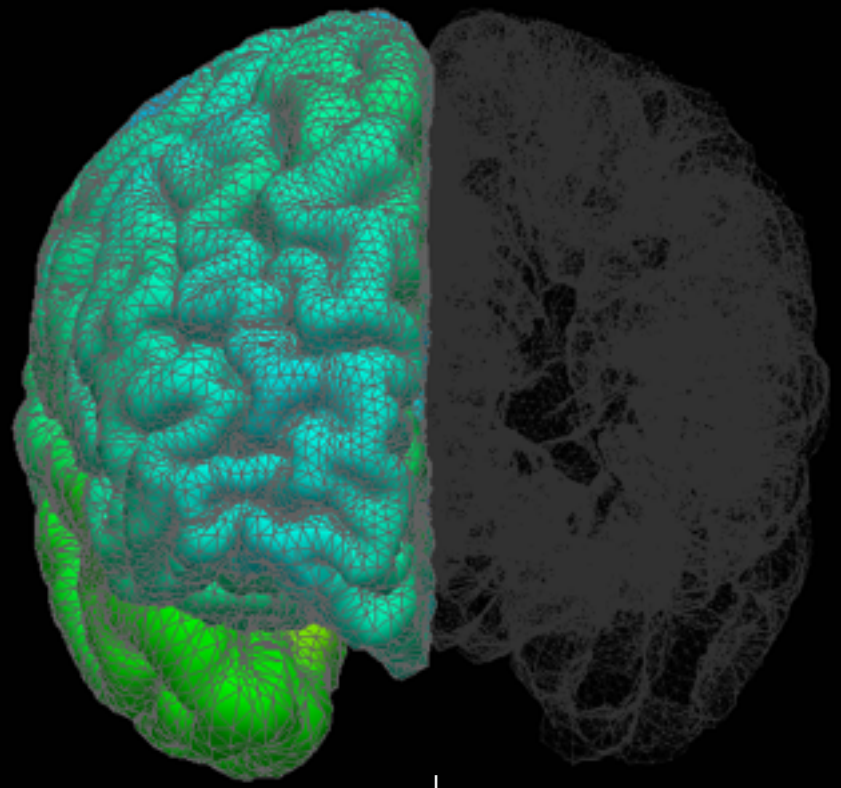


SUBTYPING EPILEPSY AND AUTISM SPECTRUM DISORDER WITH MULTIMODAL IMAGING

Boris Bernhardt, PhD

http://mica-mni.github.io

EPILEPSY AND AUTISM

HIGHLY COMMON DISORDERS

EARLY ONSET

PERSIST INTO ADULTHOOD

SYMPTOMATICALLY DIAGNOSED

CLASSIFICATIONS LARGELY IGNORE BIOLOGICAL ETIOLOGIES

LEADS TO DIVERSE COHORTS

POTENTIALLY COMPOSED OF MULTIPLE SUBTYPES

NOVEL APPROACHES FOR DIAGNOSIS AND STRATIFICATION

NEUROIMAGING AS A TRANSFORMATIVE TOOL

PROBE MULTIPLE
BIOLOGICAL PROPERTIES IN VIVO

IDENTIFY SUBTYPES

FIND COMMONALITIES ACROSS DISEASES

PROVIDE PROGNOSTIC MARKERS

MONITOR DISEASE
PROGRESSION AND INTERVENTION

OUTLINE

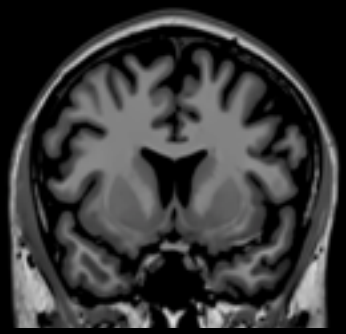
MULTIMODAL NEUROIMAGING:
STRUCTURE, FUNCTION, NETWORKS

NEUROIMAGING SUBTYPING
IN EPILEPTIC DISORDERS

NEUROIMAGING-DERIVED
AUTISM SPECTRUM SUBTYPES

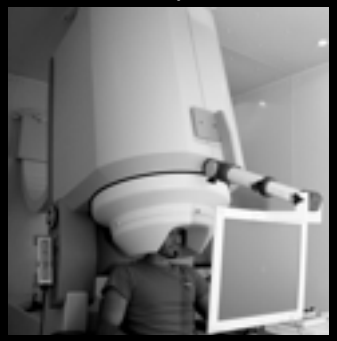
MULTIPLE NEUROIMAGING MODALITIES

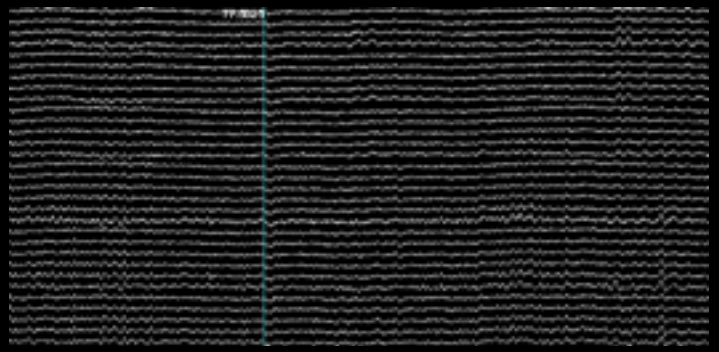
MRI



STRUCTURE
FUNCTION

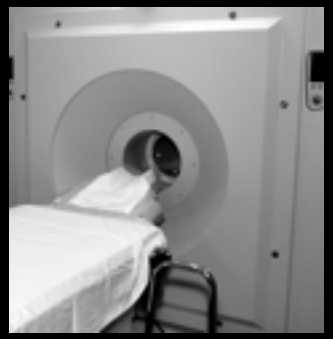
MEG/EEG

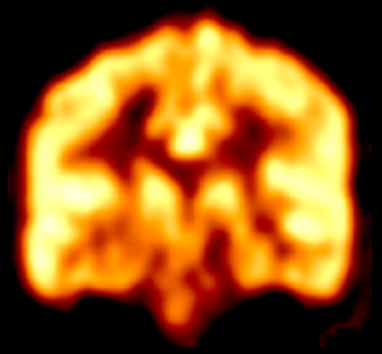




DYNAMICS

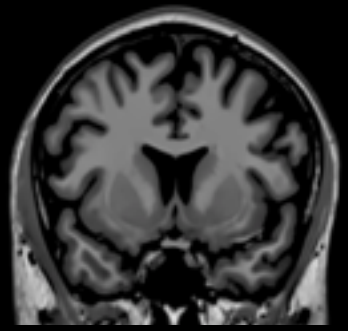
PET

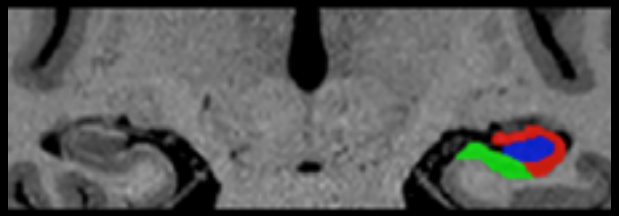




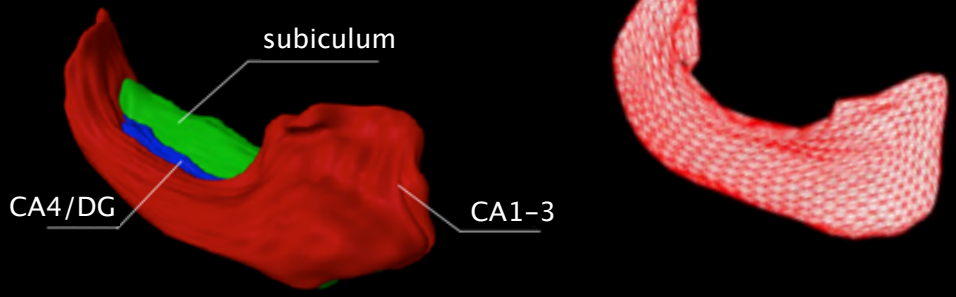
METABOLISM
TRANSMITTERS

DESCRIBING ANATOMY

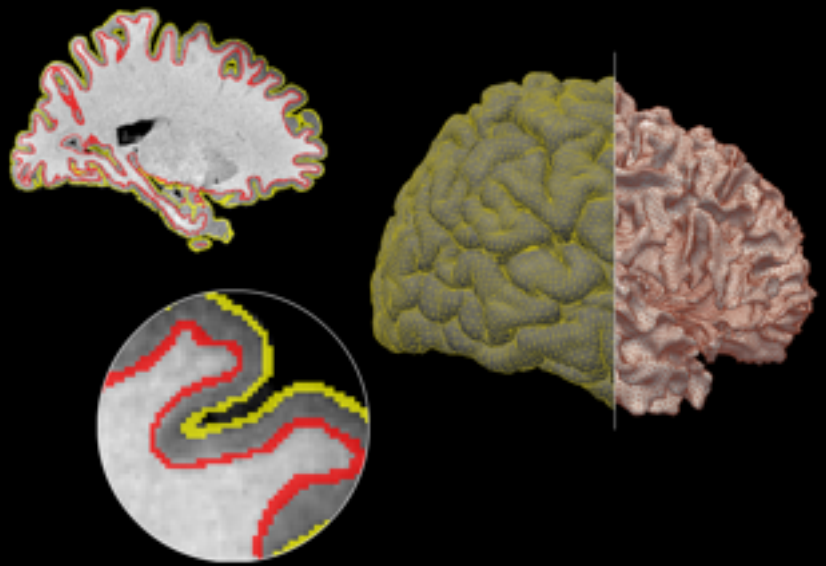




SEGMENTATION

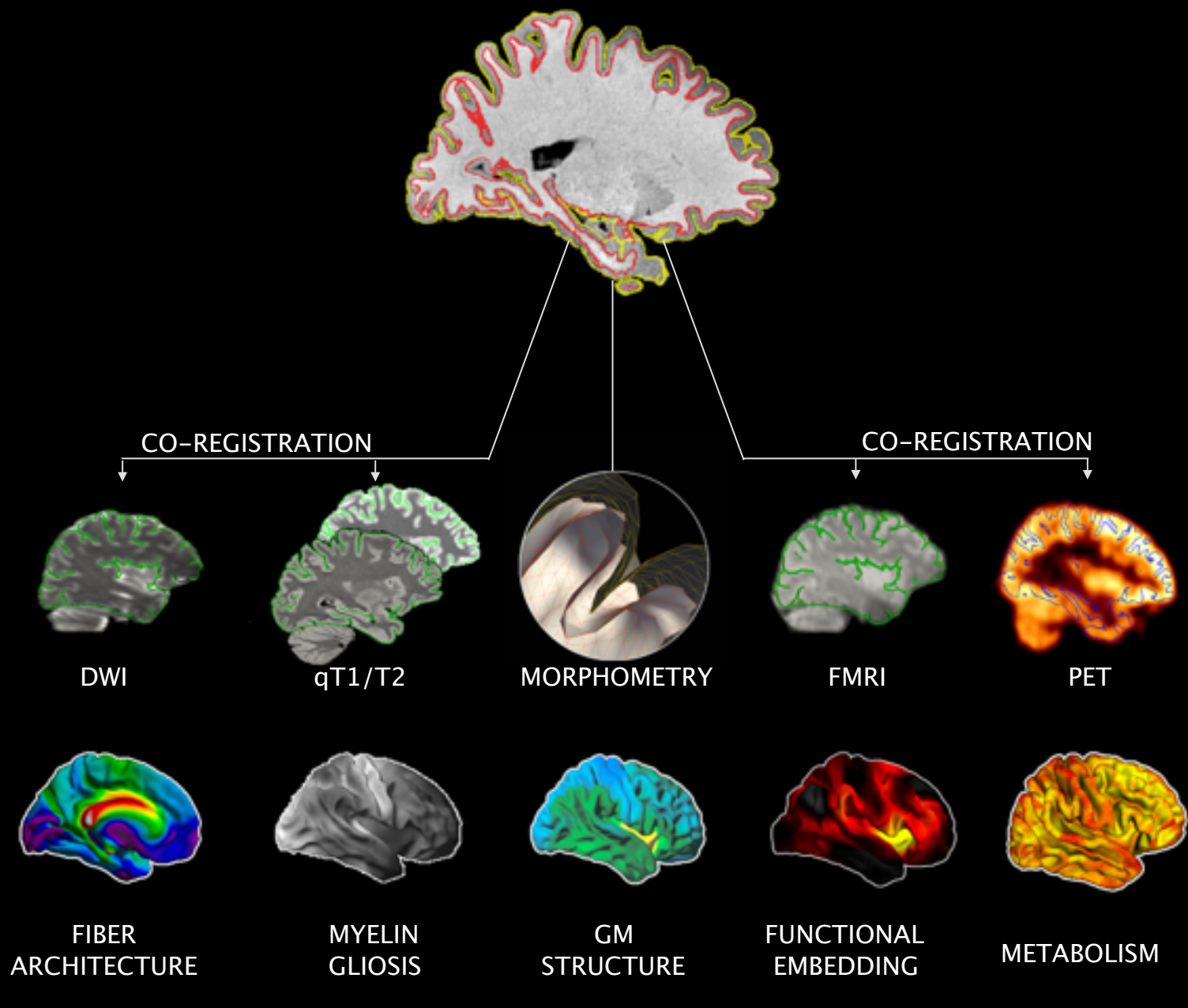


NATIVE T1w NORMALIZATION CLASSIFICATION



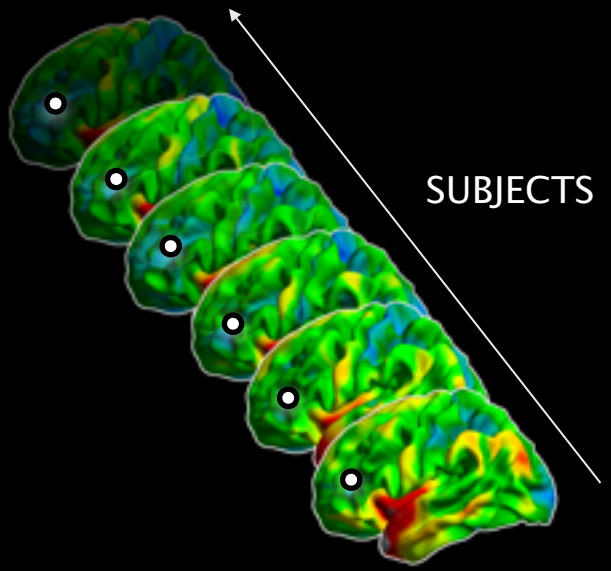
MacDonald et al. (1999) NIMG, Fischl and Dale (2000) Hum Brain Mapp, Kim et al. (2005) NIMG

