



TRAUMATIC BRAIN INJURY A NEUROPSYCHIATRIC PERSPECTIVE

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Disclosures

“Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.”

INCIDENCE

- TBI is common
 - Annual incidence 1.7 million in the US
 - 2.5-6 million live with chronic consequences of TBI
 - In 2013, there were about 2.8 million TBI-related emergency department (ED) visits, hospitalizations, and deaths in the United States
 - 56,000 TBI-related deaths
 - TBI was diagnosed in 2.5 million ED visits and 282,000 hospitalizations
- TBI leads to frequent long-term disability
 - 10-20% of mild TBI
 - 66% of moderate TBI
 - 100% of severe TBI

RISK FACTORS

- Highest risk for TBI in 15-24 y/o
- Alcohol abuse
- Motor vehicle accidents – half of TBI
- Falls – 21% - highest among 0-4 y/o and >75 y/o
- Assaults and violence – 20%
- Sports and recreation – 3%

RISK FACTORS

- Among TBI-related deaths in 2013:
 - Highest risk for TBI in 75+ y/o
 - Leading cause of TBI-related deaths by age:
 - 65+: Falls
 - 25-64: Intentional self-harm
 - 5-24: Motor vehicle crashes
 - 0-4: Assaults
- Among non-fatal TBI injuries in 2013:
 - Hospitalization rates highest in 75+ y/o
 - ED visits highest in 75+ y/o and 0-4 y/o
 - Falls are leading cause of TBI-related ED visits in all groups except
 - In 15-24 year olds, being struck by or against an object is leading cause
 - Leading cause of TBI-related hospitalizations by age:
 - 0-14 and 45+: Falls
 - 15-44: Motor vehicle crashes

Center for Disease Control (2017, April 27). "TBI: Get the Facts."

Taylor CA, Bell JM, Breiding MJ, Xu L (2017). "Traumatic Brain Injury–Related Emergency Department Visits, Hospitalizations, and Deaths — United States, 2007 and 2013."



CONSEQUENCES

- Risk of death
 - Seven times that of the general population in the first year after injury
 - 5.3 times that of the general population over the first 7 years after injury
- Conditions that promote a shorter lifespan
 - Seizures
 - Sepsis
 - Digestive conditions
 - Pneumonia
 - Other respiratory conditions
 - External causes and unintentional injury

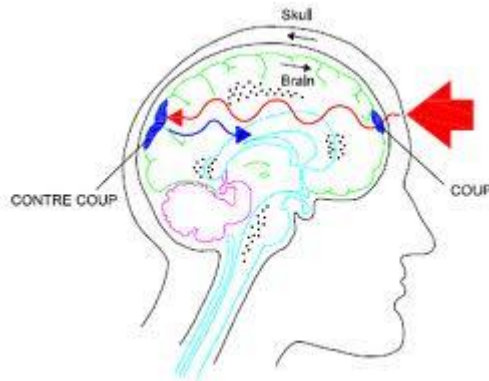
CONSEQUENCES

- Moderate TBI patients interviewed 3-5 years post injury (n=79) (1)
 - 74% of patients worked full time
 - The majority struggled with cognitive and functional limitations
- Moderate-severe TBI patients interviewed up to 10 years post injury (n=141) (2)
 - 70% returned to driving
 - 60% reported changes in cognitive, communication, behavioral, and emotional functions
 - 30% reported difficulties in personal relationships
 - 40% required more support than before injury
 - Of those studying or employed prior to injury
 - 53% studying or employed at 2 years
 - 50% at 5 years
 - 50% at 10 years
 - Overall, problems evident at 2 years post injury persisted until 10 years post injury
- Moderate-severe TBI patients interviewed up to 24 years post injury (n=306) (3)
 - 29% of them had returned to full time employment
 - Patients continued to experience limitations in activities such as managing money and shopping

PATHOPHYSIOLOGY

- Primary mechanisms
 - Contusions
 - Diffuse axonal injury
 - Hematomas
 - Epidural
 - Subdural
 - Intracerebral
- Some mechanisms of secondary injury
 - Cerebral edema
 - Hydrocephalus
 - Increased intracranial pressure
 - Infection
 - Hypoxia
 - Neurotoxicity
 - Inflammatory response
 - Protease activation
 - Caspase activation - apoptosis
 - Calcium influx
 - Excitotoxins
 - Free radical release
 - Nitric oxide

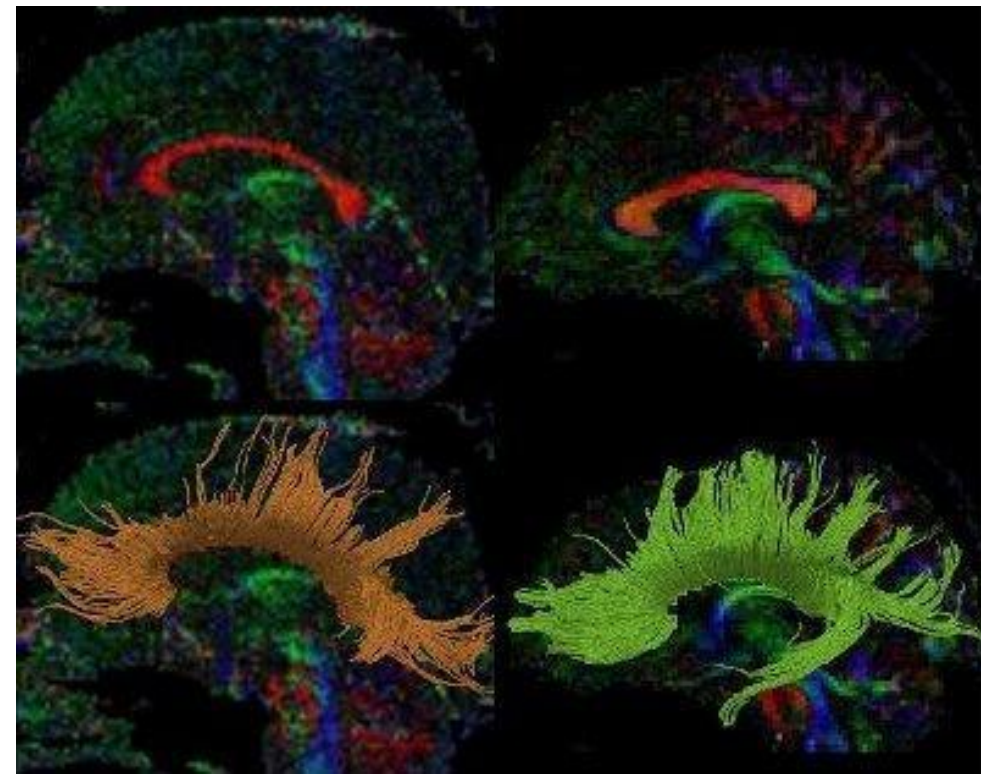
MECHANISMS OF PRIMARY INJURY



- Sudden acceleration of the head creates physical forces acting on the brain within the enclosed and rigid space of the skull
- Compressive strain – when the brain is compressed against the skull close to the impact (coup)
- Tensile strain – when brain tissue is stretched on the side opposite to the impact (contre-coup)
- Shearing strain – when brain tissues slide against one another (e.g., gray against white matter)



MECHANISMS OF PRIMARY INJURY



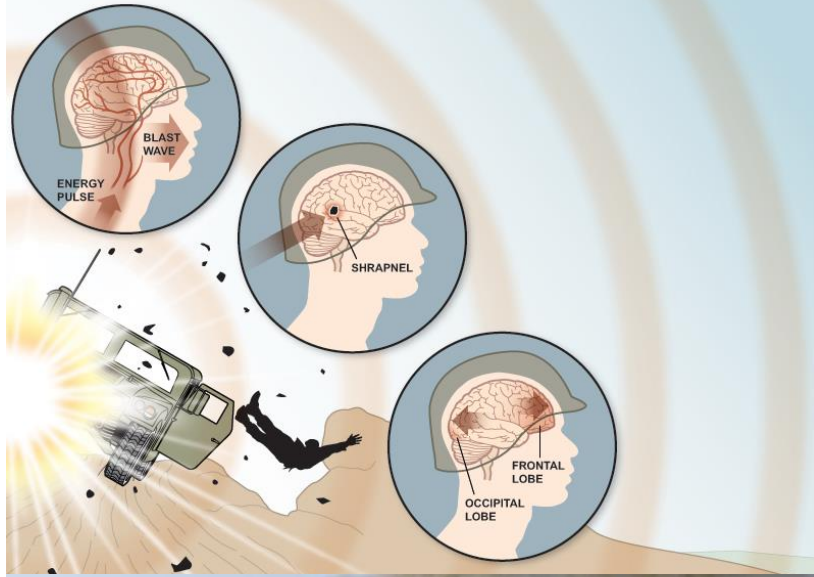
- Thinning of the corpus callosum in TBI (top left)
- Healthy Control (top right)
- 3D reconstruction of the CC in TBI (bottom left) showing fewer fiber bundles
- Healthy Control (bottom right)

