# MRI in the Diagnoses and Stratification of Acute Stroke and TBI

Larry Latour

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Acute Cerebrovascular Diagnostics
National Institutes of Neurological Diseases and Stroke, Bethesda, MD

Acute Studies Core
Center for Neuroscience and Regenerative Medicine

# Serendipity

*Dans les champs de l'observation le hasard ne favorise que les esprits prepares*

-Louis Pasteur

In the fields of observation chance favors only the prepared mind.

# Hypothesis Driven Research

**Diffusion tensor imaging of acute mild traumatic brain injury in adolescents**

EA Wilde, SR McCauley, JV Hunter, ED Bigler, Z Chu… - Neurology, 2008 - AAN Enterprises

Background: Despite normal CT imaging and neurologic functioning, many individuals report postconcussion symptoms following mild traumatic brain injury (MTBI). This dissociation has been enigmatic for clinicians and investigators. Methods: Diffusion tensor ...

Cited by 334 Related articles All 4 versions Web of Science: 213 Cite Save

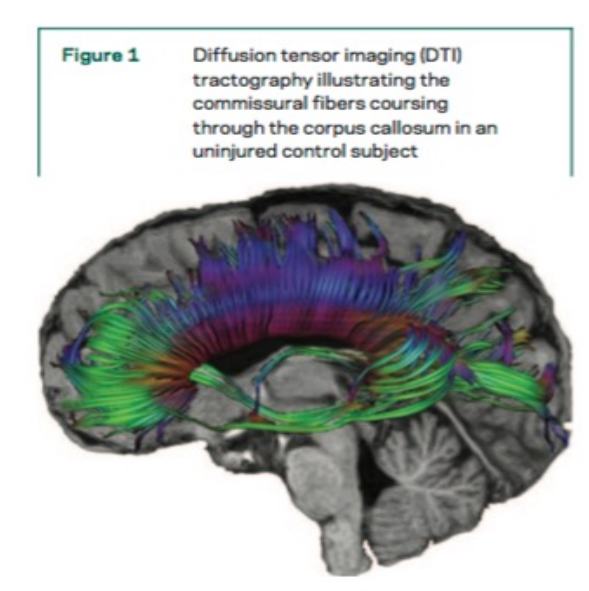


**Figure 1** Diffusion tensor imaging (DTI) tractography illustrating the commissural fibers coursing through the corpus callosum in an uninjured control subject

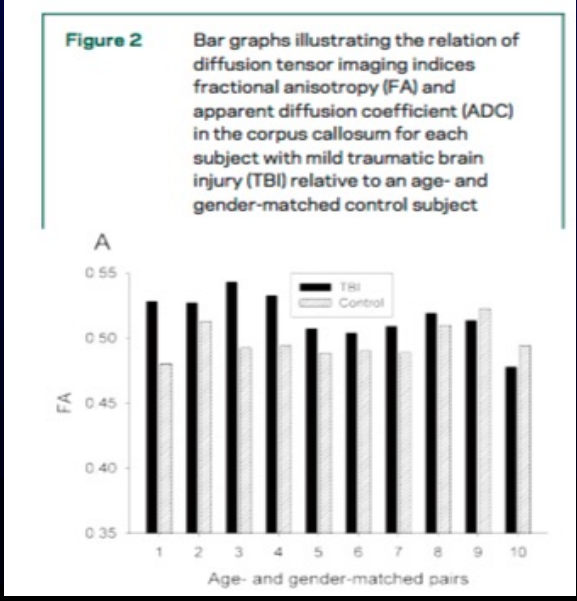
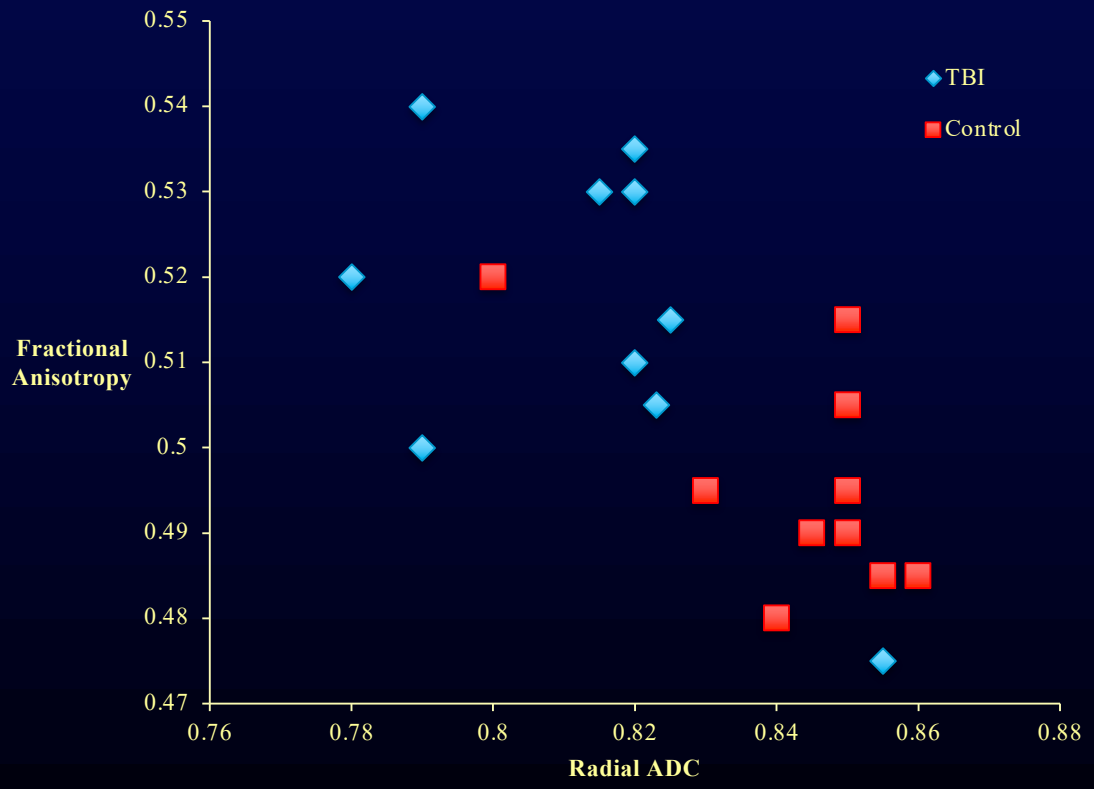



**Figure 2** Bar graphs illustrating the relation of diffusion tensor imaging indices fractional anisotropy (FA) and apparent diffusion coefficient (ADC) in the corpus callosum for each subject with mild traumatic brain injury (TBI) relative to an age- and gender-matched control subject

# Disease *vs* Control




*mTBI*
*FA = 0.516*

*Control*
*FA = 0.496*

*"Contrast"*
*E = 0.020*

*"Noise"*
*S = 0.016*

$N_o = N_1 = 14$

# Summary

- FA and/or ADC can be used to Dx mTBI…
- We can all go home now…Right?

# Summary

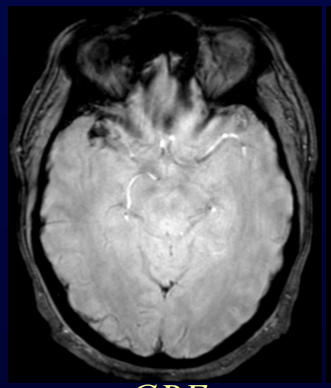
- FA and/or ADC can be used to Dx mTBI…
- We can all go home now…Right?

Wrong.

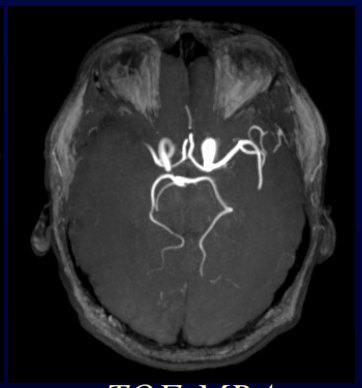
1. Diagnosis already exists, why is imaging needed?
2. Do all Dx of mTBI actually have TBI?
3. Are all mTBI the same…one phenomena?
4. Is it reasonable to expect the imaging biomarker is valid?

# Stroke Team

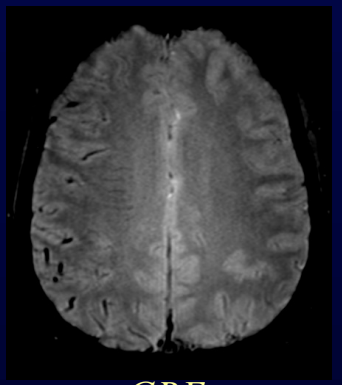
*Suburban Hospital*



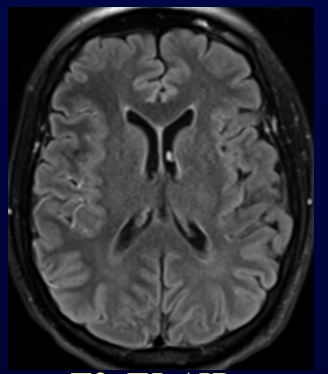
*GRE*



*TOF-MRA*

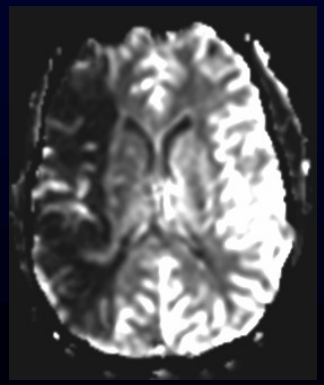


*GRE*

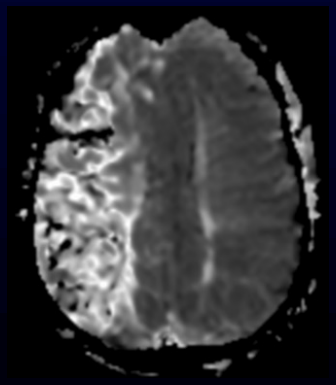


*T2-FLAIR*

*Washington Hospital Center*

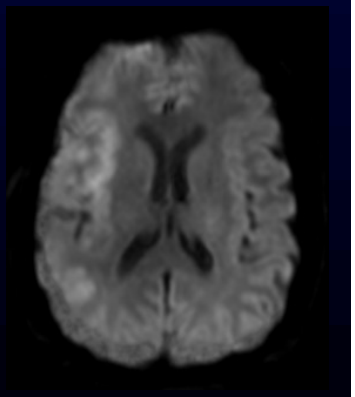



*CBF*



*MTT*

*ADC*



*DWI*

# 24 hours, 365 days

*17:17 Code one paged by Blue team for 31F with Sz disorder presented with LUE weakness, L Facial droop and dysarthria started 45min prior to arrival. Proceeded to MRI -> RMCA stroke with large perfusion mismatch -> IVtPA given DTN 44min -> IR suite: TICI 2B, first visualization showed R M1 and distal vessels re-canalized with tPA alone by the time they were able do the angio, microcatheter wire and IA tPA were given to try to recanalize M3/4 frontal branch. Patient intubated for the procedure. No NOK was available by phone or in person or NH consent. Only person at bedside of fiancée'. Admitted to ICU. Patient intubated or procedure. Blood in freezer.*

*- Alexis Simpkins*

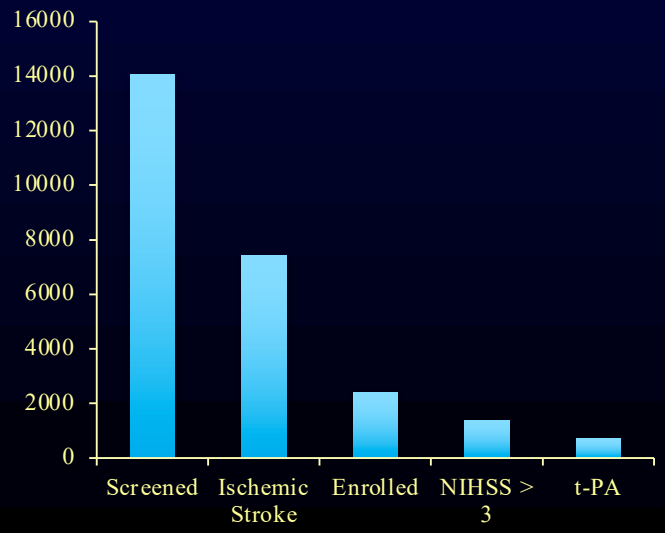
# Program – Stroke and TBI

- Attending Neurologists
- Clinical Coordinators
- MRI Technologists
- Neurology Fellows
- Neurology Residents
- Nurse Responders
- Physician Assistant
- Post-Docs
- Program Managers
- Research Nurses
- Research Assistants
- Scientists

# Natural History Studies

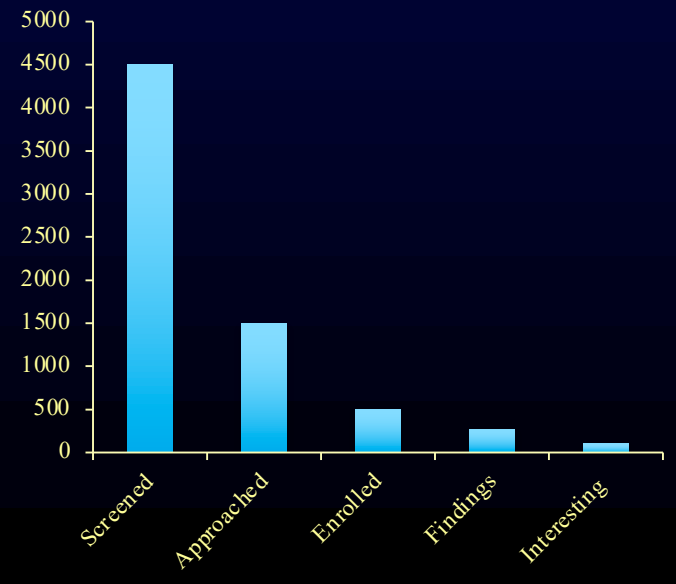
**Stroke**

- Registry
- 01-N-0007 Protocol



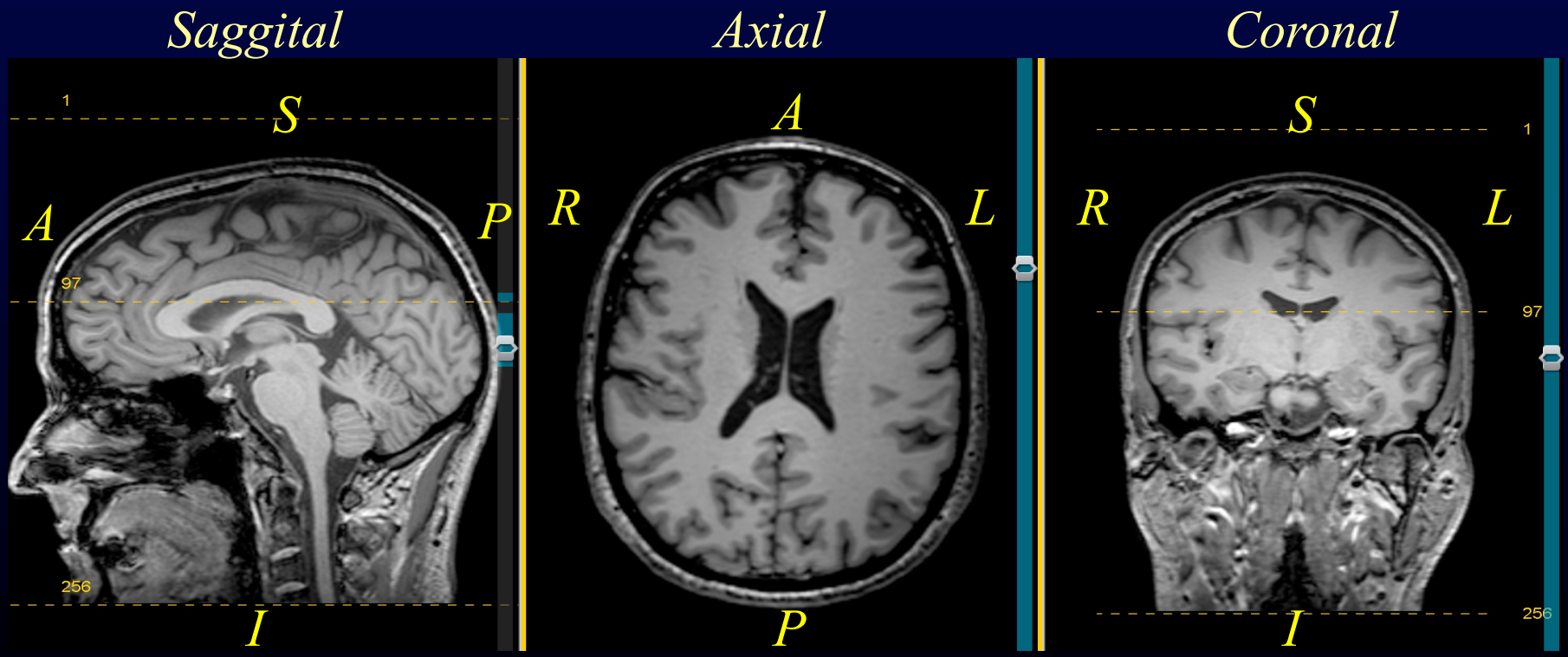

**TBI**

- 11-N-0084 “Screening”
- 10-N-0122 “THINC”



