



UNIVERSITY *of* PENNSYLVANIA



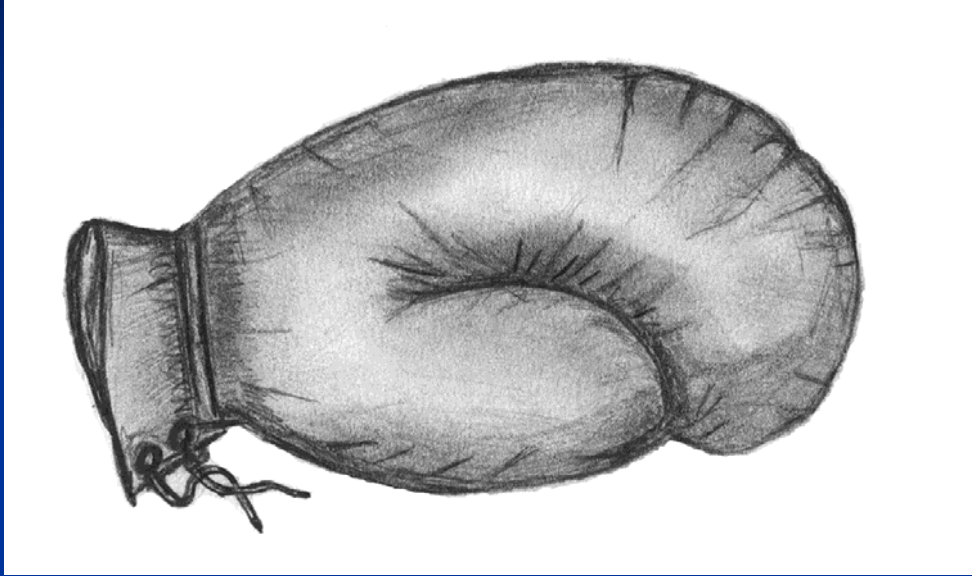
CBIR



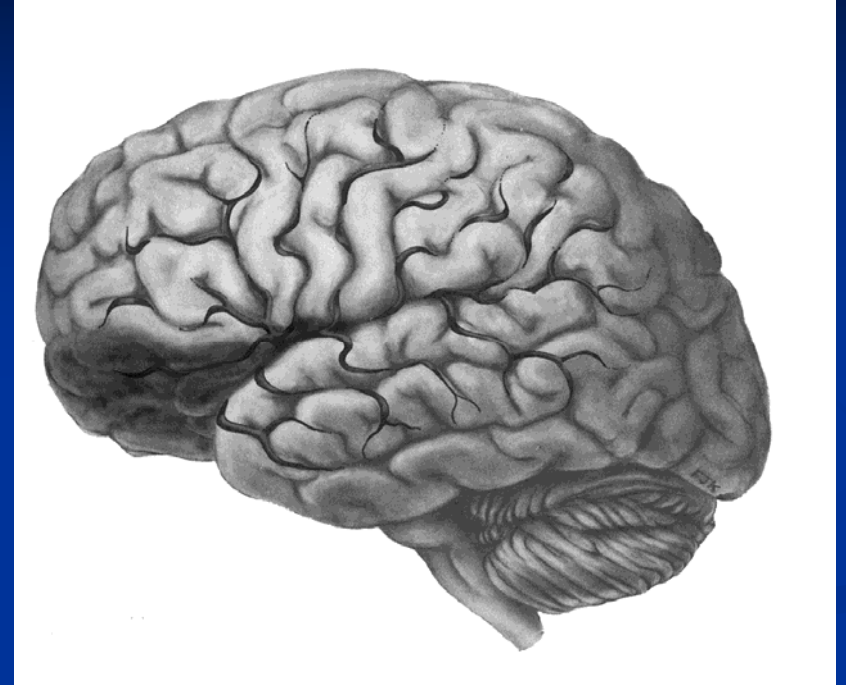
Penn Center for Brain Injury and Repair

Mild TBI: Animal to Human Translation

Douglas H. Smith
Department of Neurosurgery
Center for Brain Injury and Repair
University of Pennsylvania



1 lb. Boxing Glove

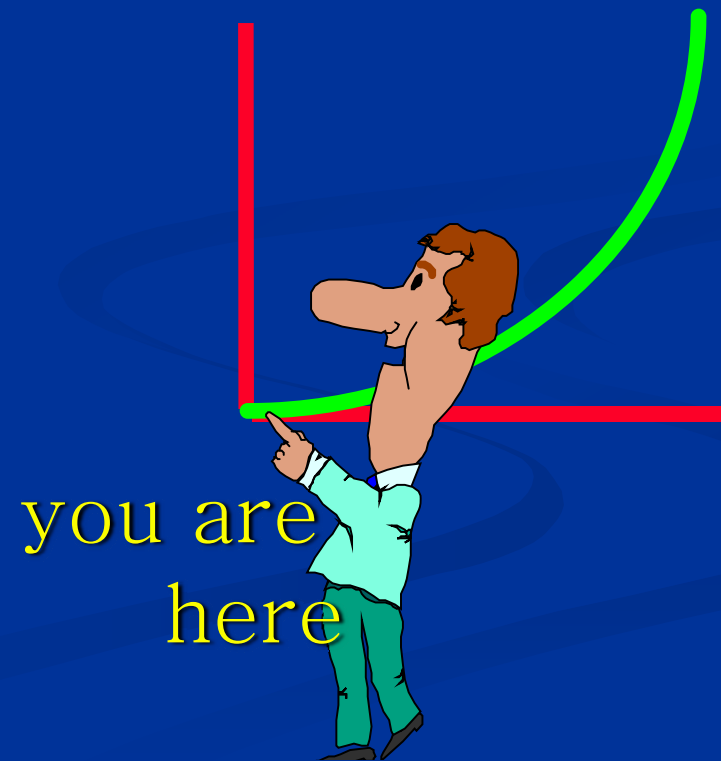


3.3 lb. Human Brain

Multiple Clinical Trials for TBI Rx

Treatments = 0

Learning Curve



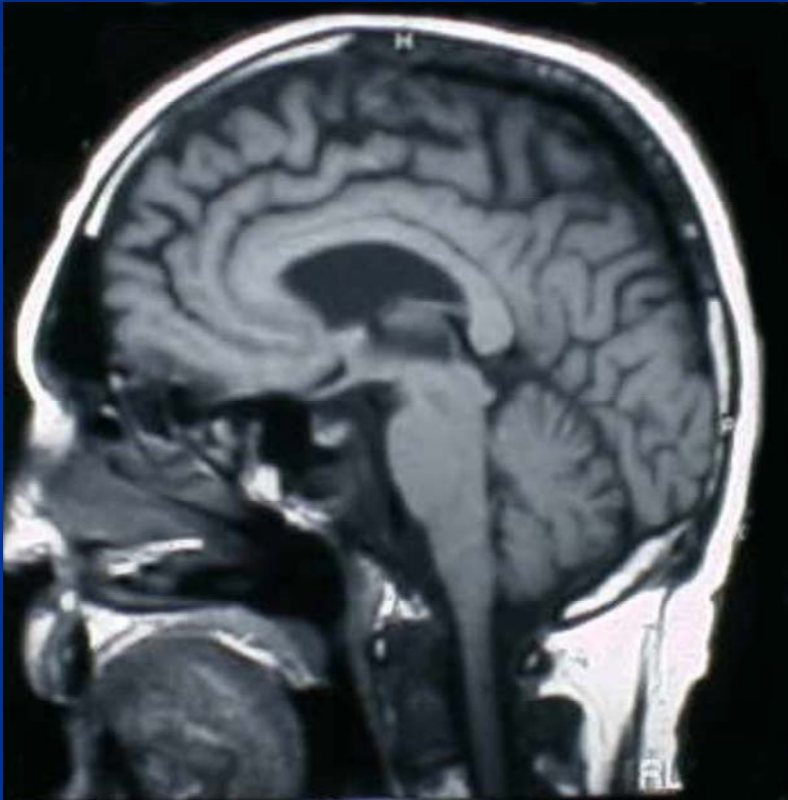


“Mild TBI” is an oxymoron
Over one million cases of mTBI
in the US each year
Approx. 15% of mTBI patients
have persisting cognitive
dysfunction



The term “concussion” is akin
to “consumption” as it was used
long ago.

What is it???



HYPOTHESIS:

mTBI = Diffuse Axonal Injury

because of what

you can't see

There are many creative ways
to induce mTBI



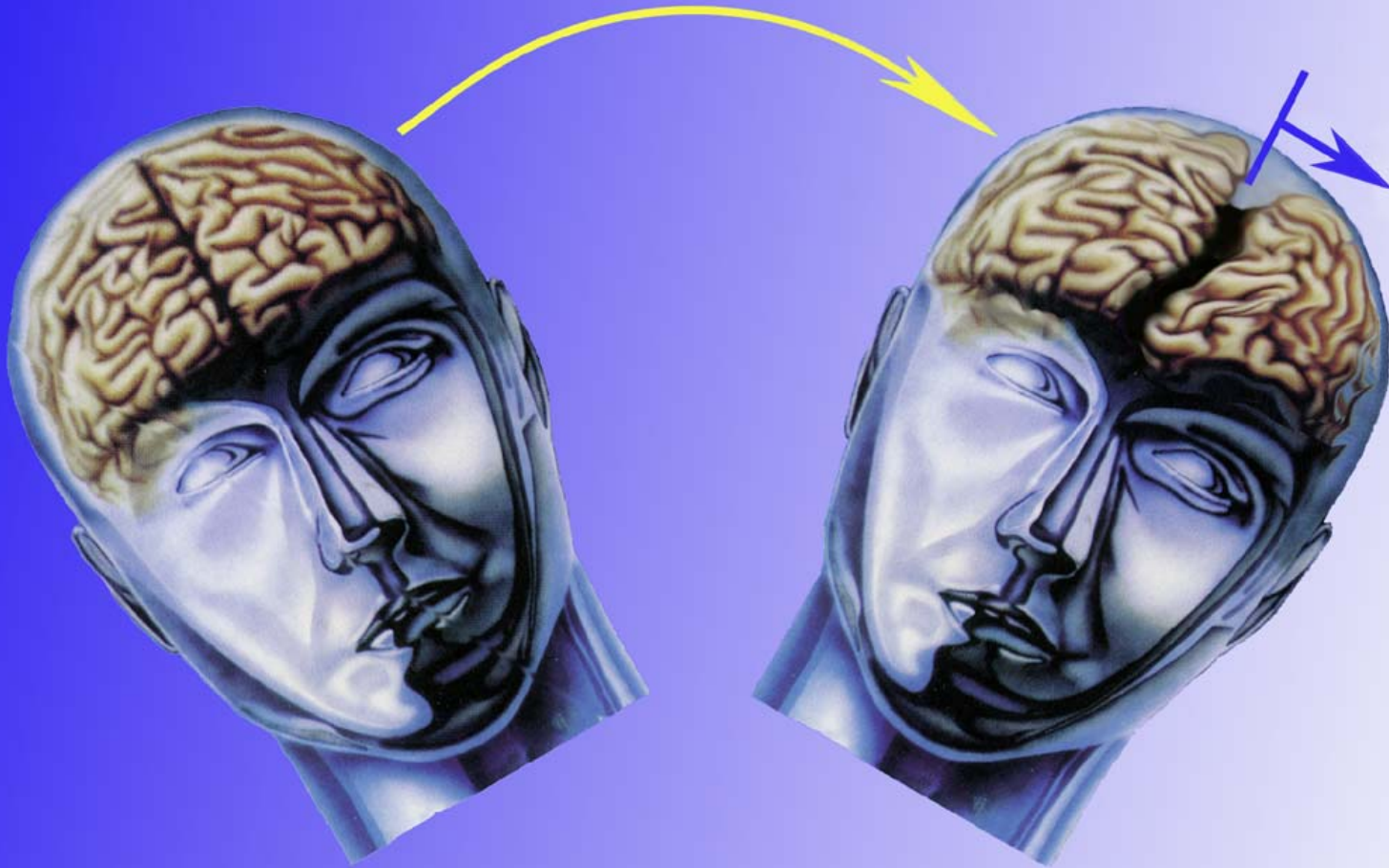


Contact Loading → Inertial Loading

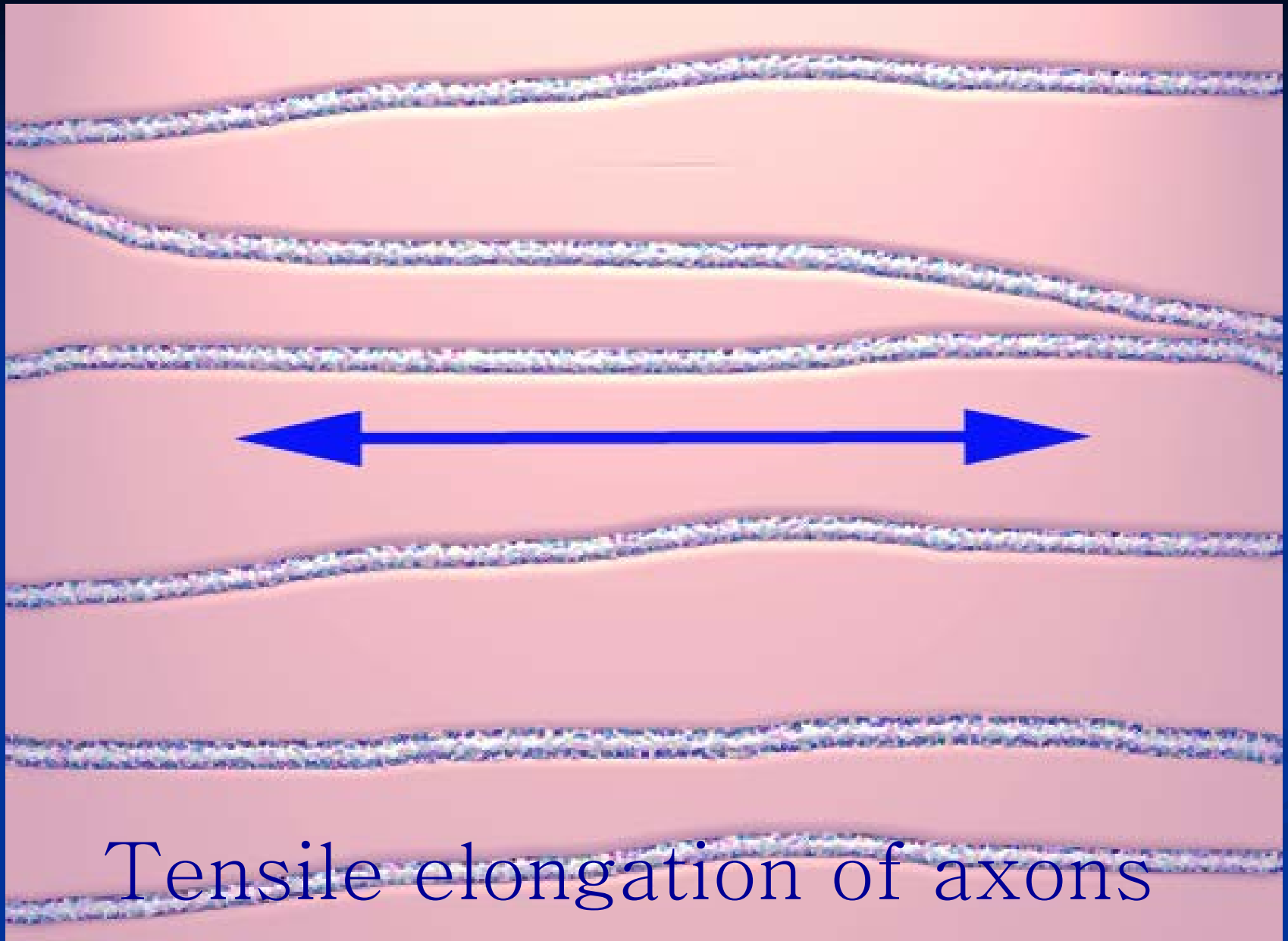


↓
Diffuse Axonal Injury (DAI)

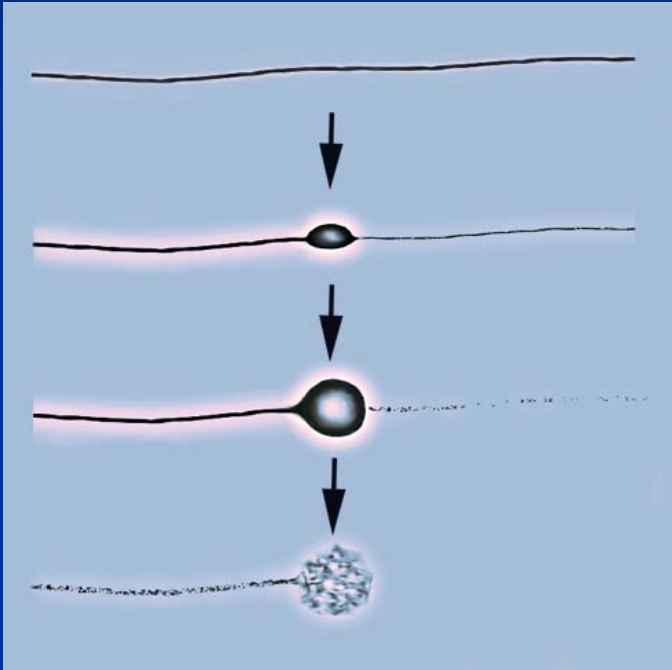
Diffuse Axonal Injury



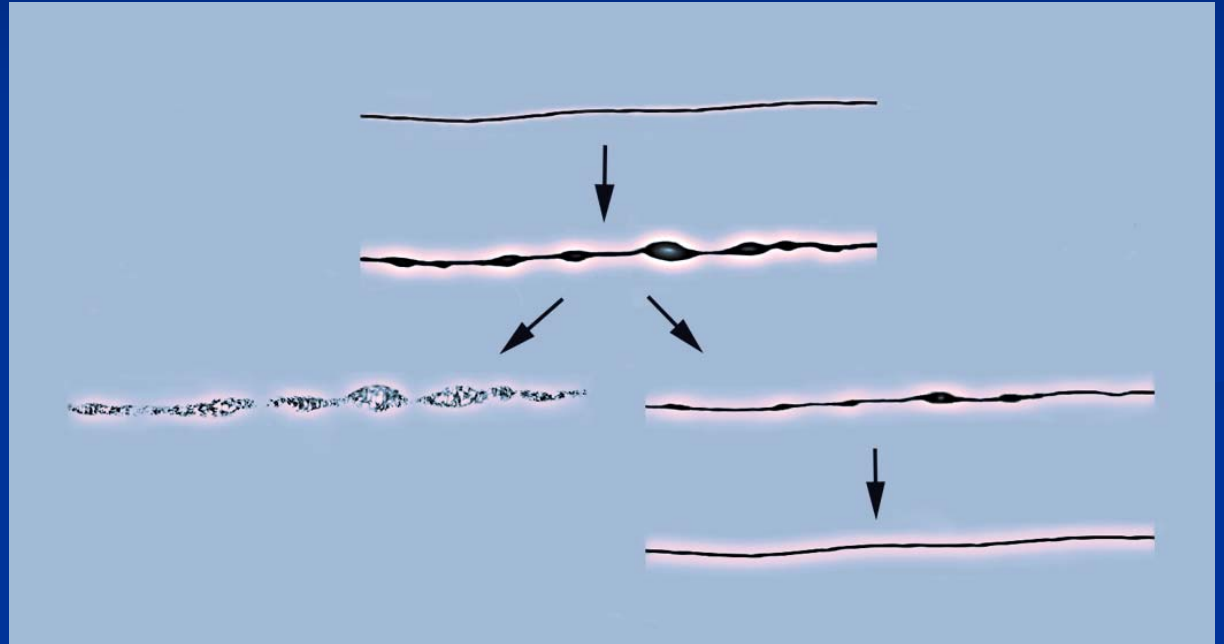
Inertial loading



Tensile elongation of axons

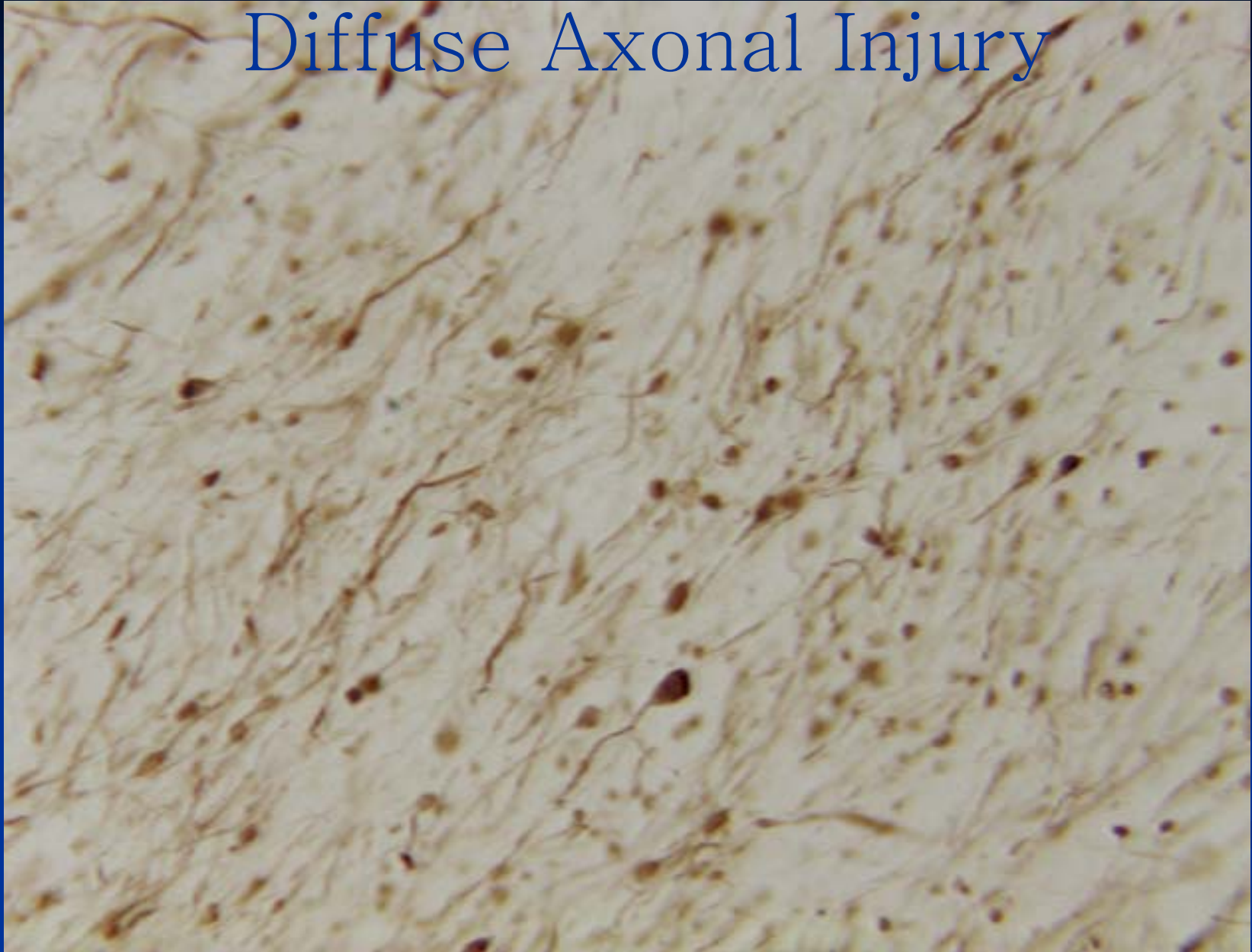


Axonal bulb evolution

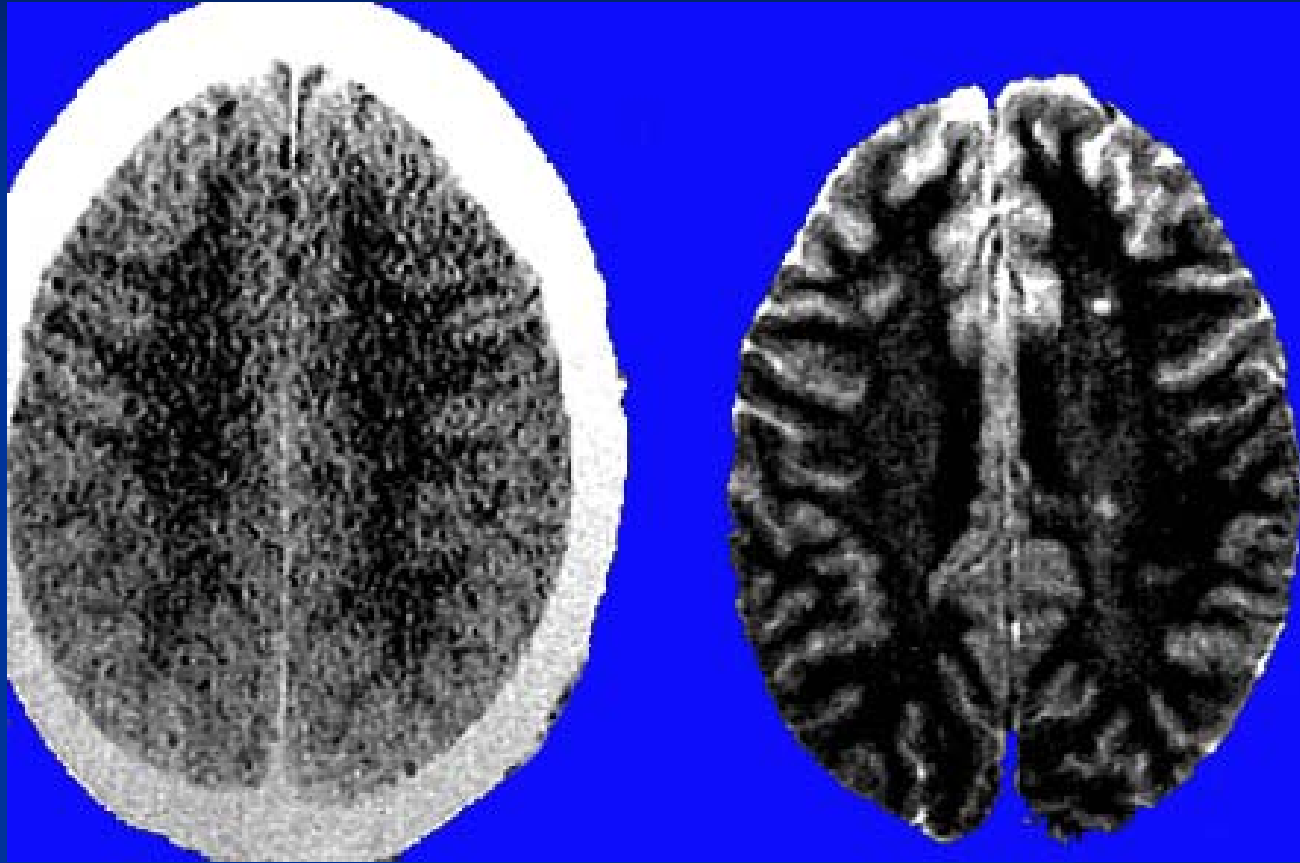


Axonal swelling evolution

Diffuse Axonal Injury



DAI: Diagnosis of exclusion



CT

T2



DAI:

The most important and
most common pathology of TBI

Difficult to detect, difficult to model

“All models are wrong.
Some are useful”

George Box, 1979



Can clinical DAI be reproduced
in a rodent model of TBI?



