

Neuroinflammation

Part 4

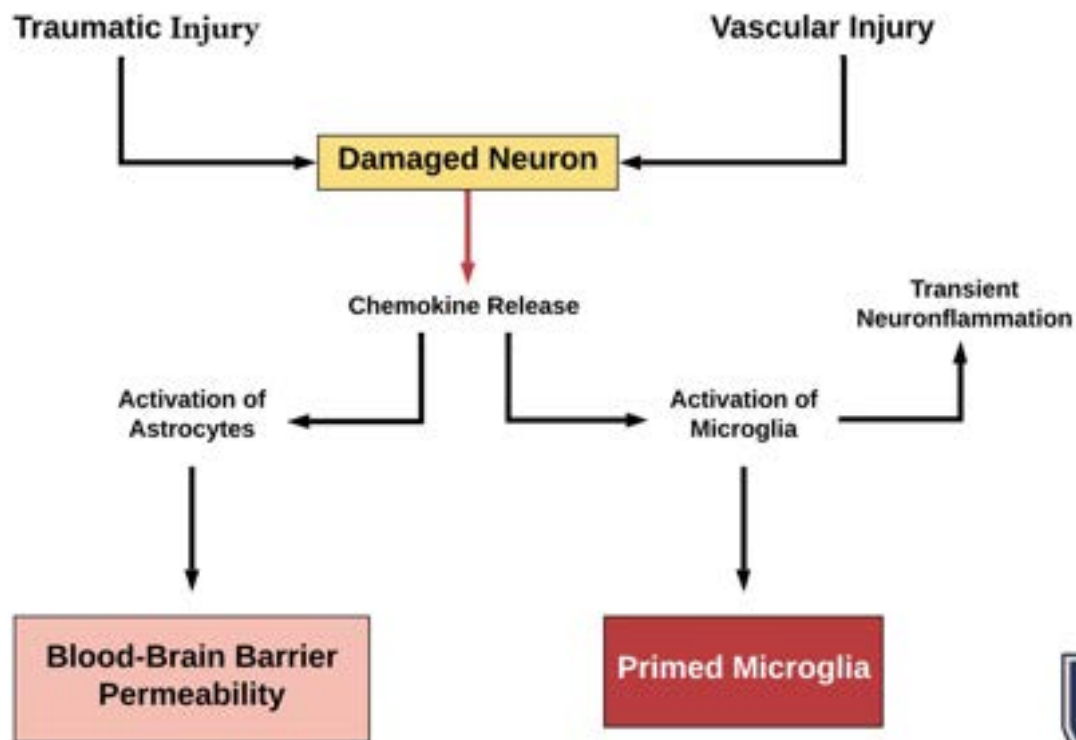
Deeper Dive

Mechanism of Neuroinflammation	Triggers	Inflammatory Response
Direct Injury to Neurons	Trauma and Stroke	Primed Microglia
Blood-Brain Barrier Breakdown	Inflammation/Oxidative Stress/Zonulin	Primed Microglia, Autoimmunity, Transient Inflammation
Peripheral Activation of Neuroglia	Systemic Inflammation	Transient Inflammation



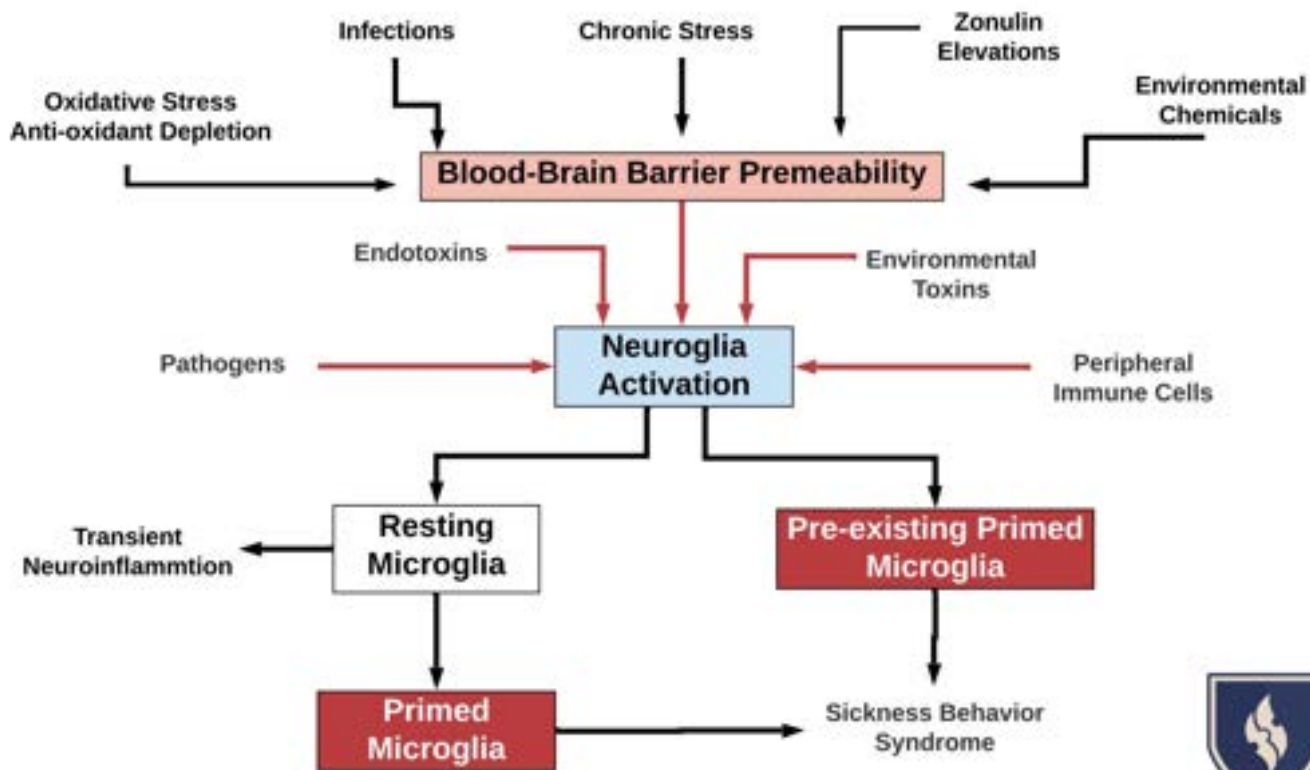
Neuroinflammation Mechanism #1

Direct Injury to Neurons (Trauma or Stroke)

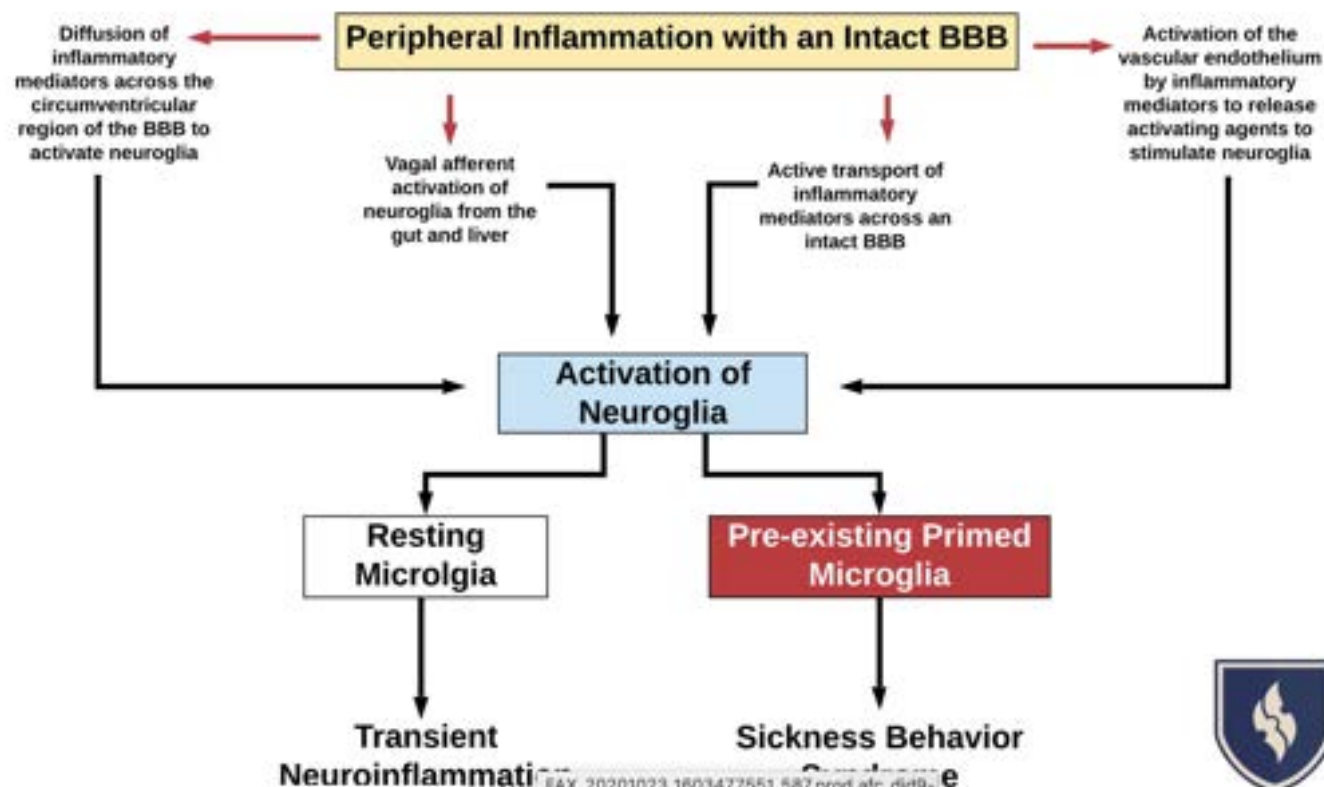


Neuroinflammation Mechanism #2

Breakdown of Blood-Brain Barrier



Neuroinflammation Mechanism #3 Peripheral Activation of Neuroglia



BBB

- Breaches are more significant than gut permeability
- Can test with large particles like GABA
 - If you take GABA and it calms the brain - likely BBB breach
- If open - constantly vulnerable to many things
 - Chemicals
 - Infections
 - Antibodies (only cross if BBB breached)
 - And more
- Silver nanoparticles in 1 study - destroyed the BBB (use with caution)
- #1 priority - heal the BBB

Example

- Celiac person
- Eats gluten - increases zonulin
- Increased zonulin → makes BBB permeable
- So leaky gut and leaky brain (due to gluten!)
- Gluten can bind to cerebellum and cross react and damage tissue
- LPS in the gut and leaky BBB - need to do all the recommendations - strictly!
-

Healing the BBB

- Decrease oxidative stress!
 - ALA, DHA and fish oils, Ginko Biloba, Resveratrol, Glutathione, turmeric
- Activate vascular endothelium
 - iNOS - destroys vascular endothelium
 - eNOS - heals BBB
 - Ginko and vinpocetine → push towards eNOS
- Support astrocyte neuroprotective pathway
 - Flavinoids (same as microglia support)
 - Resveratrol, curcumin

NeurO2

NeurO2

- Cerebral circulation
- 2 a day up to 4-6 twice daily
- Nitric balance
 - 1tsp-2tsp
 - Helps faster but not as long lasting
 - Capsules longer lasting
 - Enos



Nitric Balance™ is an advanced combination of carefully selected ingredients that work together to affect NOS (nitric oxide synthase) activity and intracellular energy production.* It also influences the related production of cell-signaling molecules and oxidants.* This formulation takes advantage of the compounding and complementary actions of its ingredients to deliver a truly effective formula backed by a decade of successful clinical use.* Nitric Balance™ is an excellent choice for individuals needing immune balance, brain function, and exercise support.* Also available in a 4 oz size (K82) and in a Chocolate Strawberry flavor (K68).

Features

- Pleasant-tasting peppermint and chocolate strawberry options
- Easy-to-use liquid formula
- Lightly and naturally sweetened with luo han guo (monk fruit) and stevia extract
- Arginine and stimulant free
- Gluten and dairy free, as confirmed by finished product testing
- Great to use 20-30 minutes before exercise*



Liquid
Formula



Micronized
& Emulsified



Healthy
Energy*



Enhanced
Taste



Advanced
Formula



Tested
for Gluten



Tested
for Dairy



BRAIN*

CARDIOVASCULAR*

CELLULAR*

OCCASIONAL STRESS*

Price QTY

NeuroO₂[™] is uniquely designed and mechanistically balanced to support the cerebral microvasculature for healthy blood flow to the brain.* By using high quality, standardized extracts with targeted "brain nutrients" such as vinpocetine at clinically studied levels, this formula can be useful to those seeking to counter the mild effects of aging on brain health and brain function.*

Features

- Includes high-potency riboflavin and is a good source of magnesium
- High-quality, standardized extracts to ensure optimal results
- Clinically studied levels of key ingredients
- Easy-to-swallow, vegetarian capsule
- Gluten and dairy free, as confirmed by finished product testing

Benefits

- Supports circulation and vascular tone*
- Supports oxygenation of the brain*
- Supports healthy cognitive function*



Vegetarian
Capsule



Great
Value



Advanced
Formula



Apex Specs
& Sourcing



Tested
for Gluten



Tested
for Dairy

Supplement Facts

Serving size 1 vegetarian capsule

Servings per container 90

	Amount Per Serving	%DV
Riboflavin	20 mg	1538%
Magnesium (as magnesium citrate)	40 mg	10%
Feverfew Extract (<i>Tanacetum parthenium</i>) (flower) (standardized to 0.7% parthenolide)	300 mg	*
Butcher's Broom Extract (<i>Ruscus aculeatus</i>) (fruit & flower) (standardized to 20% saponins)	200 mg	*
Ginkgo Extract (<i>Ginkgo biloba</i>) (leaf) (standardized to 24% flavone glycosides and 6% terpene lactones)	100 mg	*
Cayenne Extract (<i>Capsicum annuum</i>) (fruit)	40 mg	*
Vinpocetine	10 mg	*

*Daily Value (DV) not established.

