



**U.S. Army Medical Research and Materiel Command**

# **Longitudinal Characterization of Motor and Cognitive Deficits in a Military-Relevant Model of Penetrating Ballistic-Like Brain Injury**

**Dr. Deborah A Shear**

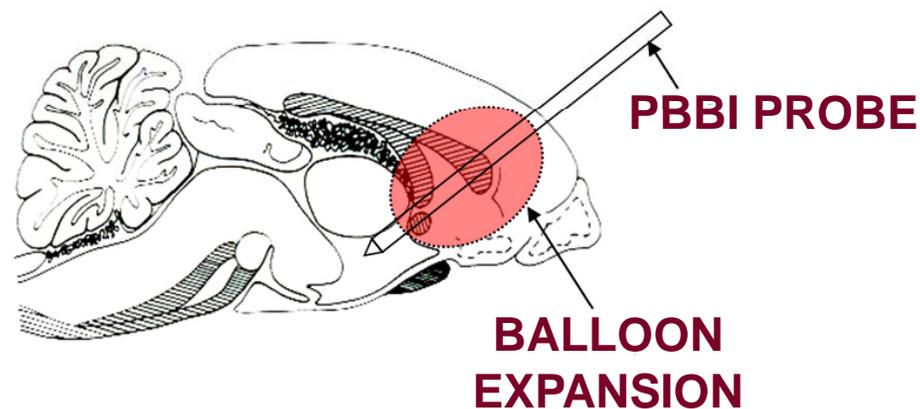
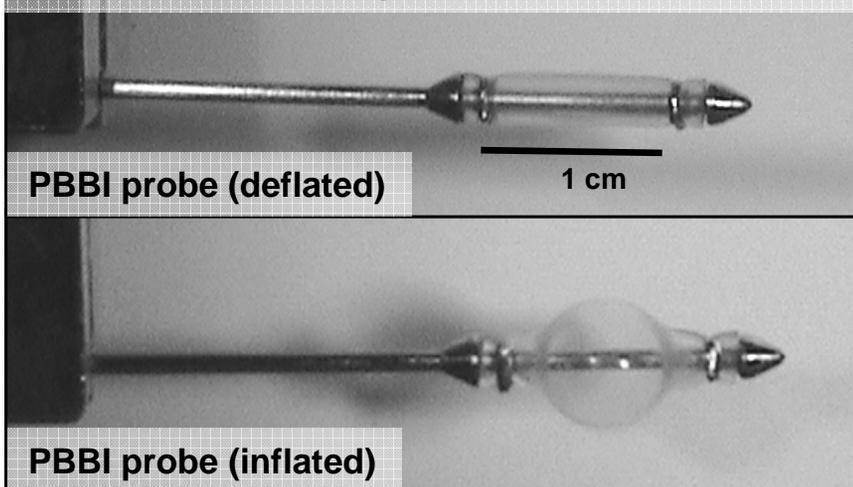
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Division of Psychiatry and Neuroscience  
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**The views expressed in this presentation are those of the author and do not reflect official policy or position of the Department of the Army, Department of Defense or the U.S. Government**

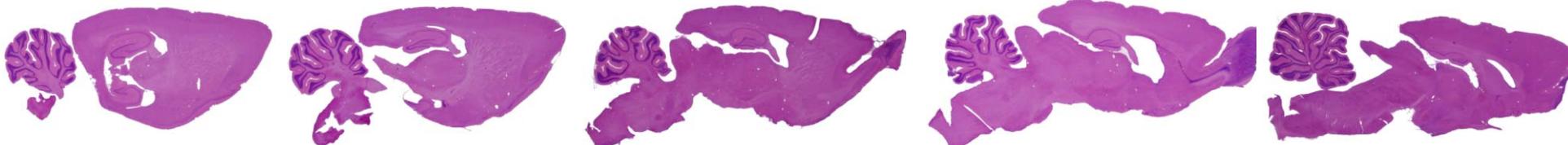


# PBBI MODEL

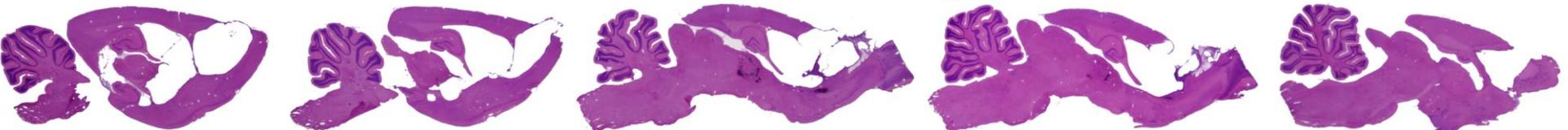
Duration of balloon expansion/contraction < 6.6 ms



SHAM



PBBI



MEDIAL



LATERAL



# BEHAVIORAL PARAMETERS

## **MOTOR:**

- **Neuroscore**
- **Balance Beam**
- **Rotarod**
- **Forelimb Asymmetry**

## **COGNITIVE:**

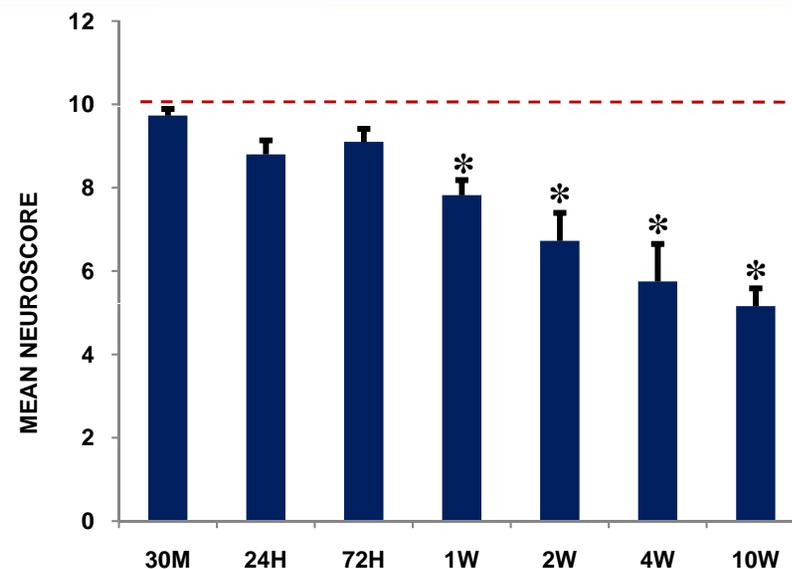
- **Novel Object Recognition**
- **Morris Water Maze**



# NEUROSCORE

Neurological deficits are scored on a 10-point (0 = normal; 10 = severely impaired) composite scale based on the following 4 categories:

1. *Contralateral forelimb flexion*
2. *Shoulder abduction*
3. *Open field circling behavior*
4. *Impaired resistance to lateral push*

