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

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

Daniel P. Perl, MD
Professor of Pathology (Neuropathology)
Uniformed Services University of the Health Sciences

November 12-13, 2015
Bethesda, MD

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?

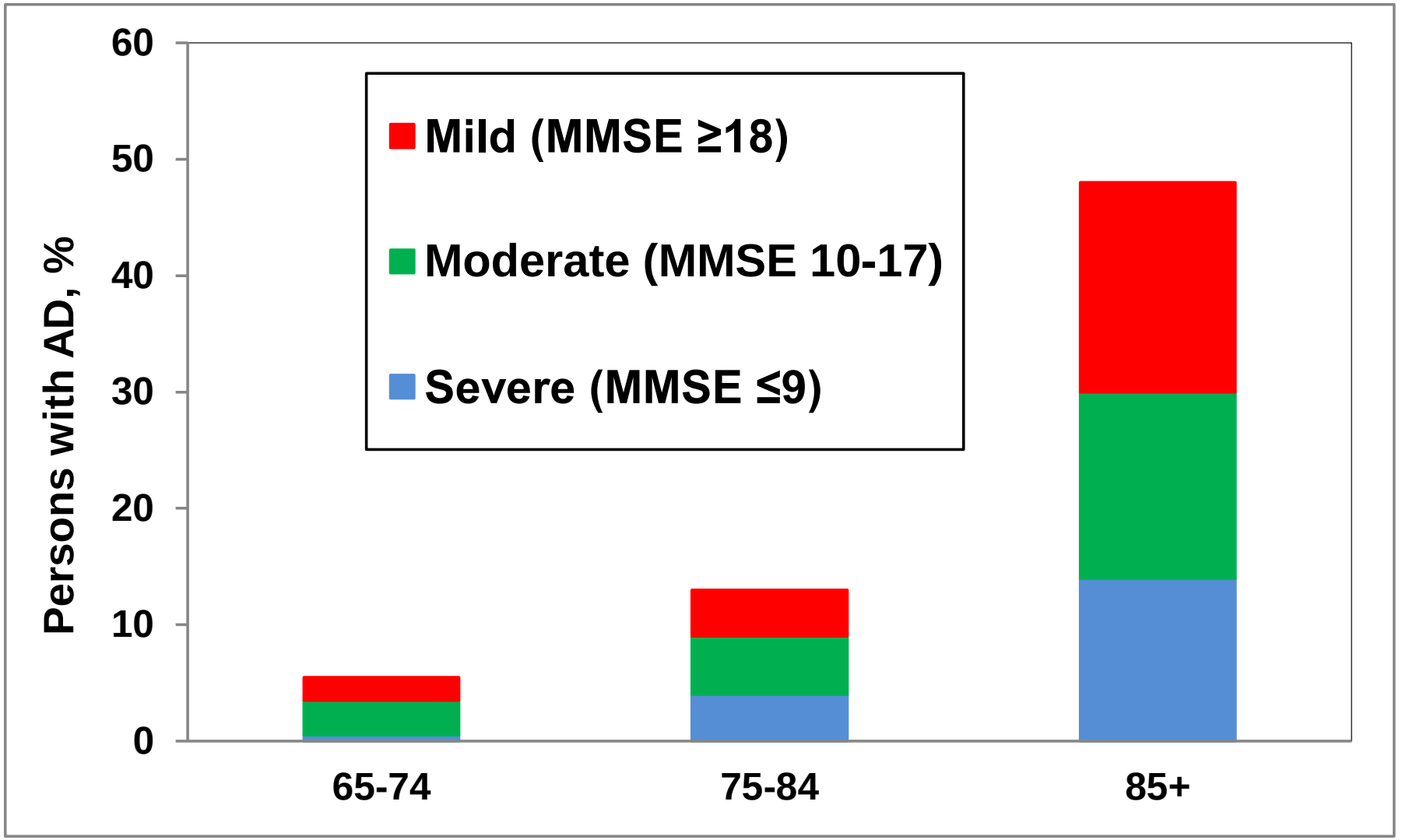
- Dementia (Alzheimer Disease, a disease of the elderly)
- Traumatic Brain Injury (TBI, both its acute and long-term effects)

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

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

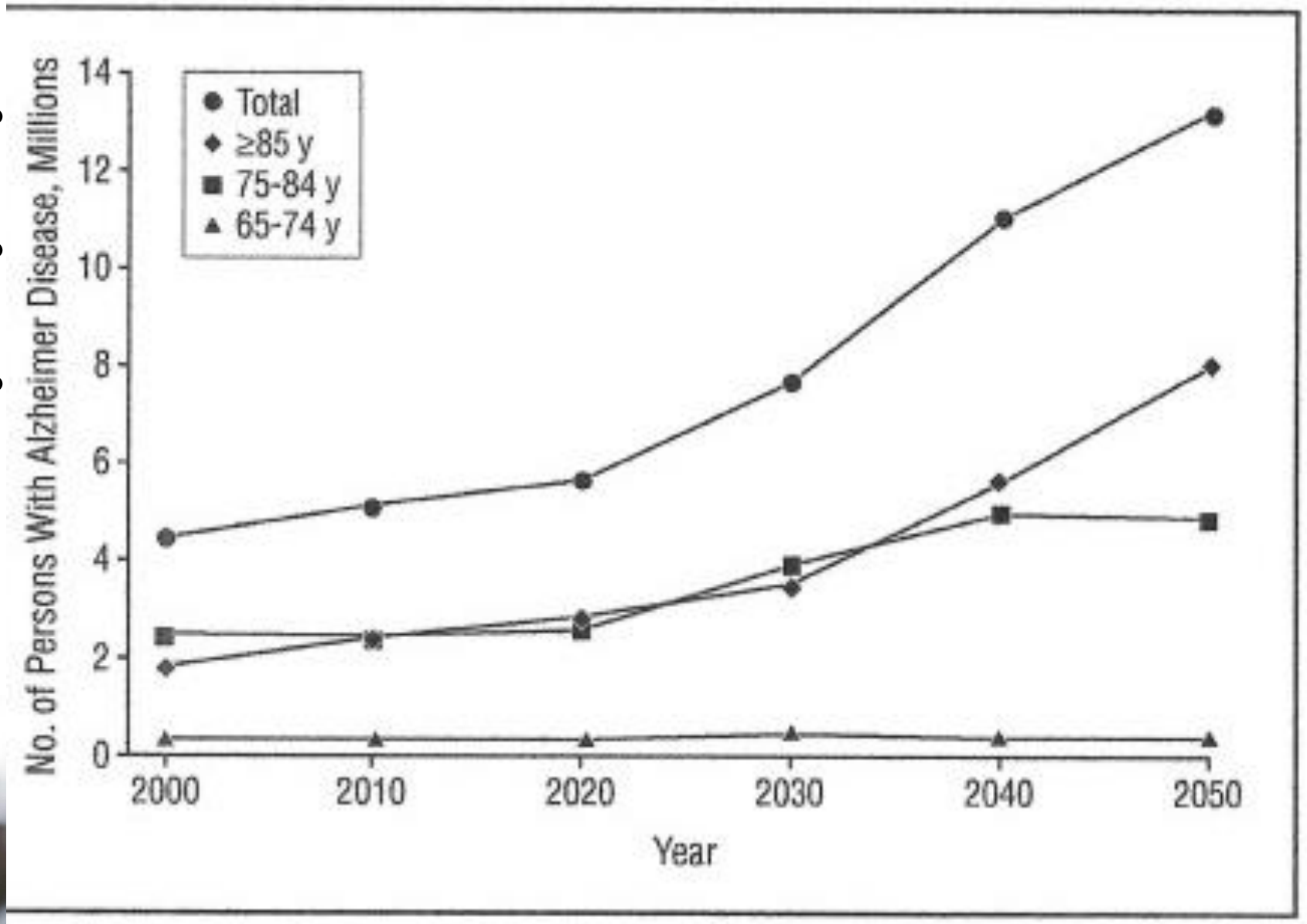
Future directions and opportunities for use of a partnership of MRI, MRS and pathology.

