Workshop – Ultrahigh Field NMR and MRI: Science at a Crossroads

Opportunities for MRI/MRS/Pathology Correlations in the Human Brain

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Required Disclaimer

The opinions expressed herein are those of the presenter and are not necessarily representative of those of the government of the United States, the Uniformed Services University of the Health Sciences (USUHS), the Department of Defense (DoD); or, the United States Army, Navy or Air Force.

No conflicts to report.
What are important disease states of the brain that will need to be addressed in coming decades?

- Dementia (Alzheimer Disease, a disease of the elderly)
- Traumatic Brain Injury (TBI, both its acute and long-term effects)

Current understanding of the underlying pathophysiology of these two conditions is limited

- Accurate diagnosis problematic (especially early)
- Lack of effective therapies

Future directions and opportunities for use of a partnership of MRI, MRS and pathology.
Age-Related Prevalence of Severe, Moderate and Mild Alzheimer Disease

The Graying of America

- In 1930, 1 in 3 Americans were 50+; 6% of the population was 65+ (6.6 million)
- Currently, 13.1% of Americans are 65+ (42.4 million)
- In 2030, 19% of Americans will be 65+ (72.1 million)
- The fastest growing segment of the population is the oldest-old (85+)
  - now 10% of the older population (5.7 million)
  - By 2050 the number of Americans 85+ will more than triple to over 19 million!!!

Source: US Census Bureau
The Graying of the World

- From 1950 to 2050, world population will increase by 3.6x; for those 60+ it will increase by 10x; those 80+ it will increase by 27x
- In 2040, the global population aged 65+ will be 1.2 billion (14% of the total population)
- By 2050, China the 65+ population will rise from the current 109 million to 350 million; India from 62 million to 240 million
- By 2050, 2/3 of people aged 80+ will be living in the developing countries (267 million)!

Source: UN Population Council
Total Health Care Costs/Patient For Last 5 Years of Life

The Bielschowskii (silver stain) method showed very characteristic changes in the neurofibrils. The fibers became more prominent through their striking thickness...forming dense bundles.”

A. Alzheimer, 1907

This was the first time that a disease of the mind was shown to be related to a morphologic change in the brain!
Tau

β-amyloid

Tau lesions and senile plaques in Alzheimer’s disease

Tau PET ([11C]PBB3)

Plaque PET ([11C]PIB)

Hippocampal formation (arrowheads)
The Cholinergic Approach to the Treatment of Alzheimer Disease

- Nucleus basalis of Meynert (NBM): the major source of cholinergic innervation of the neocortex
- Cells in NBM degenerate in Alzheimer’s disease.
- Decreased levels of acetylcholine and choline acetyl-transferase in the neocortex of AD patients.
- Most currently used treatments for AD function by enhancing CNS cholinergic activity.
- The effects of these drugs are modest, at best.
Traumatic Brain Injury (TBI)
Traumatic Brain Injury (TBI) Major Public Health Problem

- Leading cause of death and disability worldwide
- Primary cause of death among persons between ages 1-44 years
- Unknown million TBIs in U.S. annually
  - In 2010, TBI led to 2.2 million Emergency Room visits
  - 280,000 hospitalizations
  - 52,000 deaths

- 5.3 million Americans with long-term disabilities due to prior TBI
  - Equal to the number of Americans with Alzheimer’s Disease!

http://www.cdc.gov/traumaticbraininjury/
Dementia Pugilistica (Chronic Traumatic Encephalopathy, CTE)

JAMA 91: 1103-1107, 1928

PUNCH DRUNK *

HARRISON S. MARTLAND, M.D.
NEWARK, N. J.

For some time fight fans and promoters have recognized a peculiar condition occurring among prize fighters which, in ring parlance, they speak of as “punch drunk.” Fighters in whom the early symptoms are well recognized are said by the fans to be “cuckoo,” “goofy,” “cutting paper dolls,” or “slug nutty.”

Punch drunk most often affects fighters of the slugging type, who are usually poor boxers and who take considerable head punishment, seeking only to land a knockout blow. It is also common in second rate fighters used for training purposes, who may be knocked down several times a day. Frequently it takes a fighter from one to two hours to recover from a severe blow to the head or jaw. In some cases consciousness may be lost for a considerable period of time.

Psychological Medicine, 1973, 3, 270-303

The aftermath of boxing

J. A. N. CORSELLIS, C. J. BRUTON, AND DOROTHY FREEMAN-BROWNE

From the Department of Neuropathology, Runwell Hospital, Wickford, Essex
Chronic Traumatic Encephalopathy (CTE)

- Distinct neurodegenerative disease
- Associated with repeated mild TBIs in contact sports, first in boxers, then NFL, NHL amateurs
- Symptoms progress
  - Chronic headache
  - Prominent behavioral changes (impulsivity, explosive rage, depression)
  - Poor concentration, short-term memory impairment
  - Substance abuse, suicide, accidents
  - Eventual dementia
- Tauopathy
  - *Tau* protein in normal brain
  - Abnormal *tau* phosphorylation and accumulation, especially in neurons
  - Form neurofibrillary tangles (NFTs) leading to neurodegeneration

Shively, et al. *Arch Neurol* 2012
TBI in the Military
DoD Numbers for Traumatic Brain Injury
Worldwide – Totals

2000-2015 Q1-Q2

- Penetrating: 4,904
- Severe: 3,463
- Moderate: 28,192
- Mild: 274,568
- Not Classifiable: 22,042

