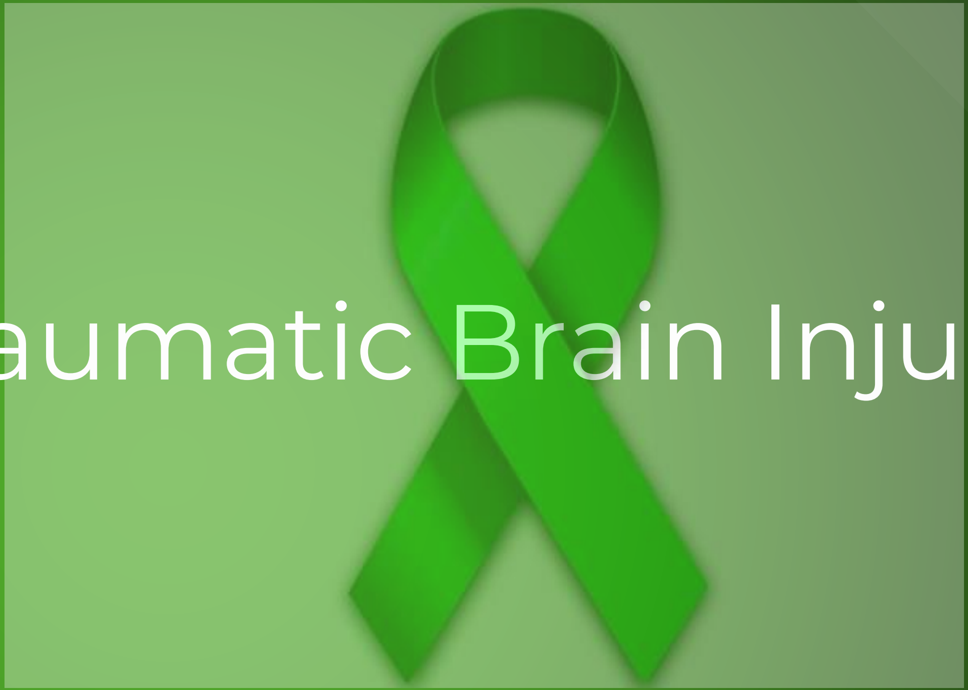
Traumatic Brain Injury



By: The Traumatic Fingerprint

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What is Traumatic Brain Injury (TBI)?

- A traumatic brain injury is an injury to the brain from an external mechanical force, that may lead to permanent or temporary damage
  - Damage can be cognitive, physical, or psychological
  - It is non-degenerative and non-congenital

- Glasgow Coma Scale (GCS)
  - Mild (score 13-15): alert and drowsy mentality, high recovery rate
  - Moderate (score 9-13): lethargic, stuporous
  - Severe (score 3-8): comatose, unresponsive to external stimuli

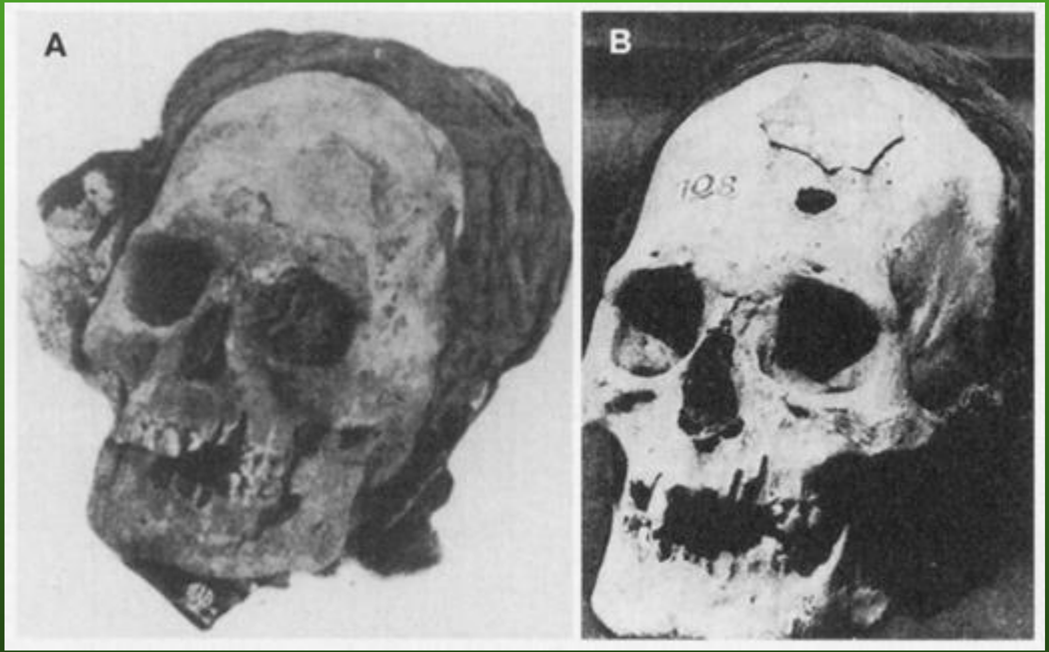
- Types of TBI
  - Open (penetrating): scalp/skull is broken, fractured, or penetrated
  - Closed: outside force impacts the head, but the skull remains intact

History of Traumatic Brain Injury in the Past

Ancient Trephination in the Egyptians

- First recorded neurosurgery burrowed holes in skulls
  - Holes covered with cranioplastic substance
    - Dependent on social rank
      - Gourd if commoner, gold if nobility
  - ~50% of patients survived, but suffered from TBI

- Dramatic Increase in 20th Century
  - Urbanization
    - More automobiles = higher probability of automobile accidents
    - Heavy machinery



Why is it relevant?

