Post-Traumatic Stress Disorder in the Controlled Cortical Impact Model of Brain Injury

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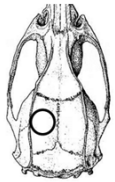
Introduction

Traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are often associated with each other particularly in a military battlefield context. Currently, there is no standardized preclinical model of PTSD with traumatic brain injury. We studied the development of PTSD behavioral phenotypes by combining two widely used preclinical models of PTSD and TBI - immobilization stress (IMO) and controlled cortical impact (CCI) in rats. Animals that received both immobilization stress and TBI show distinct behavioral phenotypes in anxiety, fear, and cognitive tests which differed from immobilization stress or TBI alone. The following results suggests that the predominant phenotype of combined IMO stress and CCI TBI is heightened activity and risk-taking behavior during the subacute period after trauma.

Methods

Animals

- Male Sprague-Dawley rats (275-325g)



Immobilization Stress

- 2 hours immobilization in decapicones
- 1 week post-stress incubation

Traumatic Brain Injury

- At 1 week after IMO stress
- 6 mm craniotomy over left parasagittal cortex mid-way between bregma and lambda
- 3 mm depth impact at 2.5 m/s with rounded 5 mm impactor

Elevated Plus Maze

- The EPM tests assess anxiety. The maze (Hamilton Kinder) consists of two closed arms and two open arms forming a cross.
- Animals were placed in the center of the maze and the computerized system monitors their movement during 5min test.
- EPM at 1 week after IMO stress
- EPM at 1 week after TBI

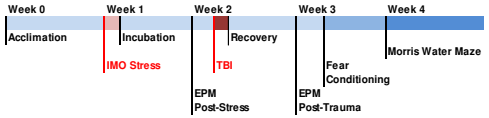
Fear Conditioning

- Cued Fear Conditioning test after 1 week post-trauma
- 5 US/CS pairings of 1mA for 0.5 sec with 30 sec 70dB tone with 90 sec interval

Morris Water Maze

- The MWM tests spatial learning and memory. Animals use visual cues to find an escape platform that is hidden beneath the surface of a pool.
- ANY-maze video tracking software monitors the animals during the test.
- Animals tested after two weeks following TBI.

Results



Elevated Plus Maze Post-Stress

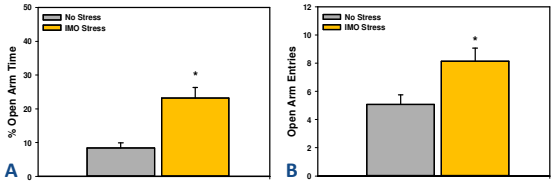


Figure 1. Immobilization stress behavioral phenotype in elevated plus maze. Animals subjected to 2 hours of immobilization stress in decapicones spend significantly more time in the open arms (A) and exhibit significantly more entries into the open arms (B) of the elevated plus maze compared to control animals with no immobilization stress when tested 1 week after stress. These data indicate that IMO animals exhibit greater risk taking behavior in the EPM. Data are presented as mean ± SEM. *p<0.05.

Elevated Plus Maze Post-TBI

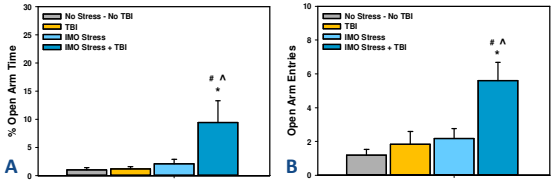


Figure 2. Elevated plus maze following traumatic brain injury with and without immobilization stress. At 1 week following TBI, animals were tested again in the elevated plus maze. Animals that were subjected to both immobilization stress and traumatic brain injury spent significantly more time in the open arms (A) compared to *No Stress-No TBI* controls, as well as compared to the *TBI* only group and the *IMO Stress* only group. Likewise, analysis of open arm entries also showed *IMO Stress + TBI* group exhibited greater entries than the other three test groups (B). These data indicate that the combination of IMO Stress and TBI triggers a sustained increase in risk taking behavior in the elevated plus maze. In contrast, animals subjected to *TBI* only or *IMO Stress* only showed attenuation of the risk taking phenotype during their second exposure to the EPM. Data are presented as mean ± SEM. *p<0.05 vs. No Stress-No TBI. #p<0.05 vs. TBI. ^p<0.05 vs. IMO Stress.

Fear Conditioning

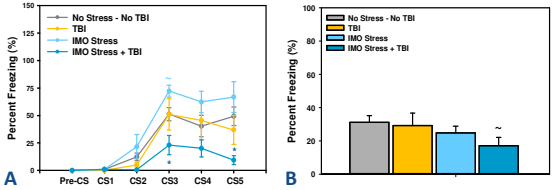


Figure 3. Combined immobilization stress and traumatic brain injury in fear conditioning. Animals subjected to 2 hours of immobilization stress exhibited evidence of elevated freezing during fear conditioning in comparison to *No Stress-No TBI* controls (A). In contrast, animals that experienced both immobilization stress and TBI exhibited significantly reduced freezing during fear conditioning (A). Presentation of the CS at 48 hours after shock training showed a trend towards reduced freezing in animals that experienced both immobilization stress and TBI (B). Data are presented as mean ± SEM. *p<0.05 and ~p<0.1 vs. No Stress-No TBI controls.

Morris Water Maze

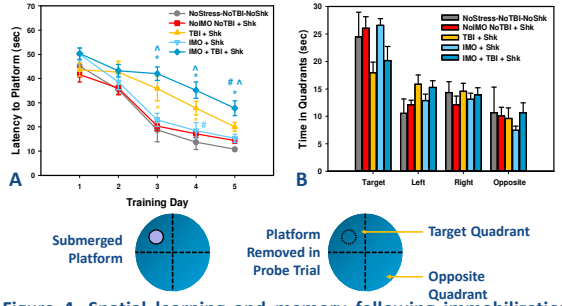


Figure 4. Spatial learning and memory following immobilization stress and traumatic brain injury. Animals subjected to shock but without prior immobilization stress nor TBI exhibited similar escape latencies to *NoStress-NoTBI-NoShk* controls. Immobilization stress alone did not appear to affect the escape latency during Morris Water Maze training. Animals subjected to TBI alone showed longer escape latency times at training day 3 and 4. Animals subjected to both immobilization stress and TBI showed significant deficits in escape latency compared to all other non-TBI groups. Data are presented as mean ± SEM. *p<0.05 vs. NoStress-NoTBI-NoShk controls. #p<0.05 vs. TBI+Shk. ^p<0.05 vs. IMO+Shk.

Summary

Animals subjected to combined immobilization stress and controlled cortical impact traumatic brain injury show enhanced risk taking behavior, reduced fear, and increased learning deficits that make this combination of trauma useful for studying the evolution of preclinical stress-TBI phenotypes over time.