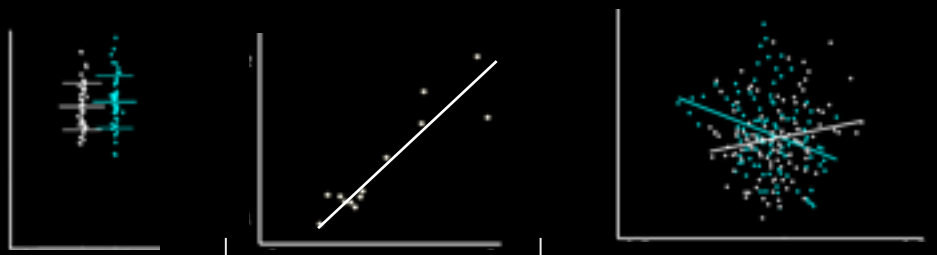
MULTI-MARKER INTEGRATION



REGIONAL STATISTICAL ANALYSIS

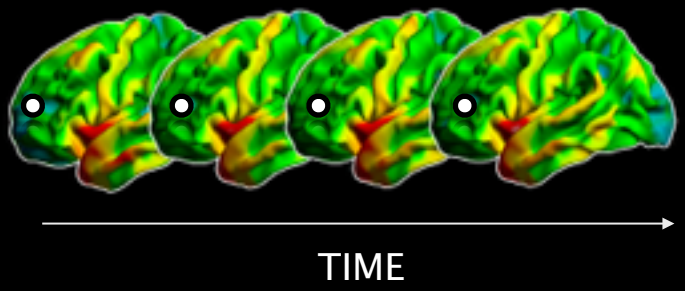
CROSS-SECTIONAL ANALYSES

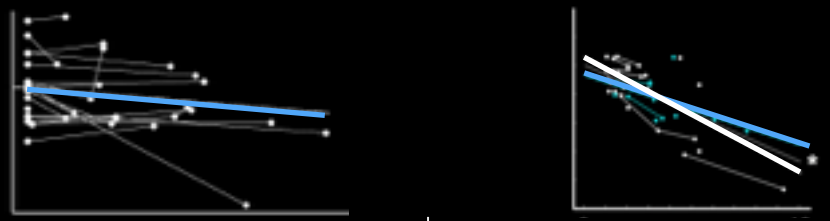




Y=1+G | Y=1+A | Y=1+G+A+G×A

LONGITUDINAL ASSESSMENTS

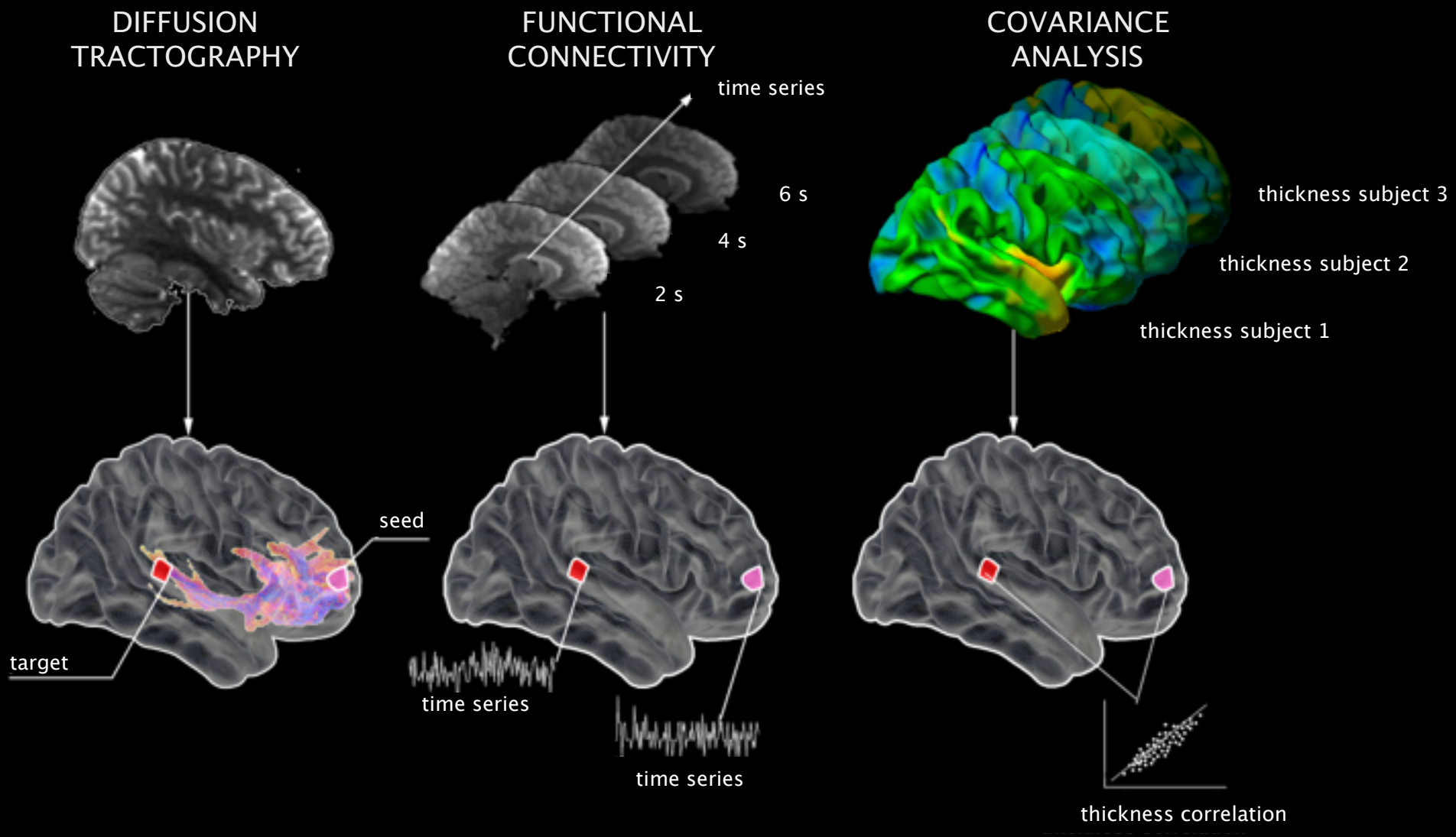




Y=1+r(S)+ISI | Y=1+r(S)+ISI+G+ISI×G

Y is univariate or multivariate data

INTER-REGIONAL CONNECTIVITY ANALYSIS

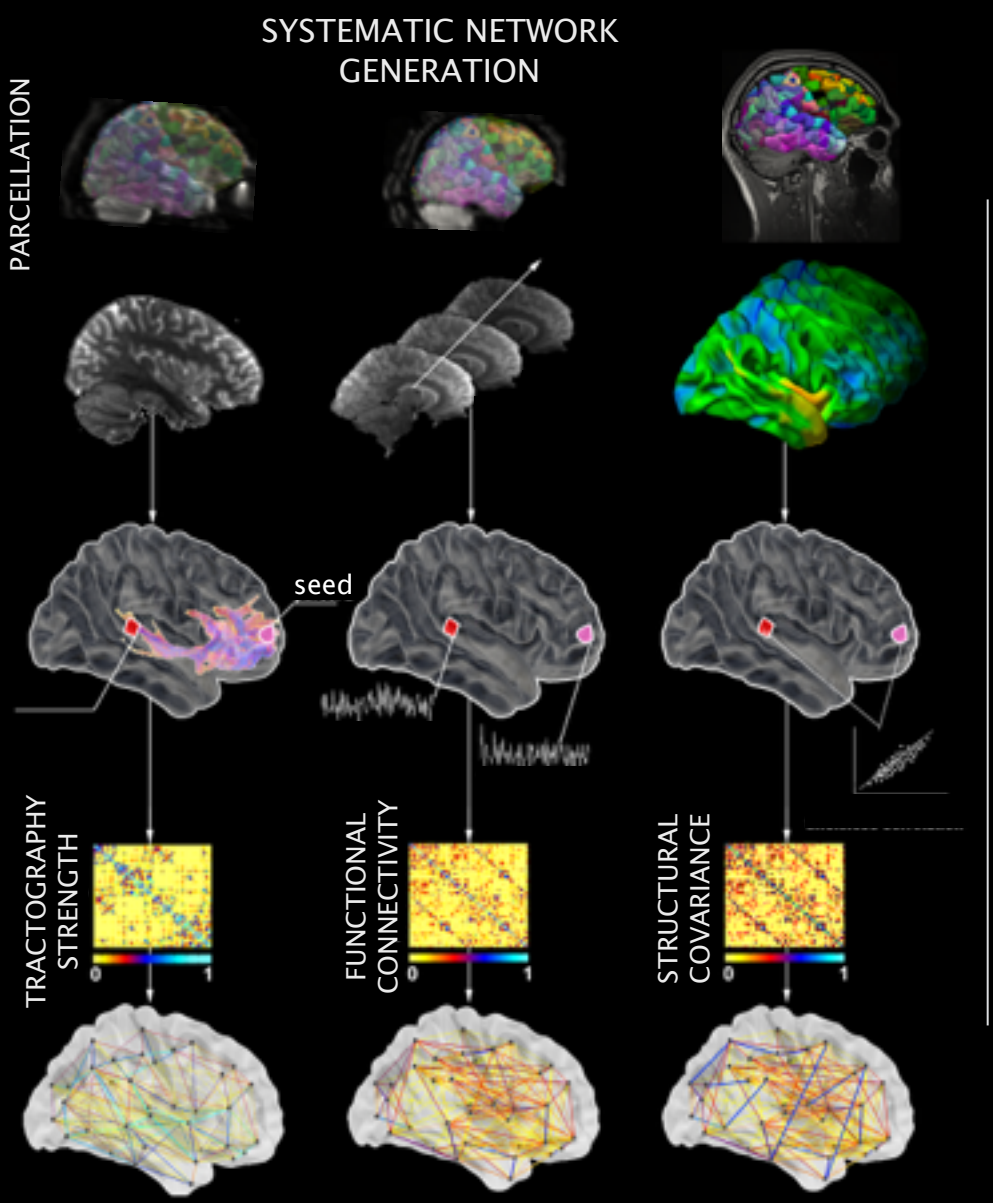


Mori et al. (1999) Ann Neu
Behrens et al. (2007) NIMG

Friston (1994) HBM
Smith (2012) NIMG

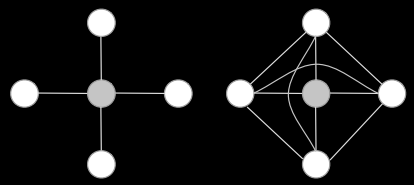
Lerch et al. (2006) NIMG
Alexander-Bloch et al. (2013) NRN

CONNECTOME ANALYSIS

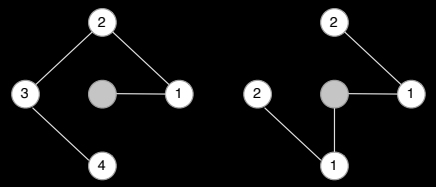


GRAPH THEORETICAL PARAMETERS

CLUSTERING C

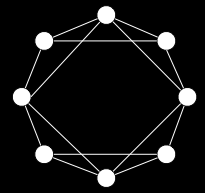


PATH LENGTH P



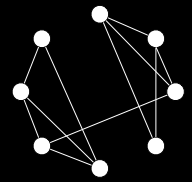
TOPOLOGY CLASSIFICATION

REGULAR



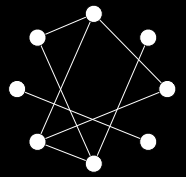
C+ P+

SMALL-WORLD



C+ P-

RANDOM

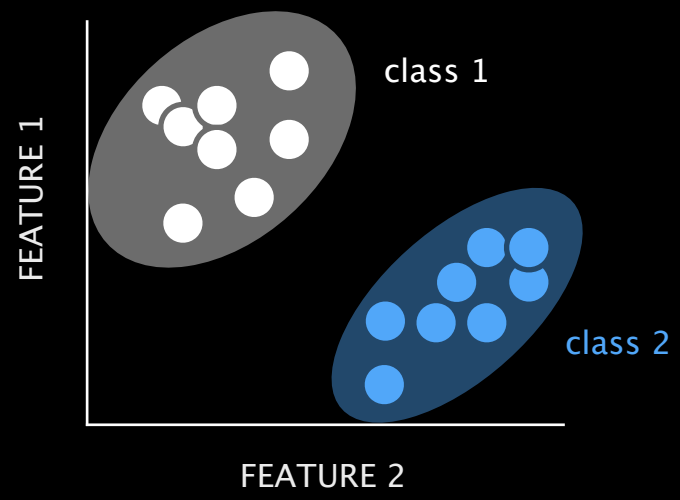


C- P-

Bullmore and Sporns (2009) NRN, Watts and Strogatz (1998) Nature

PATTERN LEARNING

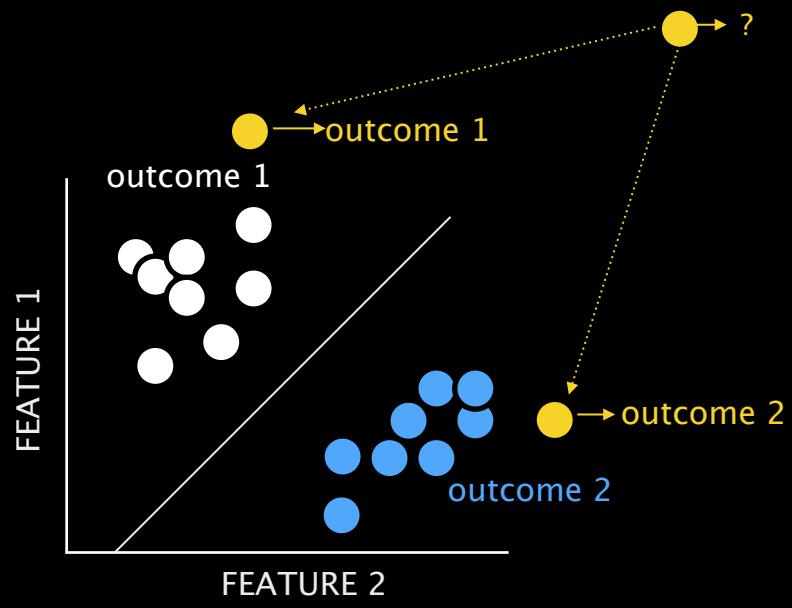
UNSUPERVISED



GROUP CASES WITH
SIMILAR FEATURES

K-MEANS, HIERARCHICAL CLUSTERING

SUPERVISED



TRAIN FEATURE-OUTCOME MAPPING
ON KNOWN CASE

PREDICT OUTCOME OF NEW CASE
BASED ON ITS LOCATION IN FEATURE SPACE

LDA, SVM

Mitchell (1997), Burgess (1999), MacKay (2002), Bishop (2006)

EPILEPSY

CHRONIC SEIZURES

0.5–1.5% OF POPULATION

HETEROGENOUS

30% OF PATIENTS ARE DRUG-RESISTANT

MULTIDISCIPLINARY ASSESSMENT

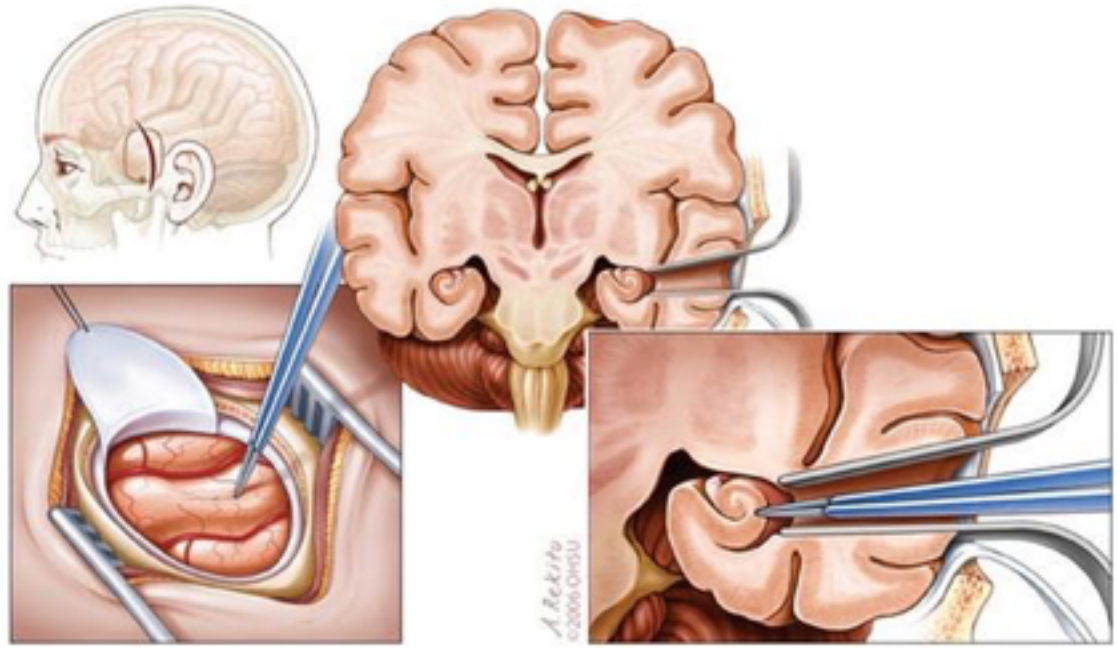
TEMPORAL LOBE EPILEPSY

MOST COMMON DRUG-RESISTANT EPILEPSY IN ADULTS

SEIZURES ARISING FROM TL

ASSOCIATED WITH HIPPOCAMPAL SCLEROSIS

SURGERY MOST EFFECTIVE TREATMENT



Spencer & Burchiel (2012) Epilepsy Research and Treatment

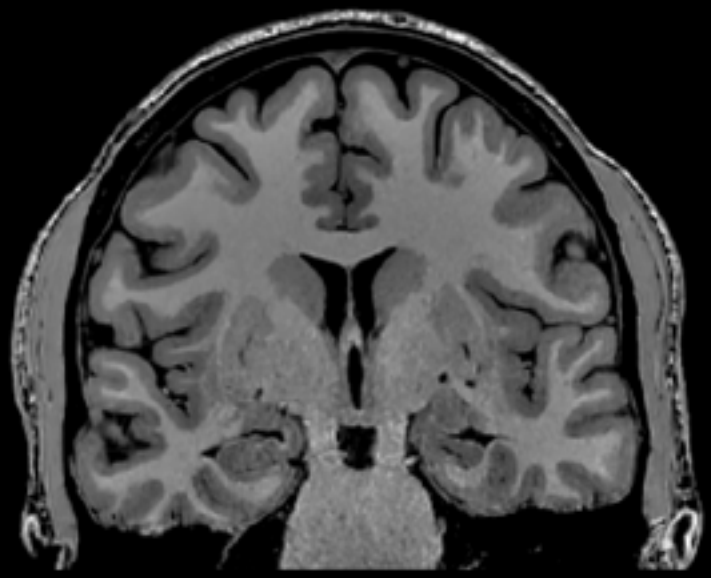
HIPPOCAMPAL PATHOLOGY AND IMAGING IN TLE

MRI plays key role in detecting HS non-invasively

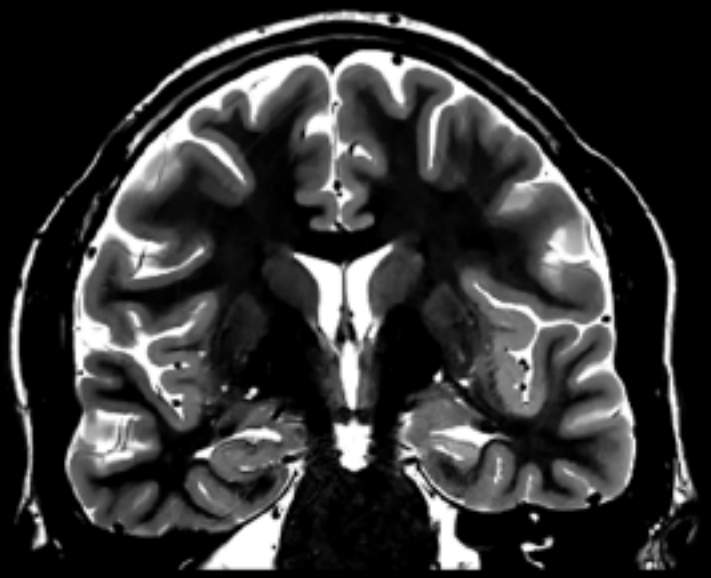
Atrophy and T2w increases can lateralize seizure focus in patients with HS

