Title: Functionally defined ROIs are superior to structurally defined ROIs for functional connectivity analysis in mild traumatic brain injury (mTBI).

R. Madhavan1, S.E. Joel1, R. Mullick1, Teena Shetty2, Luca Marinelli3
1GE Global Research, Bangalore, Karnataka, India, 2Hospital for Special Surgery, New York City, NY, USA, 3GE Global Research, Niskayuna, NY, USA

Background: mTBI patients exhibit acute symptoms including blurry vision and memory problems, though CT/MRI scans appear normal. The purpose of this study was to identify functional biomarkers of mTBI using rs-fMRI during the 3 months following mTBI. In order to study severity of the injury, imaging studies assess the change by evaluating functional connectivity between brain regions-of-interest (ROI). We correlated functional connectivity (FC) derived using either structural or functional ROIs to symptom severity, to determine which parcellation scheme was more sensitive to changes in mTBI.

Methods: After obtaining informed consent, rs-fMRI was recorded from 78 patients at four time points (3 days, 7 days, 3 weeks and 3 months) after mTBI and 26 healthy controls. Using GE 3T MRI scanner, multi-band 2D-EPI, TR/TE = 900/30 ms was acquired for 6 minutes (395 volumes), with 1.875mm² in-plane resolution and 3mm slice thickness to cover the whole brain. All participants filled a self-assessment questionnaire that was used to calculate symptom severity scores (SSS). rs-fMRI data were motion corrected, rigid registered to T1-weighted image, non-rigid registered to MNI atlas, nuisance removed, spatially smoothed using Gaussian filter (FWHM 4mm) and temporally band-pass filtered (0.01-0.1 Hz) using custom-built software. Correlation coefficients were computed between each pair of mean time courses for 86 structurally defined ROIs and 90 functionally defined ROIs. For functional ROIs, average correlation between ROIs belonging to same network (within network connectivity, WNC) and across networks (between network connectivity, BNC) were computed.

Results: FC matrices derived using structural and functional ROIs showed typical left-right (homotopic) connectivity and clustering of functional regions as expected. Average whole brain FC across 90 functional ROIs was negatively correlated with SSS (r=-0.84, p<0.05), but FC across 86 structural ROIs showed no consistent relationship with SSS. On binning the patients with low (SSS<5) and high (SSS>30) symptoms, there was a significant difference between FC in the two patient groups using functional ROIs (p<0.001, rank sum test) but not structural ROIs. Changes in BNC in higher and primary visual, executive control and precuneus networks was significantly correlated with SSS (p<0.05).

Conclusions: Correlation of whole brain FC with mTBI symptoms was observed only with functional ROIs, but not structural ROIs. Structural ROIs are typically defined using anatomical gyral boundaries and it is possible that a structural ROI can combine signal from multiple functional regions, thus diluting the information from distinct functional areas. The networks that are correlated to SSS (visual, executive control and precuneus) are related to symptoms associated with mTBI. These results validate that the use of functionally defined ROIs is superior to the use of structurally defined ROIs in whole brain connectivity analysis of neurological disorders.