

MULTIPLE CONCUSSIONS LEAD TO CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE)

CTE may develop within a short time of trauma but usually years intervene

Symptoms

- Cognitive: depression, dementia
- Movement disorders: Parkinsonism, ALS (Lou Gehrig Disease)
- Self destruction: Alcoholism, suicide



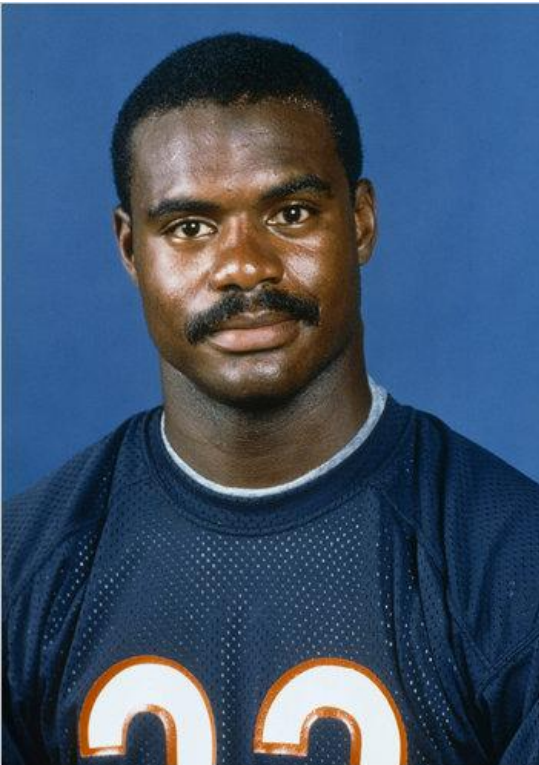
MIAMI-DADE COUNTY
MEDICAL EXAMINER DEPARTMENT
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Miami, FL 33136
Phone (305) 545-2400 Fax (305) 545-2439



AUTOPSY PROTOCOL

DUERSON, David
February 18, 2011...11:15 A.M.

Case No. 2011-00457



CAUSE OF DEATH:

Gunshot Wound of Chest

Handwritten signature
Emma O. Lew, M.D.
Deputy Chief Medical Examiner
Date: 2 / 28 / 2011



Ann McKee



Chris Nowinski

CONCUSSION

(mTBI)

Generally a closed head injury but
could include a penetrating injury

Sources of Concussion

- Blasts
- Vehicle crashes
- Projectiles
- Falls
- Sports injuries

Symptoms of concussion

- Headaches or neck pain that do not go away;
- Slowness in thinking, speaking, acting, or reading;
- Getting lost or easily confused;
- Feeling tired all of the time, having no energy or motivation;
- Mood changes (feeling sad or angry for no reason);
- Changes in sleep patterns (sleeping a lot more or having a hard time sleeping);
- Difficulty remembering, concentrating, or making decisions;
- Light-headedness, dizziness, or loss of balance;
- Urge to vomit (nausea);
- Increased sensitivity to lights, sounds, or distractions;
- Blurred vision or eyes that tire easily;
- Loss of sense of smell or taste and or ringing in the ears.

STUDY GOALS

Identify Marines at high risk to develop CTE
Distinguish between PTSD and mTBI

Methods of cerebral injury

- Acceleration and deceleration
 - Saggital (front to back)
 - Rotational acceleration and deceleration produces the most injury and appears to be the most likely factor based on the location and concentration of neurofibrillary and astrocytic tangles (dorsilateral frontal and occipital)

Neuropathology

- How is CTE distinguished from other neurodegenerative tauopathies, i.e. Alzheimer's Disease?
 - Involves superficial cortical layers
 - Patchy distribution in frontal and temporal cortices
 - Propensity for sulcal depths
 - Deposition of β -amyloid occurs in <50% of cases
 - Marked accumulation of tau immunoreactive astrocytes

Neuropathology

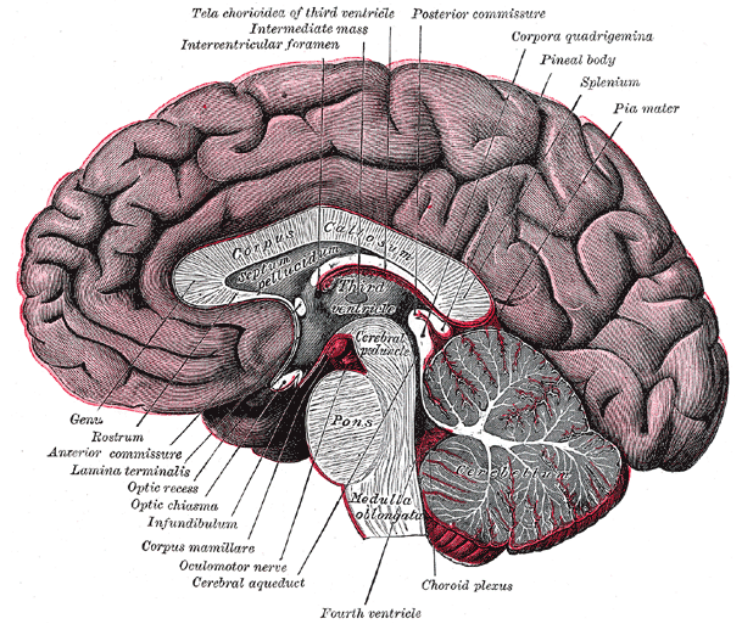
- Gross changes:

Atrophy:

