# Trauma cranico:
# Fisiopatologia e strategie terapeutiche


ISTITUTO DI RICERCHE FARMACOLOGICHE
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IRCCS

Elisa R. Zanier

# Outline

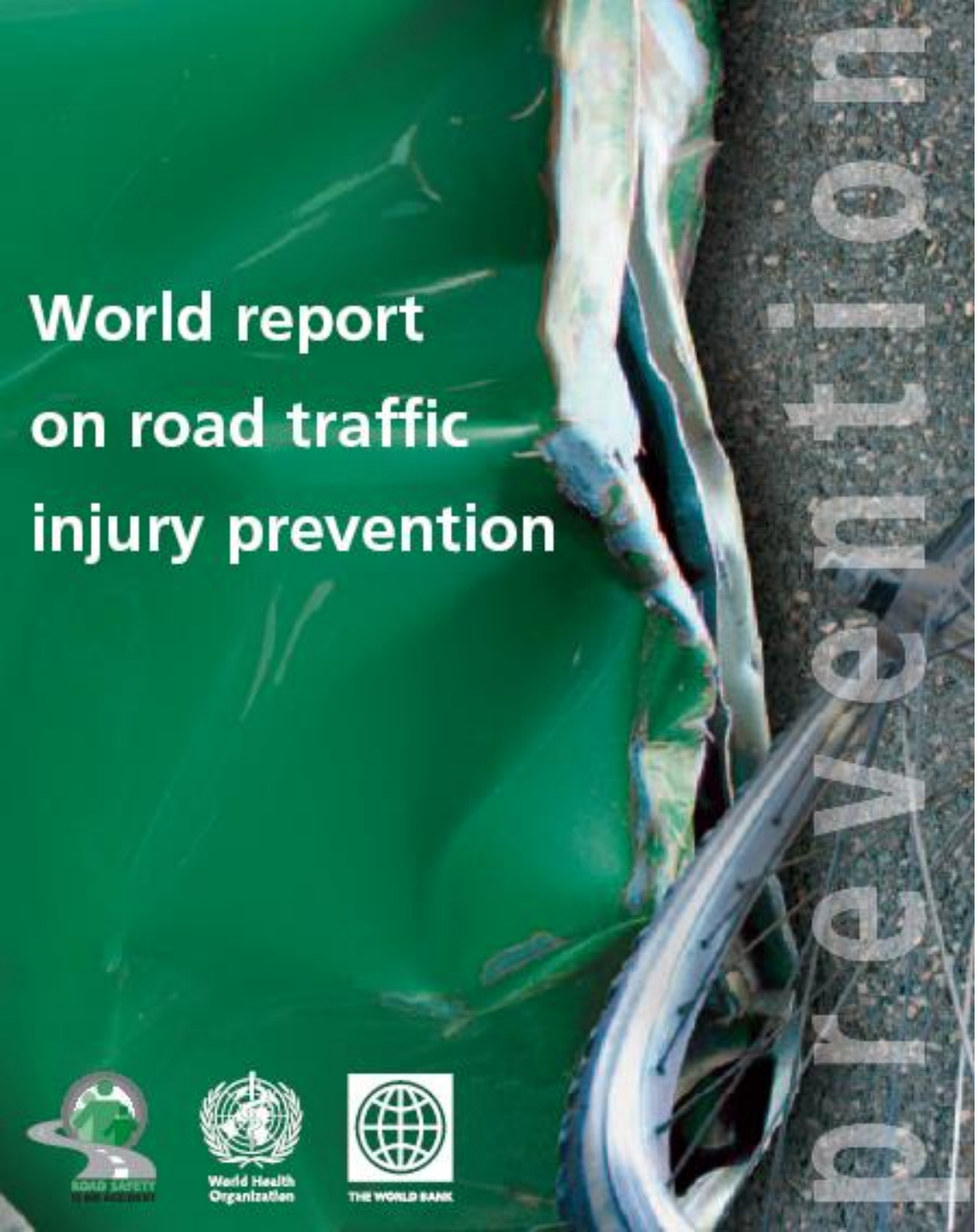
- Epidemiology
- Pathophysiology
  - Heterogeneity
  - Susceptibility
  - Chronic degenerative processes
- Therapeutic strategies
  - Secondary insults
  - Regenerative potential

OPINION

# Changing patterns in the epidemiology of traumatic brain injury

*Bob Roozenbeek, Andrew I. R. Maas and David K. Menon*

Nat Rev Neurol 2013 9(4):231-6




# Main Messages and Recommendations

2004

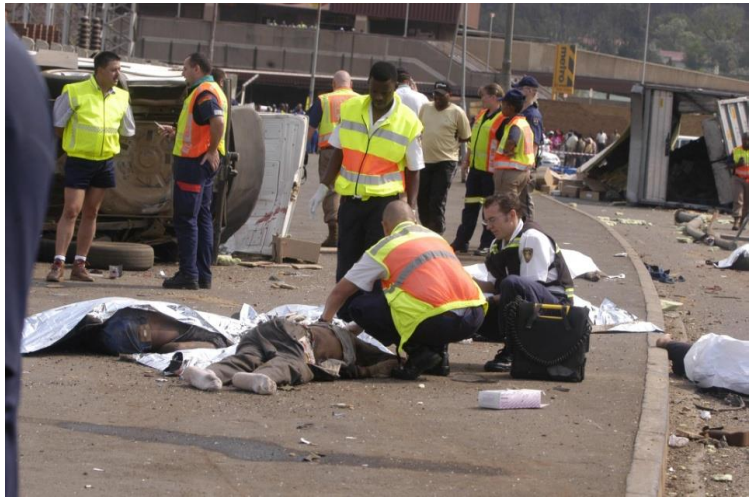
2013

# Traumatic brain injury (TBI)

- First cause of death and disabilities among young people
- 7-8 million of people affected/year in Europe
- Unfavorable outcome: 30%
- No pharmacological treatment is available to protect against the detrimental consequences of TBI

# Road traffic injuries are a huge public health and development problem

- 1.2 million die a year
- 20-50 million more are injured or disabled
- 11th leading cause of death
- account for 2.1% of all deaths globally



# Global incidence

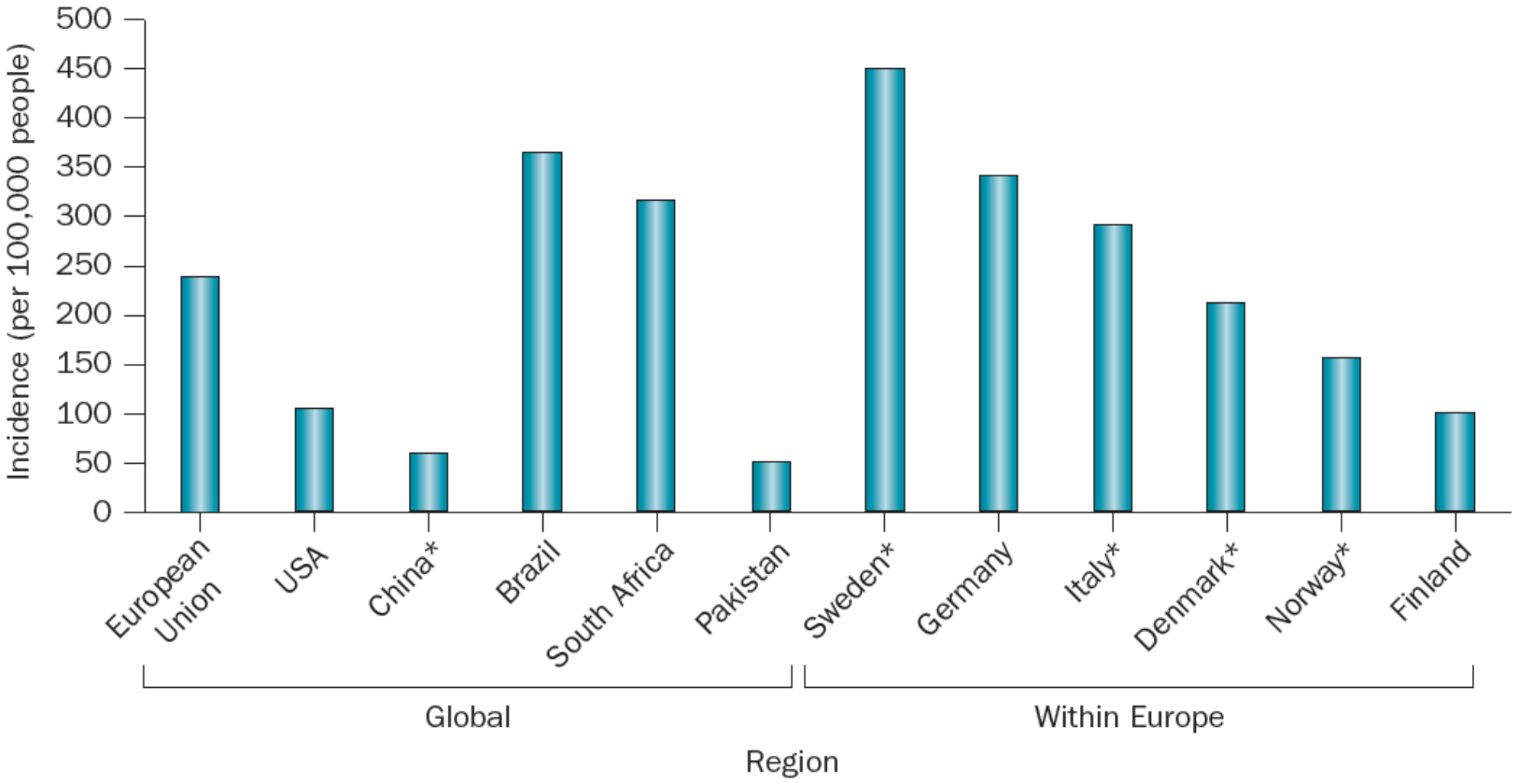
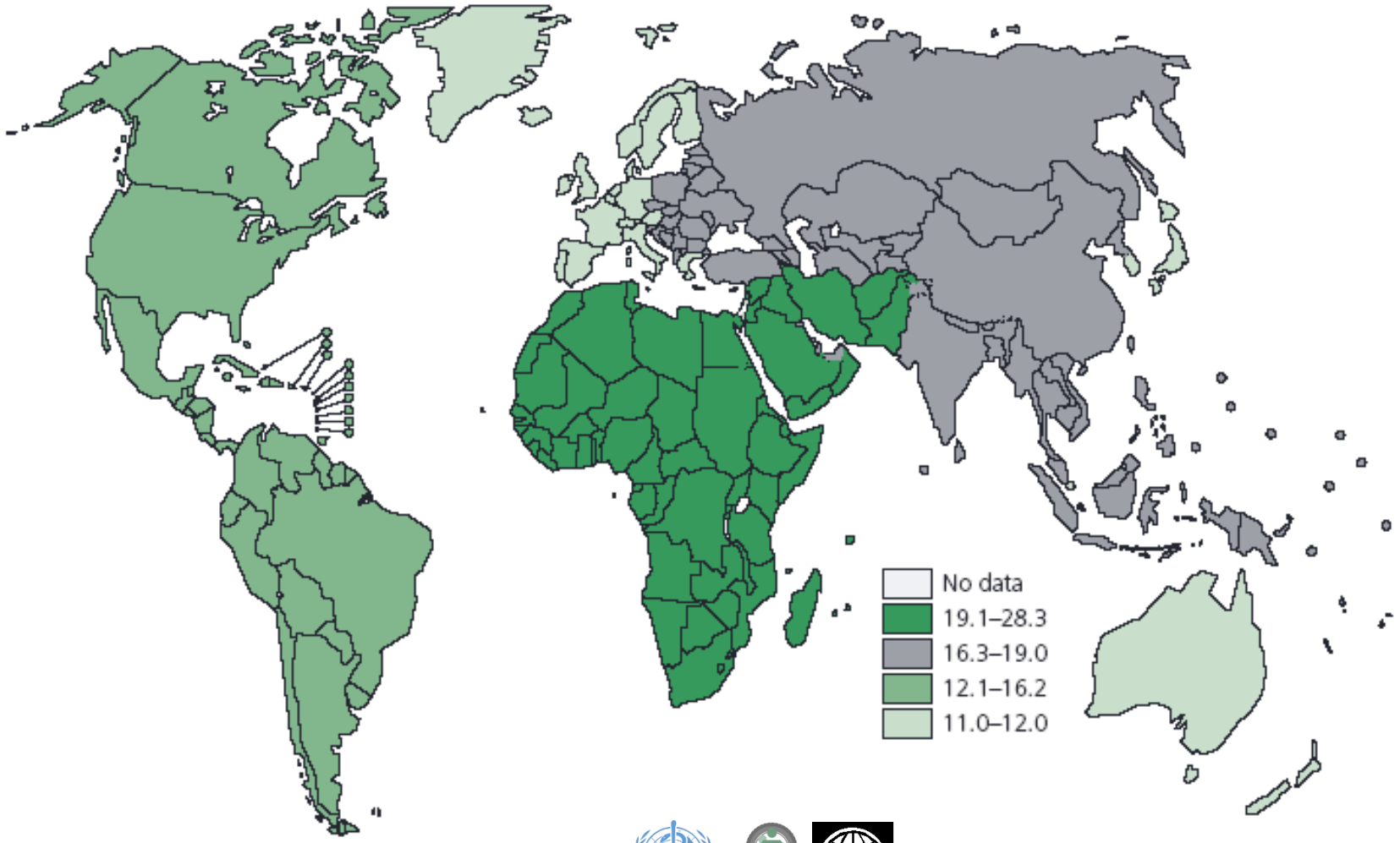


