

TOWARDS NEUROIMAGING-BASED SUBTYPING OF THE HEALTHY AND DISEASED HUMAN BRAIN

Boris Bernhardt, PhD
Montreal Neurological
Institute and Hospital



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

PROBE MULTIPLE
BIOLOGICAL PROPERTIES IN VIVO

DESCRIBE DISEASE PATTERNS
AND COMMONALITIES

IDENTIFY BIOLOGICAL SUBTYPES
WITHIN DISORDERS

MONITOR PROGRESSION AND
INTERVENTION

PROVIDE OUTCOME
MARKERS



OUTLINE

MULTI-MODAL NEUROIMAGING:
STRUCTURE, FUNCTION, NETWORKS

NEUROIMAGING SUBTYPING
IN EPILEPTIC DISORDERS

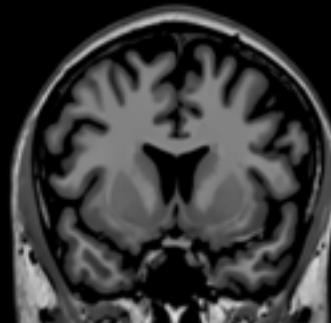
NEUROIMAGING SIGNATURES
OF AUTISM SPECTRUM DISORDERS

NEURODIVERSITY
IN HEALTHY AND DISEASED POPULATIONS

FUTURE RESEARCH DIRECTIONS

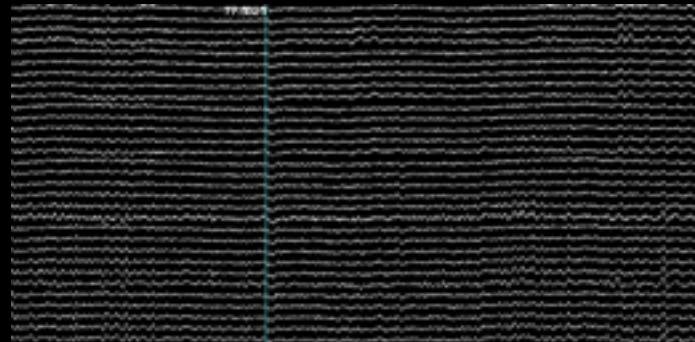
MULTIPLE NEUROIMAGING MODALITIES

MRI



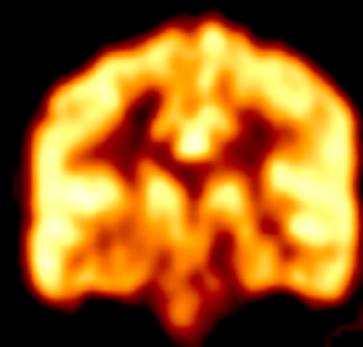
STRUCTURE
FUNCTION

MEG/EEG



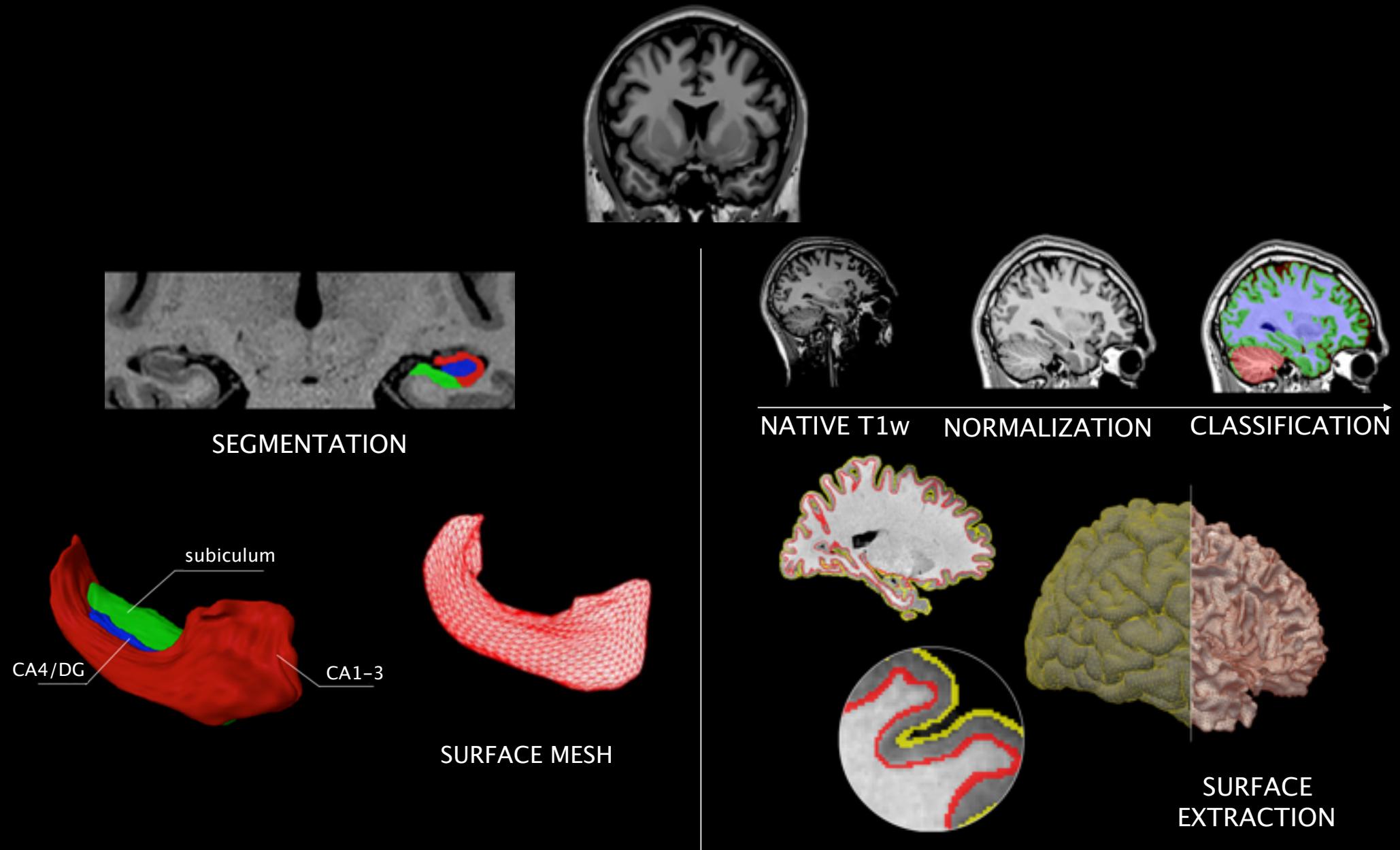
DYNAMICS

PET

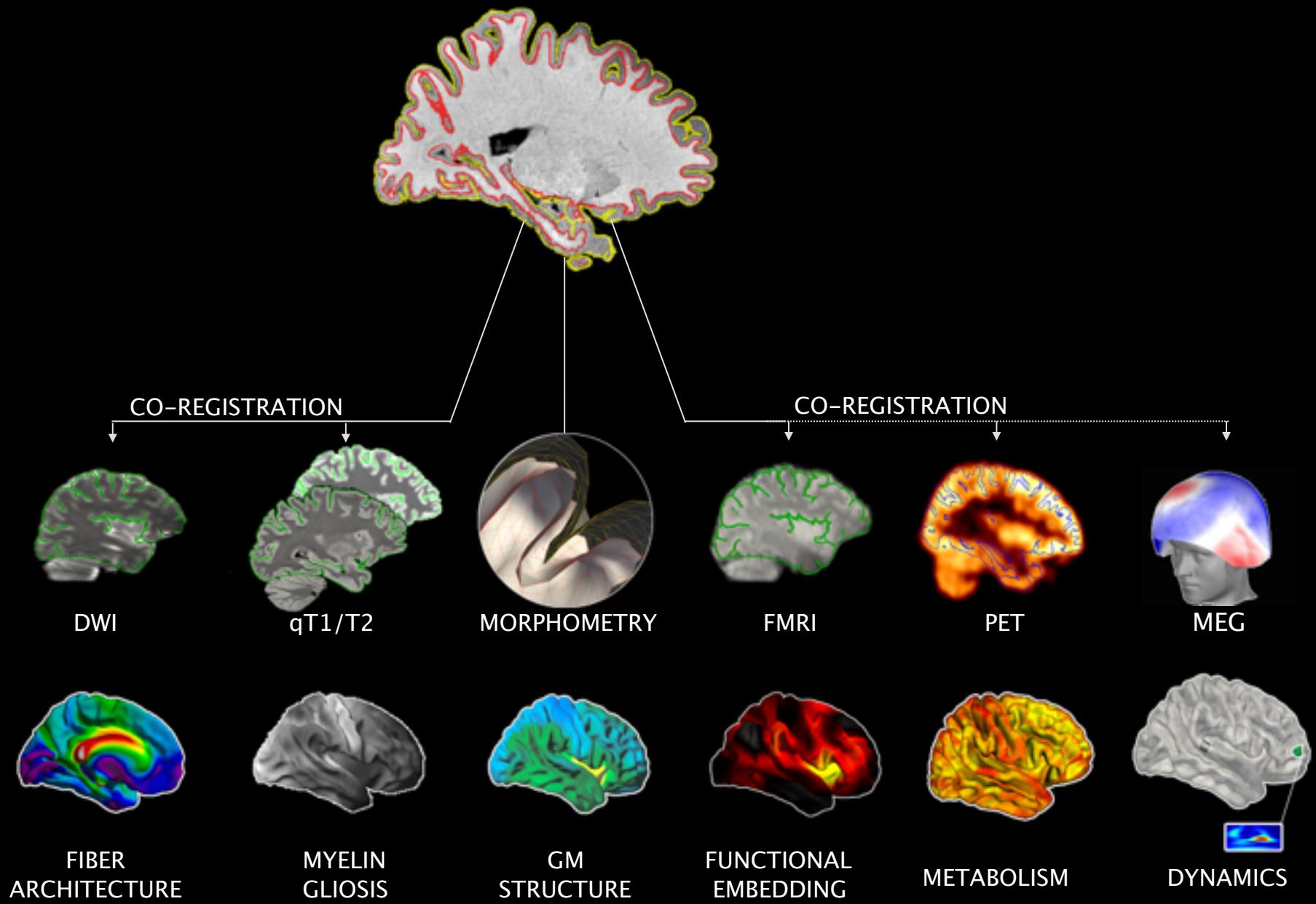


METABOLISM

DESCRIBING ANATOMY

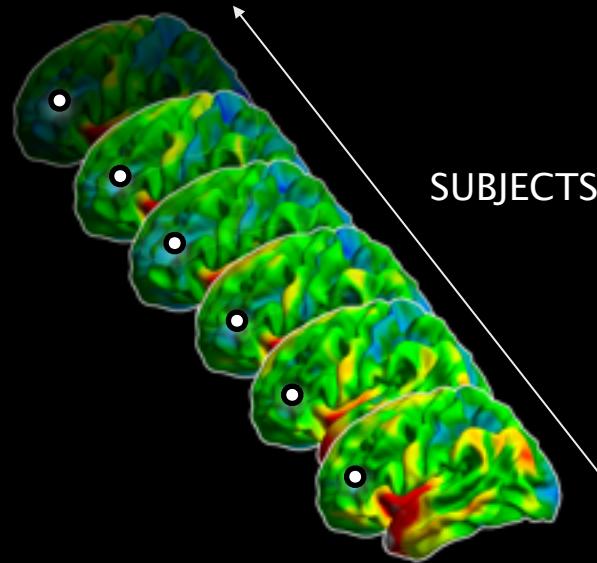


MULTI-MARKER INTEGRATION

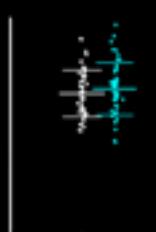


REGIONAL STATISTICAL ANALYSIS

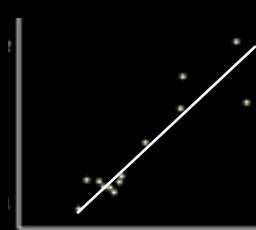
CROSS-SECTIONAL ANALYSES