- More than 10 million individuals worldwide are affected by traumatic brain injury (TBI) annually
  - The annual incidence of TBI in the United States is over 1.7 million
  - 30% of all cases result in death according to CDC
  - Survivors may have symptoms persist for a few days or the rest of their lives

- TBI is a major public health and socioeconomic concern
  - In 2009, TBI accounted for at least 2.4 million emergency department visits, hospitalizations, or deaths in the US alone
  - In 2010, TBI resulted in $11.5 billion in direct medical costs and $64.8 billion in indirect costs to the US health system

Meet Daniel...

Daniel (age 25) was involved in a collision between a work van and a 75,000 ton fuel truck

He should have been on his way to the time clock but instead was rushed to the hospital to fight for his life

His injuries included:

- Penetrating skull fracture resulting in traumatic brain injury
- Blow-out fracture to the right orbital
- Broken jaw bone
- Broken ribs
- Dislocated shoulder
- Whiplash
- Permanent loss of vision in the right eye

This accident occurred in the blink of an eye but resulted in injuries that will affect Daniel for the rest of his life.

Diagnosis

- Glasgow Coma Scale (GCS)
  - Ability to speak
  - Ability to open eyes
  - Ability to move
- Measurement for Level of TBI
  - Mild, Moderate, or Severe
- Speech and Language Tests
  - Strength and coordination of muscles controlling speech
  - Grammar, vocabulary, reading, and writing
- Cognition and Neuropsychological Tests
  - Cognition
    - Process of thinking, reasoning, problem solving, information processing, and memory
  - Neuropsychological
    - Specialized task-oriented tests for brain-behavior relationships, higher cognitive functioning, and basic sensory-motor processes
- Brain imaging
  - Computed tomography (CT): X-rays from multiple angles to create a complete picture
    - Bleeding, swelling, bruised tissue
  - Magnetic resonance imaging (MRI): Magnets and radio waves
    - More detailed images than CT, but time consuming
  - Intracranial pressure (ICP) monitoring: Probe inserted through the skull to monitor swelling
    - Pressure can cause additional damage
    - Shunt or drain placed into the skull to relieve ICP

Acute vs Delayed Traumatic Brain Injury

- Acute Injury
  - Brain tissue is destroyed upon impact
    - Neurons
    - Glia
    - Endothelial cells

- Delayed Injury
  - Toxins are released from damaged cells (necrosis) that starts a cascade in neighboring cells
    - Exacerbation of the primary injury
      - Spreads from initial point of impact

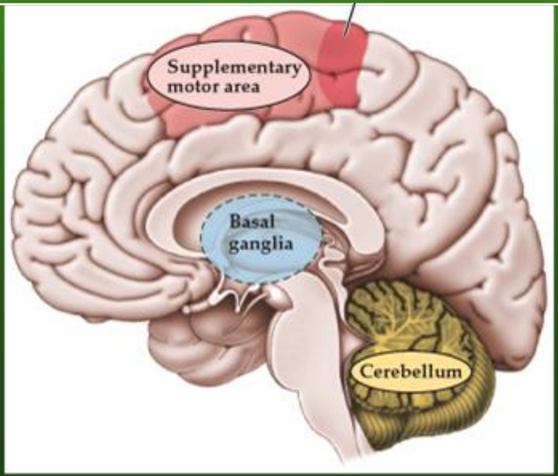
- How is the body affected?
  - Blood-brain barrier breakdown
  - Widespread neuroinflammation
  - Diffuse axonal injury
  - Subsequent neurodegeneration

Symptoms of TBI

Positive Symptoms (ex. Psychotic behavior)	Negative Symptoms (ex. "Flat affect")
❖ Sensitivity to light and noise ❖ Headaches ❖ Confusion ❖ Amnesia ❖ Slurred speech ❖ Nausea and vomiting ❖ Fatigue	❖ Impaired memory, movement, sensation ❖ Loss of balance ❖ Changes in sleeping patterns

Neuron connections affect gait and posture

- Connections to motor cortex, basal ganglia, and/or cerebellum disrupted
  - Disrupt signaling from cortices to spinal cord for smooth movements
    - Cause impaired posture, loss of balance, shakier movements