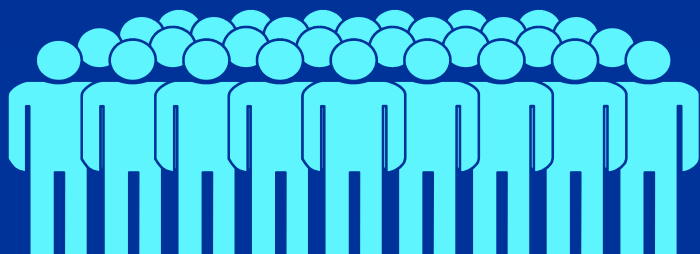
Rat Inertial Brain Injury



$$\ddot{\theta}_s = \left(\frac{M_{ref}}{M_s} \right)^{2/3} \ddot{\theta}_{ref}$$

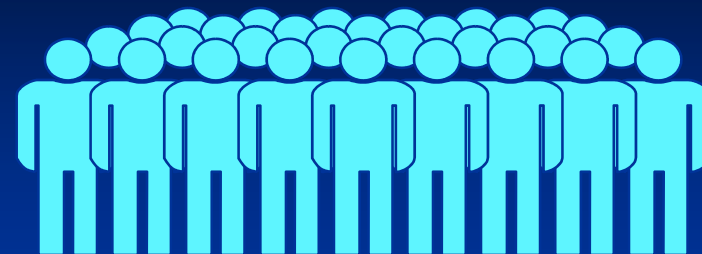
Multicenter NIH Program Grant on mTBI

>1 million mTBI per year



Current practice:
No Risk Assessment

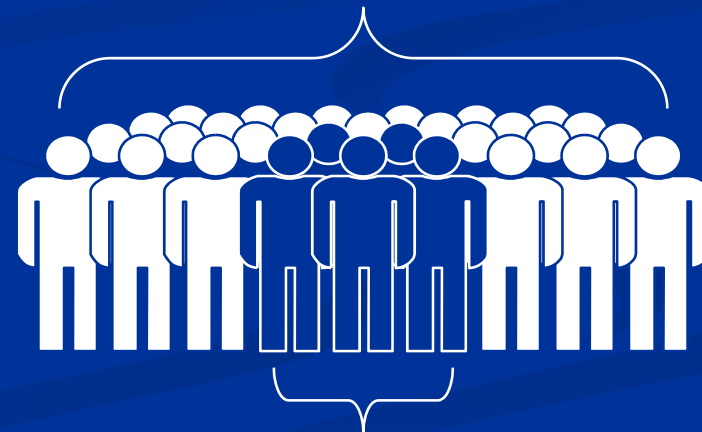
Many will suffer persistent dysfunction ...



... but no early detection

Proposed:
Risk Assessment

Early identification of those likely to recover...



...or likely to suffer persistent dysfunction

Risk Assessment Tools:

- Advanced neuroimaging
- Serum biomarkers
- Neurocognitive Assessment



A gyrencephalic animal model of mTBI via head rotational acceleration

“I like pigs.

Dogs look up to us.

Cats look down on us.

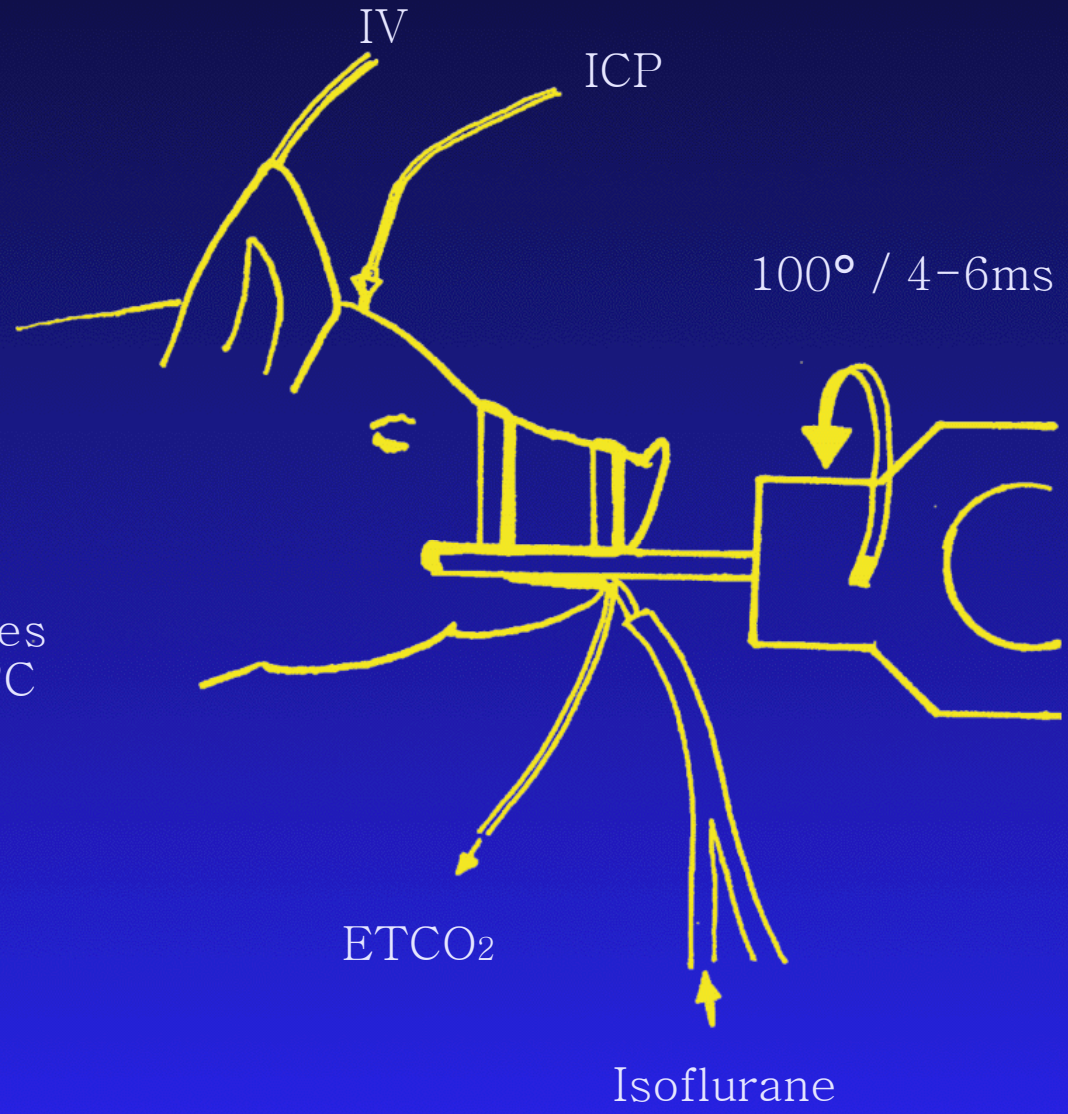
Pigs treat us as equals.”

Winston Churchill



Rotational Acceleration Brain Injury

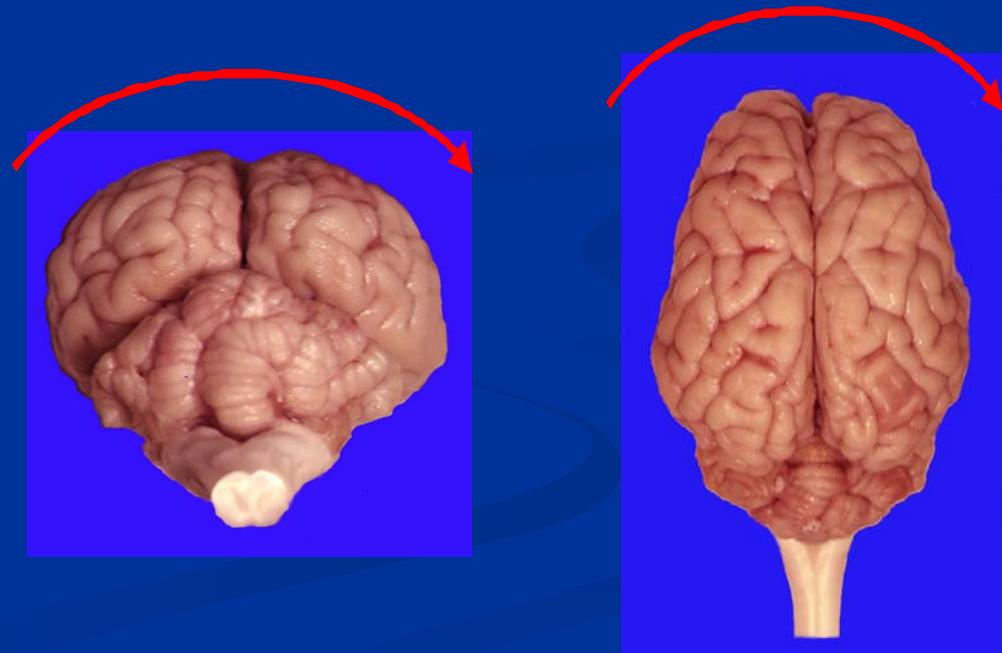
- ECG
- Pulse Ox
- A-Line:
 - MAP/HR
 - Blood Gases
 - Core Body T°C





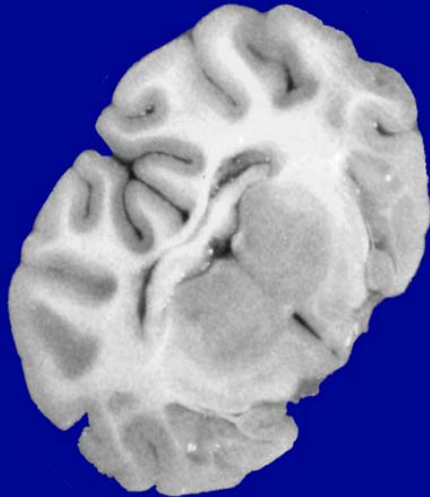
HYGE

Pneumatic actuator

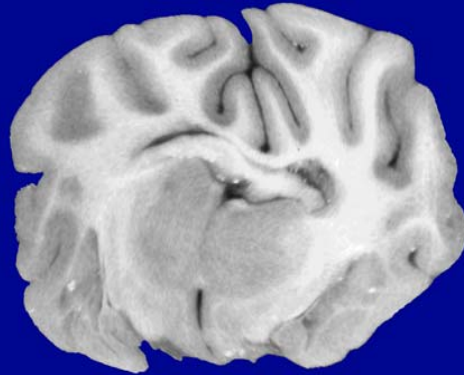


Inertial Brain Injury in the Pig

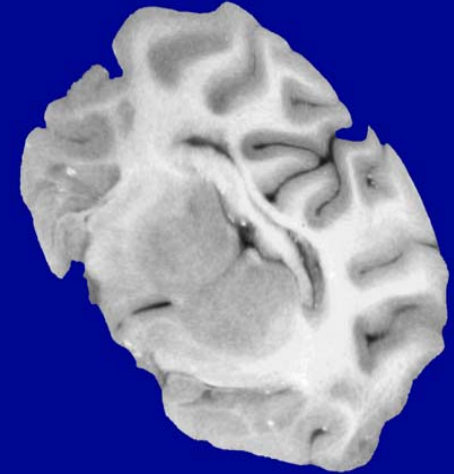
Pre-Acceleration



Acceleration



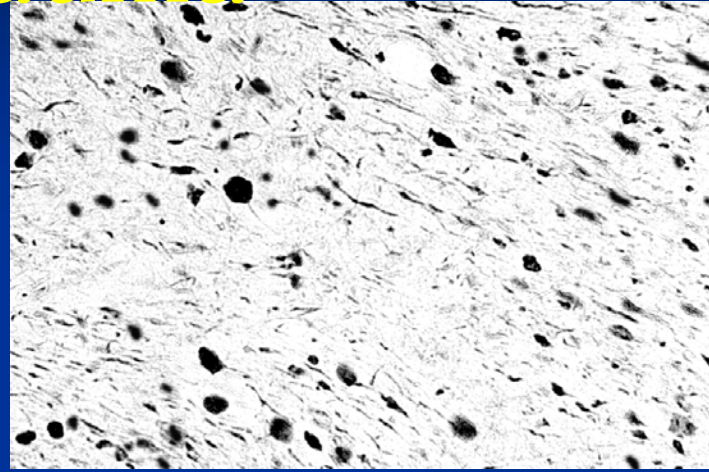
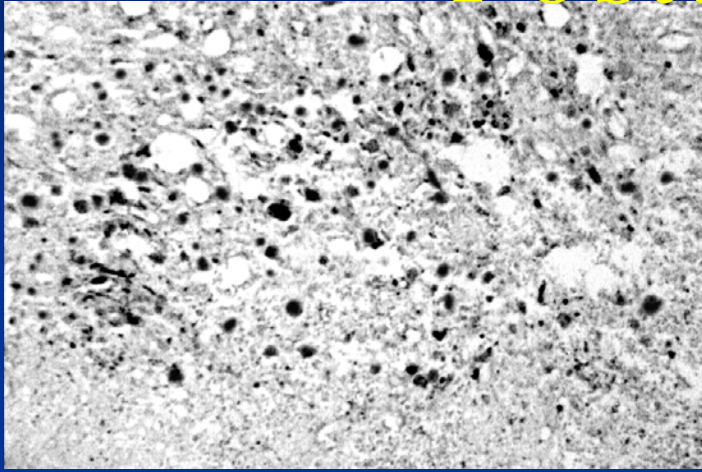
Deceleration



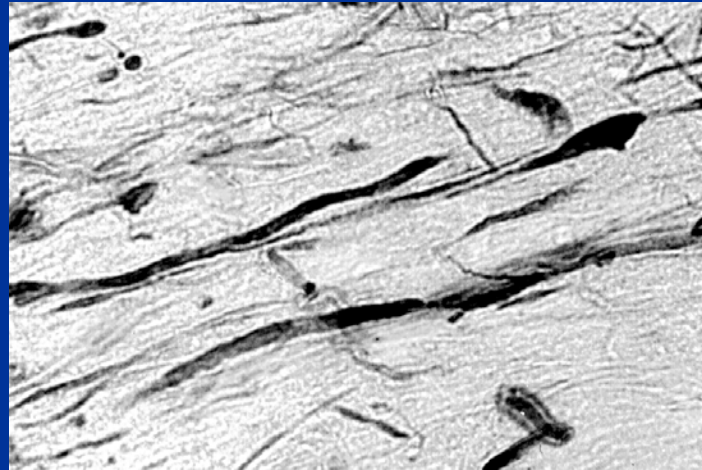
Parameters scaled to mTBI in humans

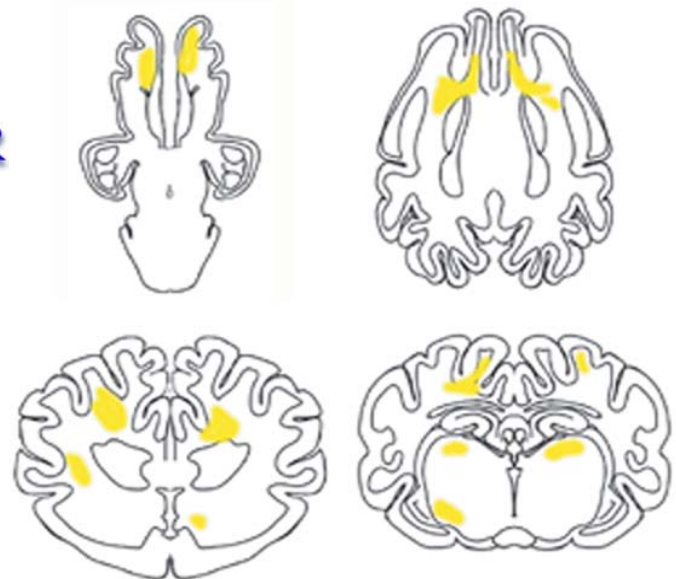
Axonal Pathologies

APP subcortical white matter NF-H subcortical white matter

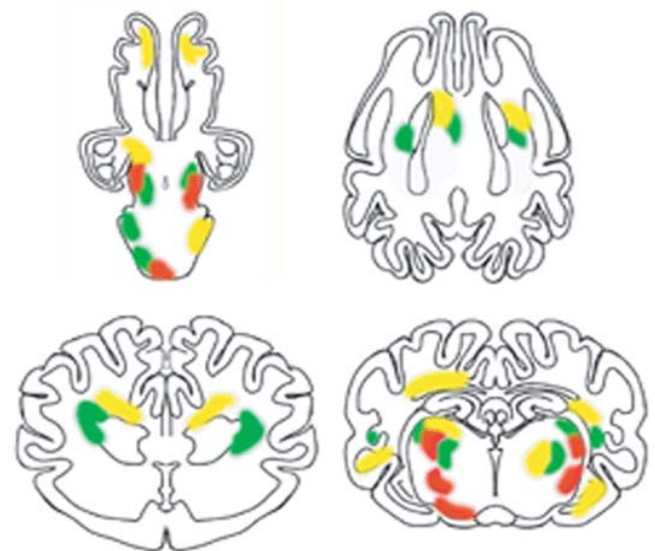


NF-H swellings deep in white matter



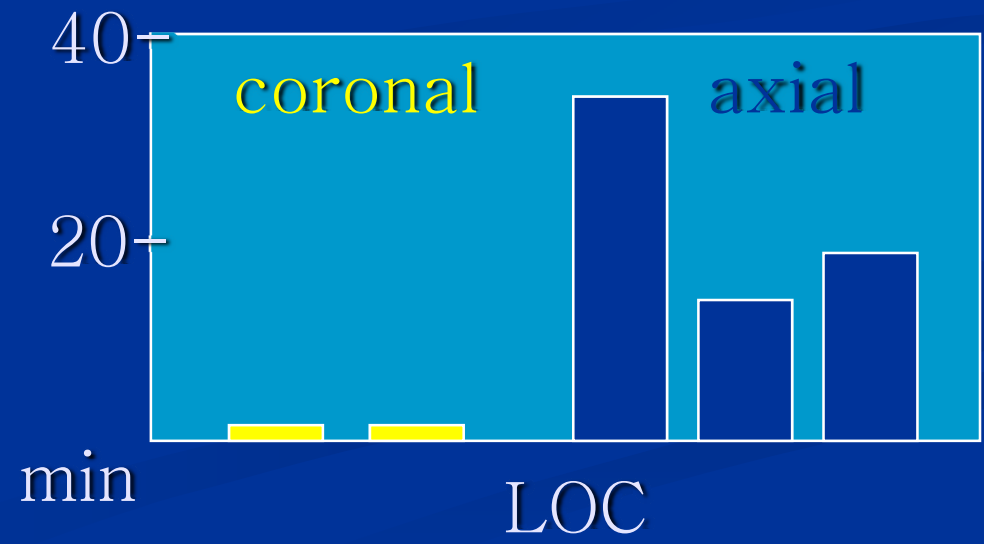
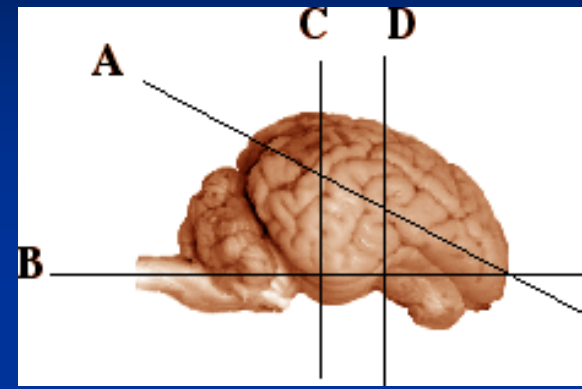


Low Level Coronal Plane Rotation (7d)

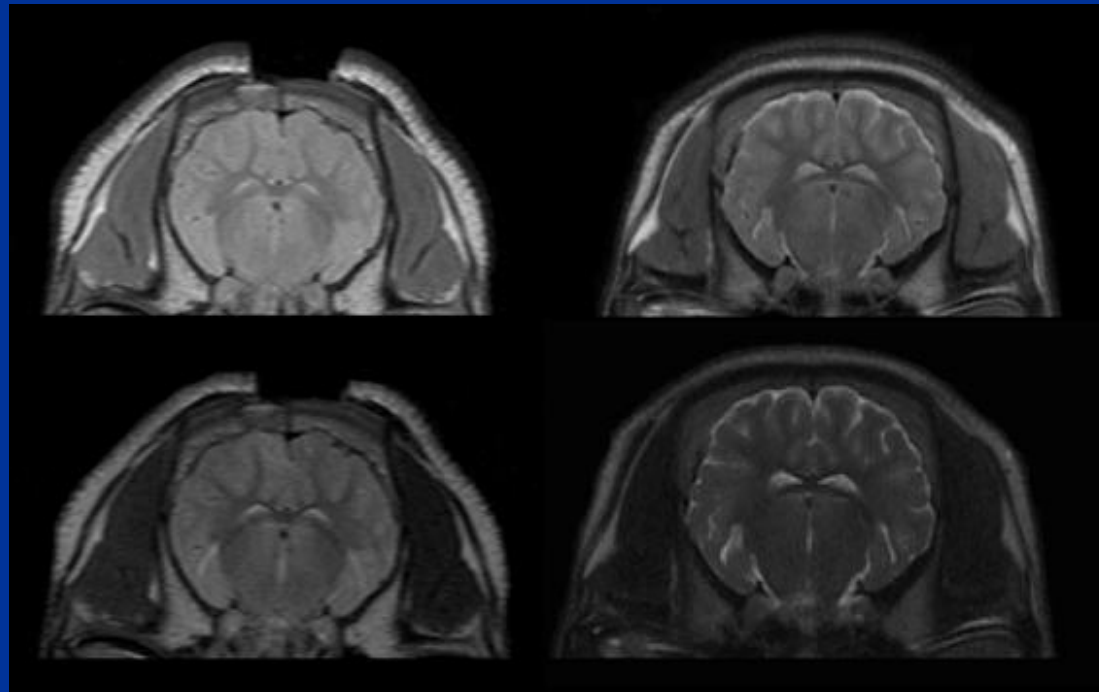


Low Level Axial Plane Rotation (7d)

Mild TBI

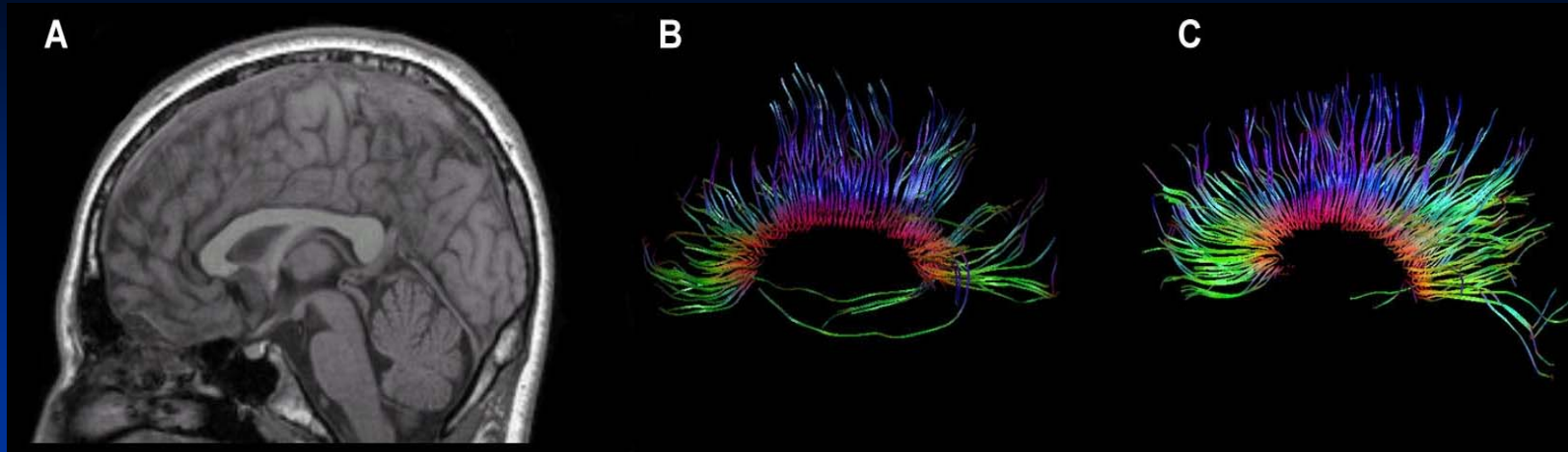


Non-Invasive advanced neuroimaging detection of mTBI...

