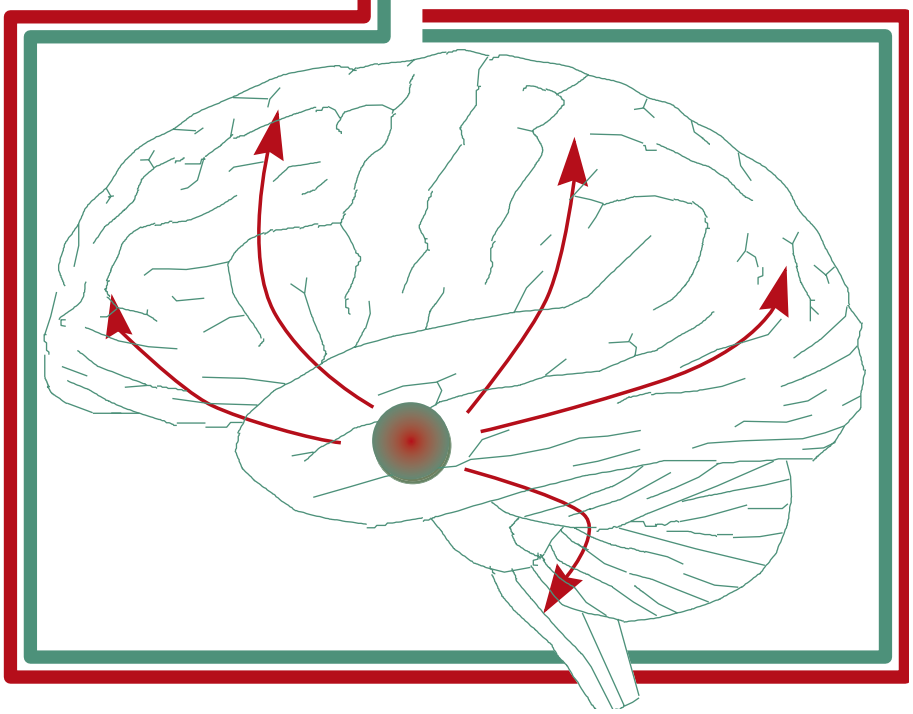
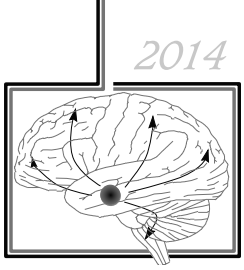
2014



# KUOPIO EPILEPSY SYMPOSIUM 2014 & TEACHING COURSE

Final Programme
April 4-5, 2014
Kuopio Music Centre, Kuopio, Finland
www.uef.fi/en/kuopioepilepsysymposium




# Welcome to Kuopio

On behalf of the Finnish Epilepsy Society and the Finnish Epilepsy Association, we cordially welcome you to participate in the KUOPIO EPILEPSY SYMPOSIUM 2014 & TEACHING COURSE, April 4-5, 2014, Kuopio Music Centre, Kuopio, Finland.

The meeting will be the seventh in a series of epilepsy meetings that are organized jointly by A.I. Virtanen Institute for Molecular Sciences (University of Eastern Finland), Neurocenter (Kuopio University Hospital), Finnish Epilepsy Society, Finnish Epilepsy Association, UEF Doctoral Program in Molecular Medicine and Department of Neurology, School of Medicine, University of Eastern Finland.

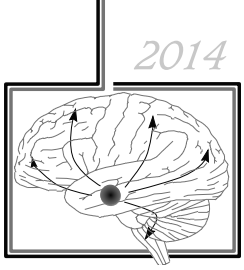
The objective of the meeting is to present up-to-date knowledge of selected topics related to epilepsy. Both experimental and clinical data will be presented. We hope to bring together people working in the different fields of epileptology to facilitate the exchange of information and ideas, and to update our understanding of basic mechanisms, diagnostics and treatment of epilepsy.

**Asla Pitkänen, Academy Professor**
Program Co-Chair of the Organizing Committee

**Reetta Kälviäinen, Professor**
Program Co-Chair of the Organizing Committee

The abstract book was edited by Dr Leena Jutila.

Kopijyvä Oy, Kuopio 2014




# Friday, April 4th 2014

## Teaching Course: Status Epilepticus

08:00- Teaching course registration

09:00-09:05 Opening of the teaching course
Course Director, Professor Reetta Kälviäinen (Finland)

09:05-09:20 How long seizure causes permanent brain damage?
Academy Professor Asla Pitkänen (Finland)

09:20-09:50 Mortality and morbidity caused by status epilepticus
Dr. Anne-Mari Kantanen (Finland)

09:50-10:30 Treatment advances in early status epilepticus
Professor Rod Scott (UK/USA)

***Coffee***

11:00-11:30 New methods for EEG monitoring of status epilepticus
Professor Esa Mervaala (Finland)

11:30-12:00 Neurointensive care of patient with status epilepticus
Dr. Stepani Bendel (Finland)

12:00-12:30 Treatment of super-refractory status epilepticus
Professor Simon Shorvon (UK)

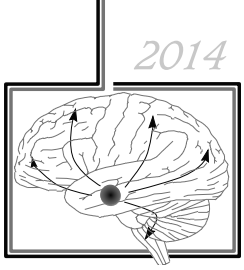
12:30-13:00 Status epilepticus after cerebral anoxia – when to treat?
Dr. Amy Crepeau (USA)

***Lunch***

## Kuopio Epilepsy Symposium 2014

### Opening of the Symposium

14:00-14:15 Welcome
Dean of the Faculty of Health Sciences Hilkka Soininen,
University of Eastern Finland (Finland)
Program Co-Chair, Academy Professor Asla Pitkänen (Finland)



## Key Note Address

14:15-14:45 Stereo-EEG – what new does it for diagnostics?
Professor Philippe Kahane (France)

## Hot Topics *(15min + 5 min for discussion)*

**Chair:** Professor Juha E Jääskeläinen (Finland)

14:45-15:05 Optogenetics – Will it replace deep brain stimulation in the treatment of epilepsy?
Professor Merab Kokaia (Sweden)

15:05-15:25 Has fMRI already replaced Wada test in presurgical evaluation?
Dr. Sallie Baxendale (UK)

15:25-15:45 Transcranial magnetic stimulation - what's new?
Professor Vasilios Kimiskidis (Greece)

***Coffee (Posters in the Hall of Light)***

## Diagnostic Challenges

**Chair:** Professor Ritva Vanninen (Finland)

16:15-16:45 Autoimmune encephalitis
Professor Simon Shorvon (UK)

16:45-17:15 Vaccines and seizures
Professor Helen Cross (UK)

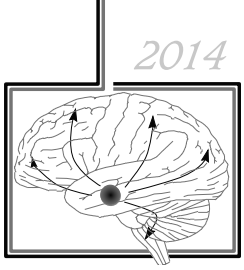
## Prebanquet Session: Interactive epileptology through challencing case studies

**Chair:** Professor Reetta Kälviäinen (Finland)

19:00-20:30 Evaluating seizures and diagnosing epilepsies and syndromes
Case presentations from Kuopio Epilepsy Center

Comments from Professors Philippe Kahane (France) and Helen Cross (UK)

**20:30-22:00 Banquet**



# Saturday, April 5th 2014

## Future of epilepsy therapy – how far is it?

**Chair:** Academy Professor Asla Pitkänen (Finland)

09:00-09:30 Non-coding RNAs
Professor David Henshall (Ireland)

09:30-10:00 Gene therapy
Professor Michele Simonato (Italy)

10:00-10:30 Cell therapy
Professor Scott Baraban (USA)

***Coffee (Posters in the Hall of Light)***

## UEF-Brain Lecture

11:00-11:45 What is good epilepsy care in 2014 in EU?
Professor Reetta Kälviäinen (Finland)
*Discussion 15 min*

## Update of epilepsy research in Finland: Selected abstracts

**Chair:** Professor Hilkka Soininen (Finland)

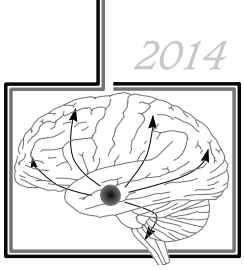
11:45-12:00 Oral presentation I
12:00-12:15 Oral presentation II
12:15-12:30 Oral presentation III
12:30-12:45 Oral presentation IV

***Lunch***

## Answers to questions that I always have wanted to ask about treatment of epilepsy

**Chair:** Professor Reetta Kälviäinen (Finland)

13.45-14.05 Febrile seizures, when to treat?
Professor Heikki Rantala (Finland)




14.05-14.25 Can we prevent cognitive decline in children with epilepsy?
Dr. Eija Gaily (Finland)

14.25-14.45 When is adverse event intolerable?
Dr. Hanna Ansakorpi (Finland)

14.45-15.05 Which patients with meningeomas should receive AEDs?
Dr. Merja Soilu-Hänninen (Finland)

15.05-15.25 How to recognize patients with long-term epilepsy associated tumors (LEAT)?
Dr. Arto Immonen (Finland)

### Awards Ceremony

15:25-15:45 Vaajasalo Foundation Young Investigator Awards
Epilepsy Foundation Awards

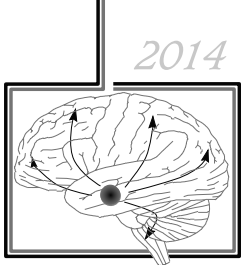
15.45-16.00 Closing of the Kuopio Epilepsy Symposium 2014
Academy Professor Asla Pitkänen, Program Co-Chair

## Organizers

A.I. Virtanen Institute, University of Eastern Finland
Neurocenter, Kuopio University Hospital
Finnish Epilepsy Society
Finnish Epilepsy Association
UEF Doctoral Program in Molecular Medicine
Department of Neurology, School of Medicine, University of Eastern Finland

## Program Committee

Program Co-Chair: Academy Professor Asla Pitkänen
Program Co-Chair: Professor Reetta Kälviäinen
Professor Heikki Rantala
Mrs. Pirkko Ulmanen
Scientific Secretary: Dr. Leena Jutila
Teaching Course Secretary: Dr. Anne-Mari Kantanen
Secretary: Ms. Tuija Parsons




## Congress Secretariat and Address for Correspondence

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Tel. +358 403552046 / secretary
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neurology.symposium@uef.fi
www.uef.fi/en/kuopioepilepsysymposium

## The Congress Venue

Kuopio Music Centre, Kuopionlahdenkatu 23, Kuopio, Finland www.kuopionmusiikkikeskus.fi. Driving instructions, parking and WLAN, please see www.kuopionmusiikkikeskus.fi.

## Meetings

The Finnish Epilepsy Society, Annual Meeting: Friday April 4th, 2014 at 13.00 in the Auditorium.

**HOW LONG SEIZURE CAUSES PERMANENT BRAIN DAMAGE?**

**Asla Pitkänen. Department of Neurobiology, A.I.Virtanen Institute, University of Eastern Finland, Kuopio, Finland.**

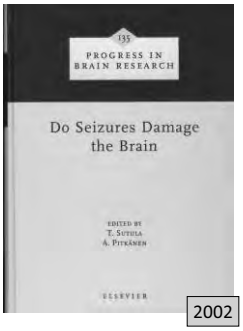
Experimental data show that seizure duration < 2 min can cause neuronal apoptosis, and duration of SE < 1 h can damage the brain to the extent which causes functional impairment. Experimental SE, however, differs from human SE in several aspects which complicates the extrapolation of data from animals to humans. In animals (a) SE is induced (chemically or by electrical stimulation) in the normal brain without any concomitant morbidity, (b) electrographic SE activity often stops spontaneously, (c) SE is not associated with peripheral morbidities (e.g., infections), and (d) SE-associated abnormalities in physiological measures are not treated. All these variables can contribute to the type, severity, and course of post-SE brain damage and functional impairments. Moreover, even though there is abundant literature demonstrating that the spatiotemporal evolution of pathological changes in morbidities causing SE (e.g., apoptosis and necrosis of different cell types, neuroinflammation, blood-brain-barrier damage) can be etiology-dependent (stroke, encephalitis, traumatic brain injury), there are no studies that had investigated whether the timing of SE relative to the occurrence/onset of underlying etiology would affect the consequent brain damage and functional outcome. This is important as some of the molecular and cellular pathologies developing over hours/days post-insult can lower the seizure threshold locally and time-dependently. Even though many of the cellular changes which modulate neuronal excitability can be monitored noninvasively, the treatment of SE still focuses on discontinuation of electrographic seizure activity, and the “molecular” environment” (etiology of SE), in which the prolonged seizure activity operates at a given time point has received little attention in the design of personalized treatment strategies for SE.

## How Long Seizures Cause Permanent Brain Damage?

*Asla Pitkänen, MD, PhD*

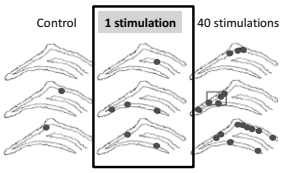
Epilepsy Research Laboratory
A.I.Virtanen Institute for Molecular Sciences
University of Kuopio, Kuopio
Finland
E-mail: asla.pitkanen@uku.fi

## Seizure-Induced Neurodegeneration




2002

**Apoptosis in hippocampal kidling**




Bengzon et al. PNAS 1997:94:10432-10437

## Variable Etiologies for SE – Variable Pathologies during SE

**TABLE 12-2 Frequency of Common Etiologies of Status Epilepticus in Adults and Children >1 Month of Age***

| Common Etiologies | Adults | Children |
|---|---|---|
| Stroke, including hemorrhagic | 20% | 10% |
| Low antiepileptic drug levels | 35% | 20% |
| Alcohol withdrawal | 15% | — |
| Drug intoxication (theophylline, imipenem, isoniazid, beta-lactams, clozapine, bupropion, 4-aminopyridine, cocaine, etc) or withdrawal (benzodiazepine, barbiturate, baclofen) | 5% | 5% |
| Anoxic brain injury | 15% | 5% |
| Metabolic disturbances (low glucose, calcium, magnesium, or sodium level; high glucose level; renal failure; liver failure) | 15% | 5% |
| Infection (meningitis, encephalitis, brain abscess, sepsis) | 5% | 5% |
| Traumatic brain injury | 2.5% | 15% |
| Brain neoplasm | 5% | 0% |
| Febrile seizures | — | 50% |
| Remote brain injury/congenital malformations | 20% | 40% |
| Idiopathic | 5% | 5% |

* Modified with permission from DeLorenzo RJ, et al. Neurology. © 1996, American Academy of neurology. www.neurology.org/content/46/4/1029.short?sid=e0855659-4863-46e8-bb78-0d96dfb06697.

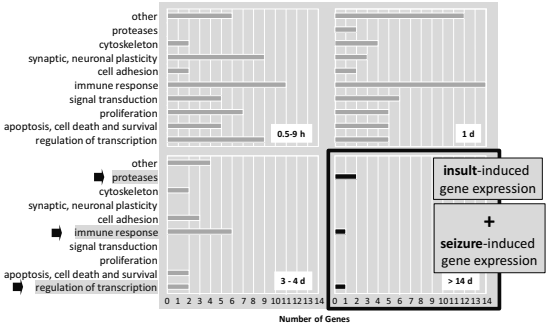
Hirsch and Gaspard, Continuum 2013:19(3):767-794

**TABLE 3. Stroke Type, Functional Disability, and Time of Onset of SE With Regard to SE Recurrence**

| | Nonrecurrent (n=12) | Recurrent SE (n=50 | P |
|---|---|---|---|
| Stroke type | | | |
| Ischemic stroke (n=12) | 7 | 5 | 0.2445 |
| Hematoma (n=5) | 5 | 0 | |
| Functional disability (Rankin scale) | | | |
| ≤3 (n=5) | 5 | 0 | 0.2445 |
| >3 (n=12) | 7 | 5 | |
| Time of onset of SE | | | |
| Early (n=7) ≤7 d | 2 | 5 | 0.00339 |
| Late (n=10) >7 d | 10 | 0 | |

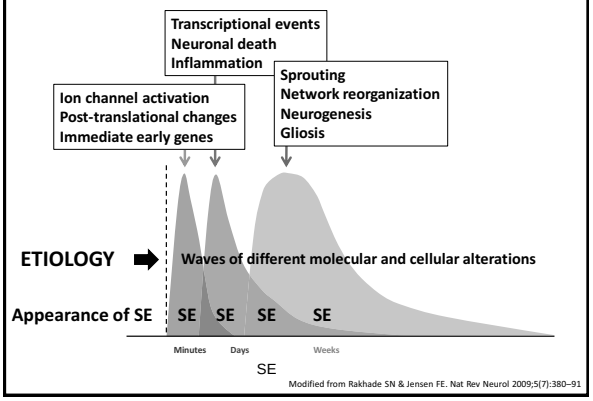
Vegioglu et al. Stroke 2001:32:1169-1172

## Gene Expression After Brain Injury Is Time-Dependent




Lukasiuk et al. Prog Brain Res 2006:158:223-241

## "Molecular and Cellular Mileau" During Occurrence of SE Can Vary




Modified from Rakhade SN & Jensen FE. Nat Rev Neurol 2009;5(7):380–91

## MORTALITY AND MORBIDITY CAUSED BY STATUS EPILEPTICUS

**Anne-Mari Kantanen. Department of Neurology, Neurocenter, Kuopio University Hospital, Kuopio, Finland.**

Most of the epileptic seizures are short, their duration is approximately 1-4 minutes and they are self-limited. Seizures that last over 30 minutes or are recurrent are considered as status epilepticus (SE), a life-threatening, medical emergency. If an epileptic seizure lasts more than 5 minutes, it is considered prolonged and the risk of getting SE is marked. Therefore seizures lasting over 5 minutes should be already treated as a SE. Any type of seizure can be prolonged. The treatment protocols of SE are agreed in local and international quidelines to consist of first line (benzodiazepines), second line (fosfenytoin/phenytoin) and third line (treatment with barbiturates or propofol in general anesthesia with EEG monitoring) treatment. Status epilepticus is considered refractory (RSE) if the first line (benzodiazepines) and second line (fosfenytoin) medical treatments fail. (1,2,3,4) Status epilepticus is called super-refractory if it lasts over 24 hours or fails third line treatment (5). In the adult population the most common aetiologies for SE are cerebrovascular disorders, traumatic brain injury, infections and previously diagnosed uncontrolled epilepsy. Less common causes, which present a clinical challenge are inflammatory causes, autoimmune diseases and errors of metabolism. Alcohol and other toxic withdrawal seizures can also lead to SE. (2,3,7) SE is important neurological emergency potentially associated with significant mortality and morbidity rates. Annual incidence is considered to be 20 /100 000. Mortality and morbidity rates of SE are influenced by the underlying aetiology. The three major determinants of prognosis are duration of SE, patients age and the underlying cause (7). The 30 days mortality rate is estimated to be 20% is lower in children (estimated 0-3%) and higher in elderly population (up to 38%) based on the underlying aetiologies (2, 3). Brain tumours as the aetiology of status are associated with greater mortality (6).

