

# Neuroinflammation

## Part 1

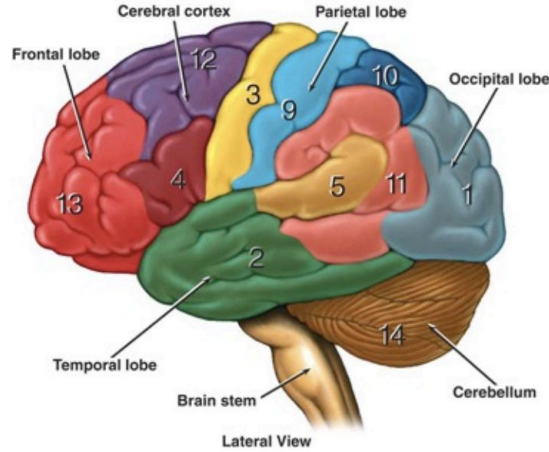
# Anatomy and Functional Areas of the Brain

## Functional Areas of the Cerebral Cortex

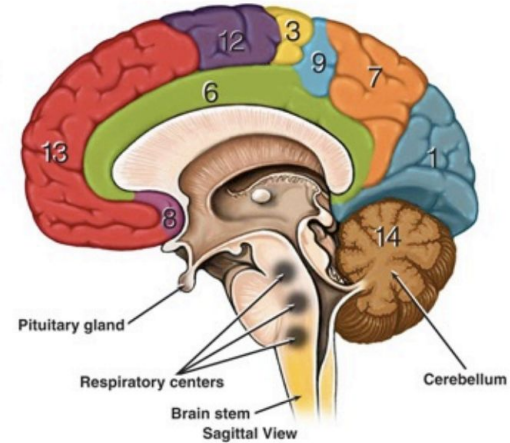
- 1 **Visual Area:**  
Sight  
Image recognition  
Image perception
- 2 **Association Area**  
Short-term memory  
Equilibrium  
Emotion
- 3 **Motor Function Area**  
Initiation of voluntary muscles
- 4 **Broca's Area**  
Muscles of speech
- 5 **Auditory Area**  
Hearing
- 6 **Emotional Area**  
Pain  
Hunger  
"Fight or flight" response
- 7 **Sensory Association Area**
- 8 **Olfactory Area**  
Smelling
- 9 **Sensory Area**  
Sensation from muscles and skin
- 10 **Somatosensory Association Area**  
Evaluation of weight, texture, temperature, etc. for object recognition
- 11 **Wernicke's Area**  
Written and spoken language comprehension
- 12 **Motor Function Area**  
Eye movement and orientation
- 13 **Higher Mental Functions**  
Concentration  
Planning  
Judgment  
Emotional expression  
Creativity  
Inhibition

## Functional Areas of the Cerebellum

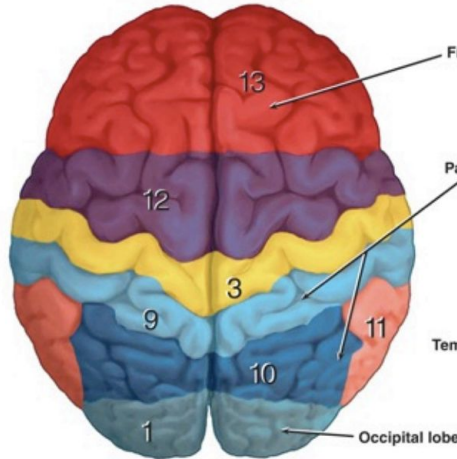
- 14 **Motor Functions**  
Coordination of movement  
Balance and equilibrium  
Posture



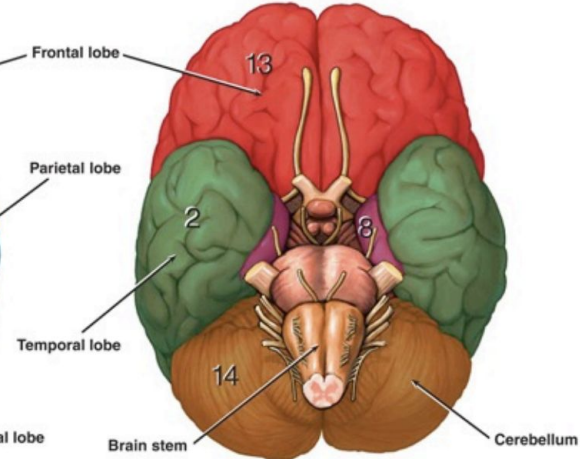
Lateral View



Sagittal View



Superior View



Inferior View

# Brain Areas

- Frontal cortex (13)
  - Executive function
  - Who a person is - personality
  - Motivation, drive and focus
- Broca's area (4) - Motor speech - in the left side
  - Full lesion - can't produce words
  - Motor part of speech
  - "The thought of speech is exhausting"
- Frontal eye motor function area (12)
  - Eye movements - check speed
- Motor strip (3) - motor on opposite side
  - "Tone" - check passive ROM. Stiffness in areas of lesion

# Brain Areas

- Parietal somatosensory (9)
  - vibration, pain, joint proprioception, pinprick
- Somatosensory Association Area (10)
  - Interprets the information from 9
  - Tells where the body is in space, textures, object recognition
- Association area (temporal) (2)
  - Olfactory, auditory, ST memory
- Occipital (1)
  - Visual pathway
  - Rare to be affected in neurodegenerative disorders
  - More often lack oxygen does damage
  - Floaters, loss of fields

