Advanced multimodal imaging in malformations of cortical development

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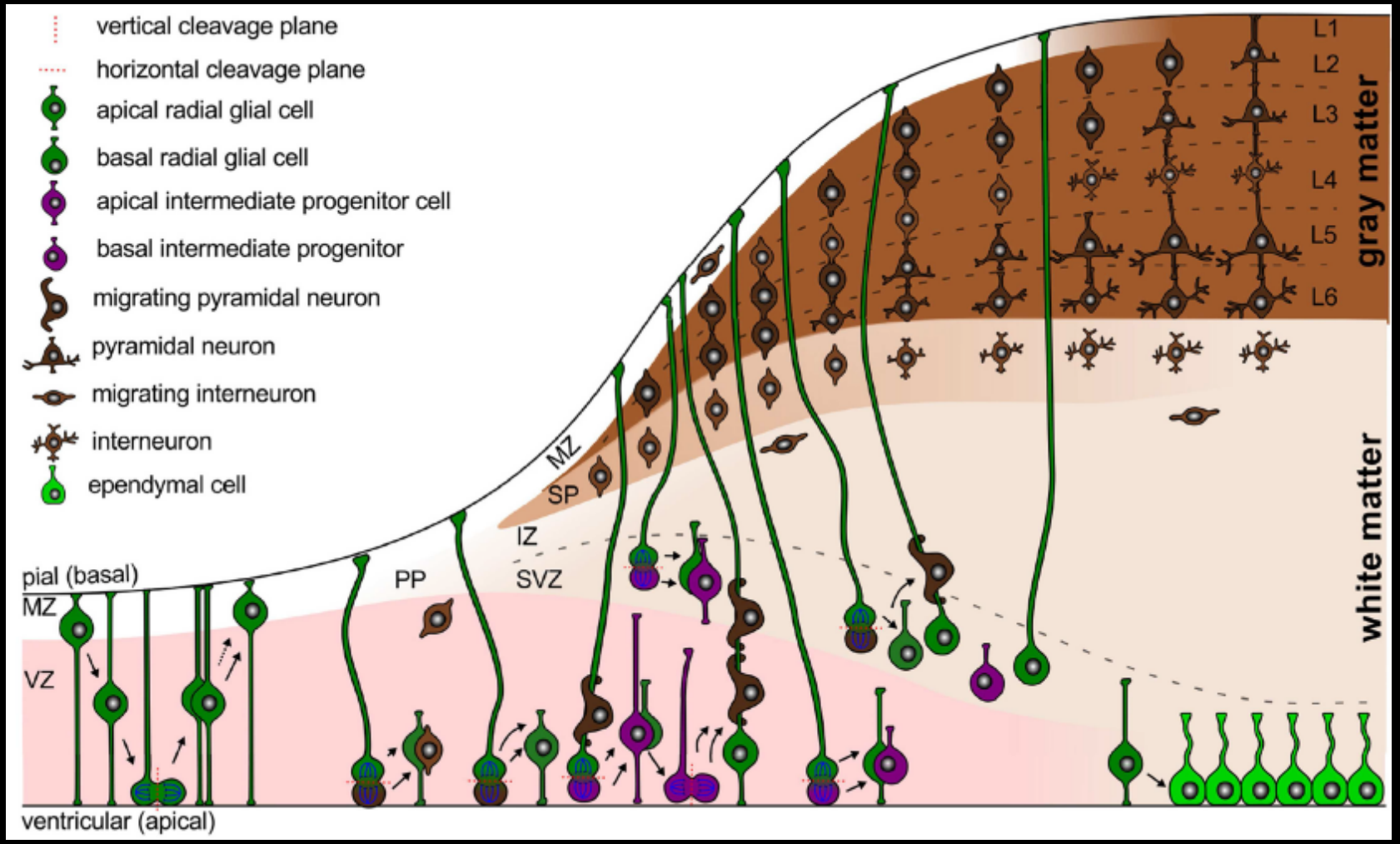
MICA – Multimodal Imaging and Connectome Analysis Lab

Normal Brain Development



w4 w5 w7 w8 w15 w18 w22 w25 w28

Neuronal progenitor cell proliferation

Neurogenesis

Onset of neuronal migration

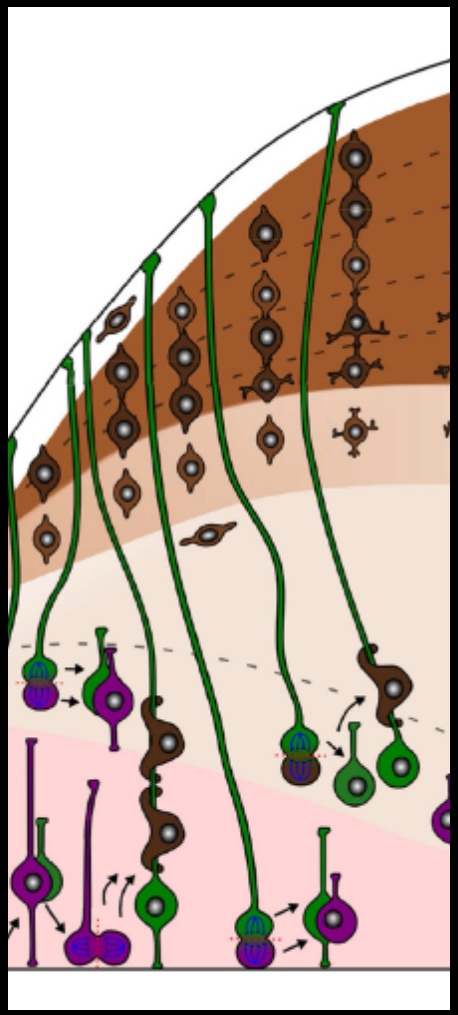
Onset of cortical organization

Budday S, et al. Fronti in Cell Neurosci 2015

Malformations of cortical development (MCD)

Blümcke I, et al. Epileptic disord, 2010
Barkovich J, et al. Brain, 2012
Guerrini R, et al. Lancet Neurol, 2014

Abnormal…



Cortical organization

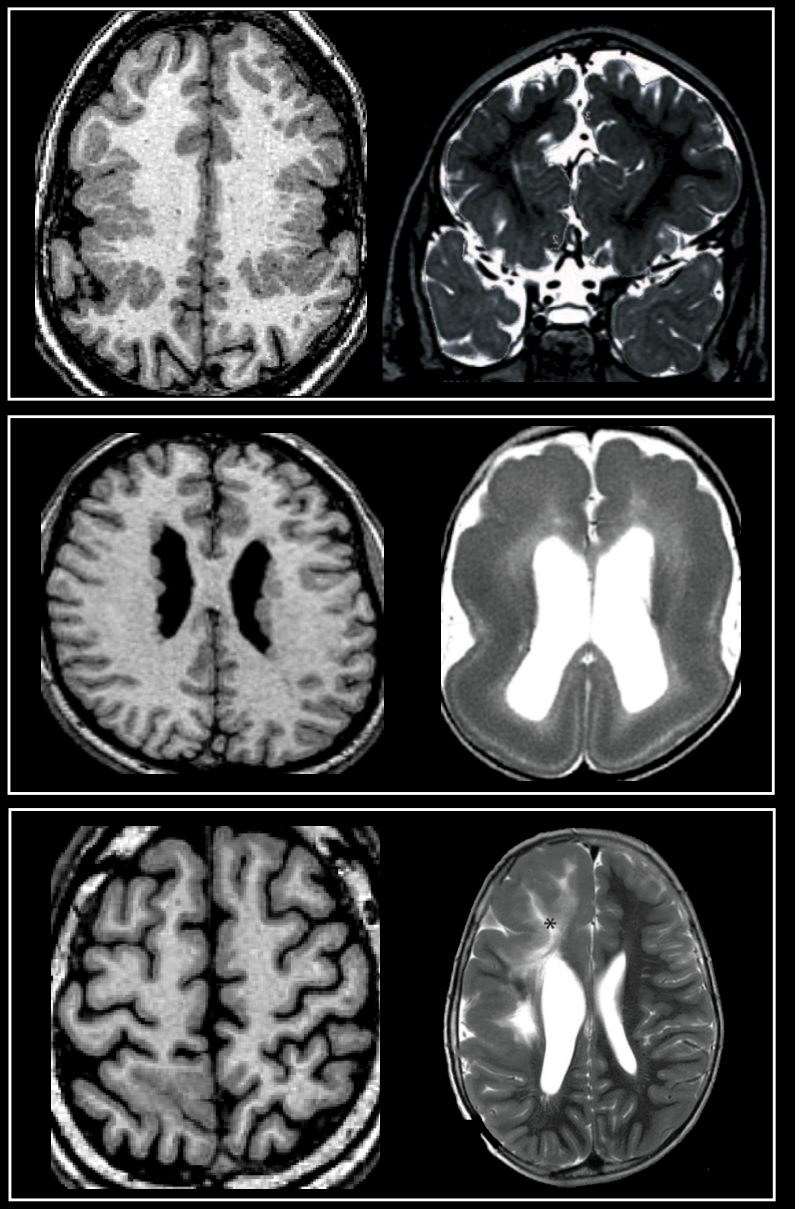
- Polymicrogyria
- Mild focal cortical dysplasia

