Static and Dynamic Functional Connectivity Impairments in Concussed Soldiers with and without PTSD

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Introduction: Military service members who sustain mild traumatic brain injury (mTBI) are at risk of developing post-concussion syndrome (PCS) and posttraumatic stress disorder (PTSD). Although PTSD has been characterized by functional hyper-connectivity[1,2], results on PCS have been mixed and inconclusive[3]. Therefore, a mechanistic neurobiological basis for PTSD with and without PCS has been elusive. In this work, we addressed this issue by performing connectivity analysis of resting state fMRI data and obtained both static functional connectivity (SFC) and dynamic functional connectivity (DFC) measures. We used these measures to test the hypothesis that PTSD with and without PCS is associated with higher connectivity strength (SFC) but lower connectivity variance (variance of DFC calculated over time) as compared to healthy controls. The basis for hypothesizing higher connectivity strength are previous studies of hyperfunctional connectivity in PTSD[1,2] whereas the latter is based on evidence that reduced temporal variance is generally associated with ill-health in biological systems; which reflects compromised ability to dynamically adjust (e.g., behavior, thoughts, etc.) to changing conditions. In addition, it has been shown that DFC is relevant to neuropathology[4] and behavioral performance in different domains (alertness, cognition, emotion, and personality traits)[5]. Further, we hypothesized that connectivities would be more extreme, i.e. higher SFC and lower variance of DFC, in subjects with comorbid PCS and PTSD compared to subjects with PTSD alone, indicative of symptom severity worsening with the degree of disorder (see Fig.1).

Fig.1 *Illustration of our hypothesis: increasing font size of SFC implies connectivity strength (SFC) is increasing from controls to PTSD to PCS+PTSD. Similar logic applies to DFC.*

Methods: Eighty-seven Soldiers, 17 with PTSD, 42 with both PCS and PTSD (PCS+PTSD), and 28 matched controls (matched in age, gender, race and education), all having combat experience in Iraq and/or Afghanistan, were recruited for the study. Subjects were scanned in a 3T MAGNETOM Verio scanner (Siemens Healthcare, Erlangen, Germany) using T2* weighted multiband EPI sequence in resting state, with TR=600ms, TE=30ms, FA=55°, multiband factor=2, voxel size= 3×3×5 mm^3 and 1000 volumes. After standard preprocessing, the data was deconvolved to obtain latent neuronal variables[6]. Mean deconvolved fMRI time series were obtained from 125 functionally homogeneous regions based on the cc200 template[7]. SFC and DFC were obtained between all pairs of regions using Pearson's correlation and its sliding windowed version, respectively. The window length was adaptively determined based on time series stationarity using augmented Dickey-fuller test[5]. Significant group differences in SFC (and variance of DFC) were obtained for all pairs of connectivity paths ($p<0.01$ FDR corrected, controlled for age, gender, race, education & head motion).

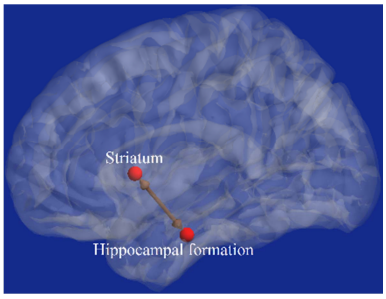

Fig.2 *Sagittal view showing the path between striatum and hippocampal formation*

Results: The connectivity path between left striatum and right hippocampal formation (includes hippocampus and parahippocampal gyrus; see Fig.2 for sagittal view) showed higher connectivity strength and lower connectivity variance in PCS+PTSD and in PTSD as compared to controls, in accordance with our hypothesis (Figs. 3 & 4). Connectivity values also correlated significantly with behavioral scores (verbal memory task by CNS-Vital Signs[8]) and symptom severity in PTSD (PTSD-Checklist-5 [PCL5] score) and PCS (Neurobehavioral Symptom Inventory [NSI] score), thus highlighting their relevance to the underlying neuropathology (Table.1). It is notable that no significant paths supporting our hypothesis were obtained from preprocessed fMRI data without hemodynamic deconvolution, indicating the value of removing HRF variability and smoothing from fMRI time series even for functional connectivity analyses. Previous literature has shown both stronger and weaker SFC in PTSD as compared to controls[1,2]. Hence we also looked for paths which had lower SFC and lower variance of DFC in disease compared to controls, but none of the paths fit this hypothesis using either deconvolved or non-deconvolved data.