In the clinics: frequently done visually

Increasing proportions of patients with less remarkable anomalies



T1-weighted

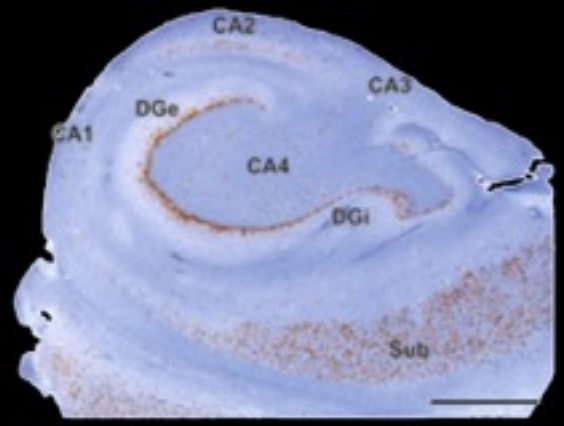


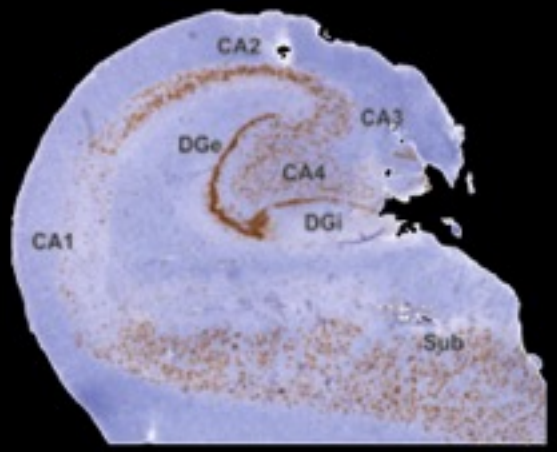
T2-weighted

TEMPORAL LOBE EPILEPSY

Pathological hallmark: hippocampal sclerosis (HS) – not a single entity

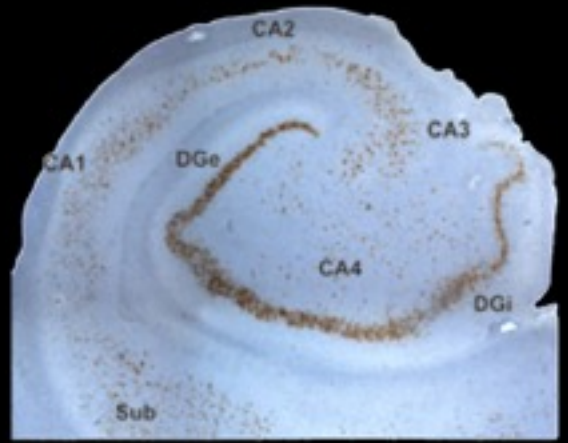
CA1+CA4 cell loss + gliosis

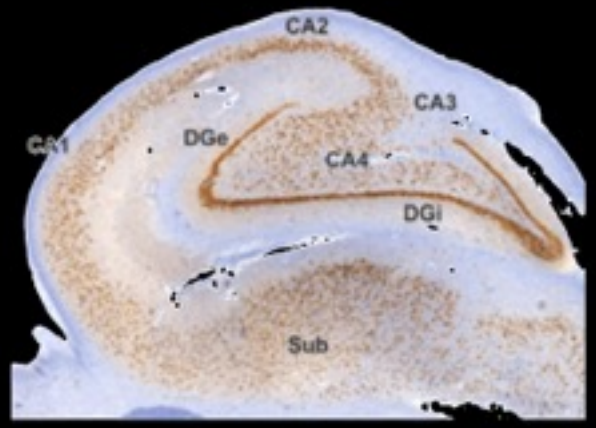




CA1 cell loss + gliosis

CA4 cell loss + gliosis





gliosis only

Blümcke et al (2013) Epilepsia

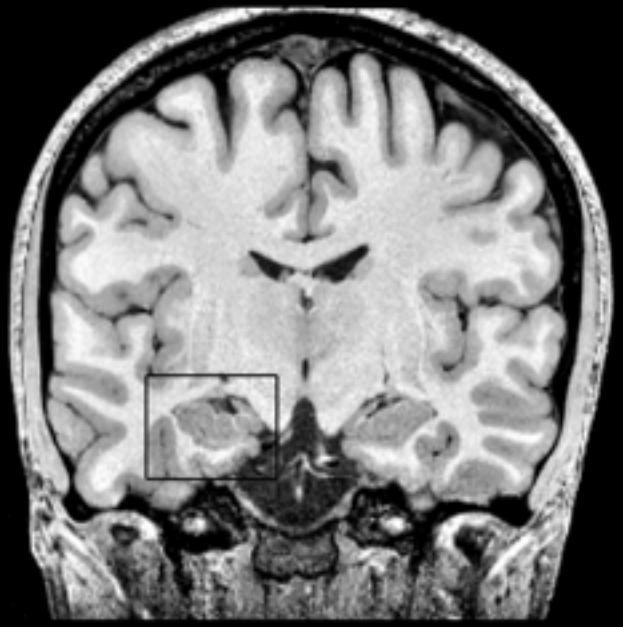
CAN WE IDENTIFY PATHOLOGICAL SUBTYPES IN VIVO?

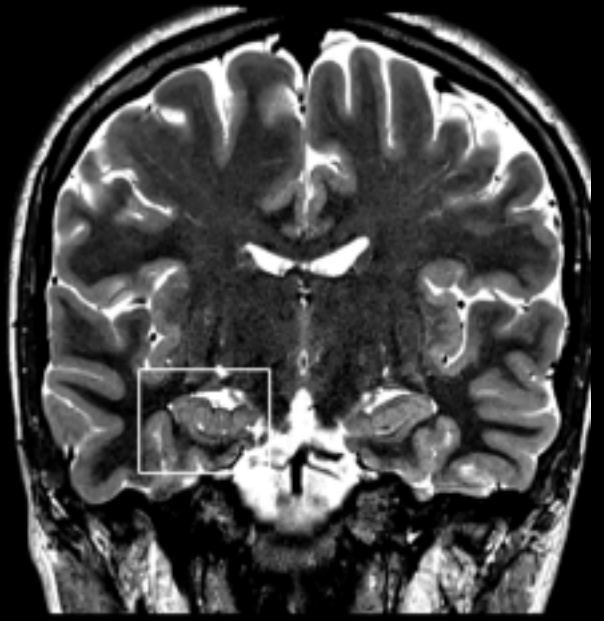
STUDY PURPOSE

IDENTIFY MRI SIGNATURES OF TLE-HS AND TLE-G

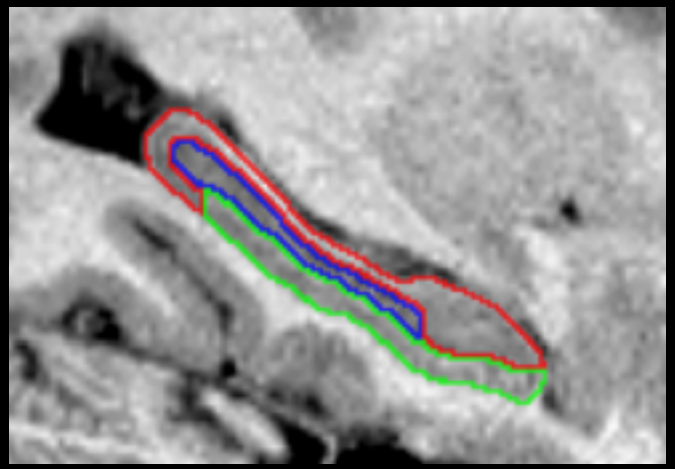
DESIGN:

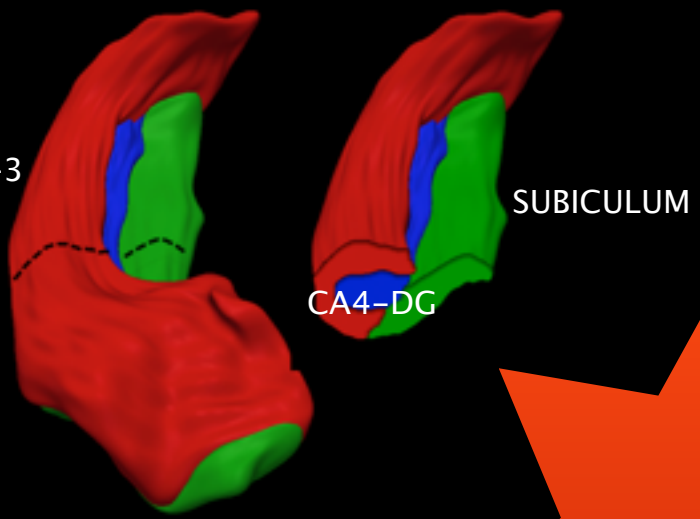
- Consecutive series of 39 unilateral TLE patients who had high resolution preoperative MRI, no mass lesions, surgical treatment, and ILAE HS scoring
  - 20 TLE-HS (10 HS-1, 6 HS-2, 4 HS-3), 19 TLE-G
  - 25 age- and sex-matched controls
- Multi-modal 3T MRI in all, in addition to clinical imaging
  - high-resolution T1w (0.6 mm, 2 averages), T2w (0.4×0.4×2.0 mm)
  - standard DWI and RS-FMRI
- Hippocampal subfield segmentations in all





https://www.nitrc.org/projects/mni-hisub25/

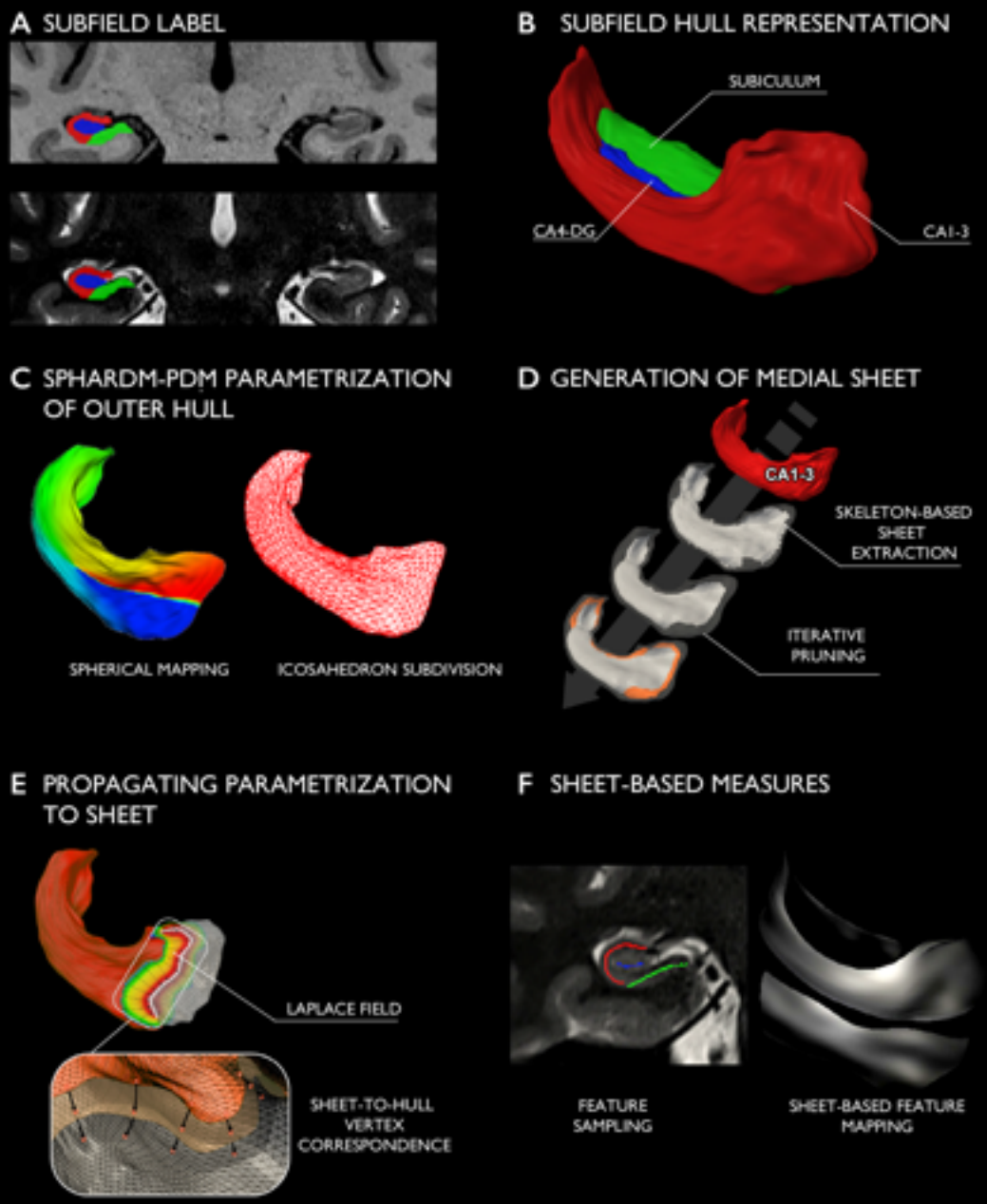




OPEN

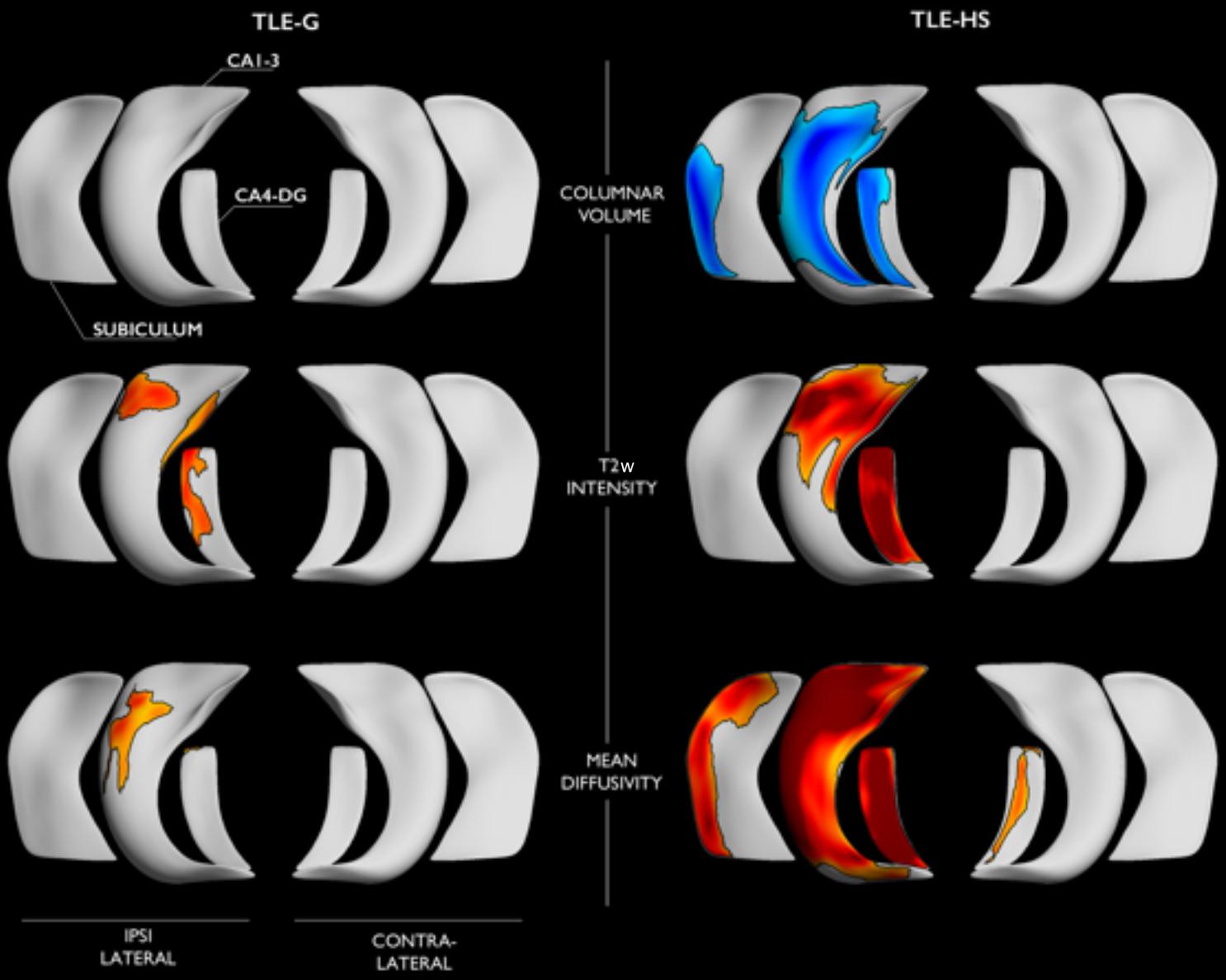
Kulaga -Yoskovitz, Bernhardt et al. (2015) Scientific Data

