

Neuropathy Update

November 12, 2010

Neuropathy Support Group

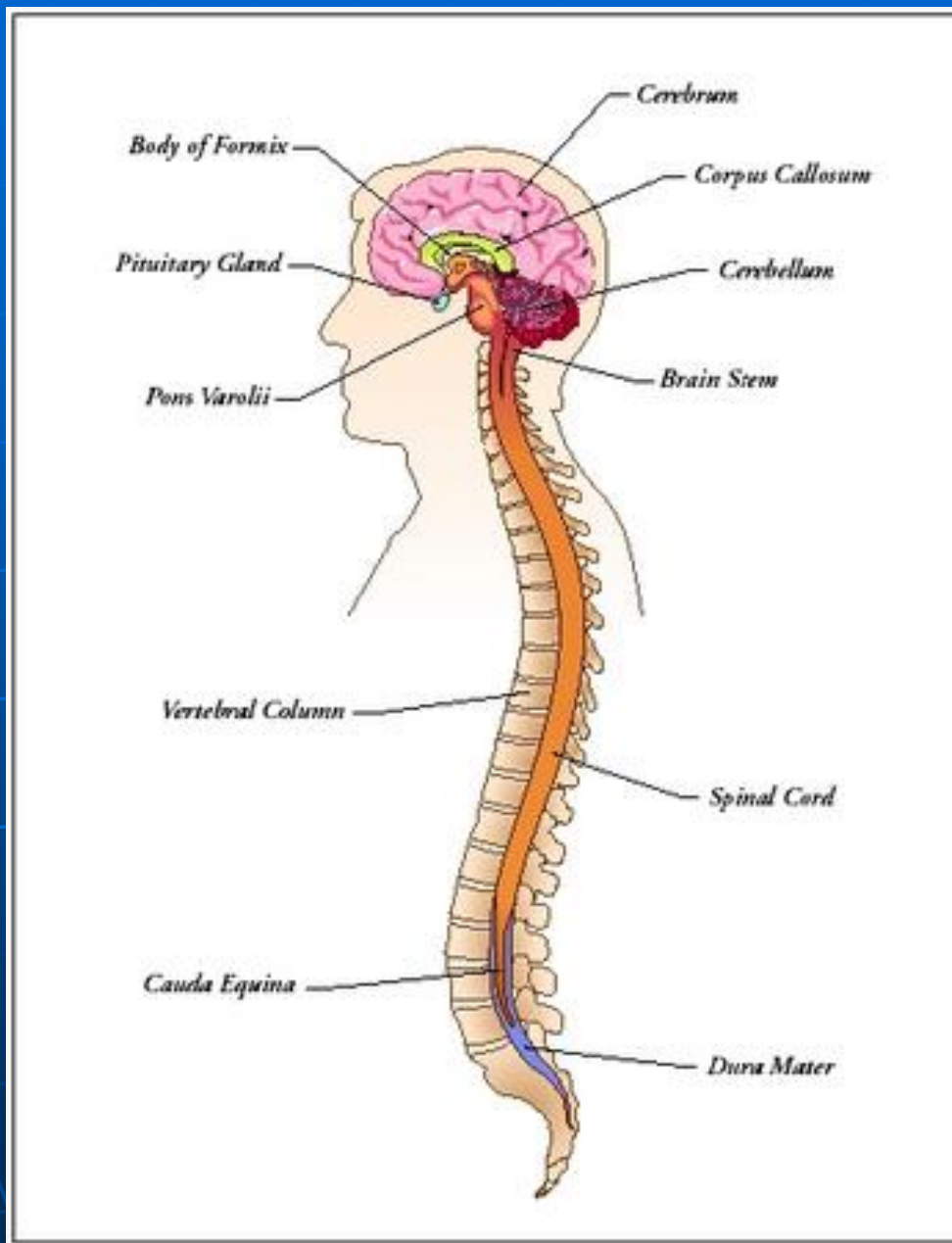
Mizell Senior Center

Overview

- Defining Neuropathy
- Classifying Neuropathy
- Mechanisms of Neuropathy
- Potential Treatments of Neuropathy

Defining Neuropathy

- Pain resulting from a lesion of the CNS or PNS
- Neuropathy is not a single disease! It is a CLINICAL entity
- Neuropathic pain can be spontaneous or evoked



Neuropathy is Unique

In most diseases the pain goes away with a cure for the disease, but in neuropathy the process persists and pain becomes it's own primary symptom.

Example: Fracture Repair vs. Diabetes

Neuropathy may not be confined to one nerve or one area of the body

Classifications

Part 1

- Focal or Multifocal
 - Post traumatic
 - Entrapment
 - Phantom Limb
 - Post herpetic Neuralgia
 - Mononeuropathy
 - Ischemia
- Generalized
 - Diabetes
 - Alcohol
 - HIV/AIDS
 - Chemotherapy
 - Hereditary

Classifications

Part 2

- Central Nervous System
 - Multiple Sclerosis
 - Spinal Cord Injury
 - Stroke
- Complex Regional Pain Syndrome
 - CRPS I
 - CRPS II

Classification

Positives and Negatives

- Positives
 - Paresthesia
 - Paroxysms
 - Hyperalgesia
 - Allodynia (hot and cold)
- Spontaneous or Evoked
- Dynamic or Static
- Negatives
 - Hypoesthesia
 - Hypoalgesia
 - Thermohypoesthesia

