

Cytotoxic Edema Following Repetitive Mild Traumatic Brain Injury: Can Minocycline Reverse It?



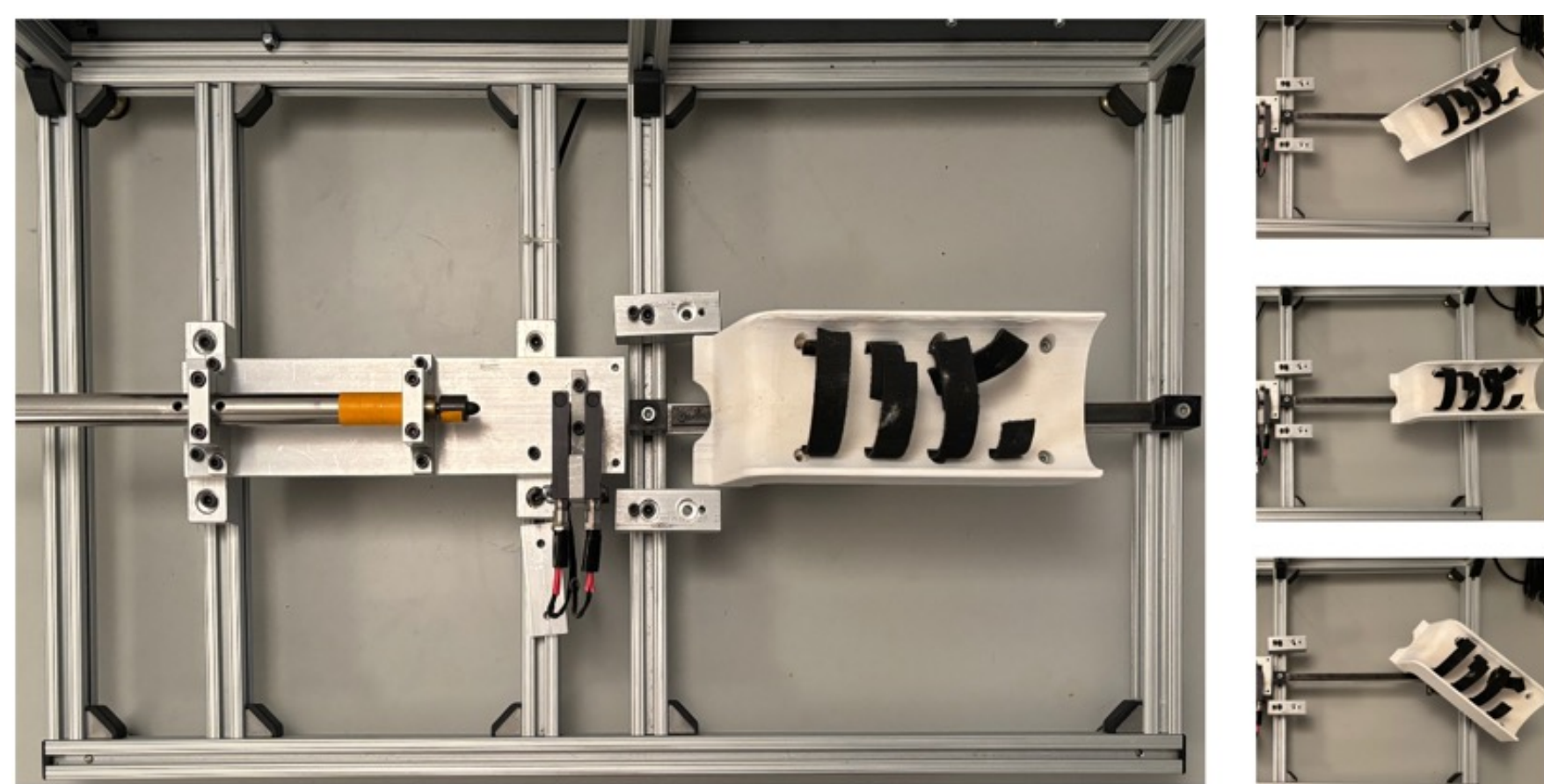
Eric Brengel, M.S., Rosemarie Hightower, Praveen Kulkarni, Ph.D., & Craig Ferris, Ph.D.
Center for Translational Neuroimaging, Northeastern University, Boston, MA

Introduction

Repetitive mild traumatic brain injury (rmTBI) is a highly prevalent risk factor for later-life neurodegenerative disease onset, yet clinical treatments remain elusive. Of interest is minocycline, an antibiotic in clinical trials for stroke that may also be useful for rmTBI due to its anti-inflammatory action. In this study, we tested the efficacy of minocycline as a treatment for rmTBI in a highly translational rat model using MRI and immunohistochemistry. Widespread cytotoxic edema was induced by rmTBI and reversed to control levels in many regions by minocycline. Clear evidence for a potential treatment and the utility of our model are discussed.

