Candidate cellular and molecular mechanisms of epileptogenesis

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An alternative and accessible version of this presentation is available at 3:10 pm in the Videocast of Day One

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Outline

I. Introduction

Evaluating cellular and molecular mechanisms of epileptogenesis

II. Stages of epileptogenesis

A. Minutes/hours

B. Days

C. Weeks/months

III. Translational approaches

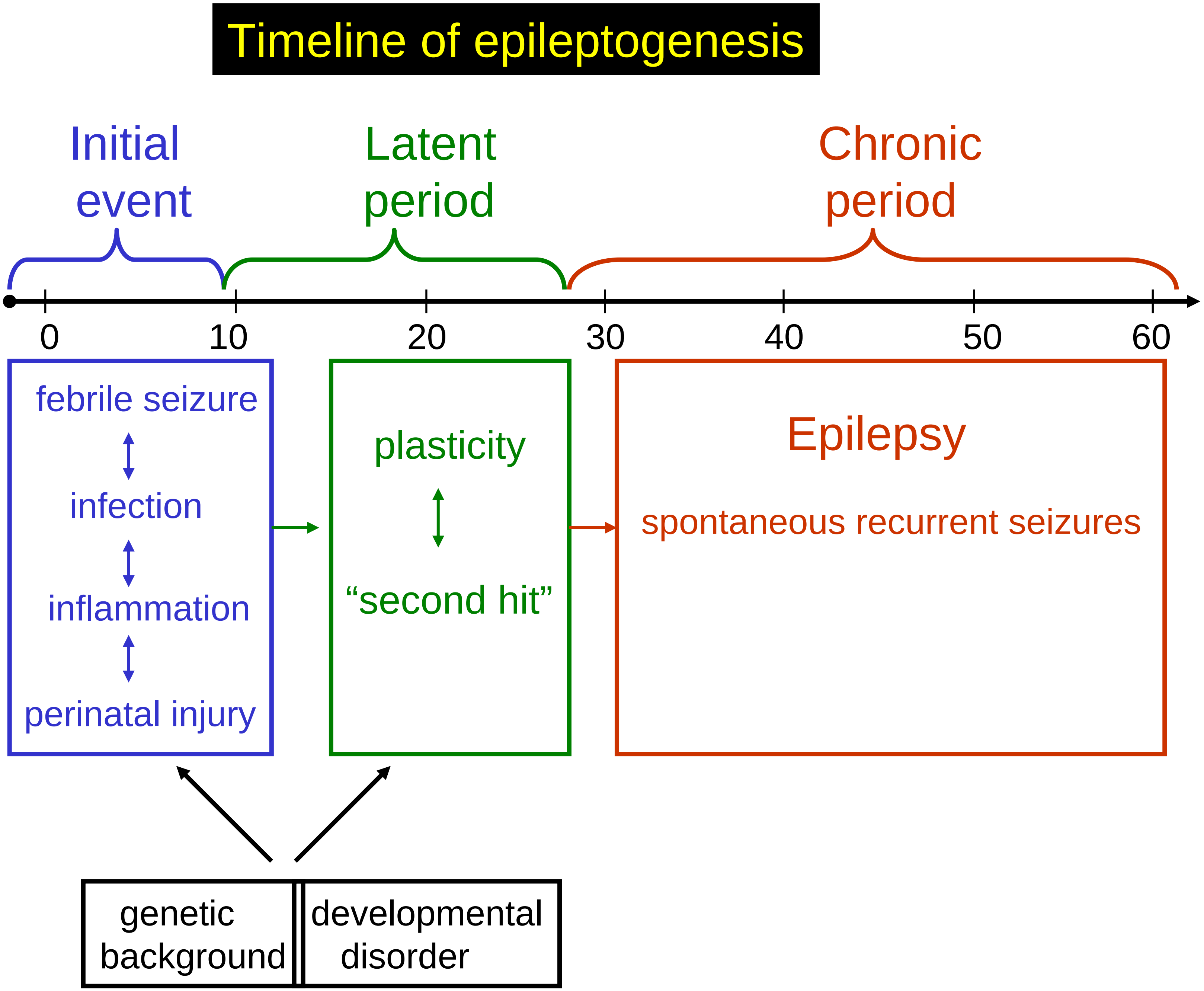