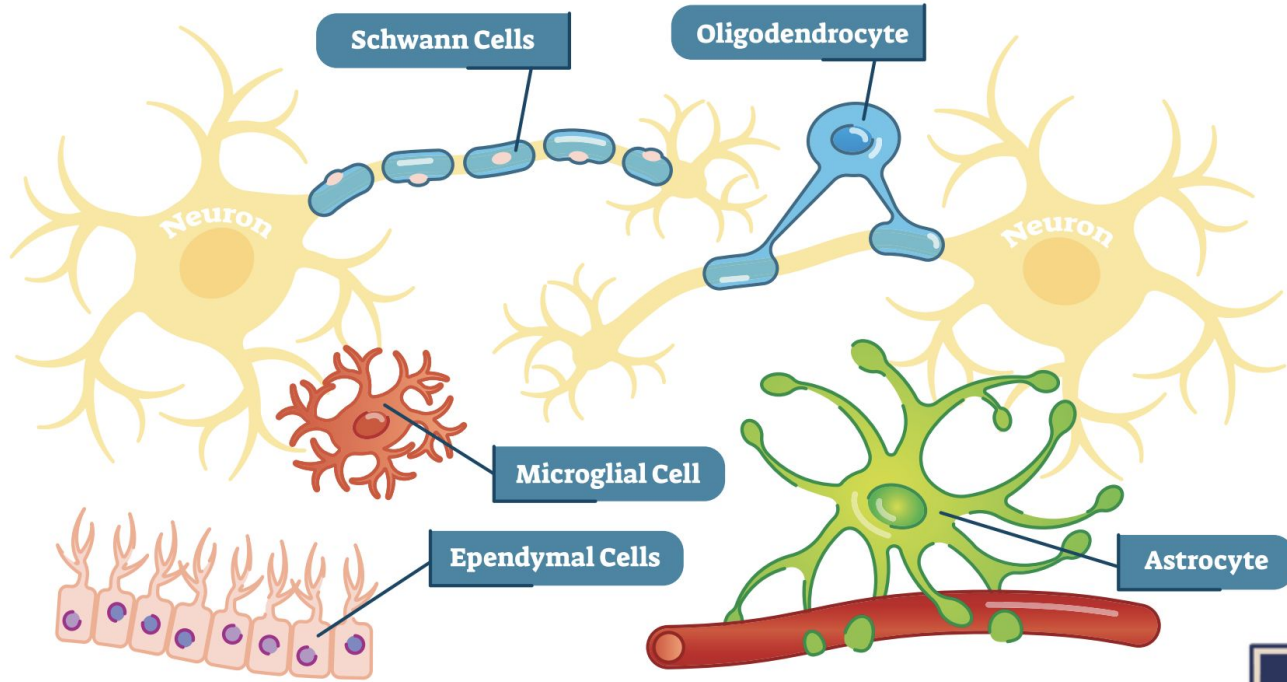
# Brain Areas

- Brainstem
  - Autonomic centers
- Corpus Collosum
  - Connects the two hemispheres
- Hypothalamus
  - Endocrine system
- Limbic (6)
  - Emotional response
  - Often unconscious patterns
- Cerebellum
  - Calibration/motion/movement
  - Common to degenerate with gluten (ataxia) and alcohol
  - Positive Romberg, ataxia

# Brain

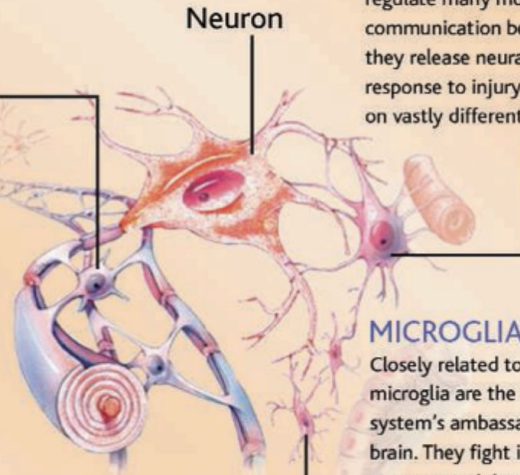
- 90% is glial cells
- 10% neurons
- We hear everything about the white matter and neurons
- Glial cells are hugely important!
  - Affected by lifestyle factors
  - Have major activity in the brain!
- Brain cells are not like liver cells or other cells. They do not regenerate.
- There is plasticity within the brain - but not new cells.
- “Use it or lose it”
  - If you don’t use a cell and there are active destroyer cells nearby - it will destroy it
  - Neurorehab is important! We need to activate those injured areas of the brain

# Glial Cells



## OLIGODENDROCYTES

These cells provide the fatty myelin sheaths that insulate axons, the long extensions that convey signals from one end of a neuron to the other. When they die off, as in multiple sclerosis, neural communication breaks down.



Neuron

## ASTROCYTES

The most mysterious glia, astrocytes have many roles in the brain. They are integral parts of synapses, where they regulate many molecules important for communication between neurons, and they release neural growth factors. In response to injury, however, they take on vastly different personae.

## MICROGLIA

Closely related to macrophages, microglia are the immune system's ambassadors to the brain. They fight infections, but in response to injury, they release a slew of compounds that may damage neurons.

# Glial Cells

- Schwann cells - coat the nerves with myelin (makes faster transmission)
  - Peripheral nervous system
  - Impacted by MS, demyelinating conditions
- Oligodendrocytes - Myelin sheath production
  - Central nervous system
- Astrocytes - 10-15%
  - Many roles - new ones being discovered
  - Part of the BBB
  - Clean out synaptic clefts
  - Dictate blood flow to neurons
  - Overall Ca ion balance
  - Lose these - don't come back → can't keep BBB intact (inflammation/OS)

# Microglial Cells - 17-20% brain

- Scavengers of the brain
- Go around and get out dead cells, particles, debris, plaques and tangles
- Have arm like projections and move around - constantly on the look out and cleaning up
- These cells are key to get rid of bad proteins (so they don't trigger an immune response) or build up
- Produce BDNF and GF's to help brain health
- Very sensitive to oxygen, stress, and injury

# Glial cells

- So much more than “glue:
- Astroglia have recently been shown to make the neurons work!!
- We have a limited number of them and when there is NI - they die and we won't get more
- Chronic NI = loss of astrocytes
- This is why we need to correct NI as early as we can!
  - Late stage dementia and loss of cells - ? improvement
- Einstein - profoundly high astroglial cells (learning, memory)
- Gut messenger pathways - can directly activate astrocytes

# Main things that impact the brain

- General inflammation - neuroinflammation (NI)
- Microglial Priming
- Breaches in the blood brain barrier
- Autoimmunity to brain cells and areas
- Vascular insults (low oxygen, clotting, etc..)

