Modulatory difference due to injury pattern in the moderate-TBI brain: Effective connectivity of working memory from preliminary findings

W J Chai¹, A I Abd Hamid¹²,³ and J M Abdullah¹²,³

¹ Department of Neurosciences, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Malaysia
² Brain Behaviour Cluster, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Malaysia
³ Hospital Universiti Sains Malaysia, Kubang Kerian, Malaysia

Abstract. Traumatic brain injury could cause cognitive deficits due to brain network disruption. The present study examined the effective connectivity of working memory in a group of moderate-TBI participants and making comparison with healthy controls. Group-level results of the n-back task with four levels of cognitive load (0-, 1-, 2-, and 3-back) identified activation in regions that corresponded with past literature of working memory, including the bilateral inferior occipital gyri, superior parietal lobules, and superior frontal gyri that were specified as regions of interest for subsequent dynamic causal model specification. The modulatory inputs were differentially defined in six models for every participant. Bayesian model selection directed to different winning models between the groups based on injury patterns. The moderate-TBI group with left hemisphere injury favoured connectivity involving a bottom-up left-to-right modulation, whereas the healthy group and TBI group with injuries involving both hemispheres preferred the connectivity model with a bottom-up modulation that is bilateral and bidirectional. The left-lateralized modulatory pattern reported in the moderate-TBI participants implies the role of the left hemisphere in attending to cognitively demanding tasks, especially in individuals with a disrupted neural network. Future studies could work on expanding the connectivity analyses based on the current finding.

1. Introduction
The neural network in the injured brain is commonly understood to be disrupted after trauma [1]. Such disruption usually manifests as cognitive impairments that could inconvenience daily life functioning. The frontoparietal region is oft-implied to be involved during higher-order cognitive tasks such as working memory [2–4]. Among the vast literature investigating the neuroscientific basis of traumatic brain injury (TBI), functional magnetic resonance imaging (fMRI) as an advanced neuroimaging tool provided promising insight to the underlying patterns of brain responses and networks [1,3].

For a start, using fMRI data, connectivity analyses that attempt to map the brain network revealed how different brain regions work in synchrony and communicate within and between hemispheres to ensure highly orchestrated neuronal activity, such as to reorganize when network disruption occurs following injury.

One such analysis, the effective connectivity, taps into the causal relationship of functional network connections between brain regions by modeling the coupling strengths and directions [5]. By estimating the posterior parameters of a model, effective connectivity explains the observed statistical
dependencies (correlations) between activated regions. Dynamic causal modeling (DCM) is a well-known method for presuming effective connectivity from neuroimaging data. DCM uses a Bayesian approach to state-space model comparison by generating parameter estimates of predefined models that best fitted the data (i.e., model with the highest evidence). It considers the time-dependence and nonlinearity of hemodynamic responses usually recorded in fMRI data. Such endogenous and exogenous inputs are modelled to test hypotheses on neural dynamics [5].

The present study examined the effective connectivity of working memory between two groups of participants: healthy and moderate-TBI. It was expected that there will be a difference in coupling strengths and modulatory influence between the two groups.

2. Materials and Methods

A 3-Tesla Philips Achieva MRI scanner (Achieva, Philips, the Netherlands) was used for data acquisition. Eighteen participants (10 healthy controls and 8 moderate-TBI patients) performed the alphabetical n-back working memory task with four levels of cognitive load (0-, 1-, 2-, and 3-back) in a block-design paradigm (see figure 1). The participants were all right-handed and right eye-dominant males who had attended at least nine years of formal education. In the moderate-TBI group, all participants sustained injury involving the frontal, temporal, or parietal lobes that ranged between 9 and 12 in the Glasgow Coma Scale (GCS) upon admittance [6].

![Figure 1. The block-design paradigm](image)

2.1. Data pre-processing

Data was pre-processed with the following steps: (1) slice-timing, (2) realignment, (3) co-registration, (4) segmentation, (5) normalisation, and (6) smoothing, using Statistical Parametric Mapping (SPM12) (Wellcome Centre for Human Neuroimaging) embedded in MATLAB 9.5 R2018b (Mathworks Inc.). These steps were undertaken to remove artefacts such as head motion and to increase the signal-to-noise ratio for statistical comparison across subjects.

2.2. Statistical analysis

Pre-processed data was statistically analysed using the general linear model in SPM12. Random-effects analysis (RFX) that takes into account the between- and within-subjects variability was performed to identify significantly activated brain regions during the task at the four different cognitive loads. The α level was set at a threshold value of .001 without correction ($p_{uncorr.} < .001$).

2.3. Effective connectivity

The DCM function (DCM12.5) in SPM12 was used to generate, estimate, and compare models.

2.3.1 VOI definitions. The volumes of interest (VOIs) were extracted based on the RFX group results and past literature that pointed to the frontoparietal network regions and visual cortex due to task nature [7-10]. The statistical outcome flagged six bilateral regions: the inferior occipital gyri (IOG), superior parietal lobules (SPL), and superior frontal gyri (SFG). The VOIs were defined within a sphere of 5mm.
2.3.2 Model space. Endogenous connections were assumed for all regions in a forward and backward direction. All visual events were regarded as the driving input. Meanwhile, the 1-back condition was modelled as a “low WM load” condition whereas the 2- and 3-back condition as the “high WM load” condition. In all models, the driving input was directed to the bilateral IOG, and modulatory inputs (low and high WM load) exerted their influence bilaterally or unilaterally (see figure 2). Six models (a – f) were specified for each subject.

