DEFENSE CENTERS OF EXCELLENCE

For Psychological Health & Traumatic Brain Injury

Today's webinar:

State of the Science: Clinical, Metabolic and Pathologic Effects of Multiple Concussions

Jan. 16, 2014, 1-2:30 p.m. (EST)

Moderator: Donald Marion, M.D., M.Sc.
Clinical Affairs Senior Advisor
Defense and Veterans Brain Injury Center
Silver Spring, Md.

DVBIC Defense and Veterans Brain Injury Center

DHCC

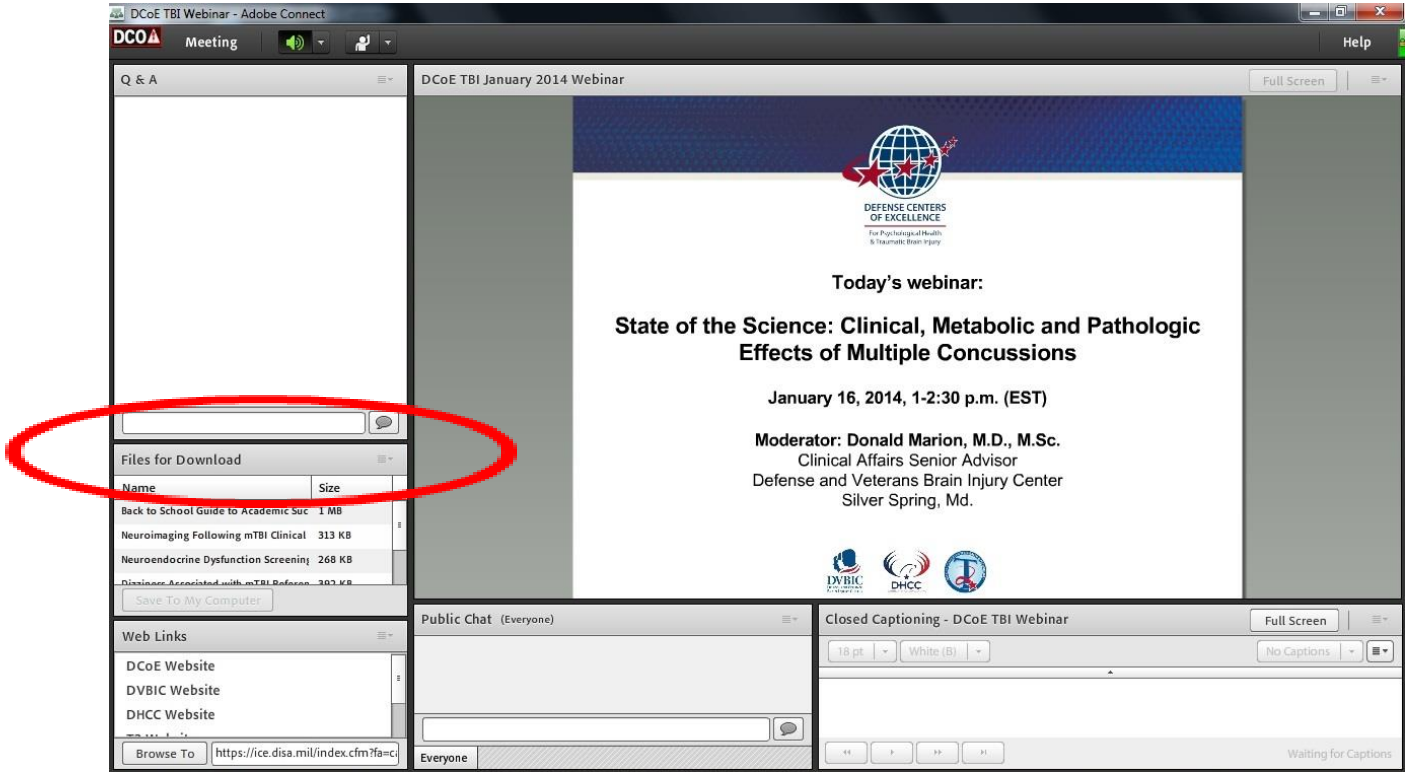
National Center for Telehealth & Technology

Webinar Details

- Live closed captioning is available through federal relay conference captioning (see the “Closed Captioning” box)
- Webinar audio is **not** provided through Defense Connect Online
  - Dial: **888-877-0398**
  - Use participant pass code: **3938468**
- Question-and-answer session
  - Submit questions via the Defense Connect Online question box

Resources Available for Download

- Today's presentation and references are available for download in the Files box on the screen, or visit **dvbic.dcoe.mil/online-education**



Continuing Education Details

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Webinar Overview

During the past few years, professional athletes and their families have become increasingly concerned about the long-term neurologic effects of repeated concussions. The premature deaths of several professional football players have drawn attention to the relationship of multiple concussions with neurocognitive disorders that occur decades after these injuries, although similar changes in the brain were associated with boxing and first described in the 1920s.

This webinar will examine the findings of laboratory and clinical studies on the mechanisms responsible for brain injury following one or multiple concussions. The presentation will address a particular focus on a class of proteins called Tau protein and its association with some of the histologic features of multiple concussions with Alzheimer's disease.

Webinar participants will learn to:

- Describe the pathophysiology of concussion
- Summarize metabolic abnormalities caused by concussion and the window of vulnerability of the brain to a second concussion
- Identify the long-term changes in patterns of protein deposition possibly associated with multiple concussions
- Articulate the possible association of multiple concussions and long-term cognitive deficits

Presenters

David A. Hovda, Ph.D.
Director, University of California, Los Angeles (UCLA) Brain Injury Research Center
Professor of Neurosurgery and Molecular and Medical Pharmacology, UCLA David Geffen School of Medicine, Los Angeles, Calif.

J. Clay Goodman, M.D., F.A.A.N.
Professor and Associate Dean, Departments of Pathology and Immunology and Neurology, Baylor College of Medicine, Houston, Texas

Steven T. DeKosky, M.D., F.A.A.N., F.A.C.P., F.A.N.A.
Visiting Professor, Department of Medical Ethics and Health Policy, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pa.
Professor of Neurology, Psychiatry and Behavioral Sciences and Director of the Alzheimer's Disease Research Center, University of Virginia School of Medicine, Charlottesville, Va.

Presenter: David A. Hovda, Ph.D.

- Director, University of California, Los Angeles (UCLA) Brain Injury Research Center
- Professor of Neurosurgery and Molecular and Medical Pharmacology, UCLA David Geffen School of Medicine
- Former president of the National Neurotrauma Society and study section committee chair for the National Institute for Neurological Disease and Stroke

Dr. David A. Hovda

The Neurobiology of Concussion and the Consequences of Repeat Injury

David A. Hovda, Ph.D.

Director, UCLA Brain Injury Research Center

Professor of Neurosurgery

Molecular and Medical Pharmacology

David Geffen School of Medicine at UCLA

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Disclaimer

- The views expressed in this presentation are those of the presenter.
- I have no relevant financial relationships to disclose.
- I do not intend to discuss the off-label/investigative (unapproved) use of commercial products or devices.
- Cited research is funded by: NS02197, NS27544, NS052406, NS058489 UC Neurotrauma Initiative, UCLA Faculty Grant Program and the Lind Lawrence Foundation.

What is Concussion?

1. It is an injury to the brain caused by biomechanical forces. It is not ischemia or stroke! These forces can be direct or indirect.

2. It results in regional and temporal cellular alterations and may produce cell death.

3. It produces a state of energy crisis and subsequent metabolic diaschisis.

4. It changes the priorities for fuel.

5. It may contribute to more chronic neurological degeneration related to disease.

20% of Energy

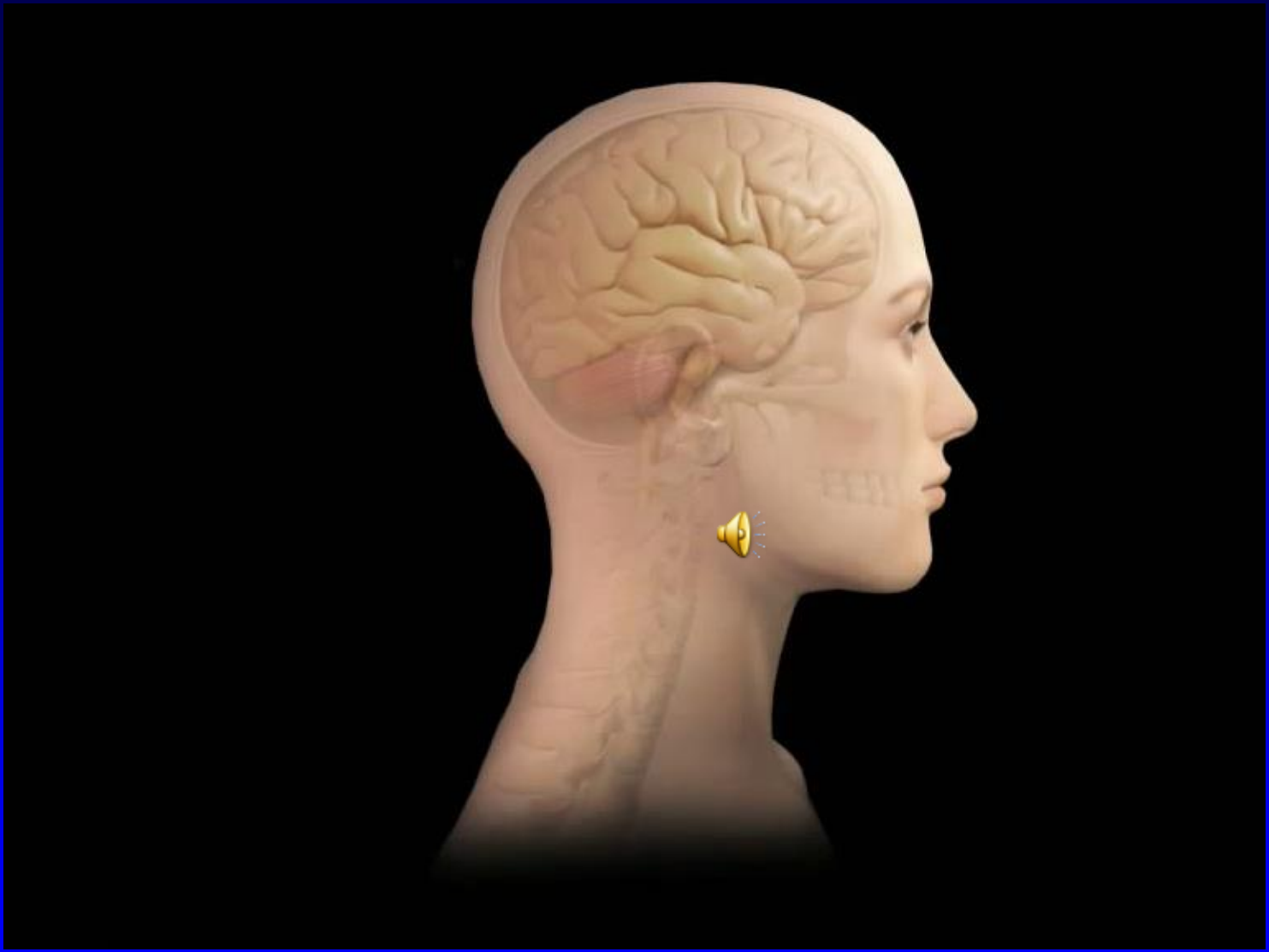
Adenosine Triphosphate (ATP)

Photo courtesy of UCLA

Fun Facts About ATP: The Cost of Living

1. 90% of the power comes from ATP synthesis: 522 amps per second
2. You make 65 kg of ATP per day
3. You consume 380 liters of oxygen per day
4. Average human: 100 kilocalories (420 kilojoules) per hour, that's about … 116 watts

Photo courtesy of UCLA



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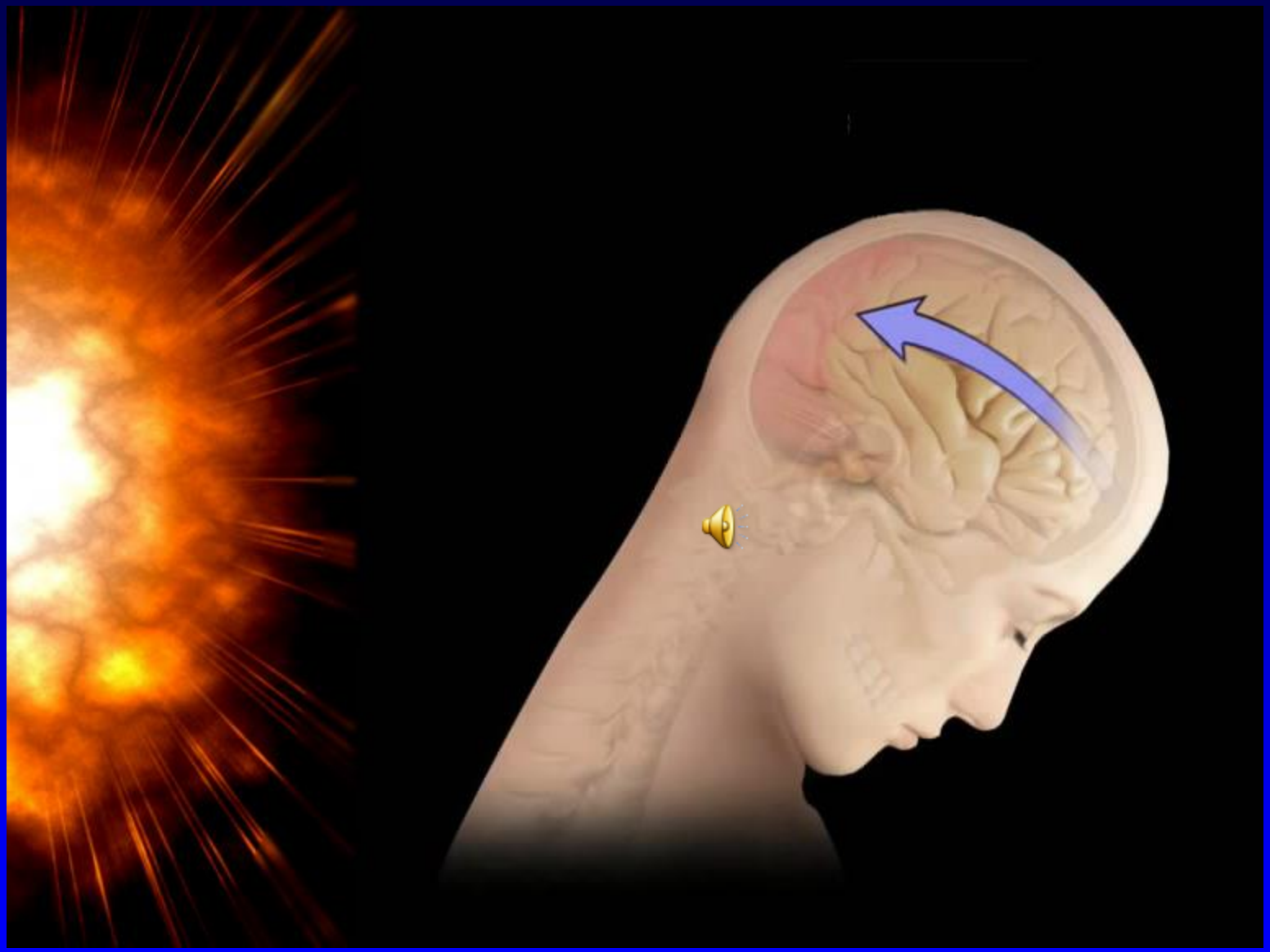