*References:*

1. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J Jr.Epileptic seizures and epilepsy: definitions proposed by the International League Against epilepsy (ILAE) and the International Bureau for epilepsy (IBE)., Epilepsia 2005 APR 46 (4):470-2
2. Mejerkord H, Boon P, Engelsen B,Göcke K,Shorvon S, Tinuper P, Holtkamp M.EFNS quideline on the management of status epilepticus in adults.European journal of Neurology Mar ;17 (3):348-55
3. Käypä Hoito suositus (Epileptinen kohtaus pitkittynyt), Käypähoito työryhmä 2009
4. Brophy GM, Bell R, Claassen J, alldredge B, Bleck TP, Glauser T, Laroche SM, Riviello JJ Jr, Shutter L, Sperling MR, Treilman DM, Vespa PM. Guidelines for the evaluation and management of status epilepticus, Neurocritical care 2012 AUG:17(1):3-23
5. Shorvon Simon, Monica Ferlisi: The treament of superrefractory status epilepticus: a critical view of available therapies and clinical treatment protocol. Brain 2011 Oct;134(Pt 10):2802-18.
6. Sutter R, Marsch S, Fuhr P,Rüegg S. Mortality and recovery from refractory status epilepticus in the intensive care unit: a 7 year observational study. Epilepsia 2013 Mar 54 (3):502 - 11
7. Trinka E, Höfler J,Zerbs A. Causes of status epilepticus. Epilepsia 2012 Sep 53 suppl 4:127-38

## What is status epilepticus?

- An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain
- Most of the epileptic seizures are short, their duration is approximately 1-4 minutes and they are self-limited. Seizures that last over 30 minutes or are recurrent are considered as **status epilepticus (SE)**, a life-threatening, medical emergency
- If an epileptic seizure lasts more than 5 minutes, it is considered prolonged and the risk of getting SE is marked. Therefore seizures lasting over 5 minutes should be already treated as a SE

ANY TYPE OF AN EPILEPTIC SEIZURE CAN GET PROLONGED!

## Etiology of status

- In the adult population the most common etiologies for SE are
  - cerebrovascular disorders
  - traumatic brain injury
  - infections
  - previously diagnosed uncontrolled epilepsy.
- Less common causes, which present a clinical challenge are
  - inflammatory causes
  - autoimmune diseases
  - errors of metabolism
- Alcohol and other toxic withdrawal seizures can also lead to SE

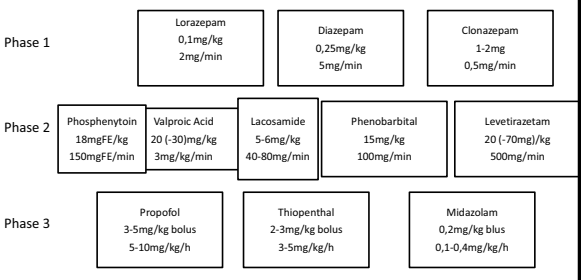
## Incidence, morbidity and mortality

- SE is important neurological emergency potentially associated with significant mortality and morbidity rates.
- Annual incidence is considered to be 20 /100 000.
- Mortality and morbidity rates are influenced by the underlying aetiology.
- The three major determinants of prognosis are duration of SE, patients age and the underlying cause.
- The 30 days mortality rate is estimated to be 20%. It is lower in children (estimated 0-3%) and higher in elderly population (up to 38%) based on the underlying aetiologies. Brain tumours as the aetiology of status are associated with greater mortality.
- Third line antiepileptic therapies themselves or hypotension requiring vasopressor therapy and duration of mechanical ventilation in the ICU may be contributing factors of the poor outcome.
- Infections during SE are also considered to be frequent and may be associated with higher mortality. Mortality associated in SE with acute ischaemic stroke seems to be three times higher than in stroke alone. In elderly population aged over 80 the mortality rate approaches 50%.
- The lack of data on outcome of RSE is well established worldwide.

## The first drugs and the timeline?

- The treatment protocols of SE are agreed in local and international quidelines to consist of
  - first line (benzodiazepines)
  - second line (fosfenytoin/phenytoin)
  - third line (treatment with barbiturates or propofol in general anesthesia with EEG monitoring) treatment
- **Status epilepticus is considered refractory** (RSE) if the first line (benzodiazepines) and second line (fosfenytoin) medical treatments fail
- **Status epilepticus is called super-refractory** if it lasts over 24 hours or fails third line treatment

## Phases of treatment of status epileticus




Modified from Trinka Nervenheilkunde 2007, Shorvon,Boulac,Cross,Trinka and Walker for ILAE Task Force on SE, Epilepsia 2008

## How to do it better?

- Learn from Stroke – take a Door to needle time to SE
- To notice and treat faster
  - Educate people
  - Educate paramedics
  - Educate doctors
  - Educate ER staff
  - Educate ICU staff
- To diagnose RSE
  - Get the EEG 24/7

- Review results on yearly basis in every hospital!

**TREATMENT ADVANCES IN EARLY STATUS EPILEPTICUS**

**Rod C Scott. University of Vermont, Department of Neurological Sciences, Burlington, Vermont, USA; UCL Institute of Child Health, London, UK.**

Convulsive status epilepticus is the most common medical neurological emergency in childhood. It is associated with significant morbidity and mortality, at least some of which is likely to be a direct result of the epileptic activity. This suggests that early intervention to terminate seizures should improve outcomes. As most seizures start in the community setting it is essential that effective non-parenteral medications are available to paramedics, parents, teachers and carers. Buccal midazolam is becoming the standard of care in many parts of Europe and the data supporting its use will be reviewed. The evidence supporting the use of lorazepam, phenytoin and sodium valproate in the hospital setting will also be discussed. However, strategies that minimize brain injury independently of seizure termination may also have a role, although this is far less studied. The efficacy of treatments that reduce excitotoxicity or manipulate inflammatory cascades will be described with emphasis on data from animal models. These data support the view that neuroprotection is possible, but antiepileptogenesis is more difficult to achieve. Finally I will discuss the long term impacts of experimental status epilepticus on hippocampal neural networks as this may drive novel approaches to minimize adverse outcomes from status epilepticus.

# Treatment Advances in Early Status Epilepticus

*Rod C. Scott*

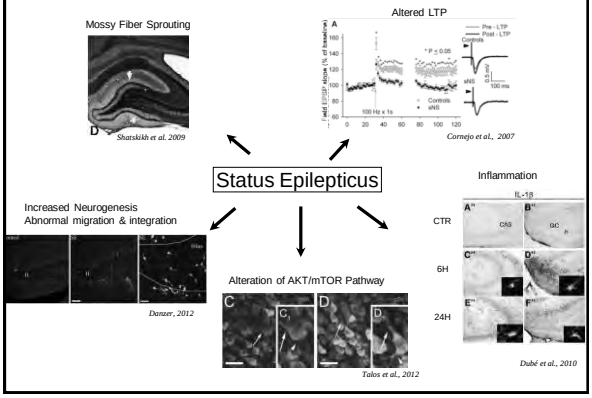
## Clinical Studies on Buccal Midazolam

- 3 RCTs
  - NCYPE Scott (1999), Lancet
    - Children with severe epilepsy (>5 years)
    - >5min seizures
    - BMDL = PRDZP
  - North and Midlands McIntyre (2005), Lancet
    - Treatment in A&E
    - All ages and aetiologies
    - BMDL > PRDZP
  - Uganda Mpimbaza (2008), Pediatrics
    - A&E
    - Primarily malaria
    - PRDZP=BMDL (malaria) and BMDL>PRDZP (other aetiologies)
- Community study required

## Difficulties implementing prehospital treatment

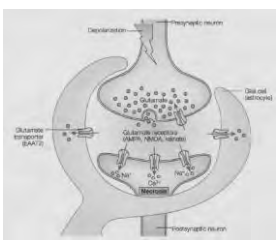
- 147/240 in NLSTEPSS
  - Majority received inadequate dose
- Pre-hospital treatment of seizures in children not universal practice
- Children admitted to PICU
  - Half treated pre-hospital
  - 30% received an adequate initial pre-hospital dose
- LAS has policy to treat children with seizures

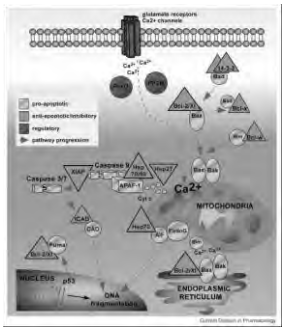
Chin (2004), JNNP




## Mechanisms of Brain Injury

Excitotoxicity






## Conclusions

- Status epilepticus is common in children
- Acute hippocampal injury occurs following status epilepticus in humans and animal models
- SE is associated with an acute inflammatory process, but causation remains uncertain
- Outcomes include
  - Epilepsy
  - Slowing of hippocampal growth
  - Cognitive and memory impairments
    - In part a function of brain network organization

**NEW METHODS FOR EEG MONITORING OF STATUS EPILEPTICUS**

**Esa Mervaala. Department of Clinical Neurophysiology, Kuopio University Hospital, Kuopio, Finland; University of Eastern Finland, Faculty of Health Sciences, Clinical Neurophysiology, Kuopio, Finland.**

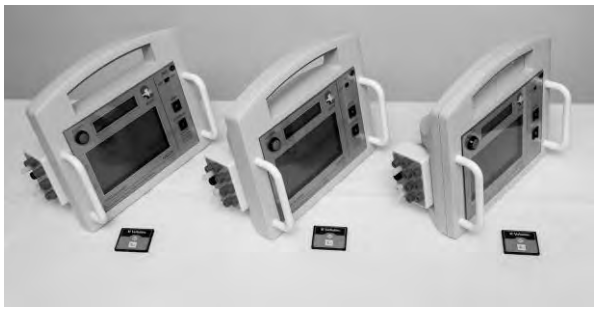
EEG should be an easily available tool for the clinician who diagnose and treat patients with Status Epilepticus (SE). However, EEG is surprisingly underutilized in acute clinical settings. The most common reason for this is simply that acute EEG is just not available when needed. In SE, optimally, EEG should be used along the complete treatment period, i.e., when entering the diagnosis, during treatment and importantly also immediately following clinically successful treatment of convulsive SE. 30-40% of successfully treated patients with convulsive SE remain in NCSE, that can be diagnosed only with EEG.

A significant proportion (~30%) of patients that have been successfully resuscitated from cardiac arrest represent NCSE that can be diagnosed only by EEG. Accordingly, the use of EEG is suggested for all patients treated with hypothermia, and that EEG recording should start from the very beginning of intensive care treatment.

The optimal situation with EEG would be similar to ECG recording: acute EEG should be available at the very first moments when clinically needed. We have designed a fast EEG electrode that is suitable for acute emergency use: it is easy to set up also by untrained Emergency and Intensive Care Units´ staff members, records high quality EEG, and can detect the most important EEG abnormalities comparable to conventional EEG. In addition to suitable electrodes for acute EEG the actual EEG recording device should also be as easy-to-use as possible. We have developed an in-house-build mobile EEG device that enables to record acute EEG practically everywhere.

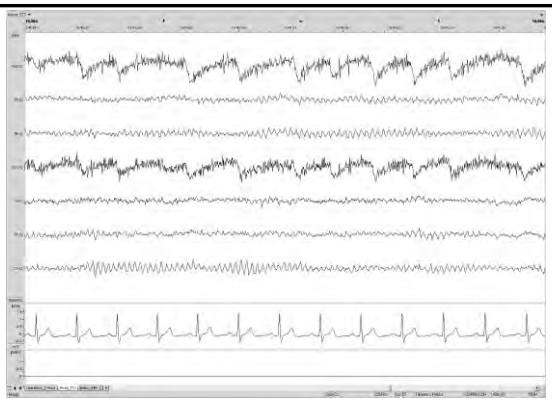

With the new electrode (turquoise), the initiation of acute EEG takes only 1-2 minutes and does not require any special neurophysiological expertise.





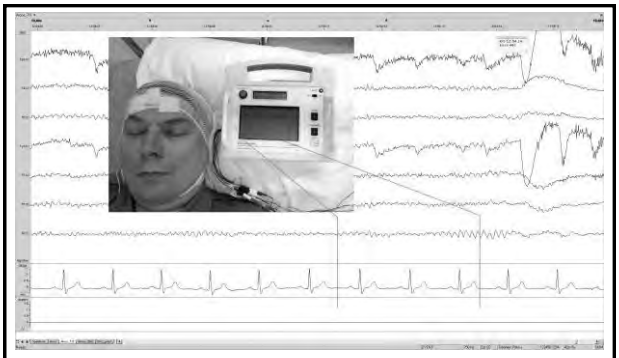
An in-house build mobile EEG device enabling EEG recordings everywhere - outside hospital and *e.g.,* in emergency medicine.





EEG example recorded with mobile EEG device showing excellent signal quality.





EEG recorded with mobile EEG device can be displayed into any EEG reading software.

## NEUROINTENSIVE CARE OF STATUS EPILEPTICUS

**Stepani Bendel. Division of Intensive Care, Kuopio University Hospital, Kuopio, Finland.**

Status epilepticus (SE) is a neurocritical emergency situation which requires immediate, targeted and aggressive treatment. Treatment guidelines for SE should be available in hospitals treating SE in ICUs. First priorities are the management of airways, breathing and circulation. Prompt intravenous access is always needed to enable drug treatment. Simultaneously with the above mentioned maneuvers one should aim to stop seizures (clinical and electrographic) and try to diagnose the underlying cause of SE. If hemodynamic instability is observed, adequate fluid resuscitation with vasoactive drugs should be initiated urgently. The need for CT/MRI should be carefully evaluated in selective patients and these examinations should not further delay seizure control. Continuous EEG should always be required for SE monitoring. If EEG shows signs of SE continuous infusions of anesthetic antiepileptic drugs should be started. Mostly thiopental, midazolam or propofol are used. There is insufficient data to recommend one of these drugs and it should be based on center and patient evaluation and experience. Propofol may cause hemodynamic instability and propofol infusion syndrome (PRIS). PRIS causes myocardial stunning and may be fatal. Thiopental may require prolonged ventilatory support. Generally, drug infusions are guided by EEG findings. SE may be present in patients treated in the ICU due to traumatic brain injury (TBI) or subarachnoid hemorrhage (SAH). Doctors must be aware of the possibility of SE also in these patient groups. SE patients should be evaluated for possible infections, early enteral nutrition and antithrombotic pneumatic devices should be applied immediately.

