Biomarkers of epileptogenesis, pharmacogenomics and functional brain connectivity in epilepsy

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Cankarjev dom, Ljubljana, Slovenia

Imaging epileptogenesis

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Epilepsy: “disorder characterised by an **enduring predisposition** to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition.”

**Biomarker:** indicator of normal biologic or pathogenic processes

**Epileptogenesis:** *both, development* of epilepsy after a pro-epileptogenic lesion, *and progression* after the condition is established

**Surrogate endpoint:** *measurement* used in therapeutic trials as **substitute** for clinically meaningful endpoint of how patient functions and predicts effect of therapy..”
Biomarkers and surrogate endpoints

Key areas – “clinical treatment gaps”

- Patient stratification: WHO?
- Prediction of outcome: WHICH DRUG?
Biomarkers and surrogate endpoints

Key requirements in epilepsy: quantification of an enduring propensity to generate seizures

- quantifiable
- objectively measured and evaluated
- reproducible
- cheap and easy to obtain
- results available quickly
- high accuracy
- good sensitivity
- good specificity
Biomarkers and surrogate endpoints

Key requirements in epilepsy: quantification of an enduring propensity to generate seizures

- quantifiable
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'Nothing is written in stone'
Biomarkers and surrogate endpoints

Relevant targets in epileptogenesis!

- Altered excitability and synchrony
- Altered neuronal function (gene expression, …)
- Altered glial function and gliosis
- Cell loss (e.g. hippocampal atrophy)
- Axonal sprouting
- Synaptic reorganisation
- Neurogenesis
- Epigenetic modulation
- Angiogenesis
- Inflammatory changes
- BBB dysfunction

on target?
Relevant targets in epileptogenesis!

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- BBB dysfunction
identify persistent measurable disturbances characterising the “enduring propensity”

*Pitkanen et al., 2013*
Biomarkers and surrogate endpoints: moving targets?

Interventions for anti-epileptogenesis

INSULT

Early latency
Late latency
Epilepsy diagnosis
Recurrent seizures w/wo progression
Cure

BM1
BM2
BM3
BM4
BM5
BM6
BM7

Target 1
Target 2
Target 3
Target 4
Target 5
Target 6
Target 7

Identify persistent measurable disturbances characterising the "enduring propensity"

No control group for at-risk anti-epileptogenesis

Pitkanen et al., 2013

Interventions for anti-epileptogenesis
Biomarkers and surrogate endpoints: moving targets?

overcoming drug resistance

identify persistent measurable disturbances characterising the "enduring propensity"

Early identification of drug-resistance or cure

Recurrent seizures w/wo progression

Epilepsy diagnosis

Early latency Late latency INSULT

Target 1 BM1 Target 2 BM2 Target 3 BM3 Target 4 BM4 Target 5 BM5 Target 6 BM6 Target 7 BM7

Pancreatic et al., 2013

Pitkanen et al., 2013

overcoming drug resistance
Prediction of outcome

- all epilepsies begin with a 1\textsuperscript{st} seizure
Prediction of outcome

- all epilepsies begin with a 1\textsuperscript{st} seizure

- EEG: high specificity, but low sensitivity
- MRI: high sensitivity, but low specificity
Prediction of outcome

Drug-refractory epilepsy?

YES

Surgically refractory?

YES

Normal MRI

NO

Normal MRI

NO

Normal MRI

Semah et al. Neurology 1998
Normal MRI: What next?

“If a lesion is not seen on the MRI study, it does not mean that a lesion cannot be seen using MRI techniques” (G Jackson)

• Volumetry
• Relaxometry
• Statistical approaches
• New MRI acquisition techniques
Prediction of outcome

Volumetry / relaxometry
Prediction of pathology
Statistical shape analysis

F. Individual analysis in TLE

Hippocampal subfields
- CA1
- CA2
- CA3-CA4

Paradoxical TLE

Unambiguous TLE

- Inward deformation
  - Z-score

Patient 1
- ipsi
- contra

Patient 2
- ipsi
- contra

Patient 3
- ipsi
- contra

Courtesy of Andrea Bernasconi
Prediction of pathology
Cortical Dysplasia - computational models

Case 1:
Female, 22 yrs, Age of onset: 17 yrs
Diffuse numbness,
left head turning, elevation left hand
EEG
Interictal - generalised slow activity
Ictal - unclear onset

Thickness
Intensity
Gradient

FCD, focal cortical dysplasia; EEG, electroencephalography

Courtesy of Andrea Bernasconi
Prediction of outcome
Role of PET / SPECT / fMRI

Drug-refractory epilepsy?