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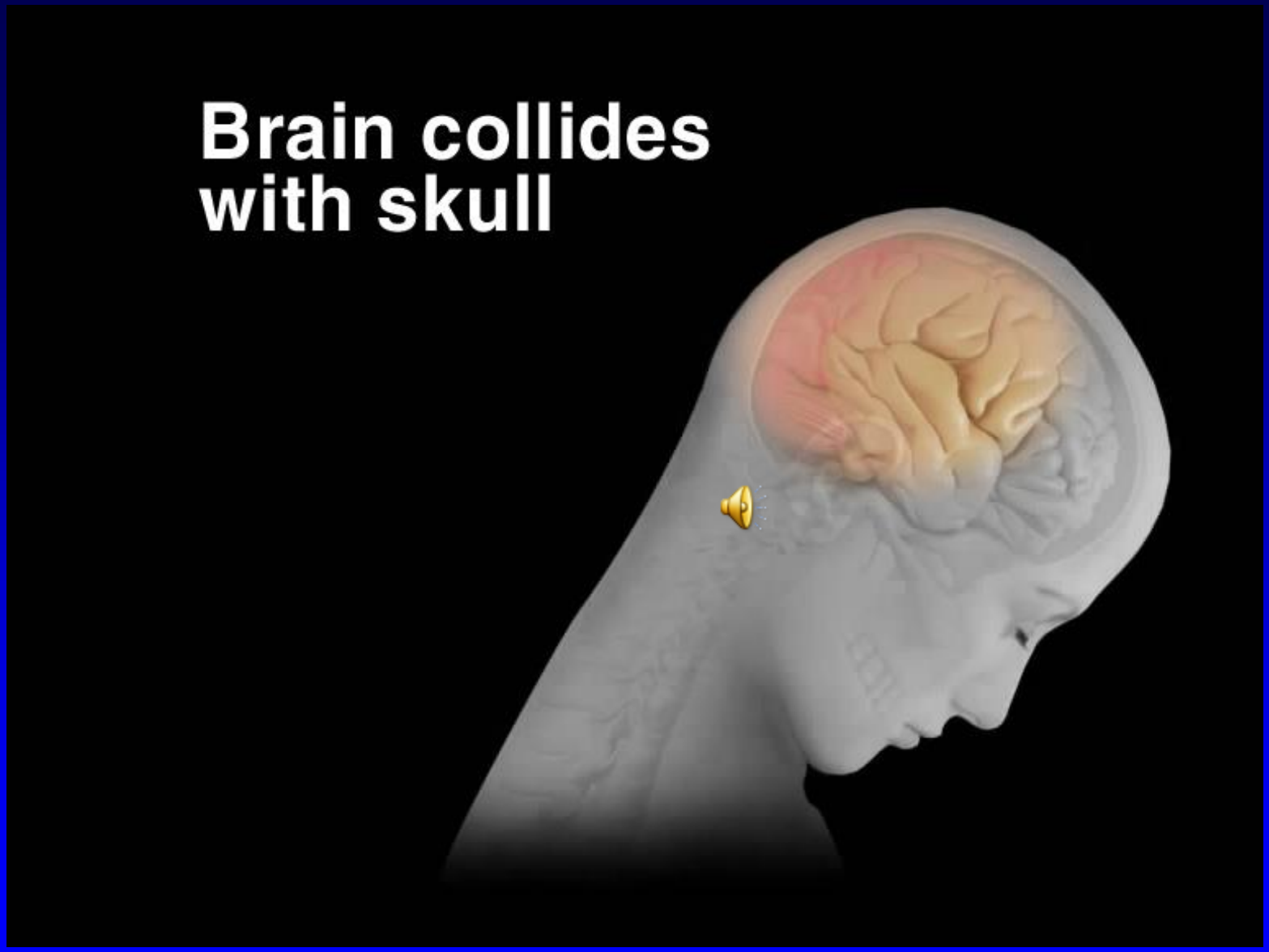

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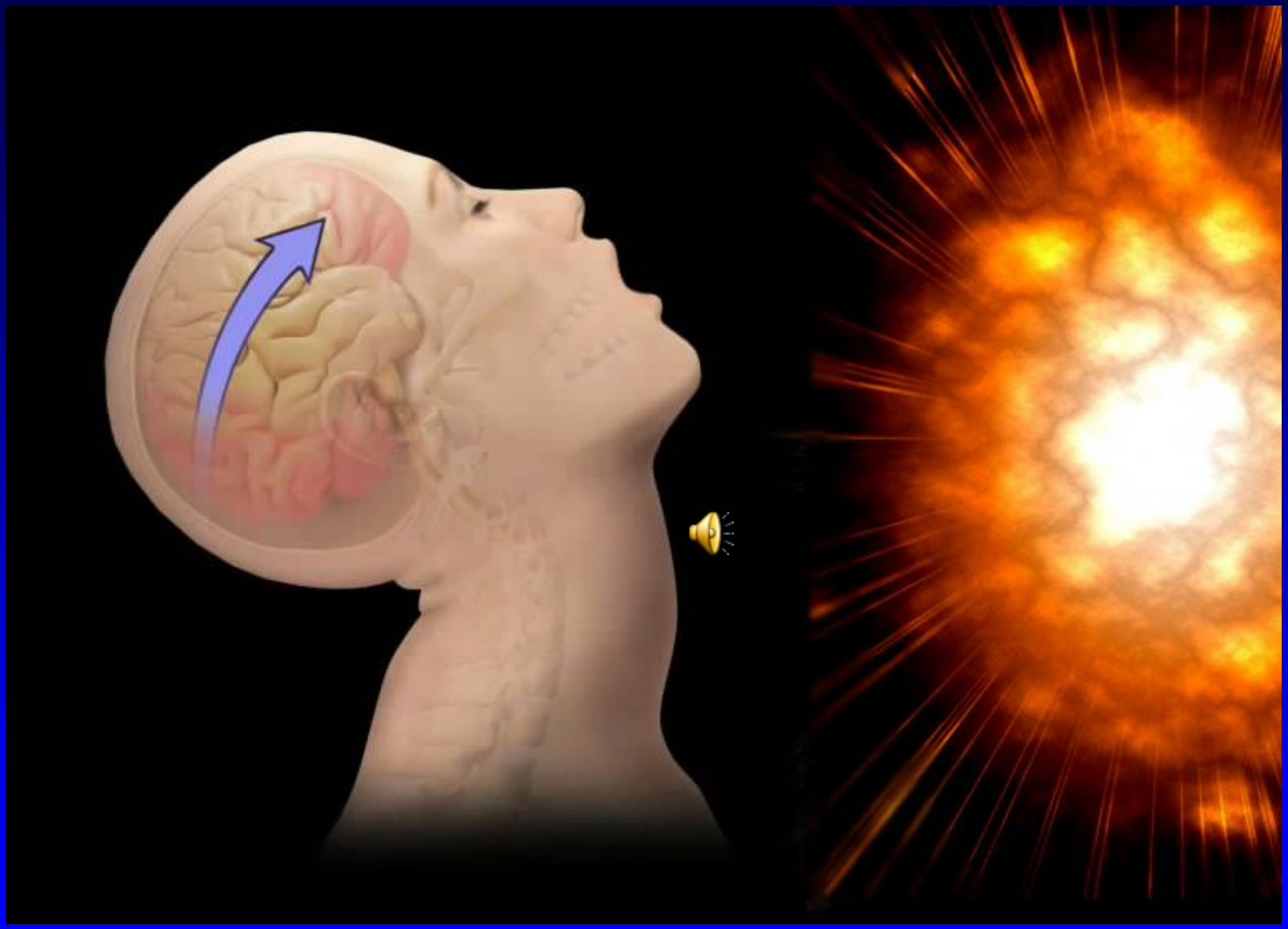

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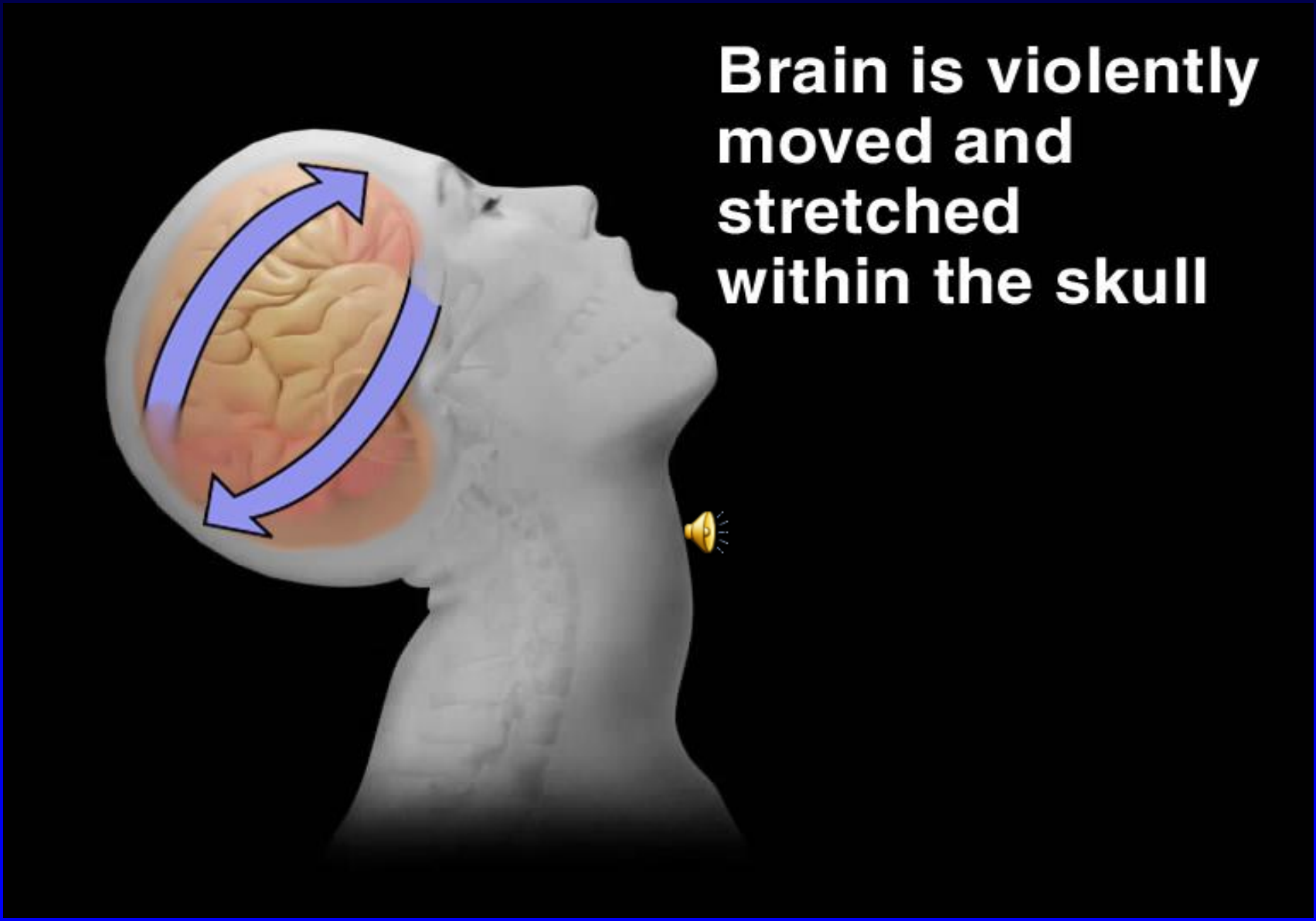

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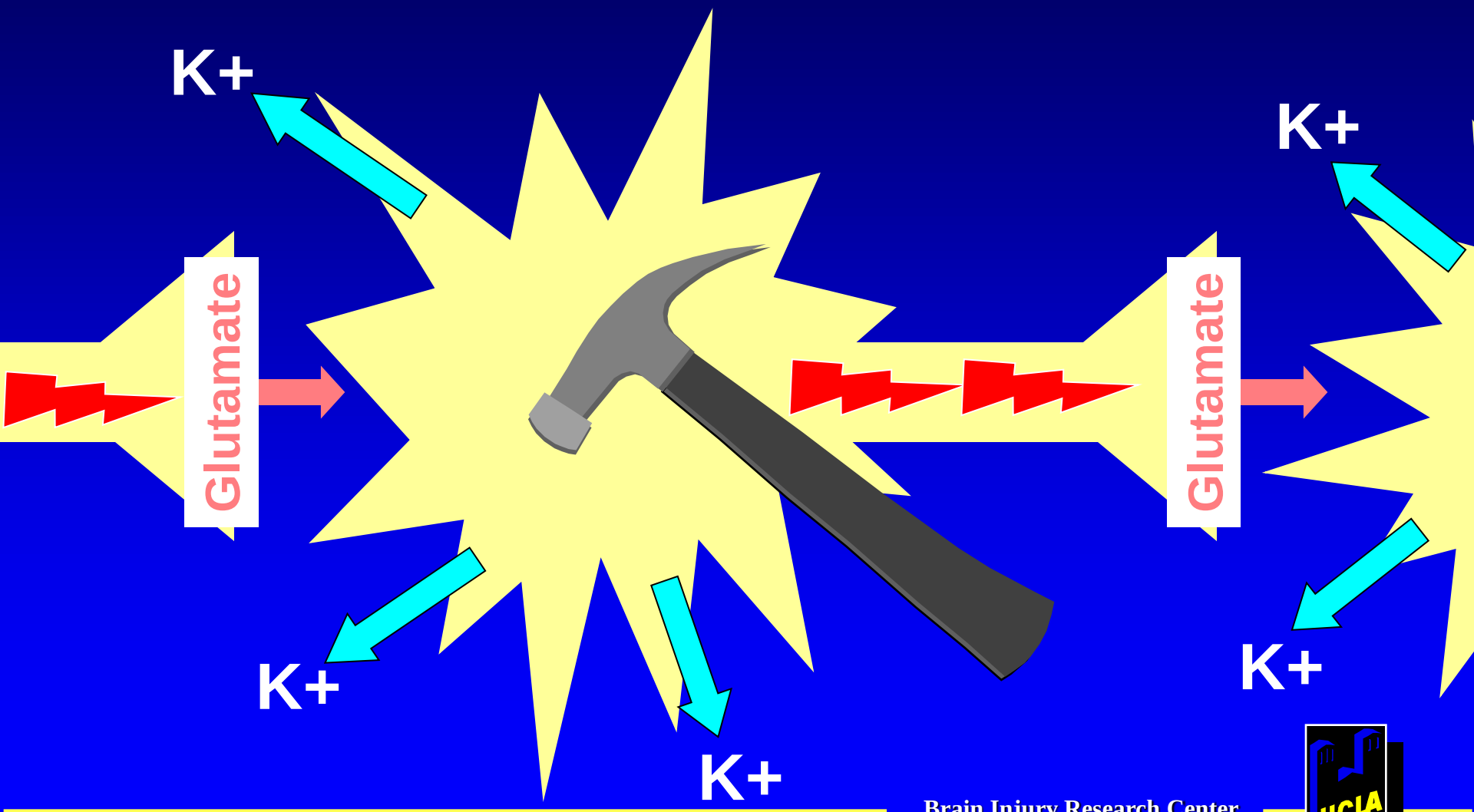
Photo courtesy of UCLA

