

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

Boris Bernhardt, PhD

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

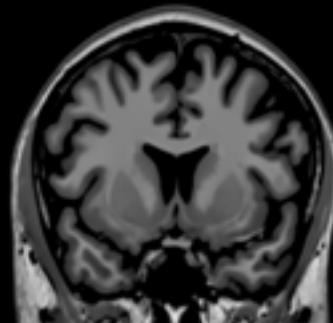
NEUROIMAGING SIGNATURES
OF AUTISM SPECTRUM DISORDERS

NEURODIVERSITY
IN HEALTHY AND DISEASED POPULATIONS

FUTURE RESEARCH DIRECTIONS

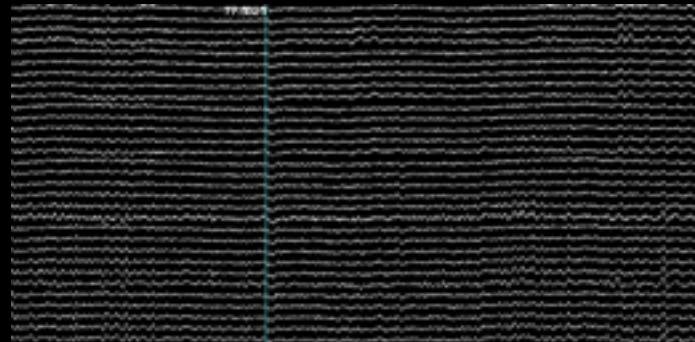
MULTIPLE NEUROIMAGING MODALITIES

MRI



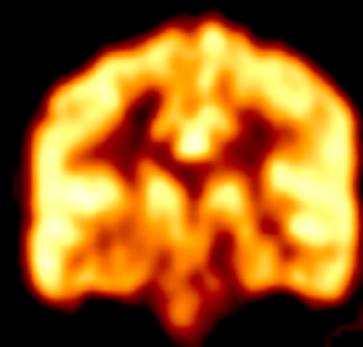
STRUCTURE
FUNCTION

MEG/EEG



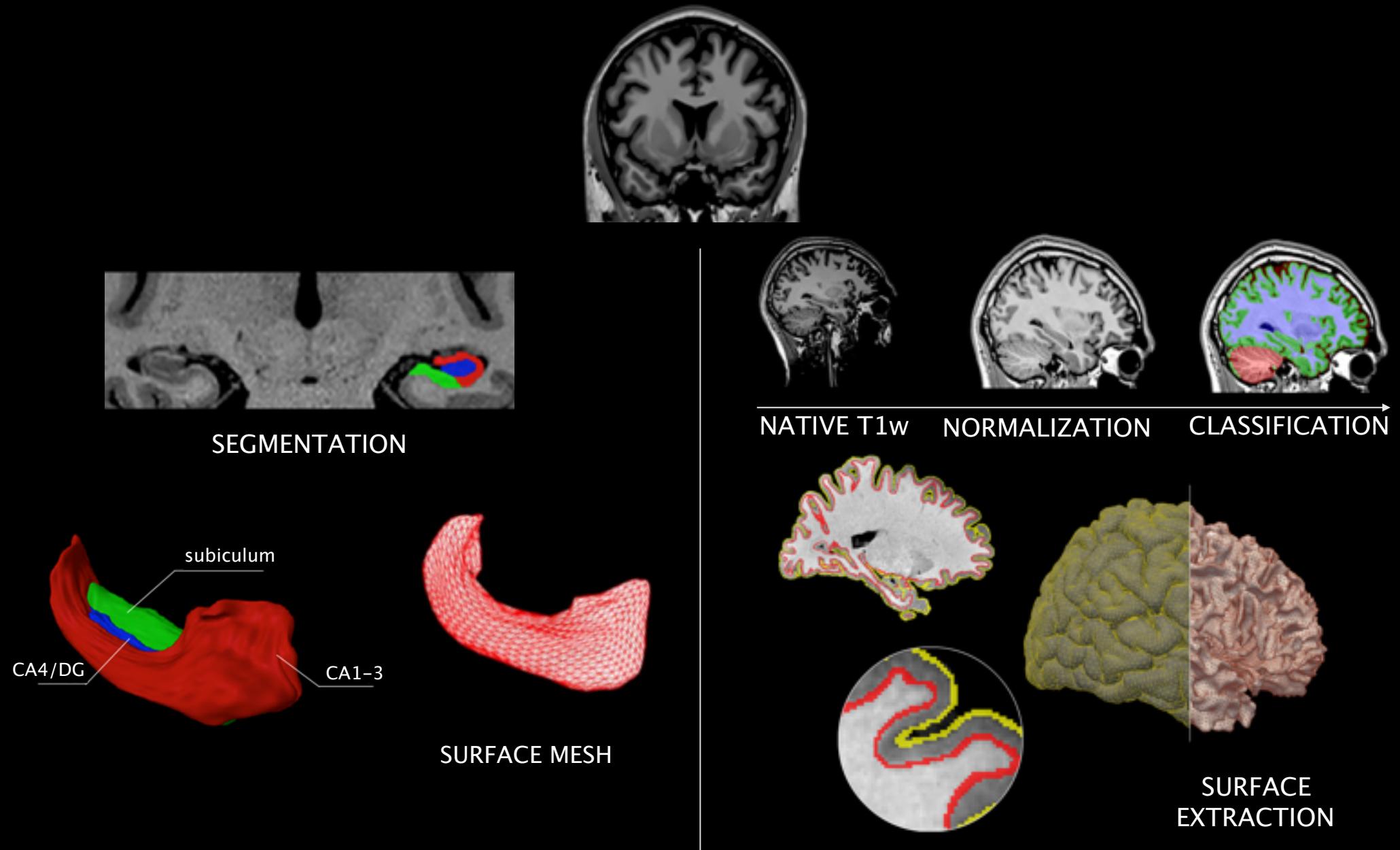
DYNAMICS

PET

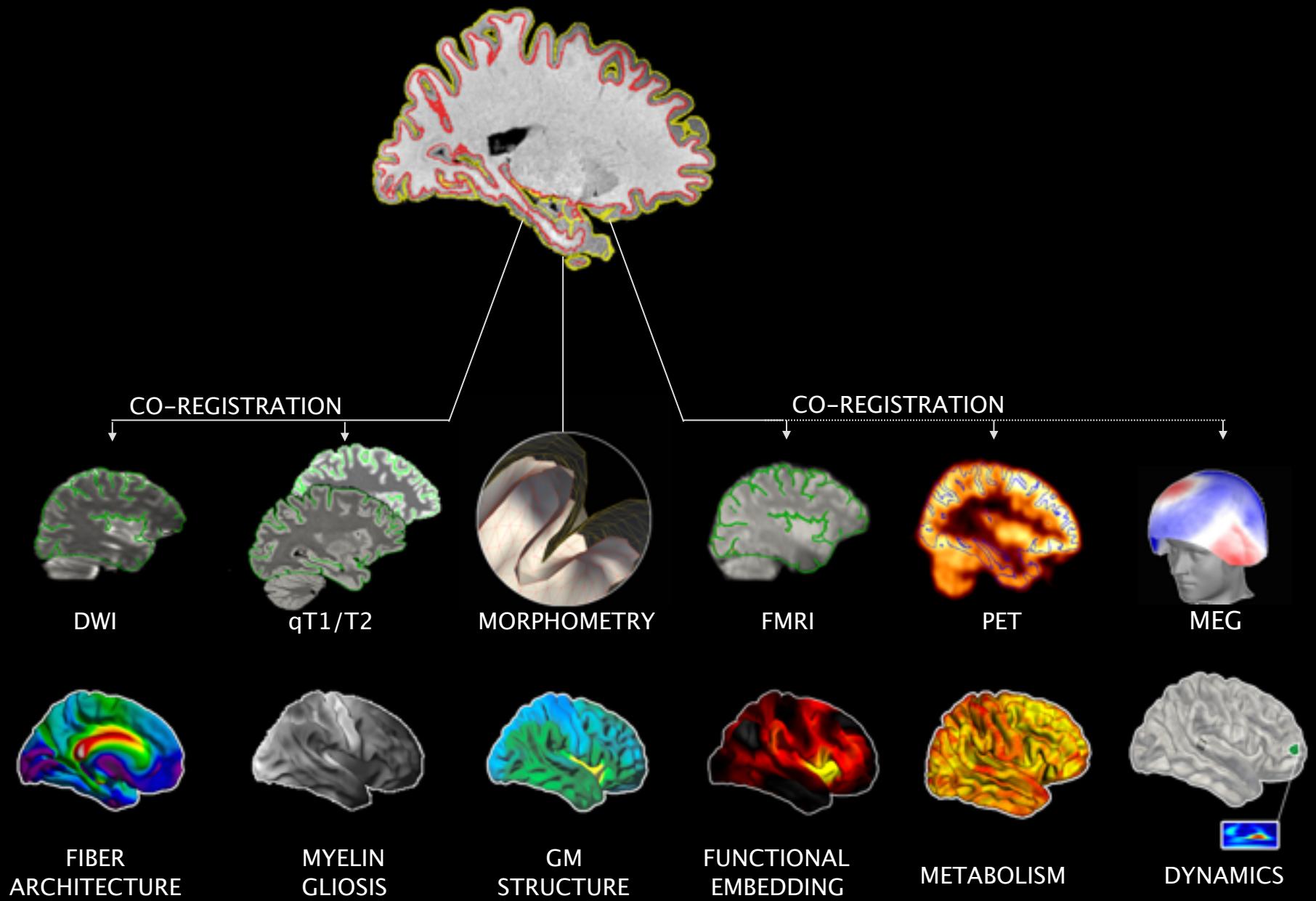


METABOLISM

DESCRIBING ANATOMY

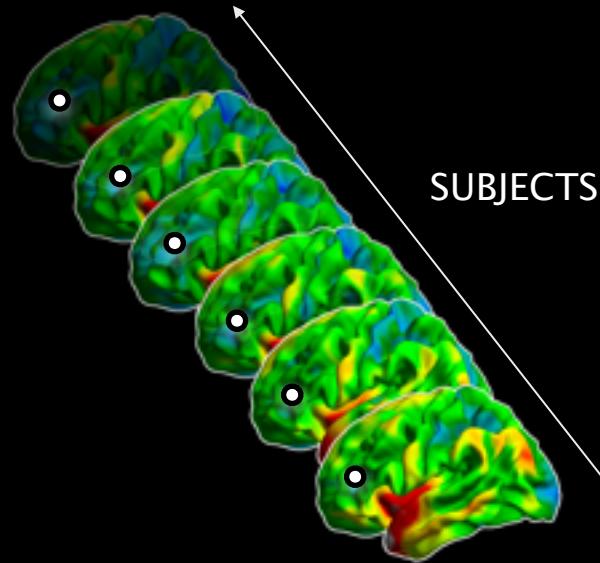


MULTI-MARKER INTEGRATION

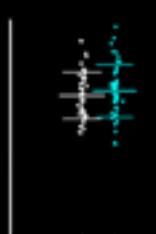


REGIONAL STATISTICAL ANALYSIS

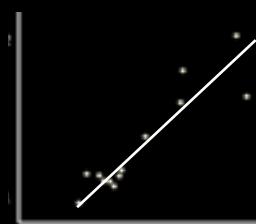
CROSS-SECTIONAL ANALYSES



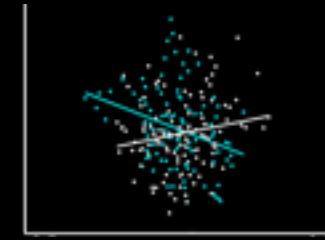
SUBJECTS



$$Y = 1 + G$$

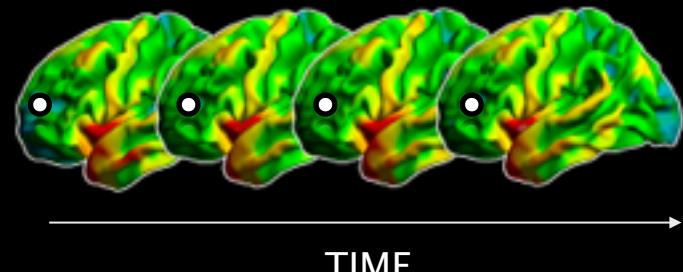


$$Y = 1 + A$$

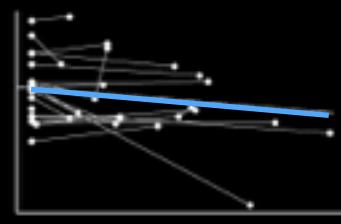


$$Y = 1 + G + A + G \times A$$

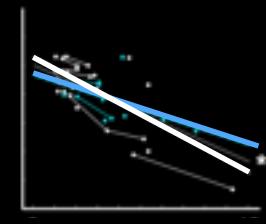
LONGITUDINAL ASSESSMENTS



TIME



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

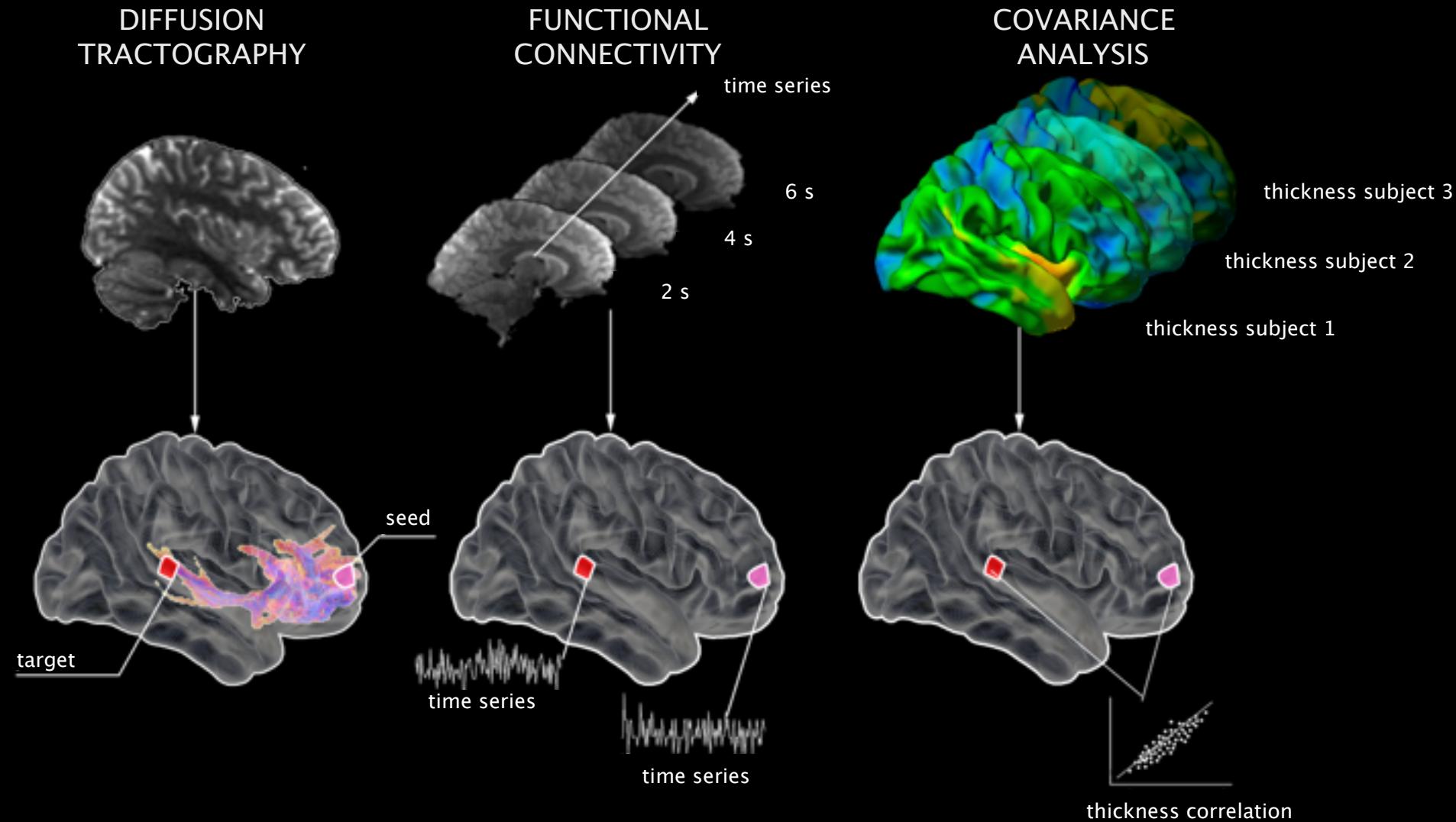


$$Y = 1 + ISI$$

Y is univariate or multivariate data

NETWORK-LEVEL ANALYSIS

SEED-BASED ANALYSIS

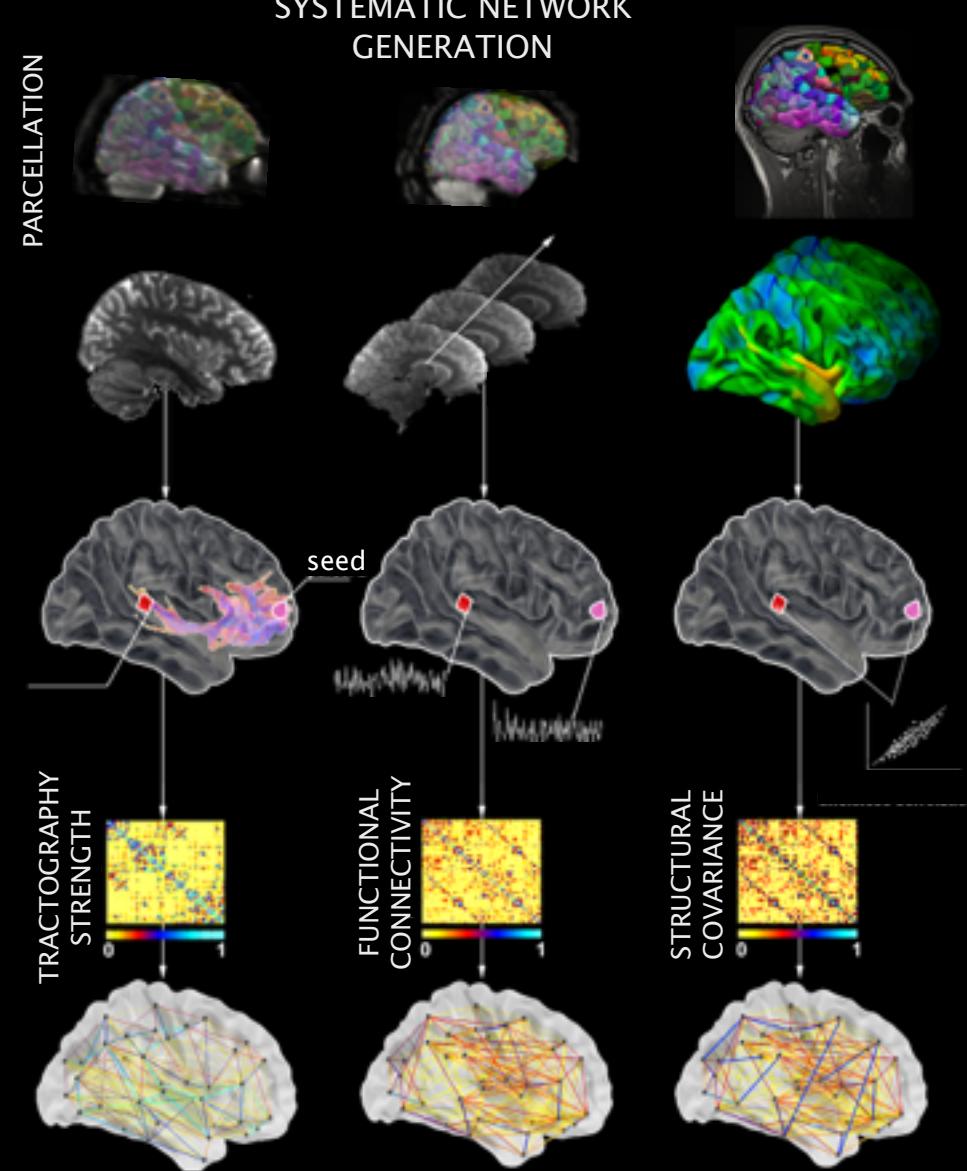


Mori et al. (1999) Ann Neu
