REDUCTIONISM *vs* HOLISM IN THE STUDY OF DRUG-RESISTANT EPILEPSY

BORIS BERNHARDT, PHD

DRUG-RESISTANT EPILEPSIES

30% OF EPILEPSIES ARE DRUG RESISTANT

TLE RELATED TO MTS

ETE RELATED TO MCD

SURGERY MOST EFFECTIVE TREATMENT

SUBSTRATE NEEDS TO BE
LOCALIZED FOR SUCCESS

LOCALIZING PATHOLOGY

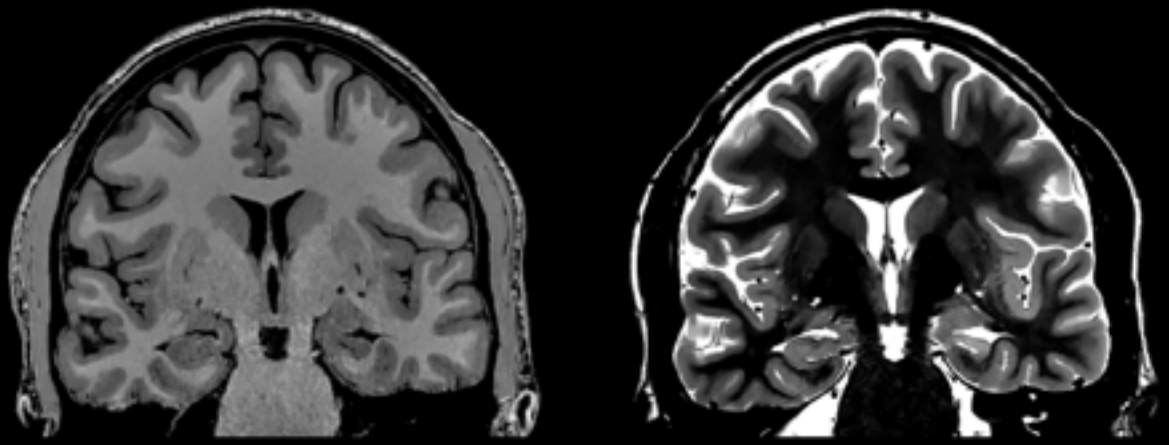
KEY ROLE OF NEUROIMAGING

MRI UNMATCHED ABILITY TO LOCALIZE LESIONS IN VIVO

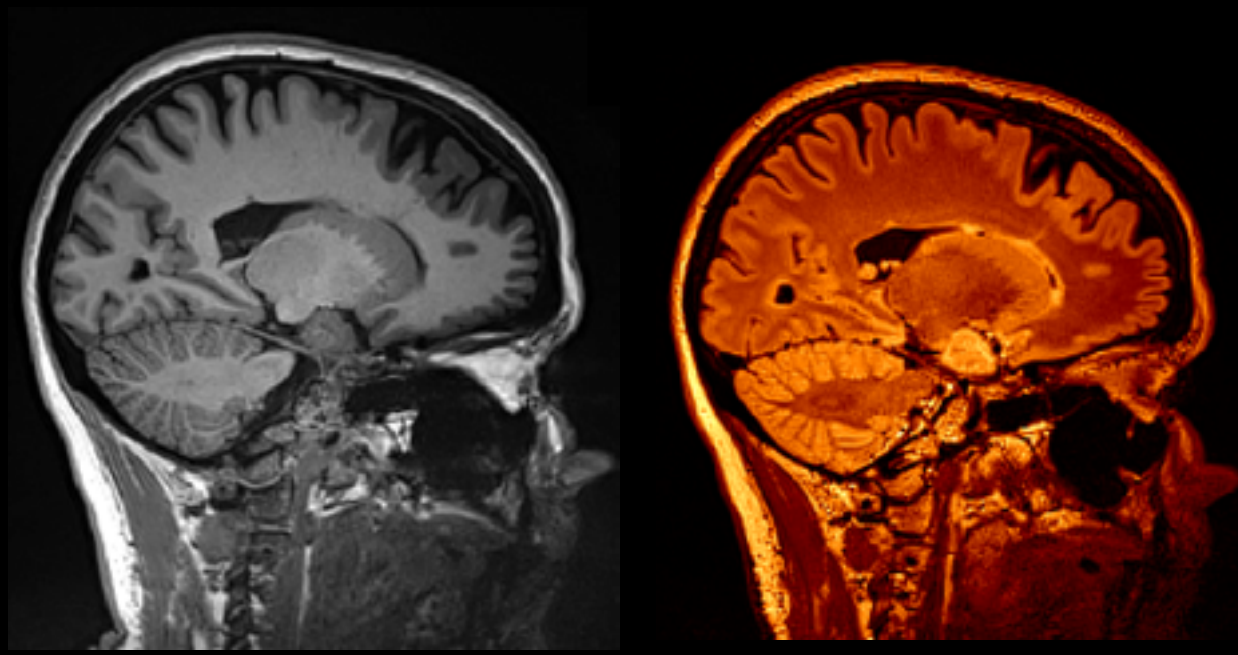
NON-INVASIVE

HIGH RESOLUTION

MULTI-CONTRAST ASSESSMENT



TLE PATIENT WITH MTS

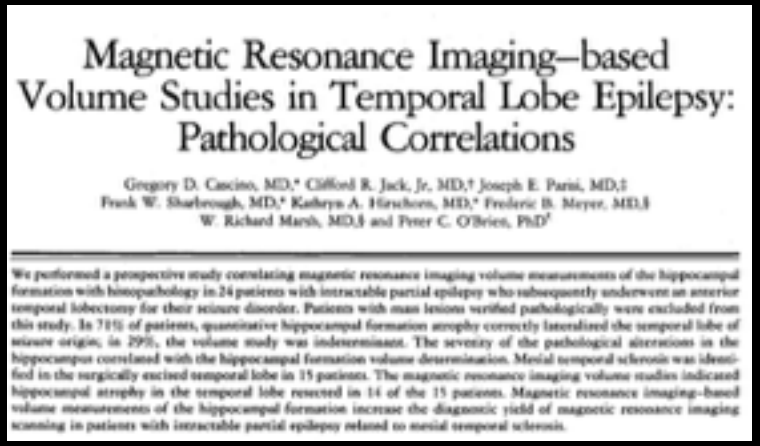


ETE PATIENT WITH FCD

THE UTILITY OF REGIONAL METHODS IN TLE
CLASSICAL STUDIES IN TLE

HISTOPATHOLOGICAL VALIDITY

Cascino, 1991, Neurology

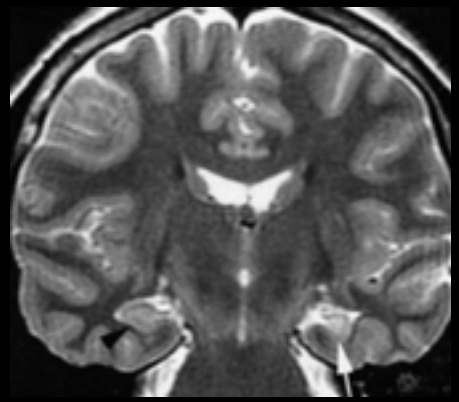


Magnetic Resonance Imaging–based Volume Studies in Temporal Lobe Epilepsy: Pathological Correlations

Gregory D. Cascino, MD,* Clifford R. Jack, Jr, MD,† Joseph E. Parisi, MD,‡
Frank W. Sharbrough, MD,* Kathryn A. Hirschorn, MD,* Frederic B. Meyer, MD,§
W. Richard Marsh, MD,§ and Peter C. O'Brien, PhD†

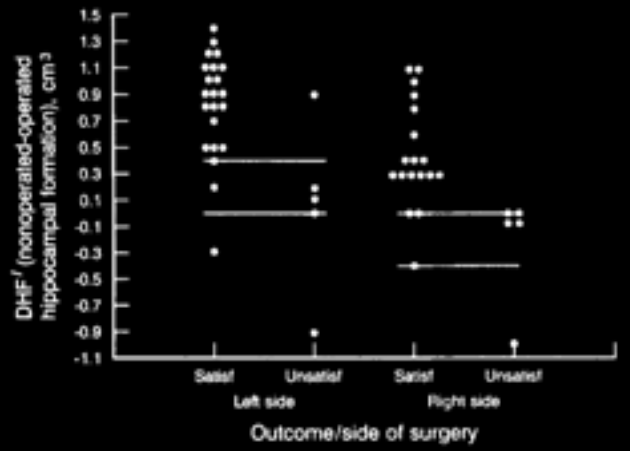
We performed a prospective study correlating magnetic resonance imaging volume measurements of the hippocampal formation with histopathology in 24 patients with intractable partial epilepsy who subsequently underwent an anterior temporal lobectomy for their seizure disorder. Patients with mass lesions verified pathologically were excluded from this study. In 71% of patients, quantitative hippocampal formation atrophy correctly lateralized the temporal lobe of seizure origin; in 29%, the volume study was indeterminant. The severity of the pathological alterations in the hippocampus correlated with the hippocampal formation volume determination. Mesial temporal sclerosis was identified in the surgically excised temporal lobe in 15 patients. The magnetic resonance imaging volume studies indicated hippocampal atrophy in the temporal lobe resected in 14 of the 15 patients. Magnetic resonance imaging–based volume measurements of the hippocampal formation increase the diagnostic yield of magnetic resonance imaging scanning in patients with intractable partial epilepsy related to mesial temporal sclerosis.