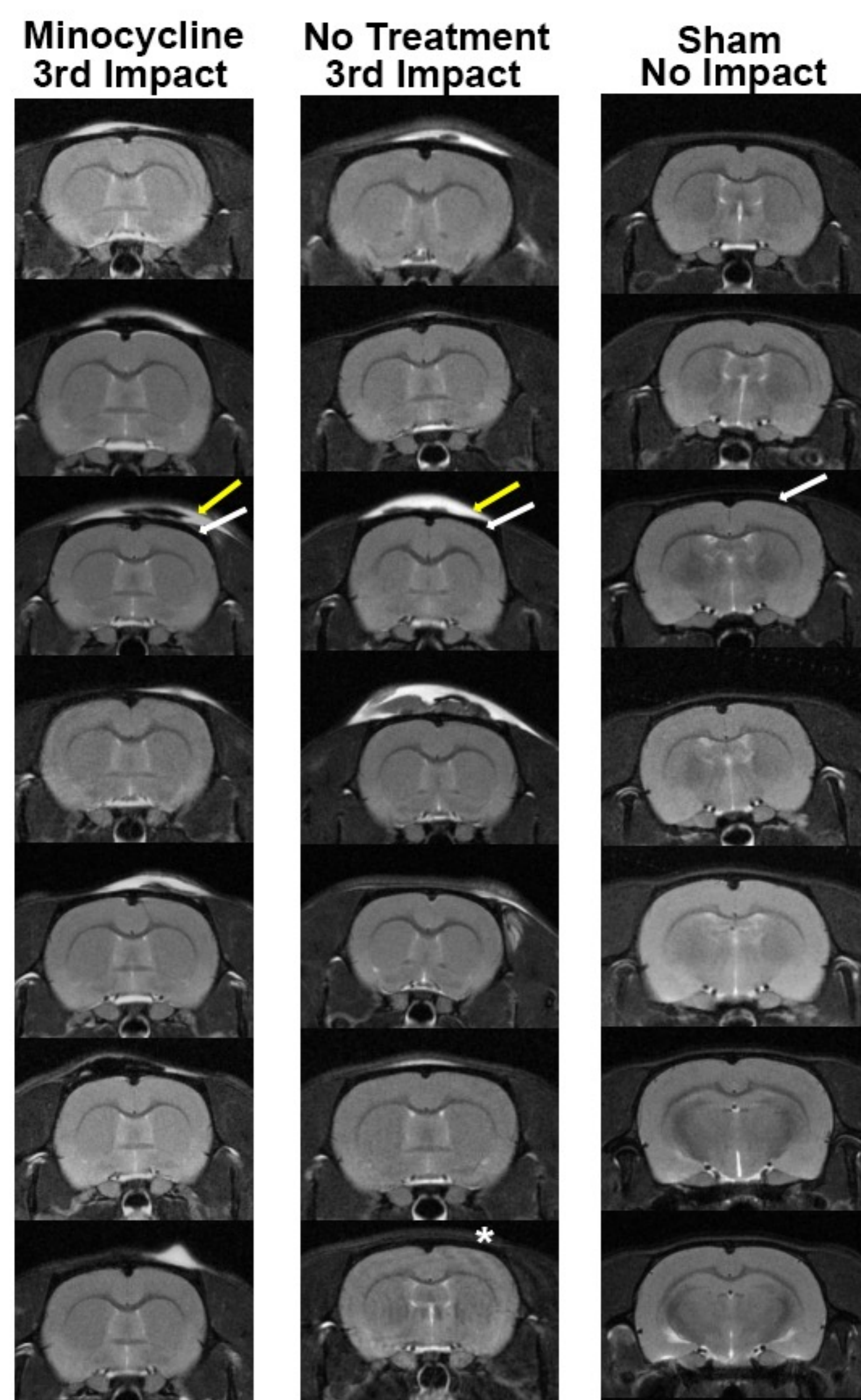
Momentum Exchange Model of rmTBI

The momentum exchange method ranks highest among preclinical rmTBI models in translational value for its ability to generate tightly regulated, ethologically valid linear and rotational forces without skull fracture or surgical procedure. The apparatus features a pneumatic rubber-tipped impactor, sensors to verify impact velocity, and a track along which the platform accelerates after impact for longitudinal use with fully awake rats, maximizing translational value.



