

Traumatic Brain Injury Increases Susceptibility to Alzheimer's Disease

QR Pharma, Inc.

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November 17, 2009

What Causes TBI?

- **Battle:** blows, explosions, shots
- **Sports:** concussions in football, boxing, all impact sports and all sports accidents
- **Car & Motorcycle Accidents:** whip lash, low and high impact collision
- **Falls in the Elderly:** concussions
- **Strokes:** brain hemorrhage, arterial occlusion, brain damage

Long term effects of mild and severe TBI

➤ **Battle:** blows, explosions, shots

64% of soldiers recently wounded in Iraq sustained blast injuries. Half of the wounded soldiers had permanent brain damage and the other half were identified with mild TBI.

Unfortunately, the soldiers with mild TBI are expected to show latent effects

80% depression

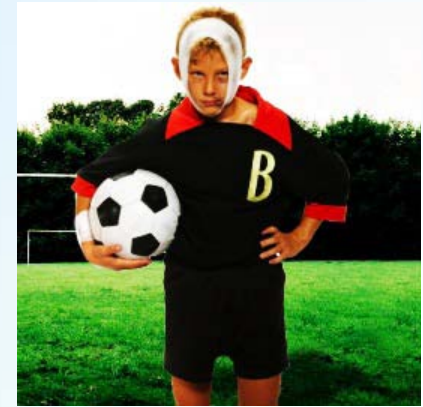
5% dementia and AD within 5 to 10 years

30% dementia and AD within 20 years

Long term effects of mild and severe TBI

➤ **Sports:** concussions

NFL statistics: in their 40ies, football players have a 19 time higher incidence of dementia than age matched controls



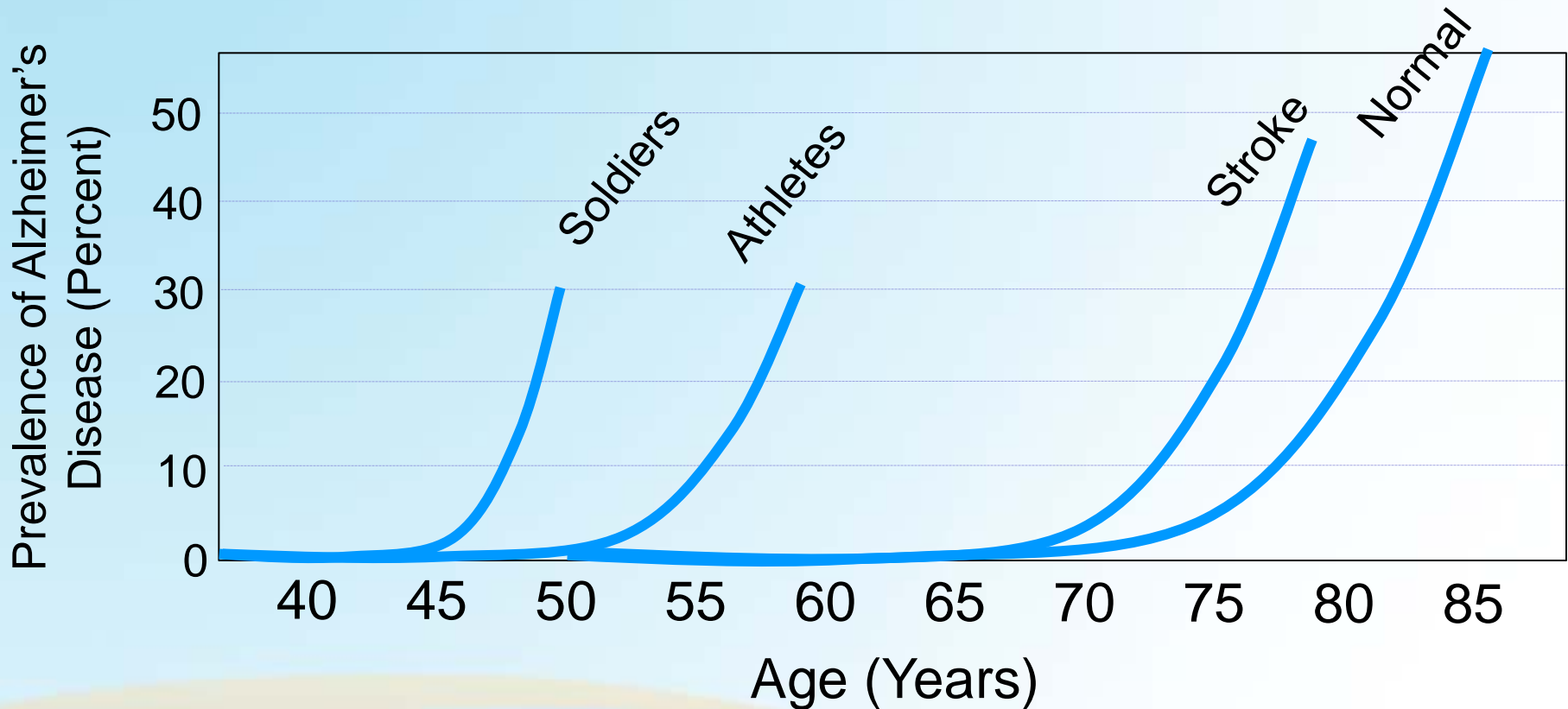
Dementia pugilistica: develops over 10 to 15 years and affects 15% of professional boxers in their 30ies

