub-cortical nuclei segmentation:**

To allow bias-free definition of seed and target areas unaffected by subjective judgments about anatomical correspondences, we will perform automated cortical and sub-cortical segmentation and labeling in subject-specific native space. High-resolution MPRAGE images will be used for anatomical reference. From the anatomical T1 weighted images, a parcellation consisting of 33 cortical regions of interest (ROIs) will be performed. Motor areas will be further segmented in dorsal (PMd) and ventral (PMv) premotor cortex; primary motor cortex (M1) and supplementary motor cortex (SMA) according to Mayka et al. (Mayka et al., 2006). For the sub-cortical nuclei, as suggested previously (Behrens et al., 2003), (Johansen-Berg et al., 2005), we will use all voxels in the basal ganglia structures and motor cortex to define seed points and target areas. An automated segmentation will be performed on high-resolution T1-weighted scans in subject specific native space using the Freesurfer software. The structures caudate, putamen, pallidum, and thalamus were considered as separate seed areas.

2. **Tractography of the cortico-subcortical motor network:**

Orientation density functions (ODFs) will be reconstructed from raw data by designing and implementing an ad-hoc algorithm. Tractography will then be performed. The connectivity between two ROIs will be measured and variation of fiber density in the 2 scans will be evaluated using suitable metrics in order to assess the reproducibility if the algorithm. In addition, the properties of the myelin characterizing the connections of interest will be evaluated through the magnetization transfer ratio (cf introduction page 1).

3. **Statistical analysis and clinical validation**

Statistical comparison of different quantitative measurements of connectivity among acute and chronic stroke phase in the patients and the controls will be performed. A correlation between connectivity modification during the follow-up and functional motor score in the acute and chronic phase after stroke will be performed.

Profile and role of the partner institution

EPFL is one of the leading institutions in Europe in many disciplines, including signal and image processing and life sciences. The EPFL partners are Prof. Jean-Philippe Thiran and Dr. Cristina Granziera.
Prof. Jean-Philippe Thiran is the head of the Signal Processing Lab. 5 (LTS5). Prof. Thiran leads the image processing group at EPFL and closely collaborates with several and hospital and research centers working in the field (CHUV, CHUG, CIBM-EPFL). Prof. Thiran is an internationally know expert in the area of medical imaging, in particular tractography. In fact the first algorithm aimed to the fibers reconstruction has been developed in his laboratory and is still the reference approach in the state-of-the-art. His contribution is therefore essential in order to succeed in this project. Prof. Thiran is an expert in the field of Diffusion MRI registration in the pre-clinical scenario, and his contribution is essential for the success of the project.
Dr. Granziera is a certified neurologist MD PhD with strong research experience in applied clinical magnetic resonance imaging. Her research interests are focusing on neuroimaging methods and their clinical application, above all concerning mechanisms of cerebral plasticity in stroke.
She has internationally recognized experience in the field and has the clinical and the scientific expertise to directly supervise the work and contribute to the achievement of the major goals of the project.

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