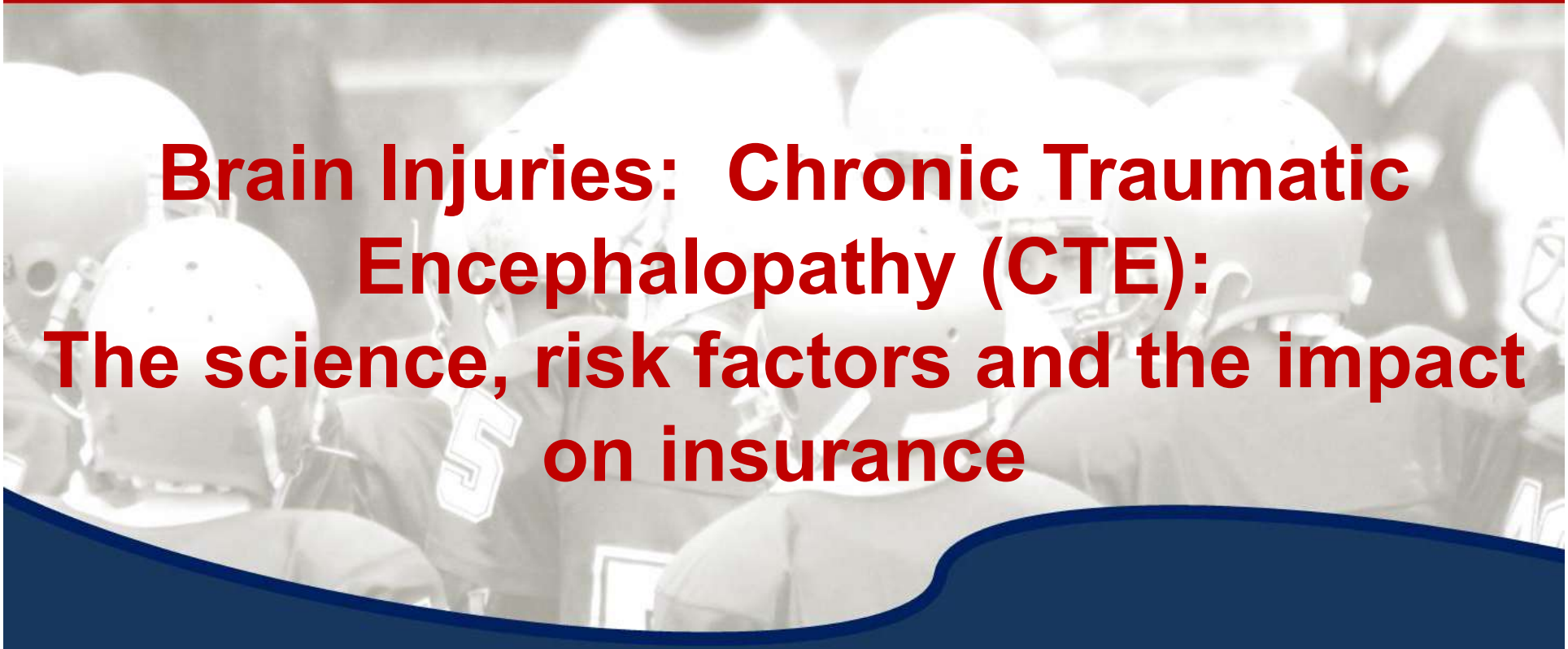


Brain Injuries: Chronic Traumatic Encephalopathy (CTE): The science, risk factors and the impact on insurance

November 13, 2018

Casualty Actuarial Society

Panelists:

Daniel H. Daneshvar, M.D., Ph.D., Neuroscientist, Chronic Traumatic Encephalopathy Center, Boston University School of Medicine/Founder, Team Up Against Concussions

Heather Schenker, Vice President-Brokerage, Nationwide

William Primps, Attorney, Partner, Locke Lord LLP

Moderator:

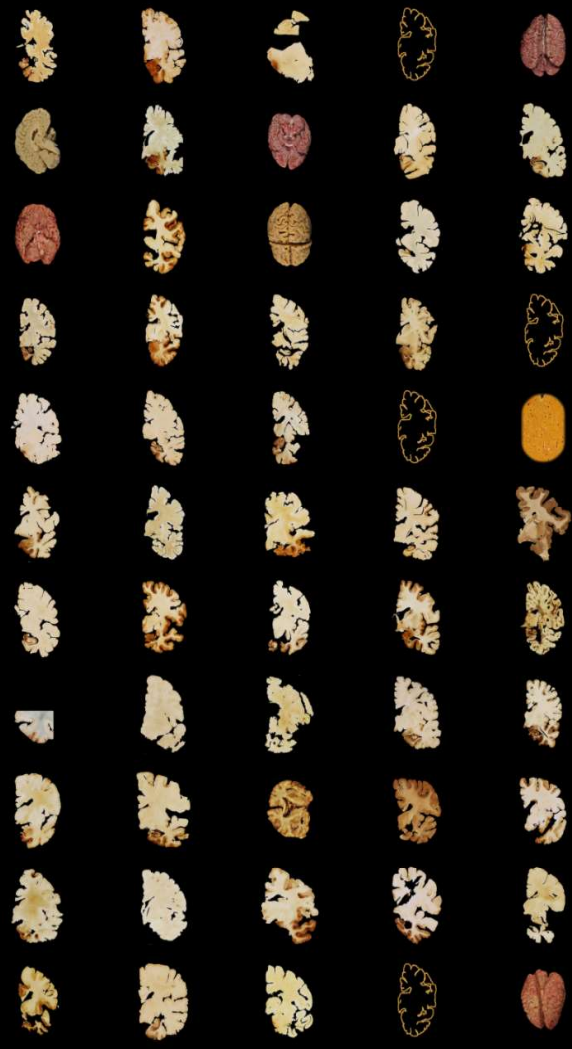
Barbara Murray, Director, PricewaterhouseCoopers