IMAGE PROCESSING



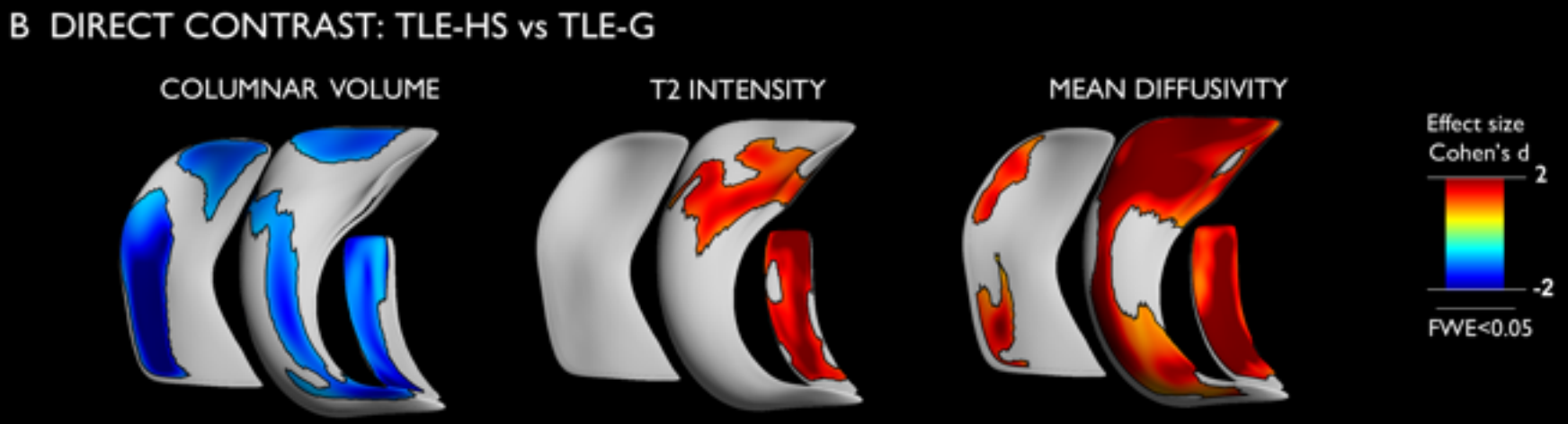
Kim, Bernhardt et al (2015) MICCAI

FEATURE-SPECIFIC COMPARISON TO CONTROLS



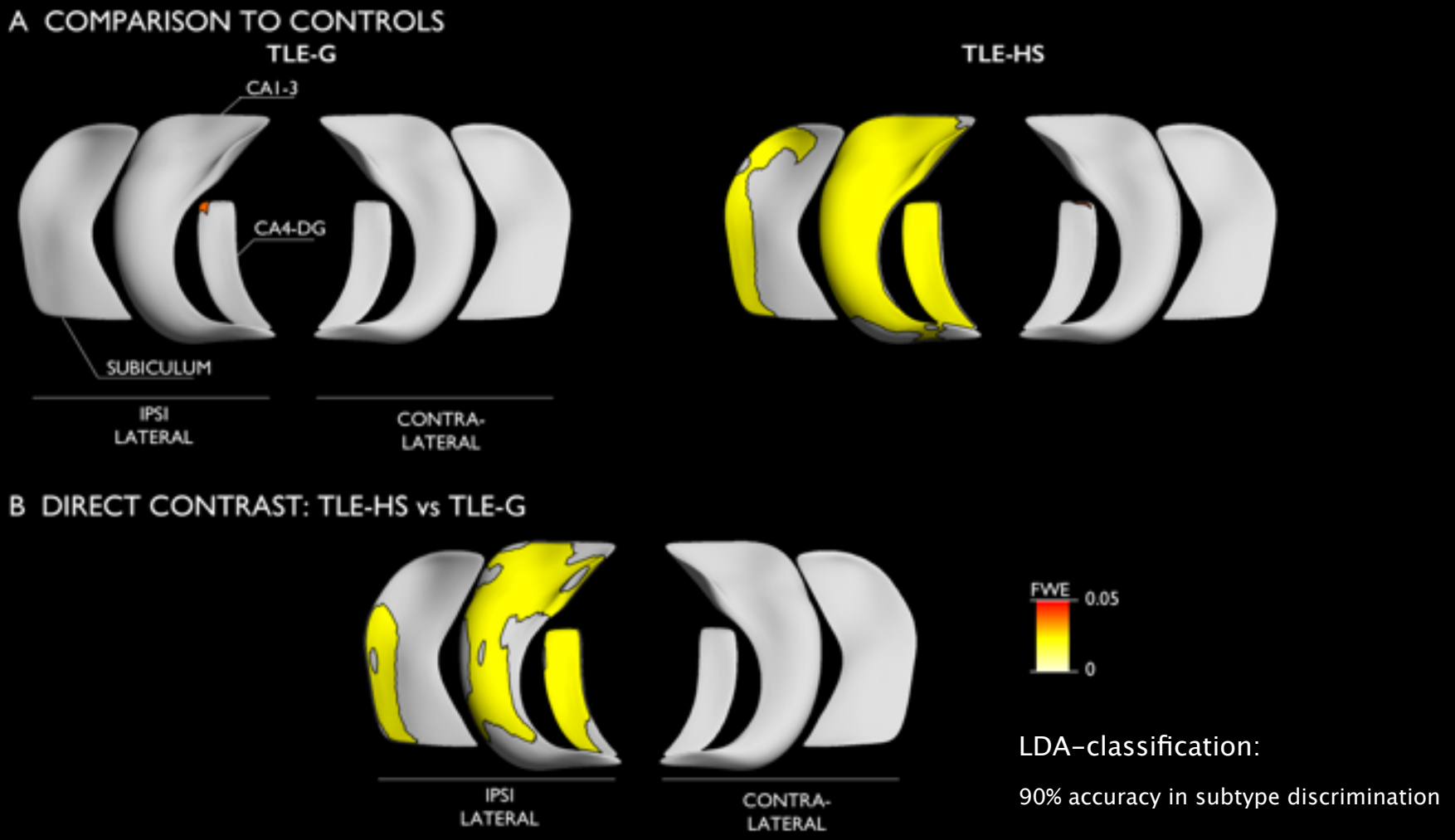
Bernhardt et al (2016) Annals of Neurology

DIRECT CONTRASTS



Bernhardt et al (2016) Annals of Neurology

MULTIVARIATE SYNTHESIS

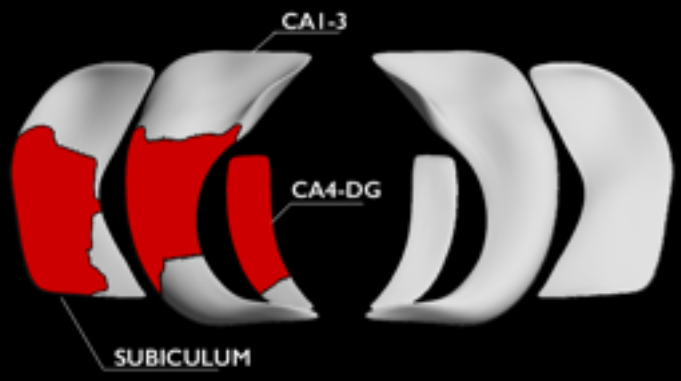


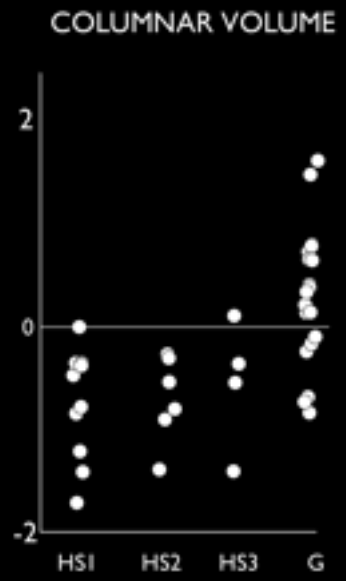
LDA-classification:

90% accuracy in subtype discrimination

Bernhardt et al (2016) Annals of Neurology

RELATION TO SPECIFIC HISTOLOGICAL HS GRADES





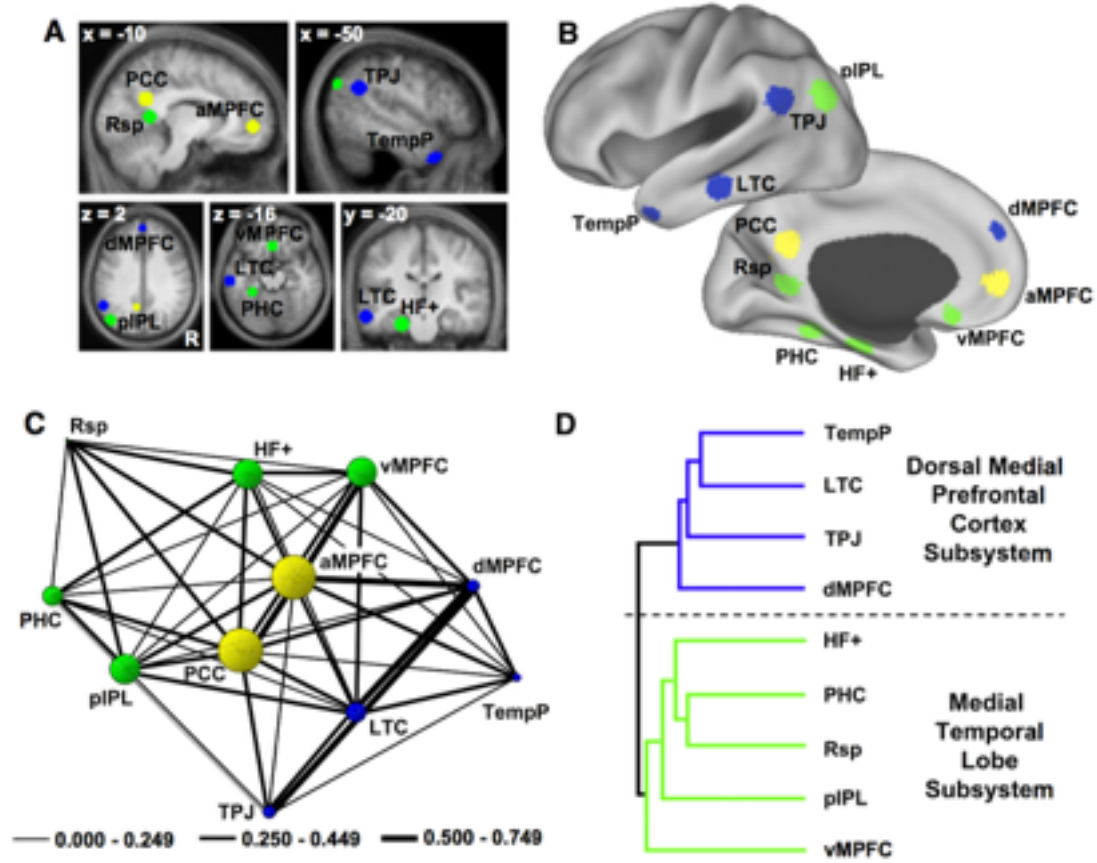
Bernhardt et al (2016) Annals of Neurology