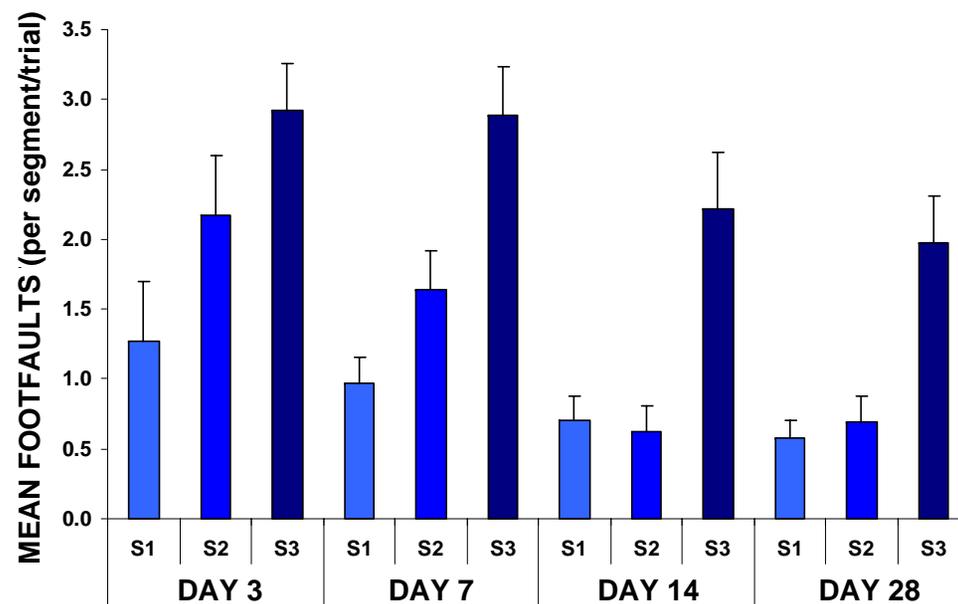
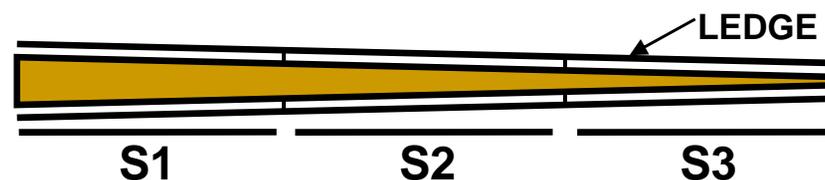


**Frontal (10%) PBBI produces severe neurofunctional deficits by 2 hours post-injury.**



# BALANCE BEAM

## Balance Beam: Day 7 Post-PBBI



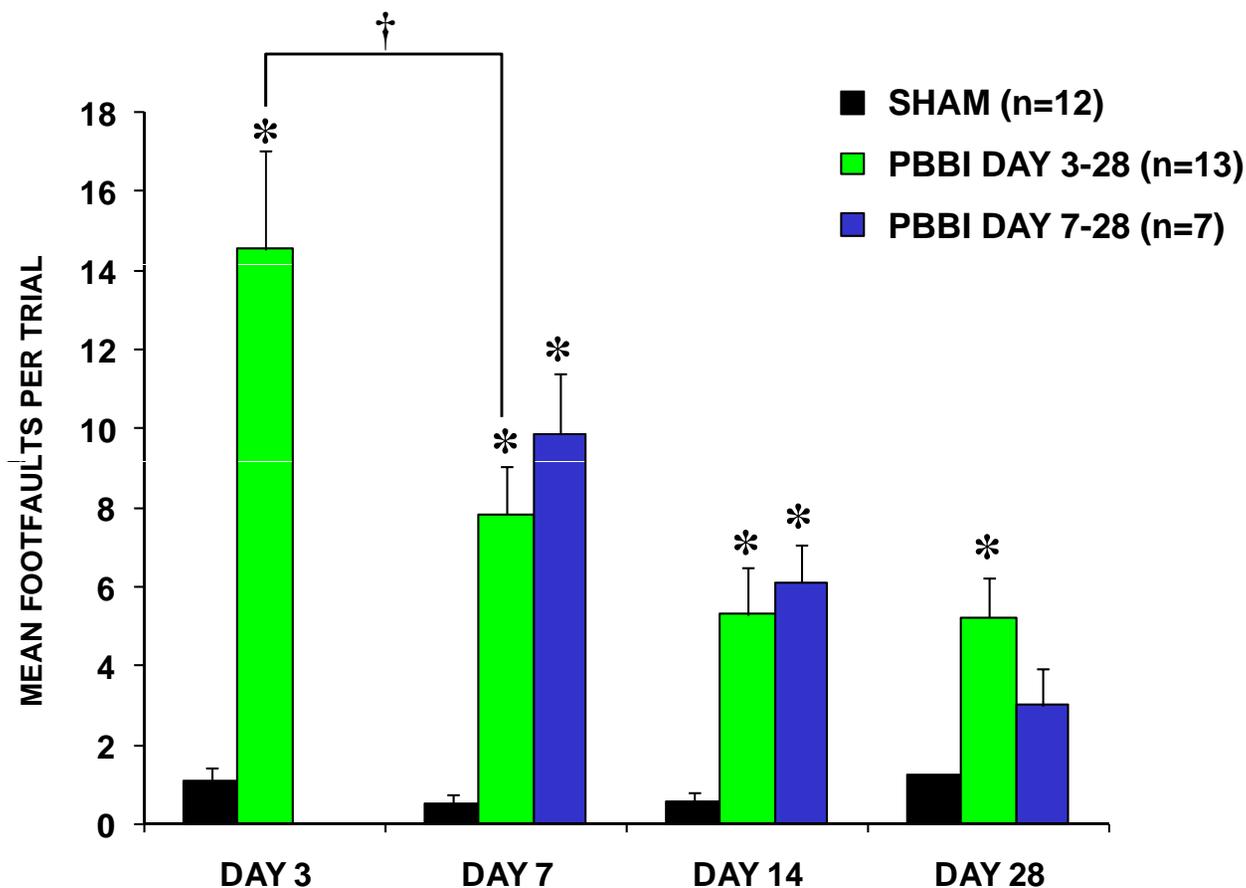
**Foot faults increase in frequency as beam narrows in width**

**(S1-S3 = widest-narrowest beam segment). Columns=means; error bars=SEM.**



# BALANCE BEAM

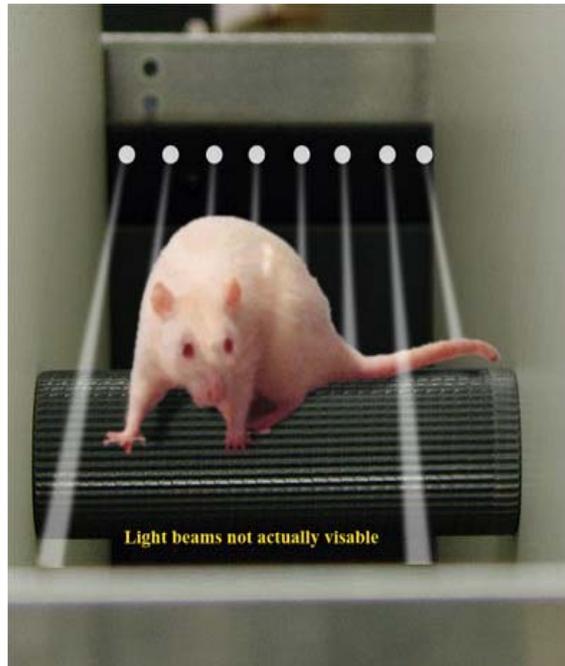
Time course profile of PBBI-induced motor deficits (total foot faults) on the tapered balance beam task