Age-Related Prevalence of Severe, Moderate and Mild Alzheimer Disease



Hebert, LE et al. Arch Neurol. 60: 1119, 2003

The Graying of America

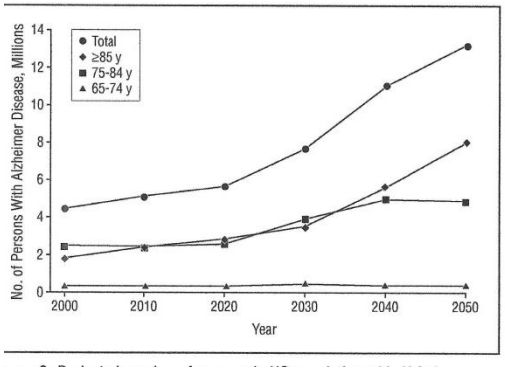


The Graying of the World

- 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

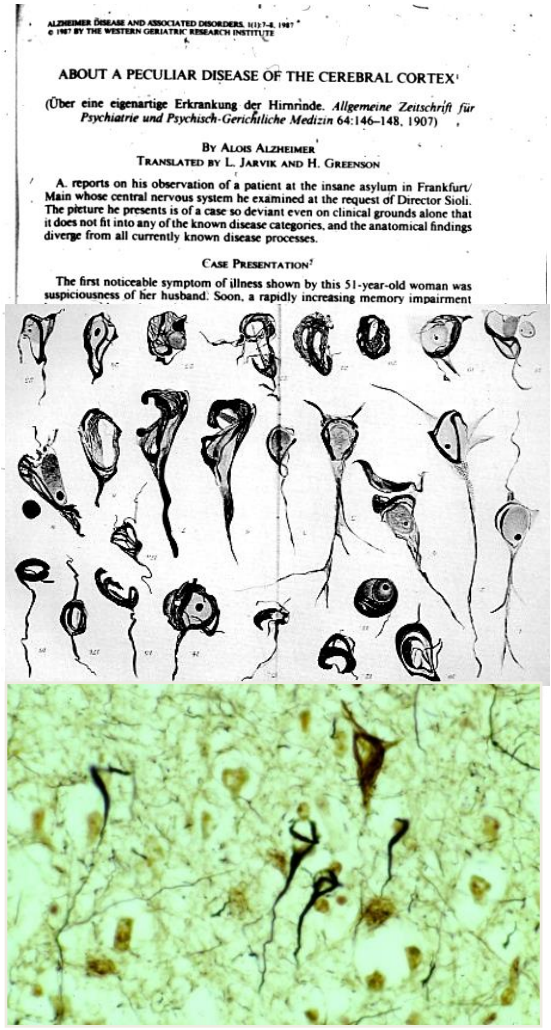
Total Health Care Costs/Patient For Last 5 Years of Life



Kelley, AS, et al. Ann. Int. Med. 2015

‘The Bielschowski (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



ALZHEIMER DISEASE AND ASSOCIATED DISORDERS, 1(1):7-8, 1987
© 1987 BY THE WESTERN GERIATRIC RESEARCH INSTITUTE

ABOUT A PECULIAR DISEASE OF THE CEREBRAL CORTEX[1]

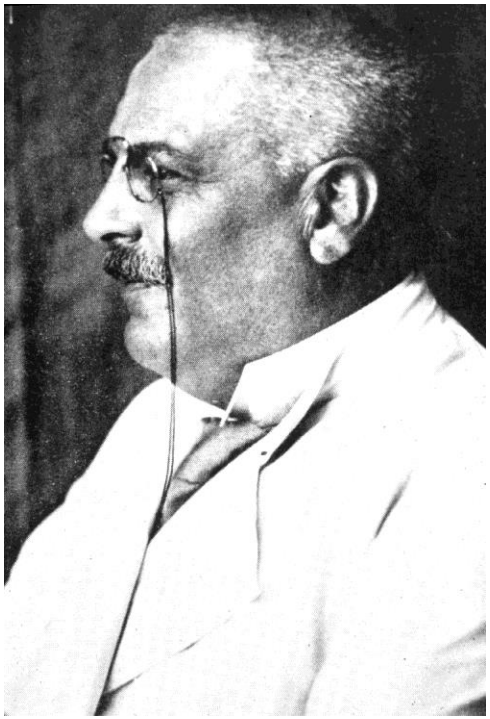
(Über eine eigenartige Erkrankung der Hirnrinde. *Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medizin* 64:146–148, 1907)

By Alois Alzheimer
Translated by L. Jarvik and H. Greenson

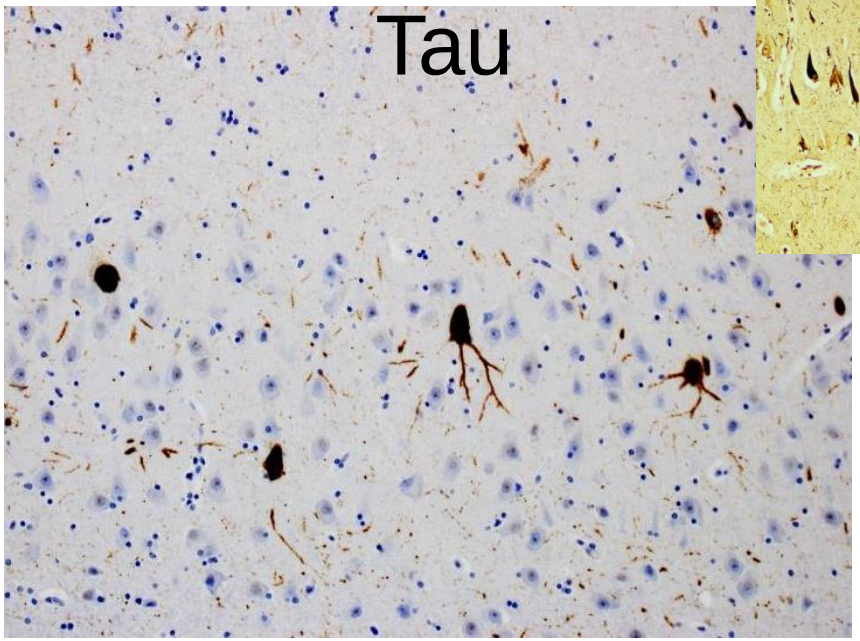
A. reports on his observation of a patient at the insane asylum in Frankfurt/Main whose central nervous system he examined at the request of Director Sioli. The picture he presents is of a case so deviant even on clinical grounds alone that it does not fit into any of the known disease categories, and the anatomical findings diverge from all currently known disease processes.

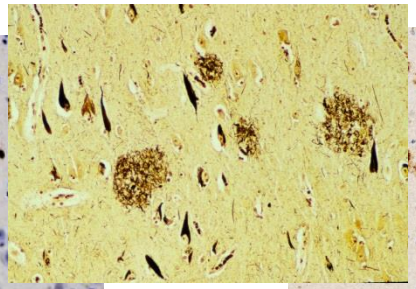
Case Presentation[2]

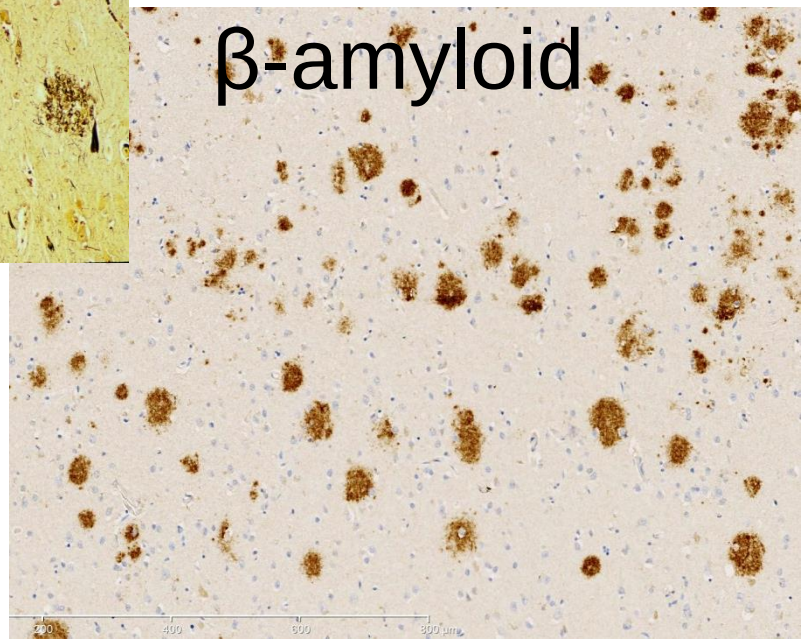
The first noticeable symptom of illness shown by this 51-year-old woman was suspiciousness of her husband. Soon, a rapidly increasing memory impairment

