A Whole Body Approach to Brain Health

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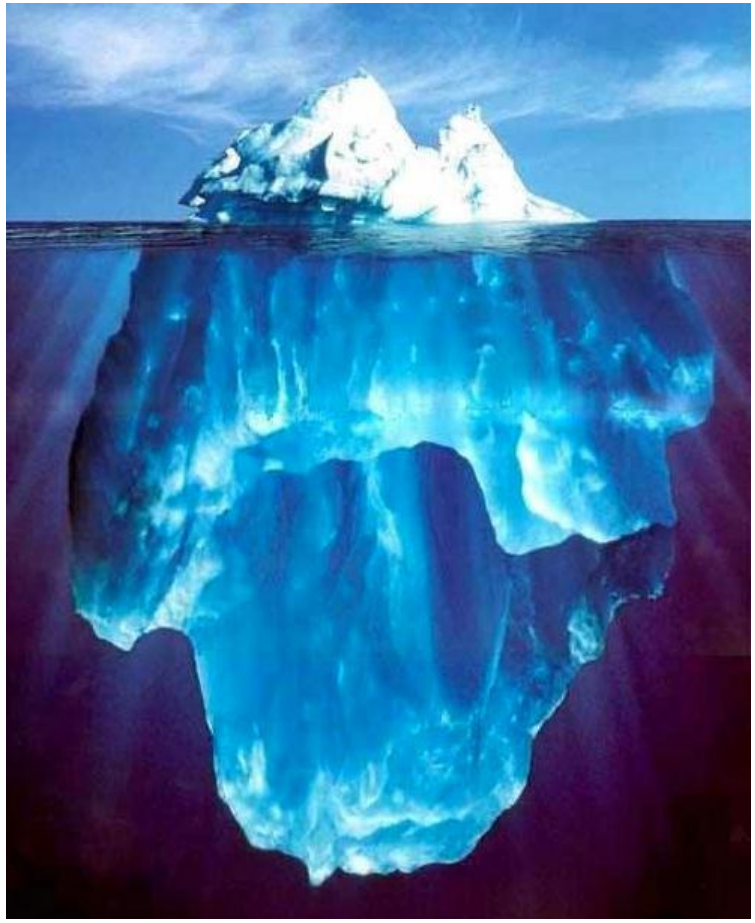
It’s not just neurons up there

In order to understand the impact of FOOD, NUTRITION and LIFESTYLE on BRAIN HEALTH, we need to understand the PHYSICAL and BIOLOGICAL aspects of the brain

Whole Body Systems Model: Symptoms Emerge from Problems with Underlying Functions

VISIBLE Social & Behavioral SYMPTOMS are OUTPUT

DISTURBANCE OF CORE UNDERLYING BODY FUNCTIONS are GENERATORS



Ziggarut model: http://www.texasautism.com/

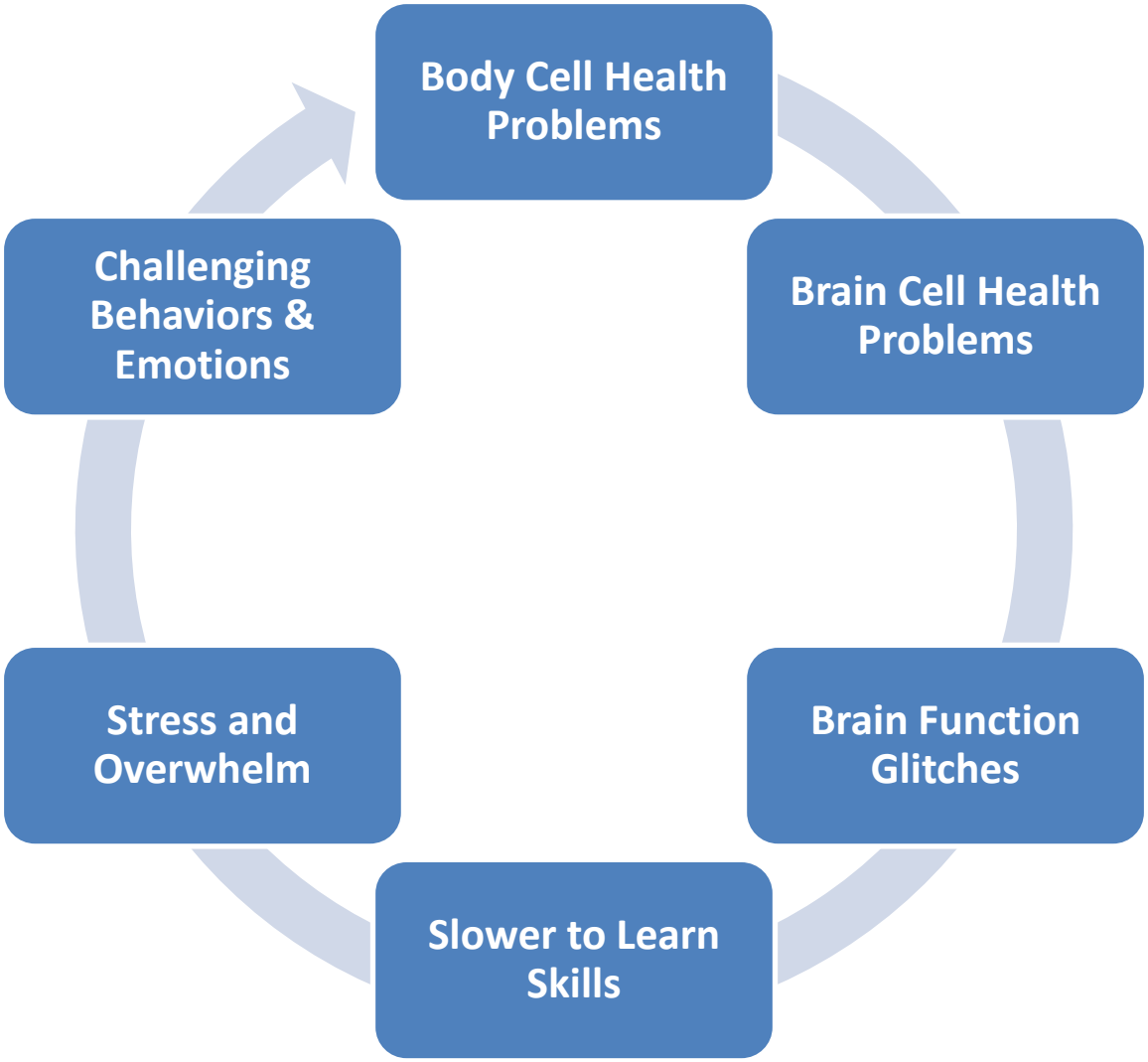
Key Points

- Physical and biological needs of the brain must be met as a precondition for “higher” functions to be performed
- These are performed by an array of cell and tissue types without which neurons could not live or function
- The quality of health, lifestyle and environment can profoundly affect these physical and biological parameters
- Transduction of biology into electrophysiological signaling is vulnerable to poor physical and biological health
- Taking a whole body approach to brain health can revolutionize health practices, medicine and research

Physical and Biological Needs of the Brain

- Energy
- Metabolic integrity
- Fluid flow
- Appropriate membrane and barrier function
- Structural integrity
  - Structures and fluids take up room
  - There is not a lot of give
  - Getting squished interferes with function

All the parts really influence each other

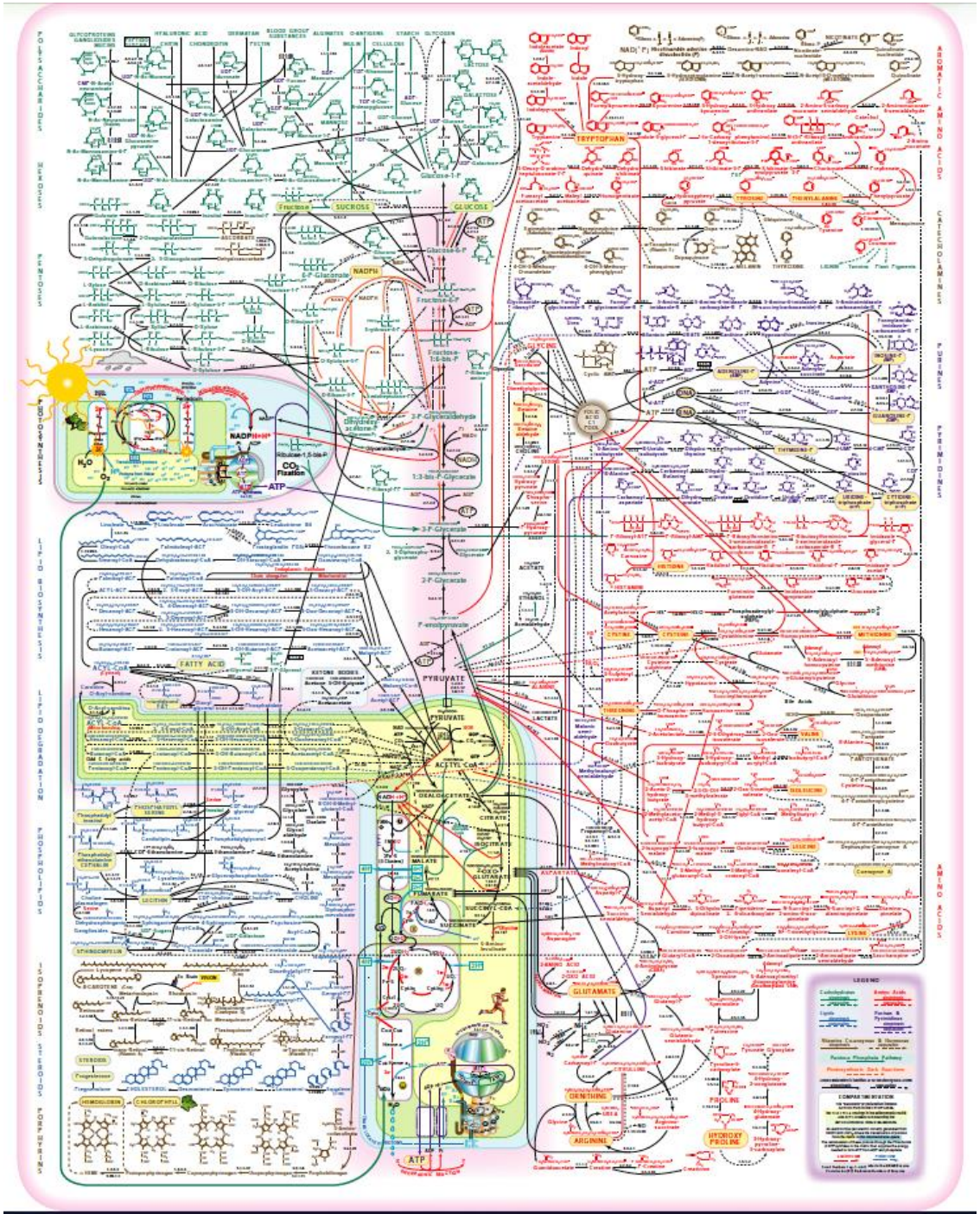


Energy in the brain

- Energy is generated by mitochondria
- It is massively burned up by neuronal signaling
- Mitochondria have huge environmental vulnerabilities
  - Nutritional needs
  - Environmental vulnerabilities
    - Toxicants, EMF, more

Metabolic integrity

- Metabolism relates to biotransformation of substances into other substances
- This requires
  - Adequate supplies
    - From the outside: nutrition
    - From the inside: circulation and transport
  - Integrity of structural frameworks in which biotransformation takes place
  - Lack of damaging interference from things that shouldn't be there
- Metabolic imbalances (too much or too little vital substances, blocked pathways, abnormal pH etc) can greatly interfere with function

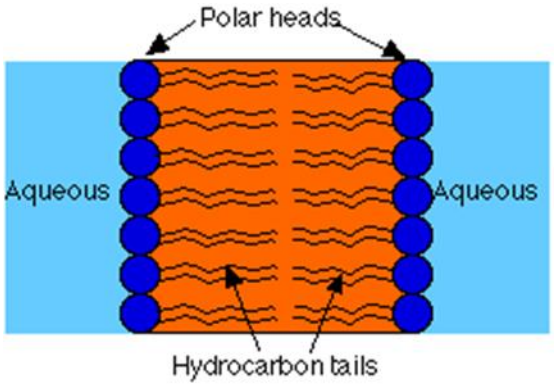


Metabolic Pathways

Fluid flow

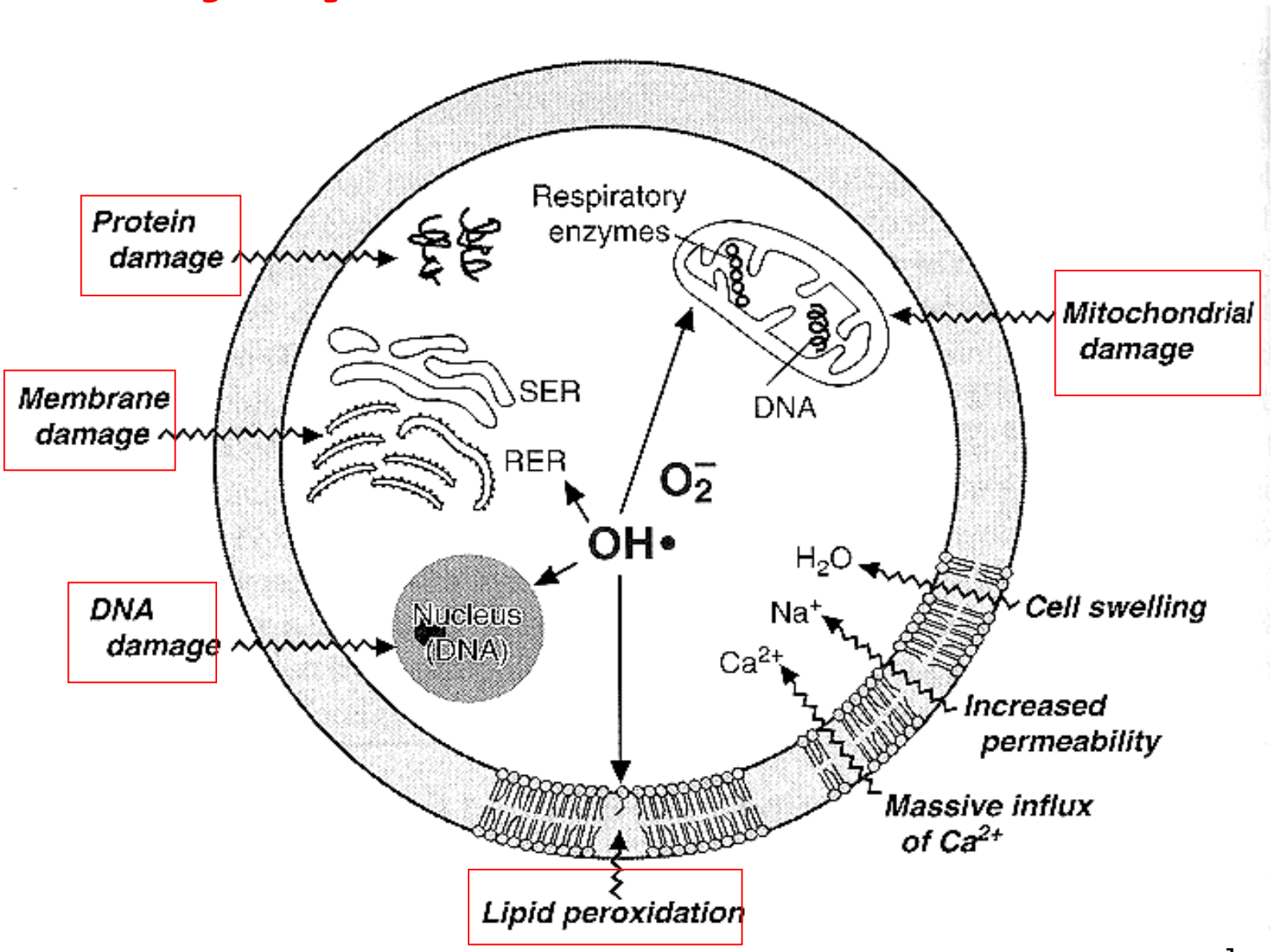
- Fluids carry supplies in and waste out
- Major fluids in the brain are
  - Blood
  - Cerebrospinal fluids
- Fluids can also carry harmful things like infectious agents, inflammatory signals and toxicants
- The fluids and the mechanisms by which they are transported and channeled need to function properly

