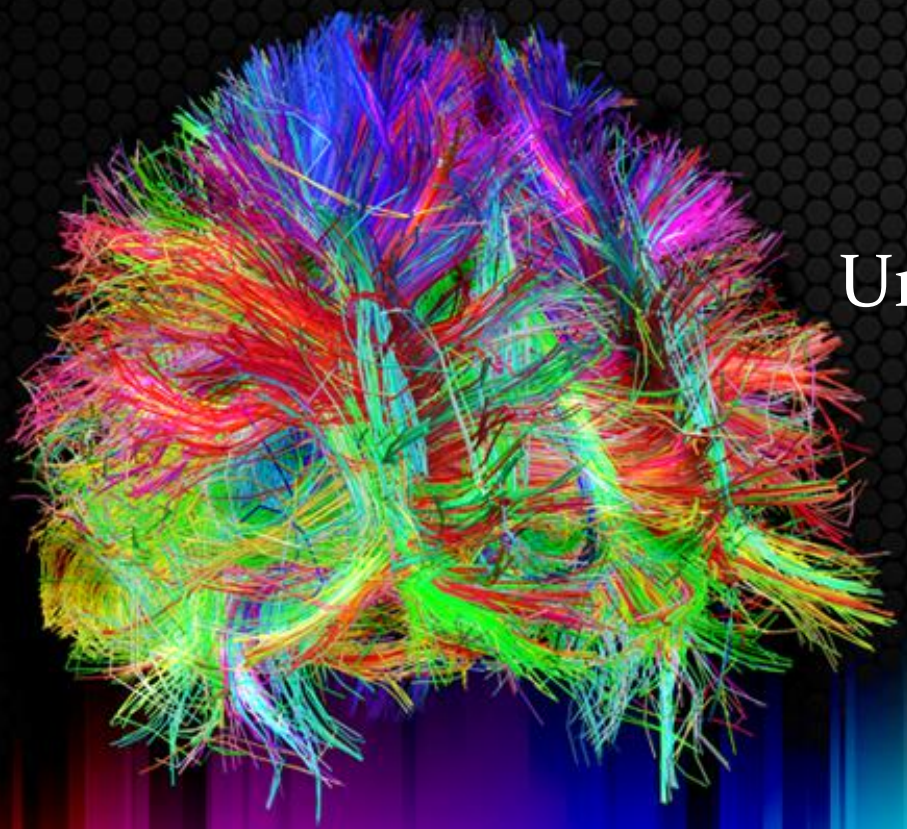
Traumatic Brain Injury Driving Biological Project

John Darrell Van Horn, Ph.D.
Laboratory of Neuro Imaging
University of California, Los Angeles



Overview

- Motivation for TBI DBP
- Why current processing tools are inadequate
- Image registration
- Cortical thickness modeling
- Lesion identification and modeling
- EEG modeling considerations in TBI
- Connectivity modeling
- An interesting application
- TBI DBP Productivity
- Plans for 2013-2014

Motivation TBI Imaging Research

Traumatic Brain Injury is a Major Health Care and Research Challenge:

- 1.5 Million TBI cases per year, half are "mild" TBI
- 650,000 hospitalizations for long-term brain injury, known as the "silent death" (unresponsiveness; coma; brain death; eventual patient death)
- $48 billion per year for management and loss to the US workforce
- **Many from automobile/workplace/battlefield**
- Returning war veterans particularly affected; NFL/NCAA taking seriously
- Neurobiology of TBI is poorly understood
- Not uncommon for patients to suffer from TBI-related epilepsy, paralysis, memory loss, etc
- 85+ clinical trials for therapy, all failed
- Few treatment options, no proven rehabilitation, but management
- Management: ~$1 million per case
- See CDC web-site: http://www.cdc.gov/TraumaticBrainInjury/tbi_concussion.html
- Opportunities to use neuroimaging for TBI assessment and prediction

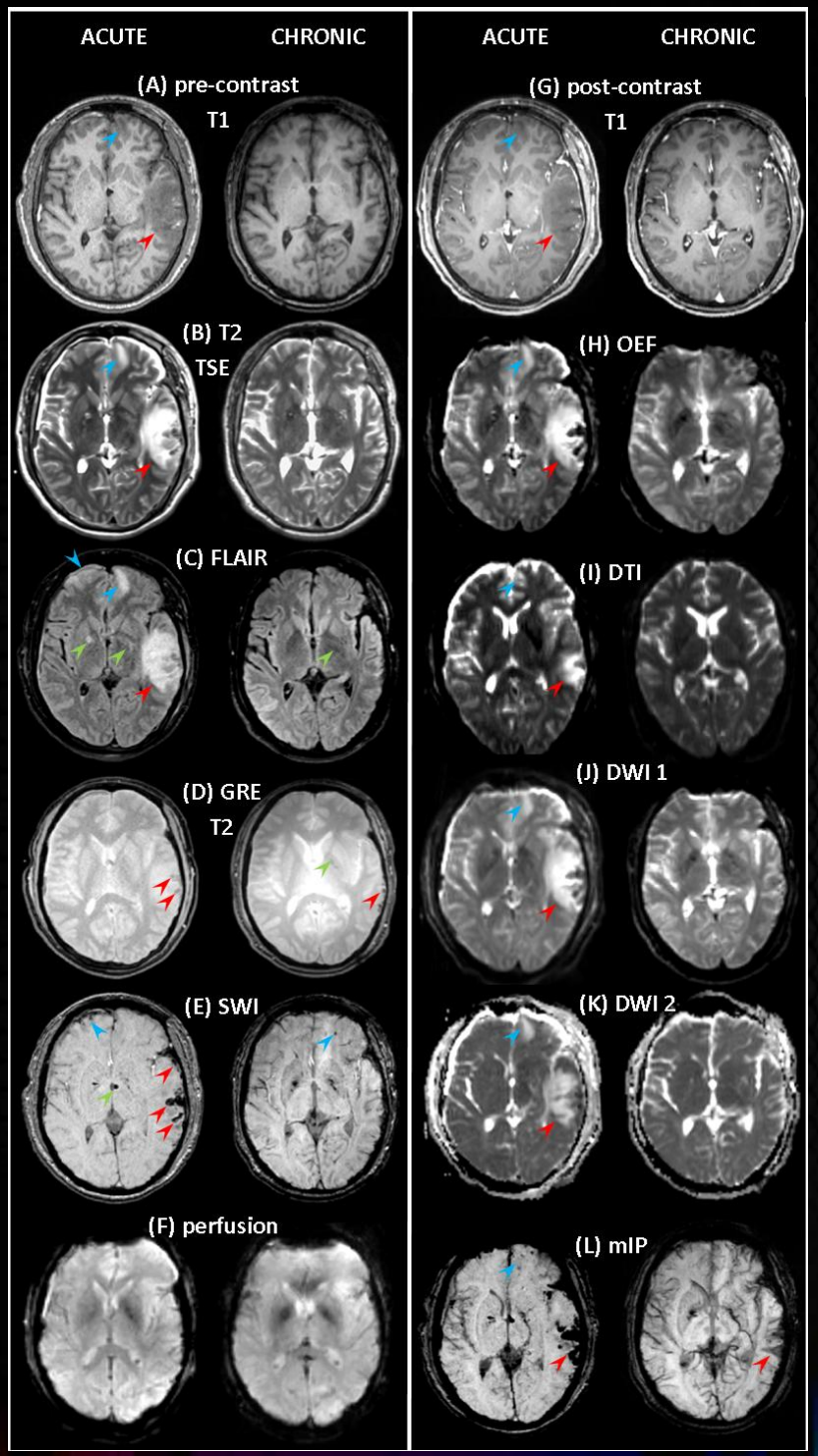
Are current methods not sufficient?

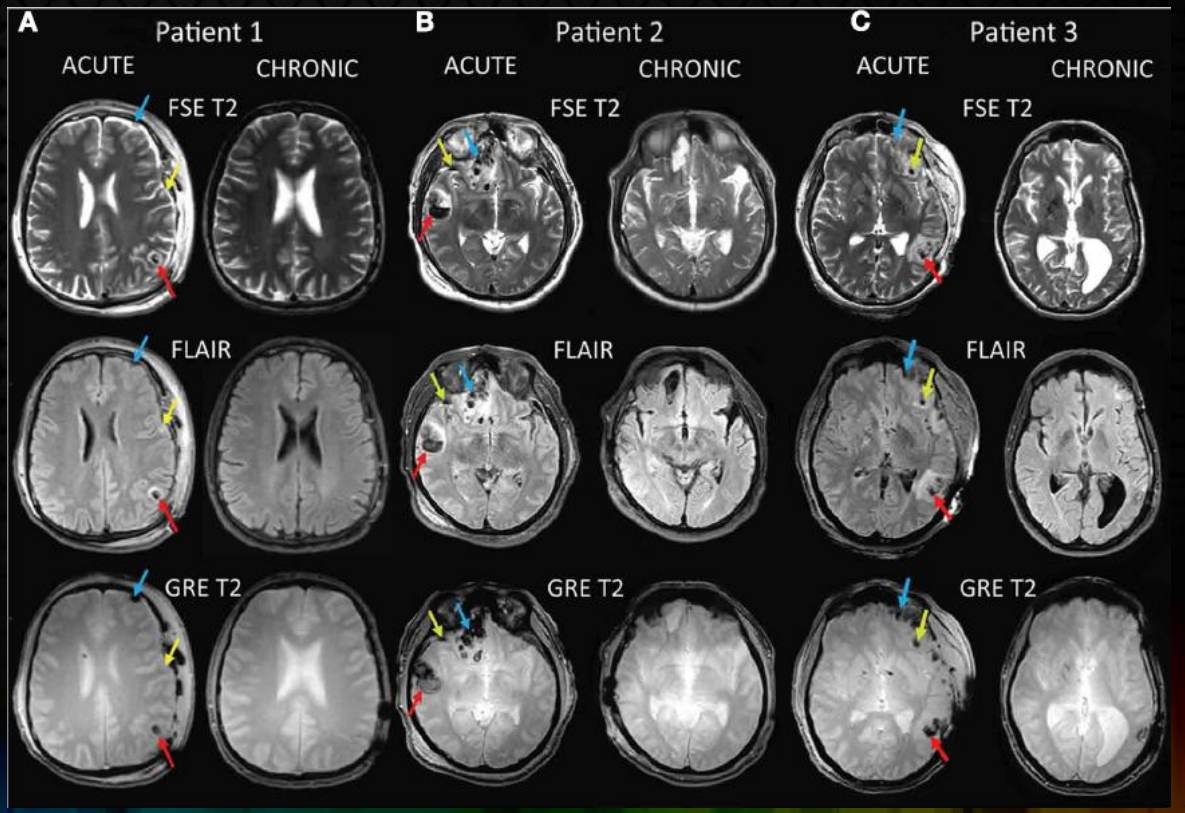
- Neuroimaging programs expect “normal” brains
- TBI deforms brain shape, so “not normal”
- More tissue classifications than GM, WM, CSF
- Non-reliance on usual brain landmarks
- Strictly atlas-based methods fail when applied to all but concussion and mild TBI
- *Murky* concept of “average” TBI
- Focus on patient-specific computation of lesion type, location, extent and effect on connectivity are needed for better characterization, treatment targeting, and outcome prediction.

Longitudinal neuroimaging of Traumatic Brain Injury and Chronic Traumatic Encephalopathy using multimodal MRI At UCLA

Brain Injury Research Center (BIRC)

Acute imaging within 1st 48 hours after admission
Chronic imaging 6 months post injury





Within-Subject Image Registration

Bhattacharyya Distance (BD) vs. Mutual Information (MI)

$$\text{BD:} \quad \mathcal{B}(I_1, I_2; \vec{u}) = \iint \sqrt{p(i_1, i_2; \vec{u}) p(i_1; \vec{u}) p(i_2)} di_1 di_2$$

$$\text{MI:} \quad \mathcal{M}(I_1, I_2; \vec{u}) = \iint p(i_1, i_2; \vec{u}) \log \frac{p(i_1, i_2; \vec{u})}{p(i_1; \vec{u}) p(i_2)} di_1 di_2$$

Notations:

- Two images $I_1(x)$ $I_2(x)$
- Deformation $u(x)$ such that $I_1(x - u(x)) \sim I_2(x)$
- Joint histogram $p(i_1, i_2; u)$
- Marginal histograms $p(i_1; u) = \int p(i_1, i_2; u) di_1$

$$p(i_2) = \int p(i_1, i_2; u) di_1$$

- The logarithm function is undefined at zero, which results in the gradient of MI being prone to numerical errors near the origin.
- The square root is continuous at zero, thus making BD more stable than MI when *p(i,j;u)* is very small.

From Yifei Lou and colleagues

Workflow for Processing TBI datasets

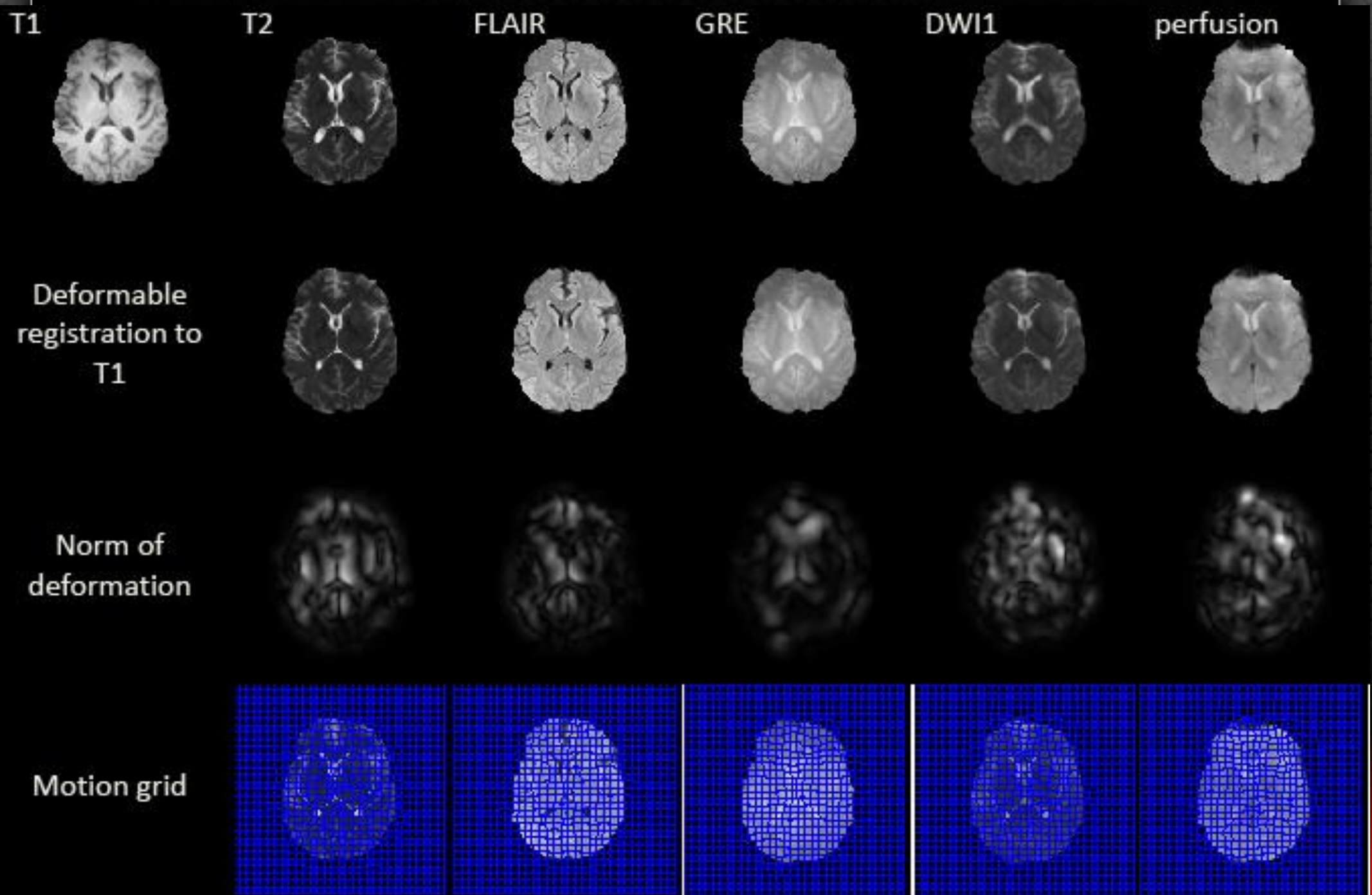
1. Rigid-body registration (all to T1 at acute stage) using *3DSlicer* to correct head tilt and reduce errors in computing local deformation fields.