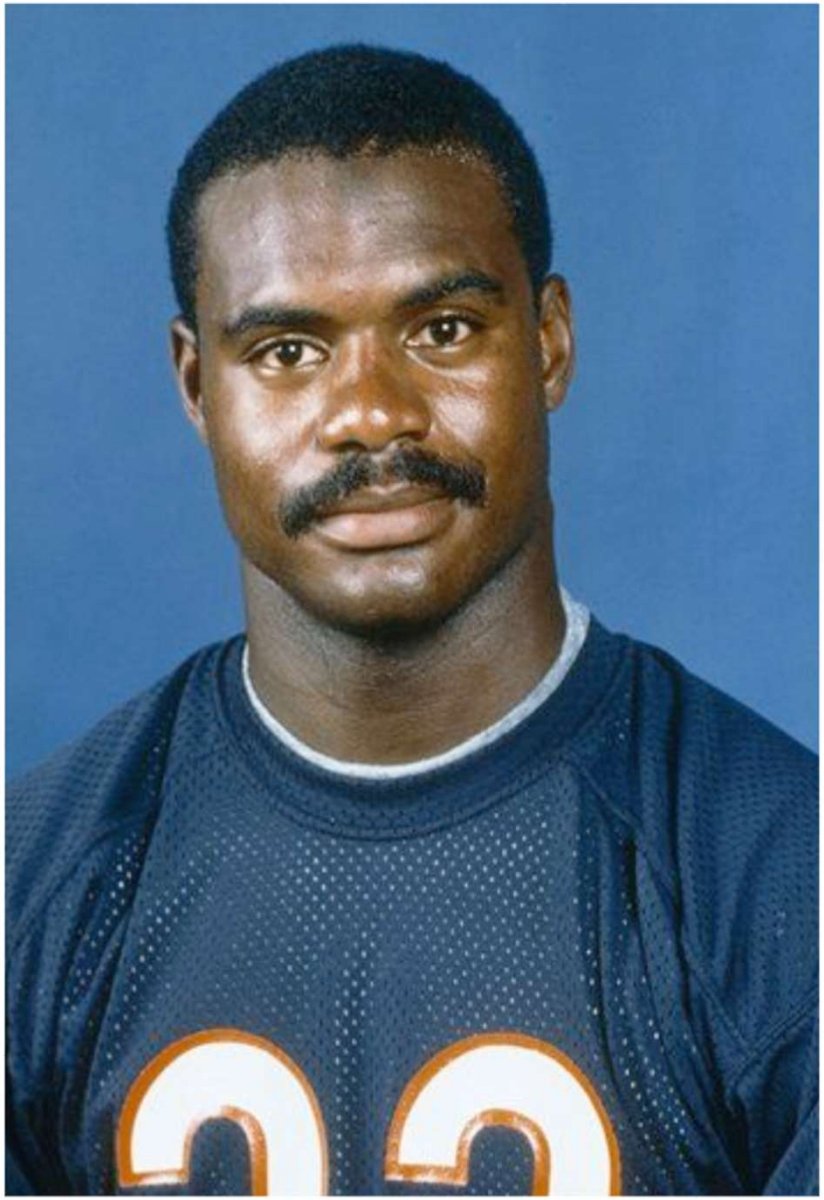
110

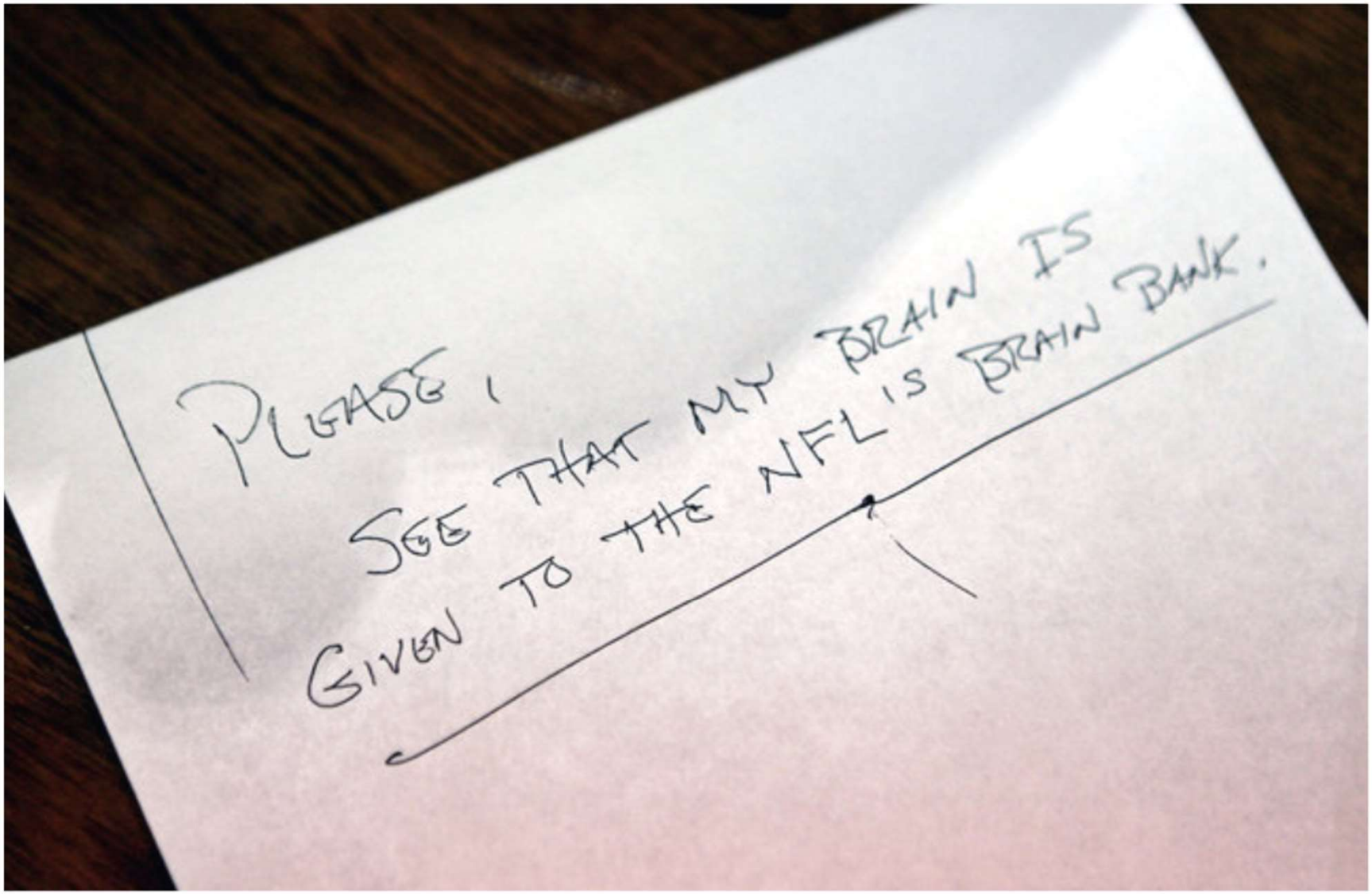
N.F.L. Brains

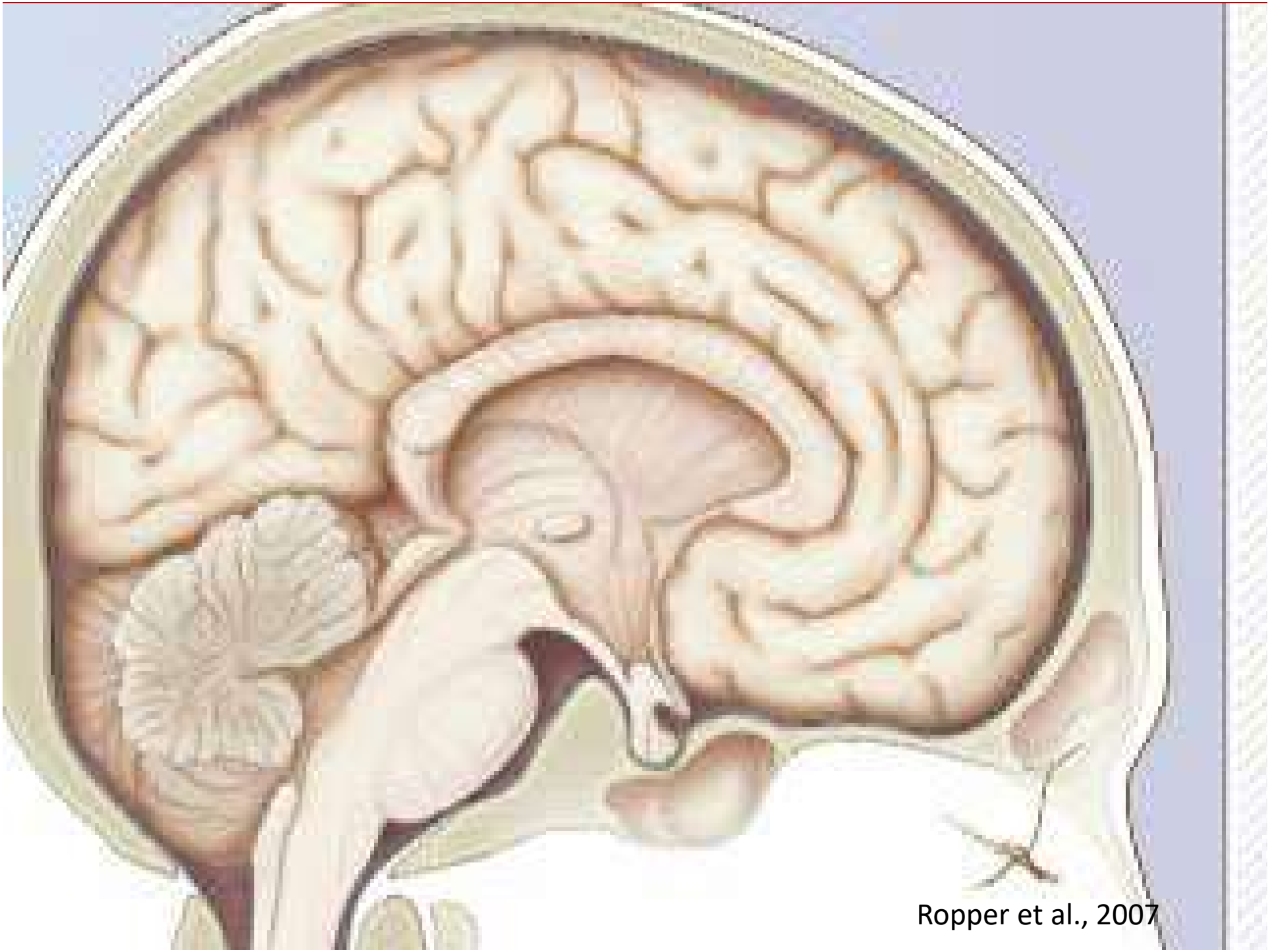
A neuropathologist has examined the brains of 111 N.F.L. players — and 110 were found to have C.T.E., the degenerative disease linked to repeated blows to the head.

By Joe Ward, Josh Williams and Sam Manchester
July 25, 2017

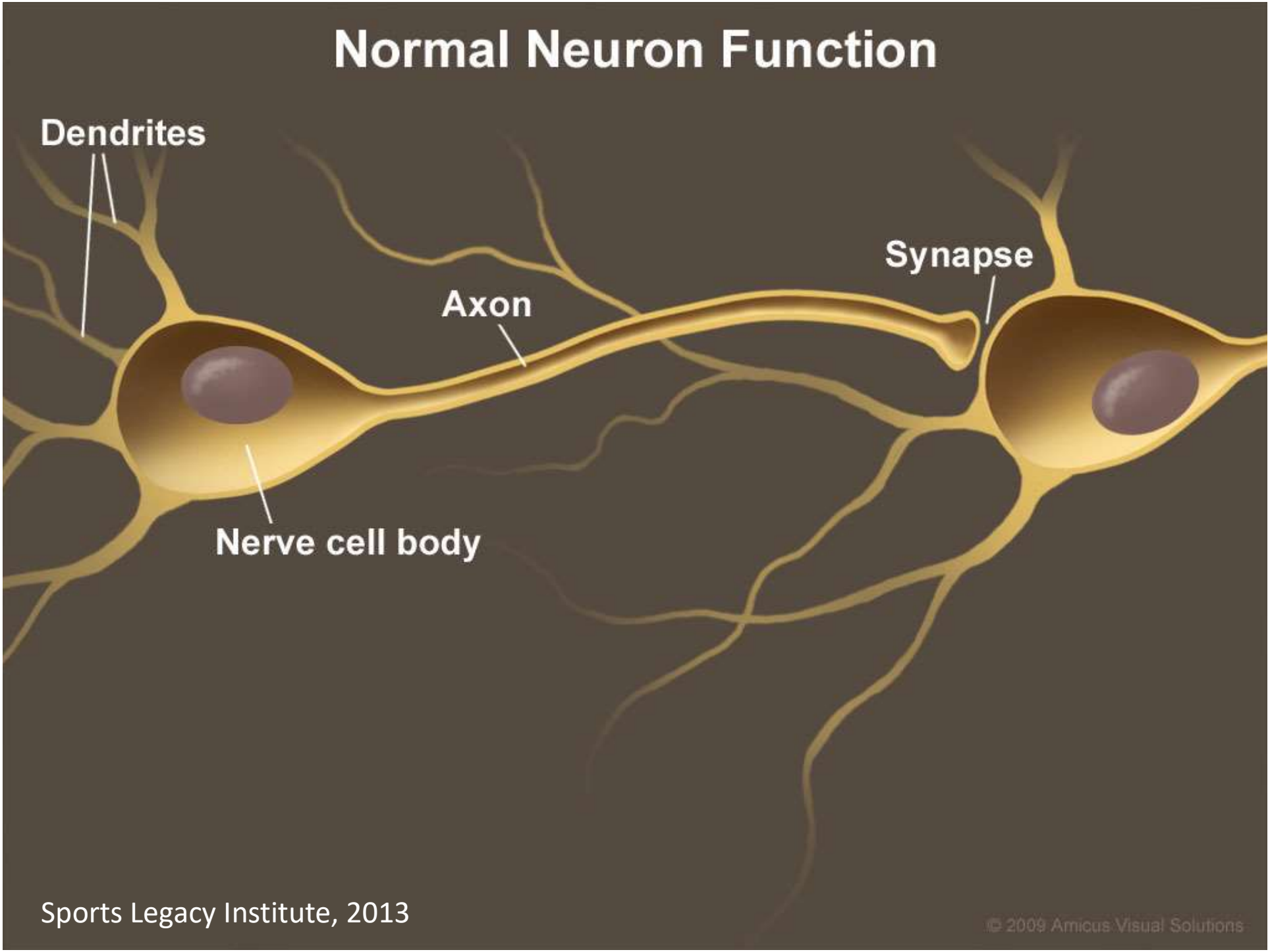




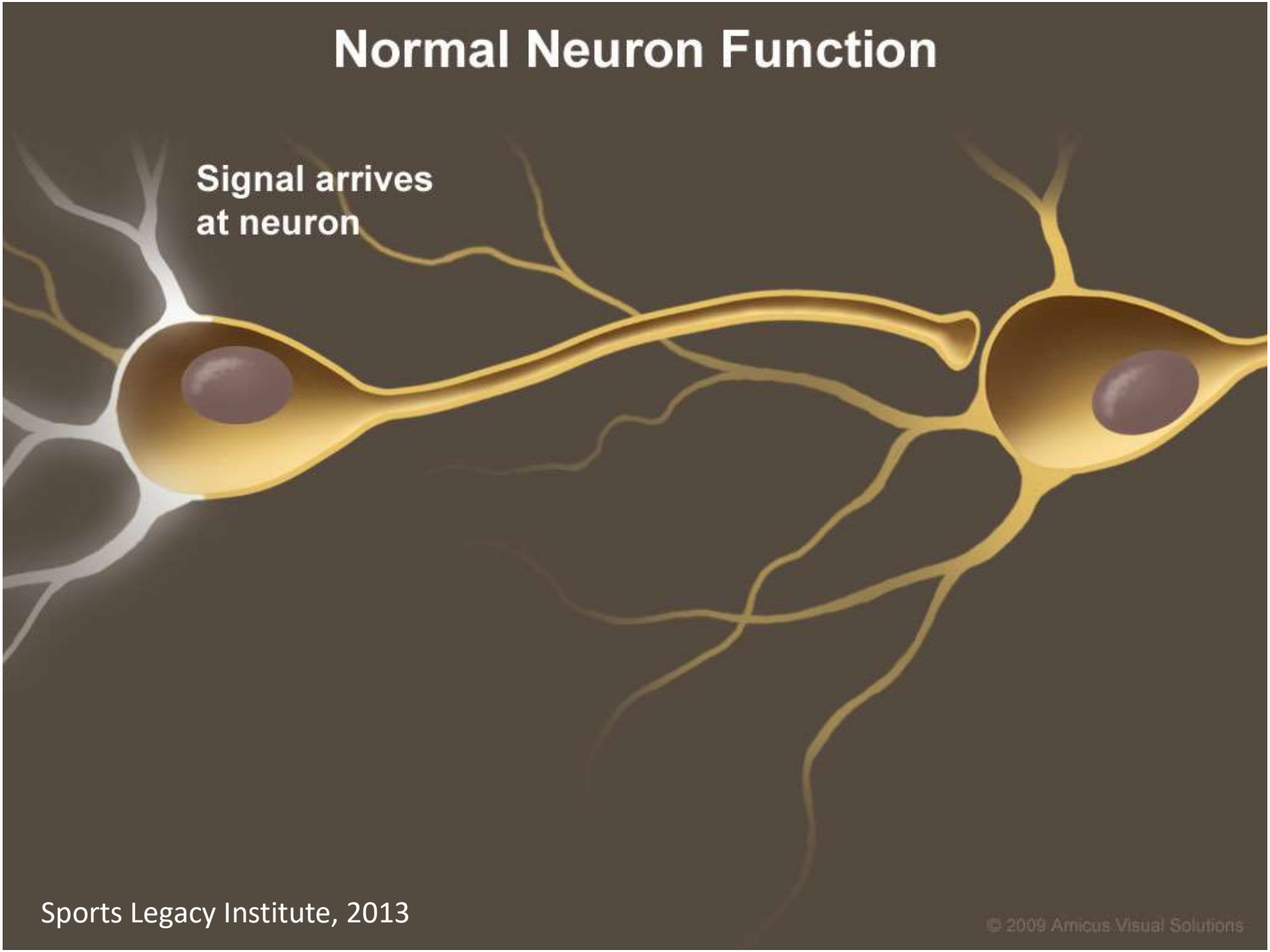

PLEASE,
SEE THAT MY BRAIN IS
GIVEN TO THE NFL'S BRAIN BANK.