Trauma, LD, Autism, seizures, Depression and anxiety, and more fall under those

# Brain Inflammation/Injury

- Symptoms will depend on area affected
  - Not a headache (vascular)
  - No pain fibers in the brain
  - So we don't know when we have inflammation besides loss of function s/s
    - Depression, lack motivation, fatigue
- Can be transient, chronic, primed or autoimmune
- Systemic inflammation will create brain inflammation
- Gut inflammation and leaky gut will create brain inflammation
- May be a cause of chronic pain
- If untreated - may lead to neurodegenerative disorders

# Brain inflammation

- Brain does not have a good anti-oxidant system
  - So good anti-oxidants and low oxidative stress is important
- Cognition and memory will be affected with NI
  - Nerve conduction speed goes down → brain fog
  - Astroglia are impacted (learning, cognition)
    - These can't monitor the synaptic clefts and clear neurotransmitters
    - We can get low or high NT's then
- Any seizure activity/disorder - is brain inflammation
- Bed wetting is often a brain related disorder

# Neuroinflammation Symptom Scale



- Brain fog (hazy thoughts and recall)
- Noticeable variations in mental speed
- Reduced brain endurance
- Brain fatigue after exposure to specific chemicals, scents or pollutants
- Brain fatigue after exposure to specific food proteins

- Depression
- Inability to concentrate especially for long periods
- Sleepiness
- Increased demand for sleep, must sleep 8 or more hours
- Lethargy/Fatigue
- Lack of motivation
- Loss of appetite
- Malaise and inability to be physically active

- Delirium/confusion/disorientation
- Dementia/personality/behavior changes
- Coma
- Seizures
- Difficulty speaking
- Trembling, tremors, involuntary twitching



# Decreased Brain Endurance

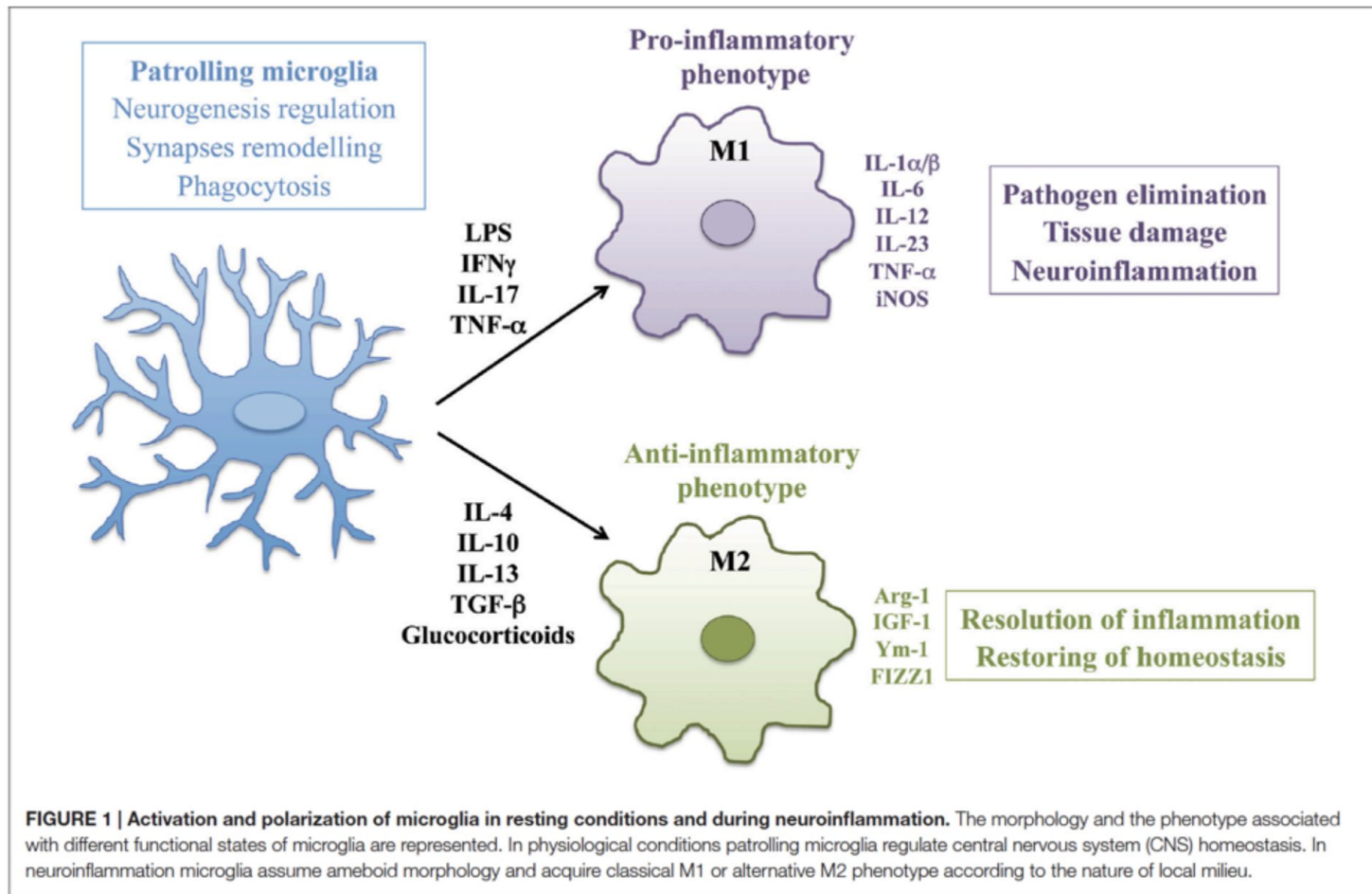
- With inflammation and glial cell activation - this creates inflammatory mediators
- These uncouple the mitochondria (energy producers of the cell)
- This results in decreased ATP (energy)
- This slows the brain and decreases endurance
- Decreased ATP available means that when it is gone - it's gone
- Uses up a lot of glucose → hypoglycemia
- Many can do an activity - but tire quickly
  - Drive - but not more than 1 hour, read but not more than a chapter
- This low endurance comes before complete loss of function