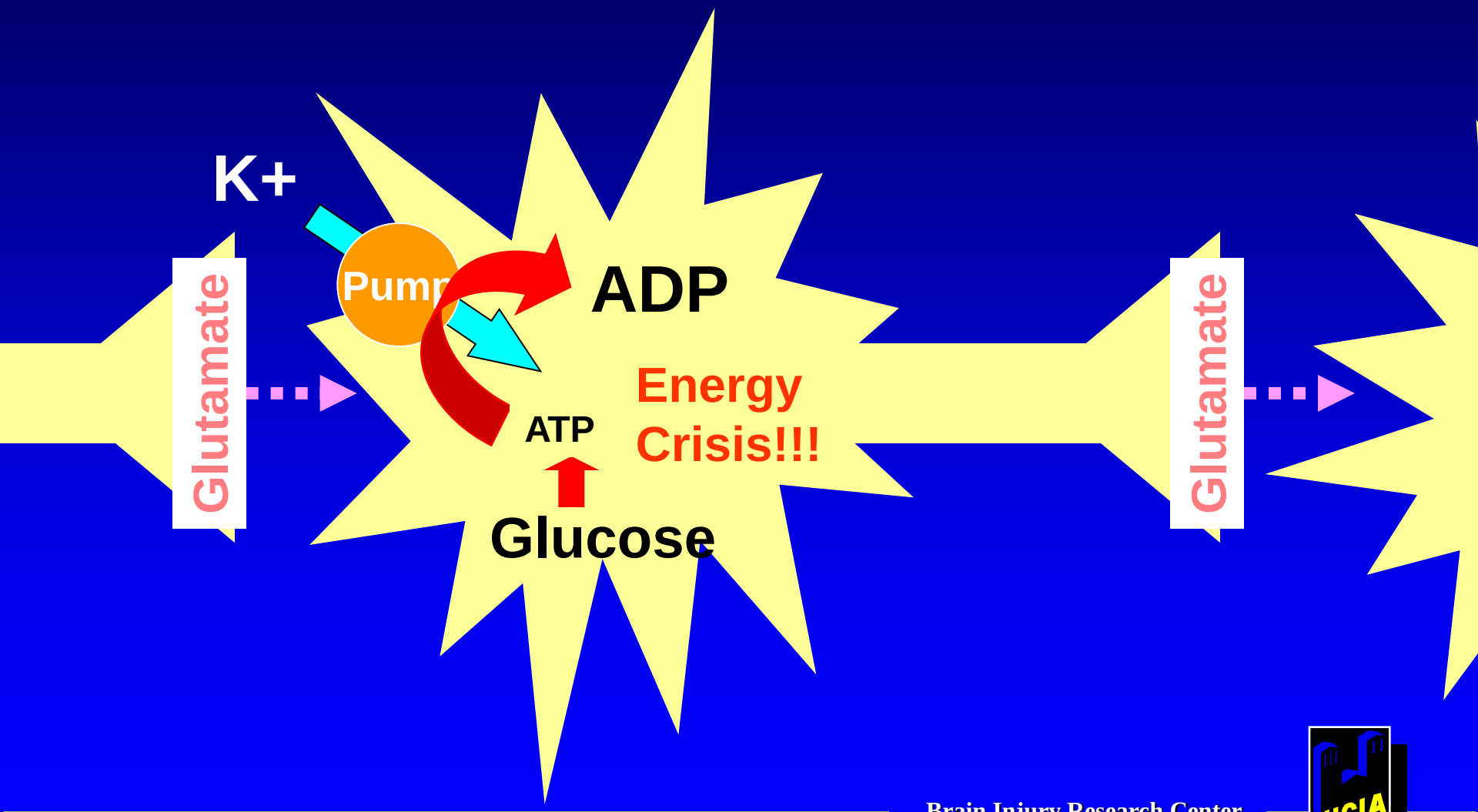
Neurometabolic Cascade:
Potassium and Glutamate Flux



Brain Injury Research Center

Katayama et.al., J Neurosurg 1990

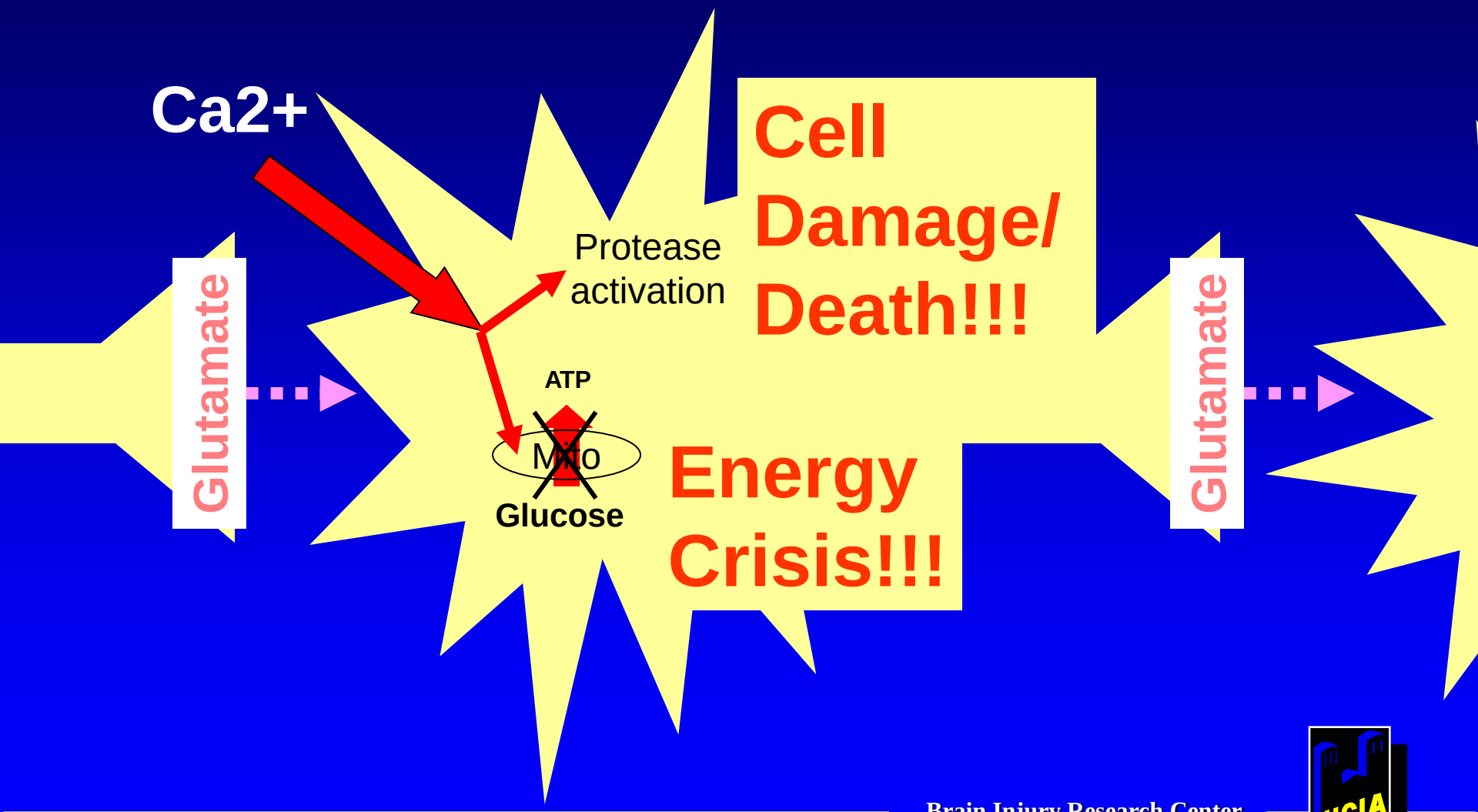
Neurometabolic Cascade:
Hyperglycolysis and Energy Crisis



Brain Injury Research Center

Katayama et.al., J Neurosurg 1990

Neurometabolic Cascade:
Calcium, Mitochondrial Dysfunction and Death

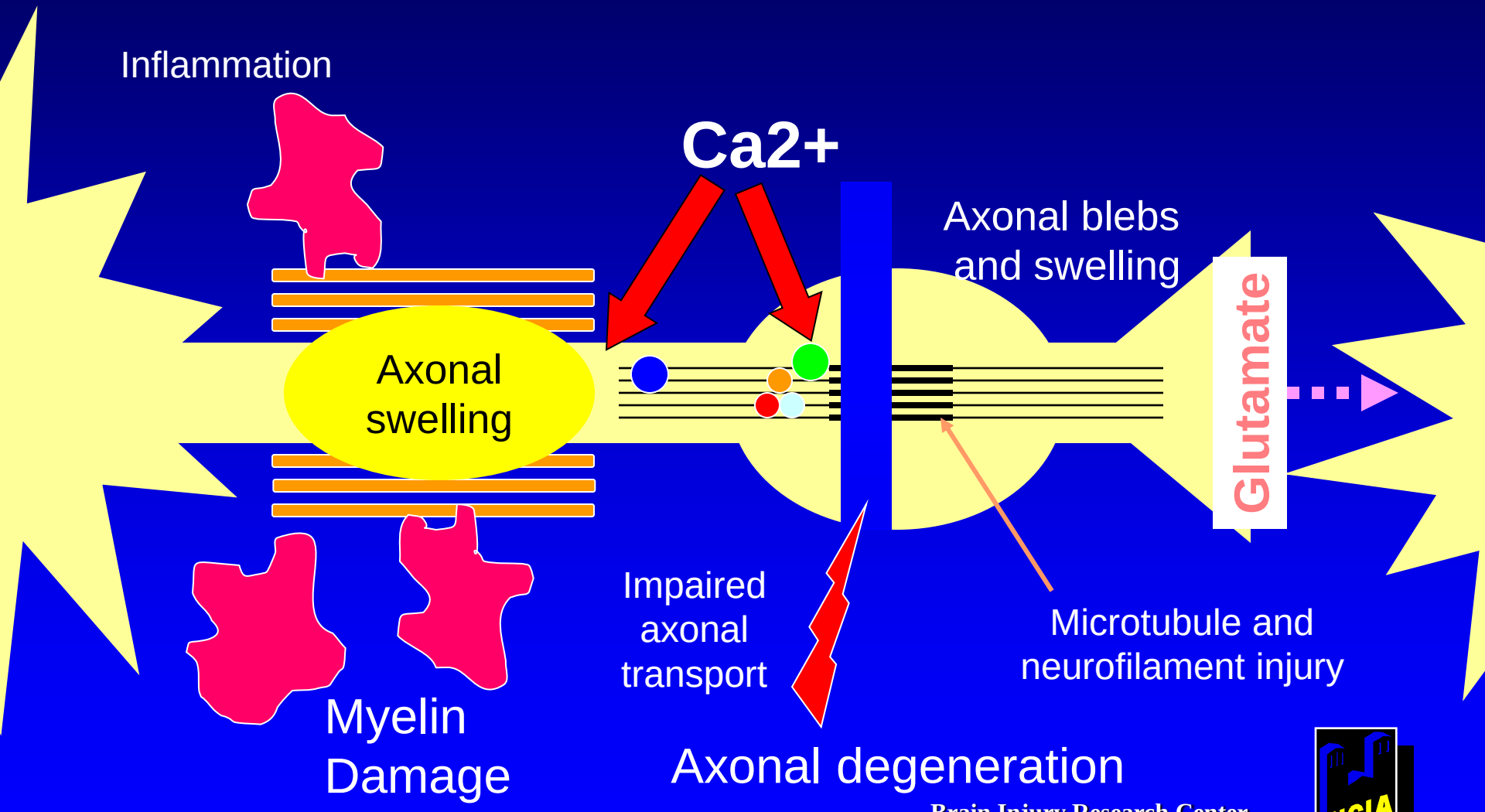


Brain Injury Research Center

Katayama et.al., J Neurosurg 1990

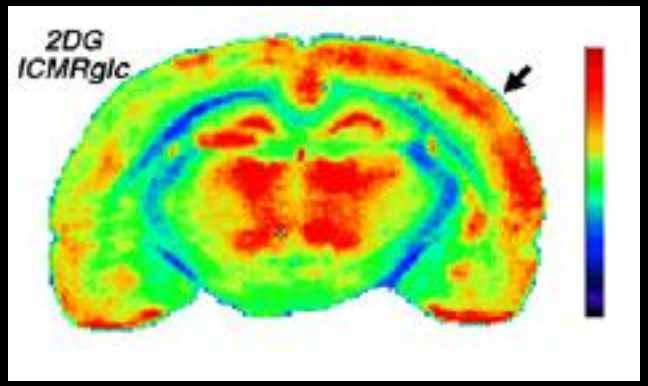
For review, see Giza and Hovda, J Athl Training, 2001

Neurometabolic Cascade:
Axonal Injury



Brain Injury Research Center

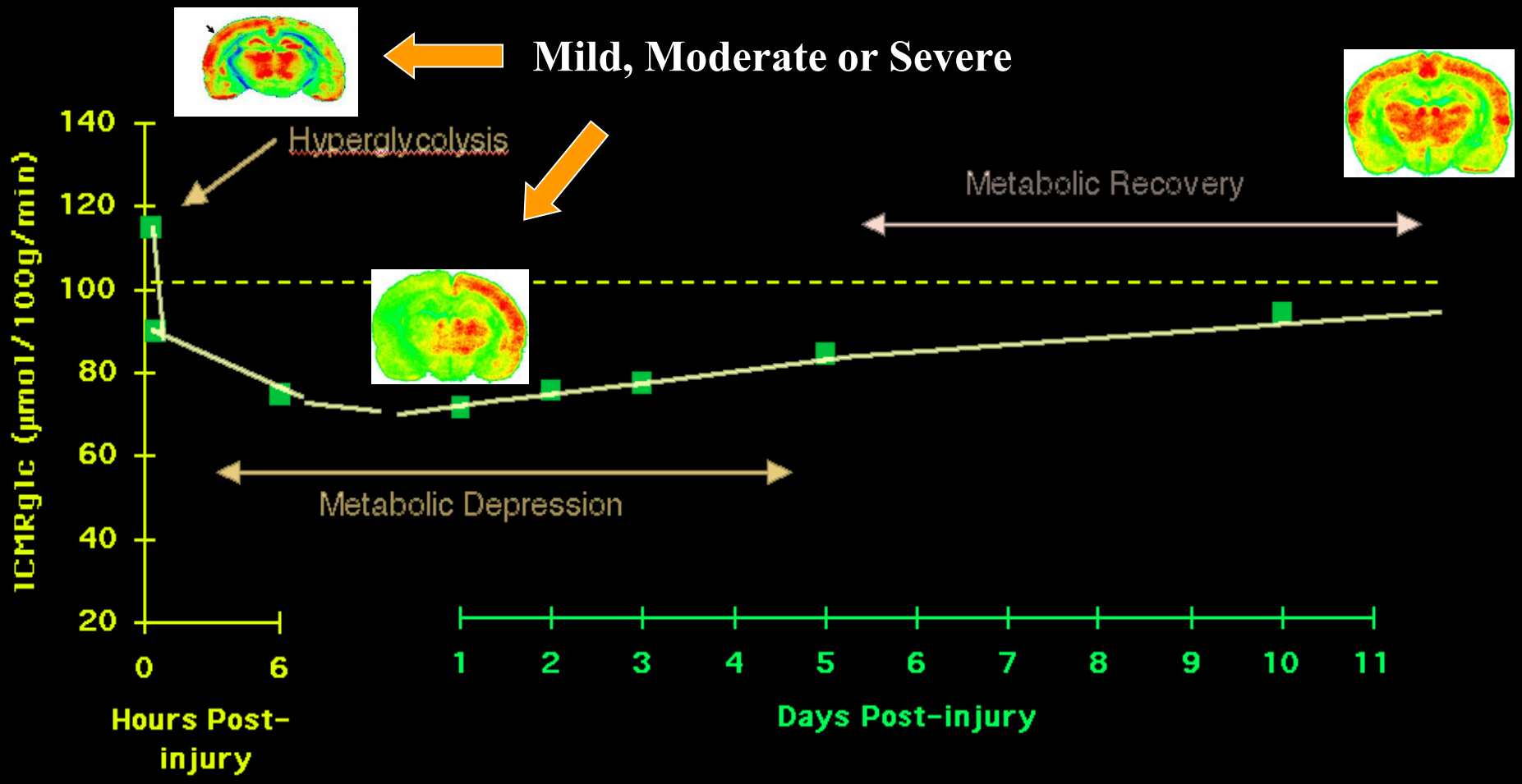
Katayama et.al., J Neurosurg 1990



TBI produces an acute increase in extracellular potassium via the stimulation of N-methyl-D-aspartate (NMDA) receptors resulting in an increased demand for glucose.