Behrens et al. (2007) NIMG

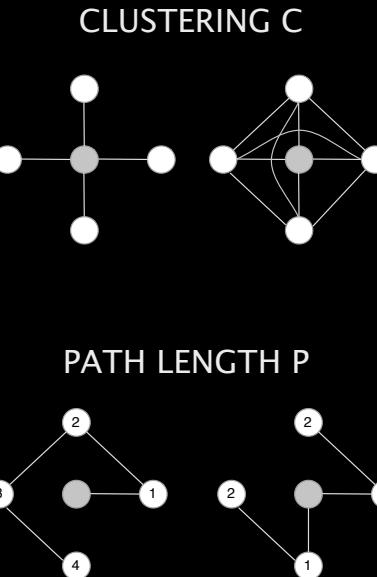
Friston (1994) HBM
Smith (2012) NIMG

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

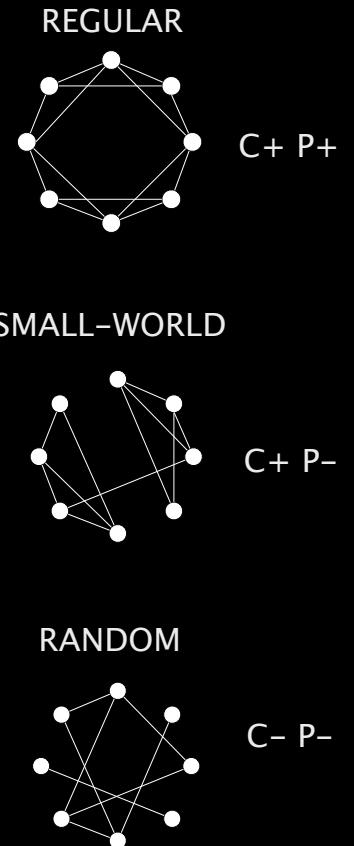
NETWORK-LEVEL ANALYSIS



GRAPH THEORETICAL PARAMETERS

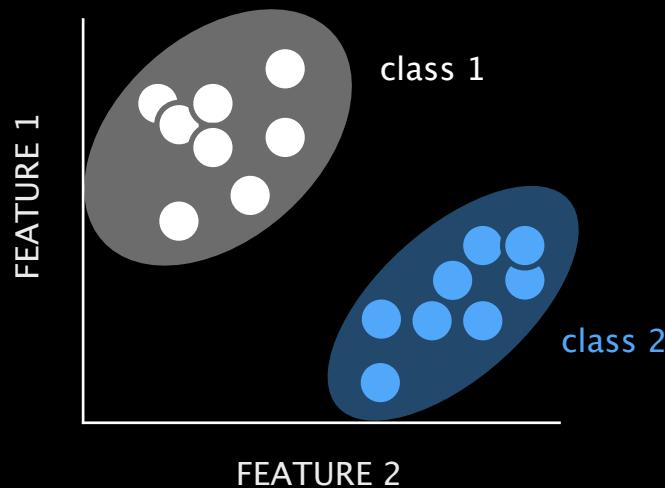


TOPOLOGY CLASSIFICATION



PATTERN LEARNING

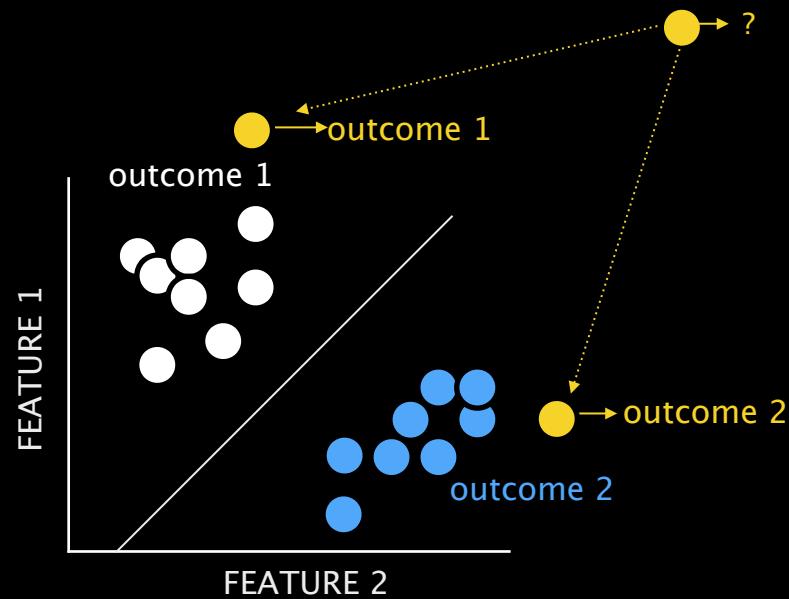
UNSUPERVISED



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



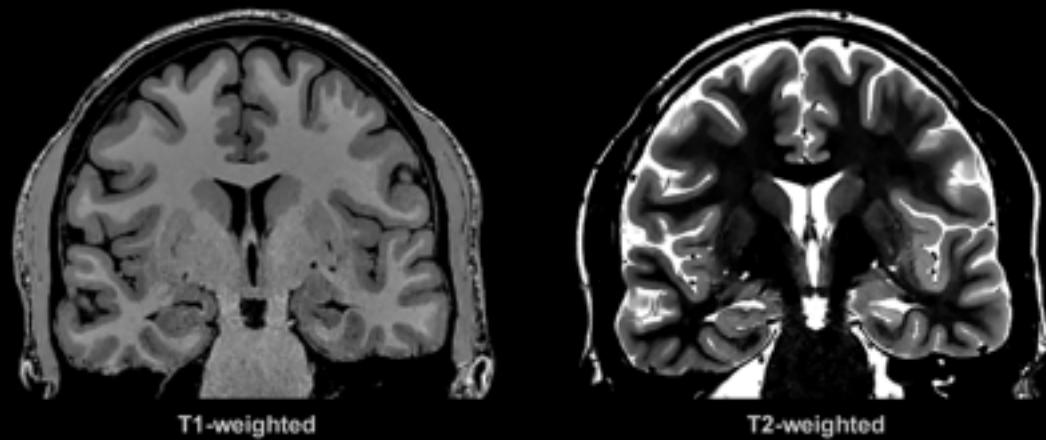
THE CASE OF TEMPORAL LOBE EPILEPSY

Most common drug-resistant epilepsy in adults

Pathological hallmark: hippocampal sclerosis, lateralizes with focus

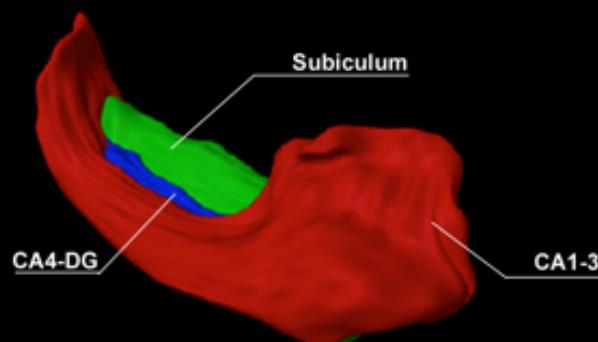
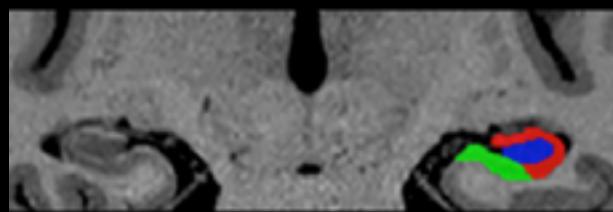
Clinical and research attention paid to hippocampus

MRI plays important role in detecting HS



QUANTITATIVE IMAGING IN THE HIPPOCAMPUS

SEGMENTATION

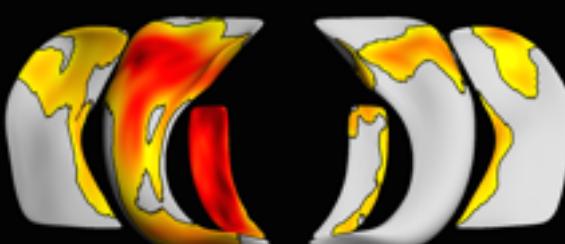


UNIVARIATE

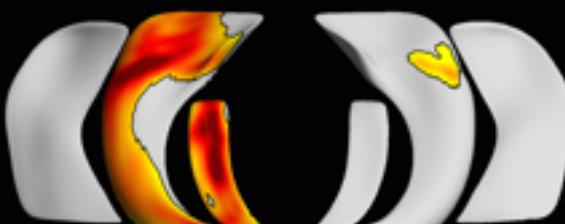
↓VOL



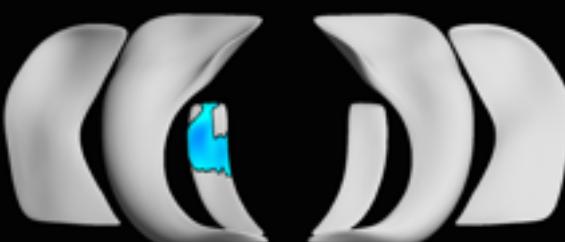
↑T2



↑MD

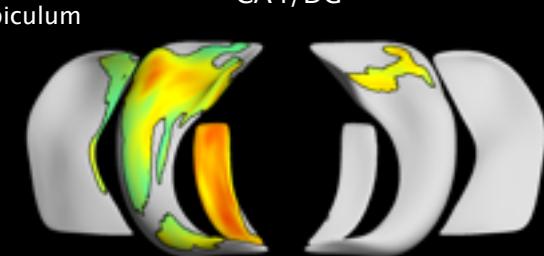


↓FA

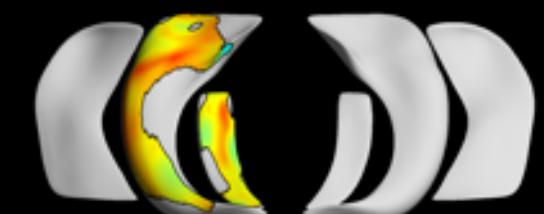


MULTIVARIATE

CA1-3
subiculum



CA4/DG



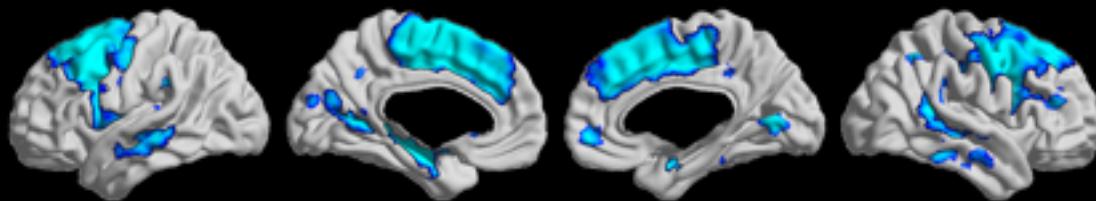
SVM-based
focus lateralization
with 100% accuracy
possible

FWE<0.05

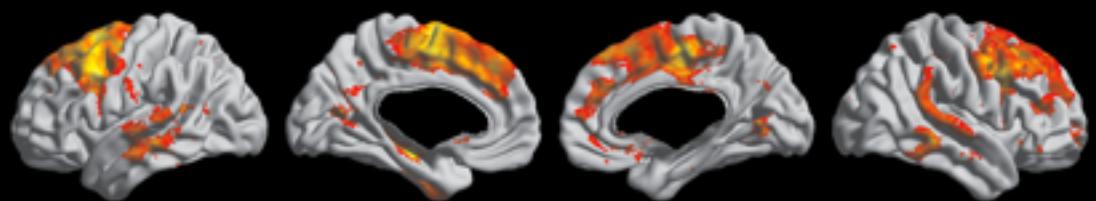
IS TLE A HIPPOCAMPAL DISORDER?

