Advancing environmental enrichment as a pre-clinical model of neurorehabilitation

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President Elect, National Neurotrauma Society

UPMC Rehabilitation Institute

Preconditioning in Biology and Medicine: Mechanisms and Translational Research
University of Massachusetts, Amherst
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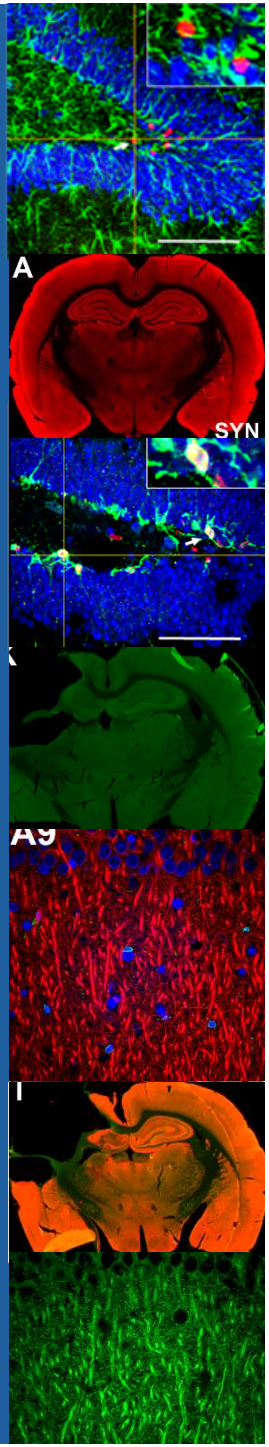
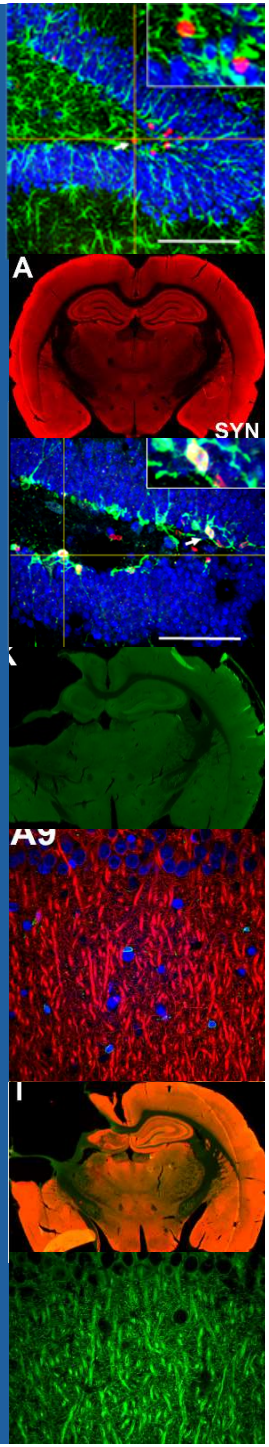
Conference Directors: Ed Calabrese, PhD and Paul Kostecki, PhD



Traumatic brain injury is a significant health care issue

Affects 1.5 to 2 million in the United States each year

- 300,000 are severe (GCS <8)
- 50,000 die
- 100,000 long-term disabilities
- Estimated cost > $75 billion
- Survivable problem
- Evaluation of potential therapies needed



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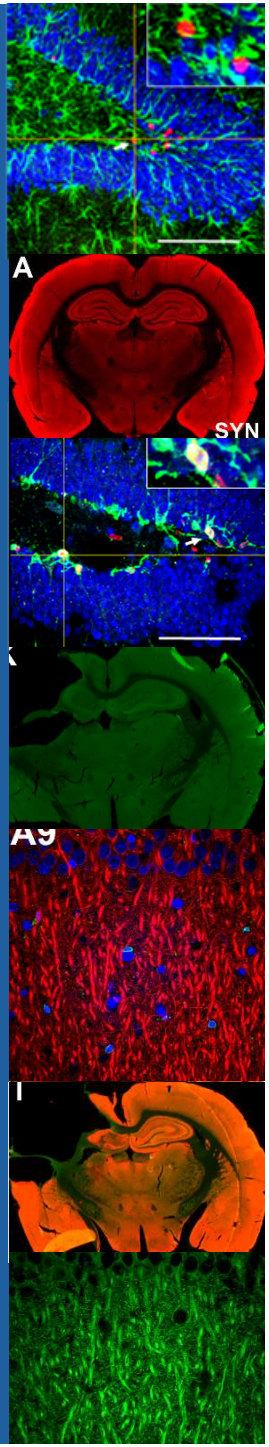

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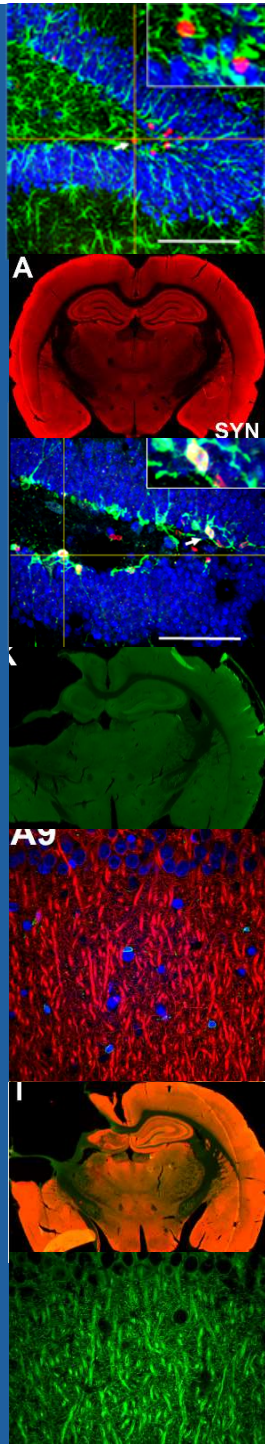

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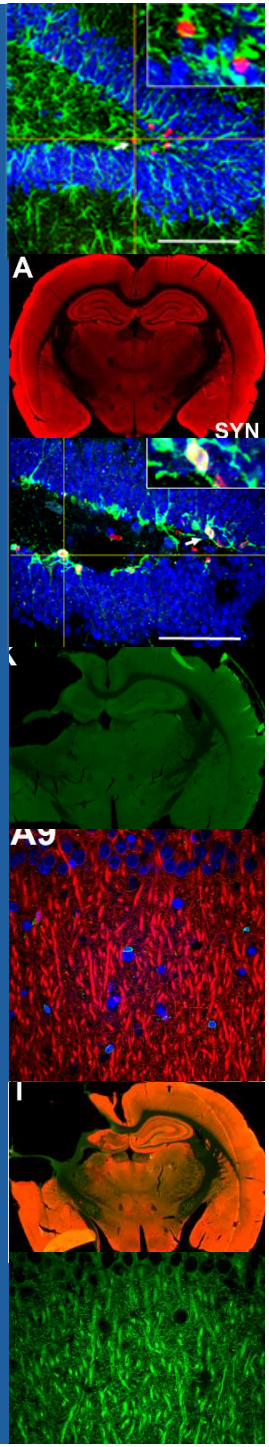

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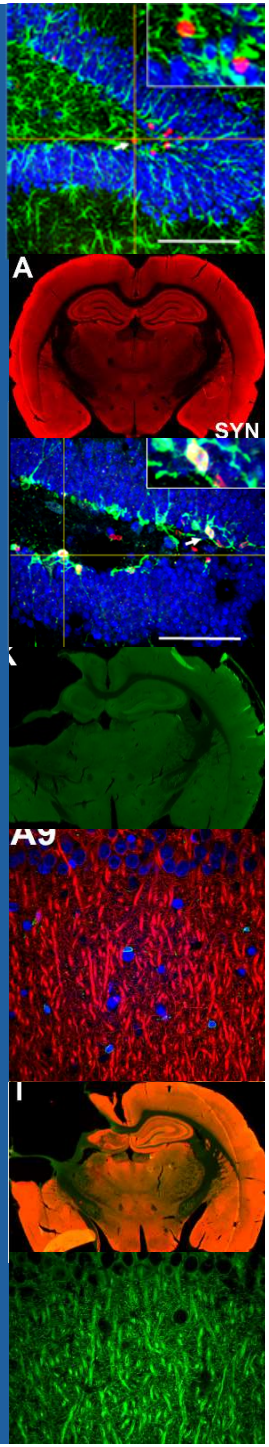

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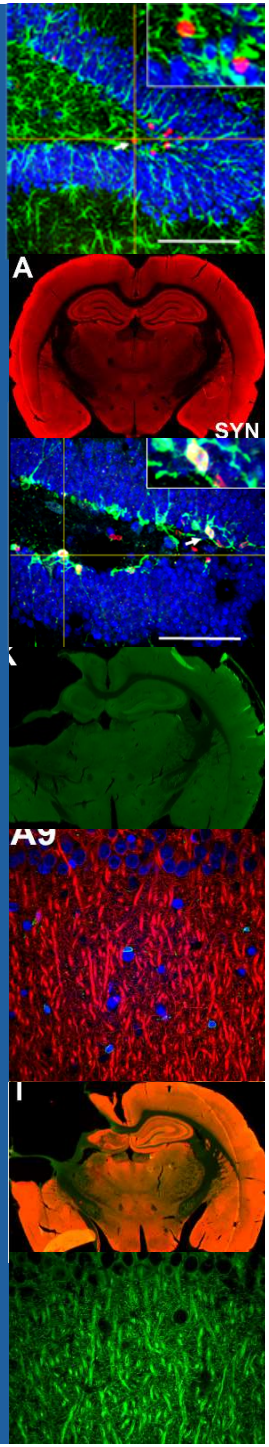

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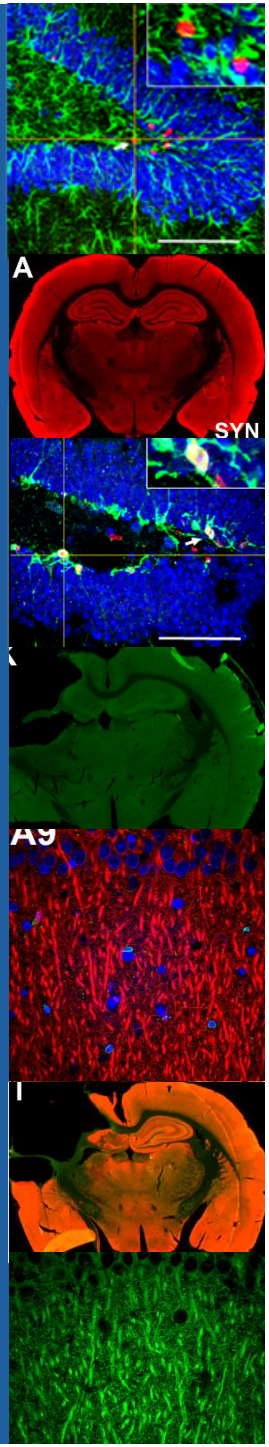

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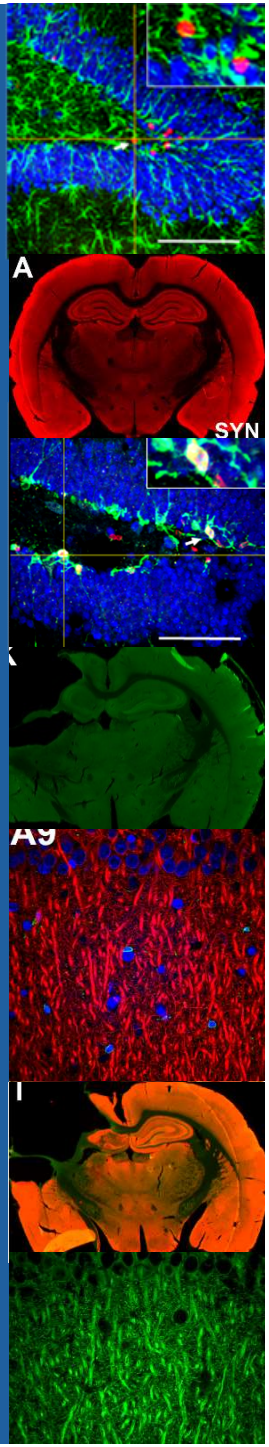

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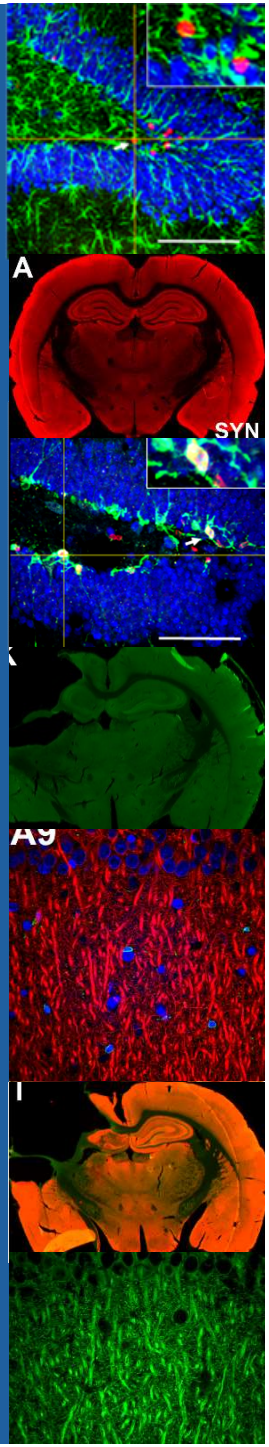
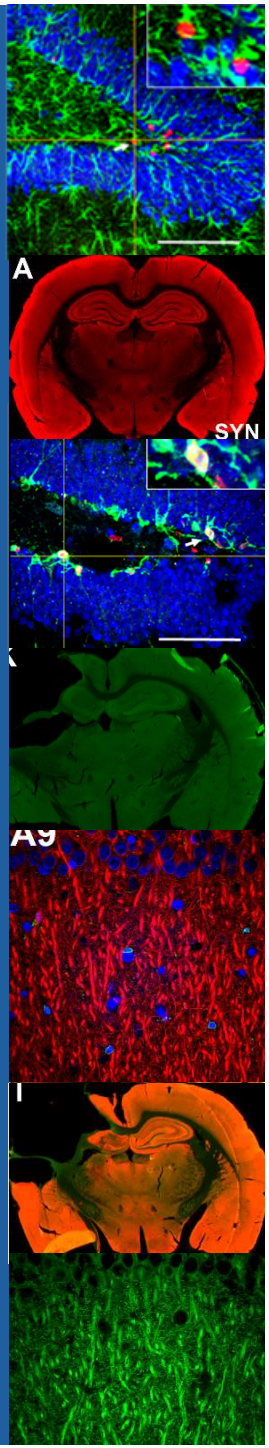


Characteristics of environmental enrichment

- 36 x 30 x 20 inches
- Various objects (i.e., toys) for stimulation
- To maintain novelty, the objects are rearranged every day and changed each time the cage is cleaned
- 10-12 rats, which includes a subset of all groups, are housed together
- Non-invasive and reasonable rodent analogue of clinical rehabilitation
- Improves spatial learning after CCI (Kline et al., 2007, 2012; Hoffman et al., 2008; Sozda et al., 2010; Matter et al., 2011; de Witt et al., 2011; Bondi et al., 2014) and FP (Hamm et al., 1996; Hicks et al., 2002; Giza et al., 2005)
- Enhances beam-walking after CCI (Hoffman et al., 2008) or cortical lesions (Held et al., 1985; Gentile et al., 1987; Rose et al., 1987)
- Reduces cortical lesion volume and hippocampal CA_3 cell loss after FP (Passineau et al., 2001) and CCI injury (Kline et al., 2007; Hoffman et al., 2008; Monaco et al., 2013; Radabaugh et al., 2016)



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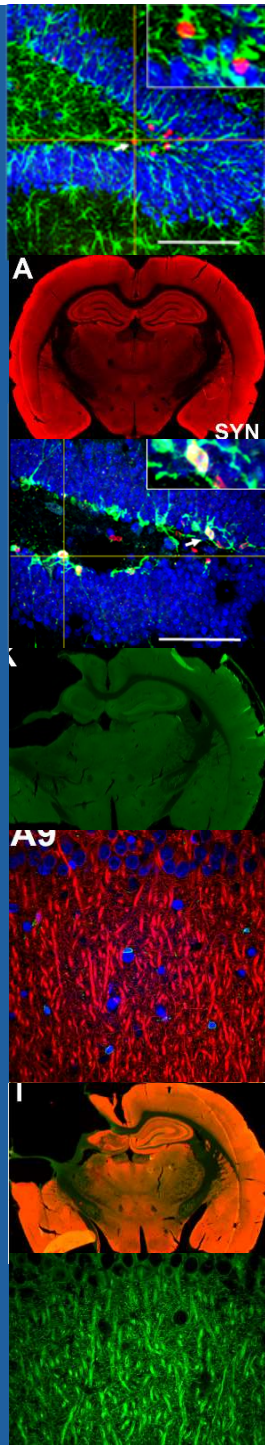
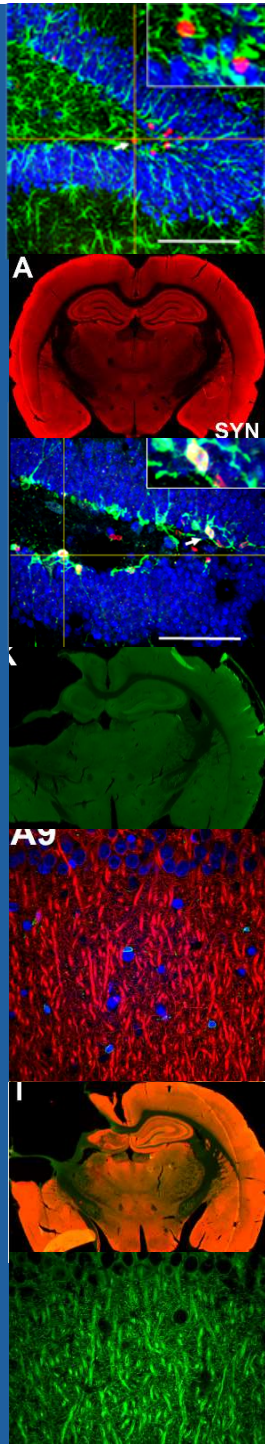
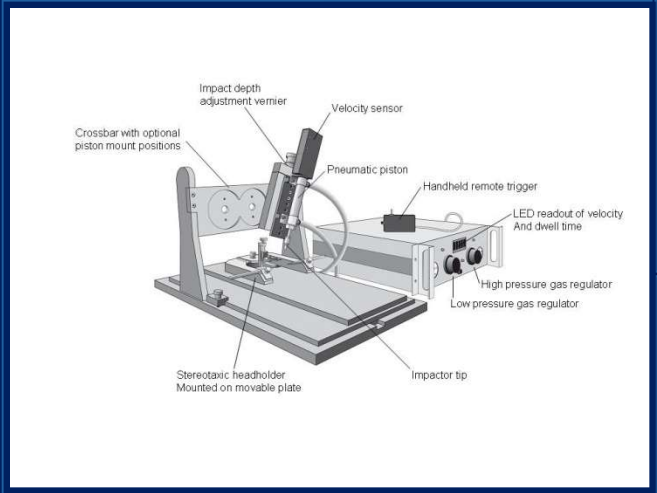


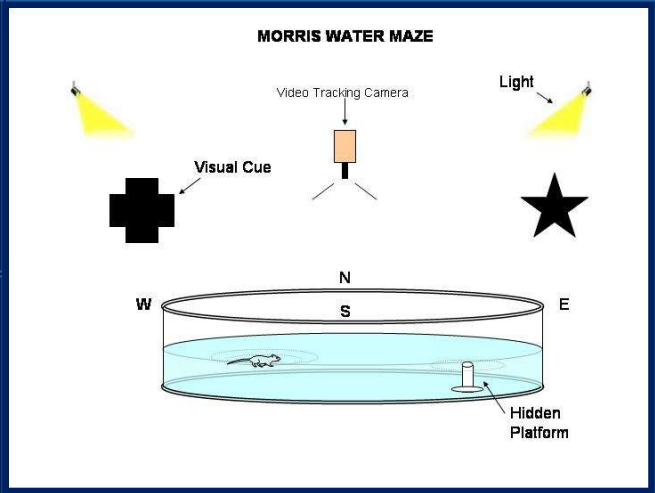
Outline

- Typical EE
- Long-term EE
- Abbreviated EE (early)
- Abbreviated EE (delayed)
- Typical EE + haloperidol



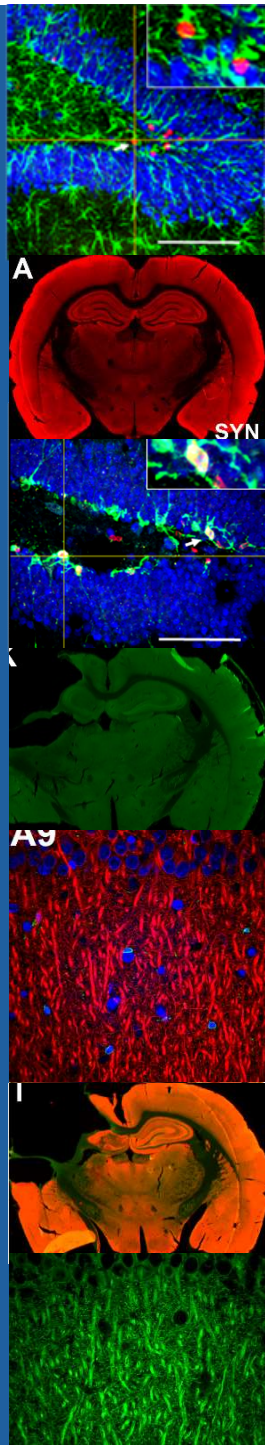
Methods: overview





Histology

Well-established model of TBI that mimics many of the characteristics of human brain injury (e.g., contusion, hemorrhage, hematoma, axonal injury, cell loss, alterations in cerebral blood flow, behavioral deficits, etc)



Environmental enrichment (typical)

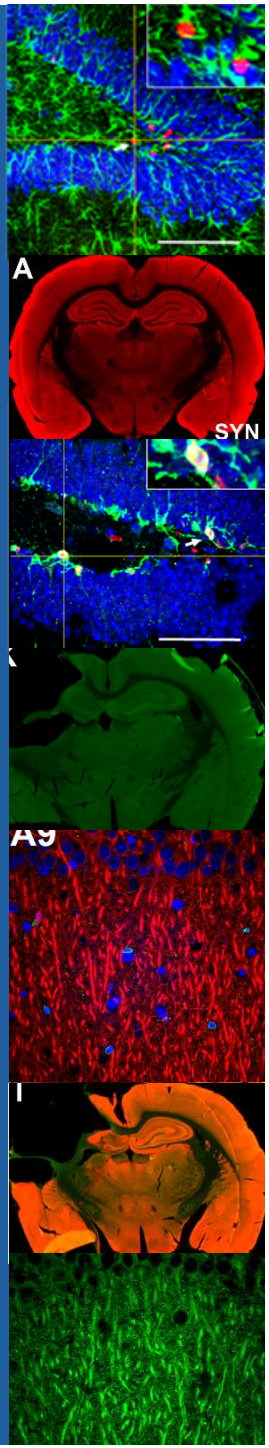
Motor training | Pre-assessment and surgery | Sacrifice

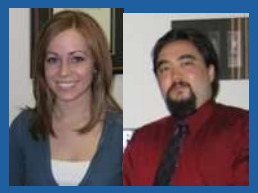
Acclimatization | Beam tests | Water maze

-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

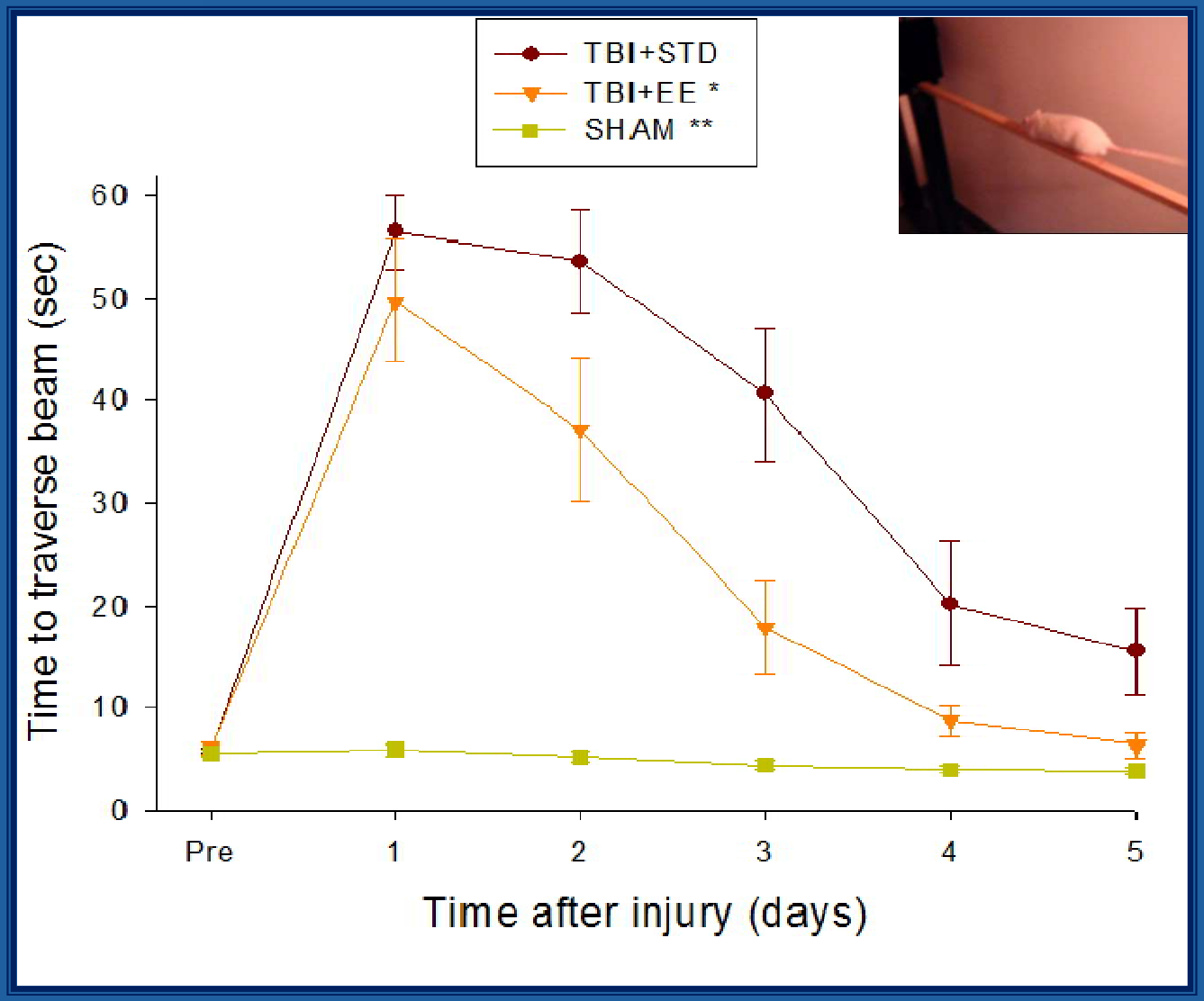
EE (typical) 36” x 30” cage; sensory stimuli (toys); social housing (10 rats)