YES

Surgically refractory?

YES

Normal MRI

NO

Normal MRI

Lesional MRI

PET / SPECT / Functional MRI

PET / SPECT functional MRI

Semah F et al. Neurology 1998
Prediction of outcome groups versus individual: FMZ PET in TLE

**Individual results:** unilateral HS normal MRI

- Hippocampal and extra-hippocampal ↓ and ↑ of FMZ binding
- Unilateral HS < norm MRI

**Group results:**

- ↓ FMZ binding
- HS bilateral
- ↑ FMZ binding
- TLWM

FMZ, flumazenil; TLE, temporal lobe epilepsy; TLWM, temporal lobe white matter

Flumazenil-PET:
• **TLE:**
  FMZ reductions more pronounced in close proximity to seizures
  *(Bouvard, Brain 2005)*
Flumazenil-PET:

- **TLE:**
  FMZ reductions more pronounced in close proximity to seizures (Bouvard, Brain 2005)

- **Focal epilepsies:**
  FMZ-PET / fMRI Correlation with seizure frequency (Laufs, Neurology 2011)
Biomarkers of altered excitability
Biomarkers of altered excitability

GE-179 PET

- binds to open (activated) ion-channel (PCP-site)

Healthy control

R TLE

Increase of $^{18}$F-GE179
AMT PET

Imaging of serotonin synthesis, tryptophan metabolism
- Inducible by inflammatory cytokines

Juhasz et al, Neursurg Focus 2013
Biomarkers of inflammatory changes

**AMT PET**

Imaging of serotonin synthesis, tryptophan metabolism

- Inducible by inflammatory cytokines
  
  Juhasz et al, Neursurg Focus 2013

**11C-TSPO - PET**

- **TLE**
  
  increased uptake in sclerotic hippocampus
  
  (Hirvonen, JNM 2012)

Juhasz et al, Neursurg Focus 2013
Biomarkers and surrogate endpoints

Key areas – “clinical treatment gaps”

• Patient stratification: drug-refractory? drug-sensitive?
• Prediction of outcome: WHICH DRUG?
Overcoming drug-resistance

“Target hypothesis”:

• Impaired GABAergic inhibition
• NMDA-receptor hyper-excitability
• Glutamate signal via NMDA activates intracellular inflammatory enzyme cascade that upregulates P-glycoprotein (P-gp)
Overcoming drug-resistance

“Target hypothesis”:
• Impaired GABAergic inhibition
• NMDA-receptor hyper-excitability
• Glutamate signal via NMDA activates intracellular inflammatory enzyme cascade that upregulates P-glycoprotein (P-gp)

“Transporter” hypothesis:
• Generic model for drug-resistance (oncology, HIV, AD, epilepsy?)
Overcoming drug-resistance transporter hypothesis

Lesson from oncology:
3rd generation P-gp inhibitor
• dissappointing!
  unselected use, wrong dose, duration?
→ increased mortality
Overcoming drug-resistance transporter hypothesis

Lesson from oncology:
3rd generation P-gp inhibitor
• disappointing!
  unselected use, wrong dose, duration → increased mortality

P-gp substrate ($^{11}$C-verapamil) proof-of-principle PET study
• Stratification: responder vs refractory
• Diagnostic tool: patient selection for Pgp modulation
• VPM low / no brain uptake
• Administration of P-gp inhibitor increases brain uptake of $^{11}$C-verapamil

JP Bankstahl et al, J Neuroscience 2011
Translation to human epilepsy

Data acquisition:

- 14 healthy controls (5 F, age 36-55 y)
- 8 drug-sensitive (5 fem, age 23-50 y)
- 14 drug-refractory mTLE patients (6 F, age 20-56 y)

PET scanning protocol:

0:00 1:00 2:00 3:00 4:00 5:00

First Scanning Session

TQD

Second Scanning Session

\[\text{[^{15}O]-H}_2\text{O followed by (R)-[^{11}C]-Verapamil}\]

\[\text{[^{15}O]-H}_2\text{O followed by (R)-[^{11}C]-Verapamil}\]

Results – $K_1$ at baseline

Higher Pgp activity:

drug-resistant vs seizure-free TLE

Correlation with seizure frequency in resistant patients

Results – $K_1$ after TQD

- increased in controls by 59%
- attenuated in patients: 26%
### Results – \( K_1 \) after TQD

- Increased in controls by 59%.
- Attenuated in patients: 26%.
- In 6/11: marked \( K_1 \) increases >36%.
- In 5/11: less remarkable (12%).

