

Characterization of Chronic Pain and Hypersensitivity in Mixed, Motor, and Sensory Nerve Terminal Neuromas in Rats.

Jason L. Kessler; Scott W. Sabbagh; Shelby Svientek, MD; Carrie A. Kubiak, MD; Jana Moon; Vincent Thieu; Brian P. Cleary; Paul S. Cederna, MD; Stephen W. P. Kemp, PhD

INTRODUCTION

- Approximately 185,000 amputations are performed annually in the United States. Symptomatic neuromas occur in approximately 30-40% of individuals after limb loss, and phantom limb pain affects 70-95% of these patients, often leading to excruciating pain and disability.
- Although pre-clinical animal studies have evaluated pain in different experimental models, it is not currently known whether different neuroma models lead to differences in pain hypersensitivity responses.

OBJECTIVES

- To create a more clinically relevant pain model, this current study sought to characterize serial pain responses utilizing sensitive functional outcome measures from terminal mixed, motor, and sensory neuroma rat models.

METHODS

- Prior to surgery, all rats underwent baseline pain sensitivity testing and were randomly sorted to one of three surgical groups of six rats each: (1) mixed nerve (tibial); (2) sensory nerve (sural), and; (3) motor nerve (femoral) neuromas.
- The distal nerve of each respective surgical group was isolated, transected, and transposed to a more superficial position in the hindlimb, creating neuromas that were accessible for testing.
- Neuromas were created in the right hindlimb (experimental group) with the left hindlimb serving as a control.
- Functional pain outcome measures were performed for eight weeks and assessed mechanical allodynia (von Frey test), heat allodynia (Hargreaves test), and cold allodynia (Acetone test).



Figure 1A: Tibial nerve transposed to a more superficial location.
Figure 1B: Black sutures were positioned where neuromas were created.

