Title: Use of the Longitudinal Model of Variance Components to Determine Hyper-Connectivity in Patients with Severe Traumatic Brain Injury Using Rs_fMRI Data

Running Title: Determine Hyper-Connectivity in Patients with TBI

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Highlights

- Traumatic Brain Injury(TBI) severely increases functional connectivity in the brain of people with the disease.
- In the group of people with TBI disease, it was observed that an acute increase in functional connectivity occurred in three pairs of areas compared to the control group.
- The acute increase in functional connectivity affected individuals' cognitive functions, including sensory and motor functions.

Plain Language Summary

Brain injury is one of the most common diseases in the field of psychiatry. Patients with brain damage will have mild, moderate, or severe diseases. The effects of brain damage on patients' brains occur in a variety of ways. This means that a person may suffer severe physical and brain injuries. The human brain is divided into several regions, and each of these regions will communicate with other areas under the influence of a specific function. The extent and intensity of these connectivities should be standard. Various diseases and procedures increase or decrease the amount of connectivity between areas of the brain. One of the complications of severe brain injury is connectivity between different regions of the brain. This effect will sometimes appear as a decrease in connectivity and sometimes as an increase in connectivity between brain areas.

Recently, several studies have shown that brain damage increases the connection between areas of the brain. This increase has occurred acutely and will lead to complications. The effects of this acute increase are not yet fully understood and are being studied in various studies. In this study, several areas of the brain were selected that were overly interconnected, and the primary purpose of this study was to identify these areas and prove this. In the present study, it was observed that three pairs of regions of the brain of patients with severe brain injury experienced an excessive increase in connectivity.

Abstract

Background: Traumatic Brain Injury (TBI) is one of the leading causes of death globally and one of the most important diseases for the World Health Organization. Several studies have concluded that brain damage can dramatically increase Functional Connectivity (FC) in the brain. The effects of this hyper-connectivity are not yet fully understood and are being studied by neuroscientists. This study aimed to identify areas of the brain where, after brain injury, we have seen an acute increase in FC in those areas.

Method: The data used in this study were downloaded from the accessible Open fMRI site. Data included fMRI data of 14 patients with severe TBI and 12 healthy individuals. The longitudinal model of variance components investigated the difference between FC in the baseline effect and the longitudinal trend between the TBI and control groups.

Result: After fitting the longitudinal model of variance components, it was observed that there is no difference between the FC of the two groups due to the baseline effect. However, in the longitudinal trend of FC, there was a statistically significant difference between the three pairs of CL and CR, SFGL and SFGR, TL and TR in the TBI group compared to the control group.

Conclusion: The results showed that FC was sharply increased in 3 pairs of areas in people with TBI. This hyper-connectivity can affect individuals' cognitive functions, including motor and sensory functions. The exact extent of this effect is unclear and needs further investigation by neuroscientists.

Keywords: Traumatic Brain Injury (TBI), Hyper functional connectivity, fMRI neuroimaging, Longitudinal model of variance components, Cognitive brain functions

Introduction

Functional magnetic resonance imaging (fMRI) is a non-invasive technique that has become a standard criterion for imaging human brain function in healthy and diseased populations(Eklund, Lindquist, & Villani, 2017). One type of fMRI is resting imaging. This type of imaging was first used by Biswal et al. And is now very popular in neuroscience(Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995). One way to discover and study the brain mechanisms that underlie behavioral changes in individuals and patients is to look at brain networks(Bittencourt-Villalpando, van der Horn, Maurits, & van der Naalt, 2021). Brain networks affect functions such as vision, cognition, or movement control(McTeague, Goodkind, & Etkin, 2016). One of these brain networks is Functional Connectivity (FC), which can lead to discovering patterns and connections between brain areas. Increasing or decreasing FC in the brain can be a way to diagnose or treat neurological diseases early(Hart, Cribben, Fiecas, & Initiative, 2018). fMRI allows indirect measurements of neural activity. Therefore, fMRI can detect changes in functional brain communication associated with neuropathology, including brain damage(Anderson, Bigler, & Blatter, 1995; Crosson, Sartor, Jenny, Nabors, & Moberg, 1993). Traumatic Brain Injury (TBI) is one of the most important diseases of the World Health Organization. It is one of the leading causes of death and disability worldwide and affects adults and children at all economic levels and society(Levin, Meyers, Grossman, & Sarwar, 1981). A 2010 study found that approximately 57 million people worldwide are hospitalized with brain injury problems each year. But the exact relationship between life and disability caused by TBI is not clear(Organization, 2010). Recently, the use of resting fMRI data in patients with TBI has been expanding. MRI data of people with TBI show abnormalities in the frontal lobes, temporal lobe, and laterals and enlarging the brain's ventricles(Crosson et al., 1993). Studies have shown that ventricular enlargement is one of the best indicators of the severity of brain damage(Henry-Feugeas et al., 2000). Cognitive control disorders have also been observed in fMRI data associated with moderate to severe TBI(Scheibel, 2017).

