

# Vasopressin Antagonists as Treatment for Repetitive Mild Head Injury

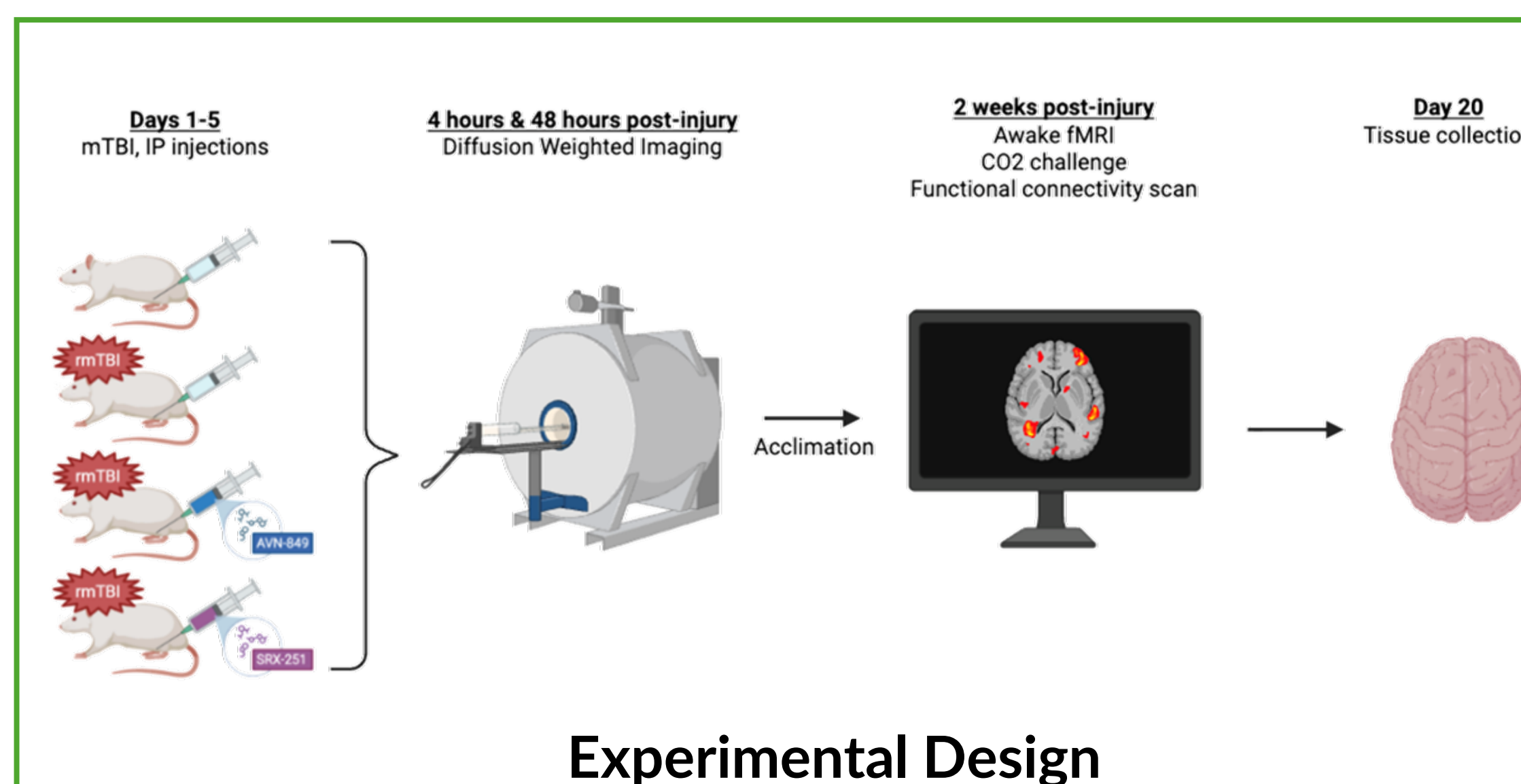
