

SUBTYPING EPILEPSY AND AUTISM WITH MULTIMODAL IMAGING AND CONNECTOME ANALYSIS

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<http://mica-mni.github.io>



EPILEPSY AND AUTISM

HIGHLY COMMON DISORDERS

EARLY ONSET

PERSIST INTO ADULTHOOD

SYMPTOMATICALLY DIAGNOSED

HIGH HETEROGENEITY



OPTIMIZING DIAGNOSIS AND TREATMENT

SYMPTOMS AND BIOLOGY

INDIVIDUAL DISORDERS MAY BE
COLLECTIONS OF SUBTYPES

DIFFERENT DISORDERS
MAY HAVE COMMON
BIOLOGICAL BASIS

BASIS INFORMS ABOUT CLINICAL,
COGNITIVE, AND AFFECTIVE OUTCOME

MATCHING CARE TO BIOLOGY
CAN LEAD TO MORE TARGETED
INTERVENTIONS



NEUROIMAGING AS A TRANSFORMATIVE TOOL

NON-INVASIVE
WIDELY AVAILABLE

QUANTITATIVE MARKERS TO PROBE TISSUE AND INTERROGATE NETWORKS

HELP TO CHARACTERIZE DISORDERS BUT ALSO TO IDENTIFY DISEASE SUBTYPES AND DISCOVER TRANS-DISEASE COMMONALITIES

PROVIDE PROGNOSTIC MARKERS MONITOR PROGRESSION AND INTERVENTION



OUTLINE

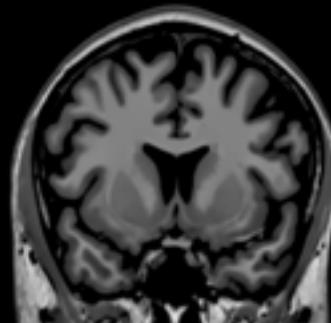
MULTIMODAL NEUROIMAGING:
STRUCTURE, FUNCTION, NETWORKS

NEUROIMAGING SUBTYPING
IN EPILEPTIC DISORDERS

NEUROIMAGING-DERIVED
AUTISM SPECTRUM SUBTYPES

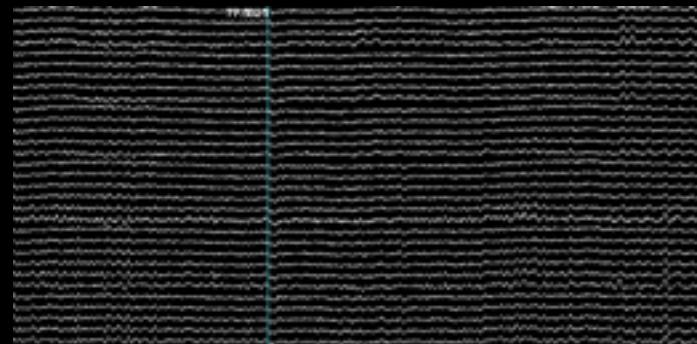
MULTIPLE NEUROIMAGING MODALITIES

MRI



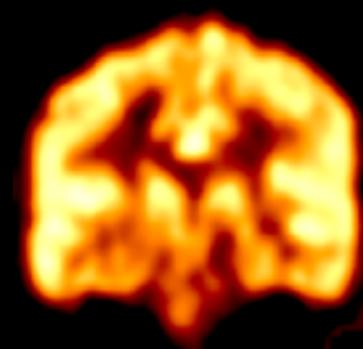
STRUCTURE
FUNCTION

MEG/EEG



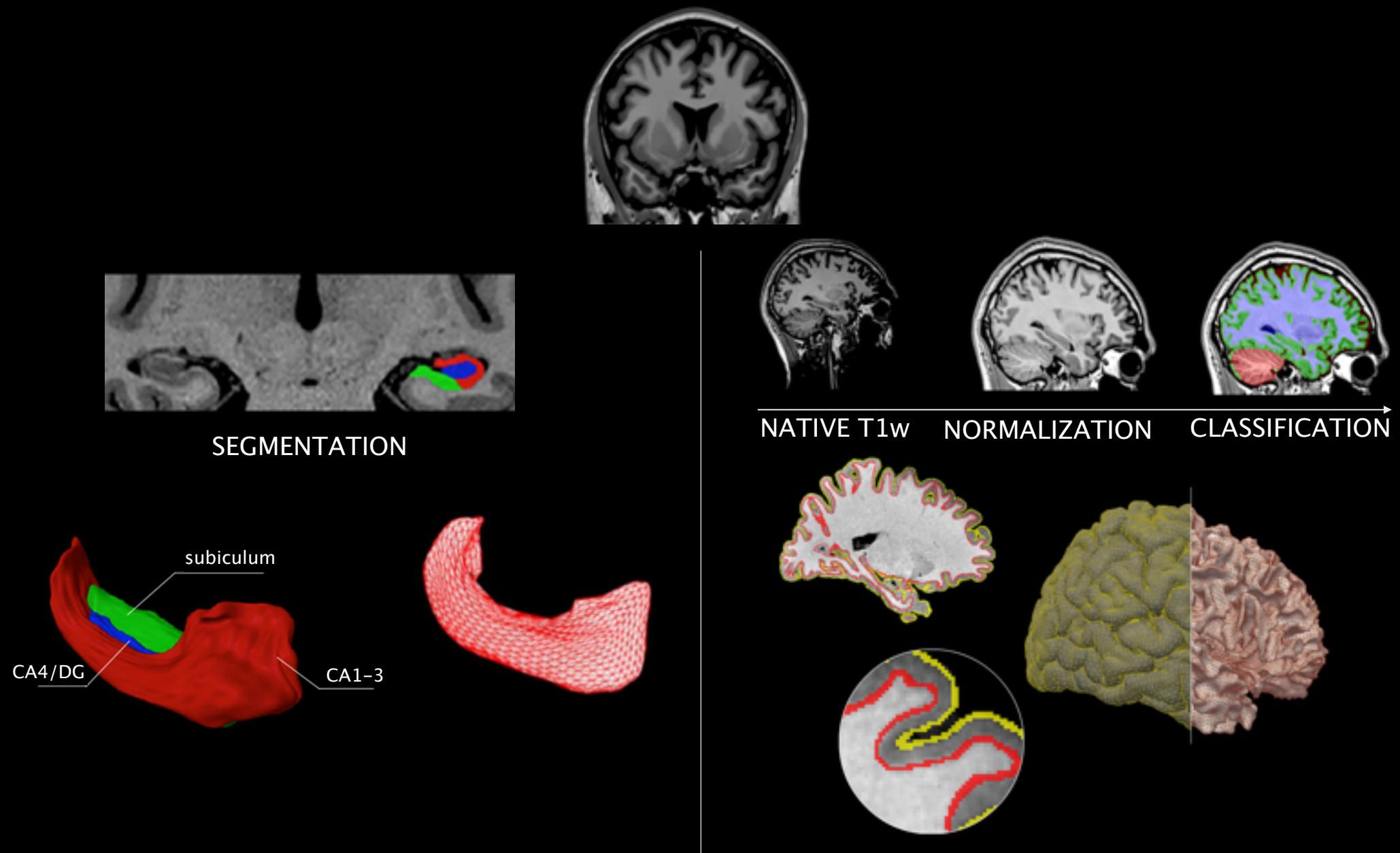
DYNAMICS

PET

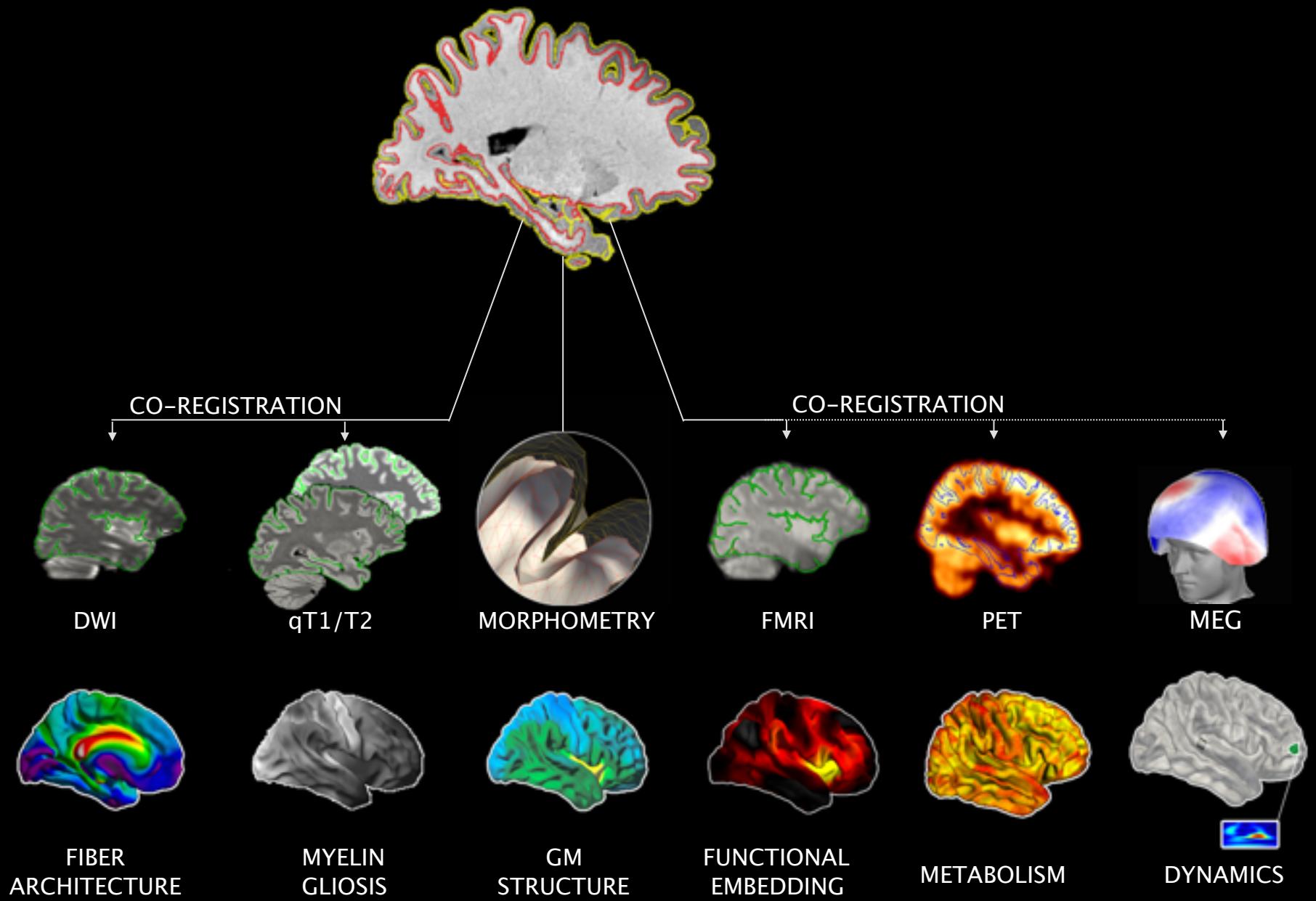


METABOLISM
TRANSMITTERS

DESCRIBING ANATOMY

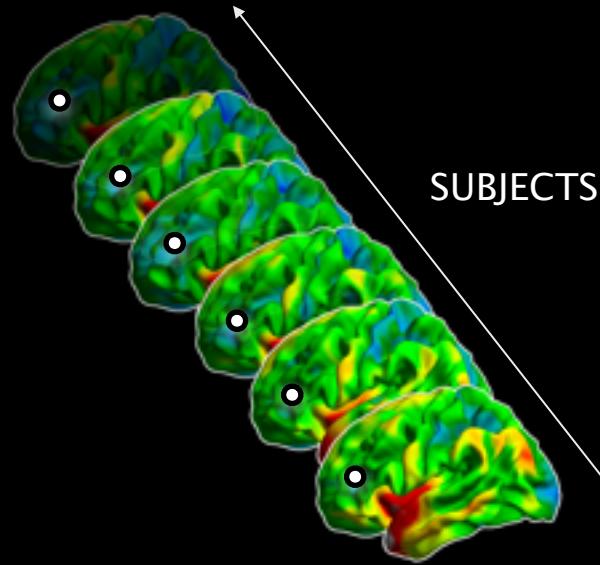


MULTI-MARKER INTEGRATION

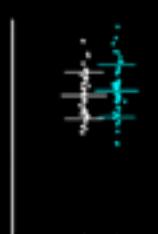
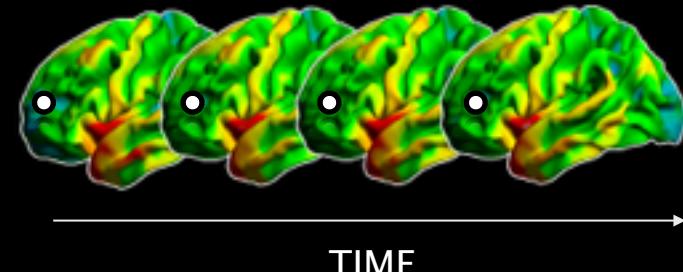