## First steps

- Airway
- Breathing
- Circulation
- Venous access
- Seizure control
  - Clinical and electric
- Continuous EEG



## Thiopental

- Effective
  - High doses needed
  - Hypotension
  - Accumulation
    - Infections
    - Prolonged ventilatory support



## Propofol

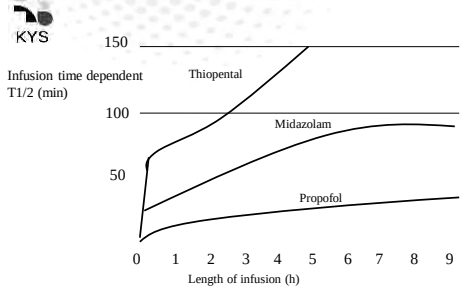
- Effective
- May be difficult to titrate
- No accumulation
- Hypotension
- Propofol infusion syndrome



## Midazolam

- Effective?
- Hemodynamically tolerable
- Accumulation








## General ICU care

- Early enteral nutrition
- Antithrombotic pneumatic devices
  - Low molecular weight heparin
- Infection control

## THE TREATMENT OF SUPER-REFRACTORY STATUS EPILEPTICUS

**Simon Shorvon. UCL Institute of Neurology, University College London and National Hospital for Neurology and Neurosurgery Queen Square, London, Great Britain.**

Super-refractory status epilepticus is defined as status epilepticus that continues or recurs 24 h or more after the onset of anaesthetic therapy, including those cases where status epilepticus recurs on the reduction or withdrawal of anaesthesia. It is an uncommon but important clinical problem with high mortality and morbidity rates. There are no controlled or randomized studies, and so therapy has to be based on clinical reports and opinion. Therapy had included: anaesthetic agents, anti-epileptic drugs, magnesium, pyridoxine, steroids and immunotherapy, ketogenic diet, hypothermia, emergency resective neurosurgery, transcranial magnetic stimulation, electroconvulsive therapy, and other older therapies. The importance of treating the identifying cause is stressed. A review of the outcome of therapies in refractory and super-refractory status epilepticus in 1168 patients is discussed. Where reported (596 cases), the long-term outcome was found to be death (35%), severe neurological deficit (13%), mild neurological deficit (13%), undefined deficit (4%) and recovery to baseline (35%). The quality of reported outcome data is generally poor. Outcome assessment is complicated by changes in co-medication, delay in response and publication bias. Given these deficits, only broad recommendations can be made regarding optimal therapy. A protocol and flowchart for managing super-refractory status epilepticus is suggested. An approach to therapy, divided into first-line, second-line and third-line therapy, is suggested.

Stage 1: First 30 minutes

Stage 2: 30-120 minutes

Stage 3: >120 minutes

After 24 hours

**Stage 1 - Early status epilepticus**
**Treat with benzodiazepines - for instance IV lorazepam, buccal midazolam, IV or rectal diazepam**

**Stage 2 - Established status epilepticus**
**Treat with IV antiepileptic drugs – for instance, phenytoin, phenobarbital, levetiracetam, valproate or lacosamide**

**Stage 3 - Refractory status epilepticus**
**Treat with general anaesthesia – for instance, propofol, midazolam, or thiopental/pentobarbital**

**Super-refractory status epilepticus**
**Status epilepticus which has continued or recurred despite therapy with general anaesthesia for ≥ 24 hours**

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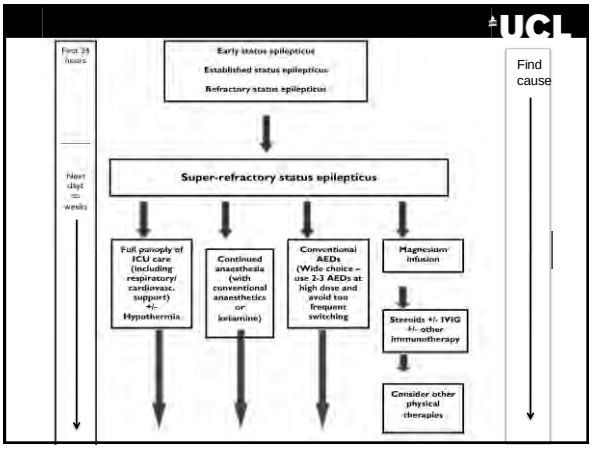


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## Super-Refractory SE – literature review and long-term outcome

- **Literature review of therapies used: 1061 pts published since 1981 with super-refractory SE**

| | |
|---|---|
| **N*** | **588** |
| **Deaths** | **205 (35%)** |
| **Severe neurological deficit** | **75 (13%)** |
| **Mild neurological deficit** | **79 (13%)** |
| **Undefined neurological deficit** | **22 (4%)** |
| **Recovery to baseline** | **207 (35%)** |
| *** = Long term outcome reported in 588 cases (52% of the total of 1130).** | |

***(From Brain 2011 134: 2802-2818; 2012 135(Pt 8):2314-28)***

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## Anaesthesia in super-refractory SE - questions

- **How long to continue**
  - **Excitotoxic damage already initiated**
  - **Do the risks of anaesthesia exceed the risks of SE ?**
- **Complications of anaesthesia**
  - **Risks include immunosuppression, cardiac depression, metabolic complications, acid-base disturbances, infection**
- **How to cycle**
  - **Initially at 24-48hr cycles, then longer.**
- **Should one switch anaesthetics ?**
  - **Prolonged propofol carries specific risk**
  - **At what stage should anaesthesia be switched**
- **Literature review**
  - **No data on any of these points**

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## New initiative: www. Status-epilepticus.net


Global Audit of Treatment of Refractory Status Epilepticus and Super-refractory Status Epilepticus

**Online audit of the treatments being used in status epilepticus around the world and their outcome**
**Short and easy to complete Questionnaires**

**!! PLEASE REGISTER AND TAKE PART !!**

## STATUS EPILEPTICUS AFTER CEREBRAL ANOXIA - WHEN TO TREAT?

**Amy Z Crepeau. Mayo Clinic, Phoenix, Arizona, USA.**

Cerebral anoxia, most typically occurring after sudden cardiac arrest, is a common condition with high mortality and morbidity. Few patients are successfully resuscitated, and of those that do survive until reaching the hospital, less than half will have good neurologic outcomes. Seizures and status epilepticus, both convulsive and nonconvulsive, are common in the patient population and have widely been regarded as being associated with a poor prognosis. Increased utilization of continuous EEG monitoring, which is often deployed within the first 24 hours after anoxic injury, has led to increased recognition of nonconvulsive seizures and status epilepticus, resulting in even more questions regarding appropriate treatment. This lecture will begin by discussing this frequency and timing of seizures and status epilepticus after cardiac arrest and anoxic injury, with a focus on those patients treated with therapeutic hypothermia. This will be followed by a review of evidence of the relationship between anoxia and seizures, with a discussion of whether seizures are simply a biomarker of a severe anoxic injury, or whether they result in secondary neuronal damage that could potentially be mediated with neuroprotective agents. Finally, there will be an overview of treatments used in clinical practice, with a proposed algorithm for the treatment of seizures after anoxic injury.

# Status epilepticus after cerebral anoxia- when to treat?

Amy Z. Crepeau, M.D.
Mayo Clinic
Phoenix, Arizona, USA

Kuopio Epilepsy Symposium and Teaching Course
April 4, 2014

## Sudden Cardiac Arrest

- Very common condition with an incidence between 0.04% and 0.13% of the population in industrialized countries.[1,2]
- Estimated mortality assessed by EMS response is approximately 94%.[3]
- If the patient survives the initial cardiac arrest, in-hospital mortality is approximately 60%.[4]

1. Becker, 1993
2. Vreede-Swagemakers, 1997
3. Nichol, 2008
4. Fugate, 2012

## Seizures After Cardiac Arrest

- Nonconvulsive seizures (NCSz) occur in 9-30% of patients treated with TH.
- The majority of seizures occur during TH.[1,2]
- Mean onset of NCSz is 15 hours after cardiac arrest.[2]
- NCSz likely to be preceded by interictal epileptiform activity.[3]

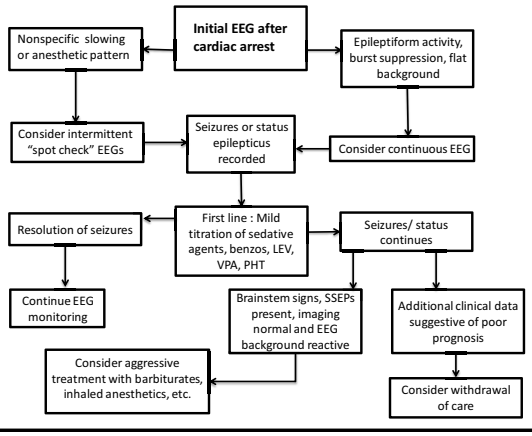
1. Crepeau, 2013
2. Rittenberger, 2012
3. Mani, 2012

## Status Epilepticus After Cardiac Arrest

- Nonconvulsive status epilepticus
  - Occurs in 10-12% of patients.
  - Typically develops during TH.
- Myoclonic status epilepticus
  - May be confused for early-onset Lance Adams myoclonus.

## Treatment

- Antiepileptic medications
  - Benzodiazepines, phenytoin, levetiracetam, valproate, midazolam, propofol, barbiturates
- Alternative treatment options
  - Hypothermia, inhaled anesthetics, ketogenic diet
- Treatment has yet to be shown to improve outcomes



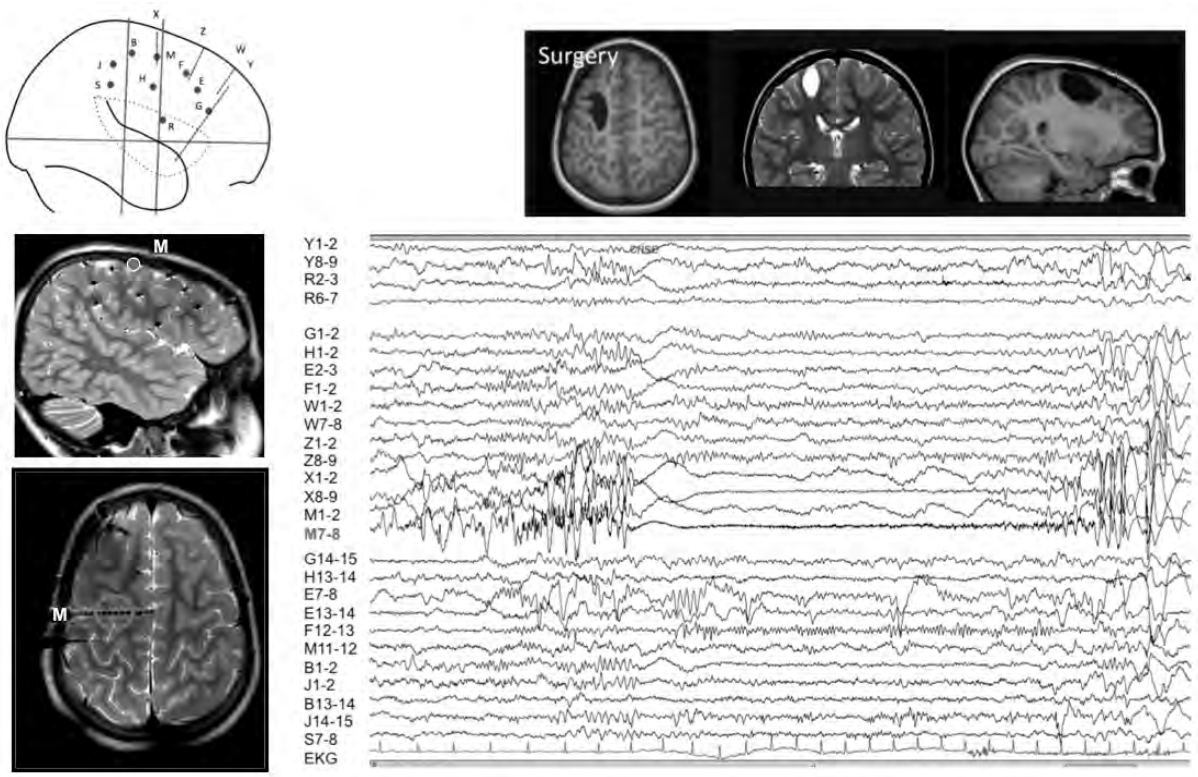
## STEREO-EEG – WHAT NEW DOES IT FOR DIAGNOSTICS?

**Philippe Kahane. Grenoble Institut des Neurosciences, Grenoble, France.**

In spite of the increasing use of non-invasive and non-electrophysiological tests in the pre-surgical evaluation of patients with refractory epilepsies, invasive EEG methods remain necessary in a number of patients, especially those suffering from MRI negative and/or extra-temporal focal epilepsies. Different types of electrodes can be used to record the intracranial EEG including intracerebral depth electrodes, subdural grids or strips, and epidural electrodes, and the intracranial method is selected depending on the question posed by a given epilepsy problem (see Table below). Among this broad group of invasive procedures, some conceptual and technical aspects make the stereo-electro-encephalography (SEEG) very particular since, from the begining, it has been conceived by Talairach and Bancaud as a comprehensive methodology and not only as a diagnostic tool. The implantation strategy was then 'custom-tailored', and electrodes were placed according to the prior hypotheses on the epileptogenic zone, in a way that enabled studying, in each individual, the origin and spread of ictal discharges (see Figure below). If the pre-implantation hypothesis is wrong, the placement of intracerebral electrodes will likely be inadequate and the interpretation of EEG findings will reflect this misunderstanding. We will see, during the presentation, what are the best indication of SEEG procedures, how the method has helped us to better understand the spatial organization of the epileptogenic networks subserving different types of focal seizures, and how to go further with SEEG using signal processing.

| Type | Recording areas | Advantages | Disadvantages |
|---|---|---|---|
| Intracerebral depth electrodes (within cortex) | Deep limbic and paralimbic buried structures: amygdala, hippocampus, entorhinal cortex and parahippocampus, insula; interhemispheric cortical structures; depth of the sulci; hypothalamus, thalamus, and basal ganglia; deep-seated and periventricular lesions | Good sampling of deep structures; findings can be standardized in a common stereotatic space allowing intersubject comparisons; well-tolerated procedure and low morbidity | Limited sampling (especially of neocortical structures); not adapted for exhaustive cortical functional mapping |
| Grids (subdural surface) | Cortical convexity, basal and interhemispheric neocortical (gyral) surface | Large number of recording channels and broad coverage of neocortical areas; well-suited for mapping of cortical function by electrical stimulation | Large craniotomy; higher morbidity; no sampling from deep buried structures; needs to be immediately followed by resective surgery |
| Strips (subdural surface) | Cortical convexity, basal and interhemispheric neocortical surface | Good coverage of neocortical areas; low morbidity | No sampling from deep buried structures |
| Epidural electrodes (pial surface) | Cortical convexity | Easy to install with low morbidity and satisfactory coverage of neocortical convexity | No sampling of basal and deep structures; no electrical stimulation |

Advantages and disadvantages of the different types of intracranial electrodes




Typical depth electrode implantation in a 6-year-old boy with negative MRI, whose seizures are characterized by asymmetric tonic motor manifestation with left oculocephalic version and mild postictal paresis of the left hand. Seizures are characterized by clusters of brief episodes of left oculocephalic version with bilateral (L > R) tonic motor signs. Interictal scalp EEG showed spikes and bursts of fast oscillations over the right fronto-central region (FP2–F4, F4–C4, Fz–Cz), and seizures started from this area. The hypothesis was to demonstrate that seizures arose from the region of the right frontal eye-field. The SEEG study confirmed the hypothesis and surgery was performed accordingly, with a class IA post-operative outcome (histology: focal cortical dysplasia type 2).

**OPTOGENETICS – WILL IT REPLACE DEEP BRAIN STIMULATION IN THE TREATMENT OF EPILEPSY?**

**Merab Kokaia. Epilepsy Center, Department of Clinical Sciences, Faculty of Medicine, Lund University, Lund, Sweden.**

**RATIONALE:** Development of novel treatments for epilepsy requires better understanding of mechanisms of epileptogenesis and ictogenesis. In particular, we need to understand what is the role various populations of neurons, both excitatory and inhibitory, in generating pathologic hyper-synchronized activity in the neuronal networks. Optogenetics provides possibility, unprecedented before, to selectively activate and inhibit certain populations of neurons, and thereby explore their role in epileptogenesis and incotegenesis. Moreover, optogenetics can be used to manipulate these populations of neurons and normalize network cavity, thereby counteracting seizures. We explored the role of different populations of hippocampal interneurons in suppressing seizure activity.

**METHODS:** Mixed interneuron population or parvalbumin (PV)- or somatostatin (SOM)-expressing interneurons were selectively transducer by ChR2 and light activation was used to elucidate the seizure-suppressant mechanisms of these interneurons in vitro.

**RESULTS:** We demonstrate that Gad2-expressing (mixed population) of interneurons is more effectively suppressing epileptiform activity in the hippocampus compared to PV- or SOM-expressing populations. This suppression is mediated by increased GABA release rather than disrupting established synchronized activity of the neuronal networks per se.

**CONCLUSIONS:** Global interneuron activation seems to exert significant seizure suppressant effect on ongoing epileptiform activity in the hippocampus, and may be used in the future for development of tailored optogenetic treatment strategies for epilepsy. Advantages of optogenetic vs electrical deep brain stimulation (DBS) will be also discussed.