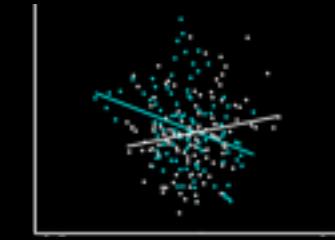
SUBJECTS



$$Y = 1 + G$$

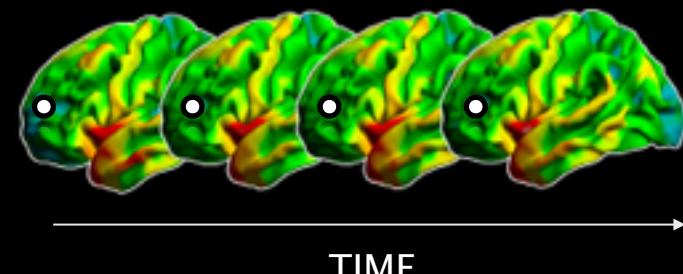


$$Y = 1 + A$$

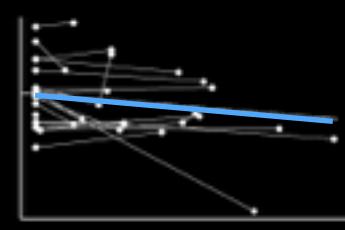


$$Y = 1 + G + A + G \times A$$

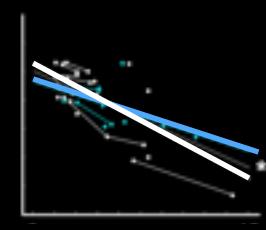
LONGITUDINAL ASSESSMENTS



TIME



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

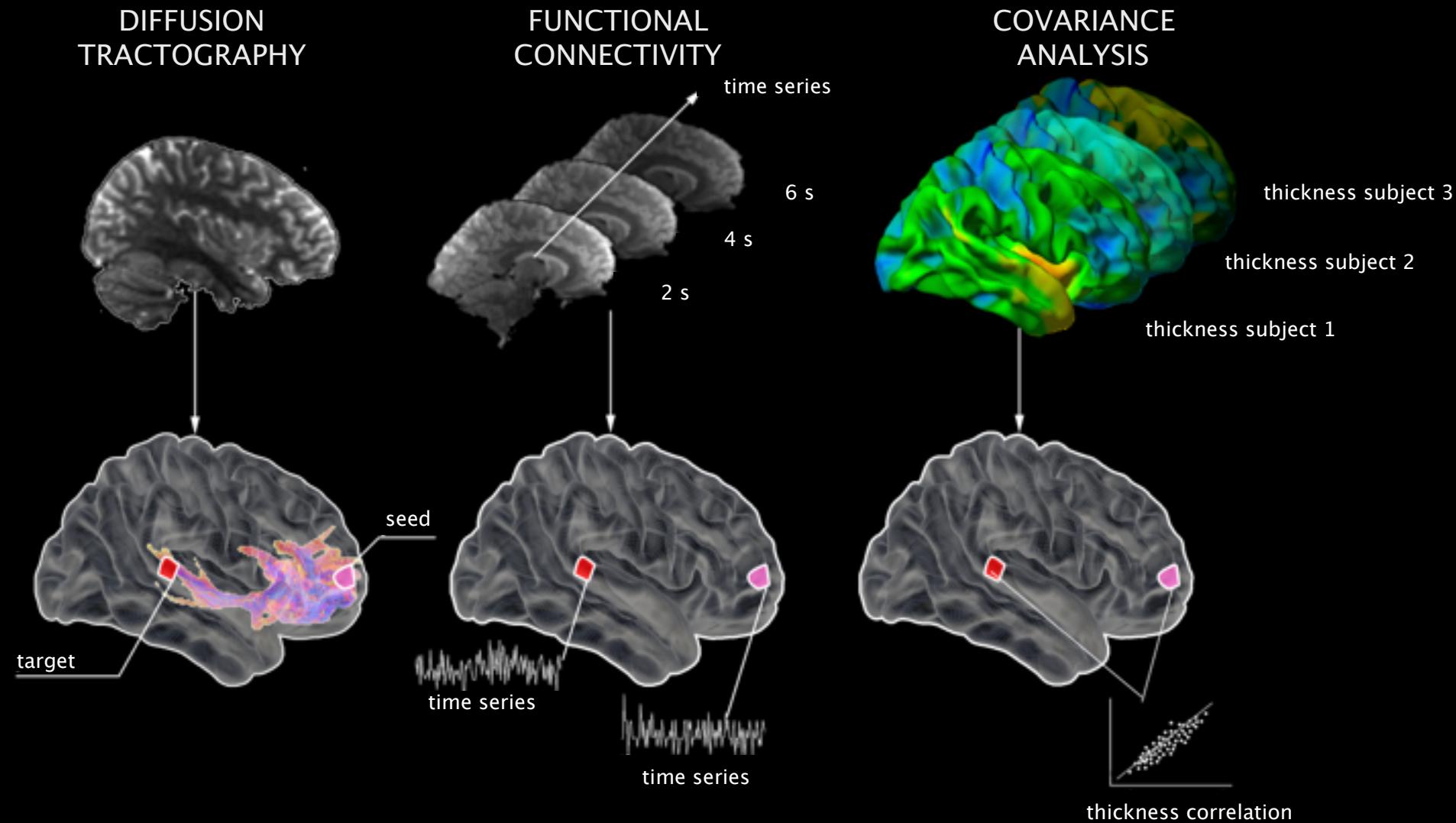


$$Y = 1 + ISI$$

Y is univariate or multivariate data

NETWORK-LEVEL ANALYSIS

SEED-BASED ANALYSIS

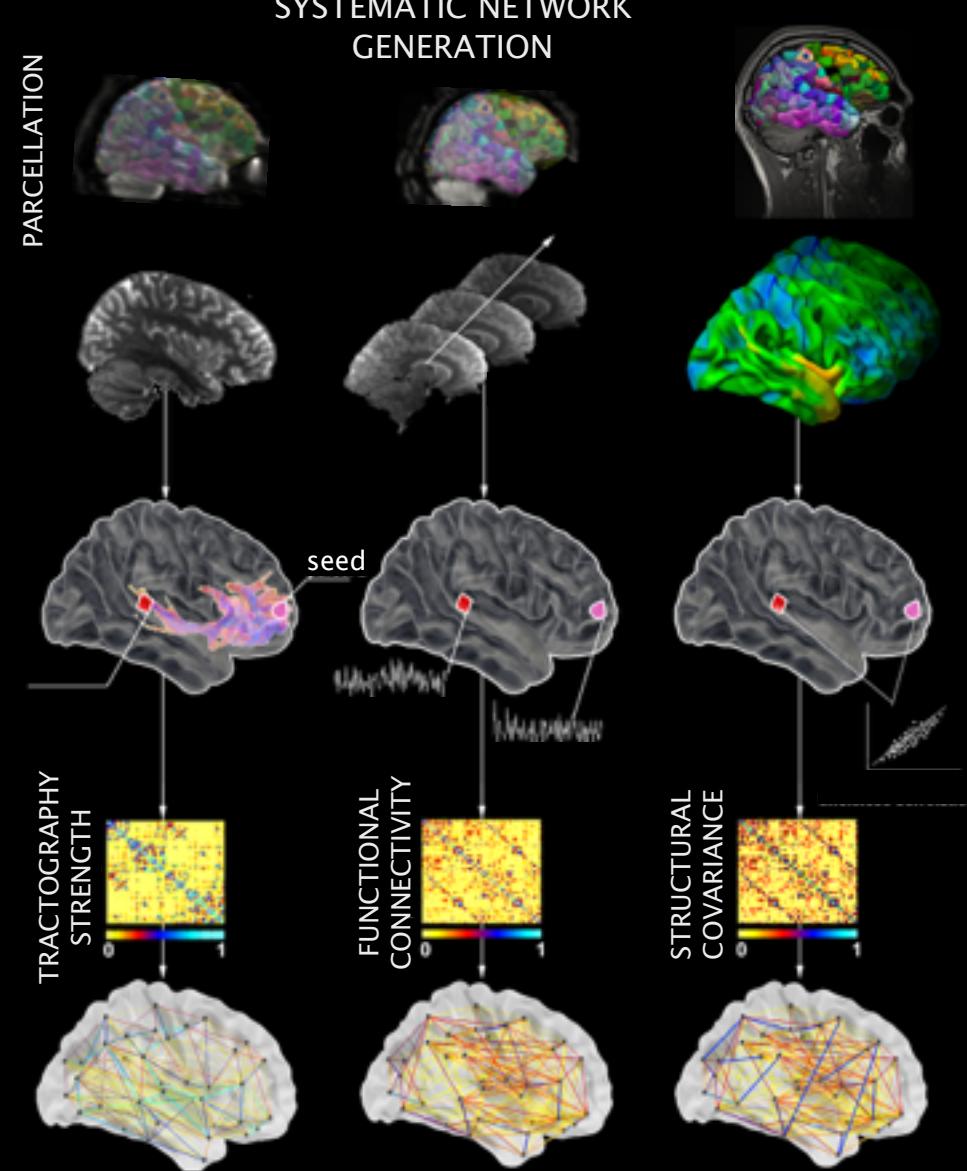


Mori et al. (1999) Ann Neu
Behrens et al. (2007) NIMG

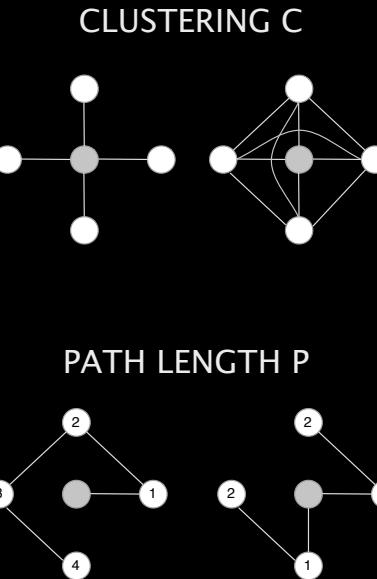
Friston (1994) HBM
Smith (2012) NIMG

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

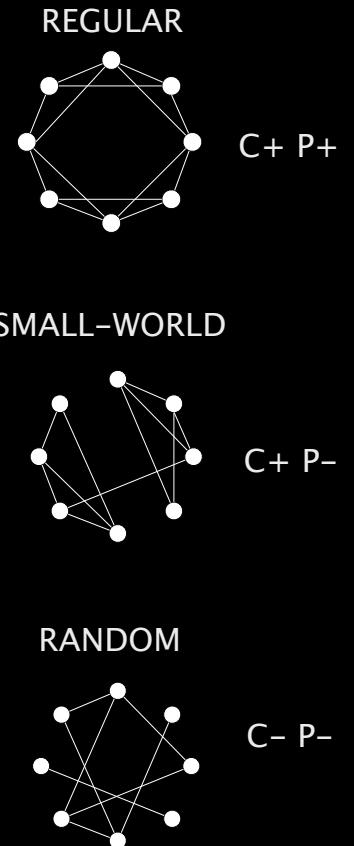
NETWORK-LEVEL ANALYSIS



GRAPH THEORETICAL PARAMETERS

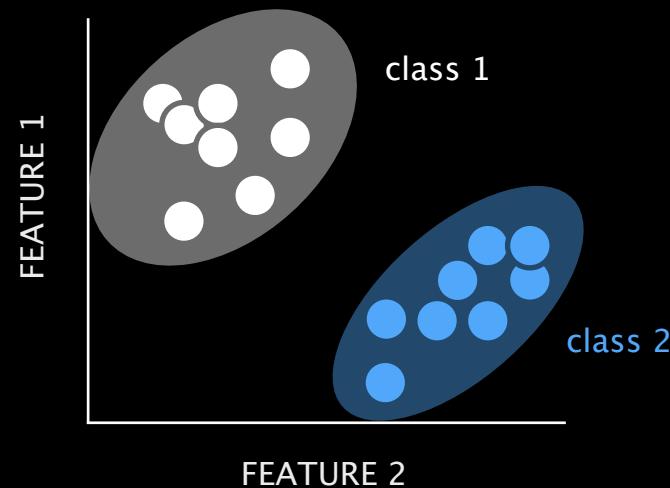


TOPOLOGY CLASSIFICATION



PATTERN LEARNING

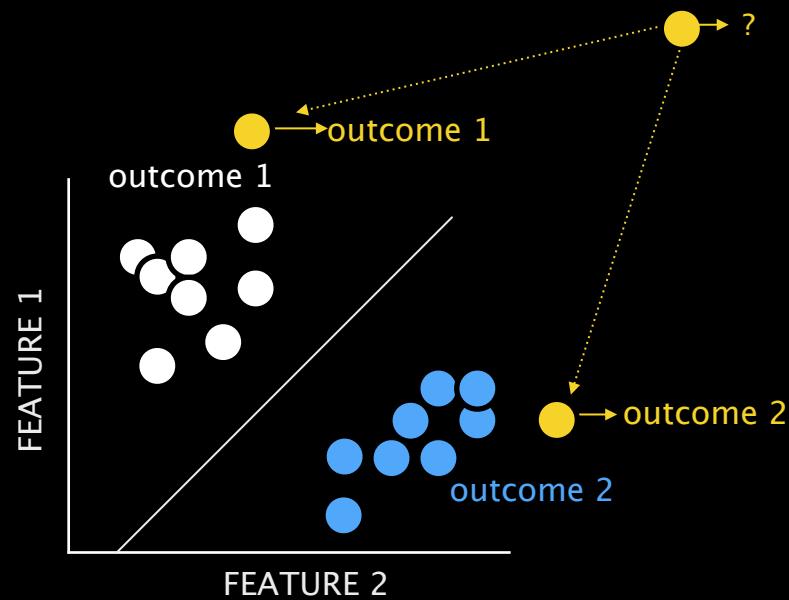
UNSUPERVISED



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, NN, Trees



APPLICATION TO BRAIN DISORDERS

EPILEPSY
AUTISM

EPILEPSY
PREVALENT DISORDER
30% OF PATIENTS ARE
DRUG-RESISTANT
SURGERY MOST EFFECTIVE
TREATMENT
MULTI-DISCIPLINARY
ASSESSMENT