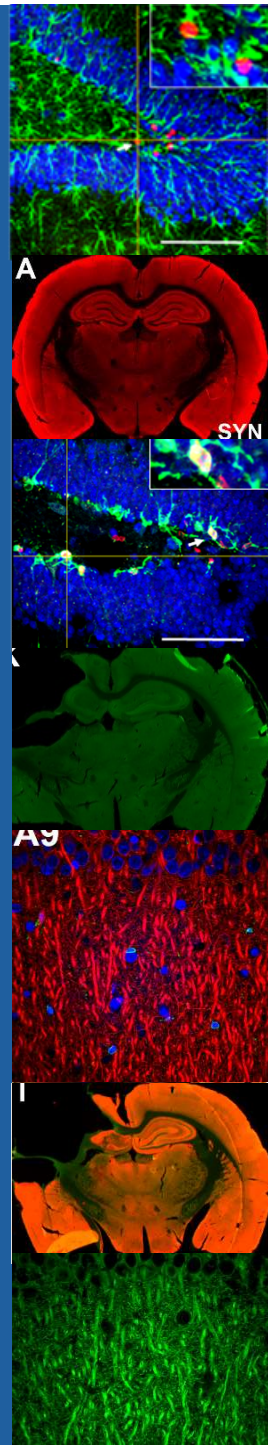
STD (typical) 8” x 9” x 15” cage; no sensory stimuli (no toys); no social housing (2 rats)



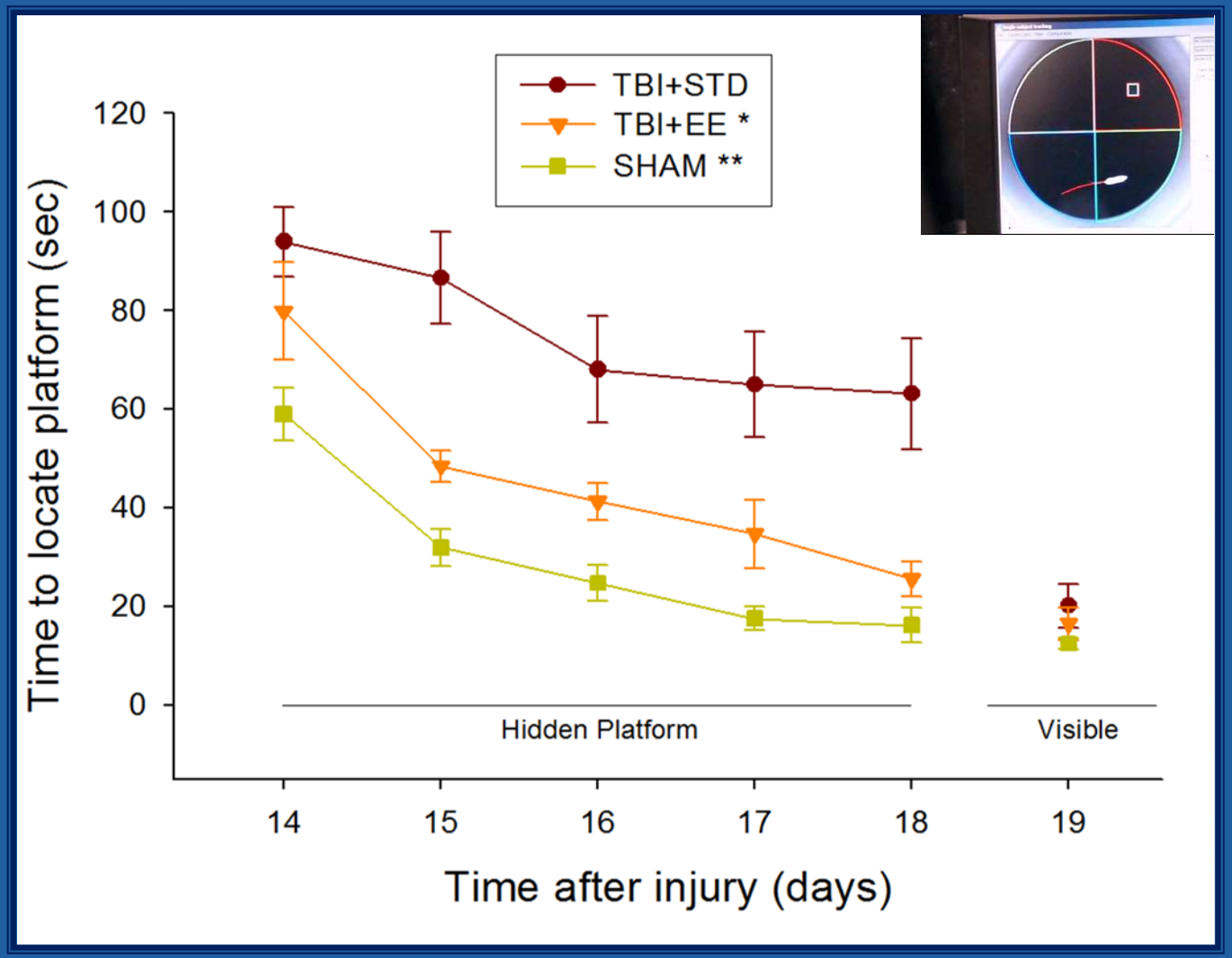


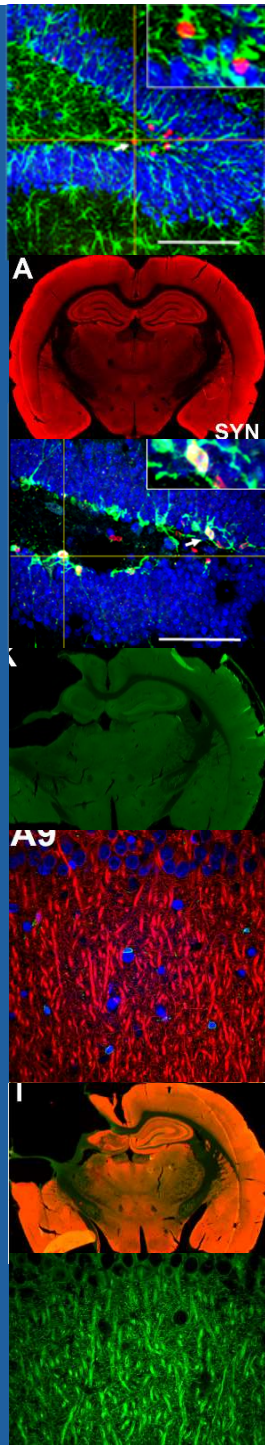
Typical EE: beam-walk (males)



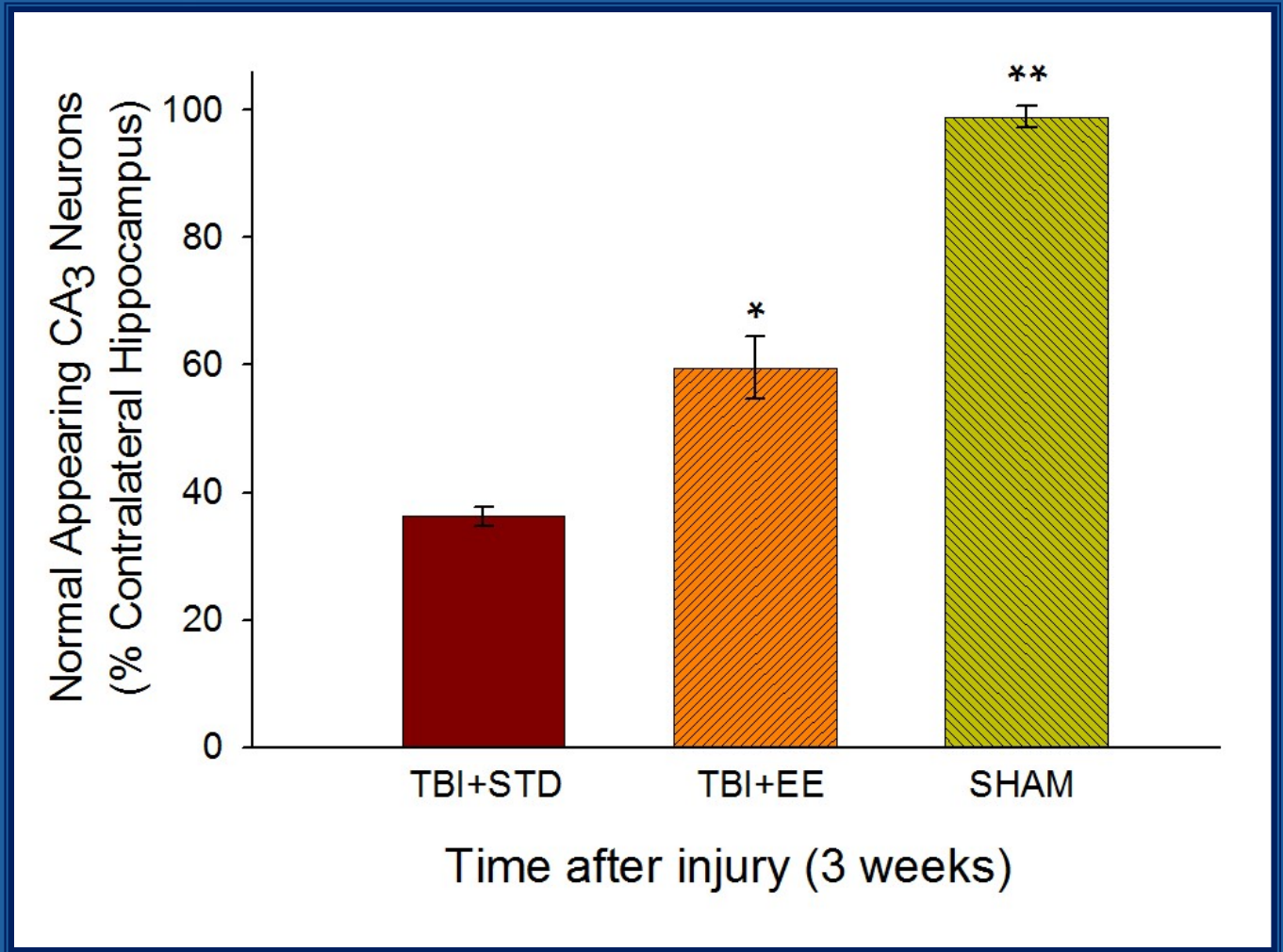


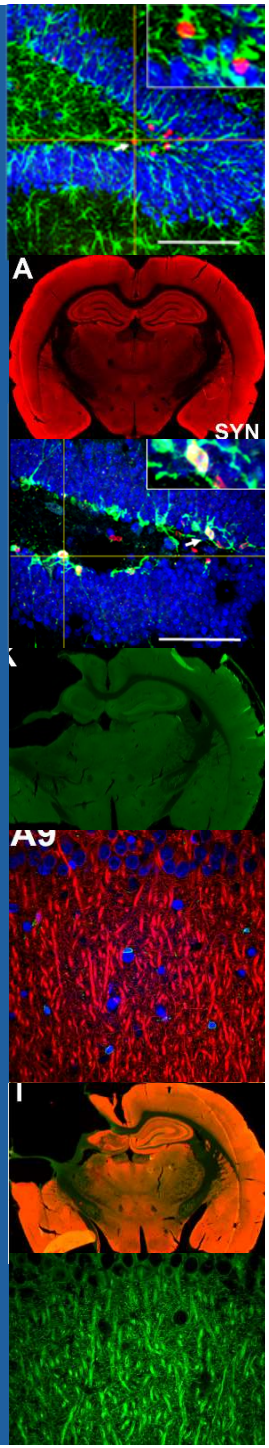
Typical EE: water maze (males)



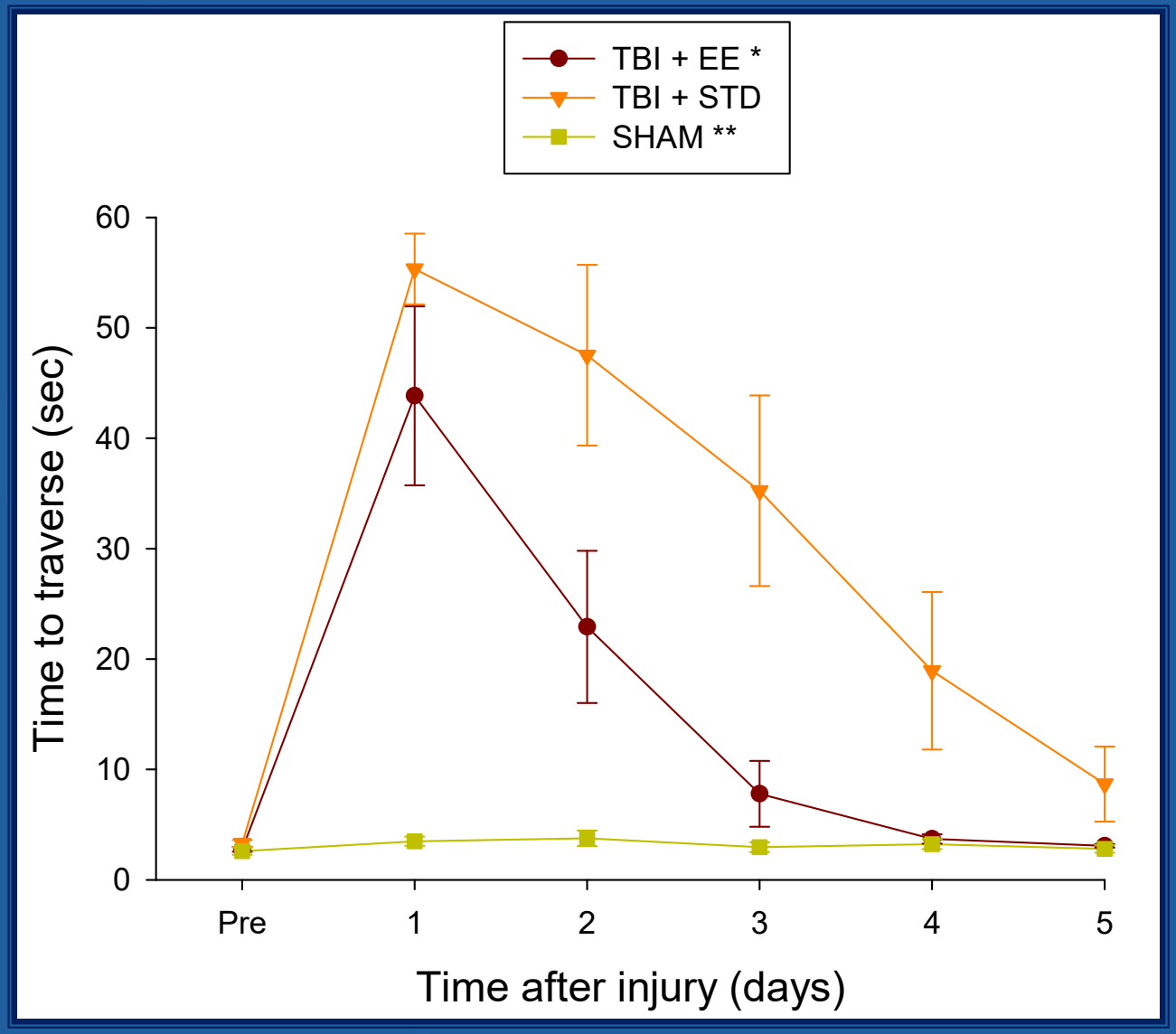


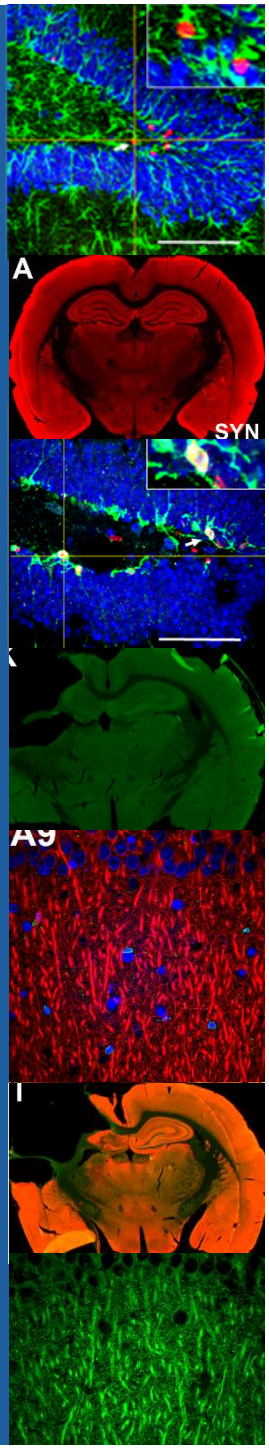
Typical EE: histology (males)



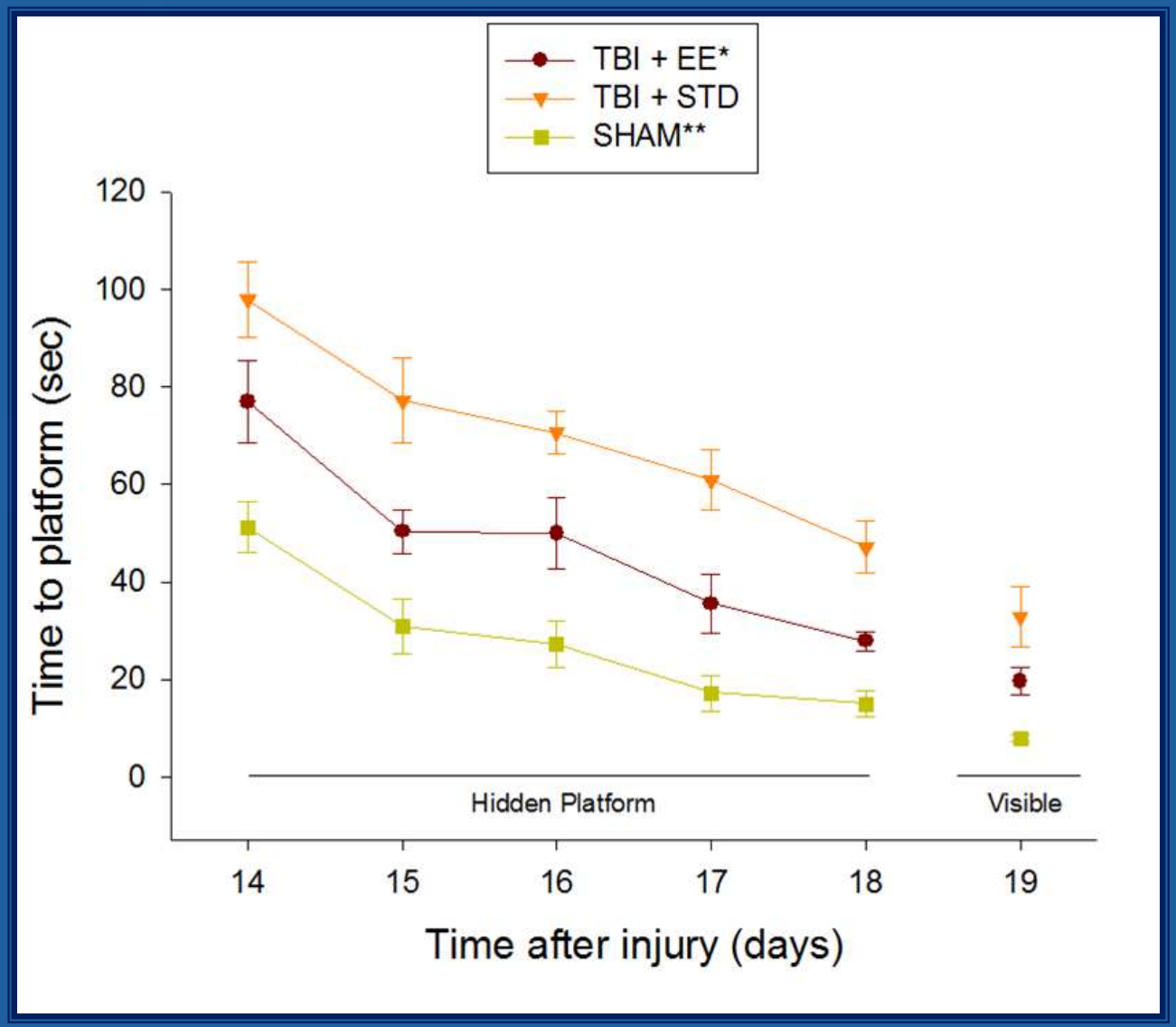


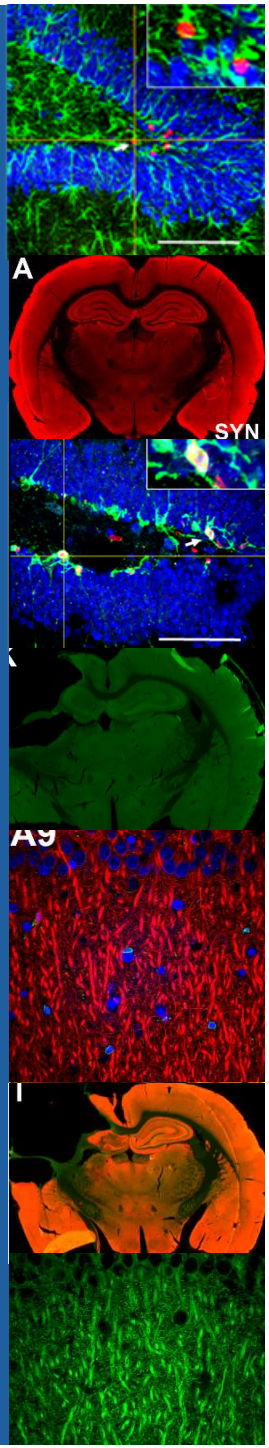
Typical EE: beam-walk (females)



