UCL INSTITUTE OF NEUROLOGY
DCEE

The National Society for Epilepsy

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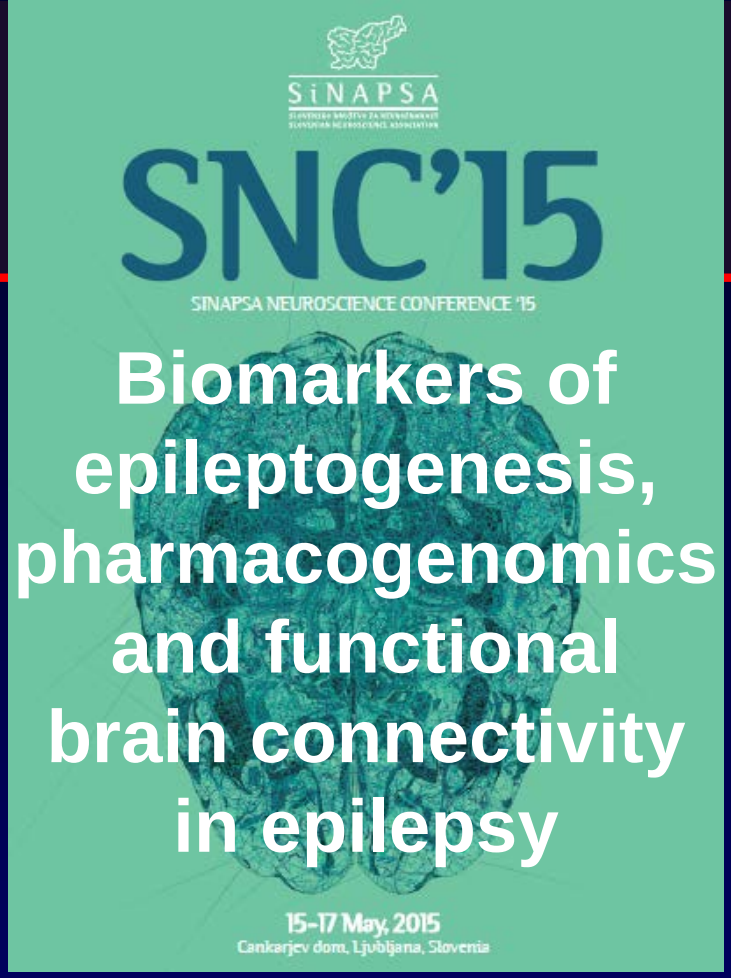

Imaging epileptogenesis

Matthias Koepp

Clinical & Experimental Epilepsy
UCL- Institute of Neurology

Definitions

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

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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 ?

Biomarkers and surrogate endpoints

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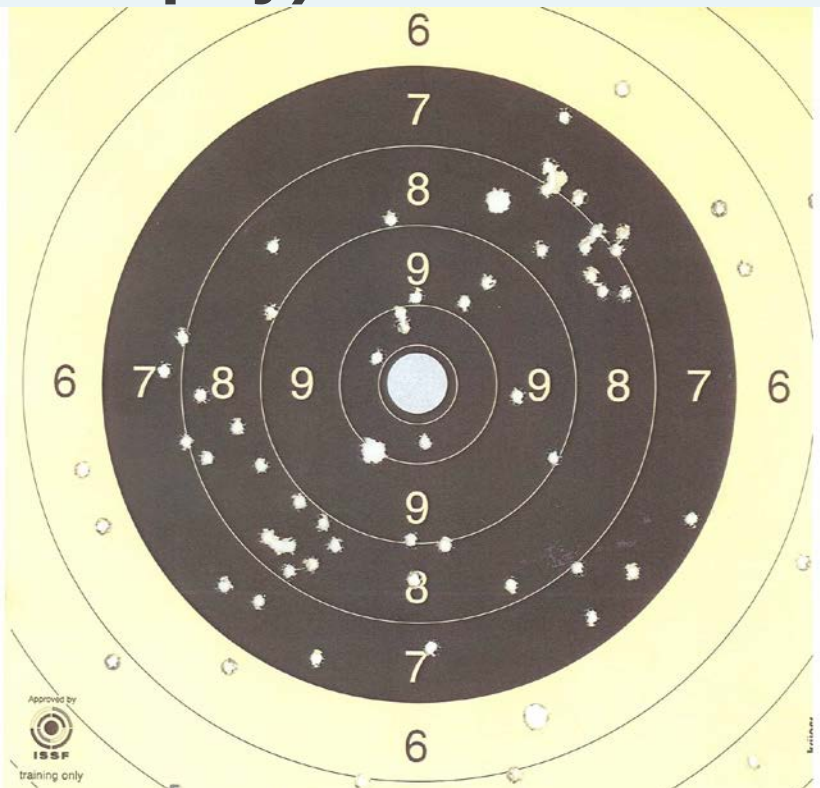
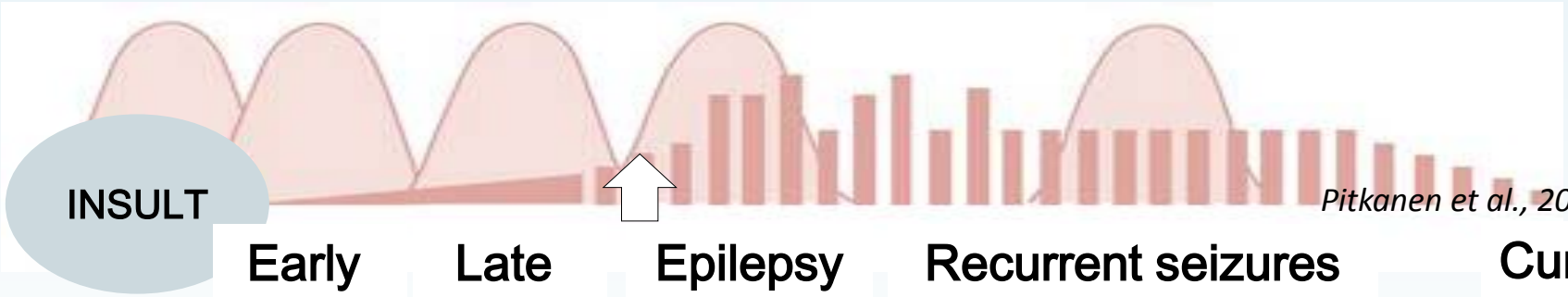


Biomarkers and surrogate endpoints

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



Pitkanen et al., 2013

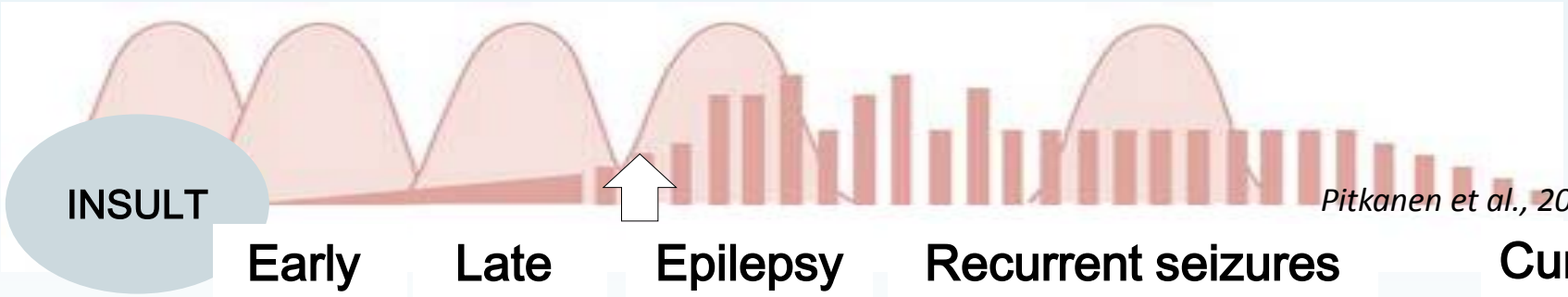
identify persistent measurable disturbances characterising the "enduring propensity"

Biomarkers and surrogate endpoints

moving targets ?

Interventions for anti-epileptogenesis

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”

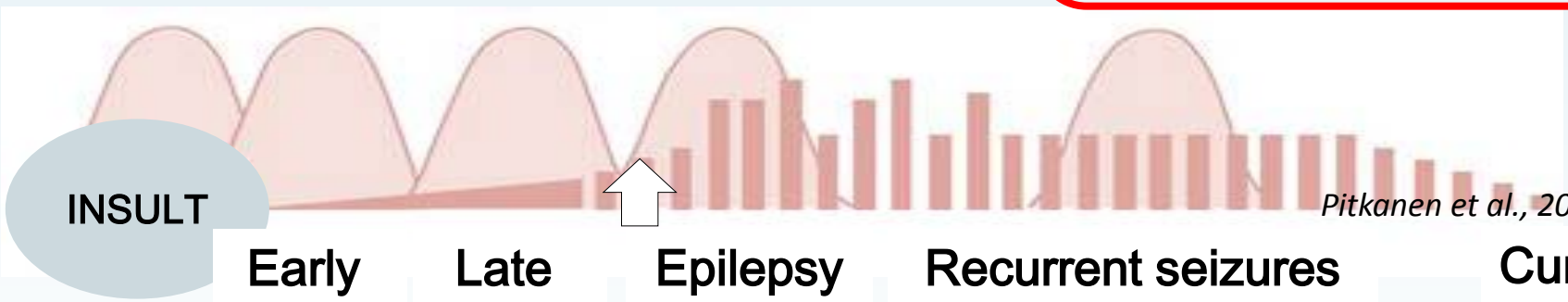
No control group for at-risk anti-epileptogenesis

Biomarkers and surrogate endpoints

moving targets ?

overcoming drug resistance

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



Pitkanen et al., 2013

identify persistent measurable disturbances characterising the "enduring propensity"

Early identification of drug-resistance or cure

Prediction of outcome

- all epilepsies begin with a 1st seizure



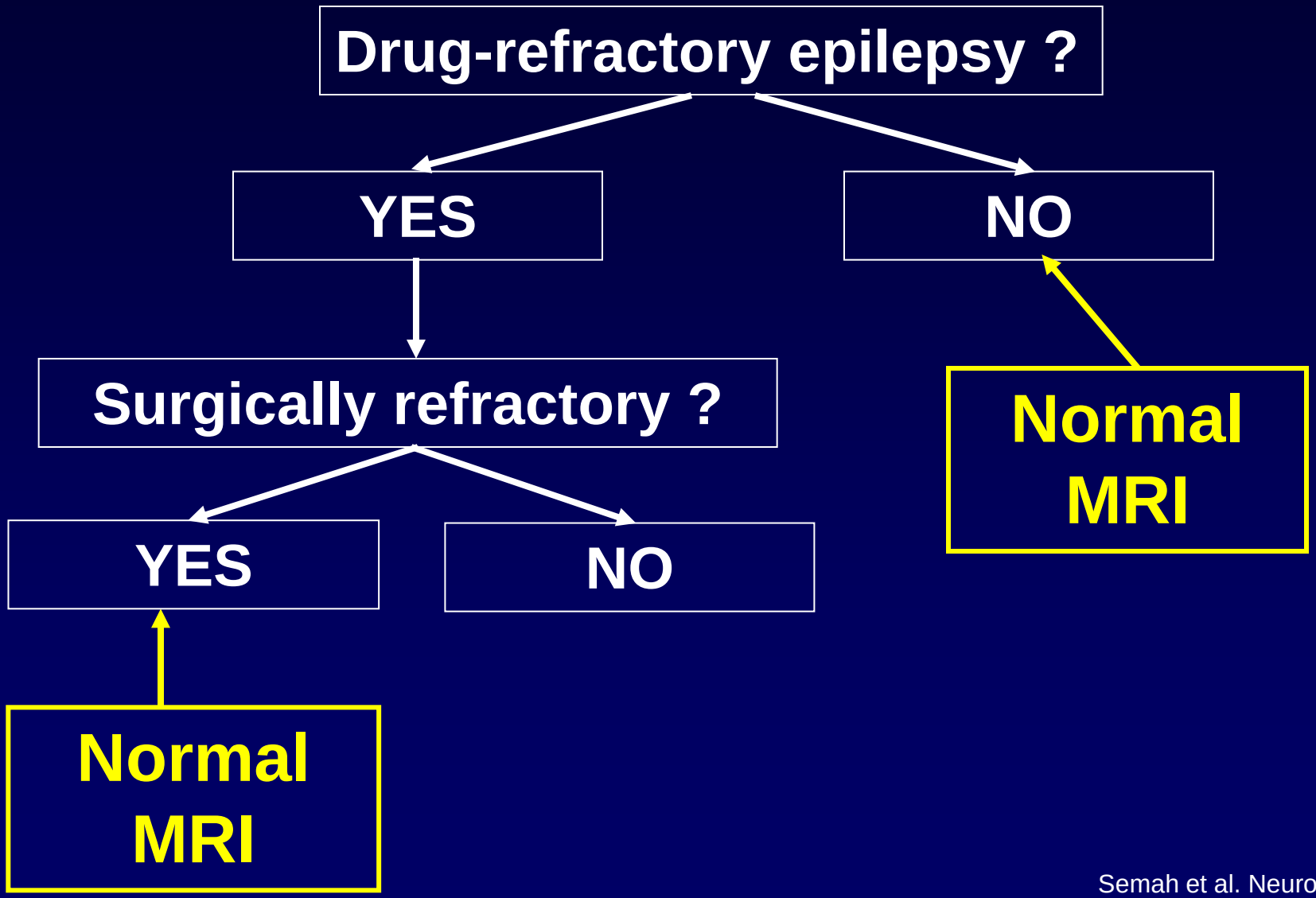
Prediction of outcome

- all epilepsies begin with a 1st seizure



- EEG: high specificity, but low sensitivity
- MRI: high sensitivity, but low specificity

Prediction of outcome



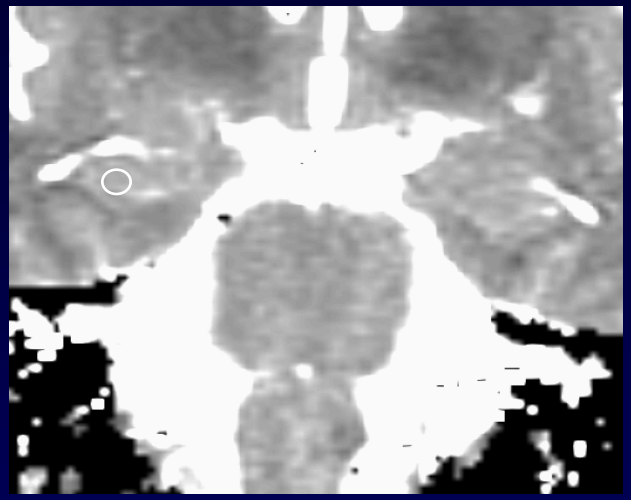
Semah et al. Neurology 1998

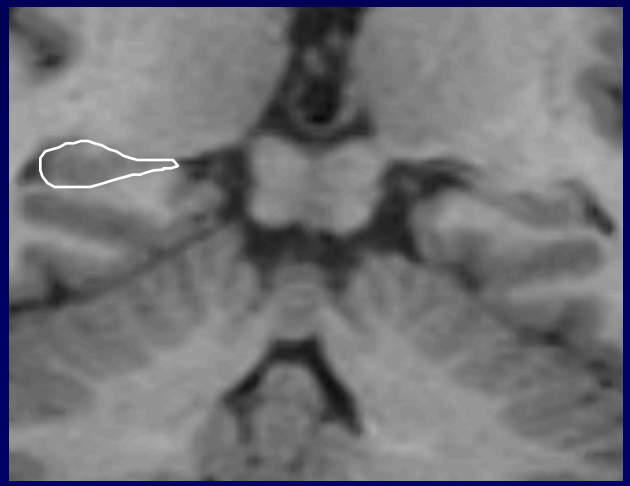
Normal MRI: What next?

"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

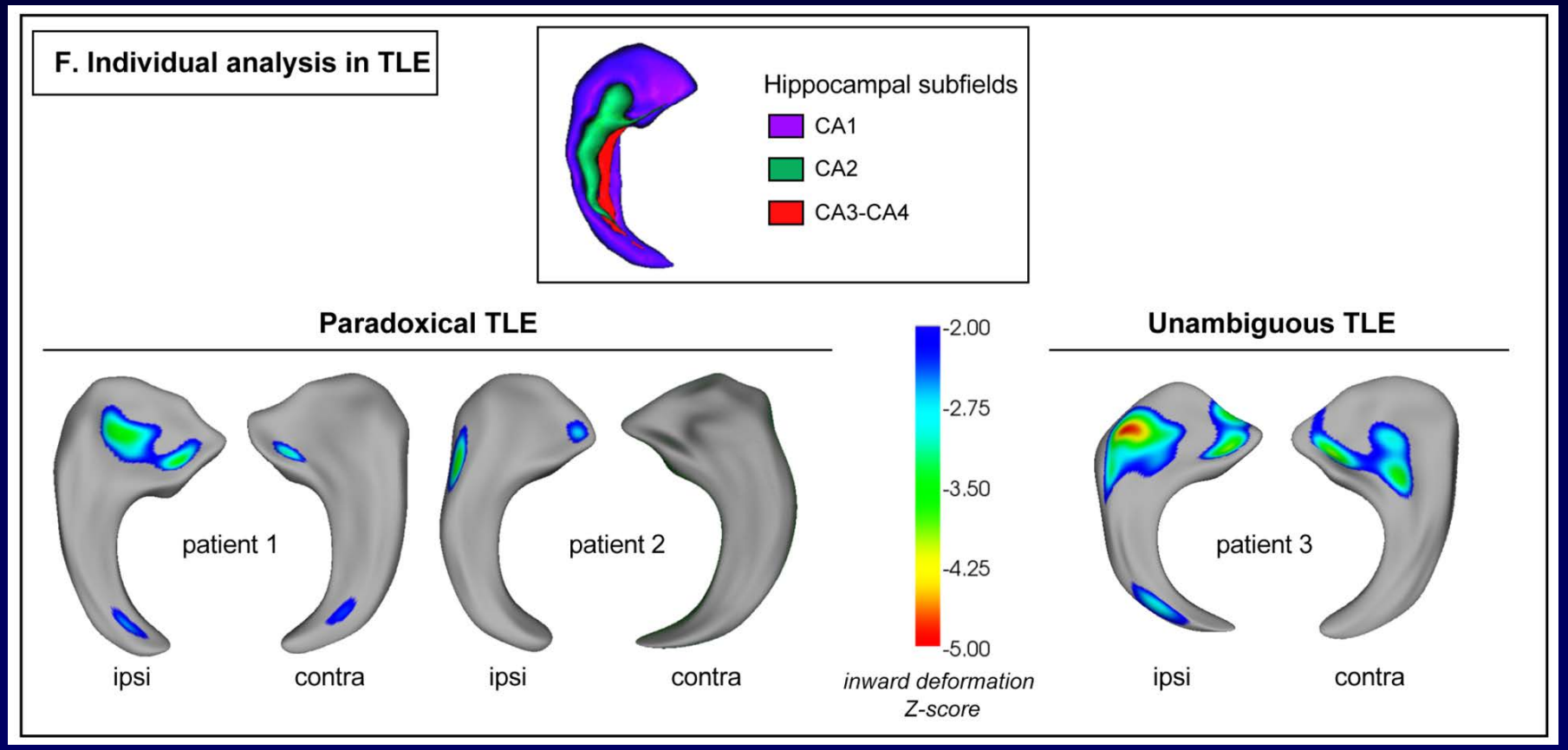




Posterior

Anterior

Prediction of pathology
Statistical shape analysis



Courtesy of Andrea Bernasconi

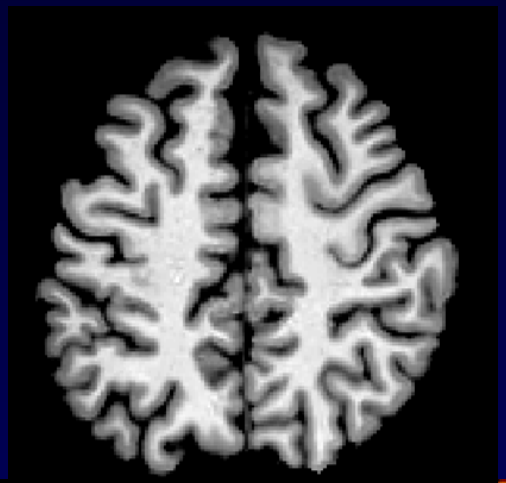
Prediction of pathology

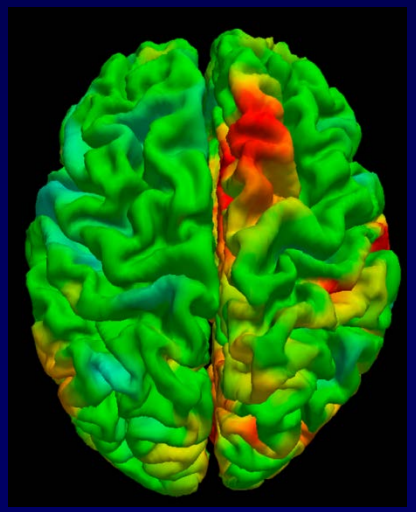
Cortical Dysplasia - computational models