Briellman, Jackson, 1991, Neurology

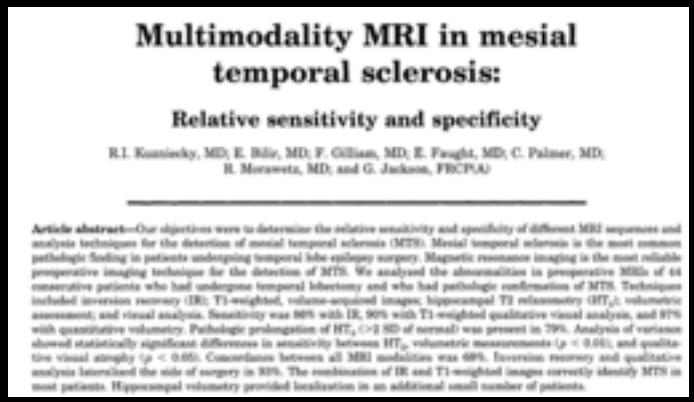


CLINICAL RELEVANCE

Jack, 1992, Neurology



Kuzniecky, 1999, Neurology



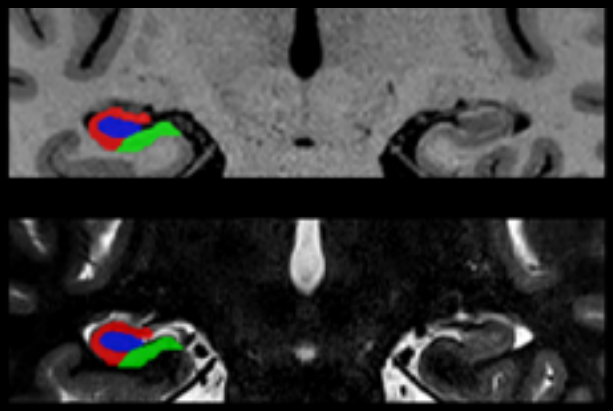
Multimodality MRI in mesial temporal sclerosis:

Relative sensitivity and specificity

R.I. Kuzniecky, MD; E. Bilir, MD; F. Gilliam, MD; E. Faught, MD; C. Palmer, MD; R. Morawetz, MD; and G. Jackson, FRCP(A)

Article abstract—Our objectives were to determine the relative sensitivity and specificity of different MRI sequences and analysis techniques for the detection of mesial temporal sclerosis (MTS). Mesial temporal sclerosis is the most common pathologic finding in patients undergoing temporal lobe epilepsy surgery. Magnetic resonance imaging is the most reliable preoperative imaging technique for the detection of MTS. We analyzed the abnormalities in preoperative MRIs of 44 consecutive patients who had undergone temporal lobectomy and who had pathologic confirmation of MTS. Techniques included inversion recovery (IR); T1-weighted, volume-acquired images; hippocampal T2 relaxometry (HT_2); volumetric assessment; and visual analysis. Sensitivity was 80% with IR, 90% with T1-weighted qualitative visual analysis, and 97% with quantitative volumetry. Pathologic prolongation of HT_2 (>2 SD of normal) was present in 79%. Analysis of variance showed statistically significant differences in sensitivity between HT_2, volumetric measurements ($p < 0.01$), and qualitative visual atrophy ($p < 0.05$). Concordance between all MRI modalities was 68%. Inversion recovery and qualitative analysis lateralized the side of surgery in 93%. The combination of IR and T1-weighted images correctly identify MTS in most patients. Hippocampal volumetry provided localization in an additional small number of patients.

