Traumatic Brain Injury

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Abstract

This study aimed to explore the impact of traumatic brain injury (TBI) on the volume of the hippocampus and its changes over time, while also examining how cognitive recovery (especially language comprehension) varies with age and gender differences. Through detailed data analysis of 155 participants (including 94 patients and 21 control group members), we used linear mixed-effects models to handle repeated measures in the dataset and applied Wald tests to assess the impact of various factors.

The results show that compared to the control group, the patient group exhibited a significant downward trend in hippocampal volume after injury. However, this rate of decrease did not significantly differ from the control group over time. Additionally, the analysis found that gender might influence the process of hippocampal volume change, particularly with males experiencing a faster rate of decline in hippocampal volume as they age. Further analysis revealed a significant positive correlation between gray matter volume and the volume of the left hippocampus, suggesting the crucial role of gray matter in supporting hippocampal functions, especially in language and memory formation.

I. Introduction

Traumatic brain injury (TBI) has been a major medical and societal challenge that affects millions of people worldwide. The recent definition of TBI is proposed by Demographics and Clinical Assessment Working Group of the International and Interagency Initiative, they said TBI is “an alteration in brain function, or other evidence of brain pathology, caused by an external force” [8]. As of 2005, approximately 3.17 million TBI survivors experience post-traumatic complications ranging from neurological, psychosocial problems to long-term disability [1]. Understanding the underlying neurobiological changes following TBI is critical to developing effective treatment and rehabilitation strategies.

The primary focus of our analysis lies in examining key brain regions impacted by TBI. Hippocampus, a bilateral structure within the middle temporal lobe, is well known for being an essential part of the neural network of learning and memory. According to the findings, the left hippocampus plays a critical role in episodic verbal memory, while the right hippocampus might be more important for spatial memory processing among non-demented older adults [6]. The internal capsule could be affected by TBI as well, it is a two-way tract for the transmission of information to and from the cerebral cortex which lies in the inferomedial portion of each cerebral hemisphere [5]. Besides, the fornix crux is an important white matter tract that supports episodic memory functions by connecting the hippocampus to other brain regions. Grey matter is also a key area, it has a large number of neurons present, which allows it to

process information and release new information through axon signaling found in the white matter [3]. The grey matter throughout the central nervous system allows enables individuals to control movement, memory, and emotions [9].Together, these structures embody the neural substrates that may undergo significant changes following traumatic brain injury, thereby affecting an individual's cognitive and emotional abilities.

In our analysis, reflected through detailed R scripting, we use the brain structures as y-variable, analyze the relationships between a set of x-variable, including patient sex, injury characteristics, recovery timelines, and other relevant factors. They represent the diverse and multifaceted aspects of TBI cases that could influence neuroanatomical and functional outcomes.By correlating TBI's impact with changes in these specific brain regions, our study leverages statistical insights to deepen our comprehension of TBI's profound effects on neural integrity and functionality. We use mixed models as our main method, this approach underpins our objective to elucidate the nuanced relationship between traumatic brain injury and subsequent changes in brain anatomy, paving the way for enhanced diagnostic and therapeutic strategies.

II. Methodology

1. Data Collection & Preparation

The dataset “TBI.xlsx” was given, and was sourced from a comprehensive study focused on individuals who have suffered from traumatic brain injuries (TBI). It contains 155 rows and 338 columns with an extensive range measurement of variables, including total brain volume ('total_brain_vol'), ventricle-to-brain ratio ('VBR'), white matter volume ('WM'), grey matter volume ('GM'), and cerebrospinal fluid volume ('CSF'). These measurements were taken at different intervals, identified by suffixes such as _1, _2, etc., corresponding to different time points post-injury. Participant IDs are numerically assigned for TBI patients and prefixed with ‘c’ for control subjects (‘c01’, ‘c02’). The variable ‘date_1’ denotes the injury date for patients, whereas ‘date_2’, ‘date_3’, etc., represent subsequent dates when brain scans were conducted.

Since the dataset displays multiple time points or conditions in separate columns for each subject, it can be called a “wide” data format. In order to do subsequent statistical analysis, we need to transform into the “long” data format, which is one column for all time points or conditions and another to identify each time point or condition. Many statistical tests and models, particularly those designed for time series, repeated measures, and longitudinal data, assume or require data to be in a long format. When dealing with complex data structure, long-format data tends to be more amenable to various types of data manipulation and subsetting. Because each observation in it can be treated individually, handling missing values would be easier. Besides, in order to compare the variables intuitively, visualization is a key tool.Many data visualization tools and libraries (ggplot2 in R) are designed to work more efficiently with long-format data.

We use the ‘tolong’ function to complete the data format transformation. After the data cleaning process, we get a new data frame containing 775 rows and 91 columns.

2. Analytical Tools and Techniques

The **Generalized Least Squares (GLS)** model is an extension of the Ordinary Least Squares (OLS) regression model. GLS for the shape parameter of the considered distributions, provides better performance than the maximum likelihood, least square and some alternative weighted least square estimation methods, for most of the considered sample sizes [10]. In OLS, this matrix is assumed to be an identity matrix scaled by a constant variance (σ^2), which implies that all errors have the same variance and are uncorrelated. GLS allows this variance-covariance matrix to have a more general form, reflecting heteroscedasticity (different variances) and correlations among errors. For longitudinal data, the variance might change over time, or some observations might be correlated. For instance, the variability in hippocampal volume measurements could increase or decrease as the study progresses. Fortunately, GLS models can handle this by allowing for non-constant variance across different time points.

We have done data visualizations between various factors and the total volume of the left hippocampus (HPC_L_TOT), which offer insightful revelations into dynamics. From the figures, it is necessary to transit linear models to mixed-effect models. The relationships depicted between HPC_L_TOT and brain structures, such as the fornix crux and the anterior capsule, differ markedly among individuals and between groups. **Linear mixed effect models** extend traditional linear models to include a combination of fixed and random effects as predictor variables. Biological datasets are often highly structured, containing clusters of non-independent observational units that are hierarchical in nature, and mixed models allow us to explicitly model the non-independence in such data [7]. Our dataset is suited to this structure, enabling the inclusion of random effects to model individual-specific variations and correlations within subjects over time. Random effects typically represent some grouping variable [2] and allow the estimation of variance in the response variable within and among these groups. This reduces the probability of false positives (Type I error rates) and false negatives (Type II error rates, [4]).

