

THE DEVIL IS IN THE DETAILS

– NORMAL MRI IN TLE?

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TEMPORAL LOBE EPILEPSY (TLE)

TLE is the most common drug-resistant epilepsy in adults

surgery most effective treatment

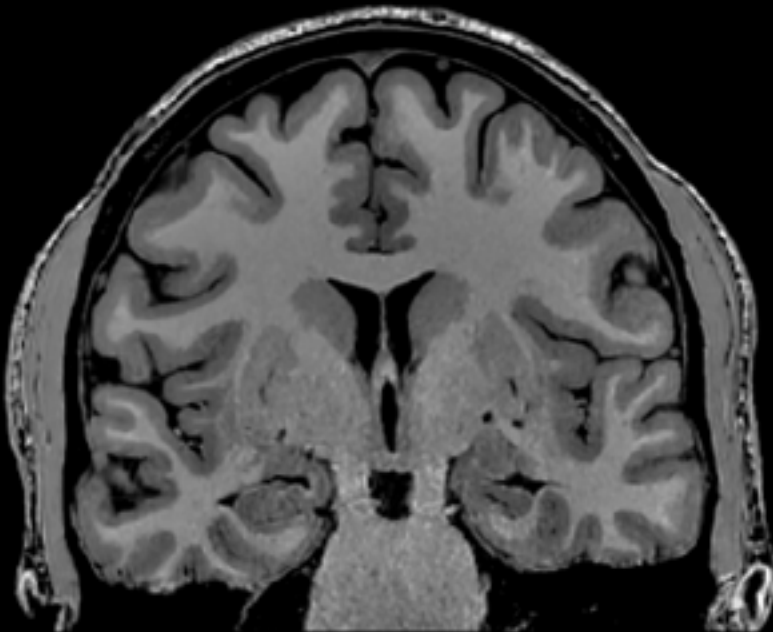
pathological analysis of resected specimen often reveals HS/MTS

MRI in TLE

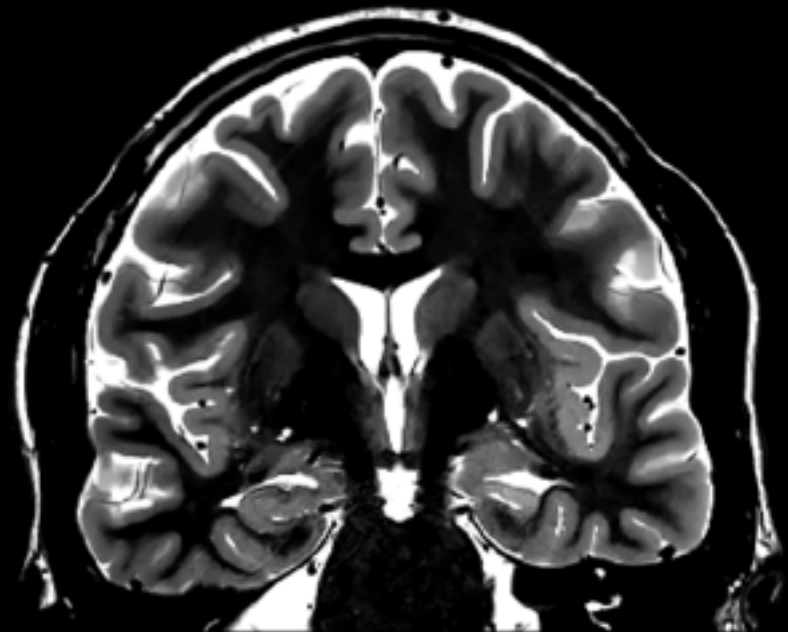
MRI has revolutionized the management of TLE

in vivo detection of HS/MTS in at least 70%

lesion identification and focus lateralization key for successful surgery



T1-weighted



T2-weighted

TLE with normal MRI

yet, a subgroup of cases are considered to have normal MRI

these patients represent important clinical challenge

- more frequently implanted
 - surgery delayed
 - generally worse outcome
- however: do these patients really have normal MRI?

Previous work 1

Pathology shows abnormalities in TLE with normal MRI

Jackson (1994) Neurology

Hippocampal sclerosis without detectable hippocampal atrophy

G.D. Jackson, FRACP; R.I. Kuzniecky, MD; and G.D. Cascino, MD

Article abstract—Six patients from three centers had MRI and pathologic evidence of hippocampal sclerosis but no detectable hippocampal atrophy. Loss of normal internal structure and T₁- and T₂-weighted signal abnormalities allowed the MRI diagnosis of unilateral hippocampal sclerosis when hippocampal volume measurements were normal and symmetric. Although accurate hippocampal volume measurements will determine the most severely affected side in most cases, volume measurements or atrophy alone will not always detect all MRI-visible pathology. Additional detailed MRI assessment is required before structural abnormality of the hippocampus is excluded on the basis of volume measurements.

NEUROLOGY 1994;44:42-46

Hippocampal sclerosis is the most common underlying pathology for which temporal lobectomy is performed in cases of intractable temporal lobe epilepsy (TLE).¹ Quantitative and qualitative MRI can detect this hippocampal pathology. The diagnosis can be made with high sensitivity and specificity using visual analysis of optimized images,^{2,4} T₂ relaxation time measurements,³ and volumetric studies of the hippocampus.⁴⁻¹⁰ Hippocampal atrophy is usually considered a characteristic feature of hippocampal sclerosis.

Volumetric evaluation of the hippocampus is an effective means of assessing hippocampal asymmetry and, to a lesser extent, hippocampal atrophy in patients with intractable partial seizures, particularly those being considered for temporal lobe surgery. This objective measurement has resolved

much of the uncertainty about the significance of small degrees of hippocampal asymmetry as evaluated subjectively. The success of hippocampal volume measurement and the increasing reliance on it in the preoperative evaluation of potential surgical candidates raise the following questions: (1) What is the role of other techniques for assessment of hippocampal abnormality? (2) Is atrophy of the hippocampus the only feature that is of clinical relevance? (3) Do all cases of hippocampal sclerosis have detectable medial temporal atrophy?

We report six patients with lateralized intractable TLE in whom both visual and quantitative analysis revealed no hippocampal atrophy but in whom the pathologically verified diagnosis of hippocampal sclerosis was made on the basis of other MRI criteria.

Bell (2009) Epilepsia

Epilepsia, Vol. 50, No. 2, 2009, pp. 2009-2016.
doi:10.1111/j.1528-1167.2009.02079.x

FULL-LENGTH ORIGINAL RESEARCH

Epilepsy surgery outcomes in temporal lobe epilepsy with a normal MRI

*Michael L. Bell, *Satish Rao, *Elson L. So, †Max Trenerry, *Noojan Kazemi, *S. Matt Stead, *Gregory Cascino, ‡Richard Marsh, †Fredric B. Meyer, ‡Robert E. Watson, ‡Caterina Giannini, and *Gregory A. Worrell

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SUMMARY

Purpose: To determine the long-term efficacy of anterior temporal lobectomy for medically refractory temporal lobe epilepsy in patients with nonlesional magnetic resonance imaging (MRI).

Methods: We identified a retrospective cohort of 44 patients with a nonlesional modern “seizure protocol” MRI who underwent anterior temporal lobectomy for treatment of medically refractory partial epilepsy. Postoperative seizure freedom was determined by Kaplan-Meier survival analysis. Noninvasive preoperative diagnostic factors potentially associated with excellent surgical outcome were examined by univariate analysis in the 40 patients with follow-up of >1 year.

Results: Engel class I outcomes (free of disabling seizures) were observed in 60% (24 of 40) patients.

Preoperative factors associated with Engel class I outcome were: (1) absence of contralateral or extratemporal interictal epileptiform discharges, (2) subtraction ictal single photon emission computed tomography (SPECT) coregistered to MRI (SISCOM) abnormality localized to the resection site, and (3) subtle nonspecific MRI findings in the mesial temporal lobe concordant to the resection.

Discussion: In carefully selected patients with temporal lobe epilepsy and a nonlesional MRI, anterior temporal lobectomy can often render patients free of disabling seizures. This favorable rate of surgical success is likely due to the detection of concordant abnormalities that indicate unilateral temporal lobe epilepsy in patients with nonlesional MRI.

KEY WORDS: Partial seizures, Epilepsy surgery, Temporal lobe, Nonlesional-MRI.

