Epileptogenic Phenotypes in Experimental Model Systems

Asla Pitkänen, MD, PhD

Epilepsy Research Laboratory
A.I.Virtanen Institute for Molecular Sciences
University of Kuopio, Kuopio
Finland
E-mail: asla.pitkanen@uku.fi

An alternative and accessible version of this presentation is available at 2:20 pm in the Videocast of Day One

Financial Disclosure

I do not have significant financial interests related to this conference

Contents

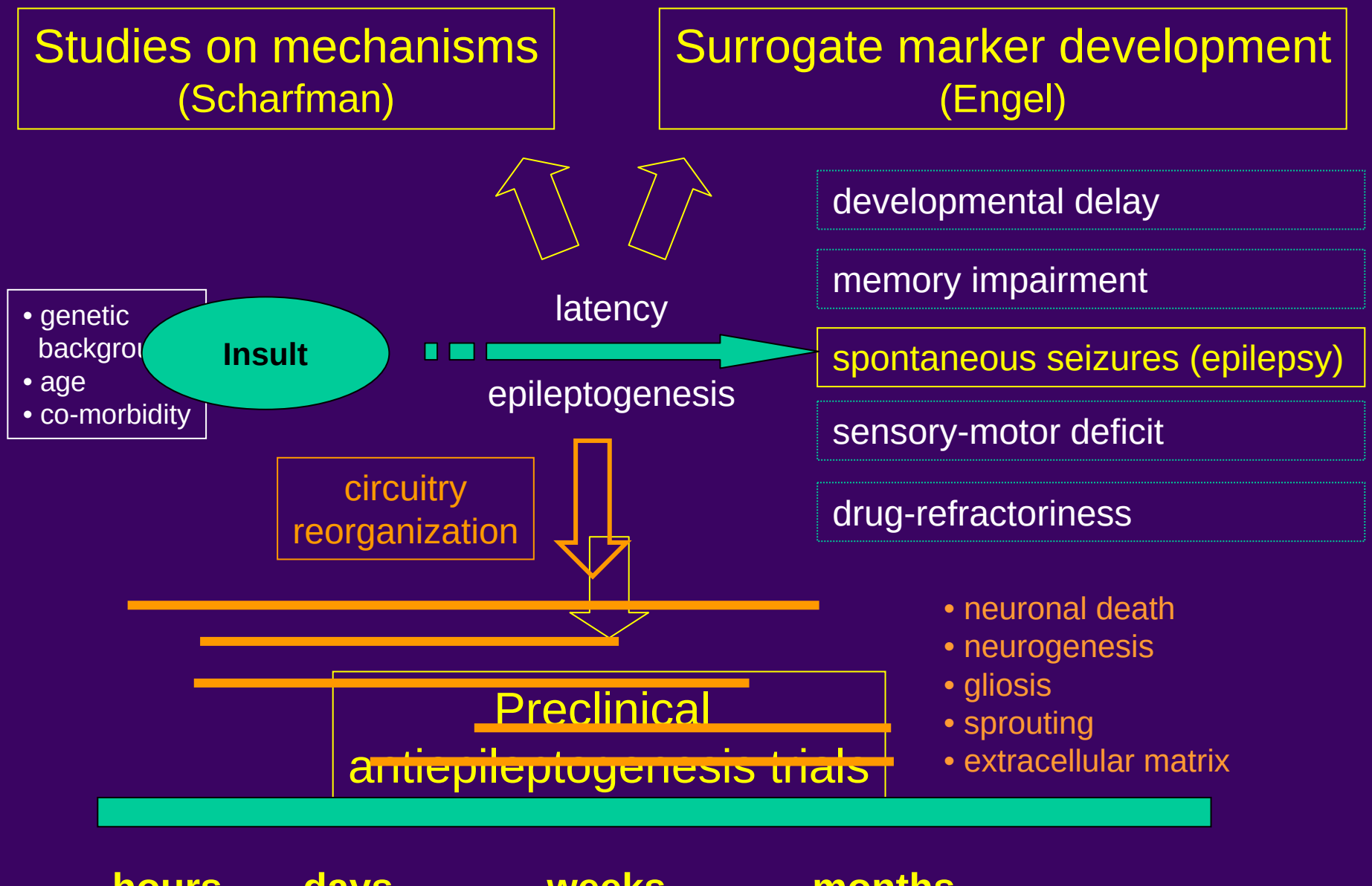
1. What kind of models do we have?