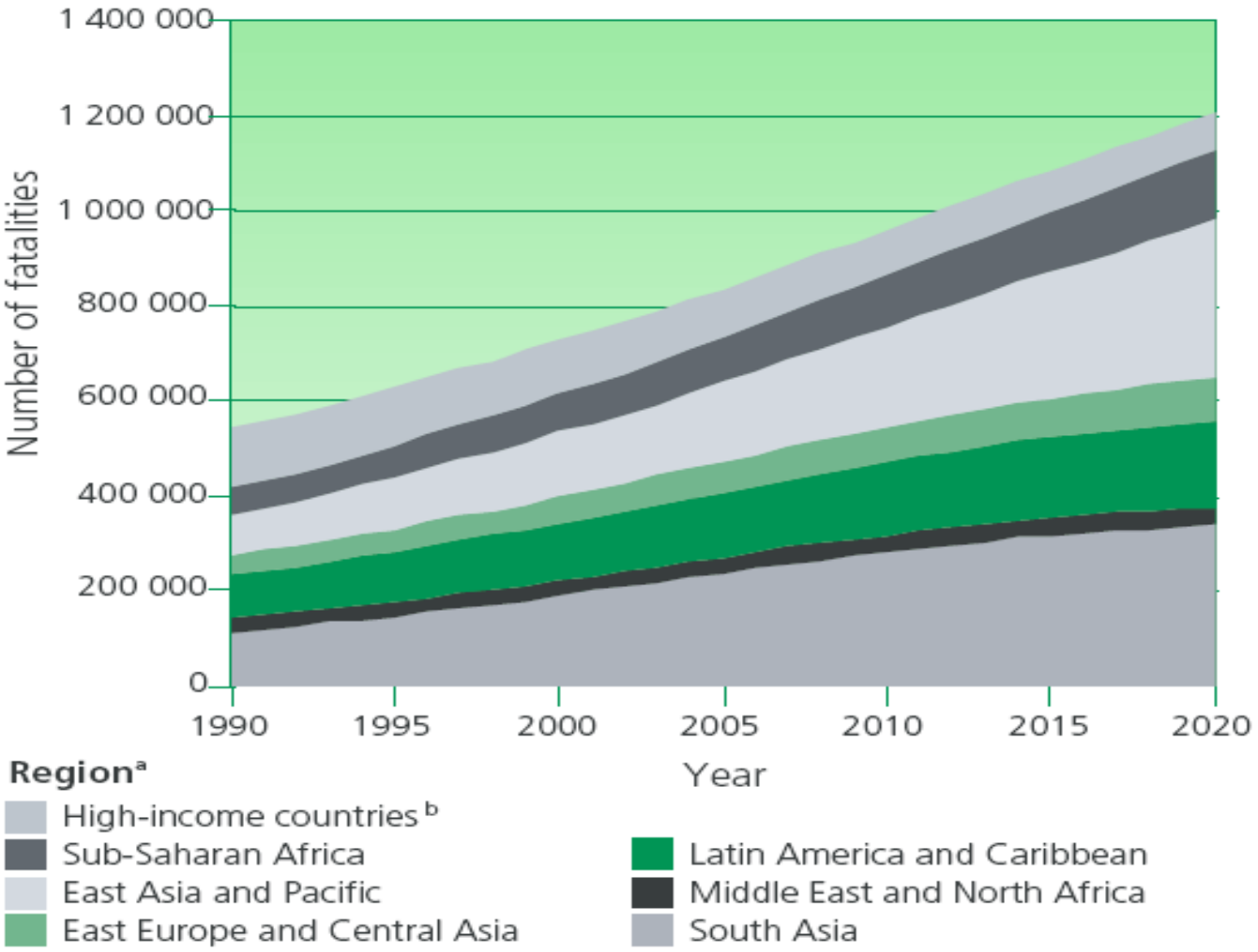

**Figure 1** | Estimates of the global incidence of traumatic brain injury. *Mean of results from two studies.

# The majority of road traffic injuries occur in low- and middle-income countries

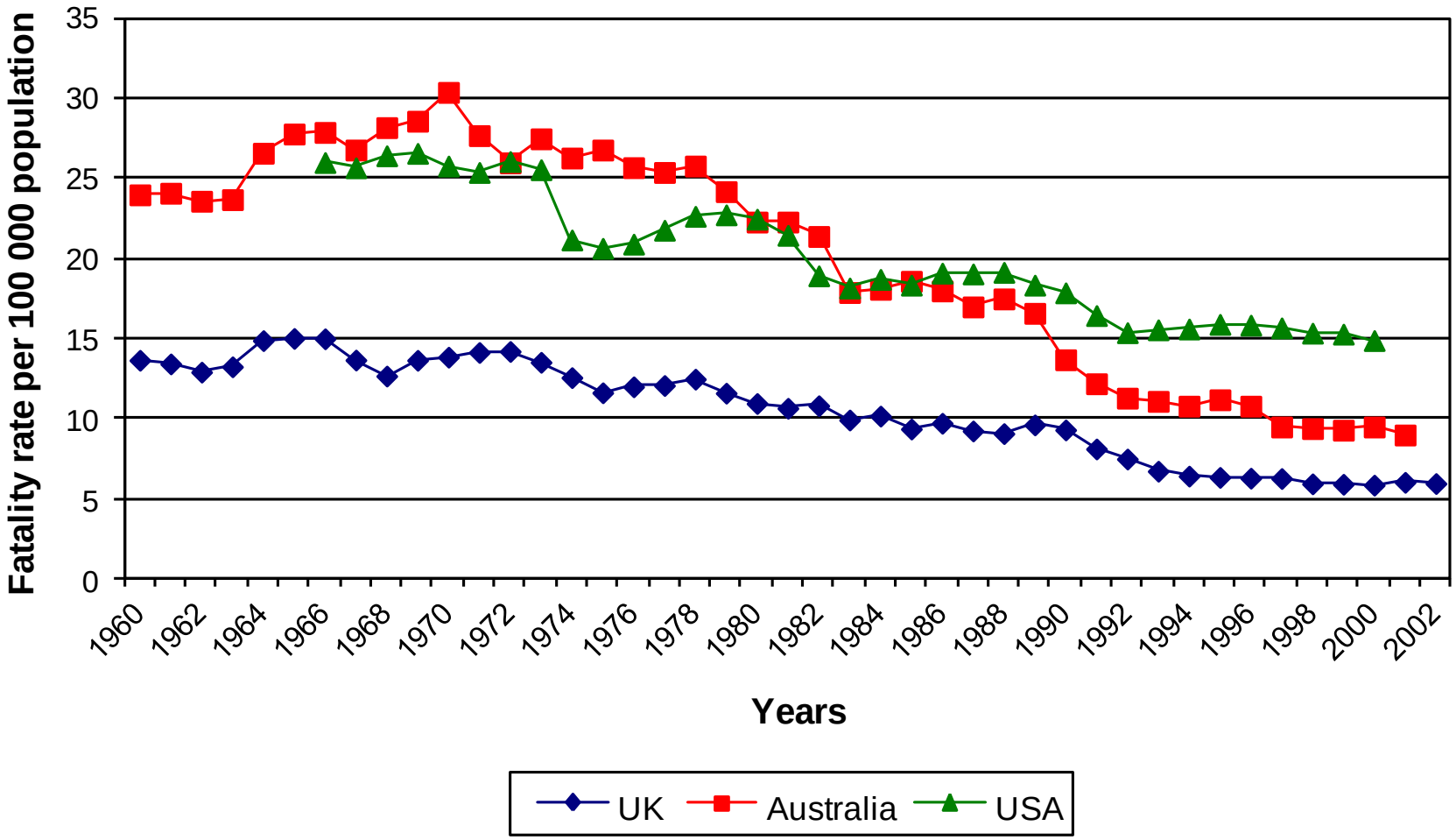
Road traffic injury mortality rates (per 100 000 population) in WHO regions, 2002