REGIONAL STATISTICAL ANALYSIS

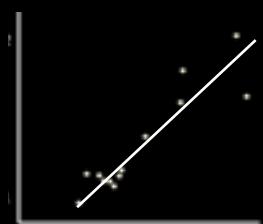
CROSS-SECTIONAL ANALYSES



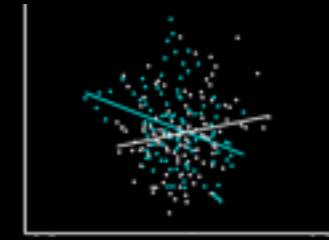
LONGITUDINAL ASSESSMENTS



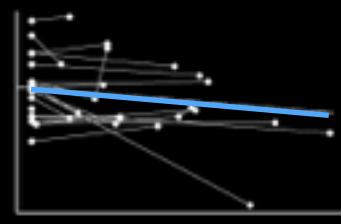
$$Y = 1 + G$$



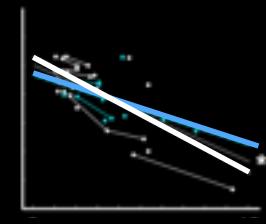
$$Y = 1 + A$$



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



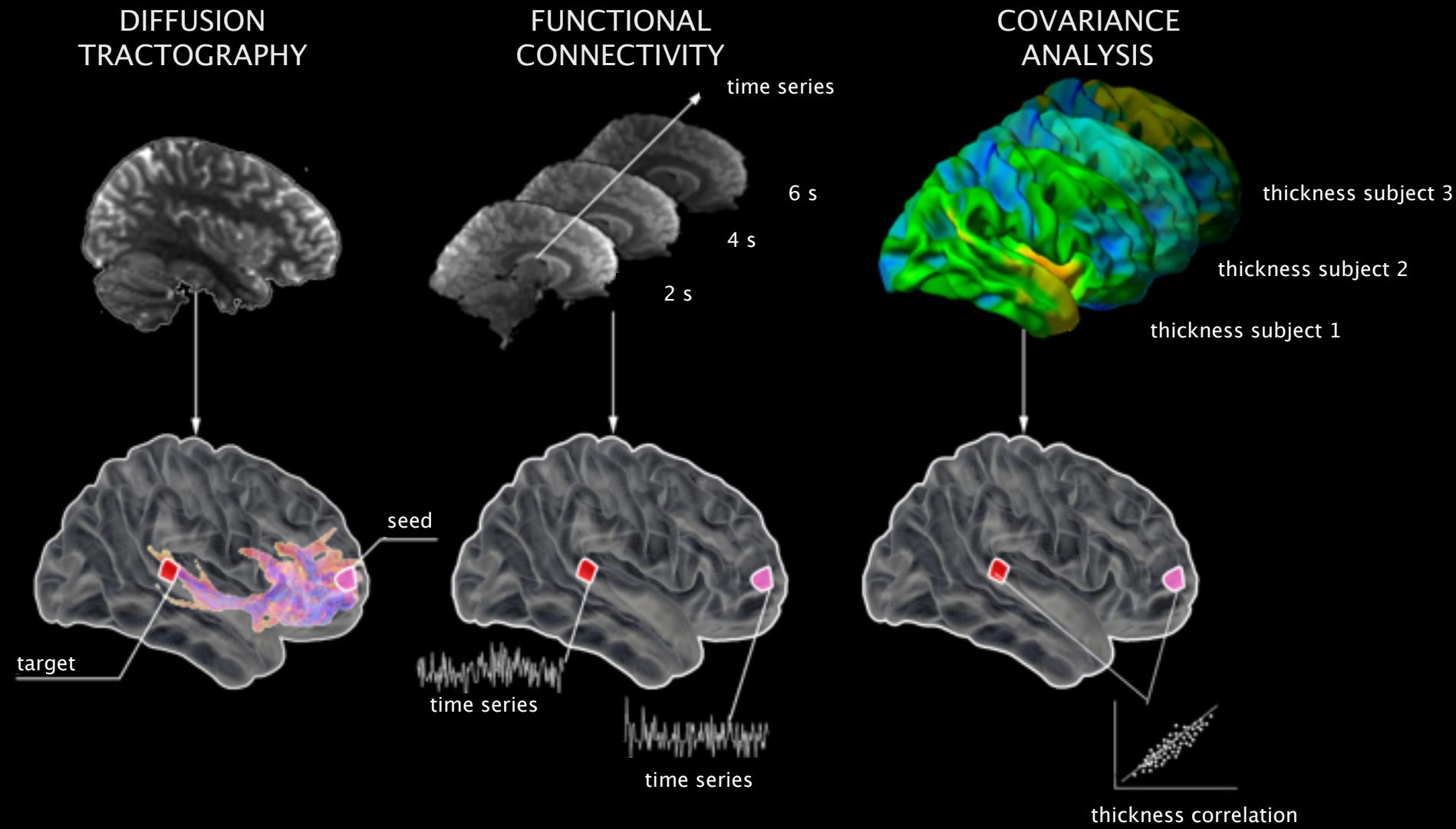
$$Y = 1 + r(S) + ISI$$



$$Y = 1 + r(S) + ISI + G + ISI \times G$$

Y is univariate or multivariate data

INTER-REGIONAL CONNECTIVITY ANALYSIS



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

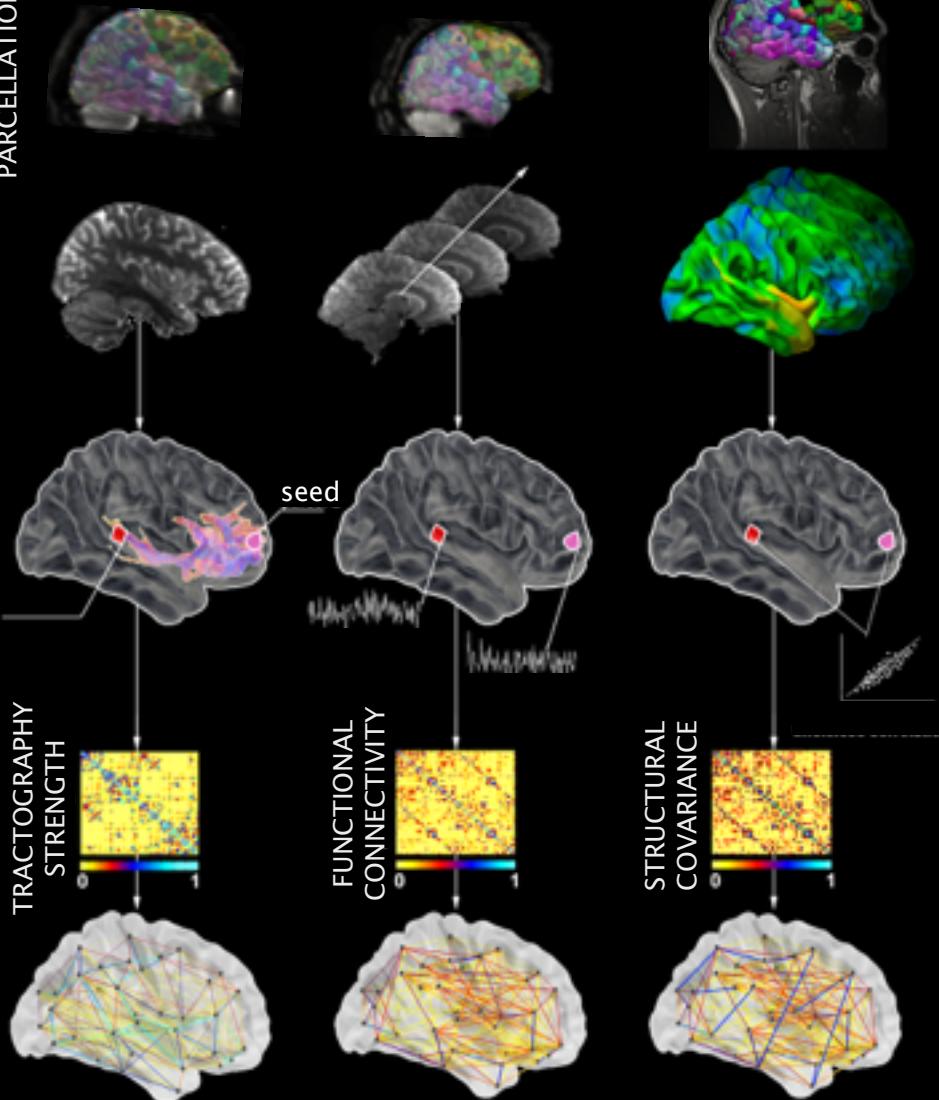
Friston (1994) HBM
Smith (2012) NIMG

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

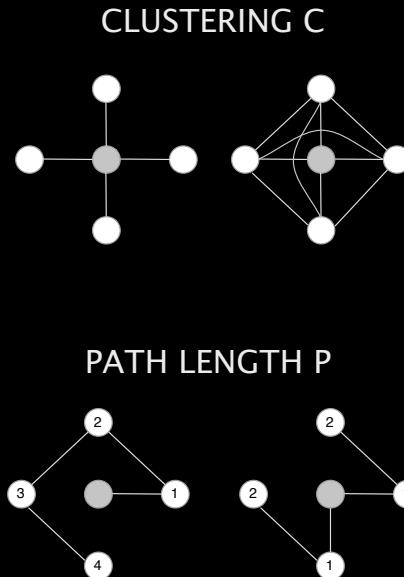
CONNECTOME ANALYSIS

PARCELLATION

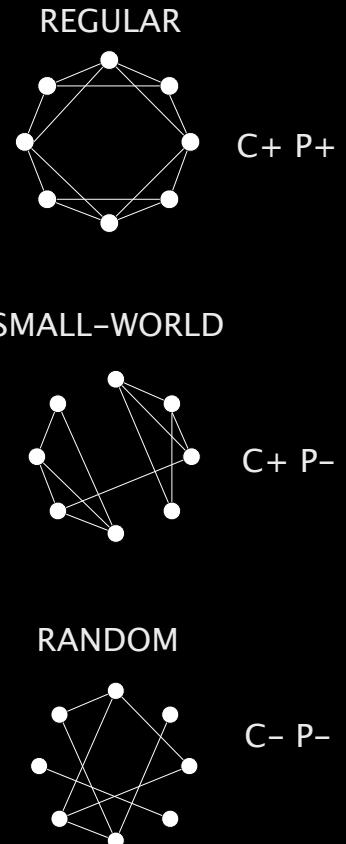
SYSTEMATIC NETWORK GENERATION



GRAPH THEORETICAL PARAMETERS

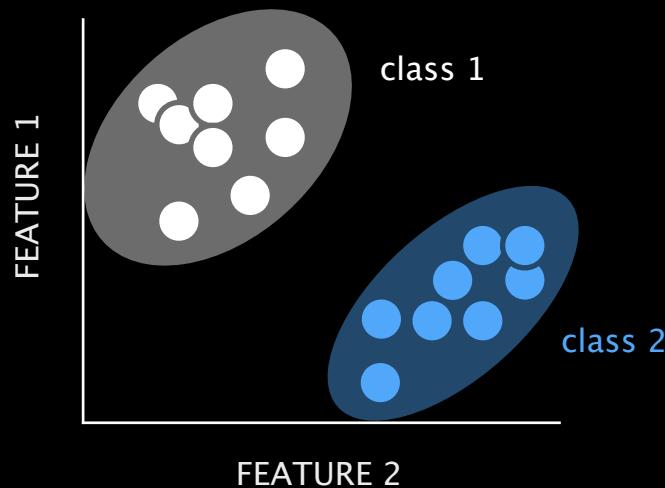


TOPOLOGY CLASSIFICATION



PATTERN LEARNING

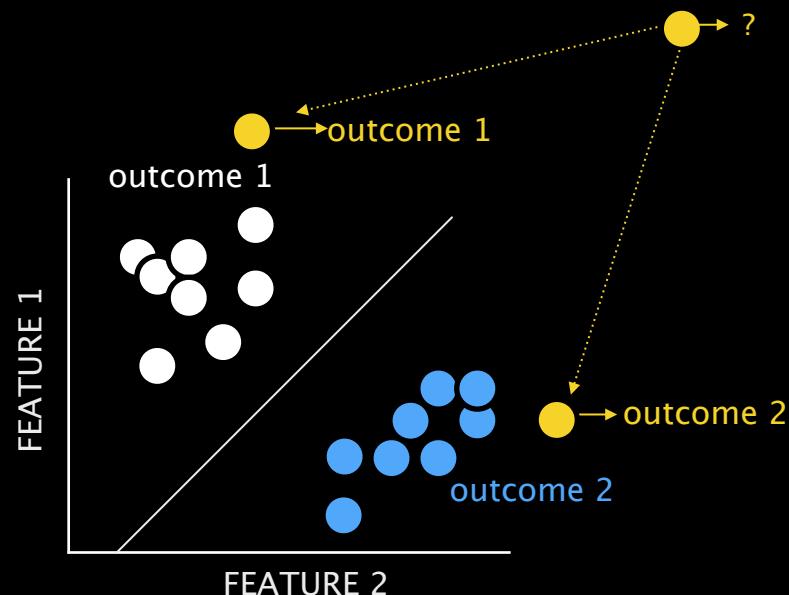
UNSUPERVISED



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



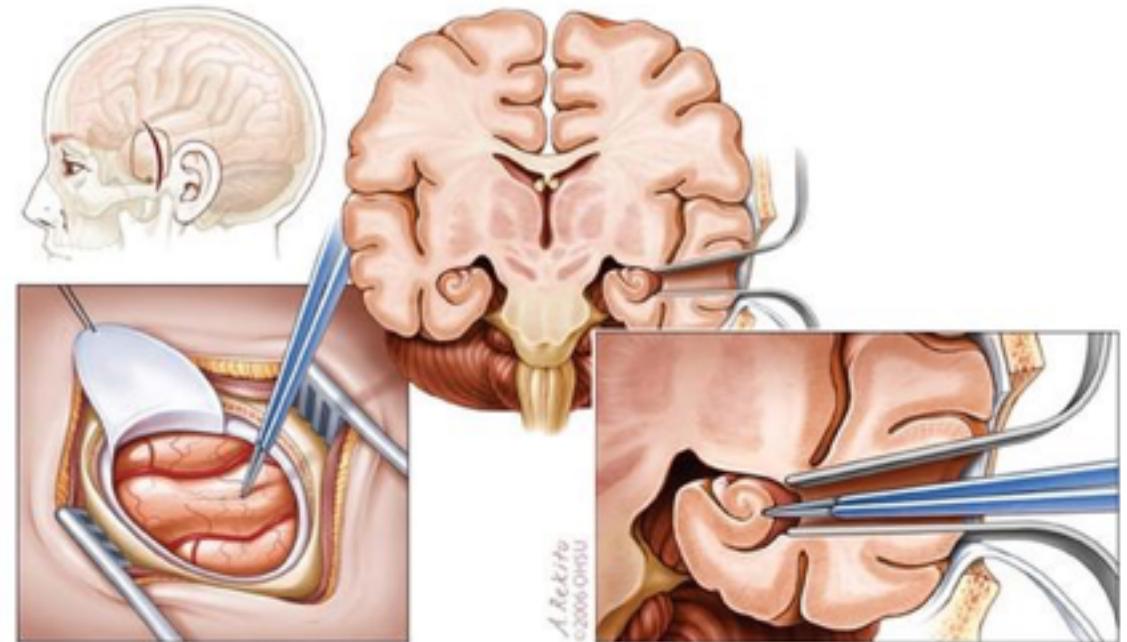
TEMPORAL LOBE EPILEPSY

MOST COMMON DRUG-RESISTANT
EPILEPSY IN ADULTS

SEIZURES ARISING FROM TL

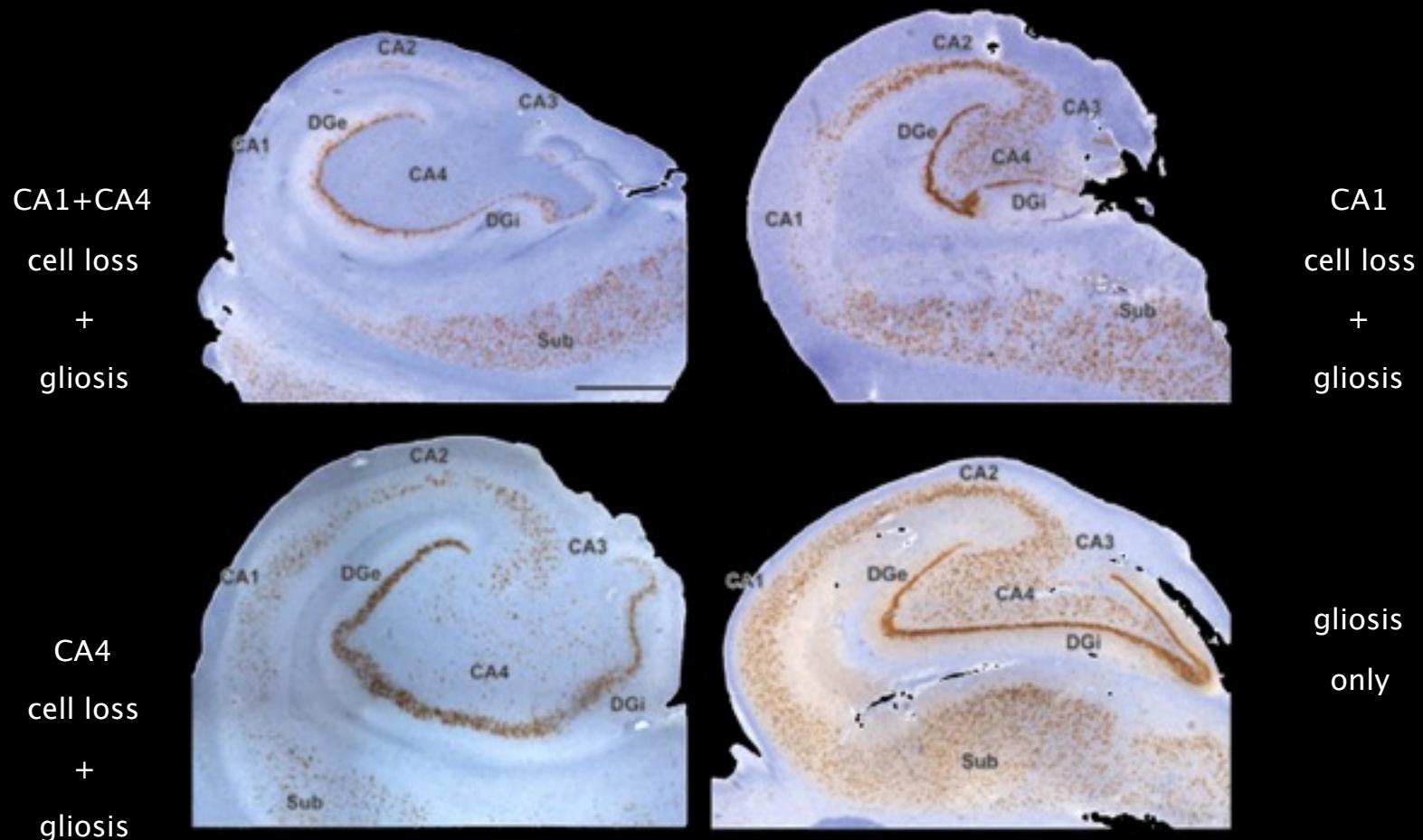
ASSOCIATED WITH
HIPPOCAMPAL SCLEROSIS

SURGERY MOST EFFECTIVE
TREATMENT



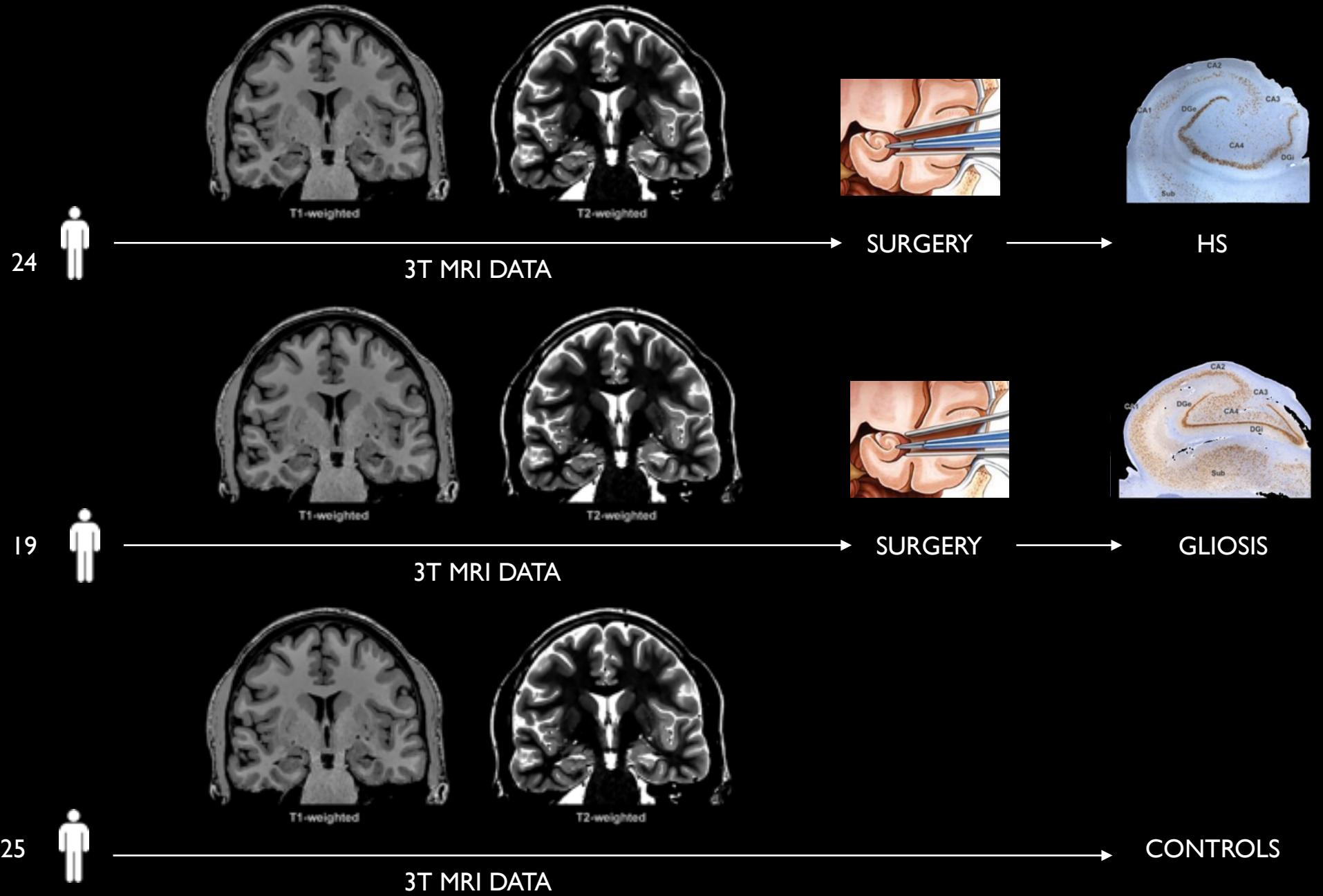
TEMPORAL LOBE EPILEPSY

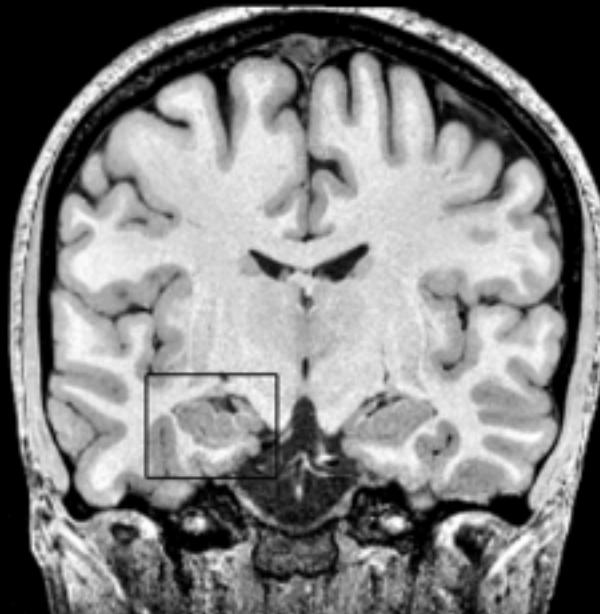
Pathological hallmark: hippocampal sclerosis (HS) – not a single entity



CAN WE IDENTIFY PATHOLOGICAL SUBTYPES IN VIVO?