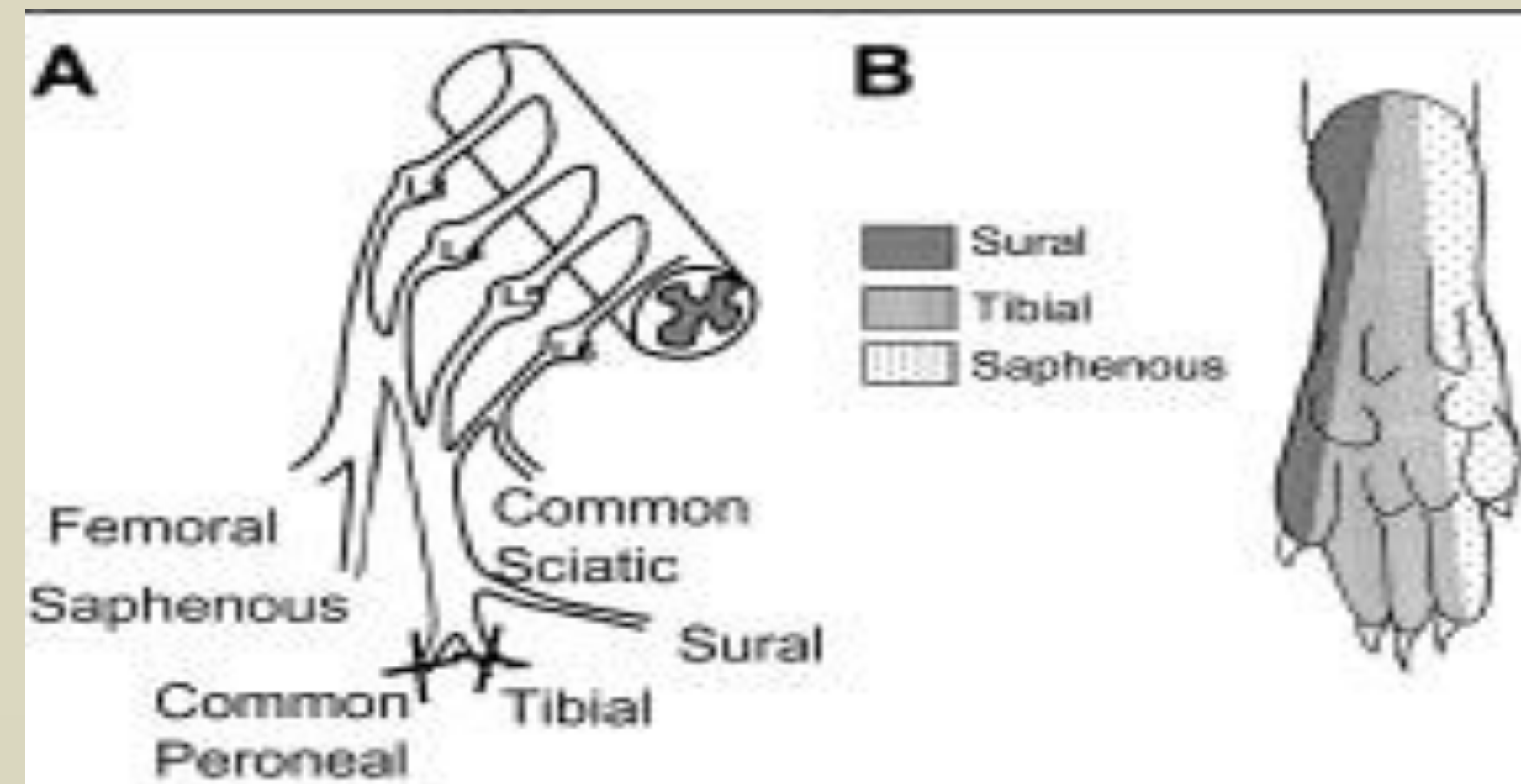


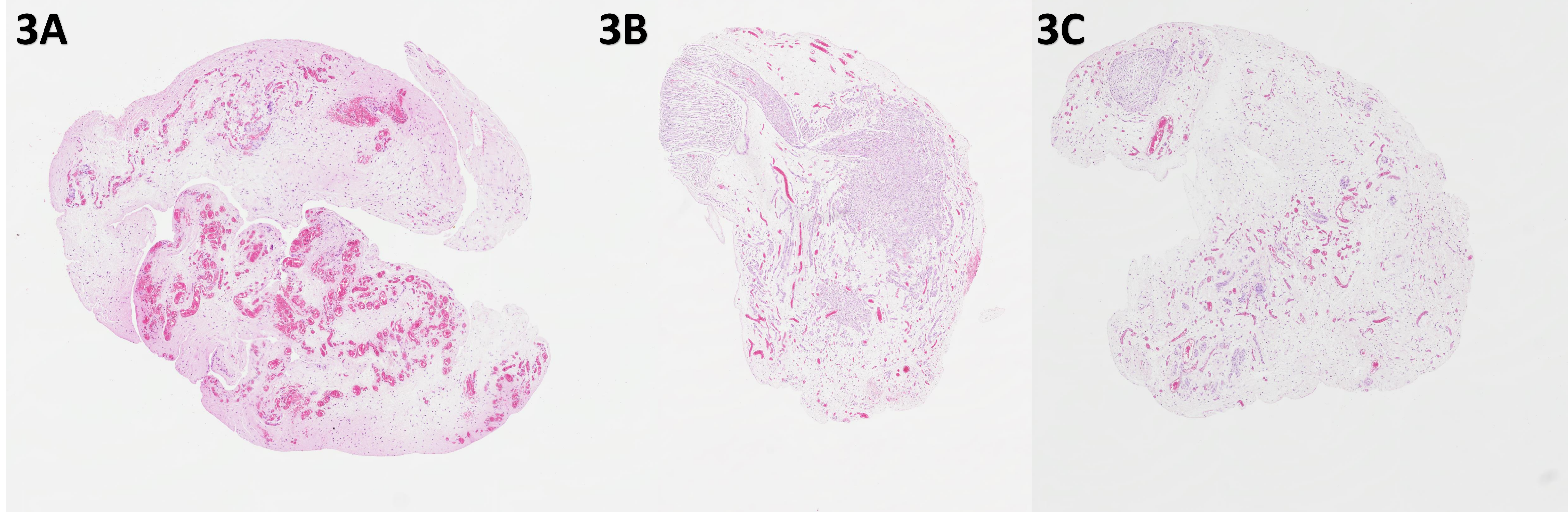
Figure 2A: Schematic of hindlimb nerve branching.

Figure 2B: Diagram of the region of paw innervation.