Long term effects of mild and severe TBI

- **Car & Motorcycle Accidents:** concussions
- **Falls in Elderly:** concussions
- **Strokes:** brain damage
 - 10 to 15 years after stroke 30% of patients develop dementia and Alzheimer's disease

Stroke was long not recognized as a condition leading to dementia and Alzheimer's disease, because stroke patients are much older than soldiers and athletes

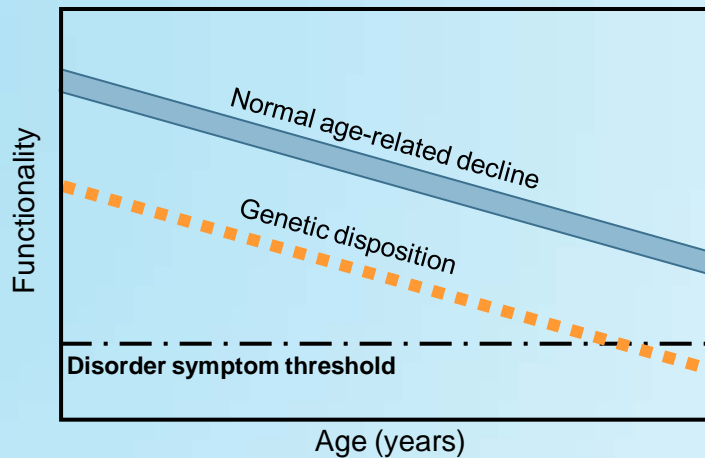
Prevalence of AD at Various Ages in Normal vs. mTBI People



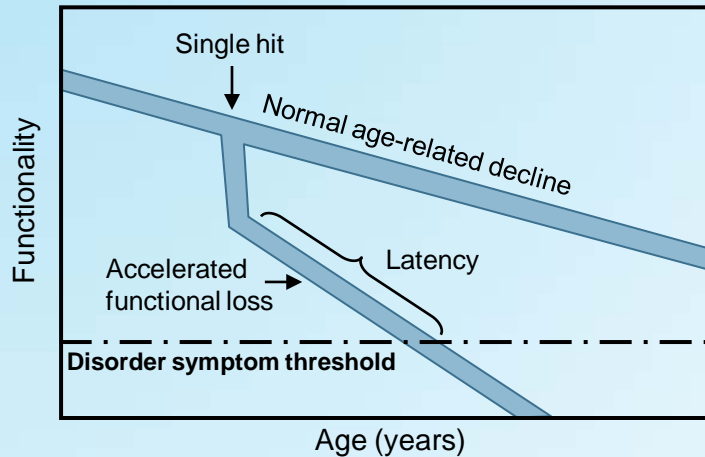
<http://www.alzheimersdisease.com>, adapted Maccacchini