FUNCTION

rs-FMRI ANALYSIS
PROVIDE INFORMATION ON
INTRINSIC FUNCTIONAL NETWORKS

HIPPOCAMPUS HIGHLY INTEGRATED
WITH DMN

TLE-HS vs TLE-G:
DISEASE MODEL TO PROBE
STRUCTURE-FUNCTION RELATIONS

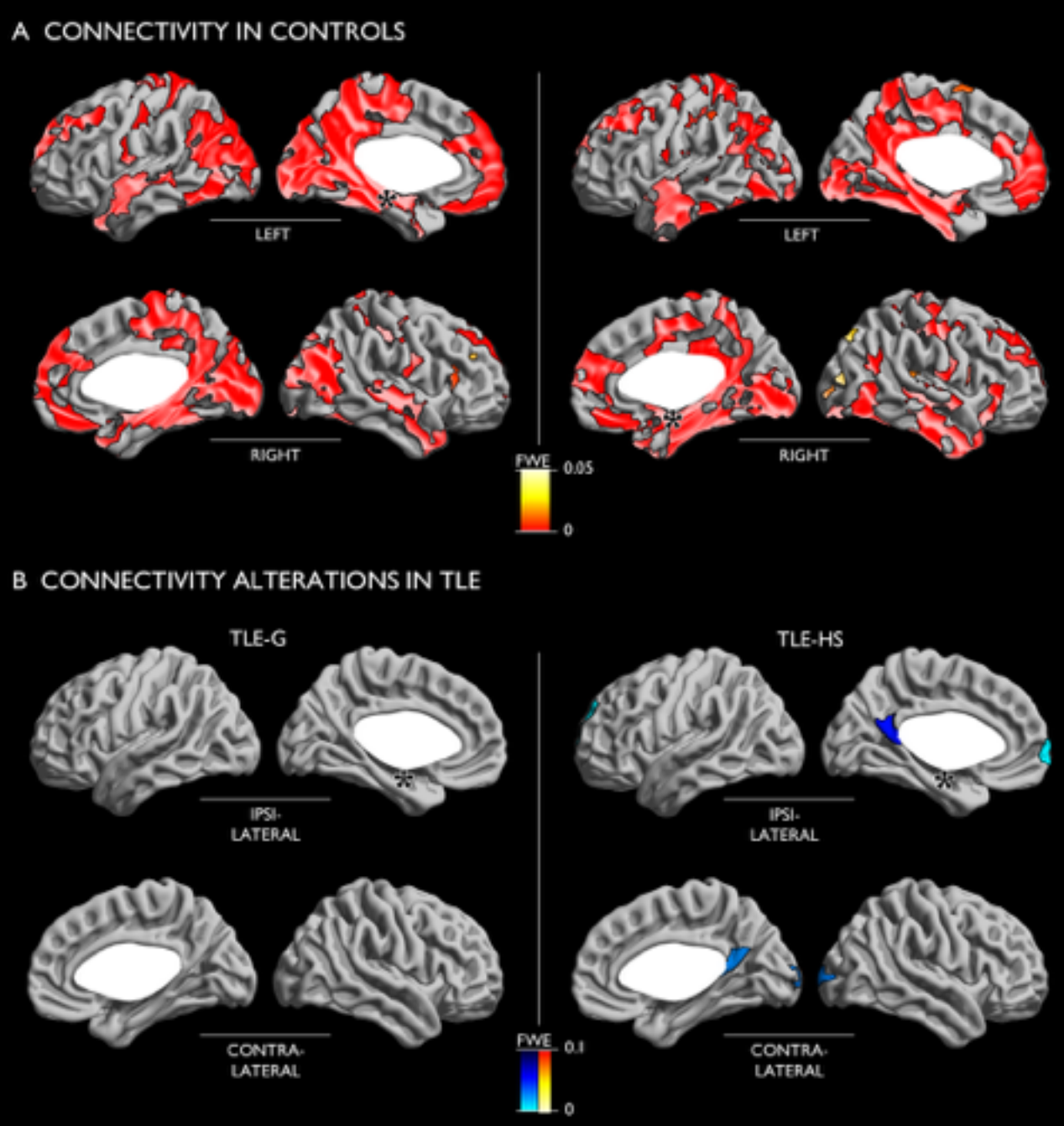


Andrews-Hanna et al (2010) Neuron

FUNCTION

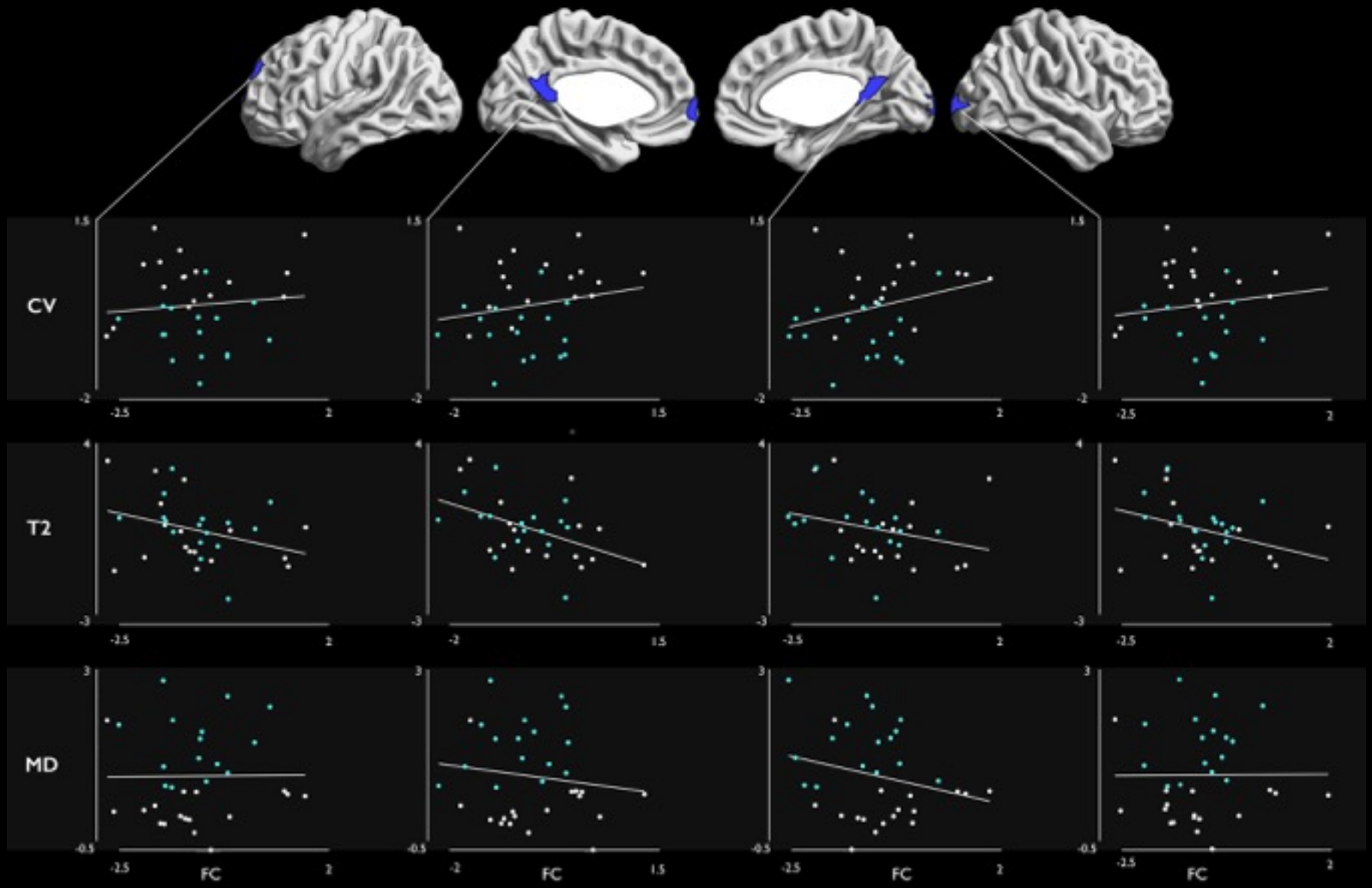
CONNECTIVITY IN CONTROLS CONFIRMS ROLE OF HIPPOCAMPUS IN DMN

DIVERGENCE BETWEEN TLE-HS AND TLE-G ALSO SEEN AT THE LEVEL OF FUNCTIONAL CONNECTIVITY



Bernhardt et al (2016) Annals of Neurology

STRUCTURE–FUNCTION RELATIONSHIPS IN TLE



Bernhardt et al (2016) Annals of Neurology

HIPPOCAMPAL SUBTYPES

MRI PROBES LOCAL
PATHOLOGICAL CHANGES

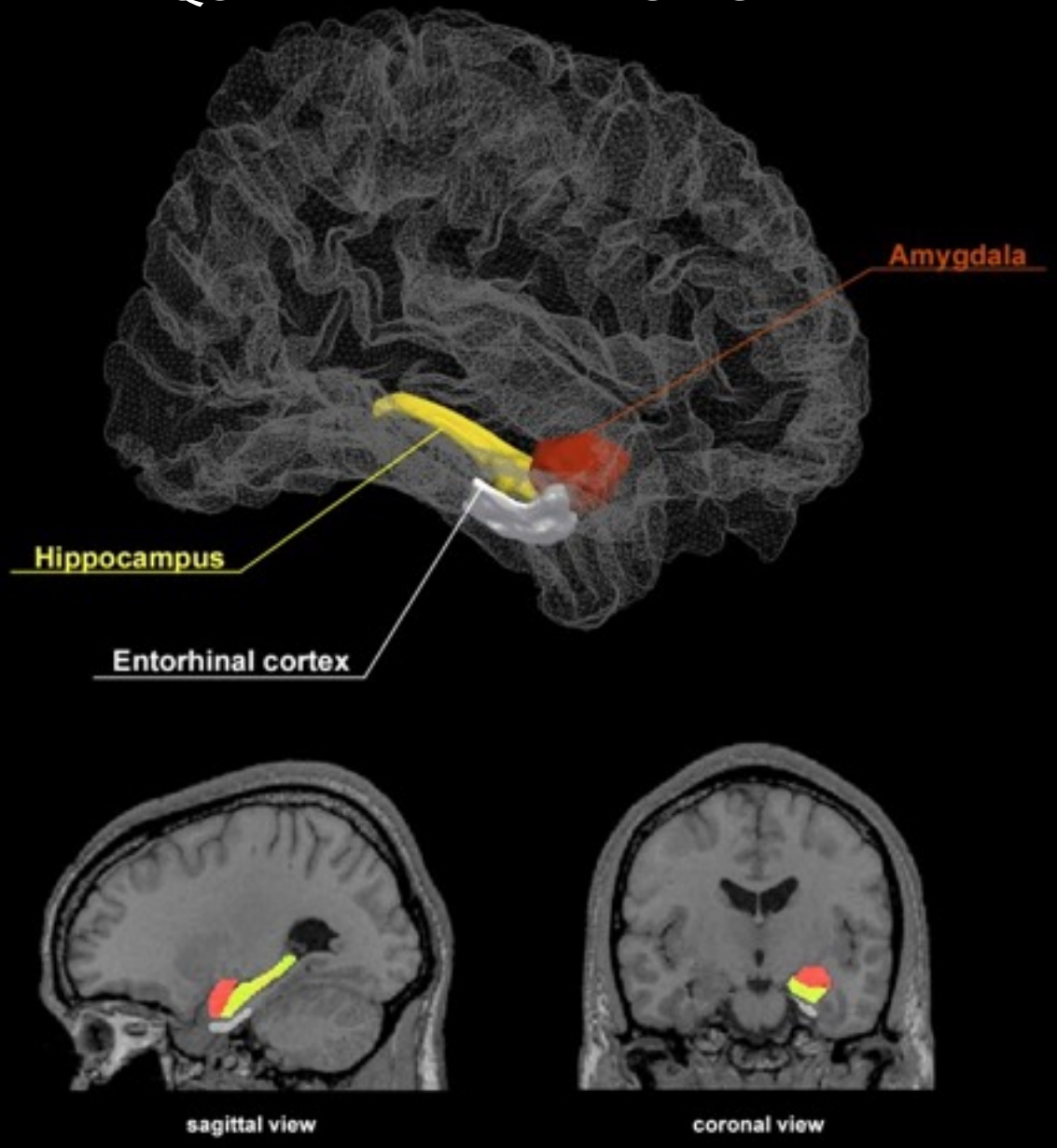
INDIVIDUALIZED PATHOLOGY
PREDICTION POSSIBLE

STRUCTURAL ANOMALIES
RELATE TO FUNCTIONAL NETWORK
EMBEDDING

TLE = SPECTRUM OF STRUCTURAL AND
FUNCTIONAL ANOMALIES

IS TLE ADEQUATELY CAPTURED BY HIPPOCAMPUS ALONE?

QUANTITATIVE IMAGING IN TLE



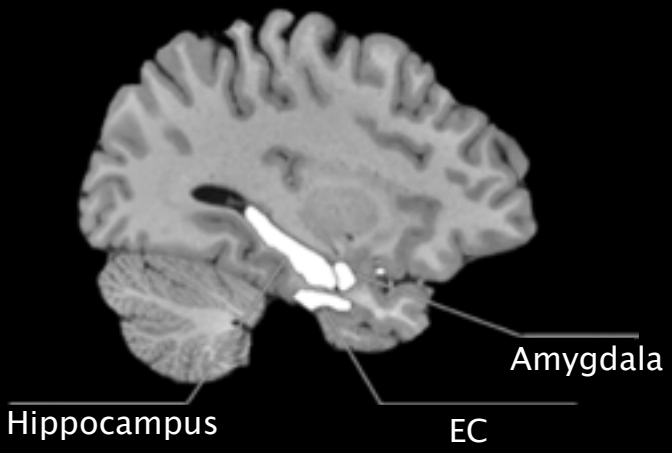
Cascino et al (1991) Annals of Neurology, Jackson et al (1995) Neurology

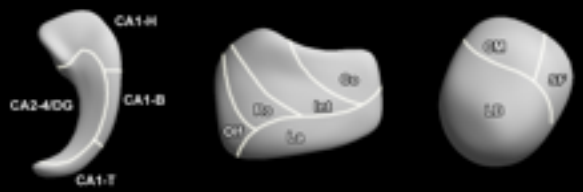
Kuzniecky et al (1999) Neurology, Bernasconi et al (2003) Brain

MRI PROFILING AND SUBTYPING

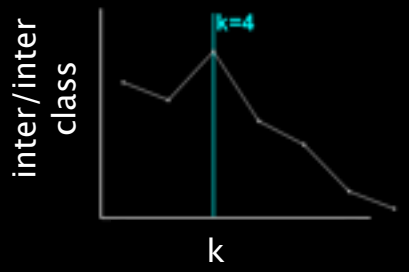
MESIOTEMPORAL PROFILING

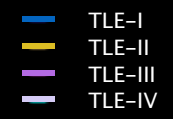
n=114

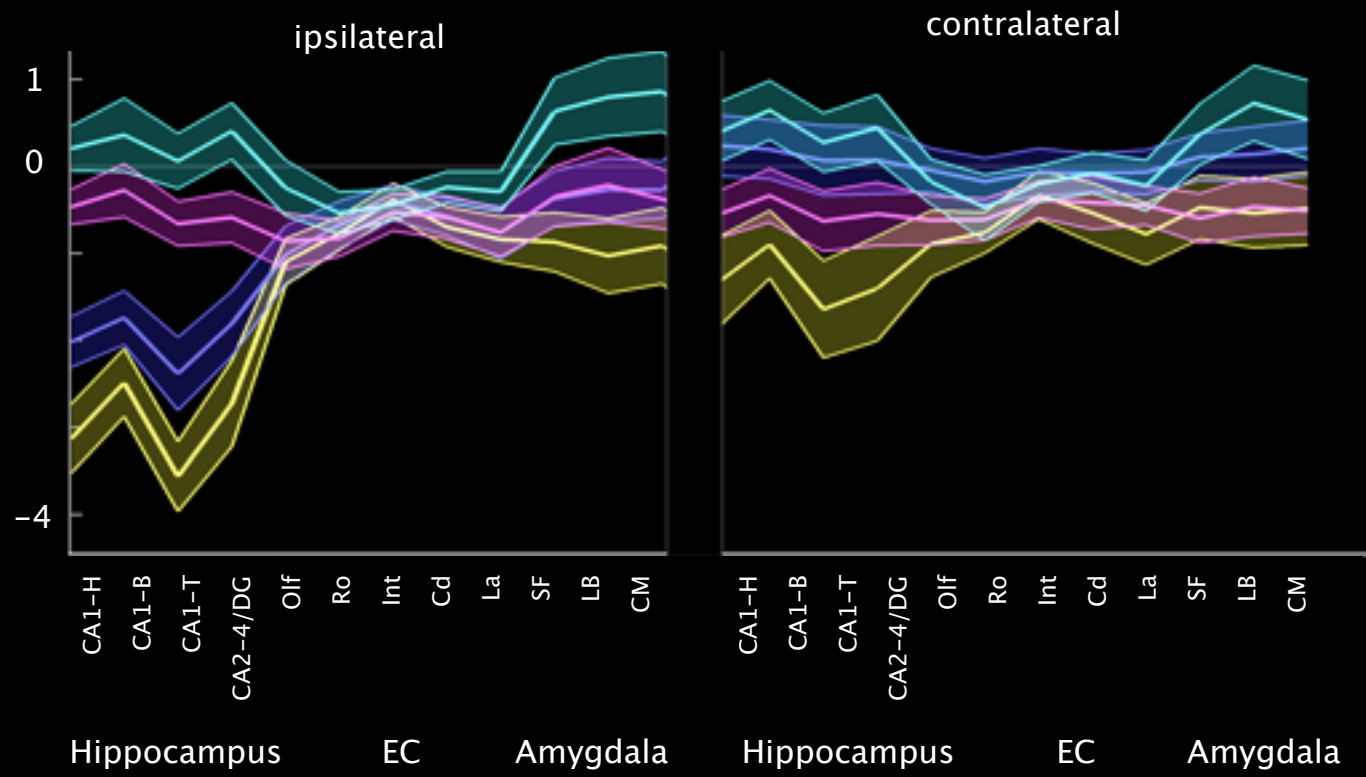




CLUSTERING PATIENT SPECTRUM BASED ON MRI MORPHOMETRY

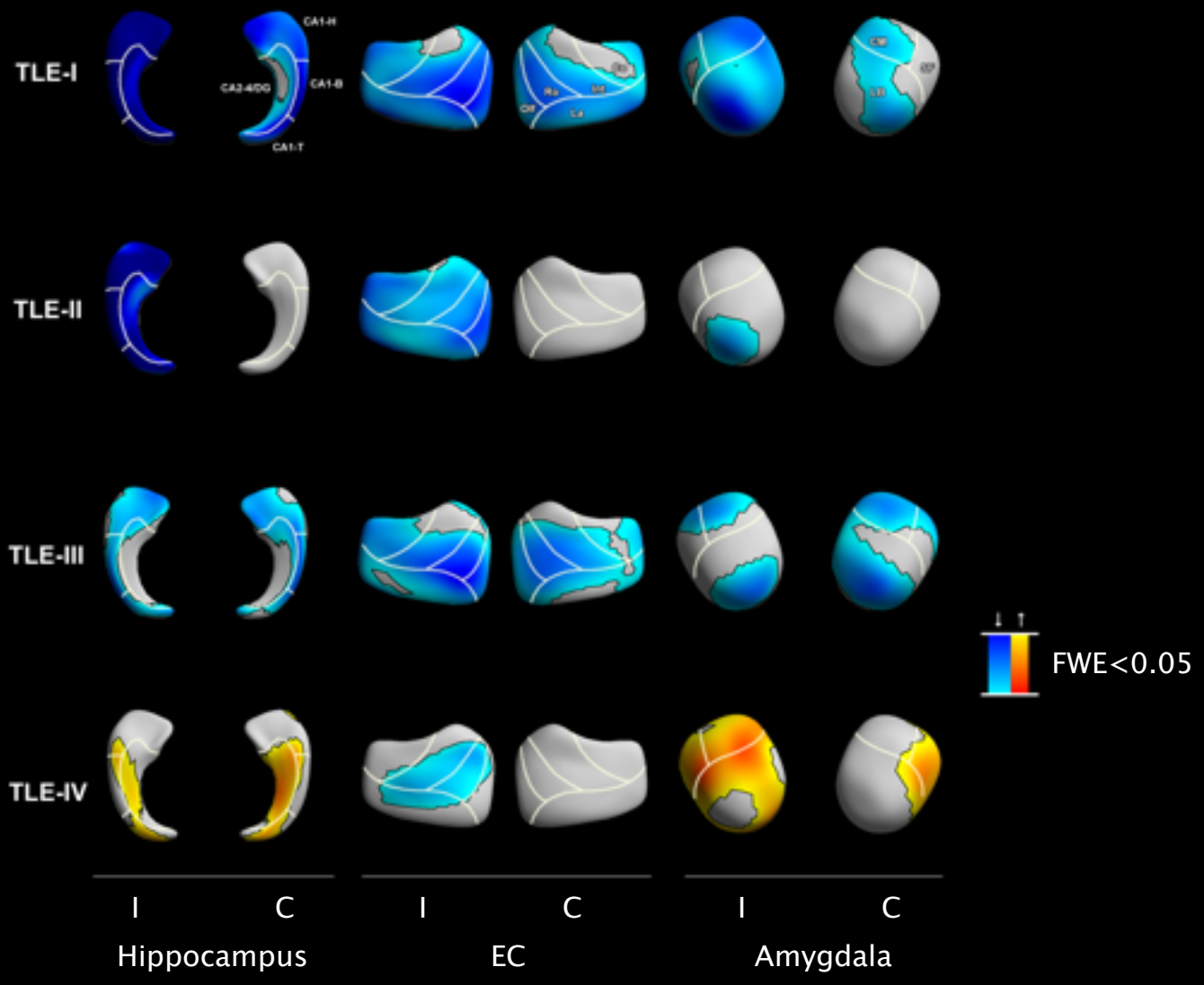






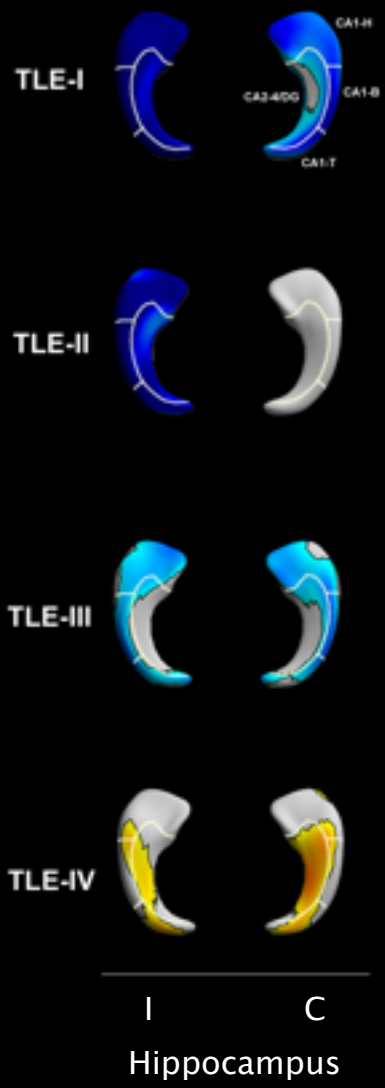
Bernhardt et al. (2015) Annals of Neurology

DATA-DRIVEN SUBCLASSES



Bernhardt et al. (2015) Annals of Neurology

RELATION TO IMAGING-INDEPENDENT CRITERIA



	HS/Gliosis	Engel-I
TLE-I	71/29%	68%
TLE-II	72/28%	89%
TLE-III	43/57%	65%
TLE-IV	17/83%	44%

LDA outcome prediction:

class + surface data: **92%**

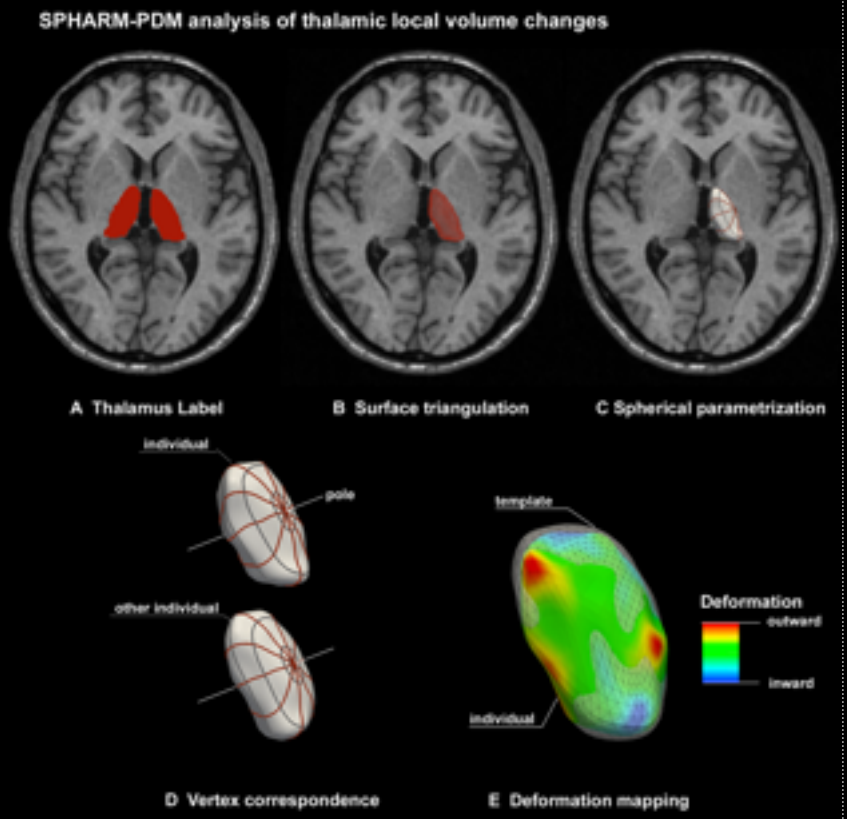
surface-measures only: **81%**

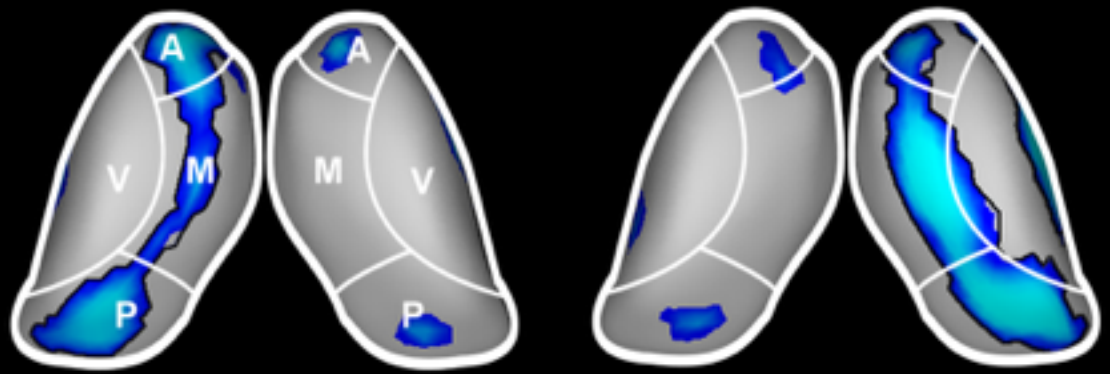
volumetry: **71%**

Bernhardt et al. (2015) Annals of Neurology

DO ANOMALIES EXTEND BEYOND THE MESIOTEMPORAL REGIONS?