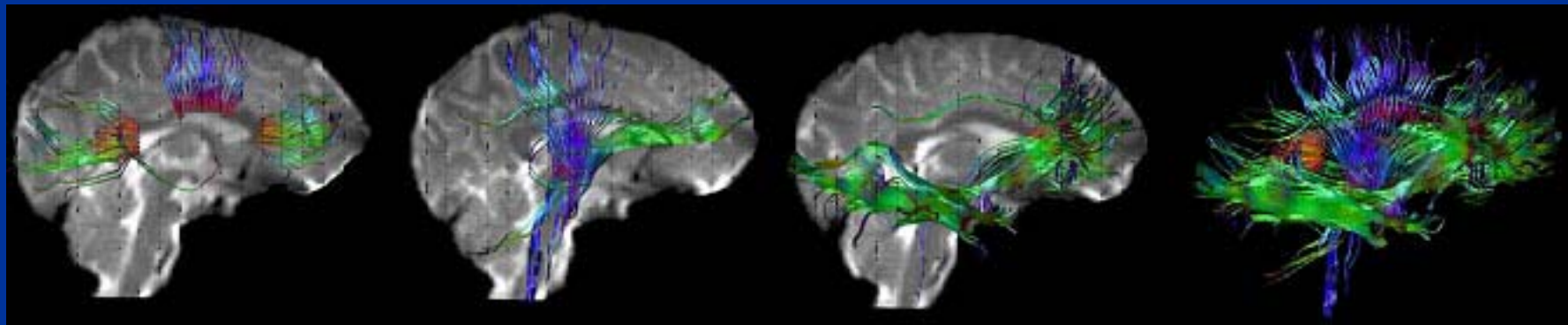


1.5T

3T



DTI Fiber Tractography Human

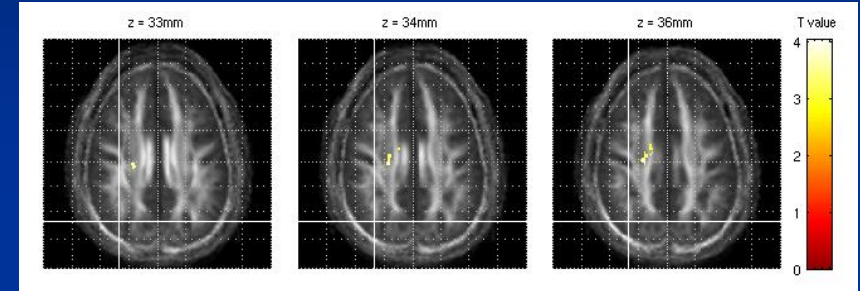
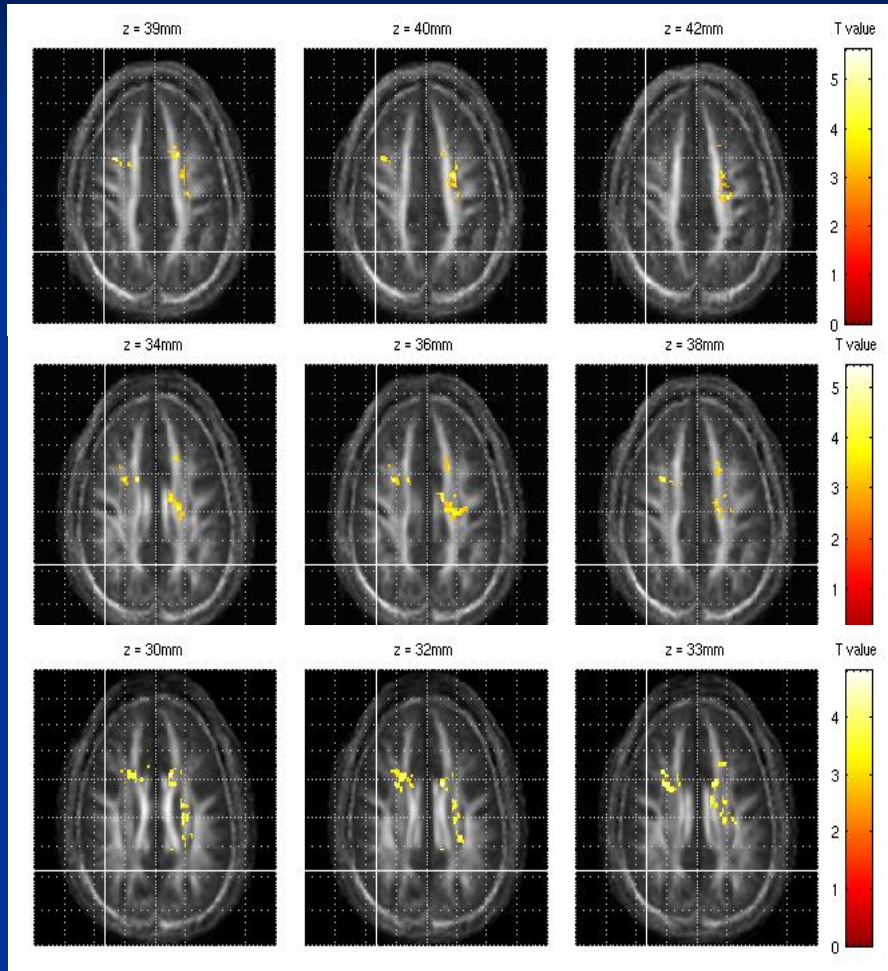


Corpus Callosum

Anterior & Posterior Internal Capsules

Frontal & Temporal Lobes

Combined ROIs for OI (left)



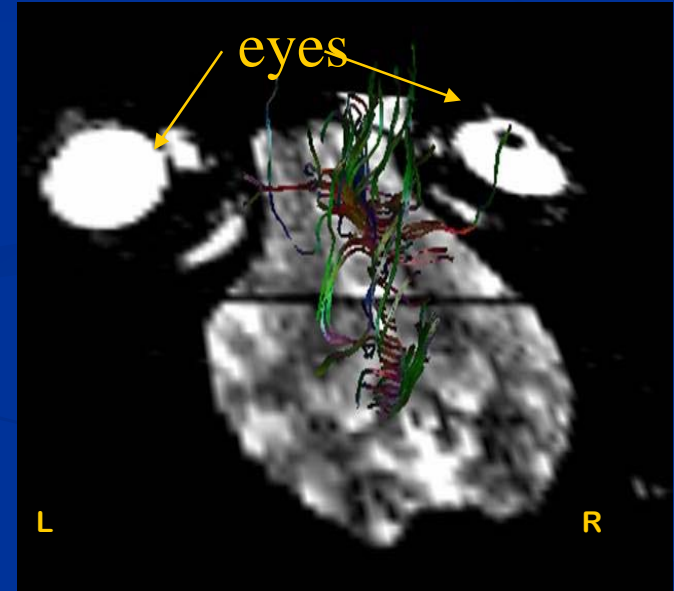
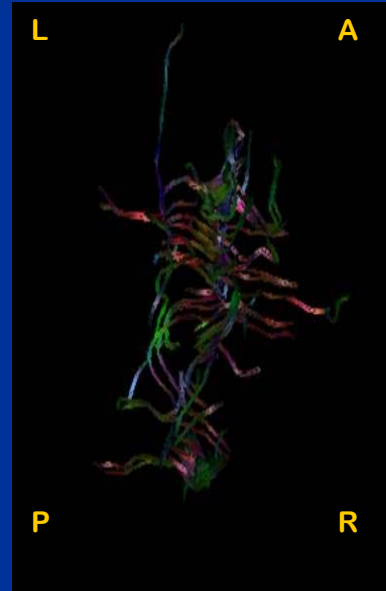
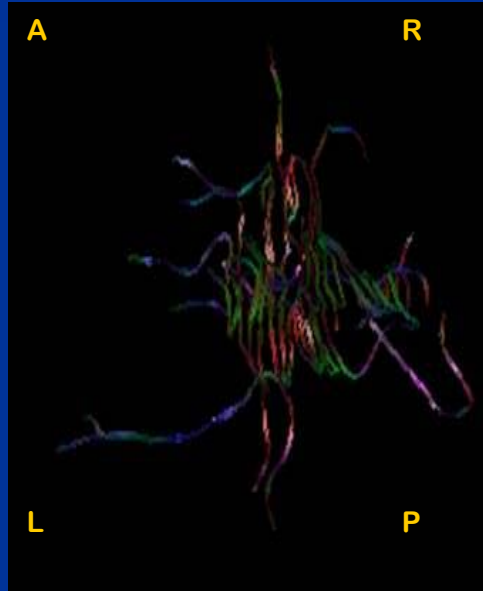
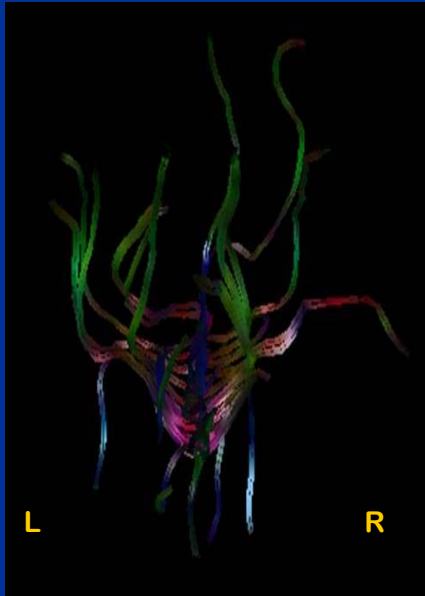
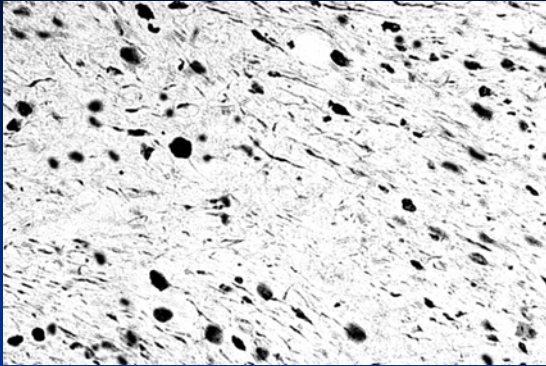
Change in FA

Change in ADC

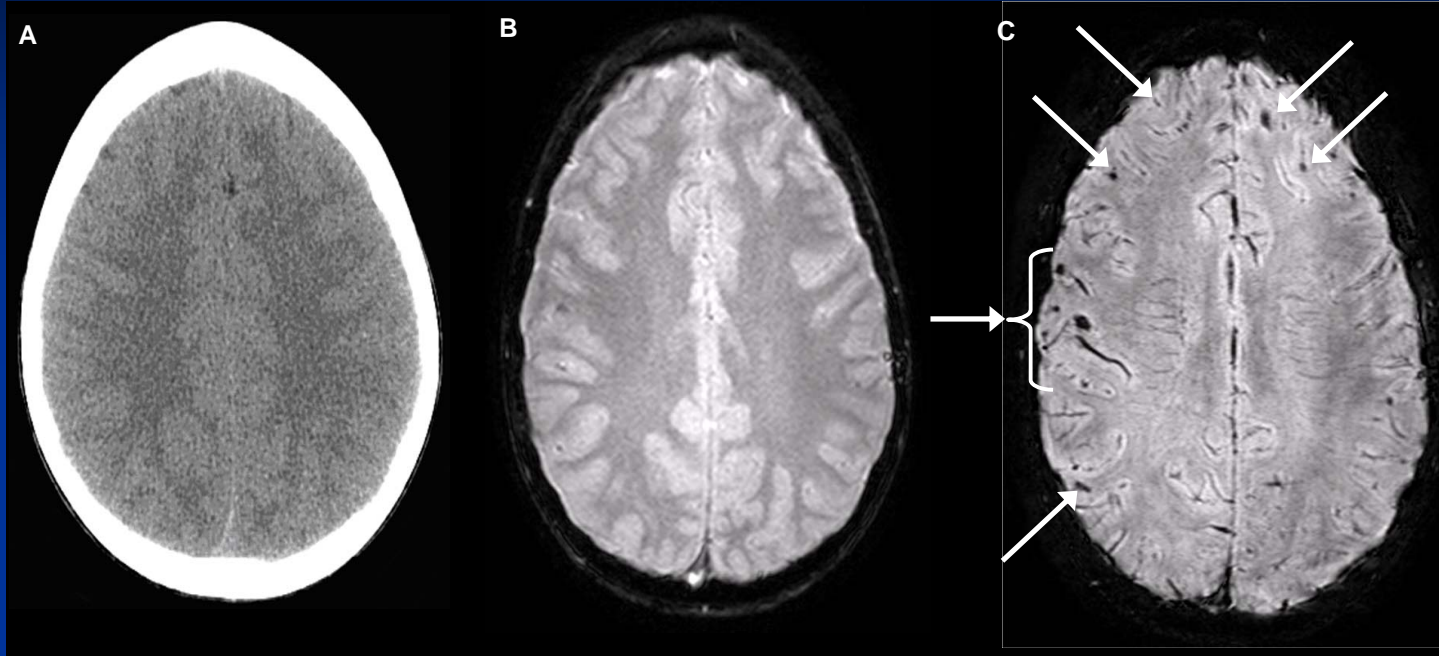
Human studies in parallel with...

mTBI = DAI?

Regional axonal pathology
matching changes in DTI



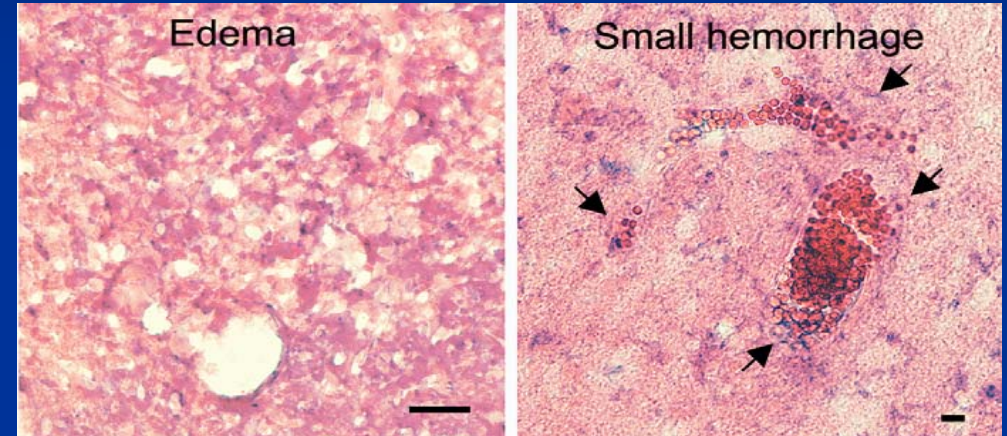
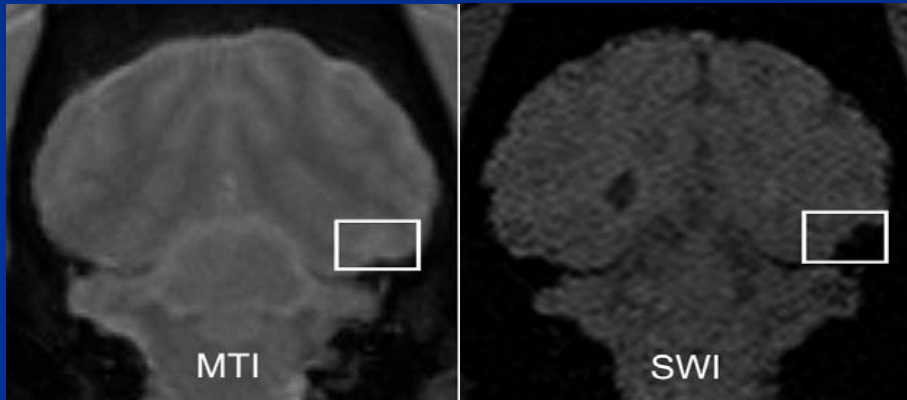
DTI Fiber Tractography Pig



CT

MRI

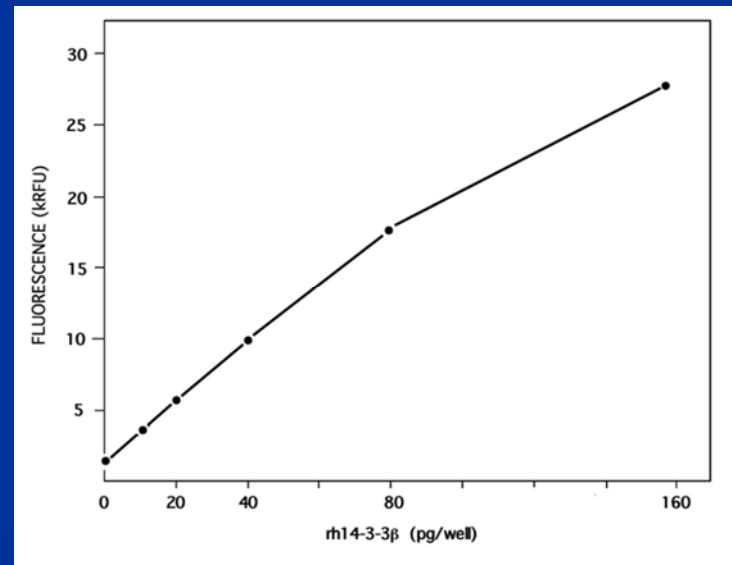
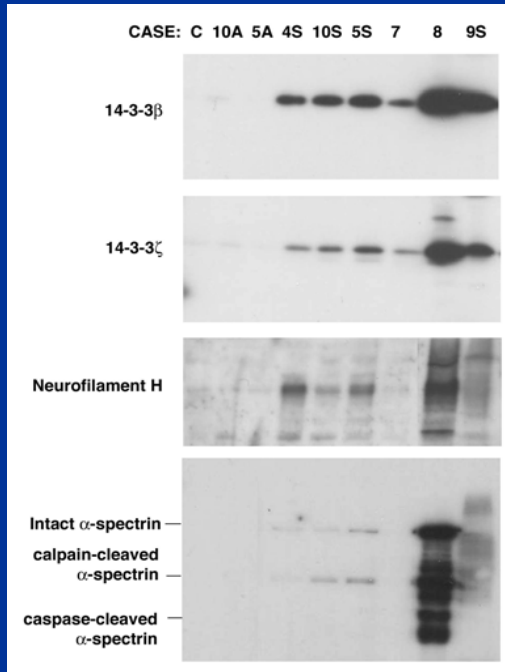
SWI



pig studies – histopathologic confirmation

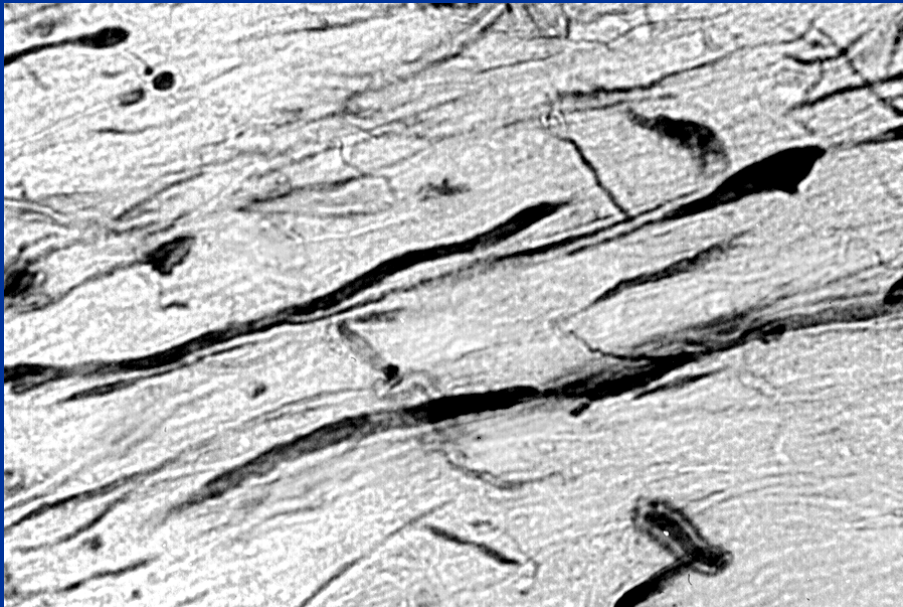
Serum biomarker detection of mTBI

Case	Time (hrs)	pNFH (U/well)
MTBI Pig	Pre-injury	2
	6	14
	72	45





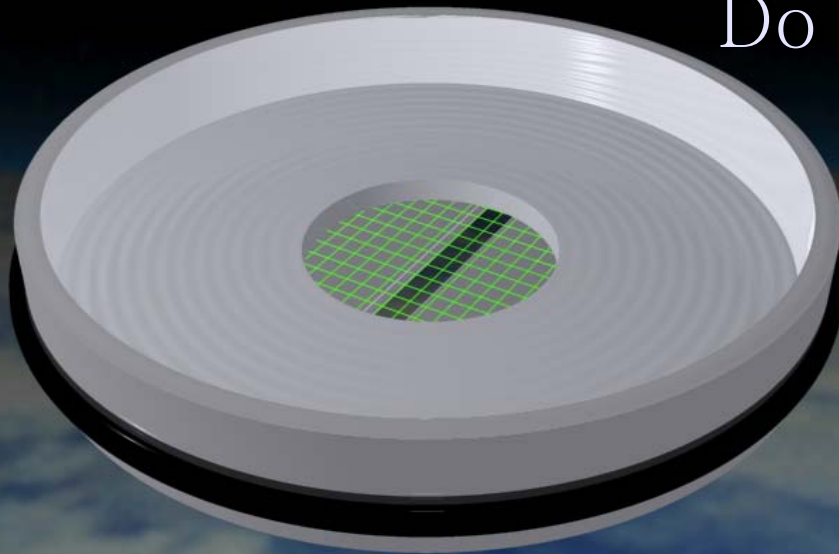
Is DAI more than swollen or degenerating axons?



