Traumatic Brain Injury:

A Clinical Approach to Diagnosis and Treatment

by Mark L. Gordon, M.D.

Chapter 2: Neurology For TBI

Hippocrates 400 BCE

"Men ought to know that from nothing else but the brain comes joy, delight, laughter and **sports**, and sorrow, grief, despondency, and lamentation.“

Therefore;

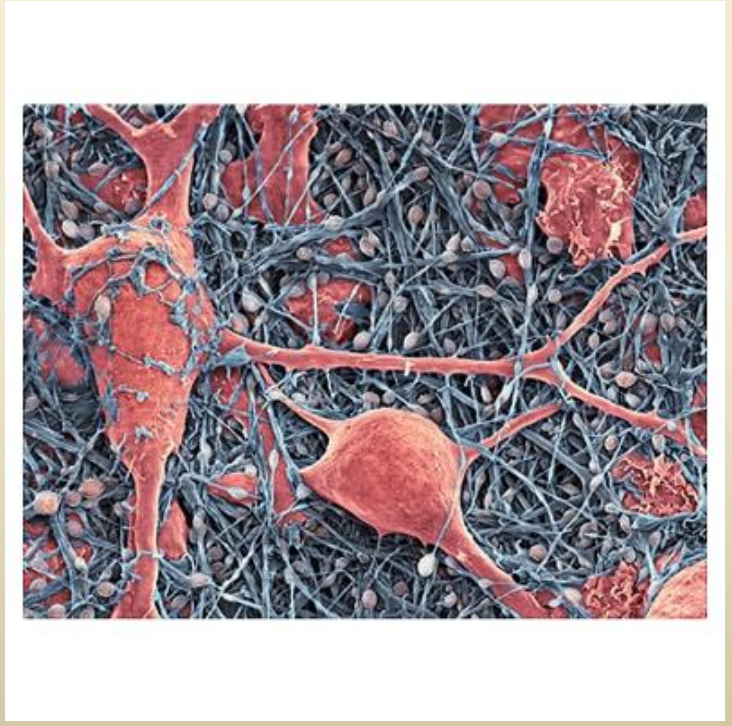
“ Women ought to know after 2500 years how to put up with our SH*T”

Introduction

- The outcome of mild closed head trauma (mTBI) on the ultimate functionality of the individual is unpredictable.
- Age and gender have been looked upon as influencing both the morbidity and mortality.
- Reports show that we can have normal appearing acute CT and MRI scans in an unconscious patient. No findings of contusion, ischemia, hematoma or structural compromise.
- Researchers are finding that impaired hypothalamic-pituitary function and general outcome can be predicted based upon the presence and degree of **Diffuse Axonal Injury** (DAI).

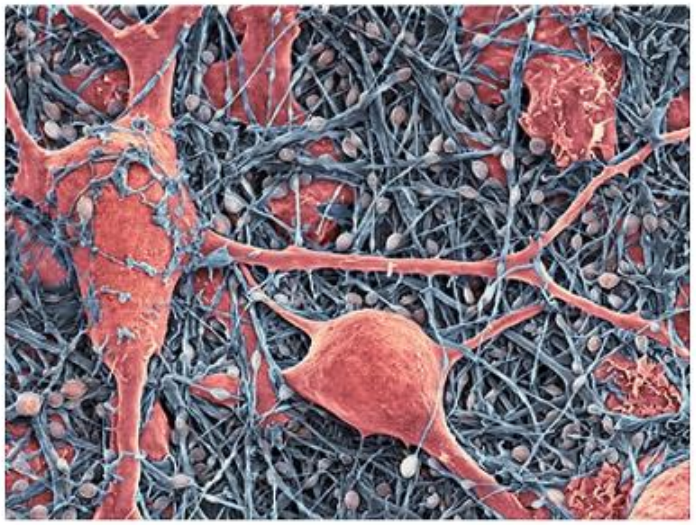
Gray and White Matters!

- The brain is an informational speedway made up of neuronal bodies (gray) and their long interconnecting appendages; axons (white).



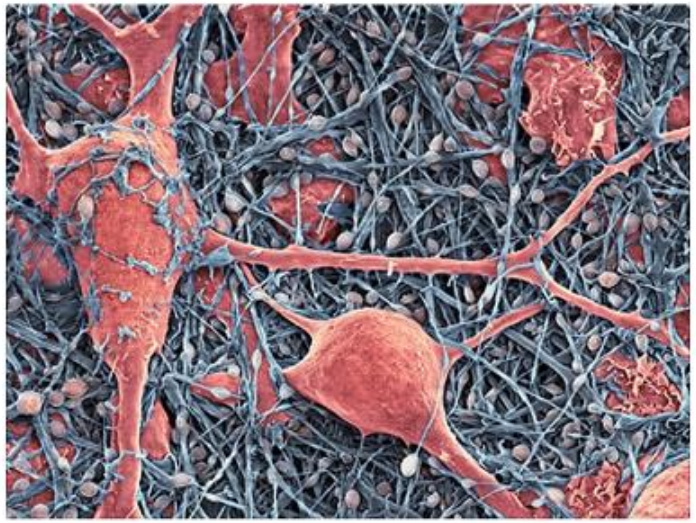
Gray Matters!

- **Gray Matter** consisting of neuronal cell bodies, neuropil (dendrites and unmyelinated axons), glial cells (astroglia and oligodendrocytes) and capillaries.



White Matters!

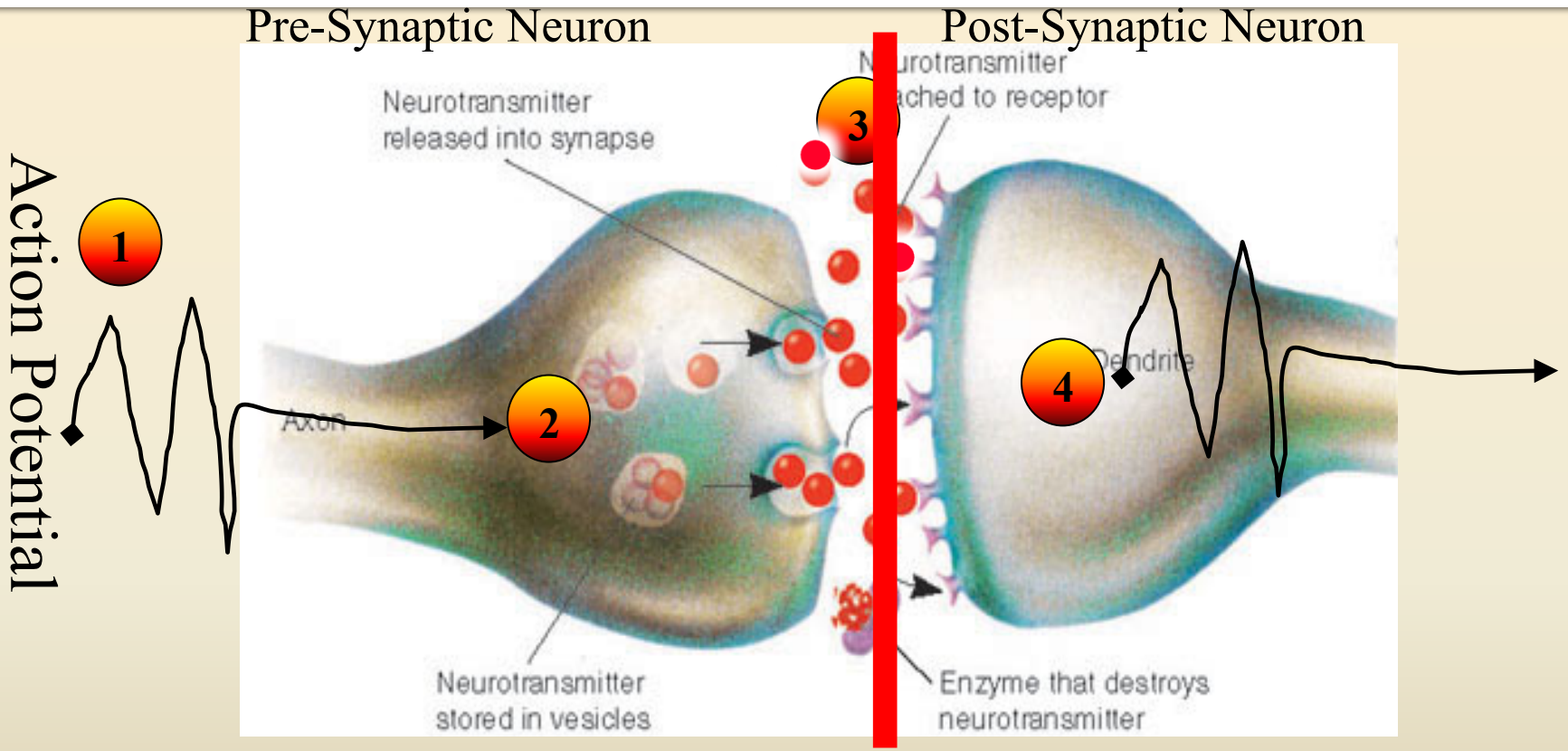
- **White matter** is one of the two components of the central nervous system and consists mostly of glial cells and myelinated axons that transmit signals from one region of the cerebrum to another and between the cerebrum and lower brain centers.



Neurons

- A neuron is an electrically excitable cell that processes and transmits information through electrical and chemical signals.
- A chemical signal occurs via a synapse, a specialized connection with other cells. Neurons connect to each other to form neural networks.
- Neurons are the core components of the nervous system, which includes the brain, spinal cord, and peripheral ganglia.

