Enhanced Context, Tone & Trace Conditioning After Traumatic Brain Injury: Support for a Rat Model of PTSD

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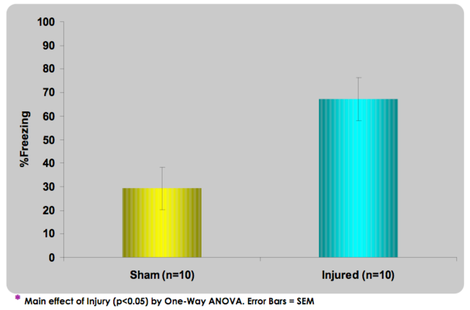
INTRODUCTION

Traumatic brain injury (TBI) is commonly known as the "silent epidemic" (Centers for Disease Control & Prevention, CDC), with mild injuries like concussion accounting for 75% of TBIs annually. The current wars only further necessitate TBI research as mild, diffuse TBI from concussion and blast injury has become the signature injury of modern combat. In humans concussion is defined as a brief change in mental status with or without loss of consciousness and is not associated with significant focal brain lesions. TBI survivors can demonstrate anxiety, affective, learning and memory problems[2], many of which go undiagnosed (CDC). Moreover, there is mounting interest in the investigation of TBI as a risk factor for the development of Post-Traumatic Stress Disorder (PTSD)[3,4,7]. Fear conditioning (FC) tasks have recently been used to model PTSD symptoms in rats[6]. Therefore, **we hypothesized that there would be enhanced fear conditioning following a concussive brain injury in rats.** We induced concussive injury in rats utilizing the well characterized lateral fluid percussion injury model (FP) and then assessed delay & trace fear conditioning acutely after injury. In Delay FC context and tone fear depend on the amygdala, however context conditioning also engages the hippocampus. Trace FC is a more difficult task because of a temporal discontinuity between the tone and shock. This discontinuity reduces associative conditioning and thus reveals a hippocampus dependent component to responding[8]. Systematic investigation of fear learning post-TBI will help us better understand the mechanisms of PTSD associated with mild TBI. This, in turn, holds promise for future development of effective interventions for post-TBI PTSD.

Delay Fear

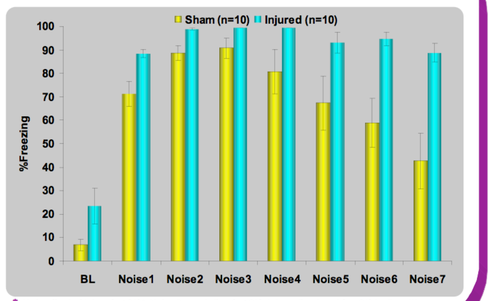
- There were no group differences in post-injury day 2 acquisition data. Nor were there differences in shock related activity bursts. (Data not shown)
- Injured rats showed *enhanced* context conditioning (Context Test)
- Injured rats showed *enhanced* tone conditioning that increased as shams extinguished (Tone Test).

Day3: Context Test



Main effect of Injury (p<0.05) by One-Way ANOVA. Error Bars = SEM

Day4: Tone Test



Main effect of Injury (p<.01)& Noise Presentation (p<.01), Interaction trend (p=.06) by Two-Way Repeated Measures ANOVA. Error Bars = SEM

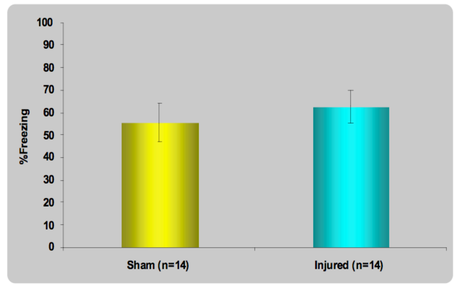
CONCLUSIONS

1. Acutely after concussive brain injury injured rats showed a general *enhancement* in both delay and trace fear conditioning despite normal acquisition data.
2. One symptom of PTSD is an exaggerated response to mild stressors or reminders of a traumatic event. Therefore these results support a Pavlovian rodent model of PTSD[4].
3. The fact that context, trace and delay conditioning fear were all enhanced suggests the effect was mediated by the amygdala, which has a role in all three sources of fear tested here.

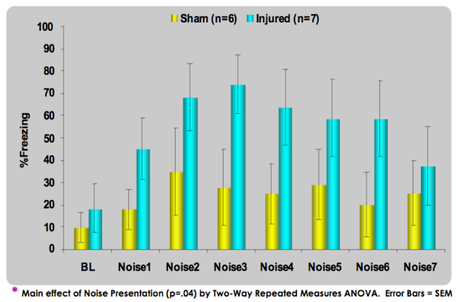
Trace Fear

- Again, injured rats showed normal trace acquisition. (Data not shown)
- Injured rats showed normal contextual fear. (Context Test)
- Injured animals showed *enhanced* conditioning during tone presentations & trace intervals. (Tone Test, Day4a&b)