Other ingredients: Vegetarian capsule (hypromellose), cellulose.

Lifestyle to support BBB

- Exercise
- Sleep
- Not smoking/benzene
 - 2nd hand can break down BBB
 - Benzene - car exhaust
 - HEPA air filter if you are around traffic, other areas
 - Smoke devastating to the BBB
- EMF
 - EMGs show changes in the brain with EMF exposure
 - Those sensitive to EMF - have glial cell priming and it is significant and severe!!
 - Get trifield meter
 - Less EMF.com
 - EMF's can make it hard to heal (take measures)

Lifestyle to support BBB

- Manage stress
- Obesity
 - Fat cells release inflammatory mediators → break down the BBB
 - High insulin also affects this
 - DM also
 - Keto recommended
 - 20 meta-analysis all show that keto is protective of chol/CV/DM/insulin

Basic Strategies to Reduce EMF Exposure

- Reduce Wi-Fi router exposure
- Use Ethernet cable rather than Wi-Fi when possible
- Keep your phone on “Airplane” mode or only use phone with wired internet connection
- Use speaker or Air Tube headsets and EMF blocking devices
- Use laptop on battery mode
- Use wired mouse and keyboard
- Create a sleep sanctuary (no cell phone or electronics, battery powered alarm clock, EMF bed canopy, etc.)



Labs

- Correct inflammation
 - High CRP, high homocysteine breaks BBB
- Glutathione pathway
 - <10 - low glutathione
 - 10-30 wnl
 - High - something is wrong with the glutathione production pathway
- All LFT elevated (AST, ALT, GGT) - tissue breakdown in the body
- Iron overload - destroys the BBB
- High complement can damage BBB

Test BBB

- S100B (Labcorp, Quest) 229
 - In the blood if BBB breaks down - but very transient and acute
 - So can get a false negative
- Array 20 - BBB
- Array 2 - Gut barrier/LPS
 - Important with joint pain, AI, NI
- Worst case scenerio - LPS, BBB breach and neuro Ab's
- Cyrex 5 - see all AI markers
- Cyrex 7 - Brain autoimmune Cyrex 7X expanded neuro Ab's (all on 5)
- Array 14 - saliva (a nice mix)
 - May not catch as well as serum but a decent test
 - BBB, gut, some AI, gluten markers



5040 N. 15th Avenue, Suite 307 . Phoenix AZ 85015
Tel 602 759 1245 . Fax 602 759 8331 . www.CyrexLabs.com

PRACTITIONER

PATIENT

KHARRAZIAN, DATIS

TEST	RESULT			
Array 7X - Neurological Autoimmune Reactivity Screen - Expanded	IN RANGE (Normal)	EQUIVOCAL*	OUT OF RANGE	REFERENCE (ELISA Index)
Myelin Basic Protein IgG + IgA	1.07			0.1-1.4
Myelin Basic Protein IgM	1.30			0.3-2.7
Asialoganglioside IgG+IgA		1.22		0.1-1.4
Asialoganglioside IgM	1.45			0.3-2.6
Alpha + Beta Tubulin IgG+IgA	0.84			0.4-1.4
Alpha + Beta Tubulin IgM		1.59		0.3-2.1
Cerebellar IgG+IgA	0.82			0.2-1.4
Cerebellar IgM	0.94			0.2-2.0
Synapsin IgG+IgA		1.15		0.1-1.2
Synapsin IgM		1.43		0.2-1.6



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PRACTITIONER

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PATIENT

TEST	RESULT			
Array 20 - Blood Brain Barrier Permeability Screen	IN RANGE (Normal)	EQUIVOCAL*	OUT OF RANGE	REFERENCE (ELISA Index)
Blood Brain Barrier Protein IgG+IgA	0.92			0.3-2.2
Blood Brain Barrier Protein IgM			3.28	0.3-2.2





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PATIENT

TEST	RESULT			REFERENCE (ELISA Index)
	IN RANGE (Normal)	EQUIVOCAL*	OUT OF RANGE	
Array 2 – Intestinal Antigenic Permeability Screen				
Actomyosin IgA **	10.69			0.0-20
Occludin/Zonulin IgG	0.79			0.2-1.5
Occludin/Zonulin IgA	0.96			0.1-1.8
Occludin/Zonulin IgM		1.66		0.1-2.1
Lipopolysaccharides (LPS) IgG	1.02			0.1-1.6
Lipopolysaccharides (LPS) IgA	0.76			0.1-1.8
Lipopolysaccharides (LPS) IgM	1.15			0.1-2.0





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PATIENT

TEST	RESULT			
Array 7X - Neurological Autoimmune Reactivity Screen - Expanded	IN RANGE (Normal)	EQUIVOCAL*	OUT OF RANGE	REFERENCE (ELISA Index)
Myelin Basic Protein IgG + IgA	0.54			0.1-1.4
Myelin Basic Protein IgM	1.12			0.3-2.7
Asialoganglioside IgG+IgA	0.63			0.1-1.4
Asialoganglioside IgM	1.14			0.3-2.6
Alpha + Beta Tubulin IgG+IgA	0.66			0.4-1.4
Alpha + Beta Tubulin IgM	1.18			0.3-2.1
Cerebellar IgG+IgA	0.51			0.2-1.4
Cerebellar IgM	0.84			0.2-2.0
Synapsin IgG+IgA	0.47			0.1-1.2
Synapsin IgM	0.89			0.2-1.6

PRACTITIONER

PATIENT

KHARRAZIAN, DATIS

TEST	RESULT			REFERENCE (ELISA Index)
	IN RANGE (Normal)	EQUIVOCAL*	OUT OF RANGE	
Array 14 - Multiple Mucosal Immune Reactivity Screen				
Lipopolysaccharides IgA+IgM			>3.50	0.2-1.8
Occludin/Zonulin IgA+IgM	0.58			0.2-2.0
Actomyosin IgA+IgM	0.45			0.2-2.0
ASCA/ANCA IgA+IgM	0.68			0.2-1.9
Calprotectin IgA+IgM	0.70			0.2-1.8
Alpha-Gliadin-33-mer IgA+IgM	0.35			0.2-2.0
Gamma-Gliadin-15-mer IgA+IgM	0.52			0.2-2.0
Glutenin-21-mer IgA+IgM	0.41			0.2-2.0
Gluteomorphin IgA+IgM	0.52			0.2-2.0
Wheat Germ Agglutinin IgA+IgM	0.79			0.2-1.9
Transglutaminase 2 IgA+IgM	0.63			0.2-1.9
Egg IgA+IgM	0.57			0.2-2.1
Soy IgA+IgM	0.91			0.2-2.0
Com IgA+IgM	0.39			0.2-2.3
Alpha + Beta Casein IgA+IgM	0.37			0.2-2.0
Casomorphin IgA+IgM	0.41			0.2-2.0
Aflatoxin IgA+IgM	0.61			0.2-2.1
Bisphenol-A IgA+IgM	0.62			0.2-2.2
Mercury IgA+IgM	0.59			0.2-2.3
Mixed Heavy Metals IgA+IgM	0.70			0.2-2.1
Rotavirus IgA+IgM	0.63			0.2-2.1
Myelin Basic Protein IgA+IgM	0.71			0.2-2.1
Blood-Brain Barrier Proteins IgA+IgM	0.55			0.2-2.4
Immune Complexes IgA+IgM	0.38			0.2-2.0

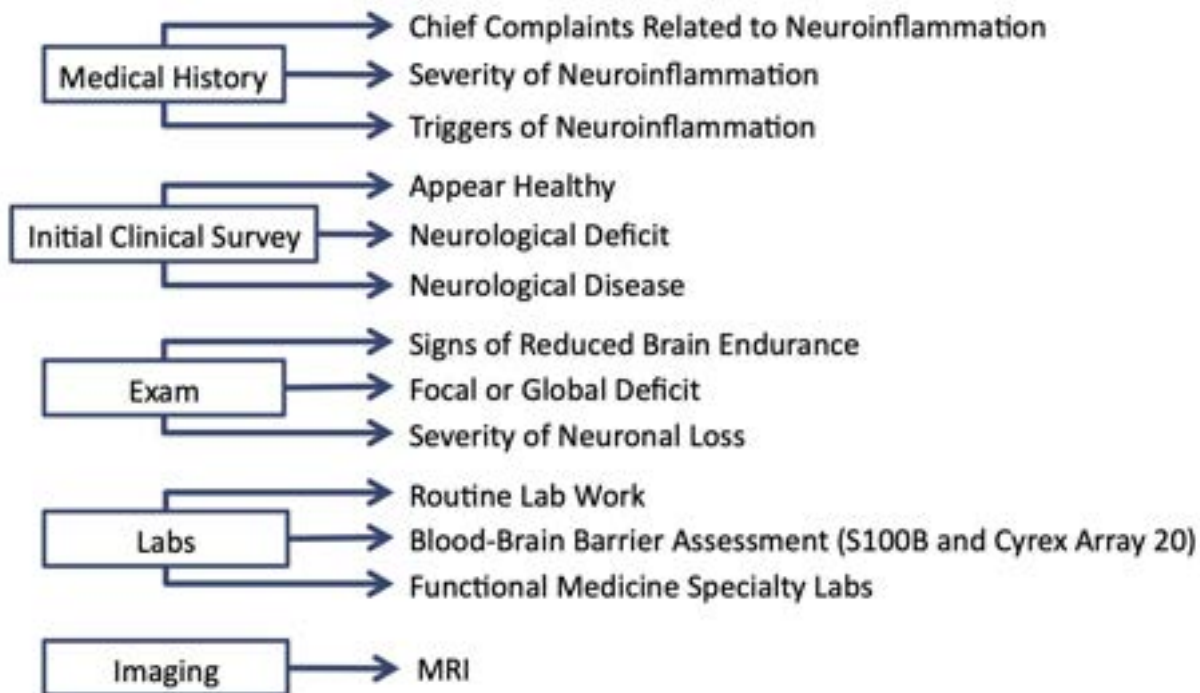


Hormones and NI

- See decreased cognitive function in menopause
- As estrogen levels decrease → greater brain inflammation
- Taking estrogen can dampen NI
- Testosterone in men can also dampen NI
- So....hormones can help - but it doesn't last long
 - So not a great long term option
- Can use in acute inflammation (helps prognosis in head injury)
 - Women - E, P, DHEA
 - Men - T, DHEA
- It is the other mechanisms that will help long term

Evaluation

EVALUATING NEUROINFLAMMATION IN A CLINICAL SETTING



EVALUATING CHIEF COMPLAINTS FOR NEUROINFLAMMATION

Functional Complaints

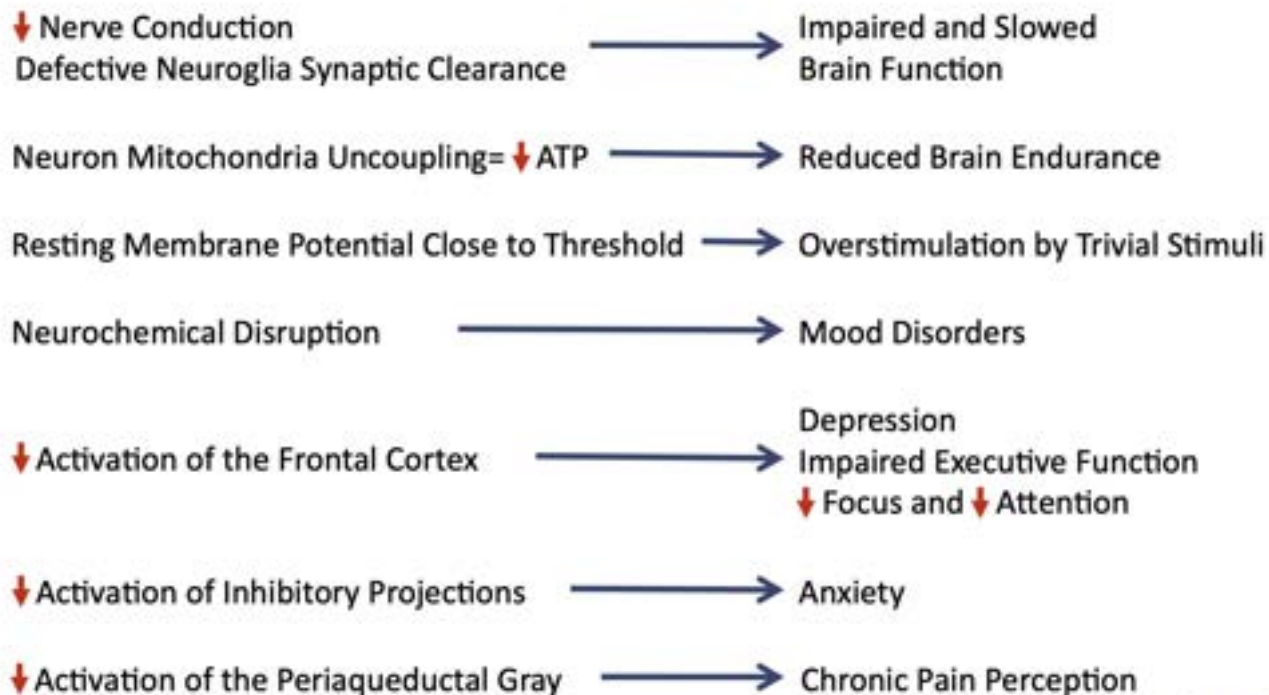
- Brain fog
- Inability to focus or concentrate
- Poor memory or recall
- Inability to handle stimulation (crowded environments, loud noises, etc.)
- A need for excessive sleep
- Fatigue
- Poor endurance with brain activities