Appropriate membrane function



- Membranes surround each cell and form compartments within each cell
- Membranes create spaces within which different types of properties can be maintained
- Membranes are made of lipids which are exquisitely vulnerable to damage
- Damaged membranes can be brittle or porous or can interfere with the function of the channels and receptors that live in them

Injury at the cellular level



James

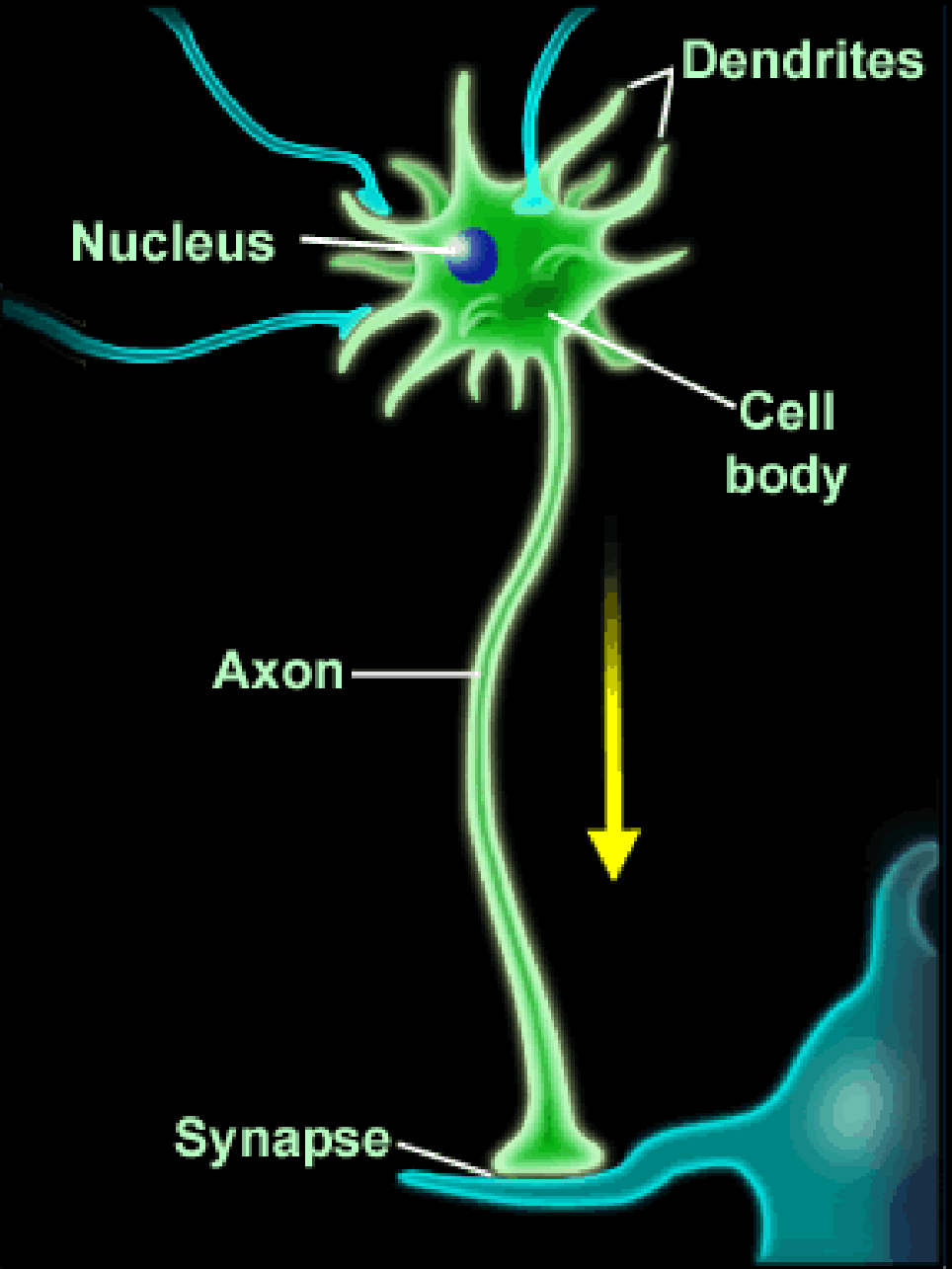
Barrier Integrity

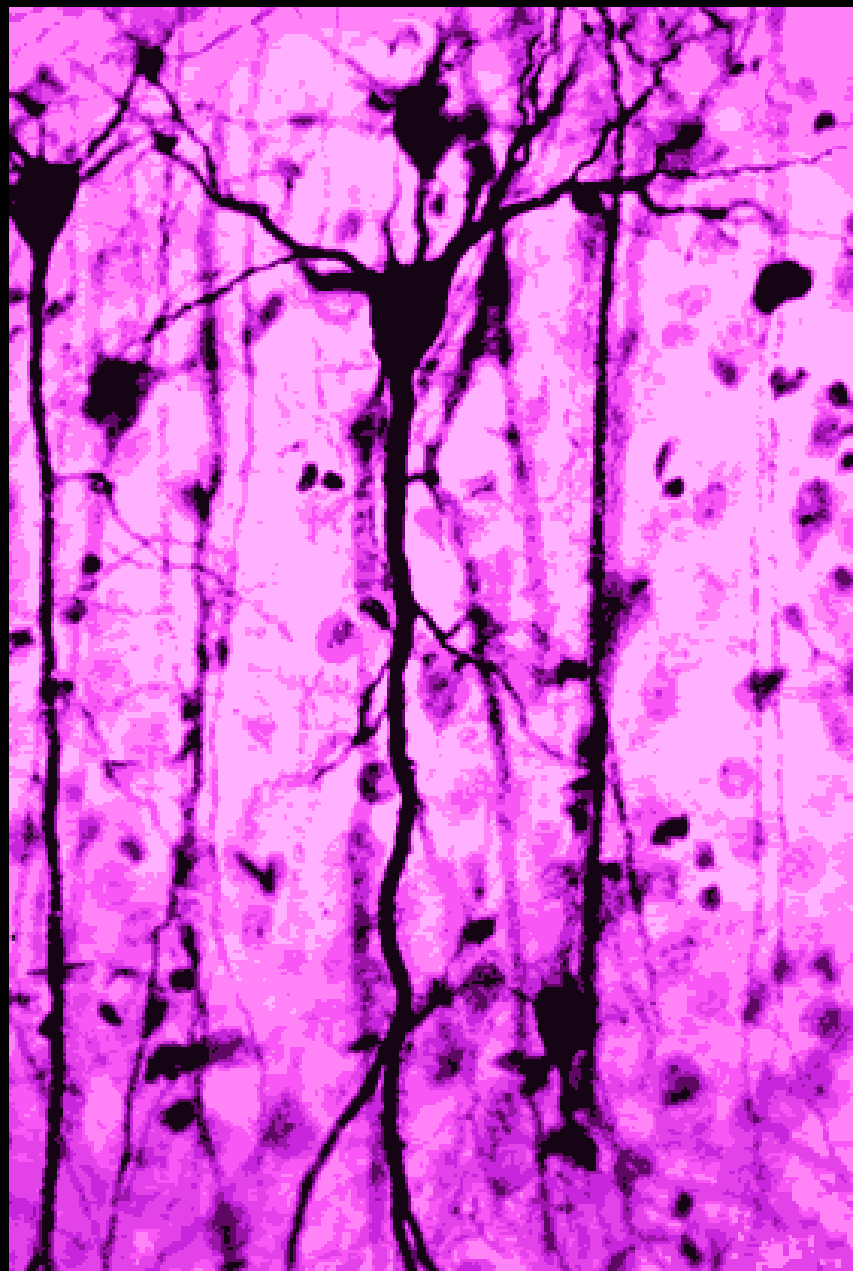
- The blood-brain barrier protects the brain from exposure to substances in the blood
- It protects the brain more intensively than most other organs are protected
- But it is not a complete barrier
- It is very immature at birth
- It can be made porous by inflammation, infection, radiation, pressure, nutritional insufficiencies, electrolyte problems and more
- It is naturally porous at certain points so chemo-sensing can occur, but these points also open the brain to exposure to noxious substances

Structural Integrity

- The brain is in the skull
- It doesn’t have room to swell
- It is also encased by tough connective tissue structures, the dura
- The brain can be physically displaced by trauma
- Even subtle displacement can interfere with fluid circulation and nerve supply, and subtle brain movements associated with health

The Neuron



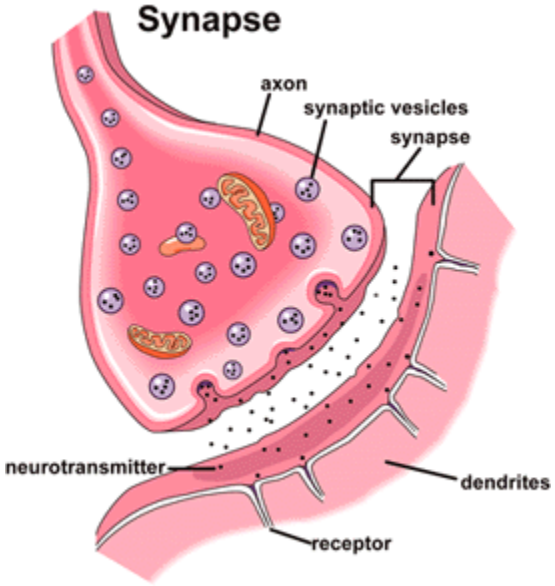


Neuron – Introduction

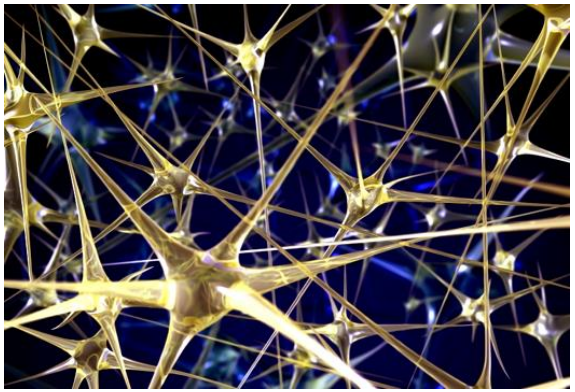
- Neurons are Core component of nervous system
- Electrically excitable:
  - process and transmit information by electrical and chemical signaling
- Types: Sensory Neuron; Motor neuron; Inter-neuron
- High energy demand
- Do not generally undergo cell division or regenerate after injury.

What is a synapse

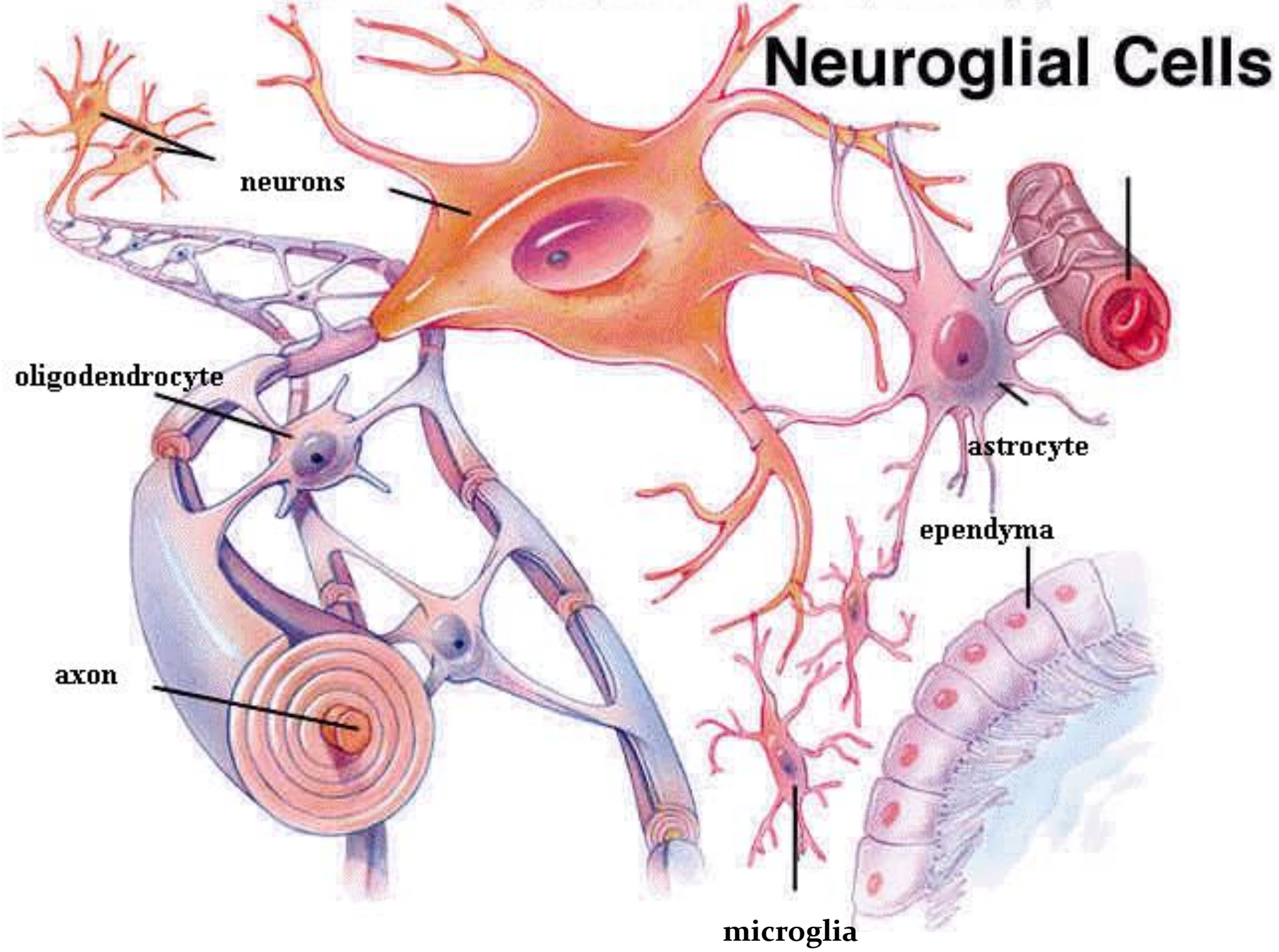
- A **synapse** is a structure that permits a neuron to pass an electrical or chemical signal to another cell (neural or otherwise)



Neuroscience and Science Fiction: Neurons in a Vacuum



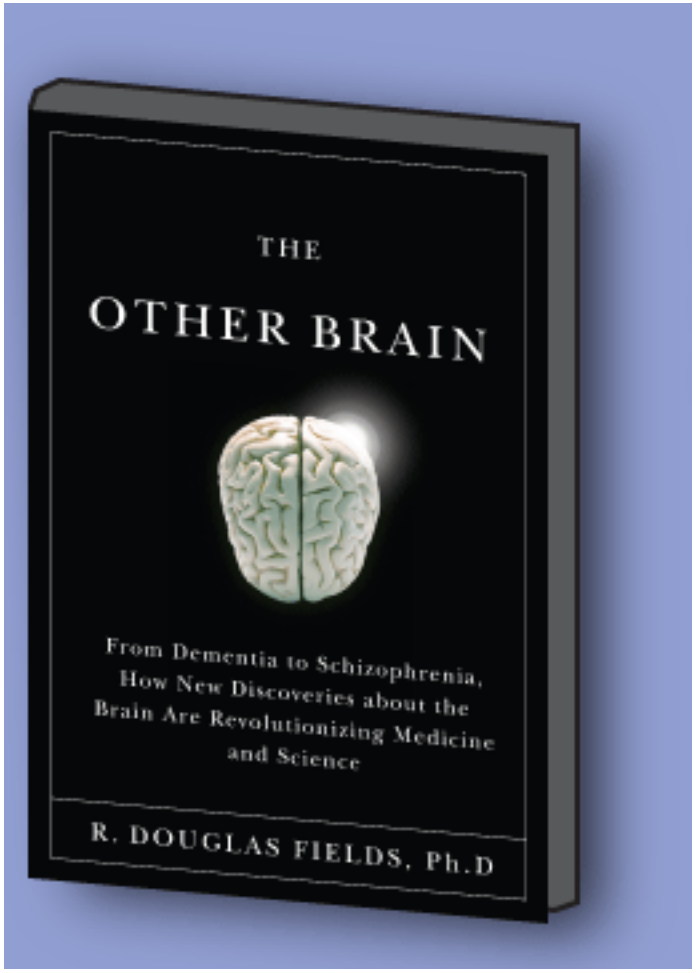
THAT VACUUM IS IMAGINARY. WHERE'S THE REST OF ME????