Cerebral hemispheres
Medial temporal lobe
Thalamus
Mammillary bodies
Brainstem

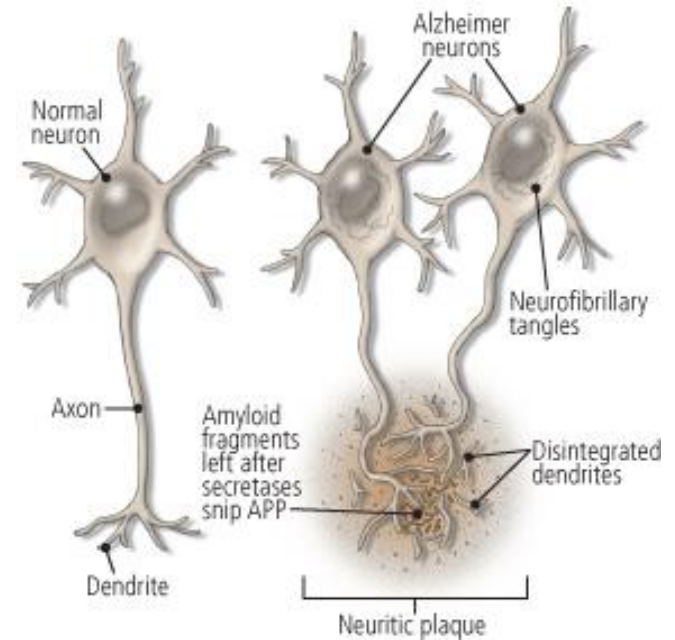
Ventricular dilatation

Fenestrated septum pellucidum



Neuropathology

- Microscopic changes
 - Tau immunoreactive neurofibrillary tangles
 - Astrocytic tangles
 - Threadlike neurites throughout the brain



Apolipoprotein E

Necessary for catabolism of triglyceride rich lipoproteins

Indirectly involved in Alzheimer's disease

The gene APOE is polymorphic and has 3 isoforms

Isoforms: APOE ϵ 2, APO ϵ 3, and APO ϵ 4

APO ϵ 2 may be protective in Alzheimers Disease and CTE

APO ϵ 4 is present in \approx 50% of those with AD

Those with 2 ϵ 4 alleles have up to 30 times greater risk for AD

Apolipoprotein enhances the breakdown of β amyloid and its deposition

It is assumed that parallels exist with CTE

Diagnosis of CTE

- Post Mortem
- Biomarkers
 - Cerebrospinal fluid examination (not practical)
 - ↓ Apo E and A β spinal fluid concentrations in acute injury



Obtain brains for gross and histologic examination through the cooperation of AFME

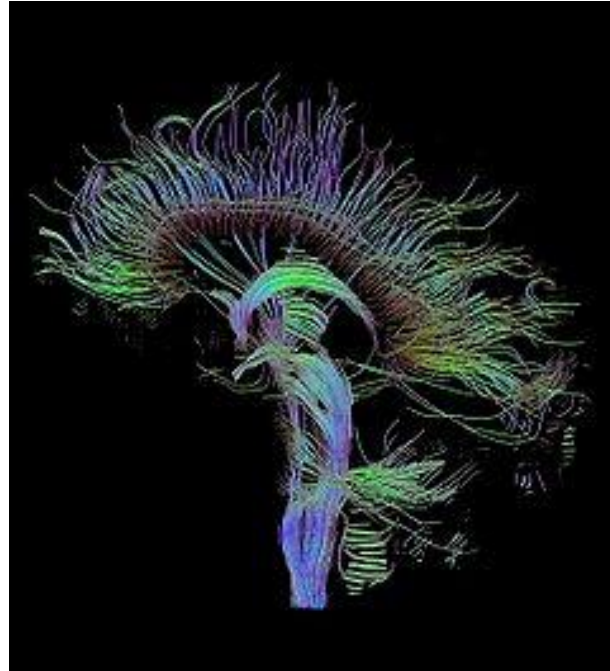
Magnetic Resonance Imaging (MRI)

- Standard MR or CT scanning cannot reveal evidence of CTE
- Diffusion Tensor Imaging (DTI)
- Functional MRI (fMRI)