2. Comparison of phenotypes (SE, TBI, stroke)
   - clinical
   - pathology

3. What have we learnt? - Implications for applications

4. Future challenges

"Ideal" Model for Acquired Epileptogenesis



In Vivo Models of Acquired Epileptogenesis

Immature Brain

Hypoxia (P10) — Jensen et al. (1992, 2007)

Hypoxia-Ischemia (P7)

- carotid artery ligation + hypoxia — Williams et al. (2004)

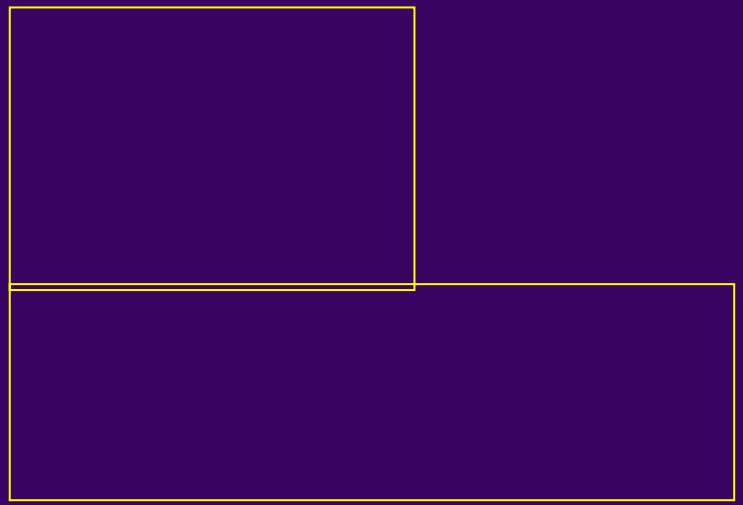
Post-stroke epilepsy (P12, P25)

- intrahippocampal endothelin-1 — Mateffyova et al. (2006)

In Vivo Models of Acquired Epileptogenesis

Adult Brain

Post-status epilepticus



Malformations (genetic)

