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Functional magnetic resonance imaging on spinal cord

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Summary. — Functional magnetic resonance imaging (fMRI) is a powerful technique for the functional investigation of the brain and spinal cord. Although some progress has been recently made, many issues still need to be solved for fMRI to be used for clinical and preclinical investigations of the spinal cord. Currently, we are developing new strategies to apply fMRI on the spinal cord of healthy subjects and in patients. These strategies include acquisition and data analysis protocols for the reduction of physiological noise (due to cardiac pulse and respiration), which is the main reason for the low signal-to-noise ratio observed in functional series of the spinal cord.

1. – Description: State of the art

Magnetic Resonance Imaging (MRI), based on the phenomenon of nuclear magnetic resonance, produces images of the human body with excellent soft tissue contrast, allowing to distinguish between grey and white matter and brain lesions. Since MRI involves no ionising radiation, the risks to the subject are minimised. In particular, functional MRI (fMRI) has become one of the most powerful tools for neuroscience research, and yet its use is limited to studies of the brain, with relatively few exceptions [1, 2]. It has been demonstrated that important neuronal activity can be identified in the spinal cord (SC) using spinal fMRI. Previous studies have shown that BOLD-based fMRI is feasible in the SC at both 1.5 T and 3 T, and the detected activation areas have good localization at the segmental level [3, 4]. In particular, areas of activity in the cervical and lumbar regions have been measured with high sensitivity and reliability, in response to thermal, sensory, motor and painful stimuli [2, 5, 6]. Although substantial advances in knowledge have arisen from these studies, the poor reproducibility of the activation patterns and their characteristics —in terms of amplitude and location— have been invoked as significant concerns by several authors [7-9]. In the clinical arena, spinal fMRI has been applied to the study of injured SCs. Spinal fMRI is indeed able to detect a neuronal response in the SC caudal to the injury site during both active and passive lower limb movement tasks, and in response to a noxious stimulus, even when subjects could not feel

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the stimulus. Thus, spinal fMRI is useful for revealing areas of impaired and preserved activity in SC-injured patients. In addition, patients' studies provide further evidence of response sensitivity to pathological changes, suggestive of a neuronal basis for the SC activity. Studies of people with SCI and multiple sclerosis (MS) have demonstrated altered activity in the SC depending on the disease state [5, 6, 10]. However, obtaining BOLD images of the SC activation remains a technical challenge. The main difficulties encountered in spinal fMRI, like for other MRI techniques, arise from the small size of the SC, from the presence of large movements due to cardiac pulsation and respiration, and from magnetic field inhomogeneities around inter-vertebral disks [9, 11, 12] which induce significant susceptibility artefacts. In addition, SC motion and the flow of cerebrospinal fluids (CSF) are thought to further confound the analysis, and therefore the interpretation of functional data [7]. Thus the vagaries of the SC fMRI activation patterns and of its characteristics can be explained, at least in part, by a poor control of physiological noise [11] and the limited overall quality of the functional series, due to geometrical distortions, signal loss, and poor contrast-to-noise ratio. However, if these challenges could be overcome, SC fMRI may be of immediate application in the clinical framework. In particular, the study of the SC system may be of immediate and fruitful application in the treatment of SC injuries, pain and neurodegenerative diseases (*e.g.*, multiple sclerosis). The application of fMRI to the SC requires specific modifications to the conventional brain fMRI methodology, with optimized experimental procedures at the 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 the SC, aimed at solving some of the problems related to physiological noise and movement's artifacts in SC fMRI.

2. – Methods

In this study, we performed a controlled motor task (graded isometric force) of the right dominant hand. fMRI data were acquired using a neurovascular coil array on a 3T scanner (Philips Medical Systems, Best, The Netherlands). 15 healthy subjects performed a block-designed motor task. Subjects were asked to grip a force-sensitive device, until a visual feedback confirmed that the target force was reached. Each run included alternating 30 s rest and motor task epochs, during which target forces of either 20%, 40% 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, 4 gradient-echo EPI runs were acquired (TE/TR = 25/3000 ms, flip angle = 80 °, FOV = 140 × 140 × 143 mm; acquisition Matrix = 96 × 96 × 34 (axial), resolution = $1.5 \times 1.5 \times 3$ mm). Anatomical reference images were acquired using T1-weighted gradient echo sequence (TE/TR 5.89/9.59 ms, flip angle 9°, FOV = $240 \times 240 \times 192$ cm, resolution $0.75 \times 0.75 \times 1.5$ mm). fMRI data underwent an optimized image pre-processing protocol; we implemented and optimized a scfMRI data analysis pipeline based on a custom Matlab routine incorporating SPM [13], AFNI [14] and FSL [15] functions (RETROICOR [16], masking, motion correction, slice timing, and smoothing).