Yoshino, et al., Brain Res, 1991

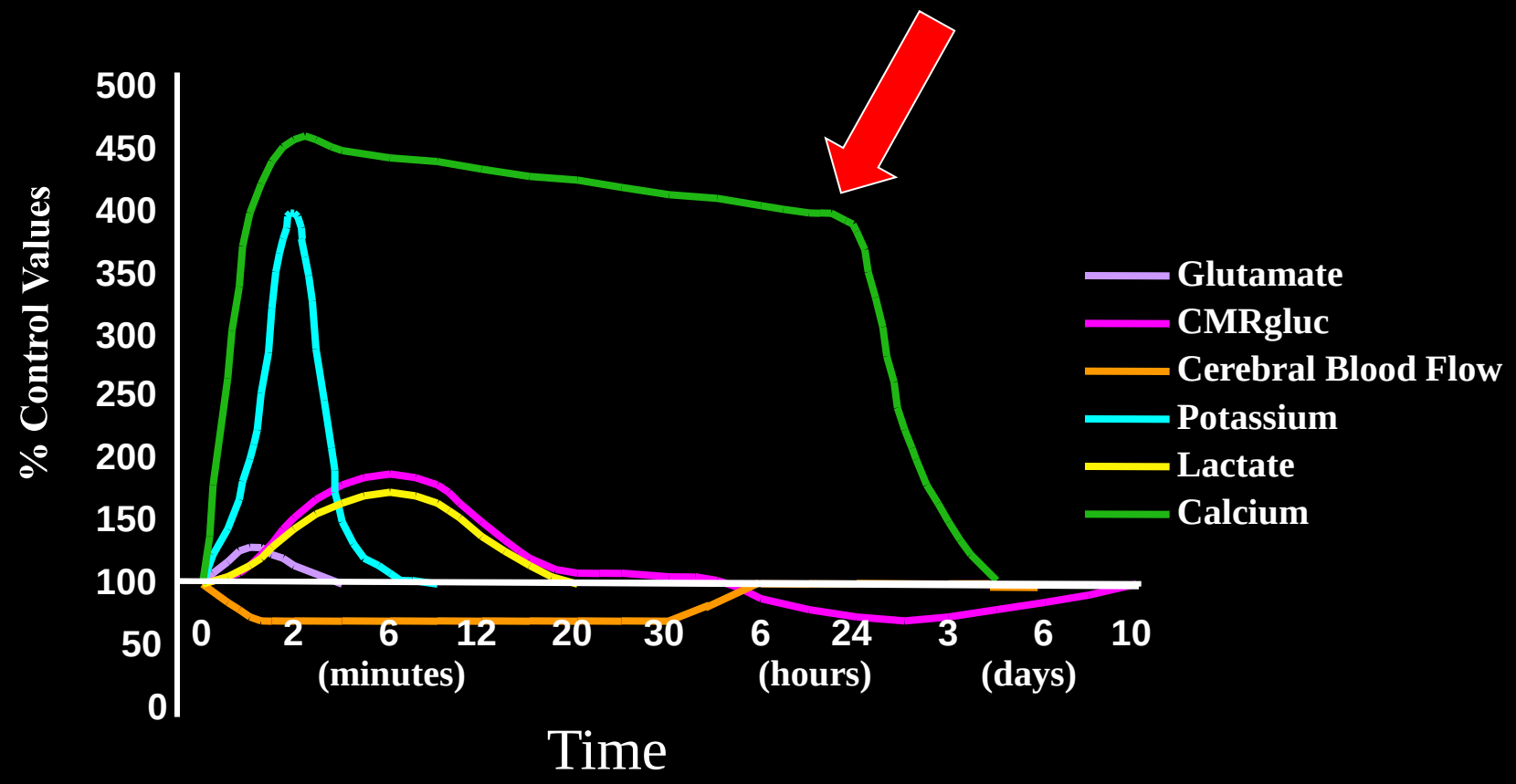
Hyperglycolysis is Followed by a Prolonged Period of Reduced Glucose Utilization



Yoshino et al: Brain Research 561:106-119, 1991

Neurochemical and Metabolic Cascade Following TBI

Cerebral Metabolic Crisis!

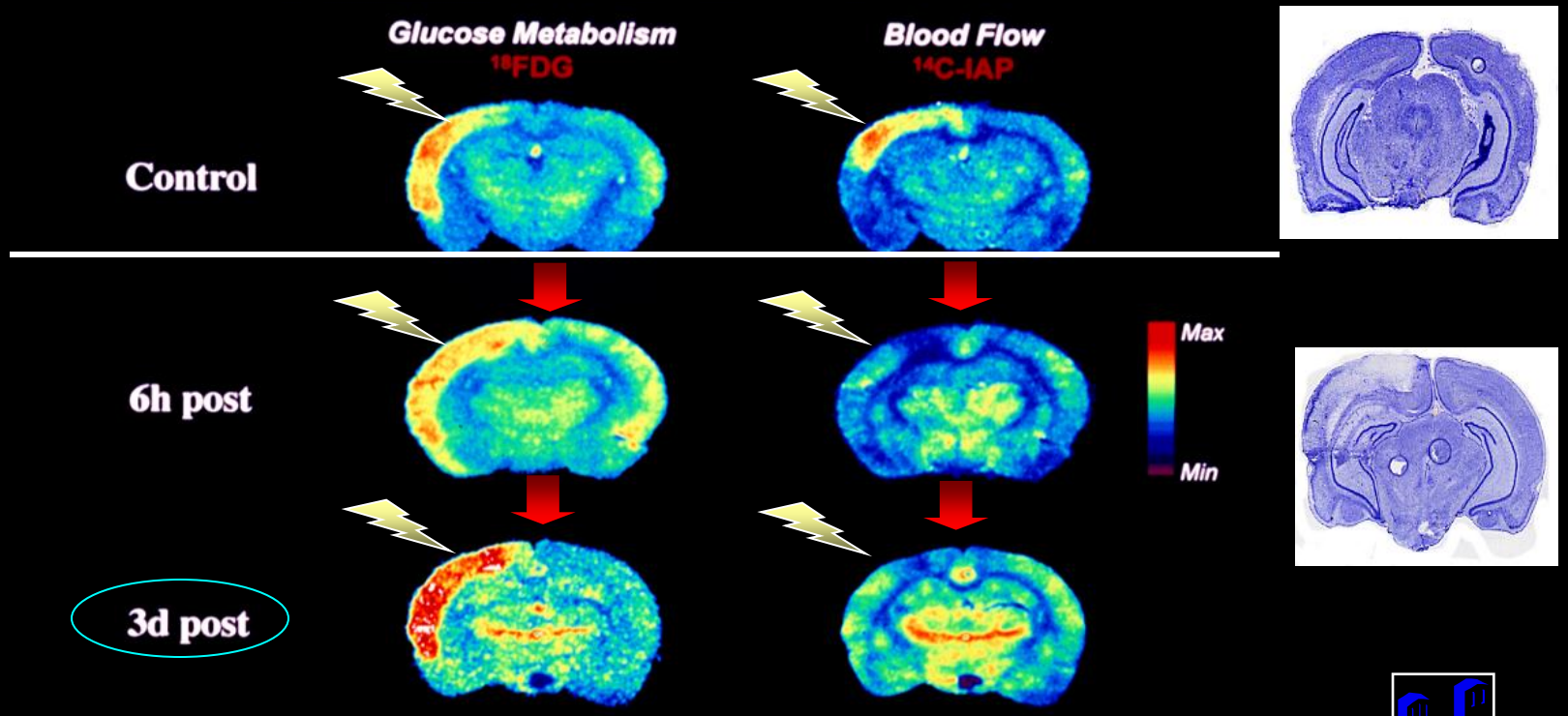


Giza & Hovda, J Athl Training, 2001

Uncoupling of Regional Cerebral Metabolic Rate for Glucose Consumption (CMRglc) and Cerebral Blood Flow (CBF) Following Experimental TBI

Duration exceeds mismatch period

Unilateral electrical stimulation following midline fluid percussion injury (FPI)



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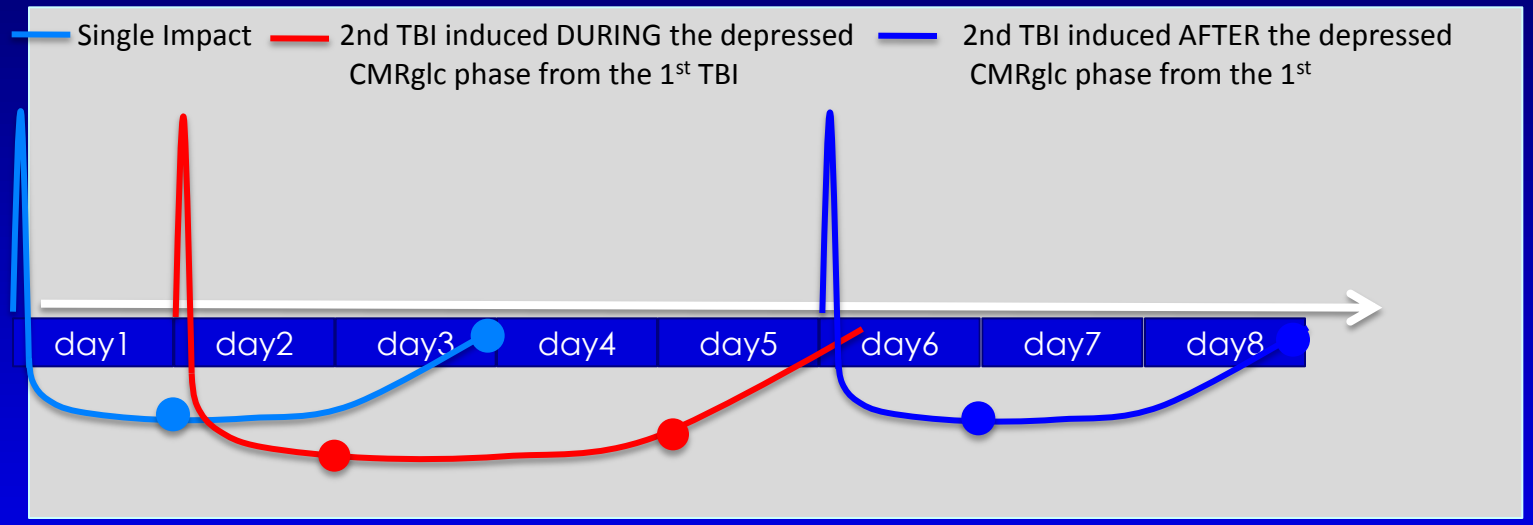
Maeda et al., 2005

Repeat Concussion and Brain METABOLISM

Does the period of glucose metabolic depression reflect the duration of vulnerability after a concussive injury?



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Prins et al, 2013, J Neurotrauma 30:30-38

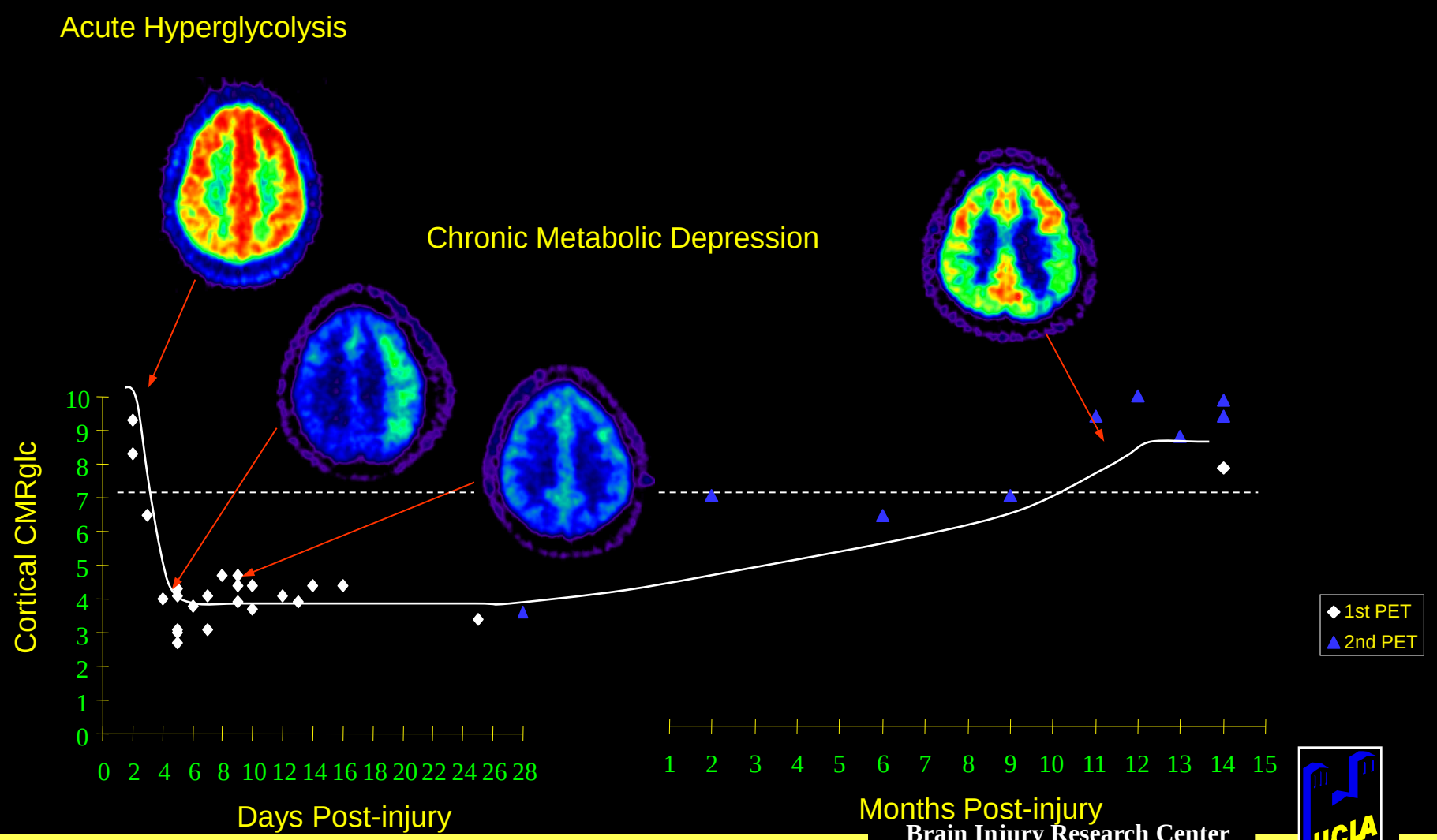
Rodent Single Concussion

1. Temporary changes in brain neurochemistry and cerebral metabolism
2. Temporary deficits in learning/memory and other post-concussive symptoms
3. Enhanced vulnerability to Post Traumatic Stress and to Parkinson's Disease

Rodent Repeat Concussion

1. Increased axonal injury with number of concussions
2. Memory deficits last longer with number of concussions
3. Interval between injuries is critically important in whether metabolic markers are cumulative
4. Pituitary functions and corresponding hormonal deficits occur with repeat concussions

TBI as a Metabolic Disorder: Clinical Studies



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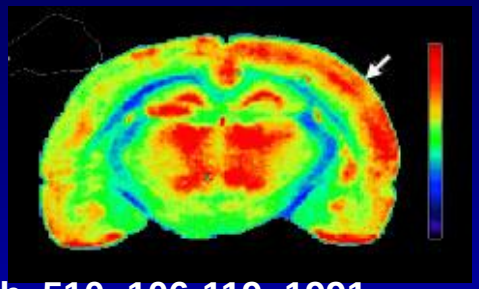
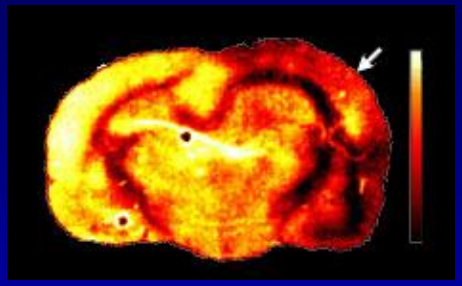
Bergsneider et al., 1997