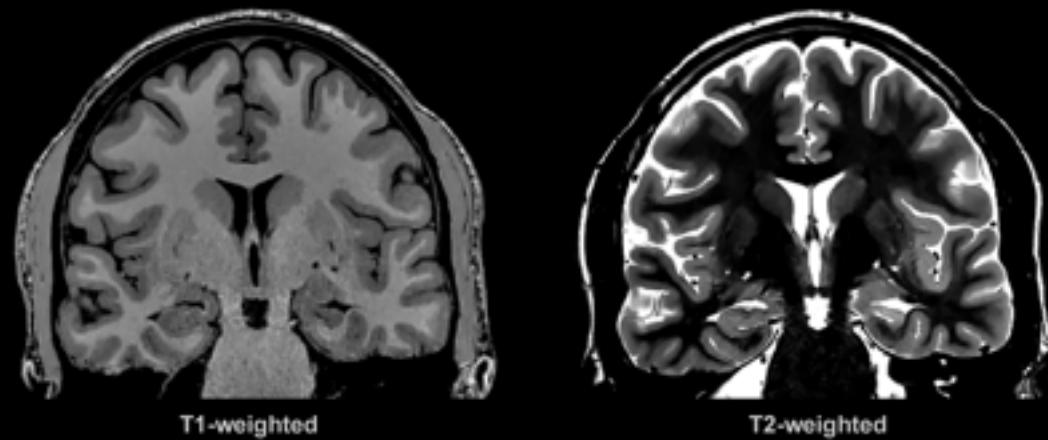
THE CASE OF TEMPORAL LOBE EPILEPSY

Most common drug-resistant epilepsy in adults

Pathological hallmark: hippocampal sclerosis, lateralizes with focus

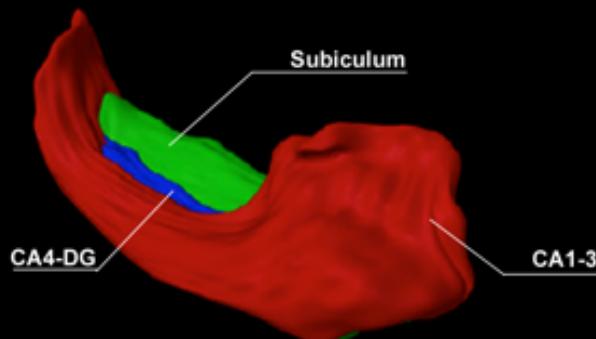
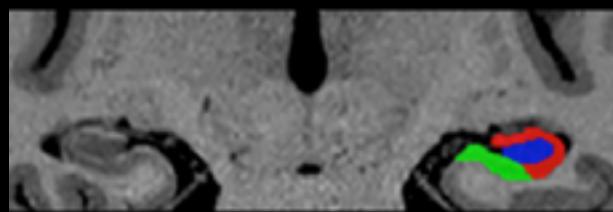
Clinical and research attention paid to hippocampus

MRI plays important role in detecting HS



QUANTITATIVE IMAGING IN THE HIPPOCAMPUS

SEGMENTATION

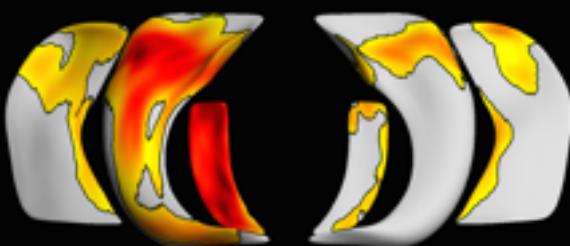


UNIVARIATE

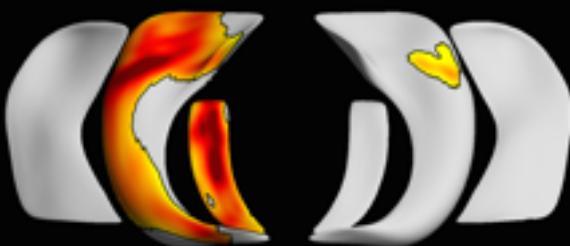
↓VOL



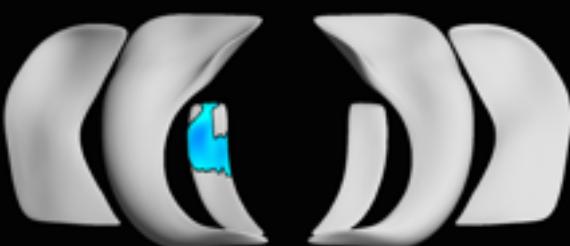
↑T2



↑MD

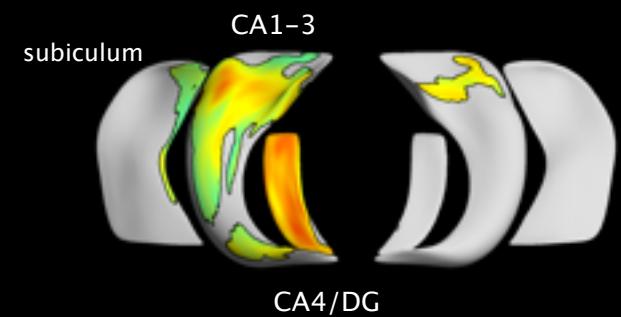


↓FA

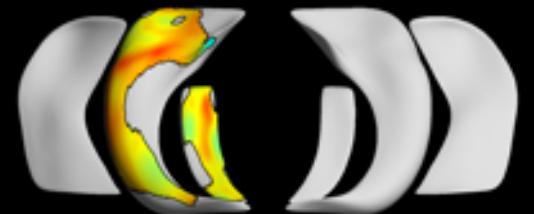


MULTIVARIATE

subiculum

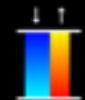
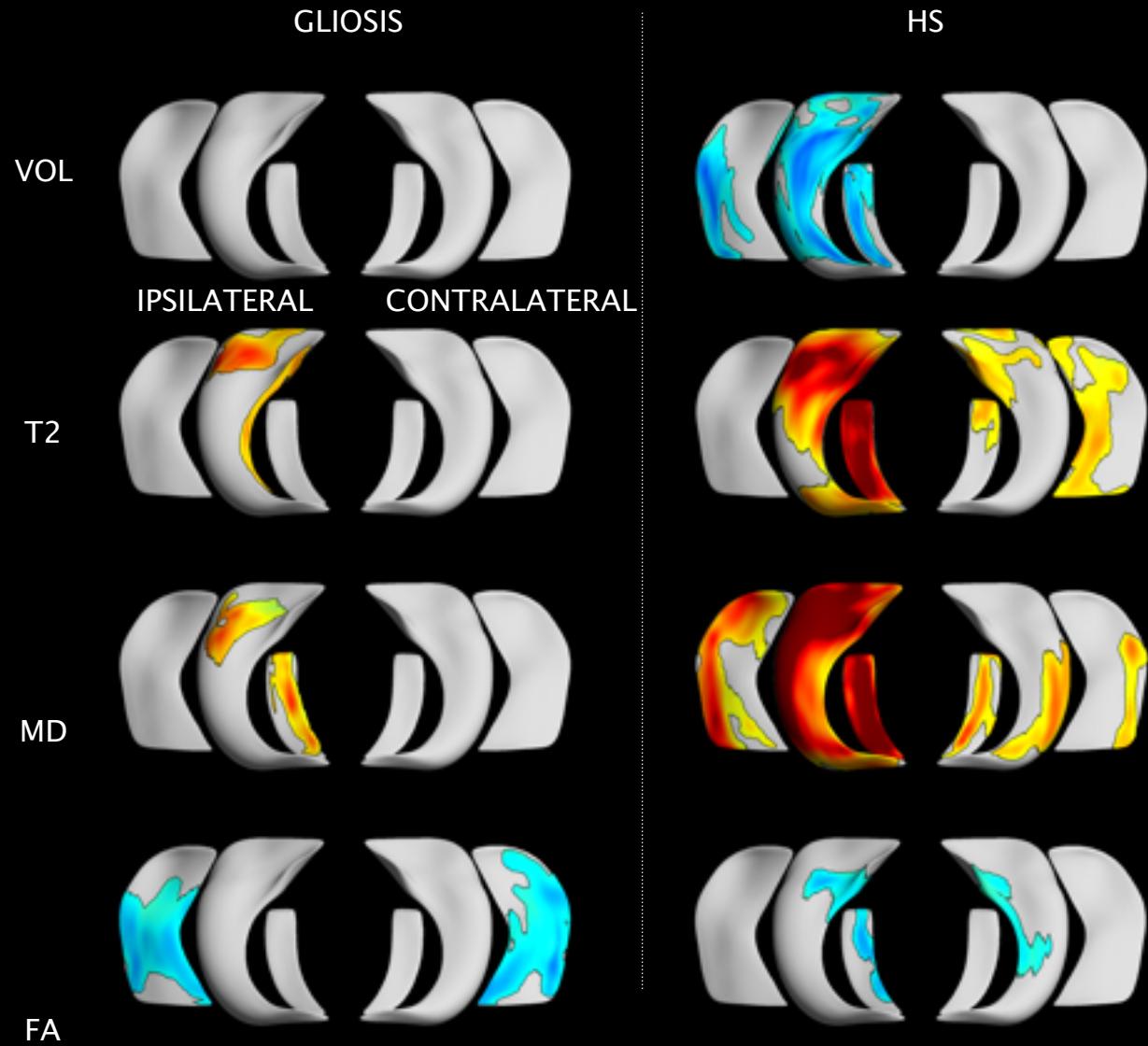


SVM-based
focus lateralization
with 100% accuracy
possible



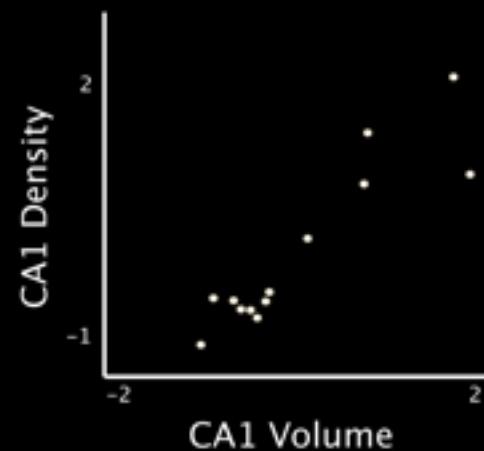
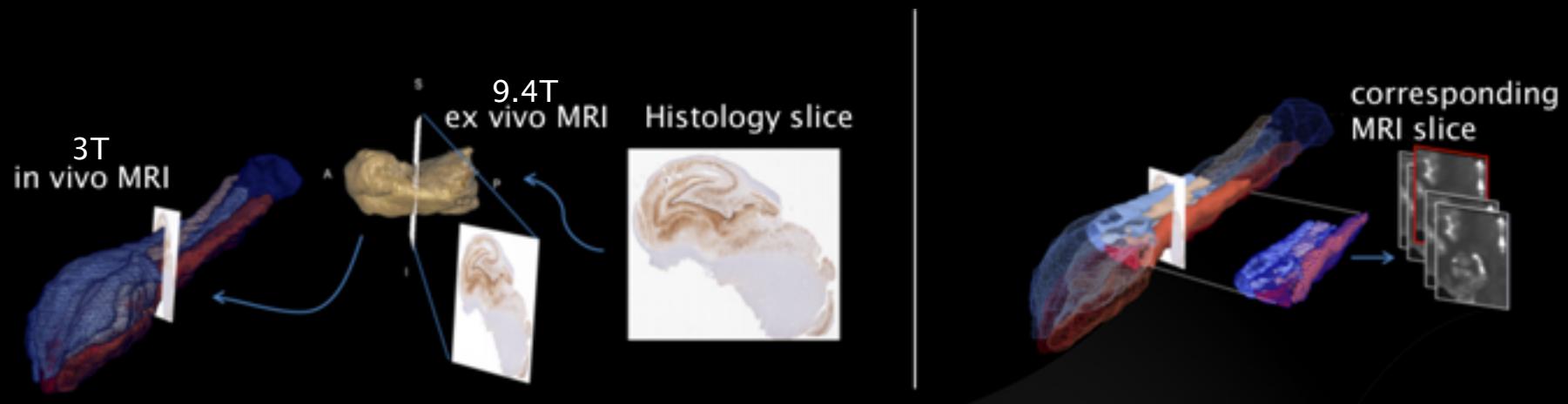
FWE<0.05

RELATION TO PATHOLOGY



FWE<0.05

VALIDATION OF SUBFIELD MRI WITH QUANTITATIVE HISTOPATHOLOGY

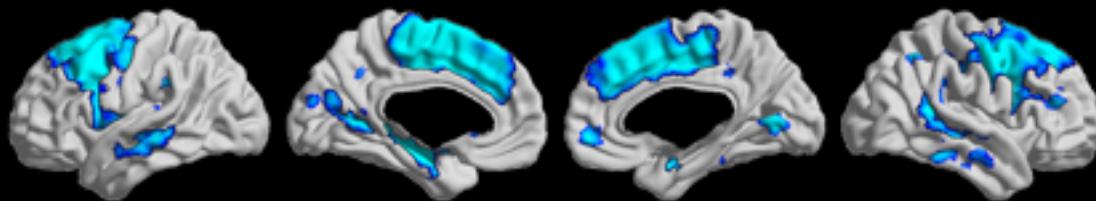


SUBFIELD-SPECIFIC CORRELATIONS BETWEEN MRI AND HISTOLOGY

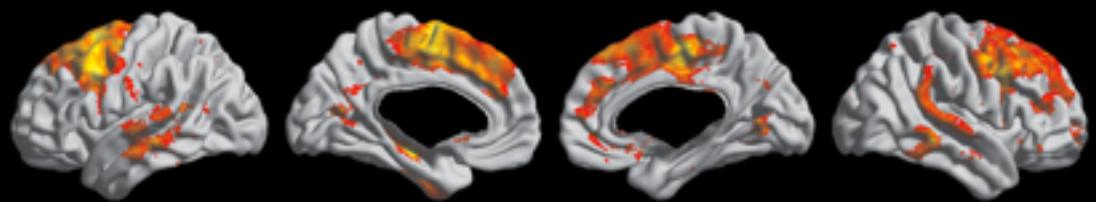
IS TLE A HIPPOCAMPAL DISORDER?