Cell migration

- Heterotopia (PVNH, SCH)
- Lissencephaly

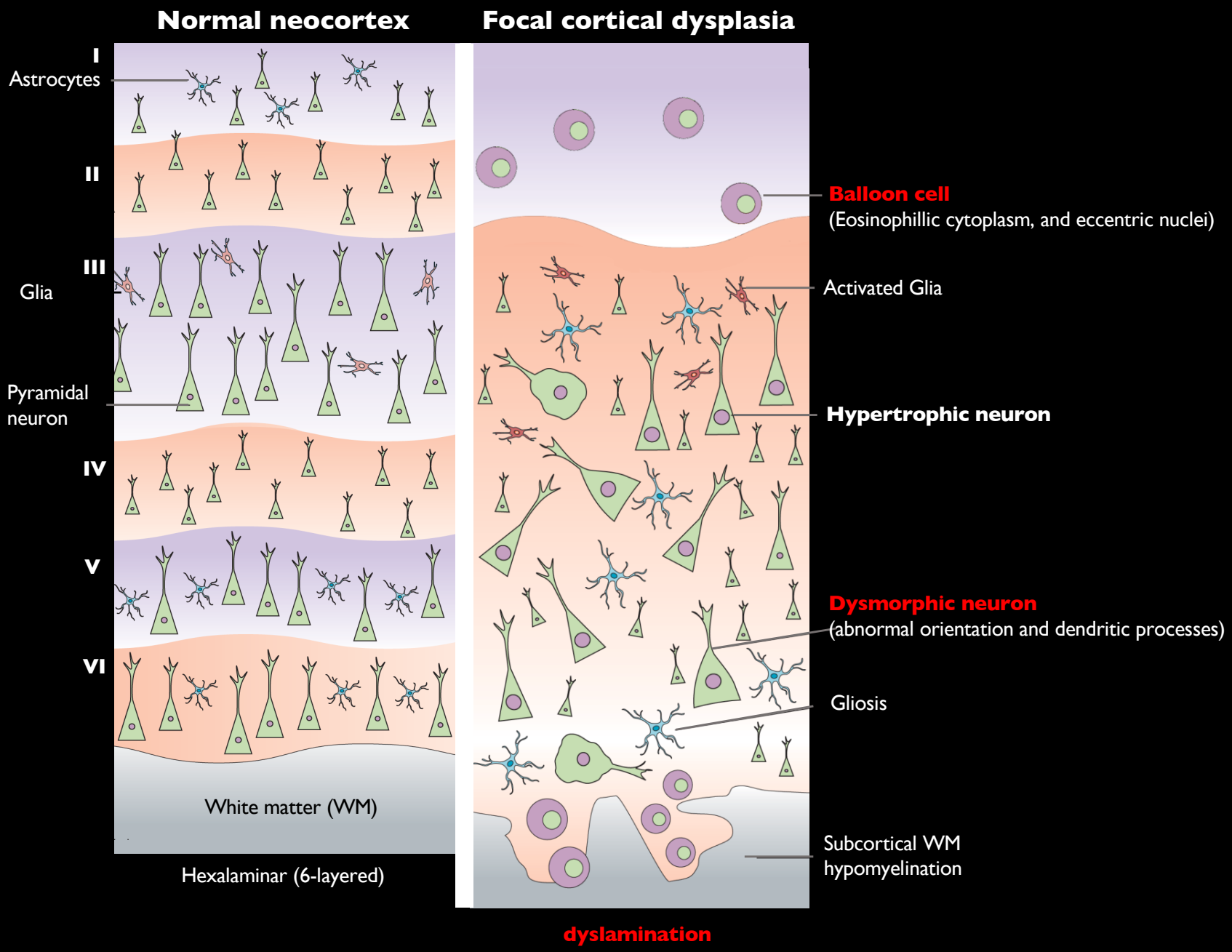
Cell proliferation

- Focal cortical dysplasia
- Micro-/Megalencephaly



Focal cortical dysplasia

- Drug-resistant neocortical epilepsy
- Amenable to surgery if localized
- 40-60% good seizure control



adapted from Sisodiya, Lancet Neurology (2009)