# ROTAROD

## Accelerating vs. Fixed-Speed Rotarod?



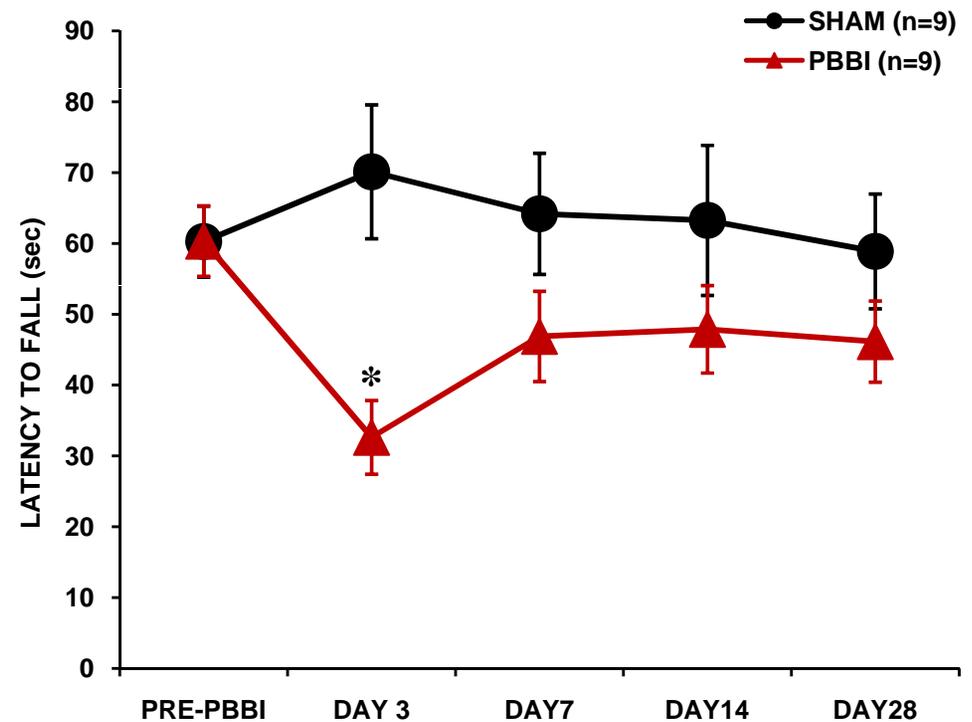
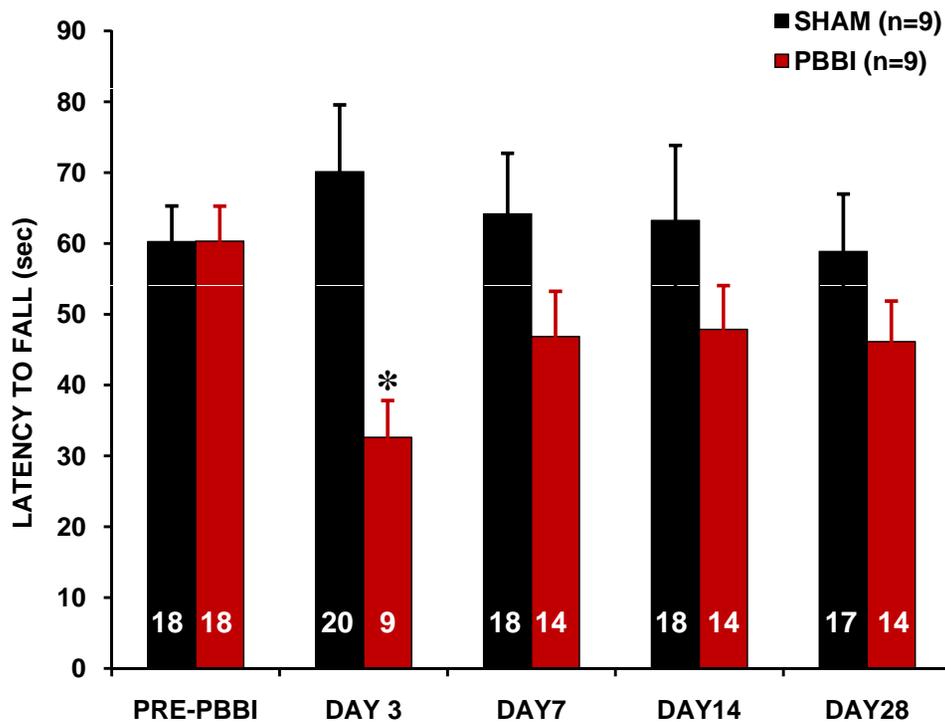
***Accelerating from 0 – 25 rpm at a rate of 0.3 rpm/s (3 rpm/10s)***

***or***

***Step-wise fixed-speed increments of 10, 15, 20, 25 rpm (2 trials/speed)***

# ACCELERATING SPEED ROTAROD

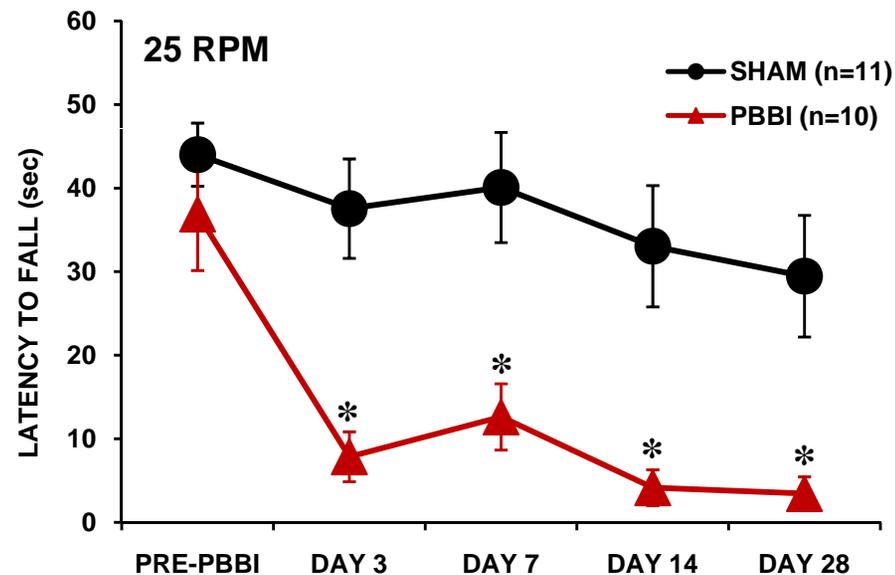
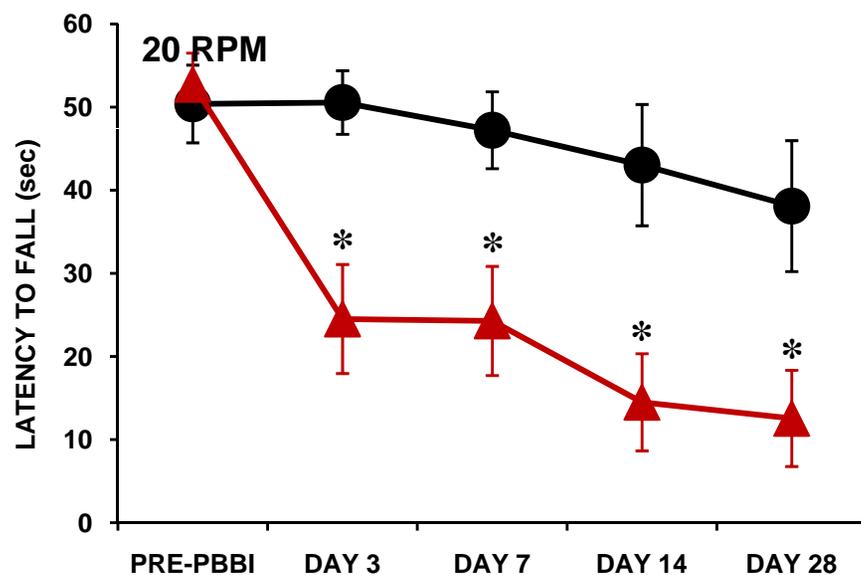
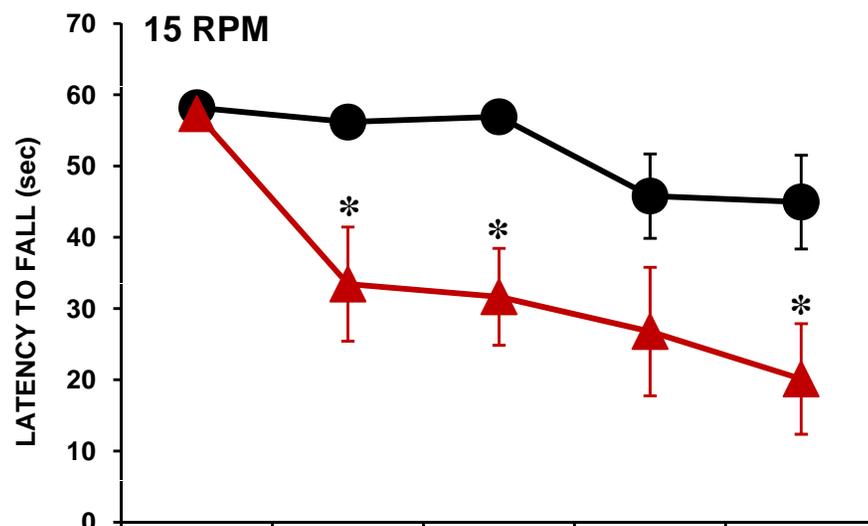
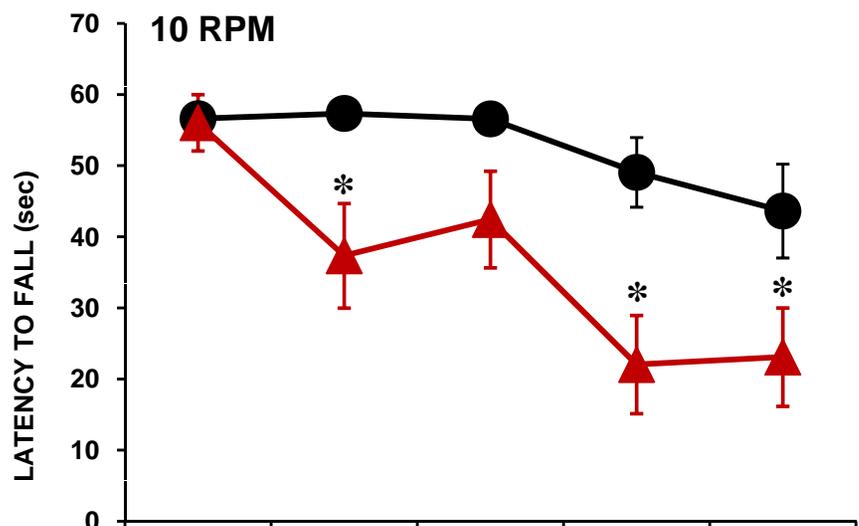
PBBI rats show significant motor deficits only at 3 days post PBBI