2. Skull stripping using *BrainSuite* to reduce extracranial swelling for image acquired at acute stage.

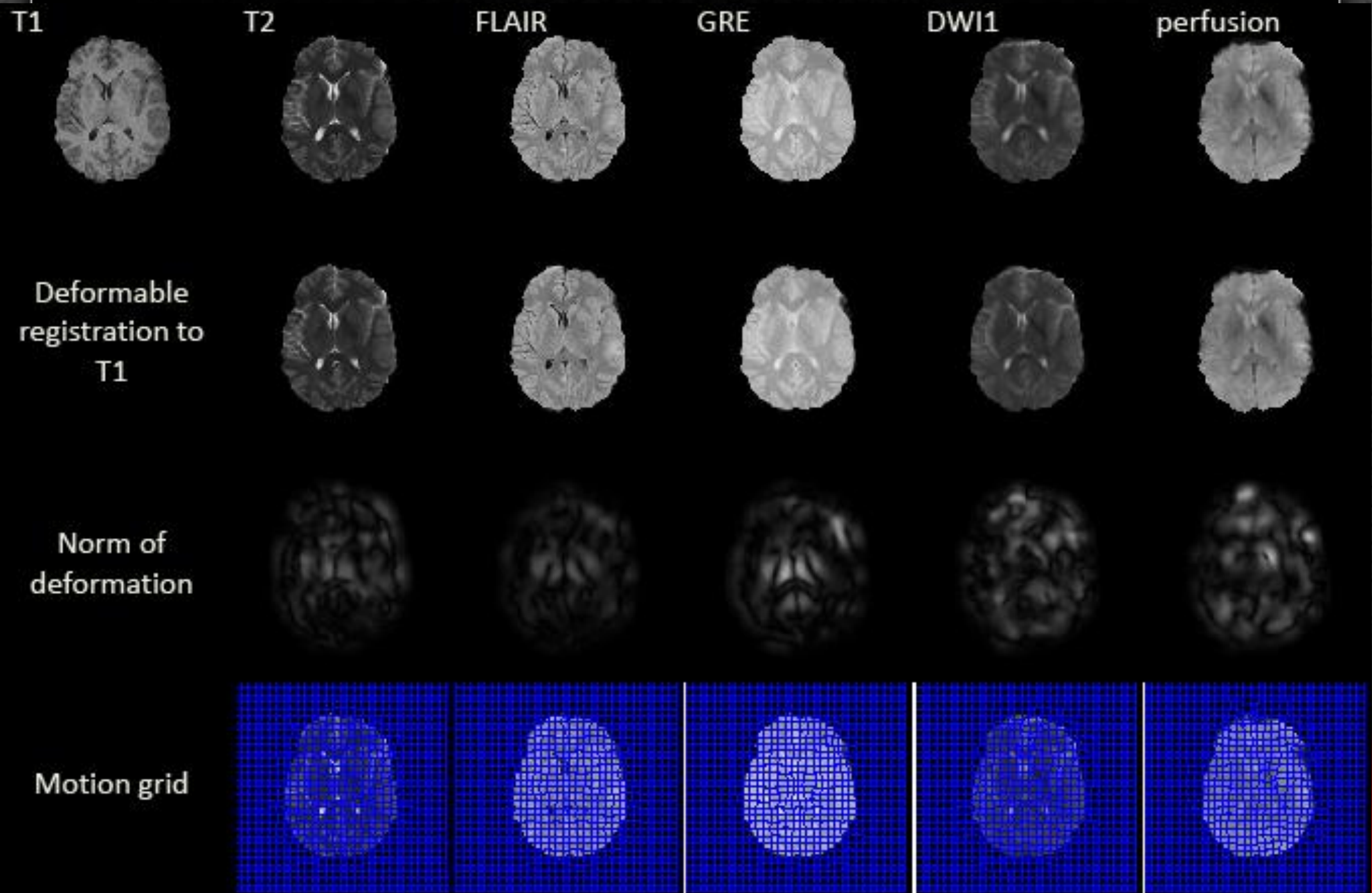
3. Deformable image registration using BD as metric.

4. Plotting deformation norms and motion to evaluate anatomical changes in TBI (see next slide for details).

Results: Acute Stage

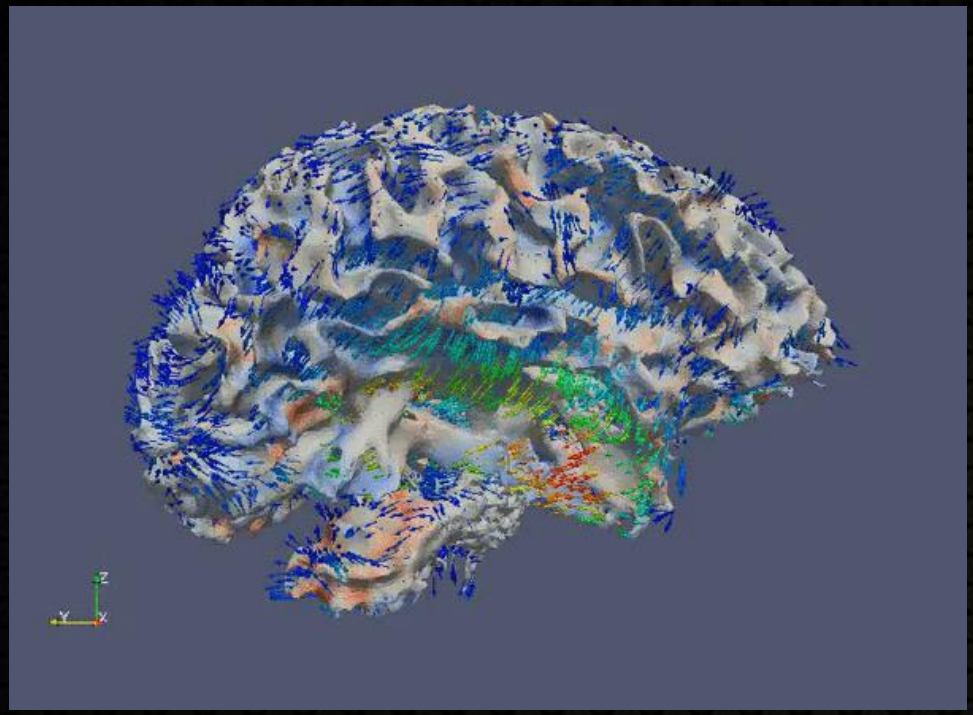


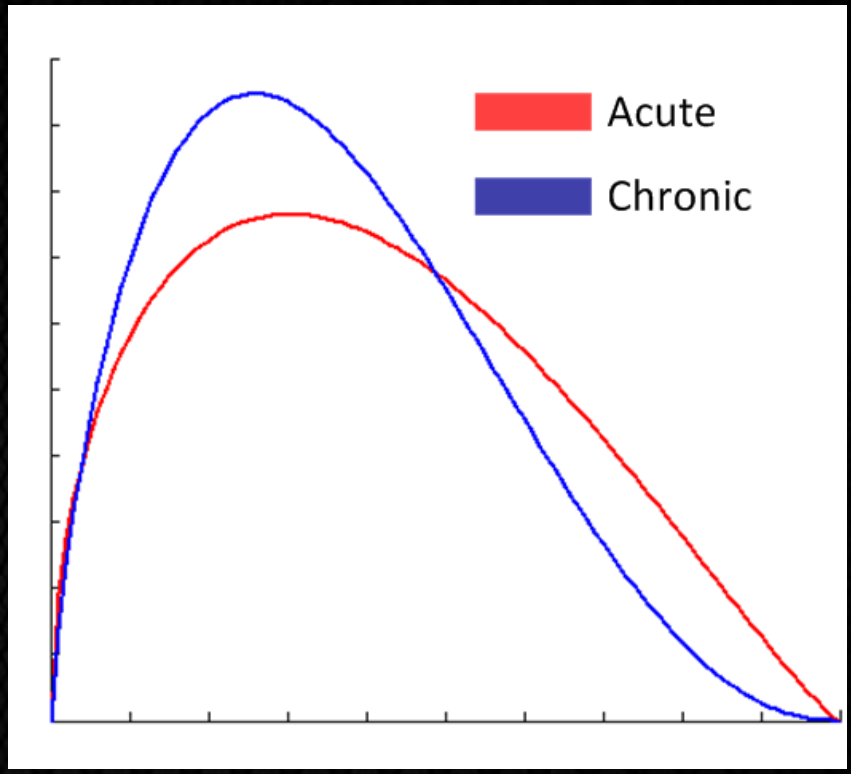
Results: Chronic Stage



Cortical Thickness Modeling

Time Dependent Changes in Cortical Thickness in TBI



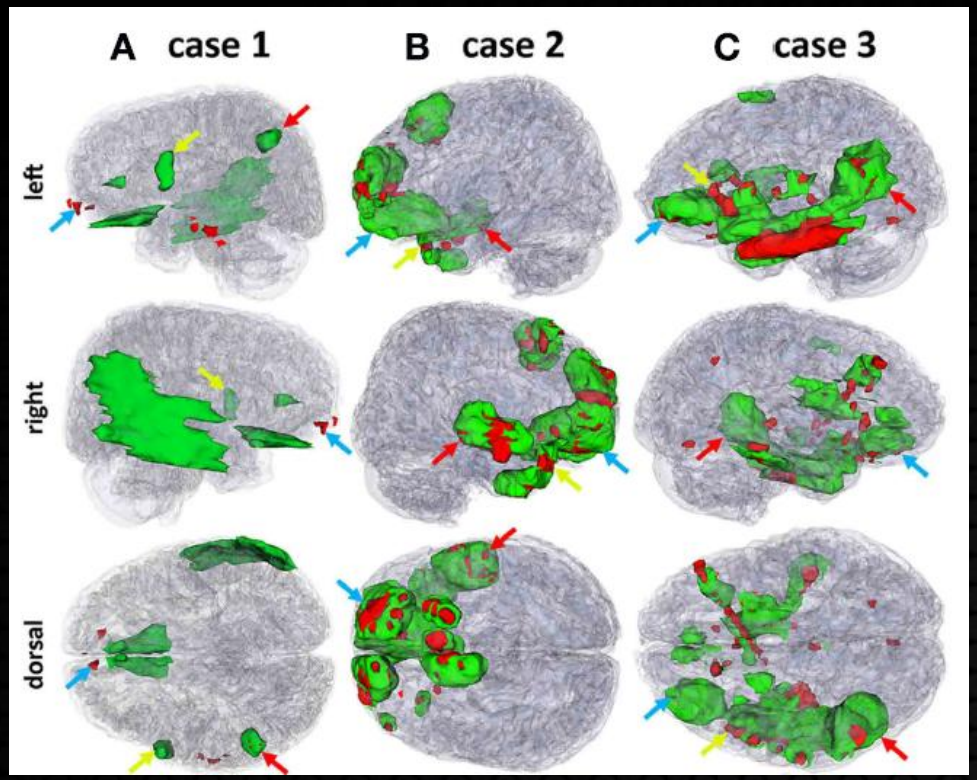


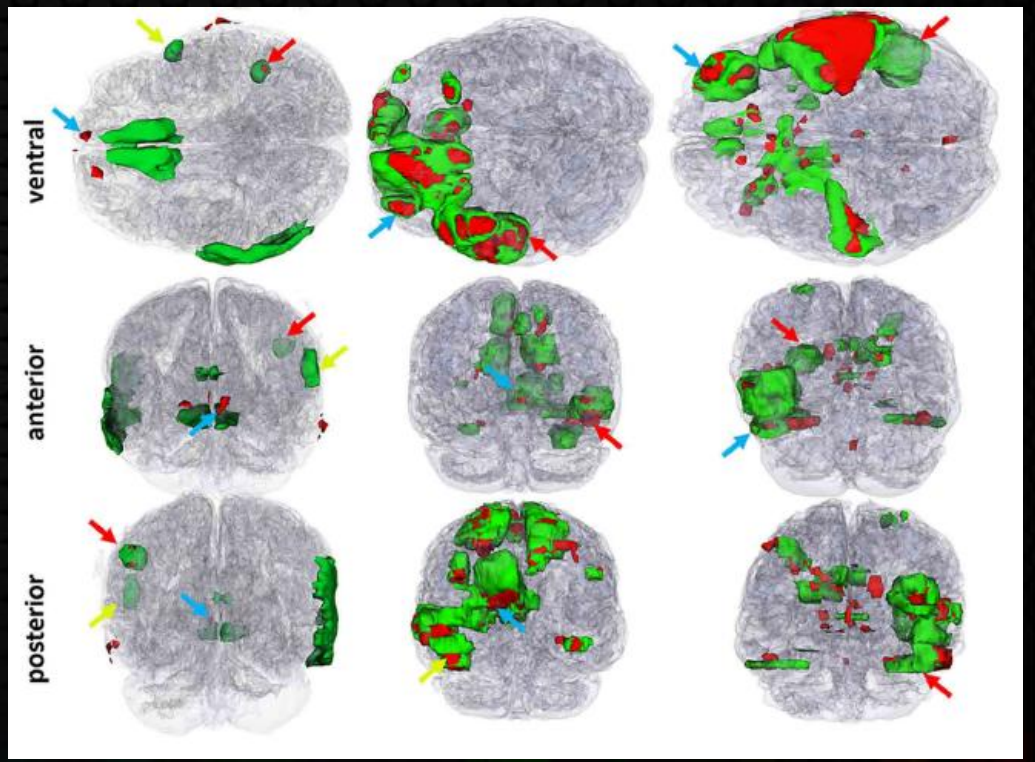
Surface-based biomarkers shown for one subject:
(a) Visualization of cortical thickness change and spatial displacement,
(b) Cortical thickness distributions at acute and chronic time points.

