Global Brain Network Alterations in Post-Traumatic Stress Disorder and Post-Concussion Syndrome

D Rangaprakash[1], Gopikrishna Deshpande[1,2], D Narayana Dutt[3], Thomas A Daniel[2], Adam Goodman[2], Jeffrey S Katz[1,2], Nouha Salibi[1,4], Thomas S Denney Jr[1,2], and MAJ Michael N Dretsch[5,6]

[1]AU MRI Research Center, Department of Electrical and Computer Engineering, Auburn University, Auburn, AL, United States, [2]Department of Psychology, Auburn University, Auburn, AL, United States, [3]Department of Medical Electronics, Dayananda Sagar College of Engineering, Bangalore, Karnataka, India, [4]MR R&D, Siemens Healthcare, Malvern, PA, United States, [5]National Intrepid Center of Excellence, Walter Reed National Military Medical Center, Bethesda, MD, United States, [6]U.S. Army Aeromedical Research Laboratory, Fort Rucker, AL, United States

Introduction: Functional segregation and integration are hallmarks of the human brain. The former allows specialized processing to occur within localized interconnected groups of brain regions, while the latter allows amalgamation of specialized information from distributed brain regions. These constructs have been measured using global network properties derived from resting state functional magnetic resonance imaging (fMRI) [1]. Specifically, transitivity (TRN), which measures functional segregation, is the ratio of triangles to triplets in a network, and is a global measure of local clustering. Global efficiency (GE), which measures functional integration, is higher for networks with shorter paths between its nodes. It has been previously shown that these measures are extremely sensitive to mental illness[2,3] as well as traits and abilities in healthy individuals[4]. However, no such studies have been carried out in two highly prevalent military injury conditions: posttraumatic stress disorder (PTSD) and post-concussion syndrome (PCS) following mild traumatic brain injury (mTBI). Military service members who sustain mTBI are at risk of developing PCS and PTSD. Although specific regional alterations have been identified in these disorders[5], alterations in global functional network properties, if any, have not been investigated. In this work, we calculated TRN and GE from both directional and non-directional functional networks to test the hypothesis that PCS and PTSD lead to impaired global functional segregation and integration.

Methods: 87 Soldiers having combat experience in Afghanistan and/or Iraq were recruited for the study. 17 of them had PTSD, 42 had both PCS and PTSD (comorbid), and 28 were healthy controls who were matched to the other groups in age, gender, race and education. Resting state fMRI data were obtained by scanning them in a 3T MAGNETOM Verio scanner (Siemens Healthcare, Erlangen, Germany) using a T2* weighted multiband EPI sequence with TR=600ms, TE=30ms, FA=55˚, multiband factor=2, voxel size= 3×3×5 mm^3 and 1000 volumes. After standard preprocessing, fMRI time series at each voxel were deconvolved to obtain hidden neuronal signals[6]. Mean hidden neural signals were obtained from 125 functionally homogeneous regions (determined via spectral clustering[7]), and were used to obtain traditional *non-directional functional connectivity* (FC) between all regions using Pearson's correlation coefficient as well as *directional effective connectivity* (EC). EC was obtained by inputting the hidden neural time series into a multivariate autoregressive model (MVAR) and estimating correlation-purged Granger causality (CPGC) [8]. FC and EC matrices from each subject were used, without thresholding, for calculating weighted TRN and GE as follows.

$$TRN = \frac{\sum_{i \in N} t_i}{\sum_{i \in N}\left[\left(k_i^{out} + k_i^{in}\right)\left(k_i^{out} + k_i^{in} - 1\right) - 2\sum_{j \in N} w_{ij} w_{ji}\right]}; \quad GE = \frac{1}{n}\sum_{i \in N} \frac{\sum_{j \in N, j \neq i} \left(d_{ij}\right)^{-1}}{n-1}$$

where N is the set of all nodes in the network, 'n' is the number of nodes, (i, j) is the link between nodes i and j ($i, j \in N$), w_{ij} is the weight of the path between i and j. Defined below are shortest path length d_{ij}, geometric mean of triangles around a node t_i, weighted out-degree k_i^{out} and weighted in-degree k_i^{in}.

$$d_{ij} = \sum_{a_{uv} \in g_{i \to j}} w_{uv}; \quad t_i = \frac{1}{2}\sum_{j,h \in N} \left(w_{ij} w_{ih} w_{jh}\right)^{\frac{1}{3}}; \quad k_i^{out} = \sum_{j \in N} w_{ij}; \quad k_i^{in} = \sum_{j \in N} w_{ji}$$

$g_{i \to j}$ is the shortest geodesic path between nodes i and j. We evaluated TRN and GE for all subjects (one value per subject) and performed two-sided t-tests, controlling for age, gender, race, education & head motion, for determining whether the differences between the groups were statistically significant.

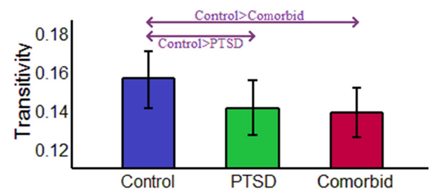

***Fig.1**. Transitivity using EC*

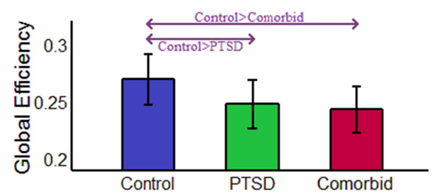

***Fig.2**. Global Efficiency using EC*

***Table.1**. p-values for the global measures using EC*

Global Measure	p-value	
	Control > PTSD	Control > Comorbid
Transitivity	0.0154	0.0088
Global Efficiency	0.0236	0.0104

***Table.2**. p-values for the global measures using FC*

Global Measure	p-value	
	Control > PTSD	Control > Comorbid
Transitivity	0.6750	0.0657
Global Efficiency	0.7697	0.0840

Results: We found that both TRN and GE for directed EC networks were significantly (p<0.05 FDR corrected) different for the following comparisons: control > PTSD and control > comorbid (see Figs 1 & 2, Table 1). However TRN and GE for directed EC networks were not significantly different between PTSD and comorbid groups. TRN and GE obtained from non-directional FC networks were not significantly different between any groups (Table.2). This indicates that causality (EC) and synchronization (FC) are two distinct modes of communication in the brain[9] and can be impacted selectively or to different degrees by PTSD and PCS. This also demonstrates the utility of characterizing both FC and EC, in contradistinction to most studies which only look at FC. Moreover, we performed the same analysis using band-pass filtered [0.01-0.1 Hz] fMRI data without hemodynamic deconvolution (which is the traditional pre-processing choice), but no significant differences were obtained with either EC or FC. This underscores the importance of removing hemodynamic variability and smoothing from fMRI time series for estimating EC networks.

Discussion: A network which simultaneously exhibits an optimal balance of functional segregation and integration is usually indicative of healthy functioning[10,11]. Our results indicate that the control group has significantly higher functional segregation (TRN) as well as functional integration (GE) compared to PTSD and comorbid groups. Since PTSD is common to both comparisons, it suggests that PTSD leads to abnormalities in functionally specialized local modular structures as well as integration between such units. Another interesting observation was the lack of significant differences between PTSD and comorbid groups. Since the two groups differ only by the diagnosis of PCS in the comorbid group, we can infer that PCS likely did not lead to significant alterations in global network properties. This makes sense given that mTBI might have a localized impact on only certain brain regions in individuals with PCS.

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