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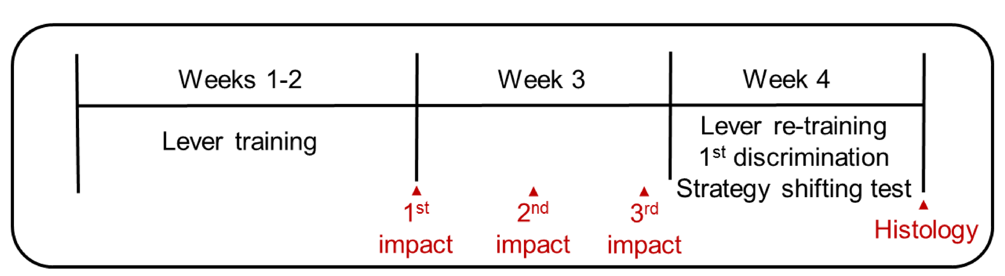
Introduction

Mild traumatic brain injury (mTBI) occurs in almost 80% of the 3 million reported cases of TBI-related emergency department visits each year in the United States. The majority of mTBIs, sometimes classified as concussions, are due to sports-related activities and typically occur repeatedly over the course of an athlete's career. mTBI symptoms are generally classified as either somatic or neuropsychiatric/cognitive in nature and include impairments in prefrontal cortex mediated functions, including attention, memory, processing speed, reaction times, problem solving, and cognitive flexibility. To date, there remains a major gap in our understanding of the behavioral manifestations, underlying neurobiology, and treatment of mTBI. An even greater gap exists in our understanding of the consequences of repeated mTBI incidents. The goal of the present study was to examine the effects of repetitive mTBI within a rodent assay of cognitive flexibility. Rats were exposed to a series of three closed head injuries (controlled cortical impact model) within a week prior to performing an automated strategy shifting task, which required rats to learn and shift strategies according to changing task demands. Rats initially acquired a visual cue strategy in which a light illuminated above one of two possible levers (left or right) indicated the correct response for reward. Twenty-four hours after initial acquisition, rats again performed the task using the visual cue strategy followed by a series of strategy shifting and reversal learning challenges.

Methods

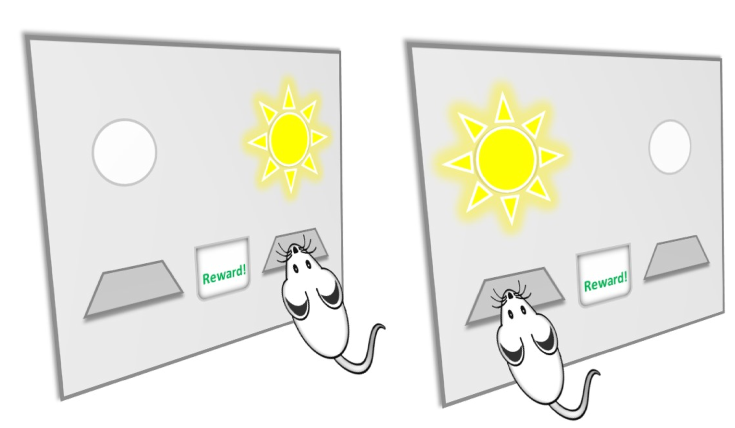
- Male Long Evans rats (n = 22, 75-100g upon arrival) were housed in a 12 : 12 hour inverted light cycle facility and placed on a food restricted diet (5 grams/100 grams body weight) with *ad libitum* access to water.
- Animal training, injuries, and testing timeline:



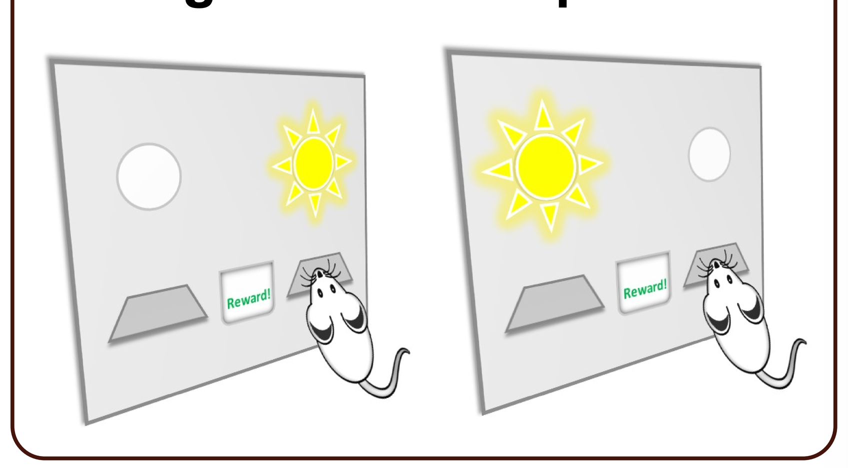
- Injury model: All rats (150-200g at the beginning of surgeries) were anesthetized and subjected to either sham surgery or mild traumatic closed head injuries using a CCI device every three days for a total of three insults. Briefly, a 5mm-diameter metal impactor tip was zeroed with the skull along the sagittal suture line so that the edge of the tip was aligned with bregma. The tip was then electronically driven into the skull at a velocity of 5.5m/s to a depth of 2.5mm below the zero point.

