

Neuroinflammation

Part 2

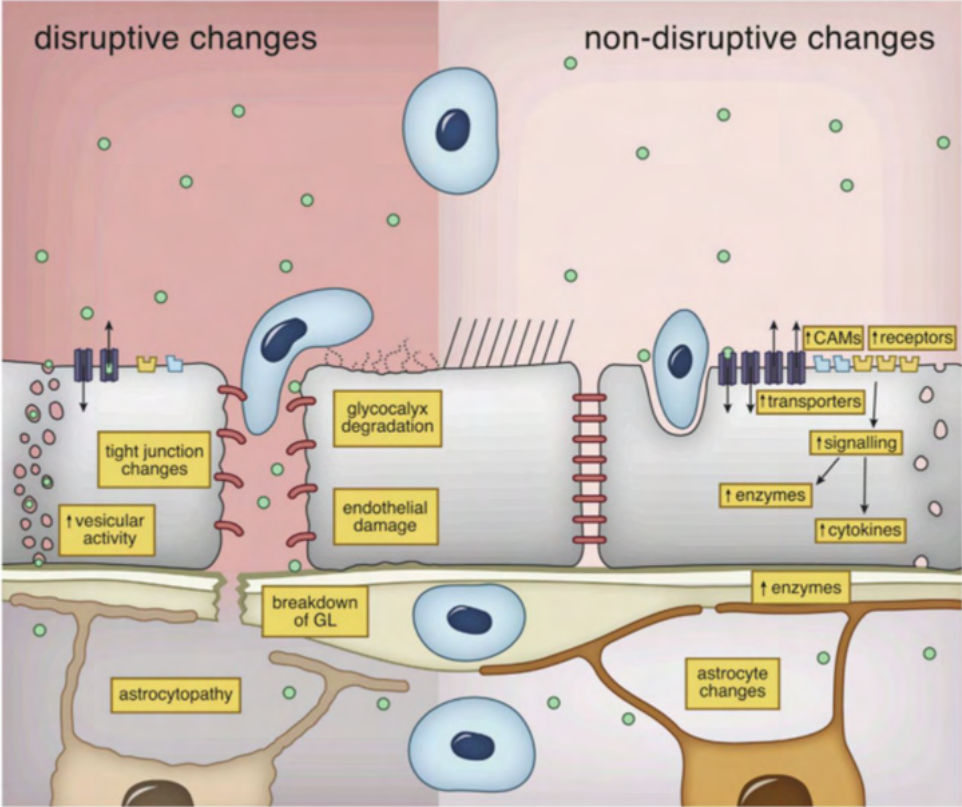
Questions to ask

- Subtle, moderate or severe
- Transient - comes and goes - more good days than bad
- Chronic - Always brain fog - a good day every once in awhile
- Primed - significant loss function with little triggers
 - Can seem like an AI flare
- Autoimmune - can see clinical evidence of this
 - Antibody testing
 - Babinski reflex
 - Double vision
 - Other hard neurological signs

Blood Brain Barrier

- Formed by blood vessels (endothelial cells), paracytes, and astrocytes
- Barrier between the rest of the body and the brain
- Many things in the body cannot pass the BBB (awesome protection)
- Many bacteria and viruses can't
- Antibodies can't
- Highly selective, semi-permeable
- We need this intact
- When leaky → many things can cross
 - Ab's, bacteria, other pathogens
 - This can be devastating!
 - Even worse with primed glial cells, BBB permeability and possible neuro AI!