THALAMIC ANOMALIES



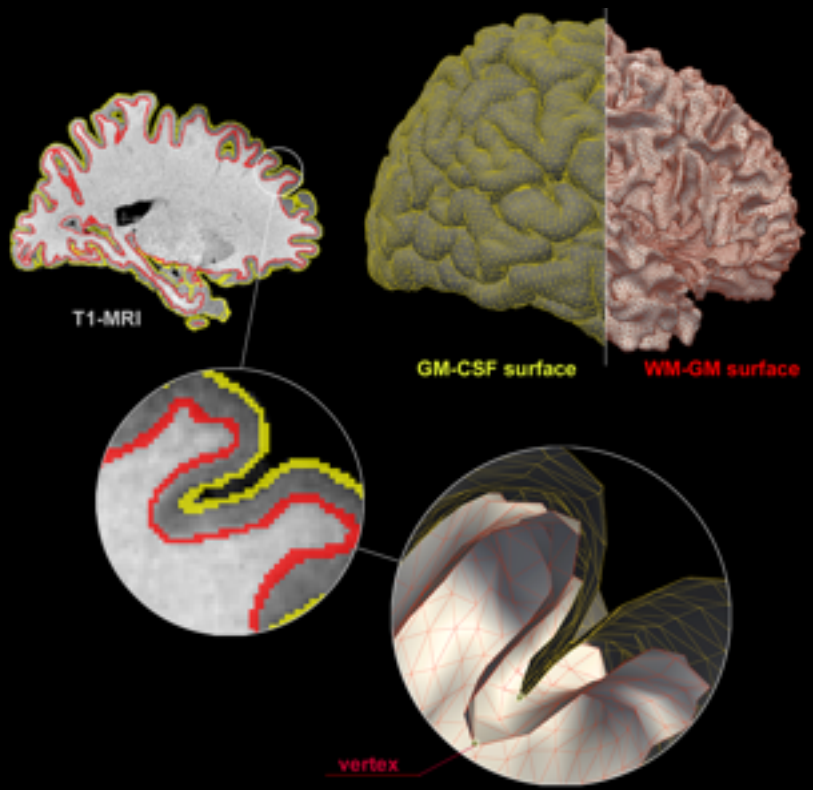


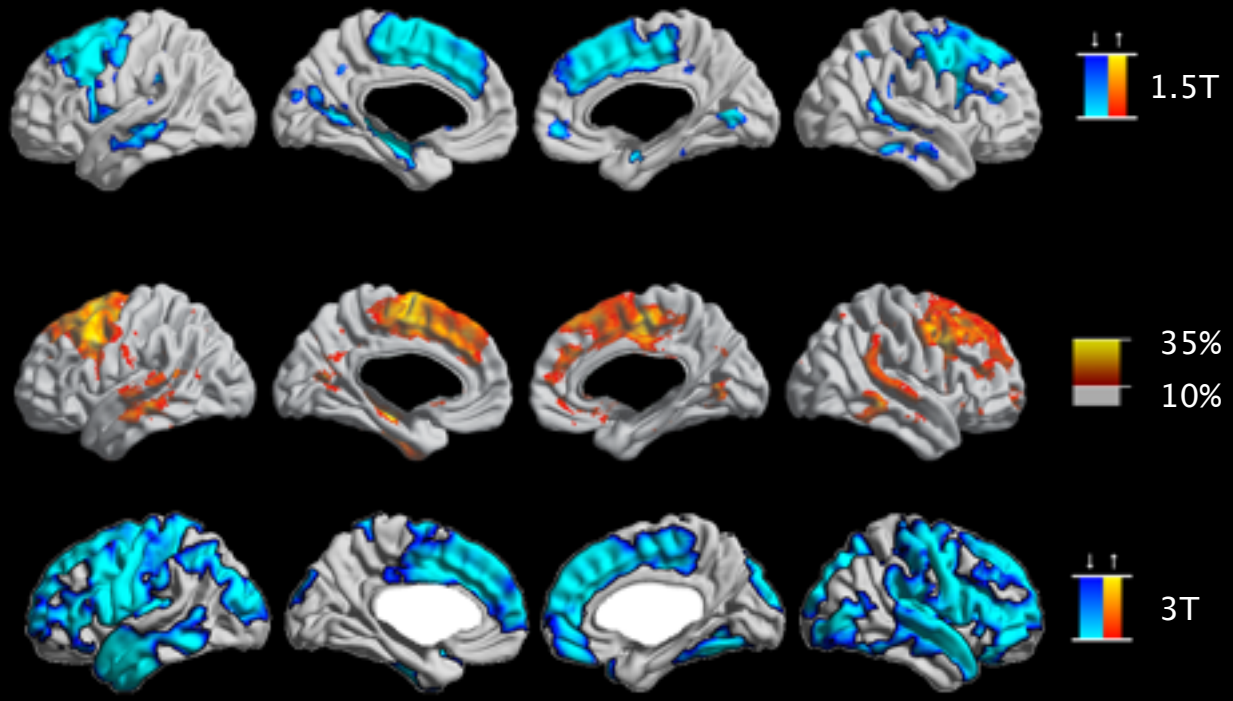
LTLE

RTLE

Bernhardt et al. (2012) Neurology

NEOCORTICAL ANOMALIES





IPSILATERA CONTRALATERA

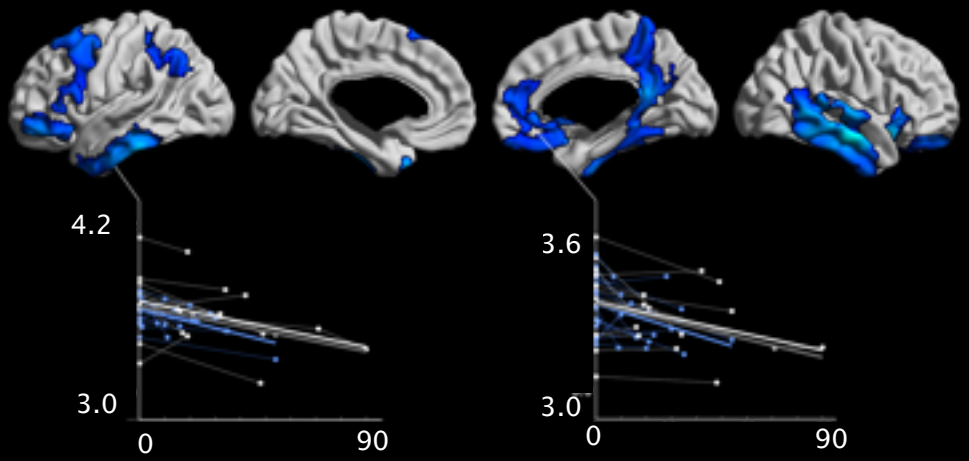
Bernhardt et al. (2008) NIMG, Bernhardt et al. (2010) Neurology

DISEASE PROGRESSION

NEOCORTEX

IPSILATERAL CONTRALATERAL

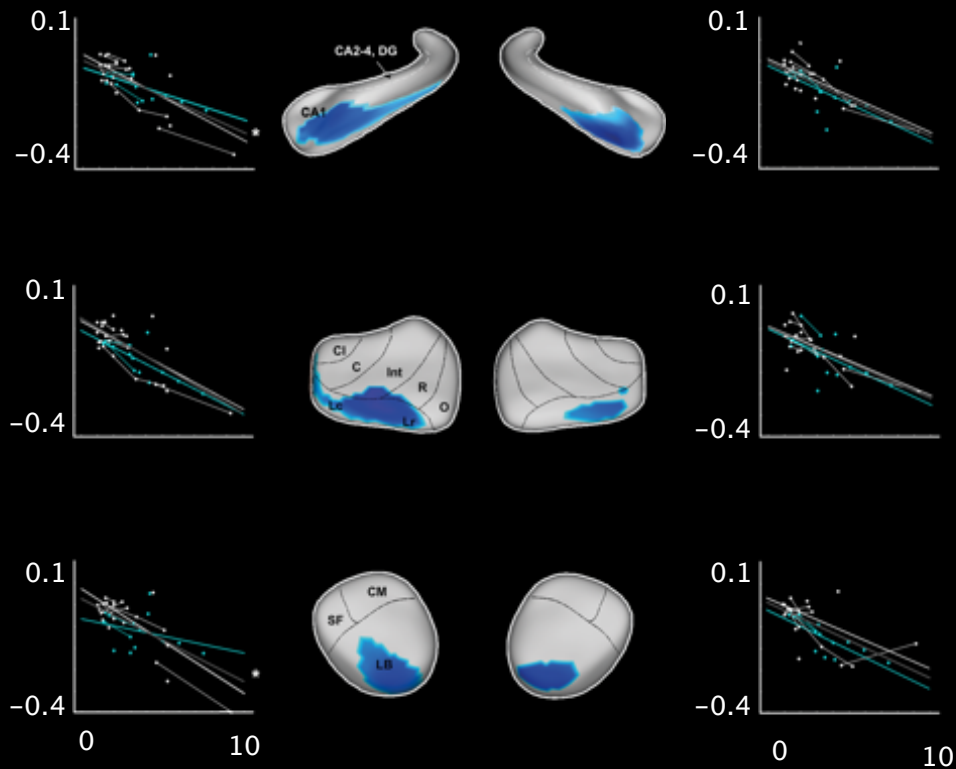
FWE<0.05



time from baseline (months)

MESIOTEMPORAL LOBE

IPSILATERAL CONTRALATERAL



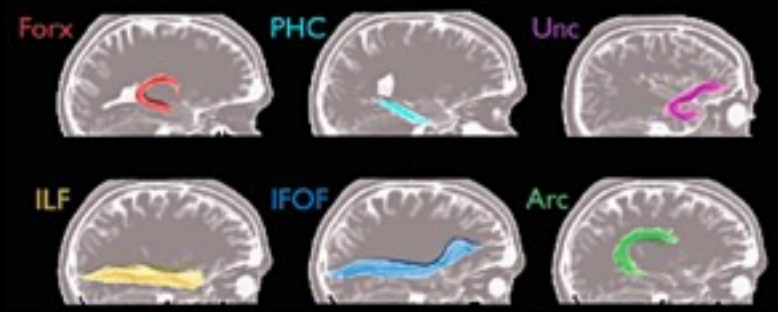
time from baseline (years)

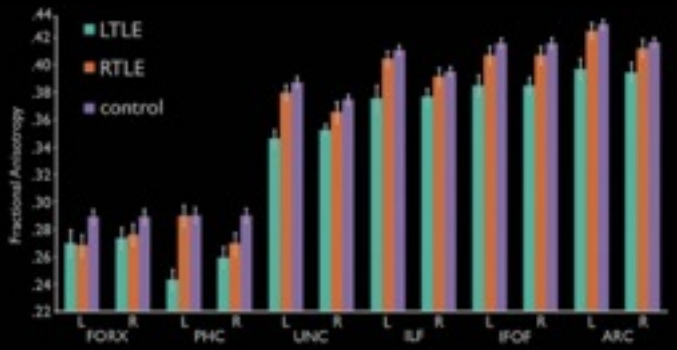
CROSS-SECTIONAL AGE-INTERACTION ANALYSIS:
MORE MARKED AGE-DECLINE IN PATIENTS

Bernhardt et al. (2009, 2010, 2013) Neurology

WHITE MATTER ALTERATIONS

TRACTOGRAPHY-BASED WM BUNDLE ANALYSIS

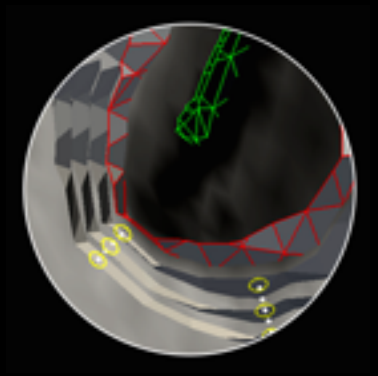




↓FA

UC San Diego

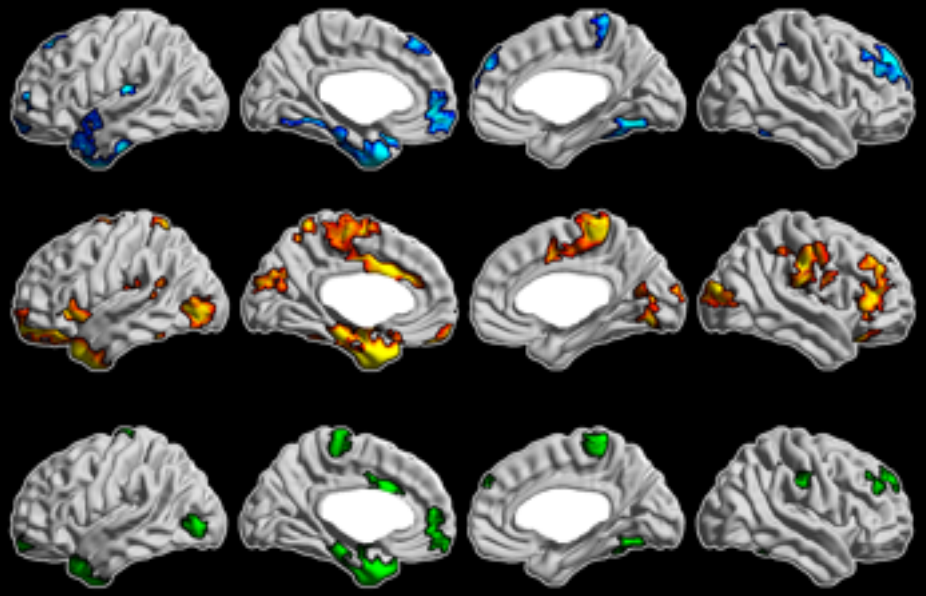
SURFACE-BASED WM SAMPLING [2MM DEPTH]



↓FA

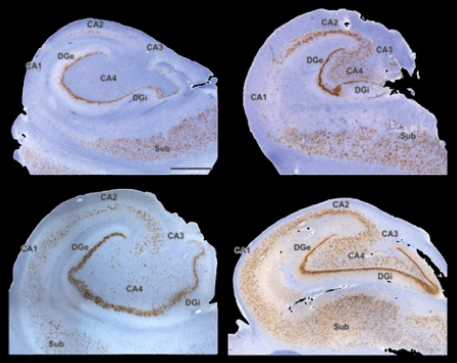
↑MD

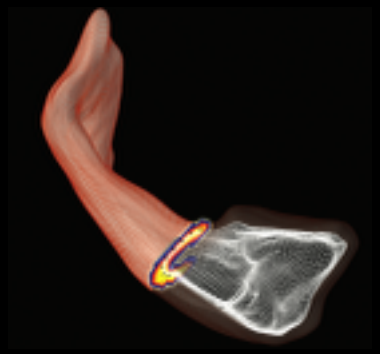
MULTI-VARIATE



FWE<0.05

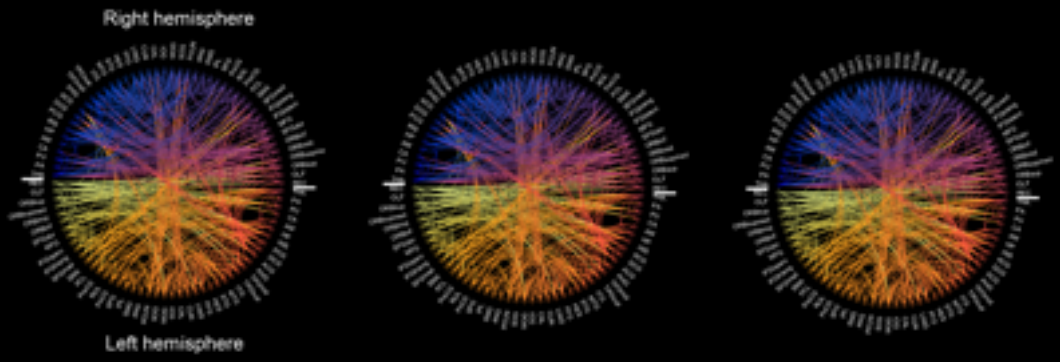
Kemmotsu et al. (2011) Epilepsia; Liu, Bernhardt et al. (2016) Brain