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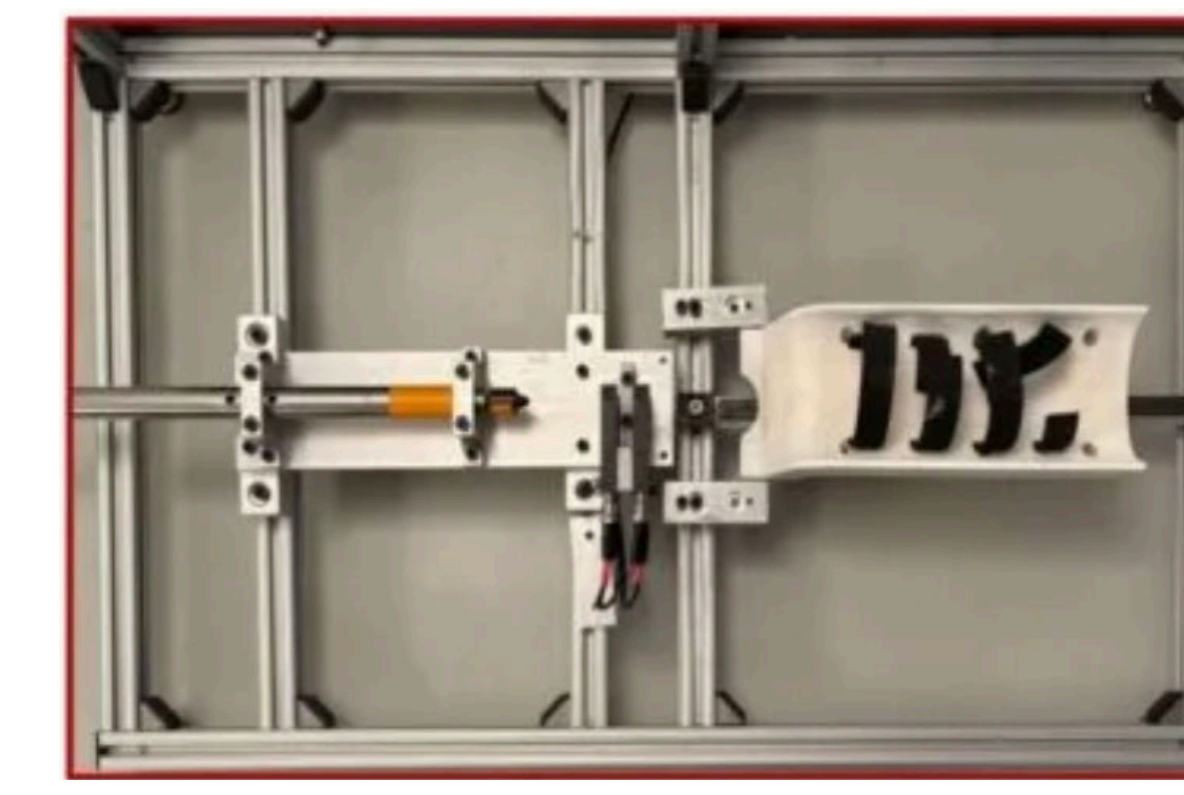
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## Introduction

