**Study of the spinal cord and brainstem functional activation in response to a controlled motor task using fMRI**

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Keywords: (Spinal cord, brainstem, isometric motor task, fMRI, motor pathway, physiological artefacts)

Functional Magnetic Resonance Imaging (fMRI) has become one of the most powerful tools in neuroscience research, with fMRI based on BOLD (Blood Oxygen level dependent) contrast [1,2] having gained a primary role in the study of human brain, both for the characterization of its activity in physiological conditions and playing an increasing role in clinical practice. Moreover, several fMRI studies of the human Spinal Cord (SC) and Brainstem in response to thermal, sensory, motor and painful stimuli have been reported [3-5], and substantial efforts have been devoted to develop appropriate methodologies [6]. Nonetheless, the application of fMRI to the SC and Brainstem remains confined to a few laboratories,
Brainstem and SC fMRI may be of immediate application in neuroradiology, specifically for the assessment and follow-up of spinal injuries, pain, and neurodegenerative diseases, as well as for the development and evaluation of new therapies. Indeed, a non-invasive tool capable of monitoring neural function, and thus complementing the available structural information, is crucially needed in these fields.
Preliminary studies of people with SC injury and multiple sclerosis have demonstrated altered activity in the brainstem and in the SC depending on the injury severity or disease state [7,8]. From the clinical perspective however, it is important to recognize that SC fMRI has been demonstrated for group analyses but there are still sources of variability or uncertainty that count against its use for individual studies. Once these sources of variability and errors are characterized and understood, it is expected that methods can be adapted to optimize the sensitivity of SC fMRI in the study and assessment of individuals.
The vagaries of the SC and brainstem fMRI activation patterns and of their characteristics can be explained, at least in part, by a poor control of physiological noise [9] and the limited overall quality of the functional series, due to geometrical distortion, signal loss, and poor contrast to noise ratio. The relevant solutions can be found in the combination of optimized experimental procedures at acquisition stage, and well-adapted procedures in post-processing. In this framework, we have developed an analysis protocol to study the motor pathway activation on spinal cord (SC) and Brainstem, aimed to solve some of the problems related to physiological and movements artifacts in SC and Brainstem fMRI. The study, performed in healthy subjects, was carried out using an ad hoc isometric motor task.
fMRI data were acquired using a neurovascular coil array, on a 3T scanner (Achieva, Philips Medical Systems, Best, The Netherlands). Healthy subjects (15 for SC fMRI and 7 for Brainstem fMRI) performed a block-designed motor task. Subjects were asked to press a force-sensitive device between their first and second finger, until a visual feedback confirmed that the target force was reached. Each run included alternating 30s rest and motor task epochs, during which target forces of either 10%, 20% or 50% of the subject's own maximal sustained force (MSF) were required in a pseudorandom order. The actual developed force was digitized and recorded. For each subject, 3 gradient-echo EPI runs were acquired (TE=25 ms, flip angle 75°, TR=2500ms, 20 parasagittal slices, 1.5 mm thick). fMRI data underwent optimized image pre-processing protocol (RETROICOR [9] and CompCor physiological noise reduction [10], masking, motion correction, slice timing, smoothing). (figure1)

In particular, we review two model-based approaches to remove the physiological noise, that rely on externally acquired respiratory and cardiac signals (RETROICOR) as well as data-driven approaches (ComCor) that estimate and correct for noise using the data themselves and without the need of recording physiological parameters. Subject specific activations were obtained by using a statistical analysis based on a general linear model (GLM). A GLM fitting was realized by using realignment parameters, denoising components and force parameters as confounding variables and a t-test was carried out by choosing as threshold a p_value of 0.001. In this way, voxels whose p-values are below 0.001 are color-coded to signify that they contain significant task-related signal. Custom Matlab routines incorporating spm8 and afni functions were used. We found a congruent task-related fMRI response in SC and Brainstem networks. Brainstem itself is an intermediate center of the motor system, receiving input from the cerebral cortex and sending pathways to spinal cord circuits. Thus, Brainstem data are of support for the study of the spinal cord activation.
Positive signal changes were mostly detected at C4–C7 vertebral levels (figure2A) and in the Brainstem and cerebral cortex (fig2B).

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The Italian Ministry of Health Young Researcher Grant 2013 (GR-2013-02358177) is acknowledged for financial support

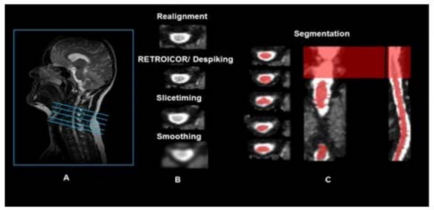


Figure 1: Preprocessing protocol_ Script Development for the data analysis *ad hoc* for the spinal cord and brainstem

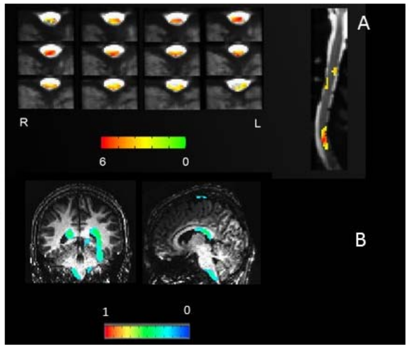


Figure 2: Activation maps of representative subjects (A) at lower cervical level and in the brainstem and in the cortex (B) during a graded isometric force