A. Genetic Predisposition

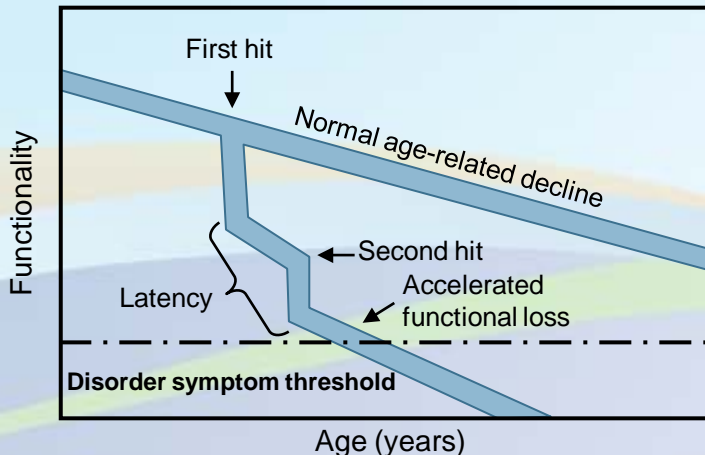
Models of Degenerative Diseases



B. “One Hit” Latent



C. “Two Hit” Latent



Molecular Psychiatry 14: 992-103, 2009

Deb Lahiri



Why does QR Pharma talk about mTBI?

- TBI increases risk of developing **Alzheimer's Disease (AD)**
- after TBI there is long term up regulation of **amyloid precursor protein (APP)** expression
- QR Pharma has a clinical candidate to treat AD in development that **inhibits expression of APP**

TBI in Animal Models

- **Mild TBI:** closed head models are good representation of human concussions
- **Gross effect of Mild TBI in mice**

mTBI neurological assessment tests:

After mild concussions all gross neurological measures and behavioral tests are normal



Nigel Greig

Gross Brain Morphology

30 g control



mTBI impact on right side:

No lesions or other gross histological differences were detected between the control and concussion mice