A. Laboratory animals → Human

B. Laboratory animals ← Human

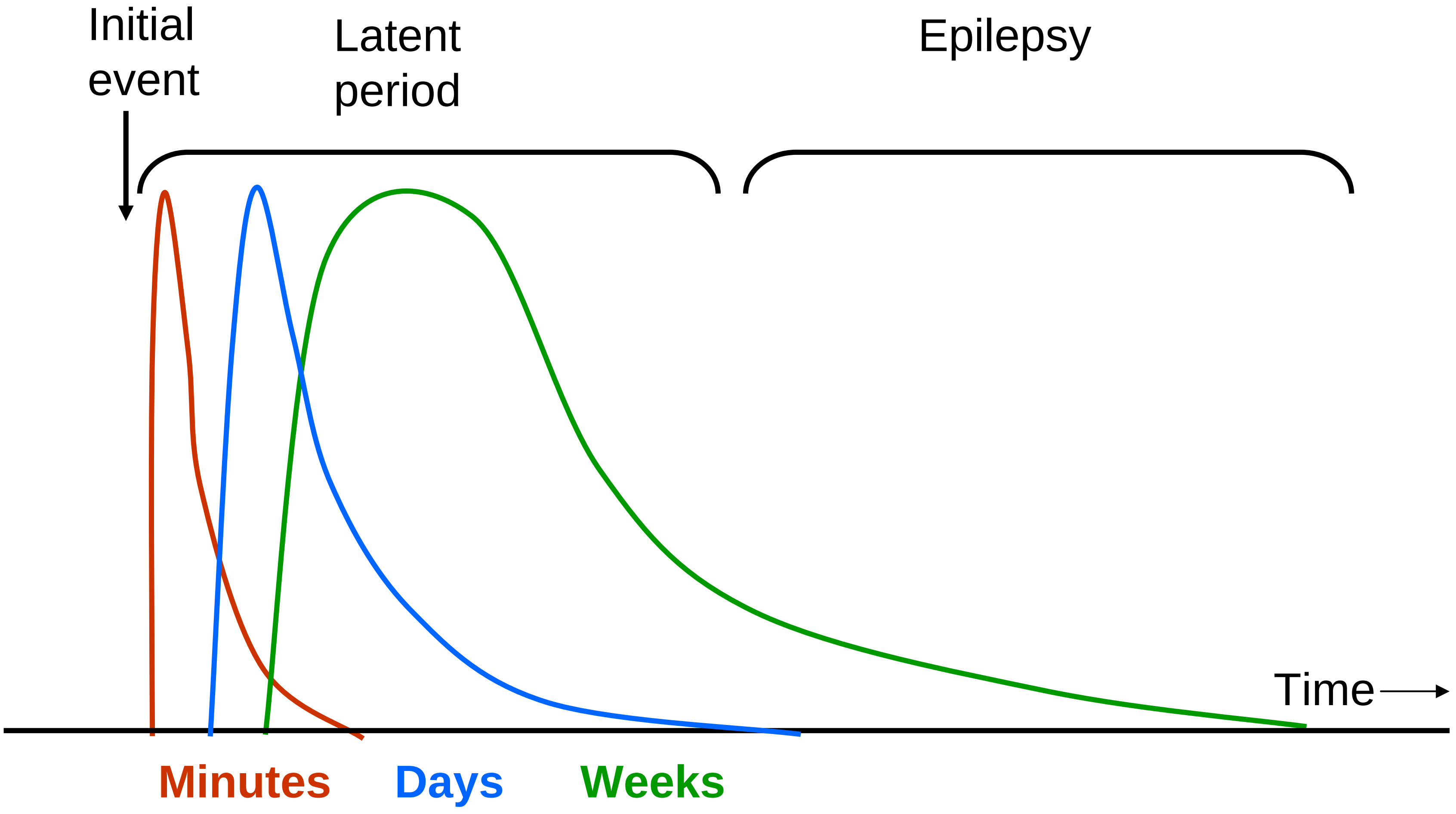
IV. Summary and Conclusions

I. Introduction

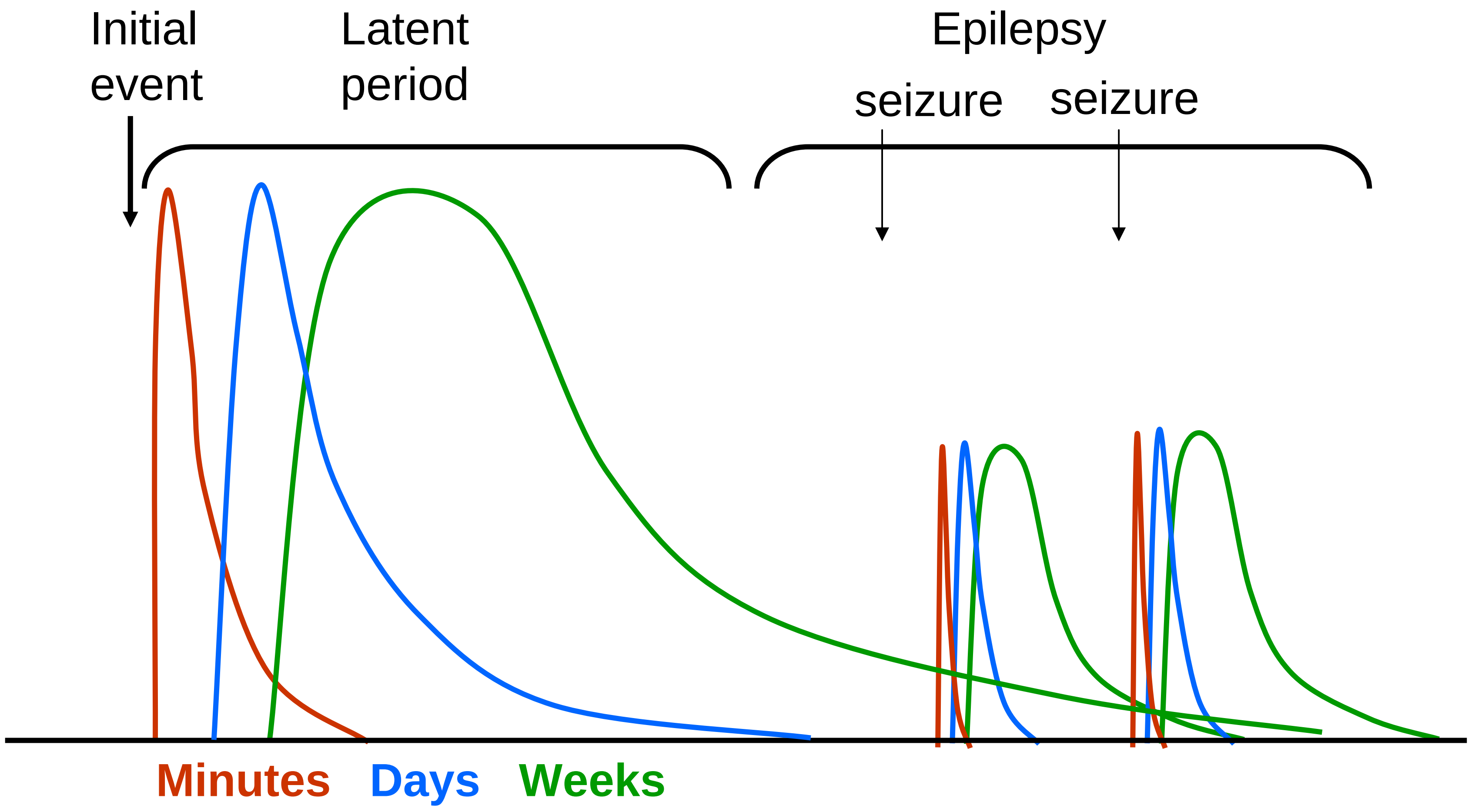
Evaluating cellular and molecular mechanisms of epileptogenesis


Timeline of epileptogenesis
Initial event
Latent period
Chronic period
0
10
20
30
40
50
60
febrile seizure
infection
inflammation
perinatal injury
plasticity
“second hit”
Epilepsy
spontaneous recurrent seizures
genetic background
developmental disorder