# Moderate neuroinflammation

- AKA Sickness behavior syndrome
- Often due to priming
- These symptoms create a syndrome that may come and go
  - After a trigger
    - influenza put me in bed a week after I was sick
    - Stressful situation - made it through and then crashed hard
  - May be chronic if NI is significant enough (more on a daily basis)
- We want to catch in the subtle and neuro stages to prevent neurodegenerative diseases
  - “I can’t think well”
  - “Can’t work full days
  - Depression and anxiety

# Microglial Activation and Priming

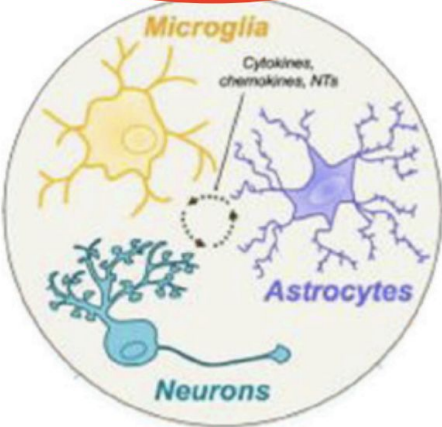
- When the brain and microglia are healthy - they are in the “rest” state
- They have arm like projections and go around and scavenge.
- They are needed for neuroplasticity, development, pruning and more.
- When they become injured and activated - they become “primed”
- They lose the arm like projections and are not able to move to scavenge
- So they are stuck in one area - eating proteins and causing destruction
- They are also not out scavenging other areas - so those areas can get build-ups
- These NEVER go back to normal - brain is forever changed
- They are either in an M1 - inflammatory/destructive state or M2 - anti-inflammatory state



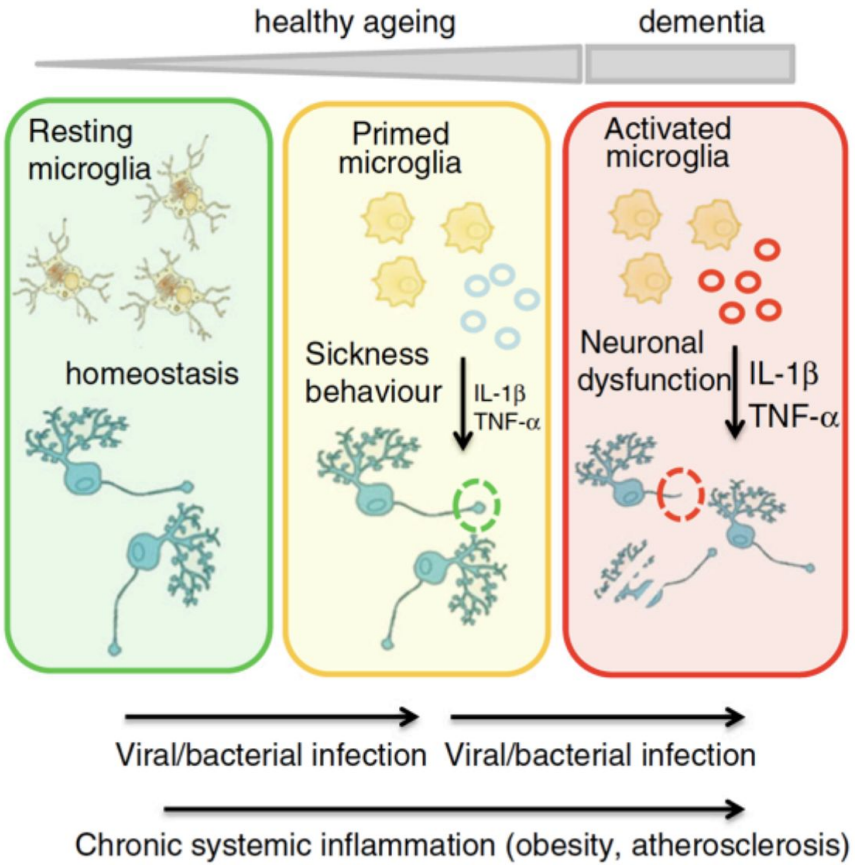
# What causes Priming?

- Significant injury
  - Trauma to the head
    - Impact not all that matters
    - Many factors prior also affect this
    - Any loss of consciousness is significant!
  - Severe psychological trauma - PTSD
  - CVA/TIA (any vascular injury) - white matter hyperintensities
  - Hypoxia
  - In utero factors - infection (autism, significant learning disabilities)
  - LPS (from a damaged gut barrier)
  
- Autism and severe learning issues - they have glial cells primed

Neuron-Glial interactions keep microglia in a down-regulated state



changes in microenvironment  
=  
changes in microglia  
adaptive/maladaptive



# Primed Cells

- Goals:
  - Not have more cells primed
  - Shift to an M2 state (anti-inflammatory state)!!!
- Many are stuck in M1 - pro-inflammatory state
- Extremely reactive to any peripheral activation
  - Stress, foods, and more
- Example - RA person - will get brain symptoms with RA flares
  - Systemic inflammation will set off primed cells
- Need to look into AI with primed cells (esp brain Ab's)

# Primed Cells

- Once you have primed cells - they are always ready
- With a seemingly trivial trigger - they reactivate
  - Generally an immune type trigger
    - Virus or infection
    - Food proteins
    - Excess stress
- Get a “second” hit (Or 3rd,4th,etc..)
  - Become non-functional after the trigger (exaggerated response to the trigger)
  - Significant loss of brain function
  - Depression, fatigue, lack of motivation, can't get out of bed
  - May feel like your body is heavy, may get increased neuropathic pain, or other neuro symptoms
- These will go away - come back - go away - come back.    MRI normal!