Case 1:
Female, 22 yrs, Age of onset: 17 yrs

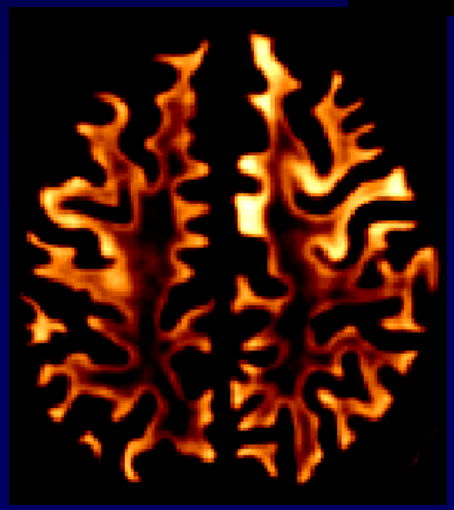
Diffuse numbness,
left head turning, elevation left hand

EEG
Interictal - generalised slow activity
Ictal - unclear onset

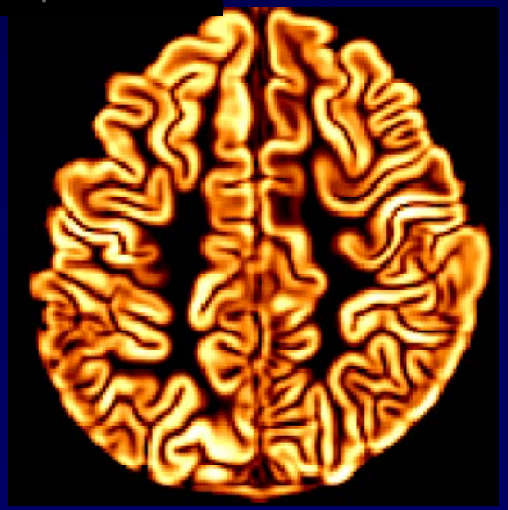




Thickness



Intensity

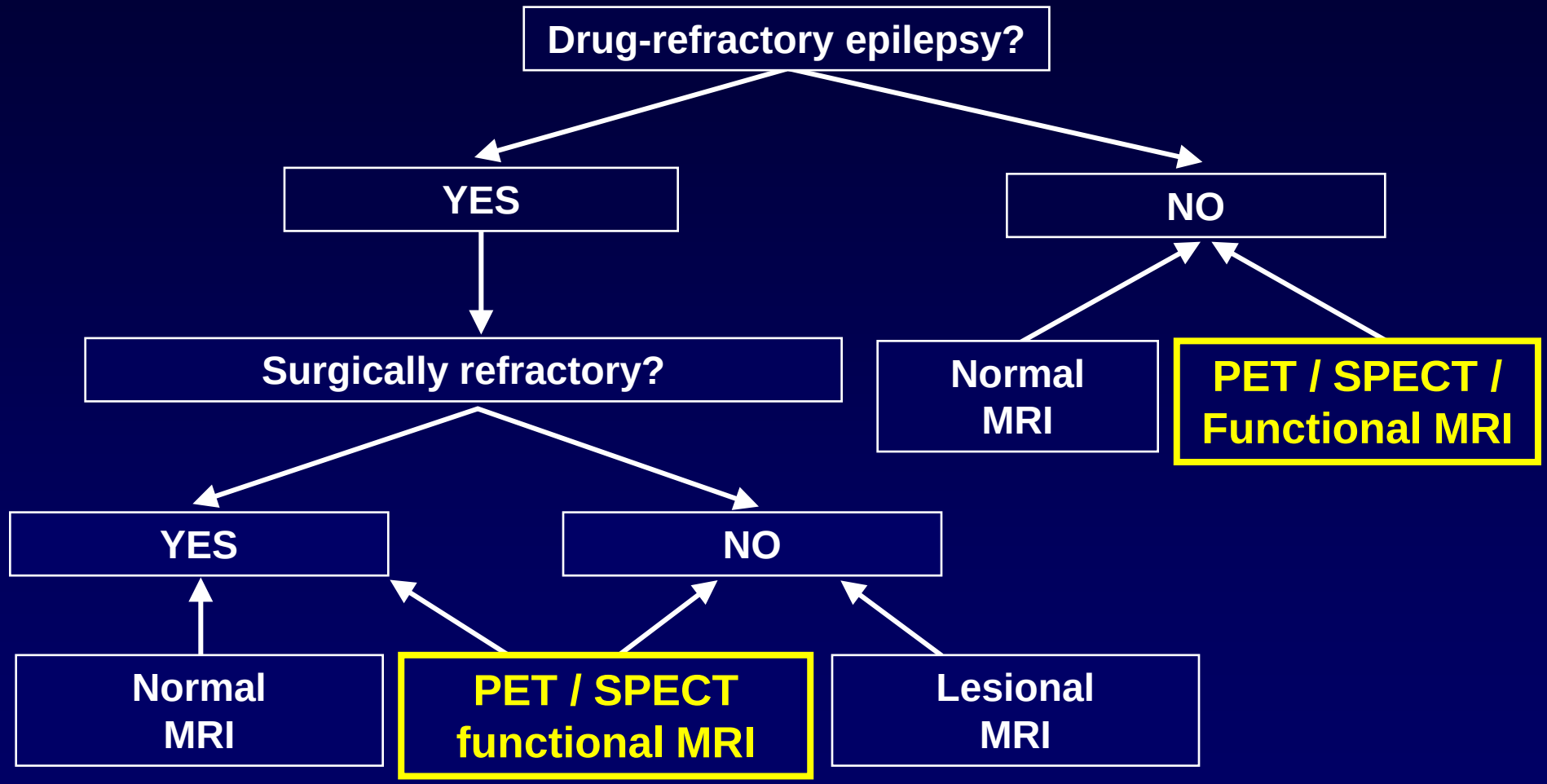


Gradient

FCD, focal cortical dysplasia; EEG, electroencephalography

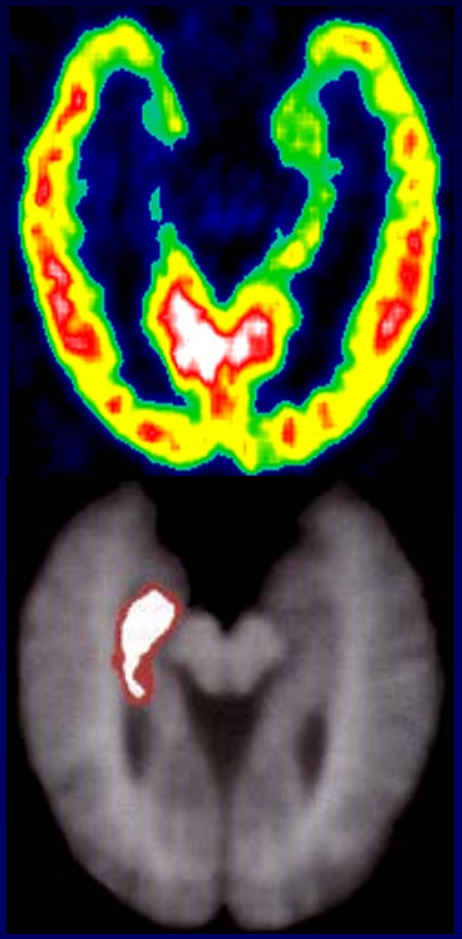
Courtesy of Andrea Bernasconi

Prediction of outcome
Role of PET / SPECT/ fMRI



Semah F et al. Neurology 1998

Prediction of outcome groups versus individual: FMZ PET in TLE

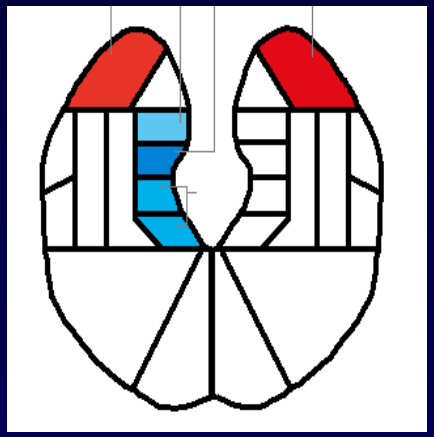


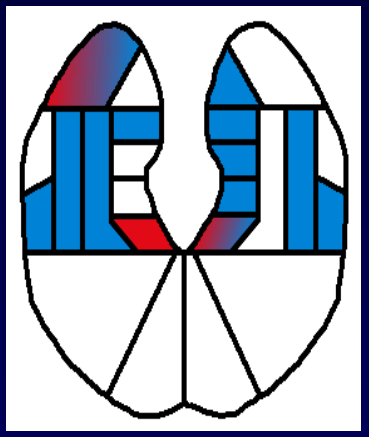
Individual results: unilateral HS normal MRI

Hippocampal and extra-hippocampal

⇓ and ⇑ of FMZ binding unilateral HS

< norm MRI

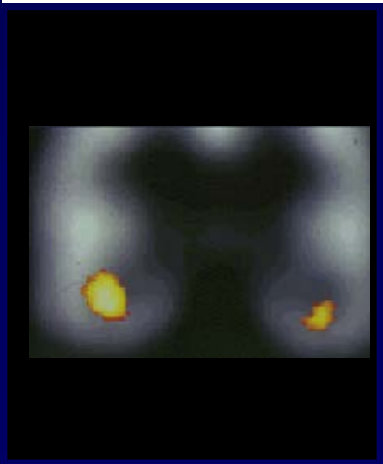


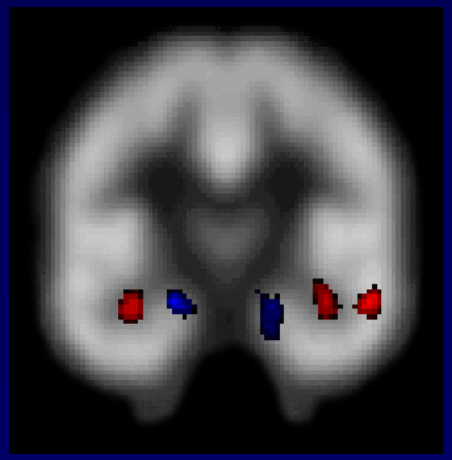


Group results:

⇓ FMZ binding HS bilateral

⇑ FMZ binding TLWM





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

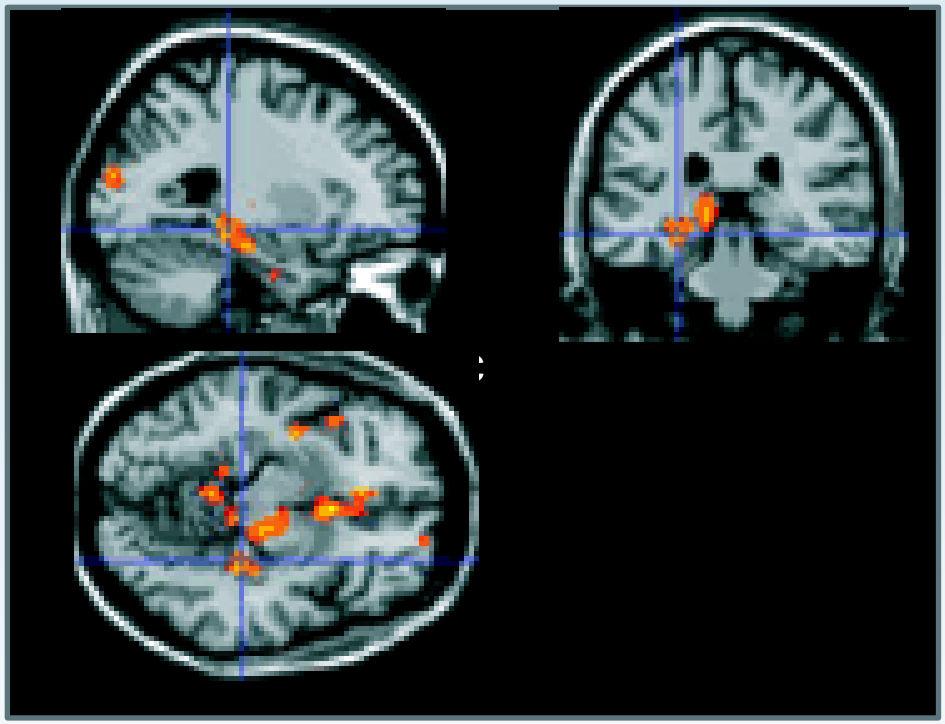
Koepp MJ et al. Brain 1997, Neurology 2000; Hammers A et al. Brain 2002

Biomarkers of synaptic plasticity

Flumazenil-PET:

- **TLE:**

FMZ reductions more pronounced in close proximity to seizures
(Bouvard, Brain 2005)



Biomarkers of synaptic plasticity

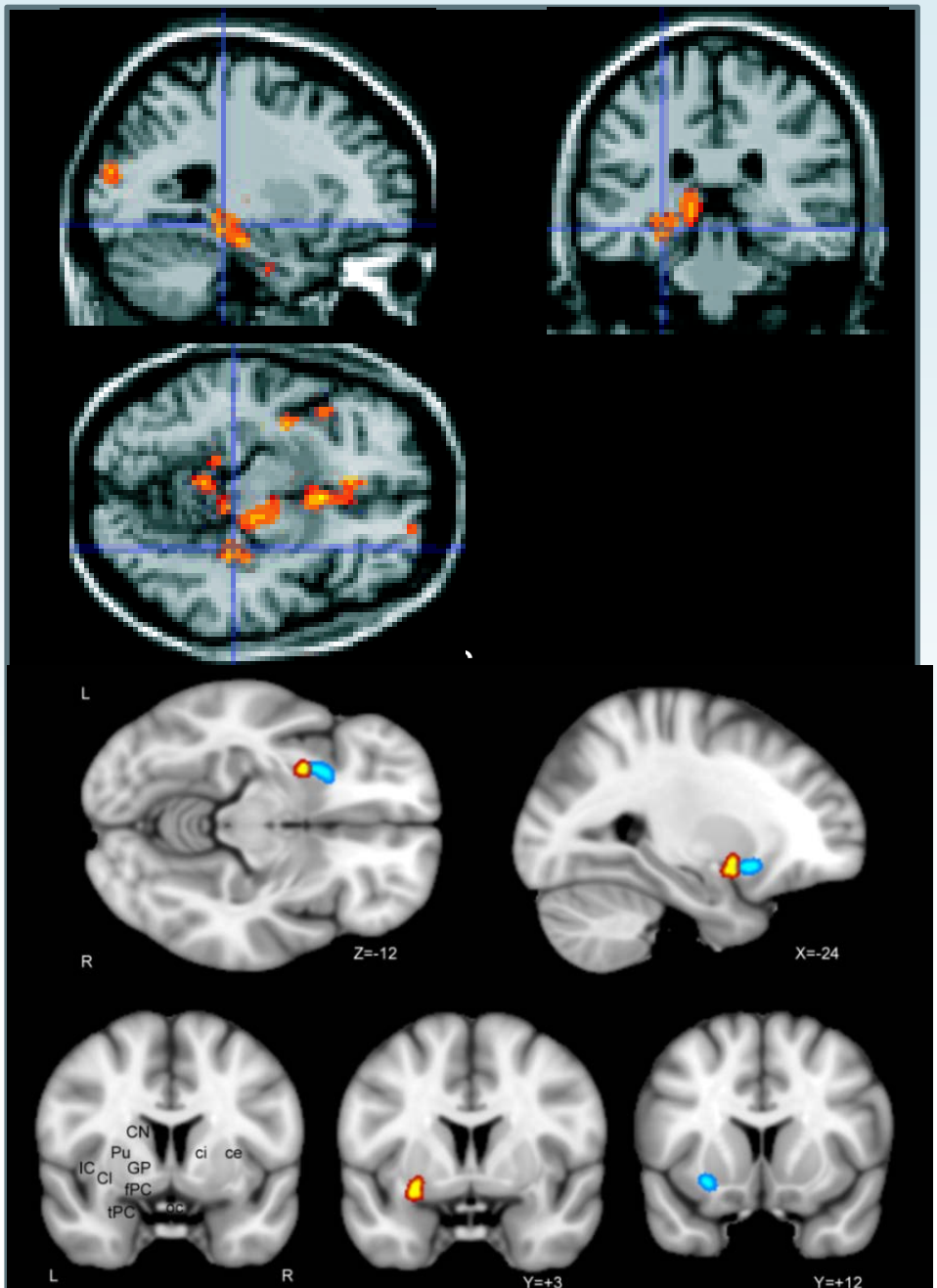
Flumazenil-PET:

