The effective connectivity of the default mode network following moderate traumatic brain injury

M R Abdul Rahman1,2, A I Abd Hamid1,3,6, N A Noh5, Z Idris1,3,4, and J M Abdullah1,3,4
1 Department of Neurosciences, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Malaysia
2 School of Medical Imaging, Faculty of Health Sciences, Universiti Sultan Zainal Abidin, 21300 Kuala Nerus, Malaysia
3 Brain Behaviour Cluster, Universiti Sains Malaysia, 16150 Kubang Kerian, Malaysia
4 Department of Neurosciences, Hospital Universiti Sains Malaysia, 16150 Kubang Kerian, Malaysia
5 Department of Basic Medical Sciences, Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, 55100 Kuala Lumpur, Malaysia

Corresponding author: aini_ismaira@usm.my

Abstract. The effective connectivity can reveal the causal relationships between nodes of the Default Mode Network (DMN), which may reveal any impairment to the network following moderate traumatic brain injury (MTBI). Eight sub-acute MTBI patients and eight controls were recruited for this study. The results indicated that effective connectivity (EC) within MTBI group was higher in number and strength compared to the controls. Moreover, the network hubs within DMN are associated with increased connection strength in MTBI group. The ECs in MTBI are also largely influenced by top-down backward connections. In conclusion, the network reorganization within the DMN reflects the effect of MTBI and may subsequently impair other brain functions. This knowledge can be used to correctly identify the patient for appropriate trauma management.

1. Introduction
Traumatic brain injury (TBI) causes debilitating effects to its victims and incurs significant socioeconomic problems on public health care [1]. Globally, its incidence has surpassed even some of the more complex diseases such as breast cancers [2]. In terms of severity, mild TBI has been suggested to affect normal brain functions [3], thus with increasing severity, TBI can seriously impair the quality of life of its survivors. Therefore, research into more severe TBI is imperative to alleviate the effects that ensue.

For over two decades, the resting-state studies have contributed to the knowledge of how TBI progresses over time. One of the most studied resting-state networks is the Default Mode Network (DMN) [4], and it has been suggested that the DMN can serve as a biomarker to the functional integrity of the brain and can predict impairments to other brain functions [4]. Through the analysis of effective connectivity (EC), influencing regions of the DMN that underlie its’ functional connections can be studied to better understand the causal effect of TBI [5], and therefore accommodate TBI survivors on maintaining a good quality of life.
In this study, we emphasize on patients suffering from moderate TBI (MTBI) in identifying and comparing the EC within the DMN with healthy control groups. We hypothesized that the DMN of MTBI patients will be altered consequent to injury, and that there will be a difference in network organisation, strength, and the number of the EC between MTBI patients and healthy controls.

2. Materials and Methods

2.1. Participants

Eight sub-acute MTBI and 8 healthy male participants (mean age MTBI: 27.63±14.7 years, control: 27.5±9.7 years) were recruited for this study. The controls were sampled randomly from the population (selected from a number of respondents to our advertisement) and matched with MTBI patients for their gender, race, age, and minimum education level. MTBI is defined as having the score of 9-12 on the Glasgow Coma Scale (GCS) [6]. All MTBI patients have no abnormal head computerized Tomography (CT) scan findings, no history of mental illness, and no history of TBI prior to the current injury.

2.2. Image acquisition

All participants were scanned using 3T MRI scanner (Achieva, Philips, Netherlands) located at Hospital Universiti Sains Malaysia using the following protocol: resting-state fMRI images were acquired using a 32-channel head coil with an echo-planar imaging (EPI) sequence (matrix size = 80 × 80, 35 oblique slices, TR = 1700 ms, TE = 33 ms, FA = 90°, field of view = 240 mm², slice thickness = 3 mm with 0 mm gap, interleaved slice acquisition) for 10 minutes. The functional DICOM data were checked for integrity by calibration process and converted into NIFTI format using MRIconvert.

2.3. Data analysis

BOLD-fMRI analysis was performed using Statistical Parametric Mapping version 12 (SPM12). Standard pre-processing steps from Seri et al. (2019) was adopted [7], except Gaussian smoothing was done at 8 mm full-width half-maximum. Statistical estimation was done using the general linear model to generate the statistical map that would be used for blood-oxygen-level-dependent (BOLD) signal extraction in the following EC analysis.