## HAS FMRI ALREADY REPLACED THE WADA TEST IN THE PRESURGICAL EVALUATION OF PEOPLE WITH EPILEPSY?

**Sallie Baxendale. Department of Clinical & Experimental Epilepsy, The Institute of Neurology, UCL, London, UK; The National Hospital for Neurology Queen Square, London, UK.**

In order to answer this question, the role of the Wada test in the presurgical evaluation of people with epilepsy must be defined. Once defined, the evidence base for using fMRI in each of these roles can be examined. The Wada test fulfils three primary roles in the presurgical evaluation.

1. **Lateralising language function.** With respect to language lateralisation, the functional imaging literature indicates that fMRI language paradigms are reliable and valid and that they can provide a more nuanced assessment of language localisation than is possible with the Wada test. Recent studies have challenged the 'gold standard' status of the Wada test in language lateralisation. fMRI has replaced the Wada test in this role

2. **Screening for amnesic risk.** The Wada test screens for amnesic risk by temporarily creating the effects of losing unilateral temporal lobe function. fMRI paradigms cannot do this. However high resolution structural MRI combined with detailed baseline neuropsychological scores and information from fMRI memory paradigms provide a detailed picture of function and structure. The combined analyses of results from these investigations can be used to screen for amnesic risk.

3. **Predicting postoperative seizure control and cognitive outcome.** Wada test scores can predict both cognitive outcome and postoperative seizure control. However the most accurate predictive outcome models are multivariate models that combine functional and structural data from the presurgical assessment. Wada data does not add sufficient power to these models to justify the invasive nature of the test.

In conclusion, fMRI has not replaced the Wada test. However the combination of fMRI data with other indices of function and structure provides a non-invasive alternative for majority of epilepsy surgery candidates.

## HAS FMRI ALREADY REPLACED THE WADA TEST IN THE PRESURGICAL EVALUATION OF PEOPLE WITH EPILEPSY?

Department of Clinical & Experimental Epilepsy
The Institute of Neurology, UCL
The National Hospital for Neurology
Queen Square
London

DR SALLIE BAXENDALE

## THE ROLE OF THE WADA TEST IN THE PRESURGICAL EVALUATION

- 1. Lateralise language function
- 2. Screen for amnesic risk
- 3. Aid prediction of postoperative outcome

## LATERALISING LANGUAGE FUNCTION

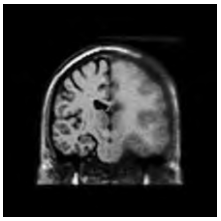
- fMRI paradigms provide more versatile, nuanced assessments of language function
- Reliable and valid
- Different methodological constraints
- fMRI presents a challenge to the concept of the Wada test as the 'gold standard'

## SCREENING FOR AMNESIC RISK

- Rationale
- No fMRI equivalent

BUT

- Structural and functional equivalents
- Case literature
  - Evidence-Based Practice: A Re-evaluation of the Intracarotid Amobarbital Procedure (Wada Test) Baxendale, Thompson, Duncan. Arch Neurol. 2008; 65(6):841-845.



## PREDICTING POSTOPERATIVE OUTCOME

- Wada Test
  - Memory function ✓
  - Seizure control ✓
- fMRI
  - Memory function ✓
  - Seizure control ✓

How is predictive data used?
Multivariate models of prediction
Added value Wada data ≠ invasive nature of test

## SUMMARY

- Has fMRI already replaced the Wada test?
  - Lateralising language YES
  - Screening for amnesic risk NO*
  - Predicting outcome YES & NO*

(*but other techniques have)

**TRANSCRANIAL MAGNETIC STIMULATION - WHAT'S NEW?**

**Vasilios K Kimiskidis. Department of Neurology & Clinical Neurophysiology, Laboratory of Clinical Neurophysiology, Aristotle University of Thessaloniki, Greece.**

Transcranial Magnetic Stimulation (TMS) entered the armamentarium of clinical neurophysiologists as a non-invasive brain stimulation technique almost three decades ago. However, the role of TMS as a research and clinical tool in the field of epilepsy is still evolving. Recent studies shed additional light on the pathophysiological substrate of epilepsies and helped better define the role of TMS in the diagnosis, prognosis and therapeutic management of epilepsy. From a pathophysiological point of view, converging lines of evidence lead to the conclusion that cortical excitability is altered in epilepsy in a syndrome-specific manner. Interestingly, cortical hyperexcitability has been recently demonstrated in asymptomatic siblings of patients with epilepsy as well. This observation suggests the existence of a genetically-defined hyperexcitability in both focal and generalized epilepsy which via a complex interaction with environmental factors leads to the expression of the ultimate phenotype (i.e. focal or generalized seizures). Pharmaco-TMS studies indicate that TMS can predict the development of pharmaco-resistance to AEDs over a long-term period at the group level. It remains to be seen, however, if optimized TMS protocols may succeed in predicting response to AEDs at the level of the individual patient thereby maximizing the usefulness of this method in every day clinical practice. Finally, the therapeutic potential of TMS in the acute setting (i.e for the interruption of clinical and/or electrographic seizures) has been further explored with encouraging results. It appears that TMS terminates epileptiform discharges by restoring, in a node-specific manner, the brain network connectivity structure to the interictal levels.

## AUTOIMMUNE ENCEPHALITIS

**Simon Shorvon. UCL Institute of Neurology, University College London and National Hospital for Neurology and Neurosurgery Queen Square, London, Great Britain.**

This talk will focus on the diagnosis and causation of autoimmune encephalitis and also cover briefly its history, and treatment. The diagnostic challenges are significant, and like many newly discovered entities, the full range of the clinical phenomenology is probably not yet fully realized. The first autoimmune limbic encephalitis was described by Brierley in 1960, when he described 3 cases of “a subacute limbic encephalitis of later life” and then in 1966, Brain discovered the association of an encephalitis with a serum antibody (Hashimoto’s encephalitis with anti-thyroid microsomal antibodies). Following this, a range of paraneoplastic antibodies were discovered. These conditions are more common than first appreciated, as was made clear in the landmark report of the clinical features of 100 cases of a severe encephalitis associated with anti-NMDA antibodies by Dalmau et al (2008). The clinical features will be described and the immunological tests that may be indicated. Challenges exist in atypical cases, not least because immunological testing may take time, whereas treatment is often urgent. A hunt for underlying malignancy often too is a diagnostic challenge. Newer forms are recently described and this is an important area of research in relation to the aetiology and treatment of epilepsy.

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## Uncommon causes of SE – autoimmune 'limbic encephalitis'

- **Autoimmune LE**
  - **First case described by Brierley 1960**
  - **First case associated with serum antibodies - thyroid microsomal AB (Hashimotos encephalitis) 1966 (Brain)**
  - **Since 1980s, a variety of ABs found, some with tumours and some 'idiopathic'**
  - **Cell surface antibodies - B-cell - and easier to treat**
  - **Intracellular antibodies - T-cell - less responsive to therapy**

| Intracellular antibodies | Extracellular antibodies |
|---|---|
| Hu/ANNA-1 | VGKA |
| Ma-2 | NMDA-R |
| CRMP-5 | Others (eg glycine, adenylate kinase 5, BR serine/threonine kinase) |
| Amphiphysin | |
| GAD | |

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## Uncommon causes of SE – autoimmune limbic encephalitis

- **Neoplastic autoimmune LE**
  - **Neurological symptoms precede tumoural symptoms in 66%; LE associated with other signs**
  - **Anti Hu: small cell lung cancer 10% have LE, others cerebellar, PN, autonomic**
  - **Ma-2: intratubal germ cell tumours of testes Other features include hypothalamic and brainstem signs**
  - **Amphyphysin: LE and 'stiff person syndrome**
  - **GAD: LE with 'stiff person syndrome'**
- **Non-neoplastic autoimmune LE**
  - **Voltage-gated potassium channel antibodies**
  - **Hashimotos encephalitis (STREAT)**
  - **NMDA-R antibodies**

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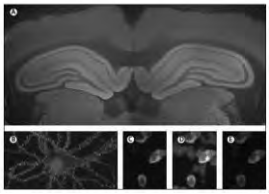
## LE due to NMDA-R antibodies

- **First described in 2007 by Dalmau**
- **Severe but treatment responsive LE; 90% young women**
- **Present with rapid deterioration with psychosis, delusions, amnesia, szs, stupor/coma, stereotyped abnormal movements**
- **Paraneoplastic; although some cases without tumour (esp male)**
- **Case series of 100 cases (Dalmau et al 2008)**
  - **59% tumours (commonest ovarian teratoma)**
  - **75% recovered or mild deficit**
  - **25% died**
  - **Main epitope is the extracellular N-terminal domain of NR1 subunit**



*Dalmau et al Lancet Neurol 2008: 1091*

## VACCINES AND SEIZURES

**J Helen Cross. The Prince of Wales's Chair of Childhood Epilepsy, UCL Institute of Child Health, Great Ormond Street Hospital for Children NHS foundation Trust, London, and Young Epilepsy, Lingfield.**

The debate as to whether vaccines cause brain damage has continued for many years. There was initial concern about a possible encephalopathy induced by pertussis vaccine on its introduction, although it was similarly recognised that such could be induced by the infection itself. Allegations have resulted in payouts for compensation from high court rulings, despite lack of evidence from epidemiological studies. It was recognised however that the so called vaccine encephalopathy had many similarities to an early onset epileptic encephalopathy. An initial study evaluated a series of individuals with 'vaccine encephalopathy' for an SCN1A mutation – 11/14 were positive. The same group then went on to evaluate two groups of individuals – those with vaccine proximate onset of seizures and those with onset of epilepsy temporally unrelated to the vaccine. Their predominant conclusion was that the vaccine appeared to trigger the onset of Dravet syndrome, but that the phenotype was not different, not more severe and the genotype was no different than in those where the vaccine was not a trigger. The vaccine did not appear to be associated as causation of brain damage. Epidemiological study of seizures following other vaccines have shown an increased risk of febrile seizures following mumps measles and rubella, as well as certain influenza vaccinations, but no increased risk of epilepsy. In summary, vaccinations my cause fever, and children are at risk if febrile seizures. The development of epilepsy following vaccination appears to be the result of what would have occurred inevitably.

## Vaccination & seizures

- Vaccination may cause first fever
  - Diphtheria/tetanus/pertussis
    Given at 2, 4, 6 months
  - Febrile seizures may occur
- Multiple epidemiological studies failed to support an association with *encephalopathy*
- *But*
  - Parents want to know why
  - Vaccination blamed
  - Drop in vaccination uptake with consequent epidemic
  - Juries very sympathetic

## Vaccine encephalopathy
*Hypothesis*

- "Vaccination encephalopathy" has features of Dravet syndrome and is associated with mutations in *SCN1A*
- Examined cases where families or doctors had regarded cases as "vaccine related"
  - Defined as within 72 hours

*Berkovic et al, Lancet Neurology, 2006*

## Conclusions 1

- Vaccine encephalopathy frequently has phenotype of Dravet
- Finding of *SCN1A* mutations shows genetic aetiology rather than immune response to vaccine
- At most, vaccine is a trigger for genetically determined disease
- Lack of family history of seizures explained by *de novo* mutations

*Berkovic et al, Lancet Neurology, 2006*

## Conclusions 2

- Children with 'Vaccine encephalopathy' frequently have Dravet phenotype
- Dravet syndrome begins shortly after vaccination in ~ 1/3 pts
- Vulnerable period is ~ 40 hours post immunization
- Vaccine-proximate group did not differ from rest
  - *Except* onset ~ 7 weeks earlier
- Vaccination may appear to trigger onset but
  - Not a different phenotype
  - Not more severe
  - Same molecular lesions
  - No evidence that vaccine causes brain damage
- Societal and medicolegal consequences

## Other vaccinations

Influenza vaccines different rates reactogenicity, varies between ethnic groups

- High rates febrile convulsions with Fluvax
- Higher rates fever with Influvac

*Petrousis-Harris et al Vaccine 2012;30:4945-52*

No significant increased risk in epileptic seizures immediate time after monovalent AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine

*Stowe et al Vaccine 2011;29:9467-72 29, Arnheim-Dahlstrom et al BMJ 2012;345:e7594*

## Summary

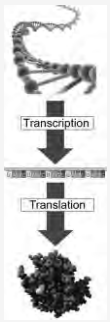
- Vaccinations may cause fever; children are at risk of febrile seizures
- Evidence seizures associated with vaccination
  - Febrile seizures
  - Consequence of inevitable course
- Careful assessment of possible epilepsy imperative, with evaluation risk:benefit prior to any decision

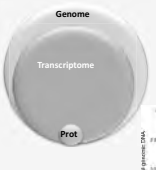
## NON-CODING RNAS

**David C. Henshall. Royal College of Surgeons in Ireland, Dublin, Ireland.**

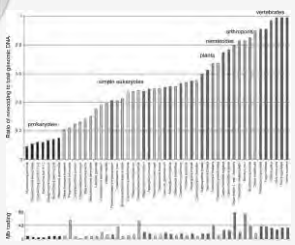
The molecular mechanisms controlling gene expression make an important contribution to the pathogenesis of epilepsy. Protein-coding genes, however, comprise only few percent of the entire transcribed human genome with perhaps 80% actively transcribed as non-coding RNA. We are gaining an increasing understanding that non-coding RNAs contribute to guiding transcription, epigenetic reprogramming and post-transcriptional interference in mRNA translation. Brain functions have been identified for several long noncoding RNAs, including regulating synapse formation and seizure thresholds. Among the short non-coding RNAs particular attention has been on microRNAs, which function post-transcriptionally to control protein levels inside cells. MicroRNAs mainly work by binding to short (7-8 nt) complementary regions of protein-coding mRNAs, resulting in down-regulation of the mRNA or repression of translation. Recent studies in experimental and human epilepsy have identified changes to over 100 different microRNAs. Consistent with their multi-targeting potential, research shows that changes to levels of a single microRNA can produce effects on hundreds of brain-expressed mRNAs. Functional studies in mouse models have demonstrated direct effects of two microRNAs on seizure thresholds and epilepsy. With microRNA inhibitors already in clinical trials these studies raise the prospect of a novel approach to epilepsy treatment. MicroRNAs are also present circulating in the blood and brain-specific microRNAs may represent potential biomarkers of epileptogenesis or seizures. In summary, non-coding RNAs represent an important contributor to gene expression control and represent potential novel therapeutic targets and molecular diagnostics for epilepsy.

## Non-coding RNA – a new gene focus in epilepsy



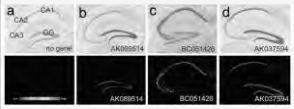




The amount of non-coding RNA increases as a function of organism complexity



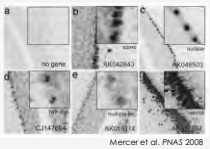

## Long non-coding RNA; emerging brain functions

lncRNAs display specific subfield expression



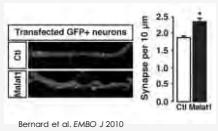

Mercer et al. *PNAS* 2008

...and specific subcellular localization



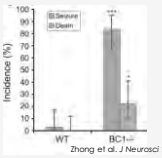

Mercer et al. *PNAS* 2008

lncRNAs regulate synapse formation




Bernard et al. *EMBO J* 2010

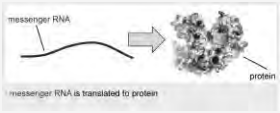
...and seizure thresholds

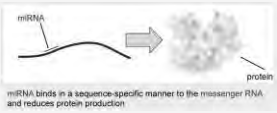


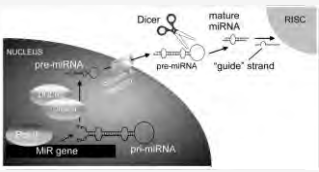

Zhong et al. *J Neurosci* 2009

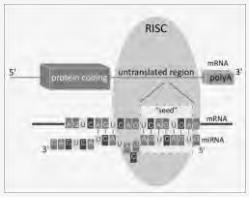
## Short non-coding RNA

**Types: microRNA (miRNA)**, snoRNA, piRNA



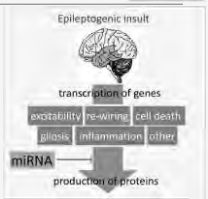




## Why look at microRNA in epilepsy?

~1500 microRNAs in human genome predicted to regulate **60%** of all proteins
→ **"meta-controllers"** of gene expression

Single microRNA can repress hundreds of proteins

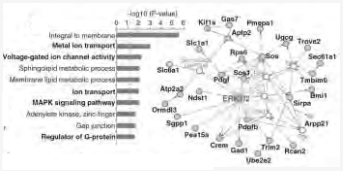
Impact of microRNA targeting **~2 fold** reduction in protein levels (**multi-targeting** up to **10 fold**)





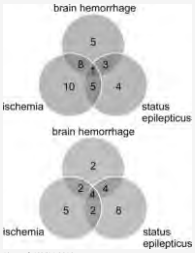
RISC-associated potential targets

mRNAs upregulated in mice lacking miR-128



Tan et al. *Science* 2013

## Epileptogenic insults trigger microRNA changes




Liu et al. JCBFM 2010

Neuronal Activity Rapidly Induces Transcription of the CREB-Regulated MicroRNA-132, In Vivo

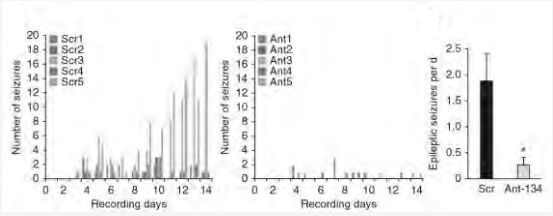
Expression pattern of miR-146a, an inflammation-associated microRNA, in experimental and human temporal lobe epilepsy

Aronica *et al.*

| Silenced miR | Brain role | EEG | Damage |
|---|---|---|---|
| miR-34a | apoptosis | — | √ |
| miR-132 | spines | — | √ |
| miR-134 | spines | √ | √ |
| miR-184 | ? | — | × |

## Silencing miR-134 *after* SE reduces later epilepsy development

92% reduction in epileptic seizures




Jimenez-Mateos et al. *Nat Med* 2012

## GENE THERAPY

**Michele Simonato. Department of Medical Sciences, University of Ferrara, Ferrara, Italy.**

Gene therapy may represent an effective alternative to standard pharmacological approaches for certain forms of epilepsy. Currently, the best candidates for this therapeutic approach appear to be epilepsies characterized by a focal lesion. Gene therapy has been attempted to produce antiepileptogenic (prevention of development of epilepsy in subject at risk after having received an epileptogenic insult), antiseizure (reduction of frequency and/or severity of seizures), and disease-modifying (alteration of the natural history of the disease) effects. An example of gene therapy aimed at producing antiepileptogenic effects is a combination therapy based on the supplementation of the neurotrophic factors brain-derived neurotrophic factor (BDNF) and fibroblast growth factor 2 (FGF-2). Antiseizure effects have been obtained by increasing the strength of inhibitory signals (by supplementing specific GABAA receptor subunits or inhibitory neuropeptides like galanin or neuropeptide Y) or by reducing the strength of excitatory signals (by knocking down NMDA receptor subunits). This review summarizes the results obtained to date using gene therapy in epilepsy models and discusses the challenges and the opportunities that this approach can offer for the treatment of human epilepsies.