Wang et al., ISBI

Multimodal Lesion Modeling

3D models of pathology



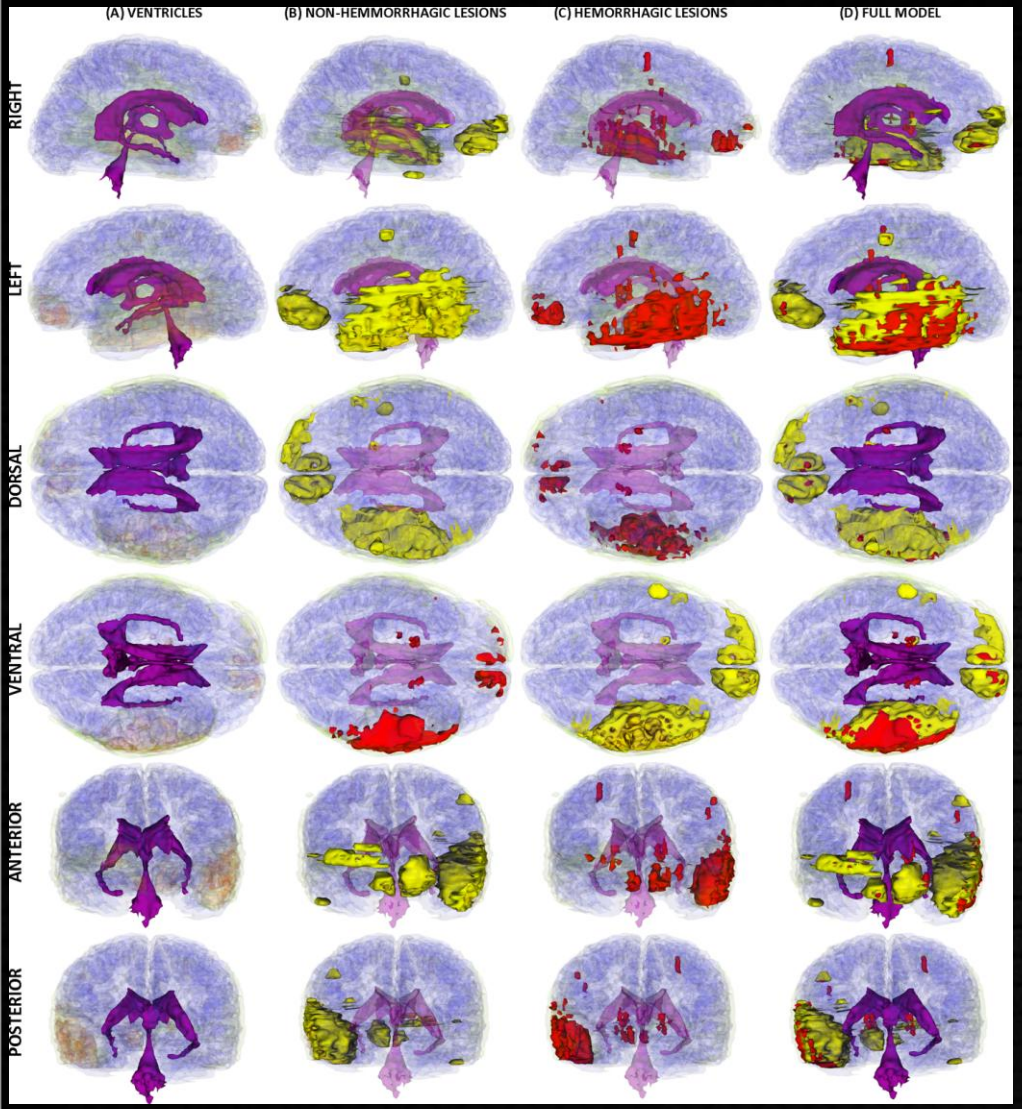


edema

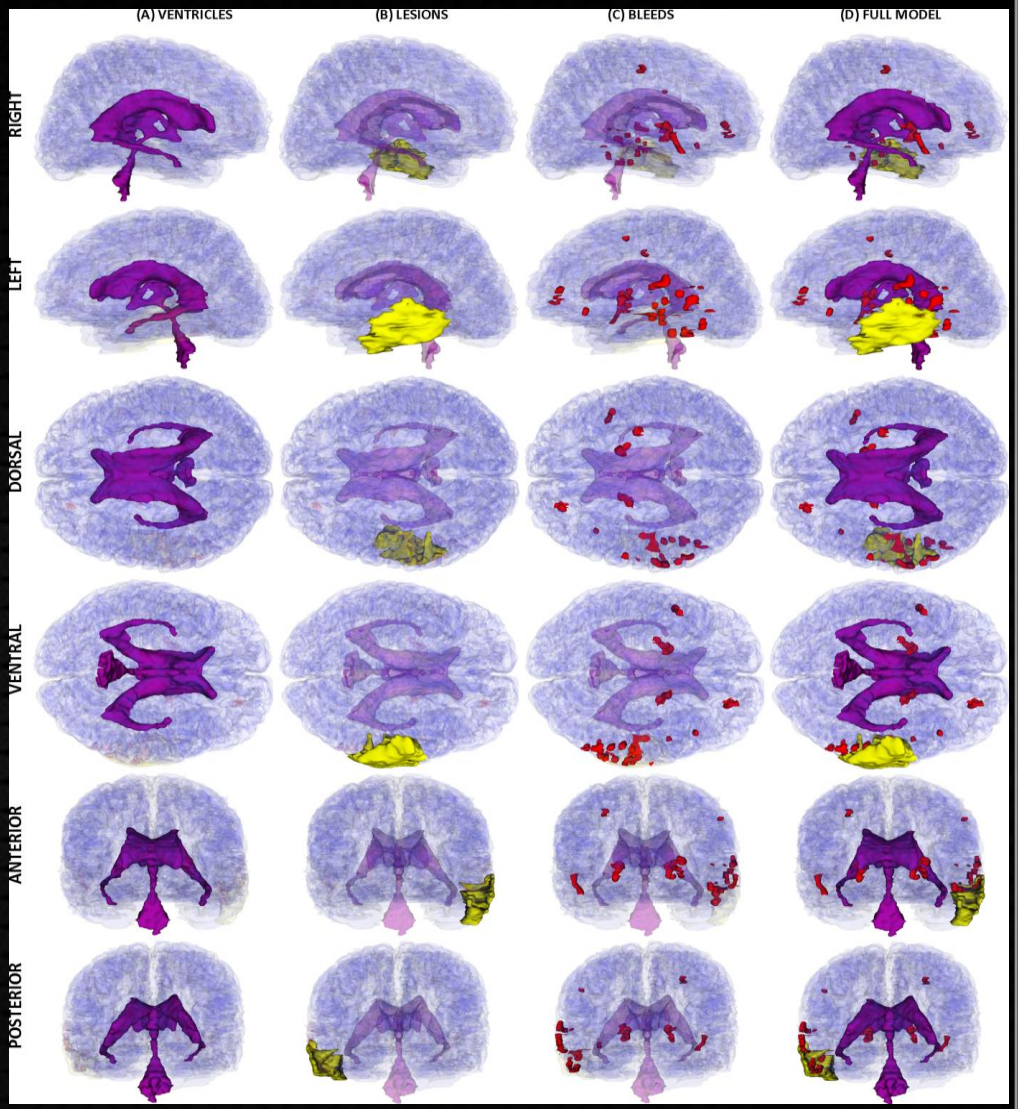
hemorrhage

Irimia et al., J. Neurotrauma, 2011

Acute



Chronic



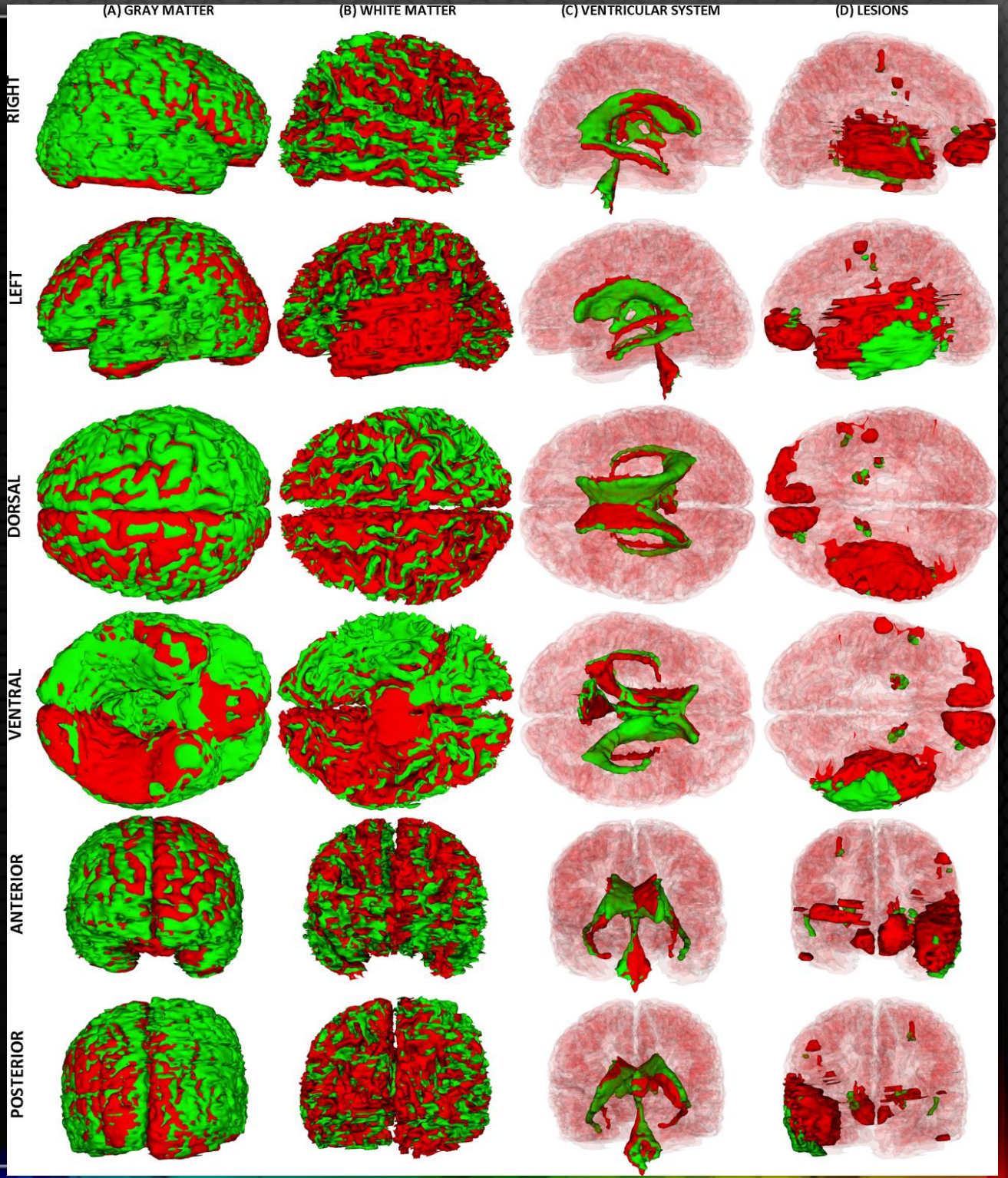
ventricular system

edema

hemorrhage

longitudinal change: acute vs. chronic

- acute
- chronic

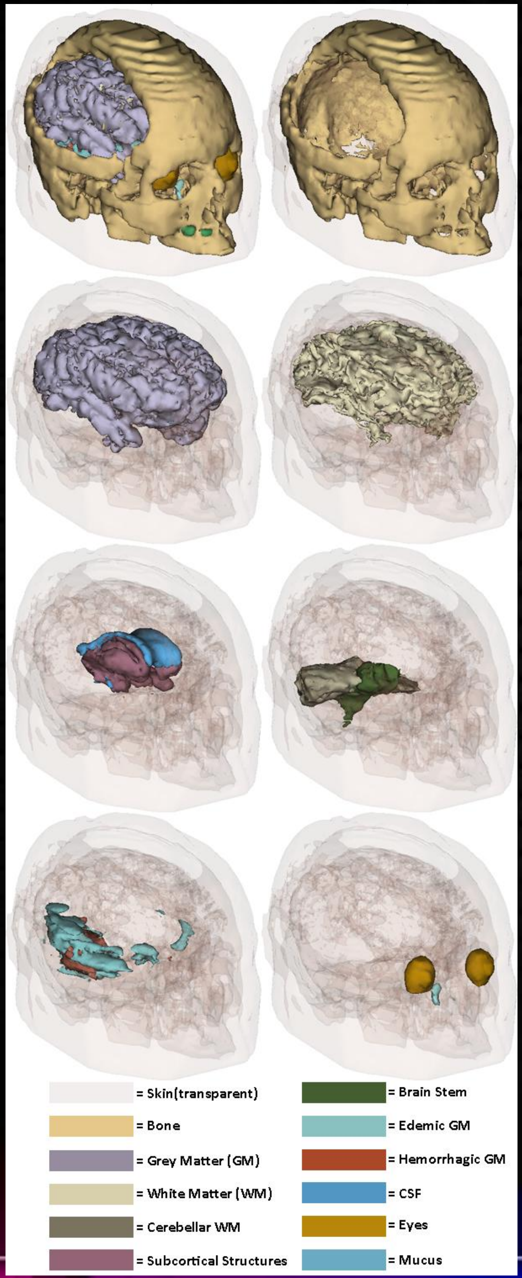


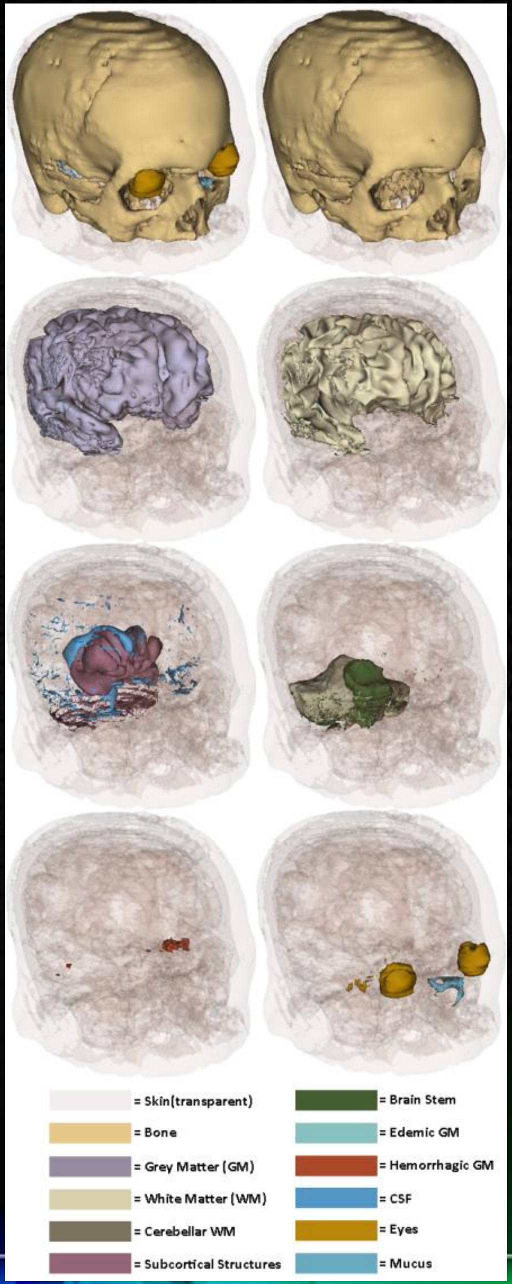
EEG Forward and Inverse Modeling

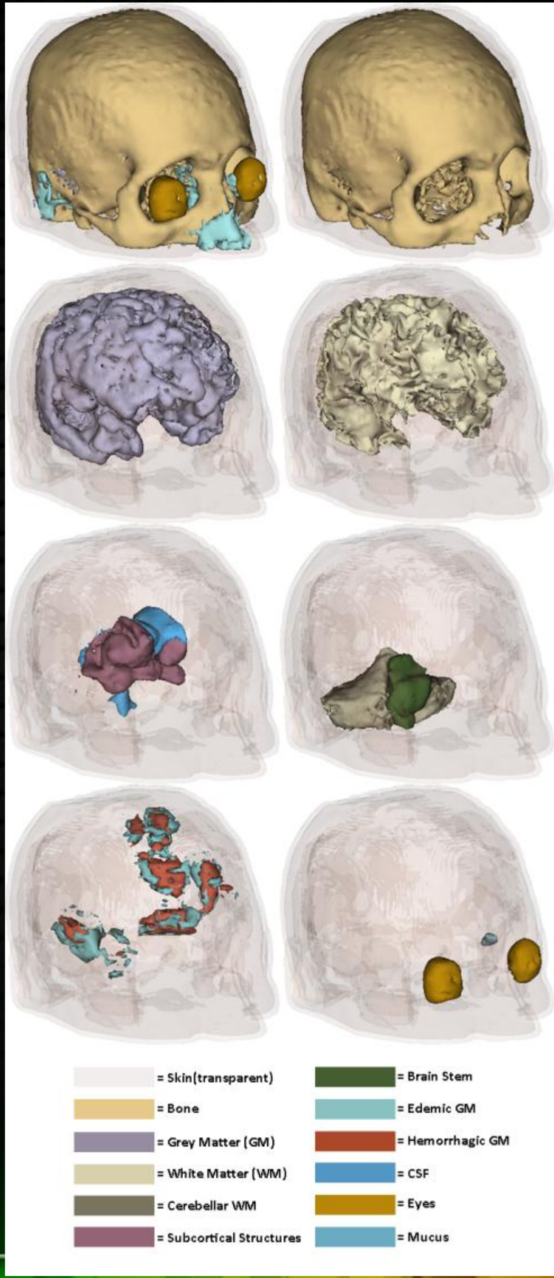
Challenges for Modeling EEG Sources in TBI

- Difficulty of accounting for TBI-related structural pathology when using EEG