Classification

- **Demyelinating** neuropathy implies injury to the myelin sheath

Think inflammatory processes

- **Axonal** neuropathy implies injury to the actual nerve endings

Think Toxins

- Persistent demyelination leads to axonal injury and a mixed neuropathy

Classification

- Small Fiber Neuropathy
- Large Fiber Neuropathy
- Sensory Neuropathy
- Motor Neuropathy
- Mixed or "sensorimotor" Neuropathy
- Autonomic Neuropathy

Diagnostic Testing

Nerve Conduction Velocity

- Demyelination causes Delayed Latencies
- Axonal injury causes decreased Amplitude

Diagnostic Testing

- Electromyography or EMG

Allows needle evaluation of neural input to muscles

Determines Denervation and Reinnervation Activity

Nerve Biopsy

- Allows tissue diagnosis by a neuropathologist
- Rarely required
- Sural nerve is the usual biopsy site

Skin Biopsy

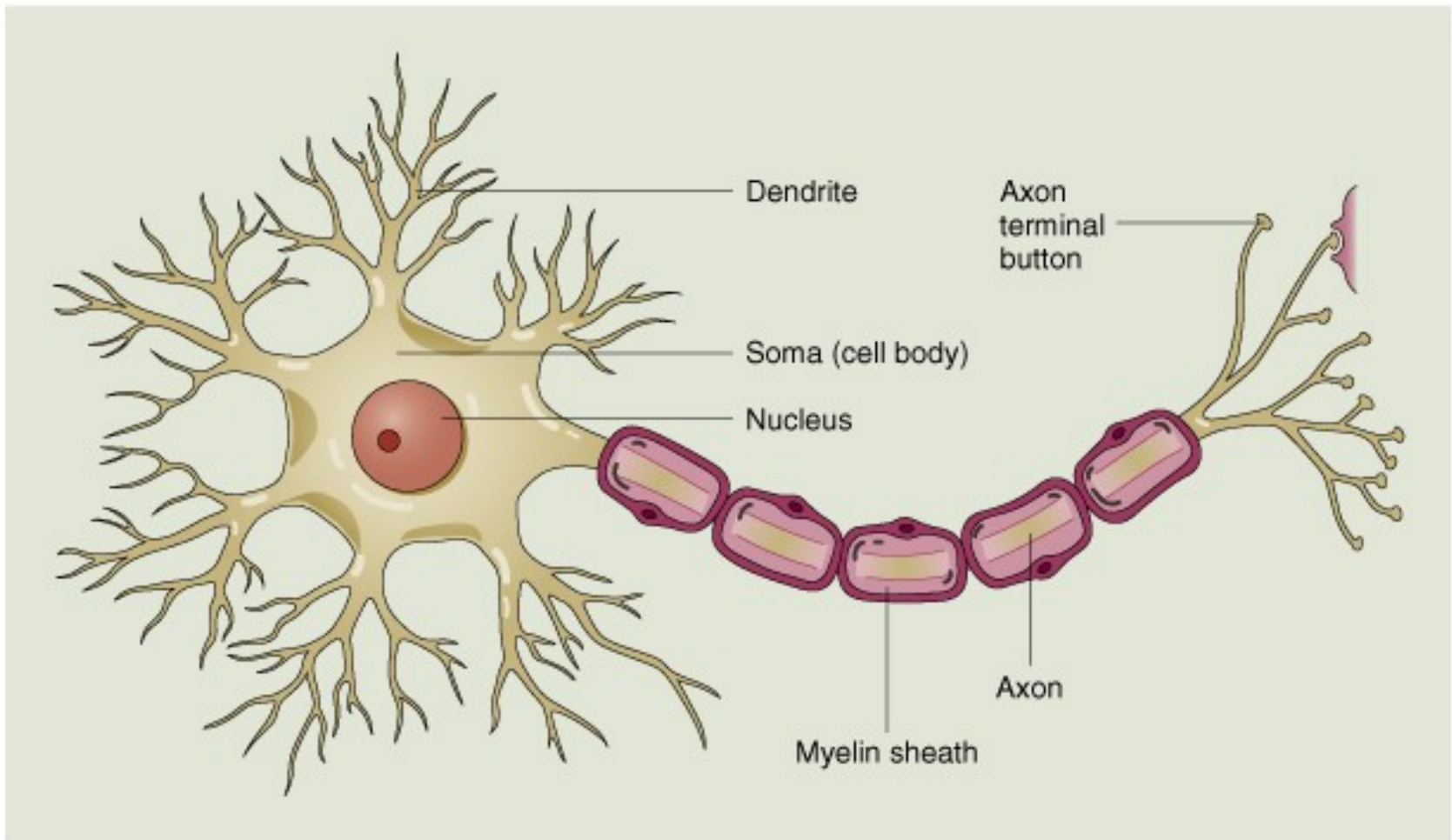
- Assess nerve fiber density
- Identify which fibers are involved
- Monitor serially over time
- Minimally invasive
- Generally not recommended
- Helpful for research protocols

Diagnostic Testing

- Confirm Diagnosis
- Exclude alternatives
- Characterize Neuropathy
- Establish Baseline Data Point