# BASIC IMAGING PRIMER

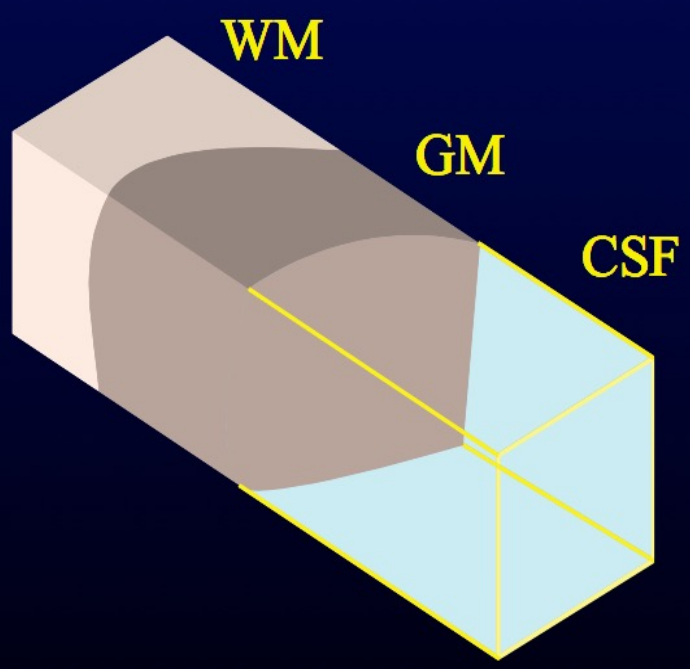
# Basic Image Orientation



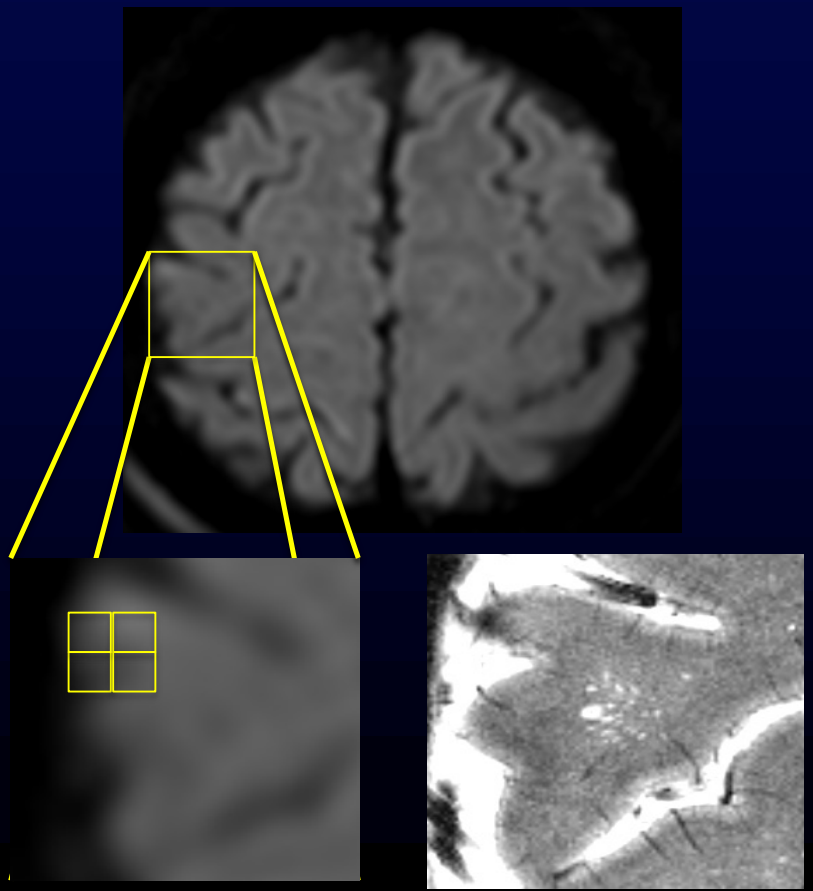
# Partial Volume Averaging

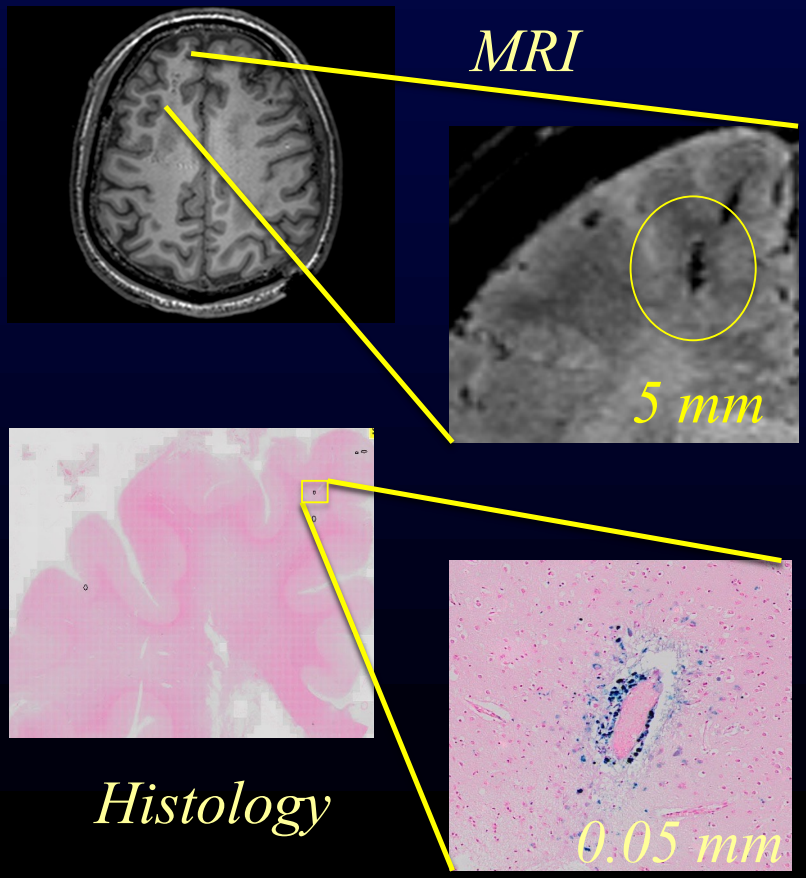
**Slices**

**One voxel, many tissues**



# Resolution *vs* Sensitivity

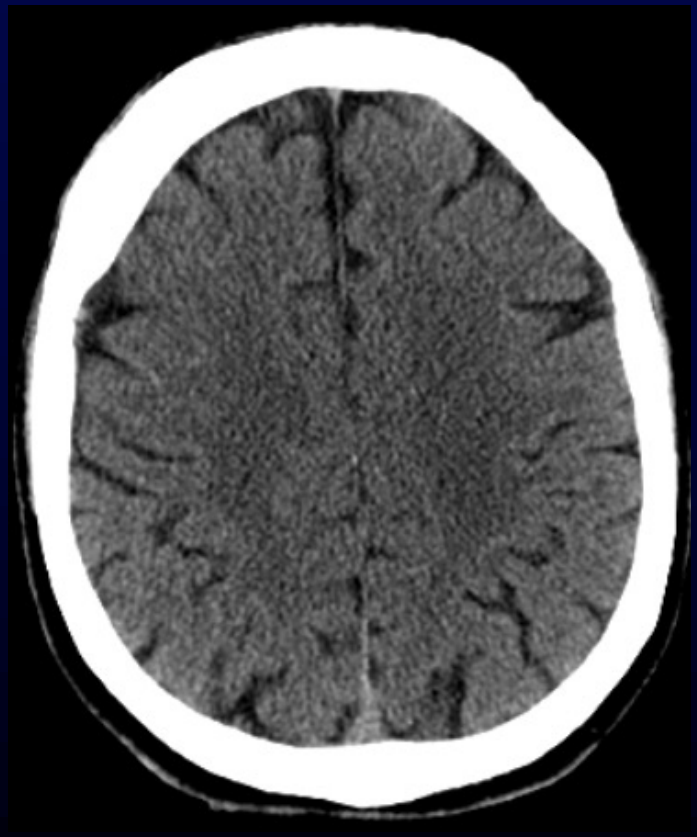


**…predementia reminder #1 … CT then Endo 1 baseline**

# CT Negative = Invisible Injury

*In a patient with post concussion syndrome*



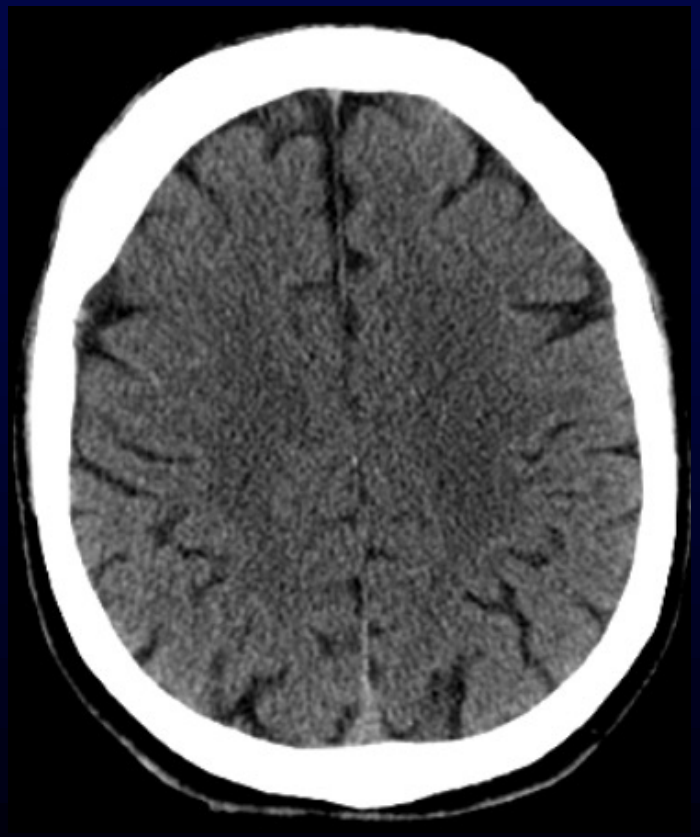
# *SYMPTOM OR BIOLOGY?*

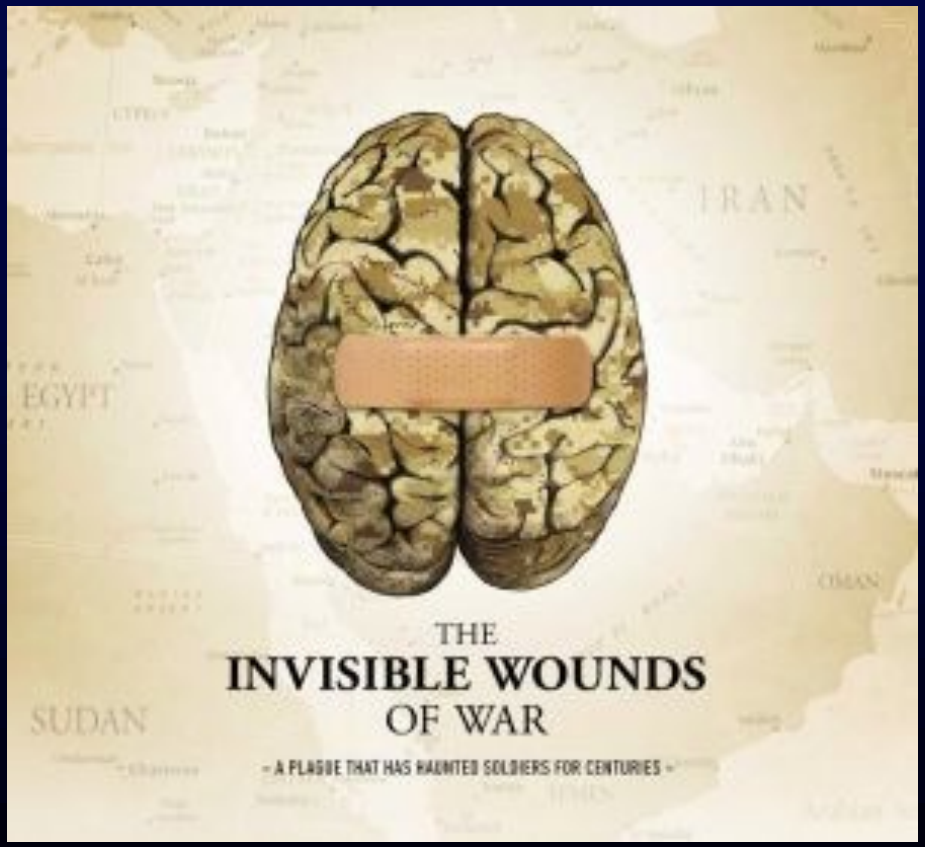
…not just with TBI or Stroke

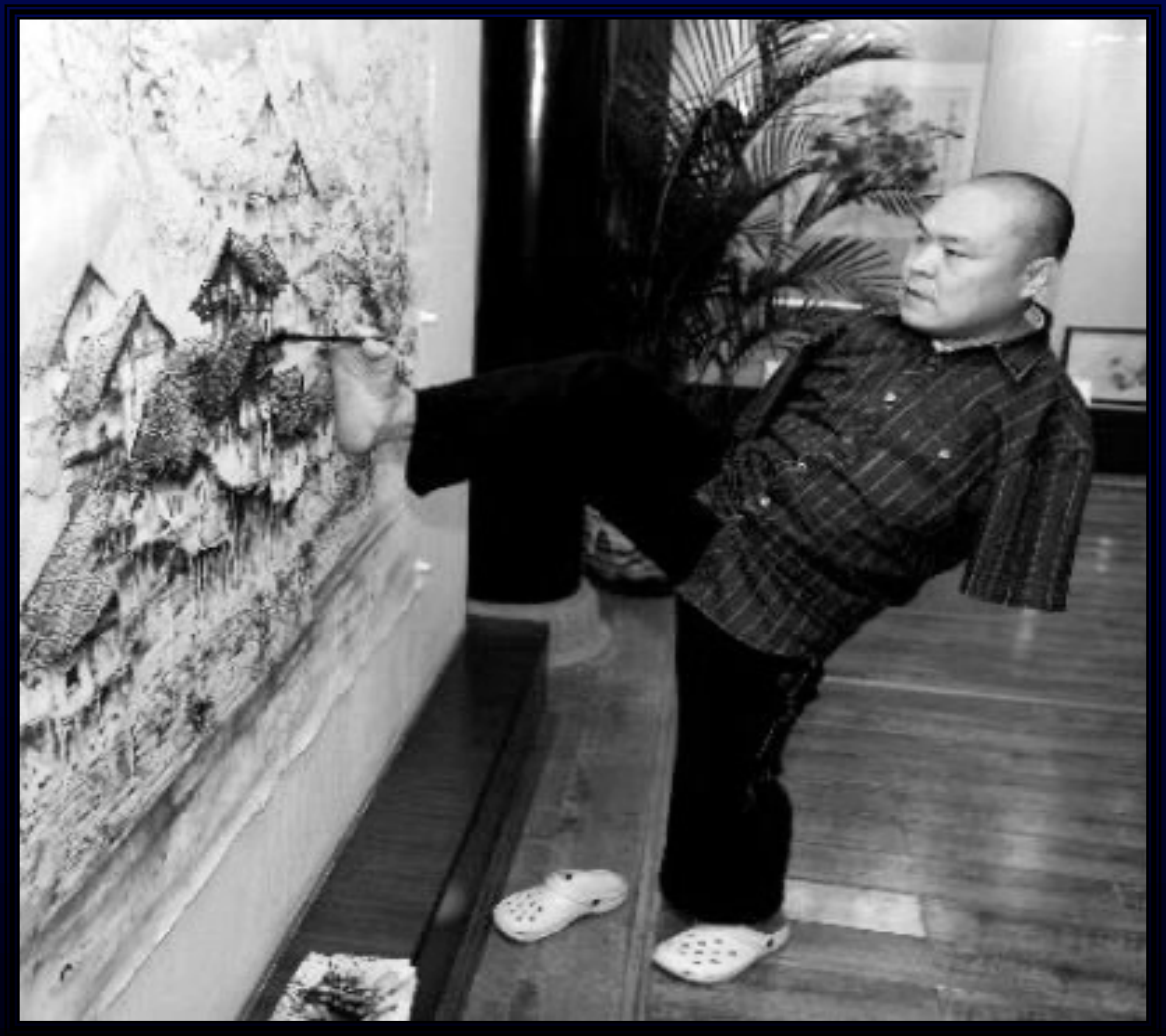
**FUNDAMENTAL PROBLEM**

# CT Negative = Invisible Injury

*In a patient with post concussion syndrome*







*Chinese artist Huang Guofu*

# “No longer Gage”

*His mind was radically changed, so decidedly that his friends and acquaintances said he was ‘no longer Gage.’*

*Graham Gordon Ramsay*
*Phineas Gage's skull and life mask, 2001Color print*
*Francis A. Countway Library of Medicine, Warren Anatomical Museum*

# 2011 NHL Playoffs

# Legislation

**Bill addressing student concussions advances**

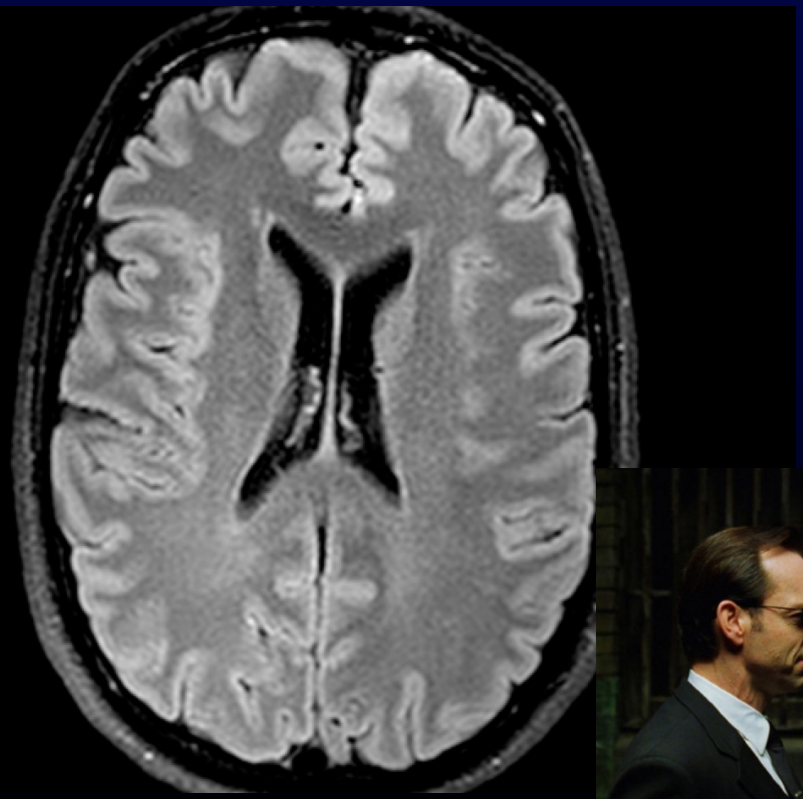
Some pro athletes push for passage

Ted Johnson, former New England Patriots linebacker, spoke at a State House rally yesterday in favor of a bill that would limit how soon a student athlete can return to play after suffering a concussion. Johnson called concussions "the invisible injury." (Essdras M Suarez/ Globe Staff)

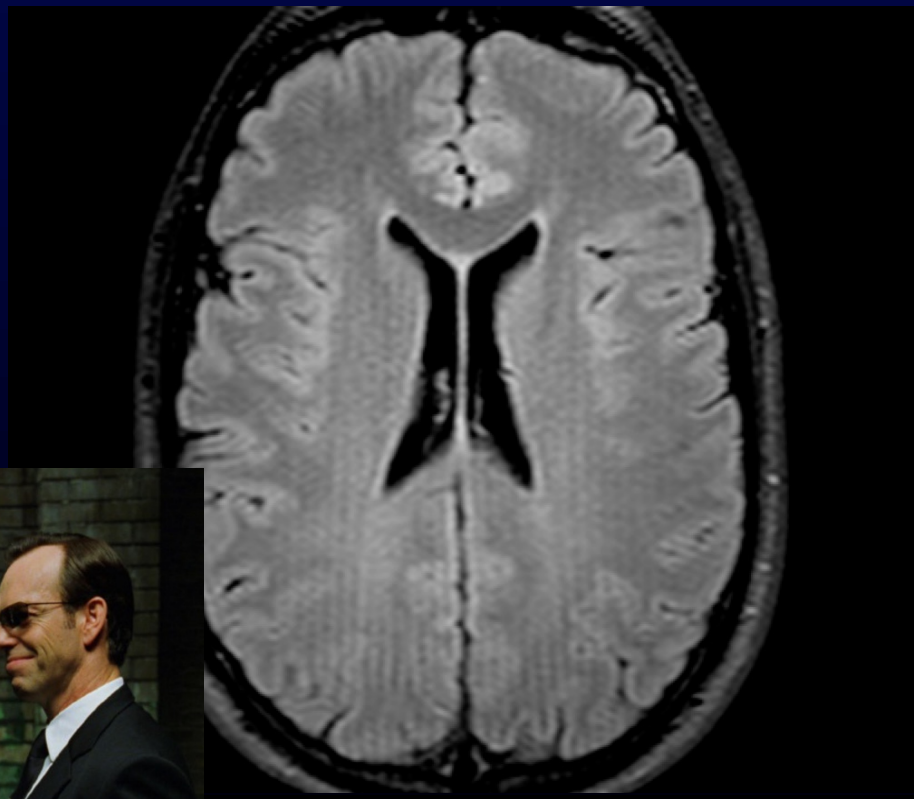
*Zack Lystedt*

# How do we diagnose disease

- Control



- Schizophrenia



# Mental Heath

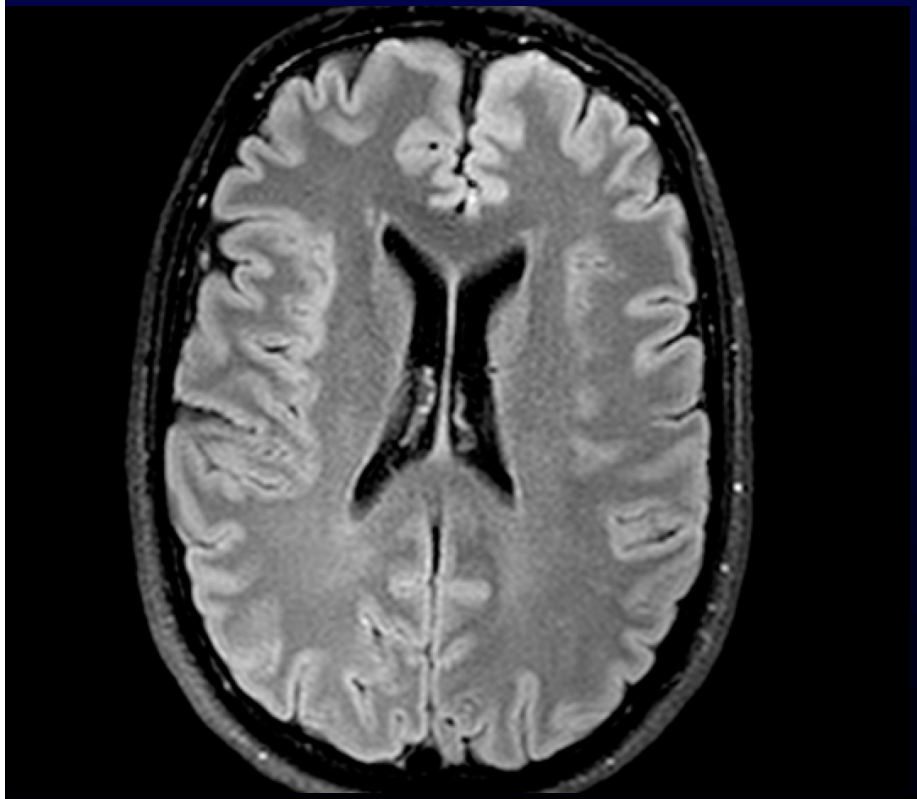
*Dr. Insel*

> *"The weakness is its lack of validity. Unlike our definitions of ischemic heart disease, lymphoma, or AIDS, the DSM diagnoses are based on a consensus about clusters of clinical symptoms, not any objective laboratory measure. In the rest of medicine, this would be equivalent to creating diagnostic systems based on the nature of chest pain or the quality of fever. Indeed, symptom-based diagnosis, once common in other areas of medicine, has been largely replaced in the past half century as we have under-stood that symptoms alone rarely indicate the best choice of treatment. Patients with mental disorders deserve better...NIMH will be reorienting its research away from DSM categories."...*

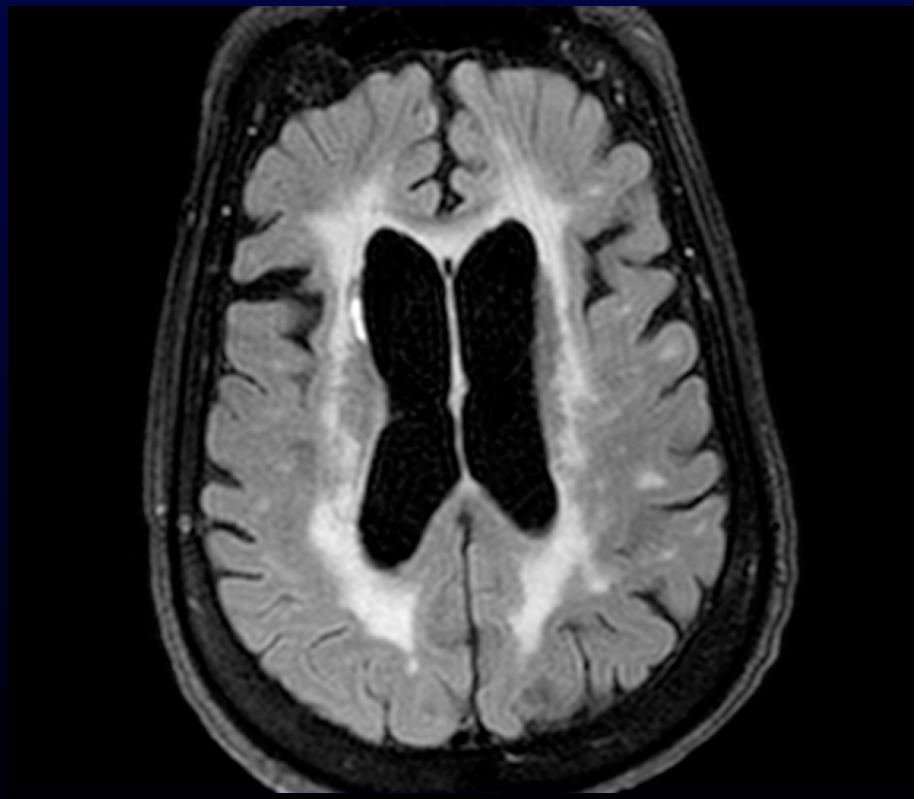
*http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml*

# Imaging "Signature"

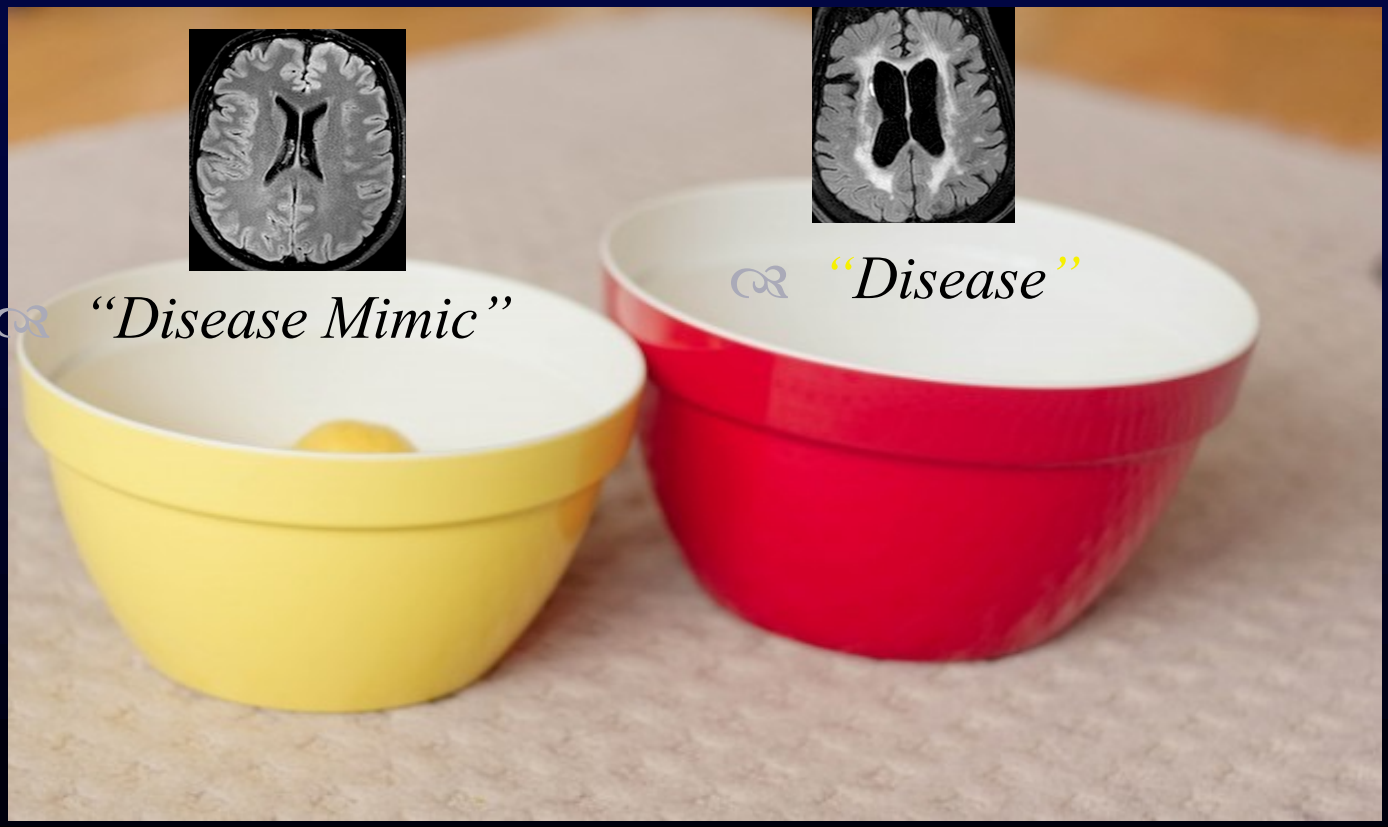
- ~~Control~~ "Mimic"



- Disease

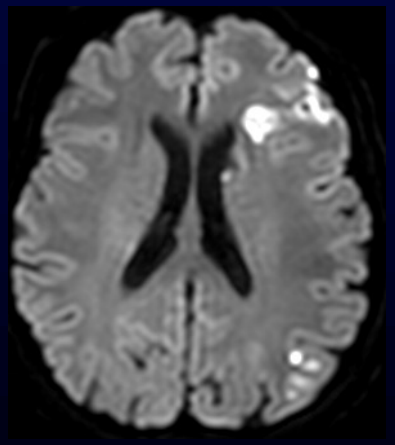


# Sorting into Containers

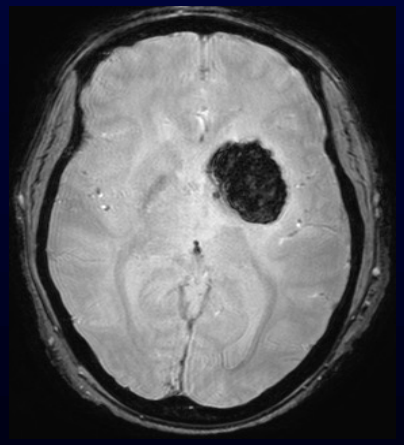


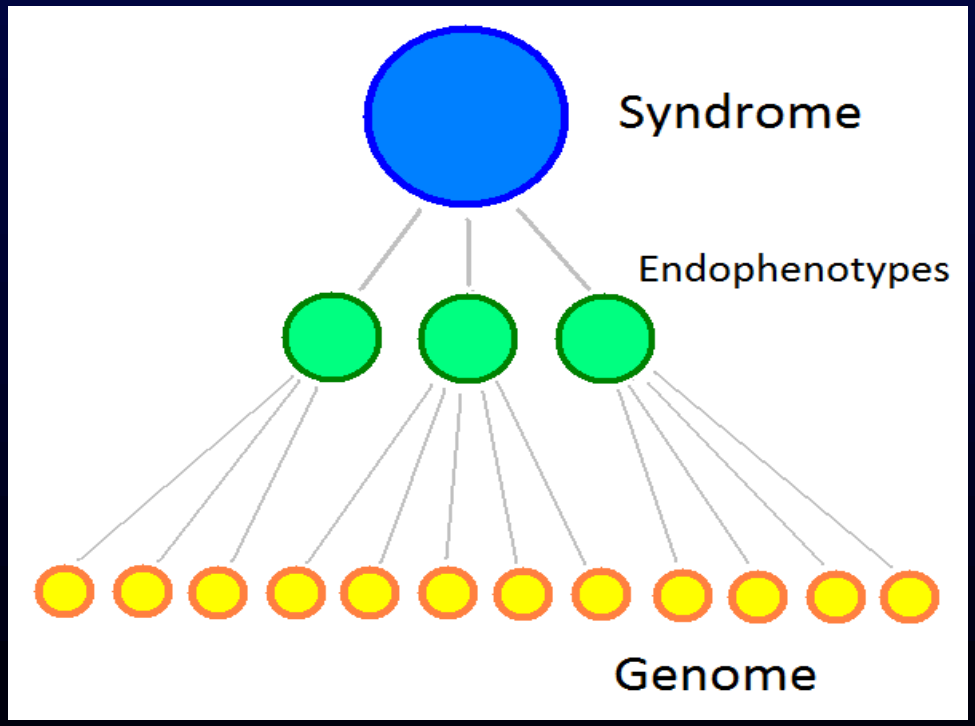
# Symptom Based Classification

*Aphasia*



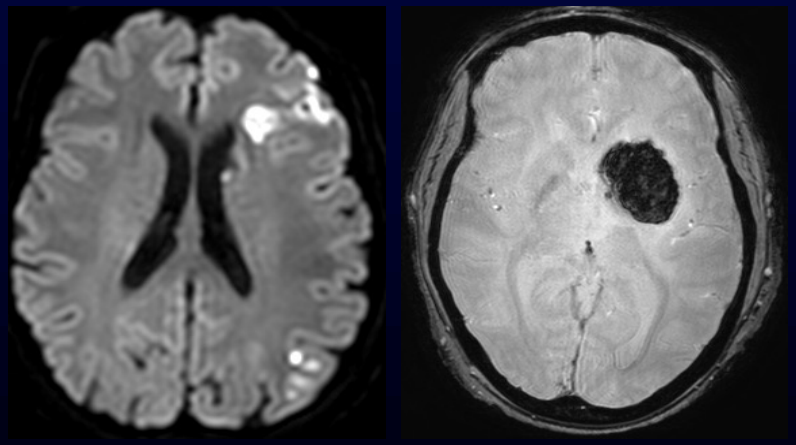
*Nausea*

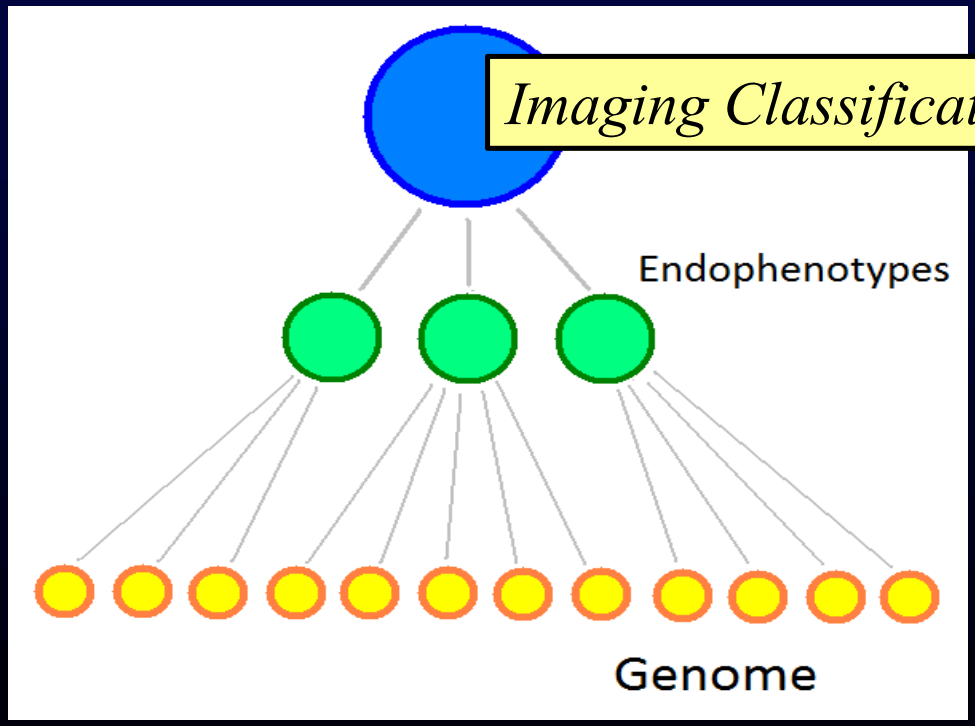




# Imaging Based Classification

*Ischemic* *Hemorrhagic*





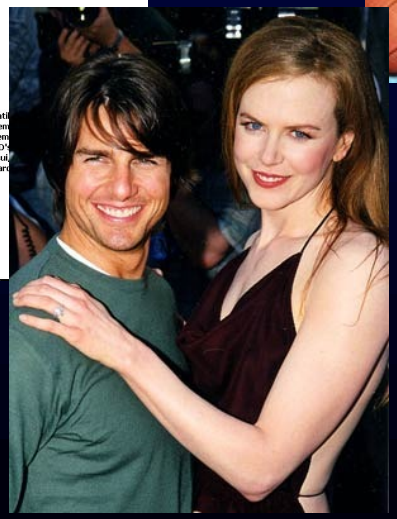
# Stroke Dx…Guiding Premise:

- Image contrast mechanisms directly attributable to pathophysiology (biology of stroke) will provide a more precise diagnosis and stratification of stroke, and thereby lead to better therapy and and improved outcome.

