

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

BORIS BERNHARDT, PHD

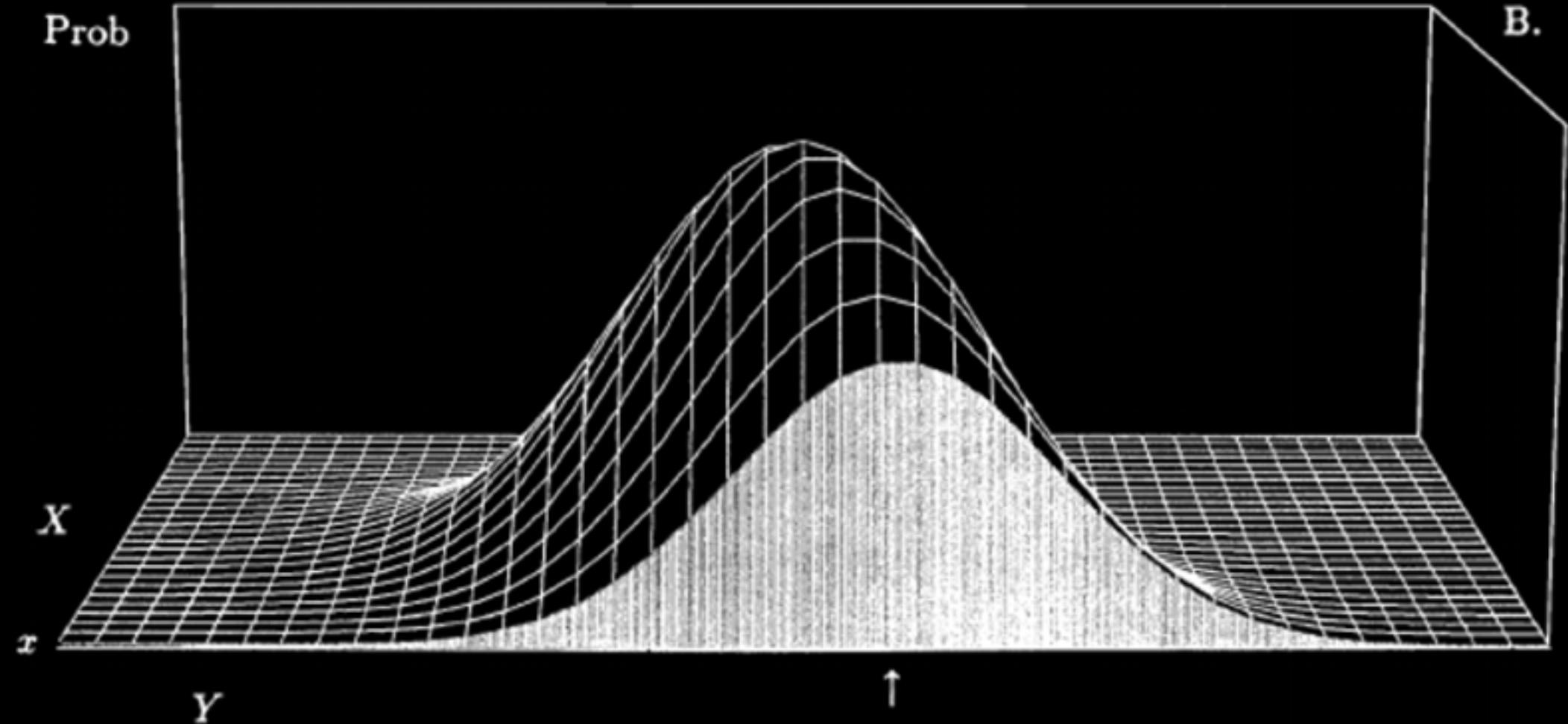
MONTREAL NEUROLOGICAL INSTITUTE

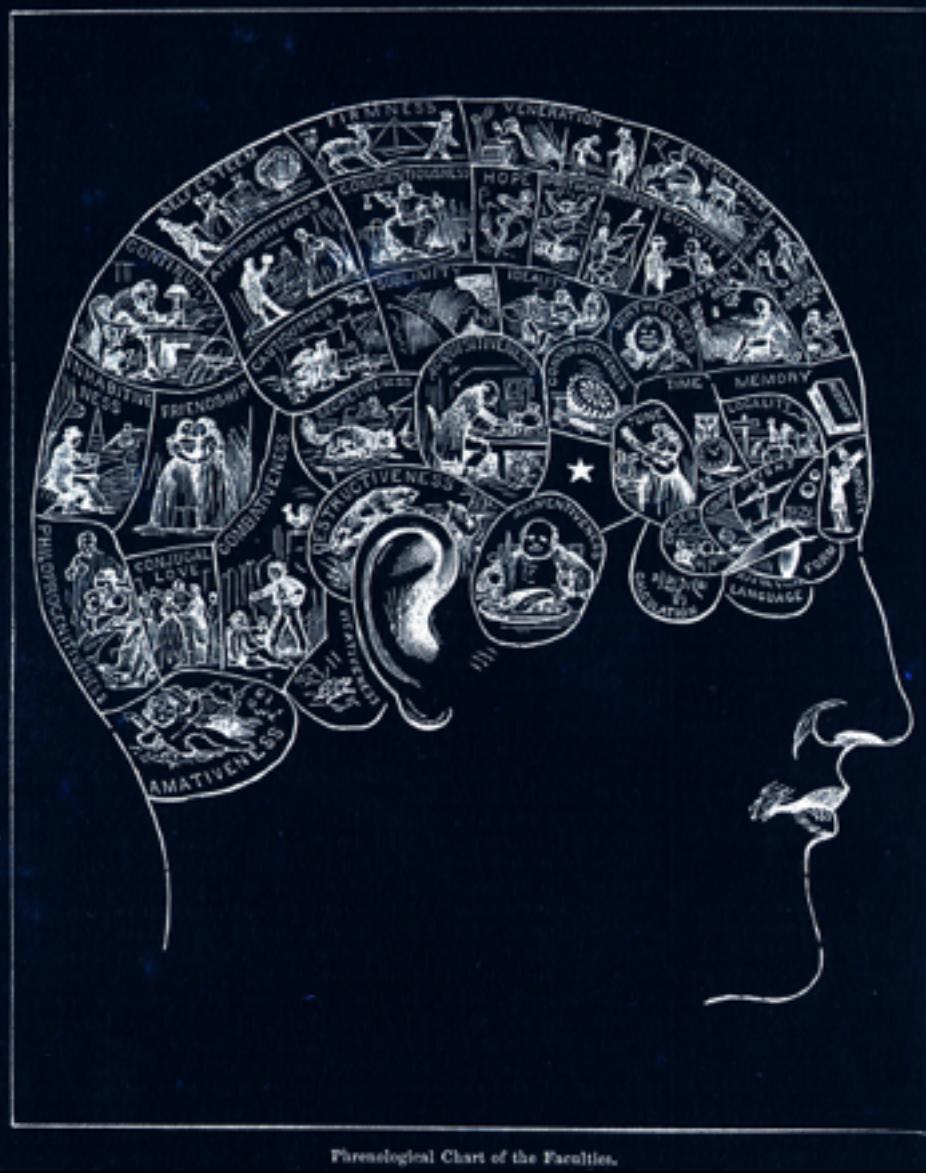
MCGILL UNIVERSITY

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

twitter: @BorisBernhardt

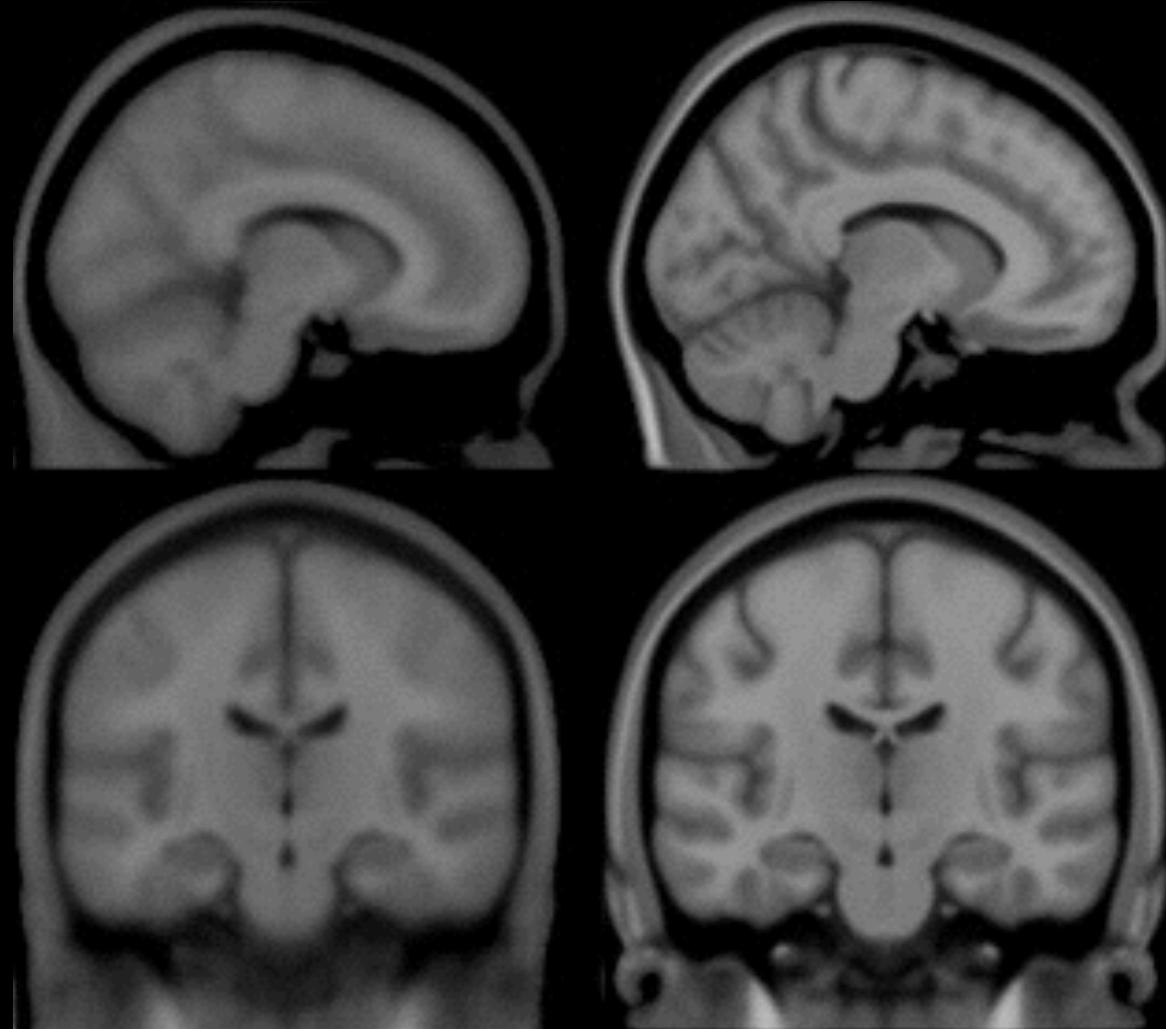




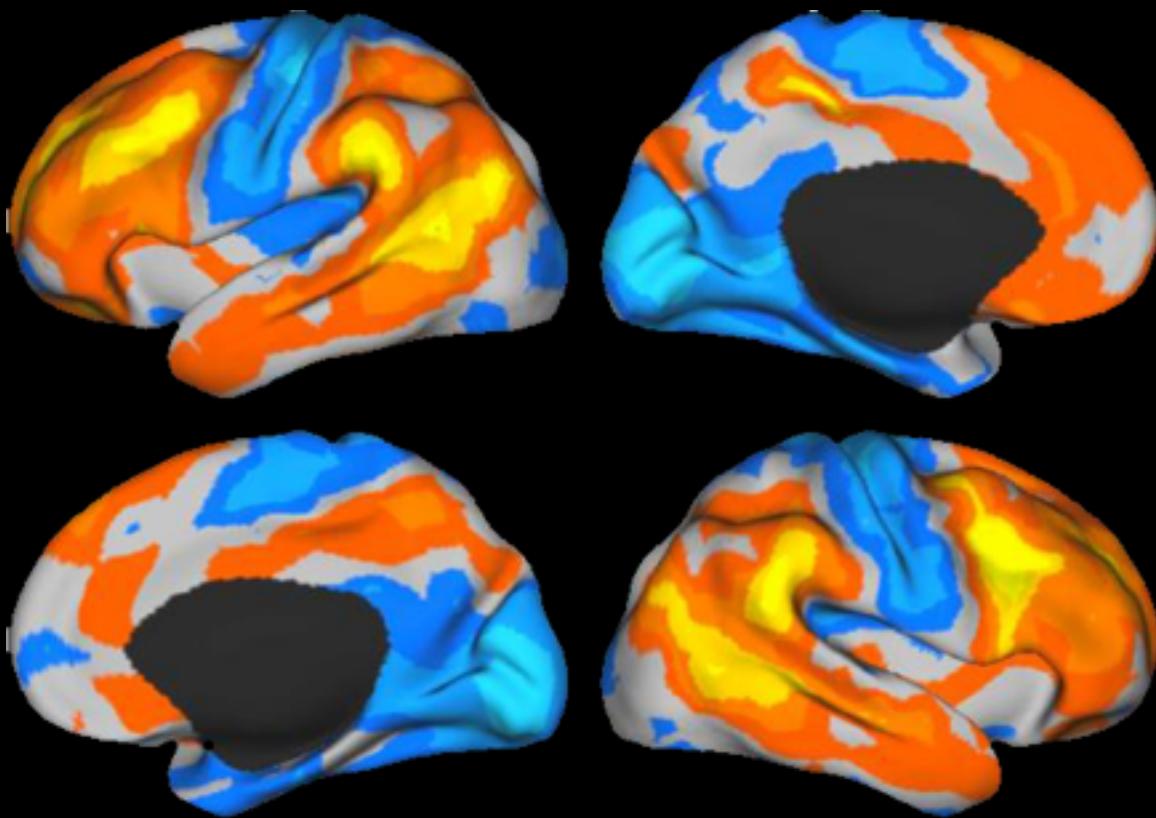


Parencological Chart of the Faculties.