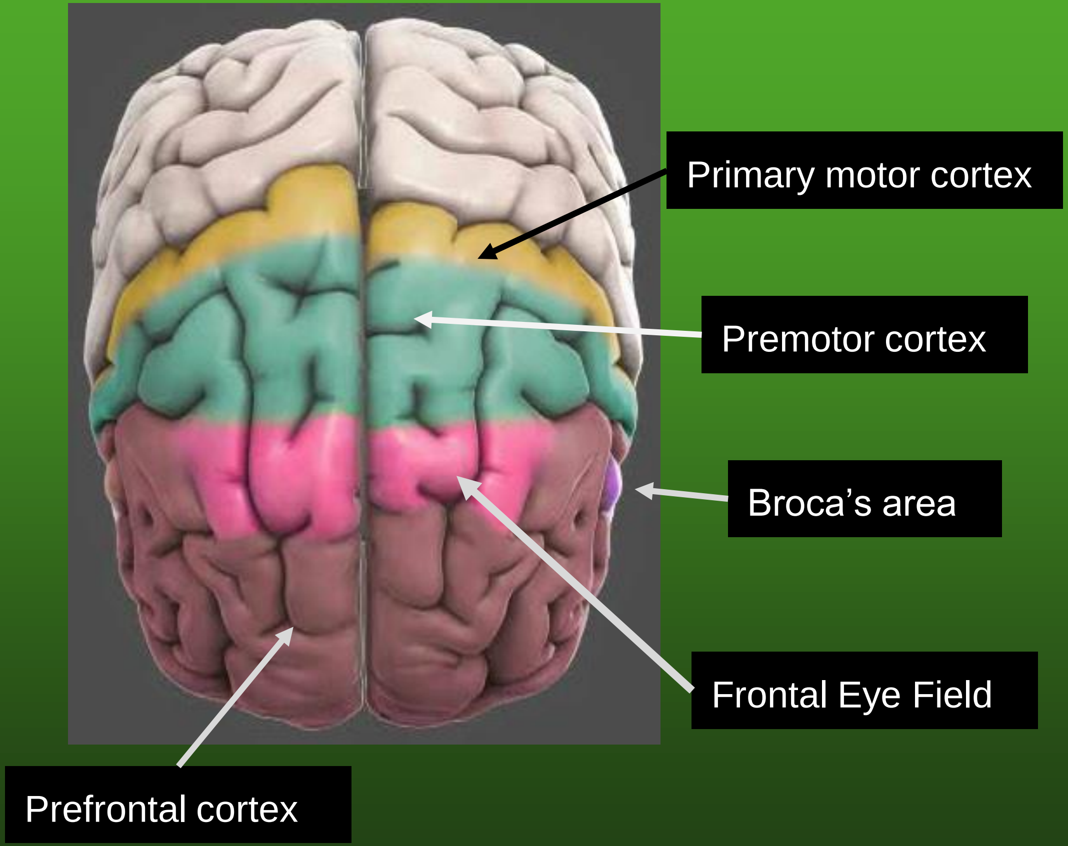
Information extracted from Brain Map

Frontal Lobe

Associated with damage:

- Paralysis
- Loss of spontaneity in social interactions
- Mood changes
- An inability to express language
- Atypical social skills and personality traits

Associated functions:
Executive processes (voluntary behavior such as decision making, planning, problem–solving, and thinking), voluntary motor control, cognition, intelligence, attention, language processing and comprehension, and many others.



Information extracted from Brain Map

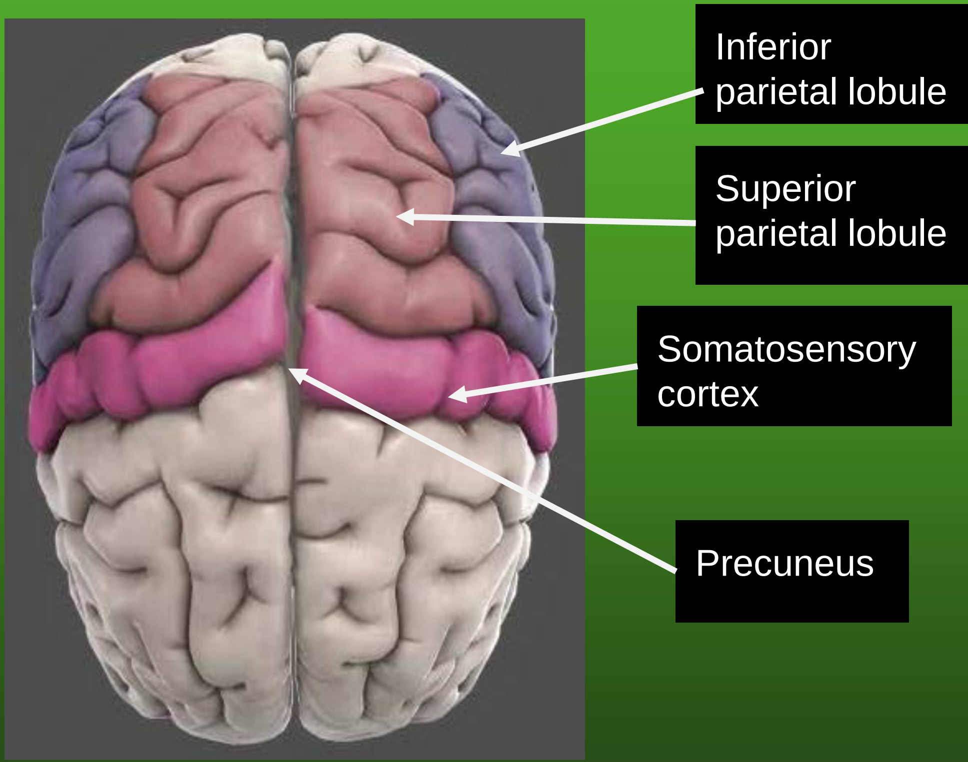
Parietal Lobe

Associated with damage:

- Inability to locate and recognize objects, events, and parts of the body (hemispatial neglect)
- Difficulty in discriminating between sensory information
- Disorientation
- Lack of coordination

Associated functions:

- Perception and integration of somatosensory information (e.g. touch, pressure, temperature, and pain)
- Visuospatial processing
- Spatial attention
- Spatial mapping
- Number representation



Information extracted from Brain Map.