0 to 30 rpm progressively increasing at a rate of 0.3 rpm/sec



# FIXED-SPEED ROTAROD

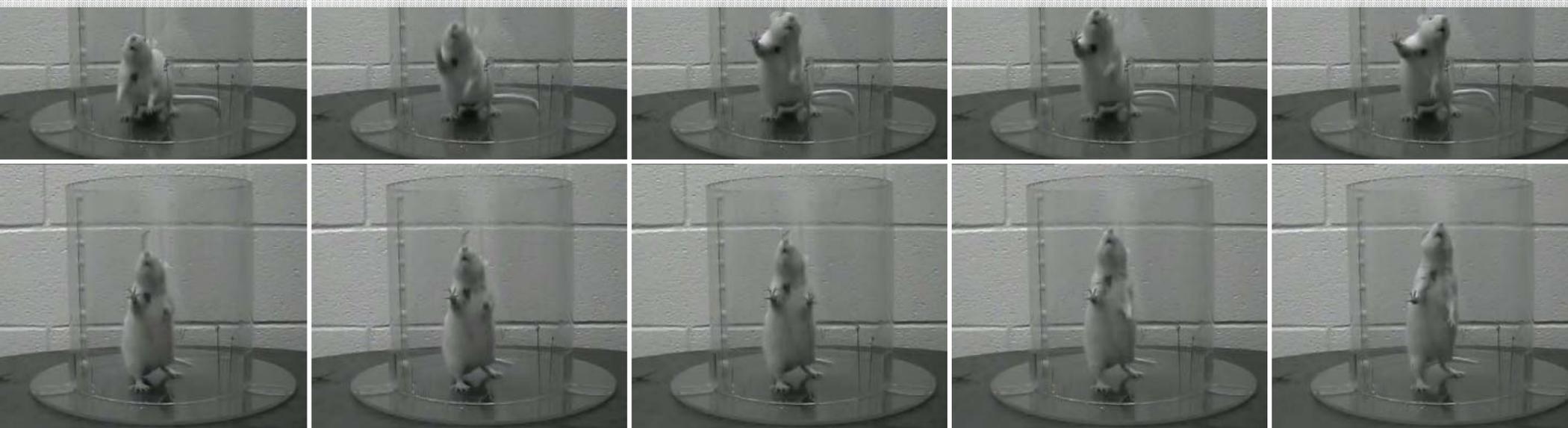




# FORELIMB ASYMMETRY

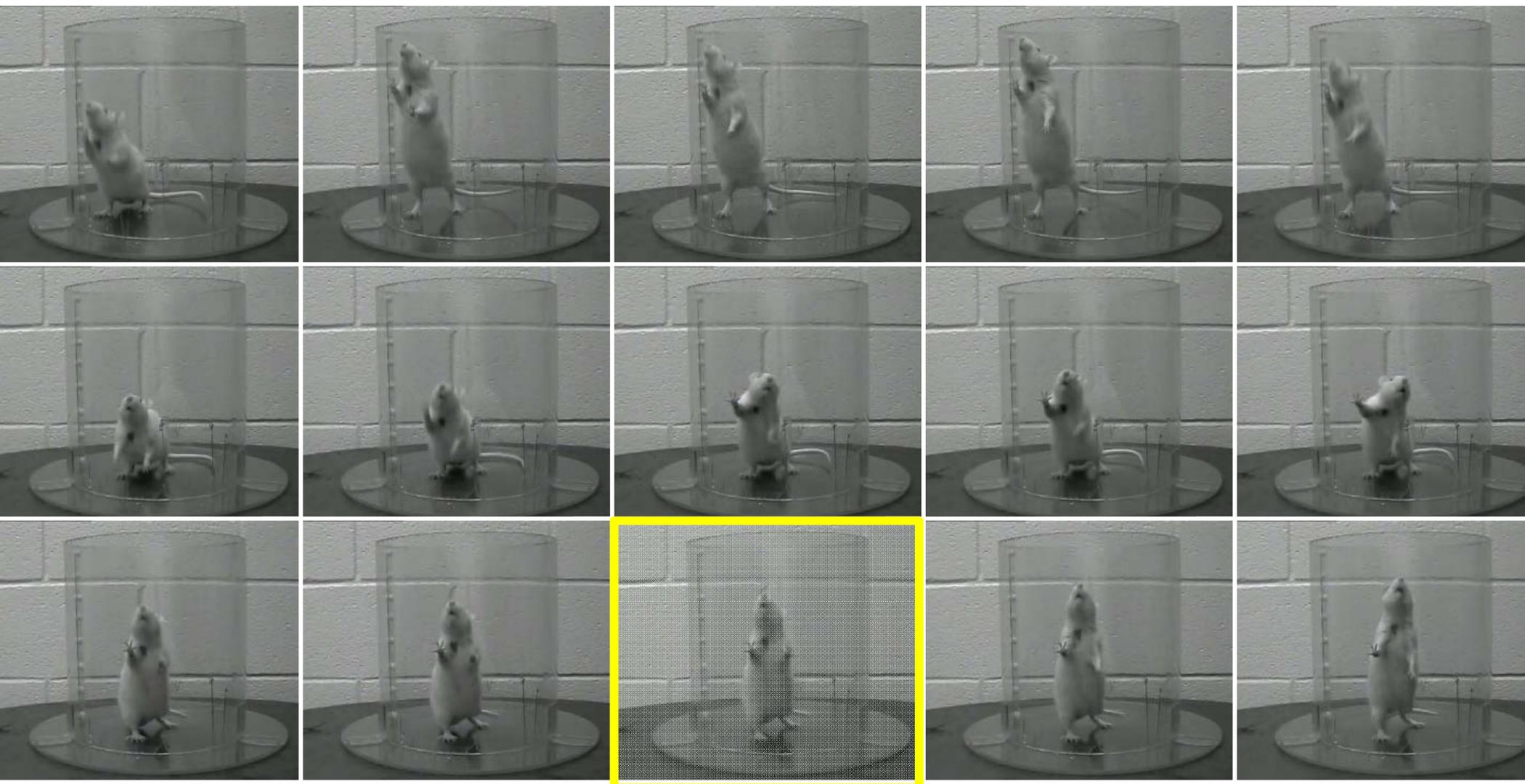
**FA Task- Index of Asymmetry (IA)**

$$IA = (\text{ipsi} + \frac{1}{2} \text{ both}) / (\text{ipsi} + \text{contra} + \text{both})$$