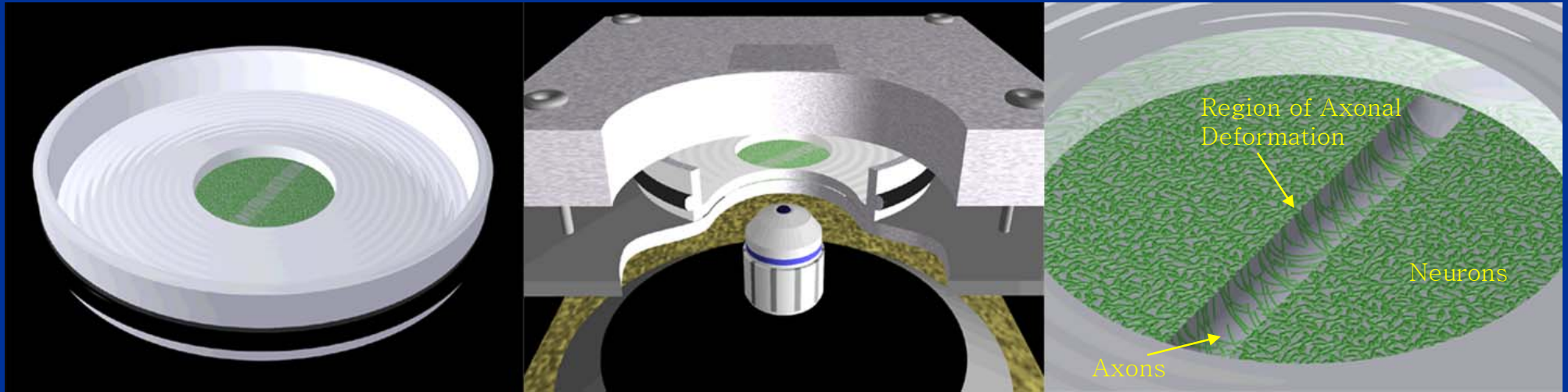
Mechanism
and potential
therapeutic
targets

Mild Axonal Stretch-Injury in Culture

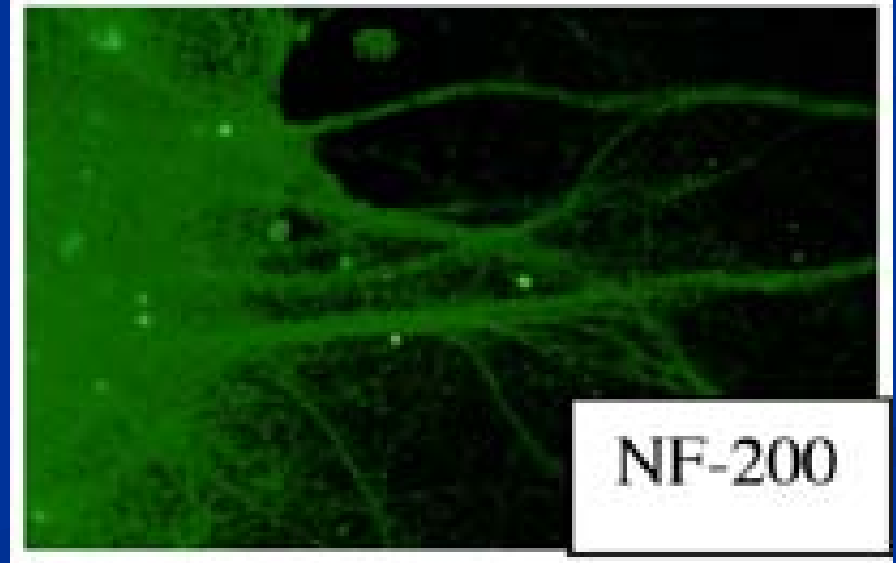
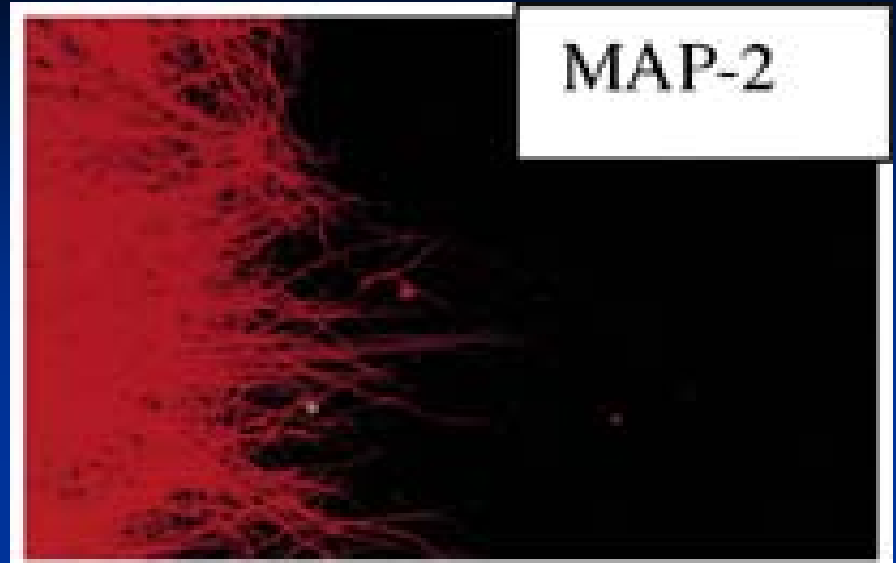
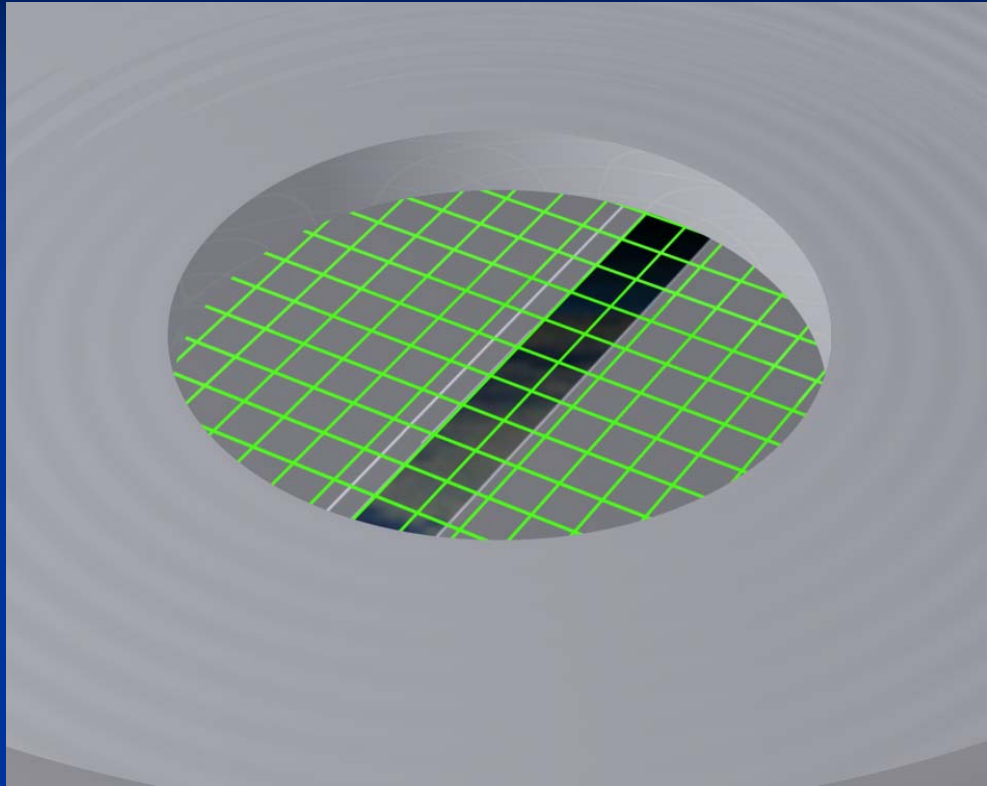
Do injured axons get nachos?

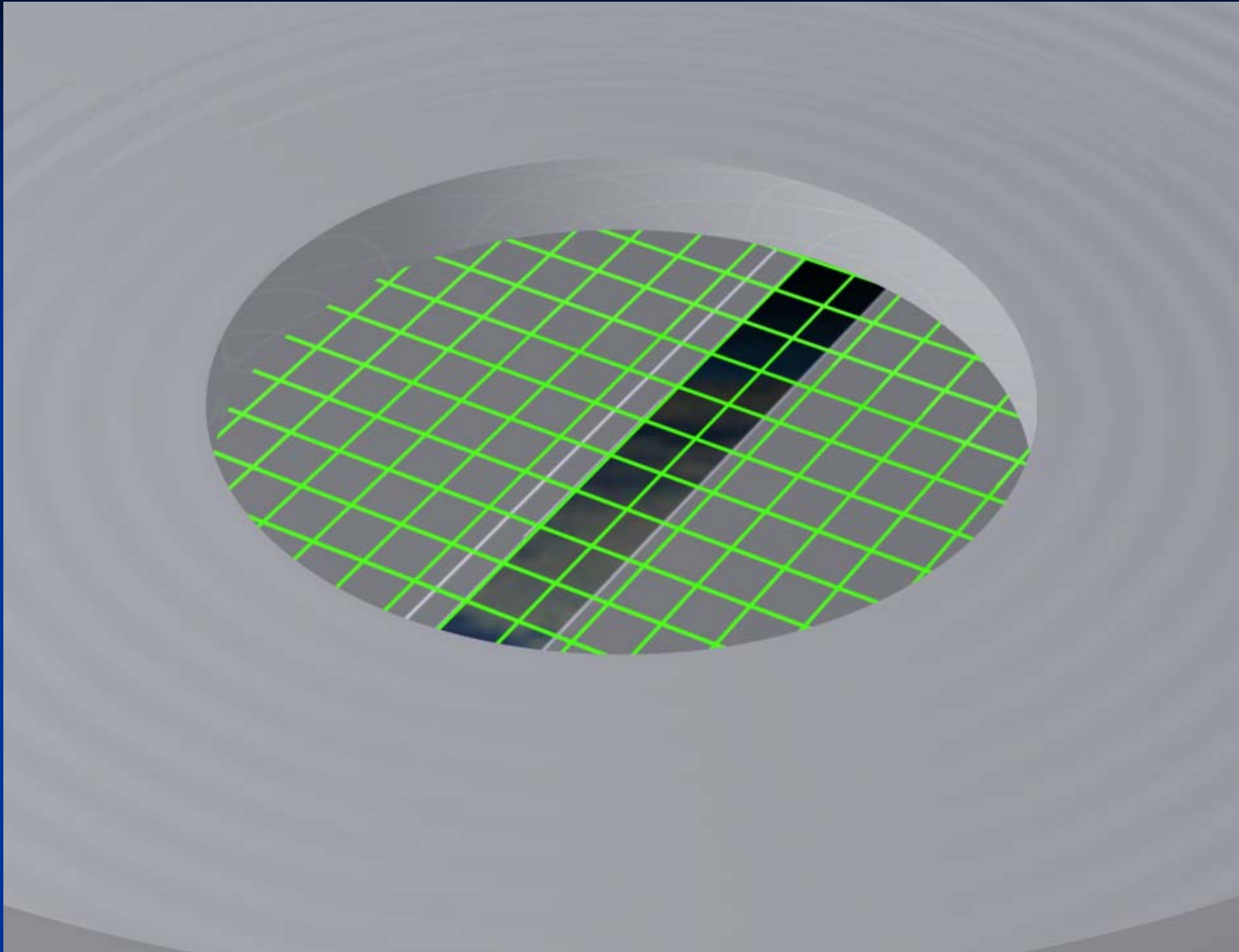


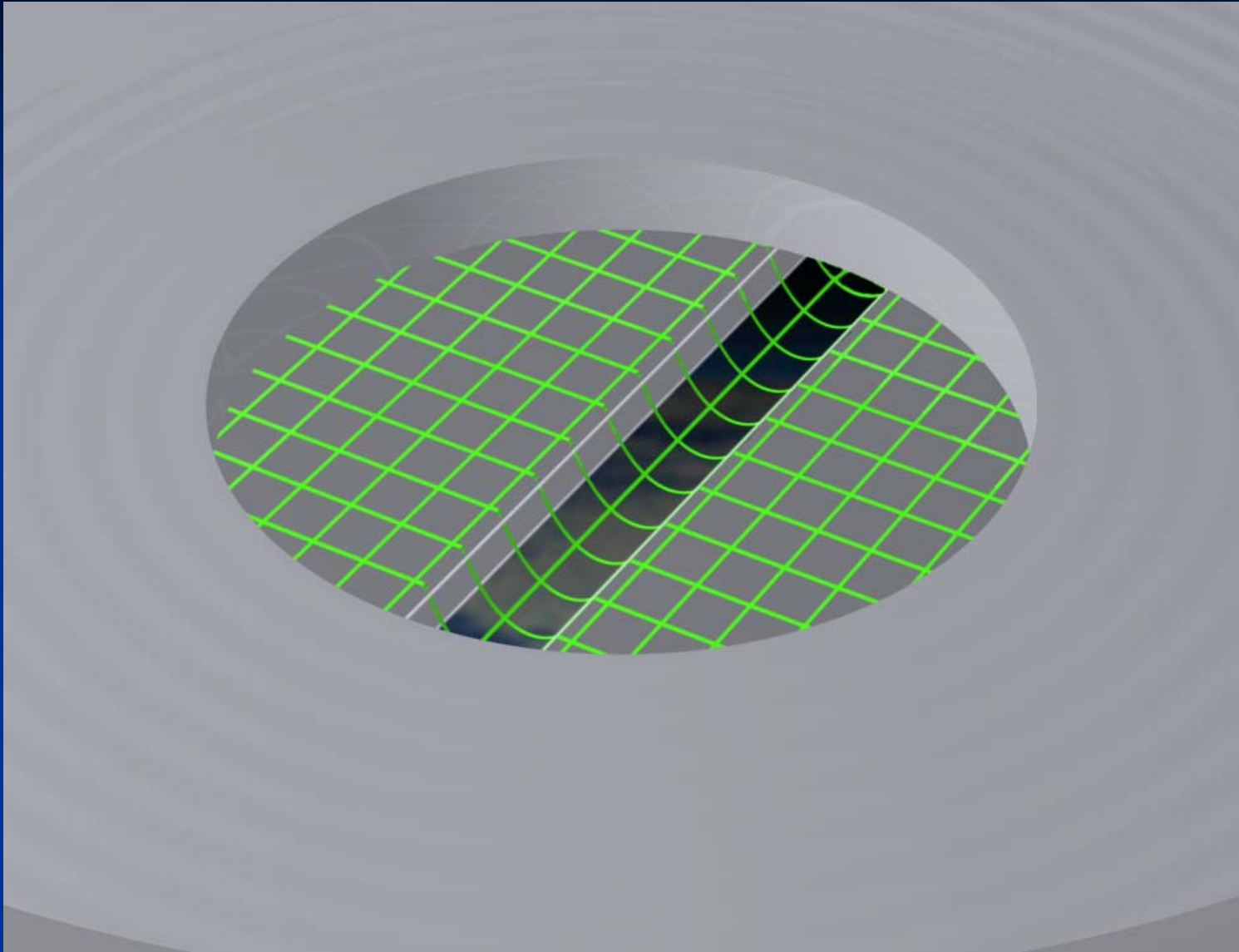
Dynamic Axonal Stretch Injury In Vitro

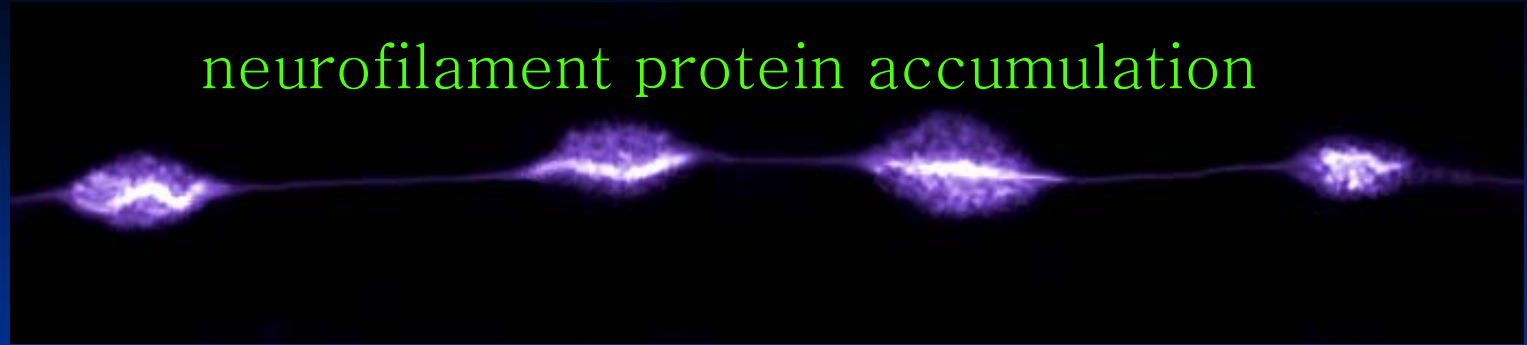
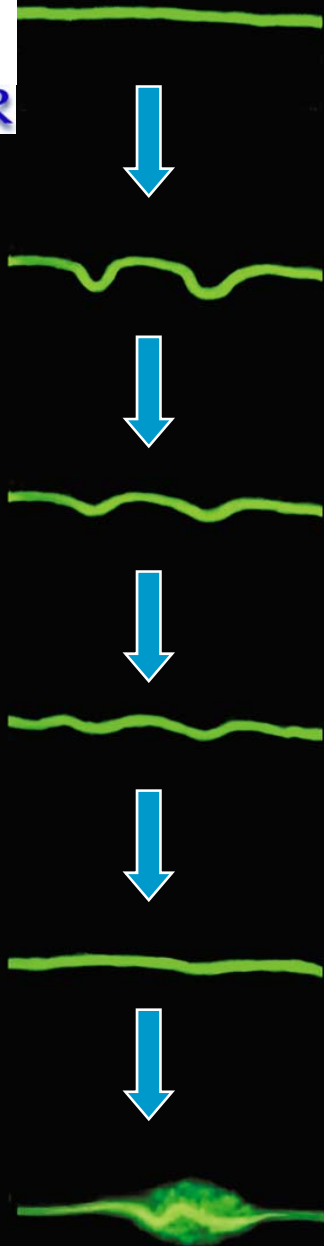


Culture Axonal Injury (CAI)









neurofilament protein accumulation

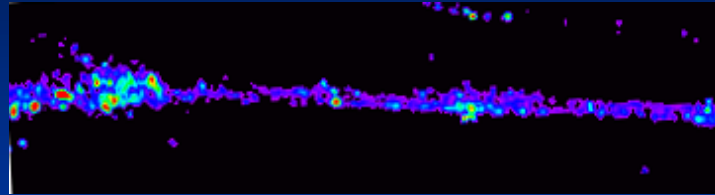
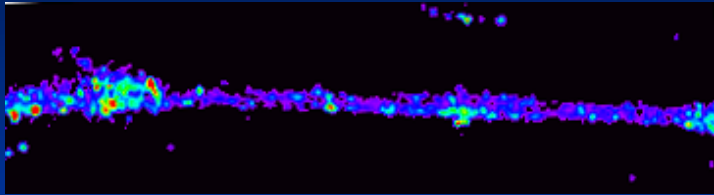
Delayed elasticity,
transport interruption,
and swelling following
tensile elongation
of axons



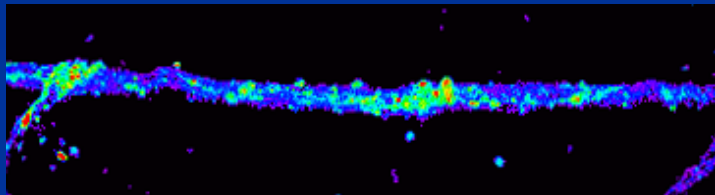
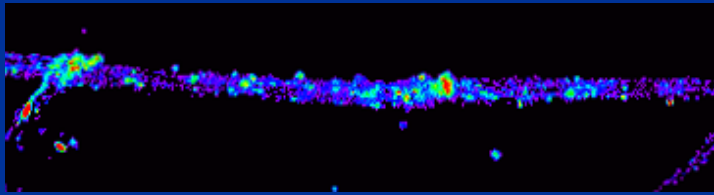
Does calcium enter
stretch-injured axons?

Pre-injury

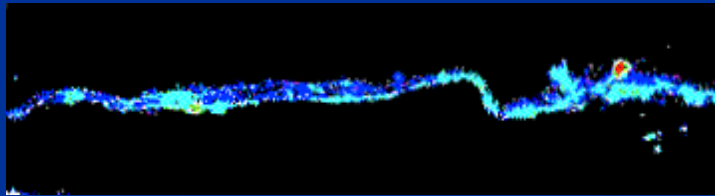
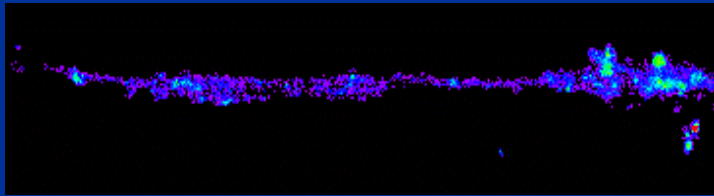
Post-injury



3% strain

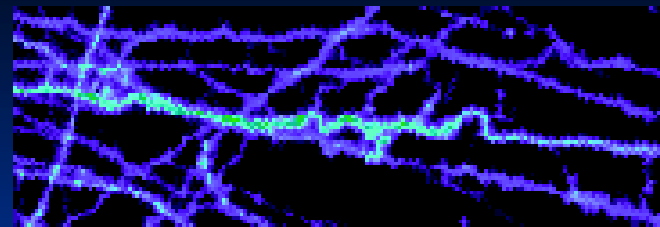
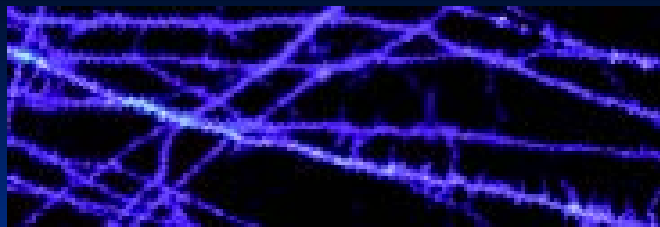


5% strain



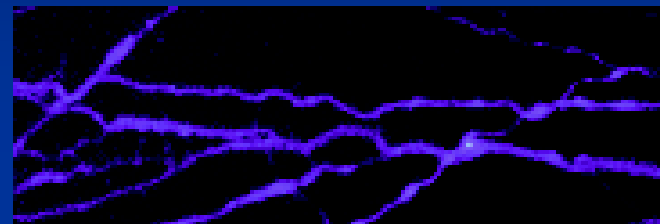
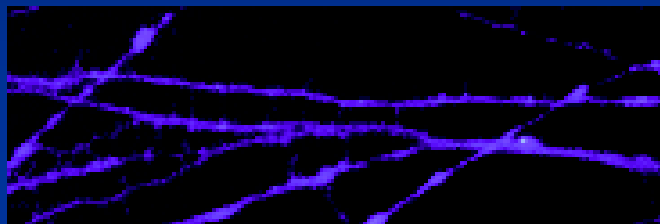
20% strain

Strain-dependent threshold for calcium influx with TAI



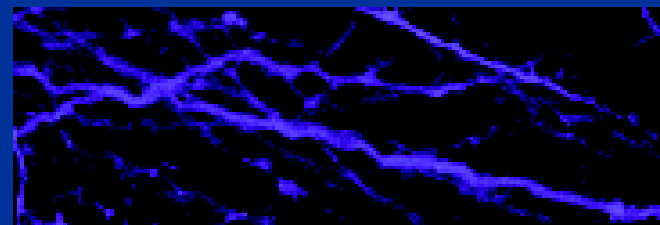
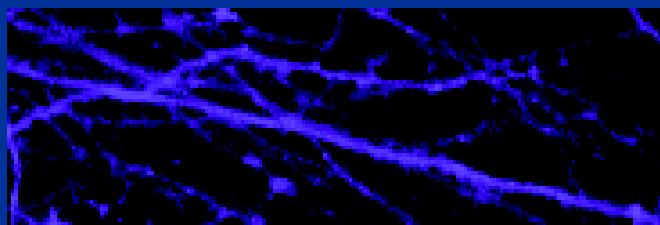
CSS

