Examining Amygdala Resting-State Functional Connectivity Alterations Associated with Depressive Symptoms in Chronic Moderate-Severe Traumatic Brain Injury

TEMERTY FACULTY OF MEDICINE
UNIVERSITY OF TORONTO

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab Michener Institute

Elfaki, Layan BSc[1,2]; Sharma, Bhanu PhD[3]; Meusel, Liesel CPsych[2]; So, Isis MSc[4]; Collela, Brenda MSc[2]; Green, Robin PhD, CPsych[1,2]

[1]Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; [2]KITE-Toronto Rehabilitation Institute, University Health Network, Toronto, Ontario, Canada; [3]Department of Medical Sciences, McMaster University, Hamilton, Ontario, Canada; [4]Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada

Background

- **Depression**: most common psychiatric sequelae of moderate-severe TBI (msTBI), affecting 26-36% of survivors.[1]
- **Only two** studies have examined the association between resting-state functional connectivity (rsFC) and depression in chronic msTBI.[2,3]

  (1) Han et al. (2015)[2]: significant hyperFC between amygdala and brain regions associated with the salience network (SN), somatomotor network (SMN), dorsal attention network (DAN), visual network (VN), and central executive network (CEN) in patients with comorbid TBI and depression.

  (2) Luo et al. (2021)[3]: positive associations between depression scores and limbic-cognitive control rsFC and negative associations between depression scores and emotion regulation limbic-frontal rsFC.

Literature Gap

Neuroimaging studies **have yet** to identify a clinical biomarker of depression in chronic msTBI, or even non-TBI related depression, which has been more widely studied.

Objectives & Hypothesis

Objective 1a, Approach 1: Correlational seed-based connectivity analyses (SBCA) between amygdala rsFC and Personality Assessment Inventory total[4] Depression (sub)scale (PAI DEP-Tot) scores

Objective 1a, Approach 2: Investigating amygdala rsFC group differences between the *msTBI-depressive*, *msTBI-nondepressive*, and *healthy control* groups

Objective 1b: Characterizing TBI-related vs. depression-related activation through exploring rsFC of brain regions implicated in both comorbidities

Aim → contribute groundwork research to aid in the identification of a neural signature of depressive symptoms in chronic msTBI

Hypothesis: significant associations between amygdala rsFC and regions of the SN, SMN, DAN, VN, and CEN in depression post-TBI[2]

Methods

Secondary analysis on longitudinal data acquired for the Toronto Rehab TBI Recovery Study[5]

Demographic, Injury-Related, and Clinical Characteristics	msTBI-Depressive Group (SD)	msTBI-Nondepressive Group (SD)	Healthy Control Group (SD)
Participants	13	19	17
Age	37.15 (13.69)	38.47 (16.71)	38.59 (15.12)
Gender (% male)	53.8%	68.4%	29.4%
Years of Education	14.15 (2.21)	15.42 (1.84)	15.12 (2.63)
Length of PTA 1-7 days 1-4 weeks >4 weeks N/A	 4 4 5 0	 3 11 3 2	 N/A
Time since injury (months)	20.23 (8.53)	18.89 (10.58)	N/A
PAI DEP-Tot scores	74.54 (13.61)	47.79 (5.96)	N/A

Data
- Clinical and neuropsychological assessments and BOLD fMRI resting-state scans acquired at 6, 12, and 30+ months post-injury.
- PAI DEP-Tot ≥60 as depressed and <60 as nondepressed

Imaging
- MRI preprocessing (FSL 6.0)
- Whole-brain seed-based connectivity analysis (SBCA)
- Group analyses: correlations and F-tests on amygdala, aPFC, PCC, and somatomotor region rsFC

Statistical analysis
- Non-parametric permutation testing; 5,000 permutations, TFCE FWE-corrected *p*-values

Results

Objective 1b:
Left aPFC rsFC Comparisons *the msTBI-depressive, msTBI-nondepressive, and healthy control* groups

After statistical correction, all group comparisons were nonsignificant, except for the **left aPFC** (LaPFC).

The LaPFC demonstrated **significantly** increased rsFC with 4 sensory/motor regions in the *msTBI-depressive* as compared to the *healthy control* group (*p*FWE < 0.05, TFCE corrected*)*.

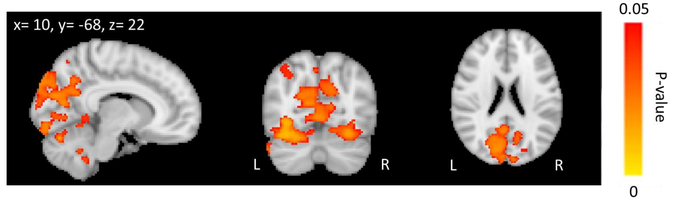

Figure 1. The left side of the image corresponds to the right hemisphere of the brain and vice versa. Images represent TFCE FWE-corrected *p*-values thresholded at an α level of 0.05, overlaid on the standardized MNI-152 brain. Group comparisons were controlled for age and YOE.

Region	Side	Peak Voxel Coordinates (MNI)	Cluster Size	TFCE Value	*p*FWE	Effect size
Fusiform gyrus	R	36, -68, -20	11,867	30,761	0.013*	1.616
Superior temporal lobe	R	54, -12, -4	685	24,941	0.032*	1.632
Fusiform gyrus	L	-30, -18, -30	119	22,729	0.041*	1.346
Precentral gyrus	R	62, 6, 36	29	22,443	0.042*	1.599

Results

Objective 1a, Approach 1 & 2: Correlations & Group Comparisons

- **No significant** correlations were found between all PAI DEP-Tot (sub)scales and bilateral amygdala rsFC (*p*FWE>0.05, TFCE corrected).
- **No significant** differences were found between the *msTBI-depressive, msTBI-nondepressive*, and *healthy controls* groups (*p*FWE > 0.05, TFCE corrected).

Summary & Conclusions

- This study is first to investigate amygdala rsFC in a group of patients with exclusively msTBI (i.e., without patients in the mild range of TBI) and in the chronic stages of msTBI.
- Although the expected group differences in amygdala rsFC were not observed, between group differences in **aPFC rsFC** converge with previous research[6] and implicates this region for depression in chronic msTBI.
- Increased aPFC-sensory/motor rsFC could be a **clue signifying vulnerability to depression** post-TBI. Whether it represents an unsuccessful compensatory mechanism to alleviate depressive symptoms[7], or an underlying etiology of depression[8] **warrants further study**.
- **Limitations**: sample size and the use of PAI DEP-Tot scores to divide the depressed and nondepressed groups.
- **Future directions**: expanding sample size, recruiting clinically depressed patients, investigating rsFC of amygdala subregions independently due to differential connectivity findings.[9]

References

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Questions? Email → Layan.elfaki@mail.utoronto.ca
Twitter: @Layan.elfaki