Blümcke I, et al. Epilepsia, 2011
Wang Z,I et al. Ann Neurol, 2015

FCD Type I: Abnormal cortical dyslamination

FCD type II: Abnormal cortical dyslamination + Dysmorphic Neurons

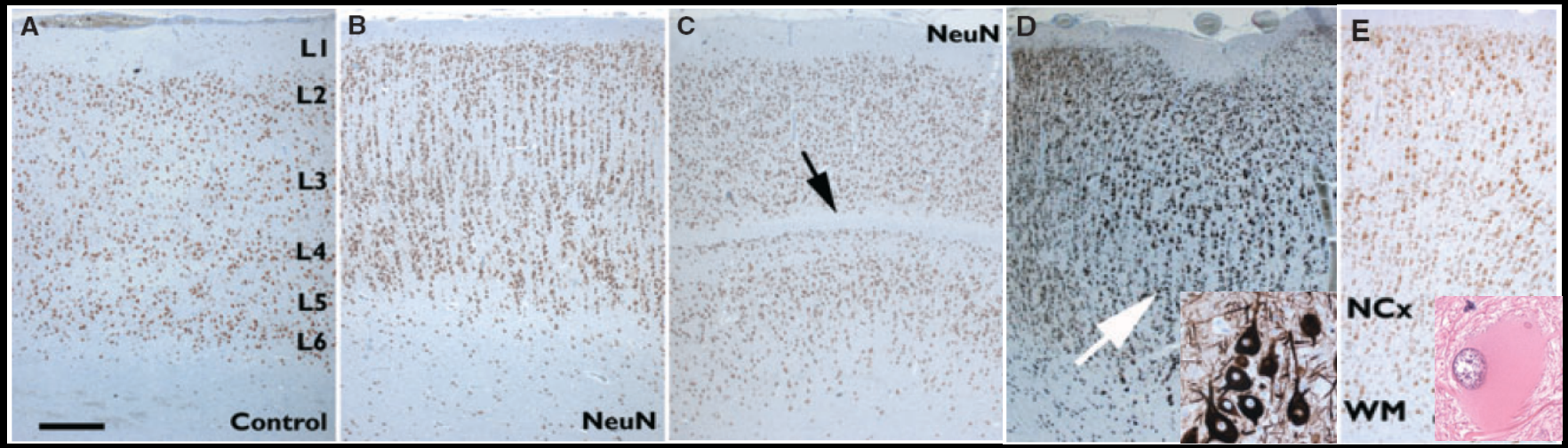
Normal

Ia: radial

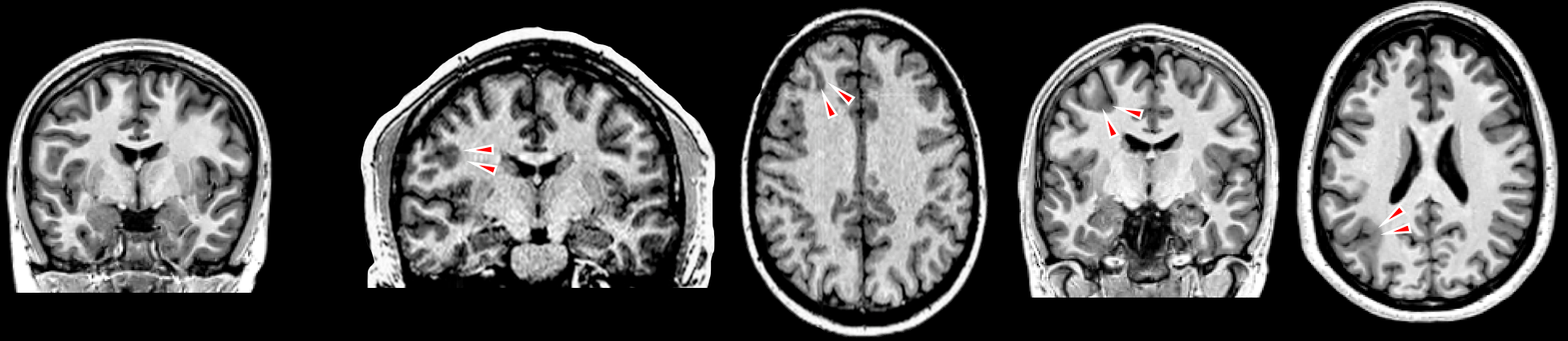
Ib: tangential

IIa: Without Balloon cells

IIb: With Balloon cells



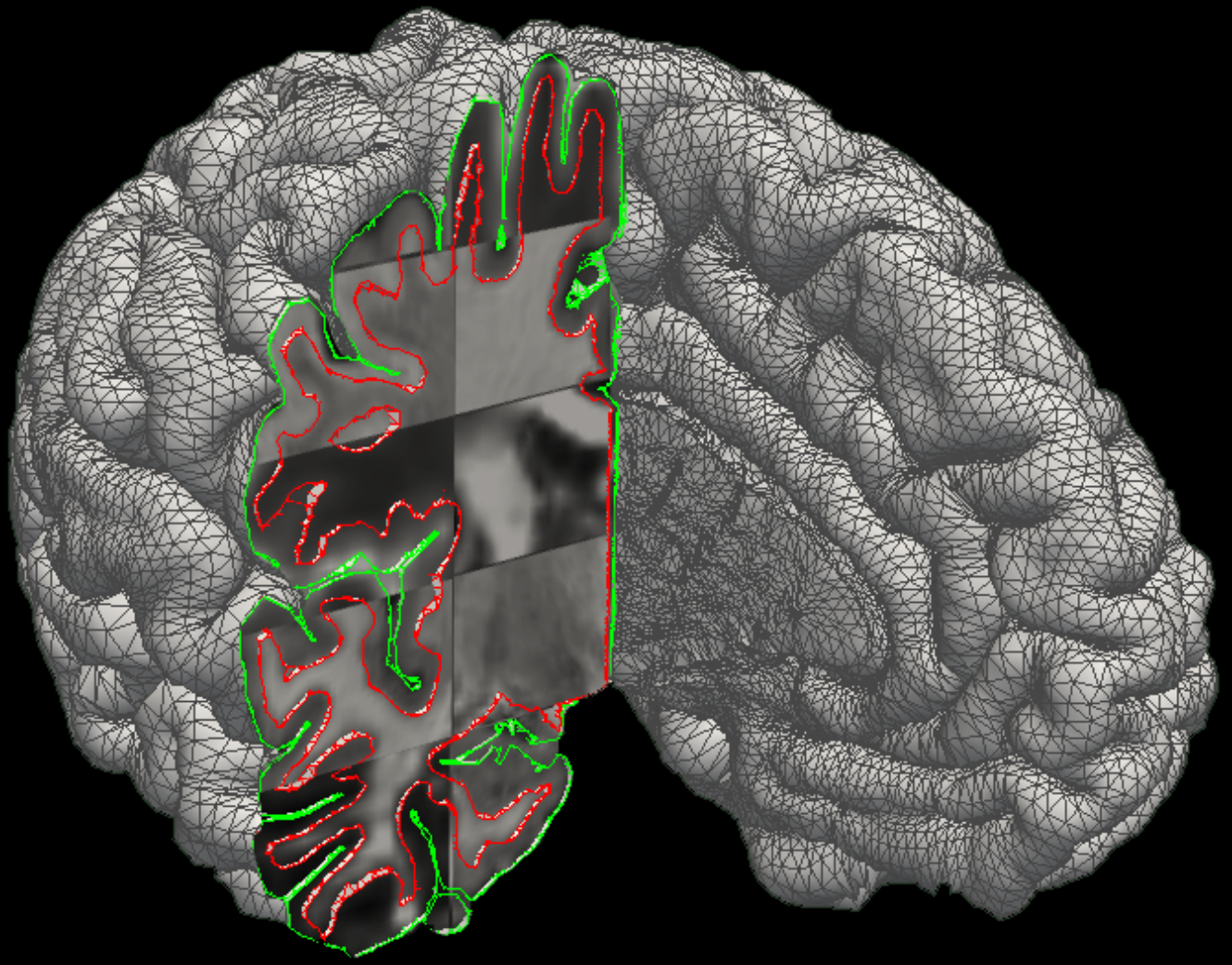
Subtle — Histological spectrum — Severe



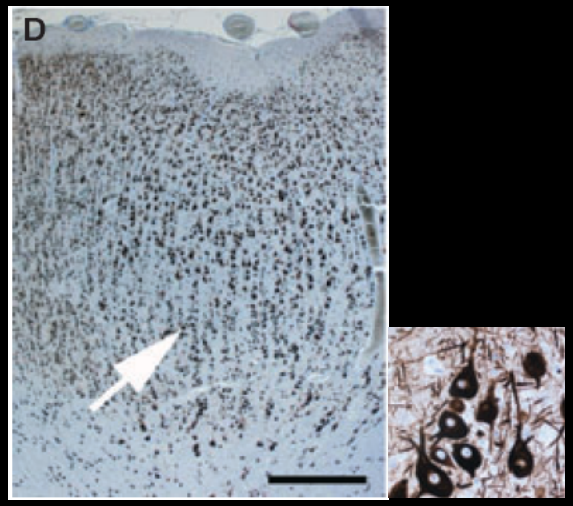
IIb Ia Ib IIa IIb

MRI-negative — MRI spectrum — MRI-positive

STUDY I MULTIMODAL LESION CHARACTERIZATION



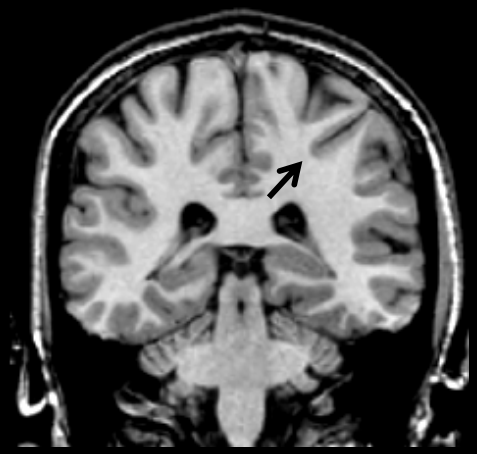
Type-IIA



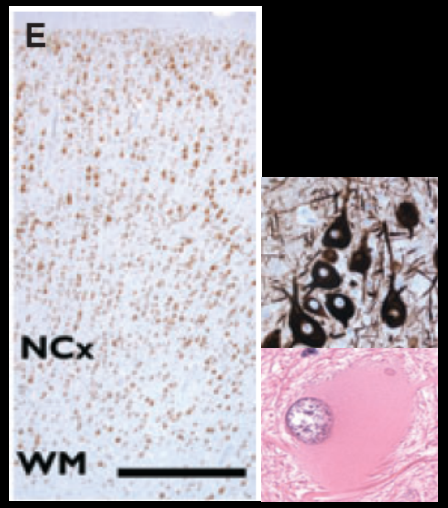
Intracortical dyslamination

+

Dysmorphic neurons



Type-IIB



Intracortical dyslamination

+

Dysmorphic neurons

+

Balloon cell

- Identifying subtype-specific imaging signatures may have potential clinical utility
  1. Optimize lesion detection (specific to certain histopathological types)
  2. Complement minimally invasive surgical procedures (e.g. thermal laser ablation)
  3. Guide and monitor pharmacological interventions (mTOR signaling inhibitor)

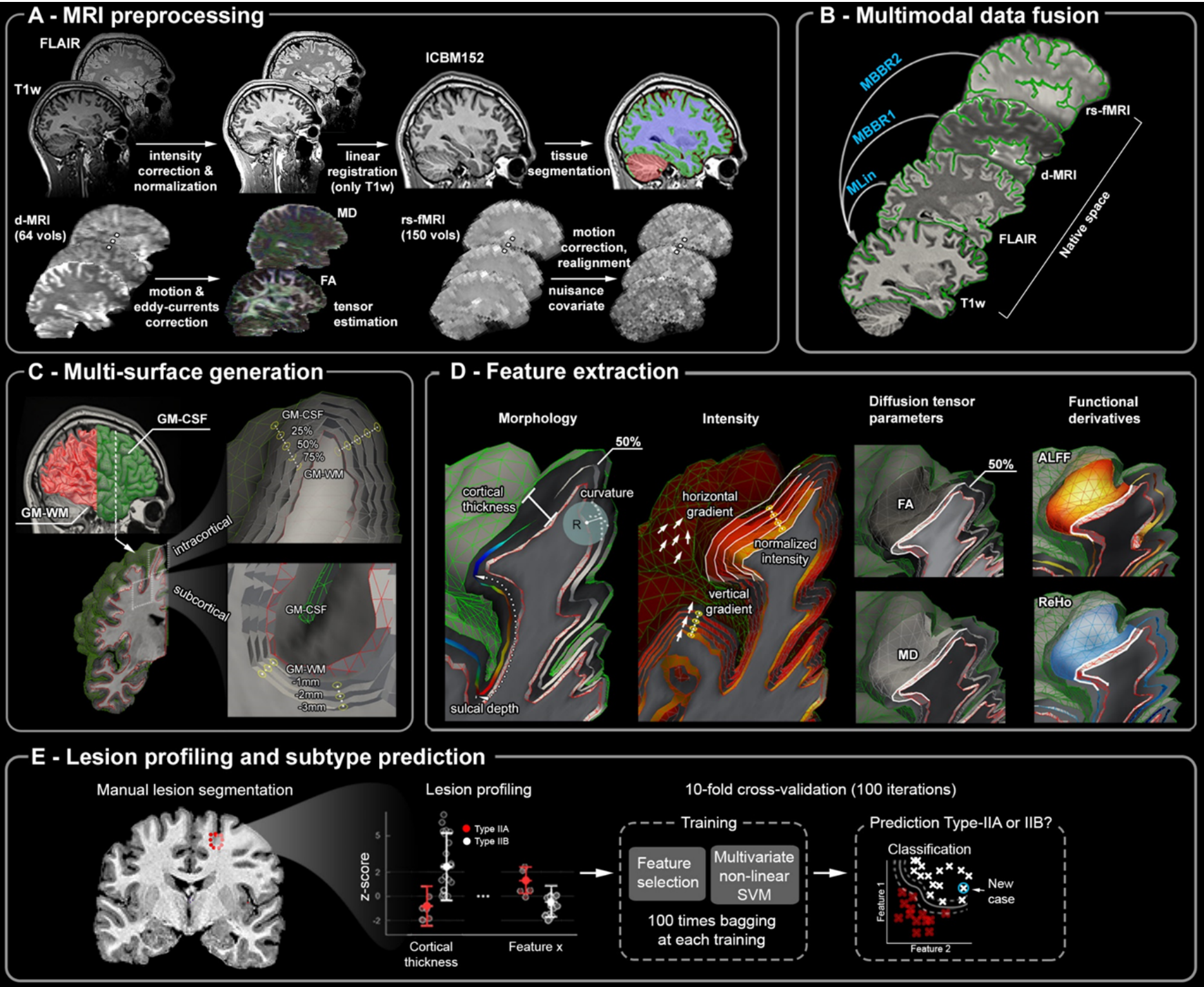
PURPOSE

In-vivo lesion profiling and subtype prediction in focal cortical dysplasia type-II

Consecutive patients with drug-resistant epilepsy and histologically verified
9 FCD Type-IIA and 24 IIB

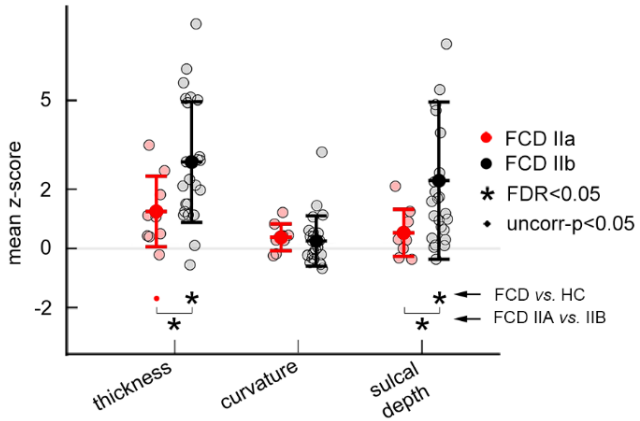
Multimodal MRIs (3T Siemens TimTrio, 32 channel head coil)