Diagnosed Conditions

- Depression
- Chronic Fatigue Syndrome
- Post-Traumatic Stress Syndrome
- Post-Concussion Syndrome
- Chronic Pain Syndrome
- Fibromyalgia
- Stroke
- Neurodegenerative Disease (Dementia #1, Parkinson's #2)



UNDERSTANDING PHYSIOLOGICAL MECHANISMS OF CHIEF COMPLAINTS



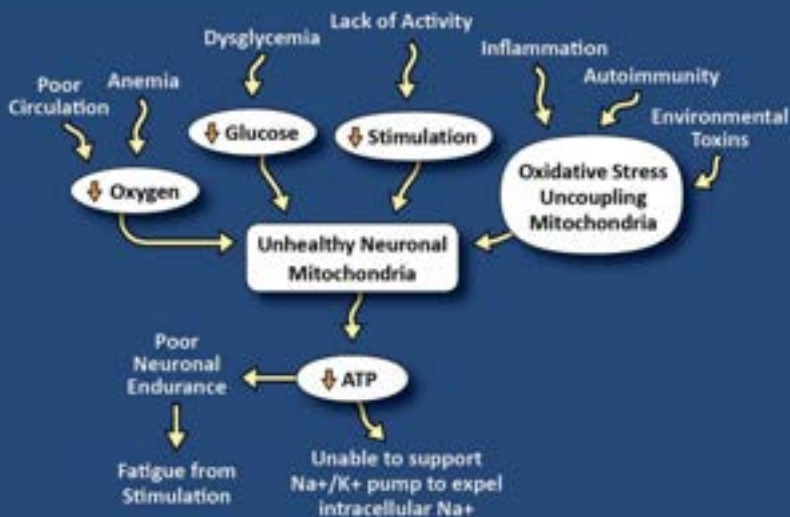
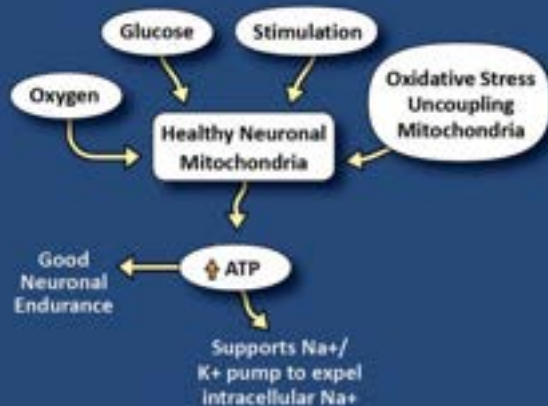
Specific Brain Areas - fatigue due to low ATP

- Limbic - sound/light
- Cerebellar - can't stand for long periods
- Vestibular - windy roads
- Frontal - Concentration
- Lack of endurance in driving, reading, focus, etc..

Resting Membrane Potential

- There is usually a certain amount of energy needed to fire a neuron at rest
 - A healthy brain - has a larger amount of energy/input needed to fire
 - An unhealthy brain - can fire with much less energy/input
- This is different than priming reactions
- Activated neurons make ATP
 - ATP involved in the Na/K pump
 - Sodium moves into the neuron -> carries a charge
 - The neuron then gets to threshold and causes activity
 - Not enough energy - threshold is not met and no activity
 - Once it reaches threshold - it needs more ATP to get the Na/K back out
 - If not enough ATP to get it out - threshold level stays high
 - Can't handle stimulus (light, sound, food, clothes)
 - Low ATP at this time equals low endurance and then a shut down

HEALTHY AND UNHEALTHY RESTING MEMBRANE POTENTIALS



Healthy Neuronal Resting Membrane Potential



Unhealthy Neuronal Resting Membrane Potential



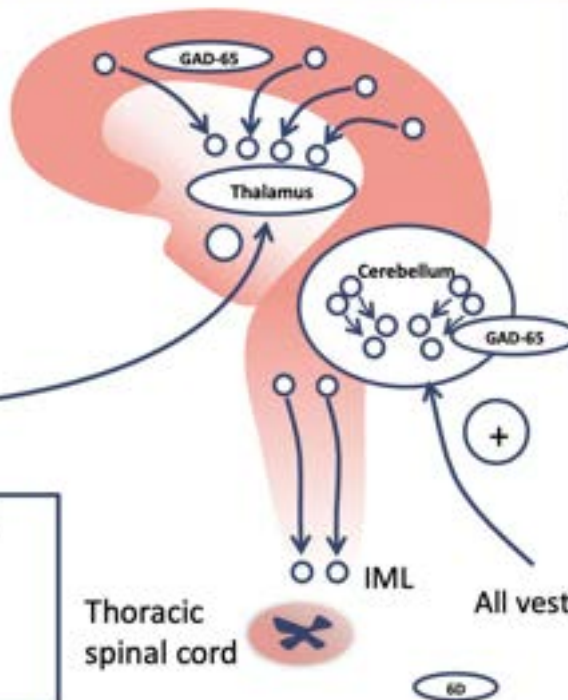
NEUROINFLAMMATION AND BRAIN GATING MECHANISMS

Cerebrum

Note: Healthy cerebrum function is needed to activate inhibition of the thalamus

All sensory input from the environment

Note: Healthy cerebrum function is needed to dampen the intermediolateral cell column (IML)



Note: GAD-65 autoimmunity also leads to failure of brain gating

Note: Gluten antibodies cross react with and degenerate the cerebellum

All vestibular and muscle-spindle input

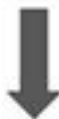


Gating

- Thalamus gets constant input
 - Cortex fires to inhibit the thalamus
 - If we lose thalamus gating - we can't handle stimuli
- Cerebellum also inhibits activity
 - Can't dampen when unhealthy
 - We see movement, muscle/vestibular input is too much
- Brain dampens autonomic patterns (sympathetic response)
 - Not working to dampen - we get increase sympathetic tone and dysautonomia
 - HR high, fight or flight response (sweat, BP up, HR up, anxiety, and more)
- Periaqueductal grey area
 - Dampens pain perception if healthy
 - Descending pain modulation - chronic pain

Descending Pain Modulation (Inhibition/Facilitation)

Cerebral Cortex (Amygdala, ACC)



Brainstem (PAG, Parabrachial Nucleus, RVM)



Spinal Cord (Dorsal Horn)



IDENTIFYING SEVERITY OF NEUROINFLAMMATION

Transient Neuroinflammation

- Episodes of Brain Fog and Cognitive Decline
- Typically Triggered by Dietary Protein or Chemicals

Chronic Neuroinflammation

- Chronic Depression, Fatigue, and Impaired Brain Function
- Underlying Inflammatory Disease
- Undiagnosed Ongoing Trigger (Dietary Protein or Chemical)

Primed Neuroglia

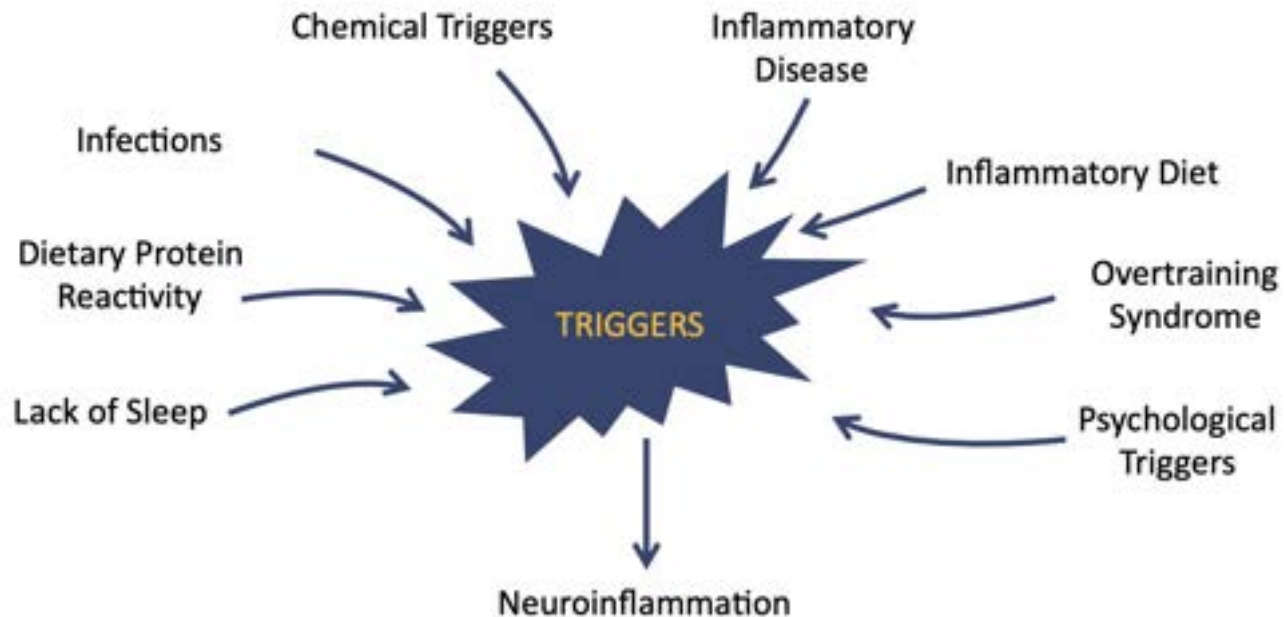
- Remitting/Relapsing Episodes of Significant Loss of Brain Function
- "Sickness Behavior Syndrome"
- History of Traumatic Brain Injury, Vascular Insult, or Infection
- Unable to Cure Current Chief Complaints

Neurological Autoimmunity

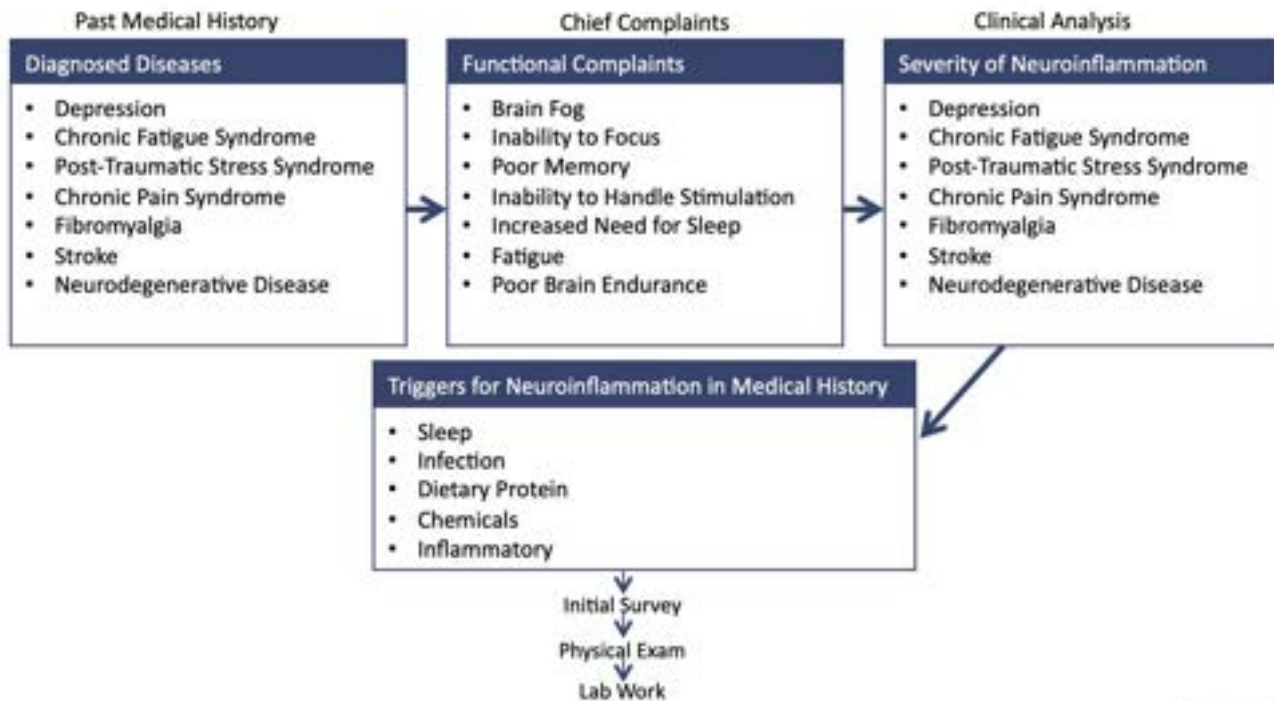
- Neurological Deficit
- History of other Autoimmune Disease
- Remitting/Relapsing Episodes of Loss of Brain Function
- Unable to Cure Current Chief Complaints