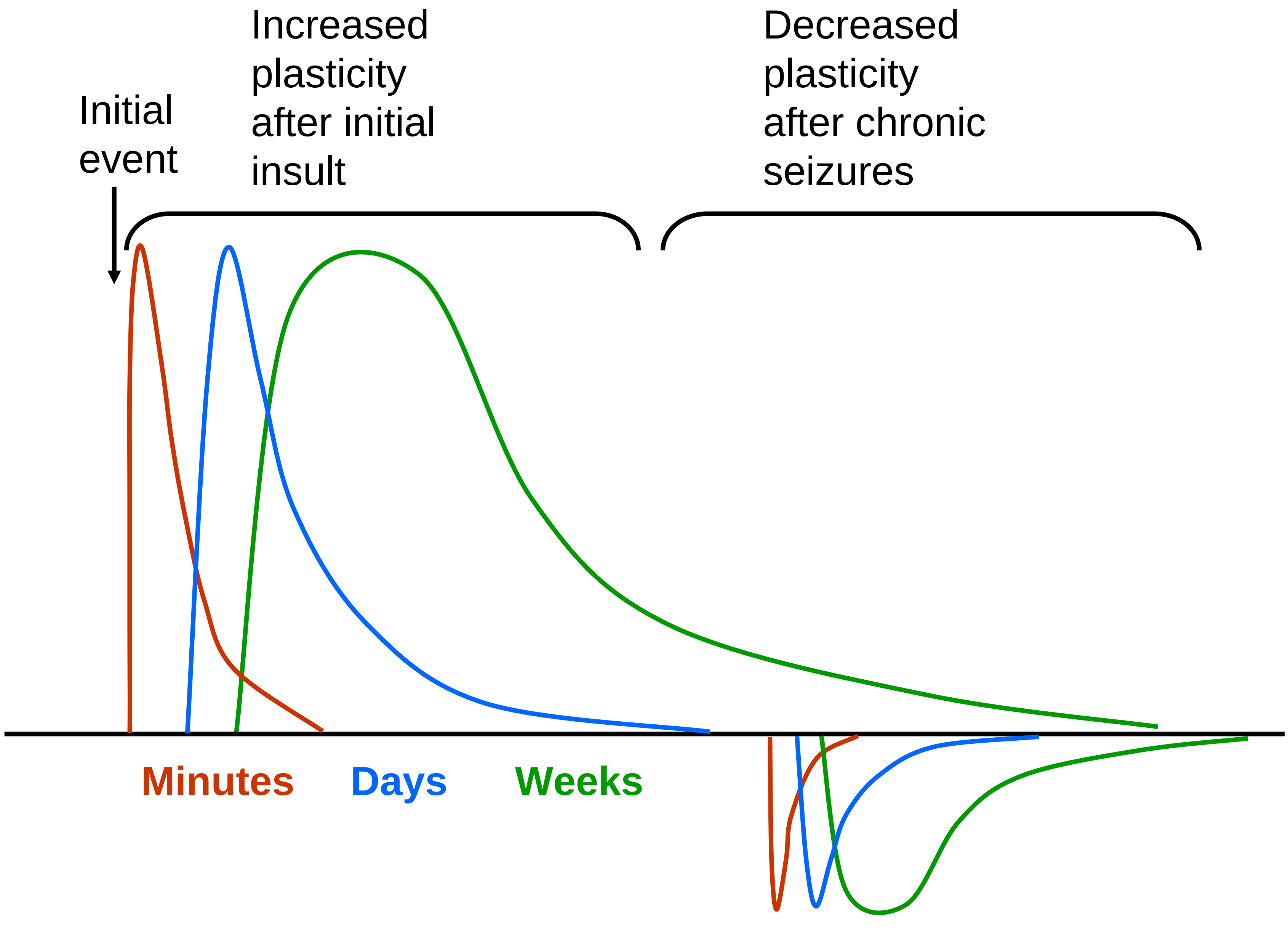
Timeline of epileptogenesis
--simplified --



Does epileptogenesis “stop” ?



Is epileptogenesis unidirectional ?