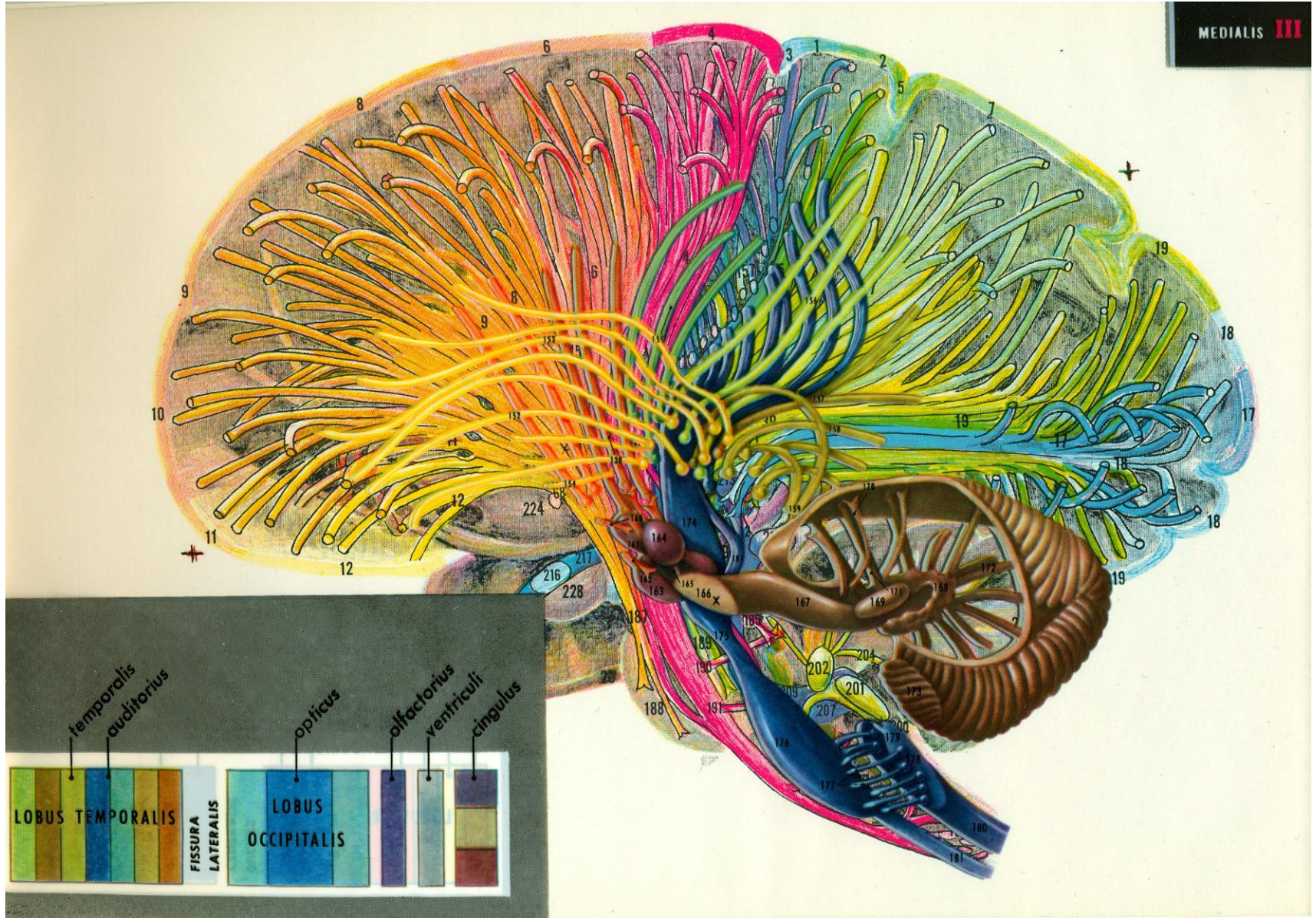
Resting fMRI

- Able to make comparisons in brain state
- Connectome Mapping
- Able to make acute distinctions

Diffusion Tensor Imaging



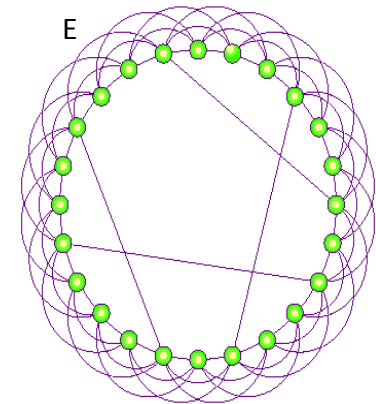
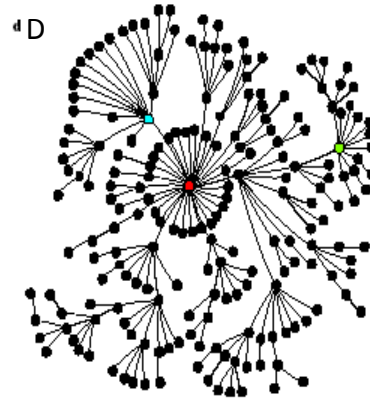
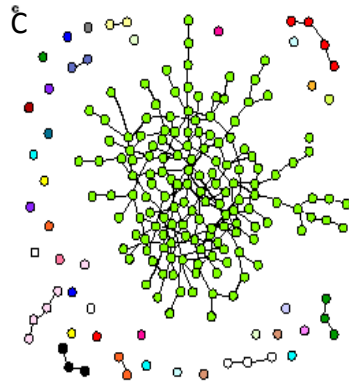
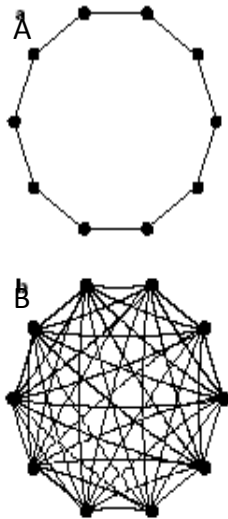
Can be used to track fibers of the nervous system (tractography) The anisotropy of long tracts can be used to facilitate the diffusion of water along their main direction by applying a number of diffusion gradients (magnetic variation) (usually 6 or more). Various algorithms are then applied. Injured white matter can be detected