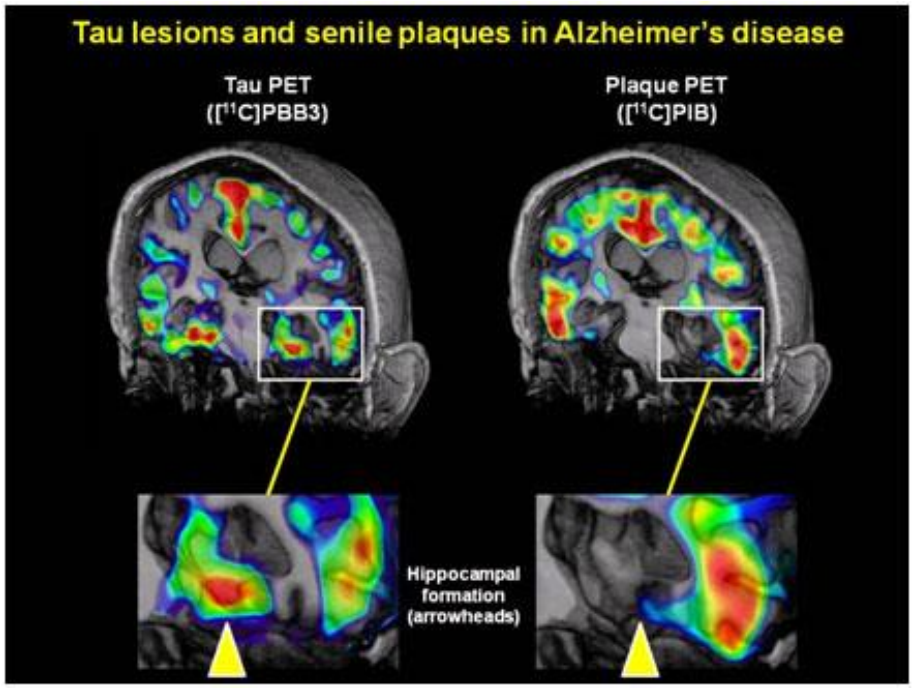


This was the first time that a disease of the mind was shown to be related to a morphologic change in the brain!

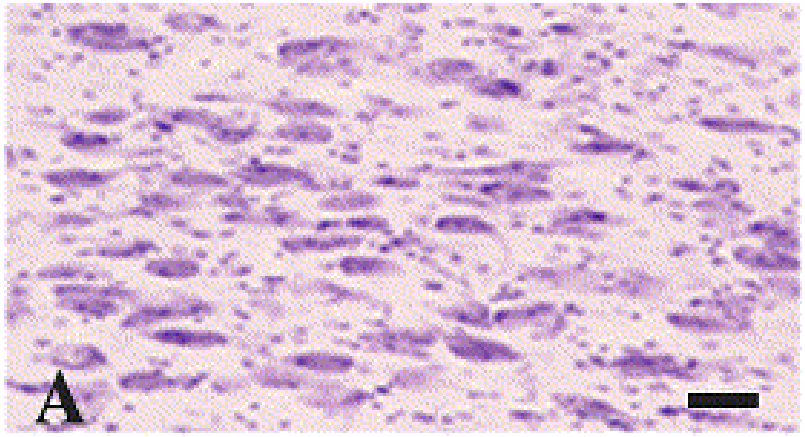

Tau

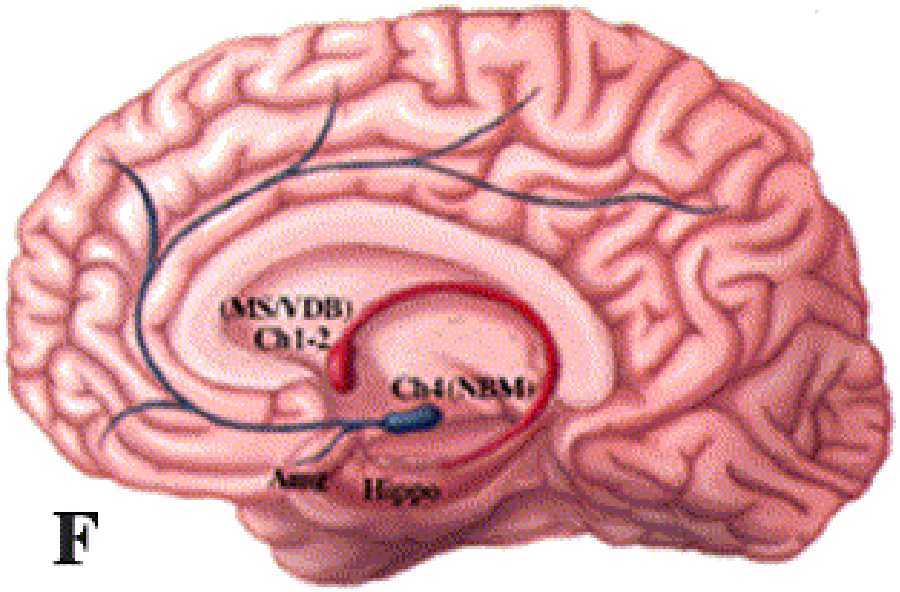



β-amyloid


Tau lesions and senile plaques in Alzheimer's disease
Tau PET
([11C]PBB3)
Plaque PET
([11C]PIB)
Hippocampal
formation
(arrowheads)

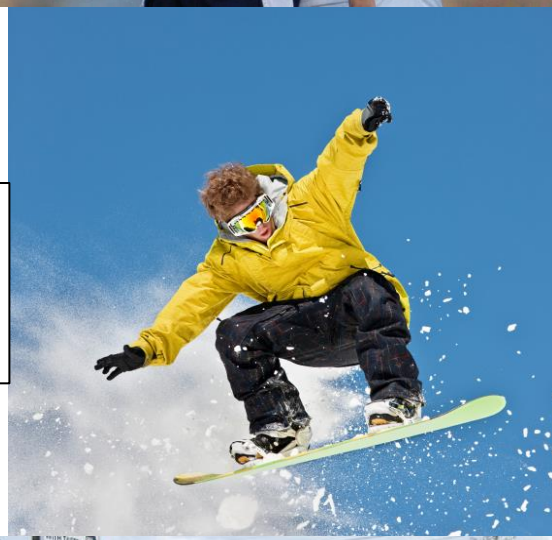
The Cholinergic Approach to the Treatment of Alzheimer Disease





- 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

Breast Cancer 40,000, Influenza 50,000

- 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

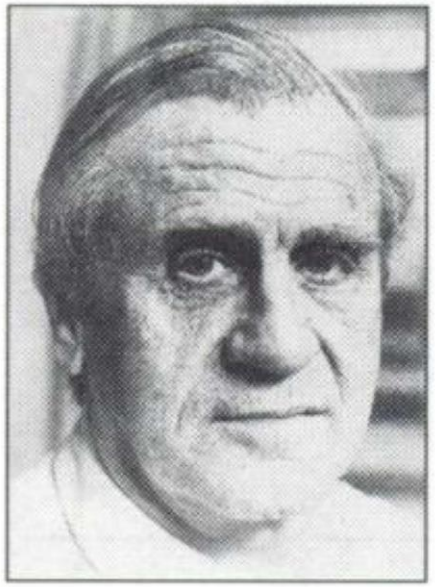
PUNCH DRUNK *

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.

