Neuromodulation to Enhance Spatial Learning Deficits After Shockwave-Induced Traumatic Brain Injury

Grace K. Nevil[1,2], Crystal M. Noller, PhD[1,2,3], Joshua P. Aronson, MD[1,2,3]
[1]Geisel School of Medicine at Dartmouth, Hanover, NH
[2]White River Junction VA Medical Center, White River Junction, VT
[3]Dartmouth-Hitchcock Medical Center, Lebanon, NH

Dartmouth GEISEL SCHOOL OF MEDICINE

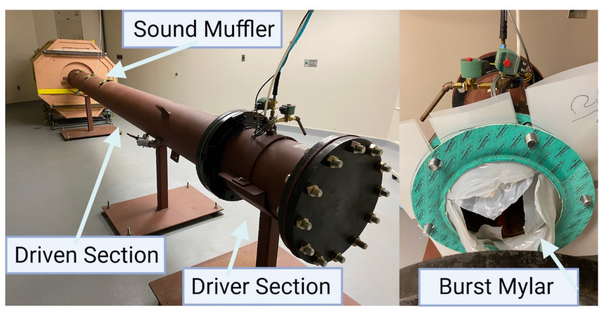
Background

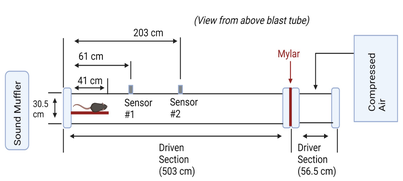
- Traumatic brain injury (TBI) is a significant problem worldwide, affecting ~69 million individuals yearly[1].
- Combat military personnel are at elevated risk for shockwave-induced blast TBI (bTBI), due to their regular proximity to improvised explosive devices.
  - Although survival has improved, bTBI can lead to neuropsychiatric complications that significantly impact the quality of life for affected persons and their families.
  - Among other deficits, bTBI can lead to significant cognitive impairment, including reduced executive functioning and spatial learning deficits, compelling the development of effective treatment[2-4].
- Neuromodulation, including deep brain stimulation (DBS) and vagus nerve stimulation (VNS), has been used to treat neurological and extrapyramidal conditions, and are under investigation for neurotrauma and neuropsychiatric illness[5].
  - Animal models of neurotrauma and post-traumatic stress disorder (PTSD) support the use of DBS and VNS to enhance recovery after bTBI.
  - Multiple stimulation targets have emerged for this promising treatment, including the amygdala, prefrontal cortex, nucleus accumbens, and hippocampus[6].
- **The focus of our laboratory is to define effective stimulation parameters, including brain targets, to enhance functional recovery after bTBI.**

Research Aims

1. Determine and compare blast injury parameters in a repeated model of bTBI.
2. Characterize spatial learning deficits associated with each injury paradigm.
3. Independently perform bTBI, behavioral assays, and microsurgical techniques.
4. Perform an extensive literature review to inform a pre-clinical review article defining neuromodulation approaches to mitigate neuropsychiatric symptoms associated with PTSD.

Methods

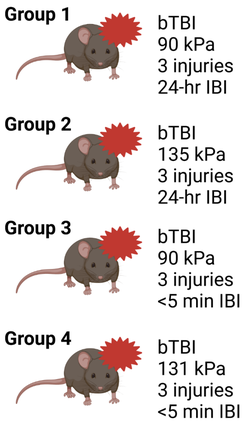




Experimental bTBI and schematic of Blast Tube. Compressed air fills the driver section, where it ruptures a Mylar membrane. A resulting shockwave is sent down the tube towards the sound muffler. Anesthetized animals are placed in a restrainer in a prone and head-forward position relative to the shockwave.

Brain Injury + Behavioral Testing

A

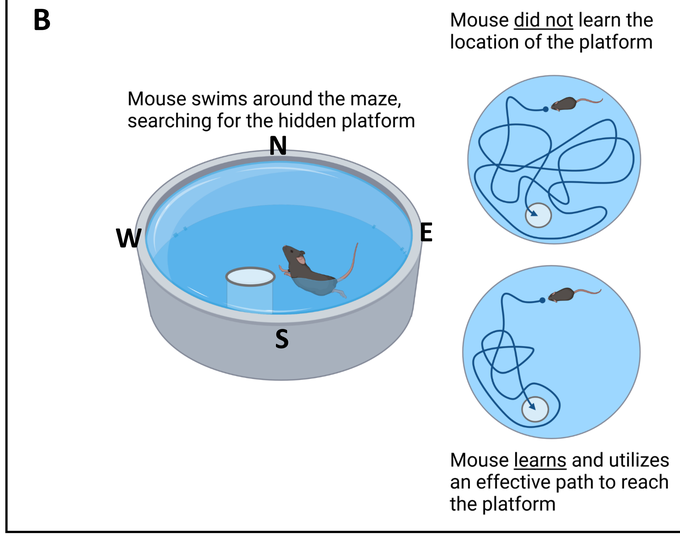


Study Design.
(A): Animals were randomly assigned to one of four experimental groups that varied according to the blast pressure (kPa) and inter-blast interval (IBI). After recovery, spatial learning deficits were assessed.