Blood-Brain Barrier Permeability



BBB Permeability

- Pathogens: toxoplasmosis, lyme, Group B strep, Syphilis
- Proteins and peptides
- Antibodies - so now cross reactions as well as brain AI
- Can check this with BBB Ab's or S100B (labcorp, quest)
- We need to check integrity and healing of the BBB
 - PANDAS, cross reaction of foods, neuro AI occur
- Leaky BBB → ALS, epilepsy, systemic disease and more

BBB Permeability causes

- Oxidative stress
- Inflammation
- Head injury
- Gut leakiness
- LPS

Inflammation pathways (with an intact BBB)

- Hypothalamus has an exposed area where the immune system can interact
 - Immune system activates this - cytokines and messengers are made to turn on the ANS → stimulates the immune response → creates neuroinflammation
- Active transport across the BBB
 - Some cytokines and messengers can get across the membrane
 - So the peripheral immune system can activate the brain
- Vascular endothelium
 - Communication in the blood vessels with cells like RBC
 - Can produce GH, immune cells
 - Direct activation of astrocytes in the BBB
- Vagus nerve (bi-directional)
 - Input in the liver, gut microbiota → activate the brain
 - Includes hepatic biotransformation

Other information

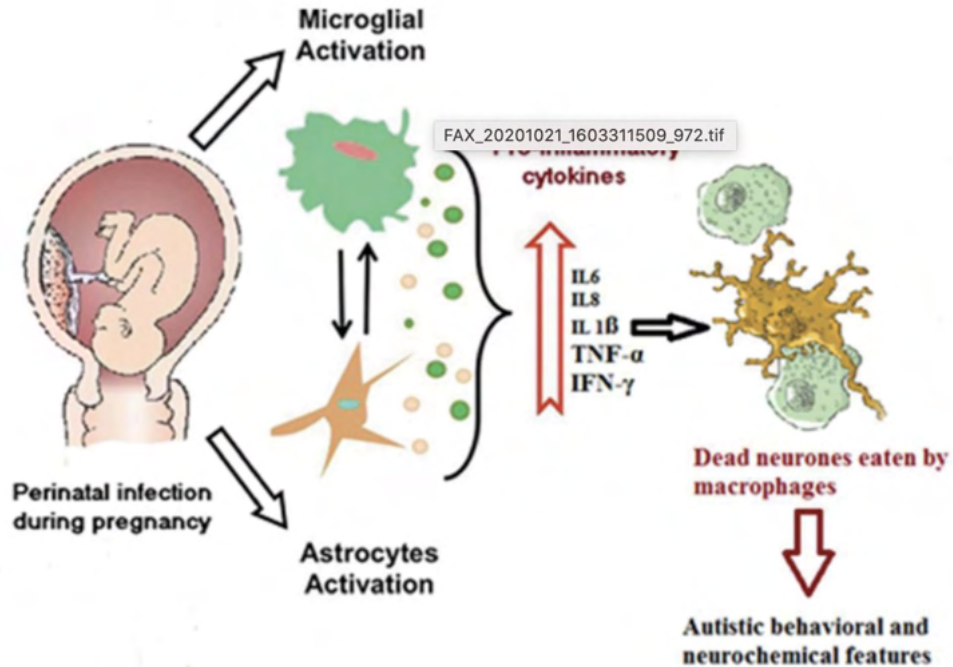
- Most of the brains neurons (90%) are there to inhibit the other 10%
- If we can't inhibit the other pathways - we can't handle input
 - Sound, light, movement
 - This is physiological - not psychological!
- So we end up with protocols for these pathways - not for every single disorder

Autism

- Neuroinflammation + glial priming
- Maternal inflammation passes to the baby
- Infections in pregnancy raise the risk
- AI, environmental and psychological factors increase risk
- So they are born with glial cells primed
 - Then they are exposed to toxins, stress, vaccines
- This creates a lot of inflammation - and glial cells are primed forever!
- Immune system reaches highest activity age 2-3
- So prenatal care targeting AI, inflammation is critical

Biomarkers-Directed Strategies to Treat Autism

Afaf El-Ansary and Hussain Al Dera



Development

- Neurons firing - cause them to develop and myelinate
- White matter develops until age 18/19 years old
- It is branching, moving, creating synapses, pruning
- Glial cells (resting) help to create and keep the good pathways
 - If primed - this has trouble
- Neurogenesis and migration depend on healthy glial cells
- If babies are born with primed cells → autism, neuropsychiatric issues, developmental delays, mental health issues