STUDY DESIGN





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

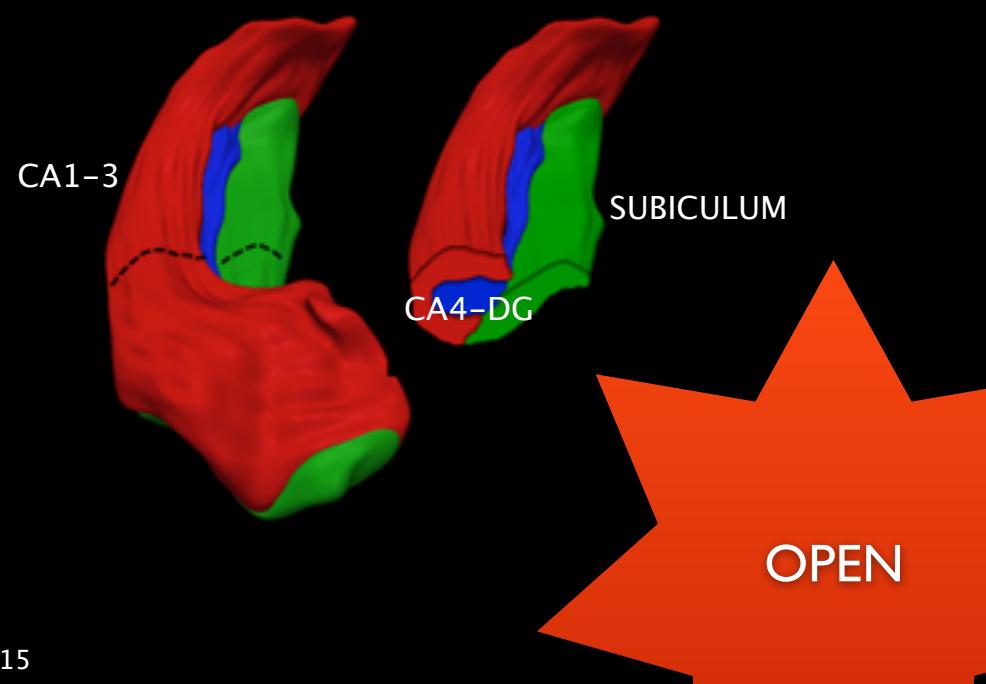
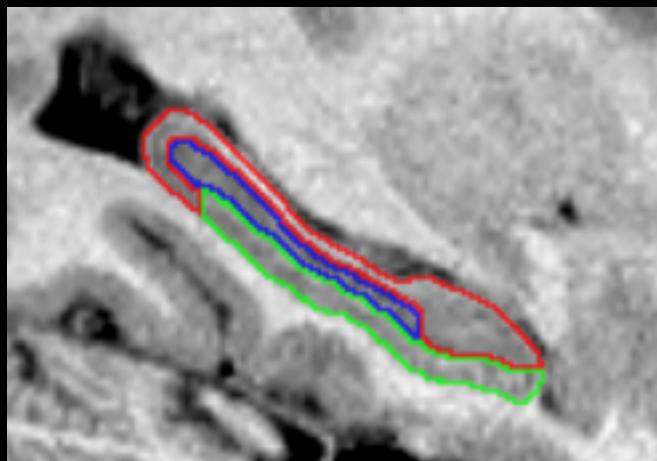
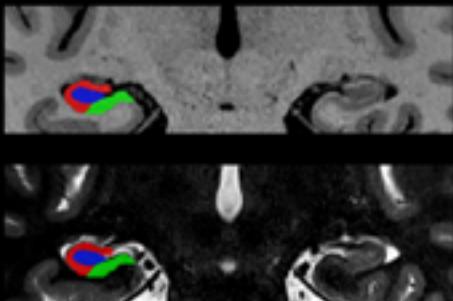
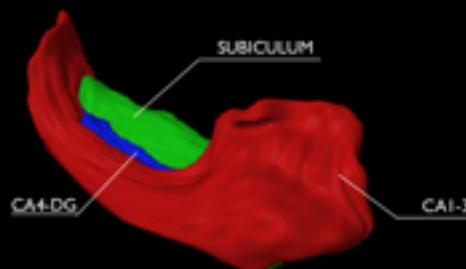


IMAGE PROCESSING

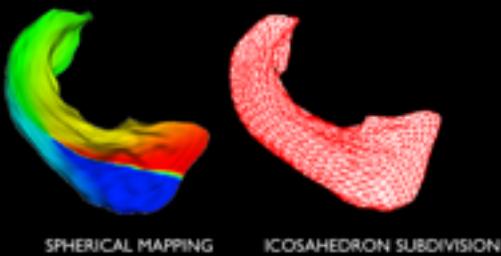
A SUBFIELD LABEL



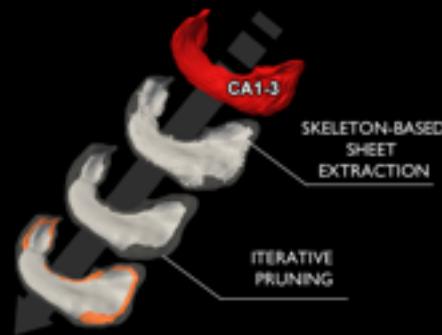
B SUBFIELD HULL REPRESENTATION



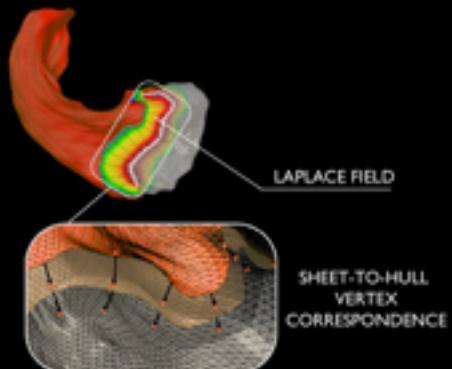
C SPHARDM-PDM PARAMETRIZATION OF OUTER HULL



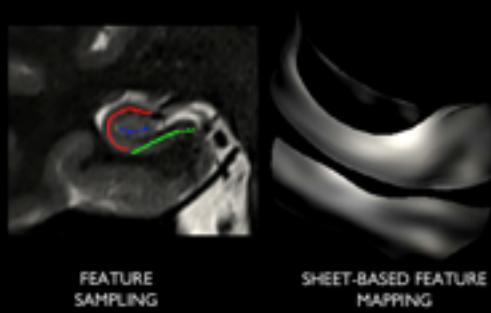
D GENERATION OF MEDIAL SHEET



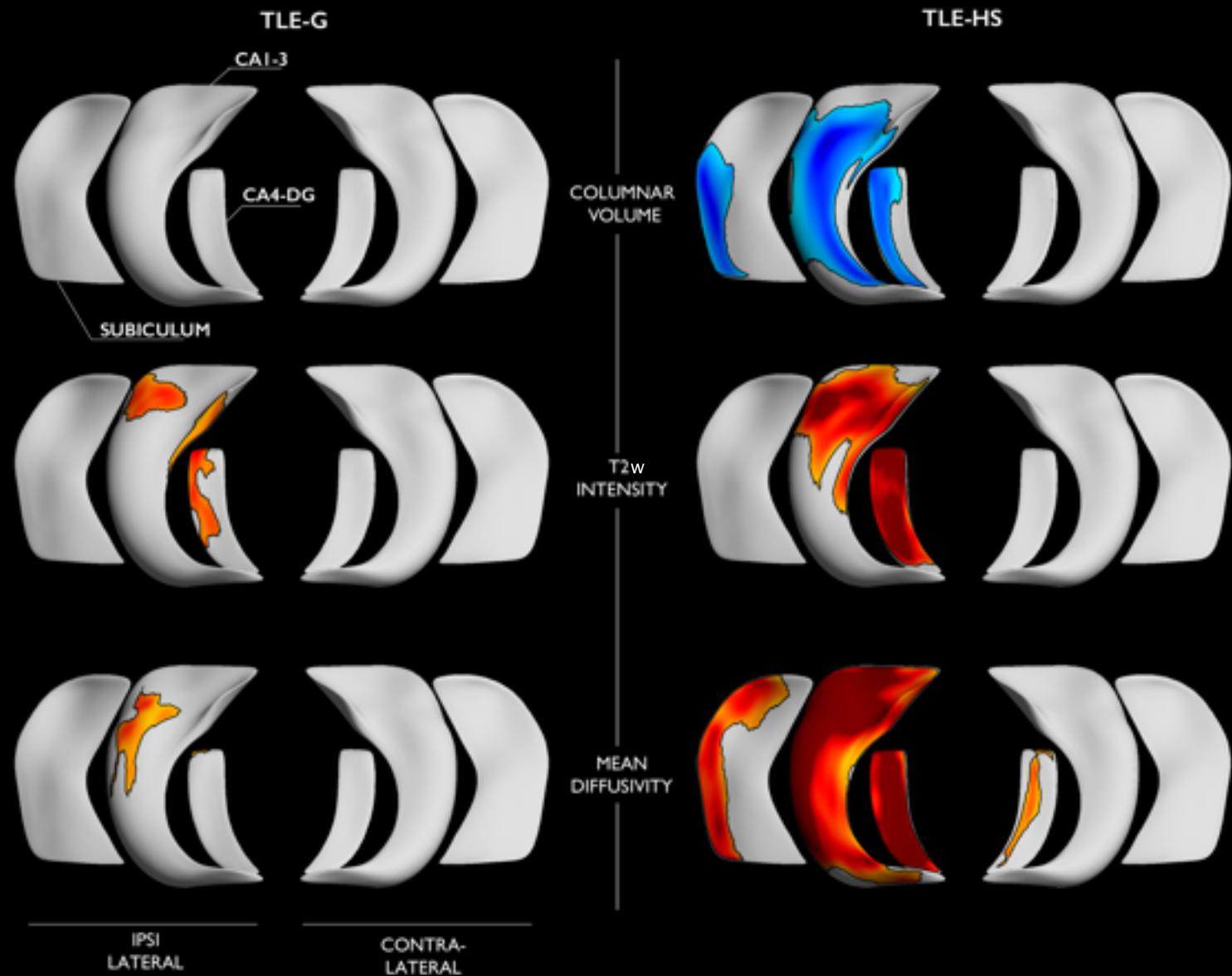
E PROPAGATING PARAMETRIZATION TO SHEET



F SHEET-BASED MEASURES



FEATURE-SPECIFIC COMPARISON TO CONTROLS



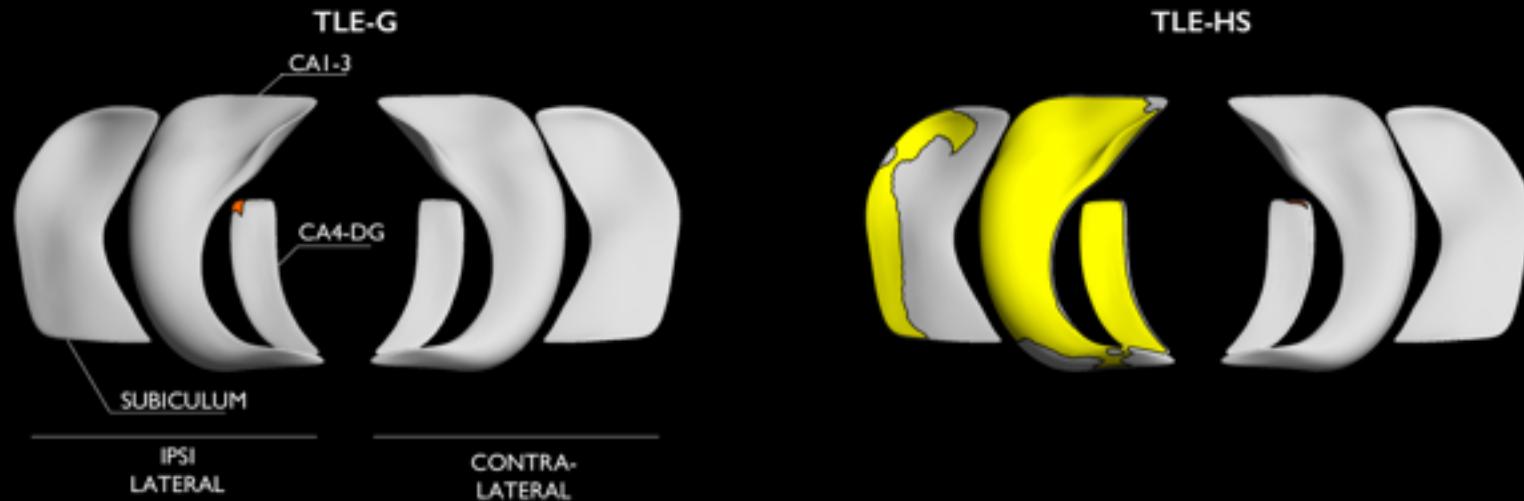
DIRECT CONTRASTS

B DIRECT CONTRAST: TLE-HS vs TLE-G

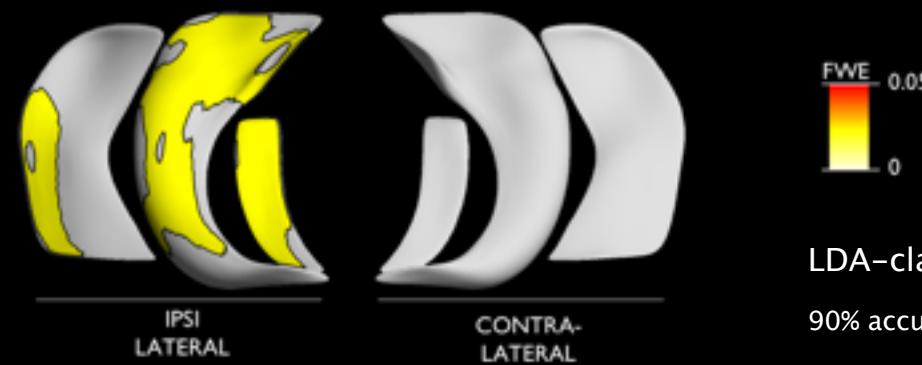


MULTIVARIATE SYNTHESIS

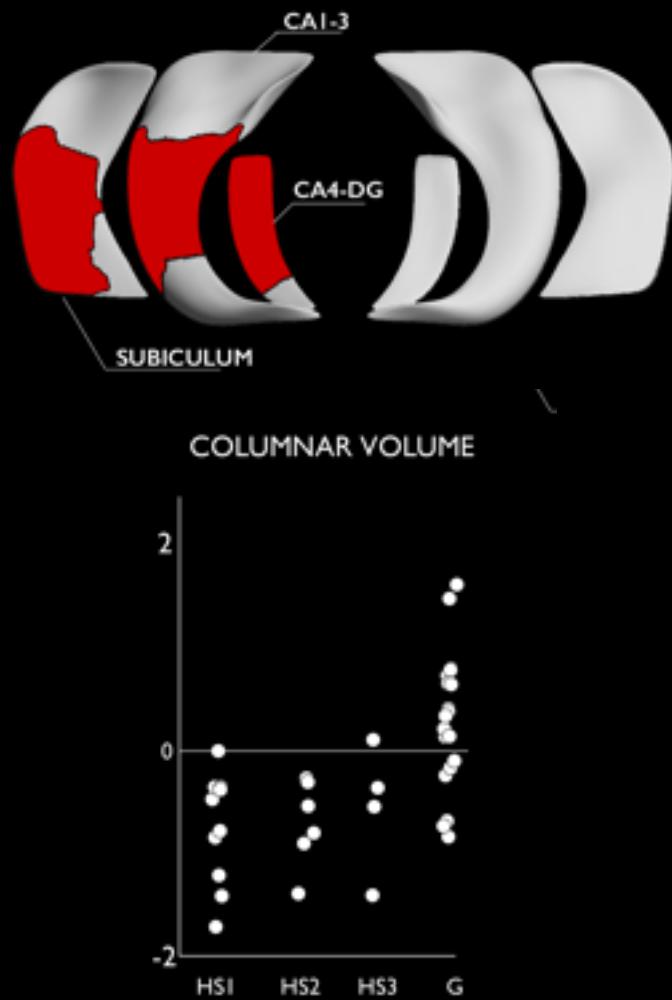
A COMPARISON TO CONTROLS



B DIRECT CONTRAST: TLE-HS vs TLE-G



RELATION TO SPECIFIC HISTOLOGICAL HS GRADES

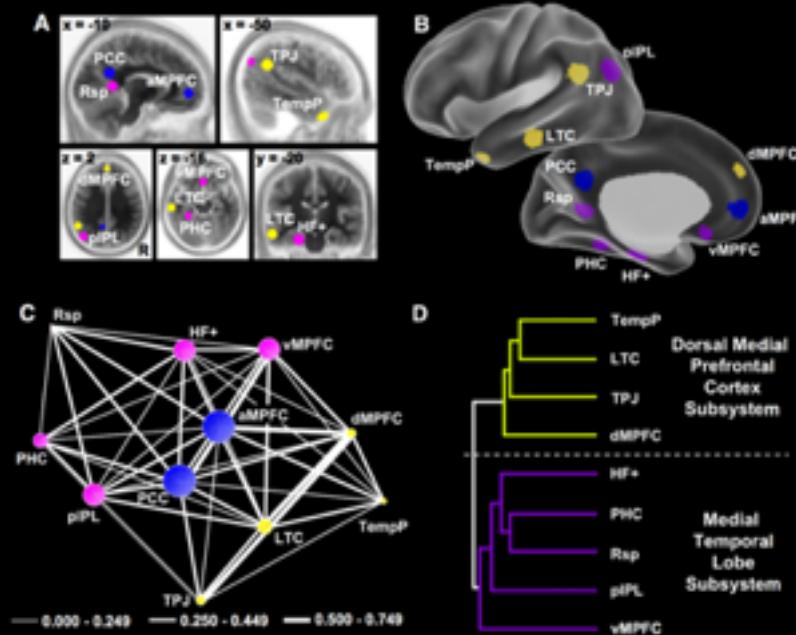


FUNCTION

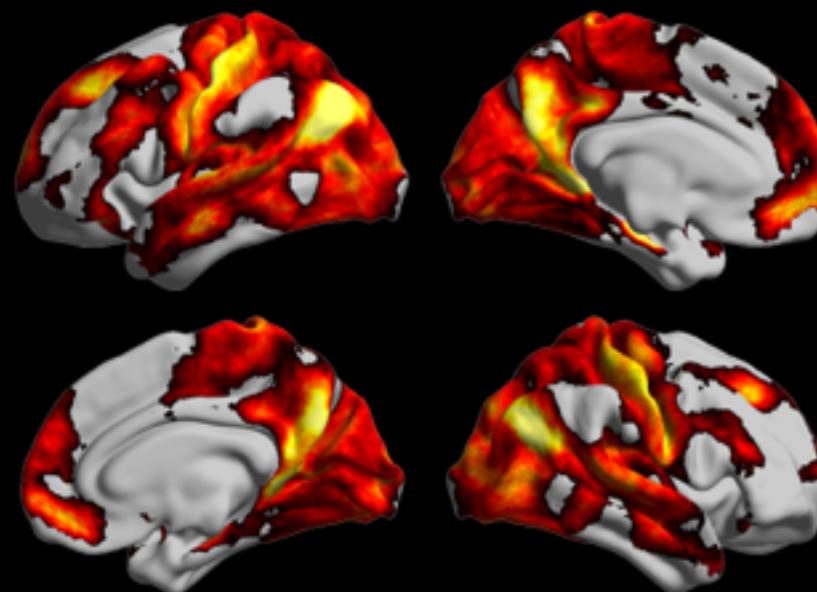
rs-FMRI ANALYSIS OF
INTRINSIC FUNCTIONAL NETWORKS