- Diffuse axonal injury
 - In accidents when there is twisting and turning of the brain around the brain stem
 - Most vulnerable sites
 - Reticular formation
 - Superior cerebellar peduncles
 - Basal ganglia
 - Hypothalamus
 - Limbic fornices
 - Corpus callosum
- Contusions and hematomas
 - From the movement of the brain against the hard and ridged internal bony surfaces
 - External or internal to the brain surface
 - Bony prominences along the base of the skull – orbital, frontal, temporal

MECHANISMS OF SECONDARY INJURY

- **Biochemical injury**
 - Disruption of the blood brain barrier and disruption of nerve cells => massive releases of neurotransmitters and free radicals
 - Excitatory amino acids act as cytotoxins => thousands of nearby cells depolarize, swell, lyse and die
 - Lysed cells release more cytotoxins => cascade of auto destructive events => progressive cell death
 - Glutamate, esp. NMDA receptors, play a major role
 - Hippocampal formation especially vulnerable to injury with or without actual neuronal death
- **Inflammatory mechanisms may contribute to the enlargement of the initial injury over days to weeks since the initial physical trauma**
 - Cellular cultures and in vivo rat brain experiments – activated macrophages and microglia in evolving brain injury
- **Nitric oxide**
 - Dilates blood vessels
 - Acts as chemototoxin in inflammatory processes
 - Damages DNA directly
 - Inhibits DNA synthesis
 - Inhibits mitochondrial respiration
- **Mitochondrial dysfunction**
 - Decreased ATP production
 - Mitochondrial swelling and membrane rupture => cell death

MECHANISMS IN BLAST INJURIES



- Shock waves cause greatest injury at air-tissue interface such as
 - Lungs (alveolae)
 - Intestines
 - Tympanic membrane
- Brain effects of blast injuries
 - Purkinje neurons of the cerebellum
 - Pyramidal neurons of the hippocampus



MECHANISMS IN BLAST INJURIES

- Primary and secondary mechanisms
 - Primary – injury caused by blast wave itself
 - Secondary – injury by flying objects or the body striking objects
- Brain – 3 possible mechanisms
 - Acceleration mechanism - Translational and/or rotational accelerations of the brain caused by exposure to a blast wave
 - Direct cranial entry - A pressure transient traverses the skull and directly injures brain tissue.
 - Thoracic mechanism - Some combination of a pressure transient reaching the brain via the thorax and a vagally mediated reflex result in bTBI
 - Hypothesis: blast wave => pressure on thorax => volumetric blood surge => increase in intracranial pressure => damage to BBB and capillaries in the brain
 - Hypothesis: Propagation of pressure waves from thorax to brain, perhaps via the soft tissues or vasculature more specifically. Pressure waves travel near the speed of sound.

DEFINITIONS OF MTBI

Diagnostic criteria for Mild TBI by the ACRM Special Interest Group on Mild TBI (1993) (1):

- A traumatically induced physiological disruption of brain function, as manifested by *at least one* of the following:
 - Any loss of consciousness
 - Any loss of memory for events immediately before or after the accident
 - Any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused) and
 - Focal neurologic deficit(s) that may or may not be transient
- But where the severity of the injury does not exceed the following:
 - Loss of consciousness of approximately 30 min or less
 - After 30 min., an initial Glasgow Coma Scale score of 13-15 and
 - Post-traumatic amnesia not greater than 24 hours

WHO definition (2004) of mTBI and operational criteria (2):

- Acute brain injury resulting from mechanical energy to the head from external physical forces
- One or more of the following:
 - Confusion or disorientation
 - Loss of consciousness for 30 minutes or less
 - Post-traumatic amnesia for less than 24 hours, and/or
 - Other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery
 - Glasgow Coma Scale score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare
- These manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury

(1) Developed by the Mild TBI Committee of the Head Injury Interdisciplinary Special Interest Group (1993);

(2) Adapted from Ruff R, 2008

DETERMINING TBI SEVERITY

- Mild – at least one of the following:
 - GCS 13-15
 - LOC 0-30 min
 - AOC momentary up to 24 hours
 - PTA 0-1 day
 - Normal imaging
- Moderate
 - GCS 9-12
 - LOC > 30 min and ≤ 24 hours
 - AOC > 24 hours (severity based on other factors)
 - PTA >1 and <7 days
 - Normal or abnormal imaging
- Severe
 - GCS < 9
 - LOC or PTA for 1 week or longer
 - LOC > 24 hours
 - AOC > 24 hours (severity based on other factors)
 - PTA >7 days
 - Normal or abnormal imaging

Veterans Health Initiative, Employee Education System, Department of Veterans Affairs.
DoD/VA Definition and Symptomatic Taxonomy Working Group Definition

GLASGOW COMA SCALE (GCS)

- Eye opening
 - None – 1
 - To pain – 2
 - To speech -3
 - Spontaneous – 4
- Motor response
 - No response -1
 - Extension – 2
 - Abnormal flexion – 3
 - Withdrawal – 4
 - Localizes pain – 5
 - Obeys commands – 6
- Verbal response
 - No response - 1
 - Incomprehensible – 2
 - Inappropriate -3
 - Confused – 4
 - Oriented - 5

POSTCONCUSSIVE SYNDROME

- Term usually used after mild TBI
- Clinical symptoms
 - Somatic symptoms
 - Headache
 - Dizziness
 - Fatigue
 - Insomnia
 - Cognitive symptoms
 - Memory difficulties
 - Impaired concentration
 - Perceptual symptoms
 - Tinnitus
 - Sensitivity to noise
 - Sensitivity to light
 - Emotional symptoms
 - Depression
 - Anxiety
 - Irritability

POSTCONCUSSIVE SYNDROME

- Time course
 - Most patients recover at 1-6 months post-injury
 - However, up to 44% of individuals report three or more symptoms 1 year following injury (2)
 - Some continue with significant complaints (1)
 - 16-49% with persistent symptoms at 6 months
 - 1-50% with persistent symptoms at 1 year
 - Professional athletes have the same symptoms as work-injured individuals

(1) Bohnen N, 1992; (2) Zgaljardic DJ, 2014

POSTCONCUSSIVE SYNDROME

- Low specificity – PCS happens in:
 - Healthy adults
 - Chronic pain patients
 - Spinal cord injury patients
 - Non-TBI trauma patients
 - Psychological distress patients
 - Orthopedic injury patients
- Low specificity makes misdiagnosis possible
- Attribution of PCS to TBI is difficult

POSTCONCUSSIVE SYNDROME

- Predictors of PCS symptoms > 3 months post-mTBI
 - mTBI does not predict PCS
 - Emotion-focused coping ⇔ increased symptom reporting
 - Problem-focused coping ⇔ decreased symptom reporting
 - Premorbid psychiatric history
 - Pre-injury neuroticism, depression, anxiety
 - Pain
 - Anxiety sensitivity - belief that sensations are signs of impending harmful consequences
 - Cognitive misattribution and “the good old times” effect
 - Individuals who had TBI reported 60% fewer symptoms pre-injury compared to healthy controls
 - Athletes underestimated their per-concussion symptoms by 97% compared to healthy controls
 - Of 30 symptoms in survey, only headache was reported more frequently by concussed athletes

PERSISTENT PCS

- **Methods**
 - Retrospective review of medical charts, questionnaire regarding recovery mailed
 - 141 of 285 patients diagnosed with concussion responded; 110 included
 - Excluded: PCS lasting < 3 months; MRI or CT abnormalities; Litigation; Known TOMM-positive cases
- **Results**
 - 30 recovered, 80 non-recovered included in analyses
 - 27% (n=30) recovered, 67% of whom within the first year
 - No one whose symptoms lasted > 3 years recovered
 - Non-recovered (n=80) more non-compliant with do-not-return-to-play recommendation (p=0.006)
 - Non-recovered group perceived higher impact of concussion on their life (p=0.001)
 - Non-recovered group perceived higher depression after concussion (p=0.015)
 - No between-group differences in demographic variables such as age or sex
 - No between-group differences in ADD/ADHD before or after concussion
 - The more symptoms, the longer time to recovery
 - Each additional symptom reduced the recovery rate by ~ 20%
- **Conclusions**
 - PCS may be permanent if recovery has not occurred by 3 years
 - Each additional PCS symptom reduces recovery rate by 20%
 - More long-term follow-up studies are needed to examine recovery from PCS