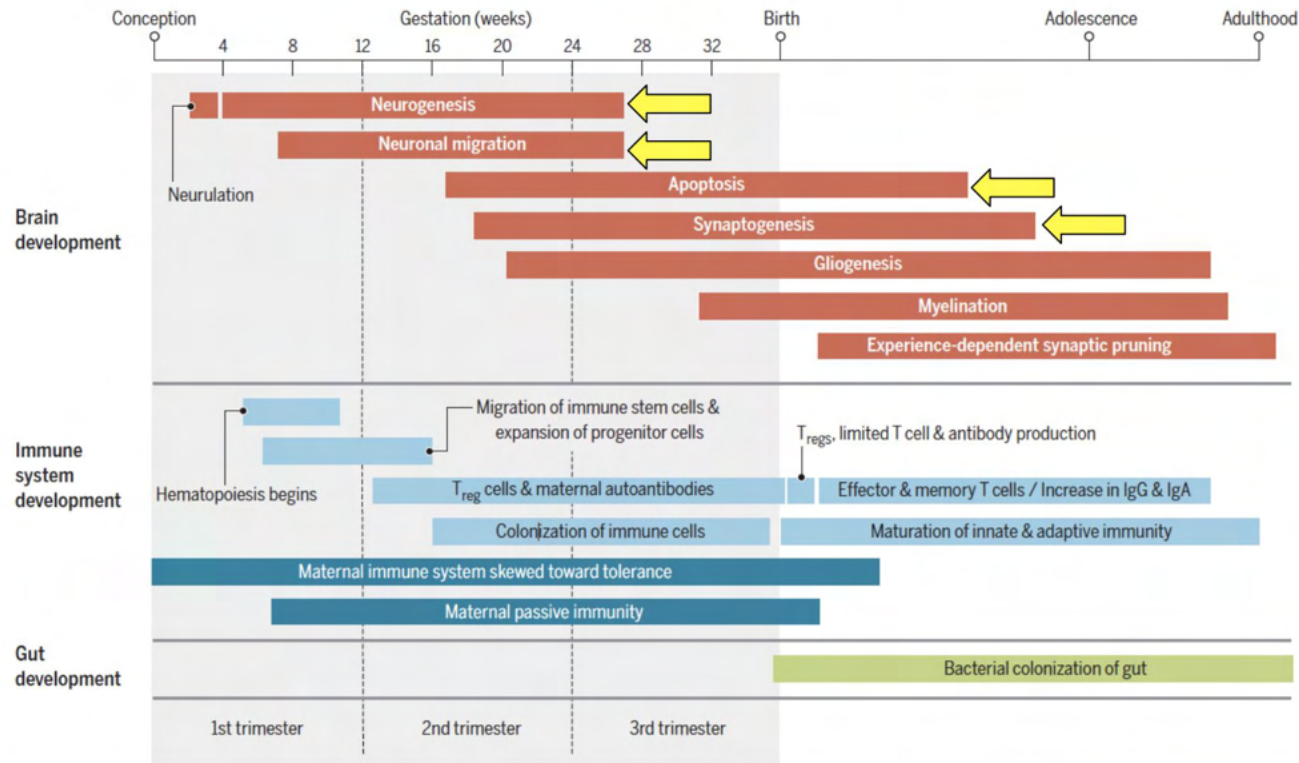


Fig. 3. Timeline of major events occurring in brain, immune system, and gut development from conception to adulthood (83–85).