THE UTILITY OF REGIONAL METHODS IN TLE
MORE RECENT WORK IN TLE

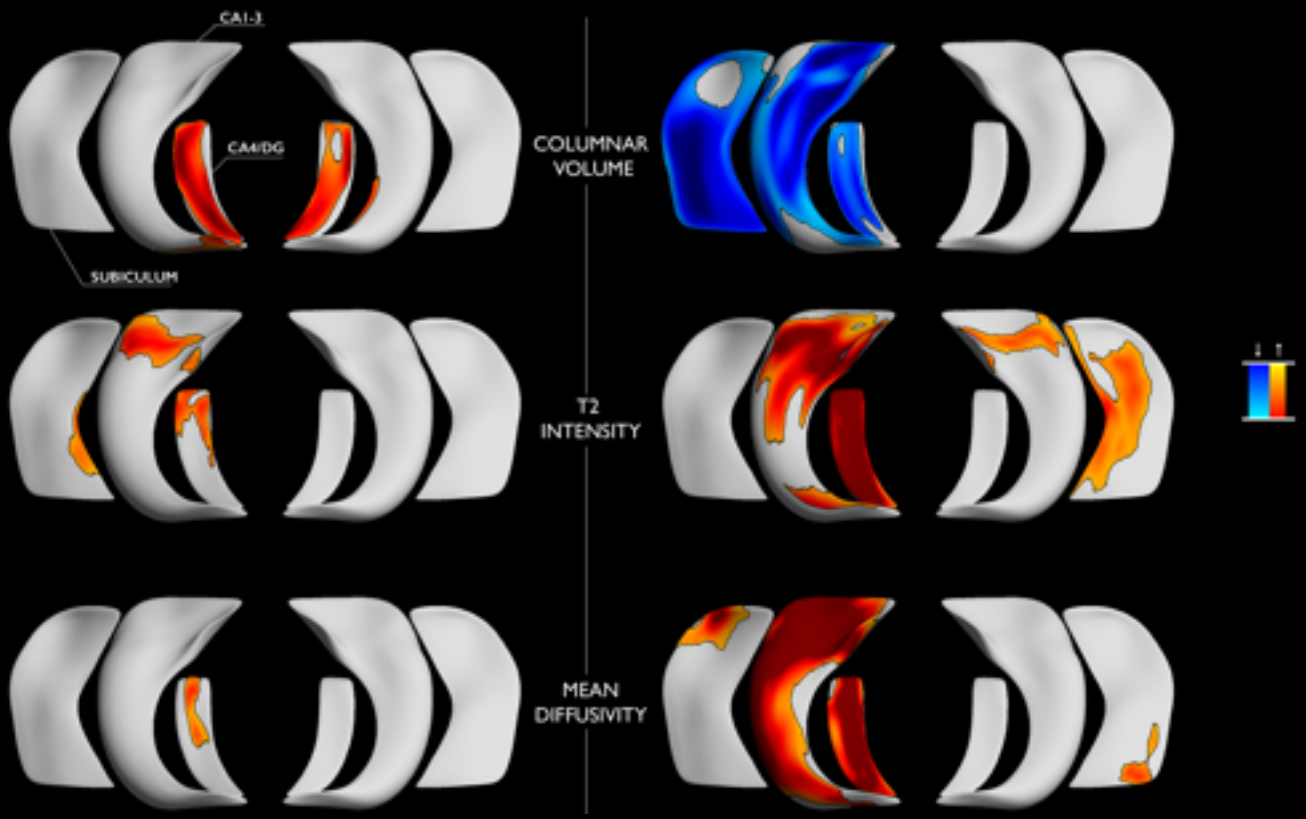


OPEN DATA ON NITRC

HISTOPATHOLOGICAL VALIDITY

GLIOSIS ONLY

CELL LOSS AND GLIOSIS

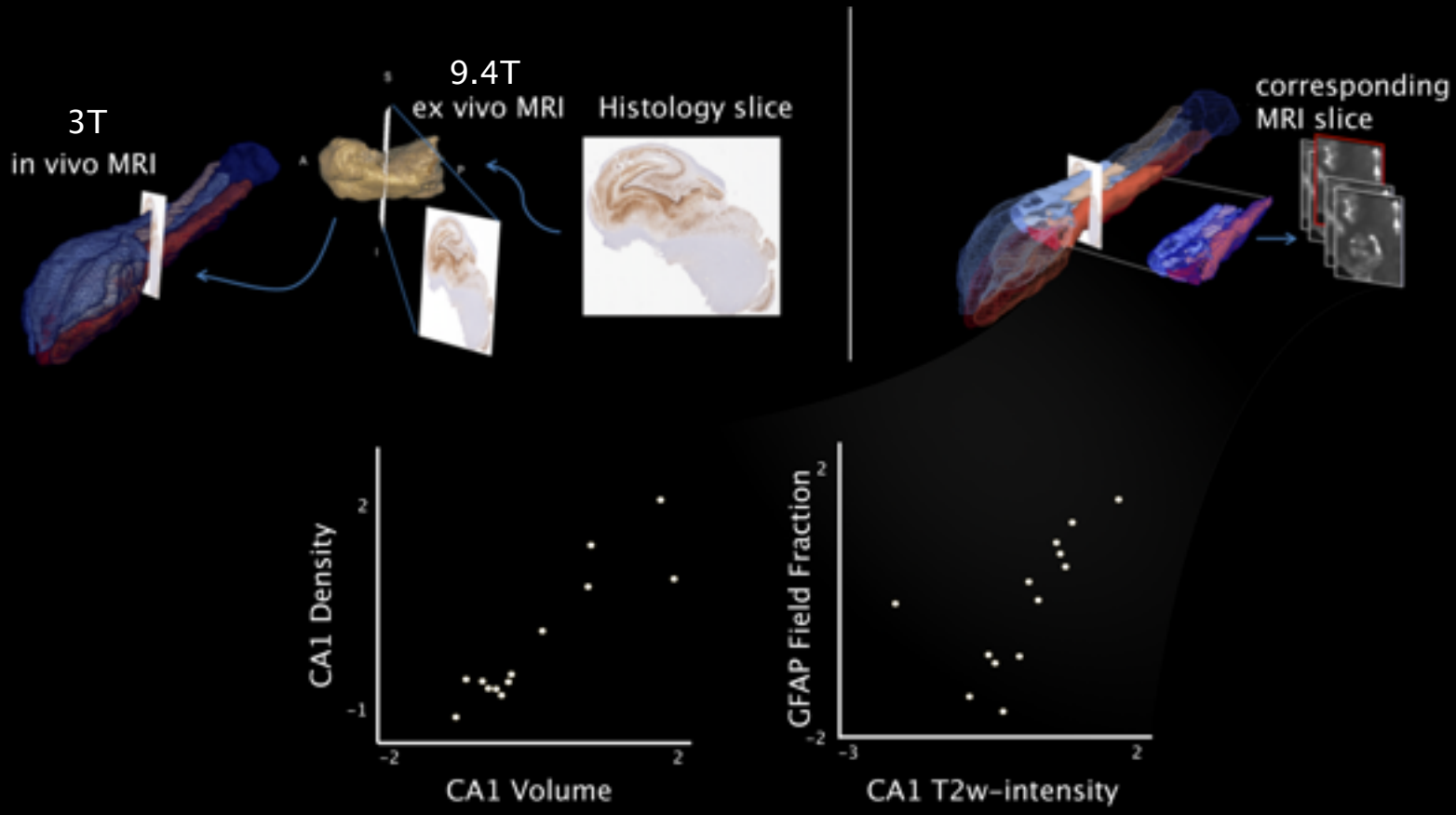


>90% LATERALIZATION AND PATHOLOGY CLASSIFICATION PERFORMANCE

Kulaga-Yoskovitz, Bernhardt et al. 2015 Scientific Data, Bernhardt et al., in preparation