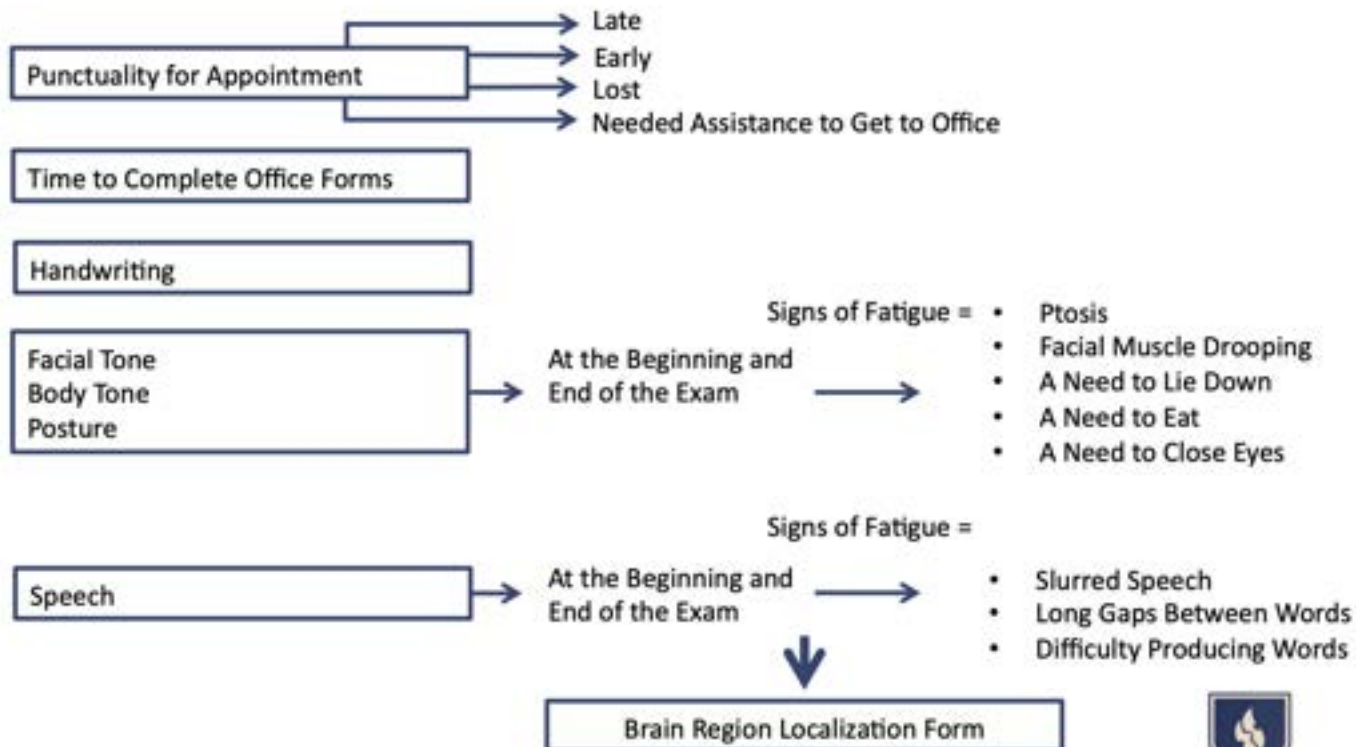
IDENTIFYING NEUROINFLAMMATION TRIGGERS FROM THE MEDICAL HISTORY

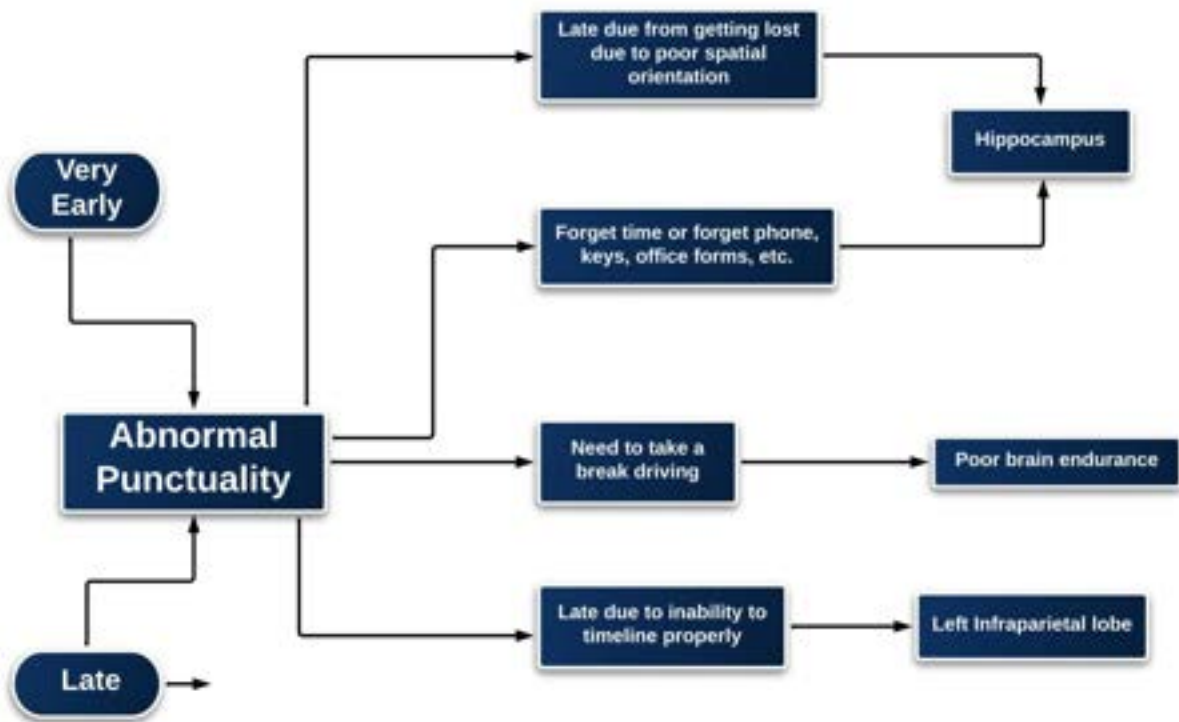


SUMMARY OF MEDICAL HISTORY OF NEUROINFLAMMATION



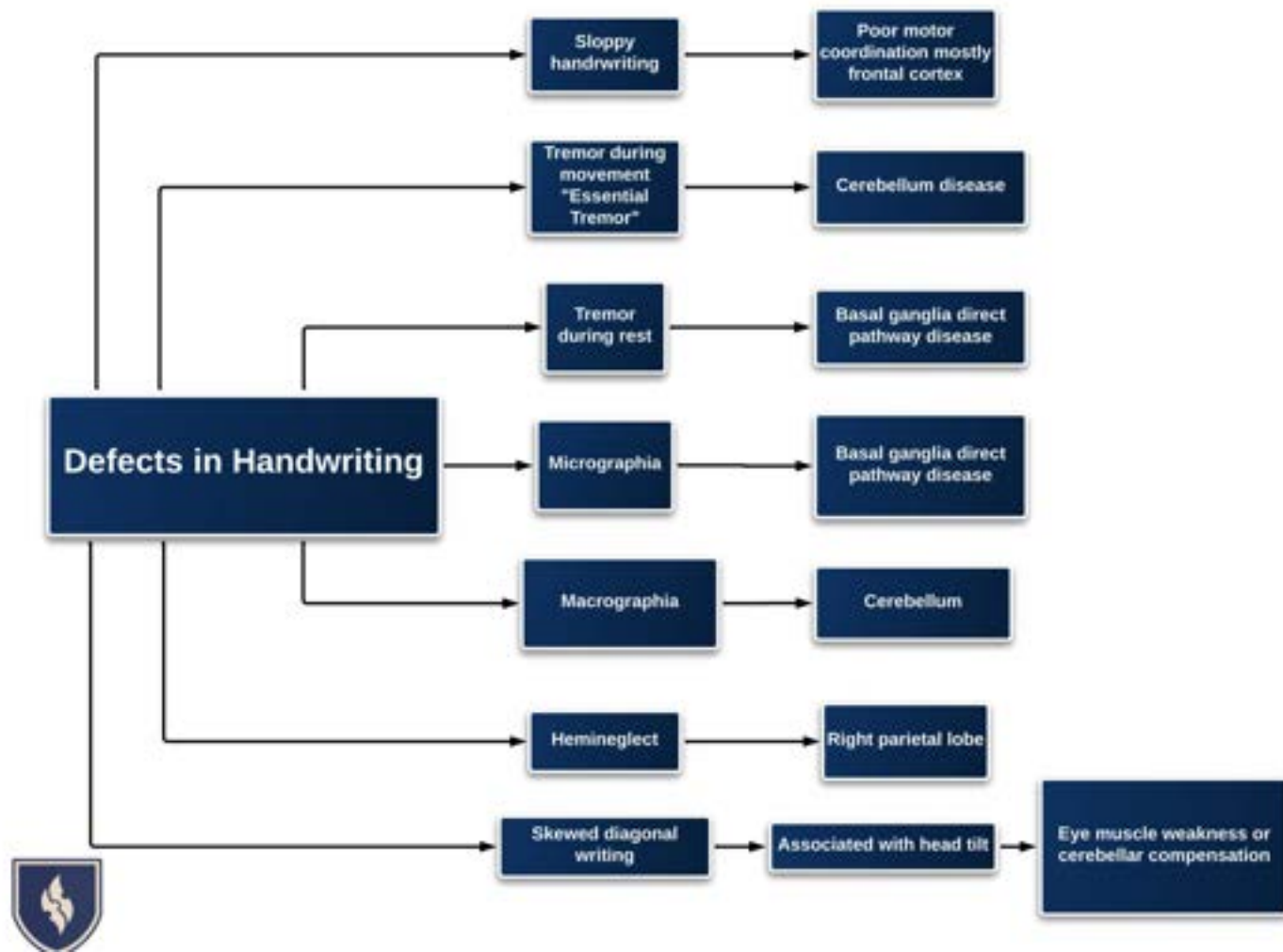
INITIAL CLINICAL SURVEY

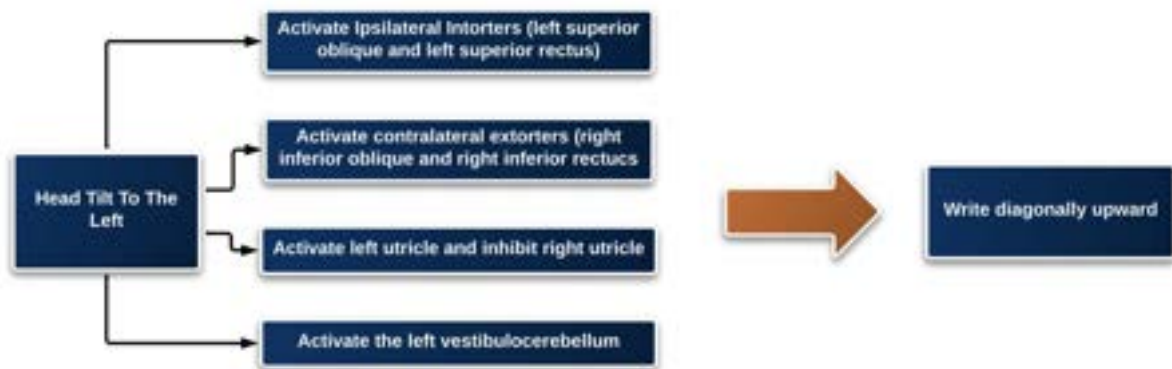




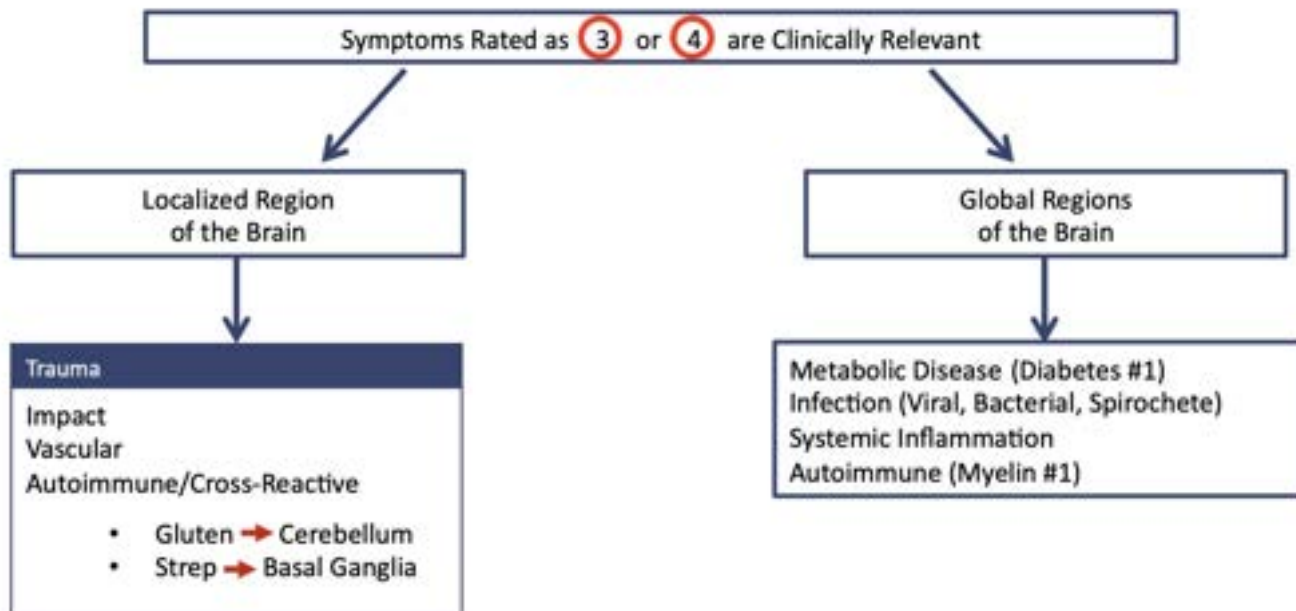
Note: If the patient needed to be driven to the office it is a red flag for brain impairment



