WRIISC
War Related Illness & Injury Study Center

VA | U.S. Department of Veterans Affairs
Veterans Health Administration
Office of Public Health

# War Related Illness and Injury Study Center (WRIISC): Insights from Comprehensive Evaluations of Traumatic Brain Injury (TBI) in Women


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Presented by the **VA War Related Illness and Injury Study Center (WRIISC)**

# Incidence of TBI - Military

- ~50% of injuries involve head or neck
  - Echelon II medical unit Mil Med 2005;170:516-520
  - Mechanized Battalion Mil Med 2005:170:546-549

- ~88-97% of injuries involve blast
  - Echelon II medical unit Mil Med 2005;170:516-520
  - Mechanized Battalion Mil Med 2005:170:546-549

- 59% of soldiers at WRAMC injured by blast had TBI (Jan03-Feb05; 44% mild, 56% mod-severe)
  - DVBIC study N Engl J Med 2005;352:2043-2047

Slide Courtesy of Katherine Taber, PhD

# Changes over Time

- Fewer fatalities due to kevlar body armor
  - More soldiers surviving with brain injuries
- Helmets are much better
  - Head injuries are more subtle, affect complex regions of the brain
- In theatre medical care, ability to evacuate quickly to higher level of care
  - More serious peripheral injuries are survived, but brain injuries are not as easily treated

# TBI – Definition

- Any extracranial mechanical force to the brain that leads to any of the following:
  - Any period of loss of consciousness (LOC)
  - Any loss of memory for events immediately before or after the event
  - Any alteration in mental state at the time of the event (AOC)
  - Focal neurological deficits*

(Kim et al., 2007; *from the ACRM)

# TBI – Definition

- Difficulties of defining severity of TBI sequelae
  - Duration of loss of consciousness (LOC)
  - Duration of post-traumatic amnesia (PTA)
  - Glasgow Coma Scale (acute level of consciousness)
  - APA-DSM-5 categories (several syndromes)
  - ACRM definition of mild TBI
  - Other approaches

# Definition of mild TBI

- Loss of consciousness (LOC) duration is relatively short: less than 1 minute versus less than 10 minutes vs less than 30 minutes
- Post-traumatic amnesia (PTA) less than 24 hours
- Glasgow Coma Scale (GCS) 13-15 (acutely)
- No penetrating brain injury
- No focal neurological findings
- (different groups use different definitions)

# Severity of Injury (VA/DOD)

| Criteria | Mild | Moderate | Severe |
|---|---|---|---|
| **LOC** | 0 - 30 mins | 31 mins - 24 hrs | >24 hours |
| **AOC** | Moment - 24 hrs | >24 hours. Severity based on other criteria | |
| **PTA** | 0 - 1 Day | 2 – 7 Days | >7 Days |
| **GCS** | 13 - 15 | 9 – 12 | <9 |
| **Structural Imaging** | Normal | Normal or Abnormal | Normal or Abnormal |

# Complicated Mild TBI

- When clinical neuroimaging findings are present following a mTBI, the classification changes to “complicated mTBI,” which has a 6-month outcome more similar to moderate TBI[1,2]

[1]Williams DH, Levin HS, Eisenberg HM. Mild head injury classification. *Neurosurgery* 1990;27(3):422-8.

[2]Kashluba S, Hanks RA, Casey JE, Millis SR. Neuropsychologic and functional outcome after complicated mild traumatic brain injury. Arch Phys Med Rehabil 2008; 89(5): 904-11.

From Belanger, 2009

# Limitations of Classification

- Not practical under the threat of enemy fire
- No one may be watching when an individual is affected, and LOC begins and ends
- PTA <24 hrs, there is no lower limit, there is no criteria for the point that it ends
- Narrow window for assessment – during most difficult time for objective observation

# Causes of Military TBI

- Blasts, Fragments, Bullets
- Motor Vehicle/Traffic Crashes
- Falls
- Assaults

# What are the Injuries?

- Most Common Primary Injuries
  - Concussion (shaking of the brain caused by any violent blow the head, usually causing loss of consciousness)
  - Contusion (bruising)
  - Subdural hematoma (a bleed immediately under the dura)
  - Diffuse axonal injury
- Most Common Secondary Injuries
  - Excitotoxicity (release of calcium, binding of magnesium)
  - Edema
  - Ischemia

# Complexities of TBI Making each Case Unique

Every Traumatic Brain Injury is Unique
(just as no 2 brain tumors, strokes, seizures are the same)

Individual Attributes

- Head attributes: age, skull thickness, protective gear
- Brain reserve: cognitive, neuronal, prior injury
- Individual repair mechanism: genetics- APOE genotype
- Education/culture

# Complexities of TBI Making each Case Unique

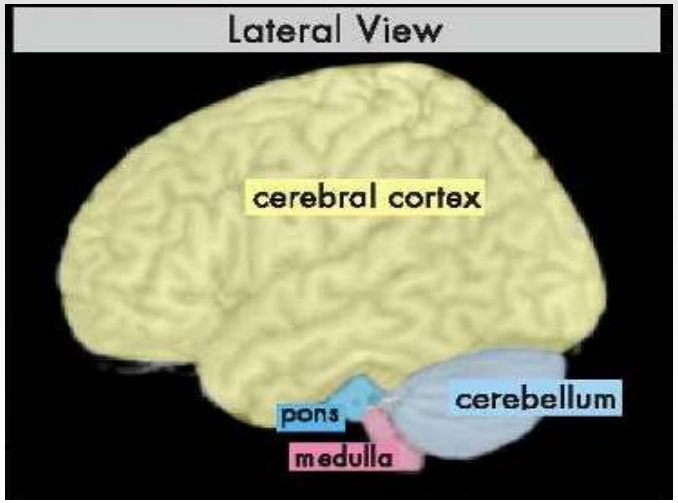
- Blast Attributes
  - Type of injury: non-penetrating, penetrating
  - Direction of physical force impacting head
  - Orientation/location of force: translational vs. rotational
  - Physical energy: amplitude, rise time, wave length, duration, reflection (shock wave bouncing around between buildings, inside of vehicles)

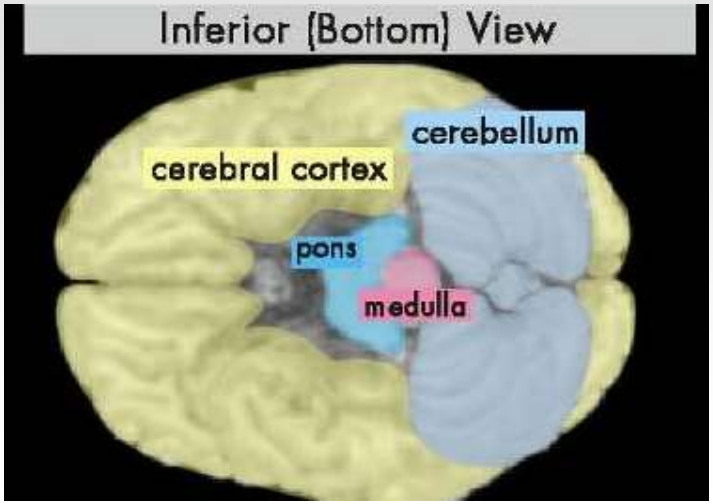
# Complexities of TBI Making each Case Unique

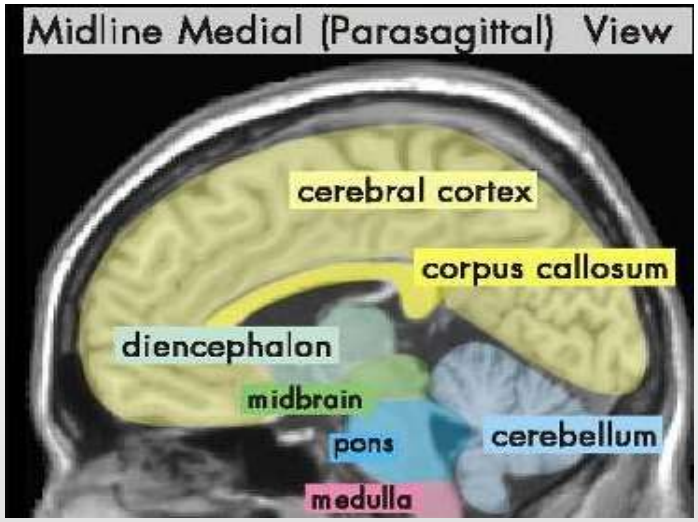
- Injury-Related Attributes
  - Complexity-multiplicity of injury; contusion, bleeding,
  - Effects on brain-brainstem, cortex, white matter
  - Psychological stress, social imperatives
  - Immediate care after injury
  - Chronic care after injury: rehabilitation, support