Post-traumatic epilepsy

Post-stroke epilepsy

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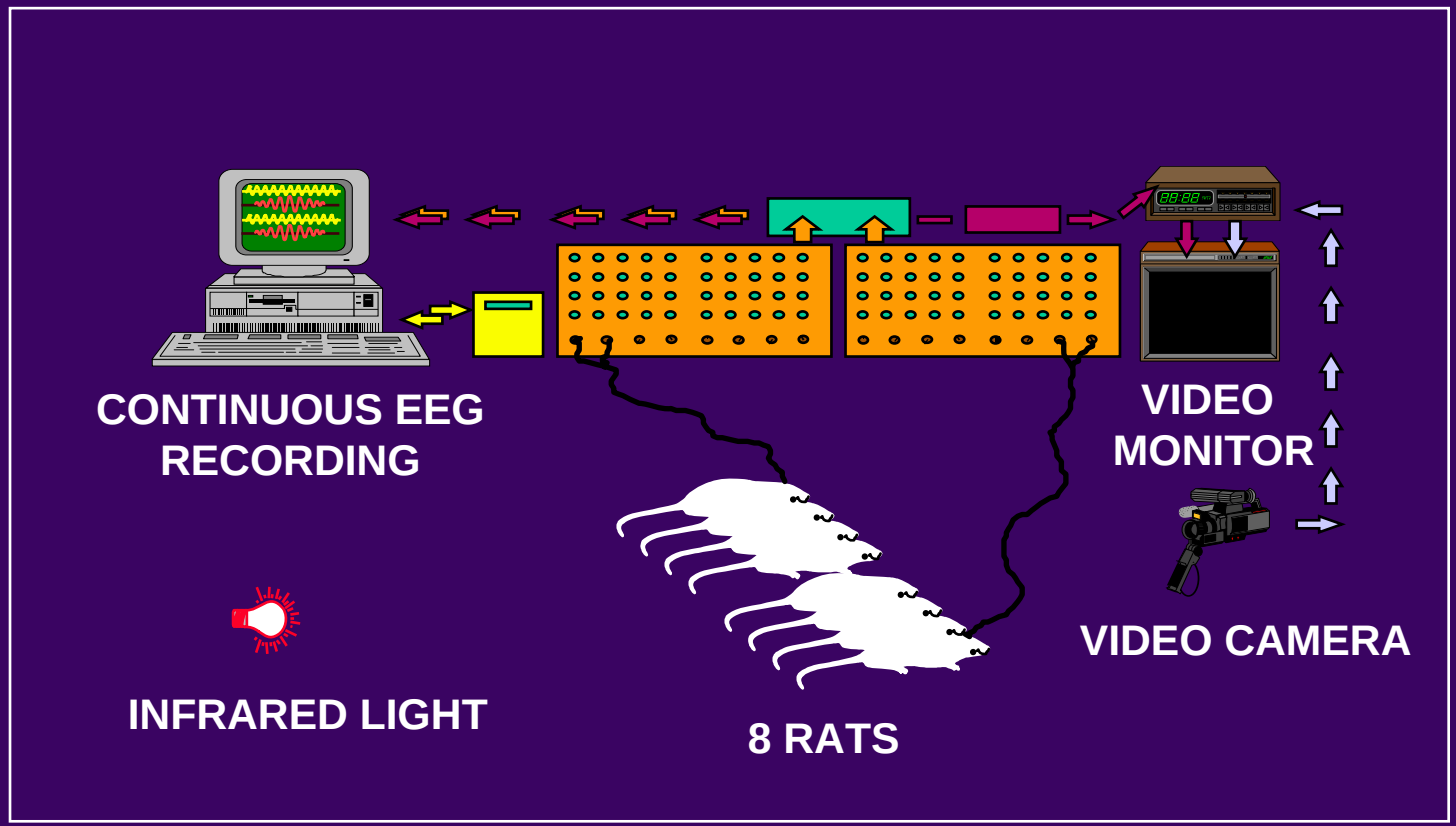
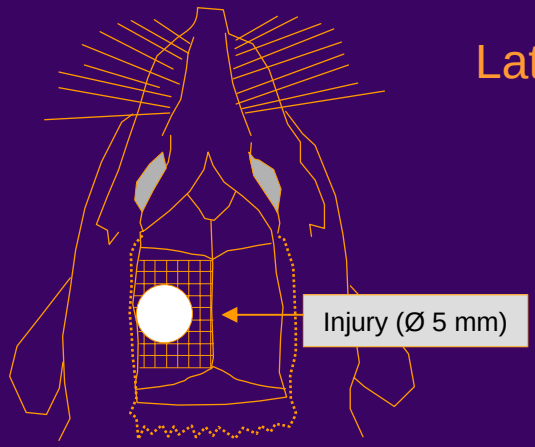
SE-induced Epileptogenesis in Rat

Video-EEG Recording System

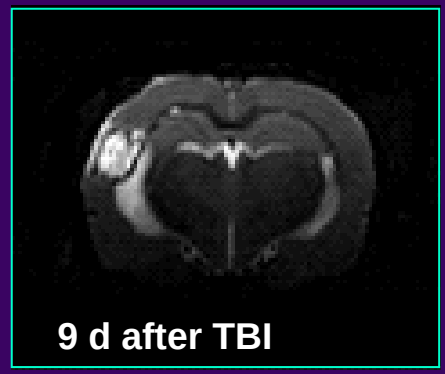


Post-traumatic epilepsy (Kharatishvili et al., 2006)



(McIntosh et al., 1989)