THE UTILITY OF REGIONAL METHODS IN TLE
MORE RECENT WORK IN TLE

HISTOPATHOLOGICAL VALIDITY



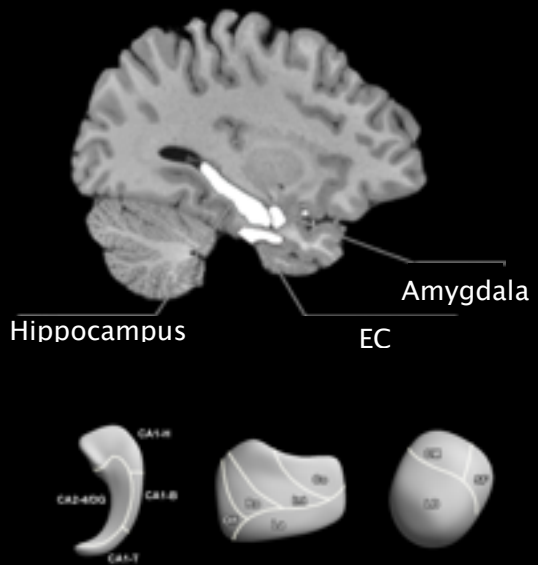
SUBFIELD-SPECIFIC CORRELATIONS BETWEEN QUANTITATIVE HISTOLOGY AND MRI

Goubran, Bernhardt, et al. (2015) Hum Brain Mapp

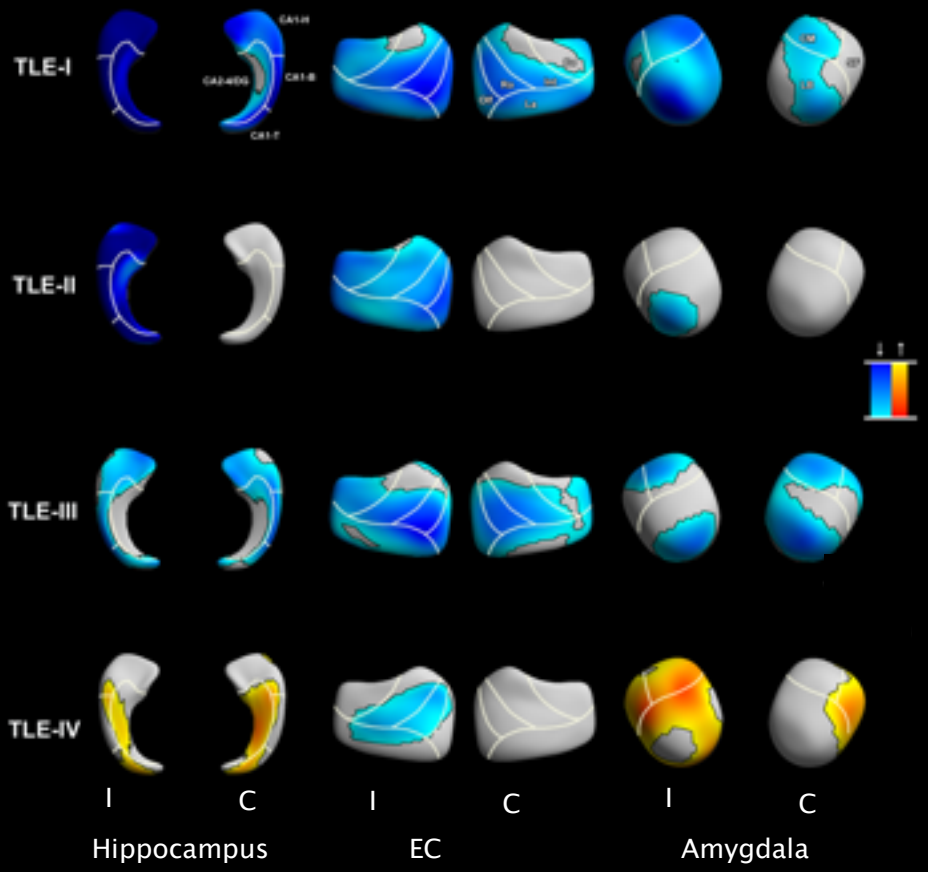
THE UTILITY OF REGIONAL METHODS IN TLE
MORE RECENT WORK IN TLE

CLINICAL UTILITY

MULTI-STRUCTURE MRI PROFILING



DATA DRIVEN CLASSIFICATION

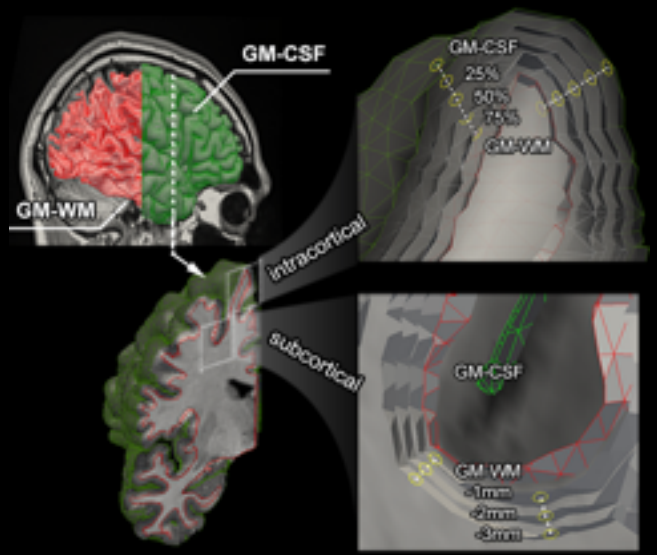


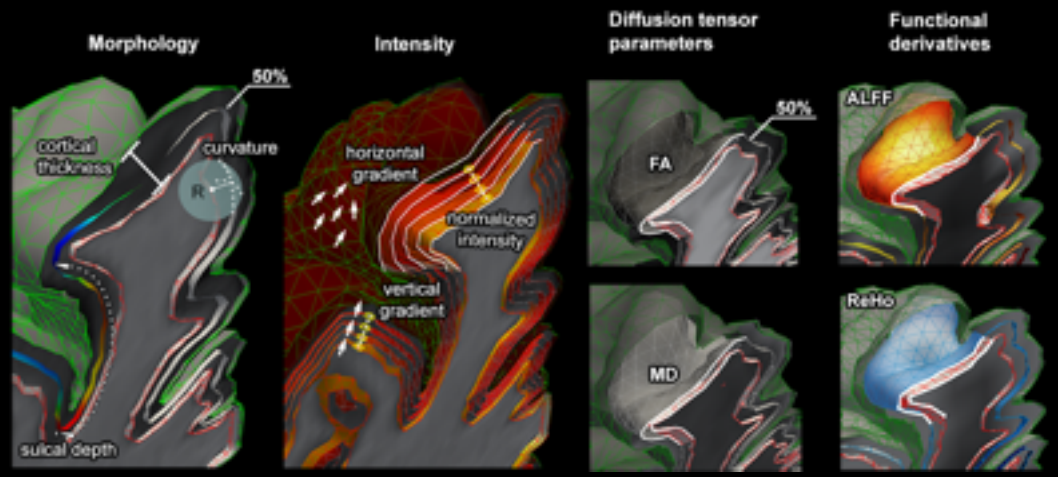
PARTITIONING OF TLE INTO DIFFERENT SUBCLASSES
>92% ACCURACY IN PREDICTING OUTCOME

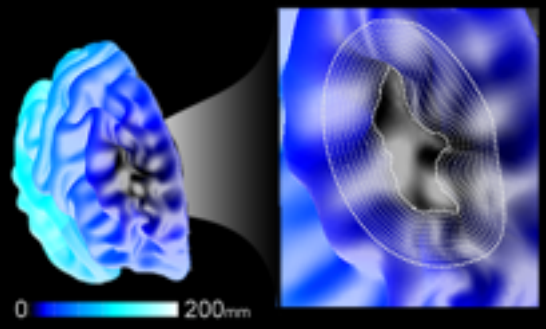
Bernhardt et al. (2015) Annals of Neurology

LOCAL METHODS IN FLE and FCD

HISTOPATHOLOGICAL VALIDITY AND CLINICAL UTILITY





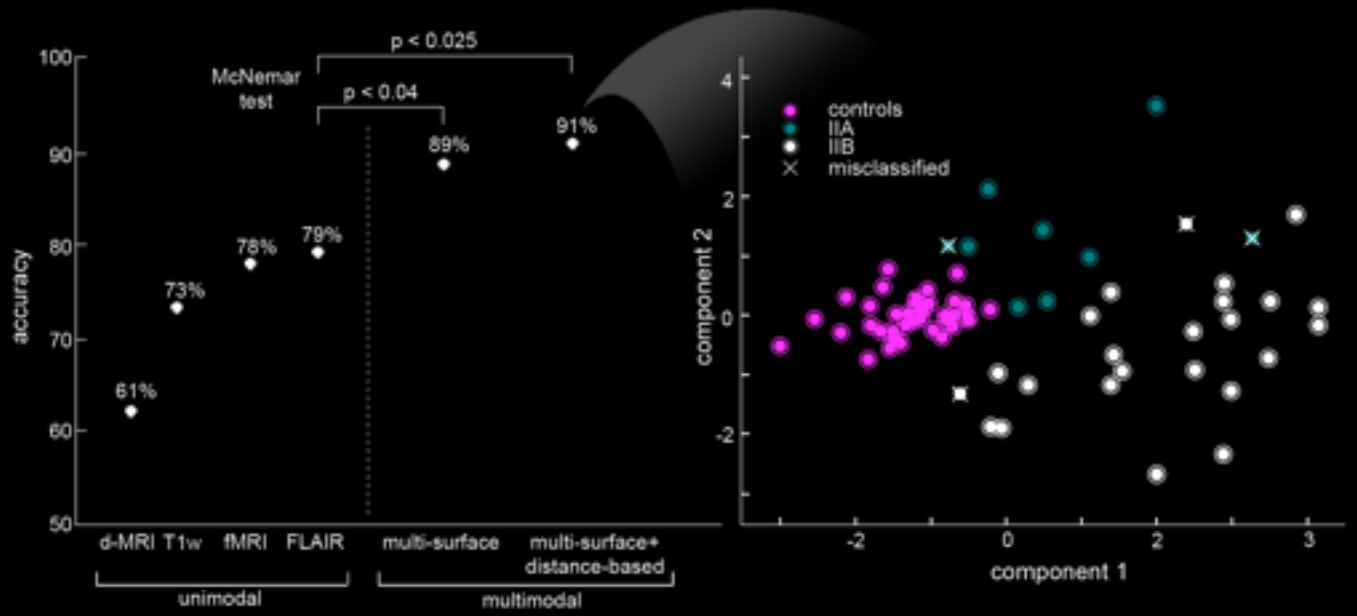


Hong*, Bernhardt* et al. (submitted)

PLATFORM
ROOM 103 3PM
2.202
MONDAY

UTILITY OF LOCAL METHODS IN FLE

HISTOPATHOLOGICAL VALIDITY AND CLINICAL UTILITY



Hong*, Bernhardt* et al. (submitted)

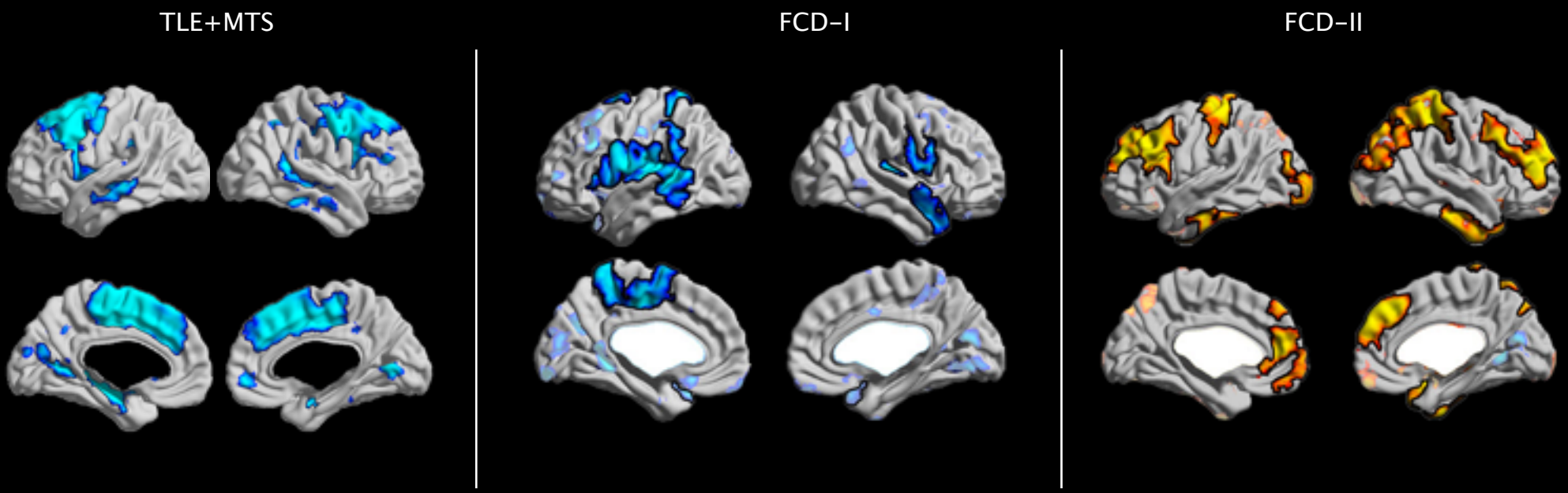
PLATFORM
ROOM 103 3PM
2.202
MONDAY

LOCALIZED MRI IN EPILEPSY

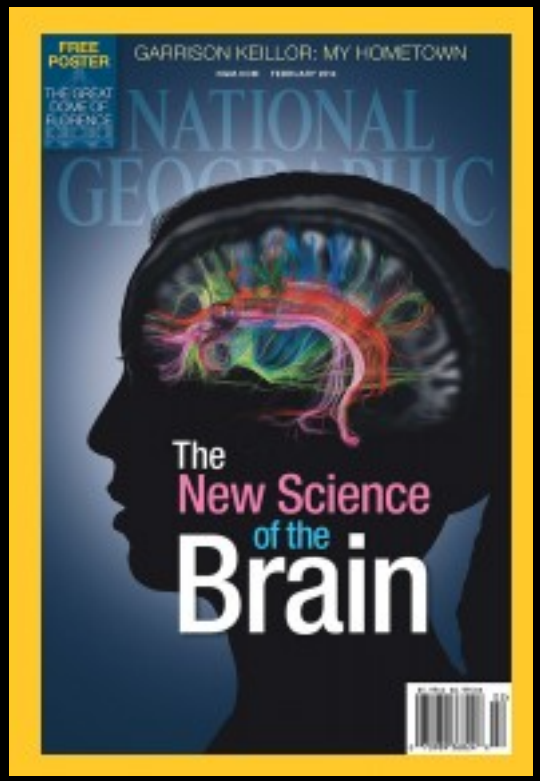
- ACCOMPLISHMENTS::
  - CROSS-VALIDATED WITH PATHOLOGICAL DATA
  - CLINICALLY USEFUL (OUTCOME PREDICTION, LATERALIZATION, CLASSIFICATION)
  - DESCRIPTION OF PATHOLOGICAL CORE AND SURROUND