- **TLE:**

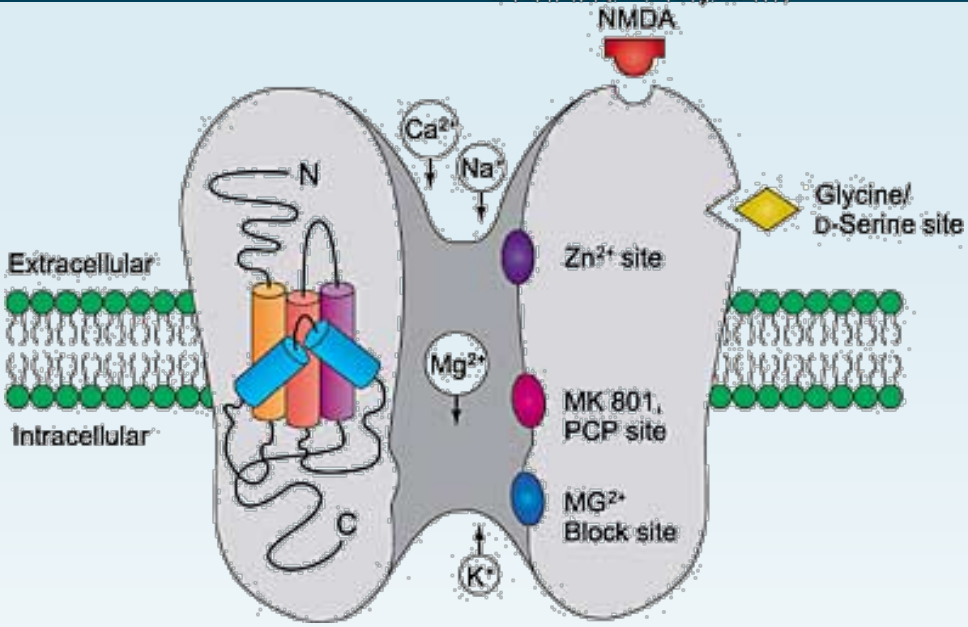
FMZ reductions more pronounced in close proximity to seizures
(Bouvard, Brain 2005)

- **Focal epilepsies**:

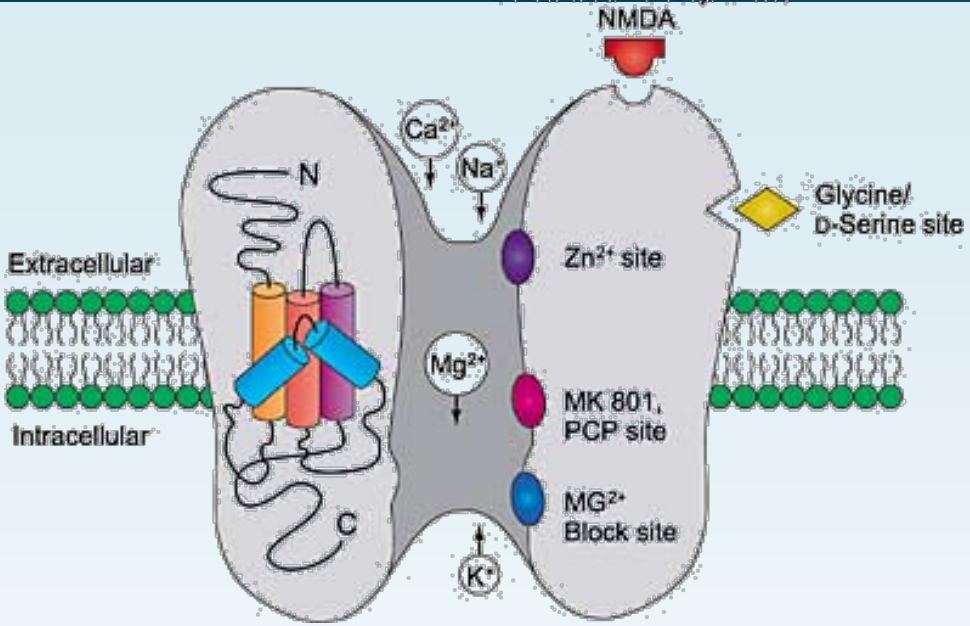
FMZ-PET / fMRI Correlation with seizure frequency
(Laufs, Neurology 2011)



Biomarkers of altered excitability

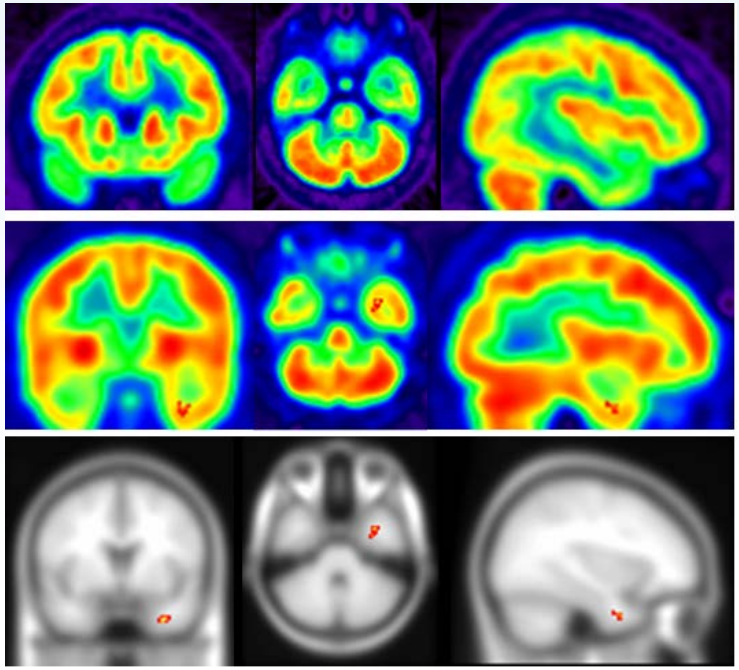


Biomarkers of altered excitability



GE-179 PET

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



Healthy control

R TLE

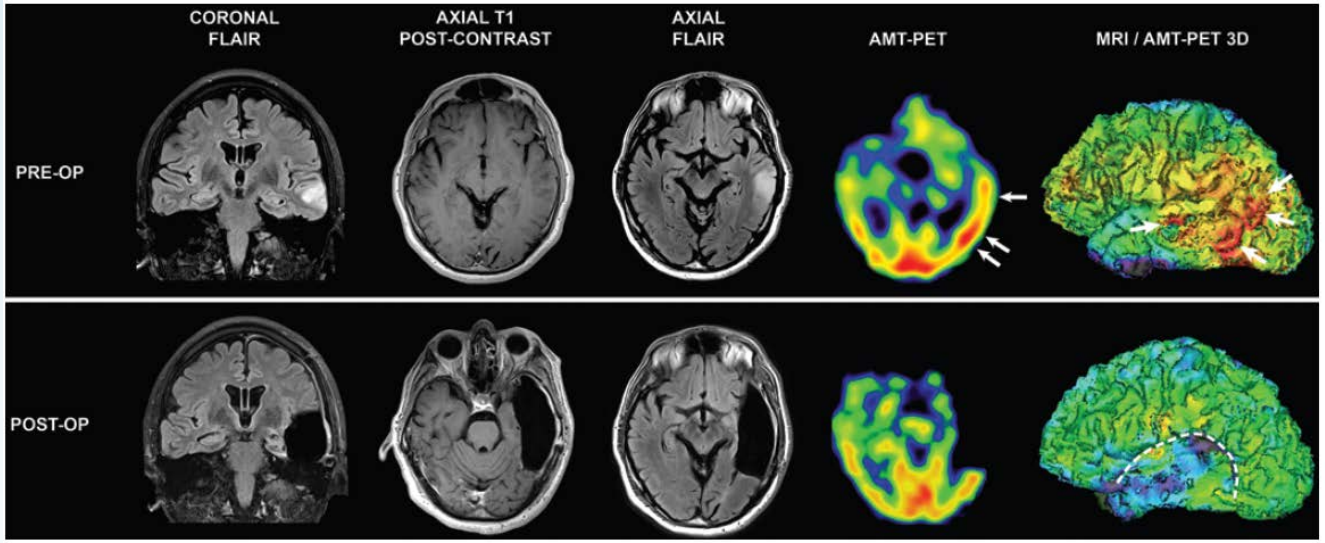
Increase of ^{18}F-GE179

Biomarkers of inflammatory changes

AMT PET

Imaging of serotonin synthesis, tryptophan metabolism

- Inducible by inflammatory cytokines

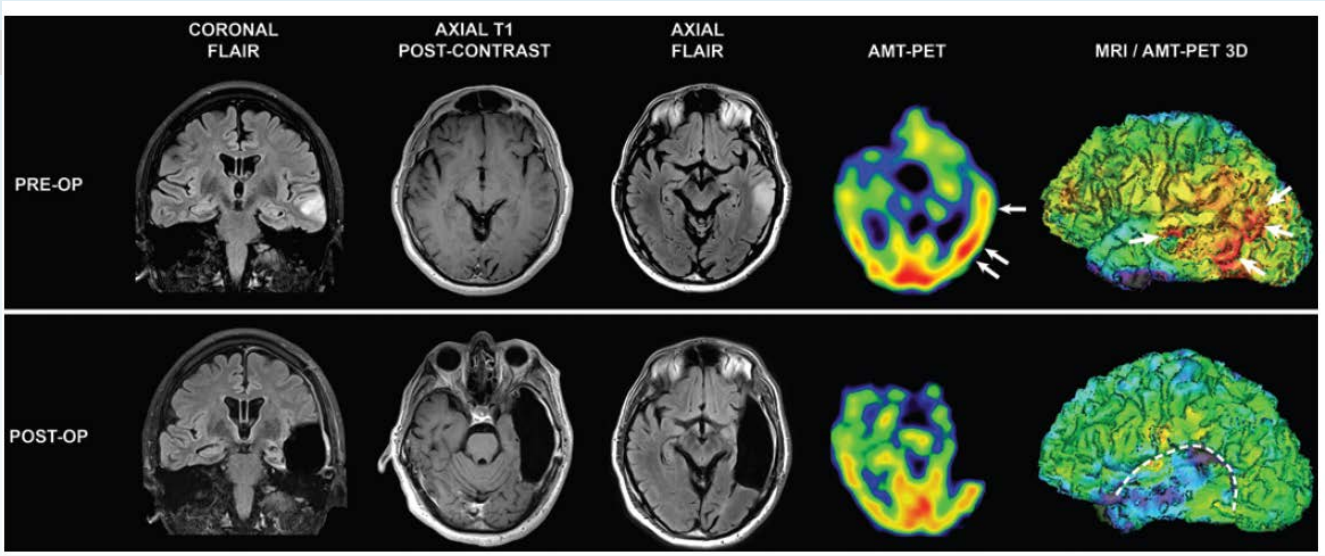


Juhasz et al, Neursurg Focus 2013

Biomarkers of inflammatory changes

AMT PET

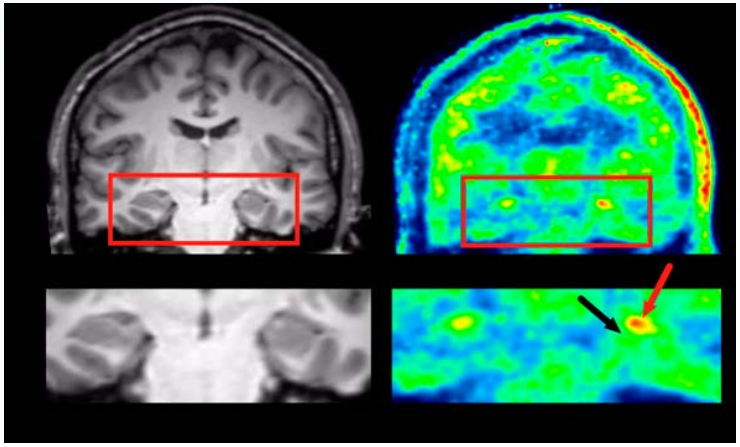
Imaging of serotonin synthesis, tryptophan metabolism



Juhasz et al, Neursurg Focus 2013

^{11}C-TSPO - PET

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



Biomarkers and surrogate endpoints

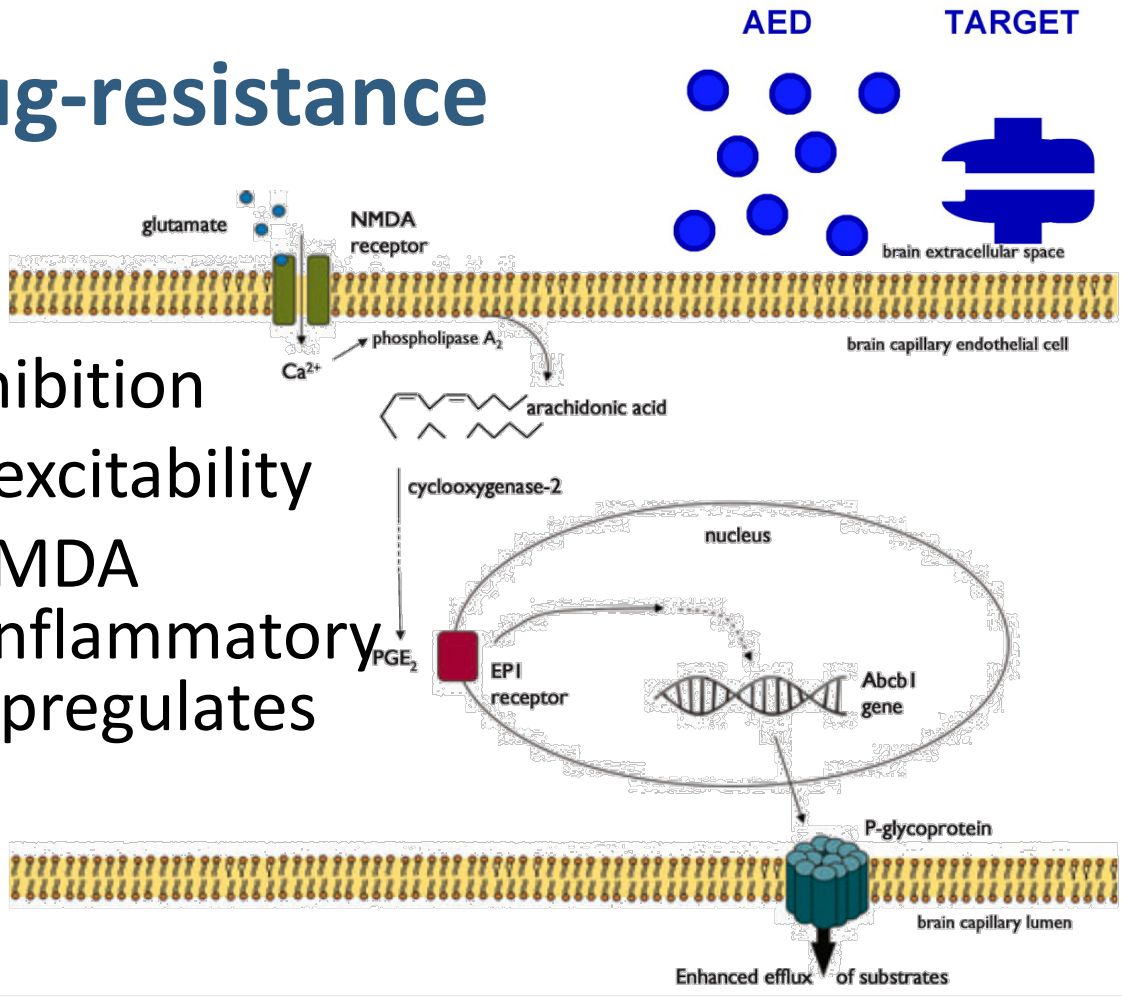
Key areas – "clinical treatment gaps"

- **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

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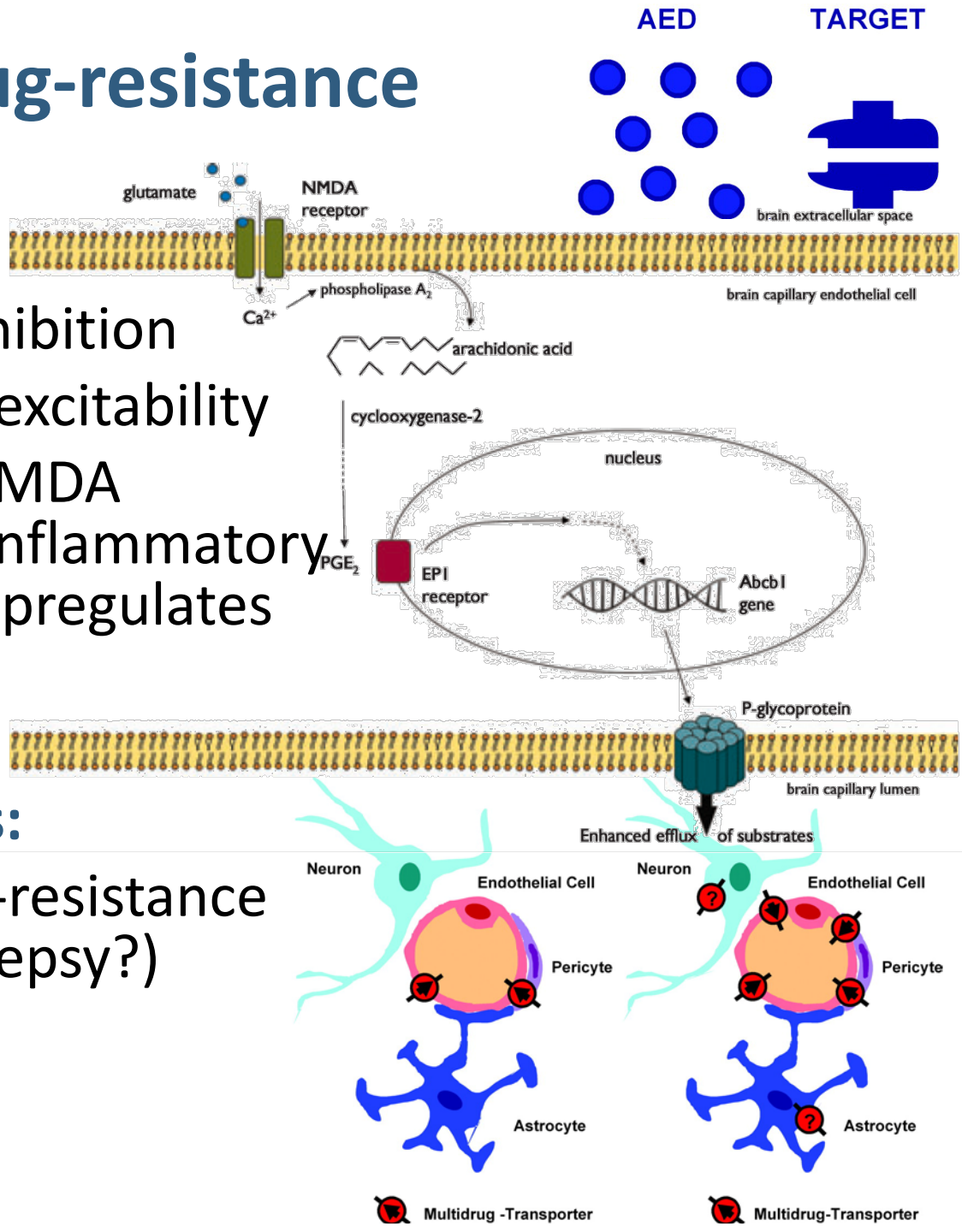
"Transporter" hypothesis:

- 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

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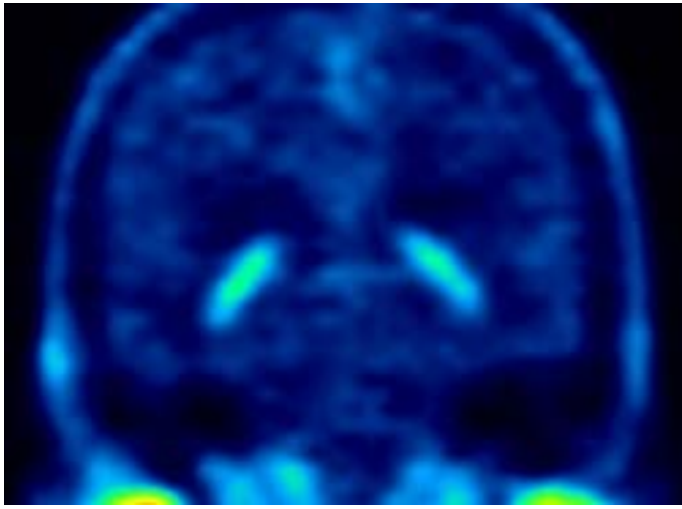
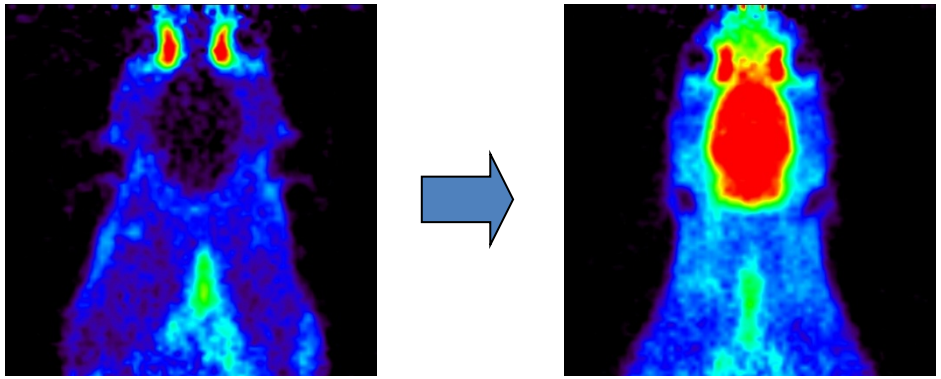


(*R*)-[^{11}C] verapamil

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



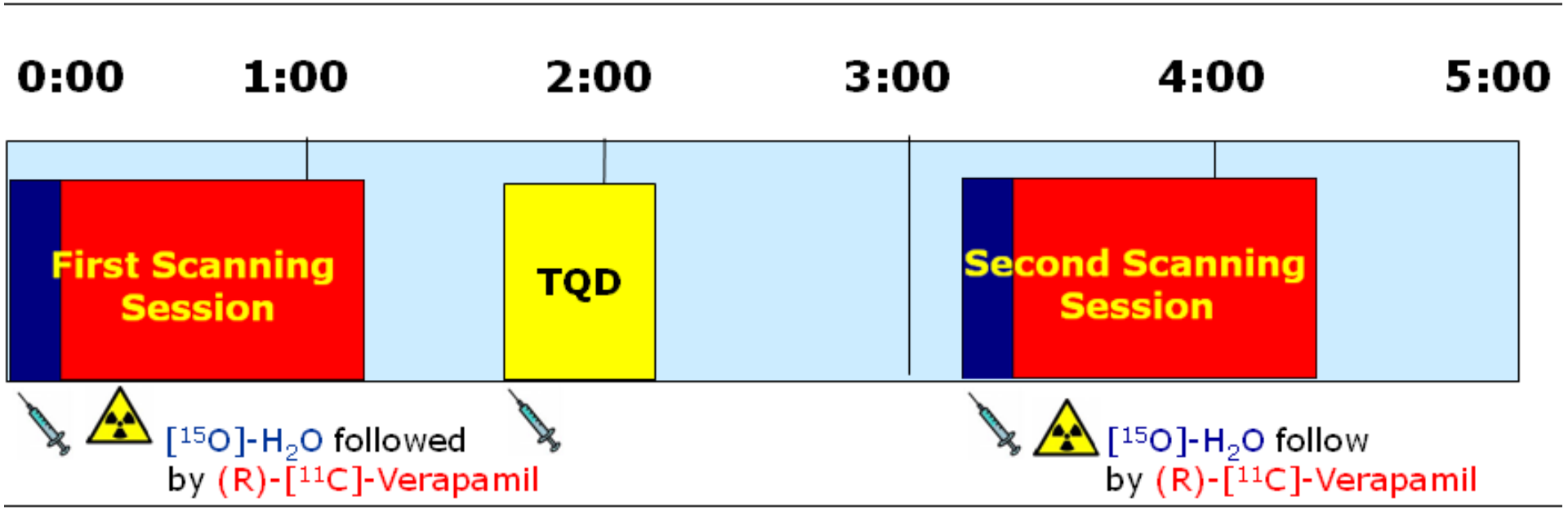
JP Bankstahl et al, J Neuroscience 2011

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:

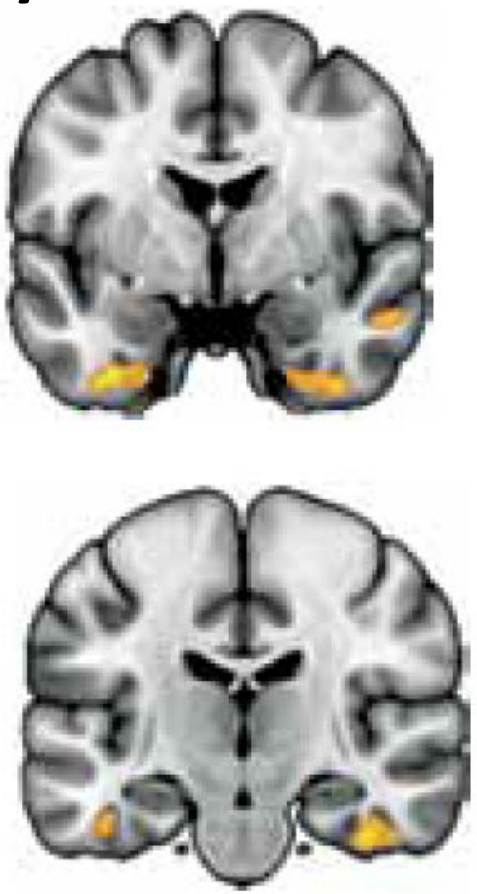


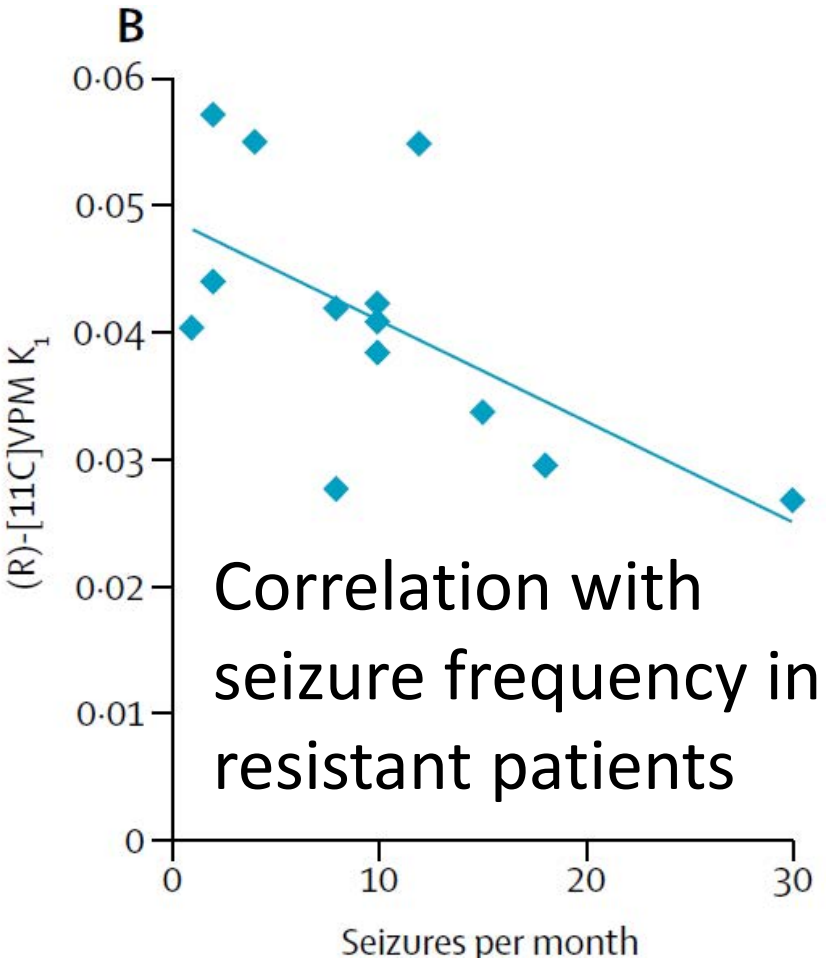
Feldmann et al, Lancet Neurology 2013 in press

Results – K_1 at baseline

Higher Pgp activity:

drug-resistant
vs
seizure-free TLE



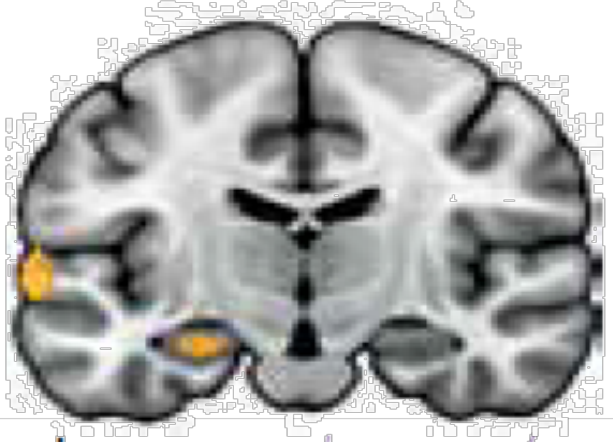


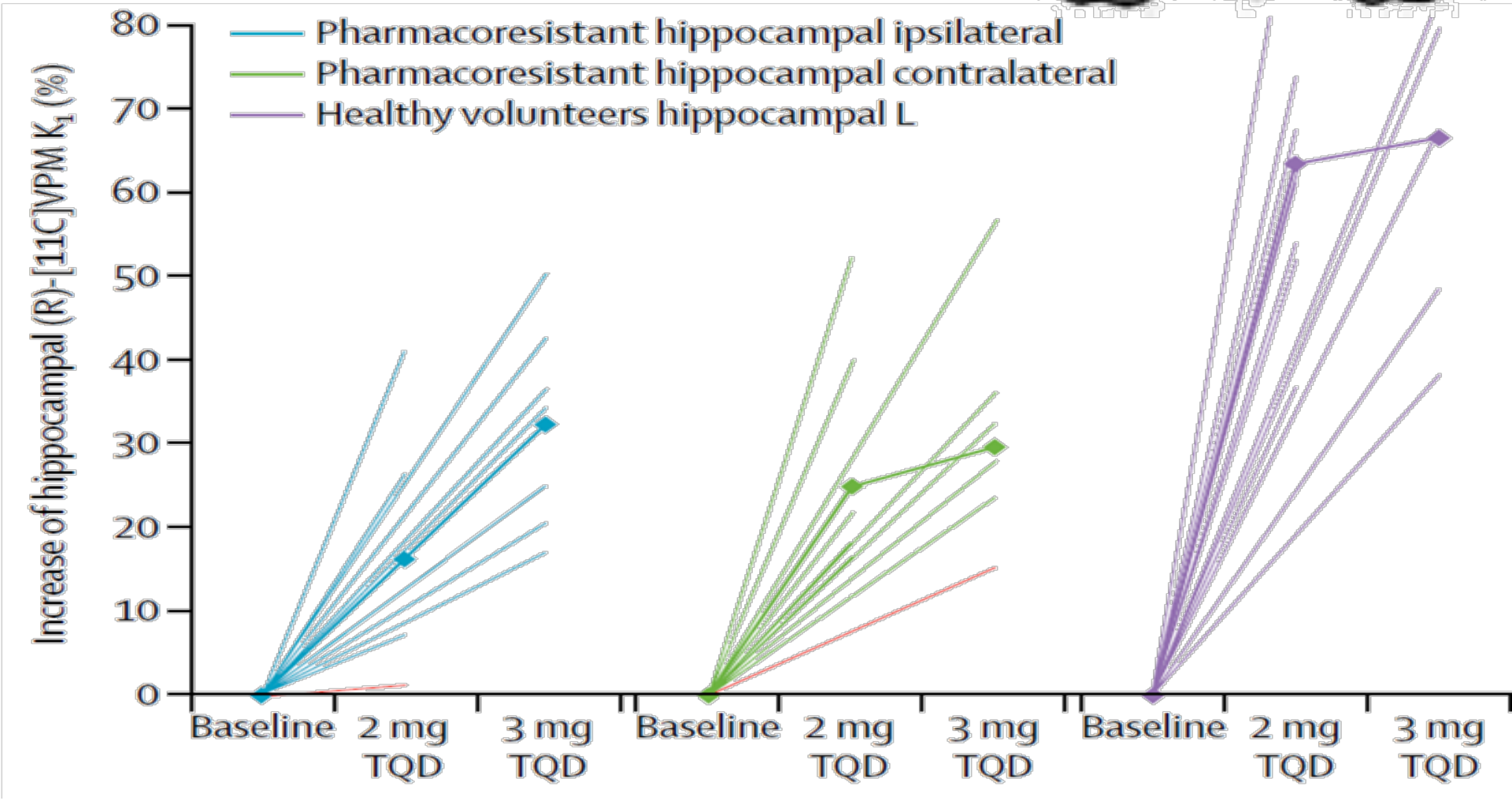
Correlation with seizure frequency in resistant patients

Feldmann et al, Lancet Neurology 2013

Results – K_1 after TQD

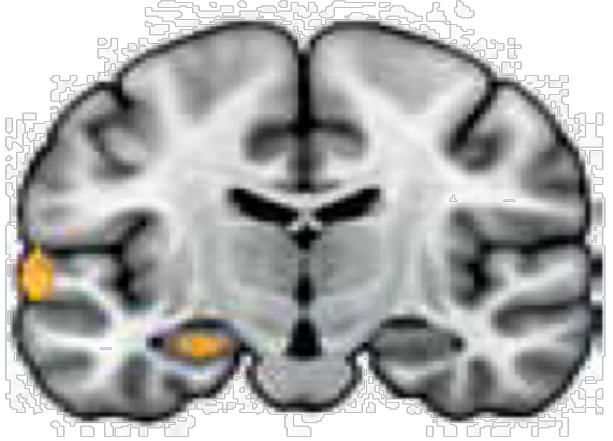
- increased in controls by 59%
- attenuated in patients: 26%

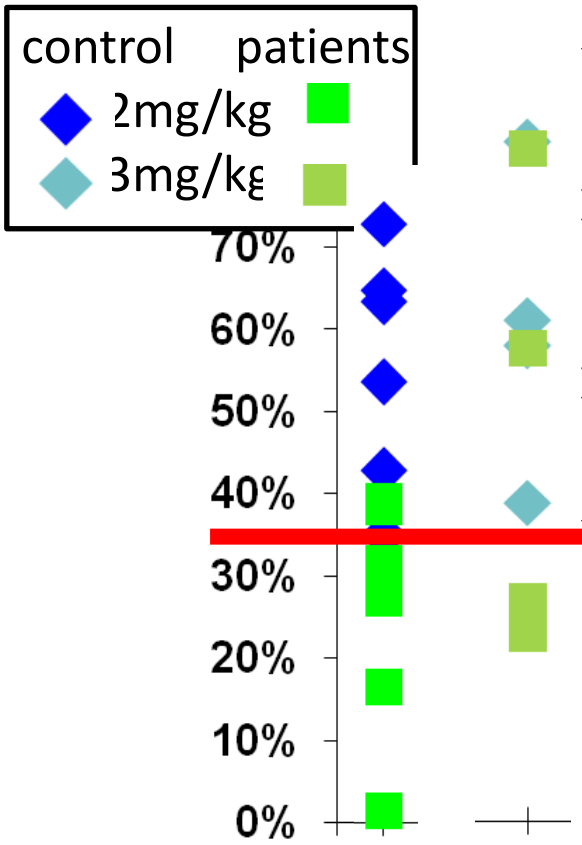




Results – K_1 after TQD

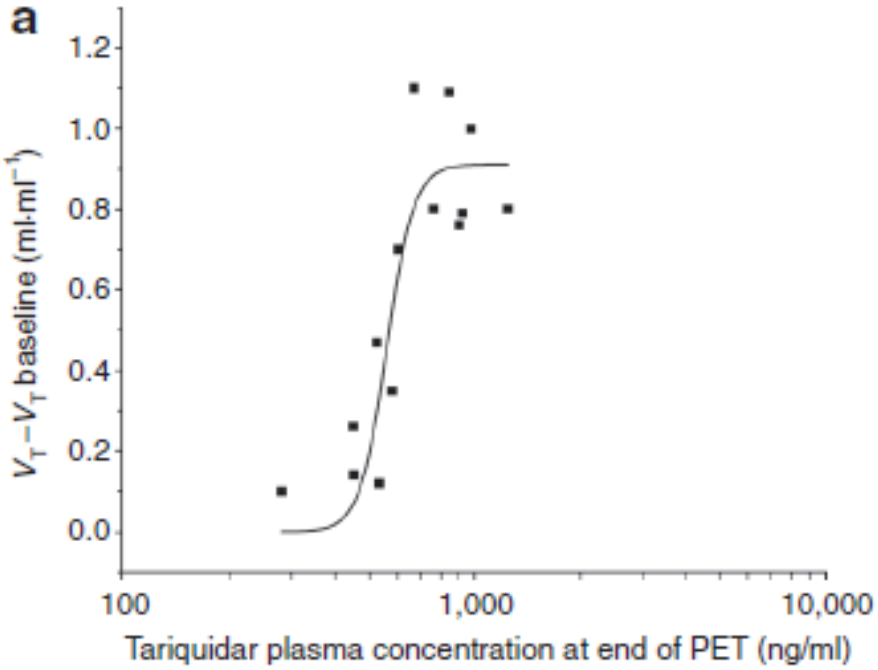
- increased in controls by 59%
- attenuated in patients: 26%
  in 6/11: marked K_1 increases >36%
  in 5/11: less remarkable (12%)

