Neuropsychiatry of Traumatic Brain Injury

Part 1

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Disclosures

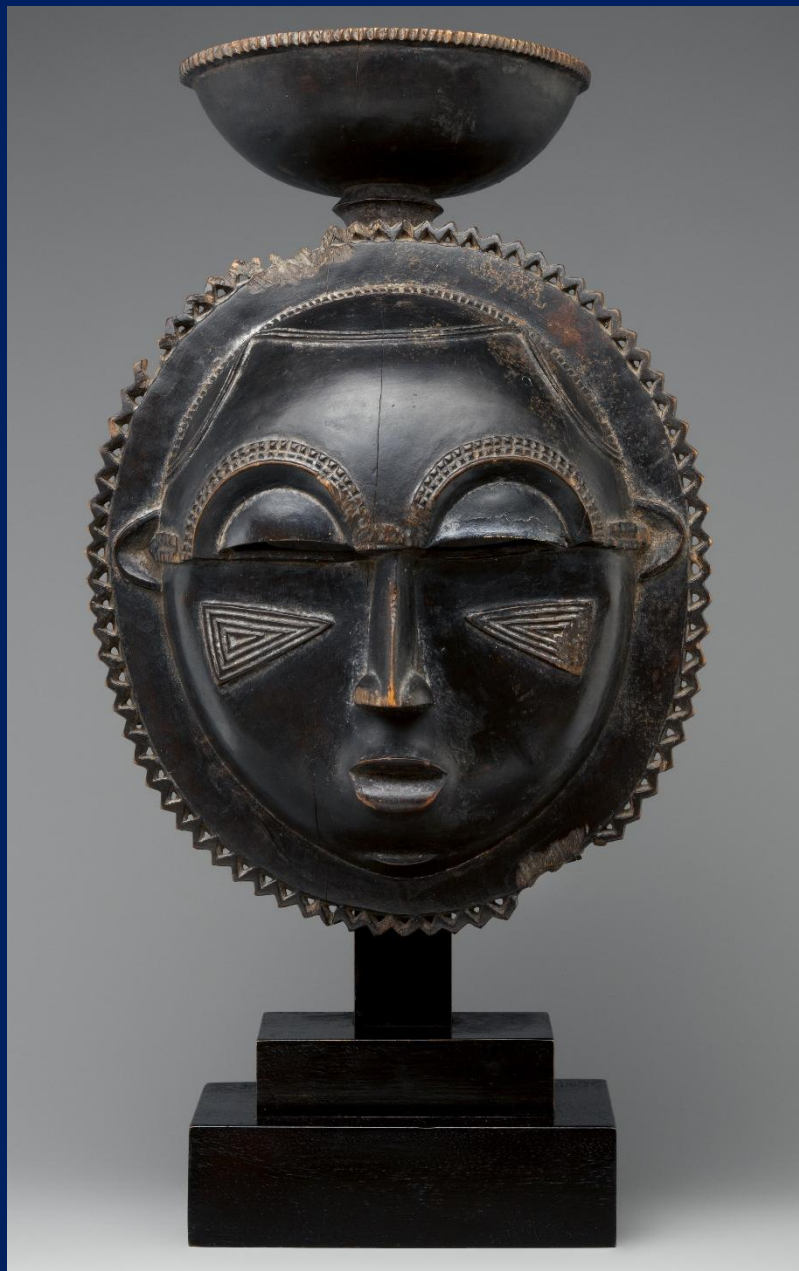
- I have nothing to disclose

Objectives

- Describe the bidirectional relationship between psychiatric disorders and TBI
- Identify how post-TBI cognitive disorders can affect individuals' psychiatric presentations and treatment
- Analyze the link between TBI and subsequent dementia

- What is a TBI?
  - Head injury due to trauma
  - HAS to alter brain function or cause other neurologic injury
    - If you hit your head and none of these things happen, it's not a TBI

- TBI and psychiatric disorders
  - TBI increases the risk of subsequent psychiatric disorders
  - Psychiatric disorders can increase the risk for TBI
  - So, all psychiatrists and mental health clinicians need to know about TBI



- TBI in the US:
  - Every year TBIs cause:
    - 2.5 million ER visits
    - 300,000 hospitalizations
    - 56,000 deaths
- > 5% of survivors have a second TBI within the next year

- TBI severity:
  - Mild
    - Makes up 70-90% of TBI
      - The rest are moderate to severe
  - Moderate
  - Severe
- TBI is graded on the MOST severe feature present
  - More severe TBI = worse prognosis

Classification of TBI severity

Mild TBI
- Same thing as concussion
- Must involve:
  - Loss of consciousness < 30 minutes
  - Confusion or amnesia < 24 hours
  - Glasgow Coma Scale score of 13-15
- If radiologic evidence of injury: COMPLICATED mild TBI

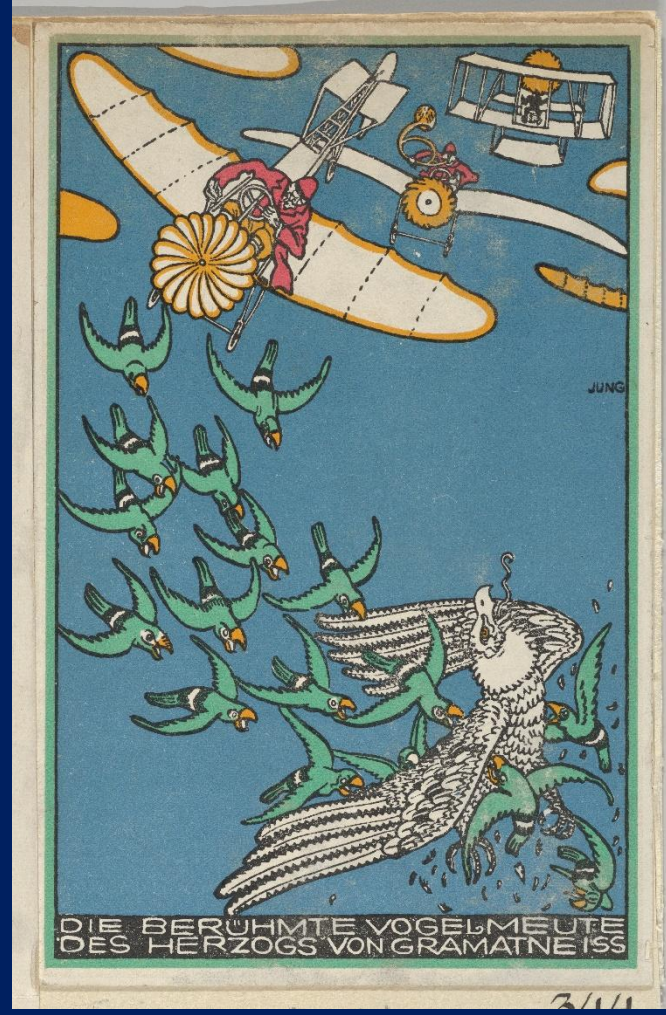
Moderate TBI
- Must involve:
  - Loss of consciousness for 30 minutes-1 day
  - Confusion or amnesia for 1-7 days
  - GCS score of 9-12

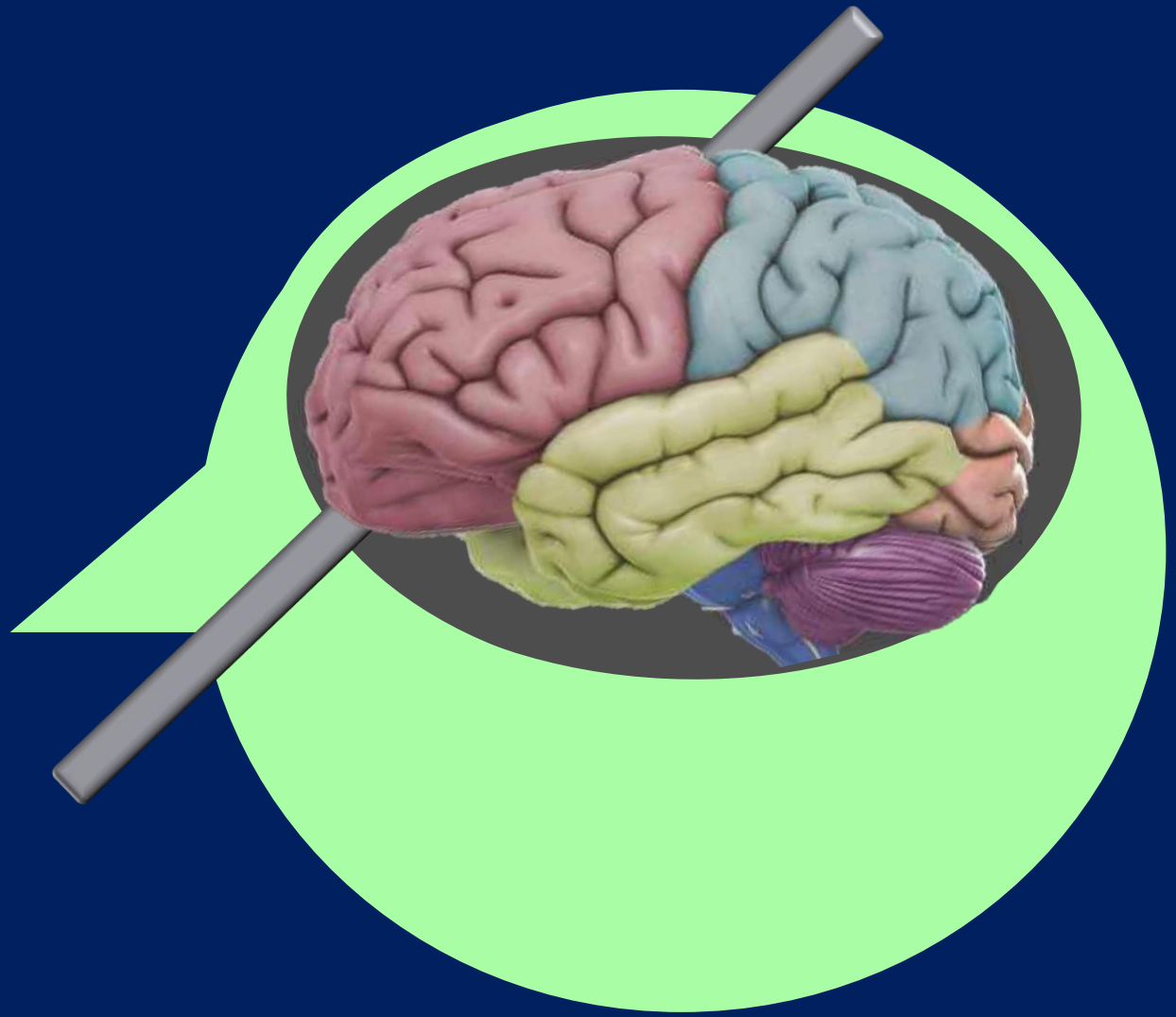
Severe TBI:
- Must involve:
  - Loss of consciousness > 1 day
  - Confusion or amnesia > 7 days
  - GCS score 8 or less