Previous work 2

multimodal quantitative MRI increases sensitivity to detect MTS

Kuzniecky et al (1997) Neurology

Multimodality MRI in mesial temporal sclerosis:

Relative sensitivity and specificity

R.I. Kuzniecky, MD; E. Bilir, MD; F. Gilliam, MD; E. Faught, MD; C. Palmer, MD; R. Morawetz, MD; and G. Jackson, FRCP(A)

Article abstract—Our objectives were to determine the relative sensitivity and specificity of different MRI sequences and analysis techniques for the detection of mesial temporal sclerosis (MTS). Mesial temporal sclerosis is the most common pathologic finding in patients undergoing temporal lobe epilepsy surgery. Magnetic resonance imaging is the most reliable preoperative imaging technique for the detection of MTS. We analyzed the abnormalities in preoperative MRIs of 44 consecutive patients who had undergone temporal lobectomy and who had pathologic confirmation of MTS. Techniques included inversion recovery (IR); T1-weighted, volume-acquired images; hippocampal T2 relaxometry (HT₂); volumetric assessment; and visual analysis. Sensitivity was 86% with IR, 90% with T1-weighted qualitative visual analysis, and 97% with quantitative volumetry. Pathologic prolongation of HT₂ (>2 SD of normal) was present in 79%. Analysis of variance showed statistically significant differences in sensitivity between HT₂, volumetric measurements ($p < 0.01$), and qualitative visual atrophy ($p < 0.05$). Concordance between all MRI modalities was 68%. Inversion recovery and qualitative analysis lateralized the side of surgery in 93%. The combination of IR and T1-weighted images correctly identify MTS in most patients. Hippocampal volumetry provided localization in an additional small number of patients.

NEUROLOGY 1997;49:774-778

Coan et al (2014) AJNR

ORIGINAL RESEARCH
BRAIN

3T MRI Quantification of Hippocampal Volume and Signal in Mesial Temporal Lobe Epilepsy Improves Detection of Hippocampal Sclerosis

A.C. Coan, B. Kibota, F.F.G. Bengo, B.M. Campos, and F. Cendes

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ABSTRACT

BACKGROUND AND PURPOSE: In mesial temporal lobe epilepsy, MR imaging quantification of hippocampal volume and T2 signal can improve the sensitivity for detecting hippocampal sclerosis. However, the current contributions of these analyses for the diagnosis of hippocampal sclerosis in 3T MRI are not clear. Our aim was to compare visual analysis, volumetry, and signal quantification of the hippocampus for detecting hippocampal sclerosis in 3T MRI.

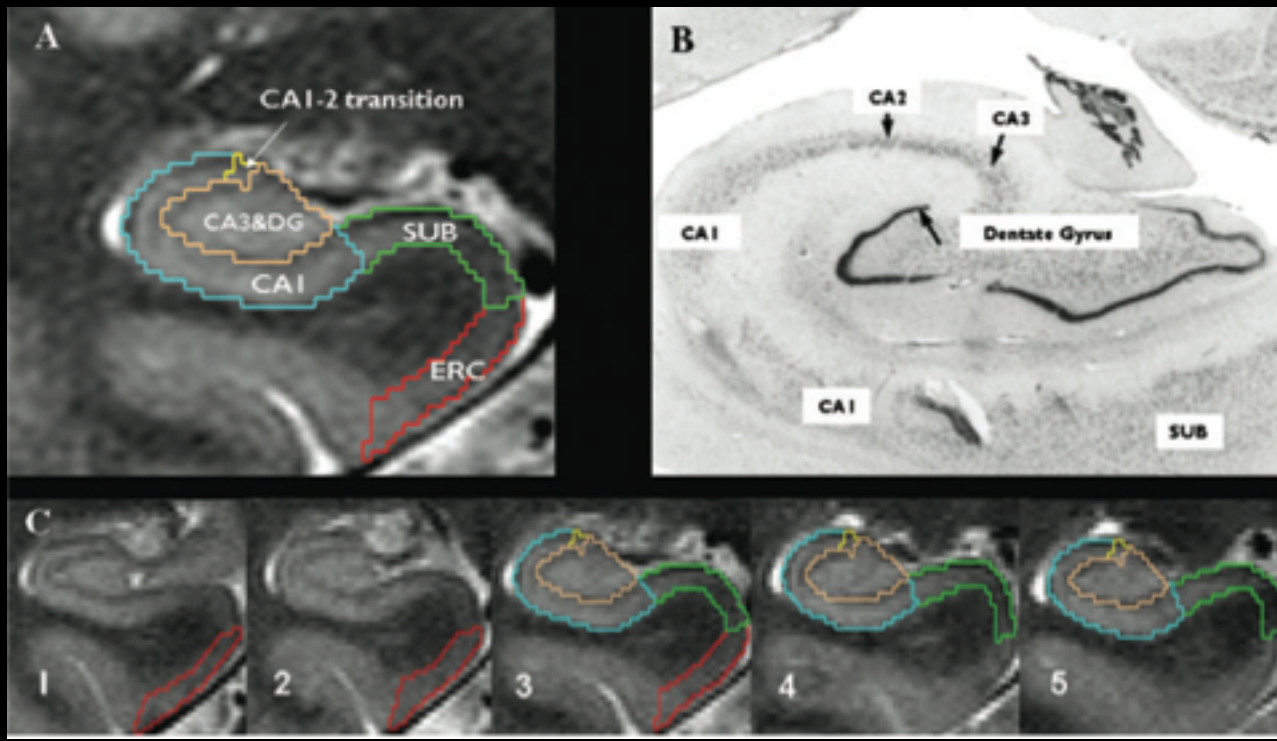
MATERIALS AND METHODS: Two hundred three patients with mesial temporal lobe epilepsy defined by clinical and electroencephalogram criteria had 3T MRI visually analyzed by imaging epilepsy experts. As a second step, we performed automatic quantification of hippocampal volumes with FreeSurfer and T2 relaxometry with an in-house software. MRI of 79 healthy controls was used for comparison.

RESULTS: Visual analysis classified 126 patients (62%) as having signs of hippocampal sclerosis and 78 (38%) as having normal MRI findings. Automatic volumetry detected atrophy in 19 (9%) patients with visually detected hippocampal sclerosis and in 10 (13%) with visually normal MRI imaging findings. Relaxometry analysis detected hyperintense T2 signal in 101 (82%) patients with visually detected hippocampal

Previous work 3

higher field strength analysis allows for more targeted assessment

Mueller et al. (2009) Epilepsia



HIPPOCAMPAL MRI SURFACE PROFILING IN TLE

MULTI-CONTRAST SUBFIELD ANALYSES

Kim, Bernhardt, Kulaga-Yoskovitz, Caldairou, Bernasconi, Bernasconi (2014)



PURPOSE

evaluate MRI normalcy in TLE cohort with normal MRI

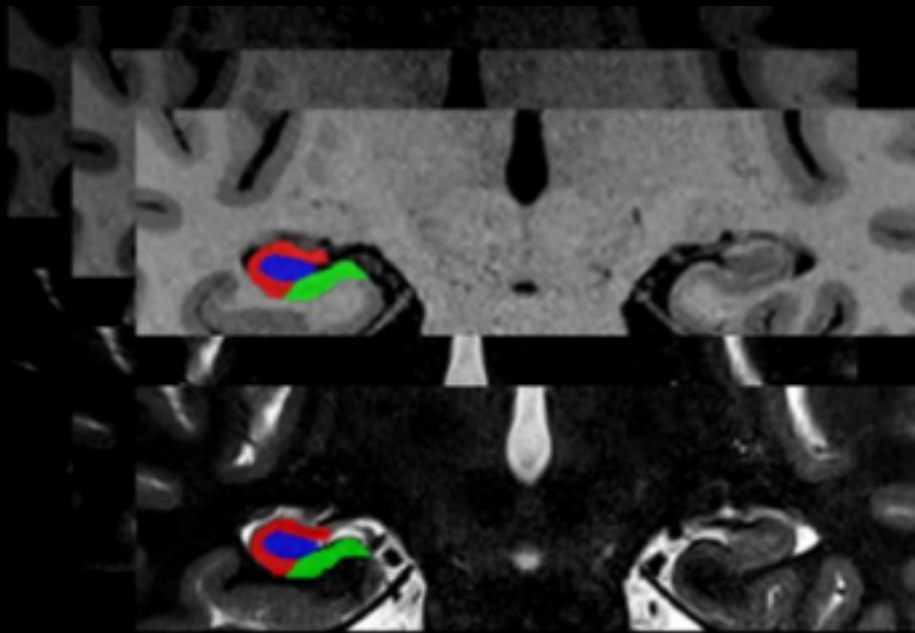
15 consecutive patients with normal hippocampal volumetry

12 underwent surgery, 10 Engel 1, HS/gliosis in all resected specimens

Multi-contrast 3T MRI + subfield surface analysis

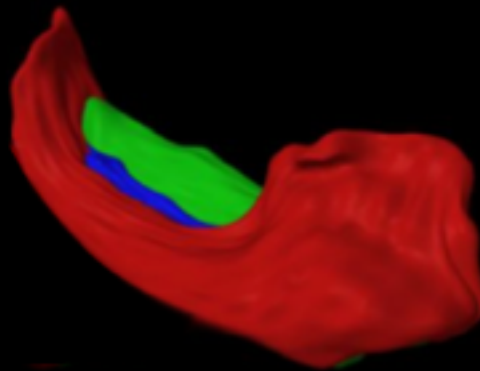
- submillimetric T1-weighted and T2-weighted MRI
- Manual subfield segmentations
- extraction of medial surfaces
- group-level analysis of T2 and volume
- automated focus lateralization in individual patients