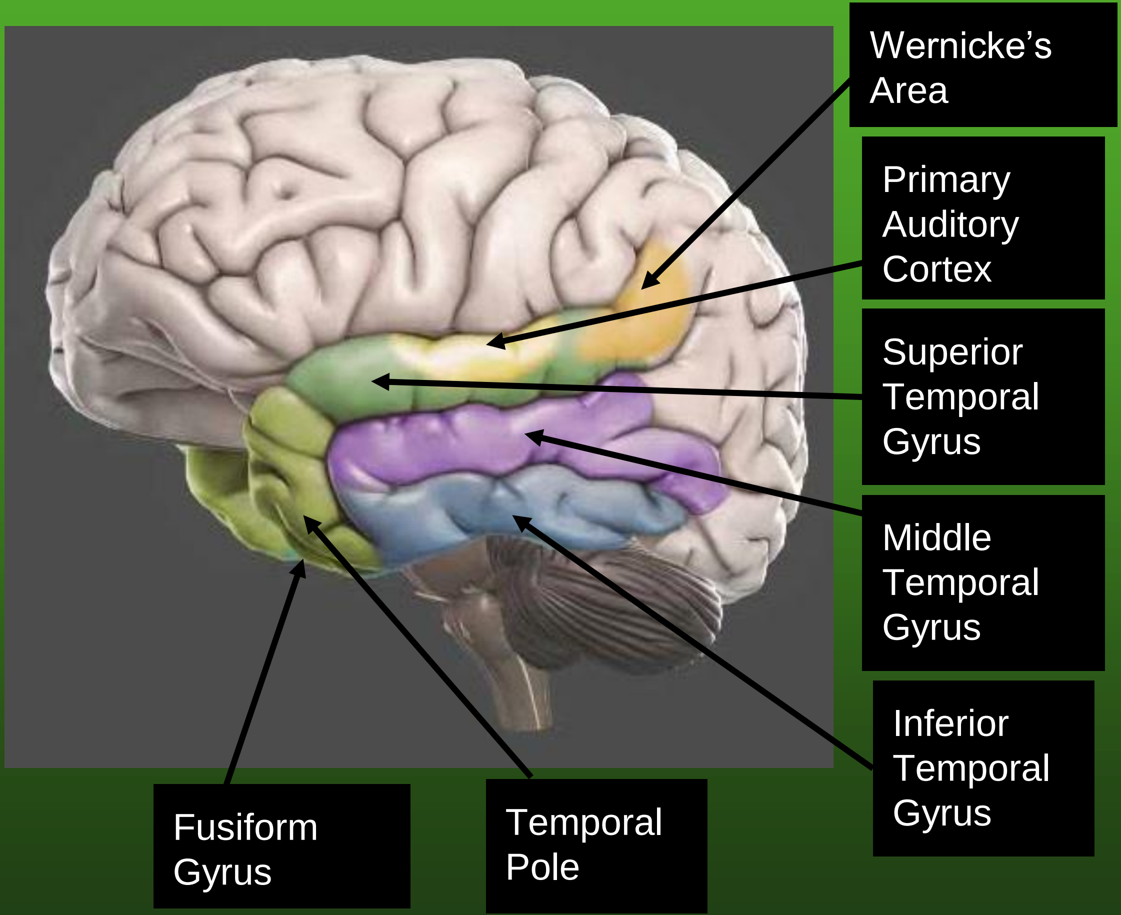
Temporal Lobe

Associated with damage

- Difficulties in understanding speech (Wernicke's aphasia), faces (prosopagnosia), and objects (agnosia)
- Inability to attend to sensory input
- Persistent talking
- Long– and short–term memory loss
- Increased/decreased interest in sexual behavior
- Aggression

Associated functions:

- Recognition
- Perception (hearing, vision, smell)
- Understanding language
- Learning and memory



Information extracted from Brain Map

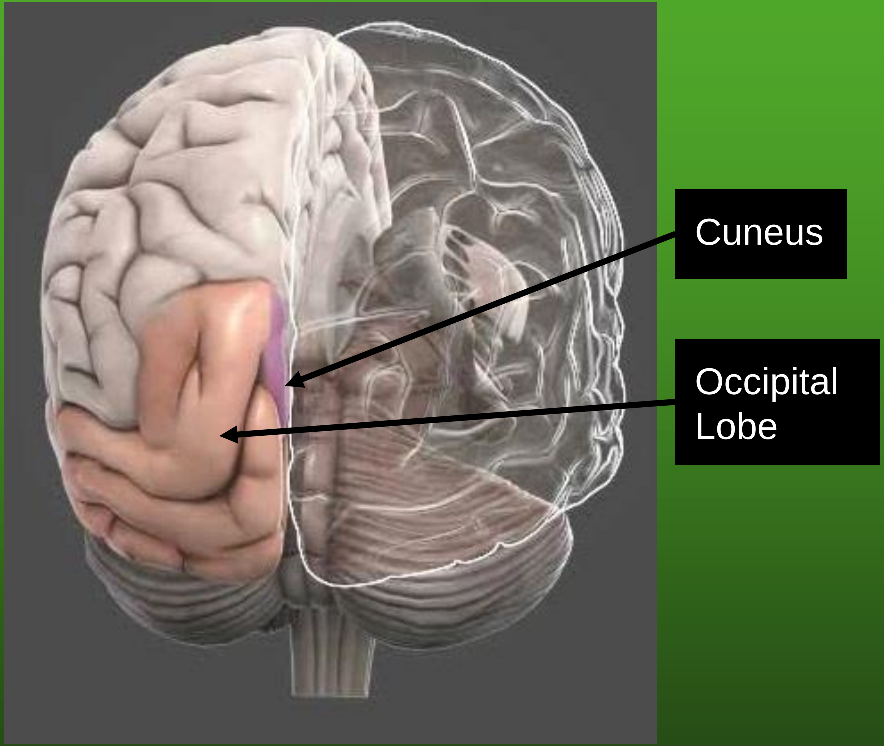
Occipital Lobe

Associated with damage:

- Hallucinations
- Blindness
- Inability to see color, motion, or orientation
- Synesthesia

Associated functions:

- Vision



Complications later in life

- Closed head
  - Mild: headaches, dizziness and short-term memory loss
  - Severe: death or permanent vegetative state
    - Can be treated with therapies and some pressure-relieving drugs (ex: diuretics)

- Penetrating
  - 4th leading cause of death in the US (ages 1-44), breaches cranium but may not exit the skull
    - Common with gunshot wounds
  - Insomnia, cognitive decline over time, seizures, hydrocephalus (excess fluid)

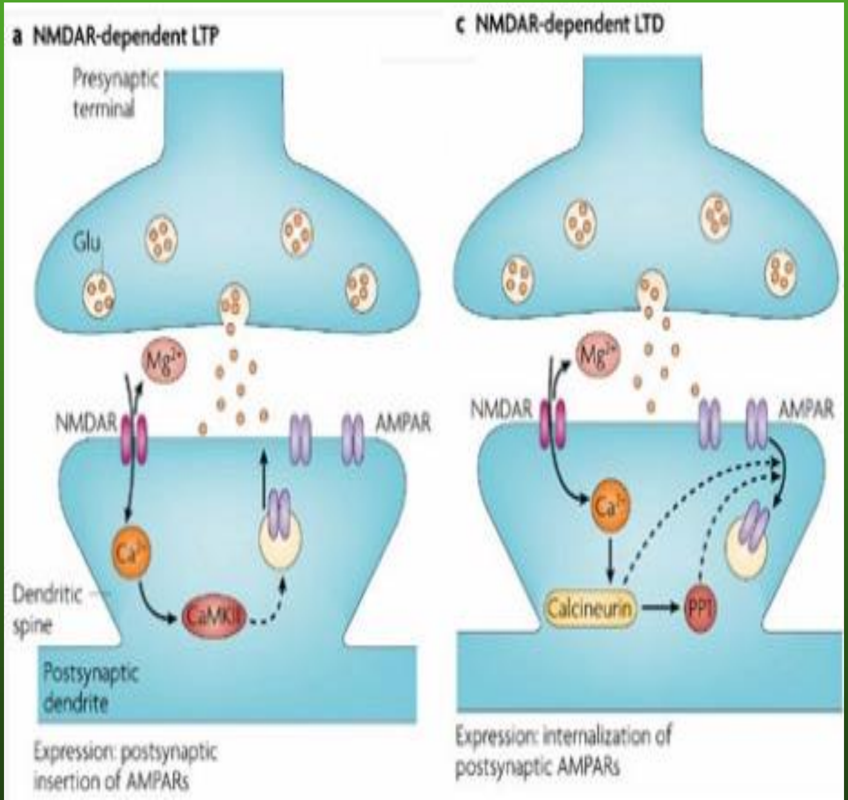
Complications later in life

- Moderate to severe traumatic brain injury is linked to a greater risk for developing Alzheimer’s disease or dementia
  - “Older adults with a history of moderate traumatic brain injury had a **2.3 times greater** risk of developing Alzheimer's than seniors with no history of head injury, and those with a history of severe traumatic brain injury had a **4.5 times greater** risk” (Alzheimer’s Disease and Dementia)
    - Brain injury can lead to increased tangles of tau protein and plaques of protein fragments which are implicated in Alzheimer’s and dementia

- Some studies show people with TBI also have an increased risk for developing Parkinson’s disease (still being proven)
  - Head injury with amnesia or loss of consciousness was associated with an increased risk for Parkinson’s in twin studie

Learning and Memory

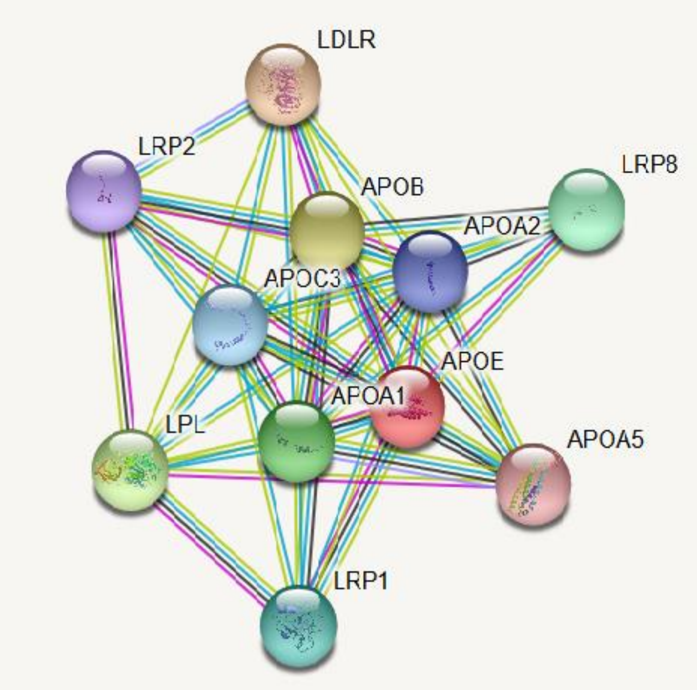
- The **hippocampus** is critical for the **formation** of **declarative memories**
  - Weeks to months following TBI, hippocampus **atrophies** and exhibits **deficits** in long-term potentiation **(LTP)**
- Study in mice to examine TBI and area CA1 LTP
  - Inability to induce LTP 7 days post-injury
  - Some forms of synaptic plasticity could still be elicited
    - Smaller N-methyl-D-aspartate potentials and glutamate-induced excitatory currents
    - Increased dendritic spine size
    - Decreased expressions of alpha-calcium calmodulin kinase II
  - Injury-induced lack of LTP contribute to cognitive impairments



