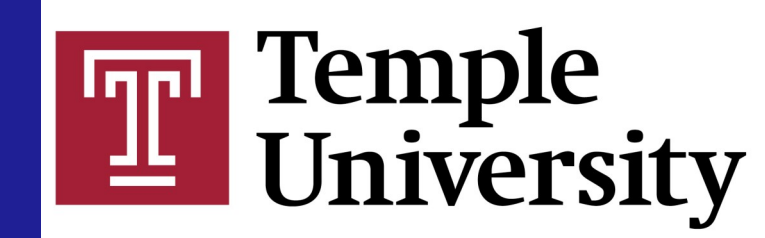


The effect of repetition pattern on sub-acute behavioral deficits following Repetitive Mild Traumatic Brain Injury



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INTRODUCTION AND OBJECTIVE

Mild Traumatic Brain Injury (mTBI), induced by a variety of mechanisms, including rapid acceleration or deceleration and blast overpressure, is a major public health issue [1]. Repeated Mild Traumatic Brain Injury (rmTBI) is when mTBI occurs more than once over a period of time and may cause long-term neurobehavioral and cognitive disorders [2]. Our main objective was to evaluate the effect of repetition pattern on sub-acute motor function deficit, anxiety, and memory loss in a novel rmTBI model in rats.

In this study, we presented two repetition patterns of rmTBI using a rat model based on applying Whole Body Deceleration (WBD) in the dorsal direction. The objective of the WBD model is to replicate mTBI in humans as in the case of repeated hits to the head in sports such as football and hockey.

MATERIALS AND METHODS

- The anesthetized animal in a freely sliding carriage on a track (Fig.1)
- The track is accelerated at 4g to the velocity of 12 m/s and decelerated with about 70g peak deceleration after the impact with a hydraulic shock absorber.
- Repetition patterns of WBD tests
 - 1) WBD1: repeated 3 times in one day
 - 2) WBD2: 4 times in one day and another 4 times after 48 hours
- Each impact and retraction took about 1s. No direct impact is applied to the head
- 20 male Sprague-Dawley rats (~ 300 grams) were randomly grouped to WBD1 (n=7), WBD2 (n=5), and sham controls (n=8).
- Animals were kept in standard housing for 21 days after injury to allow TBI symptoms to develop.
- Following behavioral tests were done on days 5, 9, 15, and 20 :
 - Rotarod to assess motor function (metric: the mean latency to fall off the rotating rod and its corresponding velocity)
 - Open field (OF) to evaluate anxiety (metric: the time spent in the central zone of the arena)
 - Novel Object Recognition (NOR) for memory (metric: the discrimination index (DI))
- TLR4 proteins were evaluated using RT-PCR to investigate the brain inflammatory response in the prefrontal cortex in day 21