- 3D T1w MPRAGE (1x1x1mm^3)
- 3D FLAIR (0.9x0.9x0.9mm^3)
- 2D EPI-DTI (2x2x2mm^3 , 64 directions)
- 2D rs-fMRI (4x4x4mm^3, 150 volumes)


A - MRI preprocessing
FLAIR
T1w
intensity correction & normalization
ICBM152
linear registration (only T1w)
tissue segmentation
d-MRI (64 vols)
motion & eddy-currents correction
MD
FA
tensor estimation
rs-fMRI (150 vols)
motion correction, realignment
nuisance covariate
B - Multimodal data fusion
MBBR2
MBBR1
MLin
rs-fMRI
d-MRI
FLAIR
T1w
Native space
C - Multi-surface generation
GM-CSF
GM-WM
intracortical
subcortical
GM-CSF
25%
50%
75%
GM-WM
GM-CSF
GM-WM
-1mm
-2mm
-3mm
D - Feature extraction
Morphology
Intensity
Diffusion tensor parameters
Functional derivatives
50%
cortical thickness
curvature
R
sulcal depth
horizontal gradient
normalized intensity
vertical gradient
50%
FA
MD
ALFF
ReHo
E - Lesion profiling and subtype prediction
Manual lesion segmentation
Lesion profiling
Type IIA
Type IIB
z-score
Cortical thickness
Feature x
10-fold cross-validation (100 iterations)
Training
Feature selection
Multivariate non-linear SVM
100 times bagging at each training
Prediction Type-IIA or IIB?
Classification
New case
Feature 1
Feature 2

Multi-surface lesion profiling

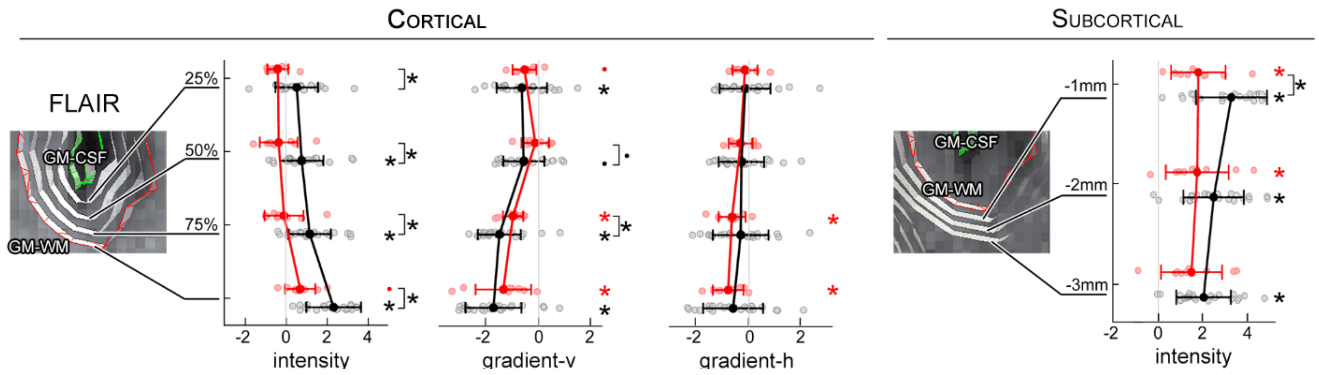
1. Morphology



2. Intensity

IIB: Abnormalities across all cortical and subcortical surfaces

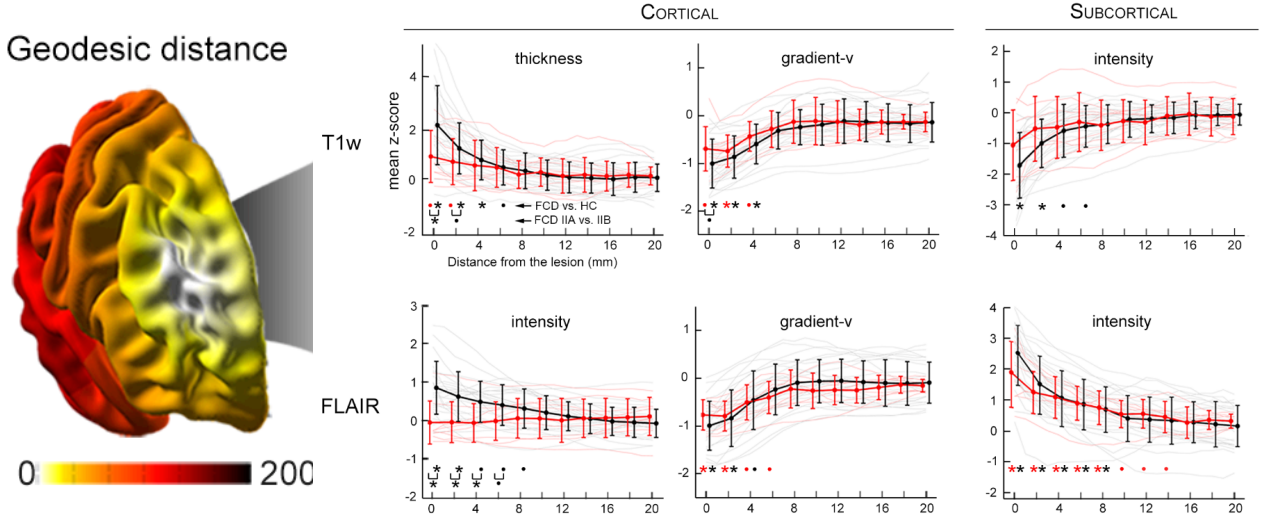
IIA: Abnormalities clustered around the GM-WM interface



Distance-based lesion profiling

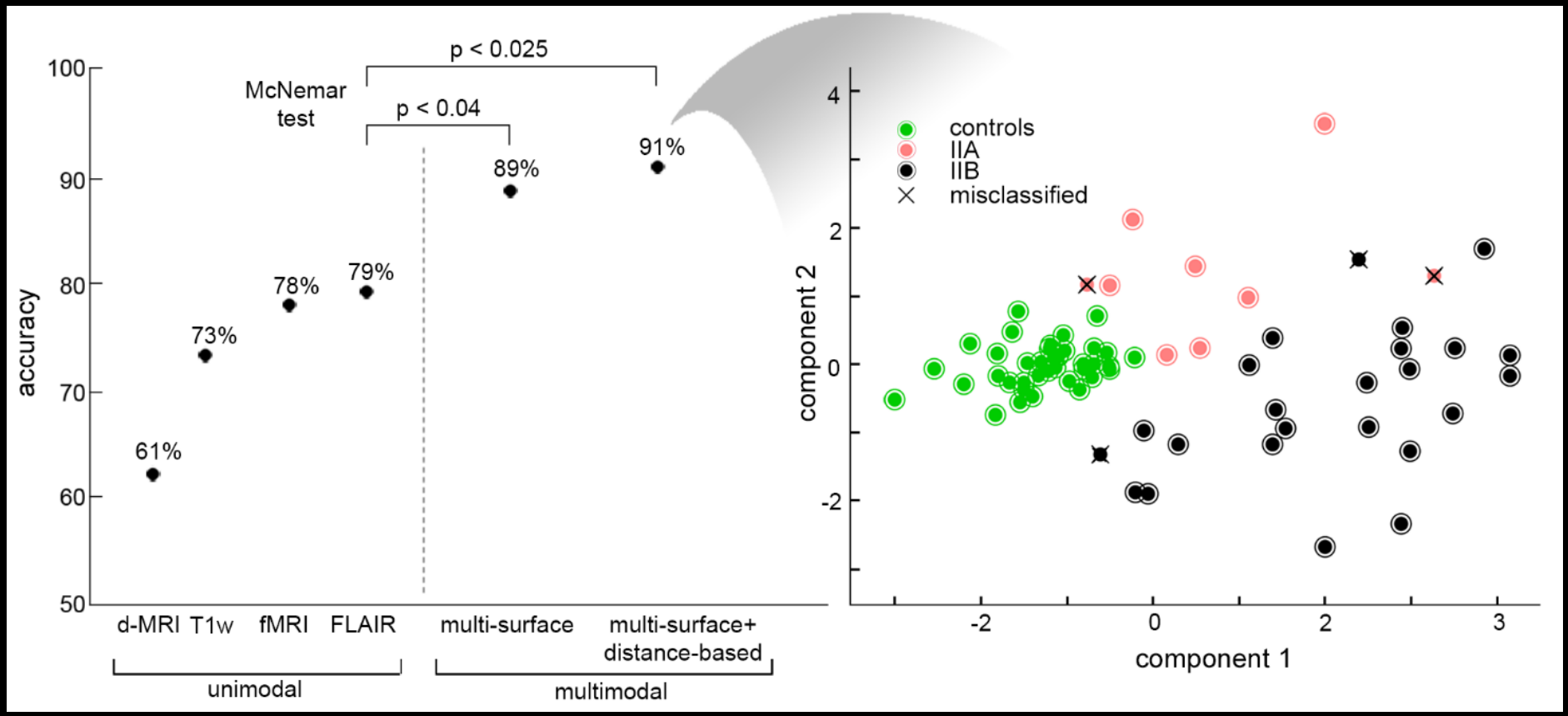
Pathological infiltration beyond the visible lesion in both subtypes

- Until 6-8 mm from the lesion
- Nevertheless, anomalies more marked in Type-IIB
- Except the reduced cortical FA specific to IIA



Hong SJ, et al. MICCAI 2015, Munich, Germany
Hong SJ, et al. Neurology 2016 (in press)