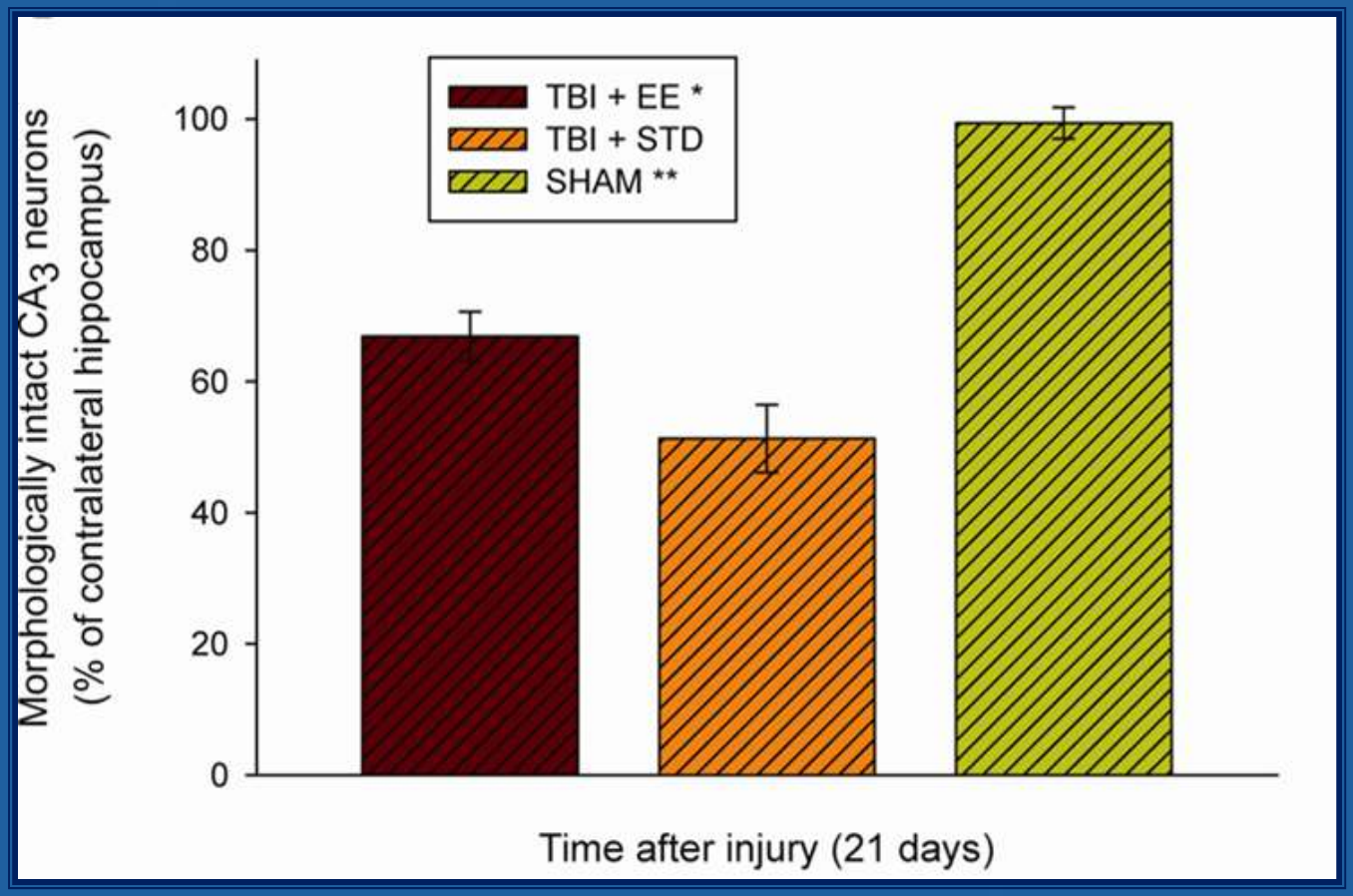


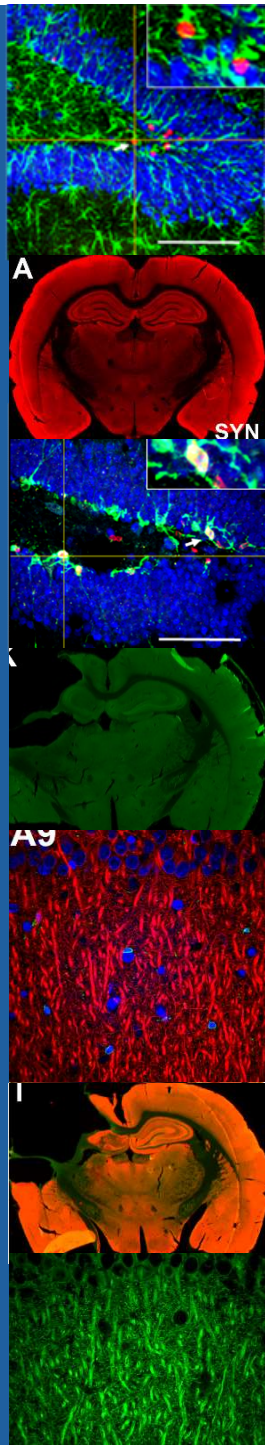
Typical EE: water maze (females)





Typical EE: histology (females)

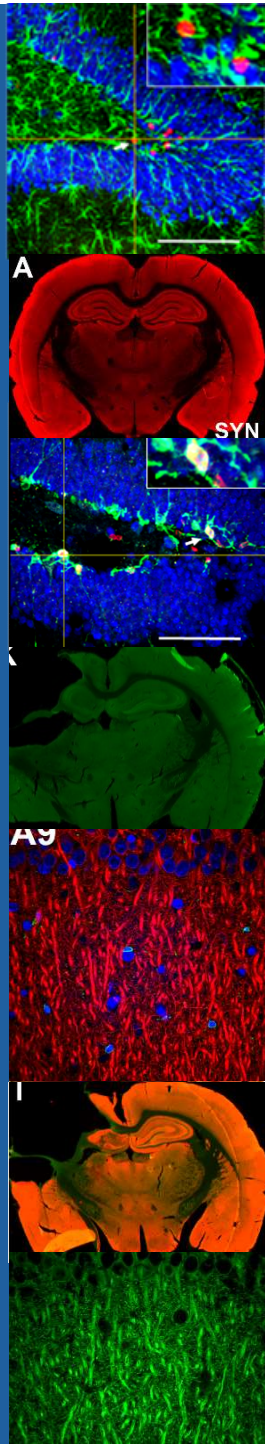




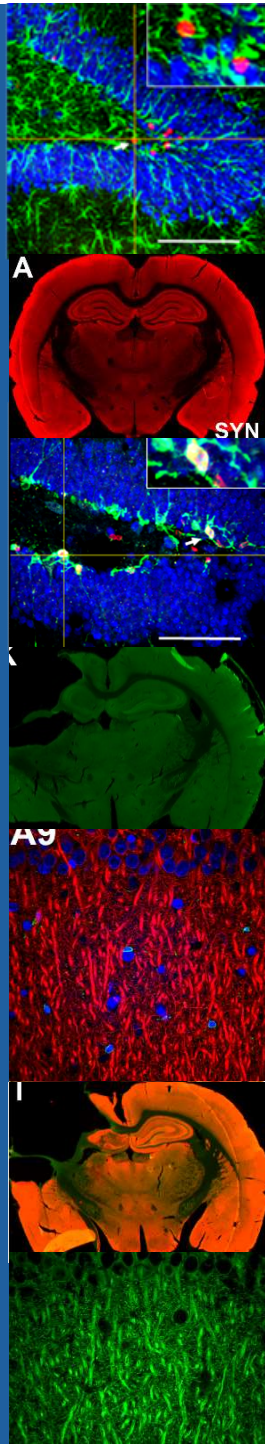
Summary

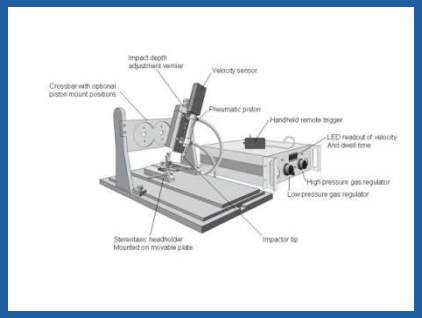
- Typical EE improves motor (beam-walking) and cognitive (Morris water maze) performance vs STD in **both male and female** rats

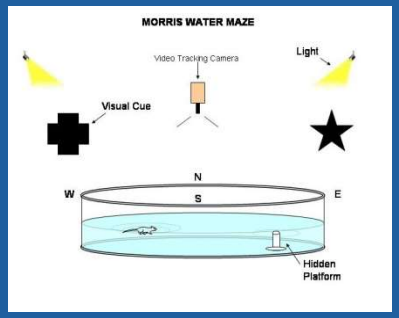
- Typical EE also protects against hippocampal CA_3 cell loss after TBI in **both male and female** rats

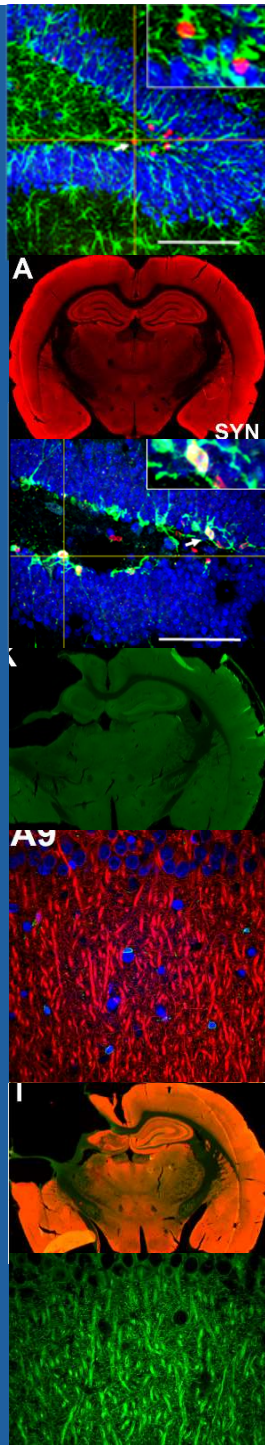


Long-term environmental enrichment







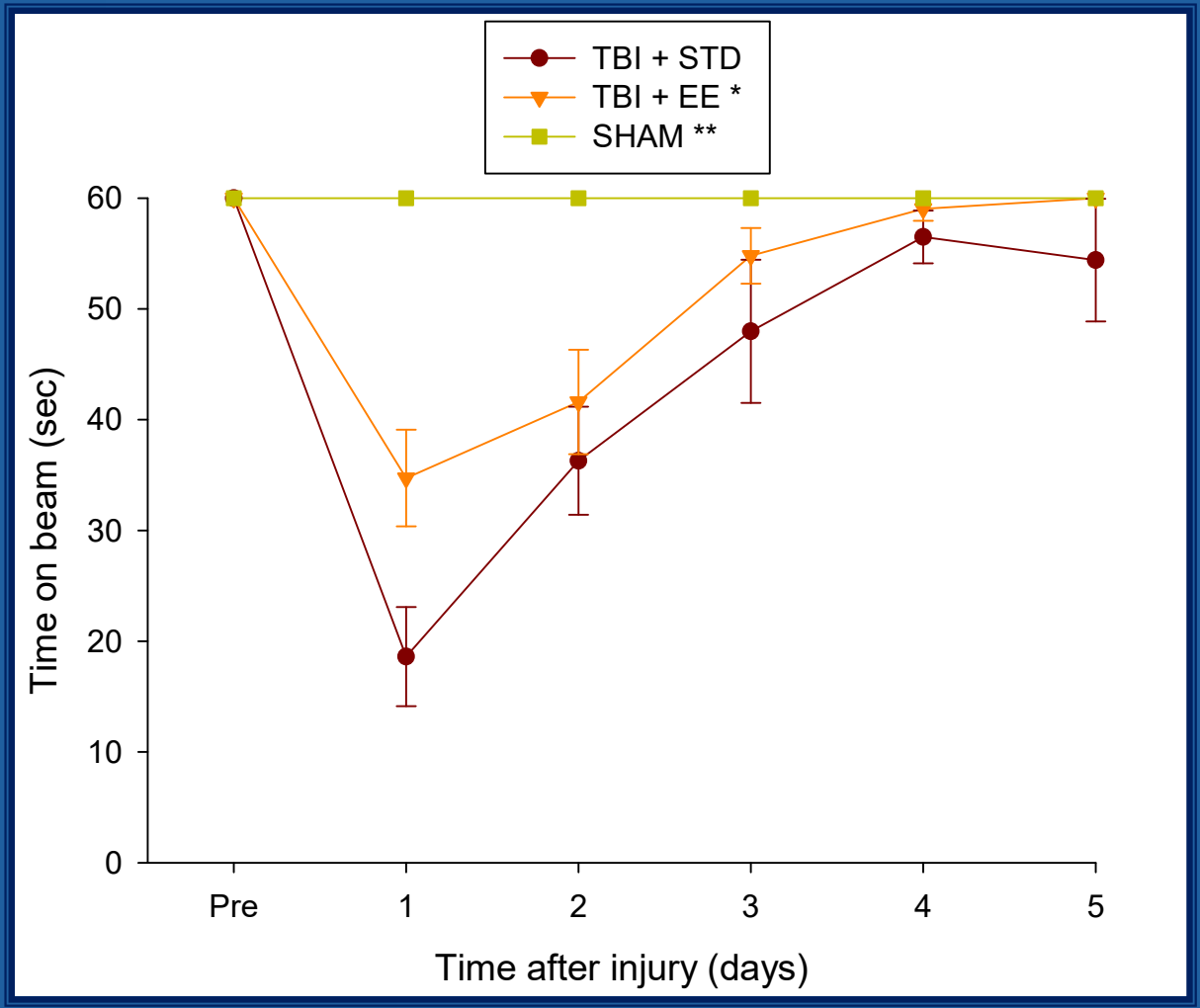


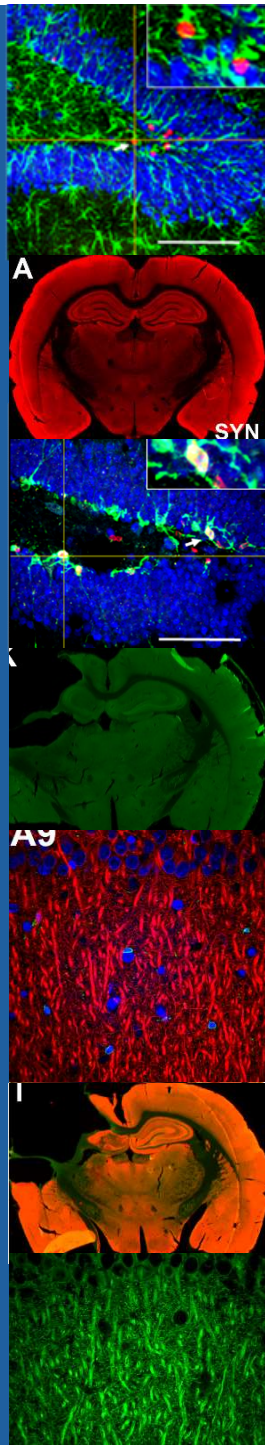
Began with 2X as many EE rats vs STD so that after 3 weeks, ½ would continue in EE for 6 months and the other ½ would be placed in STD housing.

Phase 1: TBI + STD, TBI + EE, Sham STD, Sham EE

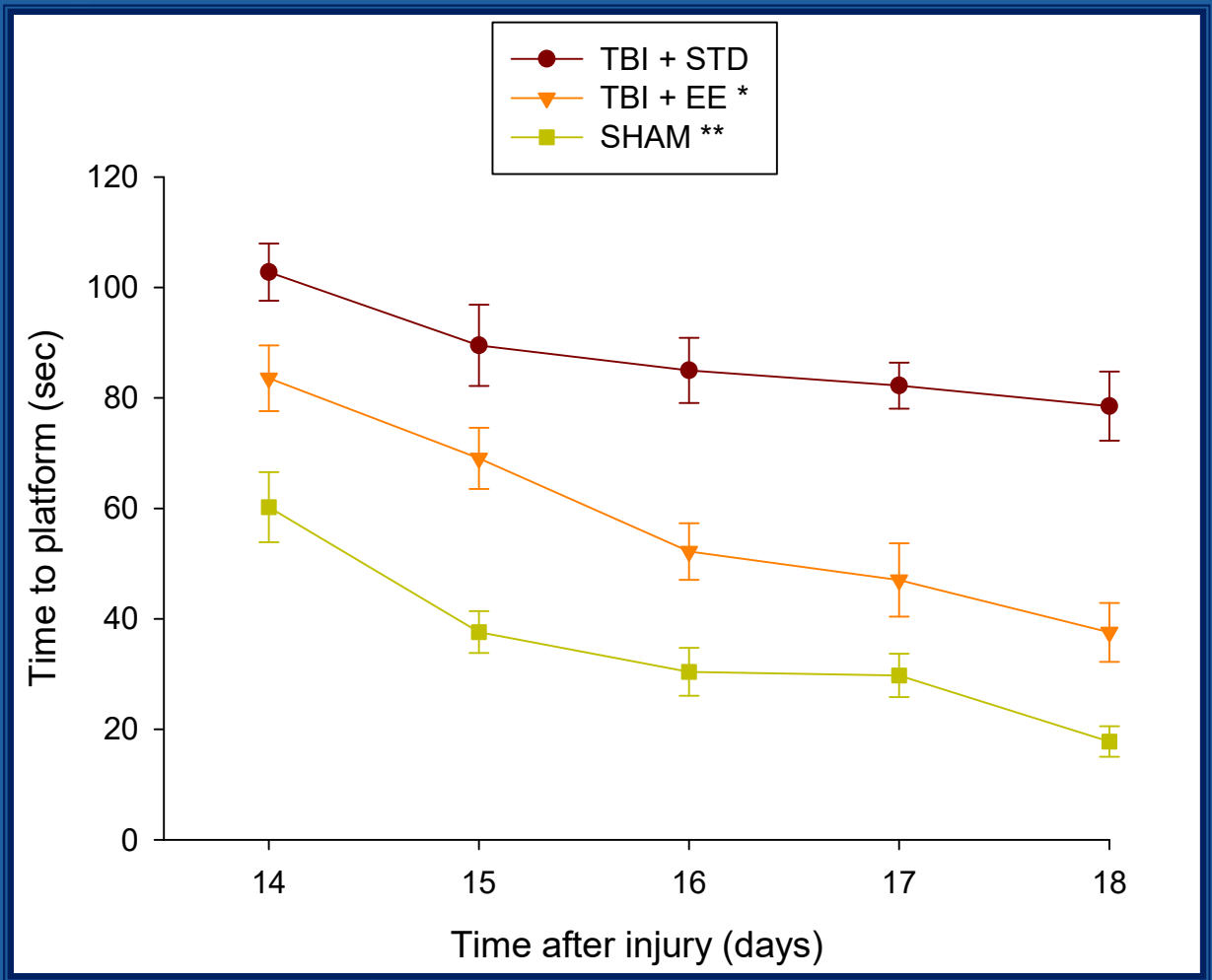
Phase 2: TBI + STD, TBI + EE, TBI + EE + STD, Shams

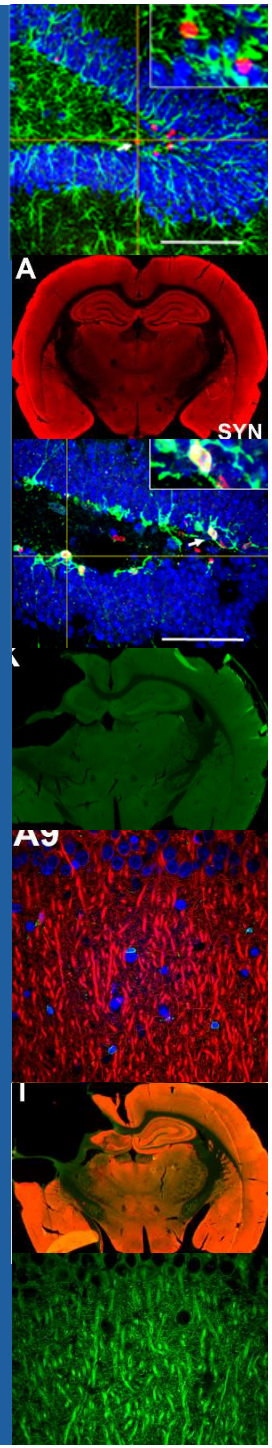
Beam balance: phase 1



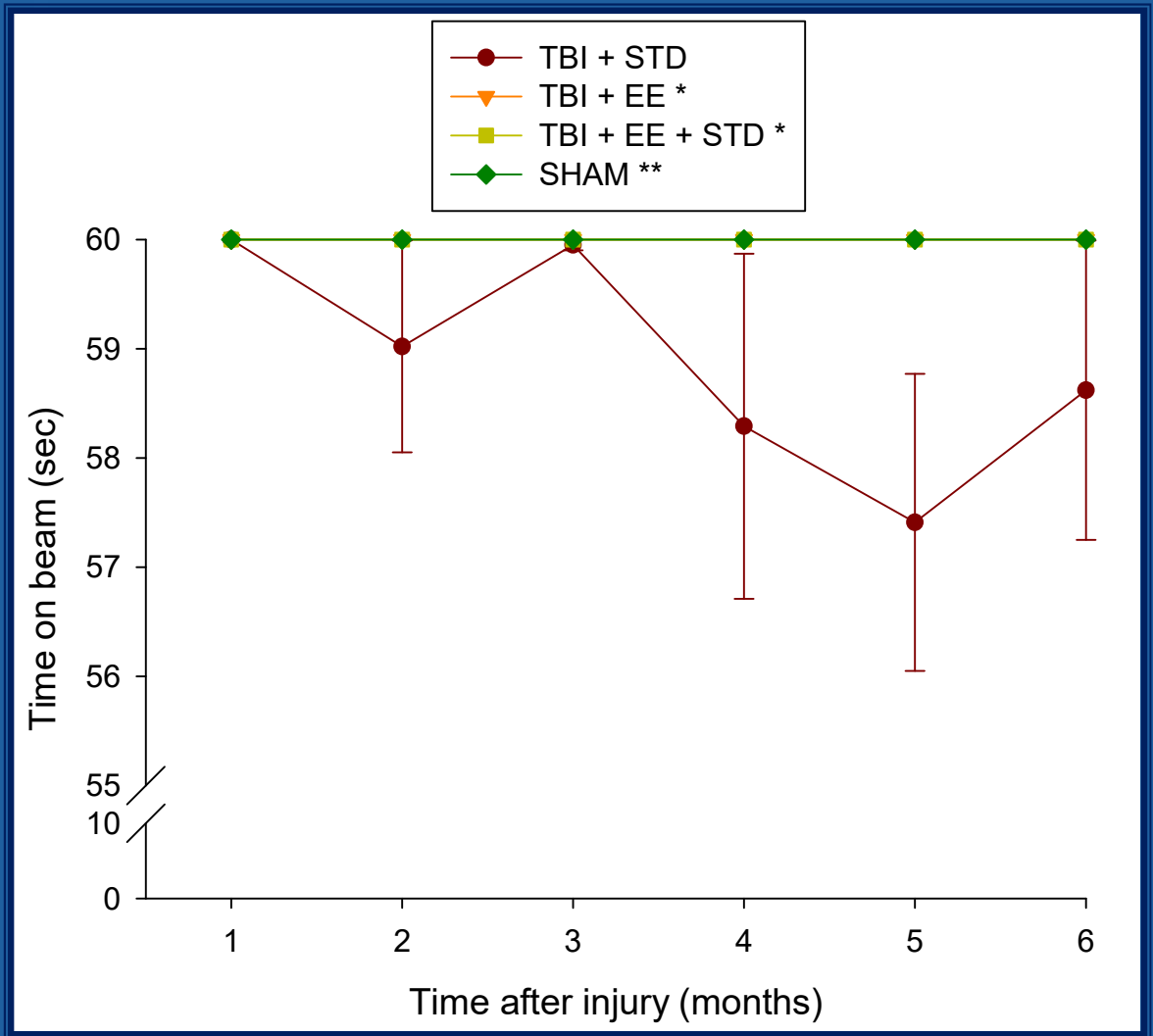


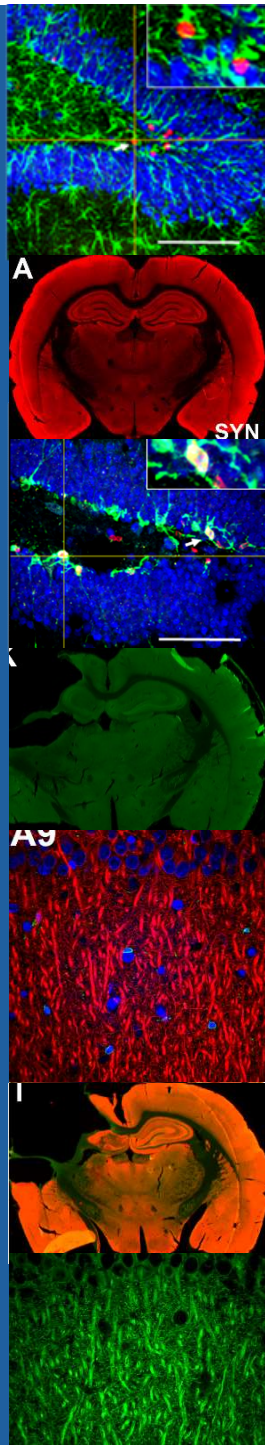
Spatial learning: phase 1





Beam balance: phase 2





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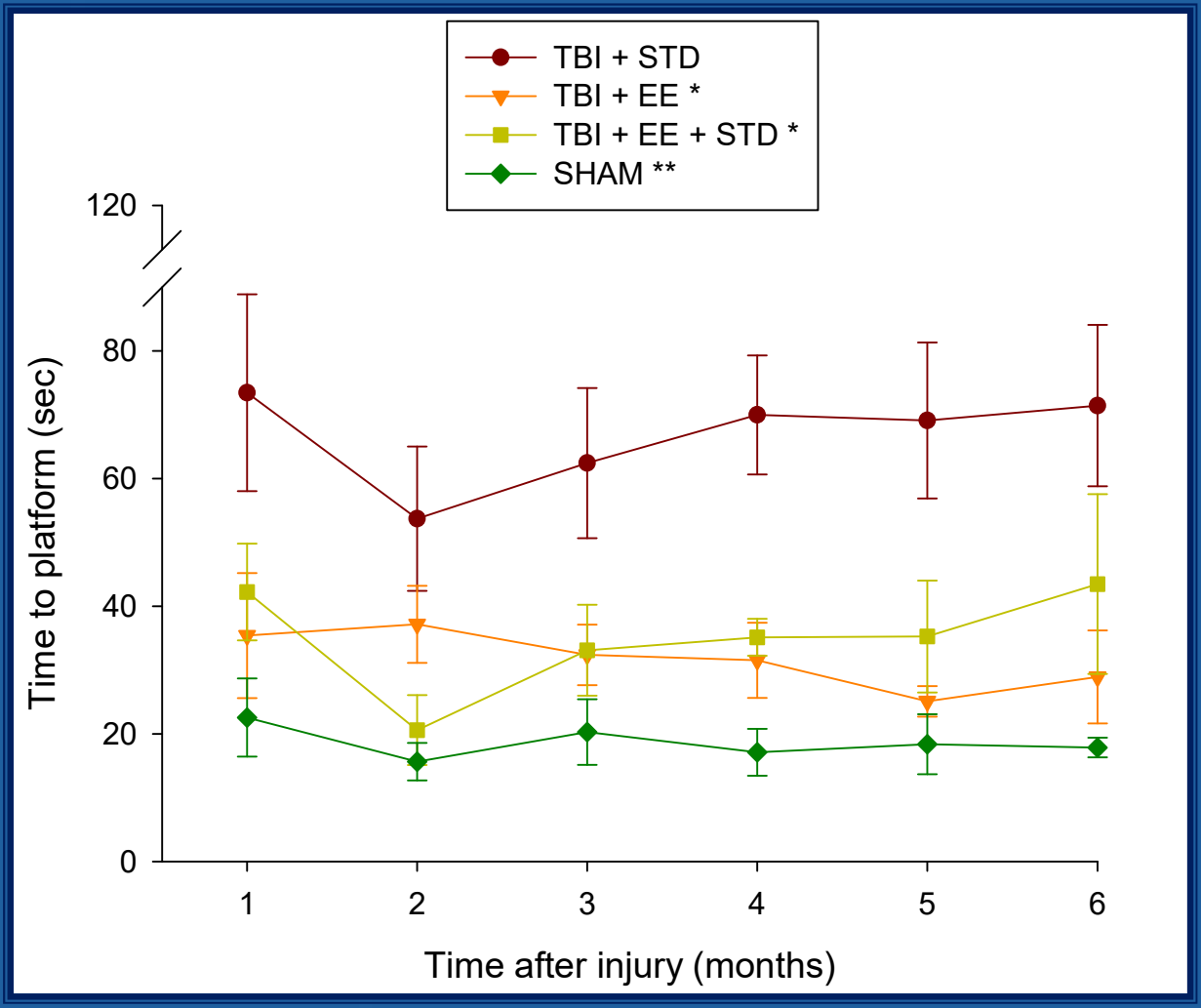
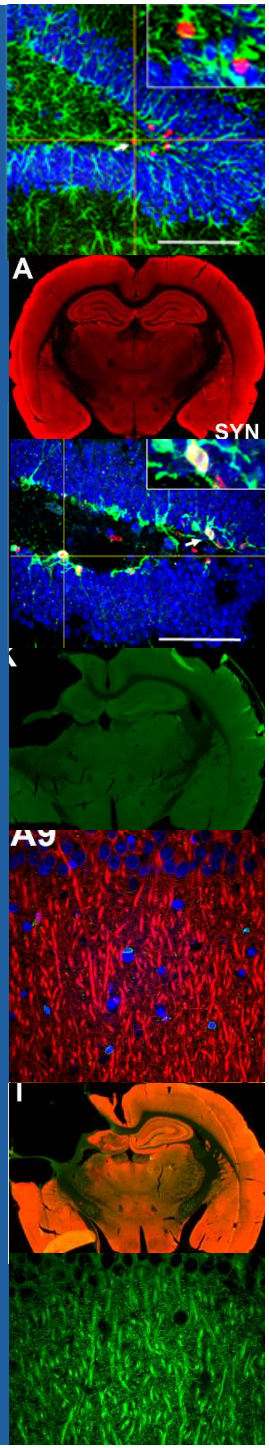
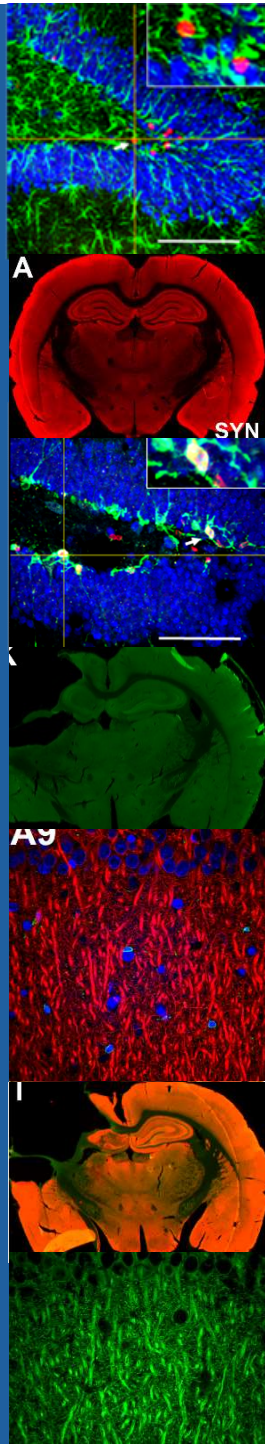




