Exploring Effective Connectivity during Unilateral Movement in Stroke using Structural Equation Modeling

W-W. Wong[1], K-Y. Tong[1], F. Meng[1,2], K-W. Tang[3], X. Gao[2], S. Gao[2], and S-T. Chan[1]

[1]The Hong Kong Polytechnic University, Hong Kong, China, People's Republic of, [2]Tsinghua University, Beijing, China, People's Republic of, [3]Queen Elizabeth Hospital, Hong Kong, China, People's Republic of

Introduction

Stroke is a leading cause of long-term disability and would result in brain reorganization to adapt the damage after stroke. Many functional MRI studies have tried to address the brain reorganization patterns following stroke which can be correlated to motor deficit or motor recovery. The activation patterns analyzed from the fMRI data however cannot sufficiently explain the causes leading to the pattern change. To improve our understanding of how the injured brain processes information to adapt the change, more knowledge about the interactions of activated brain areas, that is, functional integration is needed. Structural equation modeling (SEM) is a statistical approach to identify directional interaction among brain regions given the pairwise correlations of their time series. The parameters in the SEM model are path coefficients between different regions, which can reflect the effective connectivity in neural network model. However, conventional SEM has been used as a confirmatory analysis technique to support or not to support *a priori* model of connectivity. This would create a problem as our current anatomical knowledge often cannot constrain modeling of interactions to a sufficient degree, especially in the cases of injured brain of which its anatomical structure was largely distorted by lesions that may affect the normal interpretation of functional integration. To date, an automated elaborative approach of SEM for fMRI data has been introduced and we applied the new technique to the stroke subjects' fMRI data acquired during repeated wrist extension using unaffected wrist. The derived models were inferentially validated using a bootstrapping approach in 12 independent groups. Significant paths across the groups were used to form a validated and consistent path model.

Materials and Methods

Studies were performed on 6 stroke subjects (50-66 years) on a 1.5 Tesla Siemens MR scanner. Their lesions were found at the left basal ganglia involving cortical and/or subcortical structures. Each subject performed wrist extension using their unaffected (left) wrist in the fMRI experiment. A blocked paradigm consisting of activation and fixation epochs was used with each epoch lasting for 20s. A series of BOLD fMRI images were acquired using gradient-echo EPI sequence (TR/TE=2000/32ms, flip angle=90 degrees) while the subject performed the motor task. The data were processed using GLM approach in AFNI software to obtain general activation pattern. Structural equation modeling (SEM) was then applied to the time series extracted from the selected regions of interest (ROI) to explore the effective connectivity among the activated regions and the analysis procedures were largely followed the methods mentioned in [1] and [2]. The fMRI data of 6 subjects were randomly sampled (without replacement) 12 times to create 12 groups containing 3 subjects each. Ten brain regions in the left and right hemisphere were selected based on the activation pattern analyzed by GLM. The selected regions were left and right precentral gyrus (PrG, BA 4), left and right postcentral gyrus (PoG, BA 3), left and right premotor cortex (PMC, BA 6), supplementary motor area (SMA, BA 6), right cingulate gyrus (CG, BA 24), left thalamus (Tha) and parahippocampal gyrus (PHG). 5mm radius spherical masks were placed at the chosen coordinates as shown in Fig. 1 to extract the averaged time series within the mask for each ROI. Starting from a null model, new paths were added stepwise until an optimally explanatory, but parsimonious model was reached. For assessing the significance of individual paths, a mean and standard deviation were derived for each coefficient across all models generated from the 12 groups.

Results and Discussion

A model was independently derived from group of 3 subjects. A total of 12 models were generated from 12 different combinations of the subjects. For validating the significance of individual paths, the mean and standard deviation of automatically derived path models were calculated for all paths and recorded for those path coefficients in which the standard deviation from the mean did not cross zero. Thirty paths were found to make significant and consistent contributions across the groups. These significant paths and their corresponding coefficients are shown in Table 1 and Fig. 1. Thirteen pairs of paths were shown having bidirectional influences among the brain regions with remaining 4 paths showing unidirectional influences. The present findings showed that there were many bidirectional interactions between primary and secondary motor areas, and interactions between primary motor and sensory areas as well as the interactions of motor areas with thalamus, parahippocampus and cingulate gyrus. Using bootstrapping approach for the validation purpose, inconsistent paths were excluded and only consistent and significant paths were remained. The survived paths thus can be more typical across the subjects by reducing the errors caused by chance.

Table 1
Significant path coefficients

Path	Mean	Path	Mean
R.PoG → R.PrG	0.1678	R.PrG → R.PoG	0.5742
R.PoG → L.PrG	-0.1694	L.PrG → R.PoG	-0.1160
R.PrG → L.PoG	0.5020	L.PoG → R.PrG	0.1041
L.PrG → L.PoG	0.2079	L.PoG → L.PrG	0.3383
R.PrG → SMA	0.2682	SMA → R.PrG	0.1544
L.PrG → SMA	0.0966	SMA → L.PrG	0.4192
L.PoG → SMA	0.1208	SMA → L.PoG	0.2402
R.PrG → R.PMC	0.4500	R.PMC → R.PrG	0.4153
SMA → L.PMC	0.2246	L.PMC → SMA	0.3707
L.PrG → L.Tha	0.0853	L.Tha → L.PrG	0.3261
R.PMC → L.Tha	0.2884	L.Tha → R.PMC	0.2188
L.Tha → L.PHG	0.4882	L.PHG → L.Tha	0.7068
L.PrG → R.CG	0.1002	R.CG → L.PrG	0.2420
L.PoG → L.PHG	0.0652	SMA → R.CG	0.2033
R.PMC → R.PoG	0.7473	L.PMC → R.PoG	-0.3081

Those coefficients in which the standard deviation from the mean did not cross zero were deemed significant and are shown here. 30 path coefficients were survived after the validation test.

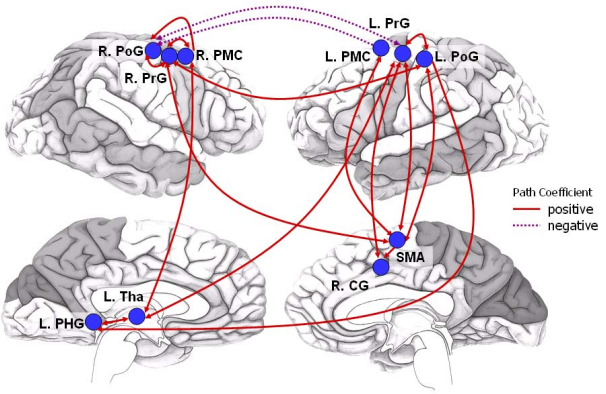

Fig.1. Automatically derived path model. Red solid lines are the paths having positive path coefficients while purple dotted lines are the paths having negative coefficients. Some brain regions have bidirectional influences with each other and these paths are represented by bi-arrow lines instead.

References

1. Bullmore, E., et al., NeuroImage, 2000. **11** : p.289-301.
2. Stein, J.L., et al., NeuroImage, 2007. **36** : p.736-745.