Impaired executive function exacerbates neural markers of PTSD

Audreyana Jagger-Rickels[1,2], Anna Stumps[1,3], David Rothlein[1], Hannah Park[1], Francesca Fortenbaugh[1,3,4], Agnes Zuberer[1,2], Jennifer R. Fonda[1,3], Catherine Fortier[3,4], Joseph DeGutis[1,3,4], William Milberg[3,4,5], Regina McGlinchey[3,4,5], and Michael Esterman[2,3,4,6]

[1]Research Service, VA Boston Healthcare System, [2]Department of Psychiatry, Boston University School of Medicine, [3]Translational Research Center for TBI and Stress Disorders (TRACTS), VA Boston Healthcare System, [4]Department of Psychiatry, Harvard Medical School, [5]Neuroimaging Research for Veterans (NeRVe) Center, VA Boston Healthcare System, [6]National Center for PTSD, VA Boston Healthcare System

Background

Posttraumatic stress disorder (PTSD) is heterogeneous in its symptom presentation, long-term outcome, response to treatment and apparent neurobiology.

Multiple sources of neurobiological heterogeneity:
1.) Nearly every large-scale brain network has been implicated in PTSD, however many of these studies used seed-based instead of large-scale whole-network based approaches.
2.) Emerging evidence for subtypes of PTSD based on dysfunction in neural network alongside cognitive impairments, that may underlie the development and maintenance of the disorder.

This study aimed to address these sources of heterogeneity by:
1.) Using a large-scale network-based approach when measuring the relationships between PTSD symptom severity and brain connectivity.
2.) Determining if subtypes of PTSD, based on normative-based cognitive dysfunction across multiple domains, had unique neural network signatures.

Methods

Imaging- 3T Siemens TIM Trio scanner (12-channel head coil), two T1-weighted anatomical MPRAGE scans and two T2* weighted fMRI scans (gradient echo-planar imaging - TR: 3000ms, TE: 30ms, flip angle: 90, 3x3x3.7 mm slices for 38 slices) were acquired during 8-12 minutes of rest.

Cognitive Composites - Using *a priori*, validated normative-based measures of memory, attention, and executive functioning, (Riely et al., 2019). Three groups for each cognitive domain were defined as impaired, average, and above average performance based on DSM-5 criteria.

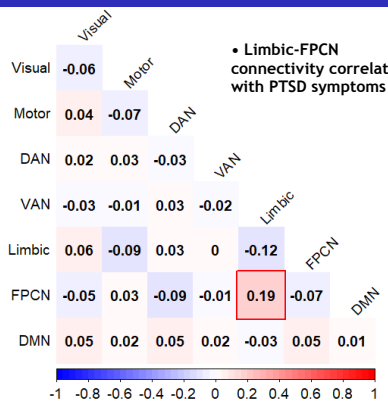
Network Correlations - Using the parcellation developed by Yeo and Colleagues, 7 networks between and within network average connectivity (28 connectivity values) were first correlated with PTSD symptom severity (CAPS-IV), followed by examination of PTSD and cognitive functioning interactions.

Hubs of Dysfunction (HoD) analysis - A graph-analytic approach to functional connectivity was employed that identified individual brain regions with a significant number of connections ("degree") related to PTSD symptom severity.

Demographics

Executive Functioning Subgroups	Total (N = 271)		Impaired (N = 35)		Average (N = 182)		Above Average (N = 45)	
	Percent							
PTSD Diagnosis	58.3		48.57		61.54		48.89	
Gender (Males)	90.0		88.57		89.01		93.33	
Mild Military TBI	42.4		34.29		42.86		46.67	
Depression Medication	21.4		22.86		20.33		22.22	
Epileptic Medication	2.6		5.71		1.65		2.22	
Sedative/Hypnotics Medication	6.6		5.71		6.59		6.67	
Pain Medication	27.3		31.43		24.73		28.89	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	31.2	8.0	32.8	7.9	31.02	8.22	30.22	6.99
Education	13.9	1.8	13.9	1.8	13.80	1.72	14.51	2.00
Depression (DASS)	8.0	8.7	9.2	9.6	7.90	8.68	6.79	8.26
WTAR**	35.2	7.3	32.3	8.3	34.75	6.99	39.71	6.31
CAPS	48.0	29.1	50.4	30.3	48.47	28.86	40.82	27.72
Memory Composite*	-0.30	0.99	-0.6	0.9	-0.29	1.02	0.09	0.87
Attention Composite**	0.10	0.58	-0.3	0.4	0.09	0.56	0.46	0.53
Executive Function Composite*	0.10	0.55	-0.6	0.4	0.08	0.42	0.75	0.34