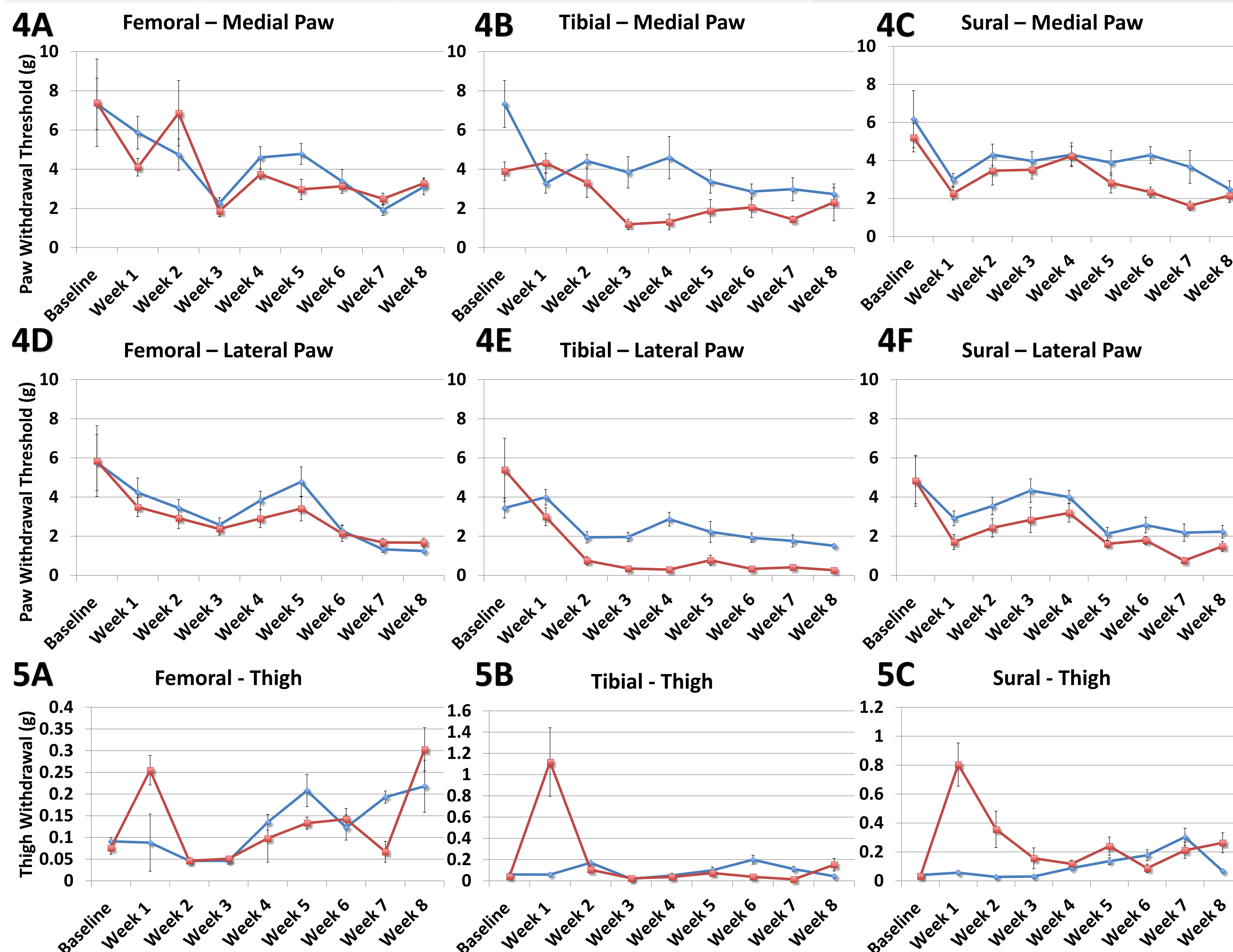
CONCLUSION

- Data from this study demonstrated that the tibial neuroma is the most appropriate model for evaluating chronic behavioral pain responses following injury.
- In the future, we will evaluate the Regenerative Peripheral Nerve Interface as a method of alleviating neuroma pain using this tibial neuroma model.

RESULTS



Figures 3A-3C: H&E staining reveals infiltration of immune cells into the terminal neuroma tissues two months following surgery. Sample femoral (3A), tibial (3B), and sural (3C) neuromas are shown.