To verify the feasibility of the models, we apply various statistical testing. Specifically, we utilized **Wald tests** within our mixed-effects model framework to evaluate the significance of various predictors such as time since injury, sex, and group status (patient vs. control) on the left hippocampal total volume (HPC_L_TOT). The Wald test is a statistical test used to assess the significance of individual coefficients (parameters) in a statistical model. The test evaluates whether each coefficient significantly differs from zero (or another specified value), which would indicate that the corresponding variable has a statistically significant effect on the dependent variable.

Further, we analyzed our model's effectiveness and comparative fit using **ANOVA tables**. This approach helped us discern which factors significantly contributed to explaining the variability in hippocampal volume. The ANOVA table is called Analysis of Variance table, it is used to

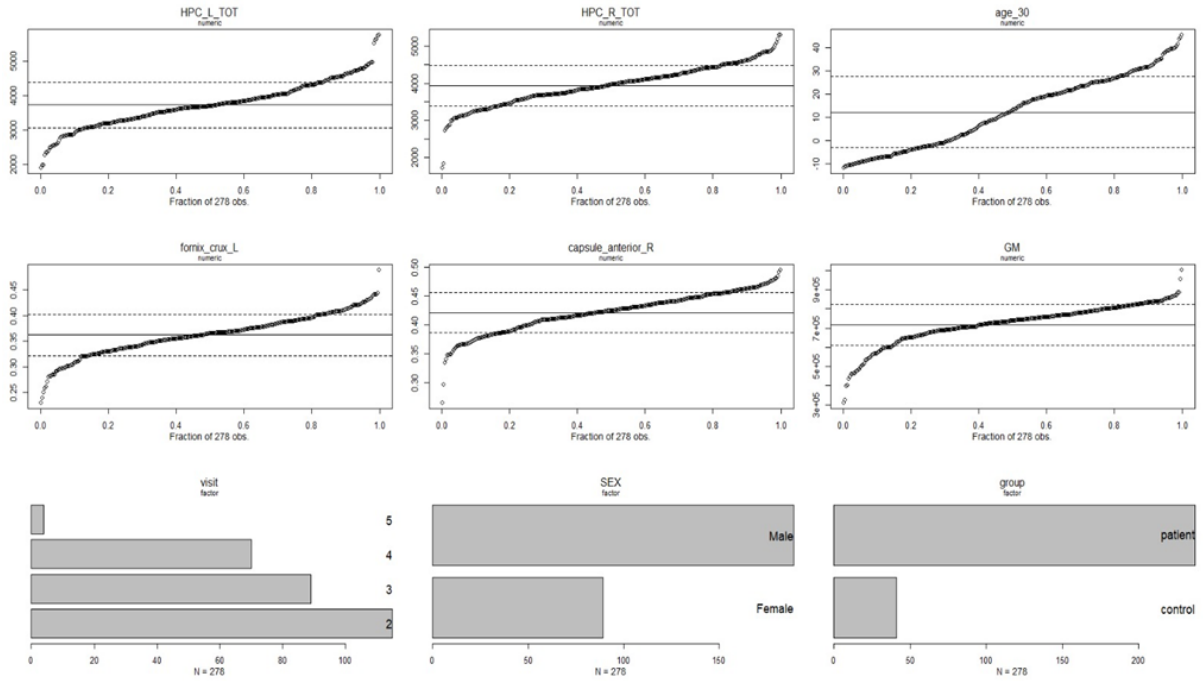
summarize the components of variance in a dataset that can be attributed to different sources, typically in the context of comparing means across multiple groups. To assess the significance, comparing the mean squares between groups (MSR) to the mean squares within groups (MSE), ANOVA determines whether the variance between groups is significantly greater than the variance within groups. Additionally, the F-statistic assesses whether the observed between-group differences are large enough to be considered statistically significant. The p-value helps make this decision more concrete by giving the probability of observing such differences if the null hypothesis were true.

Meanwhile, we conducted the **residual analysis** to ensure the reliability of our models. The Q-Q (quantile-quantile) plot can evaluate the assumptions of normality and homoscedasticity by examining plots of residuals versus fitted value, which is critical to check the validity and the appropriateness of our mixed-effects models. The horizontal axis (x-axis) of a QQ plot shows the theoretical quantiles. This means if the data were perfectly distributed according to the theoretical distribution, the points would lie along this axis. The vertical axis (y-axis) shows the actual quantiles from the dataset.

III. Analysis and Results

3. Results / Analysis

In this study, our data set consists of 38 females and 77 males. In total, 115 subjects were included, with 94 of them being patients and 21 of them in the control group. Their age ranges from 19 to 75 years old, with 21% younger than the age of 25, 47% between 25 and 50, and 32% older than 50. Hospital controls were not mandatory nor restricted to a specific time frame. Hence, the number of visits and the time of the visit are not predetermined; consequently, they vary among subjects. The minimum number of visits is 2, and the maximum is 5, with a predominantly low visit proportion. These visits occur between any time frame from the 4th of May 2004 to the 9th of Sep 2016. For each hospital check, besides the demographic information mentioned, the volumes of the hippocampus, fornix crux, capsule anterior and gray matter were measured. In our analysis, we are interested in the changes in the linguistic aspects of our brain, which is on the left side of the hippocampus [6]. We investigate whether these changes have an underlying natural relationship with age, sex, or the other parts of the brain that control communication, episodic memory recall, speech and learning, which are functioned by the capsule anterior, fornix crux, and gray matter, respectively [11][12][9]. The visual demonstration of the demographics that constitute each visit and the normal quantile graphs of the brain parts can be found in the following figure.