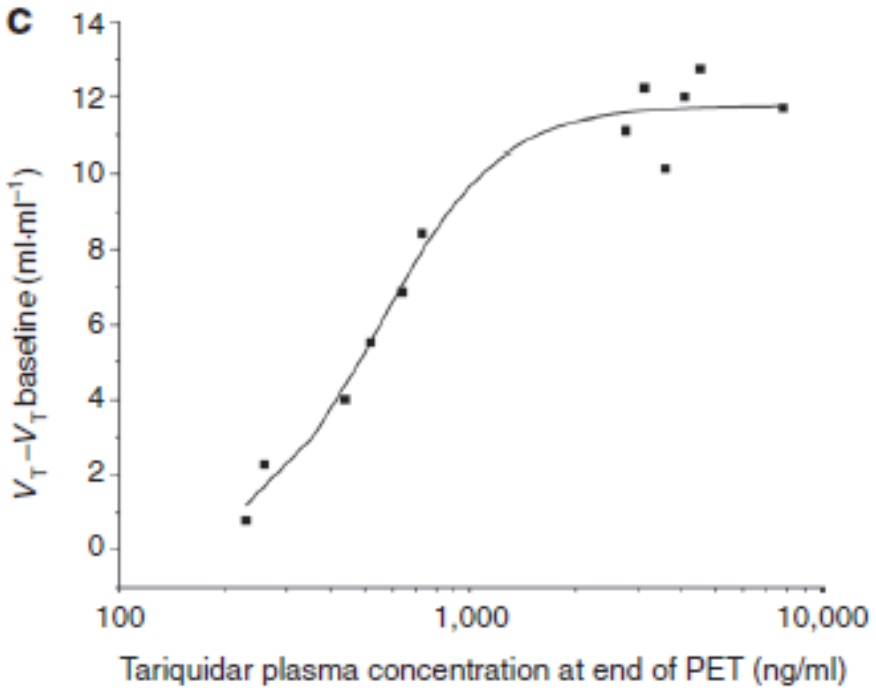




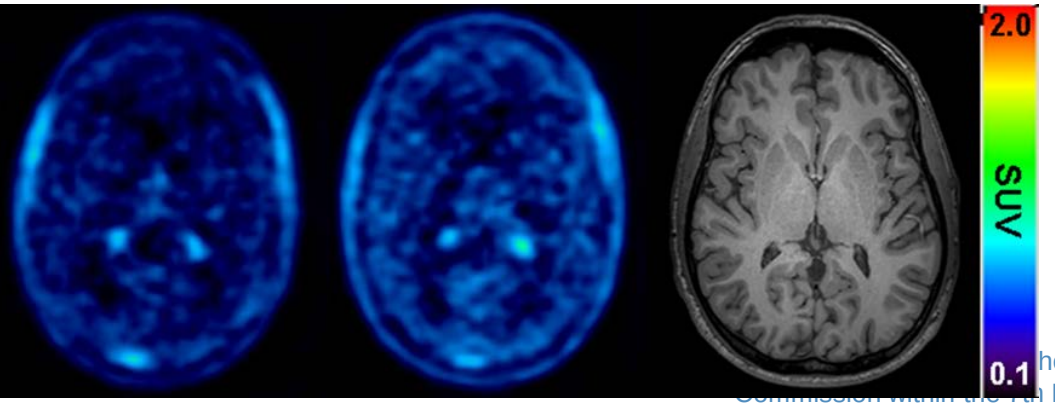
MRI	EEG	Age at onset (years)	Duration of epilepsy (years)	Average sz frequency (month)	Interval last sz to PET (days)	Current AEDs (dose: mg/day)
			2mg/kg			
L HS	LT	5	38	2	21	PHT (325), CLOB (20)
R HS	RT	11	45	18	2	LTG (200), PRG (300)
L HS	LT	19	11	15	6	LVT (750), OXC (600), CLOB (20)
			3mg/kg		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

Translation to humans

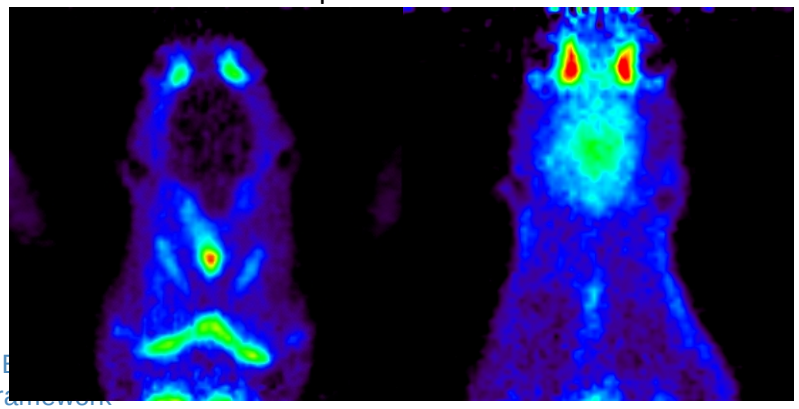




2 mg/kg (C_{plasma}: 490±166 ng/mL)

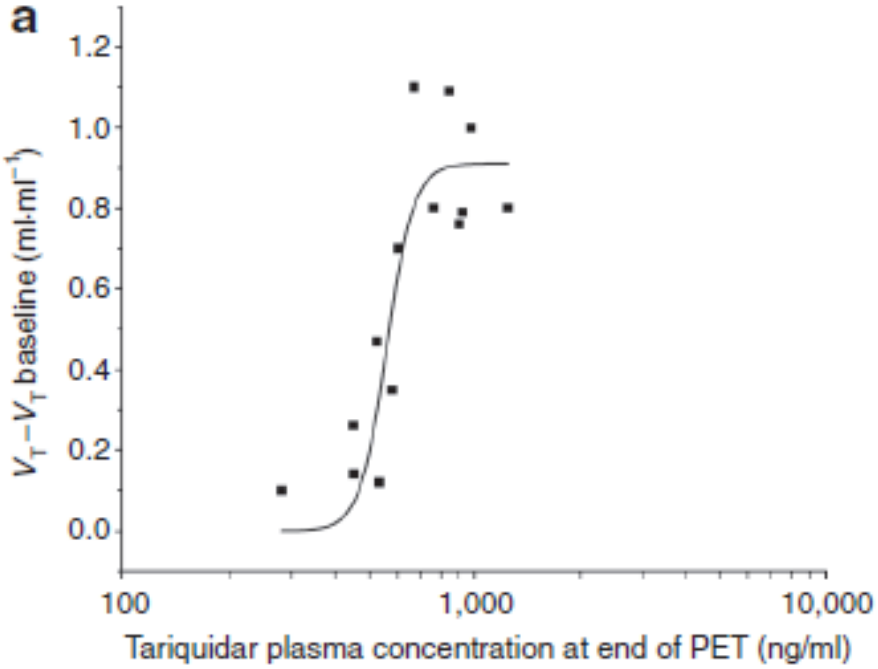


2.6 mg/kg (C_{plasma}: 480±57 ng/mL)

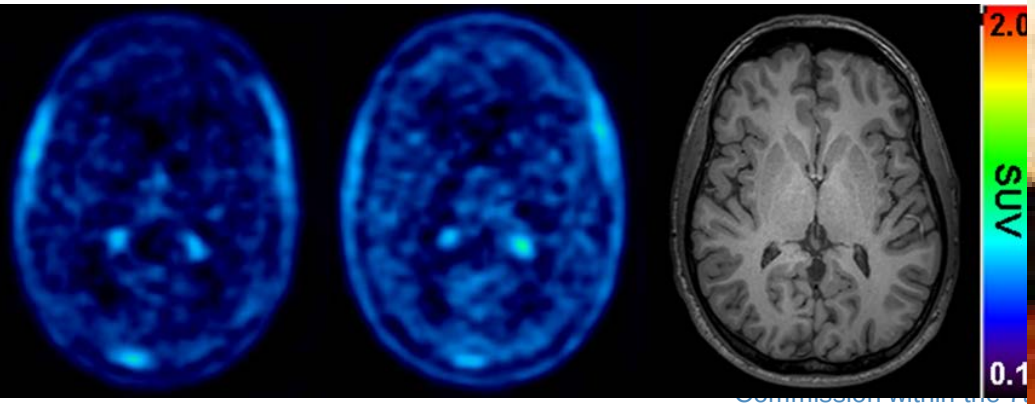


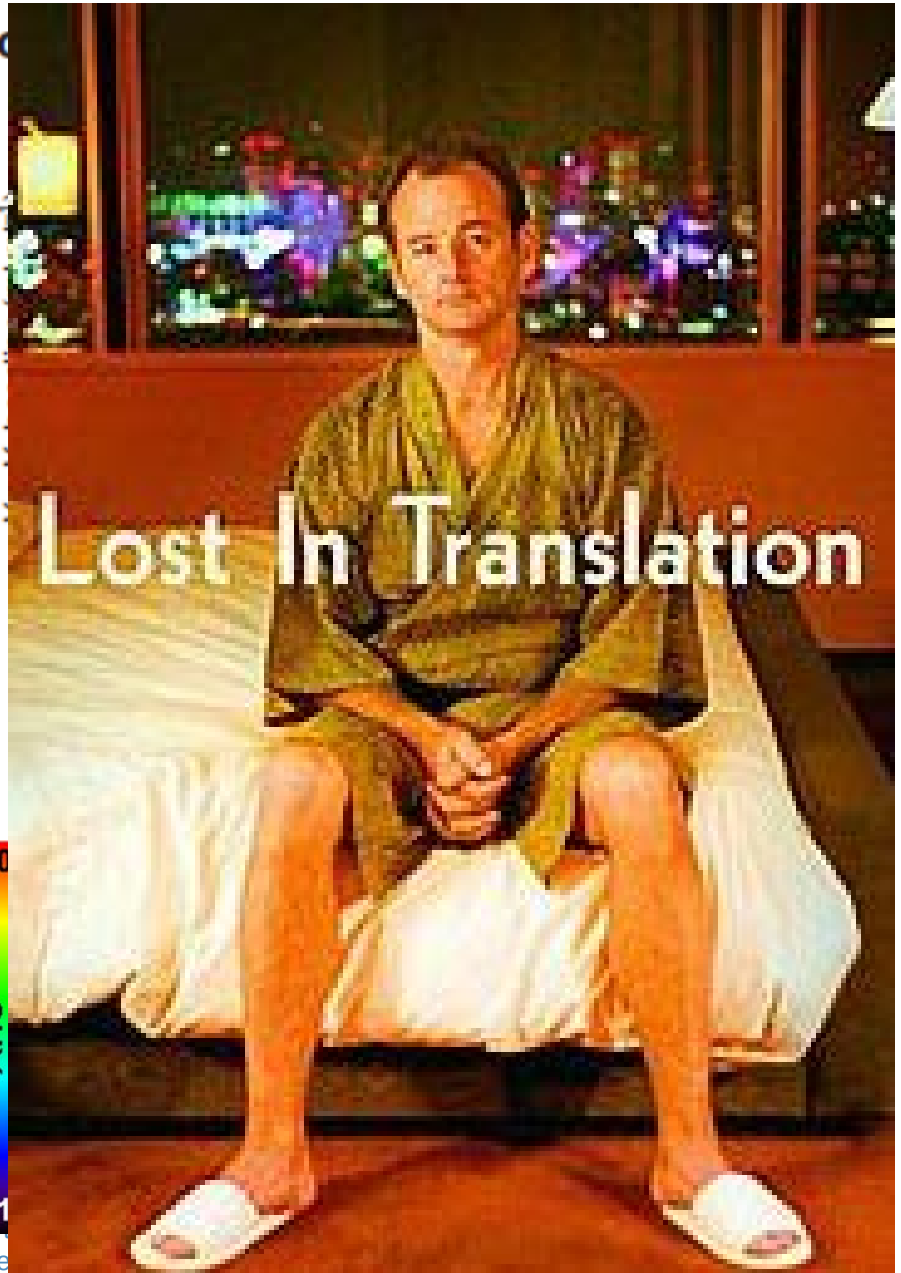
Programme

Translation to humans



2 mg/kg (C_{plasma}: 490±166 ng/mL)





Biomarkers and surrogate endpoints

Key areas – "clinical treatment gaps"

- Patient stratification — drug-refractory ?
  drug-sensitive ?
- **Prediction of outcome** — **WHICH DRUG ?**

Predict drug response

- All AEDs are designed for the same purpose

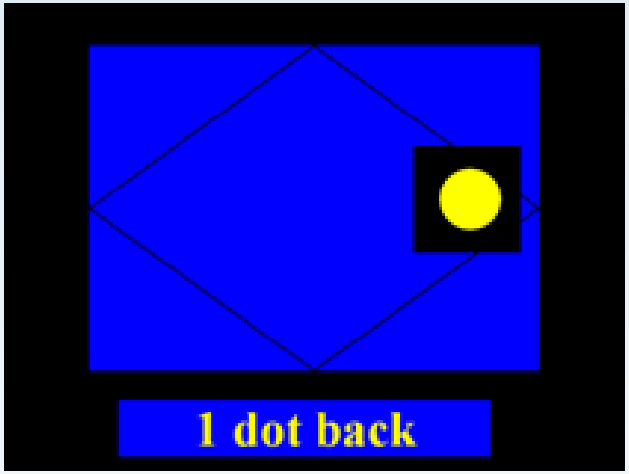
Predict drug response

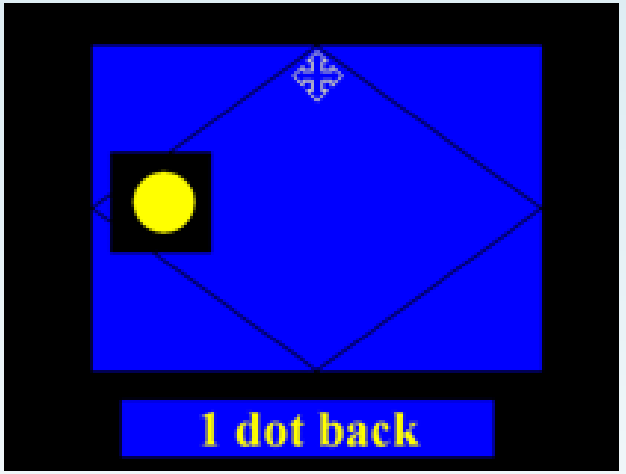
- All AEDs are designed for the same purpose

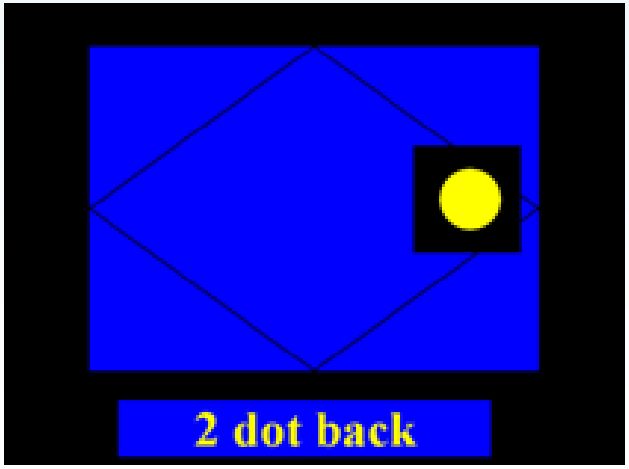
- not all AEDs are the same: “tolerability” counts!
- But: we cannot measure shoe-size

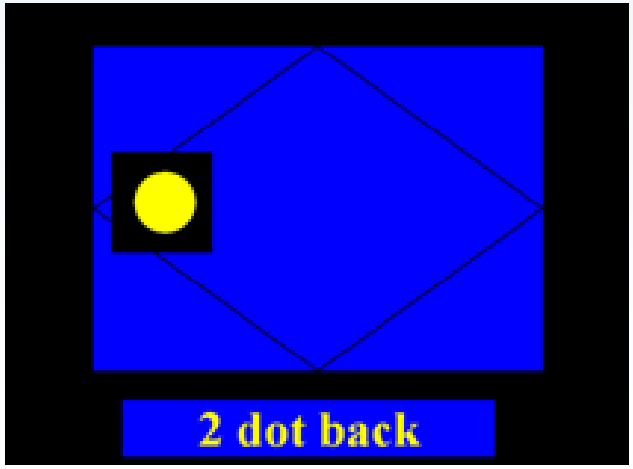
Courtesy of Martin Brodie

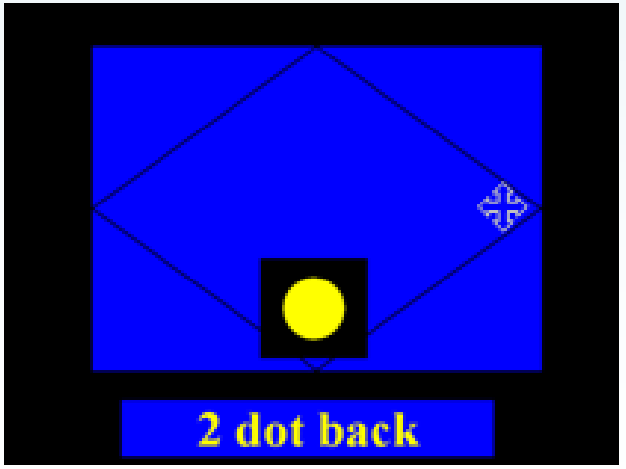
Visuo-spatial working memory paradigm





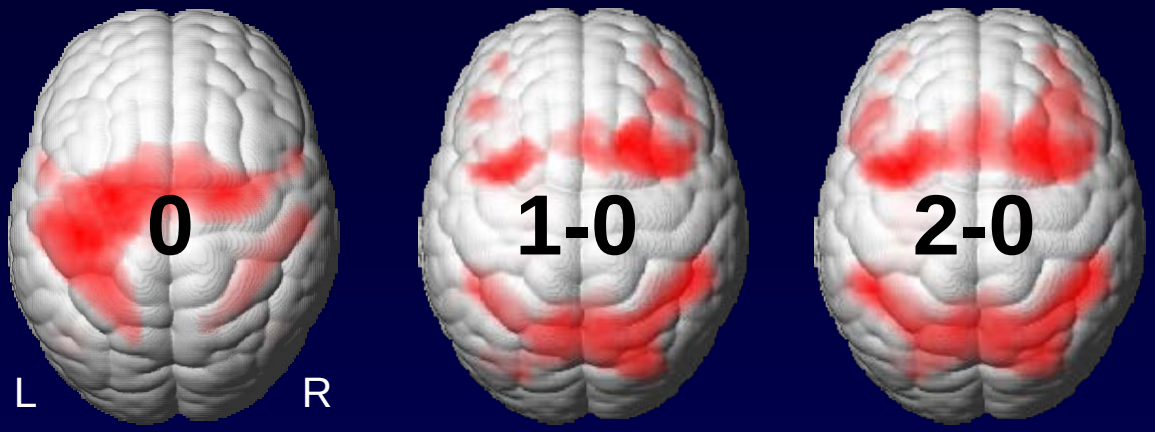






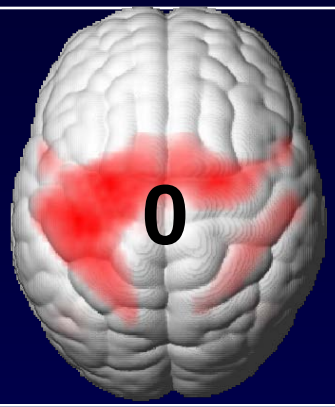
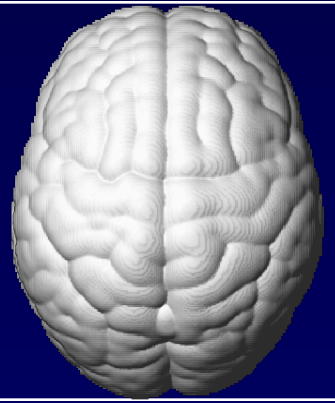
Working memory in JME