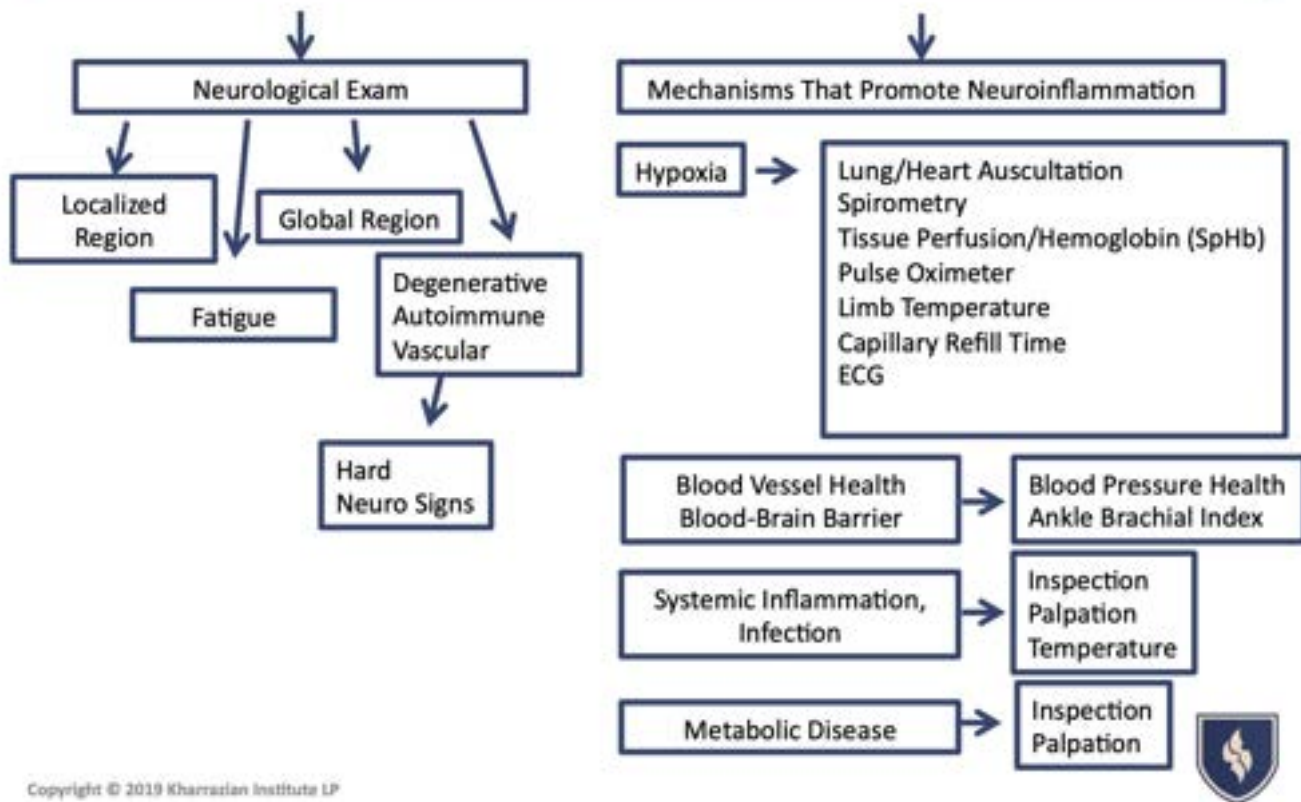




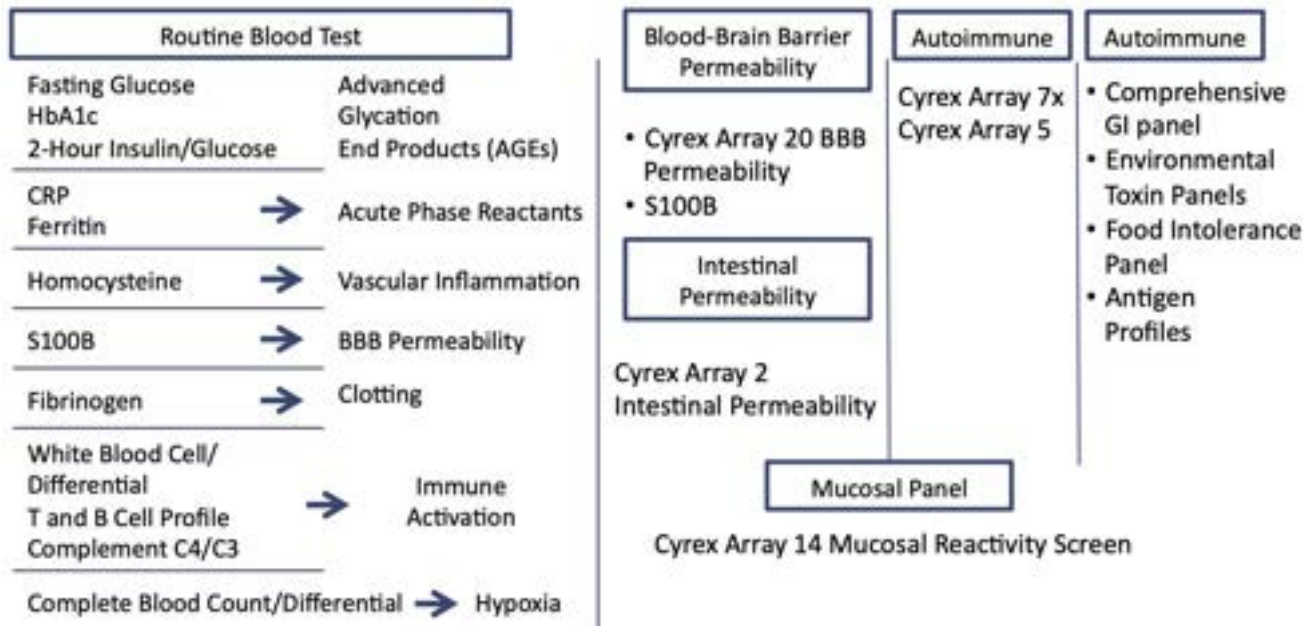
CLINICAL INTERPRETATION OF BRAIN REGION LOCALIZATION FORM



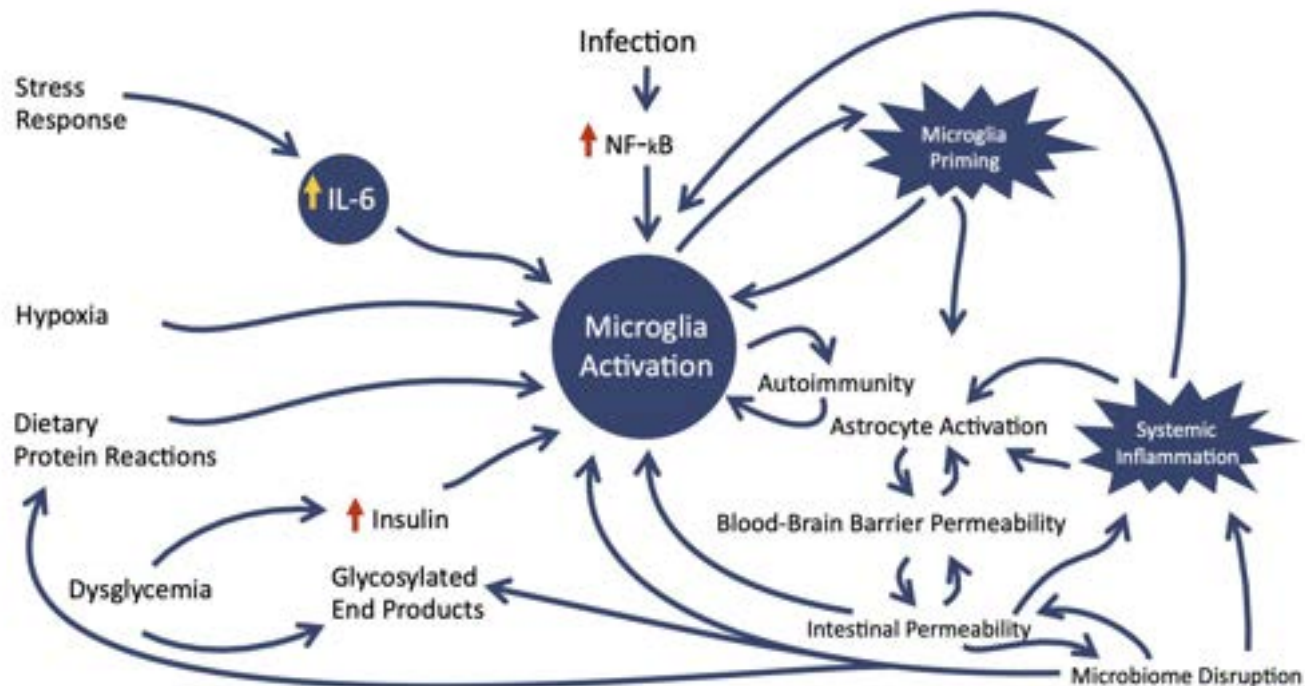
KEY PHYSICAL EXAMINATION FINDINGS FOR NEUROINFLAMMATION



LABORATORY TESTS TO EVALUATE NEUROINFLAMMATION



NEUROINFLAMMATION WEB

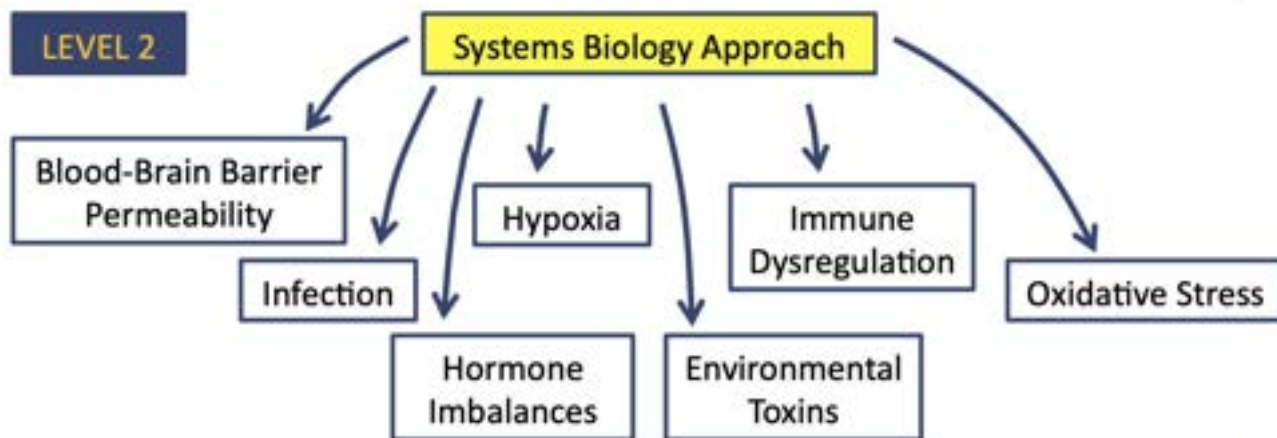


CLINICAL MANAGEMENT OF NEUROINFLAMMATION

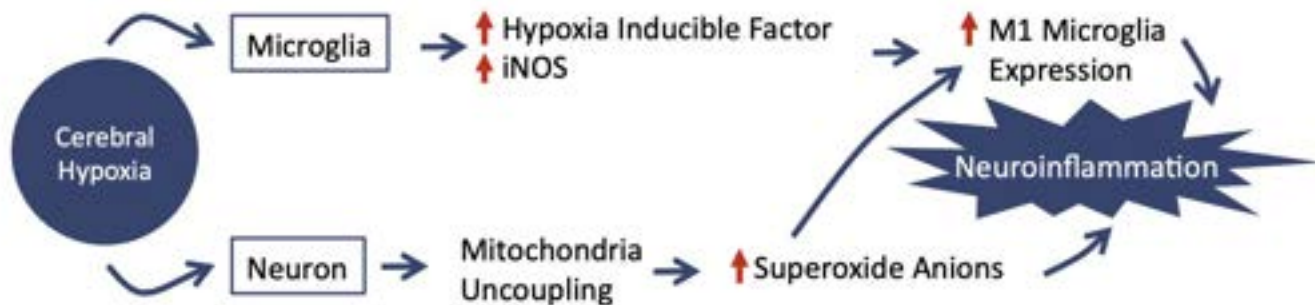
LEVEL 1

- Lifestyle
- Diet
- Anti-Inflammatory Nutraceuticals

LEVEL 2



CELLULAR MECHANISMS OF HYPOXIA-INDUCED NEUROINFLAMMATION



CLINICAL EVALUATION FOR CEREBRAL HYPOXIA

Physical Examination

Inspection

- Circulation in Limbs
- Nail Beds

Palpation

- Temperature Proximal Compared to Distal
- Capillary Refill Time

In-Office Special Studies

Pulse Oximeter

Pulse Rate= (60-100 bpm)
Oxygen Saturation/SpO₂=(95-100%)
Perfusion index= (>1%)
Total Hemoglobin= (>15)

Spirometry

ECG

Laboratory Tests

Complete Blood Count (CBC)

- Anemia
 - ↳ Microcytic
 - ↳ Normocytic
 - ↳ Megaloblastic



Circulation

- Signs of poor circulation
 - cold hands/feet/nose
 - Pallor/cyanotic fingers/toes
 - Poor nail health
 - Toenail fungus
 - Poor capillary refill
- Support circulation (all will help high BP)
 - Vinpocetine
 - Ginko
 - Butcher's broom
 - Magnesium
 - Hawthorne Extract (best for BP)
- Best way to support - exercise!