Visual Cue and Egocentric Response

Visual Cue



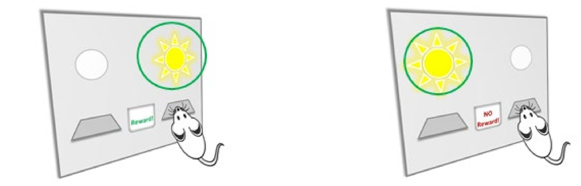
Egocentric Response



Task strategies. Visual cue discrimination example above (left; initial rule discrimination) illustrates an animal using a visual cue to guide correct lever presses for reinforcement. Egocentric response discrimination example above (right) illustrates an animal using an side response strategy (i.e. press right lever) to guide lever presses for reinforcement.

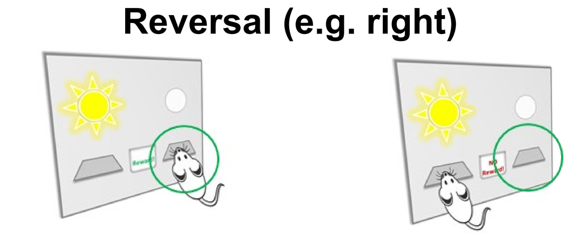
Test Progression

Cue Retrieval

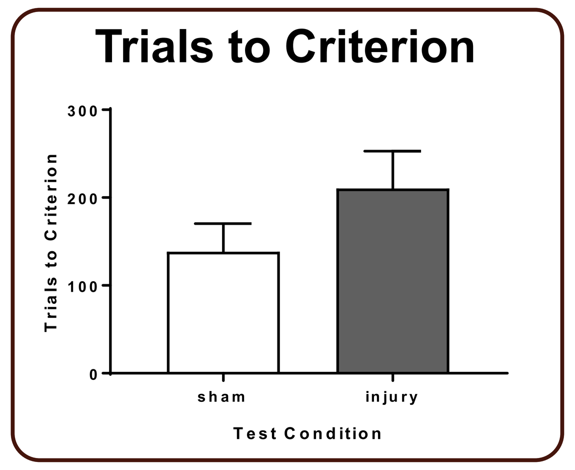


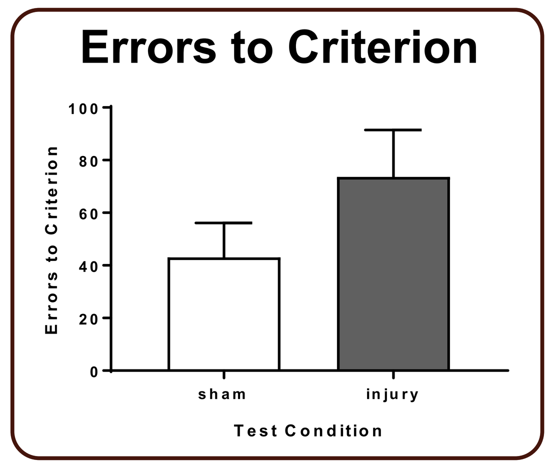
Strategy Shift to Response (e.g. left)

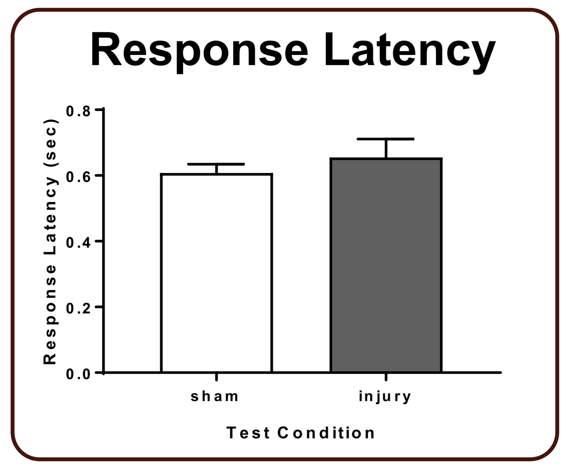
Reversal (e.g. right)