3. – Main results of the fMRI data analysis process

By combining optimized software packages, our data analysis pipeline substantially improved the otherwise problematic detection of task-activated voxels at group level, even with a relatively small number of subjects. A key reason for such good statisti-

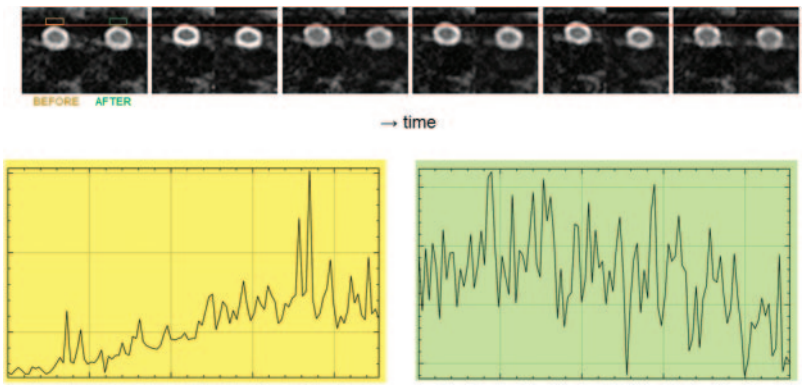

Fig. 1. – Effect of the realignment: A representative subject is shown before and after the realignment.

cal power is the algorithm for motion correction. The data were motion corrected by a rigid-body transformation, realigning all of them to the mean image. Specifically, the realignment step corrects for motion effects across and within sessions of an individual subject. This routine realigns a timeseries of images acquired from the same subject using a least-squares approach and a 6-parameter (rigid body: 3 translational + 3 rotational parameters) spatial transformation (fig. 1). Realignment is necessary because the fMRI analysis is based on signal differences induced by different stimulation conditions, therefore signal must be denoised from unrelated effects such as subject's movements. Then, a RETROICOR [16] based routine (retrospective correction technique operating in the image domain) was used for physiological noise reduction, including respiratory and car-

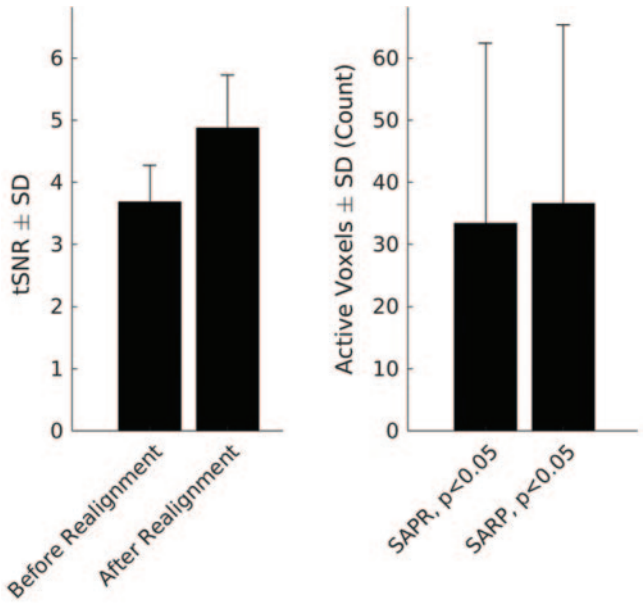

Fig. 2. – tSNR before and after the realignment (left panel). Comparison between the standard pipeline and our protocol for the spinal cord (right panel).

diac harmonics up to the 2nd order, respiration volume per unit time (RVT) and one interaction term, as well as the relevant first derivatives [7]. Voxel time courses were despiked on a voxel-by-voxel basis, and slicetiming correction was applied. Finally, data were spatially smoothed with a Gaussian kernel of $6 \times 6 \times 6$ mm^3 and temporal high-pass filtered (0.022 Hz). To test the robustness and reliability of results in more subjects we evaluated the denoising step performance before and after the realignment by calculating the temporal signal to noise ratio (tSNR) gain for each subject (see fig. 2, left panel). The positive value of tSNR between realigned and not realigned data (gain of 32%) is signaling that the denoising strategy is efficient for all the subjects. In fig. 2 (right panel) we report the gain obtained considering the number of active voxels in the standard analysis pipeline respect our pipeline, considering the RETROICOR (gain of 8%) These results confirm the solidity of the preprocessing pipeline.

4. – Conclusions

Our data analysis pipeline, combining purposely developed and optimized software packages improved the otherwise problematic detection of task-activated voxels at group level with SC fMRI. An important determinant for such good statistical power is the realignment, specifically applied for the data analysis of the spinal cord fMRI. The present approach supports the usefulness of optimized pipelines in human SC fMRI studies. Overall, the present work provides an optimized methodological tool to move the field of SC fMRI forward in basic research and towards forthcoming applications in the clinical practice.

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