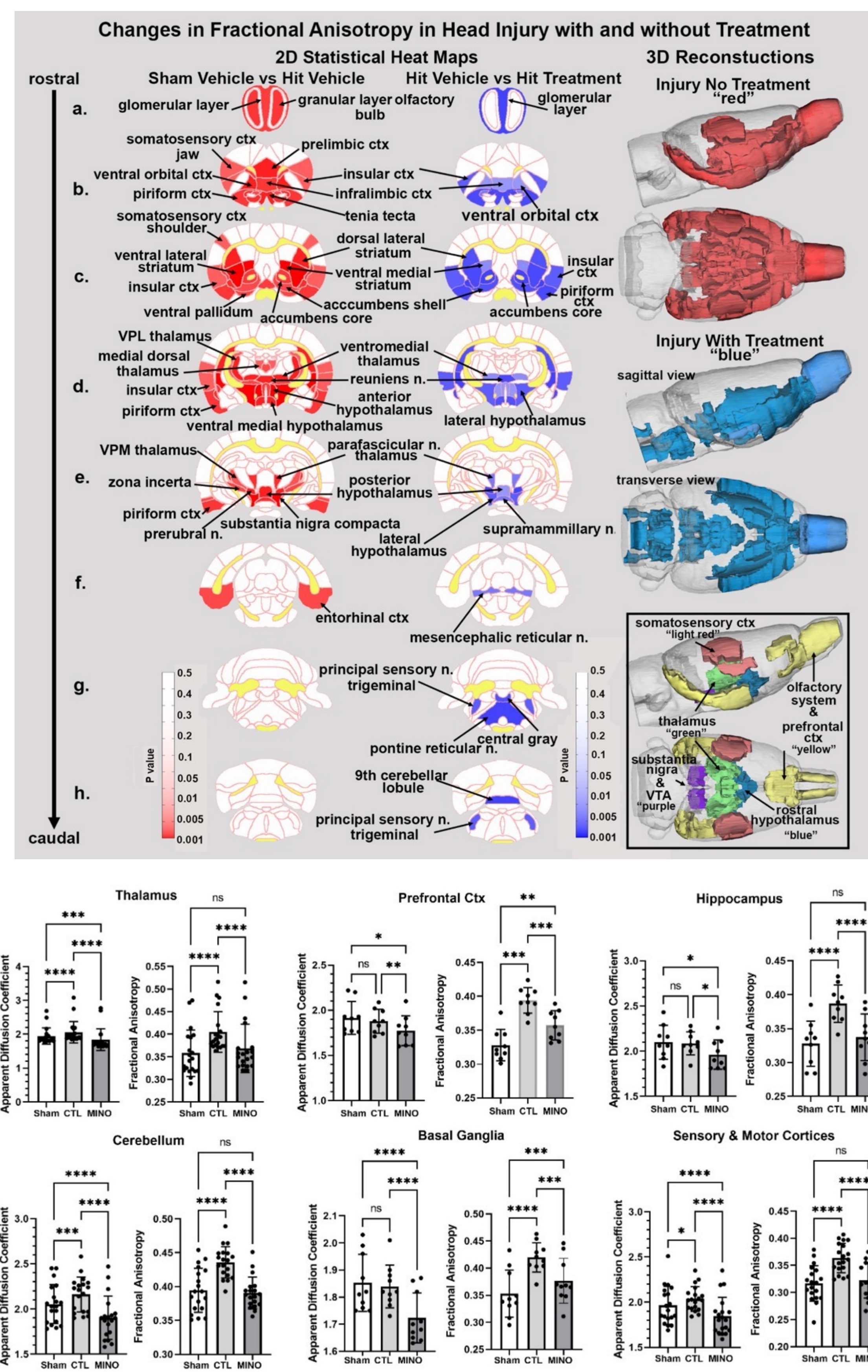
Adult female rats underwent mTBI or sham procedure once daily for three days. Minocycline or vehicle control was administered via intraperitoneal injection 30 minutes post-mTBI. On the third day, T2-weighted and DWI MRI scans were acquired within 2 hours of injury. 3 weeks post-rmTBI, tissue was acquired for histological quantification of astrocytes and microglia.

