Integrating Research into Day-to-Day Practice
December 6, 2011

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University of Bonn Medical Centre, Dept. of Epileptology
## Disclosure

<table>
<thead>
<tr>
<th>Name of Commercial Interest</th>
<th>Type of Financial Relationship</th>
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<tr>
<td>Desitin</td>
<td>Speaker Bureau Member, Consultant, received honoraria</td>
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<tr>
<td>UCB</td>
<td>Speaker Bureau Member, Consultant, received honoraria,</td>
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<td>Pfizer</td>
<td>Speaker Bureau Member, received honoraria</td>
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<tr>
<td>Medtronic</td>
<td>Received honoraria</td>
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<tr>
<td>Eisai</td>
<td>Received honoraria</td>
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<tr>
<td>DFG</td>
<td>Received federal funding</td>
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American Epilepsy Society | Annual Meeting
Learning Objectives

- To demonstrate how research can be integrated into everyday practice.
- To demonstrate how patient needs and animal research are related.
Epilepsy and the Functional Anatomy of the Human Brain

by
WILDER PENFIELD, O.M., C.M.G.
M.D. ( Johns Hopkins)
P.R.C.S. (Canada), Hon. F.R.C.S. (England), F.R.S. (London)

and
HERBERT JASPER
M.D., C.M. (McGill), B.A. (Bend), M.A. (Oregon)
Ph.D. (Iowa), D. és Sci. (Paris)

Chapter XIV by Francis McNaughton
B.A. and M.D., C.M. (McGill)

8 color plates and
314 black and white illustrations

Little, Brown and Company . Boston

www.epilepsie-bonn.de
Integrating Research into Day-to-Day Practice
- Possibilities and Problems -

- Unique approach to the human brain – “in depth sight”

- Pathology
  - epilepsy
  - cognition problems
  - comorbidities – i.e. depression

- Physiology
  - Higher brain functions

Problem: Research in Patients with a high variability in Phenotyp

Solution: „Intelligent“ experiments using the indivual situation

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WADA-Procedure

150-200 ml Amobarbital

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Integrating Research into Day-to-Day Practice
- Lessons from the WADA-Test -

- Plasticity of brain concerning speech areas
- Short term memory
- Preference for language in the human brain
Speech Dominance and the Start of Epilepsy
- Lesion-induced transfer of language (n=120) -

Chi² p>0.001
Global Wada-Procedure Left
- Carotis Interna -

before Amytal injection

injection of 200mg Amytal

after Amytal injection

F = 70 Hz   700µV
T = 0,3 s       1 s

underestimated
hit
overestimated

counted
not counted

Gleissner et al., 1997

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Crowding or Suppression Effect

Early childhood hypoxic left-hemisphere brain damage

Helmstaedter et al., Brain 1994

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Memory performance and Depth-Electrodes
Declarative Memory Formation
- Rhinal-Hippocampal Phase-Synchronization -

Hippocampus
Entorhinal Cortex
Synchronized?

forgotten
remembered

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Memory Formation
- Rhinal-Hippocampal Phase-Synchronisation -

Fell et al., Nature Neuroscience; 2001; 4: 1259-1264

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Young: < 30 years

Old: > 50 years

Fell et al., Bonn data, unpublished

www.epilepsie-bonn.de
fMRT – Memory and Age

B. Weber et al, 2004

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Research in Epilepsy Patients: Elementary Processes
Research in Epilepsy Patients: Elementary Processes

Molecular biology

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Epilepsy: A Developmental Process?
- Epileptogenesis -

Gene mutations?

Pre-disposition

“Initial hit”

Epileptogenesis

first seizure
further seizures

cell death, structural (re)-organization
Temporal Lobe Epilepsy, Cognition and “Initial Hit”

Helmstaedter and Elger, Brain, 2009

Verbal memory
[number of correctly recalled words in delayed recall]

Chronological age [yrs]

Sample

Chronological age [yrs]

N >1000 (each)

Helmstaedter and Elger, Brain, 2009

95% CI verbal memory
[number of correctly recalled words in delayed recall]

Age categories [range yrs]

N >1000 (each)
Temporal Lobe Epilepsy
- Ammon`s Horn Sclerosis -

Control

Cell loss

plasticity

Mossy fiber sprouting

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Exp. Status Epilepticus: Model for human epilepsies