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

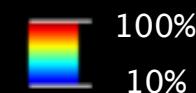
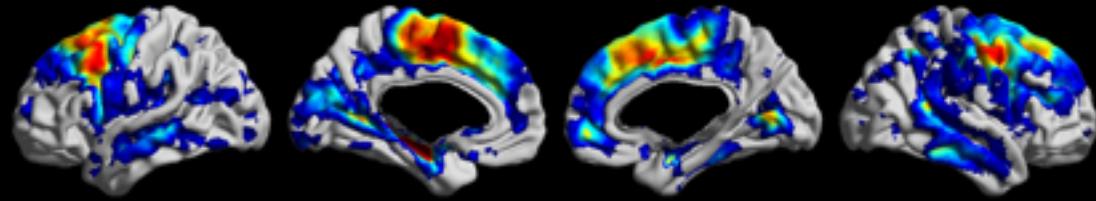
GROUP-LEVEL
THINNING AT 1.5T



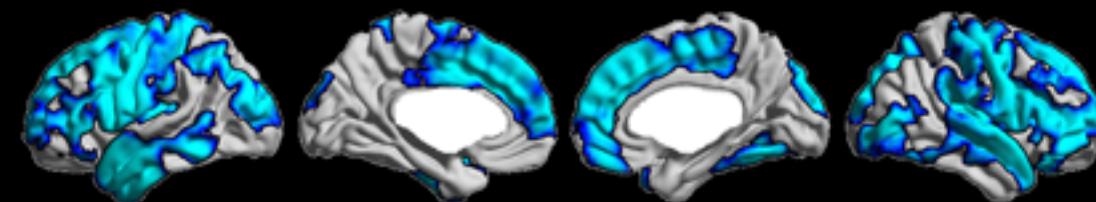
INDIVIDUALIZED
PREVALENCE



BOOTSTRAP
REPRODUCIBILITY



THINNING IN
3T COHORT

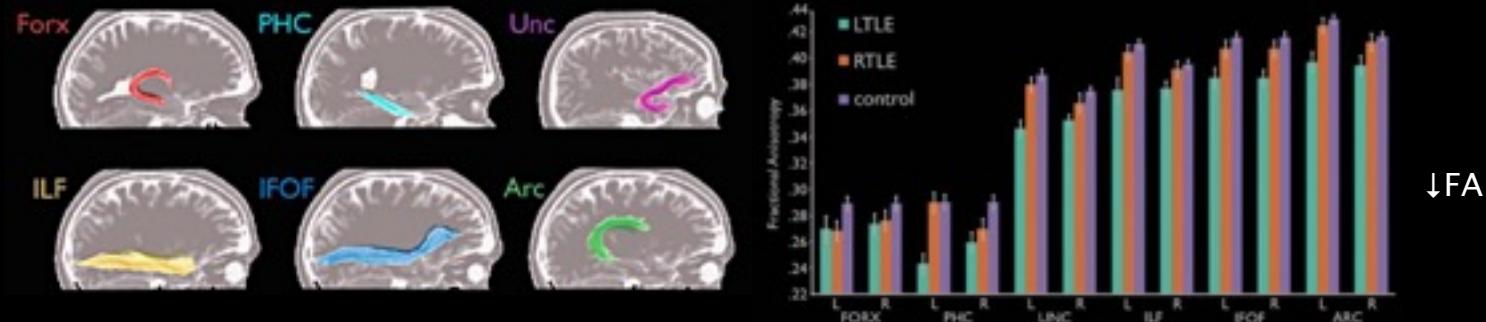


IPSILATERAL

CONTRALATERAL

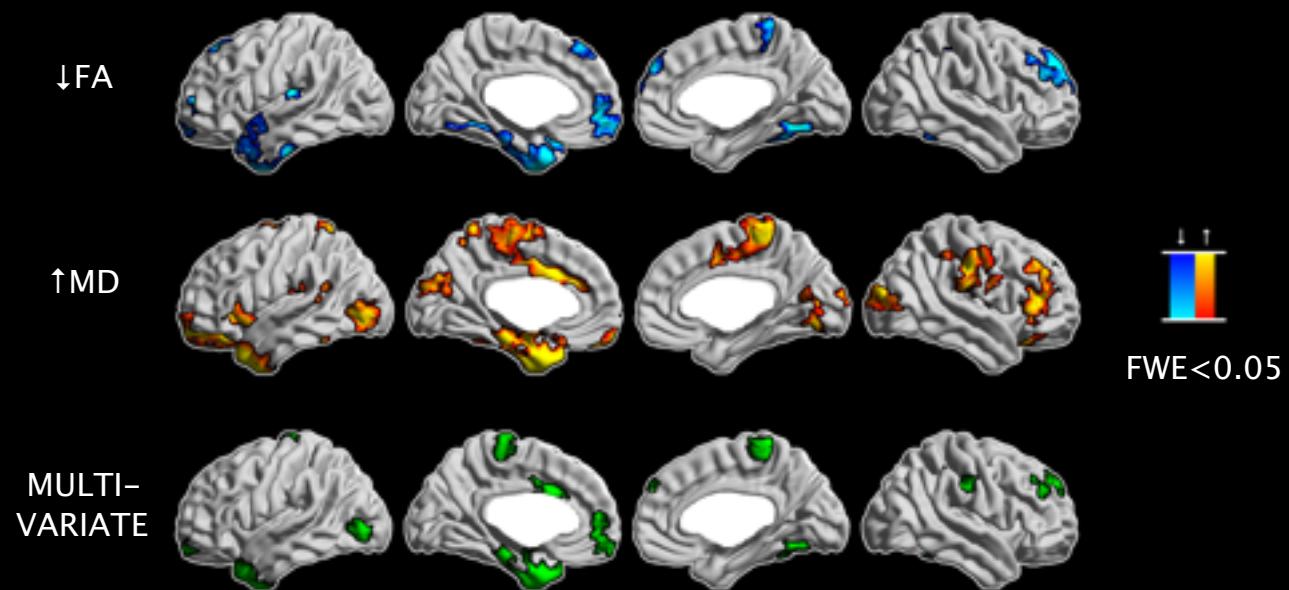
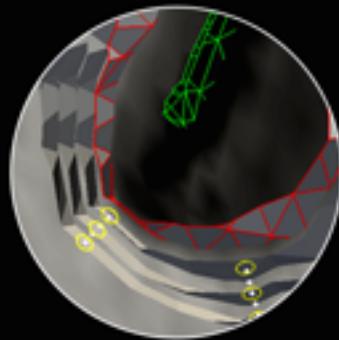
WHOLE-BRAIN PHENOTYPING OF TLE: WHITE MATTER AND FUNCTIONAL ALTERATIONS

TRACTOGRAPHY-
BASED WM BUNDLE
ANALYSIS

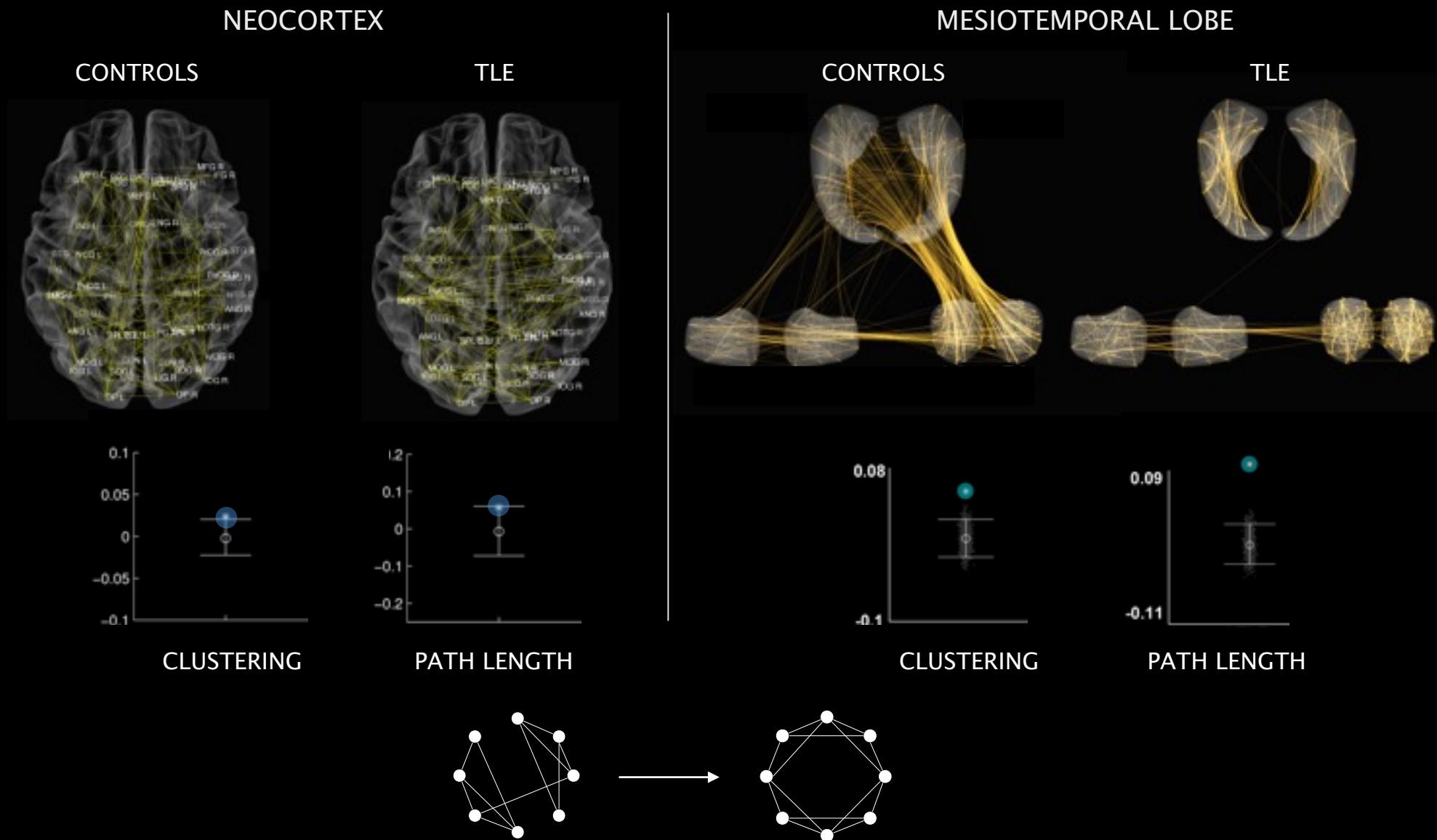


UC San Diego

SURFACE-BASED
WM SAMPLING
[2MM DEPTH]

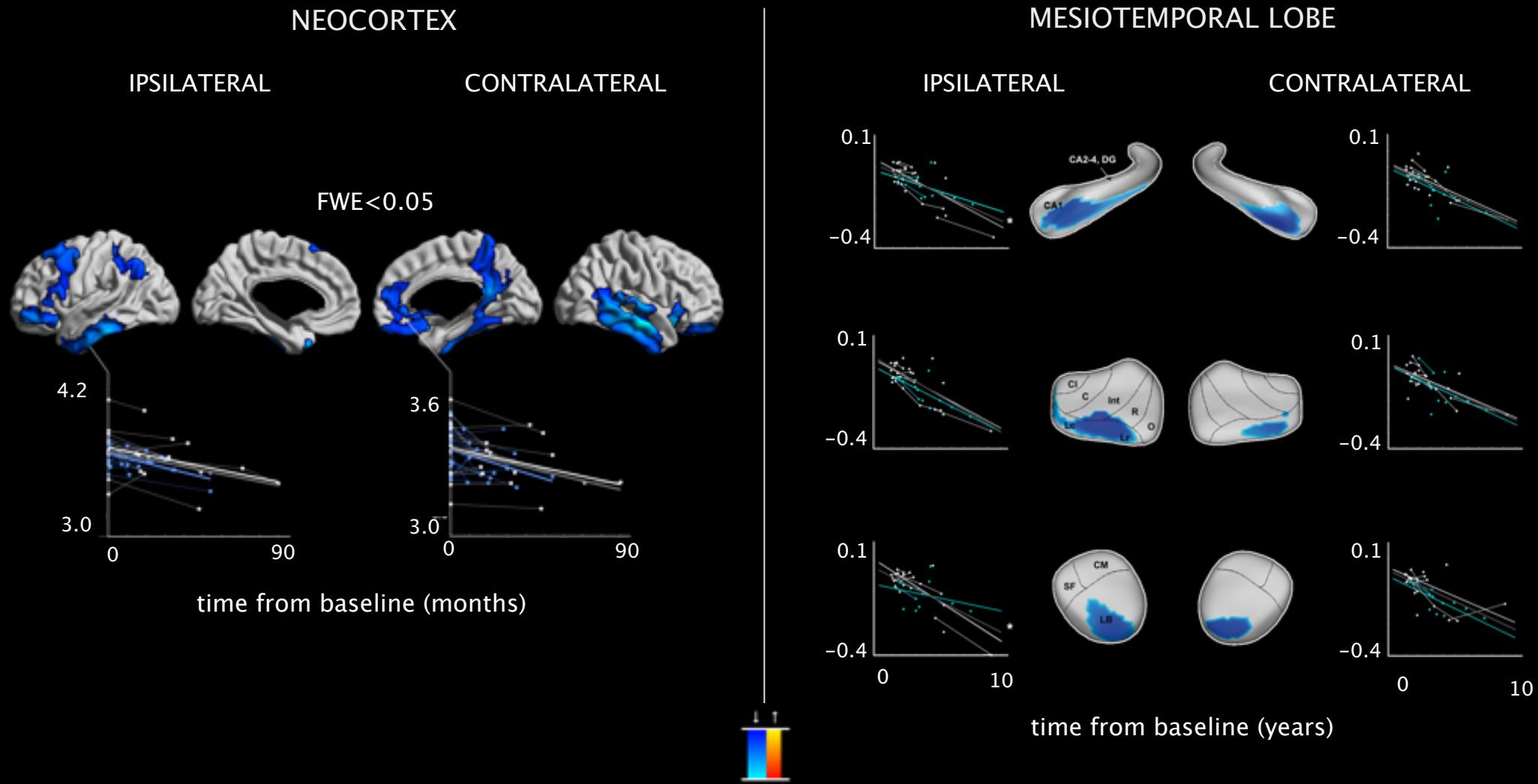


NETWORK-LEVEL PHENOTYPING



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

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reprint requests to Dr. G.D.
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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.^{2,3} The high diagnostic yield of MRI as a sensitive and specific indicator of MTS has been confirmed^{2,3}; 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.⁴ 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.

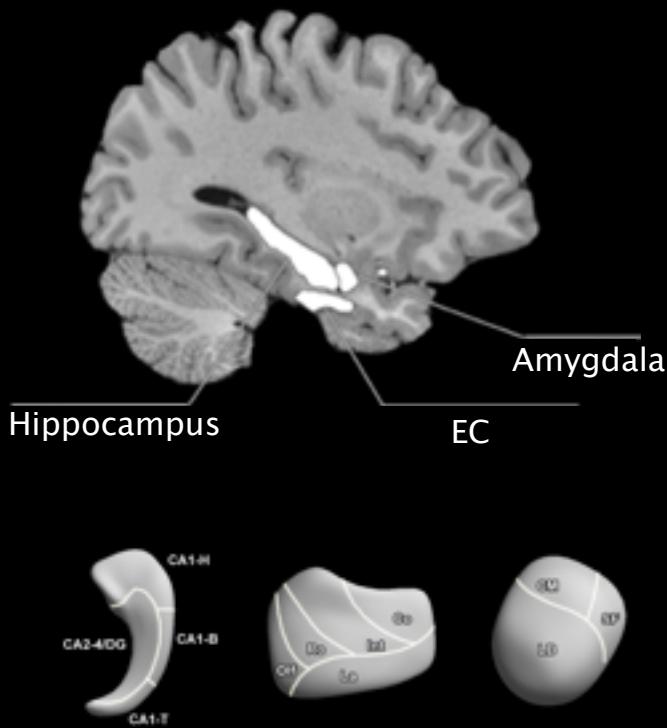
In this issue of *Neurology*®, Bernhardt et al.⁷ evaluated cortical thickness on MRI and revealed that progressive neocortical atrophy occurs in patients with intractable TLE and is correlated with epilepsy duration. A longitudinal analysis was used in 18 patients with a mean interscan interval of 2.5 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?