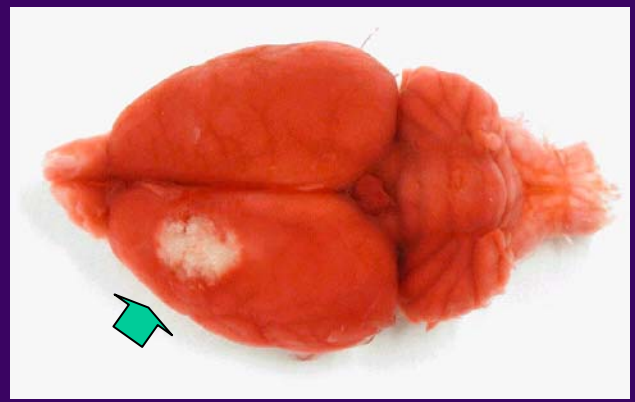
Lateral fluid-percussion brain injury

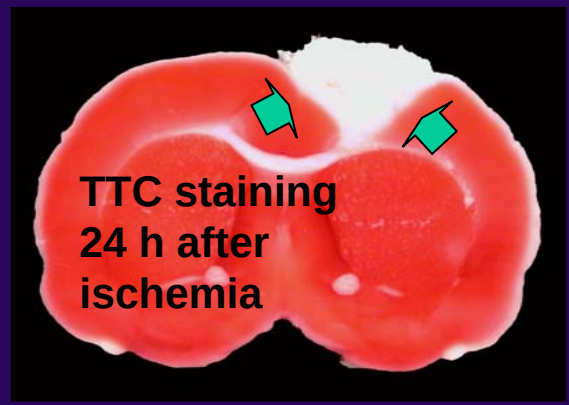


Post-stroke epilepsy (Kelly et al., 2001)

Rose bengal (i.v.)

Photothrombotic stroke





Epilepsy Phenotype Depends on Etiology

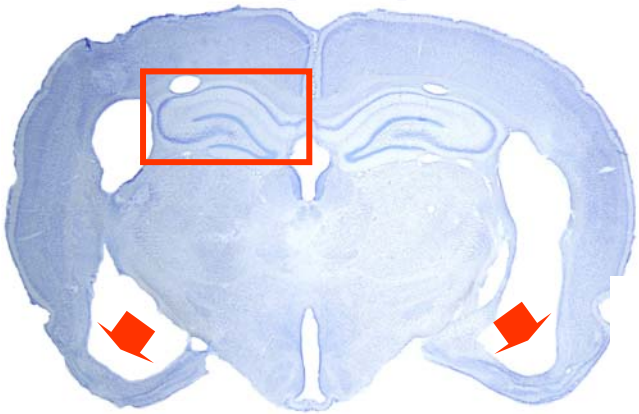
Newly Diagnosed Epilepsy in Rats

	SE	TBI	Stroke
	amygdala stimulation	lateral fluid-percussion	cortical photothrombosis
duration of latency	days -1 mo	several months	several months
% of rats with seizures	40-100%	50%	20%
mean seizure frequency	8/day	0.3/day	0.3/day
maximal seizure frequency	up to 30/day	up to 1/day	up to 5/day
mean seizure duration	49 sec	104 sec	117 sec
day-night cycle	57% lights on	44% lights on	42% lights on
memory impairment	yes	yes	no
response to AEDs	yes	?	?
drug-refrasctoriness	yes	?	?

Pitkänen et al. (2007)

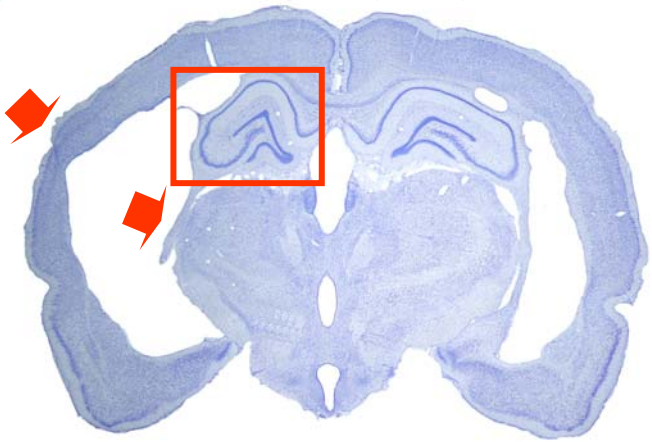
Distribution of Pathology Depends on Etiology