# Road traffic fatalities are predicted to increase by 67% by the year 2020

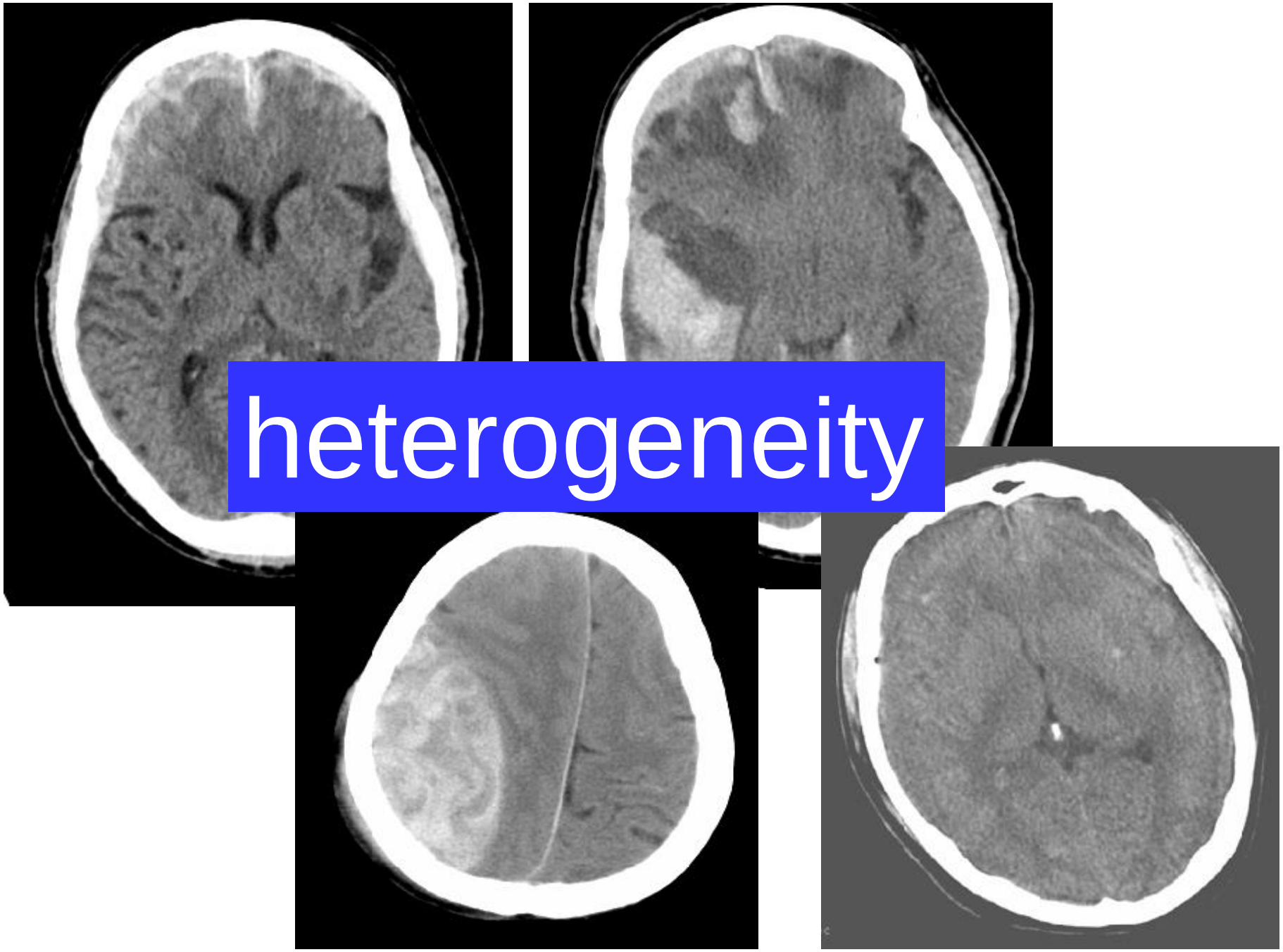


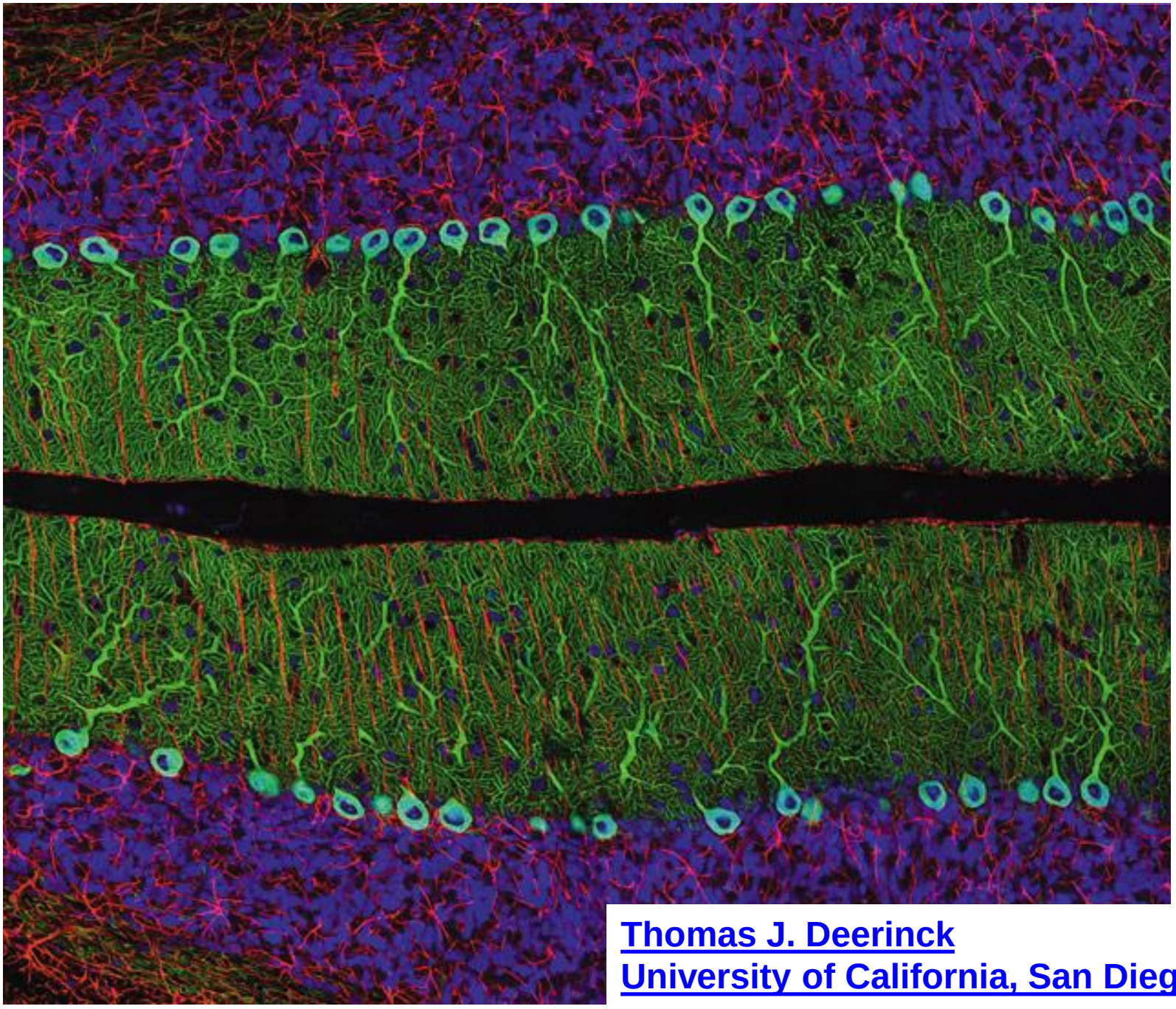
# Road traffic crashes can be prevented



# What is traumatic brain injury ?

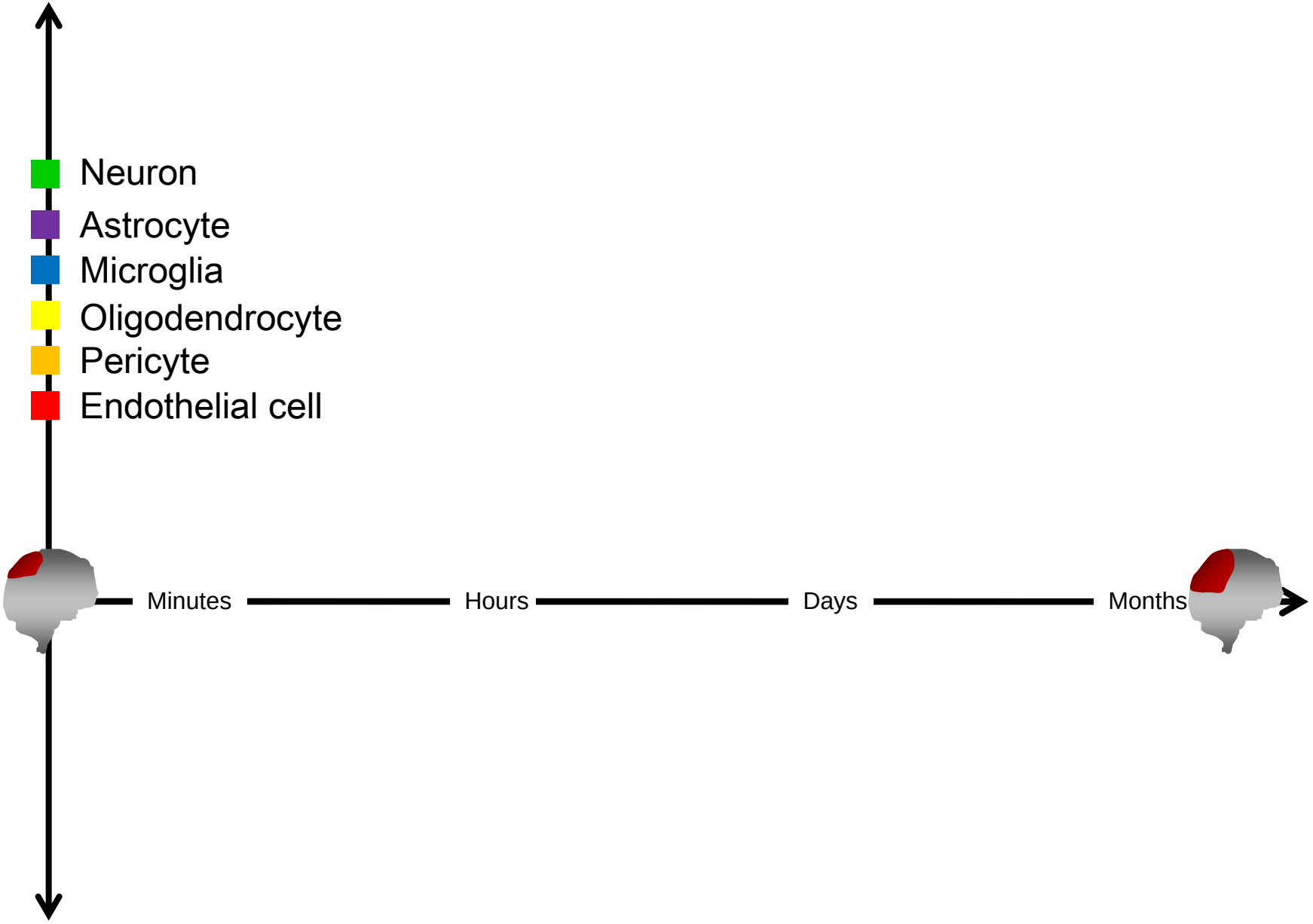

heterogeneity


heterogeneity

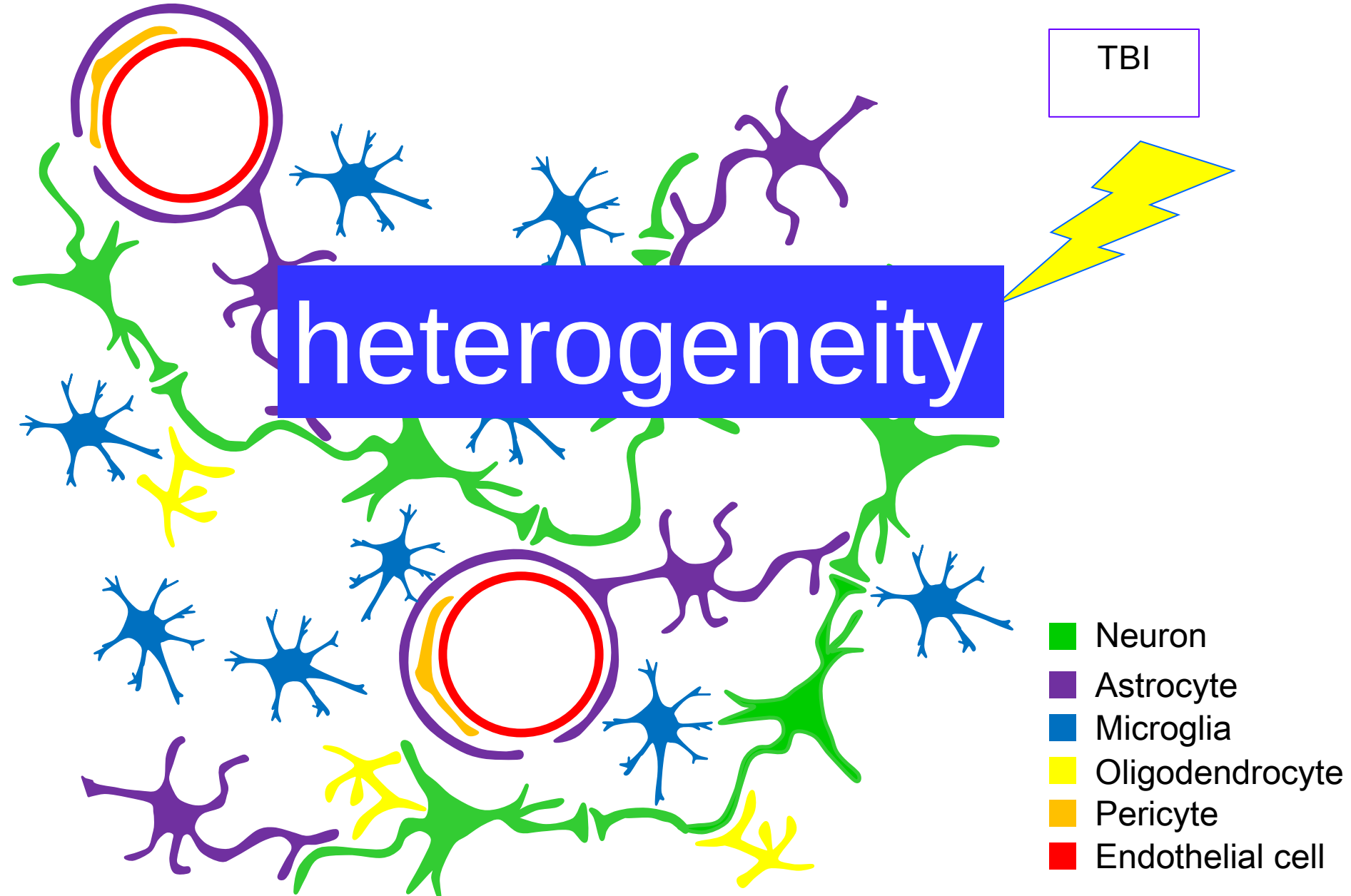


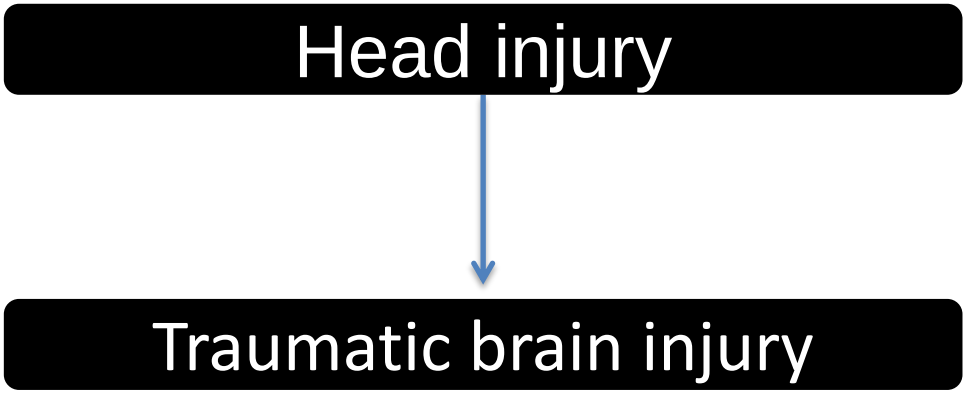
Thomas J. Deerinck
University of California, San Diego USA

# TBI and primary injury



# TBI and primary injury



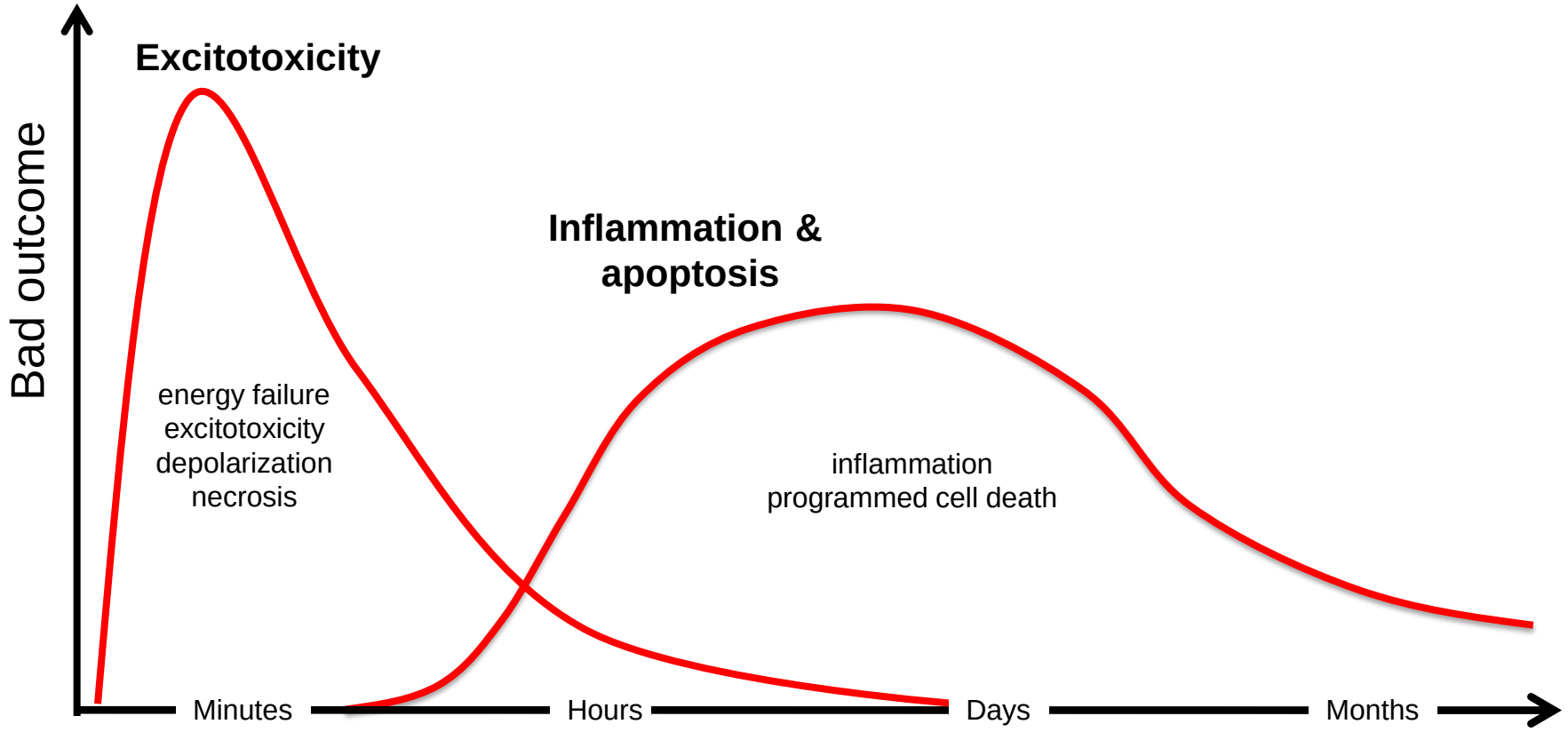



TBI: heterogeneous neurological disorder

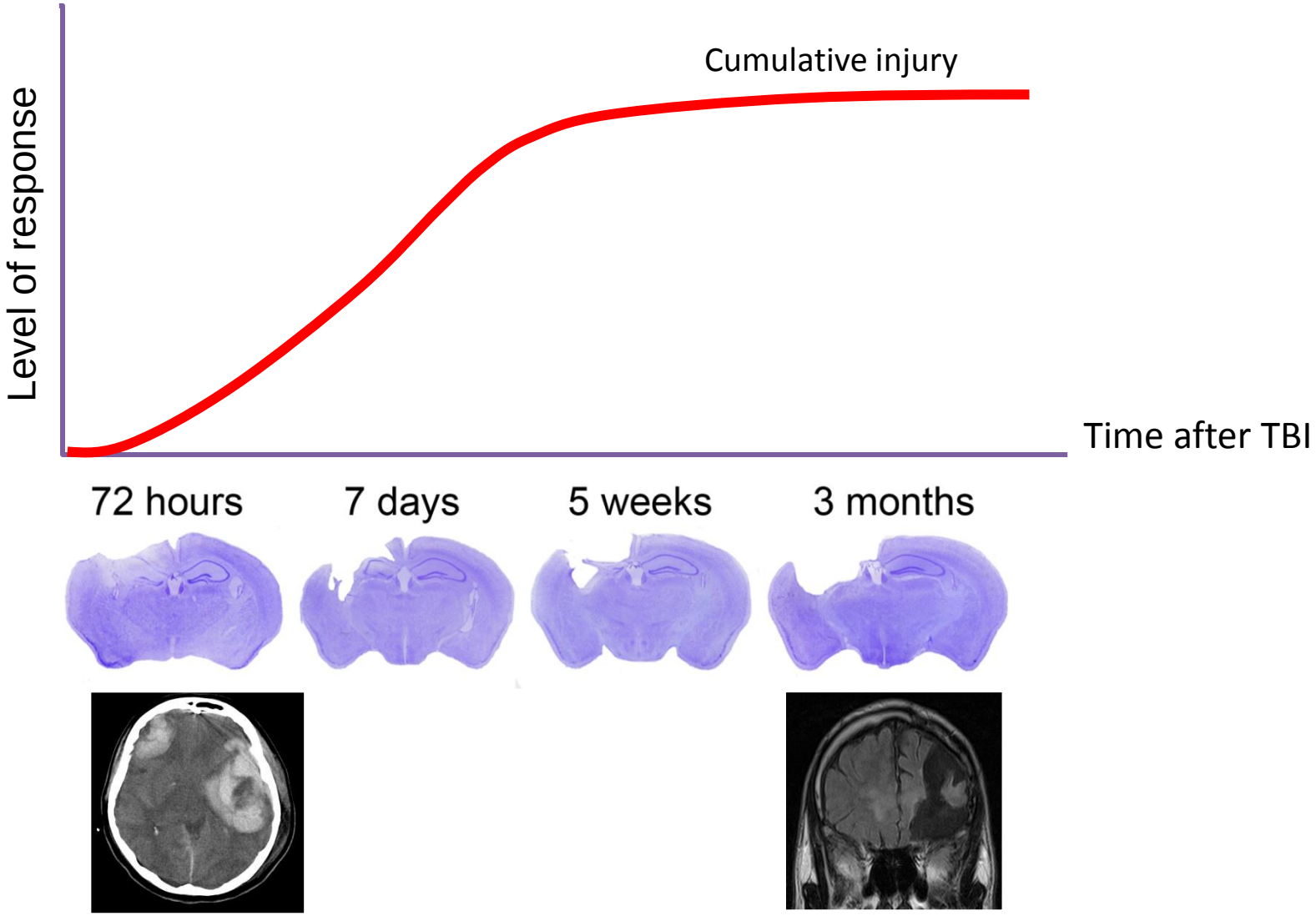
Severity
Location
Invasive versus non-invasive insults
Focal versus diffuse
Presence or absence of intracranial bleeding