WHOLE-BRAIN PHENOTYPING OF TLE: TLE \neq HIPPOCAMPAL PATHOLOGY

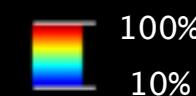
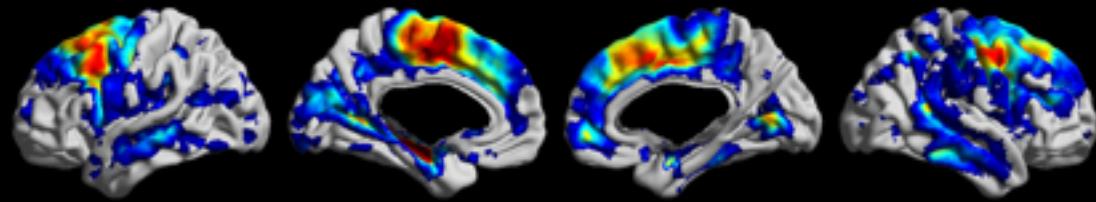
GROUP-LEVEL
THINNING AT 1.5T



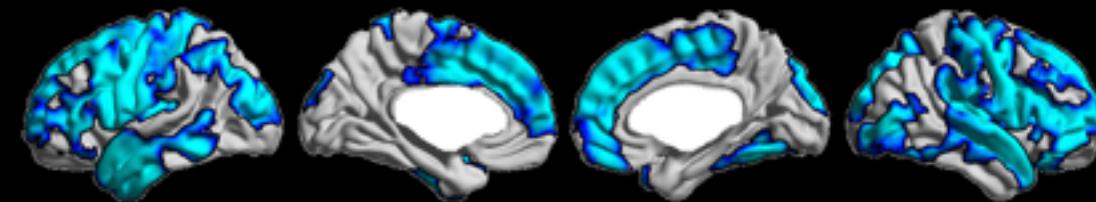
INDIVIDUALIZED
PREVALENCE



BOOTSTRAP
REPRODUCIBILITY



THINNING IN
3T COHORT

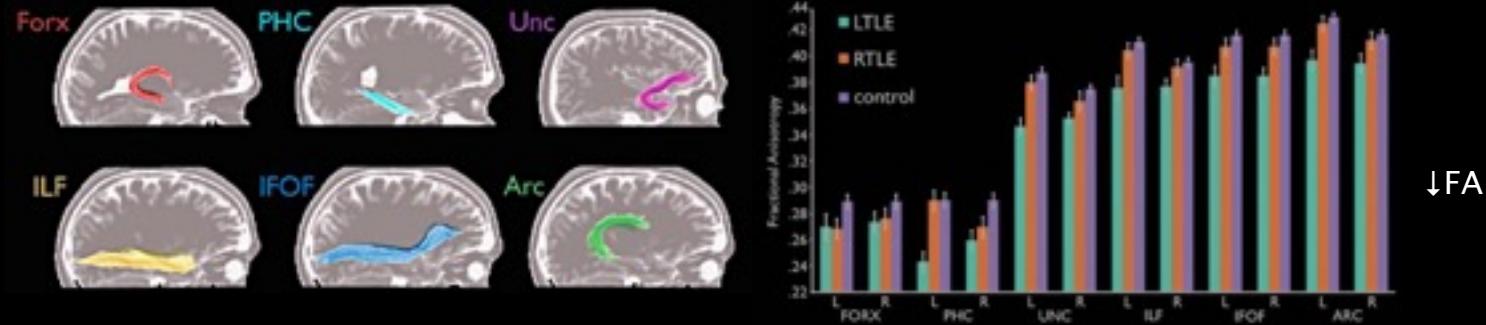


IPSILATERAL

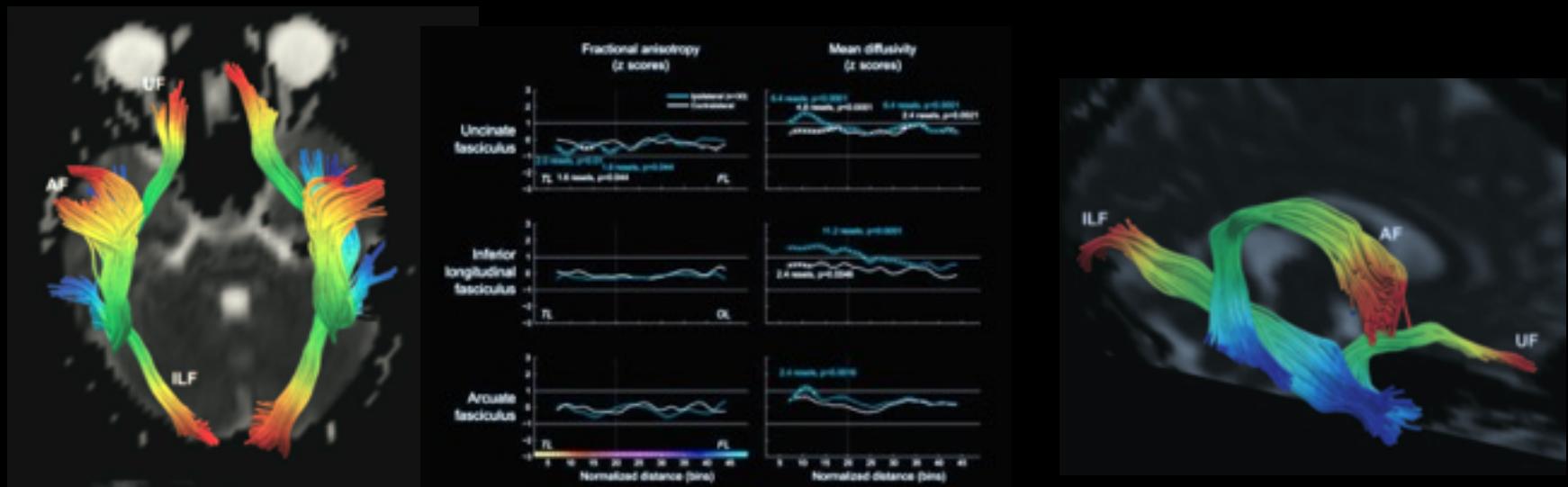
CONTRALATERAL

WHOLE-BRAIN PHENOTYPING OF TLE: WHITE MATTER ALTERATIONS

TRACTOGRAPHY-
BASED WM BUNDLE
ANALYSIS

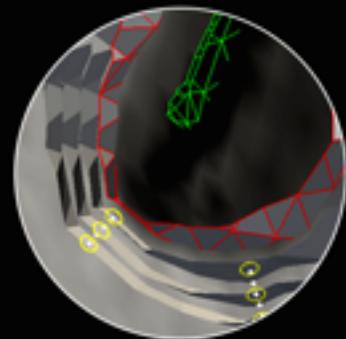


UC San Diego

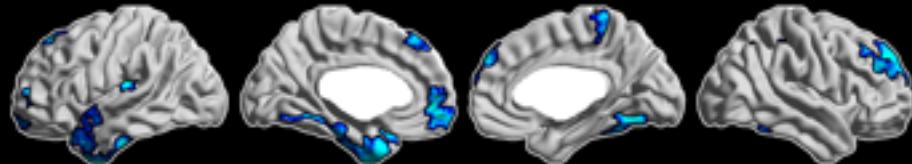


WHOLE-BRAIN PHENOTYPING OF TLE: WHITE MATTER ALTERATIONS AND FUNCTIONAL DISRUPTIONS

SURFACE-BASED
WM SAMPLING
[2MM DEPTH]



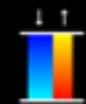
↓FA



↑MD

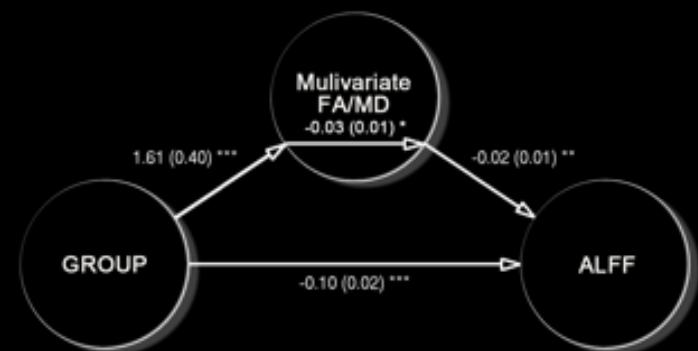
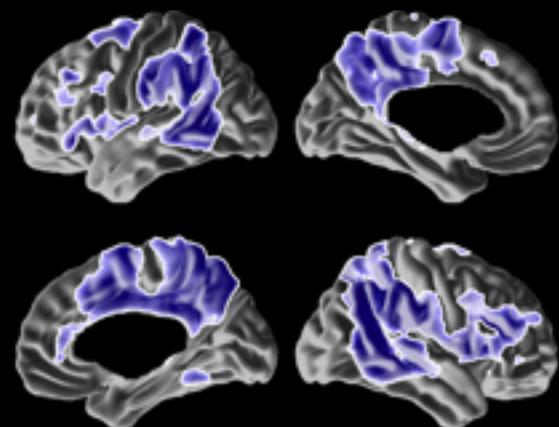


MULTI-VARIATE

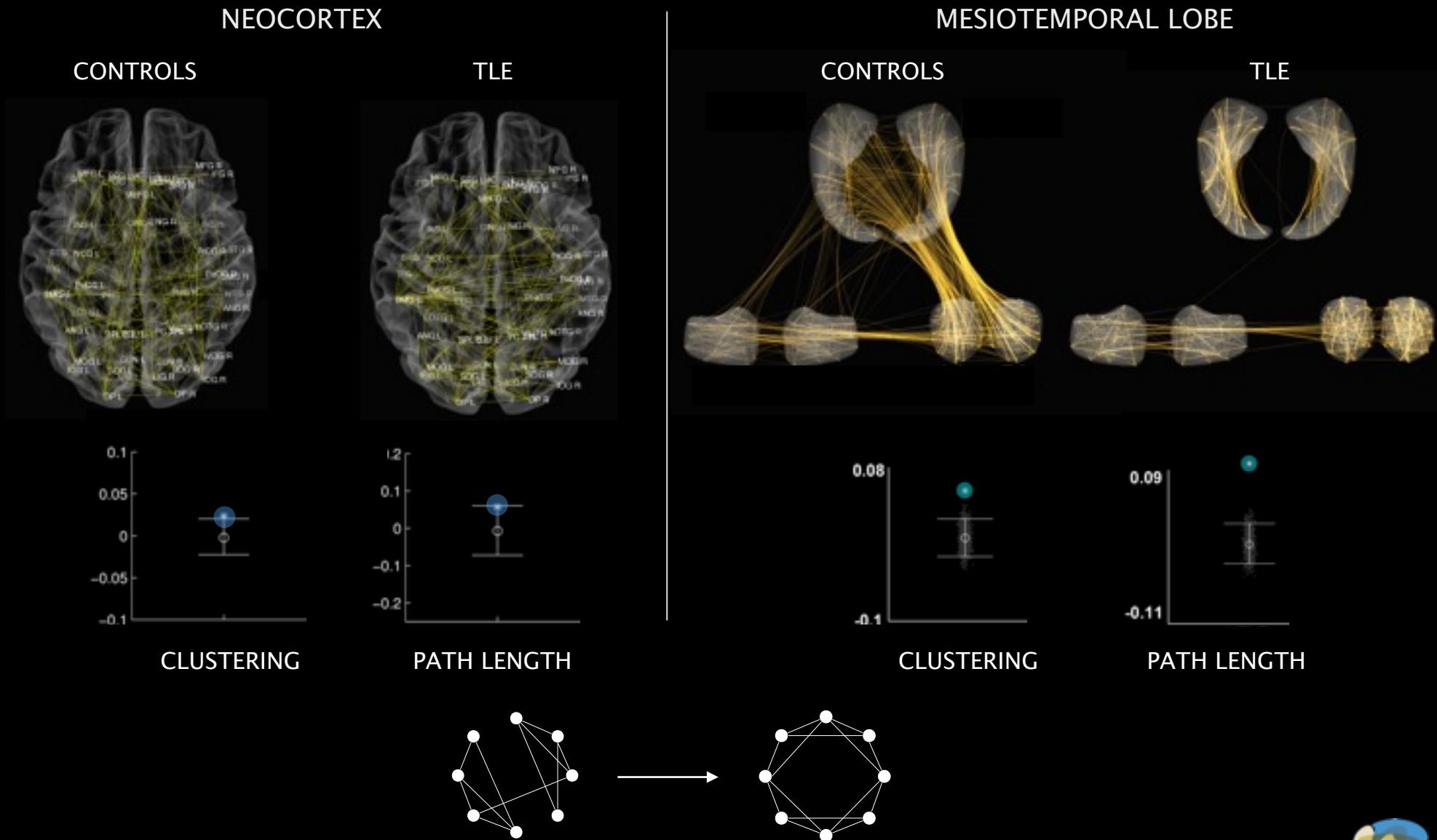


FWE<0.05

Liu*, Bernhardt* (submitted)