CLASSIFICATION OF ANEMIA FROM CBC

↓ RBC
↓ HGB
↓ HCT

= Anemia

MCV

Normal = normocytic
Depressed = microcytic
Elevated = megaloblastic

MCH
MCHC

Normal = normochromic
Depressed = hypochromic
Elevated = megaloblastic

Microcytic Hypochromic

- Iron Deficiency
- Anemia of Chronic Disease/Inflammation
- Anemia of Blood Loss
- Sideroblastic Anemia
- Thalassemia

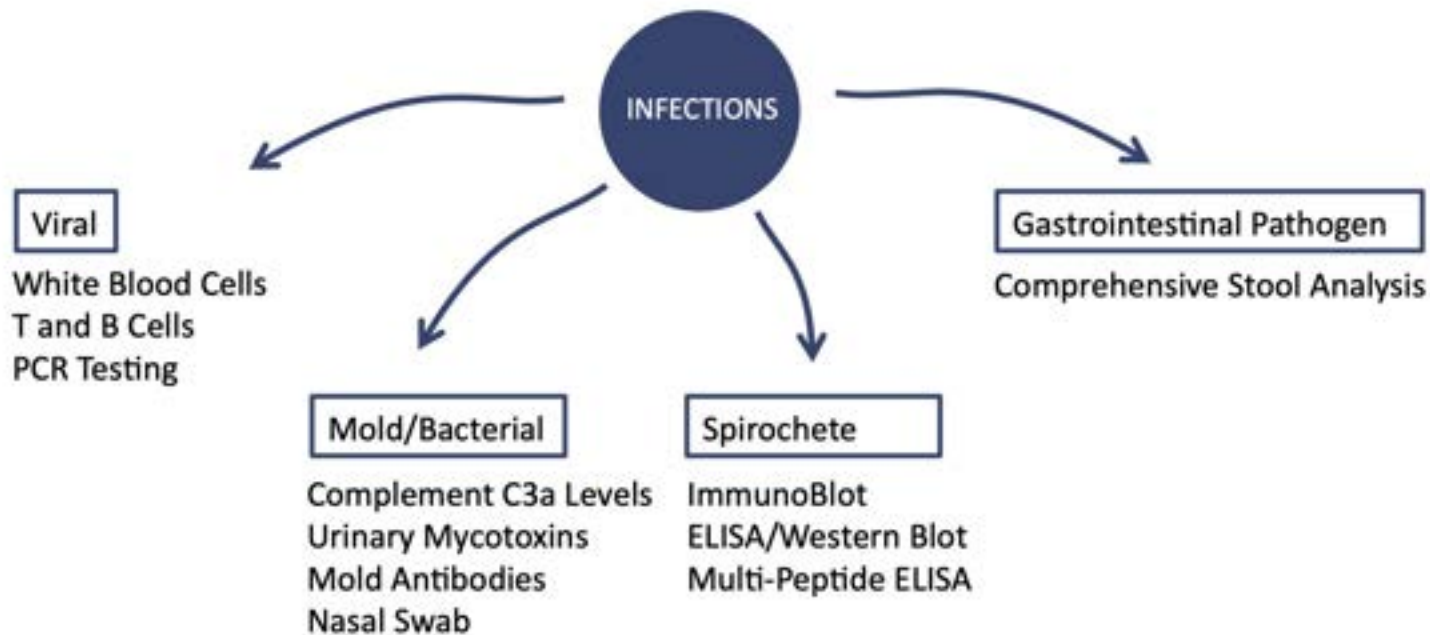
Normocytic Normochromic

- Anemia Secondary to Renal Disease
- Anemia of Chronic Inflammation/Disease
- Dyserythropoietic Anemia
- Aplastic Anemia
- Myelophthisis
- Myelodysplasia
- Anemia of Acute Blood Loss
- Hemolytic Anemia
 - Sickle Cell Anemia
 - G6PD Deficiency
 - Pyruvate Kinase Deficiency
 - Autoimmune Hemolytic Anemia
 - Hereditary Spherocytosis

Megaloblastic

- B12/Folic Acid Deficiency
- Pernicious Anemia (Autoimmune to IF)

INFECTIONS AND NEUROINFLAMMATION



KEY NUTRACEUTICALS DURING VIRAL INFECTION

TH-1

- Astragalus
- Echinacea
- Glycyrrhiza
- Maitake Mushroom

TH-2

- Grape Seed Extract
- Pine Bark Extract
- Maritime Pine Extract
- Green Tea Extract

TH-3

- Vitamin A
- Vitamin D

*These natural compounds support immune health and are not drugs



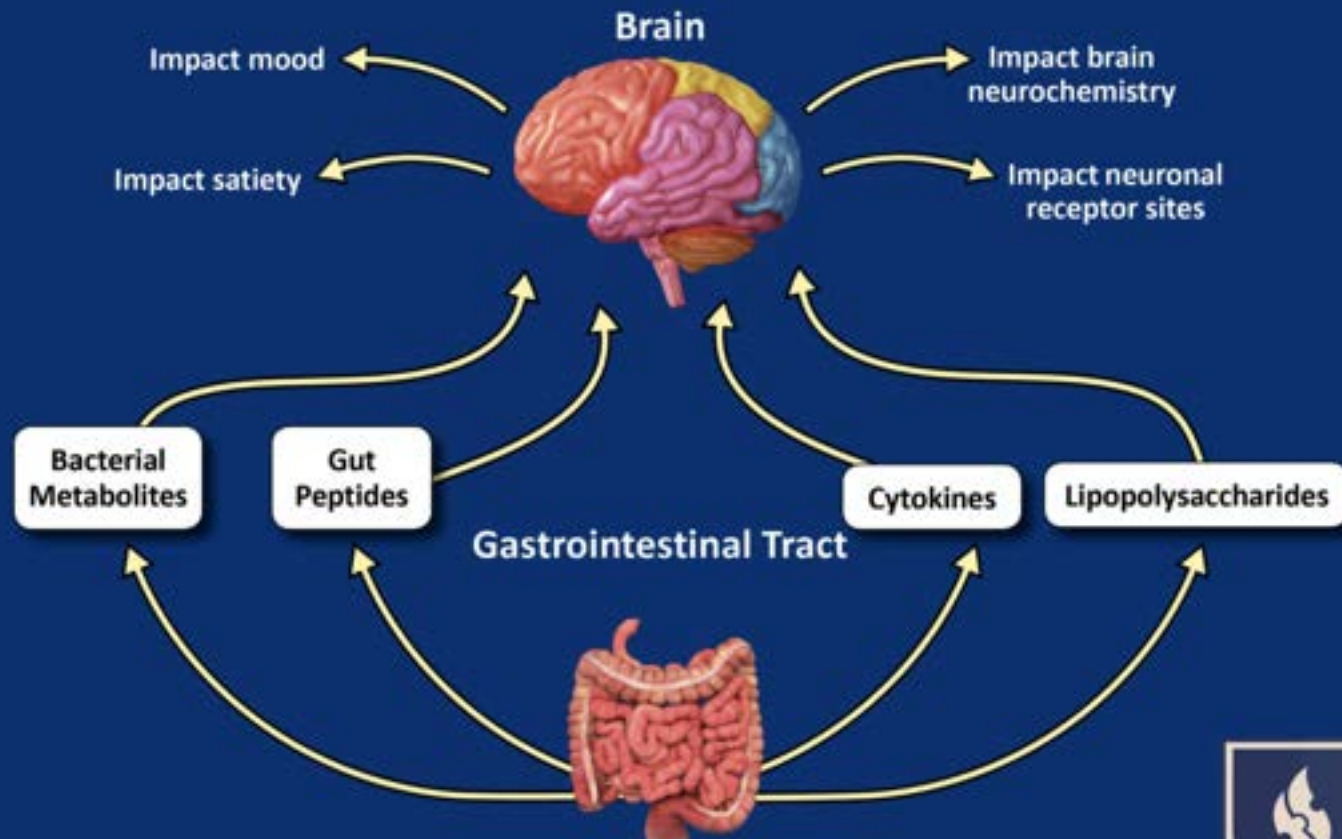
KEY NUTRACEUTICALS DURING ANTIGEN REACTION

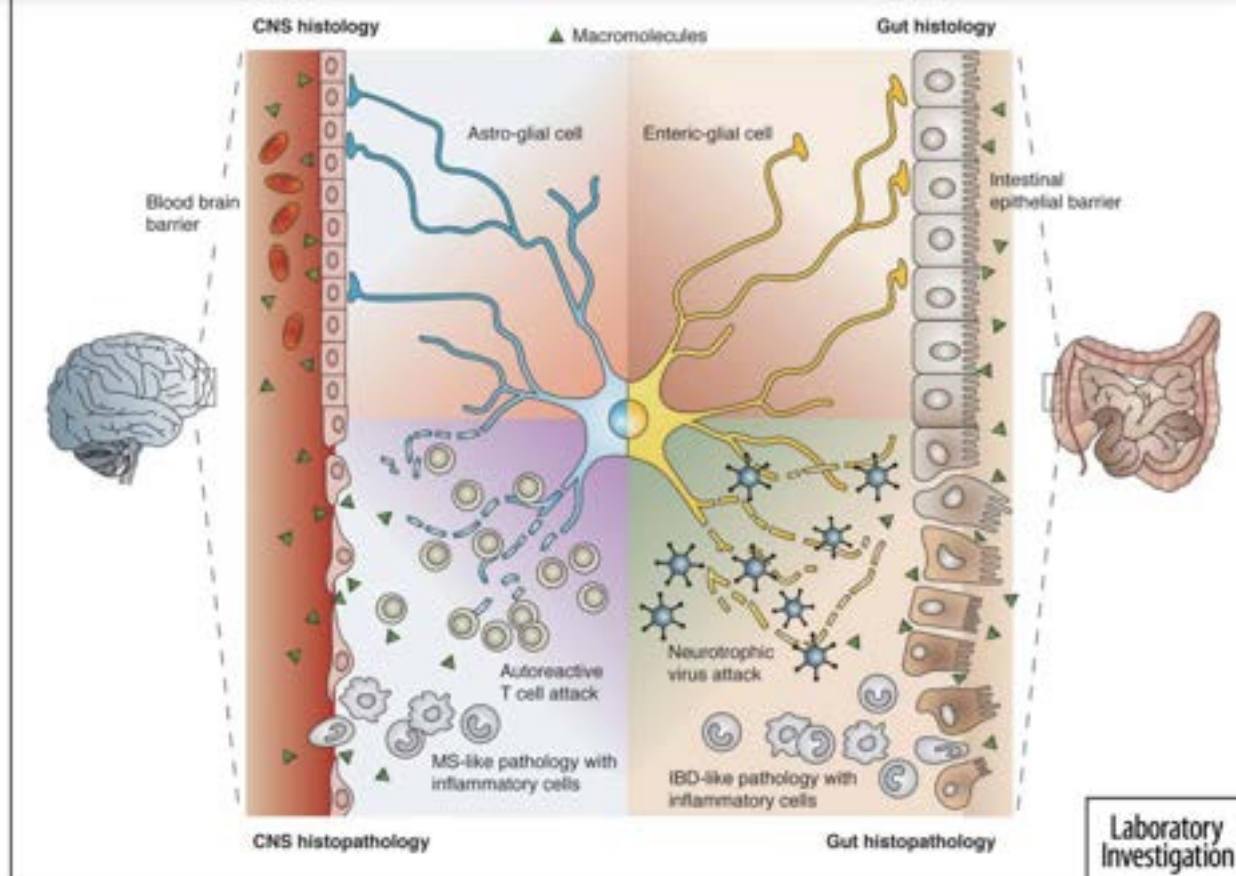
- Worm Wood Extract
- Black Walnut Extract
- Undecylenic Acid
- Caprylic Acid
- Barberry Extract
- Olive Leaf Extract
- Garlic Extract
- Uva Ursi
- Cat's Claw Extract
- Pau D'Arco Extract
- Goldenseal Extract
- Oregano Extract
- Oregon Grape Extract
- Yerba Mansa Extract