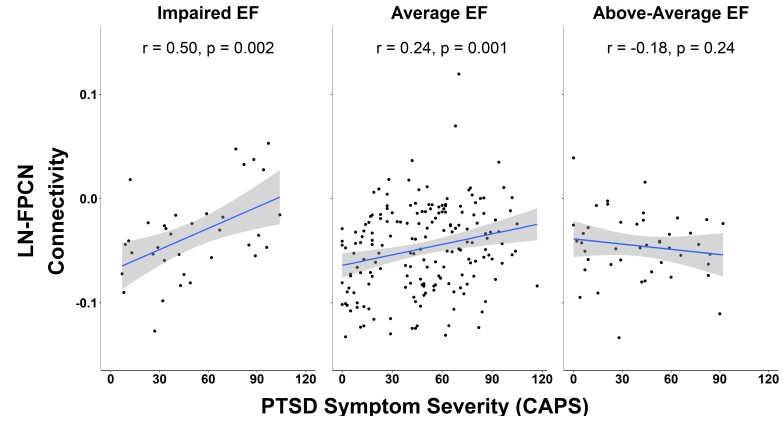
Network Correlations and the Effects of Cognition on Limbic/FPCN Connectivity



- Limbic-FPCN connectivity correlated with PTSD symptoms

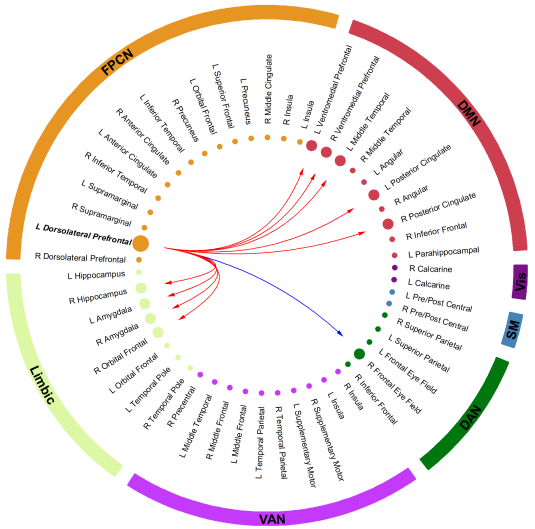
	Adjusted R^2	Predictor	β	p-value
Attention	0.03	PTSD Severity	0.23	0.17
		Attention	-0.03	0.84
		PTSD by Attention interaction	-0.02	0.93
Memory	0.03	PTSD Severity	-0.02	0.41
		Memory	-0.03	0.80
		PTSD by Memory interaction	0.24	0.31
Executive	0.07**	PTSD Severity	0.96	<0.001
		Executive	0.27	0.02
		PTSD by Executive interaction	-0.83	<0.001

- In Executive function (EF) model, main effects and interaction between PTSD and EF were significant.
- Reduced LN-FPCN coupling associated with PTSD was strongest in those with impaired EF, and absent in those with above-average EF.



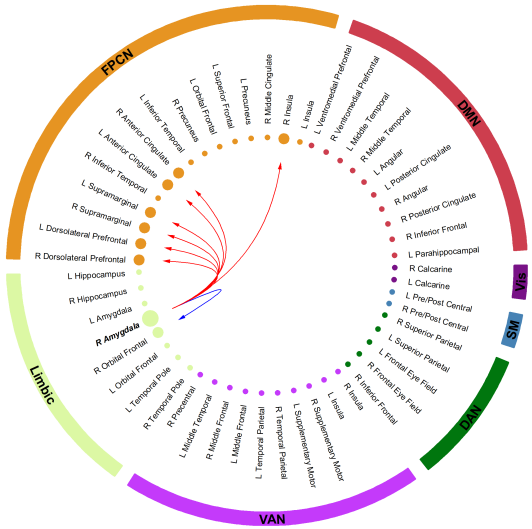
Hubs of Dysfunction Related to PTSD Symptom Severity

Left Dorsal Lateral Prefrontal Hub



- Left DLPC hub exhibited reduced negative coupling with limbic and default regions with greater PTSD.

Right Amygdala Hub



- Right Amygdala hub exhibited reduced negative coupling with multiple FPCN regions with greater PTSD.

Summary and Conclusion

- We found, through two different methods, that the PTSD symptom severity impacted regions within and between the Limbic and FPCN networks. PTSD was associated with reduced negative coupling between these networks.
- This was strongly modulated by executive functioning. Those with impaired EF showed this PTSD marker the strongest, while those with above average EF did not exhibit this neuroimaging marker of PTSD.
- This suggest that disrupted top-down regulation of emotional circuitry, alongside poor executive functioning and emotional regulation, may represent a subtype of PTSD.
- Future work should determine if EF serves as risk/protective factor for this PTSD-biomarker, and if this neurocognitive profile has implications for treatment.

Acknowledgments: US Department of Veterans Affairs through the Translational Research Center for TBI and Stress Disorders (B3001-C); VA Rehabilitation Research & Development Traumatic Brain Injury National Research Center; Merit Review Award from the VA Clinical Sciences Research and Development Service (I01CX001653); VA Rehabilitation Research & Development SPIRE Award (1I21RX002737)