# 1992

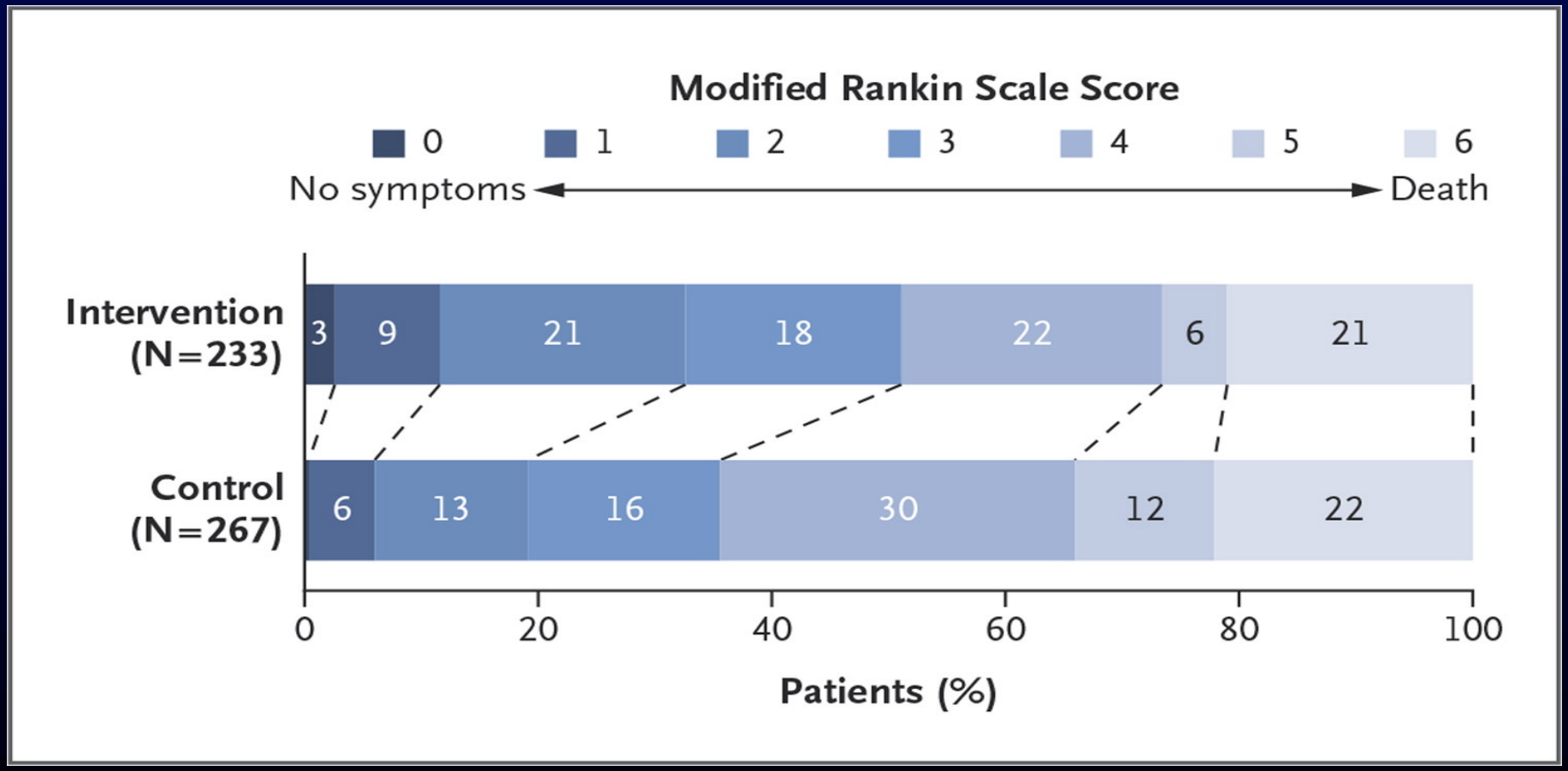

ANATOMIA DO "GRUNGE"
Decadentium pearljamis
A aparente calma do grunge deriva da erva que fuma (daí os olhos constantemente semi cerrados)
Cabelo longo e descuidado estilo ancião muçulmano.
Cara de serenidade, o Grunge atinge o seu nirvana constantemente.
Camisa decadente. Há que parecer naturalmente envelhecida, com buracos e um cor esbatida. No entanto, para alcançar o efeito mais rapidamente, o grunge pisa-a, passa-a com o carro por cima, queima-a, atira-a aos porcos, etc. Por baixo sempre uma T-Shirt da primeira tourné dos Pearl Jam, assinada pelos membros da banda.


U2 LIVE, SPRINGSTEEN PREVIEW
Rolling Stone
NEW FACES OF ROCK
1992
NIRVANA
Inside the Heart and Mind of KURT COBAIN
SEATTLE SCENE
The New Liverpool
CITIZEN GE
By William Greider



# Why doesn't anyone care?

*Modified Rankin Scale Scores at 90 Days in the Intention-to-Treat Population.*




Berkhemer OA et al. N Engl J Med 2015;372:11-20.

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# Failure of Trials in Stroke

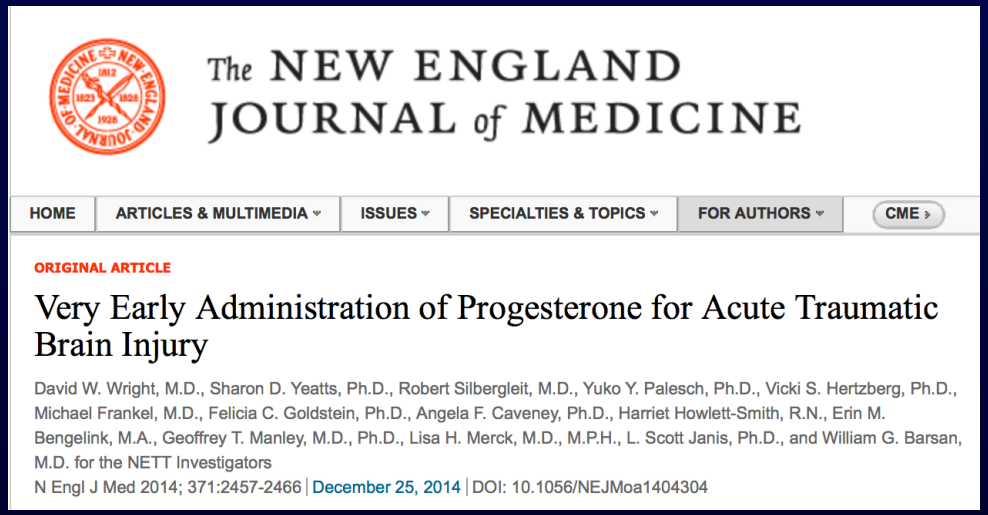
- Neuroprotective agents tested 49
- RCTs performed 114
- Patients enrolled 21,445
- Neuroprotective agents approved 0

*- Kidwell, Liebeskind, Starkman, Saver, Stroke 2001*

- Drug didn't reach brain =

$100 million (US)

# Failed Clinical Trials in TBI



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ORIGINAL ARTICLE

Very Early Administration of Progesterone for Acute Traumatic Brain Injury

David W. Wright, M.D., Sharon D. Yeatts, Ph.D., Robert Silbergleit, M.D., Yuko Y. Palesch, Ph.D., Vicki S. Hertzberg, Ph.D., Michael Frankel, M.D., Felicia C. Goldstein, Ph.D., Angela F. Caveney, Ph.D., Harriet Howlett-Smith, R.N., Erin M. Bengelink, M.A., Geoffrey T. Manley, M.D., Ph.D., Lisa H. Merck, M.D., M.P.H., L. Scott Janis, Ph.D., and William G. Barsan, M.D. for the NETT Investigators

N Engl J Med 2014; 371:2457-2466 | December 25, 2014 | DOI: 10.1056/NEJMoa1404304


## Effect of Citicoline on Functional and Cognitive Status Among Patients With Traumatic Brain Injury

### Citicoline Brain Injury Treatment Trial (COBRIT) FREE

Ross D. Zafonte, DO; Emilia Bagiella, PhD; Beth M. Ansel, PhD; Thomas A. Novack, PhD; William T. Friedewald, MD; Dale C. Hesdorffer, PhD; Shelly D. Timmons, MD; Jack Jallo, MD, PhD; Howard Eisenberg, MD; Tessa Hart, PhD; Joseph H. Ricker, PhD; Ramon Diaz-Arrastia, MD, PhD; Randall E. Merchant, PhD; Nancy R. Temkin, PhD; Sherry Melton, MD; Sureyya S. Dikmen, PhD

[+] Author Affiliations

*JAMA*. 2012;308(19):1993-2000. doi:10.1001/jama.2012.13256.

Text Size: A A A

# Stroke - Last Four Years

The NEW ENGLAND JOURNAL of MEDICINE

*2013*

ORIGINAL ARTICLE

Endovascular Treatment for Acute Ischemic Stroke

Alfonso Ciccone, M.D., Luca Valvassori, M.D., Michele Nichelatti, Ph.D., Annalisa Sgoifo, Psy.D., Michela Ponzio, Ph.D., Roberto Sterzi, M.D., and Edoardo Boccardi, M.D. for the SYNTHESIS Expansion Investigators

N Engl J Med 2013; 368:904-913 | March 7, 2013 | DOI: 10.1056/NEJMoa1213701

ORIGINAL ARTICLE

A Correction Has Been Published

Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke

ORIGINAL ARTICLE

A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke

*2015*

ESTABLISHED IN 1812 JANUARY 1, 2015 VOL. 372 NO. 1

A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

ORIGINAL ARTICLE

Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection

ORIGINAL ARTICLE

Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke

SWIFT PRIME: 'Dramatic' Benefit of Stent Retriever in Stroke

Sue Hughes

February 11, 2015

# NNT ~ 3

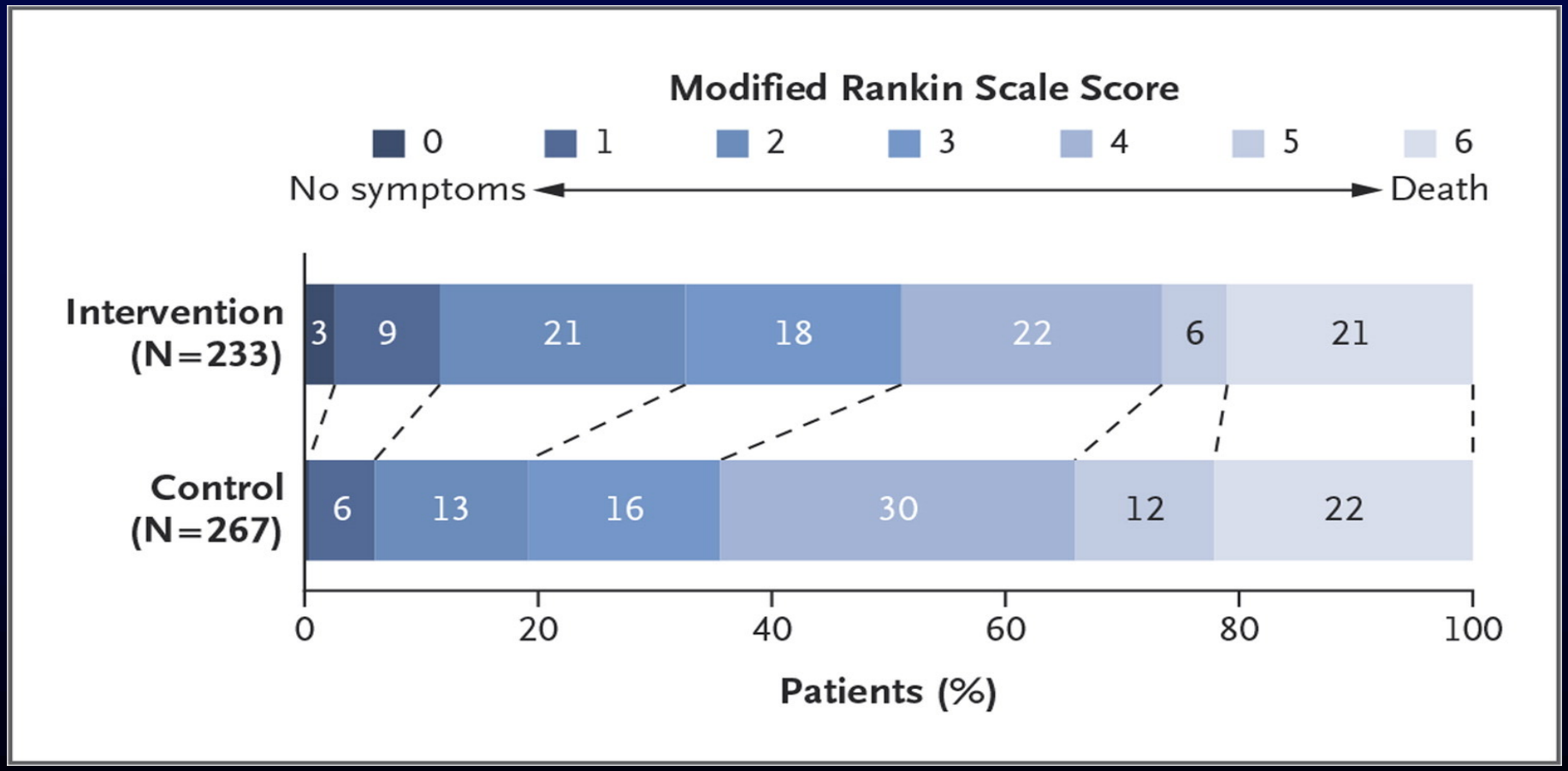
*Defibrillation NNT = 2.5*

*Screening Mammogram NNT ~ inf*

*Screening Mammogram NNH = 5*

*www.thennt.com*

*Modified Rankin Scale Scores at 90 Days in the Intention-to-Treat Population.*




Berkhemer OA et al. N Engl J Med 2015;372:11-20.

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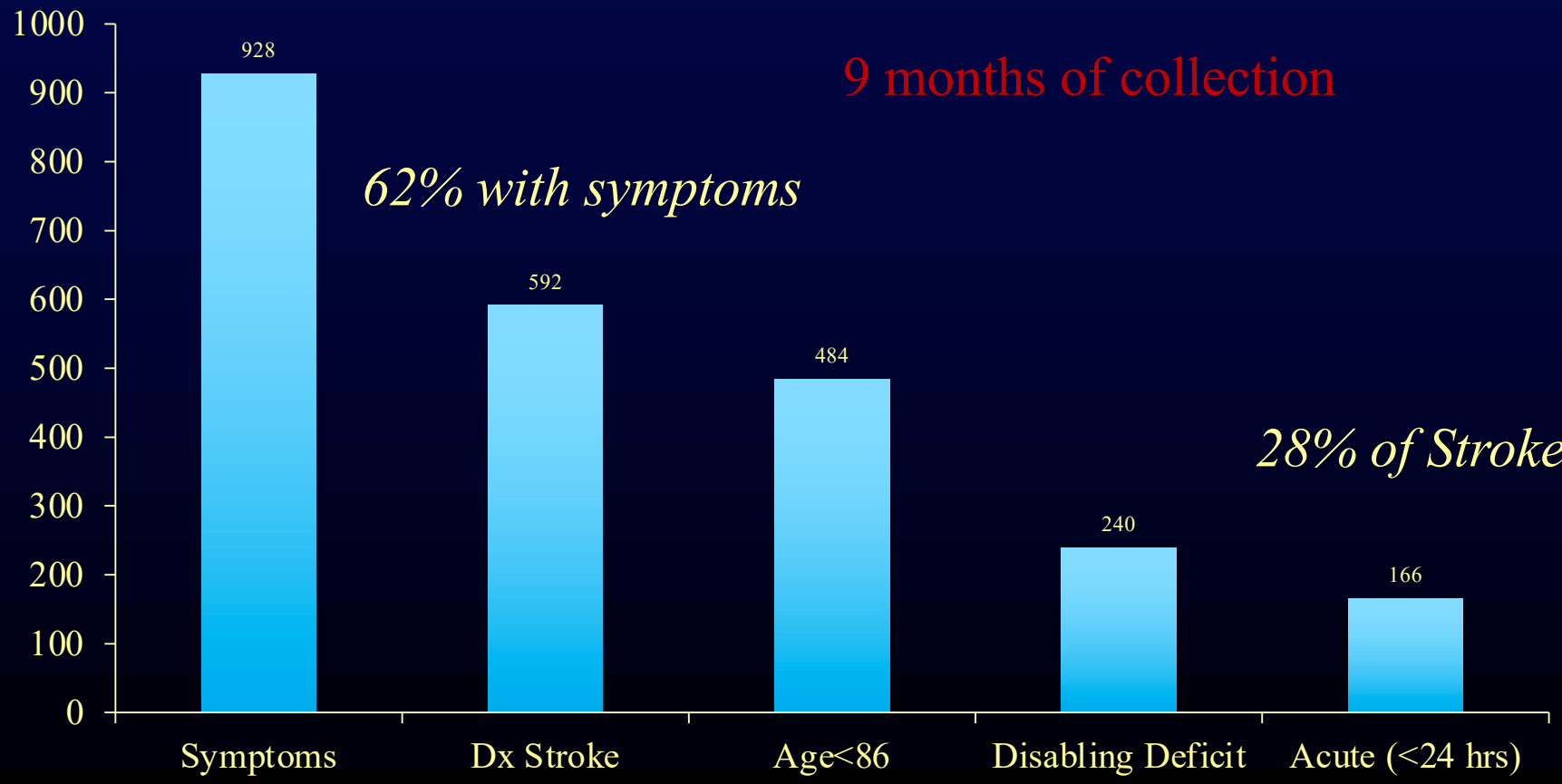
# What is best in life?

*Symptoms*

~~*Biological*~~

# Symptoms Target

*L. Davis et al, NINDS 2011*



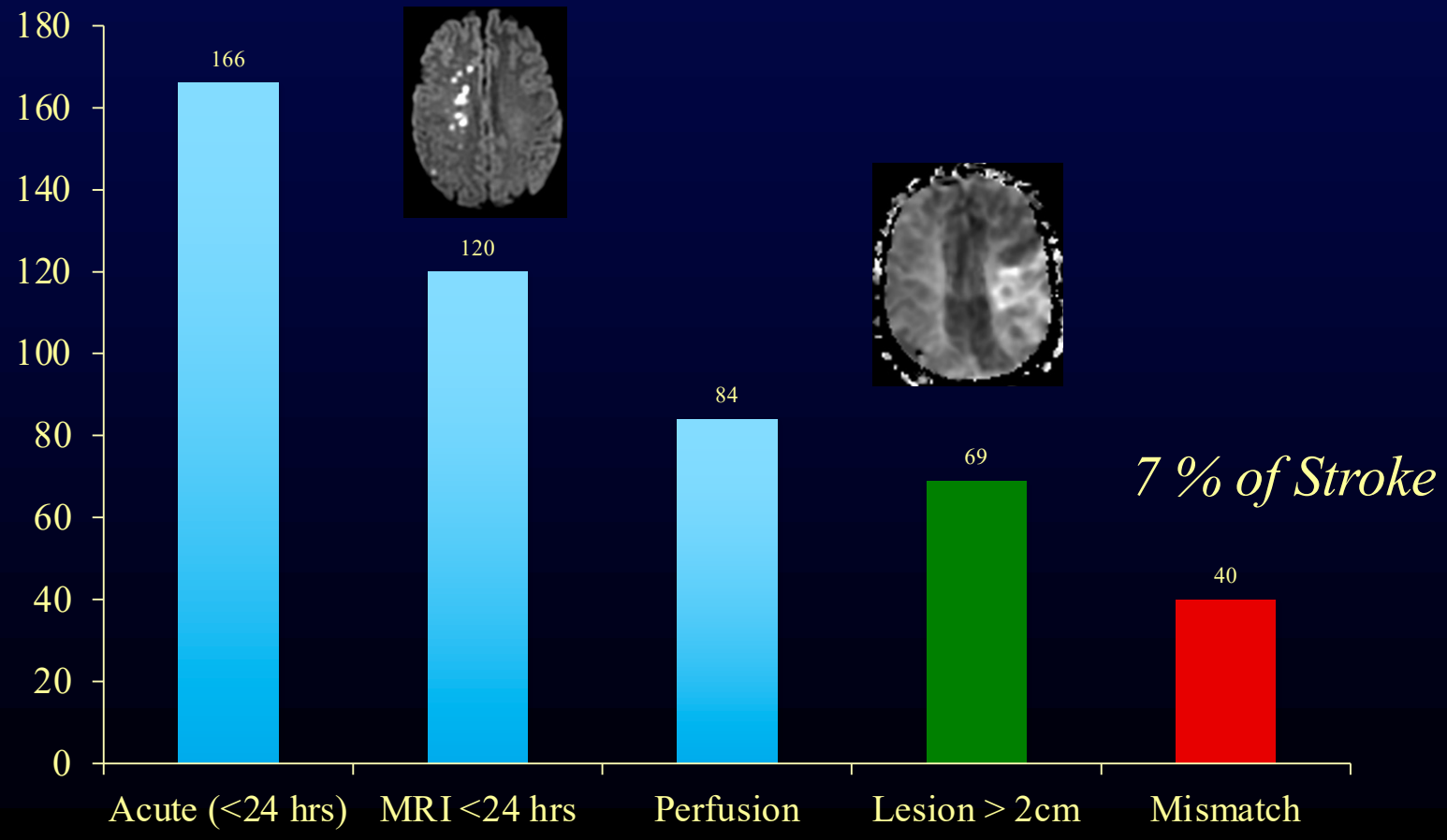
# What is best in life?

~~*Symptoms*~~

*Biological*

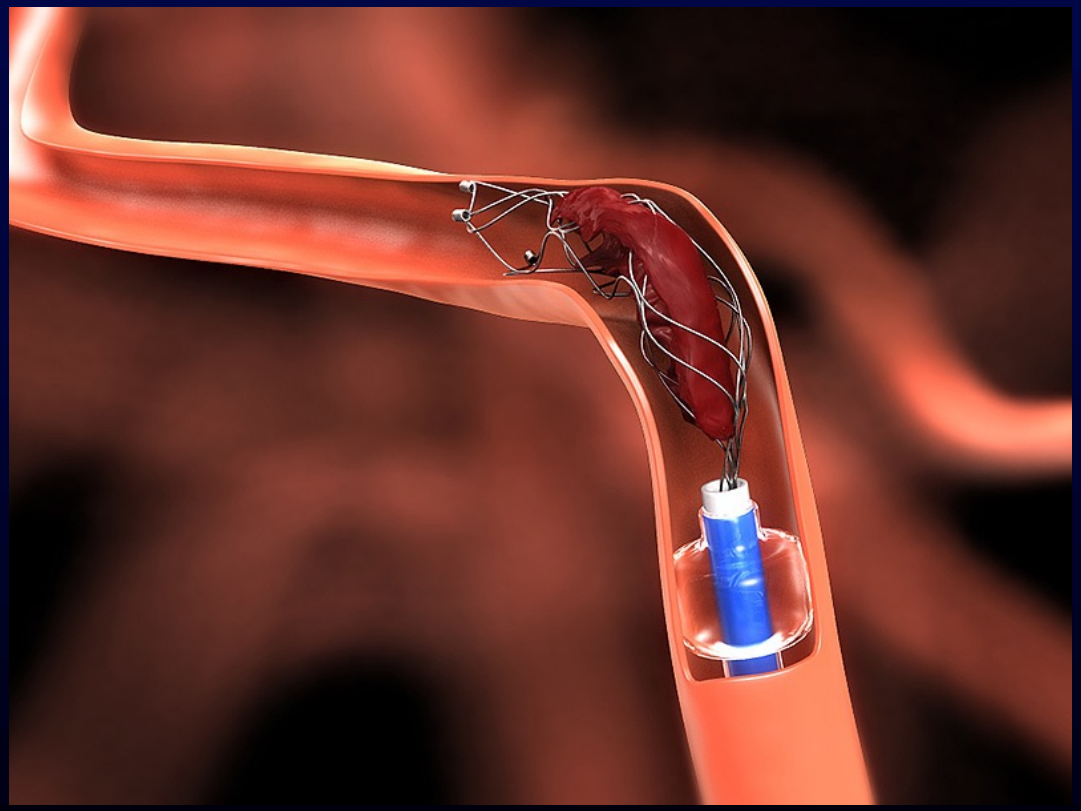
# Biological Target

*L. Davis et al, NINDS 2011*




*7 % of Stroke*

# Stent Retriever



**…predementia reminder #2 …**

**Endo 1 IR then Outcome**

**Endo 2**

# Failure of Trials in Stroke

- Neuroprotective agents tested 49
- RCTs performed 114
- Patients enrolled 21,445
- Neuroprotective agents approved 0

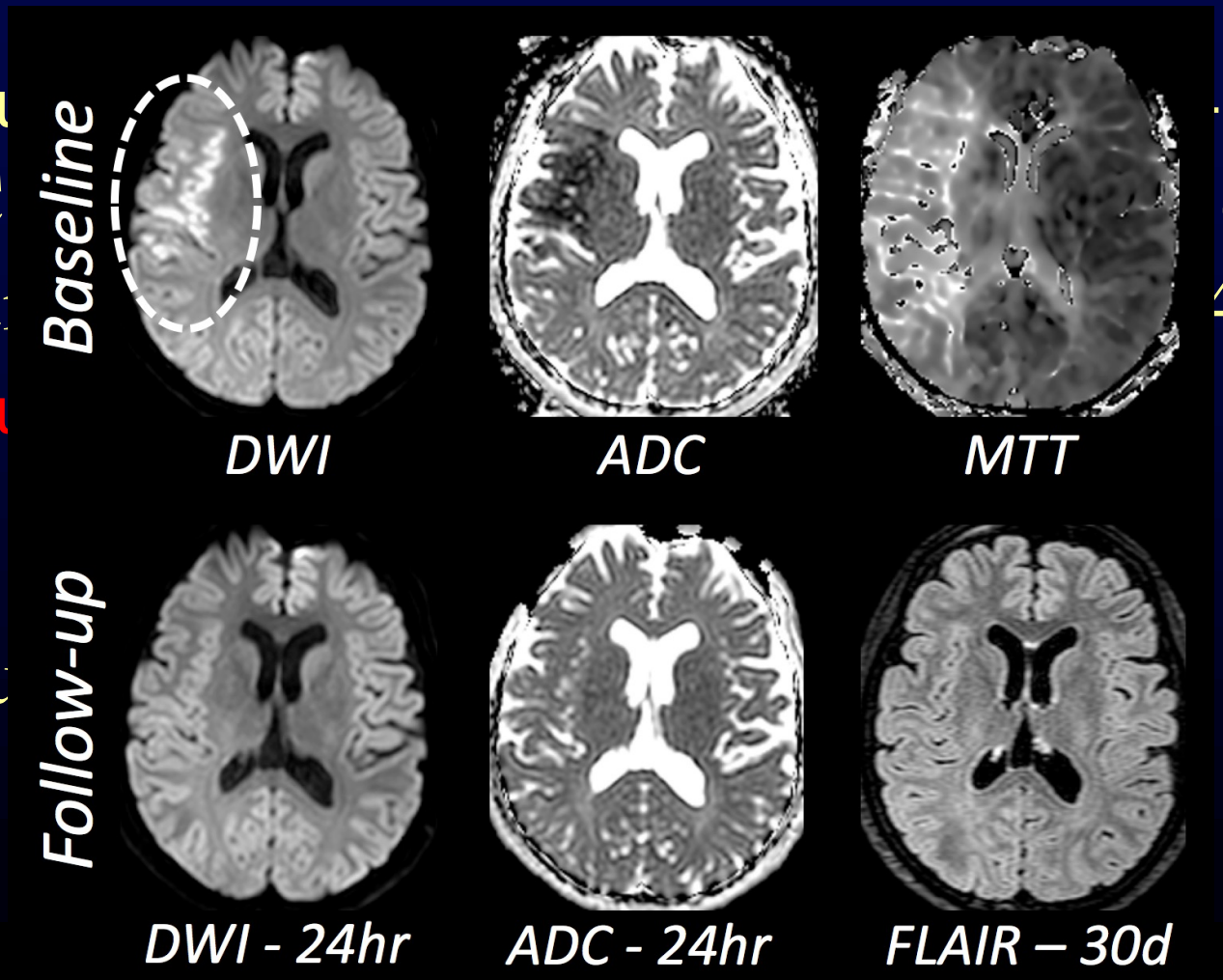
*- Kidwell, Liebeskind, Starkman, Saver, Stroke 2001*