Status Epilepticus



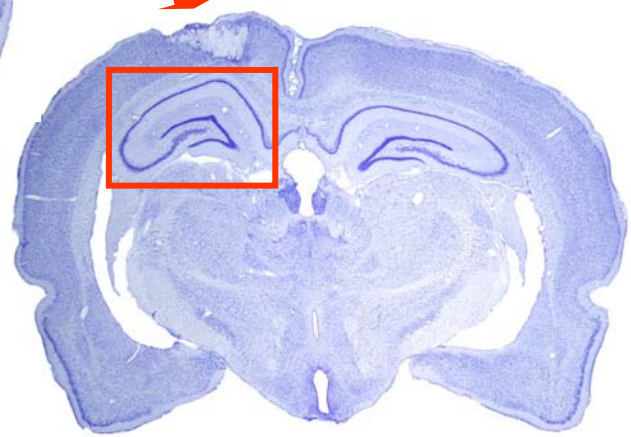
- bilateral
- temporal lobe damage

Traumatic Brain Injury



- unilateral
- lesion in cortex
- temporal lobe damage milder

Stroke



Pitkänen et al. (2007)

Type of Pathology Depends on Etiology

Hippocampus	SE amygdala stimulation	TBI lateral fluid-percussion	Stroke cortical photothrombosis
neurodegeneration neurogenesis			
astrogliosis microgliosis			
axonal sprouting axonal damage			
dendritic changes			
neovascularization			

Pitkänen et al. (2007)

Type of Pathology Depends on Etiology

Hippocampus	SE amygdala stimulation	TBI lateral fluid-percussion	Stroke cortical photothrombosis
neurodegeneration	+++	+	+
neurogenesis	++	++	+
astrogliosis	+++	+++	+
microgliosis	++	++	+
axonal sprouting	+++	++	(+)
axonal damage	(+)	+++	nd
dendritic changes	+++	(+)	n.s.
neovascularization	+	+	nd

"epileptogenesis" *vs.* "repair"

Pitkänen et al. (2007)

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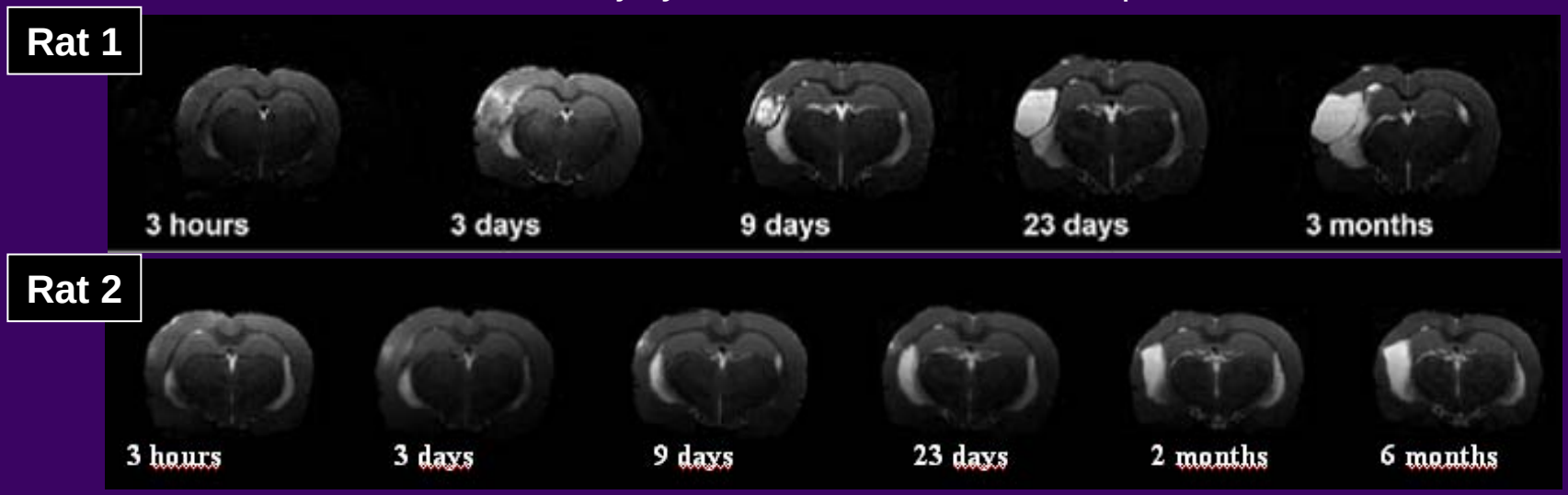
Tailoring Experiments by using MRI