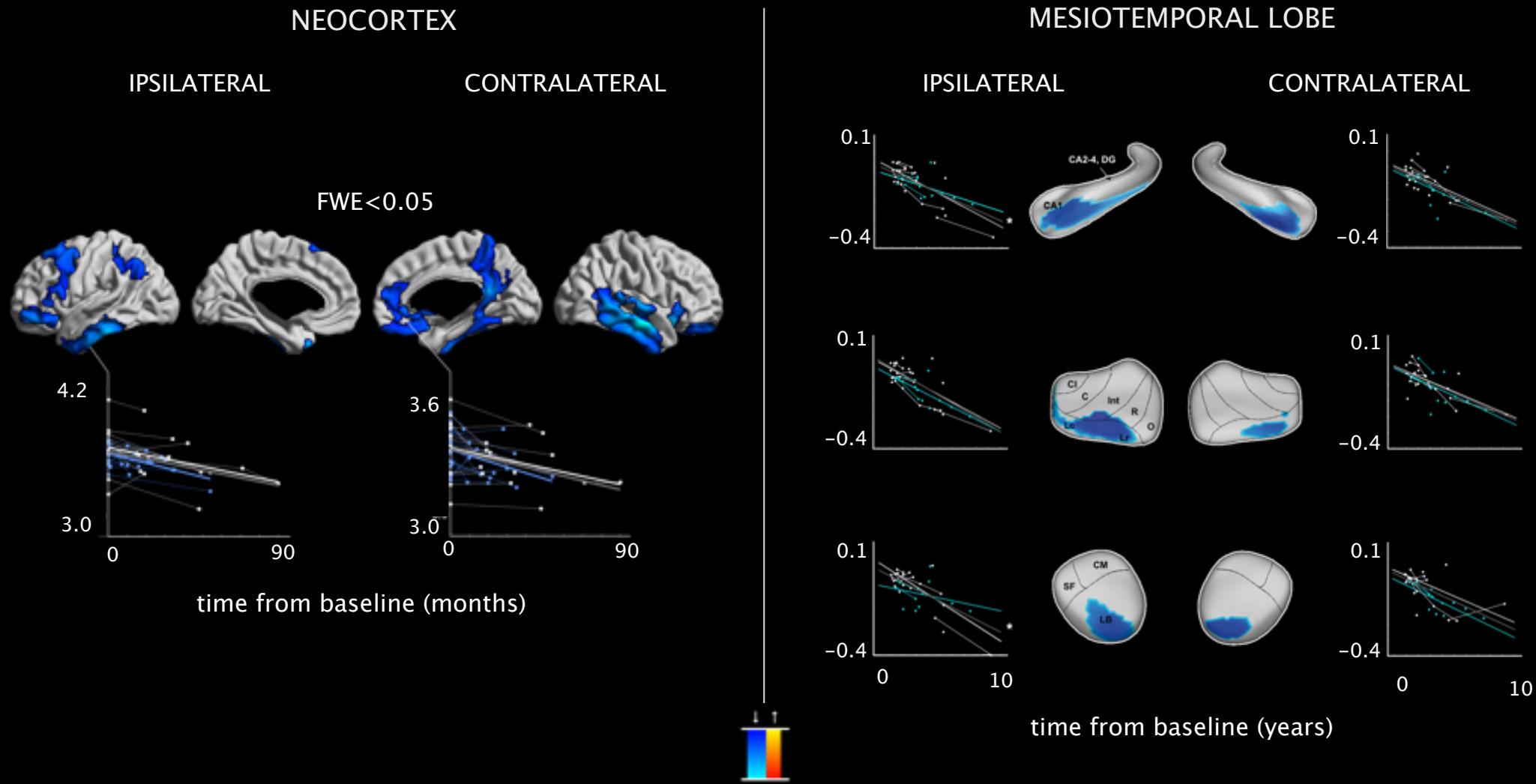


NETWORK-LEVEL PHENOTYPING



IS TLE PROGRESSIVE?

TRACKING CORTICAL DISEASE PROGRESSION



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

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



TRACKING CORTICAL DISEASE PROGRESSION

Cascino (2009) Neurology

EDITORIAL

Temporal lobe epilepsy is a progressive neurologic disorder

Time means neurons!



Gregory D. Cascino,
MD, FAAN

Address correspondence and
reprint requests to Dr. G.D.
Cascino, Mayo Clinic, 200 First
Street SW, Rochester, MN 55905
gcascino@mayo.edu

Neurology® 2009;72:1718–1719

Temporal lobe epilepsy (TLE) is the most common type of partial or localization-related seizure disorder. The amygdala and hippocampus in the medial temporal lobe are important epileptogenic regions, so it is not surprising that in individuals with partial seizures^{1,2} and TLE the most common pathology is medial temporal sclerosis (MTS) with prominent neuronal loss and gliosis in the hippocampus.^{3,4} The high diagnostic yield of MRI as a sensitive and specific indicator of MTS has been confirmed^{2,5}; the most common finding is unilateral hippocampal atrophy with a concordant signal intensity alteration.³

The initial response to antiepileptic drug (AED) therapy in partial epilepsy is highly predictive of long-term outcome, with the most effective AED treatment often being the first or second medications administered.⁶ A recent study found that for those

between the imaging findings and the site of seizure onset. Unfortunately, the duration of epilepsy in patients undergoing surgical treatment is often measured in decades and not years.⁶ This prolonged period of intractability may be associated with progressive psychosocial deprivation, cognitive impairment, and AED adverse effects.

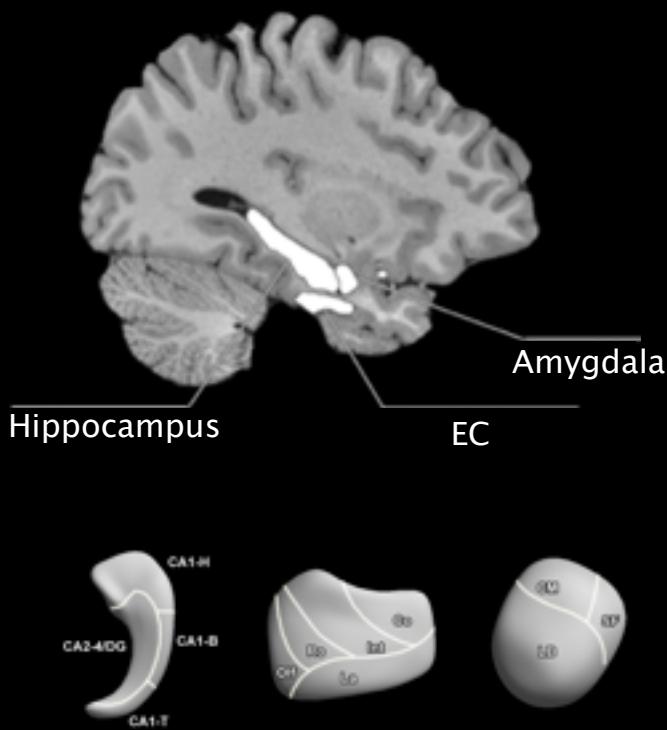
In this issue of *Neurology*®, Bernhardt et al.⁷ evaluated cortical thickness on MRI and revealed that progressive neocortical atrophy occurs in patients with intractable TLE and is correlated with epilepsy duration. A longitudinal analysis was used in 18 patients with a mean interscan interval of 2.5 years (range, 7–90 months). A cross-sectional analysis was performed in 121 patients correlating epilepsy duration and MRI. The longitudinal analysis showed that

CAN MRI PREDICT SURGICAL OUTCOME?

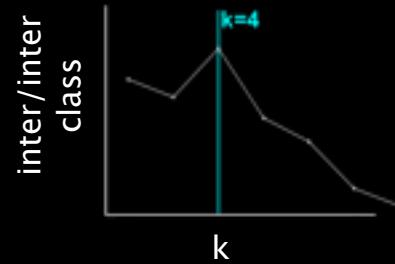
MRI PATTERN LEARNING: DISEASE SUBTYPING AND PROGNOSIS

MESIOTEMPORAL PROFILING

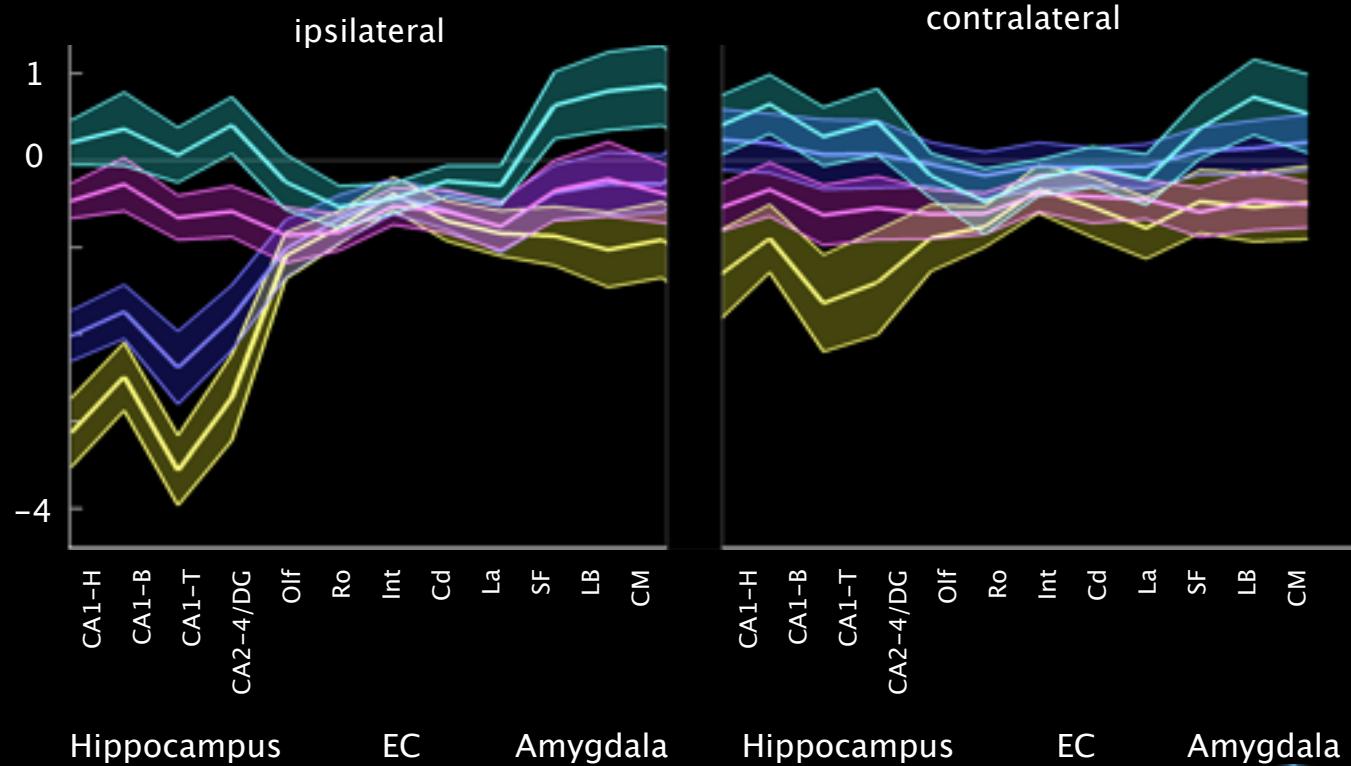
n=114



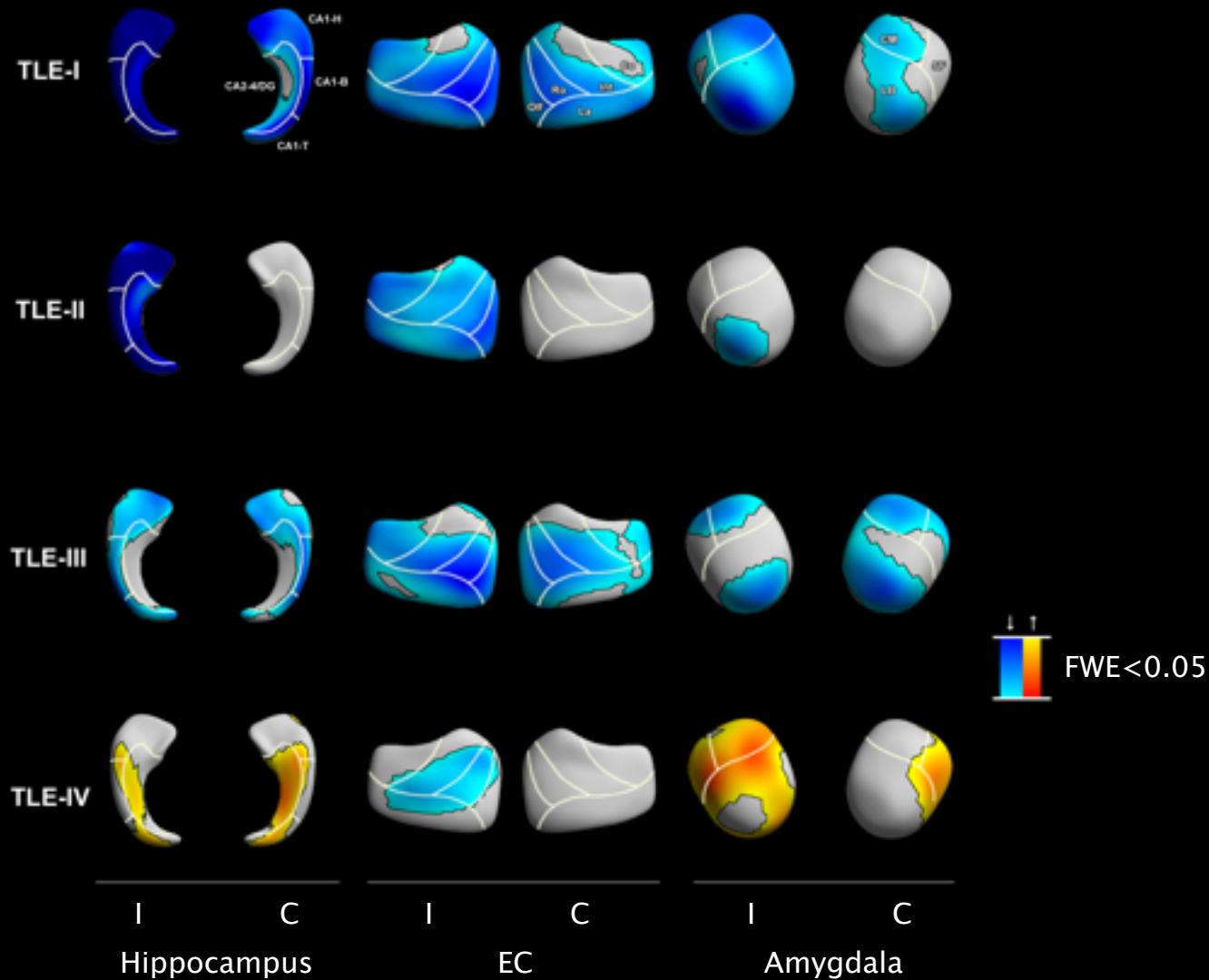
CLUSTERING PATIENT SPECTRUM BASED ON MRI MORPHOMETRY



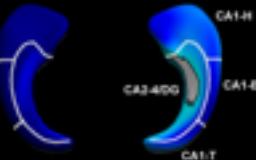
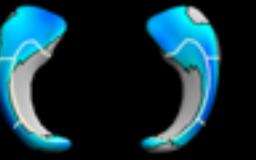
- TLE-I
- TLE-II
- TLE-III
- TLE-IV