Neuronal Synapses



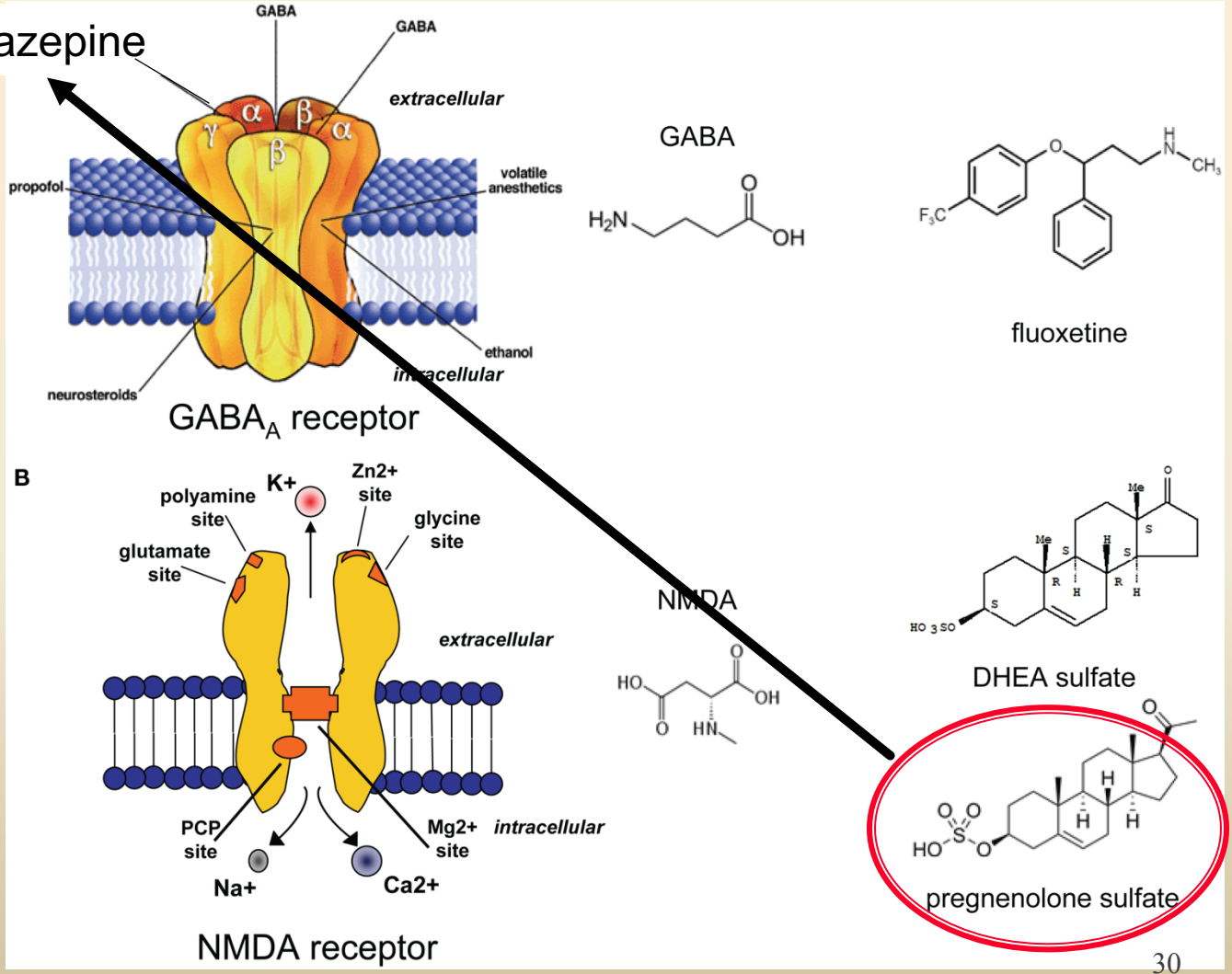
2 Neurotransmitter **diffuses** across the synapse and binds with receptor molecules on the membrane of the next neuron.

Due to inflammation and free radicals the communication is interrupted!

Neurosteroids as neuromodulators in the treatment of anxiety disorders.

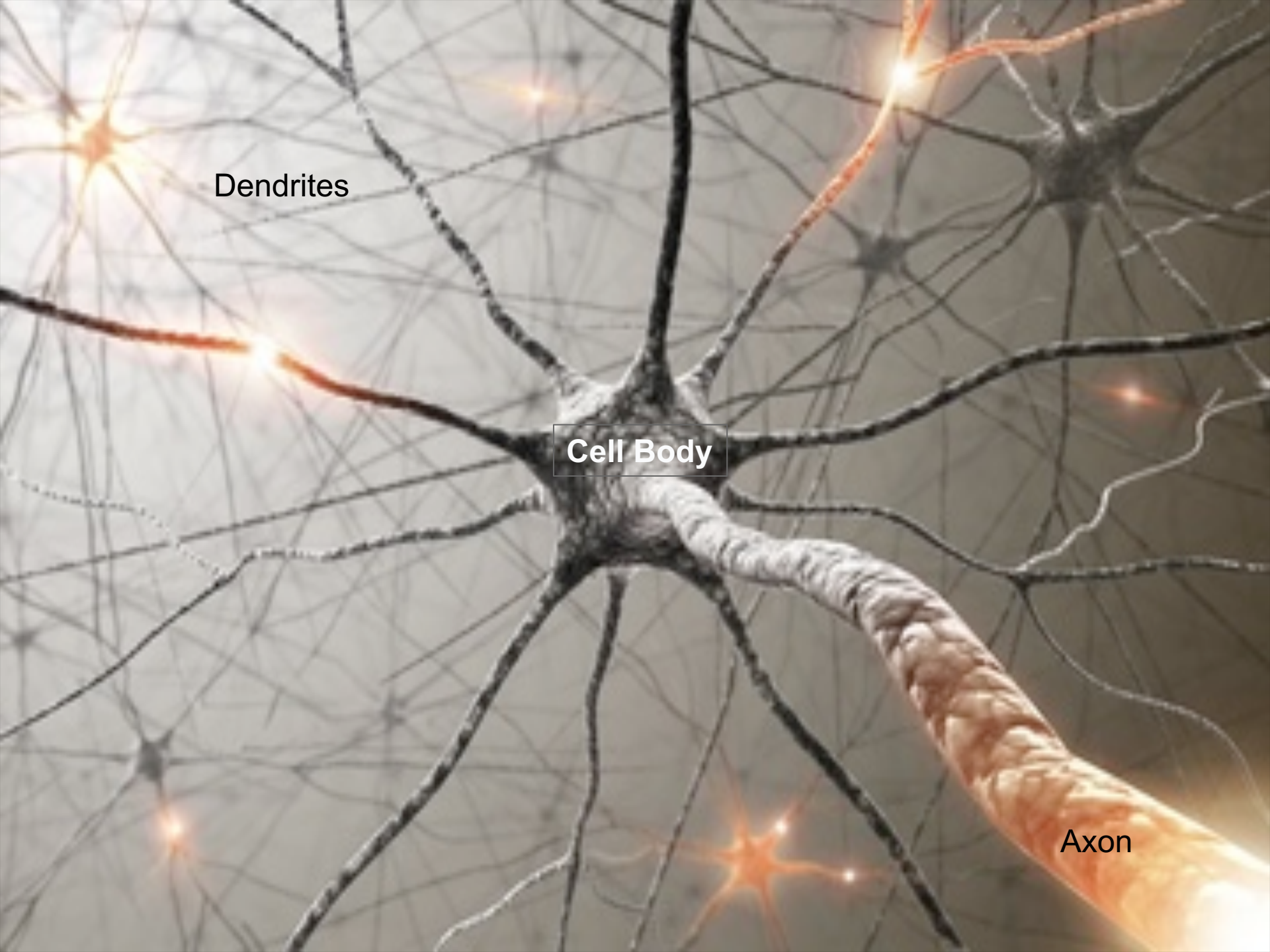
Front. Endocrinol., 2011 Patrizia Longone, et al., Rupprecht Molecular Neurobiology Unit, Experimental Neurology, Fondazione Santa Lucia, Rome, Italy. Child Neurology and Psychiatry, Dept of Neuroscience, University of Rome "Tor Vergata,", Rome, Italy. Deptt of Neuroscience, University of Rome "Tor Vergata,", Rome, Italy. Dept of Psychiatry and Psychotherapy, University Regensburg, Regensburg, Germany

Neuronal and synaptic communication is modulated by neurosteroids such as; estrogens, pregnenolone, allopregnenolone, progesterone, allopregnanolone, DHEA and their sulfated metabolites.



Neurons

- A typical neuron possesses a cell body, dendrite, and an axon.
- Dendrites are thin structures that arise from the cell body, often extending for hundreds of micrometers and branching multiple times, giving rise to a complex "dendritic tree".
- An axon is a special cellular extension that arises from the cell body and travels for a distance, as far as 1 meter in humans.
- The cell body of a neuron gives rise to multiple dendrites, but never to more than one axon, although the axon may branch hundreds of times before it terminates. At the majority of synapses, signals are sent from the axon of one neuron to a dendrite of another.


Dendrites
Cell Body
Axon

Glial Cells

- These are non-neuronal cells providing support to neurons in both the central and peripheral nervous systems.
- In general they have the ability to surround and hold neurons in place, supply nutrients and oxygen (A), produce myelin to insulate one neuron from another (O), and act as part of the immune system to destroy pathogens and remove dead neurons(MG).
- **Glial cells have been found to be the source of many of the Neurosteroids that we will discuss**.

Astrocytes

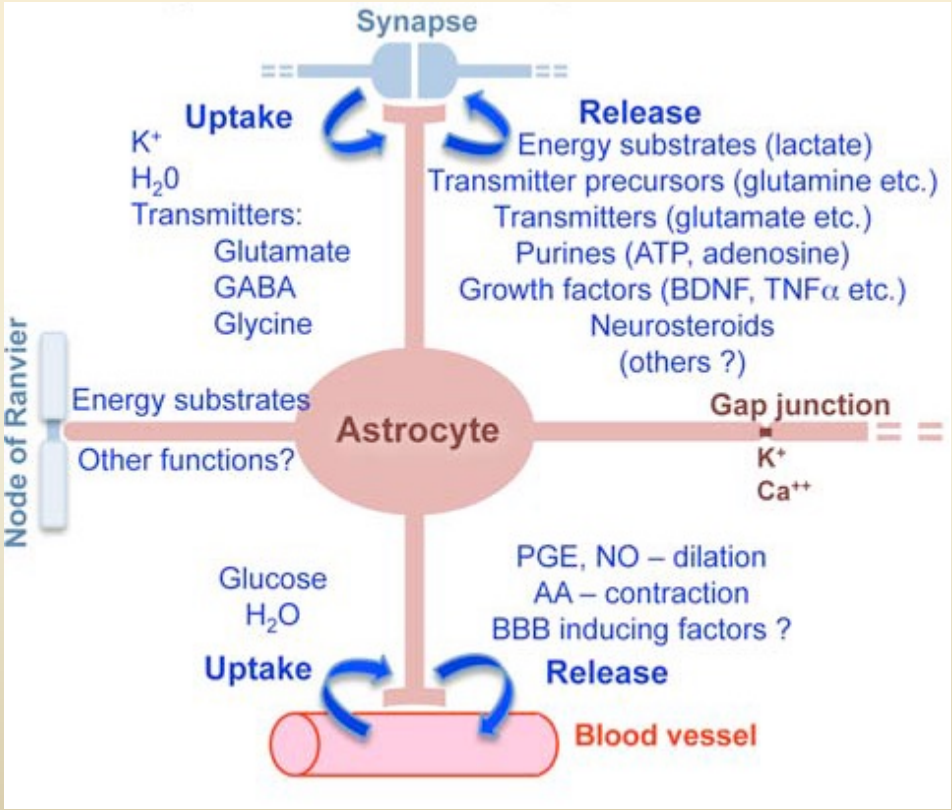
- The most abundant type of macroglial cell, astrocytes (also called astroglia) have numerous projections that anchor neurons to their blood supply.
- They regulate the external chemical environment of neurons by removing excess ions, notably potassium, and recycling neurotransmitters released during synaptic transmission.
- Astrocytes may regulate vasoconstriction and vasodilatation by producing substances such as **arachidonic acid**, whose metabolites are vasoactive.