# FORELIMB ASYMMETRY





# FORELIMB ASYMMETRY

## FA Task- Index of Asymmetry (IA)

$$IA = (\text{ipsi} + \frac{1}{2} \text{ both}) / (\text{ipsi} + \text{contra} + \text{both})$$

$$(3+2)/(3+1+4) = 0.62$$

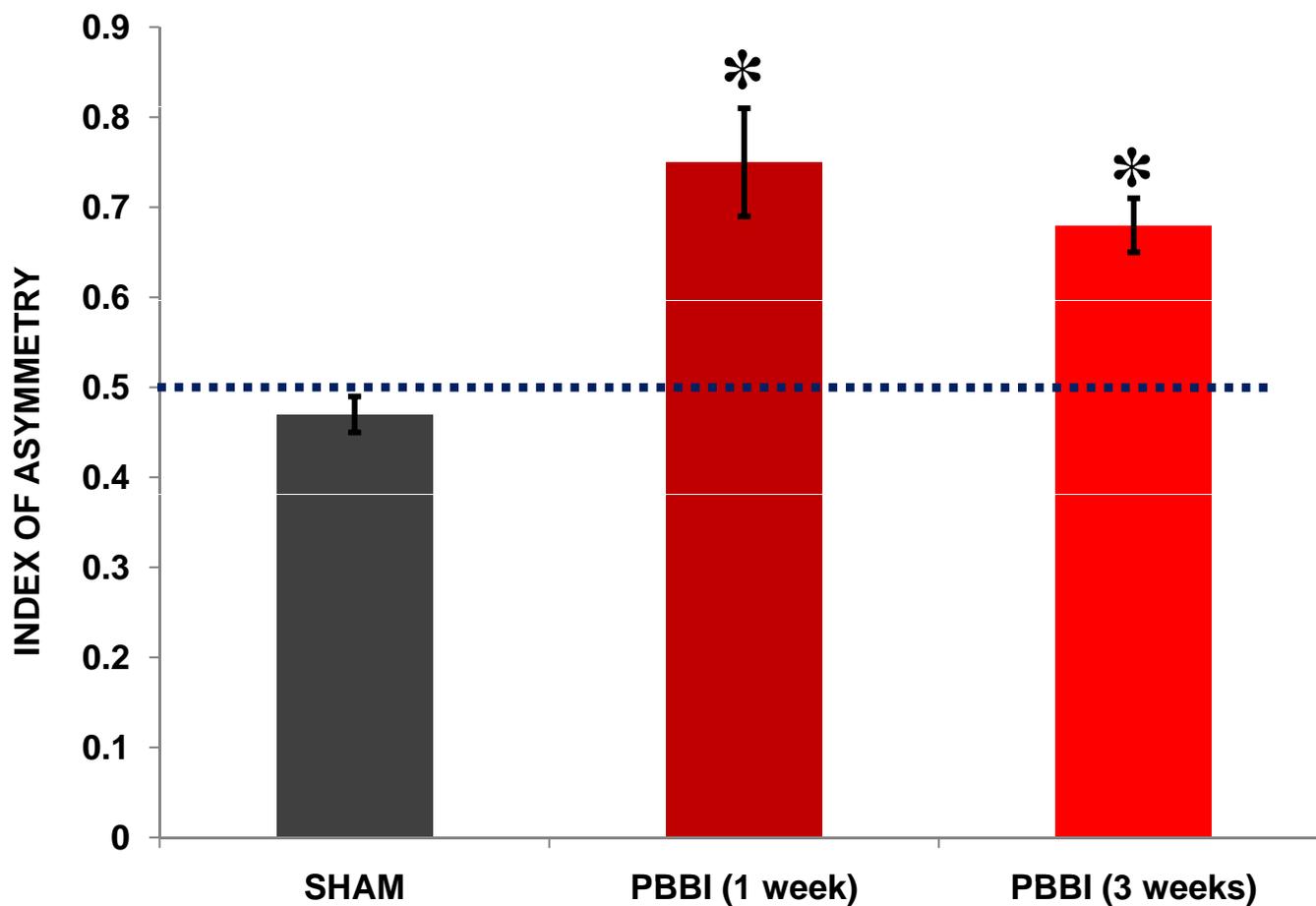
$$(3+3)/(3+3+6) = 0.50$$

**Sets nonbiased forelimb use at 0.50**



# FORELIMB ASYMMETRY

## Effects of right, frontal 10% PBBI on forelimb asymmetry





# CONCLUSIONS

- **PBBI causes significant motor deficits on the balance beam task up to 4 weeks post-injury. However the therapeutic window is greatly reduced by 7 days post-PBBI suggesting this task may be more appropriate for acute ( $\leq 3$  days) studies.**
- **In contrast, our results suggest that the fixed-speed rotarod and forelimb asymmetry tasks are more appropriate for longitudinal screening (i.e. both acute and extended recovery periods) of promising therapeutic interventions.**



# BEHAVIORAL PARAMETERS

## MOTOR:

- Neuroscore
- Balance Beam
- Rotarod
- Forelimb Asymmetry

## COGNITIVE:

- Novel Object Recognition
- Morris Water Maze



# NOVEL OBJECT RECOGNITION

The NOR task requires that the animal spontaneously explore sample objects and discriminate between a novel and familiar object during a subsequent exposure.

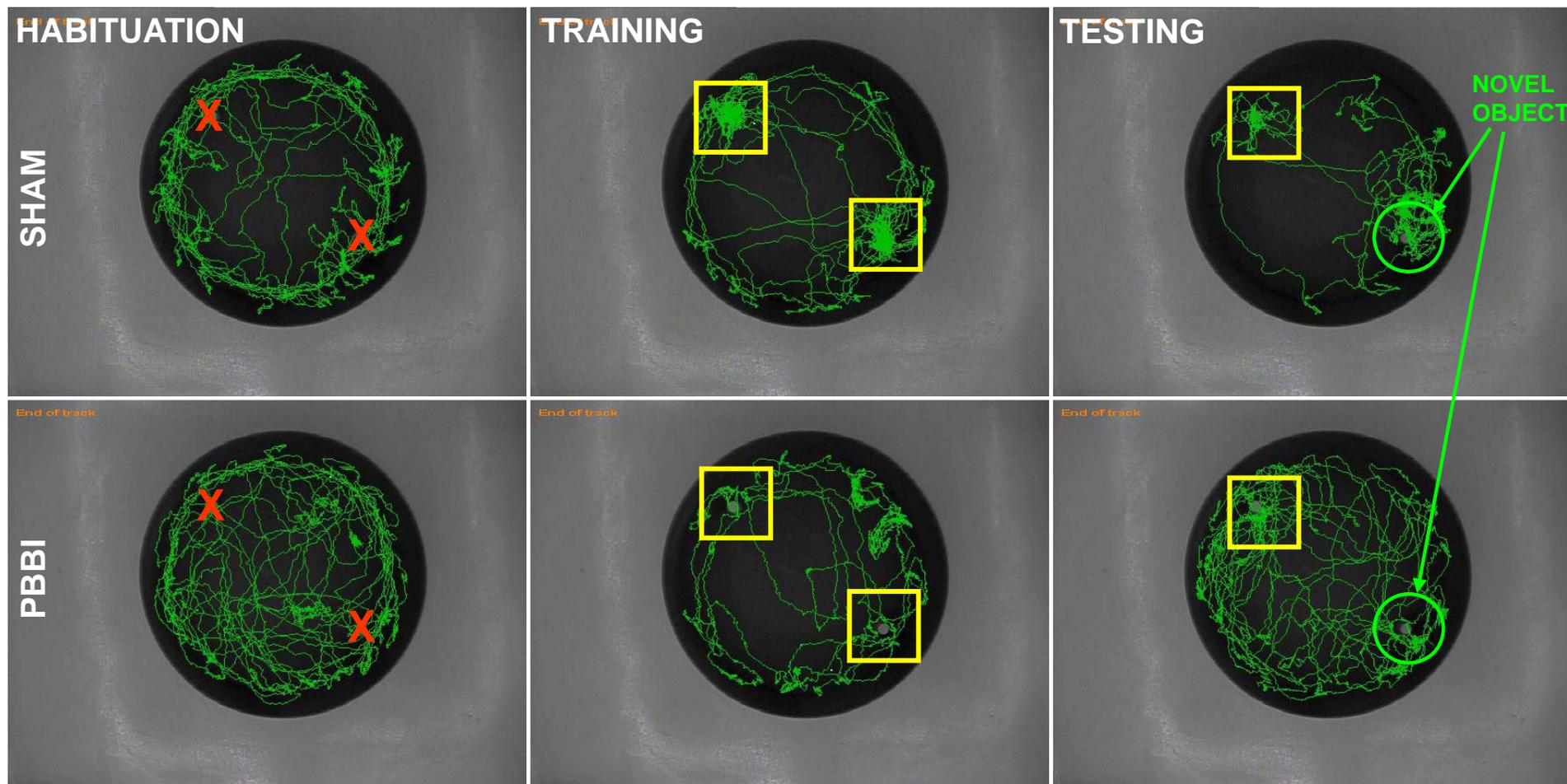
1. HABITUATION – exposed to empty open field
2. TRAINING – exposed to identical objects ( $A_1$  and  $A_2$ )
3. TESTING – exposed to one familiar ( $A_1$ ) and one novel ( $B_2$ ) object