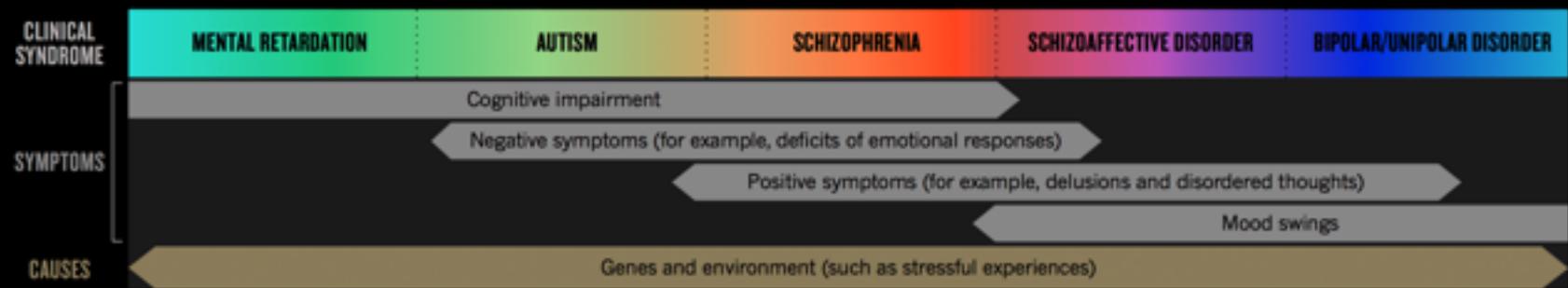


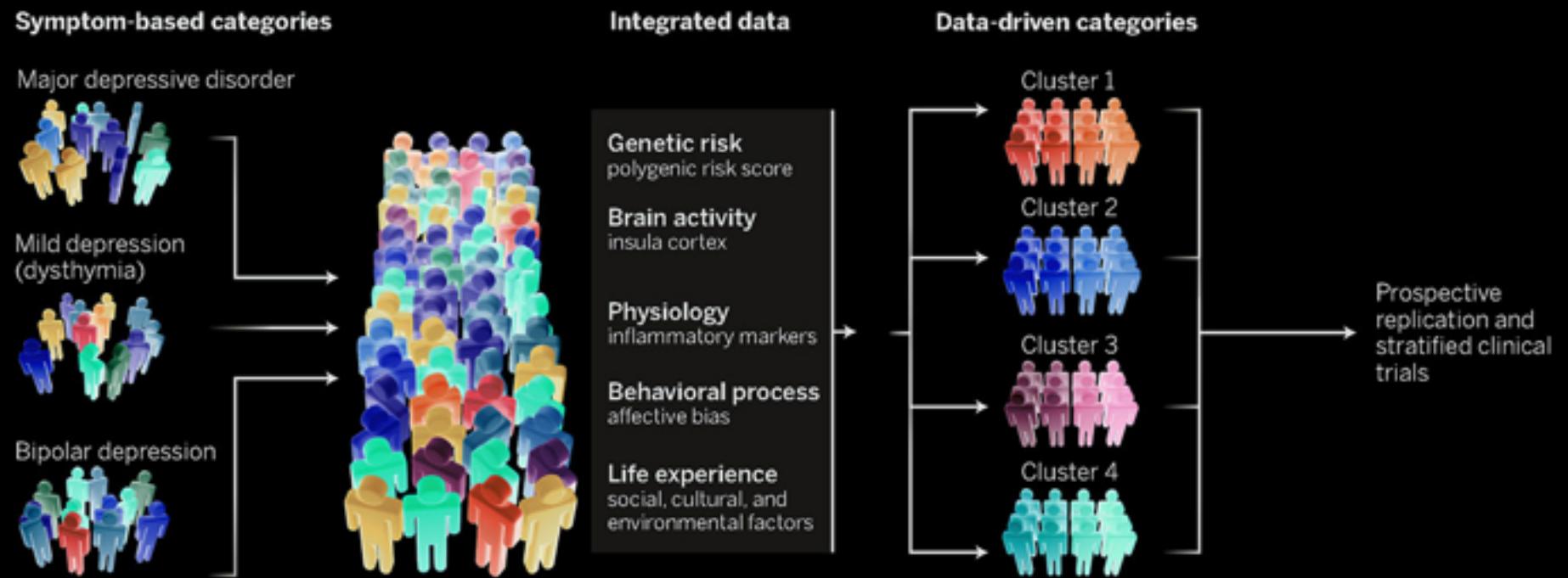


Evans, Collins, Holmes



Mueller et al 2013 Neuron





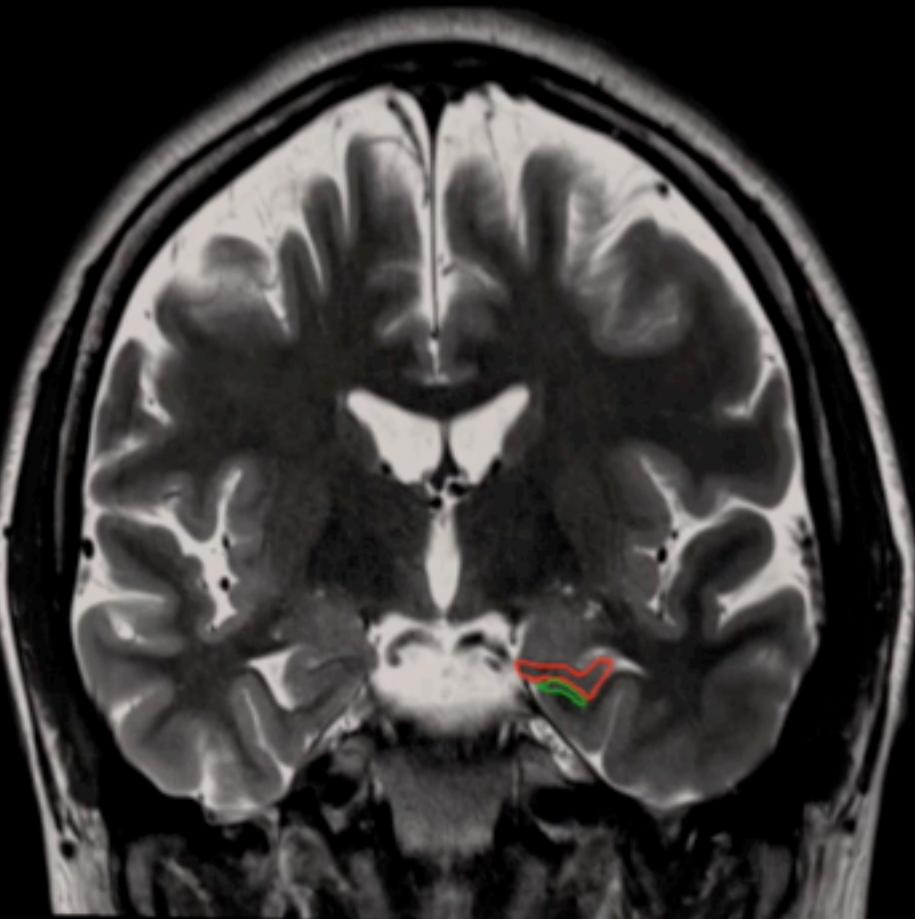
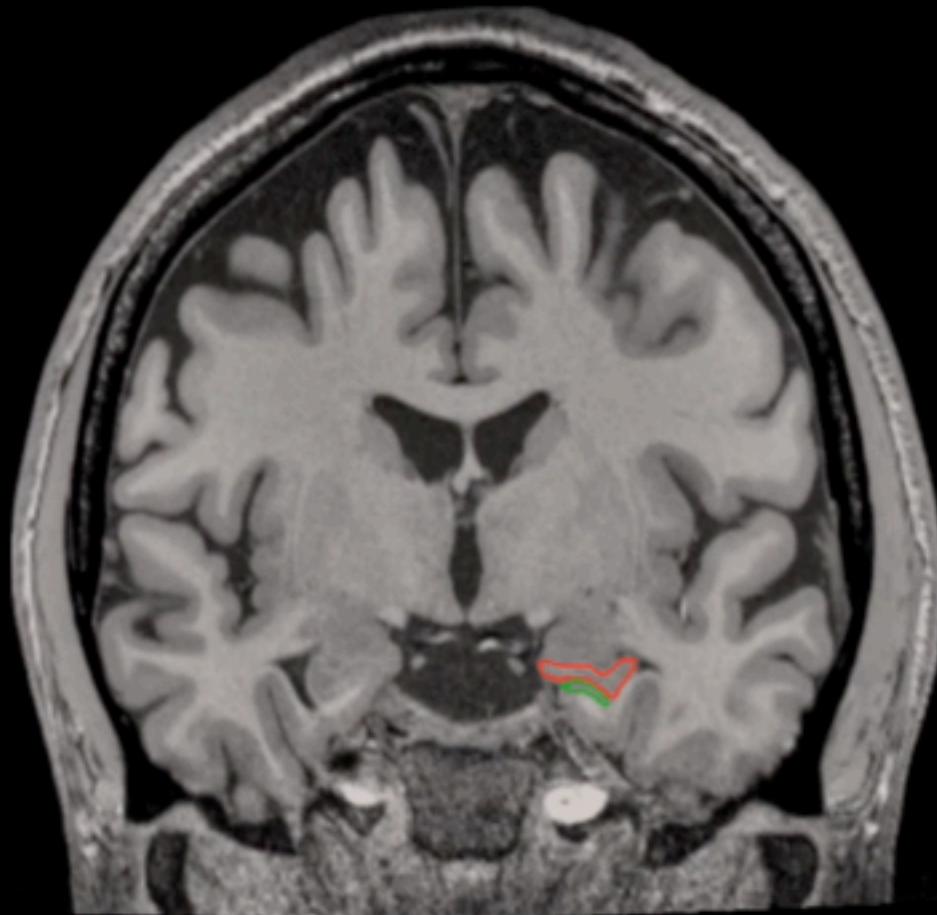
# OUTLINE

MULTIMODAL AND MULTISCALE MRI:  
FROM CORTICAL MICROSTRUCTURE TO LARGE-SCALE NETWORKS

APPLICATION TO EPILEPSY:  
INTEGRATING HIGH-DEF MRI WITH LARGE-SCALE NETWORKS  
TO INFER HISTOPATHOLOGY, SURGICAL OUTCOMES, AND DISEASE MECHANISMS