Histological subtype prediction

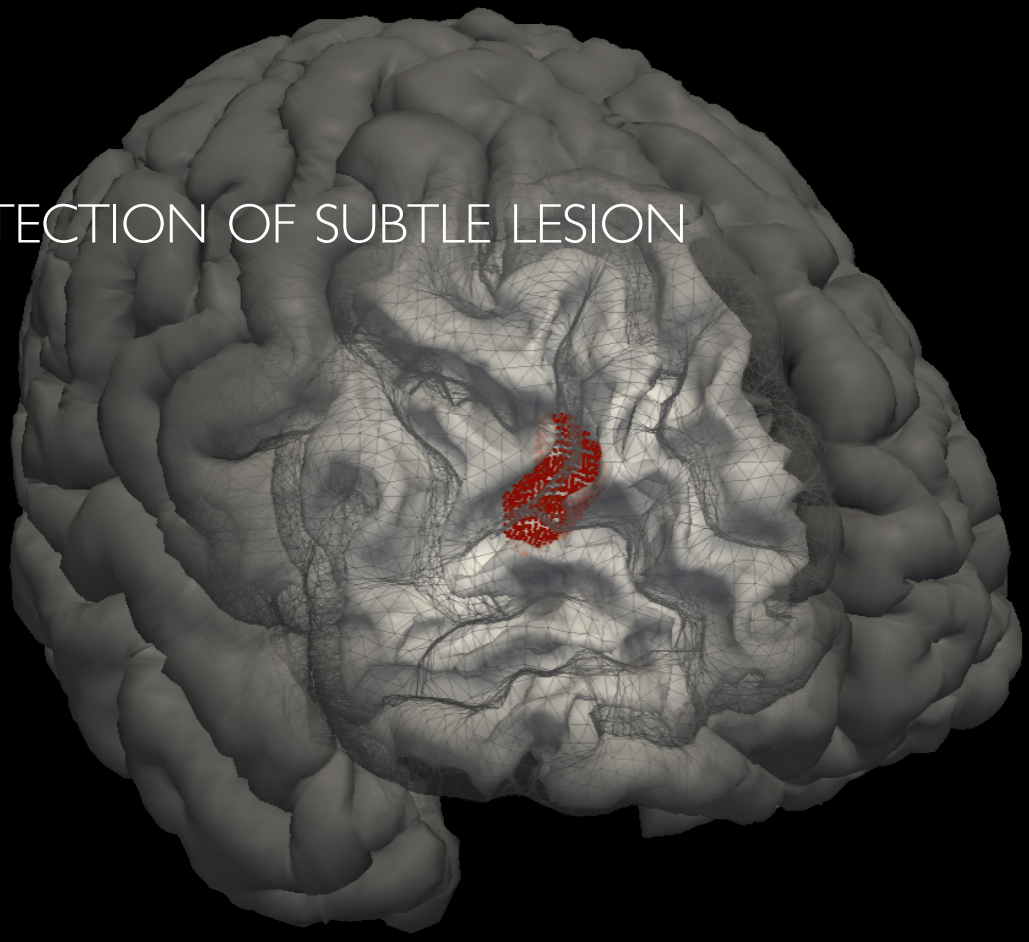


Hong SJ, et al. MICCAI 2015, Munich, Germany
Hong SJ, et al. Neurology 2016 (in press)

S1. Conclusion

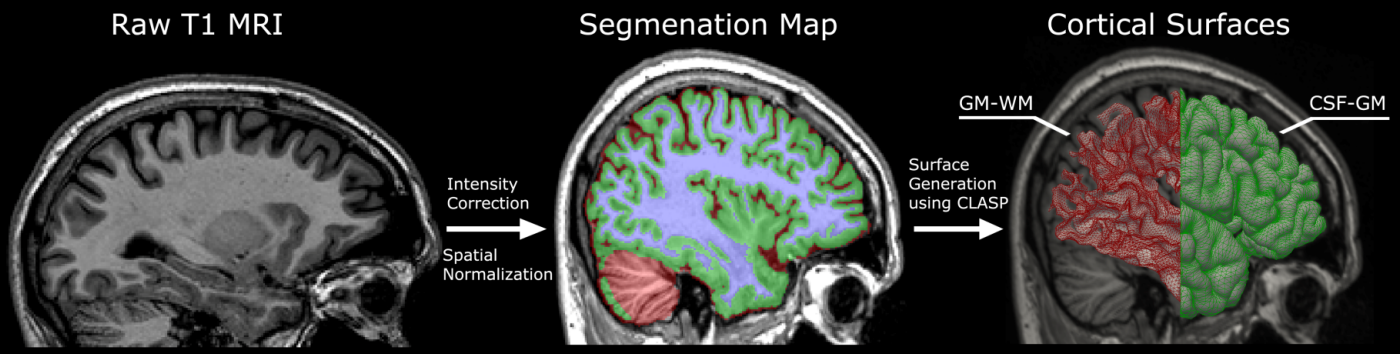
- Multimodal, multiparametric MRI lesion profiling could dissociate FCD subtypes.
- Strikingly divergent subtype-specific patterns reflect different loads of underlying histopathology.
- In-vivo MRI prediction of histology could complement pre-surgical assessment (e.g., lesion detection) and possibly monitor emerging pharmacological interventions.

STUDY2 AUTOMATED DETECTION OF SUBTLE LESION

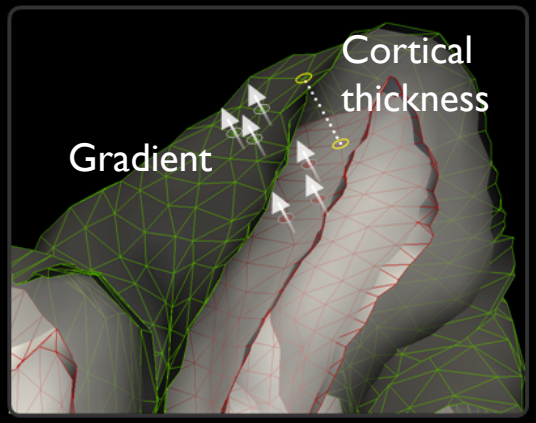


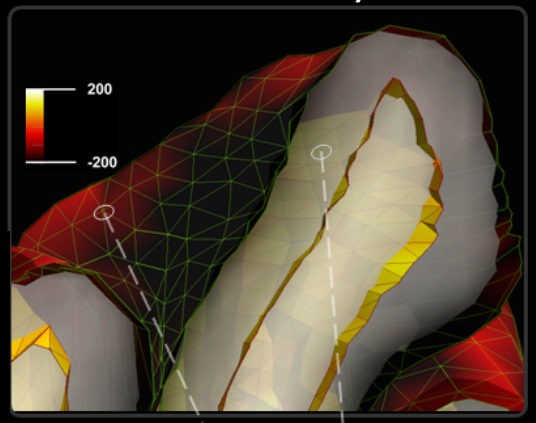
Purpose

To detect automatically FCD type II in patients with extratemporal epilepsy initially diagnosed as MRI-negative on routine inspection, both at 1.5 and 3.0Tesla

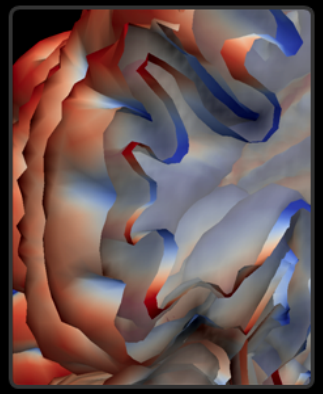


Relative intensity





$$\nabla I(x) = \frac{\partial I}{\partial x} i + \frac{\partial I}{\partial y} j + \frac{\partial I}{\partial z} k$$



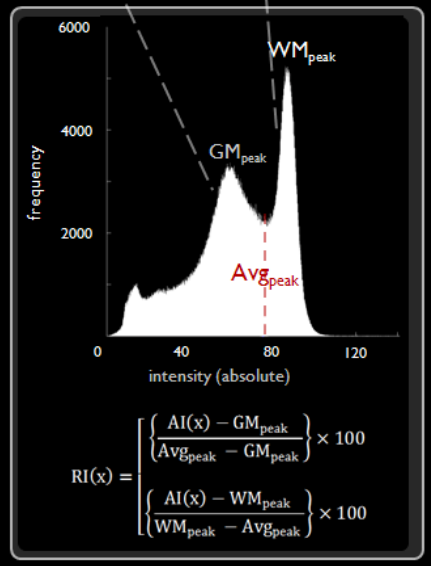
$\Delta_{surface}\ D = 2\kappa_{mean}$

$\Delta_{surface}$: harmonic energy function

D : local depth

K_{mean} : local mean curvature

Sulcal depth & curvature



$$RI(x) = \begin{cases} \left\{ \frac{AI(x) - GM_{peak}}{Avg_{gpeak} - GM_{peak}} \right\} \times 100 \\ \left\{ \frac{AI(x) - WM_{peak}}{WM_{peak} - Avg_{gpeak}} \right\} \times 100 \end{cases}$$

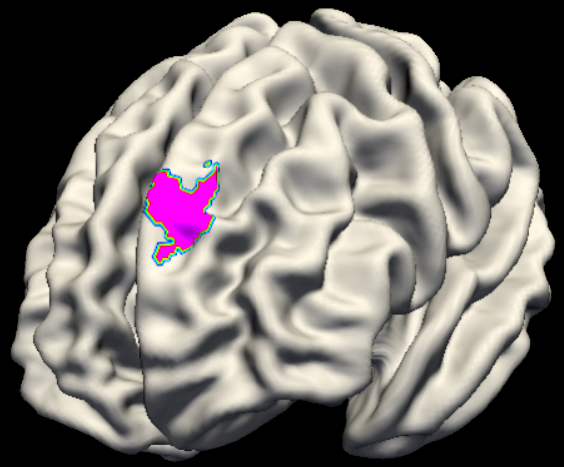
AUTOMATED LESION DETECTION USING MACHINE-LEARNING

1st CLASSIFICATION
(vertex-wise)