NaCh



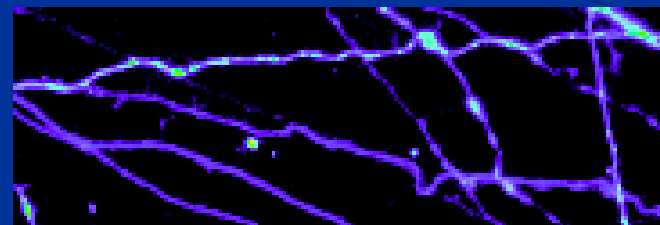
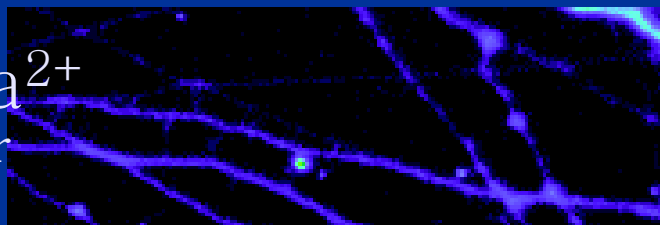
TTX

VSCC



CTX

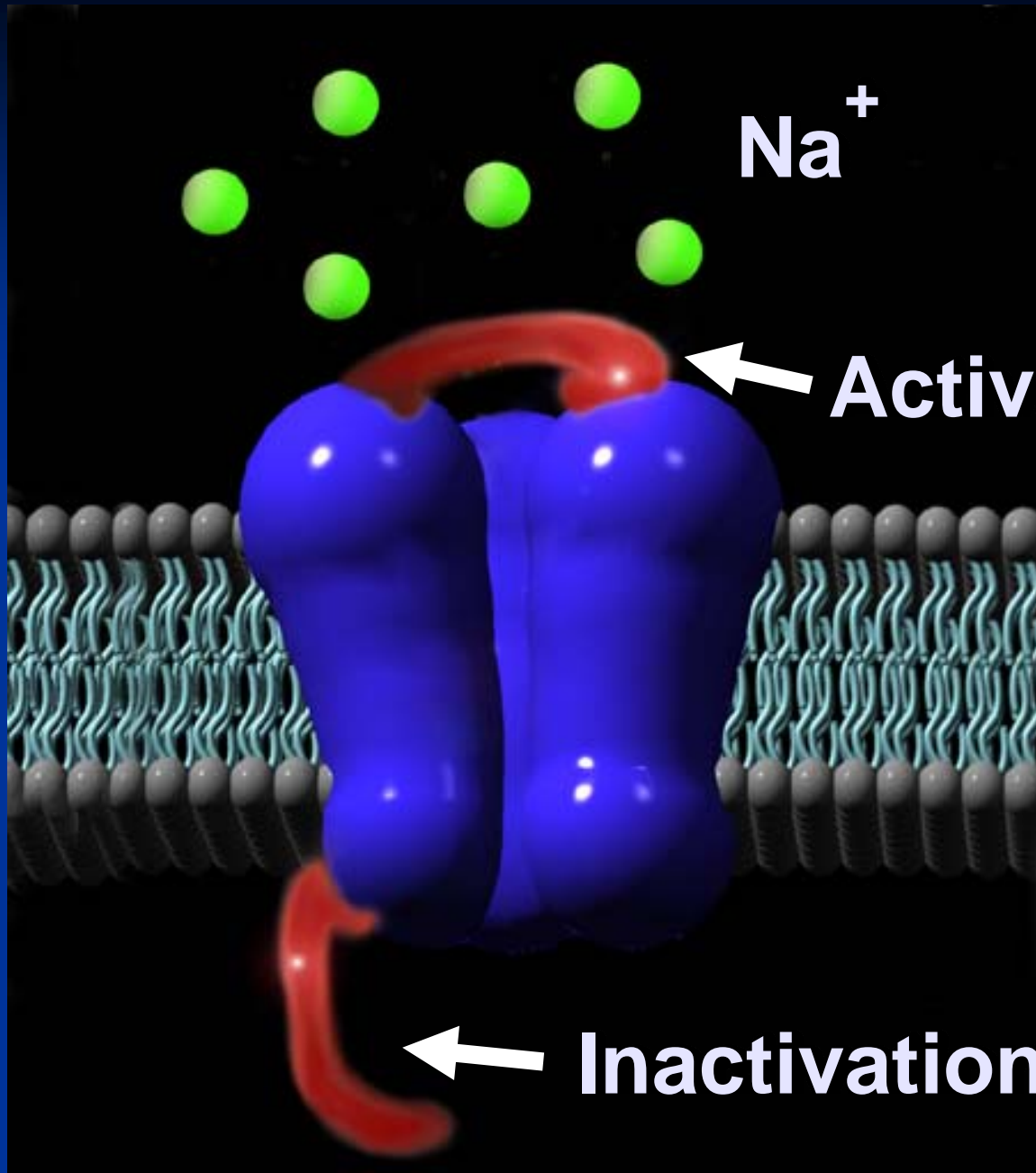
Na⁺/Ca²⁺
exchanger



BEP

Pre-injury

30s Post-injury



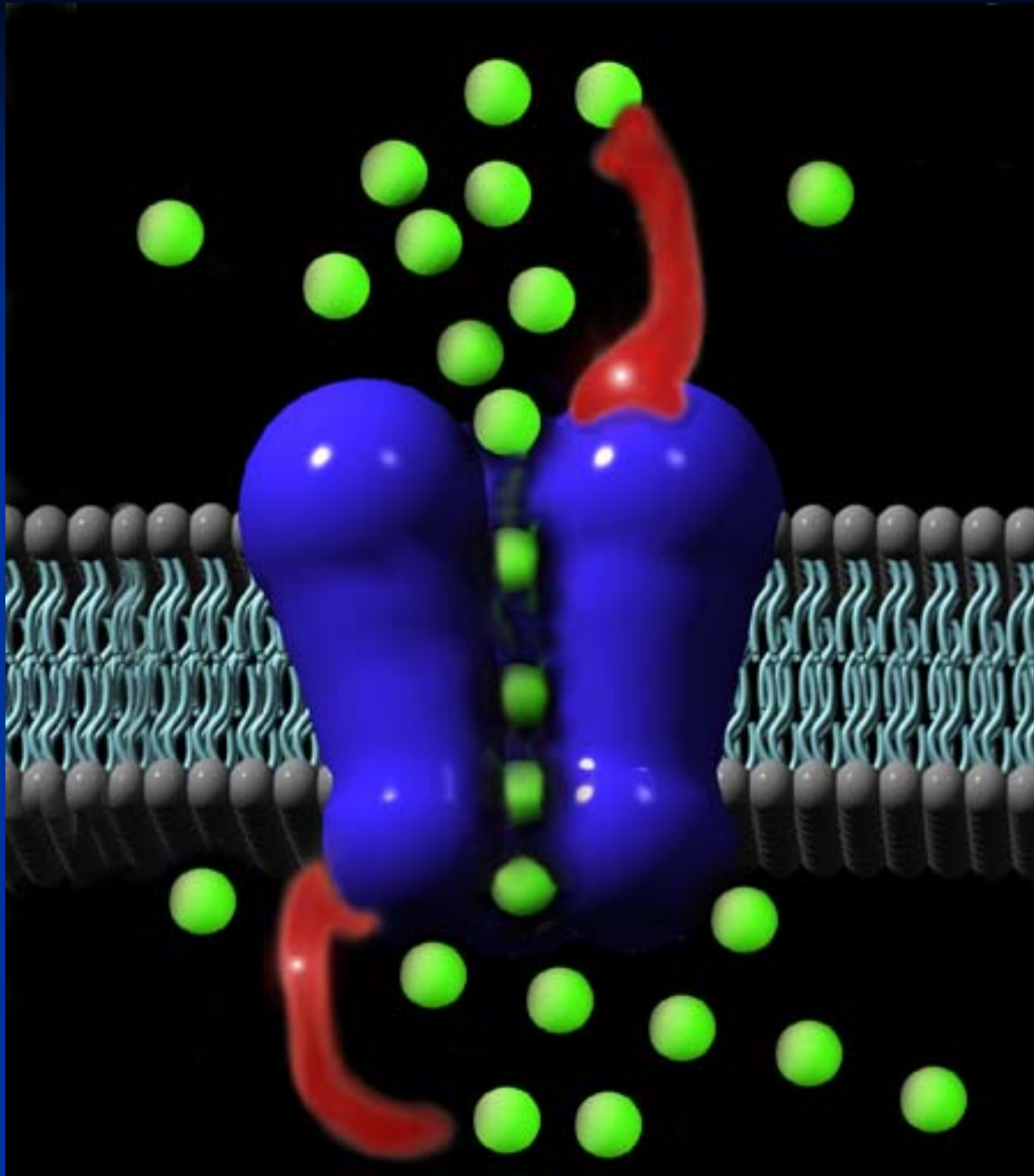
Na⁺

**NaCh
Closed State**

Activation gate

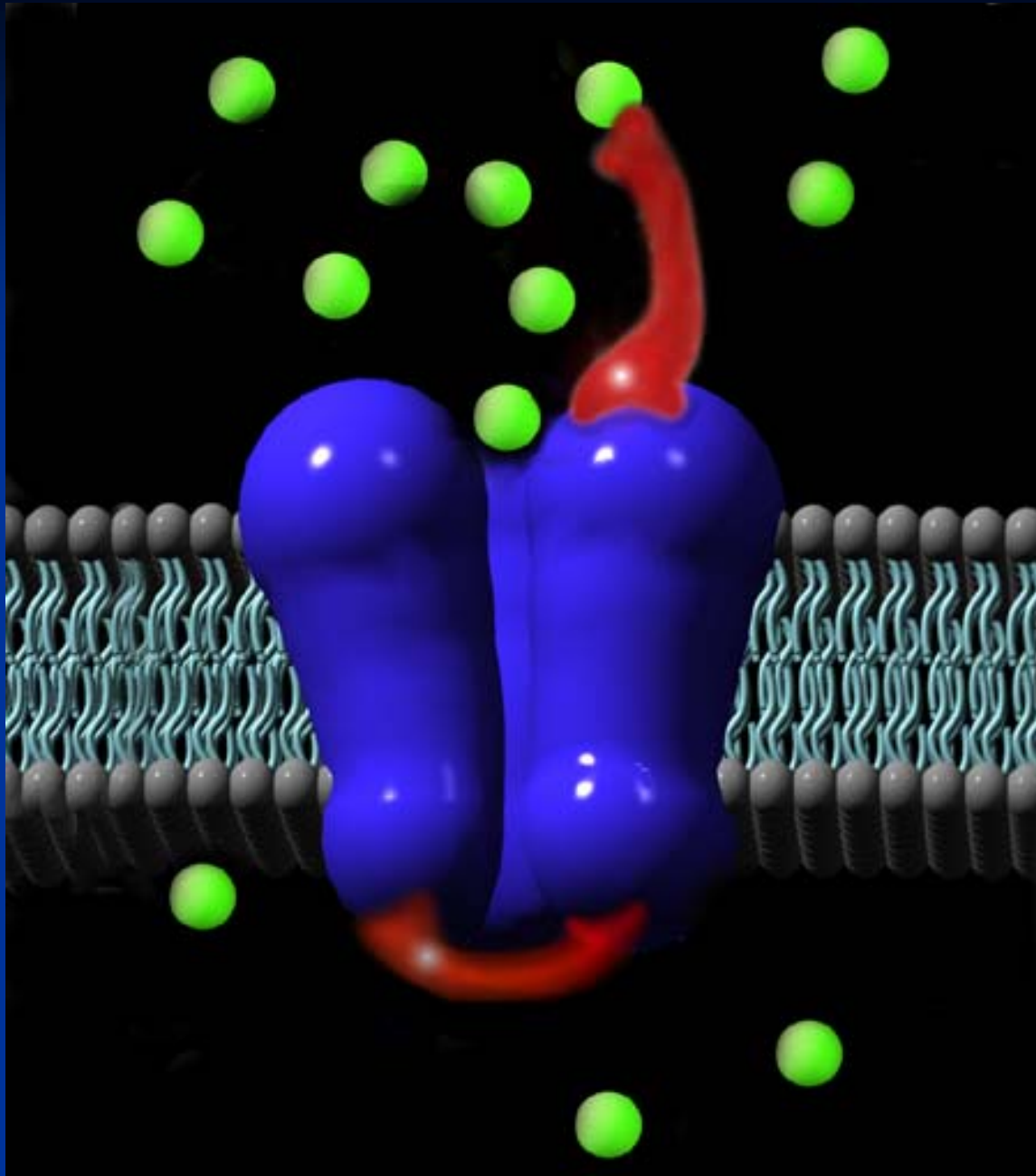
Inactivation gate





NaCh Open State

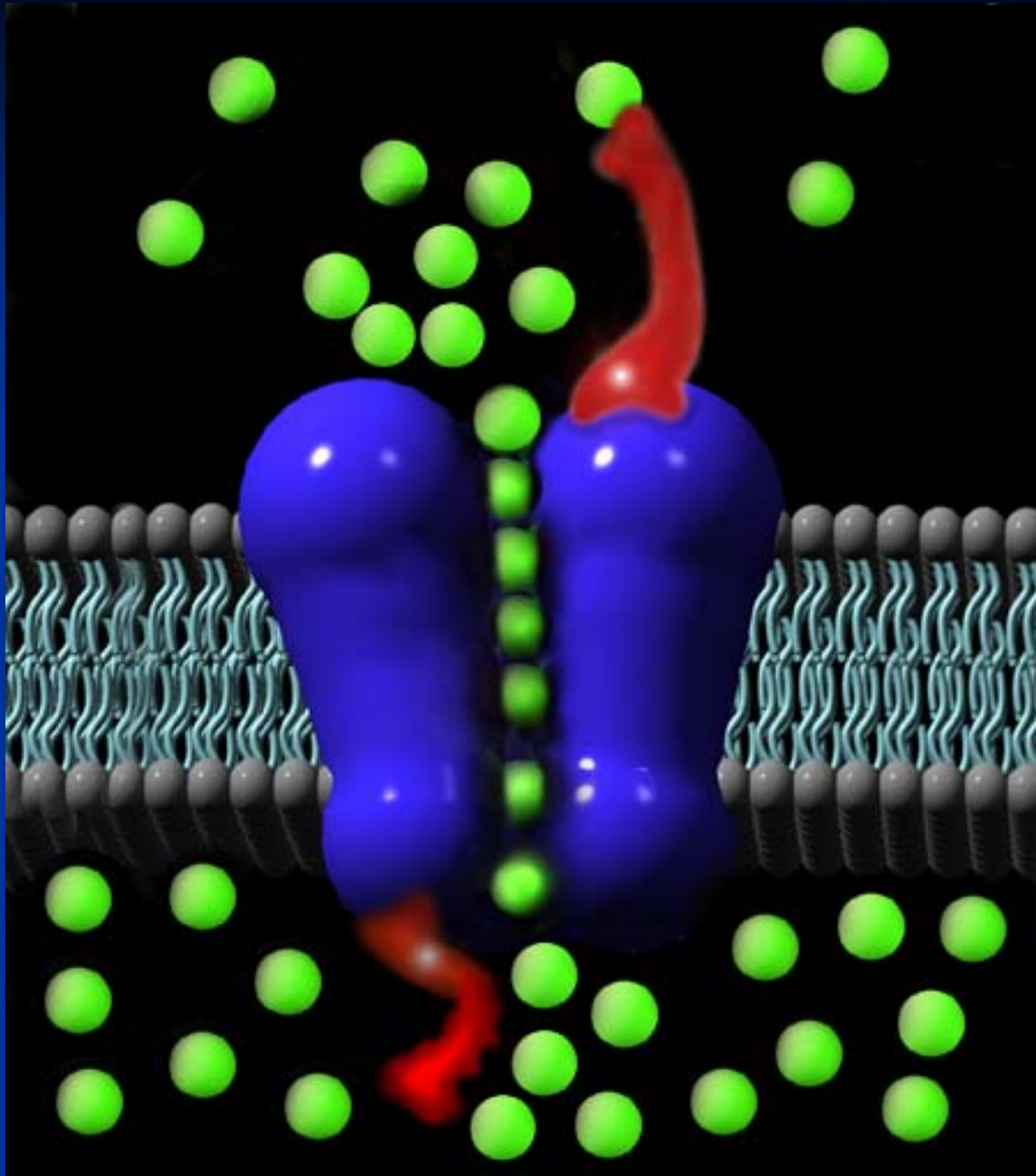
**Action Potential
Open activation
gate -
influx of Na⁺**



NaCh

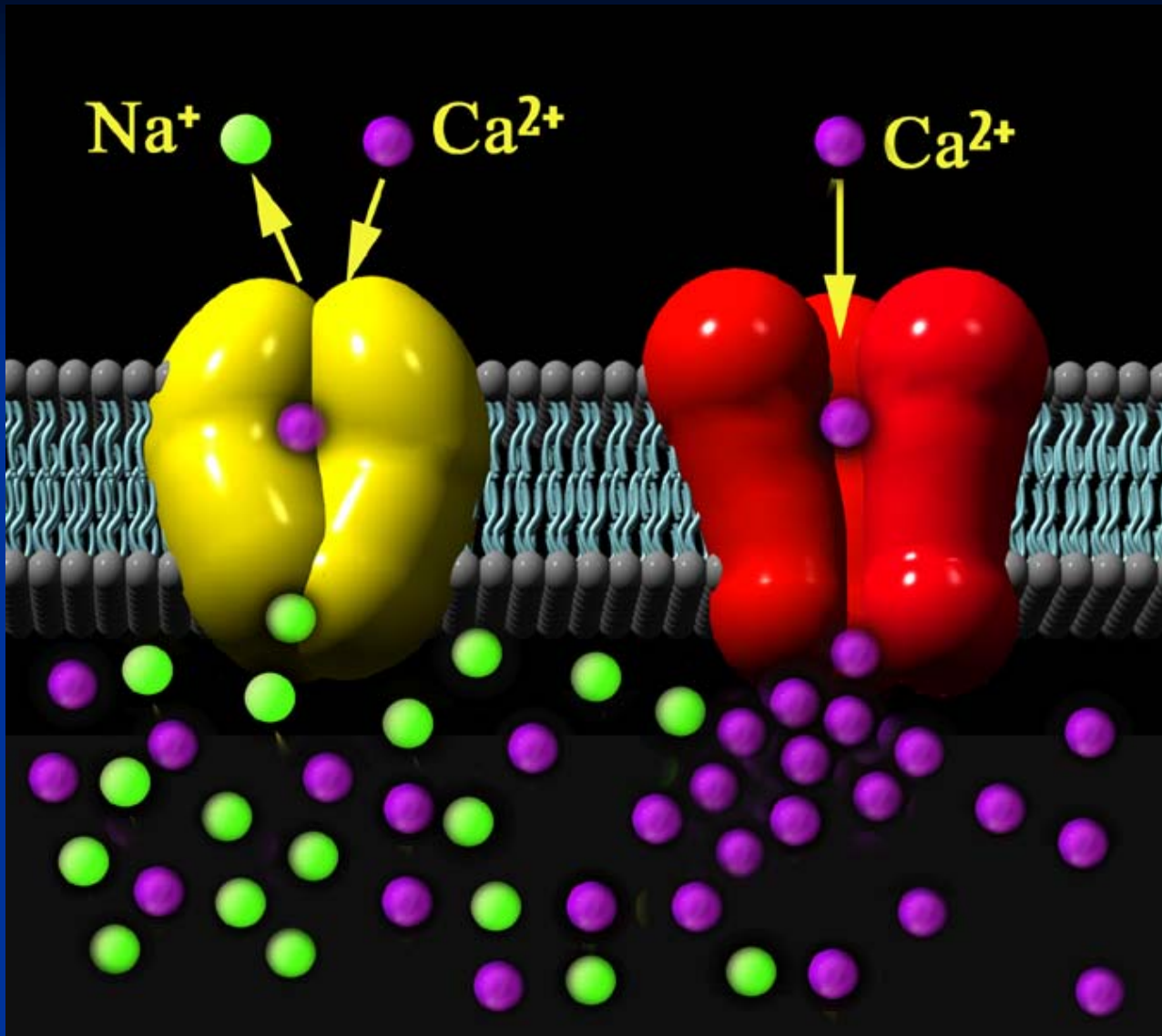
Inactivated State

**Close
inactivation
gate - block
influx of Na⁺**



NaCh
Non-inactivated
State

Trauma
immediately
damages
inactivation
gate



Massive Na⁺ influx

=

Reversal of the Na-Ca
Exchanger (NCX) and

Activation of VSCC

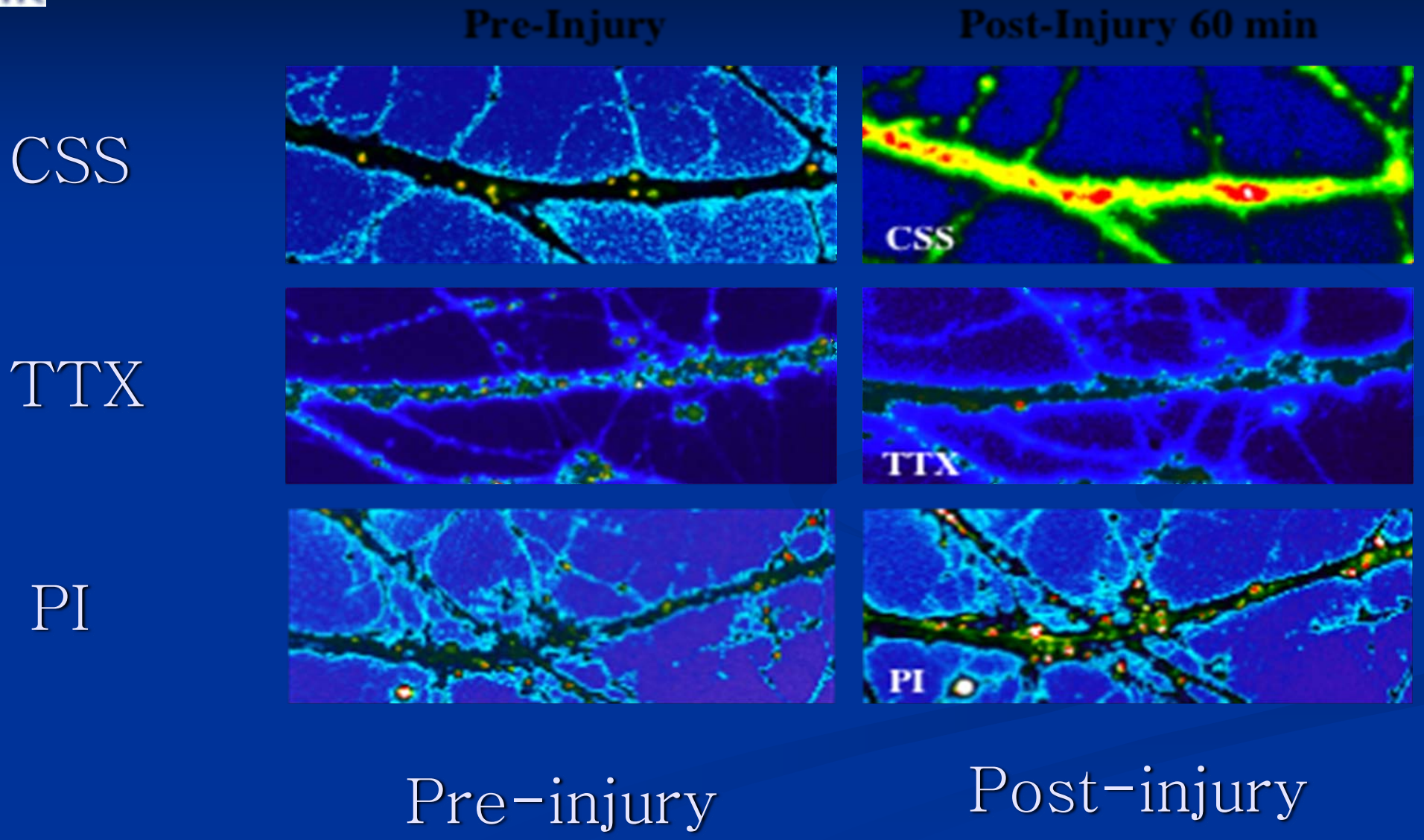
=

Massive Ca²⁺ influx



What subsequently happens to
sodium channels (NaChs)
with axonal
stretch-injury?