- METHODOLOGICAL ADVANCES: ↑ VALIDITY AND ↑ UTILITY
  - ↑ ANALYSIS RESOLUTION (FIELD STRENGTH, IMAGE PROCESSING)
  - NOVEL CONTRASTS ALLOW FOR INCREASINGLY COMPLEX TISSUE MODELS

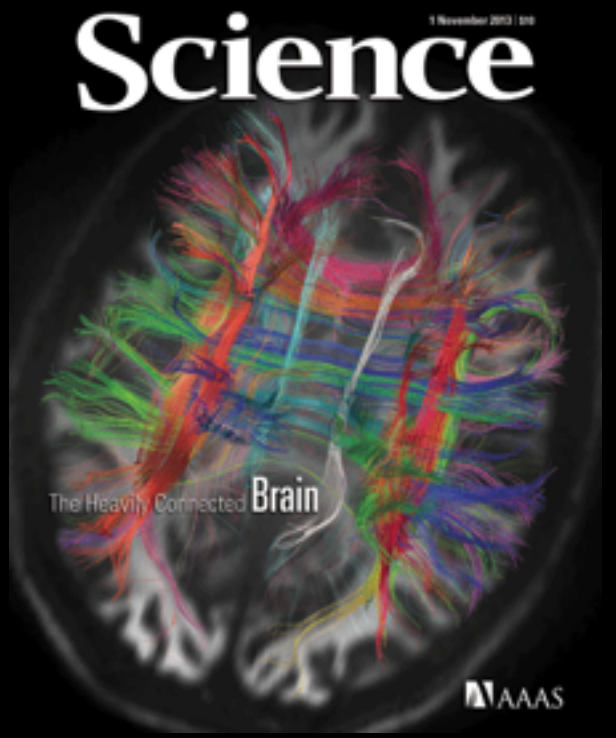
IS THAT IT?



Bernhardt et al. 2010 Neurology, Hong et al. 2015 Neurology


FREE POSTER
GARRISON KEILLOR: MY HOMETOWN
NATIONAL GEOGRAPHIC
The New Science of the Brain


Trends in Cognitive Sciences
Special Issue: The Connectome
Cell


Science
The Heavily Connected Brain
AAAS

American Epilepsy Society

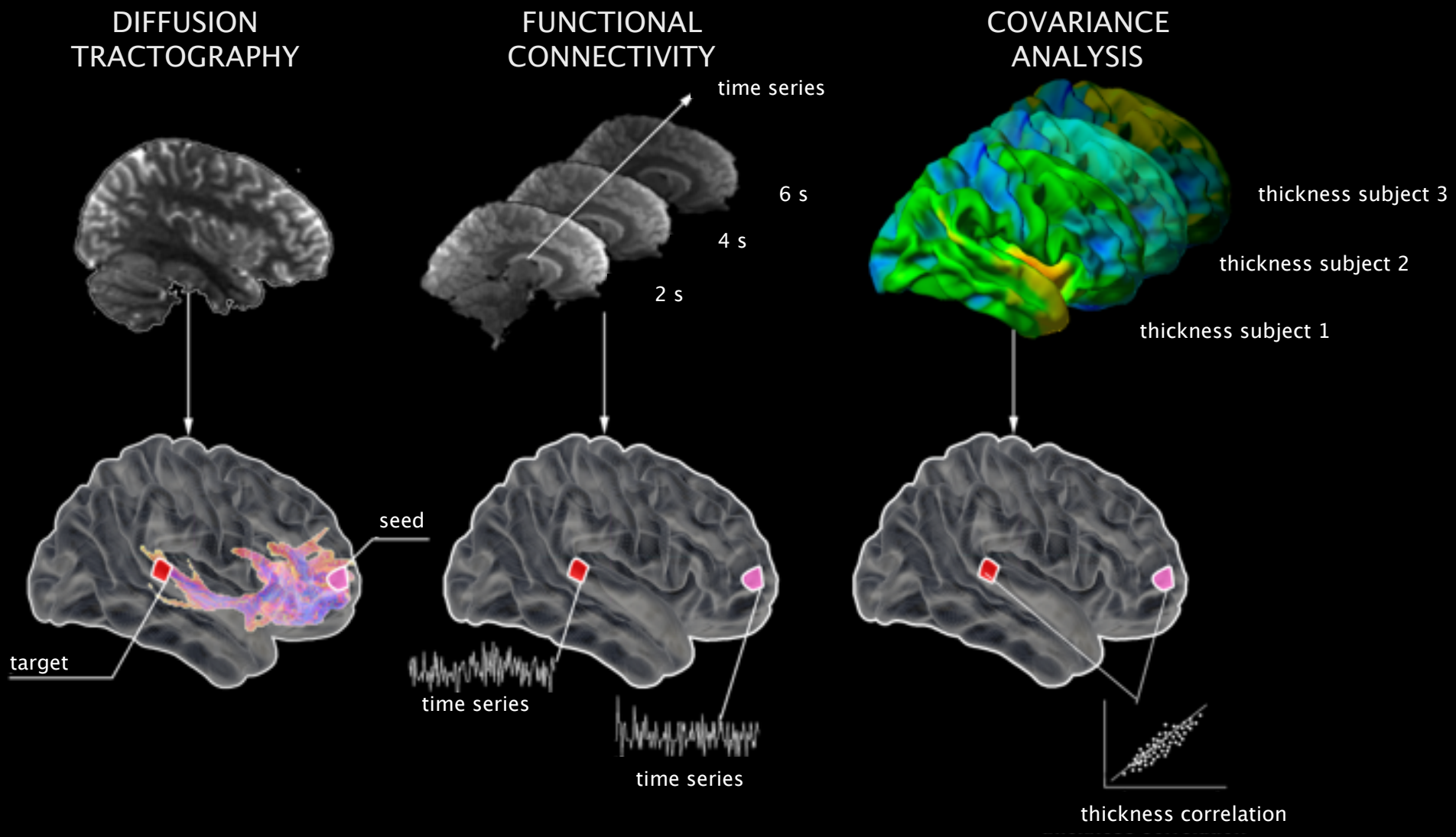
WHY STUDY NETWORKS IN EPILEPSY?

- *ADEQUACY*: NETWORK-LEVEL DESCRIPTORS CAPTURE BRAIN ORGANIZATION
  - #SYNAPSES > #NEURONS and #CONNECTIONS > #REGIONS
  - FUNCTION OF REGION LARGELY DEFINED BY ITS CONNECTIONS
  - RECONCEPTUALIZATION OF EPILEPSY AS NETWORK DISORDERS

- *NEED:* DESPITE YIELD, PURELY LOCAL APPROACH MAY STILL BE LIMITED
  - VARIABILITY ACROSS PATIENTS
  - FACTORS RELATED TO CLINICALLY-RELEVANT OUTCOMES