Momentum Exchange rmTBI Induces Microstructural Alterations Absent of Gross Anatomical Injury



T2-weighted radiography does not indicate evidence of gross neuroanatomical injury or skull fracture, consistent with the clinical phenotype of mild traumatic brain injury. Superficial edema of the skin and tissue overlying the skull is observed at the putative site of impact with high intertrial consistency.

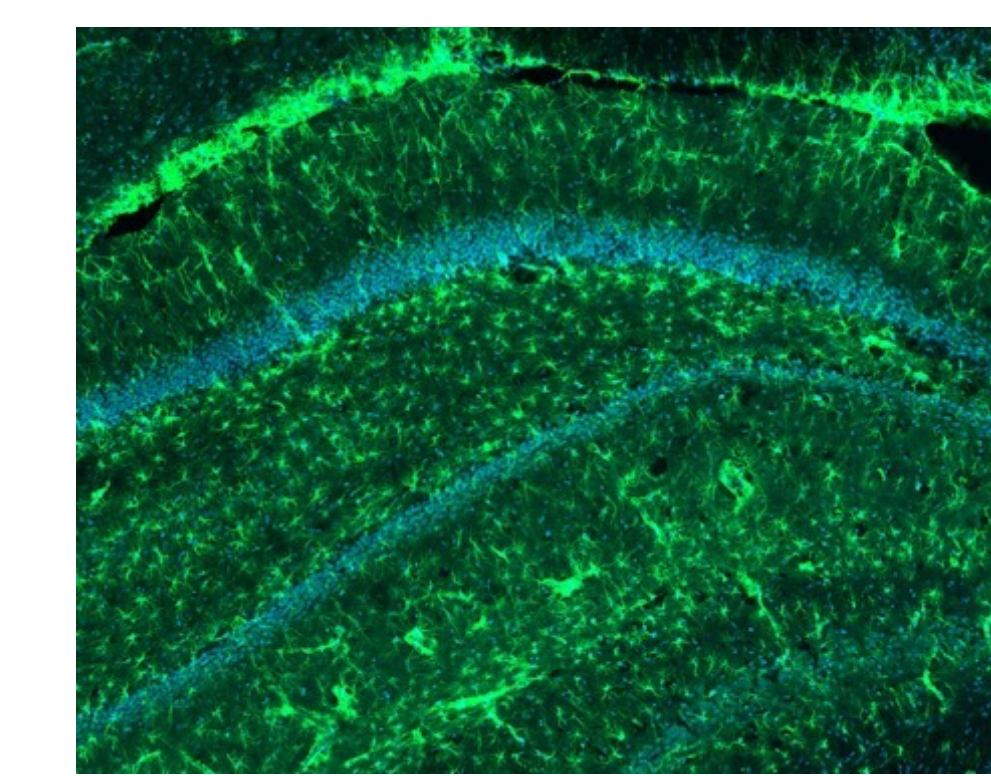
Fractional Anisotropy is Restored by Minocycline