Mechanism of Neuropathy

- An injury to the nervous system actually changes the nerve cells (neurons)
- These cells become HYPER sensitive and react spontaneously
- The injury causes inflammation which irritates surrounding cells and causes spontaneous pain



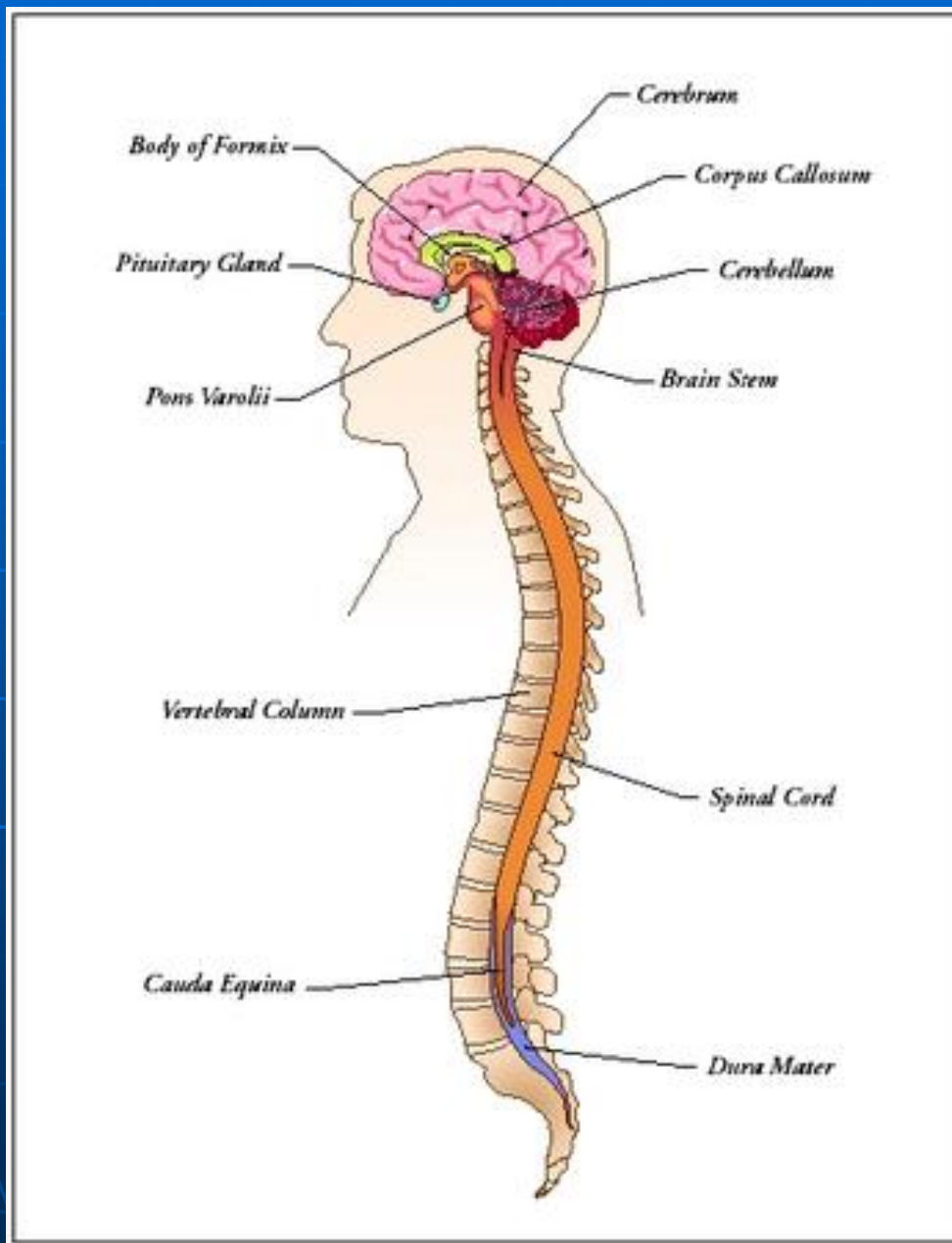
© 2000 John Wiley & Sons, Inc.

Mechanisms of Neuropathy

- If we understand the mechanism then we might find a successful treatment!

Mechanisms of Neuropathy

- These steps result in changes to cells that live in the spinal cord and brain “pain processing centers” Normal sensations are now incorrectly processed as pain
- Lastly, the CNS pain moderation system changes and becomes hyper-excitabile