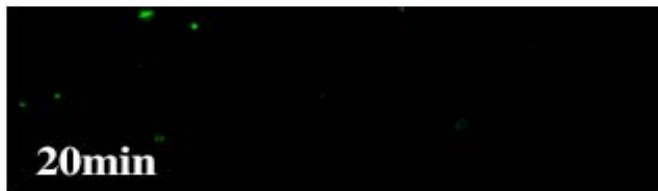
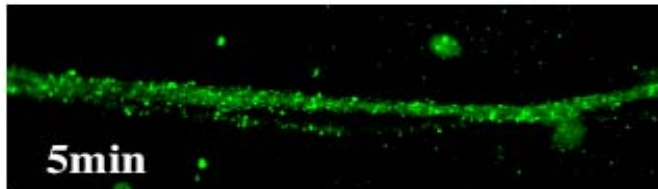
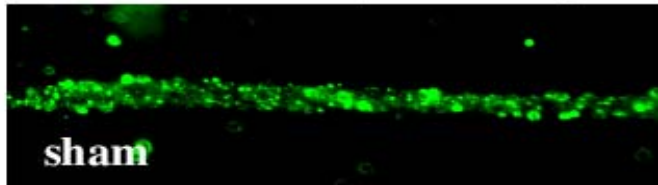




NaCh immunoreactivity

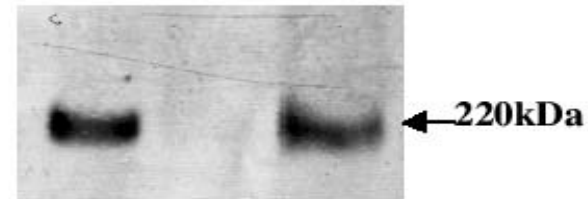
A

No Treatment (III-IV loop)

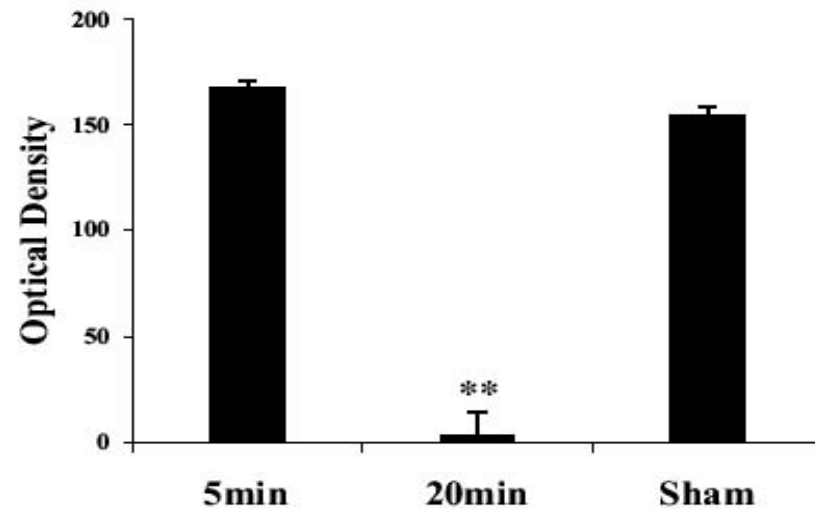


B

No Treatment (III-IV loop)

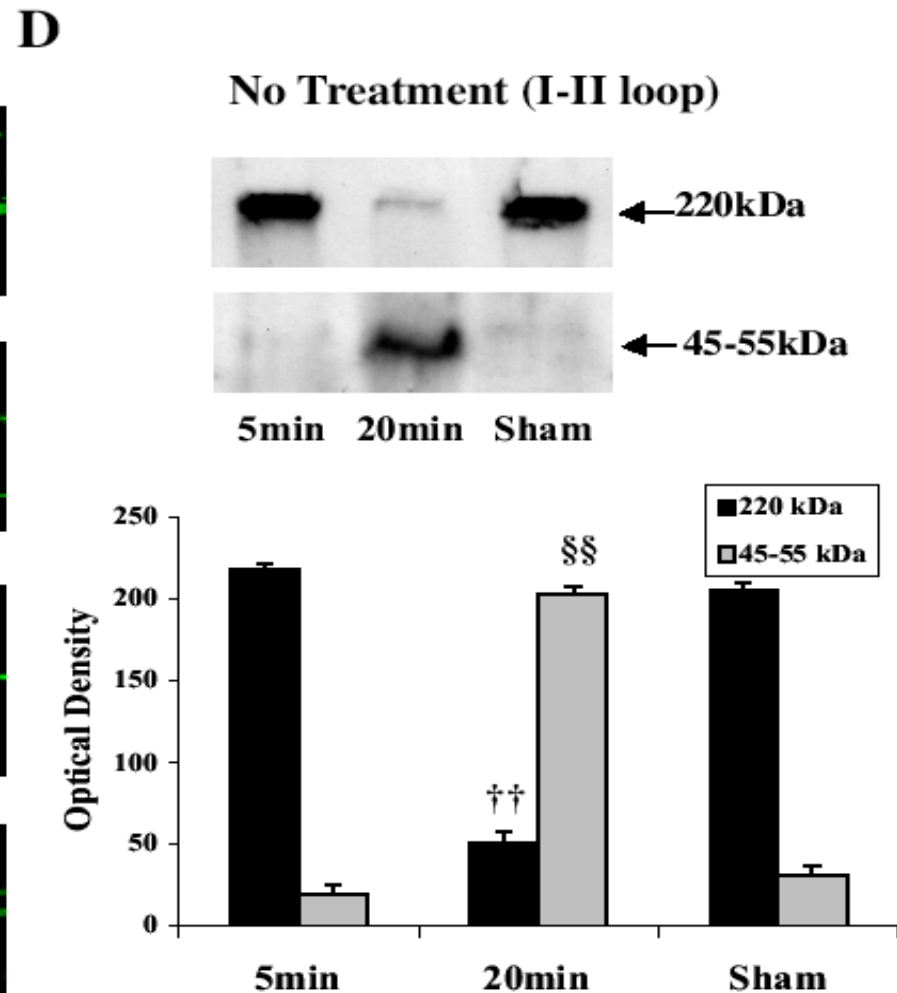
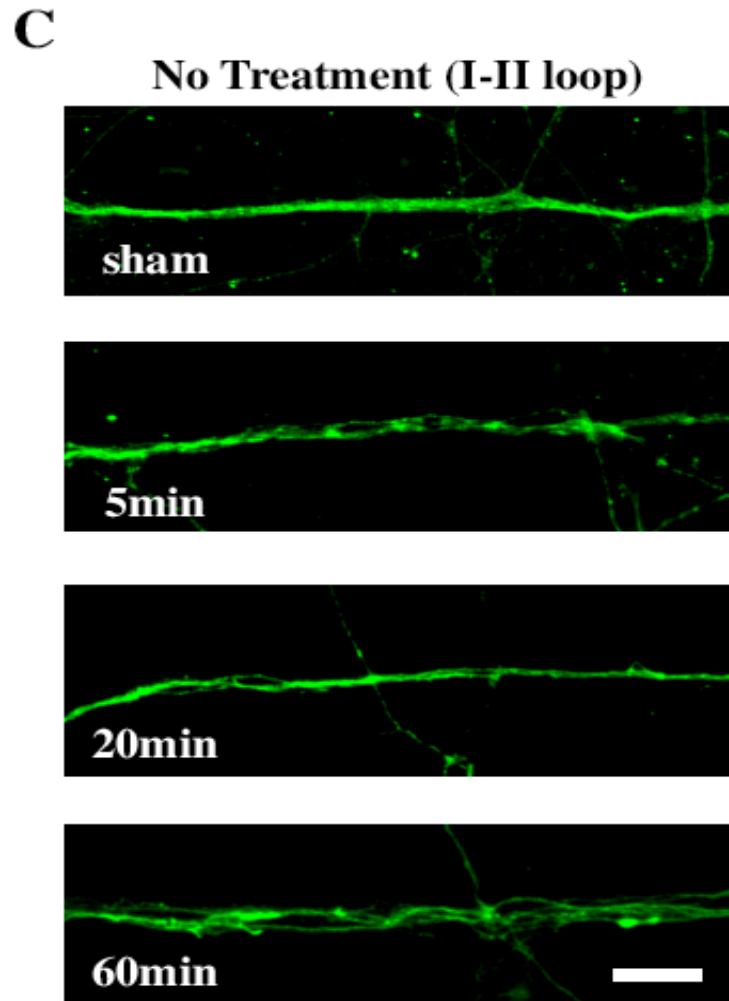


5min 20min Sham



Proteolysis of the inactivation gate

NaCh immunoreactivity

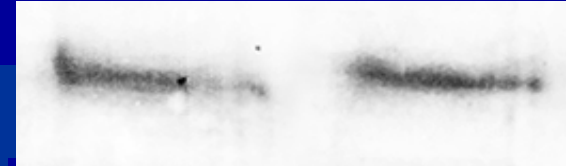
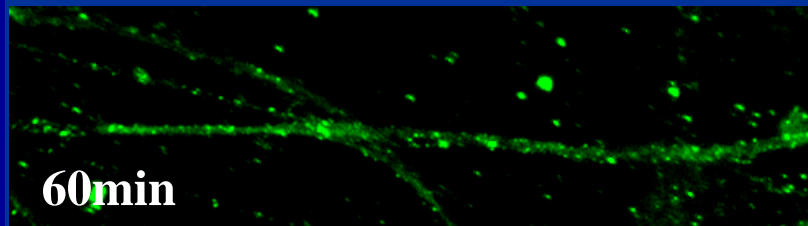
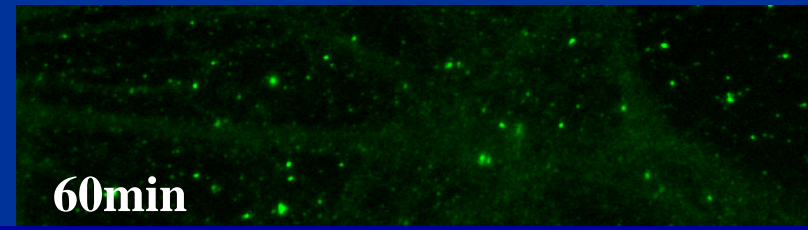
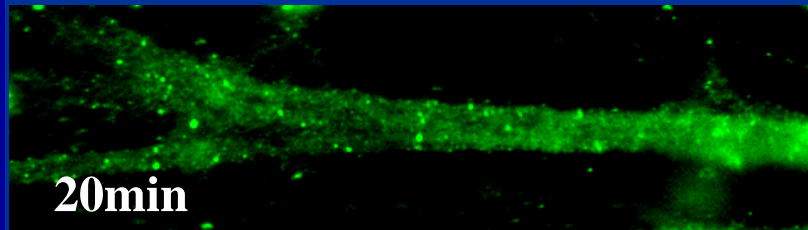
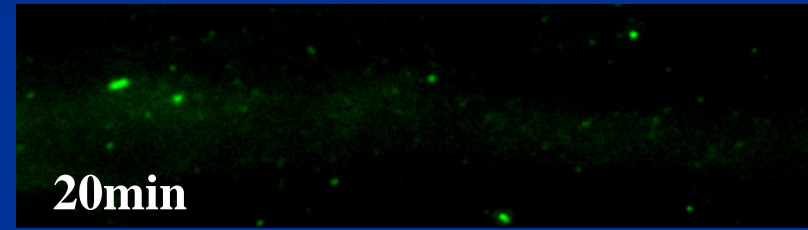
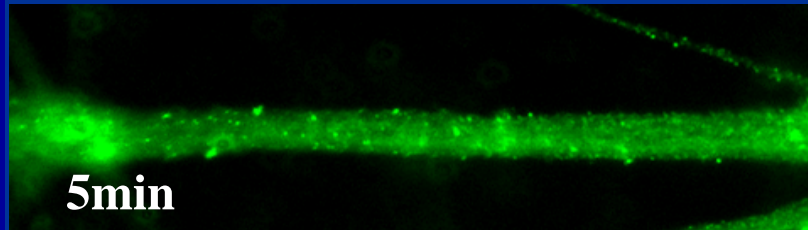
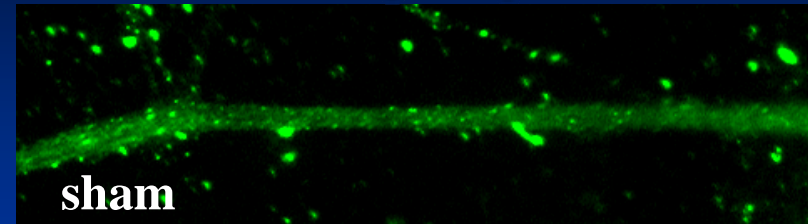
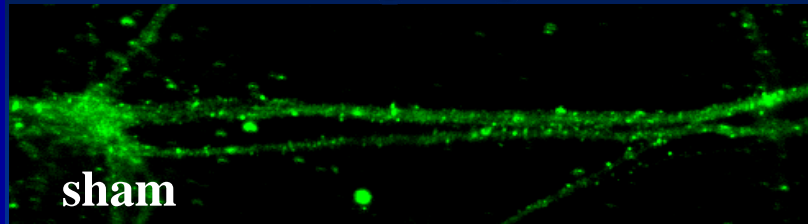


I-II loop of the alpha subunit

NaCh immunoreactivity

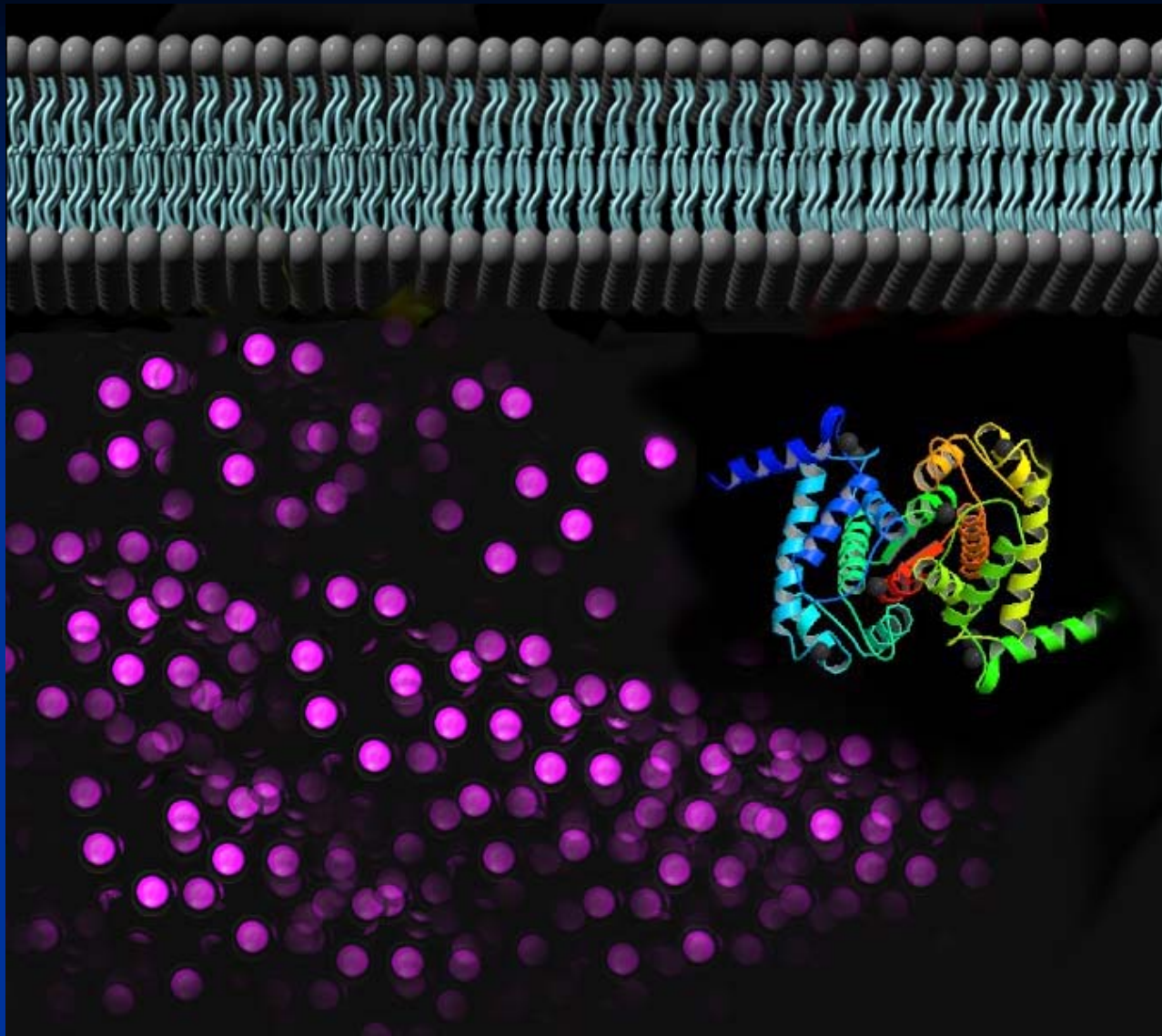
Pre-injury TTX

Post-injury TTX



Pre-injury
TTX

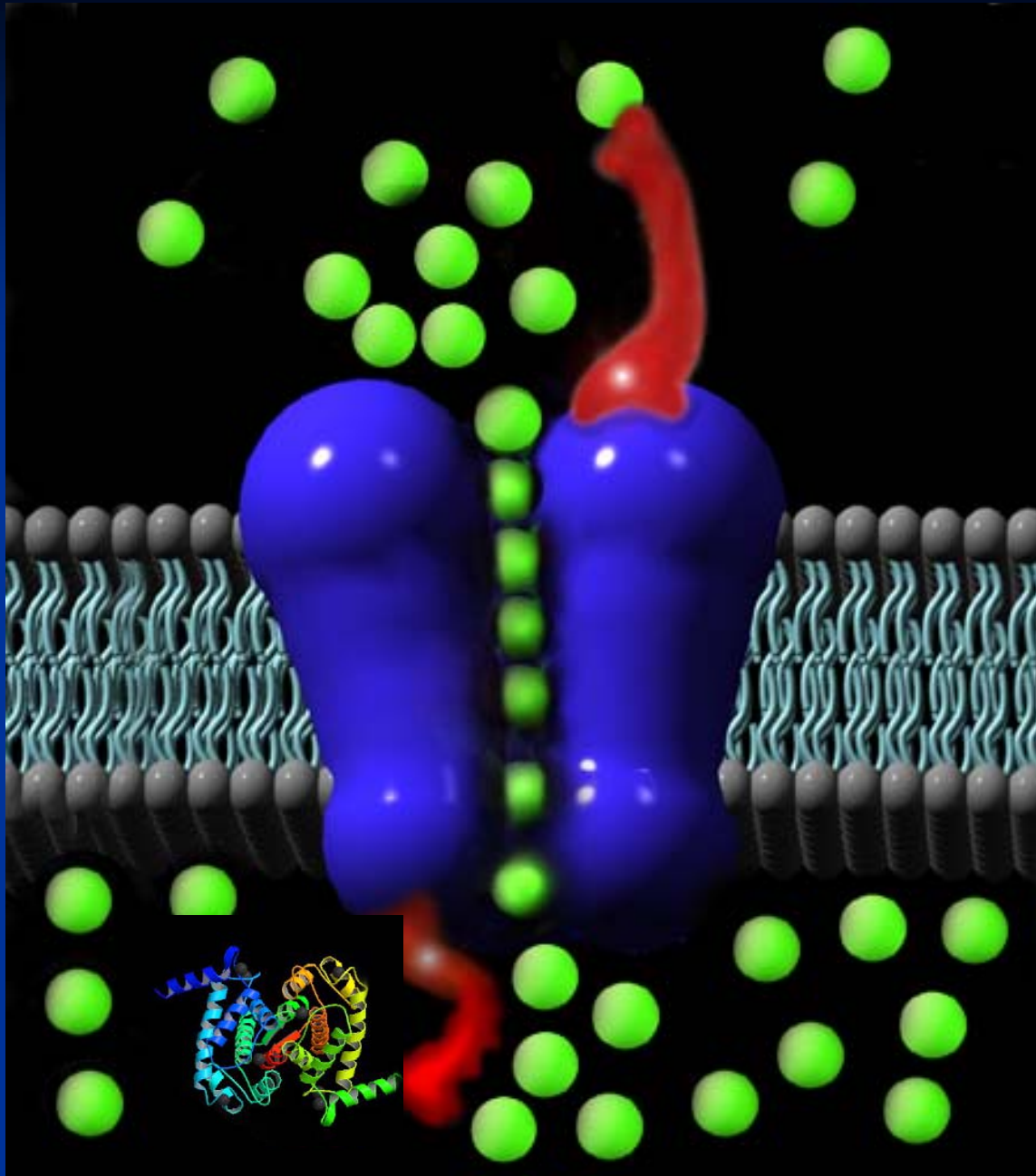
0 min 20 min



Ca²⁺ activation
of proteases -
calpain?

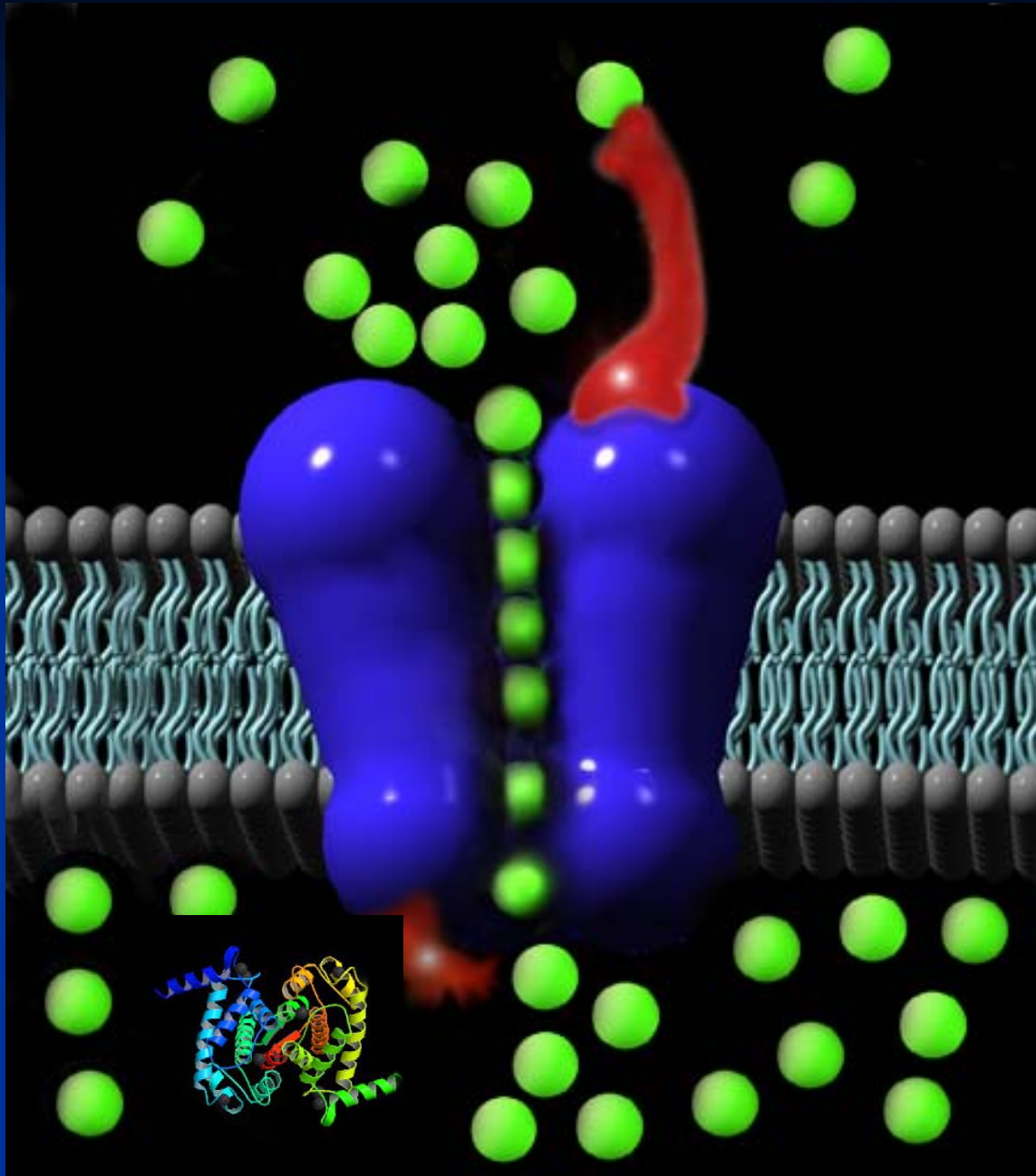
NaCh Dysregulation

Proteases
target the
inactivation
gate



NaCh Dysregulation

Proteases
target the
inactivation
gate



Repetitive mTBI

What is it???