- Drug didn't reach brain =

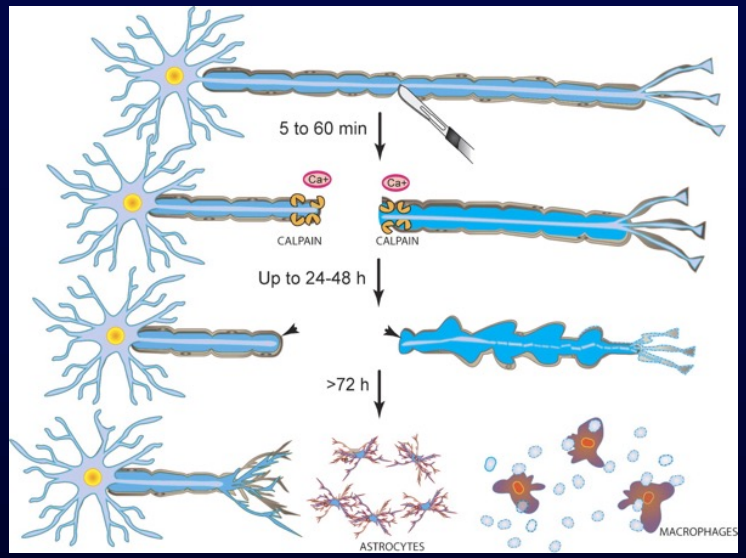
$100 million (US)

# Neuroprotection, revisited

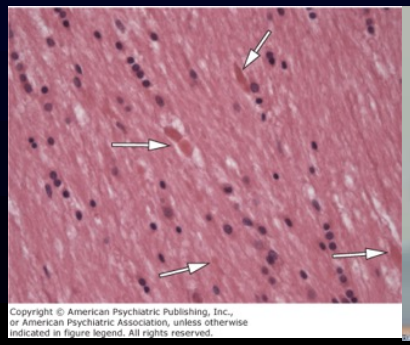
- Neu
- RC
- Pat
- Neu
- Dru



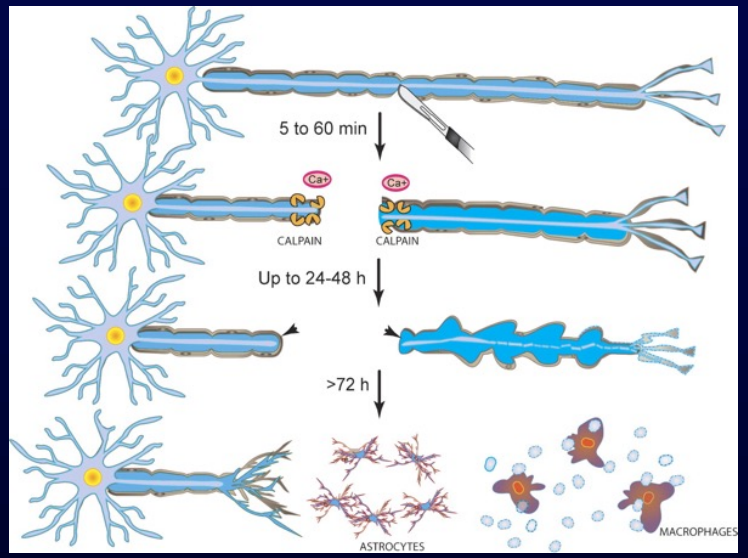
# mTBI



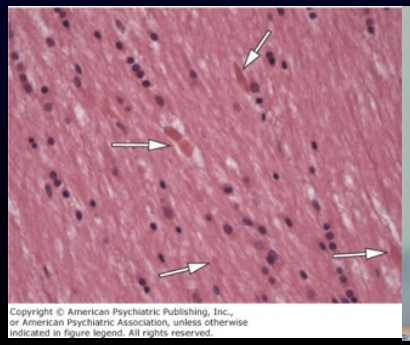

*J Wang et al, JCB vol. 196 no. 1 7-18*

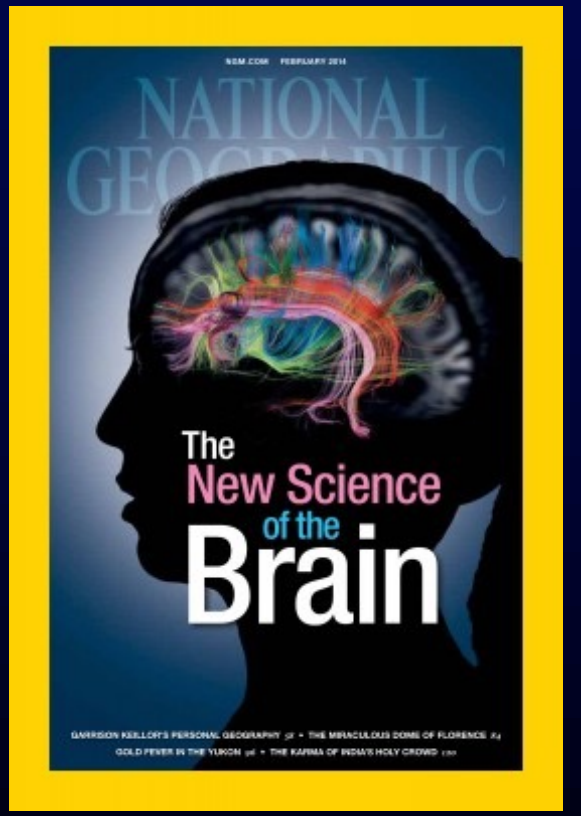



# Dominant Paradigm




*J Wang et al, JCB vol. 196 no. 1 7-18*



# Axonal injury

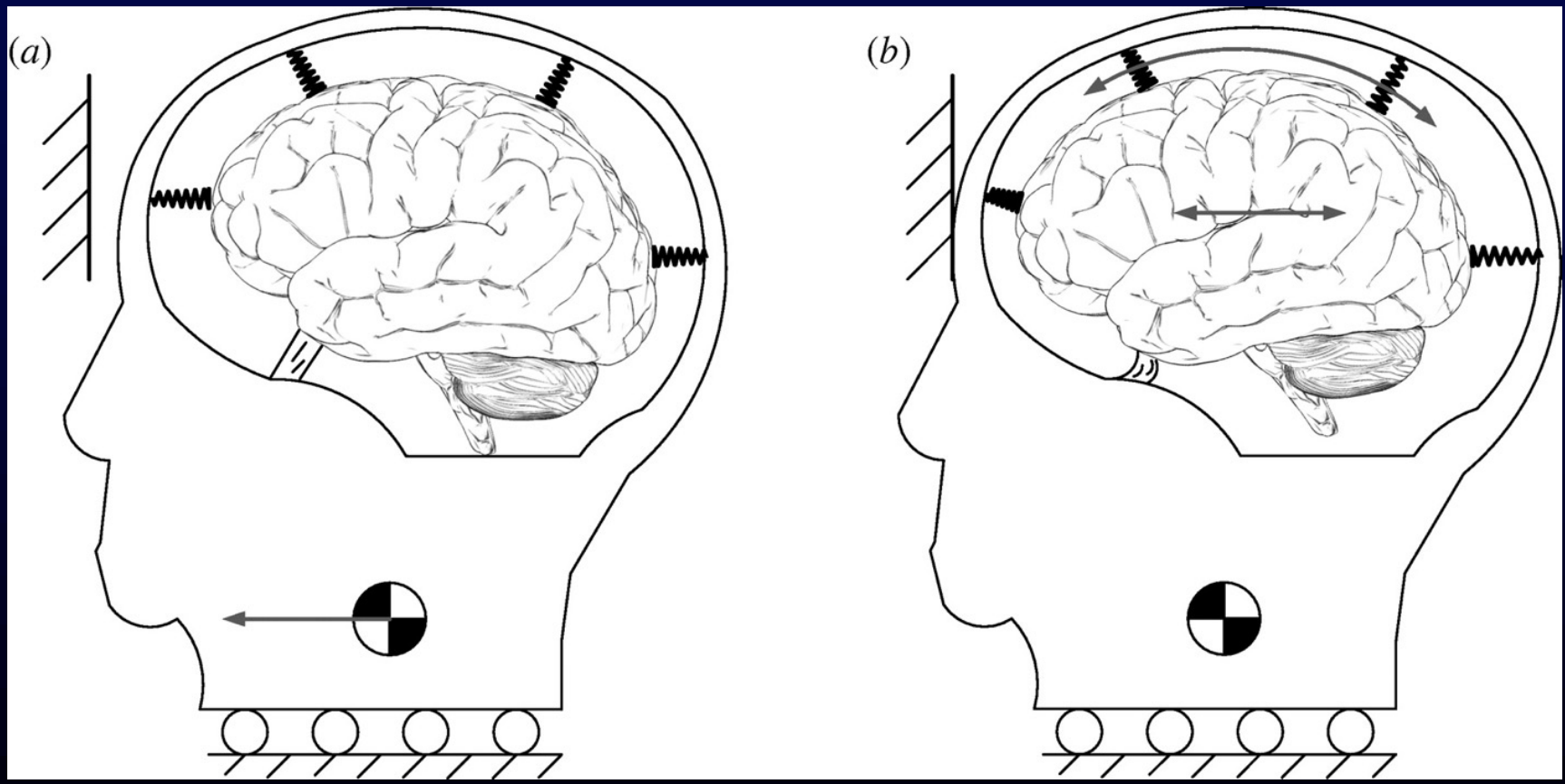
- Assumed to be the problem in mTBI
- …ergo DTI the solution
- “Ask impertinent questions…get pertinent answers”

*Mild Traumatic Brain Injury*

Postulate:

*Following head trauma, brain injury is mediate by damage to the meninges and related vasculature.*

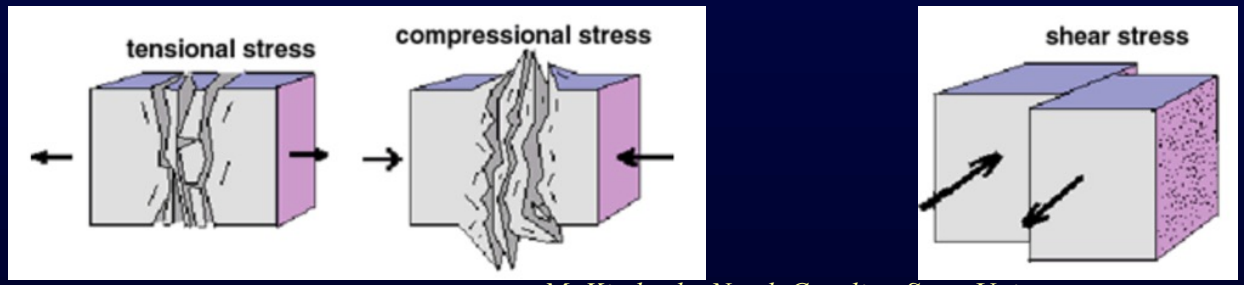
# Simplified Model for Displacement




*Y. Feng et al, J R Soc Interface. Dec 6, 2010; 7(53): 1677–1688*

# Compression and Shear Forces

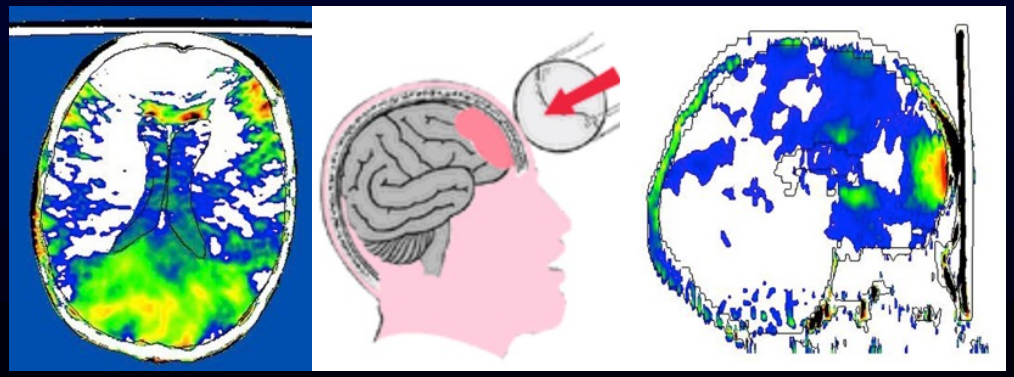
- Compression/dilatation
- Shear







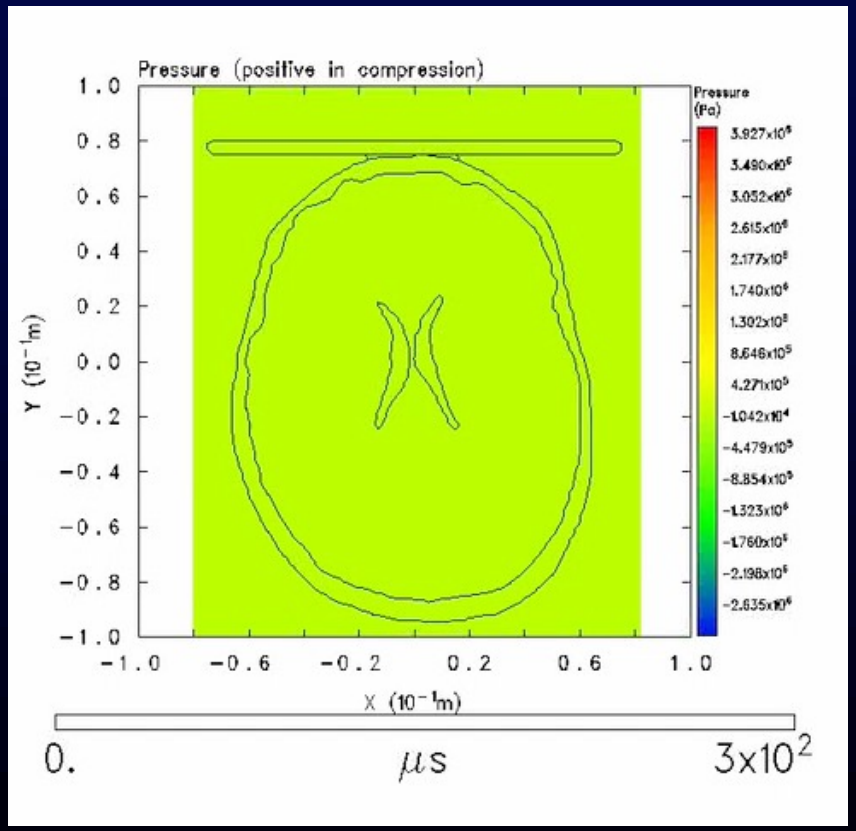
*M. Kimberly, North Carolina State Univ.*