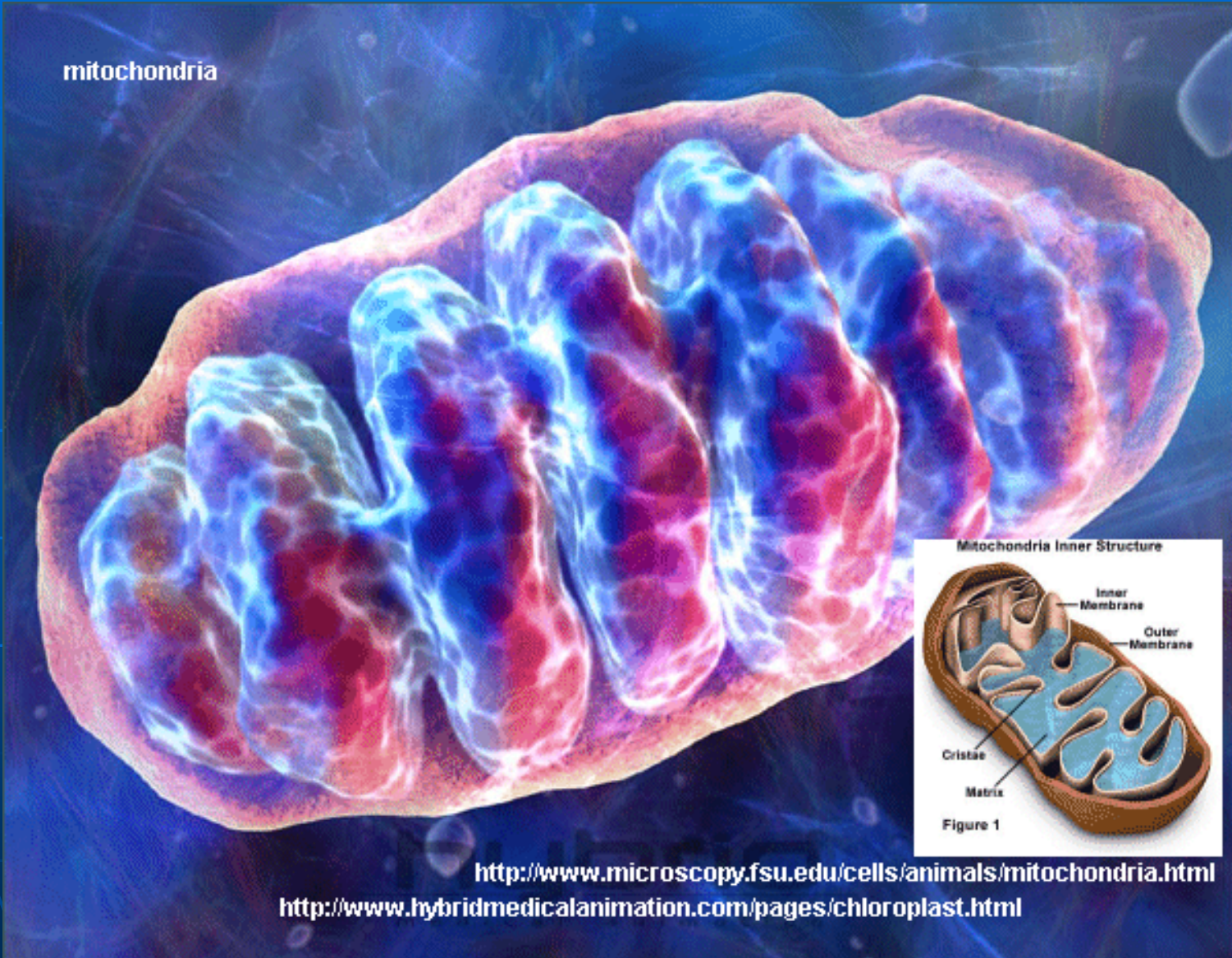
The Mitochondria Mechanism

- The "Powerhouses of Cells"

Mitochondria create the energy for nervous system tissue to function but they are poisoned by chemotherapy and in animal models even low doses of chemo caused neuropathy (with no evidence of actual damage to the nerve itself)

Once the mitochondria are damaged they can not supply enough energy to the nerve and degeneration results