STUDIES IN AUTISM:  
NEUROIMAGING-DERIVED ASD SUBTYPING AND  
THE INTERPLAY BETWEEN CORTICAL MORPHOLOGY AND CONNECTOMICS

HEALTHY BRAIN SUBTYPES  
FOCUS ON SOCIAL COGNITION

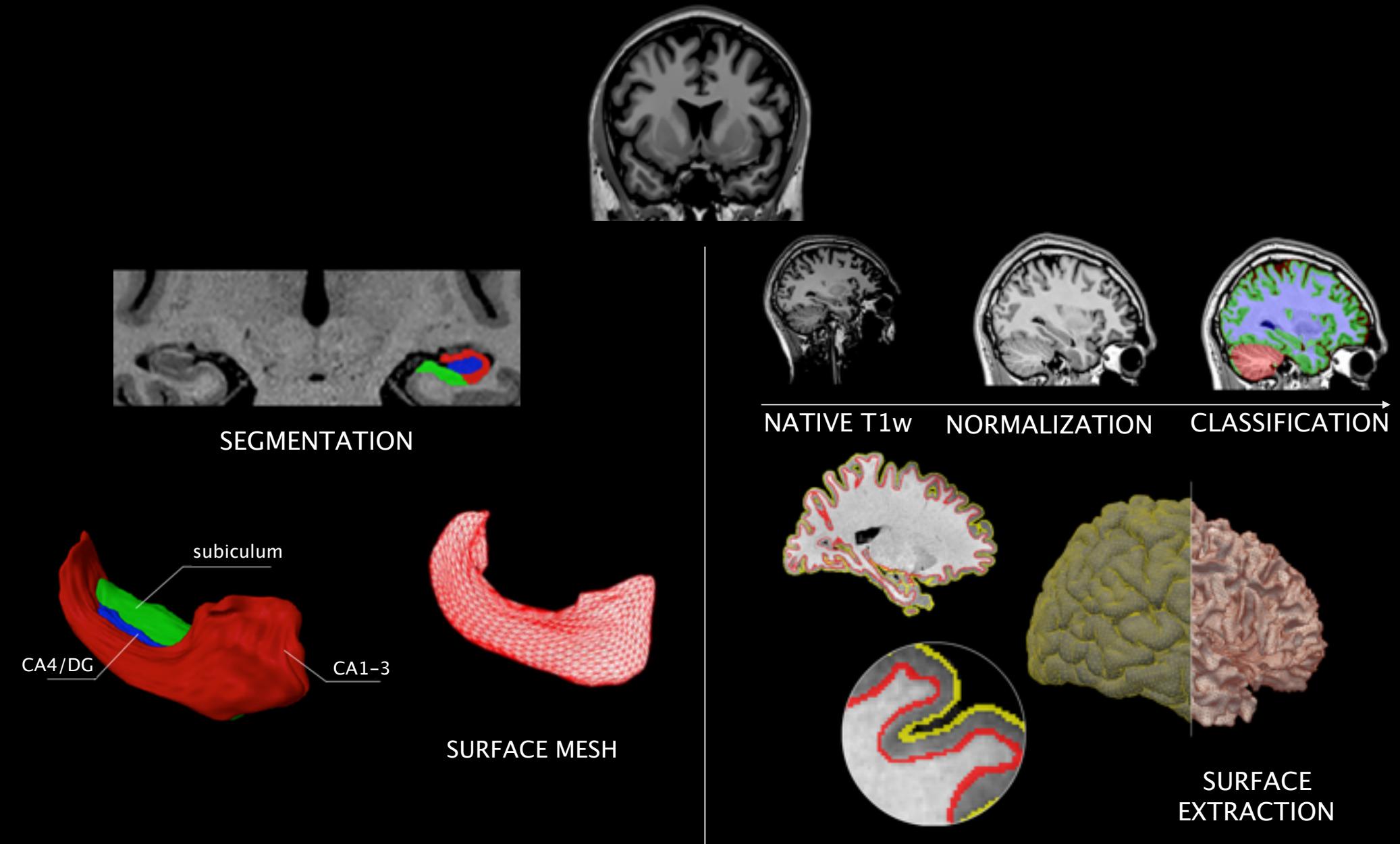


Courtesy of Jessie Kulaga-Yoskovitz



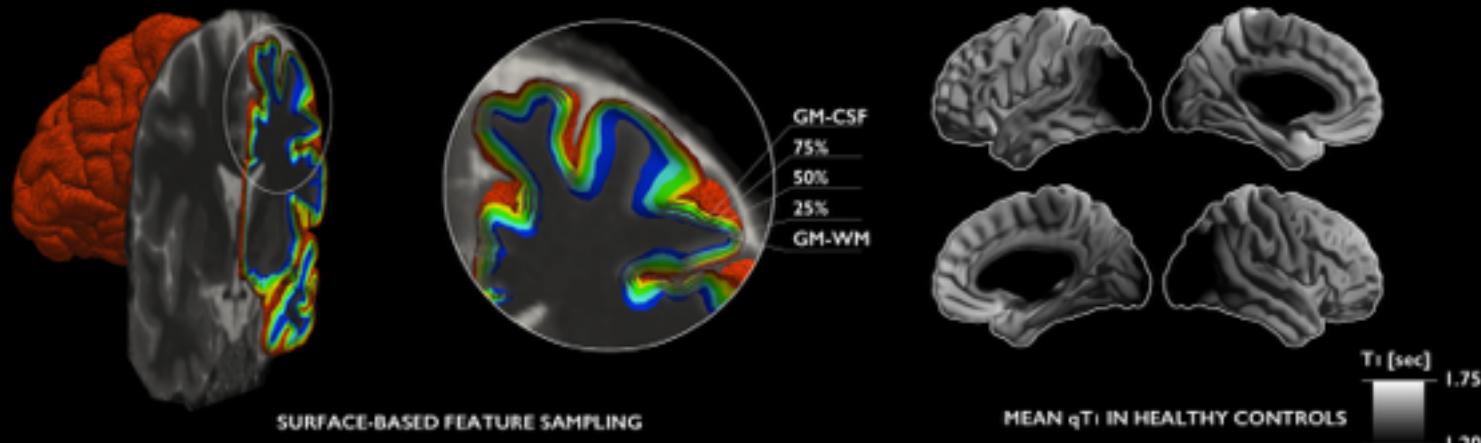
Courtesy of Alfred Anwander

# MODELLING LOCAL STRUCTURE

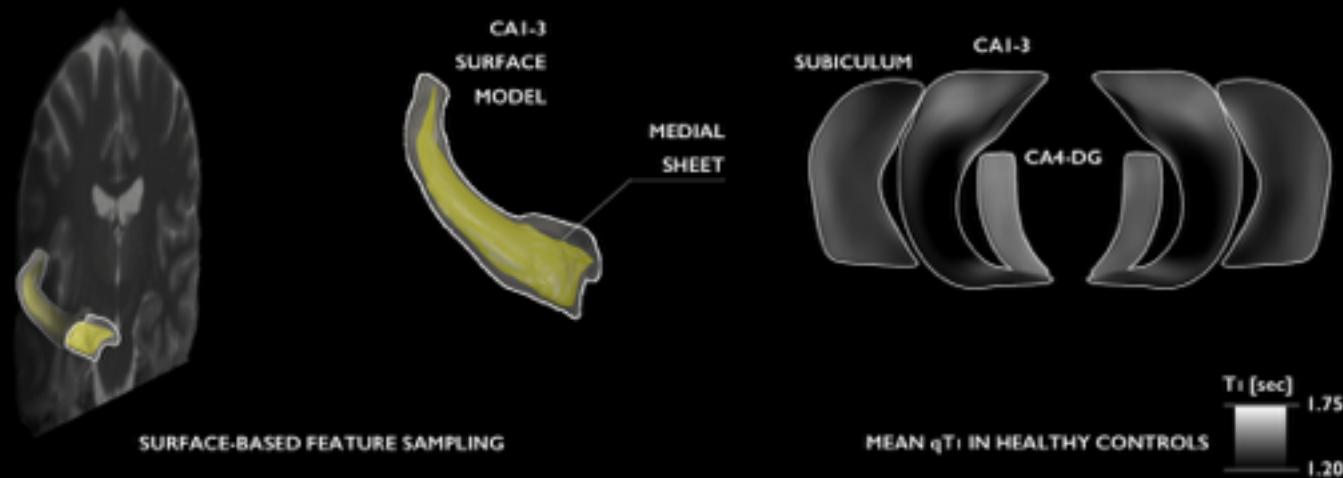


# MODELLING LOCAL STRUCTURE

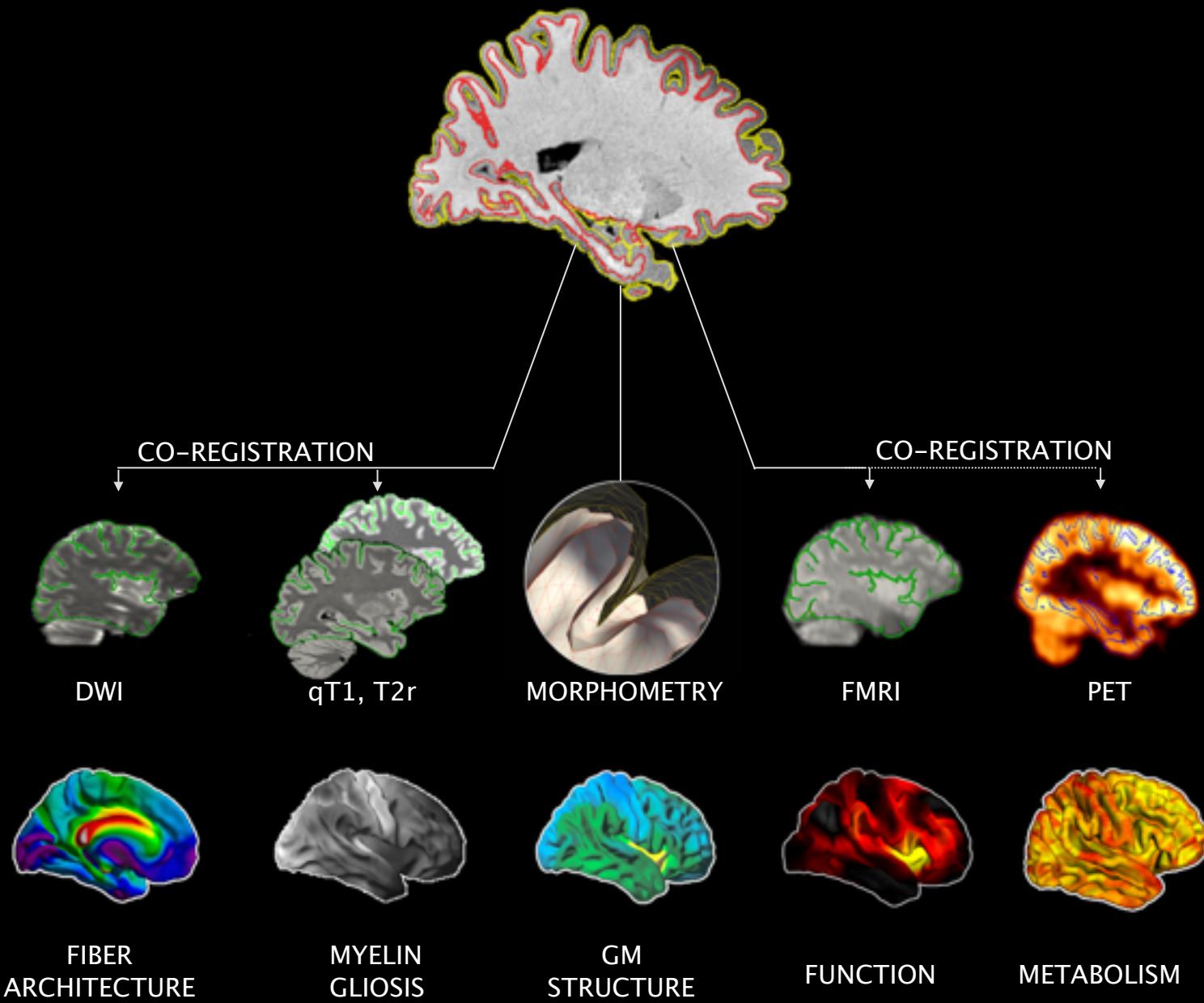
## A NEOCORTICAL $qT_1$ MAPPING



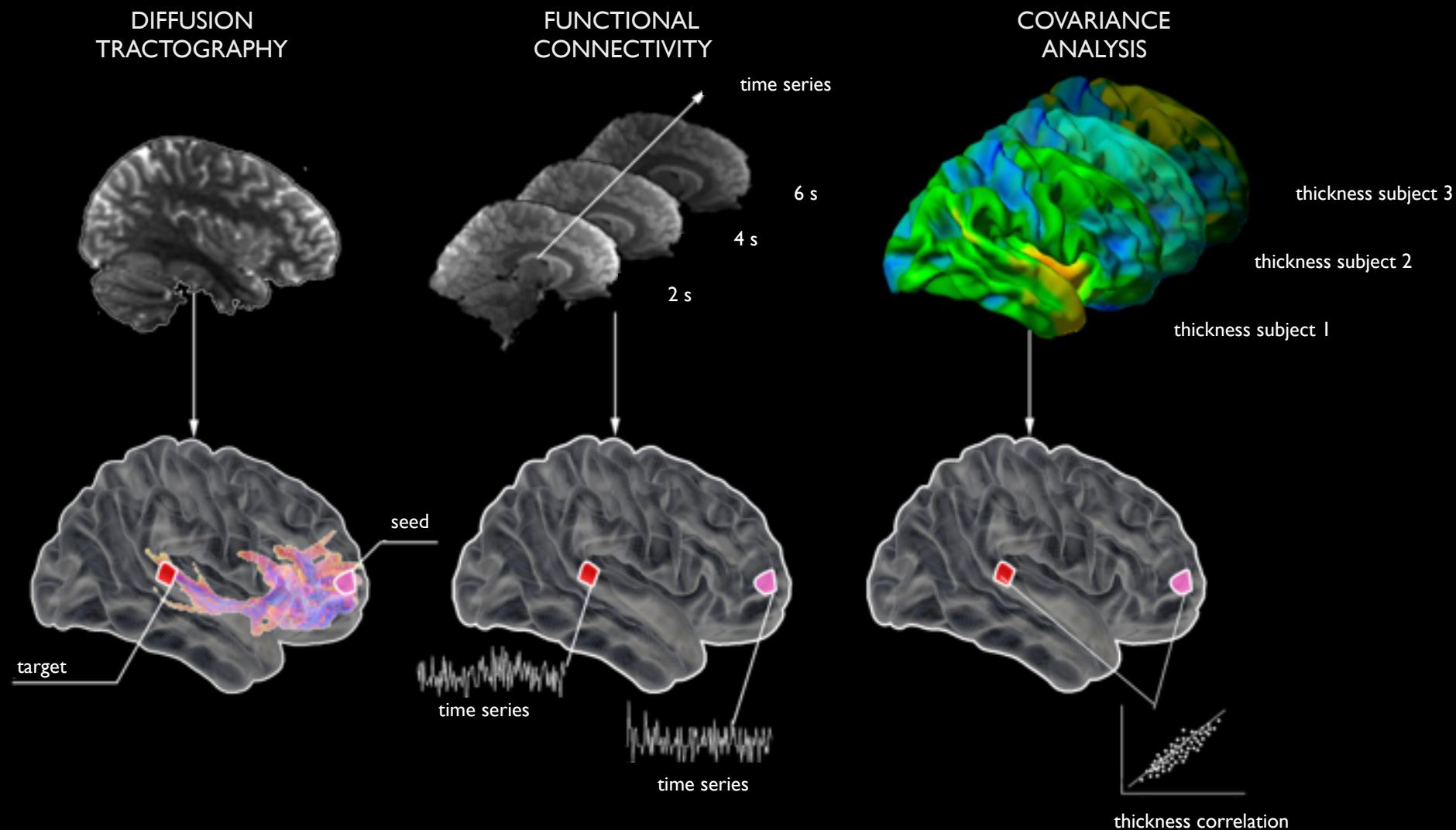
## B HIPPOCAMPAL $qT_1$ MAPPING



# MULTIMARKER INTEGRATION



# INTER-REGIONAL CONNECTIVITY ANALYSIS

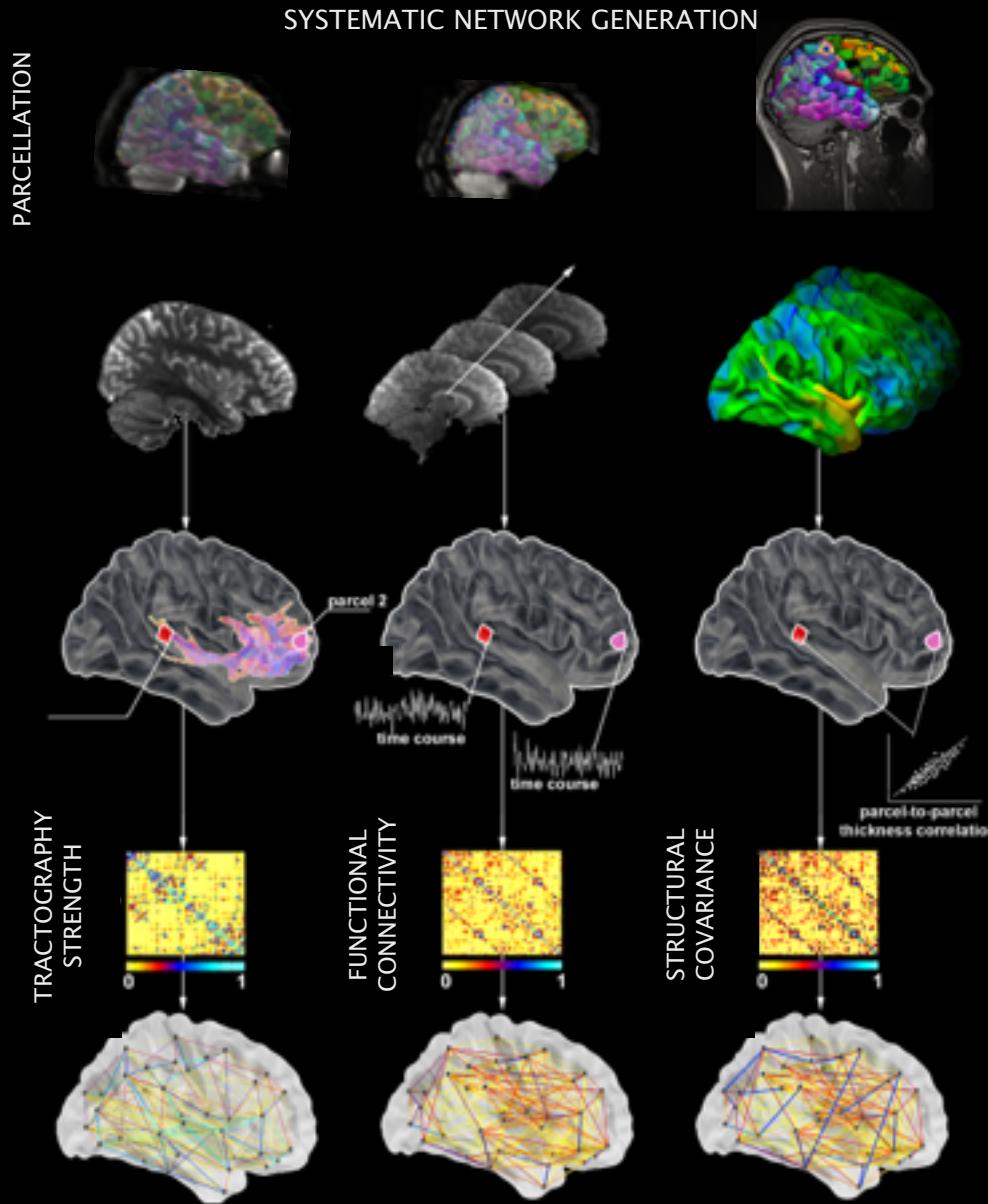


Mori et al. (1999) Ann Neu  
Behrens et al. (2007) NIMG

Biswal (1995) MRM  
Friston (1994) HBM  
Smith (2012) NIMG

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

# CONNECTOME SCALE



EPILEPSY

CHRONIC SEIZURES

0.5–1.5% OF POPULATION

HETEROGENOUS

30% OF PATIENTS ARE  
DRUG-RESISTANT

MULTIDISCIPLINARY  
ASSESSMENT



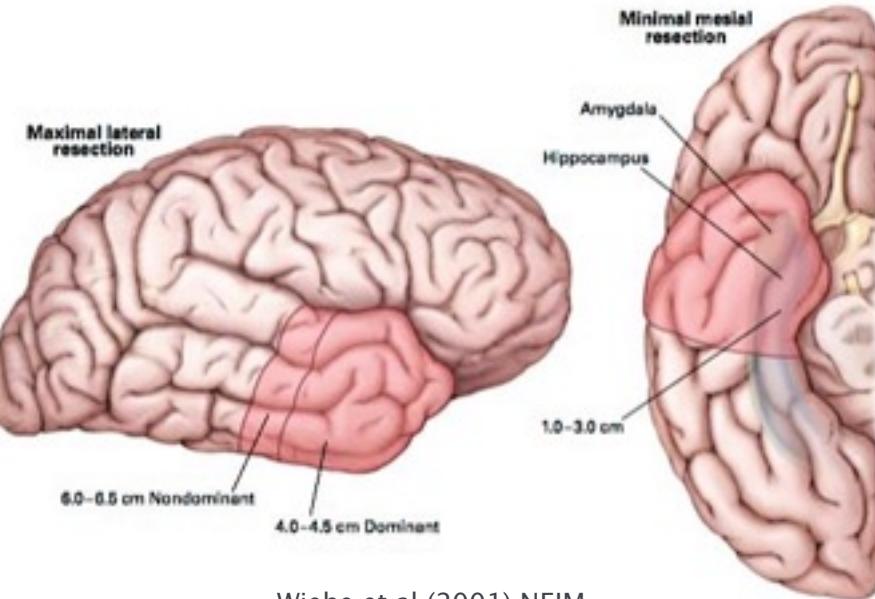
# TEMPORAL LOBE EPILEPSY

ONE OF THE MOST COMMON  
DRUG-RESISTANT  
EPILEPSIES IN ADULTS

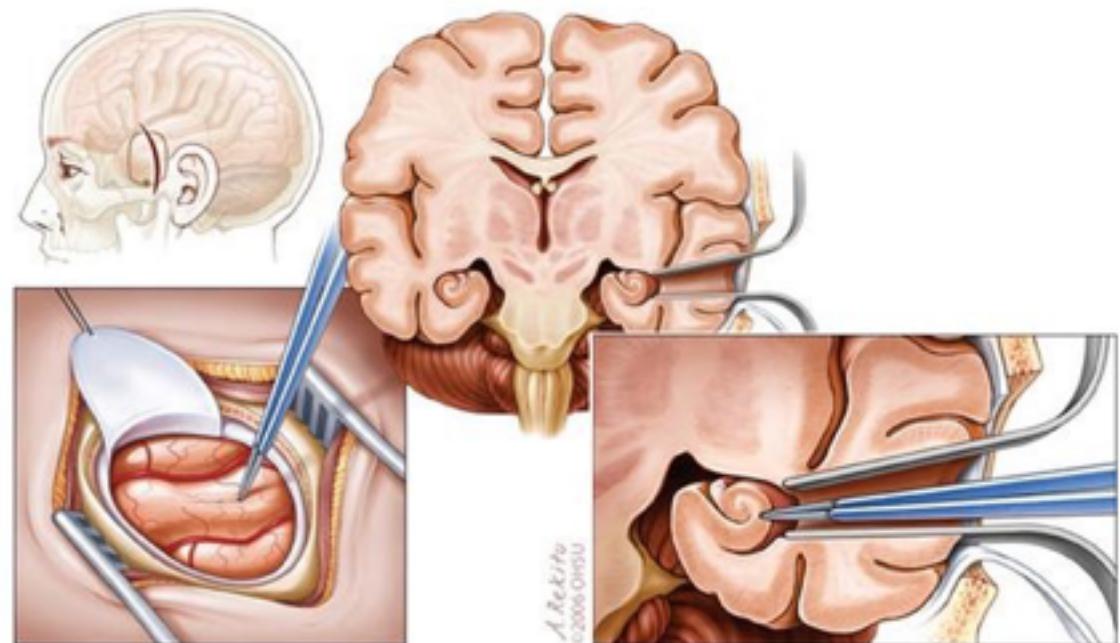
SEIZURES ARISING FROM TL

SURGERY MOST EFFECTIVE  
TREATMENT

ASSOCIATED WITH  
HIPPOCAMPAL SCLEROSIS (HS)



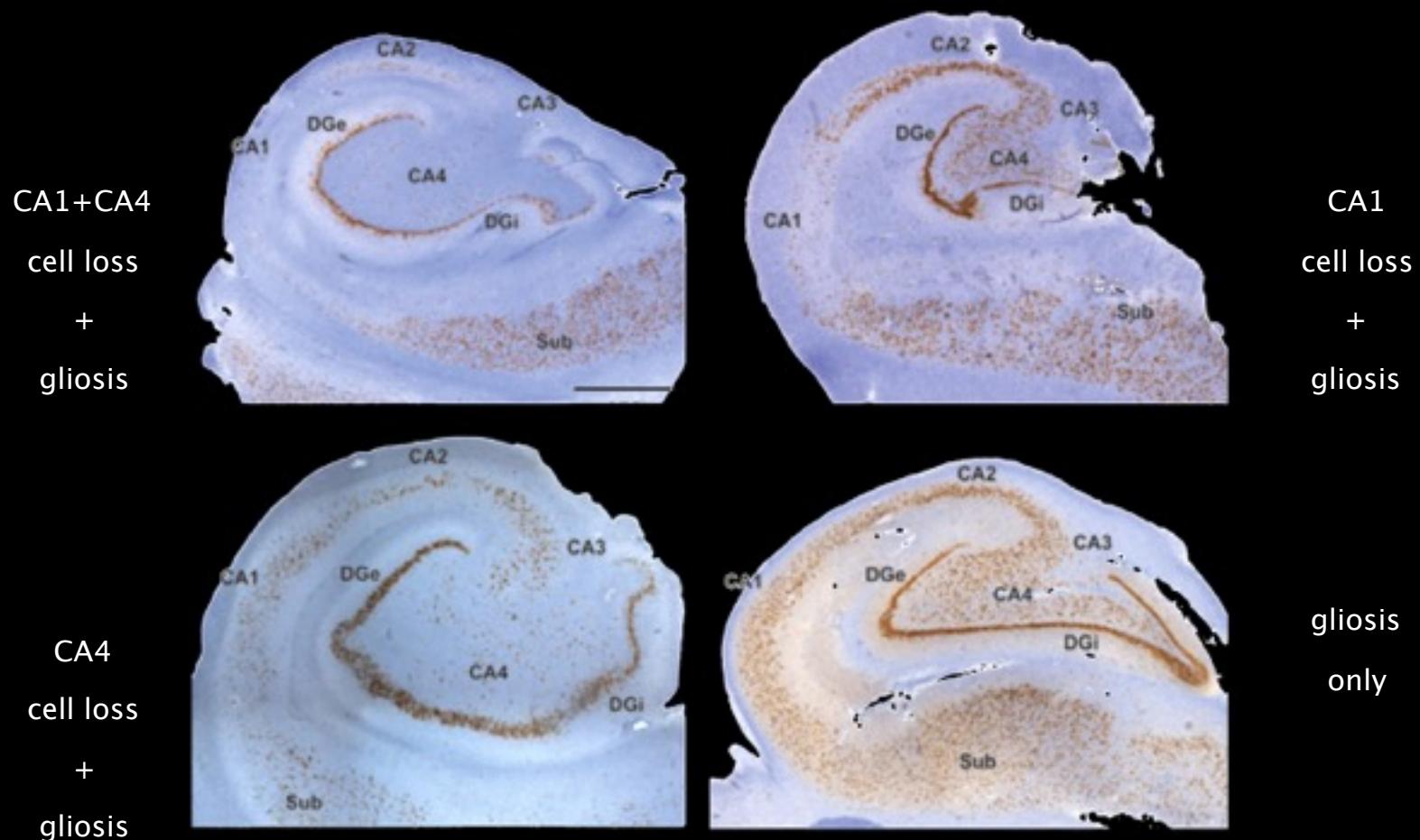
Wiebe et al (2001) NEJM



Spencer & Burchiel (2012) Epilepsy Research and Treatment

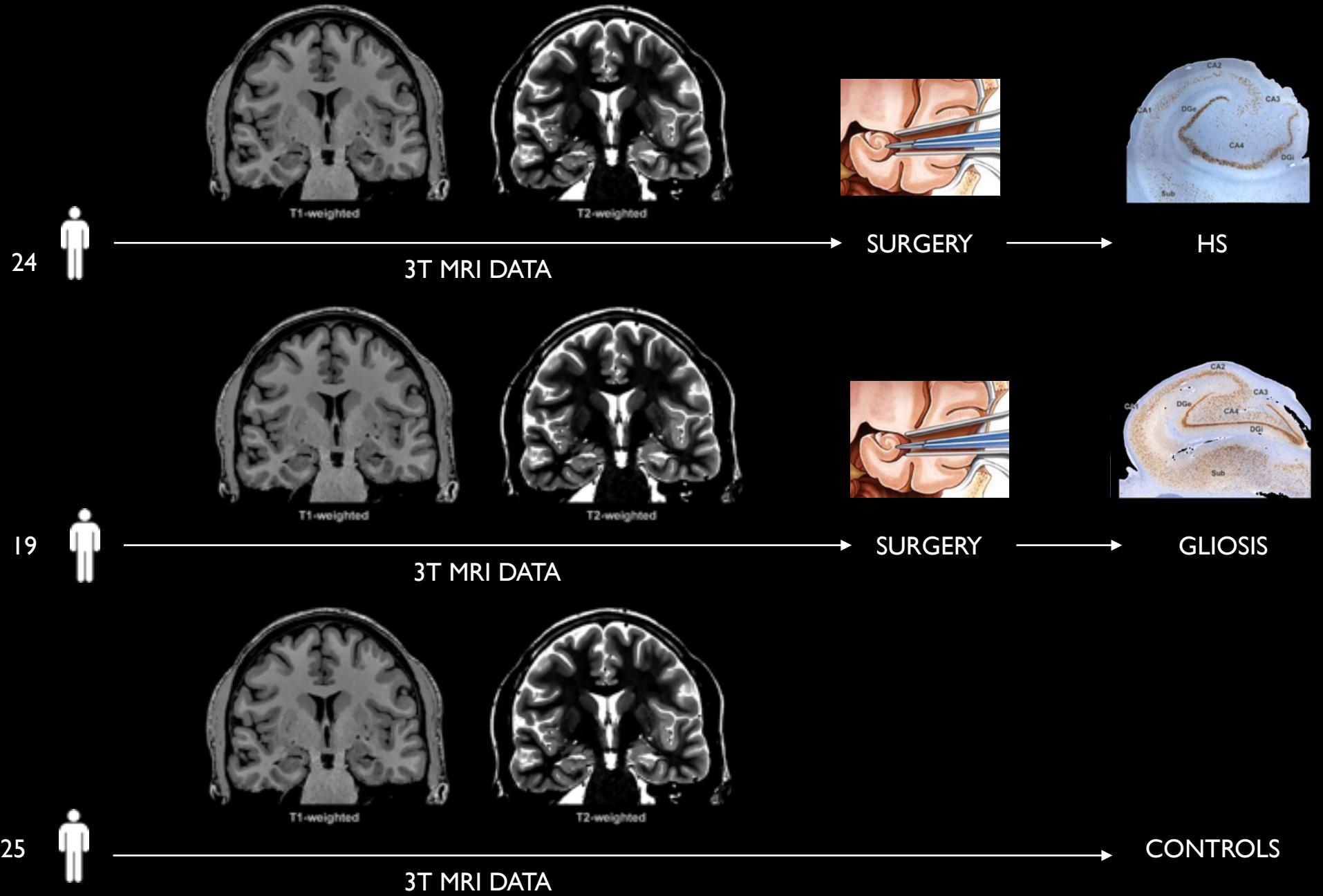
# TEMPORAL LOBE EPILEPSY

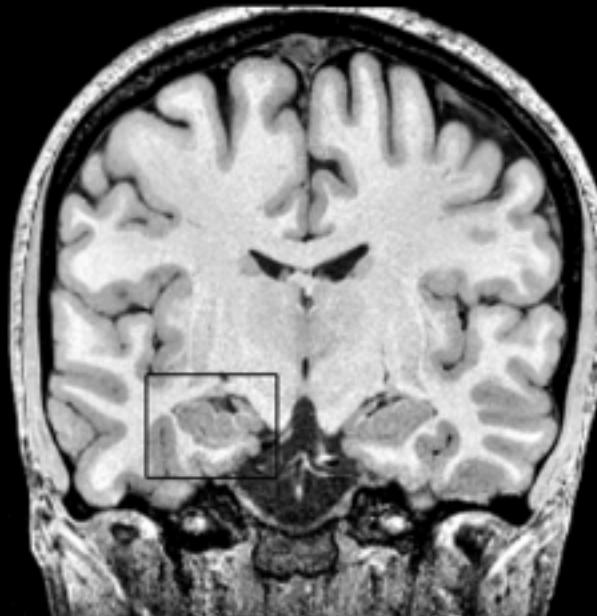
HS IS THE TLE HALLMARK BUT NOT A SINGLE ENTITY



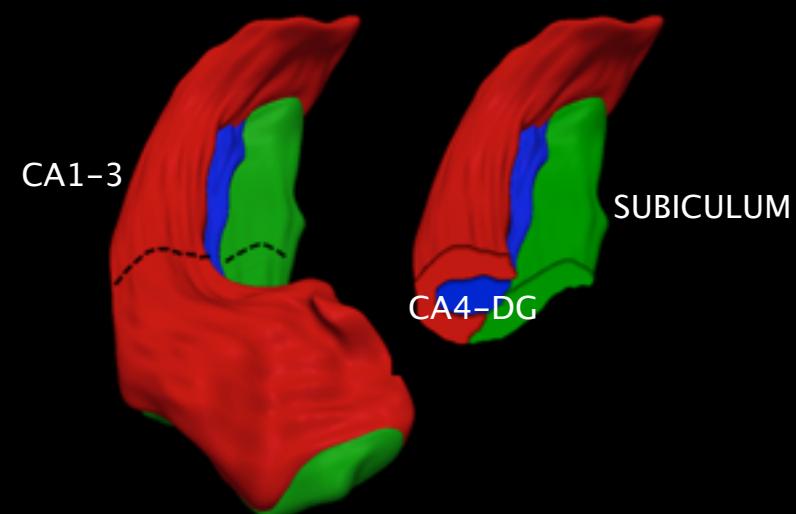
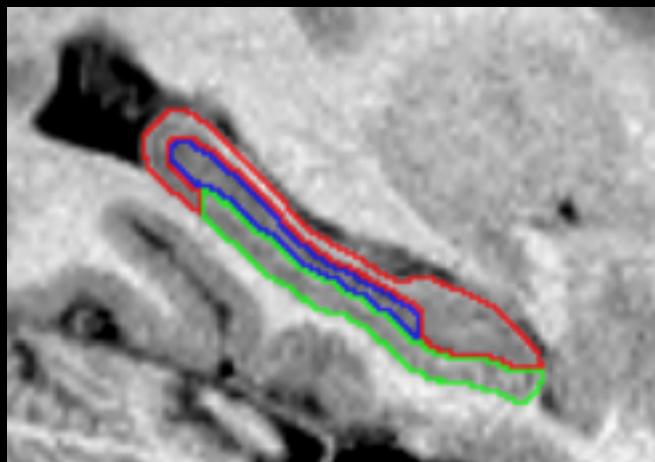
CAN WE DETECT HS SUBTYPES IN VIVO?