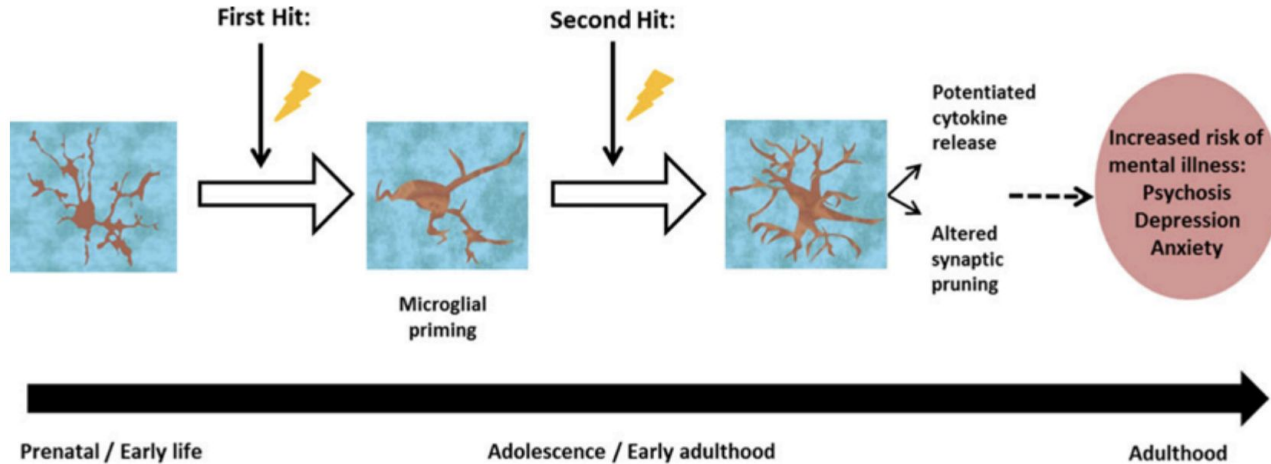
# Primed cells

- Common time we see primed cells
  - Elderly with bladder or other infection - they will get very confused (even with good BBB)
- Example- eating food - see floaters (occipital area primed)
- Trigger → right arm to feel heavy (motor strip priming)
- Eat gluten or stressful event → No motivation, heavy brain fog (frontal primed)
- 2nd hits (and more) after priming - create clinical signs
- We will see unique symptoms with priming based on the area of priming
- We will see chronic intermittent loss of brain function or patterns of sickness behavior.

# Other mechanisms to activate and prime cells

- Hypoxia
- Chronic infections
- Increased OS and AGE's
- Pre-DM and anything metabolic
- Systemic inflammation (even with intact BBB) - up the vagus nerve
  - So increased CRP = brain inflammation
  - Vagus in the gut is stimulated -> gut inflammation and LPS up the vagus → brain inflammation
- Aging alone - physical and brain activity determine how much age priming occurs
  - “ I react to stress now - I used to be able to handle it””
  - “ I never had a reaction like this before”

# Basic Concept of Microglia Priming



# Primed cells

- Once cells are primed - they will always be primed
- But...we can get them into an anti-inflammatory state (M2)
  - This is how we work towards recovery
- Chronic prednisone shuts both pathways down (M1,M2)

## MOST COMMON CAUSES OF MICROGLIA PRIMING

### Younger Adults

< 60 years old

- Traumatic Brain Injury
- Neurological Autoimmunity
- Infection (Viral, Bacterial, Spirochete, etc.)

### Older Adults

> 60 years old

- Traumatic Brain Injury
- Age-Associated Priming
- Silent Stroke



# Clinical Pearl

- Chronic intermittent loss of brain function or patterns of “Sickness Behavior Syndrome” suggest microglia priming.



## MECHANISMS THAT RE-ACTIVATE PRIMED MICROGLIA

### Triggers

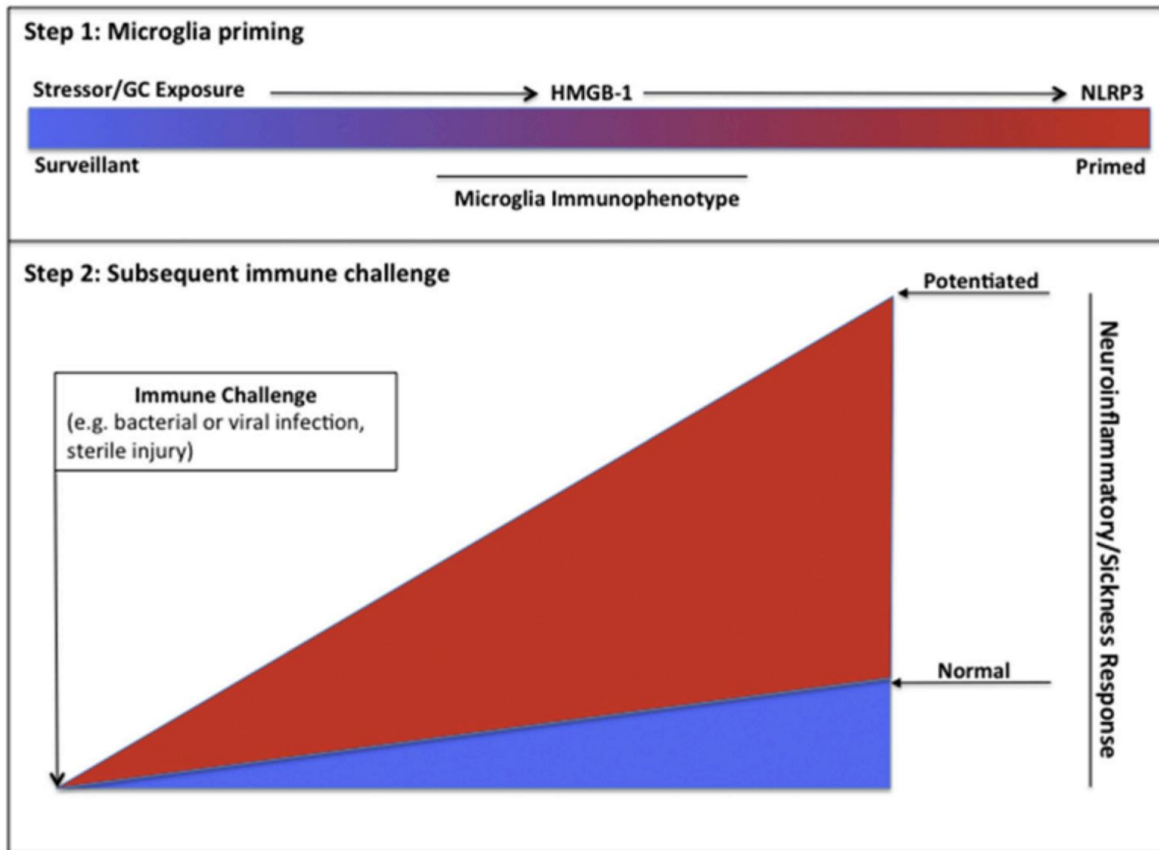
- Stress Response
- Lack of Sleep
- Overtraining
- Infection
- Dietary Protein Reaction
- Traumatic Brain Injury
- Environmental Immune Response