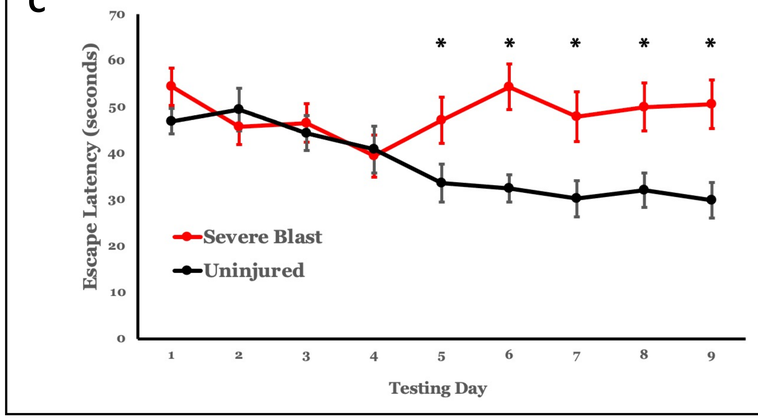
(B): The Morris Water Maze test is performed over a period of 10 days. The animal is placed at a randomly selected start point (N, S, E, W) and allowed to swim around the maze for two minutes, while searching for a platform located in the SW quadrant. The final day of testing consists of a probe trial, where the platform is removed from the maze and the animals are allowed to swim.

(C): A camera equipped with video tracking (Noldus EthoVision) records the animal's swimming patterns and time to platform (escape latency). After several days of testing, uninjured animals find the platform in a short period of time, typically employing efficient paths to the platform. They also spend more time in the platform quadrant (SW). Injured animals display significant latency to platform, inefficient paths to platform, and less time in the platform quadrant, demonstrating significant impairments in learning and memory that are often observed in humans with bTBI.

B



C



Conclusions + Ongoing Work

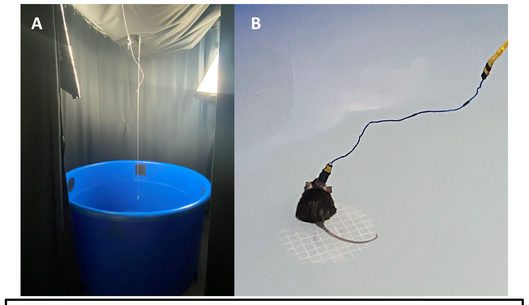
CONCLUSIONS:
- Repeated experimental bTBI can be feasibly performed in animals, with minimal mortality.
- Neurobehavioral assays can be successfully performed in injured animals after recovery.
- Animals with more severe injuries display worse spatial learning deficits compared to animals with milder injuries.

COMPLEMENTARY SUMMER RESEARCH PROJECTS:
1. Independently performed VNS implants.
2. Refined a testing protocol to assess motor deficits after bTBI using the Rotarod test.
3. Performed a literature review to inform a pre-clinical review article defining the use of brain stimulation in the recovery of neuropsychiatric symptoms associated with PTSD.

1

Vagus Nerve Stimulation. (A) The vagus nerve was isolated and placed inside an electrode cuff (inset). (B) Awake mouse receiving stimulation.

2



Deep Brain Stimulation. (A) The Morris Water Maze setup at White River Junction VA Medical Center. (B) Animal receiving stimulation after reaching hidden platform.

ONGOING WORK:
- Extend summer research in a larger study applying neuromodulation to animals with bTBI.
- Learn advanced neurobehavioral assays, including operant conditioning and hyperarousal.
- Publish neuromodulation review article with research team.

Acknowledgements + References

I would like to thank all those who made this research experience possible. Dr. Aronson, thank you for giving me the opportunity to perform research for your project and for allowing me to shadow you in the operating room this summer. Dr. Noller, thank you so much for training me on the neurotrauma procedures, behavioral assays, and microsurgical techniques. Your dedication to teaching is evident and I am so grateful for your kindness and understanding. Finally, thank you to the Geisel-sponsored research fellowship for funding my summer research efforts.

1. Dewan MC, Rattani A, Gupta S, *et al.* Estimating the global incidence of traumatic brain injury. *J Neurosurg* 2018;1-18.
2. Iaccarino MA, Bhatnagar S, and Zafonte R. Rehabilitation after traumatic brain injury. *Hand Clin Neurol* 2015;127:411-422.
3. Perry DC, Sturm VE, Peterson MJ, *et al.* Traumatic brain injury is associated with subsequent neurologic and psychiatric disease: a meta-analysis. *J Neurosurg* 2016;124:511-526.
4. Rabinowitz AR and Levin HS. Cognitive sequelae of traumatic brain injury. *Psychiatr Clin North Am* 2014;37:1-11.
5. Krauss JK, Lipsman N, Aziz T, *et al.* Technology of deep brain stimulation: current status and future directions. *Nat Rev Neurol* 2021;17:75-87.
6. Reznikov R, Bink M, Nobrega JN, *et al.* Deep brain stimulation in animal models of fear, anxiety, and posttraumatic stress disorder. *Neuropsychopharmacology* 2016;41:2810-2817.