POSTCONCUSSIVE SYNDROME

- Treatment principles
 - Education and reassurance
 - Exercise and return to activities
 - Rest may not be “the best medicine” after a concussion
 - Regular exercise may be protective against anxiety and depression
 - Graded exercise protocols under the supervision of an athletic trainer or other healthcare provider may also provide an in vivo method for anxiety desensitization
 - Vigorous exercise within 2 weeks may result in additional symptoms
 - Return to competitive sports within 1 week after concussion may result in additional concussions

AGGRESSION AFTER TBI

- Prevalence
 - 35-96% in the acute recovery period
 - In rehabilitation
 - 11-70% with agitation (7)
 - 25-39% with aggression (7)
 - Years post-injury (2,3)
 - 5-70% after mild TBI
 - 31-71% after severe TBI
- Associations
 - Depression (4, 5,7)
 - H/o substance abuse (6)
 - Orbito-frontal lesions (6,7)
 - Older males (7)
 - Poor premorbid functioning (6)
 - Language Disorders (7)
 - In noisy environments (7)
 - Within 24 hours following a seizure (7)
- Characteristics of violence after TBI
 - Reactive
 - Nonreflective
 - Nonpurposeful
 - Periodic – brief outbursts of aggression
 - Ego-dystonic
 - Explosive, without buildup

(1) Brooke MM, 1992; (2) Bogner and Corrigan, 1995; (3) Silver and Yudofsky, 1994; (4) Rao V, 2009; (5) Baguley IJ, 2006; (6) Tateno A, 2003; (7) Stefan A, 2016

AGGRESSION AFTER TBI

- Pharmacotherapy of acute aggression
 - Antipsychotics
 - Short term
 - Likely act through sedative effect
 - Possible negative effects on TBI
 - May increase length of PTA (5)
 - Benzodiazepines
 - Lorazepam 1-2mg PO/IM q 1 hour
- Pharmacotherapy of chronic aggression
 - Antipsychotics – some evidence that they may impede recovery. Newer antipsychotics preferred (1, 5).
 - Anticonvulsants – Valproate and Carbamazepine (1,2,4, 5)
 - Lithium – could be effective but possible neurotoxicity in TBI (1)
 - Buspirone may be effective (1)
 - Antidepressants – mixed results. Possible seizures with TCA's (1)
 - Beta-blockers (1, 5)
 - Propranolol – lipid soluble, nonselective – up to 520mg/day
 - Pindolol – lipid soluble, nonselective, with partial sympathomimetic activity – up to 100mg/day
 - Good when bradycardia is an issue
 - Amantadine – variable effects (1, 3, 5)
 - Methylphenidate (1, 5)

(1) Chew E, Zafonte RD, 2009; (2) Chatham-Showalter PE, 1996; (3) Hammond FM, 2014;
(4) Plantier D, 2016; (5) Williamson D et al, 2019



PERSONALITY CHANGE AFTER TBI

- 50-80% prevalence
- Abrupt onset, lasting for years
- Personality change due to TBI
 - Labile type
 - Disinhibited type
 - Aggressive type
 - Apathetic type
 - Paranoid type
 - Other type
 - Combined type
 - Unspecified type

MOOD DISORDERS

- MDD
 - Incidence 15.3-33% (1)
 - Prevalence 11.1-61% (2, 3, 4)
- Dysthymia – prevalence 5.5-14% (5)
- Minor depression (2-4 symptoms X 2 weeks) – 22% (7)
- Mania
 - Incidence 9.1%
 - Prevalence 0.83-22.2% (1)
- Depression associated with (6, 8)
 - Anxiety (77%)
 - Aggressive behavior (57%)
 - Fatigue (29%)
 - Distractibility (28%)
 - Anger or irritability (28%)
 - Rumination (25%)
- Predictors of MDD in TBI
 - Systematic review and meta-analysis (9)
 - Female gender
 - Preinjury depression
 - Postinjury unemployment
 - Lower brain volume

(1) Kim E, 2007; (2) Hibbard MR, 1998; (3) Fann JR, 1995; (4) Hart T, 2011; (5) Silver JM, 2001; (6) Jorge RE, 2004; (7) Hart T, 2011; (8) Seel RT, 2003; (9) Cnossen MC et al, 2017

MOOD DISORDERS TREATMENT

- Antidepressants
 - Choice based on SE profile
 - SSRI's first line
 - Caution for anticholinergic SE
 - Caution for apathy in SSRI's
 - Bupropion – seizures, dysphoria
 - TCA's – seizures up to 19%
- ECT can be effective (1,2)

(1) Kant R, 1999; (2) Ruedrich SL, 1983

MOOD DISORDERS MEDICATION TREATMENTS

- Most data come from open label studies and case series.
 - Single-blind placebo run-in design of Sertraline in 15 patients with MDD after TBI (1)
 - Remission (HAM-D) in 2/3 of patients
 - Cognitive improvement observed
 - Fluoxetine and sertraline, in addition to their antidepressant effects, led to improvements in attention, psychomotor speed, memory and other neuropsychological functions (3, 4)
 - Tricyclic antidepressants, sertraline, citalopram and milnacipran (a serotonin-noradrenalin reuptake inhibitor) were effective in post-TBI depression (5-7)
 - Carbamazepine beneficial for depression, inattention and confusion in a subpopulation of TBI (2)
 - Carbamazepine and valproic acid were helpful in post-TBI aggression (8, 9)
 - Antipsychotics associated with decreased cognition in animal models and human subjects (10)

(1) Fann JR, 2000; (2) Persinger MA, 2000; (3) Horsfield SA, 2002; (4) Fann JR, 2001;
(5) Meythaler JM, 2001; (6) Reinhard DL, 1996; (7) Kanetani K, 2003; (8) Chatham-Showalter PE, 1996;
(9) Dikmen SS, 2000; (10) Chew E, Zafonte RD, 2009

MOOD DISORDERS MEDICATION TREATMENTS

- Randomized controlled trials (RCT)
 - Double blind RCT comparing sertraline to placebo
 - 52 subjects with mild, moderate or severe TBI at an average of 17+/-14 years after their injury
 - Significant pre to post treatment changes in mood, anxiety and quality of life measures in both groups
 - No significant differences between the sertraline and placebo groups post treatment (2)

MOOD DISORDERS MEDICATION TREATMENTS

- **RCT – con'd:**
- **DESIGN:**
 - Level I trauma center.
 - 62 Adults with MDD within 1 year of hospitalization for complicated mild to severe TBI
 - Randomized, double-blind, placebo-controlled trial.
 - Twelve-week treatment response on the 17-item Hamilton Depression Rating Scale
- **RESULTS:**
 - 32% with severe TBI
 - 68% with significant anxiety
 - 63% with prior history of MDD, and 69% had a history of alcohol or drug dependence.
 - Depression significantly improved from baseline to 12 weeks in both treatment groups ($P < .001$).
 - No significant differences between the sertraline and placebo groups over 12 weeks on depression severity, response, or remission
 - The sertraline group had significant improvement on speed of information processing compared with the placebo group ($P < .006$)
- **CONCLUSION:**
 - Sertraline monotherapy was not superior to placebo for MDD in people with post-acute complicated mild to severe TBI

DEPRESSION MEDICATION TREATMENTS

- Meta-analysis of depression post TBI
 - 12 studies included
 - Standardized mean difference effect sizes (Cohen's d) calculated for each study and pooled using random effects model to produce a summary effect size
 - Main results
 - Mild to moderate pooled effect size: Cohen's d = -0.49 (95% CL: -0.96, -0.02, p=0.02)
 - Single-group design studies had stronger ES: Cohen's d = -1.35 (95% CL: -2.14, -0.56)
 - Independent group design had smaller ES: Cohen's d = 0.001 (95% CL: -0.59, 0.58)
 - Conclusions
 - Pharmacological treatment may be effective in post-TBI depression
 - Evidence from RCTs alone demonstrated no beneficial effect

MOOD DISORDERS PSYCHOSOCIAL TREATMENTS

- Hopelessness RCT in veterans with mod-severe TBI (1)
 - Randomized crossover trial with 3-month follow-up
 - Two-arm group CBT vs. waitlist
 - 20-hour manualized small group CBT
 - Outcomes: Beck Hopelessness scale, BDI, Beck Scale for Suicide Ideation
 - Significant group differences post-intervention in Beck Hopelessness Scale ($p=0.03$), maintained at follow-up
 - Treatment gains in decreased hopelessness ($p=0.01$) and depression ($p=0.003$) in those initially assigned to waitlist
- CBT by telephone or in-person can be helpful for depression after TBI compared to usual care (2)

(1) Brenner LA et al, 2018; (2) Fann JR et al, 2015

MOOD DISORDER PREVENTION?