# STUDY DESIGN

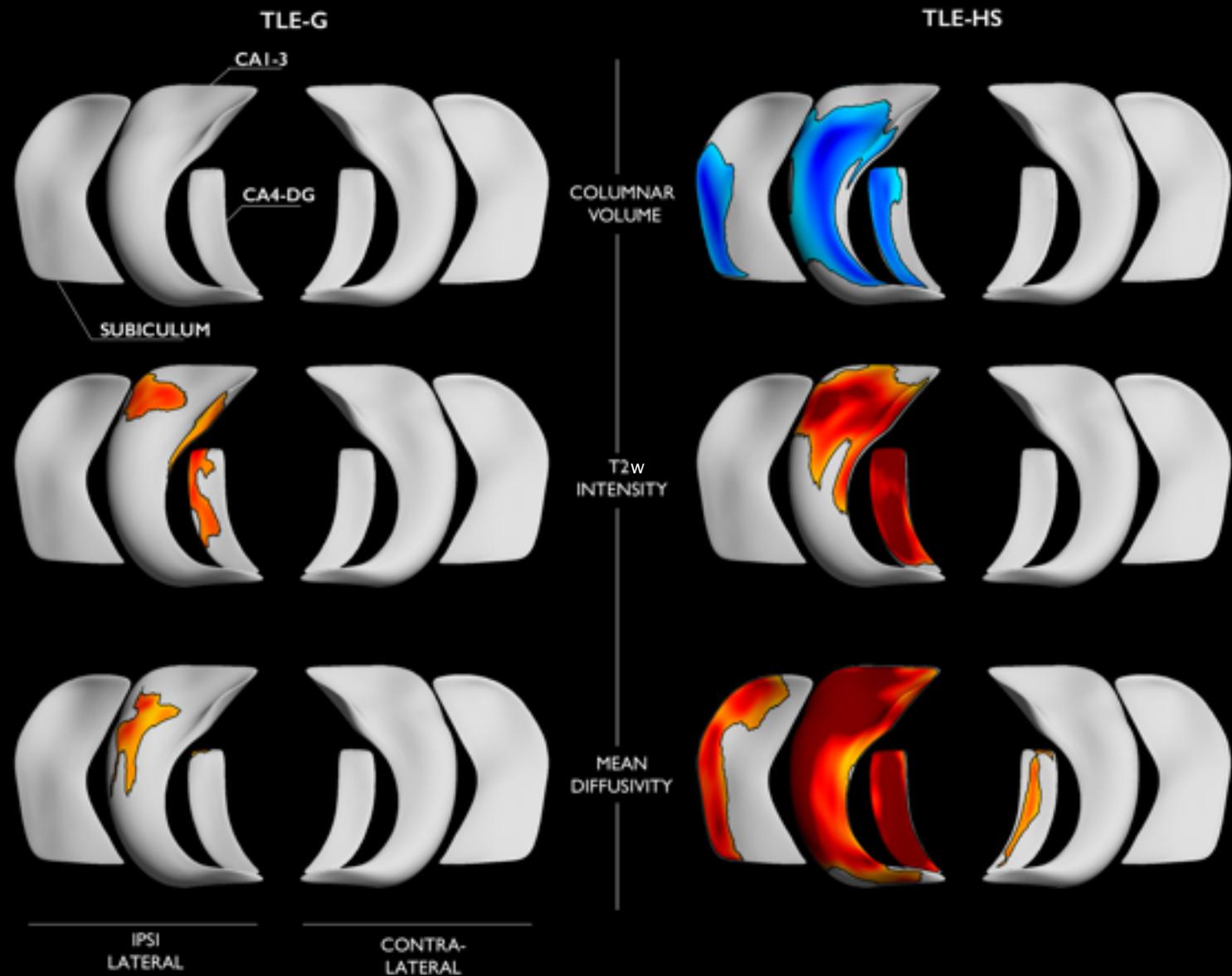




<https://www.nitrc.org/projects/mni-hisub25/>

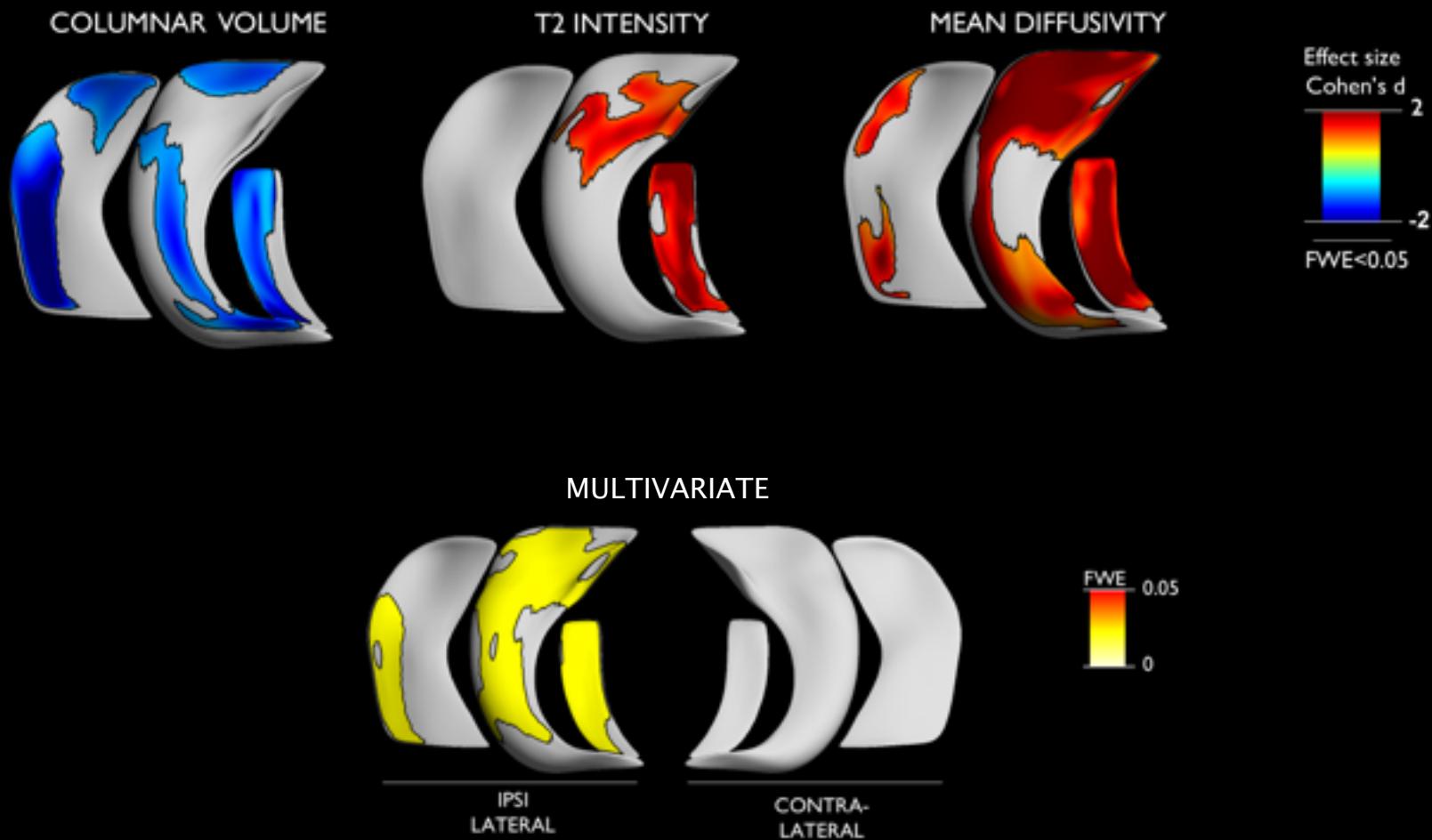


## FEATURE-SPECIFIC COMPARISON TO CONTROLS

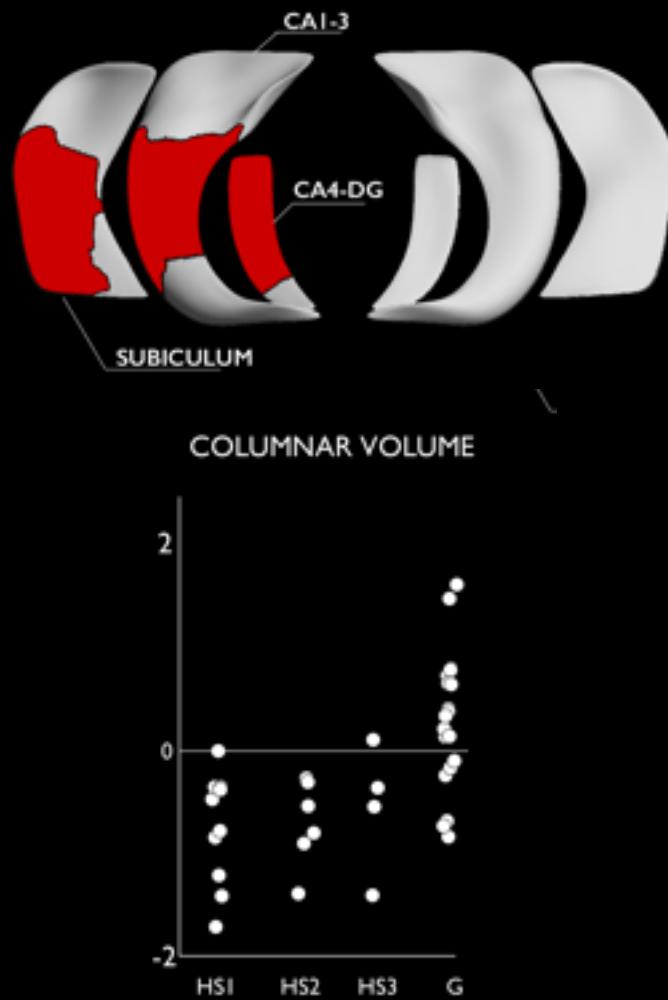


# DIRECT CONTRASTS

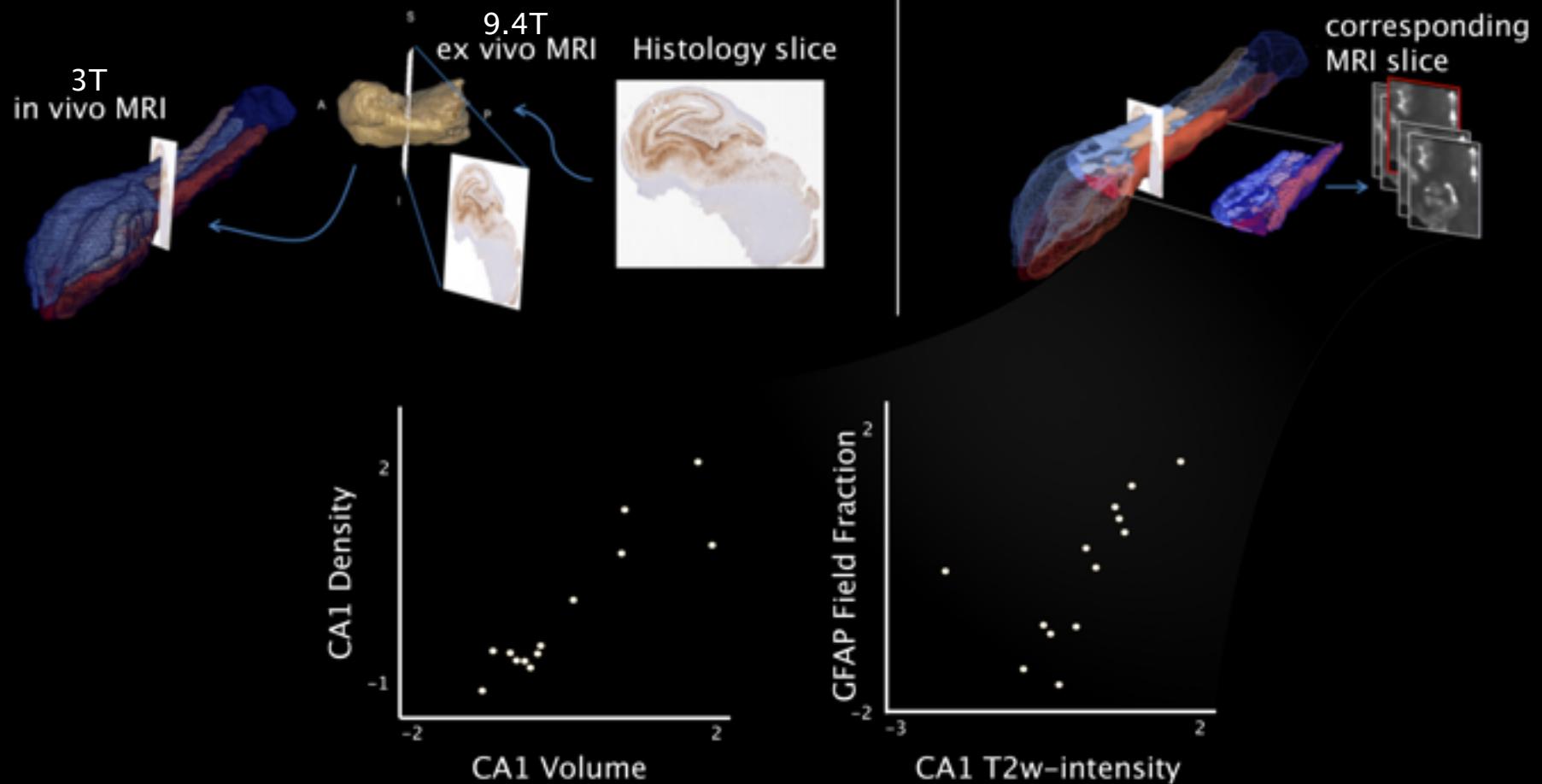
## B DIRECT CONTRAST: TLE-HS vs TLE-G



## RELATION TO SPECIFIC HISTOLOGICAL HS GRADES



# VALIDATION OF IN VIVO FINDINGS WITH QUANTITATIVE HISTOPATHOLOGY



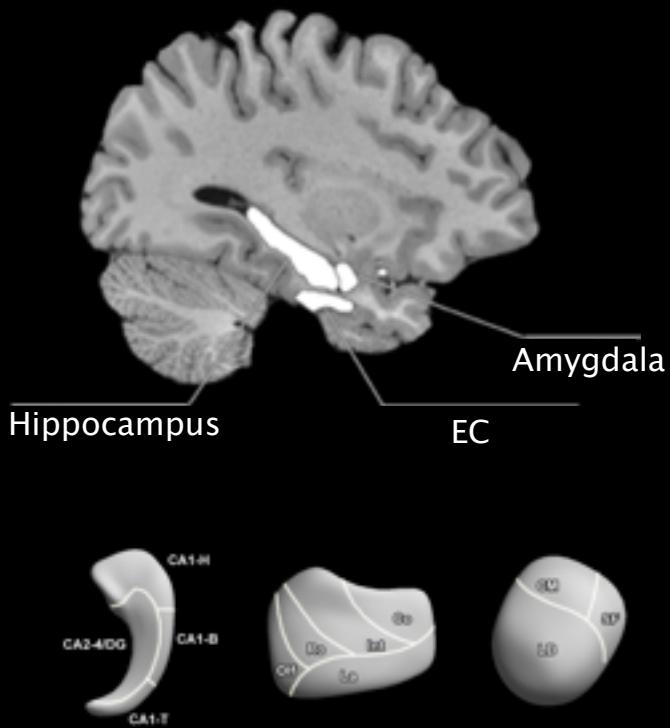
SUBFIELD-SPECIFIC CORRELATIONS BETWEEN MRI AND HISTOLOGY

IS TLE ADEQUATELY CAPTURED BY HIPPOCAMPUS ALONE?