METHODS: SUBFIELD MEDIAL SHEET GENERATION



T1-weighted MRIs

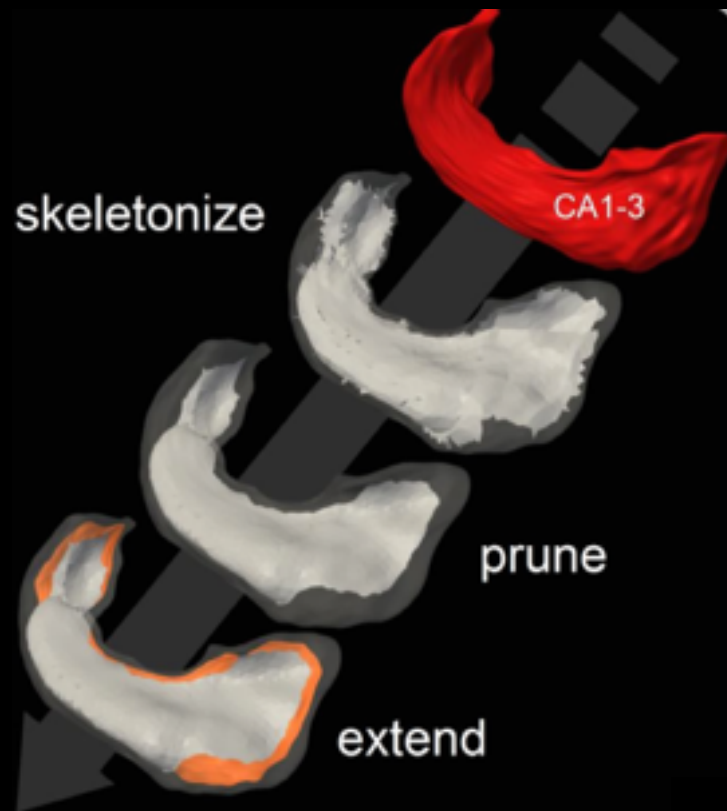
T2-weighted MRIs



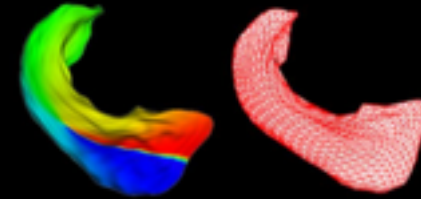
Subfield labels

- Subiculum
- CA4-DG
- CA1-3

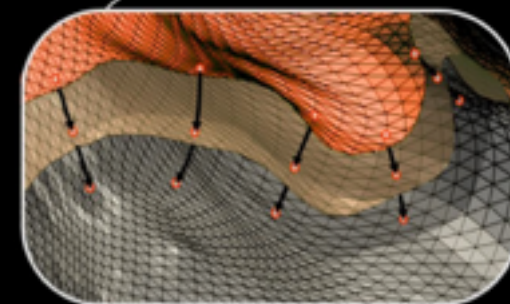
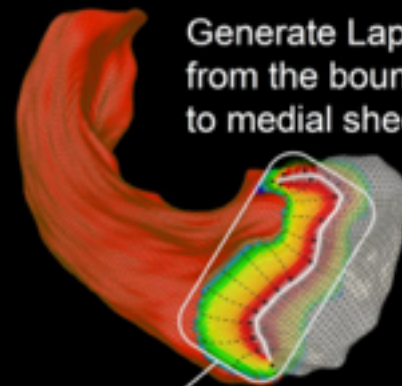
METHODS: SUBFIELD MEDIAL SHEET GENERATION