  - (1) the absence of skin and skull parts due to open head injuries
  - (2) conductivity profile alterations due to pathology
- we model the head using 25 tissue types
- we include the effects of gross pathology

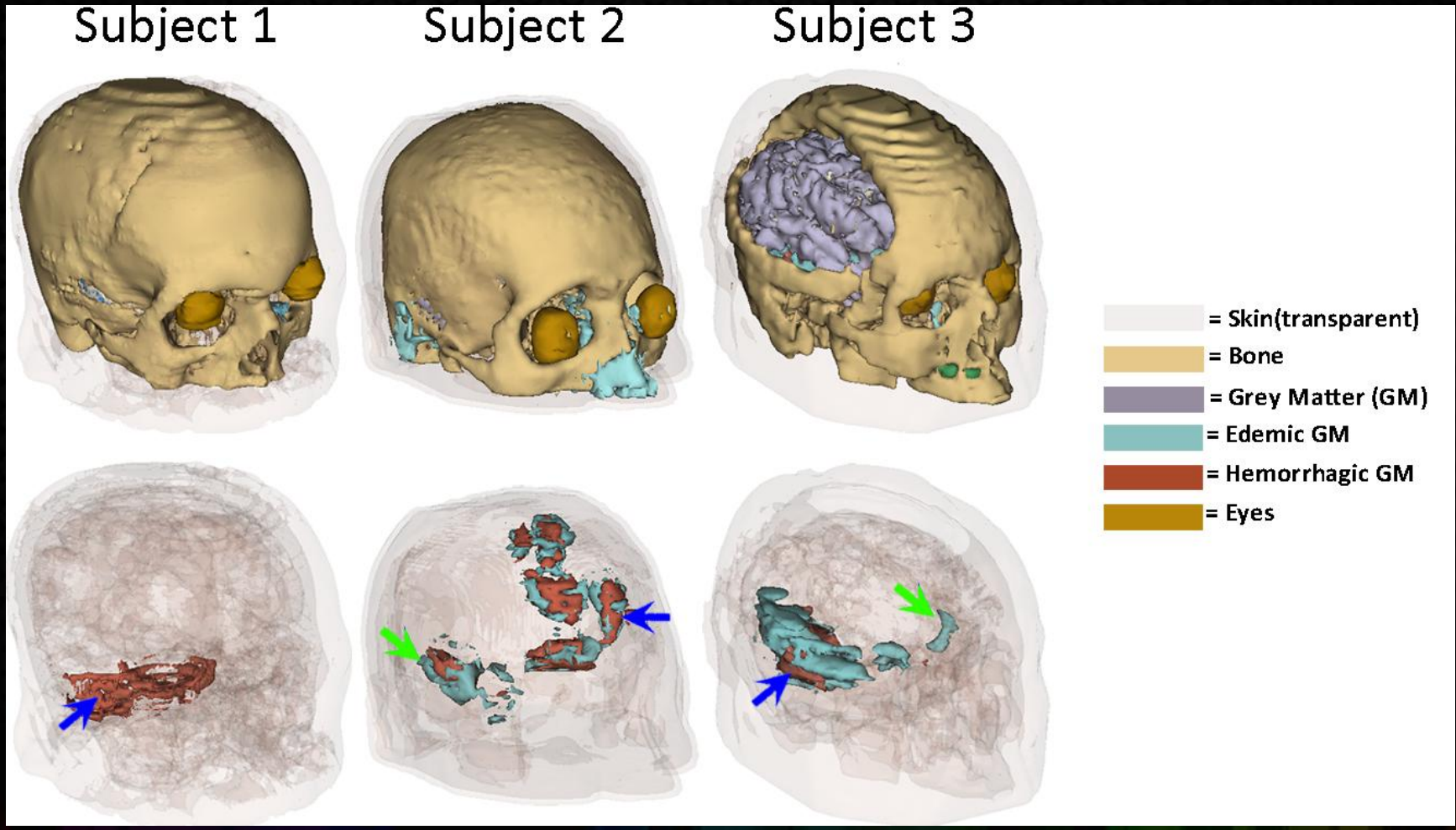
Head Models using 25 Tissue Types



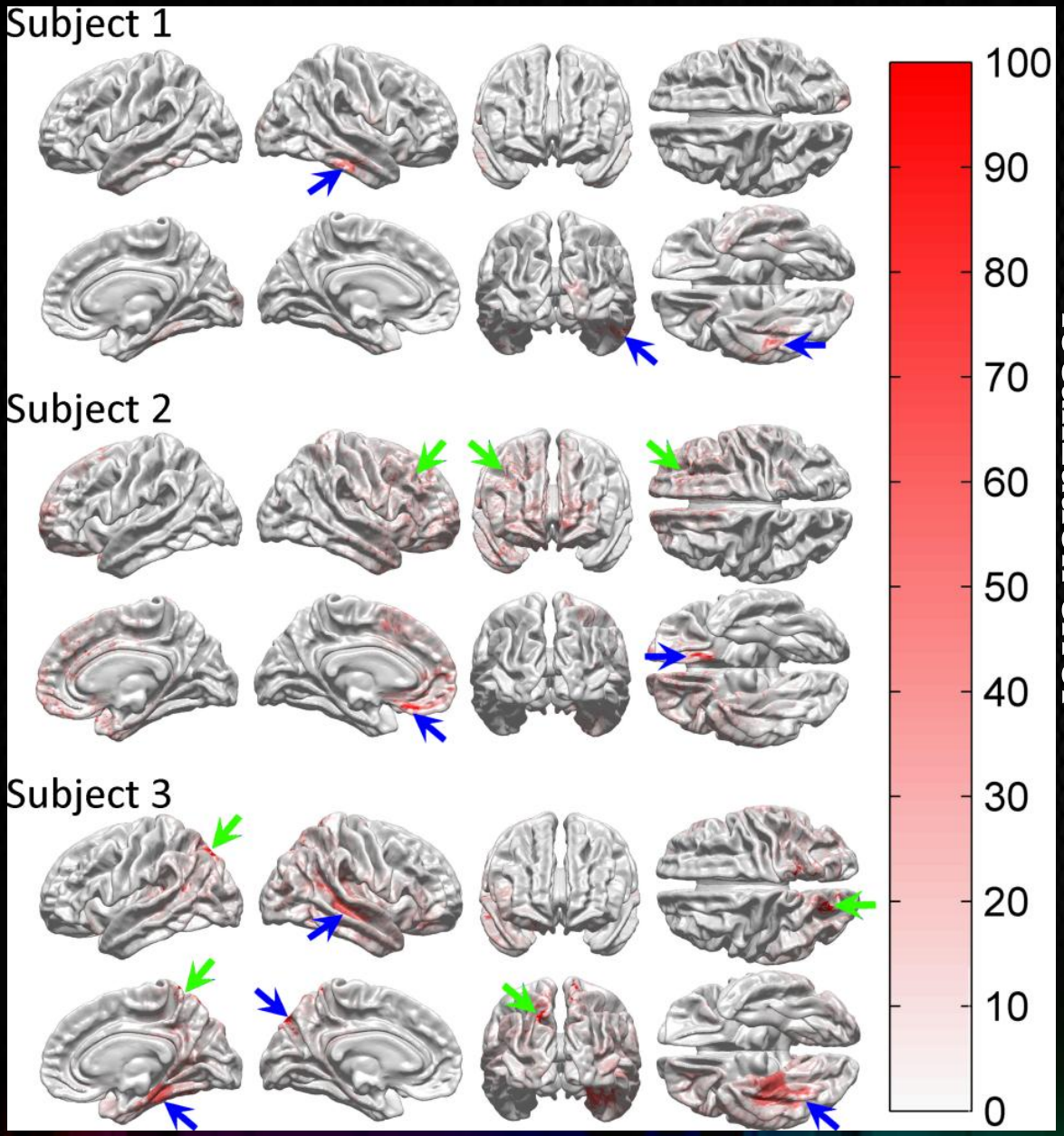




TBI effects upon localization



TBI Effects Upon Localization



- EEG forward models of TBI should account for holes in the skull
- Blood and edema can alter the conductivity profile of the head
- Accounting for lesions is important for the purpose of accurate inverse localization in acute as well as chronic TBI