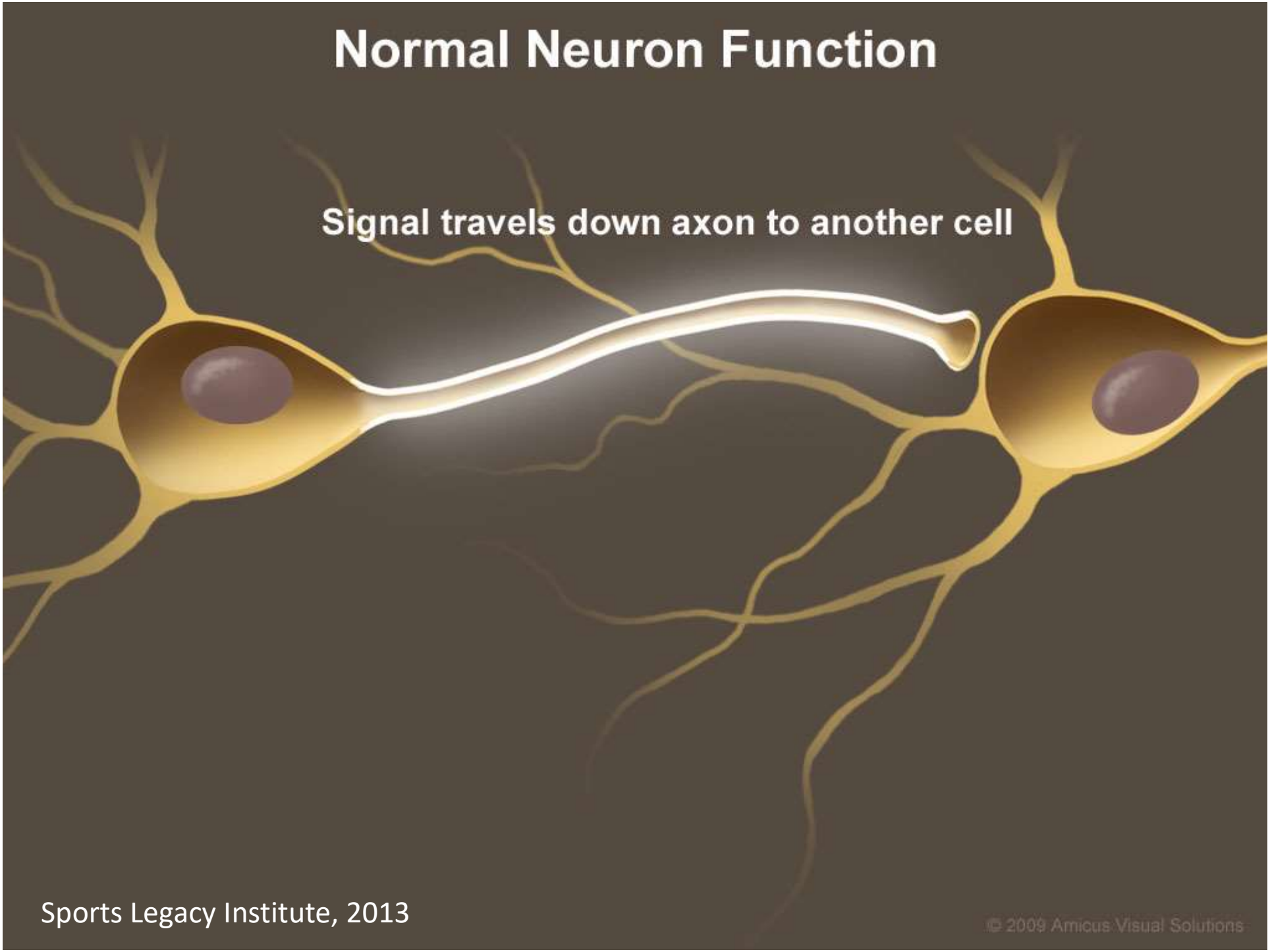
Ropper et al., 2007



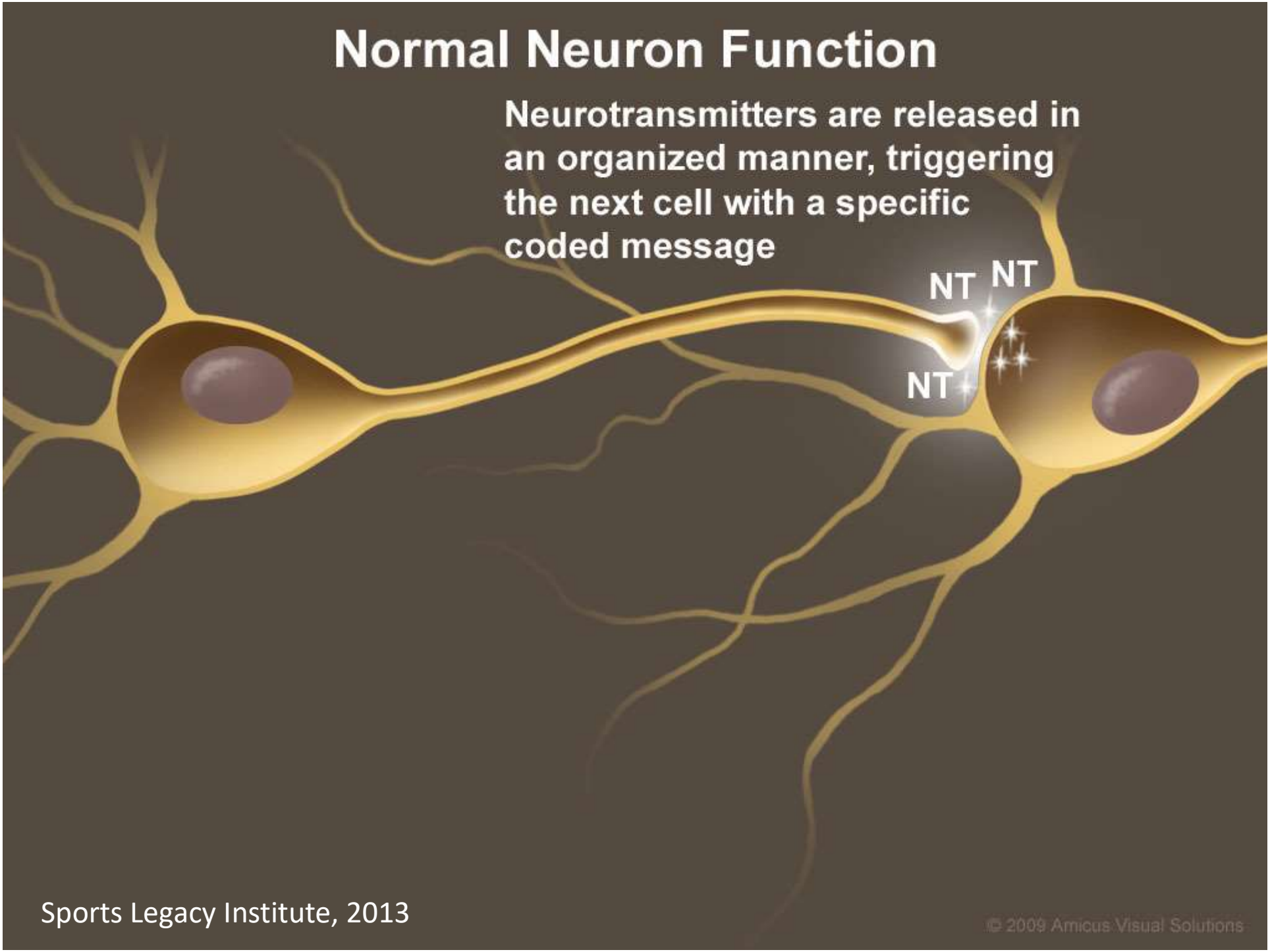
Sports Legacy Institute, 2013



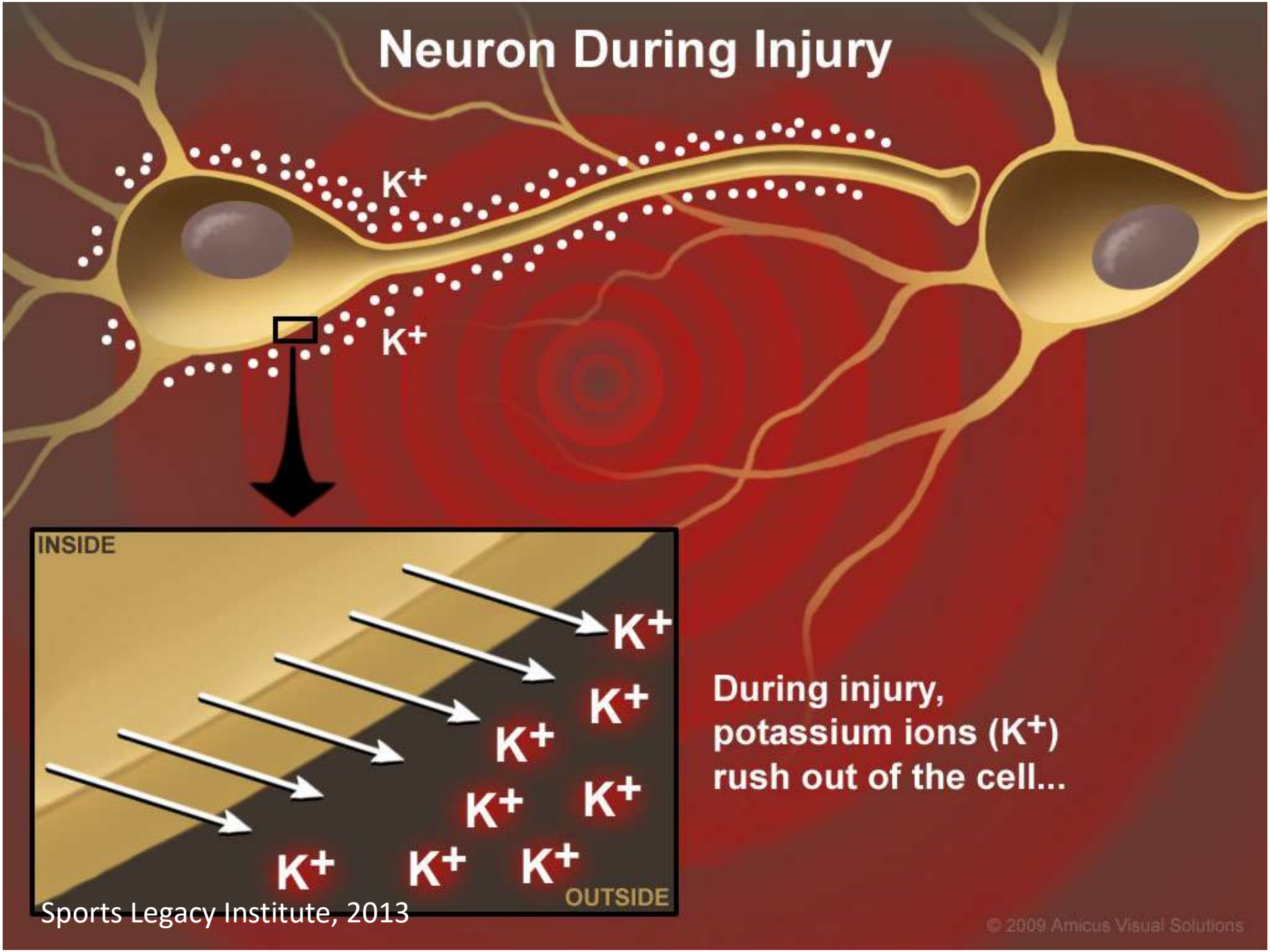
Sports Legacy Institute, 2013



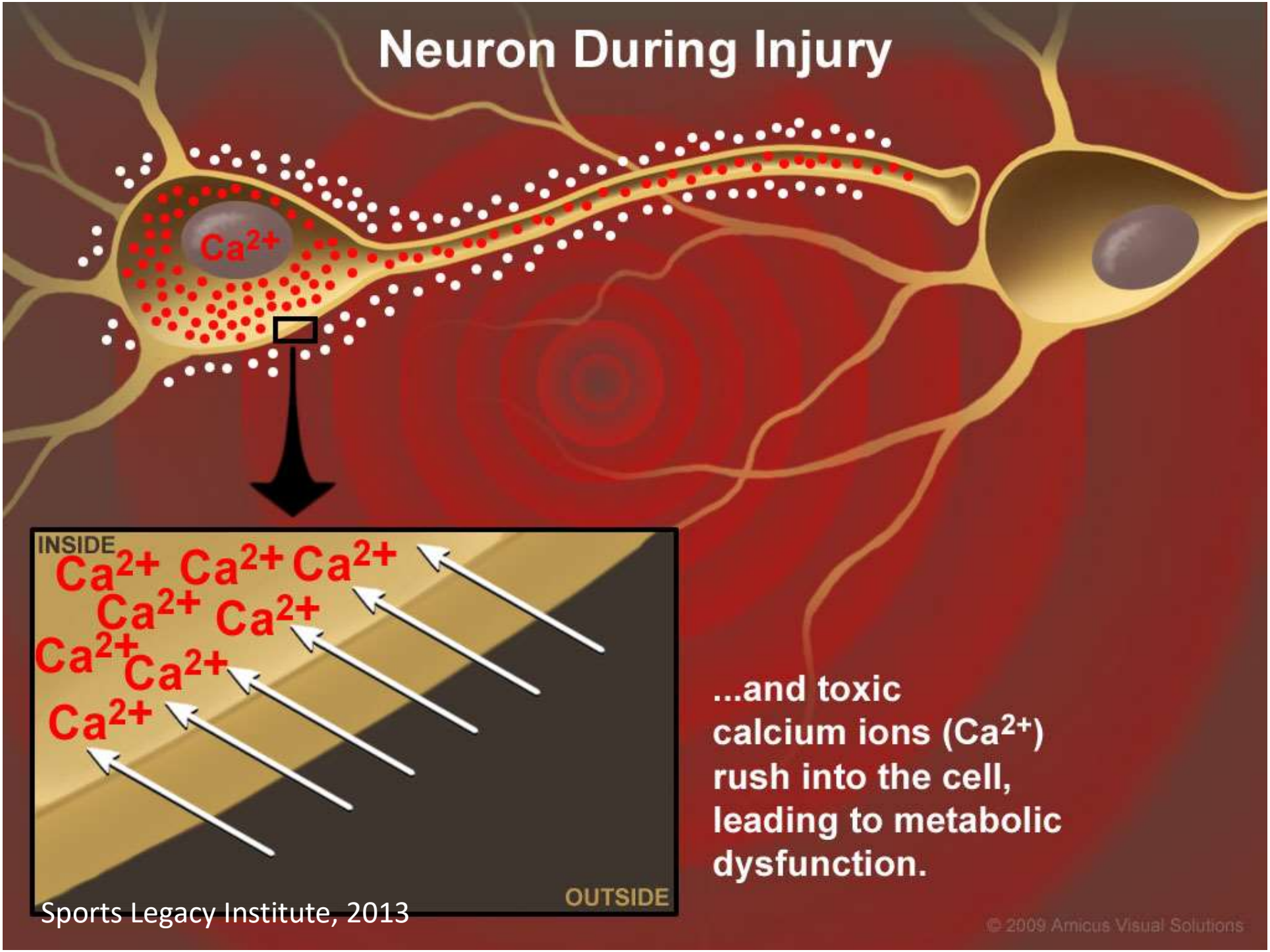
Sports Legacy Institute, 2013



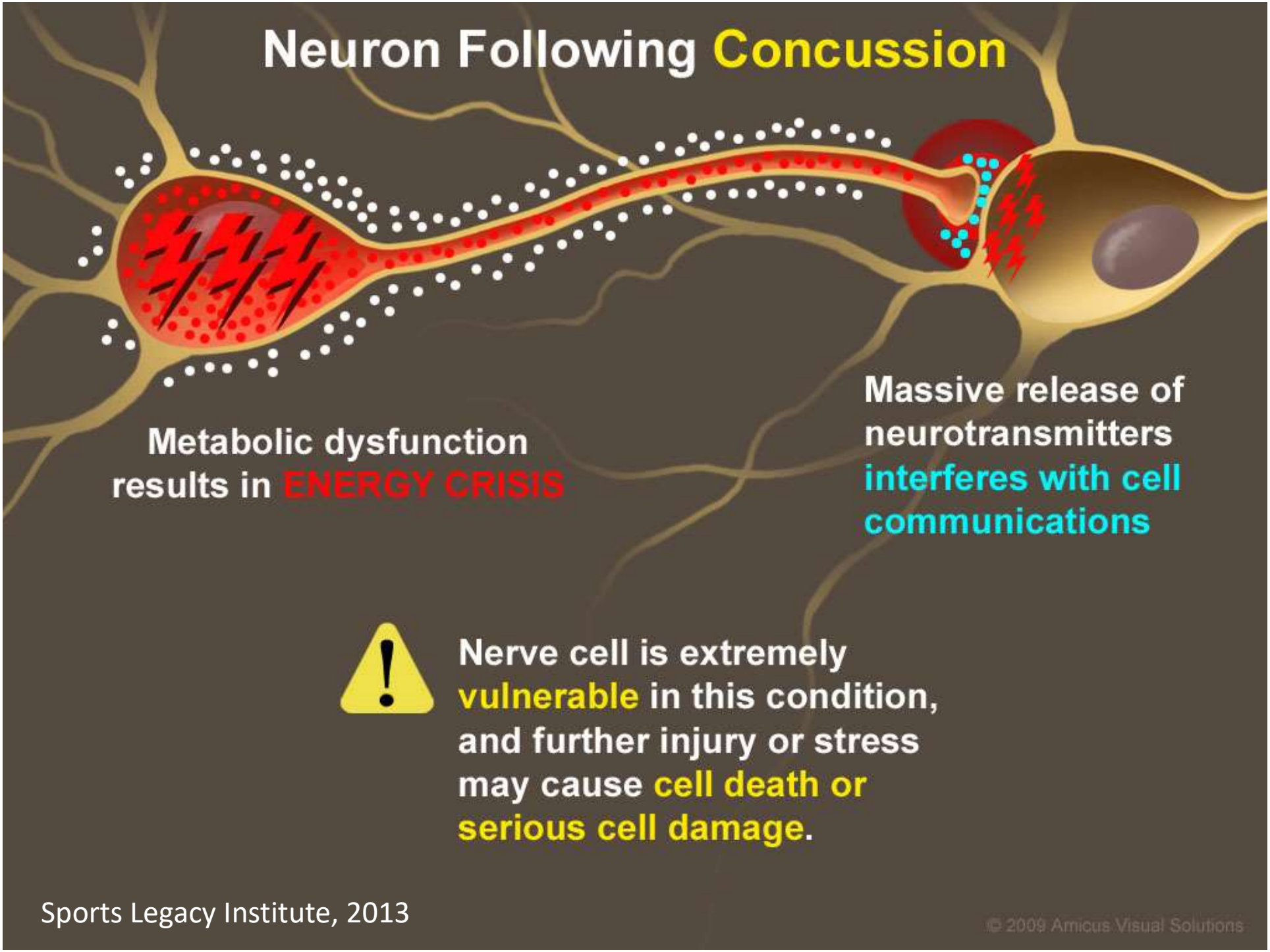
Sports Legacy Institute, 2013

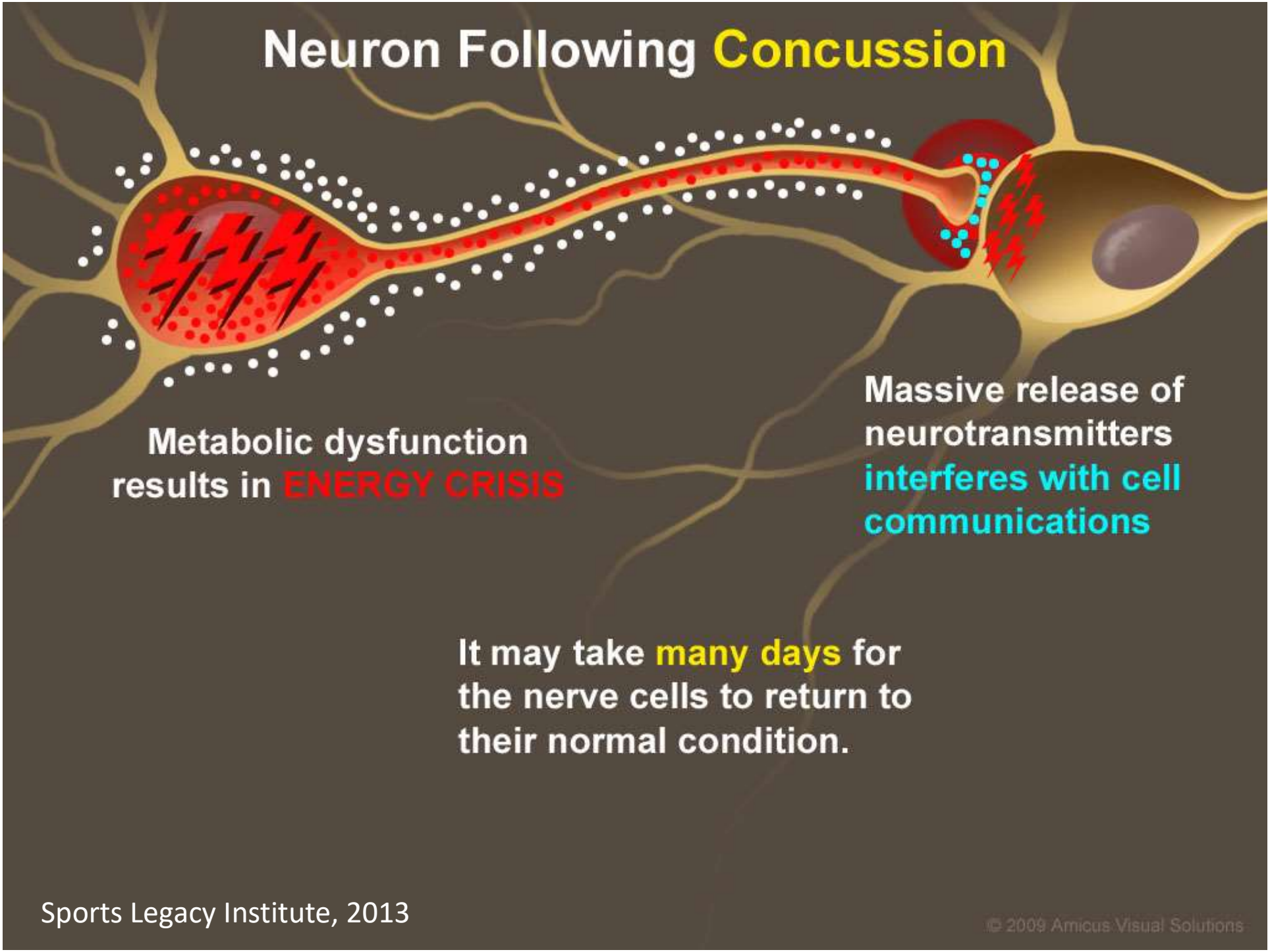


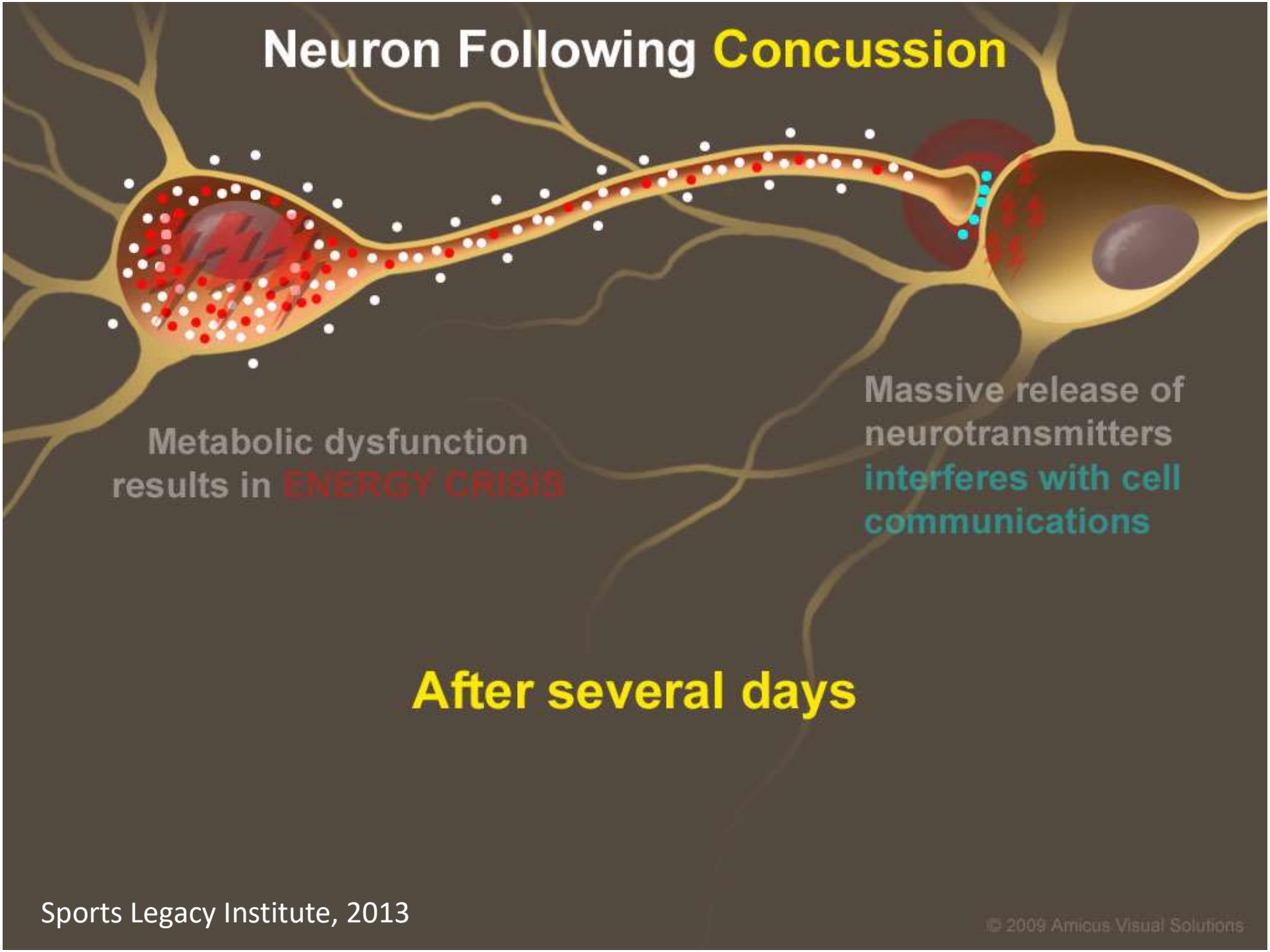
