Traumatic Brain Injury Driving Biological Project

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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)

BD: \[ \mathcal{B}(I_1, I_2; \bar{u}) = \iiint \sqrt{p(i_1, i_2; \bar{u})p(i_1; \bar{u})p(i_2)} \, di_1 \, di_2 \]

MI: \[ \mathcal{M}(I_1, I_2; \bar{u}) = \iiint p(i_1, i_2; \bar{u}) \log \frac{p(i_1, i_2; \bar{u})}{p(i_1; \bar{u})p(i_2)} \, di_1 \, di_2 \]

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
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

Irimia et al., J. Neurotrauma, 2011

- edema
- hemorrhage
Acute

Chronic

ventricular system
edema
hemorrhage
longitudinal change: acute vs. chronic

- red: acute
- green: 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

Subject 1

Subject 2

Subject 3

= Skin (transparent)
= Bone
= Grey Matter (GM)
= Edemic GM
= Hemorrhagic GM
= Eyes
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
- DTI tractography
- Connectivity matrix calculation
- Connectogram
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.)
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

<table>
<thead>
<tr>
<th>Network Type</th>
<th>Integration (Characteristic Path Length, $\lambda$)</th>
<th>Segregation (Mean Local Efficiency, $e$)</th>
<th>Small Worldness ($S$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact (I)</td>
<td>$\lambda_{\text{Obs}}(I)/\lambda_{\text{Rand}}(I) = 1.3697 \pm 0.0534$</td>
<td>$e_{\text{Obs}}(I)/e_{\text{Rand}}(I) = 6.8953 \pm 2.1672$</td>
<td>$S = 3.7226 \pm 1.0778$</td>
</tr>
<tr>
<td>Tamping Iron (T)$^1$</td>
<td>$\lambda_{\text{Obs}}(T)/\lambda_{\text{Rand}}(I) = 1.3987 \pm 0.0532^b$</td>
<td>$e_{\text{Obs}}(T)/e_{\text{Rand}}(I) = 5.7229 \pm 2.0538^c$</td>
<td>$S = 3.7289 \pm 0.9853^a$</td>
</tr>
<tr>
<td>Simulated Lesions (L)$^2$</td>
<td>$\lambda_{\text{Obs}}(L)/\lambda_{\text{Rand}}(I) = 1.4869 \pm 0.0469^d$</td>
<td>$e_{\text{Obs}}(L)/e_{\text{Rand}}(I) = 5.4062 \pm 1.5321^d$</td>
<td>$S = 3.6061 \pm 0.7094^c$</td>
</tr>
</tbody>
</table>

$^1$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).

$^a$ 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: $p(t) \leq 0.0001$
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

<table>
<thead>
<tr>
<th>Fronto-temporal dementia</th>
<th>Alzheimer’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>personality changes</td>
<td>executive function issues</td>
</tr>
<tr>
<td>irritability</td>
<td>difficulty reasoning</td>
</tr>
<tr>
<td>inappropriateness</td>
<td>changes in personality and behavior</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Mild Cognitive Impairment</th>
<th>Schizophrenia</th>
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</thead>
<tbody>
<tr>
<td>forgetfulness</td>
<td>unusual ideations/beliefs</td>
</tr>
<tr>
<td>impulsivity/poor judgment</td>
<td>working memory deficits</td>
</tr>
<tr>
<td>poor planning skills</td>
<td>executive function problems</td>
</tr>
<tr>
<td>irritability and aggression</td>
<td></td>
</tr>
</tbody>
</table>

- 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

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
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UCLA

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Utah

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