HIPPOCAMPUS HIGHLY INTEGRATED
WITH DMN

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



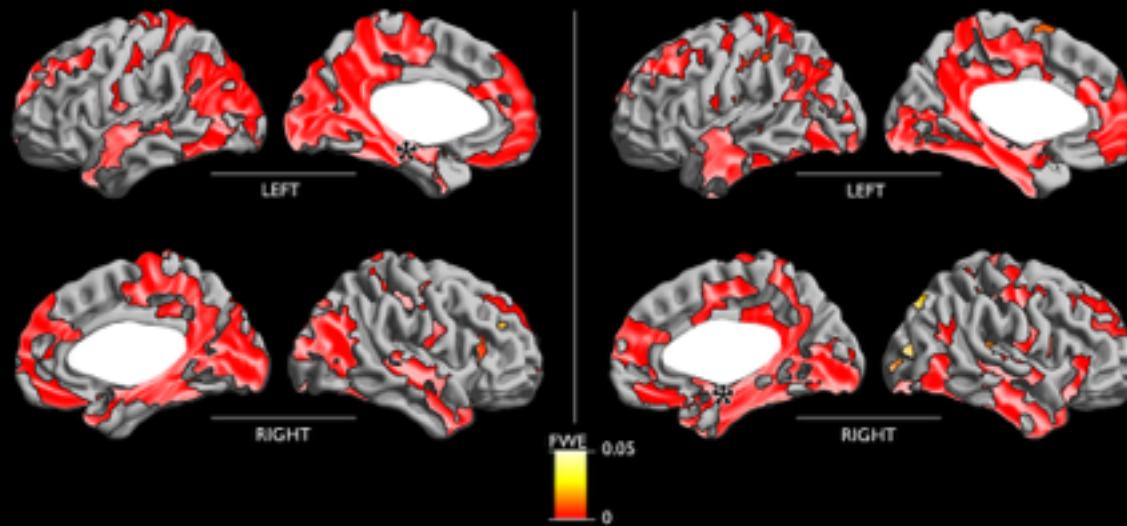
Andrews-Hanna (2013) Neuron



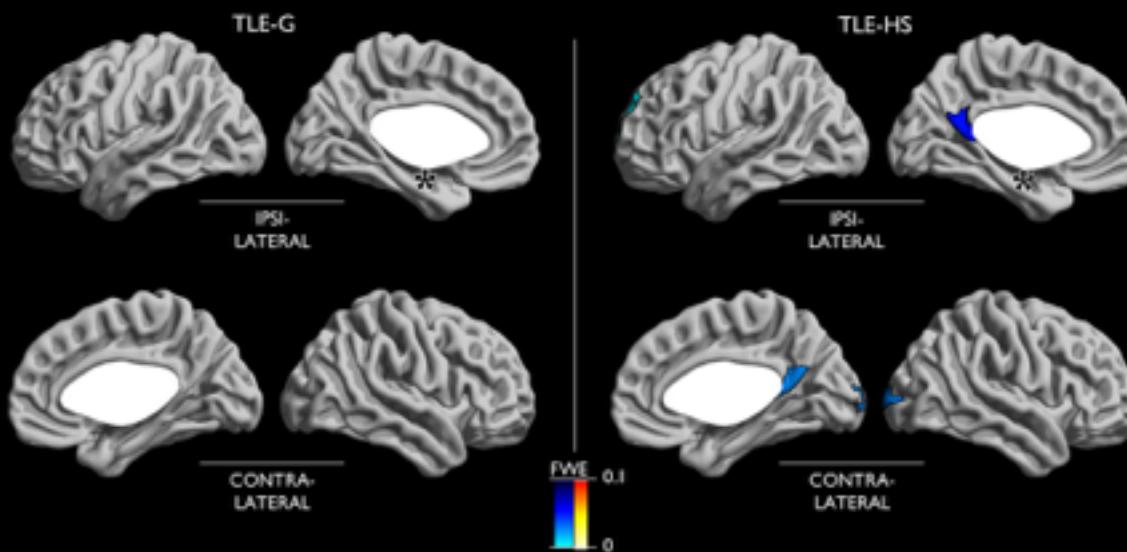
Vos de Wael, Caldairou, Jefferies, Smallwood, Bernasconi, Bernhardt (2017) SFN

FUNCTIONAL ANOMALIES IN TLE

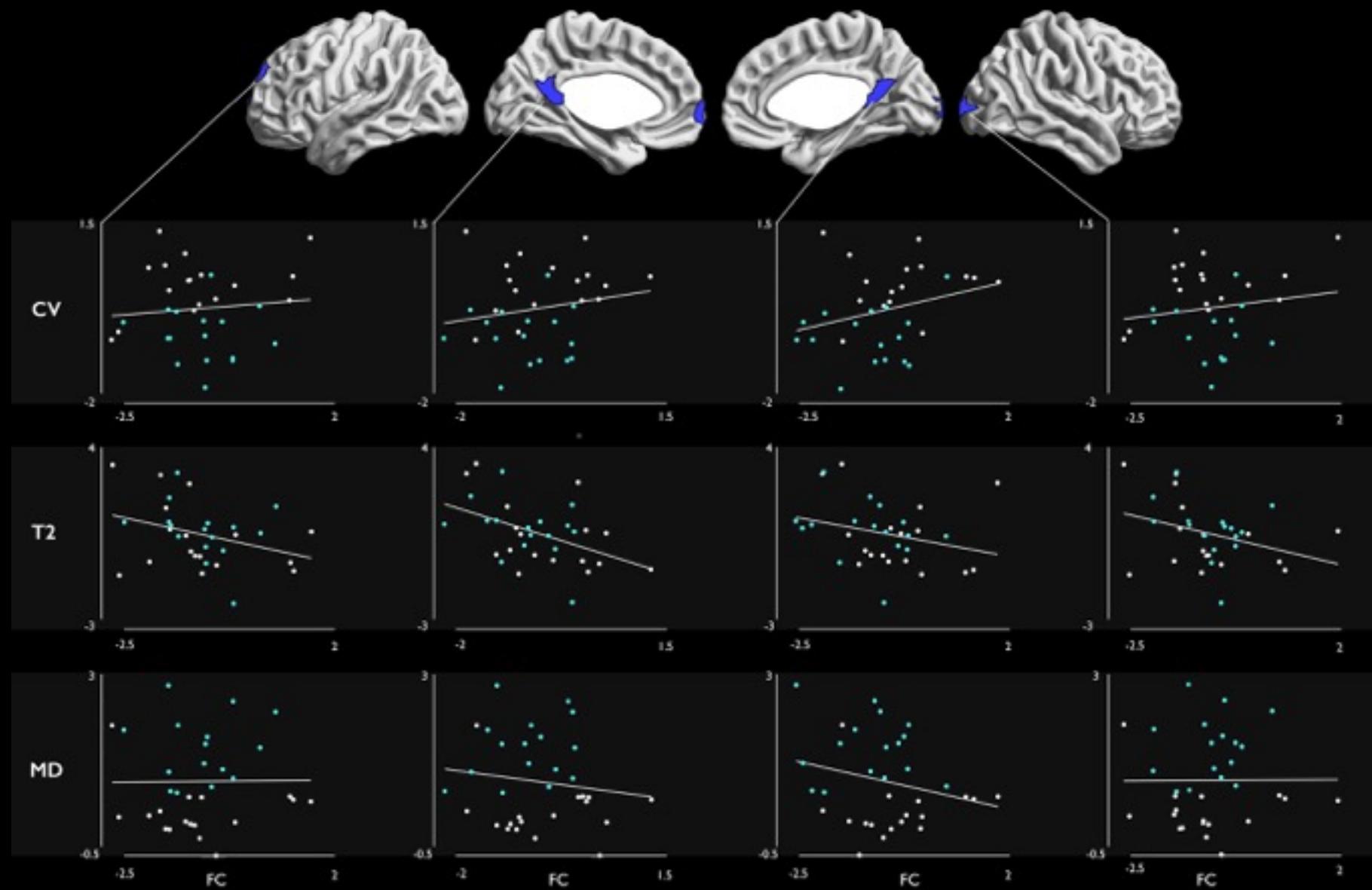
A CONNECTIVITY IN CONTROLS



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

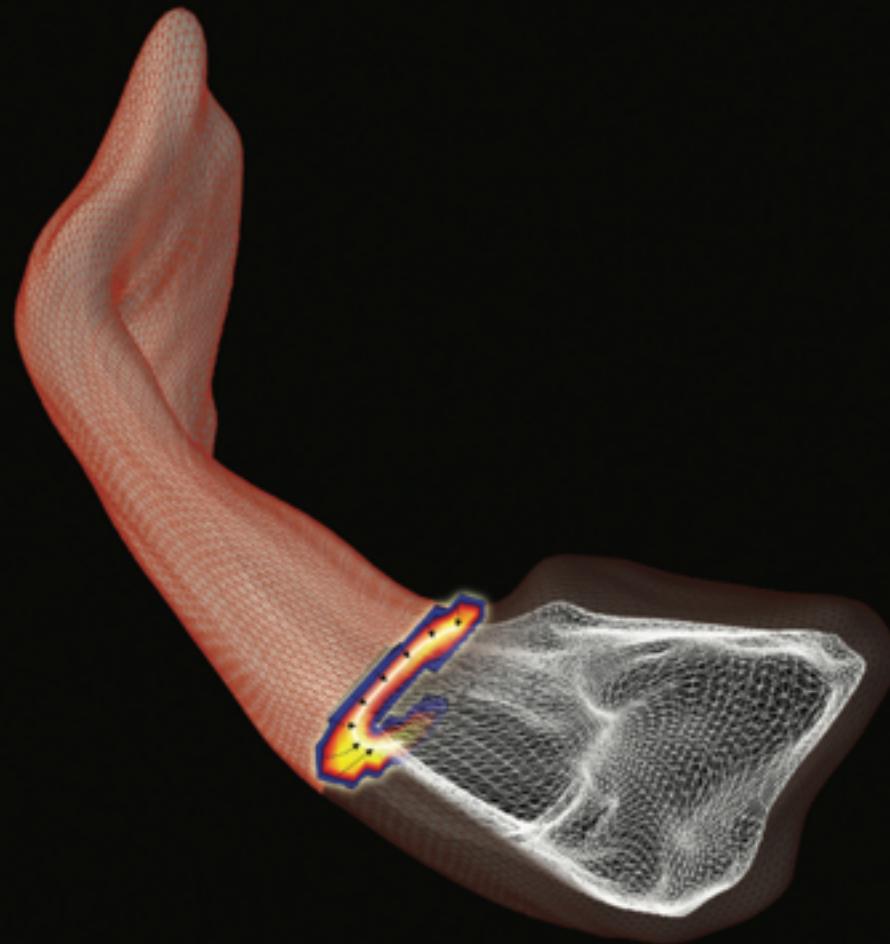
HIPPOCAMPAL SUBTYPES

MRI PROBES LOCAL
PATHOLOGICAL CHANGES

INDIVIDUALIZED PATHOLOGY
PREDICTION POSSIBLE

STRUCTURAL ANOMALIES
RELATE TO FUNCTIONAL NETWORK
EMBEDDING

TLE = SPECTRUM OF STRUCTURAL AND
FUNCTIONAL ANOMALIES



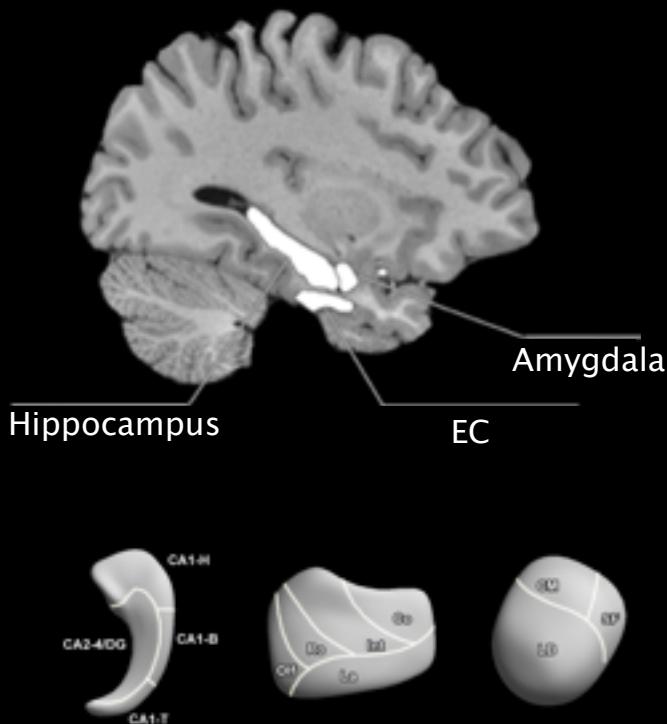
WILEY

IS TLE ADEQUATELY CAPTURED BY HIPPOCAMPUS ALONE?