**DISCRIMINATION INDEX:**  $DI = (B_2 - A_1 / B_2 + A_1)$  = the *difference between the time exploring the novel and the familiar object, corrected for the total time spent exploring both objects*. Higher DI scores indicate more time spent exploring the novel object and denote better memory retention of the familiar object.



# NOVEL OBJECT RECOGNITION

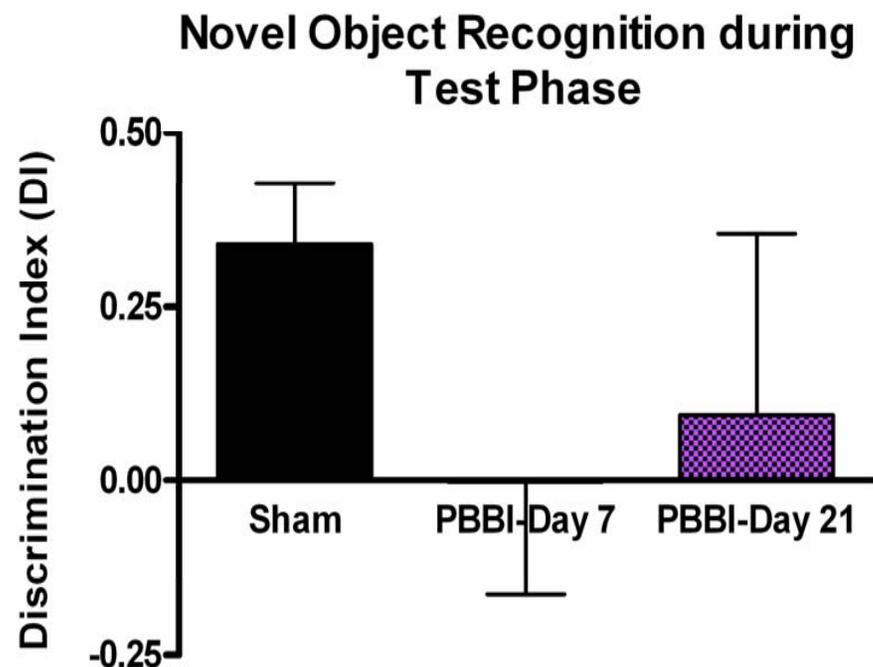
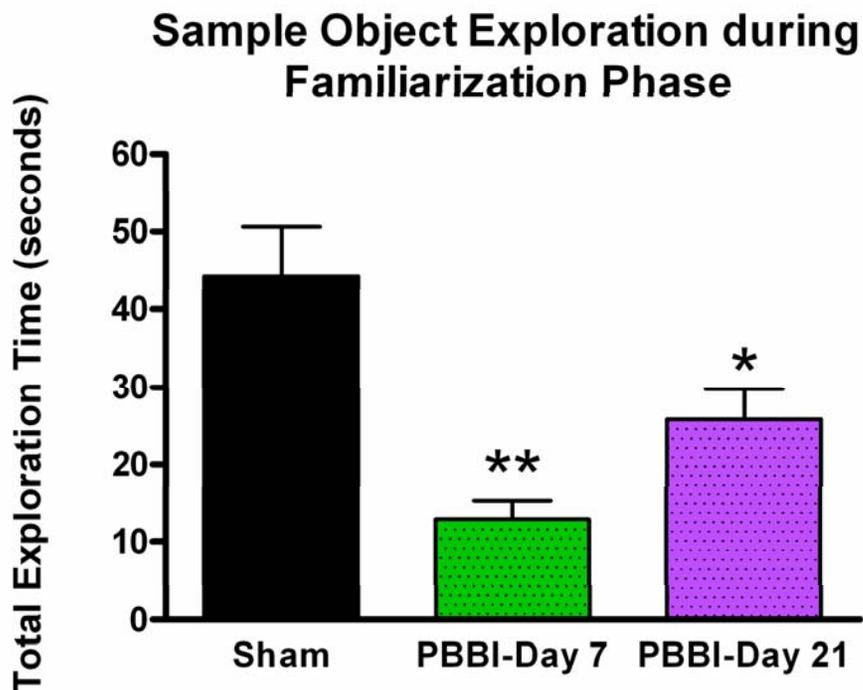
Sample pathways showing exploratory activity during Habituation, Training (2 identical objects), and Testing (3-h delay) for both SHAM (top row) and PBBI (bottom row) rats.





# NOVEL OBJECT RECOGNITION

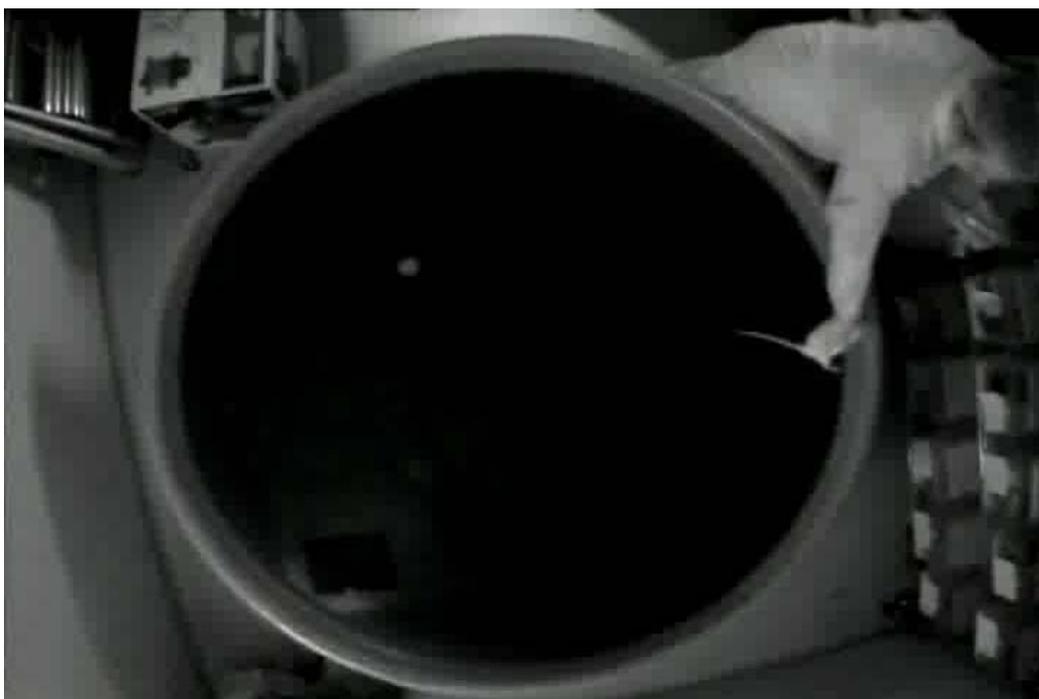
The NOR deficits observed in PBBI animals were not significant due to the large degree of within-group variability



