**ABSTRACT**

Approximately 3 million Americans sustain a traumatic brain injury (TBI) each year with a high rate of subsequent neuropsychiatric morbidity. TBI outcomes differ markedly between males and females in both clinical and preclinical studies. Nonetheless, there are limited studies examining sex as an independent variable in neuropsychiatric outcomes after TBI. We hypothesized that female mice would have attenuated post-traumatic anxiety after TBI as compared to male mice. Age-adjusted C57Bl/6j male mice (N=21) and female mice (N=20) were grouped into TBI and sham-injury groups. An open-field controlled cortical impact was used to induce a severe TBI vs. sham-injury. At 45 days post TBI, neuropsychiatric outcomes were assessed with the zero maze for anxiety-like behavior and the open field test for generalized activity levels, anxiety, and willingness to explore. Data was analyzed using one-way ANOVA and Tukey’s multiple comparison test. Contrary to our hypothesis, female mice demonstrated markedly increased levels of post-traumatic anxiety after TBI as compared to male mice. Female TBI mice spent significantly less time in the open space of the zero maze as compared to male TBI mice indicating increased levels of anxiety (22.86 ± 4.98% vs. 31.62 ± 9.7%, p=0.0171). Similarly, female TBI mice spent less time in the center of the open field demonstrating increased anxiety and less exploratory behavior than male TBI mice (12 ± 4% vs. 24.3 ± 5.4%, p=0.001). This corresponded to a more distance traveled over the course of open field testing in female TBI mice as compared to male TBI mice indicating a markedly increased in generalization activity (7515.3 ± 1335.3cm vs. 6742.2 ± 1229.2cm, p=0.0047). Female mice had increased levels of post-traumatic anxiety-like behavior, less exploratory behavior, and increased generalized activity as compared to male mice after TBI. These data suggest marked sex-linked differences in neuropsychiatric outcome after TBI. Future clinical trials should make sex as an a priori consideration in future trial design.

**INTRODUCTION**

Trauma is the leading cause of death and disability in patients between the ages of 1-44 with TBIs contributing to nearly a third of them. Presently, approximately 25% of the TBI population are females afflicted with disabilities and behavior deficits as a result of a TBI. Despite high prevalence rate, there is a severe lack of understanding on pathophysiology and mechanisms that may be sex-specific. Some recent clinical studies have also suggested possible worse long-term outcomes for females.

**RESEARCH OBJECTIVES**

Our research objective was to assess sex as an independent variable in neurocognitive tests of learning, memory, and anxiety after TBI. We hypothesized that female mice would have attenuated post-traumatic anxiety after TBI as compared to male mice.

**METHODS**

**RESULTS**

Contrary to the hypothesis, female mice had increased levels of post-traumatic anxiety-like behavior, less exploratory behavior, and increased generalized activity as compared to male mice after TBI:

- These data demonstrate marked sex-linked differences in neuropsychiatric outcome after TBI suggesting that clinical studies and possible treatment options should consider grouping by sex
- These data also show female sex-linked differences should be further researched as an independent variable in TBI outcomes

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**Sex Matters in Traumatic Brain Injury**

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