Astrocytes: biology and pathology. Acta Neuropathol (2010) 119:7–35 Michael V. Sofroniew, Harry V. Vinters. Department of Neurobiology, David Geffen School of Medicine, University of California, 10833 Le Conte Avenue, Los Angeles, CA 90095-1763, USA

- Astrocytes are specialized glial cells that out-number neurons by fivefold[+].
- They contiguously tile the entire central nervous system (CNS) and exert many essential complex functions in the healthy CNS.
- Astrocytes respond to all forms of CNS insults through a process referred to as reactive astrogliosis, which has become a pathological hallmark of CNS structural lesions.

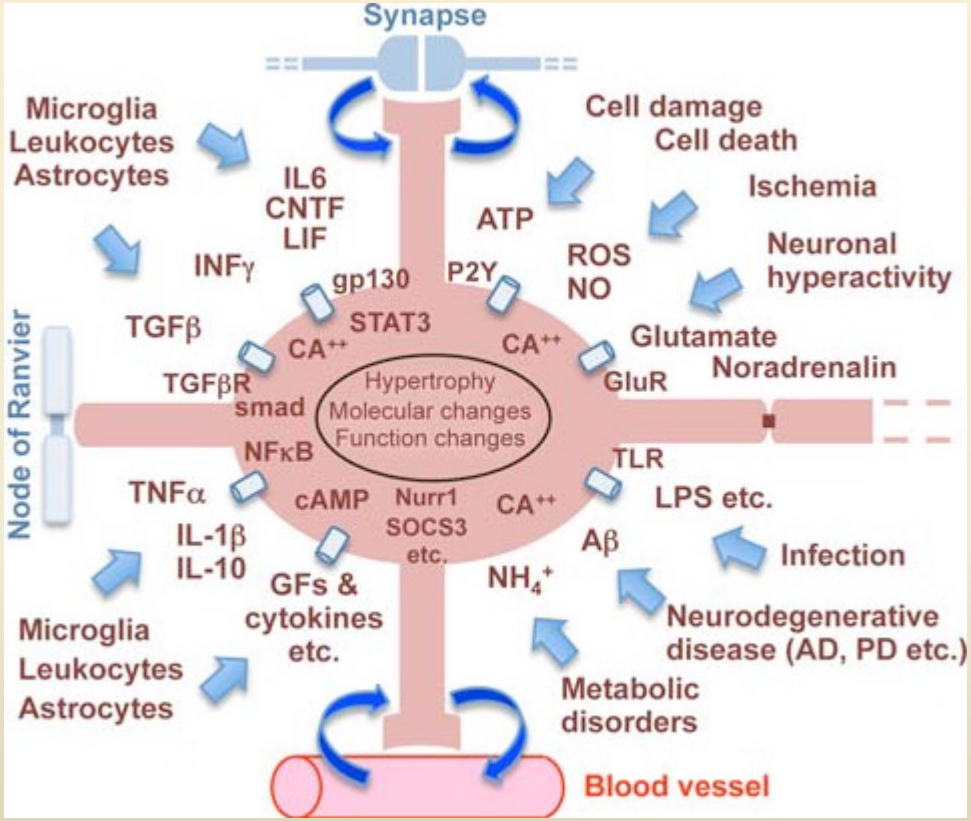
Astrocyte Functions in Healthy CNS

- Astrocytes have been found to provide more metabolic support that thought of in the past.
- They help regulate the health of the neurons as well as modulate electrochemical processes.

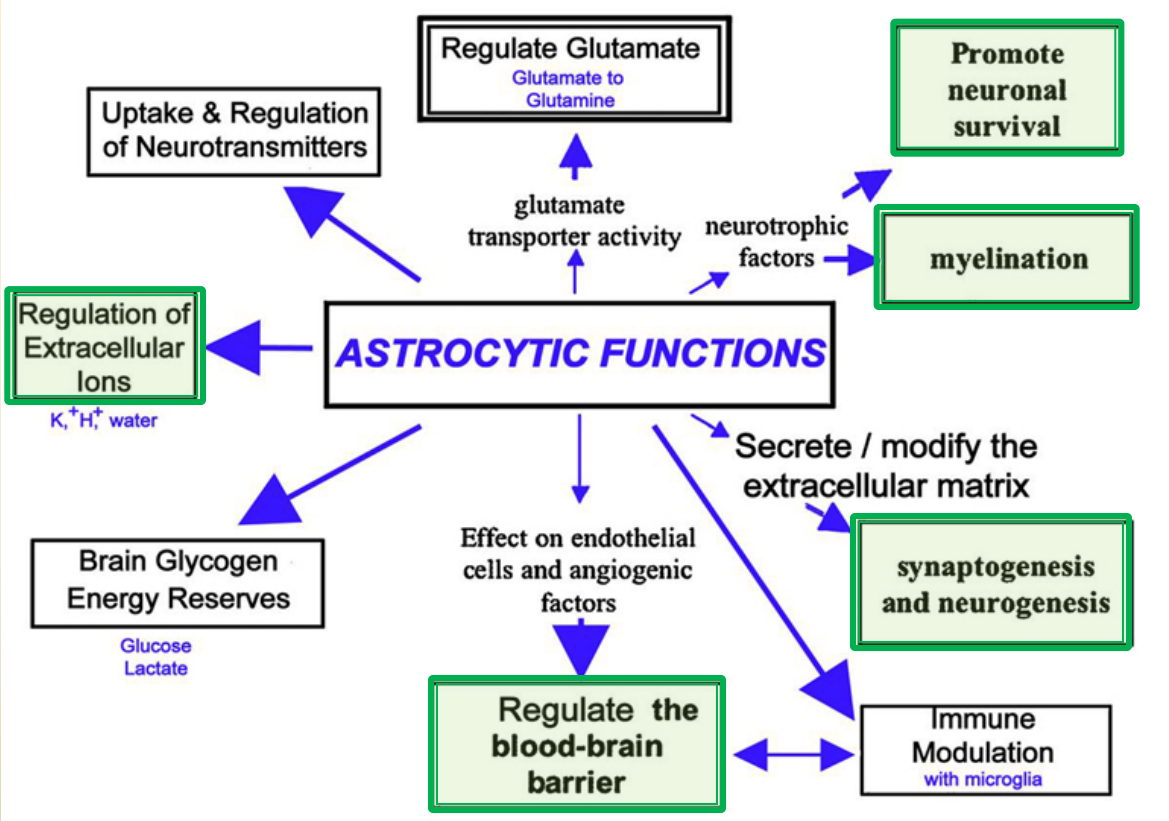


Astrocyte Functions in a Damaged CNS

- The development of a Glial Scar (reactive astrogliosis) acts as a physical impediment to the regrowth and reconnectivity of neurons.
- Early intervention to control inflammation will promote a more neuro-permissive environment fostering recovery.



Neuropermissive Environment



Oligodendrocytes

- Their main functions are to provide support and to insulate the axons in the CNS and spinal cord by producing Myelin.
- Oligodendrocytes produce the myelin sheath, which is 80% lipid and 20% protein.
- A single oligodendrocyte can extend its processes to 50 axons, wrapping approximately 1 μm of myelin sheath around each axon.
- In contrast, Schwann cells, found in the peripheral nervous system, wrap around only 1 axon.

Microglia

- Microglia constitute 15-20% of the total glial cell population within the brain.
- They act as macrophages capable of phagocytosis removing debris and bacteria. They act as the first and main form of active immune defense in the central nervous system.
- In the healthy CNS, microglia are constantly scavenging the CNS for plaques, damaged neurons, and infectious agents. (inflammation decreases this!)

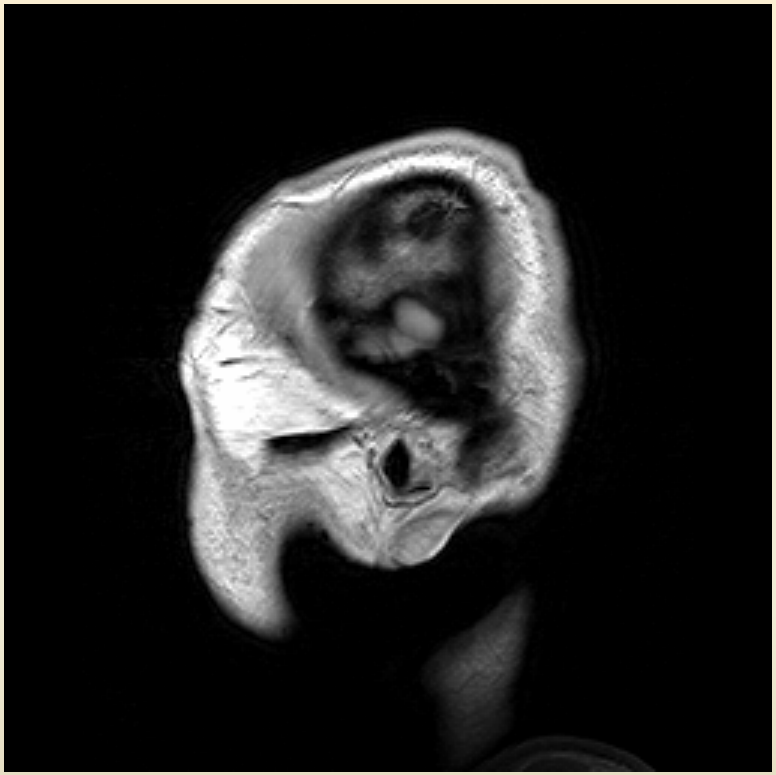
Estrogen and Microglia: A Regulatory System That Affects the Brain. J

Neurobiol 40: 484–496, 1999. Gil Mor, Jon Nilsen,Tamas Horvath, Ingo Bechmann, Santiago Brown, Luis Miguel Garcia-Segura, Frederick Naftolin, Dept of Obstetrics and Gynecology and Center for Reproductive Biology, Yale University Medical School, 333 Cedar St. FMB 202, New Haven, Connecticut 06520, USA

- The microglia are a specialized brain glial cell type, which is a target for **estrogen actions**; immune and non-immune regulatory functions are influenced directly by estrogen via expression and secretion of cytokines, and growth factors by the microglia.
- IL-1, IL-2, IL-6, TNF-Alpha, and IFN - Gamma are all products of microglia.