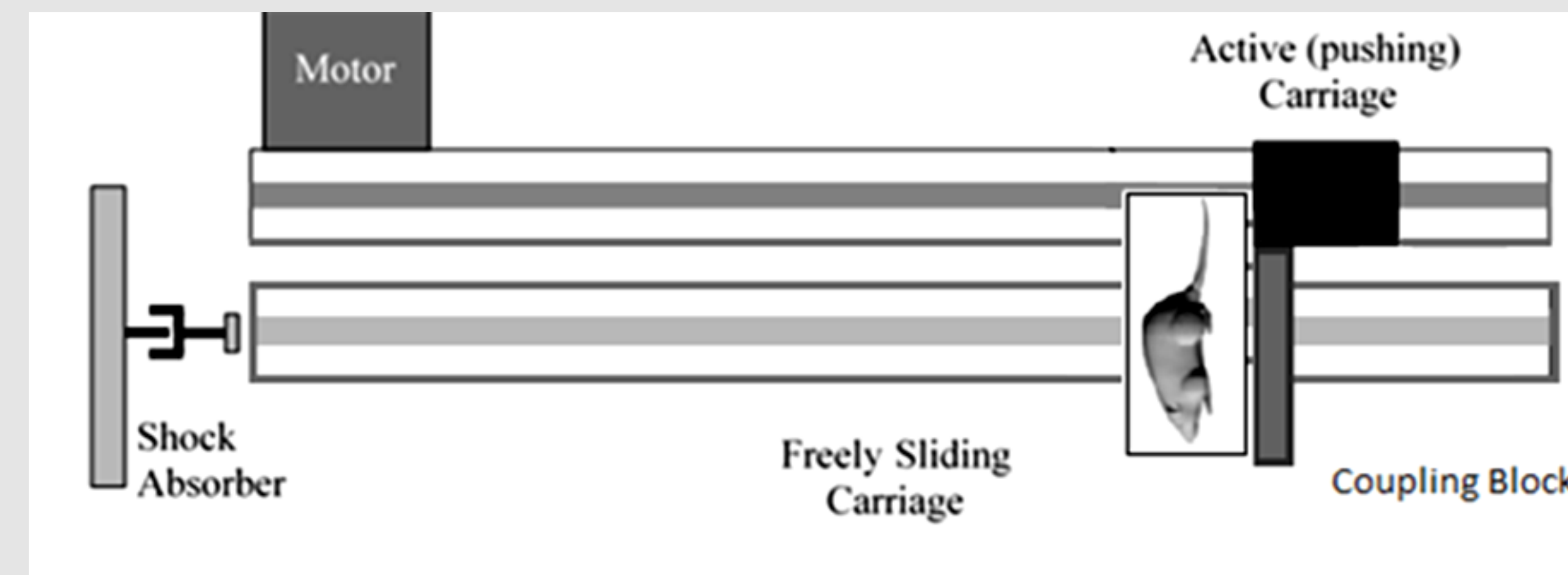


Figure 1. Schematic diagram of the experimental setup

RESULTS

Rotarod results on days 5, 9, 15, and 20 showed 15, 7, 3, and 24 % decline in performance for WBD1, and 20.5, 27.4, 34.5, 47% for WBD2 (Fig.2). WBD2 indicated significant change compared to WBD1 in rotarod performance on day 20 (p=0.04).

