Quantification of changes in resting state connectivity in monkey SI cortex following spinal cord injury

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Purpose: Resting state functional MRI signals have previously been used to identify both large and fine scale functional connectivity in brain networks, including the somatosensory (SI) cortex of monkeys [1]. Spinal cord is also a vital component of the central nervous system and is primarily responsible for transmitting sensory and motor information to and from the brain. Disruptions of the proper functions of the spinal cord following injuries are known to also affect the integrity and functions of somatic sensory networks at both the spinal cord and the brain levels [2, 3]. This study aims to determine whether the disruption of afferent inputs from the cervical spinal cord alter the fine - scale functional connectivity between sub-regions of SI cortex. Taking advantage of the high contrast and signal to noise ratios at ultra-high field (9.4T), we performed an ROI based analysis of resting state BOLD MRI signals obtained in pre- versus post- lesion conditions in anesthetized squirrel monkeys to quantify the changes in the inter-regional functional connectivity among sub-regions of the SI cortex.

Methods: Three squirrel moneys were included in this study. All scans were performed on a 9.4T, 21-cm bore magnet Varian INOVA MR imaging spectrometer, using a 3cm surface transmit-receive coil, positioned over the primary somatosensory cortex (S1). The functional EPI data (TR = 1.5s and TE = 16ms) were acquired with an in plane resolution of 547x547 μm^2 (64x64 image matrix) in 2 mm thick slices. High resolution $T2^*$ weighted anatomic images (68x68µm, 512x512 image matrix) were acquired with the same geometry. To map the digit regions in S1 cortex, an alternating tactile stimulus (8 Hz vibration, 30s off/on) was presented on distal finger pads. Resting state EPI data were acquired before the stimulation runs using an identical sequence, acquiring 300 volumes of resting state images. The functional data were slice time and motion corrected. The fMRI signal time courses were regressed with slice wise motion correction parameters and the muscle signal derived from a principal component analysis. Three major components from each masked voxel in muscle areas associated with the major eigenvectors were used as regressors, which roughly accounted for at least 70% of the cumulative variance. Seeds were identified in five regions of areas 3a, 3b, 1, 2 and a control in three different conditions: pre-lesion, post-lesion (a) and post-lesion (b). Both the stimulus driven and resting state analyses were performed using in house software compatible to SPM5/8.

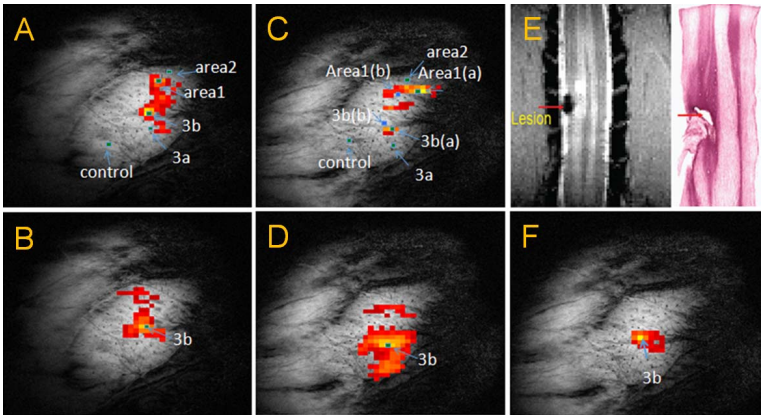

Fig. 1. Spinal cord injury altered the resting state functional connectivity of S1 subregions (areas 3a, 3b, 1 and 2). (A,C) Stimulus evoked BOLD activation map in pre- and post- lesion conditions in one monkey (thresholded at $r > 0.3$, $p < 0.001$). (B, D, F) Correlation maps of the area 3b seeds in pre- (C) and post-lesion (D, F) conditions (thresholed at $r > 0.6$, $p < 0.001$). (E) Left: sagittal MT contrast image shows the lesion as a black hole. Right: corresponding spinal cord tissue section stained with the CTB.