<table>
<thead>
<tr>
<th>control</th>
<th>patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="2mg/kg" /></td>
<td><img src="image2" alt="3mg/kg" /></td>
</tr>
</tbody>
</table>

#### Table: MRI, EEG, Age at Onset, Duration of Epilepsy, Average sz frequency, Interval last sz to PET, Current AEDs (dose: mg/day)

<table>
<thead>
<tr>
<th>MRI</th>
<th>EEG</th>
<th>Age at Onset (years)</th>
<th>Duration of Epilepsy (years)</th>
<th>Average sz frequency (month)</th>
<th>Interval last sz to PET (days)</th>
<th>Current AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>L HS</td>
<td>LT</td>
<td>5</td>
<td>38</td>
<td>2</td>
<td>21</td>
<td>PHT (325), CLOB (20)</td>
</tr>
<tr>
<td>R HS</td>
<td>RT</td>
<td>11</td>
<td>45</td>
<td>18</td>
<td>2</td>
<td>LTG (200), PRG (300)</td>
</tr>
<tr>
<td>L HS</td>
<td>LT</td>
<td>19</td>
<td>11</td>
<td>15</td>
<td>6</td>
<td>LVT (750), OXC (600), CLOB (20)</td>
</tr>
<tr>
<td>R HS</td>
<td>RT</td>
<td>4</td>
<td>48</td>
<td>8</td>
<td>2</td>
<td>LTG (500), PHT (225)</td>
</tr>
<tr>
<td>L HS</td>
<td>LT</td>
<td>8</td>
<td>19</td>
<td>10</td>
<td>6</td>
<td>CLOB (20)</td>
</tr>
<tr>
<td>L HS</td>
<td>LT</td>
<td>2</td>
<td>36</td>
<td>1</td>
<td>28</td>
<td>SVP (1000), LTG (200)</td>
</tr>
<tr>
<td>L HS</td>
<td>LT</td>
<td>0.83</td>
<td>55</td>
<td>2</td>
<td>3</td>
<td>CBZ (1000), SVP (1500), LVT (2000), ZON (150), CLOB (10)</td>
</tr>
<tr>
<td>R HS</td>
<td>RT</td>
<td>12</td>
<td>38</td>
<td>8</td>
<td>4</td>
<td>CBZ (1200), SVP (1600), TPM (150)</td>
</tr>
<tr>
<td>L HS</td>
<td>LT</td>
<td>15</td>
<td>5</td>
<td>10</td>
<td>60</td>
<td>CBZ (400), PHT (350), LTG (100)</td>
</tr>
<tr>
<td>R HS</td>
<td>RT</td>
<td>35</td>
<td>16</td>
<td>2</td>
<td>60</td>
<td>CBZ (1600), LVT (3000)</td>
</tr>
<tr>
<td>L HS</td>
<td>LT</td>
<td>15</td>
<td>5</td>
<td>10</td>
<td>4</td>
<td>CBZ (400), LVT (2250), LTG (275)</td>
</tr>
</tbody>
</table>
Translation to humans

2 mg/kg ($C_{\text{plasma}}: 490\pm166 \text{ ng/mL}$)

2.6 mg/kg ($C_{\text{plasma}}: 480\pm57 \text{ ng/mL}$)
Translation to humans

2 mg/kg ($C_{\text{plasma}}: 490 \pm 166$ ng/mL)
Biomarkers and surrogate endpoints

Key areas – “clinical treatment gaps”

• Patient stratification  drug-refractory ?
  drug-sensitive ?

• Prediction of outcome  WHICH DRUG ?
• All AEDs are designed for the same purpose
• All AEDs are designed for the same purpose

• not all AEDs are the same: “tolerability” counts!
• But: we cannot measure shoe-size

Courtesy of Martin Brodie
Visuo-spatial working memory paradigm
## Working memory in JME

### Controls

<table>
<thead>
<tr>
<th></th>
<th>0 back</th>
<th>1 back</th>
<th>2 back</th>
<th>rest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Working Memory</strong></td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td><strong>Motor</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Visual</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Controls</td>
<td>JME &gt; Ctr</td>
<td>JME &lt; Ctr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
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<tr>
<td><img src="image1.png" alt="Brain Image" /></td>
<td><img src="image2.png" alt="Brain Image" /></td>
<td><img src="image3.png" alt="Brain Image" /></td>
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</tr>
</tbody>
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## Working memory in JME