Studies have shown that FC has increased abnormally and excessively in people with moderate to severe TBI, and the consequences of this increased FC are still being studied by neuroscientists(Roy et al., 2017). Also, fMRI data, which compare two groups of healthy people with a specific neurological disease collected longitudinally, have become popular today(Esposito et al., 2013). This study aimed to use the longitudinal model of Hart et al. on fMRI data of individuals with TBI and collected longitudinally. This study investigates the excessive increase in functional communication of people with TBI. Due to the different error structures, the longitudinal model used in this study can be more reliable than other similar longitudinal models(Hart et al., 2018).

Material and Method

Data

The data used in this study were downloaded from the accessible Open fMRI site. This data has the access number ds000220 on the mentioned site. The subjects who underwent brain imaging included 14 people with severe TBI. These people were in the age range of 18 to 36 years. Severe brain injury was measured on the GCS scale. Those with spinal cord injuries or other neurological

diseases were excluded from the study. A control group was also selected, including 12 healthy individuals similar in age and literacy to the brain injury group. The subjects who were finally chosen as the TBI group were followed up three months, six months, and twelve months after the brain injury, and in all three times, brain imaging was performed. Healthy individuals also underwent brain imaging twice, each time three months apart. Brain imaging was performed using Philips Achieva 3T or Siemens Magnetom Trio 3T devices. These scanners were used to neuroimaging those in the control group or the TBI group. People were asked to have the least amount of movement in scanners. Written consent is obtained from all individuals, and all data collection steps are approved by the Pennsylvania State University Research Support Office. Also, all methods and models used in this study with the code of ethics "IR.SBMU.RETECH.REC.1397.606" were approved by the ethics committee of Shahid Beheshti University of Medical Sciences.

The image resolution of T1 was obtained with cerebral segregation weight with an isotropic spatial resolution of 1.0 mm. Echo planar imaging (EPI) evaluated blood oxygen level-dependent (BOLD) responses for performance imaging. Imaging parameters for EPI 2000 ms / 30 ms / 90 ˚ (repeat time/echo time / flip angle), 240×240 mm square field of view and 80 80 80 م acquisition matrix with 4 mm thick axial cuts parallel to the second line It was media(Roy et al., 2017). All data preprocessing steps, including temporal correction, motion correction, matching, normalization, and spatial smoothing, were performed by FSL software version 6.0.1. After using the FSL software, the output entered the MATLAB 2019 software, and the SPM package version 12 and the WFU-pickatlas module were used to exit the Region of Interest (ROI). Eleven ROI of each person's brain was extracted using the SPM package, in which brain damage had the most significant impact. The names of 11 ROI are removed, and the corresponding number of each ROI is shown in Table 1.

Table 1: Names of the ROI extracted using SPM package

ROI Number	ROI Names
١	**Brain Stem (BS)**
٢	**Cerebellum Left (CL)**
٣	**Cerebellum Right (CR)**
۴	**Inferior Temporal Gyrus Left (ITGL)**
۵	**Inferior Temporal Gyrus Right (ITGR)**
۶	**Superior Frontal Gyrus Left (SFGL)**
٧	**Superior Frontal Gyrus Right (SFGR)**
8	**Superior Temporal Gyrus Left (STGL)**
9	**Superior Temporal Gyrus Right (STGR)**
10	**Thalamus Left (TL)**
11	**Thalamus Right (TR)**