Gender
Genetic predisposition
Presence or absence of co-morbidities

# TBI associated events

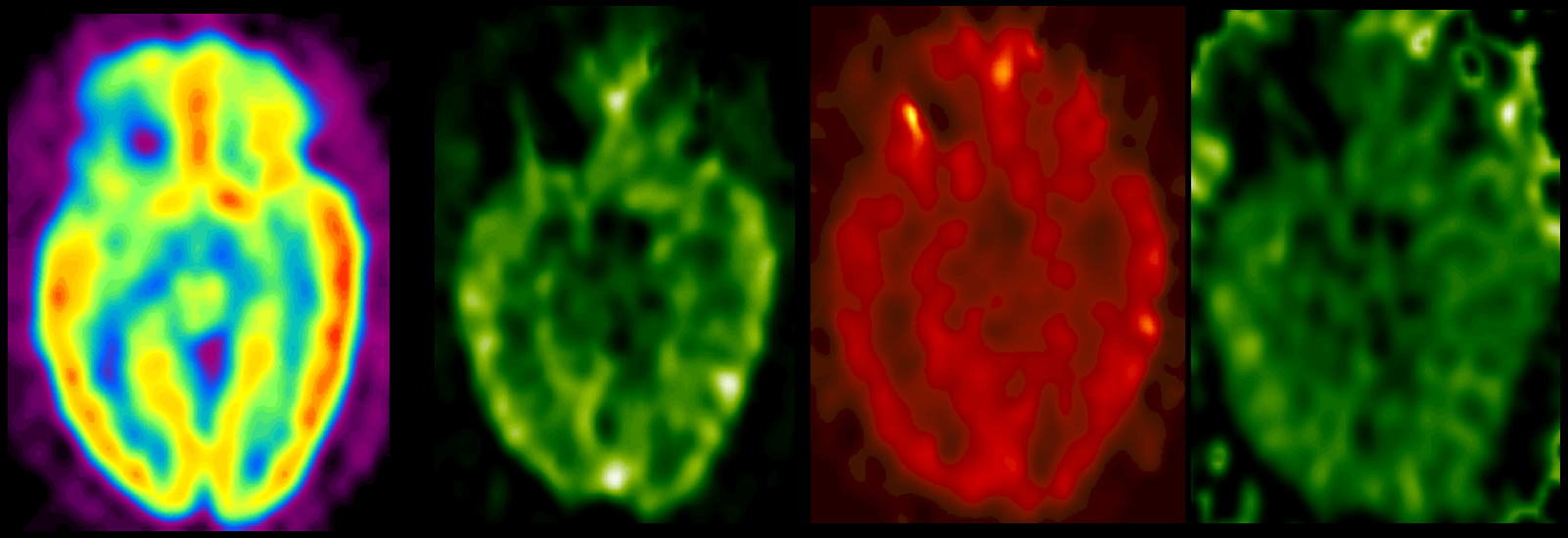


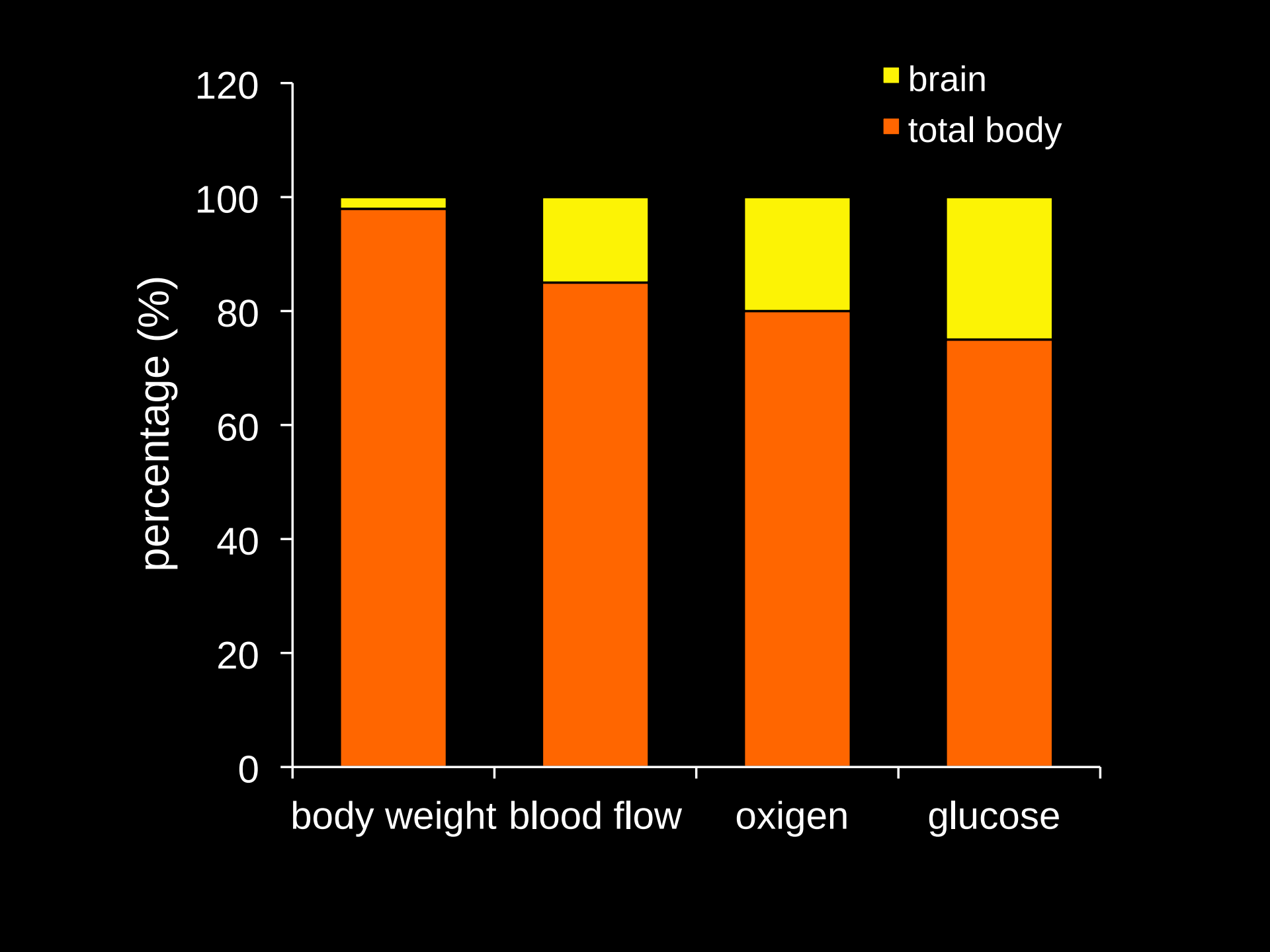
# Temporal evolution of brain damage

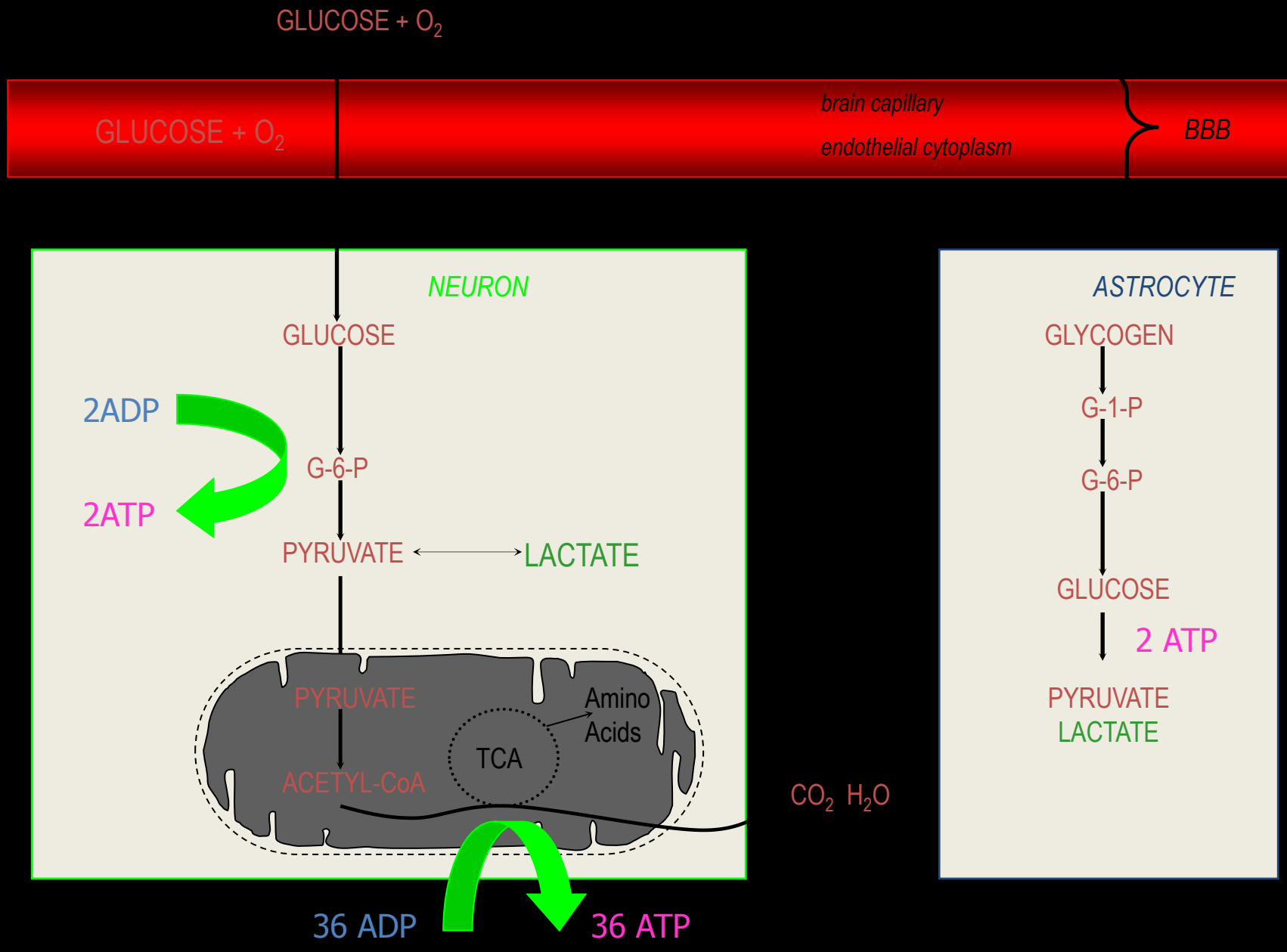


# Multitracer PET studies

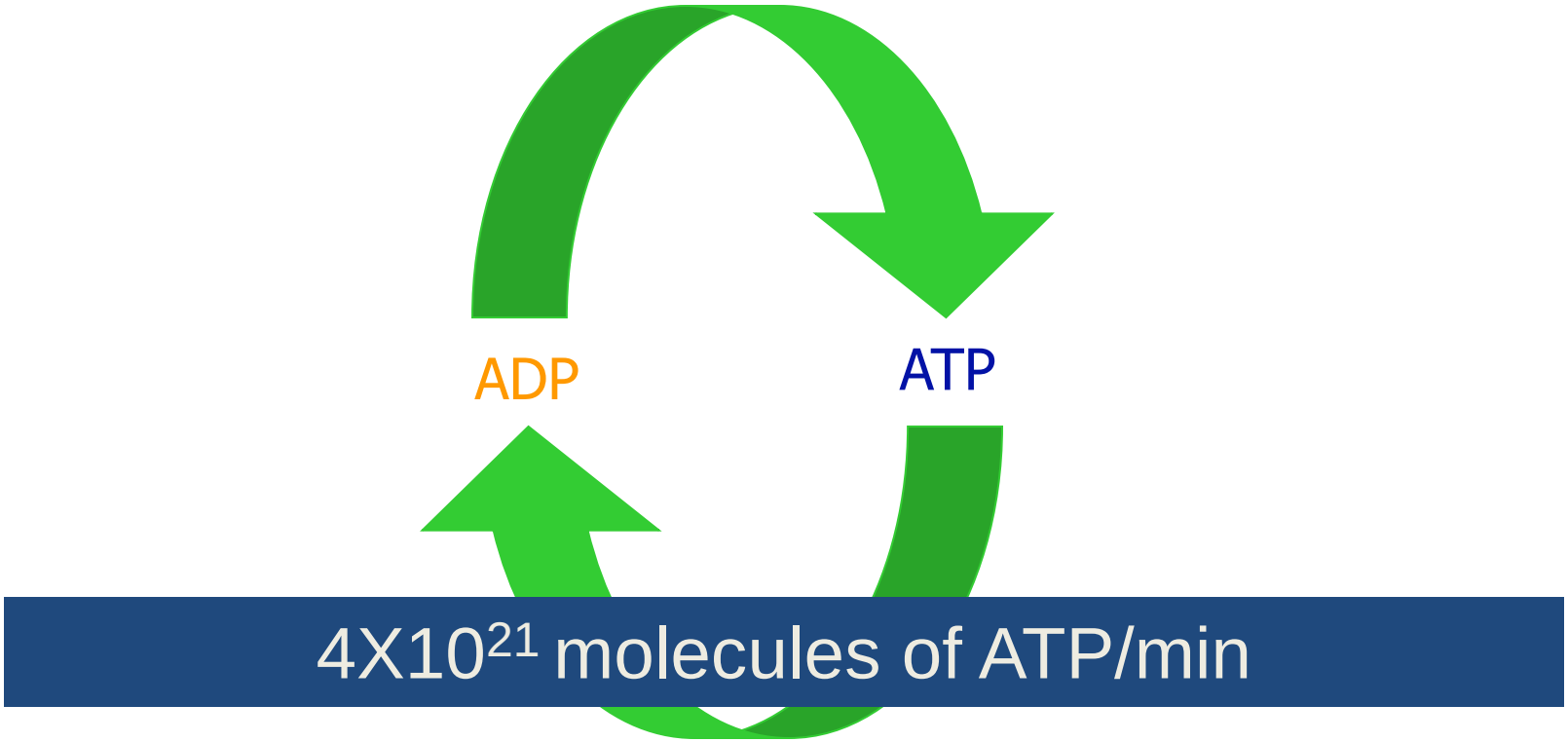
Comprehensive regional metabolic picture




brain
total body
120
100
80
60
40
20
0
percentage (%)
body weight
blood flow
oxigen
glucose


GLUCOSE + O2
GLUCOSE + O2
brain capillary
endothelial cytoplasm
BBB
NEURON
GLUCOSE
2ADP
2ATP
G-6-P
PYRUVATE
LACTATE
PYRUVATE
Amino
Acids
TCA
ACETYL-CoA
CO2 H2O
36 ADP
36 ATP
ASTROCYTE
GLYCOGEN
G-1-P
G-6-P
GLUCOSE
2 ATP
PYRUVATE
LACTATE