mitochondria



<http://www.microscopy.fsu.edu/cells/animals/mitochondria.html>

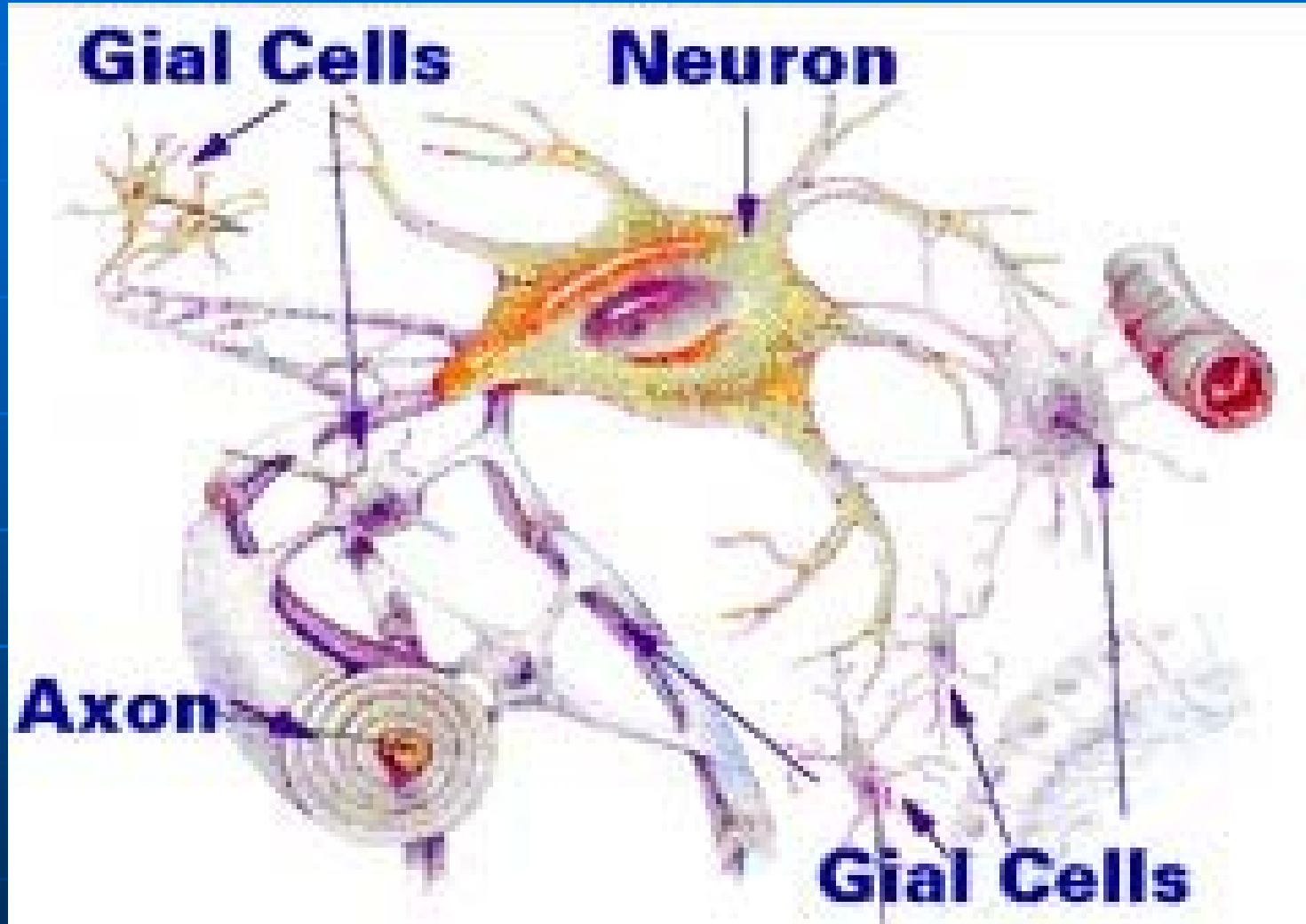
<http://www.hybridmedicalanimation.com/pages/chloroplast.html>

The Mitochondria Mechanism

- Targeting therapy at the mitochondria might optimize results.
- Medications that might work at this level include Topamax and Acetyl-L-Carnitine

The Glia Mechanism

- Glia are the cells in the nervous system that support the neurons. “Nonneuronal Elements”
- They control the “Volume” of Pain Processing



The Glia Mechanism

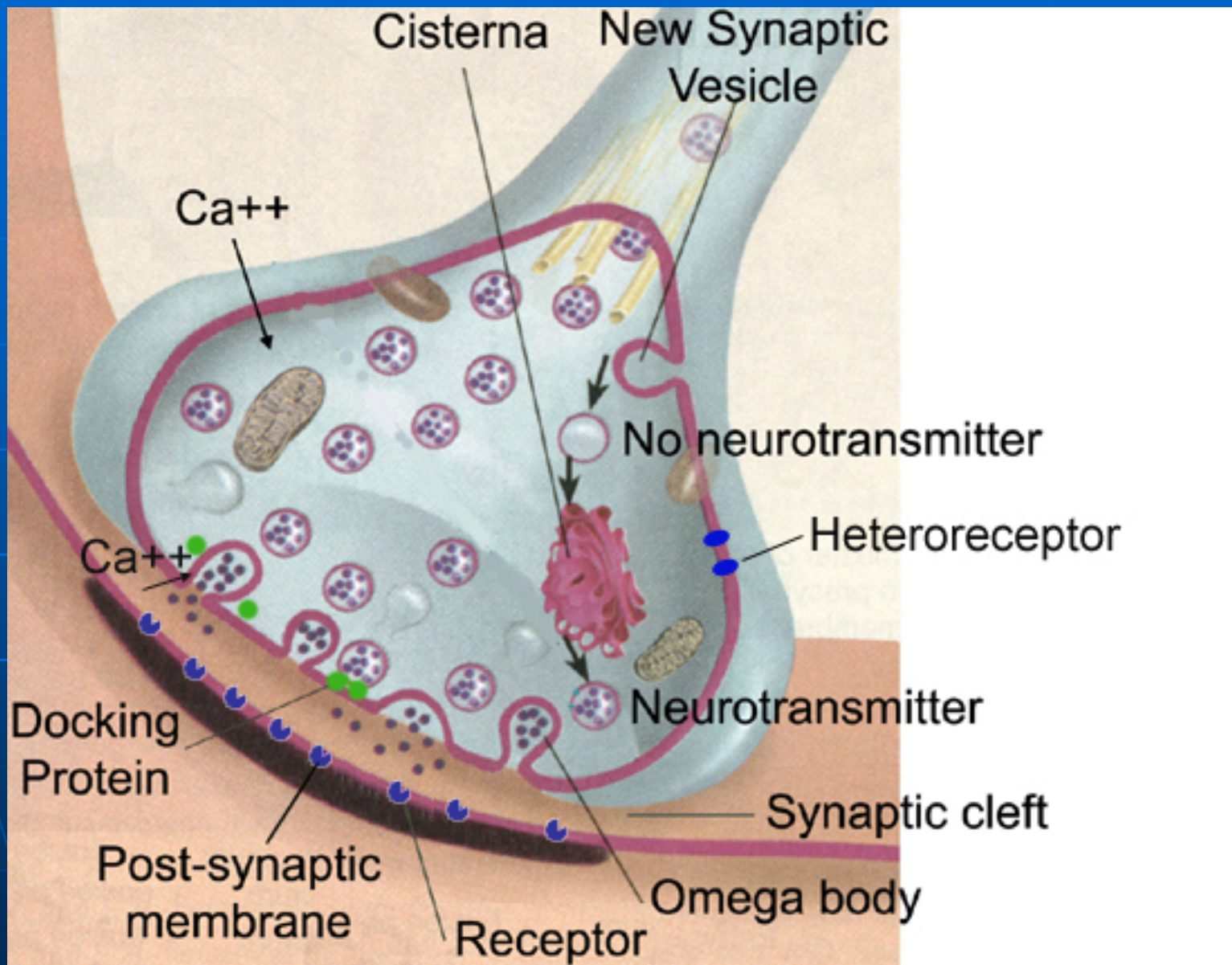
- If they are not working properly the pain volume increases. Blocking the glial system could block pain.
- Chronic opiate use activates the glia and reduces the efficacy of these drugs. Side effects and tolerance become problematic. In some cases chronic opiates result in hyperalgesia.