Triangulate boundary using SPHARM-PDM

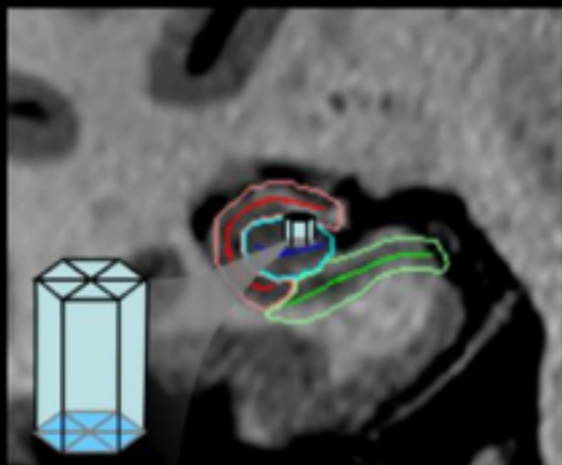


Generate Laplacian field from the boundary to medial sheet M

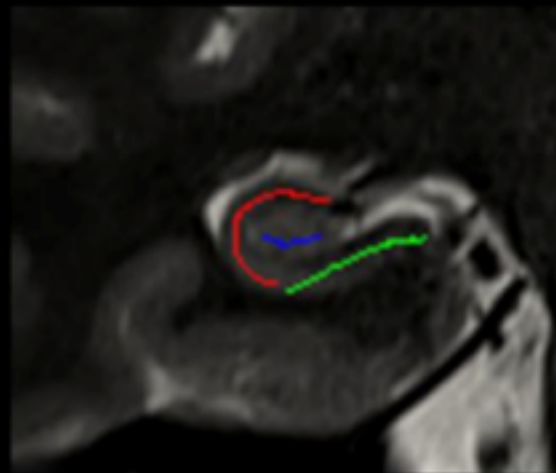


Transpose boundary's mesh to M along Laplacian field

SHEET FEATURES



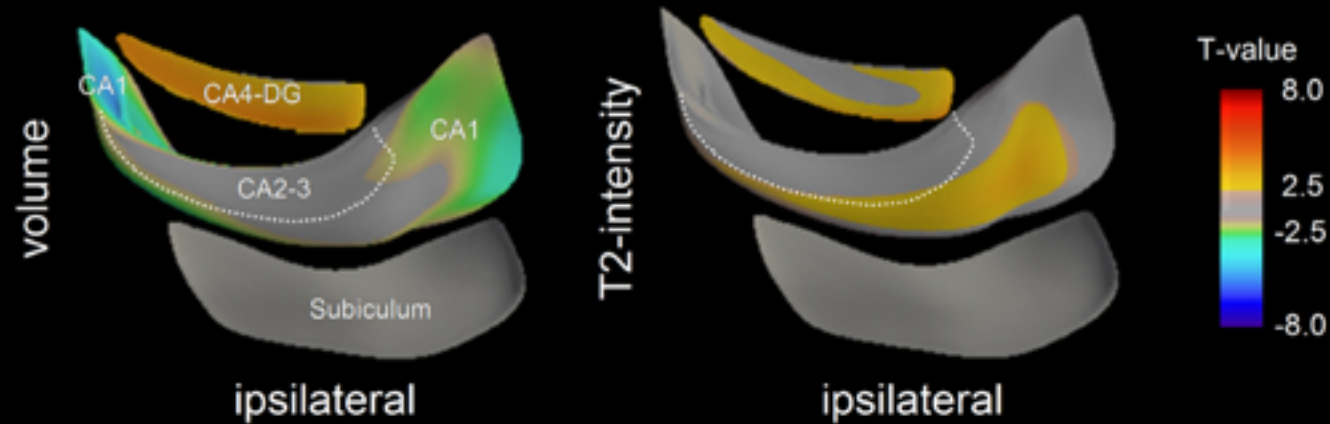
Columnar volume



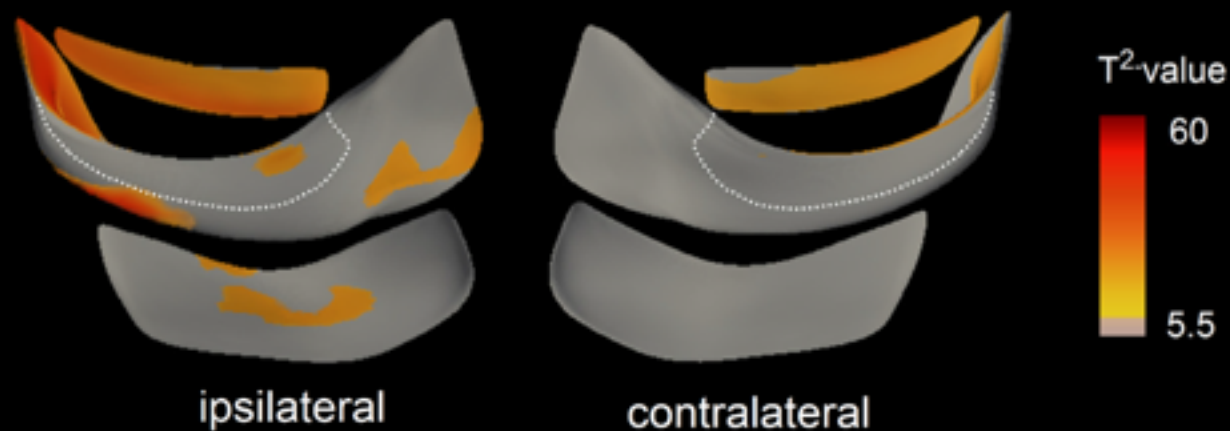
Relative intensity

GROUP-LEVEL PATTERNS OF ANOMALIES

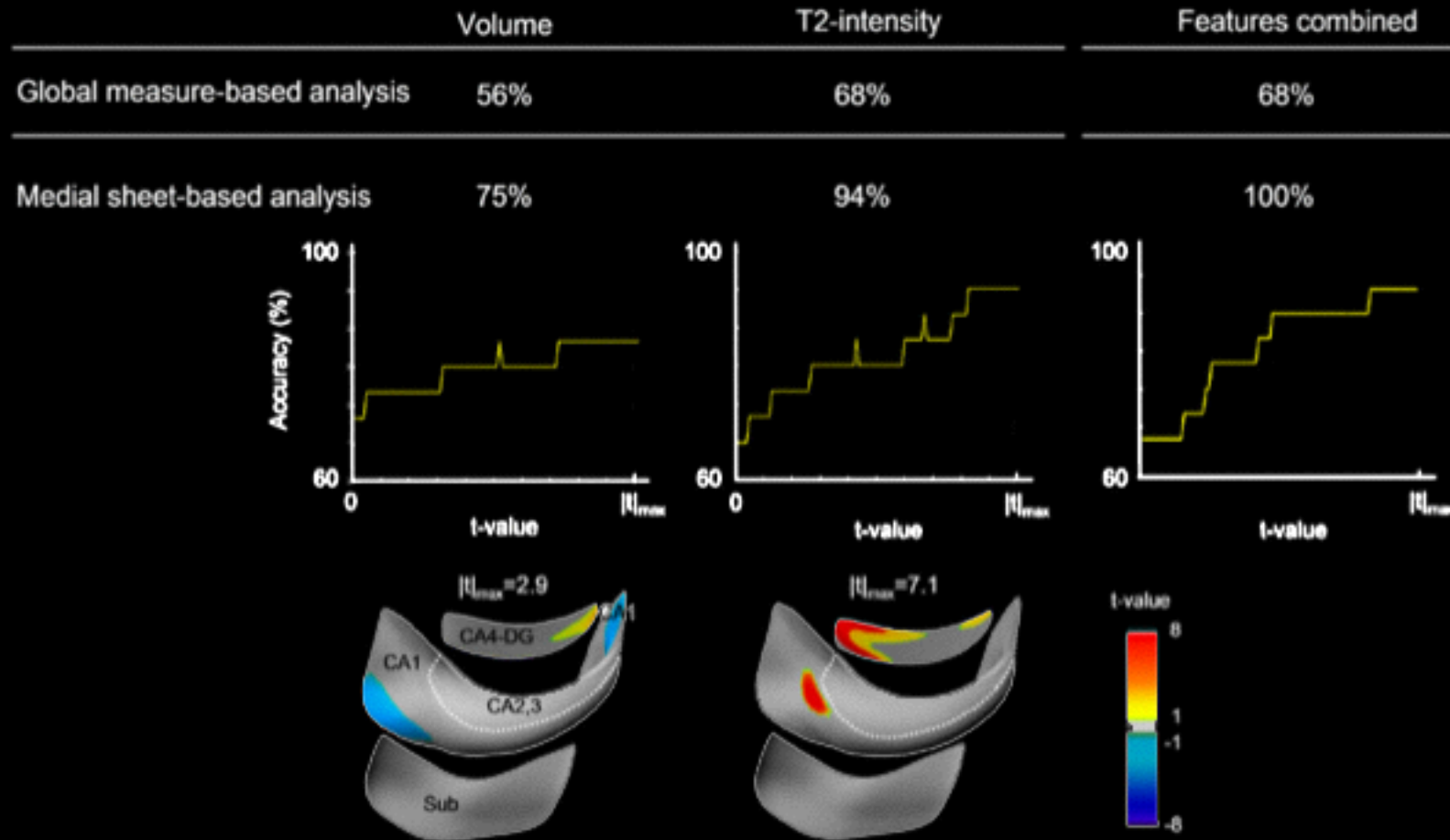
A. Univariate analysis



B. Multivariate analysis



FOCUS LATERALIZATION



INTERIM SUMMARY

Targeted assessment on hippocampus in patients with '*normal*' MRI

multi-contrast analysis unveils

- CA1 volume loss and CA4-DG volume increases
- T2 increases in same subfields, yet no 1:1 overlap

Findings clinically validated:

100% accuracy in automated seizure focus lateralization

MESIOTEMPORAL PATHOLOGY IN TLE

Pre-operative workup in TLE focusses on hippocampus, and patients dichotomized based on hippocampal findings

- Detection of atrophy permits sensitive focus lateralization
- Preoperative atrophy relates to post-surgical seizure freedom

Despite its utility in lateralization, rather limited prognostic value for outcome in individual patients

- TLE-HA may have residual seizures
- TLE-NV may have excellent outcome

MESIOTEMPORAL PATHOLOGY IN TLE

TLE-related alterations not restricted to the hippocampus!

Changes in adjacent mesiotemporal regions found in many patients

Motivates more comprehensive assessments of mesiotemporal structure

Bernasconi et al. (2001) Epilepsy

Entorhinal cortex atrophy in epilepsy patients exhibiting normal hippocampal volumes

N. Bernasconi, MD; A. Bernasconi, MD; Z. Caramanos, MA; F. Dubeau, MD, FRCP(C); J. Richardson, MD, FRCP(C); F. Andermann, MD, FRCP(C); and D.L. Arnold, MD, FRCP(C)

Article abstract—Objective: To determine whether MRI volumetric measurement of the entorhinal cortex could detect structural damage and lateralize the seizure focus in patients with temporal lobe epilepsy in whom no measurable hippocampal abnormalities were found. **Background:** A reduction in the volume of the entorhinal cortex ipsilateral to the seizure focus in patients with intractable temporal lobe epilepsy and hippocampal atrophy was recently shown. **Methods:** MRI volumetric analysis of the entorhinal cortex was performed using a T1-weighted three-dimensional gradient echo sequence in 24 control subjects and 22 patients with temporal lobe epilepsy and normal hippocampal volumes. Thirteen patients underwent surgery, with a mean postoperative follow-up of 36 months. **Results:** Group analysis (multivariate analysis of variance) showed a reduction in the volume of the entorhinal cortex ipsilateral to the seizure focus in patients with left ($p < 0.0001$) and right temporal lobe epilepsy ($p < 0.0001$). Lateralization of the seizure focus could be done in 14 of 22 patients (64%) based on entorhinal cortex volumetry. **Conclusion:** Entorhinal cortex atrophy ipsilateral to the seizure focus supports the presence of structural damage in the mesial temporal lobe in patients with temporal lobe epilepsy and normal hippocampal volumes and emphasizes the participation of the entorhinal cortex in the pathogenesis of this disorder.

NEUROLOGY 2001;56:1335–1339

Mitsueda-Ono et al. (2011) JNNP

Research paper

Amygdalar enlargement in patients with temporal lobe epilepsy

Takahiro Mitsueda-Ono,¹ Akio Ikeda,¹ Morito Inouchi,¹ Shigetoshi Takaya,² Riki Matsumoto,¹ Takashi Hasekawa,³ Nobukatsu Sawamoto,² Nobuhiro Mikuni,⁴ Hidenao Fukuyama,² Ryosuke Takahashi¹

ABSTRACT

Objective: The purpose of the study was to clarify the significance of amygdalar enlargement (AE) in patients with temporal lobe epilepsy (TLE) detected by MRI.

Methods: 11 TLE patients (eight men, mean age 45.3 (SD 18.2) years) with AE treated at Kyoto University Hospital were studied. Clinical history, ictal semiology, EEG, fluorodeoxyglucose–positron emission tomography (FDG-PET), interictal single photon emission CT (SPECT) and MRI were investigated. Amygdalar volume measured by 3 T MRI and its laterality index (LI) were compared with the three other groups: normal controls, patients with partial epilepsy of non-TLE and mesial TLE with hippocampal sclerosis (HS).

Results: Average age of onset was 39.8 years (SD 19.5). Eight had complex partial seizures and three had generalized seizures. Epileptiform discharges were found in the temporal area ipsilateral to the AE by EEG.

Accounting for laterality of the amygdala,⁵ AE could be an epileptogenic focus. However, a role for the amygdala as a focus of epilepsy has not been explicitly established, unlike hippocampal epilepsy.