Traumatic brain injury induced with lateral fluid percussion



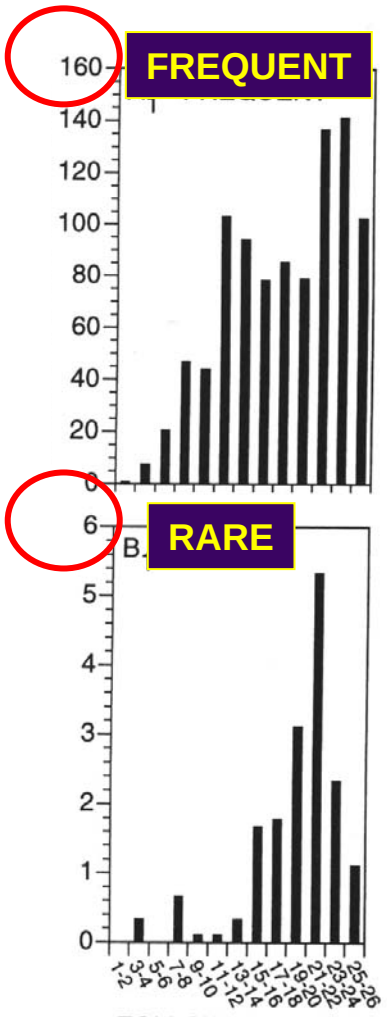
1. Adjustment of the severity of insult within the study group
2. Subpopulation analysis (mild vs. severe damage)
3. Bio/surrogate marker development

(Immonen, Kharatishvili, Gröhn, Pitkänen; unpublished)

More Detailed Analysis of Phenotype

Long-term video-EEG monitoring

Number of Seizures



Most of the seizures are partial

Implications
- subpopulation analysis
- disease modification

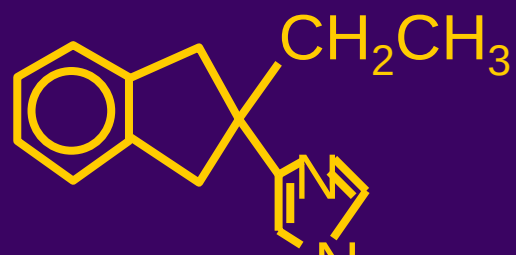
Most of the seizures are secondarily generalized

FOLLOW-UP TIME (6 months)

Disease Modification with Atipamezole

Epileptogenesis triggered by SE

Pitkänen et al. (2004)