- **CANNOT GROUP PATIENTS FOR PARAMETRIC STATISTICS – OR -**
- **COMPARE ARTIFICIAL GROUPINGS WITH NORMATIVE SCORES**

# Intro to the Brain – Divisions




Courtesy of Dr. Katherine Taber, VISN 6 MIRECC

# TBI Pathology

- Vulnerability of brain structures associated with neuropsychiatric and cognitive function:
  - Frontal cortex
  - Temporal cortex
  - Limbic system

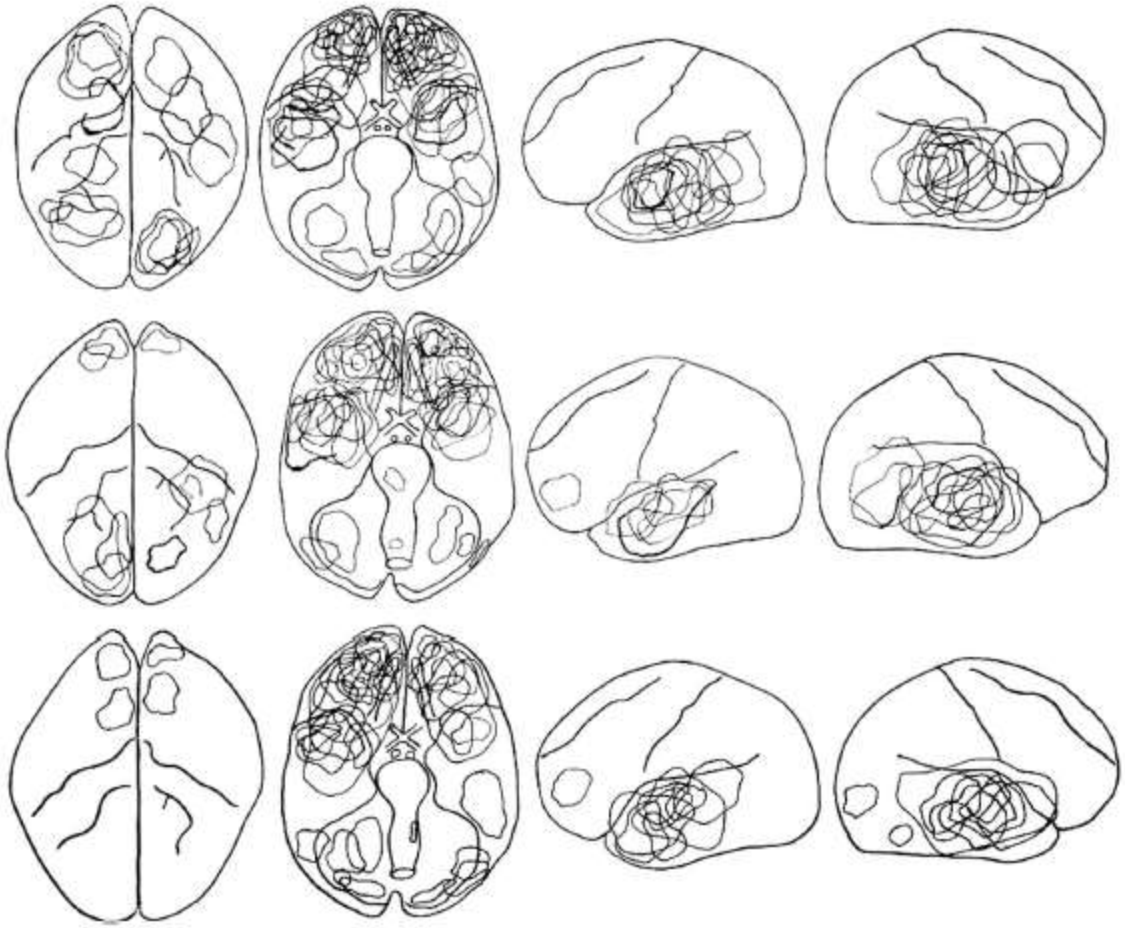


*Figure 2.* At post-mortem, both Courville (1950) and Gurdjian (1975) visually examined the location of surface contusions as depicted in Figure 1 and outlined the boundaries by hand of the contusions on a schematic of the brain to illustrate the preponderance of contusions to the frontotemporal region. From *Impact Head Injury: Mechanistic, Clinical and Preventive Correlation* (p. 244), by E. S. Gurdjian, 1975, Springfield, IL: Charles C. Thomas. Copyright 1975 by Charles C. Thomas. Reprinted with permission.

Note variations in:

- Location
- Volume
- Depth

Some commonality
Of TBI injuries:
Vulnerable regions,
Left, Right,
Front, Back,
Top, Bottom.
Size.

Bigler, Neuropsychology, 2007

# Glasgow Coma Scale (GCS)

- Comprised of 3 tests:
  - Eye responsiveness: 1-4
  - Verbal responsiveness: 1-5
  - Motor responsiveness: 1-6
- The three values separately as well as their sum are considered.
- The lowest possible GCS (the sum) is 3 (deep coma or death), the highest is 15 (fully awake person).

# Second Concussions

- It is frequently noticed that a second TBI occurs unexpectedly and soon after an initial TBI. This may be due to an unrecognized underlying condition or predisposition (e.g., being in battle).

- It is frequently observed that the deficits observed after a second TBI of a similar magnitude produces more than double the impairment.

- This synergistic effect may be because there is great neural and cognitive reserve in the brain, which contributes to recovery from the first TBI, but is not available at the time of the second TBI.

# Repeated Concussions

- Chronic Traumatic Encephalopathy (CTE) (Dementia Pugilistica)
- "…neuropathologically distinct slowly progressive tauopathy with a clear environmental etiology" McKee et al. 2009
- Can be latent for long periods before clinical symptoms manifest

# TBI Pathology / Mechanisms

- Coup-contra-coup – contusion
- Collision of medial temporal lobe structures, orbito-frontal cortex with bones of base of skull
- Breakage of blood vessels
  - Macro hemorrhages - injury to large blood vessels
    - Subdural hematoma – local pressure
    - Epidural hematoma – arterial pressure, rapidly progressing
    - Subarachnoid bleeding – herniation; normal pressure hydrocephalus
  - Small hemorrhages – arterioles (30-150 um)
  - Microbleeds at the gray-white matter junction
- Disruption of blood flow, clotting
- Local edema, increased intracranial pressure
- Shear injury - breakage of axons (0.2 – 0.5 um)
  - Vulnerability at gray-white matter junctions (Not Diffuse??)

# TBI Symptomatology

- Acute severity – mild, moderate, severe
  - Glasgow coma scale
    - Mild – GCS = 13 – 15
    - Moderate GCS = 9 – 12
    - Severe GCS = <9
  - Duration of unconsciousness
    - Mild = less than 15 min.
    - Moderate = 15 min. to 6 hours, amnesia 1 – 24 hours
    - Severe = more than 6 hours
  - Post-traumatic amnesia – Mild = less than 24 hours
  - Mild = No penetrating brain injury, no focal neurological findings.