## Possible gene therapy interventions: genetic epilepsies

- Problems:
  - rarely caused by a single mutant gene (more commonly due to inheritance of two or more susceptibility genes);
  - pathology often affects a large part of the brain (need of a widespread gene transfer).

## Possible gene therapy interventions: focal lesional epilepsies

- Features and opportunities:
  - focal (stereotaxical approach);
  - possible existence of an identifiable cause;
  - opportunity for intervention at different levels:
    preventive (antiepileptogenic) - symptomatic (anti-seizure) - disease-modifying.

## Anti-epileptogenic effects

| Gene | Vector | Model | Site of injection | Timing | Results | Reference |
|---|---|---|---|---|---|---|
| FGF-2 and BDNF | HSV-1 | pilocarpine | hippocampus | latency (4 days after SE) | DM: reduced cell loss, increased neurogenesis<br>AE: reduced s2 frequency and severity | Paradiso et al., 2009 |
| | | | | | DM: reduced neuroinflammation | Bovolenta et al., 2010 |
| | | | | | DM: reduced mossy fiber sprouting | Paradiso et al., 2011 |

## Anti-seizure effects

Anti-seizure

| Gene | Vector | Model | Site of injection | Timing | Results | Reference |
|---|---|---|---|---|---|---|
| $GABA_A$ subunit alpha1 | AAV-2 | pilocarpine | dentate gyrus of the hippocampus | before pilocarpine | AS: decreased % of animals with SRS at 4 weeks | Raol et al., 2006 |
| NMDA subunit NR1 (antisense) | | inferior colliculus stimulation | inferior colliculus | before stimulation | AS or PC (depending on the promoter and the transduced cells) | Haberman et al., 2002 |
| GDNF | AAV-2 | hippocampal kindling | hilus of dentate gyrus | before kindled | AS: no seizure generalization | Kanter-Schlifke et al., 2007 |
| | | hippocampal kindling | | fully kindled | AS: increased currents to evoke seizures | |
| | | self-sustained SE | | before SE | AC: reduction of seizure severity and mortality | |
| ADK (antisense) | AAV-8 | ADK transgenic mice | intra-CA3 | spontaneously seizing mice | AC: reduction of spontaneous seizures | Theofilas et al., 2011 |
| ICP10PK (anti-apoptotic gene) | HSV-2 | ip kainate | intranasal | before kainate | AC: prevention of seizures<br>DM: prevention of neuronal loss and inflammation | Laing et al., 2006 |
| Kv1.1 | LV | tetanus toxin in the motor cortex | cortex (seizure focus) | during or after the epileptogenic insult (together with tetanus toxin or 1 week after tetanus toxin) | AE: prevention of epileptiform events following administration during the epileptogenic insult.<br>DM: reduction of epileptiform events following administration in established epilepsy. | Wykes et al., 2012 |

## Anti-seizure effects: galanin

| Gene | Vector | Model | Site of injection | Timing | Results | Reference |
|---|---|---|---|---|---|---|
| galanin | AAV-2 | intrahippocampal kainate | hilus of dentate gyrus in the hippocampus | before kainate | AS: attenuation of seizures<br>DM: reduced hilar cell loss | Haberman et al., 2003 |
| | | inferior colliculus stimulation | inferior colliculus | before IC stimulation | AS: increased seizure threshold | |
| | | intrahippocampal kainate | hippocampus | before kainate | AS: reduction of seizure frequency and severity | Lin et al., 2003 |
| | | ip kainate | piriform cortex | before kainate | AS: reduction of seizing animals | McCown 2006 |
| | | piriform cortex kindling | piriform cortex | fully kindled | AS: increased seizure threshold | |

## Anti-seizure effects: NPY

| | | | | | | |
|---|---|---|---|---|---|---|
| NPY | AAV-2<br>AAV-1/2 | intrahippocampal kainate | hippocampus | before kainate | AS: delayed latency and reduction of seizure frequency | Richichi et al., 2004 |
| | | rapid hippocampal kindling | hippocampus | before kindling | AS: retardation of kindling development | |
| | AAV-2 | ip kainate | piriform cortex | before kainate | AS: delayed latency | Foti et al., 2007 |
| | AAV-1/2 | self-sustained SE | hippocampus (bilateral) | in the chronic period (with spontaneous seizures) | AC: reduction of seizure frequency in a subset of rats<br>DM: arrest in disease progression | Noé et al., 2008 |
| | AAV-1/2 | rapid kindling | hippocampus | before kindling | AS: retardation of kindling development<br>SE: no alteration in LTP | Sørensen et al., 2009 |
| | AAV-1 | intrahippocampal kainate | hippocampus | before kainate | AC: reduction of seizure frequency and duration<br>SE: no alteration in learning and memory, anxiety, locomotor activity | Noé et al., 2010 |
| Y2 receptor | AAV-1/2 | rapid hippocampal kindling; ic kainate | hippocampus | before kindling or kainate | AS: retardation of kindling development and reduction of kainate seizure frequency | Woldbye et al., 2010 |
| NPY + Y2 receptor | | rapid hippocampal kindling | hippocampus | before kindling | AS: potentiation | |

## Future directions

- Gene therapy for epilepsy: a wealth of opportunities.
  - Vectors can be tailored to the desired needs
    - in terms of spread from the zone of inoculation (different degrees of spread for different AAV serotypes, retrograde transport for HSV – maybe soon new vectors will be available for peripheral administration with selective localization in lesion areas for the treatment of focal epilepsies or widespread distribution in the brain for the treatment of generalized epilepsies);
    - in terms of duration of transgene expression (relatively short-lasting with HSV, long-lasting with AAV vectors);
    - in terms of targeting specific cell populations (for example population-specific promoters).
- Epilepsy for gene therapy: an important opportunity.
  - Partial epileptic patients selected for surgical resection of the epileptogenic area are ideal candidates for gene therapy:
    - pathology is focal;
    - optimal medical treatment has failed;
    - the success of surgery in leading centers supports that local and sustained release of an inhibitory molecule might be sufficient to "silence" hyperactivity;
    - gene transfer in the epileptogenic area of inhibitory factors like galanin or NPY in patients that are planned to undergo surgery does not require ad hoc stereotaxical intervention and has a built in rescue procedure (should gene therapy fail to produce any advantage, patients would simply undergo surgery as originally planned).

## CELL THERAPY

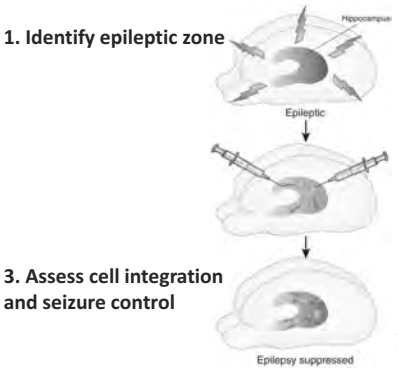
**Scott C. Baraban. Professor & William K. Bowes Jr. Endowed Chair in Neuroscience Research UCSF, University of California, San Francisco, USA.**

GABAergic interneurons play essential roles in regulating cortical excitability. In hippocampus and cortex, interneuron dysfunction is associated with many forms of epilepsy and can disrupt cognitive function. It is now known that the majority of cortical inhibitory neurons originate from a region of the embryonic ventral telencephalon known as the medial ganglionic eminence (MGE). When grafted into the postnatal brain, MGE progenitor cells migrate and functionally integrate as inhibitory interneurons. MGE-derived interneurons selectively enhance GABA-mediated inhibition in the host brain (Alvarez-Dolado et al. J. Neurosci. 2005) and were previously shown by our group to be therapeutic in a Kv1.1 mutant mouse model of epilepsy (Baraban et al. PNAS 2009). Whether MGE cells can (i) rescue chronic changes in excitability and homeostatic circuit deficit associated with a genetic loss of sub-population of GABA interneurons or (ii) functional integrate in the adult hippocampus of mouse model of temporal lobe epilepsy will be discussed. First, we show that MGE progenitors transplanted into adult hippocampus migrated up to 1500 μm from the injection site, differentiated into functional inhibitory interneurons consistent with a MGE lineage, and received excitatory synaptic input. Bilateral MGE cell transplantation into the hippocampus of adult pilocarpine-treated mice with confirmed epilepsy at the time of grafting dramatically reduced the occurrence of electrographic seizures and restored epilepsy-related deficits in spatial learning, hyperactivity, and the emotional response to handling (Hunt et al. Nat. Neurosci. 2013). Second, in Dlx1-/- mice with late-onset interneuron loss and reduced inhibition, we observed both excitatory synaptic silencing and decreased intrinsic neuronal excitability. These homeostatic changes do not fully restore normal circuit function, as synaptic silencing results in enhanced potential for long-term potentiation (LTP) and abnormal gamma oscillations. Transplanting MGE progenitors led to a restoration of hippocampal function in these animals. Specifically, miniature excitatory postsynaptic currents, input resistance, hippocampal LTP, and gamma oscillations are all normalized (Howard et al. PNAS 2014). These studies highlight the exciting potential of using MGE progenitors to correct circuit defects associated with epilepsy and other neurological disorders.

## How do we increase inhibition?

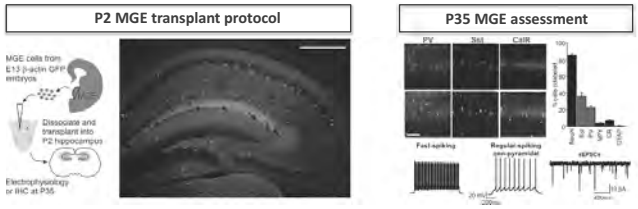
- GABA mimetic drugs
- Modulation of postsynaptic GABA receptors
- Block GABA re-uptake
- New GABA interneurons?

## A strategy for cell-based therapy

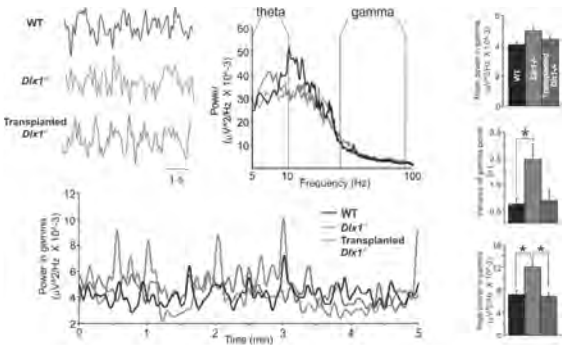



Adapted from Parent & Murphy
News & Views; Nature Neuroscience 2013

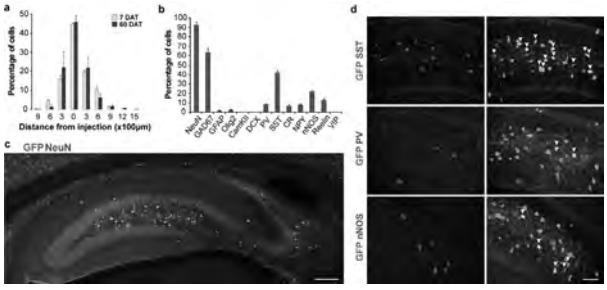
## MGE transplantation into Dlx mutant mice



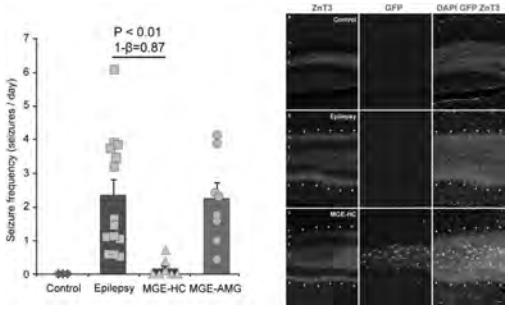

## In vivo oscillation defect in *Dlx1* mutant mice rescued by P2 MGE transplant




## MGE progenitors migrate and differentiate into GABA interneurons in adult hippocampus




## MGE rescue of epilepsy phenotype in the Pilocarpine model




Continuous 24/7 video-EEG monitoring; 7-10 days
Seizure duration > 15 sec

## WHAT IS GOOD EPILEPSY CARE IN 2014 IN EU?

**Reetta Kälviäinen. Kuopio Epilepsy Center, Department of Neurology, Kuopio University Hospital, Kuopio, Finland; University of Eastern Finland; Faculty of Health Sciences, Neurology, Kuopio, Finland.**

Epilepsy is a devastating and sometimes fatal brain disorder, yet many people with epilepsy are still not receiving the care or support they deserve. 70% of people with epilepsy are likely to respond to drug treatment but many of those in Europe are not given that chance. Many governments, communities, and health-care providers are not taking epilepsy seriously.

At least 6 million people in the WHO European region have epilepsy. The proportion of these patients who are missing out on treatment, the so-called treatment gap, is around 40% across the region and more than 90% in some areas. At present, uneven access to healthcare is increasing. There are gaps widening within and between countries and it is vital that they are rapidly addressed. Surveys in the developed EU countries have suggested that health care for people with epilepsy is fragmented and inadequately resourced.

By decreasing the treatment gap and promoting the inclusion of epilepsy care in national and EU wide health care plans, the burden of epilepsy can be significantly reduced. Legislation needs to be reviewed and revised, to remove and prevent discrimination, as with the standardization of driving license regulations across the European Union. Awareness campaigns are also needed, to educate citizens that discrimination should not be tolerated and to ensure that people with seizures are not afraid to seek help or speak out about their experiences. Early diagnosis can lead to earlier freedom from seizures and improved quality of life.

About 2 Million Europeans suffer from refractory epilepsy. Epilepsy surgery renders more than 50% of these patients seizure-free, providing hope of regaining access to normal education, driving, work and personal development. Successful epilepsy surgery in Europe is associated with an estimated direct and indirect cost-saving of about 8000€/year/operation. However, epilepsy surgery remains largely underutilised, particularly in lower-resource EU countries. Furthermore, surgery is often performed late, after a mean duration of epilepsy greater than 15 years.

The main issues responsible for this unsatisfactory situation are the following: 1) The knowledge of patients, professionals, and policy makers about epilepsy surgery is poor, with erroneous views on the risk/benefit balance, cost-effectiveness of surgery, and the appropriate patients' profile and 2) State-of-the-art epilepsy surgery programs require the collaboration of highly specialised neurology, clinical neurophysiology and neurosurgery departments, which is only available at a restricted number of sites, resulting in the greatest source of inequalities in the management of refractory epilepsy across Europe. In EU countries with limited or no access to epilepsy surgery, progress might be accomplished by fostering national epilepsy surgery programs or by facilitating cross-border healthcare by identifying patients who could benefit from referral to European reference centers.