Types of Glial Cells

- Astrocytes
- Oligodendrocytes
- Ependymal Cells
- Radial Glia
- Schwann Cells
- Satellite Cells
- Enteric Glial Cells

THE OTHER BRAIN
by Douglas Fields, PhD, NIH scientist



ABOUT GLIAL CELLS WHICH GREATLY OUTNUMBER NEURONS IN THE BRAIN AND GUT

A readable book about the non-neuron cells in the brain and how they are revolutionizing medicine

www.theotherbrainbook.com

Women in the Brain:
A History of Glial Cell Metaphors

Meg Upchurch, Simona Fojtová

NWSA Journal, 21:2, 2009 pp1-20

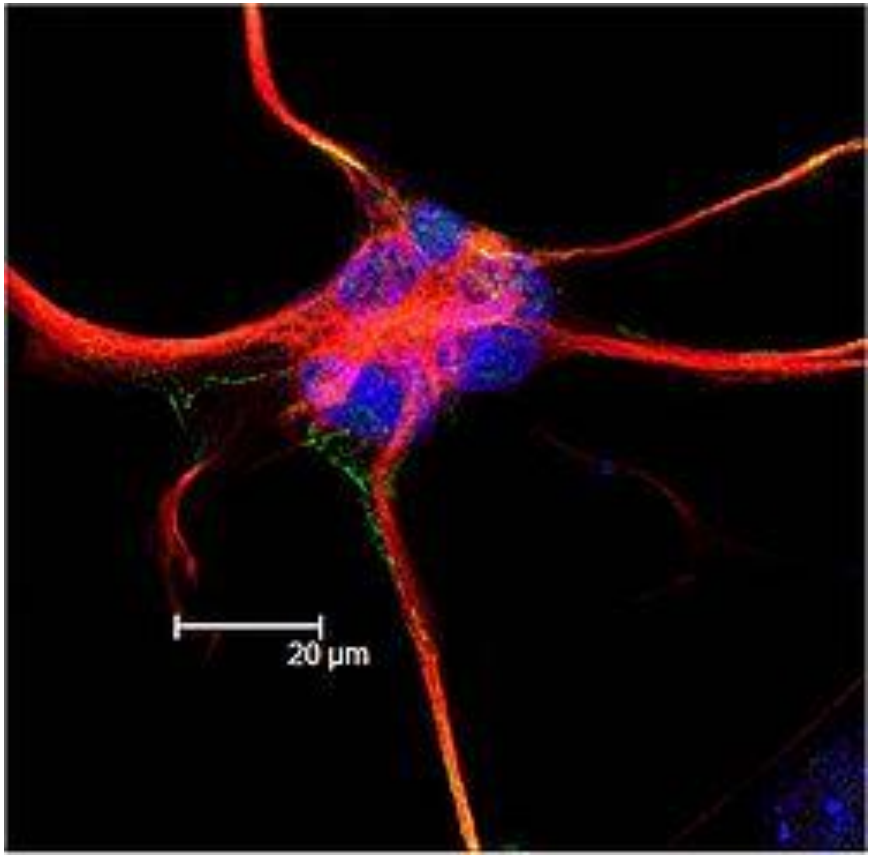
Cells within the nervous system are generally divided into two types: Neurons and glia. Neurons have the capacity to change their electrical potential, hence to be "active," and have received the bulk of attention from researchers. However, recent evidence shows that one form of glial cell, the astrocyte, contributes to communication within the nervous system in a fashion that is increasingly characterized as "active." Astrocytes were previously regarded as passive supporting elements. Metaphorical descriptions of the cells changed from lifeless "packing material" to "housekeepers," "nursemaids," and other social roles characterized by female gender and subordinate status.

A turning point in the conceptualization of glial cells came when researchers reported that chemicals released from glial cells appeared to regulate the formation of synapses, the communication points between neurons. With this evidence that glial cells not only contributed to, but actively regulated, a process highly valued by neuroscientists, glial cells moved up in social rank and changed gender, becoming "masters of the synapse" and "architects of the brain." The metaphors clearly imply that as cells become more valuable to nervous system function, they become metaphorically masculine.

Astrocytes/Astroglial cells

- Star shaped glial cells in brain and spinal cord. (“Astro” = “star”)

- Their processes envelope neuronal synapses and capillaries in brain.



Astrocytes – Structural Contributions

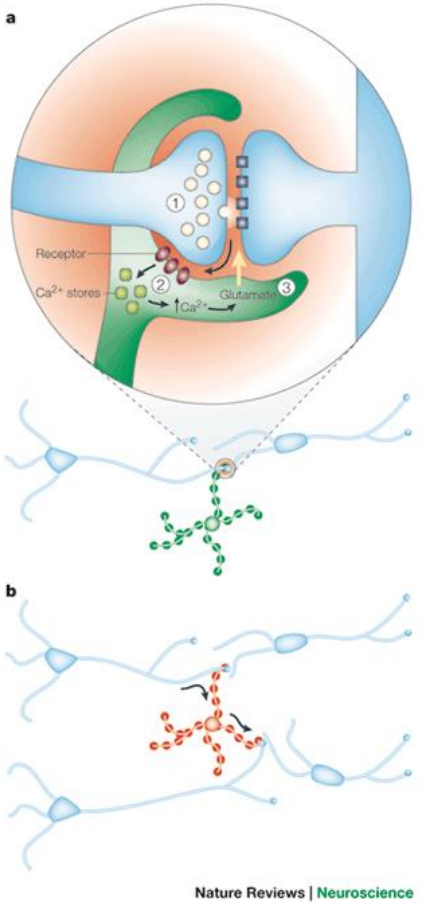
- STRUCTURE
  - Provide *Structural support* to brain.
  - Closely associated with neuronal synapses
  - Form part of Blood-Brain Barrier (BBB)
  - Cover surfaces of dendrites, cell bodies
  - Contribute to *glia limitans* in outer surface of brain and spinal cord
  - Nervous system repair: ingest damaged neurons, and create scar tissue.
  - Support myelination of oligodendrocytes

Astrocyte modulation of neuronal metabolism

- Modulation of neuronal metabolism: *Neurons are very dependent upon astrocytes.* This kind of collaboration is efficient for the organism.
  - A form of "outsourcing" of vital functions
    - Energy
    - Ion regulation
    - Neurotransmitter regulation (especially glutamate)
    - Glutathione production

The Tripartite Synapse: Neurons and Astrocytes working together

- Neurons and glial cells are intimately interrelated in the Tripartite Synapse
- Dysfunction in any aspect can cause alteration in function
- This abnormality can have local and widespread consequences
- *So it's not just neurons!*



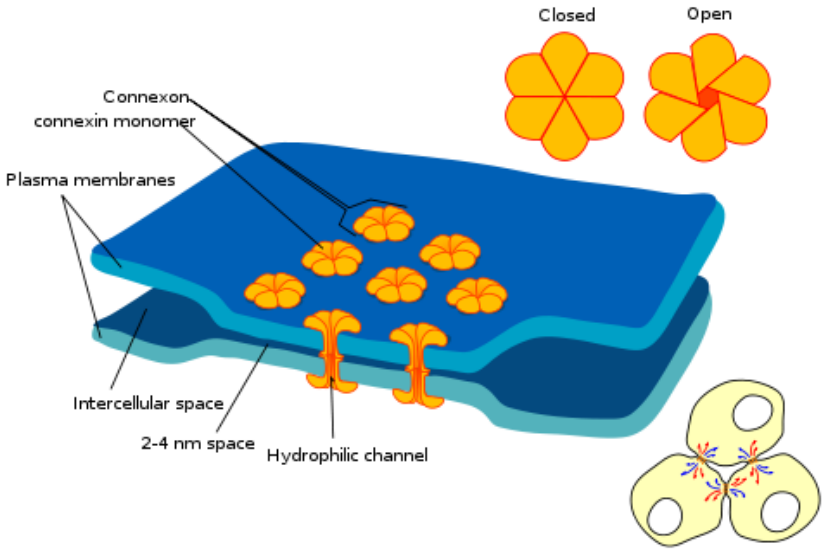
What is gliotransmission

- Glial cells play COMMUNICATION functions
- Astrocyte communication is **ANALOGIC**
- They do so in a few ways:
  - Gliotransmitters – like neurotransmitters only sent between cells by glial cells
  - Gap junctions – direct physical connections between cells that allow “calcium waves” to transmit rapidly across large areas of the brain
  - Autocrine and/or paracrine signalling can occur from glio- or neuro-transmitters in extracellular space

Verkhratsky, A. et al. (2012)

Gap Junctions

- 1-1.5 nm diameter
- Direct communication between cells
  - Electrical
  - Chemical
  - Small molecules
- Create a tight seal, preventing leaks
- Communicate when open, not when closed



Gap junctions might become closed in association to medical problems in autism

Image Source: http://en.wikipedia.org/wiki/Gap_junction

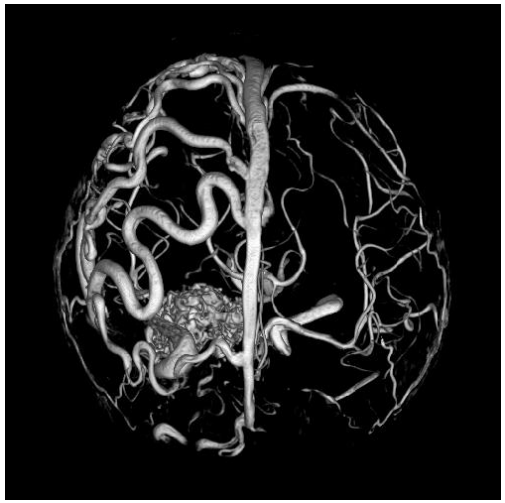
Astrocytes conspire with neurons during progression of neurological disease

James C McGann, Daniel T Lioy and Gail Mandel, Current Opinion in Neurobiology 2012, 22:1–9

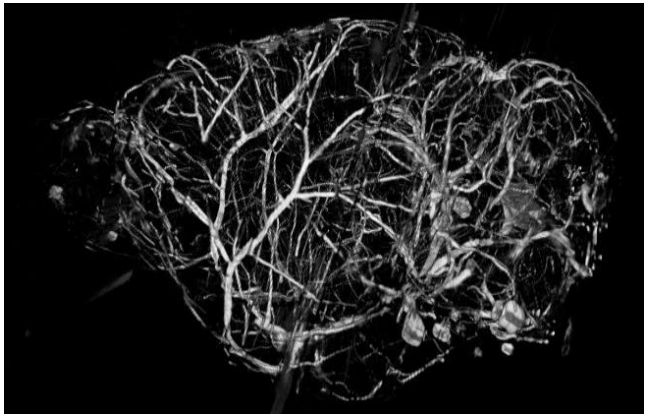
As astrocytes are becoming recognized as important mediators of normal brain function, studies into their roles in neurological disease have gained significance. **Across mouse models for neurodevelopmental and neurodegenerative diseases, astrocytes are considered key regulators of disease progression.** In Rett syndrome and Parkinson's disease, **astrocytes can even initiate certain disease phenotypes**. Numerous potential mechanisms have been offered to explain these results, but research into the functions of astrocytes in disease is just beginning. Crucially, in vivo verification of in vitro data is still necessary, as well as a deeper understanding of the complex and relatively unexplored interactions between astrocytes, oligodendrocytes, microglia, and neurons.

Astrocytes: Their Plasticity

- Astrocytes in the brain are highly mobile
- They also display structural plasticity
  - Then can undergo morphological changes *IN A MATTER OF MINUTES* (Theodosis et al., 2008)
  - This alters the extracellular space as well as relations with neurons
- Whey they are mobile, astrocytic-neuronal interactions *BECOME HIGHLY DYNAMIC*
  - This modifies extracellular homeostasis, neurotransmission, gliotransmission and neuronal function at cellular and system levels

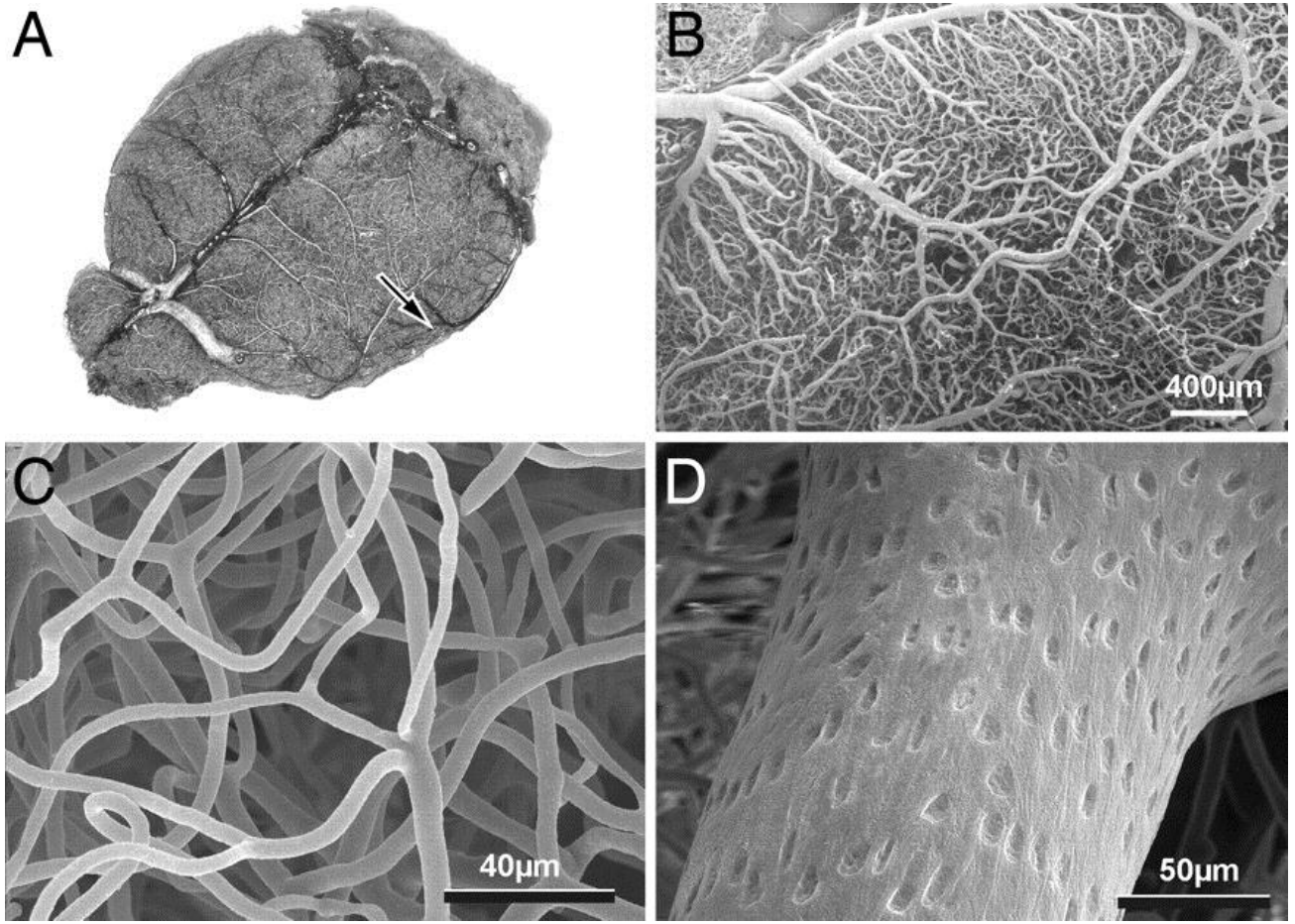


Brain blood vessels: large, medium and medium-small scales



- http://www.hitachi-medical-systems.eu/fileadmin/hitachi/onPage/at_work/ECHELON-Image2_bg.jpg
- www.jyi.org/research/re.php?id=1607
- research.cs.tamu.edu/bnl/galleryRecon.html

Brain blood vessels even smaller scales



A. Entire mouse brain vasculature.
B. Dense cortical blood vessel network.
C. Close-up of cortical capillaries.
D. Endothelial imprints on larger vessels.