### Loss of Brain Function

- Depression
- Cognitive Decline
- Dizziness
- Tinnitus
- Discoordination
- Change in Behaviors/Personality
- Change in Speech
- Change in Muscle Tone
- Tremor
- Muscle Weakness





Stress-induced neuroinflammatory priming: A liability factor in the etiology of psychiatric disorders [Neurobiology of Stress 4 \(2016\) 62–70](#)



# Inflammation vs Priming

- Inflammation may worsen after a trigger
  - Seemingly benign trigger
    - Chemicals
    - Food
  - Slight symptoms - brain fog, headache, dizziness
- Priming
  - Usually after an immune type trigger
    - Food protein, infection
  - Significant loss of function

# CLINICAL SEVERITIES OF NEUROINFLAMMATION

Transient Neuroinflammation

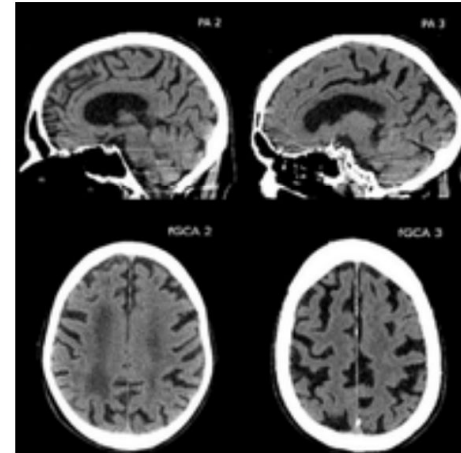
Chronic Neuroinflammation

Microglia-Primed Neuroinflammation

Neurological Autoimmunity



Neurodegeneration



# Severity

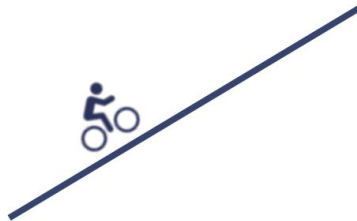
- **Transient**
  - Triggered by something - more good days than bad
- **Chronic**
  - Mostly bad days
  - Often underlying AI, etc..
- **Primed**
  - Immune trigger → overzealous response
    - Can't get out of bed, depressed, no motivation, neuro s/s
- **Autoimmune**
  - Neurological deficit (Romberg, nystagmus, weakness, numbness...)