Wendell Krieg's Functional Neuroanatomy 1966

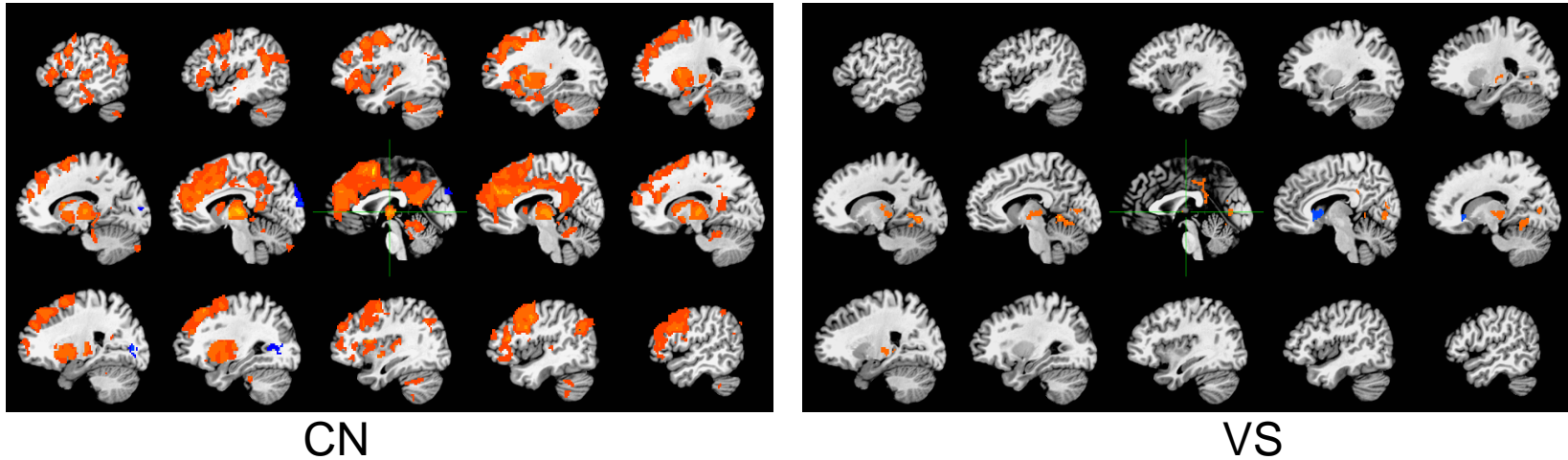
Connectivity fMRI - Definition

- **Functional connectivity:** descriptive of patterns of neural activity and Model Free
- **Effective connectivity:** Explanations of their origins. Requires a causal or acausal Model, in which regions and connections of interest are specified by the researcher



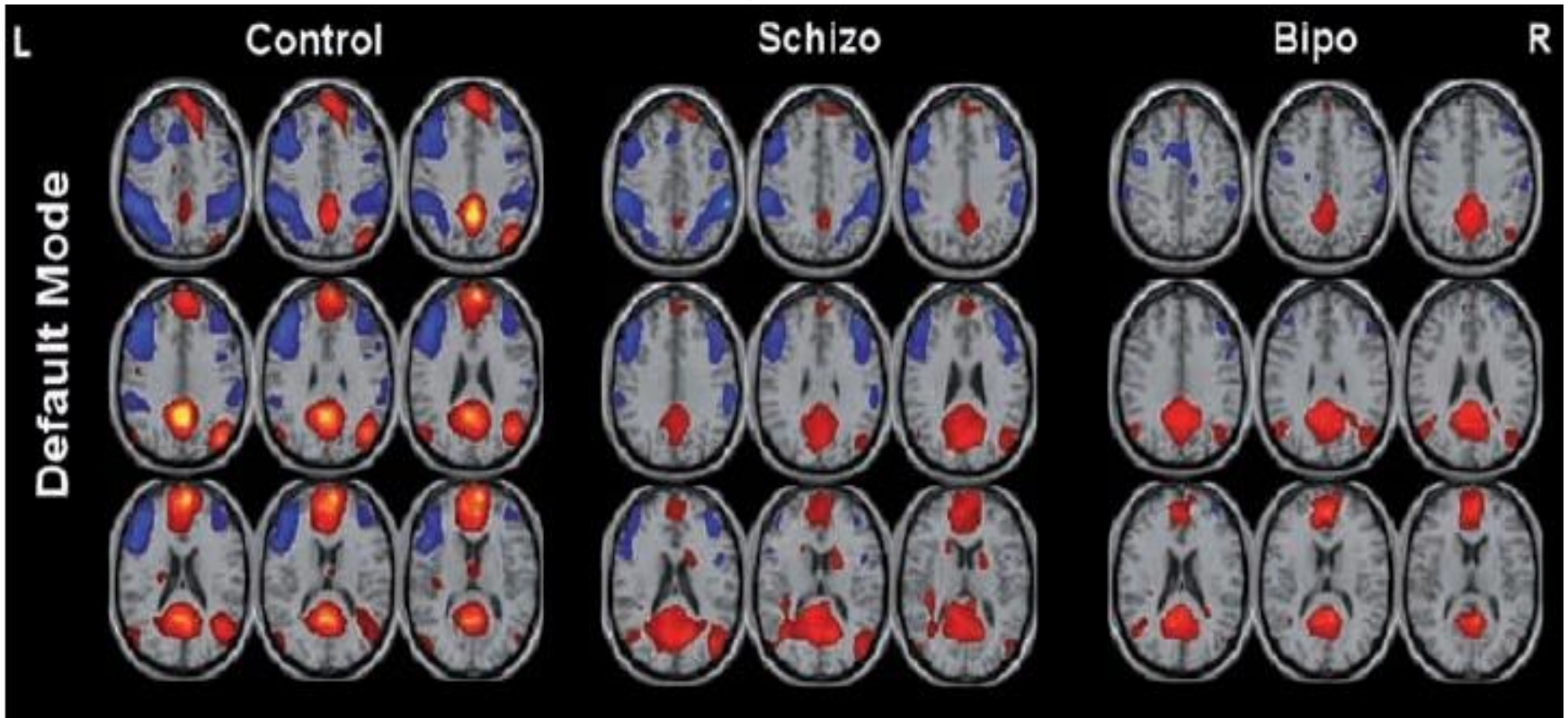
Ring; Fully connected; Random connection; Scale-free; Small-world network

Thalamus and Loss of Consciousness in VS



- Its *small-world network organizations* - disruption to only a few long-range connections may result in a breakdown of information integration, which leads to unconsciousness. VS patients with preservation of 'atypical' activation extending to higher-order associative cortices tend to have a higher likelihood toward the recovery of consciousness (*Di et al. 2008*).

