Age and sex-related changes leave female flies vulnerable to delayed harm from head injury

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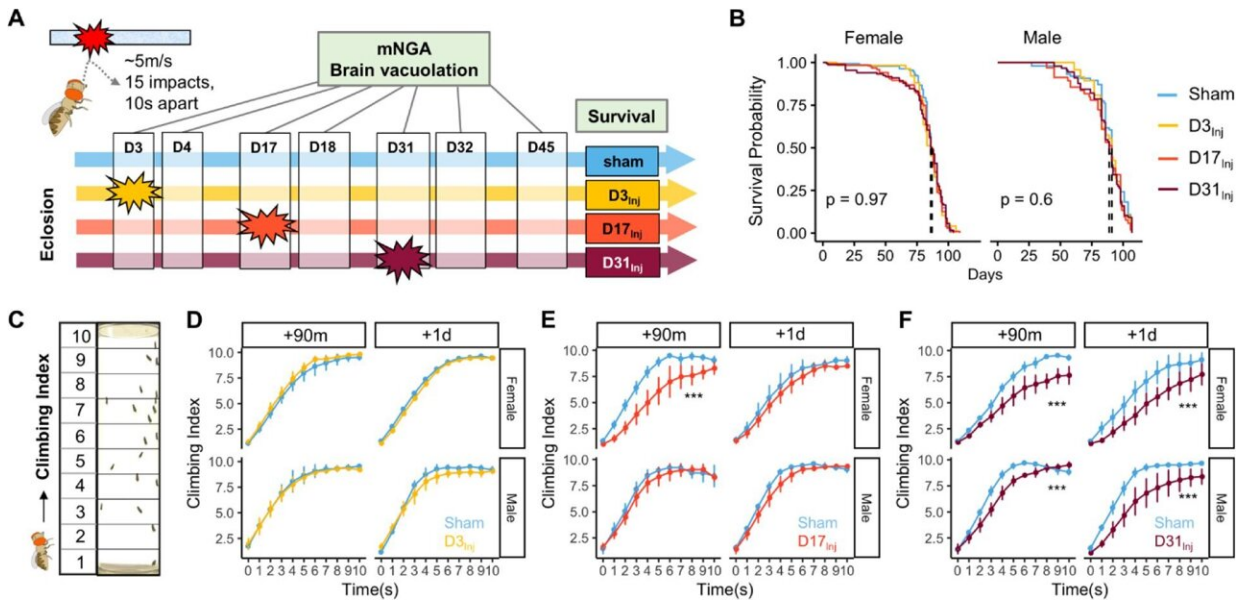

Exposure of adult fruit flies to a very mild form of repetitive head impacts at different ages elicits minimal acute effects. Credit: (2024). DOI: 10.7554/eLife.97908.1

A research team at Emory University in Atlanta, Georgia, US has discovered that even very mild, non-lethal head injuries early in life can lead to neurodegenerative conditions later in life upon aging.

Using fruit flies as a model, the researchers found that chronic immune suppression after mating might make female fruit flies susceptible to delayed brain deterioration following early-life head injuries.

The study, published today as a Reviewed Preprint in *eLife*, is described by the editors as fundamental work that advances our understanding of how sex-dependent responses to traumatic brain injury occurs. It provides what they call compelling results showing the immune and reproductive pathways that may contribute to these differences.

Environmental insults, including mild head trauma, significantly increase the risk of neurodegeneration later in life. However, identifying a causative connection between early-life exposure to mild head trauma and late-life emergence of neurodegeneration is challenging, and it remains unclear as to how sex and age compound the outcomes.

"With their short lives, fruit flies allow scientists to track brain-injury-related changes across their entire lifespan," says lead author Changtian Ye, a graduate student in the Emory Neuroscience Program, and a member of senior author James Zheng's lab, at the Emory University School of Medicine. "We recently developed a fruit fly model of mild traumatic brain injury that allows us to deliver mild headfirst impacts and then track what happens in male and female flies from the moment of injury to the occurrence of brain impairments later in life."

Using their model, Ye and colleagues monitored the impact of mild traumatic brain injury on the flies' behavior. While injury initially caused minimal acute deficits in the flies, it led to more profound brain-associated behavioral deficits and degeneration later in life, and these conditions worsened with age. Additionally, they were disproportionately elevated in females, affecting their climbing speed and ability, and leading them to have more damaged brain tissue than their male counterparts.

The researchers also found that female flies that had mated had worse outcomes than unmated (virgin) flies. They identified a protein called sex peptide—which is transferred to the female reproductive tract through semen during mating—as a key player in making these flies more susceptible to the harmful effects of brain injury.

"Our analysis of the flies' RNA data suggested that the chronic suppression of innate immune defense networks in mated females exposed to sex peptide makes them disproportionately vulnerable to neurodegeneration after mild head trauma," Ye explains.

Together, the findings support the idea that a head injury can pose a major threat to brain health, even if it is mild, and that females can be disproportionately affected. The authors say that additional studies are now needed to determine if similar processes occur in other species.

"Our work establishes a causal relationship between early head trauma and late-life neurodegeneration, emphasizing sex differences in injury response and the impact of age during and after injury," concludes senior author James Zheng, Principle Investigator at the Zheng Lab, Emory University School of Medicine.

"It will be interesting to understand if this relationship occurs in other organisms, and to dissect the genetic components and molecular players involved in the sex-different development of neurodegenerative conditions following mild head trauma."

More information: Changtian Ye et al, Sexual Dimorphism in Age-Dependent Neurodegeneration After Mild Head Trauma in Drosophila: Unveiling the Adverse Impact of Female Reproductive Signaling, *eLife* (2024). DOI: 10.7554/eLife.97908.1

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