- Methods:
 - Moderate-severe TBI subjects not depressed at study initiation
 - Double-blind RCT of sertraline (n=49) vs. Placebo (n=50)
 - Treatment X 3 months started at an average of 21 days after injury (none >8 weeks)
 - Outcome measures
 - the Hamilton Depression Rating Scale (HDRS)
 - the Depression Scale of the Neurobehavioral Functioning Inventory (NFI)
- Results
 - Greater depressive symptoms in placebo vs. sertraline group during treatment (HDRS > 6 in 10% vs. 0%; $p < 0.023$)
 - No significant difference during the remainder of the year between groups
- Conclusions:
 - Sertraline is effective in diminishing depressive symptoms even among those not clinically depressed while the medication is being taken
 - Administration early in recovery does not prevent depression after the drug is stopped

MOOD DISORDER PREVENTION?

- **METHODS (1):**
 - Patients aged 18-85 hospitalized for mild, moderate, or severe TBI
 - A double-blind RCT of sertraline 100mg/d (n=48) and placebo (n=46) for 24 weeks
 - Follow up for 24 weeks or until development of a mood disorder
 - Main outcomes: Time to onset of depressive disorders, as defined by MINI/DSM-IV
- **RESULTS:**
 - Number needed to treat to prevent depression at 24 weeks was 5.9 ($\chi^2 = 4.6$; $P = .03$)
 - Sertraline did not influence the course of neuropsychological variables
 - The intervention was well tolerated, and adverse effects were mild in both groups
- **CONCLUSIONS:**
 - Sertraline appears to be efficacious to prevent the onset of depressive disorders following TBI
 - Future studies should replicate these findings in a large sample of patients with TBI and depict their long-term physical, cognitive, behavioral, and functional outcomes
- **A SYSTEMATIC REVIEW (2)** concluded that there is mixed evidence of efficacy

(1) Jorge RE, Alcion L, 2016; (2) Clay FJ et al, 2019

SUICIDE AFTER TBI

- American Foundation for Suicide Prevention (1)
 - The annual age-adjusted suicide rate is 14.2 per 100,000 individuals
 - Men die by suicide 3.56x more often than women
- Simpson, Tate review, 2007
 - Relative risk for suicide after TBI is 3-4 times that of the general population
 - Cumulative suicide rate is 1% over the first 15 years post-TBI
 - Clinically significant SI in 21-22% of people with TBI
 - Rate of post-TBI suicide attempts among severe TBI people is as high as 18%
- Observational study of 559 adults with mild complicated through severe TBI for 1 year after TBI (3)
 - 25% reported SI at one or more points during assessments
 - 7-10% reported SI at each assessment point
 - SI highest during months 2 and 8 post-TBI
 - 53% of those with SI have probable depression at the first assessment post-TBI
- Predictors of suicidal ideation (3)
 - Having Medicaid insurance (relative to commercial or private)
 - Having a higher score on the first PHQ-8 after injury
 - A history of depression, bipolar disorder, or other anxiety disorder
 - Prior suicide attempt(s) or psychiatric hospitalization
 - Having less than high school education

(1) AFSP Website; (2) Simpson G, Tate R, 2007; (3) Mackelprang JL, 2014

SLEEP IN TBI

- 50% with some sleep disturbance
- 46% with a diagnosable sleep disorder
- 30% with Insomnia –c/w 10% in the gen. population
 - Depression and mild TBI severity correlate with insomnia
 - Pain may be a contributor
- 23% with Sleep apnea –c/w 2% in the gen. population
- 11-49% with hypersomnia –c/w 10% in the gen. population
 - Abnormalities on MSLT
 - Sleep-disordered breathing
 - Differentiate from apathy
- Circadian rhythm disorders – possibly up to 1/3
- 6% with Narcolepsy – c/w 0.047% in the gen. population
- 7% with PLMD – c/w 4% in the gen. population

SLEEP IN TBI

- More SWS than healthy controls, and reduced evening melatonin production (1)
- Insomnia ↔ neuropsychiatric sequelae of TBI
- Drugs for comorbid issues may interfere with sleep
- Post-TBI fatigue in 33-44% of individuals with mod-severe TBI (2)
- Treatment (2)
 - Caution with BZD related hypnotics
 - Sleep hygiene, physical activity, lighting
 - Treatment of specific disorders

(1) Shekleton et al, 2010; (2) Cantor JB, 2012; (3) Castriotta RJ, 2011

META-ANALYSIS OF SLEEP CHANGES IN TBI

- **Methods:**
 - Systematic search of electronic databases from inception to May 27, 2015
 - Studies were selected if they compared sleep in TBI with that of non-TBI controls
 - Data were pooled in meta-analysis
 - Outcomes expressed as the standard mean difference (SMD) and 95% confidence interval (CI)
 - Primary outcomes derived from polysomnography and subjective sleep measures
 - Sixteen studies included, combining 637 TBI patients and 567 controls, all community dwelling
- **Results (pooled data): TBI patients had:**
 - Poorer S.Eff. (SMD = -0.47, CI: -0.89, -0.06)
 - Shorter TST (SMD = -0.37, CI: -0.59, -0.16)
 - Greater wake after sleep onset time (SMD = 0.60, CI: 0.33, 0.87).
 - Sleep architecture similar between the groups, but a trend suggested that TBI patients may spend less time in REM sleep (SMD = -0.22, CI: -0.45, 0.01)
 - TBI patients reported greater subjective sleepiness and poorer perceived sleep quality
- **Conclusions:**
 - TBI associated with widespread objective and subjective sleep deficits
 - Results highlight the need for physicians to monitor and address sleep deficits following TBI

MELATONIN FOR SLEEP PROBLEMS AFTER TBI

- **METHODS:**
 - Double-blind placebo RCT crossover study
 - 33 Australian outpatients with mild-severe TBI reporting sleep disturbances post-injury
 - Mean age 37 years, 67% men
 - Prolonged-release melatonin 2 mg and placebo for 4 weeks
- **RESULTS:**
 - Melatonin significantly improved sleep quality (PSQI: melatonin 7.68 vs. placebo 9.47; $p \leq 0.0001$)
 - No effect on sleep onset latency ($p = 0.23$)
 - Melatonin associated with increased sleep efficiency on actigraphy
 - Melatonin associated with decreased anxiety on the Hospital Anxiety Depression Scale and fatigue on the Fatigue Severity Scale ($p \leq 0.05$ for both)
 - Melatonin had no significant effect on daytime sleepiness on the Epworth Sleepiness Scale ($p = 0.15$)
- **CONCLUSIONS: MELATONIN OVER A 4-WEEK PERIOD WAS**
 - Effective and safe
 - Associated with improved subjective sleep quality and some aspects of objective sleep quality in patients with TBI

COGNITIVE CHANGES

- Cognitive problems are well documented in TBI
 - Slow cognitive processing speed
 - Executive dysfunction
 - Working memory
 - Verbal memory problems
 - Within the first 6-12 months post injury, many TBI subjects experience a relatively rapid cognitive improvement due to natural regenerative brain processes
 - After about 12 months, such improvements plateau, subjects reach a new cognitive baseline that is frequently abnormal and contributes to disability