II. Stages of epileptogenesis

A. Minutes/hours

B. Days

C. Weeks/months

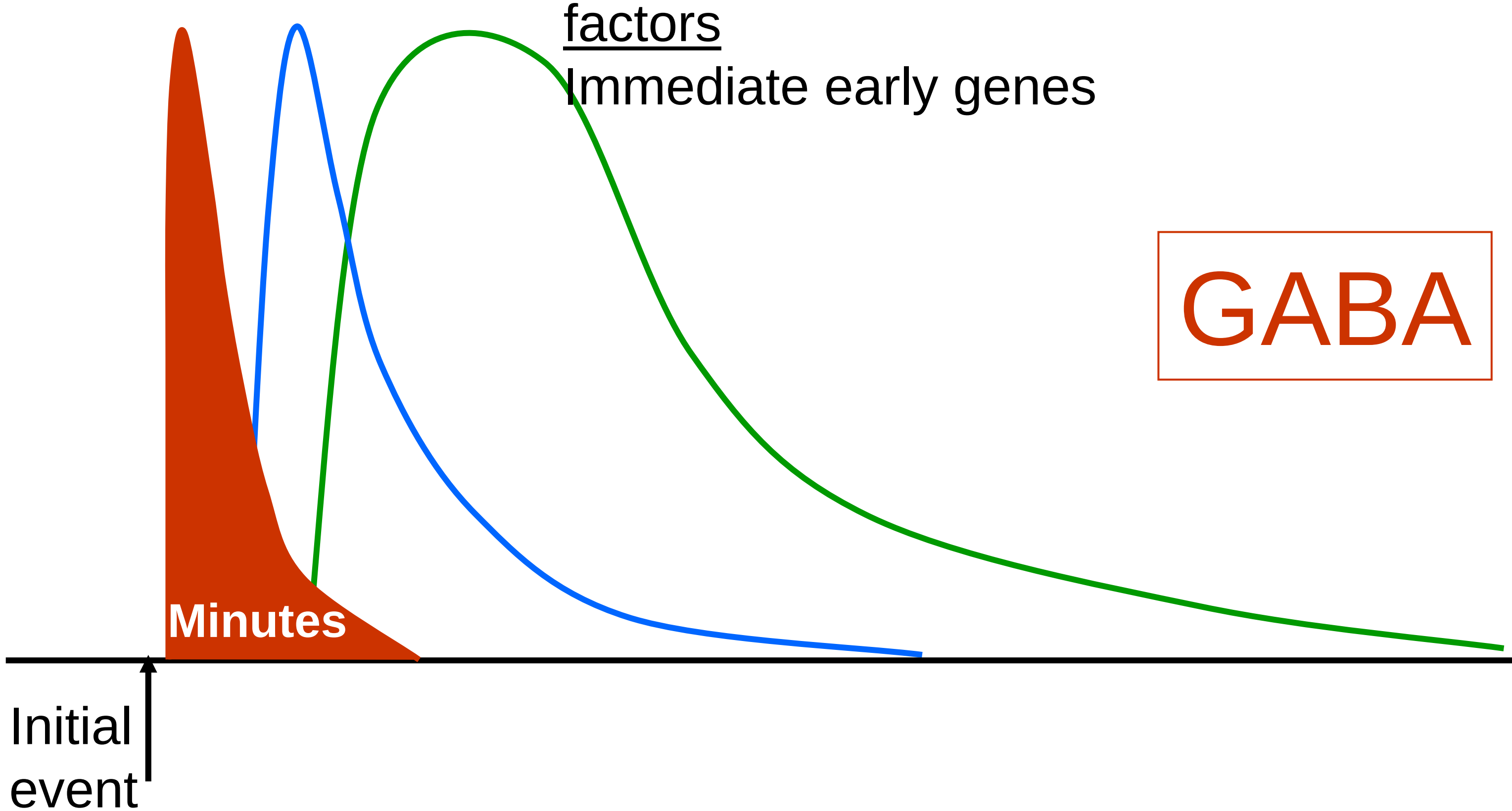
Initial changes - Minutes/hours

Glutamate - depolarization - Ca^{2+} influx

<u>Protein phosphorylation</u>
ligand and voltage-gated
ion channels

<u>Activation transcription factors</u>
Immediate early genes

<u>Excitotoxicity</u>
Neuronal and glial swelling
Mitochondrial responses
Energy depletion