Day3: Context Test

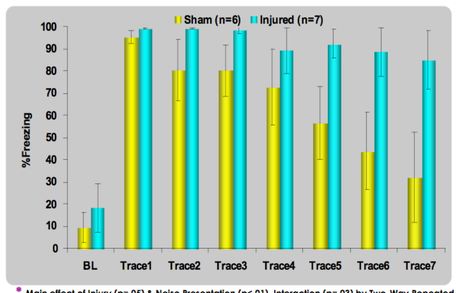


Day4a: Responding During the Tone



Main effect of Noise Presentation (p=.04) by Two-Way Repeated Measures ANOVA. Error Bars = SEM

Day4b: Responding During the Trace Interval



Main effect of Injury (p=.05) & Noise Presentation (p<.01), Interaction (p=.03) by Two-Way Repeated Measures ANOVA. Error Bars = SEM

References

1. Giza CC & Hovda DA (2001). The Neurometabolic Cascade of Concussion. *Journal of Athletic Training*, 36(3): 228-235.
2. Graham DI, Adams JH, Nicoll HA, Maxwell WL & Gennarelli TA (1995). The nature, distribution and causes of traumatic brain injury. *Brain Pathology*, 5:397-406.
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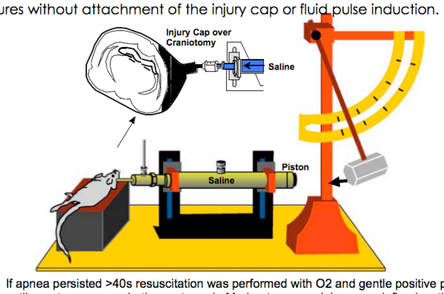
CDC Website on TBI: http://www.cdc.gov/ncipc/tbi/TBI.htm
For a Review of the Injury Model see:
Thompson HJ, Lifshitz J, Marklund N, Grady SM, Graham DI, Hovda DA & McIntosh TK (2005). Lateral fluid percussion brain injury: A 15-year review and evaluation. *Journal of Neurotrauma*, 22(1): 42-75.

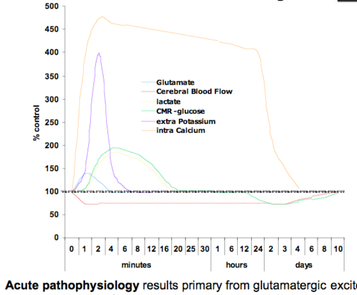
Lateral Fluid Percussion Brain Injury

Subjects. Male Sprague-Dawley rats received either Sham surgery or a moderate-severe Lateral Fluid Percussion Injury (FP). Rats were maintained on a 12hr night/day cycle and with food & water ad libitum. All procedures were approved by the UCLA Chancellors Animal Research Committee.

Surgery. FP results in a diffuse injury and was induced using our standard protocol[5]. Rats were anesthetized with a 1-2% isoflurane-O_2 mixture. Following a midline incision, a 3mm diameter craniotomy was made over the left hemisphere, centered at 3mm posterior to bregma and 6mm lateral to midline. An injury cap was cemented onto the skull, over the exposed dura. Once consciousness to toe pinch the mallet was released striking the piston of the percussion device. The subsequent pressure wave was transduced along the saline filled column of the device, entering the skull and deflecting the brain along the intact dura. Sham animals underwent all surgical procedures without attachment of the injury cap or fluid pulse induction.



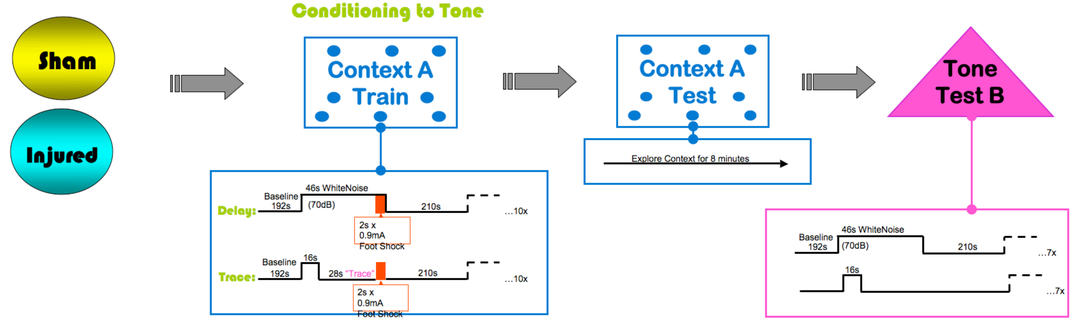
If apnea persisted >40s resuscitation was performed with O2 and gentle positive pressure, until spontaneous respirations returned. Moderate-severe injury was defined as the absence of the toe pinch withdrawal reflex for >3 min. There is little to no ipsilateral cortical lesion.



Acute pathophysiology results primary from glutamatergic excitotoxicity, neurometabolic dysfunction and edema lasting 10 days post injury and has been measured in ipsi cortx & hippocampus[1].

Fear Conditioning Behavior

Behavior. Beginning 2 days post-injury rats received one of two types of fear conditioning: (a) Delay or (b) Trace, according to Quinn et al. (2002). Both procedures consisted of 10 Tone-Shock pairing, with testing for fear to the training context and the tone cue occurring on subsequent days. Learned fear of the stimuli are measured as the percentage of test time spent "freezing" to the context or tone.



Acknowledgements

This work was supported by NS27544, NS057420, MH62122, NIMH RO1, the Winokur Family Foundation & the UCLA Brain Injury Research Center.