Statistical Inference

A longitudinal variance components model was used to compare FC in control and TBI groups(Hart et al., 2018). The longitudinal model used in this study has two basic properties. Using the longitudinal model of variance components, the automatic correlation of the data obtained from the fMRI time series, the conflict of covariance due to heterogeneity of individuals, and the clash of covariance due to the difference of each individual over time can be measured. By measuring the mentioned parameters, the results obtained from fitting the longitudinal model of the variance components will have minor errors. If we show the number of areas with **P**, we also offer the number of pairs ROI that are compared in two groups with **Q**, considering that in this study, 11 ROI have been selected, the total number of comparisons Will be calculated in two groups of control and TBI using the relation $\binom{11}{2}$. Therefore, 55 comparisons between pairs' ROI are calculated in each group. Assuming **β** is a vector of length **2Q**, **Q** will denote the first element by β_0 Which determines the group difference due to the FC baseline effect, that is, the difference in FC between the control group and the TBI group at the base time. We also show the second element, **Q,** with β_1 Which calculates the group difference in the longitudinal trend of FC, i.e., the difference in FC between the control and TBI groups over time using the longitudinal model of the variance components. The meaning of FC group difference in the baseline is to evaluate the difference in functional connectivity between the two TBI and control groups at baseline. This assessment is a difference in the degree of correlation between the ROI in the two groups of TBI and control at the base time, i.e., the first scan taken from individuals. Also, the difference between the FC Longitudinal trend means that the difference in functional connectivity over time between the TBI and control groups is evaluated. This assessment is also a difference in the degree of correlation between ROI in the two groups of TBI and control over time. More information on the details of the longitudinal model of the variance components can be found in Hart et al.(Hart et al., 2018).

Result

The longitudinal model of the variance components tests the group difference due to the FC base time and the group difference in the FC longitudinal trend. Estimation of main effects and longitudinal trend in the control group was determined with β_{HC}. Assessment of the main effects and longitudinal trend in the intervention group was shown with β_{TBI}. After fitting the longitudinal model of the variance components to the two groups, it was observed that no statistically significant difference between the control group and the TBI group due to the base time of FC and between pairs ROI. By fitting the longitudinal model of the variance components to the control and TBI groups, it was observed that there was a statistically significant difference between the control group and the TBI group in 3 pairs of ROIs in the longitudinal trend of FC. The pairs of regions, CL and CR, SFGL and SFGR, TL, and TR, had a statistically significant difference in FC over time between the control and TBI groups. So, in total, it can be concluded that out of 55 ROI, in three pairs ROI, there was a statistically significant difference between the control group and the TBI group in the longitudinal trend of FC. Table 2 shows complete information about the pair of substantial ROIs.

Table 2: Differences in the estimation of coefficients between TBI and control groups in the main effect and longitudinal trend of FC and Adjusted P-values obtained from comparison of pair ROI

Pairs of areas of interest	$\beta_{TBI} - \beta_{HC}$	$\beta_{TBI} - \beta_{HC}$	Adjusted P-value	Adjusted P-value
	Main Effect	Interaction Effect	Main Effect	Interaction Effect
۱ و ۲	0.159	0.139	0.659	0.329
۱ و ۳	0.165	0.137	0.549	0.279
۲ و ۳	-0.291	0.349	0.054	0.036*
۲ و ۴	0.095	0.080	0.710	0.549
۲ و ۶	0.041	-0.117	0.884	0.327
۲ و ۷	0.062	-0.114	0.789	0.109
۳ و ۵	0.054	0.124	0.843	0.109
۳ و ۶	0.046	-0.121	0.843	0.175
۳ و ۷	0.118	-0.128	0.672	0.175
۶ و ۷	-0.146	0.342	0.640	0.036*
۶ و ۹	0.049	-0.090	0.820	0.329
۸ و ۹	-0.270	0.206	0.073	0.079
۱۰ و ۱۱	-0.103	0.372	0.716	0.036*

* Indicates significance at the 95% confidence level.

Figure 1 at the bottom left shows the difference between the estimates of the main effects and the longitudinal trend of FC in the control and TBI groups. As can be seen in the figure, in most pairs of ROIs, the difference between the estimation of the main effects and the longitudinal trend of FC was more significant in the TBI group than in the control group. The reddish circle points indicate a positive difference, and the blueish circle points indicate a negative difference between the two groups. With these interpretations, it can be concluded that in estimating the main effects of FC, the TBI group in the two pairs of regions 2 and 3 and 8 and 9 saw a decrease in FC compared to the control group. But as mentioned, this difference was not statistically significant. Estimation of the effects of the longitudinal trend of FC also shows that in comparison with most pairs of ROIs, FC between the TBI group has increased compared to the control group. In Figure 1 at the bottom left, the top triangular diagram shows that the pairs of regions (2 and 3), (6 and 7), as well as (10 and 11) have bolder points than the other pairs of pants. This indicates an increase in FC in the TBI group compared to the control group over one year.