- *POSSIBILITY:* TOOLS FOR IN VIVO CONNECTIVITY MAPPING AVAILABLE

NETWORK-LEVEL ANALYSIS

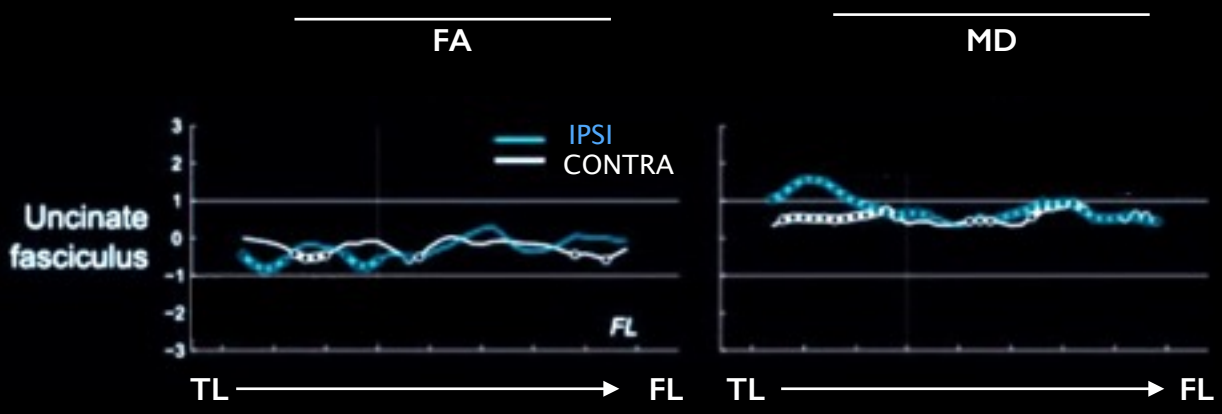


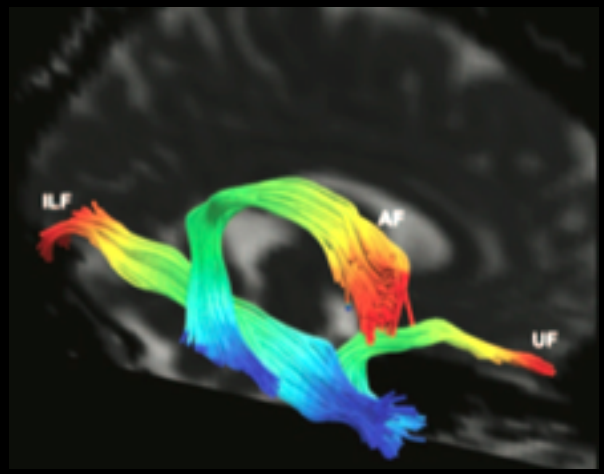
Mori et al. (1999) Ann Neu
Behrens et al. (2007) NIMG

Friston (1994) HBM
Smith (2012) NIMG

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

INTER-REGIONAL NETWORK STUDIES



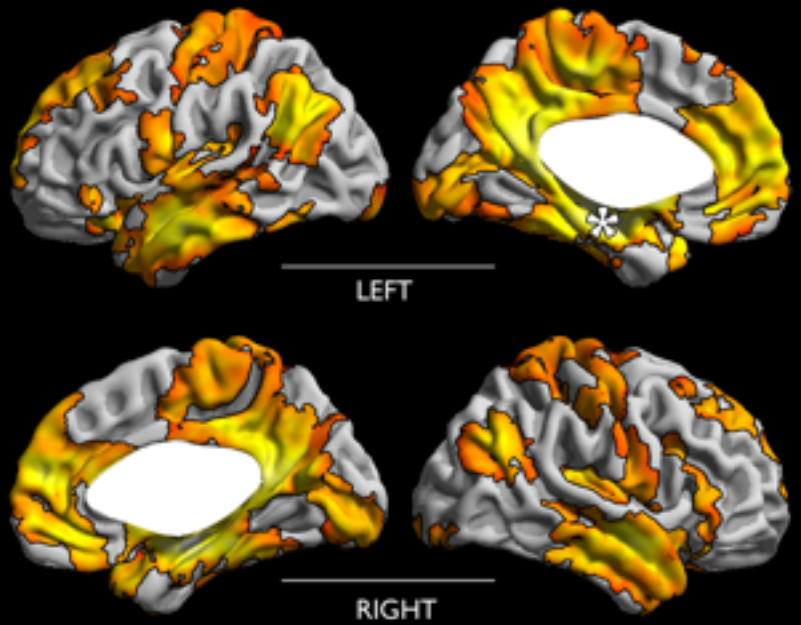


DIFFUSION ANALYSIS ALONG TRACTS: ANOMALIES TAPER OFF WITH INCREASING DISTANCE FROM TL EPICENTRE
87% LATERALIZATION PERFORMANCE

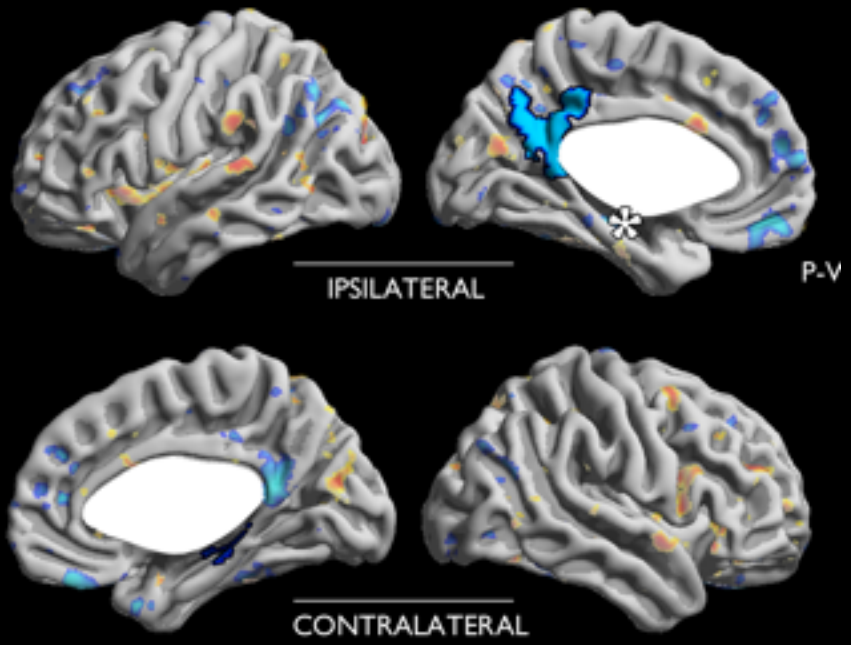
Concha et al. (2012) Neurology

FUNCTIONAL CONNECTIVITY STUDIES

CONTROLS



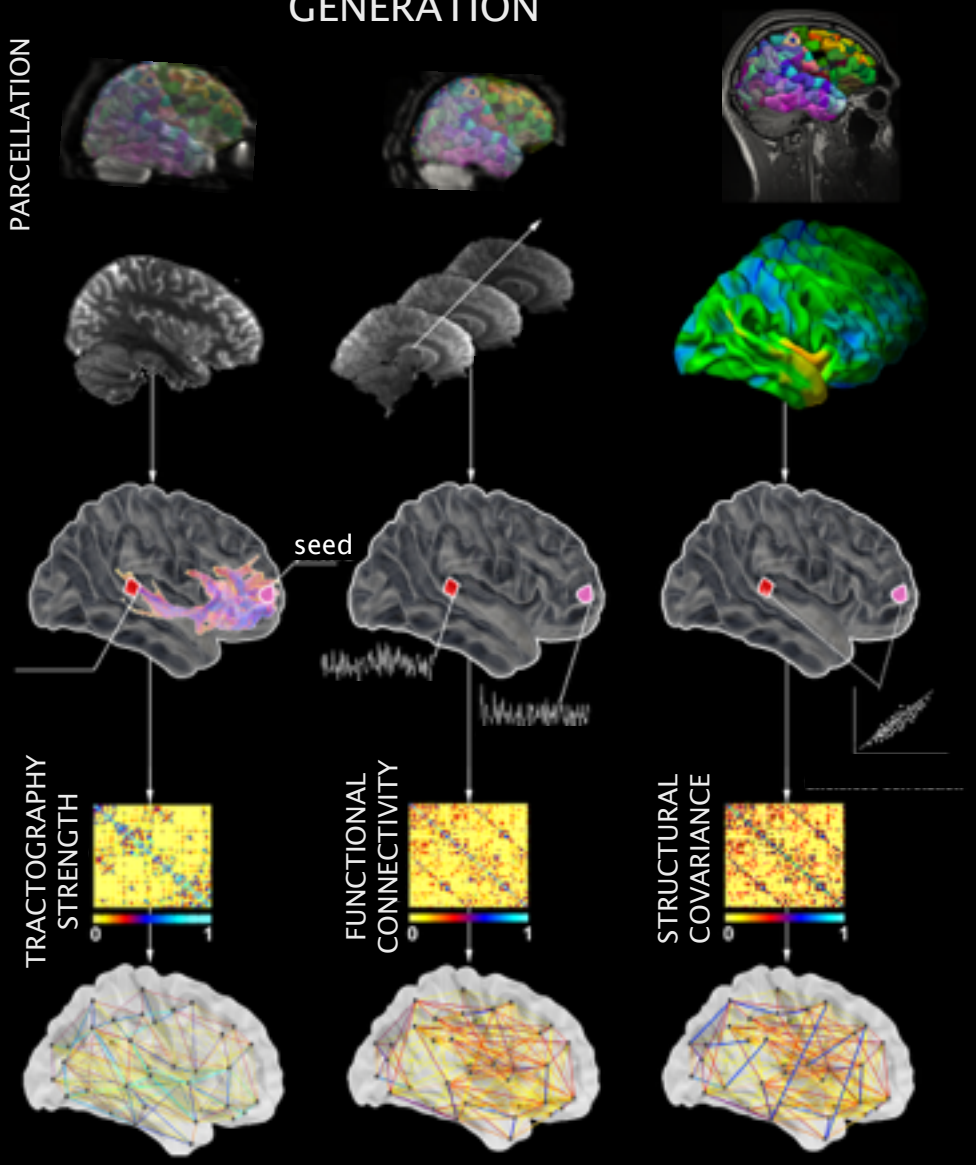
LTLE



Bernhardt et al. (in preparation)