Long term EE (summary)

- Both motor and cognitive performance was enhanced with the relatively brief EE paradigm, which replicates our previous work.
- All EE groups (even those transferred to STD housing after 3 weeks of enrichment) performed markedly better in the maze during the subsequent six month period vs. STD-housed groups.
- The persistent benefits with this paradigm provide further support for EE as a potential pre-clinical model of rehabilitation.



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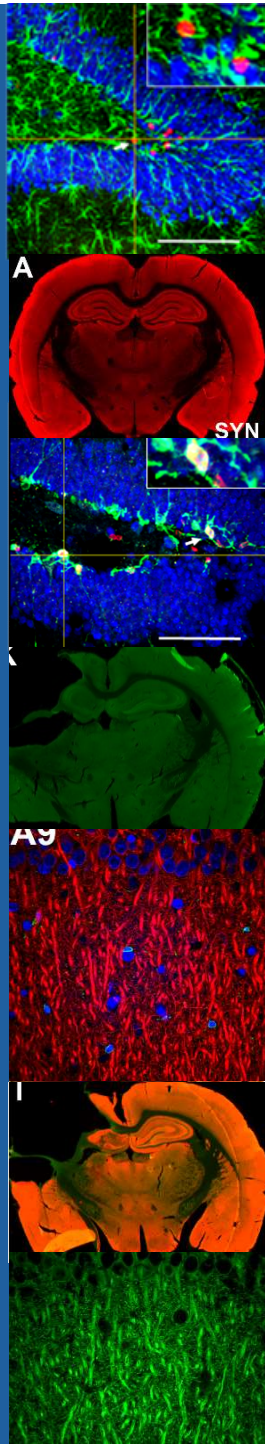

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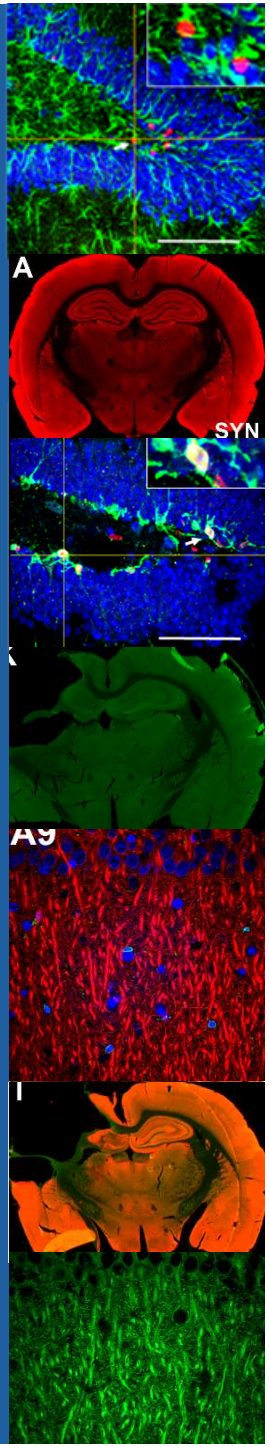

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A Relatively Brief Exposure to Environmental Enrichment after Experimental Traumatic Brain Injury Confers Long-Term Cognitive Benefits

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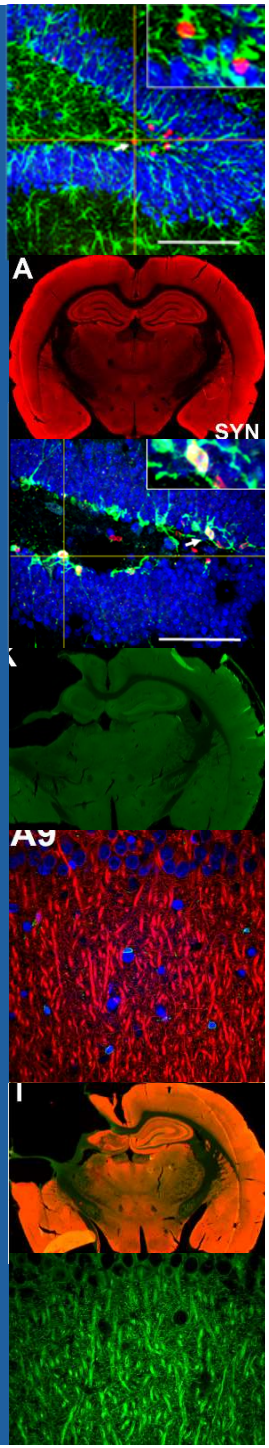
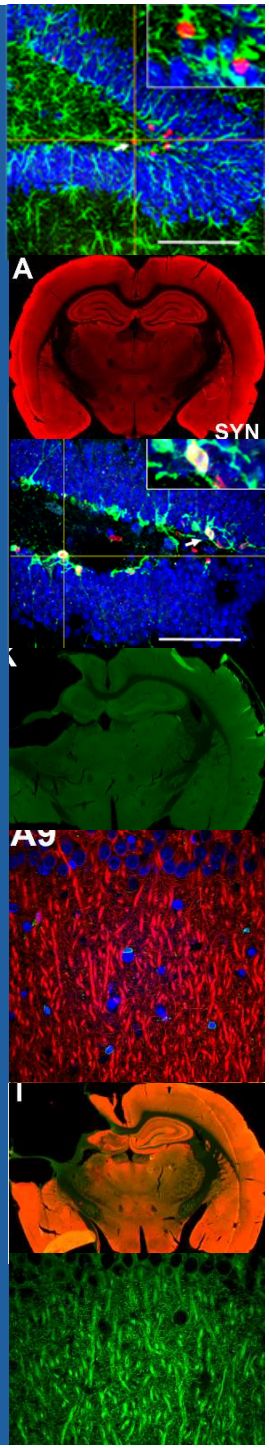


Abbreviated EE

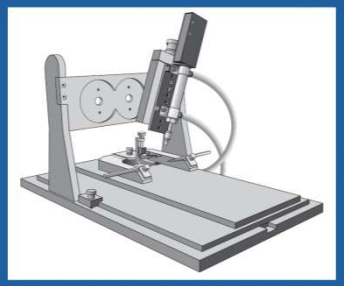
The typical EE paradigm consists of providing continuous exposure to enrichment after TBI, which is not consistent with clinical rehabilitation.

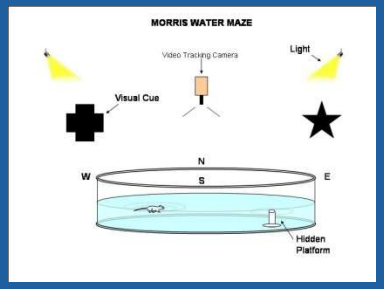
Thus, the aim of the current study was to determine whether an abbreviated EE strategy (i.e., 2, 4, or 6 hrs per day; REHAB) would confer greater recovery after TBI than STD, and whether the effects would be comparable to typical EE.



Wells Katie Mandy

Abbreviated EE



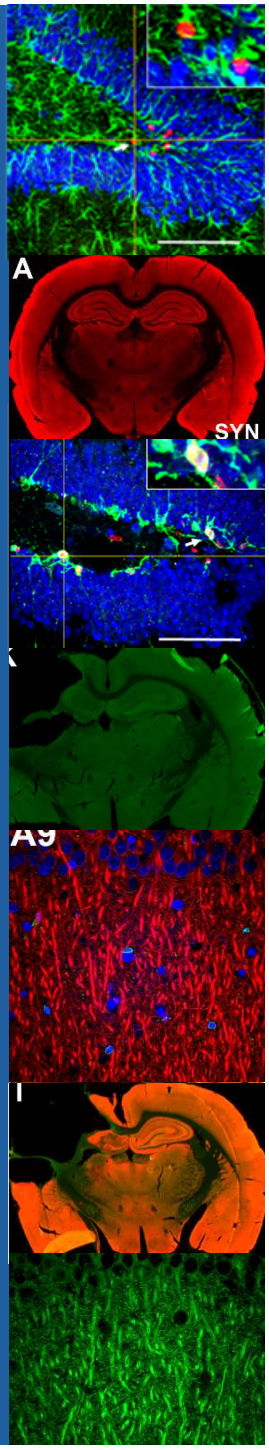


Motor training | Pre-assessment and surgery | Sacrifice

Acclimatization | Beam tests | Water maze

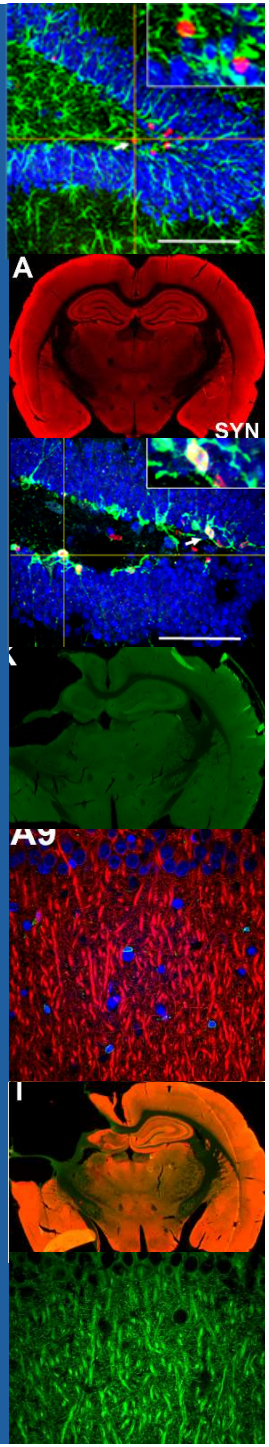
Days	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

EE	36x30x20” cage; sensory stimuli (toys); social housing (10 rats)
STD	8x9x15” cage; no sensory stimuli (no toys); no social housing (2 rats)
REHAB	STD housing + 2, 4, or 6 hours of EE daily

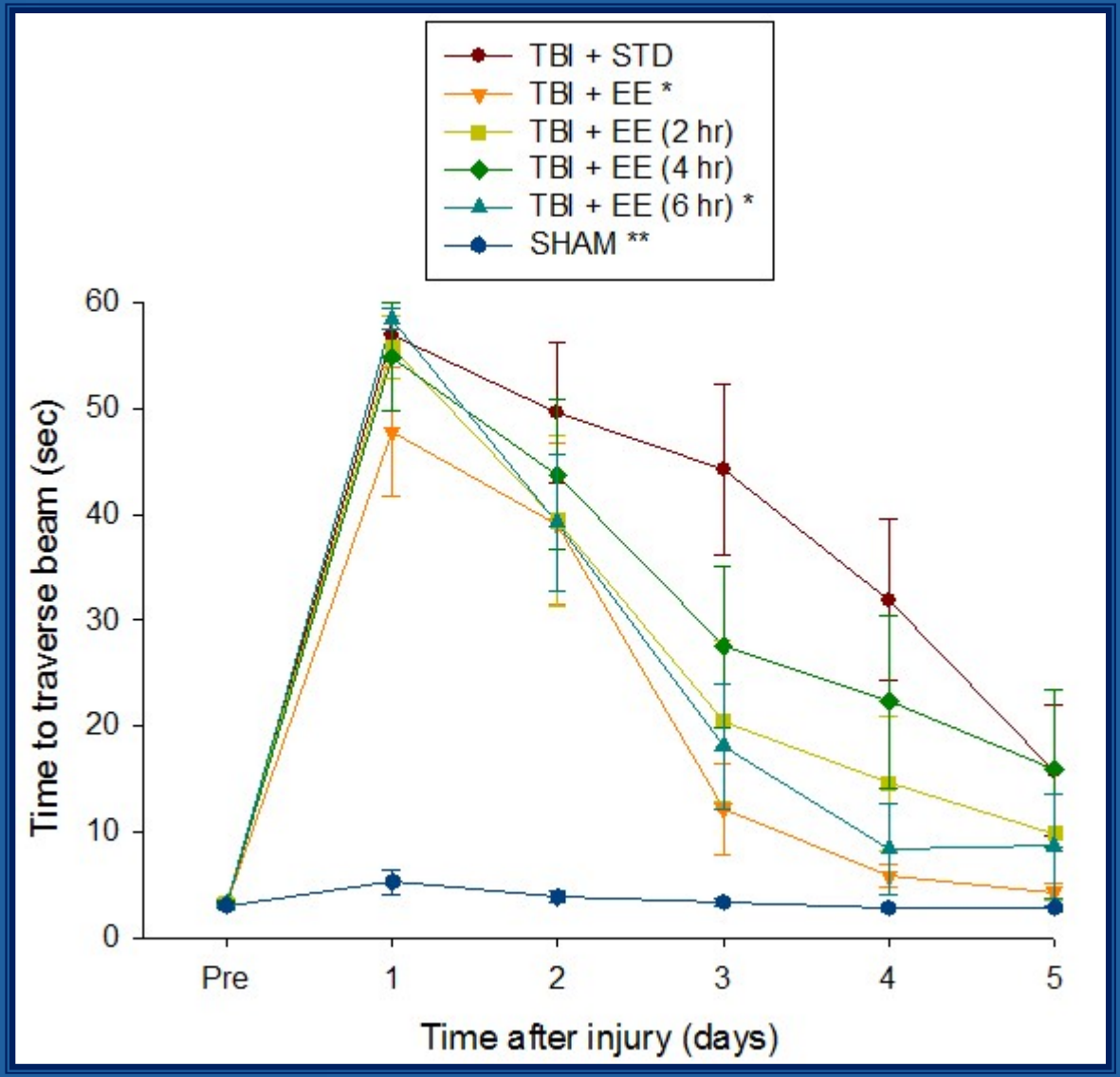


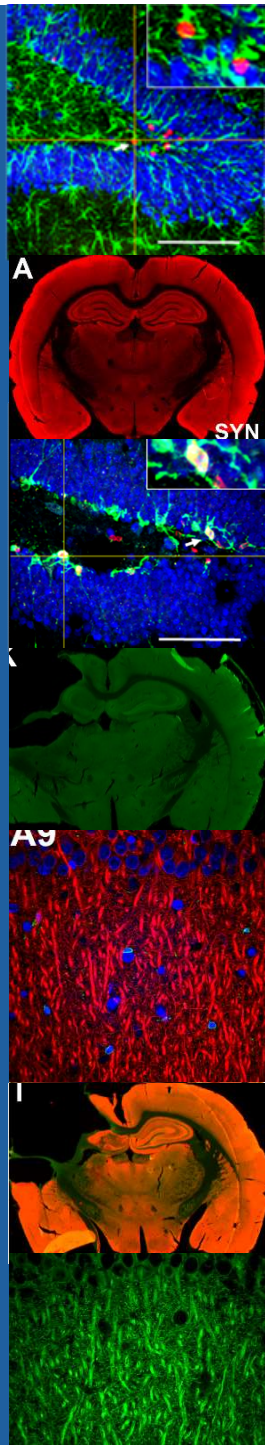
Abbreviated EE: males

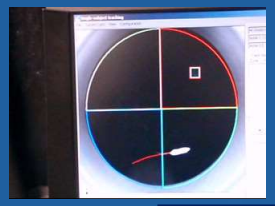
Rats were placed in their respective housing conditions (EE and STD) immediately after injury		
Groups	TBI	Sham
EE	n=10	n=5
STD	n=10	n=5
REHAB (2, 4, or 6 hrs)	n=30	n=15
N=75		



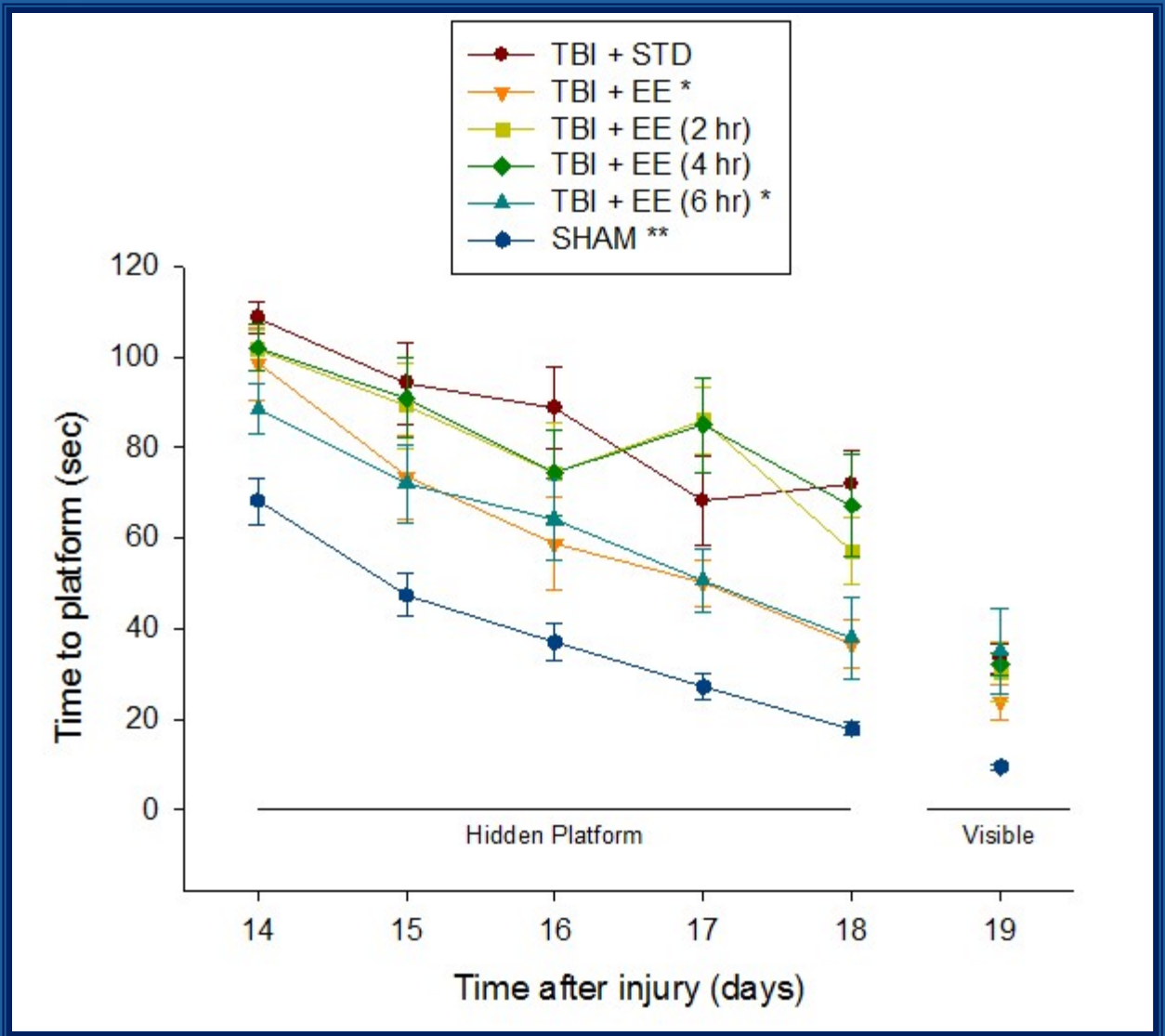
Abbreviated EE: motor

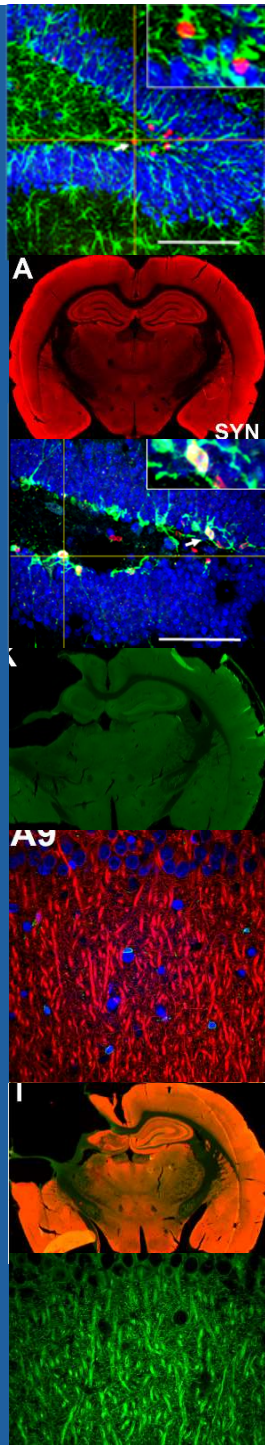






Abbreviated EE: learning

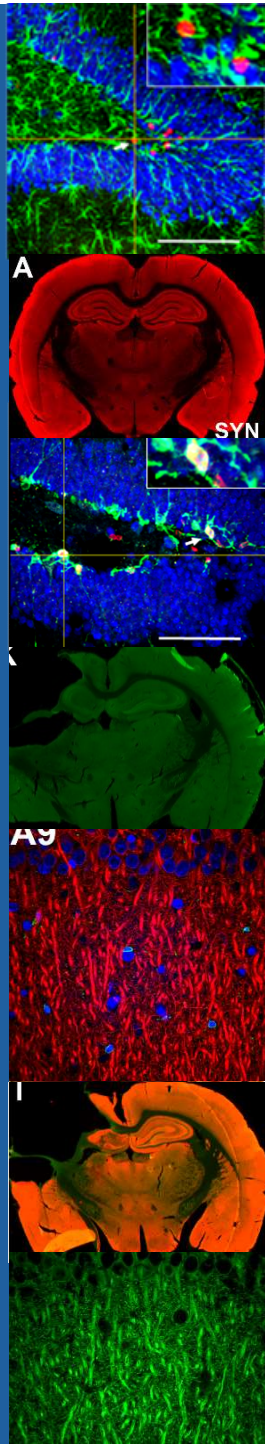




Abbreviated EE: summary

- 6 hr REHAB, but not 2 and 4 hr, comparable to typical EE on beam-walk and water maze, indicating that abbreviated EE is capable of inducing benefit