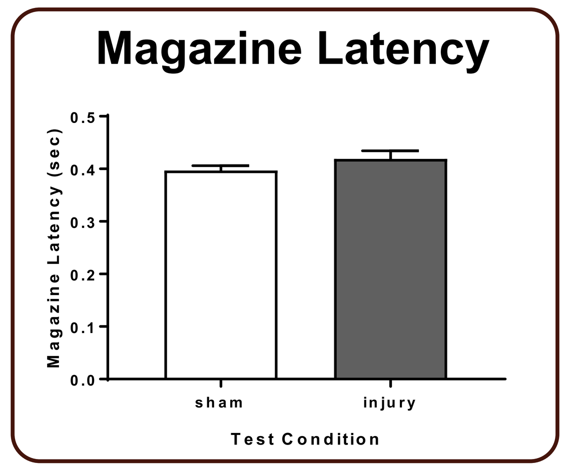


1st Rule Acquisition: Visual Cue Discrimination



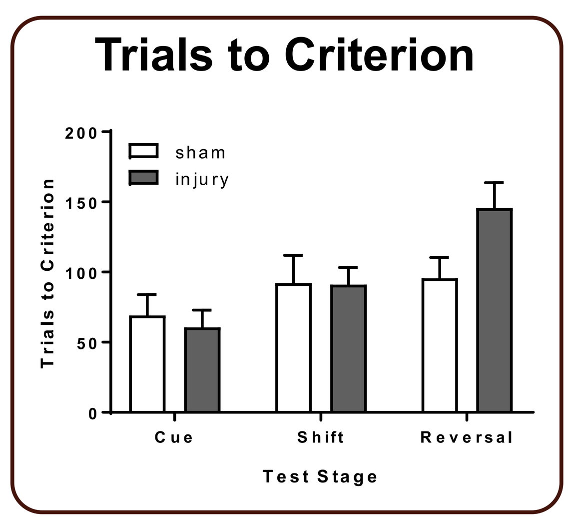


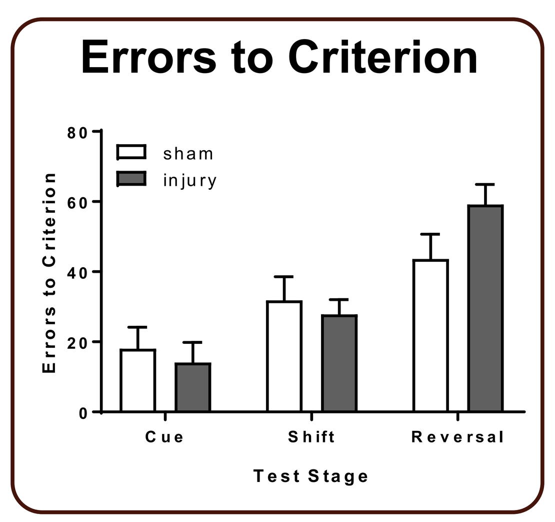


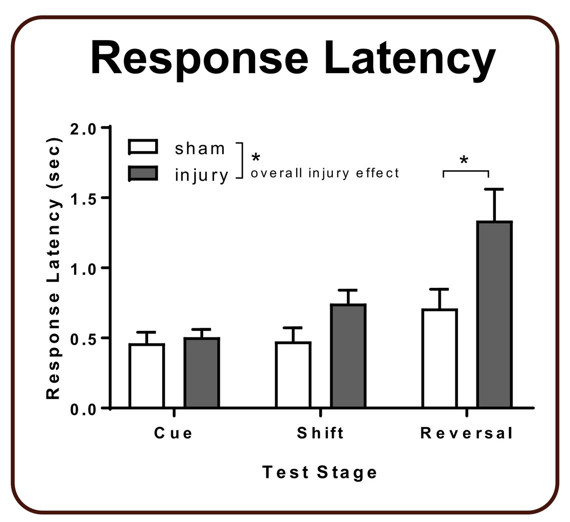


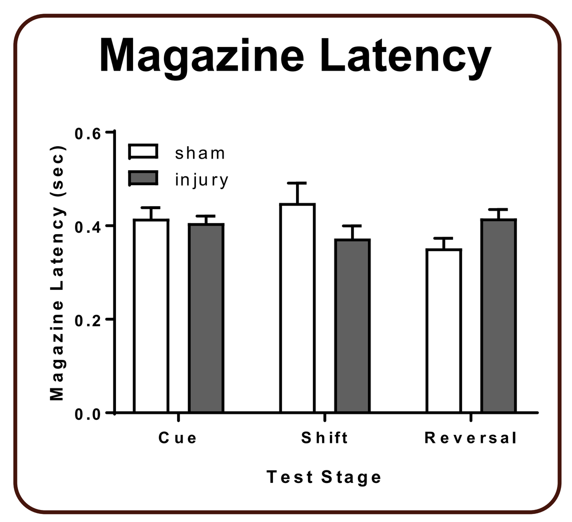
Initial rule discrimination. Bar graphs represent average test performance measures during initial visual cue discrimination (sham n = 10, injury n = 11).

