Development of a Pipeline for the Analysis of Human Spinal Cord fMRI Data Series

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Spinal cord functional magnetic resonance imaging (scfMRI) is a promising tool for the non-invasive assessment of human spinal cord function following traumatic injury or neurodegenerative disease. In spite of decades of research, the utilization of scfMRI in clinical settings has been hampered by technical and methodological limitations related to spinal cord motion (due to respiratory and cardiac-driven pulsation of spinal arteries and cerebrospinal fluid), poor spatial resolution, image distortions and signal loss (due to surrounding structures with different density, e.g. vertebrae and intervertebral discs). As a result, the development of data analysis methods and relevant software has been almost exclusively restricted to brain fMRI. The aim of the present study was to contribute filling this gap by implementing and optimizing a pipeline for scfMRI data analysis. We combined existing software libraries commonly employed for brain fMRI with further developments of Spinal Cord Toolbox (SCT). In particular, we used (i) custom-made Matlab (The MathWorks, Inc.) implementation of RETROICOR for cardiorespiratory rhythms correction using peripheral measures of respiration and cardiac pulsation; (ii) Statistical Parametric Mapping (SPM12) for slice timing as well as first- and second-level statistical analysis; (iii) Analysis of Functional NeuroImages (AFNI) and FMRIB Software Library (FSL) packages for intermediate image preparations and for testing purposes; and (iv) SCT for realignment (motion correction, hereafter MoCo), longitudinal spatial smoothing, segmentation and vertebral labeling as well as normalization (registration) to the PAM50 spinal cord template . The pipeline was applied to functional (gradient echo EPI) images acquired on a Philips Achieva 3T MR scanner using a neurovascular coil array with the following sequence parameters: TE/TR = 25/3000 ms, resolution = 3x1.5x2 mm (sagittal) or 1.5x1.5x3 mm (axial). Anatomical reference images were acquired using T1-weighted gradient echo sequence (TE/TR 5.89/9.59 ms, flip angle 9°, FOV = 240x240x192 cm, resolution 0.75x0.75x1.5mm). Images were acquired from 46 healthy subjects (all right-handed with a mean age of 35 years) while performing a block-design isometric motor task (hand-held force transducer and a visual feedback system) consisting of 5 cycles of 30s/30s rest/task epochs. In Figure 1 we report a representative example of the quality of segmentation and normalization to PAM50 template reference performed with SCT on anatomical images for guidance in manual vertebral labeling of EPI images (see below). The latter underwent the complete data analysis pipeline. We applied the pipeline to both axial and sagittal images to examine the impact of different acquisition directions on the physiological noise removal. Particularly, we investigate the performance of the de-noising strategy by evaluating the temporal Signal to Noise Ratio (tSNR). The variability of tSNR increase was assessed by computing the relative Coefficient of Variation (CV). We found that the SCT MoCo algorithm led to an increase in image tSNR of about 16% and 41% for sagittal and axial images, respectively, thus significantly outperforming available computational tools such as AFNI 3dWarpDrive (Figure 1b). Furthermore, compared with AFNI SCT MoCo substantially reduced the variability of the relative tSNR change among subjects (by 15% and 7% for sagittal and axial images, respectively). The spatial distribution map of the tSNR gain indicates that the increase is restricted to the cord and it is rather uniform across it. The segmentation and normalization of EPI images to PAM50 allowed for robust 2nd-level analysis, as evidenced by the activation maps (threshold at $p<0.001$ uncorrected), which showed consistent ipsilateral active voxels with none (sagittal) or few (axial) significant voxels outside the cord (Figure 2).Our data analysis pipeline combining recently developed and optimized software packages substantially improved the otherwise problematic detection of task-activated voxels at group-level, even with a relatively small number of subjects. Important determinants for such good statistical power are the algorithm for motion correction specifically developed for the spinal cord and the normalization to the reference template, which are two major features of SCT. Although further benchmarking is necessary to test the robustness and reliability of results in more subjects, the present approach supports the usefulness of optimized pipelines in human scfMRI studies. Overall, the present work provides an optimized methodological tool to move the field of scfMRI forward in basic research and towards forthcoming applications in the clinical practice.

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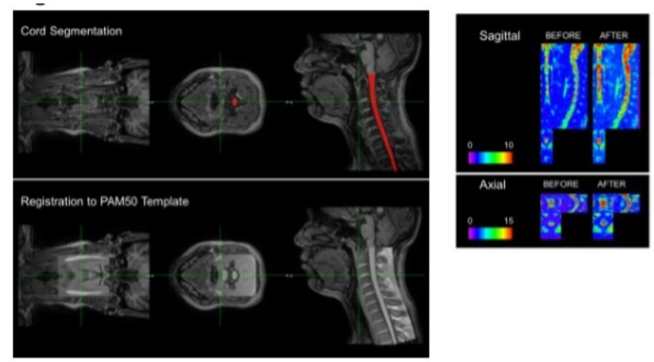

Figure 1: (a) Representative tSNR maps from a healthy subject before and after SCT fMRI MoCo (left)ical T1-weighted image covering part of the brain and cervical spinal cord. This step guided the segmentation of EPI images for manual labeling of C2/C3 vertebral disc.(b) Representative tSNR maps from a healthy subject before and after SCT fMRI MoCo

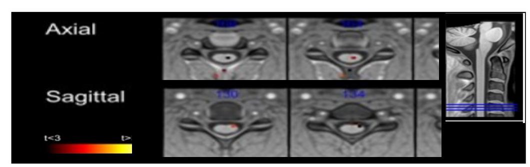

Figure 2: Activation maps after group-level analysis performed in the PAM50 template space.