Mismatch of CMRglc and CBF Following TBI

Animal Autoradiography

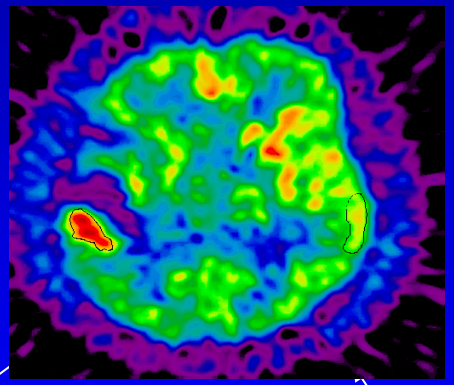




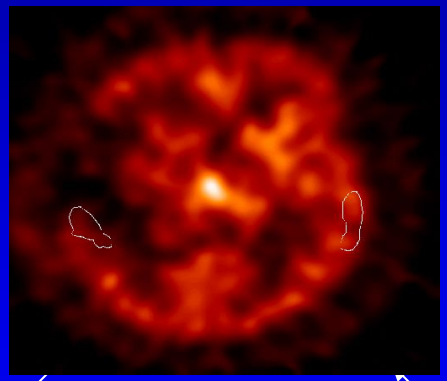
Yoshino et al. Brain Research, 510: 106-119; 1991
Ginsberg et al . American Journal of Physiology, 41: H2859-2868; 1997

Human PET

CT
(raw)



10.7 lCMRglc mg/100g/min 8.6



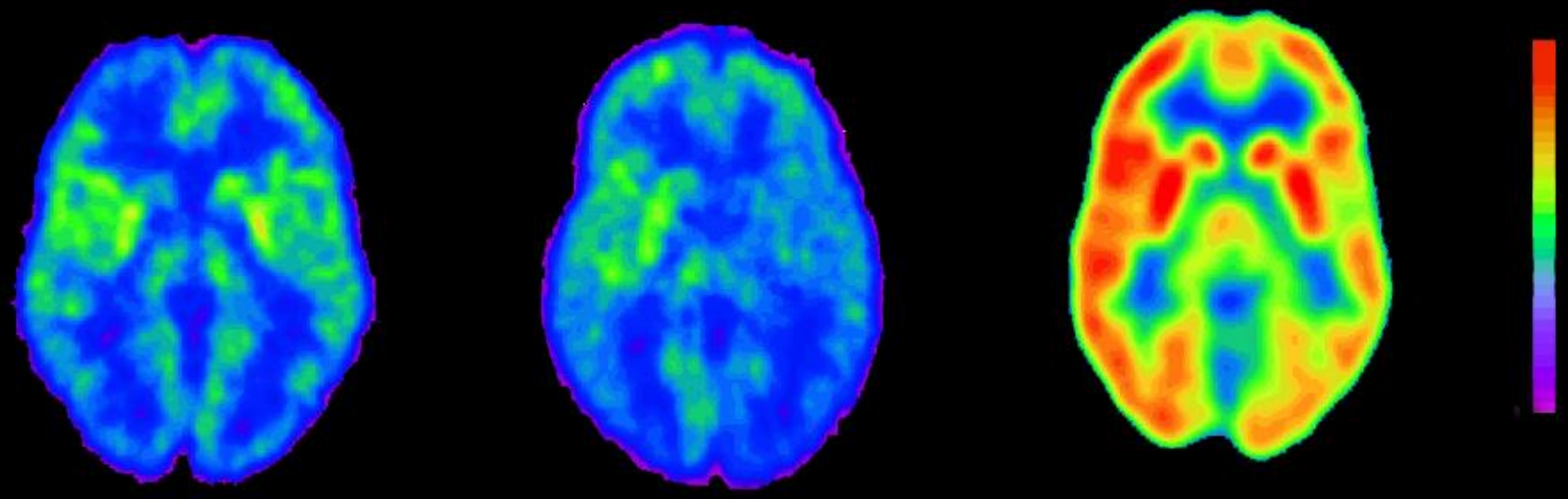
20 rCBF ml/100g/min 37

Hovda et al., J Neurotrauma 1995; 12:903-906
Vespa et al., Journal of Cerebral Blood Flow and Metabolism, 2005: 25: 763-774

Mild Glasgow Coma Scale (GCS) 15

Severe GCS 5

Normal



An Imaging Biomarker of MTBI ?

Bergsneider et al., J Neurotrauma 17:2000

Repetitive Injury and Return to Normal Activity

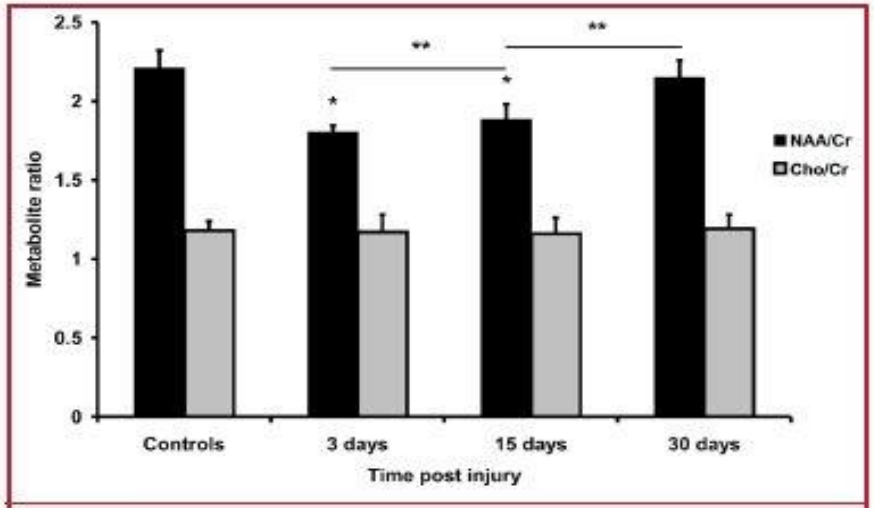


FIGURE 2. *Bar graph showing the NAA-to-Cr and Cho-to-Cr ratios determined by ¹H-MR spectroscopy in healthy control volunteers (n = 5) and in singly concussed athletes (n = 10). Time course of NAA variations indicated a minimum at 3 days postinjury, followed by a gradual, nonlinear, recovery with a slow phase until the 15th day postinjury and a fast phase (up to complete recovery) within the 30th day postinjury. Values are the mean of 10 single voxel spectra in controls (five left and five right hemispheres) and 20 single voxel spectra for each time point in singly concussed athletes (10 left and 10 right hemispheres). Standard deviations are represented by* vertical bars. Single asterisk, *significantly different from controls (P < 0.05).* Double asterisk, *significantly different from immediately preceding time point (P < 0.05).*

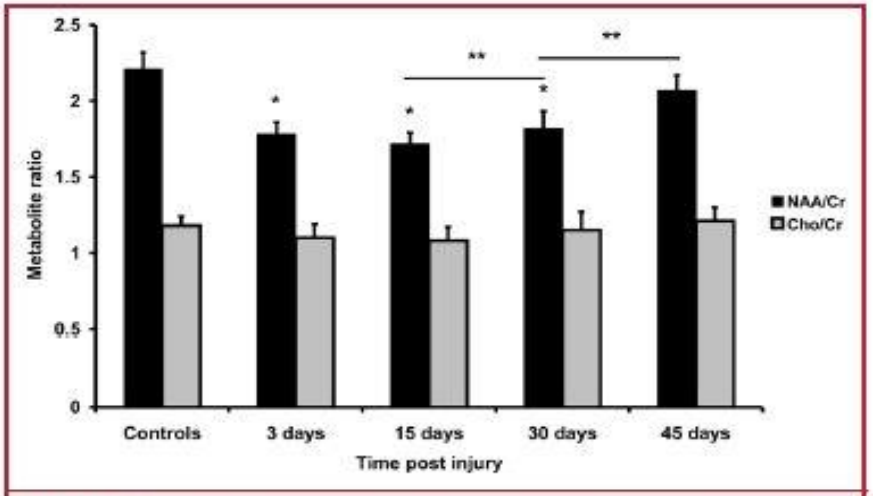


FIGURE 3. *Bar graph showing the NAA-to-Cr and Cho-to-Cr ratios determined by ¹H-MR spectroscopy in healthy control volunteers (n = 5) and in doubly concussed athletes (n = 3) in whom the second concussion occurred between the 10th and the 13th day after the first insult. Time course of NAA variations indicated a minimum at 15 days postinjury, i.e. after the occurrence of the second concussion. A subsequent gradual, nonlinear, recovery with a slow phase until the 30th day postinjury and a fast phase (up to complete recovery) within the 45th day postinjury was observed. Values are the mean of 10 single voxel spectra in controls (5 left and 5 right hemispheres) and 6 single voxel spectra for each time point in doubly concussed athletes (3 left and 3 right hemispheres). Standard deviations are represented by vertical bars.* Single asterisk, *significantly different from controls (P < 0.05).* Double asterisk, *significantly different from immediately preceding time point (P < 0.05).*

Vagnozzi, Neurosurgery, 2008

What is Concussion?

1. It is an injury to the brain caused by biomechanical forces. It is not ischemia or stroke!

2. It results in regional and temporal cellular dysfunction, including cell death.

3. In areas that survive, it produces a state of energy crisis and subsequent metabolic diaschisis.

4. Surviving brain cells alter their use of fuels and can exhibit long term dysfunction.

5. It needs to be thought of as a disease.

Presenter: J. Clay Goodman, M.D., FAAN

- Associate Dean for Undergraduate Medical Education, Baylor College of Medicine
- Professor of Pathology and Immunology and Neurology, Baylor College of Medicine
- Founding Member, National Neurotrauma Society
- Neurology Director, American Board of Psychiatry and Neurology
- Board of Directors, American Brain Foundation
- Clinical microdialysis and molecular genetics of traumatic brain injury

Dr. J. Clay Goodman

Tau in Health and Disease
Focus on Repetitive TBI

J. Clay Goodman, M.D., FAAN
Professor and Associate Dean
Departments of Pathology & Immunology
and Neurology
Baylor College of Medicine
Houston, TX

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Biology of Tau

- Abundant intracellular microtubule associated protein
- Participates in microtubule assembly, stabilization and spacing
  - Carboxy-terminal domain binds microtubule
  - Amino-terminal domain projects out from microtubule
  - Six isoforms under developmental control
  - Knock-out mice asymptomatic
- Phosphorylated tau
  - Phosphorylation diminishes interaction with microtubules

Pathology of Tau

- Major constituent of neurofibrillary tangles
- Hyperphosphorylation leads to decline in interaction with microtubules
- Hyperphosphorylation leads to filamentous aggregates
- Tau misfolding may facilitate hyperphosphorylation
- Misfolded tau may form a template which causes native tau to misfold
- Stereotypic spread on neurofibrillary tangles

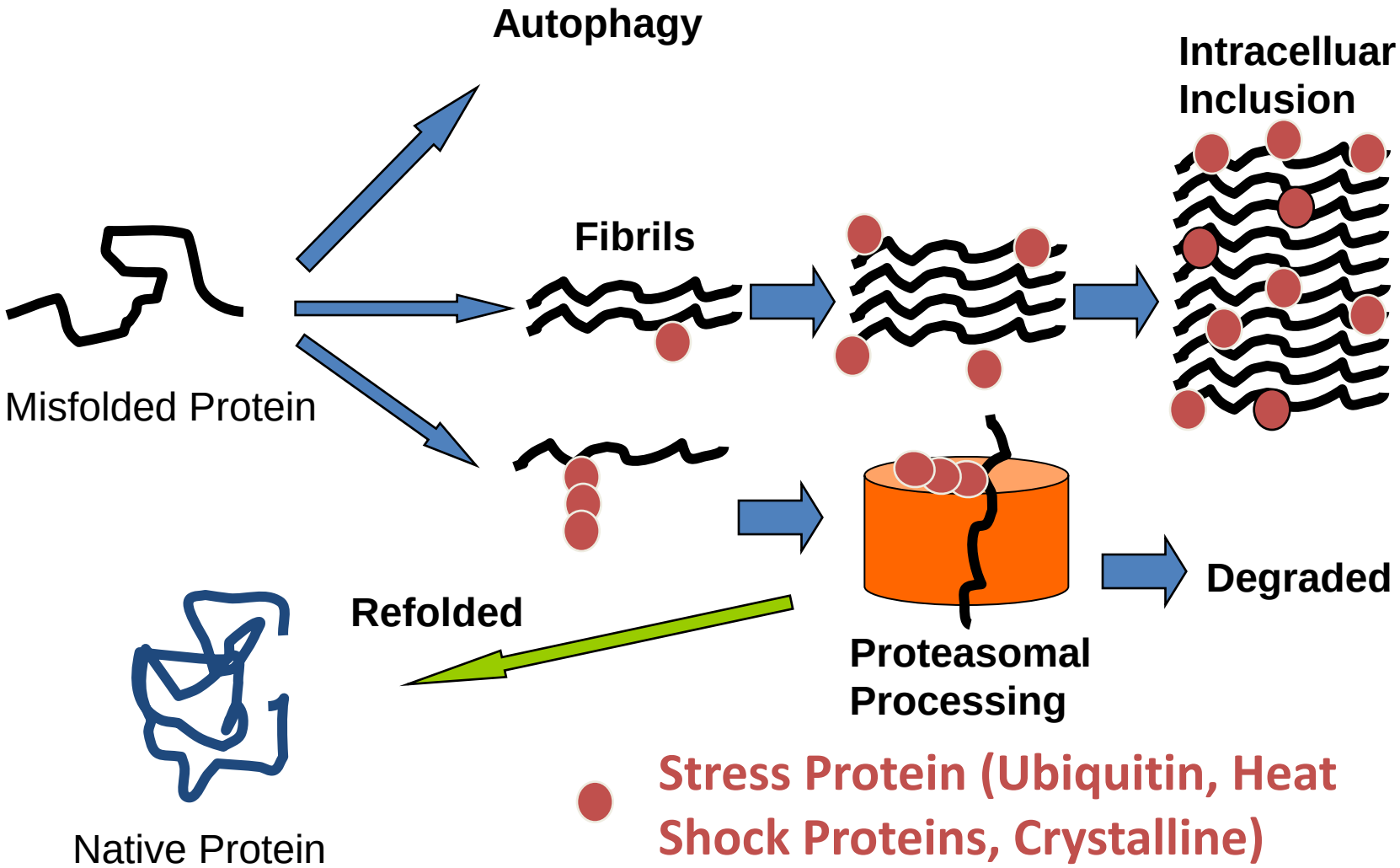
Tau in Neurodegenerative Disorders Tauopathies

- Pure tauopathies
  - Frontotemporal lobar degeneration (Pick’s disease)
  - Progressive supranuclear palsy
  - Corticobasal degeneration
  - Chronic traumatic encephalopathy (CTE)
- Mixed proteinopathy
  - Alzheimer disease (AD)
    - Beta-amyloid
    - Tau