  - Why Aromatase inhibitors are not safe!!

What we can see and what we cannot see



Lobes of the Brain

Form and Function

- Clinical assessment of the patients symptomatology can lead to an understanding of the underlying damage.
- Knowing the key functional attributes of each lobe of the brain can help in determining where the damage is even before doing sophisticated radiologic procedures.
- If the technology is unavailable, then you can use confrontational means to assess the areas of damage.

TBI Locator

Traumatic Brain Injury Locator | 2014

A comprehensive clinical assessment of a patient, with a history of head trauma, can help predict or localize the area(s) of the brain involved. Sometime this assessment will not have a radiologic confirmation and therefore, becomes the only means to assign the probable area of injury.

Name: Date:

Brain Stem [ ] NORMAL
- ☐ Decreased vital capacity in breathing (speaking)
- ☐ Swallowing food and water (**Dysphagia**).
- ☐ Difficulty with organization/perception of the environment.
- ☐ Problems with balance and movement.
- ☐ Dizziness and nausea (**Vertigo**).
- ☐ Sleeping difficulties (Insomnia, sleep apnea).

Cerebellum [ ] NORMAL
- ☐ Loss of ability to coordinate fine movements.
- ☐ Loss of ability to walk.
- ☐ Inability to reach out and grab objects.
- ☐ Tremors.
- ☐ Dizziness (Vertigo).
- ☐ Slurred Speech (**Scanning Speech**).
- ☐ Inability to make rapid movements.

Temporal Lobe [ ] NORMAL
- ☐ Difficulty in recognizing faces (**Prosopagnosia**).
- ☐ Difficulty in understanding spoken words (**Wernicke's Aphasia**).
- ☐ Difficulty with verbal ID of objects.
- ☐ Short term memory loss.
- ☐ Interference with long term memory.
- ☐ Alteration in Libido and sexual behavior.
- ☐ Inability to categorize objects (**Categorization**).
- ☐ Right lobe damage can cause persistent talking.
- ☐ Increased aggressive behavior.

Occipital Lobe [ ] NORMAL
- ☐ Defects in vision (**Visual Field Cuts**).
- ☐ Difficulty with locating objects in environment.
- ☐ Difficulty with identifying colors (**Color Agnosia**).
- ☐ Production of hallucinations.
- ☐ Visual illusions - inaccurately seeing objects.
- ☐ Word blindness - inability to recognize words.
- ☐ Difficulty in recognizing drawn objects.
- ☐ Inability to recognize the movement of object
- ☐ Difficulties with reading and writing.

Parietal Lobe [ ] NORMAL
- ☐ Inability to attend to more than one object at a time.
- ☐ Inability to name an object (**Anomia**).
- ☐ Inability to locate the words for writing (**Agraphia**).
- ☐ Problems with reading (**Alexia**).
- ☐ Difficulty with drawing objects.
- ☐ Difficulty in distinguishing left from right.
- ☐ Difficulty with doing mathematics (**Dyscalculia**).
- ☐ Lack of self awareness and/or surrounding space (**Apraxia**) that leads to difficulties in self-care.
- ☐ Inability to focus visual attention.
- ☐ Difficulties with eye and hand coordination.

Frontal Lobe [ ] NORMAL
- ☐ Loss of simple movement of various body parts
- ☐ Inability to plan a sequence of complex movements needed to complete multi-stepped tasks, such as making coffee (**Sequencing**).
- ☐ Loss of spontaneity in interacting with others.
- ☐ Loss of flexibility in thinking.
- ☐ Persistence of a single thought (**Perseveration**).
- ☐ Inability to focus on task (Attending).
- ☐ Mood changes (**Emotionally Labile**).
- ☐ Changes in social behavior.
- ☐ Changes in personality.
- ☐ Difficulty with problem solving.
- ☐ Inability to express language (Broca's Aphasia).

Abnormal Findings in:

[ ] Frontal

[ ] Parietal

[ ] Occipital

[ ] Temporal

[ ] Cerebellum

[ ] Brain Stem

1a. Lobular Functionality
Frontal Lobes

- Mood changes (Emotionally Labile).
- Changes in social behavior.
- Changes in personality.
- Diminished Executive Functions.
- Inability to sequence complex movements.
- Loss of spontaneity in interacting with others
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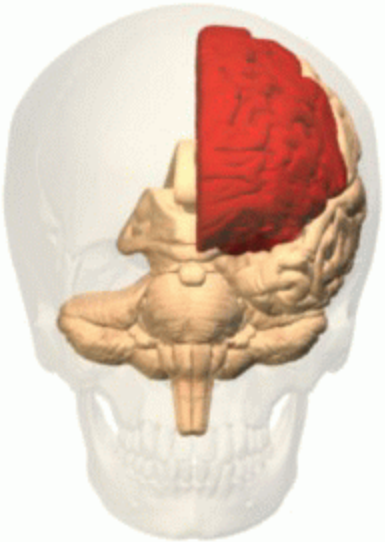

Traumatic Brain Injury Syndrome Temporal Lobes

- Increased aggressive behavior.
- Short term memory loss.
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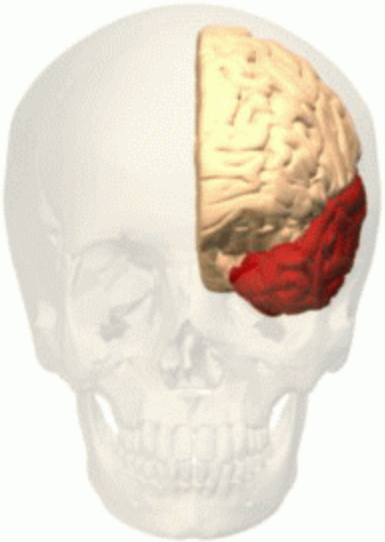

Traumatic Brain Injury Syndrome Parietal Lobes

- Problems with reading (Alexia).
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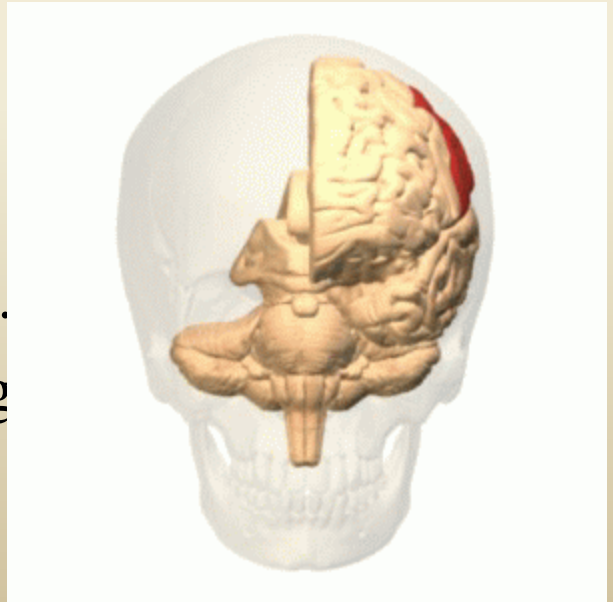

Traumatic Brain Injury Syndrome Occipital Lobes

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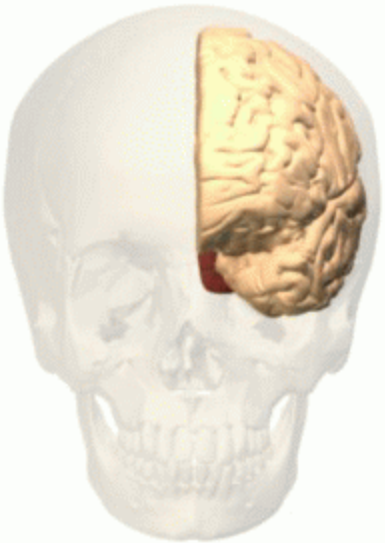

Cerebellum

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Brain Stem

- Decreased vital capacity in breathing, important for speech.
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- Problems with balance and movement.
- Dizziness and nausea (Vertigo).
- Sleeping difficulties (Insomnia, sleep apnea).

Hypothalamus

- The main function of the hypothalamus is homeostasis.
- Measurable factors such as blood pressure, body temperature, fluid and electrolyte balance, and body weight are maintained at a precise value called the set point.
- The hypothalamus does so by regulating three interrelated functions: **endocrine secretion**, **autonomic function**, and **emotions**.

The Hypocretins: Hypothalamus-specific peptides with neuroexcitatory activity.

Proc. Natl. Acad. Sci. USA Vol. 95, pp. 322–327, January 1998 Neurobiology. L. De Lecea, T.S.Kilduff, C. Peyron et al. Depts of Molecular Biology and Neuropharmacology, The Scripps Research Institute, La Jolla, CA; Center for Sleep and Circadian Neurobiology, Stanford University, Stanford, CA; Dept of Neurosurgery, Yale University, New Haven, CT ; Institute of Basic Medical Sciences, Dept of Biochemistry, University of Oslo, P.O. Box 1112, Blindern, N-0317 Oslo, Norway; and The Jackson Laboratory, Bar Harbor, ME 04609.

- Narcolepsy appears to be due to the sudden drop in the production of Orexin-Hypocretin.
- Damage to the cells of the dorsal and lateral hypothalamus leads to a variable deficiency in the production of Hypocretin (Orexin).
- In traumatic brain injury, it appears to be the cause for the primary complaint of fatigue and daytime somnabulance.
- Hypocretin has been found to be a potent neurotransmitter in the CNS regulating the ??RAS??
- New sleep medication: **Suvorexant blocks Orexin receptors 1 and 2.**

Loss of hypocretin (orexin) neurons with traumatic brain injury.