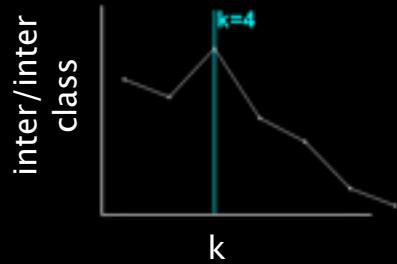
# MRI PROFILING AND SUBTYPING

## MESIOTEMPORAL PROFILING

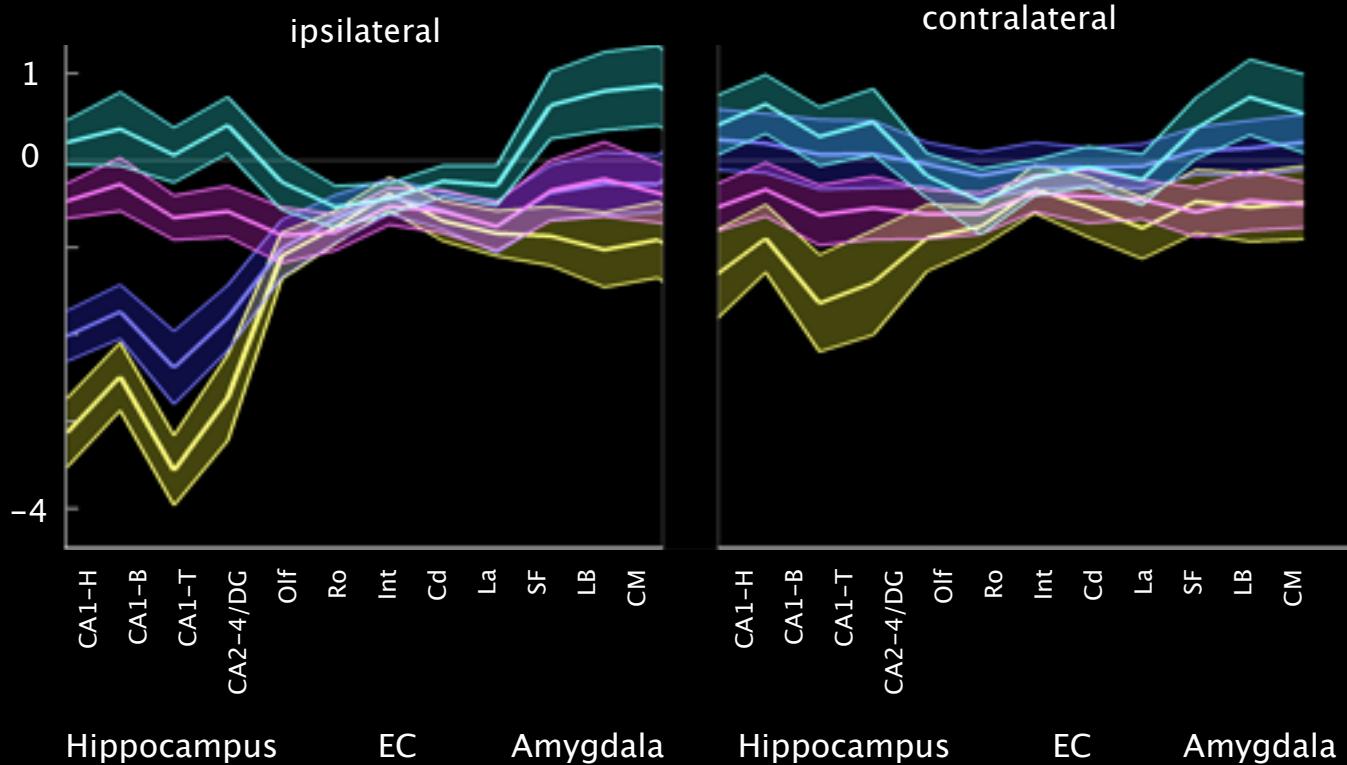
n=114



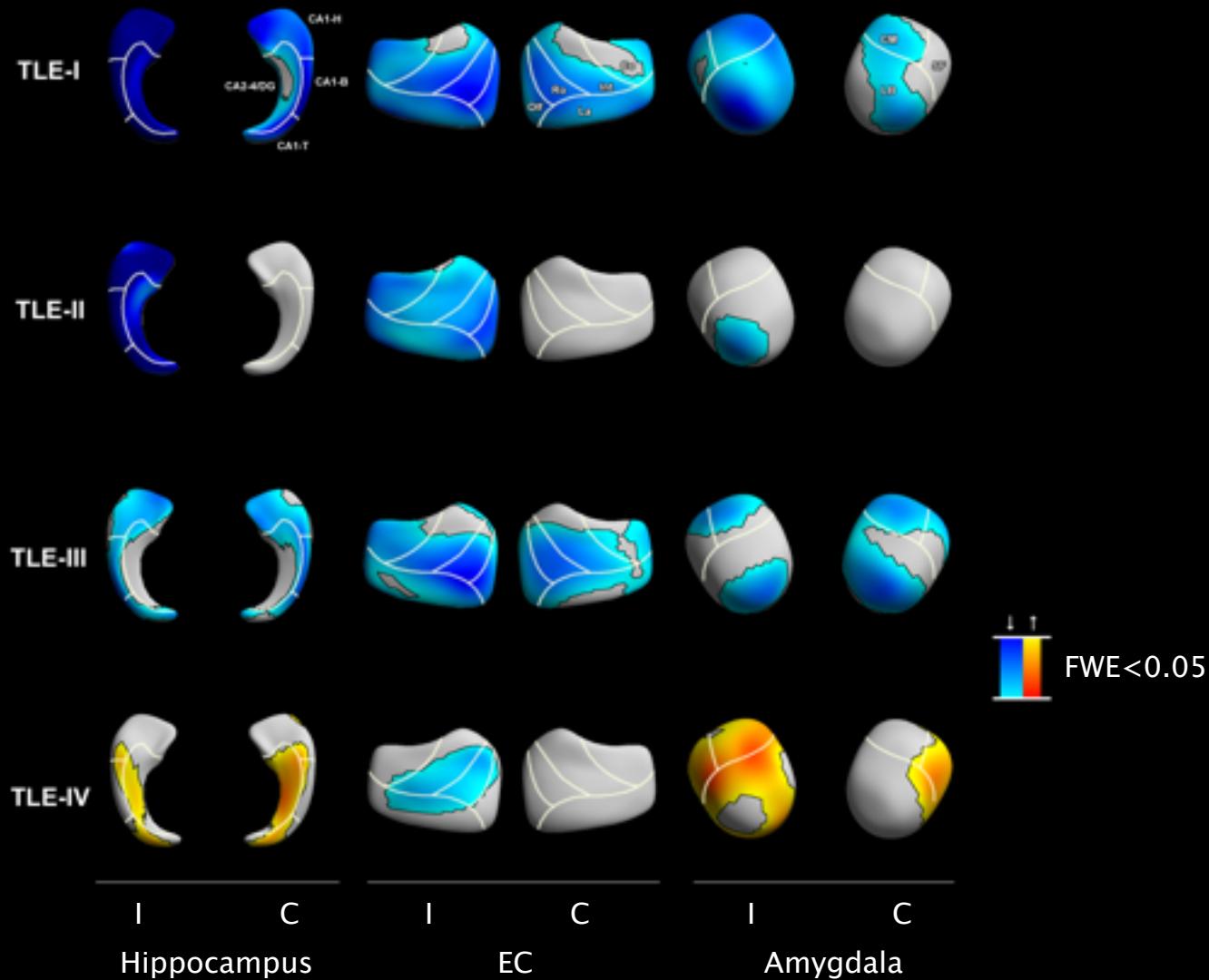
## CLUSTERING PATIENT SPECTRUM BASED ON MRI MORPHOMETRY



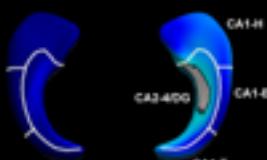
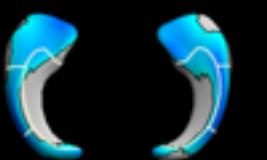
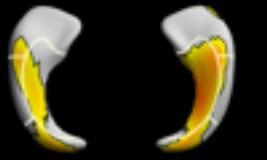
- TLE-I
- TLE-II
- TLE-III
- TLE-IV



## DATA-DRIVEN SUBCLASSES

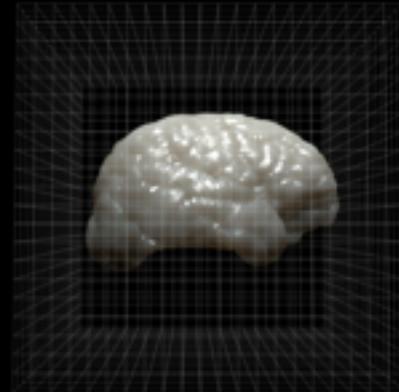


## RELATION TO IMAGING-INDEPENDENT CRITERIA

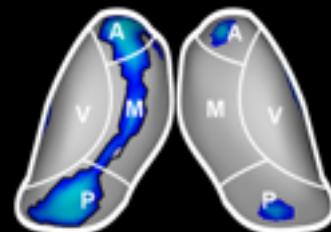
		HS/Gliosis	Engel-I	
TLE-I		71/29%	68%	<p><b>LDA outcome prediction:</b></p> <p>class + surface data: 92%</p> <p>surface-measures only: 81%</p> <p>volumetry: 71%</p>
TLE-II		72/28%	89%	
TLE-III		43/57%	65%	
TLE-IV		17/83%	44%	
	I C			
	Hippocampus			

DO ANOMALIES EXTEND BEYOND THE MESIOTEMPORAL REGIONS?

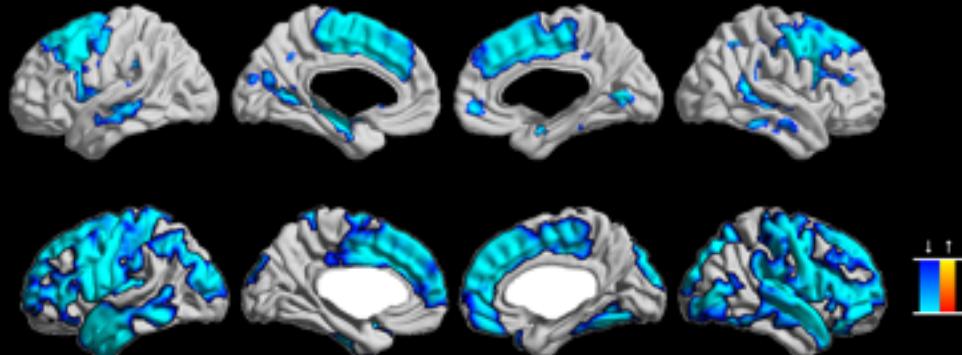
## WHOLE-BRAIN GREY MATTER



Keller 2002 JNNP, Bonilha 2004/06 NIMG, Bernasconi 2004 NIMG

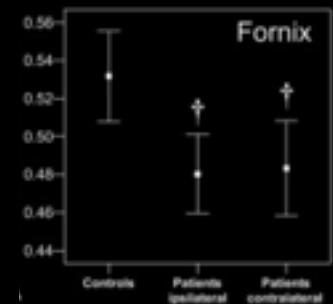
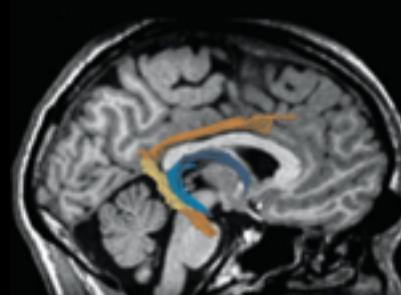


Neurology 2012

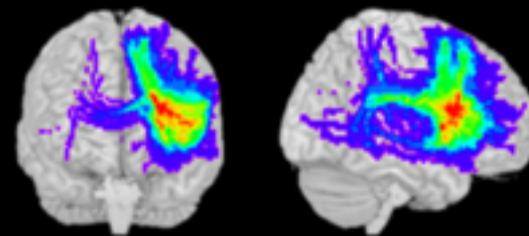


Lin 2007 CerCor, McDonald 2008 Epilepsy, Bernhardt 2008 NIMG

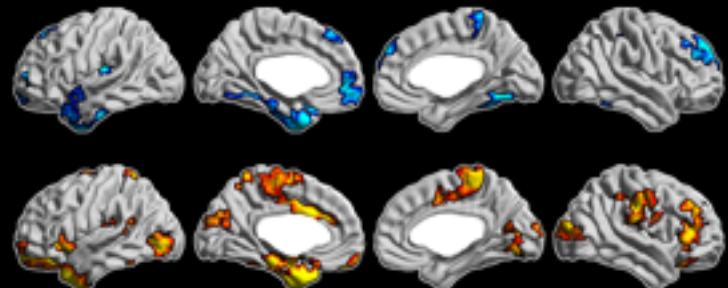
## WHOLE-BRAIN WHITE MATTER



Concha 2005 Ann Neu

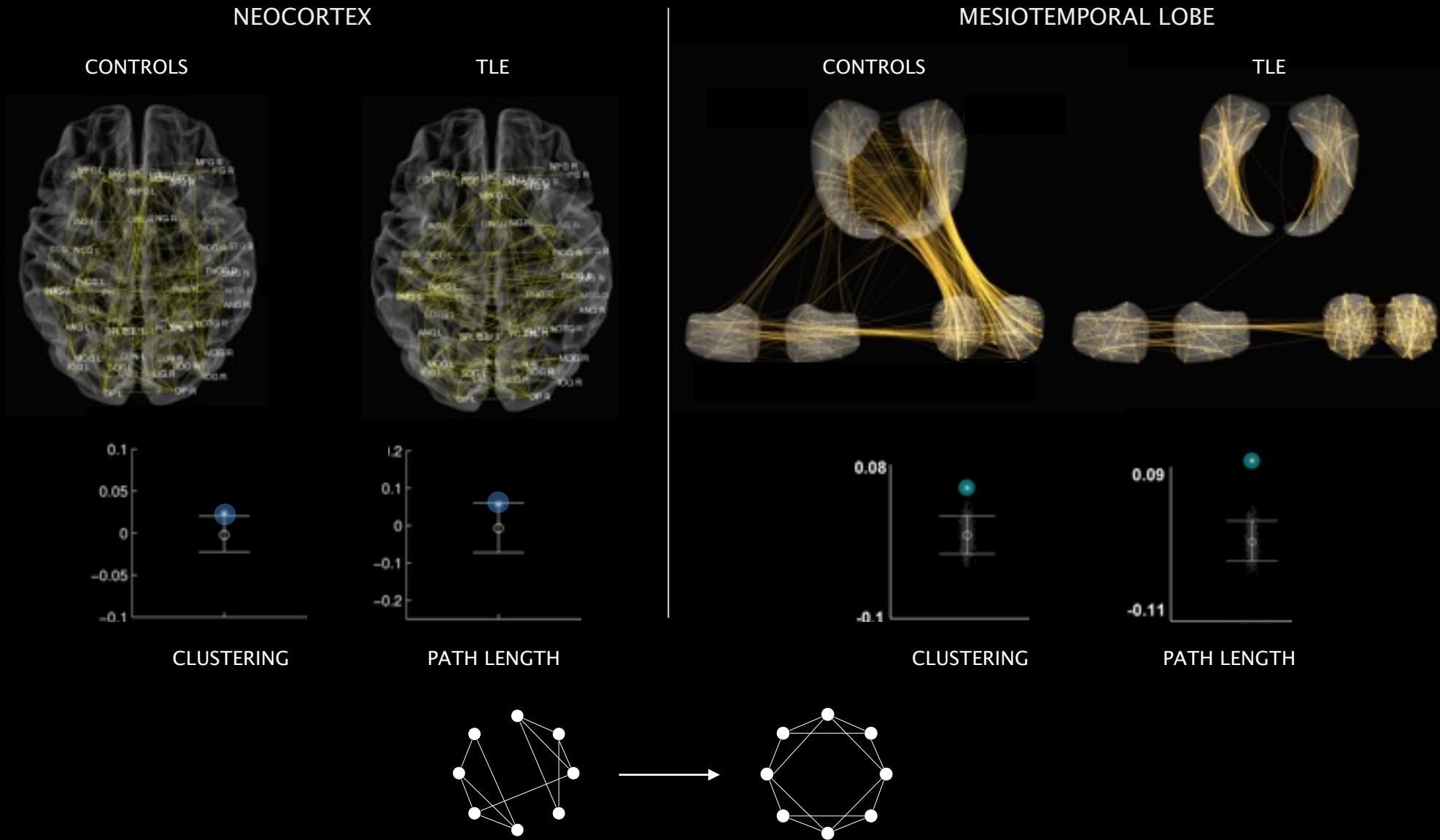


Powell 2006 NIMG

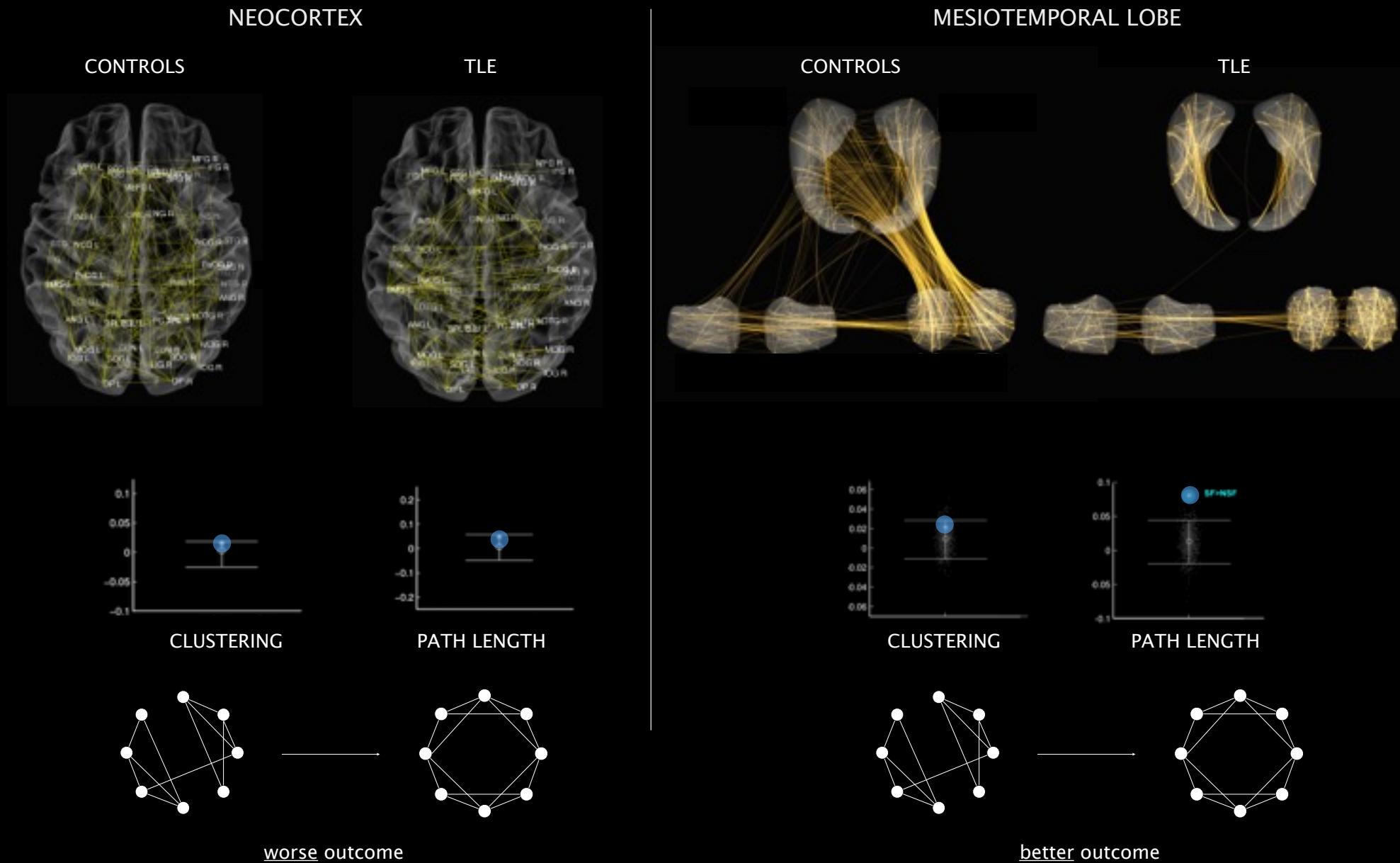


Liu 2016 Brain

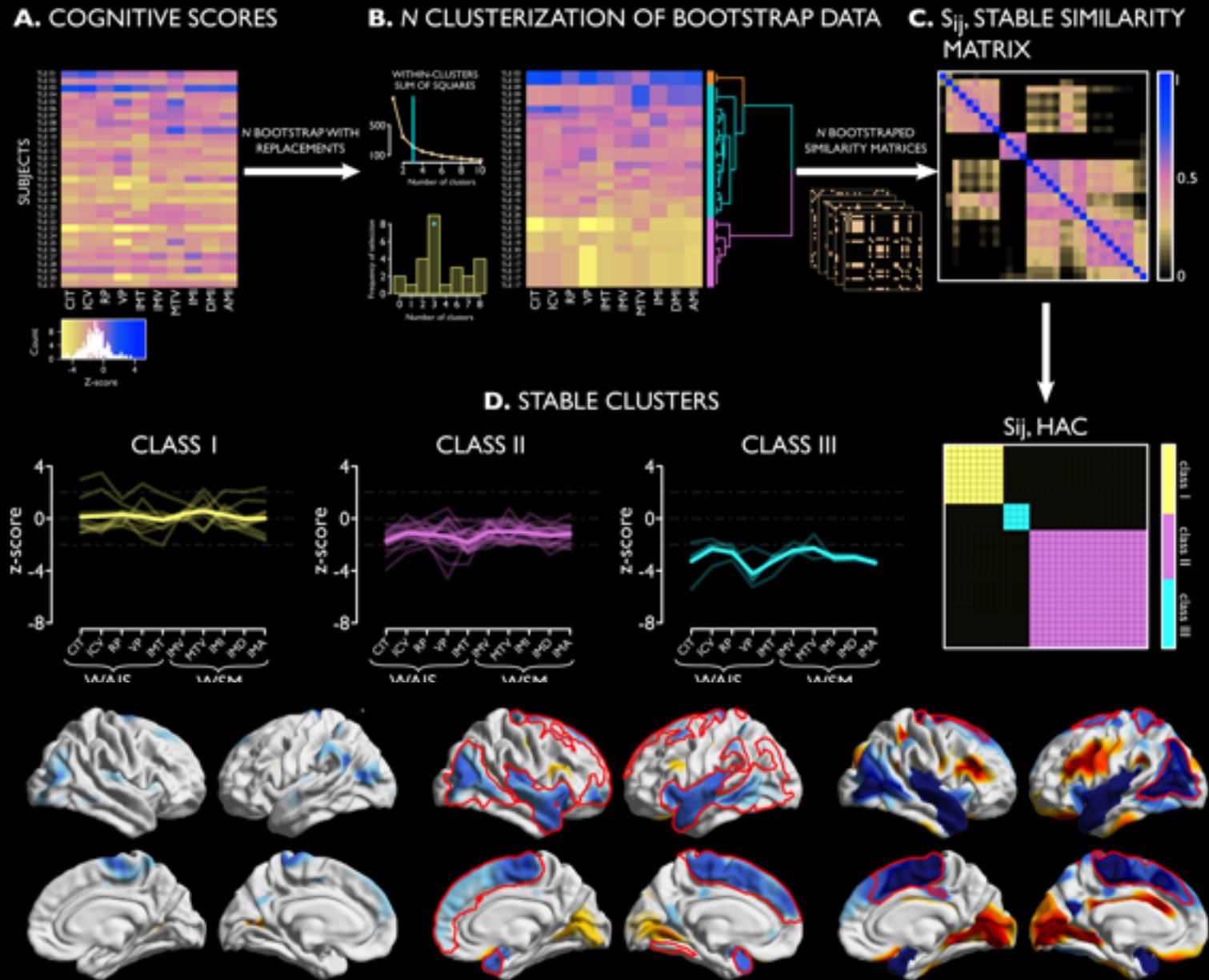
# NETWORK-LEVEL PHENOTYPING



# RELATIONSHIP TO OUTCOME



# LINKING COGNITIVE AND BRAIN PHENOTYPES



# INTERIM SUMMARY EPILEPSY

IN-VIVO IDENTIFICATION  
OF HS SUBTYPES – PREOPERATIVE STRATIFICATION

MESIOTEMPORAL SUBTYPING:  
PREDICTION OF LONG-TERM OUTCOMES

WHOLE-BRAIN ANALYSIS  
AND RELATION TO COGNITIVE PHENOTYPES

# AUTISM SPECTRUM DISORDER

COMMON  
NEURODEVELOPMENTAL DISORDER

PERSISTS UNTIL ADULTHOOD

CORE DEFICITS  
IN SOCIAL COGNITION AND  
COMMUNICATION

DIAGNOSIS AND THERAPY CHALLENGED  
BY CONSIDERABLE HETEROGENEITY



# PREVIOUS STRUCTURAL MRI WORK

INCONSISTENT LOCATION OF FINDINGS  
INCONSISTENT DIRECTION  
MIXED INCLUSION CRITERIA  
VARIABLE AGE RANGES  
ONLY SMALL SAMPLES STUDIED



