HIGH SCHOOL EDITION
Journal of Student Research
Volume 12 Issue 4 (2023)

A Multi-Modality Magnetic Resonance Imaging Model for Predicting Traumatic Brain Injury Outcomes

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ABSTRACT

Traumatic Brain Injury (TBI) is a heterogenous injury and a leading cause of long-term deficits and mortality in the United States. In order to improve TBI outcomes, an effective prognostication tool is necessary. Standard imaging modalities, computerized tomography (CT) and magnetic resonance imaging (MRI), have a limited ability to predict TBI outcomes. Currently, advanced MRI techniques are being studied for their efficacy. The aim of this study is to determine whether a multimodality MRI approach is superior to a single modality MRI approach in determining clinical outcomes of TBI. A secondary data analysis was conducted on TBI data obtained from 31 rat brains; 3-day MRI data in the Ipsilateral Perilesion Cortex and 28-day Behavioral Test data (Novel Object Recognition, Barnes Maze, and Open Field Test Total Distance and Total Act Time) were analyzed. A Best Subset Analysis was conducted for each of the behavioral tests. Three out of four behavioral tests show improved adjusted R^2 values for models containing more than one imaging modality. A Multiple Linear Regression Analysis was then conducted on the MRIs from the highest predictive model determined by Best Subset Analysis. This analysis shows that a multimodality MRI approach can explain 25.2% of the variability in behavioral outcomes in the Novel Object Recognition Test with a P value of 0.012. Thus, the study demonstrates that a multi-modality MRI approach has a potential for effectively diagnosing and predicting TBI outcomes.

Introduction

Traumatic Brain Injury (TBI), a heterogenous injury, is one of the leading causes of death and deficits in learning, memory, balance, vision, and smell in the United States. Around 50,000 people in the United States die annually from Traumatic Brain Injury, and 235,000 annual hospital admissions are attributed to TBI (Shah et al., 2020). Predicting TBI outcomes in patients is challenging for clinicians due to the heterogeneous nature of TBI severity and underlying mechanisms for varied outcomes. Standard structural magnetic resonance imaging (MRI) can provide information on the location and extent of mechanical damage and water accumulation (edema) in brain tissue but is limited in its ability to predict clinical outcome (R. Koehler, personal communication, February 16, 2023). Use of multiple modalities of advanced magnetic resonance imaging (MRI) may help to better diagnose and predict outcomes in patients with TBI. The purpose of this paper is to examine the efficacy of a multi-modality MRI approach to classify TBI severities. The paper will also demonstrate the ability of a multi-modality approach to provide diverse and complementary information to accurately predict acute and chronic TBI outcomes.

Review of Literature

Background

TBI occurs with varying severities, usually classified as mild, moderate, and severe in a research setting. Symptoms and outcomes vary in patients depending on the severity of TBI, but also vary from patient to patient with the same injury severity (Pugh et al., 2021). Clinicians analyze patients' symptoms to assess TBI severity and predict TBI outcomes, but many of these symptoms are "unreliable and/or nonspecific" (Lunkova et al., 2021). Thus, neuroimaging techniques, such as MRI and computerized tomography (CT), are utilized to evaluate TBI. But standard imaging using T1- and T2- weighted techniques is insufficient for analyzing TBI. More advanced MRI techniques have been developed, including susceptibility-weighted imaging (SWI), diffusion weighted MRI (dMRI/DWI), perfusion MRI, amide proton transfer-weighted MRI (APTw), arterial spin labeling MRI (ASL), functional MRI (fMRI), and resting state fMRI (rs-fMRI) (Zhang et al., 2017) (Koerte et al., 2016). SWI reveals hemorrhages in the brain, ASL MRI measures cerebral blood flow (CBF), diffusion-weighted MRI (DWI) and diffusion tensor imaging (DTI) identify edema and axonal injury, APTw is sensitive to tissue pH and protein abundance and differentiates between different types of stroke due to hemorrhage and occlusion of an artery (Zhang et al., 2017), fMRI measures the local changes in the concentration of deoxygenated hemoglobin in the tissue resulting from the changes in cerebral blood flow and oxygen consumption when neurons are activated while performing a task, and resting state fMRI (rs-fMRI) measures changes in local deoxyhemoglobin during spontaneous changes in activation of connected neural networks under resting conditions (Koerte et al., 2016) (R. Koehler, personal communication, February 16, 2023). Thus, each of these MRI techniques can inform about unique TBI-related changes in the brain. Whereas neuroimaging techniques can assist in diagnosis, their sensitivity and specificity for prognostication for TBI patient outcome remains uncertain.