Goh et al., ISBI

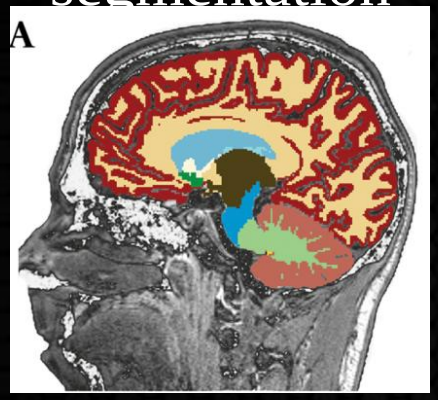
Connectivity Mapping

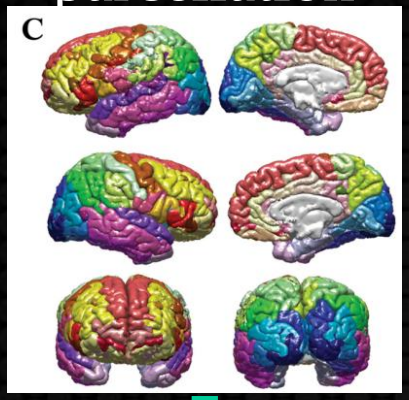
Connectomic Mapping

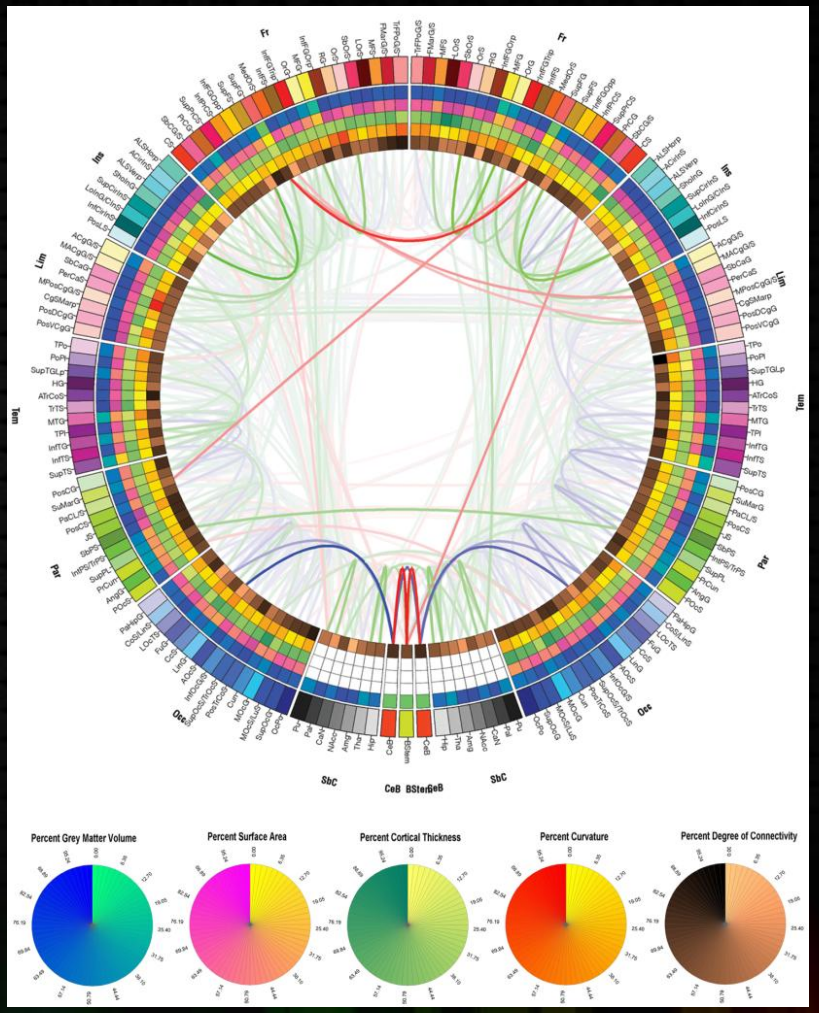
automatic segmentation

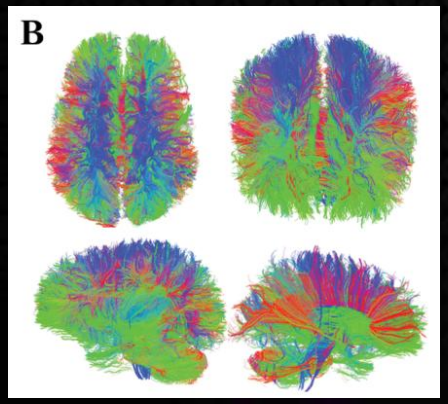
automatic parcellation

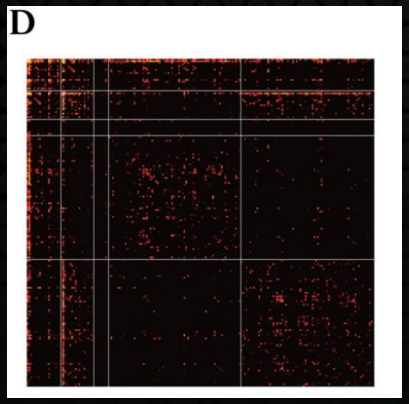
connectogram







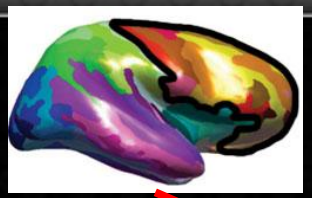




DTI tractography

connectivity matrix calculation

FRONTAL



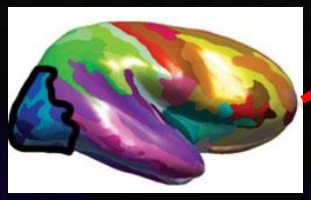
INSULAR

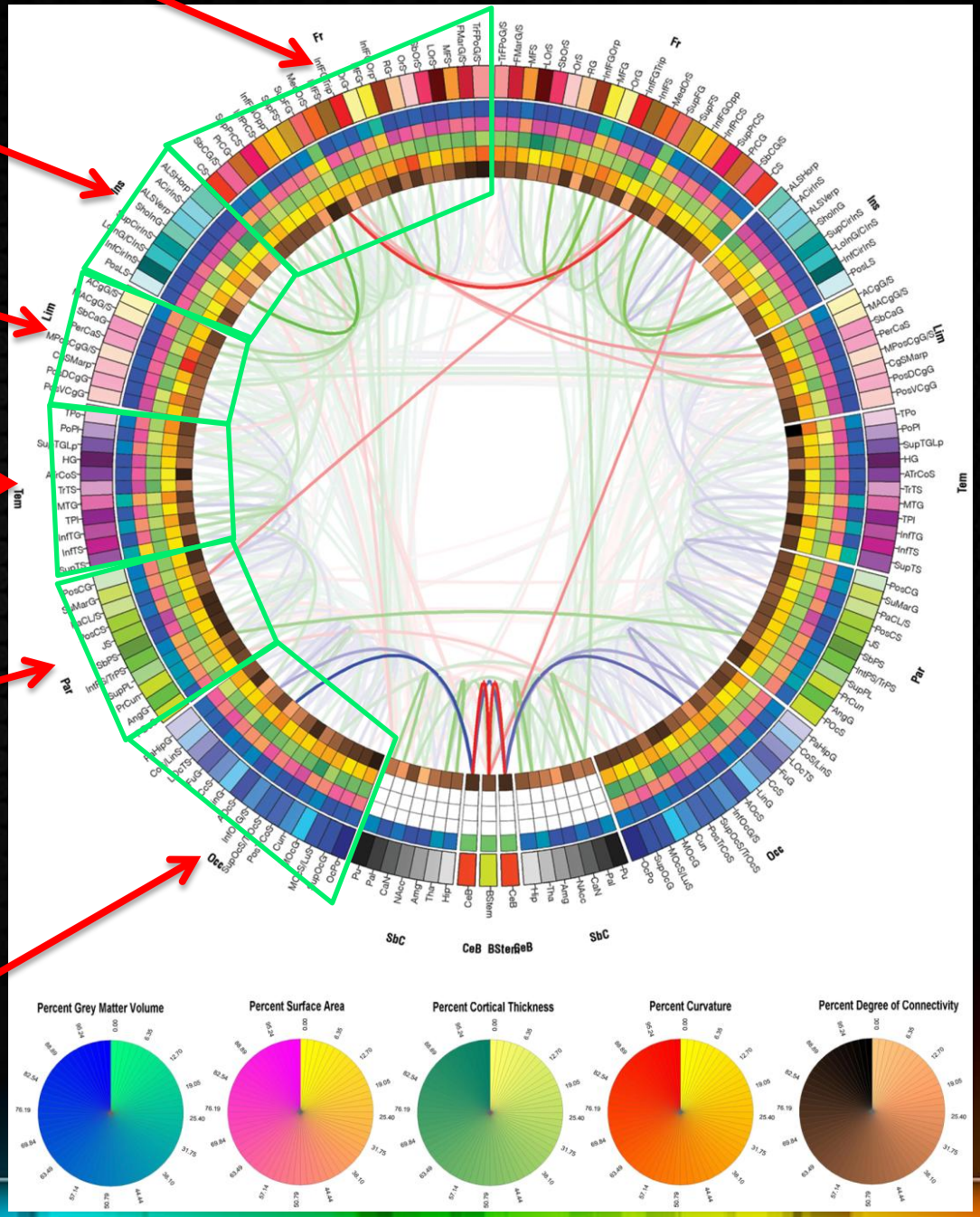
LIMBIC

TEMPORAL

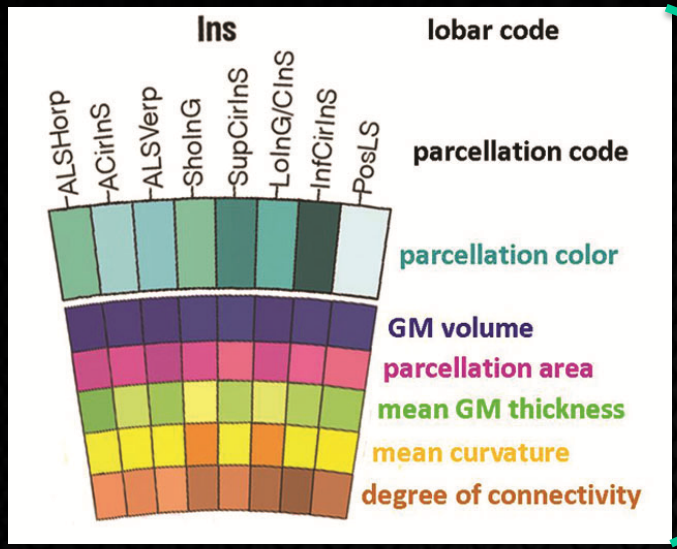
PARIETAL

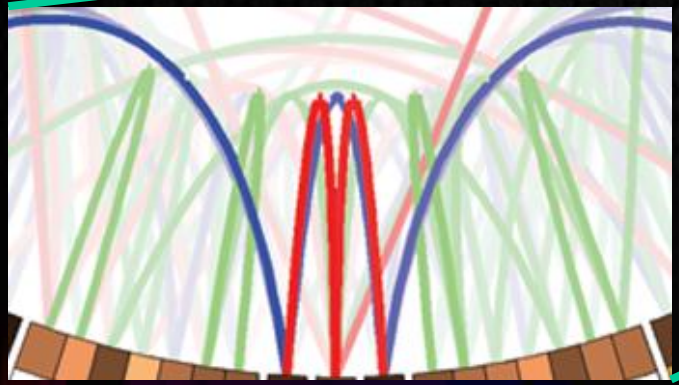
OCCIPITAL

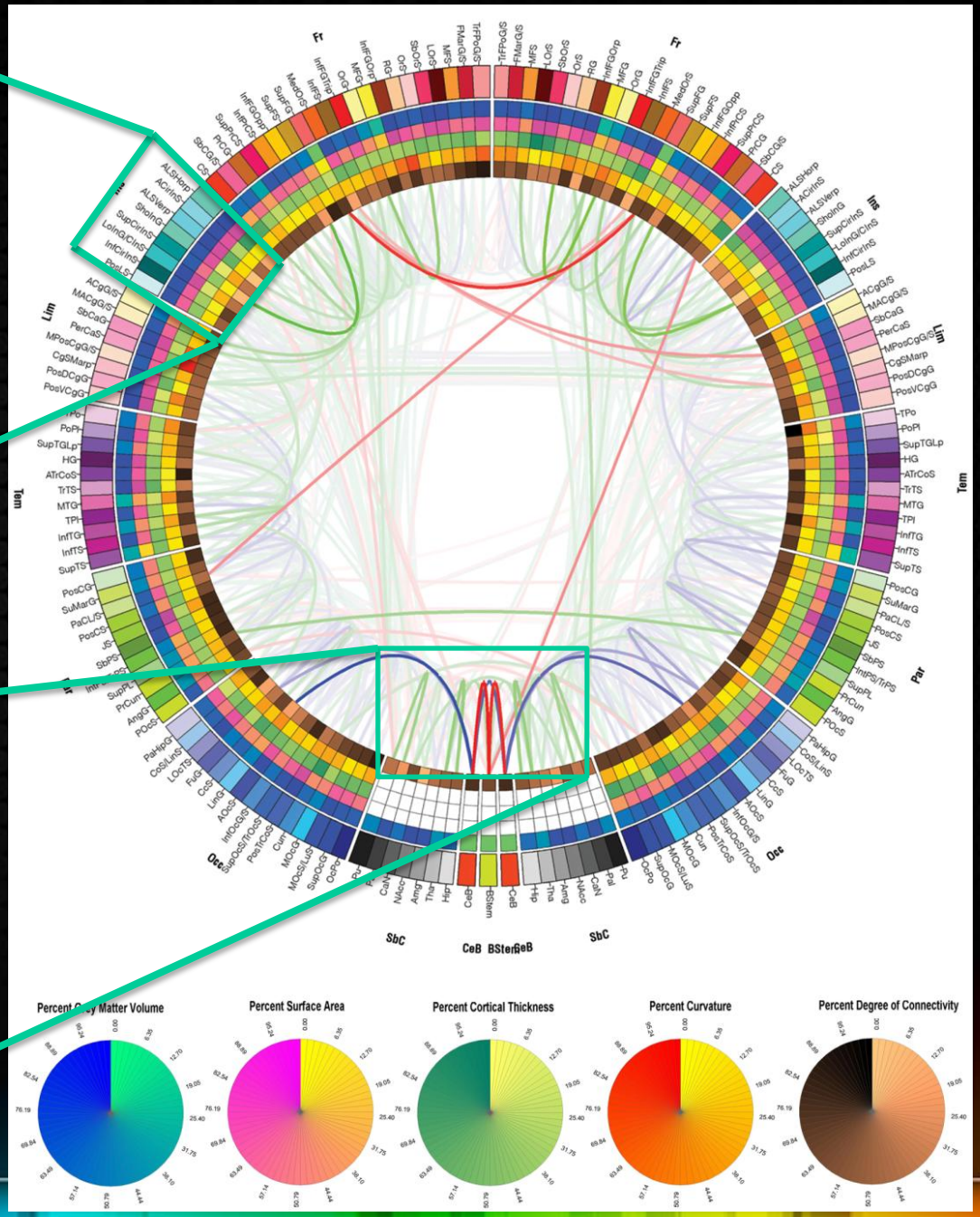


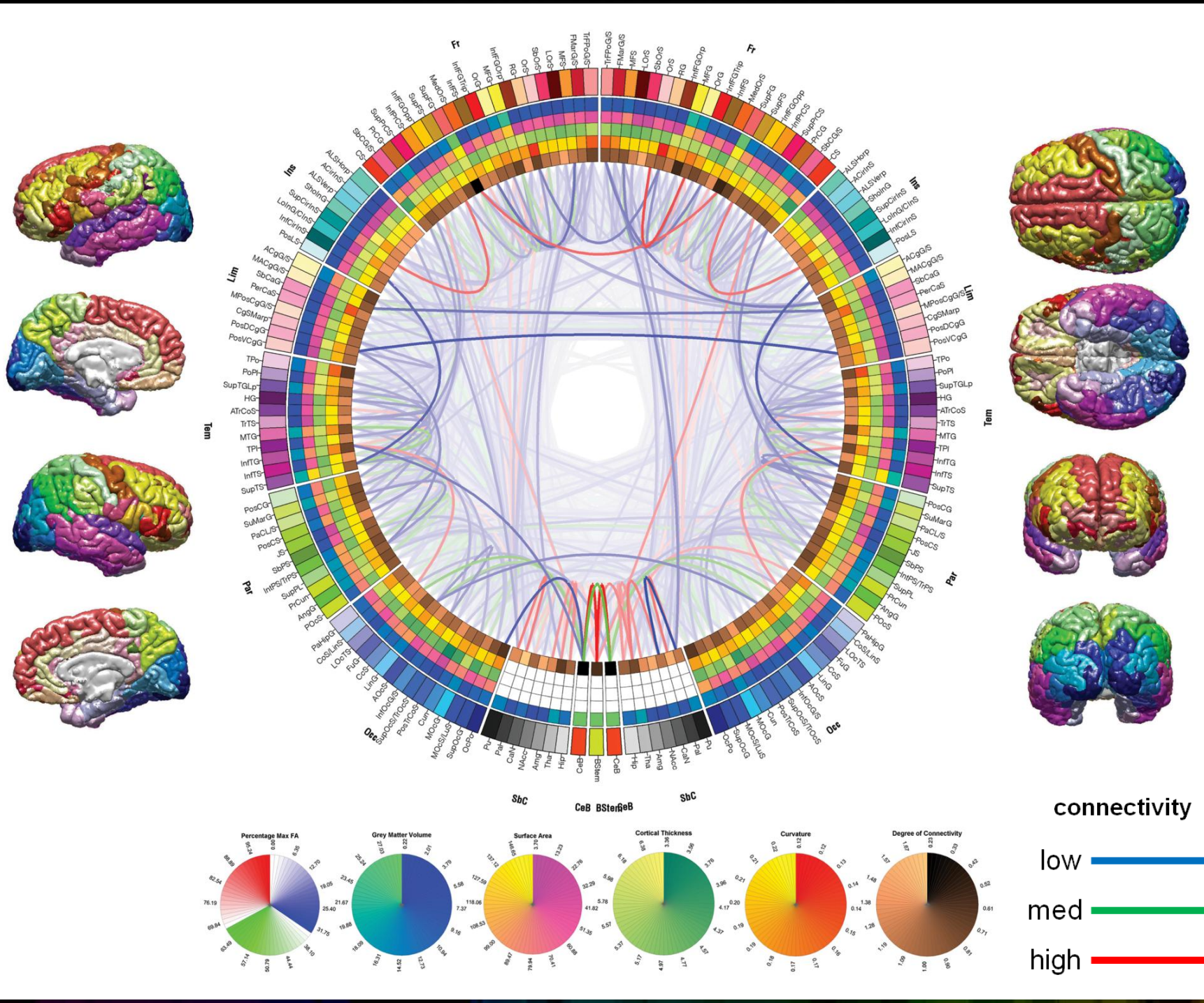


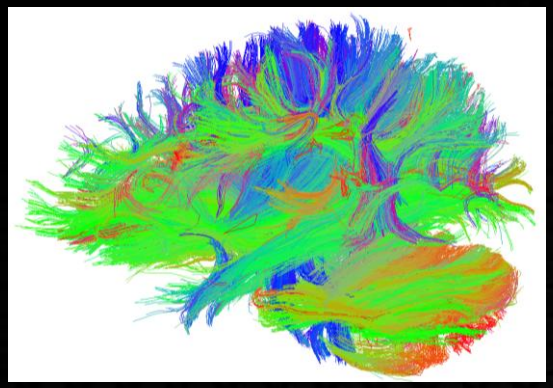
Connectogram Interpretation

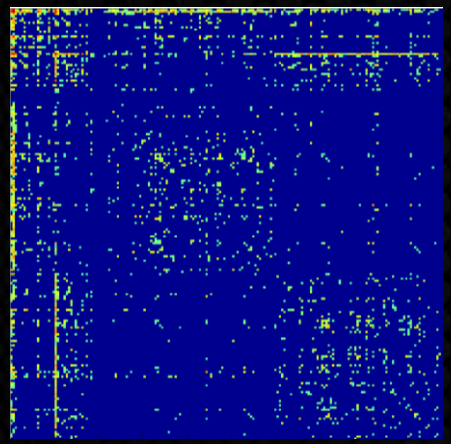




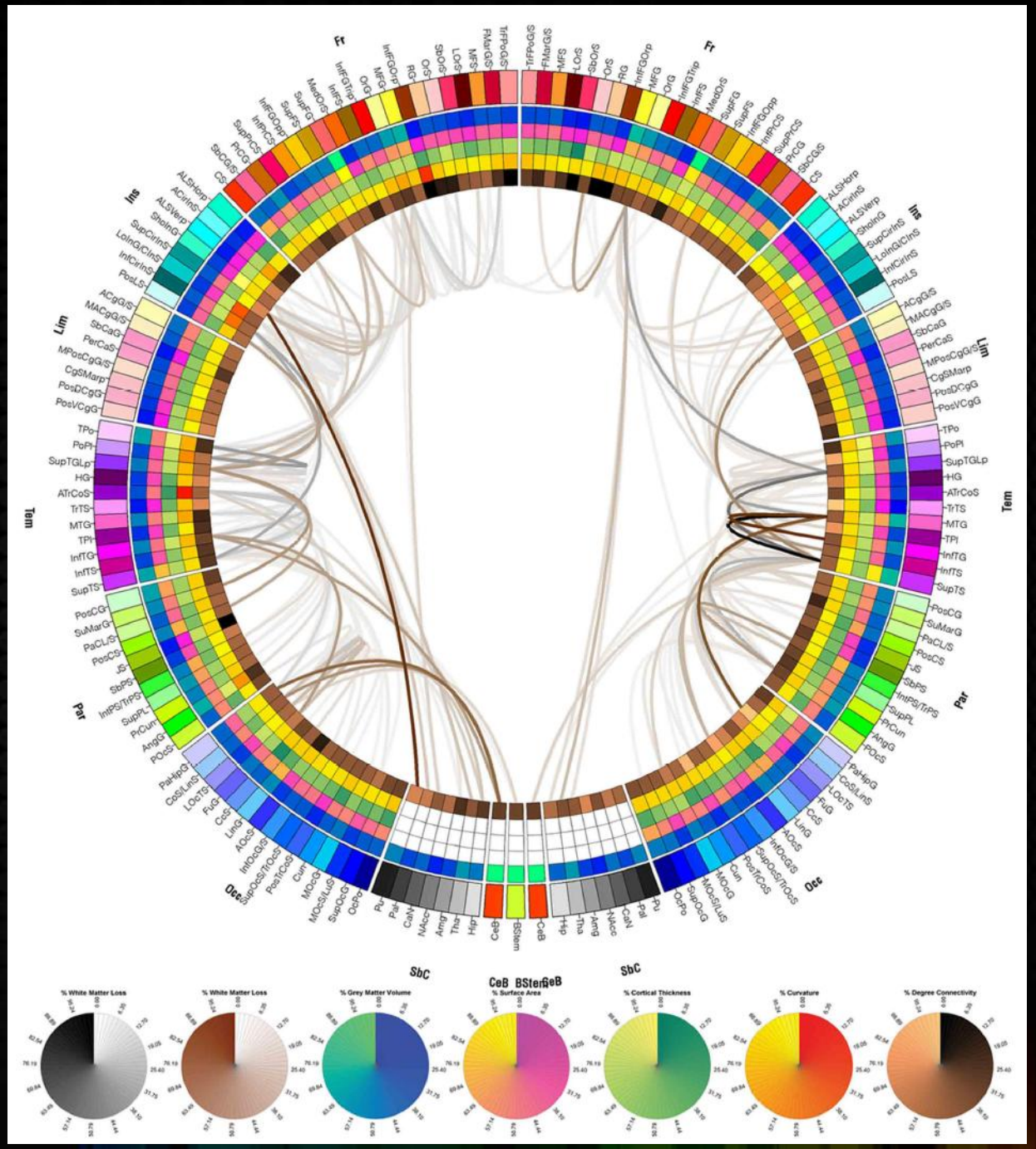



Fr
Ins
Lim
Tem
Par
Occ
SbC
CeB
BStem
Percentage Max FA
Grey Matter Volume
Surface Area
Cortical Thickness
Curvature
Degree of Connectivity
connectivity
low
med
high





Patient-tailored CONNECTOGRAM



Irimia et al., 2011 *Frontiers in Neuro Trauma*

Sets Stage for Patient Profiling

- Multimodal quantification of lesion type, location and extent visualizable using Slicer and effects on connectivity via our *connectogram* representation
- Promotes case-specific informatics and search of current literature (e.g. PubMed/Google Scholar)
- Profiles for use in clinical monitoring or for use as a research tool (e.g. correlation with blood serum assay, treatment type, outcome "forecasting", etc)
- Interoperability with the TBI Common Data Elements Project, the Federal Interagency TBI Research (FITBIR) Informatics System, and other international TBI informatics frameworks

An Interesting Example of TBI

A Notable Case

John Martyn Harlow
(November 25, 1819 - May 13, 1907)

Phineas P. Gage
(????, 1823 – May 21, 1860)

Henry Jacob Bigelow
(March 11, 1818 – October 30, 1890)

The Story…

- In 1848, 25 year old foreman preparing the roadbed for the Rutland & Burlington Railroad outside the town of Cavendish, Vermont.