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)



European Psychiatry 23 (2008) 289–299

EUROPEAN  
PSYCHIATRY

<http://www.sciencedirect.com/science/EUROPSY/>

Review

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

Andrew C. Stanfield <sup>a,\*</sup>, Andrew M. McIntosh <sup>a</sup>, Michael D. Spencer <sup>a</sup>,  
Ruth Philip <sup>a</sup>, Sonia Gaur <sup>b</sup>, Stephen M. Lawrie <sup>a</sup>

<sup>a</sup>Division of Psychiatry, School of Molecular and Clinical Medicine, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, EH10 5HF, UK  
<sup>b</sup>2790 Skypark Drive, Suite 307, Torrance, CA 90505, USA

Received 8 December 2006; received in revised form 16 April 2007; accepted 30 May 2007  
Available online 31 August 2007

doi:10.1093/brain/awq279

Brain 2010; 133; 3745–3754 | 3745

BRAIN  
A JOURNAL OF NEUROLOGY

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

Gregory L. Wallace,<sup>1</sup> Nathan Dankner,<sup>1</sup> Lauren Kenworthy,<sup>1</sup> Jay N. Giedd<sup>2</sup> and Alex Martin<sup>1</sup>



Cerebral Cortex, 2014, 1–13

doi:10.1093/cercor/cwu242  
ORIGINAL ARTICLE

ORIGINAL ARTICLE

Anatomical Abnormalities in Autism?

Shlomi Haar<sup>1</sup>, Sigal Berman<sup>3</sup>, Marlene Behrmann<sup>4</sup>, and Ilan Dinstein<sup>1,2</sup>

<sup>1</sup>Department of Brain and Cognitive Sciences, <sup>2</sup>Department of Psychology, <sup>3</sup>Department of Industrial Engineering and Management, Ben Gurion University of the Negev, Beer Sheva 84105, Israel, and <sup>4</sup>Department of Psychology, Carnegie Mellon University, Pittsburgh, PA 15213, USA

Address correspondence to Dr Ilan Dinstein. Email: [dinst@bgu.ac.il](mailto:dinst@bgu.ac.il)

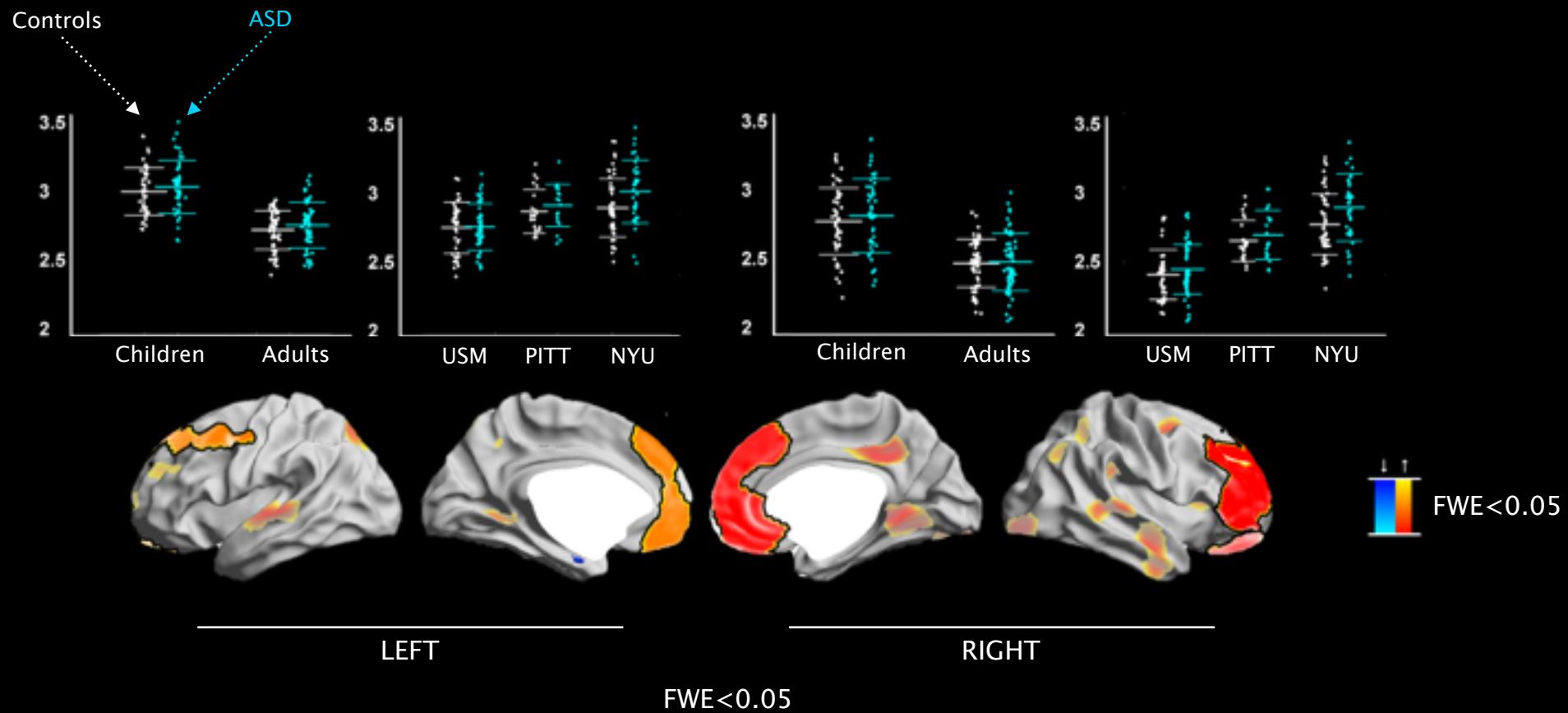
# BIG DATA ANALYSIS FOR STRUCTURAL BRAIN ANOMALIES IN AUTISM



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

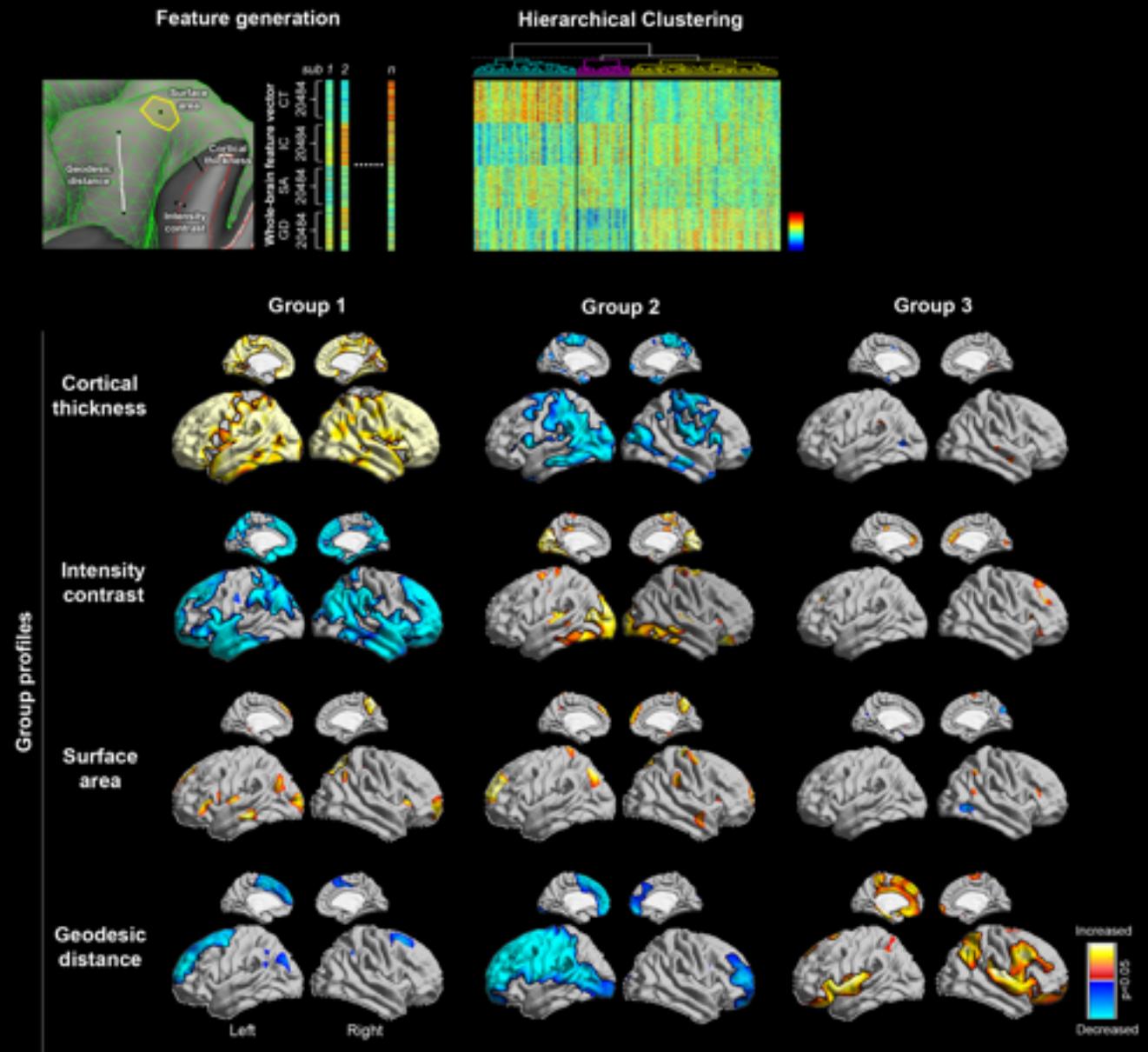
ADOS- and/or ADI-R available in all sites

# MULTI-CENTER MAPPING OF STRUCTURAL ALTERATIONS



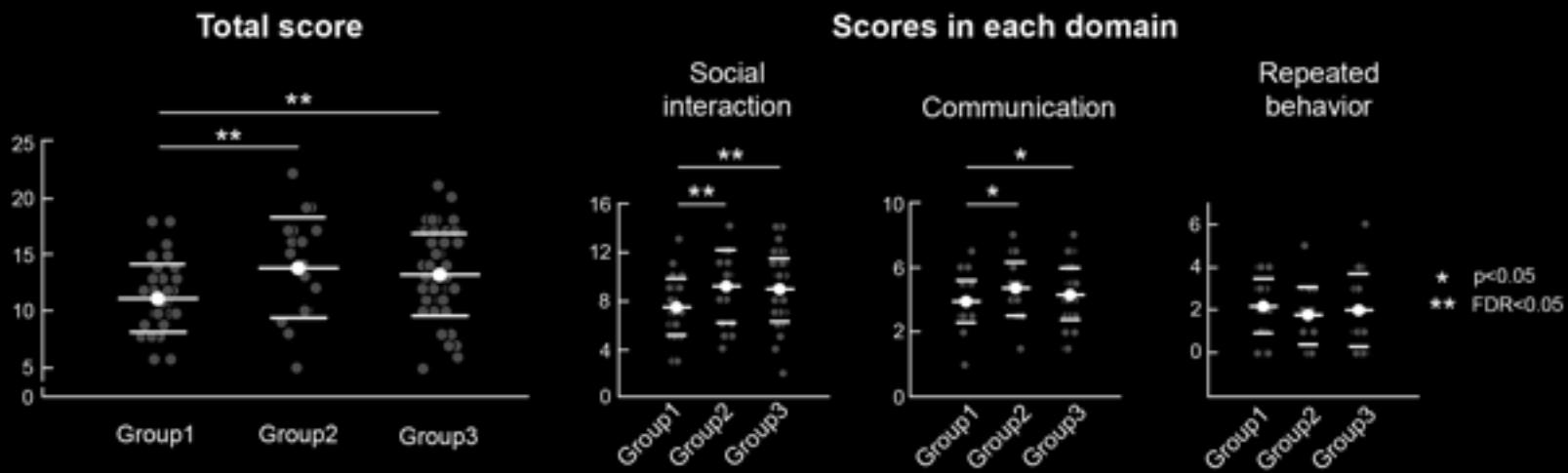
BUT DO MASS-UNIVARIATE GROUP COMPARISONS  
ADDRESS HETEROGENEITY WITHIN ASD?