Fibrillogenesis Diseases

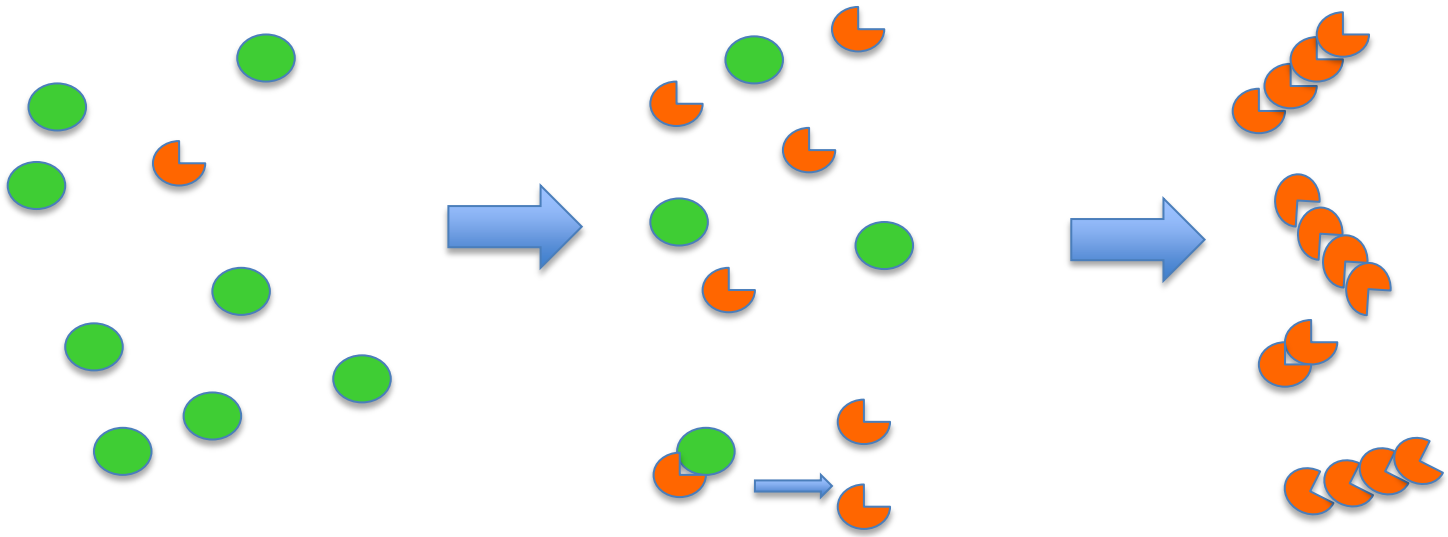
- *Concept:* Abnormal protein is produced
- As it accumulates, it aggregates into fibrils or filaments
- Identified by light or electron microscopy
- Immunohistochemistry identifies inclusions in nucleus or cytoplasm
- Accumulations lead to cellular dysfunction or cell death

Potential Fates of Misfolded Proteins



Slide Courtesy of Dr. Goodman

Neurofibrillary Tangles
Intracellular Tau Accumulation



Misfolding

Stochastic

Failure to degrade
Genetic propensity
to misfold

Templating

Misfolded protein
modifies secondary structure of
native protein

Self-replicating cycle

Aggregation

Misfolded protein
tends to aggregate

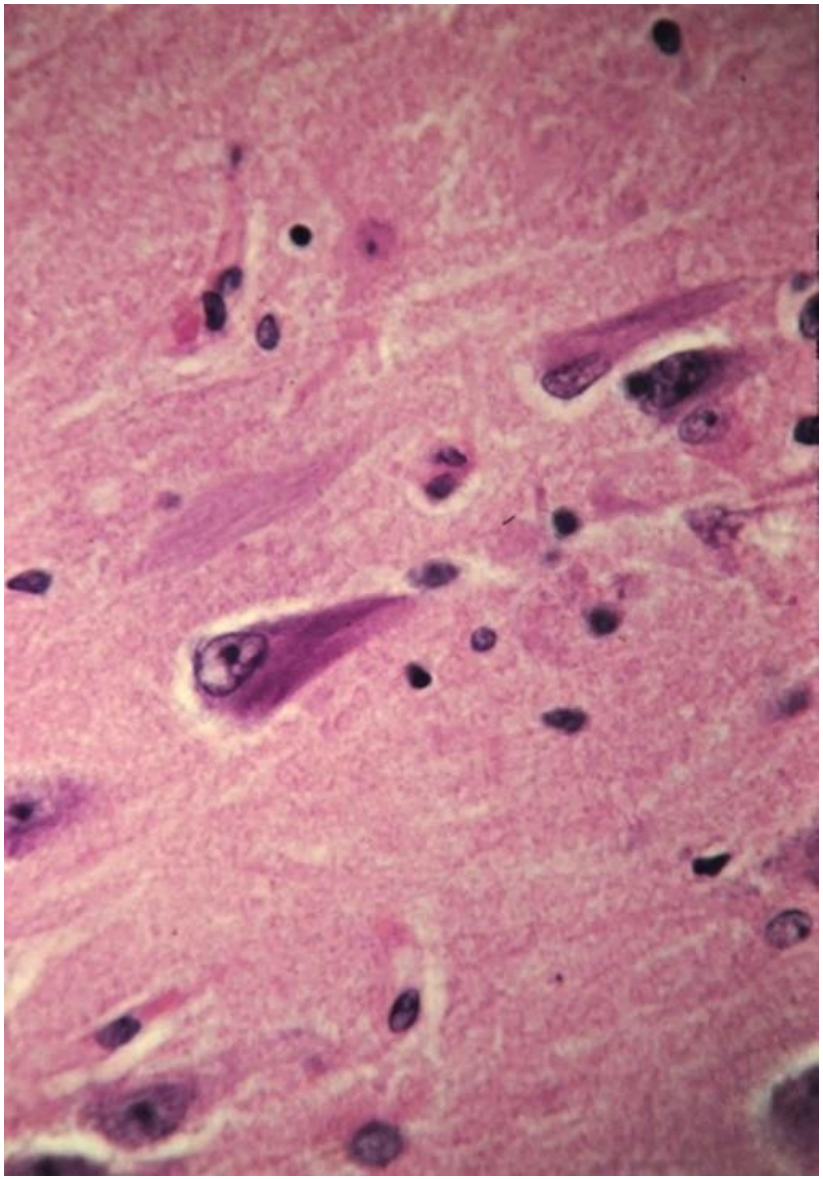
Intracellular = tangles

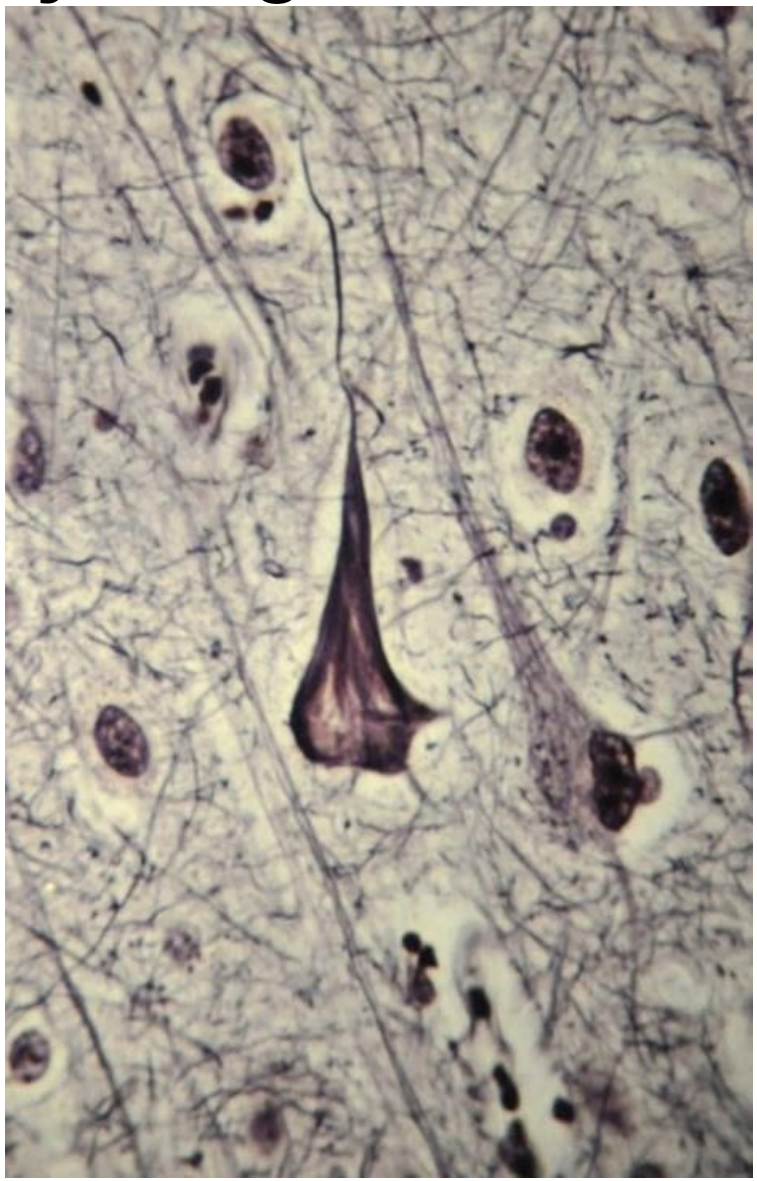
Slide Courtesy of Dr. Goodman

Aggregate of Hyperphosphorylated Tau form Paired Helical Fibers

Image courtesy and with permission of the Sydney S. Schochet, Jr. Collection

Neurofibrillary Tangles





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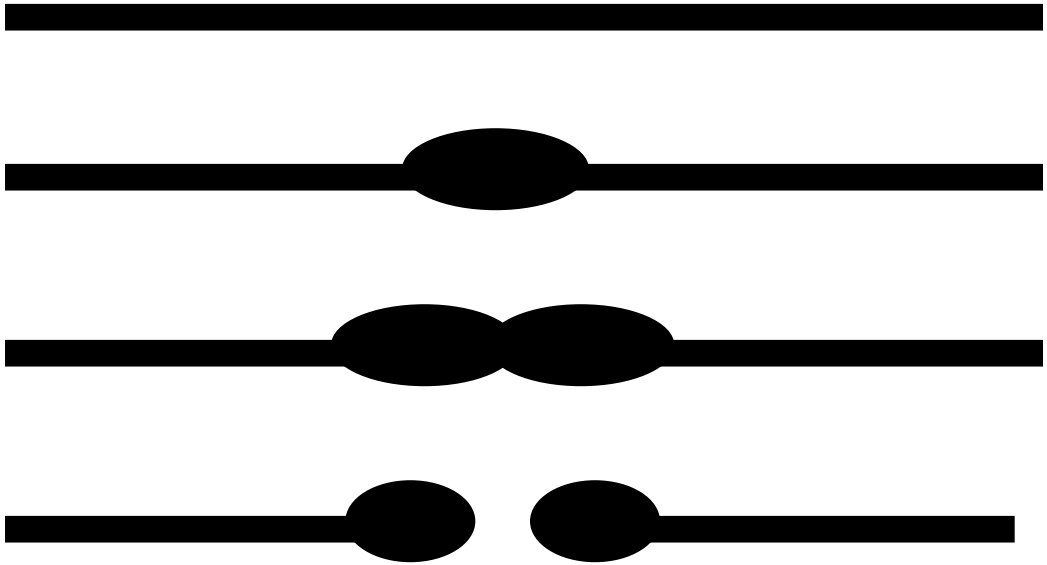
How Do Neurofibrillary Tangles Spread?

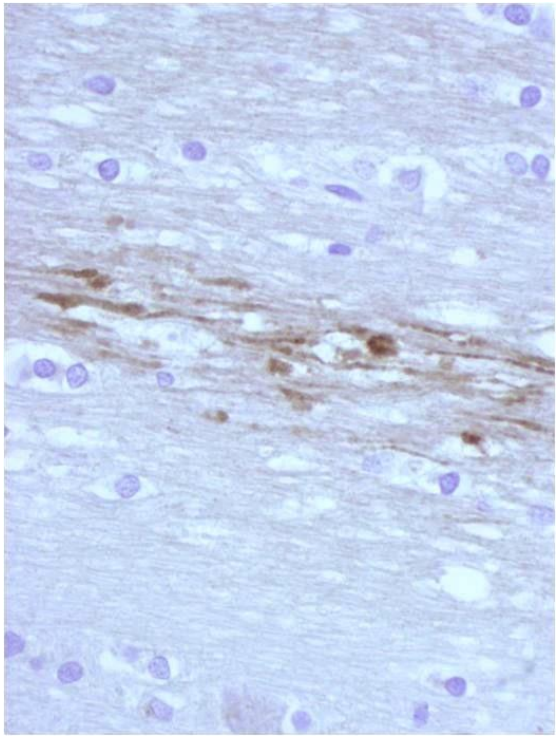
- Pathogenic tau can convert native tau to pathogenic tau through templating (prion-like mechanism)
- Neuron to neuron dissemination
  - Transsynaptic via vesicles
  - Exosomes/microvescicles
    - Extracellular membrane bound packages containing cytoplasmic constituents
    - Constantly blebbing off of cellular surface
- Corollary: Processes that increase exosome release may facilitate spread of pathogenic tau isoforms

What Does Tau Have to Do with TBI?

- Diffuse axonal injury
  - Microtubule spacing collapses
  - Tau dislodged from microtubules
  - Free tau has fewer constraints against misfolding
  - Free tau may be phosphorylated deceasing the probability to reattachment to microtubules
  - Increased neuronal blebbing – exosome release
- Clinical studies
  - Increased cerebral spinal fluid (CSF) and serum tau in boxers
  - Increased CSF tau in severe TBI
  - Increased extracellular tau in severe TBI by microdialysis

Diffuse Axonal Injury
A Process Not an Event





Slide Courtesy of Dr. Goodman

Tau in TBI

- TBI may shift the probability that tau will misfold, template, aggregate and spread
- Possible clinical correlate:

  chronic traumatic encephalopathy (CTE)
  - 1928: Punch drunk syndrome
  - 1973: Neurofibrillary tangles (NFTs)
  - 2000s: CTE
- CTE does appear to be a neuropathologically unique condition

Chronic Traumatic Encephalopathy

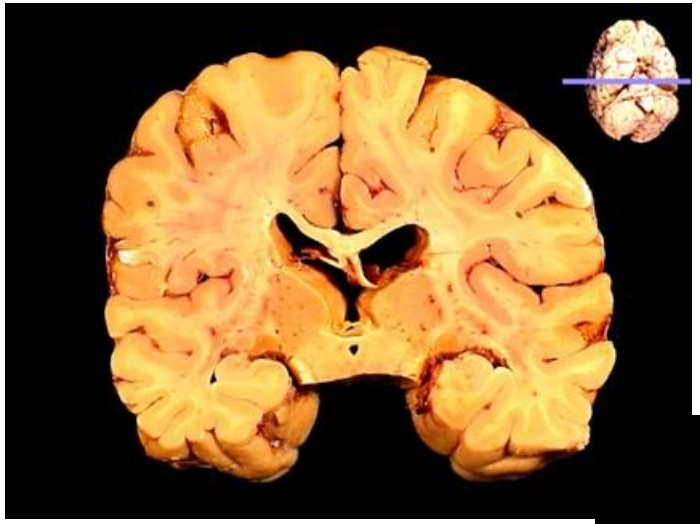
- Clinical features
  - Cognitive decline
  - Motor decline (extrapyramidal)
  - Neuropsychiatric
- Hyperphosphorylated tau inclusions
  - Uniquely at the depths of sulci initially
  - Then widespread in more advanced disease
- Few or no neuritic plaques
- Chronic traumatic encephalomyelopathy
  - Clinical features of CTE plus motor neuron disease

Chronic Traumatic Encephalopathy (CTE) Pathological Criteria as Defined by McKee et al

1. Perivascular foci of phospho-tau immunoreactive astrocytic and neurofibrillary tangles (NFTs)
2. Irregular cortical distribution of phospho-tau immunoreactive astrocytic and NFTs with predilection for the depths of cerebral sulci
3. Clusters of subpial and periventricular astrocytic tangles in the cerebral cortex, diencephalon, basal ganglia, and brainstem
4. NFTs in the cerebral cortex located preferentially in the superficial layers