- Filled a bore-hole with black powder to blast/remove rock
- Turned his attention to his men by looking slightly back over his right shoulder
- Dropped his tamping iron into the hole causing a spark and the powder to explode
- Rod was sent upward through his cheek, up through his cranial vault and out of the top of his head

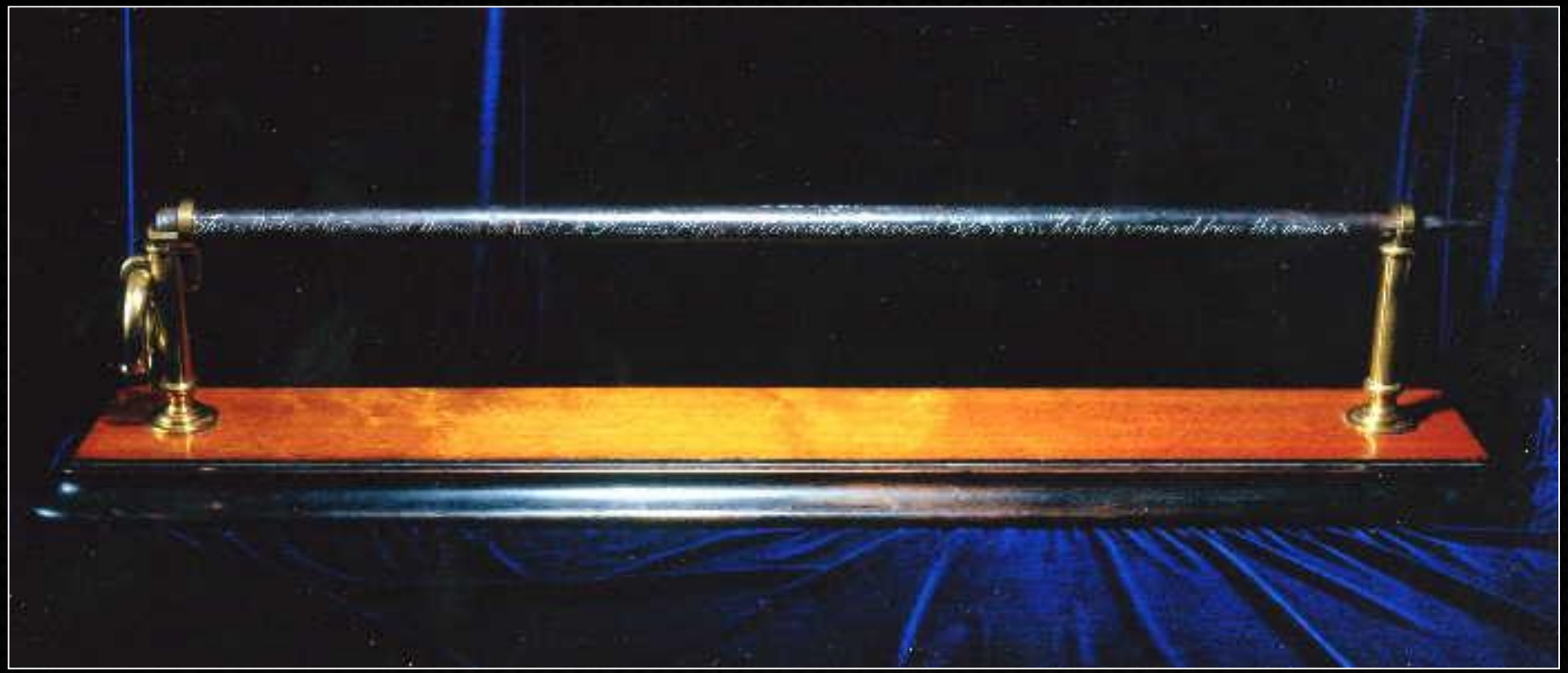
The Story…

- Taken by oxcart to Joseph Adam's tavern in Cavendish
- Is met first by Edward H. Williams of Proctorsville, VT then by Dr. John Martyn Harlow who commences treatment of Gage's wound
- Harlow can touch finger tips when inserting them in each end of the wound
- Gage struggles for days, in and out of fever/consciousness/infection
- Suffers confusion, difficulty reasoning, etc
- Eventually recovers sufficiently to return to his home
- Suffers profound personality changes

Effect of the Injury

"The equilibrium or balance, so to speak, between his intellectual faculties and animal propensities, seems to have been destroyed. He is **fitful**, **irreverent**, indulging at times in the grossest **profanity** (which was not previously his custom), manifesting but **little deference** for his fellows, **impatient of restraint** or advice when it conflicts with his desires, at times pertinaciously **obstinate**, yet **capricious** and **vacillating**, *devising many plans of future operation, which are no sooner arranged than they are abandoned in turn for others appearing more feasible*. A child in his intellectual capacity and manifestations, he has the animal passions of a strong man. Previous to his injury, though untrained in the schools, he possessed a well-balanced mind, and was looked upon by those who knew him as a shrewd, smart business man, very energetic and persistent in executing all his plans of operation. *In this regard his mind was radically changed, so decidedly that his friends and acquaintances said he was 'no longer Gage'*." *- J.M. Harlow*

Tamping Iron

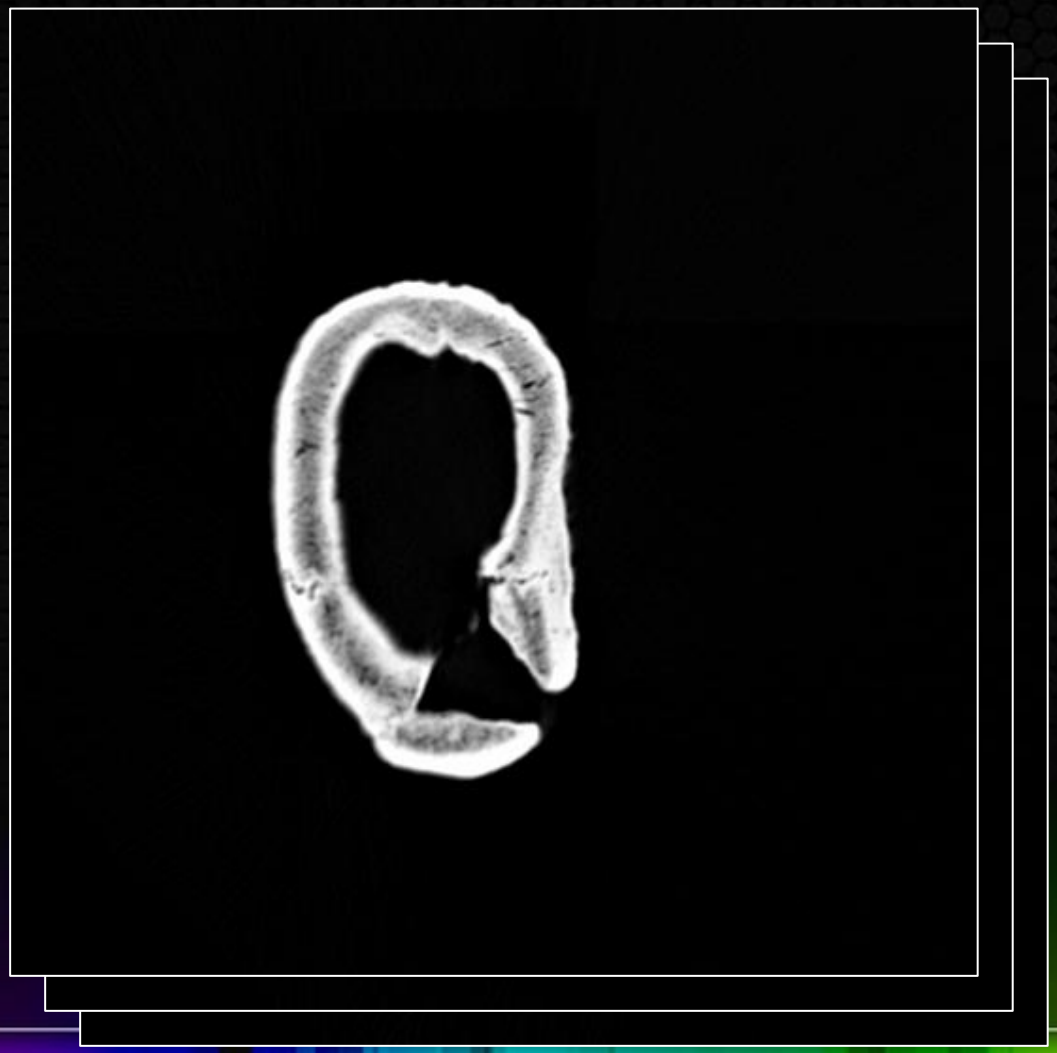


Measurements and Weight:
Length: 110cm
Circumference: 9.5cm at widest, 2.55cm diameter at tail
Rod Tip Diameter: 0.72cm
Weight: 13 lbs.