Controls

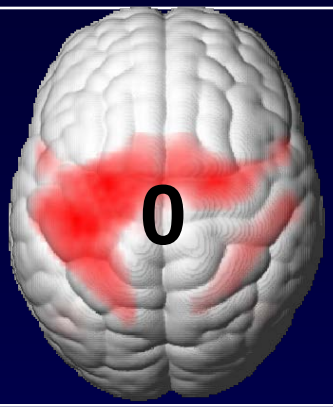
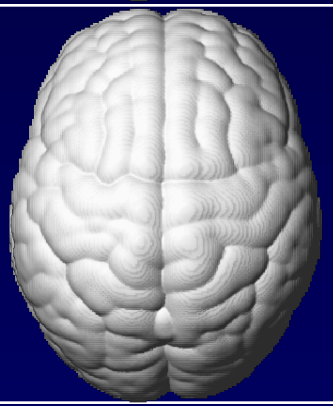
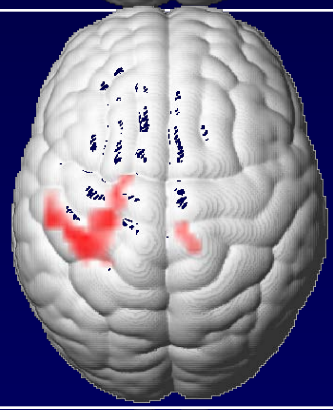


	0 back	1 back	2 back	rest
Working Memory	-	+	++	-
Motor	+	+	+	-
Visual	+	+	+	+

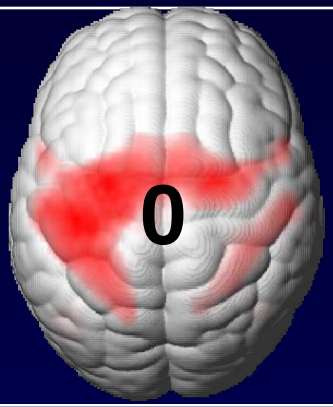
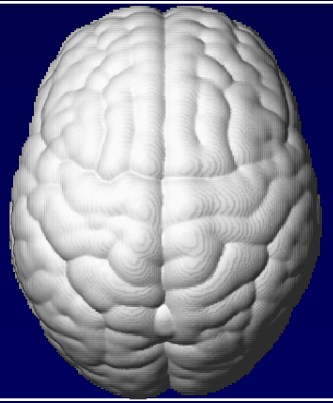
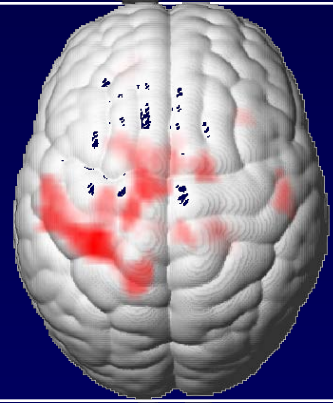
Working memory in JME

Controls	
JME > Ctr	
JME < Ctr	

Working memory in JME

Controls		
JME > Ctr		
JME < Ctr		

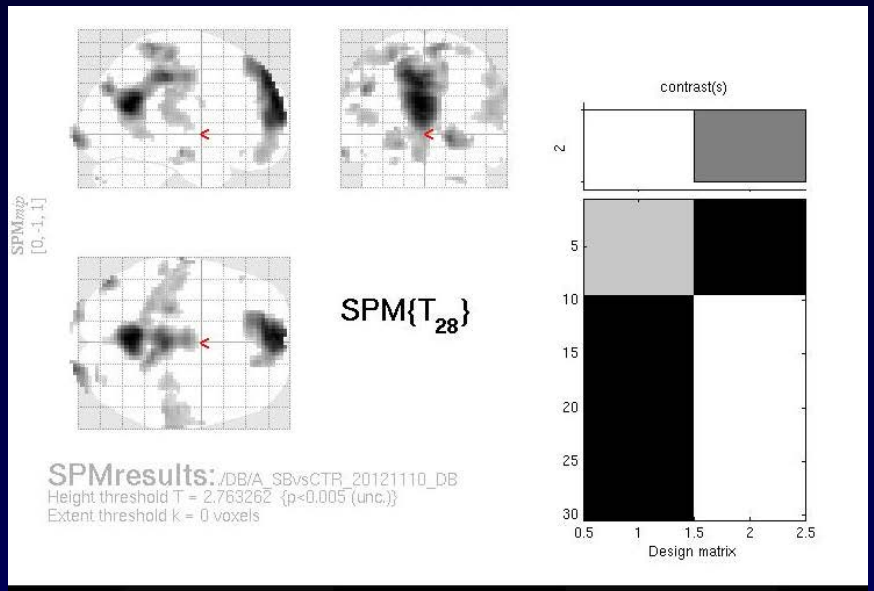
Working memory in JME

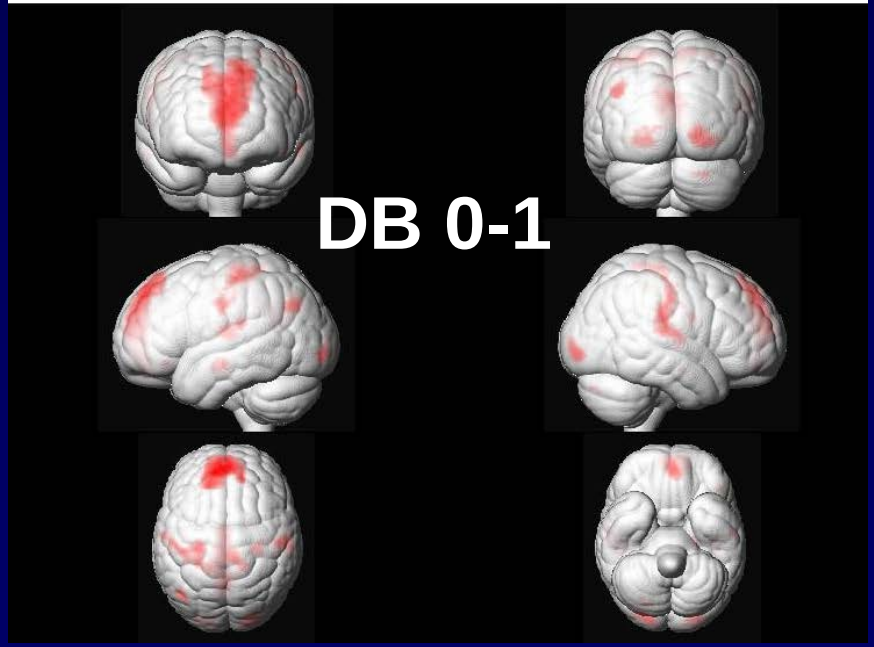
Controls	 0	 1-0	 2-0
JME > Ctr			
JME < Ctr			

"Resting state"

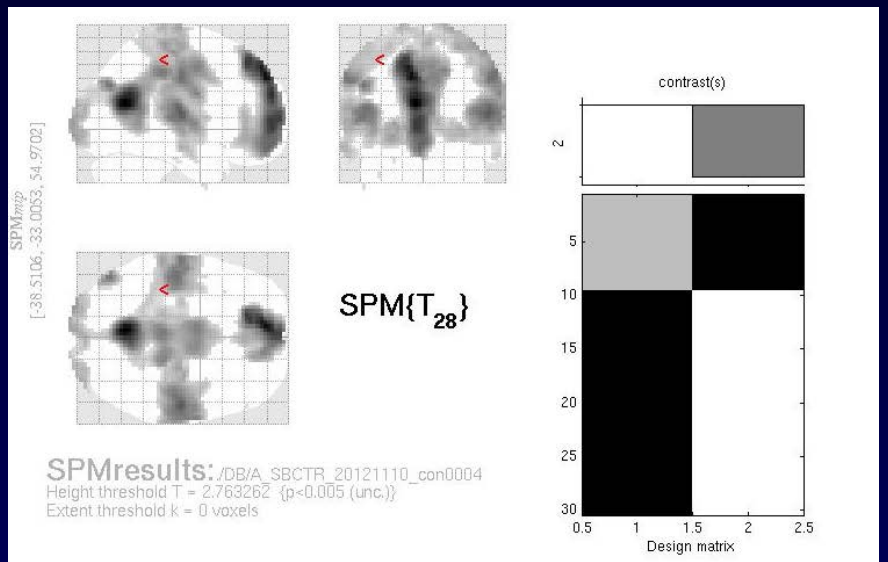
UCL

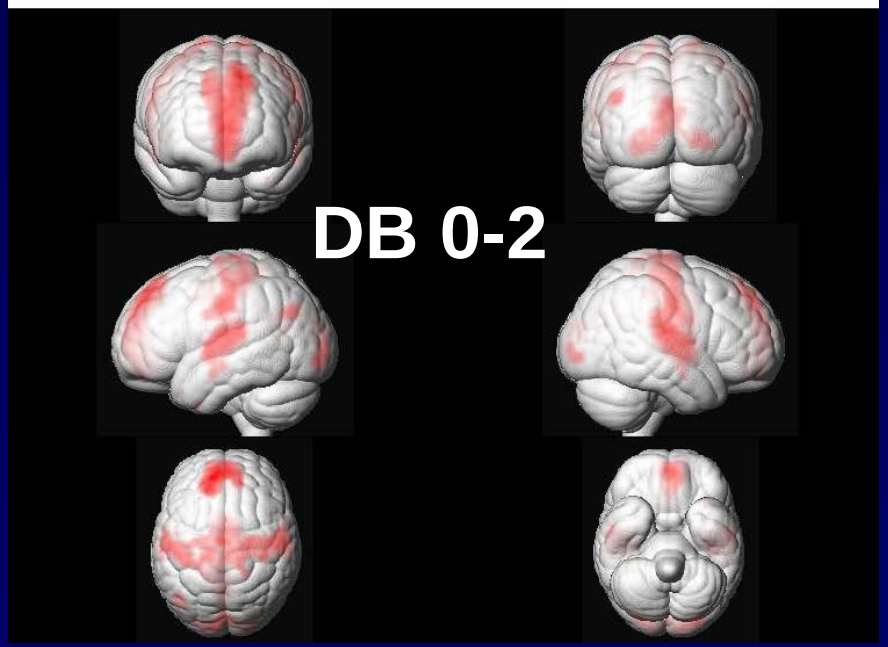
DB 0-1





DB 0-2

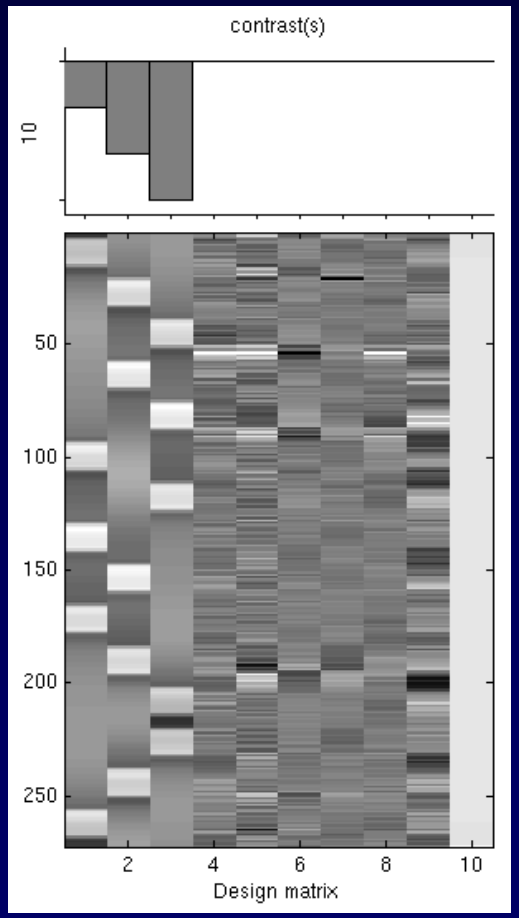


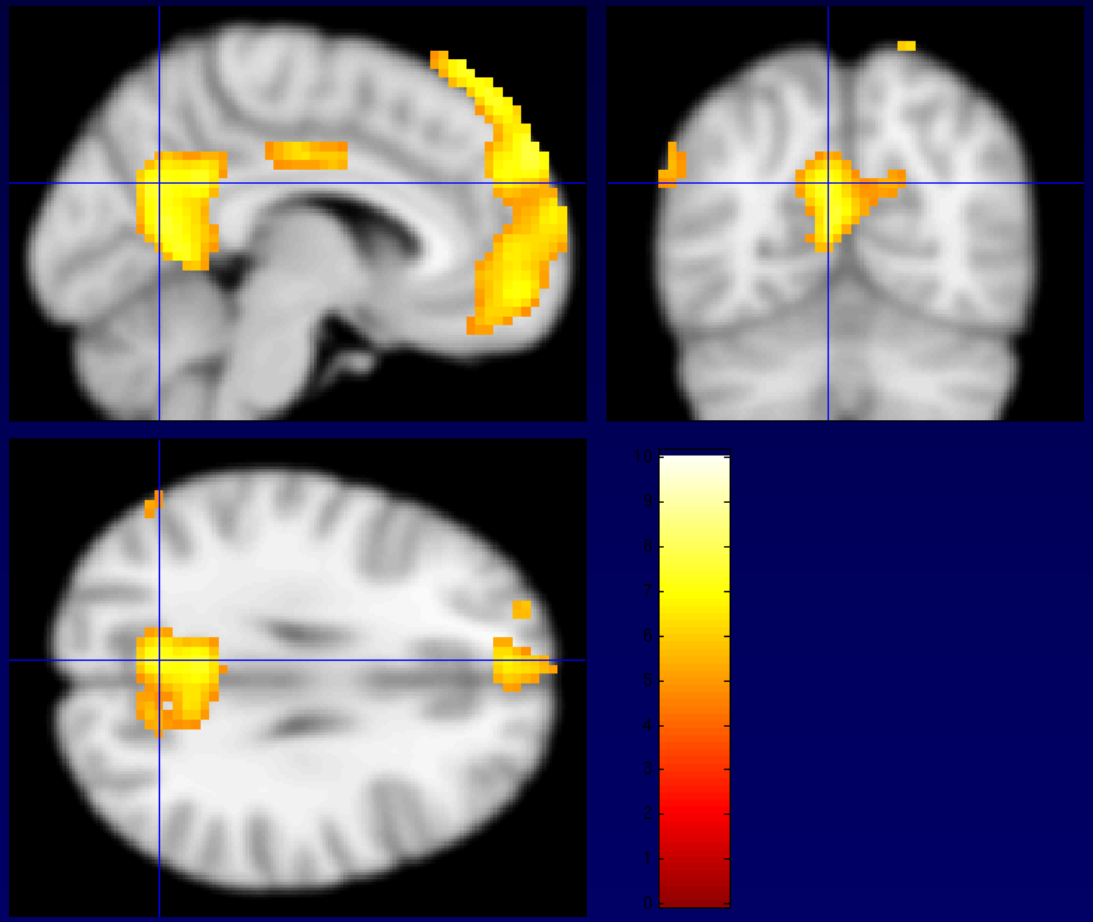


"Resting state"

Deactivation with increasing demand?