(Figure 1)

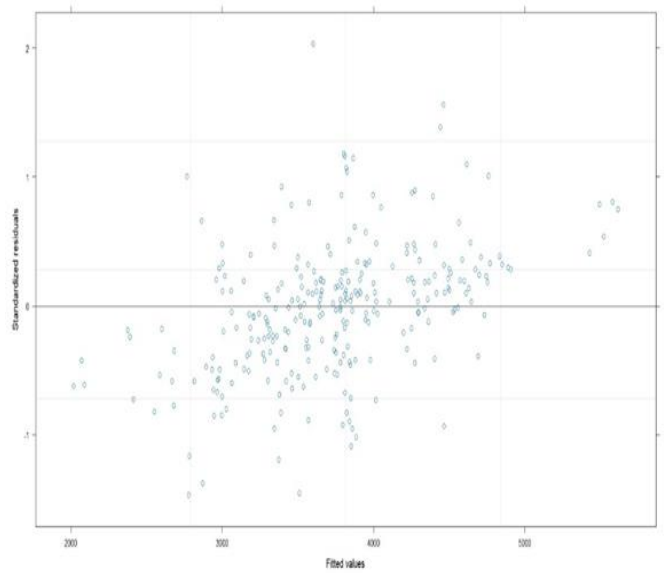
To analyze these relationships, we constructed a mixed model, which is updated through several steps to optimize the significance. For the first mixed model, the following structure was used:

- **Y variable:**
    - Left-Hippocampus-Total (Volume)
- **X variables:**
    - **Fixed Part:** Sex + Age (Centered at 30) + Sex*Age (Centered at 30) + Group + Group*Age (Centered at 30) + Capsule Anterior + Gray Matter + Fornix Crux
    - **Random Part:** Intercept + Age (Centered at 30) conditioned on the subjects
- **Auto-Correlation**: ~ Age (Centered at 30) conditioned on the subjects

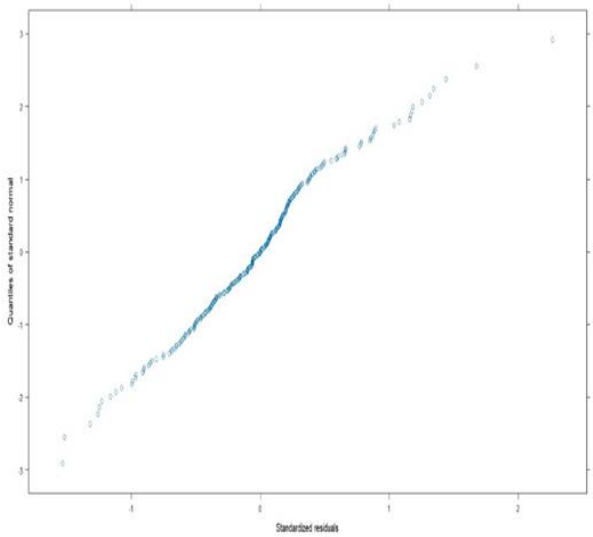
In order to ensure we are on the right path with the mixed model choice that included the random part, we tested whether the G-matrix, the covariance matrix of the random effects, was significant or not. One possible way to control it is by constructing a generalized least square model, which does not have the random part, and testing the models through ANOVA. It is important to note that ANOVA is sensitive to the difference in the number of observations and the fixed part between models. Since we had satisfied the conditions, we implemented the test. The result suggested that the G matrix was highly significant with a p-value of less than 0.0001. Consequently, the analysis proceeded with the mixed model concepts.

Moreover, some of these variables in the model are measured several times for each visit. Therefore, the cumulative measurement could vary notably between subjects, especially the measurement of the brain parts. Hence, adding each subject's average fornix crux, capsule anterior and gray matter level information would allow us to factor in the variability. However, one must consider whether these additions are significant or helping the model. Through the Wald test, we observed that only the contextual variable of the gray matter gives more information than it took for our data set. Consequently, we only added contextual variables of gray matter into our model.

With the upgraded model, the assumptions were checked through diagnostic analysis. Overall residual distribution did not signify any major issue, as Figures 2 and 3 show.

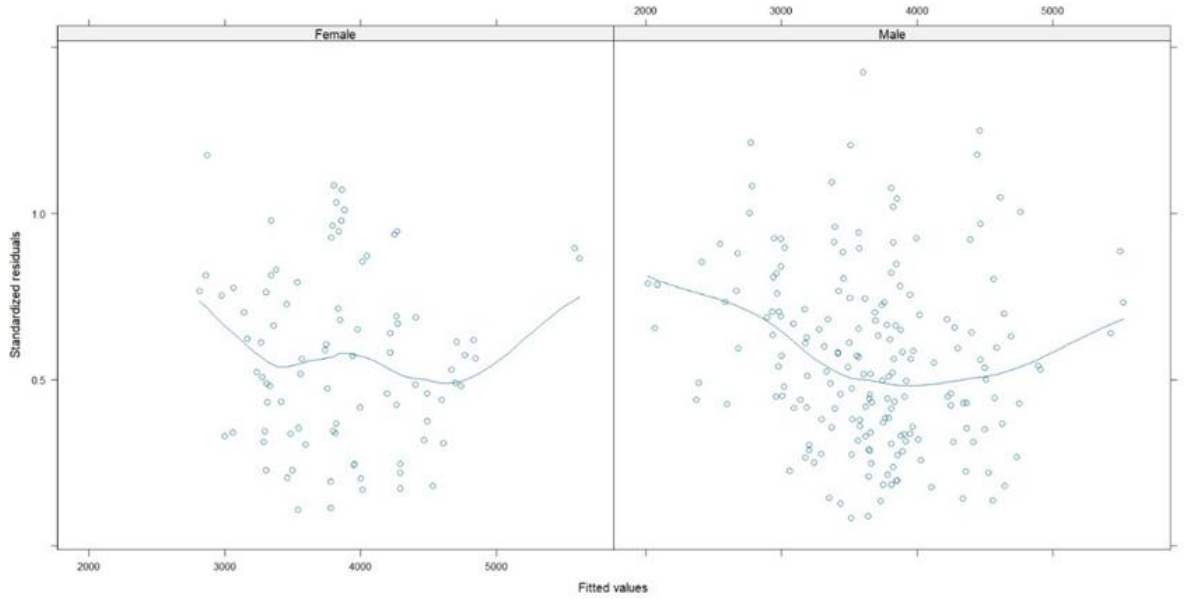


(Figure 2)



