University of British Columbia, Department of Medicine, Psychiatry , Psychiatry Research Day (10.15.2020)

# Alterations in Resting State Functional Connectivity in Patients with Traumatic Brain Injury Following a 3-Month Pilot Cognitive Intervention Program

Jessica M. Sevick[1,2], Naznin Virji-Babul[3,4], William J. Panenka[1,2,5]

## Background

Traumatic brain injury (TBI) often results in cognitive impairments related to alterations in brain structure and function. Facilitating functional recovery following TBI is a primary goal of neurorehabilitation, however the changes to the underlying neurobiological functional connections are not fully understood. Advances in neuroimaging techniques with the use of resting-state functional magnetic resonance imaging (rs-fMRI) have provided insight into the functional connectivity changes in TBI and their correlation to functional outcome following neurorehabilitation.

## Objectives

The purpose of the pilot study was two-fold:

1. To assess the differences in rs-functional connectivity in patients with TBI compared to healthy controls
2. To assess the recovery in functional connectivity following an intensive three-month cognitive intervention program in the patients with TBI.
3. To assess changes in rs-fMRI with changes with changes in cognitive function following intervention.

## Methods

Volunteers between the ages of 18-55 years who sustained a non-penetrating (mild to severe) TBI were recruited for the cognitive intervention program (n=8); all TBI participants had injuries occurring a minimum of 1 year prior to the start of the intervention, with persistent symptoms and residual deficiencies for over 1 year. Healthy controls were recruited based on age, gender and education, and were screened to ensure that they had no history of head trauma, neuropsychiatric disorders, substance abuse or any other neurological conditions (n=8). MRI scans were completed on a 3T Philips scanner and collected at baseline and at the 3-month time point, following intervention.

Rs-fMRI data processing and analysis was completed using the FMRIB Software Library's (FSL) MELODIC tool. Probabilistic independent component analysis (ICA) was used to decompose the data sets into brain networks with temporally correlated resting activity. Prior to decomposition, fMRI data was motion corrected, corrected for slice timing, spatially smoothed temporally filtered and linearly registered. Two different ICA analyses were performed to the preprocessed datasets. The first evaluated voxel-wise differences in resting-state fMRI between the TBI patients and controls using a dual regression analysis approach. The second evaluated voxel-wise differences between the TBI patients following the intensive three-month cognitive intervention. Significant group differences in functional connectivity were determined for the following networks of interest: default mode (DMN), sensory-motor (SMN), executive function (EFN), ventral attention (VAN), dorsal attention (DAN), left/right fronto-parietal (FPN), auditory, cerebellar and visual using threshold-free cluster enhancement. Group level analyses were completed using FSL's dual regression and randomise tools. Cognitive status was measured using the NIH Toolbox Cognitive Battery to assess assessing processing speed, memory, and executive function. Demographic corrected z-scores were used as the primary measure, with a global score being established for each demographic.

**Table 1:**

*Demographics of TBI patients.*

| Participant ID | Sex | Age | Years of education | Time since injury (years) | Etiology | Mechanism of Injury | Severity | Loss of Consciousness (Days) | Residual Deficiencies | Return to Work |
|---|---|---|---|---|---|---|---|---|---|---|
| S001 | M | 51 | 14 | 22 | TBI | MVA | Severe | 4 | Executive function, planning, clarity, kinetic perception, visual recognition | No |
| S002 | F | 50 | 18 | 29 | TBI | MVA | Severe | 16 | Mental fatigue, processing speed, emotional control, working and associative memory, executive function | Yes |
| S003 | M | 36 | 16 | 24 | TBI | Multiple Concussion | Mild | None | Attention, mental clarity, emotional control, substance abuse, speech, empathy and social perception | No |
| S004 | M | 41 | 12 | 8 | TBI | MVA | Severe | 14 | Mental endurance, focus, executive functioning, inability to complete activities of daily living, mental health issues | Yes (part-time, contract) |
| S005 | M | 18 | 13 | 2 | TBI | Multiple Concussion | Mild | None | Mental initiative, mental fatigue | No |
| S007 | F | 48 | 20 | 4 | TBI | MVA | Mild | Not reported | Executive function, inability to complete activities of daily living | No |
| S008 | M | 26 | 13 | 6 | TBI | Fall | Severe | Not reported | Executive function, mental organization, mental health issues | No |
| S009 | F | 35 | 13 | 8 | TBI | MVA | Severe | 3 | Non-verbal and verbal communication, mental health issues, executive functioning, time management | No |