Ann Neurol . 2009 October ; 66(4): 555–559. Christian R. Baumann, et al, Dept. of Neurology, University Hospital, Zurich, Switzerland. Dept of Neuropathology, University Hospital, Zurich, Switzerland. Dept of Forensic Medicine, University Hospital, Zurich, Switzerland. Dept of Surgical Intensive Care, University Hospital, Zurich, Switzerland. Dept of Neurology, Beth Israel Deaconess Medical Center, Boston, USA

- Chronic, daytime sleepiness is a major, disabling symptom for many patients with traumatic brain injury (TBI) but thus far, its etiology is not well understood.
- Extensive loss of the hypothalamic neurons that produce the wake-promoting neuropeptide hypocretin (orexin) causes the severe sleepiness of narcolepsy, and partial loss of these cells may contribute to the sleepiness of Parkinson's disease and other disorders.

Inflammation of the Hypothalamus Leads to Defective Pancreatic Islet Function

. J. Biol. Chem. 2011, 286:12870-12880. Vivian C. Calegari, Adriana S. Torsoni, Emerielle C. Vanzela, Eliana P. Araújo, Joseane Morari, Claudio C. Zoppi, Lourenço Sbragia, Antonio C. Boschero and Lício A. Velloso

- Type 2 diabetes mellitus results from the complex association of Insulin Resistance and Pancreatic β-Cell Failure.
- Many of the neural inputs that control β-cell activity are generated in the hypothalamus.
- The autonomic signals generated with hypothalamic inflammation can impair pancreatic islet function, and may explain the link between obesity and defective insulin secretion and the Metabolic Syndrome(Insulin Resistance) in TBI Cases.

The Limbic System

- Is a collection of structures from the cerebrum, diencephalon, and midbrain, including the hippocampus, amygdalae, anterior thalamic nuclei, septum, limbic cortex and fornix.
- It appears to be primarily responsible for our **emotional life**, and has a great deal to do with the formation of long-term **memories and provides motivation**.

A revised limbic system model for memory, emotion and behaviour.

Neuroscience and Biobehavioral Reviews 37 (2013) 1724– 1737. Marco Catania,Flavio Dell'Acquaa,Michel Thiebaut de Schottena,, Natbrainlab, Dept of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, King's College London, UK. Dept of Neuroimaging Sciences, Institute of Psychiatry, King's College London, NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King's College London, UK.

- The limbic system is a group of interconnected cortical and subcortical structures dedicated to linking visceral states and emotion to cognition and behavior.
- The role of the limbic structures includes controlling social interactions and behavior, consolidating memories, and forming emotions.

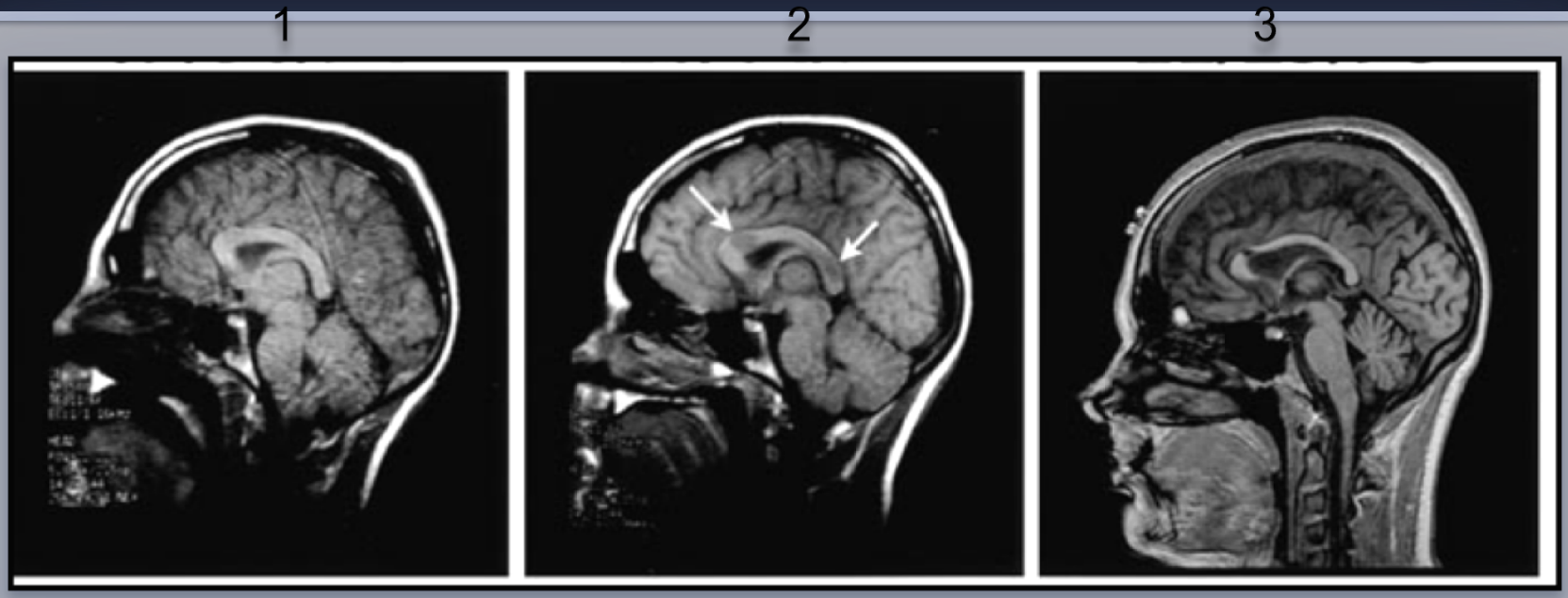
Limbic system mechanisms of stress regulation: Hypothalamo-pituitary-adrenocortical axis

. Progress in Neuro-Psychopharmacology & Biological Psychiatry 29 (2005) 1201 – 1213.
James P. Herman, Michelle M. Ostrander, Nancy K. Mueller, Helmer Figueiredo . Dept of Psychiatry, Psychiatry North, ML 0506 2170 East Galbraith Road, University of Cincinnati College of Medicine, Cincinnati, OH, Dept of Cell Biology, Neurobiology and Anatomy, University of Cincinnati College of Medicine, Reading, OH

- Limbic dysfunction and hypothalamo-pituitary-adrenocortical (HPA) axis dysregulation are key features of Affective Disorders.
- *Affective disorders* are a set of psychiatric diseases, also called *mood disorders*. The main types of *affective disorders* are **depression, bipolar disorder, and anxiety disorder**.

The lesion(s) in traumatic brain injury: implications for clinical neuropsychology

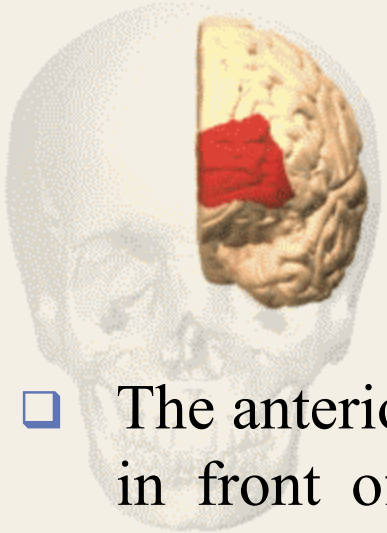
. Archives of Clinical Neuropsychology 16 (2001) 95-131. Erin D. Bigler
Departments of Psychology and Neuroscience, Brigham Young University, 1001 SWKT, Provo, UT 84602, USA



(1) DOI (2) 5-days Post-TBI (3) 4-years Post-TBI

Damage to the corpus callosum from Coup-counter coup in this patient in a front end collision:

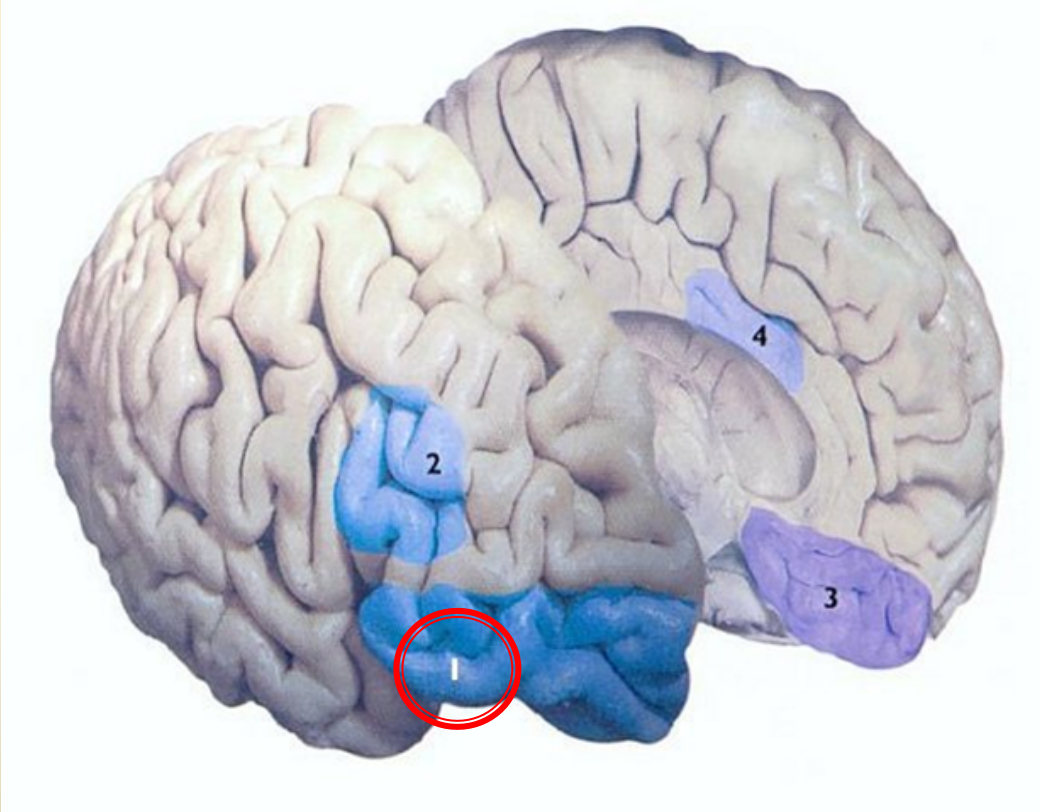
This patient developed anger, rage, and violent emotional outbursts.