The Lancet Neurology, Volume 9, Issue 10, Page 941, October 2010; http://www.epilepsyadvocacyeurope.org

A European pilot network of reference centres in refractory epilepsy and epilepsy surgery- EU project

## FEBRILE SEIZURES, WHEN TO TREAT?

**Heikki Rantala, Department of Pediatric Neurology, University of Oulu, Oulu, Finland.**

Most of the febrile seizures are short lasting only 1 – 2 minutes requiring no treatment. If the seizure last 5 minutes, it is not probable that it will stop spontaneously and therefore it should be treated promptly with the same principles as status epilepticus. The first line drugs are benzodiazepines, at the moment buccal midazolame (0,25 – 0,5 mg/kg bodyweight) that stops seizures faster than rectal or intravenous diazepam. Febrile seizures recur in about 30% of cases and therefore many drugs have been used trying to prevent them including intermittent oral or rectal diazepam, phenytoin, valproate, phenobarbitone, and pyridoxine but none of them have had any clinically important benefit. Also antipyretic drugs, ibuprofen, acetaminophen, and diclofenac have failed to prevent recurrent febrile seizures even when used promptly after fever onset. Fever should be treated with the same principles than in children without seizures. Only continuous medication with valproate or phenobarbitone is more effective than placebo in preventing febrile seizure, but given the benign nature of recurrent febrile seizures, and the high prevalence of adverse effects of these drugs, their use is not justified. Febrile seizures cause a lot of parental anxiety and therefore the most important thing in treating children with febrile seizures is to support the parents with adequate information on recurrence, first aid management, and the benign long term outcome of these children.

## Drug treatment of febrile seizures?

- Usually febrile seizures last only 1-2 minutes: no need for drugs
- If the seizure does not finish in 5 minutes
  - Diazepam as rectiol 0,5 - 0,75 mg/kg
  - or
  - Buccal midazolam 0,25 - 0,5 mg/kg
  - or
  - Intranasal midazolam 0,2 mg/kg

## Do we have to reduce the temperature in children with febrile seizures?

- Old guidelines recommend external cooling
- The effects of external cooling to a feverish person
  - Does not reduce core temperature
  - Oxygen consumption increases 35-40 %
  - Blood pressure increases
  - Norepinephrine and epinephrine concentrations increase
  - Thermal discomfort with shivering
    (Lenhardt R ym. Am J Med 1999; 106: 550-555)
- External cooling contraindicated in children with febrile seizures!

## Are antipyretic drugs able to prevent febrile seizures? -randomized controlled studies

- Oral acetaminophen 10 mg/kg x 4/day
  - not effective
    (Uhari M et al. J Pediatr 1995; 126: 991-5)
- Oral ibuprofen 5 mg/kg x 4/day
  - not effective
    (van Stuijvenberg M et al. Pediatrics 1998; 102: E51)
- Initially rectal diclofenac 1,5 mg/kg, then oral paracetamol 15 mg/kg x 4/day or oral ibuprofen 10 mg/kg x 4/day
  - not effective
    (Strengell T et al. Arch Pediatr Adolesc Med 2009; 163: 799-804)

## Are there effective drugs to prevent recurrent febrile seizures?

- Several trials on intermittent use of
  - oral or rectal diazepam, phenytoin, valproate, phenobarbitone, and pyridoxine
  - all of them have failed to prevent recurrent febrile seizures

## Are there effective drugs to prevent recurrent febrile seizures?

- Trials on intermittent use of
  - valproate and phenobarbitone
  - both are better than placebo in preventing recurrent febrile seizures, but
    - they might have serious side effects
    - given the benign nature of febrile seizures their use is not justified

## Education and reassurance of parents (both written and verbal)

- Risk of epilepsy is not increased in children with simple febrile seizures
- Children with febrile seizures have a normal cognitive outcome
- Febrile seizures recur in 20-30%
- Management of recurrent febrile seizures
  - Treatment of fever does not differ from those without seizures
  - Education of how to use buccal (intranasal) midazolam or rectal diazepam

## CAN WE PREVENT COGNITIVE DECLINE IN CHILDREN WITH EPILEPSY?

**Eija Gaily. Department of Pediatric Neurology, Helsinki University Central Hospital, Helsinki, Finland.**

In children, failure to achieve new skills (raw scores) leads to a decrease in IQ (cognitive decline). This may go unnoticed if development is not followed carefully and systematically, while regression (loss of previously achieved skills) is more easily detected.

Rarely, cognitive decline in children with epilepsy results from progressive etiology. More commonly, it is the epileptic activity itself that causes cognitive and behavioral impairments, leading to conditions known as epileptic encephalopathies. IQ decline may also occur in drug-resistant partial epilepsy.

A possible mechanism for epilepsy-related cognitive impairment is disturbance of structural development, shown by prospective morphometric methods. Due to the rapid rate and sensitive periods of early development, the very young are the most vulnerable. Alterations in resting state networks, which are important for attention and learning, may be another mechanism resulting in cognitive dysfunction.

Adverse treatment effects include the loss of an average of five IQ points after phenobarbital treatment in the first three years and cognitive impairment caused by topiramate. Polytherapy impairs cognition more than monotherapy. A syndrome-inappropriate drug acts by enhancing epileptic activity.

Cognitive decline in children with epilepsy can often be prevented. There are evidence showing that early treatment of infantile spasms and CSWS syndome is associated with favourable cognitive outcome. An accurate diagnosis for both syndrome and etiology is a prerequisite for effective therapy. In surgically remediable epilepsy, preoperative cognitive decline is halted in most children postoperatively. Children with drug-resistant seizures should be referred for evaluation of surgical and other non-drug treatment options without unnecessary delay. Detrimental drug effects should be promptly identified and avoided.

## Can we prevent cognitive decline in children with epilepsy?

Eija Gaily, Helsinki University Central Hospital

- Cognitive decline
  - In children, failure to achieve new skills (raw scores) leads to decreased IQ (**this may go unnoticed if development is not followed carefully and systematically**), OR
  - loss of previously achieved skills (regression) leads to a very rapid drop of IQ and is more easily detected

Kuopio Epilepsy symposium 5.4.2014

## What causes cognitive decline in children with epilepsy?

- Etiology
  - a direct effect is rare, limited to progressive diseases such as Rasmussen's encephalitis
  - undirect effect: certain etiologies are associated with more severe clinical presentations of epilepsy
- Epilepsy - epileptic encephalopathy
  - the epileptic activity itself contributes to severe cognitive and behavioral impairments
- Treatment of epilepsy - adverse drug effects

## Possible mechanisms

- Structural changes
  - Prospective morphometric studies show abnormal development of both gray and white matter in children with epilepsy compared to controls [Tosun et al. Brain 134:1003–1014, 2011]
  - Highest vulnerability in the very young? [Knudsen EI. J Cogn Neuroscience 16:1412–1425, 2004]
- Network alterations (fMRI studies)
  - Resting state networks show altered connectivity in children with epilepsy [eg. Mankinen et al. Epilepsy Research 100:168—178,2012]
  - Network alterations are associated with cognitive impairment in children with frontal lobe epilepsy [Braakman et al. Epilepsia 54: 446–454, 2013]

## Adverse drug effects

- Phenobarbital treatment in infancy and toddler years leads to an average 4-6 point drop of IQ [Farwell et al. 1990, Sulzbacher et al. 1999]
- Topiramate is associated with cognitive impairment also in children [Ijff and Aldenkamp, Handbook of Clinical Neurology, 2013]
- Polytherapy impairs cognition more than monotherapy
- Inappropriate drug for syndrome or etiology may exacerbate cognitive dysfunction
- Idiosyncratic reactions may lead to cognitive impairment (valproate, lamotrigine)

## Early treatment of epileptic encephalopathy is associated with favourable cognitive outcome

- Drug treatment
  - Infantile spasms [Kivity et al. Epilepsia 45(3):255-262, 2004; Eiserman et al. Epilepsy Research 55 (2003) 21–27]
  - Electric status epilepticus in sleep [Liukkonen E et al. Epilepsia 51:2023–2032, 2010]
- Epilepsy surgery
  - In surgically remediable epilepsies, cognitive decline is halted postoperatively in most children [Freitag & Tuxhorn Epilepsia 46:561-7, 2005; Loddenkemper et al. Pediatrics 119:930-935, 2007; Peltola et al. Epilepsia 52:602–609, 2011; Gaily et al. Finnish Medical Journal, in press]
  - Bilateral or generalized epileptiform abnormalities do not exclude the possibility of surgery if other studies suggest that the epileptogenic region is lateralized

## We can prevent cognitive decline in many (even if not in all) children with epilepsy

- Give appropriate treatment early
  - Make an accurate and correct diagnosis, for both syndrome and etiology
  - Refer for evaluation of surgical and other non-drug treatment options without delay (latest after failure of 2-3 drugs?) - the sooner the younger the child
- Recognize and avoid harmful drug effects
  - Do not use drugs that are inappropriate for the syndrome or etiology
  - Identify cognitive and behavioural adverse effects and avoid unnecessary polytherapy
  - Identify and stop idiosyncratic drug reactions

## WHEN IS ADVERSE EVENT INTOLERABLE?

**Hanna Ansakorpi. Department of Neurology, Oulu University Hospital, Oulu, Finland.**

The primary goal of epilepsy therapy is to achieve seizure freedom while minimizing adverse effects (AE) of the treatment. However, physicians may sometimes value seizure freedom over induced AEs. This may lead to decreased wellbeing of a patient, since the impact of AEs of therapy on quality of life is considered even greater than that of epileptic seizures in some people with epilepsy. AEs also have negative effects on compliance to therapy.

By definition, an AE is any clinical symptom, sign or laboratory dyscrasia which is deemed undesirable to the patient, the physician, or both (St. Louis 2009). These unintended effects are unfortunately common, especially during initiation of antiepileptic (AED) treatment and during polytherapy. From the medical point of view, an intolerable (serious) AE can be defined as a life-threatening event (e.g. an idiosyncratic reaction), but to the patient it can be any AE that prevents him/her from leading a normal daily life.

During the last decades, several AEDs have emerged to the market and today good guidelines exist on selecting AEDs based on the type of epilepsy. However, they do not always give practical guidance on how to recognize different patient-related factors in order to avoid intolerable AEs. In this presentation, basic principles of minimizing AEs during common clinical scenarios are discussed.

*References:* St. Louis EK. Minimizing AED adverse effects: improving quality of life in the interictal state in epilepsy care. Curr Neuropharmacol 2009;7:106-114.

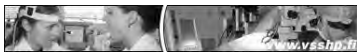
## WHICH PATIENTS WITH MENINGEOMAS SHOULD RECEIVE AEDS?

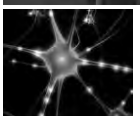
**Merja Soilu-Hänninen. Division of Clinical Neurosciences, Turku University Hospital and University of Turku, Turku, Finland.**

Meningeomas are the second most common type of brain tumours after gliomas (20% of all primary brain tumours). Over 90% of meningeomas are histologically benign and rarely recur after surgery. Meningeomas cause seizures in approximately 40% of patients. Patients who present with seizures preoperatively necessitate AED treatment. How long should these patients remain on AEDs when surgery is curative? Is there a role for prophylactic postoperative AED treatment in patients without a history of seizures?

In a large cohort of patients with preoperative seizures, seizure freedom preoperatively was strongest predictor of postoperative seizure control and successful weaning of AEDs (Caichana et al., World Neurosurgery, 2013). Patients with tumours in parasagittal, parafalcine, or sphenoid wing location, or those with cerebral oedema or uncontrolled seizures preoperatively, were more likely to have seizures postoperatively. Extent of tumour resection was not associated with seizure control. Only 40% of patients with controlled and 22% of patients with uncontrolled preoperative seizures could be weaned off AEDs at 27 months.

In a meta-analysis of outcomes in 689 patients with supratentorial meningeomas from 19 studies, no difference was found in the rate of perioperative (1.4%) or in late (8.8% vs. 9.0%) seizures in patients who received (553 patients), or did nor receive (145 patients), prophylactic AEDs (Komotar et al., J Neurosurg 2011). Only patients without preoperative seizures were included. The conclusion was that the risk of postoperative seizures is low in patients without a history of seizures, and a routine use of prophylactic AEDs provides no benefit.





## Which patients with meningeomas should receive AEDs?

Merja Soilu-Hänninen
MD, PhD, neurologist
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Turku University Hospital and University of Turku

Kuopio Epilepsy Symposium
5.4.2014

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Turun yliopisto
University of Turku

## WHO 2000 Classification of Meningiomas

**WHO Grade 1 (over 90%)**
Meningiothelial meningioma
Fibrous (fibroblastic) meningioma
Transitional (mixed) meningioma
Psammomatous meningioma
Angiomatous meningioma
Microcystic meningioma
Secretory meningioma
Lymphoplasmacyte-rich meningioma
Metaplastic meningioma

**WHO Grade 2 (5%)**
Chordoid meningioma
Clear Cell meningioma
Atypical meningioma

**WHO Grade 3 (1%)**
Papillary meningioma
Rhabdoid meningioma
Anaplastic meningioma

## Meningiomas and seizures

- Epilepsy is the initial presentation in 20-50% of patients
  - Most common in convexity meningiomas
- In addition, about 10% of patients develop late or perioperative seizures
- Mechanisms of epileptogenesis in meningeomas
  - Focal cortical hypoxia
  - Direct mass effect
  - Peritumour brain oedema
  - Perilesional cortical architectural and cellular disorganization
  - Altered levels of excitatory amino acids

## Which patients with meningeomas need AEDs?

- Patients with seizures preoperatively necessitate AED treatment BUT
  - How long should these patients remain on AEDs when surgery has been curative?
  - Is there a role for prophylactic postoperative AED treatment in patients without a history of seizures?

## Patients with preoperative seizures

- Seizure freedom preoperatively strongest predictor of postoperative seizure control
- Patients with tumours in parasagittal, palafalcine, or sphenoid wing location or patients with cerebral oedema are more likely to have seizures postoperatively
- Extent of tumour resection not associated with tumour control
- **Only 40% of patients with controlled seizures preoperatively and 22% of patients with uncontrolled seizures preoperatively succesfully weaned of AEDs at 27 months**

Caichana et al World Neurosurgery 79, 2013

## Patients without preoperative seizures

**Meta-analysis of 689 patients with supratentorial meningeomas from 19 studies**
- Prophylactic AED
  - 1.4% perioperative and 9% late seizures
- No prophylactic AED
  - 1.4% perioperative and 8.8% late seizures
  - **Conclusion: Risk of postoperative seizures is low in patients with supratential meningiomas without a history of seizure and routine prophylactic AEDs provide no benefit**

**Patients at risk for preoperative seizures:**
-Male patients
-Patients who present with headaches
-Patients with large tumous or associated cerebral oedema
-consider AEDs and/or early surgery

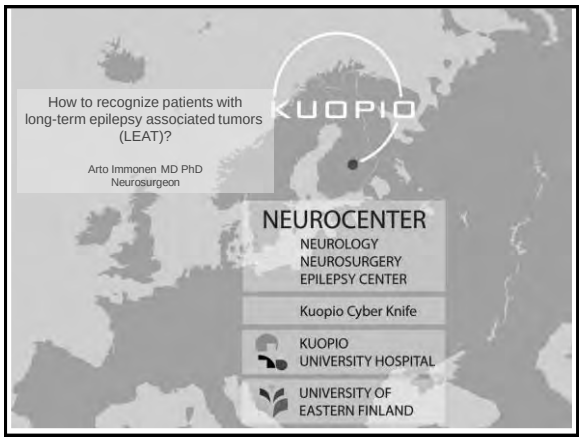
## HOW TO RECOGNIZE PATIENTS WITH LONG-TERM EPILEPSY ASSOCIATED TUMORS (LEAT)?

**Arto Immonen. Department of Neurosurgery, Neurocenter, Kuopio University Hospital, Kuopio, Finland.**

**Terminology:** A wide variety of tumor types, particularly where there is cortical extension, can manifest clinically with focal seizures. The term long-term epilepsy associated tumor (LEAT) means lesions identified in patients with chronic drug-resistant epilepsy. They are generally slowly growing, low grade, cortically based tumors, more often arising in younger age groups and in many cases exhibit neuronal in addition to glial differentiation. Gangliogliomas and dysembryoplastic neuroepithelial tumors (DNET) predominate in this group. The adjacent cortex may have lesions with some similarities to developmental focal cortical dysplasias (FCD); now grouped as FCD type IIIb in the updated ILAE classification.

**Recognition:** Diagnosis is based on two criteria 1) long history (often 2 years or more) of drug-resistant focal epilepsy and 2) imaging finding is slowly growing usually glioneuronal tumor (ganglioglioma or DNET), predominantly in the temporal lobe (or frontal lobe). Recognition LEAT is important as the main aim of surgical treatment is seizure control rather than to halt any tumor progression. The patient needs presurgical epileptological evaluation in addition to neurosurgical evaluation. Sometimes also neuro-oncological team with neuro-oncologist, neurosurgeon, neuroradiologist and epileptologist needs to evaluate the patient before treatment decisions.

**Treatment and prognosis:** After epilepsy surgical evaluation, tumor and possible adjacent epileptogenic tissue is resected. Usually at least monotherapy with antiepileptic drugs is continued. Over 80% of patients become seizure free following surgery, and only a small percentage of cases show tumor recurrence (1-3%) or represent WHO grade II or III lesions (2-6%). An interesting subgroup of LEATs are WHO grade II astrocytomas associated with a long history of epilepsy. There is probably a more benign histological subtype of astrocytoma and it seem to pose a lower recurrence rate than other astrocytomas thus showing better survival.


