Investigating functional-structural correlations in the cervical spinal cord in vivo

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TARGET AUDIENCE: Clinicians interested in spinal functional MRI (fMRI) and Diffusion Weighted Imaging (DWI). Physicists working on DWI or fMRI data analysis in the spinal cord.

PURPOSE: To investigate correlations between functional and diffusion data in the cervical spinal cord of healthy controls using a multimodal approach.

INTRODUCTION: The literature about spinal cord studies is very limited in comparison with what is published in the brain. However, the recent growing interest in investigating spinal cord function and white matter microstructure using MRI means that one has to overcome several technical issues ***[1]***. Moreover, images obtained using different sequences and parameters make it difficult to evaluate and combine results from different techniques, especially in the spine as it is very sensitive to artefacts. Here we propose a protocol in which inherently coregistered structural and functional images are acquired, aiming at making it easier to investigate possible functional-structural correlations.

MATERIALS and METHODS: **Acquisition** - Ten healthy controls (HCs; 6 male; mean age +/- SD = 35.3 +/-7.2), all right handed, were scanned with a protocol comprising 2 fMRI sessions and one DWI scan performed with a 3T scanner (Philips Achieva TX, Best, Netherlands) and a 16 channel neurovascular coil. A localized sensory stimulus was applied to the C6 dermatome over the palmar surface of the thenar eminence of each volunteer using an MR-compatible custom-built rotating brush. For each volunteer the two hands were stimulated during separate and consecutive functional sessions. The block design comprised 10 epochs of rest alternating with 10 of stimulus for a total of 200 volumes. All scans were acquired using the Spin Echo ZOnally-magnified Oblique Multislice EPI (SE-ZOOM-EPI) sequence ***[2]***. For functional scans the following parameters were used: TR=3600ms, TE=30ms, voxel size=1.19x1.19x4mm^3, FOV=76x48 mm^2 and acquisition matrix=64x40, SENSE factor=2. Nine slices were acquired axially to the cord and the field of view spanned from C5 to C7. Physiological traces were recorded for each subject using a pulse oximeter and a respiratory belt. The same SE-ZOOM-DTI sequence was used for diffusion images matching the fMRI protocol, using the same geometrical prescription and imaging parameters mentioned above, apart from the following: TE = 52 ms and TR = 9 RRs (cardiac gated). The DWI protocol comprised 30 b = 1000 s mm^{-2} DWI volumes with gradient directions evenly distributed over the sphere and 3 non–DWI (b = 0) volumes. Neck padding was applied to minimize involuntary movements. **Data analysis** - TSNR was calculated on a resting state scan. The functional analysis pipeline included: using DRIFTER toolbox ***[3]***, implemented in SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/), to reduce signal variability from cardiac and respiratory noise; 2D-realignment with FSL software (FLIRT) ***[4].*** CSF regressors from CSF masks drawn on the mean image of each subject were also added to the GLM Results are reported with p<0.01 (uncorrected) threshold significance. Only activations localized in the 6 central slices covering the whole C6 segment (with the upper slice at the bottom of C5 segment and the lower slice at the top of C7 segment) were considered. For each subject, the number of suprathreshold voxels was counted. A lateralization index (LI) was defined as: LI=number of ipsilateral/contralateral activated voxels. Similarly, LI was evaluated for left (LI_L) and right (LI_R) stimulus too. Mean signal changes were calculated. The Camino toolbox ***[5]*** was used to calculate fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (MD) and axial diffusivity (AD) and means were assessed in the ROIs drawn using JIM 6.0 software (Xinapse system, www.xinapse.com) on the b0 images of each volunteer. These ROIs outlined: whole cord (WC), right hemisphere (RH), left hemisphere (LH) and posterior column white matter (PCWM). Statistical analysis was performed with SPSS software, using the Paired-Sample T test to compare means of structural and functional indices and the Spearman's rank correlation coefficient for correlations. **RESULTS:** TSNR was 15+/-3. Neuronal activity was detected within the spinal cord of all subjects for both right and left hand stimulation ***(Fig.1)*** and, in the majority of cases, ipsilateral activity was dominant ***(Tab.1)***. Average time courses of all activated voxels for both right and left task were checked to correlate with the paradigm. LI values and number of activated voxels (ipsi- and contra-laterally) are reported in ***Tab.1*** for each subject. Mean signal enhancement calculated was: Right Hand: 3.74 +/- 1.29 % and Left Hand: 3.30 +/- 1.13 %. Means and standard deviations of all the structural parameters are reported in ***Tab.2***. Neither signal enhancement for right and left hand stimulation nor lateralization indexes LI_L and LI_R showed statistically significant difference between side. No significant correlation was found between LI and the FA, MD, RD and AD values for any ROIs .