DATA-DRIVEN SUBCLASSES



DATA-DRIVEN SUBCLASSES

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

INTERIM SUMMARY: EPILEPSY

PREVALENT NEUROLOGICAL DISORDER WITH INTER-DISCIPLINARY ASSESSMENT

Key role of neuroimaging

Multiple criteria for neuroimaging biomarker validation

ANOMALIES BEYOND HIPPOCAMPUS

Network analysis confirms system-level compromise

Longitudinal studies show progressive atrophy

NEUROIMAGING AS SUBTYPING TOOL

Mesiotemporal subtypes: clinical and pathological divergence

Neuroprognostics: accurate prediction of long-term outcome

AUTISM SPECTRUM CONDITIONS

HIGHLY HETEROGENOUS

CORE DEFICITS
IN SOCIAL COGNITION

UNCLEAR IMAGING PHENOTYPE



PREVIOUS STRUCTURAL MRI WORK

INCONSISTENT DIRECTION AND LOCATION OF FINDINGS

MIXED INCLUSION CRITERIA

VARIABLE AGE RANGES

RELATIVELY SMALL SAMPLES

AVENUES IN THE SEARCH FOR AUTISM PHENOTYPES

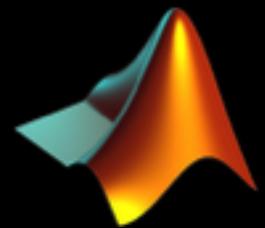
BIG DATA ANALYSIS FOR STRUCTURAL BRAIN ANOMALIES IN AUTISM



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

BIG DATA APPROACHES FOR STRUCTURAL BRAIN ANOMALIES IN AUTISM



download data

select those sites with
children and adults
and ≥ 10 individuals
per diagnostic group