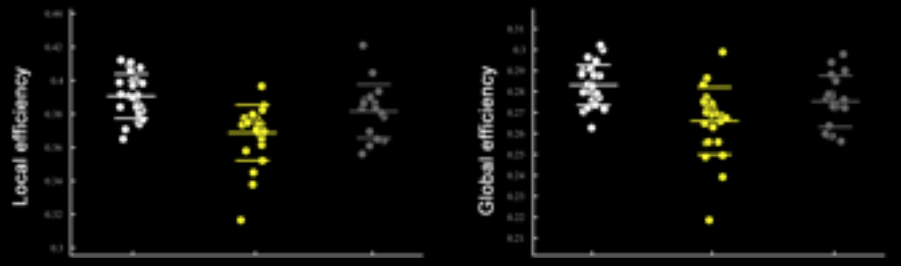




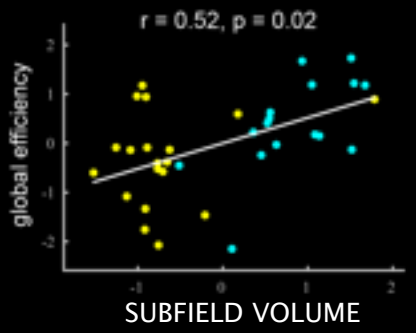
LINKING MACRO/MICROLEVEL DISRUPTIONS

CONTROLS HS GLIOSIS





CONTROLS HS GLIOSIS



Bernhardt , Liu et al. (in preparation)

INTERIM SUMMARY: EPILEPSY

ANOMALIES BEYOND HIPPOCAMPUS

- System-level compromise of grey matter, white matter
- Most marked impact in limbic network
- Longitudinal studies show progressive atrophy

NEUROIMAGING SUBTYPING

- Mesiotemporal subtypes: clinical and pathological divergence
- Neuroprognostics: accurate prediction of long-term outcome

AUTISM SPECTRUM CONDITIONS

MOST COMMON
NEURODEVELOPMENTAL DISORDER

PERSISTS UNTIL ADULTHOOD

CORE DEFICITS
IN SOCIAL COGNITION AND
COMMUNICATION

DIAGNOSIS AND THERAPY CHALLENGED
BY CONSIDERABLE HETEROGENEITY

PREVIOUS STRUCTURAL MRI WORK

INCONSISTENT LOCATION OF FINDINGS

INCONSISTENT DIRECTION

MIXED INCLUSION CRITERIA

VARIABLE AGE RANGES

ONLY SMALL SAMPLES STUDIED

Available online at www.sciencedirect.com
ScienceDirect
European Psychiatry 23 (2008) 289–299
EUROPEAN PSYCHIATRY
http://france.elsevier.com/direct/EURPSY/

Review

Towards a neuroanatomy of autism: A systematic review and meta-analysis of structural magnetic resonance imaging studies

Andrew C. Stanfield [a,*], Andrew M. McIntosh [a], Michael D. Spencer [a], Ruth Philip [a], Sonia Gaur [b], Stephen M. Lawrie [a]

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BRAIN
A JOURNAL OF NEUROLOGY

Age-related temporal and parietal cortical thinning in autism spectrum disorders

Gregory L. Wallace,[1] Nathan Dankner,[1] Lauren Kenworthy,[1] Jay N. Giedd[2] and Alex Martin[1]

BIG DATA ANALYSIS FOR STRUCTURAL BRAIN ANOMALIES IN AUTISM

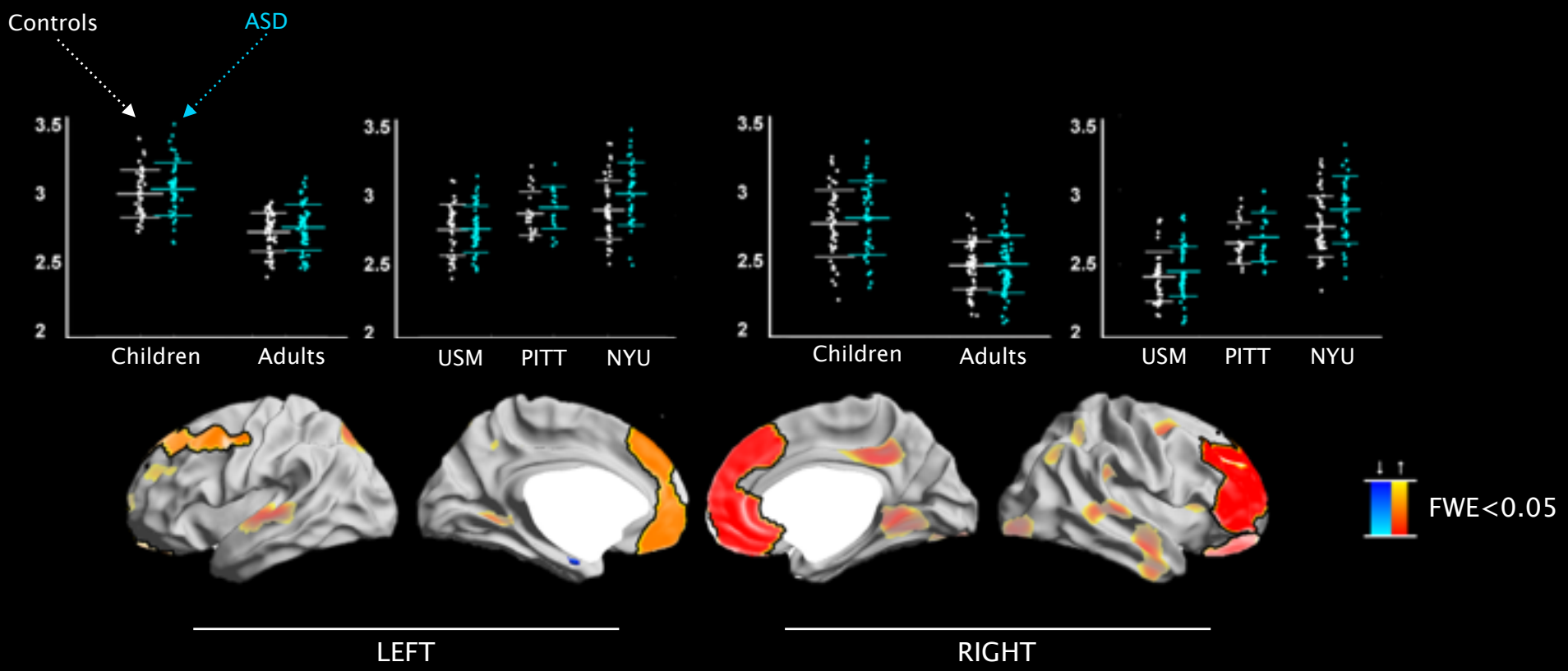
FMRI + SMRI + BASIC PHENOTYPING (AGE, SEX, IQ, DIAGNOSTIC)
in 539 ASD and 537 controls
17 sites

ADOS- and/or ADI-R available in all sites

DiMartino, et al. (2013) Mol Psy

NYU ABIDE

MULTI-CENTER MAPPING OF STRUCTURAL ALTERATIONS

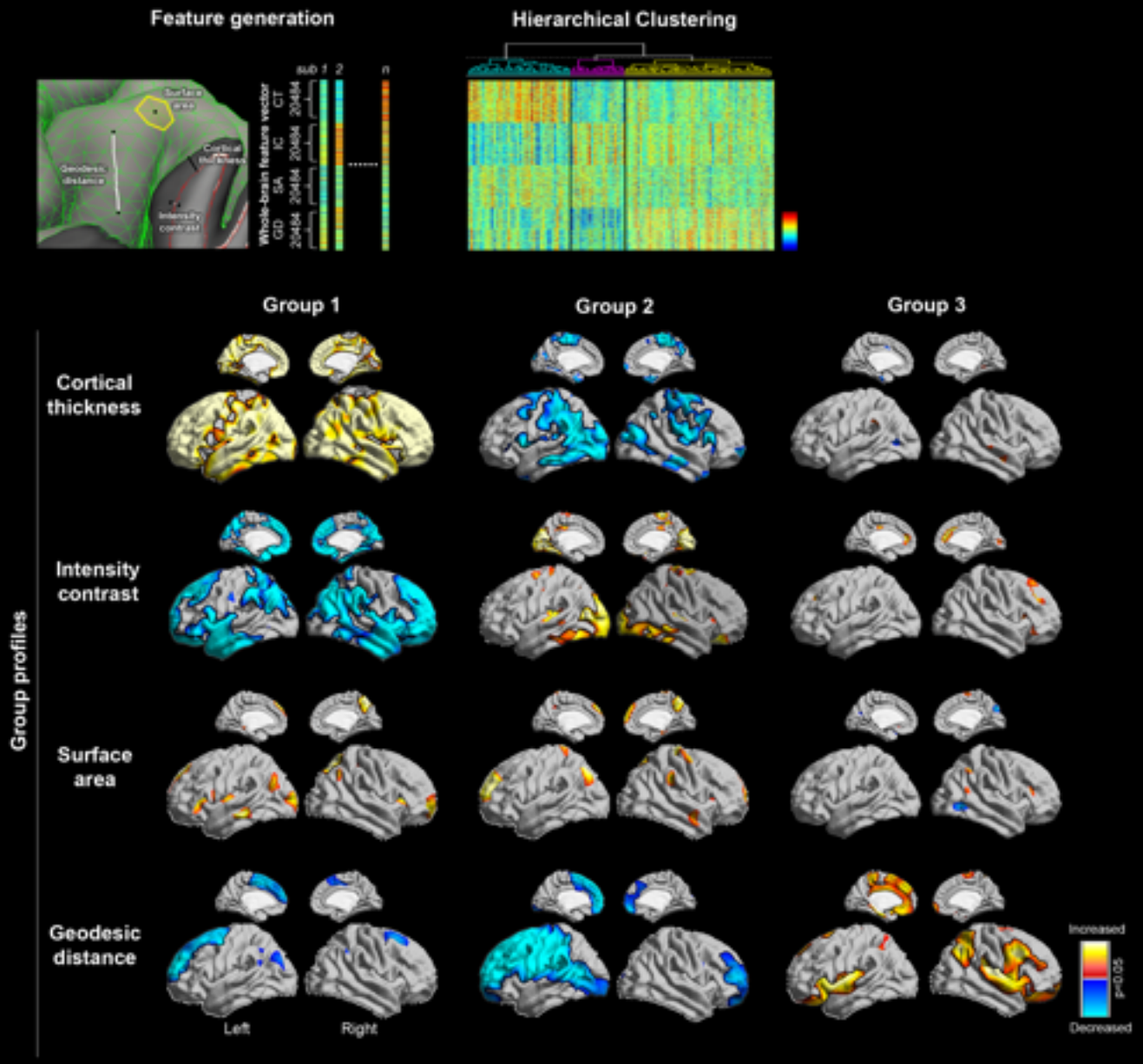


FWE<0.05

No clear relation with symptom scores

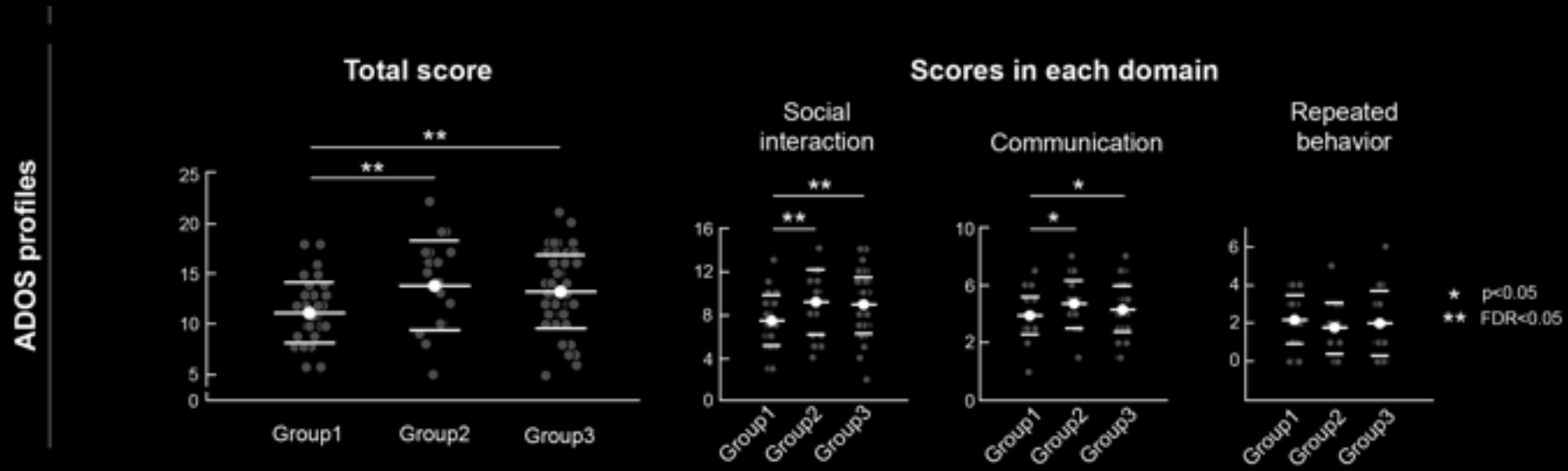
Valk, DiMartino, Milham, Bernhardt (2015) Hum Brain Mapp

SUBTYPING OF AUTISM SPECTRUM DISORDERS



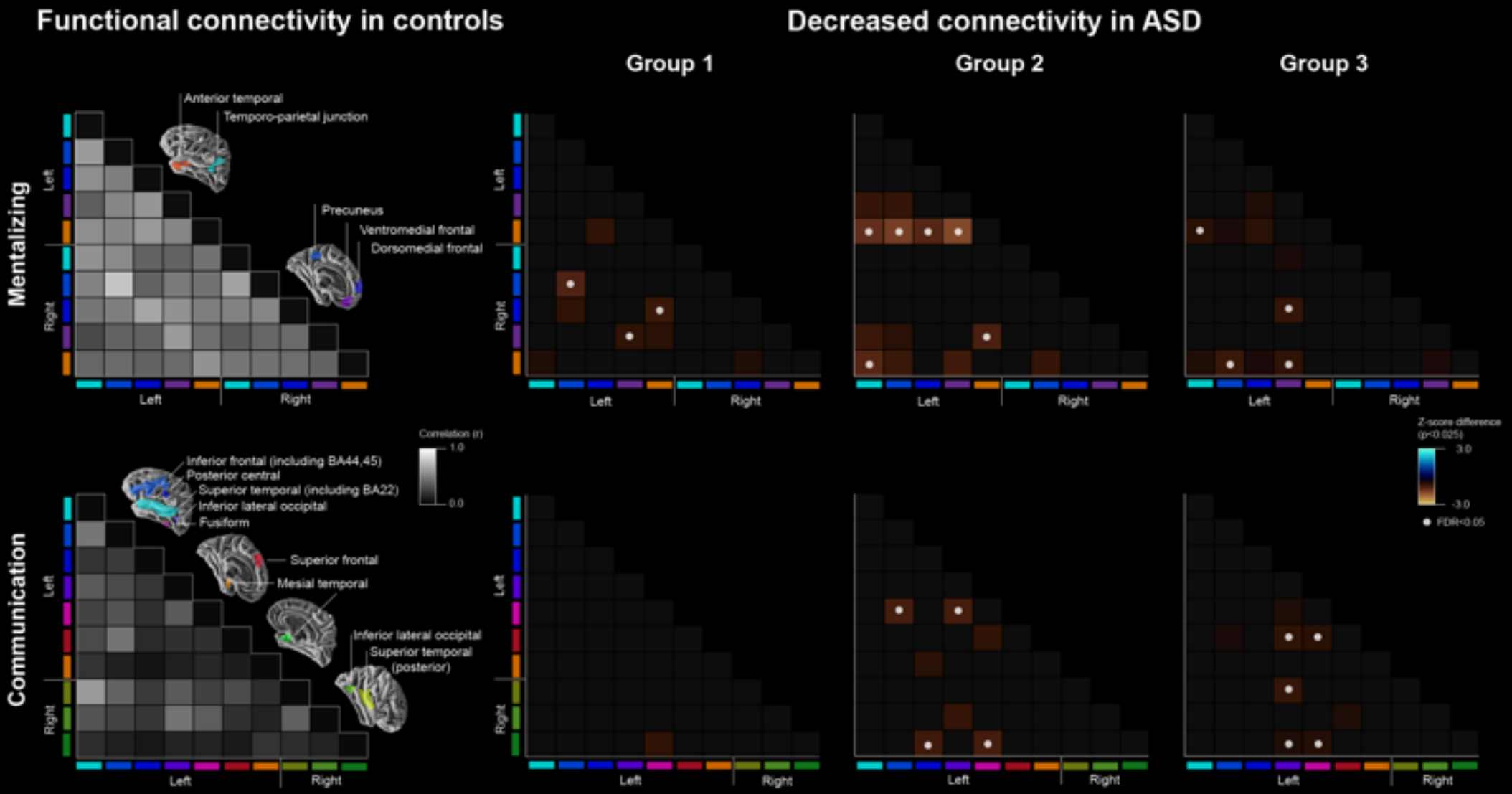
Hong, Valk, Bernhardt (submitted)