*These nutraceuticals are used to support intestinal health and are not drugs



SIGNALING AGENTS OF THE BRAIN-GUT AXIS

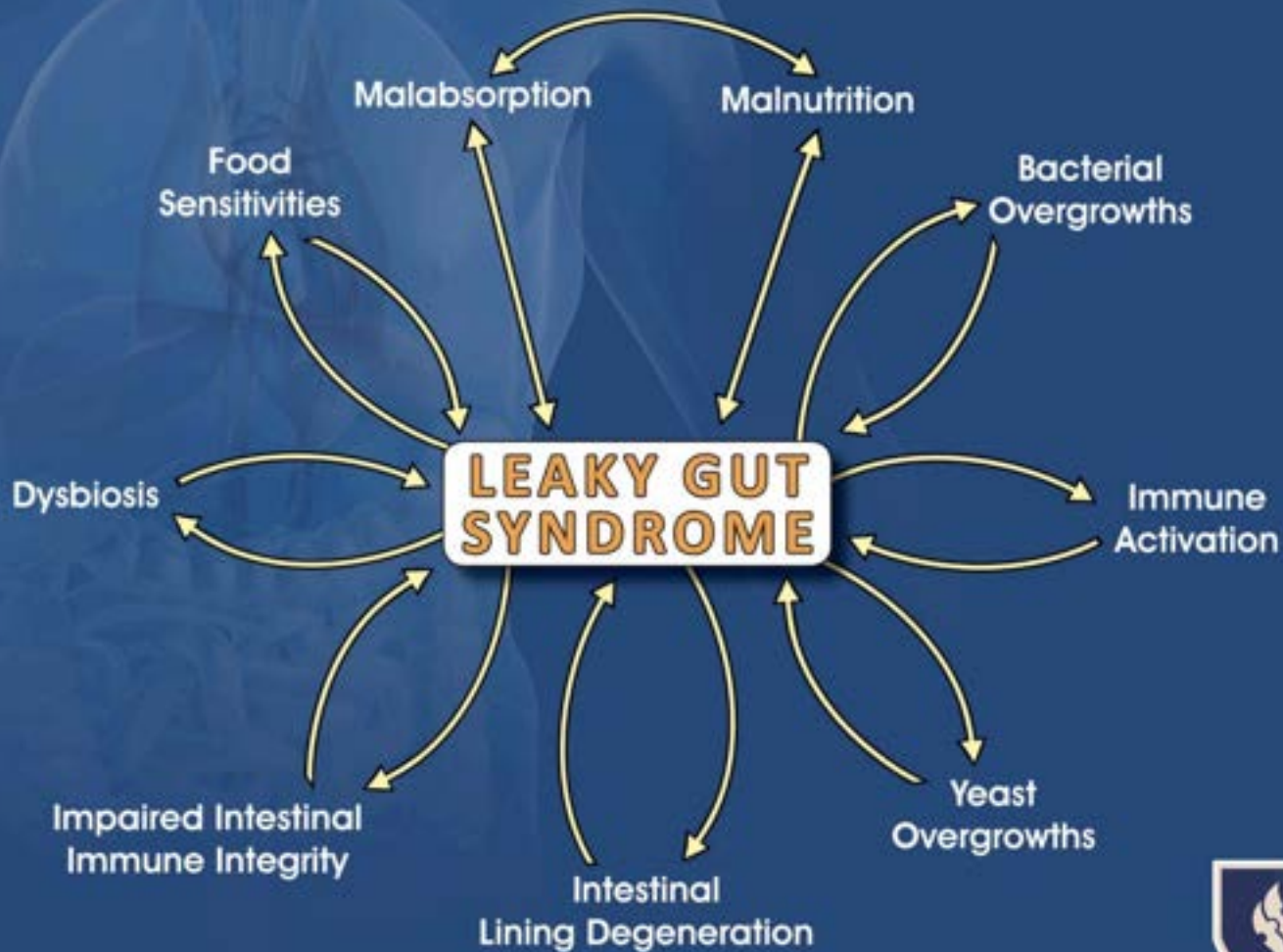




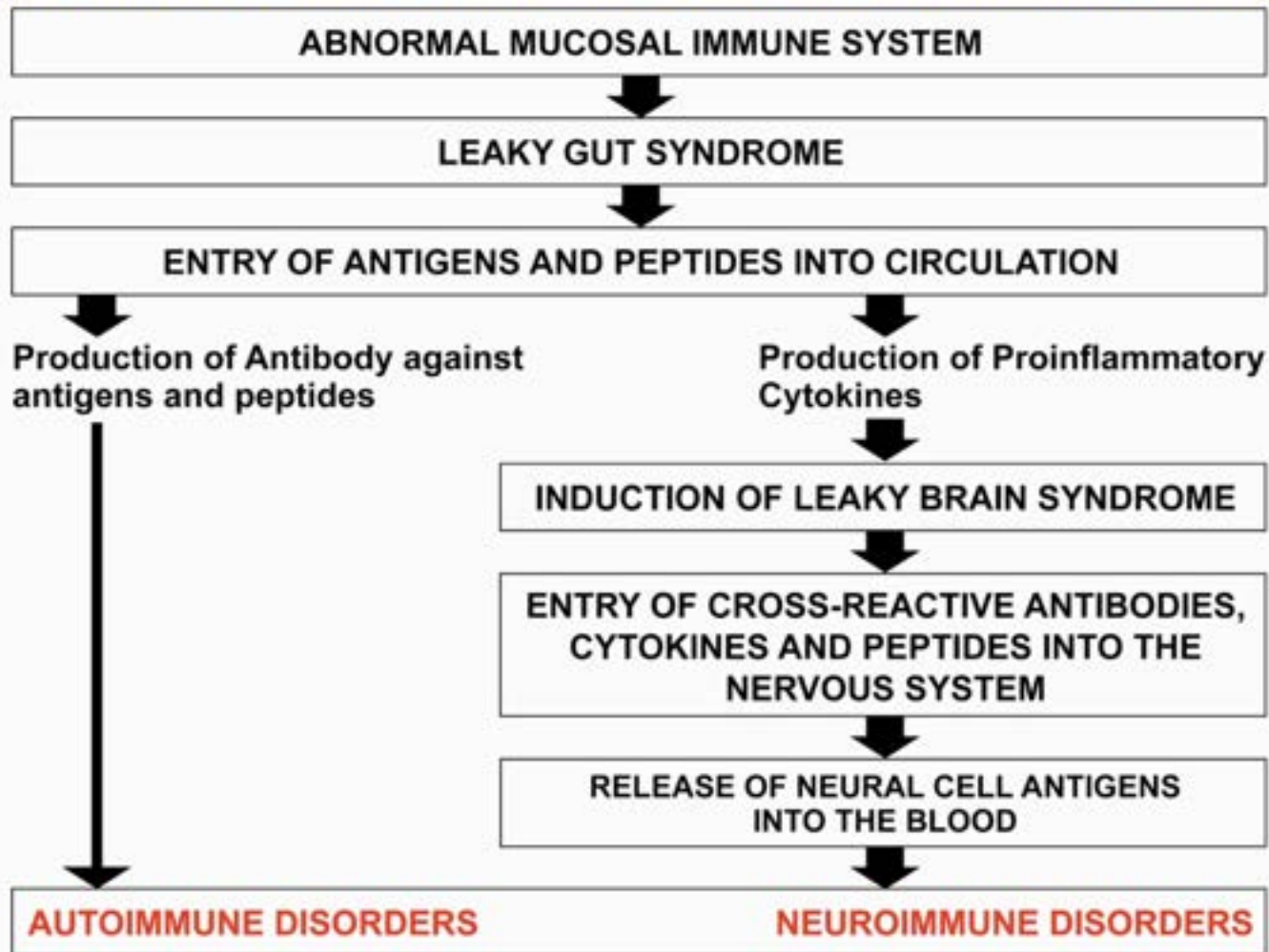
Lab Invest. 2007 Aug;87(8):731-736.

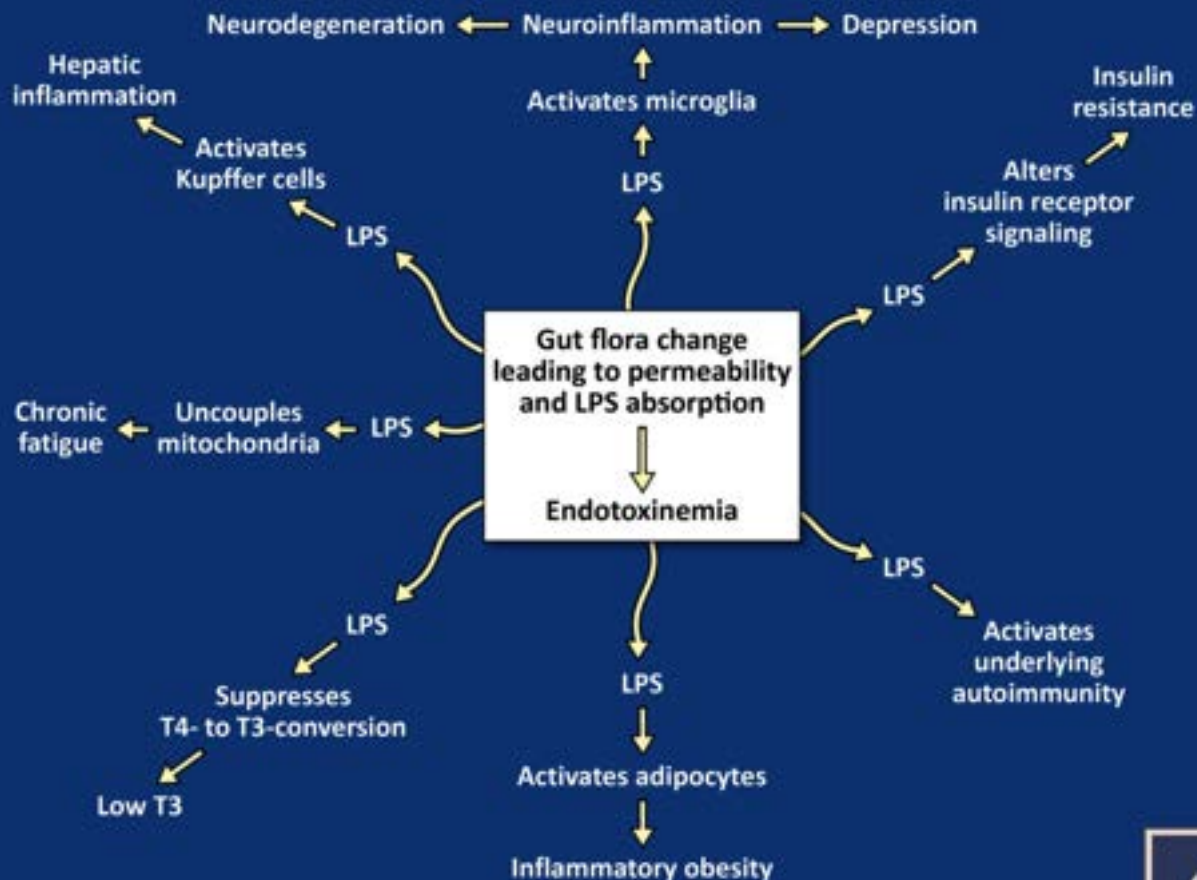
Starring roles for astroglia in barrier pathologies of gut and brain.



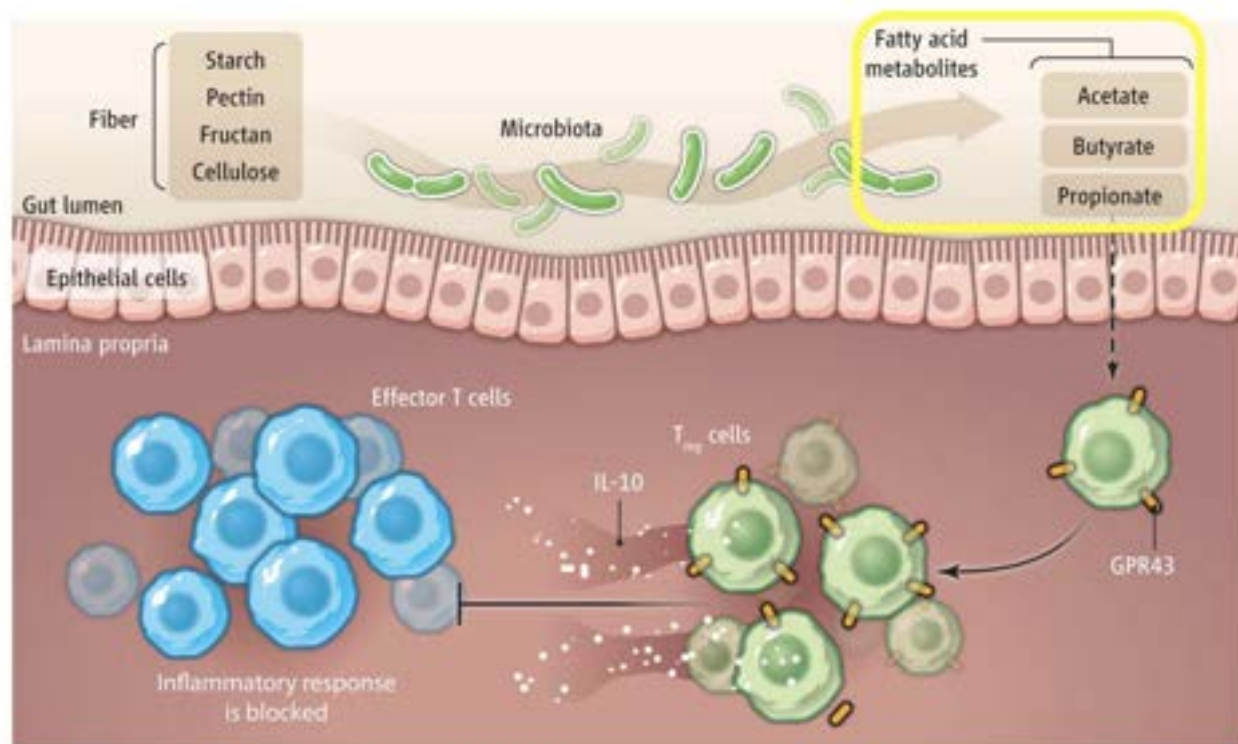


From Leaky Gut to Immune System Disorder to Leaky Brain and Neuroimmune Disorders

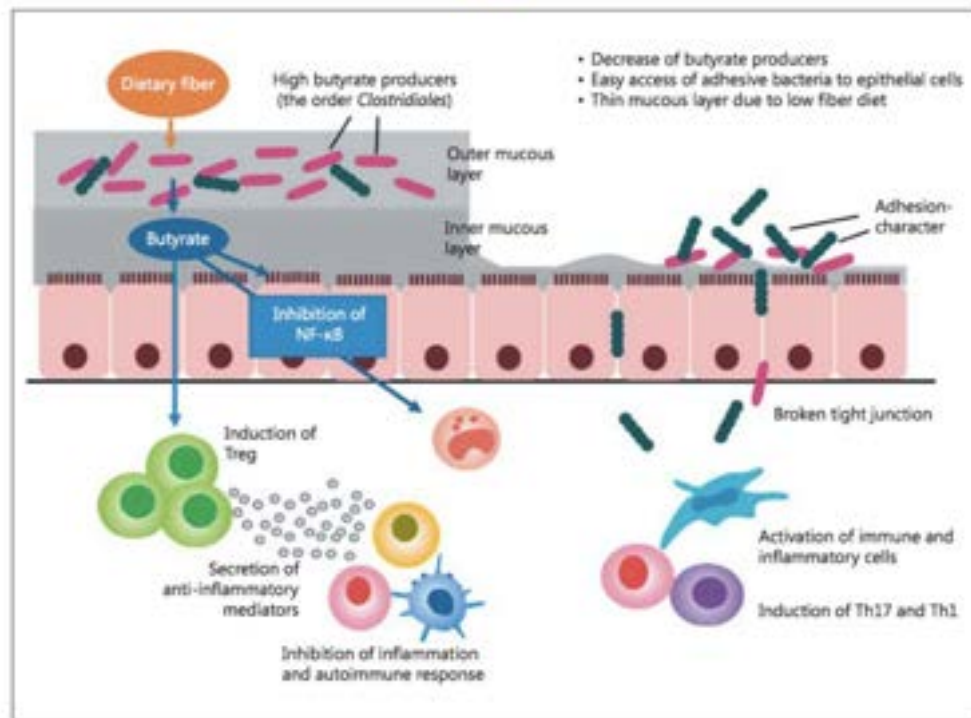




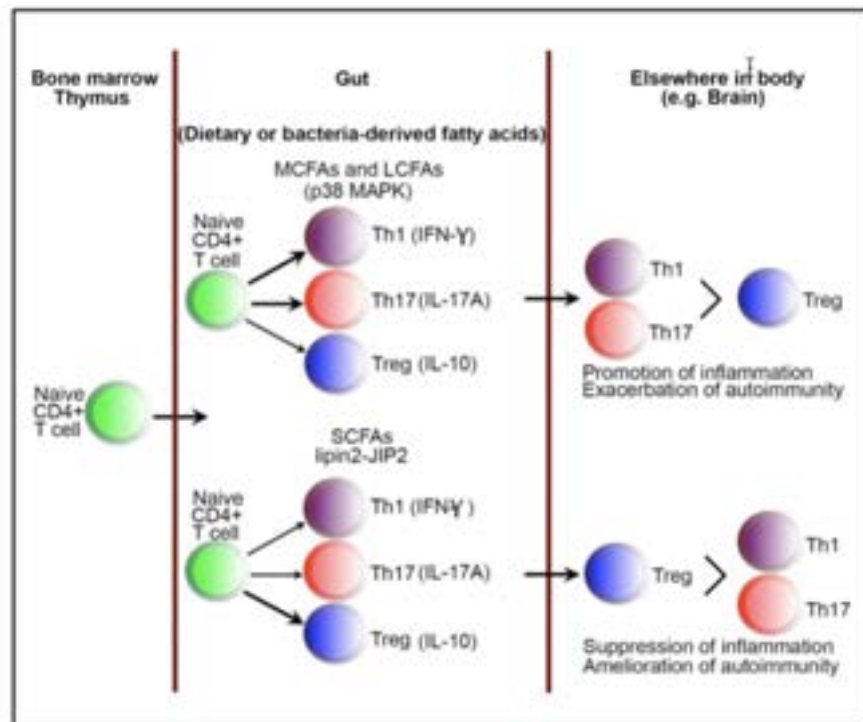
Science. 2013 Aug 2;341:463-464.
Feed your T-regs more fiber.