Peripheral Sensitization Theory

- Lesions in the Peripheral Nervous System cause a lower threshold for pain
- Pain receptors become more active and inflammatory agents increase

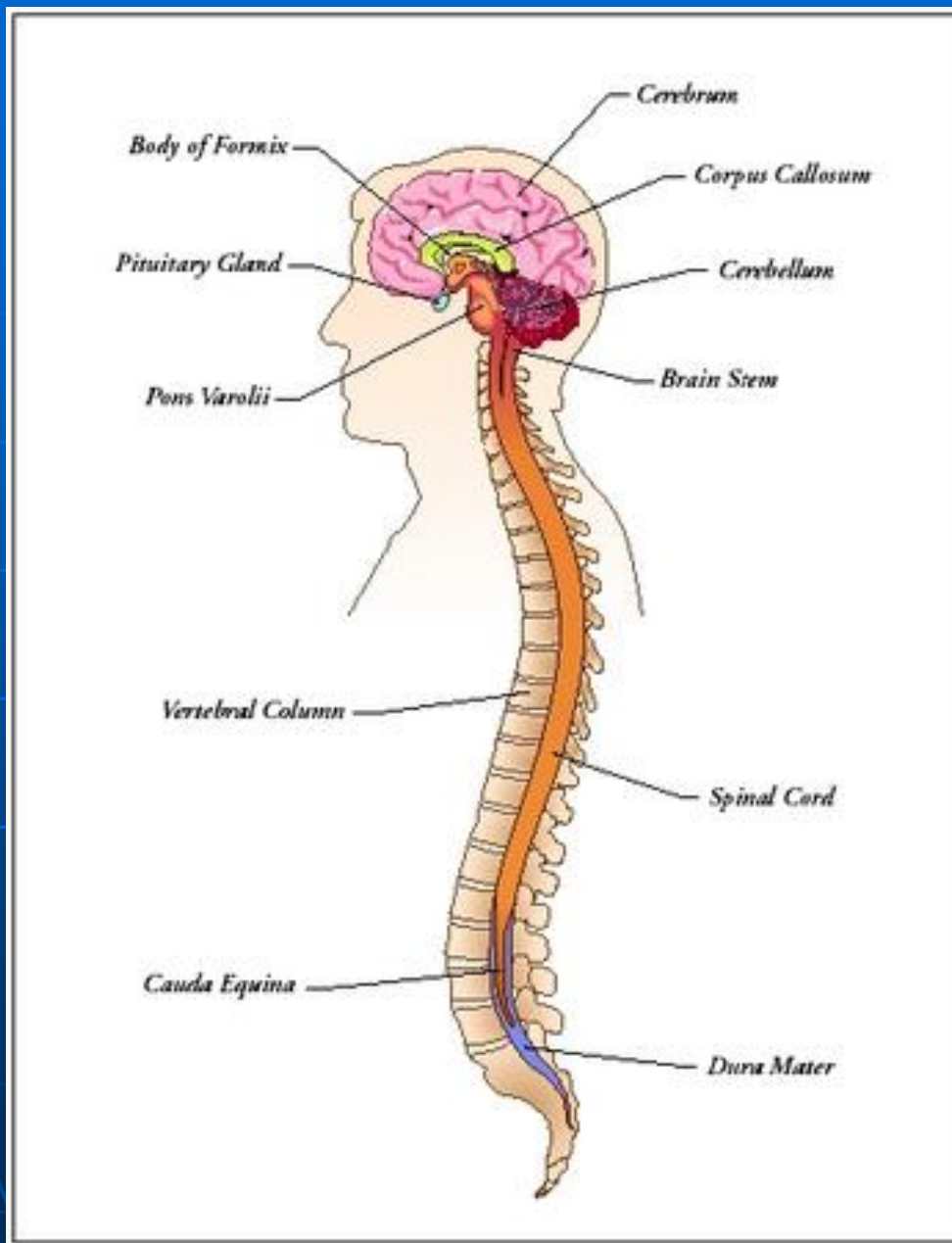
Peripheral Sensitization Theory

- Targeting these specific receptors and inflammatory agents could reduce pain
- There are many (!!!) types of receptors and many (!!!) different inflammatory agents



Central Sensitization Theory

- The Central Nervous System (Brain and Spinal Cord) becomes a pain amplifier
- Pain processing neurons become more active and expand their field of influence while spreading this process to their neighbors



Central Sensitization Theory

- Loss of CNS Inhibition Function
- Functional MRI visualizes changes in the cerebral cortex!