LATENCY PERIOD

SE
3 h

1 wk

- selective α2-adrenergic blocker

EPILEPSY

9 wk

- proconvulsant

atipamezole
via s.c. minipumps

No Effect on Epileptogenesis

vEEG for 2 wk

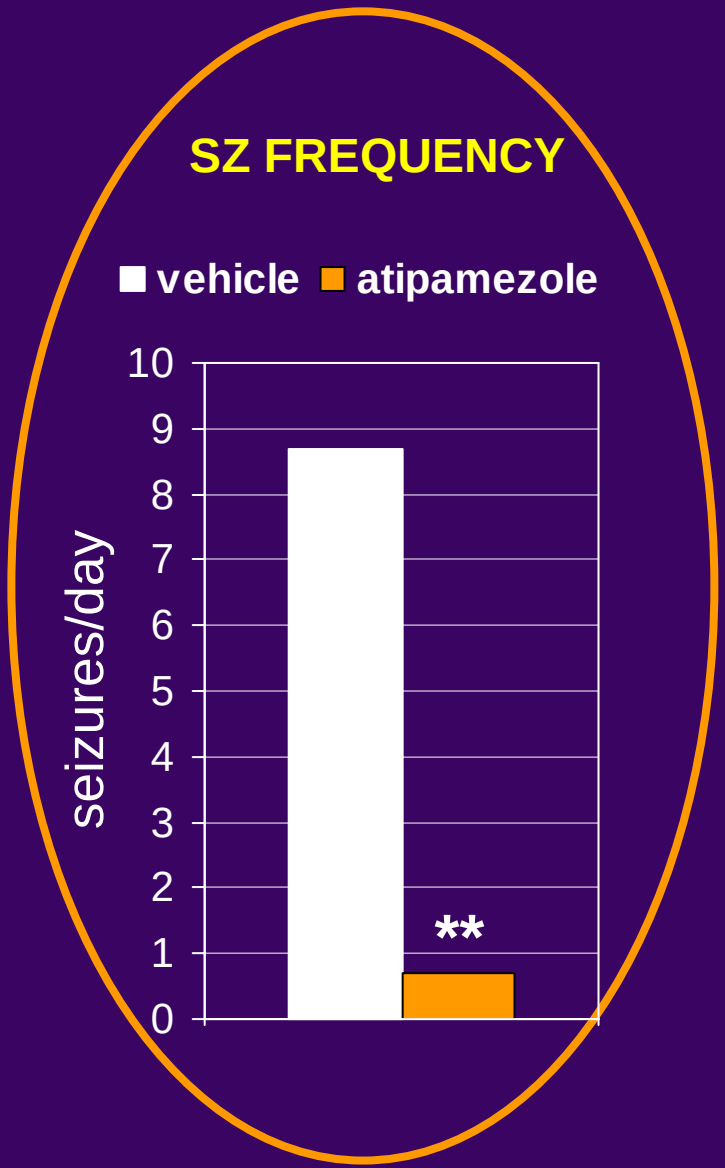
during treatment

vEEG for 2 wk

after treatment

Disease Modification with Atipamezole

Epileptogenesis triggered by SE
Pitkänen et al. (2004)



Proof-of-principle evidence that epileptogenic process can be modified

Where Are We?

1. We have models with clinically relevant etiologies
    - to investigate mechanisms of epileptogenesis
2. We are learning the "+" and "-" of models
3. We have technologies that allow the investigation of models in clinically comparable way
4. Study designs "ready for translation to clinic"
    - to find novel therapies
    - to identify bio/surrogate markers

How To Facilitate Ongoing Progress?

1. **Model development - "Ideal" Model**
   - pediatric models
   - genetic background
   - analysis of clinical relevance

2. **Development and use of new technologies in preclinical studies**
   - MRI, SPECT/CT, PET/CT
   - small-size EEG recording systems

3. **Surrogate marker development**
   - prediction of outcome
   - efficacy of therapy

4. **Development of pre-clinical study designs**
   - guidelines for preclinical studies
   - multicenter preclinical trials
   - interaction between basic and clinical scientists

5. **New thinking - taking advantage of progress in TBI and stroke fields**
   - epileptogenesis ~ recovery process

EPILEPSY RESEARCH GROUP

A.I.Virtanen Institute, Kuopio, Finland

Postdocs
Kaisa Kurkinen
Heli Myöhänen
Jari Nissinen
Tamuna Bolkvaze

Technicians
Merja Lukkari
Jarmo Hartikainen

PhD-students
Laura Kontula
Irina Kharatishvili
Heli Karhunen
Cagri Yalgin
Xavier Ekolle Ndode-Ekane
Christine Einula
Jukka Rantala
Riikka Koskinen*

NMR Research Group at A.I.Virtanen Institute
Olli Gröhn
Jaak Nairismägi
Riikka Koskinen

Gene Transfer Technology at A.I.Virtanen Institute
Jarmo Wahlfors

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