Sports Legacy Institute, 2013



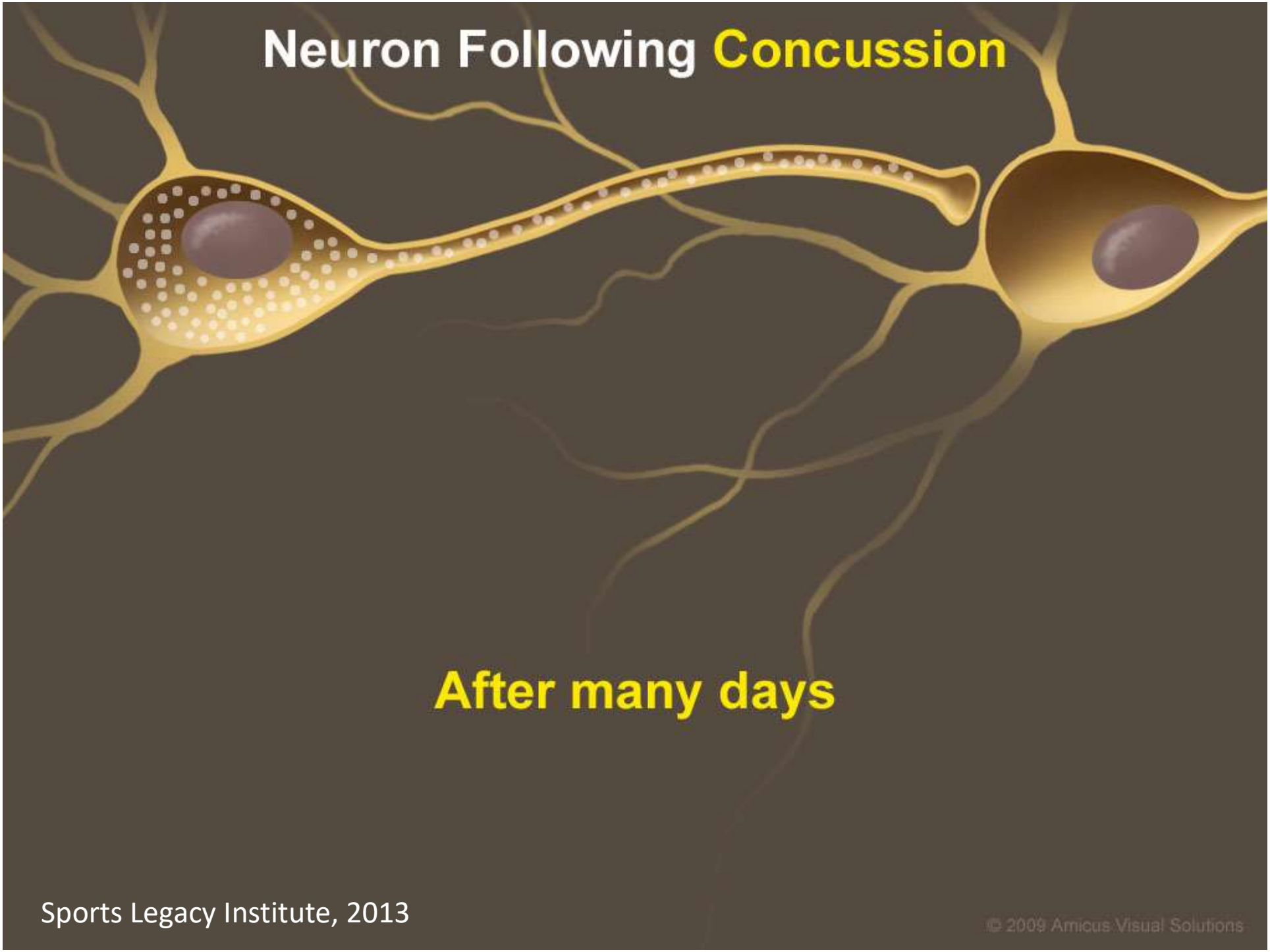
Sports Legacy Institute, 2013


Neuron Following Concussion
Metabolic dysfunction results in ENERGY CRISIS
Massive release of neurotransmitters interferes with cell communications
Nerve cell is extremely vulnerable in this condition, and further injury or stress may cause cell death or serious cell damage.
Sports Legacy Institute, 2013
© 2009 Amicus Visual Solutions