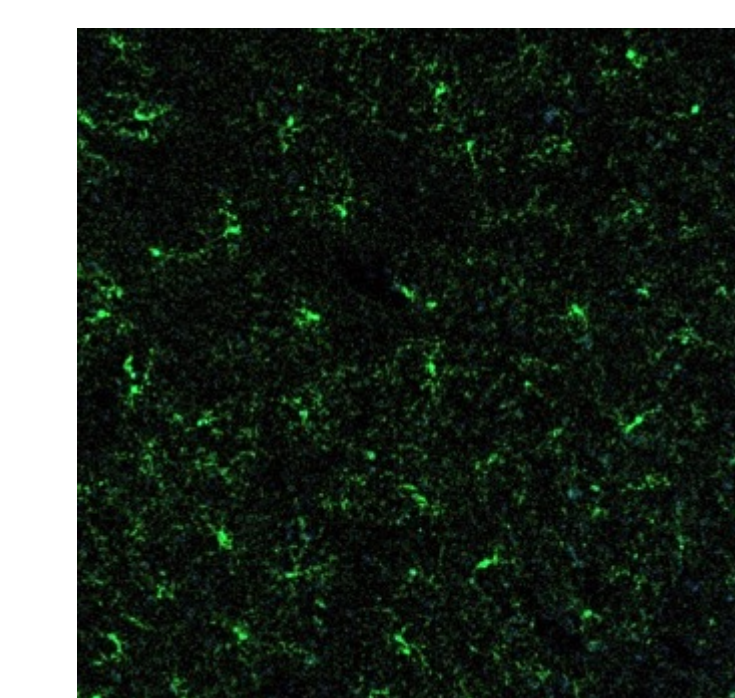
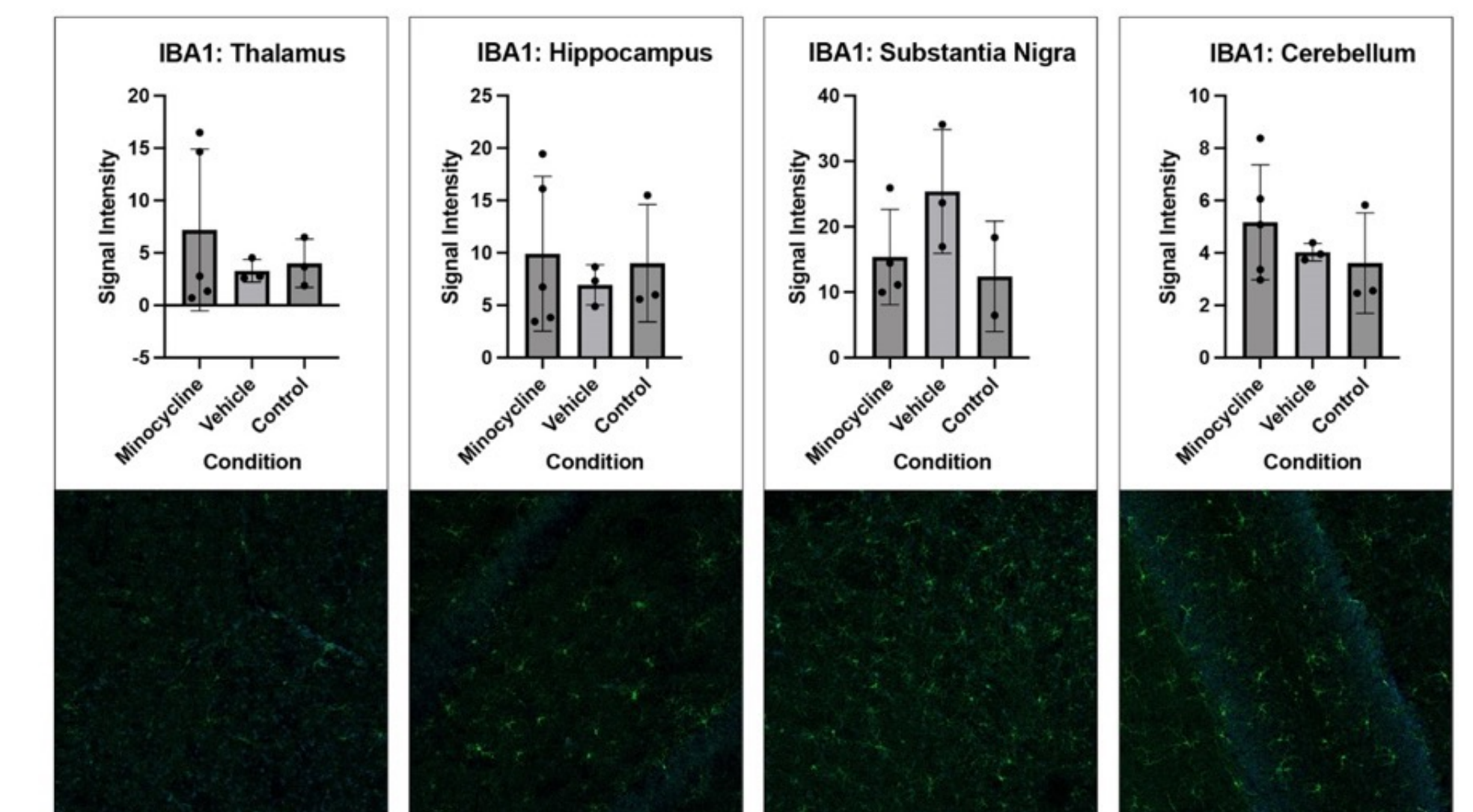
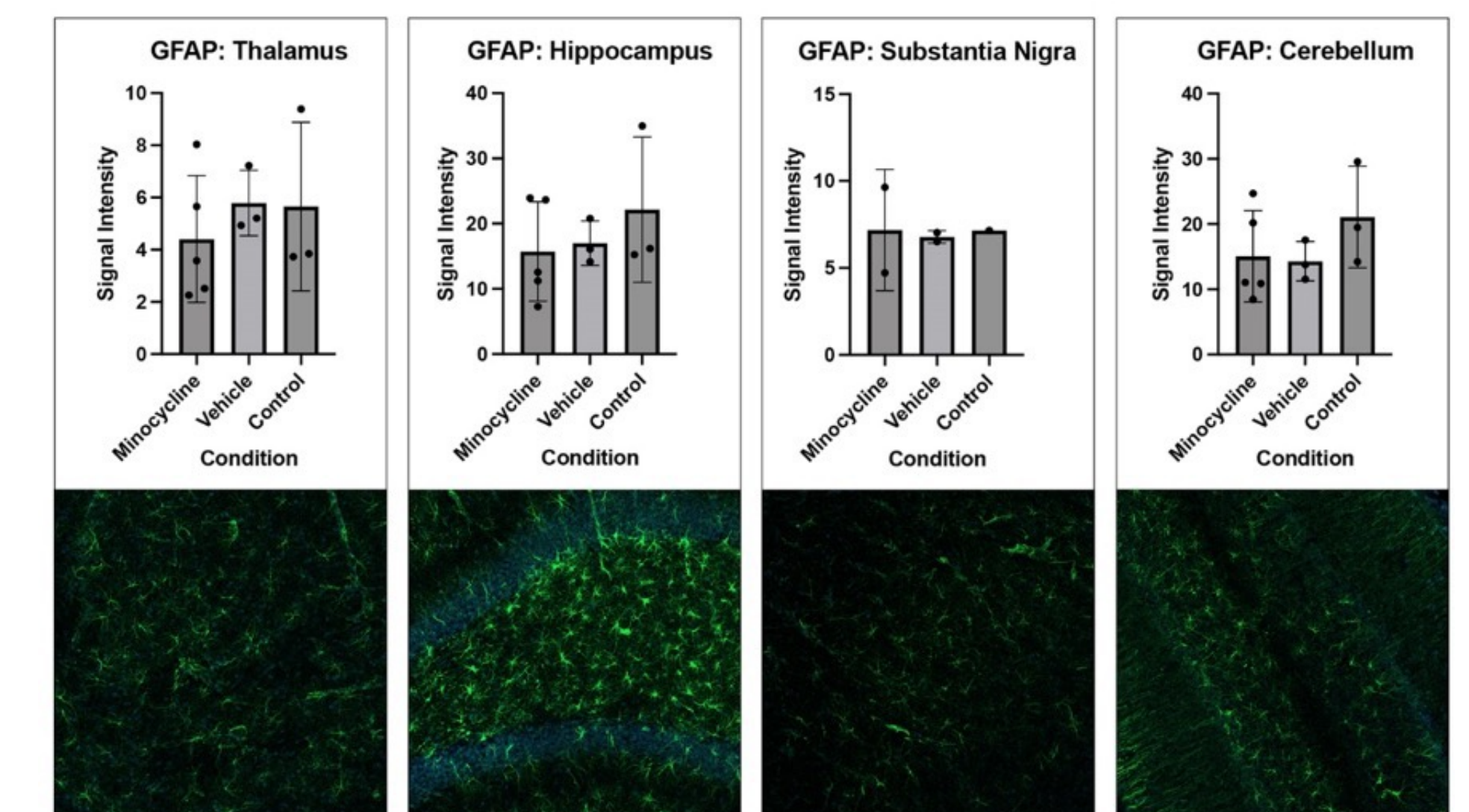
Discussion

The validity of preclinical models in guiding the development of new therapeutics for the treatment of head injury has been called into question on account of the many failed clinical trials for TBI. To that end, we have employed the momentum exchange model of rmTBI for its high translational value, further adding to it by adapting its holster for use with conscious rats. The thalamus, cerebellum, hippocampus, basal ganglia, and midbrain dopaminergic system have been identified as areas vulnerable to microarchitecture alteration, which may be treated with minocycline administered after impact.

No Evidence of Lasting Astrocytosis or Microgliosis



Astrocytosis
Signal intensity of GFAP⁺ cells was measured three weeks after rmTBI and minocycline treatment. No lasting alterations were observed.



Microgliosis
Signal intensity of IBA1⁺ cells was measured three weeks after rmTBI and minocycline treatment. No lasting alterations were observed.

Acknowledgements

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