Harrison S. Martland, MD, ca. 1940



Psychological Medicine, 1973, **3**, 270–303

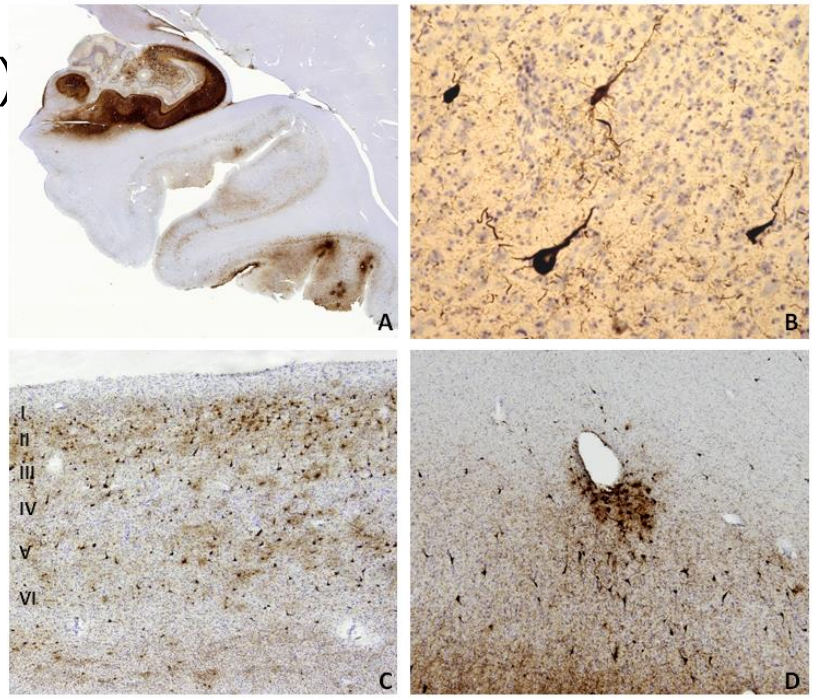
The aftermath of boxing[1]

J. A. N. CORSELLIS, C. J. BRUTON, AND DOROTHY FREEMAN-BROWNE[2]

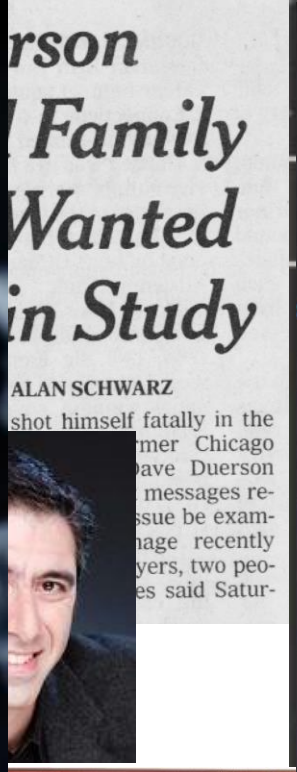
From the Department of Neuropathology, Runwell Hospital, Wickford, Essex

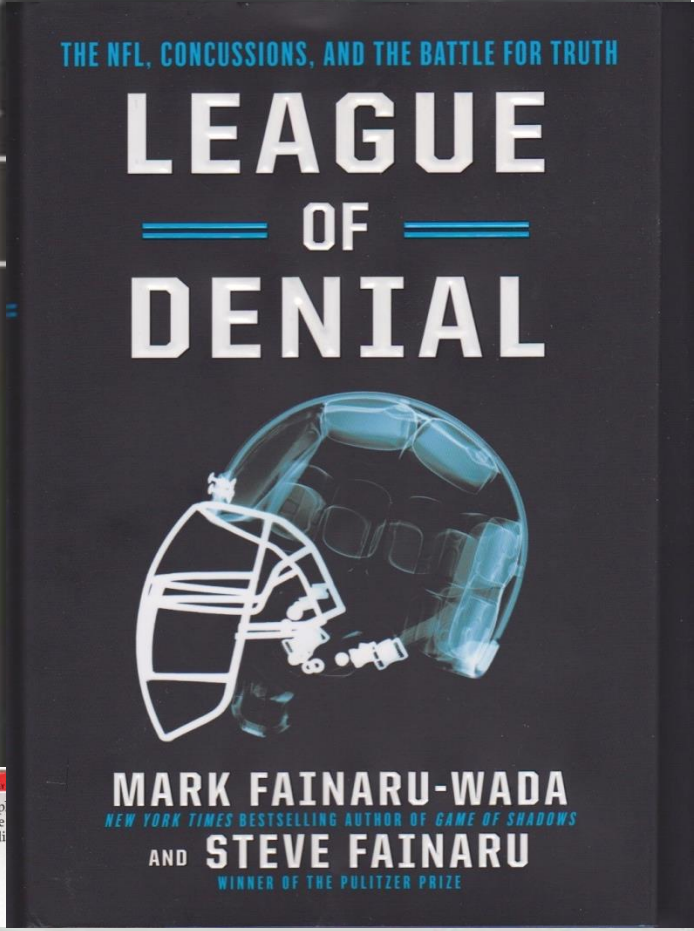
Chronic Traumatic Encephalopathy (CTE)

- 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


rson
Family
Wanted
in Study
ALAN SCHWARZ
shot himself fatally in the
mer Chicago
ave Duerson
messages re-
ssue be exam-
nage recently
yers, two peo-
es said Satur-



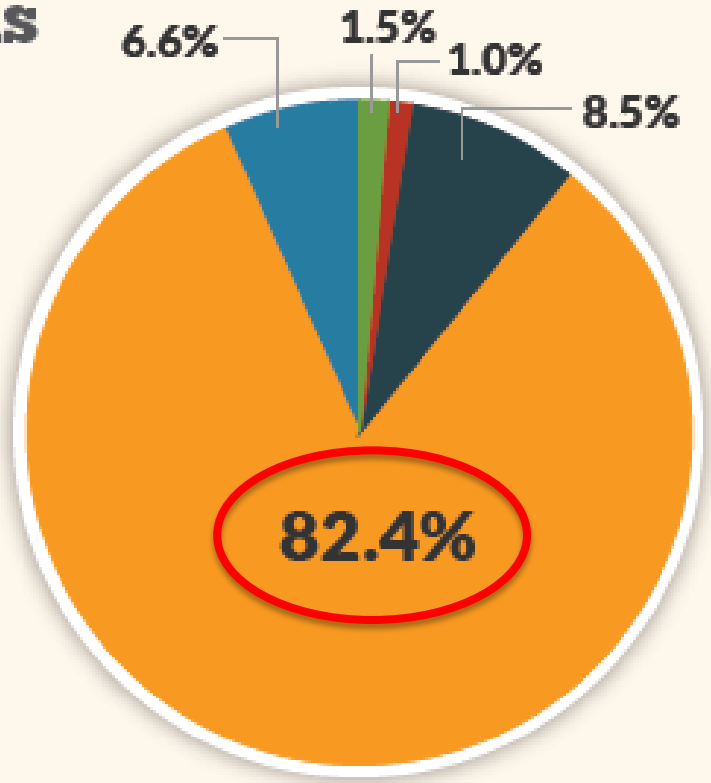
TBI in the Military

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

TBI Level→	Mild	Moderate	Severe	{Penetrating}
GCS	12-15	9-12	3-8	(any)
AoC	</= 24 hrs	>24 hrs	>24 hrs	(any)
LoC	0-30 min	31 min-24 hrs	>/=24 hrs	(any)
PTA	</=24 hrs	24H - 7 days	>/=7 days	(any)

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 Devices (IEDs)
  - Leading cause of casualties

- With modern vehicles, body armor and helmets, survival rates increased substantially
- Increased incidence of TBIs (“signature wound”)