- Chronic severity
  - Functional level established at one year (Rancho Los Amigos Scale)
  - Results of focal cortical contusion
  - Consequences of diffuse axonal injury
  - Chronic development of dementia, ? Alzheimer's disease

# Neuropsychiatric sequelae of mild TBI

- Neuropsychological, cognitive deficits (similarity to dementia)
  - Memory loss – retrograde, anterograde (? Relation to fornix damage)
  - Aphasia
  - Apraxia, slowed motor responses
  - Agnosia
  - Executive function / decision making impairment, decreased attention span
- Neurobehavioral problems
  - Depression, mood instability, mania (? Relation to norepinephrine, 5HT)
  - Apathy
  - Decreased bonding, libido
  - Inappropriate behavior, disinhibition, agitation
  - PTSD, anxiety disorders (? Relation to shearing of NE, 5HT neurons)
  - Psychosis
  - Aggression (possible relation to premorbid and predisposing factors)
- Neurophysiological symptoms
  - Disruption of sensory systems, smell, hypersensitivity to light, , dizziness, tinnitus
  - Headache
  - Sleep difficulties, fatigue (disruption/shearing of brainstem axons?)
  - Autonomic instability

# Neurobehavioral Disorders: Incidence (I) and Prevalence (P)

- Depression: (I): 15.3 %-33% , (P): 18.5%-61%
- Mania: (I): 9.1% (P): 0.83-22.2%
- PTSD:  (I): 13-27% (P): 3-59%
- Psychosis: (I): 20%, (P) un-determined range
- Aggression: (I): 33.7% (P): 20-40%

Kim et al 2007

# Cognitive Dysfunction

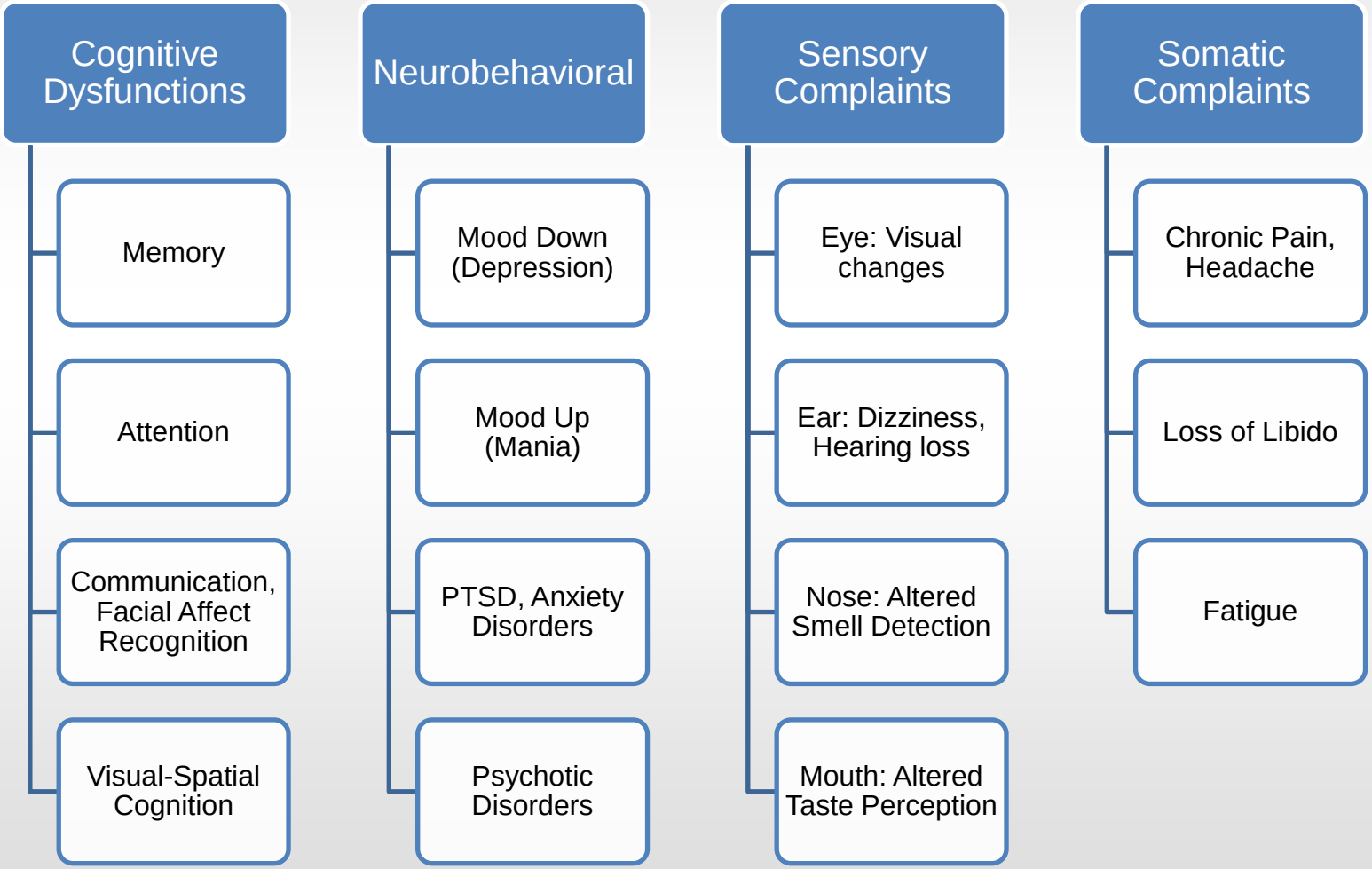
TBI can affect specific mental functions related to neuronal processing anywhere in the brain. Higher cognitive functions, particularly those associated with the tertiary association regions of the cortex in the temporal, parietal and frontal lobes of the brain.

- Temporal lobe functions relate to perception, language, and memory.
- Parietal lobe functions relate to spatial orientation.
- Frontal lobe functions include complex goal-directed behaviors such as:

  These are often called executive functions: functions of abstraction and organization of ideas; time management, insight and judgment; concept formation, categorization and cognitive flexibility

Pleasant, fun computerized testing is being developed for screening and assessment of TBI. www.memtrax.com

# Neuropsychiatric Disorders Associated with Mild to Moderate TBI



# TBI May Lead to a Chronic Disease

There is growing concern that repetitive concussive and subconcussive head injuries lead to pathogenic processes that lead to neurodegenerative disorders, including dementia pugilistica, Alzheimer's disease, and Parkinson's disease

New term:
Chronic Traumatic Encephalopathy (CTE)

# Advanced Brain Imaging - DTI

- MRI scanning allows many techniques for imaging the brain.
- A recent development is DTI (diffusion tensor imaging)
- DTI allows the examination of specific bundles of brain fibers
- Relevant to TBI, specific bundles may be damaged