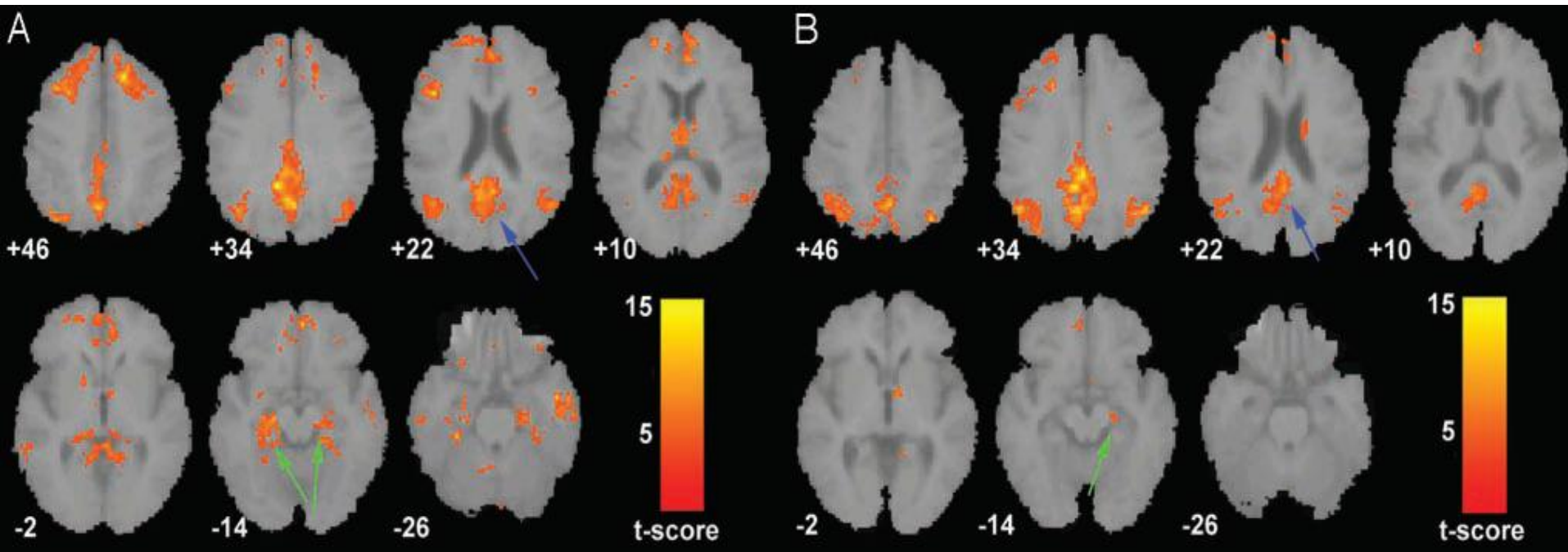
Differences of Default Model Connectivity in Controls, Schizo and Bipo



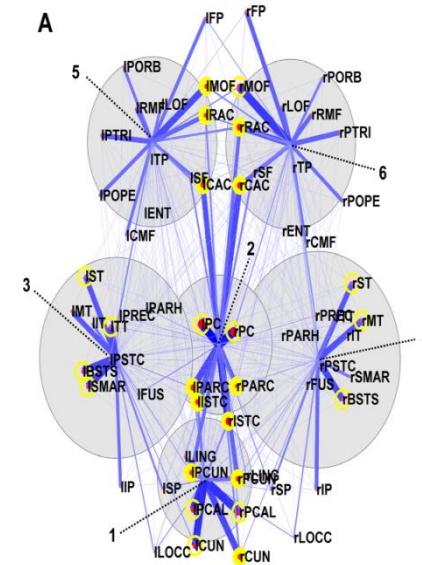
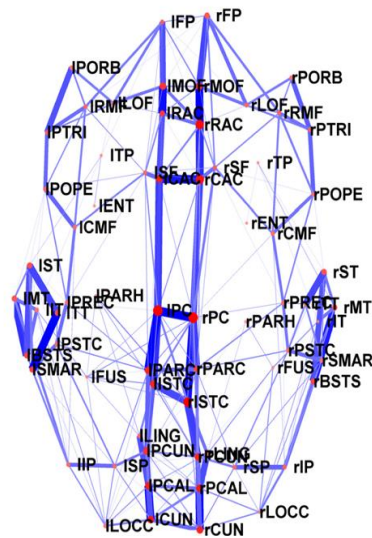
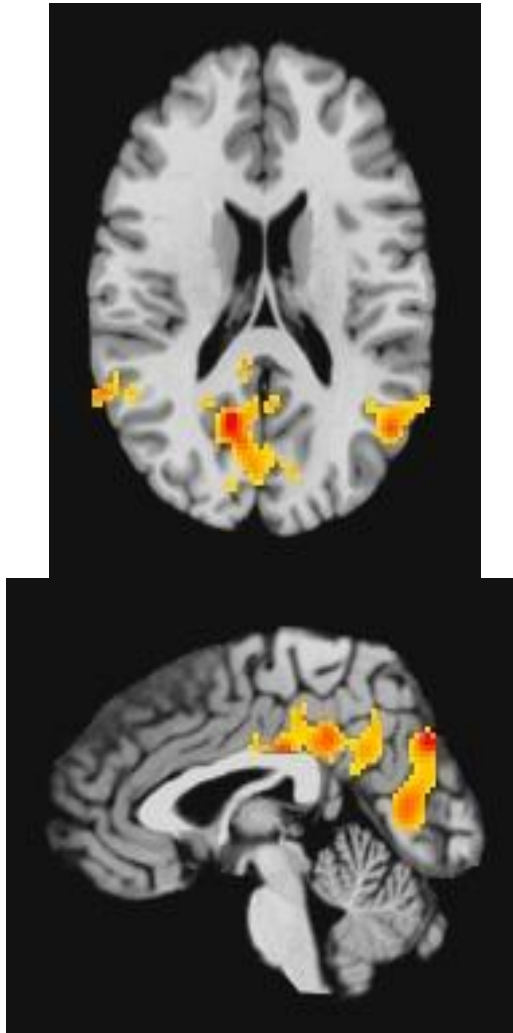
Calhoun VD et al., *Functional brain networks in schizophrenia: a review. Frontiers in Human Neuroscience* 3(17), 1-12,2009