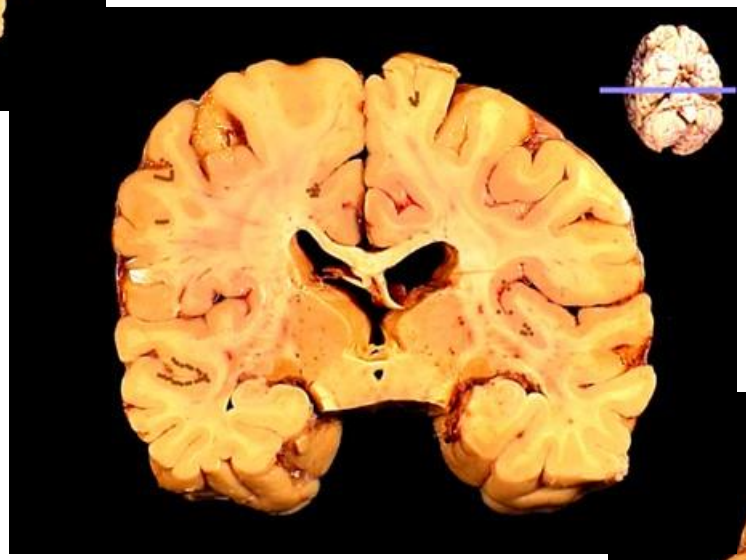
All four criteria must be met to have pathological CTE

Distribution Over Time of NFTs in CTE



Initially in focal isolated sulcal depths in frontal and temporal lobes

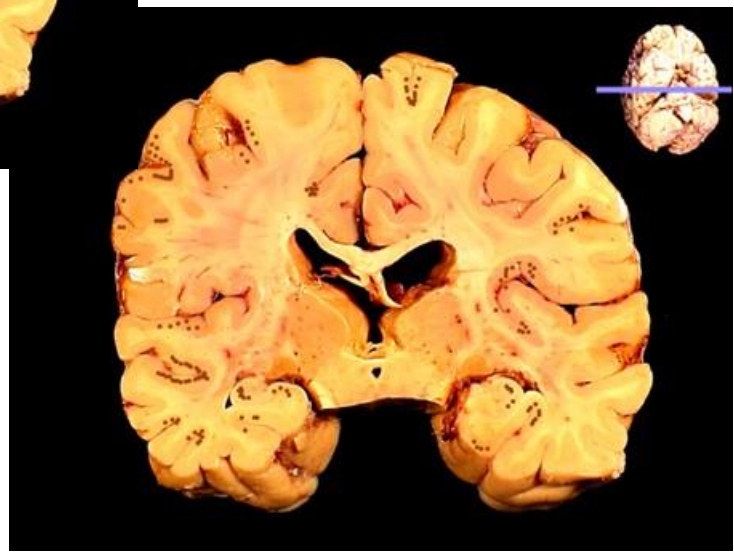
May be asymptomatic or early executive dysfunction and affective issues



More widespread confluent and in adjacent areas of cortex

Later involvement of limbic and deep structures

Cognitive, affective, motor symptom



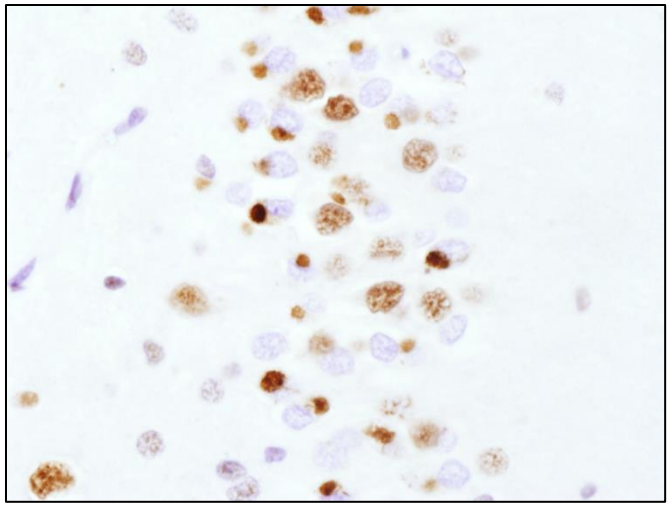
Slide Courtesy of Dr. Goodman

CTE Histopathology

- Unique distribution of NFTs
  - Sulci and superficial cerebral cortex
  - Perivascular
- Diffuse Axonal Injury (DAI) in all
- Amyloid-beta
  - Some deposition in 44%
  - Mostly diffuse plaques and perivascular
  - Age related
- TDP-43 positive > 80%

Neurodegenerative and TDP43

- TDP43 **(TAR DNA-binding protein 43)**
- Bind both DNA and RNA - transcriptional repression, pre-mRNA splicing and translational regulation.
- Normally a nuclear protein but in proteinopathies aggregates occur in the cytoplasm
- Cytoplasmic hyperphosphorylated ubiquinated TDP43
  - Frontotemporal dementia
  - Amyotrophic lateral sclerosis
- CTE: 80% TDP43 positive



Slide Courtesy of Dr. Goodman

CTE Neurodegenerative Co-Morbidity

- 37% of CTE patients have additional neurodegenerative disorders
  - 10% have features of AD
  - Motor neuron disease
  - Frontotemporal lobar degeneration
  - Parkinson disease

Tau in TBI: Unknowns

- What is the incidence of CTE?
  - Unknown
  - Current autopsy series have severe case ascertainment bias
  - CTE extremely rarely seen (if ever) in dementia brain bank series
  - CTE autopsy series use very elaborate expensive methods to exam brain

Tau in TBI: Unknowns

- Is repetitive TBI required to produce CTE?
  - Some suggestions that single hit moderate to severe TBI differs neuropathologically from repetitive TBI
    - More beta-amyloid
    - Chronic neuroinflammation
- What are the biomechanics – force magnitude, duration, frequency, number of hits required?
- Are there background pre-morbid genetic predisposing factors for development of CTE?

Tau in TBI:
How Do We Explore the Unknowns

- Tau imaging
- Autopsy studies with less ascertainment bias
- Epidemiological studies in sports and military
- What do we do in the meantime?
  - Concussion and blast guidelines are a good start
  - Stay objective and critical
  - Don’t panic and carry on

Presenter: Steven T. DeKosky, M.D., FACP, FAAN, FANA

- Professor of Neurology, Psychiatry and Neurobehavioral Sciences, University of Virginia School of Medicine
- Visiting Professor, Department of Medical Ethics and Health Policy, University of Pennsylvania Perelman School of Medicine
- Immediate Past Vice President and Dean, University of Virginia School of Medicine (2008-2013)
- American Board of Psychiatry and Neurology, Neurology Council (2004-2010)

Dr. Steven T. DeKosky

TBI and Long Term Outcomes: Neurodegenerative Dementias and Mechanisms

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Disclosures

- The views expressed in this presentation are those of the presenter.
- I have no relevant financial relationships to disclose.
- I do not intend to discuss the off-label/investigative (unapproved) use of commercial products or devices.

Topics and Questions

- What is the relationship of blast and concussive injury to long term cognitive outcomes such as CTE?
- How do the clinical and neuropathological changes relate to Alzheimer's Disease or other neurodegenerative dementias?
- How can it be treated? Prevented?

Types of Long Term Effects Based on Pathology

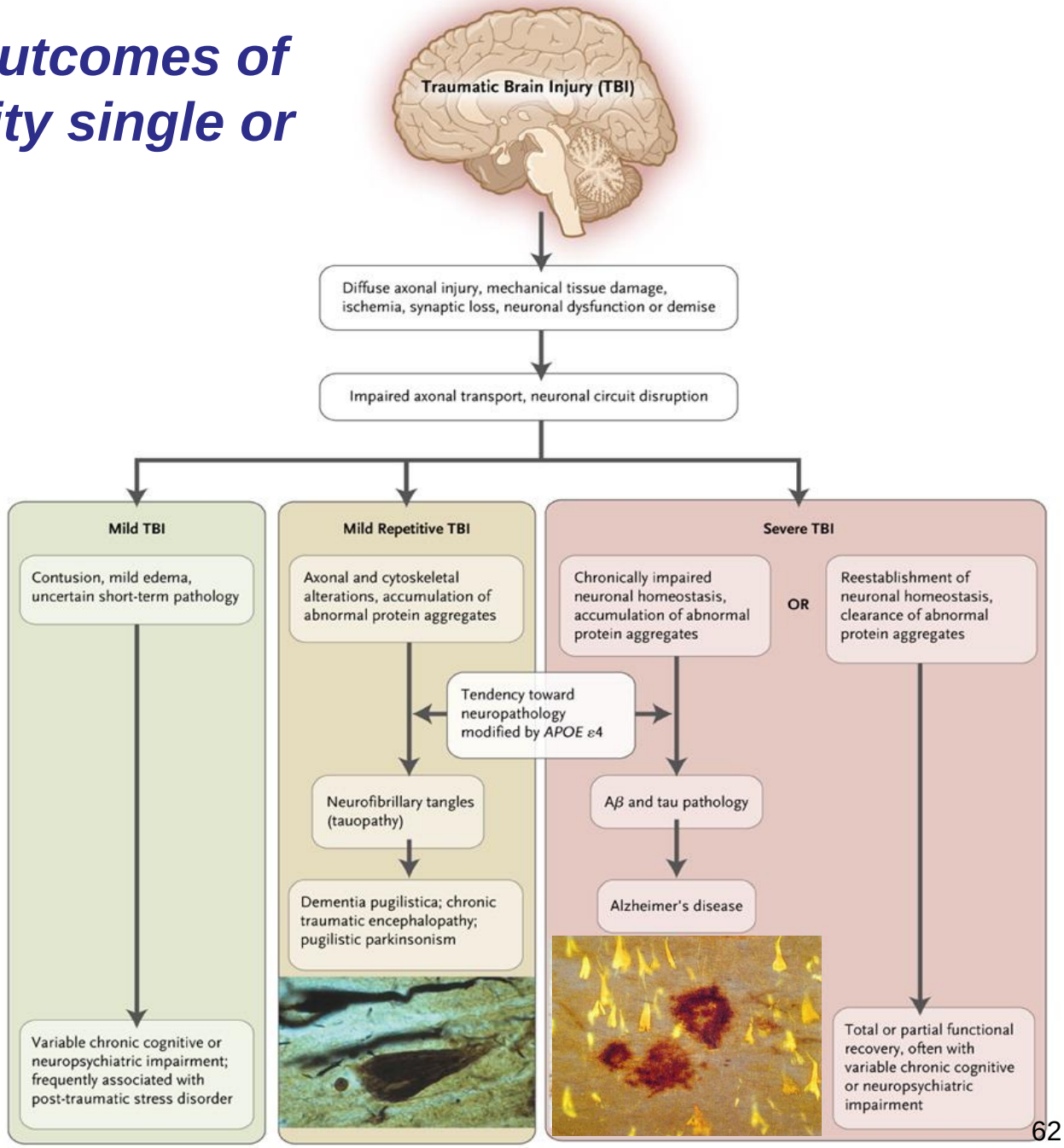
Acute, single-incident, severe (e.g., automobile crash)

- Leads to acute accumulation of amyloid deposits
- Increased long term risk for Alzheimer's disease

Repetitive injury (less severe, e.g., boxing, football)

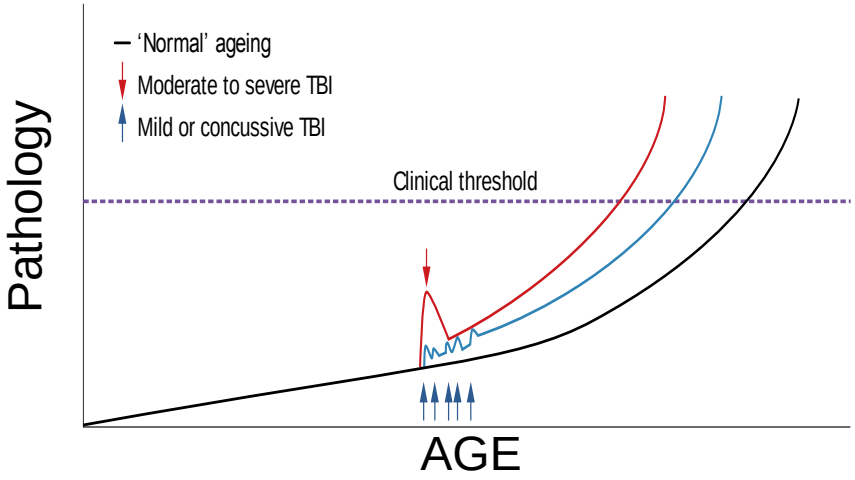
- Acute pathology not fully known
- Chronic pathology is tau/NFT-based
- Clinical spectrum of long term outcomes include dementia, parkinsonism, motor neuron disease
- "Chronic traumatic encephalopathy" (CTE)

What are the outcomes of variable-severity single or repetitive TBI?



DeKosky ST et al., NEJM, 2010

Variables Affecting TBI Outcomes



- Age
- Temporal proximity of repeated TBIs
- Number of TBIs
- Severity of injury; polytrauma; associated ischemia; breadth, extent, nature of lesions (e.g., hemorrhagic, etc.)
- ApoLipoprotein E (APOE) Genotype
- Other genetic factors (relating to injury response, regeneration…)
- *Study designs must consider all these variables*

Graphic: Smith et al., Nat. Rev. Neurol 2013

Repetitive TBI & Risk of Long Term Disease

- Contact sports, especially football, soccer, hockey, boxing are focus of studies of short and long term risk

- In boxing:
  - ~20% of boxers develop Dementia Pugilistica after boxing careers
  - Long term neuropsychological impairment is correlated with number of rounds boxed
  - Severity of impairment in boxers is related to ApoE genotype (ε4) (Jordan et al., JAMA, 2008)
- CSF markers of brain damage (neurofilament protein and tau) increased after boxing [independent of KO]

Zetterberg et al., Archives of Neurology, 2006

Mechanisms of Apoliprotein E (ApoE) in AD

- APOE is a cholesterol carrier, necessary for normal metabolism and membrane repair
- APOE (Chromosome 19) has 3 alleles: ε2, ε3, ε4
- Carrier to remove Aβ from CNS: ApoE links to LRP1 to cross into the vessel lumen
- APOE4 not as effective in this mechanism as is APOE3 or APOE2
- Single allele ε4 triples AD risk; homozygotes have 8-12X increased risk
- In AD, buildup of Aβ is <u>facilitated</u> by slower removal of Aβ from the brain

Survey of APOE and Trauma Experts at Keystone TBI meeting

TRAUMATIC BRAIN INJURY EDITORIAL

APOE ε4 Status and Traumatic Brain Injury on the Gridiron or the Battlefield

Sam Gandy* and Steven T. DeKosky*

www.ScienceTranslationalMedicine.org 16 May 2012 Vol 4 Issue 134 134ed4

- Brain Trauma and APOE Researchers:
  - = Do not believe there is sufficient evidence to use APOE genotyping for decisions re sports or armed forces
  - = <u>Would</u> use such information for family if the information came to them incidentally

What is the relationship of Amyloid to NFT in TBI?

- In brain trauma, there is upsurge of APP and Aβ after severe injury
- Amyloid plaques form acutely in 40%
- Pathology studies confirmed the presence of plaques
- Does this predispose to the neurofibrillary pathology that occurs in AD?
- Or do the NFT of CTE form by a different mechanism, for example, secondary to axonal disruption?
- Or both?