## Results

### Group Differences at Baseline

Group ICA demonstrated significant differences in voxel-wise connectivity in 10 of 30 identified components, between the TBI patients and healthy controls. The differences included not only declines in functional connectivity, but also augmentations. The decreases in functional connectivity were observed in the regions of the SMN and DAN ($p = 0.006$ to $0.036$), where-as the enhancements were observed in the regions of the visual network and the DFM ($p = 0.005$ to $0.015$). No changes were observed in the EFN, FPN, auditory or cerebellar networks.

### Changes in TBI Patients Following the Three-Month Cognitive Intervention

Analyses indicated that functional connectivity was higher in the SMN and DAN following the pilot three-month cognitive intervention program ($p = 0.001$ to $p = 0.039$). There were no changes observed in the visual or DFM networks.

### Changes in Cognitive Function Following the Three-Month Cognitive Intervention

Following the intervention, there was a statistically significant increase in the composite cognitive score in the TBI participants ( $p = 0.0002$).

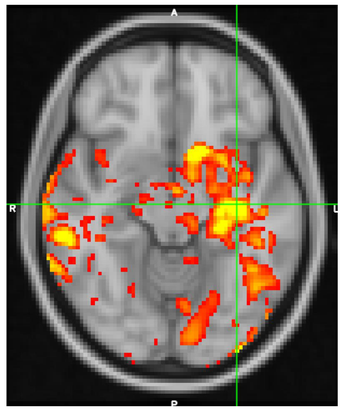


**Figure 1:**

*Dual regression and t-test analyses showing the differences in connectivity between TBI patients and healthy controls in SMN ($p<0.05$)*

## Discussion

Our findings suggest that there are multiple functional connectivity disturbances in patients with TBI, compared to controls. The data shows that while there are deficits in particular regions (as one might expect), there are enhancements in others. This suggests that there are possible compensatory mechanisms occurring in neuronal processes, exemplified further given that the patients are classified with chronic TBI. Following the pilot three-month cognitive intervention, there was a statistically significant increase in functional connectivity networks that had shown reduced connectivity compared to healthy controls. There was no change in the enhanced regions, suggesting that the compensatory mechanisms are still being implemented. The changes in cognitive scores in conjunction with the change in resting state connectivity gives evidence of changes in brain-behaviour relationship following intervention. The results from this pilot study provide preliminary evidence for functional network reorganization after cognitive rehabilitation in individuals with chronic TBI.

## Limitations

Given the small sample size of this pilot study, larger studies are warranted to validate the findings outlined above.

### References

1. Porter, S., Torres, I.J., Panenka, W., Rajwani, Z., Fawcett, D., Hyder, A., and Virji-Babul, N., 2017. Changes in brain-behavior relationships following a 3-month pilot cognitive intervention program for adults with traumatic brain injury. Heliyon 3 (2017) e00373. doi: 10.1016/j.heliyon.2017. e00373

### Acknowledgemejnts

[1] Department of Psychiatry, University of British Columbia, Canada
[2] British Columbia Mental Health and Substance Use Services Research Institute, Canada
[3] Djavad Mowafaghian Centre for Brain Health, University of British Columbia
[4] Department of Physical Therapy, University of British Columbia, Canada
[5]British Columbia Neuropsychiatry Program, Canada