Sports concussion

Second impact syndrome



Glass jaw

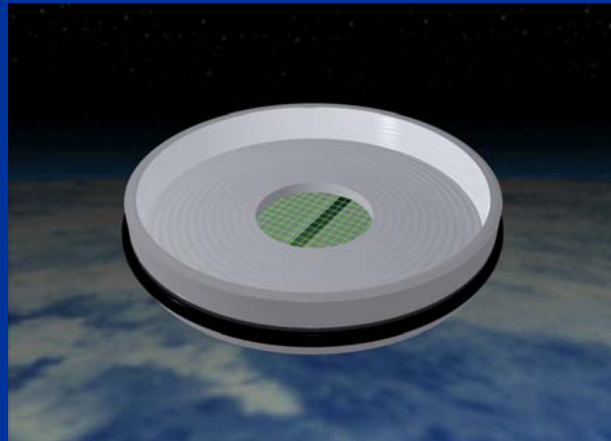


Repetitive mTBI

“period of vulnerability”, where another mild injury is thought to trigger a greatly exaggerated response

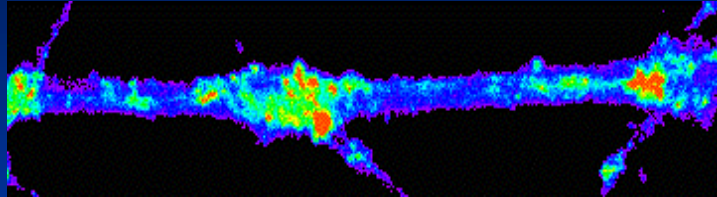
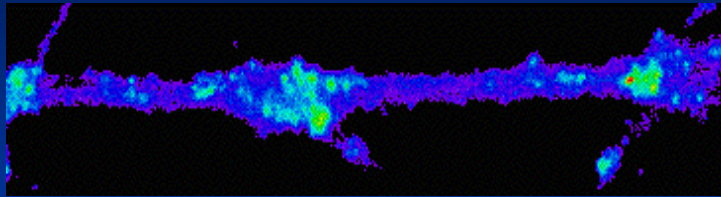


Repetitive Mild Axonal Stretch-Injury in Culture

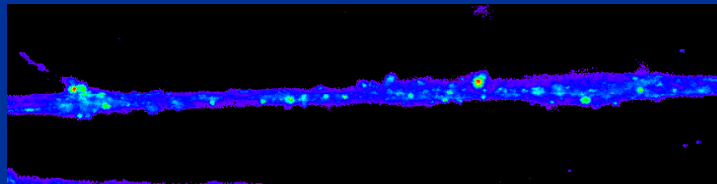
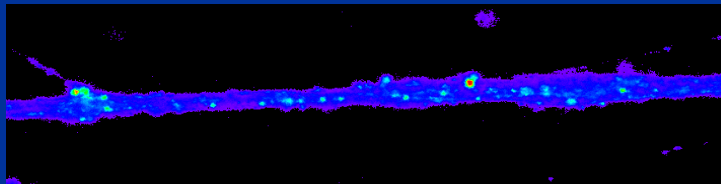


Pre-2nd injury

Post -2nd injury



Repeat
mild injury

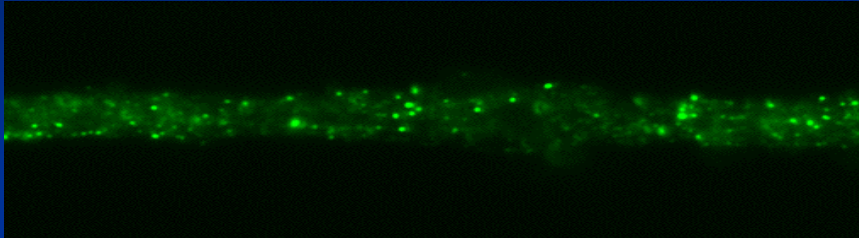


Repeat
mild injury
+ TTX

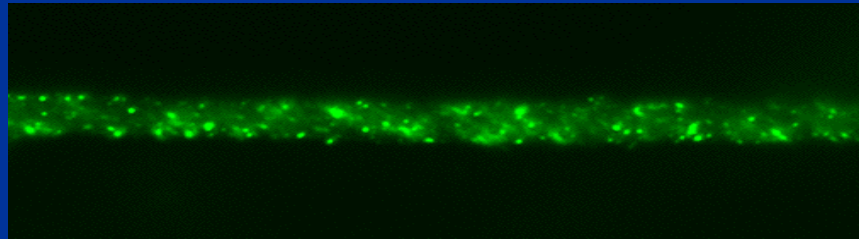
Mild TAI (below calcium influx threshold) predisposes axons to calcium influx with repeat exposure 24 hours later



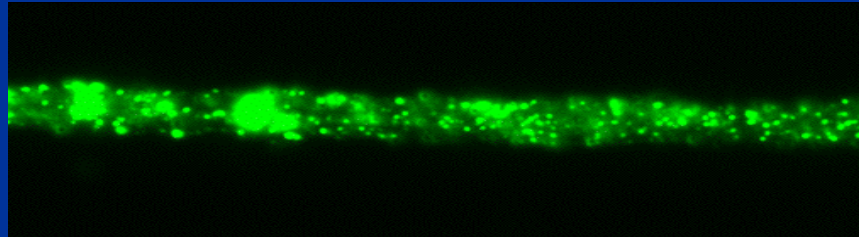
NaCh immunoreactivity



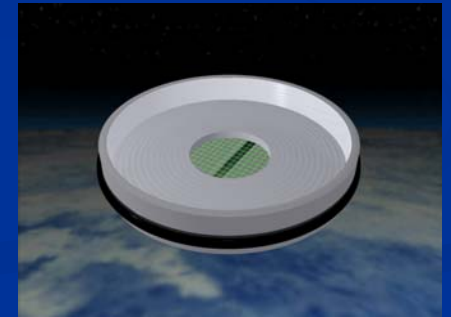
Pre-injury



1hr post-injury

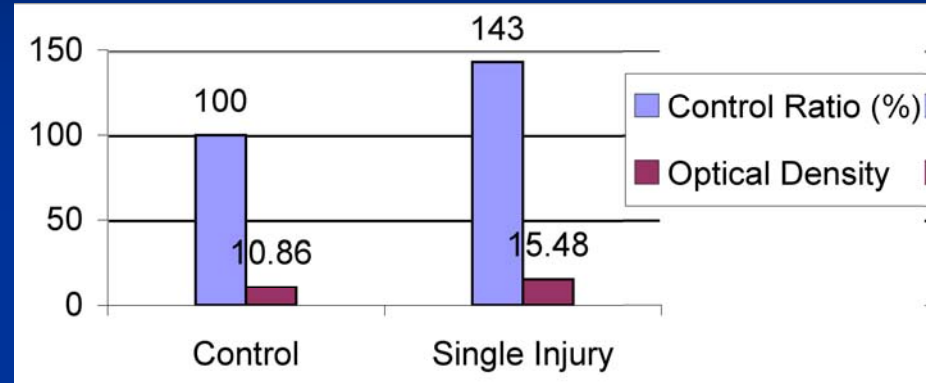
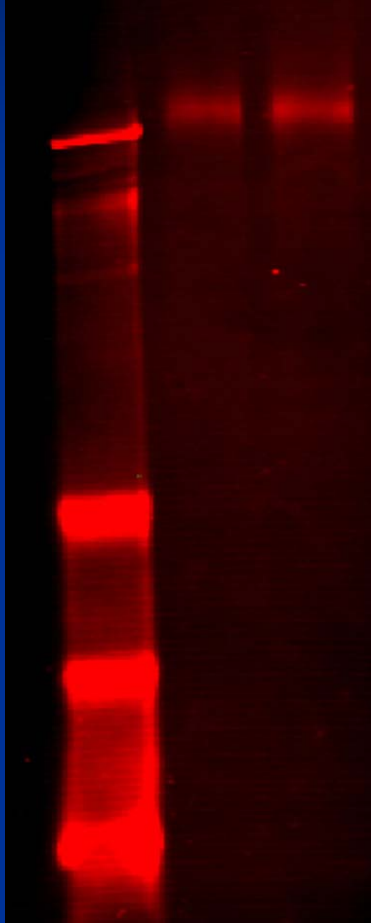


24hr post-injury

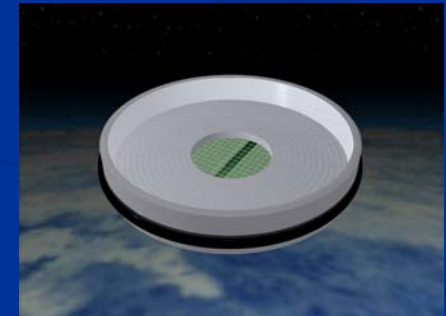


Posttraumatic increase in NaCh density = NaChO?

Control vs. 24h post mild injury



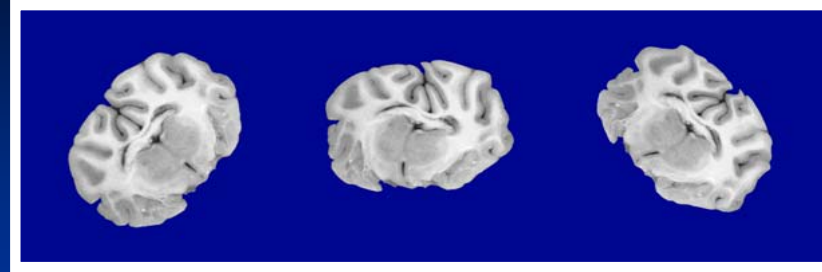
NaChO!



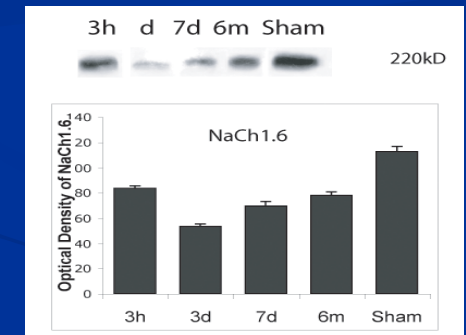
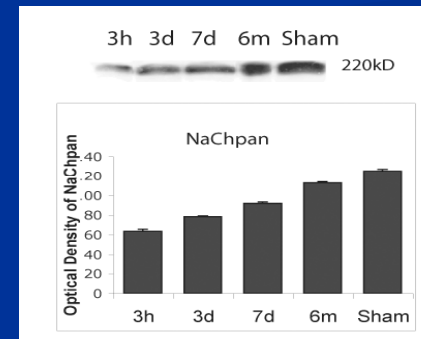
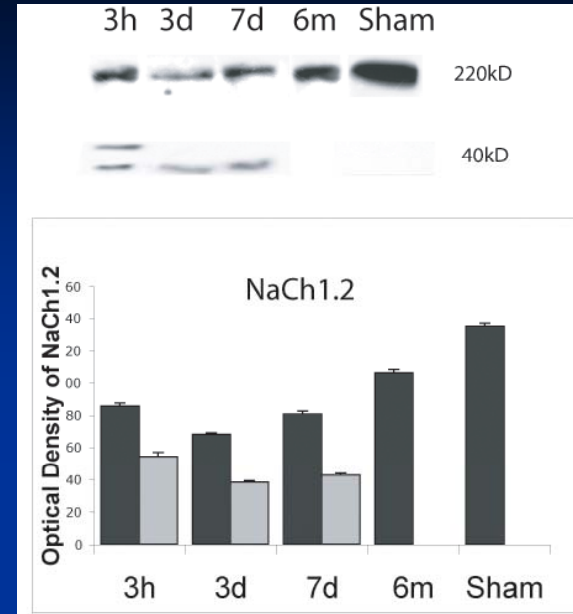
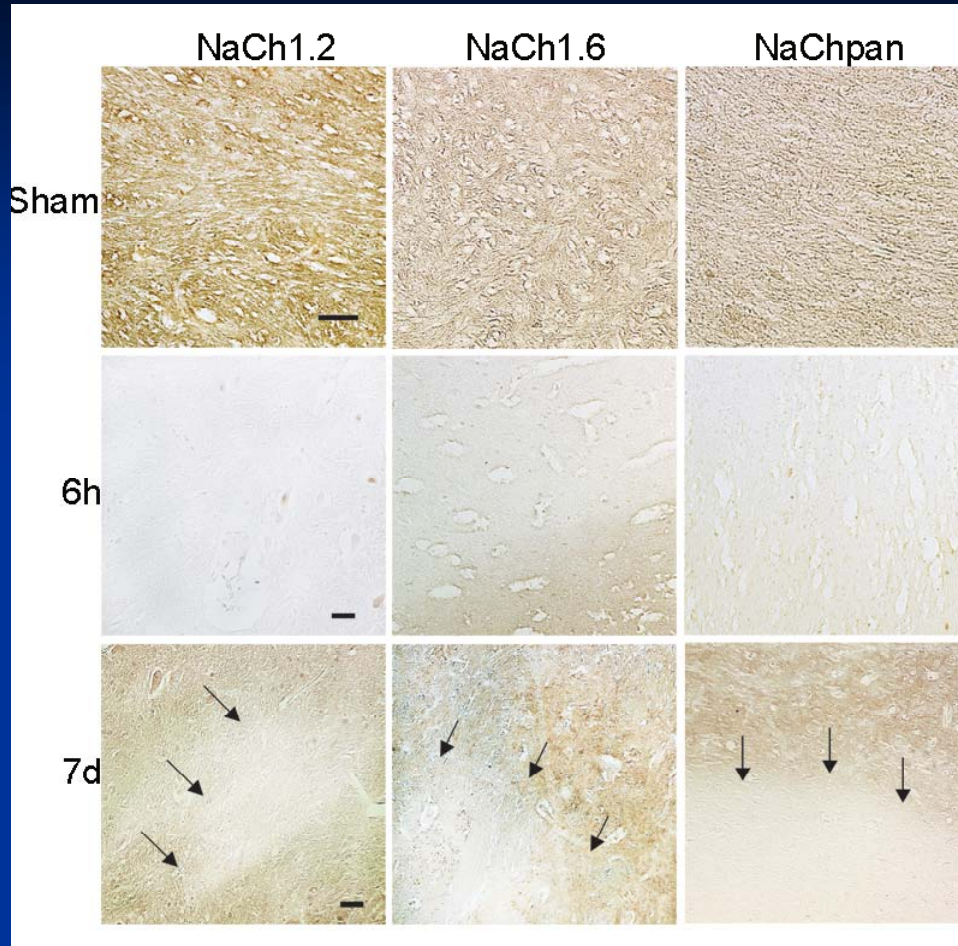
NaChO!

NaCh-opathy

A pathologic change in the
expression of NaChs

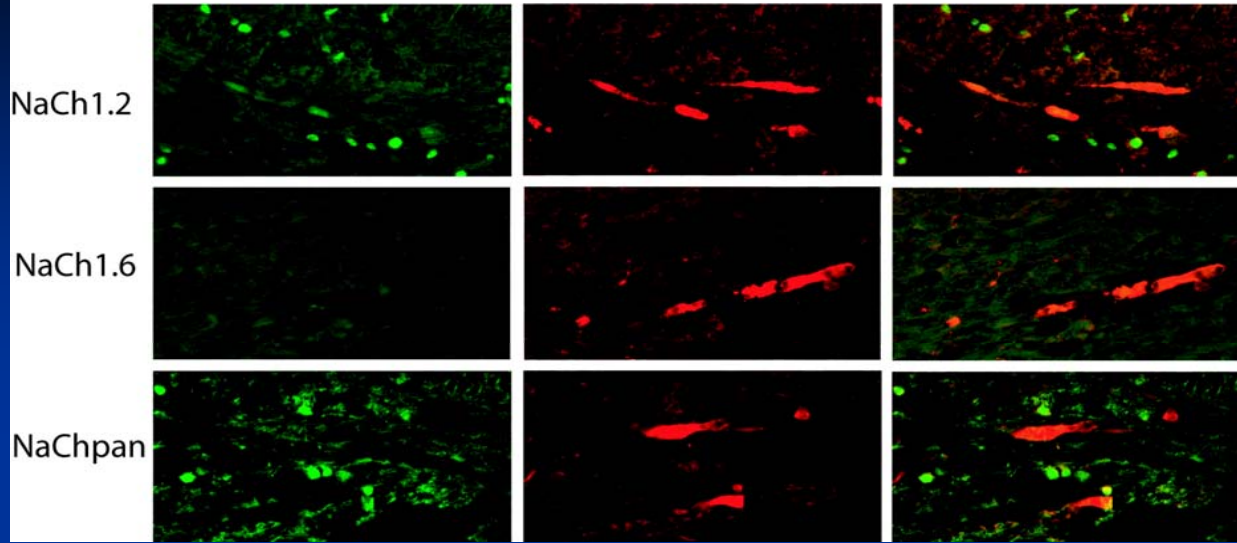


Non-inactivation
of NaChs and
NaChO after TBI
in vivo

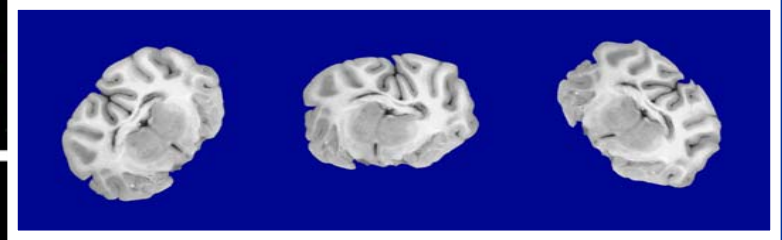
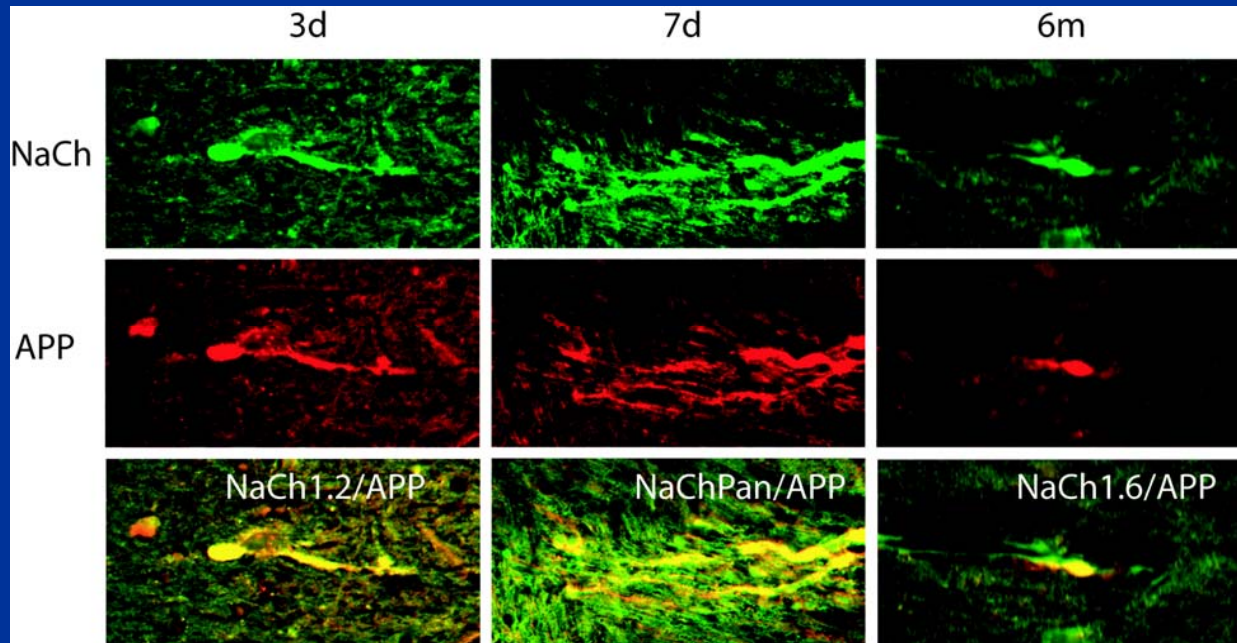