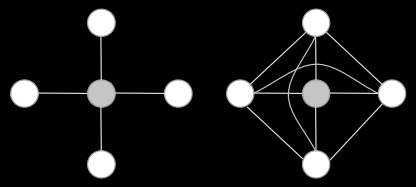
TOPOLOGY-LEVEL ANALYSIS

SYSTEMATIC NETWORK GENERATION

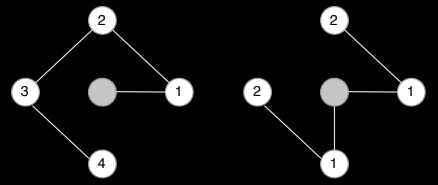


GRAPH THEORETICAL PARAMETERS

CLUSTERING C

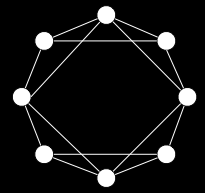


PATH LENGTH P



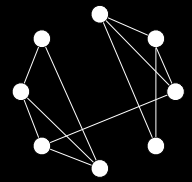
TOPOLOGY CLASSIFICATION

REGULAR



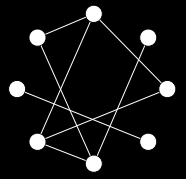
C+ P+

SMALL-WORLD



C+ P-

RANDOM



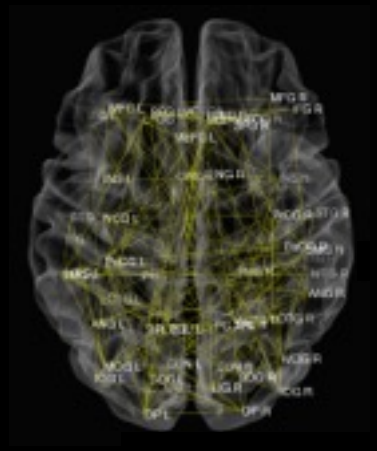
C- P-

See also: Watts and Strogatz (1998), Bullmore and Sporns (2009)

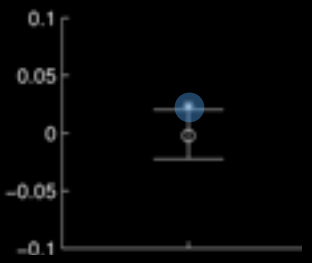
NETWORK-LEVEL PHENOTYPING IN TLE

NEOCORTEX

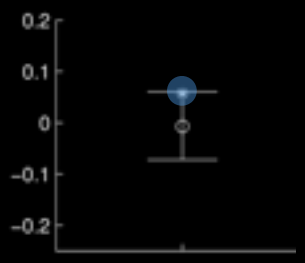
CONTROLS



TLE



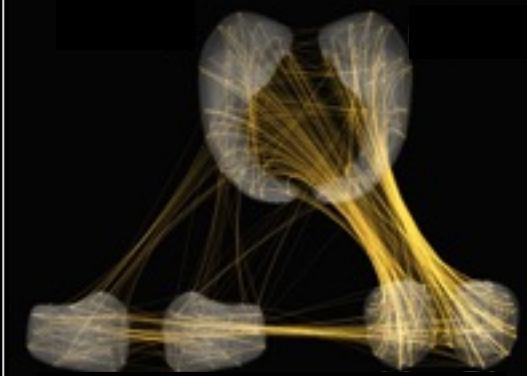
CLUSTERING



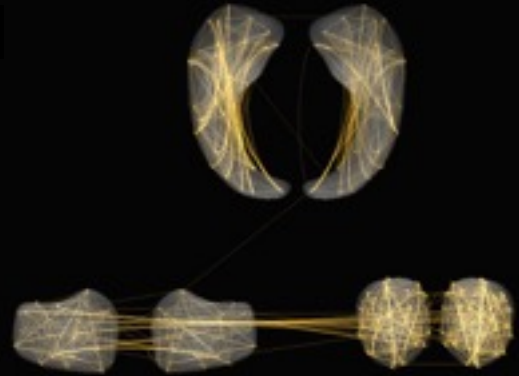
PATH LENGTH

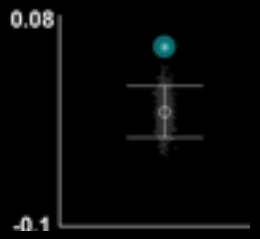
MESIOTEMPORAL LOBE

CONTROLS



TLE





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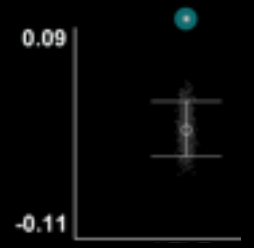

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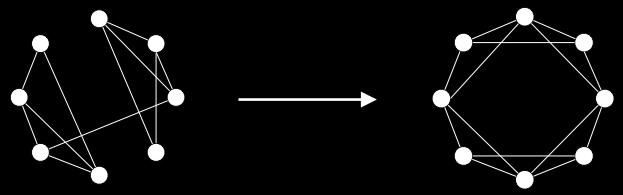


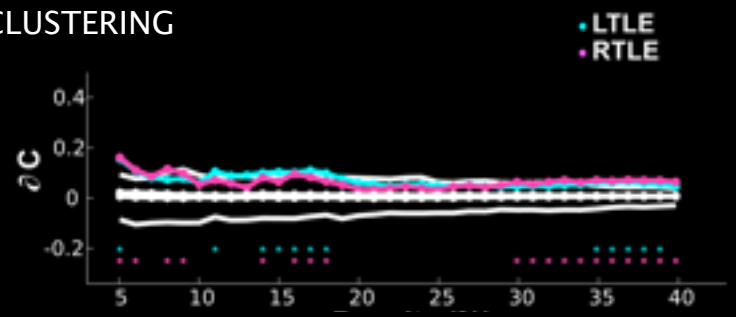
Bernhardt et al. (2011) Cerebral Cortex

Bernhardt et al. (2015) Cerebral Cortex

THRESHOLD INVARIANCE

NEOCORTEX

CLUSTERING



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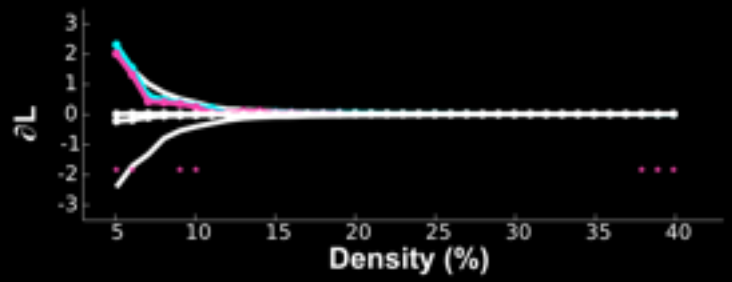
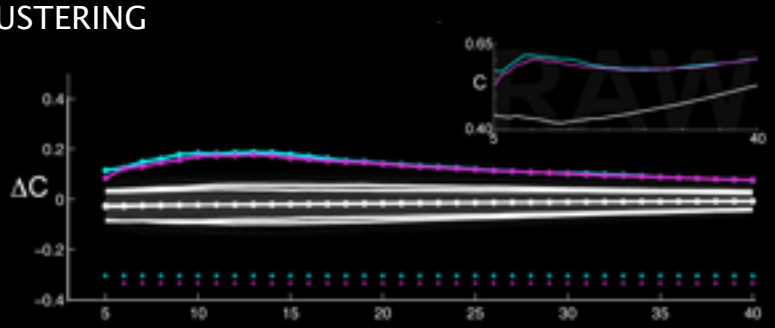


MESIOTEMPORAL LOBE

CLUSTERING



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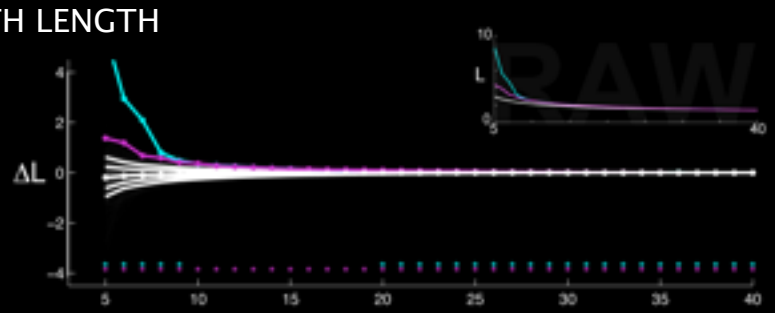
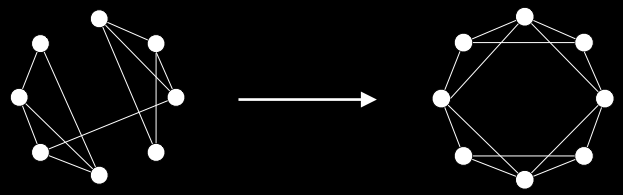