Repetitive mild traumatic brain injury (rmTBI) can lead to cerebral edema—dangerous swelling of the brain caused by fluid accumulation following overactivation of the hormone arginine vasopressin. This dysregulation can cause neurological deficits, cognitive impairment, and, in severe cases, mortality. This study investigates two vasopressin antagonists, AVN-849 and SRX-251, as potential therapeutic treatments for cerebral edema. Using a rodent rmTBI model, we evaluated the ability of these antagonists to alleviate injury-related changes in neural microstructure, cerebrovascular reactivity, and functional network integrity.



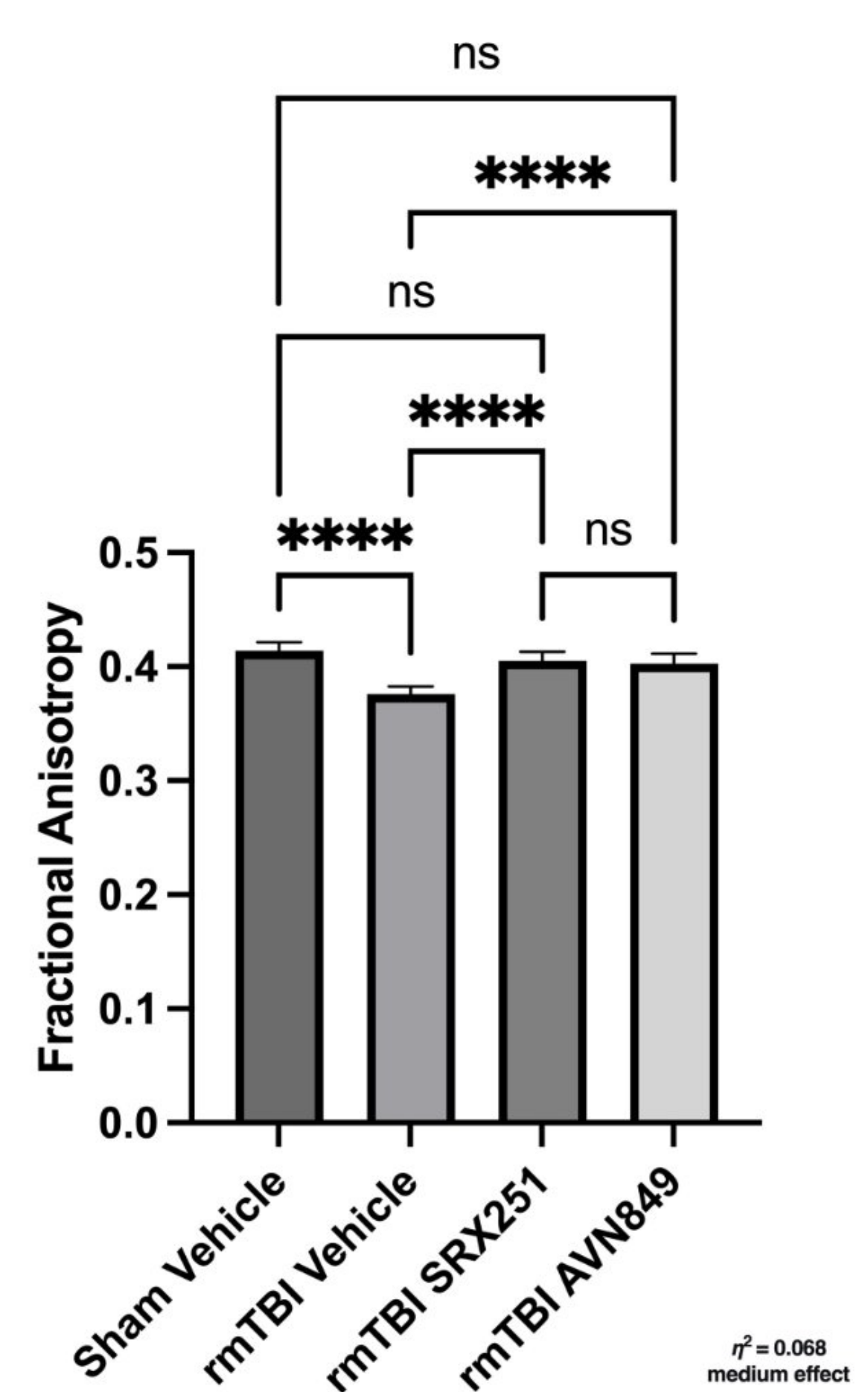
## Methods



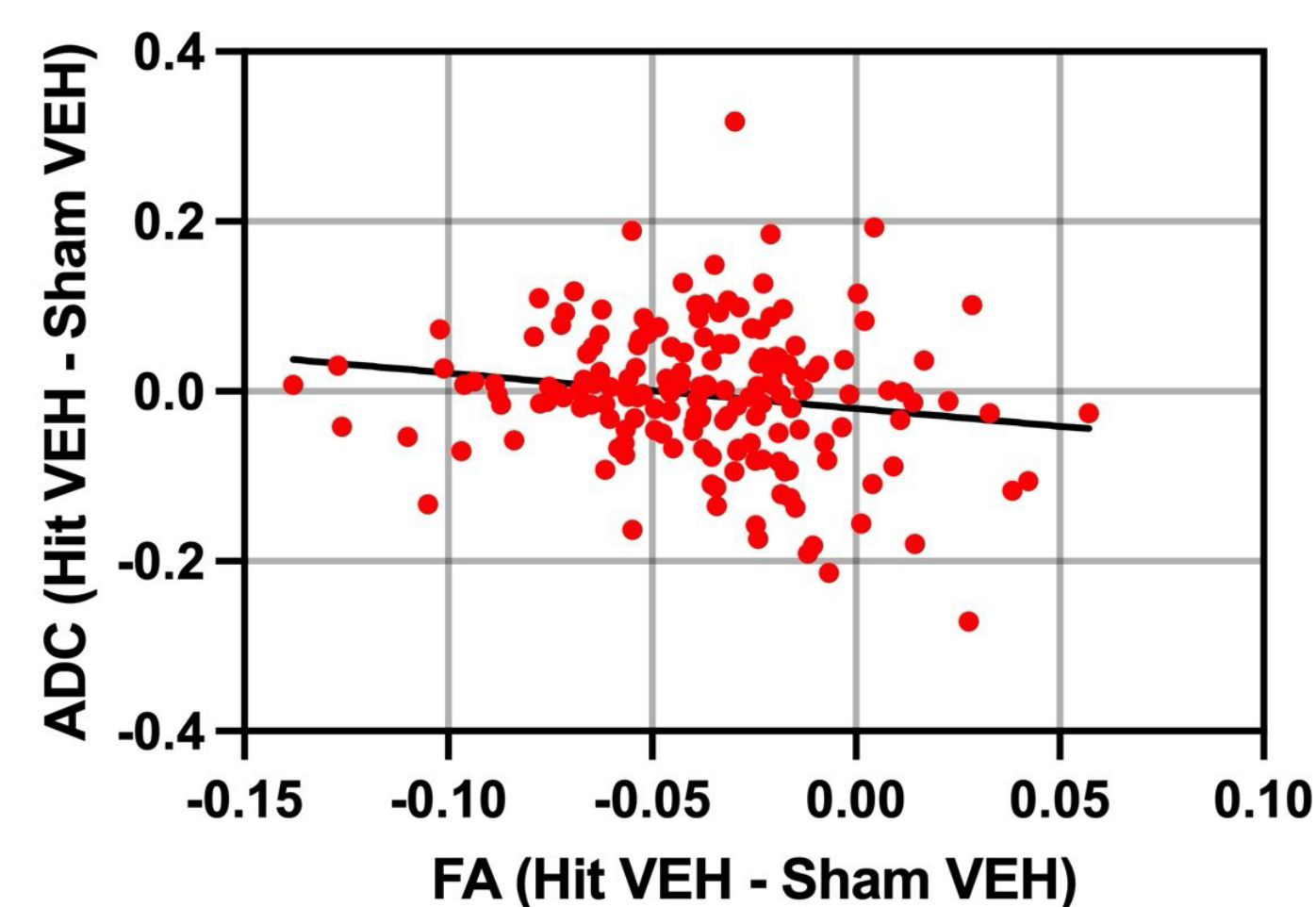
A mild traumatic brain injury (mTBI) model that produces acceleration-driven injury in awake rodents without skull fracture or neuroanatomical contusion. Rats are anesthetized with isoflurane, given buprenorphine analgesic, then placed in a holster with the head angled downward into the impact plane. After anesthesia recovery, a pneumatic piston accelerates the holster backward along a track, producing a change in velocity comparable to an average National Football League concussion. mTBI or sham was administered three times over five days.