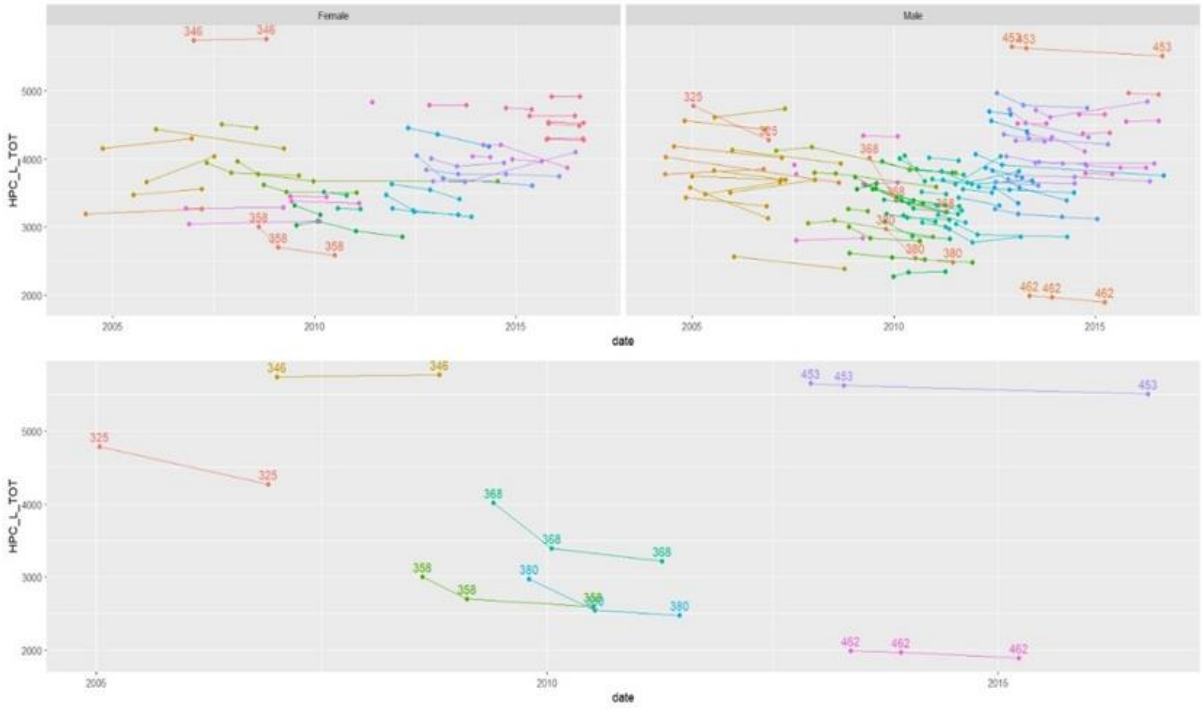
(Figure 3)

However, there is a slight upward pattern. Hence, we divided into subcategories for sex. From the result, we were suspicious about a few points on the right for females, which could possibly yield false precision.



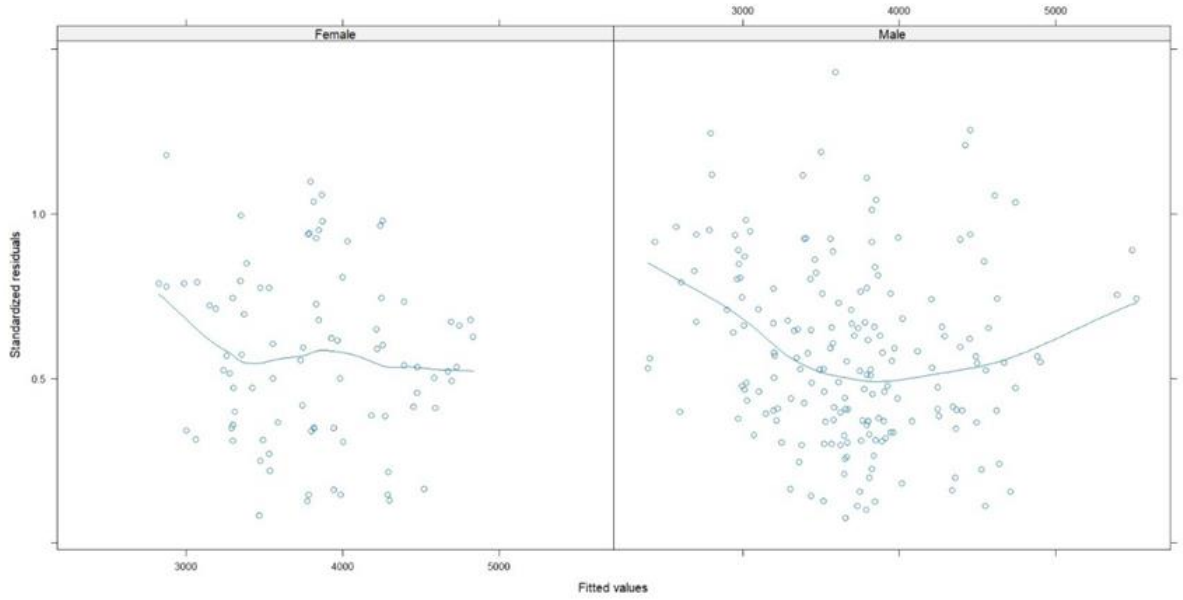
(Figure 4)

Having a closer look at the suspicious points within the whole graph, we found out that besides data point 346 on the female side, the rest were not a matter of removal.



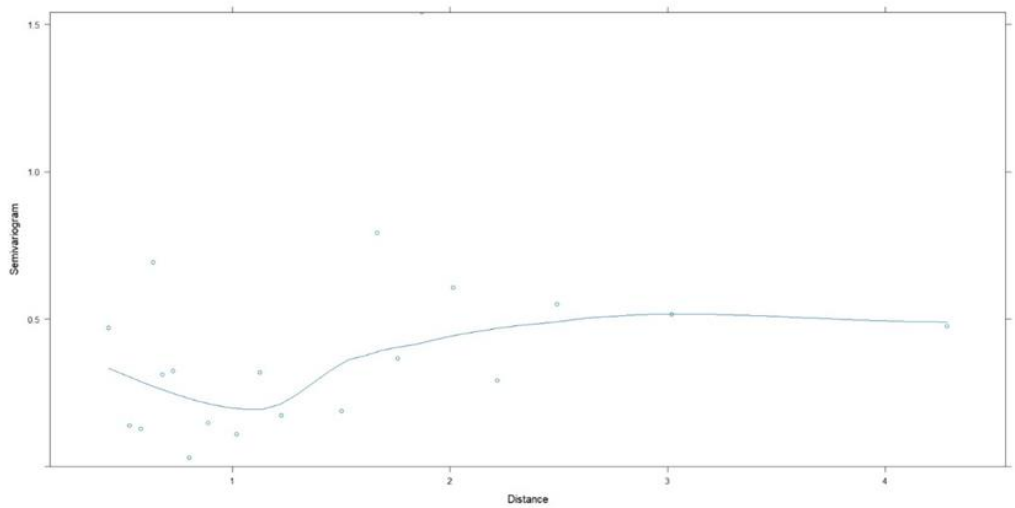
(Figure 5)

Dropping the particular point improved the residual distribution among females.