TOWARDS A SUBTYPING OF AUTISM SPECTRUM DISORDERS



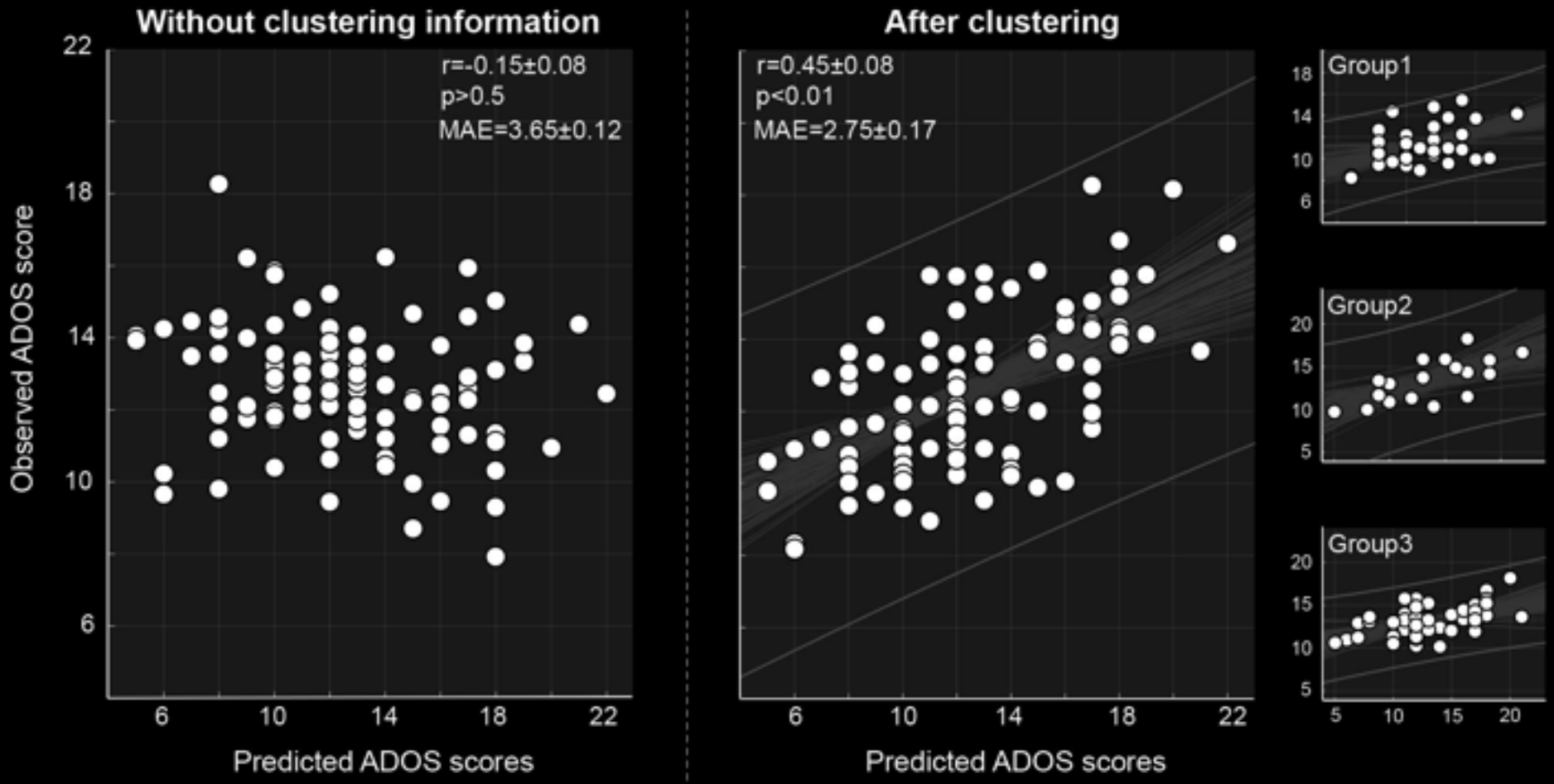
Hong, Valk, Di Martino, Bernasconi, Bernasconi, Bernhardt (in preparation)

TOWARDS A SUBTYPING OF AUTISM SPECTRUM DISORDERS



Hong, Valk, Di Martino, Bernasconi, Bernasconi, Bernhardt (in preparation)

SYMPTOM SEVERITY PREDICTION



Hong, Valk, Di Martino, Bernasconi, Bernasconi, Bernhardt (in preparation)

INTERIM SUMMARY: AUTISM

HIGH HETEROGENEITY

MOVING TOWARDS LARGE DATASETS (ABIDE1/2)

UNSUPERVISED TECHNIQUES MAY ORDER NEUROANATOMICAL VARIABILITY

MORE ACCURATE PREDICTION OF SYMPTOM LEVELS

MAY POTENTIALLY BE USEFUL TO CALIBRATE THERAPY

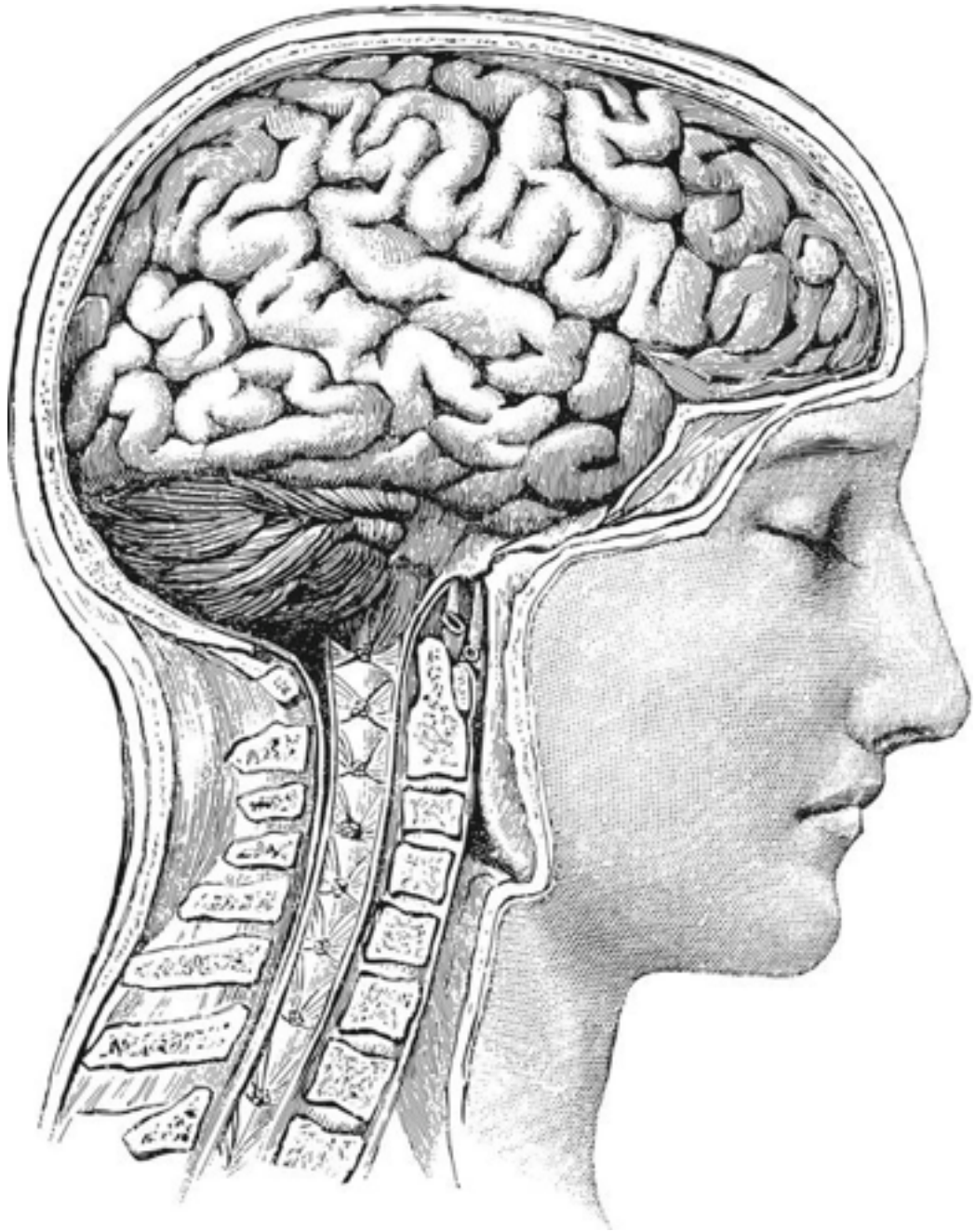
SUMMARY

MRI PROVIDES IN VIVO INFORMATION ON MICROSTRUCTURE AND NETWORKS

STRUCTURE–FUNCTION ANALYSIS

EXPLICITLY ADDRESSING VARIABILITY IN EPILEPSY AND AUTISM MAY IMPROVE DIAGNOSTIC POWER

OPPORTUNITIES FOR VALIDATION THROUGH CLINICAL PIPELINES



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Jeffrey Hall

Marie Christine Guiot

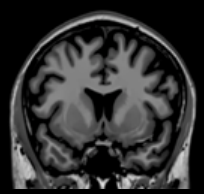
Robarts Research Institute

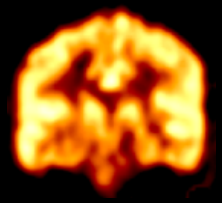
Maged Goubran

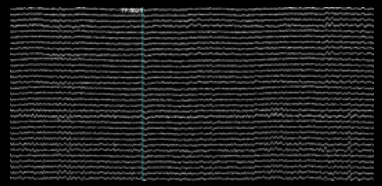
Ali Khan

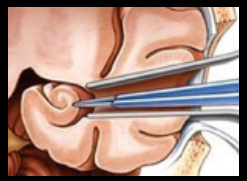
Terry Peters

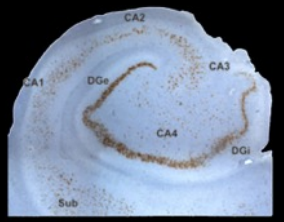
PATIENT ORIENTED RESEARCH











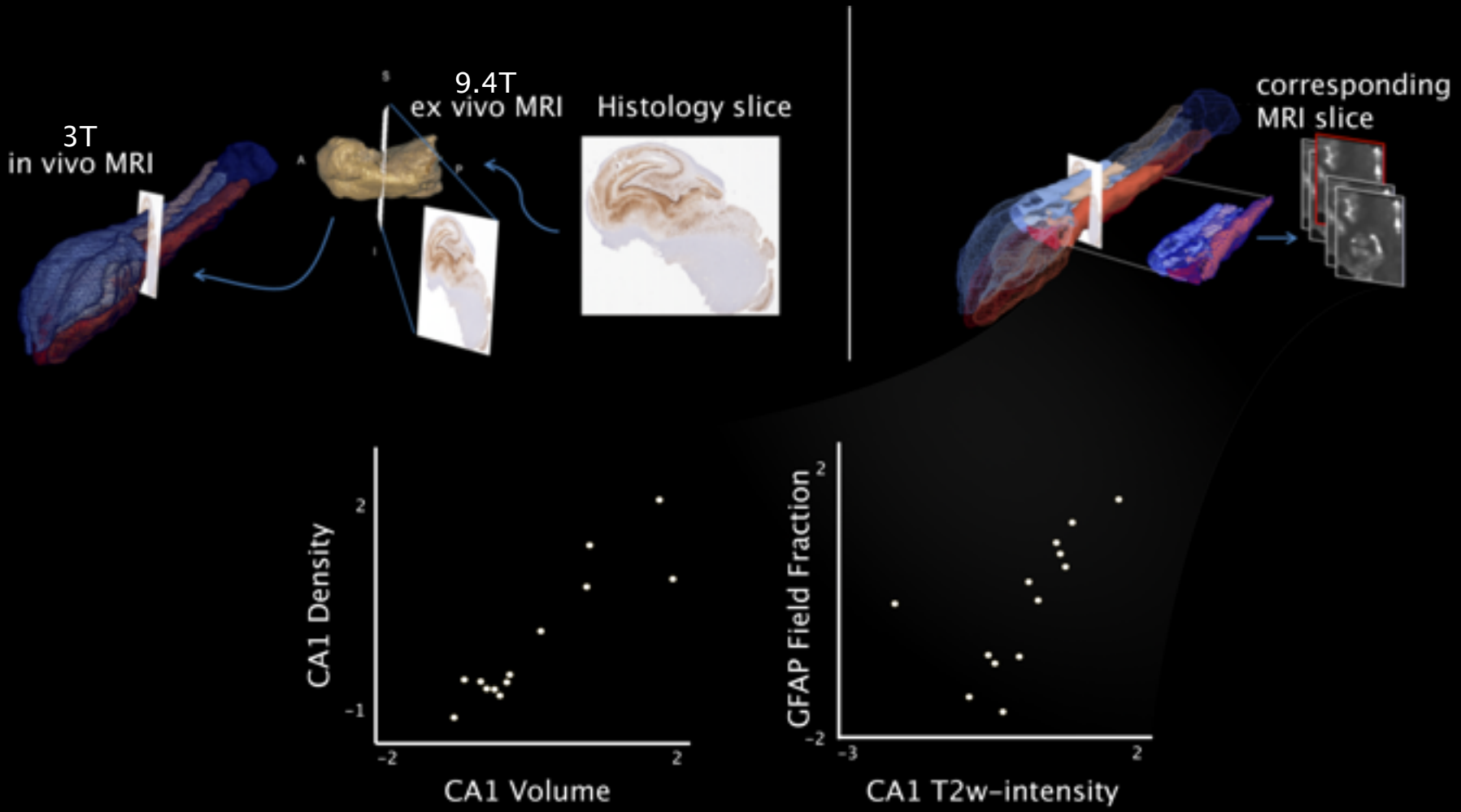
DATA COLLECTION + INTERPRETATION

CLINICAL DECISION

OUTCOME VALIDATION

INTEGRATED BIOBANK

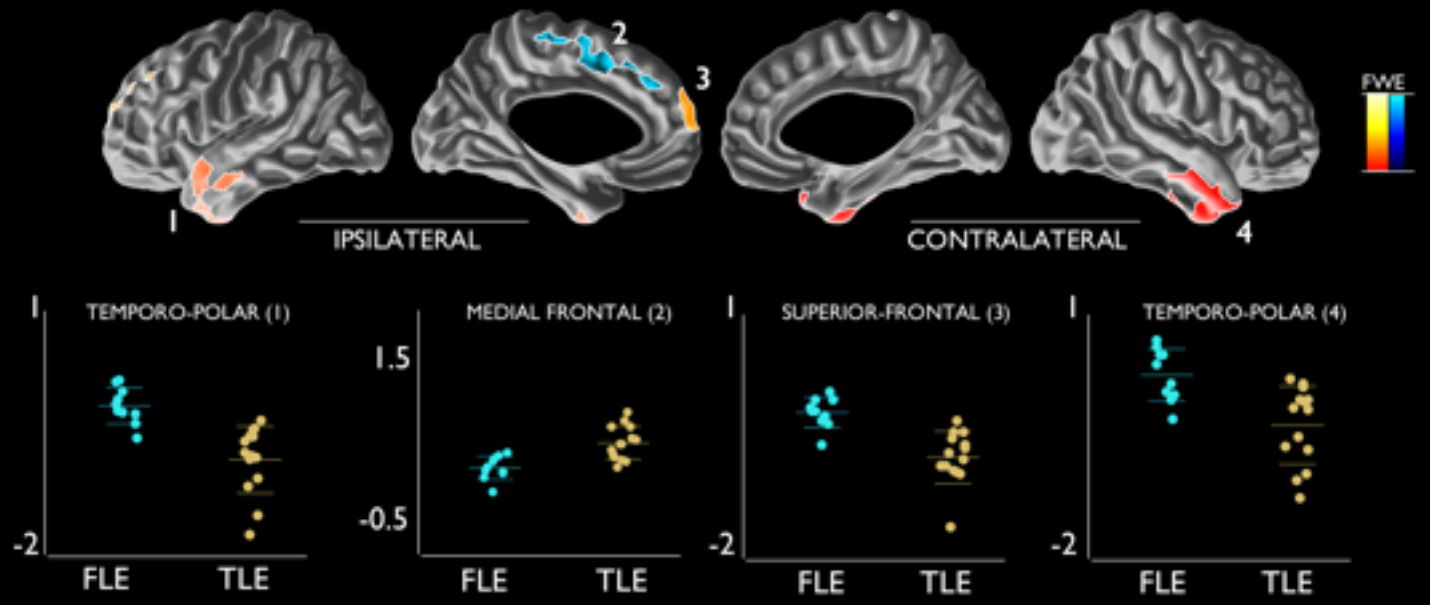
VALIDATION OF IN VIVO FINDINGS WITH QUANTITATIVE HISTOPATHOLOGY

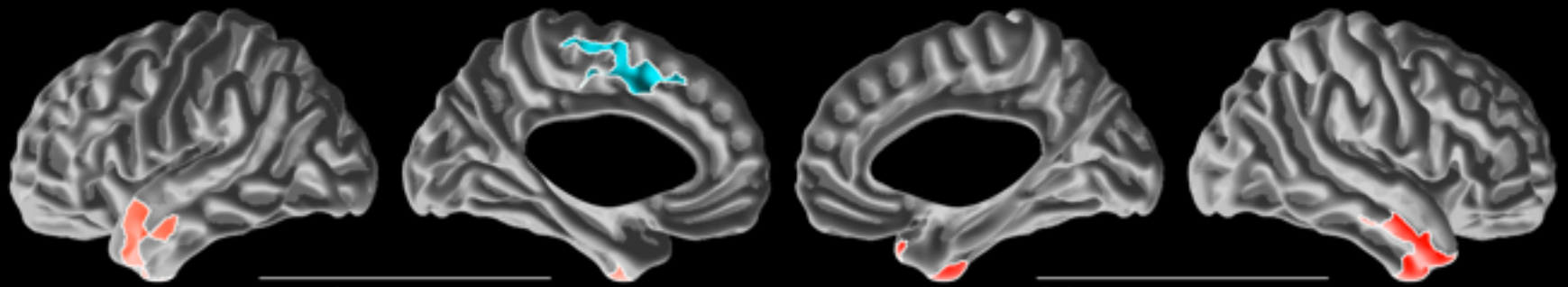


SUBFIELD-SPECIFIC CORRELATIONS BETWEEN MRI AND HISTOLOGY

Goubran, Bernhardt, et al (2016) Hum Brain Mapp

METABOLIC DIVERGENCE OF FOCAL EPILEPSY SYNDROMES





Adler, Caldairou, Soucy, Bernasconi, Bernasconi, Bernhardt (2016) AES