## Both treatments reduce immediate microstructural alterations

Scan 1 Female Whole-Brain FA



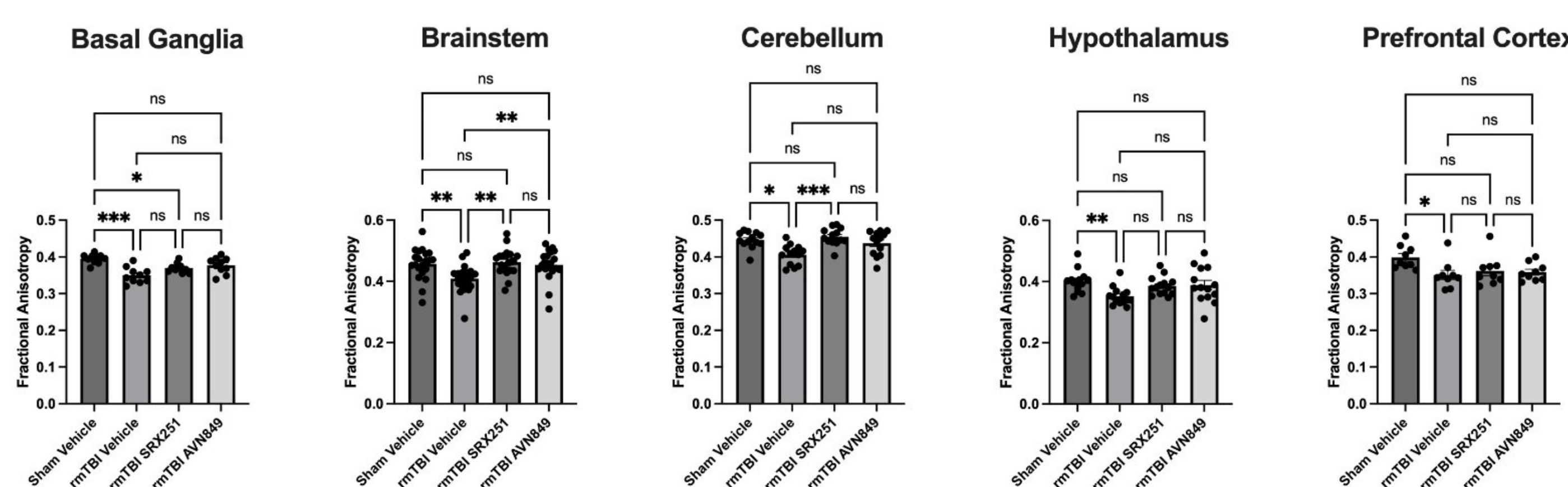
Scan 1 Female Edema Classification



$r = -0.1679$   
 $p = 0.0294 (*)$

Significant but weak negative correlation, suggesting the presence of both vasogenic and cytotoxic edema, slightly favoring vasogenic