(Figure 6)

Furthermore, we delved into the autocorrelation aspect of the diagnostics. A variogram graph is used for this part of the analysis, which is shown in Figure 7. The graph indicates that differences between pairs of close residuals have slightly smaller variances than between far-apart ones. Therefore, there is no strong correlation in our model residuals.

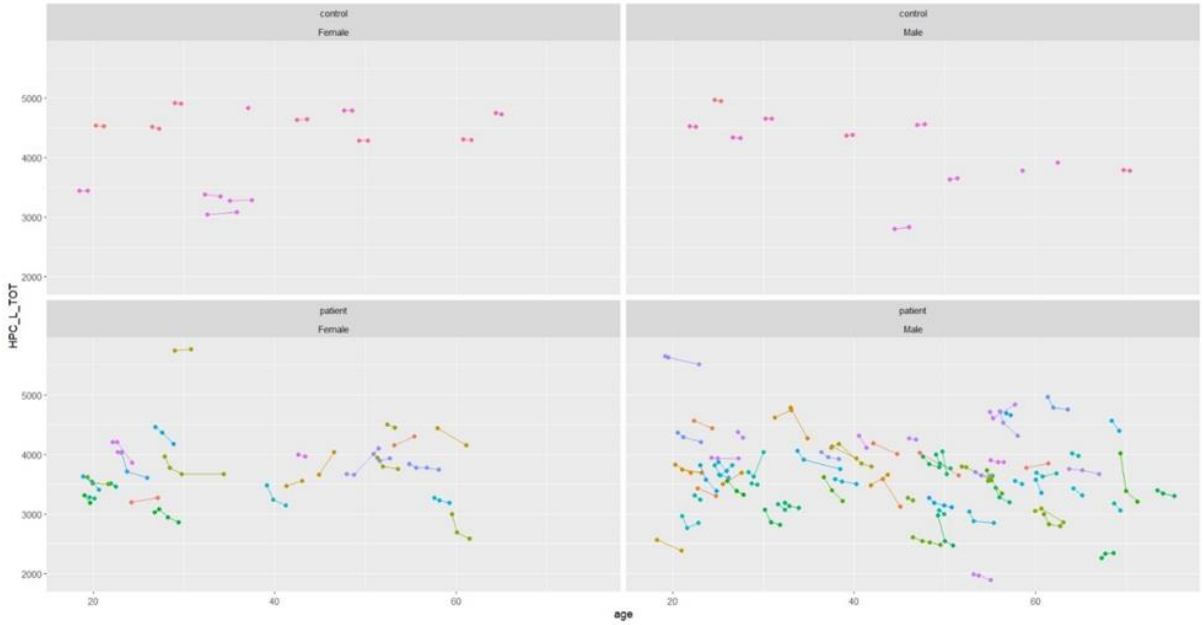


(Figure 7)

IV. Discussion

Does the hippocampus volume undergo significant changes after an injury, and do these changes vary over time post-injury?

The plot (figure 8) clearly shows a comparison of hippocampus volume between the patient group and the control group at different time points. The plot reveals that, compared to the control group, the patient group experiences a downward trend in hippocampus volume after trauma, with this change varying over time. This might reflect the brain's self-healing process or the effect of treatment following injury.



(Figure 8)

The results of the Wald test indicate that, after adjusting for age factors, the hippocampus volume of injured individuals is significantly lower than that of the uninjured control group, with an average difference of -510.7 units, which is statistically significant (p-value 0.00618). This suggests that hippocampus volume significantly decreases after injury.

Further analysis of the rate of change in hippocampus volume with age shows no statistically significant difference between the patient and control groups (p-value 0.86052). This means that although trauma leads to a significant initial decrease in hippocampus volume, the rate of this decrease over time does not significantly differ from that of the control group. In other words, the impact of injury on the rate of change in hippocampus volume with age does not show significant variation.

Therefore, we can conclude that although trauma initially causes a significant decrease in hippocampus volume, the rate of decrease does not change due to the injury, suggesting that the long-term impact of injury on hippocampus volume may primarily manifest in the initial

phase, while the subsequent recovery or further decrease in volume proceeds at a rate similar to that of uninjured individuals.

At different time points post-injury, does the level of cognitive recovery (especially language comprehension ability) improve as we age and differ between sexes?