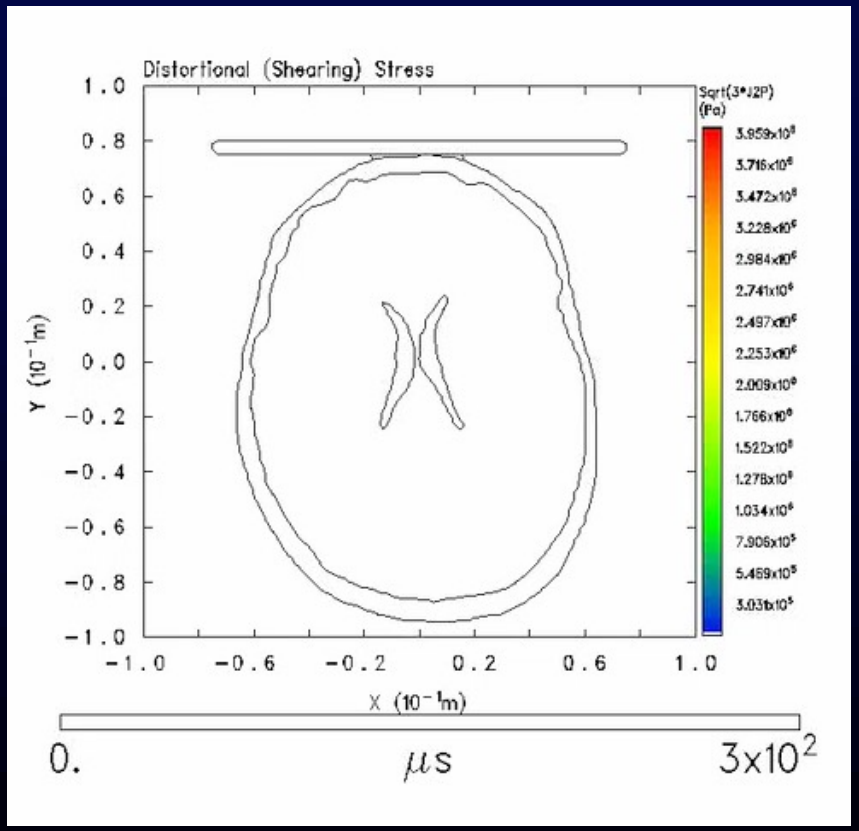


*P.A. Taylor et al., Sandia National Laboratories, 2007*

# Acoustic Elastic-plastic Deformation

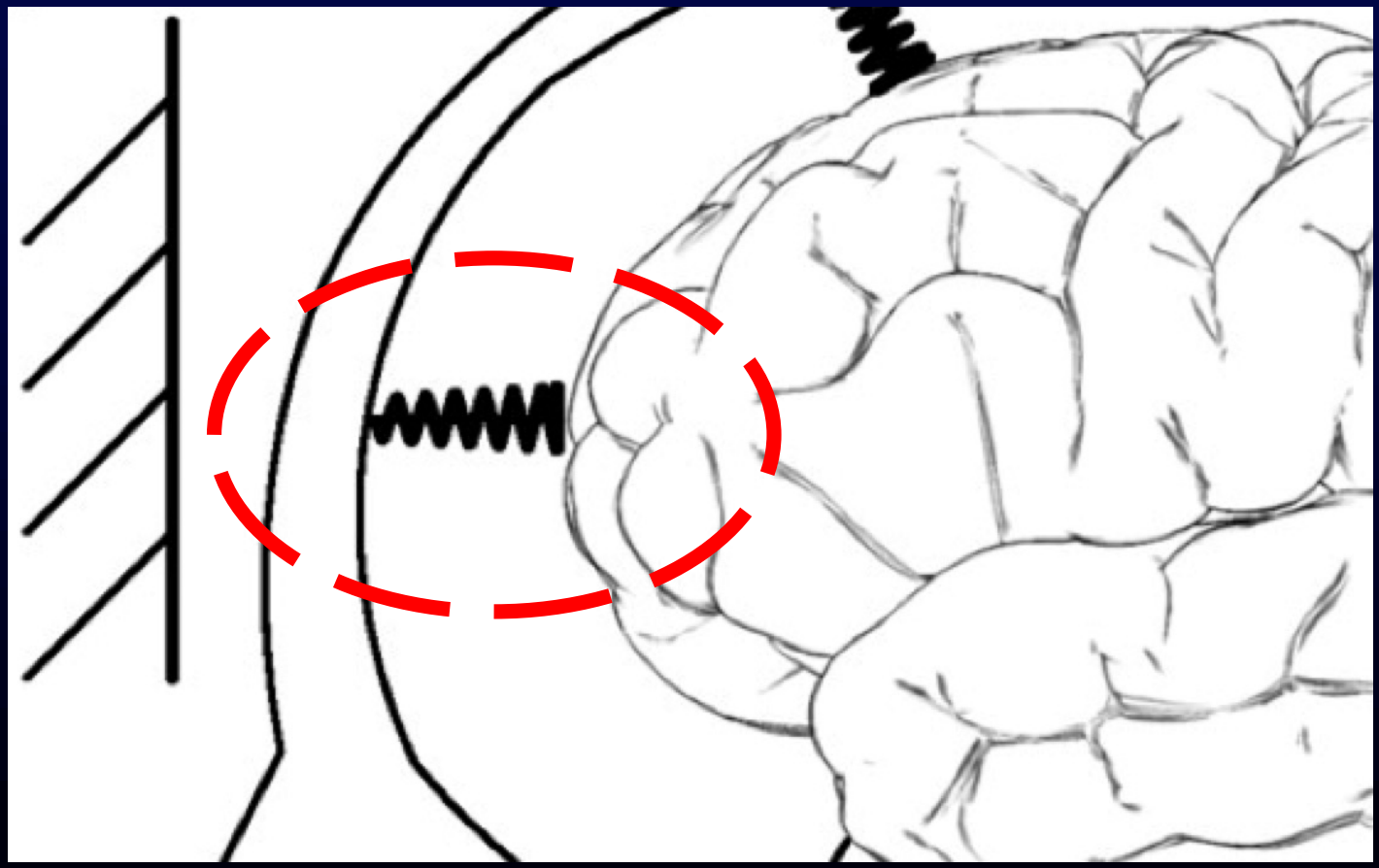
*Its all over in under 1 second.*



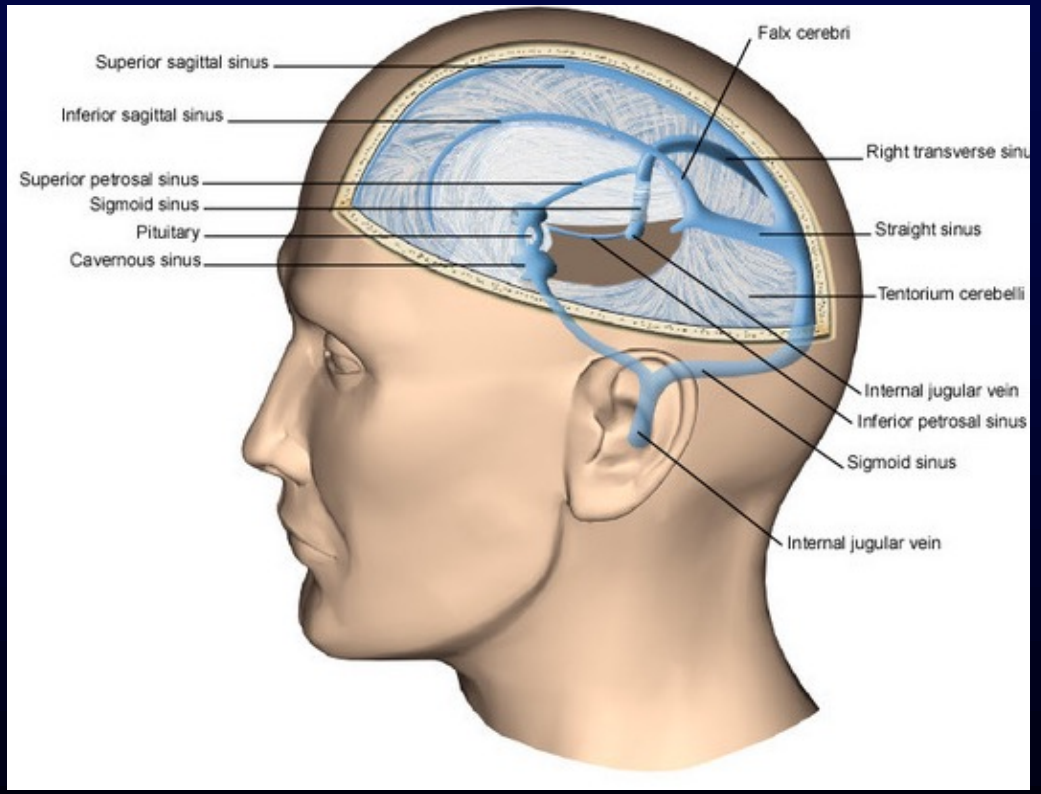




*P.A. Taylor et al., Sandia National Laboratories, 2007*

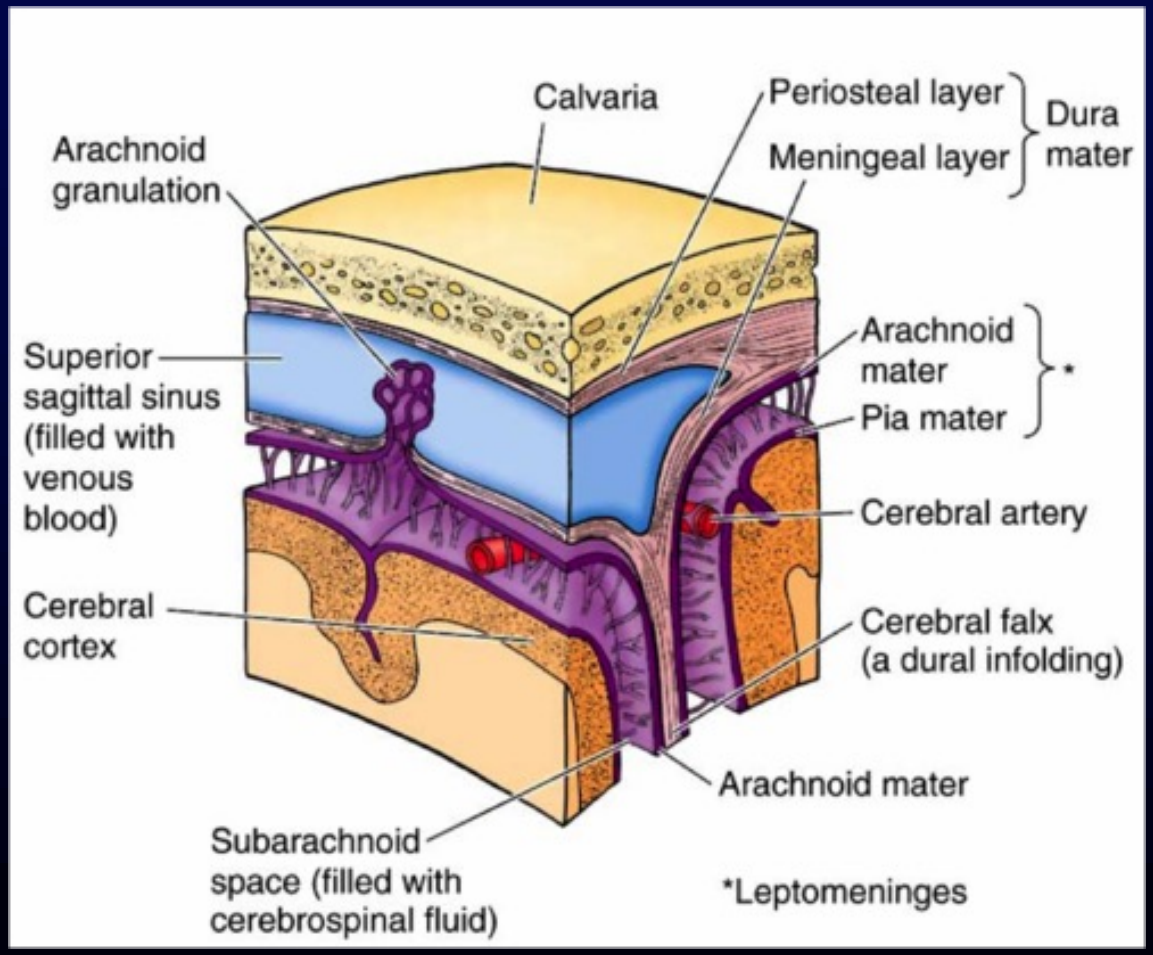
# Lets look a bit more carefully…



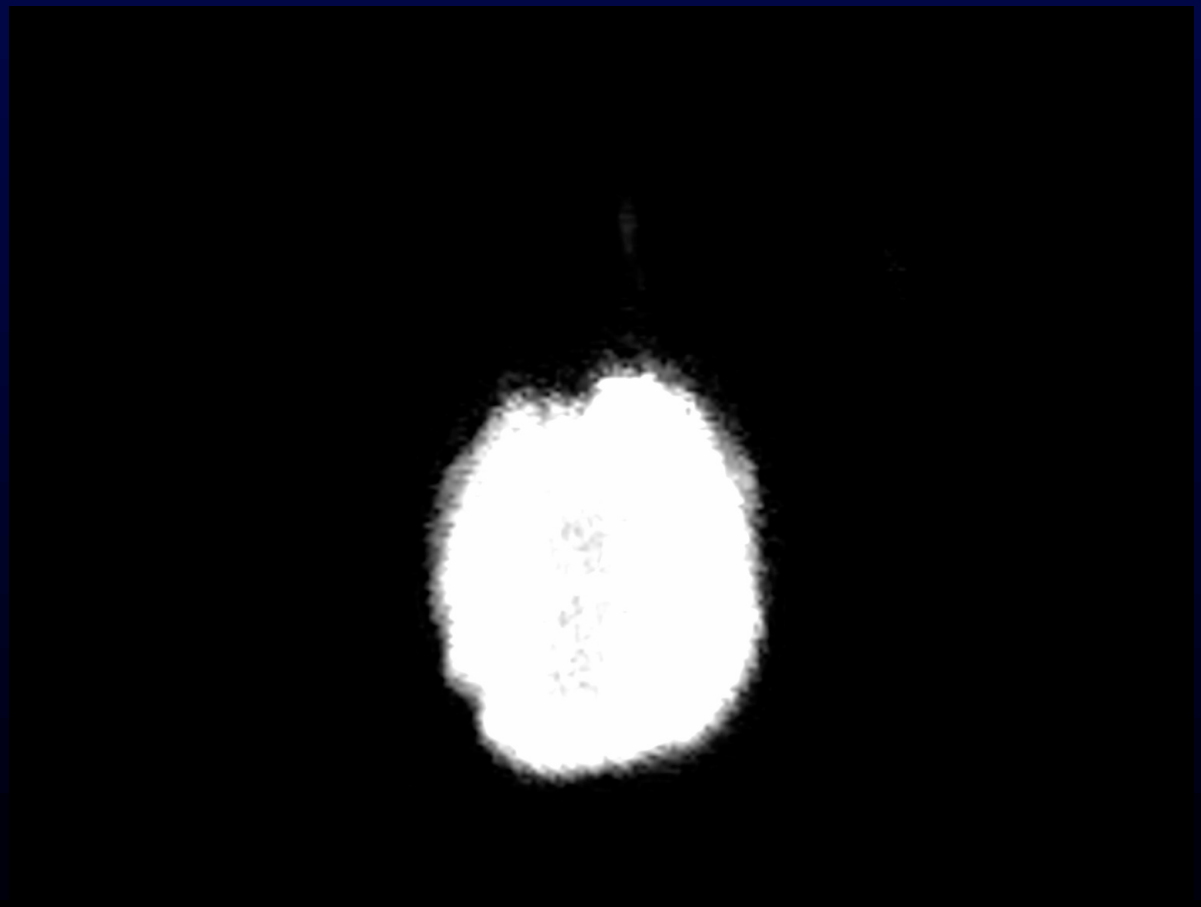
# Sinus, Falx and Tent



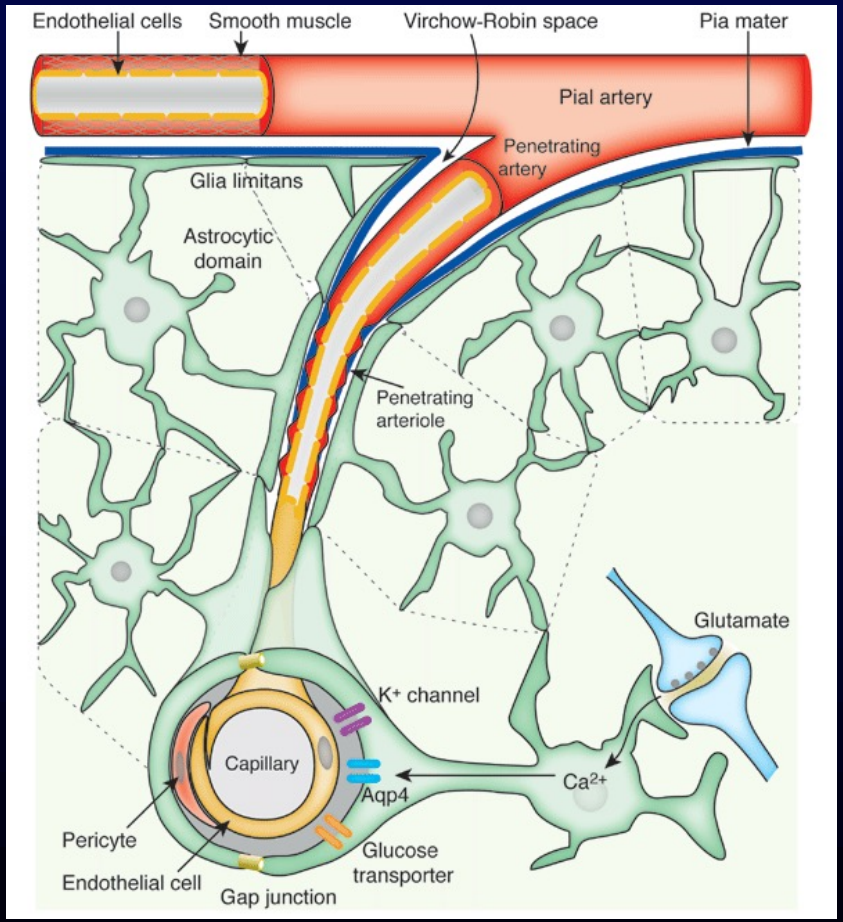
# Components of Meninges



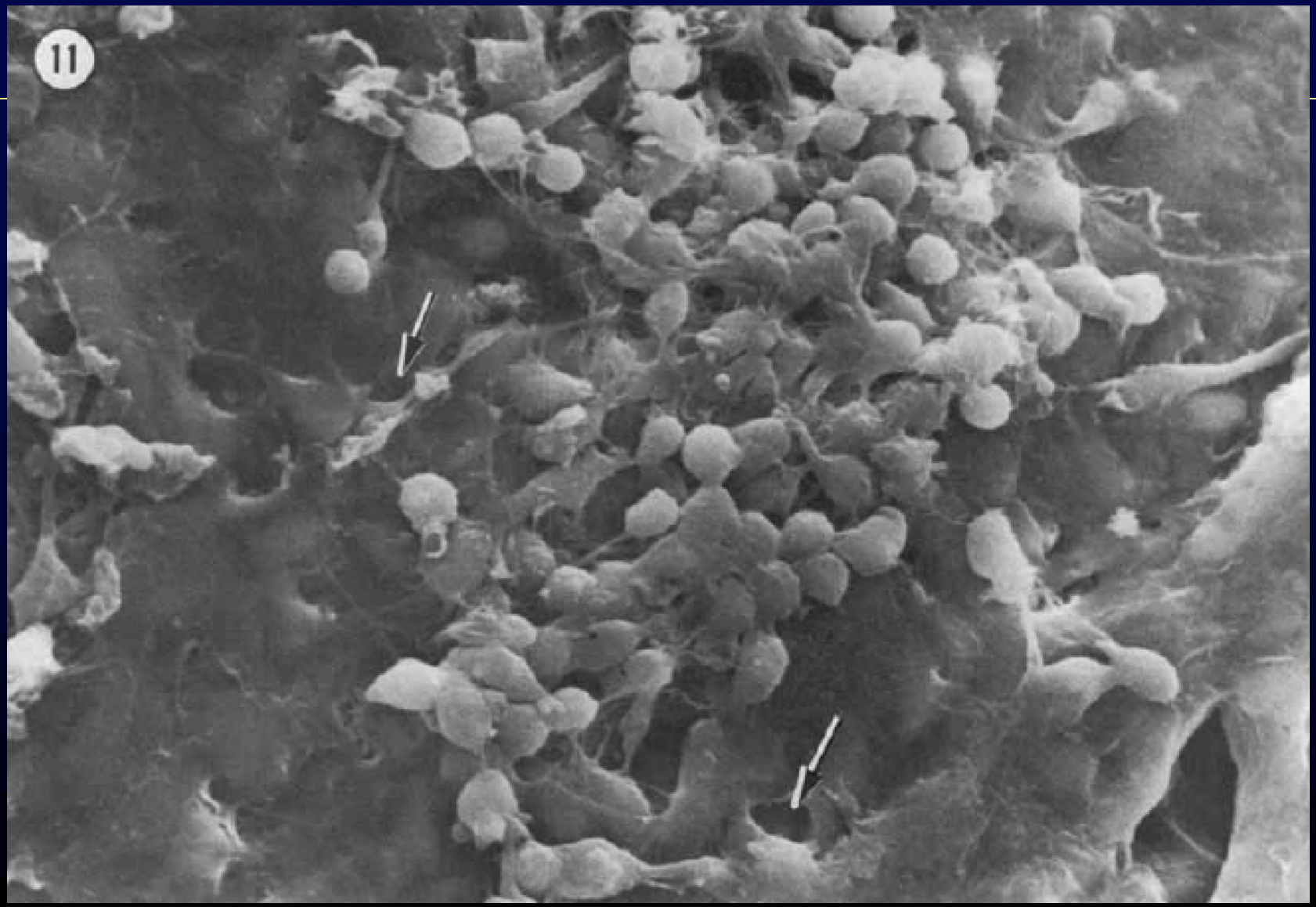
# Vessels in the Meninges



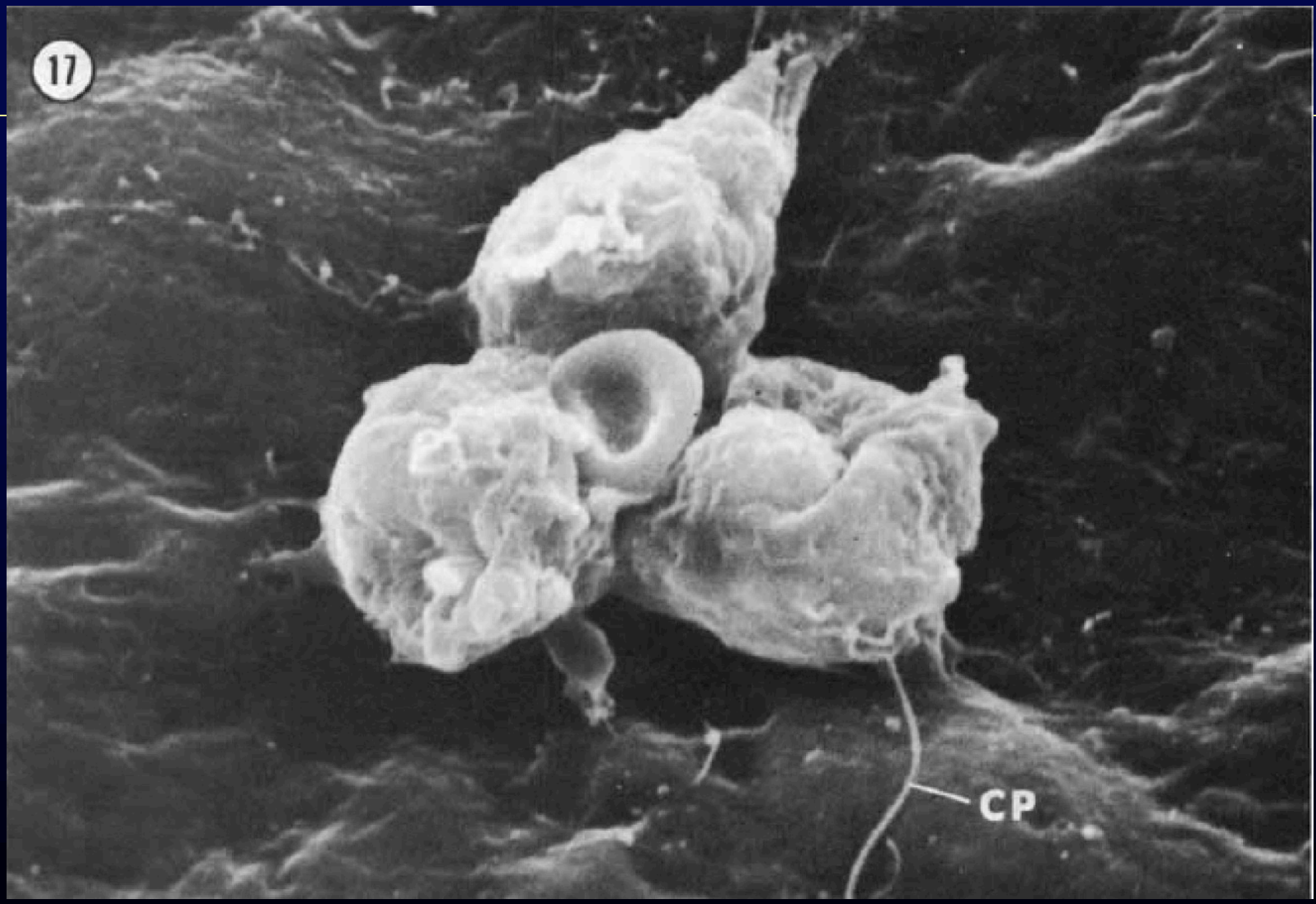
# Glial Limitans and the BBB




*Iadecola and Nedergaard, Nature Neuroscience* **10**, 1369 - 1376 (2007)

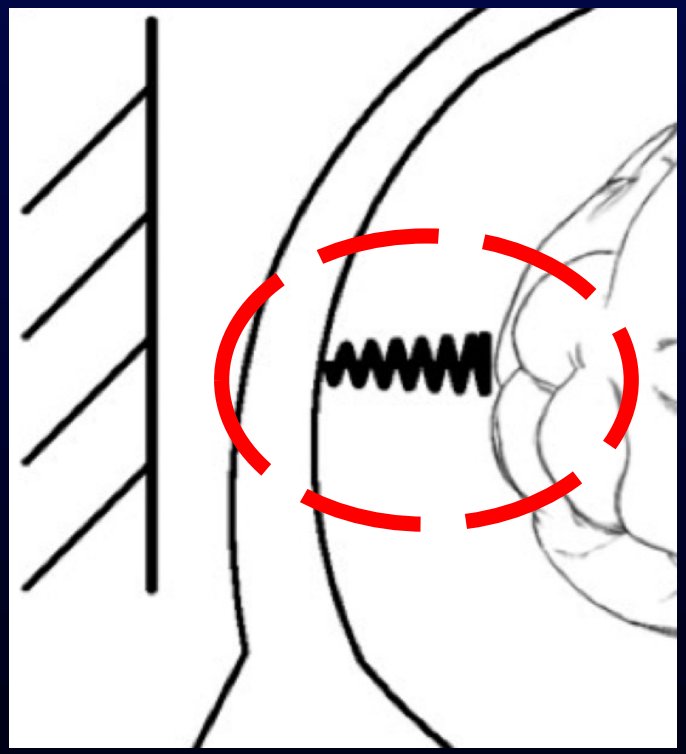



*Allen and Low, J Comp Neurol. 1975 Jun 15;161(4):515-39*




*Allen and Low, J Comp Neurol. 1975 Jun 15;161(4):515-39*

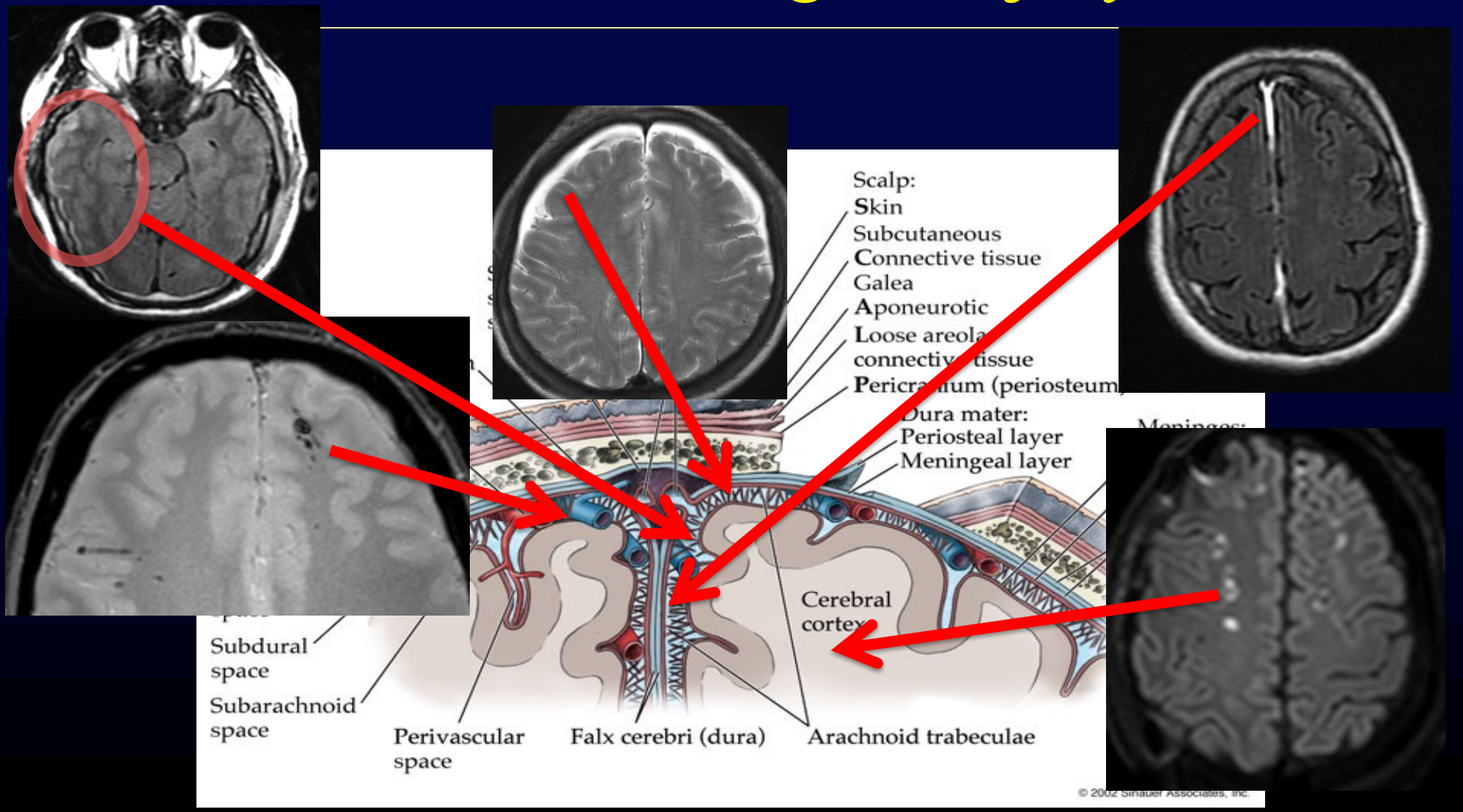
# Simple Spring? …nope



- Layers
  - Glial Limitans
  - Pia
  - Arachnoid
  - Meningeal Dura
  - Periosteal Dura
- Structures
  - Superficial vessels
  - Bridging veins
  - Arachnoid trabeculae
  - Arachnoid villi
  - Inervation
  - Falx and tentorium
- Spaces
  - Basement
  - Perivascular
  - Subarachnoid
  - Subdural (potential)
  - Venous lacuna
  - Epidural (potential)

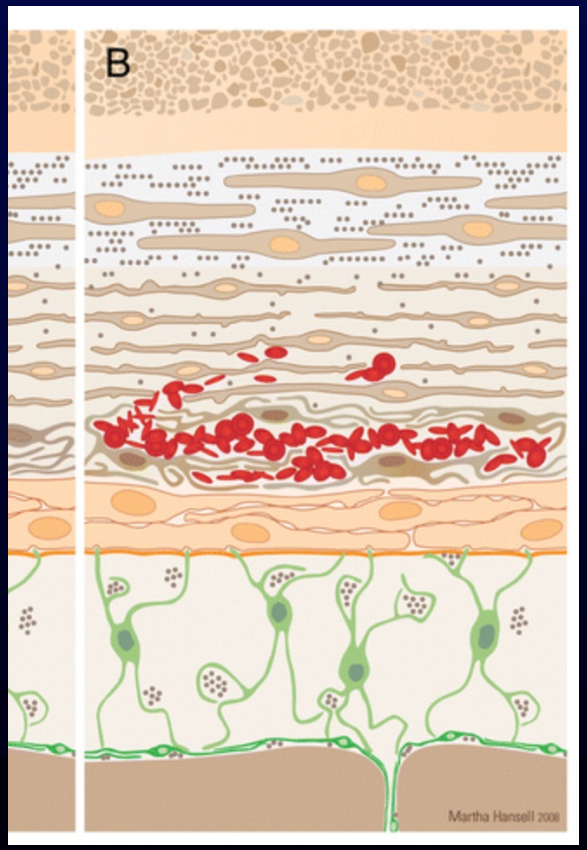
Is there evidence of damage to these structures following head injury?

# Thesis: Meningeal Injury

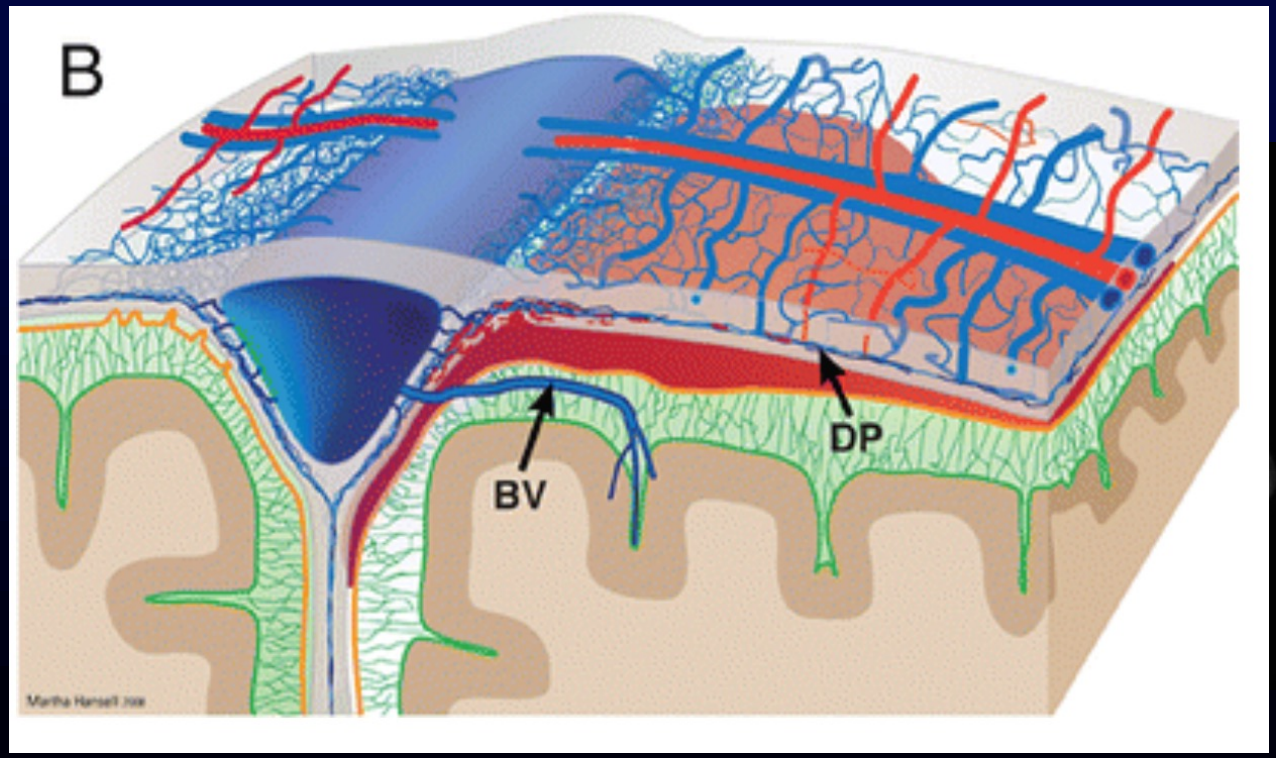



*Blumenfeld Neuroanatomy through Clinial Cases, Sinauer Assoc. Inc, 2002. , p 122.*