Network of Functional Connectivity

fMRI detected difference in resting brain network between AD and normal elderly controls in the default mode network



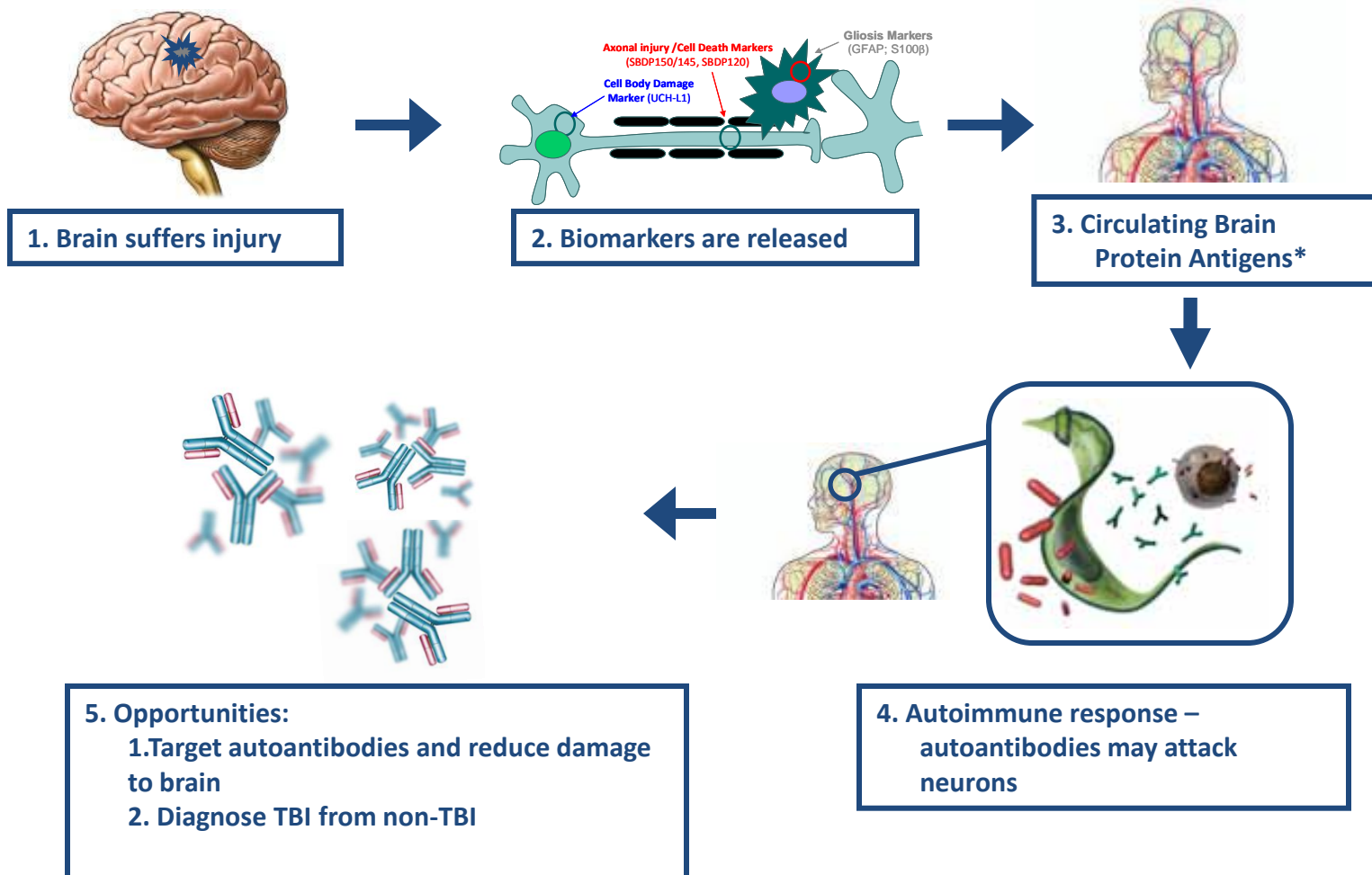
Monitoring Treatment Efficacy - Aricept



PLoS Biology 6(7): e150, 2008

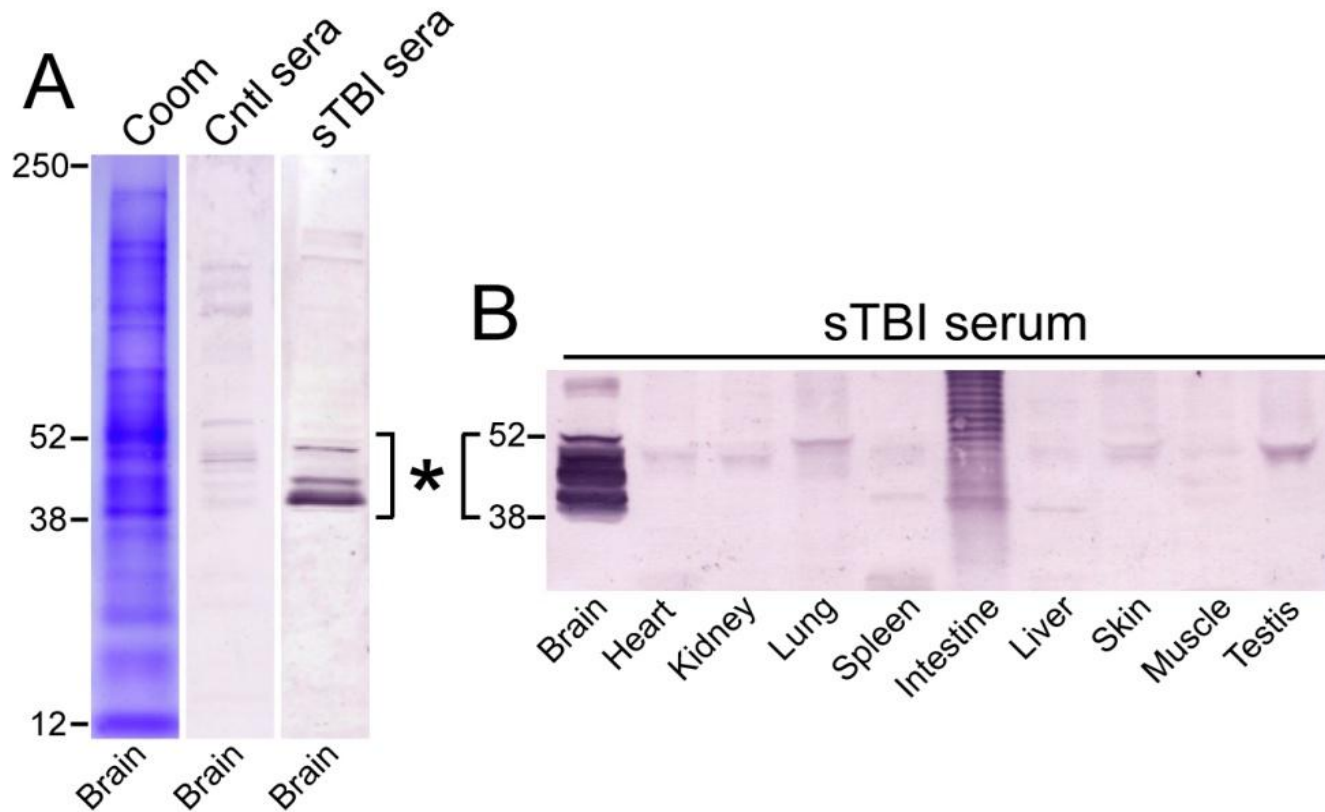
Aricept Improves Backbone and Hubs' Connectivity and the fc strength was correlated with memory improvement (N = 14 AD)

Autoantibodies: New Potential Therapeutic and Diagnostic Opportunity



* Brain is immuno privileged, thus brain proteins are foreign to the immune system

TBI serum autoantibody specific to the brain*



*Human sera (pooled) at 10 days post-TBI contains autoantibodies to unknown brain-specific human antigens

Auto-antibodies: Chronic TBI Biomarkers

- Auto-antibodies against human brain antigens (biomarkers)
- We have identified at least 4 novel auto-antigens from brain
- Identified by blood testing
- Auto-antibodies have delayed onset of 5-6 days post-injury
- Signals can persist for months and possibly years
- Quantitative and sensitive enzyme immunoassay to be developed. (funding required)