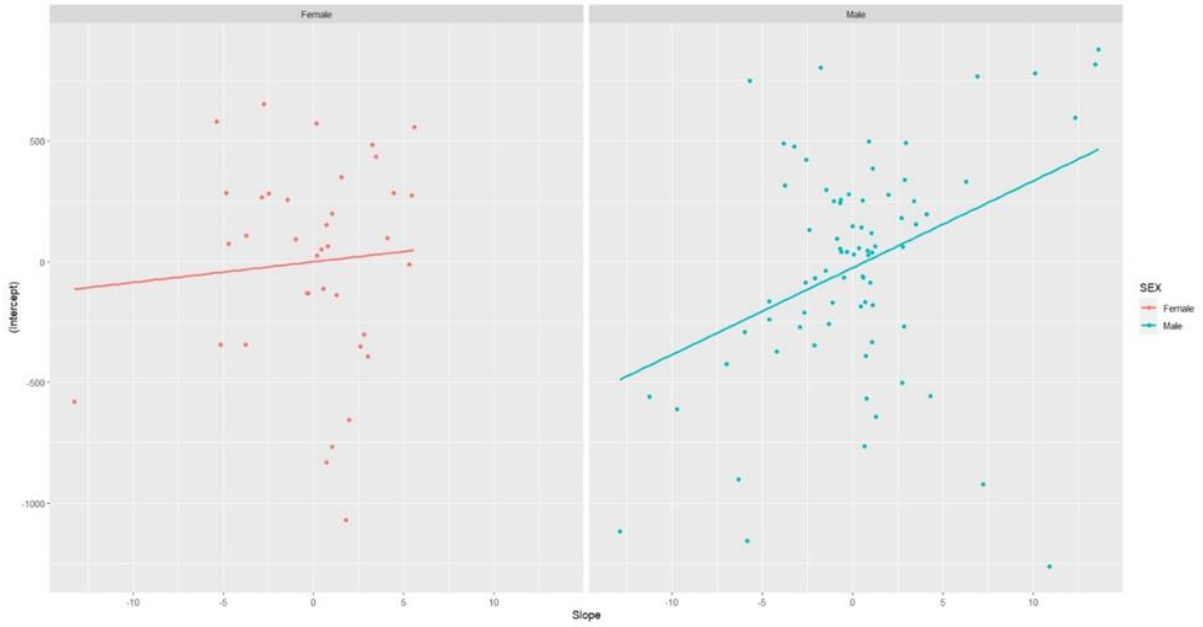
The data set consists of a broad range of ages, from 19 to 75. This opens the door to investigating what kind of role age plays. Using the Wald test once again, we find that in the patient group, female subjects only had a change of 3.94 hippocampus volume as they aged one year, holding other variables constant, which indicates that age does not play a major role in a change through the years. Meanwhile, male patients, as they age one year, have a hippocampus volume change of -11.53 units, which is a dramatic difference compared to females. The conclusion of the results is with a p-value of 0.09. Therefore, we have around 91% confidence level in claiming the relationship.

Another aspect of age is investigated through the auto-correlation. In our final version of the mixed model, the phi-value is estimated as 0.64, falling into (0.20,0.94) with the 95% confidence level. It indicates that the auto-correlation is significantly positive, which means if the hippocampus level goes down, it will likely hold that trajectory for the following days, and if it goes up, it will most likely follow a positive pattern for the near future.

Therefore, combining the results from the Wald-test and positive autocorrelation, the trend appears to be marginally straight for female patients as a relatively small positive trajectory follows a marginal positive pattern. Meanwhile, for males, the trend is downward, as a negative pattern follows the negative track.

Moreover, we have covered the relationship between age and the slope for the hippocampus level. How about starting points? Is sex a crucial factor for the intercept? Contrary to the relationship of the slope, the intercept is substantially greater for males. The effect of sex is 170 hippocampus volume for the person at the age of 30, holding everything constant.

Lastly, for the topic of age and sex, we observe the connection between the intercept and slope. . In the analysis part, we concluded that the covariance matrix of the random effects was significant. Hence, a question arose: how does that variation play in? The result can be seen in the following figure.



(Figure 9)

The graph illustrates that for females intercept is relatively unaffected by the slope. Whereas, for males, a high degree of slopes can be observed in the greater intercepts with a positive strong relationship between the two.

During the process of changes in hippocampal volume post-injury, does sex impact this process?

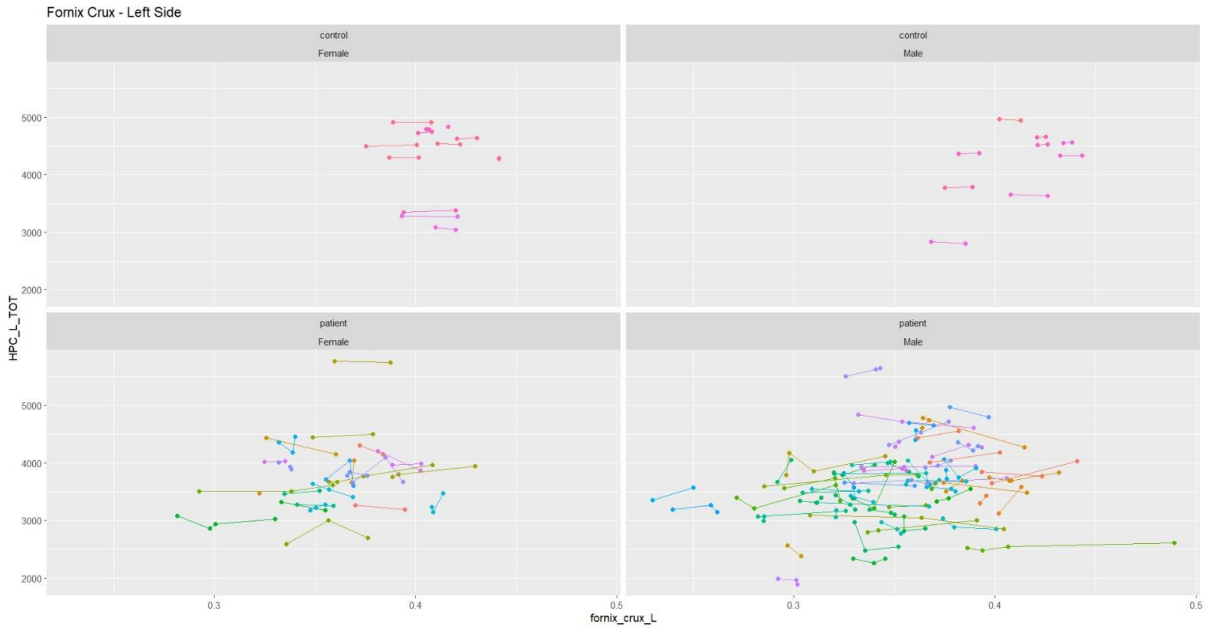
The Wald test's analysis of the interaction between sex (SEX) and age (age_30) reveals several key points. First, although the p-value for sex and its interaction effect is 0.16223, not reaching statistical significance at the 95% confidence level, the p-value for the sex and age interaction is 0.05917, showing a trend towards significance. This suggests that sex may impact the process of hippocampal volume change after brain injury to some extent.

The analysis of the interaction term SEXMale:age_30 further highlights the potential impact of sex differences. This negative estimate (-15.47152) suggests that, compared to females, males may experience a faster rate of decline in hippocampal volume as they age. This finding points out the importance of considering sex in studies examining how aging affects hippocampal volume.