COGNITIVE CHANGES PHARMACOTHERAPY

- A 24-week, randomized, placebo-controlled, double-blind crossover trial.
 - 18 post acute TBI patients with cognitive impairment.
 - Patients randomly assigned to donepezil for 10 weeks and then placebo for 10 weeks OR placebo for 10 weeks followed by donepezil for 10 weeks.
 - OUTCOME MEASURES: Short-term memory and sustained attention at baseline, week 10, and week 24
 - RESULTS:
 - Donepezil associated with increased testing scores compared with baseline
 - No significant change between baseline and the end in the placebo group during placebo period
 - Significantly improved testing scores in donepezil group over placebo group
 - Improved testing scores with donepezil sustained after the washout period and placebo phase
 - CONCLUSIONS: Donepezil associated with increased neuropsychological testing scores in short-term memory and sustained attention in post acute TBI patients

COGNITIVE CHANGES

PHARMACOTHERAPY

- Rivastigmine

- A 12 week prospective, double blind, placebo controlled trial (1)

- 157 patients > 12 months post-injury
 - Rivastigmine 3-6mg per day vs. placebo
 - Response = change > 1 SD in NP tests of verbal learning and memory (HVLT), and response time to a stimulus (CANTAB RVIP A)
 - By week 12 49% of rivastigmine and 49% of placebo were responders
 - In a subgroup of patients with moderate-severe memory impairment (n=81), rivastigmine significantly better than placebo in improving cognitive measures
 - Rivastigmine shows promising results in the subgroup of patients with traumatic brain injury with moderate to severe memory deficits

- Double blind RCT with cross over study (2)

- 102 patients >12 months post-injury
 - Rivastigmine up to 12mg vs. placebo
 - Uptitration => 8 week maintenance => washout => cross-over => uptitration => maintenance
 - Computerized neuropsychological testing and standardized clinical interviews
 - 69 completers, 17 withdrew because of side effects
 - Rivastigmine better than placebo in two measures of computerized testing - subtraction test (p = 0.034) vigilance test (p = 0.048).
 - The clinical interviews did not yield significant results
 - Subjective: 45% of patients thought rivastigmine beneficial compared to 20% with placebo

(1) Silver JM et al, 2006; (2) Tenovuo O, 2009

COGNITIVE CHANGES

PHARMACOTHERAPY

- Stimulants
 - Block reuptake of NE and DA
 - MPH helps with cognition, rate of recovery (1,2)
 - MPH helps with mental fatigue and processing speed (8)
 - SE: paranoia, dysphoria, agitation, irritability, increased BP
 - No data for increased seizures with stimulants (3, 6)
- Amantadine up to 400mg per day
 - DA-ergic action, GABA-ergic, NMDA antagonist
 - Improved motivation, concentration, alertness, executive function, behavioral dyscontrol (4, 9)
 - No significant difference in attention on amantadine 100–300 mg/d compared with placebo (6, 7, 10)

(1) Gualtieri et al, 1988; (2) Plenger et al, 1996; (3) Wroblewski et al, 1992; (4) Kraus and Maki, 1997; (5) Lal et al, 1988; (6) Chew E, Zafonte RD, 2009; (7) Schneider WN, 2009; (8) Johansson B, 2015; (9) Kraus MF, 2005; (10) Hammond FM, 2015

PHARMACOTHERAPIES FOR COGNITIVE AND BEHAVIORAL OUTCOMES

- Setting: post-acute TBI (>4 weeks)
- Methods: Meta-analysis
 - Both RCT's and open-label trials
 - 19 treatments by 30 independent studies
 - 395 treatment participants, 137 controls
- Results
 - Treatments administered in post-acute TBI:
 - Methylphenidate improved behavior (anger/aggression), psychosocial function
 - Donepezil improved cognition (memory, attention)
 - Treatments started in acute TBI and continued in post-acute TBI:
 - Methylphenidate, amantadine showed clinically useful treatment benefits for behavior
 - Sertraline markedly impaired cognition and psychomotor speed

COGNITIVE REHABILITATION

- Cognitive Task Force of the American College of Rehabilitation Medicine (ACRM) (1)
 - Systematically reviewed the literature from 2003–2008
 - 112 studies of cognitive rehabilitation interventions
- Conclusions for the effectiveness of cognitive rehabilitation in post-acute TBI (1, 2)
 - Cognitive rehabilitation is of greater benefit than conventional rehabilitation
 - Cognitive rehabilitation is the best treatment for people with neurocognitive impairment and functional limitations after TBI
 - Substantial evidence for the following interventions
 - Attention training (graded exercises to stimulate attention) (1, 2)
 - Metacognitive strategies (feedback, self-monitoring, self-regulation, strategy use) - promote generalization to real world tasks and reduce functional disability (1, 2)
 - Social-communication deficits after TBI (2)

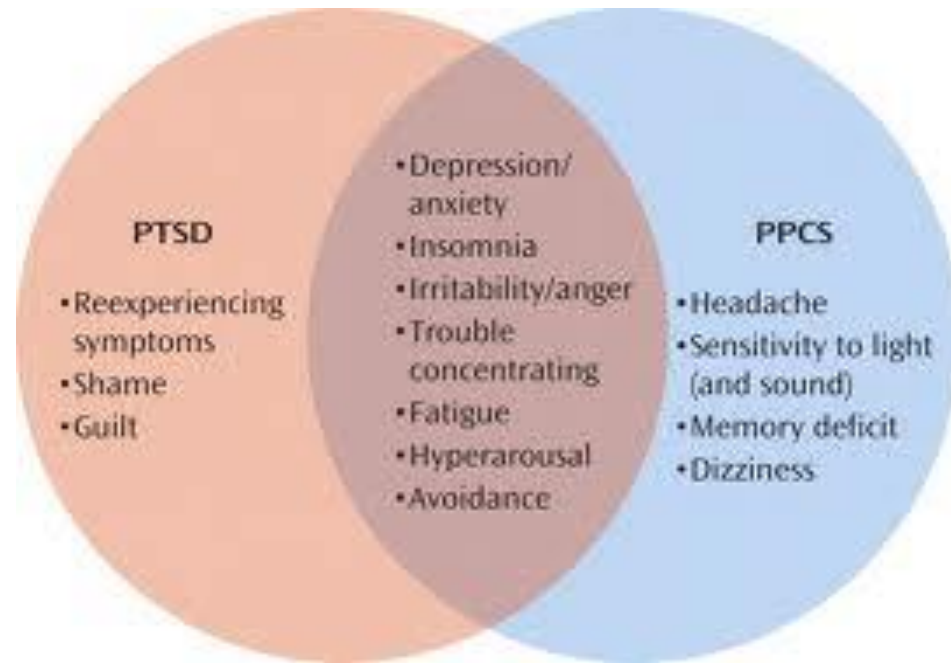
(1) Cicerone KD et al, 2011; (2) Cicerone KD et al, 2019

ANXIETY DISORDERS

- Prevalence
 - GAD – 8-24% (1-3)
 - PD – 3-11% (3, 4)
 - Phobias – 6-11% (3, 5)
 - OCD – 4.7-14% (3, 5)
 - ASD – 14% (6)
 - 73% of people with ASD have PTSD at 2 years
 - PTSD – 3-27% (7, 8)
 - Fewer intrusive memories (19%)
 - Emotional reactivity (96%)
- Predictors of PTSD after TBI
 - Systematic review and meta-analysis (9)
 - Shorter PTA
 - Memory of the traumatic event
 - Early posttraumatic symptoms

(1) Fann JR, 1995; (2) Jorge RE, 1993; (3) Hibbard MR, 1998; (4) Deb S, 1999; (5) Silver JM, 2001; (6) Harvey AG, 2000; (7) Kim E, 2007; (8) Zgaljardic DJ, 2014; (9) Cnossen MC et al, 2017

SYMPTOMS IN CO-MORBID PTSD AND TBI



- Shared symptoms (1):
 - Sleep disruption
 - Irritability
 - Difficulty concentrating
 - Slowed thinking
 - Memory impairment
- Shared co-morbidities:
 - Depression
 - Substance use disorders
 - Pain
 - Somatic disorders
- Symptom overlap can cause false positive diagnoses of PTSD after TBI. (2, 3)

SYMPTOM OVERLAP IN PTSD AND TBI

PCL-5: 20 items, rated 0-4

1. Repeated, disturbing, and unwanted memories
2. Repeated, disturbing dreams
3. Suddenly feeling or acting as if the stressful experience were actually happening again
4. **Feeling very upset when exposed to reminders**
5. Having strong physical reactions
6. Avoiding memories, thoughts, or feelings related to the stressful experience
7. Avoiding external reminders of the stressful experience
8. **Trouble remembering important parts of the experience**
9. Having strong negative beliefs about yourself, other people, or the world
10. Blaming yourself or someone else
11. Having strong negative feelings such as fear, horror, anger, guilt, or shame
12. **Loss of interest in activities that you used to enjoy**
13. Feeling distant or cut off from other people
14. **Trouble experiencing positive feelings**
15. **Irritable behavior, angry outbursts, or acting aggressively**
16. **Taking too many risks**
17. **Being “superalert” or watchful or on guard**
18. **Feeling jumpy or easily startled**
19. **Having difficulty concentrating**
20. **Trouble falling or staying asleep**

