Neuroimaging in the Assessment of Traumatic Brain Injury (TBI), Mild TBI, and PTSD*

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*A very limited presentation of some examples in the literature
Poll Question #1

• What is your primary role in VA?
  – student, trainee, or fellow
  – clinician
  – researcher
  – manager or policy-maker
  – Other
Poll Question #1

• What is your primary role in VA?
  – student, trainee, or fellow
  – clinician
  – researcher
  – manager or policy-maker
  – Other
Poll Question #2

• Which best describes your research experience?
  – have not done research
  – have collaborated on research
  – have conducted research myself
  – have applied for research funding
  – have led a funded research grant
Poll Question #3

• If you have performed imaging research, what domain did you work in (check all that apply)?
  – Structural
  – Diffusion imaging
  – Functional Imaging (task/resting)
  – CT
  – MRI
  – PET
  – EEG/MEG
  – Other
Poll Question #3

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Scope of the Problem

• Much existing epidemiology is either prior to or does not have information of the full impact of recent conflicts

• Discussion of imaging TBI generally including information from civilian as well as military populations, across a range of severity

• Thurman et al., 1999; Kraus, 1996; Ruff et al., 2009; Centers for Disease Control and Prevention:
  – Annual incidence of ~1.5 million TBIs
  – ~80% considered ‘mild’
  – ~20% moderate to severe
  – ~50,000 die
  – ~230,000 hospitalized
  – ~80,000–90,000 long-term disability

• Large economic burden
What is a ‘Diagnosis’ of TBI?

• Diagnosis and definition of TBI differs clinically and across research studies, but typically based on:
  – Information about the syndrome at time of the event
    • loss of consciousness, retrograde and post-traumatic amnesia, disorientation and confusion (Ruff et al., 2009)
  – Neurological signs: focal signs, seizure, and/or intracranial lesion (e.g., contusion, hematoma, hemorrhage, or edema)
  – Standardized Scales:
    • Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974; Jennett, 1998):
      – Motor, verbal, eye responses
      – <8: severe, 9-12: moderate, 13 to 15: mild
What is the ‘Brain Injury’ in TBI?

- Anterior cortex vulnerable to damage (Adams et al., 1980; Levin et al., 1996)
- Axonal injury due to linear and rotational forces (Buki and Povlishock, 2006; Gennarelli et al., 1982; Meythaler et al., 2001; Povlishock et al., 1992)
- Secondary biochemical, cellular, metabolic, cascades (minutes, days and months) (Giza and Hovda, 2001; Loane and Faden, 2010; Xiong et al., 1997)
Common Moderate/Severe TBI-Associated Pathology

• Contusion: blood vessels damaged by trauma; blood invades surrounding interstitial tissue resulting in necrosis
• Laceration: membranes are torn over the site of injury
• Herniation: mass effect and increase in intracranial pressure (due to above); life-threatening due to pressure of tissue to skull
• Axonal injury/diffuse axonal injury: Damage to fibers in cerebral white matter
• Cerebral swelling: Edema/extra/intracellular fluid accumulation
• Intraventricular hemorrhage: Bleeding into the ventricular system
Concussion and ‘Mild’ TBI

• Concussion: “A complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces.“ (Cantu 2006; McCrory et al., 2013)
• Often used synonymously with mTBI (e.g. Ruff et al., 2009)
• Head injury with temporary loss of ‘brain function’
  – Loss or ‘change’ in consciousness: Amnesia/Glasgow Coma Scale
• Graded depending on:
  – Loss of consciousness: present/absent
  – Duration of changes in mental status post event
• Symptoms typically resolve in weeks
• Absence of gross structural changes on ‘conventional’ imaging is may be diagnostic
  – “Complicated mTBI”: mTBI with abnormal neuroimaging
• Cumulative effect of multiple concussions/long-term consequences (Guskiewicz et al., 2003).
• Potentially linked to secondary consequences including neurodegenerative disease and dementia
TBI Is Heterogeneous

- Type of exposure?
- Force of exposure?
- Direction of exposure?
- Time since exposure?
- Time-course of injury?
Is Military/Combat-Associated TBI Unique?