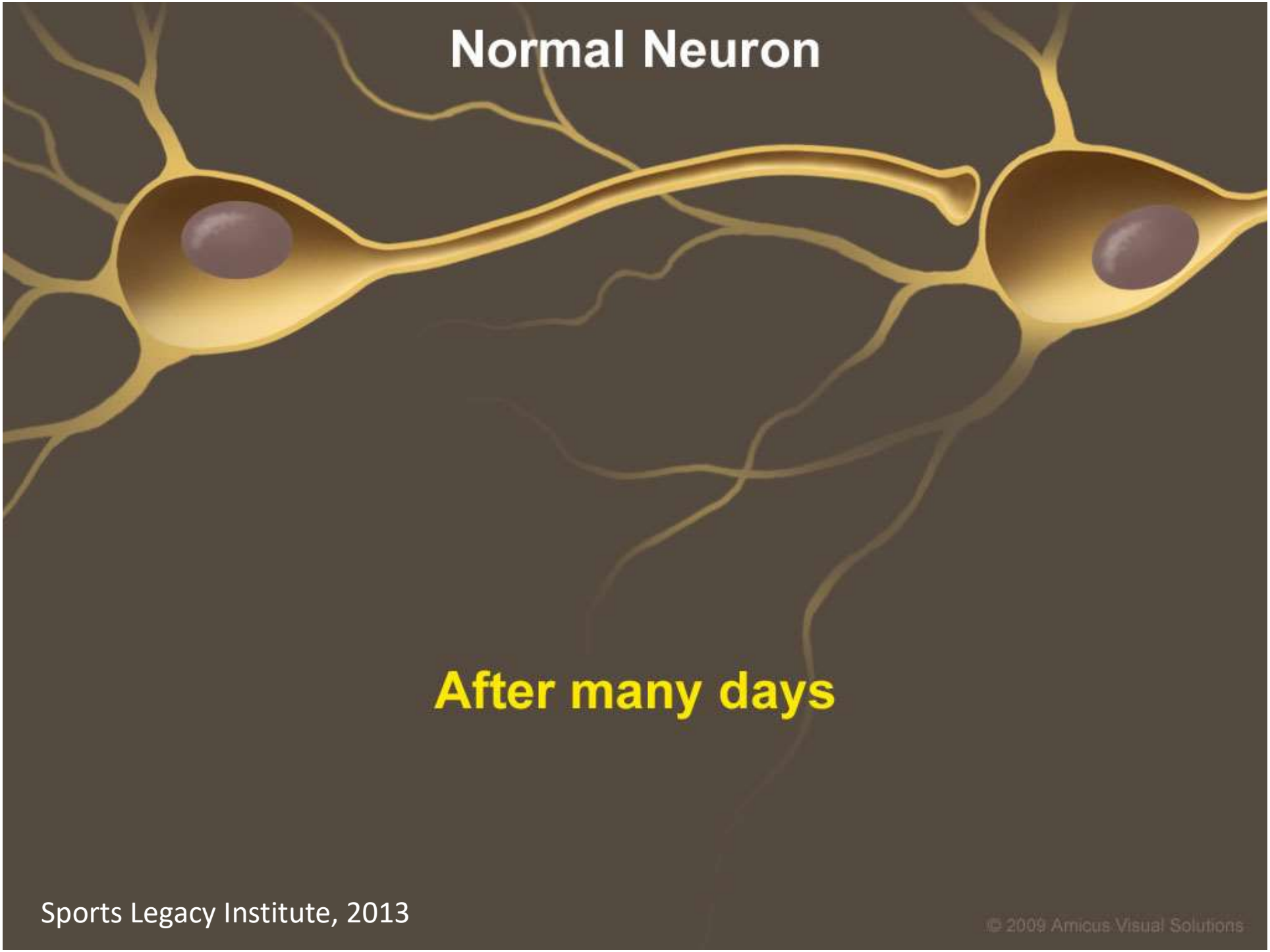

Neuron Following Concussion
Metabolic dysfunction results in ENERGY CRISIS
Massive release of neurotransmitters interferes with cell communications
It may take many days for the nerve cells to return to their normal condition.
Sports Legacy Institute, 2013
© 2009 Amicus Visual Solutions



Sports Legacy Institute, 2013



Sports Legacy Institute, 2013



Sports Legacy Institute, 2013

Window of Vulnerability

- Return-to-play during this time could cause more severe or even catastrophic brain injury

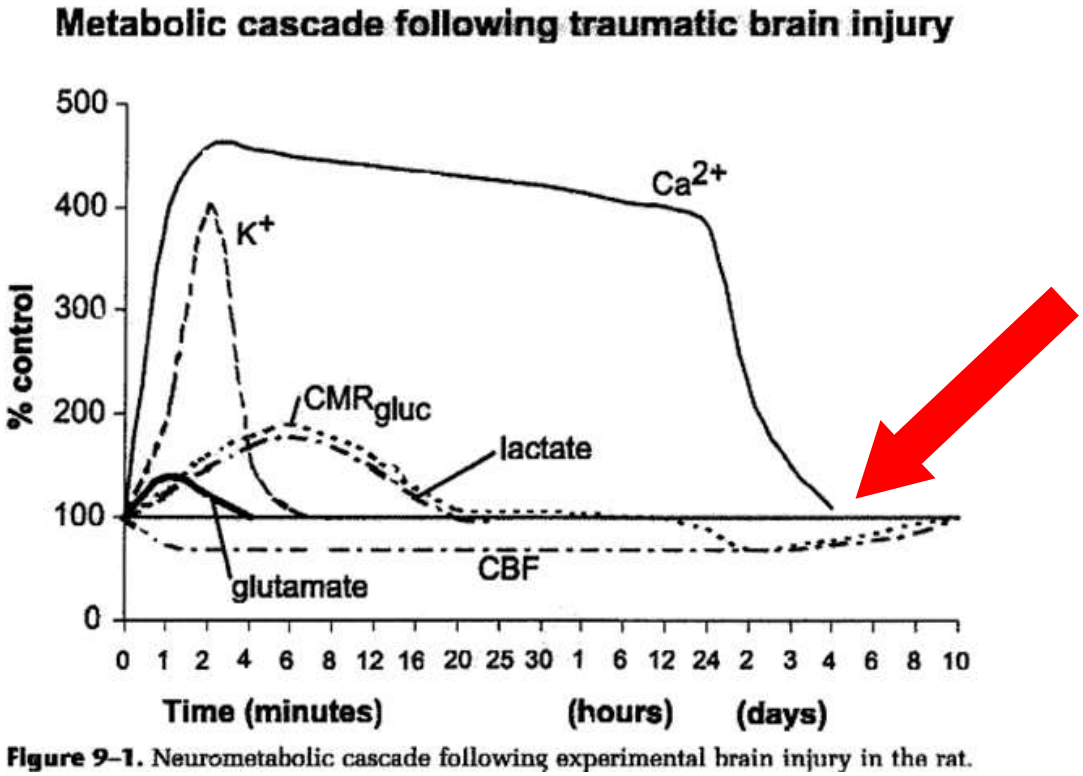
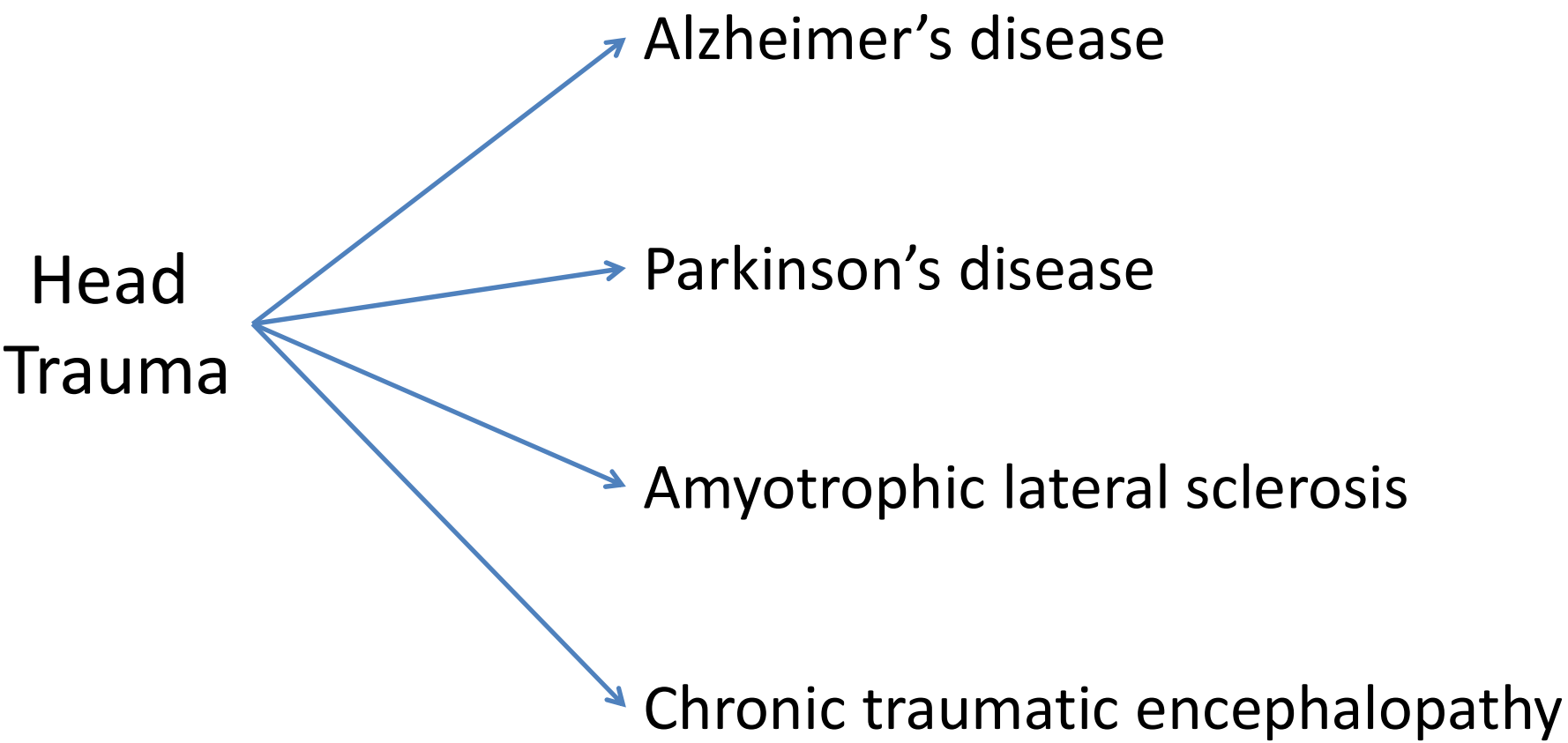


Figure 9–1. Neurometabolic cascade following experimental brain injury in the rat.