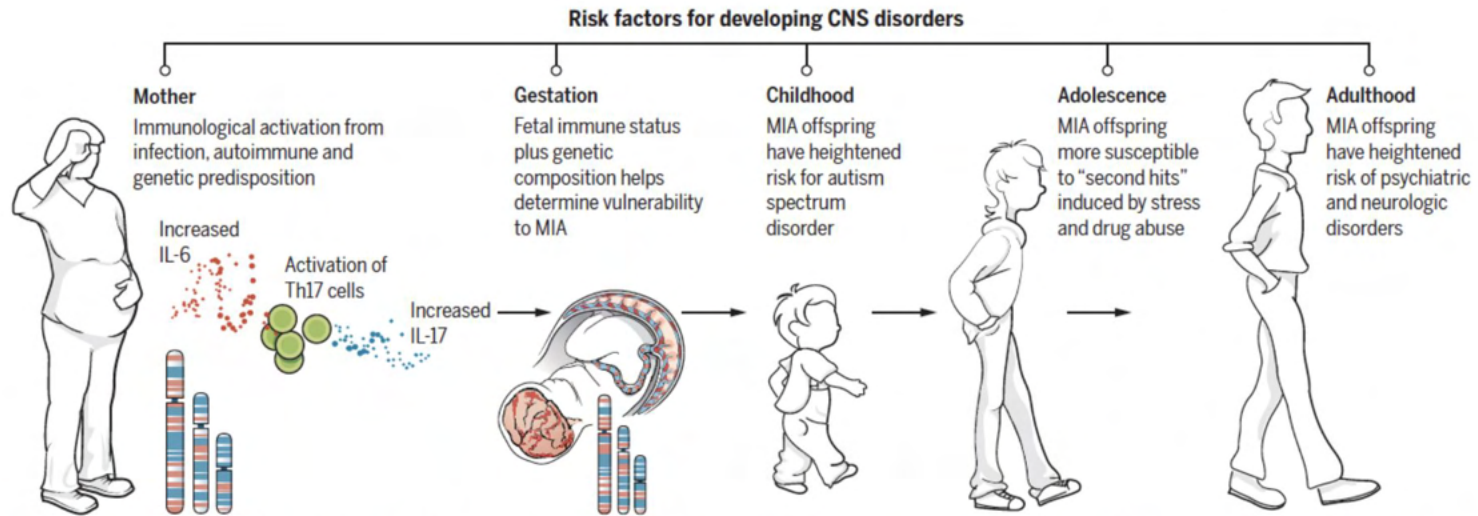
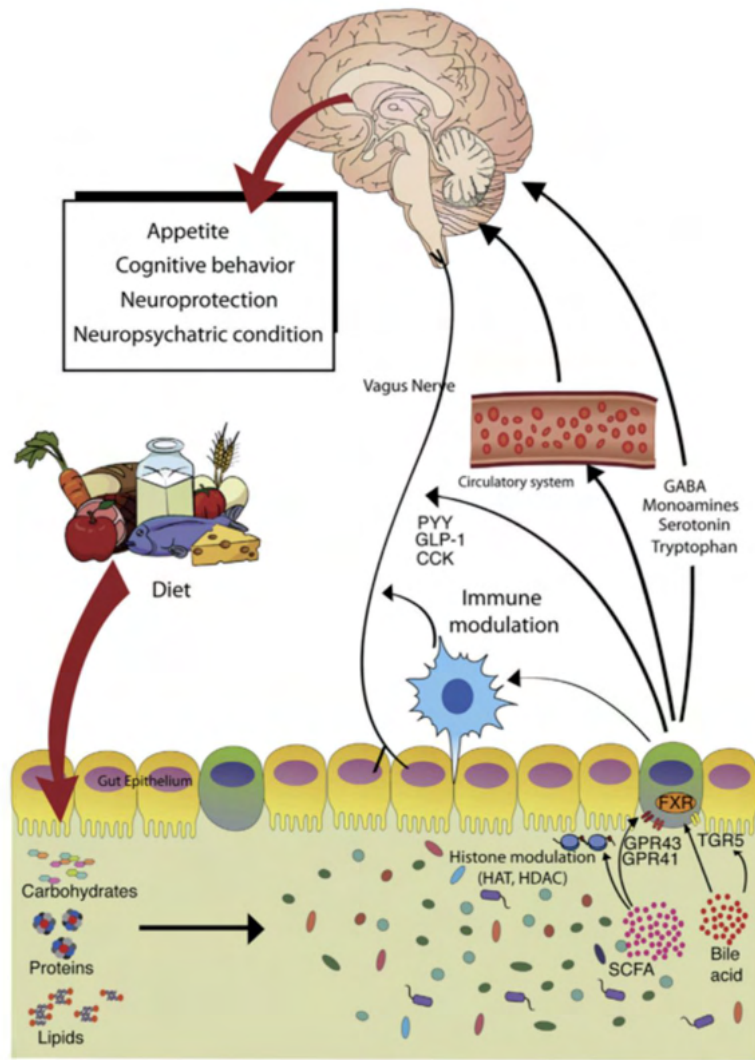
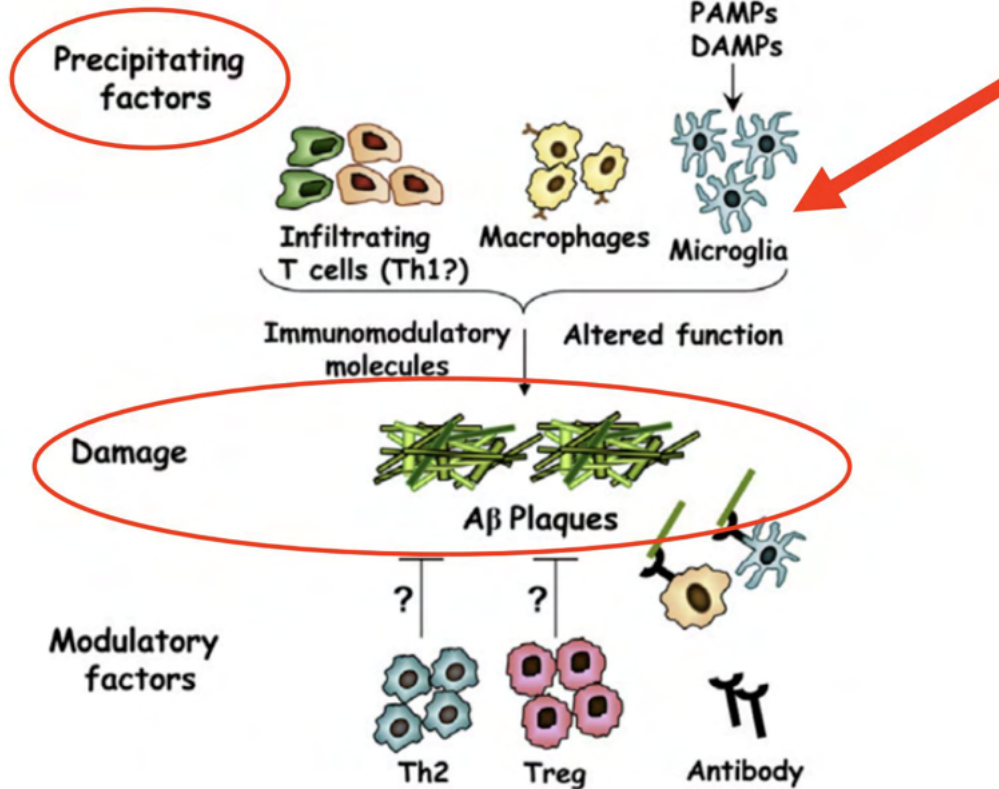