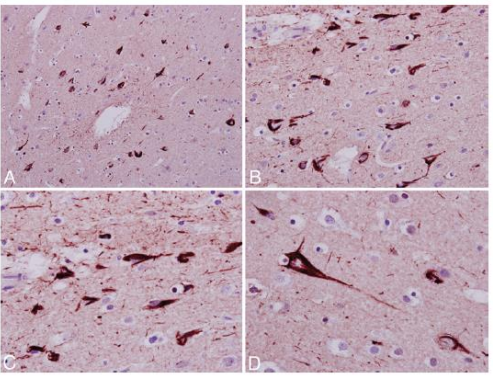
Mild TBI/Post-Concussion Symptoms (Potentially Persistent)

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

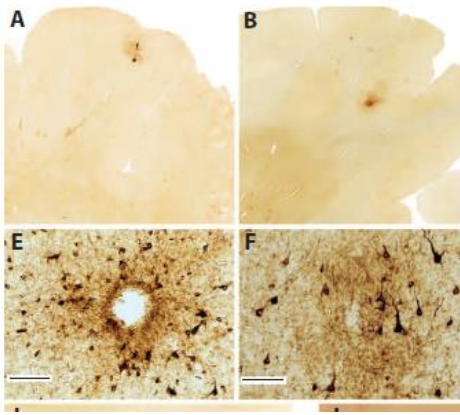
Bennet Omalu, M.D., M.B.A., M.P.H., C.P.E.,[1,2] Jennifer L. Hammers, D.O.,[1,3] Julian Bailes, M.D.,[1,4] Ronald L. Hamilton, M.D.,[5] M. Ilyas Kamboh, Ph.D.,[6] Garrett Webster,[1,2] and Robert P. Fitzsimmons, J.D.[1,7]

[1]Brain Injury Research Institute, Morgantown, West Virginia; [2]Department of Pathology, University of California, Davis, California; [3]Office of the Chief Medical Examiner, Boston, Massachusetts; [4]Department of Neurosurgery, West Virginia University, Morgantown, West Virginia; [5]Department of Pathology, University of Pittsburgh, Pennsylvania; [6]Department of Human Genetics, University of Pittsburgh, Pennsylvania; and [7]Fitzsimmons Law Offices, Wheeling, West Virginia

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. Goletiani,[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. McKee[2,8,11]*

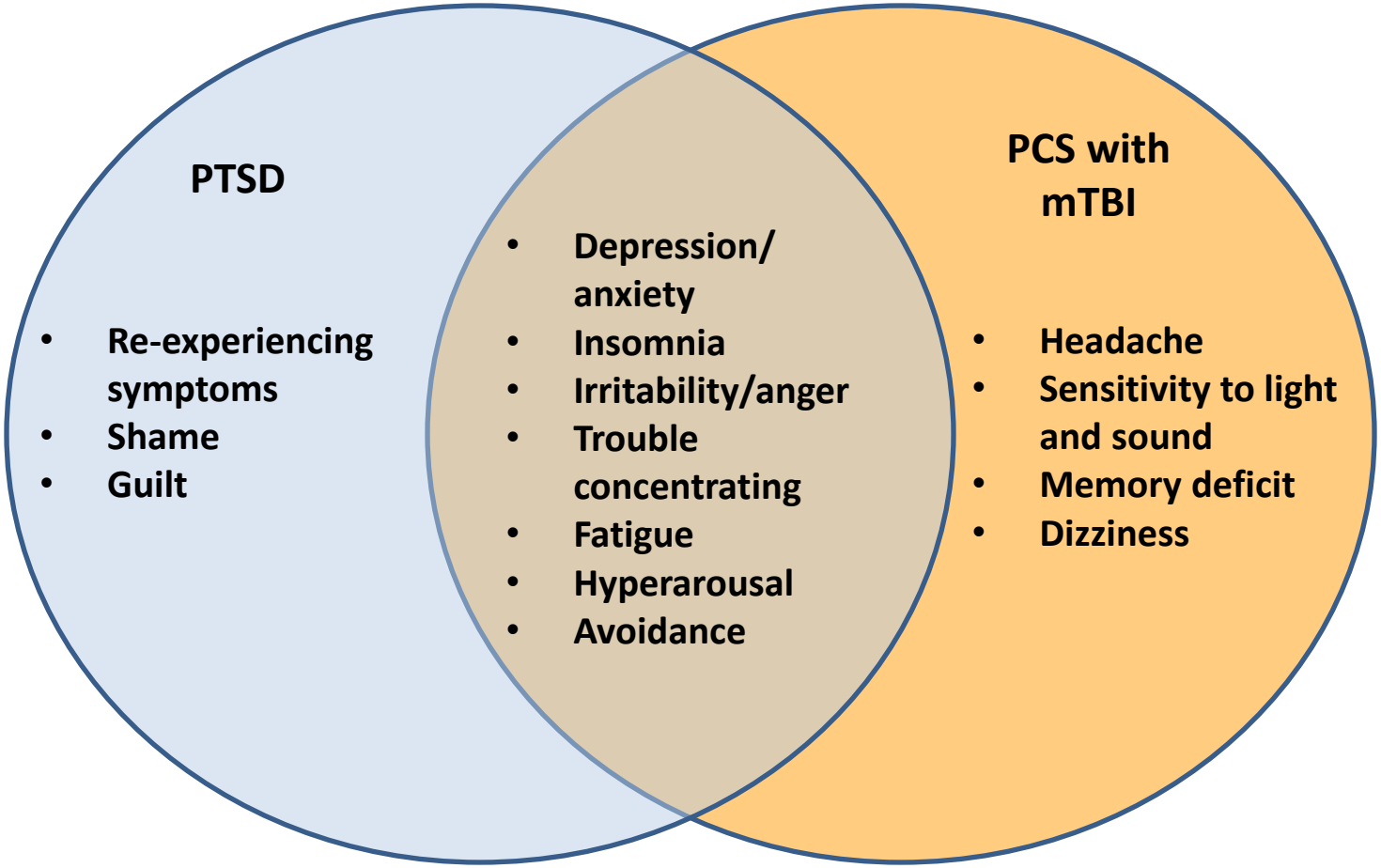
Exploring the Convergence of Posttraumatic Stress Disorder and Mild Traumatic Brain Injury

Murray B. Stein, M.D., M.P.H.

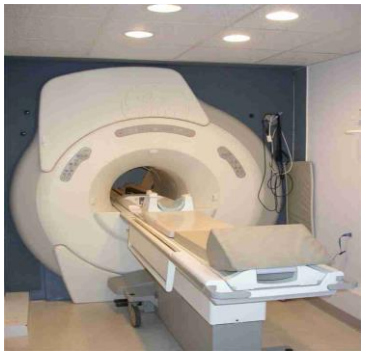
Thomas W. McAllister, M.D.

The authors examine the relationship of the two signature injuries experienced by military personnel serving in Afghanistan

dysfunction can increase the risk for these syndromes, probably by reducing cognitive reserve. Structural and functional



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



Patient

Clinical Features

Clinical Features

Pathology

At death

Imaging

In life

Funct./physiol.

