

SUBTYPING EPILEPSY AND AUTISM SPECTRUM DISORDER WITH MULTIMODAL IMAGING

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<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

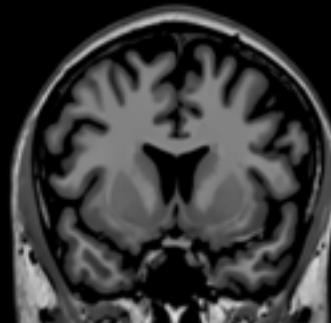
MULTIMODAL NEUROIMAGING:
STRUCTURE, FUNCTION, NETWORKS

NEUROIMAGING SUBTYPING
IN EPILEPTIC DISORDERS

NEUROIMAGING-DERIVED
AUTISM SPECTRUM SUBTYPES

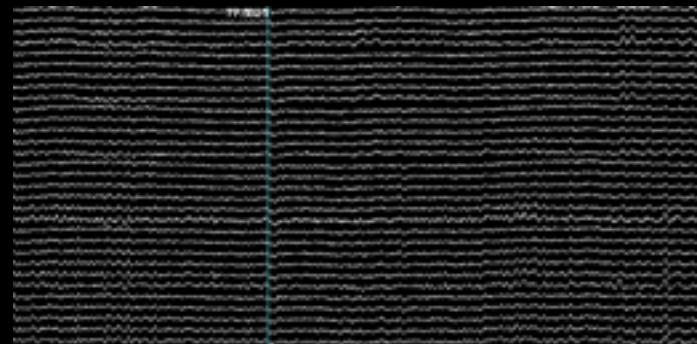
MULTIPLE NEUROIMAGING MODALITIES

MRI



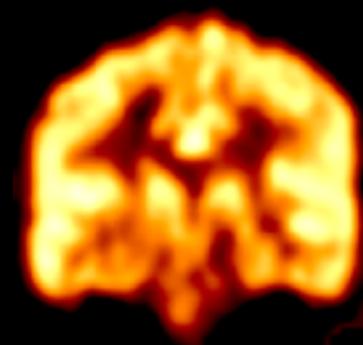
STRUCTURE
FUNCTION

MEG/EEG



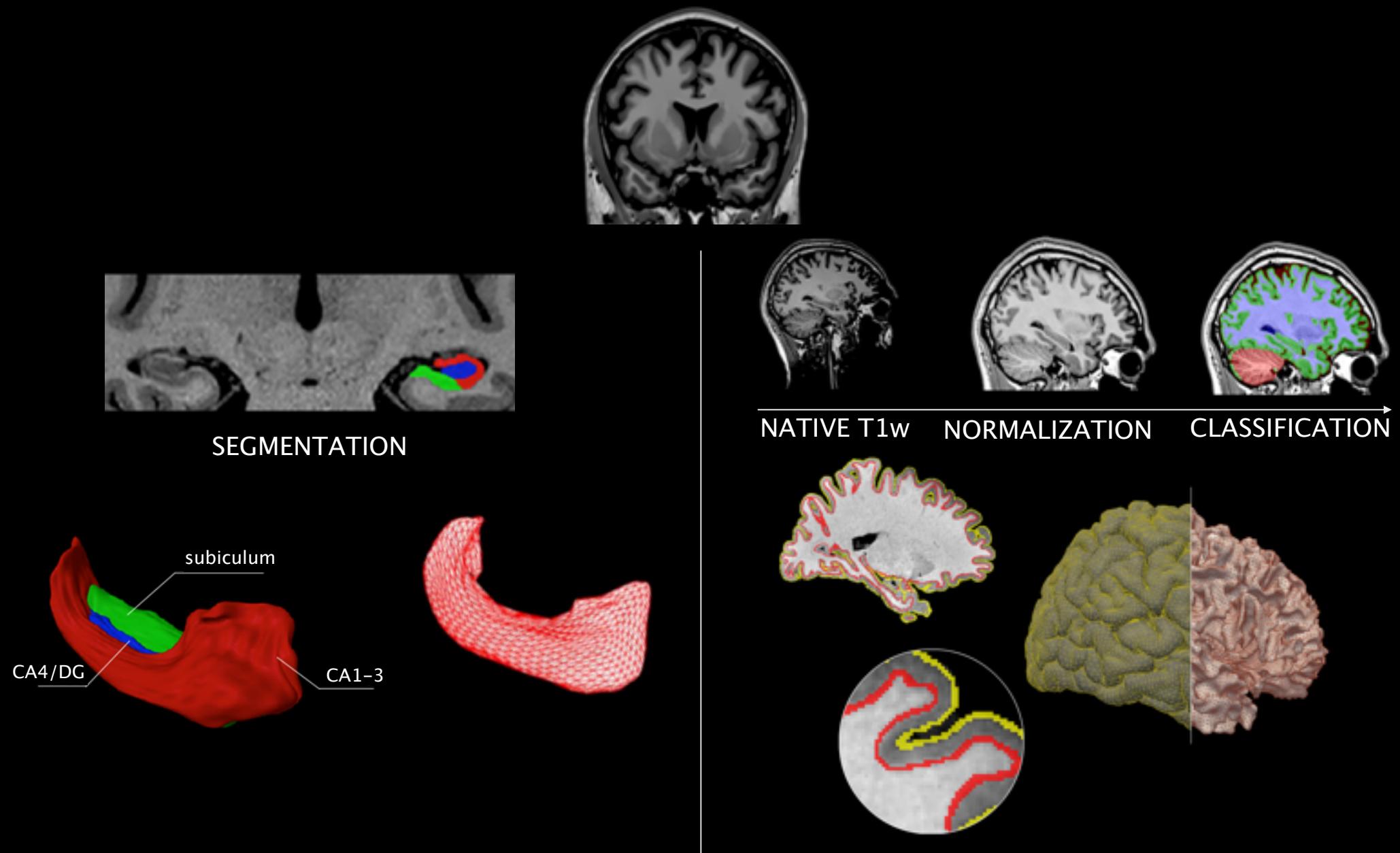
DYNAMICS

PET

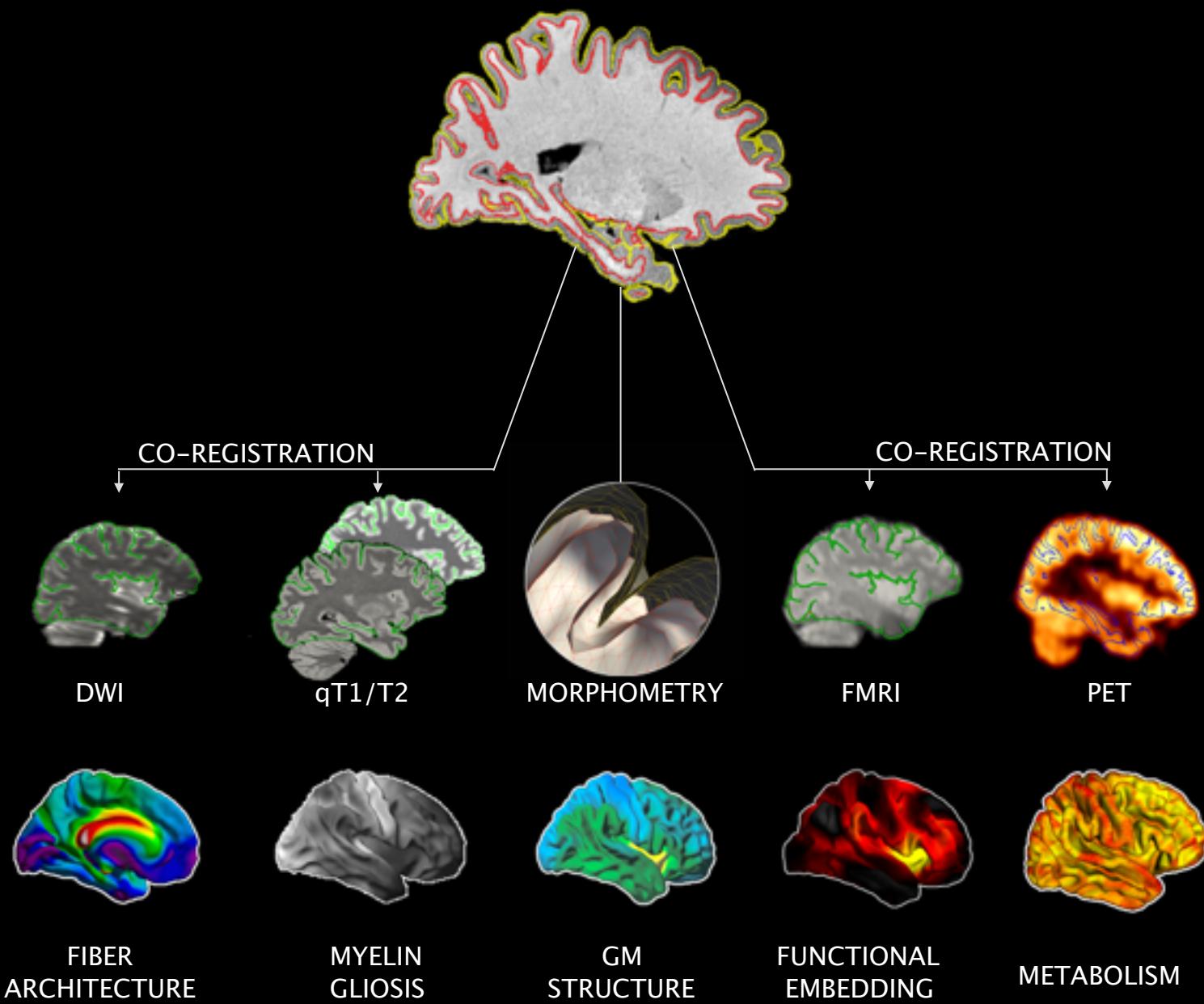


METABOLISM
TRANSMITTERS

DESCRIBING ANATOMY

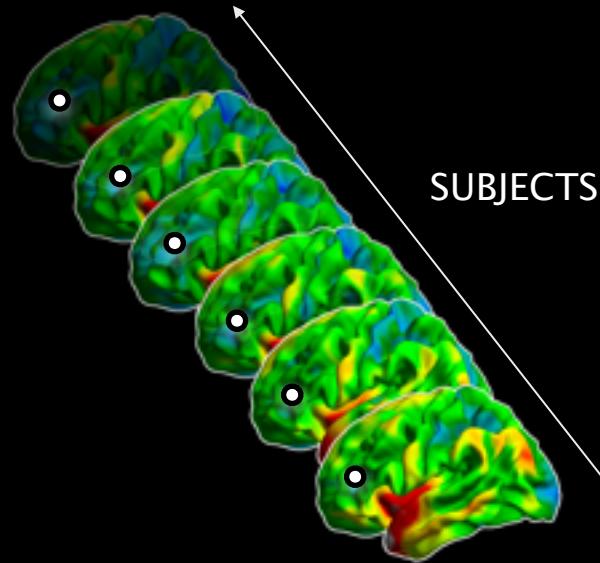


MULTI-MARKER INTEGRATION

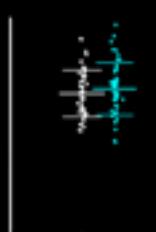


REGIONAL STATISTICAL ANALYSIS

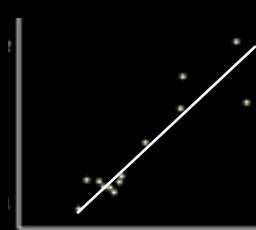
CROSS-SECTIONAL ANALYSES



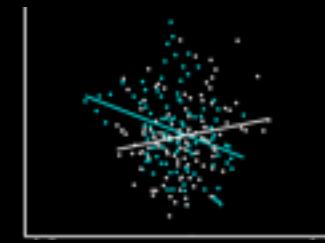
SUBJECTS



$$Y = 1 + G$$

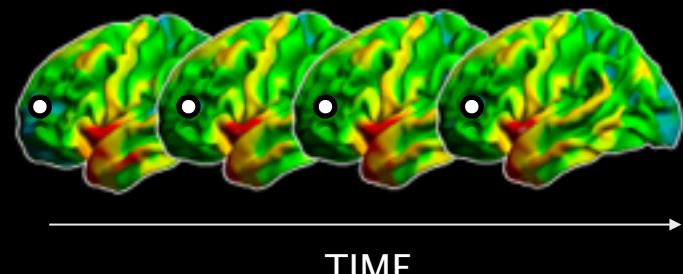


$$Y = 1 + A$$

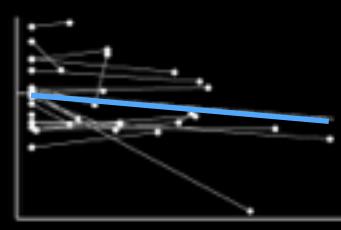


$$Y = 1 + G + A + G \times A$$

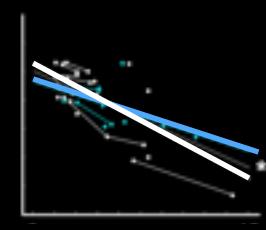
LONGITUDINAL ASSESSMENTS



TIME



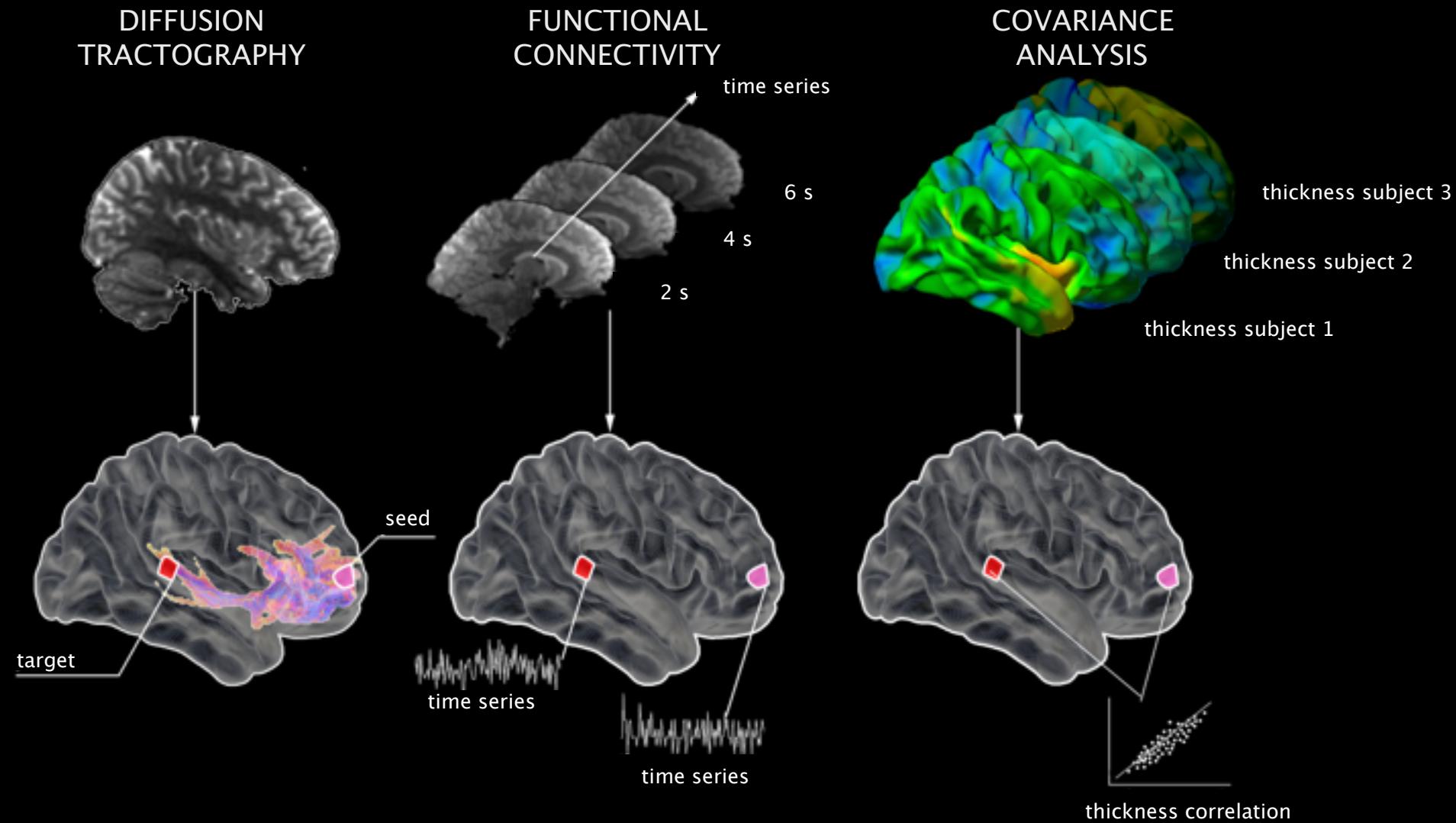
$$Y = 1 + r(S)$$



$$Y = 1 + ISI$$