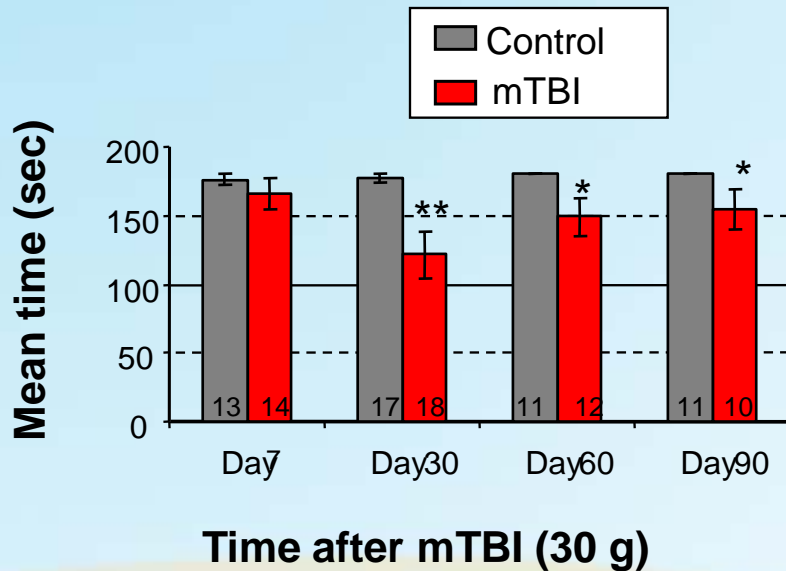
Hippocampus

J Neurosci Res. 85(4):805-15, 2007

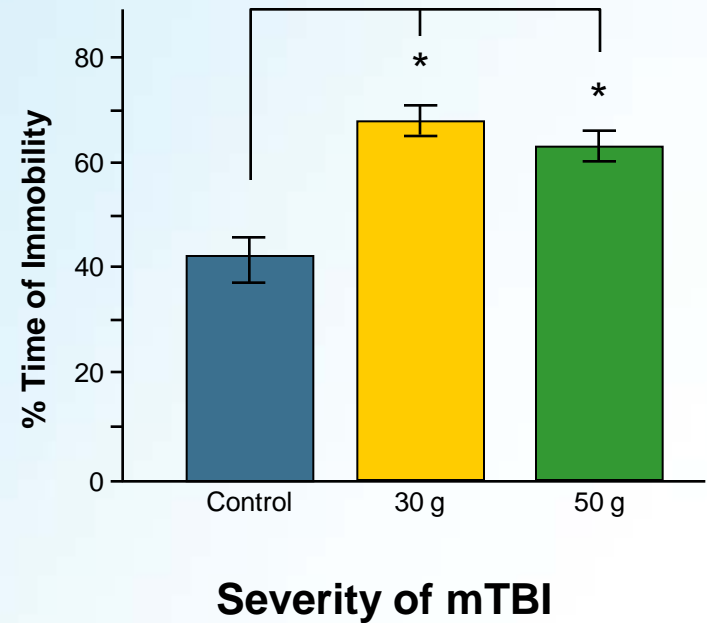
David Tweedie

Changes in Emotional Behavior

Passive Avoidance Emotional Learning



Forced Swim Test Depression



Chagi Pick

J Neurotrauma 22: 1003-10, 2005

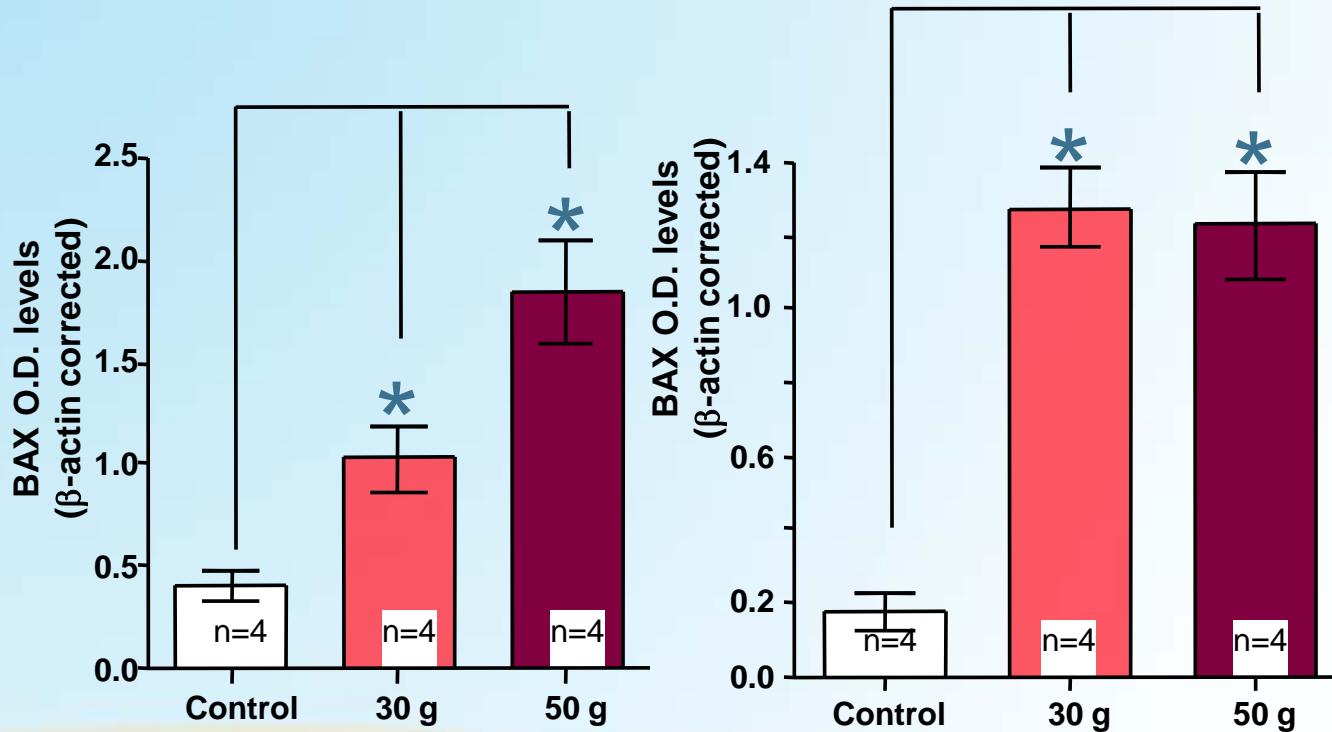
Changes in Apoptotic Markers Representing Cell Death



BAX:

8 hr

72 hr



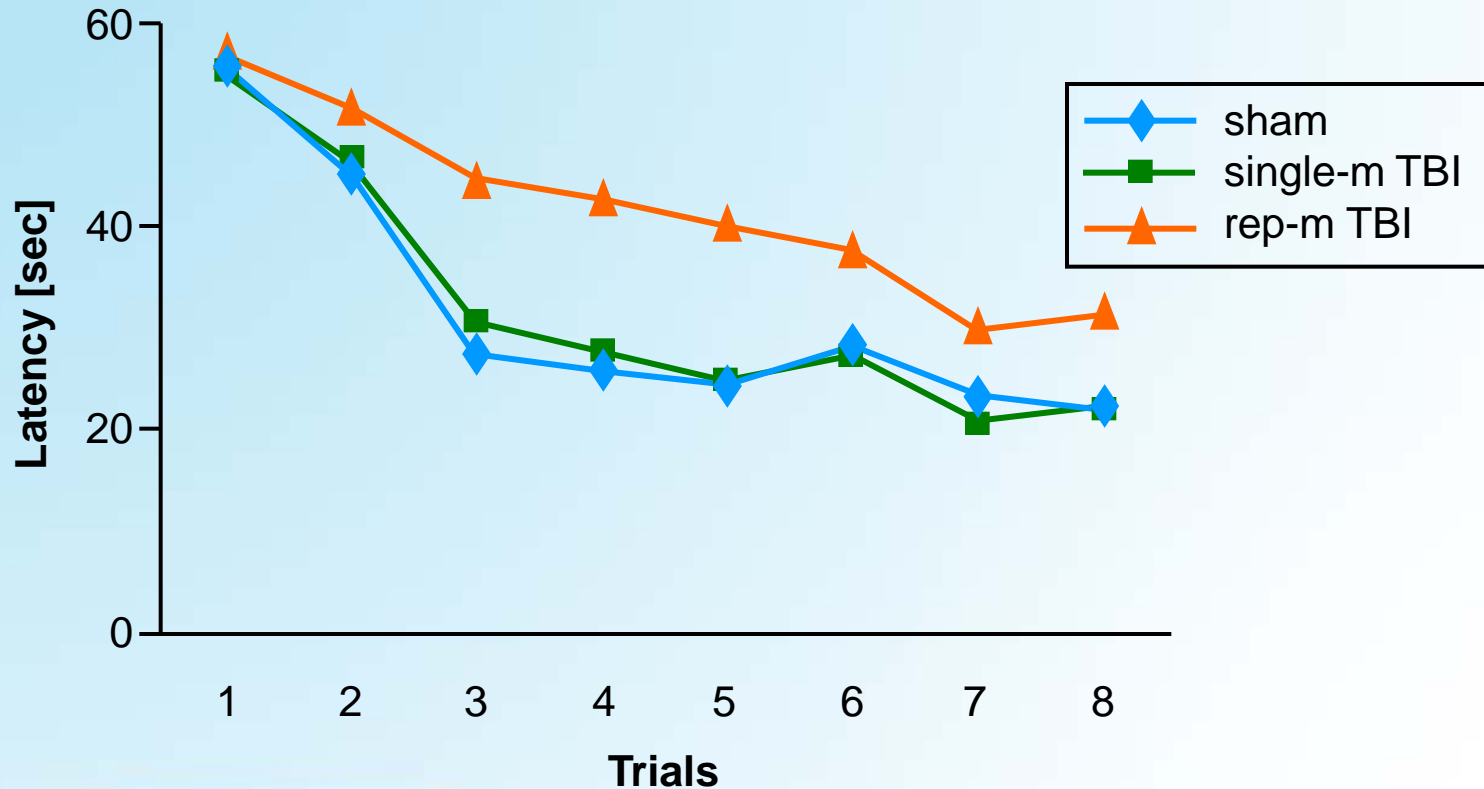
*p<0.05 Dunnett's



David Tweedie

J Neurosci Res. 85:805-15, 2007