Prefrontal Cortex

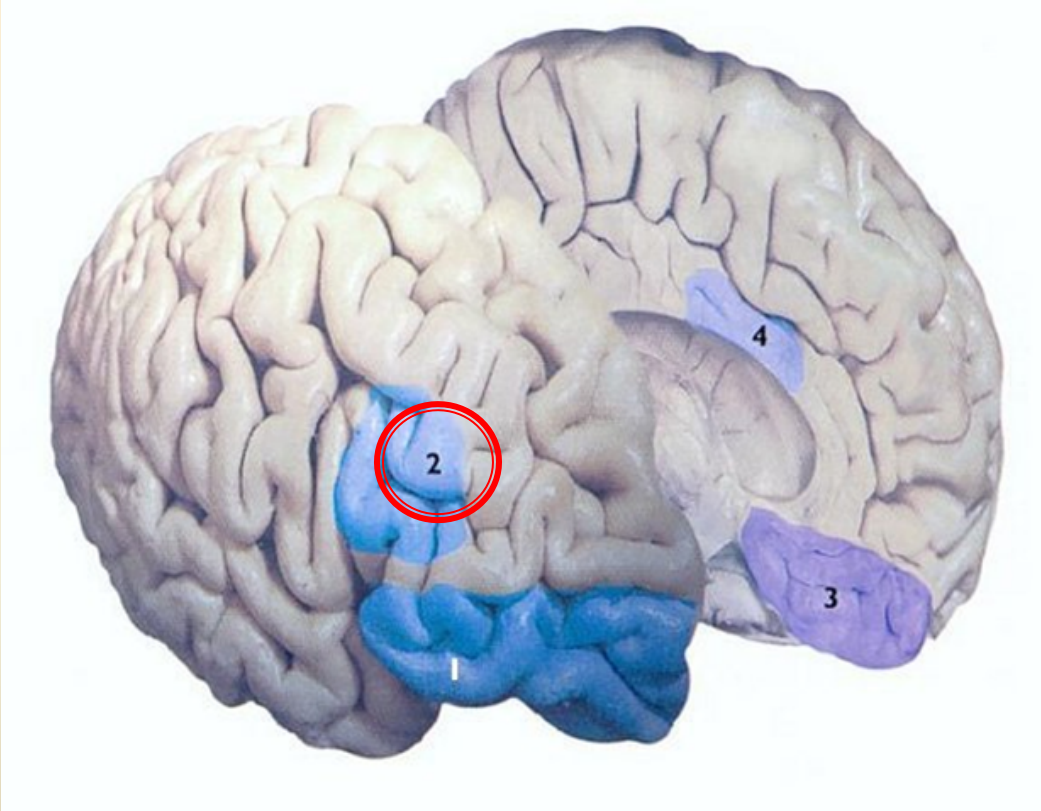
- The anterior part of the frontal lobes (prefrontal cortex), lying in front of the motor and premotor areas is implicated in planning, complex cognitive behavior, personality expression, decision making, and moderating social behavior; Executive Functions.
- Executive function relates to abilities to differentiate among conflicting thoughts, determine good and bad, better and best, same and different, future consequences of current activities, working toward a defined goal, prediction of outcomes, expectation based on actions, and social "control" (the ability to suppress urges that, if not suppressed, could lead to socially unacceptable outcomes).

Frontal Lobe Functioning in Health



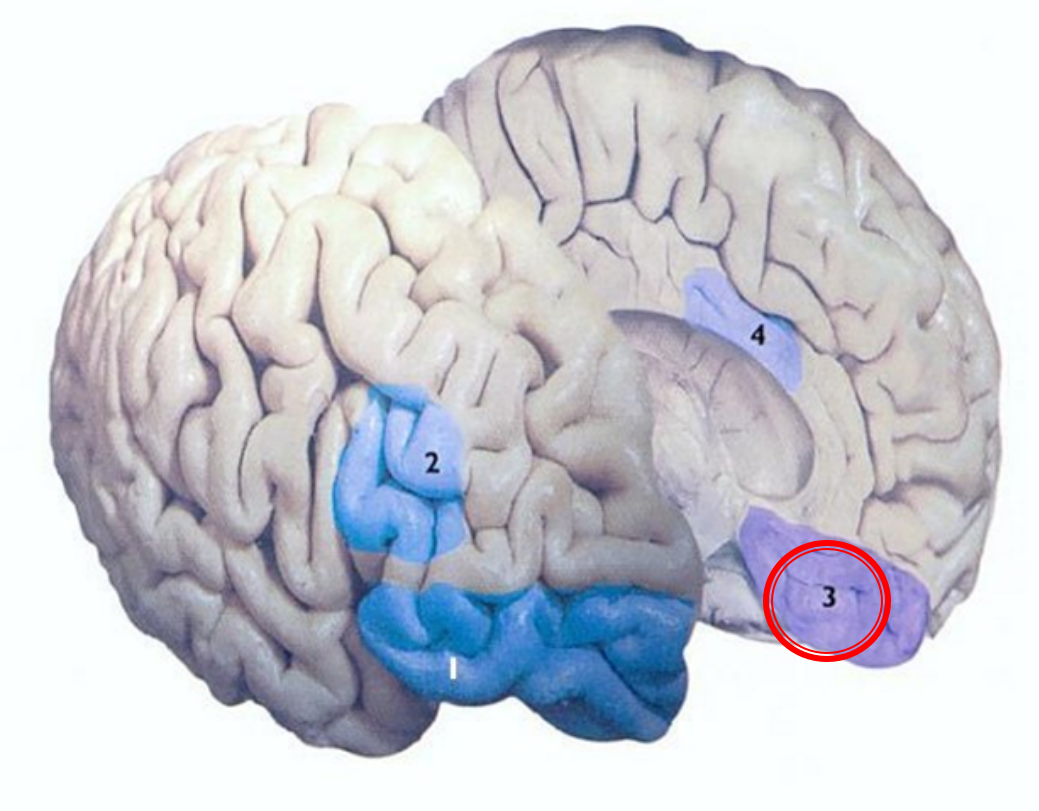
1 : **Orbito-Frontal Cortex** - This area inhibits inappropriate action, freeing us from the tyranny of our urges and allowing us to defer immediate reward in favor of long-term advantage.

Frontal Lobe Functioning in Health



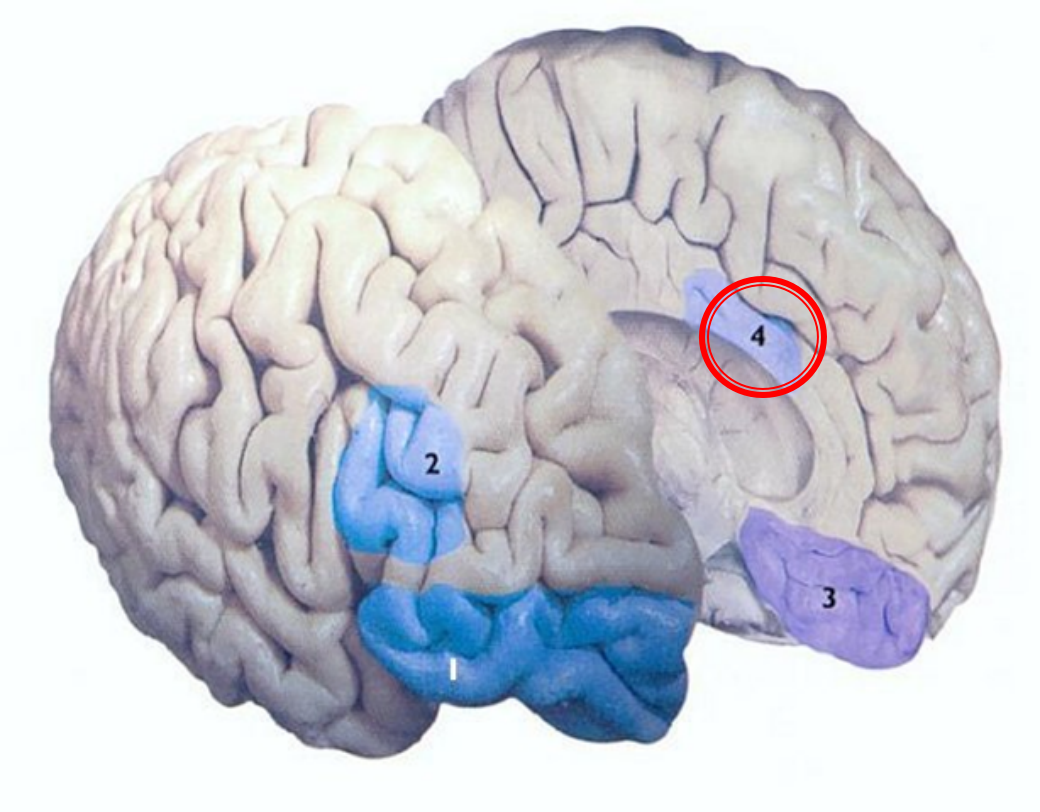
2 : Dorsolateral prefrontal cortex - Things are held "in mind" here, and manipulated to form plans and concepts. This area also seems to choose to do one thing rather than another.

Frontal Lobe Functioning in Health



3 : Ventromedial cortex - This is where emotions are experienced and meaning bestowed on our perceptions.

Frontal Lobe Functioning in Health



4 : Anterior cingulate cortex - It helps focus attention and "tune in" to own thoughts.

Hippocampal Volume and Mood Disorders After Traumatic Brain Injury

BIOL PSYCHIATRY 2007;62:332–338. Ricardo E. Jorge, Laura Acion, Sergio E. Starkstein, and Vincent Magnotta. Departmentof Psychiatry;Departmentof Radiology, University of Iowa, Iowa City, Iowa; and the Department of Psychiatry.

- TBI is characterized by pathological changes in cortical areas, subcortical nuclei, and white matter tracts with dystrophic neurons in the **CA1** subfields of the hippocampus, lasting up to 2 weeks after trauma.
- Quantitative analysis demonstrated **progressive neuronal loss** in the cerebral cortex and hippocampus over 1 year after injury.
- The occurrence of mood disorders during the first year after TBI appears to be associated with this reduction in hippocampal volumes (also memory recall and the ability to learn new information).

The Cingulate Gyrus

- It is an integral part of the limbic system, which is involved with **emotion formation** and **processing**, **learning,** and **memory**.
- The combination of these three functions makes the cingulate gyrus highly influential in linking **behavioral outcomes to motivation**.
- Daniel Coleman, author of ***Emotional Intellect*** puts the function as "Lets just say that the CG tries to help us put logic around our emotions. **Good luck**!"

