Evolution of Functional Connectivity after Transient Stroke in Rats

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INTRODUCTION

Stroke impairs neurovascular and metabolic functions, commonly resulting in acute motor deficits. Some degree of motor recovery typically occurs over subsequent weeks and months after stroke, yet the changes in neurovascular and metabolic functions that underlie this recovery are poorly understood. In particular, methodological difficulties in defining relationships between ischemic tissue damage and overall neurological deficit have impeded the development of proper diagnostic and prognostic measures. In this study, we monitored changes of resting-states functional connectivity using cross-correlation technique over a period of 30 days after transient cerebral ischemic damage.

METHOD

Two Sprague-Dawley rats (~300g) were used for inducing transient ischemia by 90-min occlusion ofthe right middle cerebral artery (MCAO). Three healthy rats were used for the control group. BOLD MRI time courses during rest (Gradient Echo Planar Imaging: TR/TE=3000/12.89ms; FOV=2.5 x 2.5cm^2; nine contiguous 1mm slices) were collected for ~15 min at 10, 20 and 30 days after MCAO. ROIs were placed over the regions corresponding to motor cortex (M1& M2), primary sensory areas (S1fl), secondary somatosensory cortex (S2), and caudate putamen (CPu) and thalamus area (TA) based on the rat brain atlas of Paxinos. Each ROI time course was detrended to the second order and bandpass-filtered between 0.01 and 0.1 Hz. Functional connectivity between ROIs was evaluated by calculating cross-correlation coefficient (CCC). T2* maps were created by conventional spin echo pulse sequences using multiple echoes where TR/TE=3000/15, 30, 45, 60, 75, 90, 105, and 120 ms. Apparent diffusion coefficient (ADC) maps were created with a diffusion-weighted EPI pulse sequence with TR/TE=9000/52.64ms and b=5, 300, 800, and 1200 sec/mm^2.

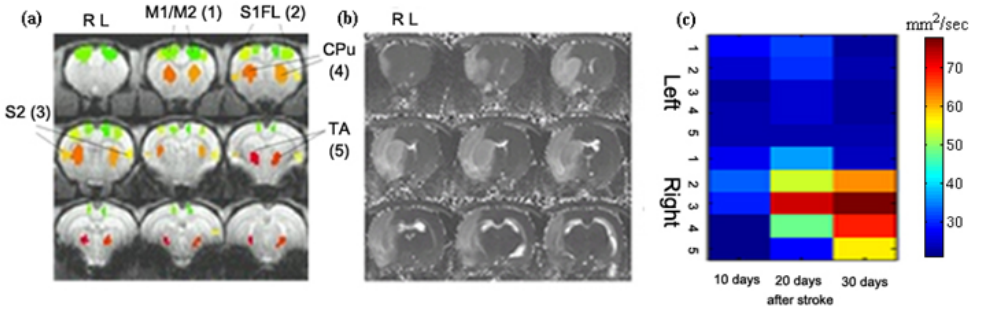

Fig. 1 (a) locations of ROIs (b) T2* map images for stroke rats (c) ADC values for each ROIs
The numbers (1-5) correspond to M1/M2, S1F1, S2, Cpu and TA, respectively

RESULTS

Figure 1 shows representative T2* map and ADC values of ROIs revealing the size and severity of lesion areas. The cross-correlation distribution matrixes at 10, 20, 30 days after the MCAO are shown in Fig. 2. Stroke rats show markedly decreased cross-correlation values among ROIs in both contra- and ipsi-hemispheres at 10 days after stroke. Although there appeared to be increased correlations among ROIs at 20 days, most CCC values associated with lesion (right) hemisphere significantly reduced at 30 days (Fig 2). The averaged correlation strengths among some ROIs in stroke rats monotonically increased within the left (contralesional) hemisphere over time, eventually matching those in control group. Despite the slight recovery, CCC values measured within ipsilesional hemisphere and between bilateral hemispheres show severely impaired functional connectivity over 30 days after stroke. (Fig. 3)

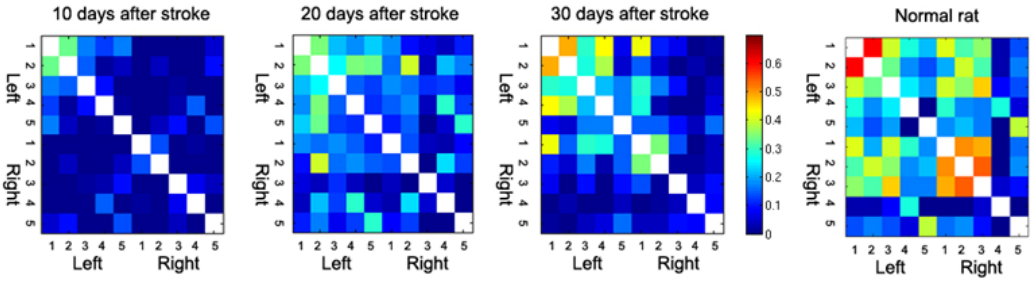

Fig. 2. Cross-correlation matrixes according to days after stroke.
The numbers (1-5) correspond to M1/M2, S1F1, S2, Cpu and TA, respectively.

DISCUSSIONS/CONCLUSIONS

We evaluated longitudinal changes in functional connectivity using resting state BOLD MRI time courses. At 10 days after transient ischemia, cross-correlation coefficient (CCC) values among the selected ROIs were severely compromised both (1) within each hemisphere and (2) between bilateral hemispheres. The initial disruption and ensuing normalization of CCC values within the contralesional hemisphere may indicate the possible contribution of altered resting state networks within the contralesional hemisphere to overall functional recovery processes. Although small, we also demonstrated temporally increasing CCC values within the lesion hemisphere. Interestingly, CCC values across bilateral hemispheres were biphasic over time and dissociated from monotonic increase of overall CCC values within each hemisphere. Although more detailed future studies are warranted for understanding the underlying mechanisms, such trends in functional connectivity may indicate possible plasticity of the functional networks during stroke recovery. In conclusion, although highly speculative, the data demonstrated that the initial limb dysfunction is related to the loss of brain connectivity in both ipsi- and contra-lesonal brain regions and that the restoration of function may be associated more with the increase of functional connectivity within the contralesional than the ipsilesional hemisphere.

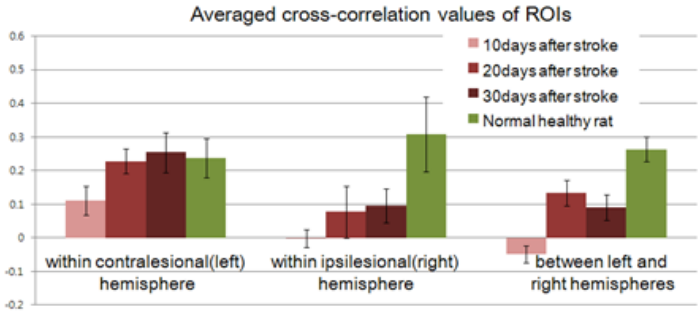

Fig. 3. Averaged cross-correlation values.

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[2] van der Zijden JP, *et al,* Neuroimage 34(4):1650-7