Classifying Injury Severity

First, a multi-modality MRI approach can distinguish between different phases and severities of TBI. Several studies show that injury severities indicated by MRI correlate with TBI outcomes as validated by behavioral tests and biomarkers.

Acute and Chronic Phase of Injury

A multi-modality approach should be employed because specific MRIs are used to classify acute and chronic phases of injury. During the acute phase of TBI, CT is utilized as it is more sensitive to acute TBI-related structural changes given its ability to detect "its ability to detect skull fractures and large intracranial hemorrhages" (Edlow & Wu, 2012) leading to displacement of healthy tissue (R. Koehler, personal communication, February 16, 2023). In addition, during the acute phase, DWI helps detect axonal injuries caused by shear forces, intracranial bleeding, and edema. On the other hand, for subacute and chronic stages of TBI, Zhang et al. (2016) note that conventional MRI is used as it provides more in-depth information regarding white matter changes and small contusions seen in the brain during these stages. Fractional anisotropy (FA) signals in DTI, an extension of DWI, can provide information on preferential direction of water movement in white matter sheaths in both the acute and chronic phases of TBI; an increase in FA is linked with the acute phase, while a decrease in FA is associated with the chronic phase as the myelin sheaths lose integrity (R. Koehler, personal communication, February 16, 2023). Similarly, rs-fMRI can provide information on neural network connectivity in the acute and chronic phases of TBI.

Degree of Injury

Specific MRI modalities are utilized to identify different severities of injury in TBI (Zhang et al., 2016). For mild severity, DTI shows associated changes in FA and mean diffusivity (MD) values of water diffusion averaged over all 3-D directions (R. Koehler, personal communication, February 16, 2023). Individuals with mild TBI are found to have low MD values and high FA values. Moreover, fMRI detects changes in the prefrontal cortex, the cerebellar tonsil, and the culmen, which is often where mild TBI-related changes occur. fMRI also reveals how patients with mild TBI show variable increases in neuronal activation when engaging in difficult, memory-related cognitive tasks. In addition, rs-fMRI can identify mild TBI in patients, without the use of T1- or T2- weighted MRI data, as its "imaging highlights the importance of baseline functional connectivity in cognitive deficits experienced by TBI patients" (Zhang et al., 2016). In contrast to mild TBI, moderate and severe TBI are typically characterized by structural changes, which can be detected by CT and conventional MRI. Specifically, CT is used as an initial diagnostic tool for detection of moderate and severe TBI associated structural changes and damage compared to mild TBI. In DTI, moderate and severe TBI is distinguished by overall lower FA values, which indicate disturbances in white matter as water diffusion is less constrained in its movement parallel to the axons and myelin sheaths (R. Koehler, personal communication, February 16, 2023).