CNS Sensitization Theory

- With no external cues the CNS produces activity!
- The Prefrontal Cerebral Cortex is the “Top Down Manager” of pain perception
- The CNS does not moderate inputs properly causing a misperception of reality

Treatment Strategies

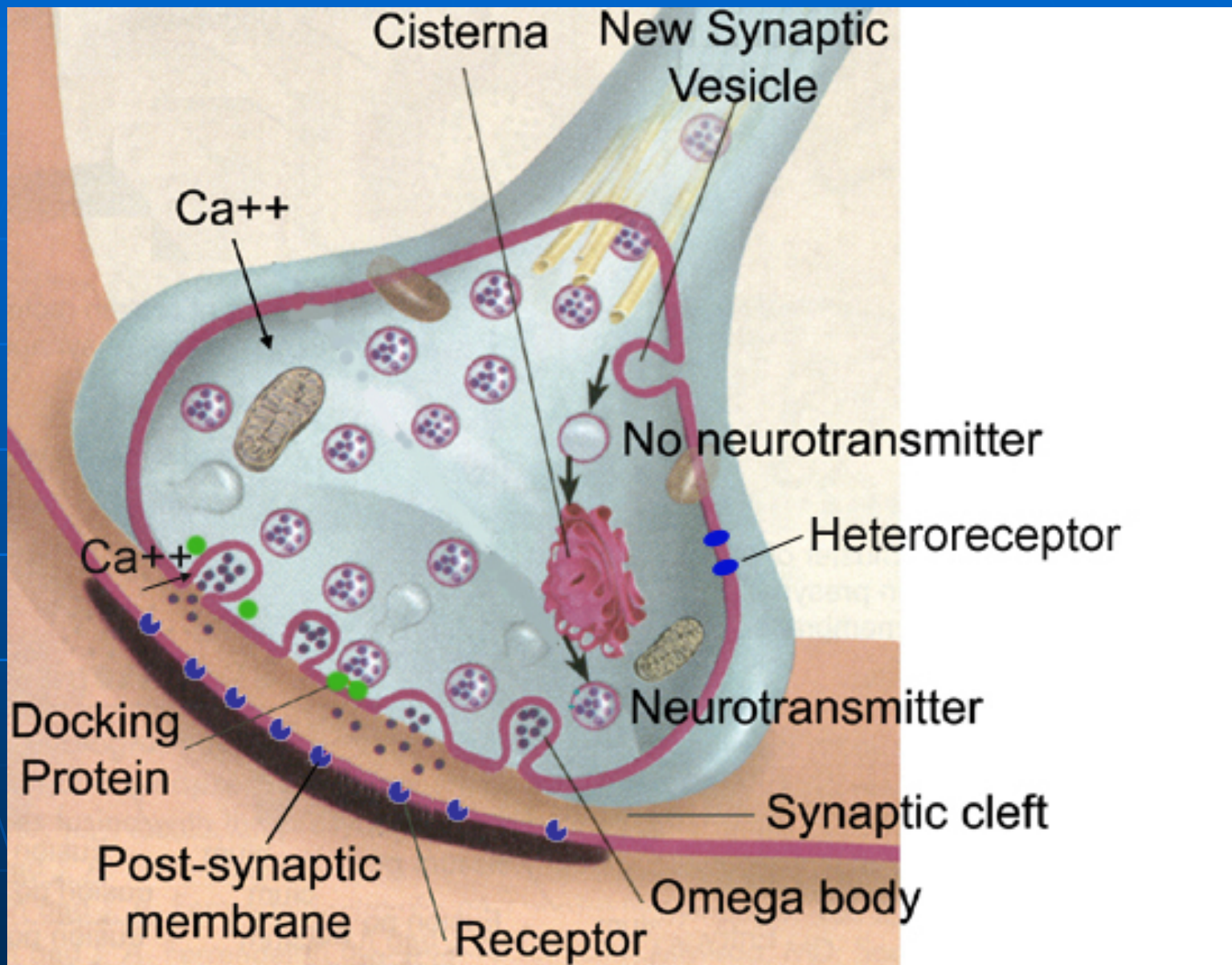
- Pitfall: A specific symptom does not imply a specific mechanism. Many different mechanisms might lead to one symptom
- In an ideal world therapy would match mechanism.

