Reproducibility of resting state spinal cord networks at 7 Tesla

Robert L Barry[1,2], Baxter P Rogers[1,2], Seth A Smith[1,2], and John C Gore[1,2]

[1]*Vanderbilt University Institute of Imaging Science, Nashville, TN, United States,* [2]*Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN, United States*

Introduction

We recently reported utilization of functional magnetic resonance imaging (fMRI) at 7 Tesla to detect resting state correlations within the gray matter of spinal cords, suggesting the potential for using high field fMRI to assess functional connectivity in the human spinal cord [1]. For practical applications in monitoring changes in the spinal cord, the within-subject reproducibility of these measurements needs to be quantified. Thus, the goal of this work is to evaluate the within-subject reproducibility of within-slice functional connectivity measurements between ventral (motor) horns and dorsal (sensory) horns. This work is a necessary first step for future studies that may use metrics of resting state connectivity to characterize changes due to aging and/or diseases of the central nervous system.

Methods

Experiments were performed on a Philips Achieva 7 Tesla scanner with a quadrature transmit and 16-channel receive coil custom-designed for spinal imaging (Nova Medical Inc.). To date, three healthy volunteers (male, 24-32 years) with no history of spinal cord injury have been scanned under a protocol approved by the institutional review board. Two back-to-back resting state runs were acquired from each subject with the following parameters to minimize T_2^* blurring and geometric distortions [1]: field of view = 160 × 160 mm, 12 4-mm slices (coverage from C3 to C5), voxel size = 0.91 × 0.91 × 4 mm^3, repetition time = 17 ms, echo time = 8.0 ms, flip angle = 12°, echo train length = 9, sensitivity encoding [2] reduction factor = 1.56 (anterior-posterior), volume acquisition time = 3.6 sec (300 ms/slice), number of volumes = 150. Functional data were processed as described in [1] except the slice-by-slice functional-to-anatomical affine registration (3dAllineate [3]; step #8 in [1]) registered each functional to its corresponding anatomical using five cost functions ('ls', 'crM', 'crA', 'crU', and 'lpa' [3]), and then applied the median transform to all volumes. These cost functions were empirically observed to produce reliable results, and use of the median value protected against possible errant transformations.

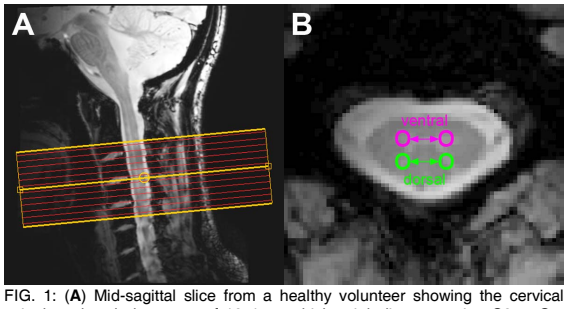

FIG. 1: (**A**) Mid-sagittal slice from a healthy volunteer showing the cervical spinal cord and placement of 12 4-mm thick axial slices covering C3 to C5. (**B**) High-resolution T_2^*-weighted axial image at C4. A pictorial representation of within-slice functional connectivity between left and right ventral (motor) horns and between left and right dorsal (sensory) horns is presented.

Gray and white matter masks were manually created from the high-resolution anatomical for each slice, and subdivided into quadrants to identify left and right ventral (motor) and dorsal (sensory) horns. To compensate for sub-millimeter co-registration inaccuracies from one run to the next, each sub-region mask was dilated in-plane by one interpolated voxel (0.31 × 0.31 mm^2) and the m individual voxel time series within each left ventral/dorsal mask were correlated with n voxel time series in the contralateral ventral/dorsal mask. The resultant m×n correlations were converted to z-scores and corrected for first-order autocorrelation [4]. To protect against spurious correlations, the 95% percentile of the z-scores was used to represent functional connectivity between left and right horns. Finally, the intraclass correlation coefficient (ICC) [5] was calculated for the two runs.

Results

Figure 1 presents the placement of slices for one subject and an illustration of the within-slice correlations of interest. The spinal cord is 11-13 mm across (left-right) and thus sub-regions are separated by ~4-7 mm. Figure 2 plots z-scores between ventral horns (A) and dorsal horns (B) for the sequential runs. The colors denote the superior (red), medial (green), and inferior (blue) segments of four slices roughly corresponding to one vertebral level. The ICC for within-slice ventral horn connectivity across slices and subjects is 0.34 (p = 0.020) and the ICC for dorsal horn connectivity across slices and subjects is 0.36 (p = 0.015).

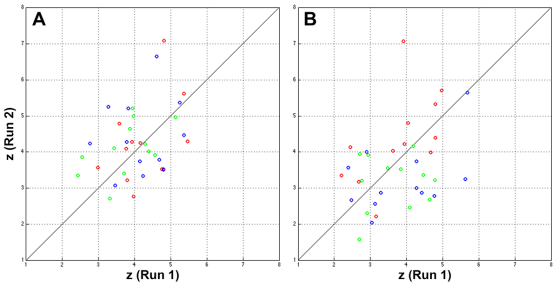

FIG. 2: Within-slice correlation between (**A**) ventral horns and (**B**) dorsal horns for two sequential runs. Each point represents a pair of z-scores for one slice in one subject. To investigate possible slice-level effects, red denotes values from the superior four slices (C2/C3), green denotes values from the middle four slices (C3/C4), and blue denotes values for the inferior four slices (C4/C5). The relatively uniform distribution of colors suggests that these networks may have similar variability of z-scores across vertebral segments.

Discussion

We have evaluated within-subject reproducibility of spinal cord connectivity, which we propose will be important for future studies that rely upon such measurements to assess into how these networks change due to aging, injury, or disease. These preliminary results suggest a moderate level of reproducibility (ICC ≈ 0.35) in the spinal cord. In previous studies, measurements of reliability for brain connectivity have ranged widely depending upon details of the methods used and the connectivity measures considered. For example, a wide range of ICC from 0-0.763 has been observed in the brain for various approaches to preprocessing and filtering [6]. Other studies have reported moderate to high within-subject reliability (Pearson correlation) between 0.38 and 0.69 [7] and between 0.71 and 0.85 [8], which similarly reflect the specific procedures and measures used. These ranges of values suggest that resting state brain networks can be highly reproducible under ideal conditions, but also can have low reproducibility when sub-optimal preprocessing choices are made. The small size of the spinal cord and inherent imaging challenges (physiological noise, B_0 inhomogeneities, etc.) suggest that measurements of spinal cord networks may inherently have lower reproducibility than networks in the brain. However, if our experiences in the brain serve as a guide for future spinal cord studies, then increases in the reproducibility of our measurements of spinal cord networks will likely be achieved through improved acquisition strategies and preprocessing methodologies. Our ongoing work will expand this study to a larger cohort of healthy subjects, and future work will investigate modulation of resting state spinal cord networks in patients with spinal cord injury and multiple sclerosis.

Acknowledgments

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References – [**1**] Barry et al. eLife 2014;3:e02812. [**2**] Pruessmann et al. MRM 1999;42:952. [**3**] Cox. Comput Biomed Res 1996;29:162. [**4**] Rogers & Gore. PLoS ONE 2008;3:e3708. [**5**] Shrout & Fleiss. Psychol Bull 1979;86:420. [**6**] Braun et al. Neuroimage 2012;59:1404. [**7**] Honey et al. PNAS 2009;106:2035. [**8**] Van Dijk et al. J Neurophysiol 2010;103:297.