Y is univariate or multivariate data

INTER-REGIONAL CONNECTIVITY ANALYSIS



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

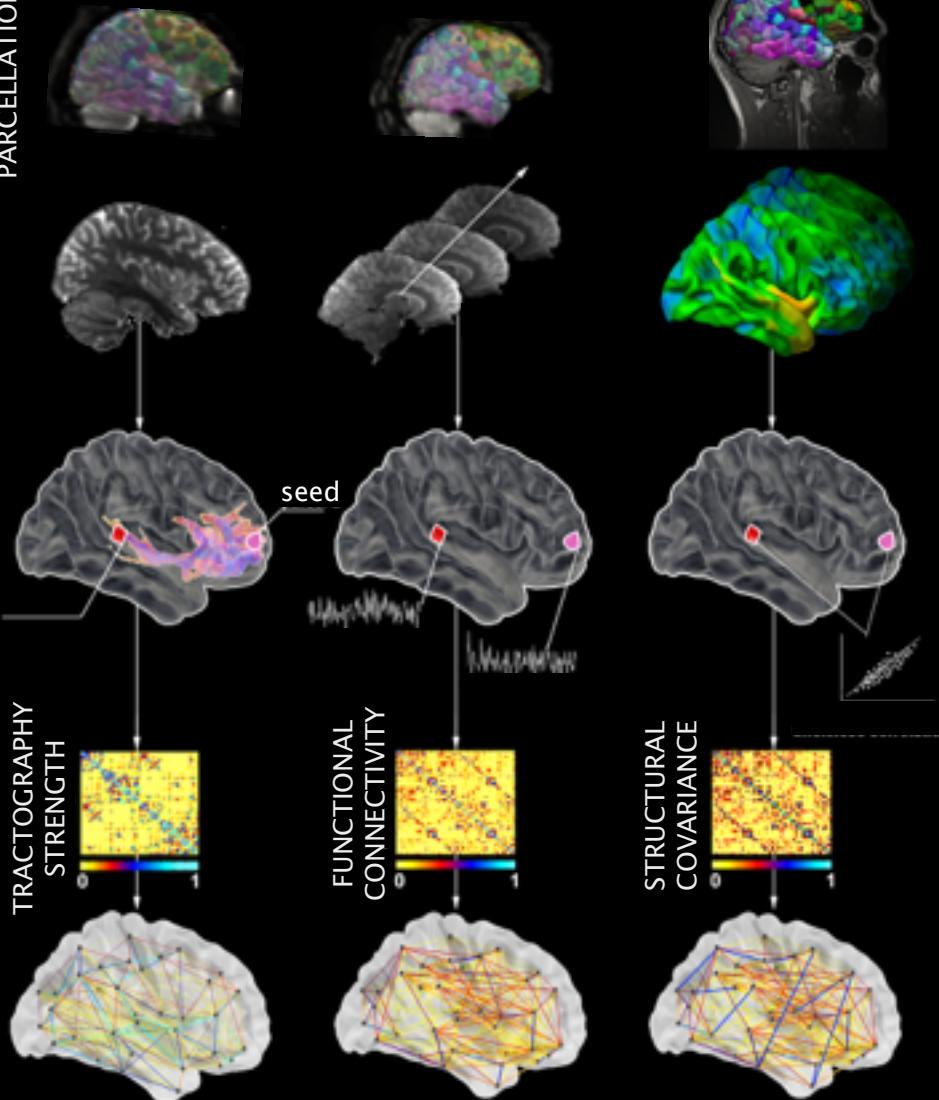
Friston (1994) HBM
Smith (2012) NIMG

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

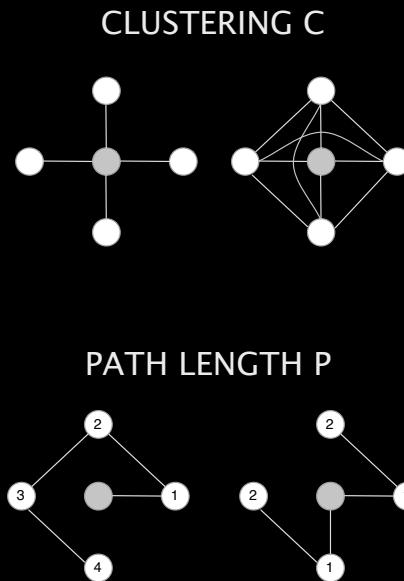
CONNECTOME ANALYSIS

PARCELLATION

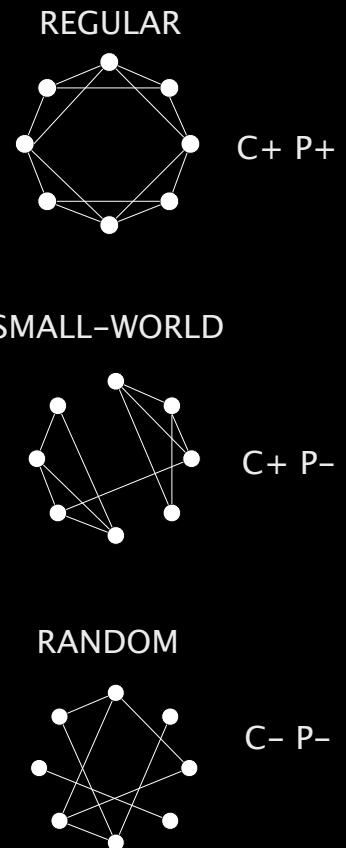
SYSTEMATIC NETWORK GENERATION



GRAPH THEORETICAL PARAMETERS

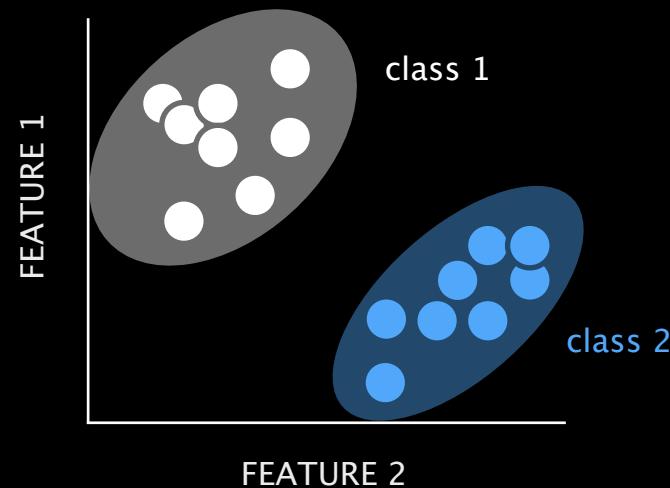


TOPOLOGY CLASSIFICATION



PATTERN LEARNING

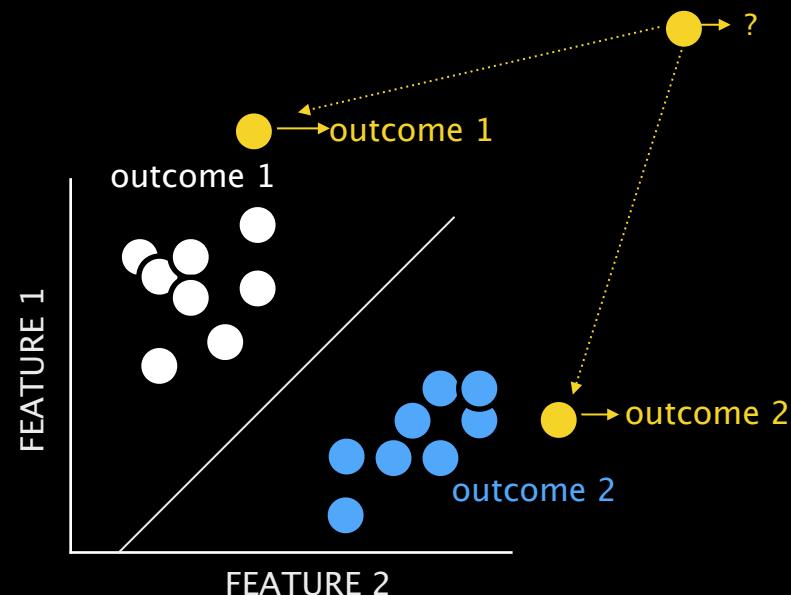
UNSUPERVISED



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

EPILEPSY

CHRONIC SEIZURES

0.5–1.5% OF POPULATION

HETEROGENOUS

30% OF PATIENTS ARE
DRUG-RESISTANT

MULTIDISCIPLINARY
ASSESSMENT



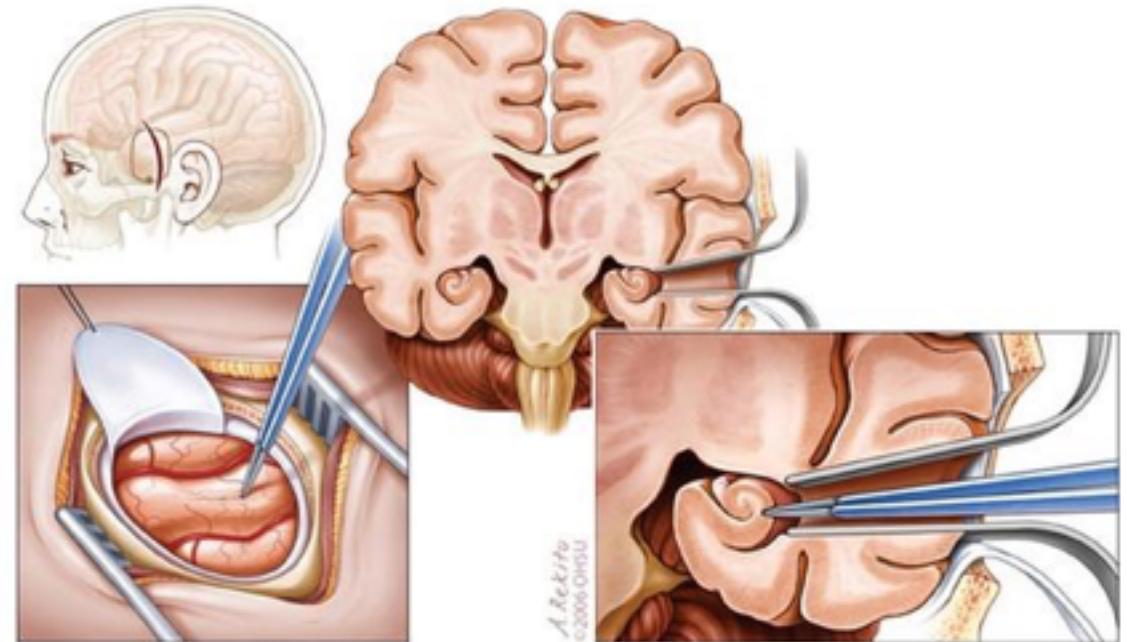
TEMPORAL LOBE EPILEPSY

MOST COMMON DRUG-RESISTANT
EPILEPSY IN ADULTS

SEIZURES ARISING FROM TL

ASSOCIATED WITH
HIPPOCAMPAL SCLEROSIS

SURGERY MOST EFFECTIVE
TREATMENT



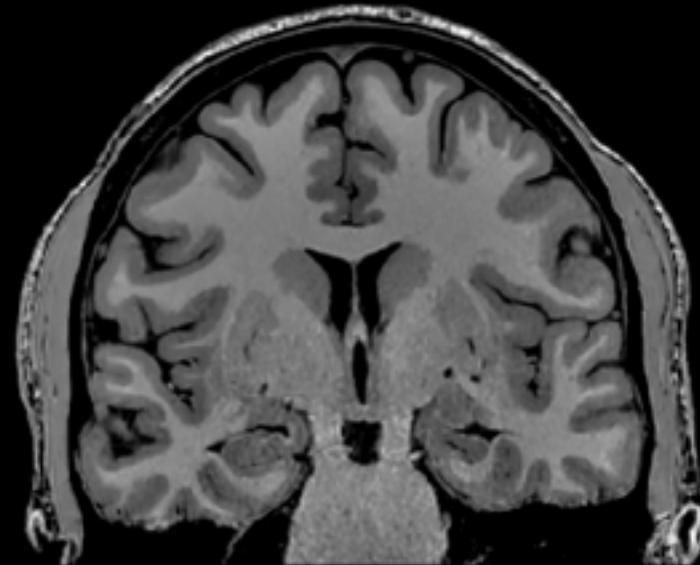
HIPPOCAMPAL PATHOLOGY AND IMAGING IN TLE

MRI plays key role in detecting HS non-invasively

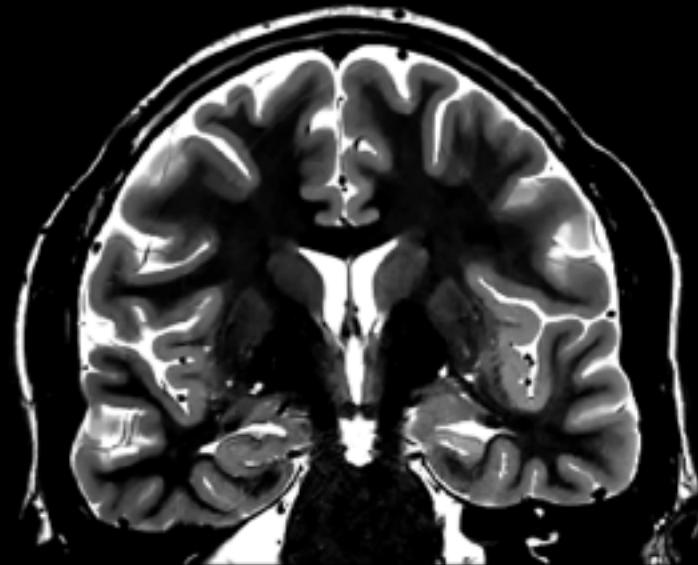
Atrophy and T2w increases can lateralize seizure focus in patients with HS