# DTI – 2 Weeks After TBI

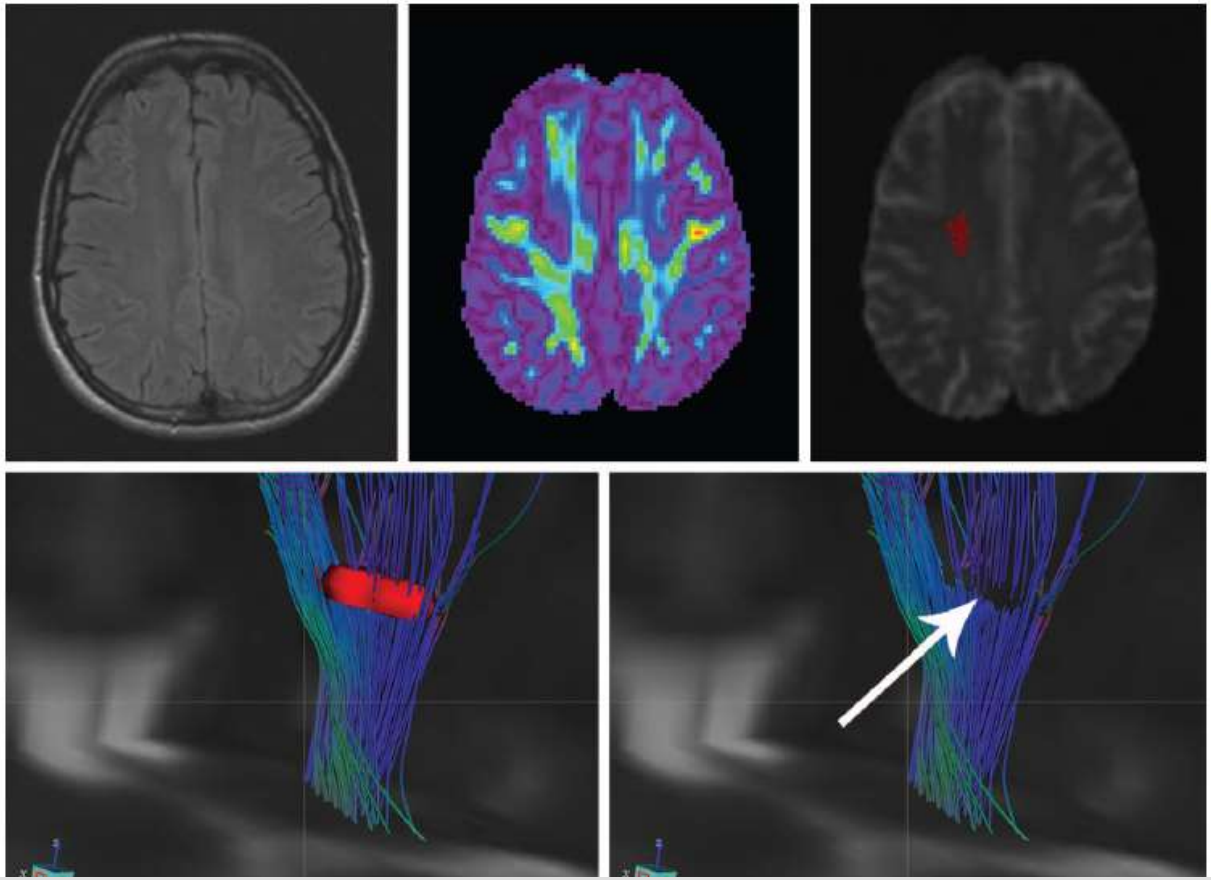


**Fig 3.** FLAIR scan, FA map, and fiber tracking in a 38-year-old patient with TBI who was imaged 2 weeks after the initial trauma. The FLAIR image shows no abnormalities in the semiovale centers (*top left image*). After analysis of the color-coded FA map (*top middle image*), a region with reduced FA was identified in the right semiovale center. This ROI, illustrated in the *top right* T2-weighted image, included projection fibers (*bottom left image*, postero-latero-superior view; the ROI is red and located in the top right quarter of the image; the fibers are superimposed on a multiplanar T2-weighted scan that shows the lateral ventricles in white). At the level of the ROI, projection fibers are discontinuous (*arrow, bottom right image*; the ROI is left out in this image).

Rutgers et al., 2008

# DTI Image 16 Months After TBI

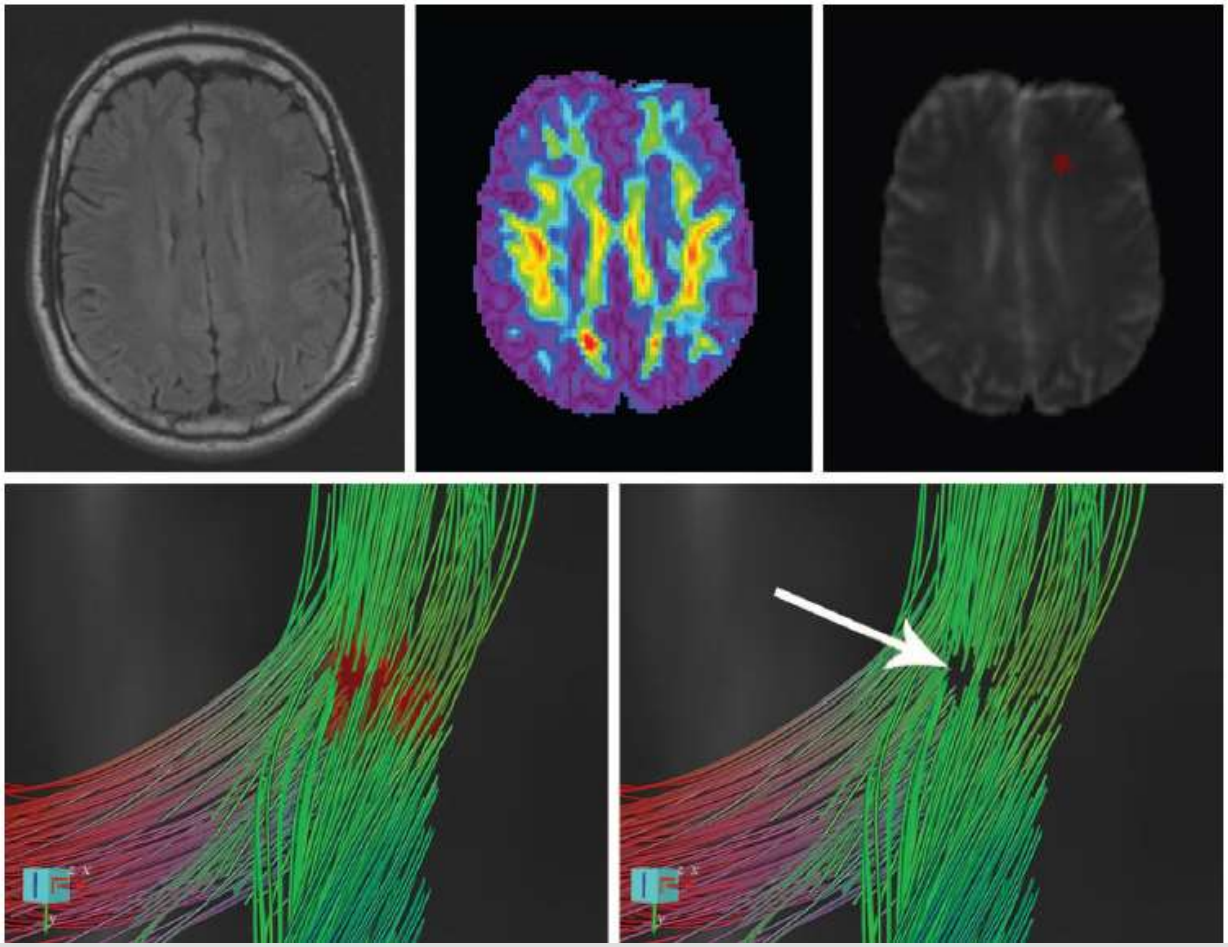


**Fig 2.** FLAIR scan, FA map, and fiber tracking in a 49-year-old patient with TBI who was imaged 16 months after the initial trauma. The FLAIR image shows no abnormalities (*top left image*). After analysis of the color-coded FA map (*top middle image*), a region with reduced FA was identified in the white matter of the left frontal lobe. This ROI, illustrated in the top right T2-weighted image, included forceps minor and fronto-temporo-occipital fibers (*bottom left image*, superior oblique view; the ROI is red and located centrally; the fibers are superimposed on an axial T2-weighted scan). At the level of the ROI, the respective fibers are discontinuous (*arrow, bottom right image;* the ROI is left out in this image).

Rutgers et al., 2008

# Case Report: WRIISC Evaluation of Female Veteran with Potential Combat-Related Condition

32 year old female, referred for: episodes of dizziness, light-headedness with loss of memory, followed by heavy feeling, chronic all-over body pain of 4-5 on a scale of 0-10, localized pain in hip and lower back, neck and head 7-10, intermittent vision loss, memory loss, problems with speech (100% Service Connected for PTSD)

- Combat location: Iraq: 3/2003 to 10/2003 and 12/2003 to 8/2004.
- Veteran was in excellent physical condition prior to military service (1997)
- Sexual assault, hit in head, LOC about 2 minutes - 1999
- In vicinity of mortar blasts in 2003-2004, including a series of 3 in which many soldiers nearby were killed and wounded - no LOC, but did feel unclear about circumstances for short period of time afterwards
- Bar-room fight resulting in LOC <1min in 2009
- Jumped out of truck with full pack 2005, injured Right hip, lower back