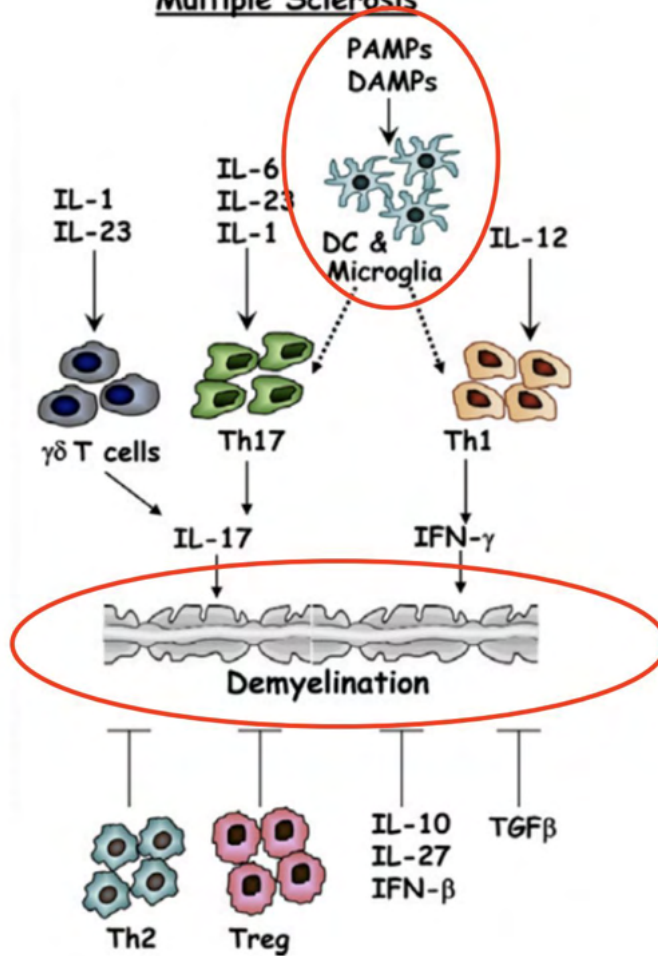
Fig. 1. MIA as a disease primer. This schematic depicts the current model for how MIA leads to psychiatric disorders in offspring. Infection leads to release of pro-inflammatory cytokines and activation of T_H17 cells in the mother's bloodstream (6, 19). A combination of genetic background, autoimmune status, and second hits during childhood and adolescence (including stress and drug abuse) combines with the consequences of maternal infection to increase the likelihood of offspring developing psychiatric disorders as adults (3, 6, 14, 37).



