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Sex Associated Differences in Neurocognitive Outcomes After TBI

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BACKGROUND

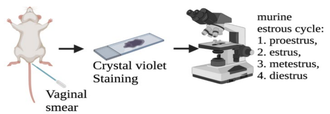
The CDC reports that every year approx. 3 million people sustain a TBI. Significant long-term complications can occur and result in motor, cognitive, and behavioral deficits. Males are disproportionately represented in most studies this is due to the higher incidence rate observed in the male population.
This has resulted in a critical unmet research need to determine whether there is a different pathophysiology of injury between men and women. The CDC has reported that 40% of TBI is sustained by women. Women TBI patients differ in severity of injury and mortality and are also 5-2 times more likely to have long-term neuropsychiatric sequelae such as anxiety and PTSD than men. Sex hormones such as estrogen and progesterone play a critical role in protecting glial cells and neurons which subsequently protects the brain from edema, necrosis, apoptosis and inflammation. Sex differences have been largely unexplored in both preclinical and clinical TBI studies.

RESEARCH OBJECTIVES

Recent work in our laboratory showed that female TBI mice disinhibited generalized anxiety compared to male TBI mice in zero maze. We also shown the microglia of male TBI mice have an increase in inflammatory gene expression than female TBI mice. However, the microglia of female TBI mice had an increase in homeostatic gene expression than male TBI mice. This data suggest a pathophysiological difference in sex and transcriptional difference following injury and an sex different response. To this end we hypothesized **that female mice would have preserved motor skills and neurocognition after TBI as compared to male mice.**

Experimental Design

Figure 2. Vaginal Smear for Estrous Cycle Staging Identification



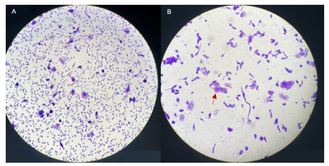


Figure 1 -TOP showing the schematic for vaginal smear and murine estrous assessment. **Bottom** (**A**) showing metestrus featured by high number of leukocytes and (**B**) proestrus featured by the presence of large nucleated cells (indicated by a red arrow). Magnification: 20X.

Figure 3. Controlled Cortical Impact

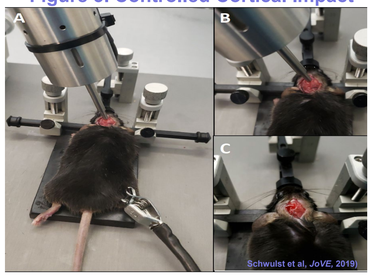


Figure 2 – (A) The grounding cable is clipped to the mouse's hind region and the impacting tip is lowered onto the dura mater. This is the zero point. (B) The impacting tip is retracted, a 2 mm depth of injury is dialed into the stereotaxic frame, and the impact is applied. (C) After the CCI is applied, the impacting tip is rotated out of the field and the mouse is recovered from the stereotaxic frame

Open Field Results

Figure 3. Female Mice Spent Less Time In The Center

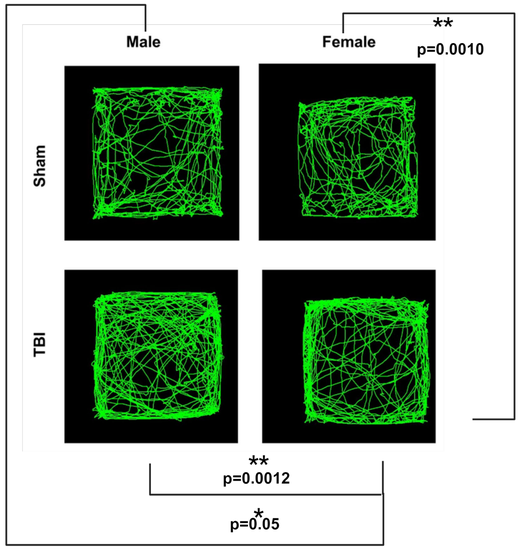


Figure 3. Female TBI mice had less time spent in the center of the OF as compared to their male TBI (34.5 ± 9.5 % time in the center vs. 40.4 ± 11.1 % time in the center, p<0.001) ,female sham TBI (34.5 ± 9.5 % time in the center vs. 46.0 ± 6.05 % time in the center, p<0.001 , and male sham (34.5 ± 9.5 % time in the center vs. 41.5 ± 5.7 % time in the center, p=0.05)