The main purpose of this study was to clarify the clinical significance of AE in patients with TLE detected by MRI. The occurrences of AE were compared with other partial epilepsies such as non-TLE and typical MTLE with HS as well as with normal controls. One of the patients (Patient 2) was shown previously as a case report.⁶

METHODS

Subjects

Subjects were 11 MTLE patients with AE (mean age 45.3 (SD 18.2) years) treated at Kyoto University Hospital from 2003 to 2007 (AE group). MTLE with AE was diagnosed by the presence of contralateral

Downloaded from <http://jnnp.bmj.com/> on November 27, 2014 - Published by group.bmj.com

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MESIOTEMPORAL MRI PATTERN LEARNING

PATIENT CLASSIFICATION AND PROGNOSTICS

Bernhardt, Hong, Bernasconi, Bernasconi (in revision)



OVERALL GOALS

Evaluate mesiotemporal damage across spectrum of TLE

- study a consecutive cohort of well-defined, unilateral TLE
- derive individualized mesiotemporal profiles
- apply unsupervised clustering to generate data-driven classification

Assess diagnostic validity of classification

- assess clinical and histopathological associations
- predict long-term surgical outcome in individual patients

METHODS: PARTICIPANTS

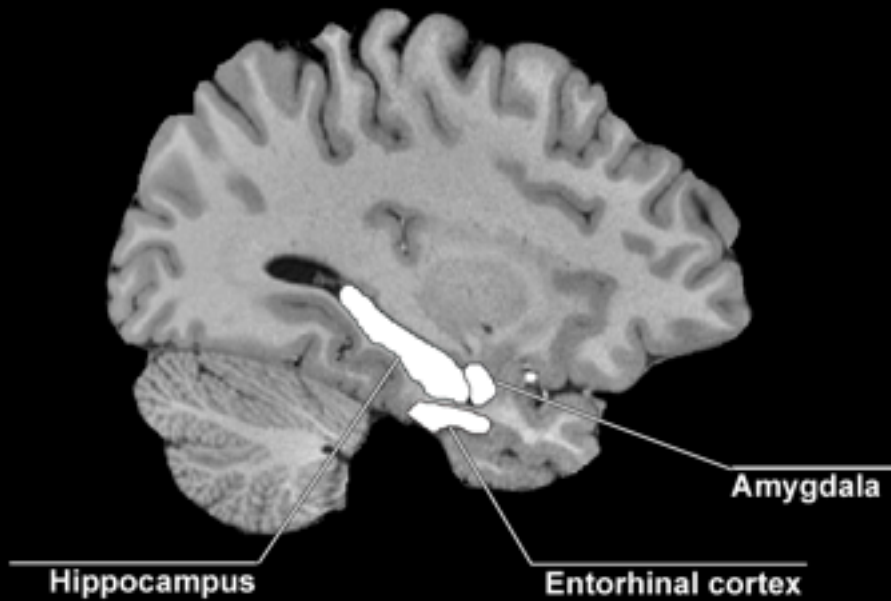
From consecutive database of 235 TLE patients (1998–2006), we excluded

- ▶ patients not evaluated on the same MRI scanner
- ▶ patients with mass lesions, history of trauma, encephalitis
- ▶ patients with seizures originating from both hemispheres

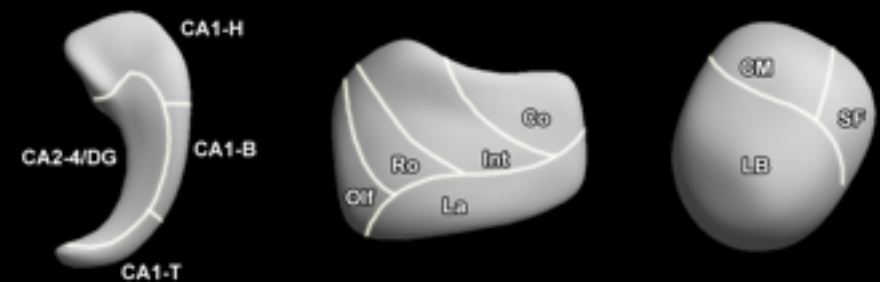
Resulting in 114 unilateral TLE patients (56/58; LTLE/RTLE; 35 ± 11 years)

- ▶ scanned on single 1.5T MRI with 1mm isotropic voxels
- ▶ 79 patients operated: 72% Engel I at 7 ± 2 years of follow up
- ▶ 66 specimens available: 60% HS+gliosis, 40% gliosis-only

METHODS: MESIOTEMPORAL PROFILING

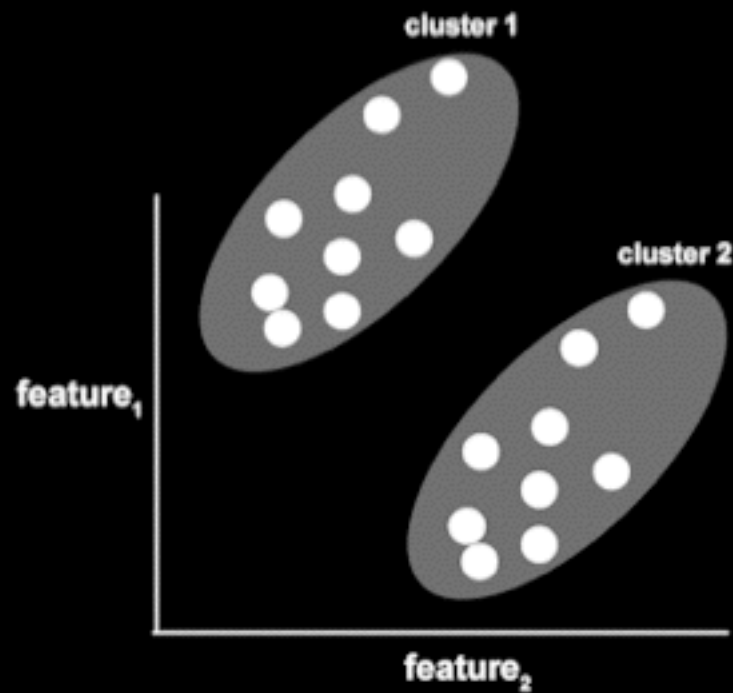


Bernasconi et al. 1999 Neurology
Bernasconi et al. 2003 Brain



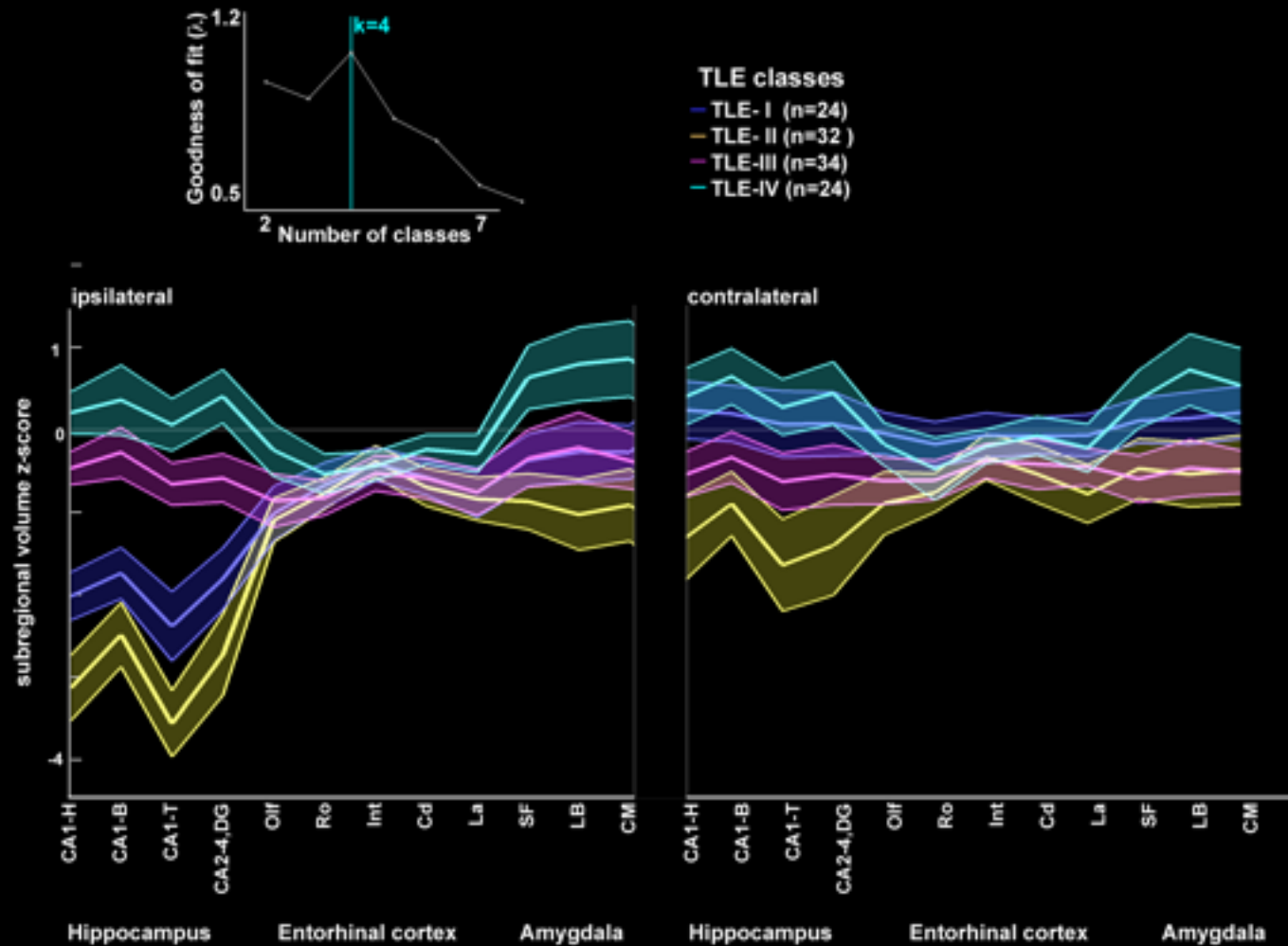
Kim et al. 2008 MICCAI
Bernhardt et al. 2013 Neurology