TBI is graded on the MOST severe feature present

- How do TBIs cause brain damage?
  - Immediate mechanical injury
  - Subacute neuropathological processes
  - Other associated injuries and sequelae

- Mechanism of acute mechanical injury affects nature of brain damage
- Types of TBI
  - Penetrating TBI
    - Foreign object (eg bullet) enters the brain
  - Closed TBI
    - Head strikes an object and the force of the collision injures the brain
      - eg car crashes and falls
  - Blast TBI
    - High pressure waves (ie from explosions) damage brain tissue



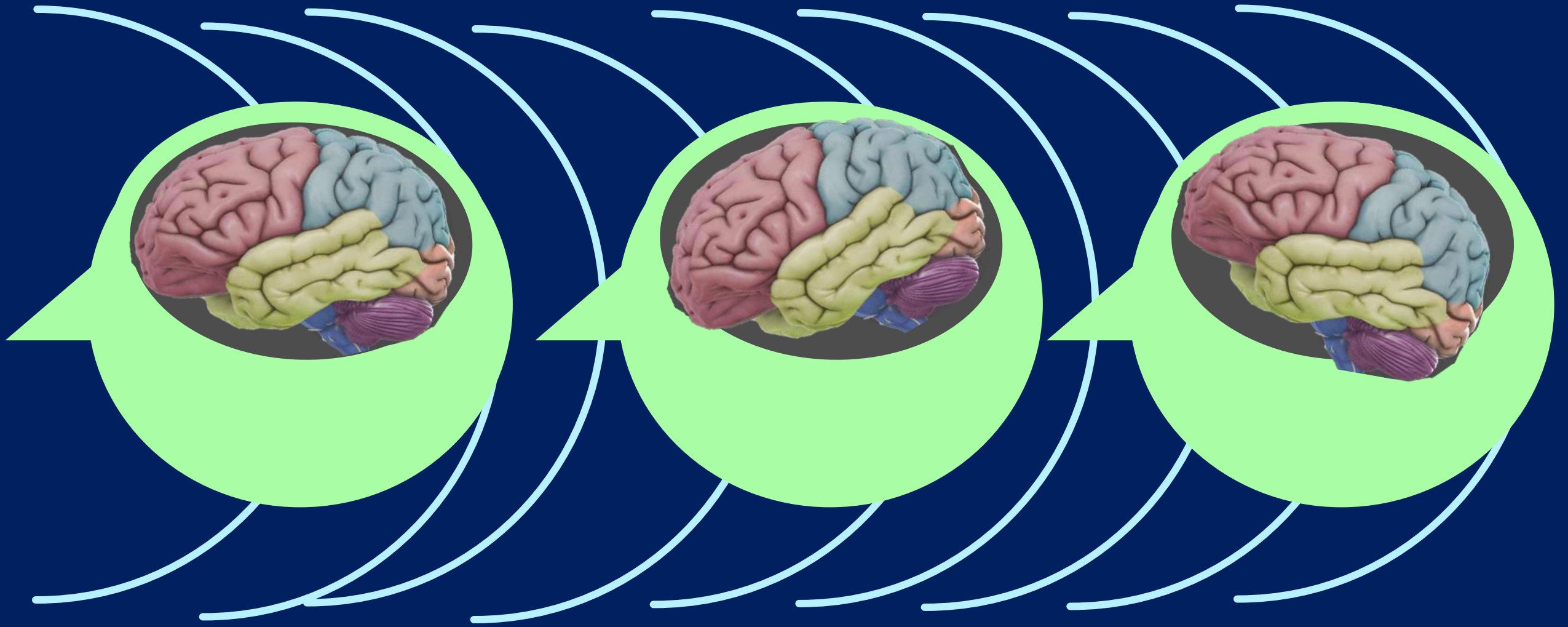


Penetrating TBI

- Destruction, displacement, or deposition of objects/bone into brain tissue
- Can have combination of closed and penetrating injuries

Closed TBI

- Rapid acceleration/deceleration of brain
- Linear and rotational forces cause brain movement lag
- Deformation and damage to brain parenchyma by bony protuberances, falx, and tentorium cerebri



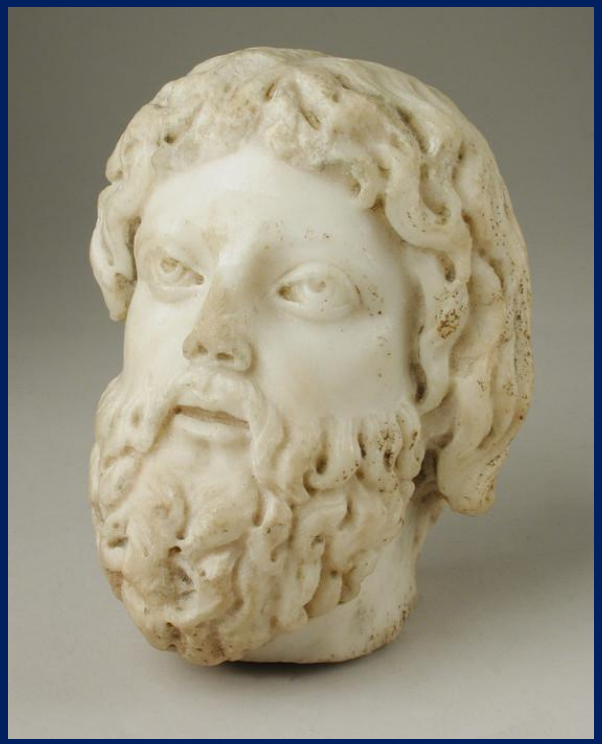
Blast TBI

- Initial pressure wave of explosion produces mechanical damage due to release of heat/acoustic/EM energy
- Followed by damage from reflection of the wave hitting the skill and repropagating back through brain

Mechanisms of acute injury

- Vascular Injuries
  - Rotational and shearing forces can lead to intracranial and intraparenchymal hemorrhages
    - Contusions at cerebral gyri, frontal, and temporal lobes
  - EDH, SDH, SAH

- Traumatic Axonal Injury
  - Multifocal white matter damage from rotational and shearing forces
  - Commonly affects upper brainstem, diencephalic structures, gray-white matter junctions, parasagittal white matter, corpus callosum
  - Clinical manifestations range from coma to mild cognitive changes



- Subacute neuropathological processes
  - Initial mechanical trauma can induce subsequent
    - Cell necrosis / apoptosis
    - Inflammation
    - Cytotoxic edema
    - Excitotoxicity
    - Neurodegeneration
  - Can continue over weeks and contribute to further brain damage
    - Someday will we have neuroprotective therapies to inhibit this secondary brain damage?
      - Hopefully someday, but does NOT exist now!

- Other associated injuries/sequelae that can accompany TBI
  - Intracranial bleeding
  - Cerebral edema
  - Hydrocephalus
    - If late worsening weeks/months after TBI, consider hydrocephalus
    - Especially if any intraventricular extension of blood at time of injury: causes scarring in ventricles that can affect CSF flow
  - Ischemic stroke
    - Can occur from:
      - Arterial dissection from neck hyperextension
      - Cardioembolism from chest injury (ie chest hitting steering wheel in MVA)
    - Posttraumatic epilepsy
    - Hypopituitarism

- TBI produces both cognitive deficits and psychiatric disorders
  - Can synergistically worsen each other
- Cognitive limitations impair:
  - Ability to cope with life stressors
  - Ability to manage their psychiatric conditions
- Psychiatric symptoms worsen cognitive problems
- So psychiatrists need to know about both post-TBI cognitive deficits and post-TBI psychiatric disorders

- 3 types of post-TBI cognitive disorders:
  - Impairment of consciousness
  - Deficits in specific cognitive domains
  - Later-onset dementias
    - Conventional dementias (AD, etc)
    - CTE / TES

- Impairment of Consciousness
  - Begins immediately or within minutes to hours after the injury
  - Generally resolves over days to weeks (if patient survives)
  - Most common cognitive problem in acute post-TBI period
  - Spectrum ranges from brief confusion to coma
    - Includes posttraumatic confusional state
      - Posttraumatic confusional state is the one you'd most likely get called about as a psychiatrist

- Posttraumatic confusional state
  - Essentially is a delirium
  - Starts immediately after TBI or after awakening from coma
  - Clinical features:
    - Impaired attention and alertness (key symptom)
    - Other potential symptoms:
      - Memory impairment
      - Disorientation
      - Agitation
      - Apathy
      - Perceptual disturbances
      - Delusions
      - Affective lability
      - Sleep disturbance.
  - Symptoms often fluctuate throughout the day