MRI Validation of Severity Using Behavioral Tests

In a 2015 study conducted by the Johns Hopkins University School of Medicine, the authors examined multiparametric MRI techniques and focused specifically on APTw to correlate with outcomes across different TBI severities in rats (Dong et al., 2022). The multiparametric MRI encompassed T1, T2, isotropic apparent diffusion constant (ADC), ASL measurements of CBF, and magnetization transfer ratio (MTR) that measures the rate of transfer of nuclear magnetic spin between protons in free water and macromolecules like myelin (R. Koehler, personal communication, February 16, 2023). In this study, the injury was induced in the rats using the Control Cortical Impact (CCI) machine. To assess neurobehavioral outcomes in rats, the sucrose preference test, Barnes maze, and modified neurologic severity score (mNSS) were employed. The sucrose preference test can indicate anhedonia, the Barnes Maze test correlates with spatial memory and learning, while the mNSS evaluates motor, sensory, reflex, and balance skills. Dong et al. (2022) observed that MRI results in the injury core and perilesion cortex were found to be predictive of TBI severity as indicated by the behavioral outcomes. Specifically, at one hour and one day post-TBI, a decrease in APTw signals in the injury core was found in rats with moderate and severe TBI; these decreased APTw signals negatively correlated with the modified neurologic severity score (mNSS) at 28 days. Furthermore, at one-day post-TBI, the APTw signal showed a positive correlation with the sucrose test and a negative correlation with Barnes maze escape time over the ensuing weeks. Conversely, in the perilesion cortex, an increase in the APTw signals was seen in moderate and severe groups at three days. This signal showed a positive correlation with the 28-day mNSS and a negative correlation with the sucrose test. Therefore, the study shows how early, one-day APTw signals in the injury core and three-day APTw signals in the perilesion cortex can correlate with injury severity and neurologic dysfunction, anhedonia, and memory decline. Overall, this study demonstrates the ability of multiparametric MRI, including APTw, in differentiating recovery of different characteristics of neurobehavioral deficits.

MRI Validation of Severity Using Biomarkers

Another study on serum biomarkers illustrates how these biomarkers can identify severities of TBI, as noted by MRI findings (McMahon et al., 2015). Conducted on 215 patients, 83% of whom had mild TBI, 4% moderate, and 12% severe, the study looked at the ability of glial fibrillary acidic protein and its breakdown products (GFAP-BDP) to diagnose TBI severity, as noted by CT and MRI findings. GFAP-BDP, a brain astrocyte cell protein released into the blood after TBI, was able to sufficiently identify intracranial injury with 81% accuracy, as shown by the radiographic

imaging. With a 95% confidence interval, GFAP-BDP had a "very good predictive ability" and showed "significant discrimination of injury severity" (McMahon et al., 2015). Given the ability of the multimodality MRI approach in identifying different TBI severities, this strategy should be employed to diagnose and prognosticate outcomes in patients with TBI.

Diverse Metrics and Complementary Information

In addition, by combining multiple MRI techniques, the number of metrics being measured is diversified and will reveal complementary information about the brain post-TBI, which is why a multi-modality approach could be more advantageous than employing a single imaging modality. This is particularly important because TBI is a heterogeneous disorder affecting gray and white matter to different degrees among patients (R. Koehler, personal communication, February 16, 2023).

Diverse Metrics

Conventional MRI methods such as T1 and T2 weighted MRI can provide important metrics that may not be detectable through the use of advanced MRI, as shown in a study conducted on 46 United States Military veterans (Gordon et al., 2019). Diffusion MRI is used to identify axonal injuries by looking at abnormalities in the white matter of the brain, where these injuries are most likely to occur after TBI. However, some axonal injuries and myelin changes resulting from TBI occur outside of the white matter of the brain, most notably the cortex. Diffusion imaging is not able to detect axonal injuries outside of white matter, so T1 and T2 weighted MRI were utilized in this study to provide additional information on the brain cortex myelination.

Other advanced MRI methods such as SWI, fMRI, and DTI can also enhance the quality of data collected following TBI as they each provide unique metrics. SWI looks at microhemorrhages. It is also sensitive "to venous blood … and iron in the brain" (Koerte et al., 2016). Furthermore, task-based fMRI is a method that measures changes in blood flow in response to the subject engaging in a cognitive task. In resting-state fMRI, changes in blood flow are measured while the subject is not performing any cognitive tasks (Lunkova et al., 2021). Also, DTI measures diffusion of water molecules and indirectly measures changes in tissue microstructure such as axonal injury. Four variables, mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), and fractional anisotropy (FA), are analyzed in DTI; "reduced FA is purported to reflect microscopic damage to myelin sheaths or axon membranes and/or axonal packing density" (Koerte et al., 2016). Each of these methods looks at different functional and structural changes in the brain as a result of TBI, providing varied information regarding the pathophysiology behind TBI and its resulting outcomes.