In the clinics: frequently done visually

Increasing proportions of patients with less remarkable anomalies



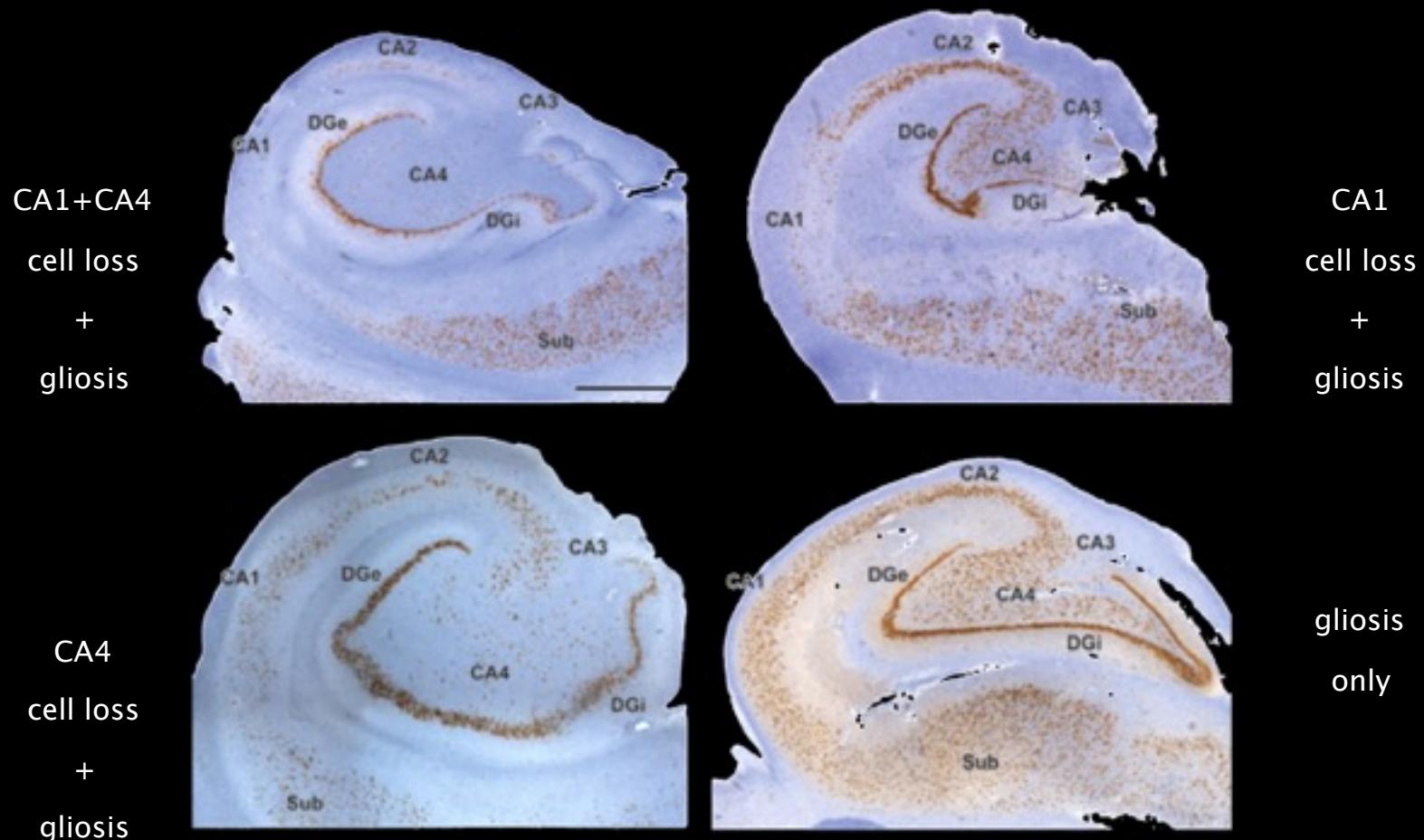
T1-weighted



T2-weighted

TEMPORAL LOBE EPILEPSY

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



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

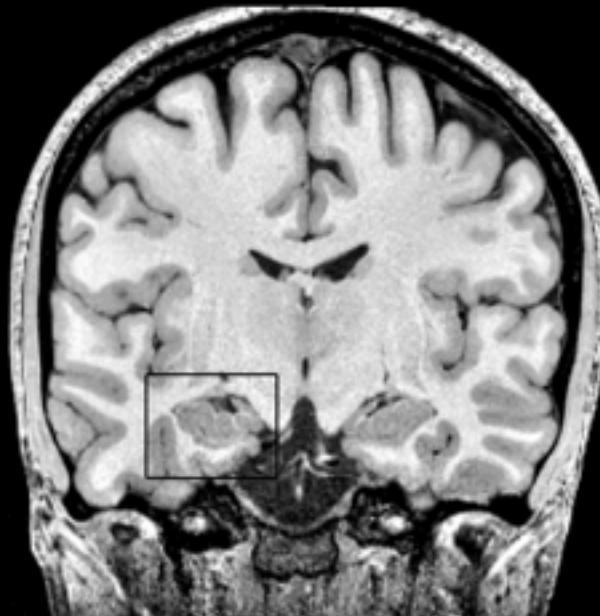
25 age- and sex-matched controls

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/>

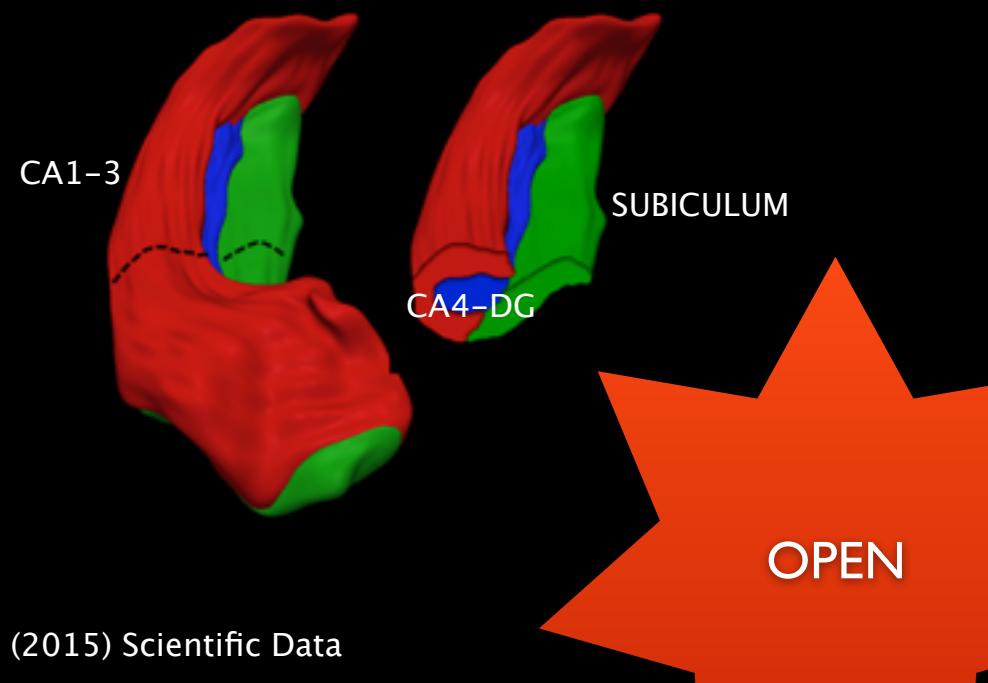
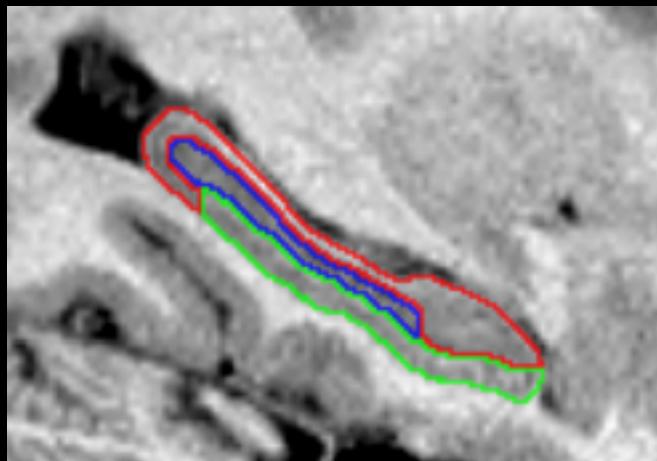
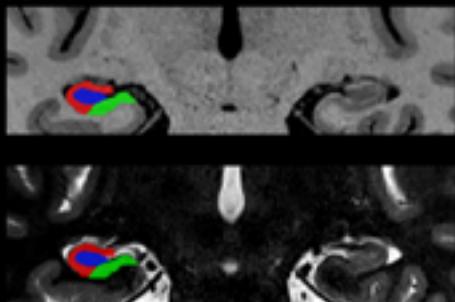
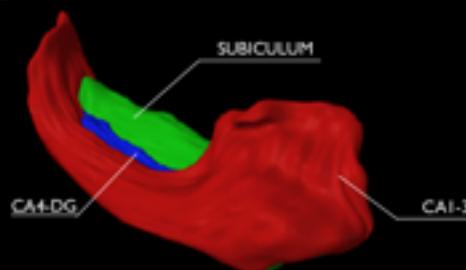


IMAGE PROCESSING

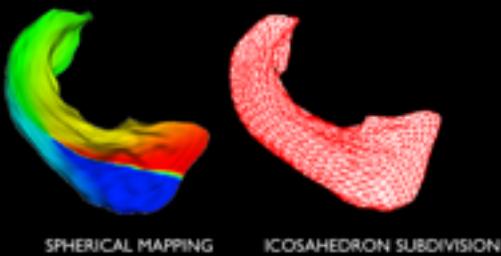
A SUBFIELD LABEL



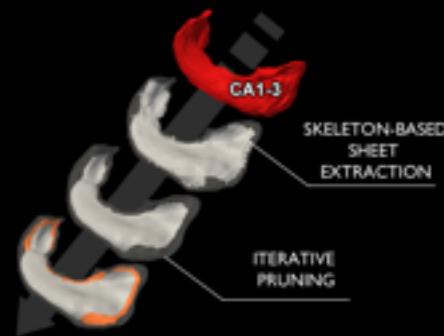
B SUBFIELD HULL REPRESENTATION



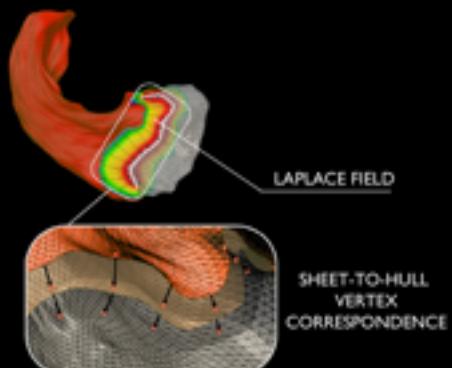
C SPHARDM-PDM PARAMETRIZATION OF OUTER HULL