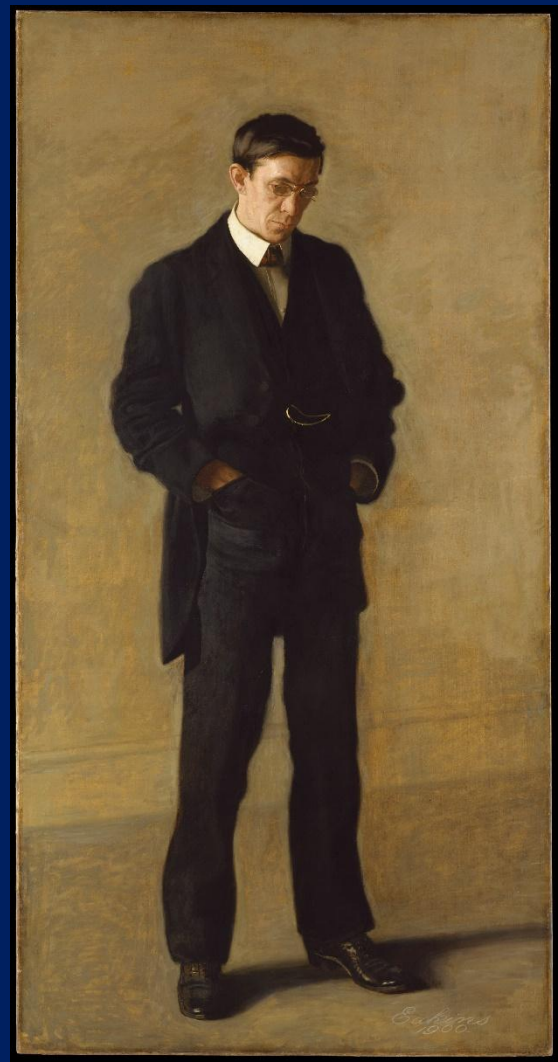
- Management of posttraumatic confusional state
  - Eventually resolves on its own, but can interfere with participation in rehabilitation therapies and negatively affect recovery
  - Important to identify and treat any additional contributors to delirium:
    - Infections
    - Endocrinopathies
    - Metabolic imbalances
    - Alcohol withdrawal
    - Medications which impair cognition
    - Nonconvulsive status epilepticus

- Make sure patient has eyeglasses and hearing aids
  - If patient can see and hear their surroundings, may reduce confusion
- Provide dark quiet environment at night, and brightly lit, appropriately interactive environment during the day
  - To help maintain sleep-wake cycles.
- Family members and friends at bedside, and/or photos and mementos, can help reduce agitation
- Frequently orient patient to situation, so they know what's going on

- Pharmacologic treatment for posttraumatic confusional state?
  - Nope!
    - Not much evidence for pharmacologic treatment for any type of delirium, including PTCS
      - EXCEPT for treatment targeting underlying problem: antibiotics for UTI, benzodiazepines for alcohol withdrawal, etc
  - Antipsychotics have limited evidence for delirium in general
    - The only drug class with evidence for delirium: but evidence is weak. Overall data suggests NOT effective in improving delirium of other etiologies (though a few studies have found mild benefits).
    - Not much studied in TBI; could theoretically impair cognition
  - Benzodiazepines and anticonvulsants potentially may impair neuroplasticity and thus hamper brain recovery
    - Haven't been shown to be of any benefit in this situation (except for for catatonia, alcohol withdrawal, and seizures)

- Static cognitive deficits
  - Can involve impairment in one or more cognitive functions.
  - Static doesn’t mean that the deficits never improve
    - Often do get better over months to years
    - But persist over the subacute to chronic period
      - Do NOT fluctuate over minutes to hours like PTCS
    - Can present immediately following the injury, or after emergence from PTCS

- Type and severity depends on the location and size of the injury
- Can occur with any brain lesion (eg stroke, tumor), not just with TBI
- Can include:
  - Memory impairment
  - Frontal-executive dysfunction
  - Aphasia
  - Anomia
  - Hemineglect
  - Impairment of attention and concentration
  - Visuospatial impairment



- Static post-TBI cognitive deficits affect psychiatric care in several important ways
  - Cognitive deficits may be confused for primary psychiatric disorders
    - Distinguishing them is key for accurate diagnosis and treatment
      - Consult I got once: “we think patient is depressed, because she won’t communicate with us”
        - On evaluation, turned out the problem is actually non-fluent aphasia
          - Aphasia ≠ mutism
            - Patients usually can talk and comprehend some
              - This can cause aphasias to be initially overlooked

- How to help sort out cognitive vs psychiatric?
  - Need to know the most common post-TBI cognitive deficits and their typical locations
    - Left frontotemporal injuries can cause nonfluent aphasias like Broca aphasia
    - Isolated occipital lobe damage wouldn’t likely cause aphasia
      - In that case should consider other explanations for the noncommunication, like depression or apathy

- Some cognitive deficits resemble psychosis
  - Most often occurs with right hemisphere lesions
  - Delusional misidentification
    - Includes Capgras syndrome
    - Patient believes that a familiar person like a spouse has been replaced by an imposter who looks and sounds identical to the original person
      - Can happen for objects too
    - May occur from damage to right hemisphere pathways connecting the areas involved in facial recognition with the areas involved in recognizing familiarity

- Asomatognosia
  - Belief that one of your limbs doesn't belong to you
- Anosognosia
  - Lack of awareness of physical and cognitive deficits
    - "I could move my left arm if I wanted to—I'm just tired right now and need to rest. Stop bothering me, doctor!"

- What causes these disorders of identity and body representation?
  - Various parts of the brain need to work together in order to recognize yourself and others, and monitor your own body
    - TBI (and other brain lesions) can damage these brain regions or disconnect them from each other
      - Breaks up the networks that support identification of self and others
  - These cognitive deficits may look like psychosis, BUT:
    - They do NOT typically respond to antipsychotics
    - Generally resolve on their own with time
    - Important to educate family and primary team
- Anosognosia (denial of neurologic deficits) is COGNITIVE deficit, NOT the psychological defense mechanism of denial
  - Knowing this can prevent futile psychotherapeutic interventions and help primary team and family understand the problem.

- Post-TBI cognitive deficits can influence how you assess the patient
  - Hemineglect
    - Stand to the patient's right, so they can notice you exist
  - Aphasia
    - Significant aphasia
      - Observing nonverbal behaviors like crying is more helpful than asking the patient questions
    - Mild aphasia
      - Many patients with mild aphasia can participate in a clinical interview if the interviewer takes their language deficits into account
        - Use yes-or-no rather than open-ended questions
        - Keep questions and comments short and grammatically simple

- Cognitive deficits influence treatment choice for post-TBI psychiatric disorders
  - Comorbid aphasia and psychiatric problems
    - Use treatments that don’t rely on verbal abilities
      - Medications
      - Pet therapy
      - Art therapy
      - Music therapy
    - Avoid language-intensive treatments like CBT

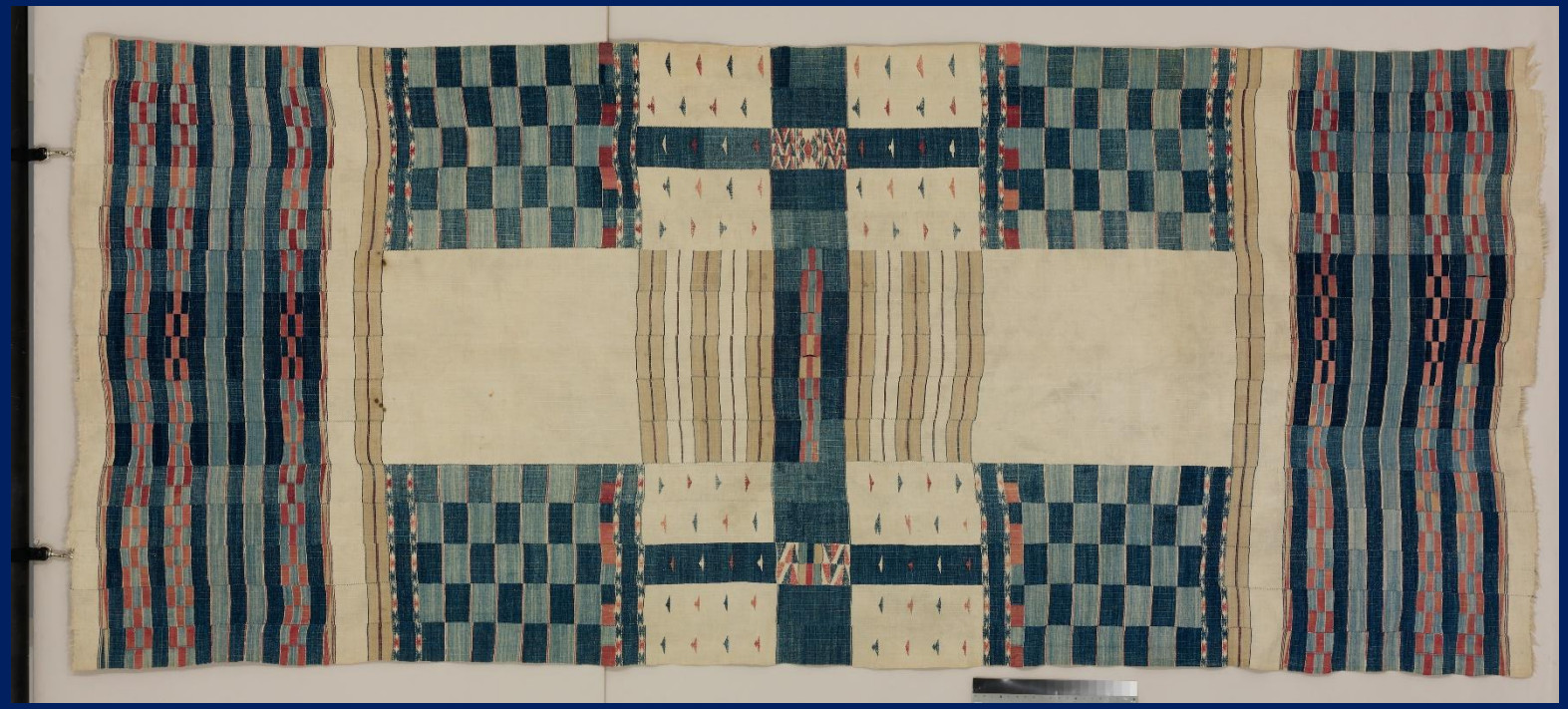
- Incorporating the treatment of cognitive deficits into the overall plan of psychiatric care and plan of recovery can help improve outcomes
  - Reduce barriers to participation in rehabilitation therapies
  - Improve independent functioning
  - Increase ability to access coping skills and other internal resources to deal with post-TBI disabilities and psychiatric disorders

