Dynamics of functional and effective brain connectivity better predicts disease state compared to traditional static connectivity

Gopikrishna Deshpande[1,2], Hao Jia[1], Xiaoping Hu[3], Changfeng Jin[4], Lingjiang Li[4], and Tianming Liu[5]

[1]*MRI Research Center, Department of Electrical and Computer Engineering, Auburn University, Auburn, Alabama, United States,* [2]*Department of Psychology, Auburn University, Auburn, Alabama, United States,* [3]*Biomedical Imaging Technology Center, Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, Georgia, United States,* [4]*The Mental Health Institute, The Second Xiangya Hospital, Central South University, Changsha, China,* [5]*Department of Computer Science, University of Georgia, Athens, Georgia, United States*

Introduction: It is well acknowledged that functional connectivity (FC) in the brain obtained from resting state fMRI dynamically changes with time [1-4]. Further, it has been shown that dynamic changes in FC [5] and effective connectivity (EC) [6] are relevant to disease processes. However, an outstanding question that remains is whether dynamic information from FC and EC provide additional sensitivity to underlying brain pathologies over and above that obtained by their static counterparts? Here, we provide answers to these questions by demonstrating that information from temporal variations in FC and EC provides better accuracy for classifying subjects with PTSD (post-traumatic stress disorder) from healthy controls. **Methods:** Individuals who were diagnosed with PTSD in the wake of the 2008 Wenchuan earthquake, Sichuan, China were recruited. Resting state fMRI data consisted of 99 runs from 76 healthy people and 146 runs from 73 PTSD patients. After standard preprocessing, mean time series from 190 functionally homogenous brain regions identified previously [7] were obtained. Dynamic FC (DFC), dynamic EC (DEC), static FC (SFC), and static EC (SEC) were computed between all possible pairs of regions. For DFC, we employed sliding windowed Pearson's correlation with window length determined by stationarity assessed through augmented Dickey-fuller test (ADF test). For SFC, Pearson's correlation calculated from the entire time series was used. For DEC, we employed a multivariate dynamic Granger causality (DGC) [8] model based on a time-varying autoregressive model embedded with a Kalman filter, while for SEC, correlation-purged Granger causality (CPGC) [9], the static counterpart of DGC, was adopted. In addition to the traditional SFC and SEC, the variance of DFC and DEC metrics over time were derived and input into four different classifiers for differentiating PTSD subjects from controls using each of the four metrics. Firstly, a two sample t-test was conducted to filter out 1000 features that were most significantly different between PTSD and controls. Next, these selected features were input into 4 different recursive clustering elimination based support vector machine (RCE-SVM) [10] classifiers. Depending on the importance of a given feature to classification, the rank of features was obtained. RCE-SVM is iterative method and in each iteration, it eliminates clusters of features with least discriminative power and then classification accuracy is updated. **Results and Discussion:** The classification performances for all the 4 metrics are shown in Fig.1. Generally, the classification accuracy increased with the removal of more uninformative features. However, for DFC and DEC, removing features beyond a point decreased accuracy since informative features were also removed. Both dynamic metrics had significantly ($p<0.05$) better accuracy in all steps of the RCE-SVM procedure compared to their static counterparts (the p values obtained by doing one-sided t-test comparing classification accuracy from dynamic and static metrics were very small). Further, the peak accuracy obtained from dynamic metrics exceeded 90% while that was not the case for static metrics. This proves that dynamics of FC and EC provides additional sensitivity to underlying pathological processes over and above that obtained from traditional static connectivities. Fig.2 presents the highest ranked features (connectivities, shown as paths) corresponding to peak accuracy, with most discriminative power. There were substantially less number of paths of PTSD > control for DEC, than vice versa. For DFC, all features were greater in controls and none in PTSD. Conversely, there were substantially more paths for which PTSD>control than vice versa, for SEC. Note there were no significant SFC paths which were greater in controls than PTSD while many SFC paths were stronger in PTSD than controls. These results support previous studies showing overall hyper-connectivity in PTSD [11]. In addition, the results surprisingly show that PTSD subjects had lower dynamic variability of both FC and EC implying that PTSD patients are prone to engage in certain negative states characterized by hyper-connectivity for longer times and cannot easily dis-engage from that state. This attribute of brain networks in PTSD seems to predict their diagnostic state better than just general hyper-connectivity. This demonstrates the clinical utility of the investigation of connectivity dynamics over and above the insights obtained from traditional connectivity.