Figure 1, bottom right, shows the -log10 p-value to compare the estimation of the main effects and the longitudinal trend of FC in the pair's ROI between the TBI and the control groups. According to the figure, it was observed that in estimating the longitudinal trend of FC between the control group and TBI, pairs of regions, (2 and 3), (6 and 7), as well as (10 and 11) have more prominent points than other points.
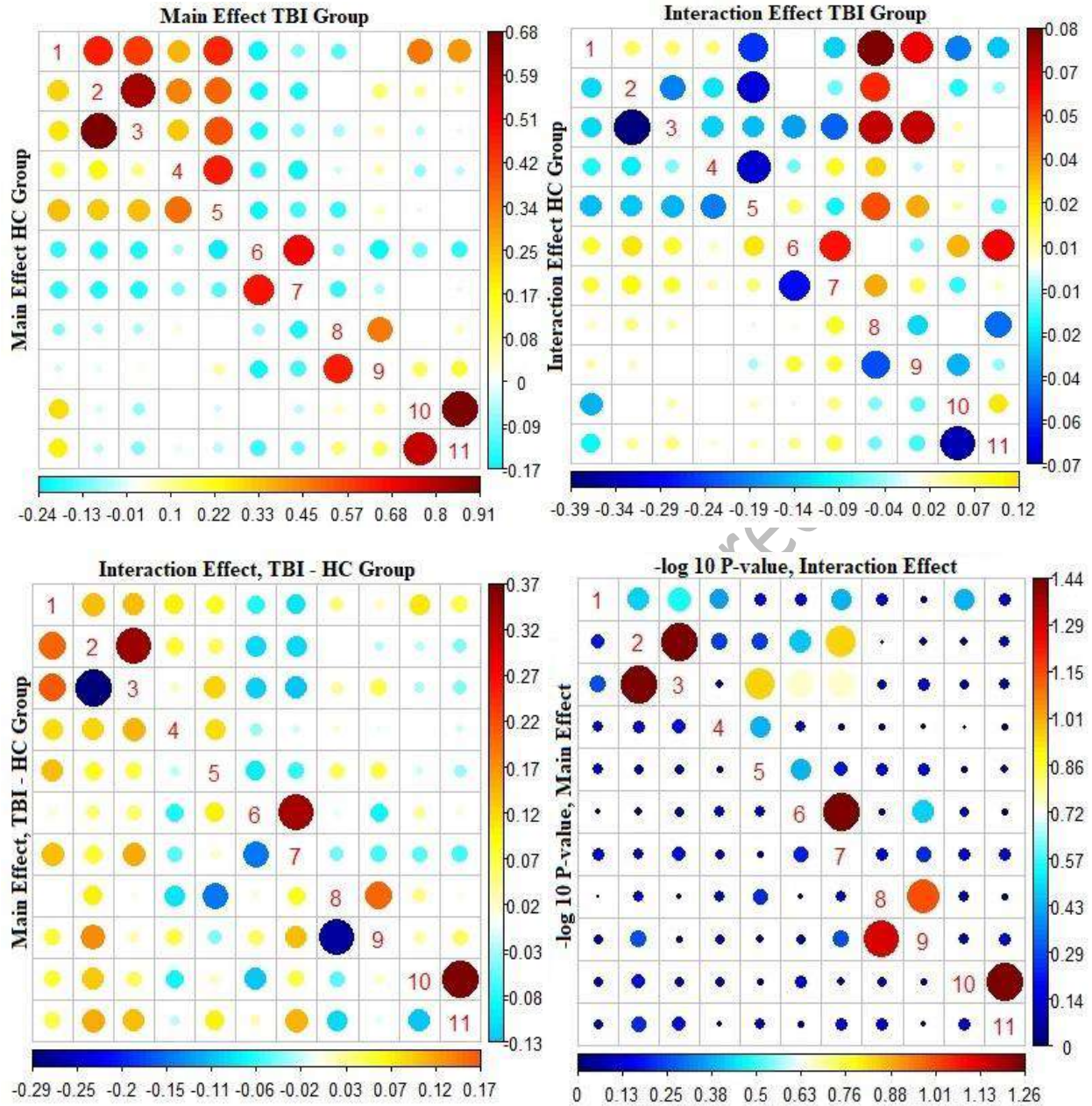
Figure 1 Top left: Estimation of baseline FC effects in pairs of ROIs (bottom triangle diagram of the control group and top triangular diagram of TBI group). Figure 1 Top right: Estimation of the longitudinal effects of FC in the pair of ROIs (the lower triangular chart shows the control group, and the upper triangular diagram shows the TBI group). Figure 1 Bottom left: The difference between the coefficients of the TBI group and the control group in the FC network survey (the upper triangular diagram shows the longitudinal trend of difference between the two groups in the FC network, and the lower triangular graph shows the base effect of the two groups in the FC network). Figure 1 Bottom right: -log10 p-value to compare pairs of ROIs in longitudinal trend and FC baseline effect (The upper triangular diagram shows the -log10 p-value for the difference in the longitudinal trend of the couples of ROIs, and the lower triangular chart shows the -log10 p-value for the difference in the baseline effect of the pairs of ROI in FC).