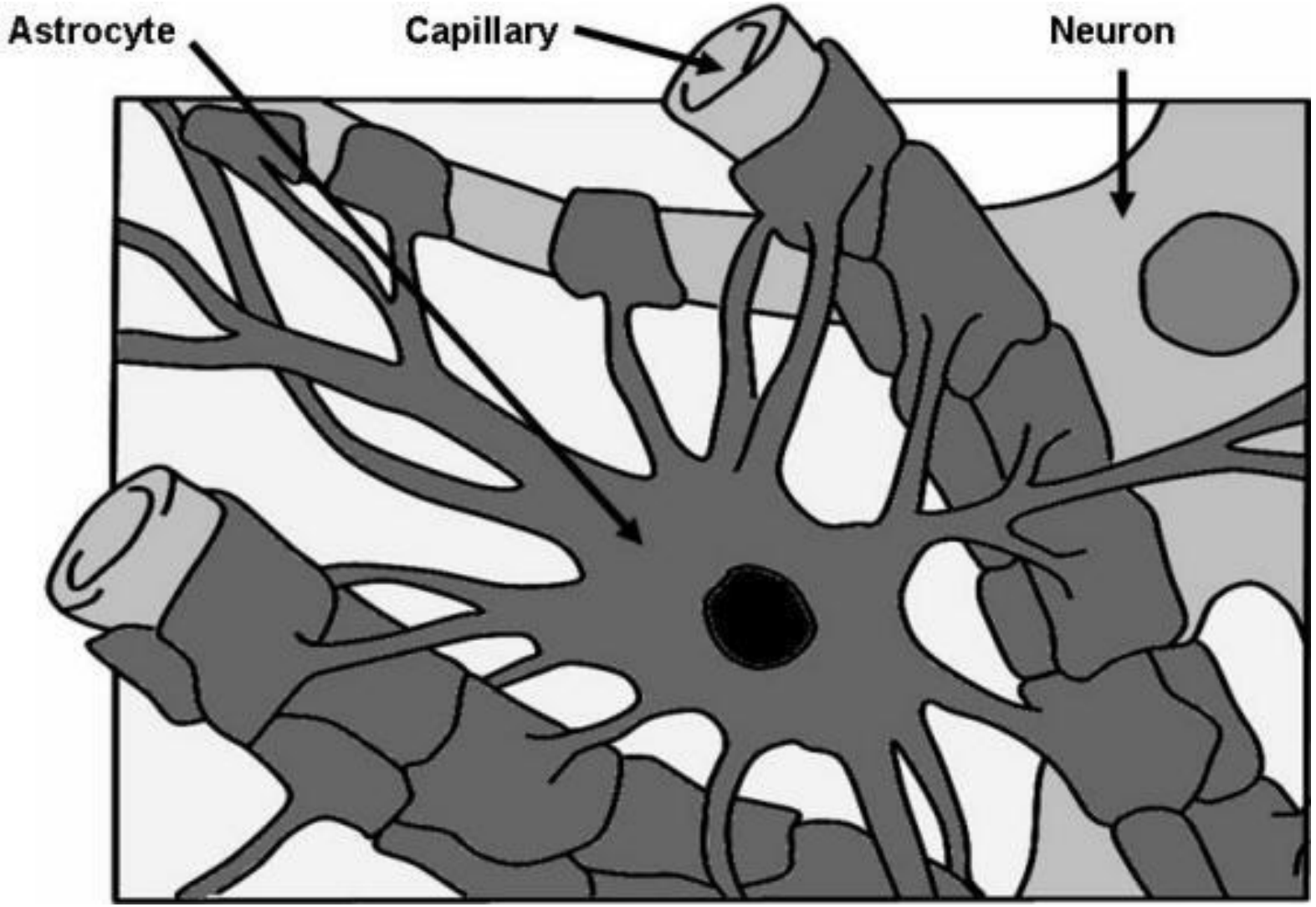
www.pnas.org/content/105/9/3587/F1.expansion.html

Blood-Brain Barrier (BBB): What it is

- Barrier that separates blood from cerebrospinal fluid in the brain
- Protects the brain from things that don't belong there
- Helps maintain a stable environment for the brain
  - Stable fluid volume and electrolytes
  - Important for brain not to swell inside skull

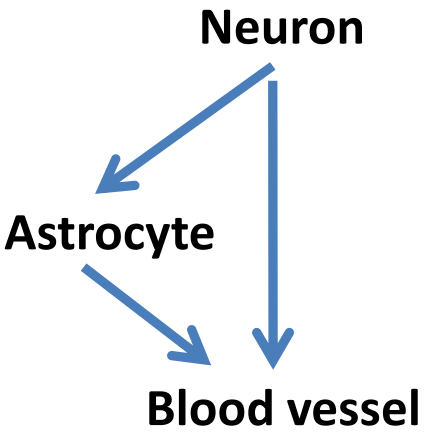
http://faculty.washington.edu/chudler/bbb.html

BBB Classic Image

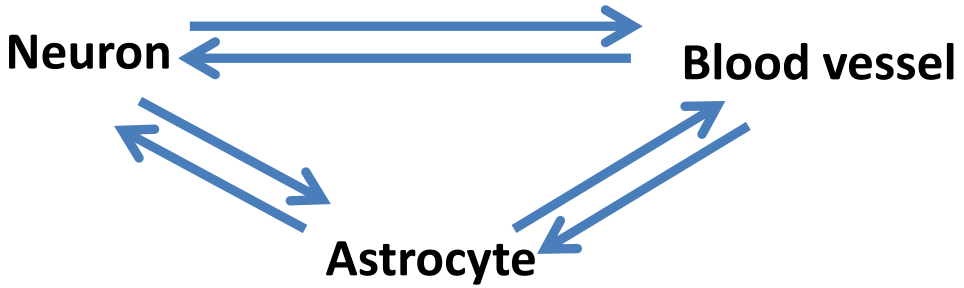


Neurometabolic regulation: Neuro-glio-vascular PARTNERS

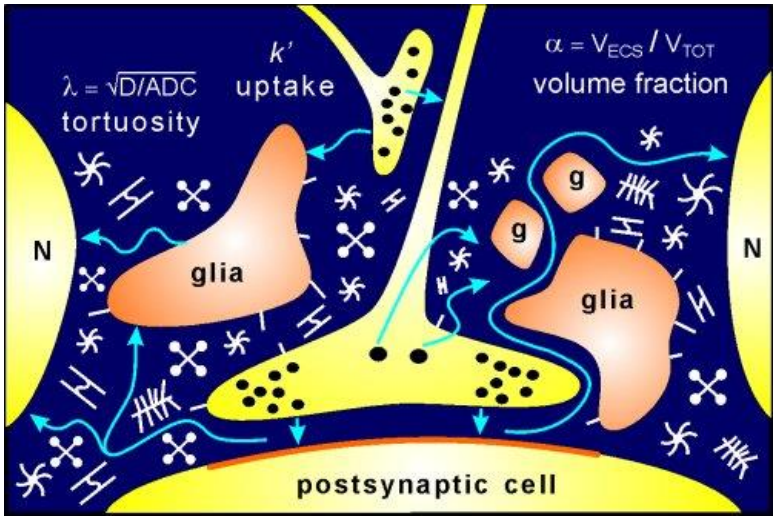
The old model:
Neuron as top-dog



The new model:
teamwork, and
A web with two-way streets

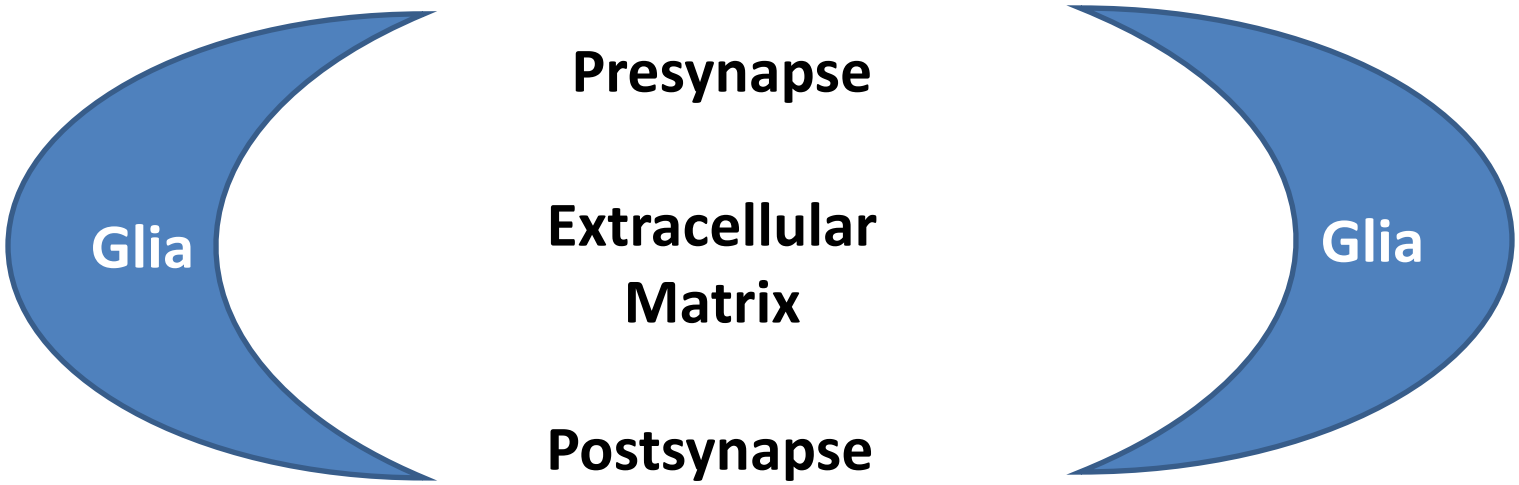


Brain "Connective tissue" – Extracellular matrix



- The "stuff" between cells
  - support structure
  - things diffuse through it and it filters (rich and complex activity)
- Previously not given much attention
- Recently getting lots of research attention
- This part of the brain plays critical roles in development and neurodegeneration
- It is also vulnerable with toxicity and with immune activation and inflammation

Tetra-partite Synapse: The Extracellular Matrix Too!

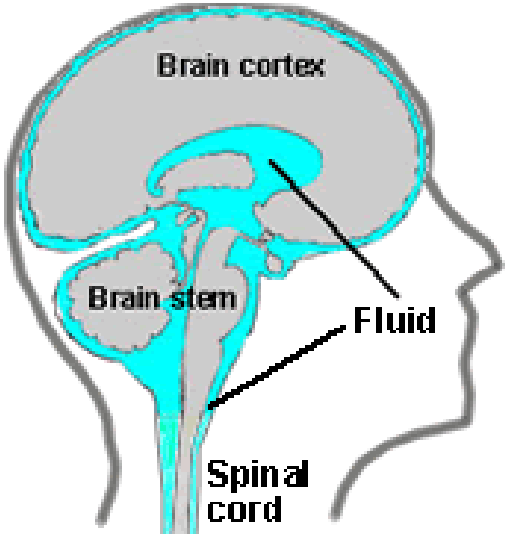


Alexander Dityatev[1,2] and Dmitri A Rusakov[3]

Molecular signals of plasticity at the tetrapartite synapse

Curr Opin Neurobiol. 2011 April; 21(2): 353–359.

Cerebrospinal fluid (CSF)

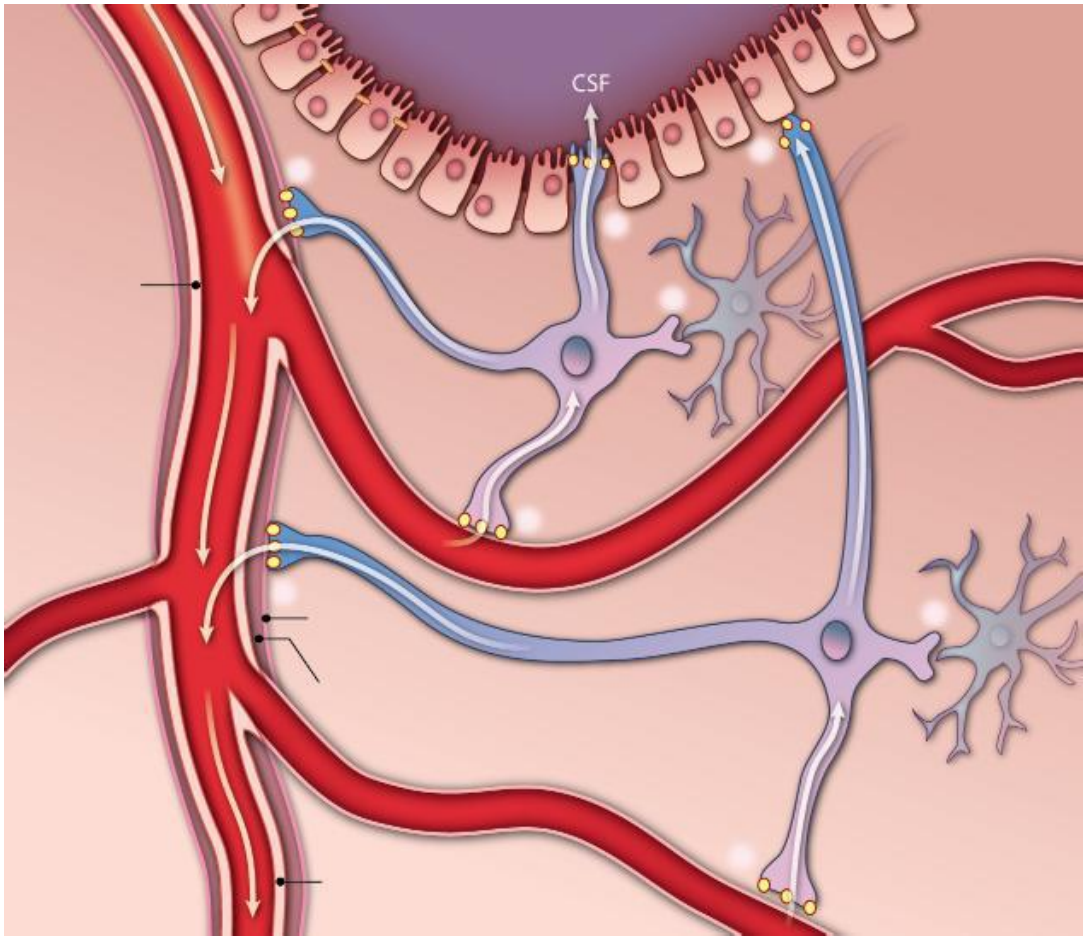


- Fluid around the brain
- Bathes the brain, carries nutrients and other substances
- Carries out waste
- Interacts with the blood stream
- Its chemical composition is influenced by health and disease