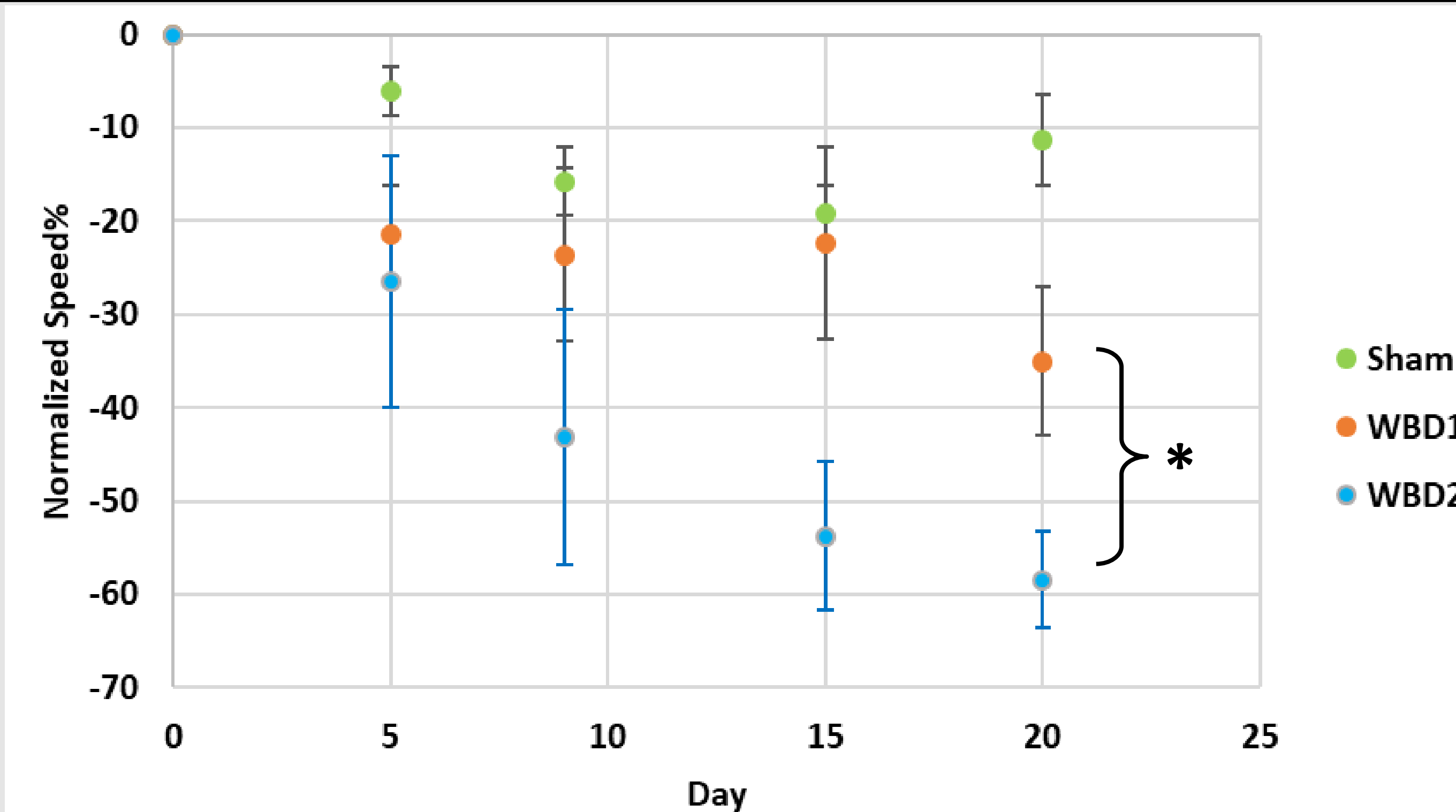


Figure 2. Rotarod results show the normalized speed at fall.

OF results showed no significant difference between two injury patterns. Injured rats spent more time in the center zone compared to shams.