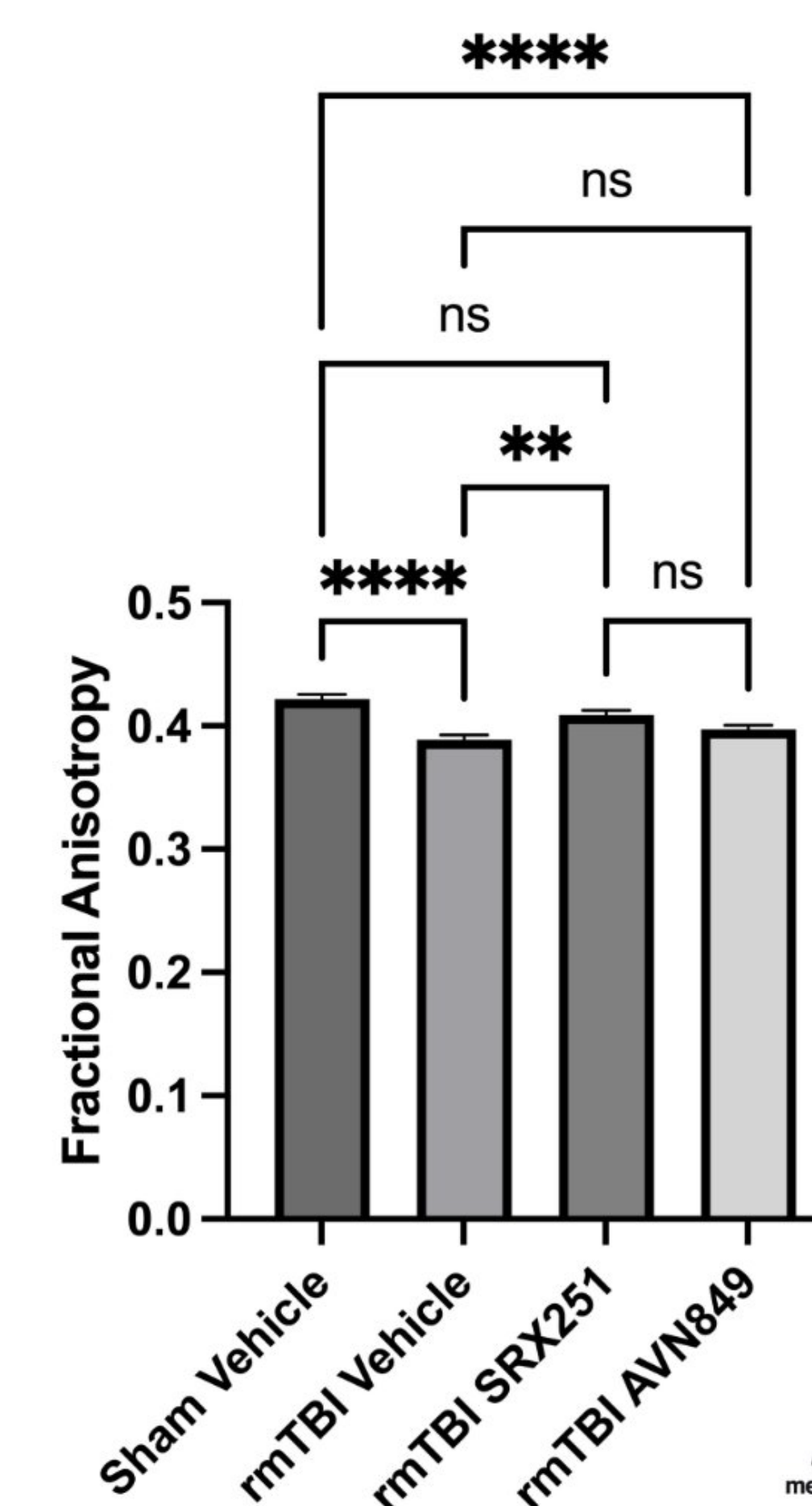
Scan 1 Female Region-Specific FA



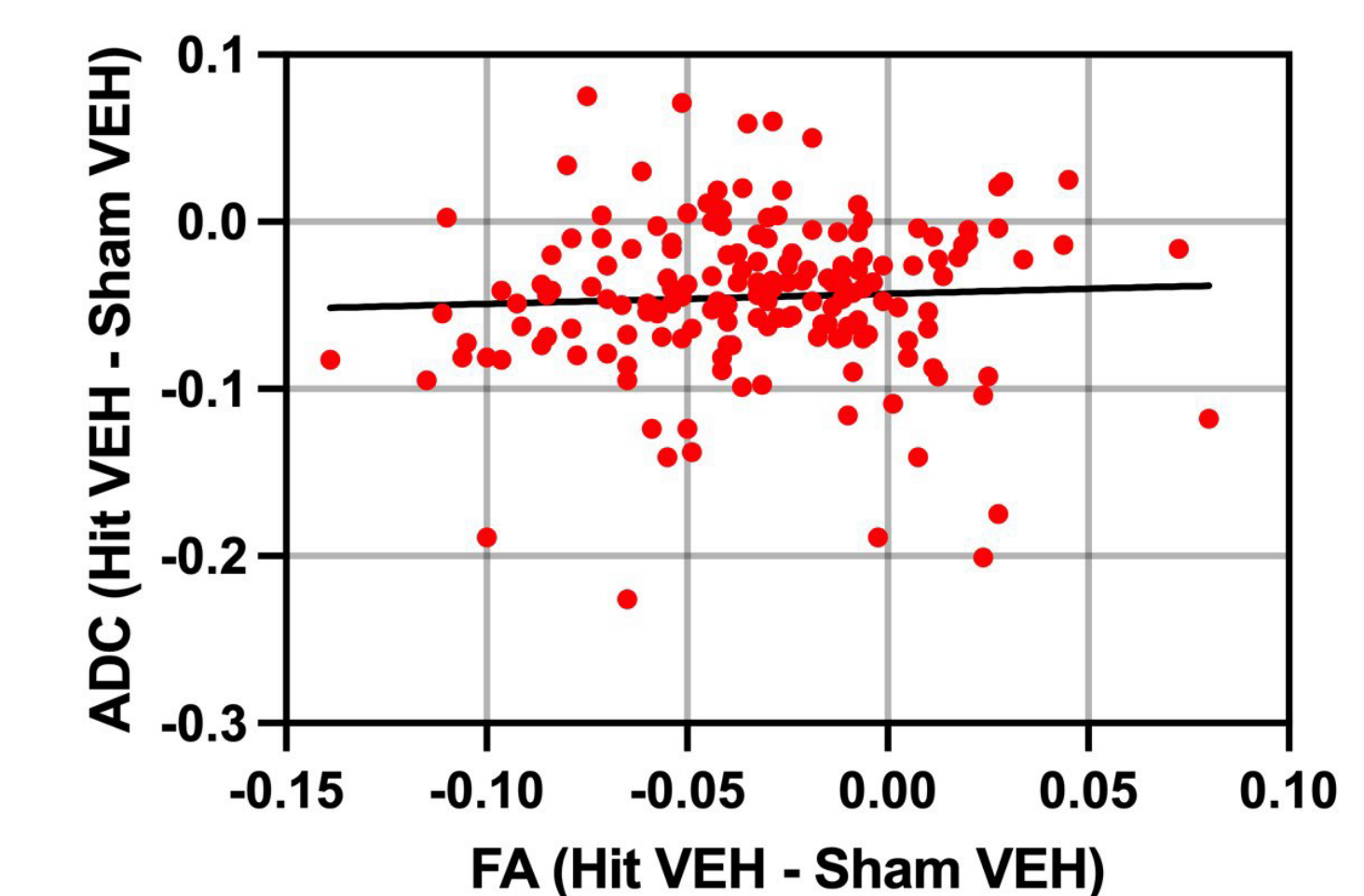
Whole Brain: FA reduction produced by rmTBI is alleviated by both treatments  
 • Basal Ganglia: Partial recovery with SRX-251 only  
 • Brainstem: Full recovery with both treatments  
 • Cerebellum: Recovery with SRX-251 only  
 • Hypothalamus & PFC: No recovery