PROFILE CLUSTERING



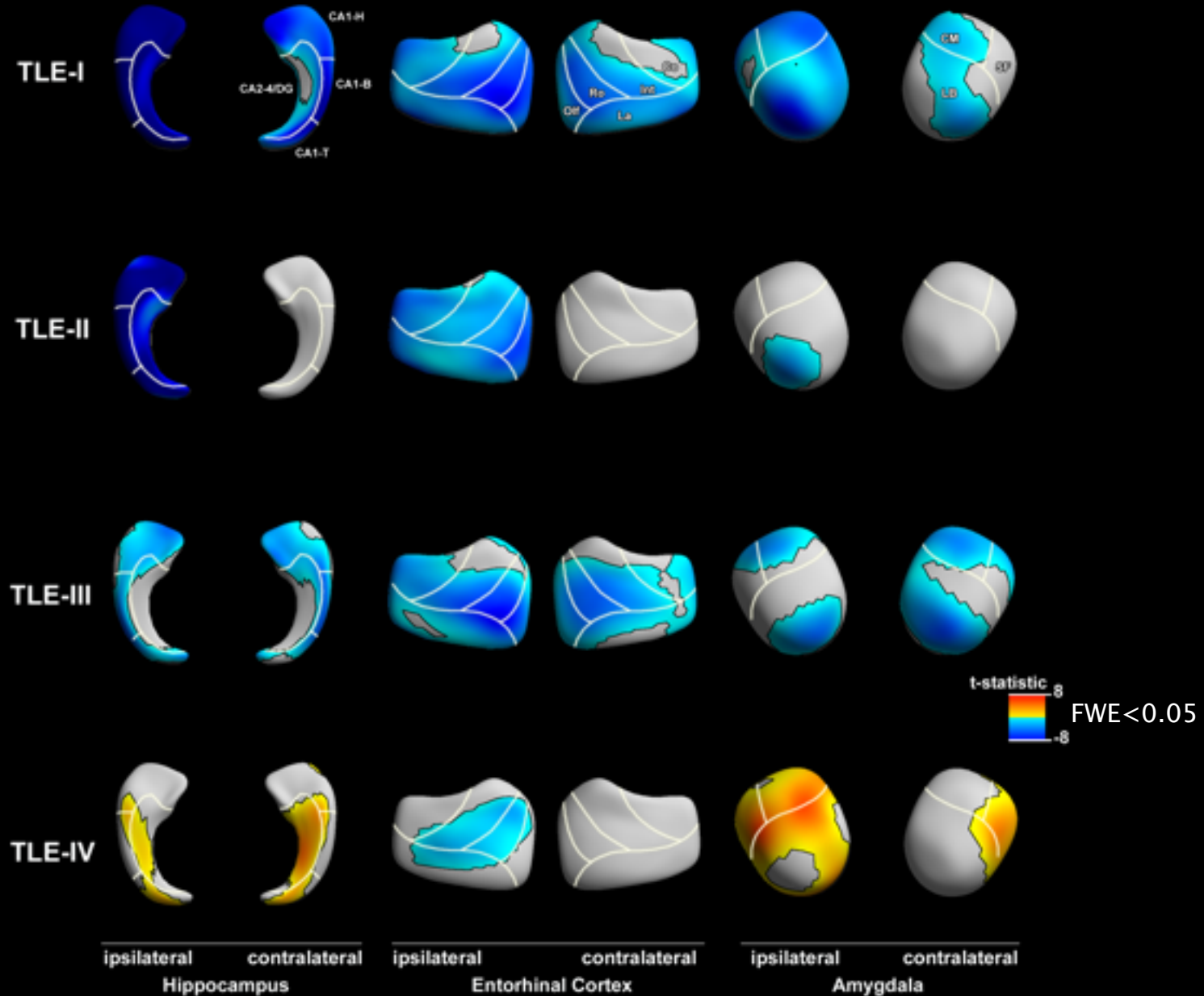
k-means = grouping of patients with similar feature profiles

MESIOTEMPORAL PROFILING

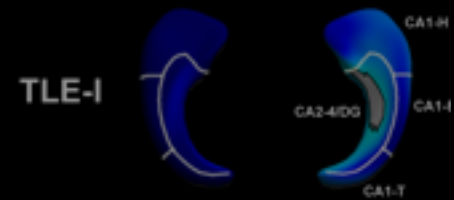


Each patient represented as a feature vector of 24 subfield volumes

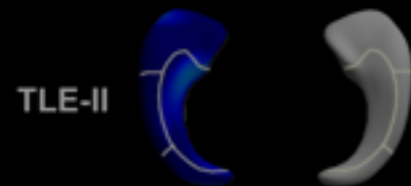
CLASS-WISE PATTERNS OF ANOMALIES



CLINICO-PATHOLOGICAL ASSOCIATIONS



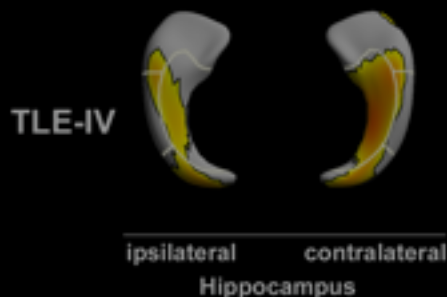
71% FC, >24 y duration, 71/29% HS/Gliosis, 68% SF