- Most evidence-based treatment for post-TBI cognitive disorders?
  - Comprehensive cognitive rehabilitation and training programs
- Other interventions for post-TBI cognitive disorders
  - Exercise
  - Medications:
    - Data is limited, but some evidence to support
      - Stimulants
        - Methylphenidate is best-studied stimulant in TBI
        - Primarily improves attention and fatigue
        - Few significant adverse effects
      - Cholinesterase inhibitors, like donepezil and rivastigmine

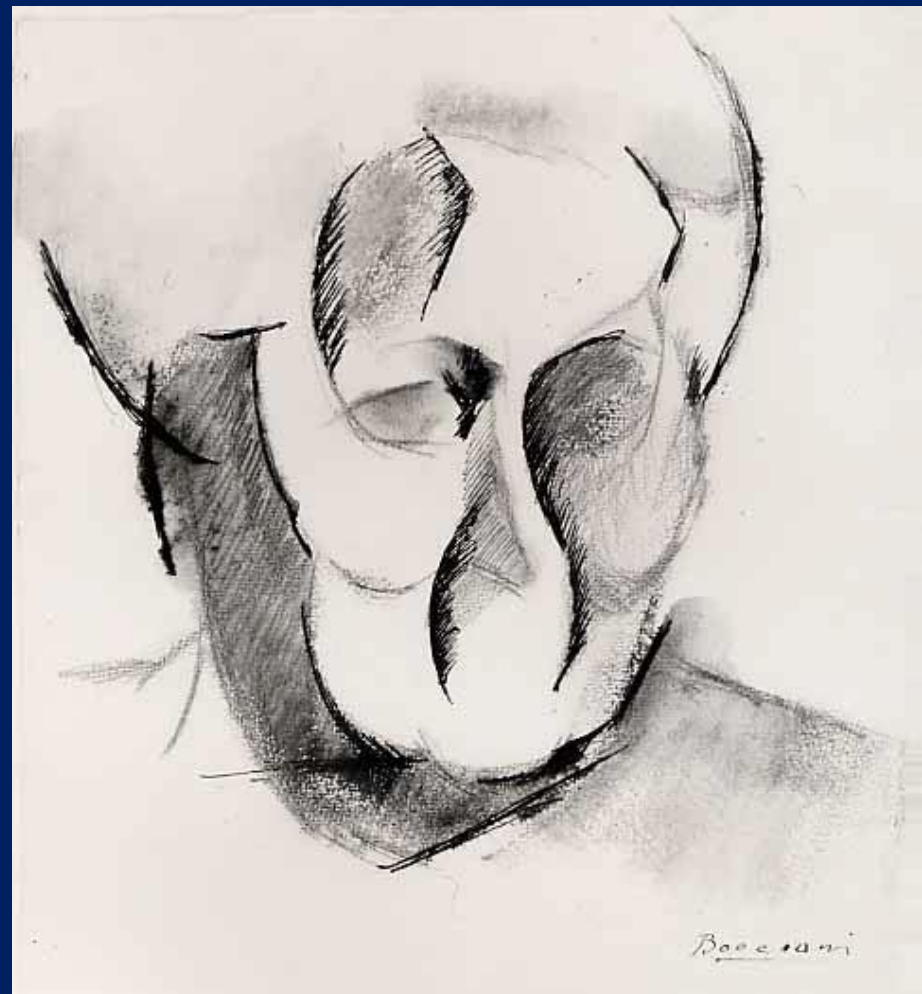
- Avoid treatments with adverse cognitive side effects
  - Good idea in all patients, but especially important in post-TBI cognitive impairment
  - Cognitively-impairing medications in patients with TBI can:
    - Iatrogenically worsen cognitive deficits
    - Impede rehabilitation participation
    - Adversely affect overall recovery

- Anticholinergic drugs inhibit the function of acetylcholine, the key neurotransmitter involved in memory
  - Anticholinergic drugs worsen cognition in individuals with TBI (actually, they do this in everyone)
    - Effects may persist even after discontinuation
  - In the general (non-TBI) population, multiple large studies have robustly demonstrated that individuals who take anticholinergic drugs have a significantly increased risk of developing irreversible dementias like Alzheimer disease
    - Risk is greater with higher doses of anticholinergic drugs and use of multiple anticholinergic agents
    - TBI is already a dementia risk factor, so let's not add any more!

- Benzodiazepines, Z-drugs like zolpidem, and the anticonvulsant topiramate can adversely affect cognition in the general population
  - May have even greater harmful effects in cognitively vulnerable or cognitively impaired patients with TBI
  - Though unlike anticholinergic drugs, not clear they cause dementia



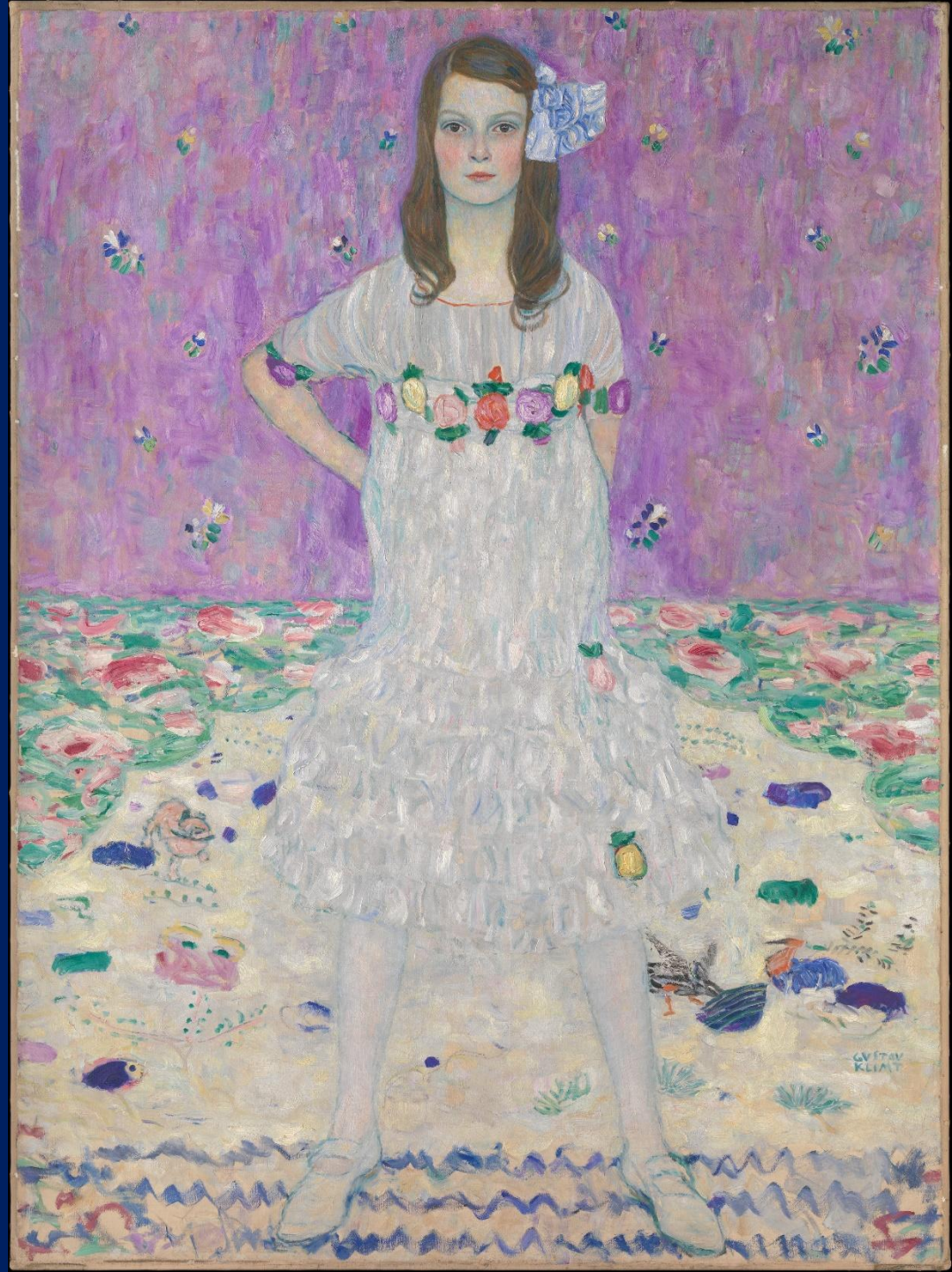
- Many individuals with TBI develop chronic migraines
  - Unfortunately, may end up on prophylaxis regimens that significantly worsen their cognition, like amitriptyline and topiramate
  - This is harmful and unhelpful, because there are many evidence-based cognitively safer options
    - Many also treat psychiatric symptoms
    - Some effective and cognitively safe migraine prophylaxis options:
      - Venlafaxine (just as effective as amitriptyline in head-to-head RCT)
      - Duloxetine
      - Propranolol
      - Magnesium



- 55-year-old woman admitted to inpatient rehabilitation following TBI
- On admission:
  - She could hardly interact with others
  - Appeared minimally aware of her environment
  - Not participating much in rehab therapies
- Her meds:
  - Oxybutynin for bladder incontinence
  - Amitriptyline for headache prophylaxis
  - Hydroxyzine for anxiety
- What are some safer medication options?