Secondary changes - Days

Excitotoxic cell death
Apotosis

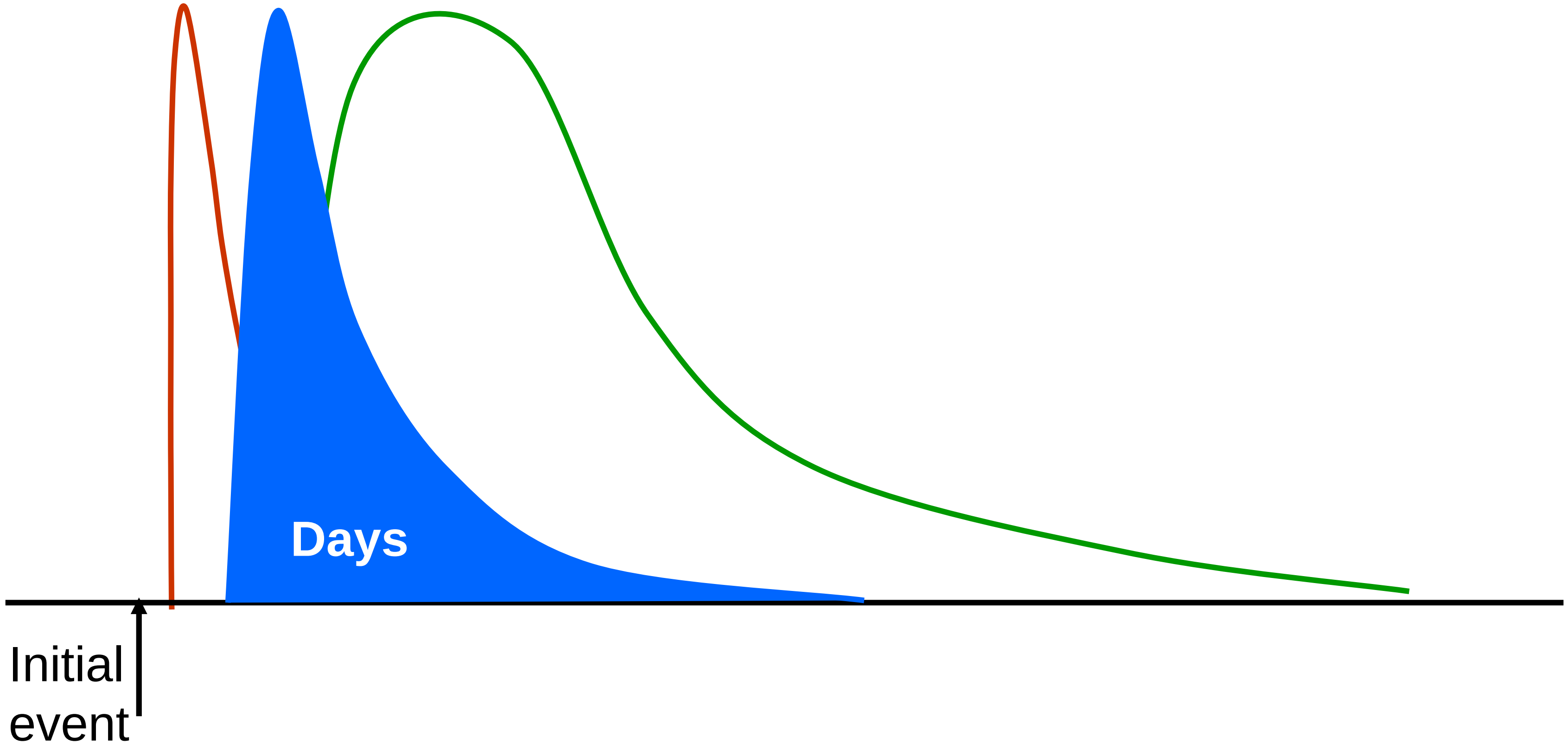
↓

Inflammation
Glial response
Vascular response

Seizure induced
gene expression

↓

Growth
Plasticity
Compensatory

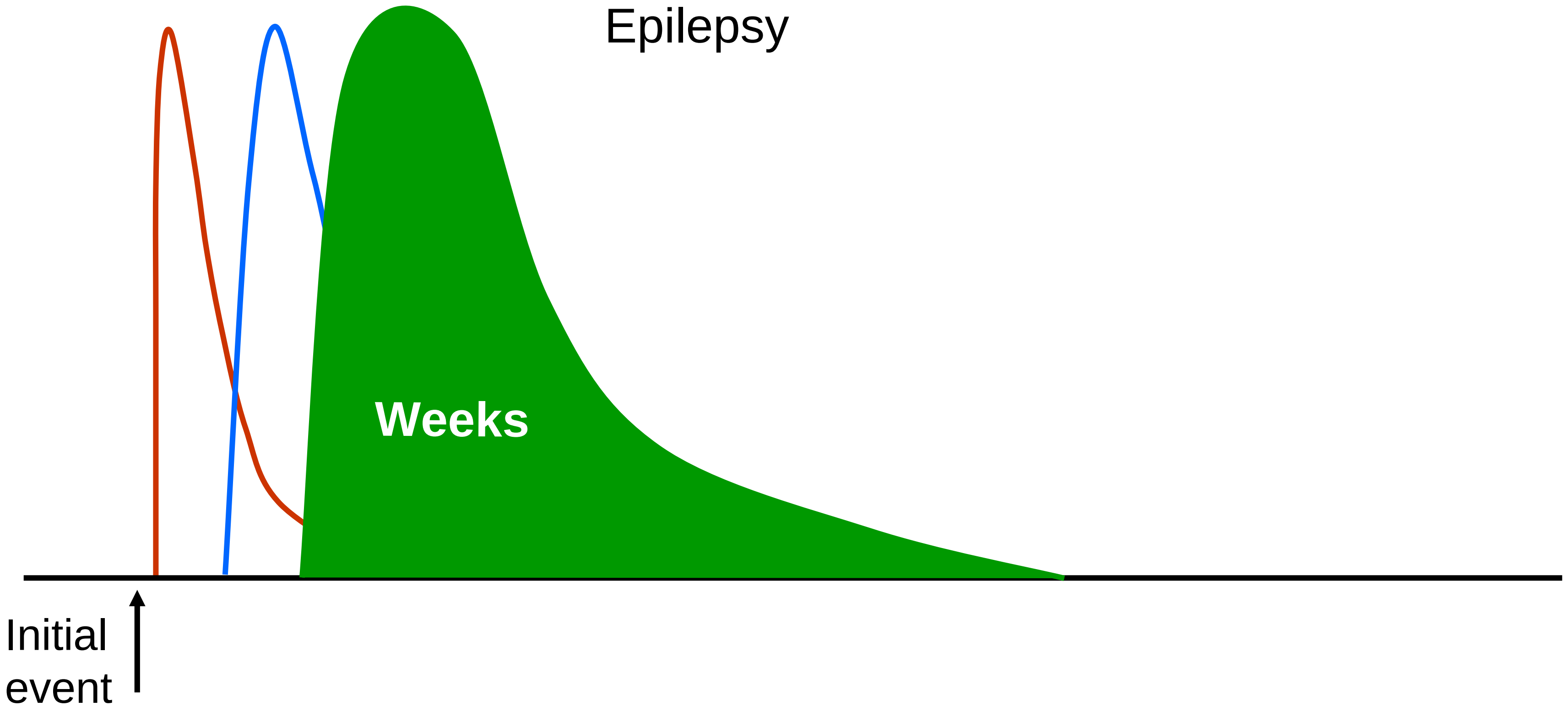


Tertiary changes - Weeks

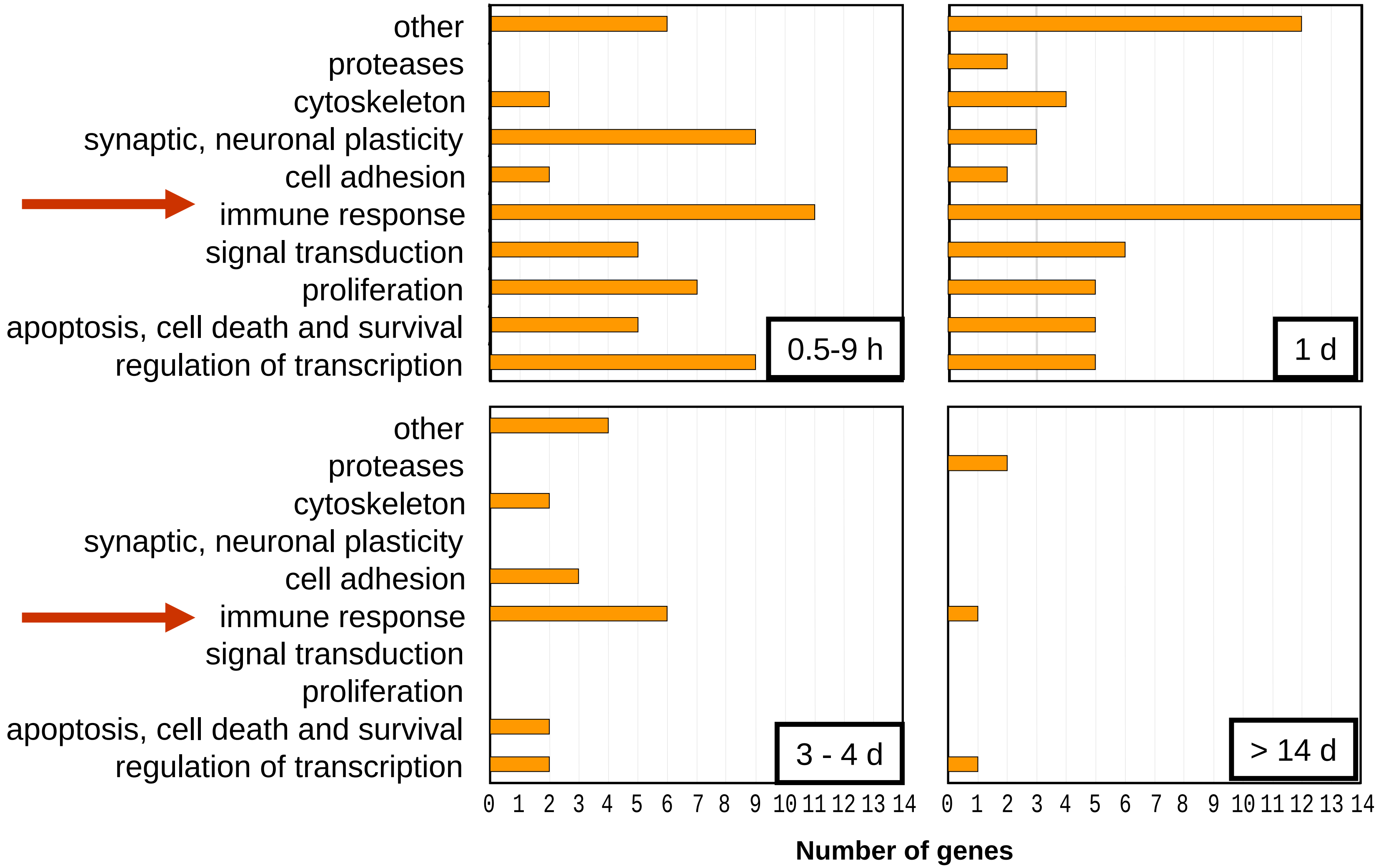
Recapitulation of development
↓
Axon outgrowth
Synaptogenesis
Angiogenesis