Genes Involved

- ❖ Influence extent of injury
  - ➢ Pro-inflammatory and anti-inflammatory cytokines
- ❖ Effect repair and plasticity
  - ➢ Neurotrophic genes
- ❖ Effect pre and post injury cognitive and neurobehavioral capacity
  - ➢ Catecholamine genes

String



Gene Cards

- ❖ Apolipoprotein E (APOE)
  - ➢ Protein coding gene
  - ➢ Mediates the binding, internalization, and catabolism of lipoprotein particles
  - ➢ Ligand for the LDL (apo B/E) receptor
  - ➢ Ligand for the specific apo-E receptor of hepatic tissues
- ❖ APOA5: minor apolipoprotein associated with HDL, determinant of plasma triglycerides
- ❖ LRP8: transmits extracellular Reelin signal to intracellular signaling processes which govern neuronal layering

Current Treatments

Electrical stimulation (deep brain)

- Non-invasive, painless brain stimulation
- Direct, electrical currents to stimulate specific regions of the brain
- Zheng et. al, 2017
  - Tested efficacy of ES in TBI cases in rats
  - MWM scores showed shorter escape latency and higher time percentage in goal quadrant in ES group
  - Increased numbers of CD34+ cells and vWF+ cells in hippocampus of injured brain tissue after three weeks of ES
  - Increased number of EPCs in peripheral blood from 3-21 days after TBI in ES group

CD34+ cells

- Type of progenitor cell (more specialized stem cell)
- Play a huge role in neovascularization and tissue repair.
- The levels of CD34+ cells in the bloodstream have been shown to increase after a TBI in rats (Guo et. al 2009).

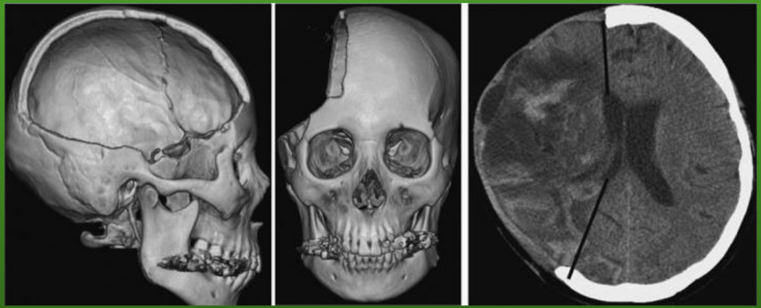
vWF+: Von Willebrand Factor

- Blood glycoprotein involved in clotting at wound sites.

Current Treatments

Decompressive Craniectomy

- ❖ Section of the skull is removed in order to allow a swelling brain to grow without restriction in an effort to relieve pressure
  - ➢ Normal intracranial pressure in human adults: below 15 mmHg. Greater than 20 mmHg, appropriate for craniectomy
- ❖ In TBI: prevent herniation, hematoma, and brain swelling
- ❖ Could possibly be therapeutic, but more research is needed
  - ➢ Cooper et. al, 2011: Increased chance of survival but relatively low quality of life (vegetative state).



Current Treatments

Medications

- Amphetamines (adderall)
  - MOA (acquired from DrugBank):
    - Stimulate release of norepinephrine from central adrenergic receptors
    - Cause release of dopamine from mesocorticolimbic system at high doses
    - Modulation of serotonergic pathways - calming affect
  - Treating TBI
    - Combined with physical rehabilitation, can increase rate and extent of motor recovery (Ramic et. al 2006)
- Cannabidiol (CBD)
  - MOA (acquired from DrugBank):
    - Acts on receptors in endocannabinoid system, which regulates physiological mechanisms like pain, memory, appetite, mood
    - Therapeutic importance of negative allosteric modulation of CB1 receptor
    - CB1 receptors: pain pathways
    - CB2 receptors: immune cells (CBD-induced anti-inflammatory response?)
  - Treating TBI (Schurman et. al, 2017)
    - Manipulations of CB1 and CB2 receptor can possibly manipulate “hallmark effects” of TBI; cell death, excitotoxicity, neuroinflammation, cerebrovascular breakdown, and cell structure and remodeling
    - TBI-induced behavior deficits also respond to receptor manipulation (learning and memory, neurological motor impairments, post-traumatic convulsions/seizures, anxiety)

Current Treatments

Hyperbaric oxygen therapy

- Promotes the body’s natural healing process through the inhalation of 100% oxygen in a total body chamber
- Oxygen is dissolved into all of the body’s tissues rather than just red blood cells
- Extra oxygen reaches all injuries and promotes the body’s own healing process
- “In CP and TBI patients, some of the injured brain tissues may be "dormant" and non-functioning. HBOT can stimulate these "dormant" tissues and return them to more normal function. In young children, cognitive function and spasticity can be improved.” -http://www.hbot.com/about-hbot#11
- Facilitates neuroprotection (improved cellular metabolism, anti-inflammation, anti-apoptosis, promotion of neurogenesis/angiogenesis)

Current Treatments

Improving quality of life:

- Physical Therapist
- Occupational Therapist
- Speech Therapist
- Neurologist
- Pharmacist
- Dietician
- Neuropsychologist
- Recreational therapist
- Anti-seizure medication
- Antidepressants
- Muscle relaxants

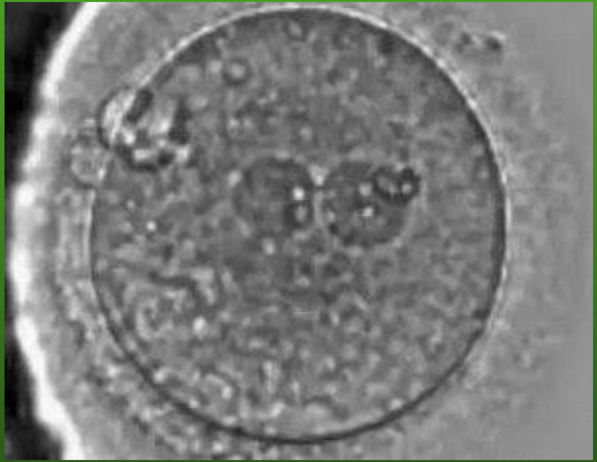
Stem cells are still being developed in their use as a treatment for TBI.