Astrocytes as trash collectors

- Toxicants accumulate in astrocytes until they can't take any more which contributes to astrocyte dysfunction
- Example: Manganese: - inhibits ability of astrocytes to promote neuronal differentiation
  - Giordano, G., D. Pizzurro, et al. (2009).
- They also dump garbage into the circulation
  - See next slide

Astrocytes facilitate CSF flow and help clear solutes

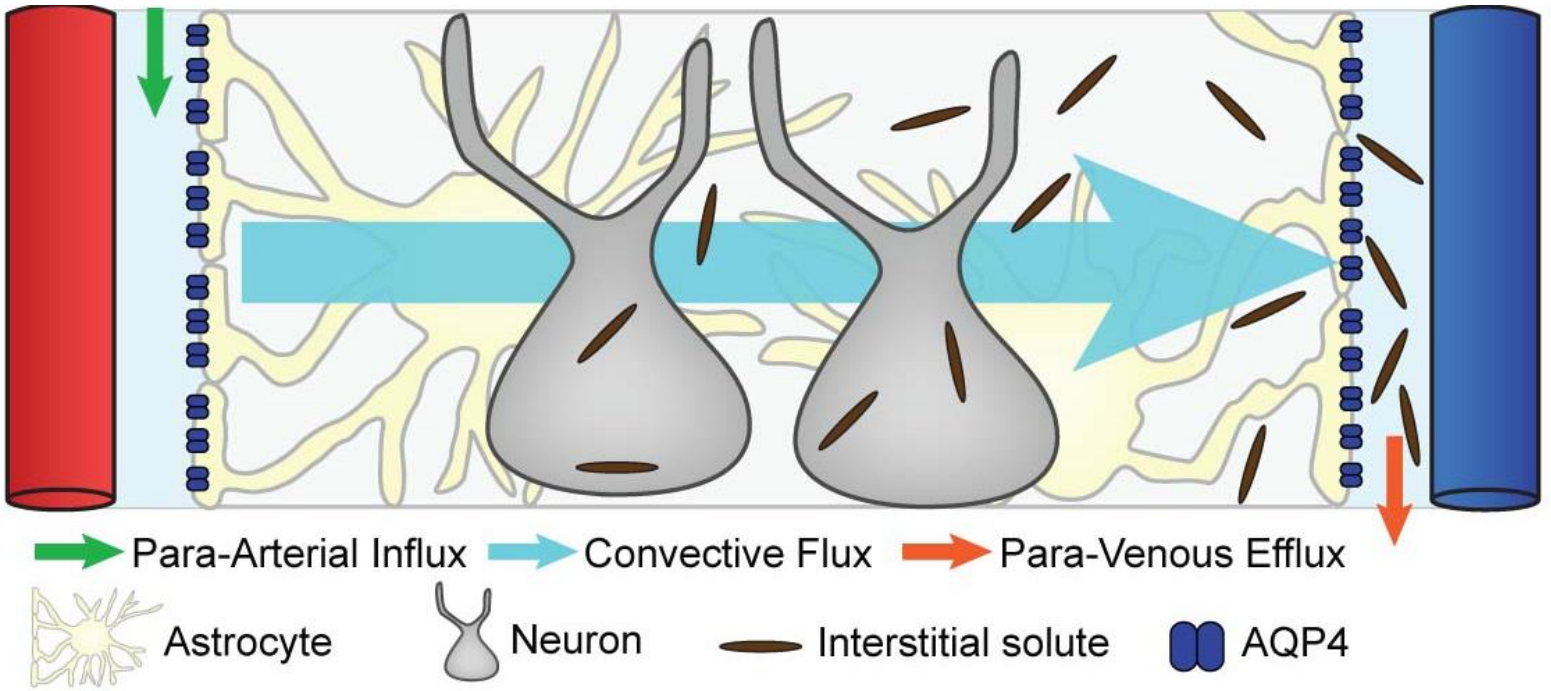


In the brain microcirculation, both astrocytes and tanycytes have long processes that run through the brain tissue and connect the cells with other structures. The tanycytes and astrocytes form endfeet (a) that are applied closely to the microvasculature that forms the BBB and express AQP4 adjacent to the endothelial basement membrane (basal lamina). The cells also bear processes that connect the cells with other brain structures. These processes may either interdigitate with the ependymal cells (c) that line the brain ventricles and directly contact the CSF (b) or may abut the ependymal cells and extend to the pial surface of the brain, which faces the subarachnoid CSF space (d). Other processes also terminate at neuronal cell bodies (e). The ependymal epithelium that covers the choroid plexuses across which CSF is secreted has tight junctions between the cells (f), as do the endothelial cells that form the BBB. Possible directions for water fl ow though the cells are indicated by the arrows.

Begley, DG, Brain Superhighways, Science translational Medicine 4:147

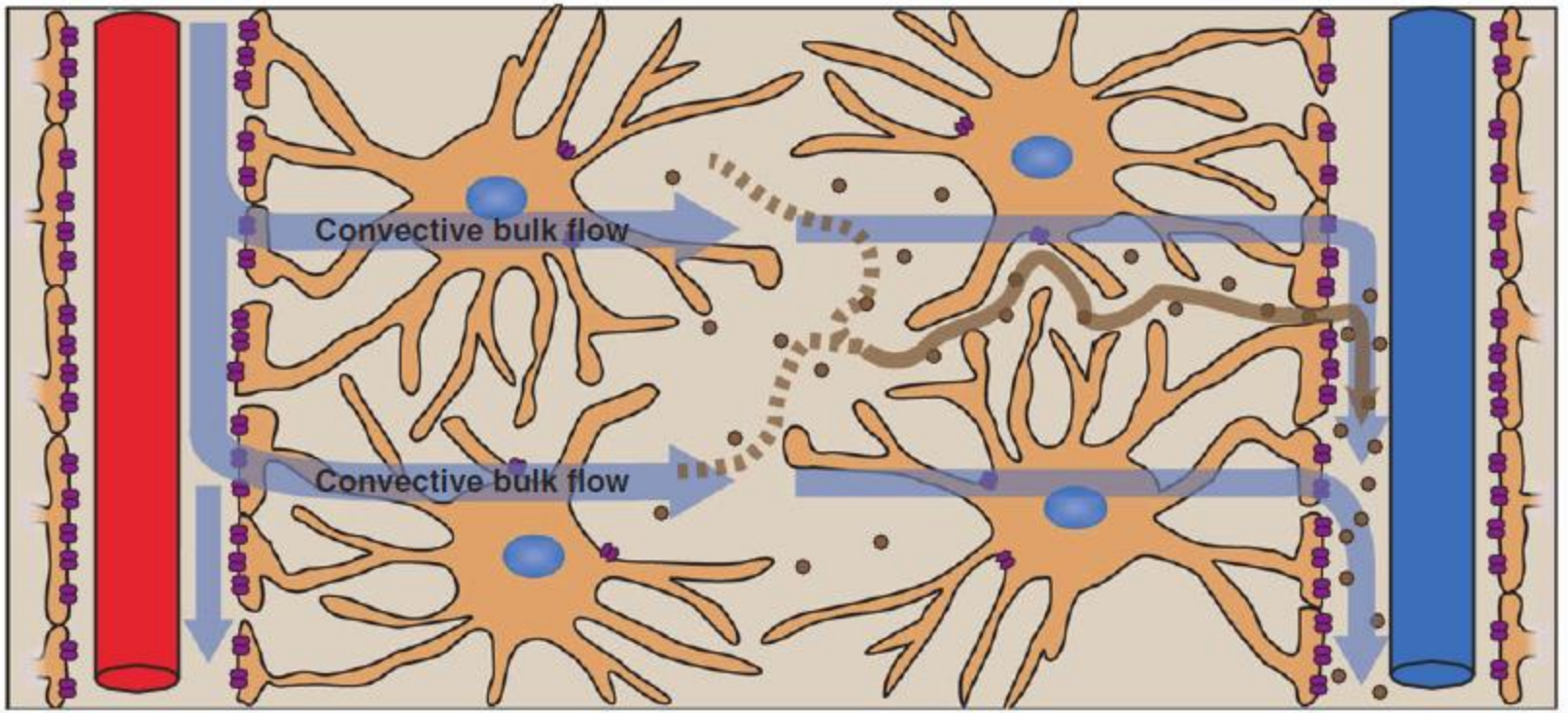
J. J. Iliff et al., A paravascular pathway facilitates CSF fl ow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci. Transl. Med. **4**, 147ra111 (2012).

Glymphatic Pathway Function



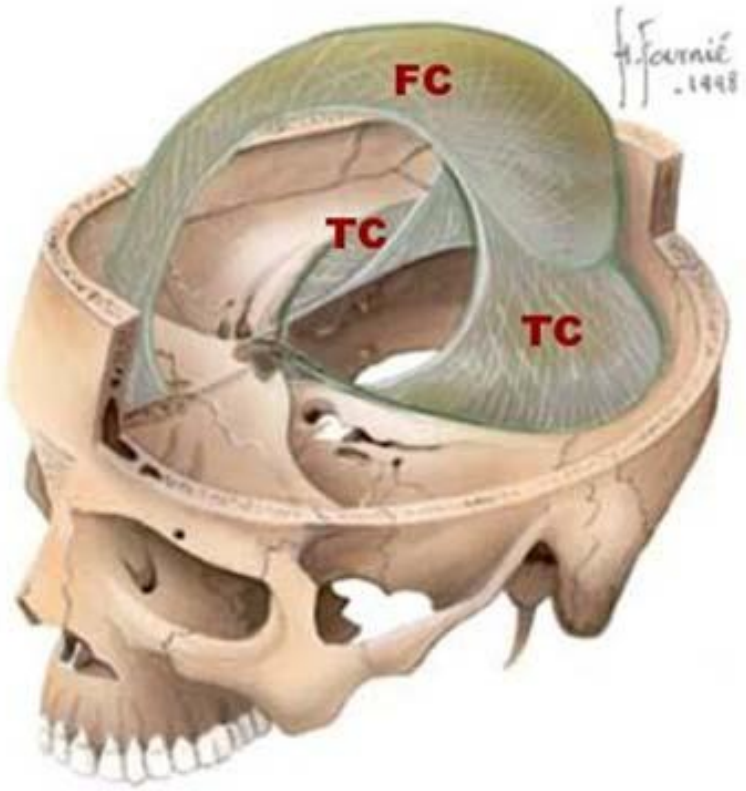
- Alzheimers, Parkinson's and Huntingtons are proteinopathies, involving pile-up of misfolded or aggregated intracellular or extracellular proteins
- The proper function of the glymphatic clearance system is necessary to remove soluble amyloid-beta and other such proteins from the brain interstitium.
  - Wikipedia

Glymphatic convective bulk flow



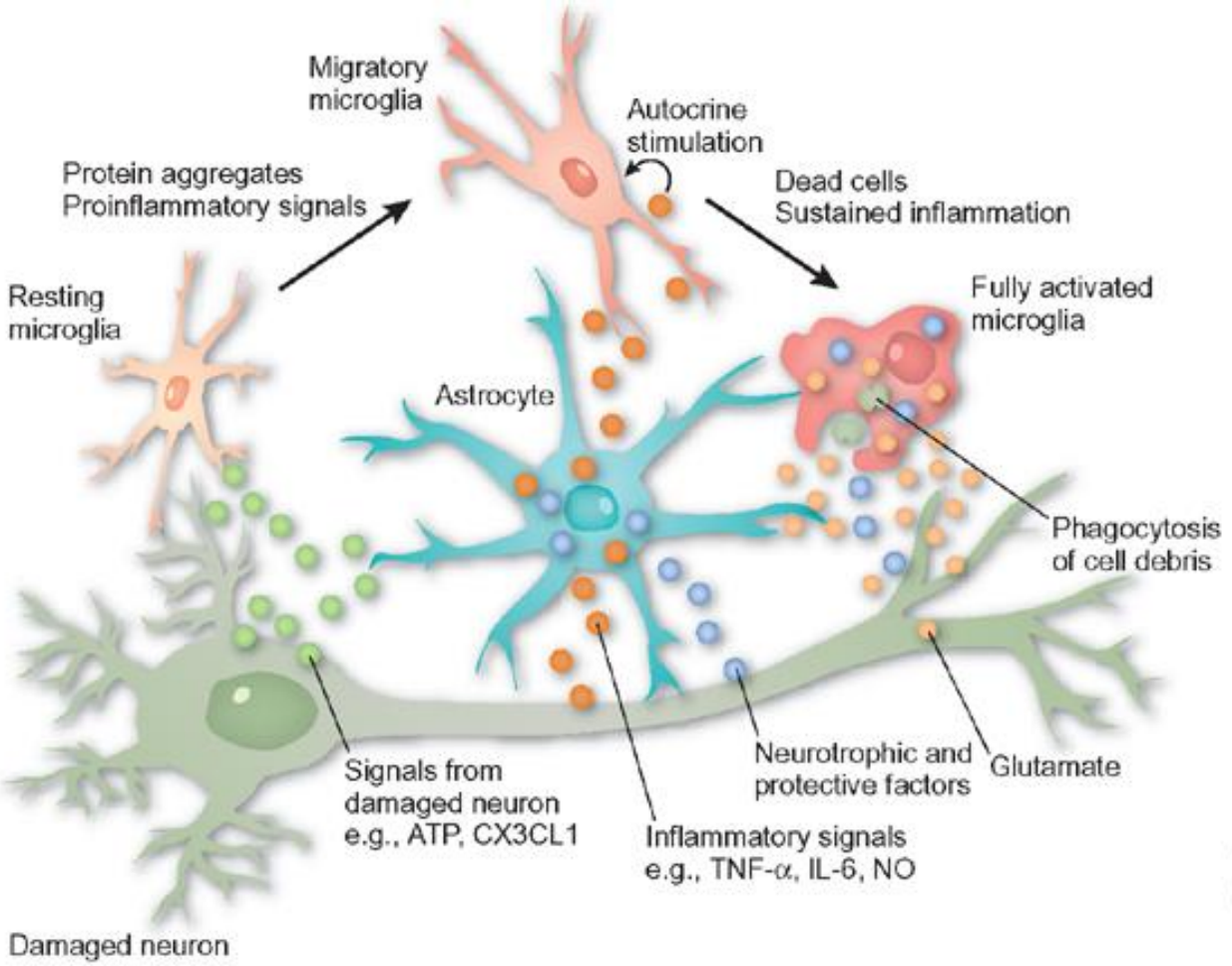
Wikipedia

Skull and membranes



- The external structures of the brain are vulnerable to strains and torques, especially in childbirth
- Cranial osteopathy has contributed greatly in understanding this