Image Courtesy of Dominic W. Hall, Warren Anatomical Museum, Harvard Medical School

Last Known CT Scan

- Ratiu and Talos, June 12, 2001, Brigham and Women's Hospital, Harvard Medical School, Boston, MA



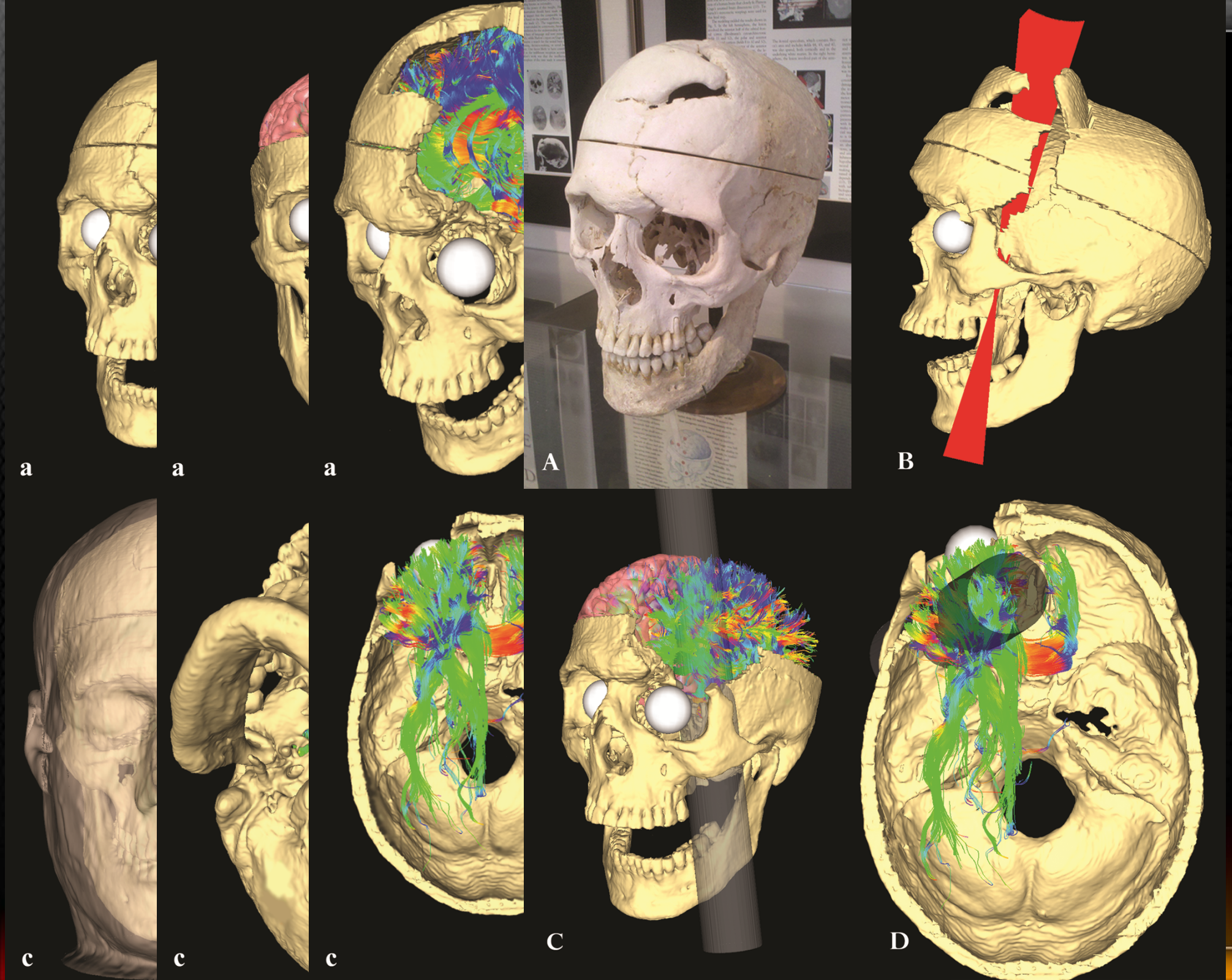
Modern MR Subjects

- Drawn from the LONI Image Data Archive (IDA)

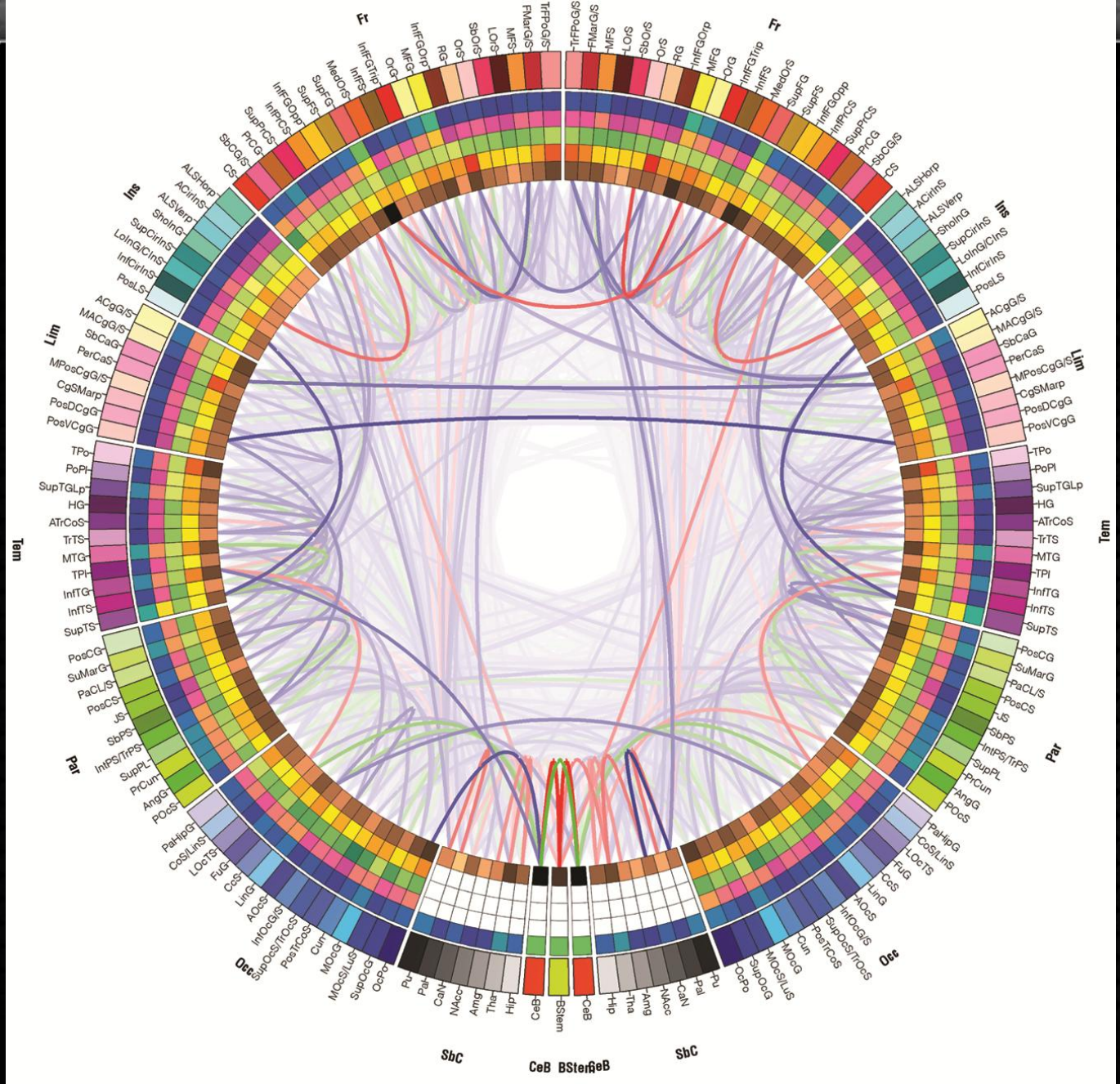
- N=110 psychiatrically/neurologically healthy males
- Age 25-36 years old
- Right handed
- Caucasian

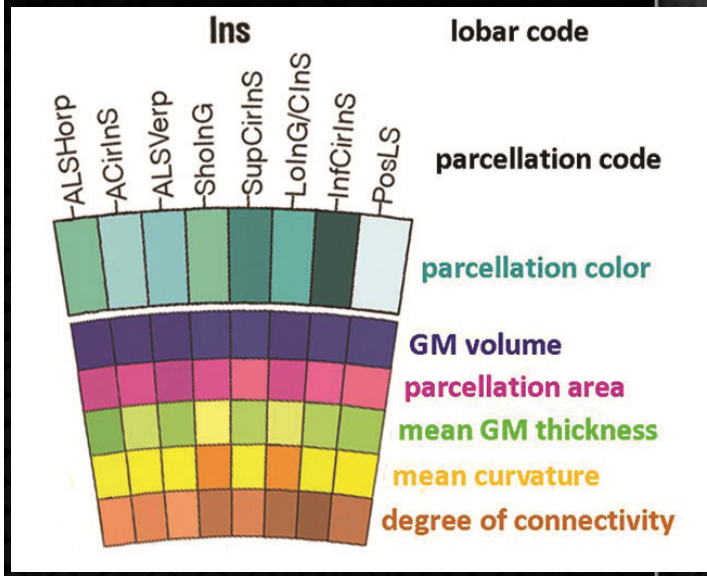
- MPRAGE T1 anatomical volumes
- 30 direction diffusion weighted imaging

- Data processed using
  - LONI Pipeline (Dinov et al., UCLA)
  - FreeSurfer (Fischl et al., MGH)
  - TrackVis (Wedeen et al., MGH)
  - Custom software
  - **Visualized using 3D Slicer (Pieper et al, NA-MIC, slicer.org)**
  - Connectogram representations (Irimia et al, 2012, NeuroImage)
  - Network analysis using Brain Connectivity Toolkit (Sporns et al.)