Figure 2. Model space (endogenous connections not illustrated).

2.3.3. Bayesian Model Selection (BMS). All models were compared using BMS at the RFX group inference level as two separate groups (healthy and moderate-TBI) to identify the optimal model. The winning model would be the one with the highest exceedance probability, which indicates the most probable model over other models.

3. Results and Discussion
Out of the 18 participants, two data had to be discarded due to instrumentation during data acquisition that resulted in incomplete scans. Sixteen sets of data from 9 controls ($M_{age} = 27.00, SD = 9.21$) and 7 patients ($M_{age} = 28.86, SD = 15.32$) underwent analysis. Of the 7 patients, 5 sustained injuries involving only the left hemisphere while the remaining 2 patients had injuries on both sides of the brain.

3.1. DCM results
Bayesian model selection reveals that the winning model for the healthy controls was Model 4 (bilateral modulation) (see Figure 2.d). However, the winning models for the moderate-TBI group differed based on the injury patterns. The TBI group with only within-left injury favoured Model 5 (see Figure 2.e), which showed left to right modulation, whereas those with bilateral injury preferred Model 4. Subsequently, Bayesian parameter averaging (BPA) was performed for the respective winning models in these groups. The averaged modulatory parameters were illustrated in figure 3.

3.2. Modulatory difference between groups
Relating the current findings to past literature, a few studies implicated the left-lateralized nature of connectivity of working memory, mostly in healthy subjects [1,3,4,8,11]. It is understood that the left hemisphere is commonly involved in the processing of verbal information or language-based (as opposed to spatial) cognitive tasks [4,8]. In fact, as load increased, connections within the left hemisphere were also reported to be enhanced [11]. Correspondingly, the nature of the working memory task in the present study might require articulatory rehearsal that engages the left hemisphere, which could explain the left to right modulatory effects observed in the left-hemisphere-injured moderate-TBI group. Yet, such conjecture on left-lateralization does not invalidate the bidirectional modulation in the healthy group. Merely, it might suggest that the working memory task was deemed more effortful and cognitively loaded for the TBI group with left-sided injury. Meanwhile, aside from
risking any comparison made negligible due to the extremely small sample size for the bilaterally injured group, the similar winning model in this group to the healthy participant’s suggested compensatory effort post-injury that engaged both hemispheres. The current connectivity analysis exerted the modulatory influence in a bottom-up manner (from the IOG to SPL then to the higher-order frontal cortex). Further analyses could examine the top-down influence by constructing models of different families.

Figure 3. Modulatory parameters for Model 4 (a) of control and (b) moderate-TBI group with bilateral injury, and Model 5 (c) of moderate-TBI with left-hemisphere injury.

4. Conclusions
The present investigation hints at the difference in the modulatory influence of working memory between the healthy and moderate-TBI groups, especially for those with injury involving only one side of the brain. Although insightful, it remains overly simplistic to be conclusive over this preliminary interpretation, and such finding should be received with caution.

5. References
[1] Hillary F G, Medaglia J D, Gates K, Molenaar P C, Slocomb J, Peechatka A and Good D C 2011 Brain 134 1555–70
[2] Dima D, Jogia J, and Frangou S 2014 Hum. Brain Mapp. 35 3025–35
[3] Dobryakova E, Boukrina O, and Wylie G R 2015 Brain Connect. 5 433–41
[4] Ma L, Steinberg J L, Hasan K M, Narayana P A, Kramer L A and Moeller F G 2012 Hum. Brain Mapp. 33 1850–67
[5] Friston K J 2011 Functional and effective connectivity: a review Brain Connect. 1 13-36
[6] Farrer T J 2017 Encyclopedia of Geropsychology ed N A Pachana (Singapore: Springer)
[7] Deserno L, Sterzer P, Wu’stenberg T, Heinz A and Schlagenhauf F 2012 J. Neurosci. 32 12–20
[8] Harding I H, Yücel M, Harrison B J, Pantelis C and Breakspear M 2015 Neuroimage 106 144–153
[9] Nissim N R, O’Shea A M, Bryant V, Porges E C, Cohen R and Woods A J 2016 Front. Aging Neurosci. 8 328
[10] Dixon M L, de la Vega A, Mills C, Andrews-Hanna J, Spreng R N, Cole M W and Christoff K 2018 PNAS 115 E1598
[11] Honey G D, Yu C H Y, Kim J, Brammer M J, Crouduc T J, Suckling J, Pich E M, Williams S C R and Bullmore E T 2002 Neuroimage 17 573–82

Acknowledgments
This research project and its presentation are financially supported by the Trans-disciplinary Research Grant Scheme (TRGS) 203/PPSP/6768003 and SfN (Kelantan Chapter). The authors wish to extend their gratitude to Hazim Omar, Athirah Rainahah Abdul Wahab, Alwani Liyana Ahmad, Sharifah Aida Shekh Ibrahim, Che Munirah Che Abdullah, Wan Nazyrah Abdul Halim, and Siti Afidah Hamat.