- Similar findings observed with female rats



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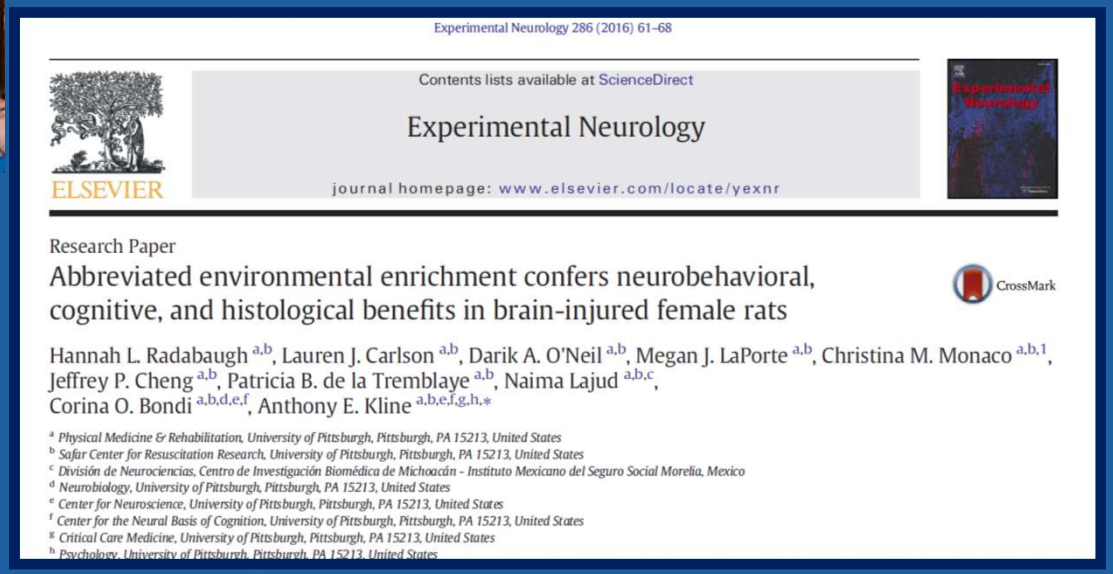

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Research Paper

Abbreviated environmental enrichment confers neurobehavioral, cognitive, and histological benefits in brain-injured female rats

Hannah L. Radabaugh [a,b], Lauren J. Carlson [a,b], Darik A. O'Neil [a,b], Megan J. LaPorte [a,b], Christina M. Monaco [a,b,1], Jeffrey P. Cheng [a,b], Patricia B. de la Tremblaye [a,b], Naima Lajud [a,b,c], Corina O. Bondi [a,b,d,e,f], Anthony E. Kline [a,b,e,f,g,h,*]

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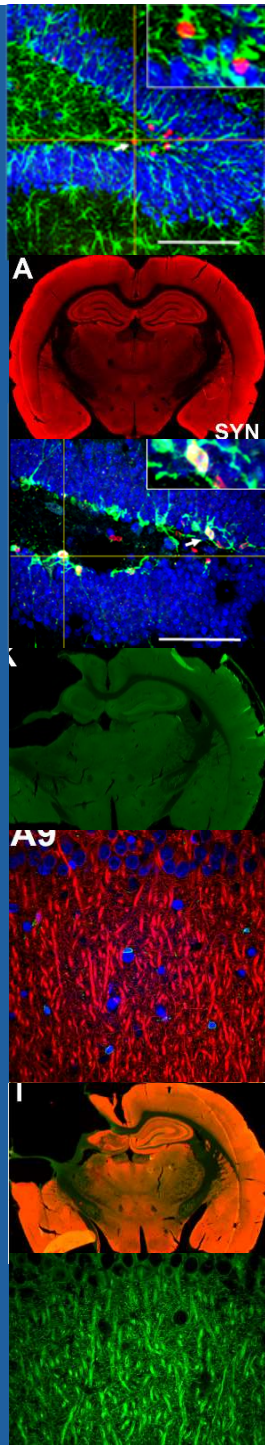
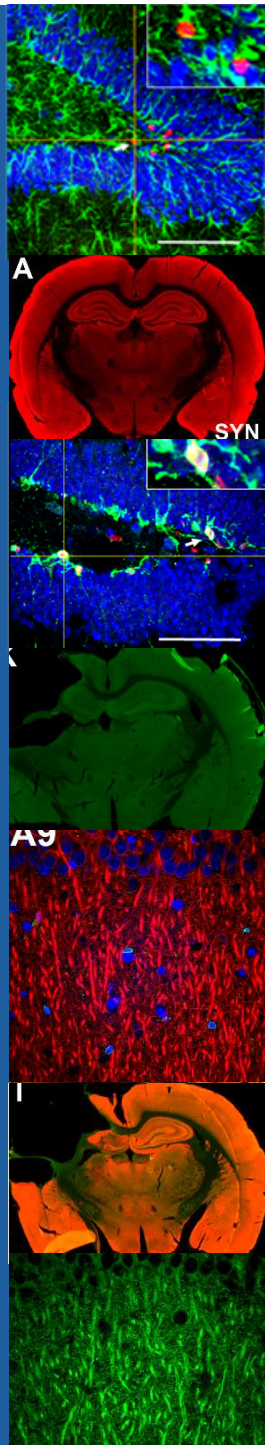


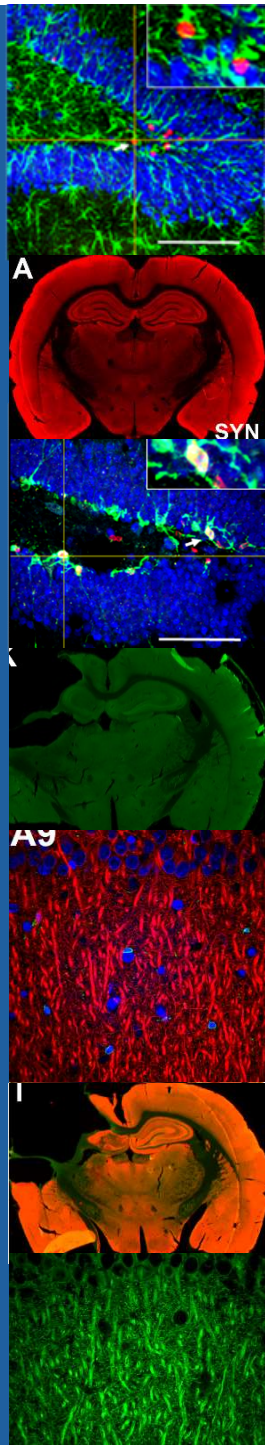
Rehabilitation-relevant EE (limited EE + pharmacotherapy)

To create a relevant preclinical model of EE therapy, the goal of the study was **to determine whether augmenting the sub-therapeutic doses of EE (2-hr and 4-hr) with the cholinesterase inhibitor galantamine would confer benefits over STD controls. Also, might the benefits be comparable to the continuously enriched rats not receiving GAL.**

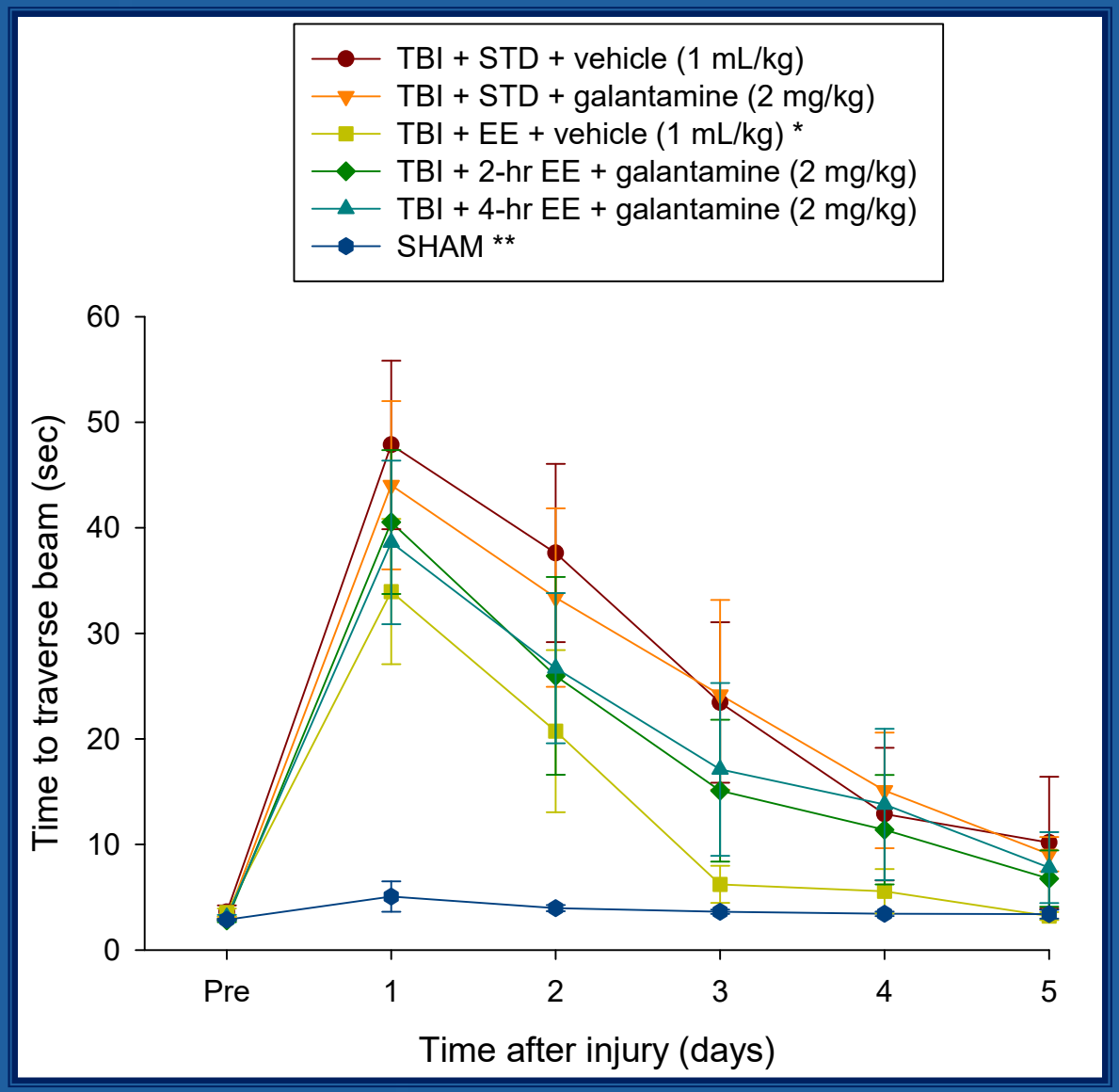


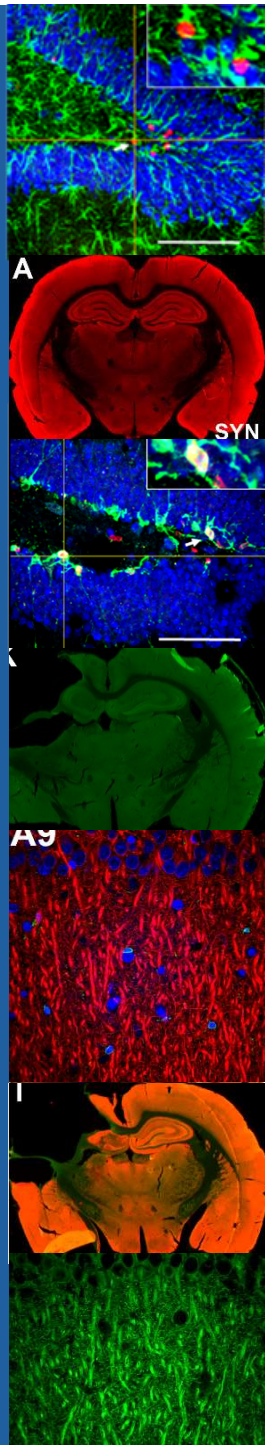
Limited EE + pharmacotherapy

Groups	TBI	Sham
Typical EE + VEH	n=9	n=4
STD + VEH, STD + GAL	n=9, n=9	n=4, n=4
2-hr and 4-hr EE + GAL	n=9, n=9	n=4
N=61		



Limited EE + pharmacotherapy





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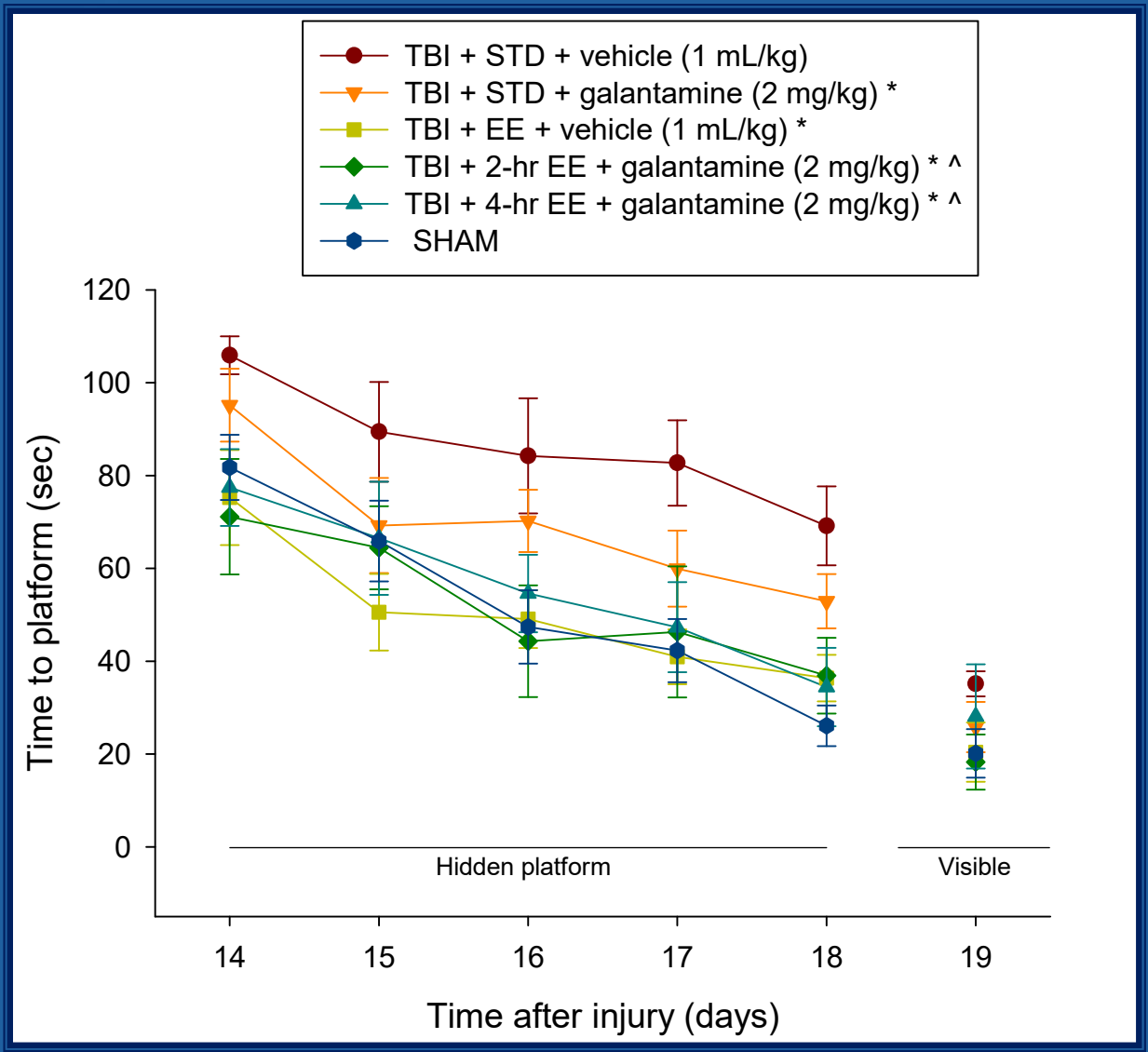
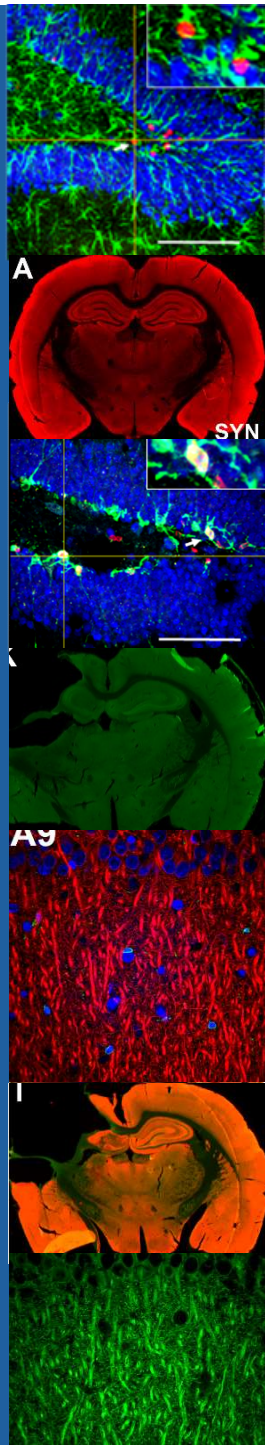
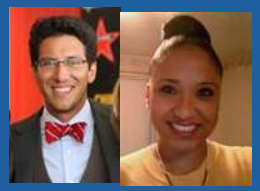
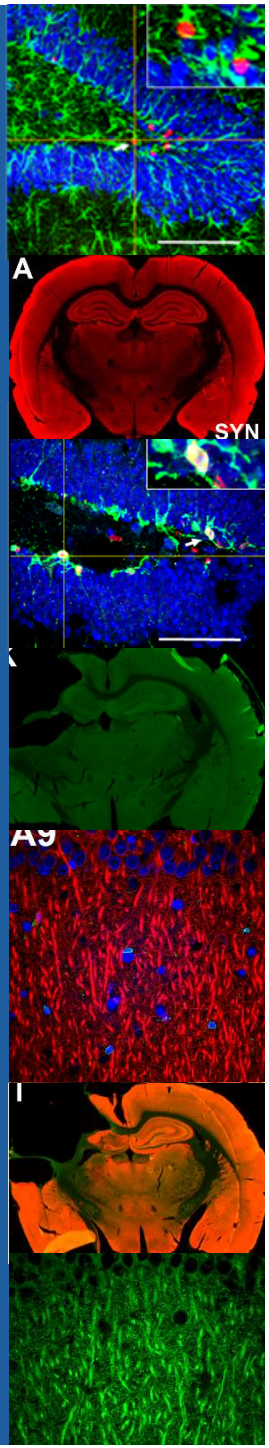






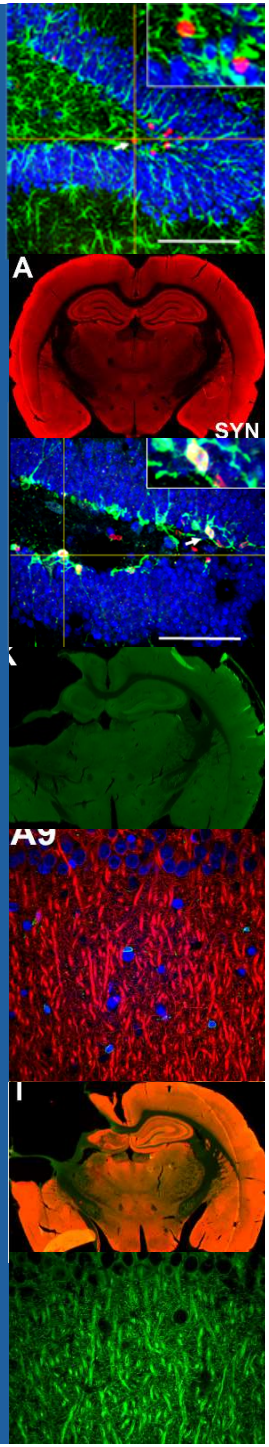
Rehabilitation-relevant EE (delaying exposure)

To further optimize a preclinical model of EE therapy, the goal of the study was **to determine whether delaying EE exposure by 3 days and abbreviating time spent (in the EE cage) to 6 hours per day would confer the same level of motor and cognitive benefits as rats housed early and continuously (i.e., typical EE).**

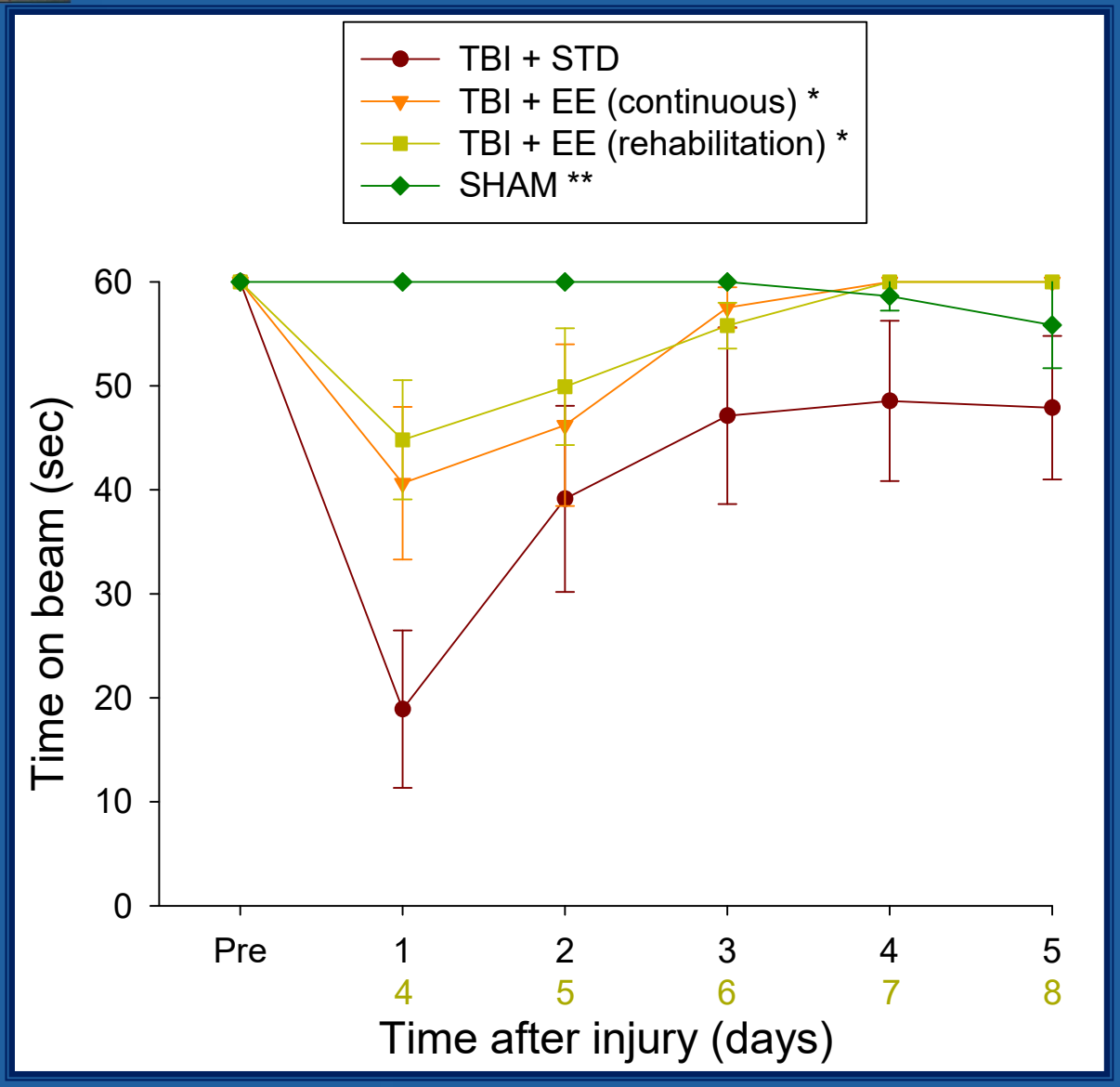


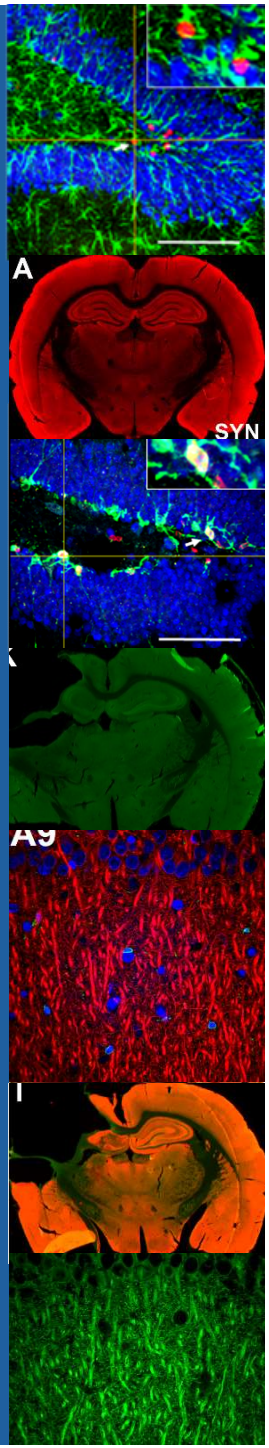
Rehabilitation-relevant EE

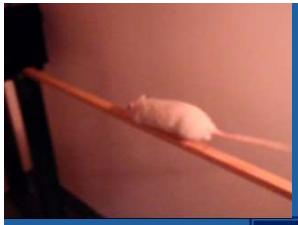
Groups	TBI	Sham
EE	n=8	n=4
STD	n=8	n=4
REHAB (3 d delay/6 hr day)	n=8	n=4
N=36		