# SUBTYPING OF AUTISM SPECTRUM DISORDERS

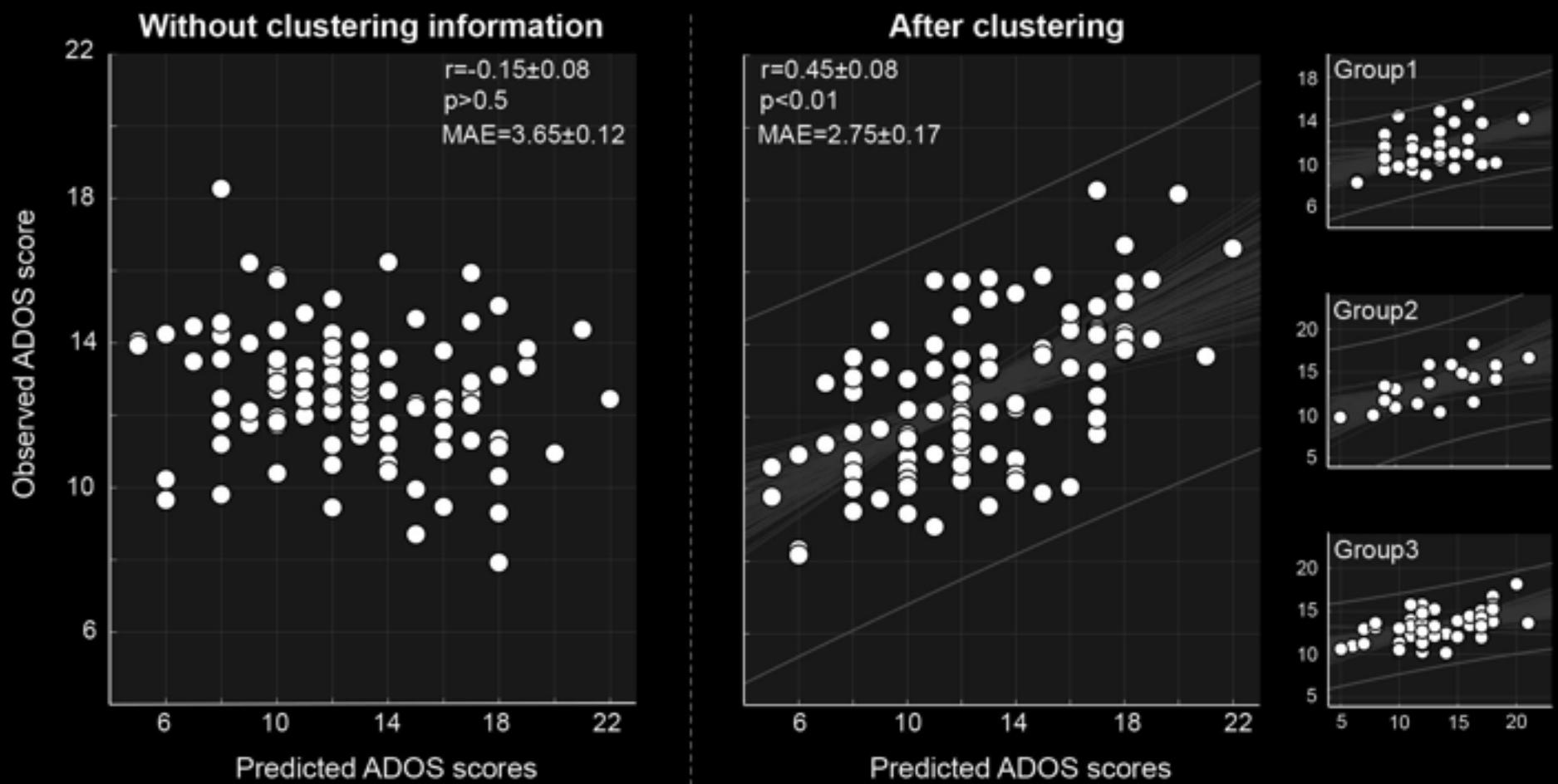


# SYMPTOM GRADIENT

ADOS profiles

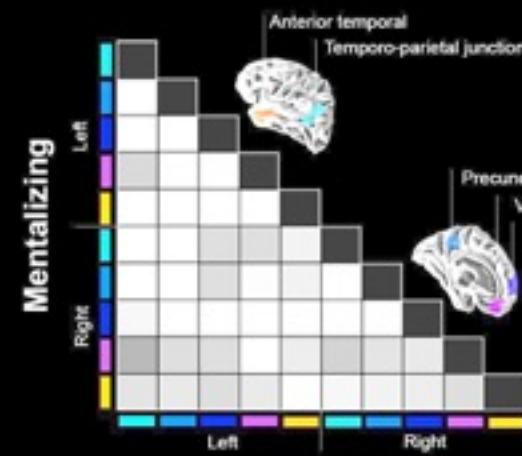


# SYMPTOM SEVERITY PREDICTION



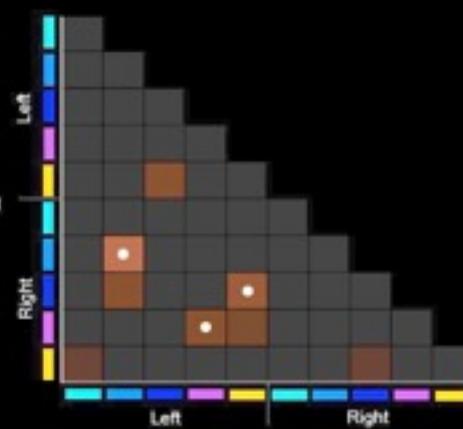
# FUNCTIONAL NETWORK ANOMALIES

## Functional connectivity in controls

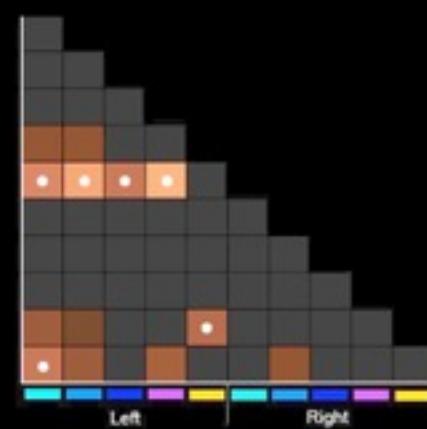


## Decreased connectivity in ASD

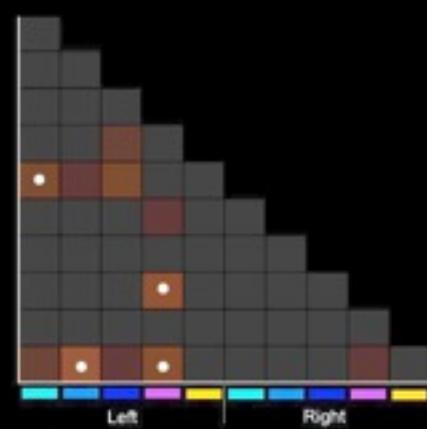
Group 1



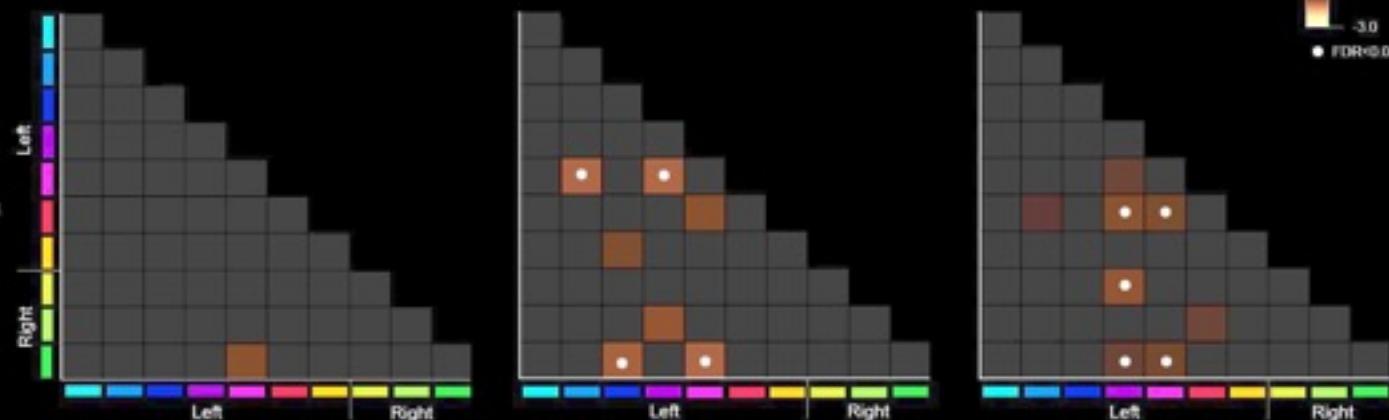
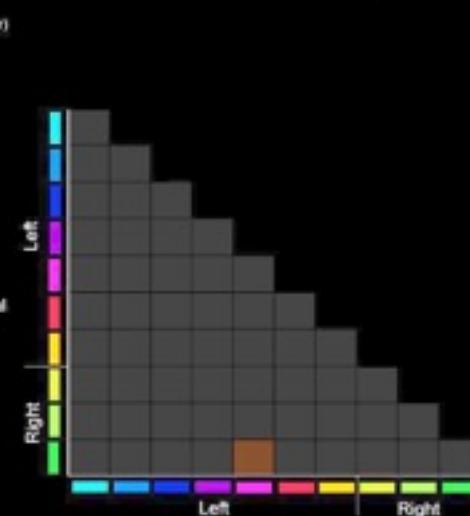
Group 2



Group 3

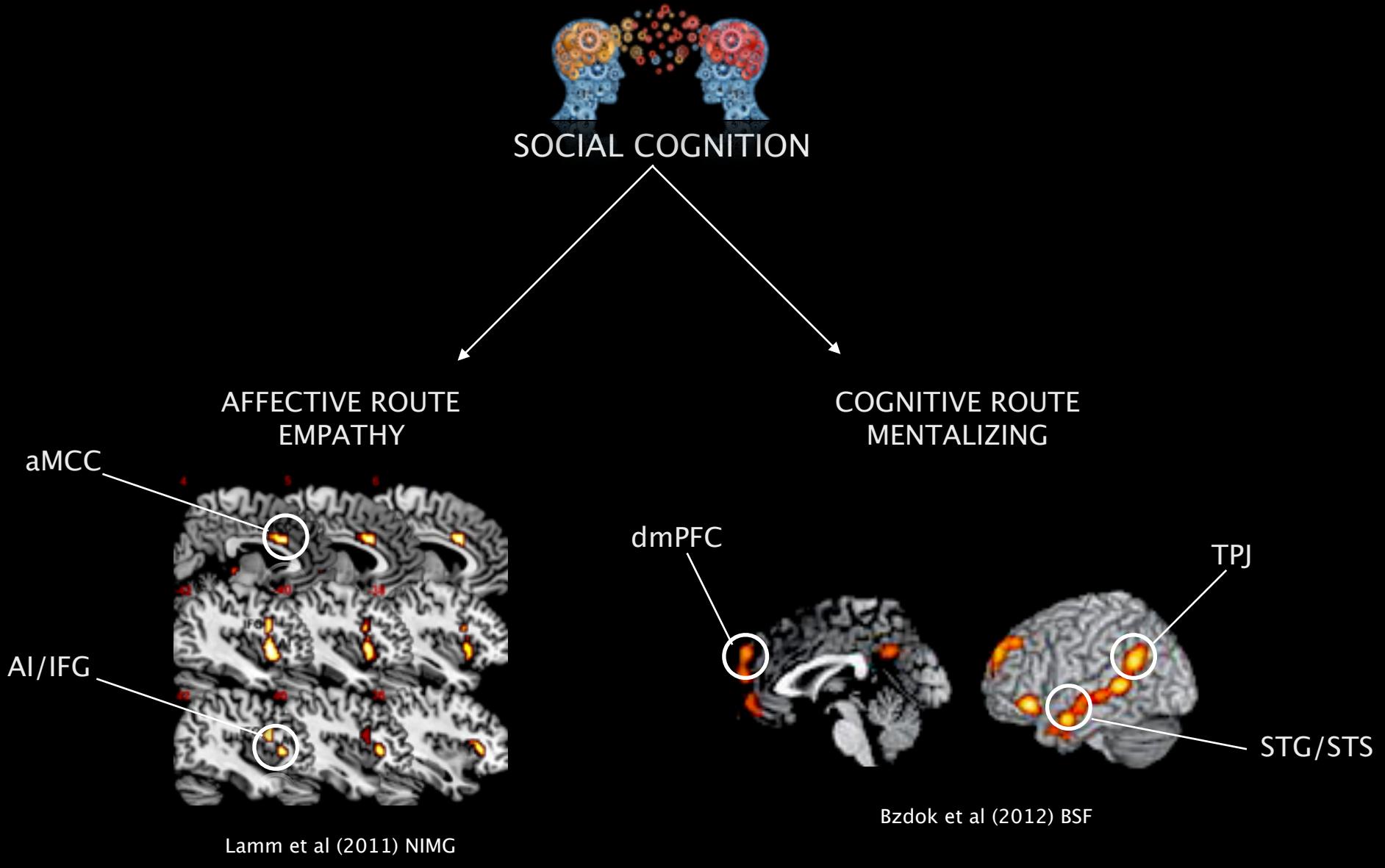


## Communication

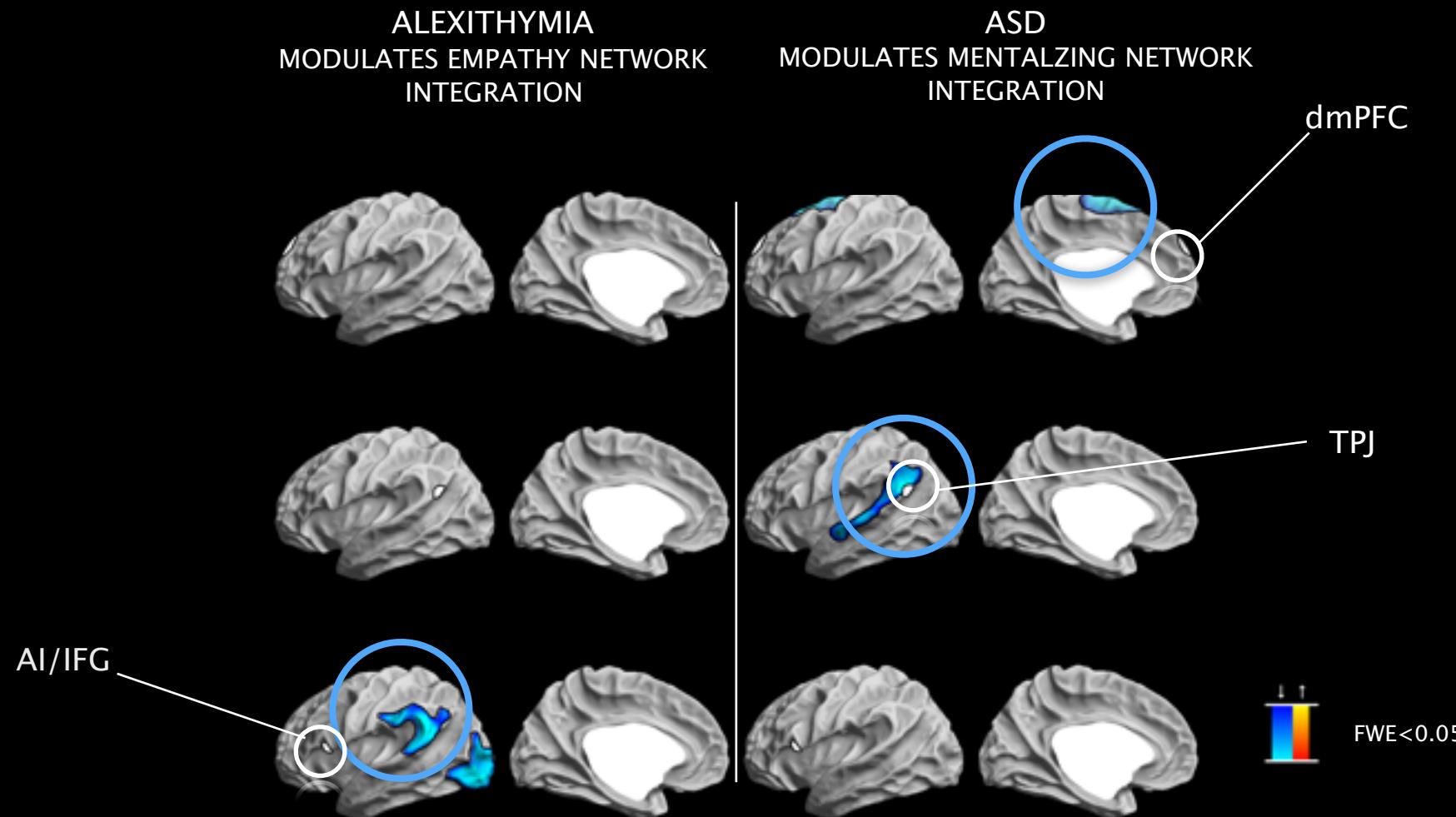


## USING AUTISM AS DISEASE MODEL

# USING AUTISM AS DISEASE MODEL



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



ASD also reported lower perspective taking but no differences in empathy

## INTERIM SUMMARY: AUTISM

MOVING TOWARDS LARGE DATASETS M  
↑ SENSITIVITY  
↑ REPRODUCIBILITY,

MAY MORE ADEQUATELY CAPTURE THE DISEASE SPECTRUM:  
SUBTYPING/BIOTYPING & DIMENSIONAL ASSESSMENTS

USING ASD AS DISEASE MODEL TO UNDERSTAND  
SOCIAL COGNITION NETWORKS:  
MENTALIZING VS EMPATHY

HEY...AND WHAT ABOUT MY  
HEALTHY BRAIN?

DISEASE MODELS CAN EFFECTIVELY  
REVEAL RELATIONSHIPS BETWEEN  
BRAIN NETWORKS AND BEHAVIOUR

HIGH PHENOTYPIC VARIABILITY  
ALSO SEEN IN HEALTHY POPULATIONS

ACCESS TO LARGE DATASETS:  
STUDY BIOLOGICAL  
UNDERPINNINGS OF NORMAL VARIABILITY  
IN SOCIO-AFFECTIVE COMPETENCES





# The ReSource Project

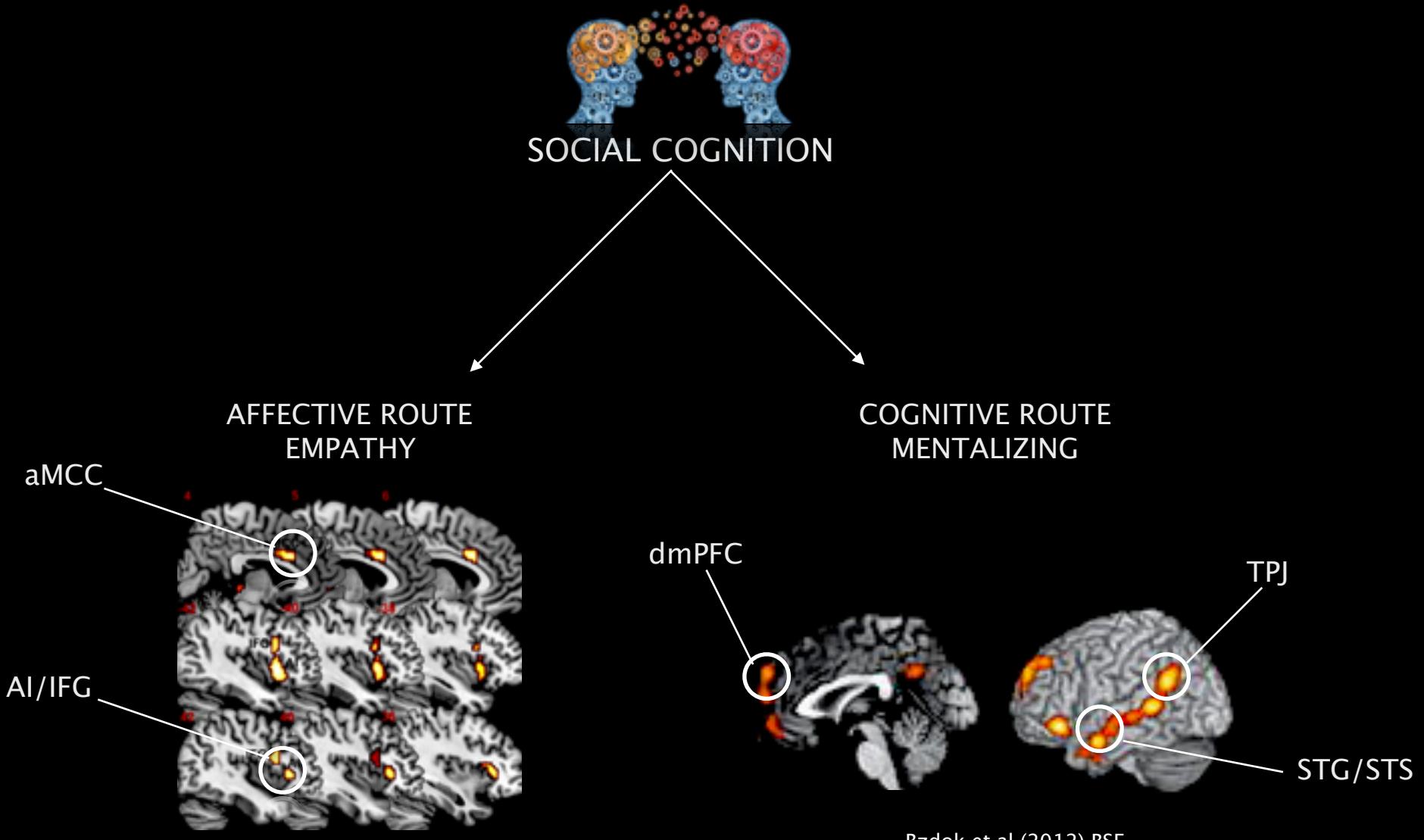
331 PARTICIPANTS  
ASSESSED AT 5 TIME POINTS OVER 12 MONTHS

>80 MEASURES PER TIME POINT:  
COGNITIVE/AFFECTIVE PHENOTYPING  
BLOOD, HAIR, SALIVA  
MULTI-MODAL 3T MRI

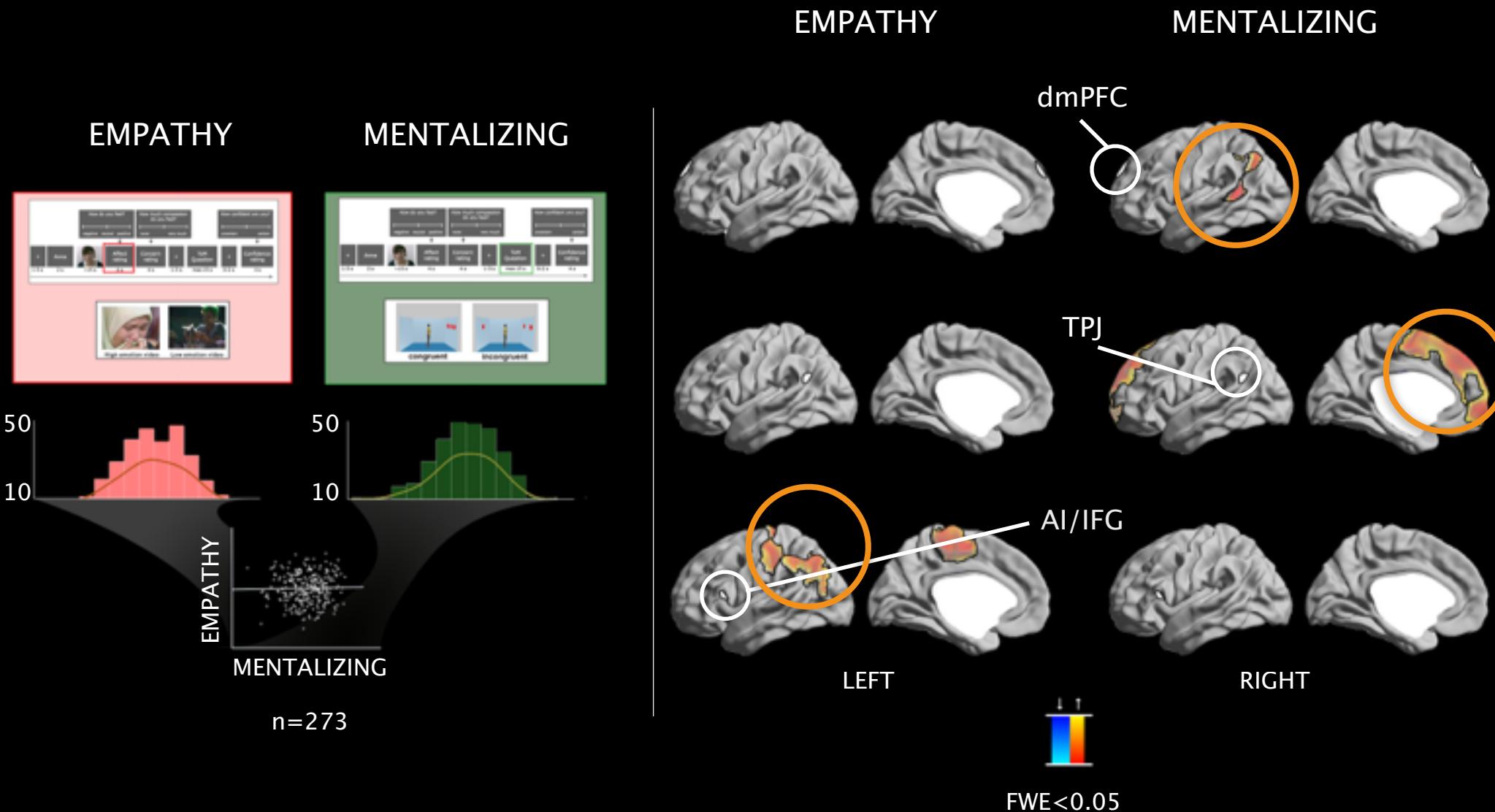
BASELINE DATA ANALYSIS:  
NEURODIVERSITY ASSESSMENT