<table>
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<th></th>
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<th>JME &gt; Ctr</th>
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<tbody>
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<td></td>
<td><img src="image1" alt="Brain Image" /></td>
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<td><img src="image3" alt="Brain Image" /></td>
</tr>
</tbody>
</table>
**Working memory in JME**

<table>
<thead>
<tr>
<th>Controls</th>
<th>0</th>
<th>1-0</th>
<th>2-0</th>
</tr>
</thead>
<tbody>
<tr>
<td>JME &gt; Ctr</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>JME &lt; Ctr</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
“Resting state”
Deactivation with increasing demand?

=> Shows default mode network

Vollmar et al, *Brain* 2011
Resting state

Vollmar et al, *Brain* 2011
- Reduced deactivation in JME
- Reduced ability to switch between task relevant and DM networks

Vollmar et al, *Brain* 2011
Resting state

- Reduced deactivation in JME
- Reduced ability to switch between task relevant and DM networks

JME: dysfunction of switching between systems

Vollmar et al, *Brain* 2011
Predict drug response
Effect of VPA in JME

negative correlation with dose

Vollmar C et al. Brain 2011
Predict drug response

Effect of VPA in JME

negative correlation with dose

positive correlation with dose

Vollmar C et al. Brain 2011
Functionally segregated WM networks

Task positive network: fronto-thalamo-parietal network
Functionally segregated WM networks

Task positive network: fronto-thalamo-parietal network

Task negative network: DMN and bilateral hippocampi

Stretton et al., Neuroimage, 2012
Progressive Deactivation Group Maps

Controls: deactivate hippocampus bilaterally
Patients: deactivate only contralateral hippocampus

Stretton et al., Neuroimage Clinical 2012
Better performance correlates with greater activation:
right middle frontal gyrus
greater de-activation:
posterior hippocampi

Stretton et al., Neuroimage Clinical 2012
Disrupted segregation of networks

Increased coactivation (red arrow) of left hippocampus with left front-parietal

Stretton et al., Neuroimage Clinical 2012
Disrupted segregation of networks

Increased coactivation (red arrow) of left hippocampus with left front-parietal

Increased coactivation (white arrow) of left hippocampus with left parietal areas correlates with worse performance

Stretton et al., Neuroimage Clinical 2012
Interim summary

Syndrome-specific activations / connectivity changes:
TLE → disrupted segregation in the diseased hippocampus – specific to TLE
JME → altered (hyper-)connectivity in motor cortex, SMA – specific to JME

Focal epilepsy disrupts connectivity of cognitive networks

Abnormalities in connectivity of cognitive networks may explain cognitive deficits extending beyond seizure focus
107 drug (53 Left) resistant TLE patients. Various pathologies Verbal / non-verbal working memory tasks

Left TLE: 26/53 on LEV (in combination with other AEDs)

Right TLE: 25/54 on LEV (in combination with other AEDs)

Wandschneider et al, Neurology 2014
Left TLE:  
26 on LEV versus 27 no-LEV  
greater suppression of LEFT ant temporal lobe

Wandschneider et al, Neurology 2014
Predict drug response
Effect of LEV in TLE

- Left TLE:
  26 on LEV versus
  27 no-LEV

greater suppression of
LEFT ant temporal lobe
dose-relationship:
lower dose =
greater suppression

Wandschneider et al, Neurology 2014
• Right TLE: 24 on LEV versus 30 no-LEV

greater suppression of RIGHT ant temporal lobe
dose-relationship: lower dose = greater suppression

Wandschneider et al, Neurology 2014
• Epilepsy is not one disease
  BUT similar generic mechanisms prevail
Biomarker of epileptogenesis

• Epilepsy is not one disease
  BUT similar generic mechanisms prevail

• Humans are different from rodents
  BUT methodologies are transferable
Biomarker of epileptogenesis

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- Patients cannot be compared to healthy controls
  BUT "control" patients are necessary
Biomarker of epileptogenesis

• Epilepsy is not one disease
  BUT similar generic mechanisms prevail

• Humans are different from rodents
  BUT methodologies are transferable

• Patients cannot be compared to healthy controls
  BUT “control” patients are necessary

• Patients are not “abnormal” at-rest / inter-ictally
  BUT pharmacological / cognitive challenge will detect specific change
THANKS

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- Action Medical Research
- DFG
- Epilepsy Research UK