Discussion

This study aimed to apply the longitudinal model of variance components to fMRI neuroimaging data of those with severe TBI disease and collected longitudinally. The data used in this study are unique in fMRI imaging studies due to the severity of brain damage and follow-up time. Also, due to the different error structures, the longitudinal model used in this study has much reliability. By fitting the longitudinal model of variance components, it was observed that there was no statistically significant difference in the baseline effect of FC between the TBI group and the control group. However, in the longitudinal course of FC between the three pairs of regions, hyper-connectivity was observed in the TBI group compared to the control group. The CL and CR regions, SFGL and SFGR, and the TL and TR regions were where hyper-connectivity was observed in the TBI group compared to the control group. The CL and CR regions are responsible for balancing and coordinating the body's muscles to perform a specific function in the brain. Eye movements and motor learning also function in the CL and CR areas(Ferrari, Ciricugno, Battelli, Grossman, & Cattaneo, 2019). The SFGL and SFGR regions play a crucial role in human self-awareness and working memory(Boisgueheneuc et al., 2006). The TL and TR regions are also responsible for amplifying sensory signals in the brain. Other functions of TL and TR include learning, episodic memory, sleep regulation, and wakefulness(Torrico & Munakomi, 2019).

This study aimed only to identify brain areas in people with severe TBI who have experienced an acute increase in FC in their areas of the brain. Numerous studies have addressed the issue of sharp FC increase in patients with moderate to severe TBI. In 2015, Sours et al. Evaluated 77 individuals with mild TBI and 35 healthy individuals for the severity of FC under the Thalamus cerebral cortex using the standard T-test and ANOVA tests. The results of their study showed that people with mTBI experienced an excessive increase in FC beneath the various layers of the thalamus, the subcortices associated with sensory processing, and the DMN[1] network. Sours et al. People with mTBI showed that they experienced cognitive, neurological, behavioral, sensory, and physical disorders. Their results suggest that this hyper-connectivity may affect brain areas related to sensory, motor, and even auditory functions. The brain is trying to heal after an injury, and time must be given for a full recovery(Sours, George, Zhuo, Roys, & Gullapalli, 2015). The present study results are also consistent with the study of Sours et al. In the present study, an acute increase in FC in the thalamus was also observed. In the study of Sours et al., Common statistical methods were used to examine group differences. In contrast, our study used a new longitudinal statistical model to examine group differences in baseline effect and FC longitudinal trend. In 2016, Iraji et al. Followed up 16 patients with mTBI for 4 to 6 weeks after injury and were given fMRI at rest. Twenty-four people were also selected as the control group. In this study, it was concluded that mTBI patients have higher FC than the control group. Iraji et al. Concluded that concussion can alter FC and that the brains of people with mTBI tend to be hyperactive to compensate for the pathophysiological abnormalities caused by the injury. This brain activity occurs in response to the problem created after a brain injury, and the brain increases these functional connections to