47% FC, >24 y duration, 72/28% HS/Gliosis, 89% SF

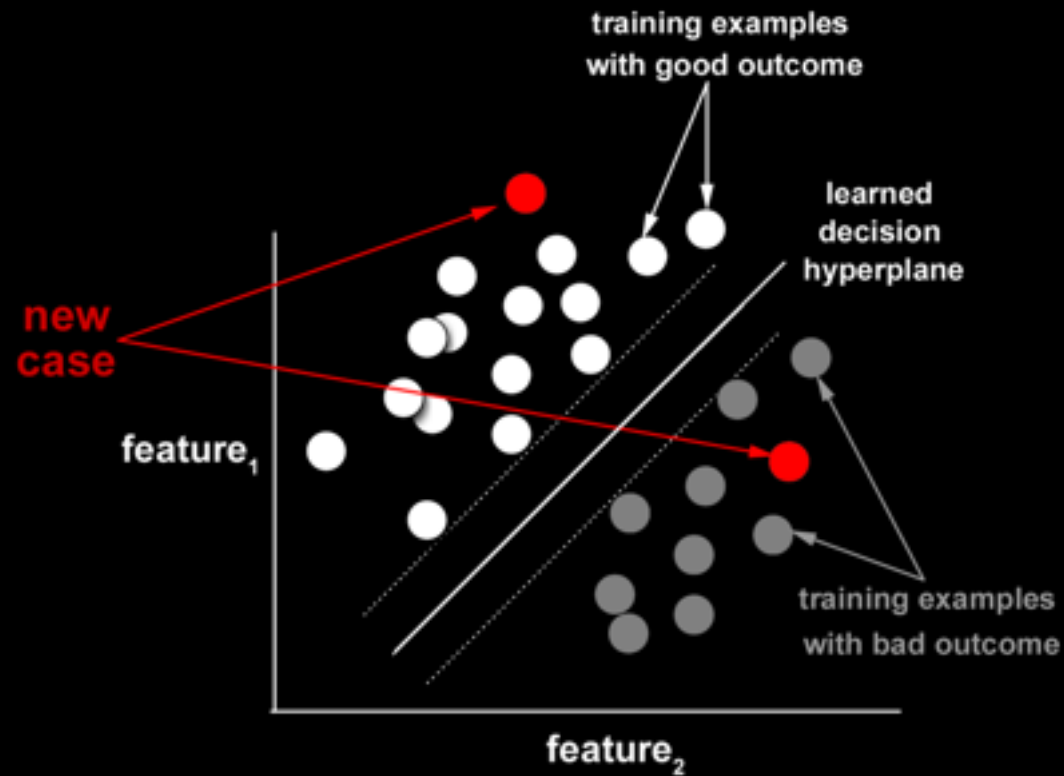


18% FC, >16 y duration, 43/67% HS/Gliosis, 65% SF



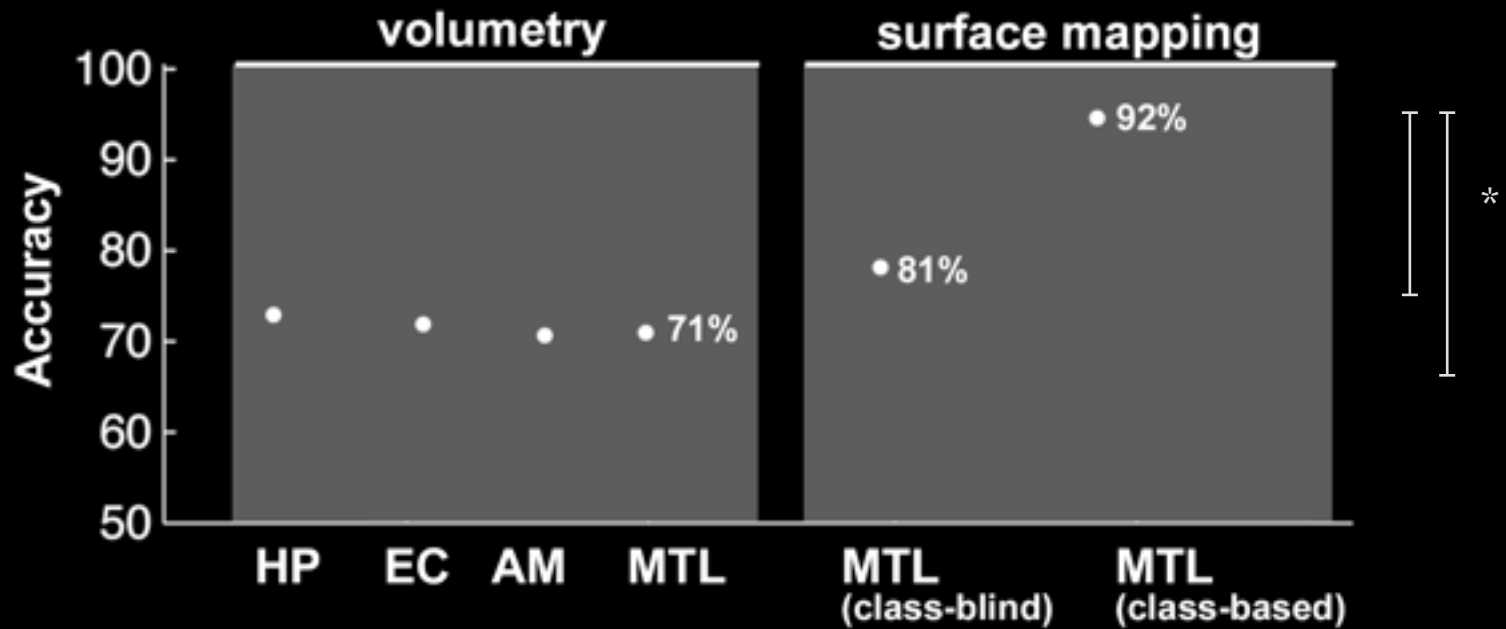
8% FC, >13 y duration, 17/83% HS/Gliosis, 44% SF

OUTCOME PREDICTION IN INDIVIDUAL CASES

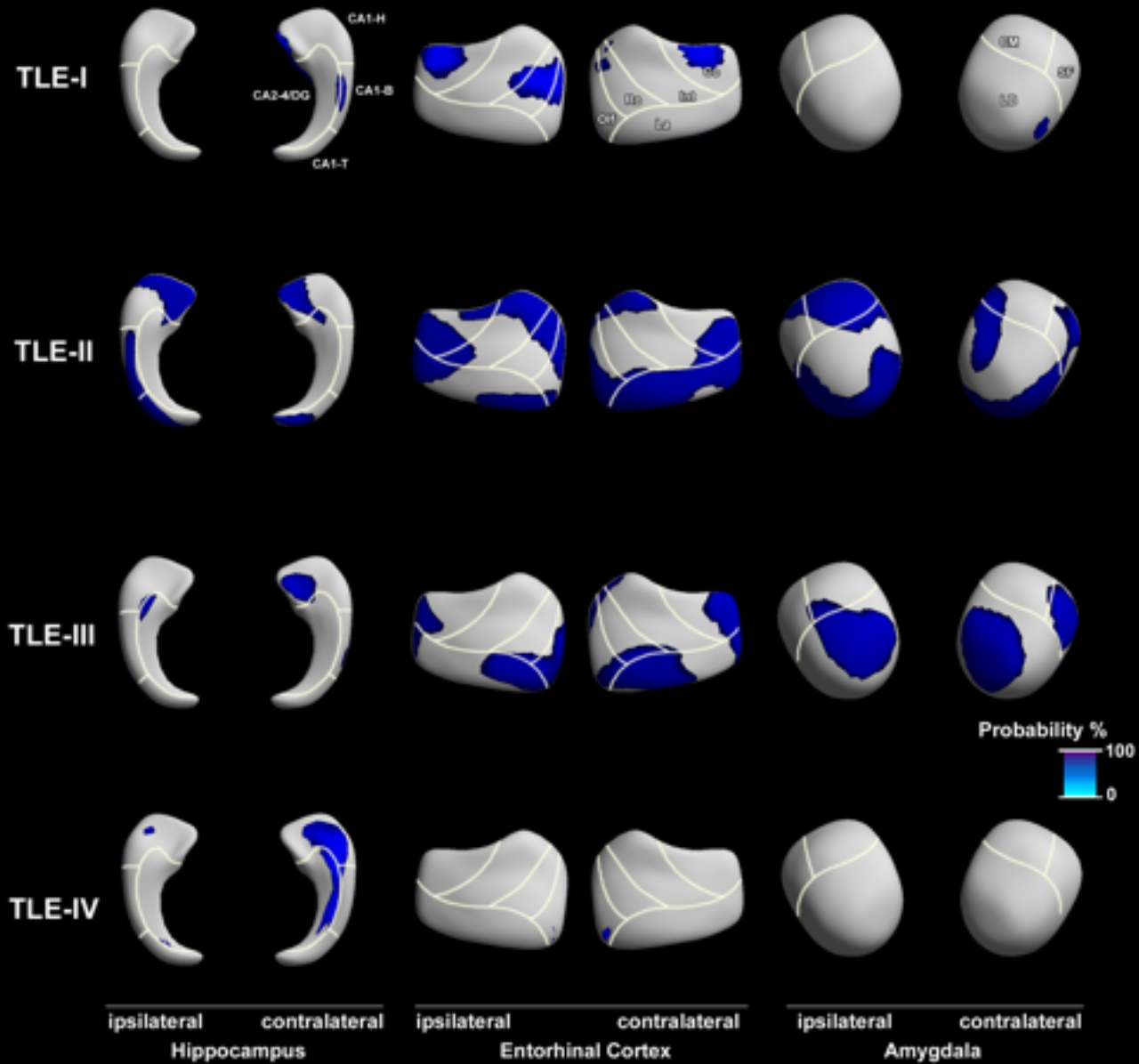


LDA = prediction of outcome based on similarity to training examples

OUTCOME PREDICTION



OUTCOME PREDICTION



VALIDATION IN INDEPENDENT DATASET

We assessed the generalizability of our approach in independent dataset

- ▶ 27 consecutive unilateral patients who underwent TLE surgery (2009–2013)
- ▶ 71% SF/29% NSF
- ▶ Preoperative 3T MRI
- ▶ Automated mesiotemporal segmentations (Kim et al. 2012)

Clustering based on patient-similarity to average 1.5 Tesla profiles

89% performance of class-blind, 96% of class-based LDA

INTERIM SUMMARY

MRI data mining in TLE: evidence for spectrum disorder

- ▶ Alterations across all mesiotemporal structures in all classes
- ▶ TLE-II strictly unilateral, all other classes bilateral
- ▶ Increases may reflect gliosis, atrophy in other classes cell loss

Outcome gradient across classes

Classification clinically validated:

- ▶ 92% accuracy in predicting outcome (n=79 patients)
- ▶ validated in independent 3T cohort with fully automated segmentation