Total - All Severities: 333,169

Source: Defense Medical Surveillance System (DMSS), Theater Medical Data Store (TMDS) provided by the Armed Forces Health Surveillance Center (AFHSC)

Prepared by the Defense and Veterans Brain Injury Center (DVBIC)

2000-2015 Q1-Q2, as of Aug 18, 2015

<table>
<thead>
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<th>TBI Level</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Penetrating</th>
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<tr>
<td>PTA</td>
<td>&lt;=24 hrs</td>
<td>24H - 7 days</td>
<td>&gt;=7 days</td>
<td>(any)</td>
</tr>
</tbody>
</table>

GCS, Glasgow Coma Scale; AoC, period of altered consciousness; LOC, period of loss of consciousness; PTA, duration of post-traumatic amnesia.
Blast Exposure

- 2.4 million service members deployed since 2001
- Multiple extended tours of duty
- High explosives
  - Improvised Explosive Device (IEDs)
  - Leading cause of casualties
- With modern vehicles, body armor and helmets, survival rates increased substantially
- Increased incidence of TBIs (“signature wound”)
Mild TBI/Post-Concussion Symptoms (Potentially Persistent)

**Physical:** headache, nausea, vomiting, dizziness, fatigue, blurred vision, sleep disturbance, sensitivity to light/noise, balance problems, transient neurologic abnormalities

**Cognitive:** impaired attention, concentration, memory, speed of processing, judgment, executive function

**Behavioral/emotional:** depression, anxiety, agitation, irritability, impulsivity, aggression

*VA/DoD Clinical Guidelines For Management of Concussion/mTBI, 2009*
Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide

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RESEARCH ARTICLE

TRAUMATIC BRAIN INJURY

Chronic Traumatic Encephalopathy in Blast-Exposed Military Veterans and a Blast Neurotrauma Mouse Model

Lee E. Goldstein,1,2,3,4* Andrew M. Fisher,1,4 Chad A. Tagge,1,4 Xiao-Lei Zhang,5 Libor Velisek,5 John A. Sullivan,5 Chirag Upreti,5 Jonathan M. Kracht,4 Maria Ericsson,6 Mark W. Wojnarowicz,1 Cezar J. Goletian,5 Giorgi M. Maglakelidze,5 Noel Casey,1,3 Juliet A. Moncaster,1,3 Olga Minaeva,1,3,4 Robert D. Moir,7 Christopher J. Nowinski,8 Robert A. Stern,2,8 Robert C. Cantu,8,9 James Geiling,10 Jan K. Blusztajn,2 Benjamin L. Wolozin,2 Tsuneya Ikezu,2 Thor D. Stein,2,11 Andrew E. Budson,2,11 Neil W. Kowall,2,11 David Chargin,12 Andre Sharon,4,12 Sudad Saman,13 Garth F. Hall,13 William C. Moss,14 Robin O. Cleveland,15 Rudolph E. Tanzi,7 Patric K. Stanton,5 Ann C. McKeel2,8,11*
Exploring the Convergence of Posttraumatic Stress Disorder and Mild Traumatic Brain Injury

Murray B. Stein, M.D., M.P.H.
Thomas W. McAllister, M.D.

The authors examine the relationship of the two signature injuries experienced by military personnel serving in Afghanistan and Iraq: posttraumatic stress disorder (PTSD) and chronic postconcussive symptoms (PCS) with mild traumatic brain injury (mTBI).

### PTSD
- Re-experiencing symptoms
- Shame
- Guilt
- Depression/anxiety
- Insomnia
- Irritability/anger
- Trouble concentrating
- Fatigue
- Hyperarousal
- Avoidance

### PCS with mTBI
- Headache
- Sensitivity to light and sound
- Memory deficit
- Dizziness

Stein MB, McCallister TW. *Am J Psychiatry* 2009 166: 766-76.
Patient

Pathology
At death
Definitive Diagnosis

Imaging
In life
Funct./physiol.

Future Approaches

Limitation: 1/10,000 of brain actually examined

Limitation: cannot visualize lesions at cellular level. New modalities must be validated microscopically
The clinical progression of signs and symptoms of neurodegenerative diseases involves progressive spread of the pathologic lesions in the brain over time.

Heiko Braak and Kelly Del Tredici

The Braak Stages of Alzheimer Disease
• To date, mostly used to construct three-dimensional renderings of normal anatomy (especially in small animals).
• The same approach can be used to construct three dimensional models of human pathology.
• These models can then be used to correlate with imaging results.
Tri-planer View of 7T MRI of moderate TBI patient’s brain (ex vivo)
Bicycle Accident, 9 month survival
Correlation of Lesions Noted on MRI to Whole Mount Neuropathology Results
Opportunities

- Exciting potential to be able to correlate imaging/spectroscopy results with digitized serial whole mount histopathologic preparations. This will help bridge the significant gaps between these technologies.
- Will lead to better diagnostic/analytic approaches
- Expand understanding of disease processes
- Permit better monitoring of the effectiveness of new therapeutics

Challenges

- Expense has limited the number of labs with these capabilities – needs a significant investment of resources
- Handling of huge digital pathology data files is a major challenge – these are much larger data sets than MRI imaging
- The approach is very labor-intensive – need to identify and train technicians, scientists in this approach. Develop more automated approaches.
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