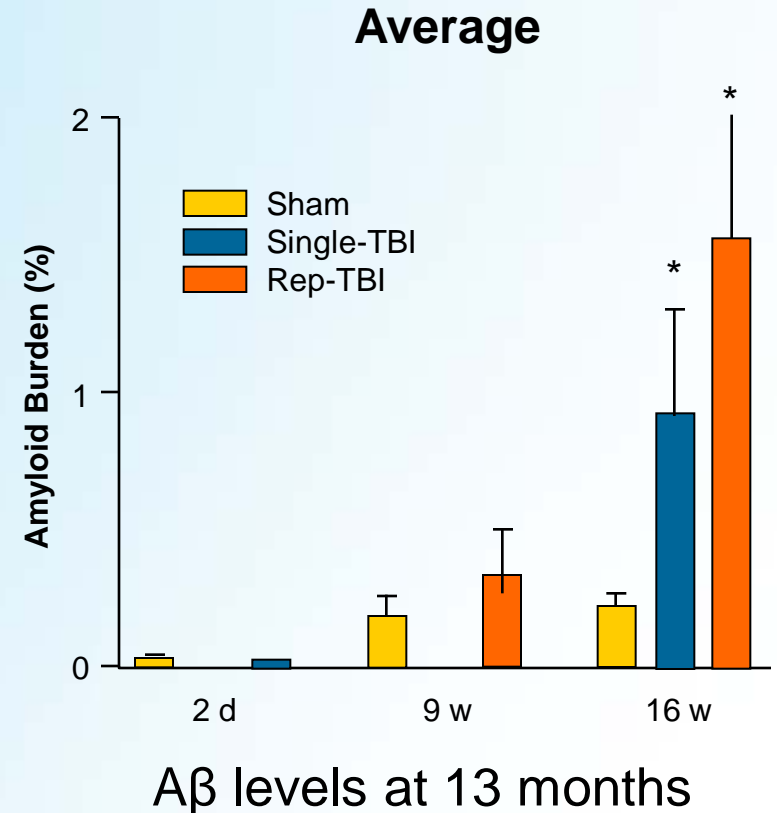
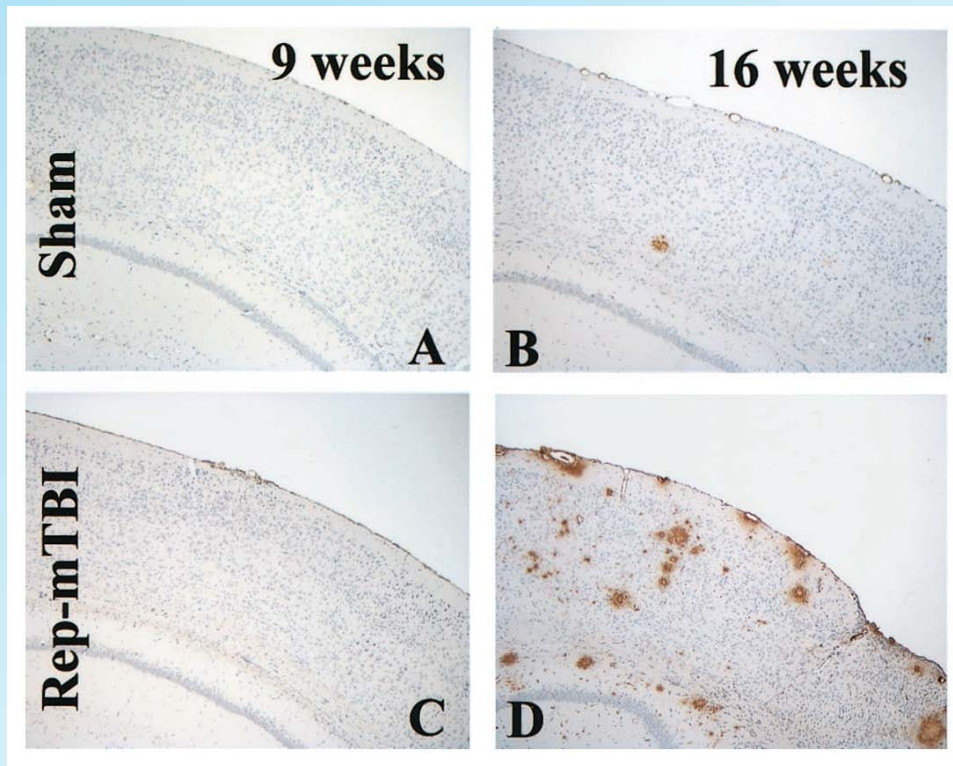
Long Term Changes in Cognition of 13 Month Old Mice