## SRX-251 shows greater acute microstructural recovery

Scan 2 Female Whole-Brain FA



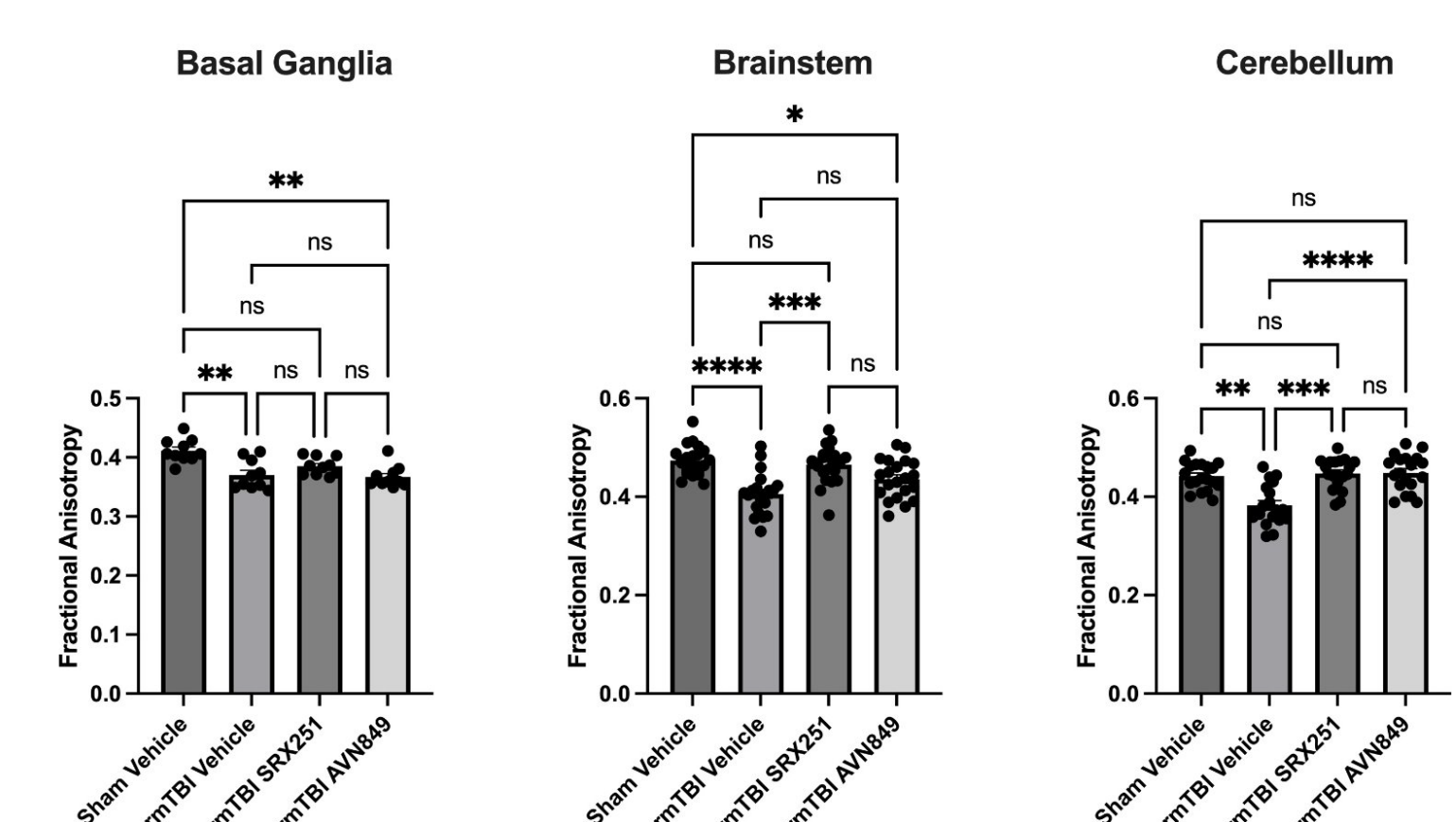
Scan 2 Female Edema Classification



$r = 0.1036$   
 $p = 0.1751 (ns)$

Non-significant correlation, suggesting progression towards mixed edema

Scan 2 Female Region-Specific FA



• Basal Ganglia: Partial recovery with SRX-251 only  
 • Brainstem: Full recovery with SRX-251, partial recovery with AVN-849  
 • Cerebellum: Full recovery with both treatments  
 • Hypothalamus & PFC: Natural recovery

Whole Brain: FA reduction produced by rmTBI is more effectively alleviated by SRX-251

## Lasting cerebrovascular hyporeactivity after AVN-849 treatment

In each of the Basal Ganglia, Brainstem, Hippocampus, Olfactory System, and Thalamus regions, non-parametric Kruskal-Wallis tests show a reduction in cerebrovascular reactivity to a vasogenic stimulus in AVN-849-treated rats, despite no effect of injury in this paradigm. This indicates an important consideration of long-term effects of AVN-849 treatment.

## Summary & Future Steps

Two candidate vasopressin antagonists have been identified as potential treatments for rmTBI. In females, SRX-251 appears to be more effective at reducing short-term cerebral edema and does so without inducing long-term alterations in cerebrovascular reactivity.

Further analyses underway:

- Awake resting-state functional connectivity (rsFC) MRI
- Evaluation of sex differences in an age-matched male cohort
- Protein analysis of fixed and flash-frozen brain tissue

## Acknowledgements

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