Figures 4A-4F: Both the tibial (4B) and sural (4C) neuroma groups showed increased mechanical sensitivity (y-axis: paw withdrawal threshold measured in grams) when the von Frey test was performed on the middle aspect of the hindpaw (blue diamond - control; red square - experimental) serially (x-axis). However, only the tibial (4E) neuroma group displayed increased mechanical sensitivity when the test was performed on the lateral aspect of the hindpaw.

Figures 5A-5C: von Frey assessment at the thigh revealed decreased mechanical sensitivity (y-axis: thigh withdrawal in grams) at Week 1 in all experimental groups (red square). This decrease normalized to baseline and control levels (blue diamond) during Week 2.

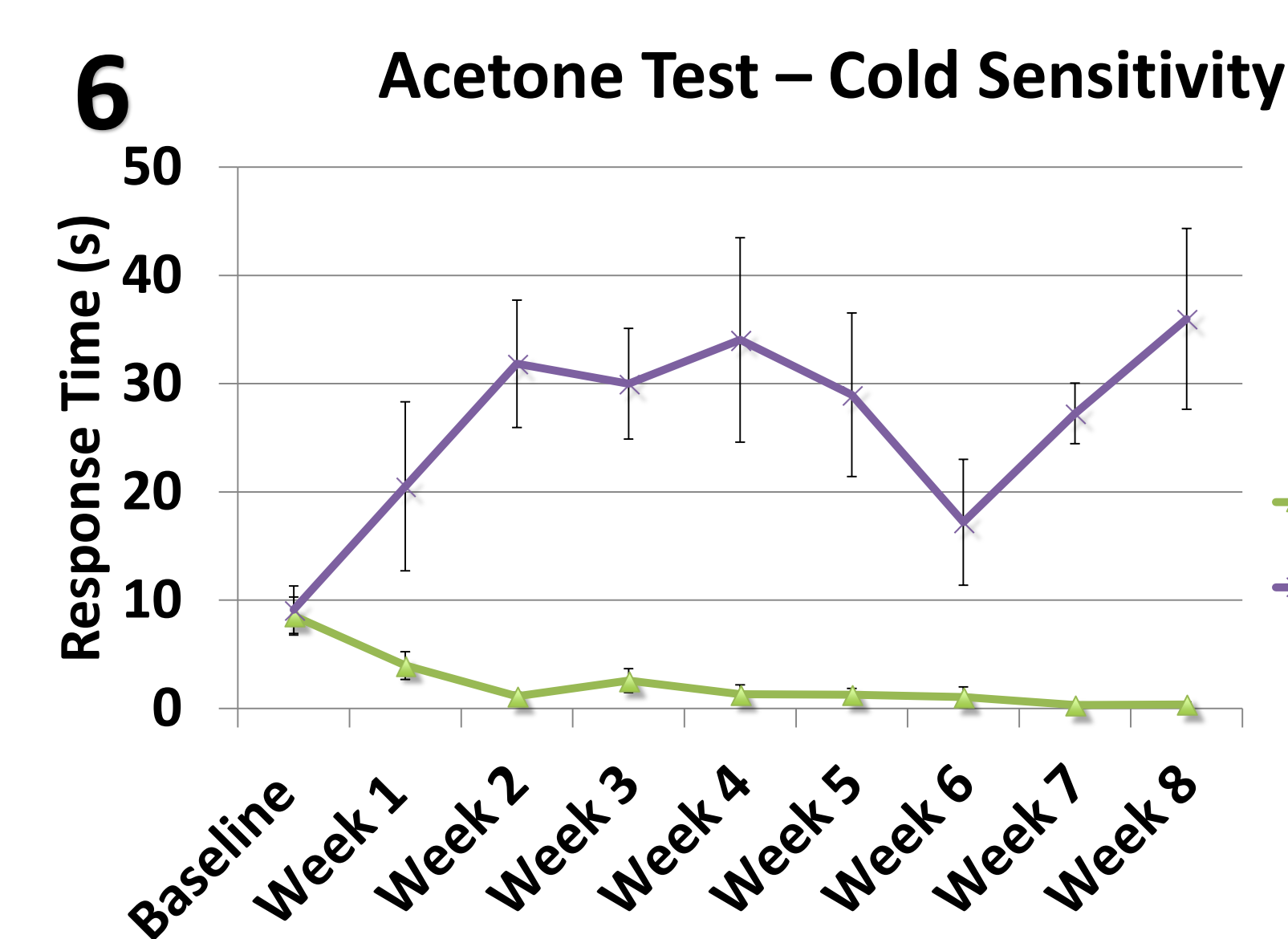


Figure 6: Only the tibial neuroma group had increased cold sensitivity (measured by response time, y-axis).