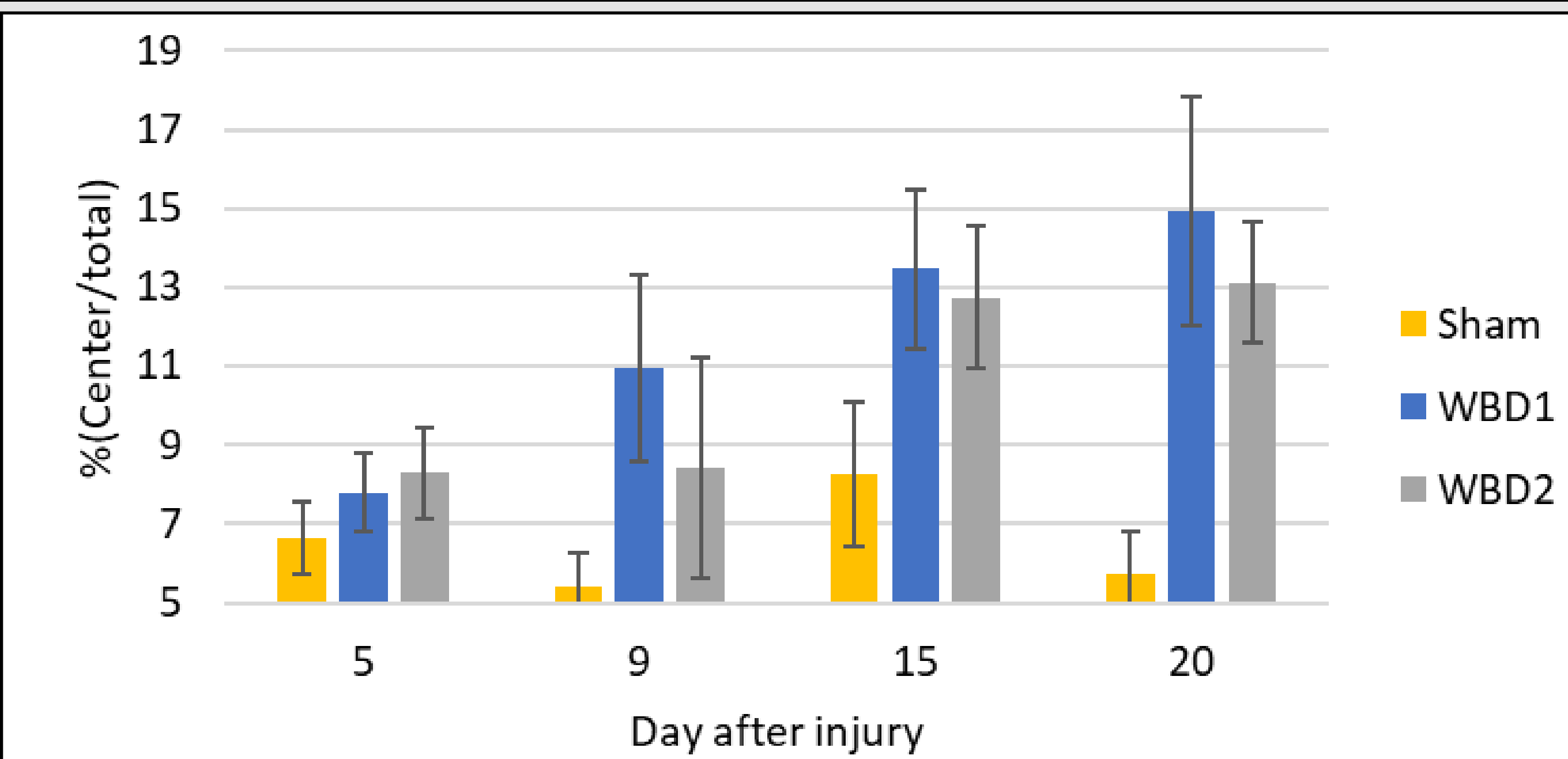


Figure 3. OF results show the percentage of time spent in the center zone

NOR results detected memory deficit on days 5 (p<0.01) and 9 (p<0.02) after both WBD1 and WBD2 (Fig.4). NOR showed significant difference between WBD2 and WBD1 on day 5 (p=0.03).