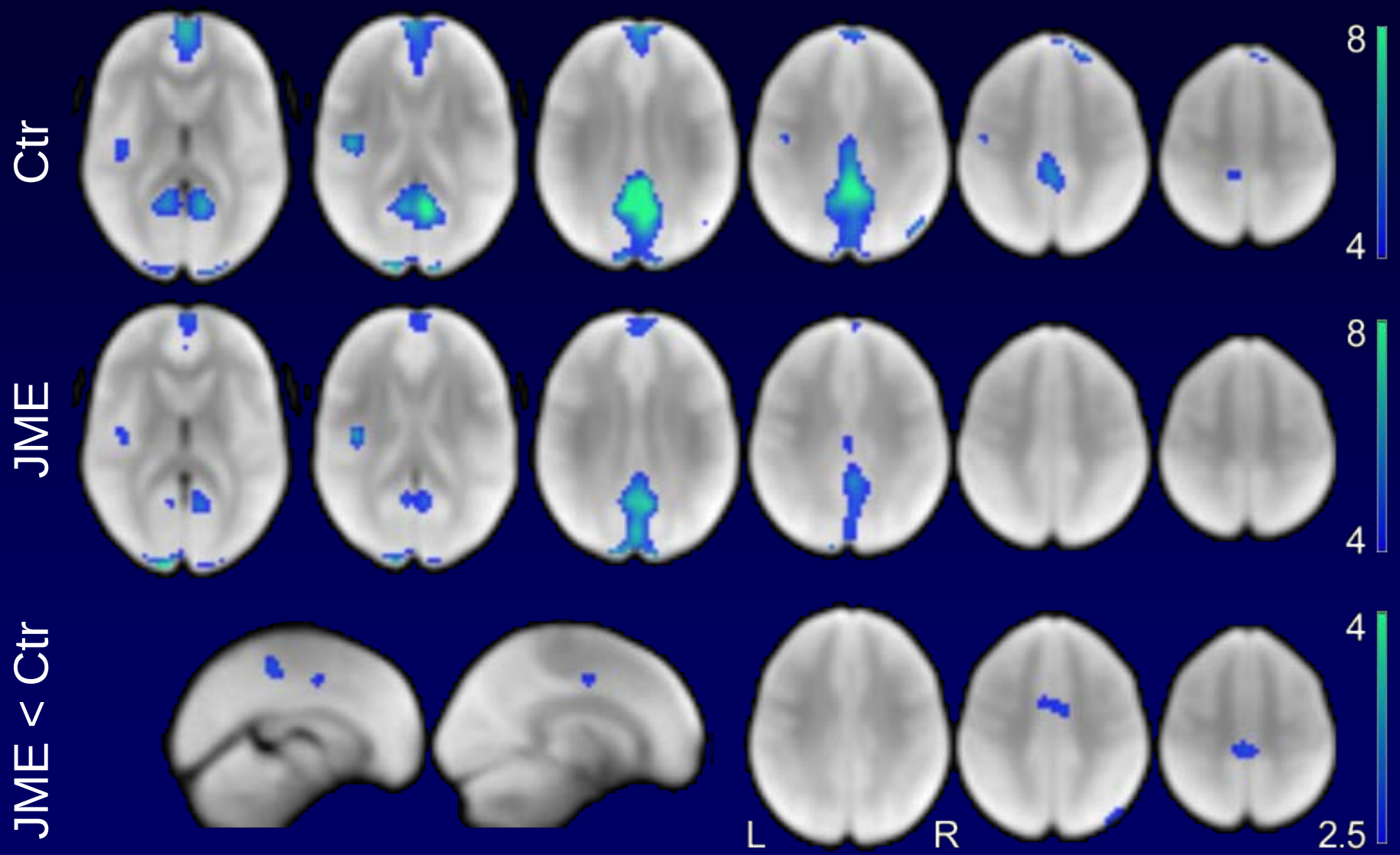
=> Shows default mode network





Vollmar et al, *Brain 2011*

Resting state

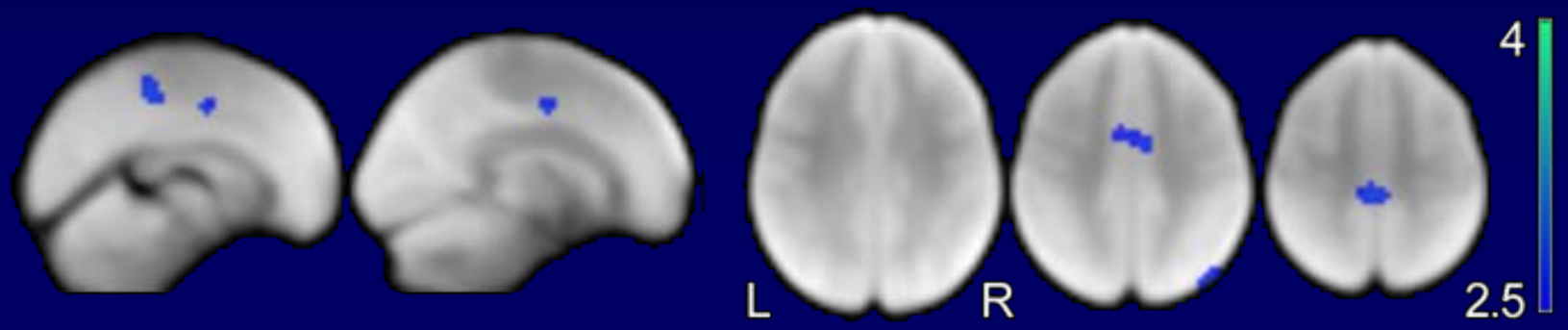


Vollmar et al, *Brain 2011*

Resting state

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

JME < Ctr

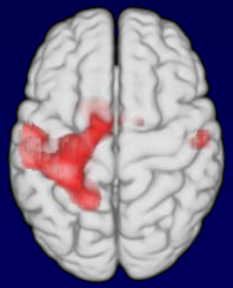


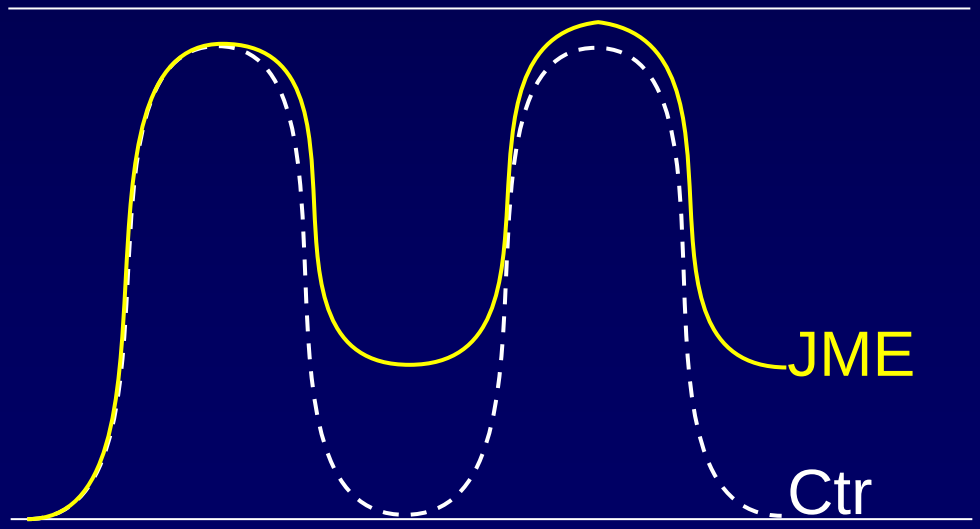
Vollmar et al, *Brain 2011*

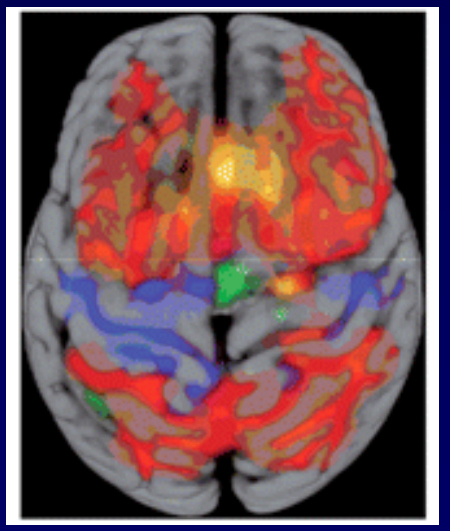
Resting state

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

JME: dysfunction of switching between systems



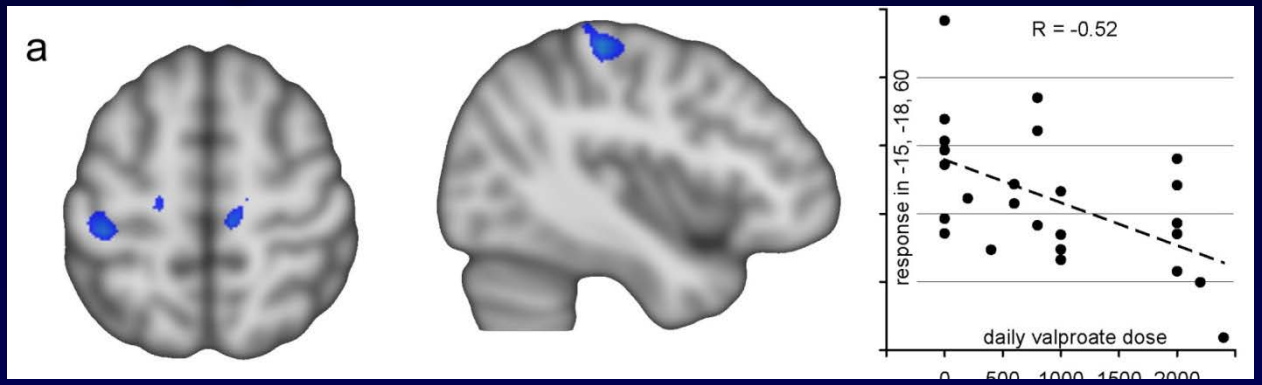




Vollmar et al, *Brain 2011*

Predict drug response
Effect of VPA in JME

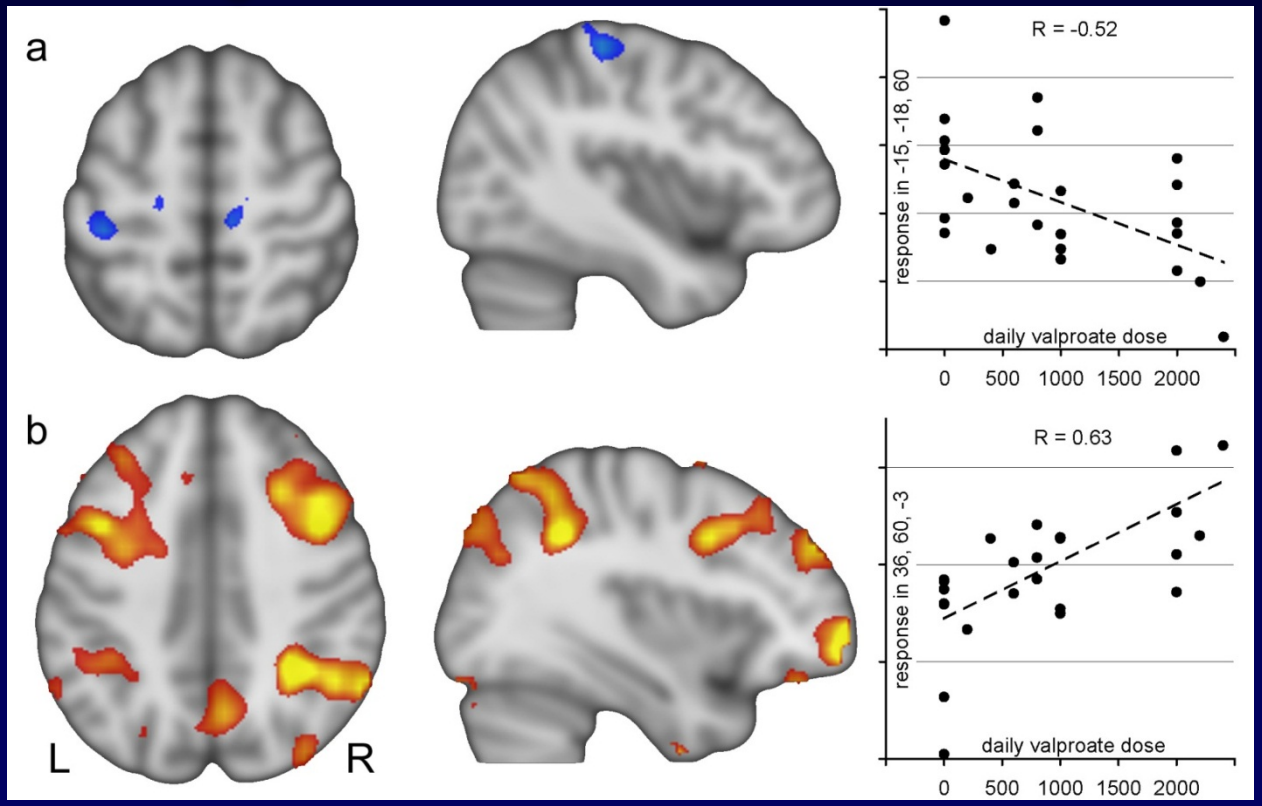
negative correlation with dose



Vollmar C *et al*. Brain 2011

Predict drug response
Effect of VPA in JME

negative correlation with dose

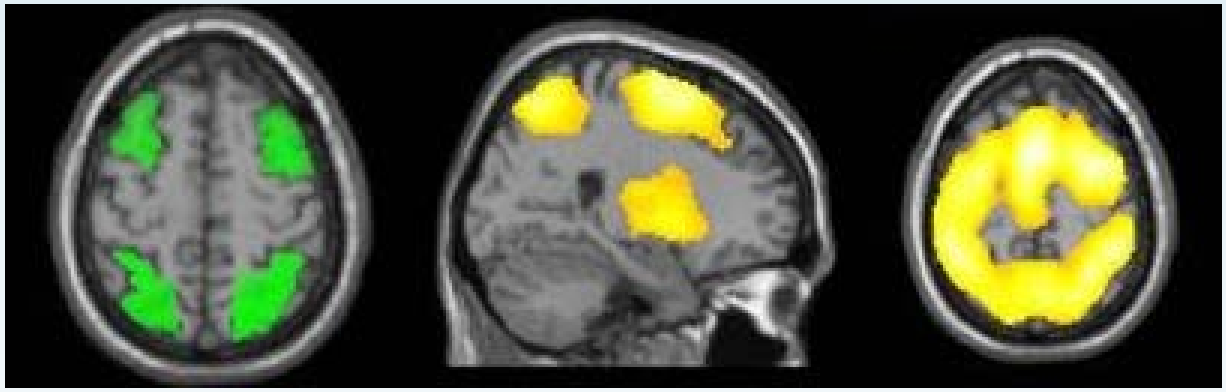


positive correlation with dose

Vollmar C *et al*. Brain 2011

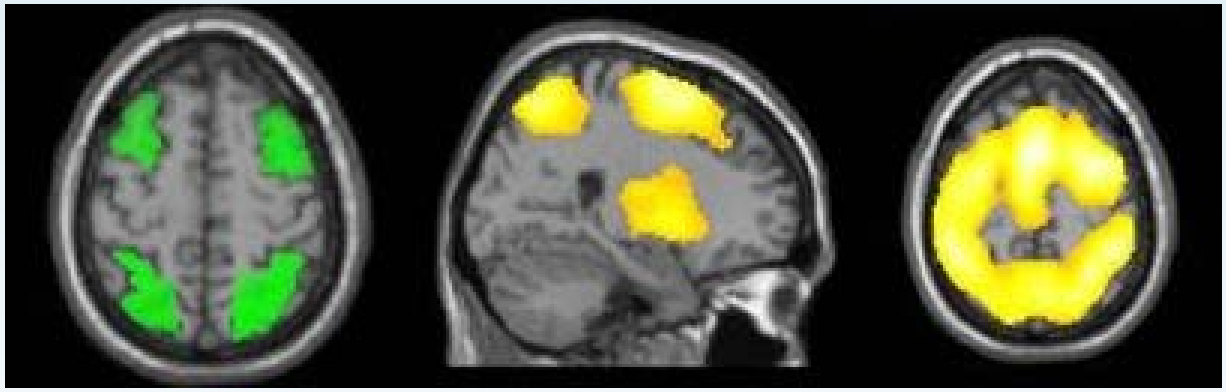
Functionally segregated WM networks

Task positive network: fronto-thalamo-parietal network

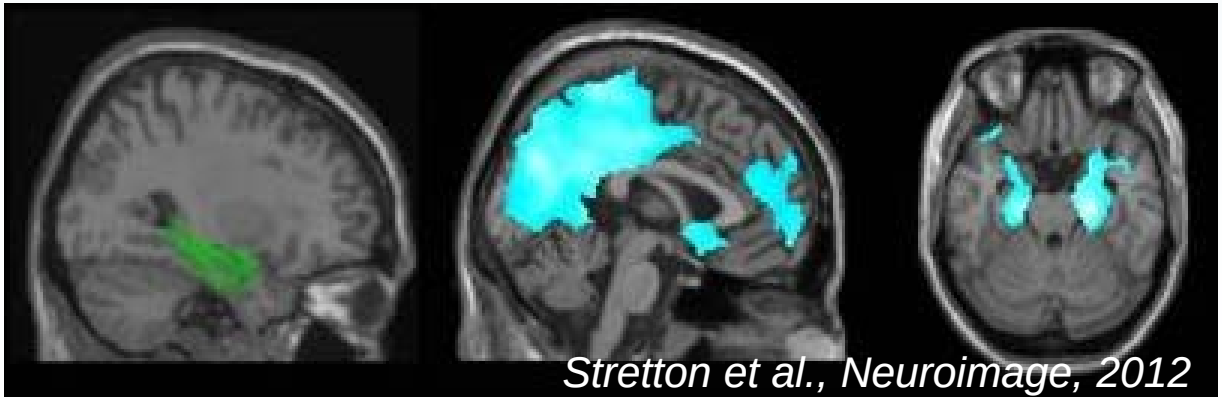


Functionally segregated WM networks

Task positive network: fronto-thalamo-parietal network



Task negative network: DMN and bilateral hippocampi

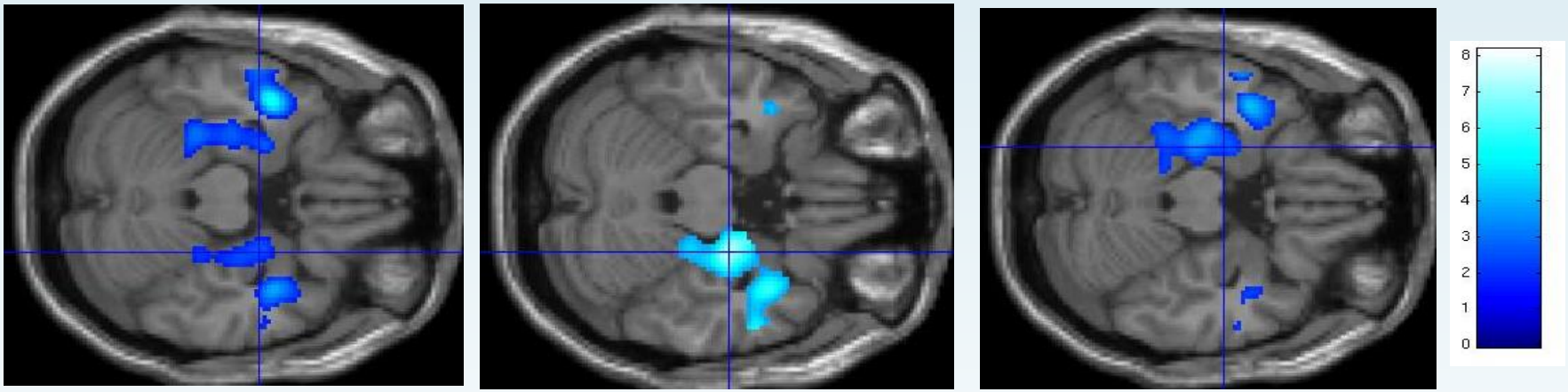


Stretton et al., Neuroimage, 2012

Working memory in TLE

Progressive Deactivation Group Maps

Controls LHS RHS



Controls: deactivate hippocampus bilaterally

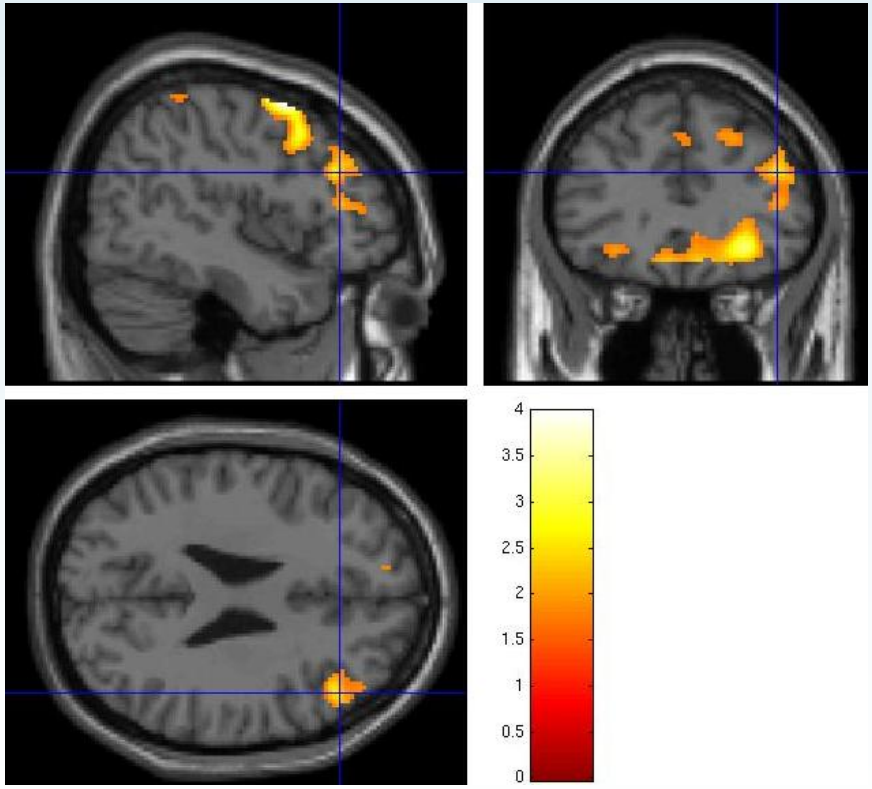
Patients: deactivate only contralateral hippocampus