- It may be unsafe to return to competition until brain activity has returned to baseline
- In rodent models, this averages ~10 days

Giza, Hovda 2000

Neurodegenerative disease and TBI



Daneshvar et al., 2015a

History of CTE

- First described in boxers by Martland in 1928

  Martland HS: Punch drunk. ***JAMA*** *91:1103–1107,* ***1928***

Harrison S. Martland

(1883-1954)

First full time paid pathologist
Newark city Hospital, 1909-1927
Chief Medical examiner
Essex county

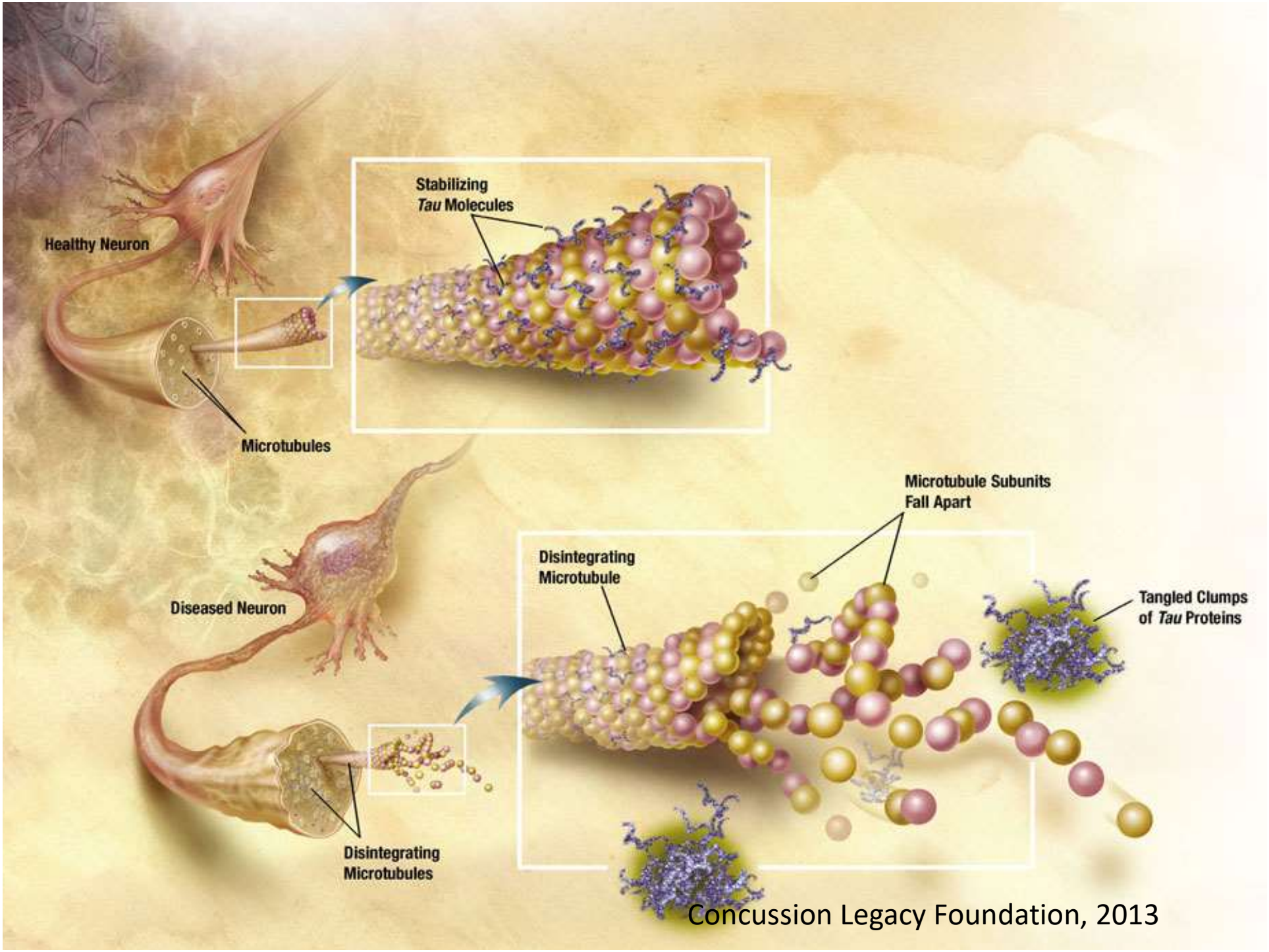
- As of 2008, there were only **45 cases of CTE** in the medical literature. **All had histories of repetitive brain trauma**

Primary Trauma Source	45
Boxing	39
Soccer	1
Battered spouse	1
Head banging behavior	2
Circus clown	1
Epilepsy	1

McKee et al., 2009

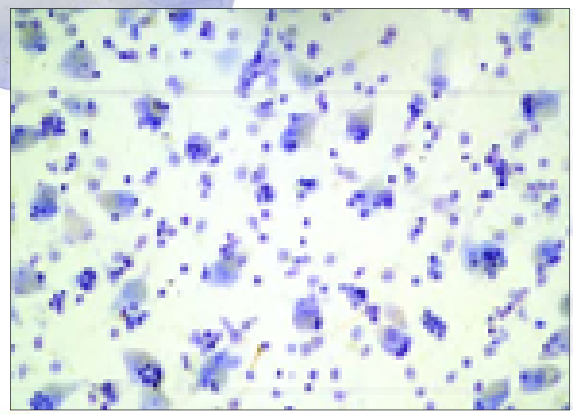
Current Status of the Brain Bank

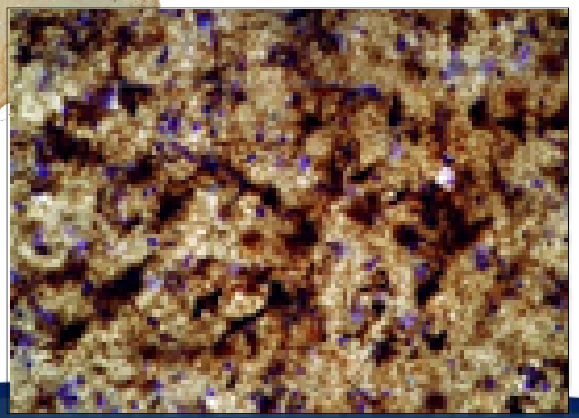
- Over 630 brains of former athletes, veterans, and individuals otherwise exposed to repetitive head impacts
- Published first 85 donors in *Brain* in 2013
- Published first 202 football players in *JAMA* in 2017 (177 with CTE) and first 246 in Annals of Neurology in 2018 (211 with CTE)



Concussion Legacy Foundation, 2013

What do we know: Pathology





McKee et al., 2013

What do we know: Pathology

Substantia Nigra

Locus ceruleus

Midbrain

Pons

Medulla

Cord

McKee et al., 2013

Neuropathologic Review

- Expert neuropathologists independently analyzed slides from cases of CTE and other tauopathies, blinded to the clinical history and gross neuropathological features
- 25 cases of various tauopathies, including:
  - CTE, Alzheimer's disease, progressive supranuclear palsy, argyrophilic grain disease, corticobasal degeneration, primary age-related tauopathy and parkinsonism dementia complex of Guam
- All slides processed by same laboratory to provide uniform processing of the cases
- A total of 675 slides were digitally scanned at Mayo Clinic Jacksonville

McKee et al., 2015

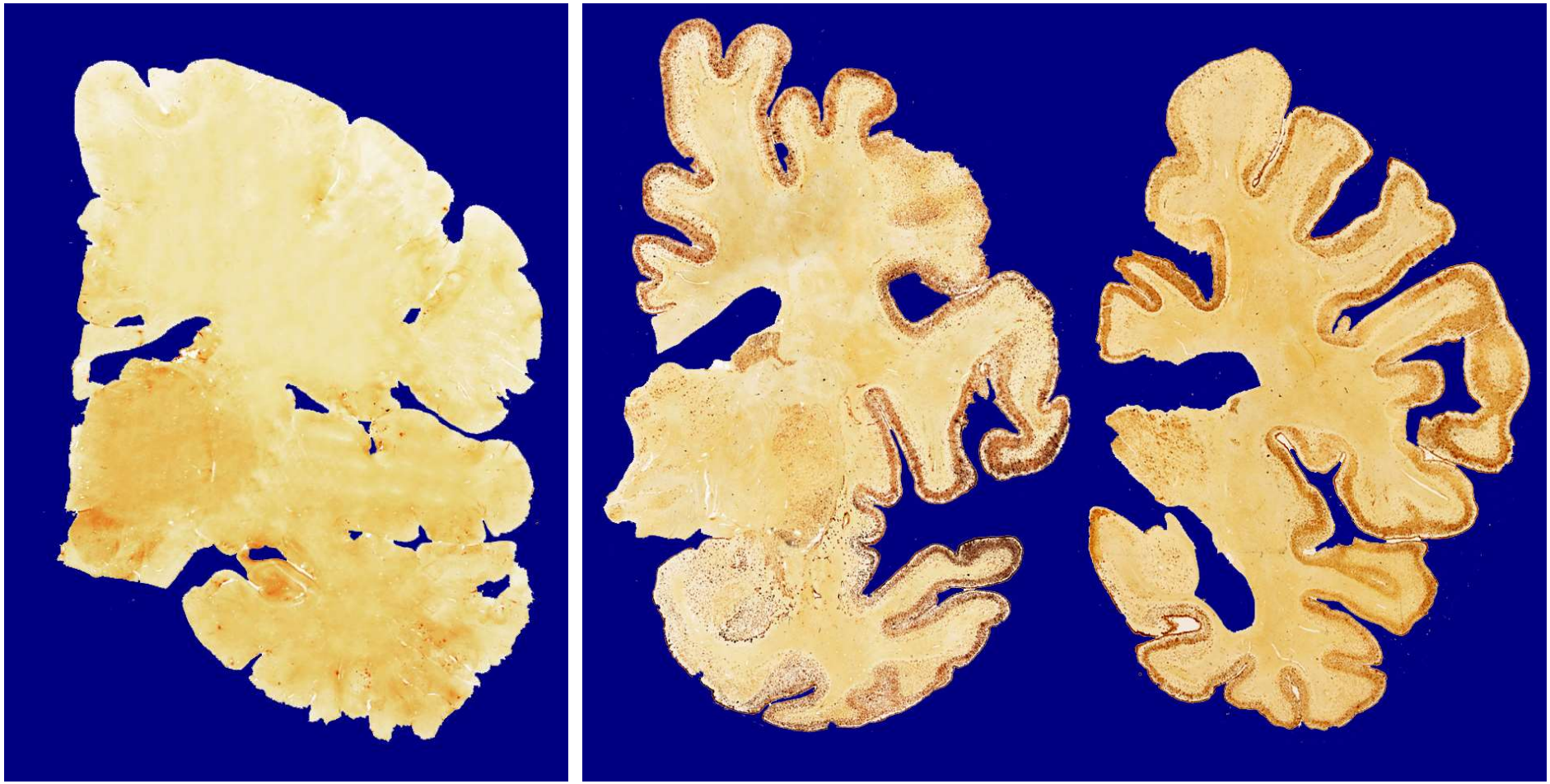
Stanford MEDICINE

Consensus Results

- Substantial agreement between pathologists (overall kappa: 0.67) and substantial agreement between pathologists and CTE diagnosis (overall kappa: 0.78) using the proposed CTE criteria
- Pathognomonic lesion of CTE was defined:
  - an abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes in an irregular pattern at the depths of the cortical sulci.

McKee et al., 2015

Beta-amyloid deposition



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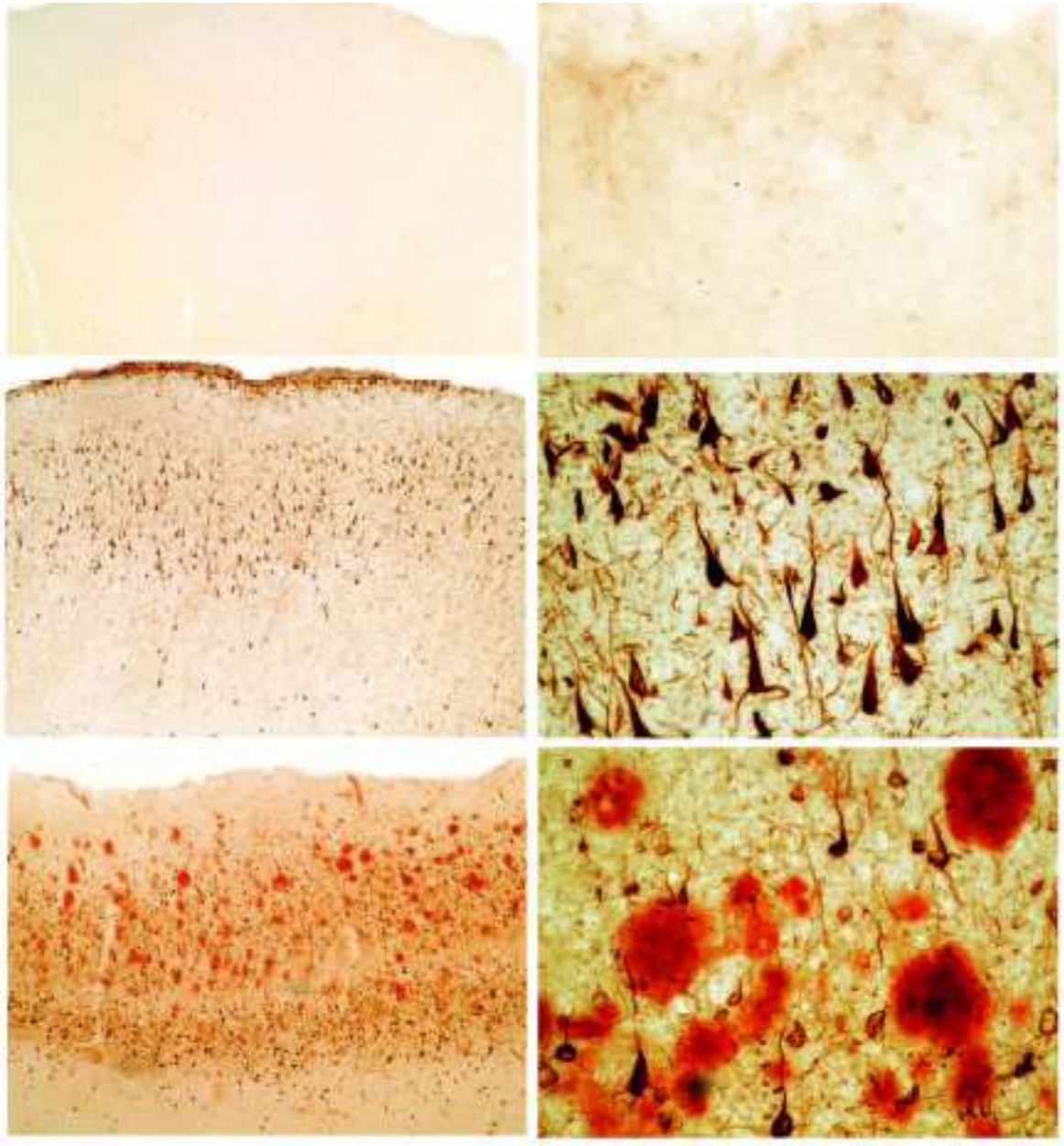
Stein et al., 2015