Complementary Information

A multimodality approach also provides complementary, "mutually informative" data about the brain's pathophysiological processes (Hao et al., 2011). In an experiment to study pinocembrin drug efficacy, four MRI signals from functional and molecular MRI techniques were identified as successful biomarkers of TBI and TBI recovery (Wang et al., 2017). The authors state that "to the best of our knowledge, this is the first study to use multiparameter MRI to assess TBI-induced secondary brain injury over time" (Wang et al., 2017). The four MRI signals used in the study were ASL, APTw, ADC, and MTR. During the experiment, pinocembrin, a natural extract, was found to combat the effects of neuroinflammation stemming from the secondary phase of TBI. The authors subjected some of the rats (TBI rats) to controlled cortical impact. Next, pinocembrin was administered to a subset of rats, which showed recovery on behavioral testing, as opposed to the TBI rats not given pinocembrin. MRI brain signals were also measured to correlate with pinocembrin-induced recovery. In rats that were given pinocembrin, the TBI-induced changes in ASL-

derived CBF, APTw, ADC, and MTR levels were mitigated. Thus, the use of the 'multiparameter' MRI with four signals could identify drug treatment effects on neuroinflammation and behavior recovery in the rats.

Another study analyzed MRI and DTI biomarkers that could be used for studying TBI in ferrets that underwent controlled cortical impact (Hutchinson et al., 2016). T2 MRI and DTI changes during the acute phase of TBI were studied. The authors found that T2 MRI and DTI signals should be taken together as they provide complementary information about "pathophysiology and cellular alterations that emerge during the acute time period" (Hutchinson et al., 2016). Strong statistical correlations between T2 and TR values were found in most lesioned areas but showed varied data in other areas. Similarly, T2 and FA also showed a statistically significant correlation with one another. When looking at individual areas, T2 and TR as well as T2 and FA provided complementary information to one another.

In a different study, MRI, fMRI, and DTI were identified as potential biomarkers for predicting TBI outcomes, and a combination of these techniques was proposed to improve outcome prediction (Irimia et al., 2012). Predominantly, clinicians use CT and MRI together to assess TBI patients. Although this combination of techniques has improved the assessment of TBI patients, it still lacks specificity in certain areas. Other advanced neuroimaging methods like DTI and fMRI fill in these gaps by measuring structural and functional abnormalities in the brain. By using CT, MRI, and advanced neuroimaging techniques together, researchers can combine volumetric measurements with structural and functional measurements of the brain to reveal pathological processes that occur following TBI and improve the prediction of outcomes.

Based on the results of these studies, a multi-modality approach is shown to provide varied, complementary information and should be used more widely to assess TBI.

Predicting TBI Outcomes

Additionally, data obtained from multiple MRI techniques can help predict TBI outcomes, including acute and chronic cognitive and motor deficits.

Acute Cognitive Outcomes

The ability to predict acute cognitive outcomes in TBI patients was studied by measuring diffuse axonal injury on MRI (Humble et al., 2018). These outcomes were measured using the FIM, or hospital-discharge Functional Independence Measure, score. The study found that diffuse axonal injury can only accurately prognosticate short-term functional outcomes, not long-term. The study used a modified FIM score which is "a total of self-feeding, locomotion, and expression scores" (Humble et al., 2018) obtained at discharge. As observed by the data from 240 patients, lower FIM scores, which indicated worse cognitive outcomes at discharge, were associated with diffuse axonal injury on MRI.