a
a
a
A
B
c
c
c
C
D

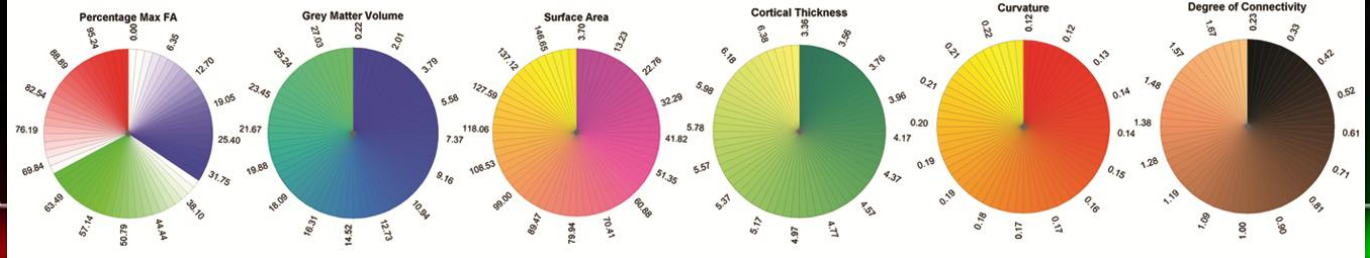
Van Horn et al., PLoS ONE

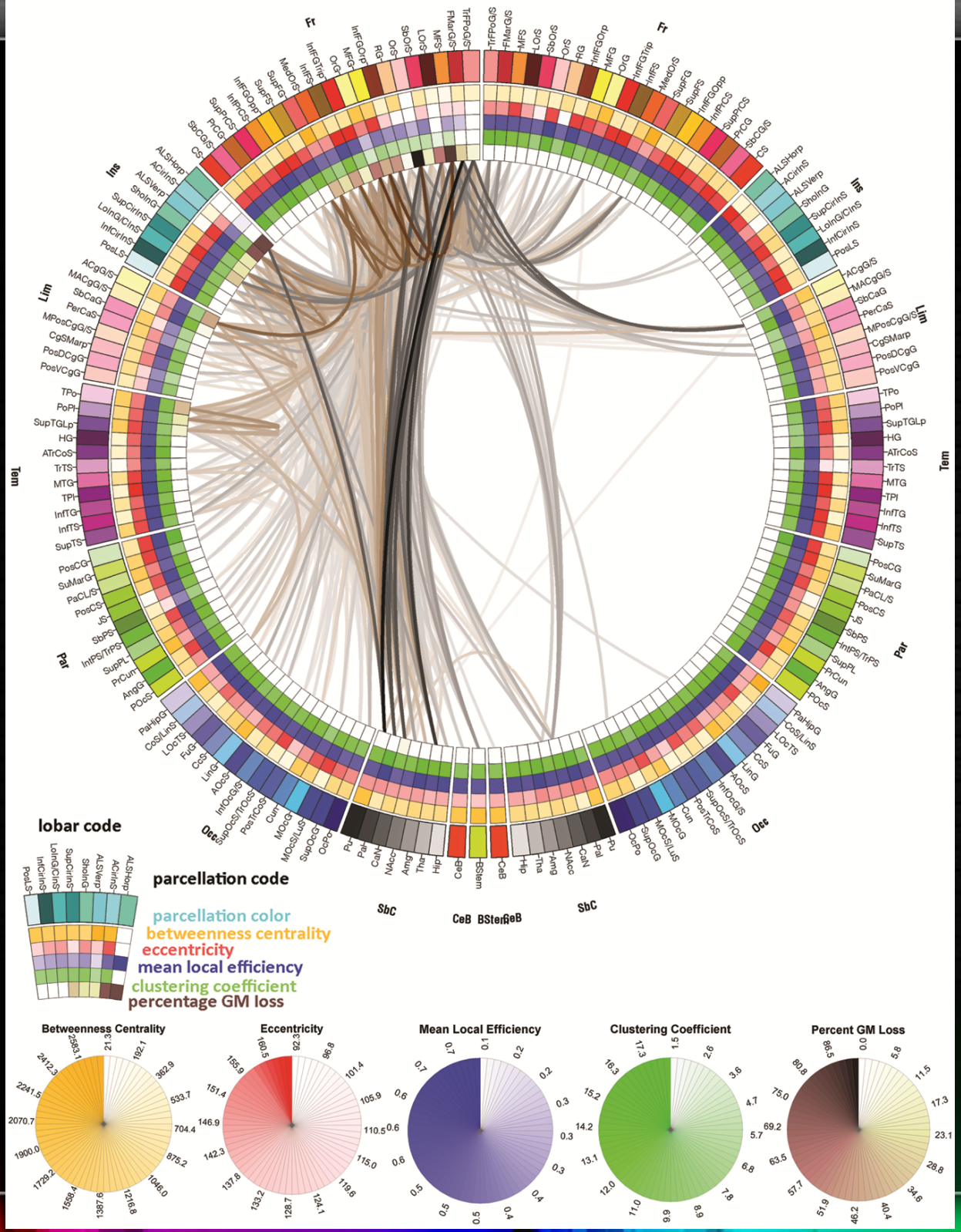




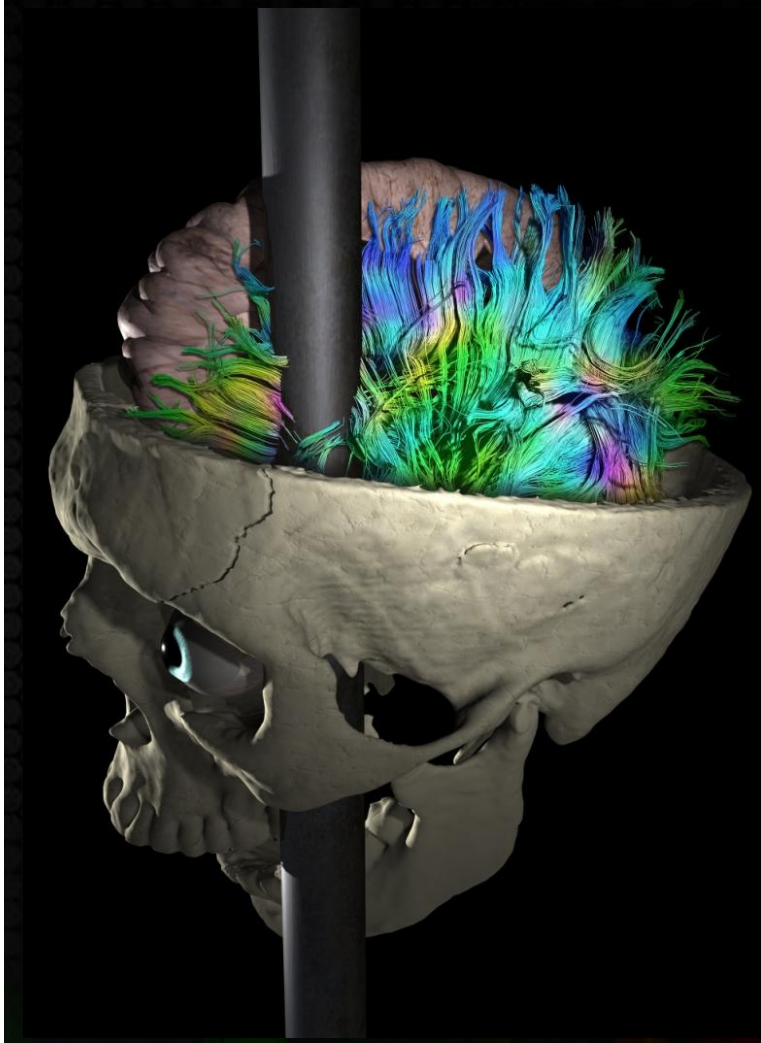
N=110 Healthy,
Right handed males
25-36 years old

Van Horn et al.,
PLoS ONE





White matter fiber connections affected by the passage of the tamping iron



Van Horn et al.,
PLoS ONE

Effects on Global Network Integration and Segregation

Table 5: Comparison of Intact, Tamping Iron, and Simulated Network Attributes

Network Type	Integration (Characteristic Path Length, λ)	Segregation (Mean Local Efficiency, e)	Small Worldness (S)
Intact (I)	$\lambda_{Obs}(I)/\lambda_{Rand}(I)$ = **1.3697±0.0534**	$e_{Obs}(I)/e_{Rand}(I)$ = **6.8953±2.1672**	S = **3.7226±1.0778**
Tamping Iron (T)[1]	$\lambda_{Obs}(T)/\lambda_{Rand}(I)$ = **1.3987±0.0532**[b]	$e_{Obs}(T)/e_{Rand}(I)$ = **5.7229±2.0538**[c]	S = **3.7289±0.9853**[a]
Simulated Lesions (L)[2]	$\lambda_{Obs}(L)/\lambda_{Rand}(I)$ = **1.4869±0.0469**[d]	$e_{Obs}(L)/e_{Rand}(I)$ = **5.4062±1.5321**[d]	S = **3.6061±0.7094**[c]
	[a] T vs. I: $p(t)$ = ns [b] T vs. L: $p(t) \leq 0.0001$	[c] T vs. I: $p(t) \leq 0.001$ [d] L vs. I: $p(t) \leq 0.0001$	

[1]Means and standard deviations are reported as computed over N=110 subjects included in the study (see text for details). Paired-sample Student's t-tests were used to compare the damaged and intact networks; subscripts refer to "observed" (Obs) and "random" (Rand); df=109.
[2]Means and standard deviations are reported as computed over N=110 subjects included in the study, after first averaging metric values over 500 simulated lesions of the cortex (see text for details).

Diseases Linked to Frontal Lobe White Matter Degeneration

- As noted by Damasio and others, Gage's personality changes similar to modern patients with damage to frontal cortex
- However, changes also not unlike neurological and psychiatric diseases involving frontal white matter degeneration

Fronto-temporal dementia
- personality changes
- irritability
- inappropriateness

Mild Cognitive Impairment
- forgetfulness
- impulsivity/poor judgment
- poor planning skills
- irritability and aggression

Alzheimer's Disease
- executive function issues
- difficulty reasoning
- changes in personality and behavior

Schizophrenia
- unusual ideations/beliefs
- working memory deficits
- executive function problems

- While Harlow comments that Gage's mental state was "nothing like dementia", the extensive white matter network damage may have contributed to many of Gage's reported behavioral and personality changes.

TBI DBP Productivity

Recent Publications

OPEN ACCESS Freely available online

PLoS one

Mapping Connectivity Damage in the Case of Phineas Gage

John Darrell Van Horn[1]*, Andrei Irimia[1], Carinna M. Torgerson[1], Micah C. Chambers[1], Ron Kikinis[2], Arthur W. Toga[1]

1 Laboratory of Neuro Imaging (LONI), Department of Neurology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, United States of America, 2 Surgical Planning Laboratory, Department of Radiology, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States of America

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

ELSEVIER

Full Length Articles

Circular representation of human cortical networks for subject and population-level connectomic visualization

Andrei Irimia *, Micah C. Chambers, Carinna M. Torgerson, John D. Van Horn

Laboratory of Neuro Imaging, Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles, 635 Charles E Young Drive South, Suite 225, Los Angeles, CA 90095, USA

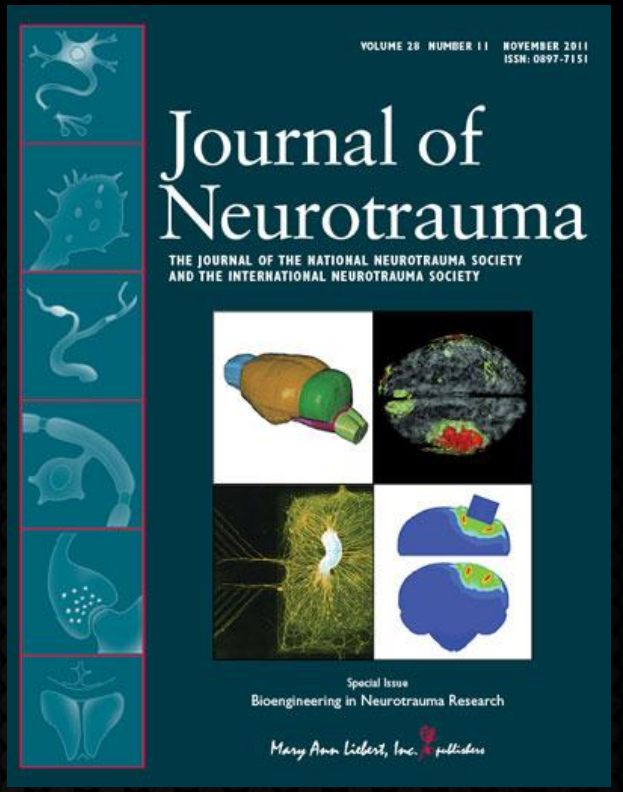
frontiers in NEUROLOGY

METHODS ARTICLE
published: 06 February 2012
doi: 10.3389/fneur.2012.00010

Patient-tailored connectomics visualization for the assessment of white matter atrophy in traumatic brain injury

*Andrei Irimia[1], Micah C. Chambers[1], Carinna M. Torgerson[1], Maria Filippou[2], David A. Hovda[2], Jeffry R. Alger[3], Guido Gerig[4], Arthur W. Toga[1], Paul M. Vespa[2], Ron Kikinis[5] and John D. Van Horn[1]**

[1] *Laboratory of Neuro Imaging, Department of Neurology, University of California Los Angeles, Los Angeles, CA, USA*
[2] *Brain Injury Research Center, Departments of Neurology and Neurosurgery, University of California Los Angeles, Los Angeles, CA, USA*
[3] *Department of Radiology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA*
[4] *Scientific Computing and Imaging Institute, University of Utah, Salt Lake City, UT, USA*
[5] *Surgery Planning Laboratory, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*



8 journal articles
4 conference proceedings
14 conference abstracts
28 posters

In addition, we have (as of 1/10/2013):
2 journal manuscripts under review
3 conference manuscripts under review
6 conference abstracts under review
6 journal manuscripts in preparation

Plans for 2013-2014

Outreach: Relevant TBI Conferences and Symposia

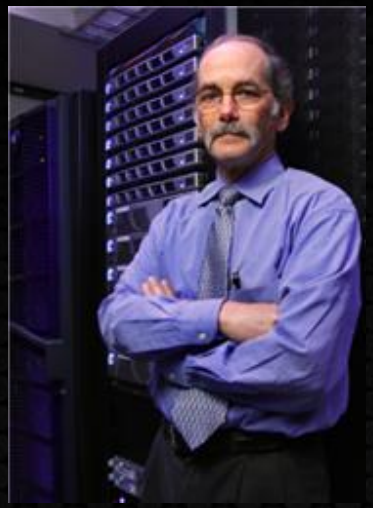
- UCLA 3D Slicer 4.x Demo Day
- 14th Annual UC Neurotrauma Meeting, Sonoma, CA
- The 4th Annual TBI Conference, Wash DC
- American Society of Neuroradiology, San Diego, CA
- 8th Annual Brain Injury Rehabilitation Conference, Carlsbad, CA
- An educational session on TBI featuring Slicer at the 2014 Organization for Human Brain Mapping (OHBM), Berlin, Germany
- Other targets of opportunity

Grants Building on DBP Activities

- Phase I STTR TBI project with Kitware, UCLA, and UNC – funded!
- NA-MIC Collaborative RO1 with UCLA and Utah – under review
- Participation in NA-MIC 2.0 - we hope!

Collaborators

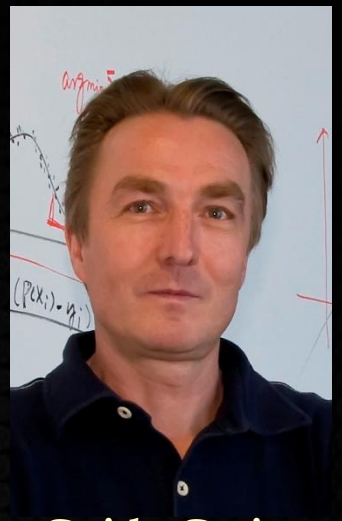
Ron Kikinis
Harvard Medical School



Arthur Toga
UCLA

David Hovda
UCLA

Paul Vespa
UCLA



Guido Gerig
Utah

Andrei Irimia

Carinna Torgerson

Micah Chambers

Special thanks to Dominic W. Hall, Chief Curator, Warren Anatomical Museum, Harvard Medical School

UCLA: Maria Filippou, Jeffrey Alger, Matthew Goh

University of Utah: Marcel Prastawa, Bo Wang , Sylvain Gouttard

Harvard Medical School: Sonja Pujol

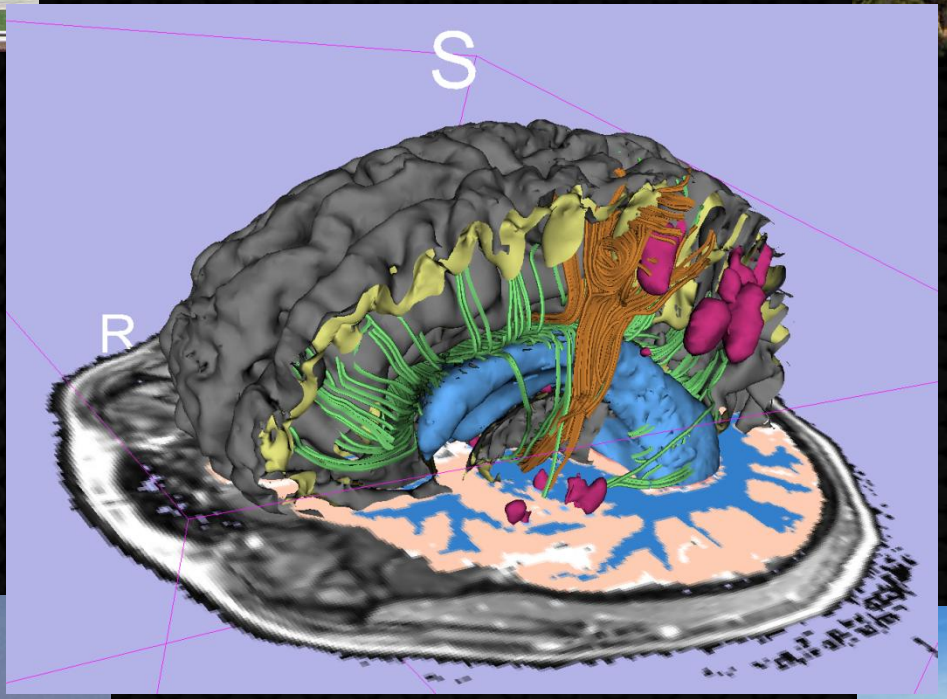
UNC Chapel Hill & Kitware, Inc.: Stephen Aylward, Danielle Pace

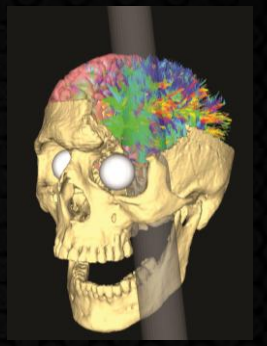
UCSD: Yifei Lou

Georgia Tech: Patricio Vela

Boston University: Allen Tannenbaum

Supported by NIBIB/NINDS (grant 2U54EB005149), the NINDS (grant P01NS058489)





Thank you