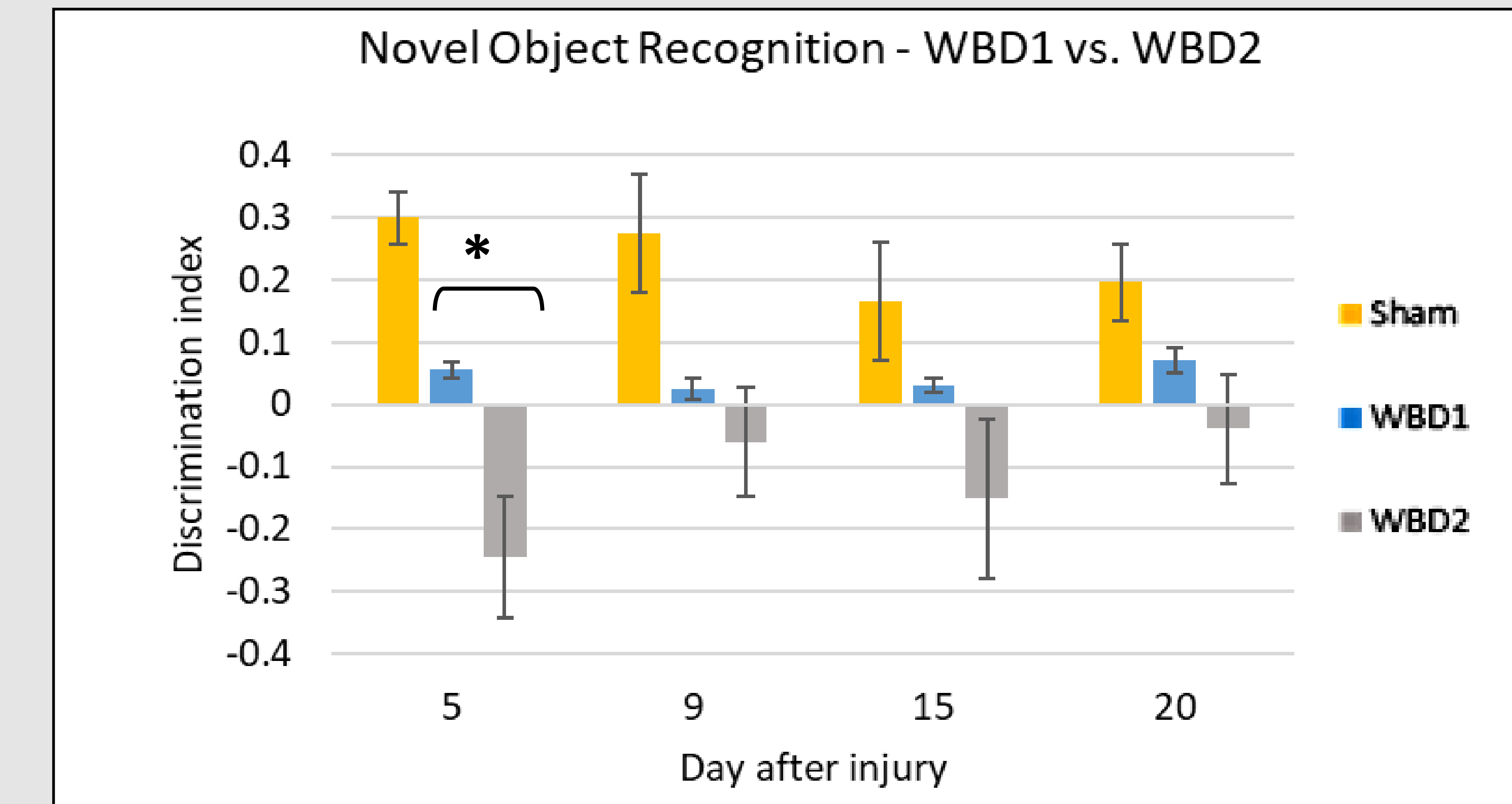


Figure 4. NOR results show the discrimination index

RT-PCR showed no significant change in TLR4 following both repetition patterns compared to sham groups.

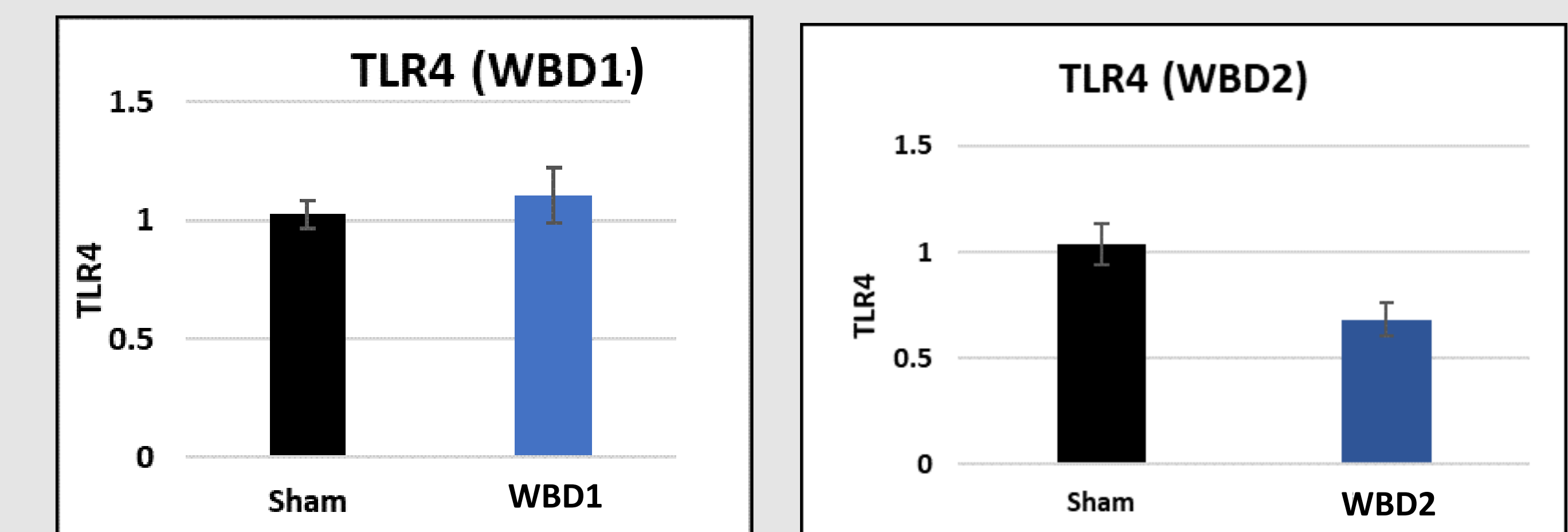


Figure 5. RT-PCR results for assessing TLR4

CONCLUSIONS AND FUTURE WORKS

- The cumulative effect of WBD2 on motor function and memory is more severe than WBD1.
- rmTBI can cause sub-acute impulsivity over time
- While no histological difference was found on day 20, behavioral assessments showed measurable differences at this time point
- In OF, injured animals compared to sham spent more time in the center zone which can be described as impulsivity or risk-taking behavior. This can also be an indication of increased anxiety in rodents [3].
- Using a greater number of samples as well as employing more than one type of behavioral test for each function can help to reach to more robust conclusions.

ACKNOWLEDGEMENT

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