The effects of altered hemodynamics on measurements of functional connectivity following ischemic stroke

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Introduction Stroke is a major health concern in the United States, where it is the fourth leading cause of death and the leading cause of adult disability. It is becoming increasingly apparent that a global assessment of functional connections throughout the brain may provide better insight into recovery potential than a simple assessment of anatomic infarction. While recent findings suggest that homotopic interhemispheric connectivity is associated with behavioral and functional recovery [1,2], signal regression can influence interpretation of functional connectivity (fc) patterns. For example, regression of a whole-brain signal (a common signal shared across the brain) from all voxels can reveal anticorrelations between brain regions that may not have been present prior to regression. Further, the notion of a global signal becomes less well defined in the context of stroke. Presumably, all regions of the brain are not affected uniformly by the insult, and a common, shared signal between the ipsilesional hemisphere (containing the infarct) and the contralesional hemisphere (the healthy hemisphere) may not exist. Neglecting to distinguish unique signals shared within and across hemispheres may confound potentially recovery-relevant information provided by fc. In this study, we applied a novel fc optical intrinsic signal imaging (fcOIS) technique to a mouse model of ischemic stroke before and 72 hours after transient middle cerebral artery occlusion (tMCAO) to evaluate altered regional hemodynamics and how they can affect measurements of fc after stroke.

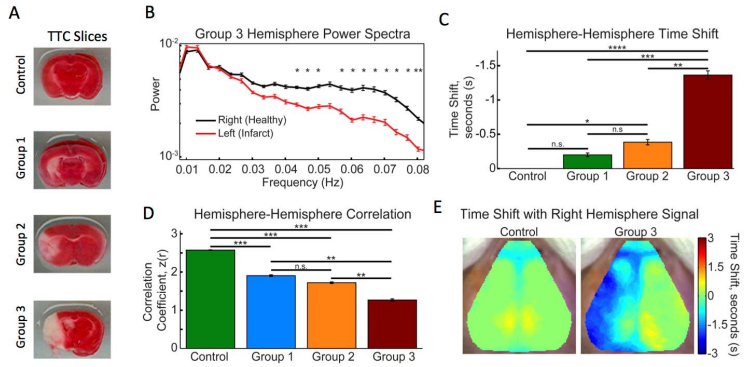

Figure 1: **Altered hemodynamics following ischemic stroke**. (**A**) Representative TTC slices in each group after tMCAO. (**B**) Average power spectra of the ipsilesional hemisphere signals in Group 3 mice exhibit significantly attenuated higher frequency components compared with the contralesional side. (**C**) Cross-correlation analysis of hemisphere signals show that the ipsilesional hemisphere signals are gradually delayed in time with respect to the contralesional hemisphere. (**D**) Group-averaged hemisphere-to-hemisphere correlation (zero-lag) in each group indicates a lack of hemisphere-wide synchrony. (**E**) Regional time lag after cross correlation analysis of every brain pixel with the contralesional side shows altered hemodynamics residing in damaged cortex.

Methods Mice were imaged and data were analyzed before and 72 hours after tMCAO following our published fcOIS methods[3]. After the final imaging session, brains were harvested and stained with TTC to assess infarct volume; mice were then separated into three groups according to infarct size and location. Group 1 had either no discernible or small infarcts involving subcortex, Group 2 had moderate infarcts involving lateral/ventral cortex and subcortex, and Group 3 had large infarcts involving portions of cortex and subcortex (**Fig. 1A**).

Results Evaluation of time traces from the ipsi- and contralesional hemispheres after stroke reveals different spectral and temporal characteristics within the fc band (**Fig. 1B-E**). As a function of stroke severity, we found an overall attenuation of high frequency content (**Fig. 1B**) and an increase in temporal delay (**Fig. 1C**) in the spontaneous activity exhibited by the healthy and injured hemispheres. The source of the delay was observed to reside in brain regions within the MCA territory exhibiting significantly altered hemodynamics (**Fig. 1E**). These findings suggest that whole brain regression is not optimal for evaluating fc after ischemic insult; failure to account for the difference in hemisphere signals was found to substantially affect fc patterns (**Fig. 2**, only Motor and Somatosensory cortices shown). While bilateral fc disruption was commensurate with stroke severity, whole brain regression produced strong anticorrelations between contralateral brain regions and increased ipsilateral connectivity in the most injured mice. As it is unlikely that injured and contralesional brain regions become more connected during the acute stage of recovery, as other studies have suggested[2], we sought an alternative regression approach. A dual-hemisphere regression method, which regresses the individual hemisphere signals simultaneously from both hemispheres, preserves ipsilateral connectivity in the healthy hemisphere, and produces contralateral homotopic connectivity patterns that approach zero in regions most affected by stroke, a result that should be anticipated from behavioral data reporting loss of function after stroke [1,2].

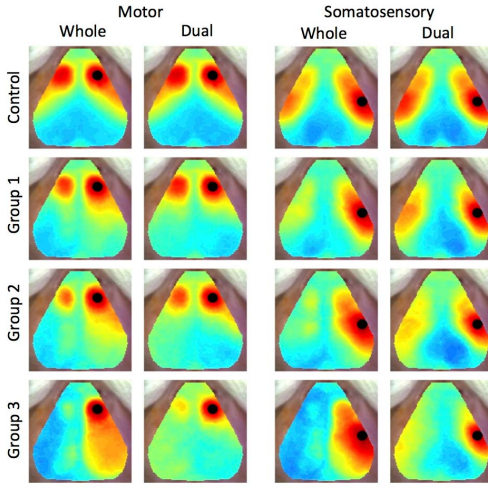

Figure 2: Observed functional connectivity after stroke is affected by method of regression. Two types of regression procedures (**Whole** and **Dual**) were performed on mice with incrementing degrees of stroke injury (**Groups 1-3**) and compared with control mice (**top row**). Only Motor and Somatosensory cortices shown for brevity.

Summary and Conclusions Our data suggest that accounting for the separate hemodynamics occurring in the healthy and damaged hemispheres may provide a more accurate method for calculating fc between regions affected by stroke. Given that resting-state fc measures have provided valuable information regarding functional organization in the human brain, we are now in a unique position to probe questions about post-stroke recovery mechanisms and the role of ipsilesional and contralesional connectivity on functional remapping after stroke using fcOIS.

References

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