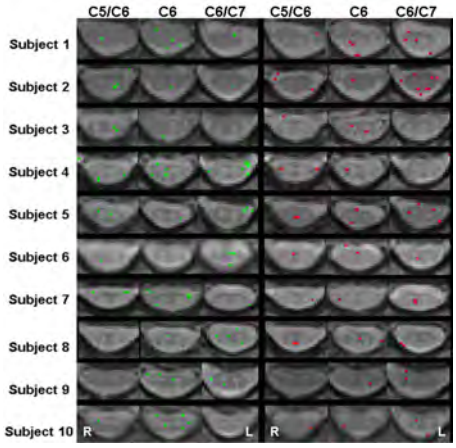

Fig.1: Spinal activity overlaid on the mean image for 3 slices of each subject. Results concerning left (in green) and right (in red) hand stimulation are shown.

	R_ipsi-contra	L_ipsi-contra	LI_R	LI_L	LI
Subject 1	8 – 6	6 – 3	1.33	2.00	1.56
Subject 2	7 – 4	7 – 2	1.75	3.50	2.33
Subject 3	3 – 4	5 – 1	0.75	5.00	1.60
Subject 4	6 – 2	8 – 7	3.00	1.14	1.56
Subject 5	6 – 5	5 – 2	1.20	2.50	1.57
Subject 6	2 – 1	2 – 1	2.00	2.00	2.00
Subject 7	3 – 1	2 – 1	3.00	2.00	2.50
Subject 8	3 – 3	3 – 3	1.00	1.00	1.00
Subject 9	2 – 2	3 – 2	1.00	1.50	1.25
Subject 10	3 – 1	3 – 3	3.00	1.00	1.50
Mean +/- std			1.80 +/- 0.90	2.16 +/- 1.26	1.69 +/- 0.46

Tab.1: Number of both ipsi- and contra- laterally activated voxels for right (R_ipsi-contra) and left (L_ipsi-contra) hand stimulation; values of lateralization index for right (LI_R) and left (LI_L) hand stimulation and for both of them (LI) for all subjects. Means and standard deviations are reported too.

	FA	RD (x10^{-3} mm^2/s)	AD (x10^{-3} mm^2/s)	MD (x10^{-3} mm^2/s)
WC	0.65 +/- 0.03	0.56 +/ -0.06	1.86 +/- 0.07	0.99 +/- 0.05
RH	0.66 +/- 0.03	0.55 +/- 0.06	1.85 +/- 0.08	0.98 +/- 0.05
LH	0.65 +/- 0.03	0.58 +/- 0.07	1.86 +/- 0.07	1.01 +/- 0.05
PCWM	0.76 +/- 0.04	0.43 +/- 0.07	2.09 +/- 0.14	0.98 +/- 0.06

Tab.2: Means and standard deviations of: fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD) and mean diffusivity (MD). Values refers to the ROIs drawn over: whole cord (WC), right hemisphere (RH), left hemisphere (LH) and posterior column white matter (PCWM).

CONCLUSION and DISCUSSION: We proposed a protocol for functional and structural assessment of the spinal cord with geometrically matched sequences. The methods applied in this study allowed detection of task-related neural activity in the spinal cord of all subjects. No functional-structural relationship was found for healthy controls. Nevertheless, the multimodality of this study and its geometrically matched functional and diffusion protocols have the potentiality to detect functional-structural changes in patients affected by spinal damage, as shown in a recent preliminary study performed on MS patients ***[6]***.

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