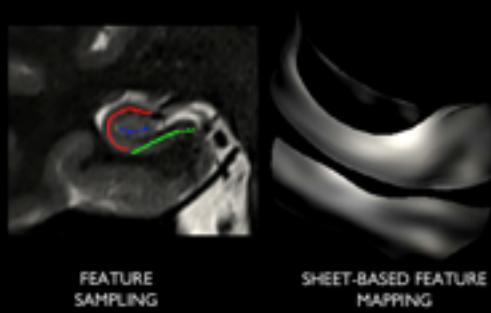
D GENERATION OF MEDIAL SHEET



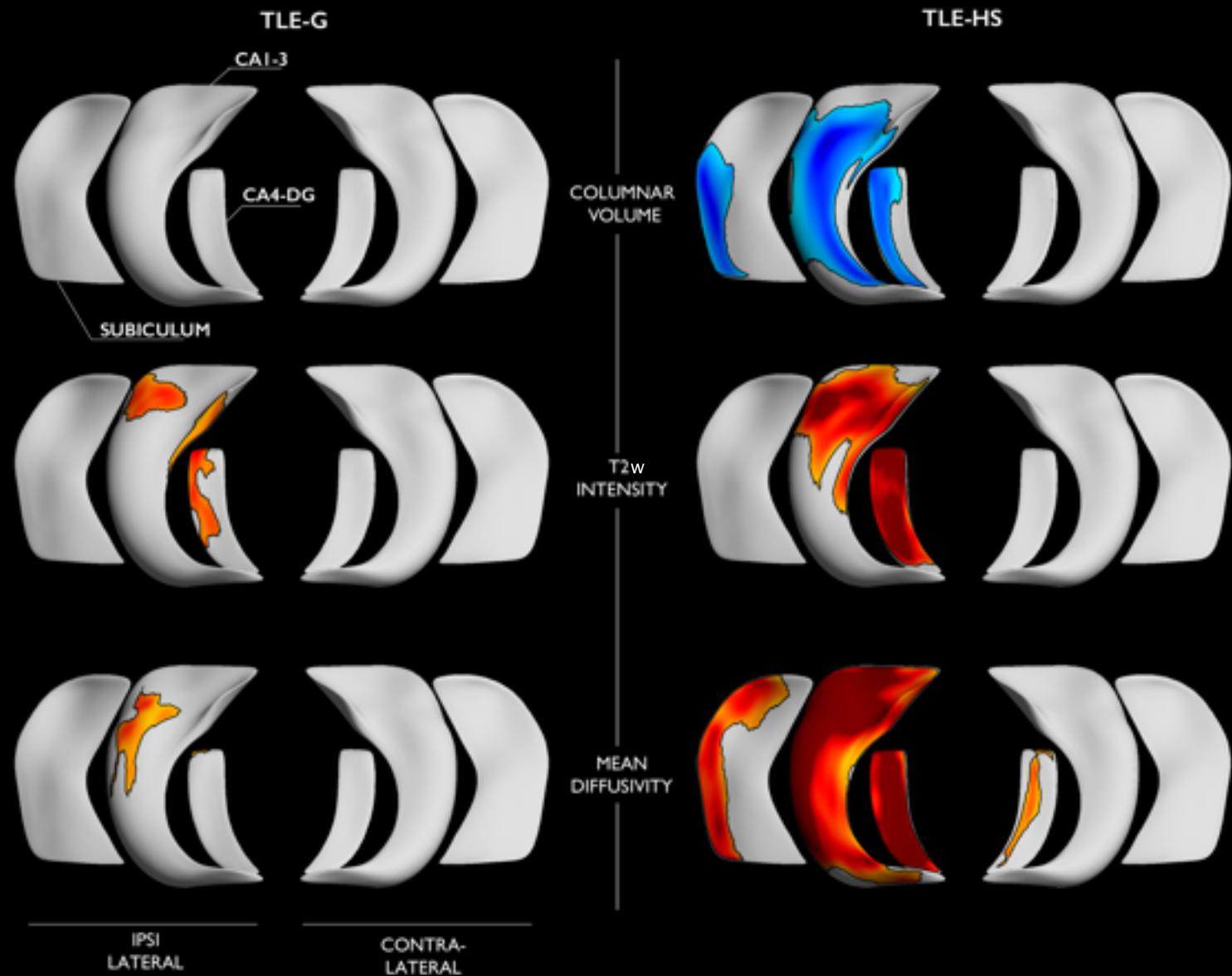
E PROPAGATING PARAMETRIZATION TO SHEET



F SHEET-BASED MEASURES



FEATURE-SPECIFIC COMPARISON TO CONTROLS



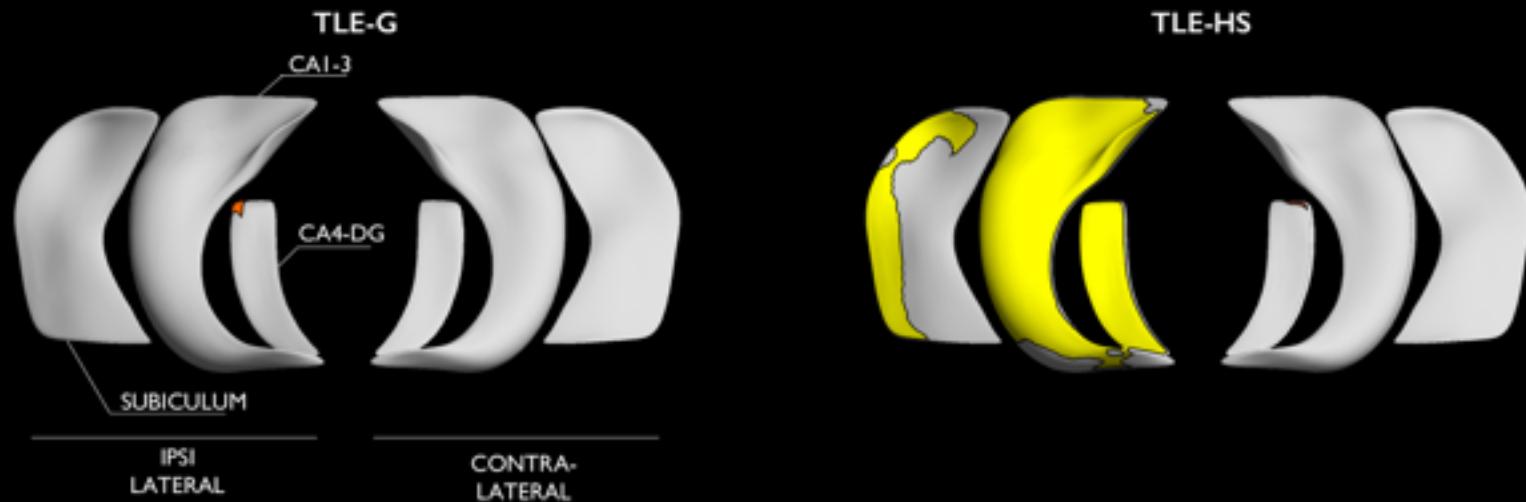
DIRECT CONTRASTS

B DIRECT CONTRAST: TLE-HS vs TLE-G

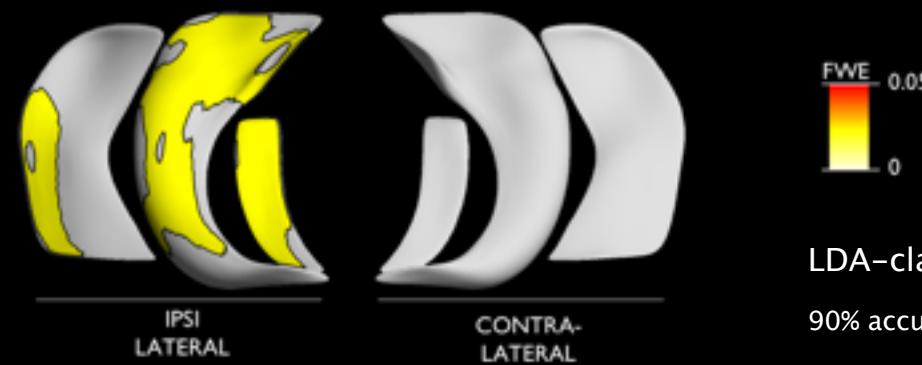


MULTIVARIATE SYNTHESIS

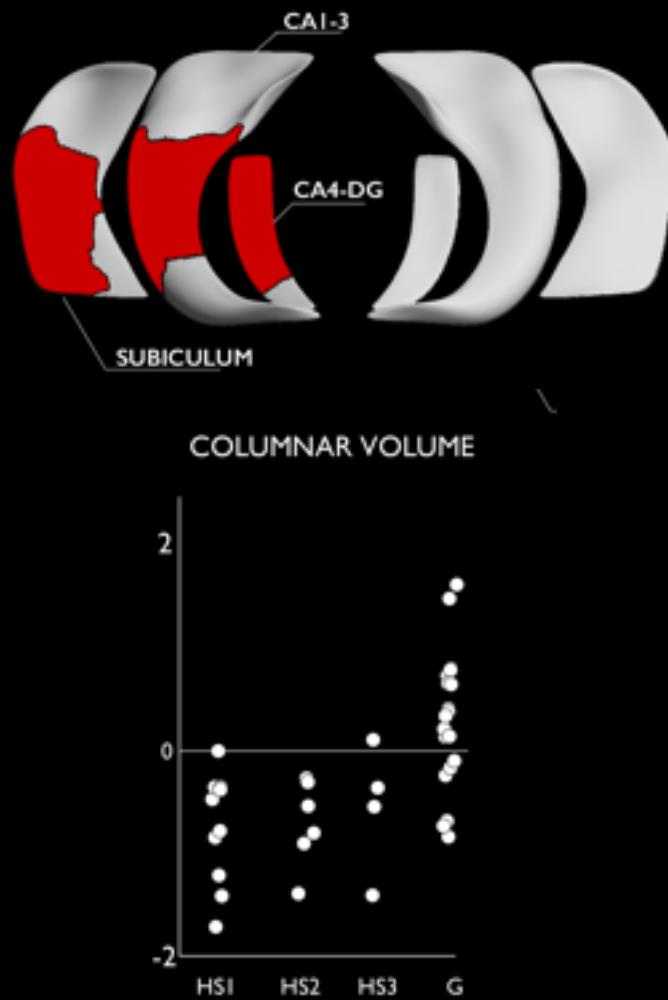
A COMPARISON TO CONTROLS



B DIRECT CONTRAST: TLE-HS vs TLE-G



RELATION TO SPECIFIC HISTOLOGICAL HS GRADES

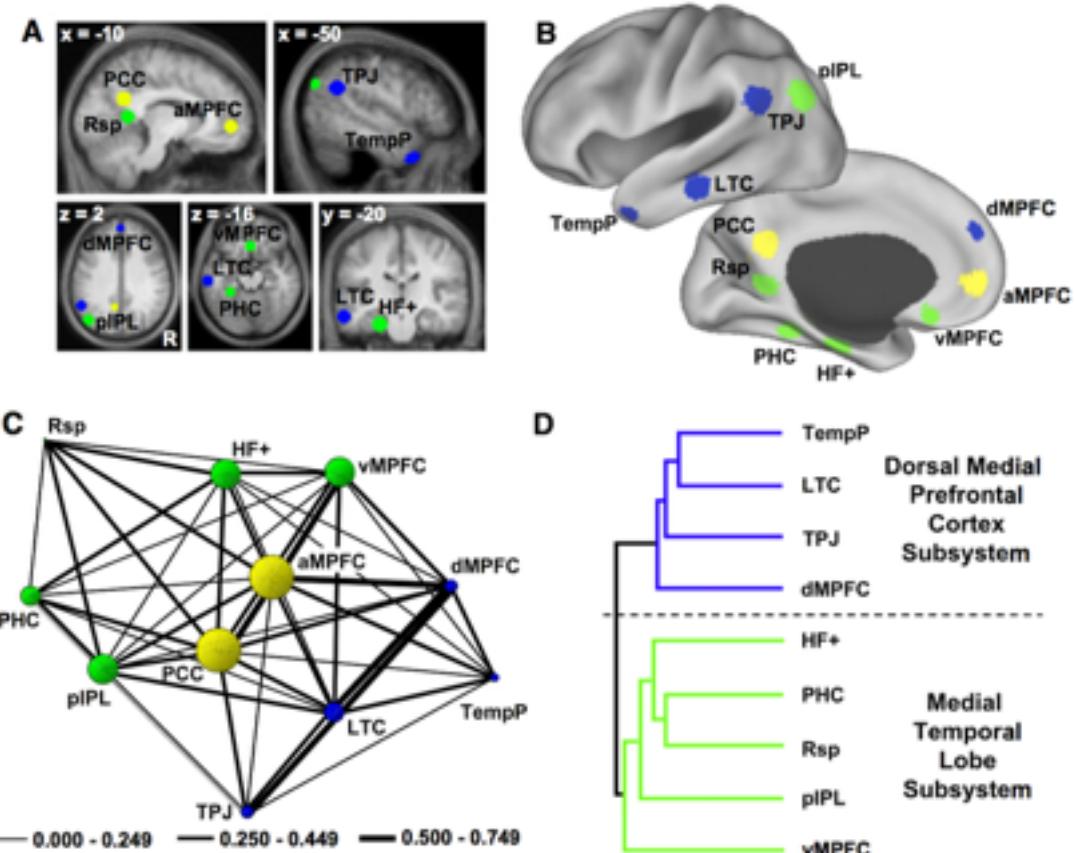


FUNCTION

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

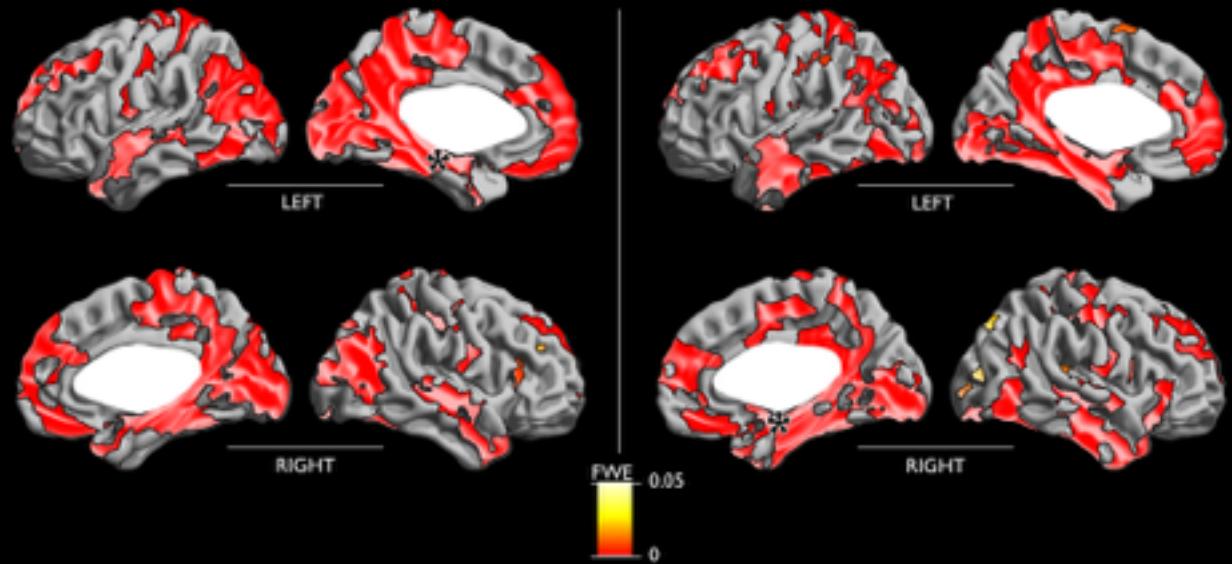


FUNCTION

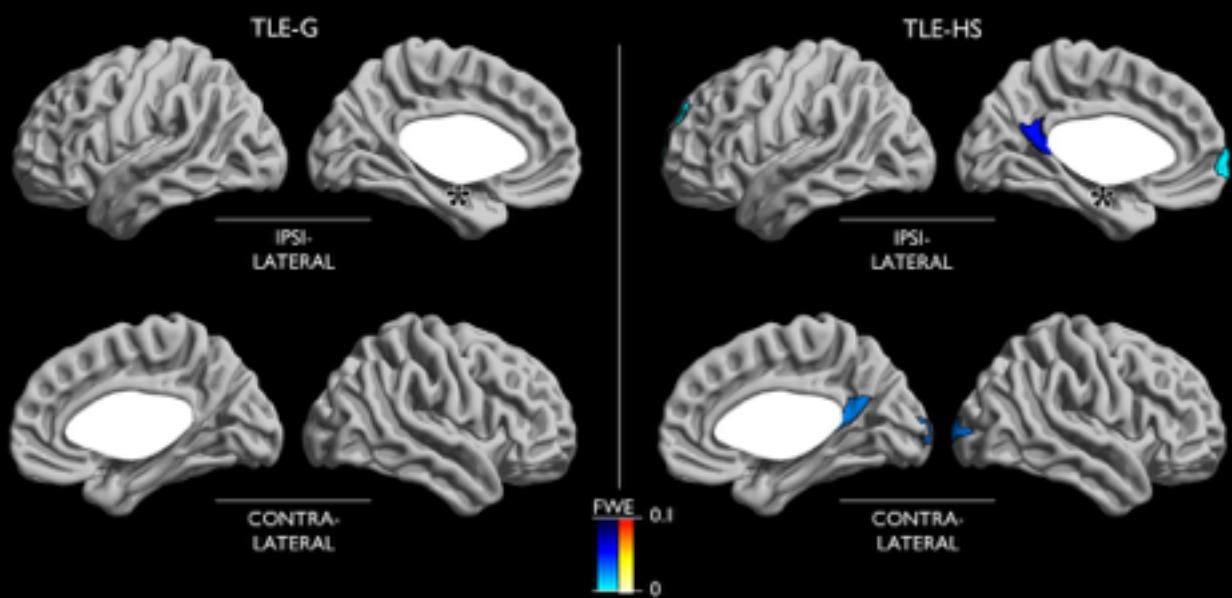
CONNECTIVITY IN CONTROLS
CONFIRMS ROLE OF HIPPOCAMPUS
IN DMN

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

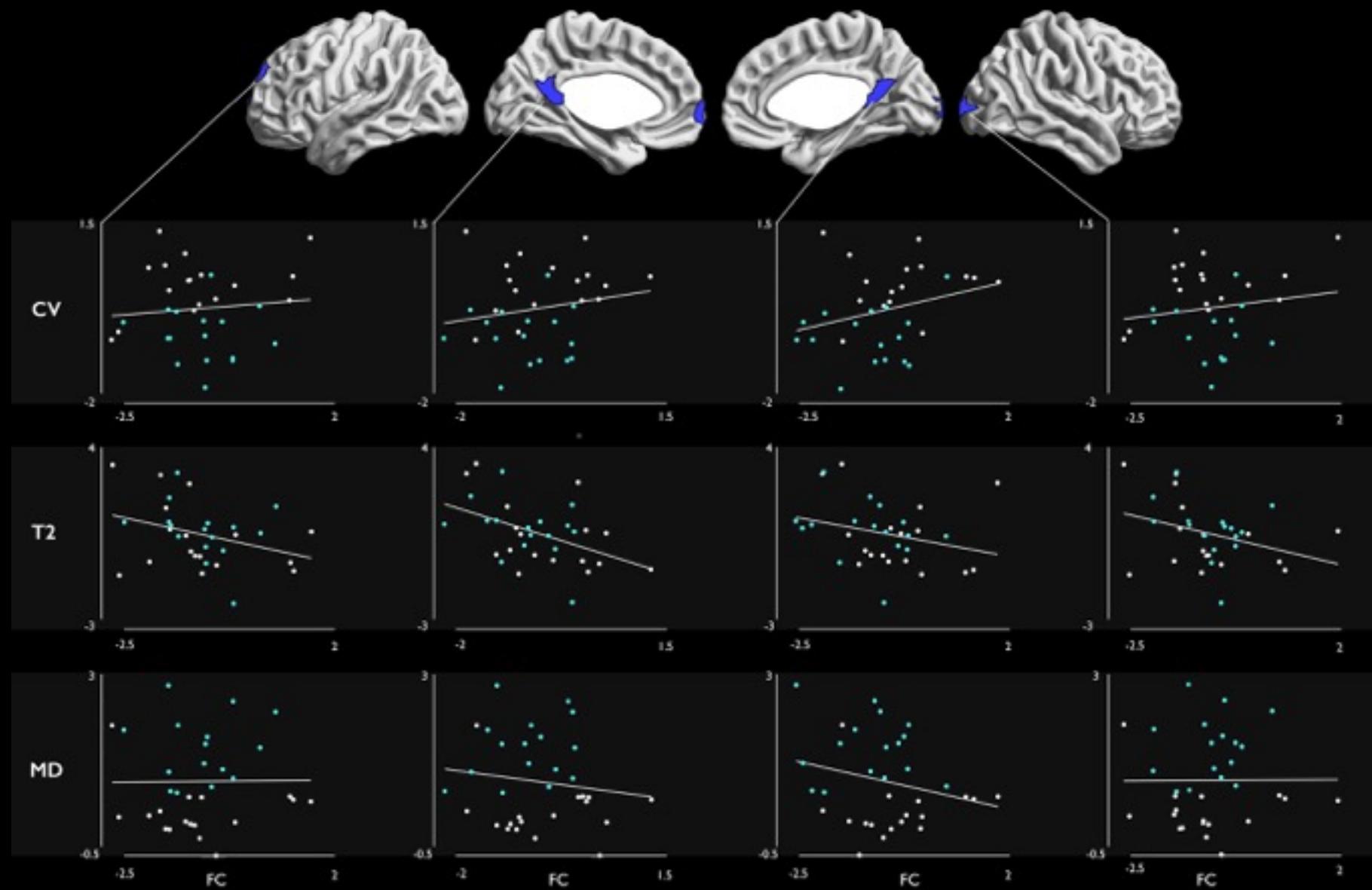
A CONNECTIVITY IN CONTROLS



B CONNECTIVITY ALTERATIONS IN TLE



STRUCTURE-FUNCTION RELATIONSHIPS IN TLE





Annals of NEUROLOGY

An Official Journal of the American Neurological Association and The Child Neurology Society

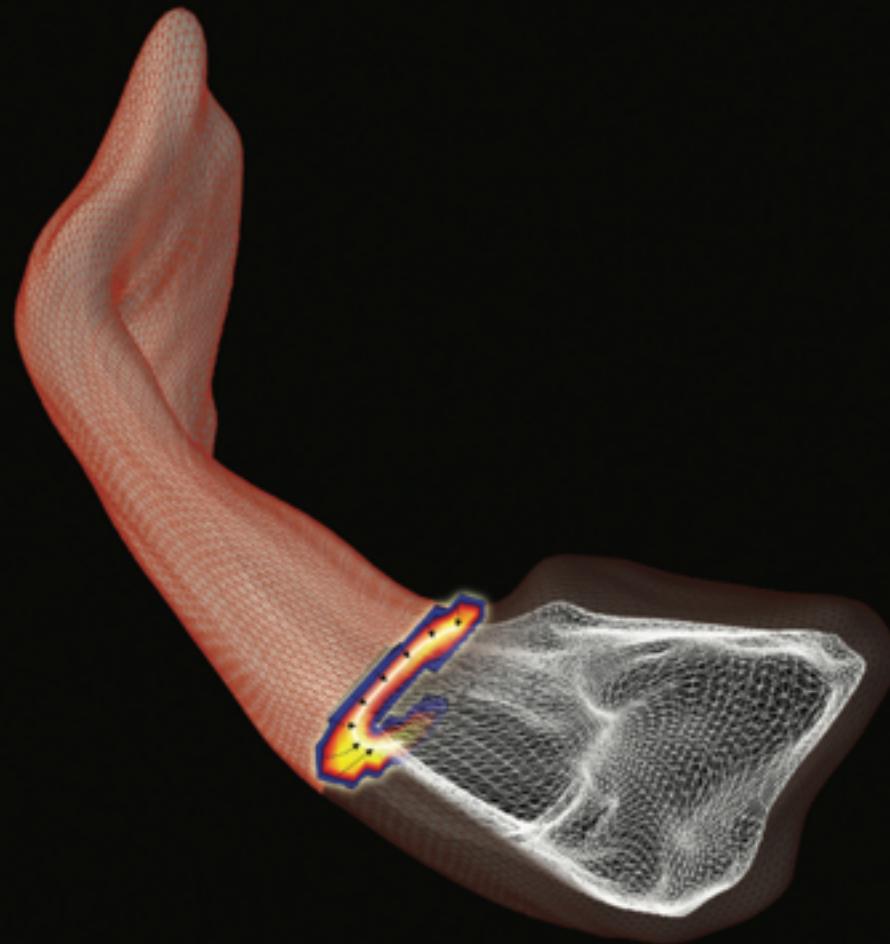
HIPPOCAMPAL SUBTYPES

MRI PROBES LOCAL
PATHOLOGICAL CHANGES

INDIVIDUALIZED PATHOLOGY
PREDICTION POSSIBLE

STRUCTURAL ANOMALIES
RELATE TO FUNCTIONAL NETWORK
EMBEDDING

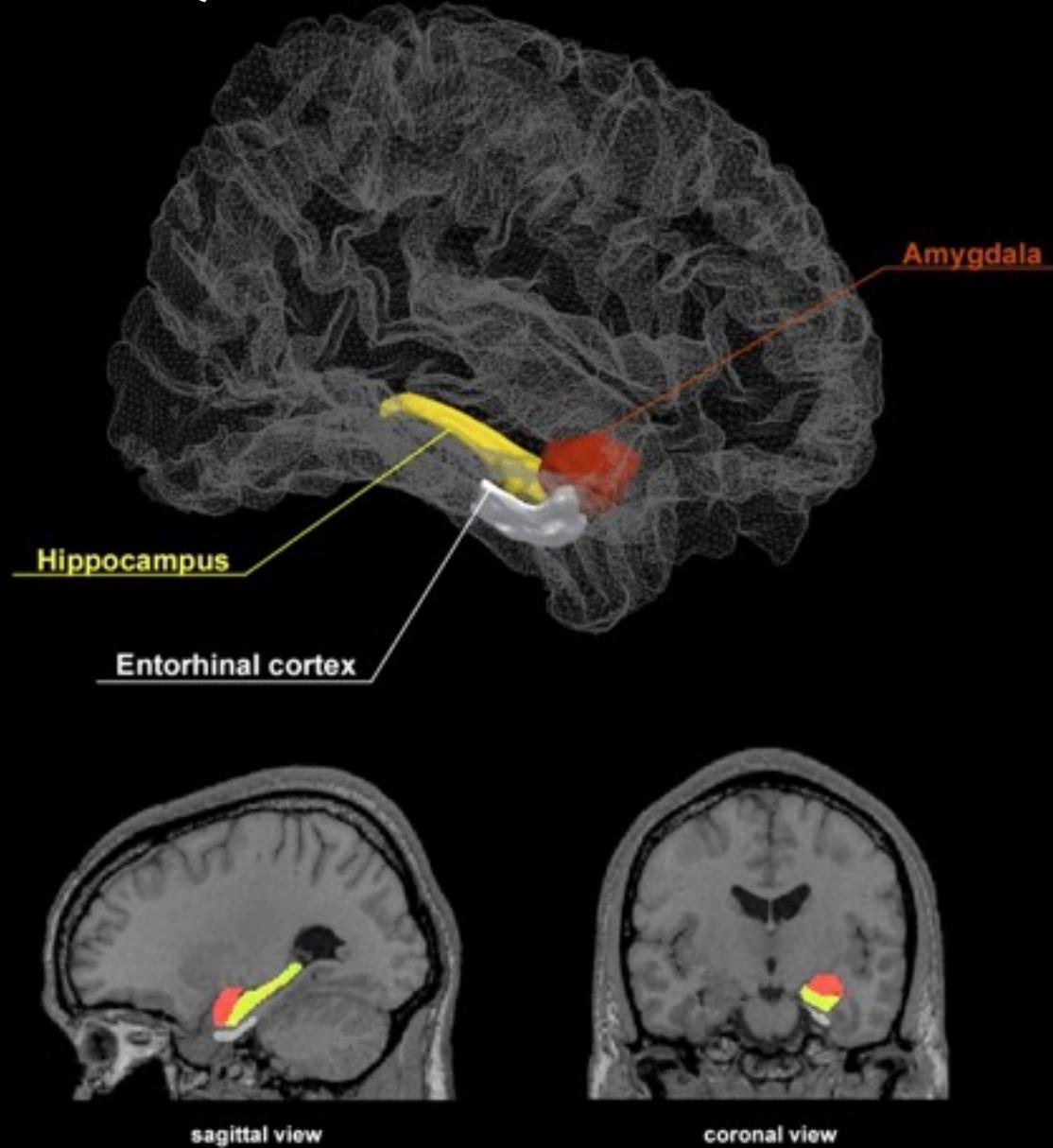
TLE = SPECTRUM OF STRUCTURAL AND
FUNCTIONAL ANOMALIES



WILEY

IS TLE ADEQUATELY CAPTURED BY HIPPOCAMPUS ALONE?