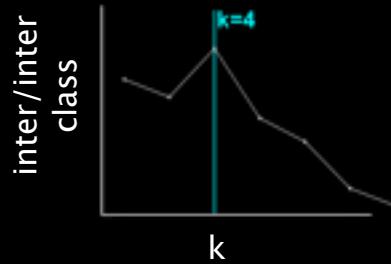
MRI PROFILING AND SUBTYPING

MESIOTEMPORAL PROFILING

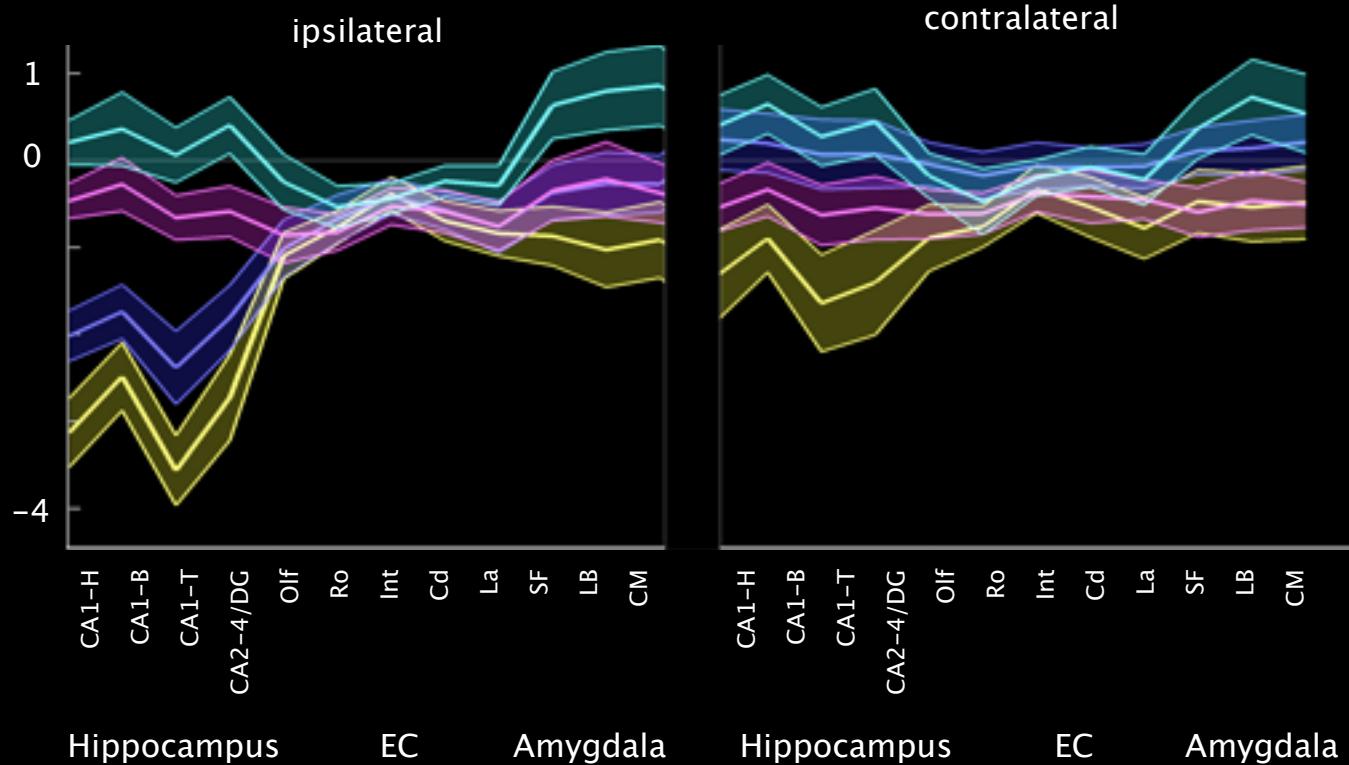
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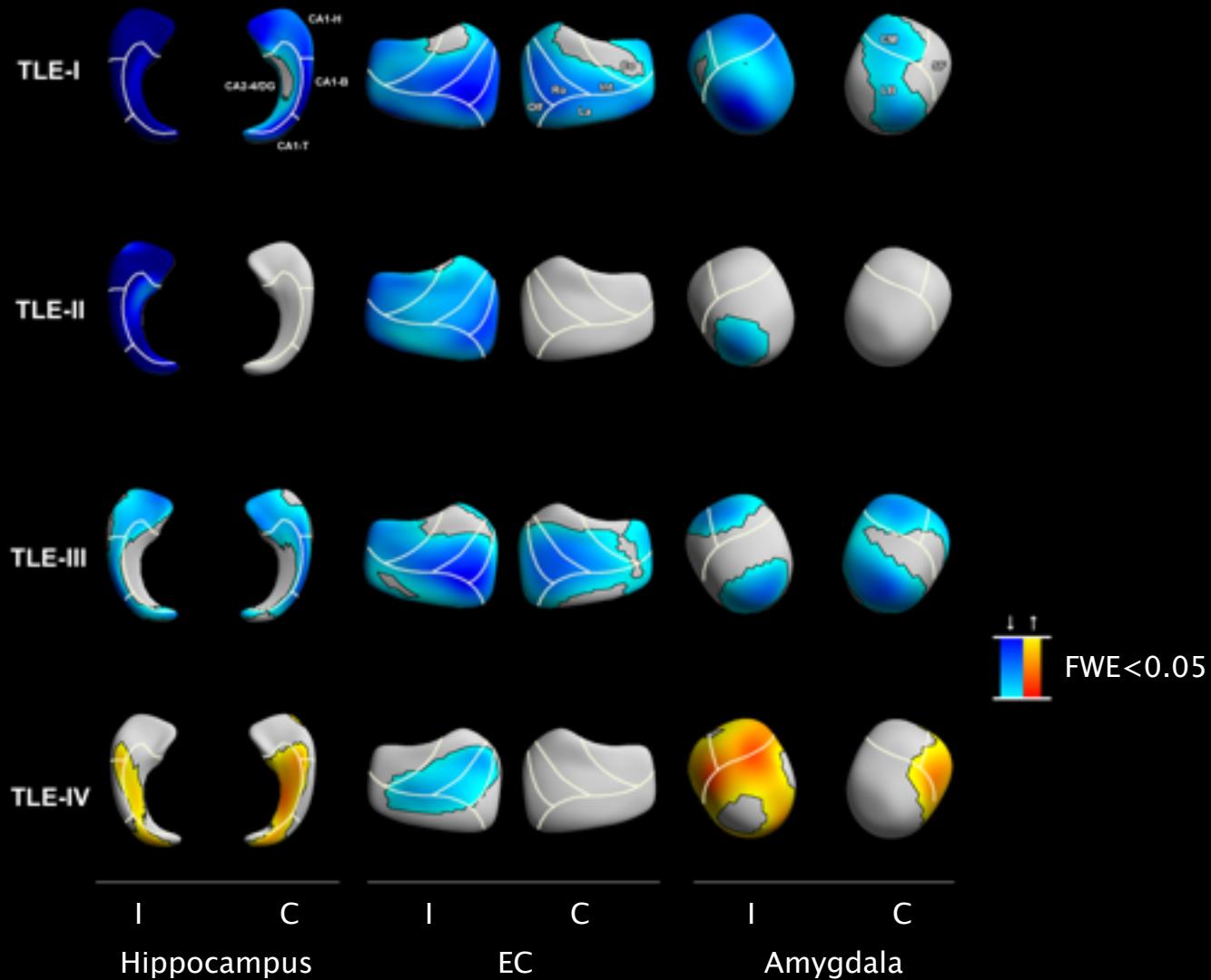
CLUSTERING PATIENT SPECTRUM BASED ON MRI MORPHOMETRY



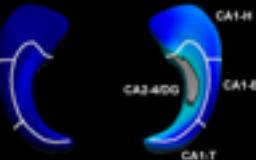
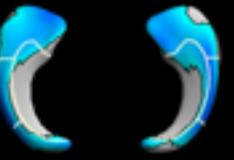
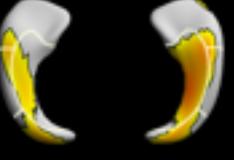
- TLE-I
- TLE-II
- TLE-III
- TLE-IV



DATA-DRIVEN SUBCLASSES

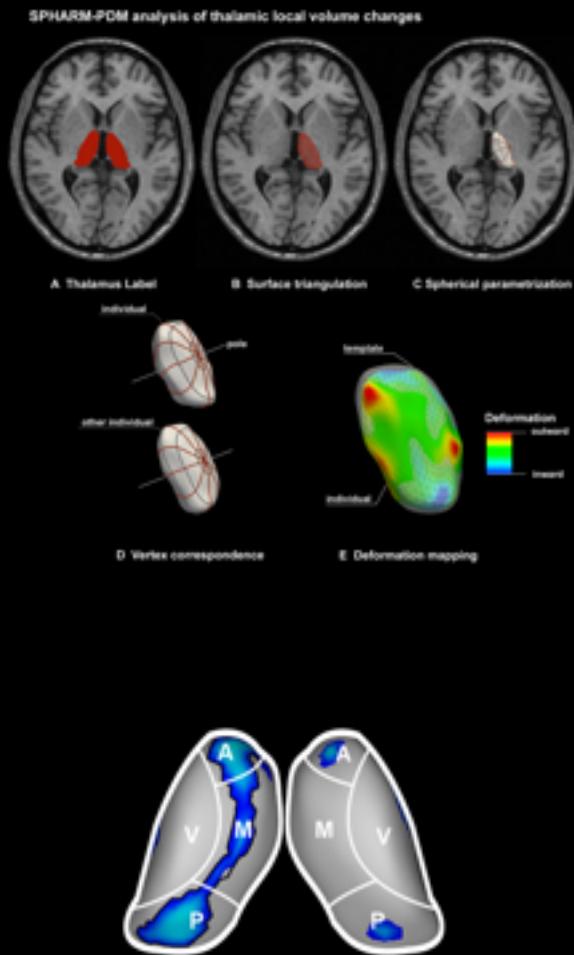


RELATION TO IMAGING-INDEPENDENT CRITERIA

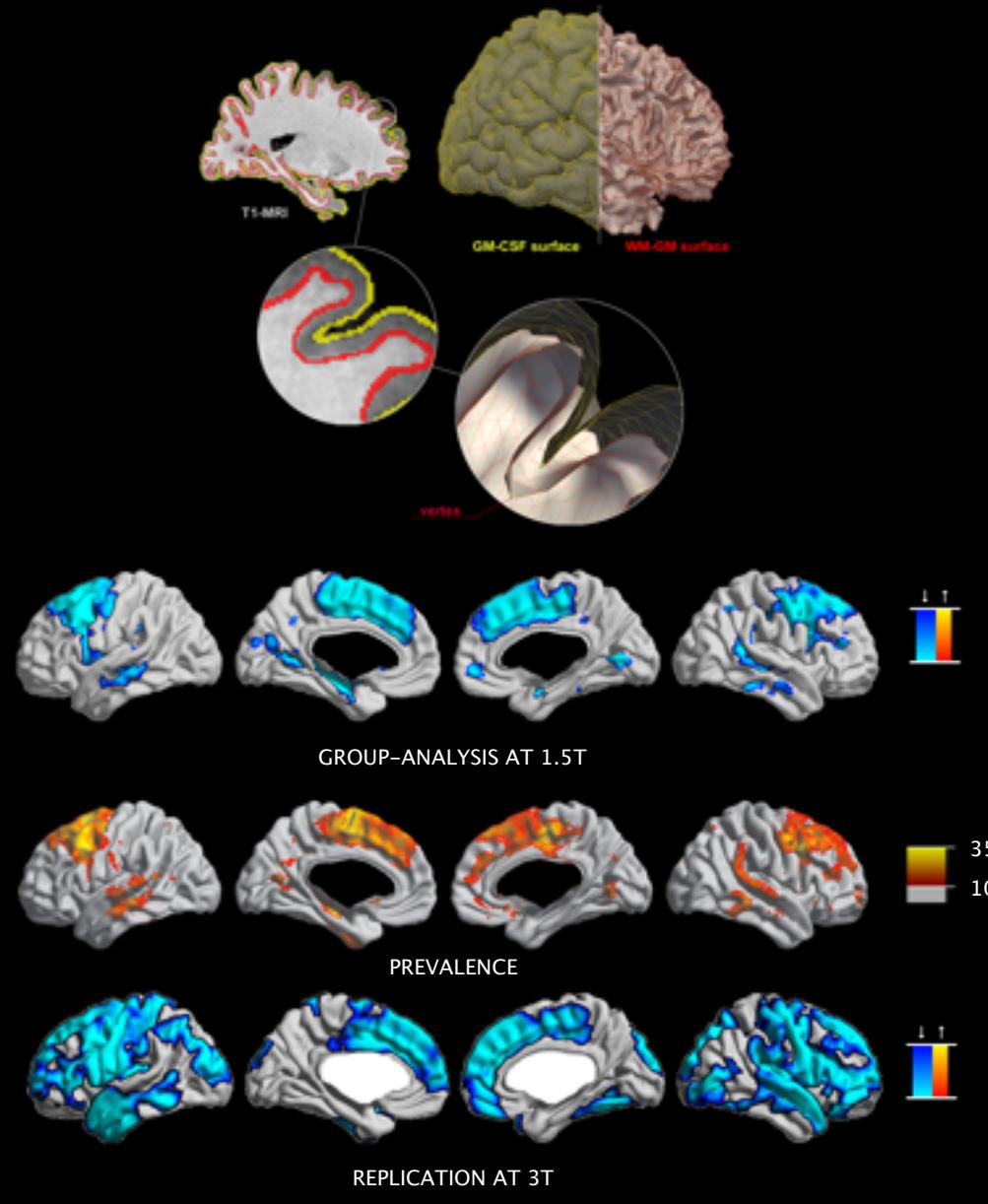
		HS/Gliosis	Engel-I	
TLE-I		71/29%	68%	<p>LDA outcome prediction:</p> <p>class + surface data: 92%</p> <p>surface-measures only: 81%</p> <p>volumetry: 71%</p>
TLE-II		72/28%	89%	
TLE-III		43/57%	65%	
TLE-IV		17/83%	44%	
	I C			
	Hippocampus			

DO ANOMALIES EXTEND BEYOND THE MESIOTEMPORAL REGIONS?