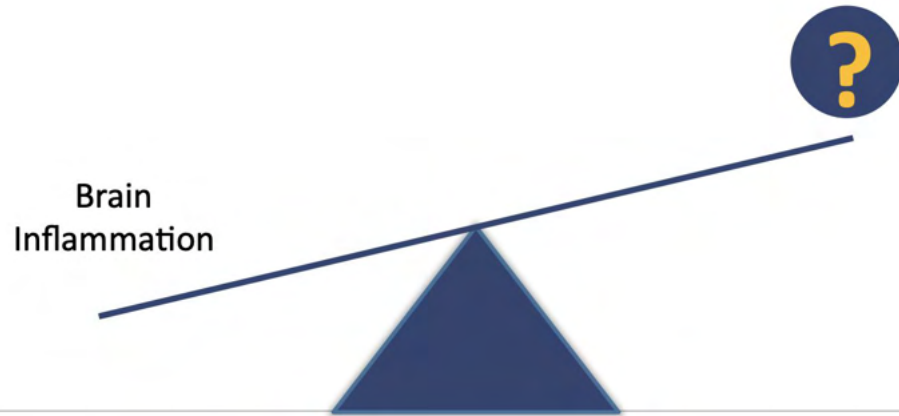
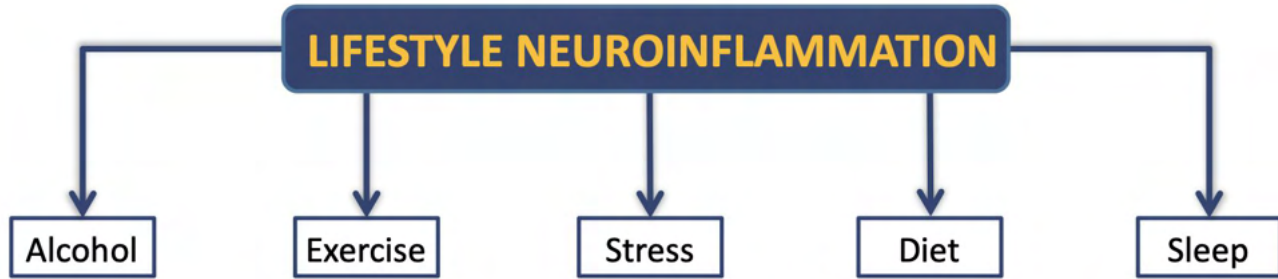
Alzheimer's Disease