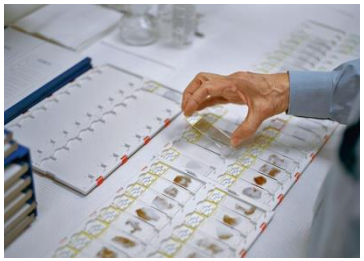
Future Approaches

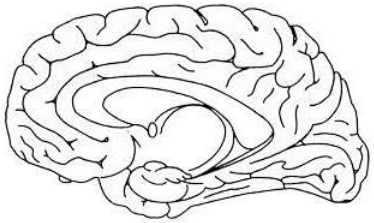
Definitive Diagnosis

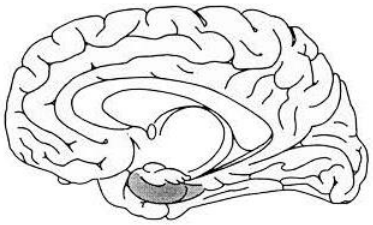
Presumptive Diagnosis

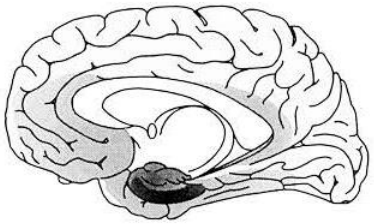
Limitation: 1/10,000 of brain actually examined

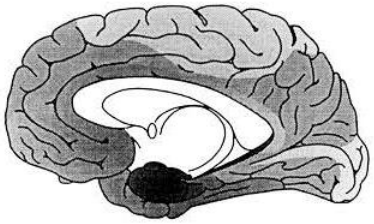
Limitation: cannot visualize lesions at cellular level. New modalities must be validated microscopically