• Combat-associated blast exposure is highly prevalent (Okie 2005)

• Patients admitted to Walter Reed who have been exposed to a blast evaluated for brain injury:
  – 59% TBI diagnosis
    • 56% moderate or severe TBI
    • 44% mild
Mechanisms of Blast Injury

Taber et al., 2006

• Brain injuries occur:
  – Direct result of blast wave-induced changes in atmospheric pressure (barotrauma/primary blast injury)
  – Objects put in motion by the blast (secondary blast injury)
  – People being forcefully put in motion by the blast (tertiary blast injury)

• Stress and shear waves
Nonpenetrating Injuries

Taber et al., 2006

Figure 2. The most common types of nonpenetrating traumatic brain injury are diffuse axonal injury, contusion, and subdural hemorrhage. The most common locations for diffuse axonal injury (pink) are the corticomedullary (gray matter-white matter) junction (particularly frontotemporal), internal capsule, deep gray matter, upper brainstem, and corpus callosum. The most common locations for contusions (blue) are the superficial gray matter of the inferior, lateral and anterior aspects of the frontal and temporal lobes, with the occipital poles or cerebellum less often involved. The most common locations for subdural hemorrhage (purple) are the frontal and parietal convexities.

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What does clinical imaging contribute?

• Computed tomography (CT) of the head is the study of choice to evaluate TBI (Brown et al., 2004)
• Evaluate need for surgical intervention
• Repeat CT in patients with a neurologic deterioration after TBI for assessment of injury progression (Patel et al., 2000)
• Classification of injury by pathophysiologic mechanisms for targeted by interventions (Saatman et al., 2008)
Classification of Injury by CT

- Most often clinically for first 24 hours after injury
- ‘X-Ray’ imaging
- Edema/infarction: dark
- Calcifications, hemorrhage, bone trauma: bright
- Pros:
  - Available, cost effective, short imaging times, can be performed with life support hardware, implants, sharpnel, etc.
  - Most appropriate for determining immediate medical needs
- Cons:
  - Reduced resolution
  - Limited contrast/information
  - Ionizing radiation (considered moderate to high)
- Lack of imaging findings on CT may be used to classify ‘mild’ TBI
- CT findings may not be correlated with outcome

Epidural hematomas (EDH), contusions and parenchymal hematomas (Contusion/Hematoma), diffuse axonal injury (DAI), subdural hematoma (SDH), subarachnoid hemorrhage and intraventricular hemorrhage (SAH/IVH), and diffuse brain swelling (Diffuse Swelling): From Saatman, et al, J Neurotrauma, 2008
Clinical Imaging: MRI

- Edema: bright on T2/FLAIR MRI
- Hemorrhage: time-course from bright to dark to bright again
- Microhemorrhage: gradient echo MRI
What can research neuroimaging contribute?

• A range of imaging procedures exist that may not be practical for routine clinical assessment, but may provide valuable information for:
  – Future diagnostics
  – Tracking injury progression
  – Tracking novel therapeutic interventions
  – Understanding mechanisms of injury
• Different imaging modalities that vary in spatial and temporal resolution and contrast mechanisms
• Research imaging procedures may target specific aspects of brain tissue structure, function, physiology or chemistry
• Various ways to process and analyze data
  – ‘Group’-based comparisons to control populations
  – Association between imaging findings and neuropsychological and clinical scales
• Particular application to mTBI where conventional imaging findings are limited
• Significant effort, yet limited consistent information about mTBI based on imaging
• Present *procedures and trends* as opposed to detailed information about work to date
Research Imaging

‘Structural’
- Structural/Morphometry (T1-MRI)
  - Volume, thickness, curvature etc.
- ‘Lesion’ or abnormal tissue (e.g. edema) (T2/FLAIR-MRI)
- ‘Microstructural’
  - Diffusion tensor imaging (DTI)
  - Magnetization transfer imaging (MTI)
  - Relaxometry
- Receptor/protein densities (Positron Emission Tomography; PET radioligands)
- ‘Susceptibility’ weighted imaging: Hemorrhage/axonal injury

‘Functional’
- Brain ‘activity’
  - Functional magnetic resonance imaging (fMRI)
  - Electroencephalography
  - Magnetoencephalography
  - PET
    - Glucose metabolism
    - CMRO2
- Magnetic resonance spectroscopy (MRS)
- Cerebral blood flow
  - Arterial spin labeling (ASL)
  - PET
Recent mTBI Publication Expansion

