Reliability of functional and effective connectivity of the resting state motor network in healthy subjects

T. Kavallappa[1], S. Roys[2], A. Roy[3], J. Greenspan[2], R. Gullapalli[2], and A. McMillan[2]
[1]Dept. of Nuclear Medicine and Diagnostic Radiology, Univeristy of Maryland School of Medicine, Baltimore, MD, United States, [2]University of Maryland School of Medicine, [3]University of Maryland Baltimore County

Introduction: Resting state functional connectivity of the cortical motor network has been shown to be reliable and consistent; however, the same has not been shown for measurements of effective connectivity. In this study, we use structural equation modeling (SEM), a frequently used method to evaluate effective connectivity, to evaluate reliability of these measurements in the human resting state motor network. Because connectivity measurements have shown sensitivity to physiological noise, we performed our reliability assessment using four different filtering methods. The filtering methods used were i) Standard preprocessing with no physiological filtering ii) retrospective correction of physiological effects using RETROICOR iii) White matter + CSF mean signal filtering and iv) whole brain mean signal filtered data.

Methods: Multiple resting state data sets were obtained from 7 healthy right-handed subjects during three separate sessions spanning over two months using a Siemens Tim-Trio 3T scanner. During each of the 3 sessions, three resting state scans were obtained using a single-shot EPI acquisition with 24 axial slices (TE = 30ms, TR = 2s, FOV = 22cm, slice thickness = 6mm with no gap), yielding 171 time points in 342s. Respiratory data was acquired during scanning via a nasal cannula at a sampling rate of 500Hz. Standard data preprocessing included slice timing correction, spatial registration, linear detrending, and spatial smoothing using a 6mm FWHM Gaussian blur. 3D structural brain images were automatically segmented into gray matter (GM), white matter (WM) and CSF component images which were used to extract average GM, WM and CSF time series from the resting state scans. Further processing of the data was performed to yield separate data sets that included (i) Preprocessed data with no physiological filtering (ii) Respiratory noise filtered from the data using retrospective image correction (RETROICOR), (iii) White matter + CSF mean signal filtered data where the average time series of white matter and CSF (WM-CSF) was regressed from individual voxels, since the WM-CSF signals are expected to be independent of the BOLD signal fluctuations present in the gray matter, and (iv) Global mean brain signal filtered data where the average time series from all brain voxels (GM+WM+CSF) was regressed from each individual voxel time series. In this analysis the local signal changes are of interest, and the global signal is assumed to represent non-neuronal noise. Five ROI's were chosen as part of the resting state motor network in the cortex: left & right primary motor areas (LM1, RM1), dorsal premotor areas (LPMd, RPMd), and the supplementary motor area (SMA). After preprocessing, LM1 was chosen as seed region using data from the motor paradigm to obtain functional connectivity maps. Spherical ROIs (radius ranging from 7-13 mm) were manually drawn in the LM1, RM1, RPMd, LPMd, and SMA using calculated functional connectivity maps as a guide. Group correlation matrices were obtained from the concatenated ROI time series (for all subjects and sessions). The correlation coefficients, along with an initial causal model (Fig 1) were used as input to SEM. The SEM package in R was used to test and refine the causal model for the resting state motor network using modification indices and goodness-of-fit indices (we define RMSEA<0.05, AGFI>0.99 as a good model fit). A resampling test was performed to examine the reliability of the model, and determine the distribution of the path coefficients using different combinations of the subjects' data. In the resampling test the path coefficients were determined for combinations of pooled data from all 7 subjects, taken 6 subjects at a time, to assess group functional and effective connectivity.