Normal

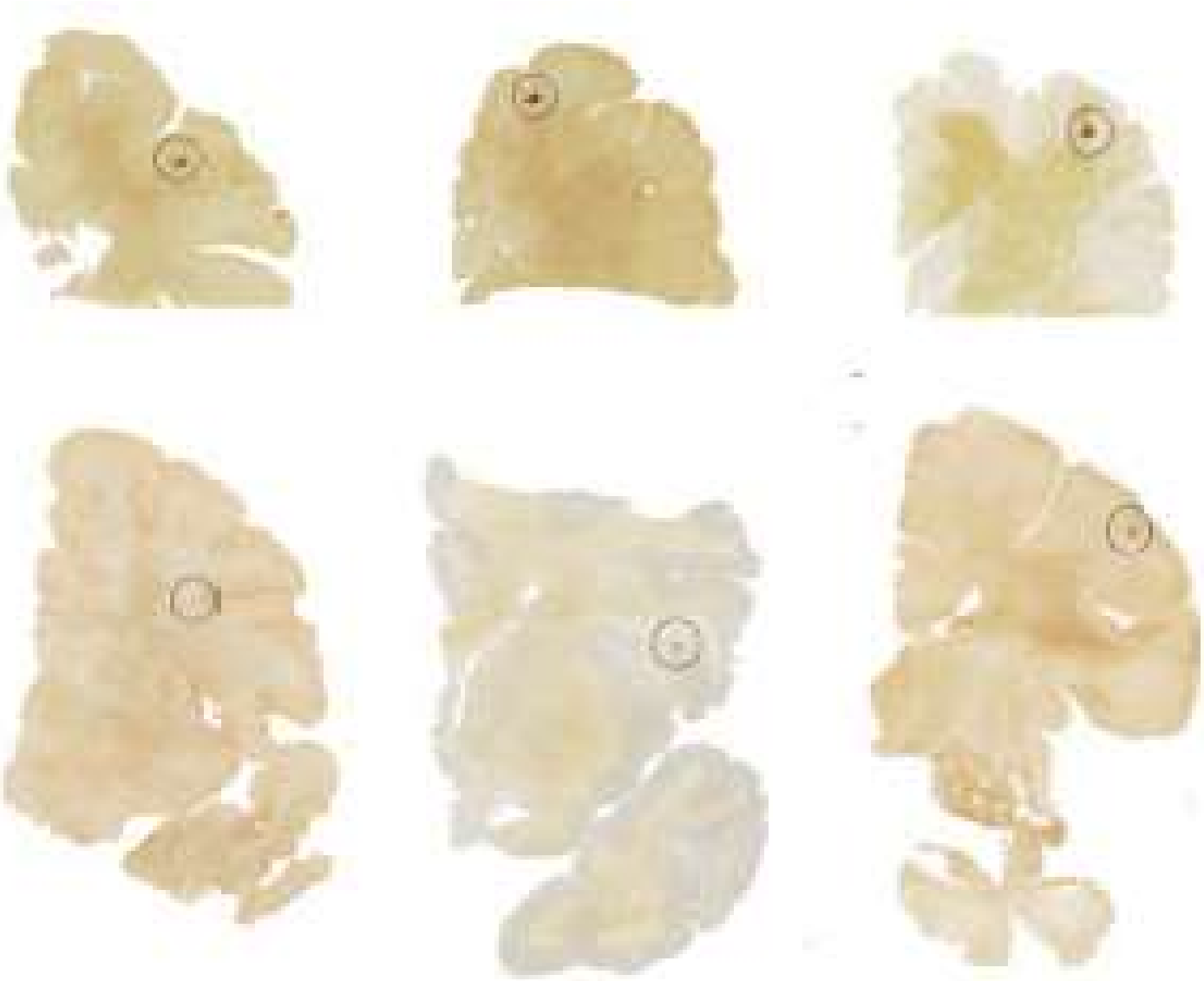
CTE

AD



Stanford MEDICINE

McKee, 2010



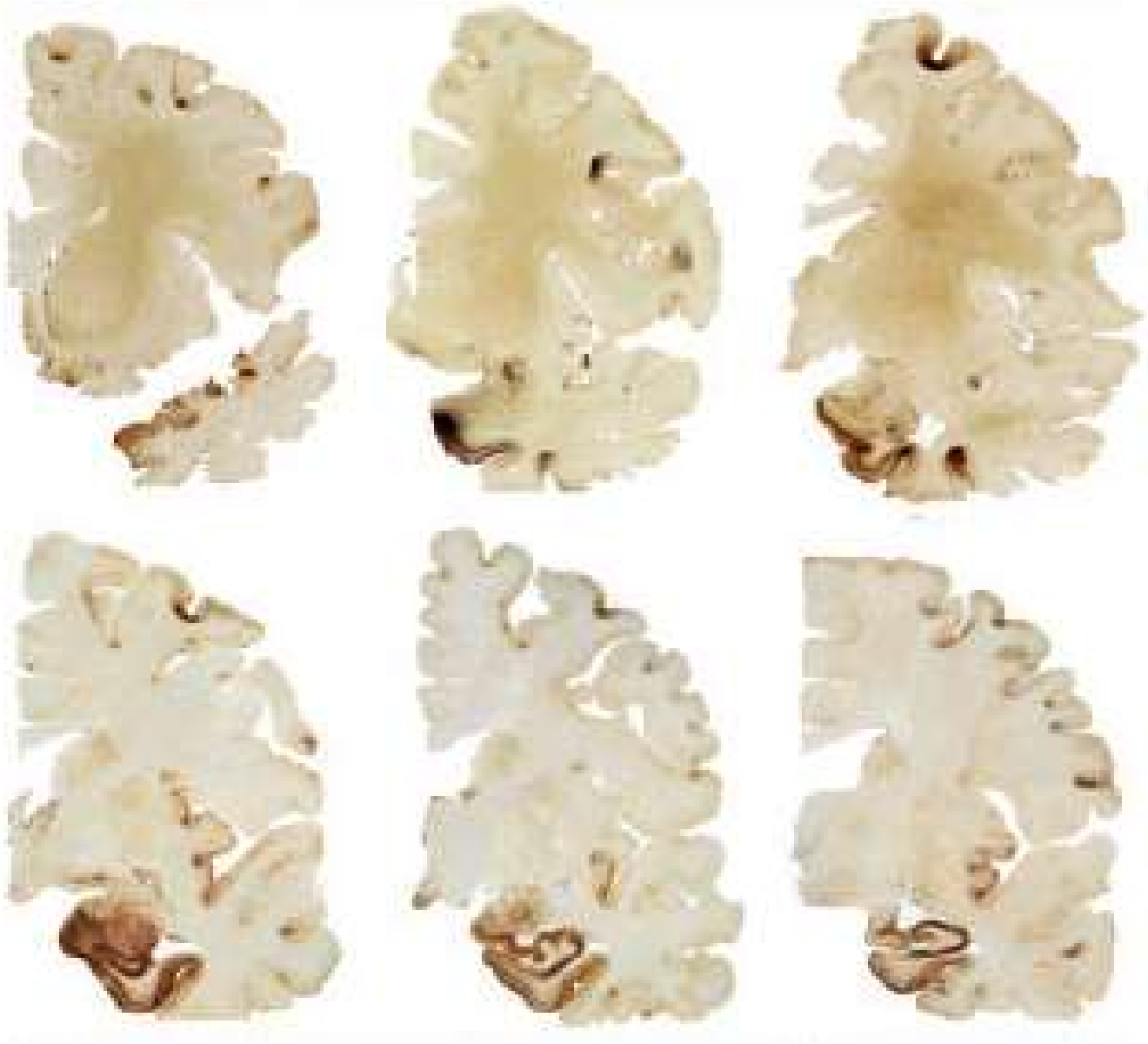
McKee et al., 2013

II.

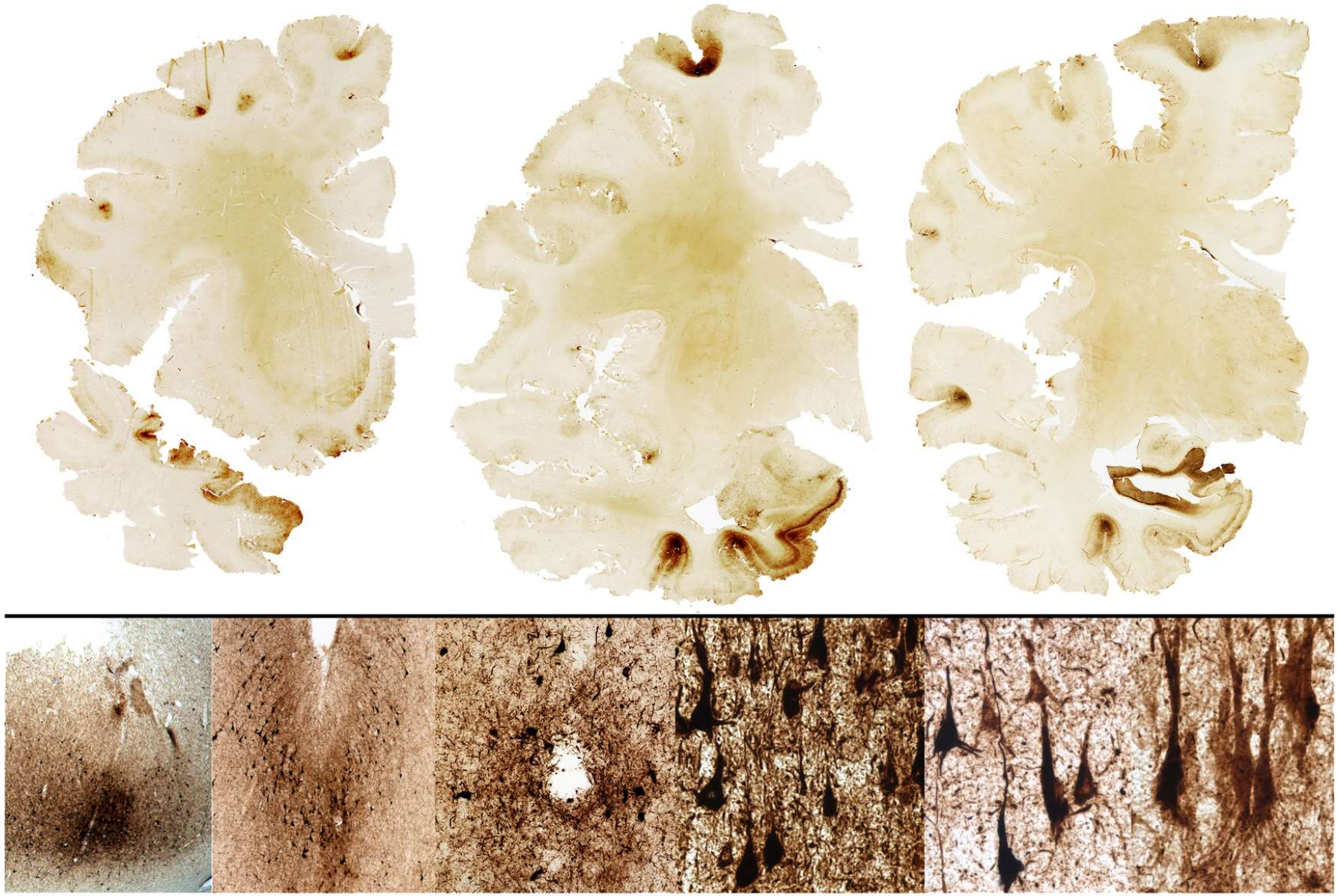
Stanford MEDICINE

McKee et al., 2013

III.



McKee et al., 2013



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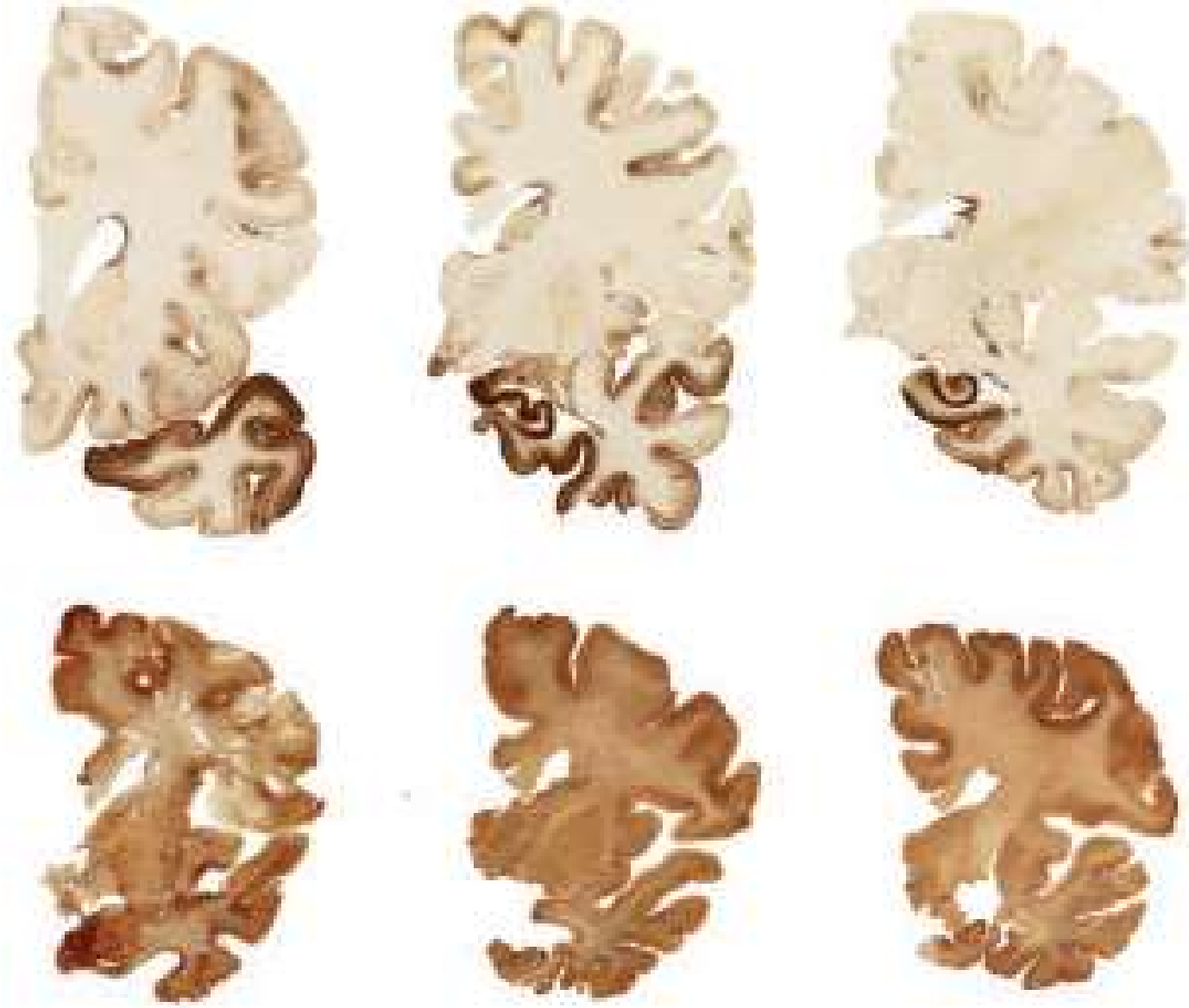
IV.