- Methyl-scopolamine
- Pilocarpine
- Diazepam

One of the models resembling features of temporal lobe epilepsy

2 hours

15 days

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Molecular Basis of Increased T-type Currents
- Selective increase in transcription of $Ca_v 3.2$ -

A

Ca$_v$3.2 protein (Immuno)

B

Ca$_v$3.2 protein (Western)

Becker et al., J. Neuroscience, 2008
Altered Intrinsic Neuronal Properties
- Conversion of regular to burst firing in CA1 -

<table>
<thead>
<tr>
<th>Sham-control</th>
<th>SE-experienced</th>
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<tbody>
<tr>
<td><strong>Day 1</strong></td>
<td><strong>Day 1</strong></td>
</tr>
<tr>
<td><strong>Day 5</strong></td>
<td><strong>Day 5</strong></td>
</tr>
<tr>
<td><strong>Day 30</strong></td>
<td><strong>Day 30</strong></td>
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- **10.5 nA**
- **10 mV**
- **50 ms**
- **10 ms**

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Dlo Ca$_v$3.2 knock-out animals help to understand?

- Missing Ca$_v$3.2-channels do not influence the SE.
- Missing Ca$_v$3.2 leads to animals being less seizure prone later on.

- What is the impact of Ca$_v$3.2 up-regulation on the development of an Ammon`s horn sclerosis?
Altered Intrinsic Neuronal Properties
- Role in epileptogenesis - **Cell Loss** -

Ca\(\text{v}3.2\) +/- Ca\(\text{v}3.2\) -/-

sham

SE

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Becker et al., J. Neuroscience, 2008
Altered Intrinsic Neuronal Properties
- Role in epileptogenesis – **Mossy Fiber Sprouting** –

Becker et al., J. Neuroscience, 2008

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Plasticity in Chronic epilepsy
- Conclusions -

Role of Cav3.2 in epileptogenesis after SE:

- Cav3.2 up-regulation causes increased T-type currents.
- Loss of Cav3.2 related T-type currents prevents neuro-pathological changes characteristic for AHS.

Potential implications:
Basis for *therapeutic* interventions during early epileptogenesis?
Effect of Treatment by AED
- Untreated Patients (n= 470) -

Carbamazepine is the most often used AED in focal epilepsies.

Epilepsy: A Developmental Process?

- Epileptogenesis -

Gene mutations?

Pre-disposition

“Initial hit”

cell death, structural (re)-organization

Epileptogenesis

first seizure

further seizures

Reduced drug response

Pharmacoresistance
Mechanisms of Pharmacoresistance
- “Transporter” versus “Target” Mechanism

Transporter Mechanism

AED responsive
- Neuron
- Endothel cell
- Perizyte
- Astrozyte

AED resistant
- Neuron
- Endothel cell
- Perizyte
- Astrozyte

Target Mechanisms

AED responsive
- AED
- TARGET

AED resistant
- AED
- altered TARGET

Multidrug Transporter

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Reduced Pharmacosensitivity of Drug Targets
- Target mechanisms must exist – *Slice Preparation* -

**CBZ-responsive chronic epilepsy – human brain slice**

Potent inhibition of seizure activity
control  | CBZ 50 µM  | Washout
20 min   | 60 min    |

**CBZ-resistant chronic epilepsy - human brain slice**

Reduced inhibition of seizure activity

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Remy and Beck, Brain, 2006
Reduced pharmacosensitivity of drug targets
- Voltage-gated sodium channels -

Remy et al., Ann Neurol, 2003
Mechanisms of Pharmacoresistance
- Alterations of Na+-channels? - Recovery from Inactivation -

Responsive

Resistant

Human brain tissue

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Remy et al., Ann Neurol, 2003
Mechanisms of Pharmacoresistence
- Alterations of Na+-channels? -

*Loss of use dependent block by Carbamazepine*
  – one reason for pharmacoresistance

*But .....*

*No resistance to other sodium channel blockers such as*

- PHT
- LTG
- OXC/ESL (metabolite - MHD)

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Epilepsy provides unique opportunities for performing specific research of the human brain and its diseases.

Epilepsy had opened the doors of the operating room at the M.N.I to the study of physiology of the brain in conscious man

(Wilder Penfield, 1891-1976)
J. Axmacher
H. Beck
A. Becker
C. E. Elger
J. Fell
G. Fernandez
U. Gleissner
T. Grunwald
C. Helmstaedter
M. Kurthen
F. Moormann
S. Schoch

J. Schramm
J. Zentner
V. Coenen

and many others

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