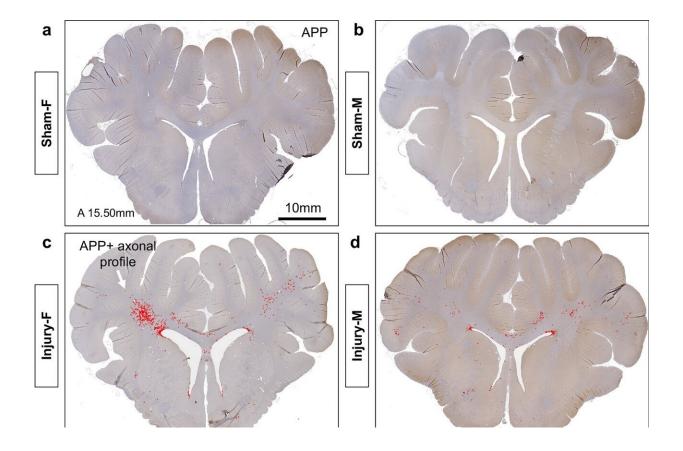


## Axons in female mammal brains may be more prone to concussions

May 13 2024



Extent of APP axonal pathology following experimental concussion. Representative whole brain section map of annotated APP-immunoreactive profiles (at A 15.50 mm level) in sham female (a) and male (b) swine, as well as injured female (c) and male swine (d). Red-dot labels annotate individual APPimmunoreactive axonal profiles. Scale bar = 10 mm. e Significantly greater



numbers of APP-immunoreactive axonal profiles per whole brain section were observed in injured females than injured males at 24 h post-injury. Each dot represents individual animal's mean. Credit: *Acta Neuropathologica* (2024). DOI: 10.1007/s00401-024-02735-9

Important brain structures that are key for signaling in the brain are narrower and less dense in females, and more likely to be damaged by brain injuries, such as concussion. Long-term cognitive deficits occur when the signals between brain structures weaken due to the injury. The structural differences in male and female brains might explain why females are more prone to concussions and experience longer recovery from the injury than their male counterparts, according to a preclinical study led by the Perelman School of Medicine at the University of Pennsylvania, <u>published</u> in *Acta Neuropathologica*.

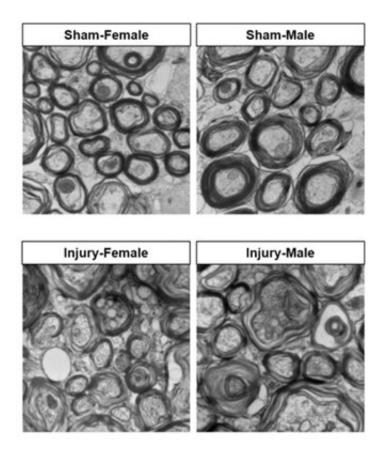
Each year, approximately 50 million individuals worldwide suffer a <u>concussion</u>, also referred to as <u>mild traumatic brain injury</u> (TBI). However, there is nothing "mild" about this condition for the more than 15% of individuals who suffer persistent cognitive dysfunction, which includes difficulty concentrating, learning and remembering new information, and making decisions.

Although males make up the majority of emergency department visits for concussion, this has been primarily attributed to their greater exposure to activities with a risk of head impacts compared to females. In contrast, it has recently been observed that <u>female athletes</u> have a higher rate of concussion and appear to have worse outcomes than their <u>male counterparts</u> participating in the same sport.



"Clinicians have observed for a long time that females suffer from concussion at higher rates than males in the same sports, and that they take longer to recover cognitive function, but couldn't explain the underlying mechanisms of this phenomenon," said senior author Douglas Smith, MD, a professor of Neurosurgery and director of Penn's Center for Brain Injury and Repair.

"The variances in brain structures of females and males not only illuminate why this disparity exists, but also exposes biomarkers, such as axon protein fragments, that can be measured in the blood to determine injury severity, monitor recovery, and eventually help identify and develop treatments that help patients repair these damaged structures and restore cognitive function."



Top: Axons in female and male subject brains Bottom: damaged axons in male



and female brains after injury. Credit: Perelman School of Medicine at the University of Pennsylvania

If neurons are telephones that send messages between brain cells, axons are the lines that connect them, allowing communication across the brain. These axons form bundles that make up <u>white matter</u> in the brain and play a large role in learning and communication between different brain regions. Axons are delicate structures and are vulnerable to damage from concussion.

Communication between axons in the brain is powered by sodium channels that serve as the brain's electric grid. When axons are damaged, these sodium channels are also impaired, which causes loss of signaling in the brain. The loss of signaling causes the cognitive impairment experienced by individuals after concussion.

In this study, researchers used large animal models of concussion to identify differences in brains of males and females after a concussion. They found that females had a higher population of smaller axons, which researchers demonstrated are more vulnerable to injury. They also reported that in these models, females had greater loss of <u>sodium</u> channels after concussion.

"The differences in brain structure not only tell us a lot about how brain injury affects males and females differently but could offer insights in other brain conditions that impact axons, like Alzheimer's and Parkinson's disease," said Smith. "If female brains are more vulnerable to damage from concussion, they might also be more vulnerable to neurodegeneration, and it's worth further research to understand how sex influences the structure and functions of the brain."



**More information:** Hailong Song et al, Sex differences in the extent of acute axonal pathologies after experimental concussion, *Acta Neuropathologica* (2024). DOI: 10.1007/s00401-024-02735-9

## Provided by Perelman School of Medicine at the University of Pennsylvania

Citation: Axons in female mammal brains may be more prone to concussions (2024, May 13) retrieved 8 June 2024 from https://medicalxpress.com/news/2024-05-axons-female-mammal-brains-prone.html

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