# Bleeding at the Dural Border




**Subdural**

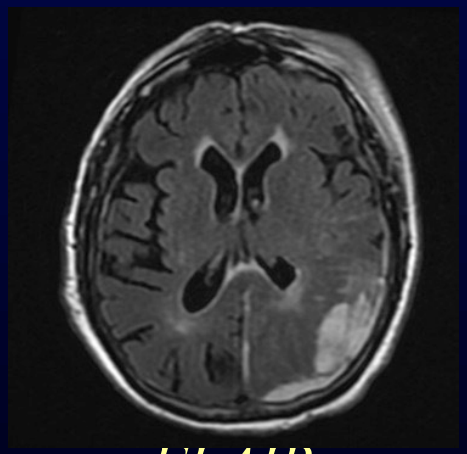



*J. Mack, Pediatr Radiol. 2009 Mar;39(3):200-10*

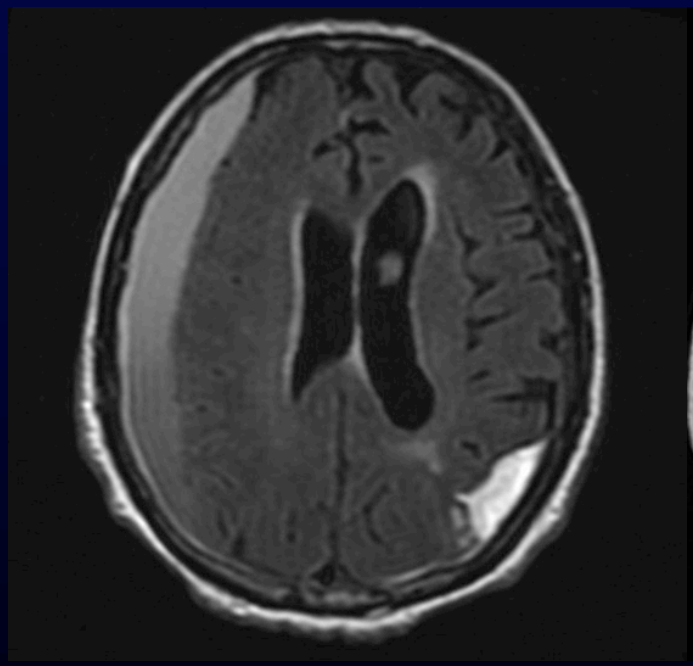
# Subdural Effusion

*90 Day Follow-up*

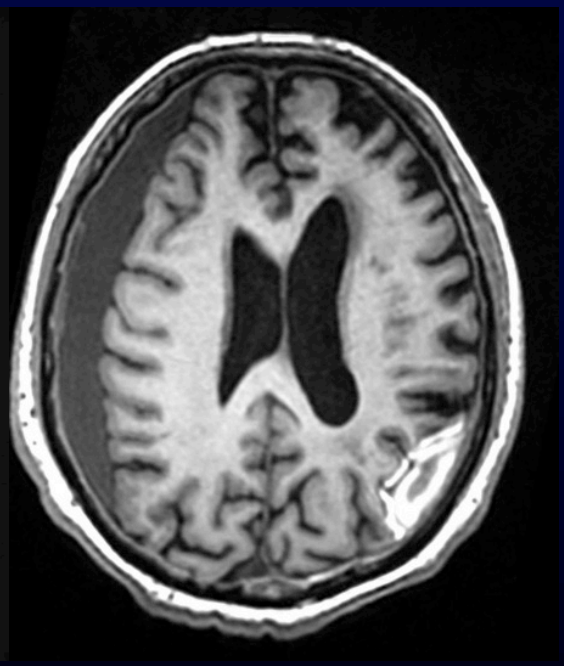
*Acute*



*FLAIR*



*FLAIR*



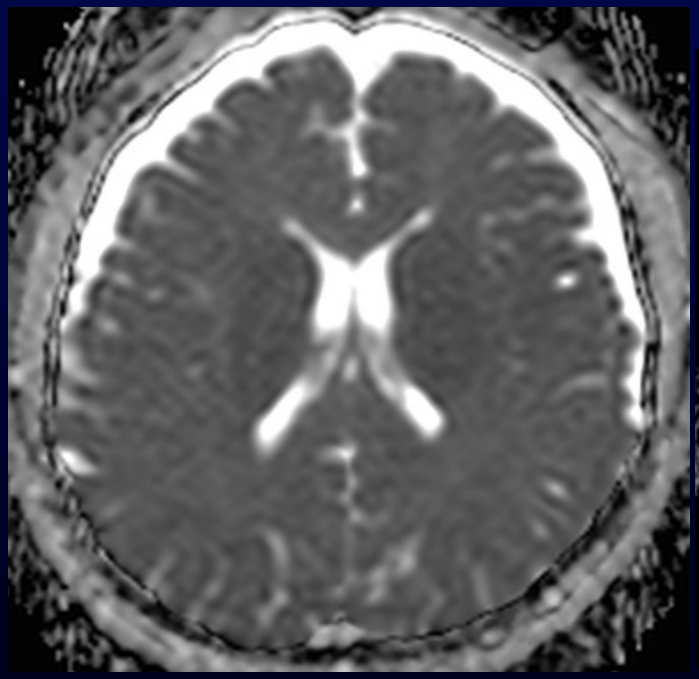
*3D T1*

# Shaken Baby Syndrome – SDH?

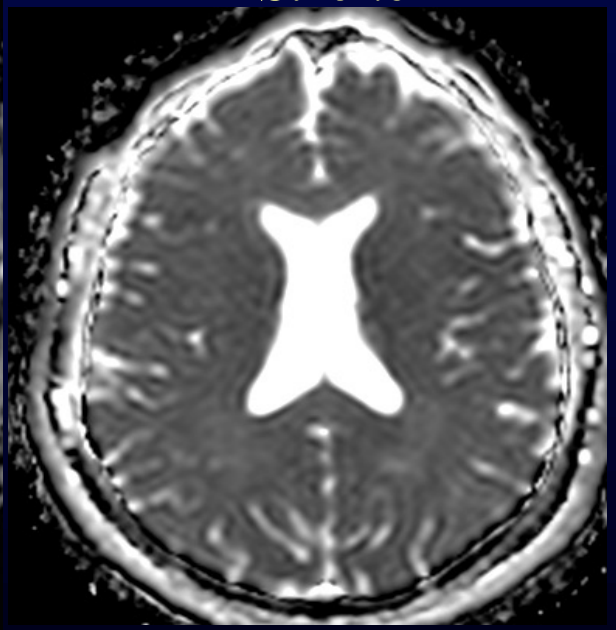
*6-mo old*

*http://www.asnr.org/neurographics/2/1/1/3.shtml*

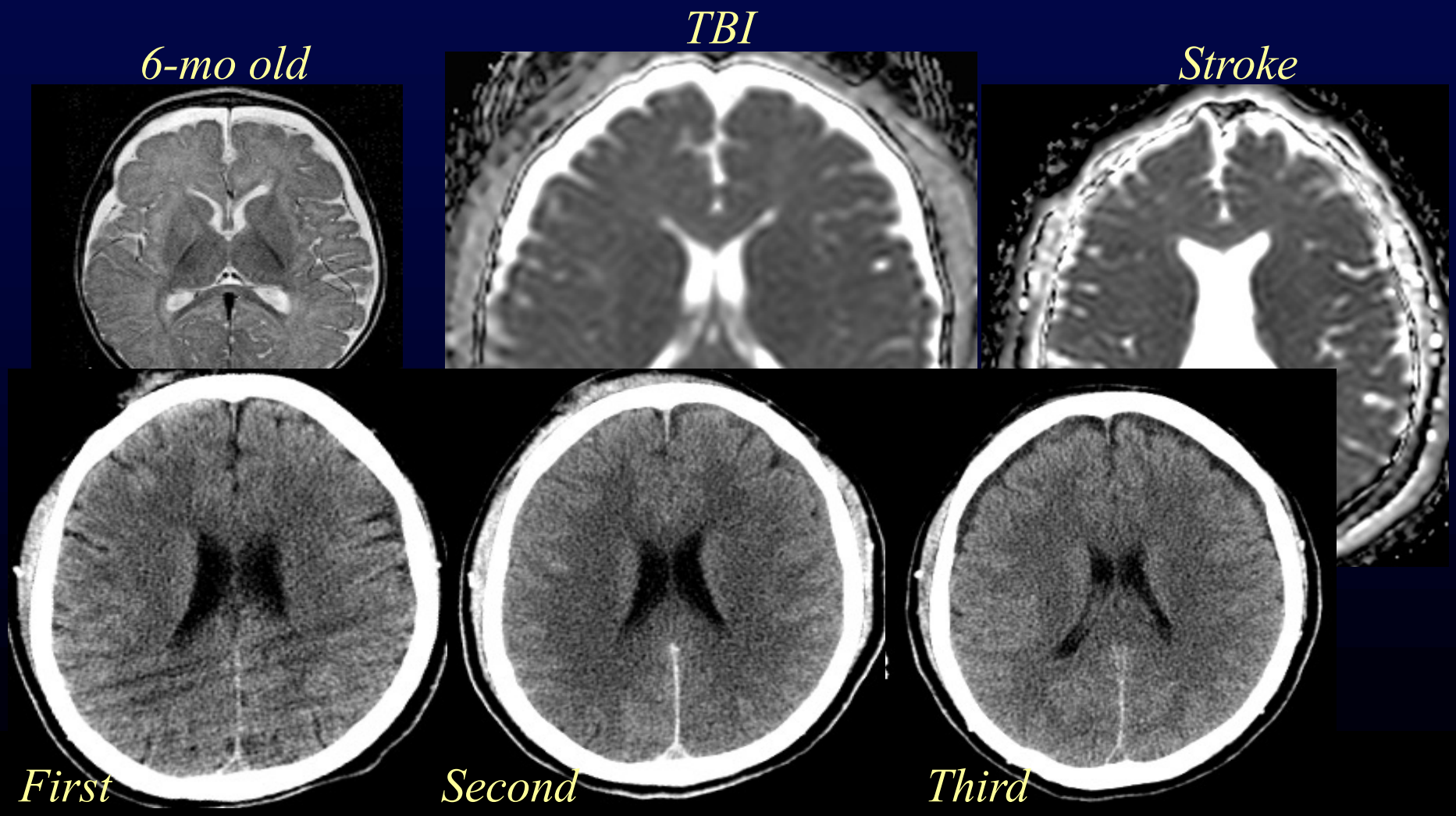
*TBI*



*Stroke*

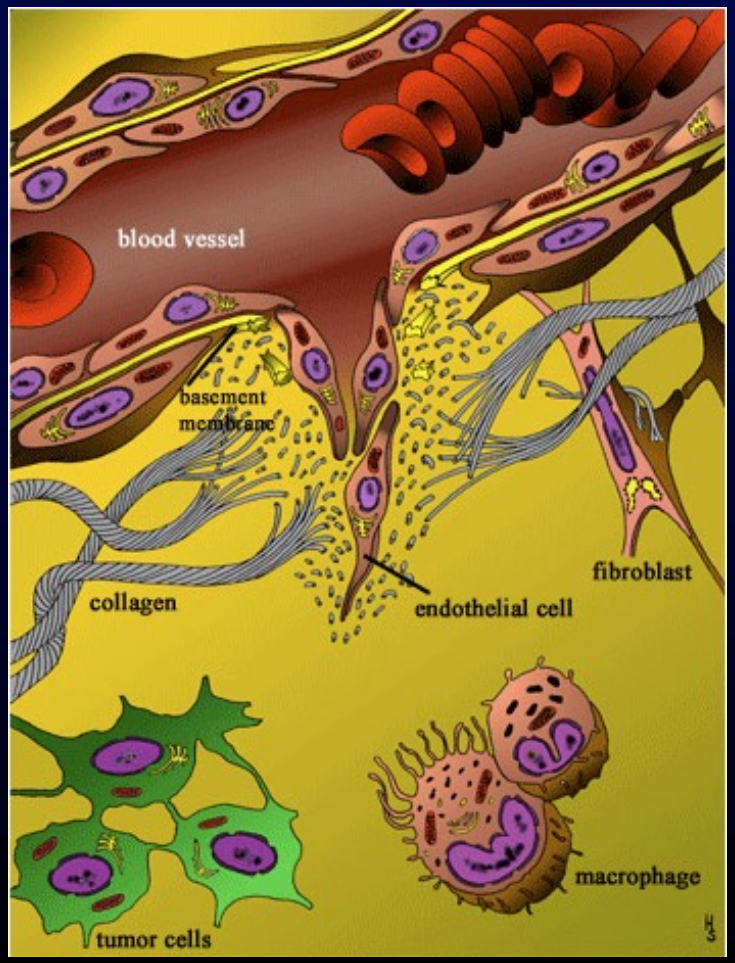


# Injury to the SAS



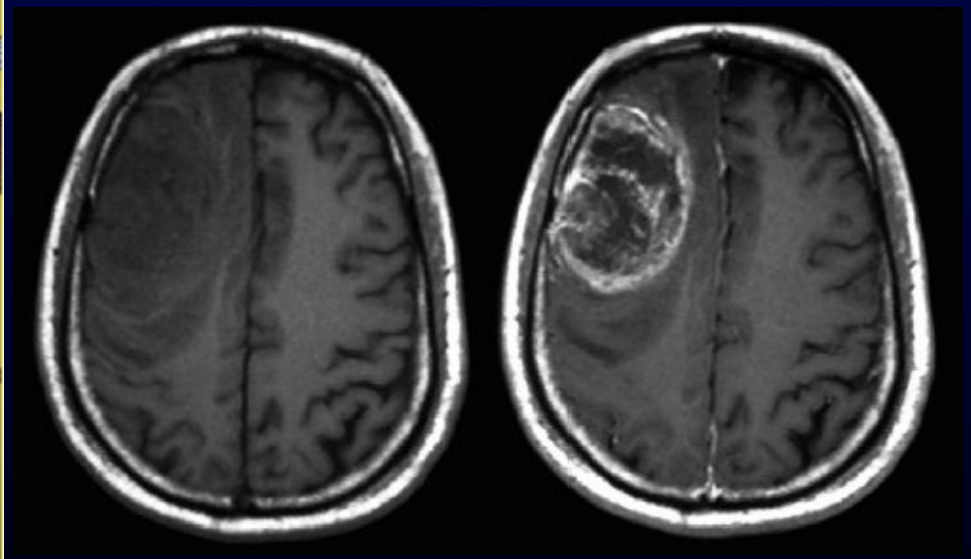
# TMI (Traumatic Meningeal Injury)

# Angiogenesis and Fenestrations




*Tumor*

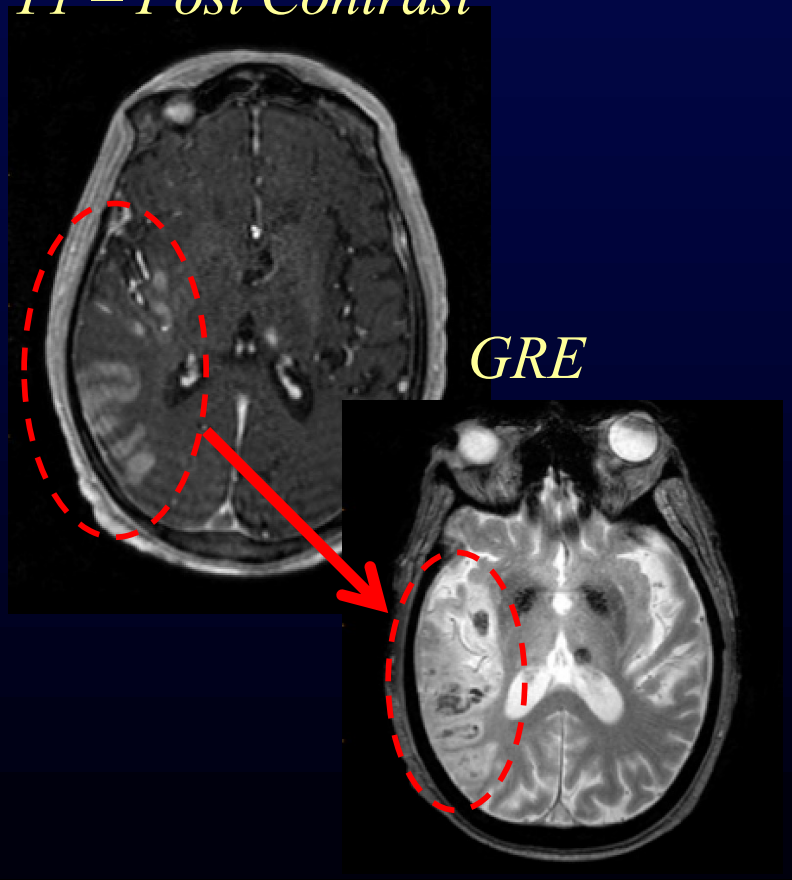
*T1-weighted*



*Pre-contrast* *Post-contrast*

# BBB Disruption - Stroke

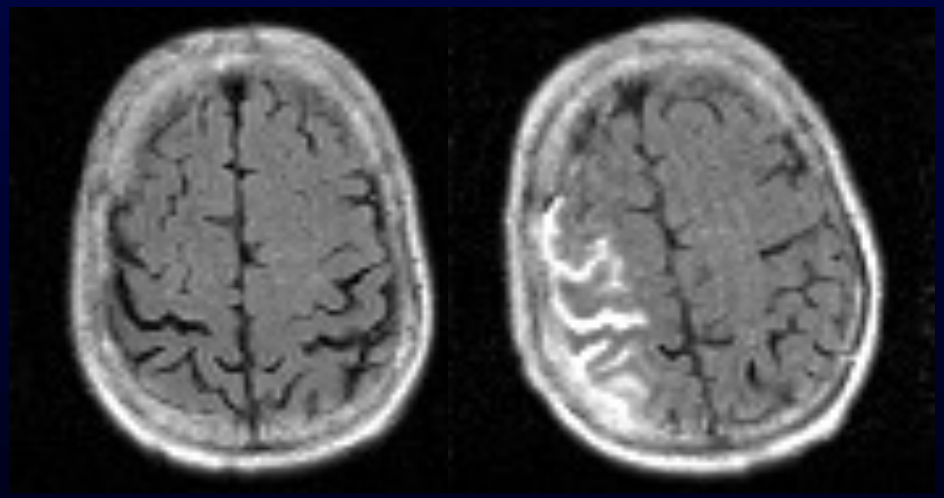
*T1 – Post Contrast*



*GRE*

*FLAIR*

*HARM*



# Nothing!

Nothing on T1 – Post, and no HARM

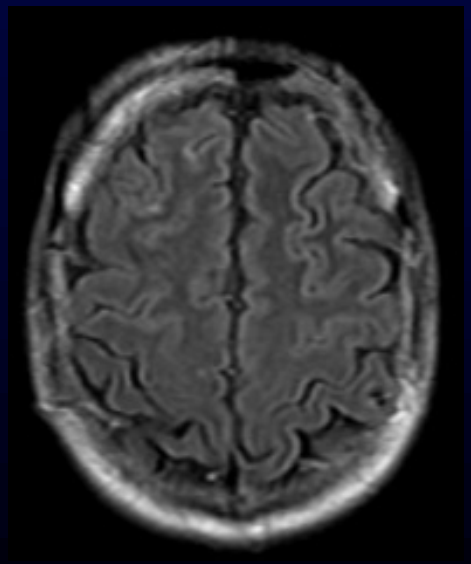
No BBB disruption

# Acute Dural Enhancement in mTBI

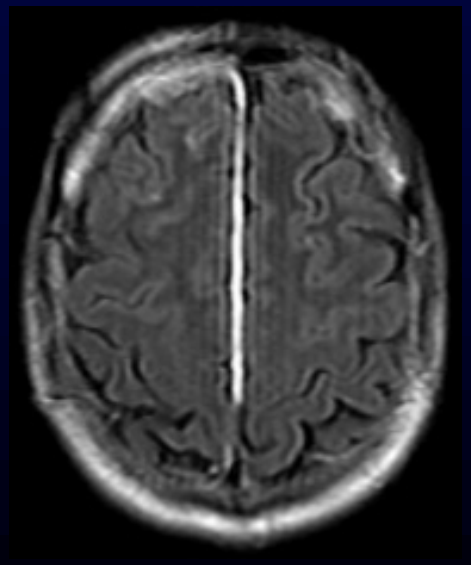
*FLAIR*

*Acute*

*Pre-*

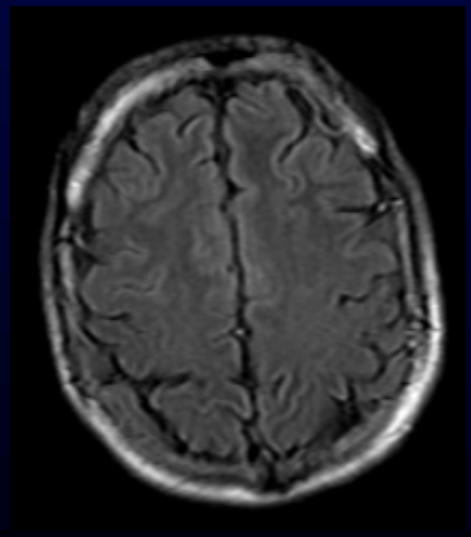


*Post-contrast*

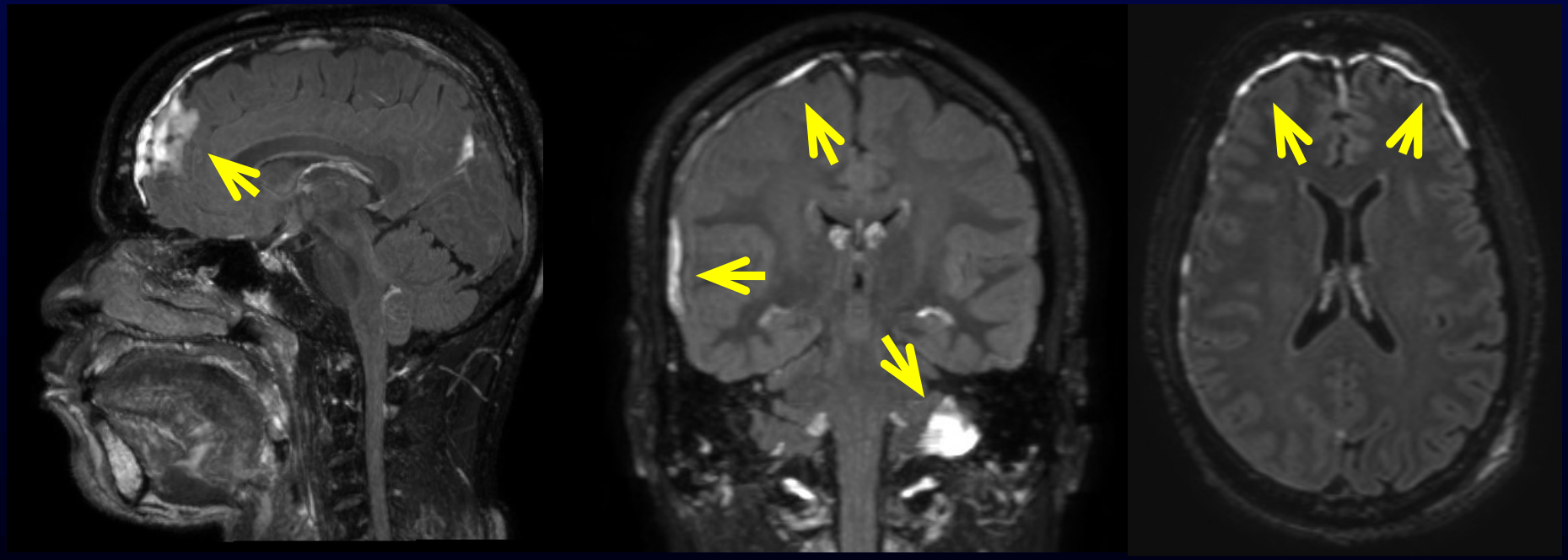


*Follow-up*

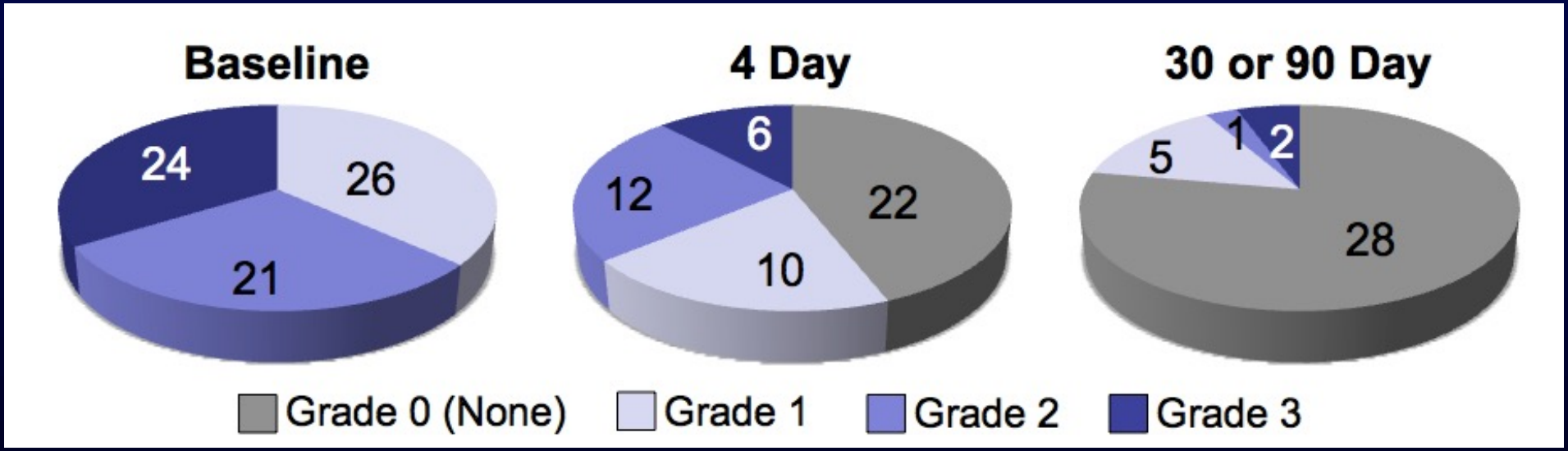
*Post-contrast*



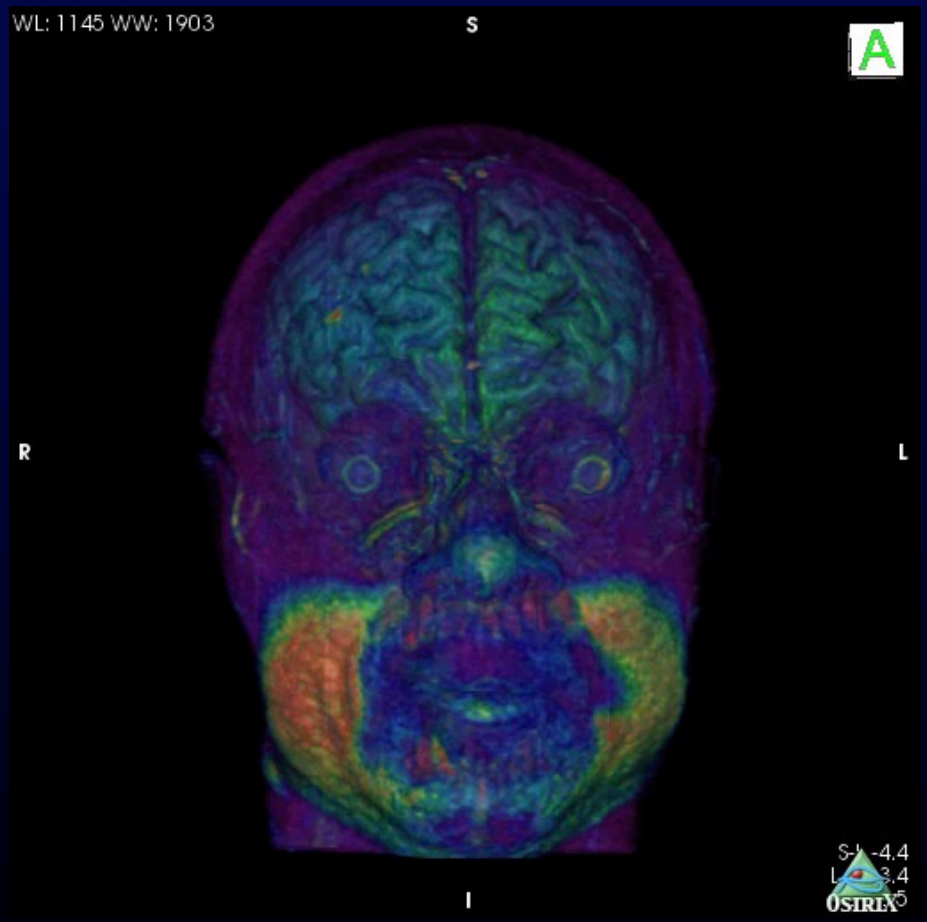
# Traumatic Meningeal Injury (TMI)