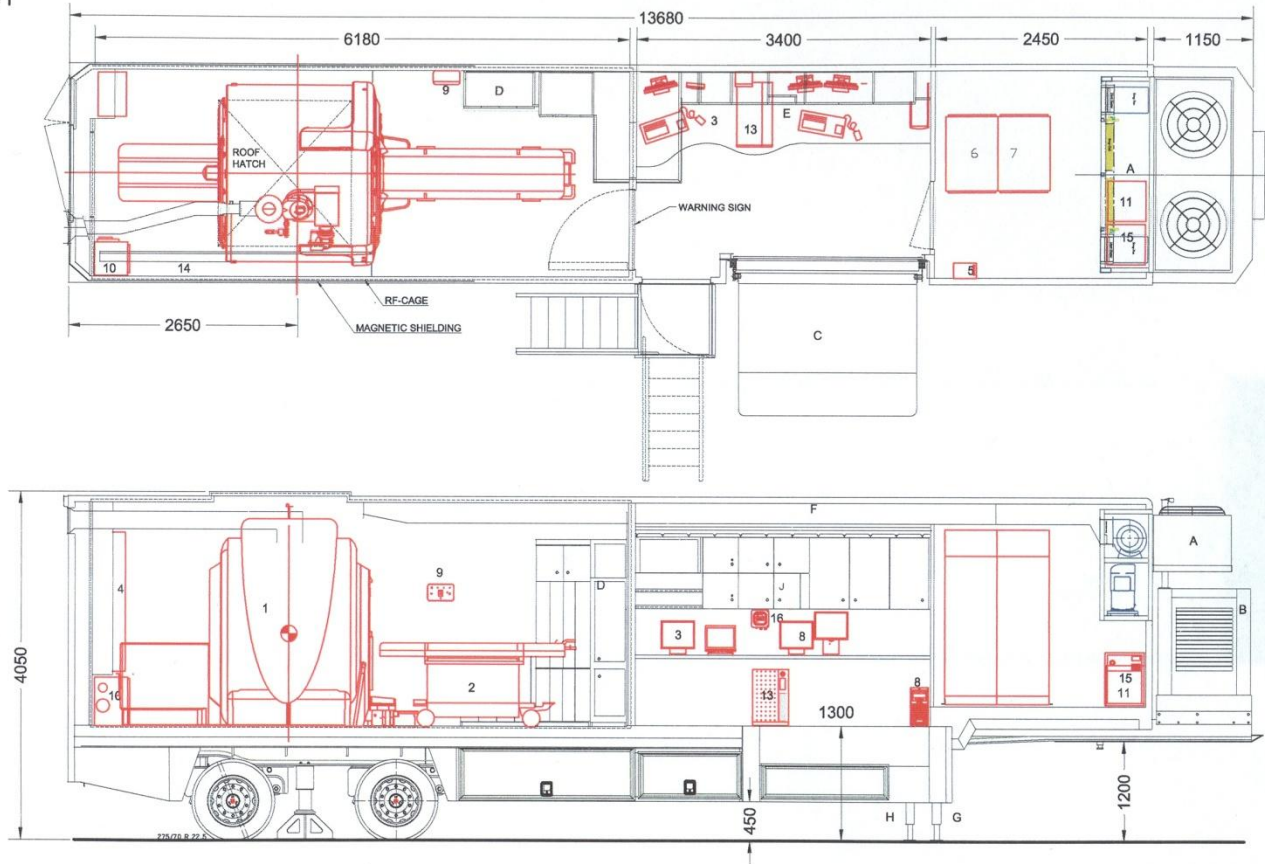
Application of fMRI

- Marines undergo fMRI pre and post deployment as well as in theater scanning (if available).
- Resting fMRI should be able to distinguish mTBI, PTSD as it has with 80-90% accuracy distinguished AD and mCD from CN

Application of fMRI

- Four 3.0 tesla MR scanners
- Modules
- Leased or Purchased
- Scan 12-15 Marines/day/scanner
- Scanning needs to be done during waking hours (sleep deprivation—negative effect)
- Scanners located at Lejeune and Pendleton

GE MOBILE MRI SIGNA EchoSPEED 1.5T HDX NO LASER IMAGER
MIDDLE EAST



GENERAL ELECTRIC MR/I SIGNA EchoSPEED 1.5T HDX

- | | | |
|---------------------------------|--|--------------------------------|
| 1 MAGNET ENCLOSURE (MG2) | 10 BLOWER BOX (MG6) | A AIRCONDITIONER |
| 2 PATIENT TABLE (PT1) | 11 SHIELD COOLER (MS5) | B DIESEL GENERATOR |
| 3 OPERATOR WORKSPACE | | C PATIENT LIFT |
| 4 PENETRATION PANEL (PP1) | | D PHANTOM CABINET |
| 5 MAGNET MONITOR (MSM) | 13 GLOBAL OPERATOR CABINET (Excite II) | E WORKTOP |
| 6 RFS CABINET (MR2) | 14 COLDHEAD TOOL | F CABLE DUCT |
| 7 HFD/PDU CABINET (MR3) | 15 HEAT EXCHANGER | G HYDRAULIC LEVELLING SUPPORTS |
| 8 ADVANCED WORKSTATION (OPTION) | 16 GE OXYGEN MONITOR (OPTION) | H MECHANICAL SUPPORT |
| 9 MAGNET RUNDOWN UNIT | | |

PATENTS PENDING

OSHKOSH EXHIBIT B

Protocol

Pre deployment:

ANAM testing

Standard MRI

fMRI

Genotyping (Apo E4 allele)

Auto antibody testing?

Deployment

Strict reporting of all concussive episodes

MACE testing

Auto antibody testing?

Field scanner fMRI? 1.5T (not ideal)

Post Deployment

fMRI

ANAM testing

Auto antibody testing

Two groups of Marines

Concussion

Symptomatic (priority analysis)

No symptoms

No concussion

Symptomatic (PTSD?)

No symptoms

The Ideal Study

Pre Deployment

Organ donor status to allow postmortem exam

Concussion history

Thorough neuropsychology evaluation

Genetic Testing for ApoE 4 allele

Scanning in dedicated scanner pre deployment (3T fixed scanner)

Parallel biomarker study

Deployment

Scanned in theater post concussion (3T fixed scanner)

Anam evaluation

Parallel biomarker study

Helmet, vehicle blast sensors

Post Deployment

Repeat scanning post deployment in same scanner as pre deployment

Thorough neuropsychology evaluation

Brain examination KIA

Continued surveillance in civilian status through Veteran's Administration

Parallel biomarker Study

Conclusions

RfMRI, through connectome mapping, will detect organic changes in functional neural architecture after significant mTBI.

The presence of these changes should serve as a warning that repeated exposure to concussive forces may lead to the development of chronic traumatic encephalopathy and its debilitating and possibly lethal results.

The pairing of RfMRI with other biomarker studies will provide cross validation of methods and the development of less complex methods of detection of significant mTBI, i.e., easily obtained serum biomarkers.

Persons and Institutions interested in project

Ann McKee, Boston University
Center for the Study of Traumatic Encephalopathy

Christopher Nowinski
Sports Legacy Institute, Boston

Shi Jiang Li, Medical College of Wisconsin
Director, Center for Imaging Research

University of California, San Diego

Duke University

Washington University, St. Louis

Banyan Biomarkers