- After neuropsychiatry consult:
  - Anticholinergic drugs were stopped
  - Started on a cognitively safer regimen:
  - Mirabegron for incontinence
  - Magnesium oxide for migraine prophylaxis
  - Sertraline for anxiety*
- Outcome: her functioning markedly improved
  - She eventually resumed most of her usual prior life activities

*Could have used venlafaxine to also target migraines; however patient had good response to prior trial of sertraline several years earlier; had stopped prior to TBI because no longer needed



Cognitive symptoms after a mild TBI (aka postconcussive cognitive symptoms)

- Debate on whether isolated mild TBI can produce significant and permanent cognitive changes
- Reports of concentration and memory deficits in the first weeks post-injury
- Objective cognitive deficits persisting up to 3 to 6 months post-injury in some studies
- Spontaneous recovery within the first 3-12 months for most patients with single uncomplicated TBI

Cognitive symptoms after mild TBI: caused by the TBI or something else?

- Post-mild-TBI cognitive symptoms occur at similar rates in healthy individuals and patients with non-brain-related ortho injuries
- Individuals with premorbid psychiatric conditions more likely to experience long-lasting cognitive symptoms after mild TBI
  - Why???
    - Psychiatric conditions can cause cognitive symptoms

    AND/OR
    - Baseline disruptions to neural circuitry could predispose to both psychiatric symptoms and cognitive vulnerability

Imaging abnormalities in “uncomplicated” mild TBI: could reflect injuries that directly cause cognitive changes

- Complicated mild TBI generally refers to abnormalities on conventional clinical imaging: routine CT, routine MRI
- Advanced imaging may show abnormalities even in “uncomplicated” mild TBI
  - DTI, DTI tractography, volumetric MRI, functional imaging, etc
- Structural and functional findings in uncomplicated mild TBI
- Decreased white matter integrity in corpus callosum; may spread during first year after injury
  - Associated with worse executive functioning
- Reduced blood flow in cingulate gyrus
- Reduced hippocampal volume in athletes with a history of concussions
  - More concussions = less hippocampal volume

Correlation ≠ causation in neuroimaging (and otherwise)

- Mediating variables:
  - Different amounts of head movements during MRI acquisition in individuals with schizophrenia and healthy controls
  - Volume averaging gives rise to erroneous conclusions about brain volumes in schizophrenia
- Directions of causation can be opposite of what we assume:
- Vietnam Veteran twin study of hippocampus volume and PTSD
  - Combat veterans with PTSD had smaller hippocampal volumes than combat veterans without PTSD
  - BUT: non-combat exposed twins of veterans with PTSD also had smaller hippocampal volumes than non-combat-exposed twins of veterans without PTSD

Mild TBI and persistent cognitive symptoms: why the uncertainty?

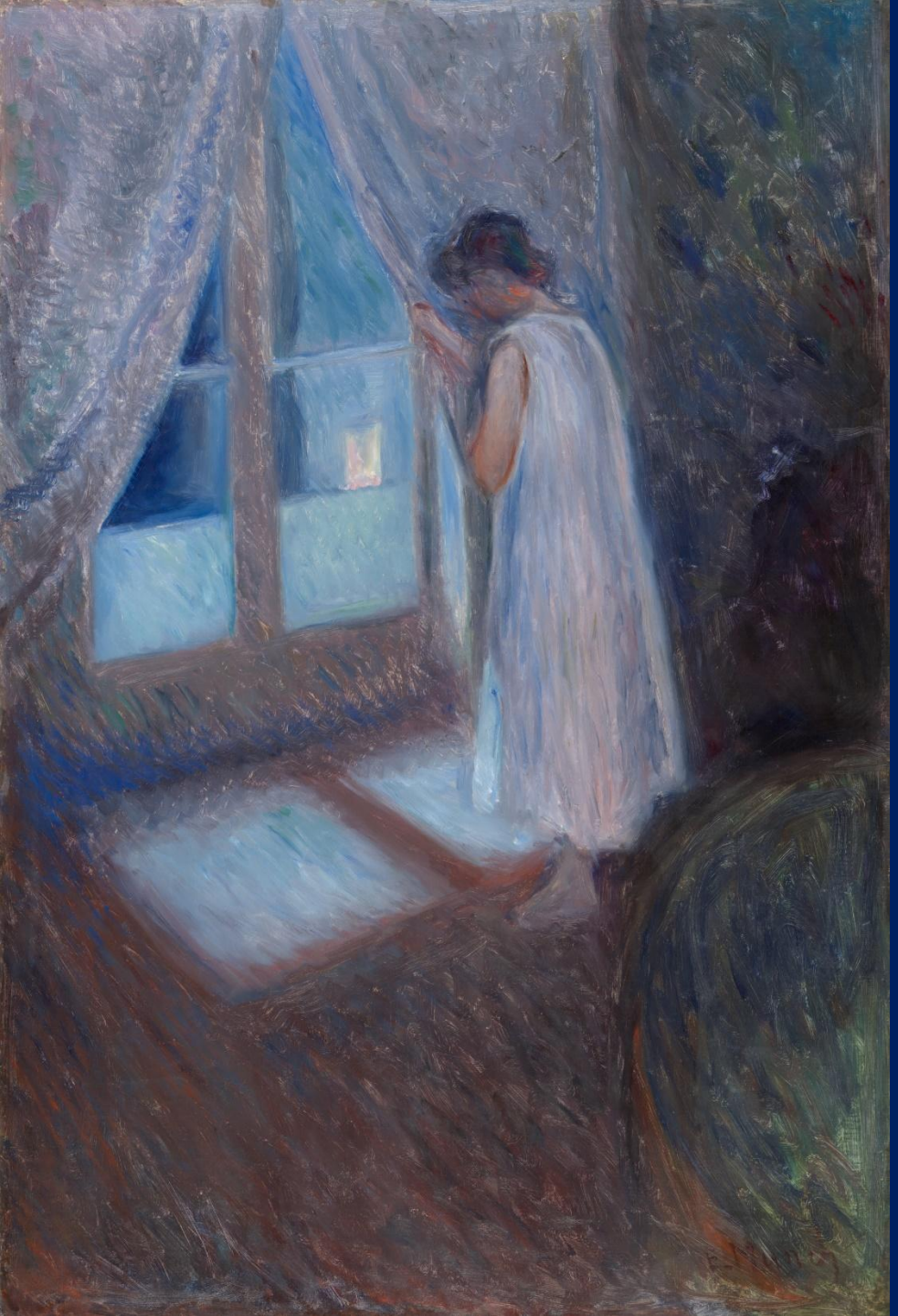
- Mild TBI encompasses a broad range of severity
  - Symptoms at time of event can range from momentary confusion or disorientation, to LOC for up to 30 min followed by hours of post-traumatic confusional state
- Rate of persistent cognitive issues may vary with the severity of the mild TBI
- Long-lasting cognitive deficits more frequent in patients with complicated TBI

Mild TBI and persistent cognitive symptoms: what to do?

- Educate patients on the expected course of improvement after mild TBI.
- Treat comorbid psychiatric conditions in patients with persistent cognitive symptoms following mild TBI.
- Stop anticholinergic drugs and other medications with adverse cognitive effects
- Consider other causes of cognitive impairments, such as obstructive sleep apnea, vitamin deficiencies, substance use, neurodegenerative disorders, other treatable causes of cognitive disorders
- Refer patients to specialists for further assessment, treatment, and/or rehabilitation of cognitive, somatic, and sleep complaints, as appropriate.

- TBI and later-onset dementia
  - TBI may cause or contribute to dementia
    - Specifically, TBI can cause/contribute to the types of dementia seen in the general population, like Alzheimer disease
      - Data discussed here refers to these general types of dementia (NOT to the TBI-specific syndrome of CTE)
  - Can begin decades after injury
  - Can occur in individuals who had no immediate significant post-TBI cognitive symptoms.

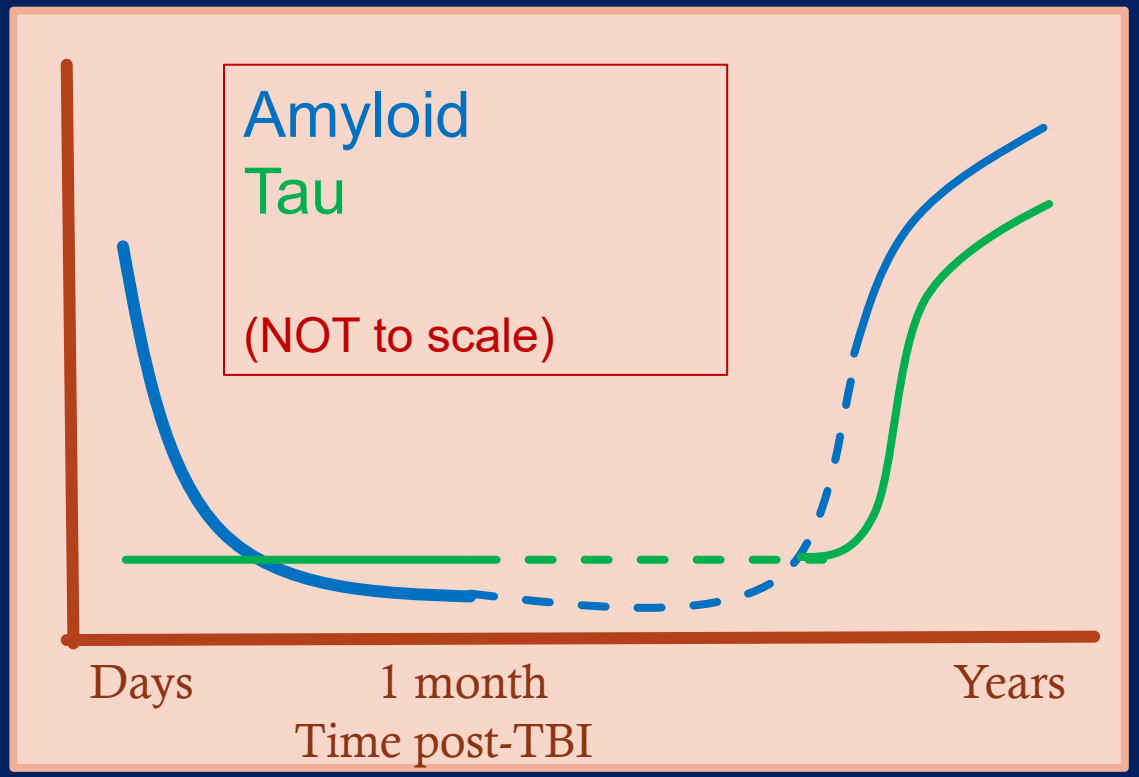
- Most (though not all) studies show that TBI increases the risk for Alzheimer disease and other dementias over the next several decades
  - Even if returned to their normal cognitive baseline following TBI
  - How much does TBI increase risk for dementia?
    - 80%-300% for all TBIs considered together
      - Even higher in moderate-severe TBI or with multiple TBIs