Objective
recognize lesional vertices with highest detection rate

Features
z-scores of GM thickness, GW-WM gradient, intensity, sulcal depth, sulco-gyral curvature

Classifier
Linear discriminant



2nd CLASSIFICATION
(cluster-wise)

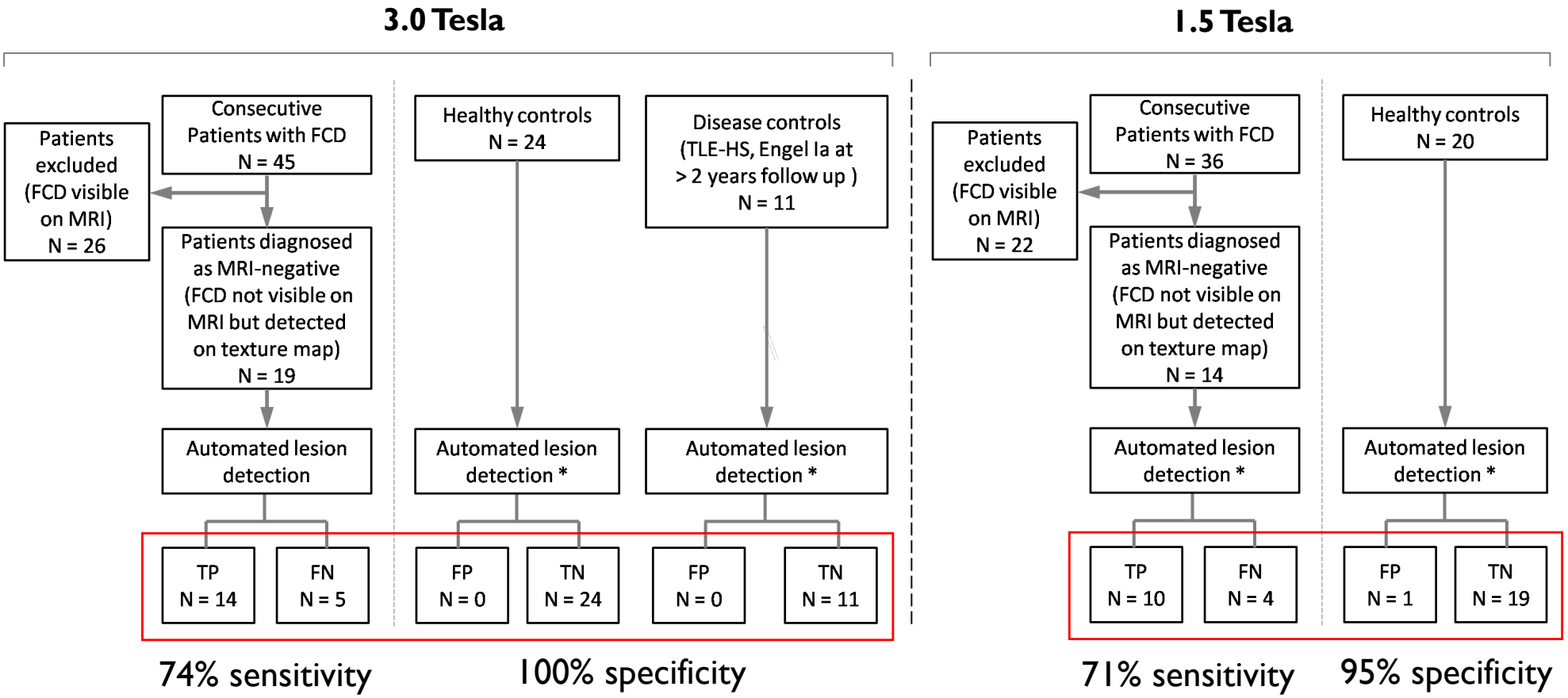
Objective
reduce false positives while maintaining high sensitivity

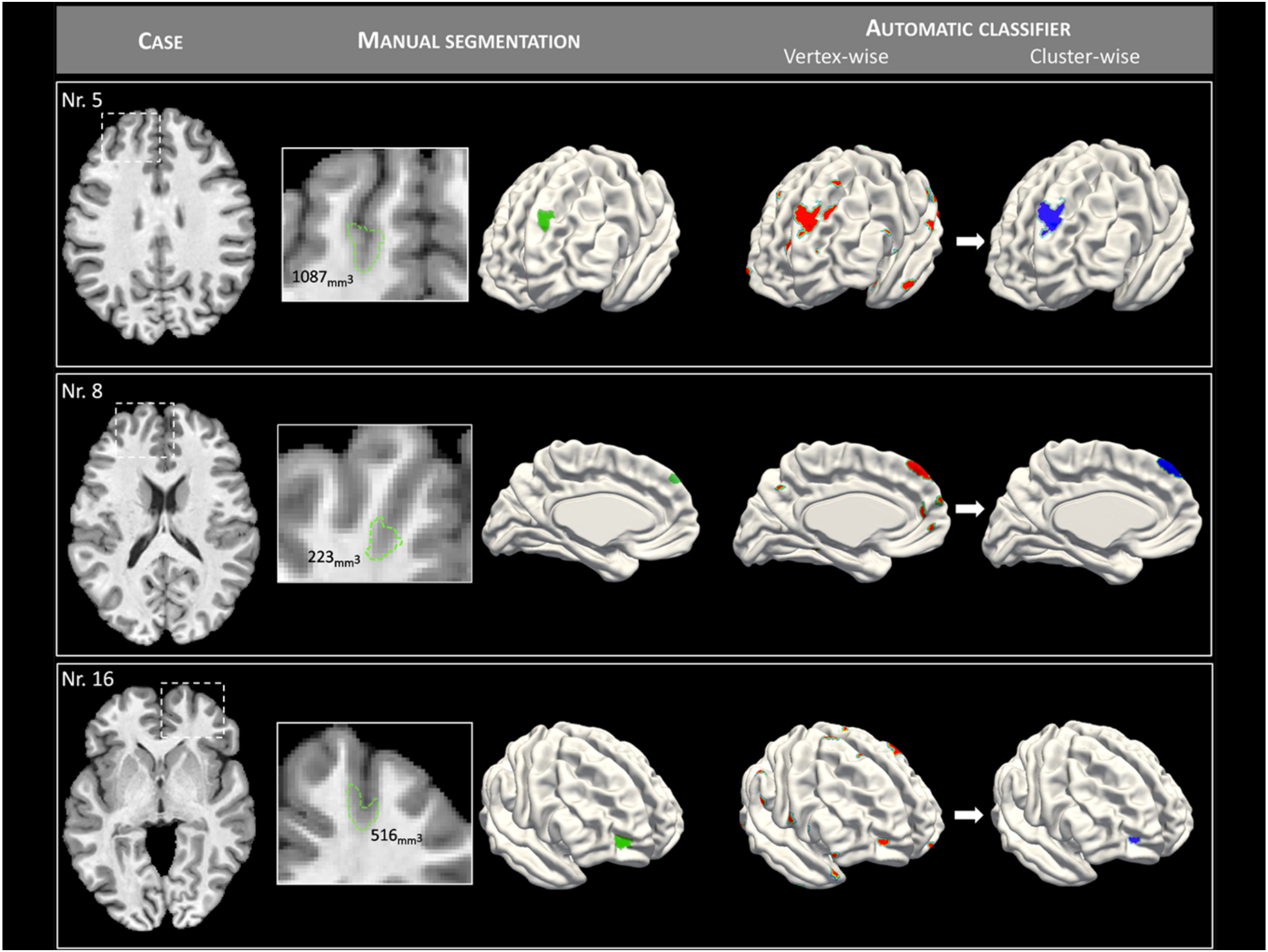
Features
mean, SD
skewness and kurtosis (texture)
spatial priors