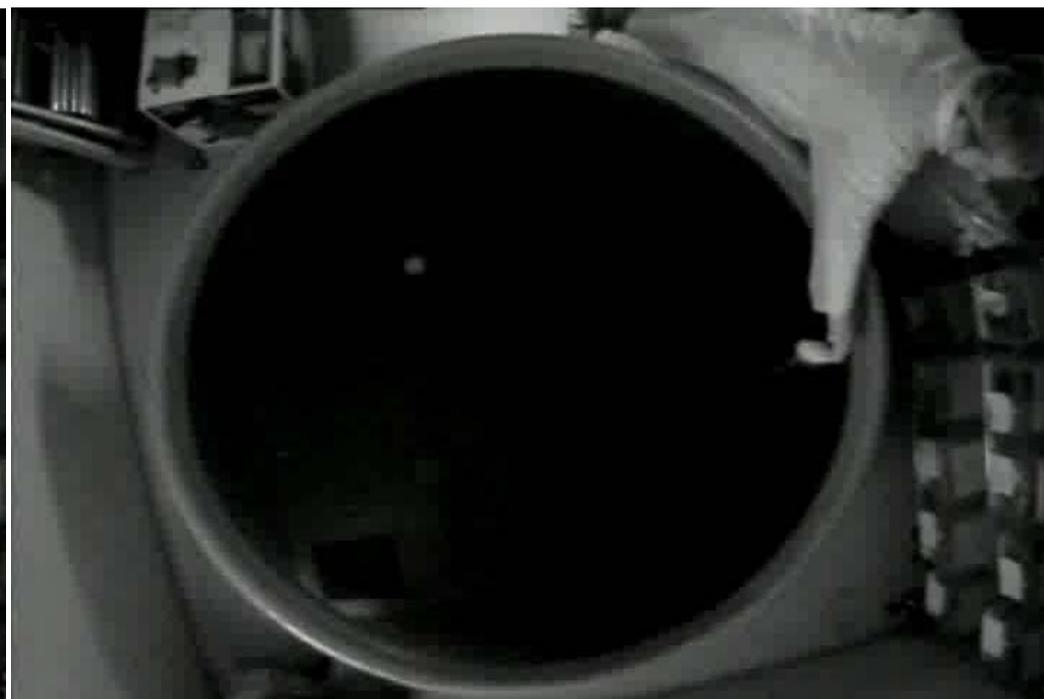


# MORRIS WATER MAZE

Animals are given 4 trials per day (30-m ITI) for 5 consecutive days.



**SHAM**  
(2X normal speed)

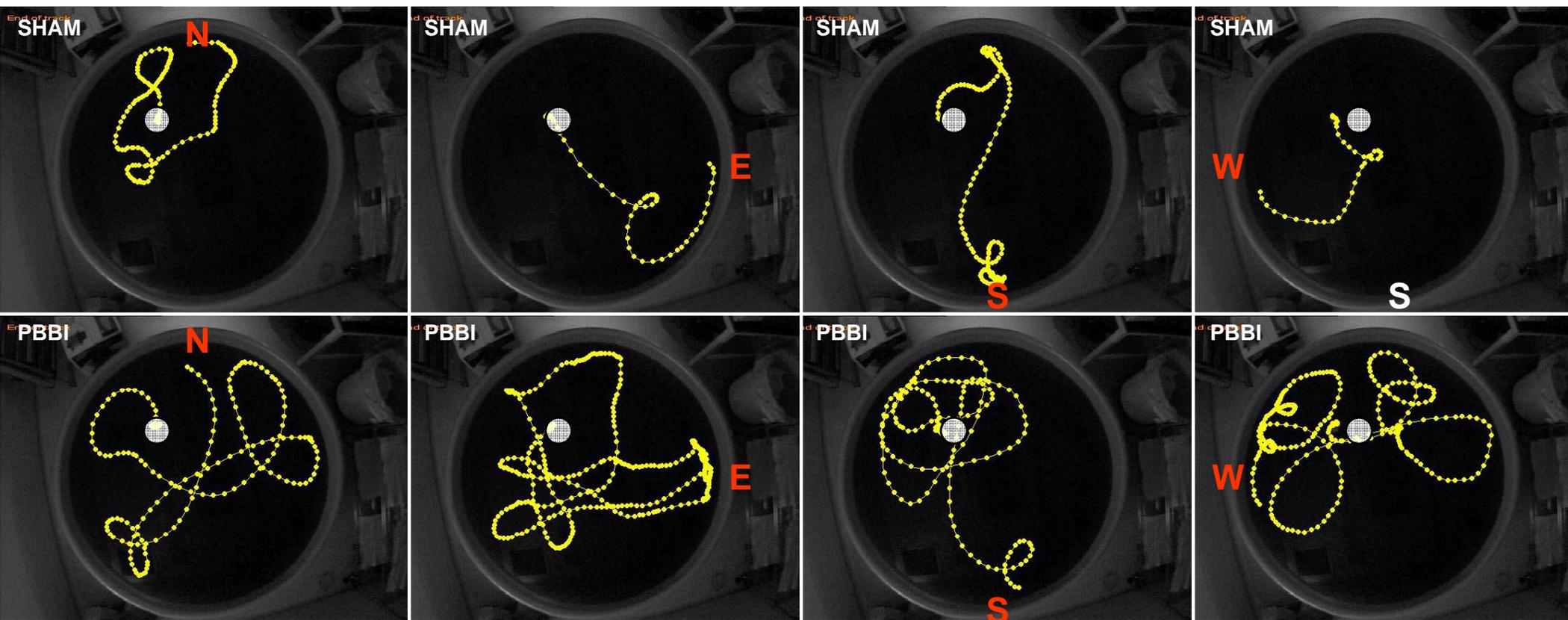


**PBBI**  
(4X normal speed)



# MORRIS WATER MAZE

Sample pathways on the final day of MWM testing (1 week post-PBBI)