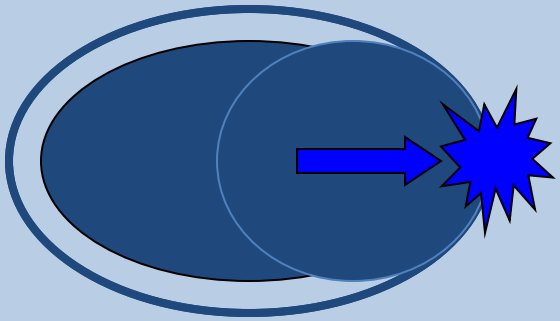
# Energy generation



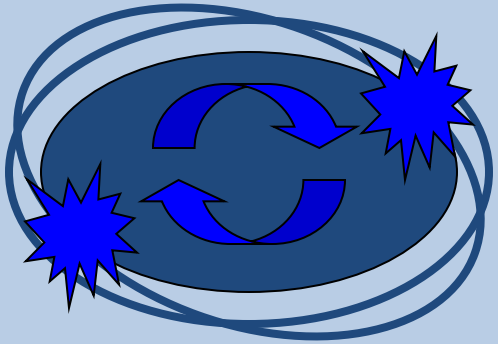

# Functional activity

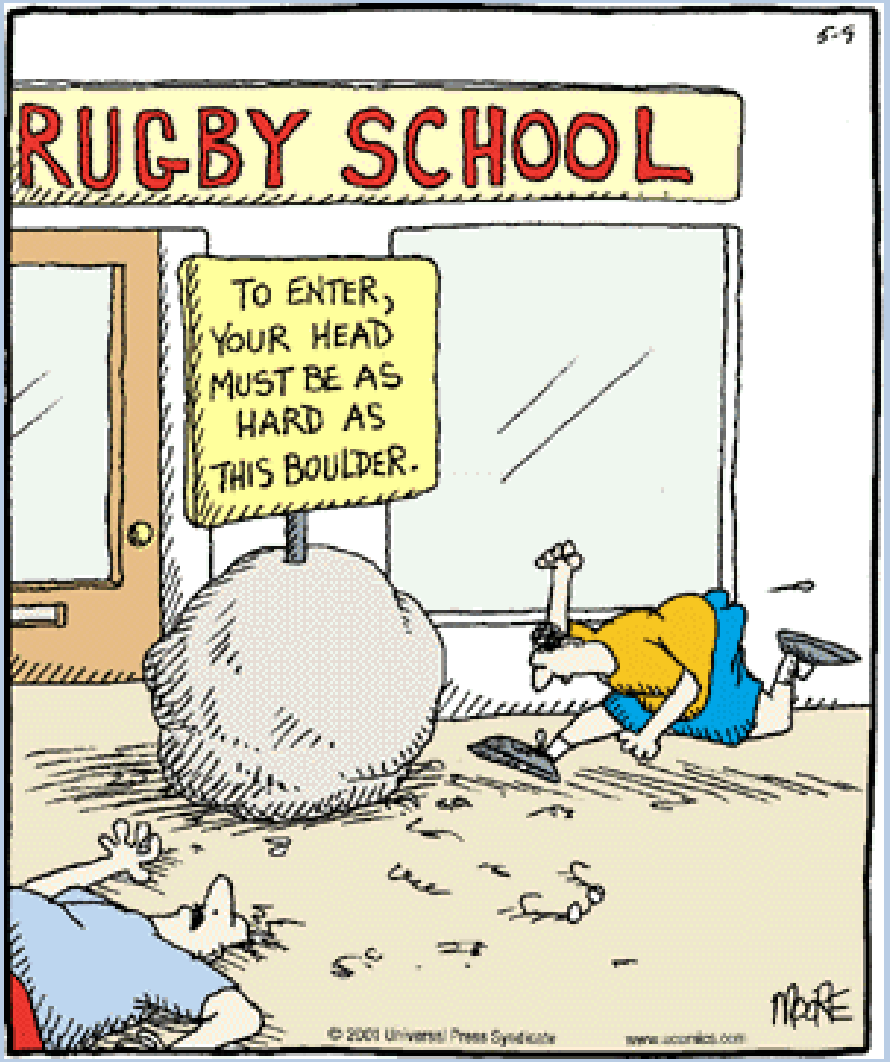
# Traumatic brain injury: concussion

Acceleration - Deceleration

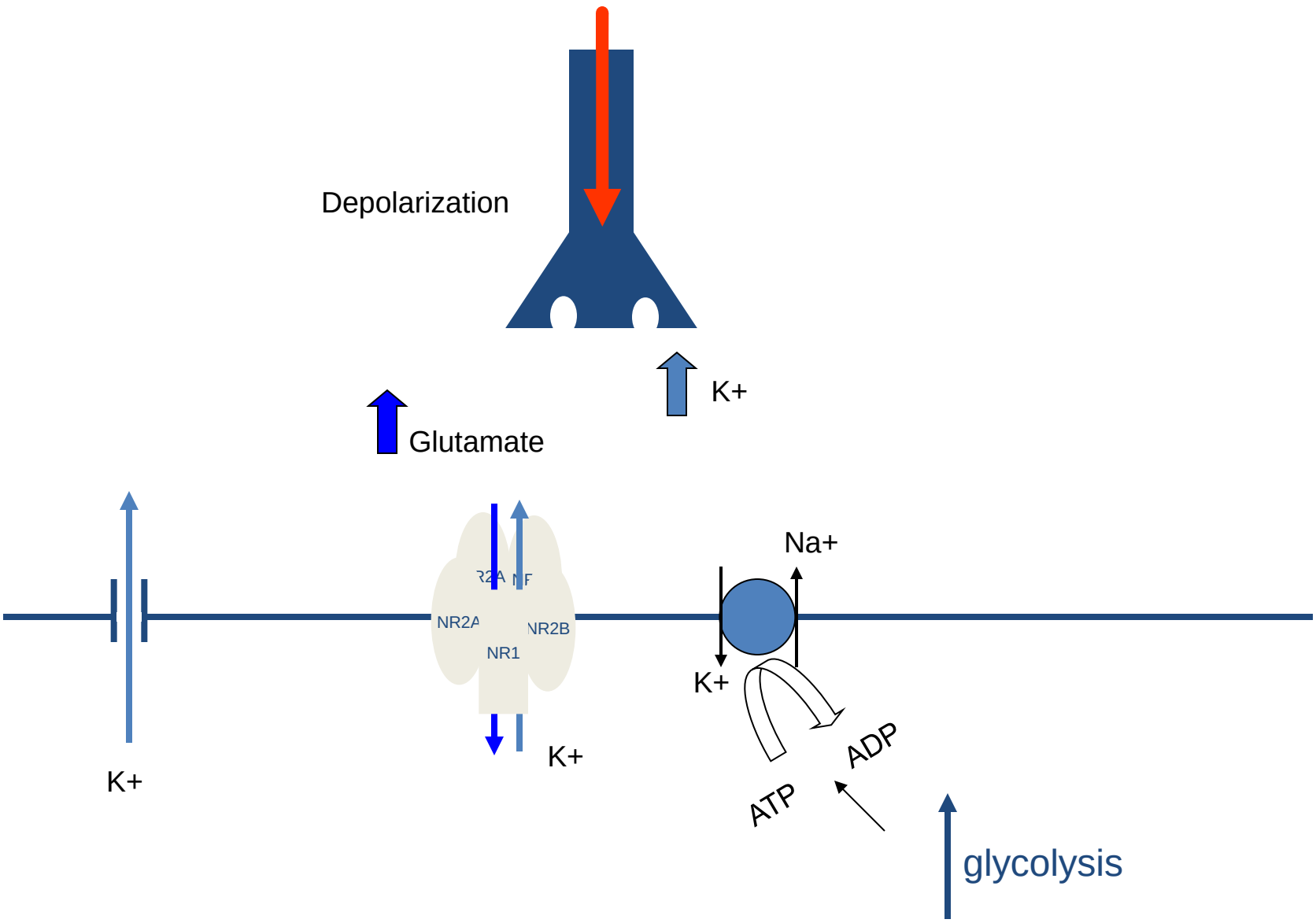


Rotation

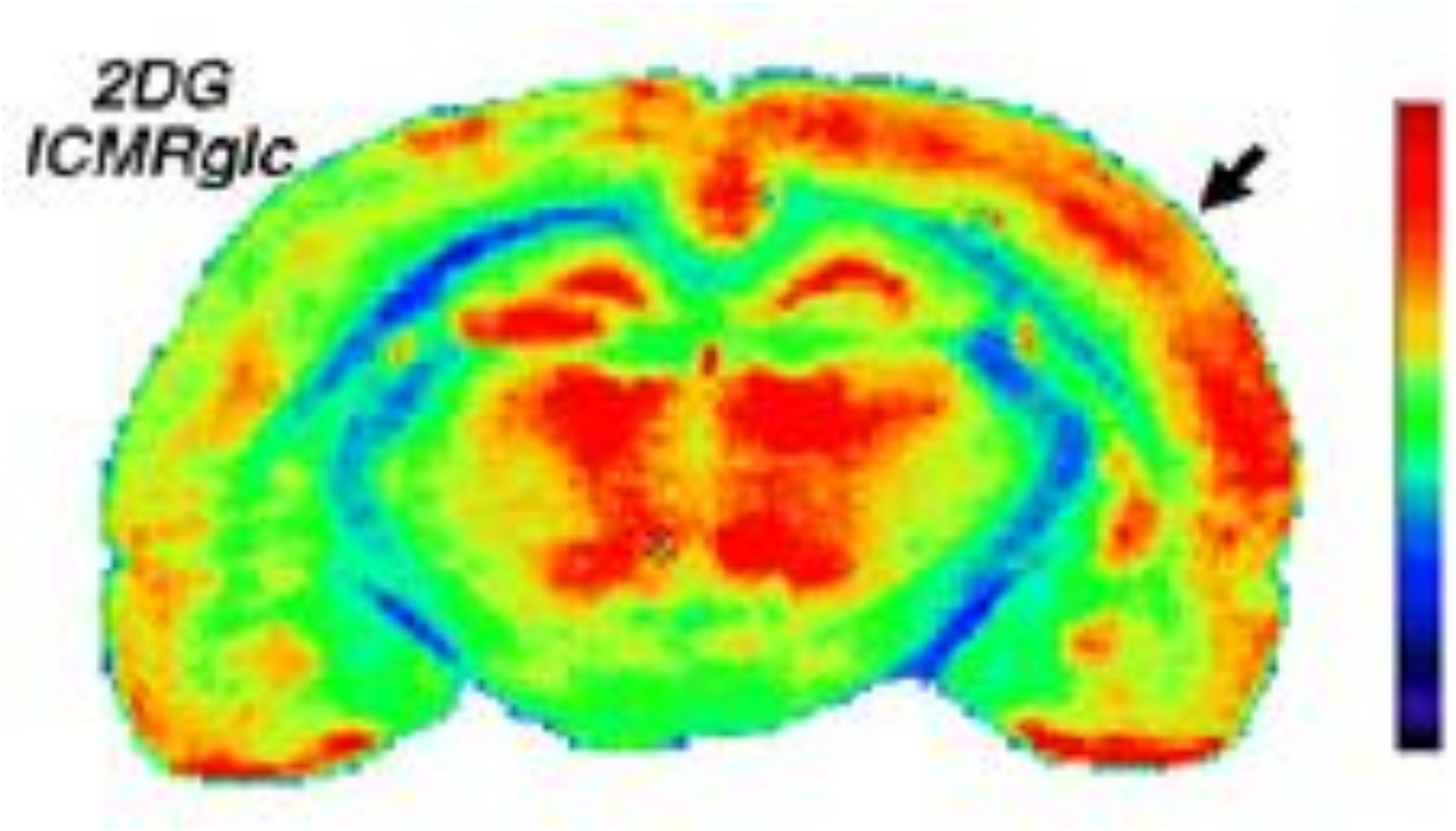




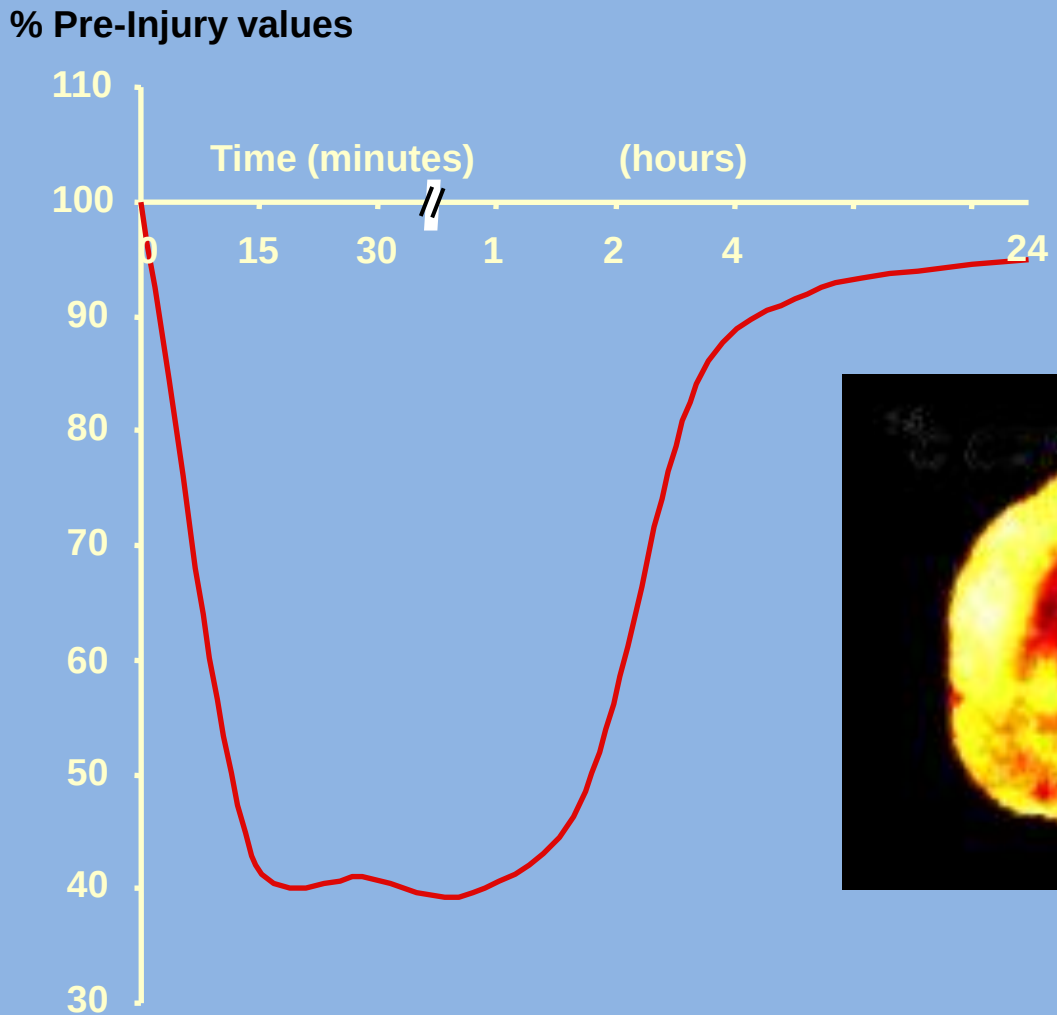
# Traumatic brain injury: concussion



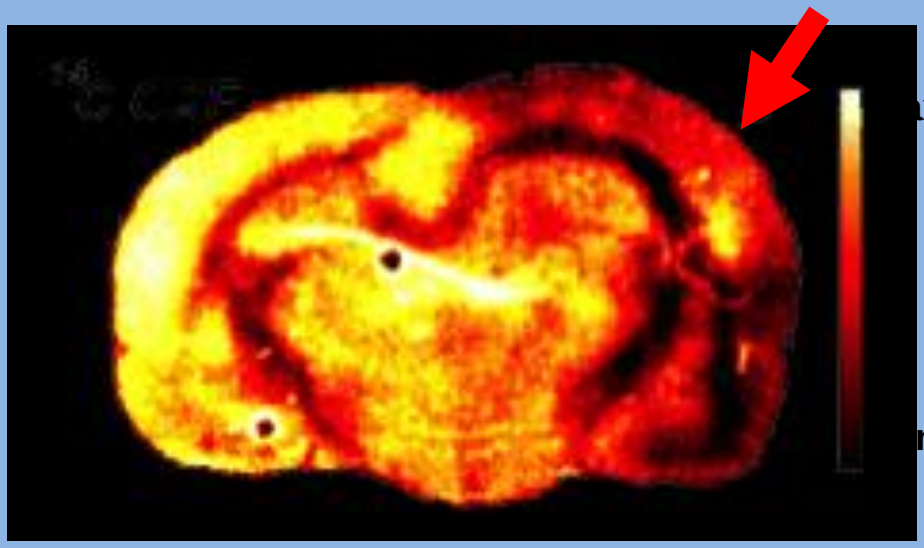
# Increased brain glucose utilization following TBI in the rat



# Decreased cerebral blood flow following TBI in the rat



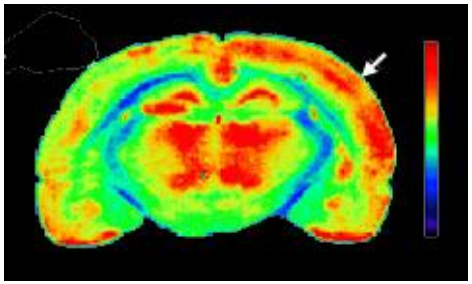

(Yamakami & McIntosh, 1991)

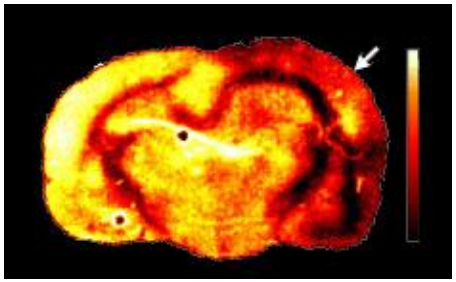


[$^{14}$C]-iodoantipyrine autoradiography

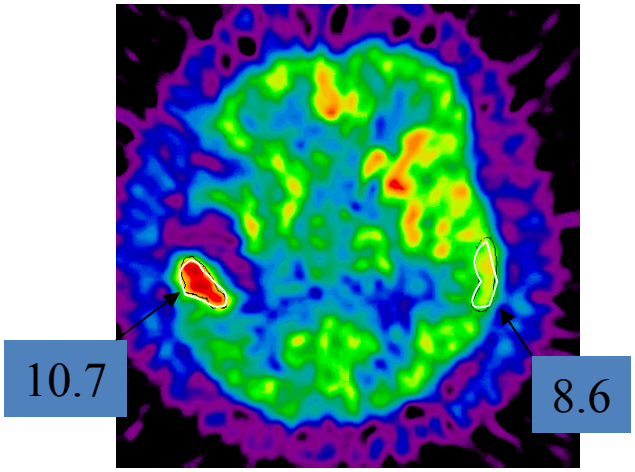
# Mismatch of CMRglc and CBF following TBI

Animal
Autoradiography

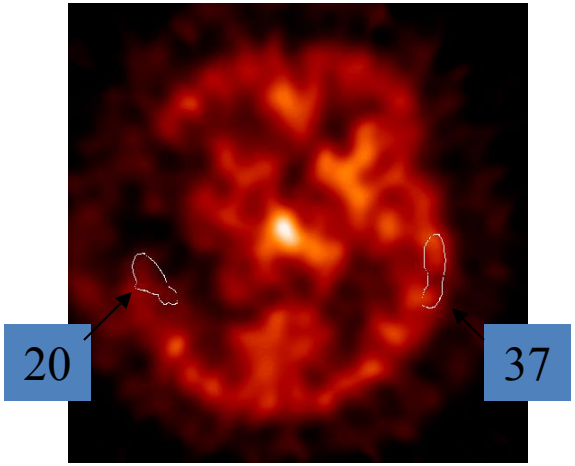




CT
(raw)