Results and Discussion: The initial anatomical model for the resting state network is shown in Figure 1 with bold and dotted arrows. Using modification indices in R, the model that demonstrated the best fit to the data (for all four filtering methods) included all of the connections from the anatomical model except connections from SMA to the bilateral dorsal premotor areas. This model is shown in solid lines in Figure 1. The resting state motor network obtained demonstrates reciprocal connections across bilateral primary motor areas, and the premotor areas. The model follows a symmetric structure with the premotor areas influencing the SMA and the ipsilateral primary motor areas. The SMA influences both the primary motor areas. Coefficient of variation was calculated for each connection at combination level 6 (7 different combinations). While functional connectivity was more consistent across the 4 filtering methods used (COV <= 0.08) as shown in Table 1, it was not so with effective connectivity (Table 2). Although the model yielded a good fit for all the filtering methods, the path coefficients were only stable for certain connections (e.g variability of LM1->RM1 path coefficients greater than RPMD->RM1). The correlation coefficients from the RETROICOR filtered dataset and the dataset with no physiological filtering had higher path coefficients, and lower variability, than that of the global mean signal regressed and WM-CSF mean signal regressed datasets. The path coefficients, in general, displayed higher variability for the WM-CSF and the global mean filtered datasets.

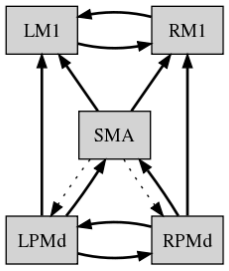

Figure 1 Anatomical model used as base for SEM analysis

Conclusion: It is seen that while a single causal model fit all the datasets considered, the path coefficients demonstrated high degree of variability. The variability of both functional connectivity and effective connectivity was less for the physiologically filtered dataset and the dataset with no filtering, compared to the WM-CSF and global mean filtered datasets. Given the variability of effective connectivity from SEM, interpretation of such data should be treated with caution.

Correlation Coefficients				
Connections	I	II	III	IV
LM1 – LPMd	0.70	0.72	0.47	0.44
LM1 – RM1	0.80	0.81	0.67	0.60
LM1 – RPMd	0.64	0.66	0.42	0.37
LM1 – SMA	0.74	0.75	0.52	0.43
LPMd – RM1	0.64	0.67	0.41	0.36
LPMd – RPMd	0.72	0.78	0.61	0.57
LPMd – SMA	0.67	0.68	0.38	0.35
RM1 – RPMd	0.70	0.74	0.55	0.51
RM1 – SMA	0.76	0.76	0.55	0.47
RPMd – SMA	0.63	0.67	0.39	0.33

Table 1: Correlation coefficients for all subjects for the 4 filtering methods (Mean (sd)) at combination level 6 [COV<0.03, 0.03<COV<0.1]

Path Coefficients				
Connections	I	II	III	IV
LM1 → RM1	0.14 (0.07)	0.16 (0.07)	0.20 (0.08)	0.14 (0.06)
RM1 → LM1	0.38 (0.05)	0.35 (0.04)	0.33 (0.05)	0.34 (0.04)
RPMd → LPMd	0.43 (0.02)	0.48 (0.01)	0.34 (0.02)	0.32 (0.02)
LPMd → RPMd	0.43 (0.02)	0.48 (0.01)	0.34 (0.02)	0.32 (0.02)
LPMd → LM1	0.27 (0.02)	0.29 (0.02)	0.24 (0.02)	0.25 (0.02)
RPMd → RM1	0.31 (0.03)	0.37 (0.04)	0.34 (0.03)	0.36 (0.03)
LPMd → SMA	0.44 (0.03)	0.41 (0.02)	0.23 (0.04)	0.23 (0.04)
RPMd → SMA	0.31 (0.03)	0.35 (0.02)	0.25 (0.03)	0.19 (0.03)
SMA → RM1	0.46 (0.05)	0.39 (0.03)	0.32 (0.04)	0.29 (0.03)
SMA → LM1	0.27 (0.03)	0.28 (0.03)	0.25 (0.02)	0.18 (0.02)

Table 2: Path coefficients of the final causal model (Mean (sd)) at combination level 6 [0.03<COV<0.1, 0.1<COV<0.2, COV>0.2]

References: [1] Gonzalez-Lima ARMF, Human Brain Mapping 2 (1-2) (1994) 2–22. [2] Fox J, With the SEM Package in R, Structural Equation Modeling 13 (3) (2006) 465–486. [3] Zhuang J, LaConte S, Peltier S, Zhang K, Hu X, Neuroimage 25 (2) (2005) 462–470.