Physiological Role of Gut Microbiota for Maintaining Human Health



Short, but Smart: SCFAs Train T Cells in the Gut to Fight Autoimmunity in the Brain.



KEY NUTRACEUTICALS TO SUPPORT INTESTINAL PERMEABILITY

- Butyrate, Acetate, Propionate (SCFAs)
- L-Glutamine
- Deglycyrrhizinated Licorice
- Marshmallow Extract
- Slippery Elm
- Gamma Oryzanol
- MSM
- Spanish Moss Extract
- Chamomile Extract
- Calendula Extract

*These nutraceuticals are used to support intestinal health and are not drugs



Help for microbiome, tolerance, Gut/brain

Microbiome mashup

Not matter how much - but diversity!

Sherataki noodles with avocado, OO, AO and more

SCFA (even preventatively) - more powerful than L-glutamine**

1-2 weeks later - add in other polyphenols

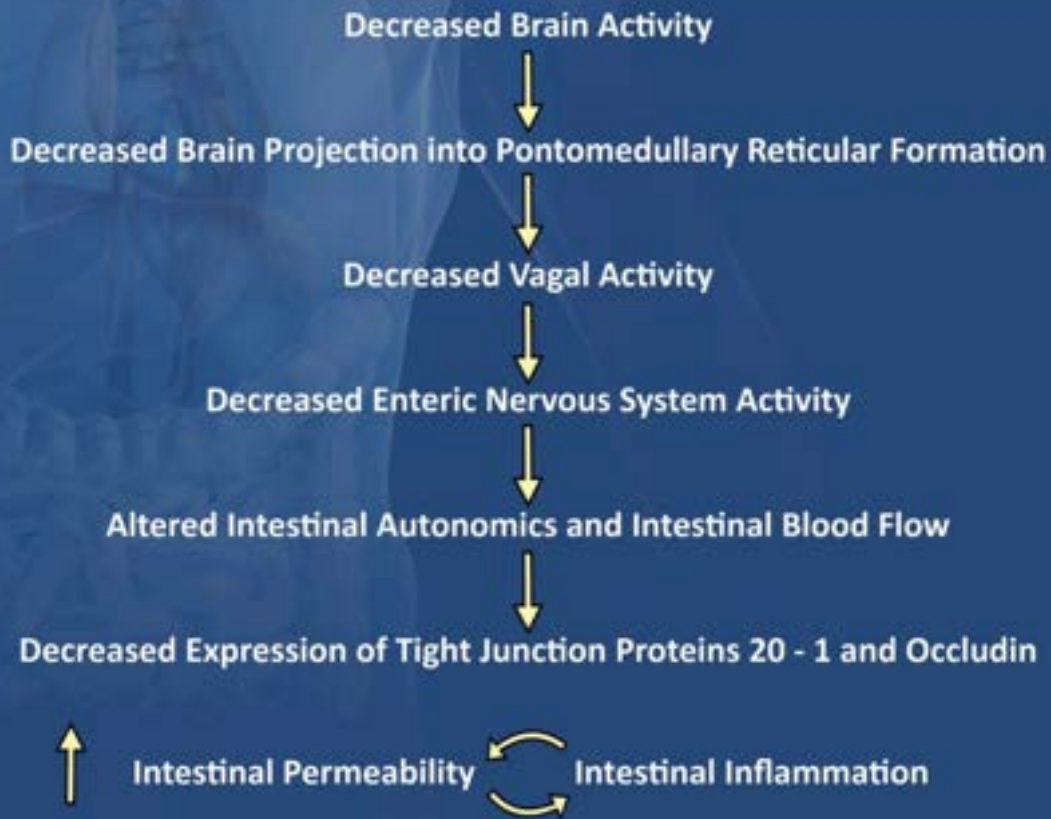
SCFA actually help build tight junction proteins (L glutamine does not)

MECHANISMS FOR LEAKY GUT

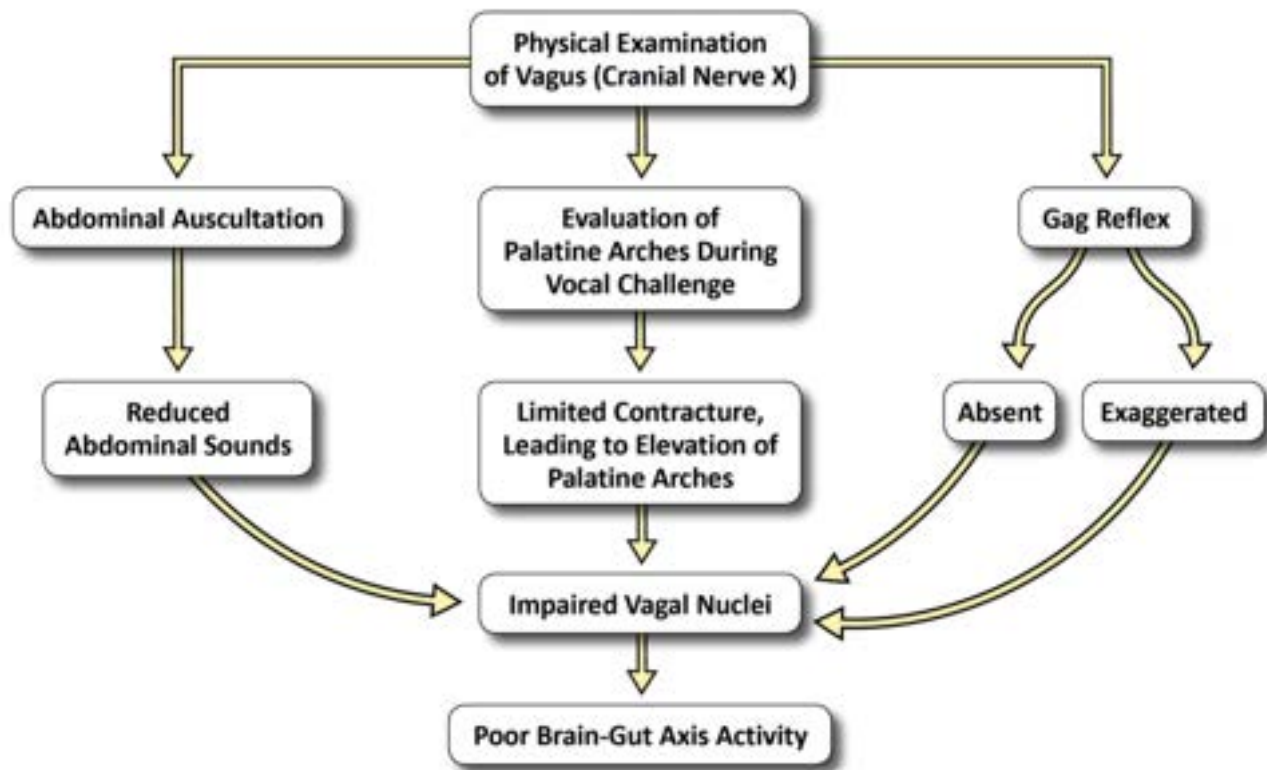
Diet	Medications	Infections	Stress	Hormonal	Neurologic	Metabolic
<ul style="list-style-type: none"> • Alcohol • Gluten • Casein • Processed Foods • Excess Sugar • Fast Food 	<ul style="list-style-type: none"> • Corticosteroids • Antibiotics • Anti-acids • Xenobiotics 	<ul style="list-style-type: none"> • H. Pylori • Bacteria Overgrowth • Yeast Overgrowth • Intestinal Virus • Parasitic Infection 	<ul style="list-style-type: none"> ⚡ Cortisol ⚡ CRH ⚡ Catecholamines 	<ul style="list-style-type: none"> ⚡ Thyroid ⚡ Progesterone ⚡ Estradiol ⚡ Testosterone 	<ul style="list-style-type: none"> • Brain Trauma • Stroke • Neurodegeneration 	<ul style="list-style-type: none"> • Glycosylated End Product • Intestinal Inflammation • Autoimmune



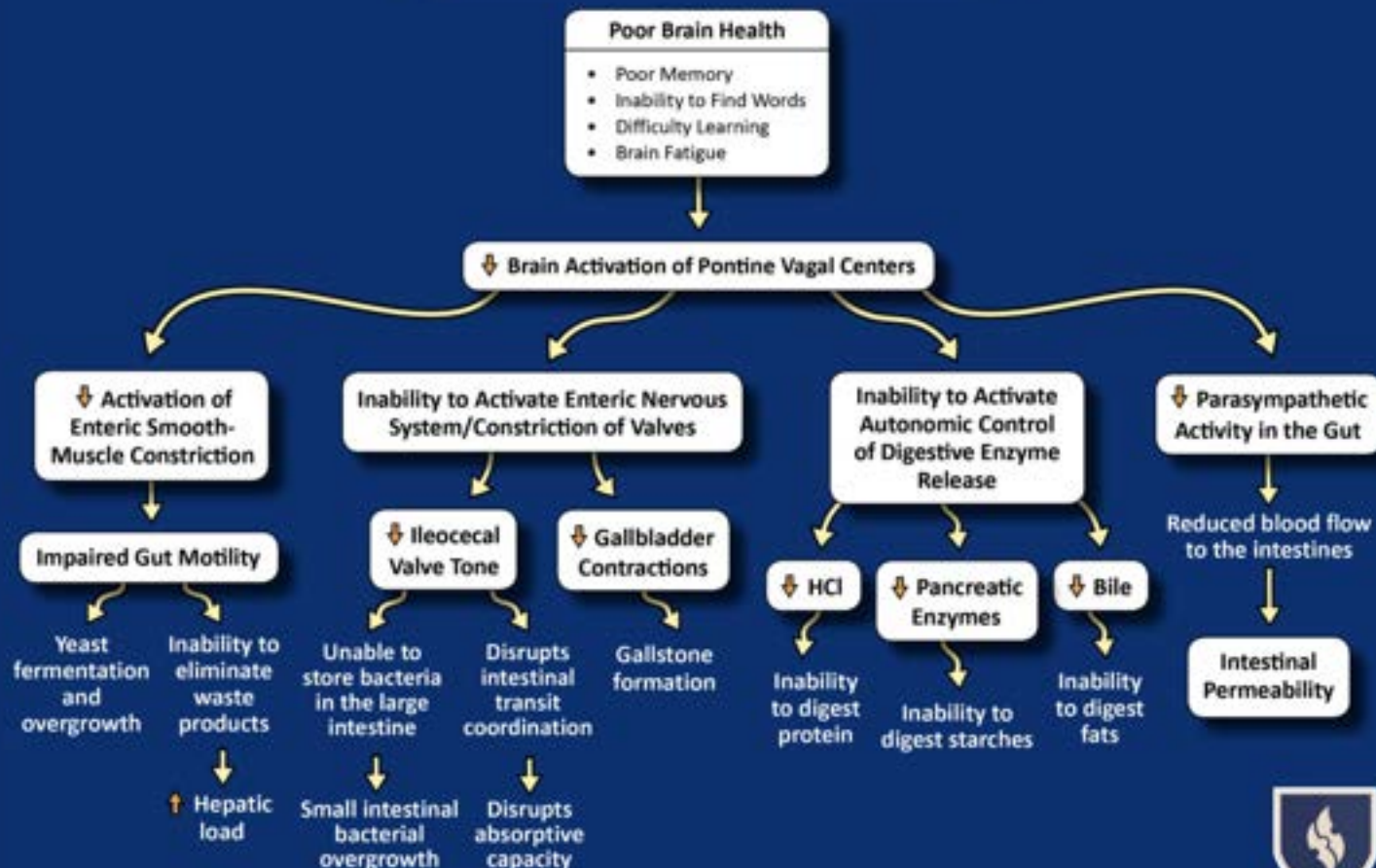
BRAIN/LEAKY GUT MECHANISMS



EVALUATING VAGAL INTEGRITY



BRAIN-GUT AXIS DISRUPTION



ACTIVATING THE VAGAL NUCLEI

Gargling With Water

Gag Reflexes on Back of Tongue

Singing Loudly to Raise Palate

Coffee Enemas



Activate Vagal Nuclei



Increase Postsynaptic Activation
of the Enteric Nervous System



↑ Motility

↑ Sphincter Contraction

↑ Digestive Enzyme Release

↑ Blood Flow to the Intestines