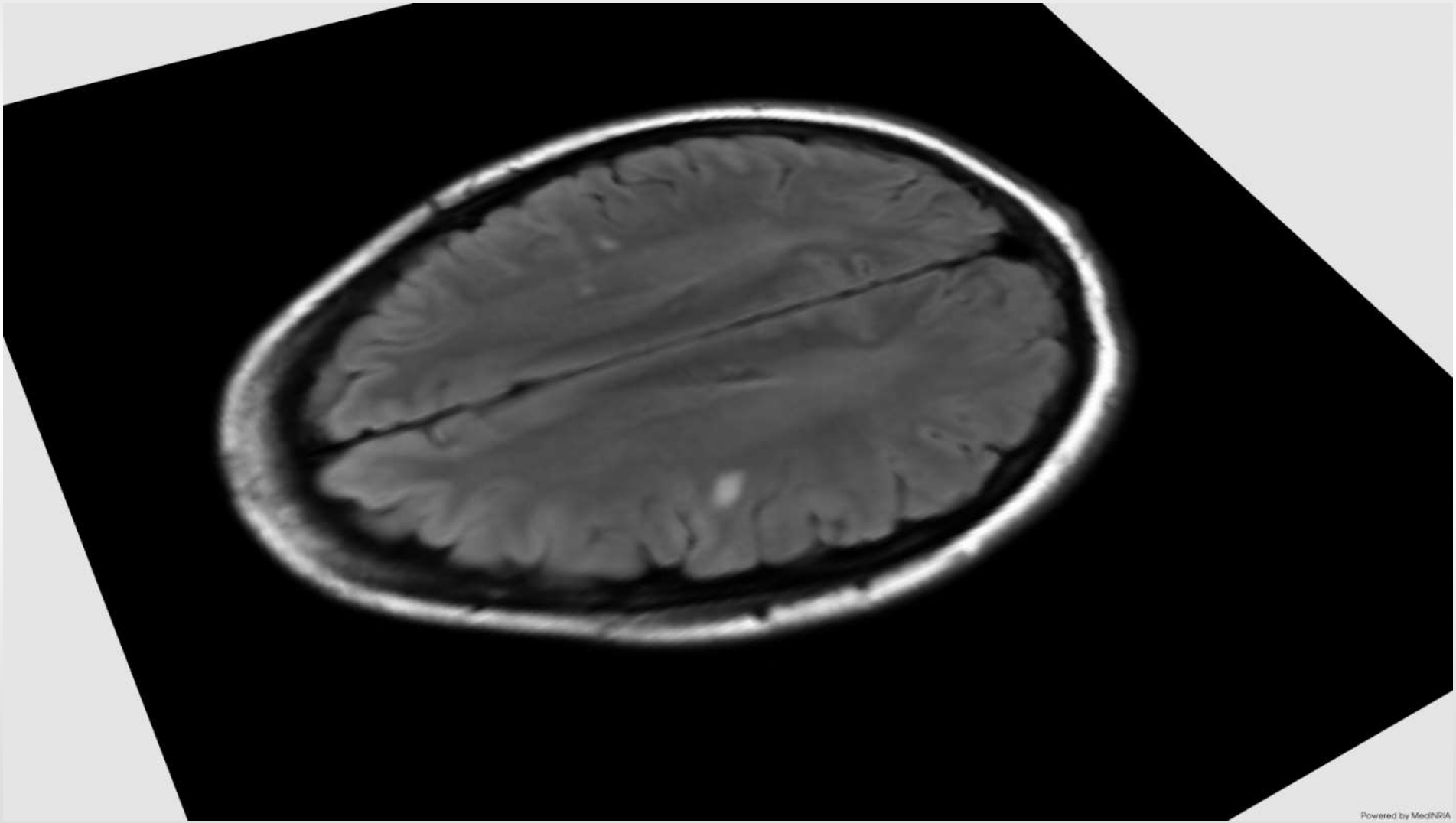
# Case Report (continued)

On neuropsychological testing of cognitive functioning:

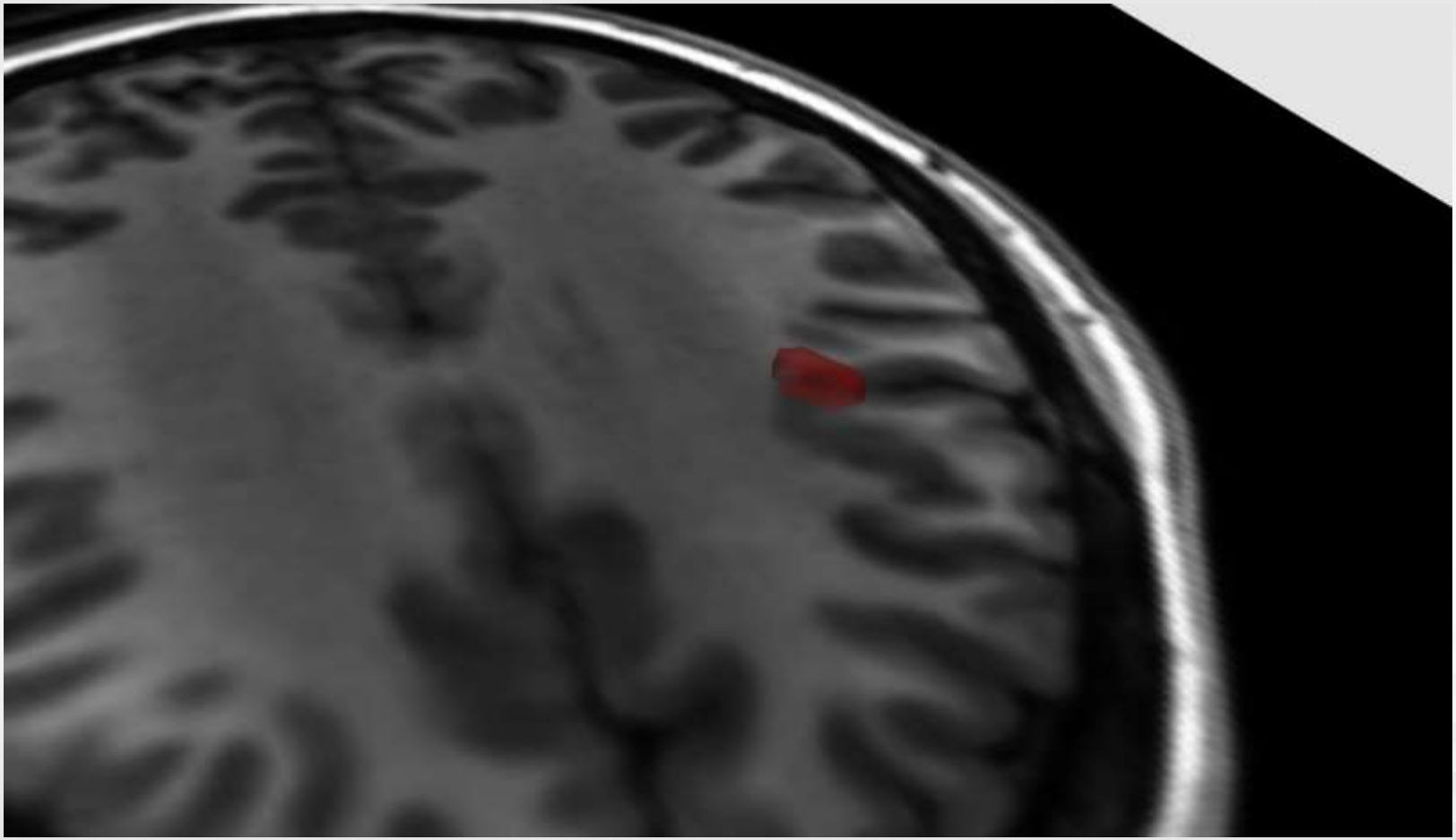
- Inconsistencies were found in
  - Processing speed (low average to average range) and
  - Semantic fluency (severely impaired to low average)
  - Visual memory (discrimination errors)
- Impaired or lower than expected:
  - Phonemic fluency (mildly impaired)
  - Executive functioning (mildly impaired to low average range)

- MRI of brain: Multiple punctate foci of T2 and FLAIR signal abnormality in the bifrontal subcortical and deep white matter, without associated abnormal enhancement or susceptibility. Findings are nonspecific and likely represent sequelae of prior traumatic brain injury.