Eierud et al., 2014

Fig. 1. mTBI publications between 1990 and 2011: The levels of mTBI studies have been increasing over the past two decades and the focus on neuroimaging has increased proportionately with the field as a whole. (A) The histogram shows 1314 mTBI articles published from 1990 to 2011. (B) Focuses on the 122 imaging-based studies, and provides a graphical breakdown of what imaging modalities were used. To date the predominant imaging modalities have been CT and MRI.
Diffusion Weighted/Tensor Imaging (DWI/DTI)

- Magnetic Resonance Imaging (MRI) procedure
- Quantification of diffusion of molecules (water) in tissue
- Water diffusion in tissue is influenced by macromolecules, membranes, tends to follow fibers
- Diffusion measures can modeled to provide information about tissue ‘microstructural’ properties
- Extensions of DWI such as DTI provide information that can be used to model the anatomy of large fiber bundles
- Different ways of modeling the diffusion data providing different types of ‘contrast’ linked to tissue properties
  - ‘Axial’ versus ‘radial’ diffusivity
- In vivo and non-invasive
- Thought to be potentially sensitive to diffuse axonal injury
- See Le Bihan and Johansen-Berg 2012 for recent review
Diffusion ‘Maps’

Microstructure: Fractional Anisotropy

Anatomy: Tensormap
Example: DTI in mTBI

Lipton et al., 2009

- DTI and neuropsychologic assessment in 20 patients with mTBI within 2 weeks of injury
- mTBI due to motor vehicle accidents or falls and were evaluated to rule out conventional brain injury
- Whole brain analysis of DTI parameters
- Clusters of lower frontal white matter FA/higher MD
- Lower dorsolateral prefrontal FA correlated with worse executive function
Example: Blast mTBI

Levin et al., 2010

- 37 veterans/service members
- Post-injury interval 871.5 days
- Mild to moderate blast TBI
- Standard ‘region-of-interest’ and ‘voxel-based’ analysis showed no group difference
- Regional diffusion measures associated with total words consistently recalled
- Correlations of DTI variables with symptom measures were nonsignificant and inconsistent.
Meta-analysis of Diffusion Findings

Eierud et al., 2014

Anisotropy Abnormalities and ROI Spatialities

Studies with significant mTBI abnormalities
Complicated Diffusion Timecourse?

- Anisotropy is increased in the acute phase and decreased in the chronic phase in symptomatic TBI (Niogi and Mukherjee, 2010)
- Animal models demonstrate changes in diffusion signal hours to weeks or longer after injury (e.g. Assaf et al., 1997; Albensi et al., 2000)
Functional MRI (fMRI)

- Used to measure brain ‘activity’
- Contrast based on blood oxygenation
- Signal can be measured in response to cognitive or behavioral stimuli ‘hemodynamic response’
- In the ‘resting’ state

Riecker et al., 2003
Example: fMRI/DTI in Blast mTBI

Matthews et al., 2007

- 11 MDD and 11 non-MDD
- Emotional face matching fMRI task
- DTI
- MDD had greater amygdala activity during fear matching trials
- lower activity during fear matching trials in emotional control structures (DLPFC)
- Lower diffusion measures in SLF
- Depressive symptom severity associated with SLF integrity
Meta-analysis of fMRI Findings

Eierud et al., 2014

- ‘Anterior-to-posterior’ pattern: reduced in anterior regions and increased in posterior regions
- Six regions consistently more active in mTBI
  - MFG, ACC, and right precentral gyrus
- Seven regions with lower activity in mTBI
  - Cerebellum/insula/parietal (BA 40)
Positron Emission Tomography (PET)

- Nuclear medicine technique
- Detection of gamma rays emitted by a positron-emitting radionuclide
- Radionucleotide (PET ligand) is a biologically active molecule injected into the body (invasive)
- Can be used to measure receptor concentrations, metabolic activity (FDG), blood flow, inflammation (diverse contrast)