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[1] Default Mode Network

compensate for the damage. This increase is too much for the affected areas responsible for executive functions and working memory(Iraji et al., 2016). The results of our study are mainly similar to those of Iraji et al. Because the areas in the present study that experienced an excessive increase in FC affect organizational performance and working memory. The data used in our study are similar to the study of Iraji et al., but our data's follow-up time is one year and is more valid in terms of time. The model used in our study may provide stronger results due to the different error structure than the common methods used in the study by Iraji et al. In 2017, Bernier et al. Examined FC at rest using fMRI images. They analyzed 14 people with moderate to severe TBI and 19 healthy people. They used a 264-area atlas to identify areas of the brain. Finally, they concluded that the FC in the group with TBI was much higher than the FC in the control group. Bernier et al. Hypothesized that this hyper-connectivity after brain injury might have been due to dedifferentiation. Dedifferentiation means the loss of specialization and function in a specific network of the brain that occurs most often in old age(Bernier et al., 2017). The areas used in the study by Bernier et al. Were different from our study. Also, the data used in their study were cross-sectional, while the data used in the present study were collected longitudinally. A new longitudinal model was used in our study, while in Bernier et al., Common statistical methods such as T-test and Analysis of Variance were used. But the results of both studies showed a hyper-connectivity in the TBI group. In 2019, Konstantinou et al. Examined the correlation between brain regions in two groups of people with moderate to severe TBI. There were 11 people in both groups. They found that those with moderate to severe TBI had impaired executive function, verbal memory, and visual memory, which were associated with differences in FC in the cerebral cortex(Konstantinou, Pettemeridou, Stamatakis, Seimenis, & Constantinidou, 2019). Our study also showed that hyper-connectivity occurs in areas of the brain that are responsible for executive functions. In a 2020 study by Liyan et al., 27 people with moderate TBI and 43 healthy people with FC in several brain areas were compared using fMRI imaging. This study was cross-sectional and showed a decrease in FC in SFG[2]. The results of Liyan et al.'s study showed that decreased FC in the thalamus and SFG caused headaches in people with mTBI(Lu, Li, Wang, et al., 2020). The results of our study are different from those of Liyan et al. Because they observed a decrease in FC in the TBI group, while we observed hyper-connectivity in the TBI group. Their study is cross-sectional, while our study is longitudinal. In 2020, Liyan et al. Conducted another study on 53 patients with mTBI and 37 healthy individuals. Resting fMRI was used to compare FC in the two groups. The results showed that hyper-connectivity in RPI[3] and IFG[4] was observed in the mTBI group compared to the control group(Lu, Li, Chen, et al., 2020). Their study is a cross-sectional study, and common statistical methods such as the Pearson correlation coefficient test have been used. However, longitudinal data have been used in the present study, and a newer statistical model has been fitted to the data. The results of both studies show an excessive increase in FC in many areas of the brain. In 2021, Sheth et al. Analyzed 49 veterans with mTBI and 25

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[2] Superior Frontal Gyrus
[3] Right Posterior Insula
[4] Inferior Frontal Gyrus

veterans without cerebral palsy for FC using fMRI neuroimaging. They found that FC was significantly increased in veterans with mTBI compared with veterans without cerebral palsy. Sheth et al. Eventually concluded that this sharp increase in FC in veterans with mTBI could be a mechanism for maintaining overall brain network function(Sheth, Rogowska, Legarreta, McGlade, & Yurgelun-Todd, 2021). Also, in 2021, Amir et al. Examined the FC network of resting fMRI neuroimaging among 27 patients with mTBI and 26 in the control group. They observed hyper-connectivity in patients with mTBI compared to the control group. Amir et al. Argued that this hyper-connectivity could be due to post-injury protective mechanisms, which are nerve compensation in the brain system. There are also signs that this acute increase in FC may be causing psychological distress or headache. The nature of this hyper-connectivity can depend on some factors, including age, pre-injury cognitive function, or nervous system(Amir et al., 2021). The results of Amir et al.'s study are in line with the present study. However, the differences between our study and Amir et al.'s study are in the length of the data and different statistical methods to examine the difference between FC in the two groups. There is still no convincing evidence for the claims of hyper-connectivity in patients with moderate to severe TBI. Researchers and neuroscientists need to investigate the nature and cause of this acute increase(Amir et al., 2021).

Conclusion

Using neuroimaging data from people with severe TBI and collected longitudinally and Applying the longitudinal model of variance components for these data, due to the different nature of the error structure compared to similar models, can make the results of the error structure this study highly cited. By fitting the longitudinal model of variance components, it was concluded that in the longitudinal trend of FC in the TBI group, hyper-connectivity compared to the control group was observed in the pairs of CL and CR, SFGL and SFGR, as well as TL and TR. This hyper-connectivity can affect people's cognitive functions, but the extent and manner of this effect have not been determined to date and requires more detailed studies.

Ethics approval and consent to participate

Written consent is obtained from all individuals, and all data collection steps are approved by the Pennsylvania State University Research Support Office.

Authors' contributions

KO designed this study and participated in data extraction, data analysis, data interpretation, and manuscript writing; HAM and NB participated in data analysis, data interpretation, and manuscript writing; MH participated in manuscript preparation and literature research. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring accuracy or integrity.

Availability of data and materials

All data generated or analyzed during this study are included in this published article," The evolution of cost-efficiency in neural networks during recovery from traumatic brain injury (https://doi.org/10.1371/journal. pone.0170541)."

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable

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