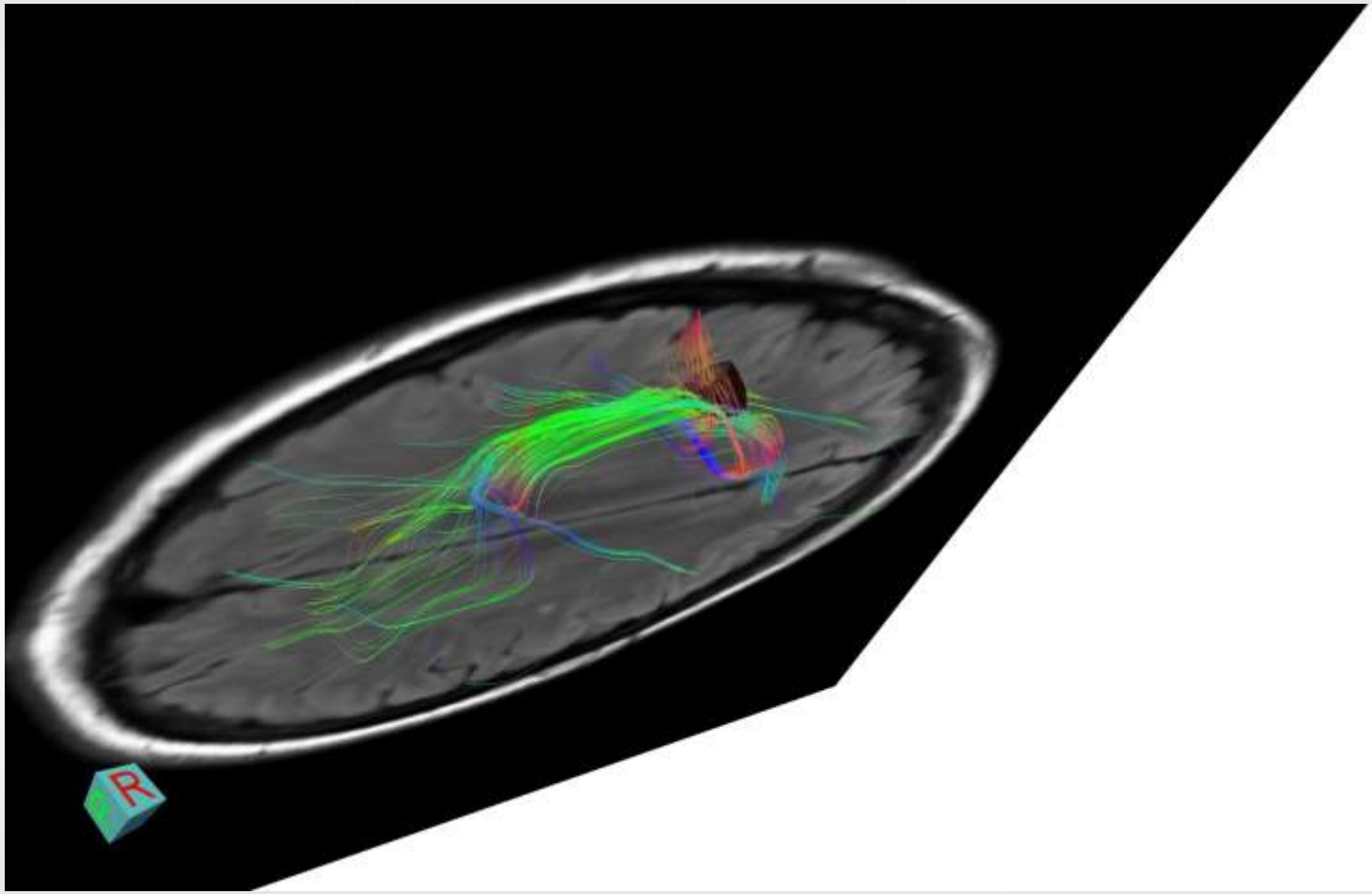
# MRI Scan Showing Non-specific White Matter Changes



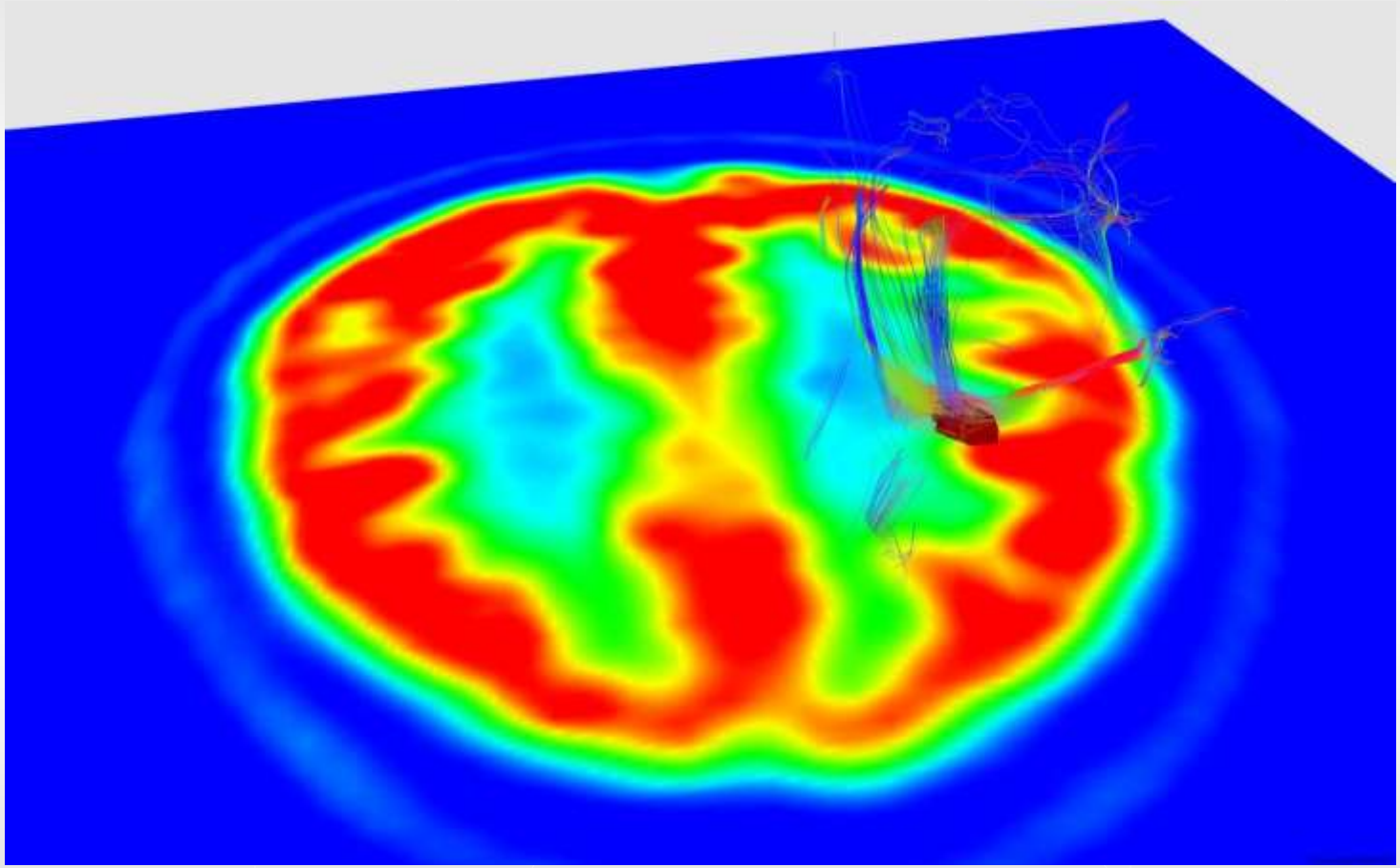
# Customized Fiber Tracking Based on Pathology/Complaint