Responses to initial stages
↓
Homeostatic mechanisms

Predisposition for synchronization
↓
Epilepsy



Functional Classification of Individual Genes
16 datasets - TBI and status models

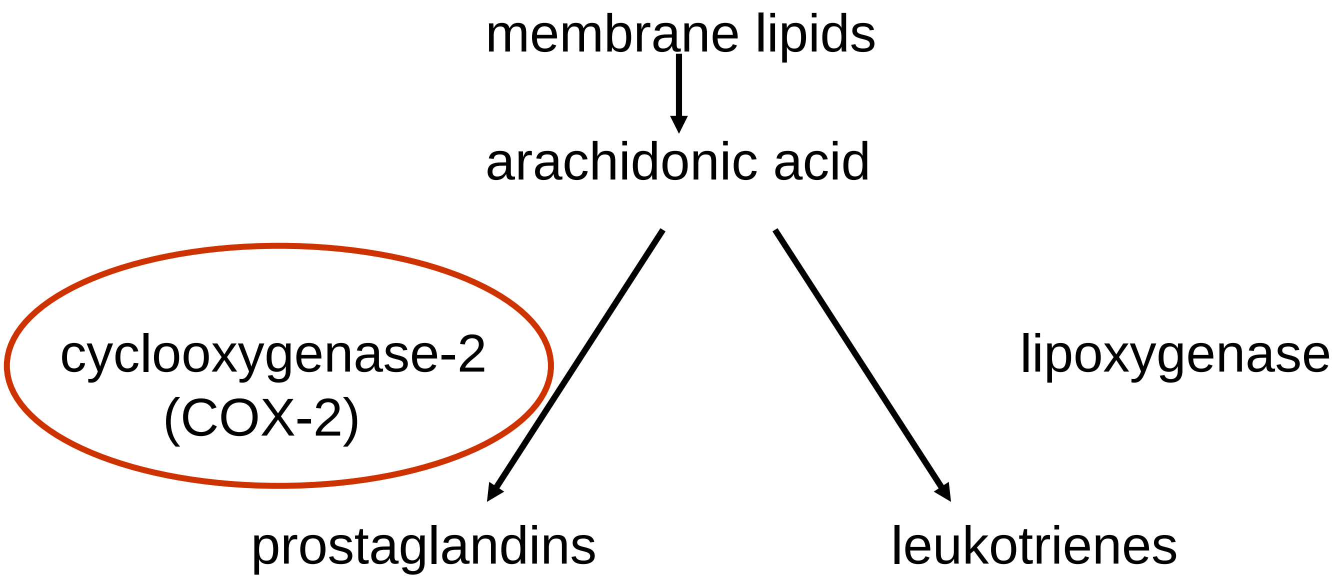


Lukasiuk et al. (2006)

Changes that are critical to epileptogenesis

Inflammation

Eicosanoids



Changes that are critical to epileptogenesis

Inflammation

Day 0 — Status

Day 1 — START intake COX-2 inhibitor

Day 28 — START MONITORING

Day 42 — END

	Vehicle	Celecoxib	
Frequency (seizures/day)	1.92 ± 0.6*	0.68 ± 0.32*	↓
Duration (sec)	14.82 ± 3.50	7.12 ± 2.82	↓
N	9	9	

Jung et al. (2006) Neurobiol. Dis.

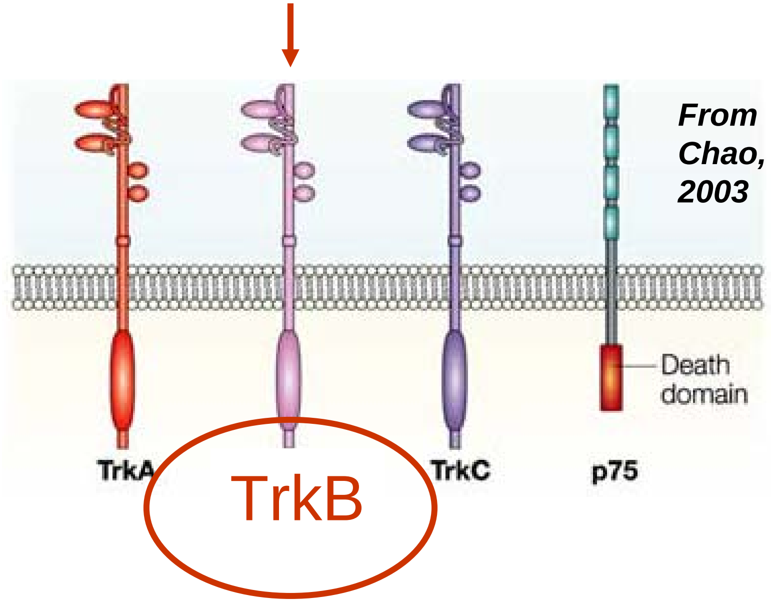
COX-2 inhibition reduces epileptogenesis