Microglial cells



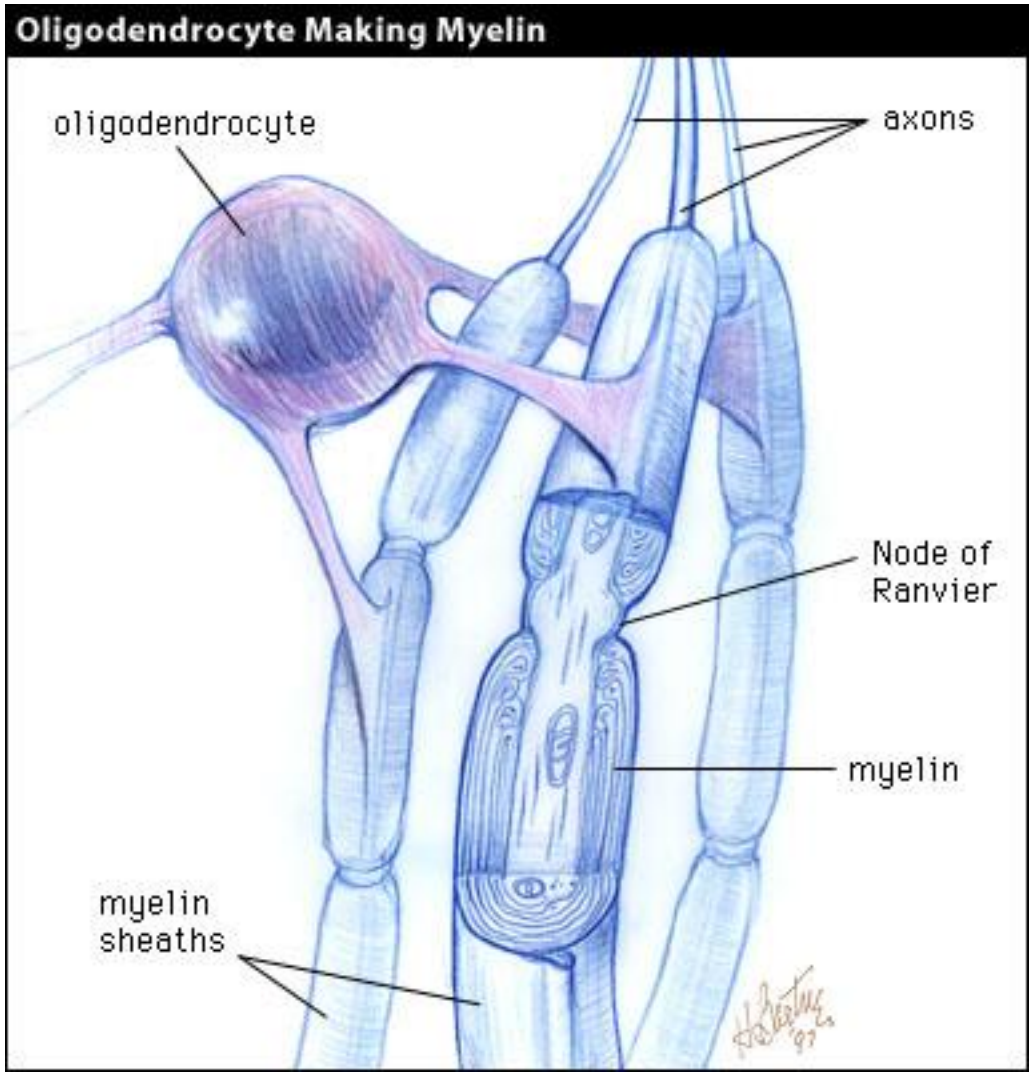
Microglial cells in action – along with Astroglial cells.

Source: http://www.nature.com/nm/journal/v12/n8/fig_tab/nm0806-885_F1.html

Microglia – Introduction

- First line of immune response in central nervous system.
- ORIGIN: originate in bone marrow from hematopoietic stem cells.
- Resident macrophages of brain and spinal cord.
- CNS is “immune privileged”, that is, blood brain barrier keep out most infections and antibodies
- Microglia are extremely sensitive to even small amount of pathological change – acting through their unique potassium channels.

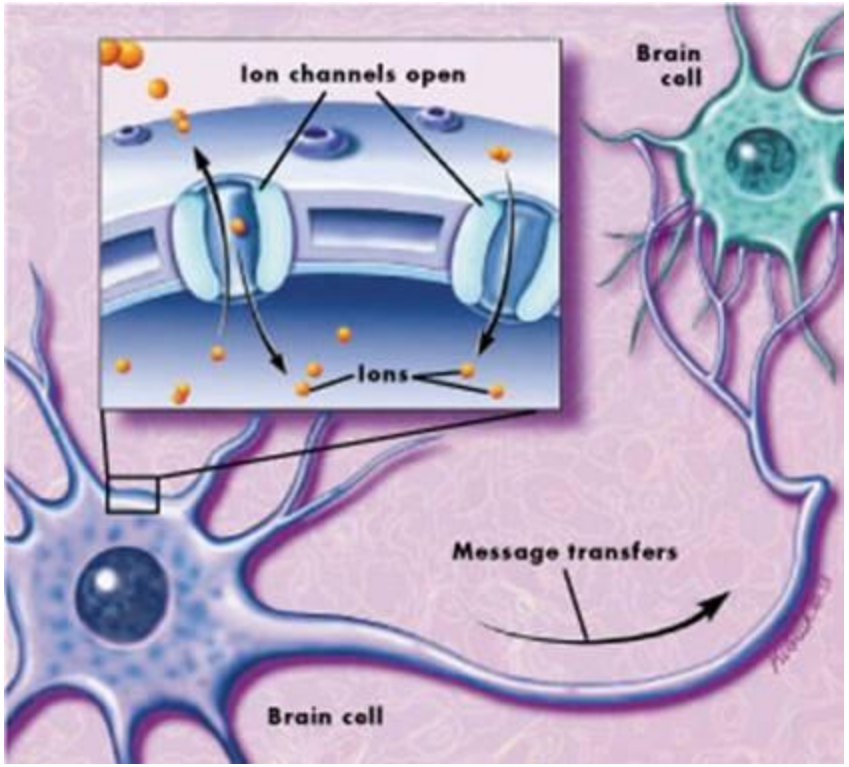
The White in White Matter: Myelin



- Oligodendrocytes are glial cells in the brain that wrap around axons (the “wires” or cell processes that connect neurons with each other)
- The wrapping is “myelin,” a fatty substance that is white—hence “white matter.”
- Myelin insulates axons and speeds nerve conduction.
- Oligos help coordinate signals.

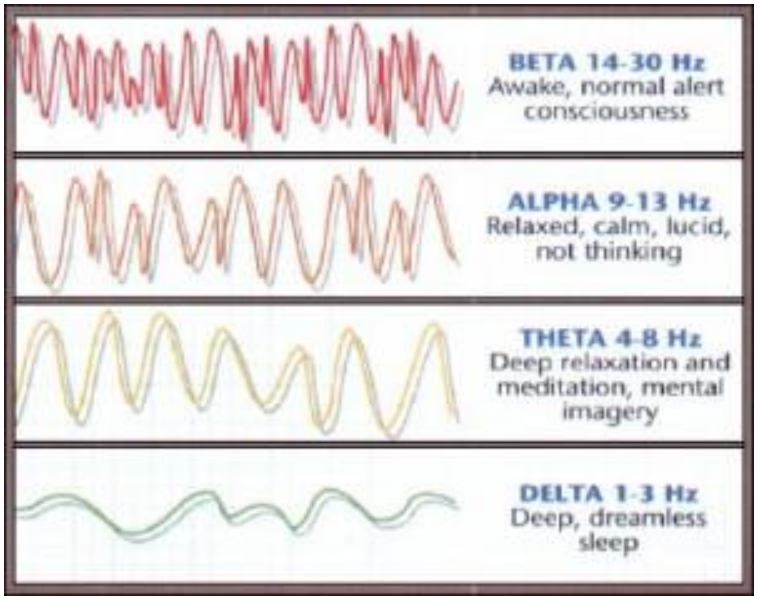
Ion channels

- Ions (like sodium, potassium, chloride) pass in and out of cells through ion channels.
- CALCIUM CHANNELS are thought to be critical and vulnerable to toxicants, EMF, mutations



What are brain oscillations (or, “brain waves”)

- Electrical activity in brain
- Occurs at different rates
- Different frequencies related to different levels of consciousness
- Rates relate to different kinds of neurons and other things that affect how neurons function



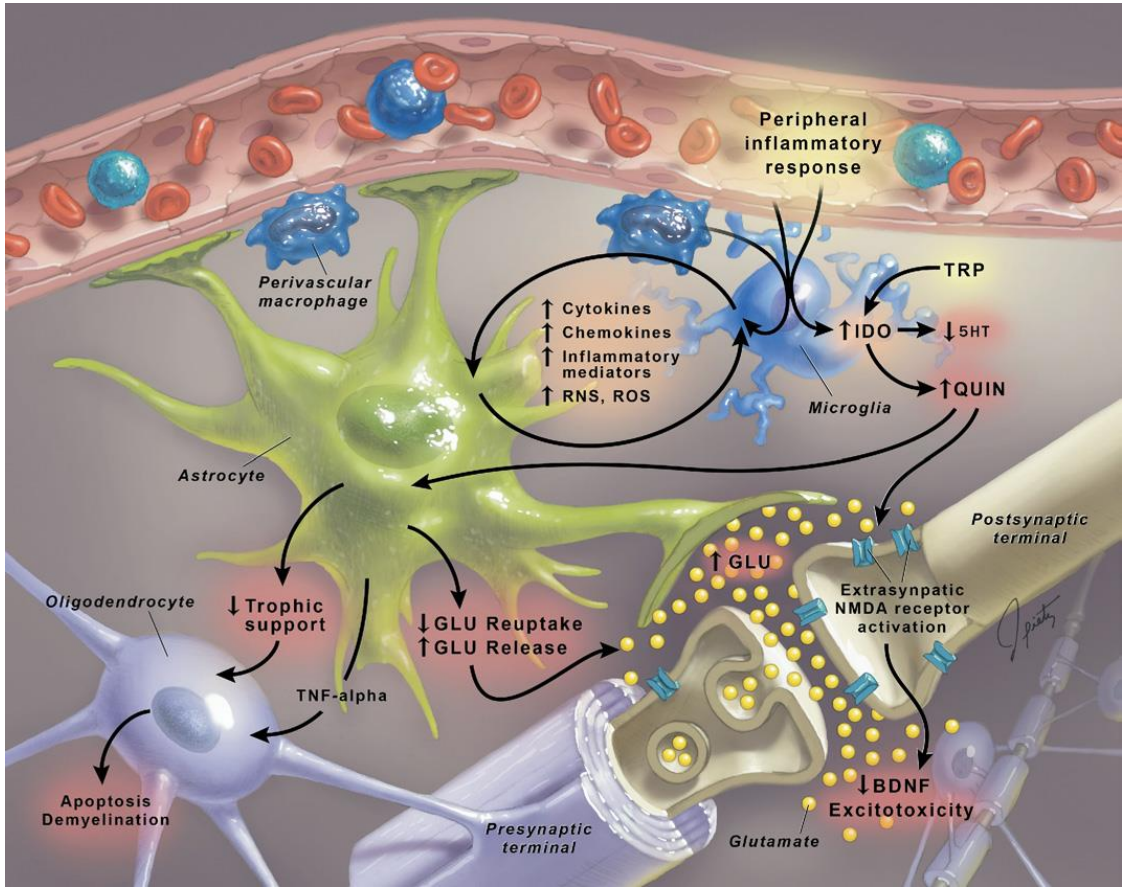
Delta, theta, alpha, beta
Gamma is even faster

What is synchronization and why is it important?

- When different parts of the brain oscillate together at the same frequencies, this gets information transferred

- Synchronization is not just a function of hardware (like neuronal cables) but also of waves that move rapidly across the brain

Inflammation in the brain creates cellular noise that interferes with information processing



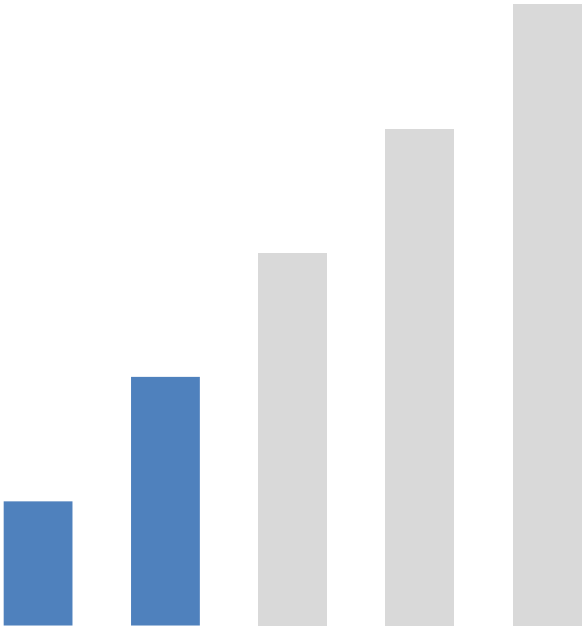
- Excitatory chemicals created by activated glial cells
- Normal housekeeping functions of glial cells get neglected
- Chronic inflammation is irritating and promotes excitotoxicity
- Chronic inflammation can cause damage

Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression.
Miller et al., BIOL PSYCHIATRY 2009;65:732–741

Worse brain cell health:
More noise and static, Less signal
Yielding Poor Bandwidth

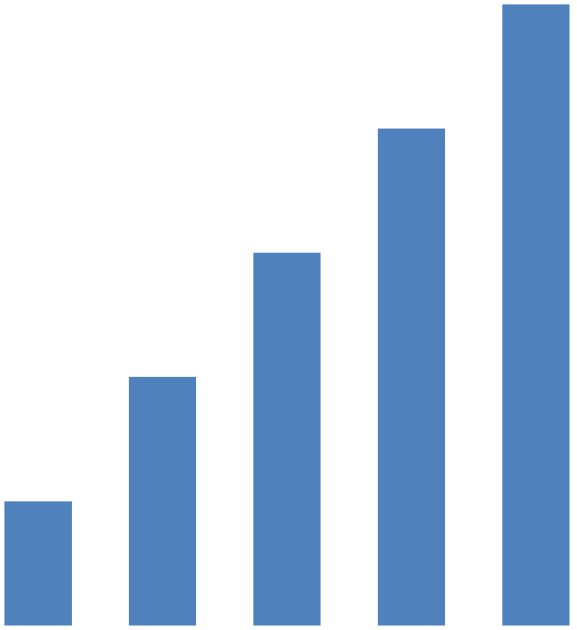
Poor Bandwidth:

Limited Reception



Lots of Bandwidth:

Good Reception



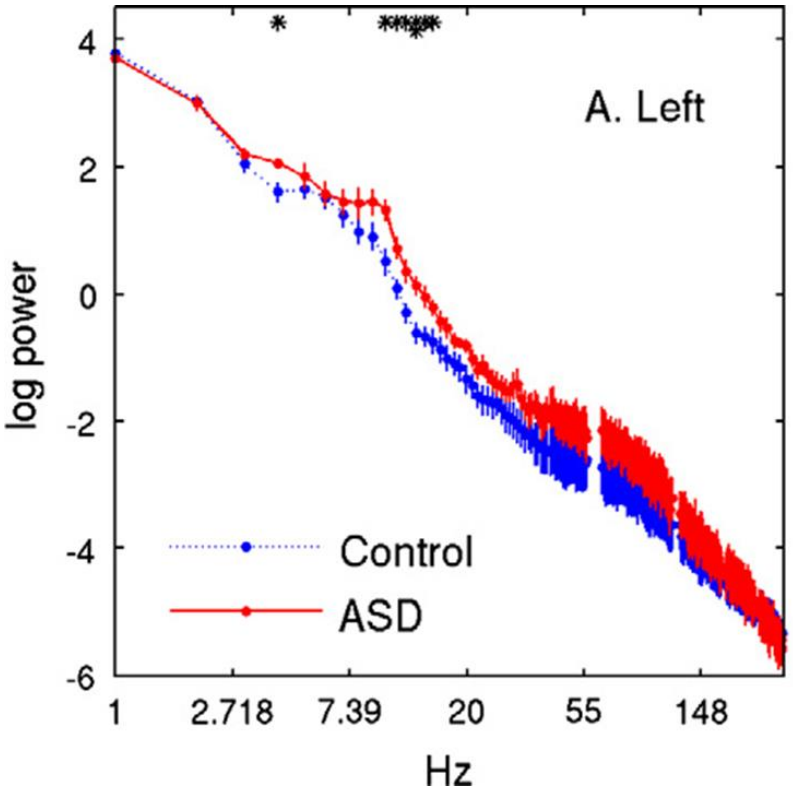
Better Reception Allows Better Discernment of Differences and More Spontaneous Learning