Treatment Strategies

- Genetics and health status of an individual also play a role in both the symptom complex and the response to therapy

Potential Treatment of Neuropathy

- Understanding the mechanism of neuropathy may allow for targeted therapy



Potential Treatment of Neuropathy

- Examples
 - Sodium channels on neurons blocked by lidocaine, tegretol, trileptal, lamictal, tricyclic antidepressants
 - Calcium channels blocked by neurontin and lyrica
 - GABA stimulants (reduce inhibition): baclofen

Potential Treatment of Neuropathy

- Examples (continued)
 - Mu receptors: opioids
 - Alpha 2 receptors stimulated by Clonidine, Cymbalta, Effexor, tricyclic antidepressants
 - Descending CNS pathway inhibition altered by SSRI and other antidepressants

Other Treatments

Targeting Treatment to Mechanism

PLEX

IVIG

Reduce active inflammation and demyelination

Treatment of Neuropathy

- On average it takes 8 trials of medications to get one success
- Success is defined as a 30% reduction in pain
- Combination therapies are likely more successful than singular therapies pushed to the max

Ongoing Treatment

- Many therapeutic failures reflect poor understanding of the physiology of pain
 - Sub therapeutic Dosing
 - Erroneous Dosing Schedules
 - Early termination of trial
 - Failure to escalate dose properly

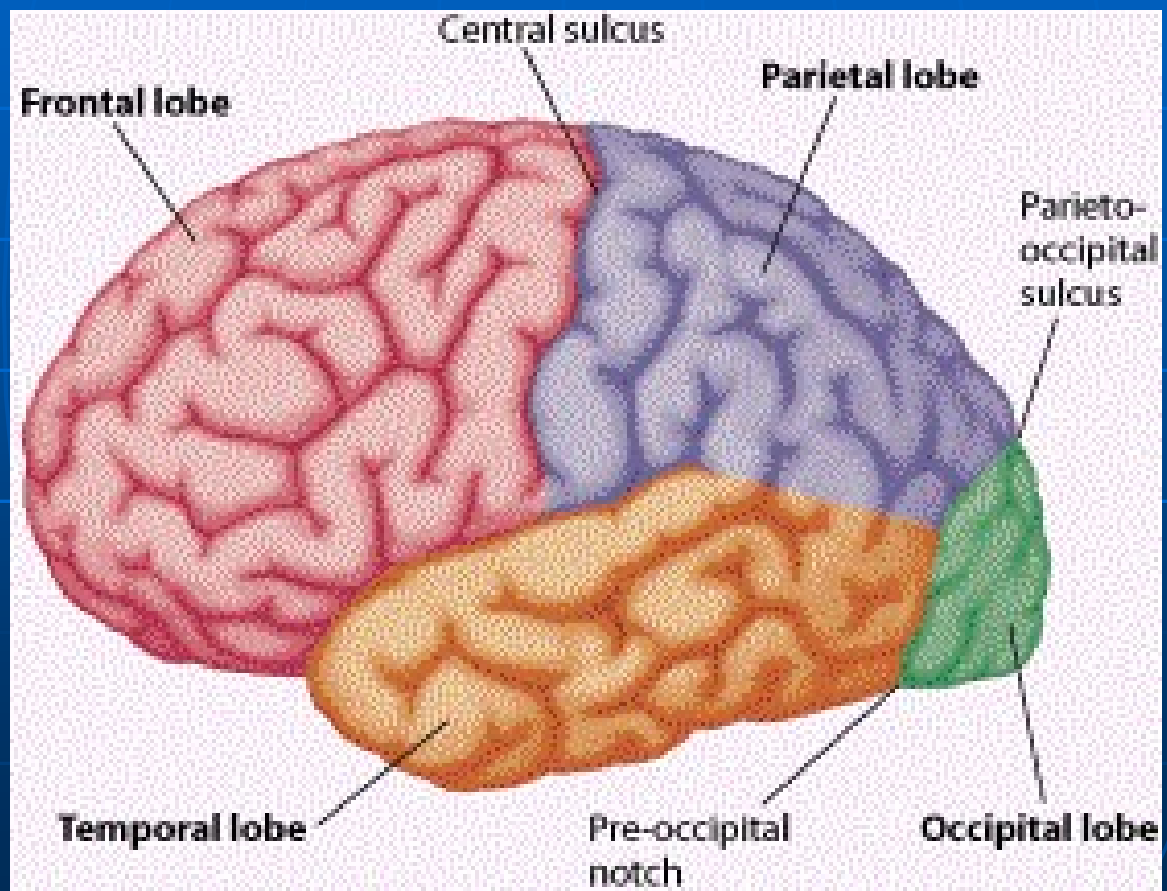
Non-Prescription Options

- NOT PROVEN!!!
- Some suggestive/circumstantial evidence:
 - Soy Diet
 - Vegan Diet
 - Alpha Lipoic Acid (600-1800 mgs per day)
 - Acetyl-L-Carnitine (1-2 grams per day)
 - Vitamin E
 - Iyengar Yoga

Smoke Gets in Your Eyes

- Cannabananoids
 - Definite evidence not available
 - May be helpful for central pain
 - Oral formulas sometimes utilized

Questions?



Credits

- 12th International Conference on Mechanisms and Treatment of Neuropathic Pain 2009
- Mechanisms of Disease: Neuropathic Pain-a clinical perspective Ralf Baron
www.nature.com/clinicalpractice/neuro February 2006 vol 2 no 2