QUANTITATIVE IMAGING IN TLE



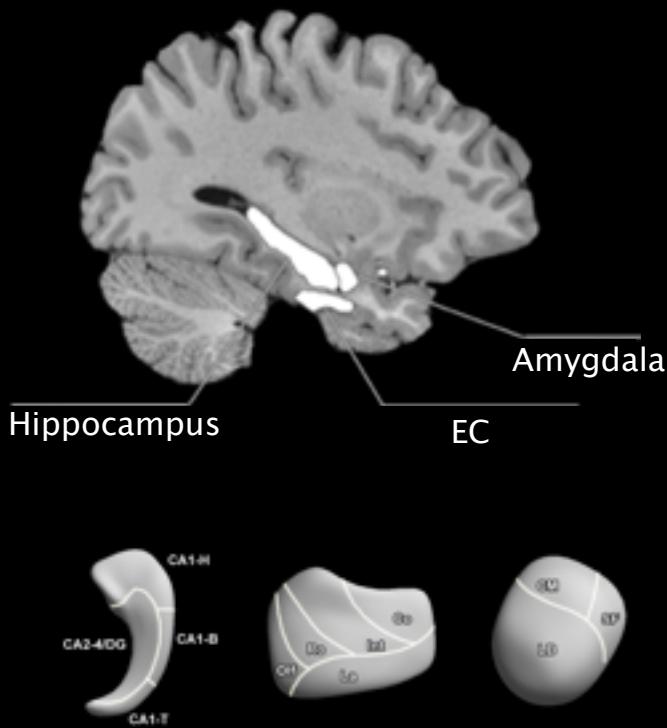
Cascino et al (1991) Annals of Neurology, Jackson et al (1995) Neurology

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

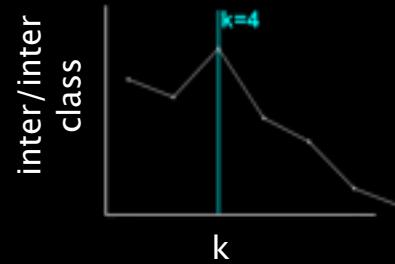
MRI PROFILING AND SUBTYPING

MESIOTEMPORAL PROFILING

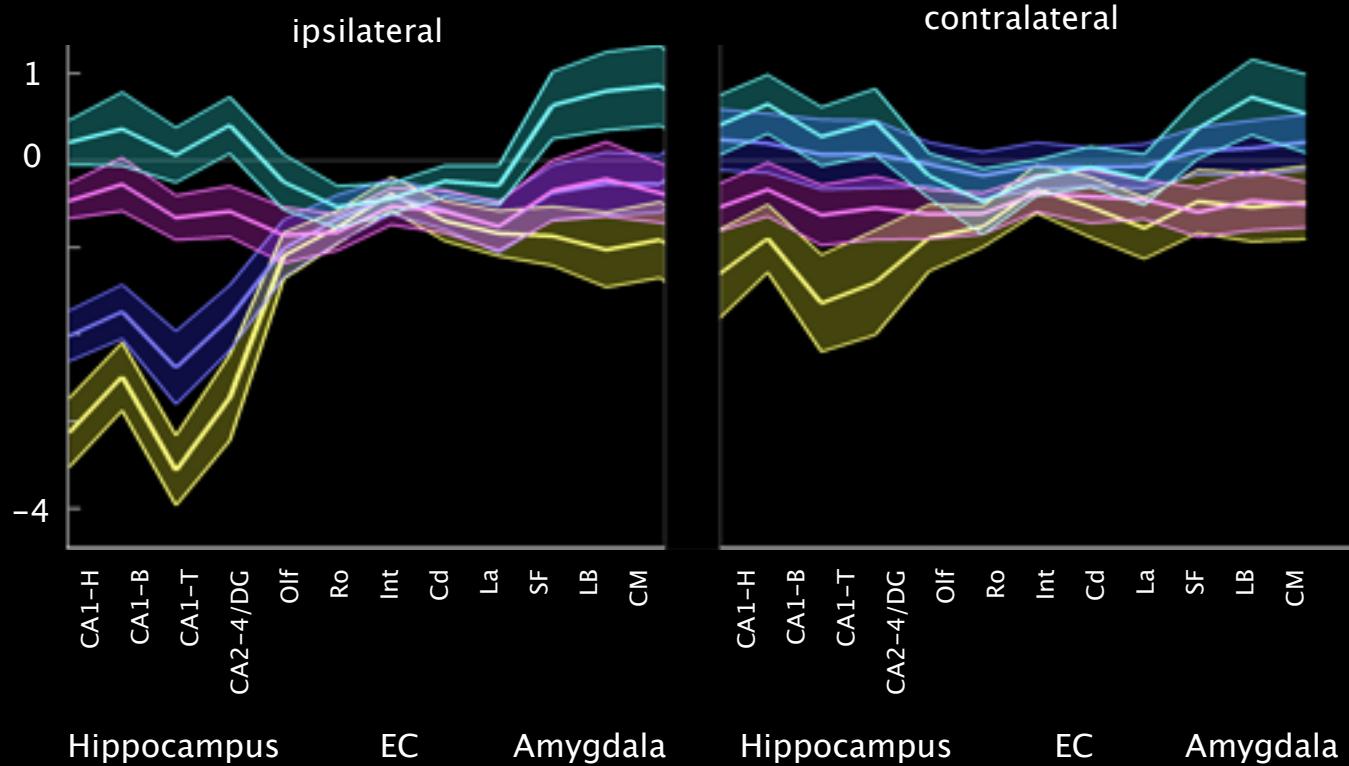
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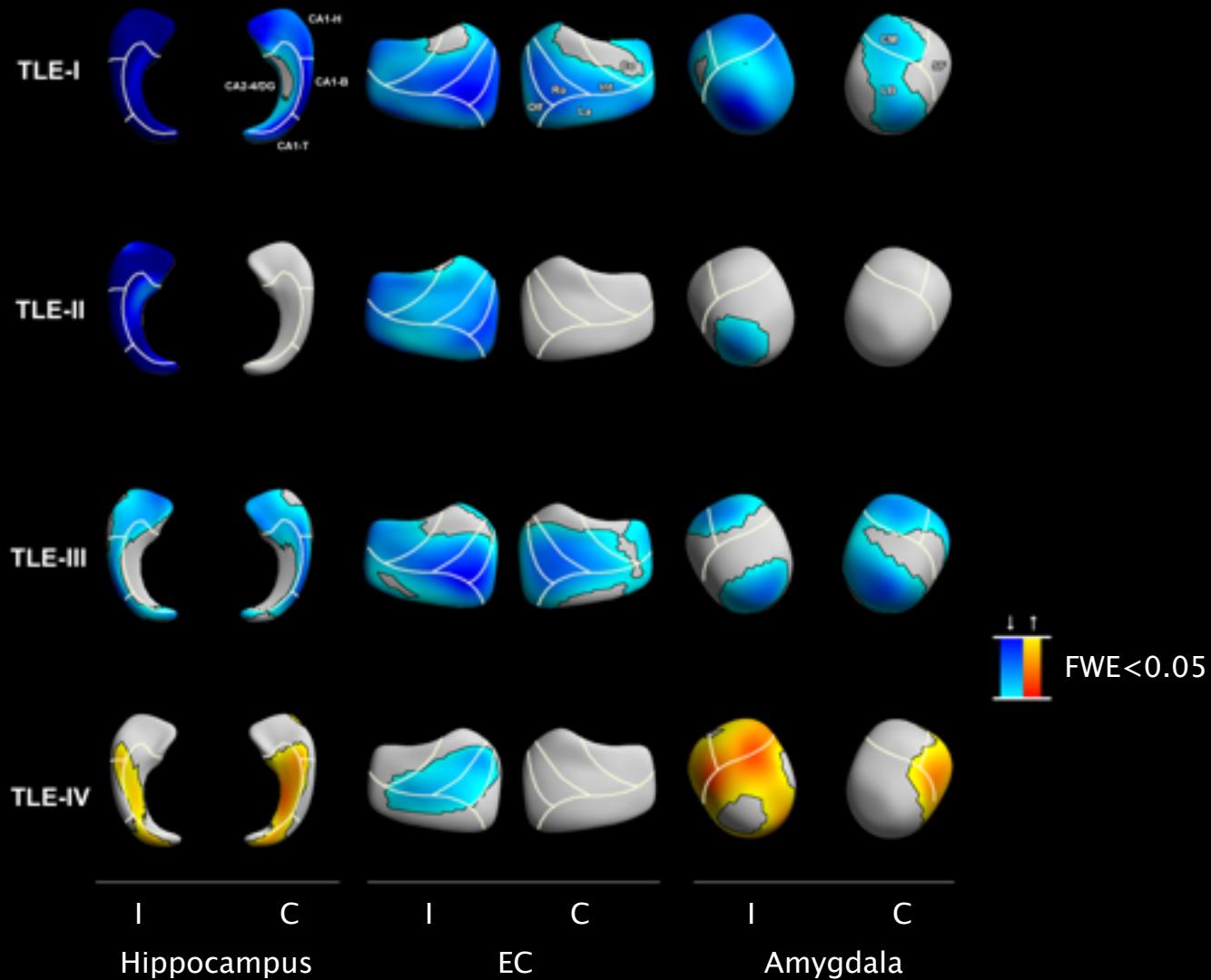
CLUSTERING PATIENT SPECTRUM BASED ON MRI MORPHOMETRY



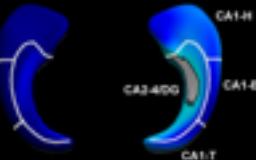
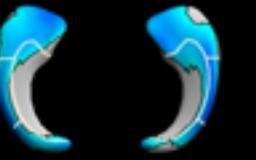
- TLE-I
- TLE-II
- TLE-III
- TLE-IV



DATA-DRIVEN SUBCLASSES



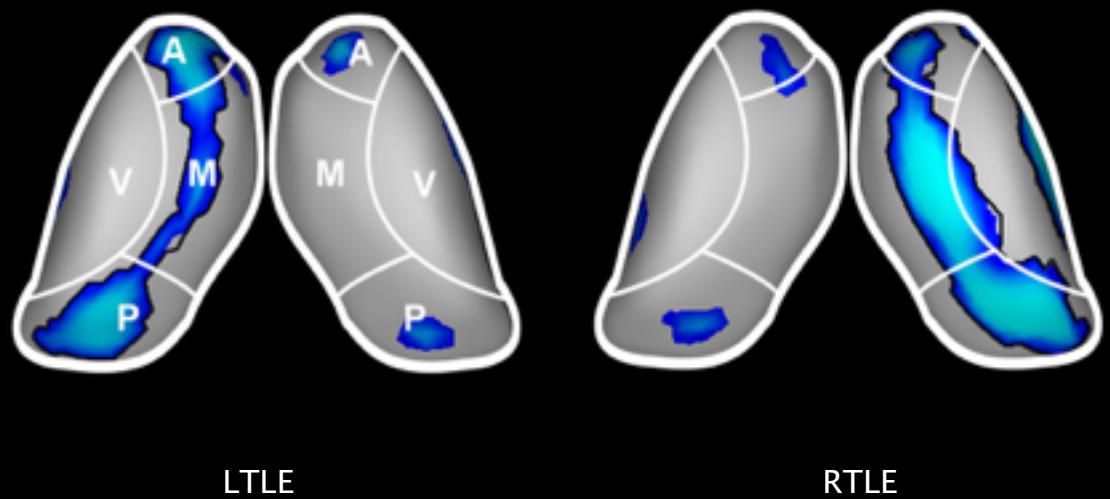
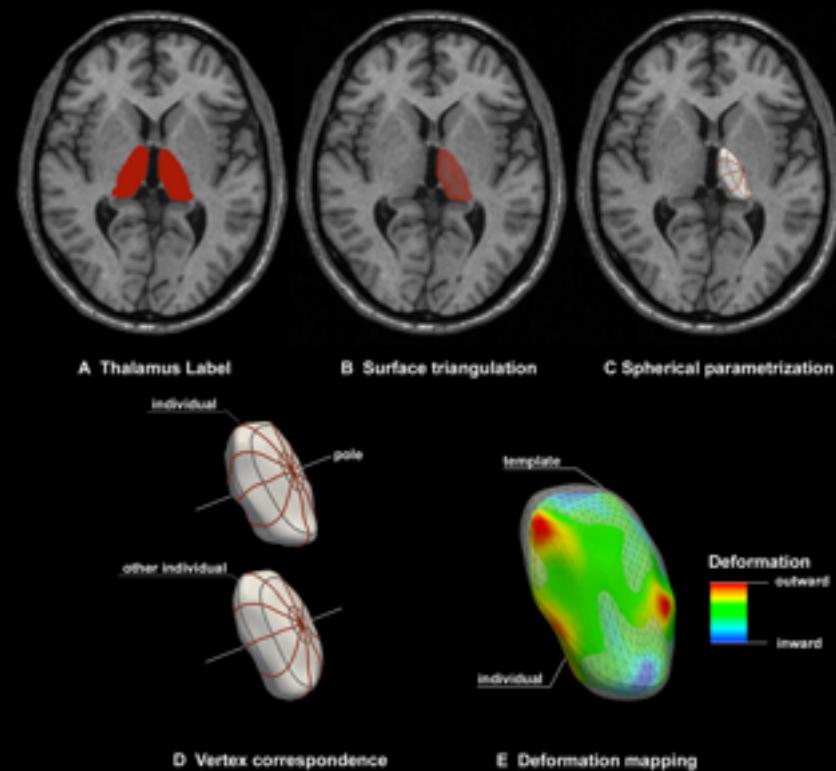
RELATION TO IMAGING-INDEPENDENT CRITERIA

		HS/Gliosis	Engel-I	
TLE-I		71/29%	68%	<p>LDA outcome prediction:</p> <p>class + surface data: 92%</p> <p>surface-measures only: 81%</p> <p>volumetry: 71%</p>
TLE-II		72/28%	89%	
TLE-III		43/57%	65%	
TLE-IV		17/83%	44%	
	I C			
	Hippocampus			