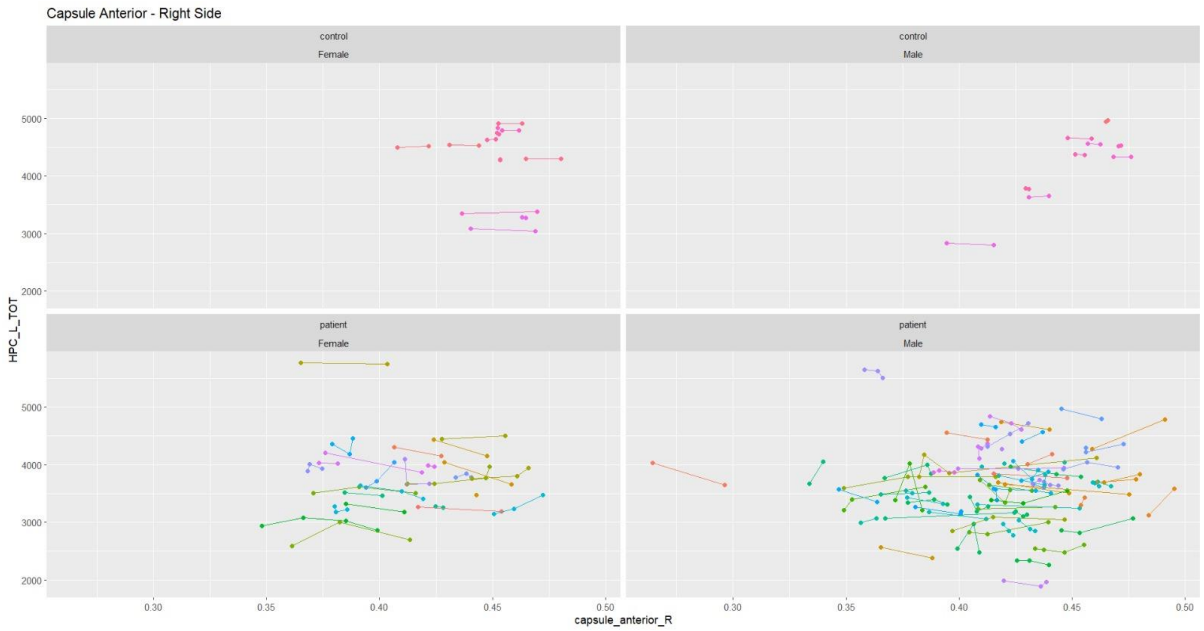
In summary, our analysis suggests that sex, especially for males, might have a significant impact on the process of hippocampal volume change following brain injury. Males might face a more rapid decrease in hippocampal volume after injury.

Is the deep communication pathway region and episodic memory of the brain, capsule anterior and fornix crux, respectively, related to decreased hippocampal volume and reduced cognitive function?

The scatter plots show a complex link between the size of the hippocampus and the volumes of the capsule anterior and the fornix crux. There's no clear straight-line trend, hinting that other interactions might be at play. Different patterns seen with gender and illness status add to this complexity, especially the variations in the patient group, which might show different stages of the disease.



(Figure 10)

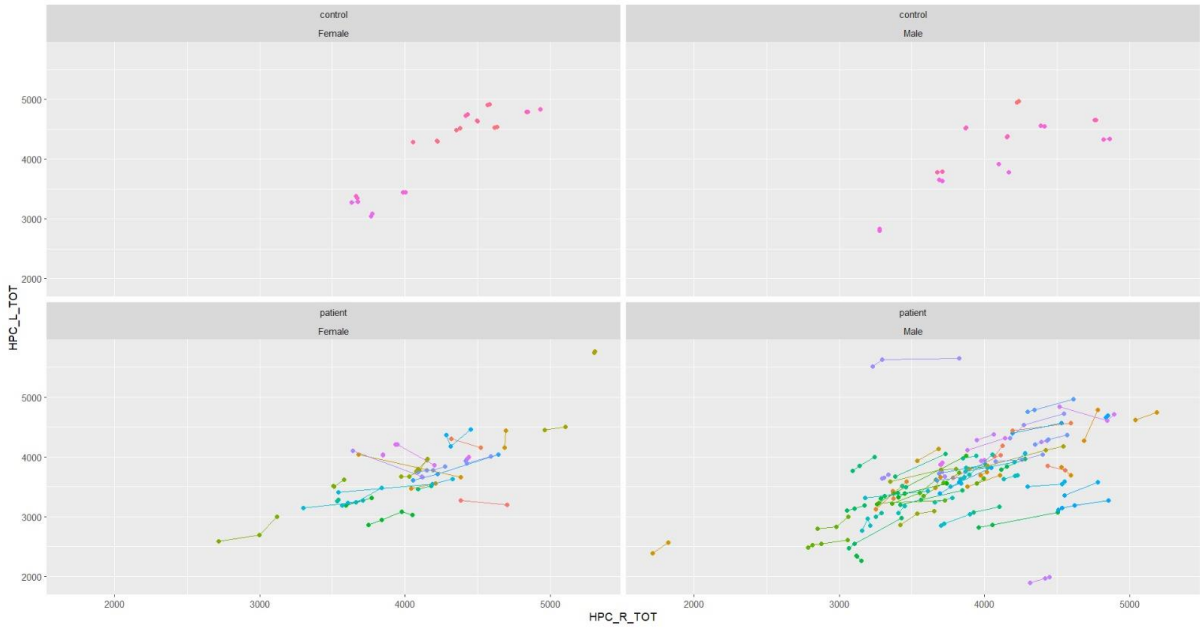


(Figure 11)

Although the change in the volume of the capsule anterior doesn't hit the usual level for being significant in stats (with a p-value of 0.06652), the trend it suggests shouldn't be ignored. As for the fornix crux, with a p-value of 0.17388, the results don't back up a significant statistical link to a decrease in hippocampus size. These insights hint that there could be some connection between the capsule anterior and changes in hippocampus size, while the impact of the fornix crux isn't as clear.

Considering that the right side of the hippocampus is related to spatial perception abilities, is there a connection between spatial perception abilities and language comprehension and production?

Based on this graph, we can see that there is a positive relationship between the volume of the left and right hippocampus in both the patient and control groups. This might mean that changes in the volume of the right hippocampus happen together with changes in the volume of the left hippocampus. If we assume that the right hippocampus is linked to spatial perception abilities, then the positive relationship shown in the graph could suggest that there is some connection between spatial perception abilities and the ability to understand and produce language.