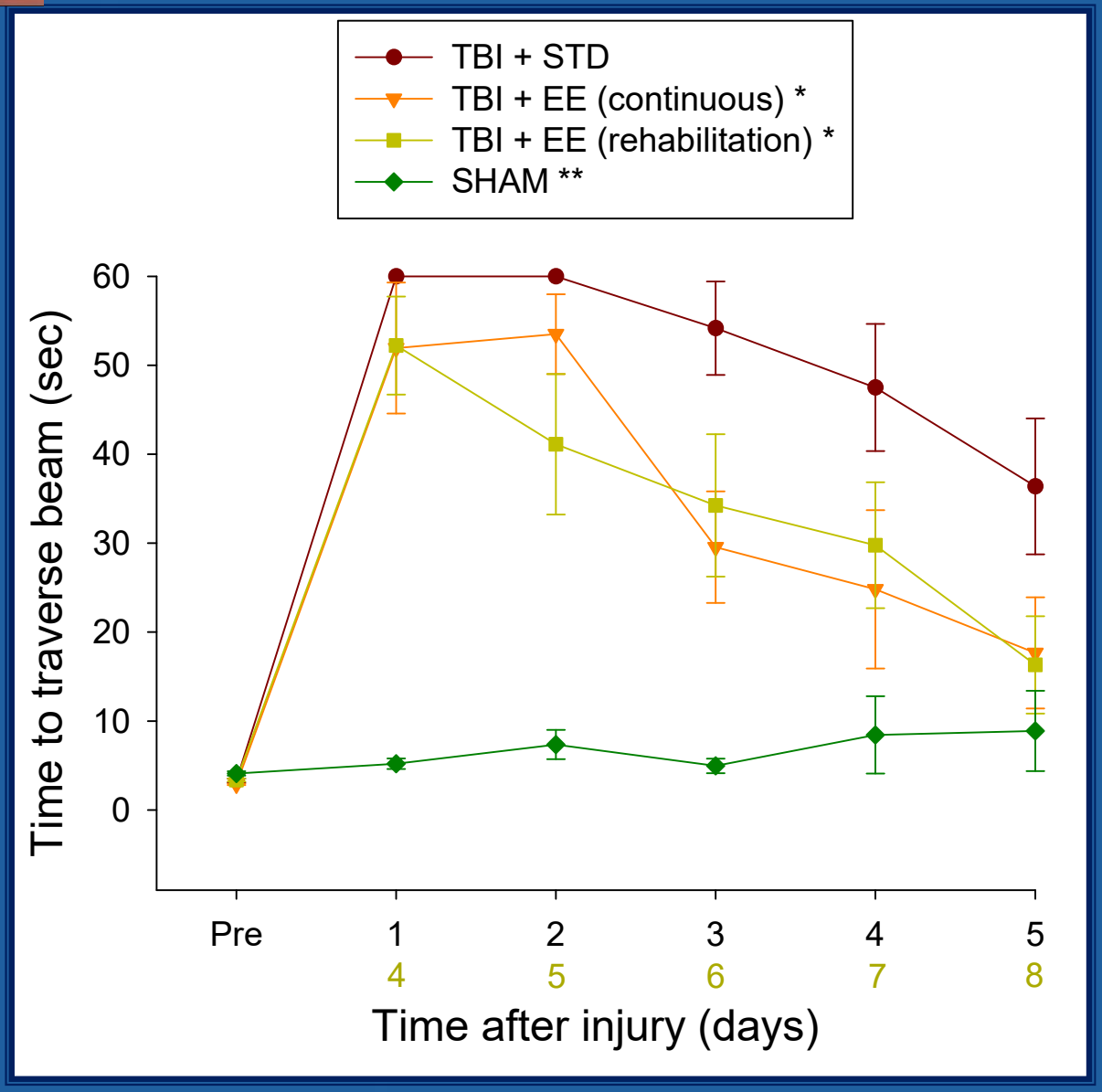
Rehabilitation-relevant EE

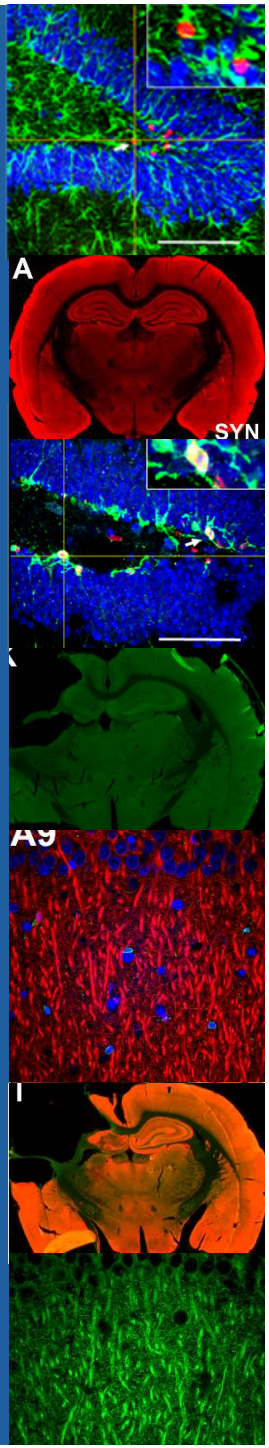


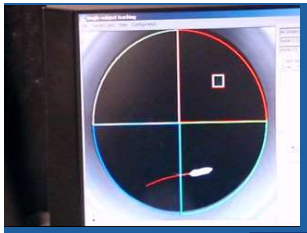




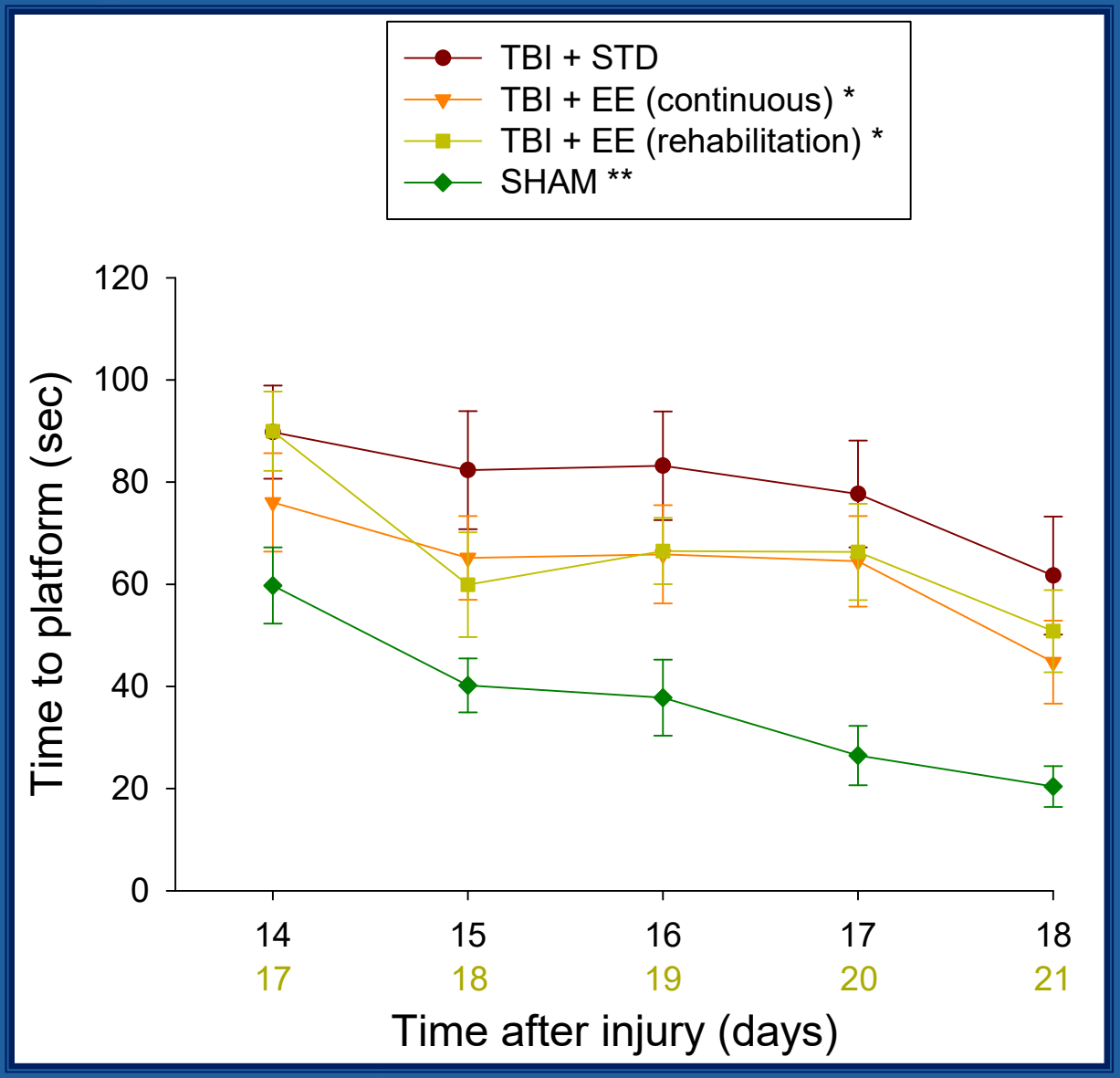
Rehabilitation-relevant EE

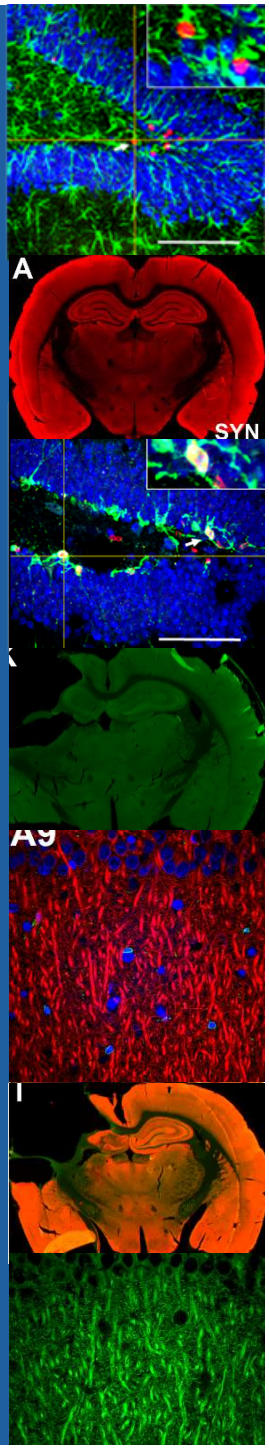






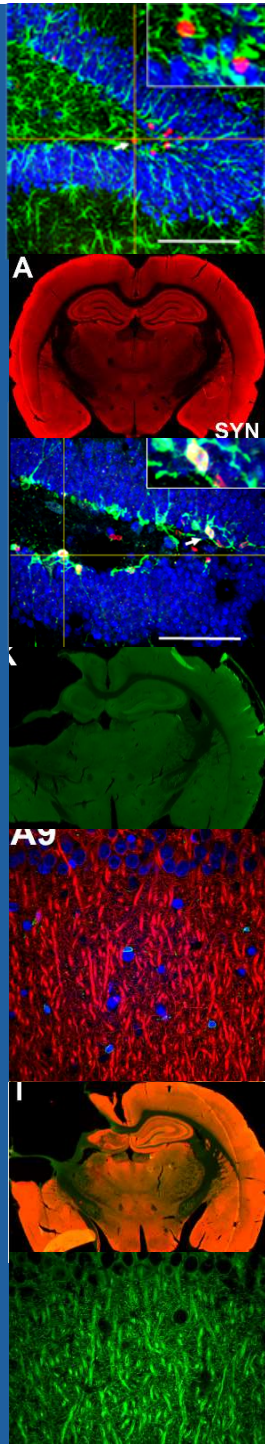
Rehabilitation-relevant EE





Rehabilitation-relevant EE

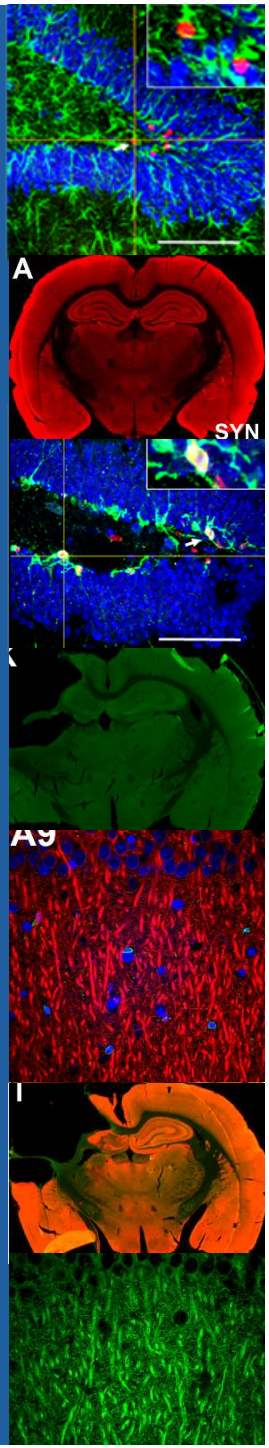
- Both EE conditions significantly enhanced motor and cognitive performance vs. STD
- The rehabilitation relevant EE group did not differ from the typical EE group in any task, which suggests that the benefits mediated by EE do not require early and continuous exposure



Refining EE to advance rehabilitation based research after experimental TBI

Breaking the therapy into two shorter sessions may increase novelty and ultimately enhance recovery.

Hence, the aim of the study was to test the hypothesis that functional and histological outcomes will be significantly improved by daily preclinical neurorehabilitation consisting of two 3-hr periods of EE vs. a single 6-hr session.



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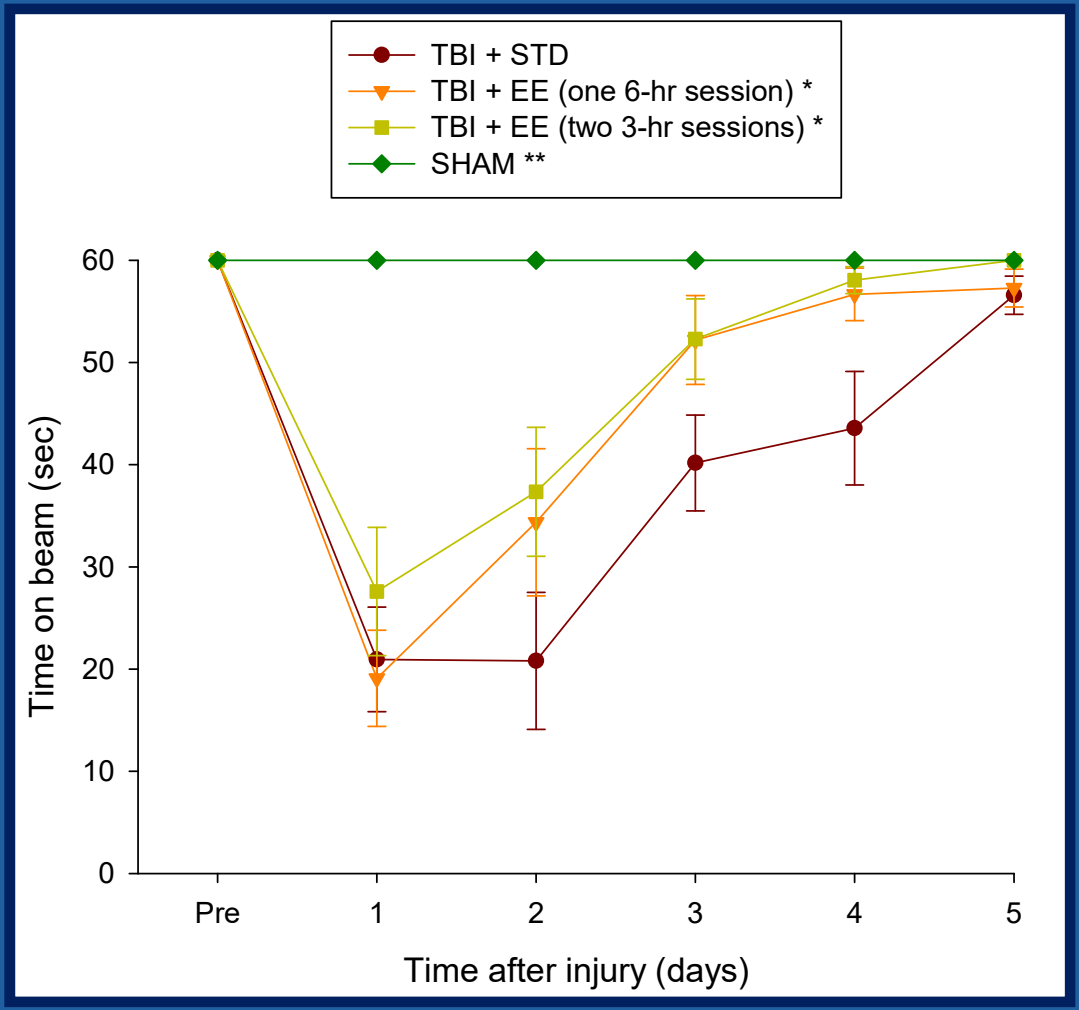

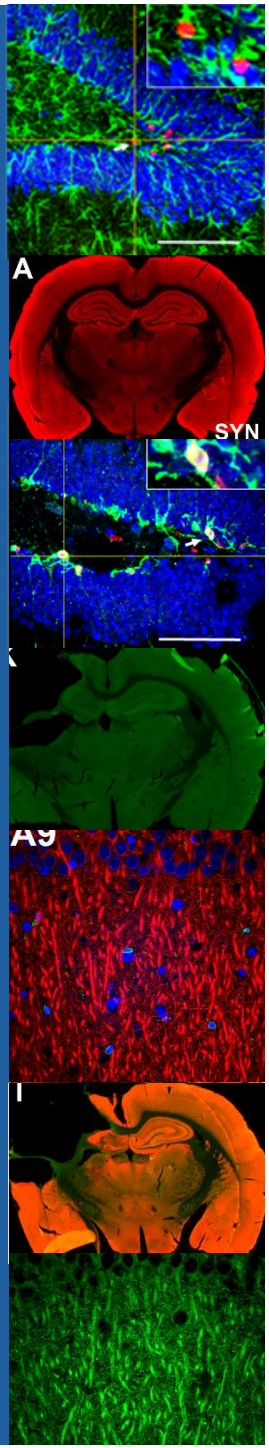

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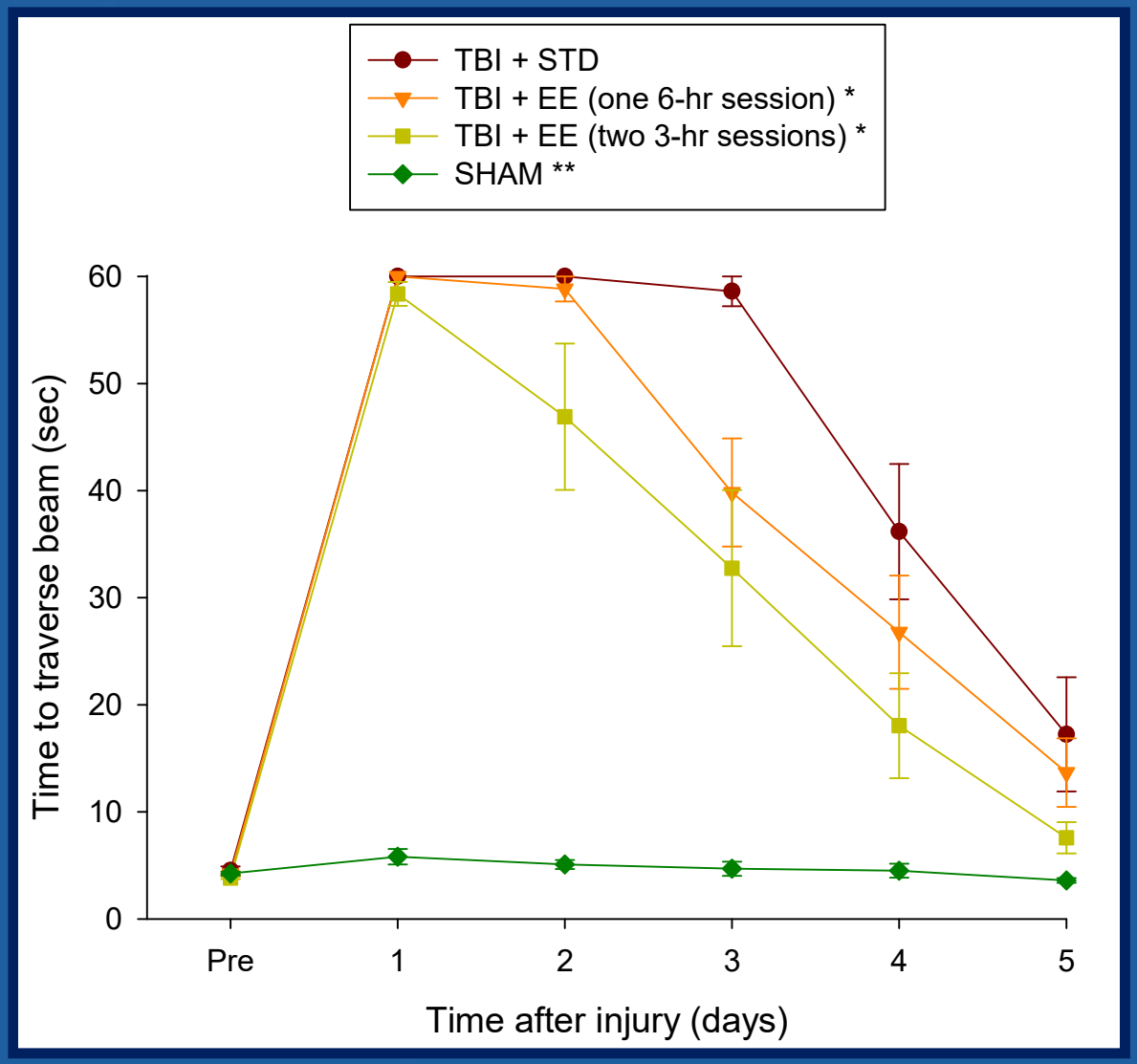

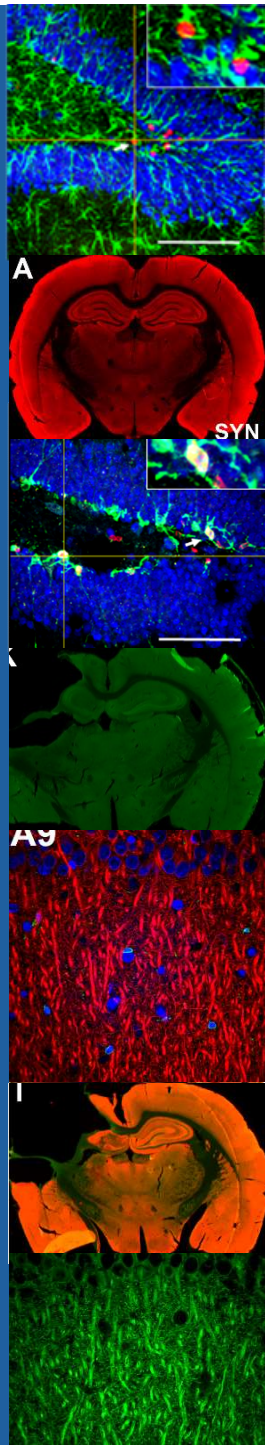

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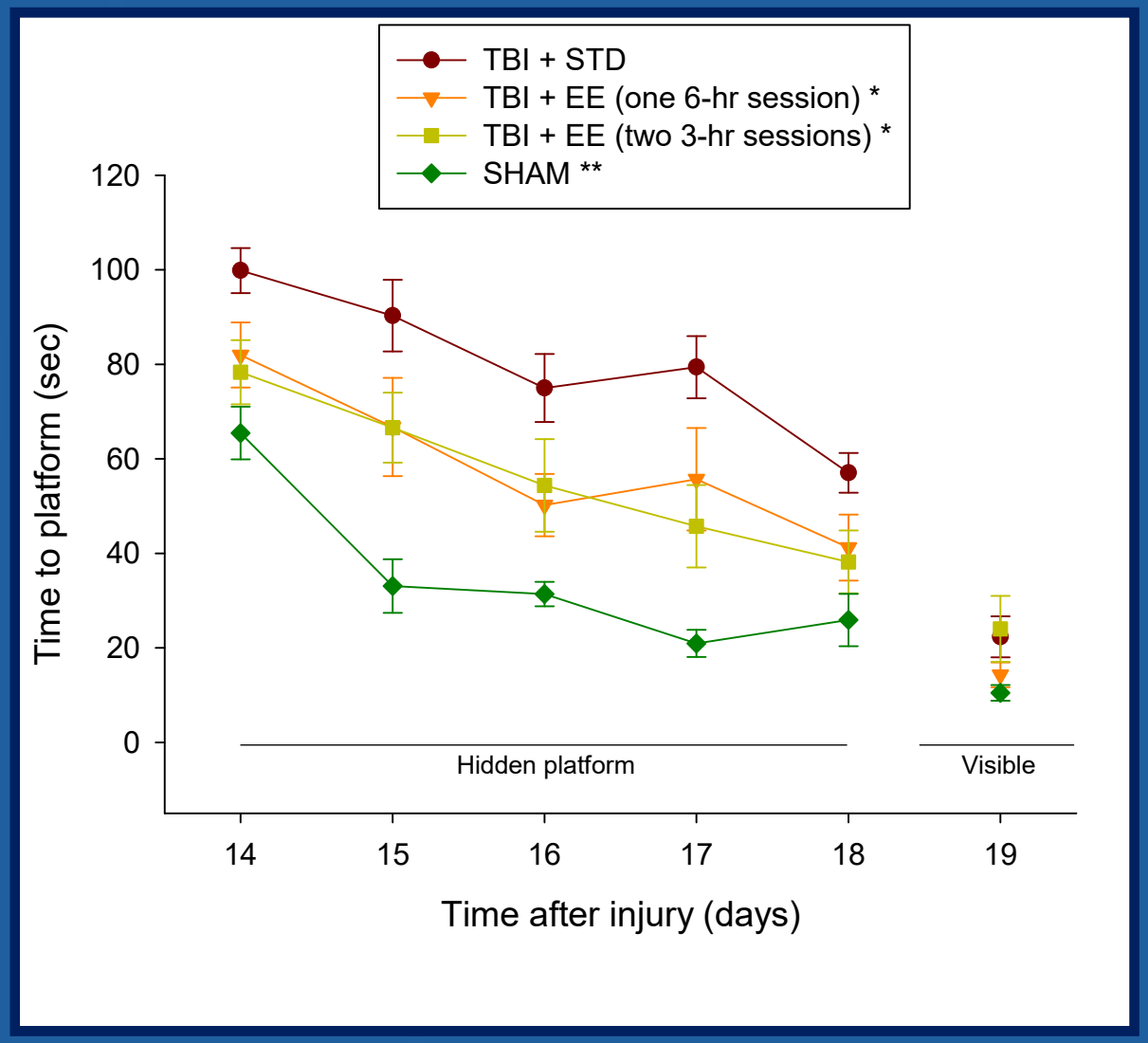