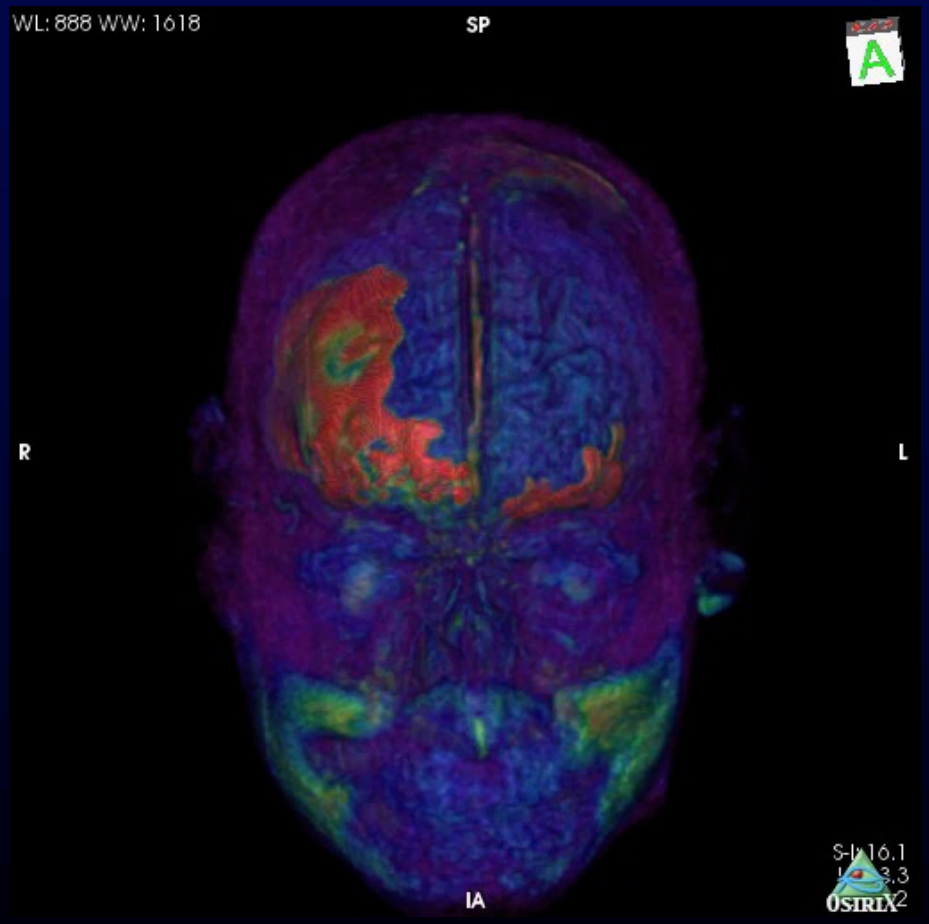
# Resolution of TMI

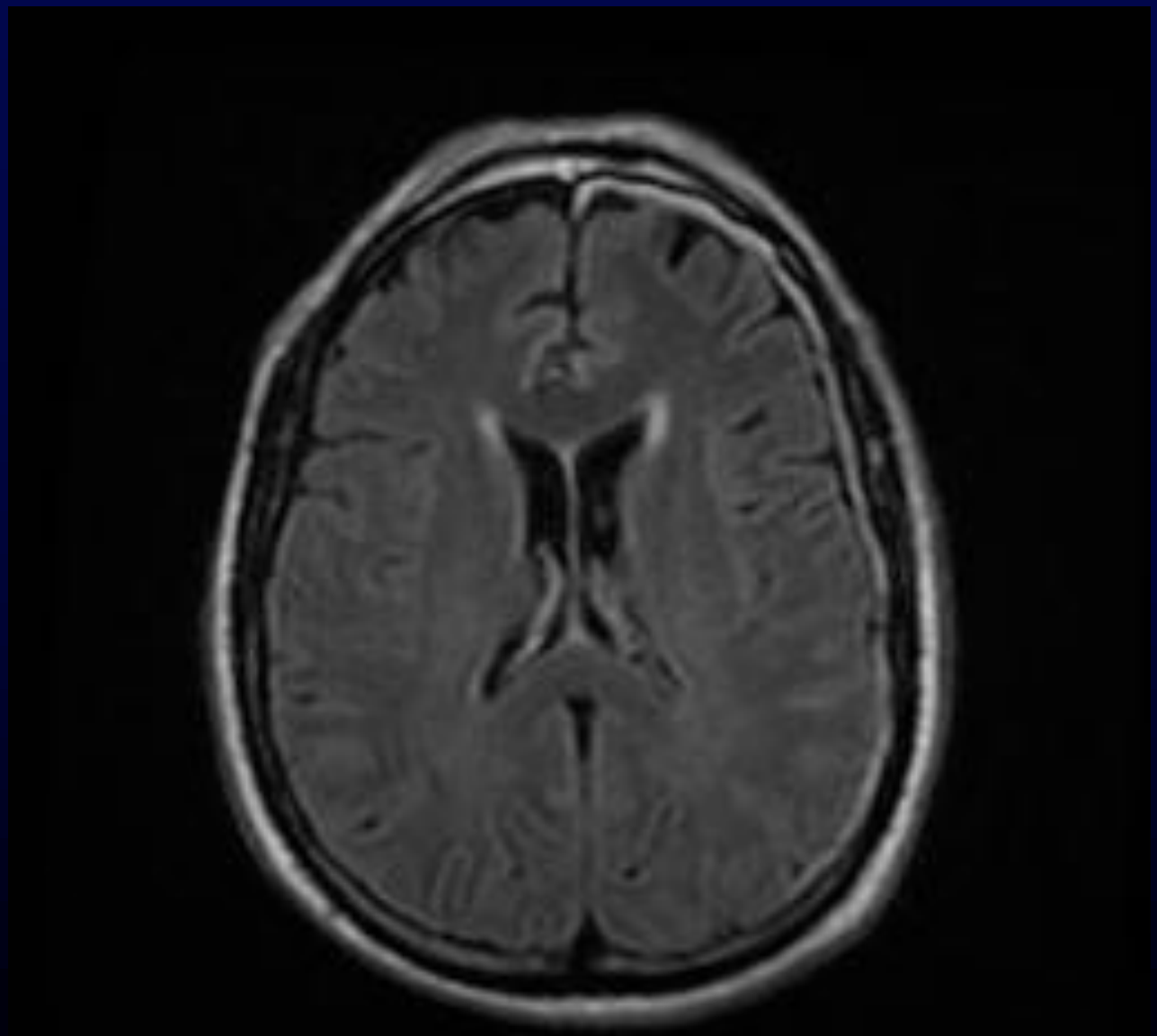


# 3D FLAIR - Normal



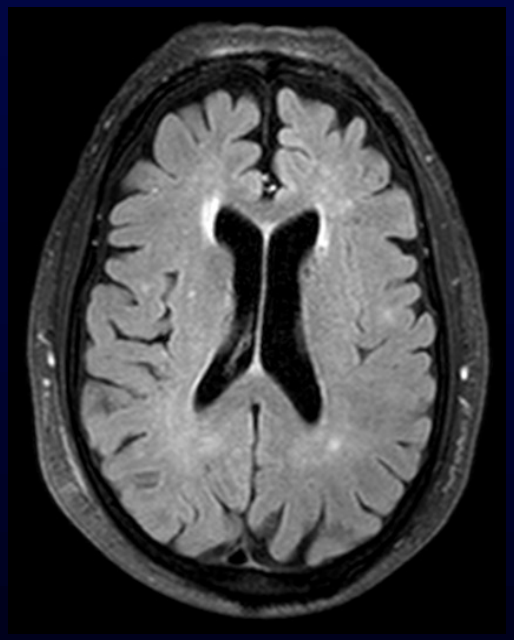
# Acute TMI





# Potential Progression

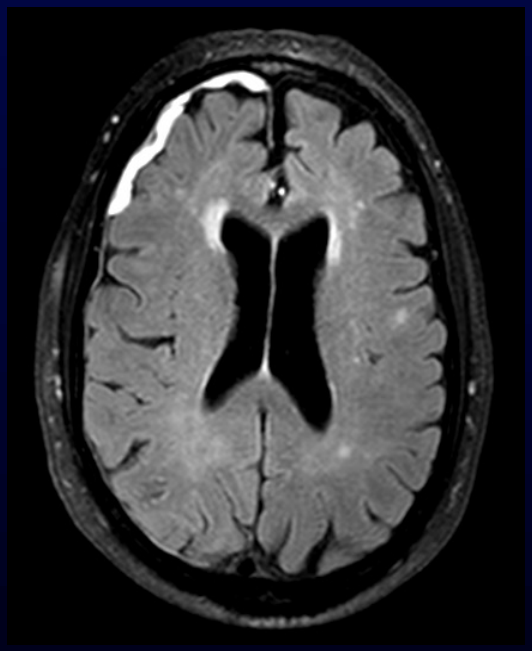
*Acute TMI*



*FLAIR-pre*

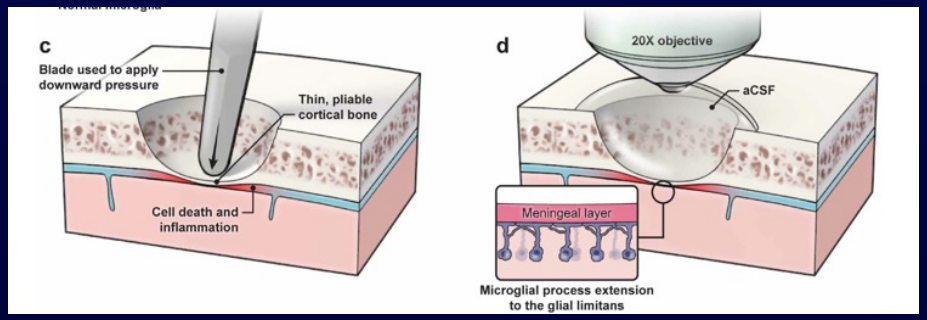
*FLAIR-post*

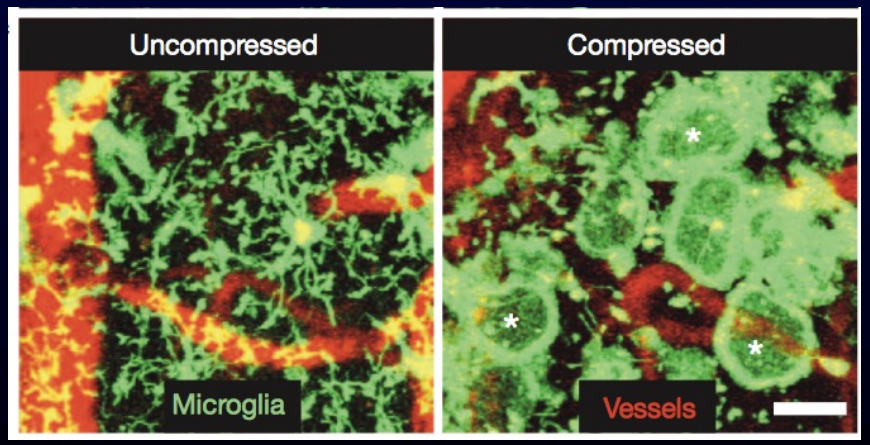
*Chronic SDH*

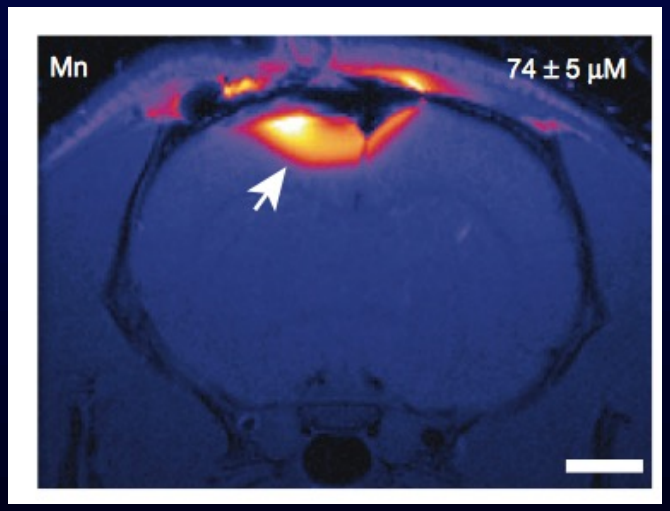


*FLAIR-pre*

# Dorian McGavern




Nature. 2014 Jan 9;505(7482):223-8. doi: 10.1038/nature12808. Epub 2013 Dec 8.

**Transcranial amelioration of inflammation and cell death after brain injury.**

Roth TL, Nayak D, Atanasijevic T, Koretsky AP, Latour LL, McGavern DB.

# TVI (Traumatic Vascular Injury)

# Brainwashing

Evidence for a 'Paravascular' Fluid Circulation in the Mammalian Central Nervous System, Provided by the Rapid Distribution of Tracer Protein Throughout the Brain from the Subarachnoid Space

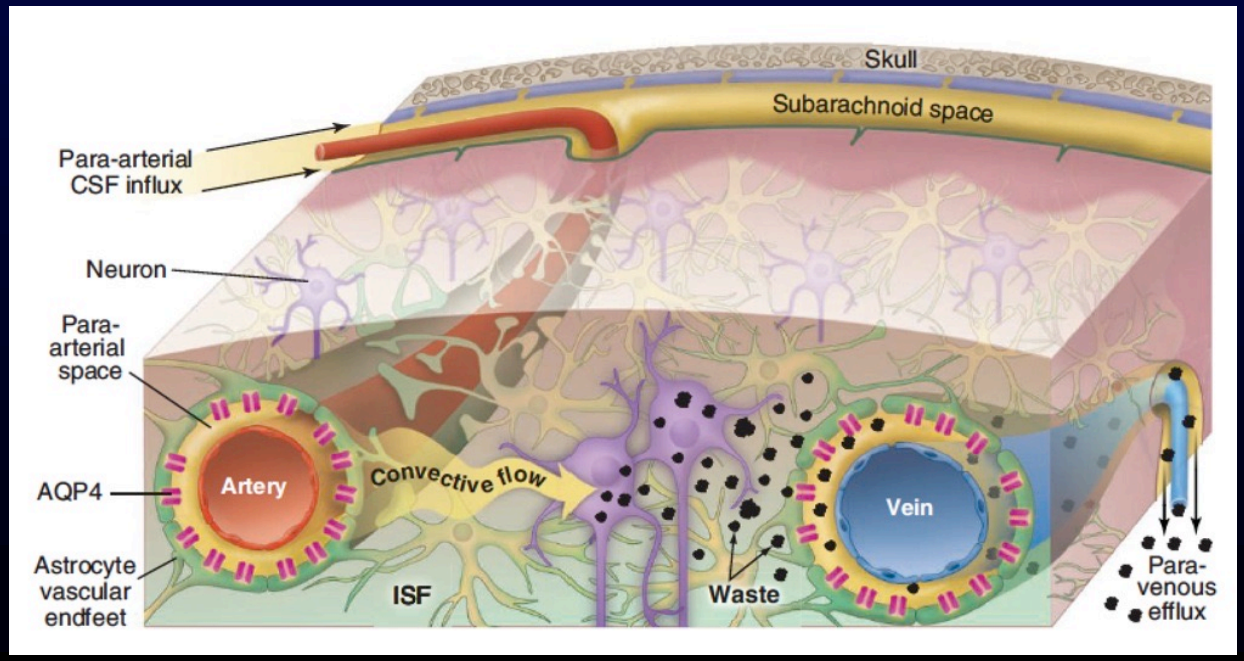
MARSHALL L. RENNELS, THOMAS F. GREGORY, OTIS R. BLAUMANIS, KATSUKUNI FUJIMOTO and PATRICIA A. GRADY

*Departments of Anatomy and Neurology, The University of Maryland School of Medicine, Baltimore, MD (U.S.A.)*

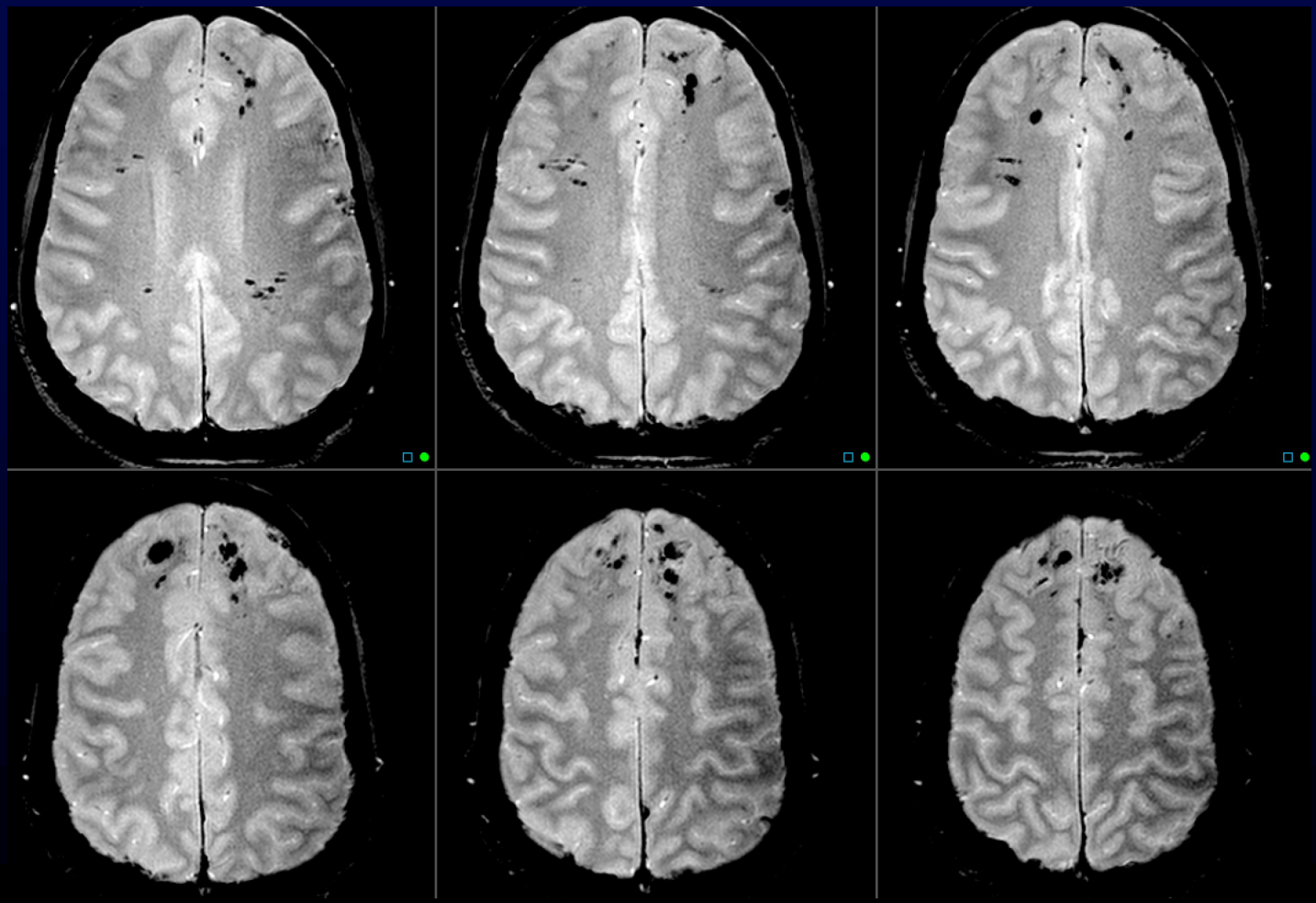
(Accepted May 1st, 1984)

**Garbage Truck of the Brain**

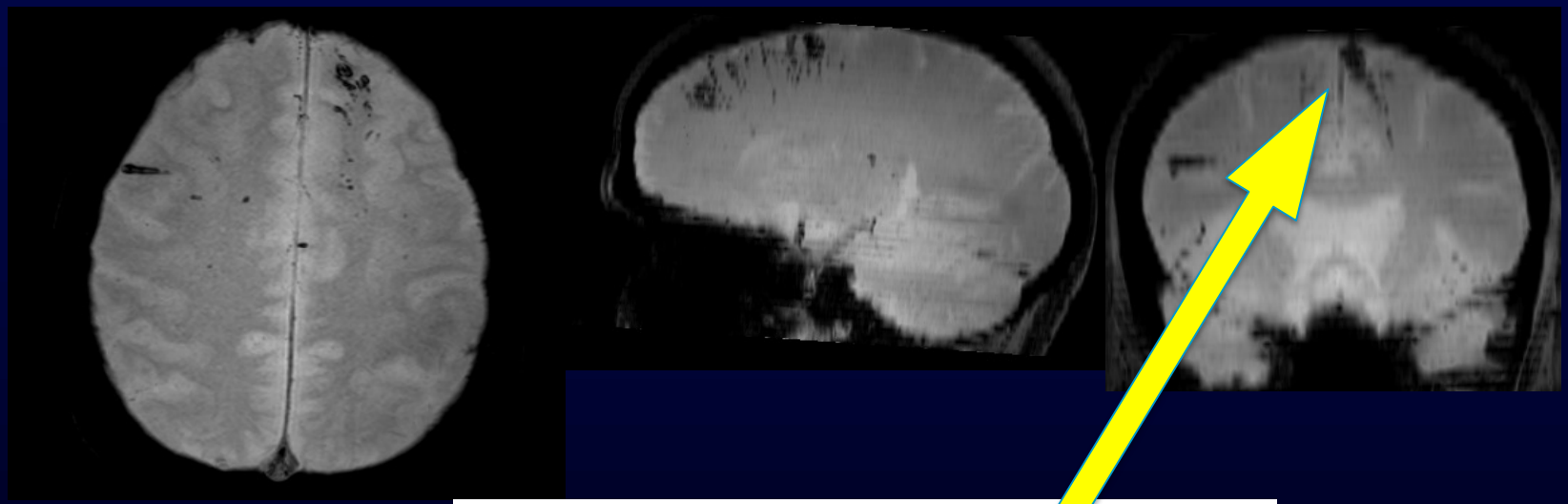
**Maiken Nedergaard**

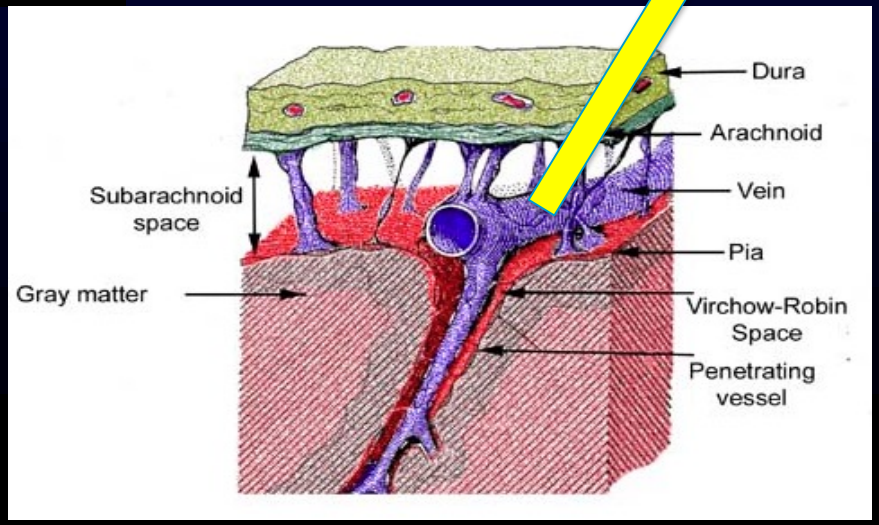


# So Called Traumatic Microbleeds

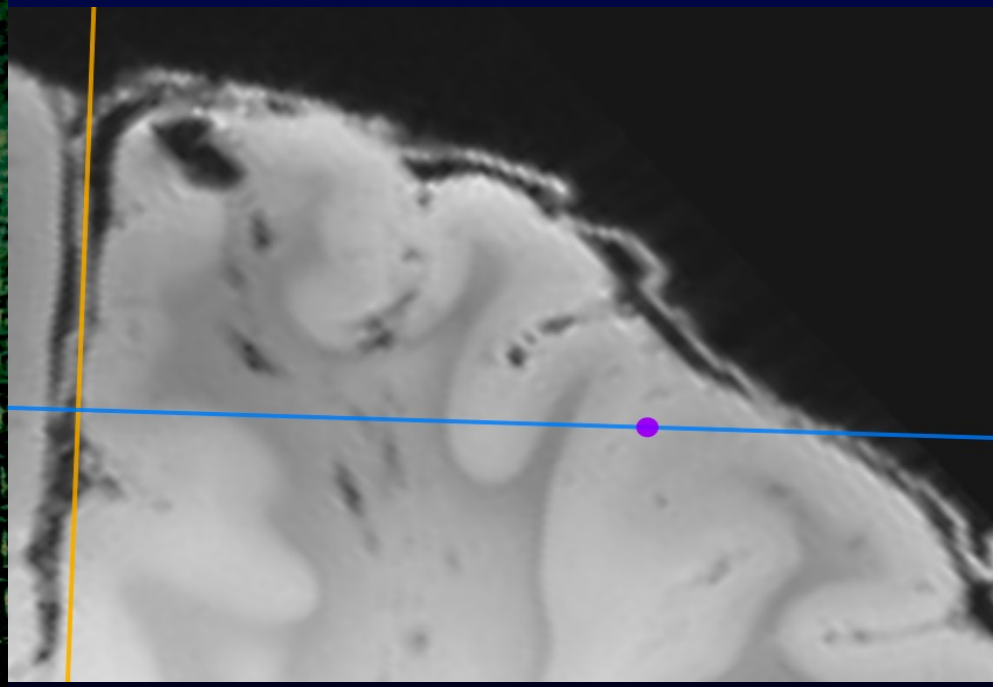


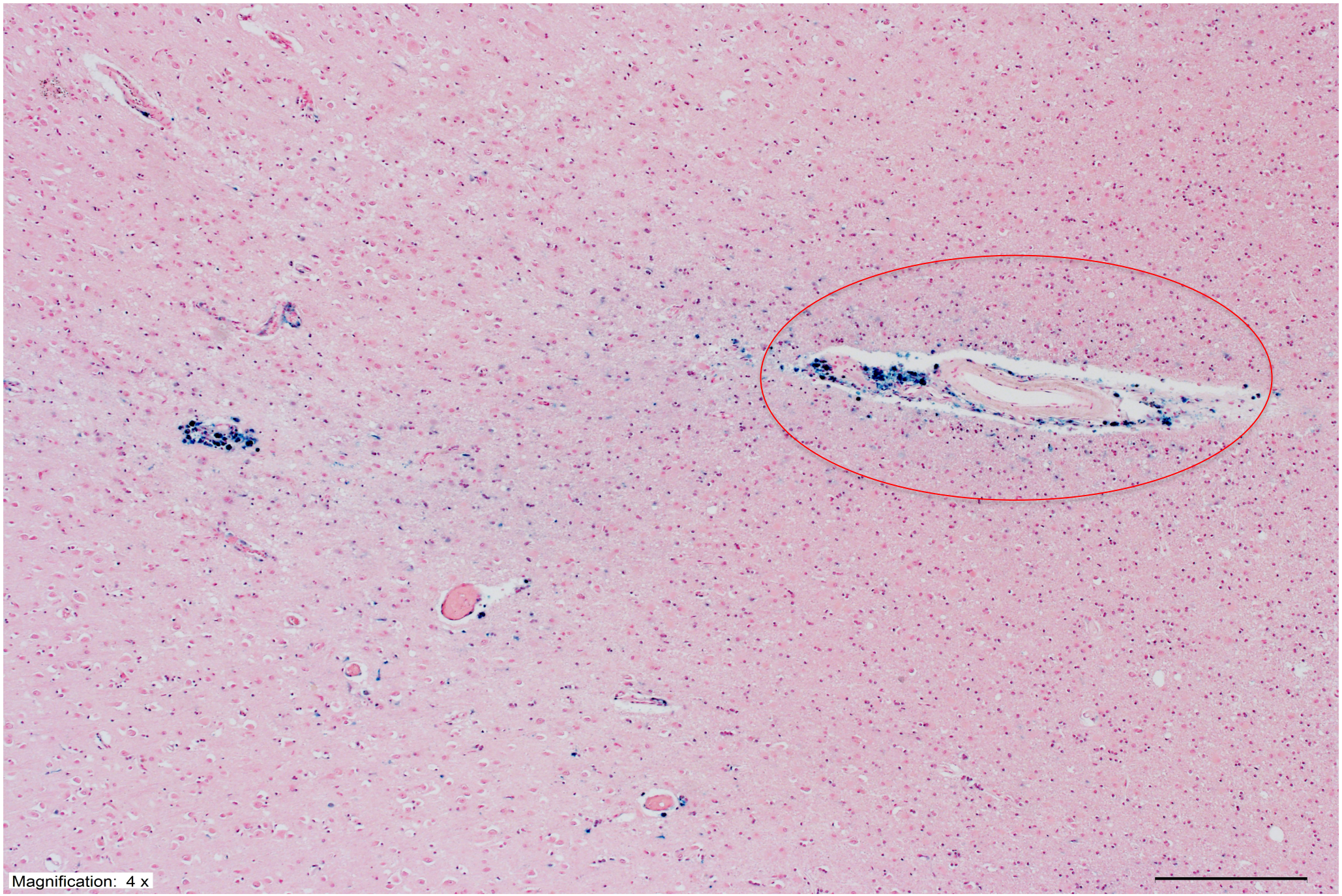
# Traumatic Vascular Injury (TVI)