Results: In pre-lesion normal conditions, a seed in area 3b (digit region, the yellow voxel in the bottom of the image in Fig 1A) showed strong correlations with its immediately adjacent voxels and voxels in area 1, where the corresponding digit showed the strongest correlation (see the yellow voxel in the top portion of the image). After a spinal cord injury that disrupted over 90% of the ascending afferents, the activation map to identical stimuli altered (Fig 1C), compared to the pre-lesion activation map (Fig 1A). The foci of digit responses shifted somatotopically as we have previously shown [2]. Using these two different stimulus-evoked activation maps, we identified three sets of seeds for ROI based resting state analysis. All the seeds are indicated by small green boxes in Fig 1A&1C. The correlation map of the seed in area 3b (Fig 1B) in normal conditions appeared to be quite similar to the stimulus activation map (Fig 1A). However, the correlation map of the area 3b seed at a shifted location (identified as the post-lesion activation peak) (Fig 1D) looked similar but somatotopically shifted toward the area 3b-area 1 border, just as the activation map (Fig 1C). In contrast, the area 3b seed at the pre-lesion location (Fig 1E) showed only local correlation with reduced connectivity to the rest of the S1 subregions, which was quite different than the pre-lesion map. At the group level, comparisons between the pre- and post- lesion (a) conditions showed that the pair-wise correlation strengths (z scores) altered after the spinal cord injury (Fig 2). Across animals, the correlation strength varied drastically in the injury condition (green bars in Fig 2). The inter-ROI distribution of z-scores in post lesion data had larger variation and lower median value in comparison to the corresponding pre-lesion data pairs, although ROI-control z-scores possess similar distributions. Different trends of changes were also present for different ROI pairs. There was an overall decrease in the connectivity between area 3b and the rest of S1 subregions and the control (the first three and the 5th column groups in Fig 2). But, the connectivity between area 1 and area 2 appeared to be increased (the 4th column in Fig 2).

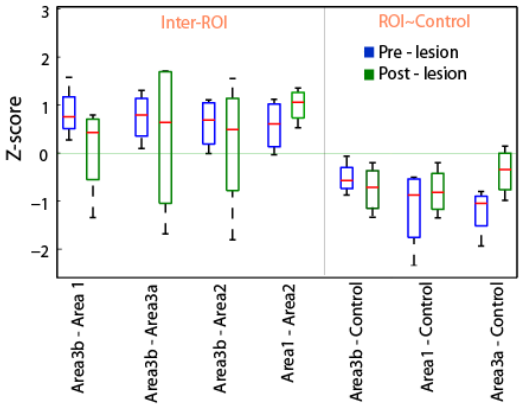

Fig. 2. Whisker box plots of the distribution of the z-scores of the inter-ROI correlation between sub-regions within the SI cortex and subregion - control region. Red lines present median values.

Discussion and conclusion: Following a spinal cord injury, we observed somatotopically shifted stimulus activation maps and resting state functional connectivity maps in SI cortex. Inter-regional correlation strengths altered in different directions. The quantitative group analysis of the functional connectivity patterns of BOLD signal showed comparable differences in the correlations of inter-S1 subregions vs. S1 subregions-control pre- and post- injury conditions as have been reported previously [3]. We will next examine the relationships between the reduced resting state functional connectivity and the behavioral deficit in a larger sample size of animals.

References: [1] Wang Z. et al. (2013): The relationship of anatomical and functional connectivity to resting-state connectivity in primate somato-sensory cortex, Neuron, 19;78(6):1116-26. [2] Chen et al. (2012): Dynamic reorganization of digit representations in somatosensory cortex of nonhuman primates after spinal cord injury. J of Neursci, 32(42):14649-63. [3] Mishra et al. (2014): Functional connectivity of intrinsic networks in monkey spinal cord revealed by resting state BOLD signals at 9.4T. ISMRM14, Milan: 3813.