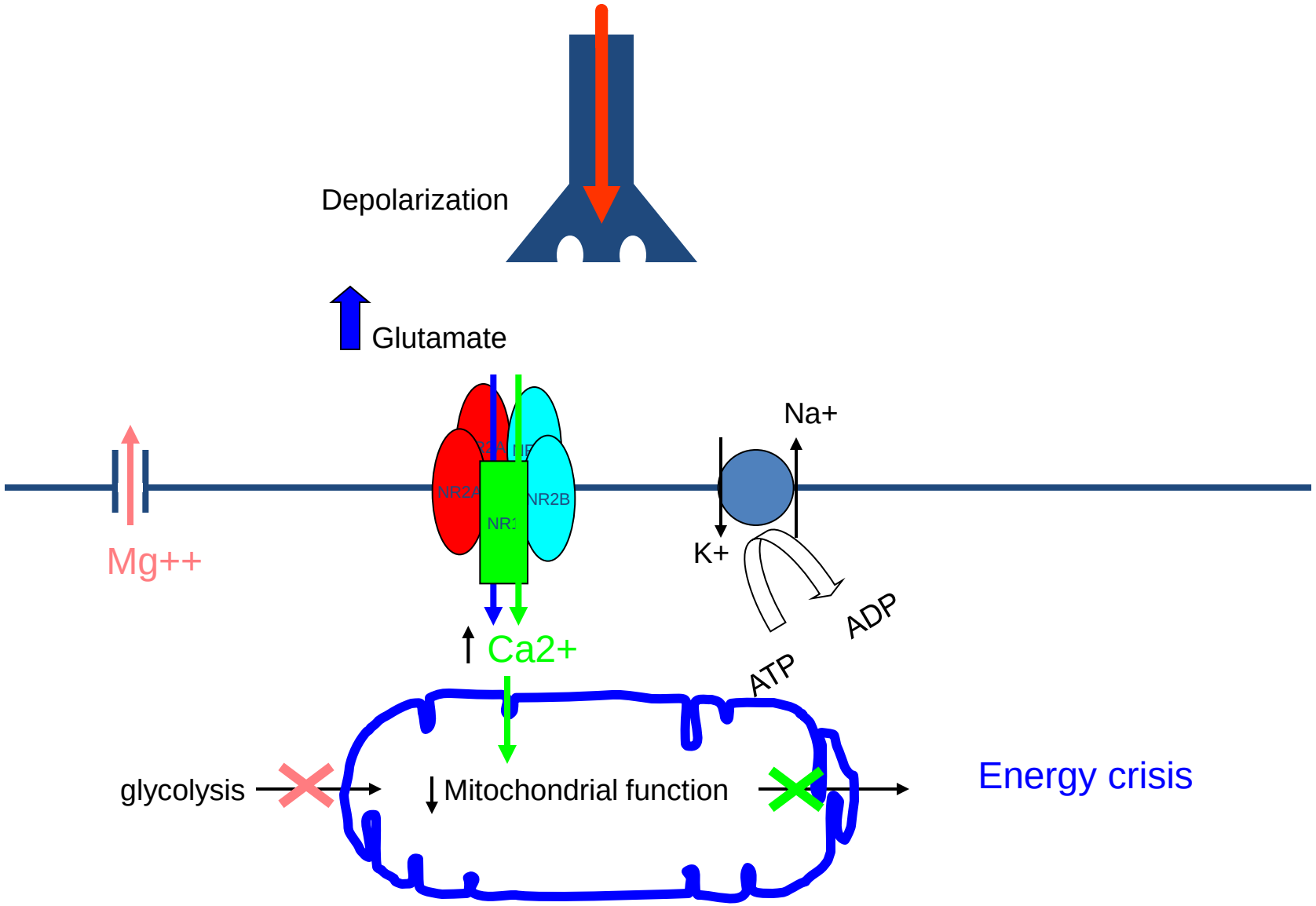



lCMRglc
mg/100g/min

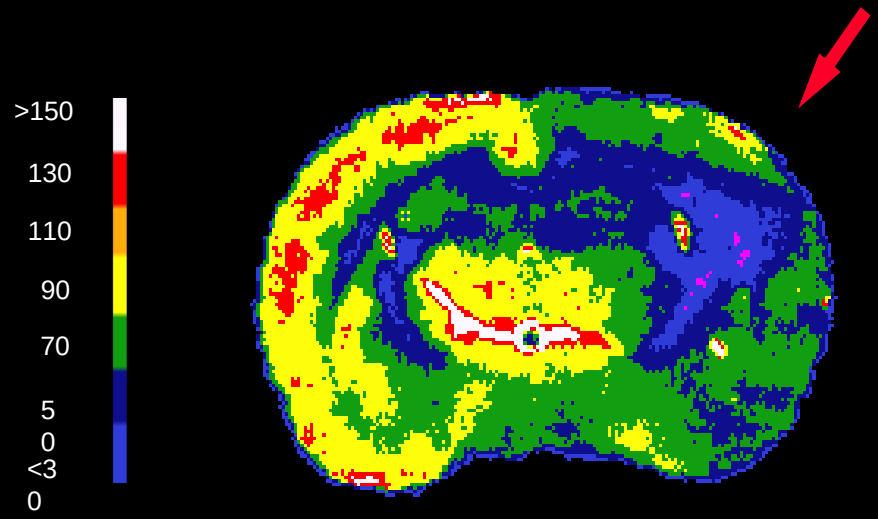



rCBF
ml/100g/min

# Traumatic brain injury: concussion

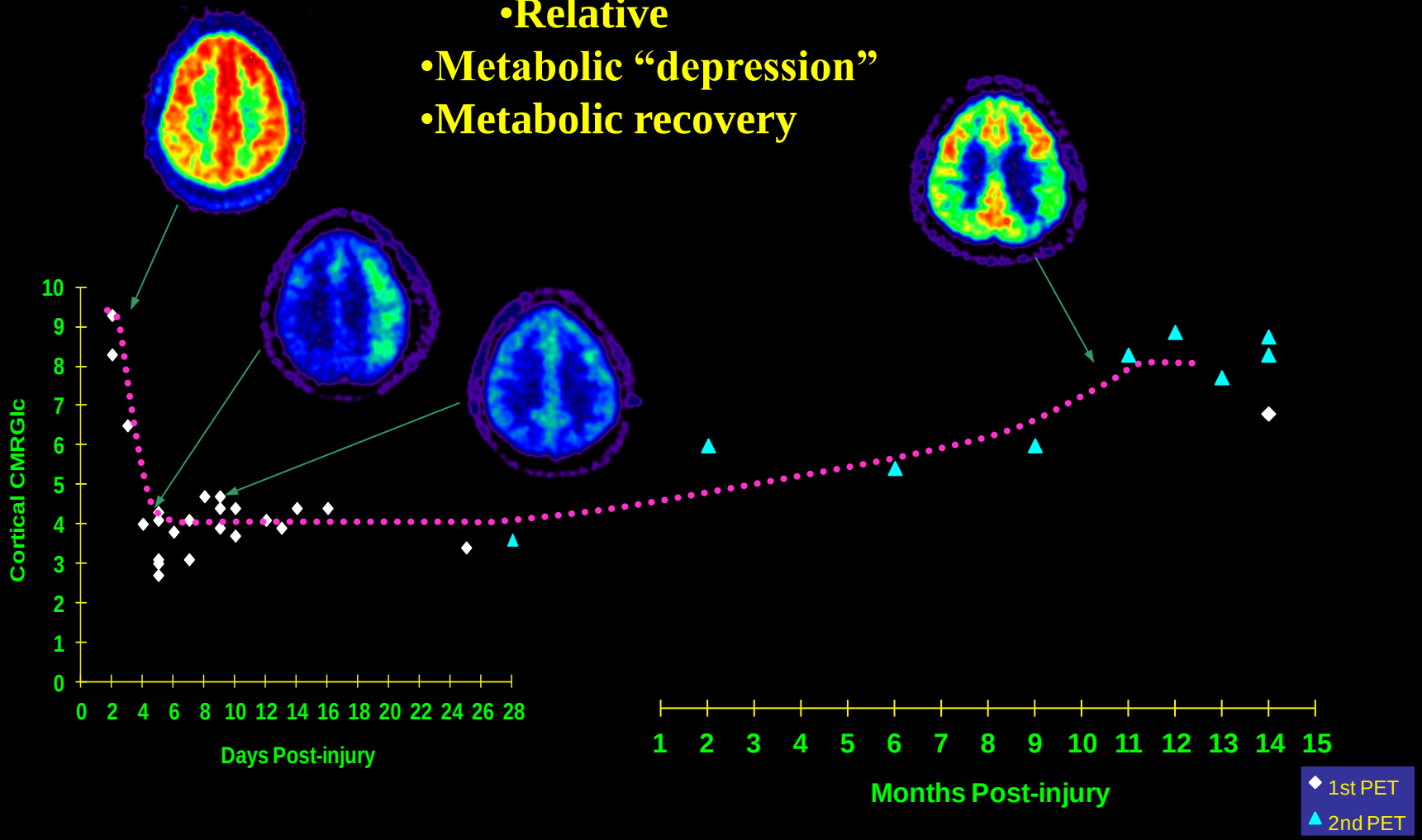


# Depression lCMR $_{glc}$ 3 Days Following Lateral F-P Brain Injury




lCMR $_{glc}$
(µmols/100g/min)

- Triphasic metabolic response
  - Hyperglycolysis
    - "Absolute"
    - Regional
    - Relative
  - Metabolic "depression"
  - Metabolic recovery

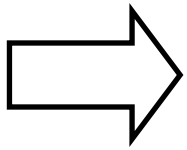


# Enhanced VULNERABILITY after TBI

The injured brain is vulnerable to even otherwise tolerable alterations

- vascular factors that increase the likelihood of ischemia (SUSCEPTIBILITY)

- altered ability to withstand insults (SENSITIVITY)



lower threshold for energy failure

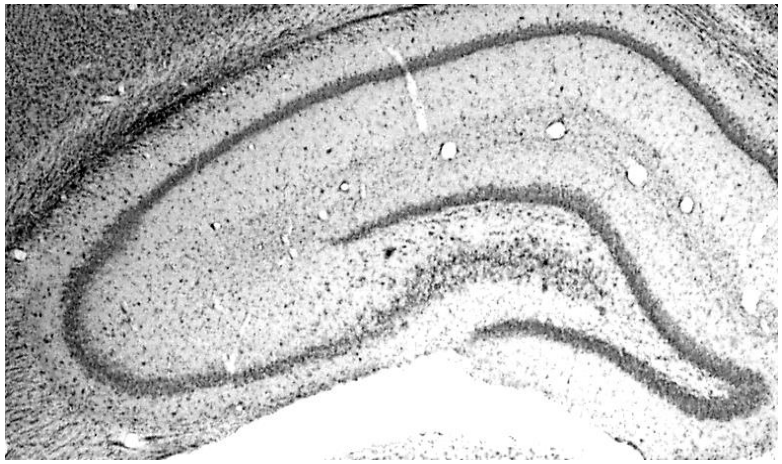
DeWitt DS: New Horizons 1995

# Brain vulnerability

Zanier ER, et al., J Neurotrauma, 2003

# Brain vulnerability

LFP+saline



Subtreshold level

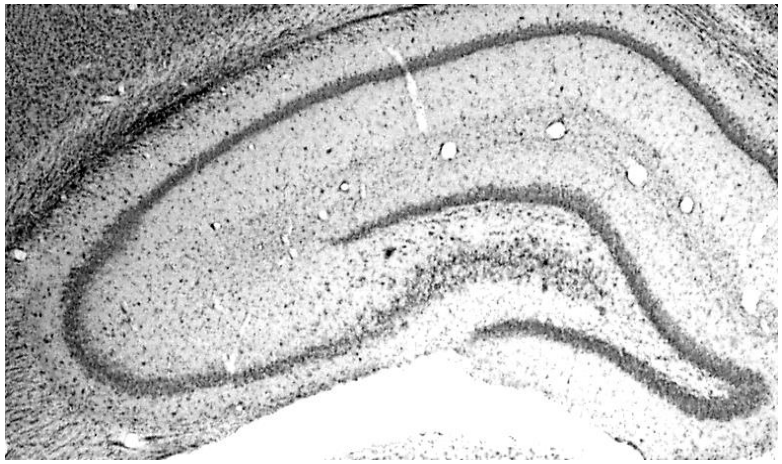
7d

Lateral fluid percussion injury (LFP)

Zanier ER, et al., J Neurotrauma, 2003

# Brain vulnerability

LFP+saline



sham+KA

Subtreshold level 7d

Lateral fluid percussion injury (LFP)

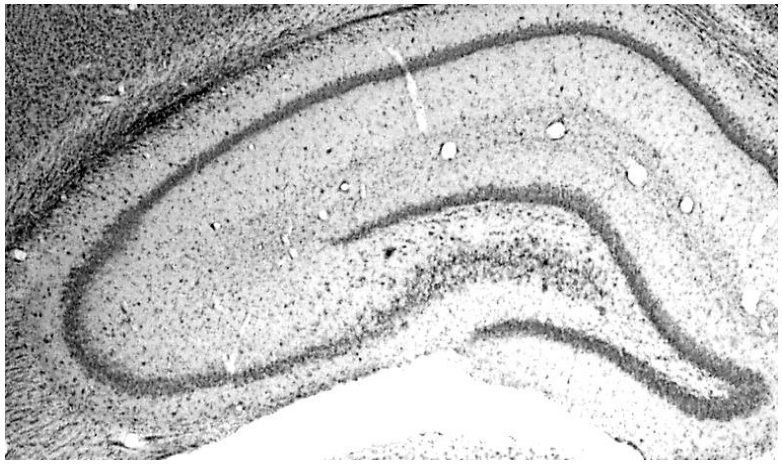
Subtreshold level 7d

Excitotoxic injury (KA)