# CLINICAL MANAGEMENT OF NEUROINFLAMMATION

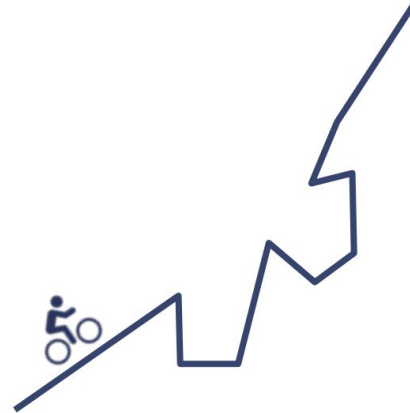
Transient  
Neuroinflammation



Chronic  
Neuroinflammation



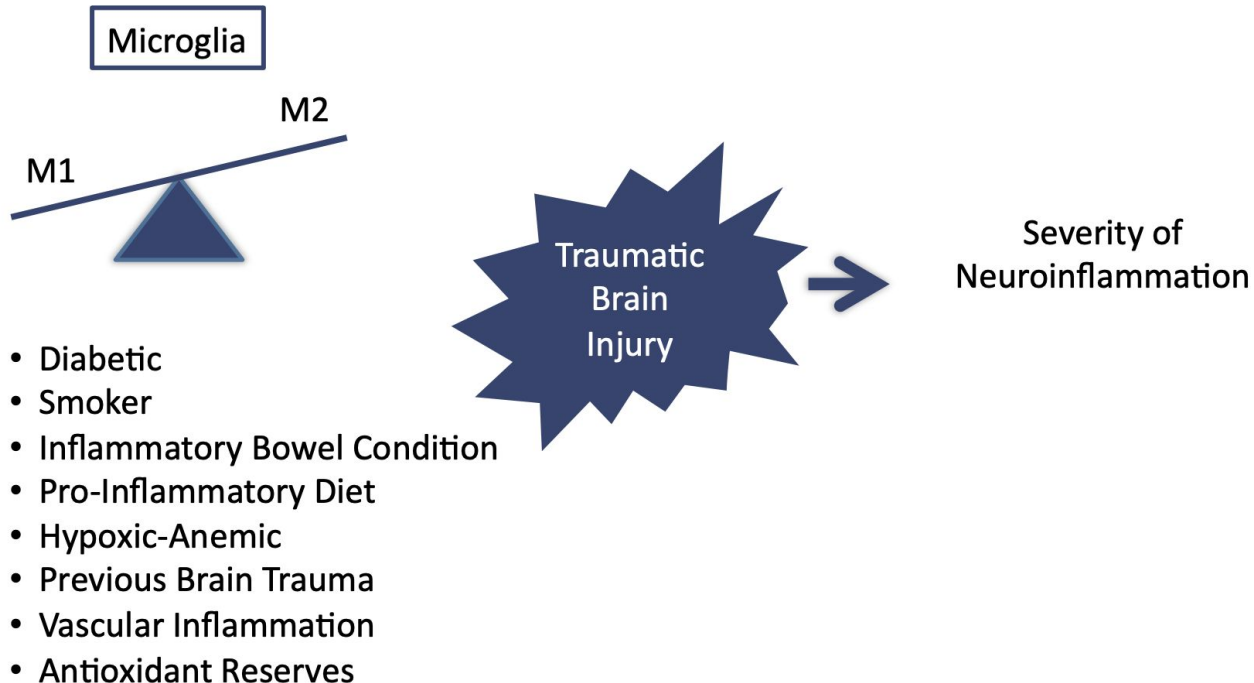
Primed Glia



# TBI

- Causes microglial priming
- Can show up years later. 5...10...20 years after
- Lose consciousness - it is a big deal!
  - Increased correlation with priming and degree of priming
- Factors at the time of the head injury make a big difference - not just the impact
  - Inflammation at the time of the injury matters
  - Oxidative stress at the time matters
  - Diet, smoking, stress, sleep, meds, and all the lifestyle factors
- All brain injuries cause increase in M1 and M2 initially
- At 2-3 months - M1 is still up
- If baseline M1 is high prior to injury - it can go really high and impact
- BBB opens up within 3-5 minutes

## VARIABLES THAT IMPACT BRAIN INJURY



# TBI

- Can create tau phosphorylation → Alzheimer's disease
  - More inflammation in and around a TBI - the faster tauopathy
- Can lead to chronic traumatic encephalopathy
  - See in NFL players
  - See personality changes → anger , rage
- Want to catch early (see chart)
- TBI also opens up gut barrier - may leave this vulnerable for many years
- Injures the brain structure itself - and then damage due to chemical mediators released
  - Decreased ATP → hypoxia.
  - Chemokines activate astrocytes - open up BBB. Immune system can get in.
  - Great acutely to clear debris - but can then develop AI and have cross reactions

# Chronic traumatic encephalopathy (CTE)

- See personality changes - anger and rage common
- I - asymptomatic
- II - rage, impulsivity, depression, focus and attention issues
- III - confusion and memory loss (LT memory loss)
- IV - dementia
- Often missed until later stages
- Sooner we treat the inflammation, slower the progression

# Symptomology of CTE

Symptomatology of CTE [8].

Cognitive features	Behavioural features	Mood features	Motor features
Memory impairment	Physical violence	Depression	Ataxia
Executive dysfunction	Verbal violence	Hopelessness	Dysarthria
Impaired attention	Explosivity	Suicidality	Parkinsonism
Dysgraphia	Loss of control	Anxiety	Gait
Lack of insight	Short fuse	Fearfulness	Tremor
Preservation	Impulsivity	Irritability	Masked facies
Language difficulties	Paranoid delusions	Apathy	Rigidity
Dementia	Aggression	Loss of interest	Weakness
Alogia	Rage	Labile emotions	Spasticity
Visuospatial difficulties	Inappropriate speech	Fatigue	Clonus
Cognitive impairment	Boastfulness	Flat affect	
Reduced intelligence	Childish behaviour	Insomnia	
	Socially inappropriate behaviour	Mania	
	Disinhibited behaviour	Euphoria	
	Psychosis	Mood swings	
	Social isolation	Prolix	

Chronic Traumatic Encephalopathy: The cellular sequela to repetitive brain injury



# CVA TIA White matter hyperintensities

- Just like in a TBI - an inflammatory cascade occurs when there is a lack of oxygen
- A forest fire of inflammation in the area of the CVA
- Then the CVA area heals - but NI is still on (especially with priming)
- Many may have silent strokes
  - Tinnitus, headaches, dizziness, grip strength decreased (all signs of NI)
- Even small infarcts prime glial cells
- RF: >60, hypertension, metabolic syndrome
  - Unmanaged stress, high BP in the am, CRP high, homocysteine high
  - ETOH, BMI high, CAD
- White matter hyperintensities - it is NI and neuronal injury

# Subtle Findings of Silent Stroke

- Dizziness
- Headaches
- Memory problems or other cognitive (thinking) problems
- Weakness in a limb (including loss of grip strength)
- Blurry vision
- Tremors
- Balance problems
- Problems with coordinated movements
- Extreme fatigue



# Other factors

- We cannot fix the BBB if there is hypertension
  - It damages the vascular endothelium → debris → neuroinflammation → opens the BBB
- Need to fix hypertension first
- Same with hypoxia, blood sugar dysregulation, etc..
- PTSD - treat from a NI model

# Brain and Gut axis

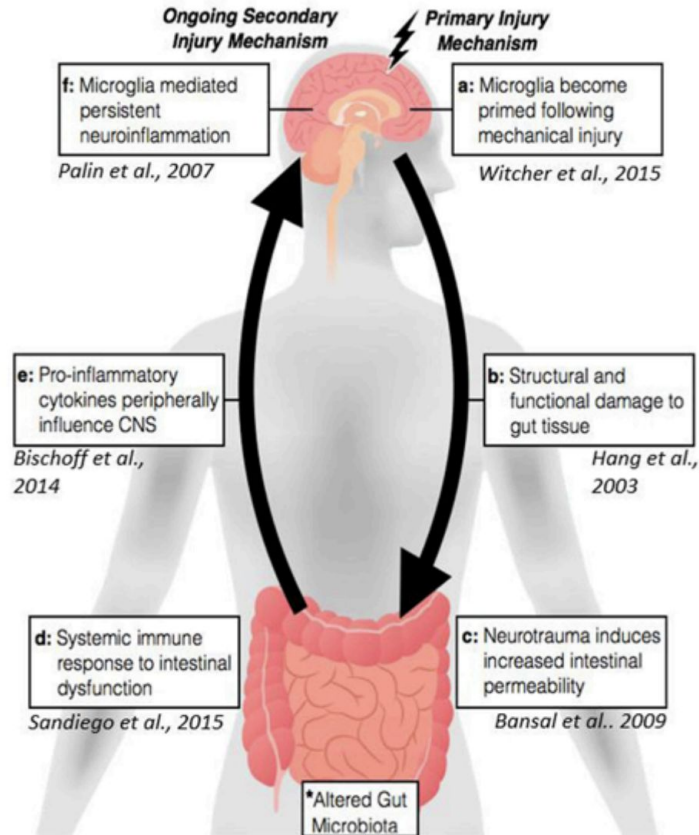
- Microglia are primed → vagus nerve carries the inflammatory cascade to the gut.
- Gut has microglia also (neural plexus)
- Within hours - the gut barrier can be breached and damaged
- Intestinal dysfunction → LPS → up the vagus to cause NI
- Many cases of leaky gut are due to NI/CTE
- Cannot fix it by fixing the gut alone - need to settle down the priming
- Fix the gut to fix the brain - fix the brain to fix the gut
- Supplements can't work if they are not absorbed due to gut damage
- Also need those to cross the BBB (target the microglial cells)