n=342

select only males

n=297

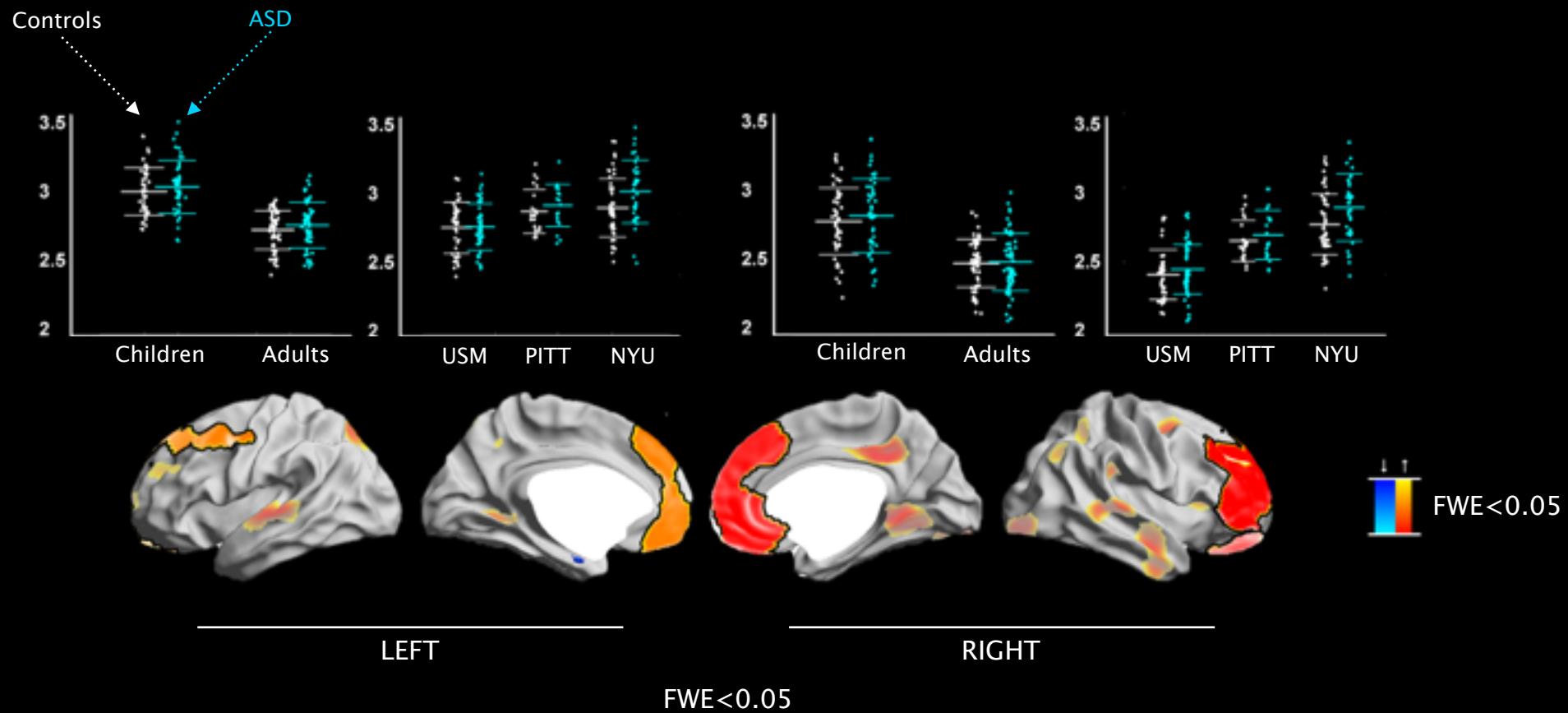
processing

QC

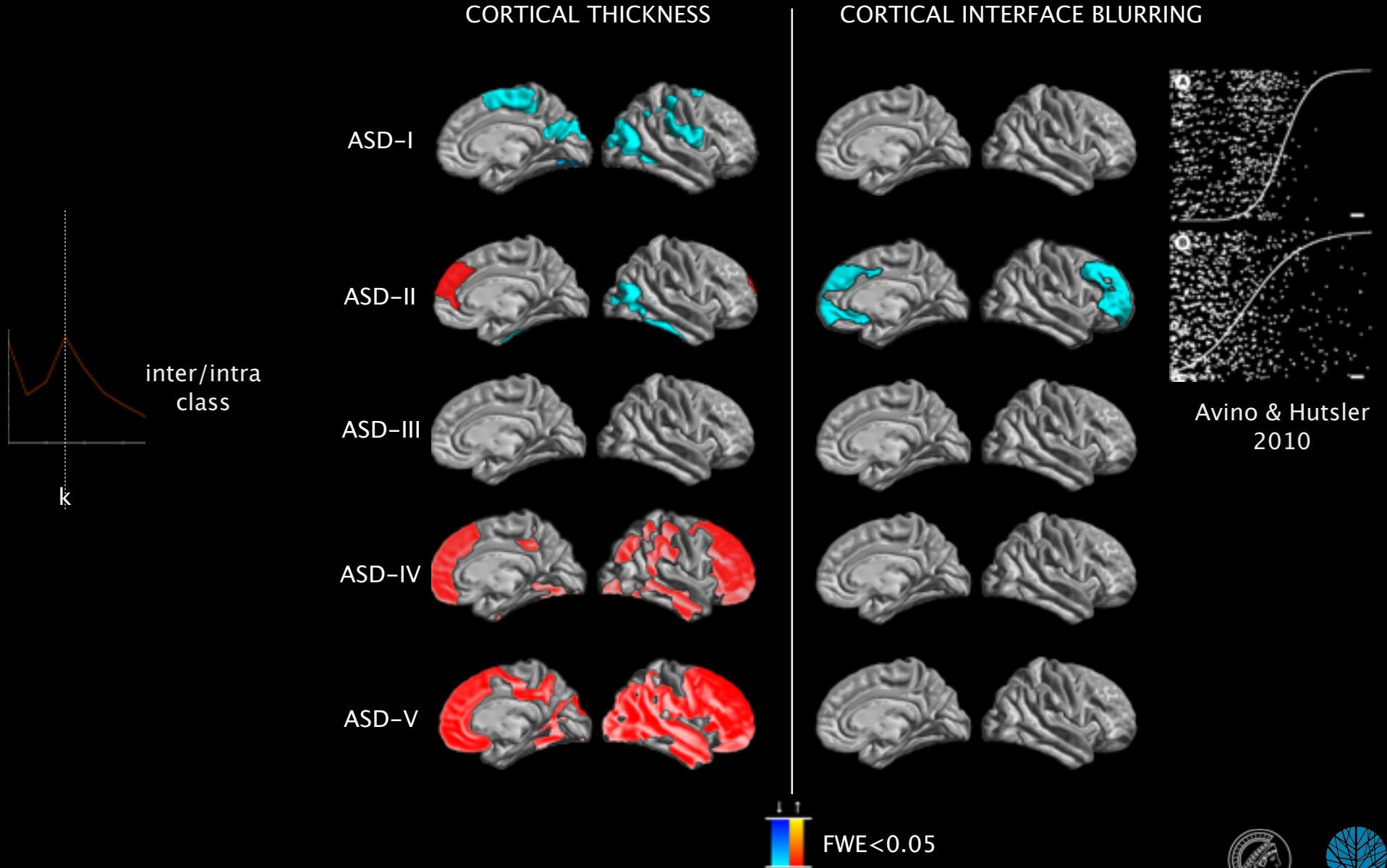
n=220



MULTI-CENTER MAPPING OF STRUCTURAL ALTERATIONS

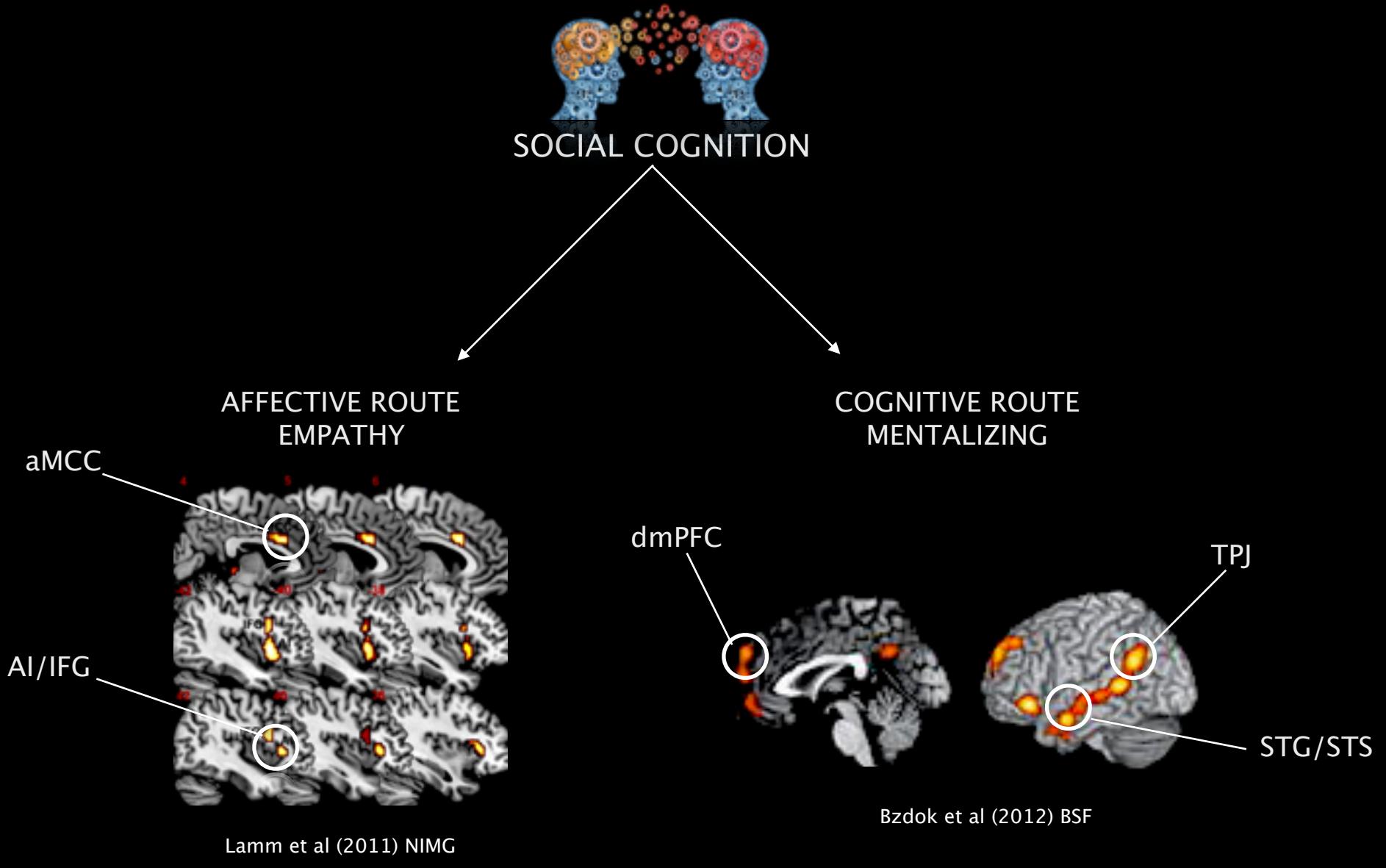


TOWARDS A SUBTYPING OF AUTISM SPECTRUM DISORDERS

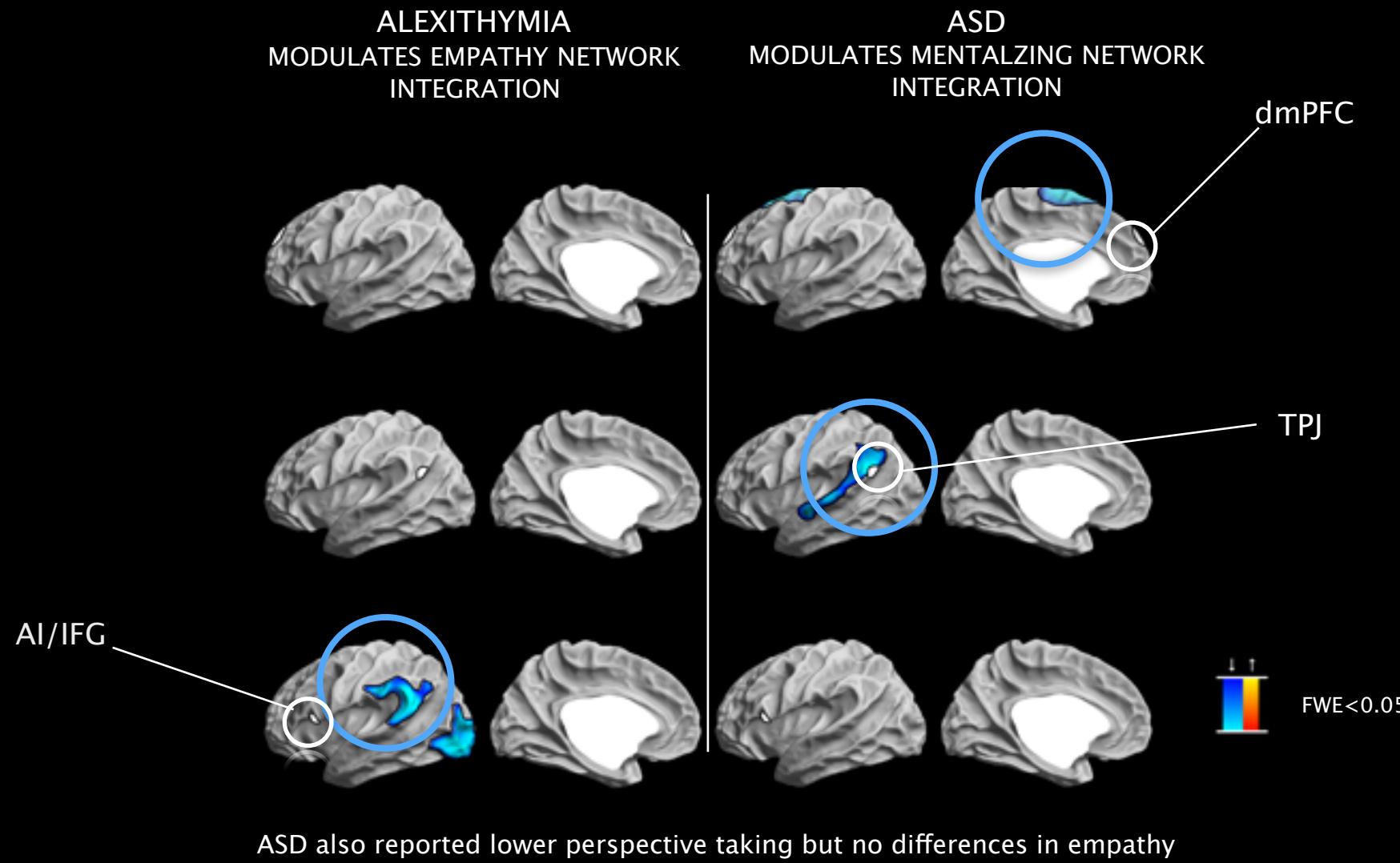


USING AUTISM AS DISEASE MODEL

USING AUTISM AS DISEASE MODEL



USING AUTISM AND ALEXITHYMYIA AS DISEASE MODELS TO PROBE SOCIAL COGNITION NETWORKS



INTERIM SUMMARY: AUTISM

BIG DATA APPROACHES IN AUTISM

Identify commonalities across spectrum and sites

Address heterogeneity through clustering techniques

CORTICAL INTERFACE BLURRING

Migrational anomalies and atypical cortical organization

AUTISM AS DISEASE MODEL TO STUDY SOCIAL COGNITION NETWORKS

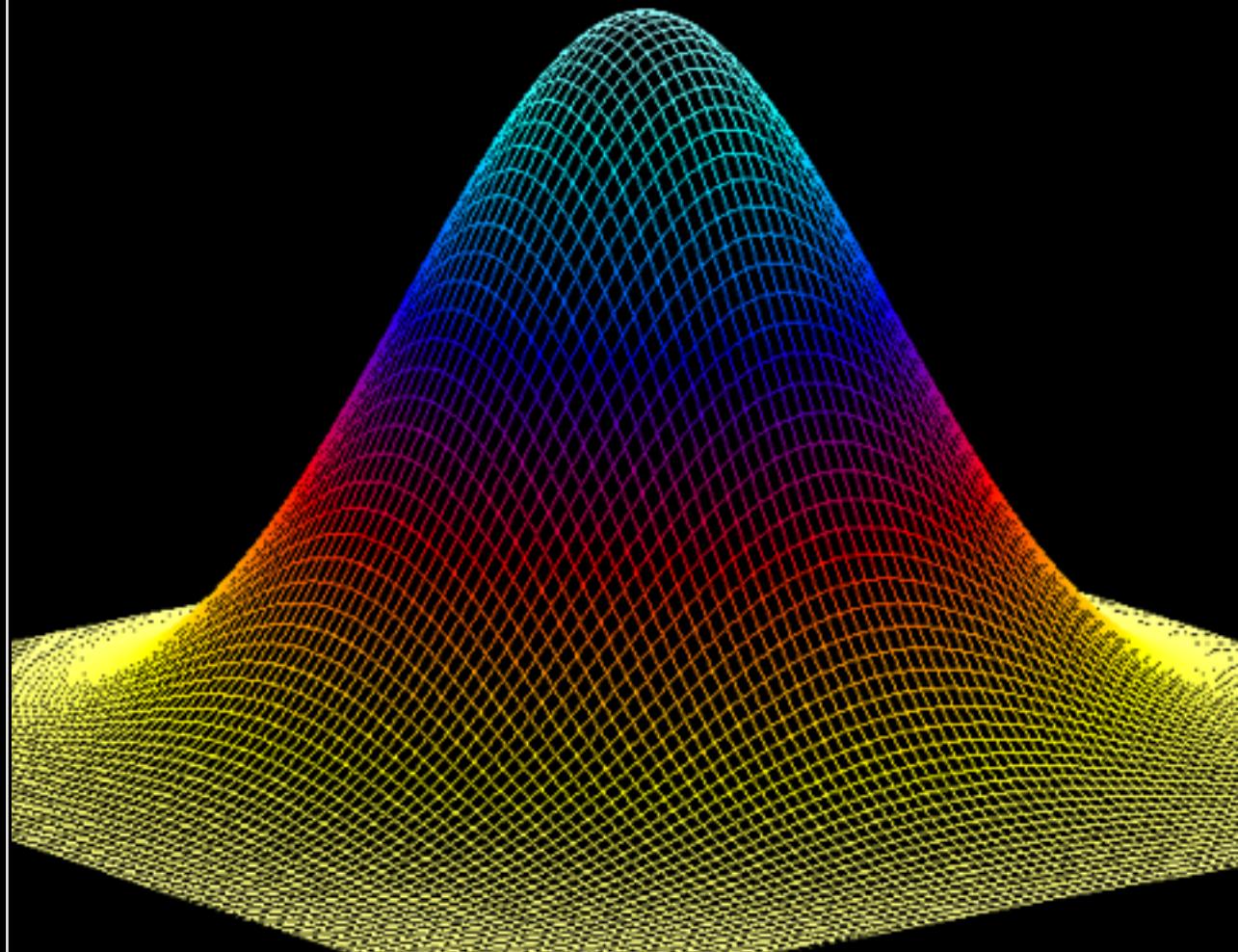
Divergence between socio-affective and socio-cognitive networks

NEURODIVERSITY

DISEASE MODELS CAN EFFECTIVELY
REVEAL RELATIONSHIPS BETWEEN
BRAIN STRUCTURE AND BEHAVIOUR

HIGH VARIABILITY
IN BEHAVIOUR, AFFECT, COGNITION
ALSO PRESENT IN HEALTHY INDIVIDUALS

ACCESS TO LARGE DATASETS:
STUDY BIOLOGICAL
UNDERPINNINGS OF NORMAL VARIABILITY



THE RESOURCE PROJECT

LARGE SCALE STUDY (n=331)