Acute Motor Outcomes

Another study aimed to identify MRI biomarkers that correlate with functional acute motor outcomes 24 hours after TBI (Wang et al., 2021). T1, T2, DWI, and DTI MRI techniques were used at 24 hours. During this same period, gait analysis, which looked at stride and step length, was also conducted. An increase in lesion size correlated with a decrease in stride and step length with $P = 0.03$ and $P = 0.02$ respectively; an increase in midline shift of the brain hemispheres also negatively correlated with stride and step length, with $P=0.03$ for both. The data suggest that MRI can predict reduced motor skills at 24 hours post-TBI.

Long-term Cognitive Outcomes

Structural MRI was used on 63 patients one year post-injury across all severities to prognosticate chronic TBI outcomes with neuropsychological testing (Levine et al., 2013). It was found that in "tests of speeded attention, working memory, and verbal learning and memory," the results on MRI "robustly covaried with a distributed pattern of volume loss over temporal, ventromedial prefrontal, right parietal regions, and cingulate regions" (Levine et al., 2013). These correlations in outcomes were seen in patients with both focal and diffuse injuries on MRI. In a similar study, 45 ice hockey players with acute concussion were studied for persistent post-concussive symptoms six days post TBI (Shahim et al., 2020). Serum neurofilament light (NfL) correlated with outcomes, as indicated by Glasgow Outcome Scale Extended (GOSE) score, and MRI changes in DTI. A GOSE score is a standard method for the evaluation of cognitive outcomes in patients with TBI. Serum NfL correlated with long-term outcomes at 90 days (low GOSE scores). Shahim et al. (2020) concluded that "Serum NfL distinguished patients with TBI from controls at 30, 90, and 180 days with high accuracy and showed an association with functional outcome."

Long-term Motor Outcomes

MRI biomarkers that correlate with long-term functional outcomes in pigs at 12 days post TBI were identified (Wang et al., 2021). At 12 days post TBI, T1, T2, DWI, and DTI MRI techniques were used and gait analysis was conducted. An increase in lesion size and midline shift negatively correlated with stride and step length at 12 days, suggesting that MRI can predict reduced motor skills at 12 days post-TBI. Another study was conducted on 391 patients with acute mild TBI at two weeks and six months post TBI for long-term outcomes (Palacios et al., 2022). White matter changes on DTI were analyzed using four parameters, AD, FA, MD, and RD. In order to assess long-term outcomes, patients were evaluated with a GOSE score. AD and MD values at two weeks correlated with long term deficits at six-months, as noted by a GOSE score less than eight. Palacios et al. (2022) state that "higher AD and MD at two weeks are both independently associated with better long-term outcome." A multi-modality neuroimaging approach thus has the ability to provide key information on TBI outcomes, both short term and long term, allowing for improved prognostication.

Counterargument

There are limited studies conducted on a multi-modality MRI approach to diagnose and predict TBI outcomes, and many of these studies were conducted on animal models or a small sample size of human subjects. However, a multi-modality MRI approach has several advantages over a single modality approach given its superior ability to provide a range of information about TBI and to predict TBI outcomes.

Conclusion

Traumatic Brain Injury is a widespread problem affecting diverse groups of people from varying age groups. TBI can cause long-term debilitating effects. Although there are various imaging techniques available including advanced MRI for diagnosis of TBI, there is still a limited ability to effectively prognosticate outcomes for patients. Without an accurate diagnosis and prognosis, patients may not get the proper care in a timely manner. As demonstrated by several studies, a multi-modality MRI approach has high potential for diagnosing and predicting acute and chronic TBI outcomes given its ability to differentiate between severities and provide a diverse set of information. In the future, the principles of using a multi-modality MRI approach can be applied to various other neurological conditions.