NSI 22 items, rated 0-4

1. Feeling Dizzy
2. Loss of balance
3. Poor coordination, clumsy
4. Headaches
5. Nausea
6. Vision problems, blurring, trouble seeing
7. Sensitivity to light
8. Hearing difficulty
9. **Sensitivity to noise**
10. **Numbness or tingling on parts of my body**
11. **Change in taste and/or smell**
12. **Loss of appetite or increased appetite**
13. **Poor concentration, can't pay attention, easily distracted**
14. **Forgetfulness, can't remember things**
15. **Difficulty making decisions**
16. **Slowed thinking, difficulty getting organized, can't finish things**
17. **Fatigue, loss of energy, getting tired easily**
18. **Difficulty falling or staying asleep**
19. **Feeling anxious or tense**
20. **Feeling depressed or sad**
21. **Irritability, easily annoyed**
22. **Poor frustration tolerance, feeling easily overwhelmed by things**

PCL – posttraumatic symptoms checklist; NSI – Neurobehavioral symptoms inventory

COGNITIVE DYSFUNCTION IN PTSD

TABLE 3. Summary of Positive and Negative Findings for Association of Cognitive Domains, by Type of Sample Subject

Cognitive Impairment	Sample	Positive	Negative
Attention	Veterans	5	1
	Abused individuals	1	1
	Refugees/war victims	2	0
	Undergraduates	0	2
	Disaster survivors	1	0
	Other	0	0
	Total	9	4
Learning	Veterans	5	2
	Abused individuals	1	1
	Refugees/war victims	1	1
	Undergraduates	0	0
	Disaster survivors	0	1
	Other	0	1
	Total	7	6
Memory	Veterans	3	5
	Abused individuals	2	2
	Refugees/war victims	0	3
	Undergraduates	0	0
	Disaster survivors	1	1
	Other	0	1
	Total	6	12
Executive Function	Veterans	4	3
	Abused individuals	1	1
	Refugees/war victims	1	1
	Undergraduates	1	1
	Disaster survivors	2	0
	Other	0	1
	Total	9	7
Visuospatial Function	Veterans	0	7
	Abused individuals	0	1
	Refugees/war victims	1	0
	Undergraduates	0	0
	Disaster survivors	0	1
	Other	0	0
	Total	1	9

- Definite attentional impairment
- Mixed evidence for impairment in
 - Learning
 - Memory
 - Executive functions
 - Visuospatial function
- Attention and new learning both impaired in veterans with PTSD

SUBSTANCE USE DISORDERS

- Prevalence

- Initial reduction in substance use in the 1st year post-injury, and greater abstinence
- Return to pre-injury alcohol (7-48%) and drug misuse (6-28%) over time
 - > 25% consuming alcohol at hazardous levels
 - 15% demonstrated alcohol dependence at 2 years post-injury
 - 8.4% reported problem drug use
 - 53% reported both alcohol and drug misuse

SUBSTANCE USE DISORDERS

- Risk factors
 - Substance use and misuse (esp. alcohol) is a risk for TBI
 - Risks for continued post-TBI use/misuse
 - Pre-injury history of an SUD
 - Intoxication at the time of injury
 - Family history of an SUD
 - Denial of dangers associated with continued substance use
 - Younger age (i.e., < 25 years)
 - Male gender
 - Fewer cognitive and physical impairments stemming from injury
 - Less involvement in productive activities that produce income
 - Less community access
 - Risk factors for a new use/misuse after TBI
 - Most had an extensive pre-injury history of substance misuse
 - Some evidence that TBI may be a risk factor for developing an SUD
 - Children with mTBI more likely to demonstrate SUD during adolescence
 - New alcohol misuse after TBI in 11-30% of those without such pre-injury

SUBSTANCE USE DISORDERS

- Consequences
 - Greater cerebral cortical atrophy
 - Post-traumatic seizures
 - Poor psychosocial functioning
 - Mood disorders
 - Poor long-term vocational outcomes
 - Decreased life satisfaction
 - Increased risk for suicide
 - Increased risk for sustaining a second TBI
- Treatment
 - Education about the negative effects of continued substance use
 - Motivational interviewing and multimedia psychoeducational materials may enhance retention of information
 - Pharmacological treatments – as adjunct to traditional therapies: Naltrexone, acamprosate, and disulfiram

Zgaljardic DJ, 2014

www.mghcme.org

TBI EVALUATION

- History of the accident(s)
 - When, where, type
 - Alteration in consciousness, LOC
 - Post Traumatic Amnesia
 - GCS at scene or ER if available
 - Associated trauma to other body parts/systems
 - Neurological/neurosurgical complications
 - Focal neurological findings
 - Hematomas, contusions, etc.
 - Sensory-motor deficits
 - Speech/language deficit
 - Surgical procedures – craniotomies, shunts, etc.
 - Post-traumatic epilepsy

TBI EVALUATION

- History of the accident(s)
 - Hospitalization and rehabilitation
 - Length of acute hospital stay
 - Functional recovery
 - Residual deficits
 - Rehabilitation hospitalization, interventions
 - Rehabilitation efforts since discharge from post-acute facility – residential rehab, vocational rehab, etc.
- Overview of life since TBI
 - Living situation
 - Employment
 - Rehabilitation activities – OT, PT, SLP, HI support groups
 - Finances –attempts to work, disability, workman’s compensation, lawsuits
- Collateral information from family
 - Patients report more physical impairment
 - Relatives report more behavioral problems

TBI EVALUATION

- Neuropsychiatric syndromes
 - Cognitive disturbances
 - Memory loss, external cueing, naming and word finding difficulties
 - Attention/concentration problems
 - Speed of information processing
 - Cognitive rigidity
 - Mood syndromes
 - Depression
 - Mania/hypomania
 - Personality changes
 - Dyscontrol – irritability, sexual behavior, apathy
 - Psychotic syndromes
 - Anxiety syndromes
 - Seizures and their consequences