ORIGINAL CONTRIBUTION

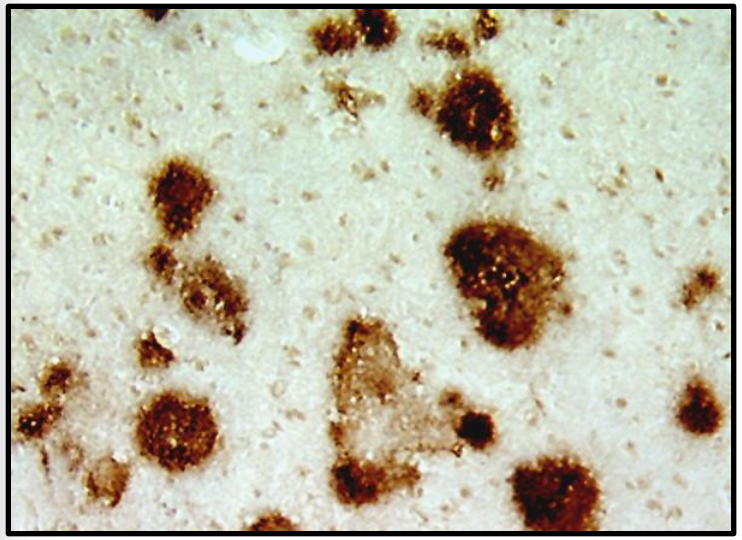
Association of Increased Cortical Soluble $A\beta_{42}$ Levels With Diffuse Plaques After Severe Brain Injury in Humans

Steven T. DeKosky, MD; Eric E. Abrahamson, PhD; John R. Ciallella, PhD; William R. Paljug, MS; Stephen R. Wisniewski, PhD; Robert S. B. Clark, MD; Milos D. Ikonomovic, MD

APP and Aβ are increased in acute TBI, and amyloid plaques are seen within hours after injury.

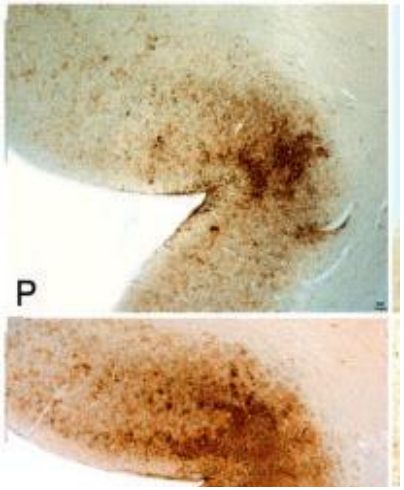
How does Acute Trauma Lead to NFT? Through Amyloid?

Acute…



Years…

Chronic…



Distribution of NFT is different than the laminar pattern in the cortex in AD:
NFT predominant in bottom of sulci

McKee et al., Brain 2012

Brain Injury Mechanisms in TBI

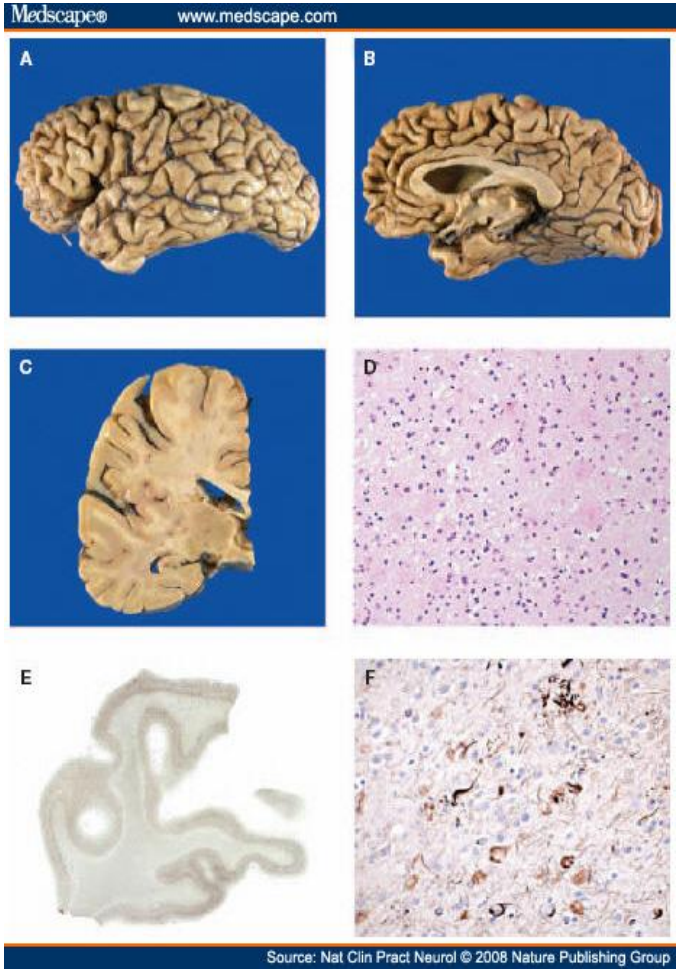
- The mechanism of longer term cognitive & neuropsychiatric disorders is unknown
- Disrupted tau metabolism and axonal loss, genetic and epigenetic vulnerabilities, regional cell and neurotransmitter system loss/disruption
- *HYPOTHESES:*
  - *Loss of cognitive reserve by injury-induced structural loss*
  - *Cortical Aβ, upregulated with repeated injuries, drives tau pathology, is resorbed, and the visible end stage pathology involves largely NFT*

Lessons Learned & More Nuanced Views…

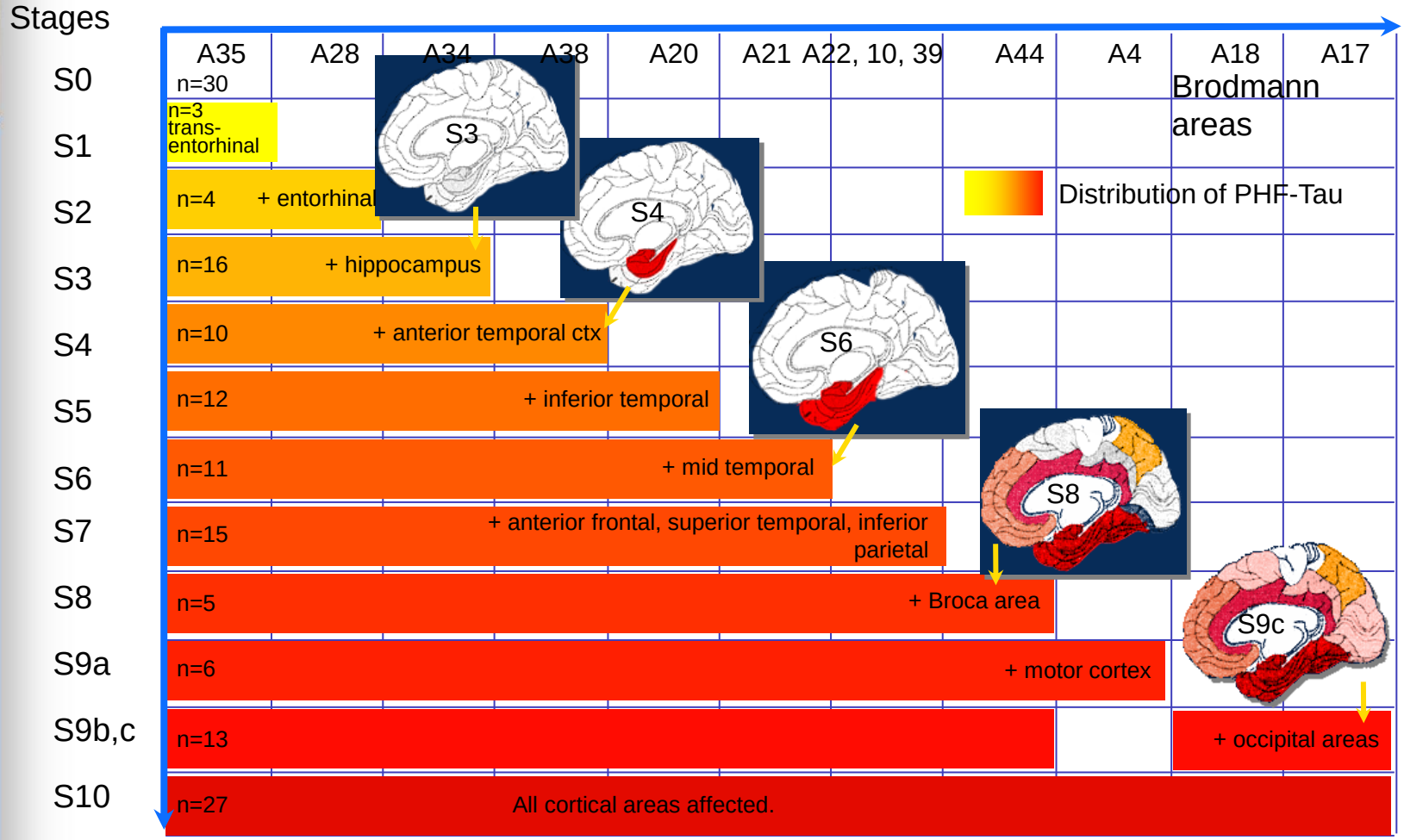
- High variability of TBI related injury: sports, combat, falls, auto accidents; single or repetitive; recall bias
- Pathology: regional neuronal death, axonal loss, NFT
  - Two neuropath classifications proposed (Omalu, McKee)
- Comorbid neurodegenerative disorders & protein deposits
- **Cross sectional ≠ longitudinal studies**
- Biomarkers: blood/CSF/neuroimaging
  - Predictive use in short term
  - Serial imaging for therapy (e.g. anti-amyloid therapy)
- Treatment and prevention of long-term adverse outcomes are a focus

Changing Times:
Neuropathology and Clinicopathological Correlation was the Standard

- Autopsy was king
- Required patience
- Only got one point in disease progression
- No prospective studies
- *Longitudinal/serial protein imaging (PET) & MR Imaging change the paradigm*



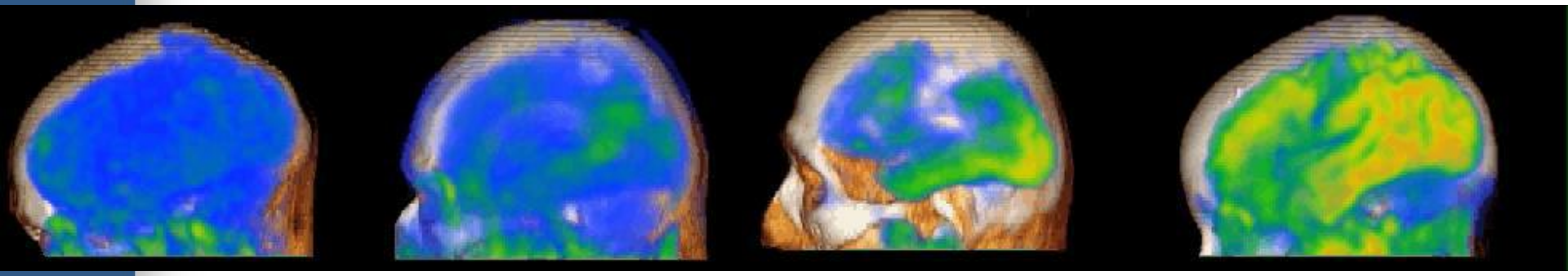
Initiation and spread of neurofibrillary degeneration in AD: Different from CTE



Delacourte A, et al., Neurology. 1999;52:1158-1165

18F-T807 PET Across the AD Severity Spectrum: Imaging Tau *In Vivo*

Healthy	Mild MCI	MILD AD	Severe AD
	MMSE=26	MMSE=21	MMSE=7

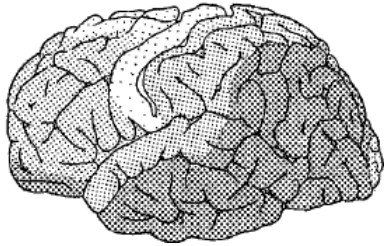


58 yo	69 yo	88 yo	72 yo

rSUV

Target/Cerebellum)

Images 80-100 min post injection



Cortical NFT density in end stage AD (Neuropath)

Courtesy of Mark Mintun, Avid Pharmaceuticals

Conclusions

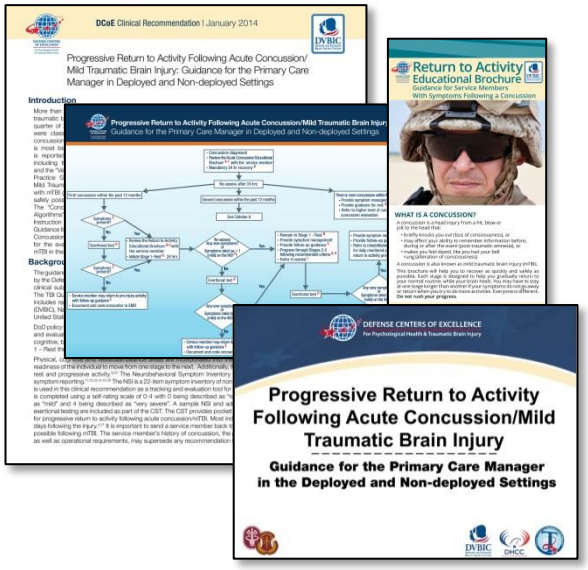
- The main genetic risk factor for AD (*APOE* ε4) increases brain accumulation of Aβ and increases DP/CTE risk and severity
- Aβ-lowering agents (statins, γ-secretase inhibitors) improve outcome in TBI in rodents
- Anti-tau and anti-amyloid drugs being developed for AD may be useful in TBI, both acute and chronic treatment
- Longitudinal assessment of acute and chronic TBI for Aβ and tau pathology will provide direction for improved interventions

How can we diagnose, prevent, treat, and delay adverse long term outcomes in the future?

- Understand the time course (and variability) of the biomarkers in relation to the cognitive changes
  - Prospective studies of people at risk for TBI
  - New in vivo biomarkers: serum, imaging, genetic
- Roadmap for collaborative studies:
  - For short term single severe and repeated TBI
  - For longer term outcomes: DOD and VA, athletes
- Why do some TBI subjects develop CTE or ALS or PD?
- What causes the comorbid neurodegenerative diseases—in some but not all cases?

Progressive Return to Activity

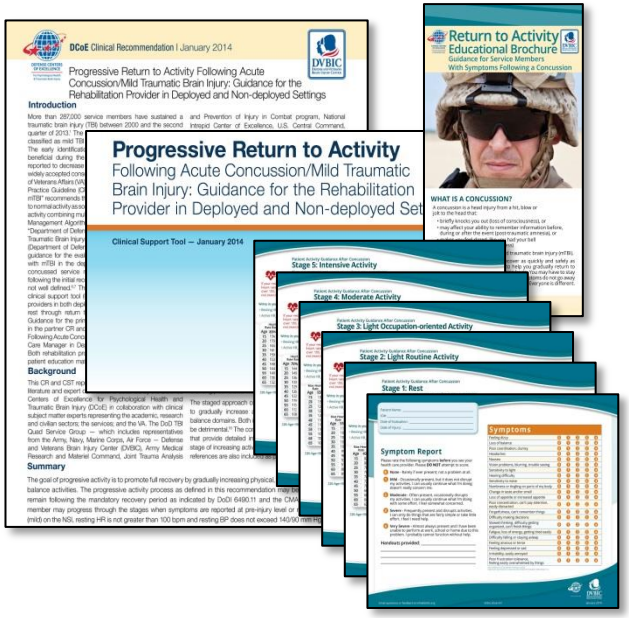
Primary Care Manager Suite



Coming Soon

Each suite includes:
clinical recommendation
clinical support tool
provider educational slide deck
patient education products

Rehabilitation Provider Suite



- Guidelines provide a standardized staged approach from rest to unrestricted activity for service members who remain symptomatic after sustaining an acute concussion/mild TBI
- Each suite of tools are tailored specifically to primary care providers and rehabilitation specialists for managing the progressive return of activity following an acute concussion/mild TBI

Questions?

- Submit questions via the Defense Connect Online question box located on the screen.
- The question box is monitored and questions will be forwarded to our presenter for response.
- We will respond to as many questions as time permits.

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Save the Date

Next DCoE Psychological Health Webinar:

Sleep Disturbance: Assessment and Evidence-based Clinical Interventions in the Active-duty and Veteran Populations

Jan. 23, 2014
1-2:30 p.m. (EST)

January						
S	M	T	W	T	F	S
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5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

Save the Date

Next DCoE Traumatic Brain Injury Webinar:

Joint Theater Trauma Systems Practice Guidelines and Recommendations

Feb. 13, 2014
1-2:30 p.m. (EST)

February						
S	M	T	W	T	F	S
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
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