- How does TBI increase risk for later-onset dementia?
  - No one knows for sure
  - But may involve amyloid plaques and neurofibrillary tangles and their associated biomarkers
    - These are also the neuropathology associated with Alzheimer disease

- In AD:
  - Hyperphosphorylated tau protein clumps together into neurofibrillary tangles
    - Neurofibrillary tangles are relatively specific to neurodegenerative disease
    - May represent the underlying neuropathologic mechanism
  - Amyloid plaques
    - Found in AD
    - Also found in cognitively healthy older adults
    - May represent a downstream consequence of neurodegeneration, rather than a cause of it
- Neuropathology of TBI
  - Studied from autopsy brain tissue, or resected tissue from living patients

- TBI brain tissue shows abnormalities similar to those seen in Alzheimer disease
- Several days post-TBI:
  - Increased amyloid deposits
  - Generally NO tau abnormalities
- 1 month post-TBI: month after TBI
  - NO increased amyloid plaques
  - NO increased neurofibrillary tangles
- Several years post-TBI
  - Increased amyloid plaques
  - Increased neurofibrillary tangles
- CSF in living patients with TBI:
  - Shortly after TBI: increased tau protein
  - During recovery from TBI: tau protein decreases as clinical condition improves

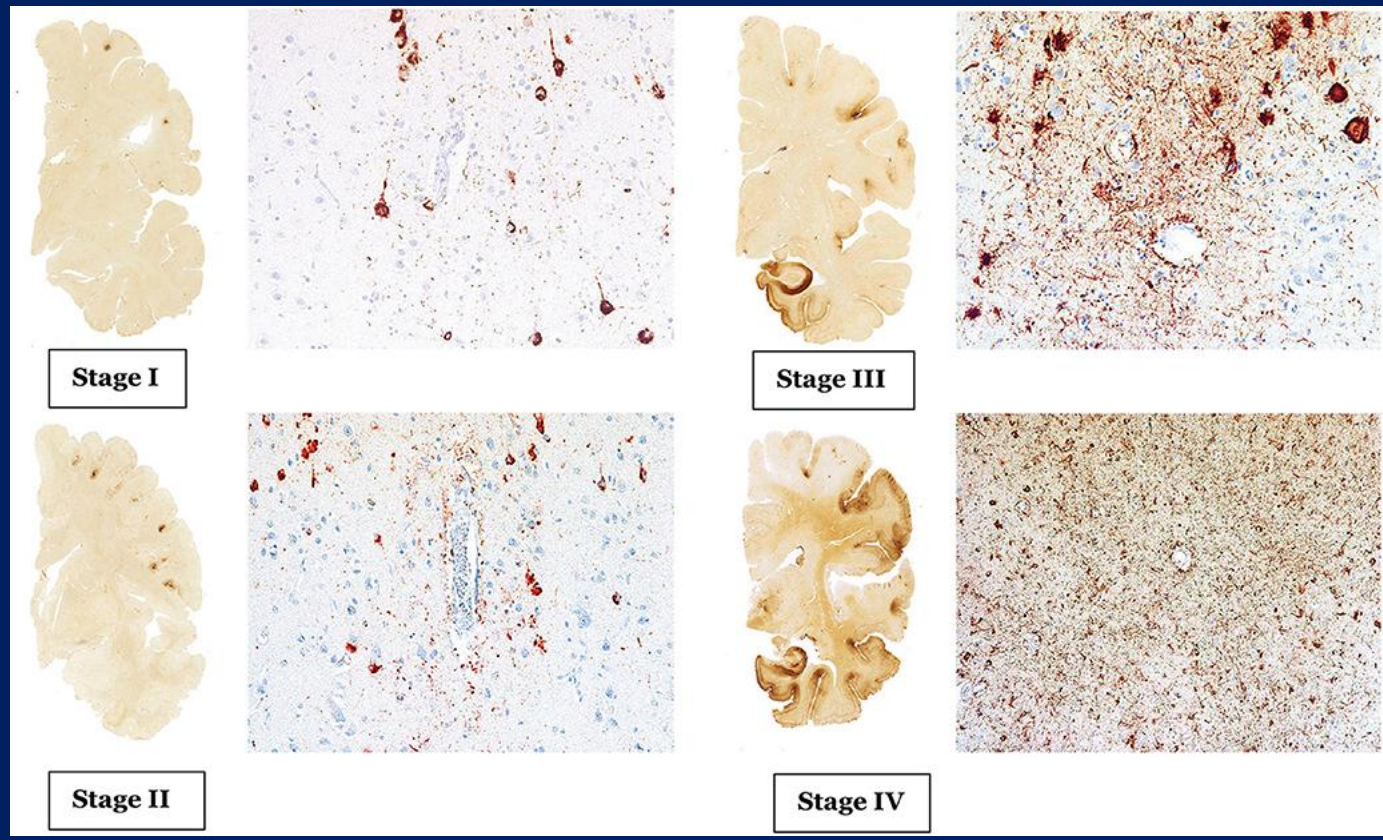


- One hypothesis for link between TBI and dementia:
  - TBI sets in motion some neuropathologic process that doesn't happen immediately but rather develops over time

Chronic traumatic encephalopathy

- Type of late-onset dementia caused by repetitive head trauma
- Clearly many individuals who suffer repeated head traumas (like football players) subsequently develop dementia later in life
- BUT:
  - Is CTE represents a distinct type of dementia?
    - ie, does it have:
    - Unique causative mechanism
    - Distinct clinical presentation
    - Specific neuropathology
  - Or do the cognitive / psychiatric / motor / neuropathologic findings seen in these individuals represent conventional dementia syndromes that can occur in the absence of TBI?
- Longstanding controversy, but we are finally starting to get some answers

- CTE originally described by neuropathologists, based on neuropathologic data showing novel patterns of tau accumulation not seen in other conditions
  - CTE neuropathology involves abnormal tau accumulation, like AD
  - But occurs in different brain locations than in AD and other conventional tauopathies:
    - In CTE, “p-tau aggregates in neurons, with or without glial tau in thorn-shaped astrocytes, at the depth of a cortical sulcus around a small blood vessel, in deeper cortical layers not restricted to subpial and superficial region of the sulcus” (2016 NINDS/NIBIB criteria)
    - This neuropathology is relatively specific to individuals with a history of repeated head trauma



CTE neuropathology

- Until recently, CTE neuropathology was much better-established than the clinical features
  - Most investigations had looked at brain findings in deceased individuals, and then worked backwards by interviewing their families about symptoms during life
    - Reported clinical symptoms were vague and nonspecific (ie common in all types of dementia)
      - “cognitive problems”, “psychiatric symptoms”
    - Subject to recall bias
- Large prospective studies of individuals with repeated head trauma are now underway
  - 2021: New consensus CLINICAL criteria for traumatic encephalopathy syndrome

Traumatic encephalopathy syndrome

- TES = clinical correlate of the neuropathologic condition of CTE
  - DIAGNOSE CTE Research Project: criteria for TES developed by expert consensus panel of clinician-scientists (neurology, neuropsychology, neurosurgery, psychiatry, PM&R)
  - Looked at RHI exposure history, symptom profiles, and clinical course to identify features SPECIFIC to PATHOLOGICALLY CONFIRMED cases of CTE

- ie, NOT just symptoms seen in anyone with any kind of head injury who developed any kind of cognitive impairment
- Goal to identify clinical features commonly present in pathologically confirmed CTE but not in other forms of dementia/neuropsychiatric disorders or in the general population

REQUIRED criteria for diagnosis of traumatic encephalopathy syndrome

I. Substantial Exposure to Repetitive Head Impacts

History of substantial exposure to repetitive impacts to the head is required. Impacts may or may not have been associated with clinical symptoms/signs of TBI. Examples of substantial exposure include:

- Involvement in high-exposure contact or collision sports such as boxing, American football, ice hockey, soccer, rugby, professional wrestling, mixed martial arts, motocross, or bull riding
  - For American football, minimum of 5 y of organized play; should include ≥2 y at the high school level or beyond
  - Exposure risk thresholds for other sports not yet established but should be a substantial number of years (e.g., ≥ 5 y) at a level of play involving routine RHIs
- Military service involving RHIs, including combat exposure to multiple blast and other explosions, noncombat exposure to explosions (including blasting and forced opening of locked doors), or multiple blows to the head over an extended period of time (e.g. repeated blows with a padded military training weapon)
  - Exposure risk thresholds for military service not yet established.
- Other sources involving multiple head impacts over an extended period of time, including domestic violence, head banging, or vocational activities such as breaching locked doors and other barriers by first responders.
  - Exposure risk thresholds for these sources not yet established.