(Figure 12)

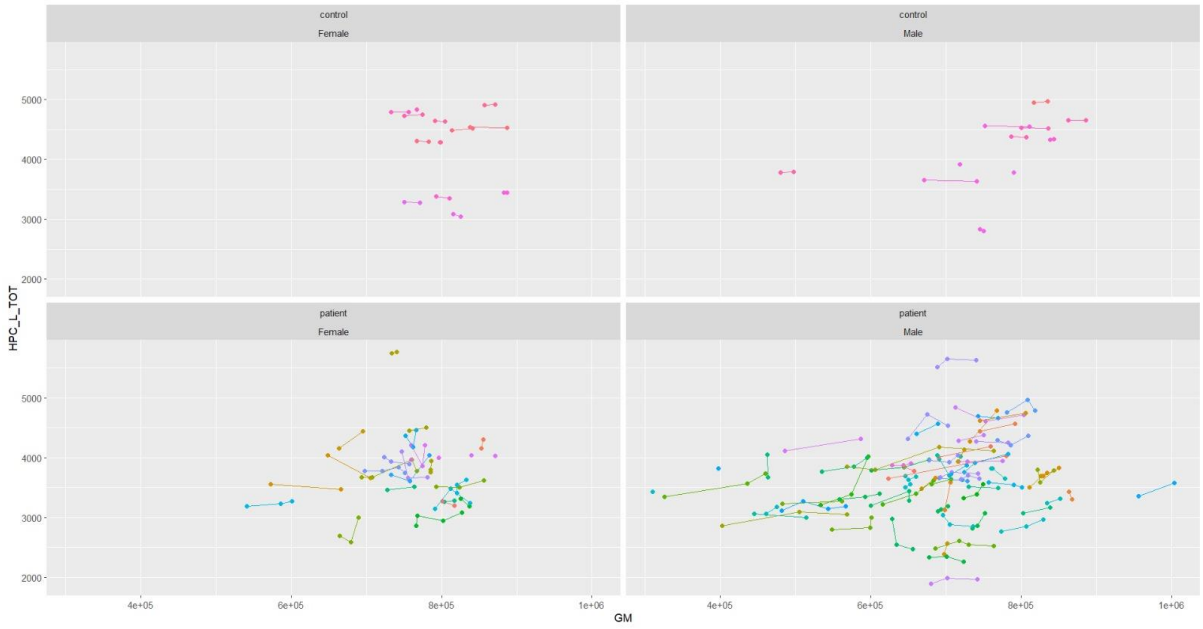
The hippocampus is an important part of the brain related to memory and navigation. Its role in language and spatial processing might be connected, but we need more experiments and data analysis to check this further.

What is the connection between the Gray Matter, where processing sensation, perception, voluntary movement, learning, speech and cognition happens, and the hippocampus left-side, where the brain constructs the languages?

The Wald test reveals the significant role of gray matter in predicting the volume of the left hippocampus, indicating a strong positive correlation between increases in gray matter volume and increases in the volume of the left hippocampus. Gray matter is the core area of the brain responsible for processing sensations, perceptions, voluntary movements, learning, speech, and cognition. Meanwhile, the left hippocampus plays a crucial role in the brain's language construction abilities and memory formation, especially in building long-term memories. This discovery highlights the close connection between the two, suggesting that processing activities in gray matter might support the key role of the left hippocampus in language and memory formation.

Further analysis with "cvar(GM, SubID)" assessed the variability in the effect of gray matter on the volume of the left hippocampus among individuals, meaning the increase in gray matter volume might have varying impacts on the volume of the left hippocampus in different individuals. The Wald test results show that this variability among individuals is not statistically significant (p-value of 0.21255), indicating that while the overall effect of gray matter is significant, this effect does not vary significantly among individuals. This result might mean that the role of gray matter in supporting hippocampal functions is relatively consistent across the population.

The positive correlation between gray matter and the volume of the left hippocampus might reflect an improvement in brain network efficiency and functionality, especially in processing and storing language-related information. This connection emphasizes the collaborative work between gray matter and the left hippocampus in processing sensory inputs and executing cognitive tasks, particularly during language processing and memory building. As the brain's demand for these functions increases, more neuronal resources might be needed, with the role of gray matter being particularly crucial.



(Figure 13)

What would be the predicted Hippocampus level for a male at the age of 20 with a traumatic brain injury who has an average fornix crux, capsule anterior, and Gray Matter Level?

How about a female with the same features?

In discussing a 20-year-old with traumatic brain injury and average levels of the anterior capsule, gray matter, and fornix crux, the predicted hippocampus volume for males is 4568.826, while for females under the same conditions, it's 4243.967. This comparison reveals that in young adults, males have a higher hippocampus volume relative to females.

How about middle-aged (50) people?

As age increases to 50, the predicted hippocampus volume for males decreases to 4166.299, while for females, it rises to 4305.585. This reflects a change in the impact of gender on hippocampus volume during middle age, with females surpassing males.

How about someone in their 70s?

By the time individuals reach 70, the predicted hippocampus volume for males further declines to 3844.276, in contrast, for females, it increases to 4346.663, intensifying the difference between genders. Elderly females not only have a higher hippocampus volume compared to males of the same age but also show a greater advantage over middle-aged males.

These results indicate that the gender differences in hippocampus volume become more pronounced with aging, especially among the elderly, where females tend to maintain a higher hippocampus volume relative to males. This trend might be related to various factors like physiology, hormones, and lifestyle, but further research is needed to explore the specific mechanisms.

Visit and improvement - Do people who show improvement still visit?

According to the analysis, we can observe a specific pattern between the number of visits and improvements. Specifically, patients who showed an increase in the volume of the left hippocampus (i.e., improvement) between the second and third visits often do not continue to the fourth visit. In other words, all the patients who showed improvement by visit 3 (6 out of 6) did not appear for visit 4. By contrast, only a very small number of patients who did not show improvement stopped attending subsequent visits.

This finding could have several implications. Firstly, patients who showed improvement might believe that they no longer need further treatment or follow-up, hence choosing not to continue with subsequent visits. Moreover, there could be other factors influencing these patients' decisions to continue with follow-ups, such as personal scheduling, transportation convenience, treatment costs, etc.

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