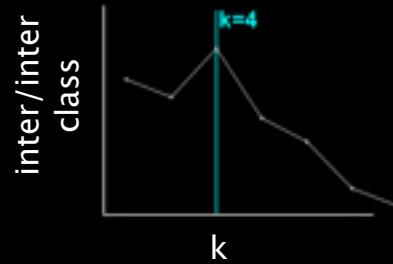
MRI PATTERN LEARNING: DISEASE SUBTYPING AND PROGNOSIS

MESIOTEMPORAL PROFILING

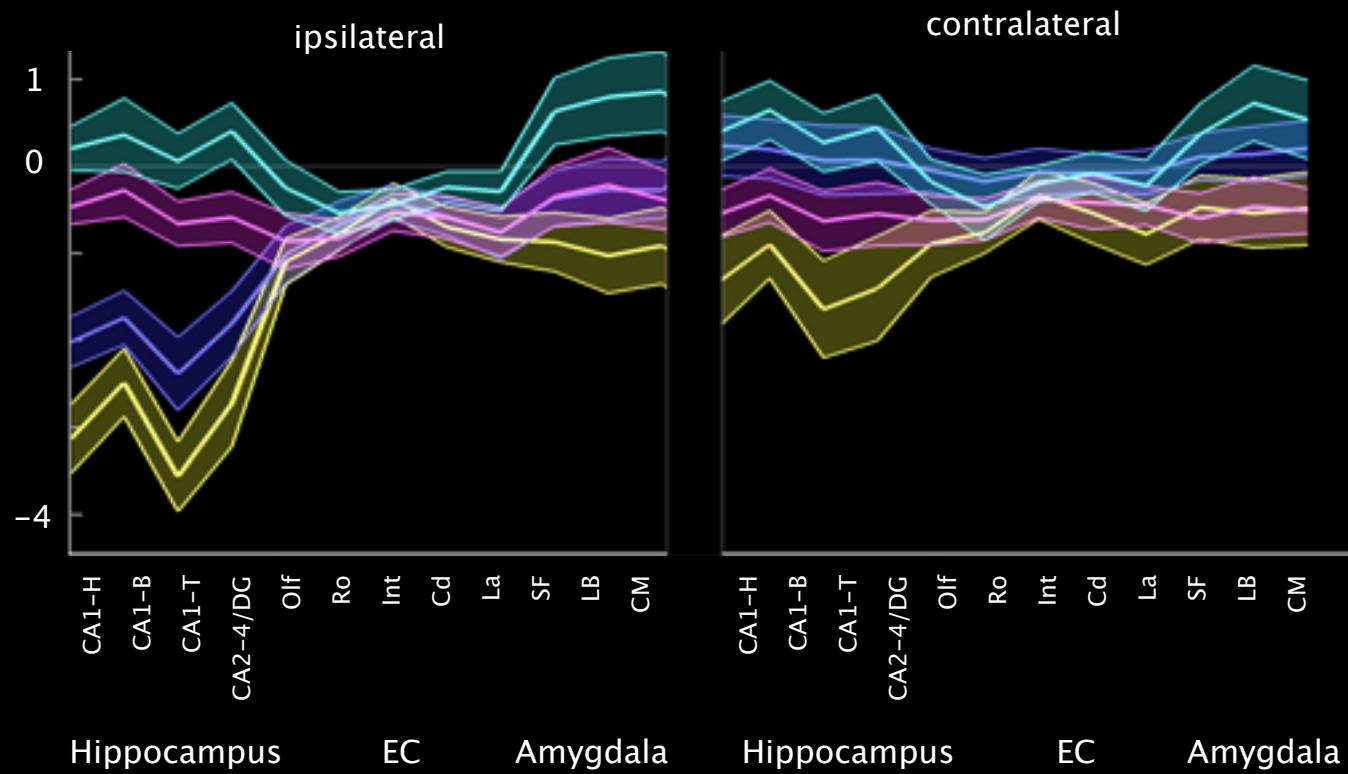
n=114



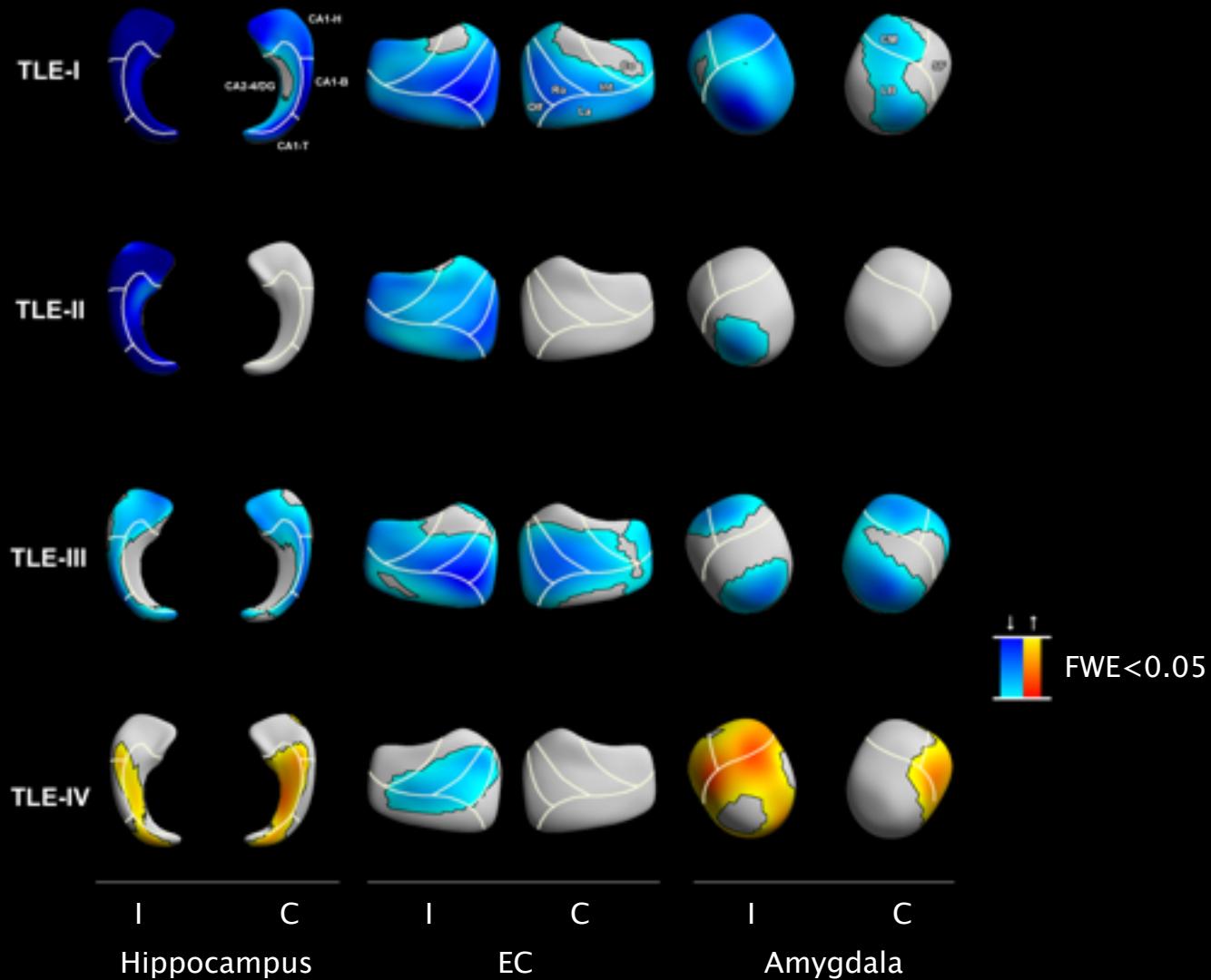
CLUSTERING PATIENT SPECTRUM BASED ON MRI MORPHOMETRY



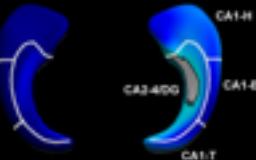
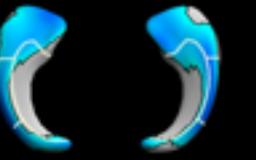
- TLE-I
- TLE-II
- TLE-III
- TLE-IV