Changes that are critical to epileptogenesis

Growth

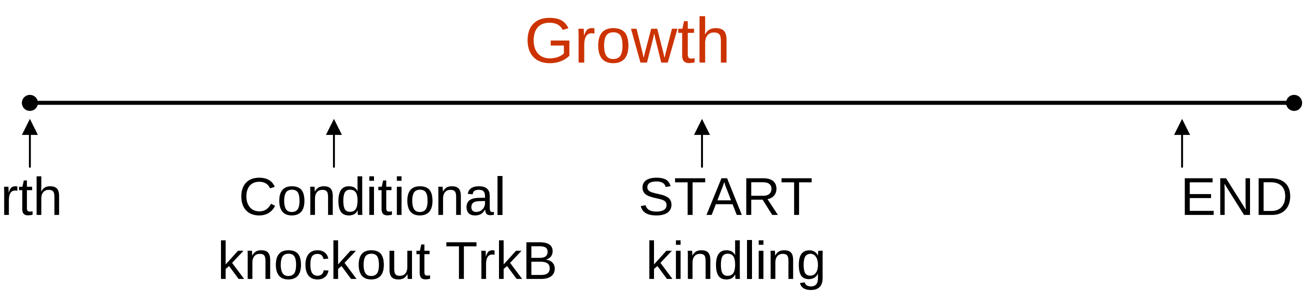
Neurotrophins

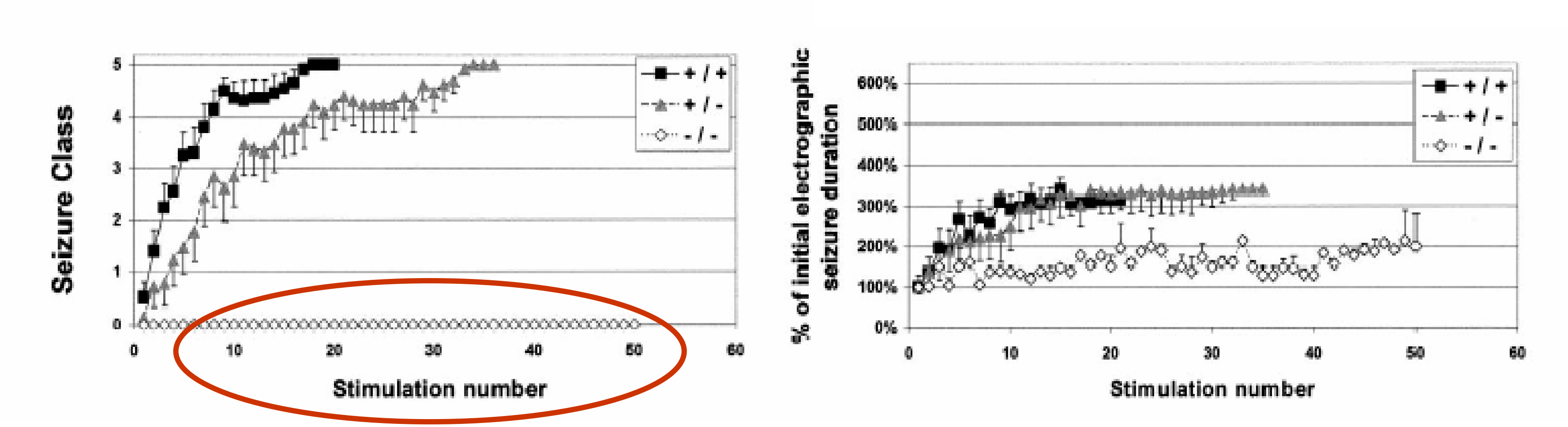
Brain-derived neurotrophic factor (BDNF)



From Chao, 2003

Changes that are critical to epileptogenesis





Animals can not kindle

He et al. (2004) Neuron

TrkB inhibition reduces epileptogenesis

Summary- critical changes

glutamate - depolarization - Ca2+ influx

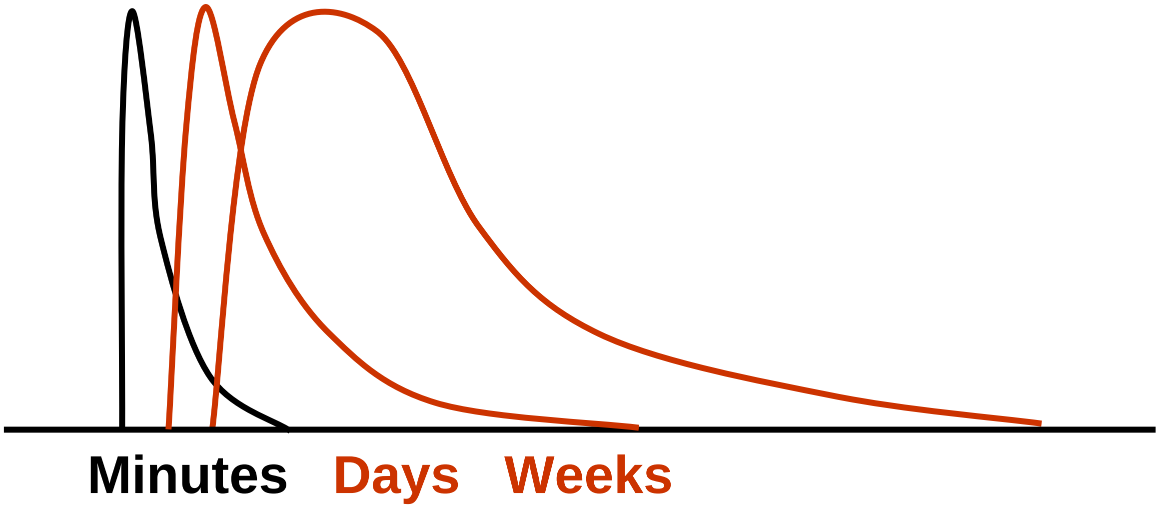
Excitotoxic cell death
Apotosis

Inflammation: COX-2

Seizure induced
gene expression

Growth: TrkB

Synchronization



III. Translational approaches

Laboratory animal

↕

Human

Translational research: Laboratory animal → Human

Inflammation

Kanemoto et al. Epilepsia (2003)

Increased frequency of interleukin-1β-511T allele in patients with temporal lobe epilepsy, hippocampal sclerosis, and prolonged febrile convulsion.

Jin et al. Epilepsia (2003)