Dynamic causal modelling (DCM) analysis was performed to identify the EC. Four nodes associated with DMN [8] were identified for each participant; posterior cingulate cortex (PCC) (0, -52, 26), left inferior parietal lobule (LIPL) (-50, -63, 32), right inferior parietal lobule (RIPL) (47, -68, 35), and medial prefrontal cortex (MPFC) (3, 54, -2). BOLD signals were extracted from a spherical volume of interest set at 8 mm radius from the coordinates and analysed using DCM 12.5. In identifying the EC, approach by Di and Biswal (2014) was adopted where endogenous connectivity parameters were varied between the previously defined four nodes, with three different sets of possible combinations: PCC ↔ MPFC, LIPL ↔ RIPL, and LIPL/RIPL ↔ PCC/MPFC [8].

Using this approach, a total of 30 connectivity models were generated and analysed. Afterwards, all models were compared using Bayesian Model Selection (BMS) to determine the best model for MTBI and control group. Each model had undergone random-effects inference method and the likeliness probability graph was plotted (See Supplementary Material). Finally, the connectivity values of the best models were averaged across subjects in respective groups using Bayesian Parameter Averaging (BPA), in which the average parameters of connections were derived by combining the posterior precision matrices and the posterior mean of the winning models across the subjects in their respective groups [9,10].

3. Results and Discussions

Figure 1 illustrates the averaged endogenous connections of the best model for each group. There is a higher number of endogenous connections in MTBI patients, compare to healthy participants. Based on the winning models, we found influencing relationship between LIPL/RIPL and PCC/MPFC for both groups, with the addition of bilateral connections between LIPL and RIPL. However, the best model for the control group did not demonstrate significant connections between PCC and MPFC,
though the connection was alluded in the winning model. Furthermore, the connections between RIPC and PCC, though present in the winning model of the control group, did not survive statistical significance.

Additionally, overall connectivity parameters showed increased connectivity strength in MTBI than controls. This can be seen especially in connections directed towards the network hubs of the DMN; PCC and MPFC. The highest averaged strength was from PCC to MPFC (mean strength: 0.90) followed by LIPC to PCC (mean strength: -0.75). In contrast, the largest EC in controls was from MPFC to LIPC (mean strength: -0.60). There were also higher numbers of negative EC in MTBI (7 connections) compared to controls (3 connections). The sign of EC value indicated the nature of connection; positive value suggested a forward bottom-up influence, while negative value suggested backwards top-down influence [5].

The main findings suggested that the ECs of the DMN were altered in organisation, number, and strength within the MTBI group when compared with the controls. Interestingly, our controls show different EC compared to the previous study; reciprocal influence between LIPC/RIPC and PCC/MPFC as opposed to one-way EC found by Di and Biswal [8]. Their study also suggested a causal connection from MPFC to PCC, which we did not find in our control cohort – instead, we found non-significant EC from PCC to MPFC. This could be caused by our small sample (8 participants) compared to the previous study (64 participants). Additionally, our sample is fairly homogeneous; participants are all male and racially similar. Therefore, our different findings might be inclined towards the Malay males, and further studies should be done to validate this observation.

The winning model for the MTBI group showed that there were significant reciprocal EC between all four nodes of the DMN, with higher connectivity strength compared to the control group. This could be attributed to the compensatory mechanism of the DMN following injury, where an increase in the number of functional connections and strength signals the brain’s adaptive process in compensating for impaired structural connection [11]. Furthermore, from our model, PCC and MPFC – two network hubs of the DMN – were associated with most of the higher connection strength. This was in line with literature which suggested that most rerouting of functional connections will go through network hubs, in order to minimise network cost [11]. This compensatory mechanism might predict impairment in other brain functions, especially when DMN maintains activation in the presence of resource-demanding tasks [4].

It is interesting to note that the higher presence of negative connections in MTBI may suggest that the ECs were influenced by top-down processing; higher-order information was passed to the lower order nodes to infer context [12]. However, the largest EC value in MTBI was a forward connection.
from PCC to MPFC, which was supported by the role of PCC in integrating bottom-up forward processing [13]. In a similar fashion, the top-down connections within the control group were appropriately influenced by MPFC; a higher-order node of DMN [12].

The main limitation of the current study was the small number of MTBI participants. Due to our purposive method of sampling, we rely on the admission and consent of patients that meet our inclusion criteria, which yielded a small number of participants. Therefore, our findings should be treated as preliminary at best, and future studies with a larger sample size should be conducted to establish these results for the general population.

4. Conclusion
The causal connectivity of the DMN provides valuable information into the extent of TBI on normal brain functions. Our results of network reorganisation and increased functional connectivity in DMN subsequent to MTBI may be used to predict deterioration in other brain functions, thus offering a better post-trauma prognosis. However, our findings are preliminary and future studies with a larger sample size should be conducted in order to translate this knowledge to the general population.

5. References
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