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

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

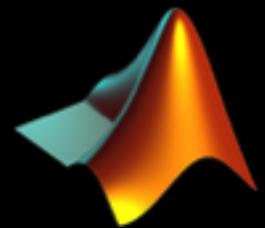
BIG DATA ANALYSIS FOR STRUCTURAL BRAIN ANOMALIES IN AUTISM



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

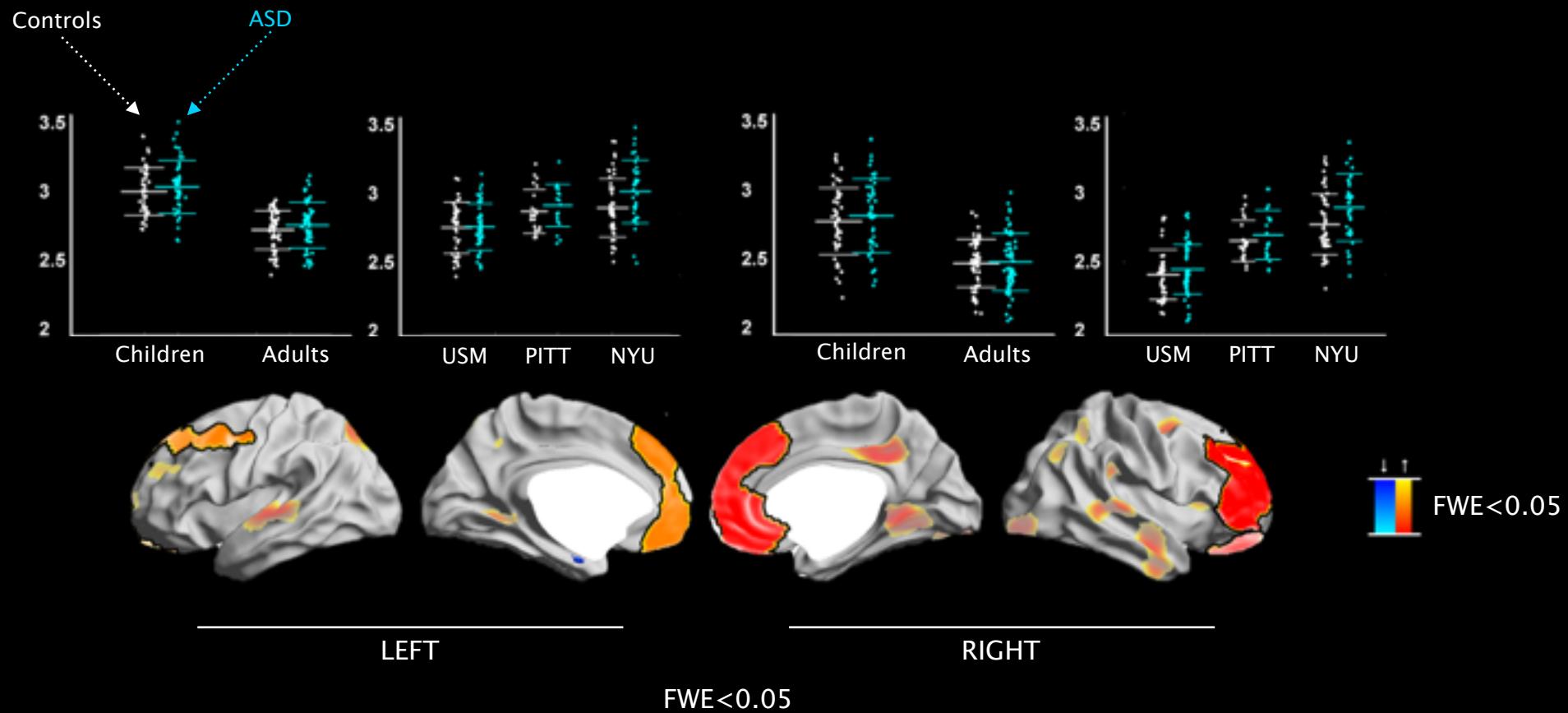
processing

QC

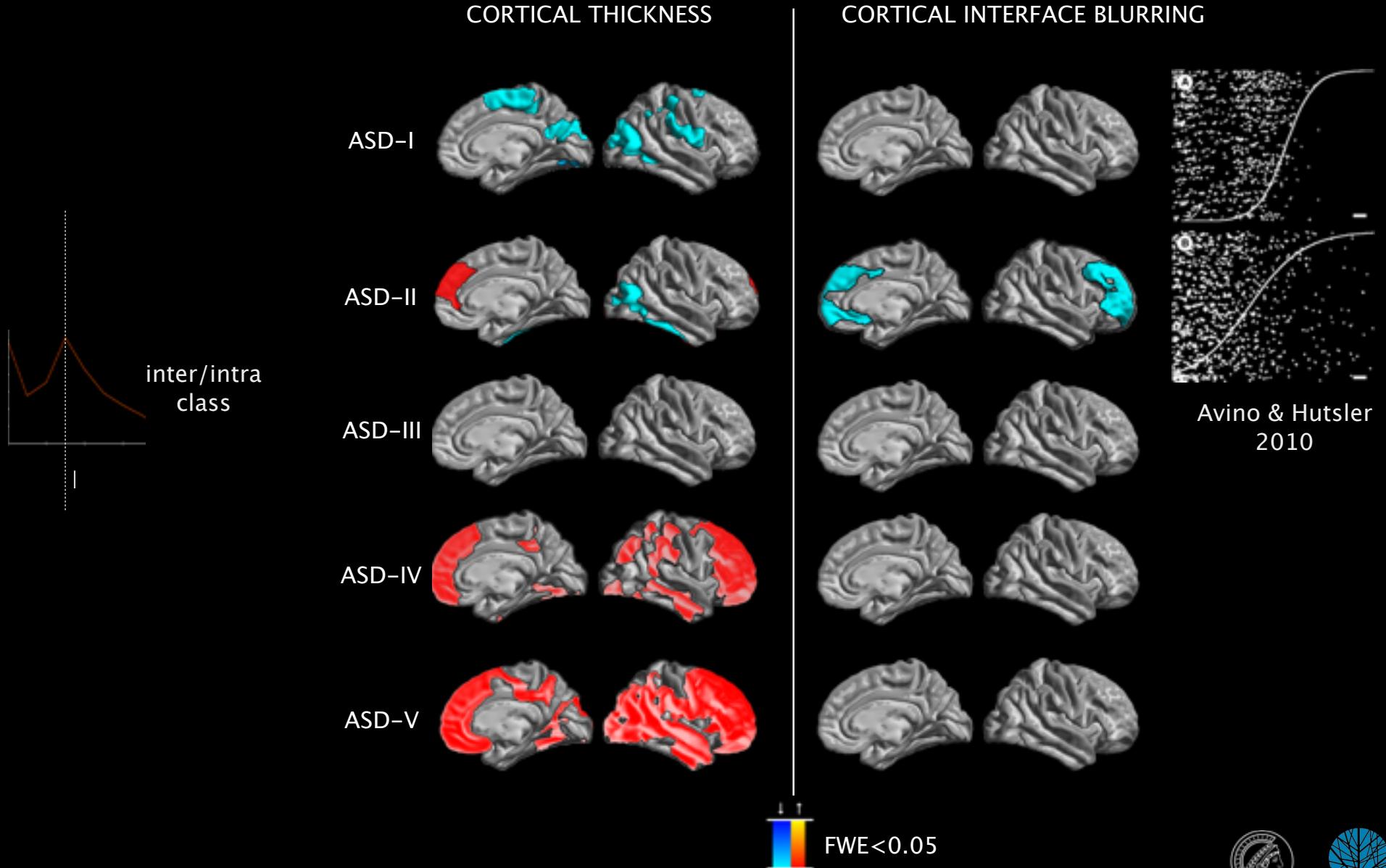
n=220



MULTI-CENTER MAPPING OF STRUCTURAL ALTERATIONS

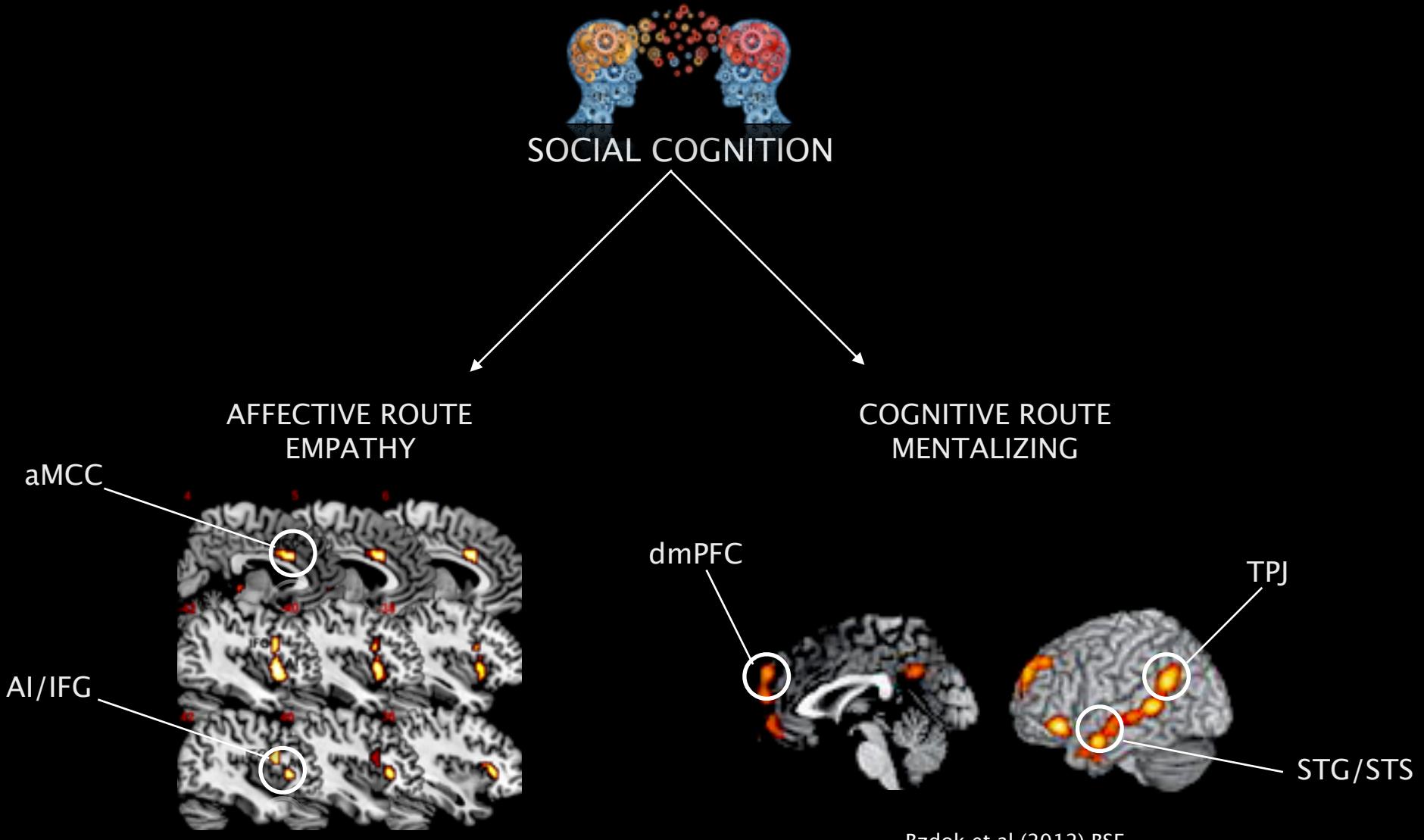


TOWARDS A SUBTYPING OF AUTISM SPECTRUM DISORDERS

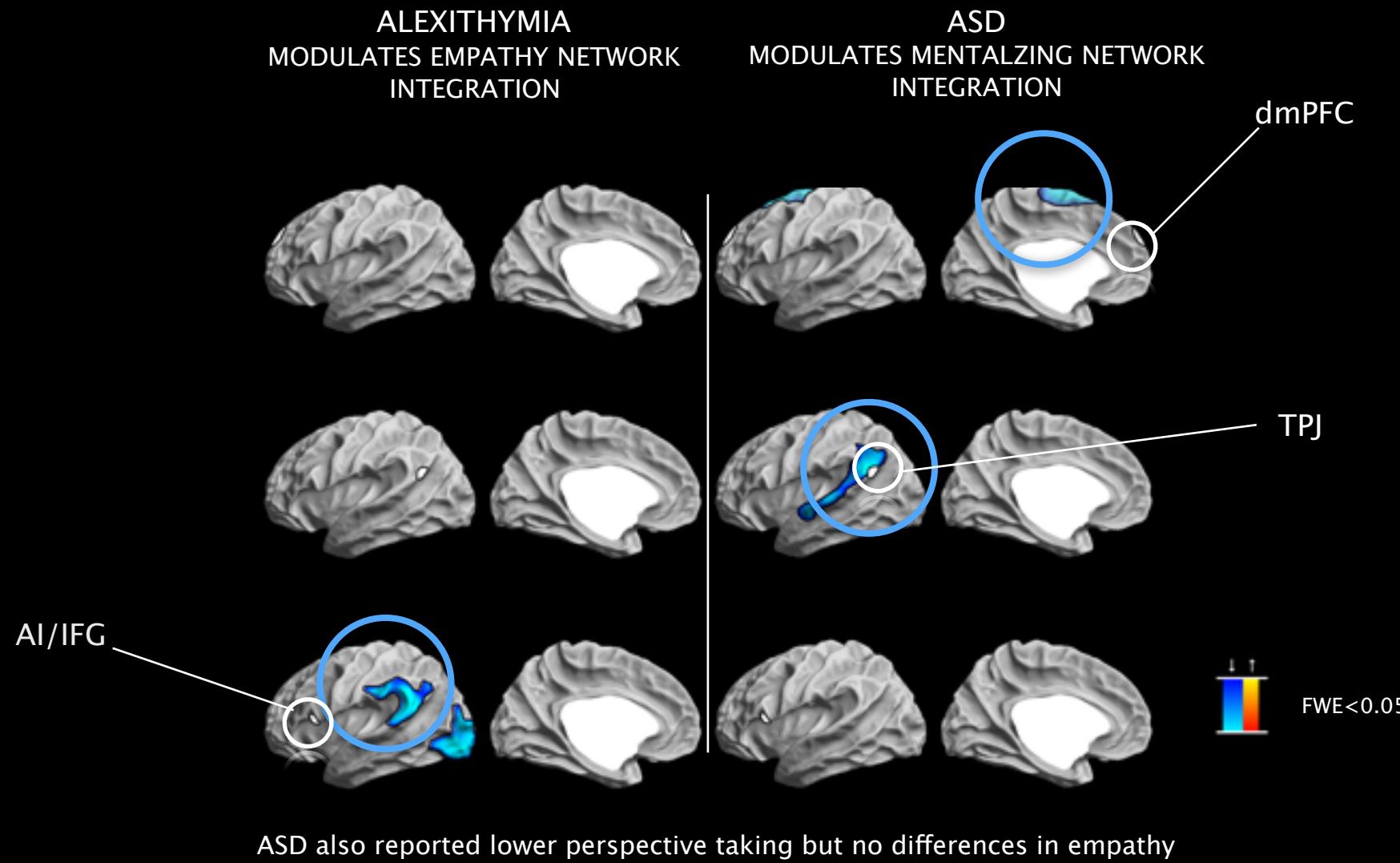


USING AUTISM AS DISEASE MODEL

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

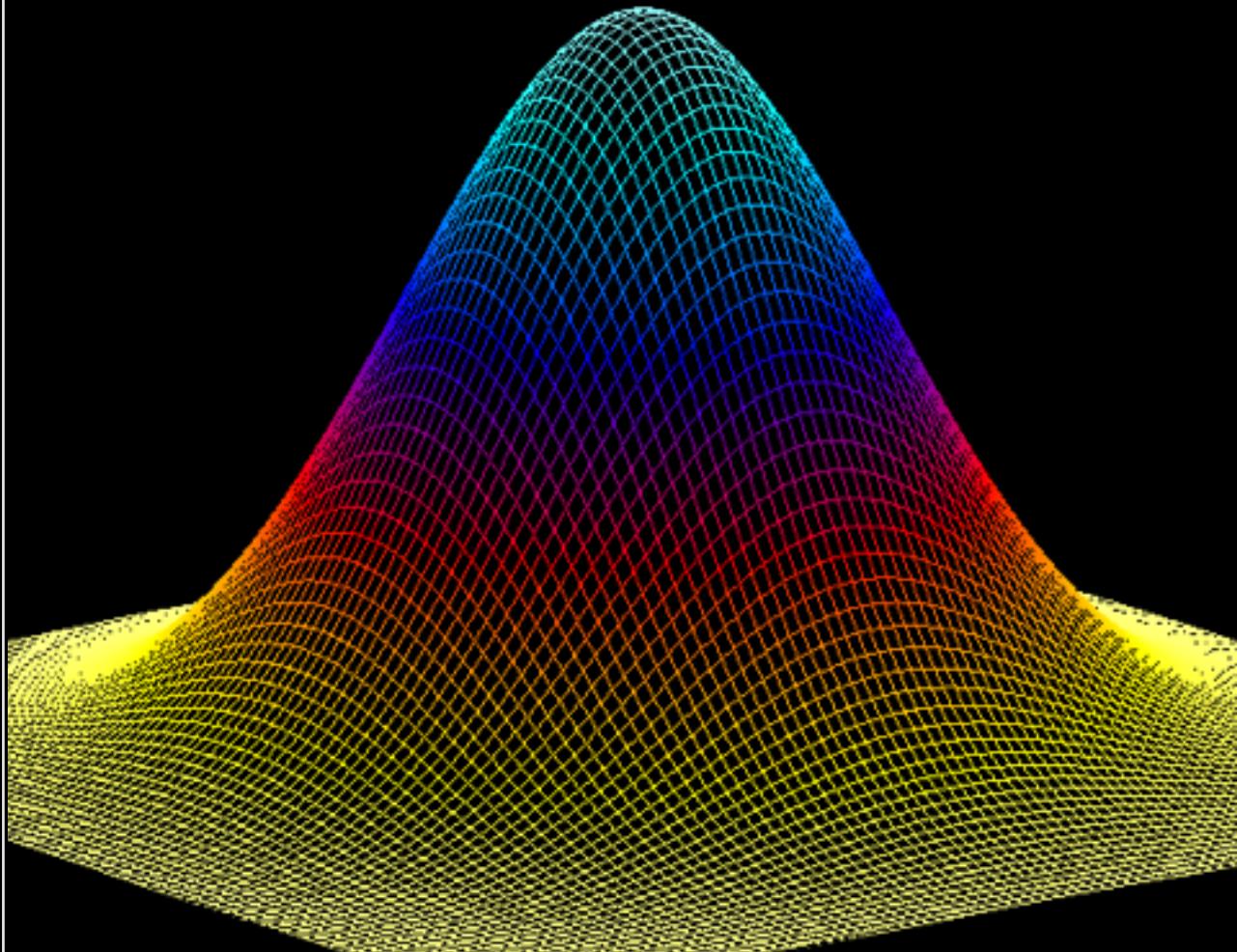
Divergence between socio-affective and socio-cognitive networks

NEURODIVERSITY

DISEASE MODELS CAN EFFECTIVELY
REVEAL RELATIONSHIPS BETWEEN
BRAIN STRUCTURE AND BEHAVIOR

HIGH VARIABILITY
IN BEHAVIOR, 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