TBI EVALUATION

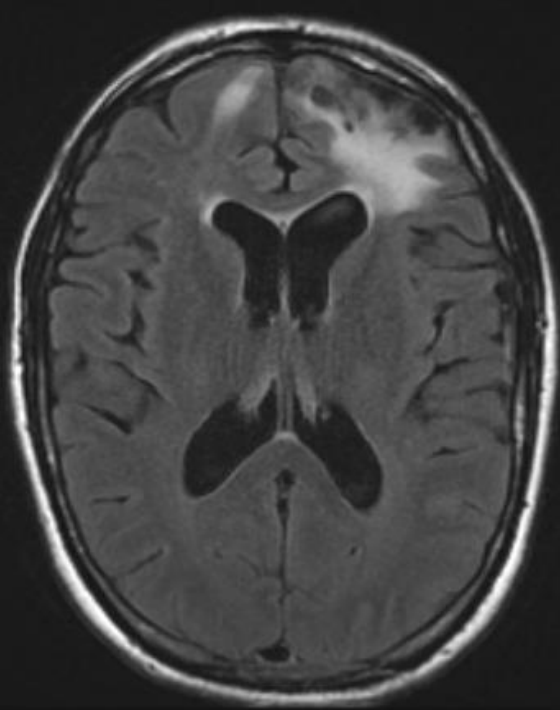
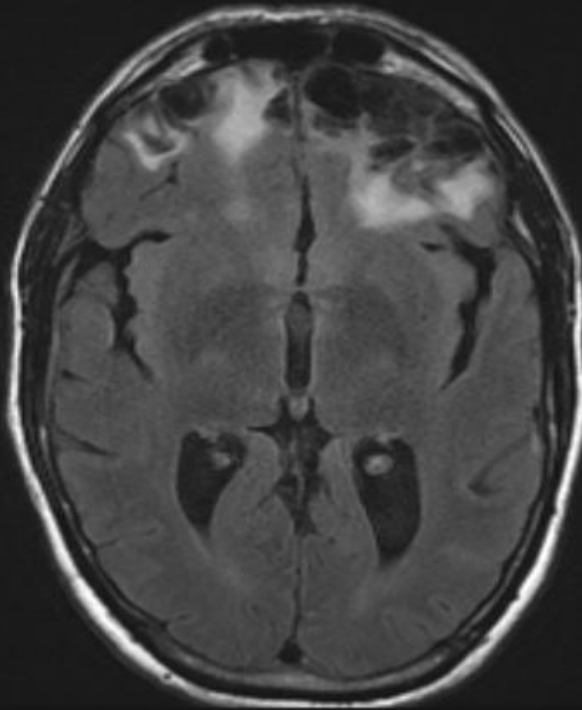
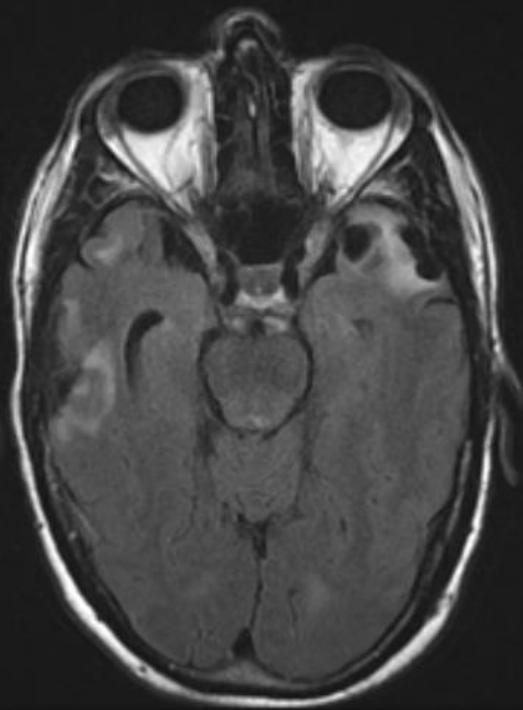
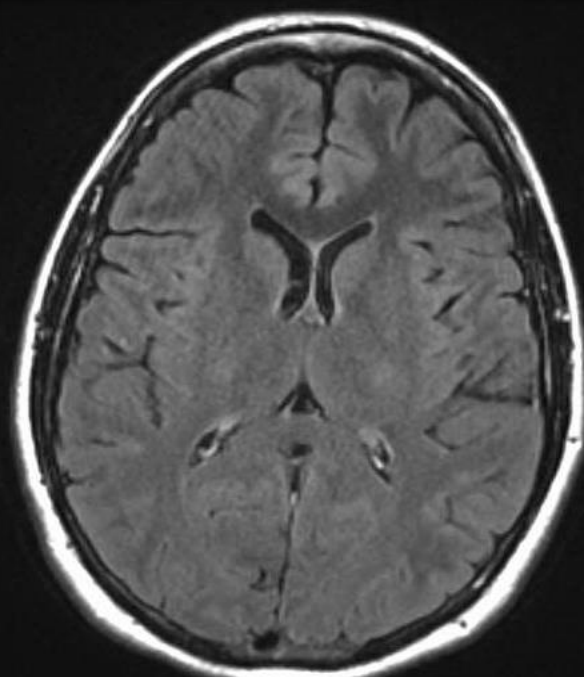
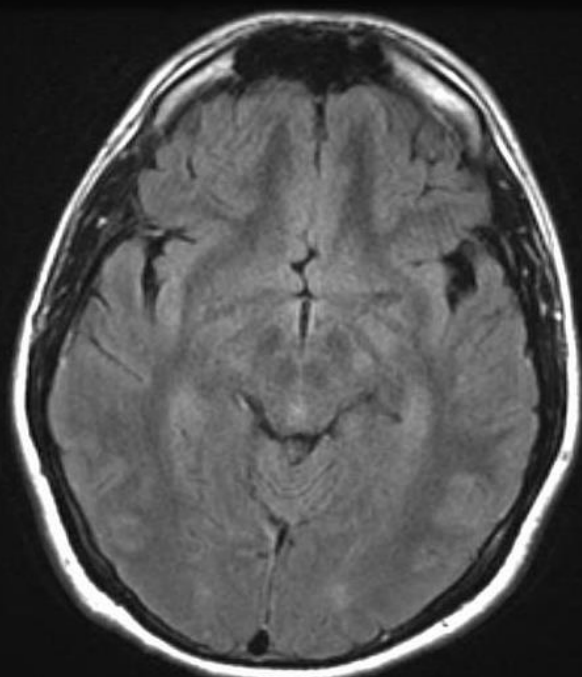
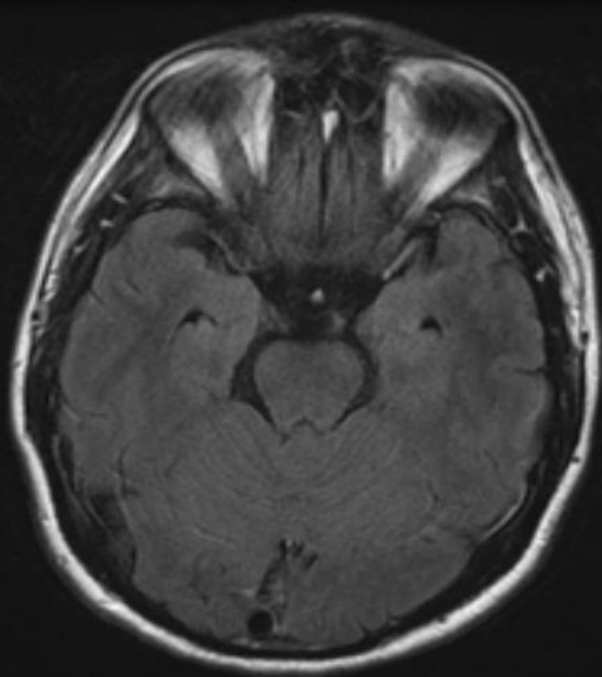
- MSE
 - Appearance
 - Psychomotor activity
 - Involuntary movements
 - Motor, gait, speech deficits
 - Dress
 - Speech/language function
 - Coherence/articulation
 - Repetition
 - Naming
 - Prosody
 - Thought processes
 - Circumstantiality
 - Thought content
 - Mood/affect
 - Stability
 - Appropriateness to thought content

TBI COGNITIVE EXAMINATION

- **MOCA +/-**
- **Additional “bedside” tests:**
 - Attention:
 - Days of the week forward and backward
 - Months forward and backward
 - Digits forward and digits backward
 - Trails A
 - Complex attention/executive functioning:
 - Trails B
 - Speed of information processing
 - SDMT
 - Word generation:
 - FAS test – phonemic fluency
 - Groceries, animals – semantic fluency
 - Short-term memory:
 - Important to note how many words remembered with cues and with multiple choice
 - Language:
 - Reading, repetition, writing
 - Praxis:
 - Test for apraxia
 - Luria’s motor sequencing task
 - Visual-spatial function
 - Clock drawing – good test, part of MOCA; CLOX 1 and 2 for further examination
 - Rey-Osterrieth complex figure test

ANCILLARY TESTS: NEUROIMAGING

- Structural
 - CT – tissue density
 - MRI – magnetic properties of tissue
- Functional
 - fMRI – BOLD
 - MRS – metabolite concentrations in tissue
 - PET – radioactive tracers
 - SPECT – radioactive tracers
 - EEG, Quantitative EEG – summed neuronal discharges



CT VS. MRI

- Sensitivity good
 - Average time for examination 1 minute
 - Plane of section axial
 - Preferred conditions
 - Acute hemorrhage
 - Calcifications
 - Screening exam
 - Bone injury
 - Identifying path of missile
 - Foreign objects
 - Cost - \$675-\$1750 (1)
- Sensitivity superior
 - Average time for exam 30-45 minutes
 - Plane of section any
 - Preferred conditions
 - Temporal lobe detail
 - Frontal lobe detail
 - Posterior fossa, pituitary
 - Contusions
 - Shearing injury
 - SDH and epidural hematomas
 - Diffuse axonal injury
 - Sequences – FLAIR, DTI, SWI, volumetric analyses
 - Cost - \$600-\$1550 (1)