Classifier
Linear discriminant

Hong SJ, et al Neurology, 2014

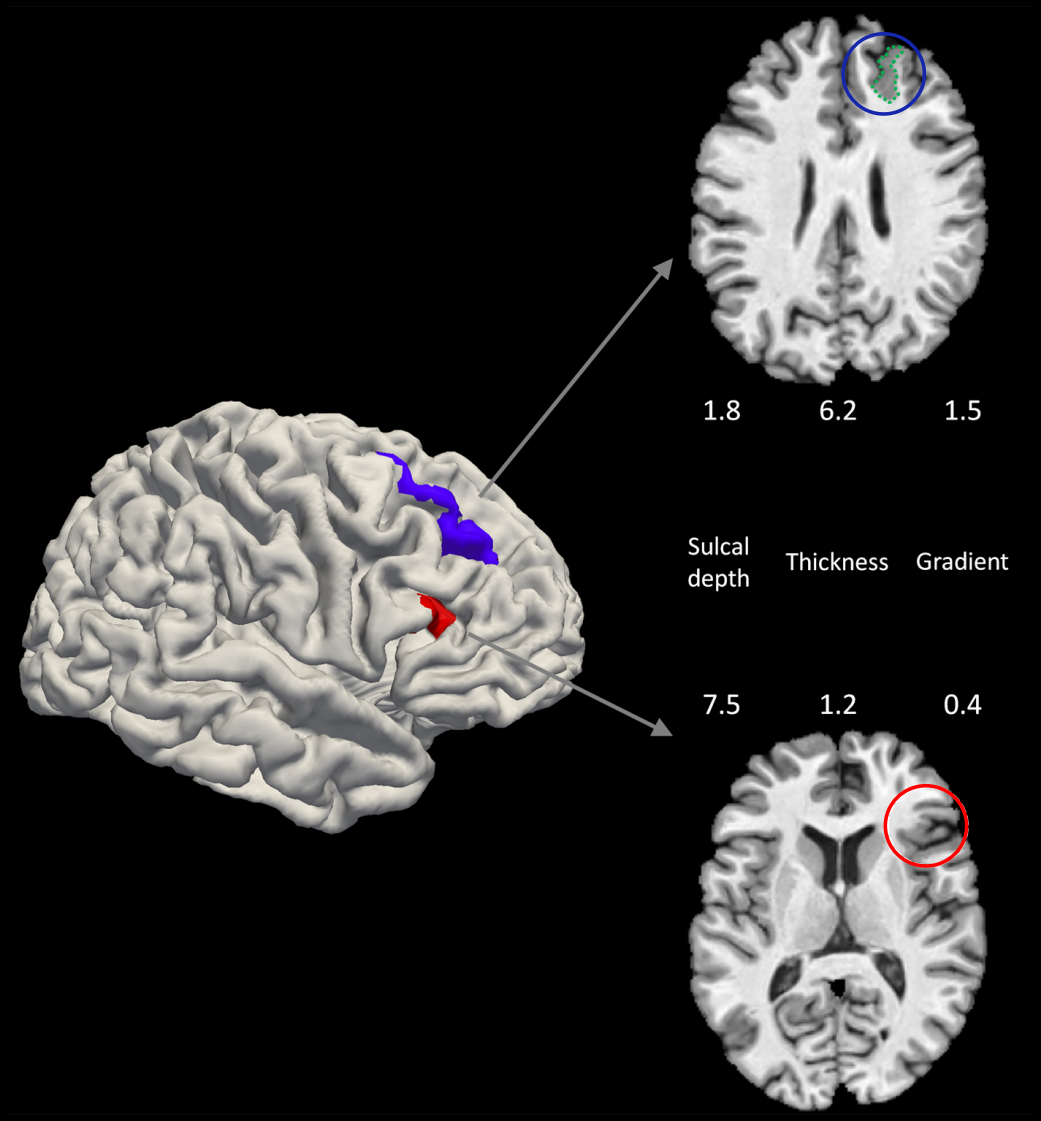
RESULTS


3.0 Tesla
Patients excluded (FCD visible on MRI) N = 26
Consecutive Patients with FCD N = 45
Patients diagnosed as MRI-negative (FCD not visible on MRI but detected on texture map) N = 19
Automated lesion detection
TP N = 14
FN N = 5
Healthy controls N = 24
Automated lesion detection *
FP N = 0
TN N = 24
Disease controls (TLE-HS, Engel Ia at > 2 years follow up) N = 11
Automated lesion detection *
FP N = 0
TN N = 11
74% sensitivity
100% specificity
1.5 Tesla
Patients excluded (FCD visible on MRI) N = 22
Consecutive Patients with FCD N = 36
Patients diagnosed as MRI-negative (FCD not visible on MRI but detected on texture map) N = 14
Automated lesion detection *
TP N = 10
FN N = 4
Healthy controls N = 20
Automated lesion detection *
FP N = 1
TN N = 19
71% sensitivity
95% specificity


CASE
MANUAL SEGMENTATION
AUTOMATIC CLASSIFIER
Vertex-wise
Cluster-wise
Nr. 5
1087mm3
Nr. 8
223mm3
Nr. 16
516mm3

S2. Conclusion

- Substantially increased sensitivity and specificity
- Generalizability across different cohorts, scanners and field strengths
- Machine learning may assist presurgical decision-making



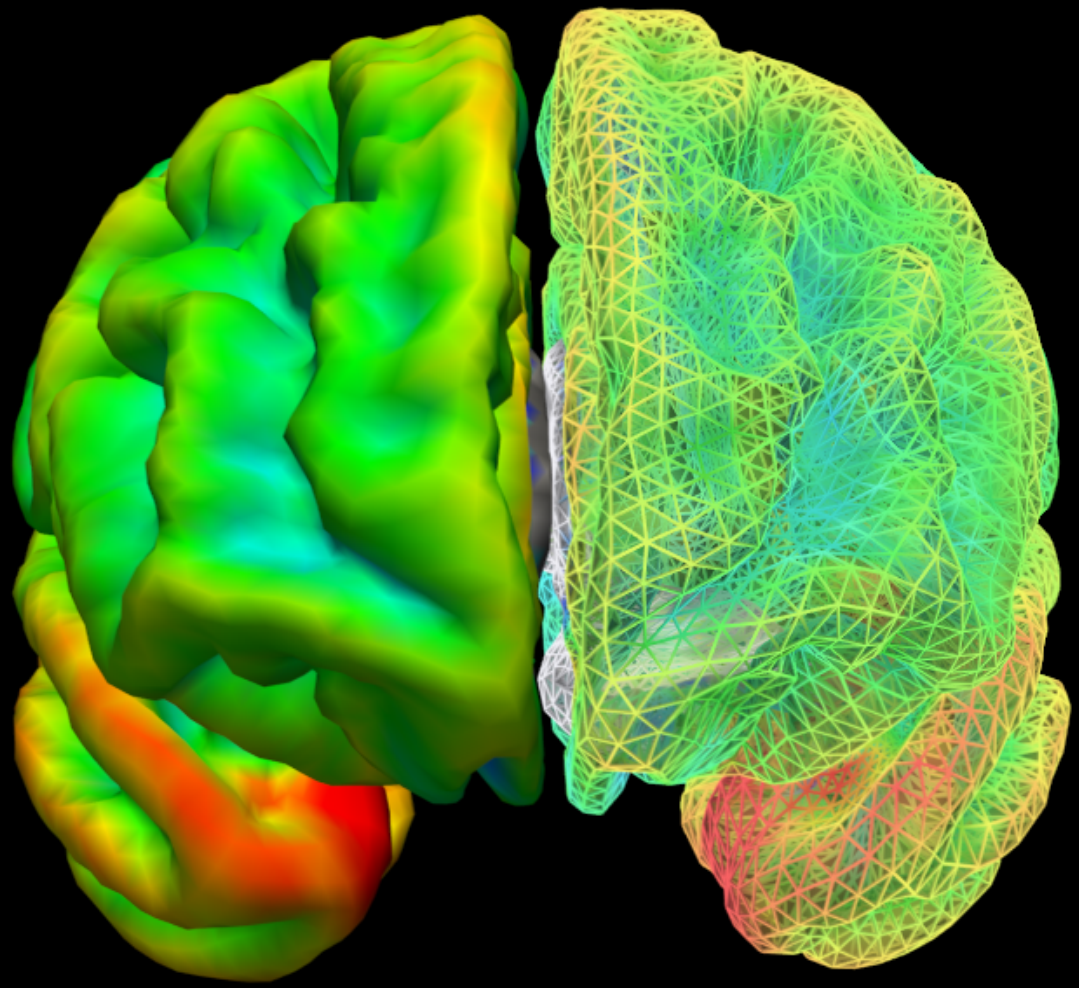
Extralesional findings

- 50 % patients had 1-3 extra-lesional clusters
- Localized in frontal or central areas
- Same lobe as the primary lesion in 2 patients; contralateral hemisphere in 3; bilateral in 2

- Less abnormal features than primary FCD
- Most abnormal feature: sulcal depth

- No EEG correlates

- Almost all previous assessments have focused on primary lesion alone
- Integrity of whole-brain anomalies have not been systematically evaluated



STUDY3 WHOLE-BRAIN MORPHOMETRY

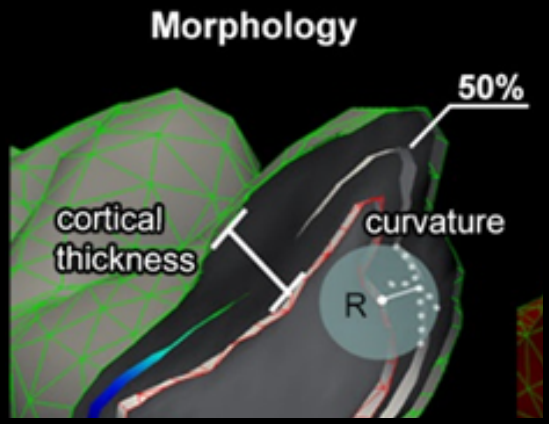
PURPOSE

1) To assess whole-brain morphology in patients with dysplasia-related frontal lobe epilepsy
2) To compare the cohorts between FCD Type-I and II

- Two frontal lobe epilepsy cohorts with histologically-verified FCD (13 Type-I; 28 Type-II) & closely-matched 41 controls

- 1.5 T, 3D T1-FFE (isotropic voxel size of 1 mm^3)

- Cortical thickness
- Gyral complexity (mean curvature)