CROSS-SECTIONAL AND LONGITUDINAL:
5 TIME POINTS OVER 12 MONTHS

>80 MEASURES PER TIME POINT:
COGNITIVE/AFFECTIVE PHENOTYPING

BLOOD, HAIR, SALIVA MARKERS:
CORTISOL, CYTOKINES, GENES

MULTI-MODAL 3T NEUROIMAGING

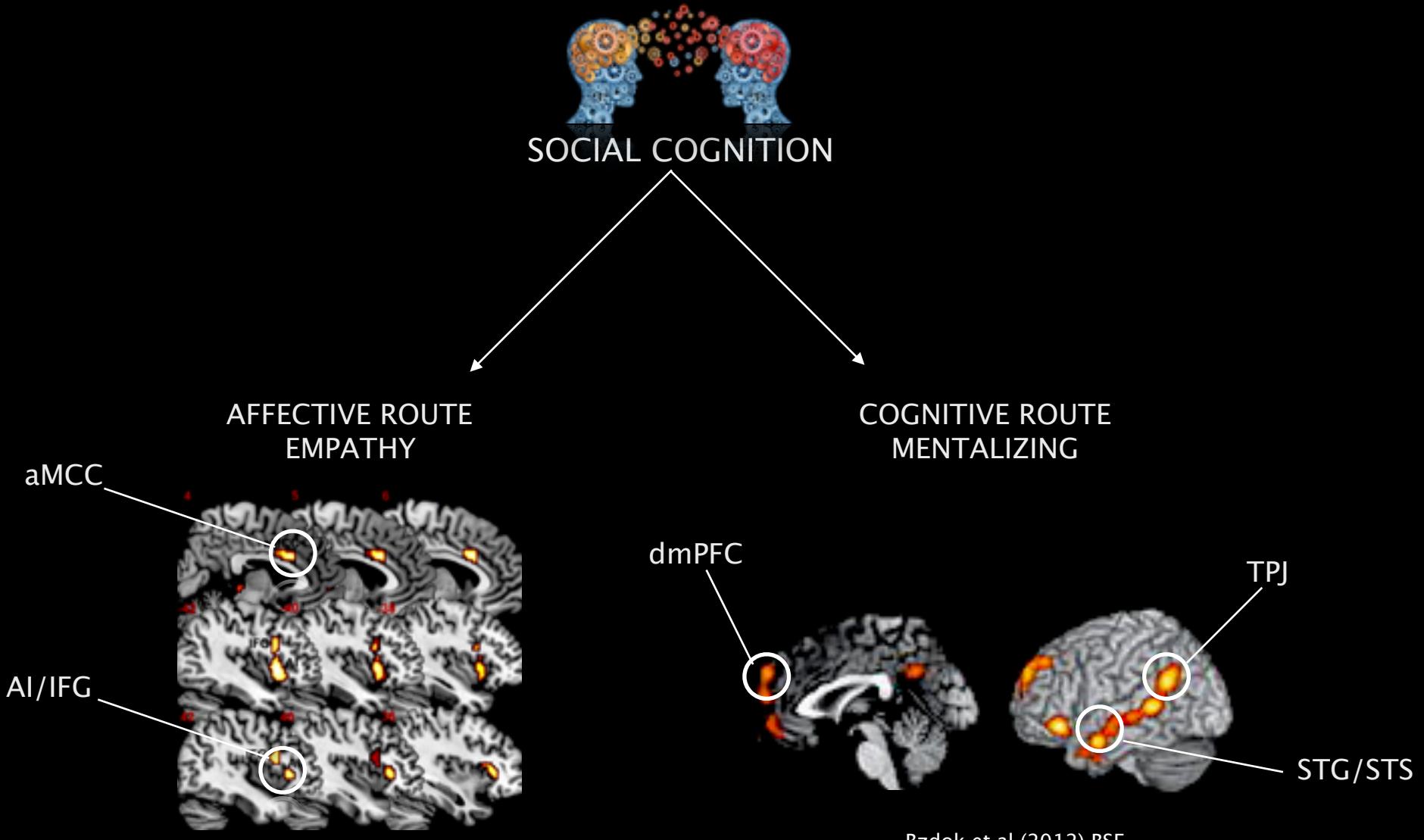
BASELINE DATA ANALYSIS:
NEURODIVERSITY ASSESSMENT



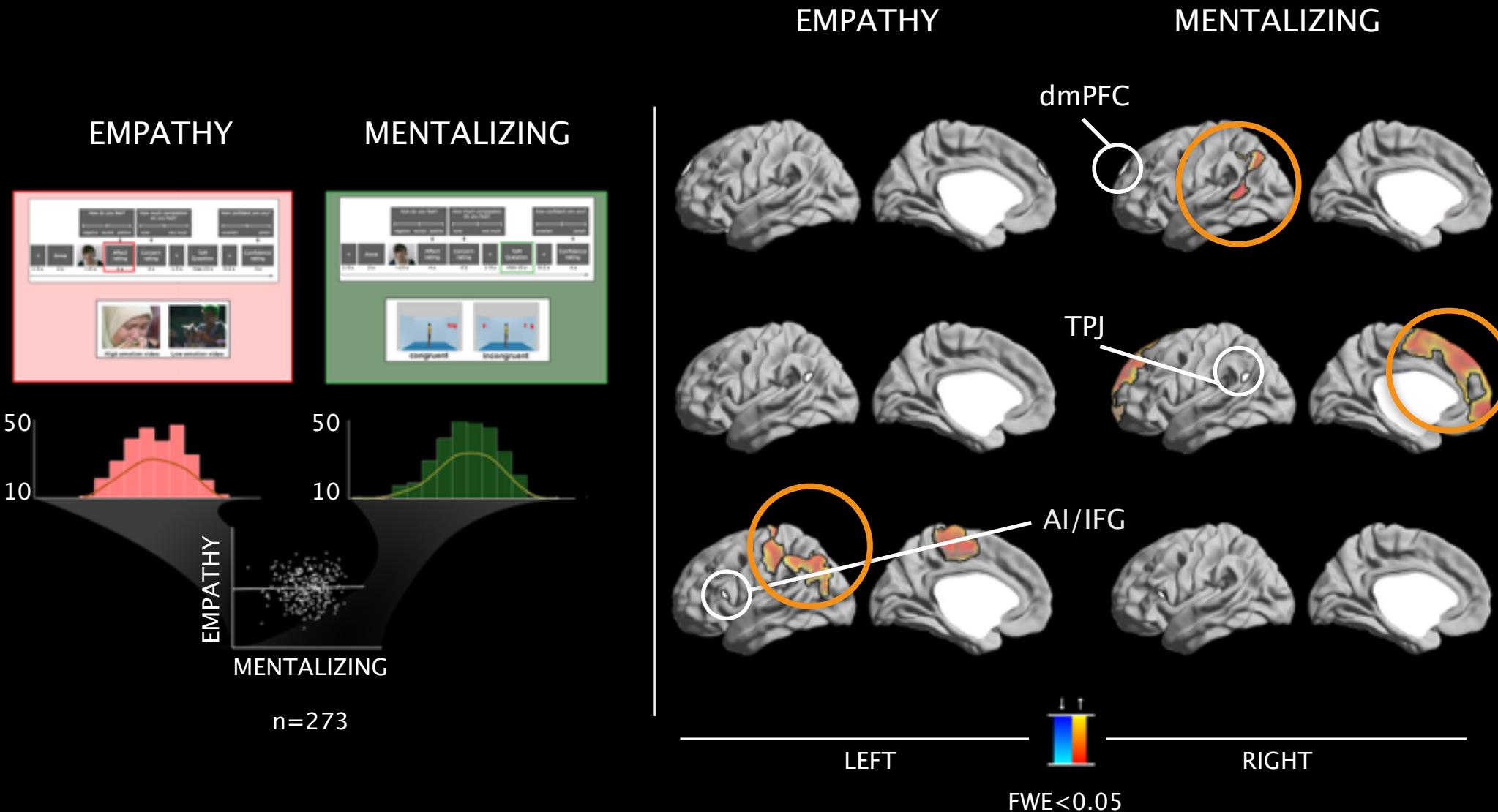
The ReSource Project



USING AUTISM AS DISEASE MODEL



PHENOTYPING SOCIO-COGNITIVE NETWORKS: CROSS-SECTIONAL EVIDENCE



PRIVATE COGNITION

COGNITION MAY ALSO OPERATE
INDEPENDENT FROM INPUTS

MW CAN DERAIL PERFORMANCE
YET, POSSIBLE ADAPTIVE VALUE

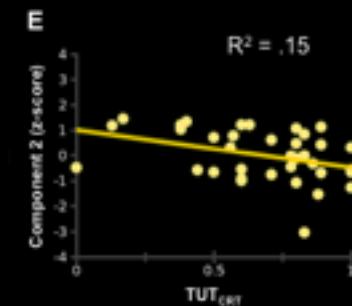
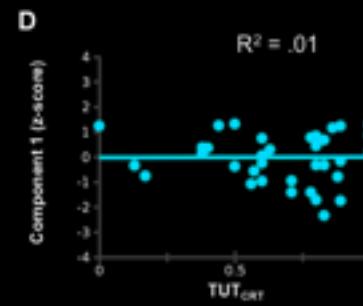
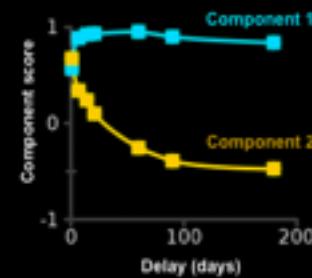
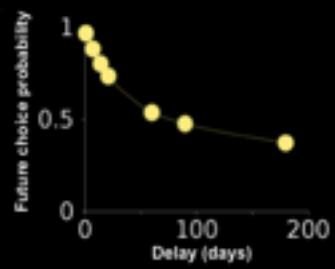
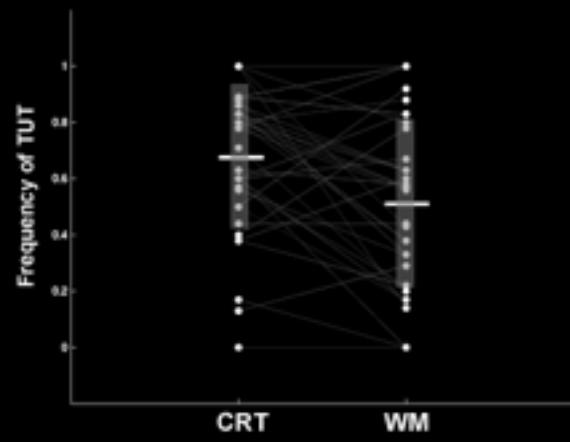
FUNCTIONAL STUDIES RELATED
MIND WANDERING TO MPFC PROCESSING

STRUCTURAL SUBSTRATES
NOT WELL UNDERSTOOD



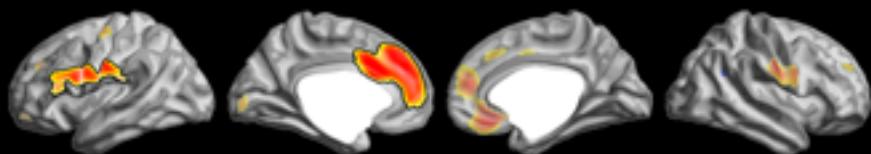
UNIVERSITY of York

MIND WANDERING AND PATIENT DECISION MAKING

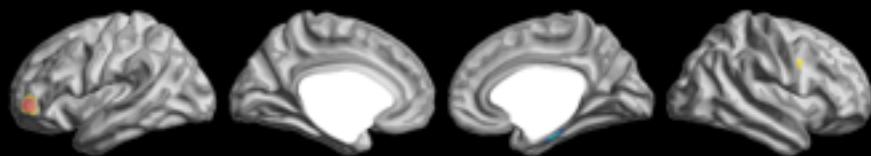


SUBSTRATES OF TUT

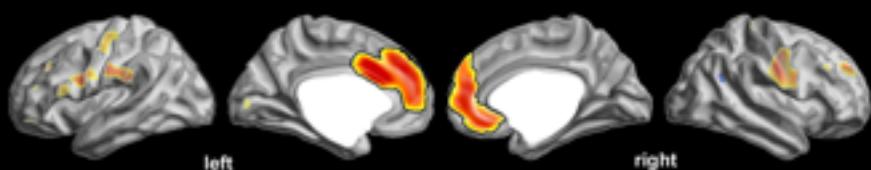
A Effects of TUT_{CRT}



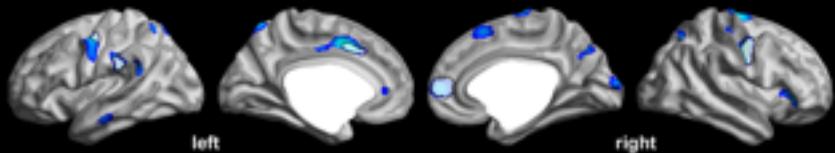
B Effects of TUT_{WM}



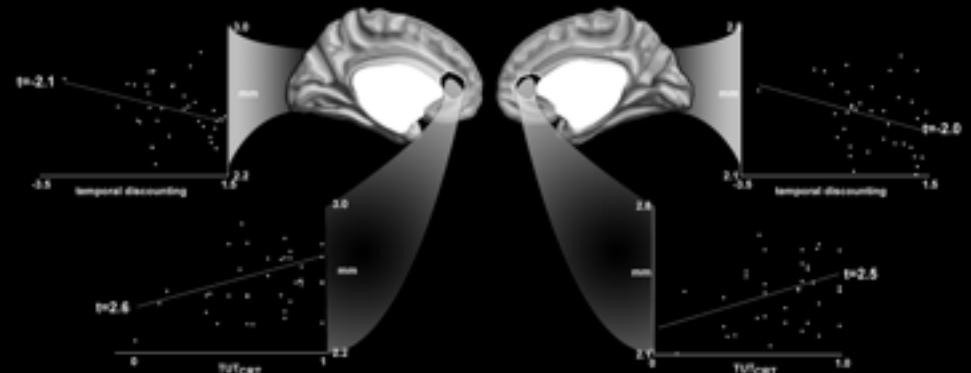
C Effects of TUT_{CRT} controlled for TUT_{WM}



A Whole brain analysis: Effects of TD (blue) and overlap with $TUT-CRT$ (white)



B Region-of-interest analysis: Kable and Glimcher (2007)



C Region-of-interest analysis: effects of TD in clusters of $TUT-CRT$ findings



NEUROIMAGING
MODELLING
MACHINE LEARNING

COGNITIVE AND AFFECTIVE
PHENOTYPING
BLOOD, HAIR, SALIVA

CLINICAL INFORMATION
PATHOLOGY
OUTCOME

NEURODIVERSITY BRAIN DISORDERS

SUBTYPING
PREDICTION
VALIDATION



Andrea Bernasconi
Neda Bernasconi
Epilepsy Group

Terry Peters
Maged Goubran
Ali Khan

Uta Frith
Giorgia Silani
Geoffrey Bird

Jonathan Smallwood
Florence Ruby
Beth Jeffreys

Michael Milham
Adiana di Martino
INDI

Carrie McDonald
Nob Kemmotusu

Tania Singer
Sofie Valk
Anne Boeckler
Philipp Kanske
Mathis Trautwein

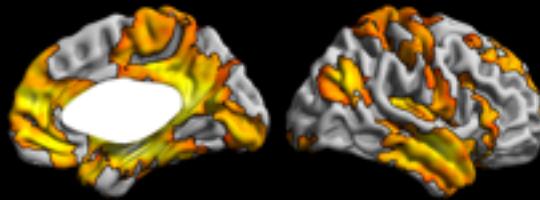
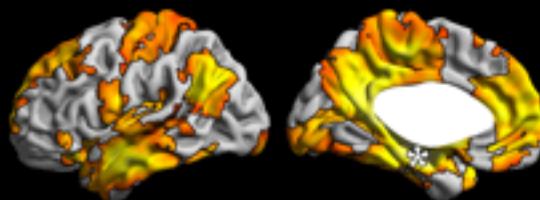
Alan Evans
Jean Paul Soucy
Louis Collins
Felix Carbonell
Seok-Jun Hong
Min Liu
Benoit Caldairou

Sylvie Neubert
Sandra Zurborg
Haakon Engen

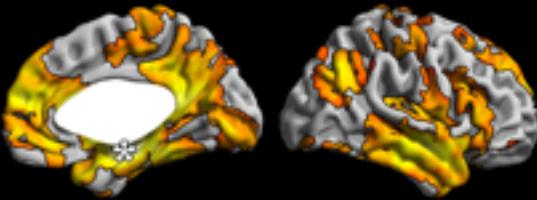
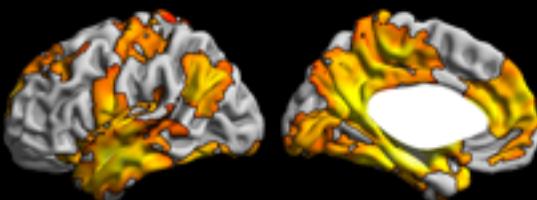


WIDESPREAD HIPPOCAMPAL FUNCTION

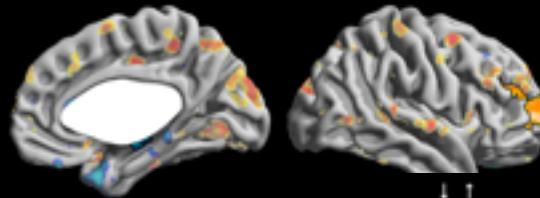
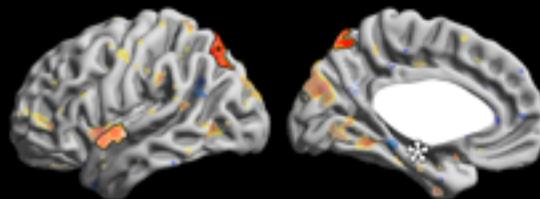
LEFT



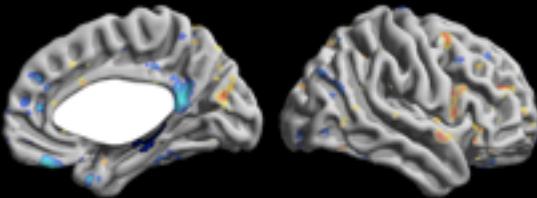
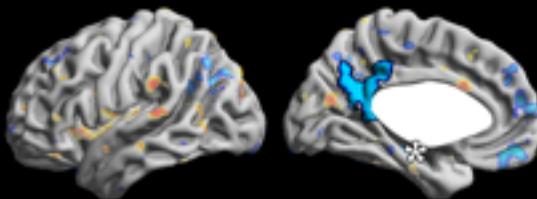
RIGHT



GLIOSIS



HS



FWE<0.05

Bernhardt et al. (in preparation)