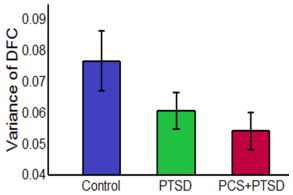

Fig.3 *Variance of DFC values for the three groups*

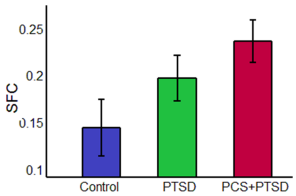

Fig.4 *SFC values for the three groups*

Table.1 *Correlation value (R) and corresponding p-value for the correlation of behavioral measures and symptom severity with SFC and variance of DFC*

Behavioral Measure	SFC		Variance of DFC	
	R	p-value	R	p-value
Verbal memory	-0.4239	5.57×10^{-09}	0.5482	4.89×10^{-15}
Symptom Severity				
PCL5 score	0.5884	1.37×10^{-17}	-0.5112	5.71×10^{-13}
NSI score	0.5671	3.43×10^{-16}	-0.4909	6.15×10^{-12}

Discussion: Our results are interesting given that individuals with PTSD (and PCS) have cognitive impairments[1-2]. Habit learning and memory, associated with perseverative thinking, involves the striatum while declarative memory involves hippocampus. Previous studies have showed that traumatic experiences[9] and stress[10] respectively increase activation of striatum and decrease activation of the hippocampus, leading to a shift from declarative to habit formation[11]. Subjects with PTSD frequently perseverate on traumatic memories, more frequently and intensely than they do for memories of other events. There might exist a fine balance between hippocampal and striatal memories, which determines relative emphasis received by each of the memories. An imbalance in this mechanism could be indicative of stress related conditions[12].

Memories of stressful negative life events, necessary for PTSD, have been found to increase the structural connectivity between striatum and hippocampus[13], which might explain our findings of higher SFC in PTSD and PCS+PTSD. Moreover, Cisler et al.[14] show that there is increased SFC between hippocampus and striatum during a 'repeated exposure to traumatic memory' task in PTSD subjects, which supports our results. A critical point is that the lower variance of DFC indicates that there is a lack of adaptability and regulation between these regions, suggesting that PTSD is associated with a hyper-connectivity state from which it is difficult to disengage, often observed with habit formation. This characterization fits well with behavioral manifestations in co-occurring PTSD and PCS.

References: **1.** Larson et al., Rehab Psych. 8(3):245-52,2013. **2.** Hayes et al., Front Integ Neurosci. 9;6:89,2012. **3.** Eierud et. al., Neuroimage Clin. 4:283-94,2014. **4.** Sakoğlu et al., MAGMA 23(5-6):351-66,2010. **5.** Jia et al., Brain Conn. 2014 (in press). **6.** Wu et al., Med Image Anal. 17(3):365-74,2013. **7.** Craddock et al., Hum Brain Mapp. 33,1914–1928,2011. **8.** http://www.cnsvitalsigns.com/AcademicResearch.html **9.** Goodman et al., Rev Neurosci. 23(5-6):627-43,2012. **10.** Schwabe et al., Biol Psychiatry. 74(11):801-8,2013. **11.** Packard, Brain Res. 1293:121-8,2009. **12.** Ghiglieri et. al., Prog Neurobiol. 94(2):102-14,2011. **13.** Favaro et al., Psychiatry Res. 223(2):157-63,2014. **14.** Cisler et al., J Psychiatr Res. 48(1):47-55,2014.