Corroborates in vitro results

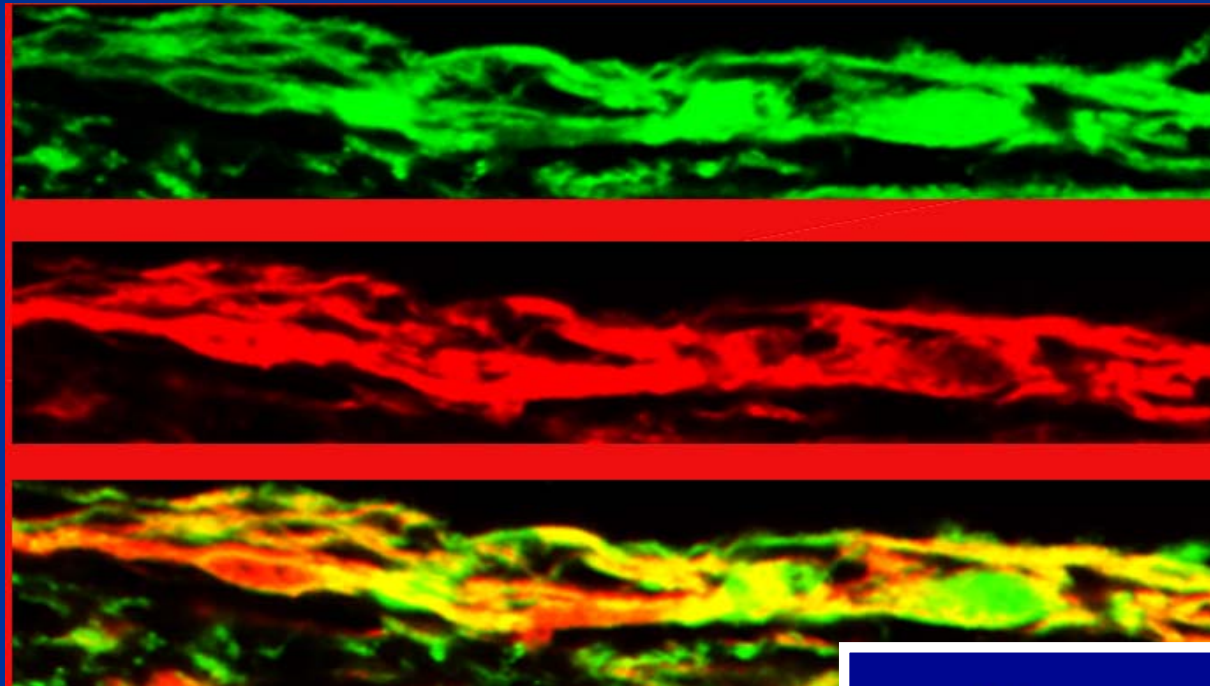
6-8h Following Axial Plane Rotation



Temporal NaChO
after DAI

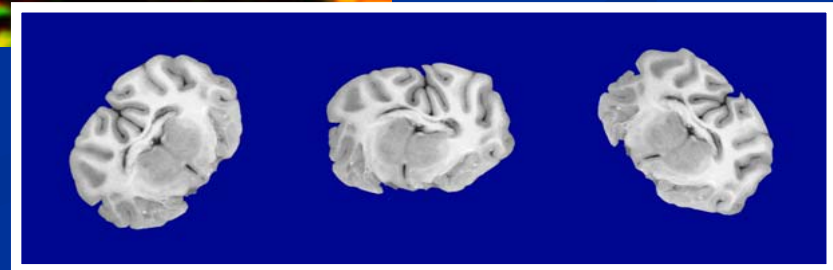


Long-term NaChO after TBI



Nav1.2

APP



mTBI = mDAI

Feed forward cycle of NaCh dysfunction

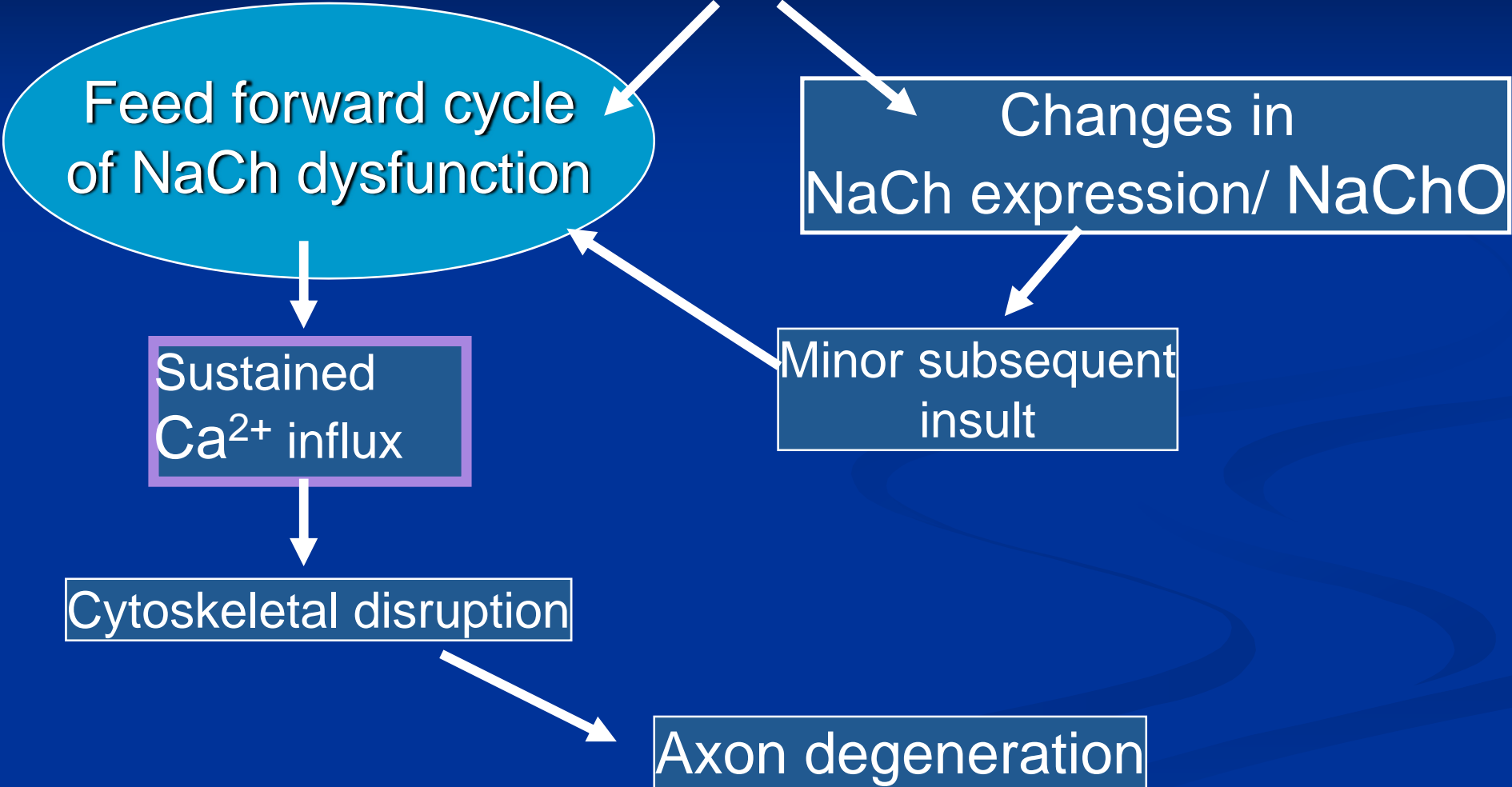
Changes in NaCh expression/ NaChO

Sustained Ca²⁺ influx

Minor subsequent insult

Cytoskeletal disruption

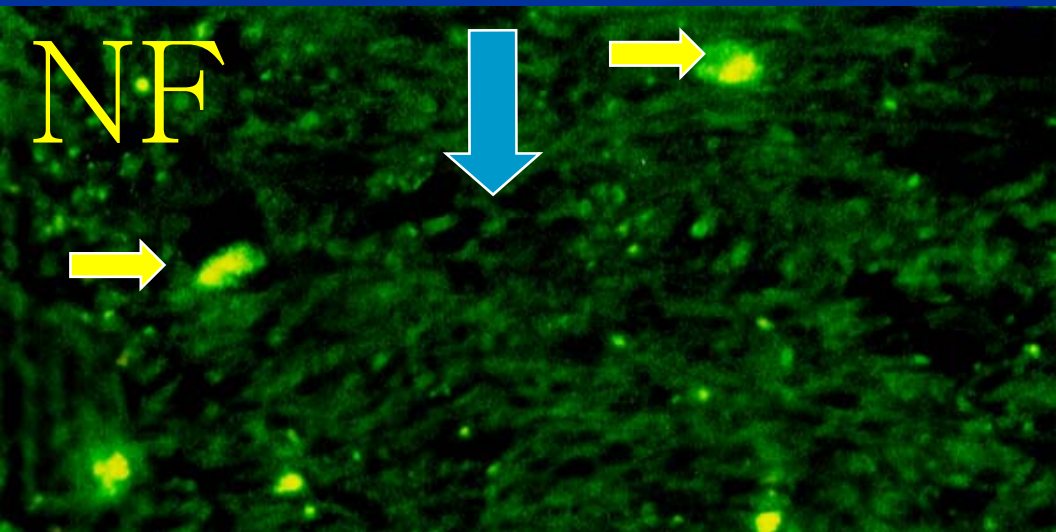
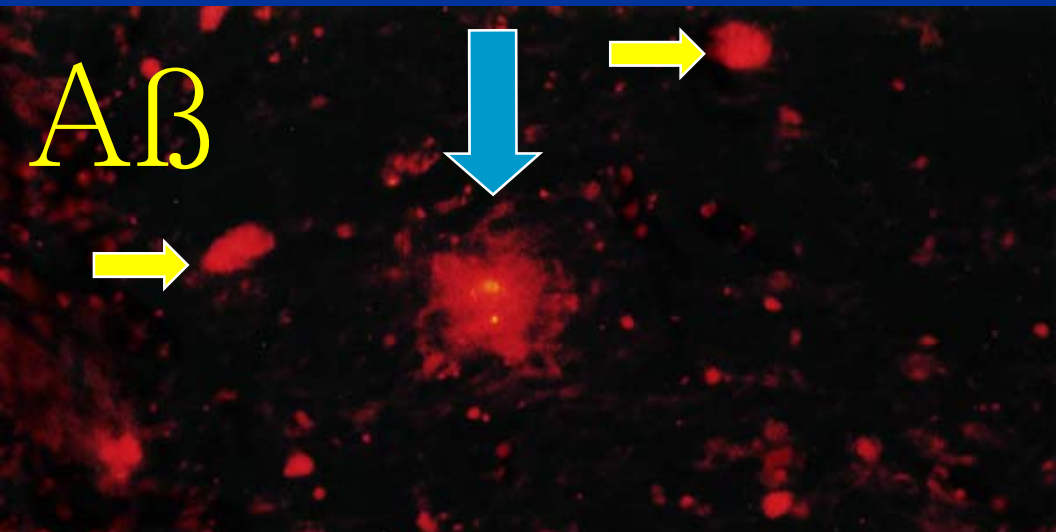
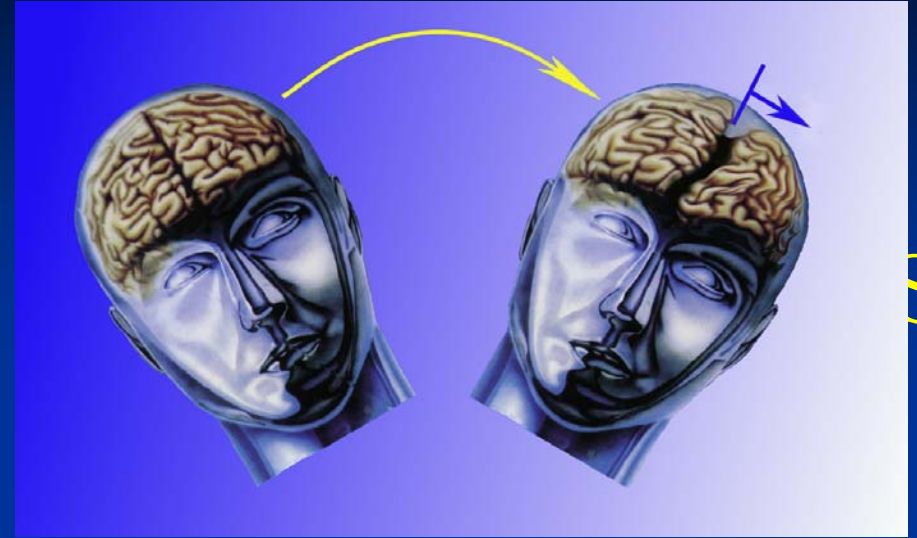
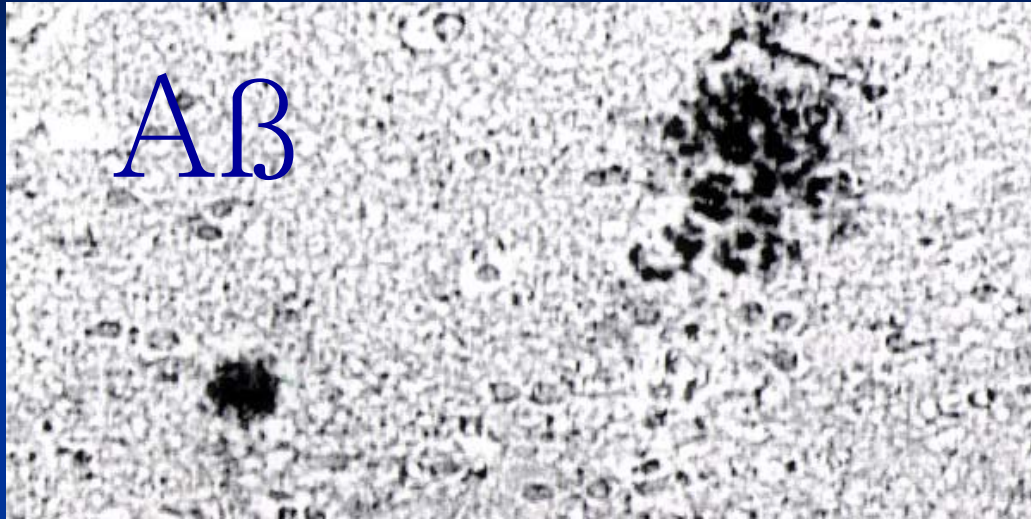
Axon degeneration





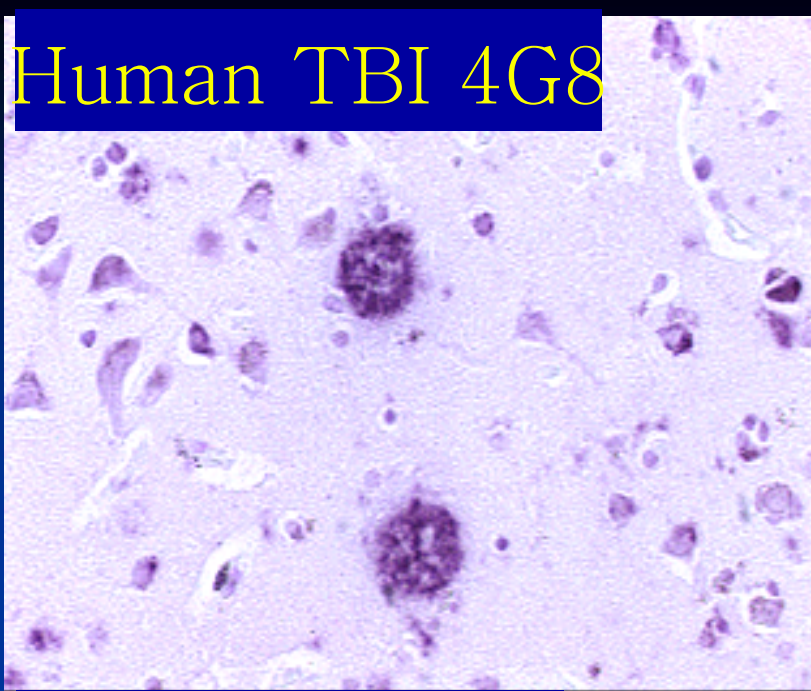
Other therapeutic targets:

The link between TBI and
Alzheimer's disease

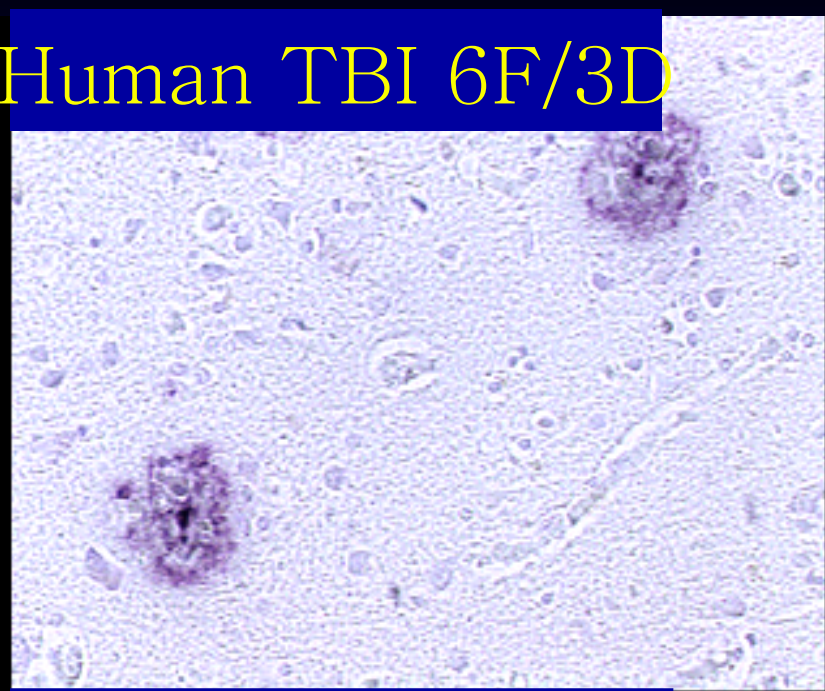




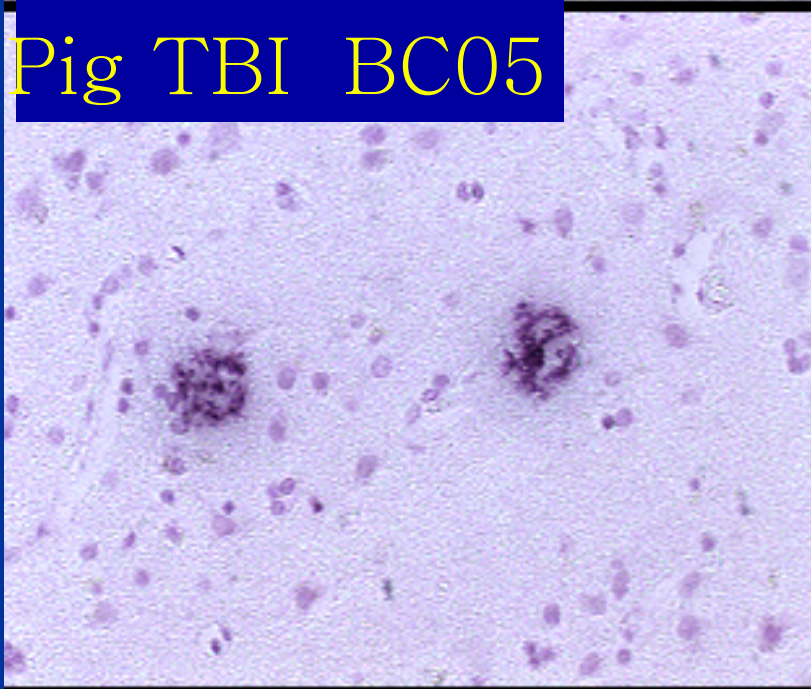
Human TBI 4G8



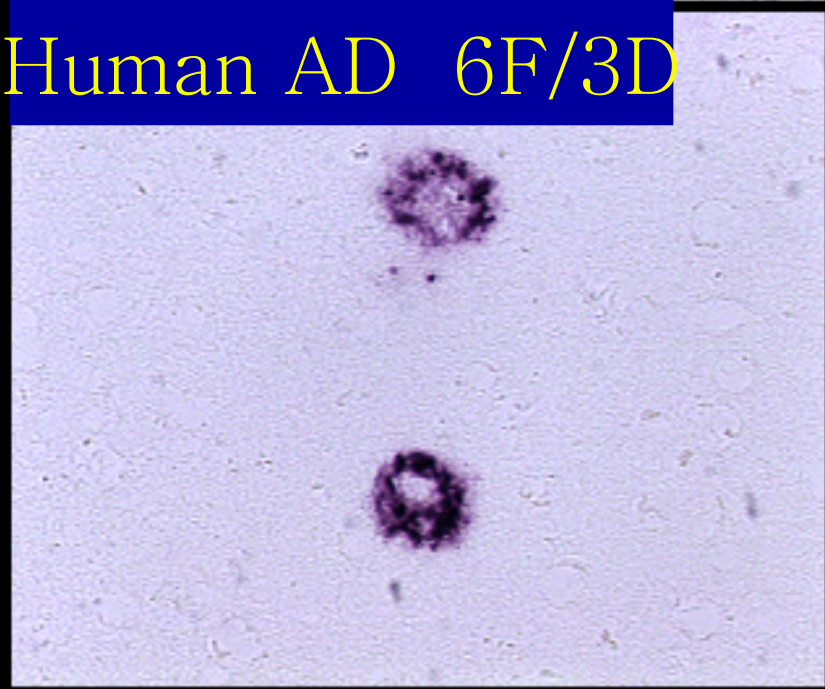
Human TBI 6F/3D

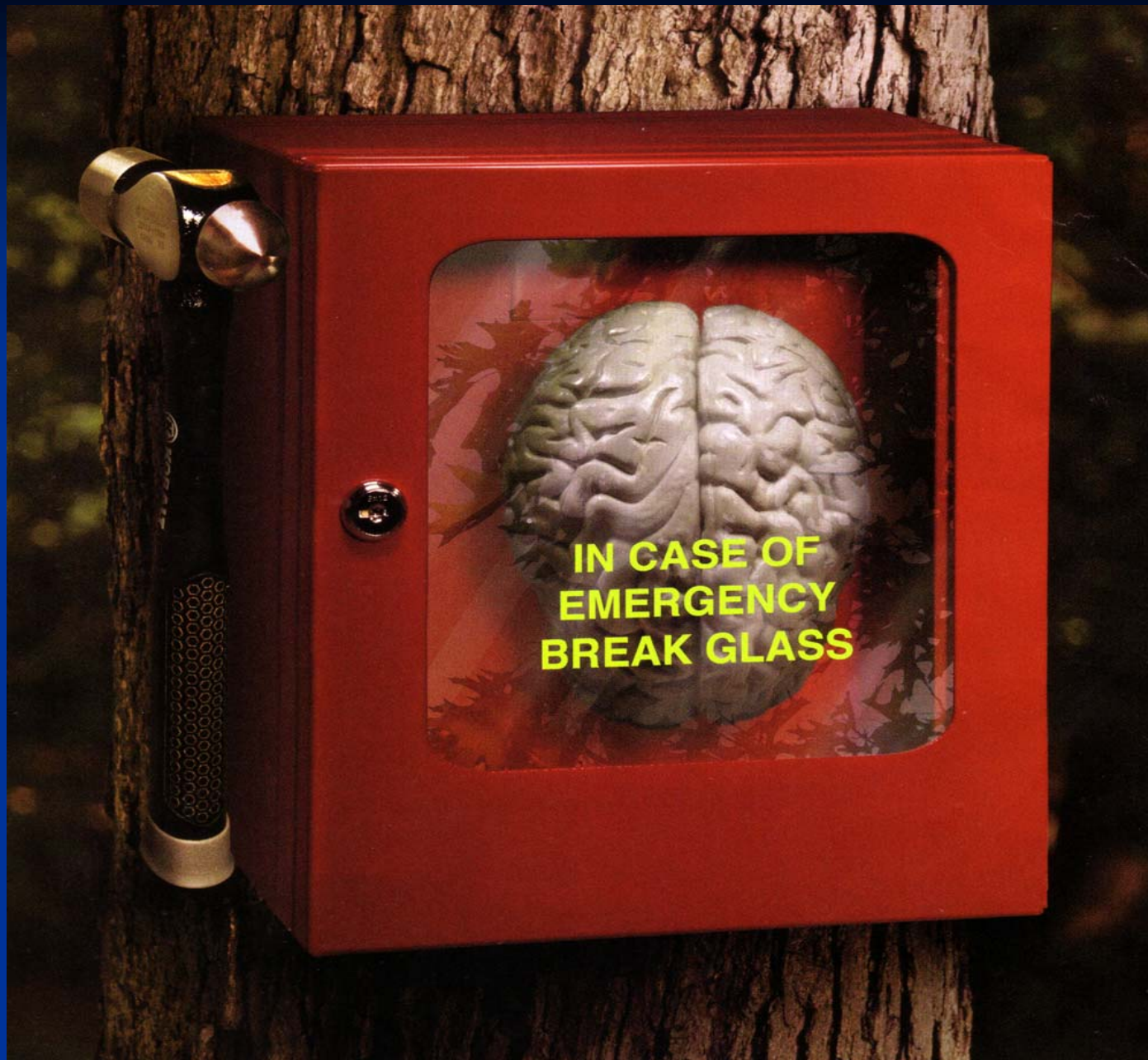


Pig TBI BC05



Human AD 6F/3D

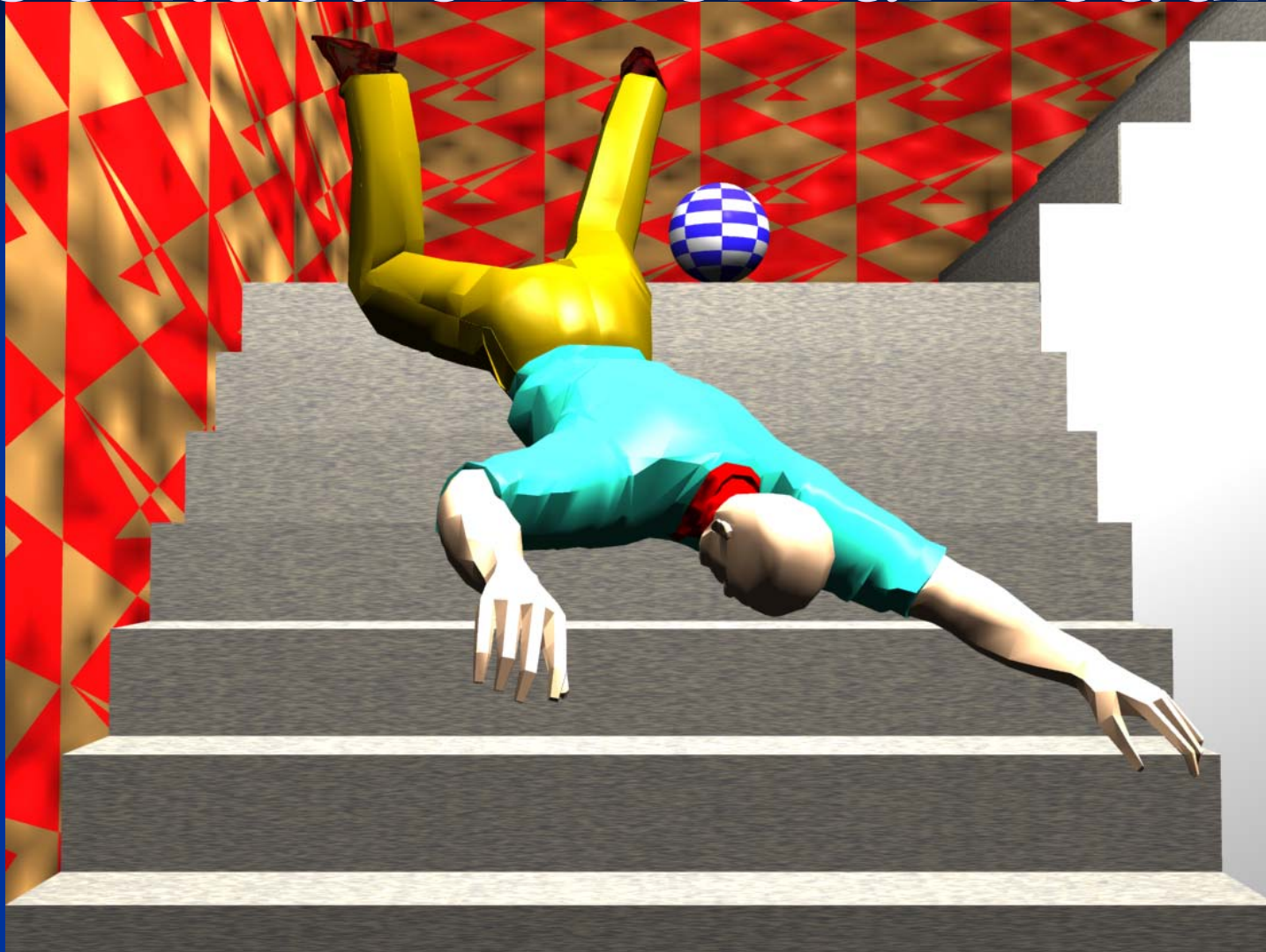




Mind
your
brain!



Contact or Inertial Loading?



Rapid repetitive TBI



The Lab



Wallow Maze?