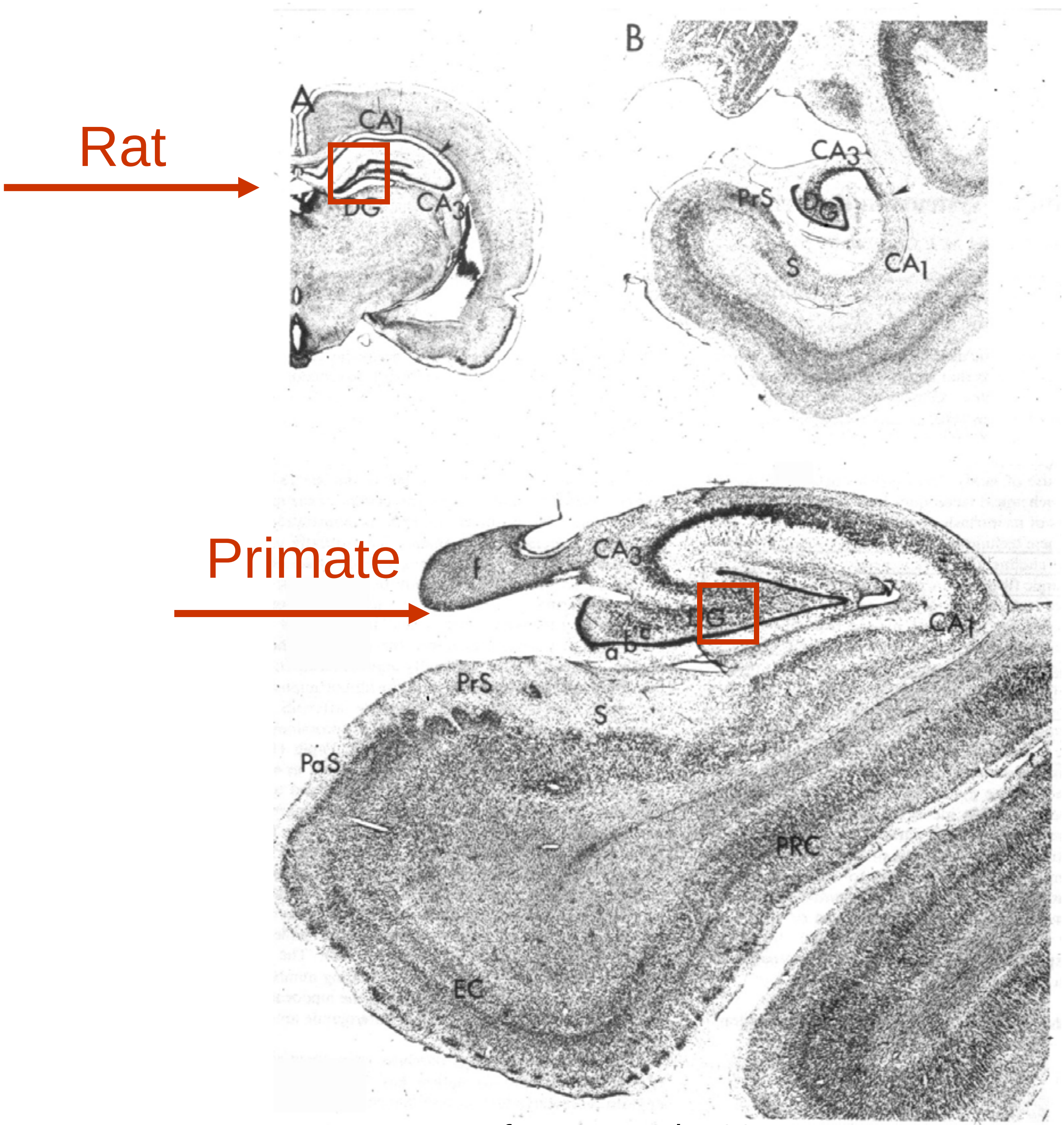
Association analysis of a polymorphism of interleukin 1β gene with temporal lobe epilepsy in a chinese population.

Translationalresearch: Laboratory animal ← Human

Dube et al. Ann. Neurol. (2005)

Interleukin 1β contributes to the generation of experimental febrile seizures

Dentate gyrus Rodent → Dentate gyrus Human



from Amaral, 1981

Translational research: Laboratory animal ⟷ Human

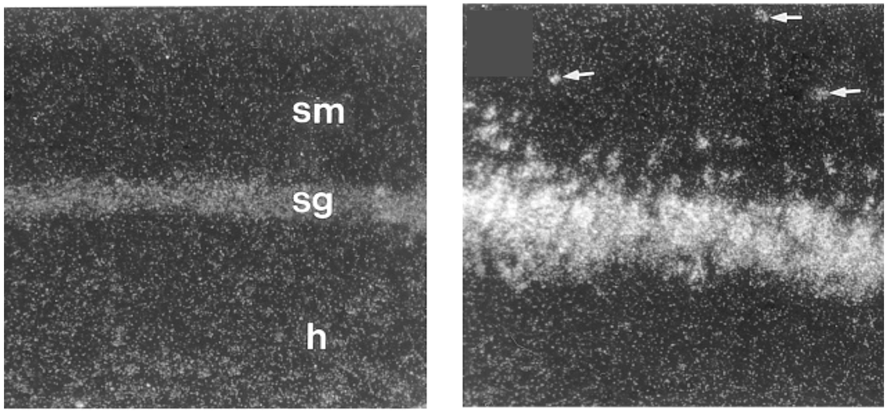
Growth

Control Epileptic

RAT

Scharfman et al (2002) J Comp Neurol

Control Epileptic



HUMAN

Murray et al (2000) J Comp Neurol

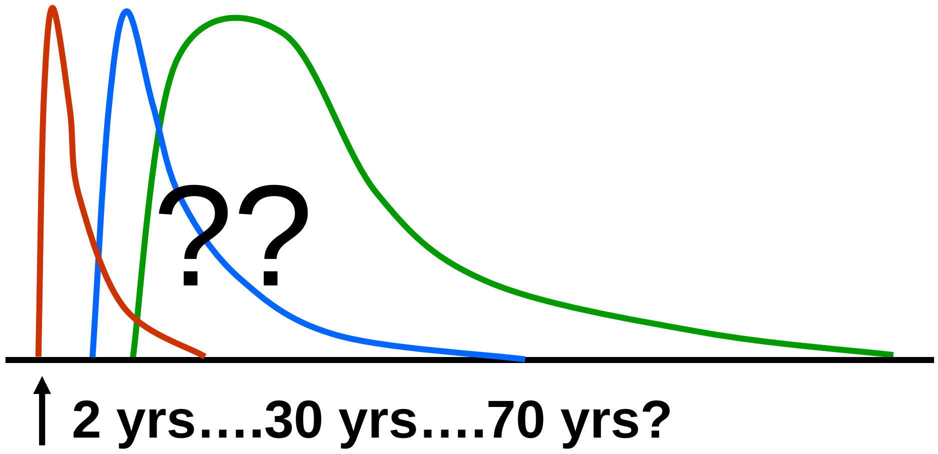
Evidence for ↑ BDNF in patients with epilepsy

Translational research: Human ⟷ Laboratory animal

Epileptogenesis appears different across ages…

↓

What can animal models tell us?



Insult early in life	Insult after maturity	Insult in old age
↓	↓	↓
Less damage More plasticity	More damage Less plasticity	Less epileptogenesis

Conclusions

I. Epileptogenesis as a complex process

Simplified view

Minutes/hours	Rapid mechanisms
↓	↓
Days	Secondary changes
↓	↓
Weeks/Months	Tertiary changes

II. Data from animal models of epileptogenesis provide insight into the clinical condition and vice-versa

III. New opportunities for therapeutic targets for antiepileptogenic agents

A. Immune response, Inflammation - COX-2, interleukin 1β

B. Growth - BDNF/trkB

GABARα1, Calcineurin, K^+Cl^- cotransporter, CB1

Raol et al (2006) Sanchez et al (2005) Dzhala et al (2005) Schuchmann et al (2006) Chen et al (2007)

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