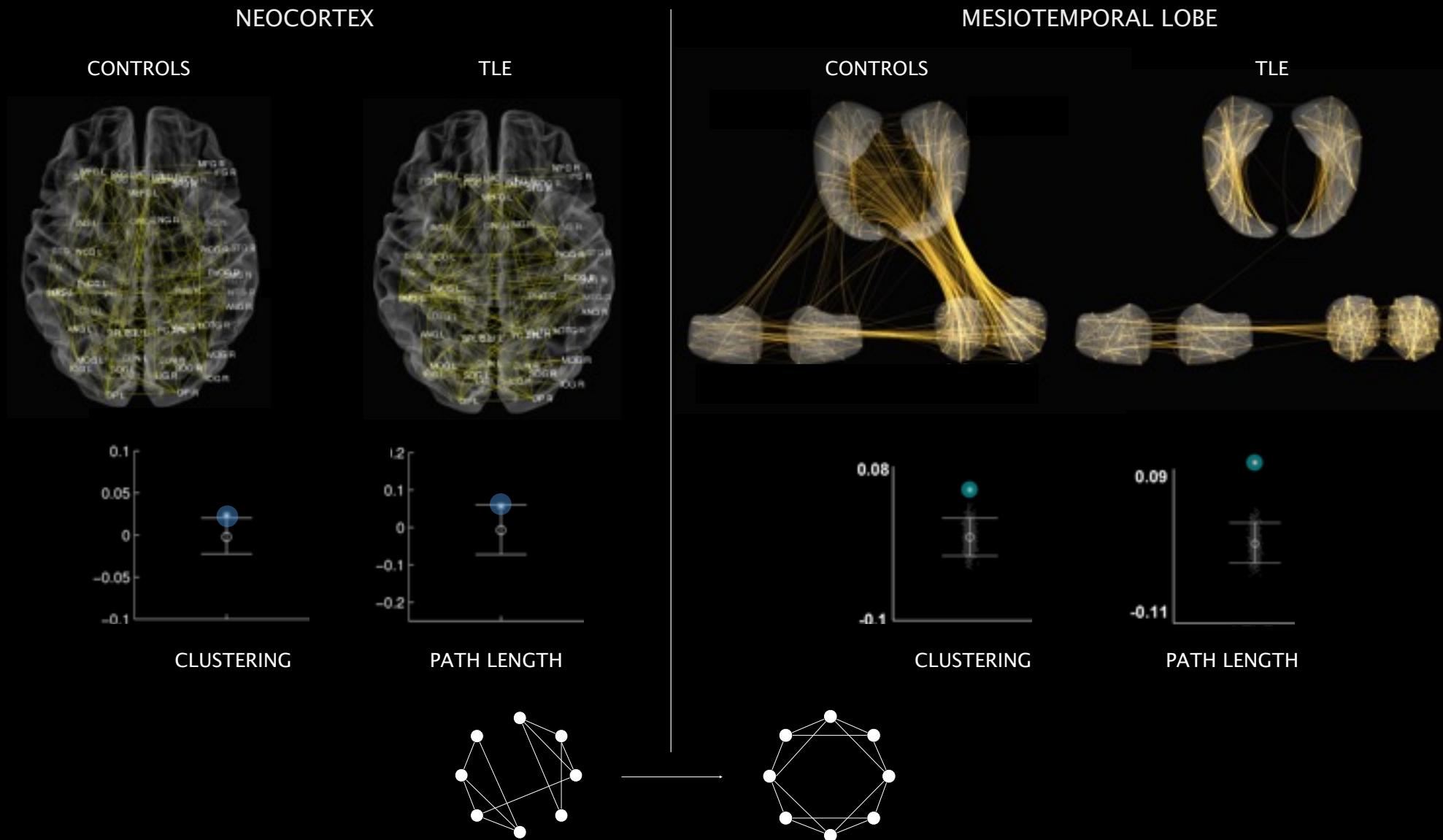
THALAMUS



NEOCORTEX

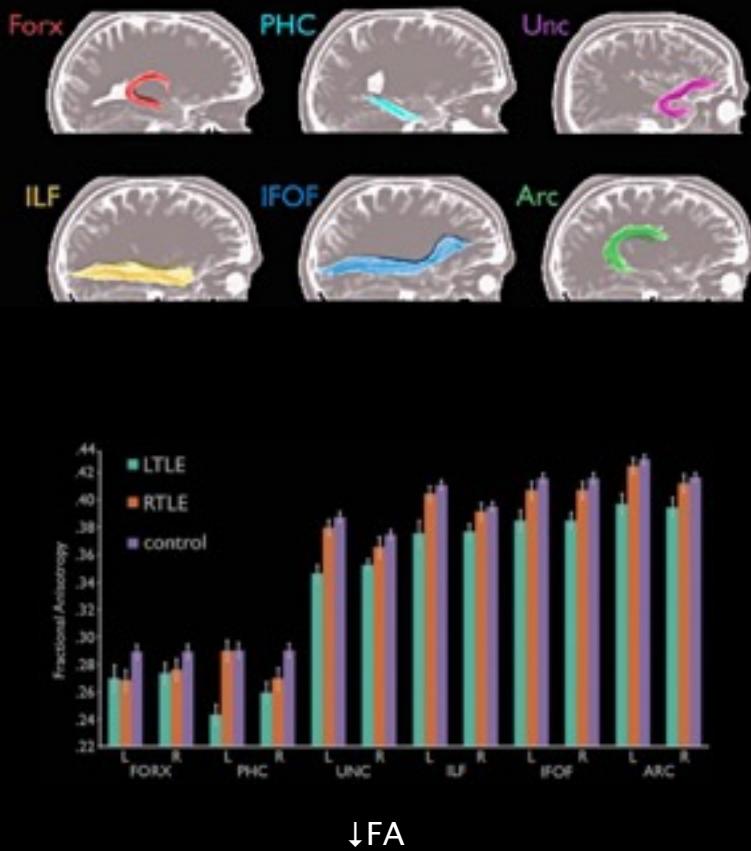


LARGE-SCALE CHANGES: STRUCTURAL COVARIANCE NETWORKS

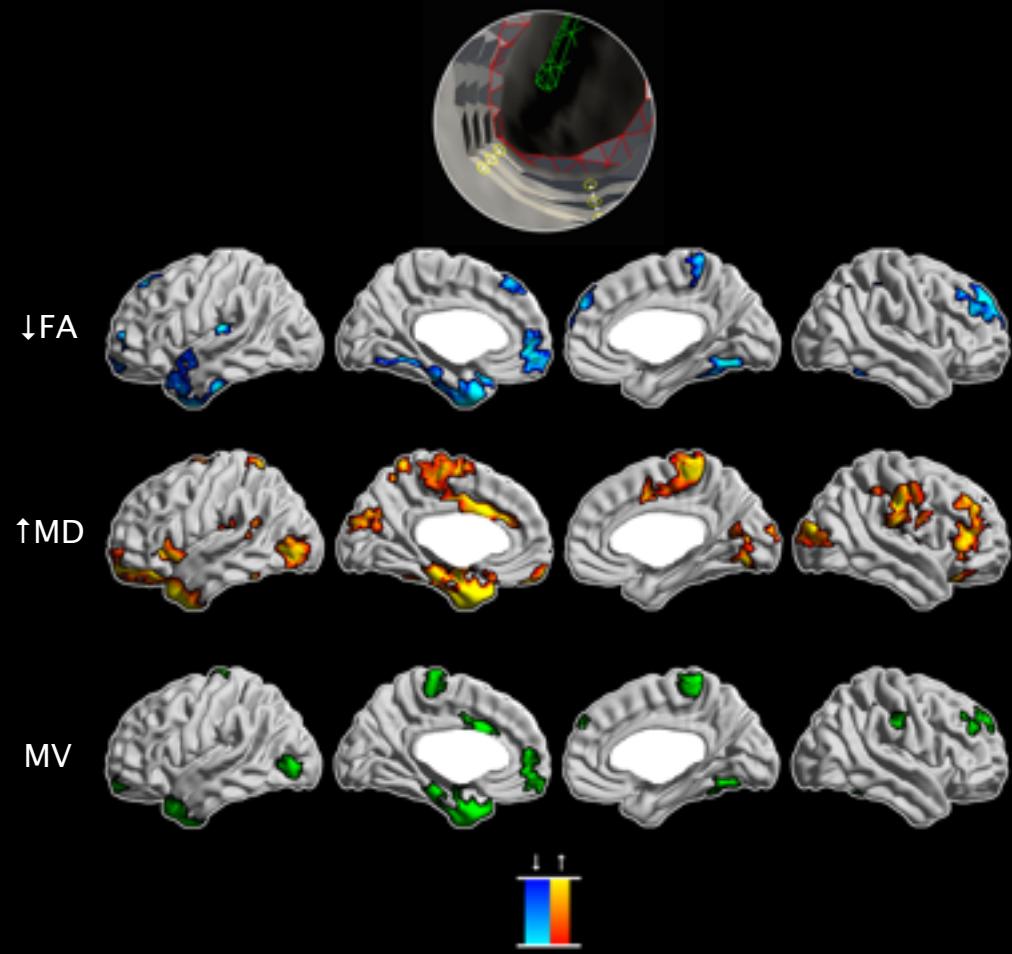


WHITE MATTER ALTERATIONS

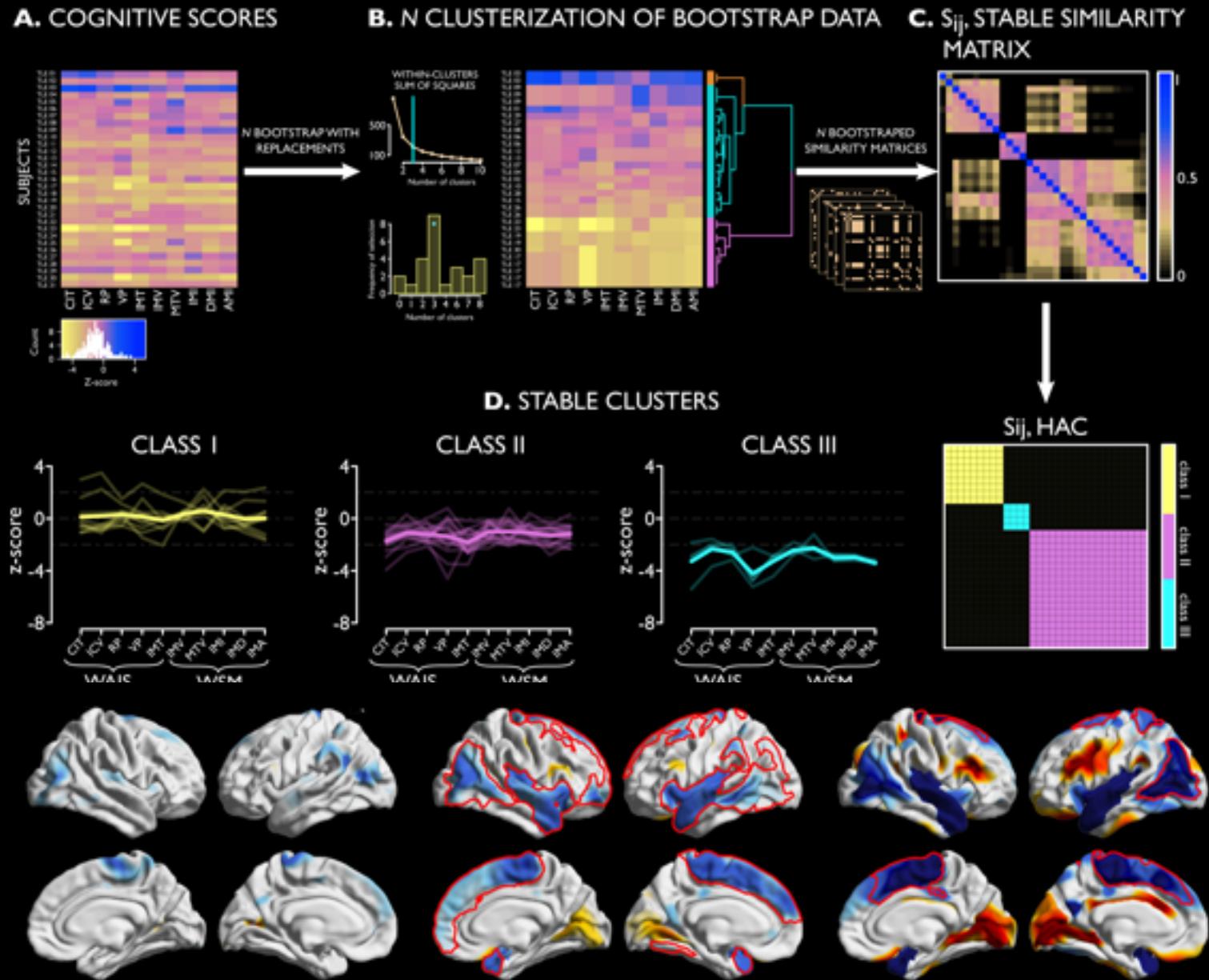
TRACTOGRAPHY-BASED WM BUNDLE ANALYSIS

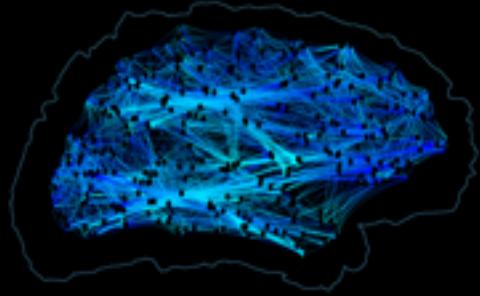
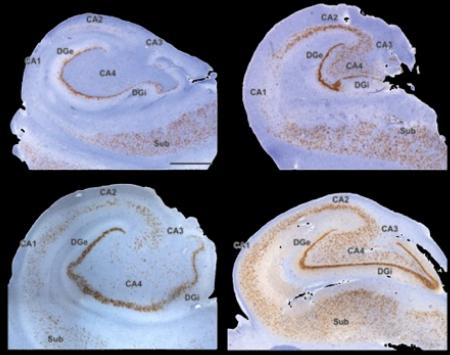


SURFACE-BASED WM SAMPLING [2MM DEPTH]



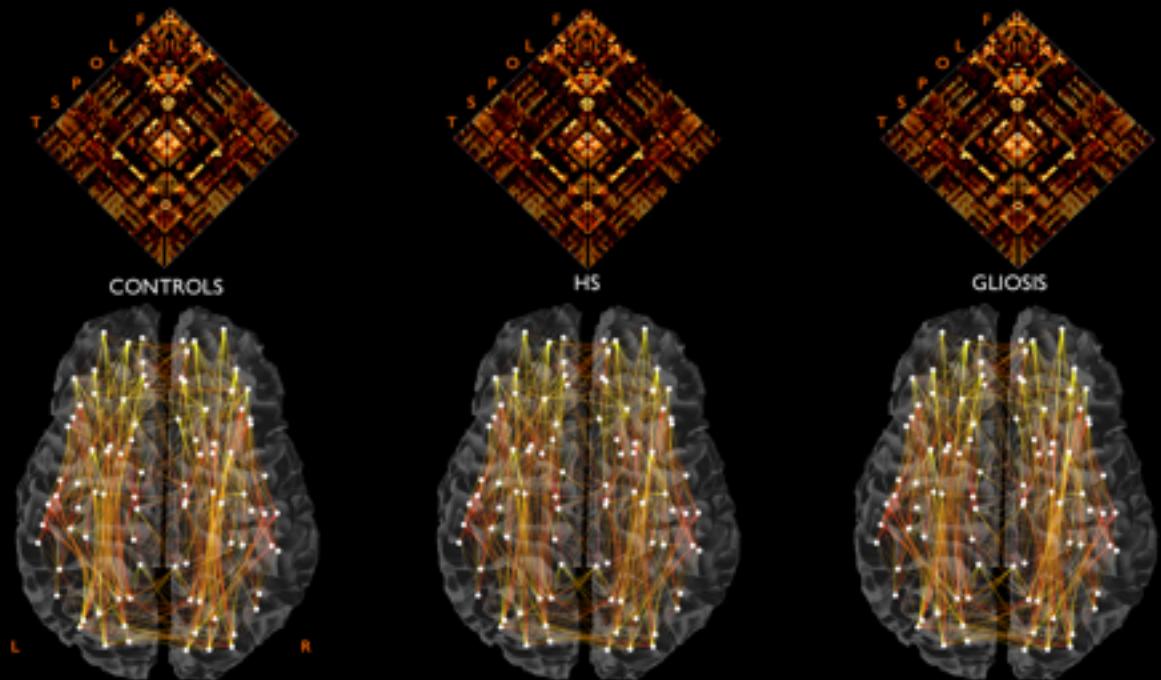
LINKING COGNITIVE AND BRAIN PHENOTYPES



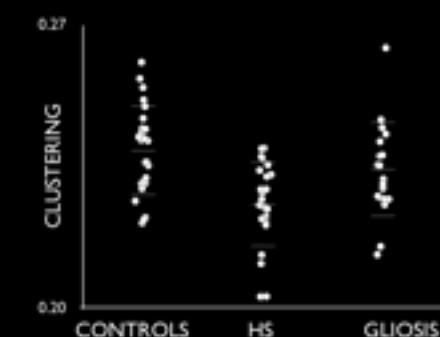
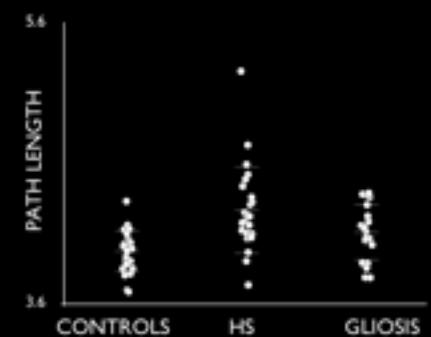


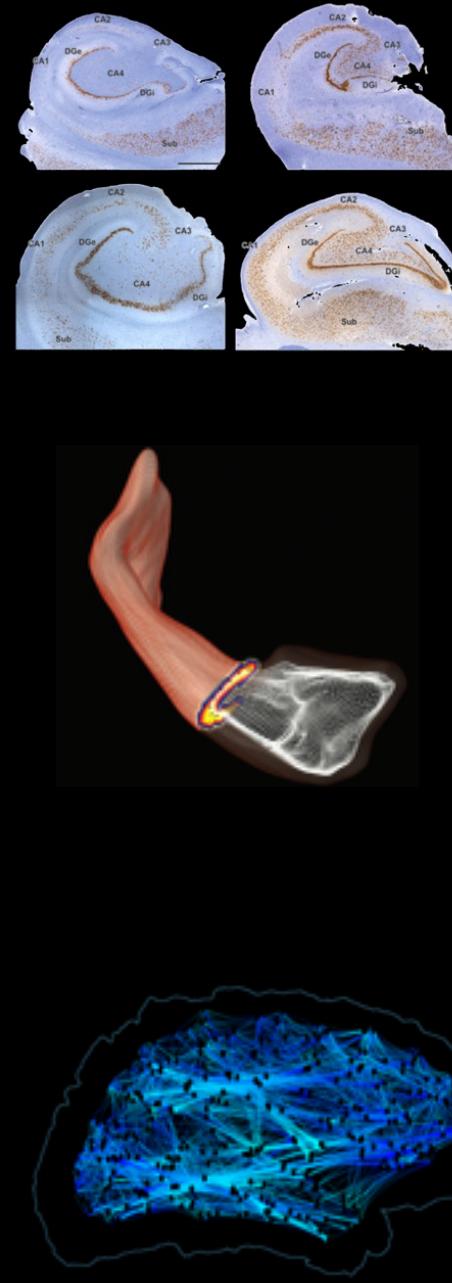
LINKING MACRO/MICROLEVEL DISRUPTIONS

A STRUCTURAL CONNECTOMES



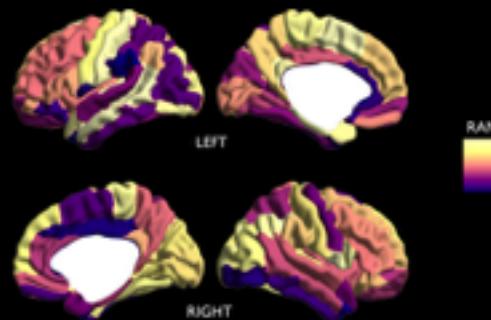
B TOPOLOGICAL PARAMETER ANALYSIS



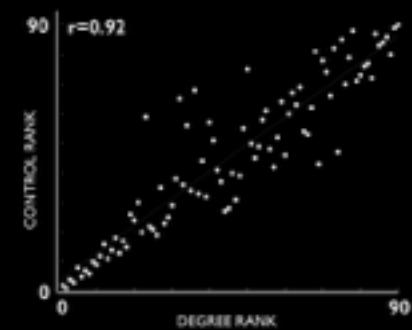


LINKING MACRO/MICROLEVEL DISRUPTIONS

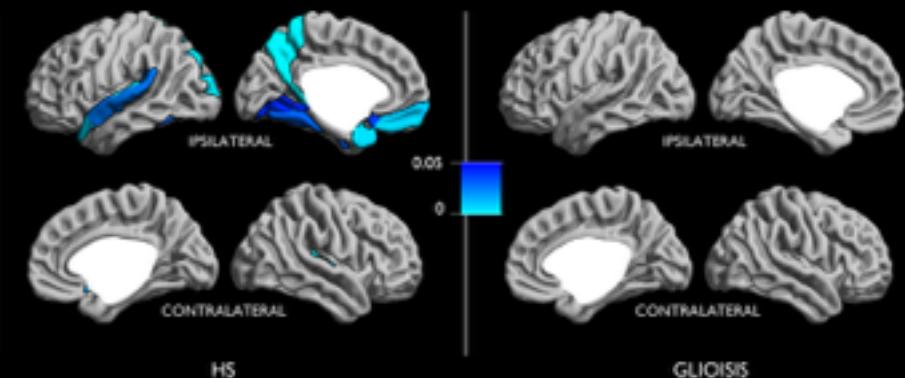
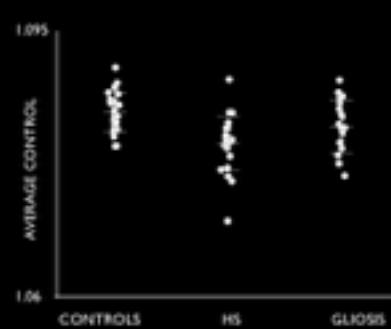
A NETWORK CONTROLLABILITY

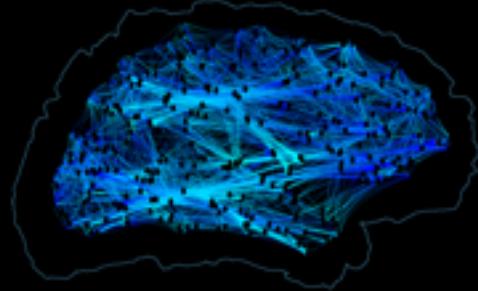
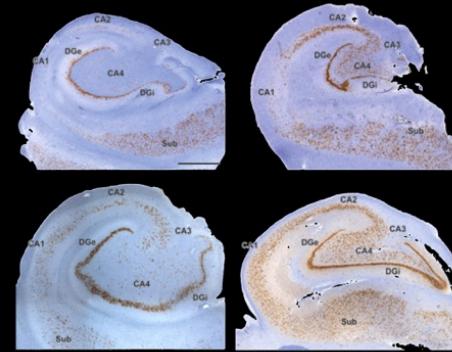


B RELATION TO CENTRALITY



C CONTROLLABILITY ALTERATIONS IN TLE





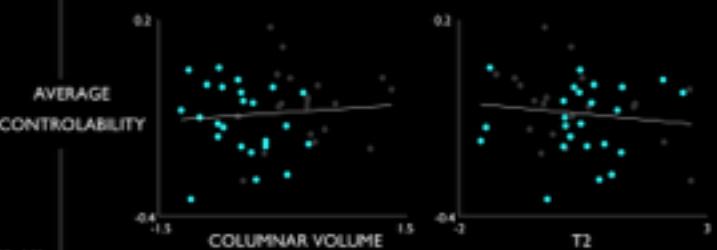
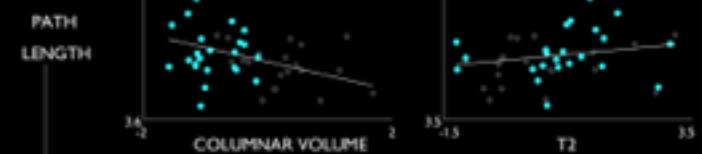
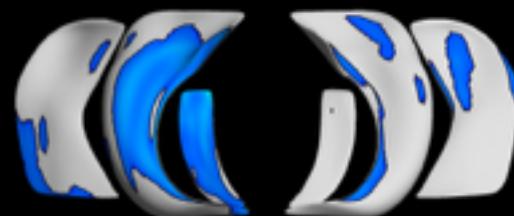
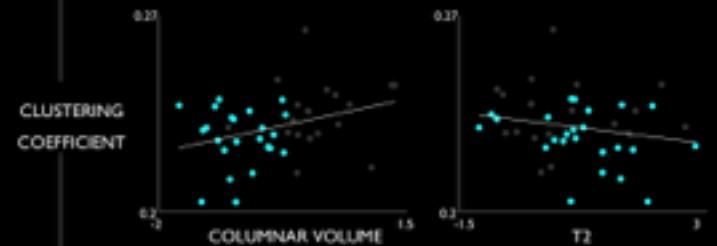
LINKING MACRO/MICROLEVEL DISRUPTIONS

RELATION BETWEEN NETWORK MARKERS AND HIPPOCAMPAL SUBFIELD FEATURES

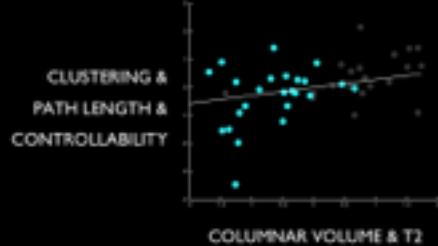
MULTIVARIATE SURFACE-WIDE



UNIVARIATE POSTHOC



MULTIVARIATE POSTHOC



IPSILATERAL

CONTRALATERAL

submitted

INTERIM SUMMARY: EPILEPSY

ANOMALIES BEYOND HIPPOCAMPUS

SYSTEM-LEVEL COMPROMISE OF GREY MATTER & WHITE MATTER

MOST MARKED IMPACT IN LIMBIC NETWORK

NEUROIMAGING SUBTYPING

MESIOTEMPORAL SUBTYPES: CLINICAL AND PATHOLOGICAL DIVERGENCE

NEUROPROGNOSTICS: PREDICTION OF LONG-TERM OUTCOME

LINK TO COGNITIVE PHENOTYPES

ASSOCIATION BETWEEN HIPPOCAMPAL PATHOLOGY AND CONNECTOME PHENOTYPES

AUTISM SPECTRUM CONDITIONS

MOST COMMON
NEURODEVELOPMENTAL DISORDER

PERSISTS UNTIL ADULTHOOD

CORE DEFICITS
IN SOCIAL COGNITION AND
COMMUNICATION

DIAGNOSIS AND THERAPY CHALLENGED
BY CONSIDERABLE HETEROGENEITY



IS THERE A CONSISTENT PATTERN OF REGIONAL ANOMALIES?