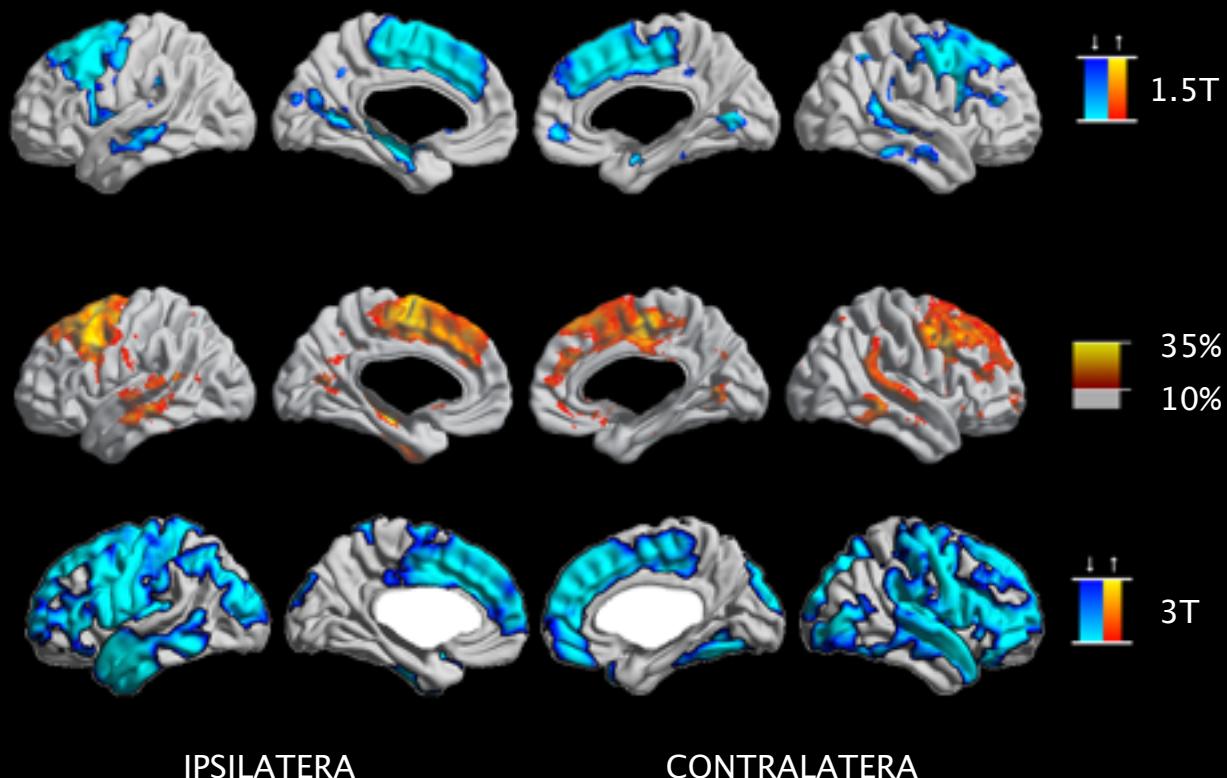
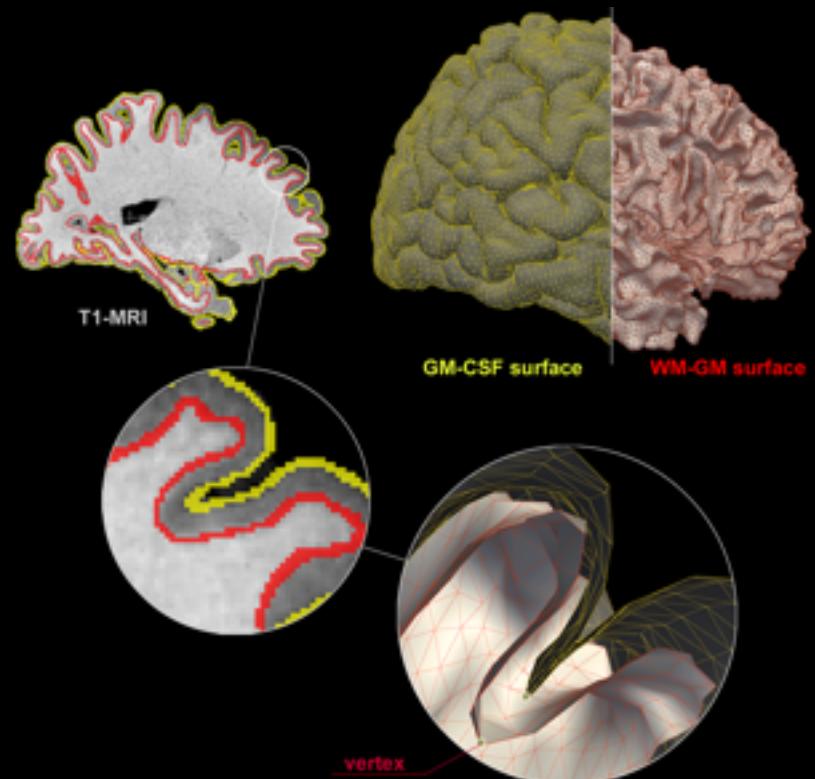
DO ANOMALIES EXTEND BEYOND THE MESIOTEMPORAL REGIONS?

THALAMIC ANOMALIES

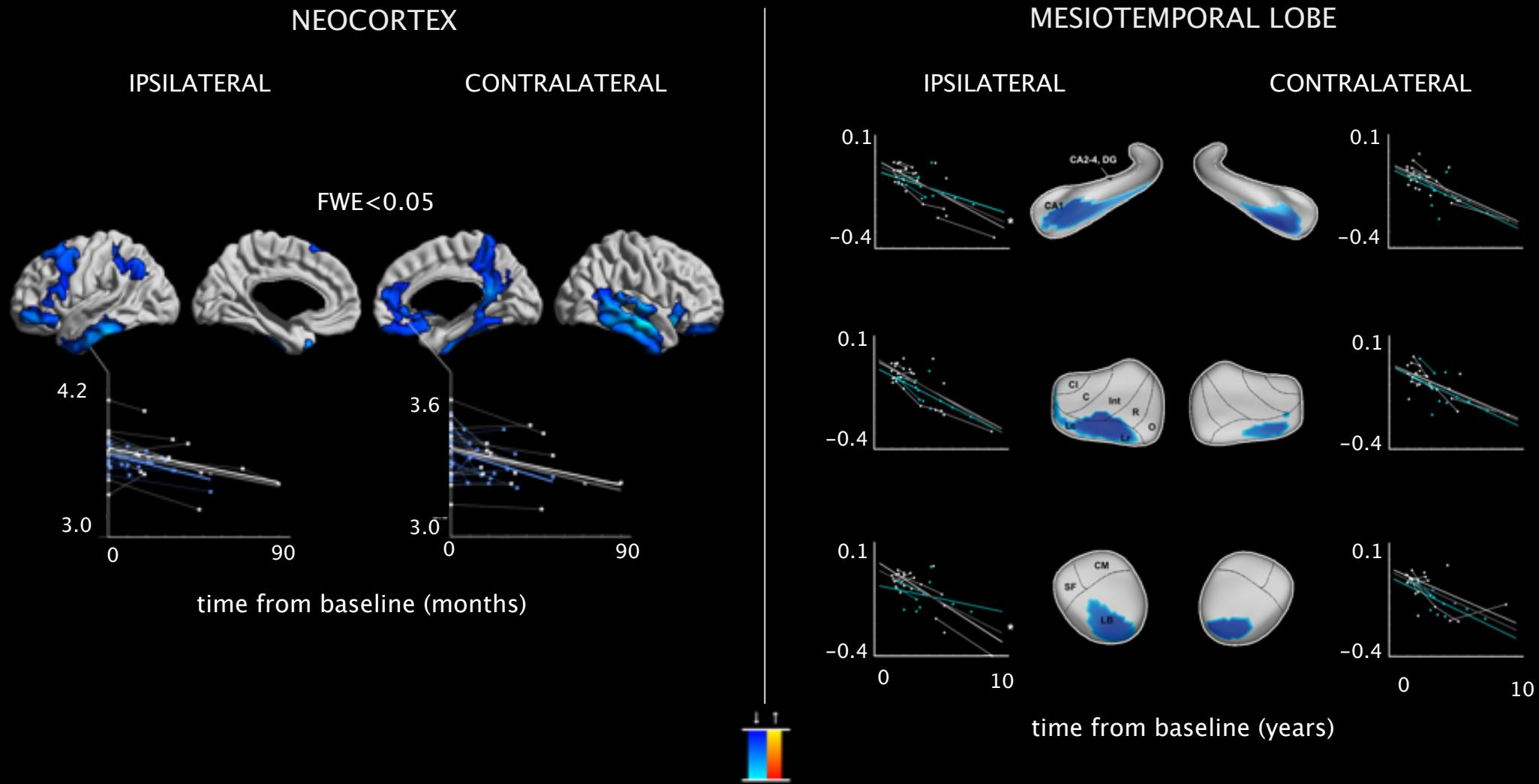
SPHARM-PDM analysis of thalamic local volume changes



NEOCORTICAL ANOMALIES



DISEASE PROGRESSION

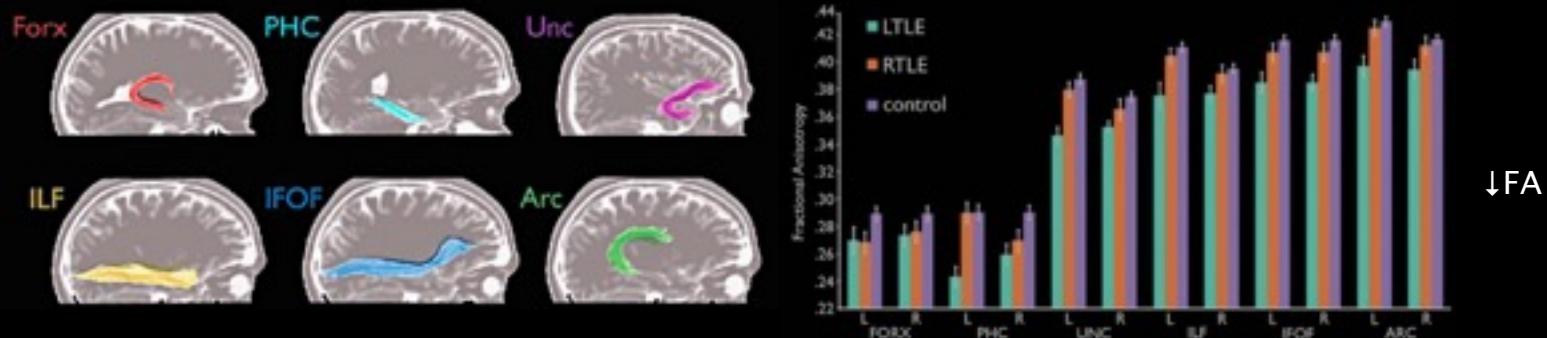


CROSS-SECTIONAL AGE-INTERACTION ANALYSIS:
MORE MARKED AGE-DECLINE IN PATIENTS

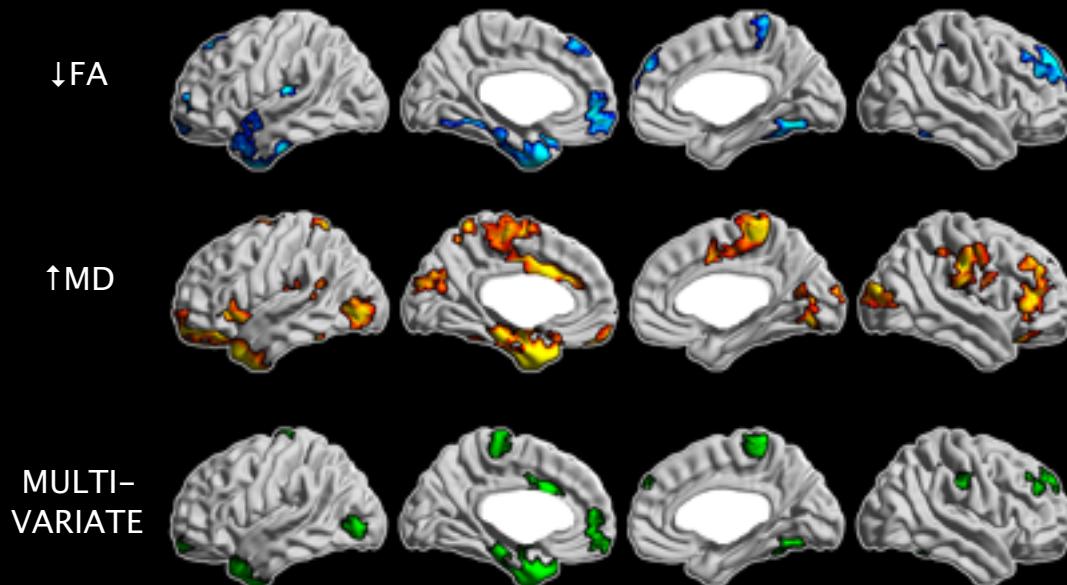
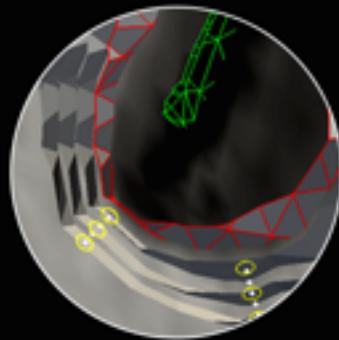
Bernhardt et al. (2009, 2010, 2013) Neurology

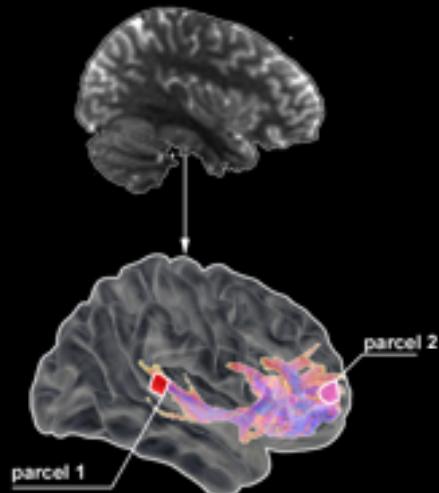
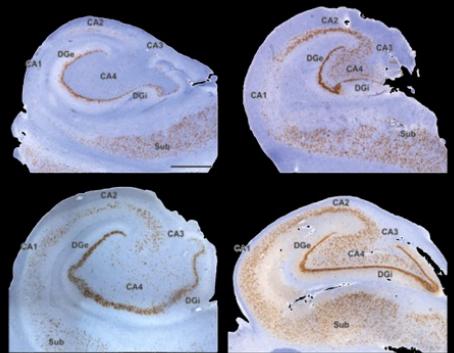
WHITE MATTER ALTERATIONS

TRACTOGRAPHY-
BASED WM BUNDLE
ANALYSIS

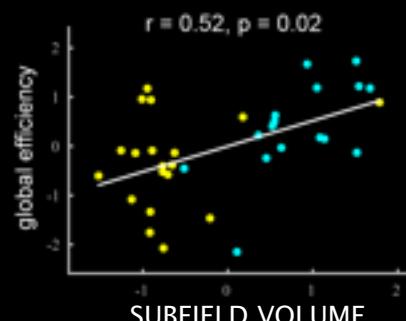
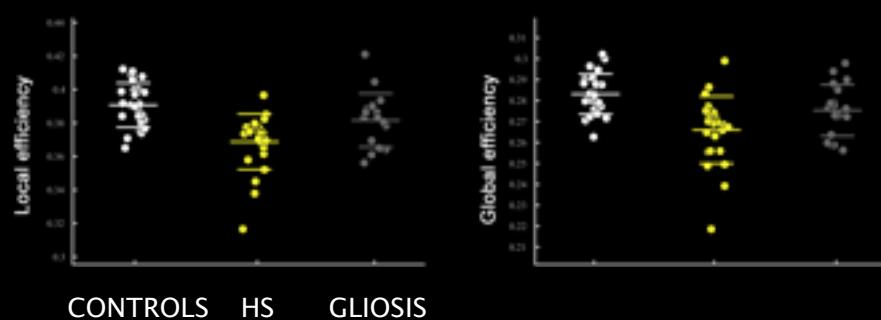
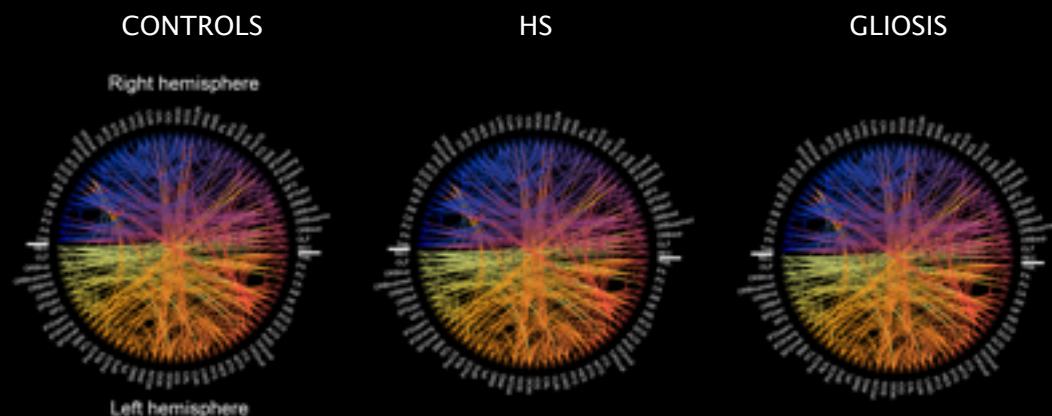


SURFACE-BASED
WM SAMPLING
[2MM DEPTH]





LINKING MACRO/MICROLEVEL DISRUPTIONS



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



European Psychiatry 23 (2008) 289–299

EUROPEAN
PSYCHIATRY

<http://www.sciencedirect.com/science/ELJ/EPSY/>

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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Received 8 December 2006; received in revised form 16 April 2007; accepted 30 May 2007

Available online 31 August 2007



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

Gregory L. Wallace,¹ Nathan Dankner,¹ Lauren Kenworthy,¹ Jay N. Giedd² and Alex Martin¹