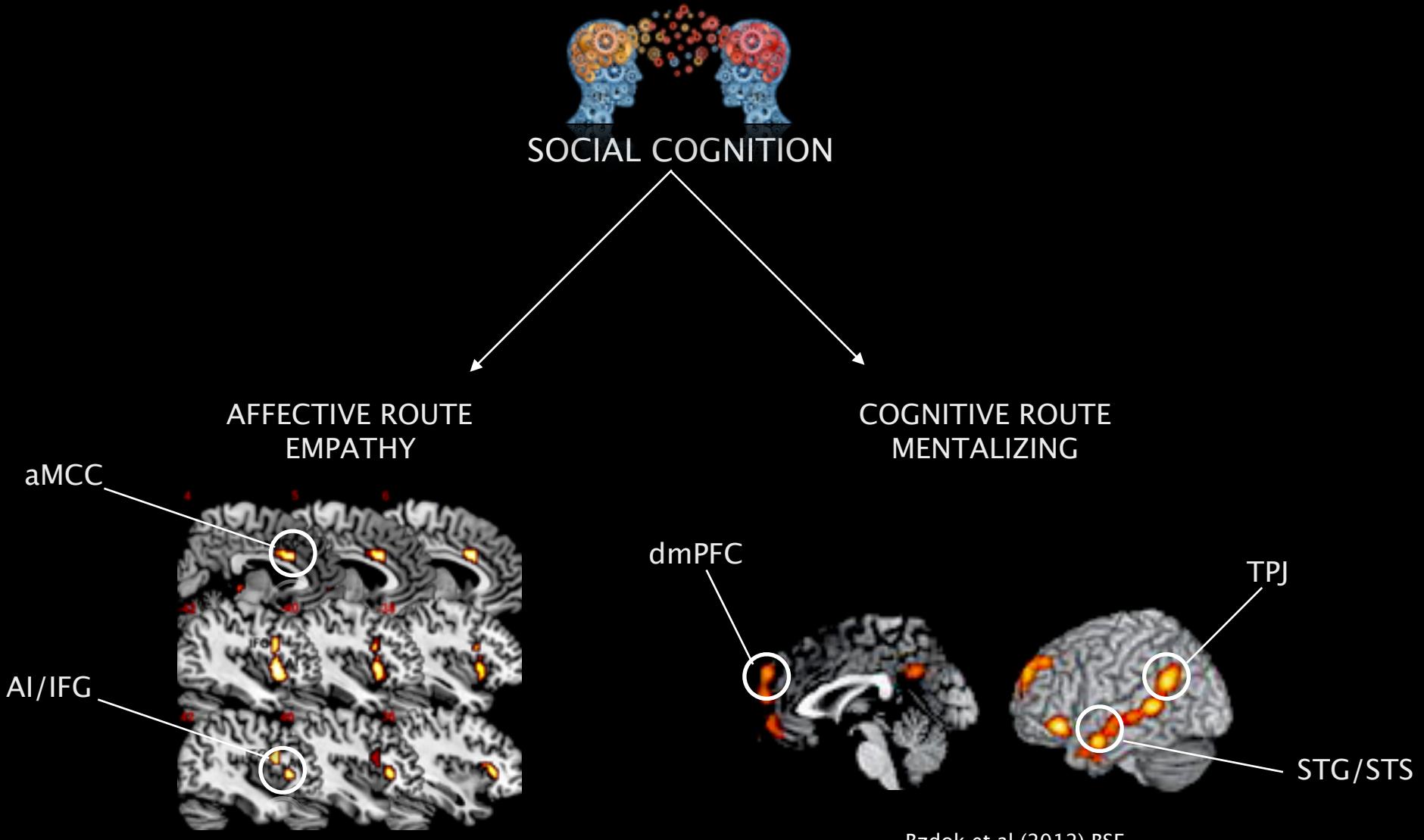
The ReSource Project



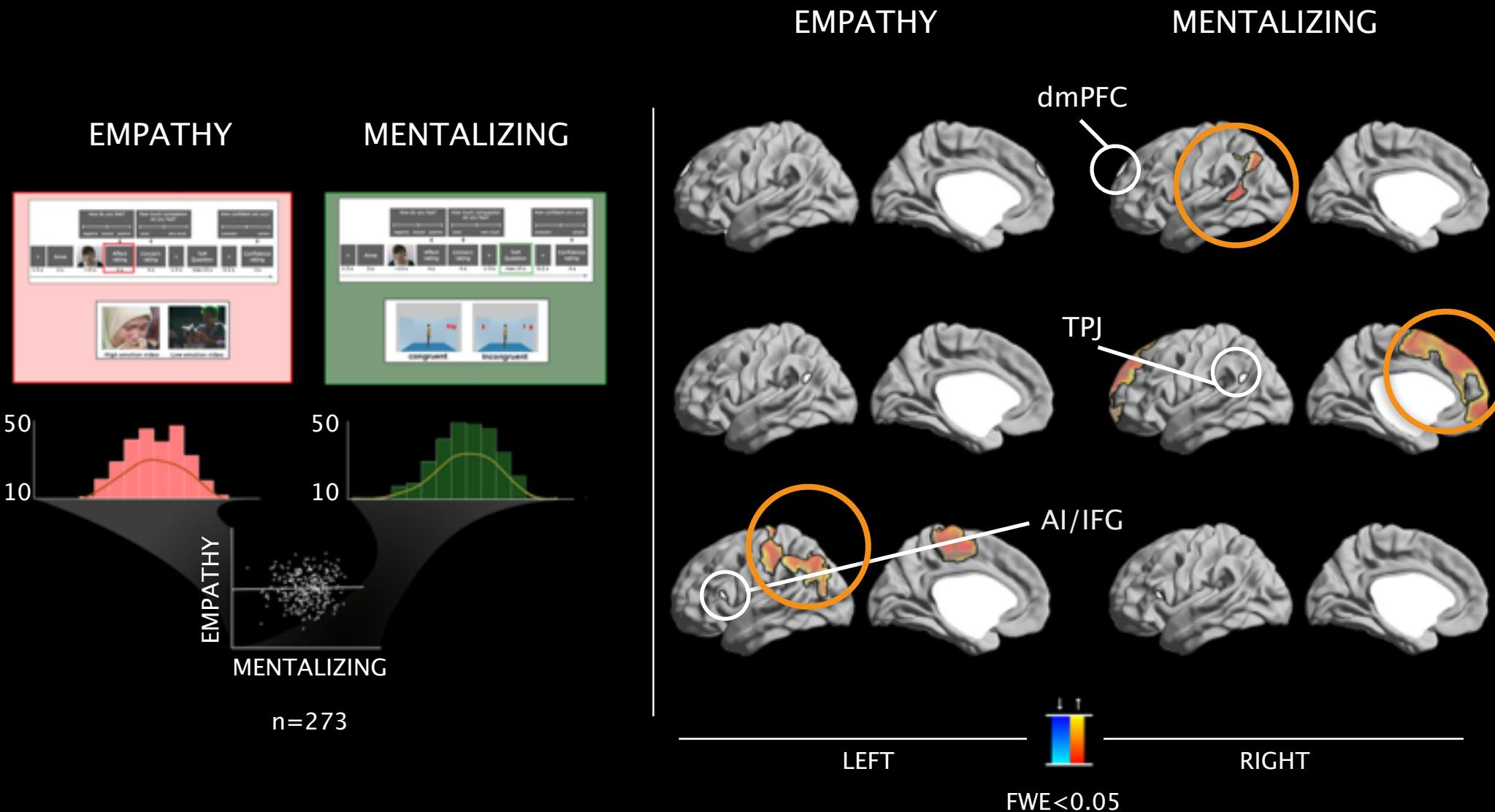
PI: Tania Singer



USING AUTISM AS DISEASE MODEL



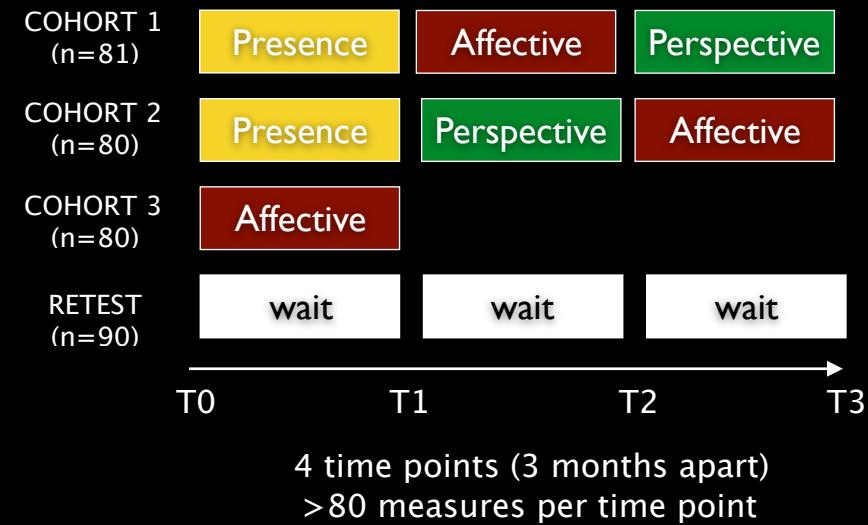
PHENOTYPING SOCIO-COGNITIVE NETWORKS: CROSS-SECTIONAL EVIDENCE



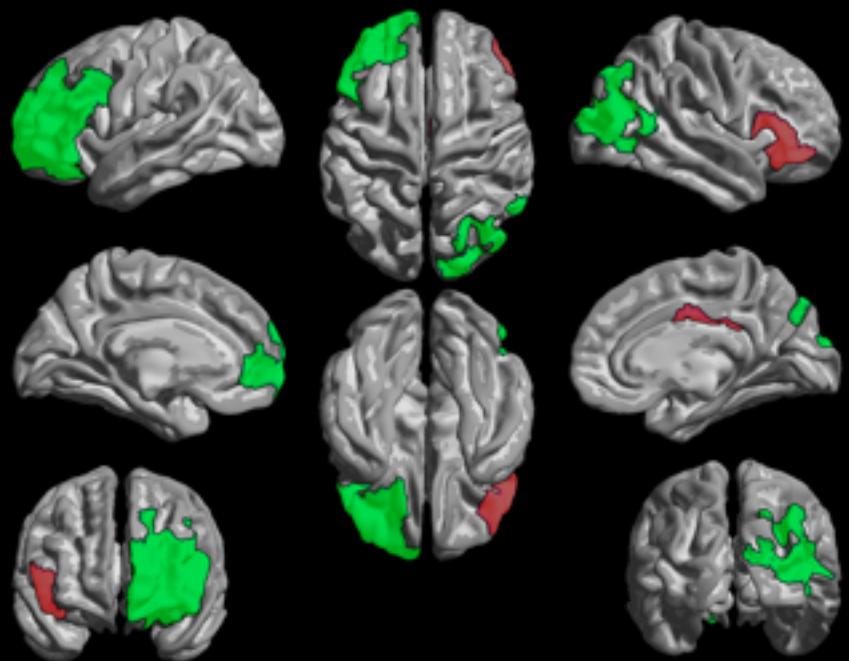
Valk*, Bernhardt*, Boettger, Trautwein, Kanske, Singer (in preparation)
Bernhardt, Klimecki, Leiberg, Singer (2014) Cerebral Cortex



PHENOTYPING SOCIO-COGNITIVE NETWORKS: LONGITUDINAL EVIDENCE



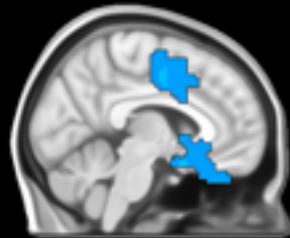
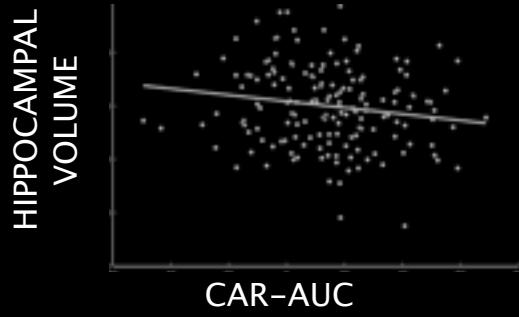
PRELIMINARY CORTICAL THICKNESS FINDINGS



Mixed effects models:
Differential change affective vs perspective
T1-T2

NEURODIVERSITY ACROSS DIFFERENT DOMAINS

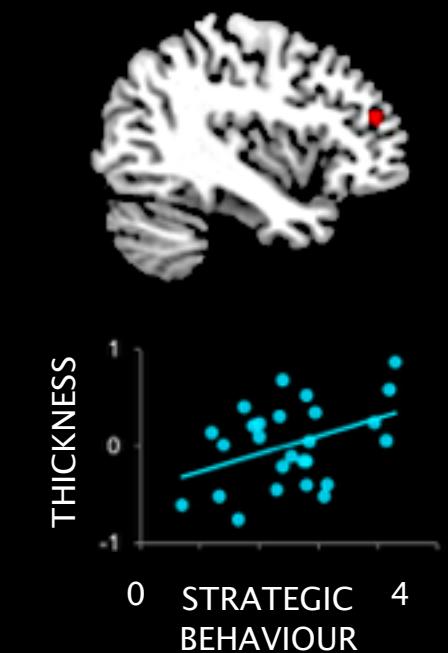
CORTISOL AWAKENING RESPONSE



DECREASED HIPPOCAMPAL VOLUME
AND FUNCTIONAL CONNECTIVITY
IN PARTICIPANTS WITH HIGHER
CORTISOL AWAKENING RESPONSE

Bernhardt, Engert, Singer
(in preparation)

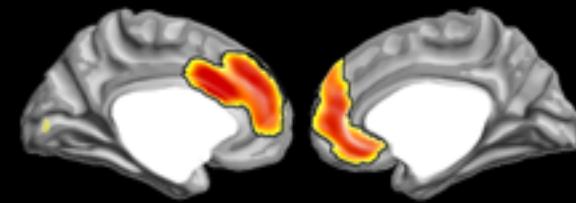
STRATEGIC BEHAVIOUR



DLPFC THICKNESS GREATER
IN INDIVIDUALS WITH
MORE STRATEGIC DECISION MAKING

Steinbeis, Bernhardt, Singer
(2013) Neuron

PRIVATE COGNITION



THICKNESS IN INDIVIDUALS
WHO TEND TO MIND-WANDER
IN EASY TASK COMPARED
TO HARD TASK

Bernhardt, Smallwood, et al.
(2014) NIMH

NEUROIMAGING
MODELLING
MACHINE LEARNING

COGNITIVE AND AFFECTIVE
PHENOTYPING
BLOOD, HAIR, SALIVA

CLINICAL INFORMATION
PATHOLOGY
OUTCOME

NEURODIVERSITY BRAIN DISORDERS

SUBTYPING
PREDICTION
VALIDATION

FUTURE DIRECTIONS

DISEASE MODELS AND NEURODIVERSITY TO STUDY COGNITION AND AFFECT

IMPACTS OF LESIONS IN CONTEXT OF
WHOLE-BRAIN PHENOTYPES

BRAIN MARKERS OF COGNITIVE
RESERVE AND RESILIENCE

PREDICT COGNITIVE AND
AFFECTIVE OUTCOME



TRACKING AND PREDICTING DISEASE PROGRESSION

MULTI-COHORT
LONGITUDINAL DESIGNS

PATIENT STRATIFICATION
BASED ON PROGRESSION

PREDICT
COGNITIVE DECLINE
AND QUALITY OF LIFE

COMBINE NEUROMARKERS
WITH BIOMARKERS



MULTI-CRITERIA BIOMARKER VALIDATION

MRI vs HISTOLOGY

MRI vs ELECTROPHYSIOLOGY

MULTI-SITE OPEN ACCESS DATABASES:
GENERALIZABILITY AND SCALABILITY

7T IMAGING





MAX-PLANCK-GESELLSCHAFT



Tania Singer

Sofie Valk

Anne Boeckler

Philipp Kanske

Mathis Trautwein

Nikolaus Steinbeis

Boris Bornemann

Veronika Engert

Sylvie Neubert

Sandra Zurborg

Haakon Engen

Terry Peters

Maged Goubran

Ali Khan

Uta Frith

Giorgia Silani

Geoffrey Bird

Carrie McDonald

Nob Kemmotusu

Michael Milham

Adiana di Martino

INDI

Jonathan Smallwood

Beth Jeffreys

Andrea Bernasconi

Neda Bernasconi

Epilepsy Group

Alan Evans

Jean Paul Soucy

Louis Collins

Felix Carbonell

Seok-Jun Hong

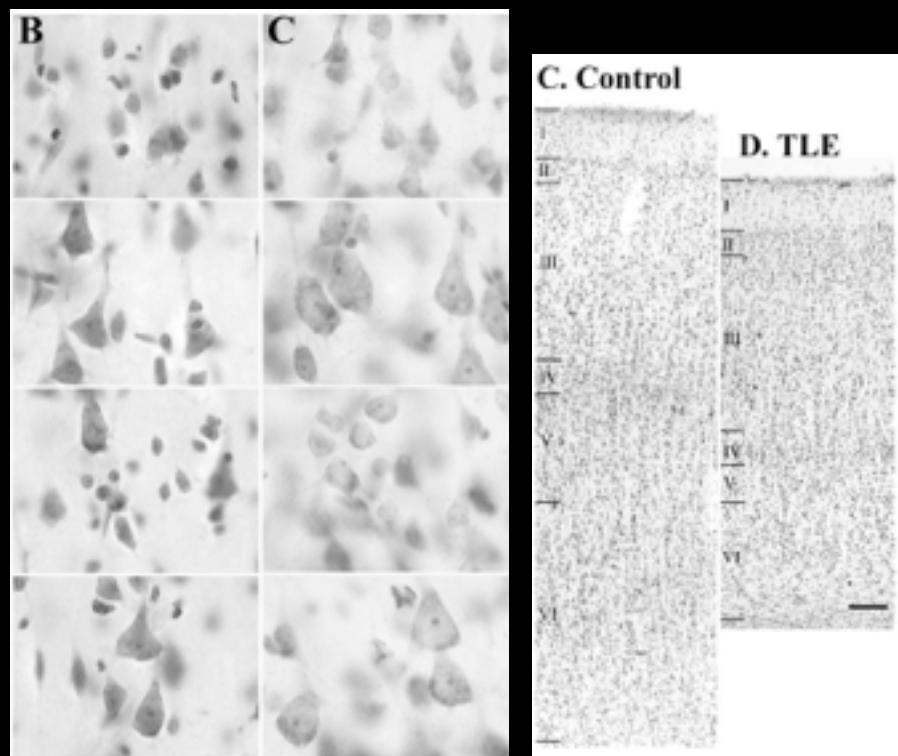
Min Liu

Benoit Caldairou



TLE AND CORTICAL PATHOLOGY

Bothwell 2001 JN



The Journal of Neuroscience, July 1, 2001, 21(13):4799–4800

Neuronal Hypertrophy in the Neocortex of Patients with Temporal Lobe Epilepsy

Sarah Bothwell,^{1,4} Gloria E. Meredith,^{1,2} Jack Phillips,² Hugh Staunton,¹ Colin Doherty,² Elena Grigorenko,² Steven Glazier,³ Sam A. Deadwyler,⁴ Cormac A. O'Donovan,² and Michael Farrell¹

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Blanc 2011 Epilepsia

Table 4. Mean field fraction staining in all cortical regions and white matter regions from both hemispheres for individual cases in the three groups: classical hippocampal sclerosis, no hippocampal sclerosis, and controls