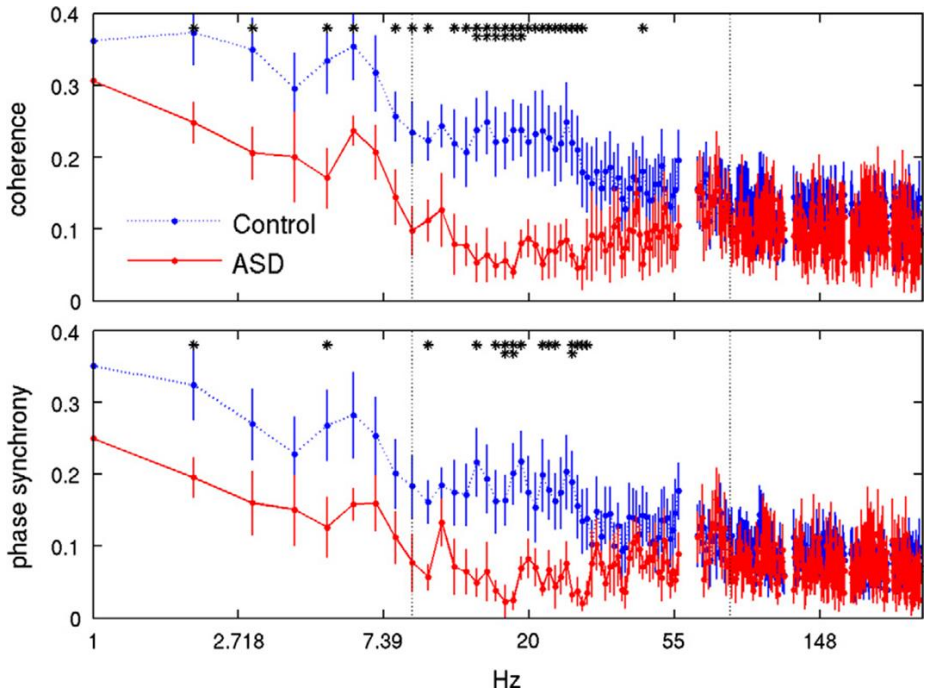
"Inefficiency" in brain signaling in autism

J.R. Isler, K.M. Martien, P.G. Grieve, R.I. Stark, M.R. Herbert

Clinical Neurophysiology 121 (2010) 2035–2043

ASD has more power than controls… but *less coherence*





Too much noise, not enough signal

BETTER BANDWIDTH SHOULD IMPROVE THIS

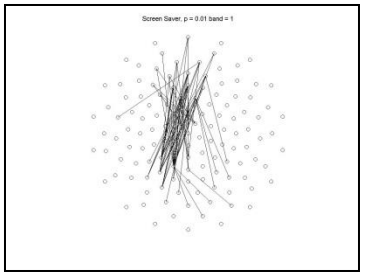
EEG of Sensory Responses

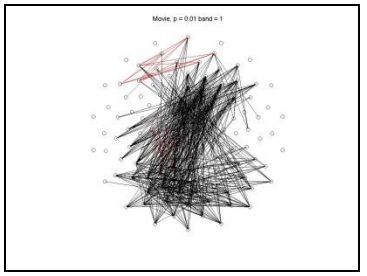
- Sensory stimulation can be overwhelming

Lines indicate differences between ASD and age-matched controls

- **Much more dysfunction when more stimulation**
- **Looks milder in older kids**

5-8 years old

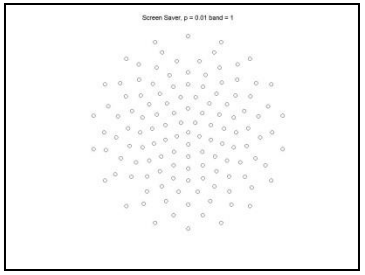


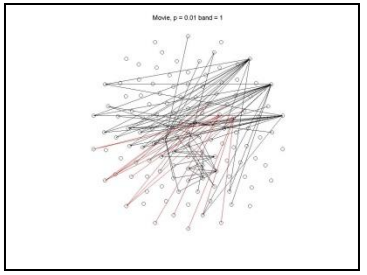


Screen Saver: **Less Stimulation**

Movie: **More Stimulation**

9-11 years old

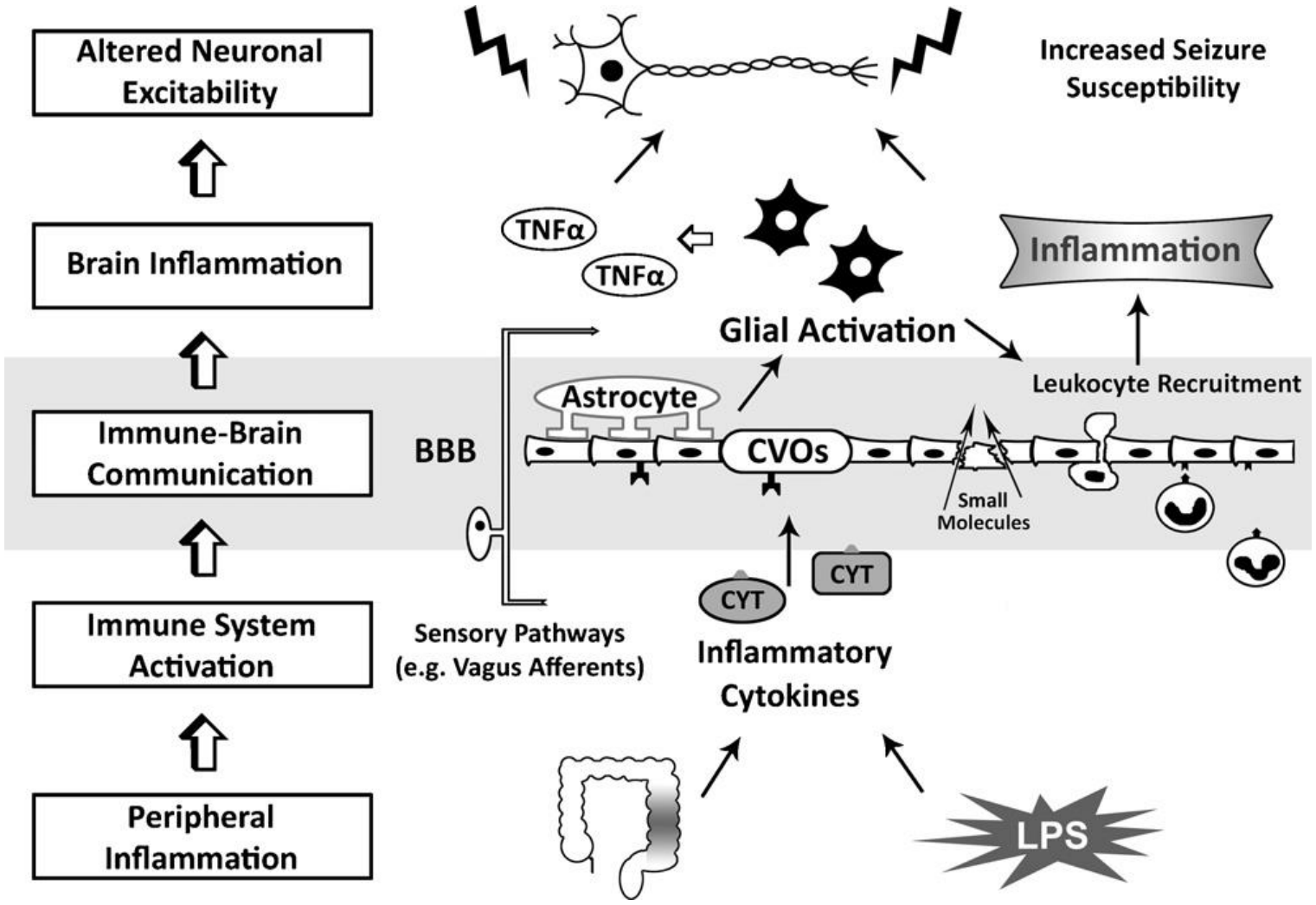




Prediction: Improved connectivity with effective treatment

Martien et al. 2008

Peripheral Inflammation and Neuronal Excitability

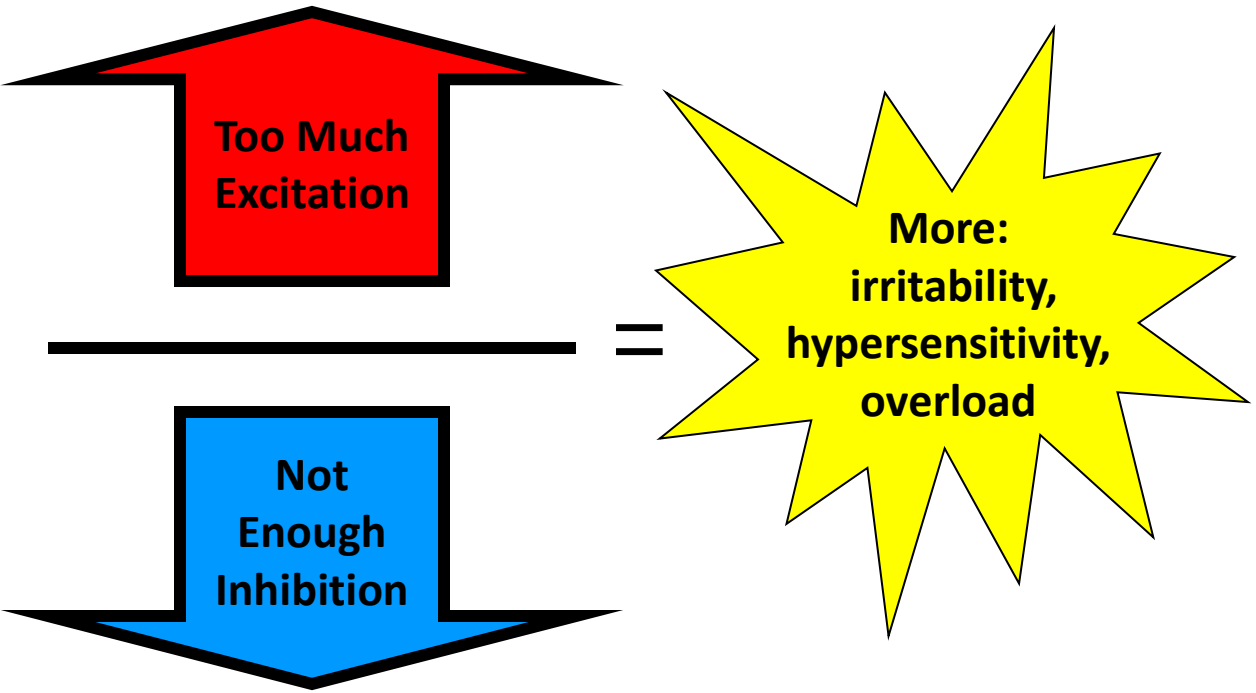


Riazi 2010, doi:10.1016/j.eplepsyres.2009.09.004

Environmental Stressors are contributing to an *ONGOING, CHRONIC* DEGRADATION OF BRAIN AND BODY FUNCTION and increase in ENTROPY

Model of autism: Increased ratio of excitation / inhibition in key neural systems

Rubenstein & Merzenich, *Genes, Brain and Behavior (2003) 2: 255-267*



Reduced informational complexity and organization

Reduced signal to noise ratio

Increased chaos and confusion

This excitation/inhibition ratio can be increased by inflammation, oxidative stress and toxicants, as well as genetic dysfunction

"Wild-type microglia arrest pathology in a mouse model of Rett syndrome"

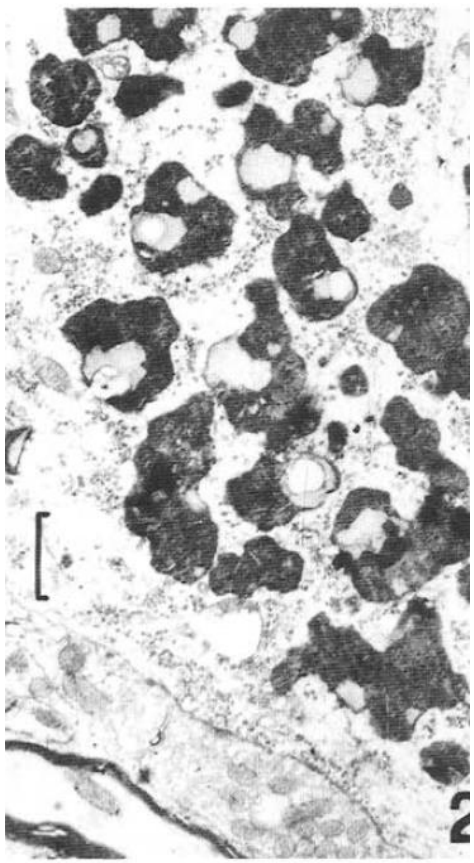
Derecki et al, Nature, 2012

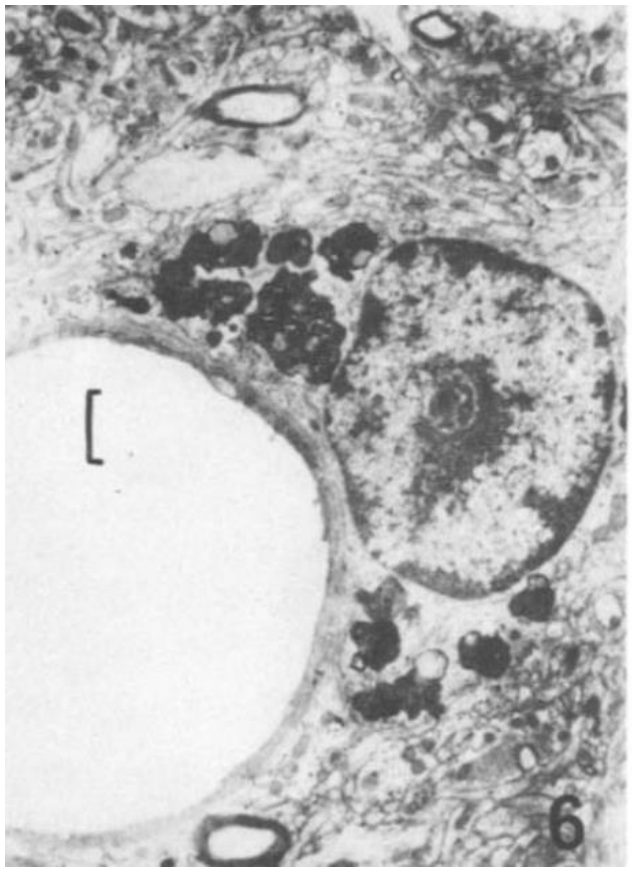
- Rett features had been attributed to neuronal dysfunction related to MECP2 mutation
- Astroglial cells now known to contribute
- Now microglia shown to contribute as well: bone marrow transplant of wild type microglia
  - Increased lifespan, normalized breathing, increased body weight, improved locomotor activity
  - *Improvement even without direct change to neurons*
  - Improvements lost when microglial phagocytic (garbage-collecting) activity inhibited

Electron microscopy of therapeutically activated glia turning into “brain garbage collectors and transporters”

CELLS PICK UP CELLULAR DEBRIS, SIDLE OVER TO BLOOD VESSEL, AND DUMP DEBRIS INTO BLOOD VESSEL
They do this after receiving an intensive nutiritional stimulation program

RIGA, S. et al., *Ann. N.Y. Acad. Sci.* 1067: 383–387 (2006)
RIGA, S. et al., *Arch. Gerontol. Geriatr.* suppl. 4 (1994) 227-234





Why does garbage pile up?