AND

II. Core Clinical Features (REQUIRED)

Cognitive impairment or neurobehavioral dysregulation, or both, is required to meet TES criteria. A progressive course is also required to meet TES criteria.

- **Cognitive impairment (all 4 are required)**
  - As reported by self or informant, or by clinician's report.
  - Representing a significant decline from baseline functioning.
  - **With deficits in episodic memory and/or executive functioning** (additional domains may be impaired in addition to these).
  - Substantiated by impaired performance on formal neuropsychological testing (if available), as defined by performance at a level of at least 1.5 SDs below appropriate norms, accounting for the individual's estimated premorbid functioning. If formal neuropsychological testing is not available, there should be substantial evidence of impairment on a standardized mental status examination (e.g., Montreal Cognitive Assessment and Mini-Mental State Examination) by a clinician experienced in the evaluation of cognition.
- **Neurobehavioral dysregulation (all 3 are required)**
  - As reported by self or informant, or by clinician's report.
  - Representing a significant change from baseline functioning.
  - **With symptoms and/or observed behaviors representing poor regulation or control of emotions and/or behavior, including explosiveness, impulsivity, rage, violent outbursts, having a short fuse (exceeding what might be described as periodic episodes of minor irritability), or emotional lability.** These symptoms and/or observed behaviors do not appear to represent a transient response to life events, e.g., divorce, death of loved one, and financial problems.
- **Progressive course**
  - Evidence of progressive worsening of these clinical features over a period of at least 1 year in the absence of continued exposure to RHIs or TBI. The evidence should be supported by serial standardized testing or clear history supporting a change in functioning over time.

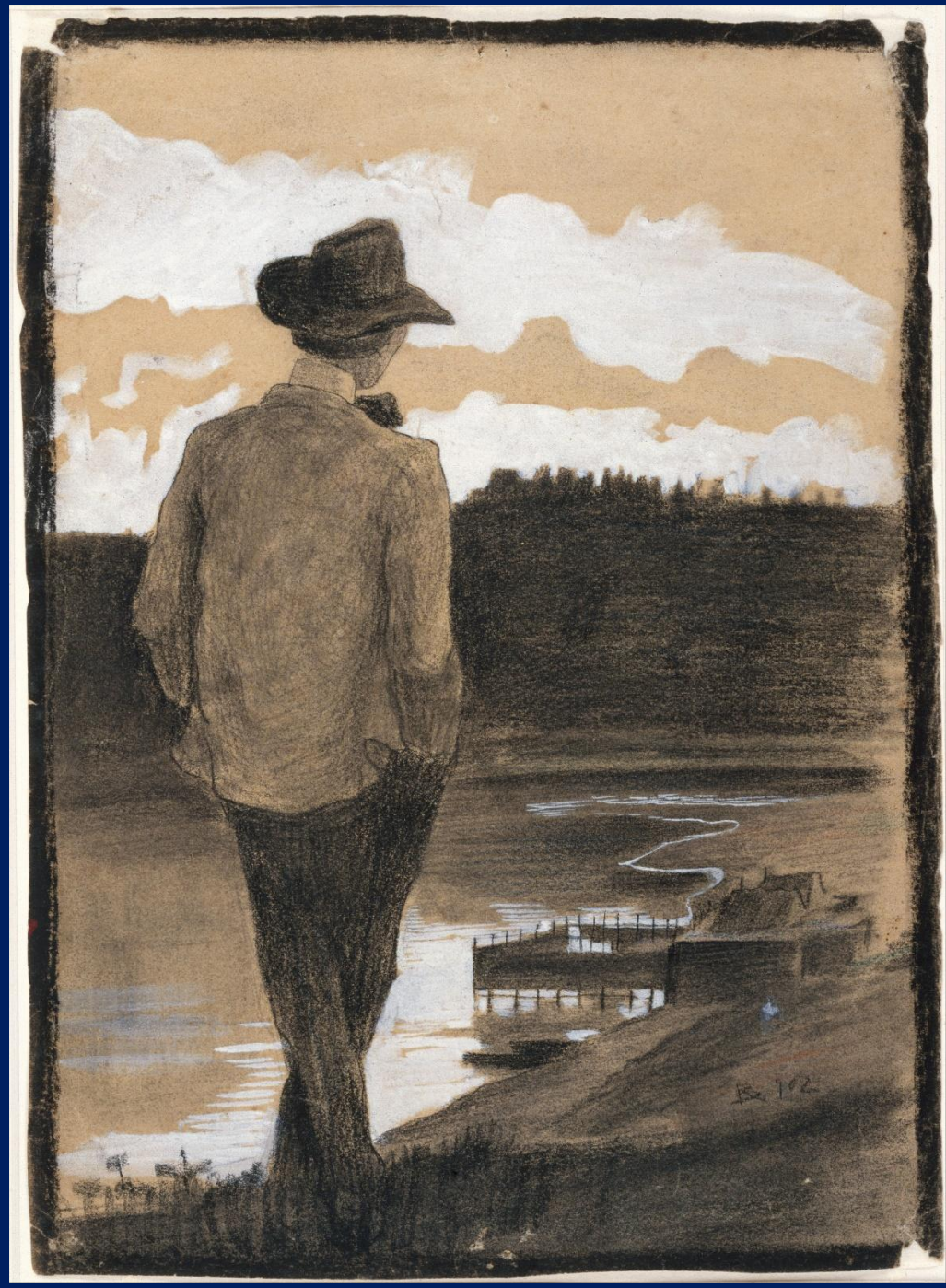
AND

III. Not Fully Accounted for by Other Disorders

- Pattern of cognitive deficits and/or neurobehavioral not fully accounted for by other preexisting, established, or acquired nondegenerative nervous system, medical, or psychiatric disorders and conditions.

Repetitive head injury ≠ TBI

- RHI criteria for TES does NOT require a history of clinically apparent TBI
- Even multiple clinical TBIs don't necessarily meet criteria for RHI for TES
- Though, many individuals with TES do have a history of both RHI and clinically apparent TBI
- Reason: CTE neuropathology occurs in individuals with RHI regardless of if they also had clinical TBI; and CTE neuropathology not generally seen in individuals with multiple TBIs who don't meet the RHI threshold
  - However, a few cases of individuals with single moderate-severe TBI who have a CTE/TES like phenotype



RHI and TES: need RHI to get CTE/TES

- Causes of RHI exposure in CTE data:
  - American football: 73%
  - Boxing: 16%
  - Others (military exposure, domestic violence, other sports, etc): 11%
- Brain bank study looking at individuals with neurogenerative disease:
  - 1/3 of individuals with a history of contact sports (mostly amateur football) had CTE pathology
  - 0 individuals without contact sports exposure history had CTE pathology
- More RHI exposure = higher likelihood of CTE pathology and worse pathological severity
  - Risk of CTE doubles for every 2.6 years of football

Cognitive findings in TES

- Cognitive domains most commonly involved: episodic memory, attention, and executive functioning (over 60% of cases)
  - Other domains like language and visuospatial functions can also be affected, but not as common
- Progressive worsening of cognition / functioning in >95% of cases

Psychiatric symptoms in TES

- "Neurobehavioral dysregulation", not just any mood and behavior change
  - Neurobehavioral dysregulation: violent, impulsive, or explosive behavior; aggression, rage; impulsivity; emotional lability
    - Present in over 40% of autopsy-confirmed CTE cases; much lower prevalence in general population or other forms of dementia
- Other psychiatric symptoms (anxiety, depression, apathy, paranoia): don't count towards TES diagnosis; but if present, are supporting features that can increase the diagnostic confidence
  - Why don't they count towards diagnosis?
    - These symptoms occur in 30% or more of CTE cases
    - BUT also common in general population and other forms of dementia
      - So not SPECIFIC to TES
    - Counting these nonspecific symptoms towards diagnosis could lead to a lot of false positives

Supportive Features Used in Determining Provisional Levels of Certainty for CTE Pathology

- Not used to make TES diagnosis
- Among individuals diagnosed with clinical TES, supportive features used to establish the likelihood that the problem is indeed due to CTE pathology
  - These supportive features are frequently present in individuals with underlying CTE pathology but are too nonspecific to qualify as core clinical features

SUPPORTIVE FEATURES

- Delayed onset:
  - Core clinical features begin after a period of stable functioning following RHI exposure
- Motor signs:
  - Parkinsonism: bradykinesia, rigidity, rest tremor, and parkinsonian gait disorder
  - Other motor signs: dysarthria, ataxia, and imbalance (not due to another cause)
  - Motor neuron disease features (UMN + LMN signs)
- Psychiatric features:
  - Anxiety
  - Apathy
  - Depression
  - Paranoia

Further classify TES based on:

- Level of functional dependence/dementia
- Level of diagnostic confidence

LEVEL OF FUNCTIONAL DEPENDENCE/DEMENTIA

Independent:
- Able to perform job, household responsibilities, and social/community roles at usual level
- Fully independent in instrumental and basic activities of daily living (ADLs)

Subtle/Mild Functional Limitation:
- Slightly reduced performance in responsibilities and interests
- Mostly independent but may face challenges in some instrumental ADLs
- Fully independent in basic ADLs

Mild Dementia:
- Definite impairment in instrumental ADLs
- Engaged in some home, family, social, and community activities
- Needs cues for some basic ADLs

Moderate Dementia:
- Not independent but can attend some functions outside the home
- Preserves only simple chores
- Restricted interests
- Requires assistance with basic ADLs

Severe Dementia:
- Unable to participate in functions outside the home
- No significant function in the home
- Impaired basic ADLs
- Not independent in self-care
- Frequent incontinence

PROVISIONAL LEVELS OF CERTAINTY FOR CTE PATHOLOGY

Possible CTE
- Substantial exposure to a contact/collision sport: exposure to American football ≥5 y (including at least 2 y at high school or beyond the high school level) or other contact/collision sport (e.g., boxing) to an equivalent extent.