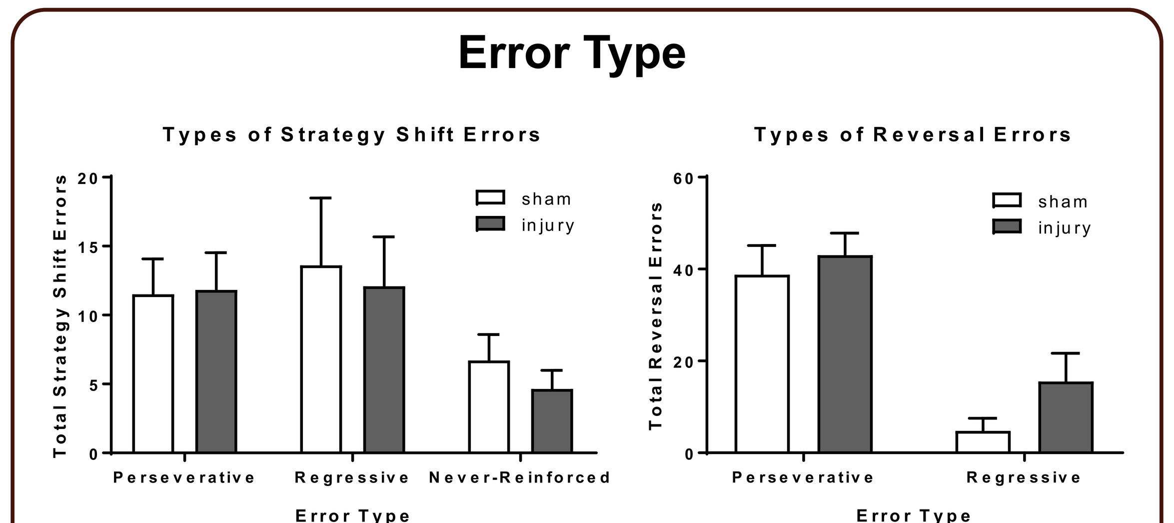
Strategy Shifting Test

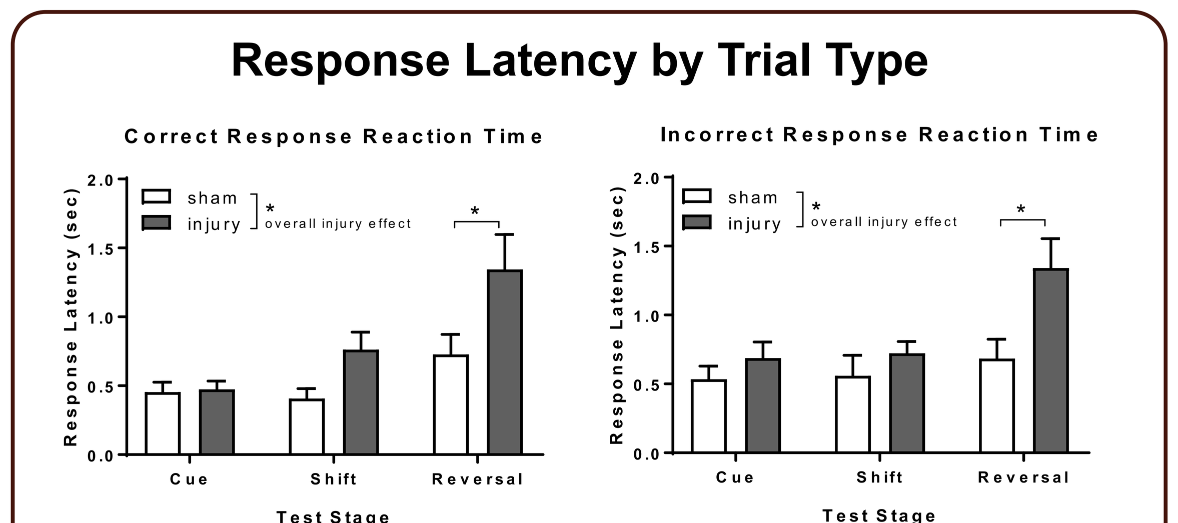






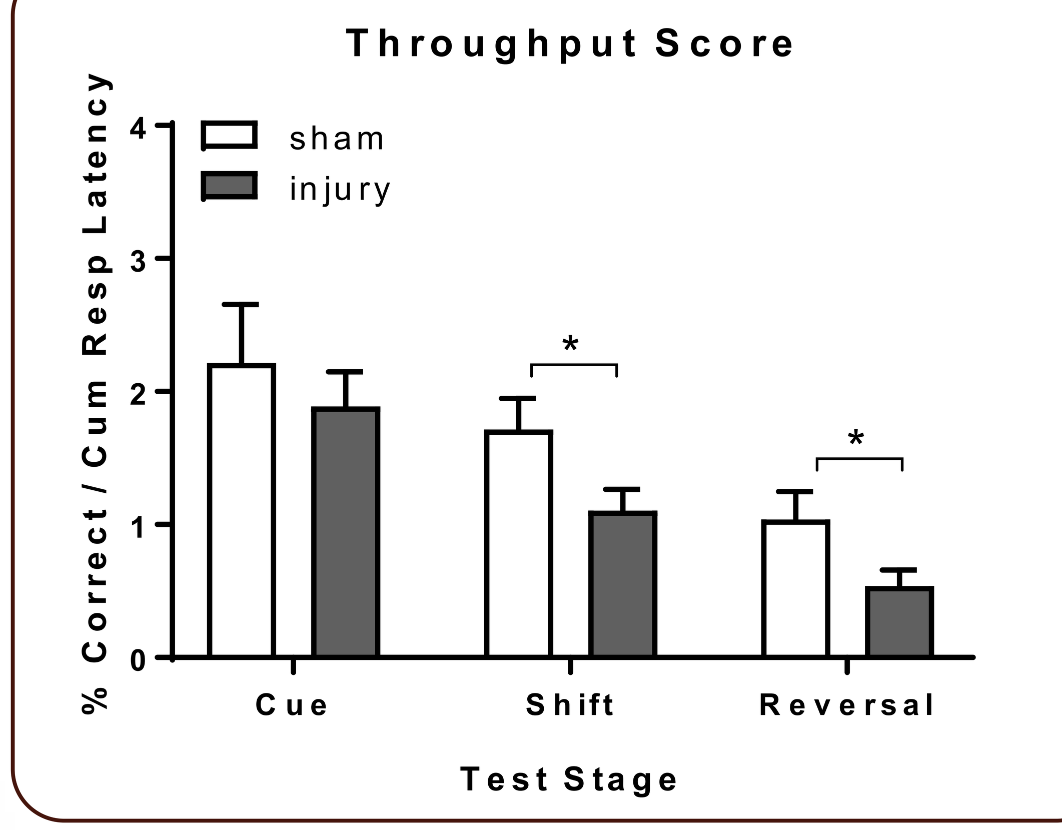






Strategy shifting test. Bar graphs represent average performance measures during each test stage (sham n = 10, injury n = 11). * denotes $p < 0.05$ for an overall injury group effect on response latency analyzed by two-way ANOVA (adjacent to treatment legends) and between injury groups at specific test stages analyzed by Sidak's multiple comparisons tests.

Throughput Scores



Throughput scores. Bar graph represents average throughput scores during each test stage split into injury groups (sham n = 10, injury n = 11). The throughput score is a performance index that blends accuracy and response speed into a single measurable unit of behavior and derived from the number of correct responses / cumulative reaction time for both correct and incorrect responses [1]. * denotes $p < 0.05$ for an overall injury effect analyzed by two-way ANOVA.

Conclusions

Summary

Repetitive mTBI increased reaction times and reduced throughput scores, a performance index that blends accuracy and response speed [1].

Significance

These results indicate that performance and task efficiency in an operant test of cognitive flexibility are impaired after repetitive mTBI. As such, this model presents a useful approach for further investigating the behavioral deficits and potential treatment strategies for patients who have experienced multiple mTBI insults.

Acknowledgements and Support

1. McCrea, M., Prichep, L., Powell, M. R., Chabot, R. & Barr, W. B. (2010). Acute effects and recovery after sport-related concussion: a neurocognitive and quantitative brain electrical activity study. *J Head Trauma Rehabil* 25, 283-92.

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