Figure 4. Male Mice Demonstrated High Levels of Exploratory Velocity

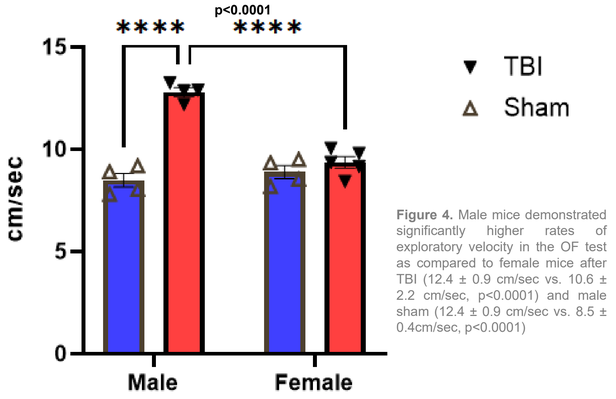


Figure 4. Male mice demonstrated significantly higher rates of exploratory velocity in the OF test as compared to female mice after TBI (12.4 ± 0.9 cm/sec vs. 10.6 ± 2.2 cm/sec, p<0.0001) and male sham (12.4 ± 0.9 cm/sec vs. 8.5 ± 0.4cm/sec, p<0.0001)

Fear & Conditioning Results

Figure 5. Female Mice Have Preservation Of Contextual Fear

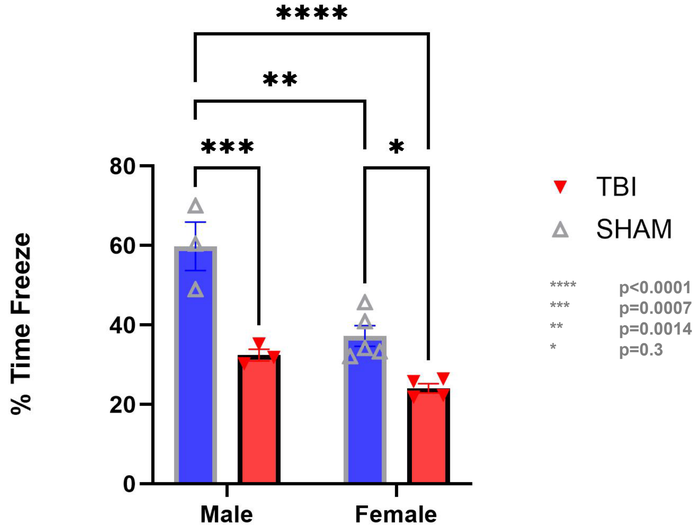


Figure 5. Female TBI mice had attenuation of associative learning and memory deficits after TBI as compared to sham (31.4 ± 2.9 %time vs. 37.0 ± 4.5 %freezing, p=0.03) and male sham (31.4 ± 2.9 % time freezing vs. 61.0 ± 6.3% time freezing, p<0.0001). Male TBI mice had a 45% decline decrease in associative learning and memory as compared to sham (34.8 ± 7 % time freezing vs. 61.0 ± 6.3 % time freezing, p<0.0007).

CONCLUSION

In conclusion:

- There are sex-linked differences in anxiety-like behavior, motor coordination, and contextual fear
- This data suggests many mechanisms are involved in this difference
- This aligns with what is seen clinically in human patients after injury

Sex should be a priori consideration in future studies

ACKNOWLEDGMENTS

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