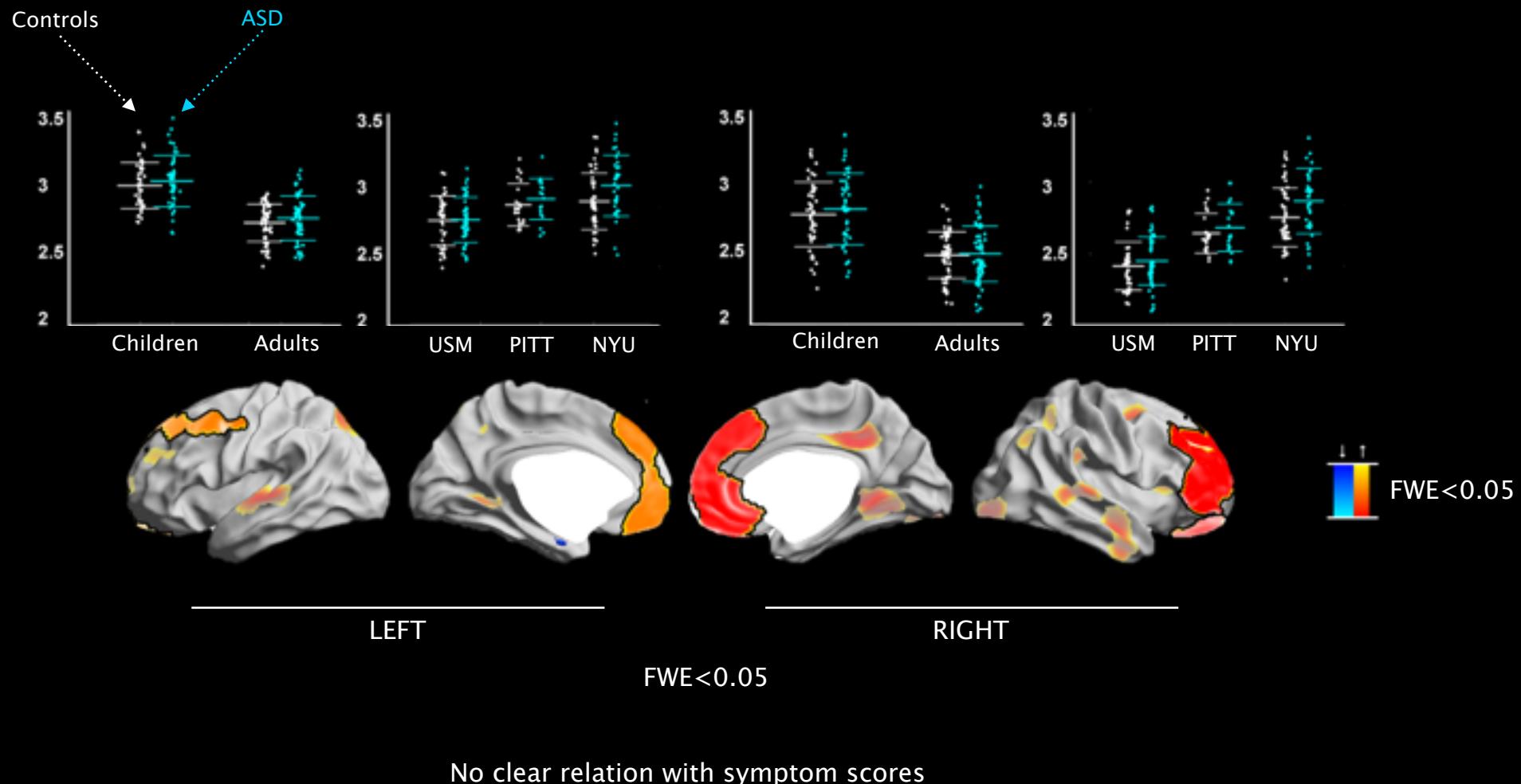
BIG DATA ANALYSIS FOR STRUCTURAL BRAIN ANOMALIES IN AUTISM



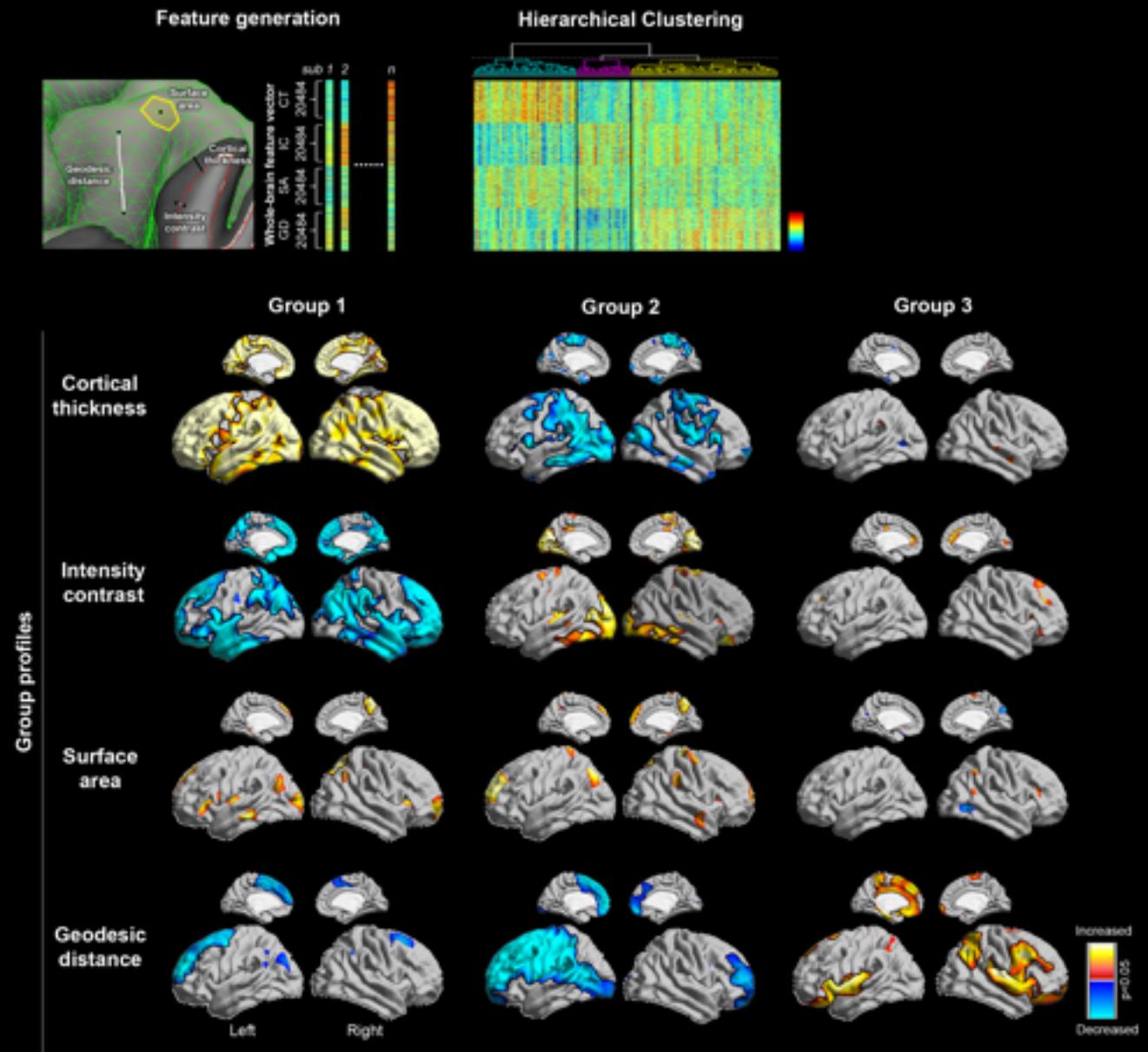
FMRI + SMRI + BASIC PHENOTYPING (AGE, SEX, IQ, DIAGNOSTIC)
in 539 ASD and 537 controls
17 sites

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

MULTI-CENTER MAPPING OF STRUCTURAL ALTERATIONS

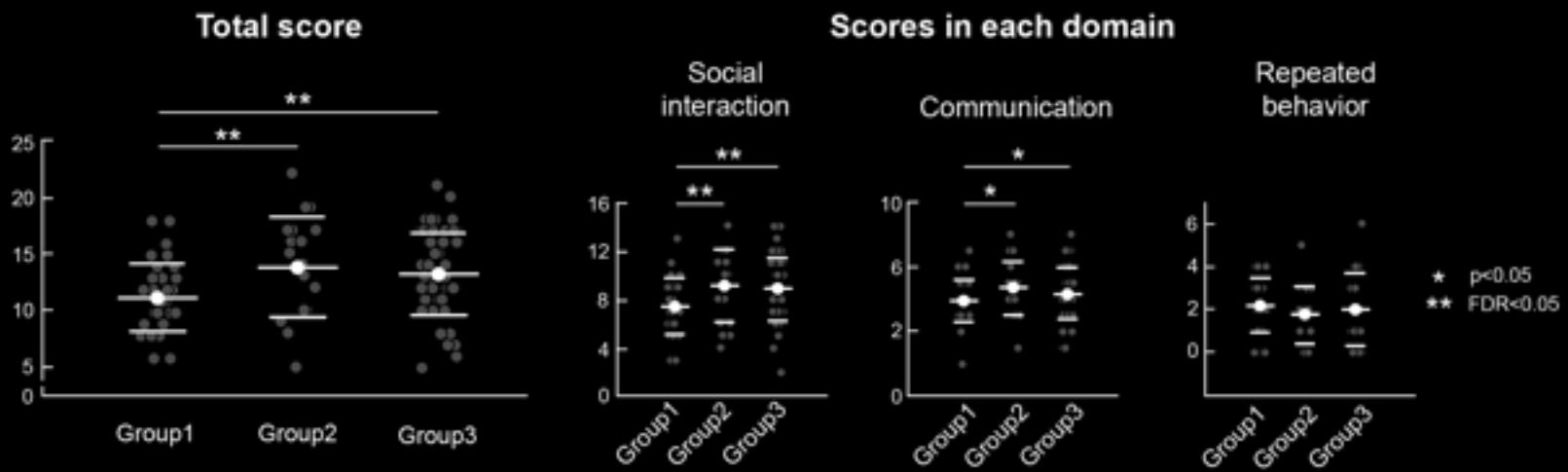


SUBTYPING OF AUTISM SPECTRUM DISORDERS



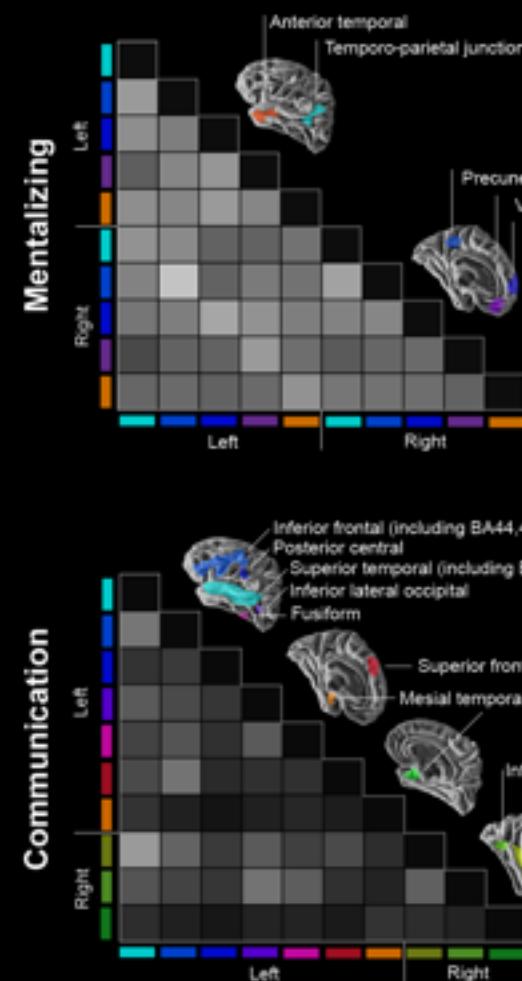
TOWARDS A SUBTYPING OF AUTISM SPECTRUM DISORDERS