AND
- Cognitive impairment as defined in Core Clinical Features

AND
- A minimum of 2 of the following 5 criteria:
  - Delayed onset
  - Supporting motor signs
  - One or more supporting psychiatric features
  - Neurobehavioral dysregulation as defined in Core Clinical Features
  - Severity of functional dependence = subtle/mild functional limitation or worse

Probable CTE
- Extensive exposure to a contact/collision sport: exposure to American football ≥11 y (including at least some at college level); or boxing or other sports with high-level exposure to RHIs to an equivalent extent

AND
- Cognitive impairment as defined in Core Clinical Features

AND
- A minimum of 3 of the following 5 criteria:
  - Delayed onset
  - Supporting motor signs
  - One or more supporting psychiatric features
  - Neurobehavioral dysregulation as defined in Core Clinical Features
  - Severity of functional dependence = mild dementia or worse

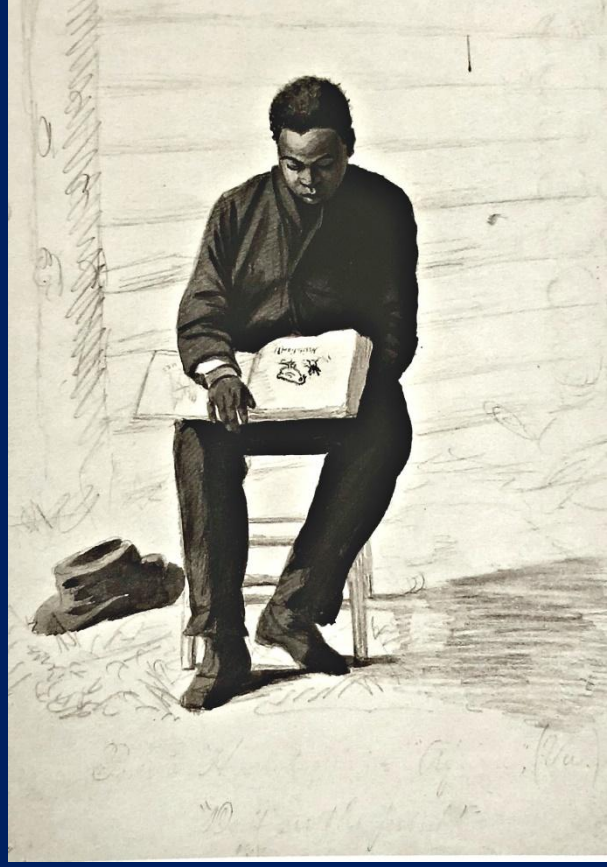
Definite CTE with TES
- Meets TES criteria as well as CTE, confirmed by postmortem neuropathologic diagnosis based on current NINDS criteria for neuropathologic diagnosis of CTE

TES vs. CTE

- TES is a clinical syndrome diagnosed in life; CTE is a neuropathologic diagnosis made at autopsy
  - Not everyone with CTE pathology at autopsy had TES symptoms in life
- TES criteria primarily for research purposes at this point; need more data to understand how to best use them clinically
- Be VERY careful about diagnosing TES
  - Criteria not 100% sensitive or specific; clinicians and patients need to understand that neuropathologic CTE much better established than clinical TES criteria
  - Avoid premature diagnostic closure: “you played football, so your dementia must be TES/CTE; we don’t need to look for any treatable etiologies”
  - TES diagnosis (like any dementia diagnosis) can be devastating for patients and families; important to provide support

Preserving cognitive health in individuals with a history of TBI

- TBI can increase dementia risk, but this doesn't mean patients with TBI will inevitably get dementia
  - We need to let patients know this!
  - Lifestyle modifications may reduce the risk of dementia in general:
    - Regular exercise
    - Quit smoking
    - Treat hearing loss
    - Avoid heavy alcohol use
    - Mediterranean diet, DASH diet or Mediterranean-DASH diet
    - Cognitively stimulating activities
    - Increase social contact
    - These lifestyle modifications haven't been studied in TBI
      - But safe, cheap, and improve health outcomes in noncognitive areas like cardiovascular disease and depression
      - So might as well give them a try!



- Avoid medications that increase risk of dementia (anticholinergic drugs)
- TBI and stroke
  - TBI increases the risk of future (ie, not in immediate acute TBI phase) ischemic stroke by 1/3-2 times
  - Cerebrovascular disease increases the risk of both vascular and neurodegenerative dementia
    - So need to optimize control of vascular risk in patients with TBI (and everyone else) to help them maintain good cognitive health throughout their lifespan
      - Smoking cessation
      - Control HTN/DM
      - Avoid drugs with adverse metabolic side effects (eg quetiapine, olanzapine) unless no response to other options
        - ie, ok for otherwise-treatment-refractory schizophrenia, NOT for sleep

Treatment of TBI-associated dementia / TES

- Currently no evidence that conventional dementias, like Alzheimer disease, require different treatments in people with a history of TBI than in people with no history of TBI
- No specific treatments for CTE / TES
  - Reasonable options include the treatments used in:
    - Other types of dementia such as Alzheimer disease
    - Acute post-TBI cognitive deficits
    - Idiopathic psychiatric syndromes
  - Since no real evidence-based treatments:
    - Monitor for improvement or worsening with various interventions
    - Avoid medications with significant side effects

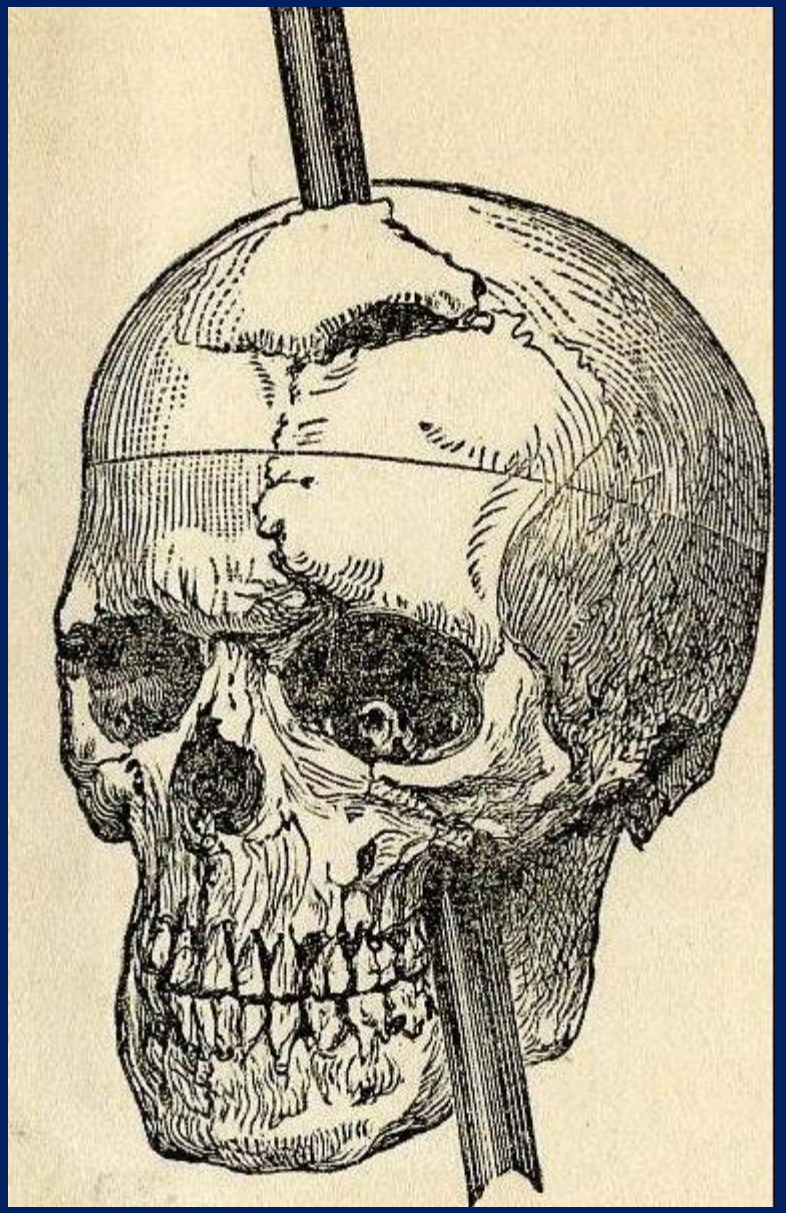
There is hope after TBI

- Meaningful recovery is possible
  - Even in patients with persistent neuropsychiatric deficits
- Nearly 2/3 of individuals with severe TBI (who survive their injuries) return to work within 2 years
  - 3/4 of those who return to work, go back to their prior job
  - Those who change jobs often took jobs that required less qualifications
- Often still have neuropsychiatric symptoms, but still able to work and resume other normal life functions

Phineas Gage: the real story

- 25-year-old construction foreman for a railroad company who suffered a severe penetrating TBI.
  - 43-inch long, 13.5-pound iron rod passed through his left frontal lobe, exiting the top of his skull
- Despite being able to talk and walk away from the accident with assistance, Gage's physician (who cared for him immediately following the TBI and for a few years afterwards) described him as inconsiderate, capricious, obstinate, and profane after the accident.
  - Experienced significant changes in behavior and personality, even though his intellect remained relatively intact: "He was no longer Gage."
- He got fired from his railway job

BUT…



- 4 years after the accident, Phineas Gage returned to skilled employment as a stagecoach driver
  - This work required good executive functioning and social skills:
    - He had to “rise early in the morning, prepare himself, and groom, feed, and harness the horses; he had to be at the departure point at a specified time, load the luggage, charge the fares and get the passengers settled; and then had to care for the passengers on the journey, unload their luggage at the destination, and look after the horses. The tasks formed a structure that required control of any impulsiveness he may have had.”
- Worked successfully in this job for 6 years until he developed intractable epilepsy and then died from status epilepticus.

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