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McKee et al., 2013

Progressive?

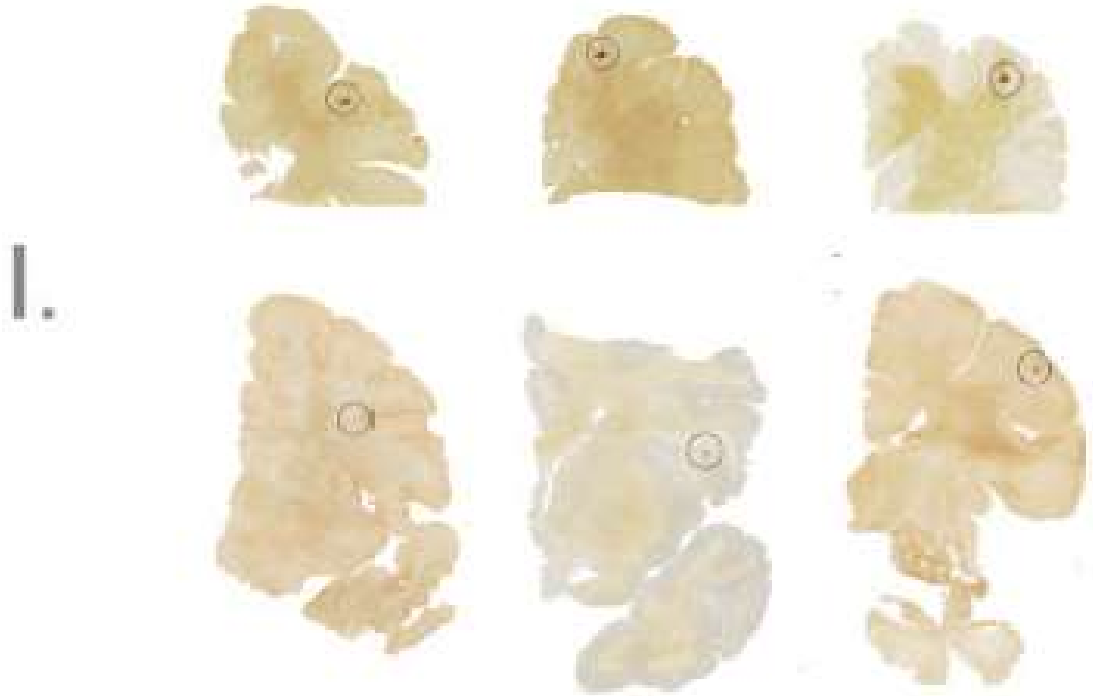
- Although clinical symptoms appeared to be slowly progressive in most individuals diagnosed with CTE, CTE may not progress, or may not progress at the same rate, in all individuals with the disease.

- 11-14 years between stages

McKee et al., 2013; Mez, Daneshvar, et al., 2017

Stage I

- Headaches and issues related to attention and concentration



McKee et al., 2013

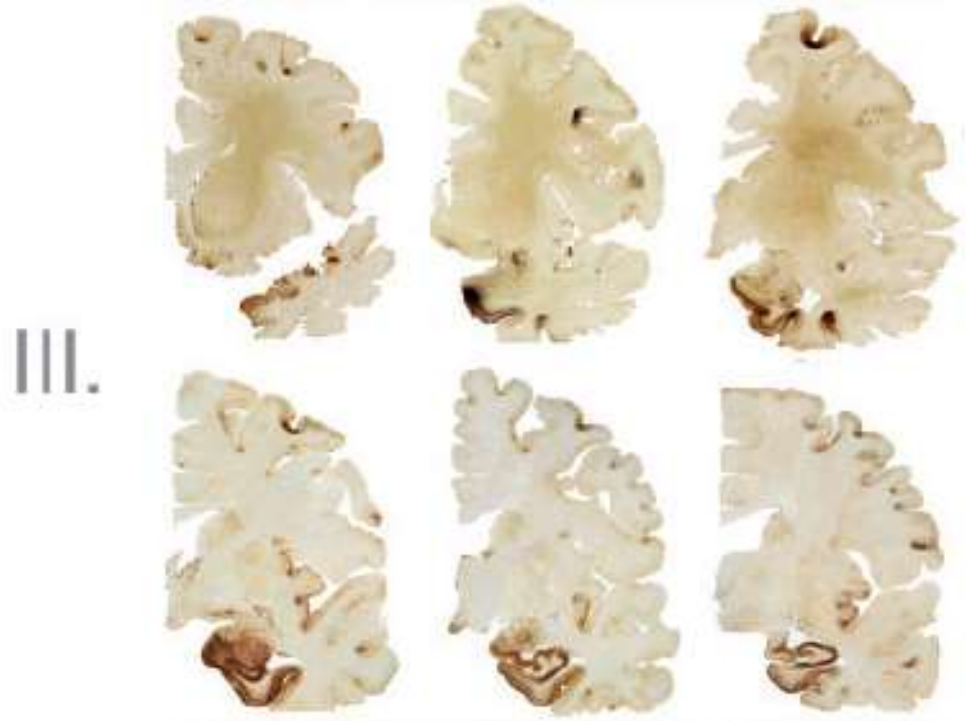
Stage II

- Symptoms expanded to include depression, explosivity and short-term memory impairment

McKee et al., 2013

Stage III

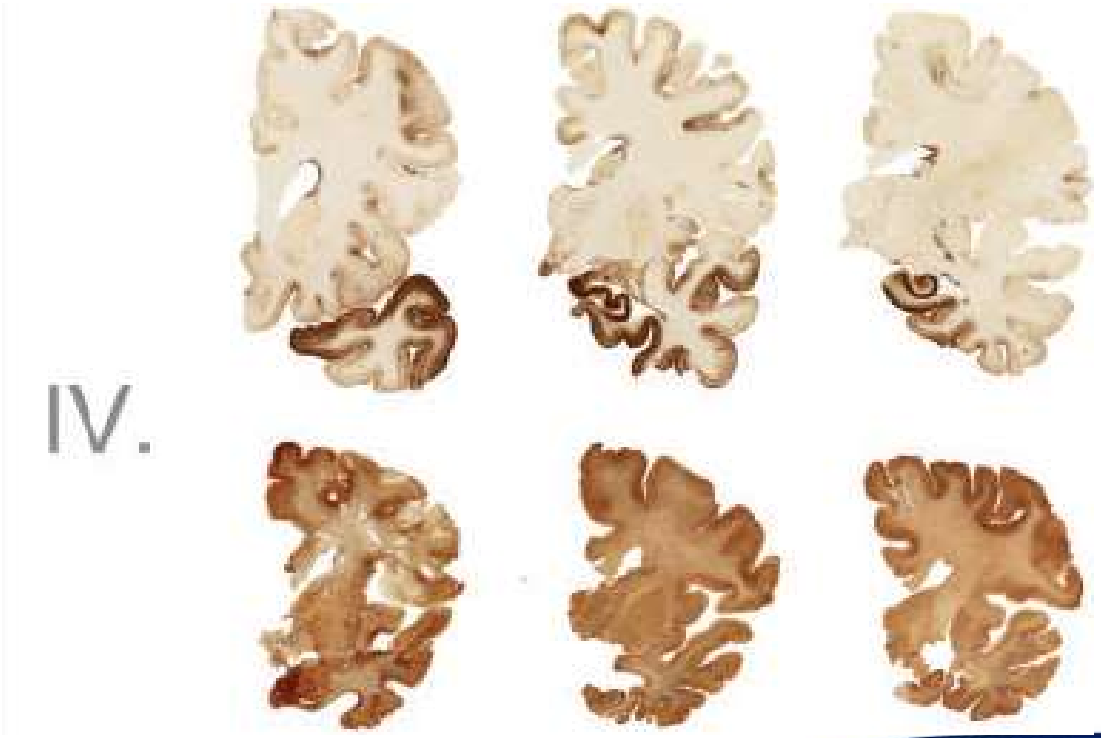
- Cognitive impairment and problems with executive functions, specifically planning, organization, multitasking and judgment



McKee et al., 2013

Stage IV

- Dementia (i.e., memory and cognitive impairments severe enough to impact daily living) in 90% of subjects



McKee et al., 2013

Clinical Features	No. (%) of Brain Donors		
	Mild CTE	Severe CTE	Total
Progressive course	23 (85)	84 (100)	107 (96)
Cognitive symptoms[b]	23 (85)	80 (95)	103 (93)
Memory	19 (73)	76 (92)	95 (86)
Executive function	19 (73)	67 (81)	86 (79)
Attention	18 (69)	67 (81)	85 (78)
Language	10 (39)	54 (66)	64 (59)
Visuospatial	7 (27)	44 (54)	51 (47)
Fluctuating cognition	2 (8)	17 (21)	19 (18)
Dementia[b]	9 (33)	71 (85)	80 (72)

Mez, Daneshvar, et al., 2017

Clinical Features	No. (%) of Brain Donors		
	Mild CTE	Severe CTE	Total
Behavioral or mood symptoms[b]	26 (96)	75 (89)	101 (91)
Impulsivity	23 (89)	65 (80)	88 (82)
Depressive symptoms	18 (67)	46 (56)	64 (59)
Explosivity	18 (67)	38 (45)	56 (51)
Apathy	13 (50)	43 (52)	56 (51)
Anxiety	14 (52)	41 (50)	55 (51)
Hopelessness	18 (69)	36 (46)	54 (52)
Verbal violence	17 (63)	28 (34)	45 (41)
Social inappropriateness	13 (48)	26 (32)	39 (36)
Physical violence	14 (52)	23 (28)	37 (34)
Paranoia	11 (41)	26 (31)	37 (34)
Suicidality (ideation, attempts, or completions)	15 (56)	21 (25)	36 (33)
Visual hallucinations	6 (23)	22 (27)	28 (26)
Mania	6 (22)	3 (4)	9 (8)

Mez, Daneshvar, et al., 2017

Clinical Presentation of CTE

- 36 male athletes, ages 17 to 98, diagnosed with CTE after death, and who had no other brain disease, such as Alzheimer's.
- The majority of the athletes had played amateur or professional football, with the rest participating in hockey, wrestling or boxing
- Data suggests two presentations:
  - A younger age of presentation (34.5 years) with initial symptoms of behavioral (e.g., impulsivity, violence) and/or mood changes (e.g., depression, hopelessness)
  - An older age of presentation (58.5 years) with initial symptoms of cognitive impairment (e.g., episodic memory deficits, executive dysfunction)

Stern, Daneshvar et al., 2013

Playing football before age 12

- 246 tackle football players (211 with CTE, 126 without comorbid neurodegenerative diseases)
- Age of exposure not associated with CTE (or AD or LBD)
- In those with CTE, every one year younger AFE to football predicted earlier cognitive symptom onset by 2.44 years ($p<0.0001$) and behavioral/mood symptoms by 2.50 years ($p<0.0001$)
- AFE before 12 predicted earlier cognitive ($p<0.0001$) and behavioral/mood ($p<0.0001$) symptom onset by 13.39 and 13.28 years
- Similar effects observed in the CTE only participants

Alosco et al., 2018

Biomarkers to improve diagnosis

- Brain and CSF biomarkers
  - CCL11, a protein linked to age-associated cognitive decline
  - 23 football players with CTE, 50 subjects with AD, and 18 controls
  - CCL11 levels significantly increased in DLFC in CTE (fold change = 1.234, $p < 0.050$) compared to AD and controls
  - CCL11 correlated with years of exposure to football ($\beta = 0.426$, $p = 0.048$) independent of age ($\beta = -0.046$, $p = 0.824$)
  - CSF CCL11 trended towards increase in CTE ($p = 0.069$), significant association with years of football ($\beta = 0.685$, $p = 0.040$) independent of age ($\beta = -0.103$, $p = 0.716$)
- To date, 6 PET studies examining ~50 subjects with promising findings
- MRS, DTI, also promising future directions

Cherry et al., 2018; Lee et al., 2018

What do we know: Overall

- All individuals ever diagnosed with CTE have had some history of head impacts:
  - From sports
  - From occupation, and
  - From other sources
- Not all individuals diagnosed were known to have experienced concussion, suggesting that acute symptoms may not be necessary for pathogenesis

McKee et al., 2009; Daneshvar et al, 2015b; Mez et al., 2017

Acknowledgements

- Ann McKee, MD
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- Our donors and their families


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