How to recognize patients with long-term epilepsy associated tumors (LEAT)?
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EPILEPSY CENTER
Kuopio Cyber Knife
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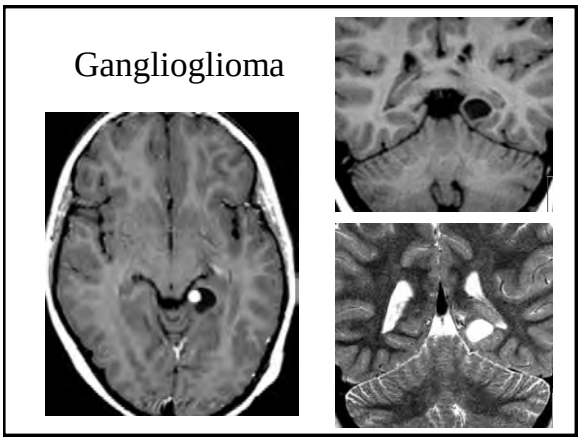
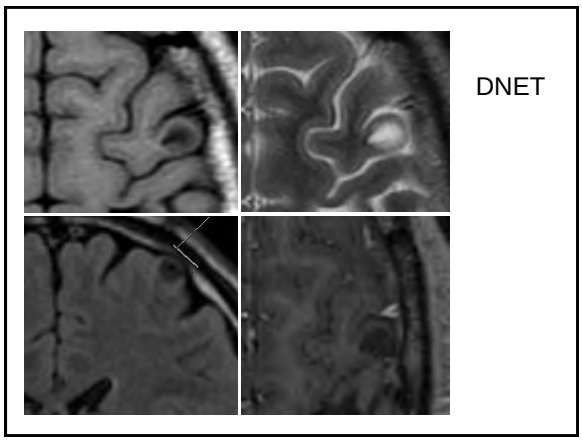

Ganglioglioma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# SCIENTIFIC ABSTRACTS

## Oral Presentations I-IV Saturday April 5th, 2014 11:45- 12:45

**I**

### POST TRAUMATIC ALTERATIONS ON DNA METHYLOME AFFECTS EXPRESSION OF EPILEPTOGENESIS RELATED GENES

N Huusko, A Lipponen, A Pitkänen. University of Eastern Finland, Faculty of Health Sciences, A.I Virtanen Institute for molecular sciences. Kuopio, Finland; Department of Neurology, Kuopio University Hospital, Kuopio, Finland.

**RATIONALE:** Traumatic brain injury (TBI) is estimated to cause 10-20% of all acquired epilepsies. After the initial damage caused by direct mechanical force to the head, secondary damage develops over time consisting of molecular changes that underlie the subsequent reorganization of neuronal networks. The little evidence available suggests that epigenetic regulation controls some part of the alterations found in the expression of hundreds of genes after TBI. We hypothesize that DNA methylation alters gene expression which regulates post-injury reorganization of neuronal circuits, eventually leading to the development of hyperexcitability and epilepsy. **METHODS:** TBI was induced with lateral fluid-percussion injury in adult rats (n=5). Five sham-operated rats served as controls. At 3 months after TBI sampling of the hippocampus and cortex was done for DNA extraction. Sequencing of methylome was carried out with Illumina Genome Analyzer IIx. **RESULTS AND CONCLUSIONS:** After TBI, methylation was changed in the gene body area in 21 genes in the hippocampus and in 45 genes in the cortex (adj.p-value<0.05). Three promising candidate genes with altered gene expression and methylation level were identified for further validation. Our results demonstrate long-lasting change after TBI in DNA methylation which can explain altered gene expression levels of known epileptogenesis related genes.

**II**

### NOVEL EPILEPSY GENE LGI2 IN ANIMAL MODELS OF EPILEPSY

EH Seppälä, M Segerstråle, T Jokinen, E Nevalainen, T Taira, H Lohi. Research Programs Unit, Molecular Neurology, University of Helsinki, Helsinki, Finland; Department of Veterinary Biosciences, University of Helsinki, Helsinki, Finland; Folkhälsan Institute of Genetics, Helsinki, Finland; Department of Biosciences, University of Helsinki, Helsinki, Finland; Department of Clinical Veterinary Sciences, University of Helsinki, Helsinki, Finland.

**RATIONALE:** Idiopathic childhood epilepsies with benign outcomes are well-known in human medicine. However, the genetic basis of benign epilepsy in many families is still unknown. Dog breed Lagotto Romagnolo (LR) manifest benign juvenile epilepsy with focal seizures. Identification of the causative gene and understanding how dysfunction of a mutant protein leads to epileptogenesis might help both humans and dogs. **METHODS:** To map the gene a genome-wide association analysis was performed in LRs and candidate gene was sequenced. To study the pathophysiology of the mutation, a knockout

mouse model was generated. In order to look for alterations in the electrophysiological properties in the hippocampal network, voltage clamp recordings were made from CA3 pyramidal cells from neonatal wildtype and knockout mice. **RESULTS:** *LGI2* gene located in CFA3 was sequenced from LRs. A homozygous nonsense mutation was identified from epileptic dogs leading to a secretion deficient LGI2 protein. The hippocampal activity was altered in Lgi2 -/- mice. The occurrence of spontaneous excitatory postsynaptic currents (PSCs) was increased and the occurrence of inhibitatory PSCs decreased, resulting as an increased frequency of synchronous network bursts. **CONCLUSIONS:** Identification of the LGI2 gene establishes dogs as an important model for human epilepsies. We aim to discover the role of LGI2 in epileptogenesis. Next we are going to test if the decreased interneuronal output is due to attenuated interneuronal excitability. Recordings will also be done from older animals to see if the changes persist and if there are permanent changes in the interneuron function.

**III**

## EPILEPSY-RELATED CLINICAL CHARACTERISTICS AND MORTALITY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF OBSERVATIONAL COHORT STUDIES

O Nevalainen, H Ansakorpi*, M Simola* (*equally contributed), J Raitanen, J Isojärvi, M Artama, A Auvinen. School of Medicine, University of Tampere, Tampere, Finland; Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland; UKK Institute for Health Promotion, Tampere, Finland; School of Health Sciences, University of Tampere, Tampere, Finland; Lundbeck, Deerfield, IL, USA; University of Helsinki, Helsinki, Finland; Pediatric Research Center, Tampere University Hospital and University of Tampere, Tampere, Finland.

**RATIONALE:** A systematic review and meta-analysis on mortality risk in patients with epilepsy with emphasis on epilepsy-related clinical characteristics. **METHODS:** A systematic review of 15 electronic databases, complemented with browsing reference lists and direct author contact. We included cohort studies reporting mortality in representative epilepsy populations relative to the general population, with exclusion of cohorts of highly selected subpopulations, such as epilepsy surgical series. Random effects meta-analyses were used to pool the estimates. **RESULTS:** Mortality was threefold (relative risk 3.33, 95% CI 2.83 - 3.92) in 38 epilepsy cohorts including 165,879 patients. Among incident cases, idiopathic epilepsies did not associate with materially increased mortality (RR 1.29, 95% CI 0.75 – 2.20), whereas mortality was almost twofold in cryptogenic epilepsy (1.75, 1.20 – 2.54), highly elevated in patients with symptomatic epilepsy (4.73, 3.27 – 6.83) and in epilepsies due to congenital or developmental causes (10.3, 4.03 – 26.2). Newly diagnosed patients who attained seizure freedom did not have elevated mortality (0.97, 0.73 – 1.30). **CONCLUSIONS:** Epilepsy-associated excess mortality was highly attributable to the etiology of epilepsy in all ages. In patients without neuroradiological abnormalities or other identifiable cause of epilepsy, risk of death depended on the differentiation between idiopathic epilepsy and cryptogenic epilepsy.

**IV**

## TEMPORAL ANTEROINFERIOR ENCEPHALOCELE: AN UNDER-RECOGNIZED ETIOLOGY OF TEMPORAL LOBE EPILEPSY?

T Saavalainen, L Jutila, E Mervaala, R Kälviäinen, R Vanninen, A Immonen. Departments of Clinical Radiology, Neurology, Neurosurgery and Clinical Neurophysiology, Kuopio University Hospital, Kuopio, Finland.

**RATIONALE:** To report increasing frequency of temporal anteroinferior encephalocele diagnosis in our tertiary care epilepsy centre and to illustrate the clinical and imaging characteristics of this condition in a series of 23 patients. Previously only 18 similar patients have been reported in the English literature, largest series being 3 patients. **METHODS:** Epilepsy patients diagnosed with temporal anteroinferior encephalocele during the study period (January 2006 - December 2013) in our hospital were included.
**RESULTS:** Twenty-three epilepsy patients (14 females, mean age 40 years) were diagnosed with temporal anteroinferior encephalocele. Thirteen patients had two or more encephaloceles, bilateral in seven cases. The estimated prevalence of this condition was 0.3% in MRI examinations performed due to newly diagnosed epilepsy (n=6) and 1.9% in drug-resistant patients referred to our institute as epilepsy surgery candidates (n=17). High-quality, thin-slice, preferably three-dimensional 3T MRI according to an epilepsy protocol and computed tomography studies facilitated the detection of this condition. Histologically gliosis was present in temporal lobe samples in all 10 surgically treated patients and some also showed cortical laminar disorganization. Eight patients with local encephalocele disconnection (n=3) or anterior temporal lobectomy and amygdalohippocampectomy (n=5) have become seizure free in a mean 2.8 years (range 3 months – 6.2 years) of follow up. Two local encephalocele disconnection patients were almost seizure free or had a worthwhile improvement. **CONCLUSIONS:** The possibility of temporal encephalocele should be considered when interpreting MRI examinations of patients with medically intractable temporal lobe epilepsy. These patients can significantly benefit from epilepsy surgery.

# Poster presentations

**Authors present on Friday April 4th, 2014 at 15.45-16.15 and Saturday April 5th, 2014 at 10.30-11.00.**

### 1. MOLECULAR PLASTICITY IN UPA-UPAR INTERACTOME AFTER TRAUMATIC BRAIN INJURY

T Bolkvadze, A Pitkänen. Epilepsy Research Laboratory, Department of Neurobiology A.I.Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland; Department of Neurology, Kuopio University Hospital, Kuopio, Finland.

**RATIONALE:** Increasing evidence suggest that urokinase-type plasminogen activator (uPA) and its receptor (uPAR) play a significant role in tissue remodeling after epileptogenic brain insults, such as traumatic brain injury (TBI). The regulation of post-injury expression of different components of uPAR-interactome (ligands and receptors) is, however, poorly understood. Here we assessed the effect of uPA deficiency on the expression of its receptor, uPAR, after TBI. **METHODS:** TBI was induced by controlled cortical impact (CCI) in 12-wk old male Wt (n=8) and uPA -/- (n=10) mice. Injury velocity was 5 m/s and depth 0.5 mm. For qRT-PCR, mice were decapitated at 4 days post-CCI. Expression of uPA and uPAR genes was assessed in the perilesional cortex, hippocampus, and thalamus. **RESULTS:** The expression of uPA mRNA in the perilesional cortex was elevated 4-fold in the Wt-CCI group as compared to that in controls ($p<0.05$). The expression of uPAR mRNA was similarly upregulated in the perilesional cortex both in the Wt CCI (4-fold, $p<0.05$) and uPA -/- CCI groups (4-fold, $p=0.01$). Importantly, there was no difference between the injured groups. In the uPA -/- CCI group uPAR mRNA was elevated also in ipsilaterally in the hippocampus (6-fold, $p=0.01$) and thalamus (4-fold, $p<0.05$). **CONCLUSIONS:** The present study shows that expression of uPAR mRNA after CCI-induced TBI is not compromised by genetic deficiency of its ligand uPA. Consequently, uPAR may stay functional for mediating the signaling initiated by other components of uPAR-interactome.

### 2. STIMULATION OF STEREO-EEG ELECTRODES: RESPONSES FROM INSULA

T Hirvonen, L Metsähonkala, M Peltola, E Gaily, R Roivainen, A Karppinen, A Laakso, G Blomstedt, L Lauronen. Departments of Clinical Neurophysiology, Pediatric Neurology, Neurology and Neurosurgery, Helsinki University Central Hospital, Helsinki, Finland.

**RATIONALE:** We have established a database of clinical responses induced by stimulations of stereo-EEG (SEEG) depth electrodes in patients with intractable partial epilepsy undergoing evaluation for epilepsy surgery. Here we report our experience on stimulating the insula. **METHODS:** 16 patients (8 male, 6-45 years, four with insular epilepsy) with 2-8 electrode contacts in the insula were included in this study. Eight patients had contacts in the anterior and all 16 in the posterior insula. Nine patients had right and 7 had left-sided implantation. The stimulus was a 1-5 second duration, 50Hz train with a current of 0,5-3,0 mA. Both the subjective and objective responses were documented. Responses during afterdischarges were not excluded, but stimulations leading to seizures were not included. **RESULTS:**

The most frequent responses were variable somatosensory sensations contralaterally to the stimulated side. Patients reported warm or cold sensations as well as prickling in the extremities, face, head or teeth to stimulation of the posterior or anterior insula. Other responses included feeling of twitching, numbness or muscle stiffness in the extremities. Several stimulations caused oral sensations like burning or prickling, but also unpleasant gustatory sensations. One patient had a feeling of difficulty in breathing. **CONCLUSIONS:** Variable contralateral somatosensory sensations were the most frequent responses from insular stimulation -both anteriorly and posteriorly. These sensations were sometimes unpleasant but not clearly painful. Unlike previous reports, no speech disturbance, auditory or autonomic responses were evoked in these patients.

### 3. KNOWLEDGE OF CLINICAL DRUG TRIALS AMONG PATIENTS WITH EPILEPSY

E Itkonen, A Halkoaho, A-M Pietilä, R Kälviäinen, T Keränen. University of Eastern Finland, Faculty of Health Sciences, Kuopio, Finland; Kuopio University Hospital, Science Service Center, Kuopio, Finland; Kuopio Social and Health Care Services, Kuopio, Finland; Kuopio Epilepsy Center, Department of Neurology, Kuopio University Hospital, Kuopio, Finland; Institute of Clinical Medicine, Neurology, University of Eastern Finland, Kuopio, Finland; Department of Neurology, Kanta-Häme Central Hospital, Hämeenlinna, Finland.

**RATIONALE:** Clinical trials (CT) are essential for the development of new medical treatments. Ethically sound conduct of CT requires that the study participants are aware of the differences in the goals and methods of standard therapy and research. **METHODS:** A questionnaire was sent to a random sample (N=2000) of the members of the Finnish Epilepsy Association aged at least 18 years. General knowledge about CT and the research methods were assessed. The survey included statements, which the participant responded using a Likert scale from 1 (strongly disagree) to 5 (strongly agree). **RESULTS:** Of the 325 respondents, 52% were aware of the meaning of CT and 82% knew that participation is always voluntary. Half of the respondents thought that CT primarily seek to find the best treatment for the individual participant. Additionally, 50% of the respondents thought that the research physician knows which study treatment (new medication, placebo, or a standard drug) is given. Moreover, 40% of the respondents thought that the investigator had an option to choose the trial medication for each participant. **CONCLUSIONS:** Patients with epilepsy are not completely aware of the concept of by CT or the differences between research and standard treatment. Furthermore, the awareness of research settings is either insufficient or biased. Information about CT, presented in common language, should be distributed on various patient forums to increase awareness among patients and potential research participants.

### 4. DOG AS AN ANIMAL MODEL FOR HUMAN IDIOPATHIC EPILEPSY: IDENTIFICATION OF COMMON RISK VARIANTS IN THE ADAM23 GENE

LLE Koskinen, EH Seppälä, M Arumilli, P Jokinen, E Nevalainen, R Viitmaa, T Jokinen, H Lohi. Research Programs Unit, Molecular Neurology, University of Helsinki, Helsinki, Finland; Department of Veterinary Biosciences and Department of Medical Genetics, University of Helsinki, Helsinki, Finland;

Folkhälsan Institute of Genetics, Helsinki, Finland; Department of Clinical Veterinary Sciences, University of Helsinki, Helsinki, Finland.

**RATIONALE:** Idiopathic epilepsy (IE) is a common neurological disease in human and dog. Relatively few risk genes have been identified for common IE to date. We have used dog as an animal model for human focal and generalised epilepsy to identify disease risk genes. The seizure characteristics are similar between the two species and reduced genetic heterogeneity of purebred dogs is advantageous for genetic studies. **METHODS:** Recently, we identified a risk locus for IE in Belgian Shepherds on CFA37 in a genome-wide association study (GWAs). GWAs meta-analysis of 158 cases and 179 controls in three other breeds suggested association to the same locus (p=2.9e-07). To investigate this locus further, we performed targeted next-generation sequencing. Twelve Belgian Shepherd cases and twelve controls were selected for the sequencing based on homozygosity for the risk and non-risk haplotypes. **RESULTS:** Thirty-six variants unique for the cases were identified in the sequencing experiment. All variants located in the ADAM23 gene region. Twenty-seven variants were selected for validation in 235 cases and 320 controls from four dog breeds. Association analysis yielded a strong signal at the locus (p=5.3e-11). Haplotype analysis suggests a common risk haplotype in all studied breeds. **CONCLUSIONS:** The results indicate that there is a common genetic risk factor for epilepsy in several dog breeds. ADAM23 plays a role in synaptic transmission and interacts with LGI1 and LGI2, both known causative genes for Mendelian forms of epilepsy. Based on the genetic association and gene function, ADAM23 is a potential risk gene for epilepsy.