Morris Water Maze results from mice exposed to no, one or multiple mTBI at 9 months and tested 16 weeks later at 13 months of age

Uryu, Laurer et al, J Neuroscience; 22: 446-454, 2002

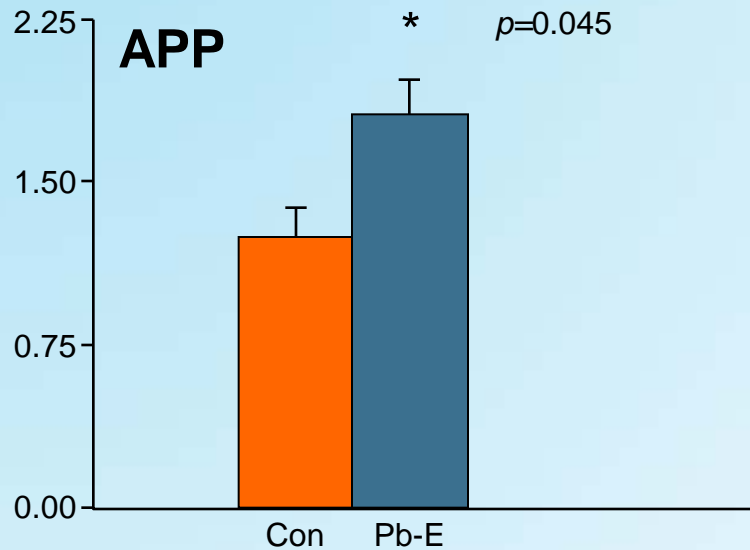
Long Term Changes in AD Markers of 13 Month Old Mice



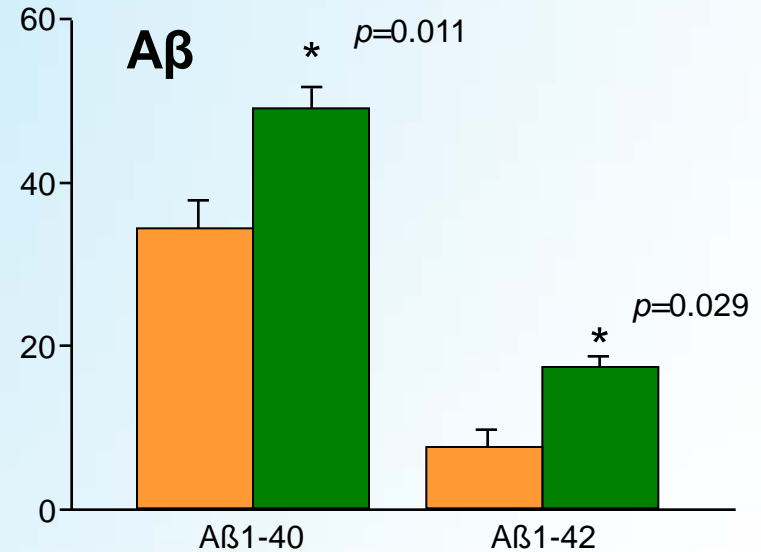
Amyloid Deposition in mice exposed to no, one or multiple mTBI at 9 months and tested 16 weeks later or 13 months of age

Uryu, Laurer et al, *J Neuroscience*; 22: 446-454, 2002

Long Term Changes in AD Markers in 23 Year Old Monkeys



APP mRNA expression in 23 year old monkeys treated with lead at birth



A β 40 and 42 protein levels in 23 year old monkeys treated with lead at birth

Summary of Biochemical Assessment

- **Apoptotic markers** are elevated short term
(*J Neurosci Res.* 85:805-15, 2007)
- **Inflammatory markers** are elevated medium term
(*Brain Res* 1185:45-58, 2007; *J Neurotrauma* 25:959-74, 2008)
- **Alzheimer's marker** is elevated after 3 days and stays elevated for life
(*Mol Cell Biochem* 2009 Jan 7 E-online)



**QR Pharma's compound,
Posiphen, inhibits expression
of this AD marker**

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