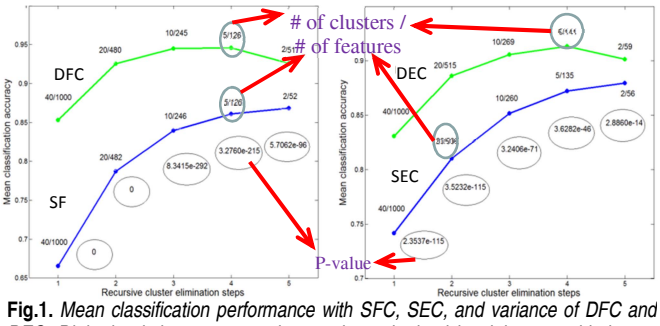

Fig.1. *Mean classification performance with SFC, SEC, and variance of DFC and DEC. Digits in circles represent the p values obtained by doing one-sided t-test comparing classification accuracy of dynamic and static metrics.*

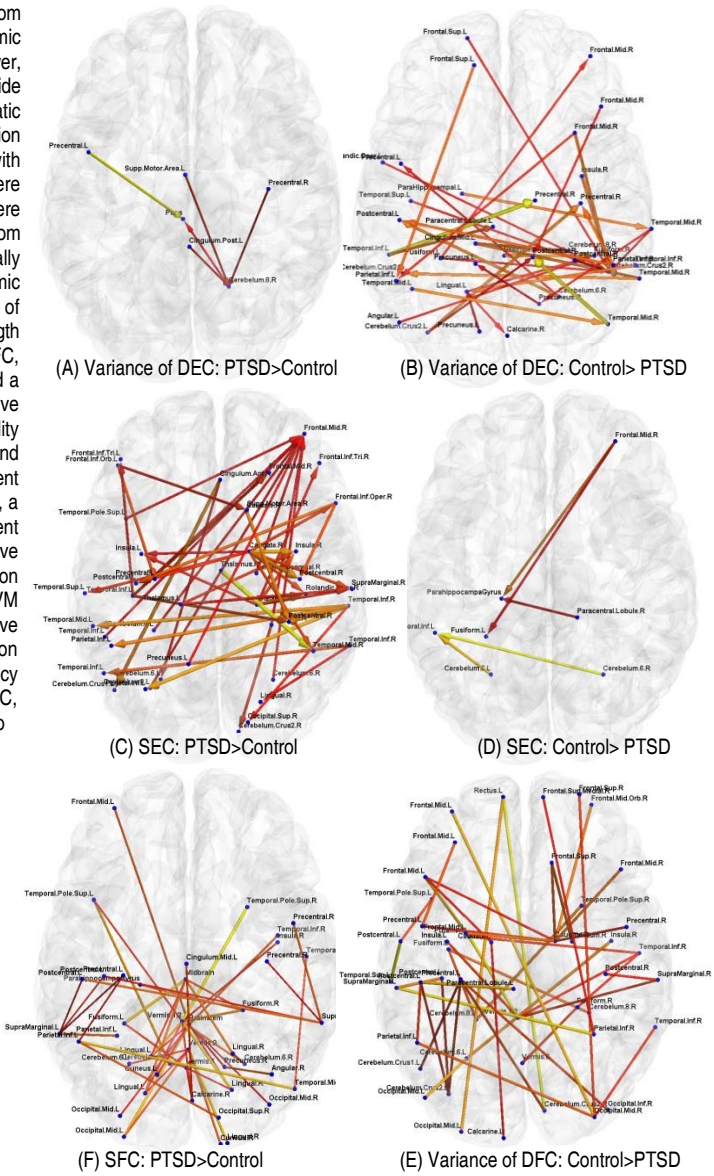

Fig.2 *Brain networks with top-ranked paths for predicting the diagnostic label of a given subject with peak accuracy using FC & EC. The thickness and color of paths correspond to their rank from RCE-SVM (top rank: yellow, bottom rank: red). (A) and (B) show paths where variance of DEC for controls is significantly less (A)/more (B) than PTSD. (C) and (D) show paths where SEC for controls is significantly less (C)/more (D) than PTSD. (E) shows paths where SFC for controls is significantly less than PTSD. (p=0.05). (F) shows paths where variance of DFC for controls is significantly more than PTSD.*

References: **1**. Chang *et al*, Neuroimage, 50(1): 81–98, 2010. **2**. Handwerker *et al*, Neuroimage, 63(3):1712-9, 2012. **3**. Deshpande *et al*, Lecture Notes in Computer Science, 4091:17-24, 2006. **4**. Hutchison *et al*, Neuroimage, 80: 360-78, 2013. **5**. Sakoğlu *et al*, MAGMA, 23(5-6): 351-66, 2010. **6**. Li *et al*, HBM, *in press*. **7**. Craddock *et al*, HBM, 33(8):1914-28, 2012. **8**. Havlicek *et al*, Neuroimage, 53(1): 65-77, 2010. **9**. Deshpande *et al*, IEEE Trans. Biomed. Eng., 57(6): 1446-56, 2010. **10**. Deshpande *et al*, PLoS One, 5(12): e14277, 2010. **11**. Sripada *et al*, Psychosomatic Medicine, 74(9): 904-11, 2012.