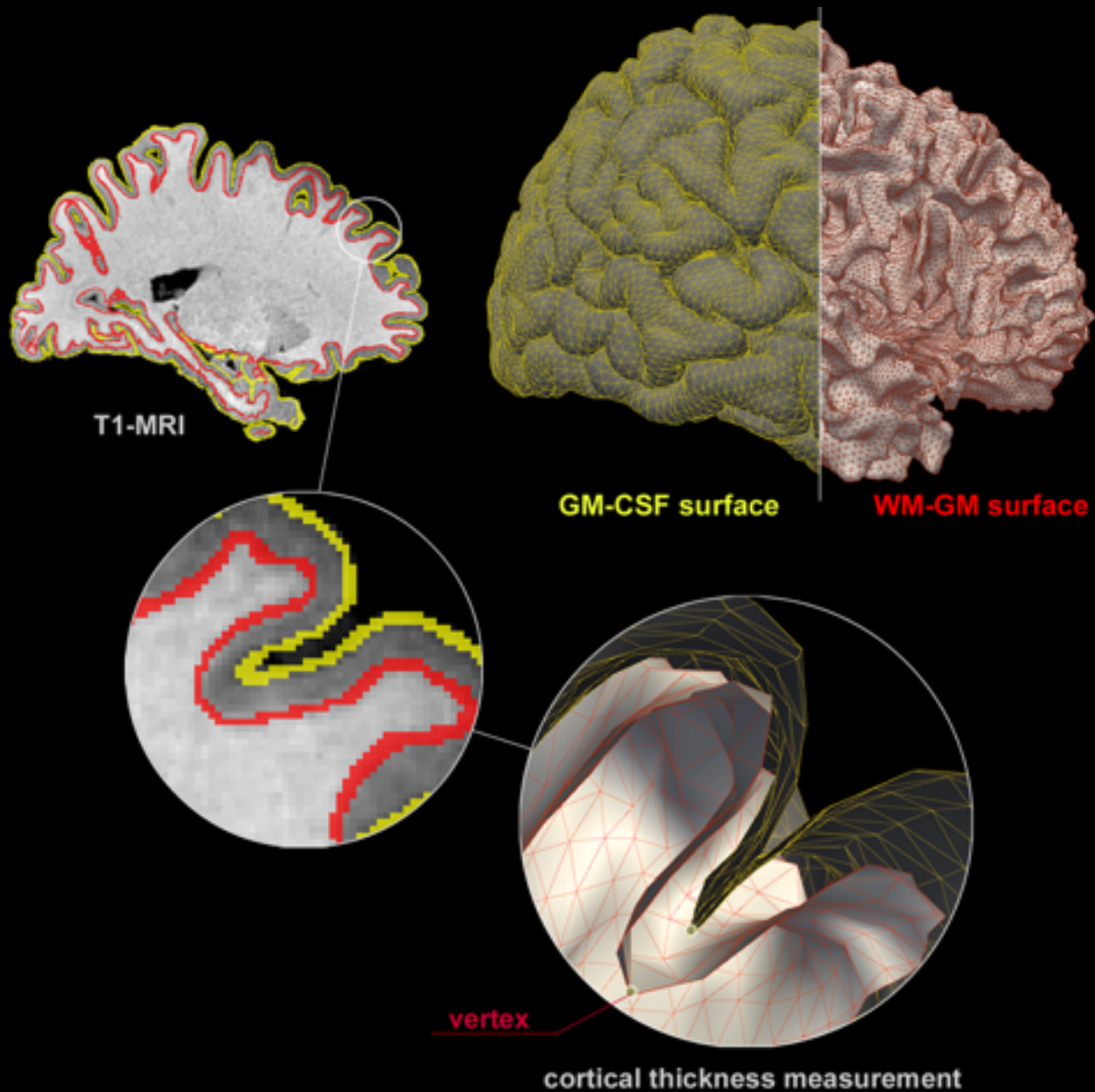
NEOCORTICAL FINDINGS ACROSS TLE SPECTRUM

Bernhardt et al. (2008) NIMG

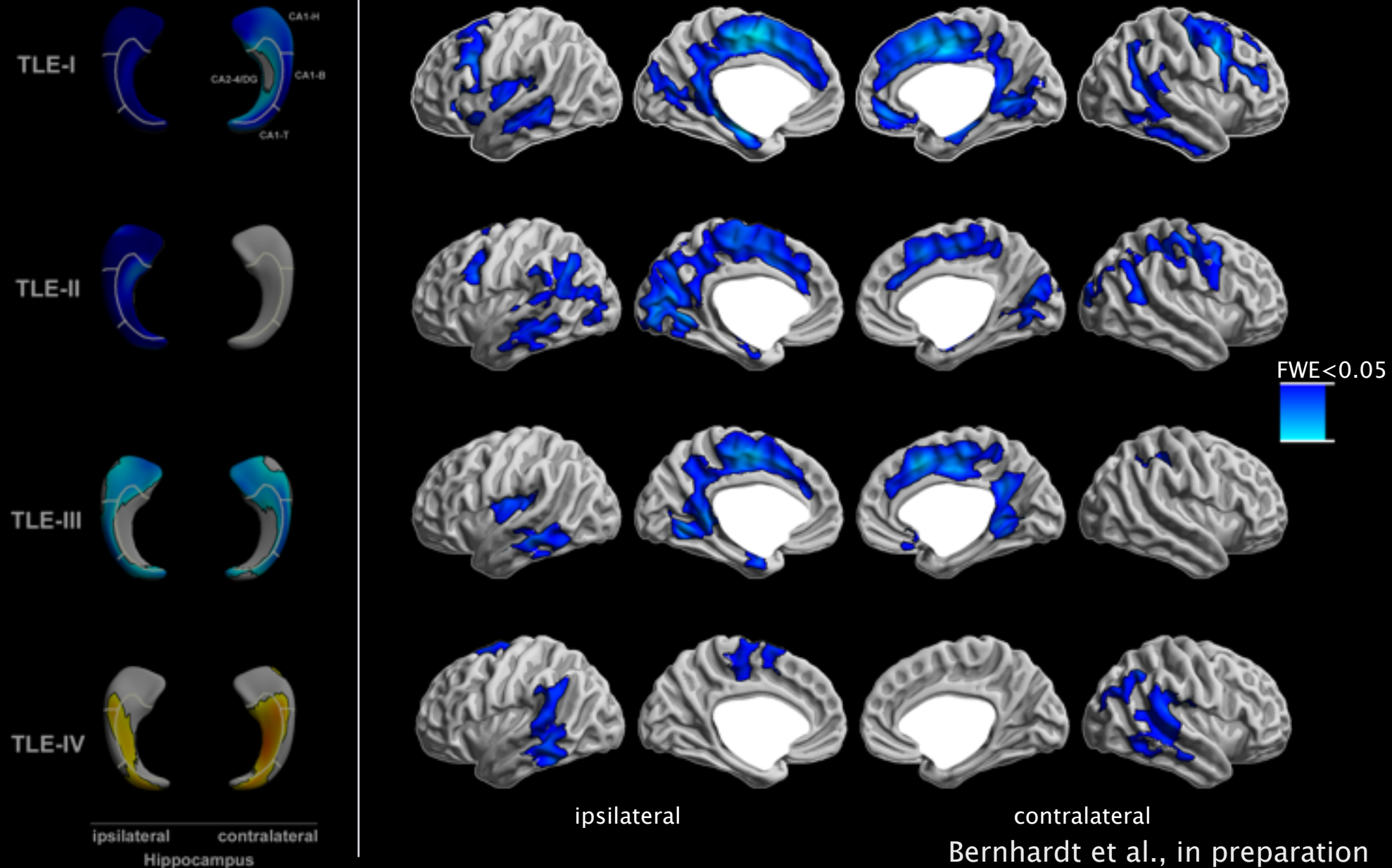
Bernhardt et al. (2010) Neurology



CORTICAL THICKNESS ANALYSIS



NEOCORTICAL THINNING ACROSS TLE SPECTRUM



CONCLUSIONS

CONCLUSIONS

Quantitative MRI challenges notion of MRI normalcy in TLE

- ▶ Multi-contrast hippocampus subfield assessment in 15 TLE-NV
 - ▶ subfield-specific patterns of anomalies
 - ▶ 100% lateralization performance, (*i.e.*, there is damage in all!)
- ▶ Clustering of unilateral patients based on mesiotemporal profiles
 - ▶ All mesiotemporal structures affected in all TLE classes
 - ▶ bilateral mesiotemporal assessment lends highly accurate predictors surgical outcome across two independent cohorts
- ▶ Marked and bilateral thinning across unilateral TLE spectrum

MERCI!

Neda Bernasconi

Andrea Bernasconi

Seok-Jun Hong

Hosung Kim

Jessie Kulaga-Yoskovitz

Min Liu

Benoit Caldaïrou

Anton Plavski

Dewi Schrader

François Dubeau

Frederick Andermann

Jeffery Hall

Martin Vielleux

Marie-Christine Guiot

JTC Fellowship of MNI

CIHR



MOST REPRESENTATIVE CASE