(1) <https://www.newchoicehealth.com/places/massachusetts/boston/>

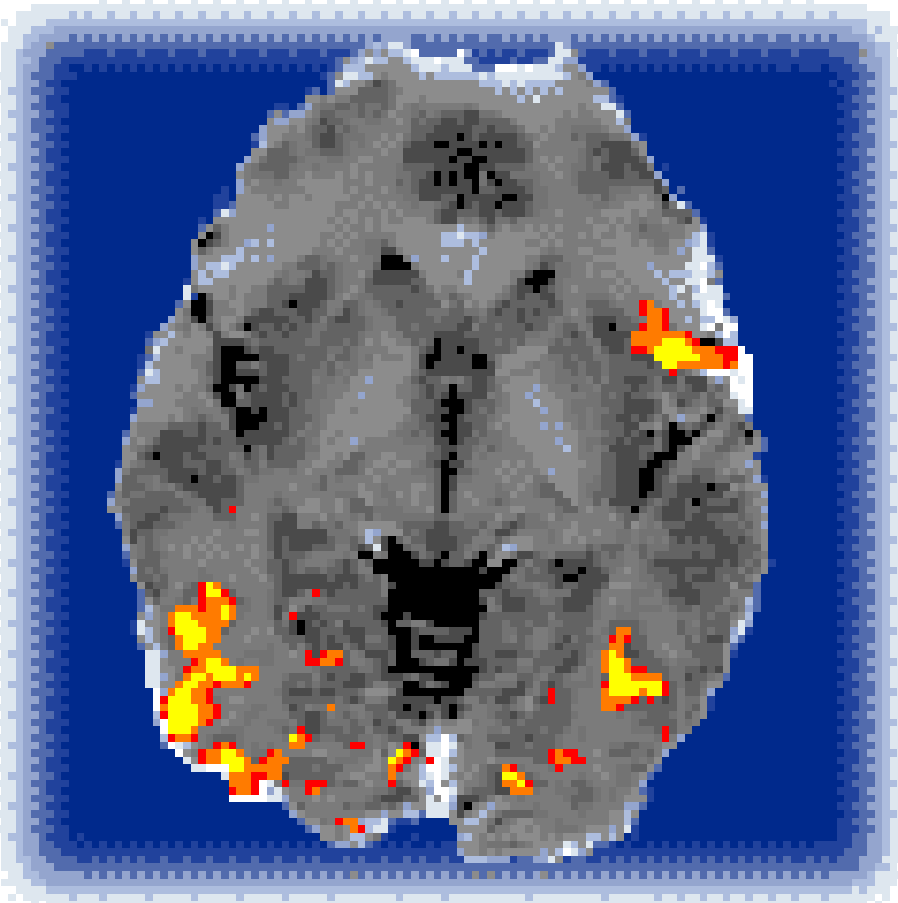
ANCILLARY TESTS: NEUROIMAGING

- CT – tissue density
 - Sensitive for identifying intracranial hemorrhages that may require neurosurgical interventions in moderate and severe TBI patients presenting to the ED
 - Not useful for the prediction of functional recovery, even in moderate and severe TBI
 - Limited usefulness in the clinical evaluation of mTBI patients presenting to the ED
 - Likely overused in the evaluation of mTBI

ANCILLARY TESTS: NEUROIMAGING

- MRI
 - Moderate clinical utility in both CT-negative and CT-positive TBI
 - Significant utility for research into the evaluation of TBI
 - Increased sensitivity of MRI compared to CT – only 10% of DAI positive on CT because it is non-hemorrhagic
 - Findings rarely affect management in acute TBI
 - Utility in post-acute TBI to evaluate neurological symptoms not explained by CT findings
 - Sequences valuable in TBI:
 - DWI – acute ischemia and white matter injury
 - DTI – mainly for research
 - T2, FLAIR – edema
 - SWI – hemorrhage, though does not determine age of lesion

fMRI



- Mechanism – BOLD
- Uses (1)
 - During tasks
 - Resting state
 - Before and after treatment
- Limitations
 - Movement of subjects
 - Low signal to noise ratio
 - BOLD contrast relies on small changes of 1-5%
- fMRI in TBI (2)
 - WM tasks in mild TBI vs. healthy controls
 - Mild TBI with increased activation of R PL and R DLPFC during high memory load
 - No differences in performance
 - Mild TBI “work harder” to recall things

(1) Amyot F, 2013; (2) McAllister T et al, 1999

PET AND SPECT

- PET
 - Measures glucose metabolism, oxygen metabolism, neuroreceptor abnormalities, neuroinflammation, amyloid deposits
 - Relationship between clinical deficits and brain abnormalities in chronic TBI
 - Unclear clinical utility
- SPECT
 - Measures cerebral blood perfusion
 - Frequently co-registered with structural imaging
 - Affordable and available
 - Strong evidence for determining a positive prognosis in mTBI patients with normal SPECT perfusion imaging
 - SPECT can identify perfusion/blood deficits in mild, moderate, and severe TBI that anatomic imaging inaccurately identifies or misses altogether

ANCILLARY TESTS: ELECTROPHYSIOLOGY

- Techniques
 - EEG can detect seizures or abnormal functioning
 - qEEG
 - MEG
 - ERP
- Measures brain activity with temporal resolution superior to functional imaging
- Insufficient evidence to support use of these techniques in detection and diagnosis of TBI

NEUROPSYCHOLOGICAL TESTING

- Orientation
- Mental ability, e.g., WIS
- Speech and language
- Attention
- Memory
- Perception and neglect
- Visuospatial and constructional abilities
- Agnosia and apraxia
- Executive functions
- Conceptual functions, e.g., similarities, WCST

NEUROPSYCHOLOGICAL TESTING

- Group norms
- Indications for NP testing in TBI
 - To establish a baseline or as a follow up
 - To establish pre-injury intelligence
 - To establish ability to go back to work
 - To differentiate functional (i.e., psychiatric) from neurologic (i.e., from TBI) symptoms
 - To help establish whether disability should be covered
- Factors affecting NP test findings
 - Original baseline
 - Environment
 - Motivation and effort
 - Physical health
 - Psychological distress
 - Psychiatric disorders
 - Medications
 - Experience of neuropsychologist
 - Errors in scoring
 - Errors in interpretation

FACTORS AFFECTING TBI FUNCTIONAL OUTCOME

- Factors linked to worse post-injury functional outcomes and greater disability
 - Older age
 - Severity of injury
 - Longer post-traumatic amnesia
 - Anosmia
 - Apolipoprotein E status
 - Pre-injury unemployment
 - More disability at rehabilitation discharge
 - Pre-injury psychiatric history and substance abuse
 - Substance abuse history
- Protective factors
 - Higher baseline intellectual functioning
 - Social support
 - Higher income level
 - Higher education
 - Higher socioeconomic status

FACTORS AFFECTING TBI FUNCTIONAL OUTCOME

- Post-injury factors influencing patients' functional status
 - Challenging behaviors associated with lower levels of community integration
 - Cognitive impairment and depression strongly and independently related to problems in everyday functioning but weakly related to each other
 - The relationships between depression, cognitive impairment and social adjustment are inadequately studied
 - Appropriate post-injury interventions ?
 - Access to rehabilitation programs ?
 - Community and family supports ?
 - Vocational reintegration ?
 - Cognitive rehabilitation ?

TREATMENT

- Pharmacotherapy general principles
 - Review prior treatments for effectiveness, dose, side effects
 - Review diagnoses
 - Review indications and SE of meds
 - Review past/current nonpharmacological treatments
 - TBI patients are sensitive to SE of medications
 - Start low, go slow
 - Brain regenerative processes => continued reassessments of medication needs
 - Few double-blind RCT => treatment based on extensions from non-TBI patients

TREATMENT

- Behavioral treatments
 - 75% Effective in disruptive behaviors after TBI (1)
 - The importance of someone in charge of behavioral approaches
- Cognitive rehabilitation
 - Teaching patients new strategies
- Psychosocial interventions
 - Supportive psychotherapy with patient
 - Supportive therapy and education of family
 - 40% of TBI relatives showed depressive symptoms within 1 month;
 - 25% showed physical or psychological illness within 6-12 months (2)
 - Working with existing community resources
 - Rehabilitation programs
 - Communication strategies
 - Vocational rehabilitation

(1) Eames and Wood, 1985; (2) Oddy M, 1978

SUMMARY

- TBI is common
- Consequences of TBI are severe, long-lasting, under-recognized and under-treated
- Role for psychiatry in TBI treatment
 - Neuropsychiatric symptoms
 - Psychological, social, vocational consequences important
- Treatment model
 - Acute and chronic rehabilitation
 - Collaboration between many specialties

THE END