ADOS profiles

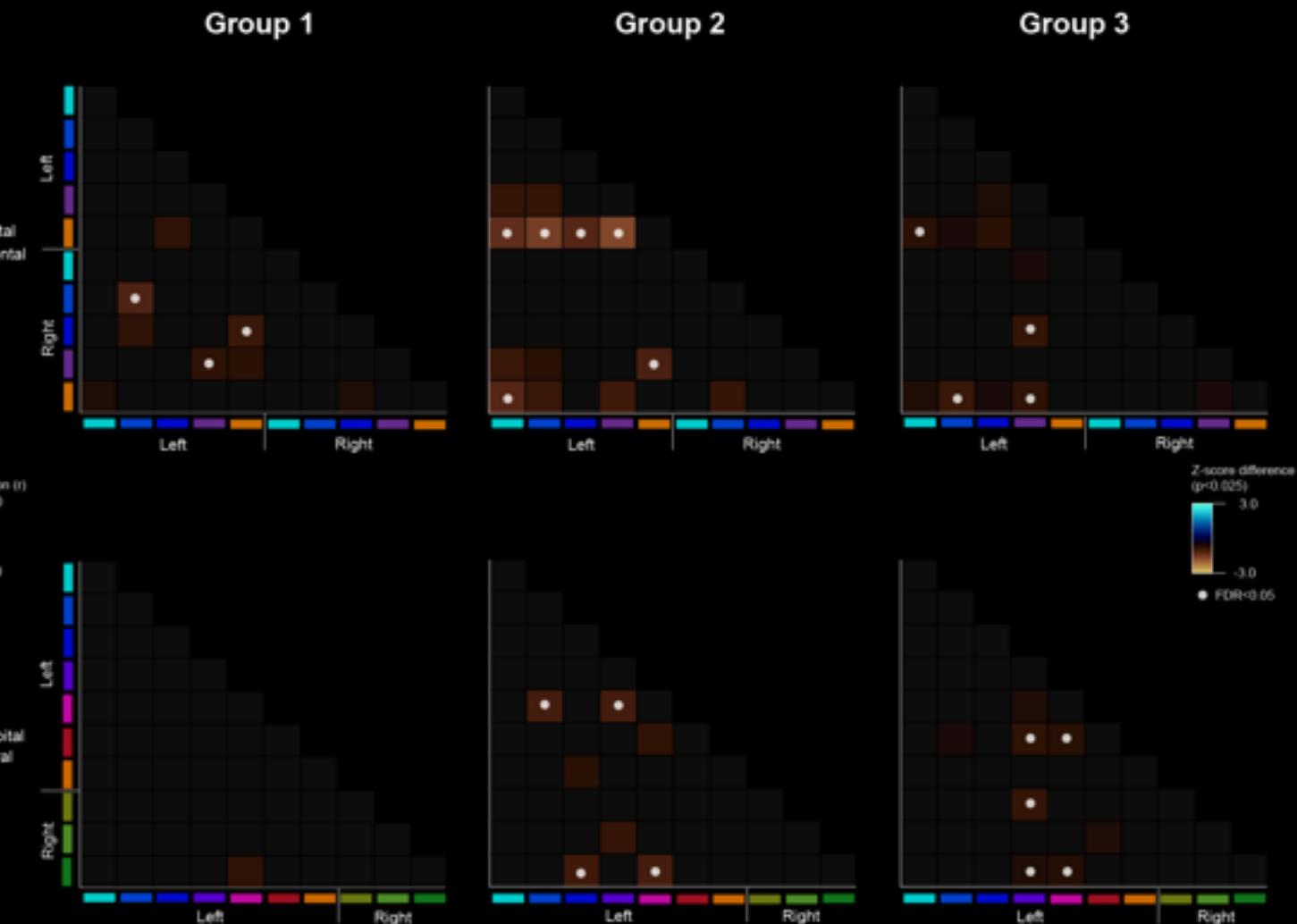


TOWARDS A SUBTYPING OF AUTISM SPECTRUM DISORDERS

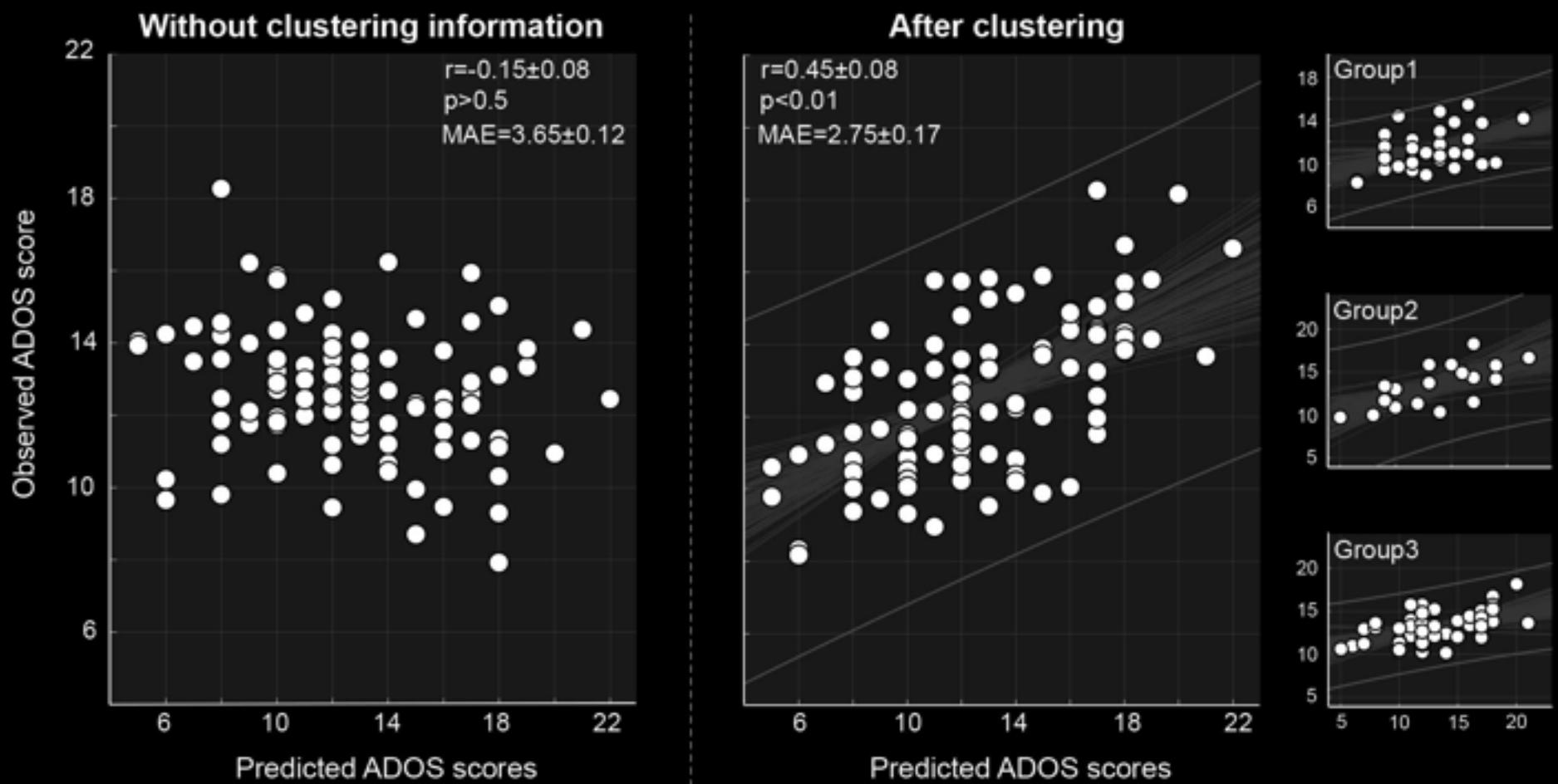
Functional connectivity in controls



Decreased connectivity in ASD



SYMPTOM SEVERITY PREDICTION



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

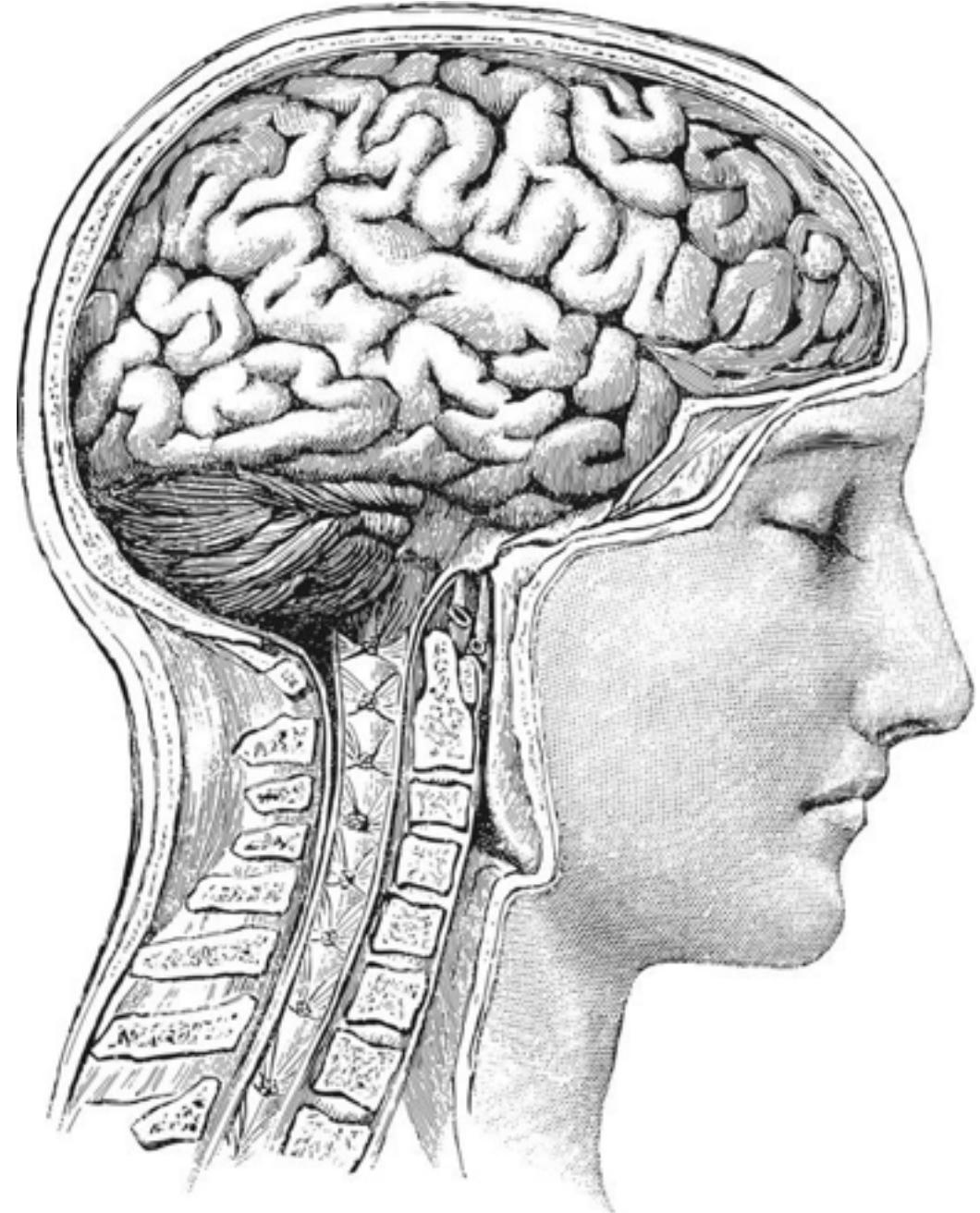
SUMMARY

MRI PROVIDES IN VIVO INFORMATION ON
MICROSTRUCTURE AND NETWORKS

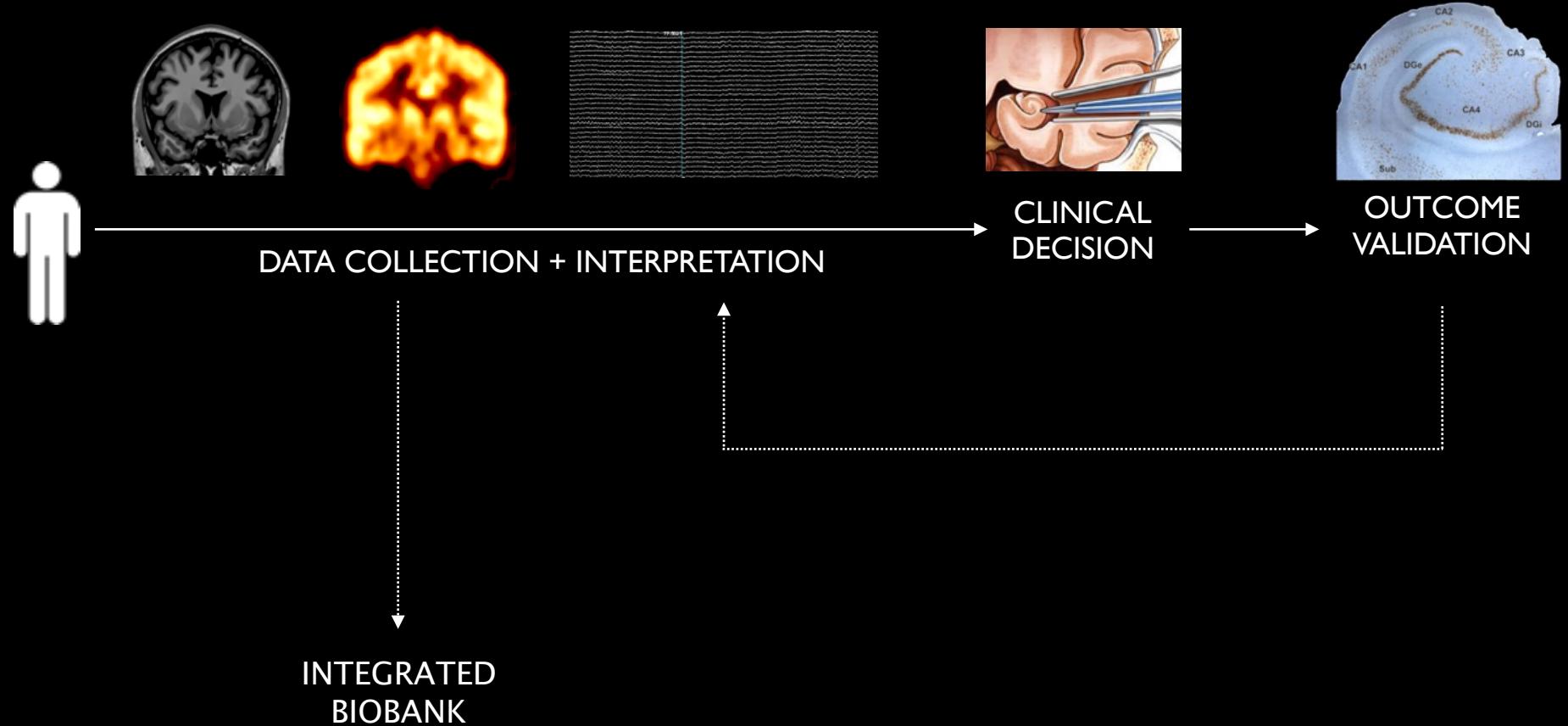
STRUCTURE-FUNCTION ANALYSIS

EXPLICITLY ADDRESSING VARIABILITY
IN EPILEPSY AND AUTISM MAY
IMPROVE DIAGNOSTIC POWER

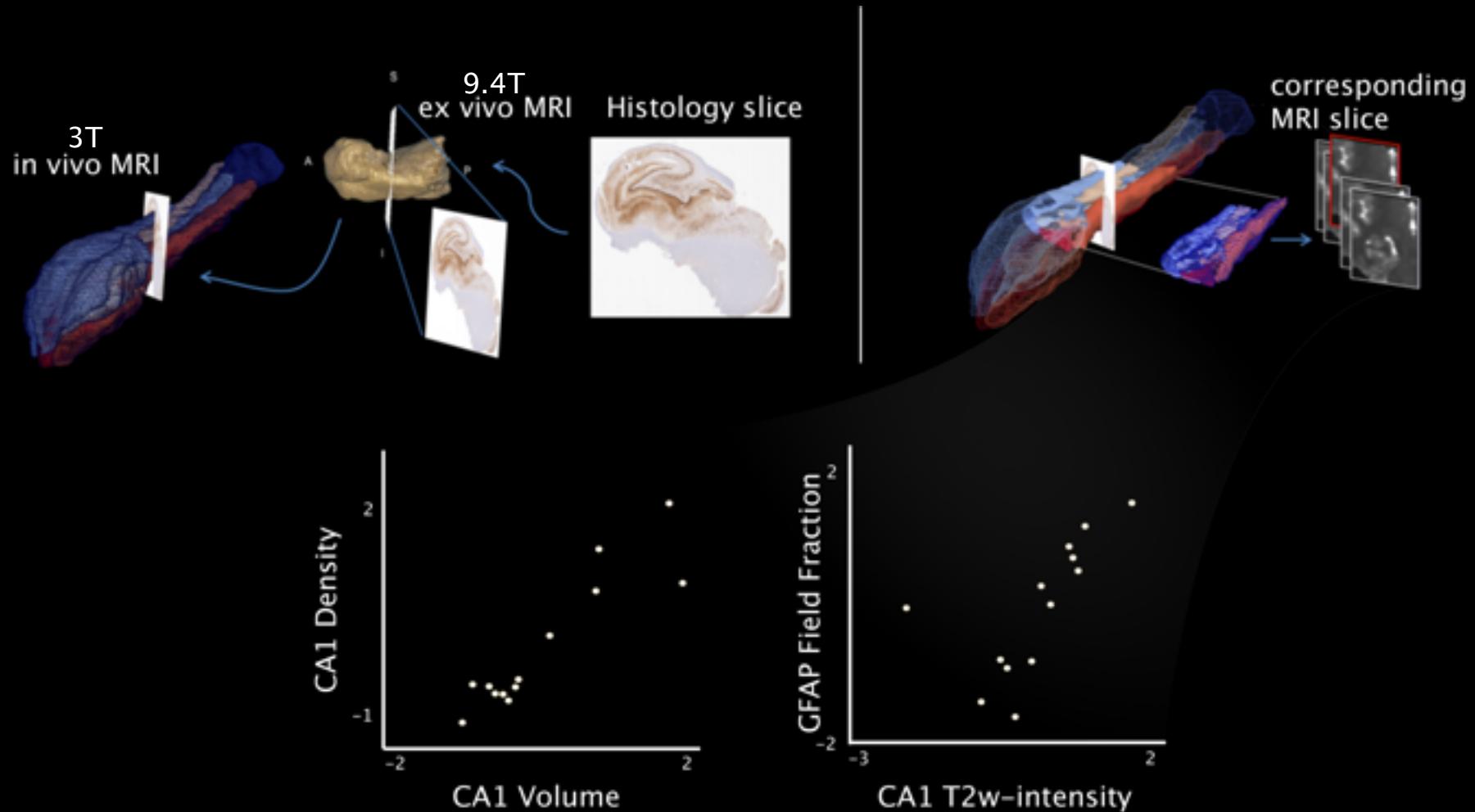
OPPORTUNITIES FOR VALIDATION
THROUGH CLINICAL PIPELINES



PATIENT-ORIENTED RESEARCH



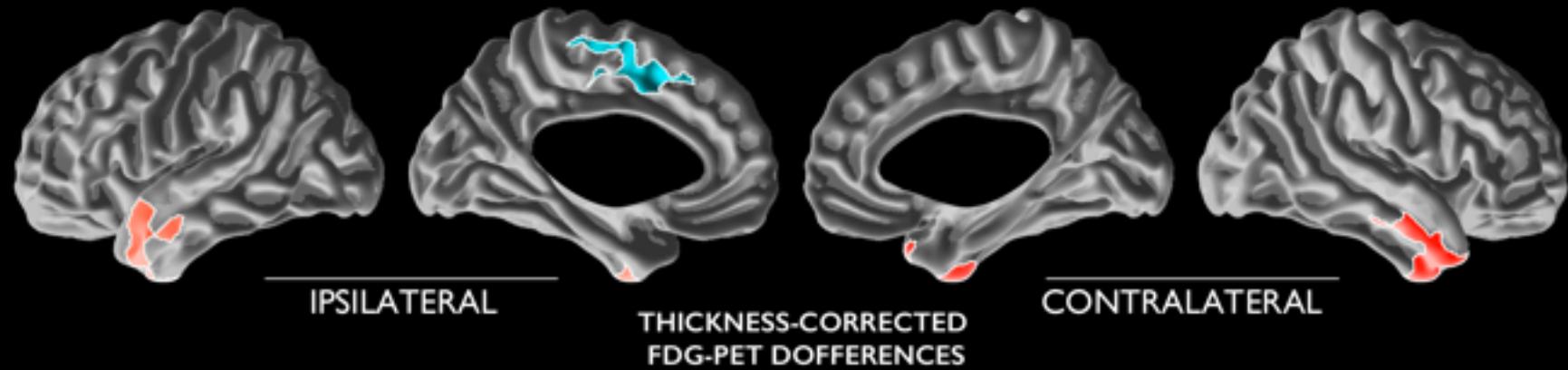
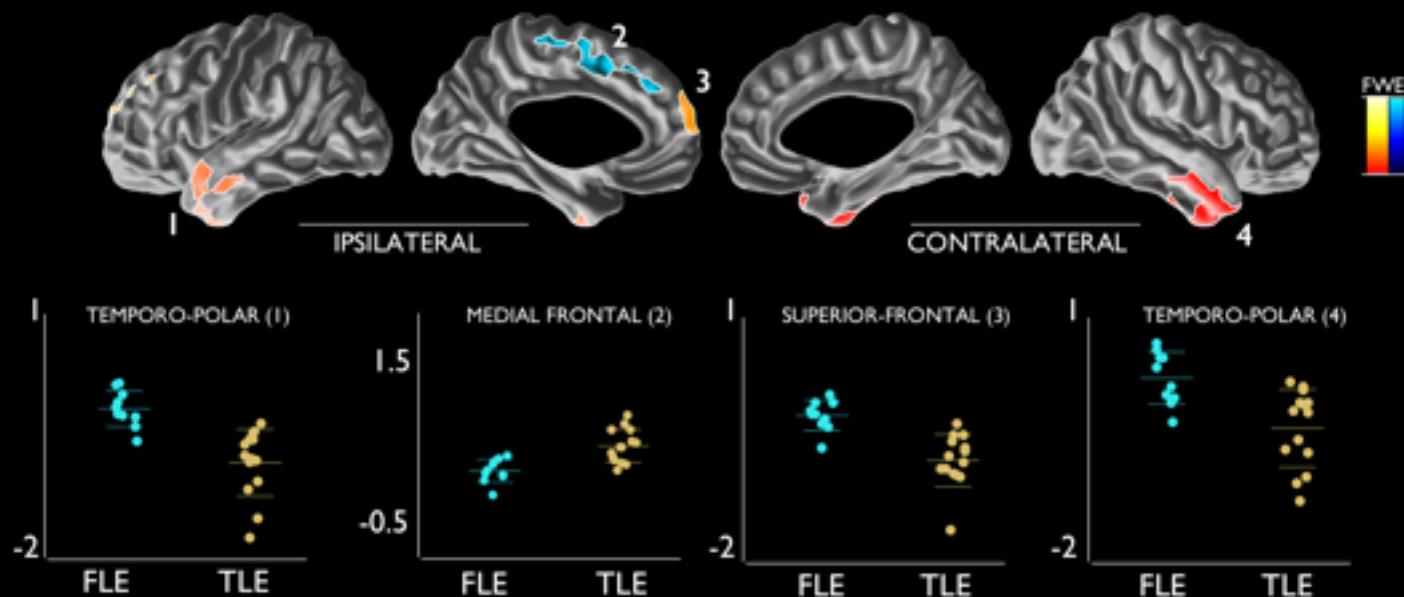
VALIDATION OF IN VIVO FINDINGS WITH QUANTITATIVE HISTOPATHOLOGY



SUBFIELD-SPECIFIC CORRELATIONS BETWEEN MRI AND HISTOLOGY

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

METABOLIC DIVERGENCE OF FOCAL EPILEPSY SYNDROMES



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