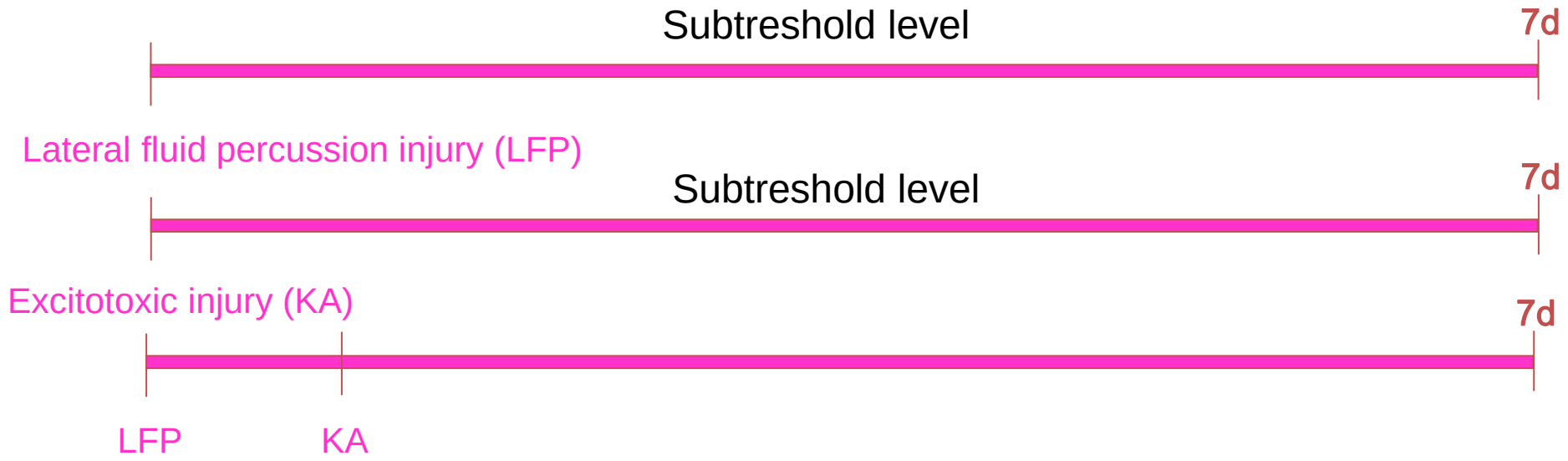
Zanier ER et al., J Neurotrauma, 2003

# Brain vulnerability

LFP+saline

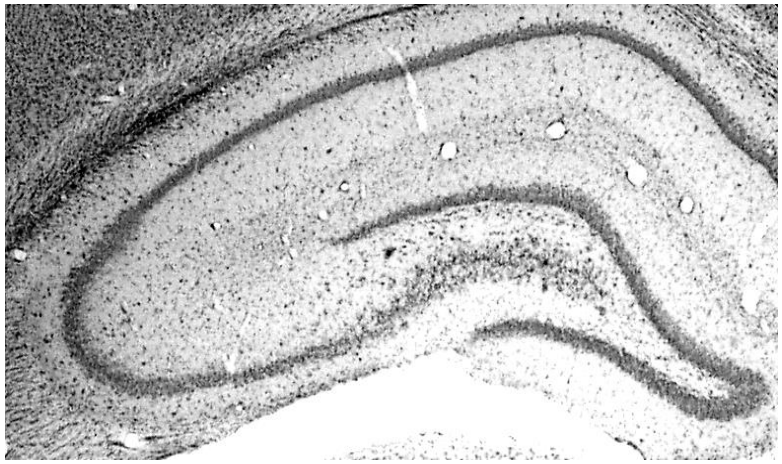


sham+KA

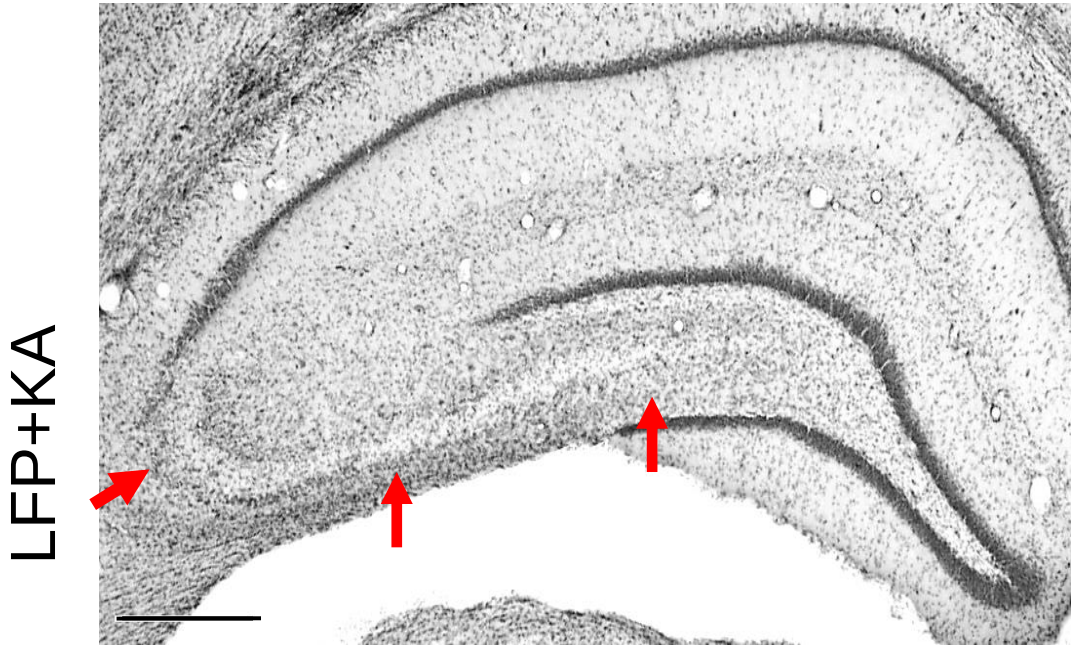



Zanier ER et al., J Neurotrauma, 2003

# Brain vulnerability

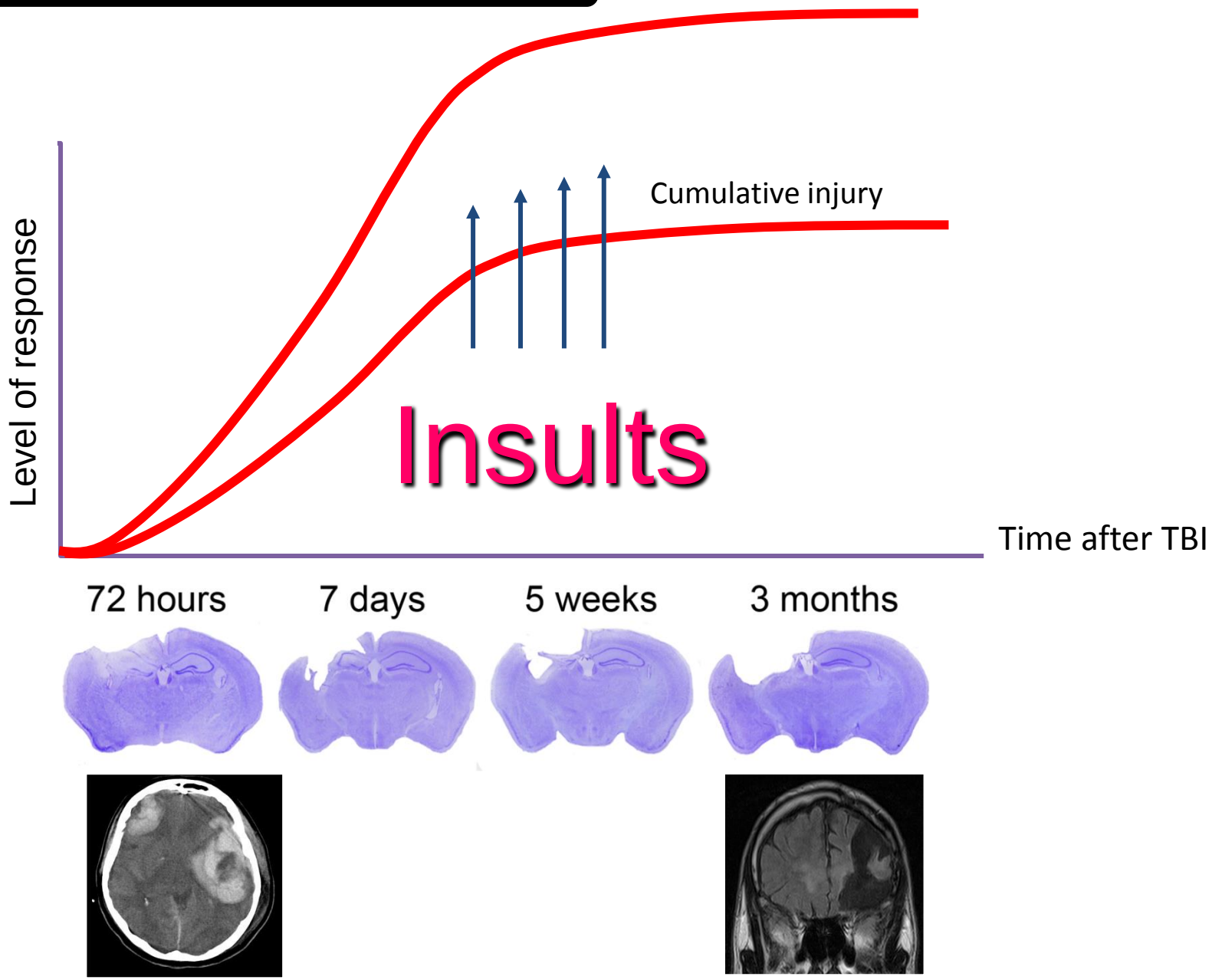




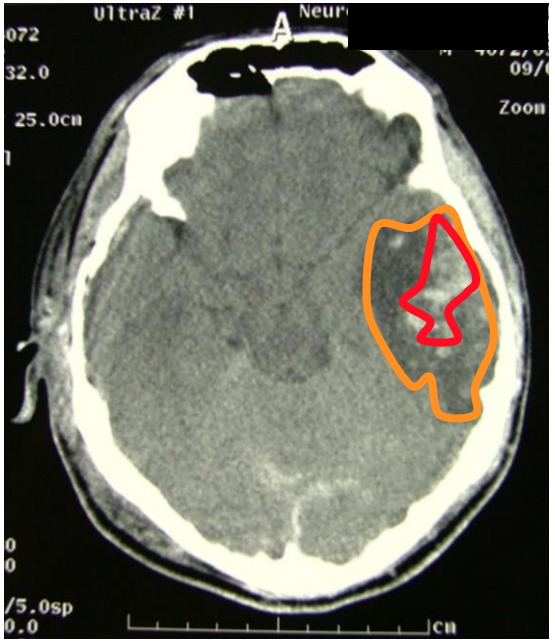



Zanier ER et al., J Neurotrauma, 2003

# Temporal evolution of brain damage



# Secondary insults




*Crisi comiziali*

*Febbre*

*Carenza di ossigeno*

*Riduzione della pressione*

Metabolismo depresso

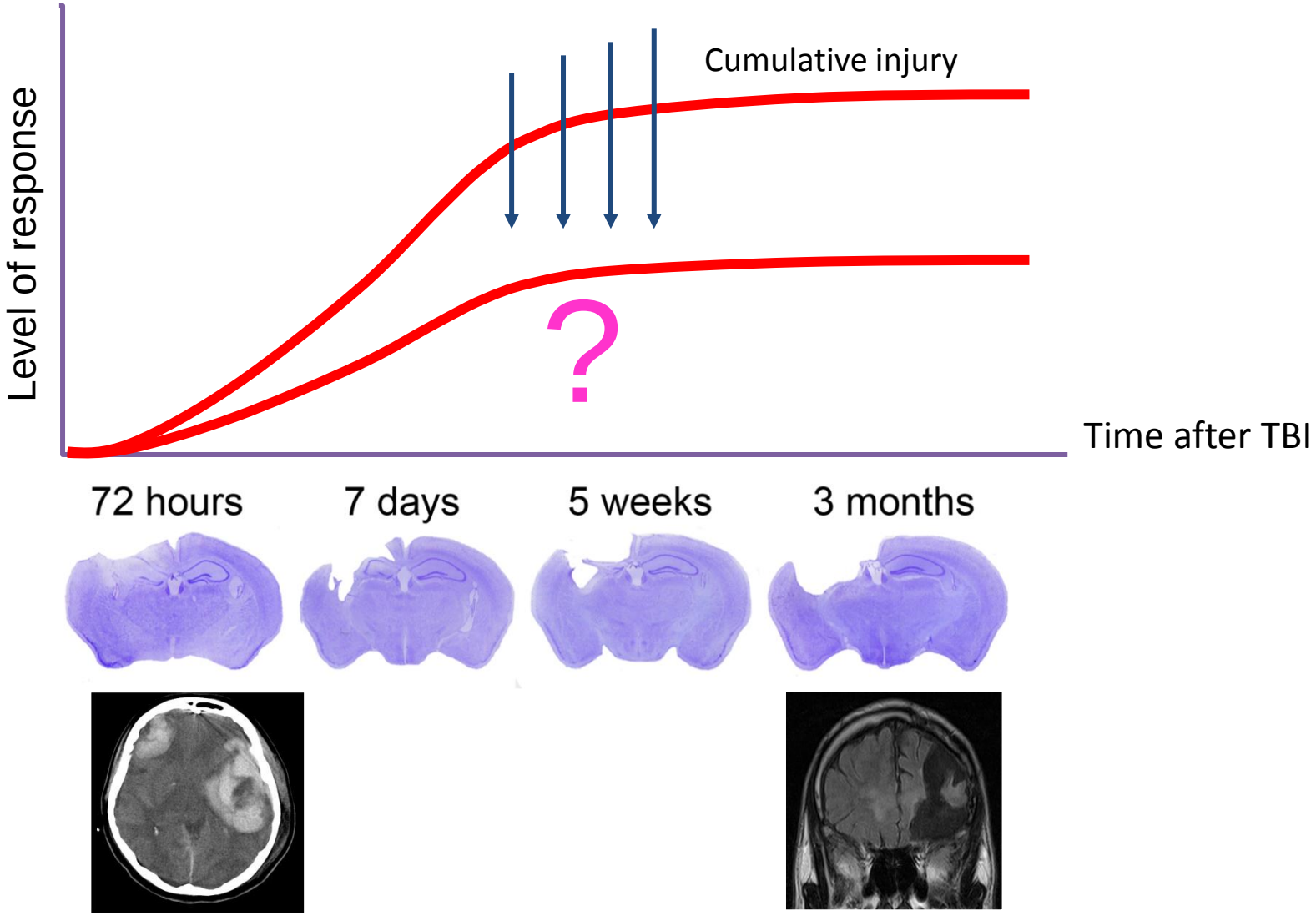
**Fallimento energetico**

Ridotto flusso ematico cerebrale

**Morte cellulare e danni neurologici**

# Temporal evolution of brain damage

## Brain protection and repair

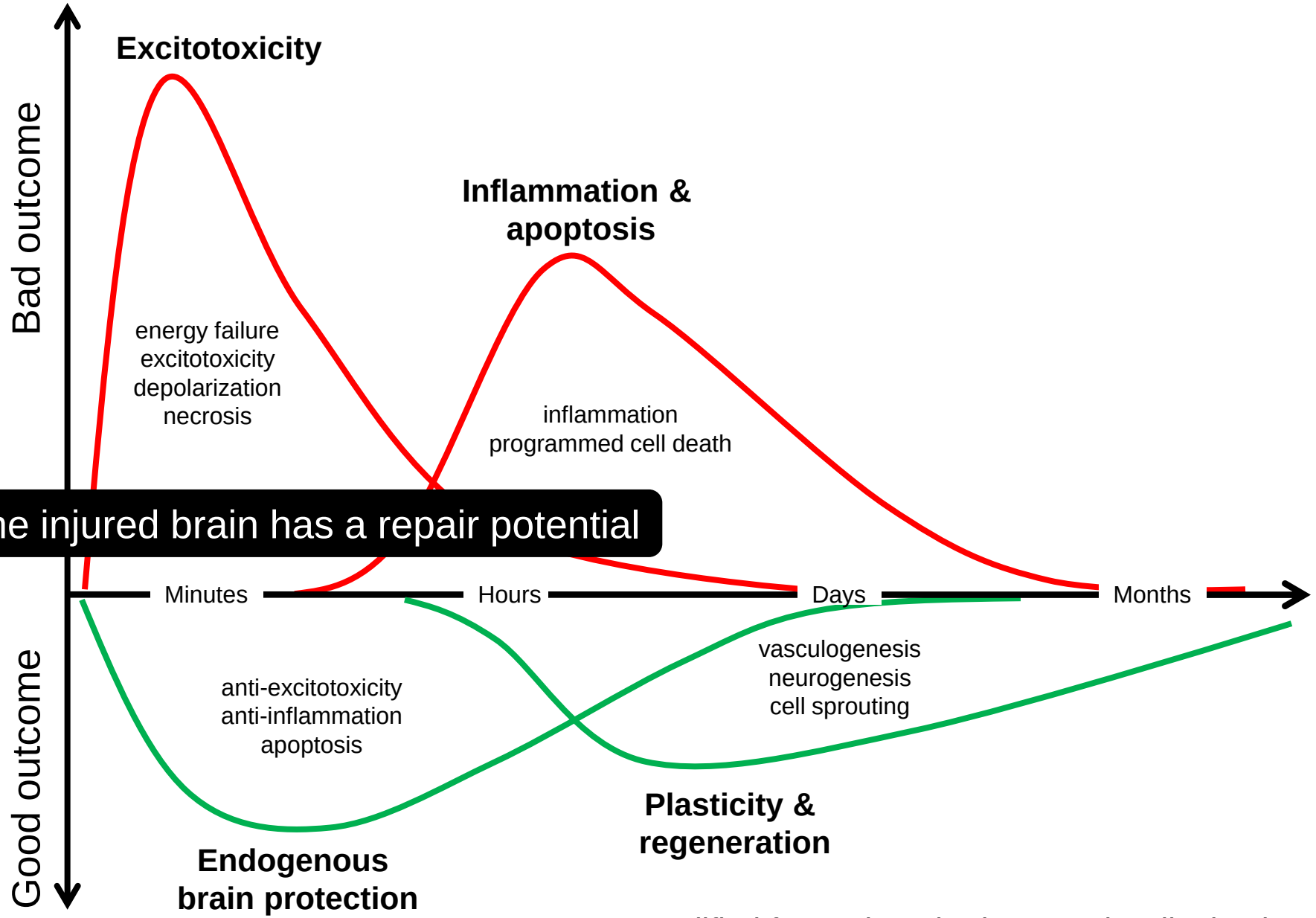


# Therapeutic strategies for TBI

More than **30 Phase-3 trials have failed** to show significance for their primary end point.

Most of these trials **targeted single factors** proposed to mediate secondary injury.

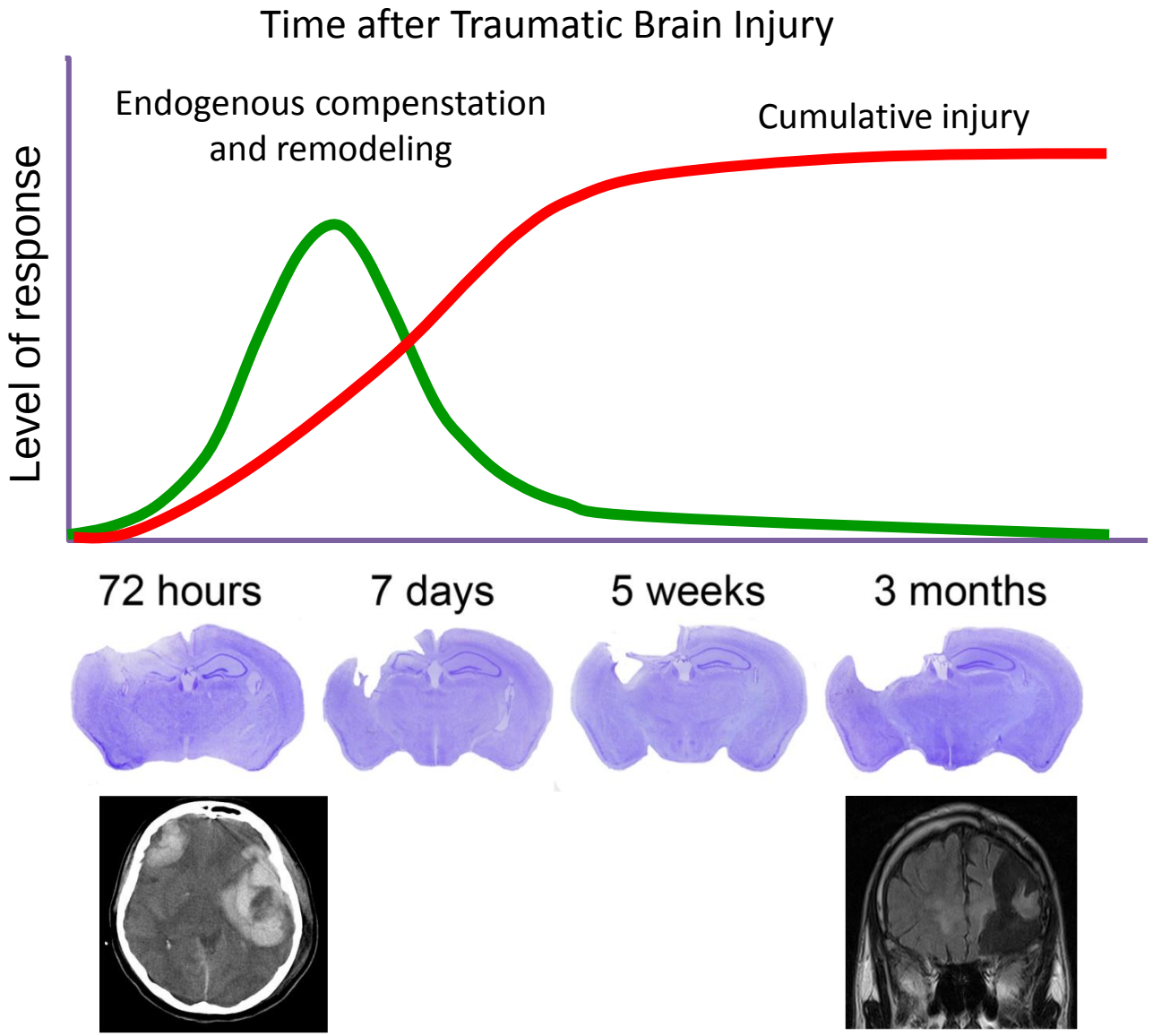
# TBI associated events




## The injured brain has a repair potential

Modified from Dirnagl, Simon and Hallenbeck 2003

# TBI associated events



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Need to focus on:

Strategies that **affect simultaneously multiple injury mechanisms.**

Neurorestorative strategies that **enhance endogenous restorative brain plasticity processes** to improve functional recovery.