Stretton et al., Neuroimage Clinical 2012

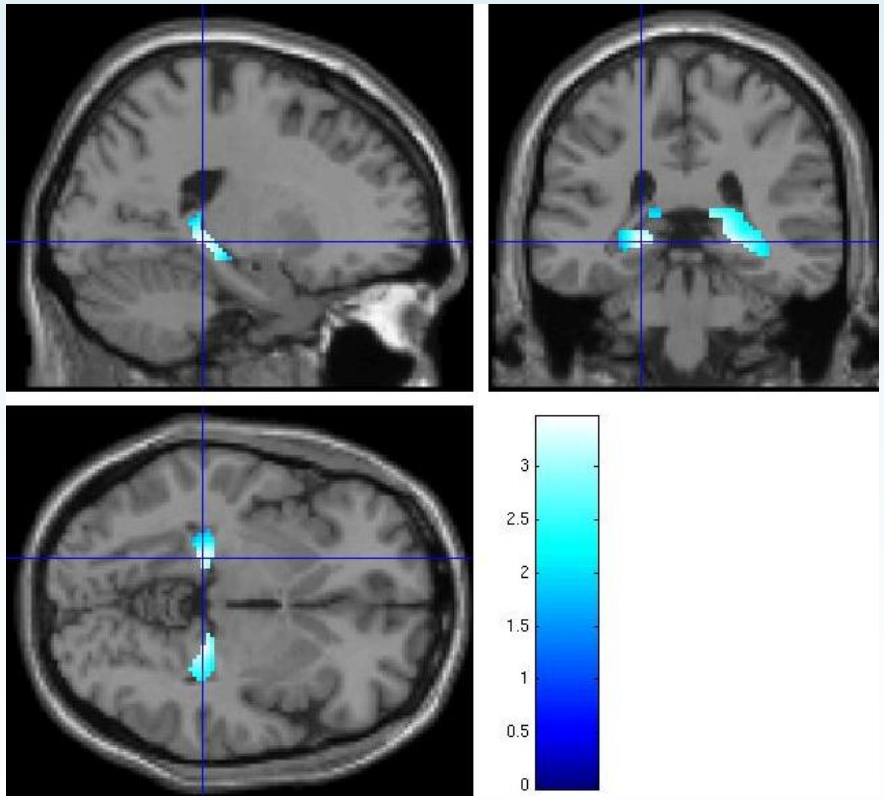
Working memory in TLE

Better performance correlates with

greater activation:
right middle frontal gyrus

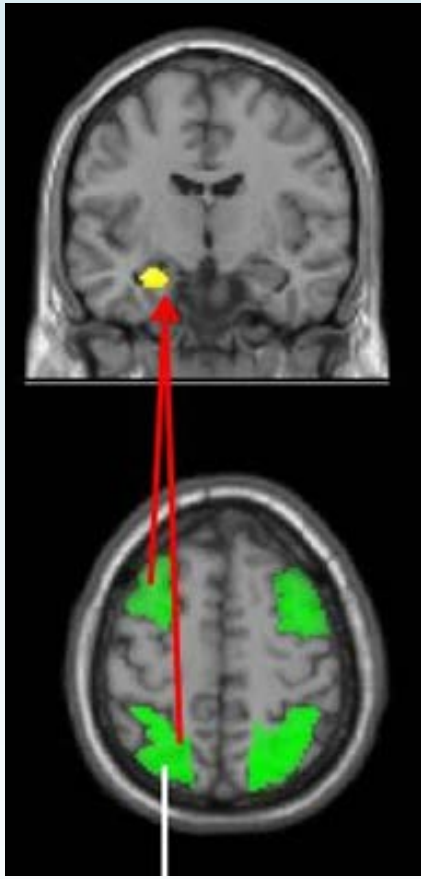


greater de-activation:
posterior hippocampi



Stretton et al., Neuroimage Clinical 2012

Disrupted segregation of networks



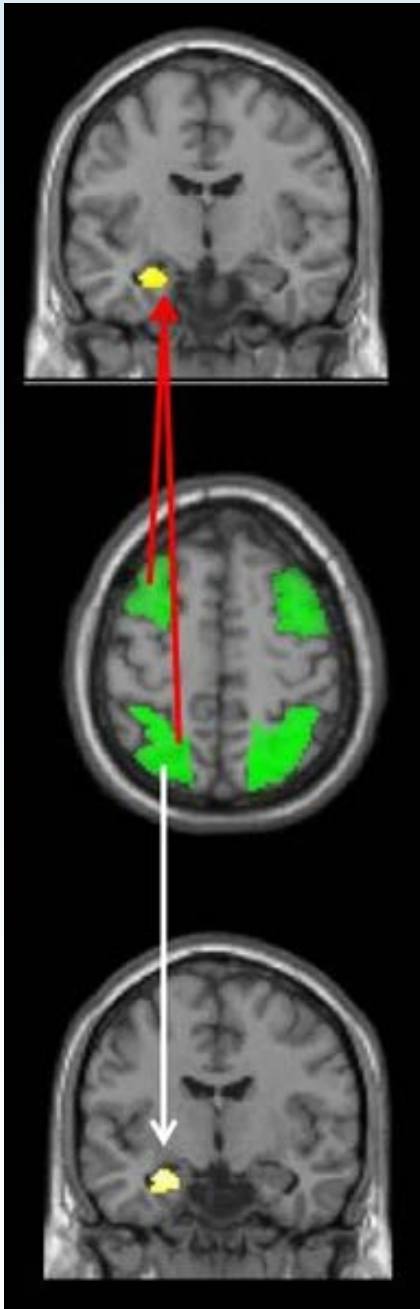
Increased coactivation (red arrow) of left hippocampus with left front-parietal

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

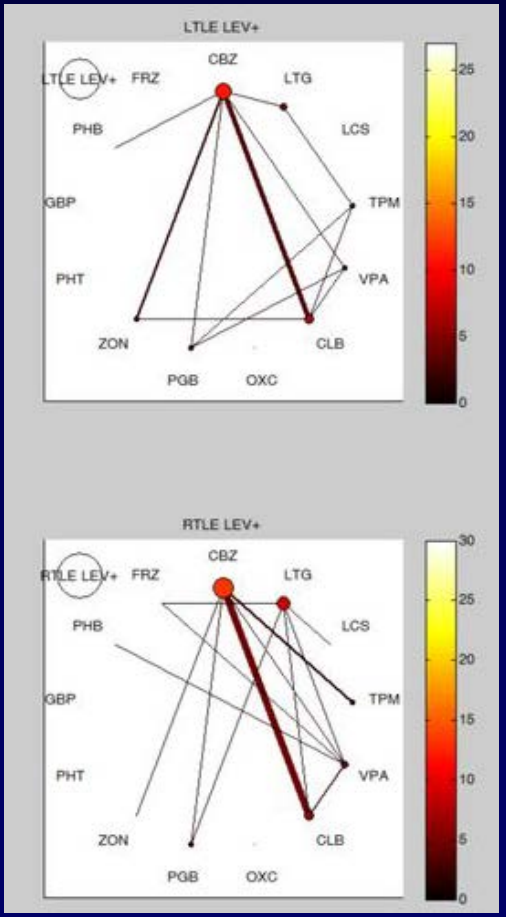
JME → altered (hyper-)connectivity in motor cortex, SMA – specific to JME

Focal epilepsy disrupts connectivity of cognitive networks

Abnormalities in connectivity of cognitive networks may explain cognitive deficits extending beyond seizure focus

Predict drug response
Effect of LEV in TLE

- 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)

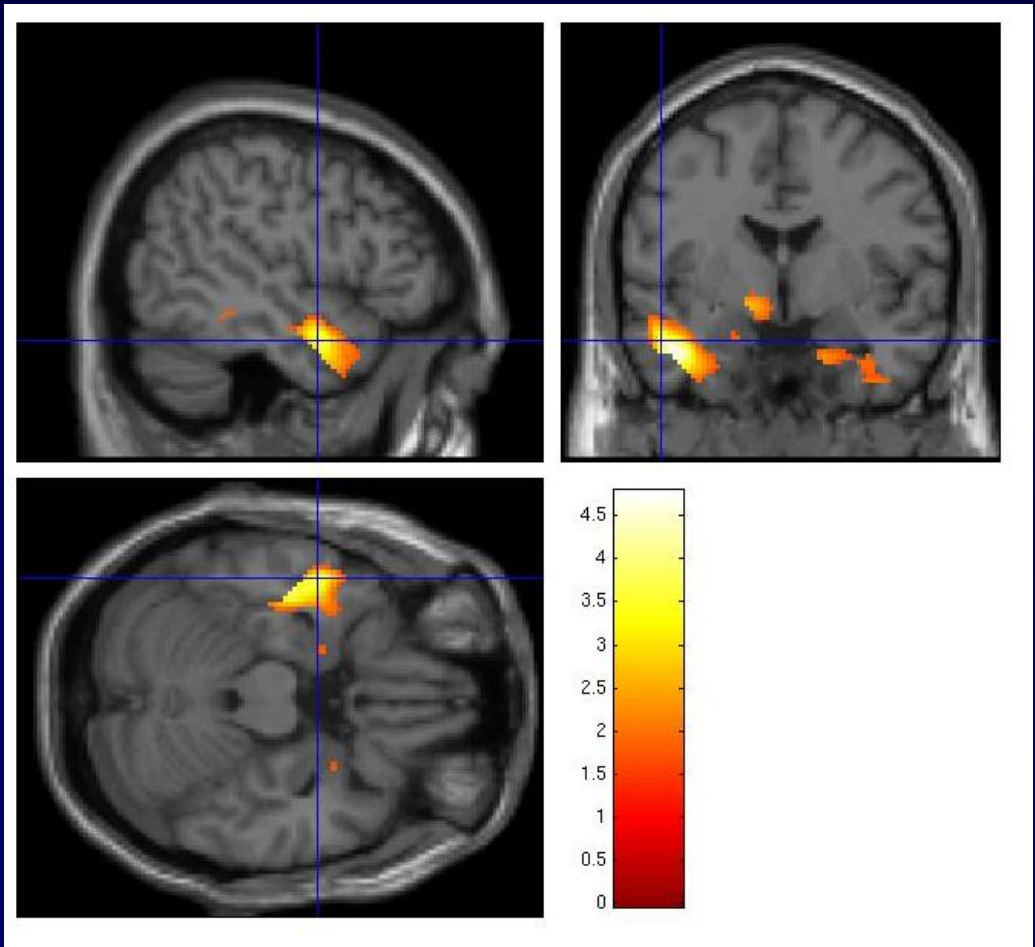


Wandschneider et al,
Neurology 2014

Predict drug response
Effect of LEV in TLE

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

  greater suppression of
  LEFT ant temporal lobe



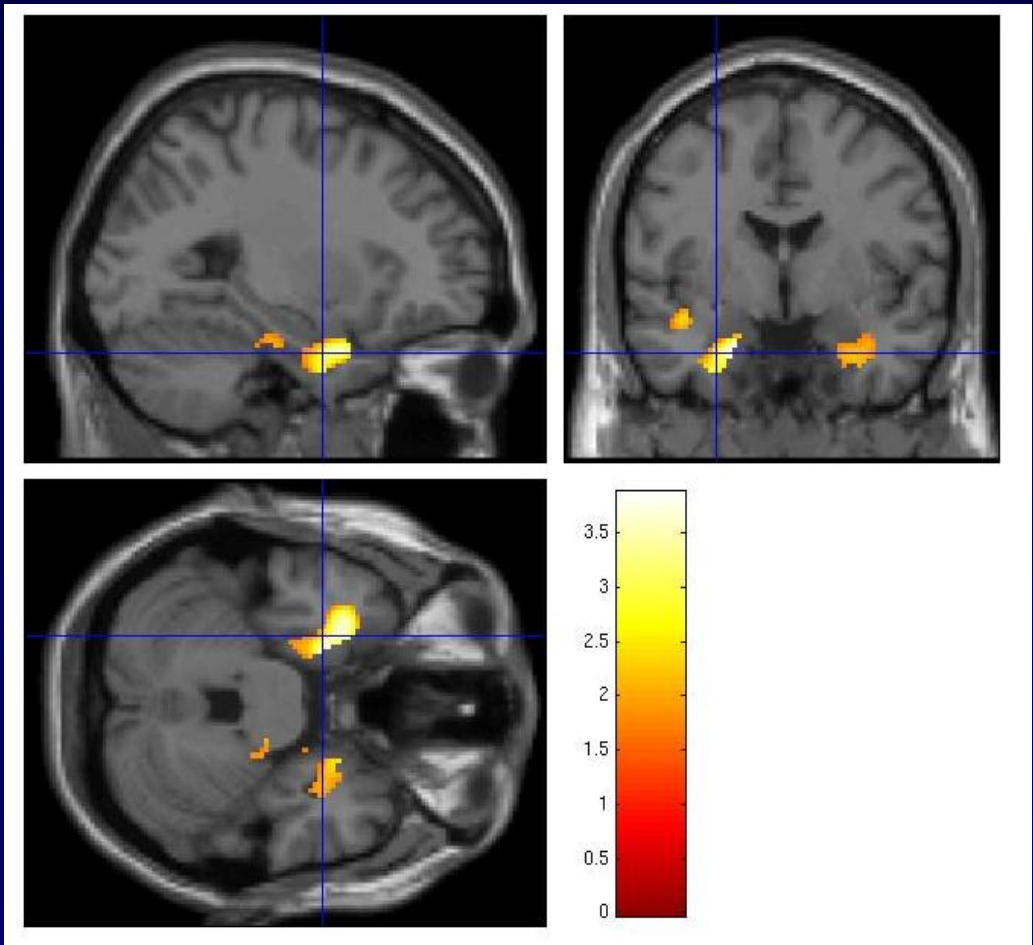
Wandschneider et al,
Neurology 2014

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



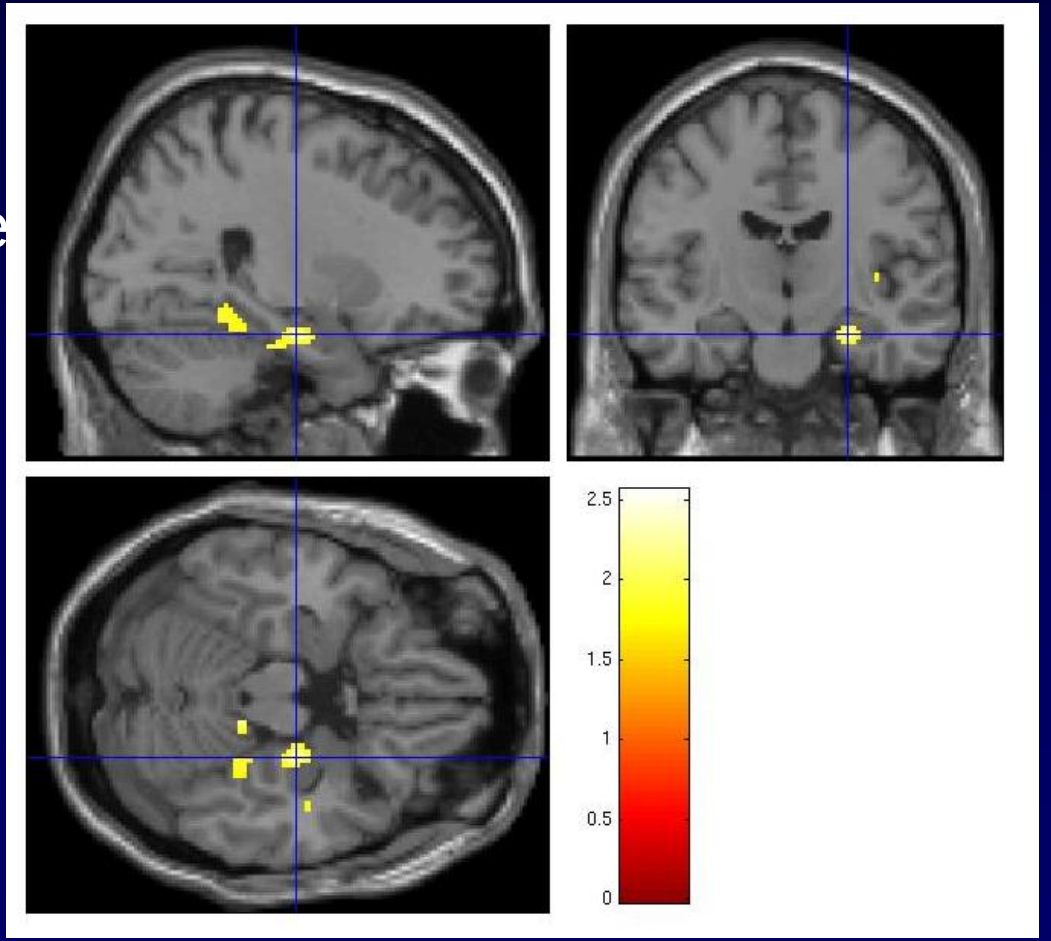
Wandschneider et al,
Neurology 2014

Predict drug response
Effect of LEV in TLE

- 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

Biomarker of epileptogenesis

- Epilepsy is not one disease

  BUT **similar generic mechanisms prevail**

Biomarker of epileptogenesis

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  BUT **similar generic mechanisms prevail**

- Humans are different from rodents

  BUT **methodologies are transferable**

-

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  BUT **methodologies are transferable**

- 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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Wellcome Trust
Medical Research Council
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Epilepsy Research UK