## 5. EXPRESSION OF PLATELET-DERIVED GROWTH FACTOR B RECEPTOR AFTER INTRAHIPPOCAMPAL KAINIC ACID-INDUCED STATUS EPILEPTICUS IN MICE

J Kyyriäinen, XE Ndode-Ekane, A Pitkänen. Epilepsy Research Laboratory, A. I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland; Department of Neurology, Kuopio University Hospital, Kuopio, Finland.

**RATIONALE:** Composition of the extracellular matrix (ECM) is a master regulator for injury-induced plasticity. Previous data suggest that the ECM-derived signaling -induced interaction between platelet-derived growth factor receptor β (PDGFR-β) and urokinase-type plasminogen activator receptor (uPAR) increases neuronal survival. As the first step to understand the PDGFR-β/uPAR interaction, we characterized the location of PDGFR-β in the hippocampus after an epileptogenic brain insult. **METHODS:** Status epilepticus (SE) was induced in adult male C57BL/6JOlaHsd mice by intrahippocampal injection (60nl) of 10mM kainic acid (KA). Animals were sacrificed at 24h, 4d and 7d post-KA, and the brains were processed for immunohistochemistry. The total number of PDGFR-β immunoreactive (ir) cells was estimated by unbiased stereology. **RESULTS:** In the ipsilateral hippocampus, the total number of PDGFR-β-ir cells in mice with SE did not differ from controls (60160±4307) at any time point (24h: 45158±6288; 4d: 60288±1868; 7d: 59264±4765; $p>0.05$). Interestingly we found that as PDGFR-β-ir cells were relatively homogeneously distributed in the normal hippocampus, after SE they clustered in the hilus as well as in the infrapyramidal and suprapyramidal regions of the CA3 and CA1. Contralaterally, the number of PDGFR-β-ir cells was reduced at 24h (control: 76032±5798, SE: 44083±5063, $p<0.05$), 4d (54784±4186, $p<0.05$) and 7d post-SE (61312±2917, $p<0.05$). Interestingly, contralaterally they remained evenly distributed through the follow-up.

**CONCLUSIONS:** PDGFR-β expressing cells were ipsilaterally re-distributing to hippocampal subfields known to experience severe neurodegeneration post-SE. The cells expressing the receptor can be involved in neuroprotection by moving to areas that are more vulnerable after SE.

## 6. SIMILARITIES IN TRANSCRIPTOME ALTERNATIONS BETWEEN HIPPOCAMPUS AND CORTEX DURING POST TRAUMATIC EPILEPTOGENESIS

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**RATIONALE:** Traumatic brain injury (TBI) is a significant cause of acquired epilepsies. After the initial damage by direct mechanical force to the head, secondary brain damage leads to molecular changes affecting reorganization of neuronal networks in epileptogenesis. We hypothesize that expression of genes that control formation of neuronal circuits alters network features after TBI in both, hippocampus and cortex, leading to increased seizure susceptibility and epilepsy. **METHODS:** TBI was induced with lateral fluid-percussion injury to adult rats (n=5). Five sham-operated rats served as controls. At 3 months post-TBI two 2-mm-thick coronal slices were sectioned to sample the hippocampus and cortex for RNA extraction. Sequencing of transcriptome was carried out with Illumina Genome Analyzer IIx. **RESULTS AND CONCLUSIONS:** In the hippocampus, 4280 genes and cortex 176 genes were expressing differently when compared to controls (adj.p<0.05). The expression of 140 same genes was altered significantly in both brain areas. Most common functional terms in among of these differential expressing genes were glycoprotein, signal, plasma membrane and ion/metal/cation binding. Our result reveals long-lasting alternations after TBI in gene expression in the hippocampus and cortex.

## 7. EFFECTS OF SEROTONIN DEPLETION ON KAINATE-INDUCED MORTALITY, SEIZURE SUSCEPTIBILITY AND EPILEPTOGENESIS

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**RATIONALE:** Despite many advances in epilepsy-related research, the etiology of this disorder is not fully understood. Serotonin depletion is one of the potential mechanisms associated with epileptogenesis. In this study, we tested the hypothesis that serotonin depletion is capable of modifying the mortality rate, expression of seizures and epileptogenesis in kainate-treated rats. **METHODS:** Adult rats were treated during 4 consecutive days with L-p-chlorophenylalanine (PCA) in order to inhibit serotonin synthesis. Then, they received single injections of kainic acid at doses ranging between 6.5 mg/kg and 12.5 mg/kg. The severity of provoked seizures and the rat's mortality were registered. Following the treatments, rats were observed during 5 months for the presence of spontaneous motor seizures. **RESULTS:** The loss of approximately 90% serotonin-positive neurons in the dorsal raphe nuclei after the treatment with PCA was confirmed using immunocytochemical procedures. At the highest kainate doses, practically all PCA-pretreated rats showed severe tonic convulsions, frequently terminated in animal's death. In rats that were not pretreated with PCA, kainate induced seizures were milder and only a few rats had died. Kainic acid

injected at a dose of 6.5 mg/kg induced status epilepticus only in PCA-pretreated rats. Significantly more PCA-pretreated rats showed spontaneous motor seizures later in life, when compared to kainate dose-matched non-PCA groups. **CONCLUSIONS:** Serotonin depletion increases mortality and enhances motor seizures in the kainate model of epilepsy. These data support the idea that ascending 5-HT pathways may play protective role against excitotoxicity-induced epileptogenesis.

## 8. SEIZURE OUTCOME OF EPILEPSY SURGERY BASED ON INTRACRANIAL STEREO-EEG-INVESTIGATIONS (SEEG)

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**RATIONALE:** Noninvasive investigations are insufficient to identify all patients that may benefit from epilepsy surgery. We report the one-year postoperative seizure outcome in patients who had epilepsy surgery based on sEEG in HUCH. **METHODS:** All patients with epilepsy surgery at HUCH have prospective clinical follow-up. The seizure outcome is reported according to Engel criteria. **RESULTS:** Altogether 33 patients were investigated with sEEG since 2011 in HUCH. These patients had refractory partial epilepsy and after thorough non-invasive work-up, further investigations were considered necessary to delineate the epileptogenic zone. 24 patients proceeded to surgery based on sEEG and at least one year post-operative follow-up was available for 17 patients. The mean age of the 17 patients was 10.6 years at the onset of epilepsy and 17 years at the time of the sEEG. The operations were two standard and three modified temporal lobectomies, four frontal, three parietal, three fronto-insular and two multilobar resections. Eleven patients (65%) had Engel I seizure outcome and three patients (17%) Engel IV outcome, eg. no benefit from surgery. A small nonsymptomatic intracerebral hemorrhage was identified after the sEEG- electrode removal in one patient. Two patients with polymicrogyria had ischaemic complications in the final resections. They are seizure free but have residual motor impairment. **CONCLUSIONS:** Seizure-freedom was obtained in 65% of patients after epilepsy surgery based on sEEG.

## 9. THE DYNAMICS OF T CELL INFILTRATION INTO THE BRAIN PARENCHYMA FOLLOWING TRAUMATIC BRAIN INJURY IN RATS

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**RATIONALE:** T cell infiltration into the brain parenchyma following traumatic brain injury (TBI) may contribute to the progression of epileptogenesis and the development of post-traumatic epilepsy (PTE). Our objective here is to elucidate the dynamics of T cell infiltration into the brain after TBI and whether the magnitude of infiltration is associated with post-traumatic somato-motor deficits. **METHODS:** TBI was induced in adult rats using lateral fluid-percussion injury. A neuroscore test was performed at 24h, 2d, 4d, and 7d after injury. Then, the brains were processed for immunohistochemical analysis of the number of T cells in the ipsilateral cortex, hippocampus and thalamus. **RESULTS:** In controls there were

practically no T cells in the brain. The number of T cells in all regions increased dramatically at 24h post-injury. At 2d the number was even higher, being 154% of that at 24h post-TBI. At 4d and 7d, their number dropped to 77% and 10%, respectively, of that at 24 h. The highest number of T cells was observed in the cortex when compared to other areas ($p<0.05$). There was a strong inverse correlation between the total number of T cells at any time-point and the neuroscore at 24h or 2d post-injury reflecting the severity of injury ($p<0.05$). **CONCLUSIONS:** Our data shows that the severity of post-traumatic neurological deficit is associated with the magnitude of T cell infiltration in to the brain parenchyma. Furthermore, it demonstrates that acute phase post-TBI is most likely the time window during which T cells can influence post-traumatic epileptogenesis.

## 10. IN VIVO HIGH-RESOLUTION DIFFUSION TENSOR IMAGING SHOWS PROGRESSIVE CHANGES IN THE RAT BRAIN AFTER STATUS EPILEPTICUS

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**RATIONALE:** Diffusion tensor imaging (DTI) is an MRI technique which provides a high contrast based on tissue microstructure in both white and grey matter. In this study, our hypothesis was that *in vivo* DTI is able to detect the progression of microstructural alterations in hippocampal subfields as well as in other white and grey matter areas during the early stages after status epilepticus (SE) of which could potentially serve as biomarkers for epileptogenesis. **METHODS:** Adult male Wistar rats (n = 17) were scanned using *in vivo* DTI in a 7T magnet before and 10, 20, 34 and 79 days after SE induced by kainic acid or pilocarpine injection (n = 13). For DTI data, we conducted region-of-interest and tract-based spatial statistics (TBSS) analyses. Fourier analysis of histological images was performed to determine the fiber orientation and anisotropy of myelinated axons and astrocytes. **RESULTS:** In the dentate gyrus, we detected an increase in fractional anisotropy (FA) (day 34, $p<0.001$; day 79, $p<0.001$) along with an increase in axial diffusivity ($D_{\parallel}$) (day 34, $p<0.01$; day 79, $p<0.001$) during the observation period. In the CA3bc, we also found FA increased (day 79, $p<0.01$), and a progressive change in the diffusion orientation from rostral-caudal to more dorsal-ventral (day 34, $p<0.001$; day 79, $p<0.001$). Fourier analysis revealed changes in the orientation in both myelinated axons and astrocytes, which might contribute to the DTI signal in these two subfields. TBSS analysis showed an increase in FA in the hippocampus and thalamus and a decrease in FA in the fimbria, external capsule and optic tract ($p<0.05$) when compared animals before SE to the same animals at the latest time point. **CONCLUSIONS:** We were able to detect progressive microstructural alterations in different hippocampal subfields and in other white and grey matter areas related to epileptogenesis using in vivo DTI. These changes correlate with damage and plasticity during the early stages of the epileptogenic process. The value of these findings as potential predictive biomarkers for epilepsy has to be tested in the future.

## 11. EPILEPTIC SEIZURES IN FINNISH HUNTINGTON'S DISEASE PATIENTS

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**RATIONALE:** Seizures are not more prevalent in adult-onset Huntington's disease (HD) than in the general population, unlike the situation in Alzheimer's disease or juvenile HD. **METHODS:** Patients treated for HD between the years 1986-2010 were identified using national registries. Patient records of the ascertained patients were reviewed in order to identify subjects with seizures. **RESULTS:** Four patients with HD and seizures were identified (table) with mean age of HD onset 48.0 years. All patients manifested with generalized seizures and Patient 4 also exhibited myoclonic jerks for which the medication was started four months after her first generalized seizure. EEG of Patient 4 revealed several isolated spike-wave discharges over the convexity, some of which are associated with muscle jerks and that of Patient 2 revealed irregular intermediate velocity complexes with sharp waves laterally to the left with a short paroxysm after hyperventilation. In all cases treatment with anticonvulsive medication resulted in total remission even at low serum concentrations. The seizure activity of Patient 2 was well controlled after reinstitution of the same medication after unsuccessful attempts to taper it off. In addition, one patient was identified with a juvenile-onset HD and with first symptoms at 14 years of age. She has had no manifest seizures during the 6 years of follow-up before her death. **CONCLUSIONS:** Seizures are uncommon in Finnish patients with HD and can be well controlled with anticonvulsive medication. Tapering off may be attempted.

| | | | *Repeat length* | | *Age (years) at* | | |
|---|---|---|---|---|---|---|---|
| *Patient* | *Gender* | *Inheritance* | *CAG (affected)* | *CAG (wild type)* | *HD diagnosis* | *Seizure onset* | *Medication* |
| 1 | Male | Paternal | 40 | 19 | 76 | n.d.[1] | Phenytoin[2] |
| 2 | Male | Maternal | n.d. | n.d. | 49 | 33 | Carbamazepin[3] |
| 3 | Female | Paternal | 55 | 22 | 32 | 33 | Carbamazepin[4] |
| 4 | Female | Maternal | 44 | 17 | 35 | 40 | Valproic acid |

[1]Decades before the onset of HD; [2]Tapering off successful; [3]Tapering off, two unsuccessful attempts; [4]In addition, clonazepam for chorea; n.d., not determined

## 12. A NOVEL MAGNETOENCEPHALOGRAPHY TEST COMPARED WITH WADA TEST IN ASSESSING LANGUAGE LATERALIZATION IN EPILEPSY-SURGERY CANDIDATES

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**RATIONALE:** The Wada test is the current gold standard in the assessment of language lateralization in epilepsy-surgery candidates. It is, however, invasive and has several limitations. Here we searched for a new language-lateralization test based on magnetoencephalography (MEG). **METHODS:** From 14 epilepsy patients who had undergone the Wada test, we recorded whole-scalp auditory MEG responses to pairs of vowels and tones. For each individual, we selected the sensor with the strongest response to vowels (at 100–200 ms) and —from the vector sum of responses of this gradiometer pair—quantified the vowel/tone amplitude ratio in the left (L) and right (R) hemisphere. and then calculated the laterality index: LI = (L–R)/(L+R). LI > 0.1 indicated left-hemisphere dominance, LI < –0.1 right-hemisphere dominance, and –0.1 < LI < 0.1 bilateral language function. A "typical" left-hemisphere-dominance pattern, earlier observed in healthy subjects, comprised stronger responses to vowels than tones in the left hemisphere and *vice versa* in the right hemisphere. **RESULTS:** In eleven (79%) patients, language lateralization was similar in MEG and Wada test; this group included all five patients who showed the "typical" left-hemisphere-dominance pattern. The MEG LI and the Wada results correlated statistically significantly (Spearman rank correlation, r = 0.55, p = 0.04). **CONCLUSIONS:** This simple MEG paradigm shows promise in assessing language lateralization feasibly and noninvasively in epilepsy-surgery candidates. The data analysis can be partly automated for clinical settings. However, further elaboration is needed to improve the accuracy needed in individual-level diagnostics.

## 13. THE TREATMENT OF EPILEPSY IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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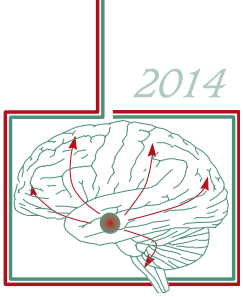
**RATIONALE:** Patients with Alzheimer's disease (AD) have an increased risk of unprovoked seizures. Seizures in AD are associated with a faster cognitive decline and a more severe neuronal loss. We investigated different treatments against AD related epilepsy, including valproic acid (VPA) and supplementation with oxidative energy substrates (OES) in a mouse model of AD. **METHODS:** In experiment 1, 15-wk-old male APP/PS1 mice (n=12) were injected (i.p.) with 30 mg/kg VPA (low dose) for one week. After a 3–wk wash-out, the same animals were treated with 300 mg/kg VPA (higher dose) for 1 wk. The control group was injected with saline. In experiment 2, 12-to 13-week-old APP/PS1 mice (n=9) were fed with pyruvate and beta-hydroxybutyrate enriched chow for 5 weeks, while the control group (n=8) received regular chow. The antiepileptic action of treatments was evaluated using long-term (24/7) video-EEG monitoring. As outcome measures we assessed the occurrence of spontaneous seizures

and epileptiform discharges (EDs). **RESULTS:** Occurrence of spontaneous seizures was reduced during the low-dose treatment with VPA ($p<0.05$), but no longer after treatment discontinuation. The high-dose VPA, but not the low-dose, suppressed EDs during the treatment ($p<0.001$), and for one week after treatment discontinuation ($p<0.05$). OES diet reduced EDs during the dietary intervention and for 2 wk thereafter ($p<0.05$). **CONCLUSIONS:** Both VPA and OES diet reduced spontaneous epileptiform discharges in a mouse model of AD. OES diet was more efficient that low-dose VPA, while the efficacy of high-dose VPA was comparable to that of OES diet.

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