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,
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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

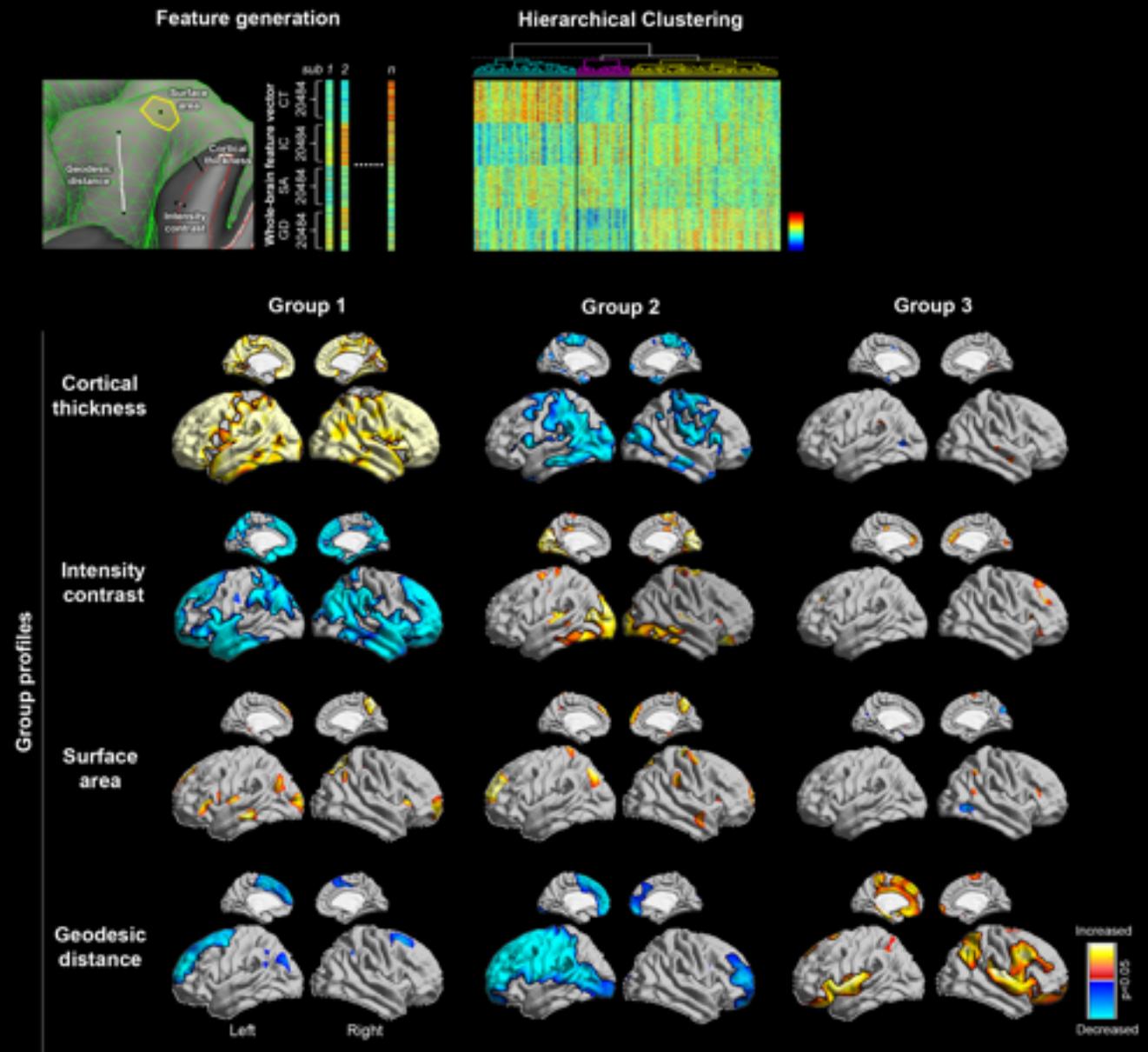
BIG DATA ANALYSIS FOR STRUCTURAL BRAIN ANOMALIES IN AUTISM



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

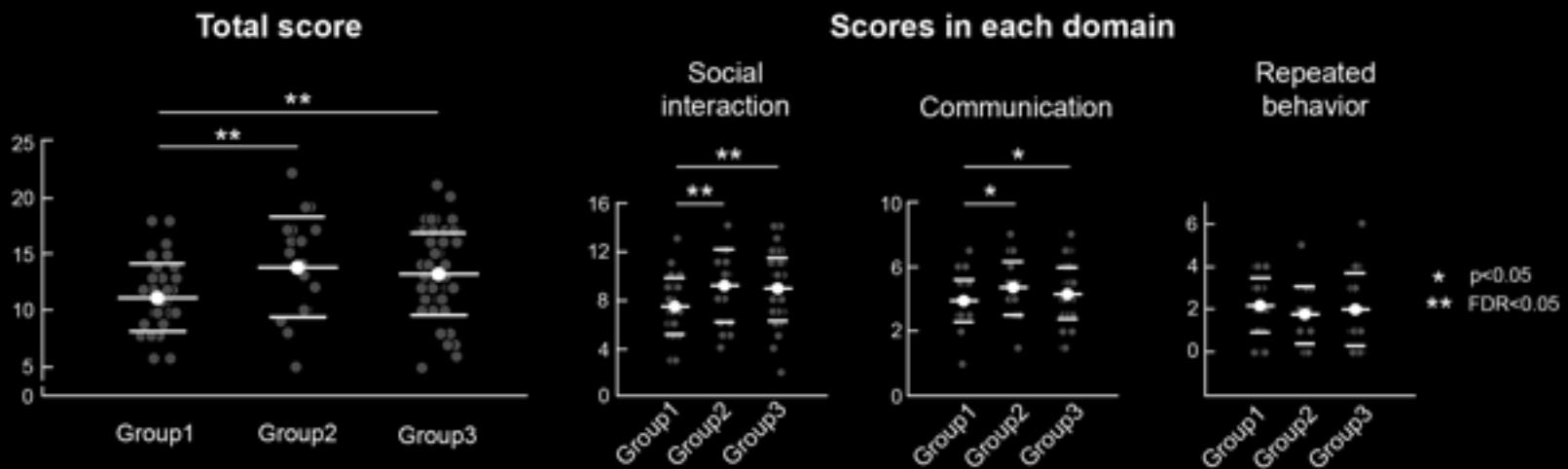
ADOS- and/or ADI-R available in all sites

SUBTYPING OF AUTISM SPECTRUM DISORDERS



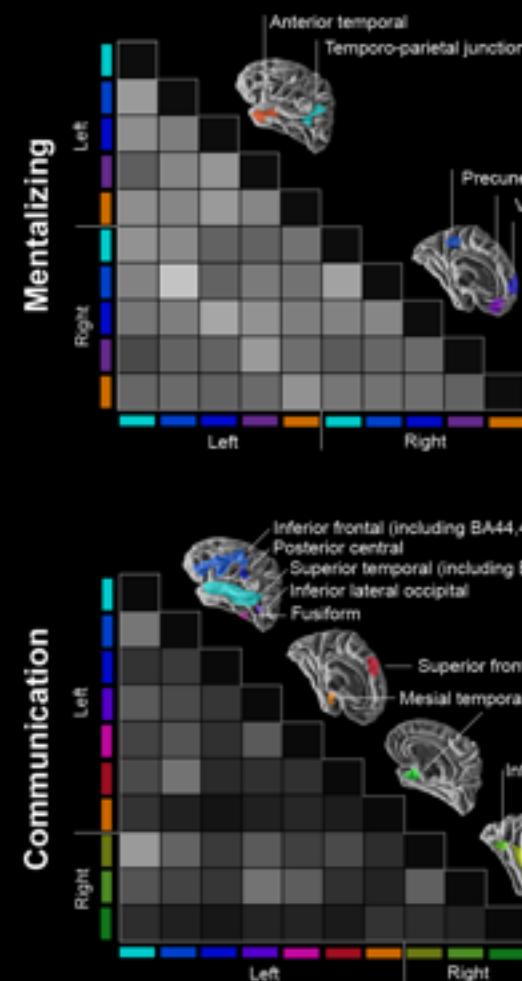
TOWARDS A SUBTYPING OF AUTISM SPECTRUM DISORDERS