Bernhardt et al. (2011) Cerebral Cortex

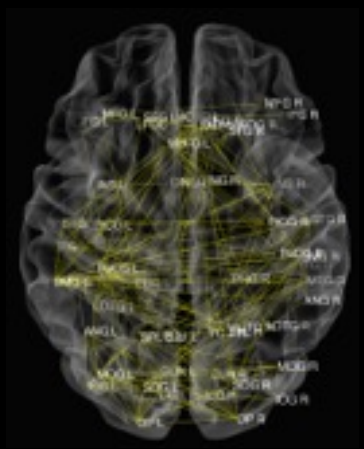
Bernhardt et al. (2015) Cerebral Cortex

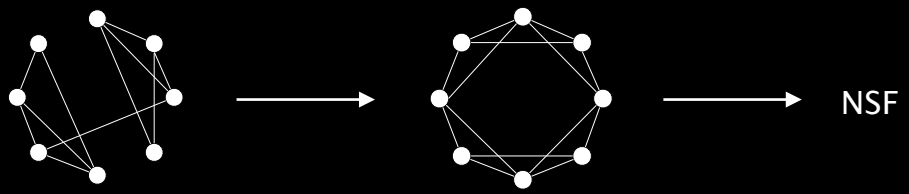
NETWORK MARKERS OF OUTCOME

NEOCORTEX

CONTROLS

TLE



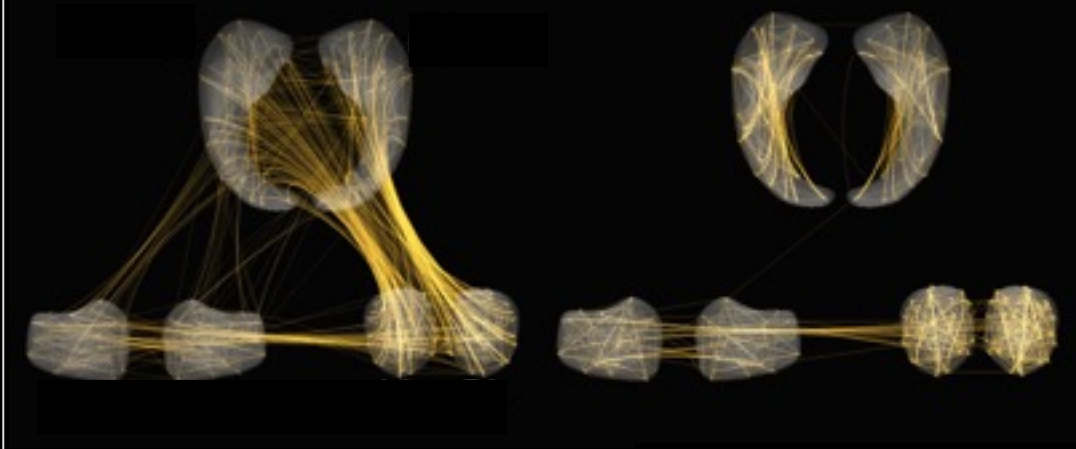


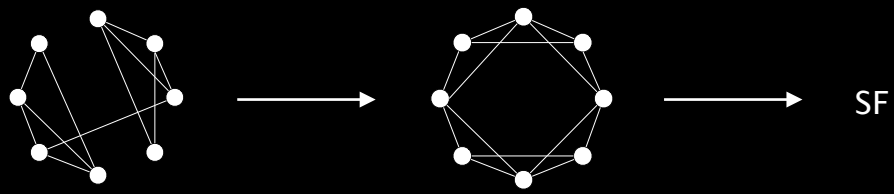
Bernhardt et al. (2011) Cerebral Cortex

MESIOTEMPORAL LOBE

CONTROLS

TLE





Bernhardt et al. (2015) Cerebral Cortex

NETWORK METHODS

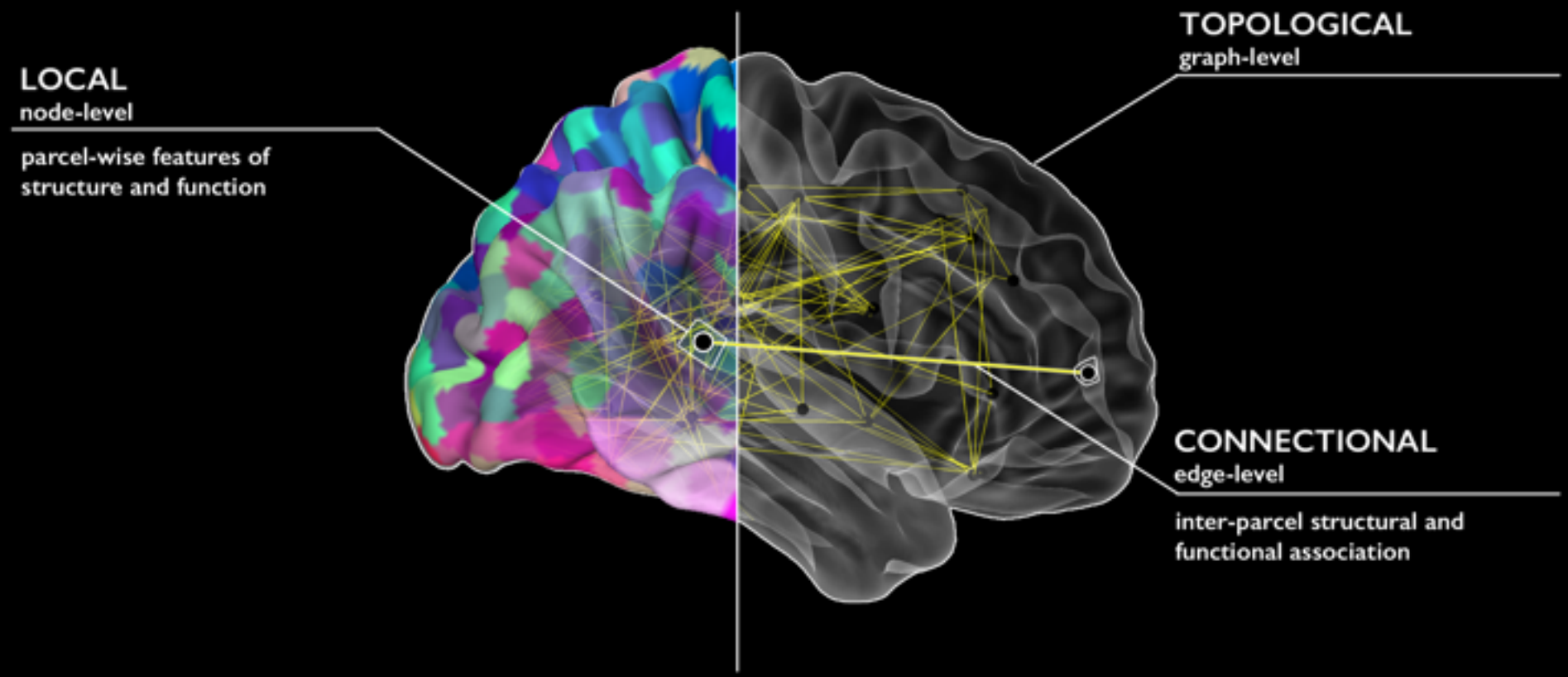
ADVANTAGES

- THEORETICALLY MEANINGFUL
- DIFFERENT LEVELS OF ANALYSES
  - REGIONAL
  - INTER-REGIONAL
  - TOPOLOGICAL
- UTILITY:
  - SYSTEM-LEVEL ANOMALIES IN 'FOCAL' EPILEPSIES
  - DISSOCIATING BETWEEN OUTCOME CLASSES

CHALLENGES

- INTERPRETATION AND VALIDATION IN VIVO CONNECTIVITY MARKERS
- TRANSFORMING NETWORK FINDINGS INTO MECHANISTIC MODELS
- HOW CAN NETWORK-LEVEL FINDINGS GUIDE CLINICAL DECISION MAKING

LOCAL + NETWORK



THANKS

Neda Bernasconi
Andrea Bernasconi
Seok-Jun Hong
Min Liu
Maged Goubran
Benoit Caldairou
Luis Concha
Sophie Adler
Lorenzo Caciagli
Dewi Schrader
Ravnoor Gill
Anton Plavski

Epilepsy Group at MNI
Brain Imaging Center

CIHR
Savoy Foundation for Epilepsy