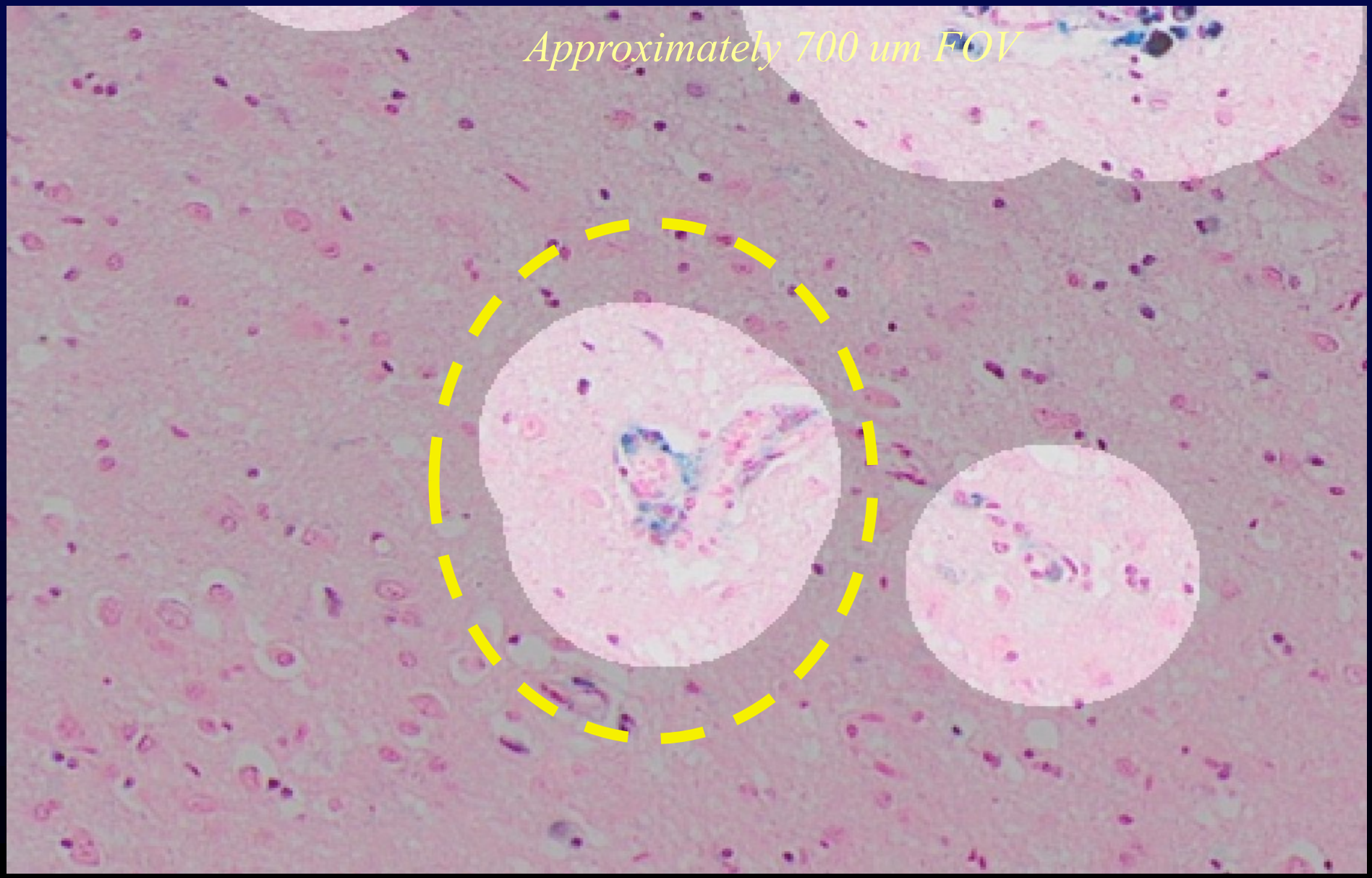


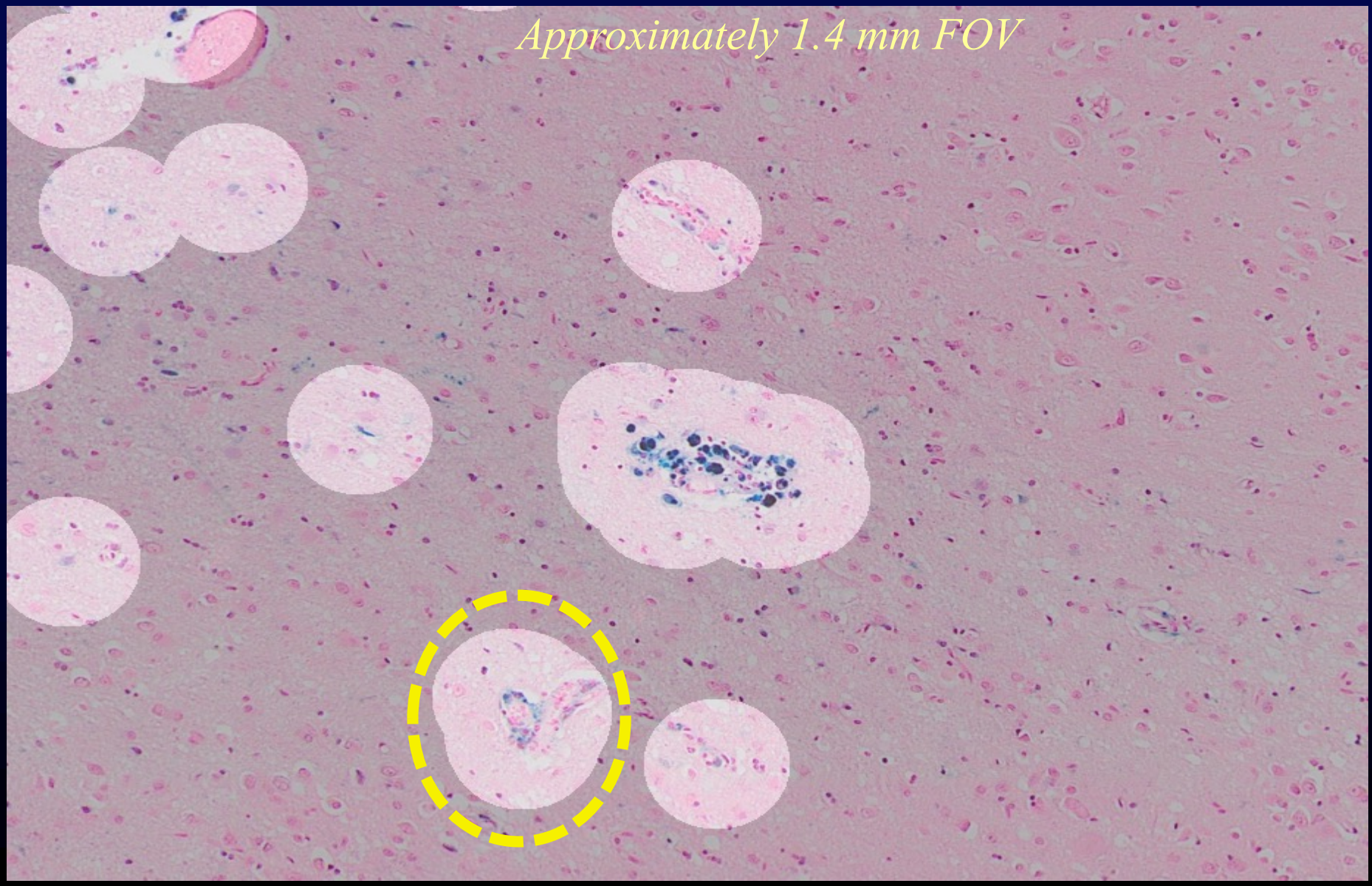


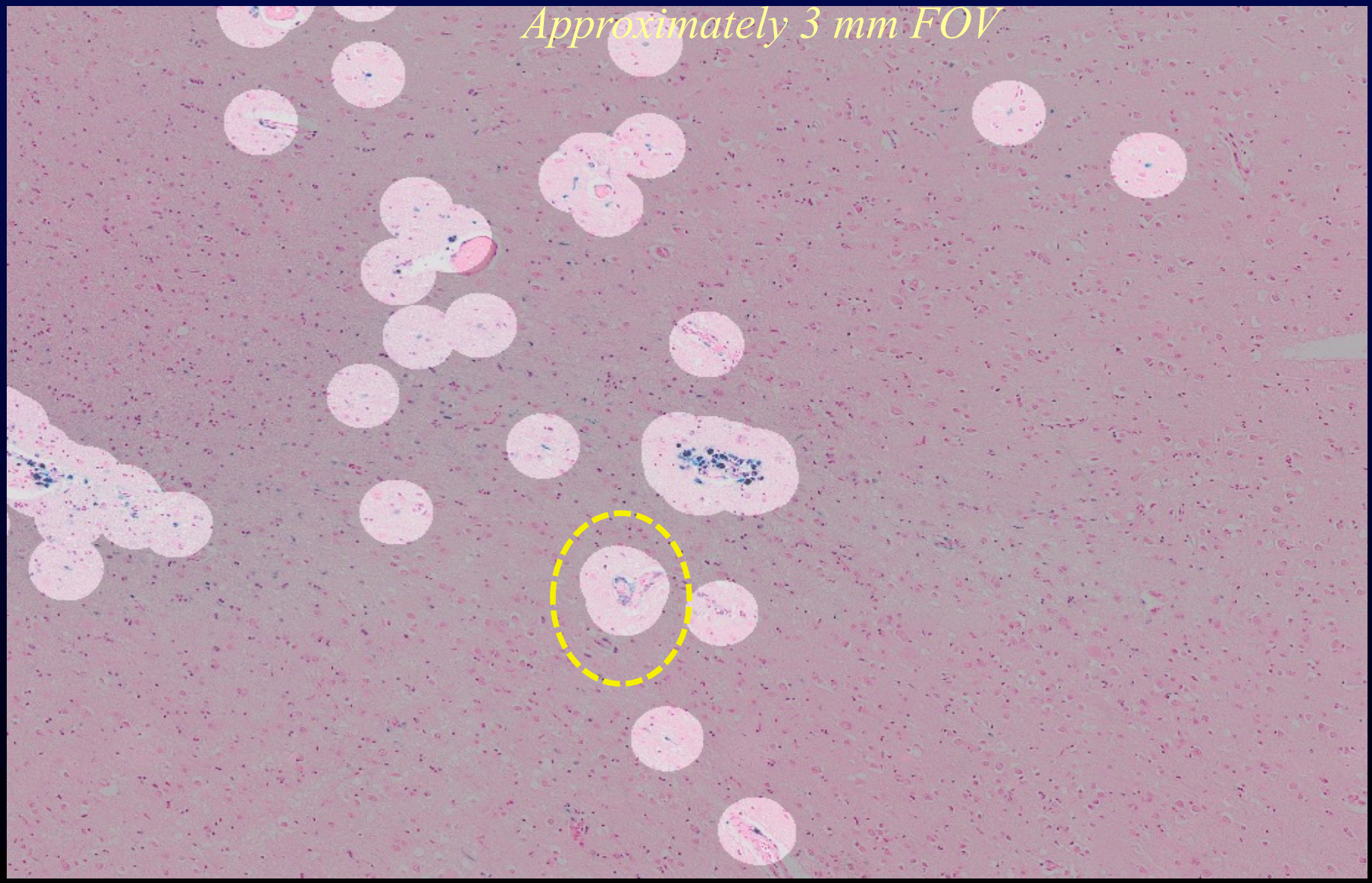
# Vascular Injury

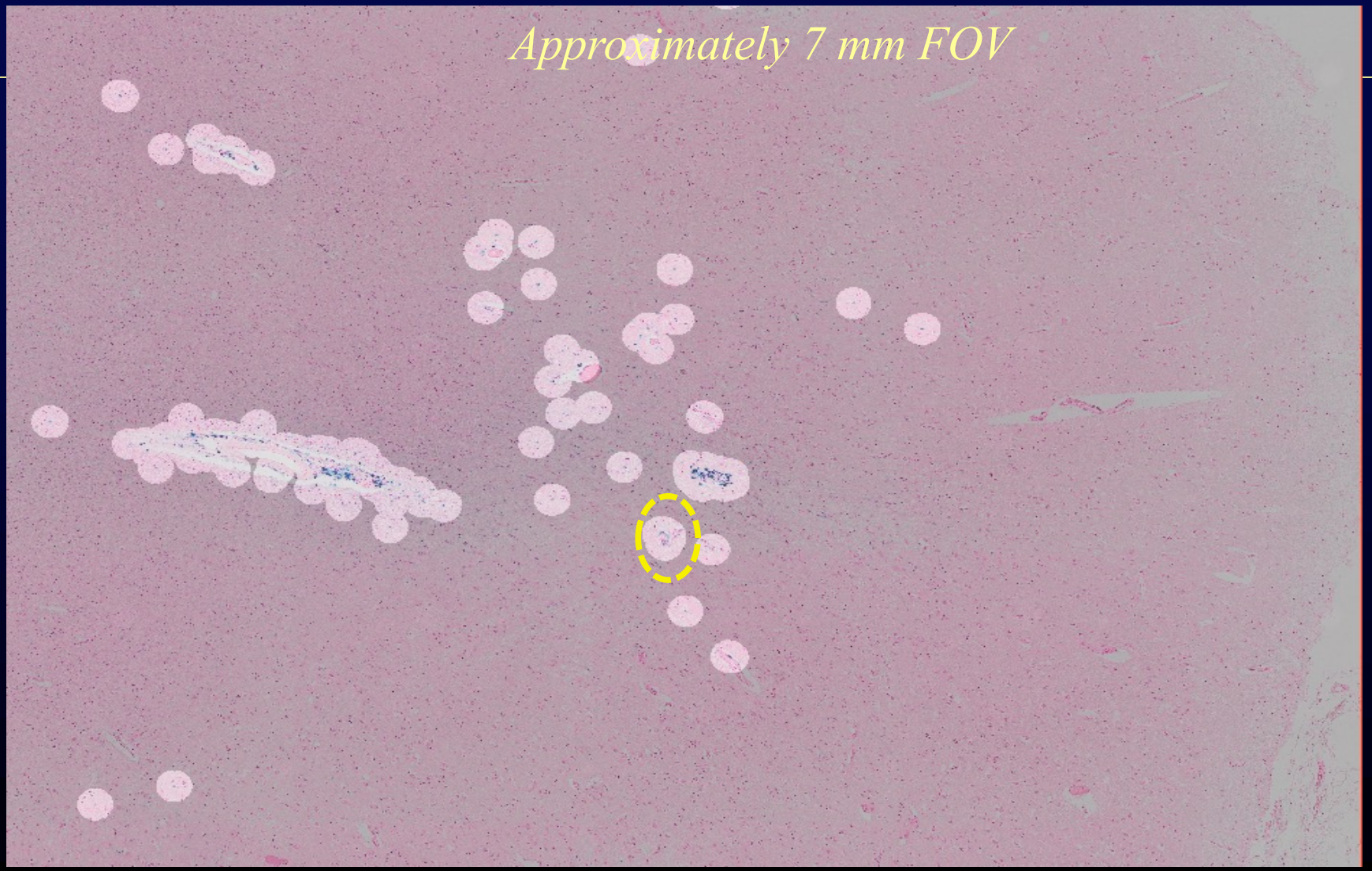



Magnification: 4 x

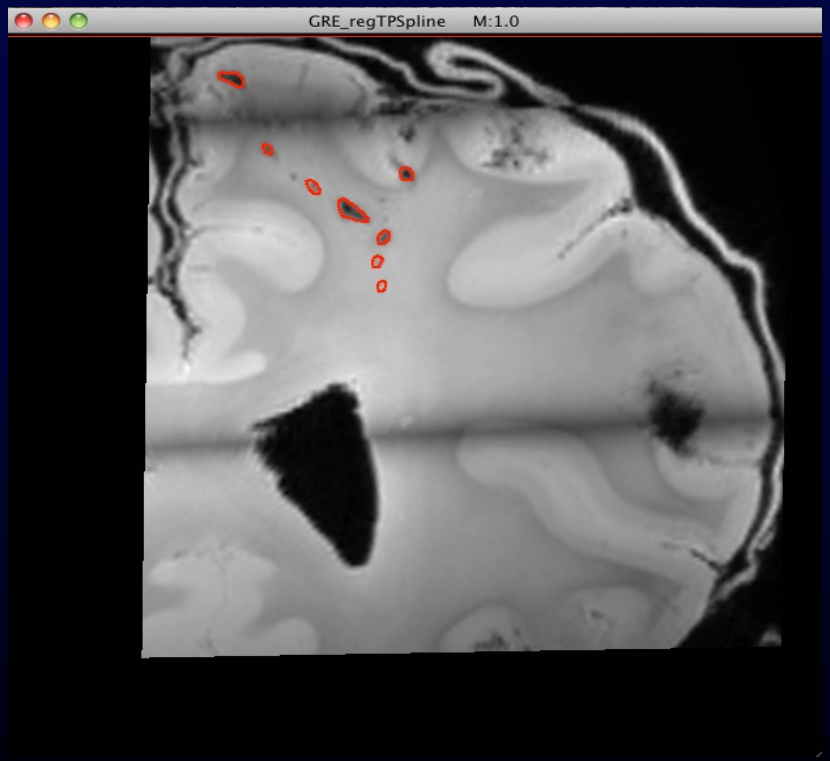

Approximately 700 um FOV

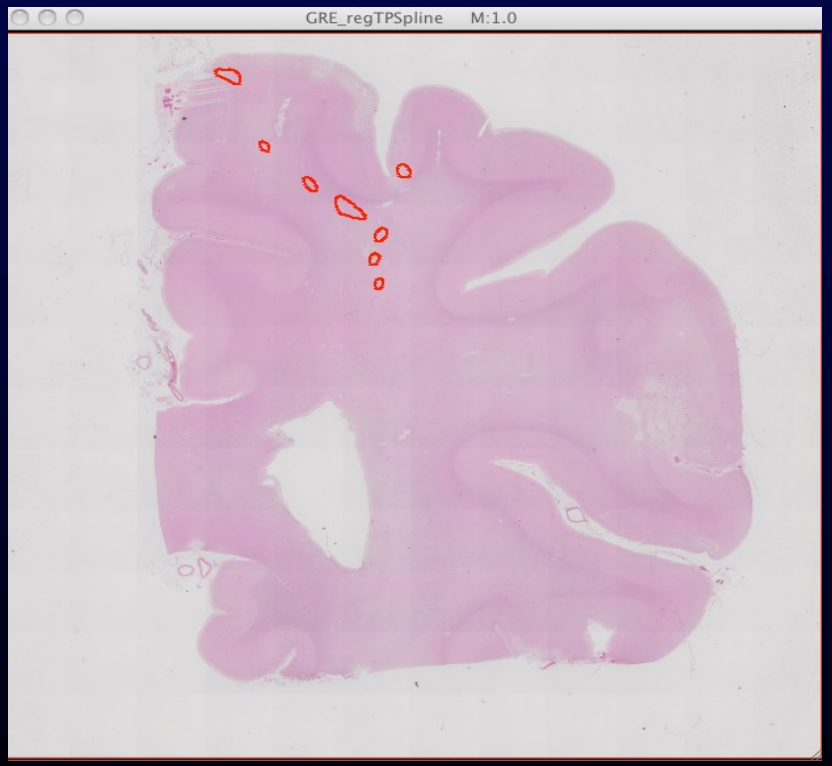

Approximately 1.4 mm FOV

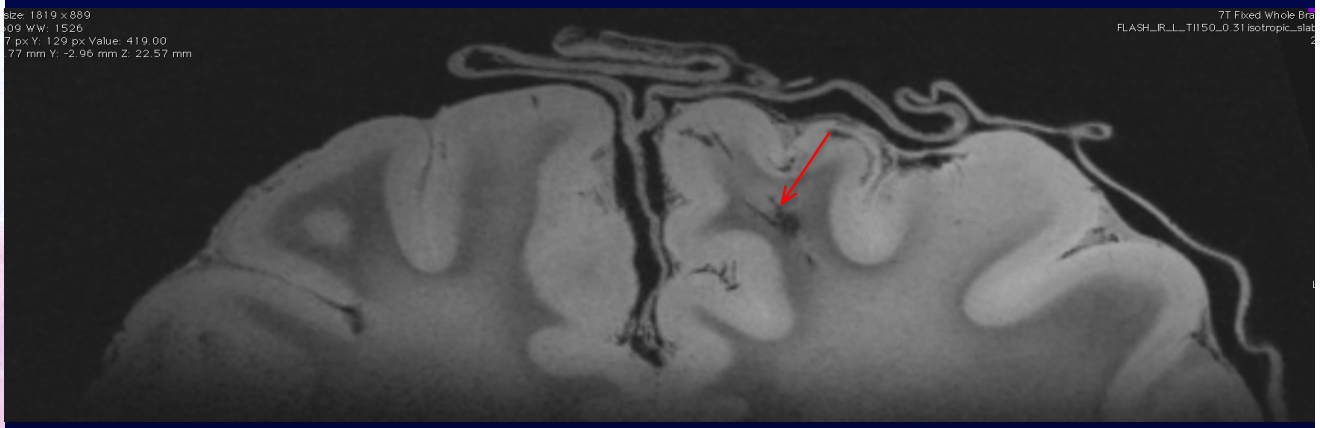

Approximately 3 mm FOV


Approximately 7 mm FOV

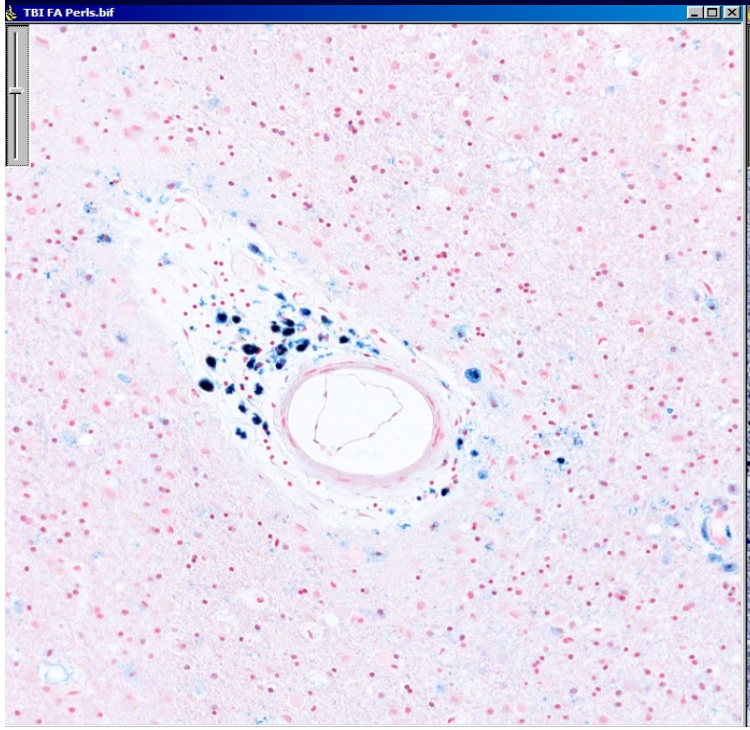
# Segmentation of Lesions on MRI

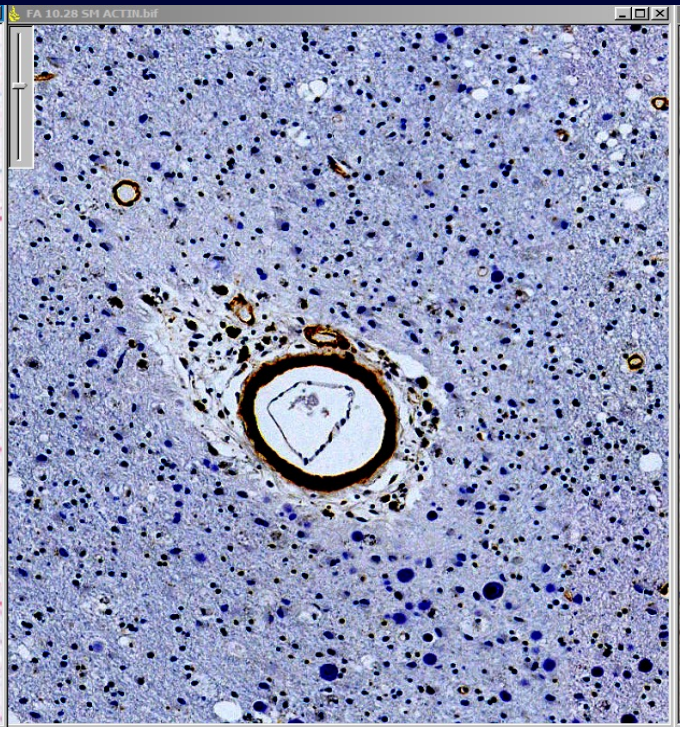


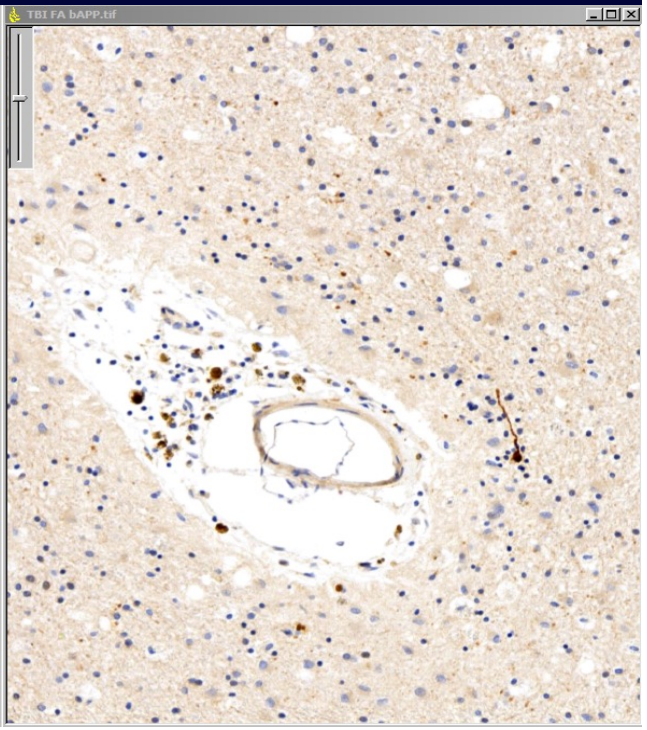




Size: 1819 x 889
.09 WW: 1526
7 px Y: 129 px Value: 419.00
.77 mm Y: -2.96 mm Z: 22.57 mm
7T Fixed Whole Bra
FLASH_IR_L_TI150_0.31isotropic_slab

*Parikh et al*


TBI FA Perls.bif


FA 10.28 SM ACTIN.bif


TBI FA bAPP.tif

# Amyloid Beta PET