Marker	GFAP		CD68		NPY	
	Region	Cortex	White matter	Cortex	White matter	
Classical hippocampal sclerosis						
EP019		2.86	3.89	0.07	0.29	0.61
EP038		5.88	12.62	0.29	0.46	1.22
EP266		5.43	23.07	0.19	0.44	0.54
EPI41		20.9	30.90	0.08	0.21	0.77
EP294		26.84	37.36	1.09	2.48	1.31
EP286		16.96	27.90	0.48	0.92	2.03
Average		13.15	22.62	0.37	0.80 ^a	1.08 ^a
Epilepsy cases						
No hippocampal sclerosis						
EP210		2.39	5.57	0.04	0.1	0.47
EP039		3.91	10.02	0.22	0.29	0.65
EP290		7.71	18.01	0.51	0.53	3.34
Average		4.67	11.2	0.25	0.3	1.48
Control cases						
PMC1		4.73	12.37	0.27	0.35	0.54
PMC2		8.81	11.73	0.15	0.20	0.66
PMC3		4.78	13.28	0.072	0.06	0.52
PMC4		0.72	1.24	0.11	0.12	0.52
Average		4.76	9.66	0.15	0.18	0.56

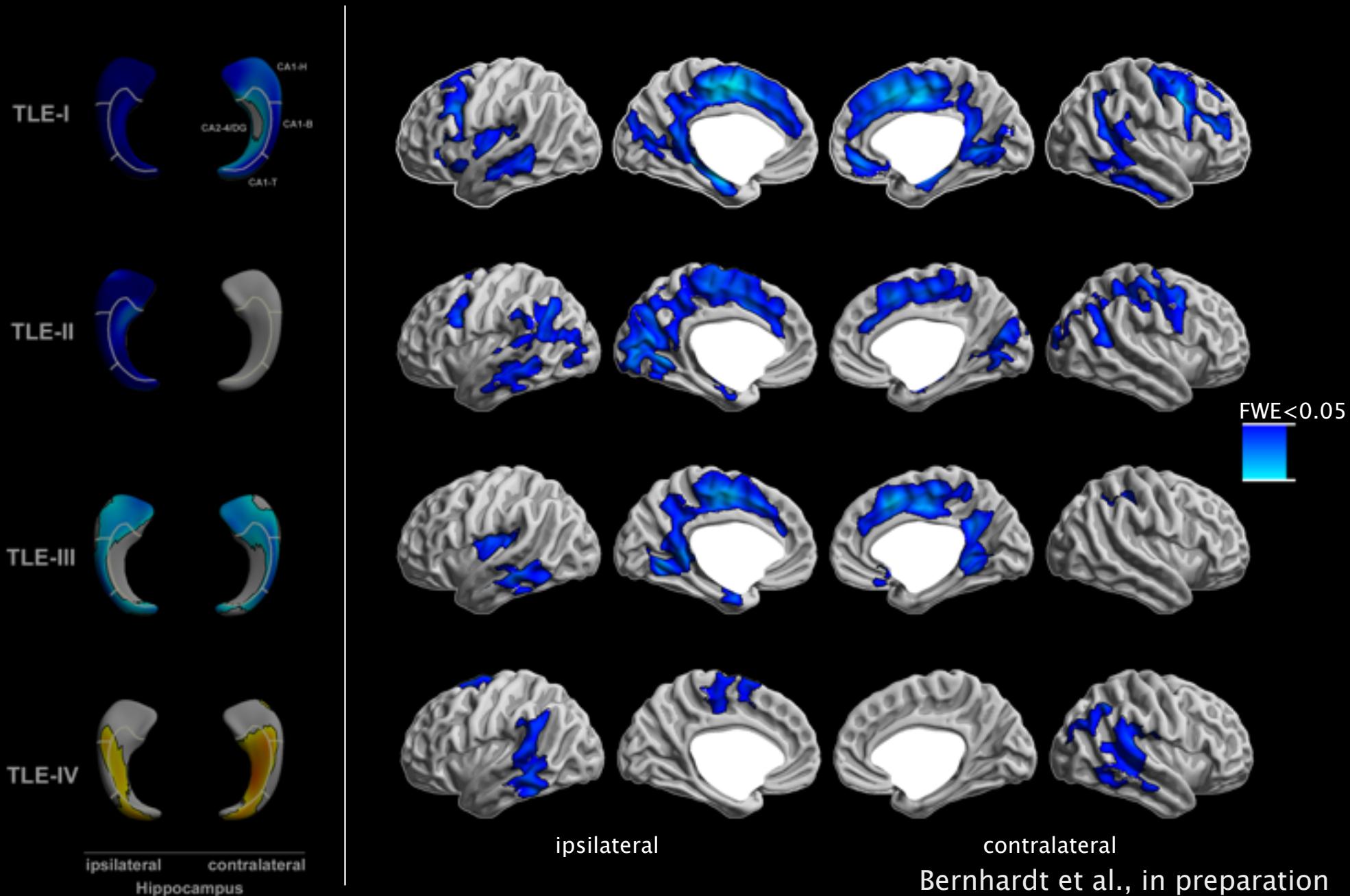
All values are shown as percentage of staining (field fraction).

PMC, postmortem control; EP, epilepsy postmortem.

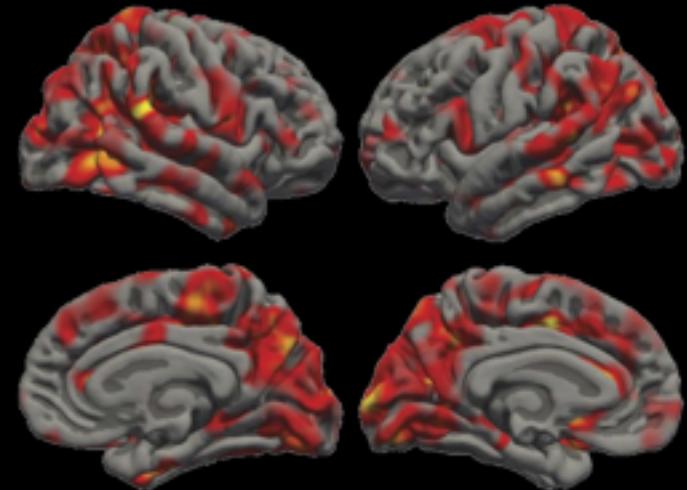
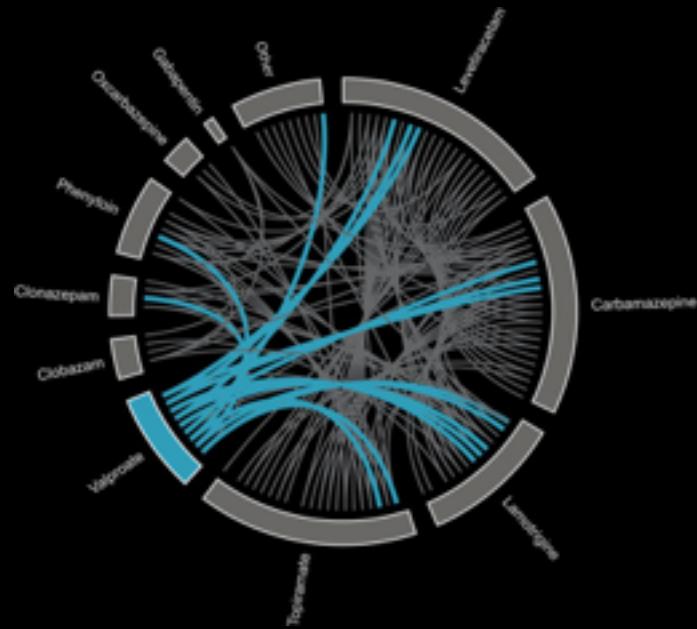
^aResults significantly different from controls ($p < 0.05$).

This study supports acquired neocortical pathology in epilepsy patients both with and without CHS. Cortical pathology does not show lateralization to the side of CHS. Preferential involvement of the temporal and frontal poles may relate to other factors, such as cortical injury associated with seizures, rather than involvement through hippocampal pathways.

NEOCORTICAL THINNING ACROSS TLE SPECTRUM



EPILEPSY AND AED



Sodium valproate use is associated with reduced parietal lobe thickness and brain volume

▲

Heath R. Pardoc, PhD
Anne T. Berg, PhD
Graeme D. Jackson, MD

ABSTRACT

Objective: We hypothesized that total brain volume, white matter volume, and lobar cortical thickness would be different in epilepsy patients. We studied valproate relative to nonvalproate by using patients with epilepsy and healthy controls.

Methods: Patients with focal intractable epilepsy from a tertiary epilepsy center were the primary group for analysis. A confirmatory analysis was carried out in an independent group of subjects imaged as part of a community-based study of childhood-onset epilepsy. Total brain volume; white matter volume; and frontal, parietal, occipital, and temporal lobe thickness were measured by processing whole-brain T1-weighted MRI using FreeSurfer 5.1.

Results: Total brain volume, white matter volume, and parietal thickness were reduced in the valproate group relative to controls and nonvalproate users (valproate, n = 9; nonvalproate, n = 27; controls, n = 45; all male). These findings were confirmed in an independent group (valproate, n = 7; nonvalproate, n = 70; controls, n = 20; all male).

Conclusions: Sodium valproate use in epilepsy is associated with parietal lobe thinning, reduced total brain volume, and reduced white matter volume.

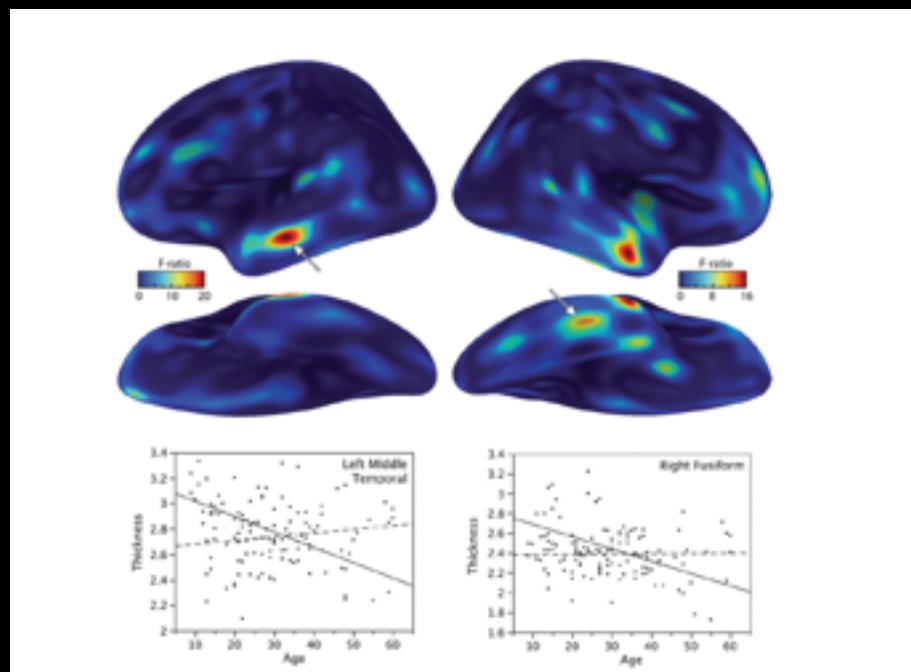
Level of evidence: This study provides Class IV evidence that use of valproate in epilepsy is associated with reduced parietal lobe thickness, total brain volume, and white matter volume.

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AUTISM AND AGE

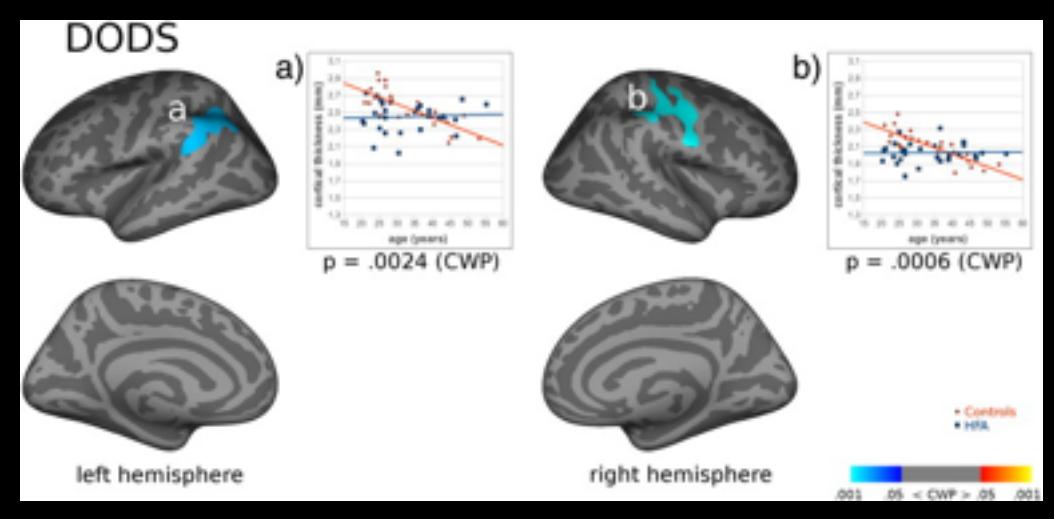
Raznahan 2011 CC

Protracted aging in 76 ASD vs 51 controls (10-76)



Scheel 2011 NIMH

Protracted aging in 28 High Functioning Autism vs 28 controls



ABIDE and SMRI

Toro 2014 MolPsy

“Our analyses of **Abide** did not show any statistically significant difference. The difference that we observed was „.02 standard deviations for CC size and „.04 standard deviations for BV”

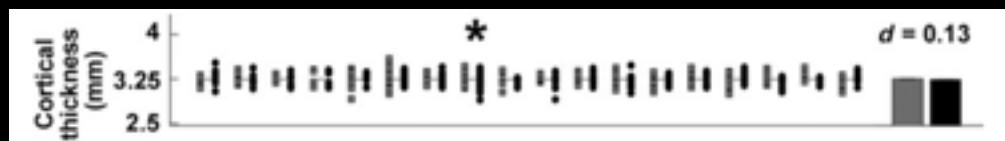
This contrasts with the global effect size found in our meta-analysis: .5 standard deviations, more than 20 times larger.

Combined with a selective report of positive findings, this makes meta-analyses based on small studies tend to overestimate the true effect size.”

Dinstein 2014 CerCor

“Analyses using volumetric, thickness, and surface area measures of over 180 brain areas, revealed significantly larger ventricular volumes, smaller corpus callosum volume, and several cortical areas with increased thickness in ASD.

Multivariate classification analyses yielded modest decoding accuracies of individuals’ group identity, suggesting that examined anatomical measures are of limited diagnostic utility for ASD.”