# USING AUTISM AS DISEASE MODEL



# PHENOTYPING SOCIO-COGNITIVE NETWORKS: CROSS-SECTIONAL EVIDENCE



Valk, Bernhardt, et al. (2017) Cerebral Cortex  
Bernhardt, Klimecki, Leiberg, Singer (2014) Cerebral Cortex

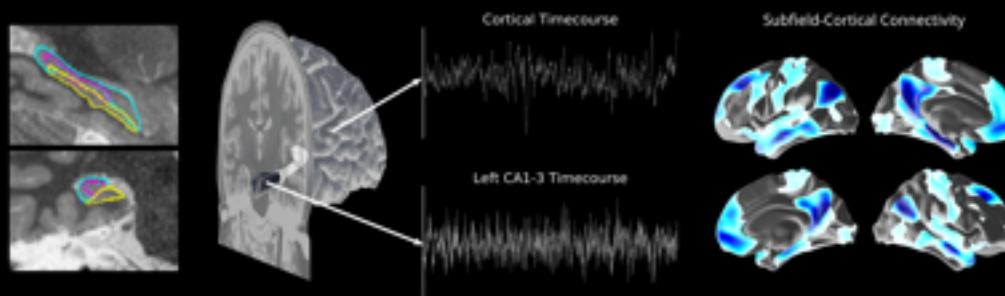




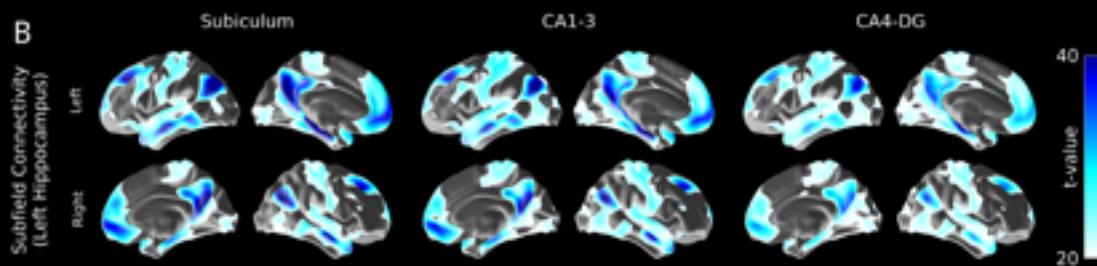
HUMAN  
**Connectome**  
PROJECT

# BACK TO THE HIPPOCAMPUS

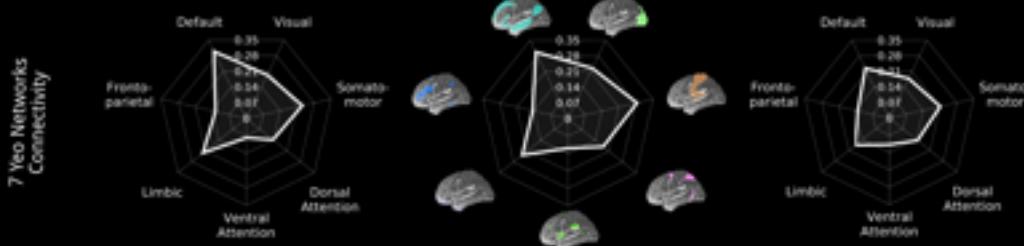
A



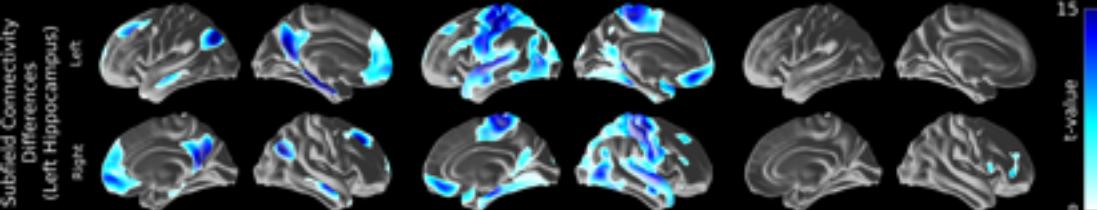
B



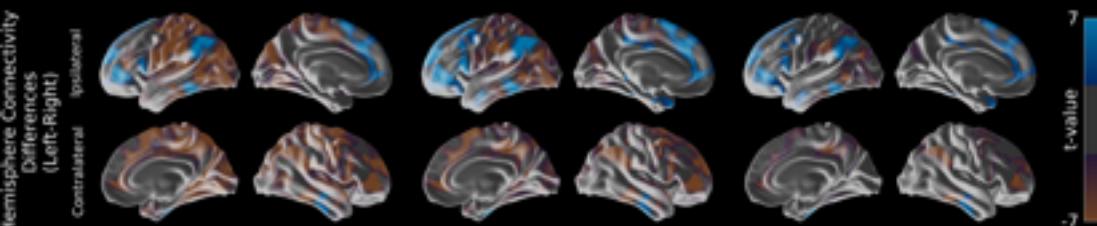
7 Yeo Networks  
Connectivity



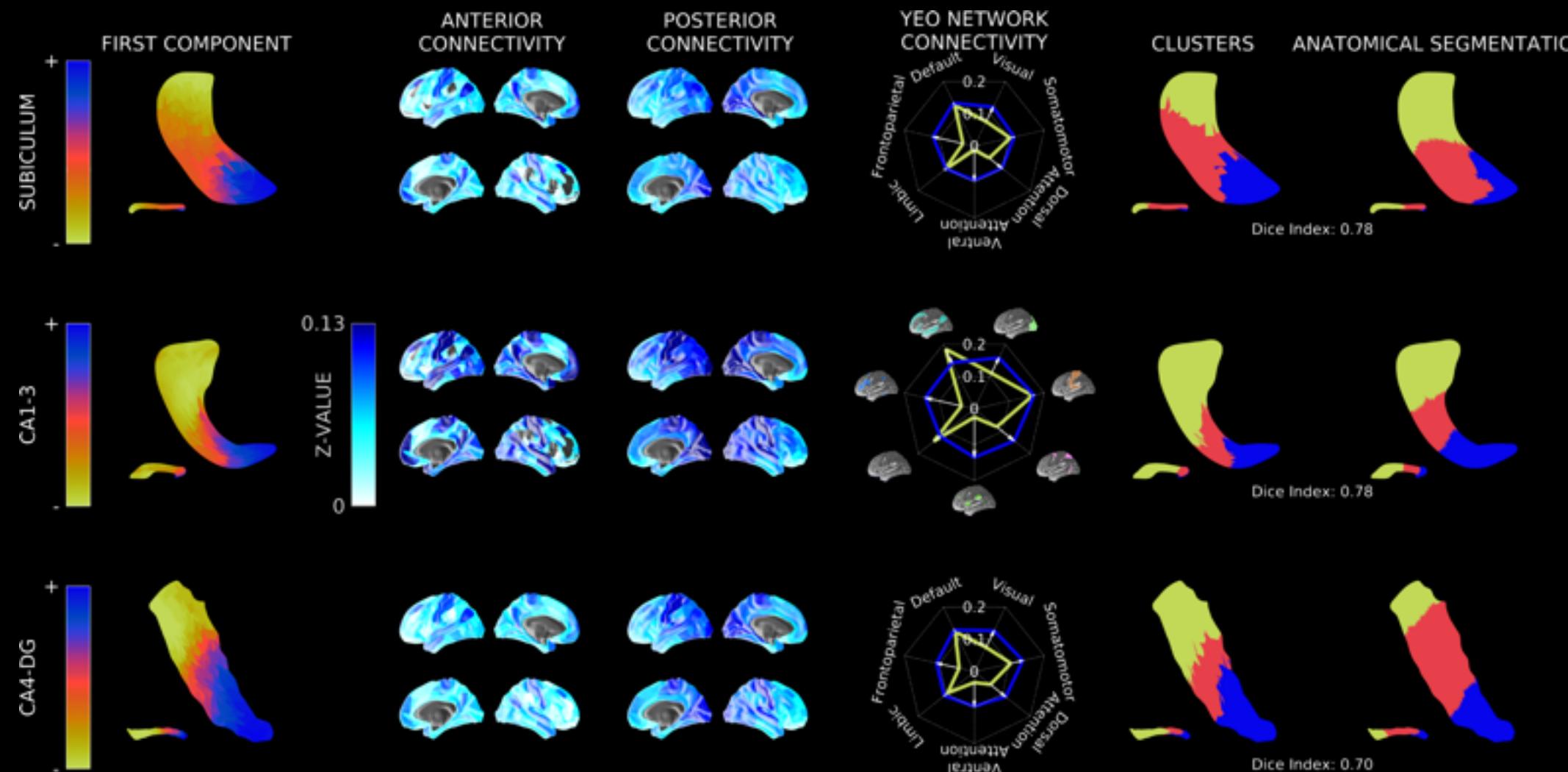
Subfield Connectivities  
(Left Hippocampus)



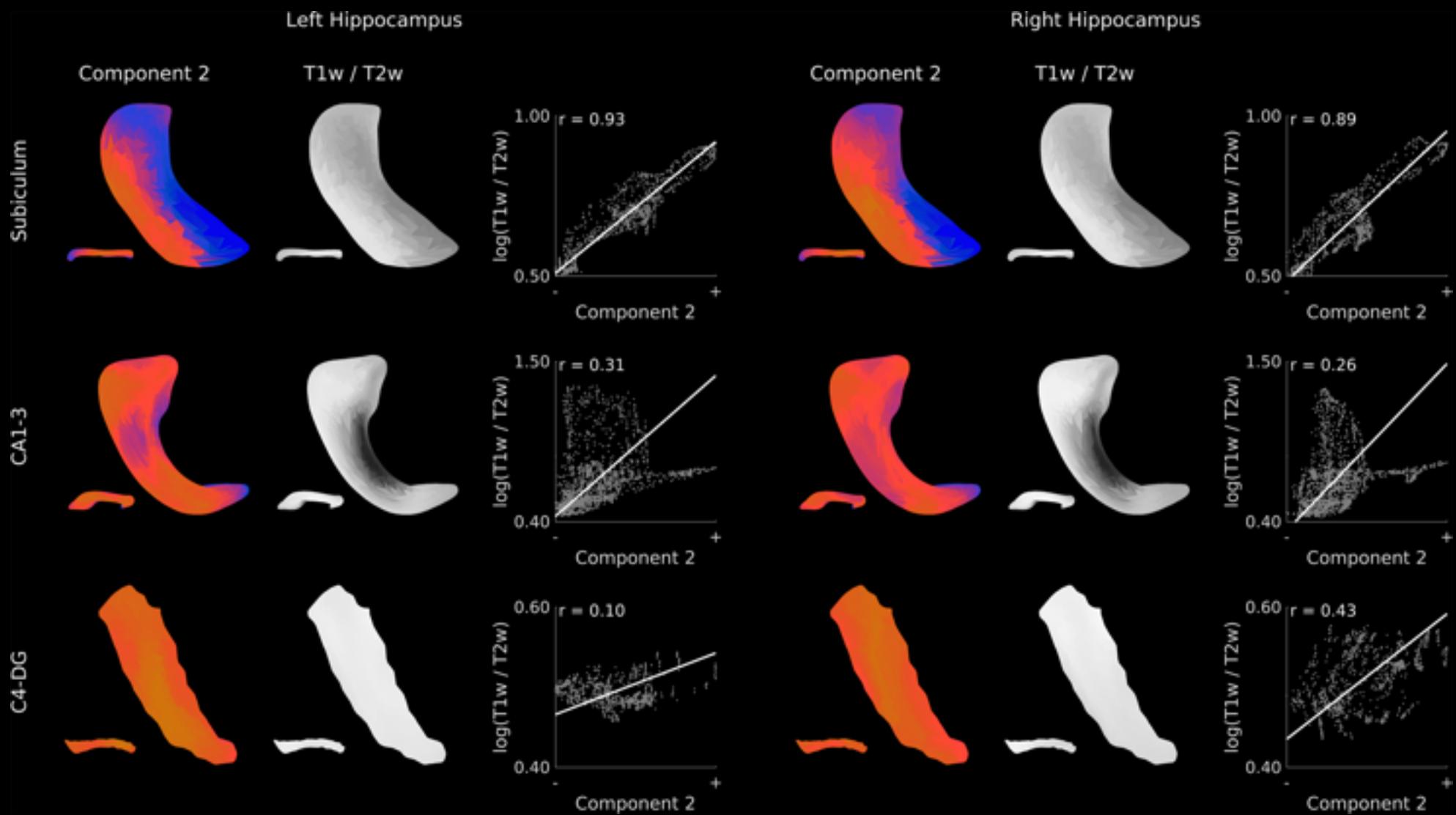
Hemisphere Connectivities  
Differences (Left-Right)



# BACK TO THE HIPPOCAMPUS



# BACK TO THE HIPPOCAMPUS

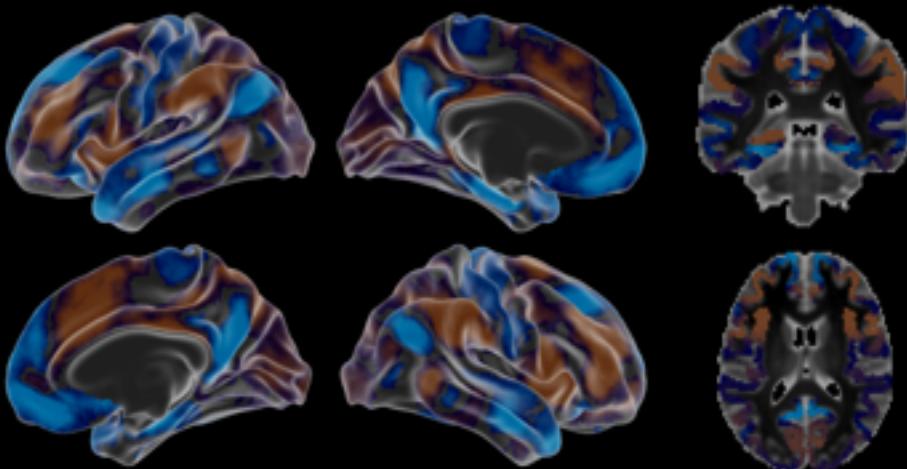
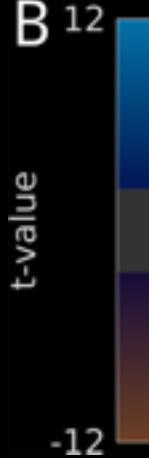


# BACK TO THE HIPPOCAMPUS

A



B



C

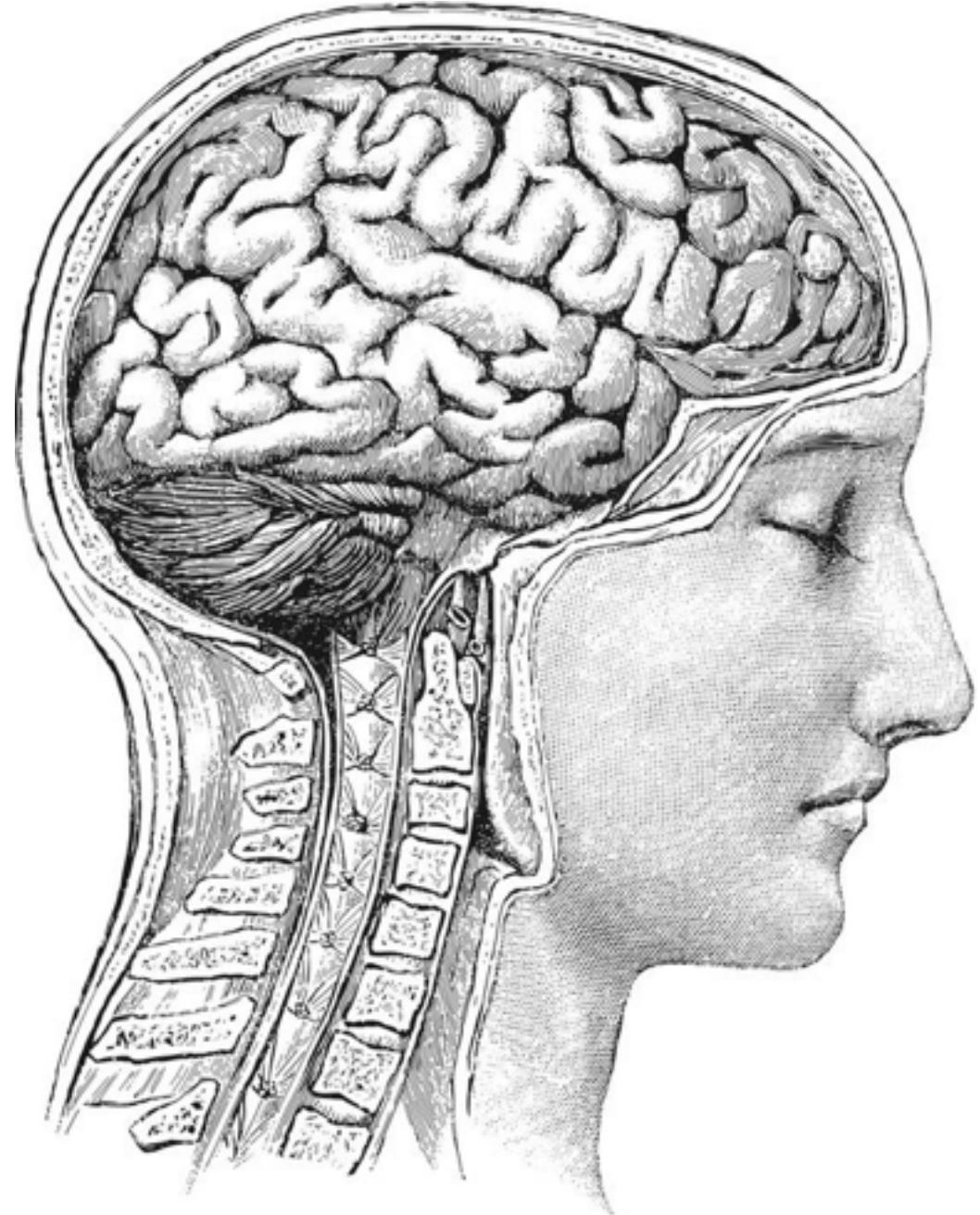
autobiographical	parietal
medial	anterior insula
autobiographical memory	inferior parietal
default	working memory
medial prefrontal	task
memories	working
default mode	insula
mode	dorsolateral prefrontal
remembering	parietal cortex
episodic	dorsolateral

## SUMMARY

MRI PROVIDES IN VIVO INFORMATION  
ON MICROSTRUCTURE AND  
MACROSCALE NETWORKS

DESCRIBE ANATOMICAL-FUNCTIONAL  
HETEROGENEITY  
IN EPILEPSY AND AUTISM

UNDERSTANDING  
HEALTHY BRAIN  
NETWORK DIVERSITY





Neda Bernasconi

Andrea Bernasconi

Jessie Kulaga Yoskovitz

Ravnoor Gill

Benoit Caldairou

Min Liu

Jeffrey Hall

Marie Christine Guiot



Sofie Valk

Tania Singer

Alfred Anwander

Daniel Margulies



Together We Will.  
TOGETHER WE WILL.



Canadian League Against Epilepsy  
Csapatnak a reakció Állományának Egyesülete



Reinder Vos de Wael

Sara Lariviere

Seok-Jun Hong

Shahin Tavakol

Zhengge Wang

Brian Hyung

Tabea Haas Heger



Luis Concha

Raul Cruces



Jonathan Smallwood

Beth Jeffreys



Michael Milham

Adriana DiMartino

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

twitter: @BorisBernhardt