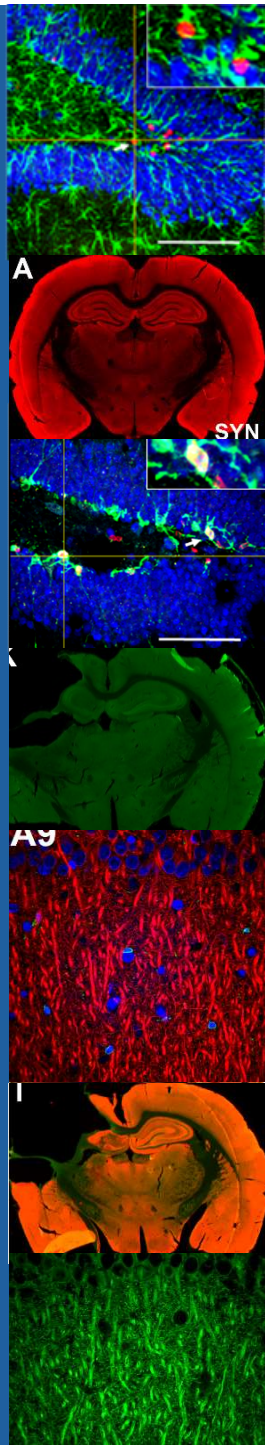

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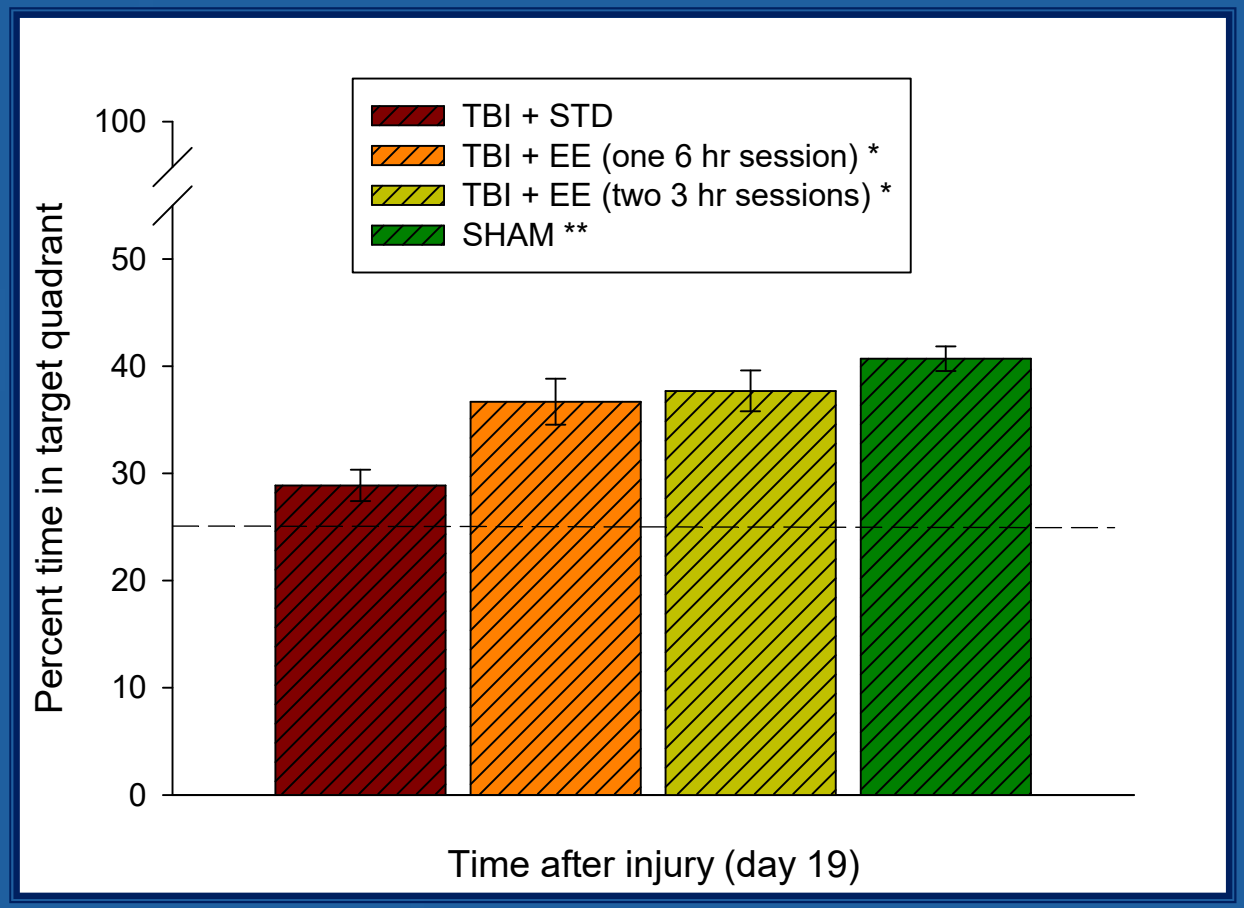
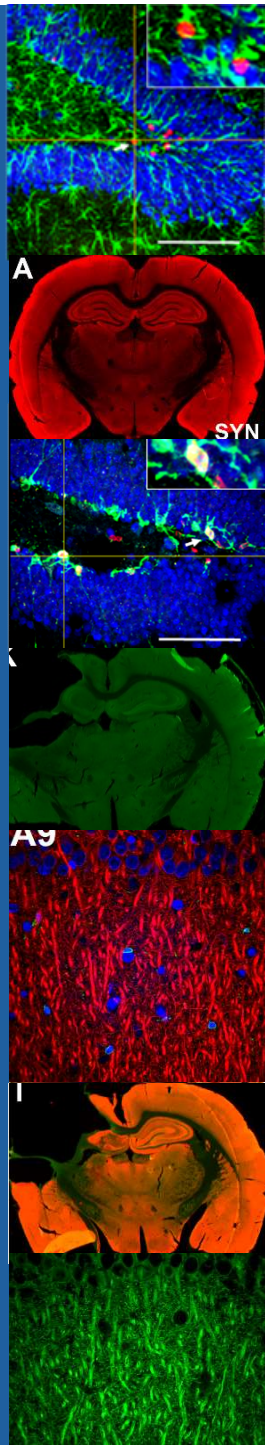
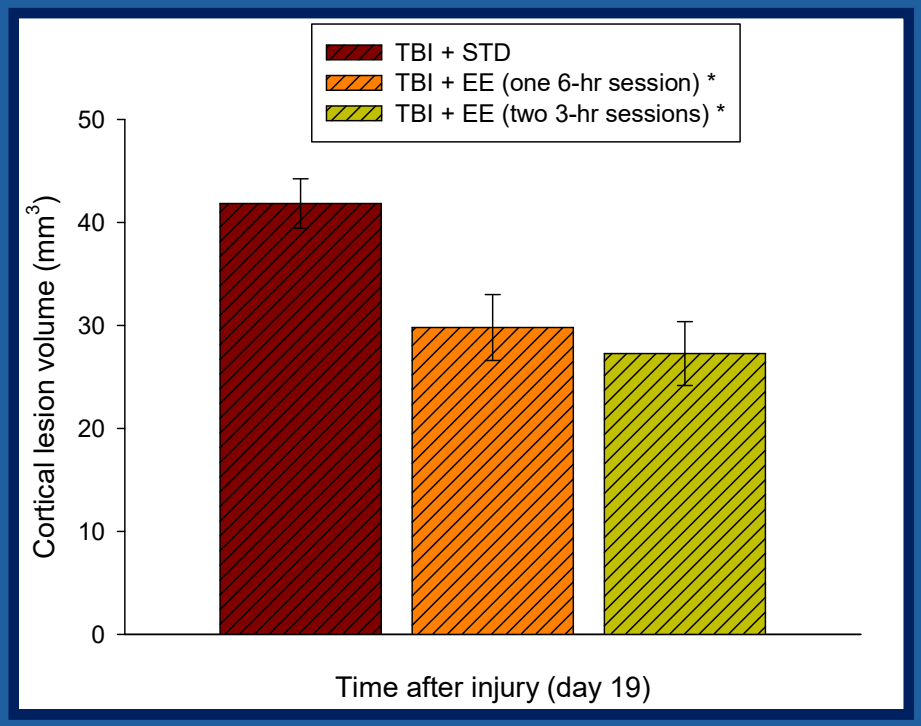




Refining EE to advance rehabilitation based research after experimental TBI

A



B

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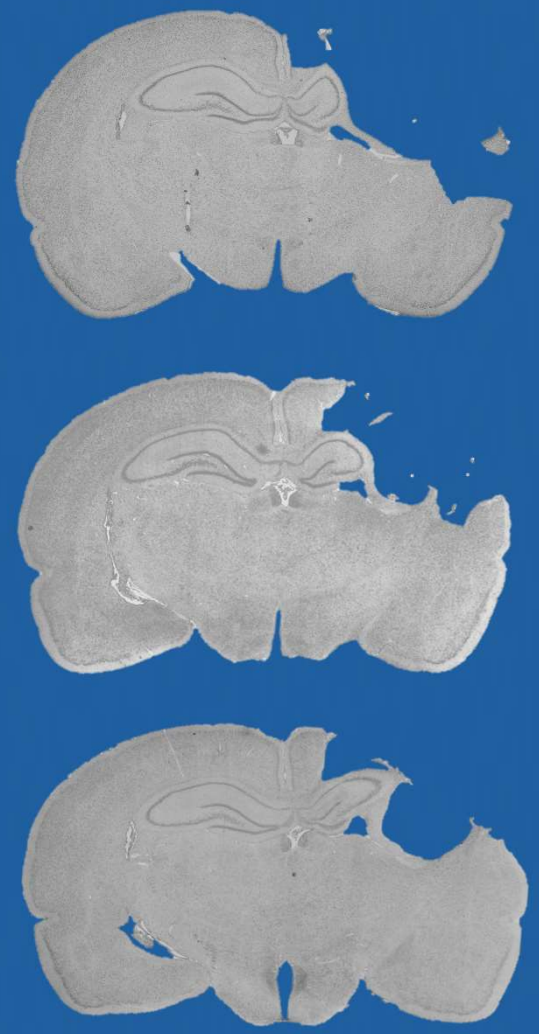
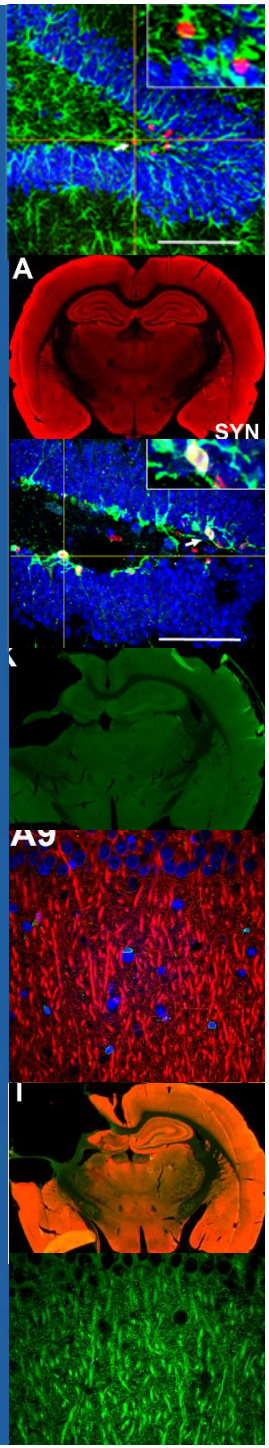
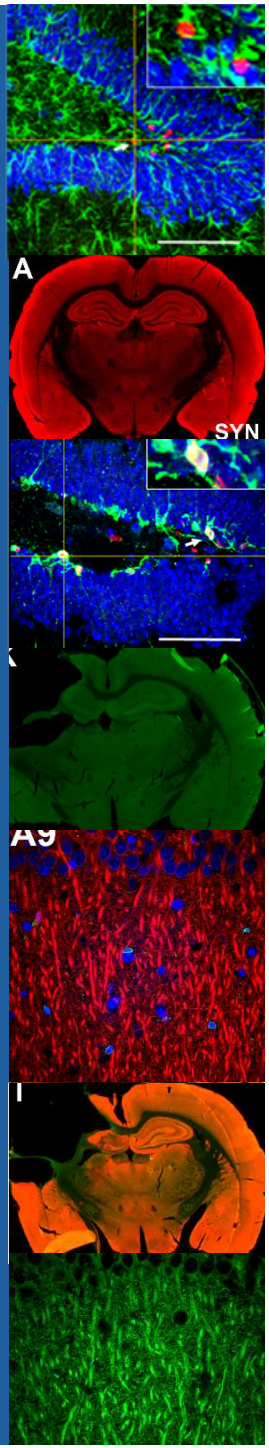
D



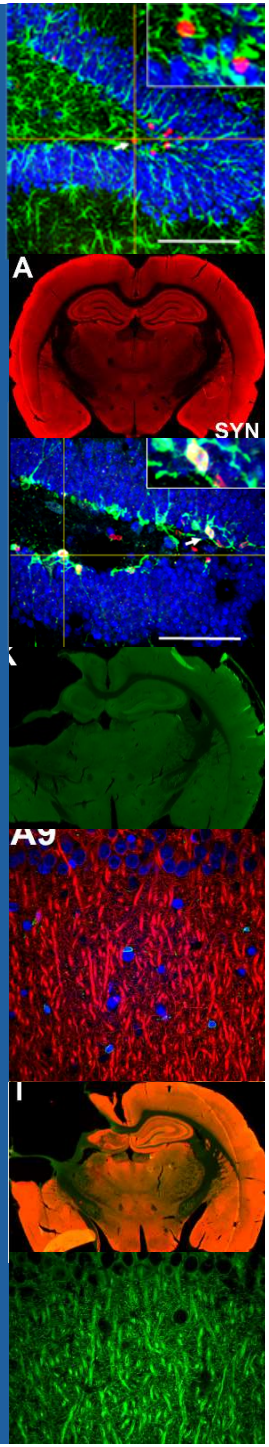


Agitation and aggression after TBI



Agitation and aggression after TBI

- 24% - 96% of patients exhibit agitated behavior
- 11% exhibit aggression
- Agitation and aggression can interfere with assessment, acute treatment, and rehabilitation
- Patient management is imperative
- Pharmacological agents first choice
  - Antipsychotics



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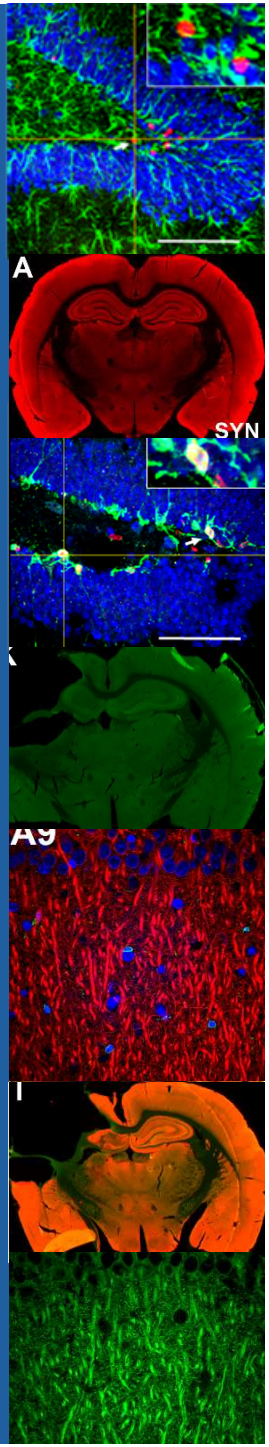

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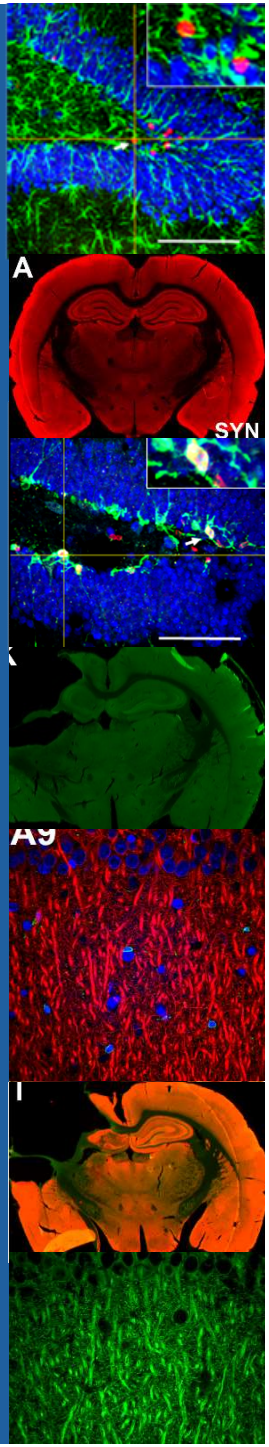

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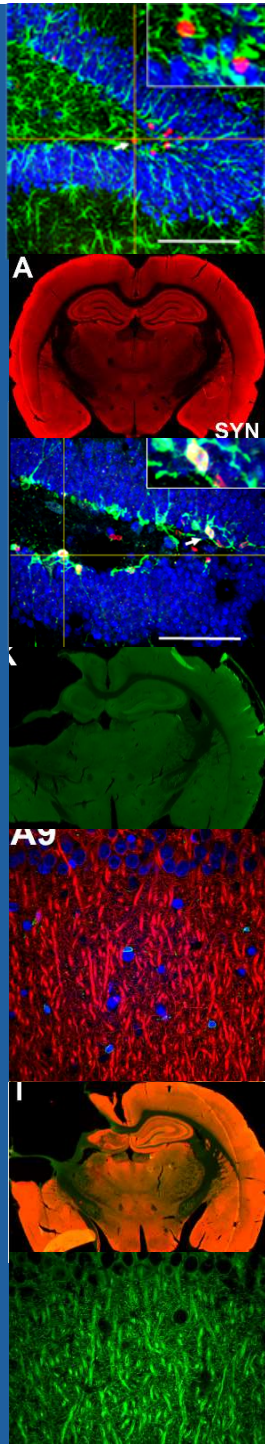
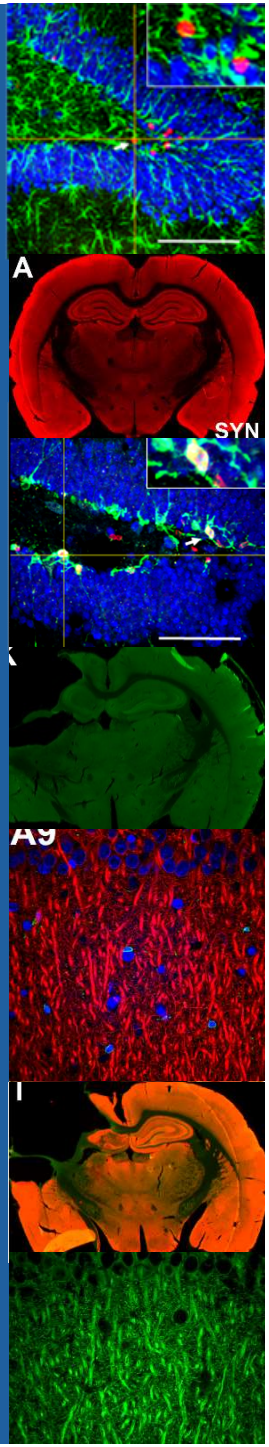
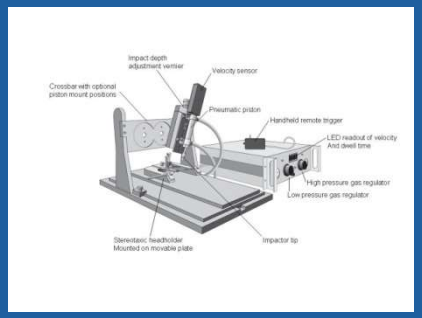


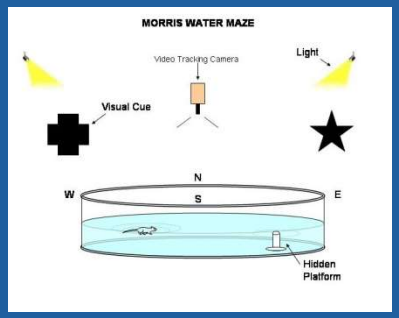
Agitation and aggression after TBI

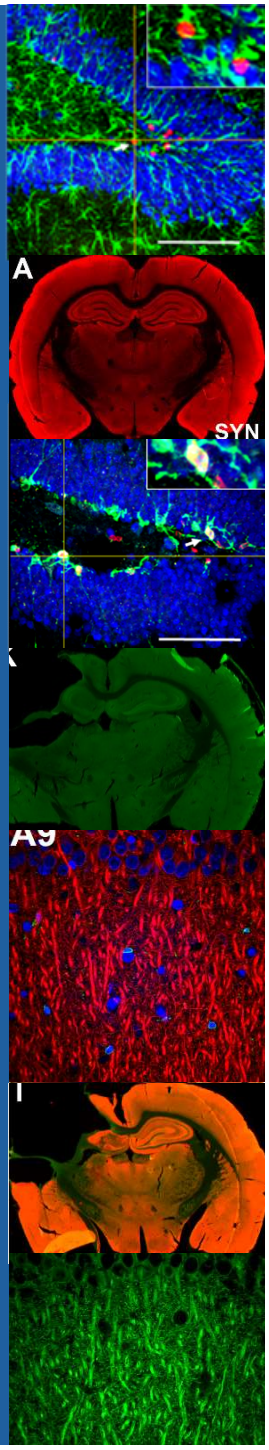
- 24% - 96% of patients exhibit agitated behavior
- 11% exhibit aggression
- Agitation and aggression can interfere with assessment, acute treatment, and rehabilitation
- Patient management is imperative
- Pharmacological agents first choice
  - Antipsychotics



HAL + environmental enrichment





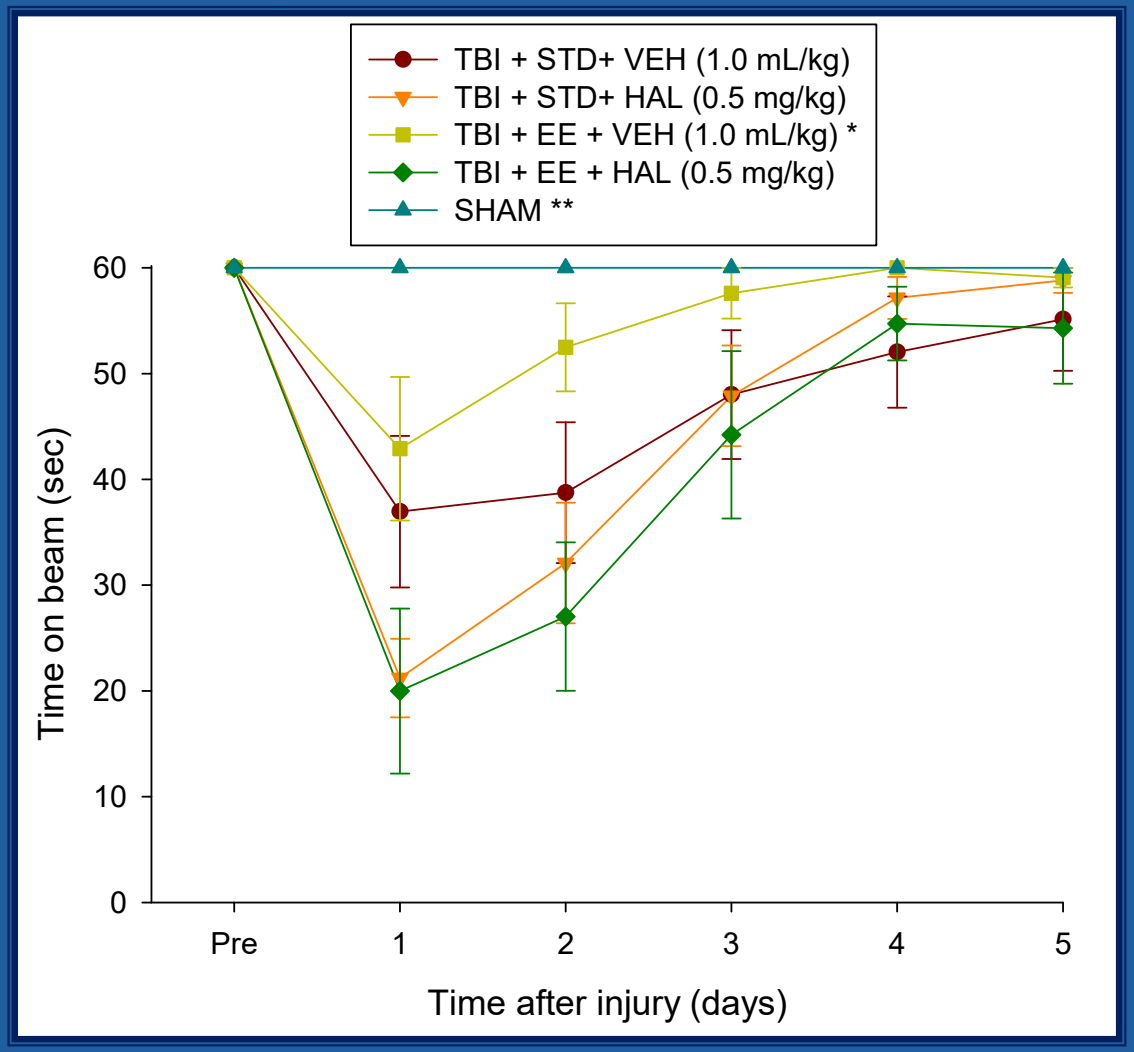


TBI + STD + VEH (1 mL/kg), TBI + STD + HAL (0.5 mg/kg)