Amygdala.1

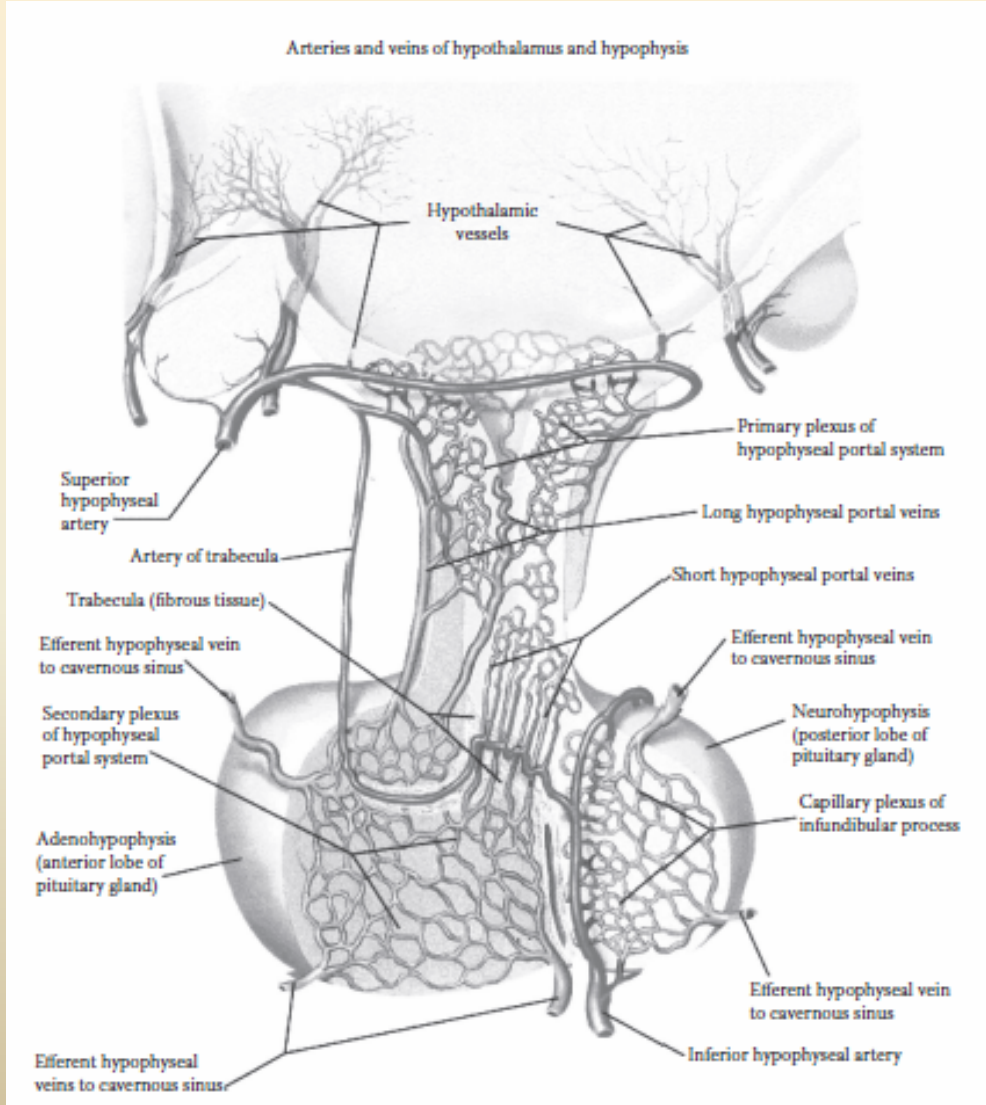
- Located deep inside the anterio-inferior region of the temporal lobe, the Amygdala connects with the hippocampus, the septal nuclei, the prefrontal area and the medial dorsal nucleus of the thalamus.
- These connections make it possible for the **amygdala to control the major affective activities** like friendship, love and affection, on the expression of mood and, mainly, on fear, rage, and aggression.
- TBI can lead to the loss of connectivity.

Amygdala.2

- The amygdala, is the center for the identification of danger, and is fundamental for self-preservation.
- **When triggered, it gives rise to fear and anxiety which lead to a heightened stage of alertness, getting ready to fight or for flight.**
- Experimental destruction of both amygdales tames the animal, which becomes **sexually non-discriminative**, deprived of affection and indifferent to danger.

Damage to blood supply to AP

- Compromised blood supply to the pituitary is seen in **Sheehan's, repetitive or prolonged surgery, stokes, and with increase intracranial pressure.**
- This can lead to selective anterior pituitary hormone deficiencies.

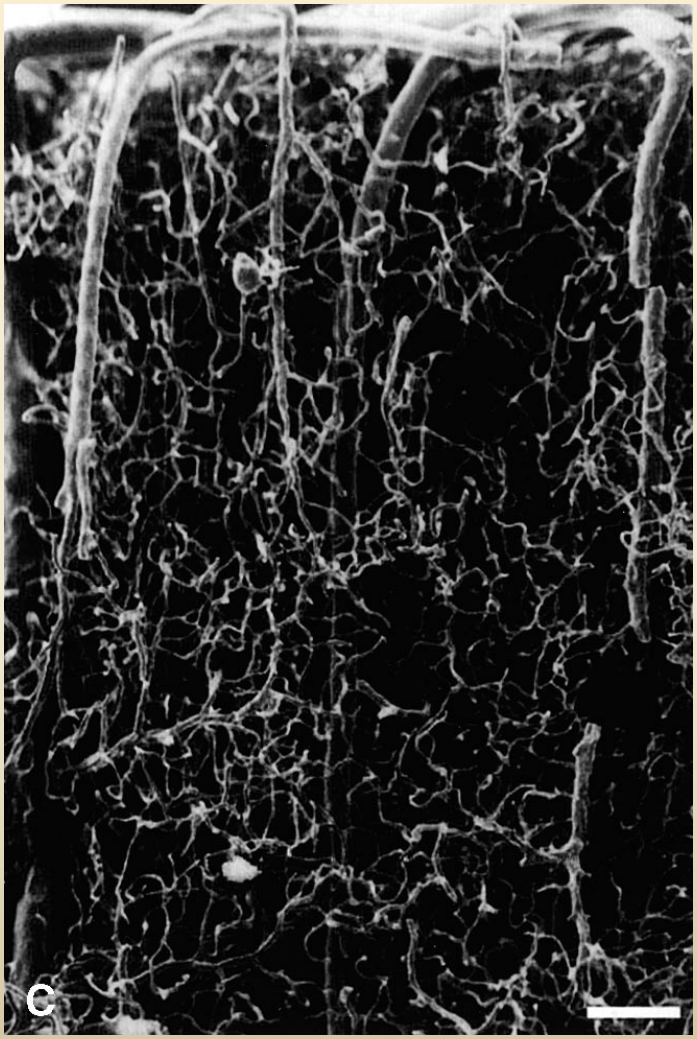


The lesion(s) in traumatic brain injury: implications for clinical neuropsychology

. Archives of Clinical Neuropsychology. 16 (2001) 95-131. Sept 2000.

Erin D. Bigler. Depts of Psychology and Neuroscience, Brigham Young University, 1001 SWKT, Provo, UT 84602, USA

- Many times in TBI micro vessels permeating the gray to white matter are sheared along with neurons.
- The added insult of **free blood** in the brain augments the production of inflammation with free radical damage induced by the iron released from hemoglobin.



Diffuse Axonal Injury

- Diffuse axonal injury (DAI) is caused by acceleration–deceleration and rotational forces during the primary head injury.
- This injury causes a stretching and shearing of the neurons (white matter tracts) throughout the brain, disrupting neuronal transmission and connectivity.
- DAI is only visible on the MRI scan however, there is a high index of suspicion when multiple small cerebral contusions appear on CT scan.
- DAI can be clinically diagnosed when the patient has experienced a prolonged coma (> 6 hours) and does not have signs of a mass lesion or ischemia.

The lesion(s) in traumatic brain injury: implications for clinical Neuropsychology

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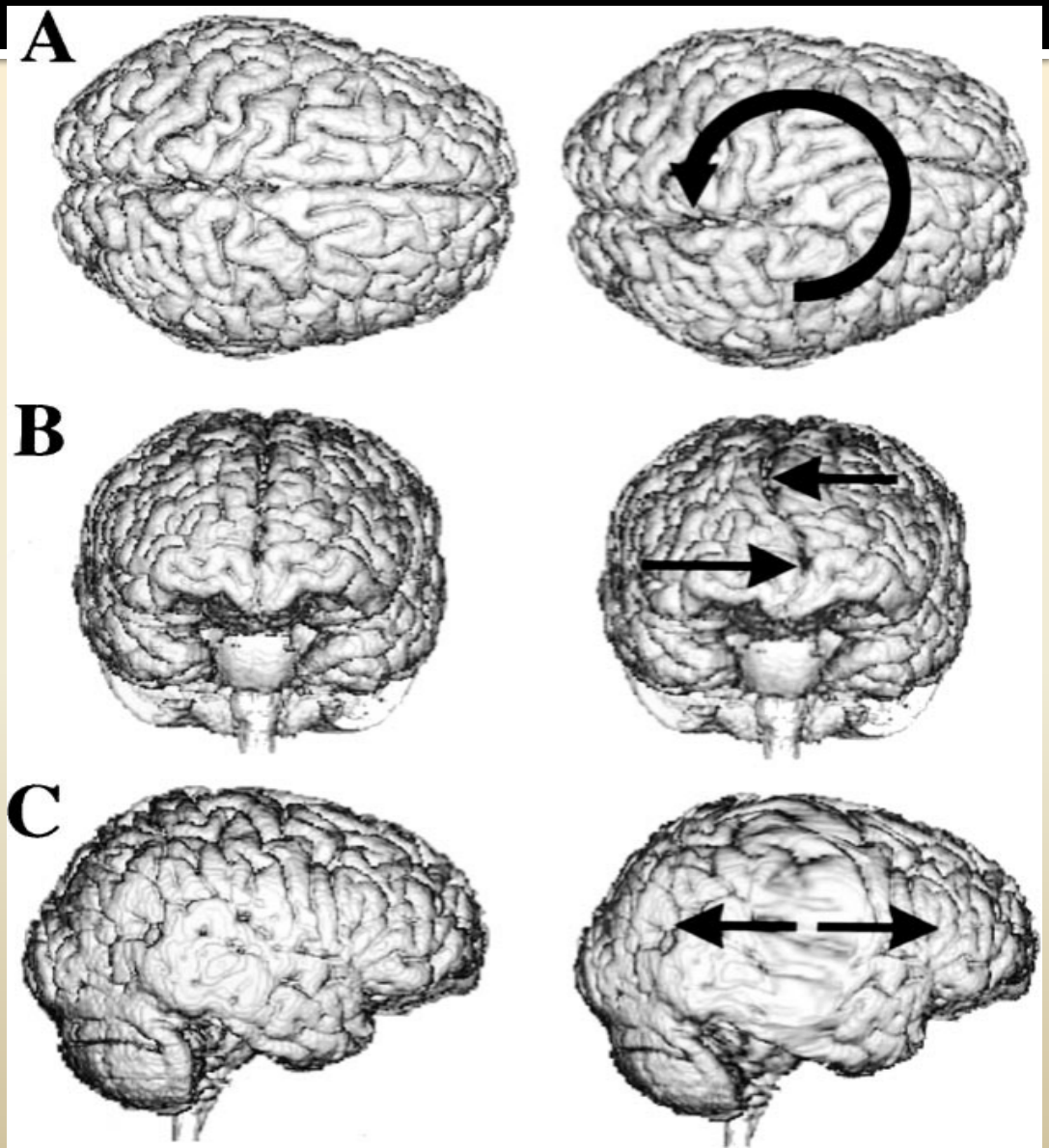
(A) Dorsal View of a high velocity side impact that is rotating the brain with twisting action.