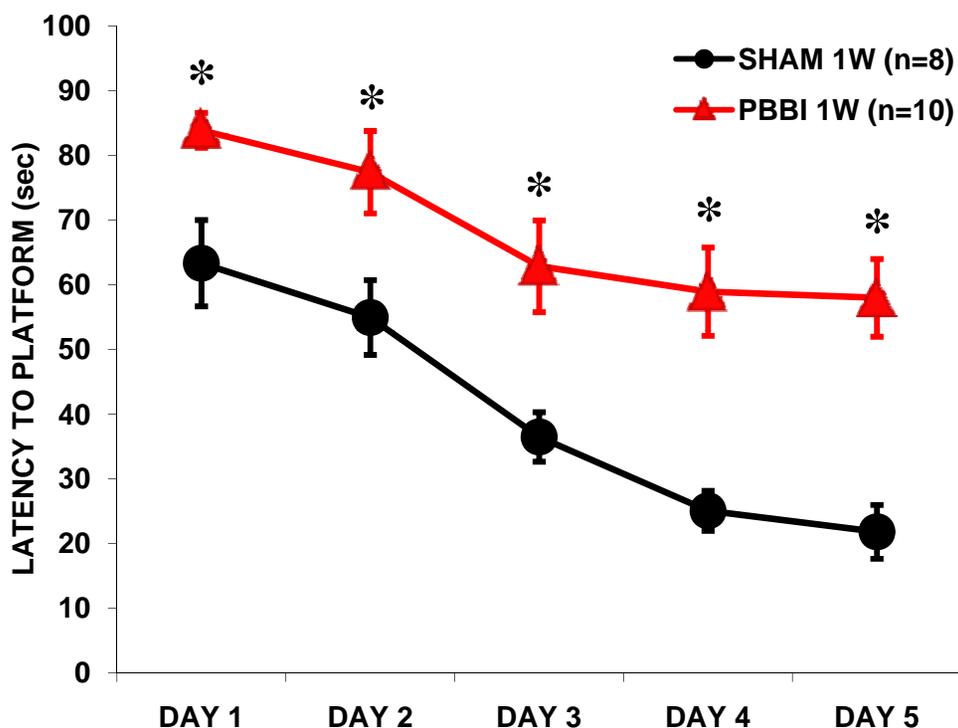




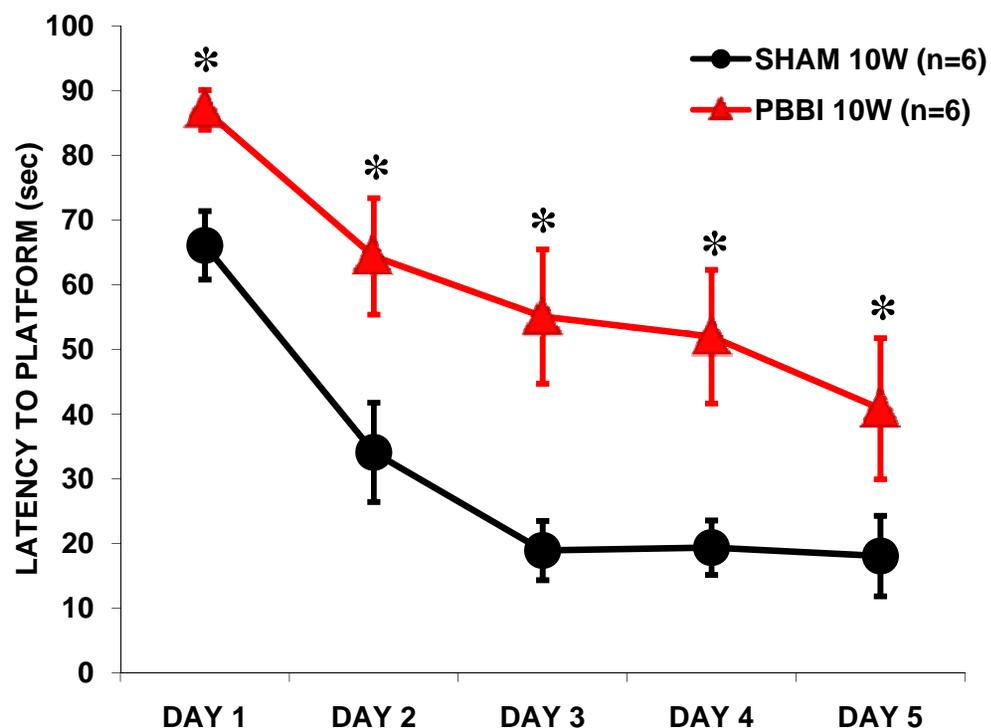
# MORRIS WATER MAZE

**PBBI produces significant cognitive deficits in the MWM sustained out to 10 weeks post-injury**

**A. MWM: 1 week post-PBBI**



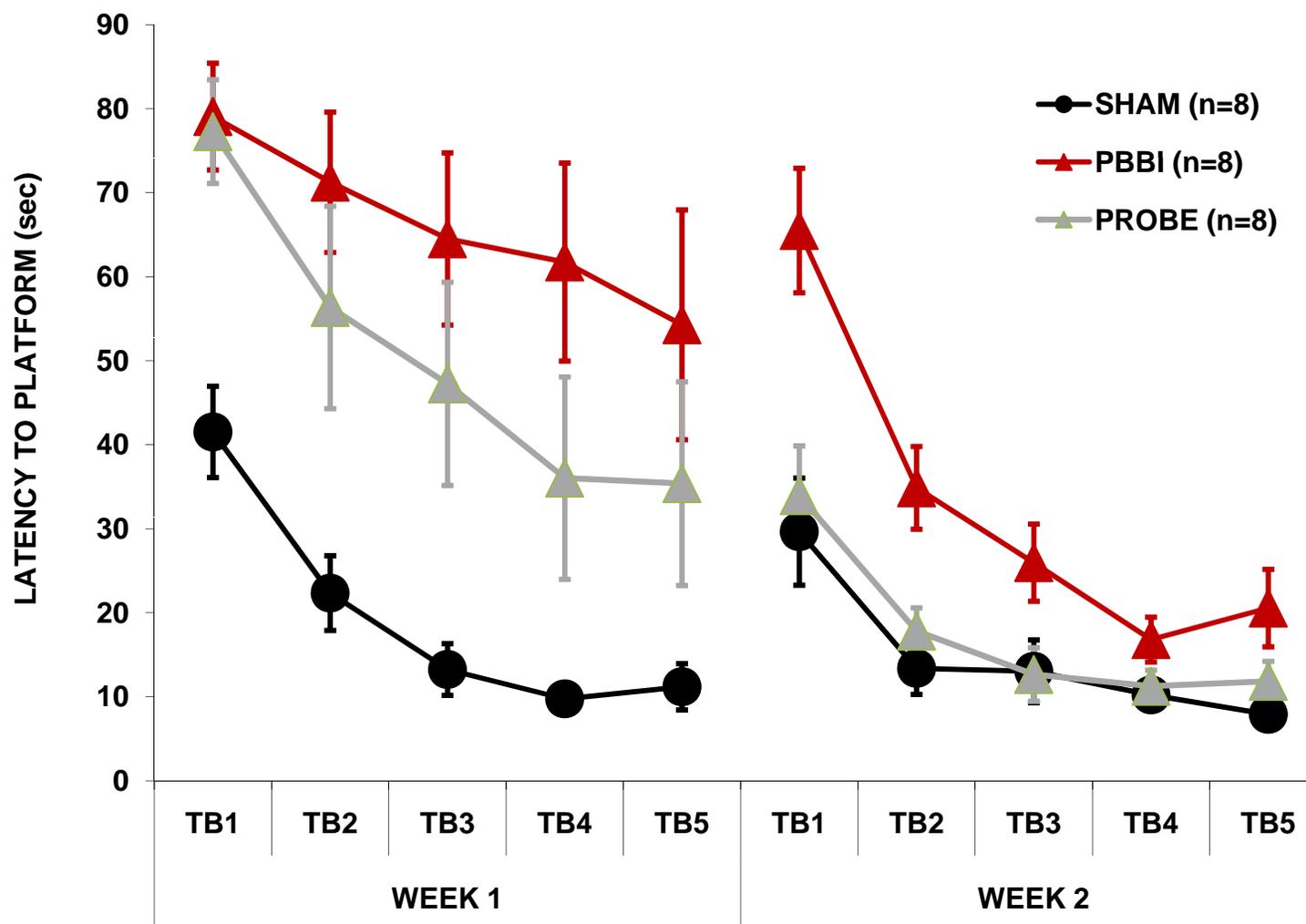
**B. MWM: 10 weeks post-PBBI**





# MORRIS WATER MAZE

## Effects of repeated testing (2 weeks) on PBBI-induced cognitive deficits





# CONCLUSIONS

- **The NOR deficits observed in PBBI animals were not significant, due to the large degree of within-group variability, indicating this task may not be appropriate for the PBBI model.**
- **PBBI consistently produced significant cognitive deficits in the MWM at comparable rates during both the acute (1 week) and chronic (10 weeks) post-injury phase.**
- **The slow learning curve of the PBBI animals in the MWM provides a large window of opportunity for therapeutic intervention.**



# POSTER SESSION

- N13:** *A Comparison of Two Cognitive Test Paradigms in a Military-Relevant Traumatic Brain Injury Model.* Davis A, Shear DA, Chen Z, Lu X-C M, & Tortella FC.
- N15:** *Longitudinal Characterization of Cognitive Deficits in an Experimental Model of Penetrating Ballistic-Like Brain Injury using the Morris Water Maze.* Shear DA, Pedersen RC, Bombard MC, Lu X-C M, & Tortella FC.
- N14:** *Dose-Response Profile of NA-1, a Novel PSD-95 Blocker, in a Military-Relevant Model of Penetrating Ballistic-Like Brain Injury.* Shear DA, Lu X-C M, & Tortella FC.



# ACKNOWLEDGMENTS

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