- MGH Radiology Rounds:
Example: PET/FDG in mTBI

Peskind et al., 2011

- 12 Iraq war Veterans
- one or more blast exposures
- Diagnosis of mTBI and persistent PCS
- 12 cognitively normal community volunteers without head trauma
- FDG PET tomography (FDG-PET)
- Neuropsychological/clinical assessment
- mTBI had decreased cerebral metabolic rate of glucose in the cerebellum, vermis, pons, and medial temporal lobe
TRACTS

• ‘Translational Research Center for TBI and Stress Disorders’
• A Rehabilitation Research and Development Center of Excellence, Director: McGlinchey
• Goal: Understand the complex changes in the brain, thinking, and psychological well-being that result from TBI and PTSD
• Veterans from Operation Enduring Freedom, Operation Iraqi Freedom (OEF/OIF)
Morphometry: Cortical Thickness
Example: Cortical Thickness, PTSD, and mTBI

Lindemer et al., 2013

- 104 OEF/OIF veterans
- PTSD symptoms assessed: Clinician Administered PTSD Scale (CAPS): previous month (“current”)
- Cumulative Lifetime Burden of PTSD/integration of lifetime CAPS scores
- Mild TBI: Boston Assessment of TBI-Lifetime (BAT-L)
- Negative relationship between current PTSD severity and thickness
- Stronger association when lifetime burden was considered
- Stronger regional associations in individuals with mTBI
- Various factors (e.g. lifetime stress; mTBI) interact and demonstrate need for extremely well matched groups or very large cohorts
But TBI Is Heterogeneous

- Type of exposure?
- Force of exposure?
- Direction of exposure?
- Time since exposure?
- Time-course of injury?
Imaging Groups or Individuals?

Davenport et al., 2012

- American military service members with (n=25) or without (n=33) blast-related mTBI
- Individuals with more than one blast mTBI had greater number of low FA voxels than individuals with a single blast injury
- Effects were not apparent when using ‘region of interest’ procedure
- Blast mTBI is associated with disrupted integrity of several white matter tracts
- Findings are diluted by averaging across the large number of voxels within an ROI
- Neurological effects of blast mTBI are diffuse, widespread, and spatially variable
Caveats to Neuroimaging TBI

- Who are the study participants?
  - Premorbid conditions?
    - Prior psychological or physical trauma?
    - Medical comorbidities?
    - Drug and alcohol use?
- What type of TBI?
  - Blast?
  - Blunt?
  - Mild, moderate, severe?
- How was the TBI diagnosed?
  - GCS?
  - +/- Imaging?
- Time since injury?
  - Acute?
  - Chronic?
- Mechanism of injury?
  - Primary?
  - Secondary?
  - Interaction with comorbidities/genetics?
- Any given finding in neuroimaging may be limited to a very specific population and not generalizable to overall TBI
- Imaging techniques are indirect
- The mechanistic basis of any imaging finding can be complex
- Imaging procedures can be influenced by various technical limitations resulting in artifactual results
- Many tests are performed with imaging data increasing the likelihood of statistical error
- Small participant samples can lead to spurious results
Conclusions

• Eierud et al., 2014

4. Discussion

An obvious key limitation of this paper (and any review that attempts to report a snapshot of a vibrant field) is that components of it are immediately outdated. Although we believe that the conclusions we draw here will be qualitatively accurate for the next few years, the literature we sampled just barely supported any meaningful fMRI meta-analyses, and the issue of the anisotropy values’ dependence on time post-injury is far from conclusive. Part of what we have hoped to accomplish here is an assessment of the modalities, questions, and times post-injury that recent publications have examined. Based on this we hope that research teams can use this to strategically bolster areas of this field that would most benefit from additional effort. We are optimistic that we and/or others will improve our literature analysis approaches in the future to continue what has the potential to become an ongoing, reflective process.
Conclusions

- Neuroimaging provides a window into brain pathology
- Procedures facilitate measurement of brain structure, function, tissue integrity, metabolism, chemistry and other aspects of physiology
- Potential to uncover mechanisms of TBI-associated cognitive, behavioral, and psychiatric conditions
- Advances in novel acquisition and analysis procedures, participant characterization, and multimodal image integration will be necessary
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Questions?

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References/Suggested Reading 1

References/Suggested Reading 2

References/Suggested Reading 3