# TBI and the gut

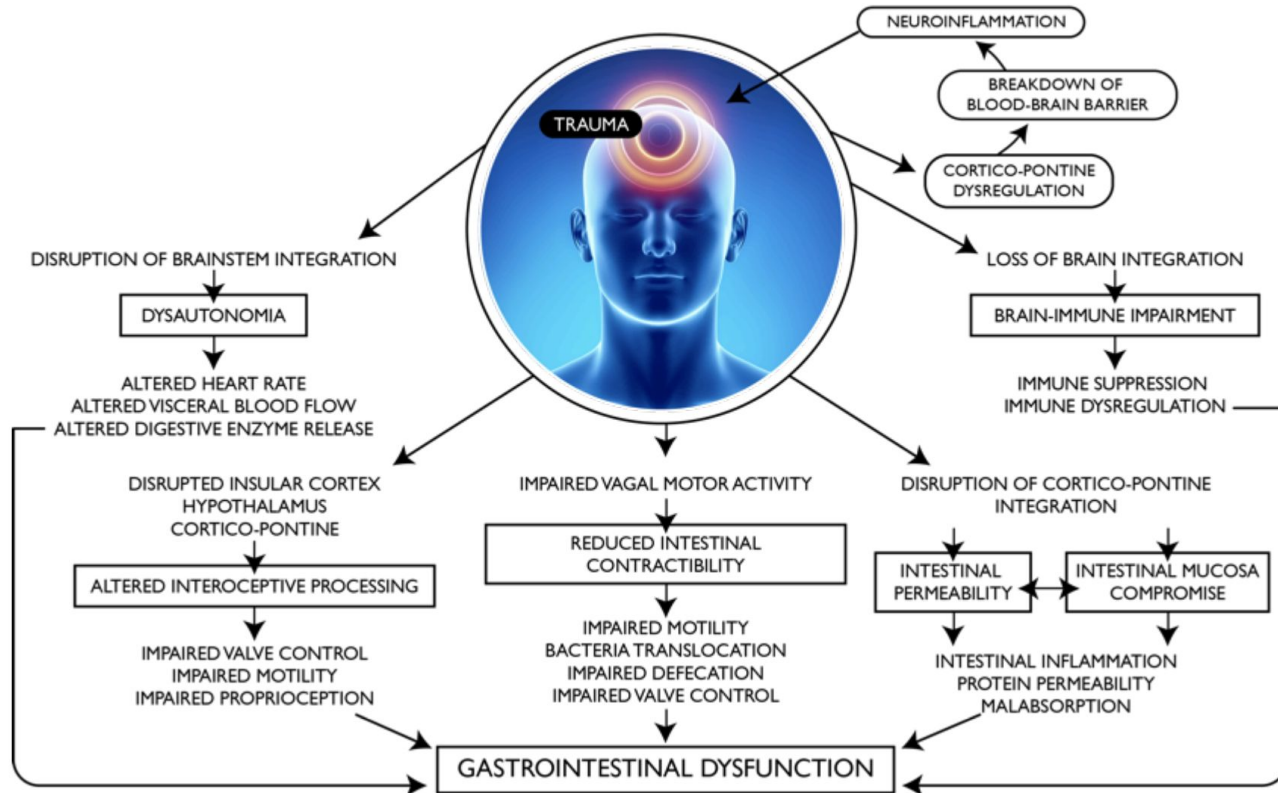
- TBI causes leaky gut and damage
- Can cause food sensitivity, SIBO and more
- Can cause the constipation and motility issues, enzyme issues

# The bidirectional gut-brain-microbiota axis as a potential nexus between traumatic brain injury, inflammation, and disease

Brain, Behavior, and Immunity 66 (2017) 31–44



# TRAUMATIC BRAIN INJURY MECHANISMS OF GASTROINTESTINAL TRACT



# GI Manifestations of NI

- Due to vagus nerve
- Gut dysmotility
  - Constipation
  - This is a huge clue to loss of gut/brain axis
  - Smooth muscle activity impacted
  - Likely priming
- Lose the ability to produce digestive enzymes
  - So we see yeast, dysbiosis and SIBO
- May have difficulty swallowing pills

# Other GI Issues

- With damage of the gut barrier - we lose mitochondria in the smooth muscle of the gut
- We can then see mucosal atrophy within a week
- Common reason for SIBO
- We will see neuroinflammation and priming in a SIBO patient!
- After injury - LPS will be released from the damaged gut → turn on glial cells
- Directly talk to astrocytes in the brain and can activate
- Liver, gut, both increase NI
- We will talk treatment - but SCFA and diversity -> increase T reg cells → decrease gut and brain inflammation

# Vagus Issues

- Vagal stimulation if these are issues
- Especially right after injury - but helpful anytime
- Gargle multiple times a day
- Tongue blades - gag
- Hum - “om” chanting style
- Face in cold water - or cold water plunges
- Coffee enemas (holding as long as you can)
- Fix the gut
- Fix the BBB