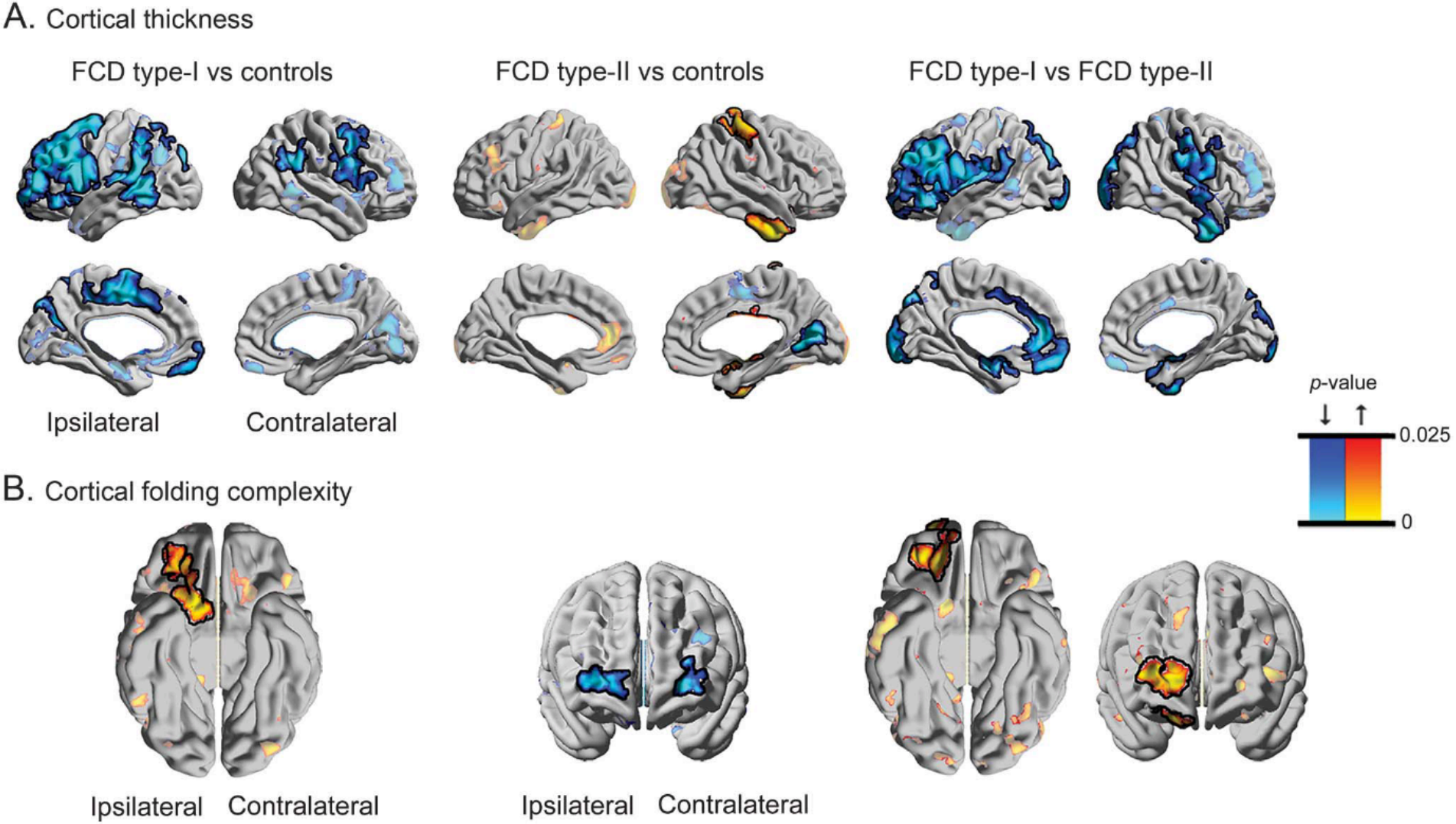


- Cross-sectional group comparison analysis (patients vs. controls; FCD Type-I vs. Type-II)

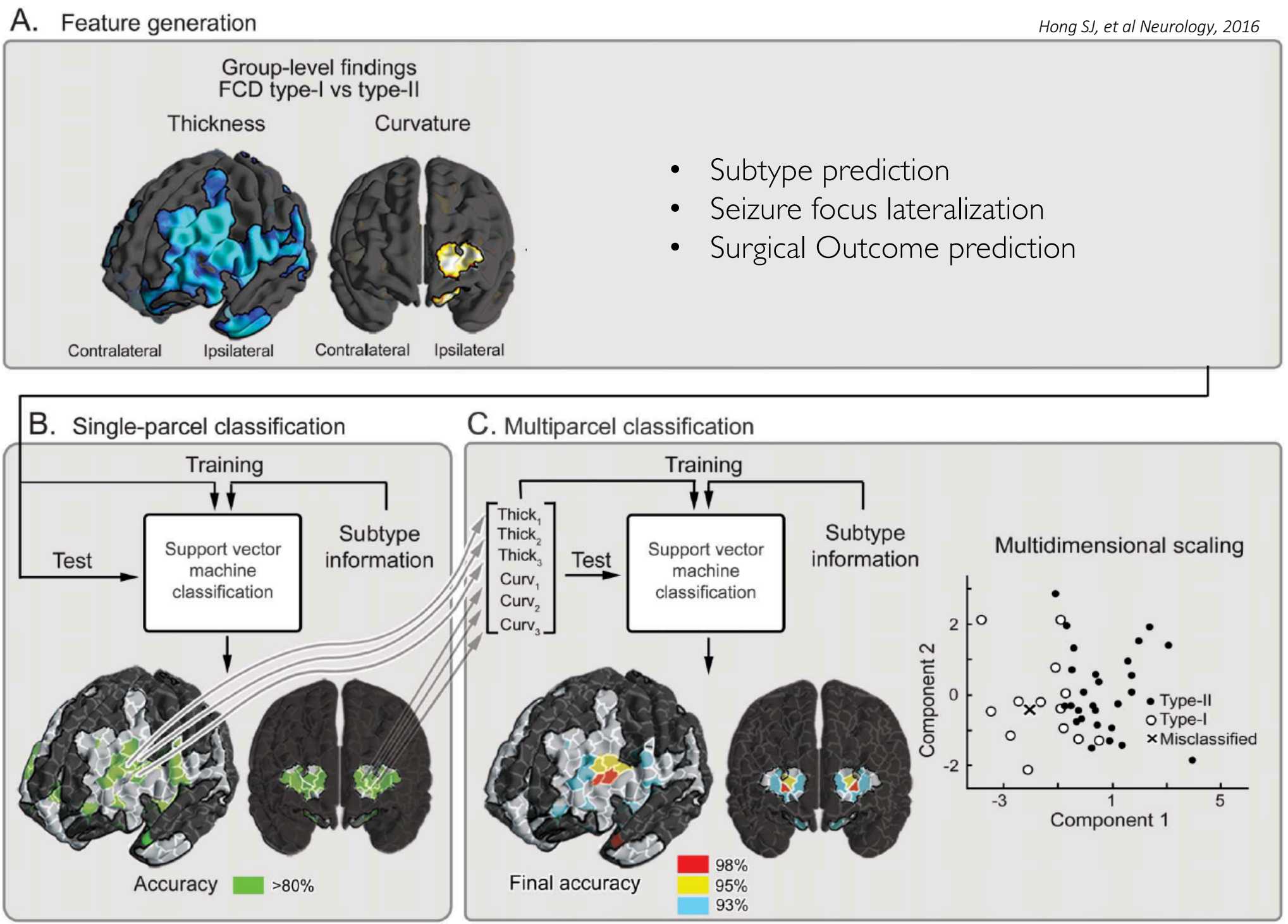
S3. Group-level comparisons

Hong SJ, et al Neurology, 2016

Figure 1 **Group-level alterations in cortical thickness (A) and folding complexity (B) in patients with FCD**



Hong SJ, et al Neurology, 2016



S3. Conclusion

- Extensive structural damage beyond the visible lesion
- Distinctive patterns between Type-I and Type-II.
- By successfully guiding multiple clinical tasks, our findings demonstrated high translational value for individualized diagnostics

SUMMARY

P1. In vivo profiling and subtype prediction of FCD Type-II:

- Reliable imaging markers to clearly dissociate histopathological subtypes

P2. Automated detection of FCD Type II in MRI-negative epilepsy

- Highly accurate detection performance across two different datasets

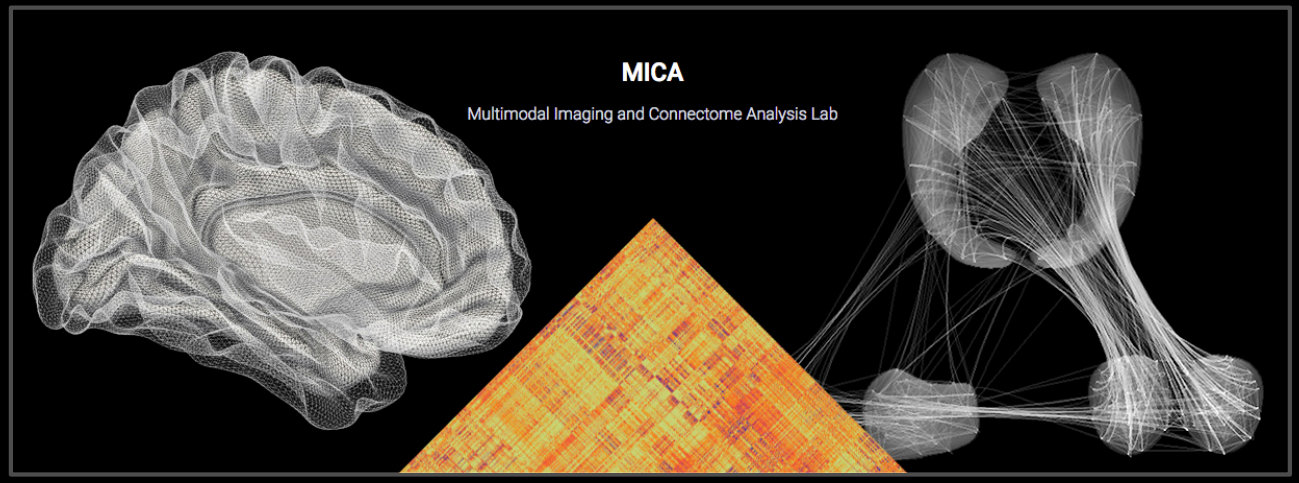
P3. Whole-brain MRI phenotyping in dysplasia-related frontal lobe epilepsy

- First demonstration that FCD is associated to whole-brain structural alterations.

SIGNIFICANCE

1. The power of multimodal MRI and image postprocessing

2. A new avenue to better understand fundamental pathological mechanisms in MCD, and clinically improve lesion detection and treatment strategies.



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