What are Stem Cells?

Stem cells

- After fertilization, rapid cell divisions create the gastrula
  - Contains 3 cell layers that become all regions of the organism
    - Until differentiated to their given roles they are **stem cells**
      - Fate of each cell (differentiation) depends on location in 3 germ layers
        - Ex: Ectoderm → nervous system (neurons)

- Embryonic stem cells have been targeted for isolation
  - Inserted into humans who need tissue replacement but have fully differentiated cells



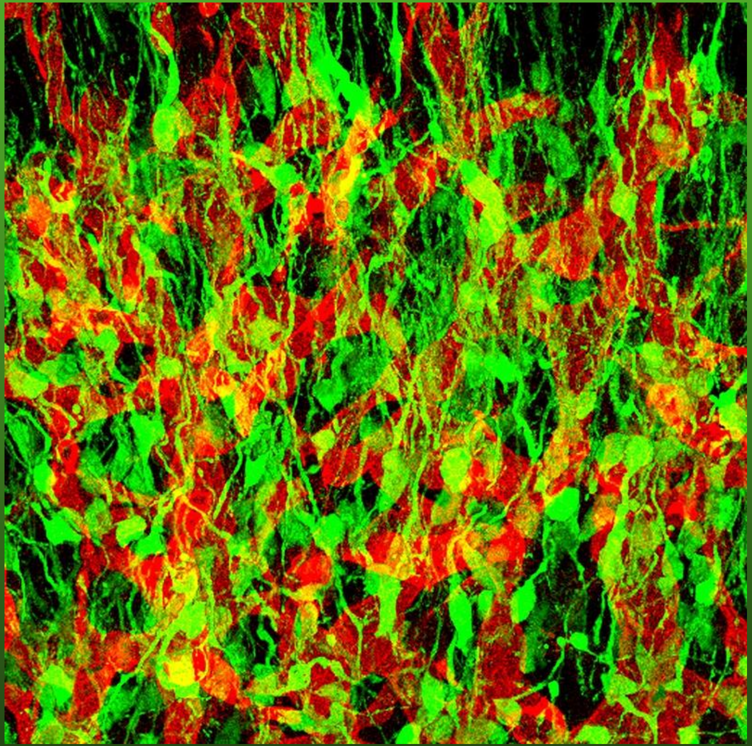
Ex: heart tissue after damage to cardiac muscle following heart attack

Stem Cell Transplantation as a Treatment Method for TBI

- Stem cell transplantation is being explored as a preventative measure for brain damage following injury
  - Protect neurological cells from secondary damage and aid in cell regeneration
  - Neural stem cells (NSC) are self-renewing cells that create the cells of the nervous system in all animals
  - This creation of cells may counter the degeneration of cells caused by the injury
- There is a large amount of conflicting evidence regarding the effectiveness of stem cell therapy
  - Some sources support stem cell research and claim it improves neurological function after experiencing a TBI, for either humans or rodents
  - Some sources claim stem cell therapy had little to no effect when used for treating a TBI
- Ethical concerns of using stem cells
  - Embryonic stem cell extraction destroys embryos
- Differentiation
  - How do we make sure it turns into a neural cell? Use **neural stem cells.**

Neural Stem Cells

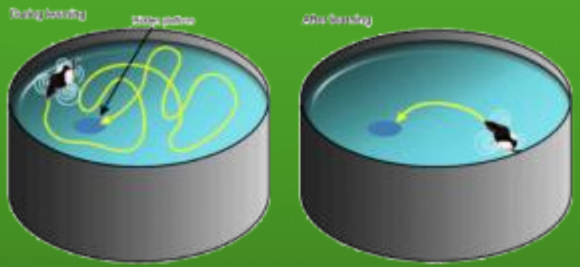
- Self-renewing, multi-potent
  - Found in the neural crest of an embryo
- Create neurons and glia of nervous system during embryonic development
- Some persist in adult vertebrate brain and continue to differentiate and create new cells throughout life
  - In adult subventricular zone and dentate gyrus
- Primarily differentiate into astrocytes, neurons, and oligodendrocytes
  - Create neural connections that act as the basis for cognitive function



Clinical Trials Using Stem Cells

- Anabari et. al (2014)
  - Significant improvements in motor deficits after two weeks in rats in the treatment group versus the sham
- Galindo et. al (2011)
  - Pro-inflammatory cytokines IL-6 and TNF-α levels were significantly increased in treatment groups compared to sham groups.
    - High levels implies a healing brain
- Guan et. al (2013)
  - Significant functional improvement (lower mNSS scores) after two weeks observed in stem cell treatment groups
    - Lower score indicates significant neurological recovery
- Wang et. al (2017)
  - Subjects who received SCT had improved GCS and NIHSS scores (2-6 points and 10-22 points higher, respectively)
    - Higher score = higher neurological functioning
- Yan et. al (2013)
  - Behavioral and therapeutic advancements from SCT
  - Significant cognitive function improvement in stem cell treatment groups when compared to sham in MWM test