Methods

This study aims to test whether a multimodality MRI approach is superior to a single MRI modality to predict TBI outcomes. Secondary data analysis was performed on data obtained from a prior study that sought to observe the efficacy of TPPU (a potent and highly selective soluble epoxide hydrolase inhibitor) on reducing neuroinflammation after TBI in rats. From the data set, 3-day MRI data in the Ipsilateral Perilesion Cortex and 28-day Behavioral Test data were analyzed. For this study, the MRI data from all experimental groups (Sham, Moderate, and Moderate with TPPU) were combined to mimic a heterogenous human population.

Data were obtained from a research study conducted by the Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine. The data set contains behavioral test data (Novel Object Recognition, Barnes Maze, and Open Field Test Total Distance and Total Act Time) at 28 days post Controlled Cortical Impact (CCI) Injury and MRI data (T2, T1, CBF, APTw, ADC, and MTR) for 1 hour, 3 days, 7 days, and 28 days in five regions of the brain: Core Area, Ipsilateral Perilesion Cortex, Contralateral Cortex, Ipsilateral Hippocampus, and Contralateral Hippocampus. The original data set had 31 rats with complete MRI and behavioral data which were selected for this study. The statistical analysis was conducted using the SigmaPlot software.

For each of the behavioral tests, individual Linear Regression analysis was conducted between each of the six MRI modalities and the behavioral test. Next, a Best Subset Analysis was conducted for each of the behavioral tests. The Best Subset Analysis produces models for all possible combinations of the independent variables. If the number of variables is k, there will be 2^k models produced. However, in Best Subset Analysis, only the best model for one variable, two variables, etc. to k variables is considered leaving only k number of models to compare. After conducting the Best Subset Analysis, the model with the highest adjusted R^2 value for each behavioral test was identified. The MRIs in these models were used as independent variables in a Multiple Linear Regression analysis to evaluate their predictive value of each behavioral test; for Barnes Maze a simple Linear Regression, not a Multiple Linear Regression, analysis was conducted because the best subset model with the highest adjusted R^2 had only one MRI variable.

Results

Individual Linear Regression analysis between each of the six MRI modalities shows a strong covariance between APTw and CBF (Table 1). Individual Linear Regression analysis between each of the six MRI modalities and behavioral tests were also conducted (Table 2). The MRI modalities are ranked in predictive order for each behavioral test.

Next, the Best Subset Analysis identified the six models with the best predictive value for TBI outcomes for each of the behavioral tests (Table 3). Each of the best subset models for a particular behavioral test has a Mallows' Cp value equal to or less than the number of independent variables plus one (Cp </= k+1). This indicates that each of these models is an unbiased predictor of the dependent variable, the behavioral test.

The R^2 value improves every time an independent variable is added to the regression, so a model with the maximum number of variables will always have the highest R^2 value. To avoid this problem, the best overall model is chosen based on the adjusted R^2 value.

Table 1. Linear Regression Analysis conducted with six different MRI modalities.

MRI Type	ATPw	CBF	MTR	ADC	T2	T1
APTw	1					
CBF	0.784 **0.615** 0.602	1				
MTR	0.601 **0.361** 0.339	0.436 **0.190** 0.162	1			
ADC	0.621 **0.386** 0.365	0.682 **0.466** 0.447	0.657 **0.432** 0.412	1		
T2	0.283 **0.0801** 0.0484	0.108 **0.0116** 0.000	0.233 **0.0542** 0.0216	0.120 **0.0144** 0.000	1	
T1	0.211 **0.0444** 0.0115	0.0337 **0.00114** 0.000	0.634 **0.402** 0.381	0.263 **0.0691** 0.0370	0.471 **0.222** 0.195	1
Key: R **Rsqr** Adj Rsqr						

Table 2. Linear Regression Analysis between each of the six different MRI modalities and the behavioral tests.