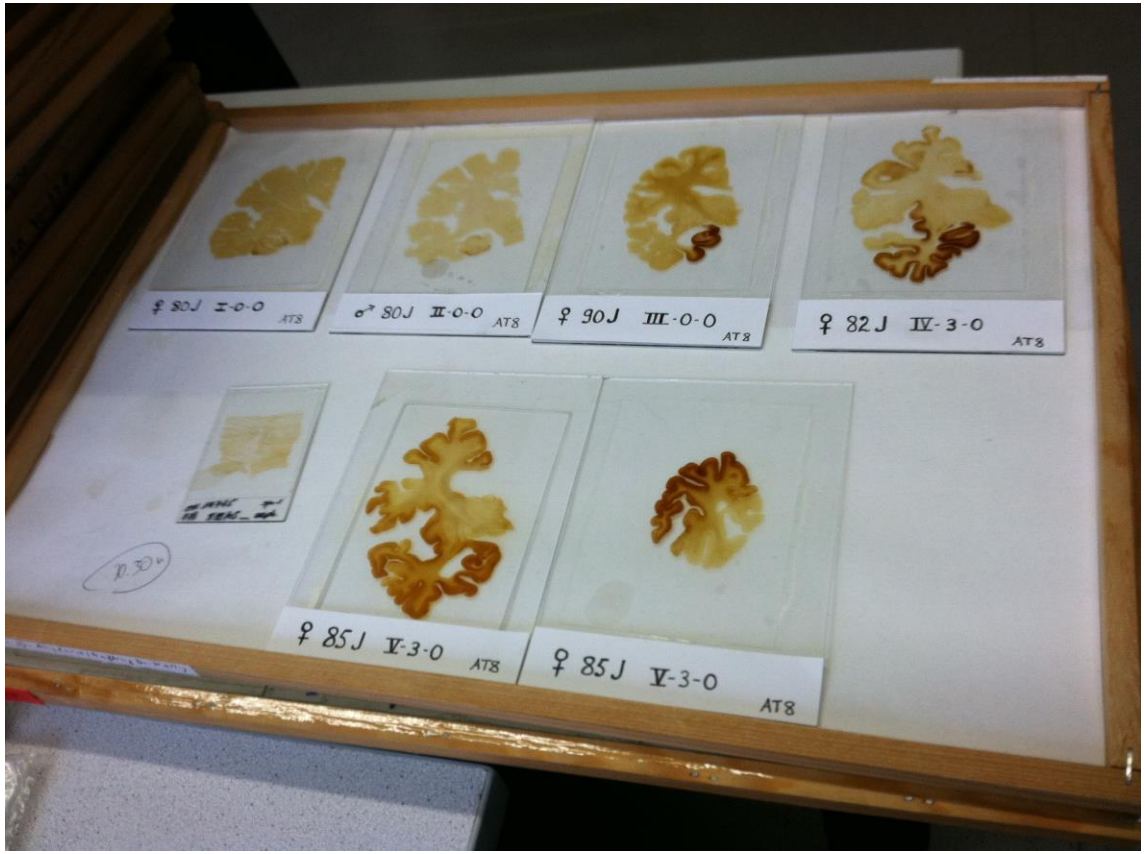


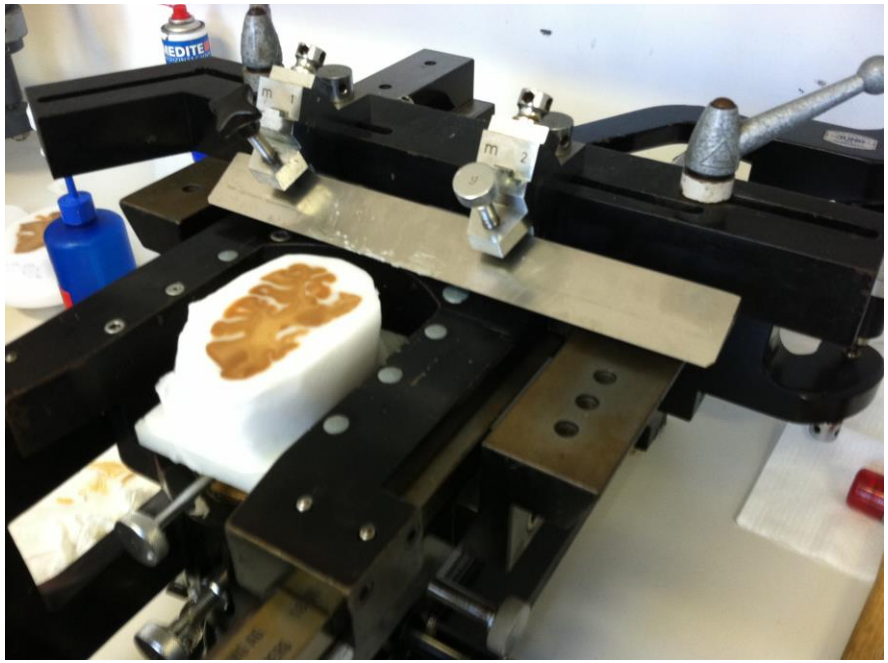


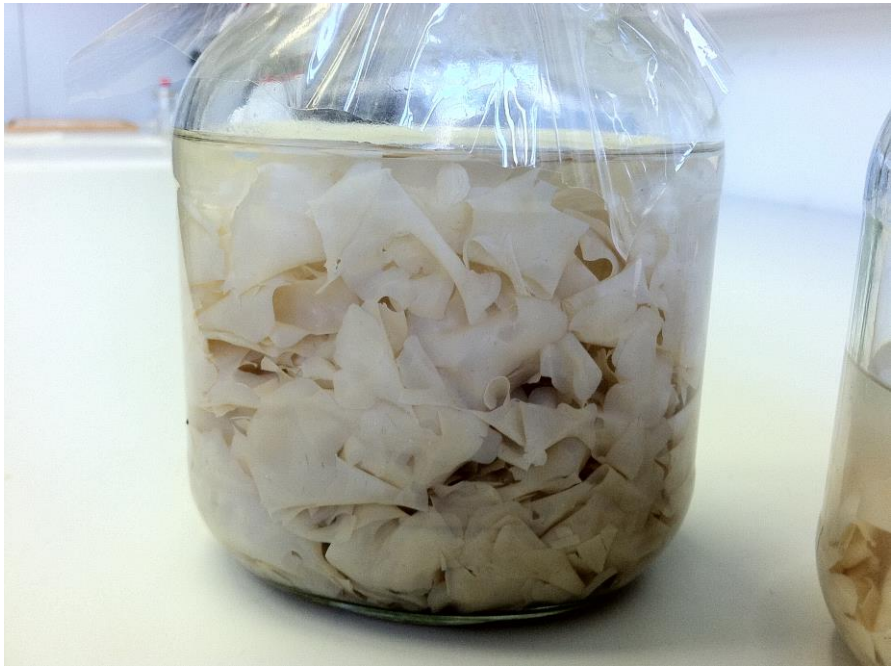
The Braak Stages of Alzheimer Disease

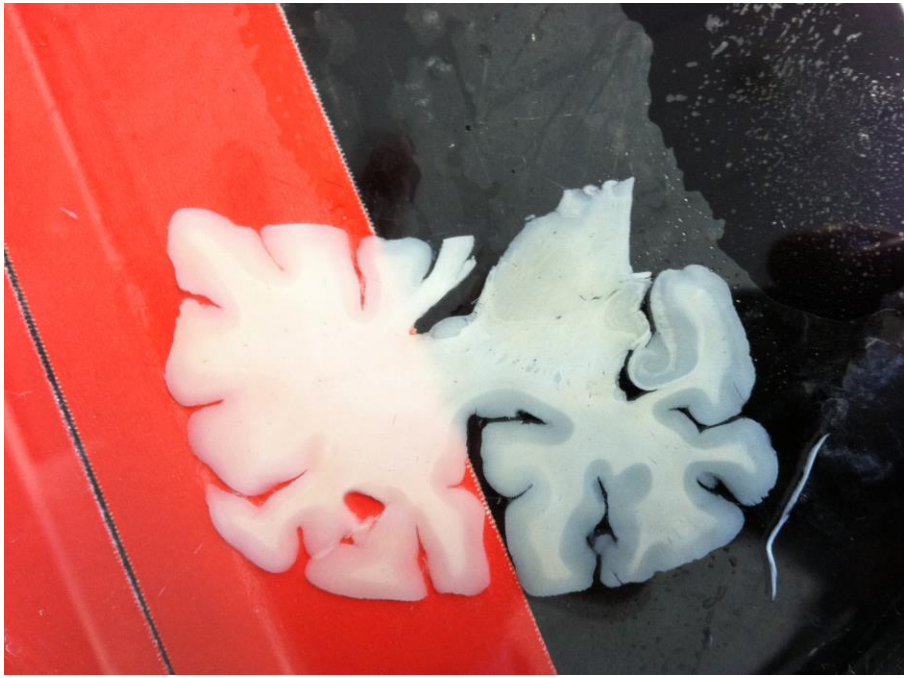
The clinical progression of signs and symptoms of neurodegenerative diseases involves progressive spread of the pathologic lesions in the brain over time.