# Therapeutic strategies for TBI

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Need to focus on:

Strategies that **affect simultaneously multiple injury mechanisms.**
Mesenchymal stem cells: induce multiple protective mechanisms

Neurorestorative strategies that **enhance endogenous restorative brain plasticity processes** to improve functional recovery.
Mesenchymal stem cells: induce mechanisms of repair

# Mesenchymal stromal cells to reprogramme the local microenviroment

- In different injury models it has been shown that MSC can induce multiple mechanisms of protection and repair

- Distinctive advantages of mesenchymal stromal cells (MSC):
  - Safe
  - Easily available
  - Free of ethical problem
  - Already used in the clinical setting for non-neurological conditions

# Mesenchymal stem cells for TBI

## Human umbilical cord blood mesenchymal stem cells protect mice brain after trauma*

Elisa R. Zanier, MD; Mery Montinaro, BS; Mariele Vigano, PhD; Pia Villa, PhD; Stefano Fumagalli, BS; Francesca Pischiutta, BS; Luca Longhi, MD; Matteo L. Leoni, MD; Paolo Rebulla, MD; Nino Stocchetti, MD; Lorenza Lazzari, PhD; Maria-Grazia De Simoni, PhD

Crit Care Med 2011 Vol. 39, No. 11

## Immunosuppression does not affect human bone marrow mesenchymal stromal cell efficacy after transplantation in traumatized mice brain

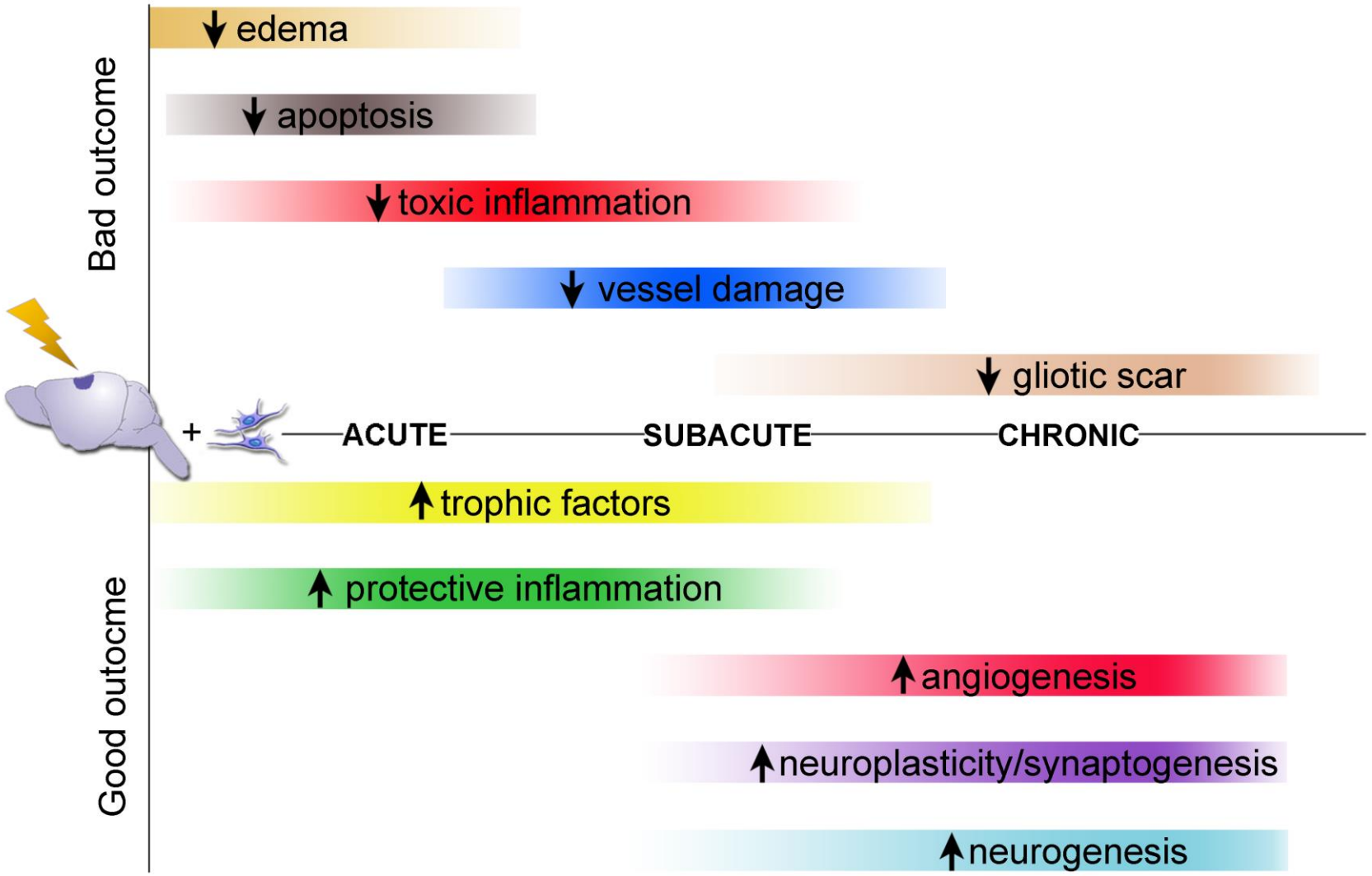
Francesca Pischiutta [a], Giovanna D'Amico [b], Erica Dander [b], Andrea Biondi [b], Ettore Biagi [c], Giuseppe Citerio [d], Maria Grazia De Simoni [a,*], Elisa R. Zanier [a]


## Bone Marrow Mesenchymal Stromal Cells Drive Protective M2 Microglia Polarization After Brain Trauma

Neurotherapeutics 2014

**Elisa R. Zanier · Francesca Pischiutta · Loredana Riganti · Federica Marchesi · Elena Turola · Stefano Fumagalli · Carlo Perego · Emanuela Parotto · Paola Vinci · Pietro Veglianese · Giovanna D'Amico · Claudia Verderio · Maria-Grazia De Simoni**

# Toxic and protective events affected by MSCs




Zanier et al., Cellular Therapy for Stroke and CNS Injuries. Springer in press

# Systematic review on MSC and experimental TBI: in progress…

PubMed.gov 7/5/2014

EMBASE® 18/12/2013

Records identified through PubMed searching (n=305)

Records identified through EmBase searching (n=102)

Records screened after duplicates removed (n=407)

Full-text articles assessed for eligibility (n=136)

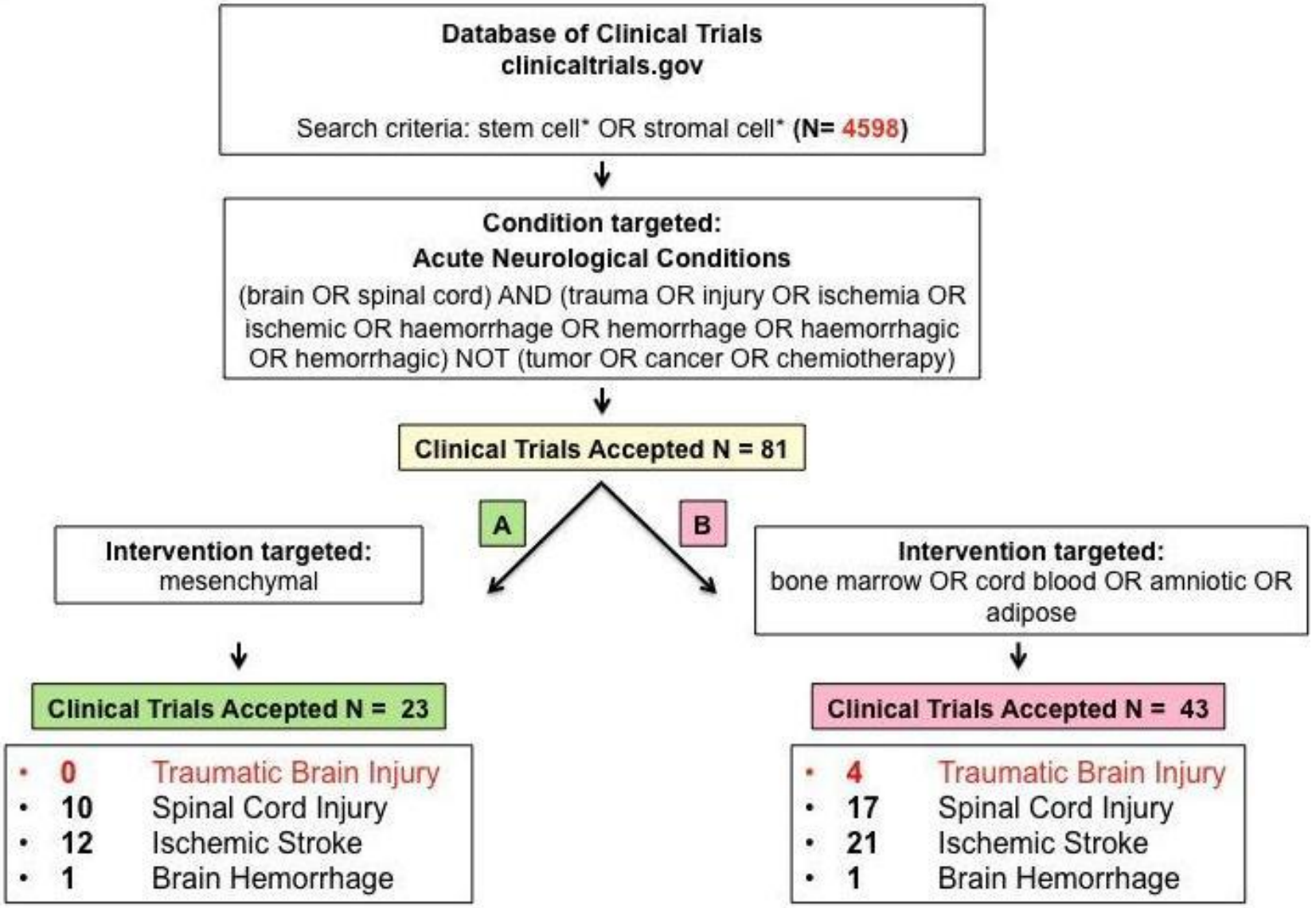
**MSC + TBI:**

**136 references**

**MSCs protect the brain after acute brain injury promoting both protective and reparative processes**

Search criteria adapted for TBI from Oliveri RS et al., Neurobiol of disease 2013

# Clinical Trials (CTs) registered in ClinicalTrials.gov on stem/stromal cells. Search performed on 12-2-2014.




Zanier et al., Cellular Therapy for Stroke and CNS Injuries. Springer in press

# MSC and experimental TBI

| Motor deficit | Cognitive deficit | Contusion volume |
|---|---|---|
| Improvement 20/27 | Improvement 15/27 | Improvement 10/27 |

| | | |
|---|---|---|
| Improvement | Improvement | Small effect |

Maximize efficacy

REVIEW

**Mesenchymal stromal cells: misconceptions and evolving concepts**

DONALD G. PHINNEY[1] & LUC SENSEBÉ[2,3]

*Cytotherapy*, 2013; 15: 140–145

- MSC isolated from different tissues are NOT equivalent

- Protocols used to prepare the cells affect their properties

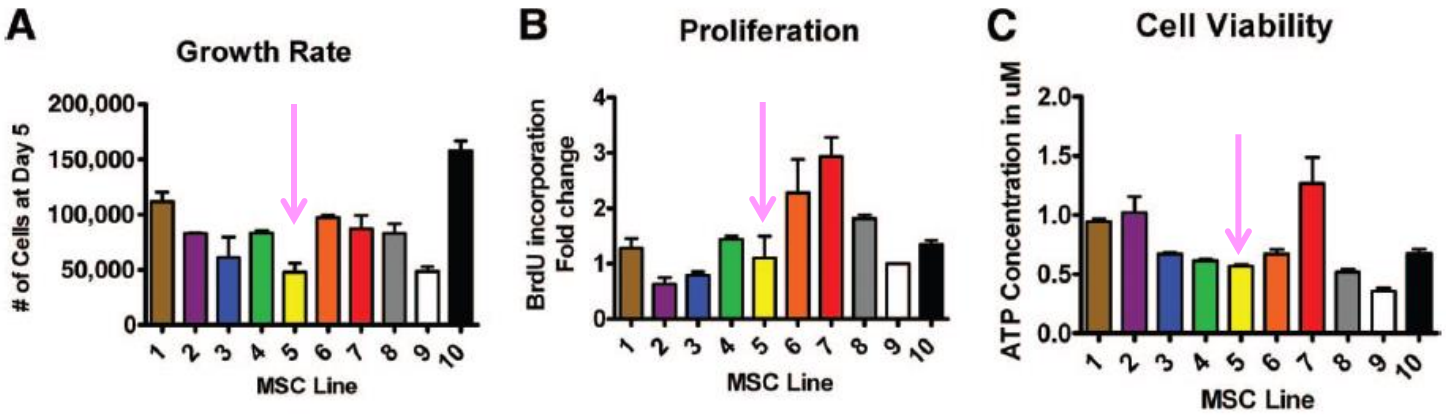
# Maximize efficacy

**Human Mesenchymal Stromal Cells: Identifying Assays to Predict Potency for Therapeutic Selection**

Desirae L. Deskins,[a,b,*] Dikshya Bastakoty,[a,*] Sarika Saraswati,[a] Andrew Shinar,[c] Ginger E. Holt,[c] Pampee P. Young[a,b,d]

Stem Cells Translational Medicine 2013;2:151–158 www.StemCellsTM.com

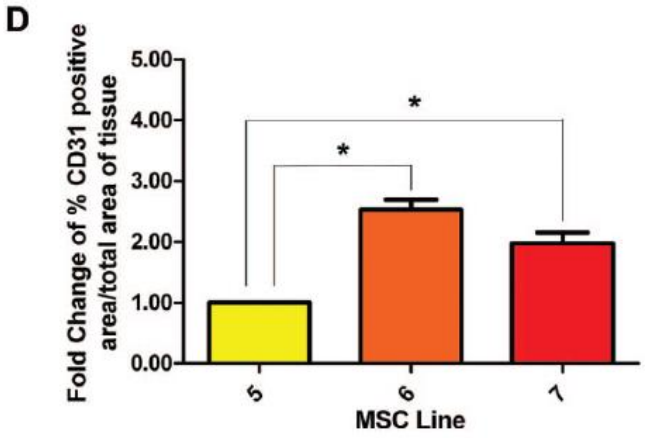
## *In vitro*


## *In vivo*

Mouse wound model

Vascular density of the granulation tissue generated by MSC lines at 3 weeks




The ability to poduce large quantities of MSC with predictable quality and quantifiable potency is necessary for successful clinical use

# What is needed to translate stem cells into effective therapies following TBI

- Maximum information about efficacy and safety must be obtained from ongoing and planned clinical trials
- Mechanism of actions:
  - To select the optimal cell type/source/culture condition
  - To induce maximum recovery
  - To select the most suitable patient

# Outline

- Epidemiology
- Pathophysiology
  - Heterogeneity
  - Susceptibility
  - Chronic degenerative processes
- Therapeutic strategies
  - Secondary insults
  - Regenerative potential

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