TOO MUCH BAD STUFF

- Toxicants
- Molecular debris from cellular stress and inflammation

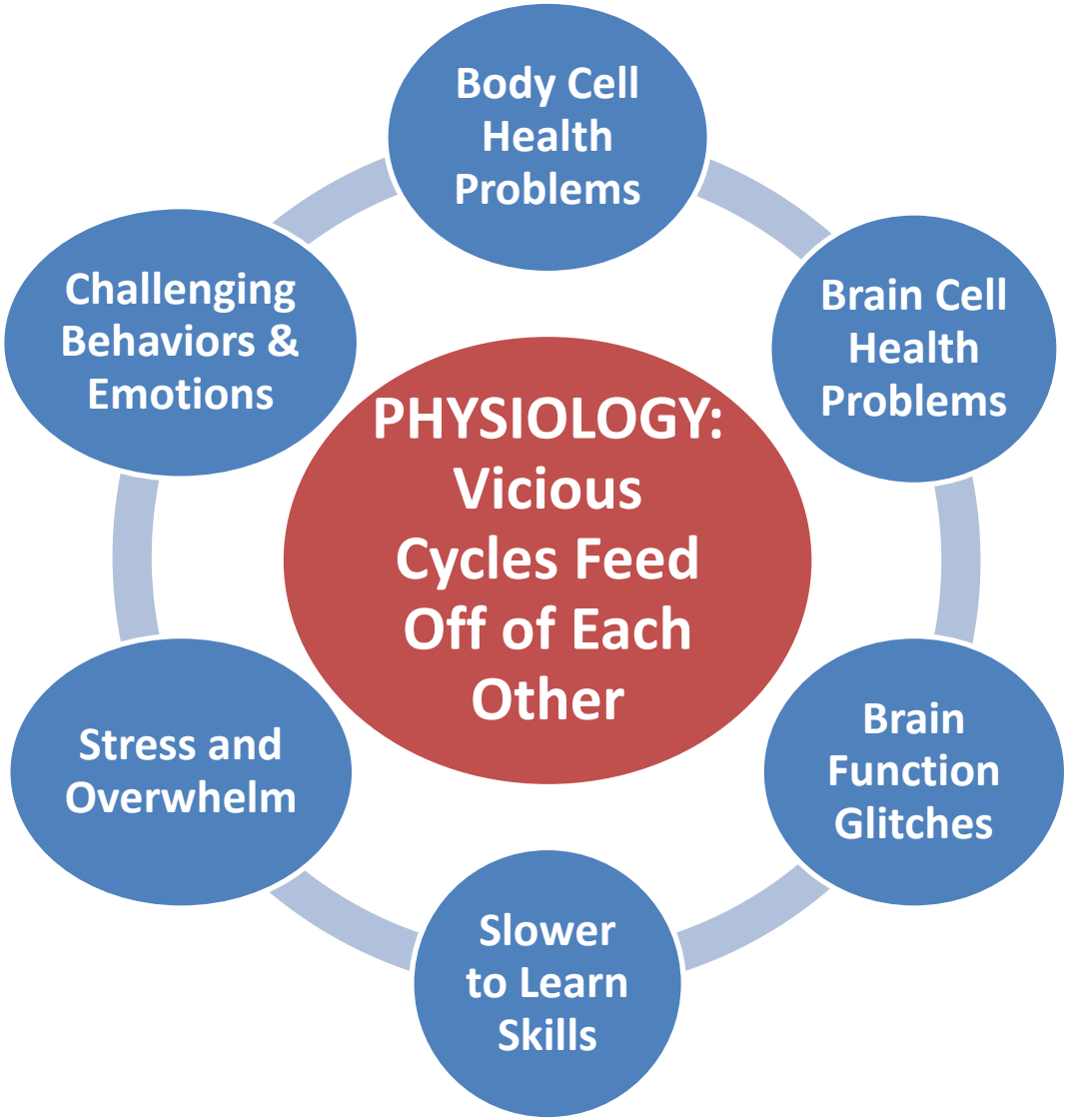
NOT ENOUGH GOOD STUFF

- Not enough nutrients needed to run clean-up operations
- Blood flow that is less than it should be due to sickness or poor nutrition

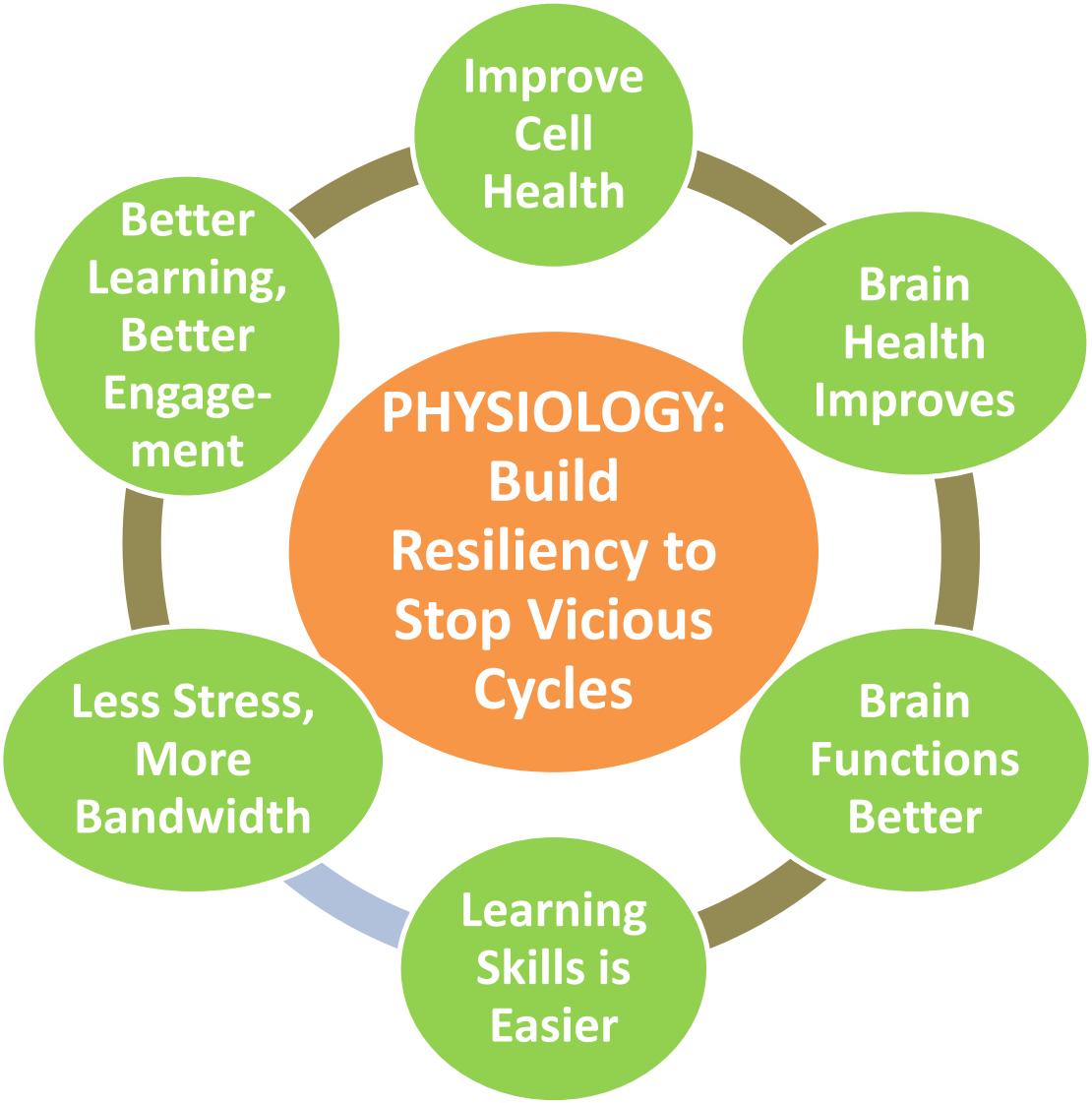
The brain needs energy and nutrition supplies

- Abundant supplies allow the brain to
  - work at its best
  - protect it from being dragged down by inflammation and other health problems.
  - TAKE OUT THE GARBAGE!
- Better brain health will help restore the brain's full powers.
- We can support brain health through "nutrient flooding" – high nutrient density diet

Problems in each area make trouble for the other areas



Dialing back the problems and Moving Toward Whole Body-Brain Health

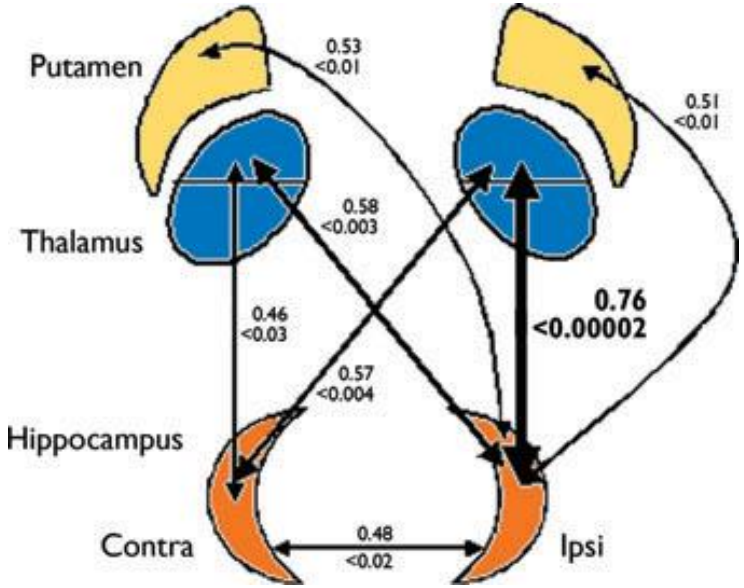


Are seizures on a continuum with sensory hypersensitivity?

- Does excitotoxicity drive sensory intolerance?

- This is poorly understood at present from a neurobiological point of view.
- But biomedical treatment anecdotally appears to reduce sensory issues in at least some cases.

Reversibility of reduced NAA after epilepsy surgery



- NAA (marker of neuronal density or function) reduced on the side opposite of a seizure focus
- After surgical resection of seizure focus, NAA on the other side returns to normal

Pan, 2008
Neurometabolism in Human Epilepsy

NAA = n-acetylaspartate

IMPLICATION: The persistent aberrant electrical charges afflicting the opposite side appear to have stunned those cells and taken them off line, but not "taken them out" since they came back online after the seizure electrical activity stopped.

A model of possible role of glial cells in autistic regression

- **Degradation of metabolic supports for healthy glial function through chronically poor food, toxins, allergens and stress**
- **Degradation of blood supply- narrow small vessel lumen, stickier blood**
- **Reaching a tipping point possibly through acute stressors**
- **Change of system "attractor state" into autism**
- **Lots of coordinated work needs to be done to change "attractor state" back to better connectivity and greater options**

- See chapter 5 of THE AUTISM REVOLUTION for more details
- Also see Herbert chapter in Chauhan 2009 book AUTISM: OXIDATIVE STRESS, INFLAMMATION AND IMMUNE ABNORMALITIES

HYPOTHESIS

For at least many, “autism” involves “obstruction” of capacities rather than “impairment” or lack of capacities.

Testing the model: Studying brain change

- If autism develops over the first year or two of life rather than being present from birth this challenges the “it’s all prenatal development” assumption
- If brain changes can be reversed through environmental/medical intervention this challenges the hard-wired assumption

- Testing: Using measures of different aspects of the brain (structure, tissue metabolism, electromagnetic function, blood flow) to see how the different levels of function/dysfunction relate to each other.

www.transcendresearch.org

Treatment Research And
NeuroSCience Evaluation
of Neurodevelopmental Disorders

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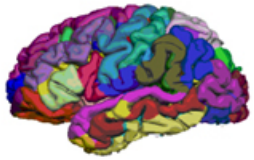


Transcend is a Verb
To climb
To surmount
To exist above and independent of
To be transcendent
To excel

Our Mission

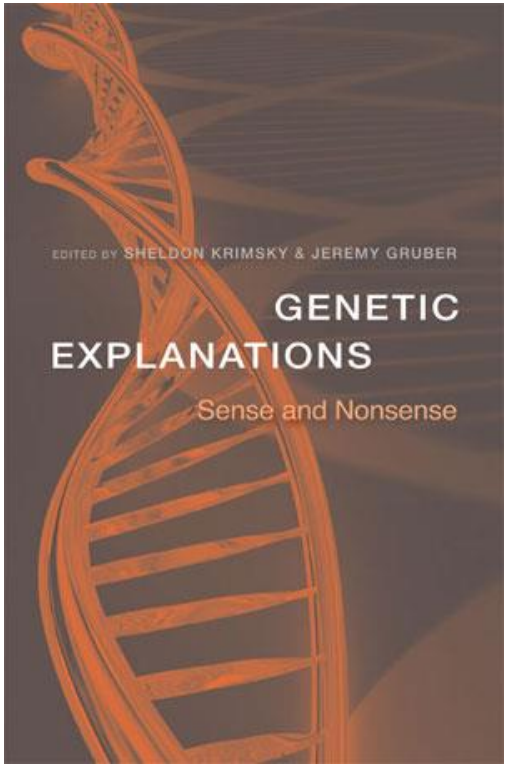
TRANSCEND's mission is to generate new scientific evidence about neurodevelopmental disorders. We built an integrative brain and body research tool kit to shed light on real-life issues. Our goal is to bring clarity and find practical solutions to relieve hurt and speak to the hopes of individuals and families affected by neurodevelopmental disorders.

BLOG:

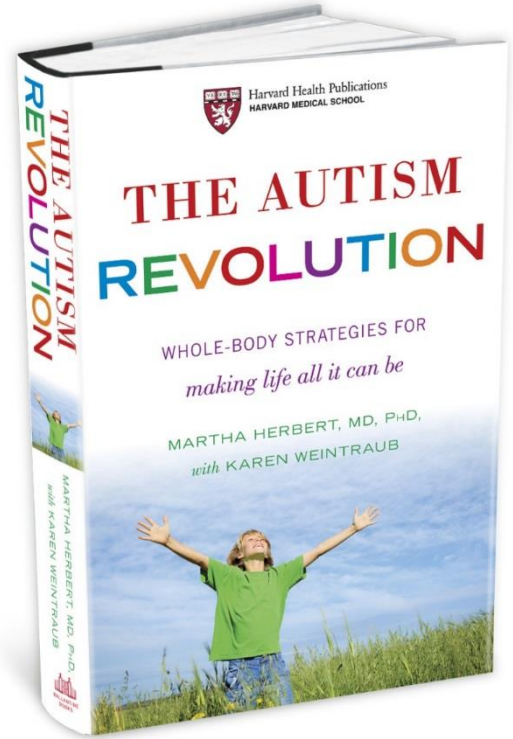
Housekeeping and Higher Function are Profoundly Intertwined

www.autismWHYandHOW.org

Sources detailing these arguments



GENETIC EXPLANATIONS: Sense and Nonsense
S Krimsky and J Gruber, Eds
Chapter 10, on autism, by Martha Herbert



THE AUTISM REVOLUTION: Whole-Body Strategies for Making Life All It Can Be
Random House/ Harvard Health Publications
By Martha Herbert
with Karen Weintraub
www.AutismRevolution.org
Now in paperback

Also, for more technical detail:
"Autism and EMF? Plausibility of a Pathophysiological Link"
Published as Section 20 in Bioinitiative 2012,
www.bioinitiative.org and presently in revision

De-tuned or Optimally Tuned?

- Taking care of brain health is practical
- It emerges from healthy choices about whole-body health
- A brain with cell health problems will get de-tuned very easily
- A healthy brain has the best chance of being optimally tuned electrically
- Everyday lifestyle modifications can make a BIG DIFFERENCE.