Shearing actions

(B) Frontal View of a high velocity side impact that is twisting the brain.

Shearing actions

(C) Lateral View of a high velocity side impact that is stretching and twisting the brain.



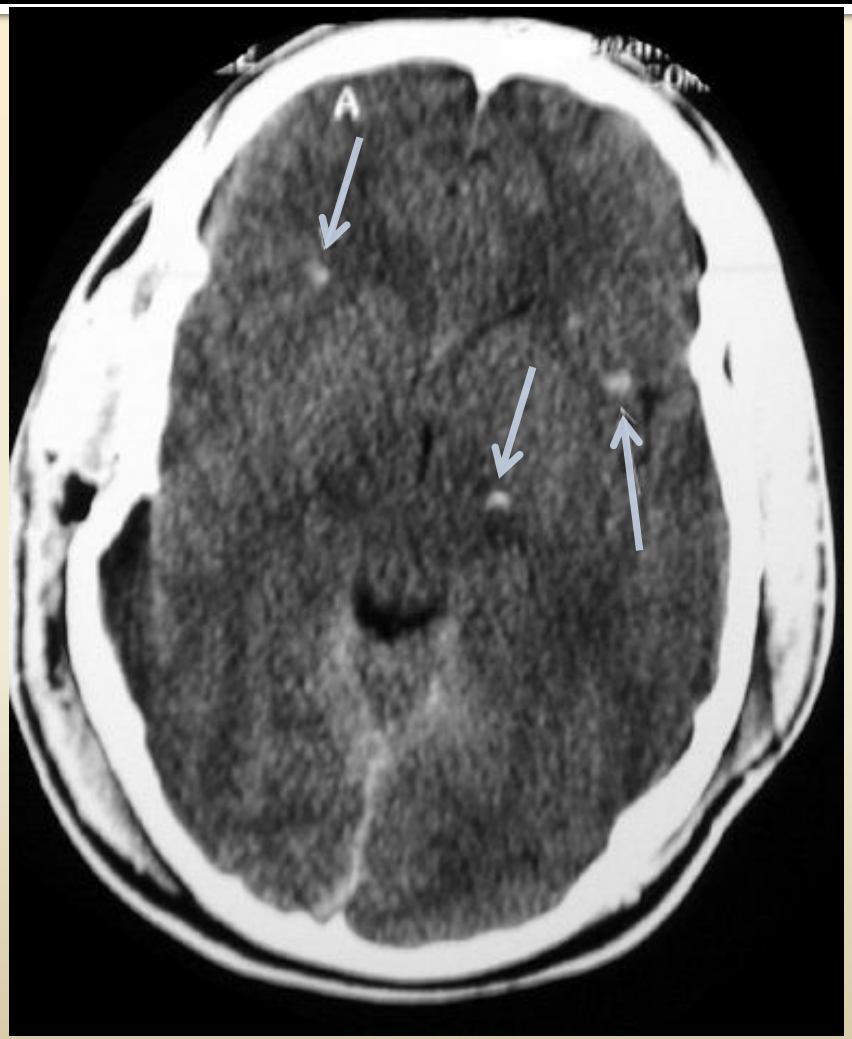
Diffuse Axonal Injury

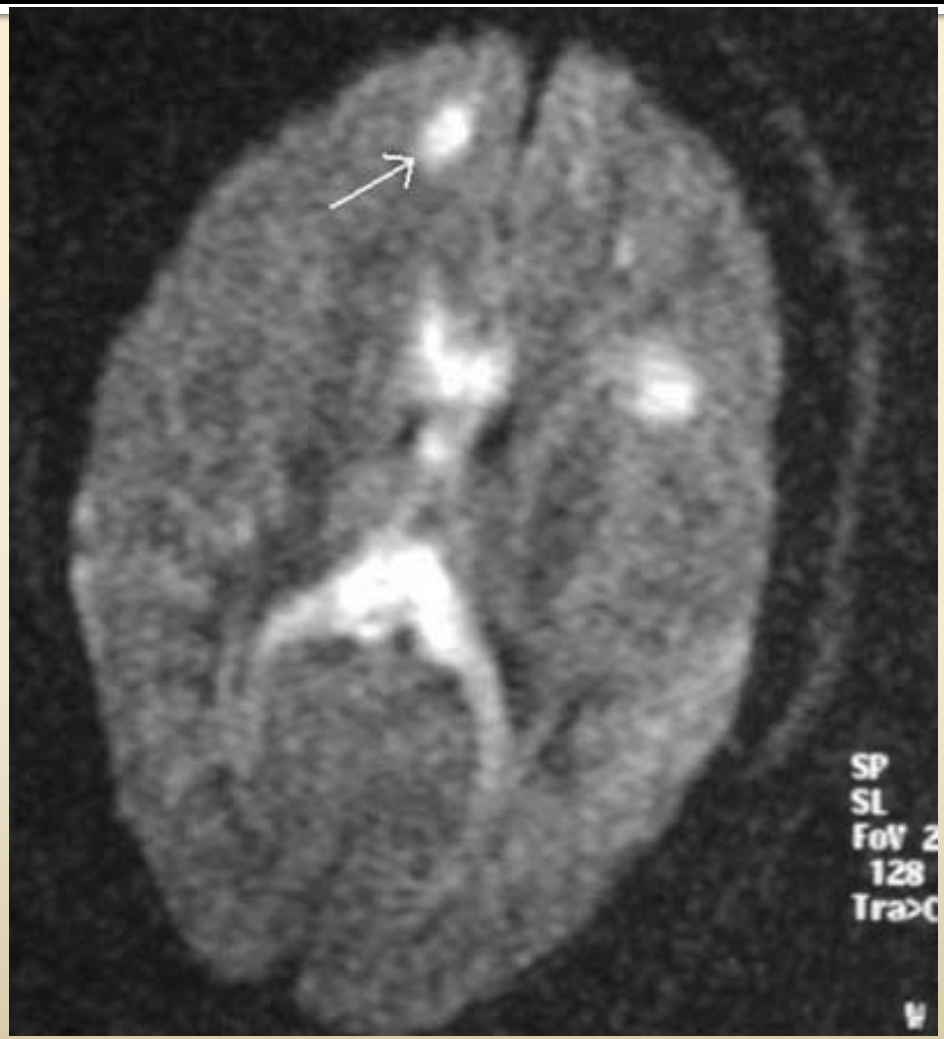
- Typically, diffuse and bilateral involving the lobar white matter (FL) at the gray-white matter interface.
- Most Common areas involved:
  - Frontal and Temporal White Matter
  - Corpus Callosum
  - Caudate Nuclei
  - Tegmentum
  - Thalamus
  - Hypothalamus
  - Internal Capsule

Mechanism of Head Injuries. Holbourn A., Lancet. **1943**;2:438-41

- Sudden acceleration-deceleration impact can produce shearing injury which is not found to be induced by linear or translational forces but only by rotational forces.
- Greater than 60% of the shearing injuries produced by rotational force is at the gray-white matter junction.
- When shearing forces occur in this area of greater density differential, the axons suffer trauma resulting in edema and axonal leakage which is most **severe in the 2 week post trauma period.**
- Loss of consciousness is associated with DAI.

Diffuse Axonal Injury. Jeffrey R Wasserman, DO, Diagnostic Radiologist, Manatee Memorial Hospital and Lakewood Ranch Medical Center Robert A Koenigsberg, DO, MSc, FAOCR, Professor, Director of Neuroradiology, Program Director, Diagnostic Radiology and Neuroradiology Training Programs, Department of Radiology, Hahnemann University Hospital, Drexel University College of Medicine. **2010**





Classification of DAI

DAI is classified as mild, moderate or sever:

- **Mild DAI**: Coma lasting 6-24 hours, mild to moderate memory impairment, and mild to moderate disabilities.
- **Moderate DAI**: Coma lasting > 24 hours, followed by confusion and long-lasting amnesia. Withdrawal to purposeful movements, and mild to severe memory, behavioral, cognitive, and intellectual deficits.
- **Severe DAI**: Deep prolonged coma lasting months with flexion and extension posturing. Dysautonomia can occur. Deficits are noted in cognition, memory, speech sensorimotor function and personality.

Summary

- TBI affects functioning at subcellular and cellular levels influencing the integration of the different lobes of the brain. Connectivity.
- At the subcellular level **neurotransmitters and neurosteroids** are affected along with their ability to modulate gated-ion channels and receptors, thereby altering both cognition and neurobehavior.
- On the cellular level, destruction of neurons and glial cells further flame the fires of inflammation with the progression and expansion of cell death and loss of cerebral tissue = Cavitation.

Summary

- Compromise of the hypophyseal blood supply can lead to the loss of anterior pituitary hormones (Sheehan's-like syndrome).
- Bleeding into the brain not only causes local ischemic, hypoxia, and hypoglycemia but deposits iron which initiates free radical production raising OS.
- All adverse reactions are modifiable with the use of NS, NAS and supplements that address inflammation and Oxidative Stress.