ADOS profiles

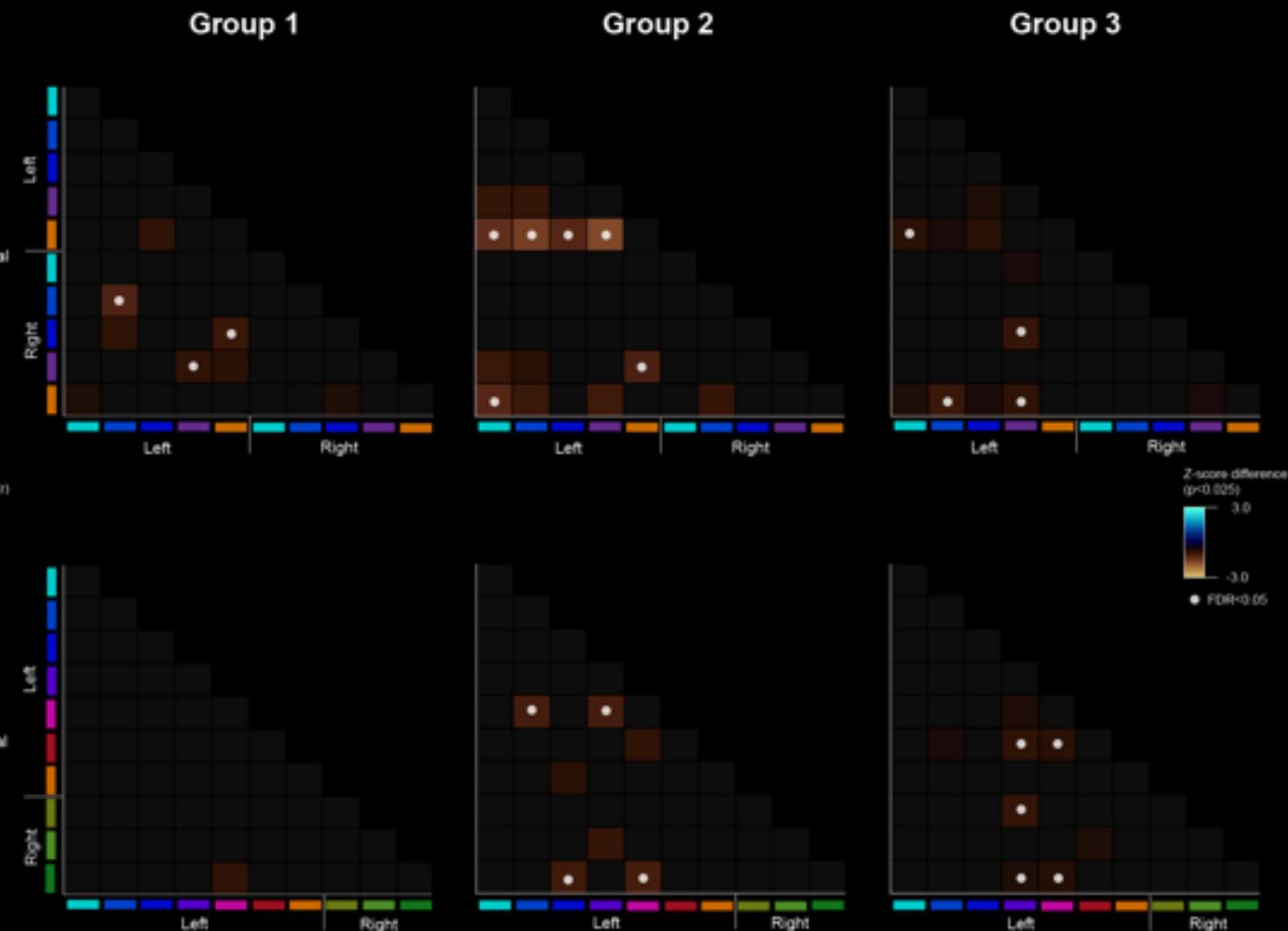


TOWARDS A SUBTYPING OF AUTISM SPECTRUM DISORDERS

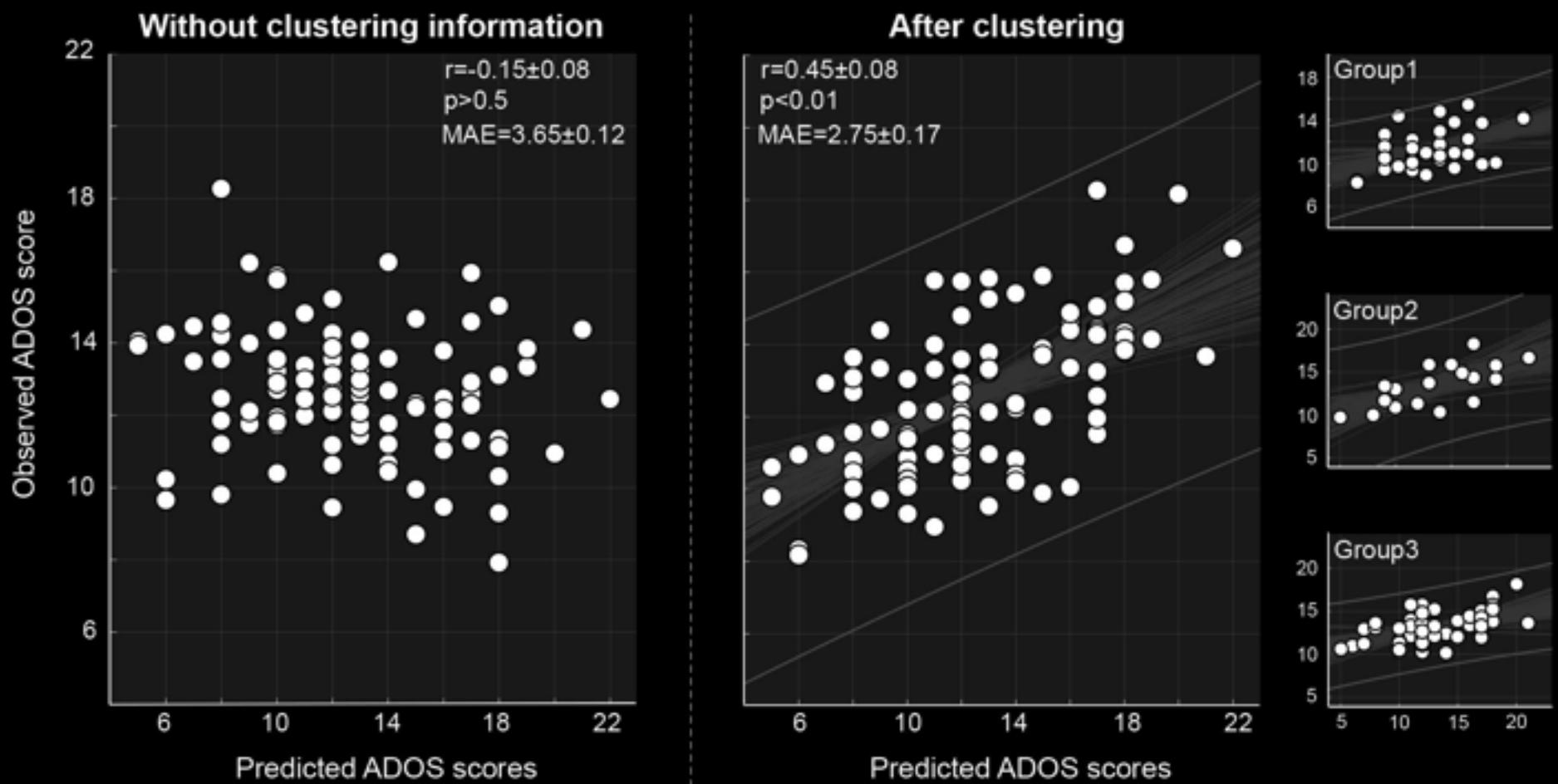
Functional connectivity in controls



Decreased connectivity in ASD

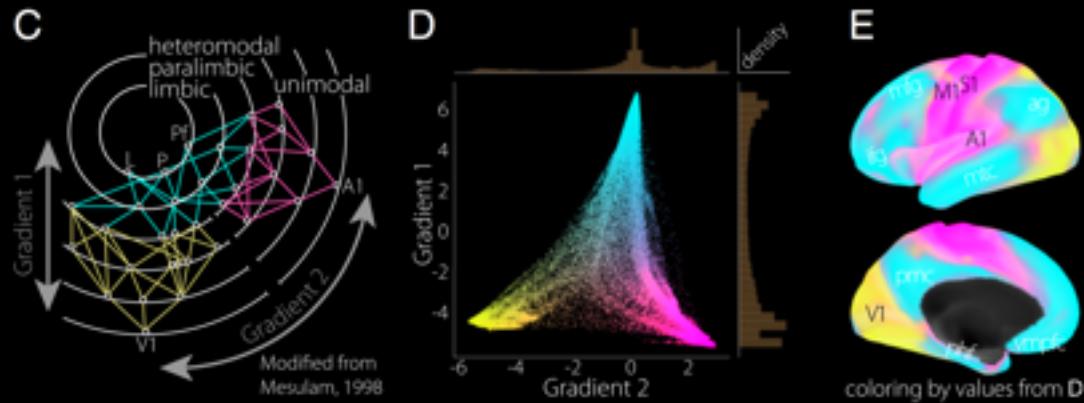


SYMPTOM SEVERITY PREDICTION

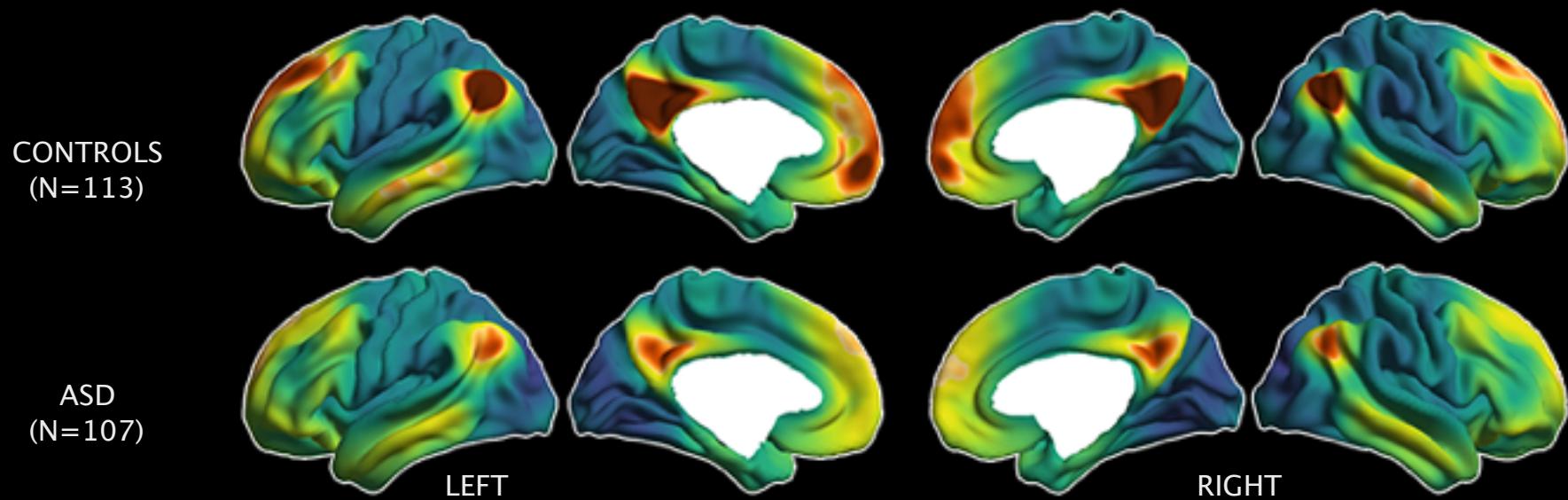


CAN WE EXTEND ASD ASSESSMENTS TO THE CONNECTOME LEVEL

ALTERED CONNECTOME HIERARCHY IN AUTISM



Margulies et al. (2016) PNAS



ASD
(N=107)

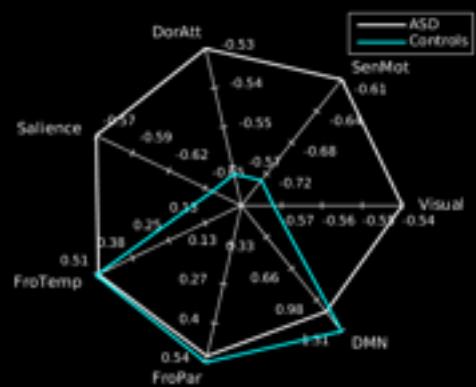
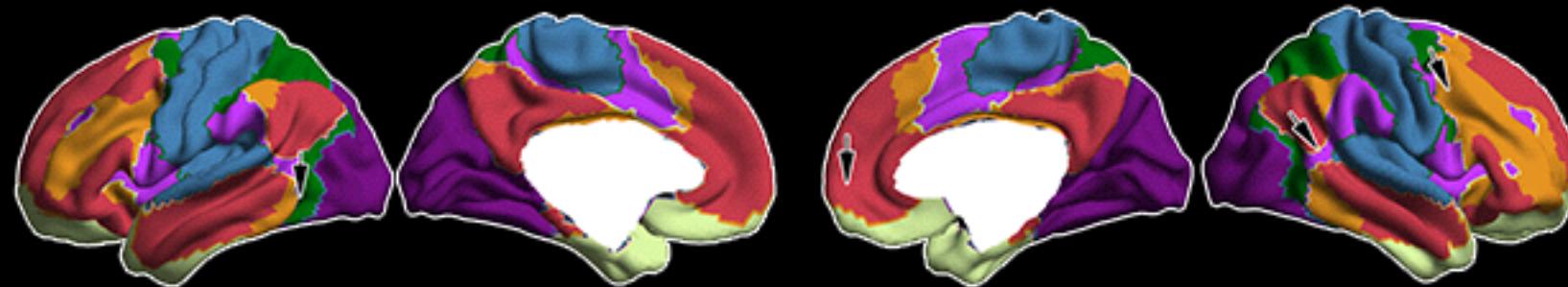
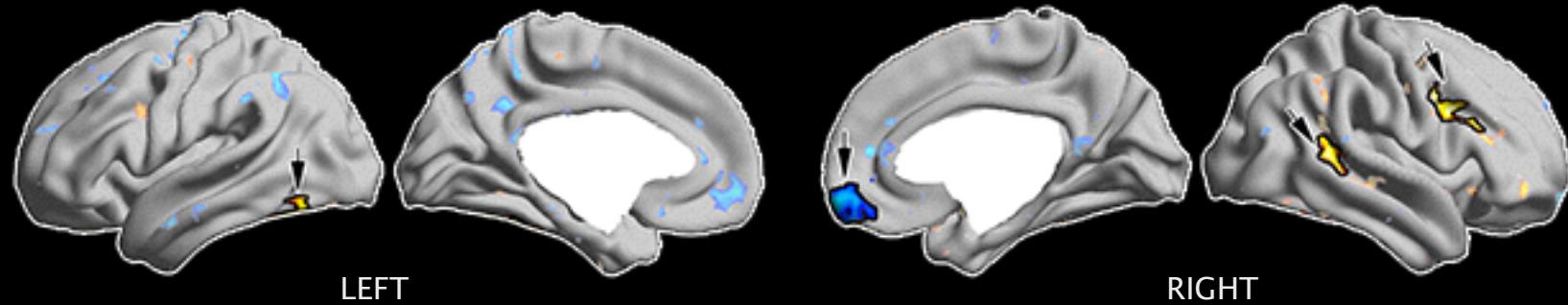
LEFT

RIGHT

Hong, Vos de Wael, Valk, Margulies, Bernhardt (2017) SFN

ALTERED CONNECTOME HIERARCHY IN AUTISM

ASD
VS
CONTROLS



INTERIM SUMMARY: AUTISM

MOVING TOWARDS LARGE DATASETS MAY BETTER CAPTURE HETEROGENEITY

MULTI-SITE REPRODUCIBILITY ANALYSES

UNSUPERVISED TECHNIQUES MAY IDENTIFY MRI SUBTYPES

CONNECTOMICS MAY PLACE DISRUPTIONS ALONG FUNCTIONAL HIERARCHIES

CONSOLIDATE PREVIOUS FINDINGS

BETTER PREDICTION OF SYMPTOM LEVELS

POTENTIALLY USEFUL TO CALIBRATE THERAPY

MAY FACILITATE THE LINK OF IMAGING FINDINGS WITH GENOMICS

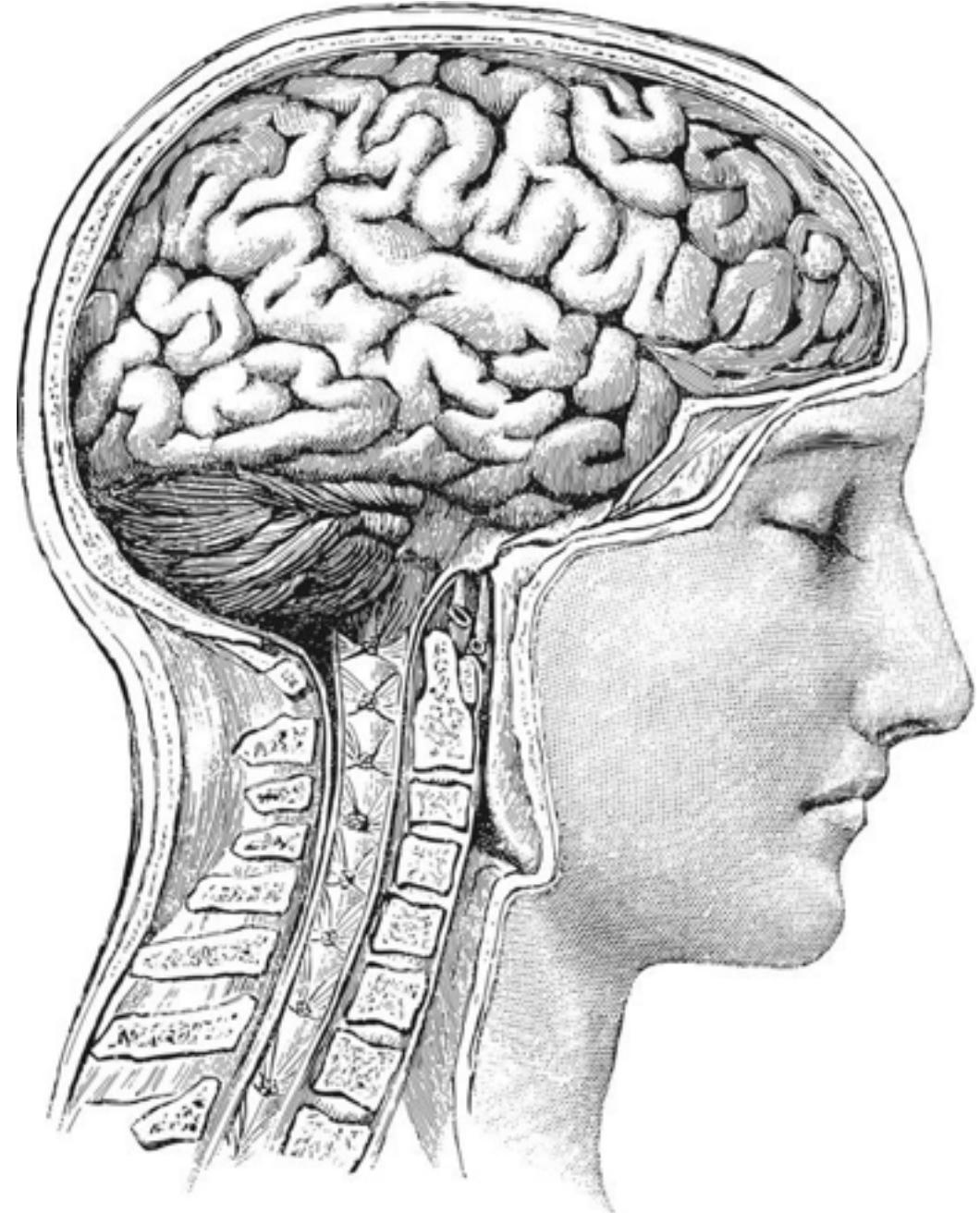
SUMMARY

MRI PROVIDES IN VIVO INFORMATION ON
MICROSTRUCTURE AND NETWORKS

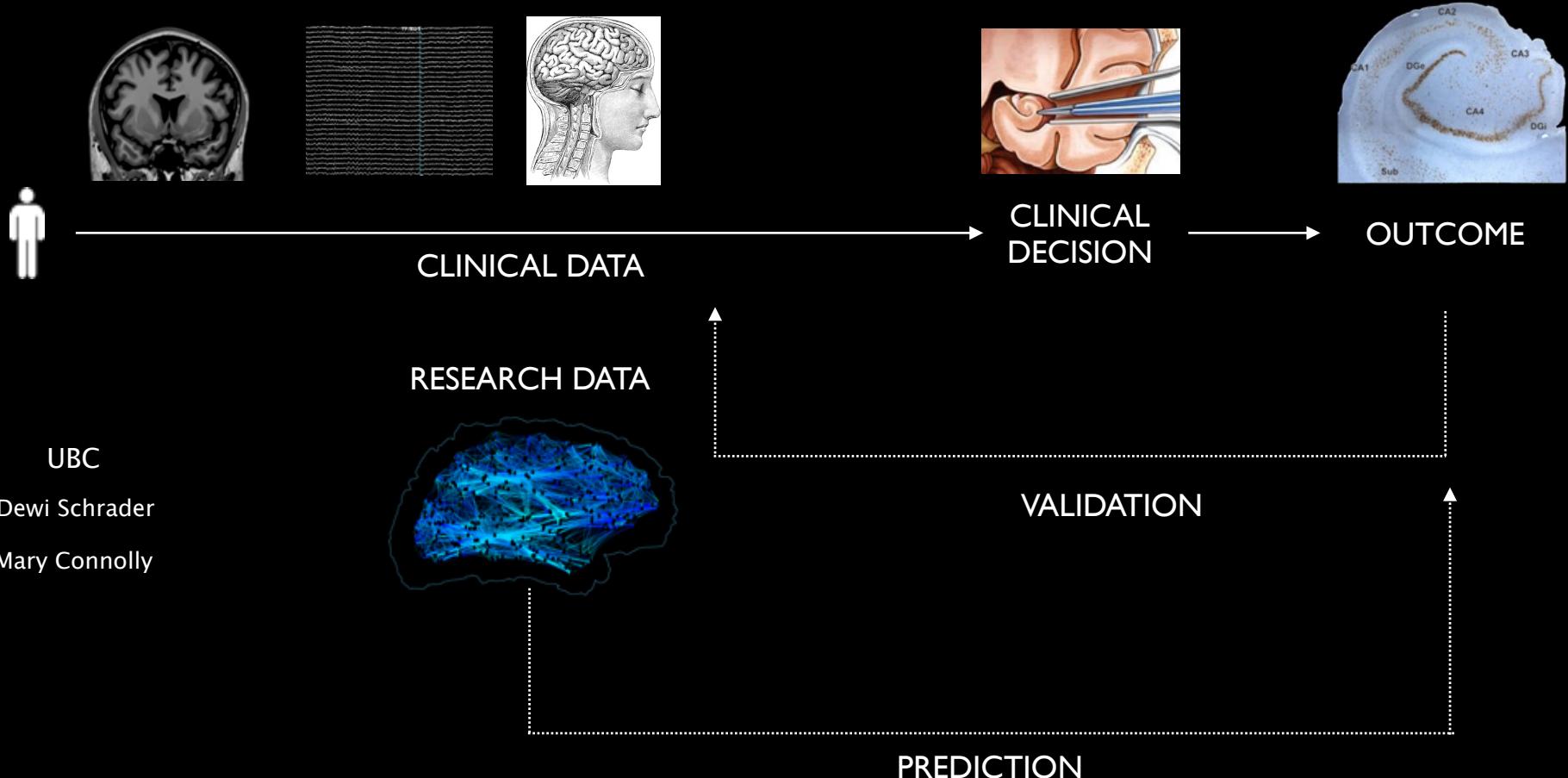
STRUCTURE-FUNCTION ANALYSIS

EXPLICITLY ADDRESSING VARIABILITY
IN EPILEPSY AND AUTISM MAY
IMPROVE DIAGNOSTIC POWER

OPPORTUNITIES FOR VALIDATION
THROUGH CLINICAL PIPELINES



TOWARDS PATIENT-ORIENTED PREDICTIONS



MICA

Reinder Vos de Wael
Sara Lariviere
Raul Cruces
Seok-Jun Hong
Brian Hyung
Tabea Haas Heger

MNI

Neda Bernasconi
Andrea Bernasconi
Fatemeh Fadaie
Benoit Caldairou
Min Liu
Sophie Adler
Mauricio Giradi-Schappo
Jeffrey Hall
Marie Christine Guiot

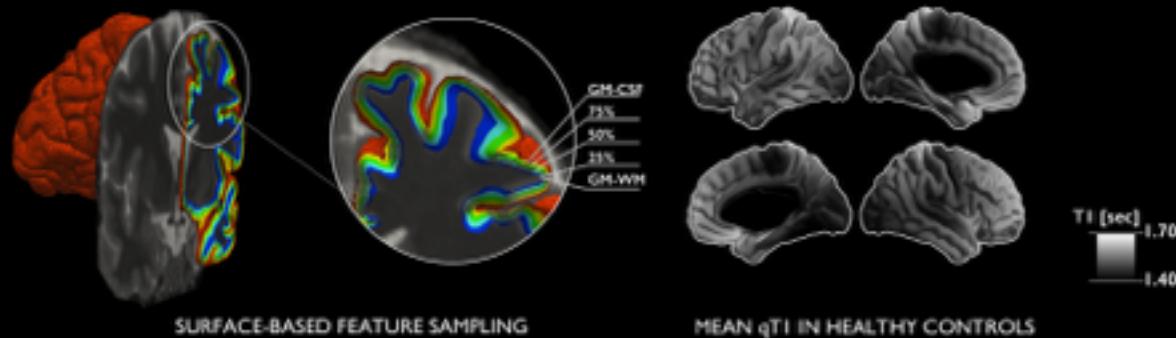
MPI

Sofie Valk
Alfred Anwender



MICROSTRUCTURAL CORTICAL ANOMALIES

A qT_i SAMPLING PROCEDURE



B qT_i GROUP COMPARISON