Heiko Braak and Kelly Del Tredici



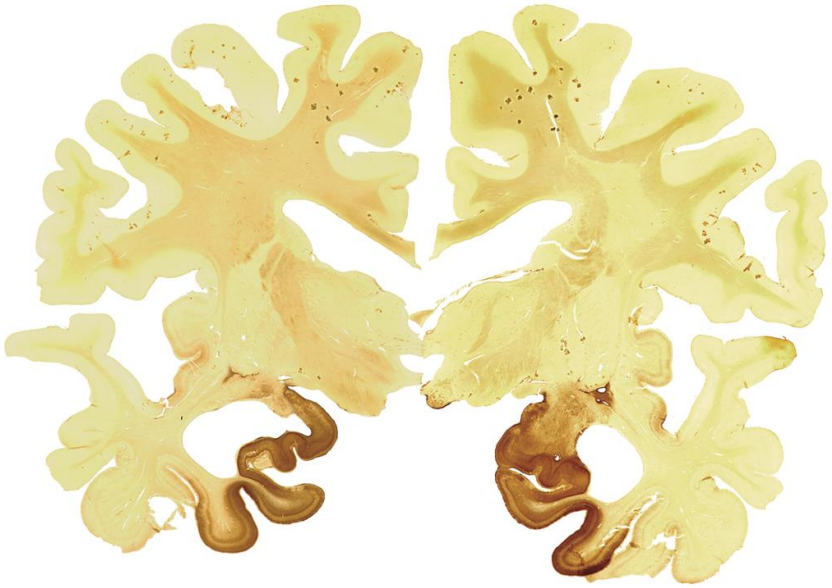


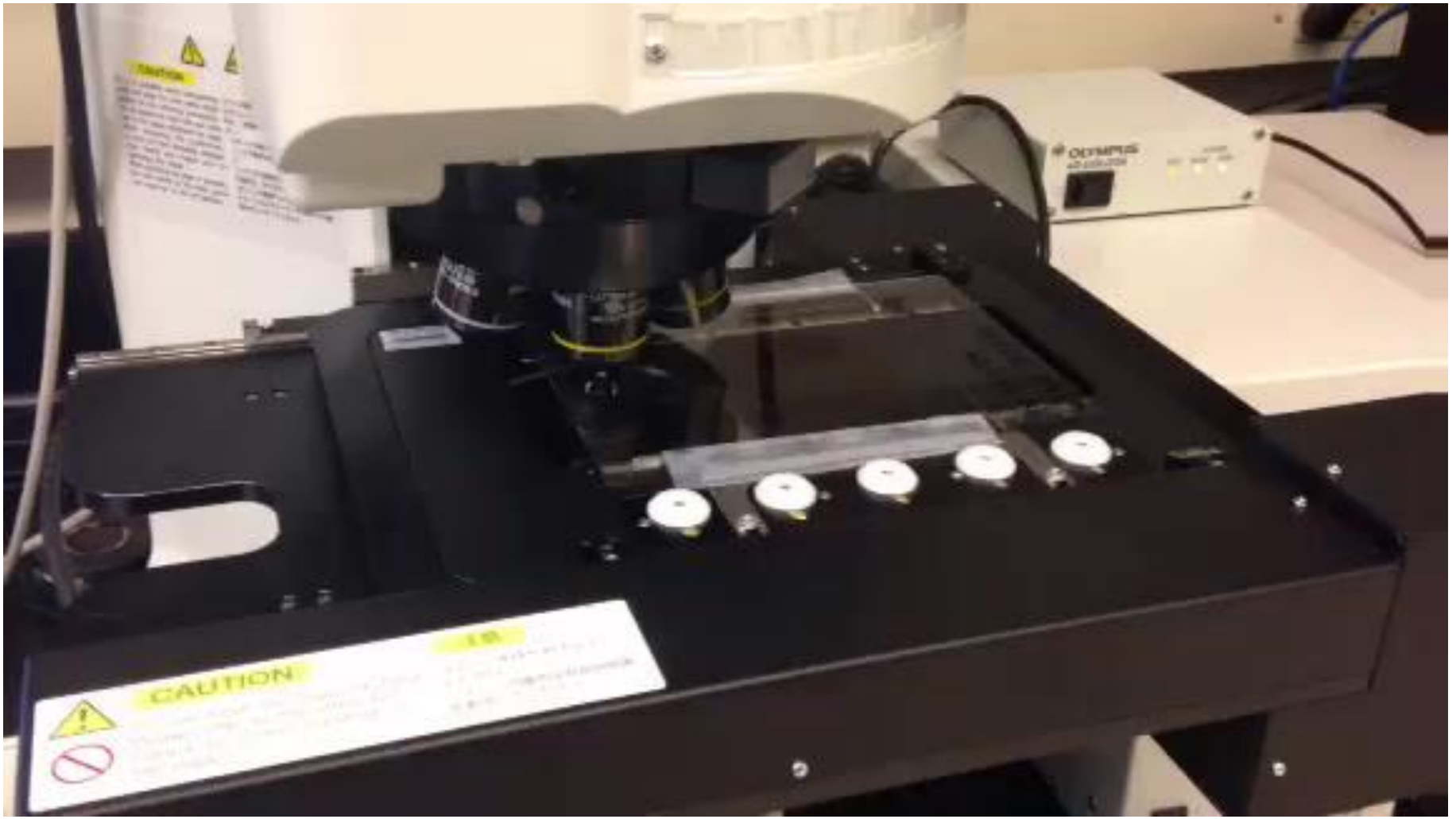




B

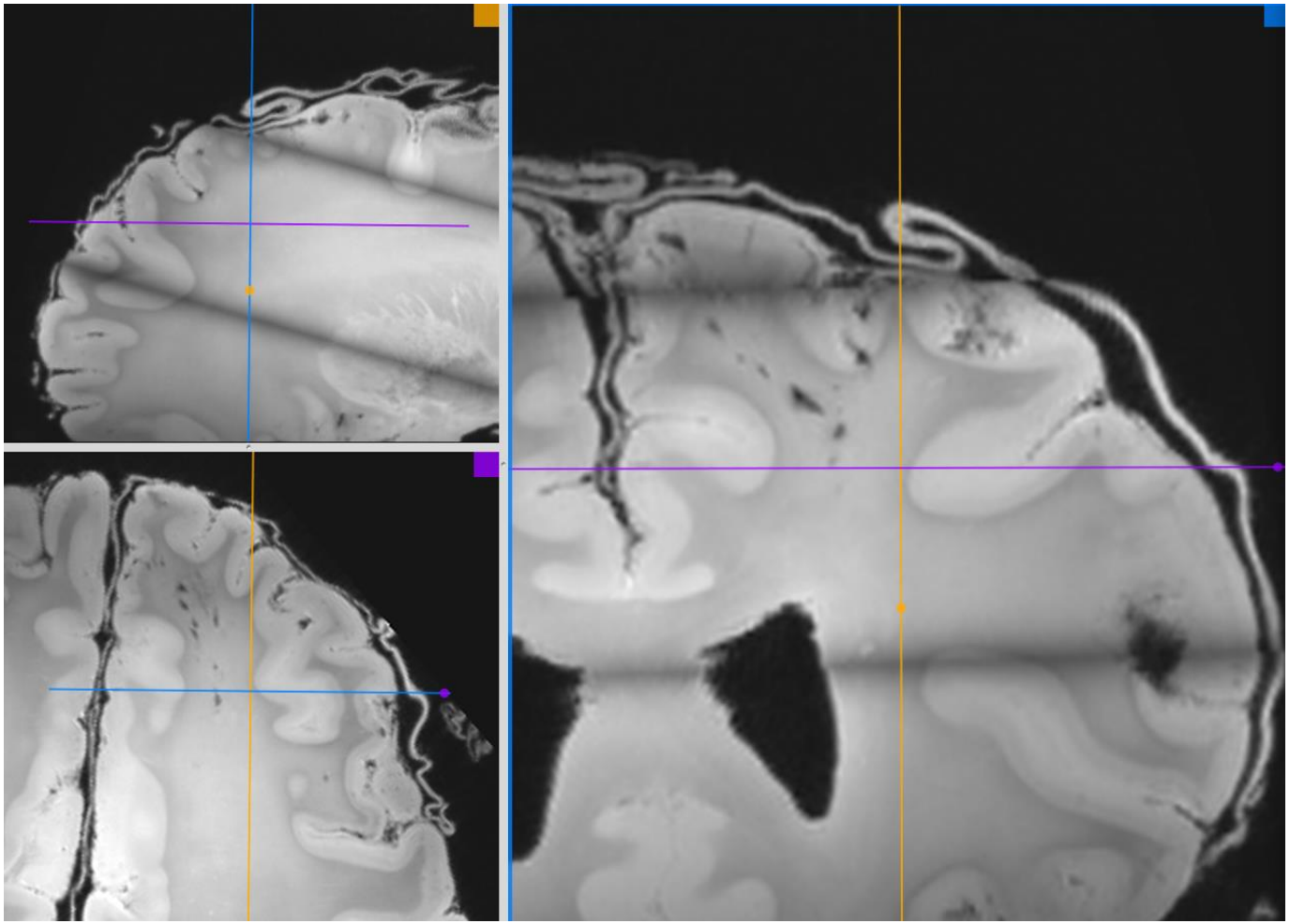
NFT stage III



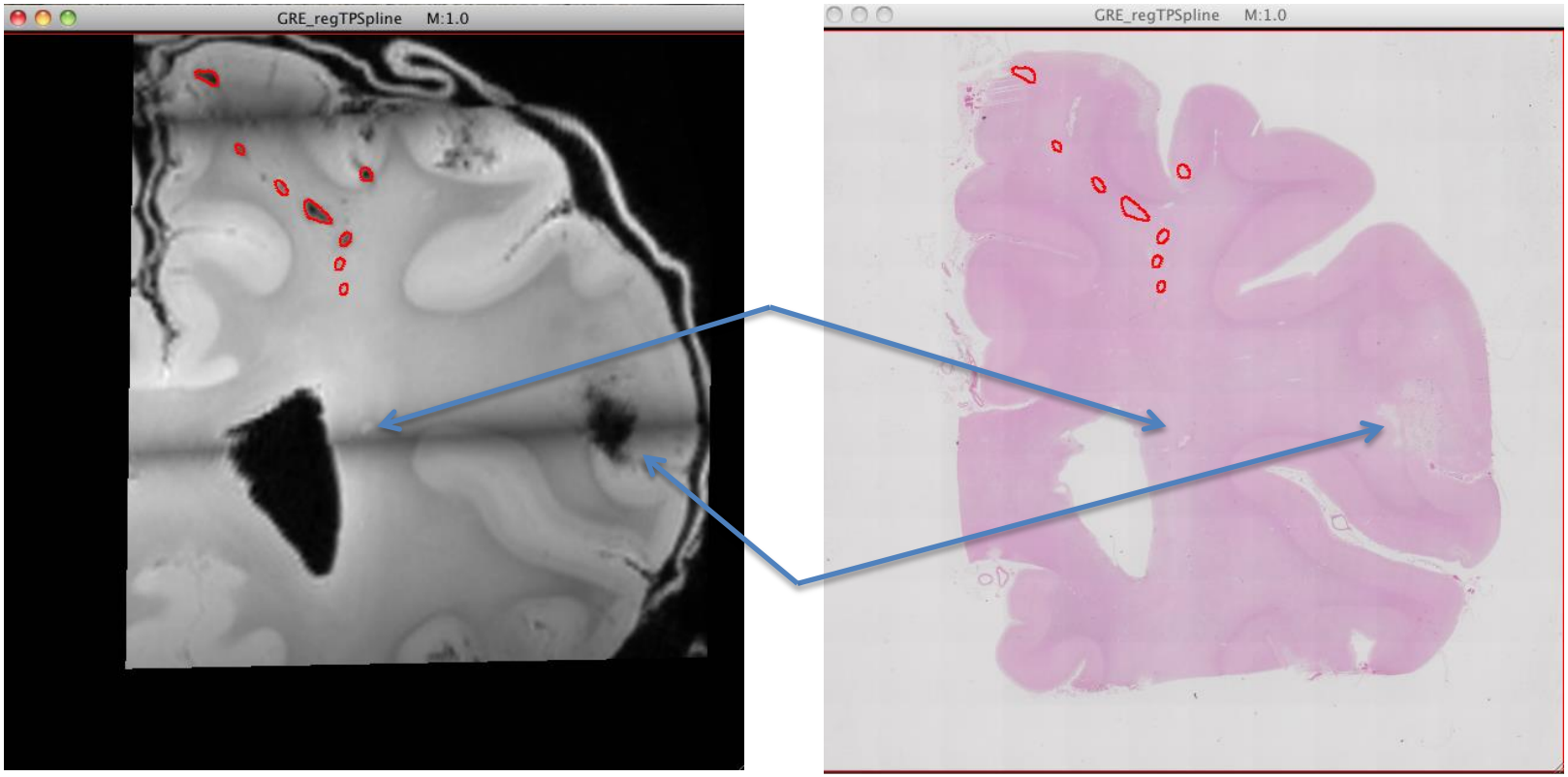

CAUTION

- 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 (e*x 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.

Acknowledgements

Sharon B Shively, MD, PhD (USUHS)

Heiko Braak, MD (Ulm University, Germany)

Kelly Del Tredici, PhD (Ulm University, Germany)

Regina Armstrong, PhD (USUHS-CNRM)

Bernard Dardzinski, PhD (USUHS-CNRM)

Brian Edlow, MD (MGH, Martinos Center)

Bruce Fischl, PhD (MGH, Martinos Center)

Rebecca Folkerth, MD (Brigham-Women's Hosp.. Boston)

Dirk Keene, MD (Univ. Washington)

Patricia Lee (USUHS-CNRM)

Lawrence Latour, PhD (NIH, CNRM)

Gunjan Parik, MD (Univ. Maryland, NIH)

And grant support from the CNRM, NIH-NINDS and US Army MRMC