TBI + EE + VEH (1 mL/kg), TBI + EE + HAL (0.5 mg/kg)

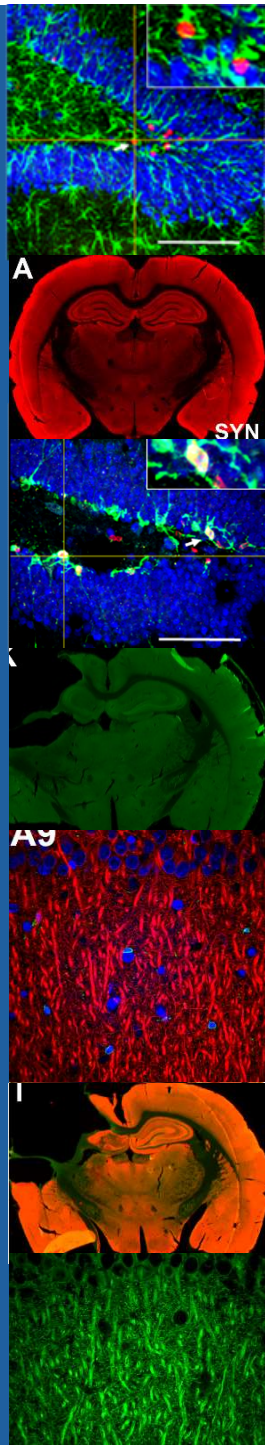
Sham STD + VEH and HAL, Sham EE + VEH and HAL

HAL + environmental enrichment



*$p < 0.05$ vs. all TBI groups

**$p < 0.05$ vs. all TBI groups



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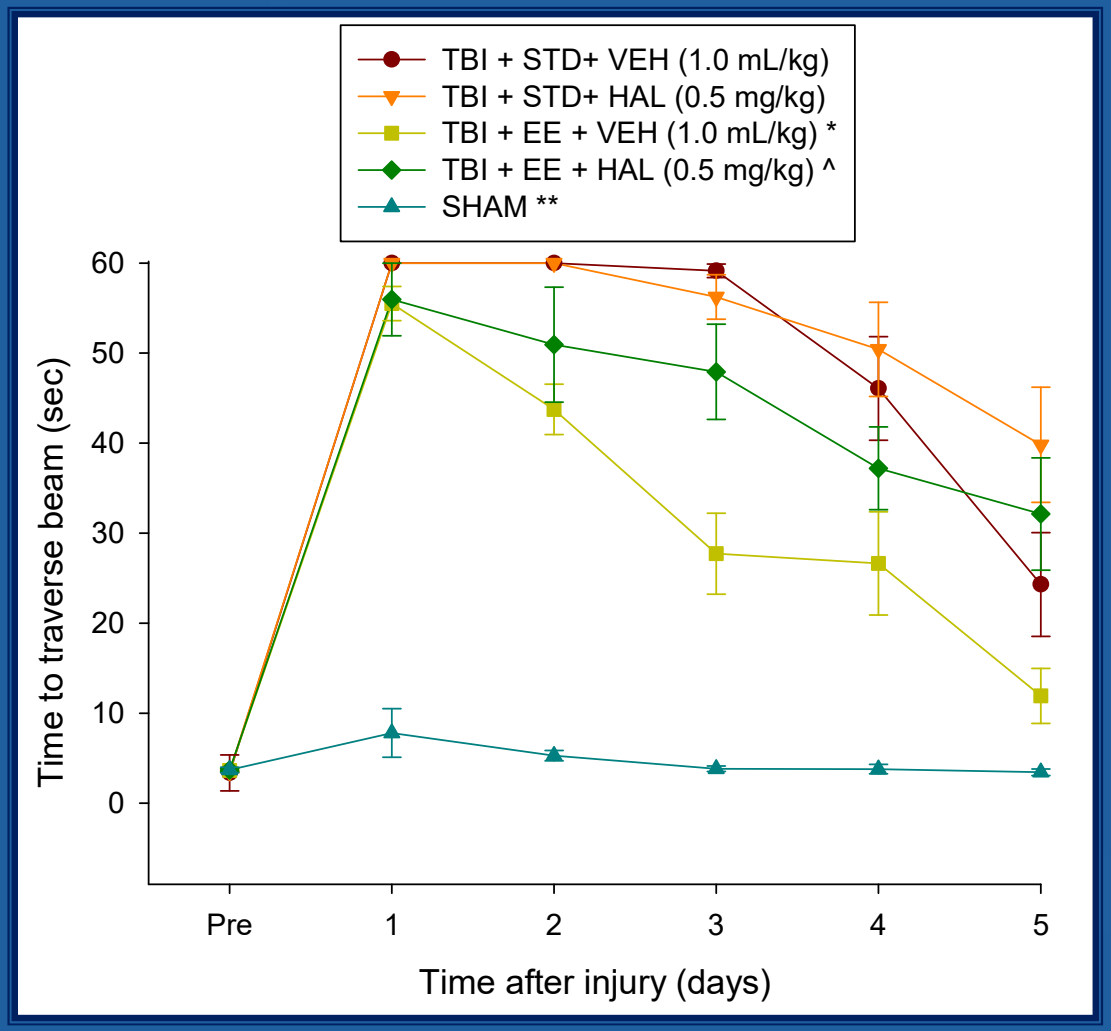
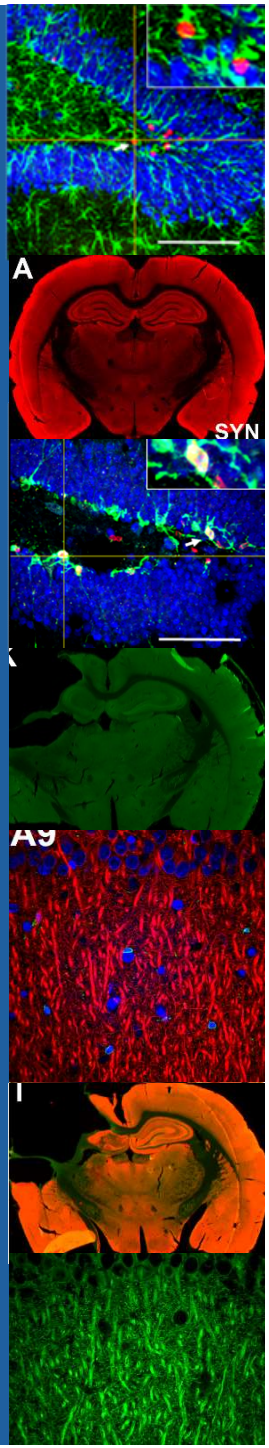


*$p < 0.05$ vs. all TBI groups

^$p < 0.05$ vs. TBI+STD+HAL

**$p < 0.05$ vs. all TBI groups



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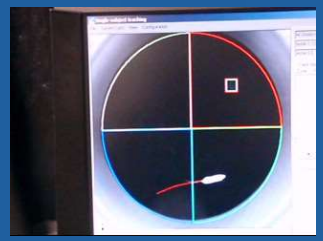

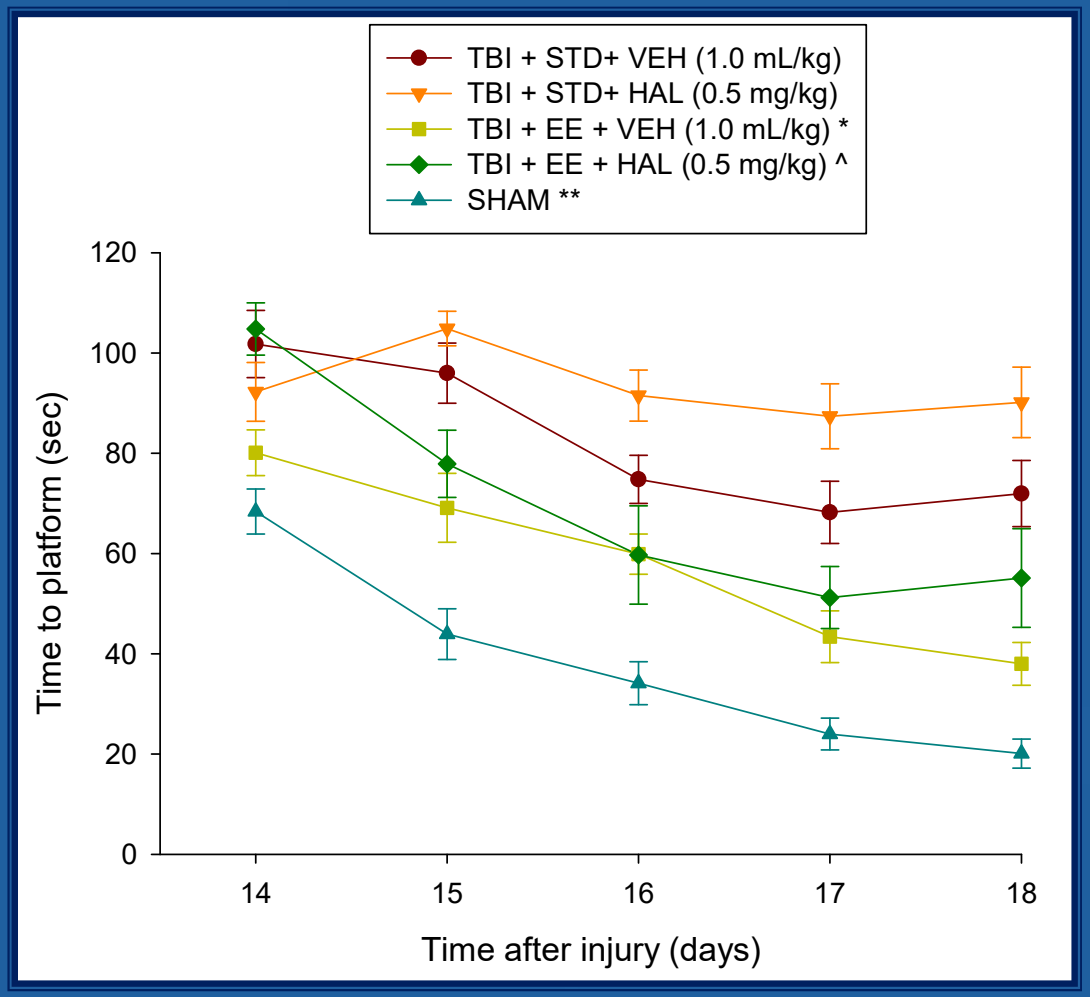

*$p < 0.05$ vs. all TBI

^$p < 0.05$ vs. TBI+STD+HAL and TBI+STD+VEH

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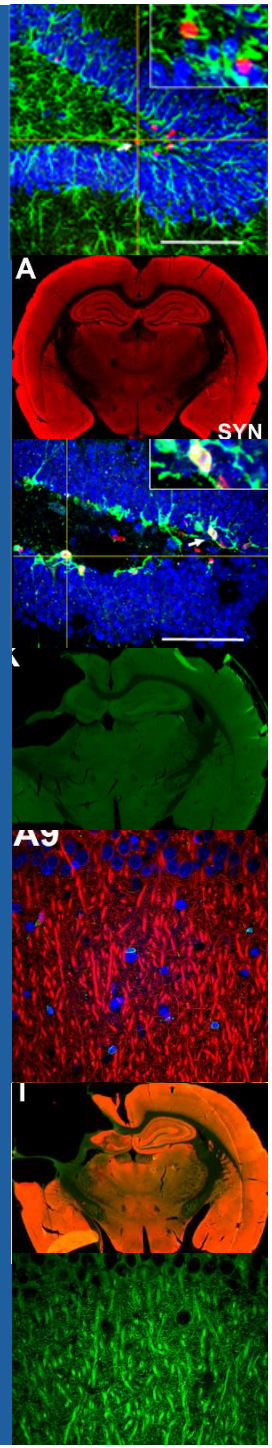
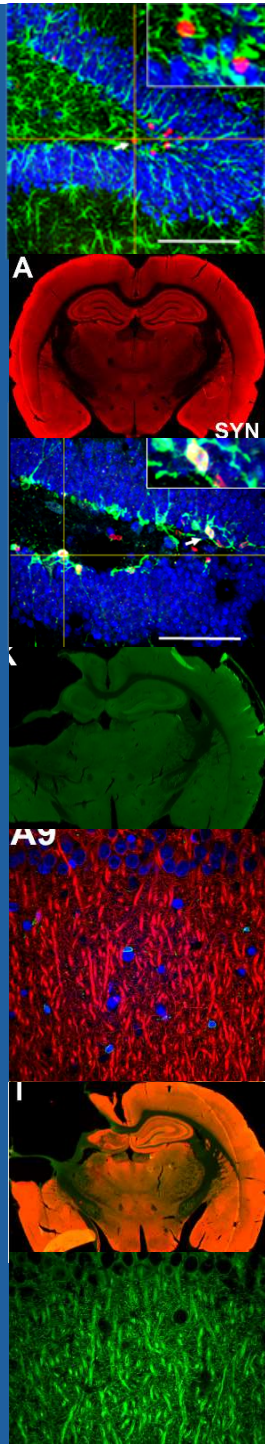


HAL + environmental enrichment (summary)

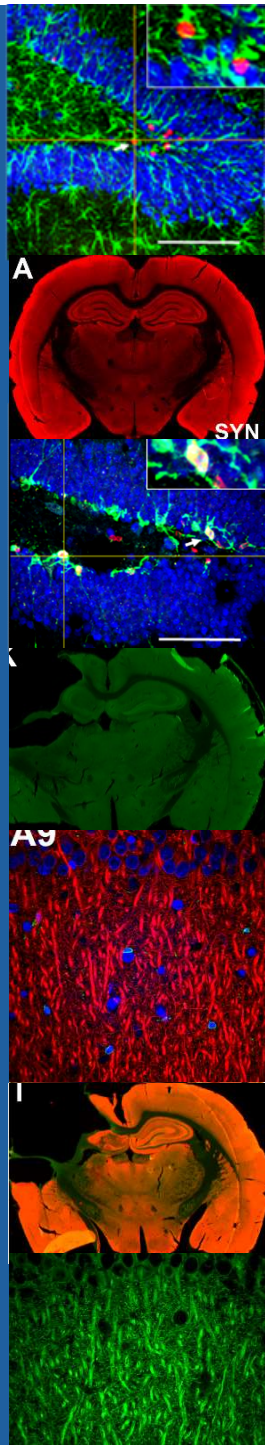
The data show that EE can attenuate the negative effects of HAL on cognition, but HAL in turn reduces the efficacy of EE.

Clinically, this suggests that if providing HAL chronically while in rehabilitation, the intensity of rehabilitation may need to be increased (to compensate for the reduced efficacy mediated by HAL).



Take home points

- Typical EE improves motor / cognitive performance, and hippocampal cell survival vs. STD in males and females
- The benefits of typical EE persist for up to 6 months
- Abbreviated EE confers significant benefits in both sexes
- Sub-therapeutic doses of EE combined with GAL synergize to promote benefits beyond GAL treatment alone
- Delaying / abbreviating EE (3 days / 6 hours per day) is as effective as typical EE in male rats
- No significant differences observed whether EE (i.e., rehab) is provided in 1 longer exposure or 2 shorter sessions (both are equally effective)
- EE can reduce the deleterious effects of HAL, but HAL in turn reduces the benefits of EE



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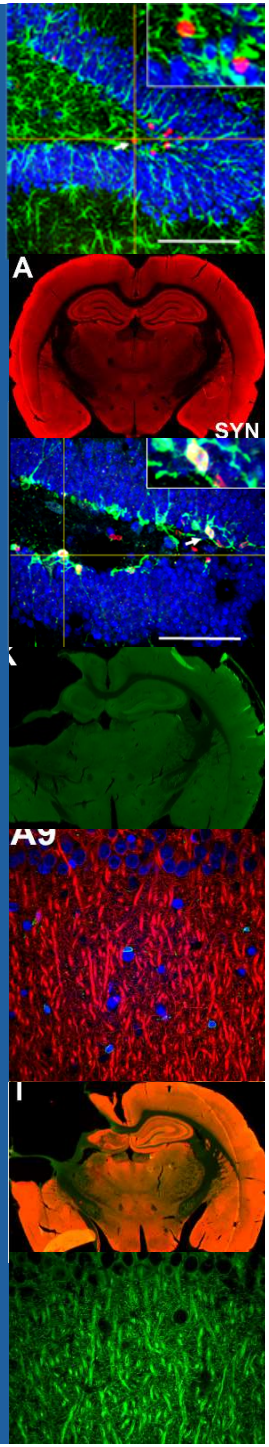

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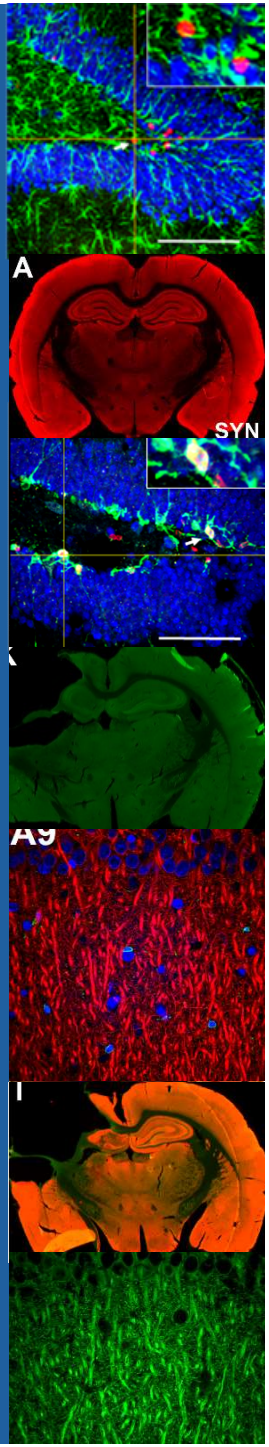

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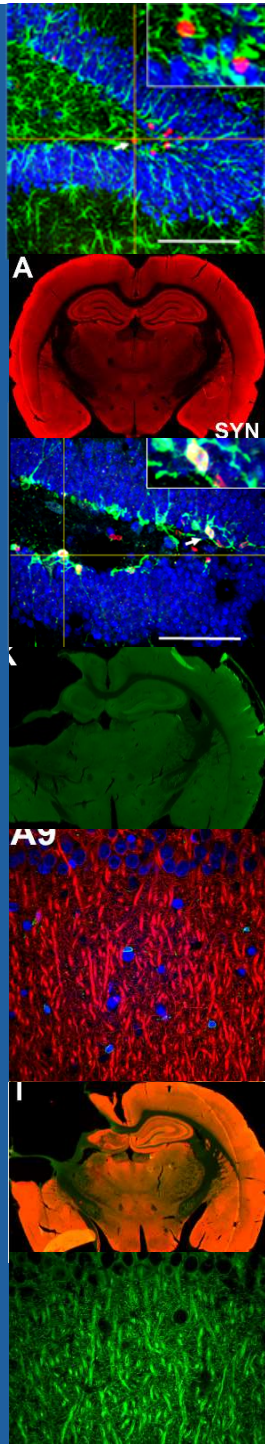

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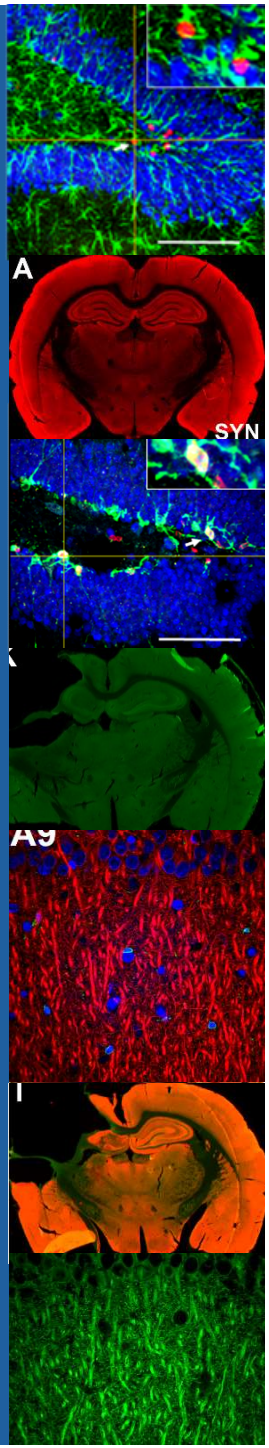

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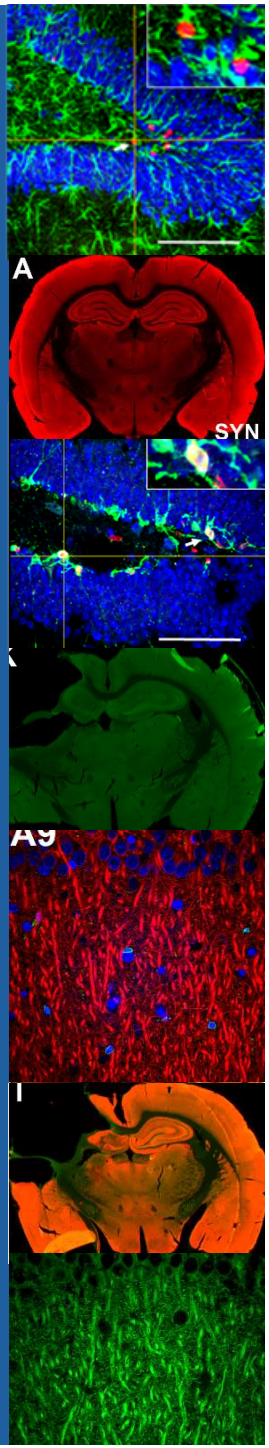

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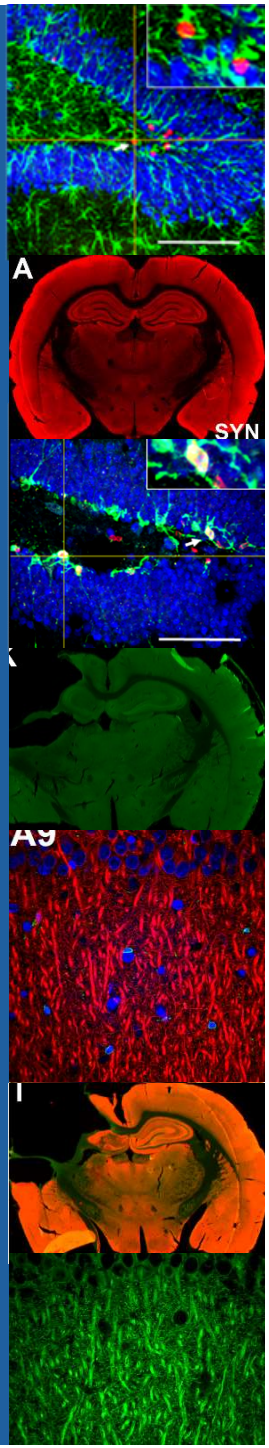

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C. Edward Dixon (Neurosurgery; Safar Center)
Phil Empey (Pharmacological Sciences)
Robert Gibbs (Pharmacological Sciences)
Milos Ikonomovic (Neurology)
Patrick Kochanek (Critical Care Medicine; Safar Center)
Mioara Manole (Critical Care Medicine; Safar Center)
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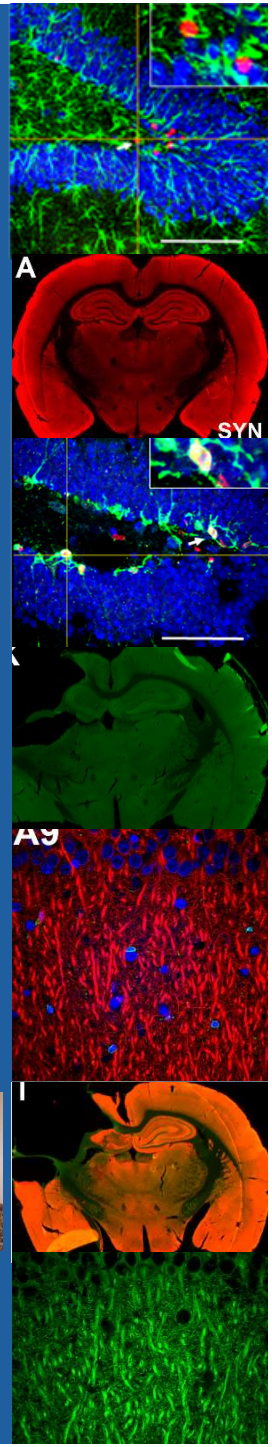

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Children's Hospital of Pittsburgh of UPMC

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