Behavioral Test and Analysis/MRI modality		T2	T1	ADC	CBF	APTw	MTR
Novel Object Recognition	Linear Regression (P & R^2 value)	0.296 0.0376	0.419 0.0226	0.279 0.0403	0.047 0.129	0.003 0.263	0.027 0.158
	Predictive Order (1 is the highest)	5	6	4	3	1	2
Barnes Maze	Linear Regression (P & R^2 value)	0.264 0.0428	0.791 0.00247	0.142 0.0727	0.002 0.297	0.009 0.214	0.294 0.0379
	Predictive Order (1 is the highest)	4	6	3	1	2	5
Open Field Total Distance	Linear Regression (P & R^2 value)	0.844 0.00135	0.394 0.0252	0.806 0.00211	0.453 0.0195	0.462 0.0188	0.476 0.0177
	Predictive Order (1 is the highest)	6	1	5	2	3	4
Open Field Total Act Time	Linear Regression (P & R^2 value)	0.947 0.000154	0.531 0.0137	0.854 0.00119	0.409 0.0236	0.405 0.0240	0.645 0.00740
	Predictive Order (1 is the highest)	6	3	5	2	1	4

For the Novel Object Recognition Test, Model 3 which includes APTw, MTR, and ADC has the highest adjusted R^2 value, 0.252. For the Barnes Maze Test, Model 1 which includes CBF has the highest adjusted R^2 value, 0.273. For Open Field Test Total Distance, Model 2 which includes ATPw and MTR has the highest adjusted R^2 value, 0.008. For Open Field Test Total Act Time, Model 2 which includes ATPw and MTR has the highest adjusted R^2 value, 0.027. The Best Subset Analysis on three out of four behavioral tests shows improved adjusted R^2 values for models containing more than one MRI modality.

Table 3. Best Subset Analysis for behavioral tests.

Novel Object Recognition											
Model #	Variable	Cp	Rsqr	Adj Rsqr	MSerr	T2	T1	ADC	CBF	APTw	MTR
1	1	-.0229	0.263	0.238	100.585					*	
2	2	0.945	0.286	0.235	100.966			*		*	
3	3	1.462	0.327	0.252	98.718			*		*	*
4	4	3.226	0.333	0.231	101.526		*	*		*	*
5	5	5.086	0.337	0.205	104.977	*	*	*		*	*
6	6	7.000	0.340	0.175	108.961	*	*	*	*	*	*
Barnes Maze											
Model #	Variable	Cp	Rsqr	Adj Rsqr	MSerr	T2	T1	ADC	CBF	APTw	MTR
1	1	-1.301	0.297	0.273	4327.080				*		
2	2	-0.114	0.319	0.271	4339.886	*			*		
3	3	1.067	0.342	0.269	4352.411	*		*	*		
4	4	3.017	0.343	0.242	4510.370	*		*	*	*	
5	5	5.009	0.343	0.212	4689.272	*		*	*	*	*
6	6	7.000	0.344	0.179	4882.846	*	*	*	*	*	*

Open Field Total Distance											
Model #	Variable	Cp	Rsqr	Adj Rsqr	MSerr	T2	T1	ADC	CBF	APTw	MTR
1	1	-1.356	0.024	-0.010	5434.283					*	
2	2	-.0677	0.074	0.008	5338.292					*	*
3	3	1.181	0.080	-0.023	5503.800			*		*	*
4	4	3.005	0.086	-0.054	5673.780			*	*	*	*
5	5	5.001	0.087	-0.096	5899.780	*		*	*	*	*
6	6	7.000	0.087	-0.142	6145.424	*	*	*	*	*	*

Open Field Total Act Time											
Model #	Variable	Cp	Rsqr	Adj Rsqr	MSerr	T2	T1	ADC	CBF	APTw	MTR
1	1	-0.993	0.025	-0.008	627004.634		*				
2	2	-0.763	0.092	0.027	605198.419					*	*
3	3	1.168	0.094	-0.007	625828.160			*		*	*
4	4	3.053	0.098	-0.040	646792.970			*	*	*	*
5	5	5.038	0.099	-0.081	672253.469	*		*	*	*	*
6	6	7.000	0.100	-0.124	699155.933	*	*	*	*	*	*