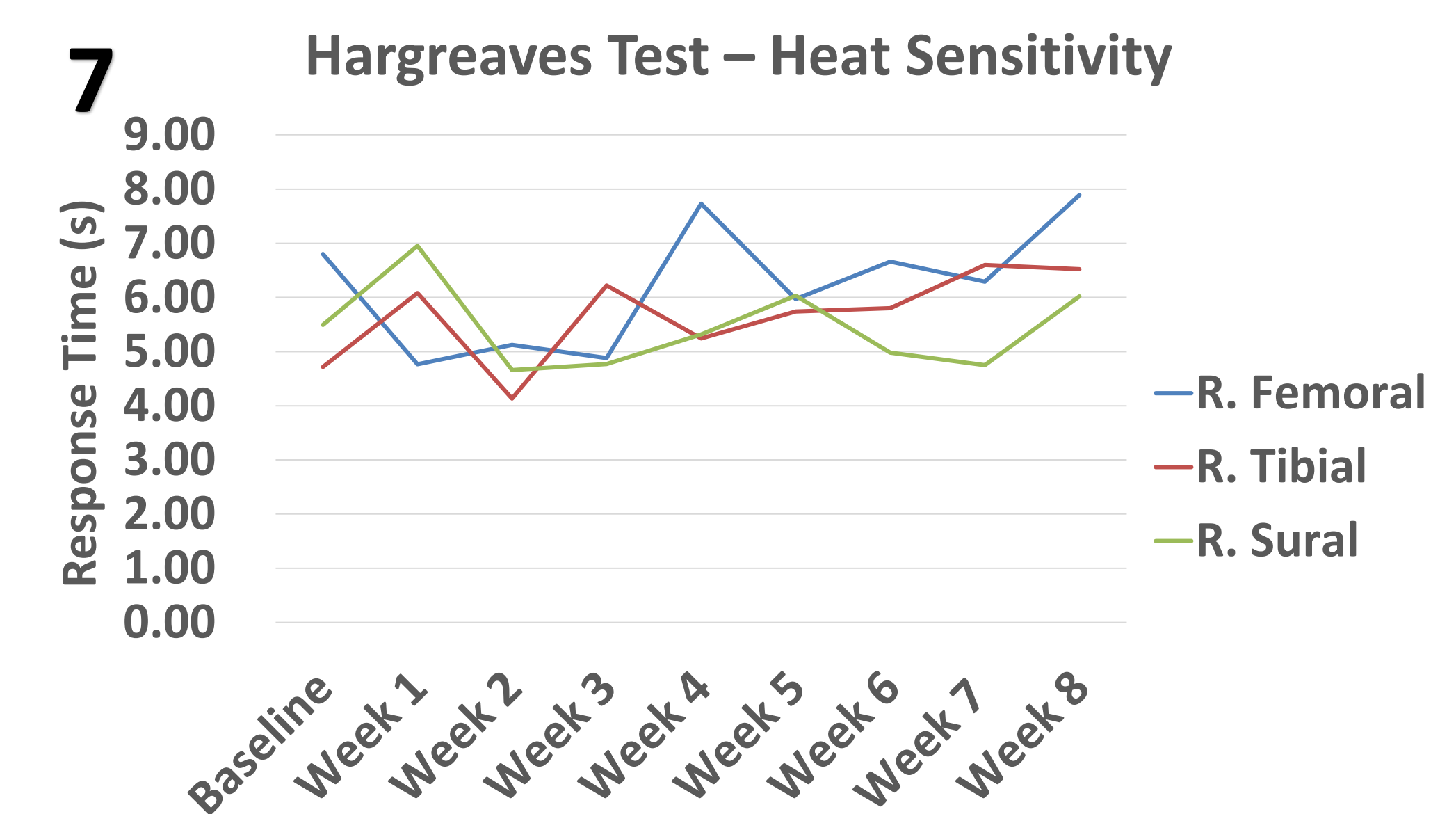


Figure 7: The Hargreaves Test revealed no significant differences in heat sensitivity (measured by response time, y-axis) for all neuroma groups when compared to controls.