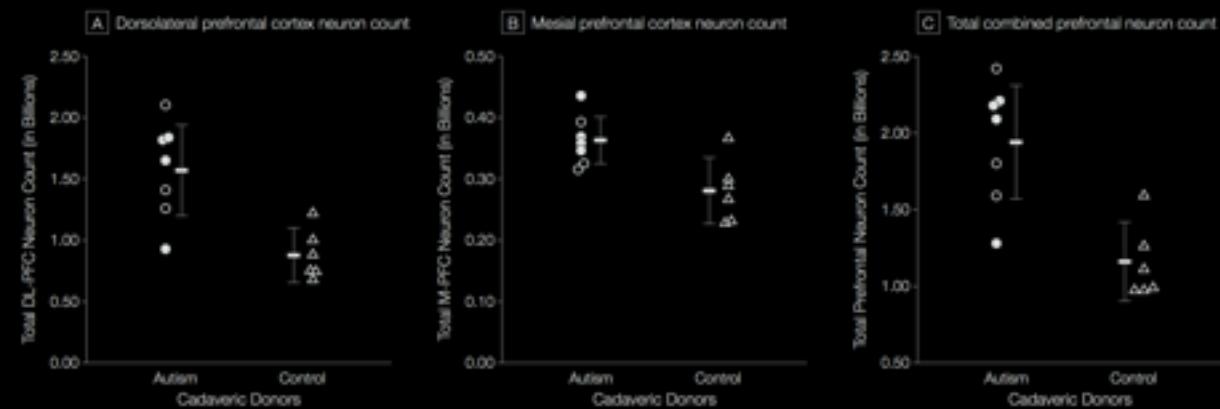
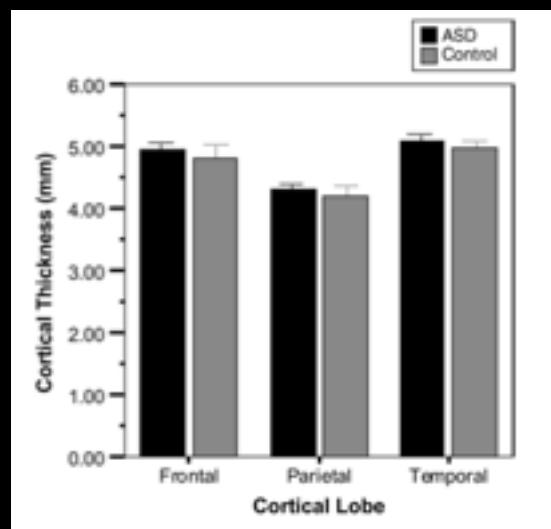


AUTISM: PATHOLOGICAL FINDINGS

Hutsler (2007) Biol Psy

Small increases in post-mortem cortical thickness

Courchesne (2011) HAMA
increased PFC neuronal numbers in autism



Histological and Magnetic Resonance Imaging Assessment of Cortical Layering and Thickness in Autism Spectrum Disorders

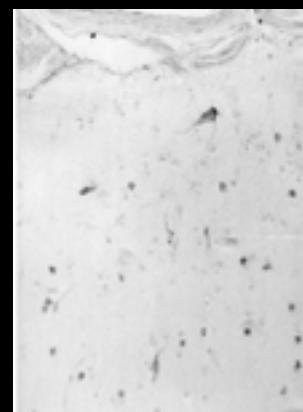
Jeffrey J. Hutsler, Tiffany Love, and Hong Zhang

Background: Qualitative reports of the cerebral cortex in a small number of autism spectrum disorder (ASD) cases have suggested an increase in thickness and disruptions in migration and lamination patterns.

Methods: We examined postmortem ASD individuals and age-matched controls using magnetic resonance imaging (MRI) to evaluate total cortical thickness, and histological samples to evaluate the pattern of cortical layering.

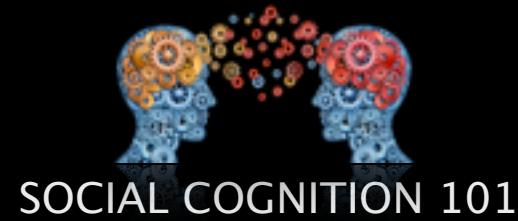
Results: Overall, thickness measures from ASD subjects were equivalent to control cases. Individual regions showed marginal but nonsignificant thickness differences in the temporal lobes. Cortical thickness values in ASD subjects decreased significantly with age. Quantitative examination of proportional layer thickness in histological sections indicated that the pattern of cortical layering was largely unaffected, while qualitative examination of these same samples revealed evidence of cell clustering and supernumerary cells in layer I and the subjacent.

Conclusions: These findings support limited disturbances in cortical cell patterning, but do not indicate a major deficit in the orderly migration of cortical neuroblasts during development, or their subsequent aggregation into the laminar pattern found in typically developing individuals.

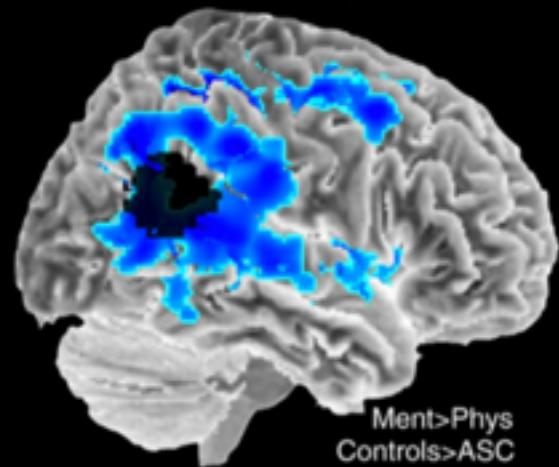


Bailey (1998) Brain
increased neuronal numbers,
organizational abnormalities

USING AUTISM AS DISEASE MODEL



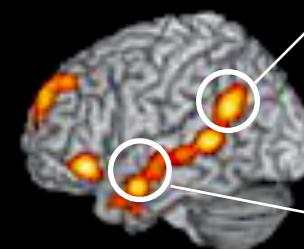
COGNITIVE ROUTE
MENTALIZING



dmPFC



TPJ



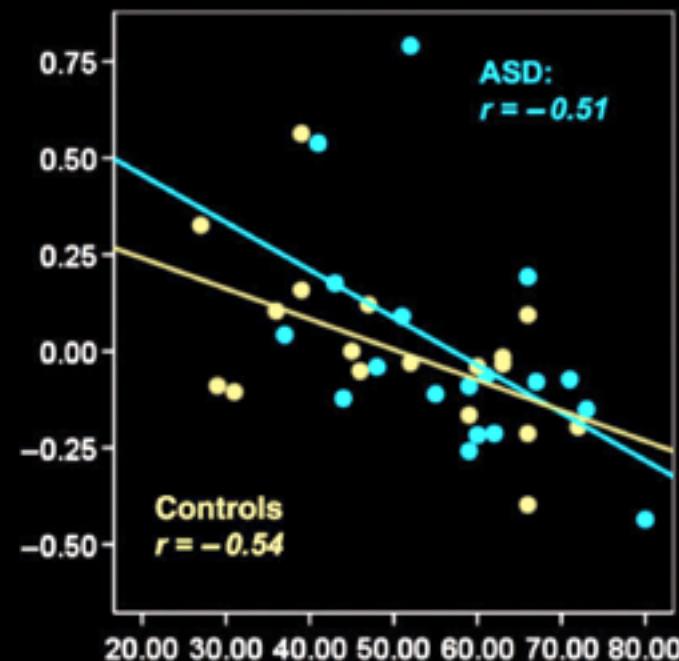
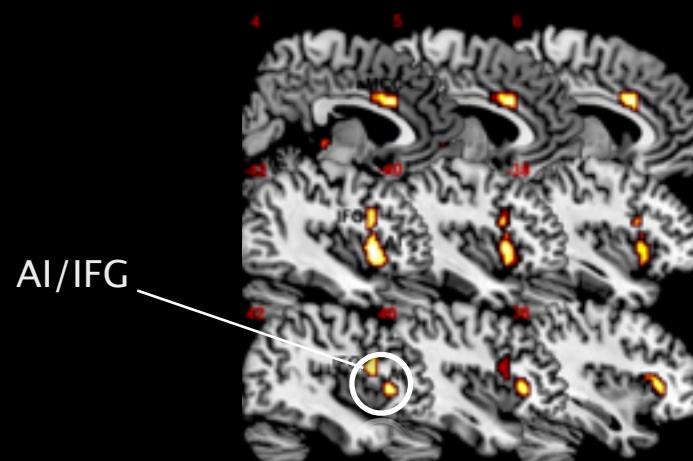
STG/STS

Bzdok et al (2012) BSF

USING AUTISM AS DISEASE MODEL TO PROBE SOCIAL COGNITION NETWORKS

FMRI DURING EMPATHY FOR PAIN PARADIGM

IN INDIVIDUALS WITH HIGH AND LOW ALEXITHYMIA IN
ASD AND CONTROL GROUPS



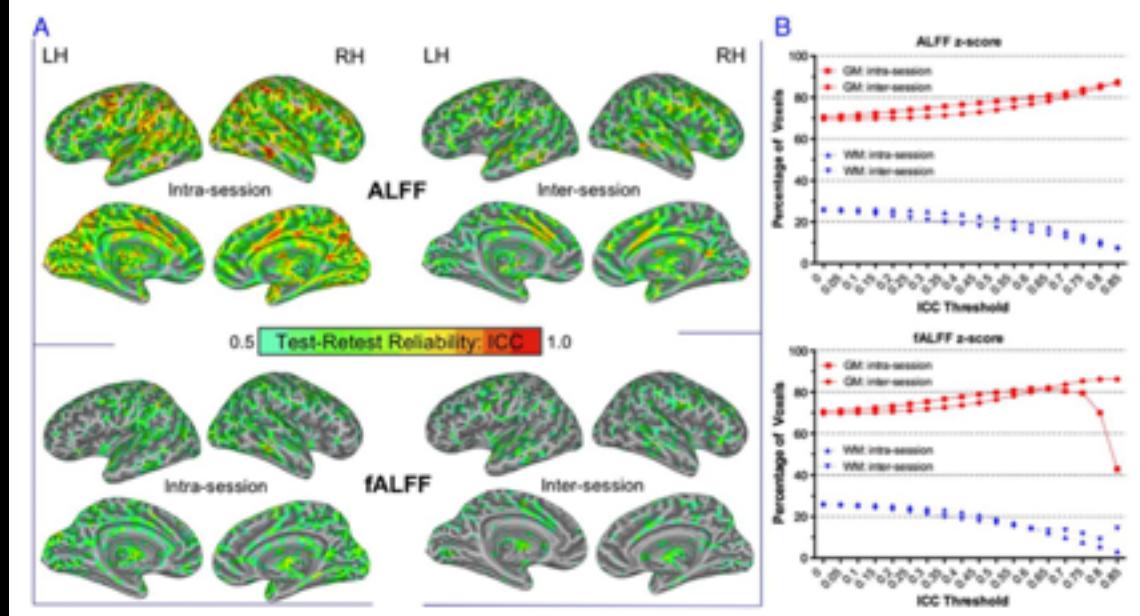
ALEXITHYMIA:
deficit in identifying feeling states
linked to altered interception and empathy
usual prevalence: 10% healthy controls, 50% ASD

ALFF vs fALFF

High ALFF in cysterns
controllable by fALFF



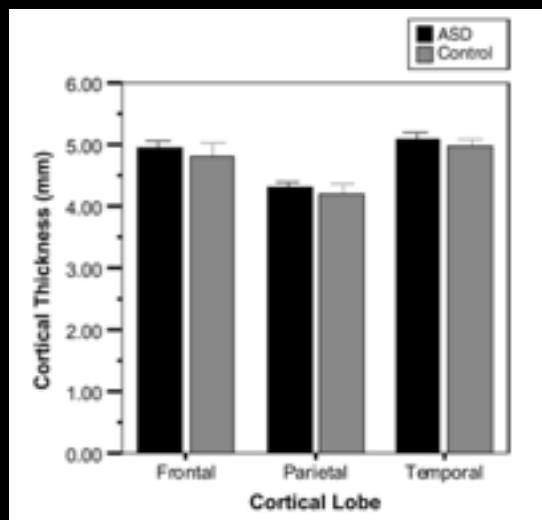
Higher test-retest reliability
for ALFF than fALFF



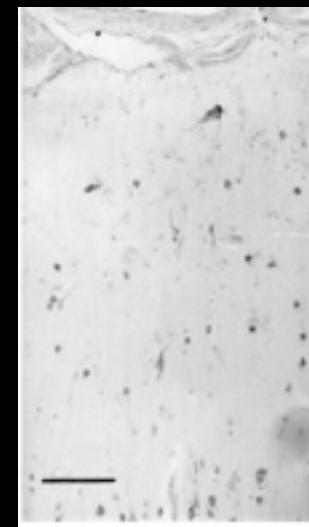
AUTISM: PATHOLOGICAL FINDINGS

Hutsler (2007) Biol Psy

Small increases in post-mortem cortical thickness



Bailey (1998) Brain



Brain (1998), 121, 889–905

A clinicopathological study of autism

Histological and Magnetic Resonance Imaging Assessment of Cortical Layering and Thickness in Autism Spectrum Disorders

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Conclusions: These findings support limited disturbances in cortical cell patterning, but do not indicate a major deficit in the orderly migration of cortical neuroblasts during development, or their subsequent aggregation into the laminar pattern found in typically developing individuals.

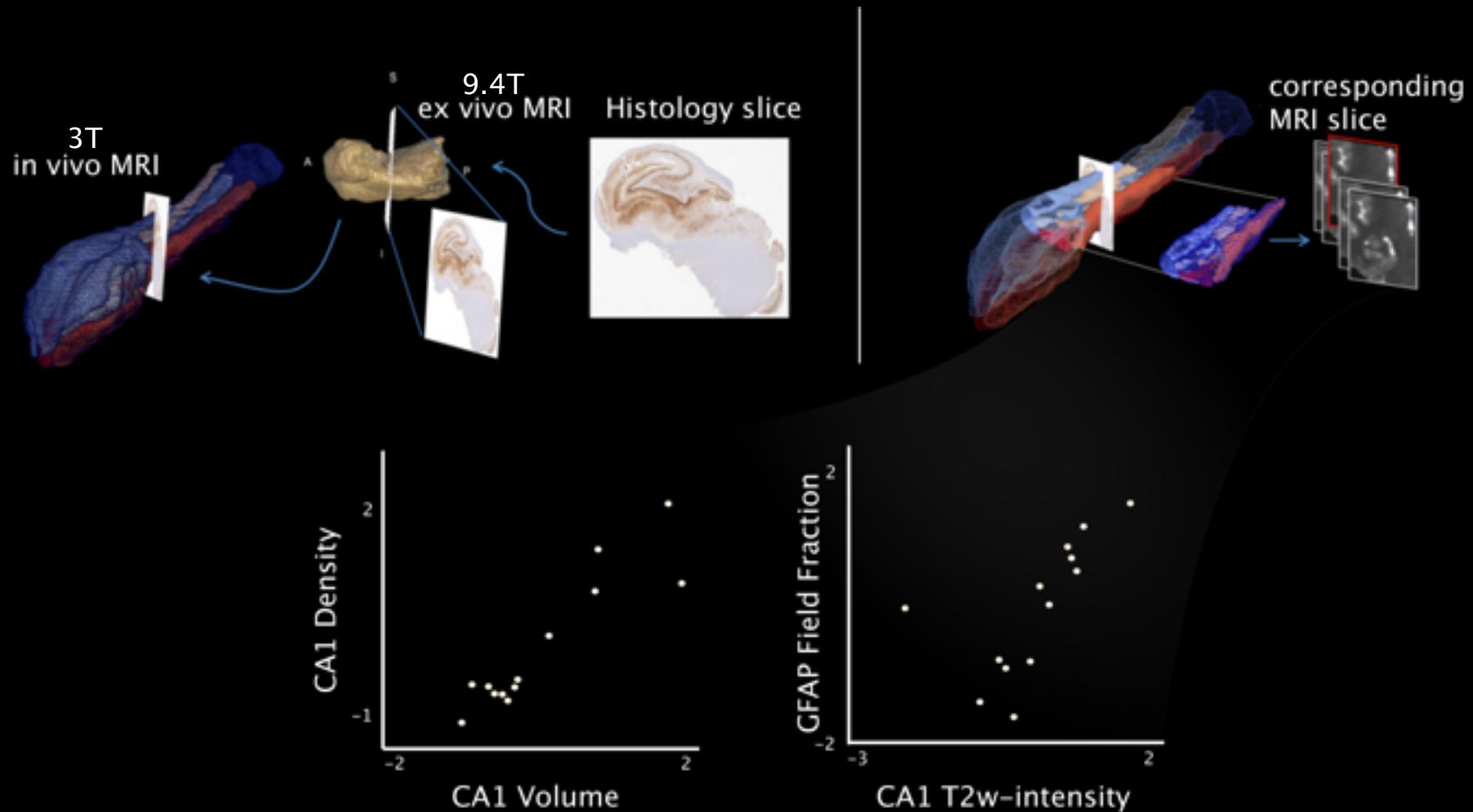
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¹MRC Child Psychiatry Unit, and ²Department of Neuropathology, The Institute of Psychiatry and ³Department of Histopathology, Institute of Child Health, London, UK

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*Present address: The Department of Pathology, The Institute of Ophthalmology, University College, London, UK

VALIDATION OF IN VIVO FINDINGS WITH QUANTITATIVE HISTOPATHOLOGY



SUBFIELD-SPECIFIC CORRELATIONS BETWEEN MRI AND HISTOLOGY