# Customized Fiber Tracking Based on Pathology/Complaint (cont'd)



# Cross-modality Integration (MRI & PET)



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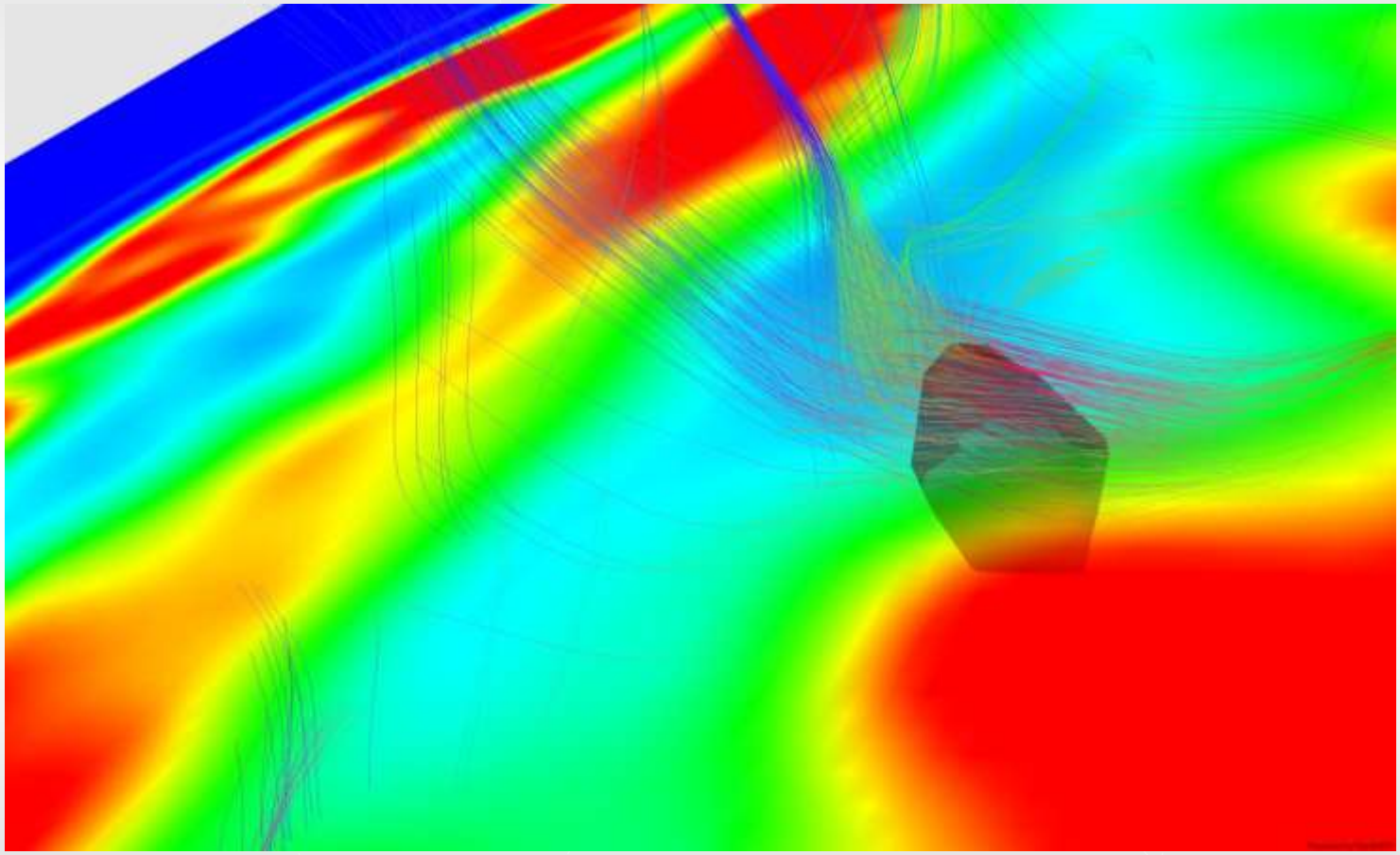
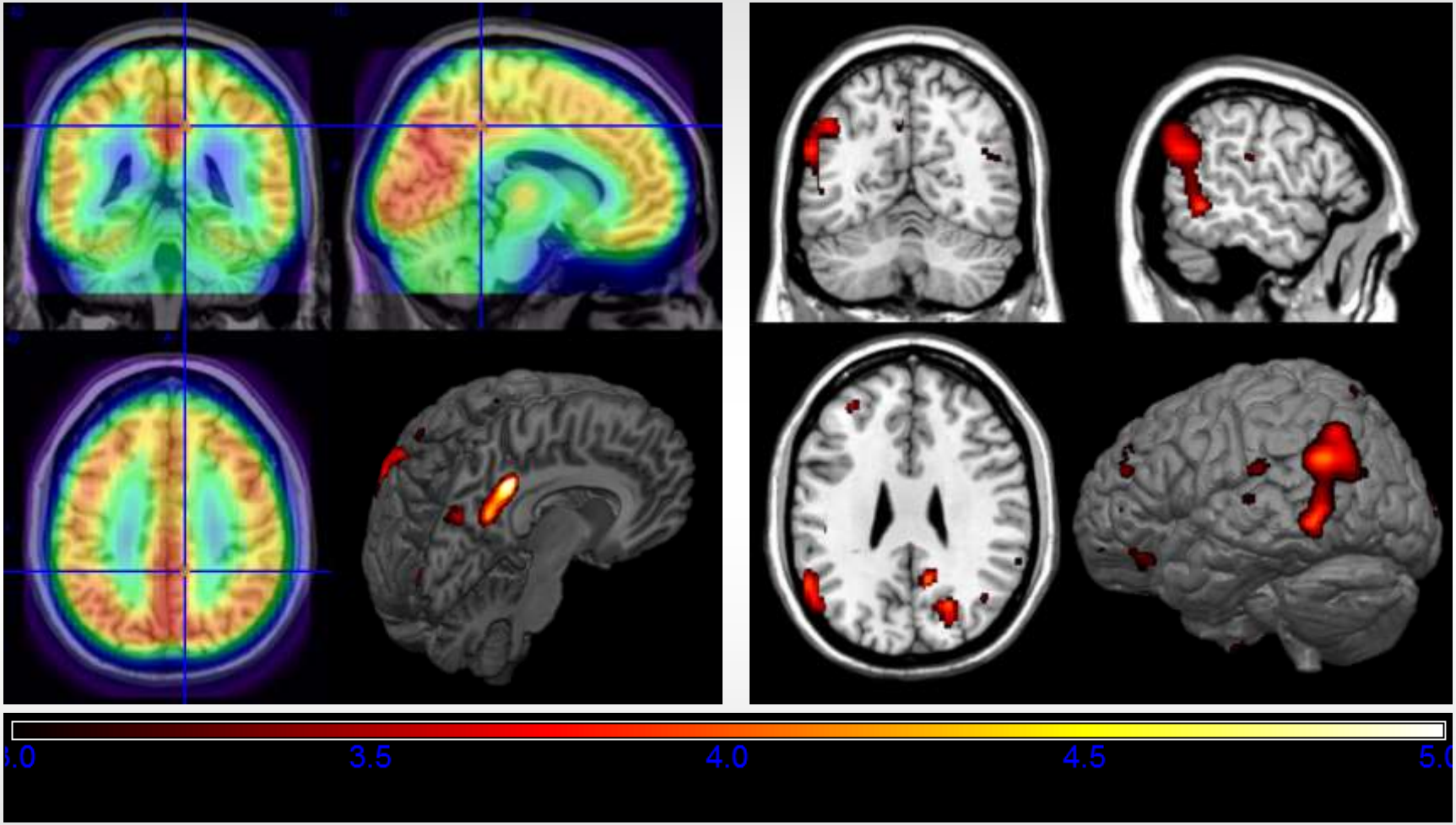


# PET scan in WRIISC Veterans with TBI




Evaluation of WRIISC Veterans (n=50, mean age 46), with history of varying degrees of TBI (mild=27, moderate=5; GW1=15) or not (18; GW1=11) demonstrating areas of hypometabolism in precuneus and angular gyrus when controlling for age, CAPS score.

# Clinical Relevance

- Developing new diagnostic techniques can improve our ability to not only diagnose underlying brain damage but to focus rehabilitation on these areas

# How will this Benefit our Veterans?

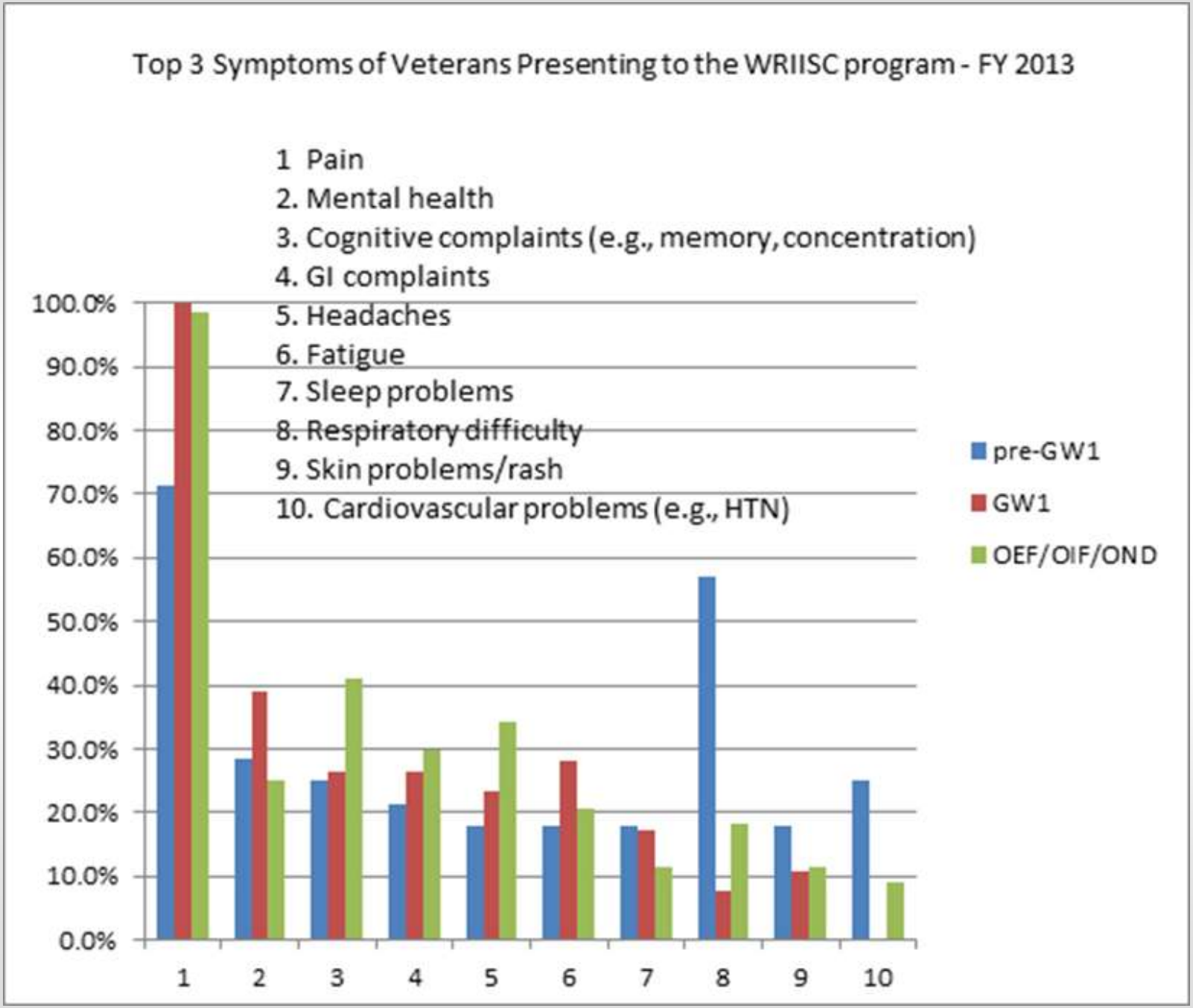
- By better diagnosing mild TBI we can better treat Veterans who have suffered damage
- In addition knowing where the damage has occurred can also help focus rehabilitation programs