A Multiple Linear Regression analysis was conducted using the MRIs identified in the model with the highest adjusted R^2 value in the Best Subset Analysis (Table 4). The Multiple Linear Regression analysis for Novel Object Recognition using the MRI variables APTw, MTR, and ADC has an adjusted R^2 of 0.252 and a P value of 0.012. The Multiple Linear Regression analysis for Open Field Total Distance using the MRI variables APTw and MTR has an adjusted R^2 of 0.0267 and a P value of 0.261. The Multiple Linear Regression analysis for Open Field Total Act Time using the MRI variables APTw and MTR has an adjusted R^2 of 0.00822 and a P value of 0.339. The Novel Object Recognition test is the only behavioral test with a significant result from the three Multiple Linear Regression analyses.

Table 4. Multiple Linear Regression for Novel Object Recognition, Open Field Total Distance, and Open Field Total Act Time tests. Linear Regression for Barnes Maze test.

Behavioral Test (Y)	**MRIs[1] (Xs)**		**Analysis of Variance**	DF	SS	MS	F	P
Novel Object Recognition	APTw MTR ADC		Regression	3	1294.465	431.488	4.371	0.012
R^2	0.327		Residual	27	2665.373	98.718		
Adj R^2	0.252		Total	30	3959.838	131.995		

Behavioral Test (Y)	**MRIs[1] (Xs)**		**Analysis of Variance**	DF	SS	MS	F	P
Barnes Maze	CBF		Regression	1	53039.449	53039.449	12.258	0.002
R^2	0.297		Residual	29	125485.325	4327.080		
Adj R^2	0.273		Total	30	178524.774	5950.826		

Behavioral Test (Y)	**MRIs[1] (Xs)**		**Analysis of Variance**	DF	SS	MS	F	P
Open Field Total Distance	APTw MTR		Regression	2	1707596.843	853798.421	1.411	0.261
R^2	0.0915		Residual	28	16945555.739	605198.419		
Adj R^2	0.0267		Total	30	18653152.582	621771.753		

Behavioral Test (Y)	**MRIs[1] (Xs)**		**Analysis of Variance**	DF	SS	MS	F	P
Open Field Total Act Time	APTw MTR		Regression	2	12004.707	6002.354	1.124	0.339
R^2	0.0743		Residual	28	149472.187	5338.292		
Adj R^2	0.00822		Total	30	161476.894	5382.563		

[1]MRIs chosen from the best subset model with highest adjusted R^2 value for a given Behavioral Test

Discussion

Based on the results from the Multiple Linear Regression analysis, it cannot be definitively concluded whether a multimodality MRI approach is a better predictor of TBI-related behavioral outcomes as opposed to a single modality approach. Out of the three Multiple Linear Regressions, only the Novel Object Recognition test has a significant P value; its adjusted R^2 value is 0.252, which means 25.2% of the variability in the behavior outcome is explained by the combined MRI modalities and 74.8% is not explained by the MRI modalities. The latter could be partially due to the fact that MRI measurements are only indirect biomarkers of behavior. The other two behavioral tests do not have significant P values. Several studies on Traumatic Brain Injury (Irimia et al., 2012) (Wang et al., 2017) (Hutchinson et al., 2016) have suggested a multimodality MRI approach is superior to a single modality, but the results of this data analysis are not able to support this conclusion.

This data analysis has a few limitations. The MRI data were collected from rats, which may not translate well to clinical settings. The sample size of 31 is very low. Moreover, the MRI data may be affected due to inherent limitations of the technique and positioning of the rat while collecting the data. MRI data varies within a rat brain over time and among individual rats. Similarly, there are inherent limitations when collecting behavioral data. Behavior is the combination of multiple neurological processes; hence, behavioral data has high variability in measurement. Although a multimodality MRI approach needs to be further studied, it has the potential to improve clinical outcome prediction in patients with TBI. In the future, the multimodality MRI approach can be expanded to predict not only various other cognitive and motor functions post-TBI but also other neurological conditions.

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