Data Collection in Clinical Trials



- Types of data collected:
  - NSS (neurological sensitivity score)
    - Evaluate damage after a closed head trauma
    - Assess motor function and behavior
  - mNSS (modified neurological severity score)
    - Rate behavior and motor function on a scale of 14 (mice) or 18 (rats)
    - A lower score indicates higher neurological functioning)
  - NIHSS (National Institute of Health Stroke Scale)
    - Determine stroke severity
    - Assess patient’s level of consciousness, language abilities, motor impairments, and impairments relating to vision or facial movements
    - Higher scores (ranging from 1-42) represent more severe stroke symptoms
  - GCS (Glasgow Coma Scale)
    - Determine level of consciousness in patients in response to certain stimuli
    - Ability to open their eyes, respond verbally in a coherent manner, and obey motor response commands
    - Higher scores (ranging from 3-15) equates higher neurological function
  - MWM results (Morris Water Maze)
    - Evaluate cognitive function in rats
  - Neurotrophic factors
    - Molecules that support the growth and survival of neurons

Comparing the Research

- Methods for measuring the effectiveness of stem cell therapy
  - Neurological Tests
    - Measure cognitive and motor improvement over specific time frames
  - Radiological resources
    - Measure stem cell distribution and survival in the brain
  - Laboratory methods
    - Measure cytokinesis (cell division resulting in two daughter cells)
    - Measure levels of neurotrophic factors (facilitate brain cell growth)
    - Measure growth of nervous tissue

- Subjects
  - One source utilized human beings (Wang et al, 2017)
  - The majority of the sources chose to use rats or other animal subjects
    - Ethically easier
    - Comparable to humans because symptoms can be replicated in rats and mice

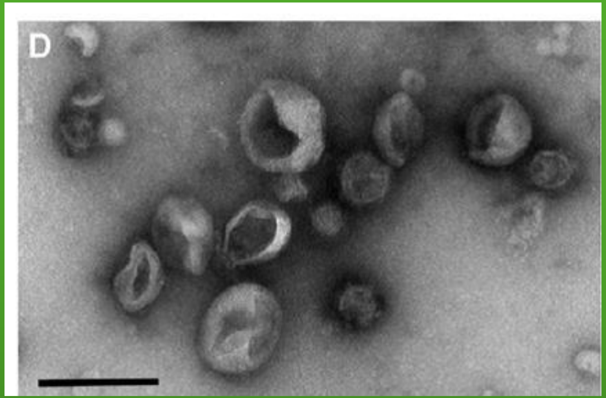
Table I. Baseline characteristics and clinical follow-up of patients.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Sex	Male	Male	Female	Male	Female	Male	Male	Male	Female	Male
Age (years)	39	50	21	55	52	29	27	47	22	39
Etiology	fall accident	traffic accident	traffic accident	fall accident	traffic accident	traffic accident	traffic accident	traffic accident	fall accident	fall accident
Pathological features	CC, SAH, IVH, DAI	CC, SAH, IVH, DAI	CC, SDH	EDH, SAH, SF	CC, BSI, DAI	CC, BSI, DAI	CC, ICH	CC, SDH, SF	CC, SAH, SDH	CC, SAH
Acute treatment	Conservative	Conservative	Conservative	DC	Conservative	DC	DC	DC	DC	Conservative
Days since TBI	46	35	20	60	43	59	42	57	29	32
GCS/NIHSS scores										
Infusion day	7/25	8/24	7/24	8/23	6/25	7/31	8/31	8/29	7/22	8/26
Day 1	7/25	8/24	15/3	8/23	6/25	7/31	8/31	8/29	7/22	8/26
Day 3	7/25	9/23	15/3	8/23	6/25	7/31	8/31	8/29	7/22	8/26
Day 7	7/25	14/6	15/3	8/23	6/25	7/31	8/31	8/29	7/22	10/18
Day 30	10/15	14/6	15/3	15/8	6/25	7/31	10/21	8/29	10/20	12/15
Day 60	10/15	14/6	15/2	15/8	6/25	7/31	10/21	8/29	14/7	14/7
GOS at follow-up day 180	2	5	5	4	2	2	3	2	4	5
No. of injected cells	4×10^7	2×10^7	4×10^7	4×10^7	2×10^7	2×10^7	4×10^7	4×10^7	4×10^7	4×10^7
Delivery route	intravenous	intrathecal	intravenous	intravenous	intrathecal	intrathecal	intravenous	intravenous	intravenous	intravenous

CC, cerebral contusion; SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; DAI, diffuse axonal injury; SDH, subdural hematoma; EDH, epidural hematoma; SF, skull fracture; BSI, brain stem injury; ICH, intracerebral hemorrhage; DC, decompressive craniectomy; GCS, Glasgow Coma Scale; NIHSS, National Institute of Health Stroke Scale; GOS, Glasgow Outcome Scale; TBI, traumatic brain injury.

Wang et. al, 2017

Future Stem Cell Therapy: What about exosomes?



Previously, exosomes and stem cells as treatments have gone hand in hand.

Exosomes-cell-derived vesicles in eukaryotic fluids (blood, urine, etc.)

- ❖ Therapeutic improvements from stem cells may be in part caused by exosomes
  - ➢ Exosomes are important for intercellular signaling
    - ■ Used in rats and promoted neuroplasticity after TBI
  - ➢ Reduced safety risk of uncontrolled growth
    - ■ Exosomes cross blood brain barrier and are more stable than stem cells
      - ● Contain miRNAs to regulate gene expression at the post-transcriptional level

Cell-free exosome-based therapy emerging as new, possibly more efficient and effective treatment for TBI.

Researchers are asking: are exosomes *better* than stem cells as treatment?

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