# The War Related Illness and Injury Study Center (WRIISC) Palo Alto, CA

A national program in the Department of Veterans Affairs (VA), initially established in 2001 to address post-deployment health issues from the Gulf War.  Palo Alto site established in 2007

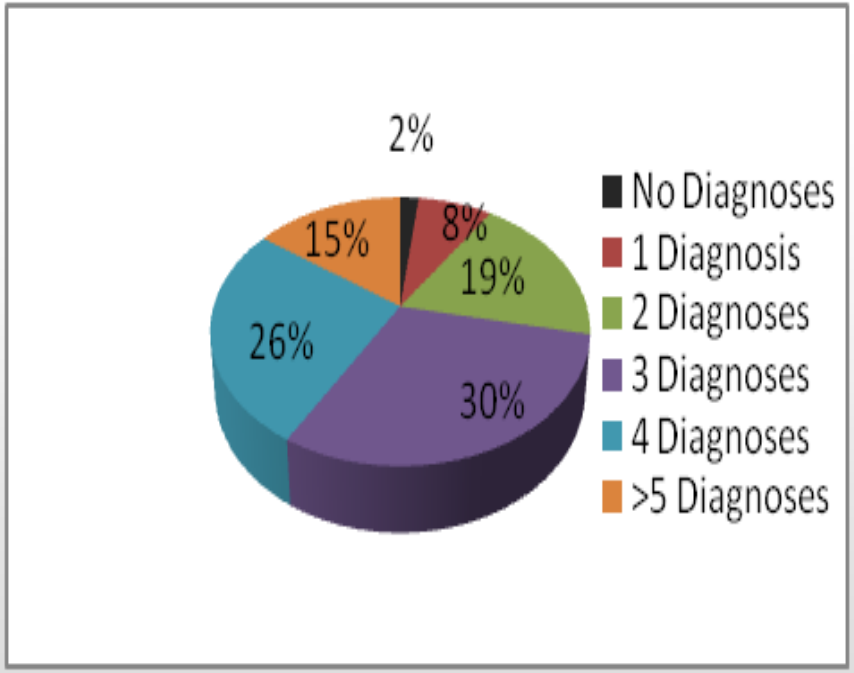
# ABOUT THE WRIISC

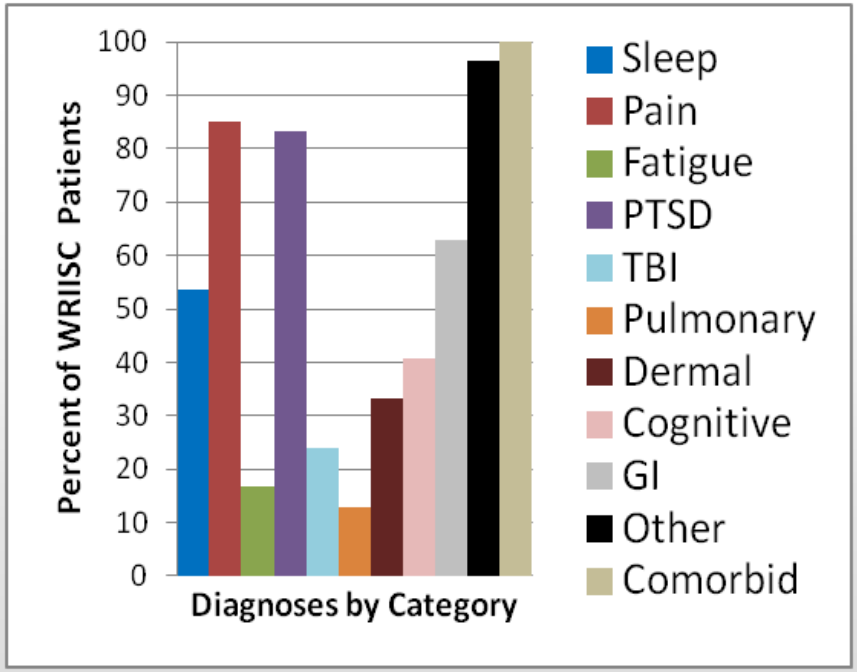
Deployed Veterans have unique healthcare issues and concerns. The WRIISC now serves Veterans from any era or conflict with war related illnesses and injuries through clinical assessments, education, and research.


Top 3 Symptoms of Veterans Presenting to the WRIISC program - FY 2013
1 Pain
2. Mental health
3. Cognitive complaints (e.g., memory, concentration)
4. GI complaints
5. Headaches
6. Fatigue
7. Sleep problems
8. Respiratory difficulty
9. Skin problems/rash
10. Cardiovascular problems (e.g., HTN)
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
1
2
3
4
5
6
7
8
9
10
pre-GW1
GW1
OEF/OIF/OND

# WRIISC-CA

- Since its creation in 2007, WRIISC-CA has evaluated over 200 complex referrals routed through Central Office from most States West of the Mississippi River (and all States West of the Rockies).
- Of these referrals, 42% have been Veterans of the Gulf War.
- The largest single problem in the WRIISC referrals has been PAIN!!



# WRIISC REGIONAL MAP

# REASONS TO REFER

- Complex health history with no known etiology (medically unexplained symptoms—MUS)
- History includes many tests and treatment with little to no symptom improvement
- Possible deployment-related environmental exposures
- Second opinion is not available locally
- Providers frustrated with lack in progress

# THE WRIISC CLINICAL TEAM

- Physicians
- Physician assistants
- Nurses
- Nurse practitioners
- Specialists in environmental exposure assessments
- Psychologists
- Neuroscientists
- Neuropsychologists
- Social workers
- Risk communication specialists
- Health education specialists
- Health care professionals that specialize in Complementary and Alternative Medicine (CAM) such as:
    - Acupuncturists
    - Yoga instructors

# CA WRIISC Team

- J. Wesson Ashford, MD, PhD - WRIISC Director (Psychiatrist)
- Stacy Moeder, MHA, MBA - Administrative Officer
- Sandra Bell, RN, MSN - Nurse, Clinical Coordinator
- Valerie Darcy, RN, BSN - Nurse
- Louise Mahoney, MS - Education & Risk Communication & Yoga
- Maheen Adamson, PhD - Neuroscientist, Research Director
- Ansgar Furst, PhD - Neuroscientist – Neuroimaging
- Peter Bayley, PhD - Psychologist – Memory researcher
- Joseph Cheng, MD, PhD - Neurologist, Neuroscience
- Steven Chao, MD, PhD - Neurologist, Neuroscience
- Ahmad Salehi, MD, PhD - Neuroscientist., PTSD Researcher
- Janet Baldwin, BA - Research Assistant
- Jennifer Kong, BA - Research Assistant
- Jerome Yesavage, MD - ACOS for Mental Health