Multiple Sclerosis



Lifestyle approach - Level 1



NI

- Lifestyle is huge in the management of NI, primed cells, BBB issues
- If primed - diet and lifestyle are critical and lifelong!
 - May mean the difference between functioning and not functioning
 - May mean the difference between progression and stability
- Not supplement only
- Education, lifestyle and supporting your body

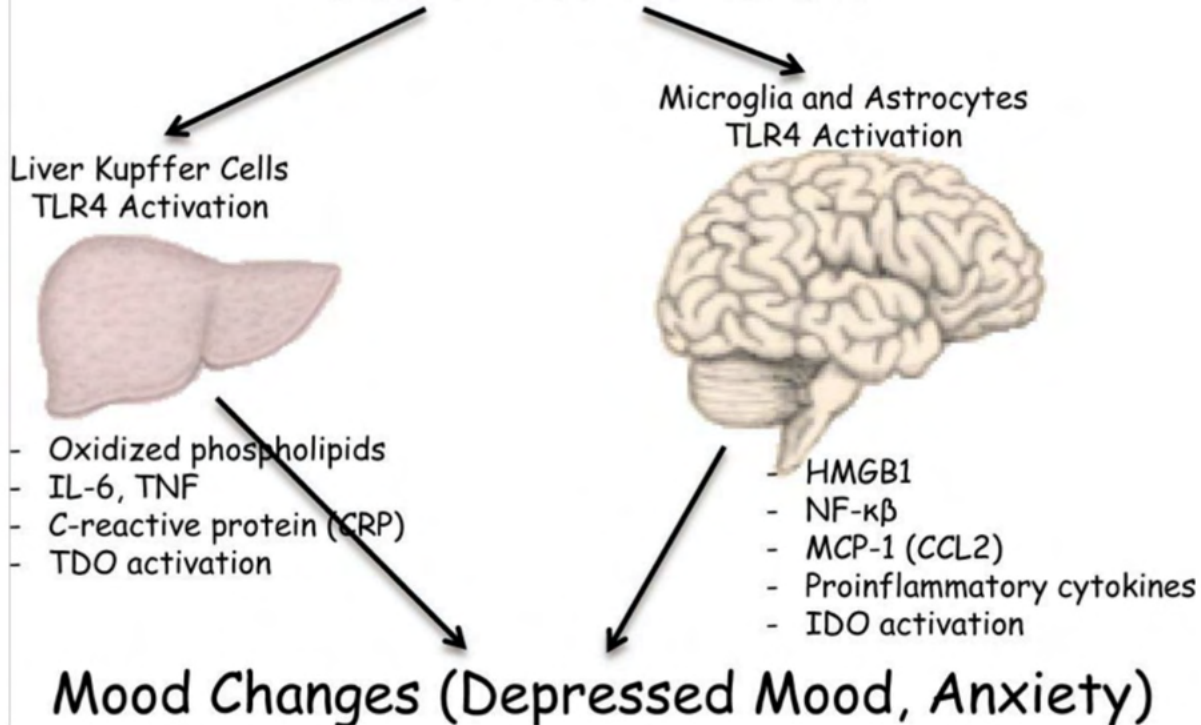
Alcohol

- Cerebellum is the most sensitive part of the brain to alcohol (Purkinje cells)
- In NI and neurodegenerative diseases - the midline cerebellum degenerates first
- Many notice they are “sensitive to alcohol”
 - This can be due to primed cells - it quickly activates these - dizzy, balance, not feel well
- Those with gluten ataxia (off balance due to degeneration of the cerebellum due to gluten or NI- can't handle alcohol)
- Can cause leaky BBB
- Alcohol is never good for the brain - but especially if primed!!
- Increases Kupffer cells in the liver - which stimulates the vagus nerve and creates further inflammation (Kupffer regenerate - brain cells do not)

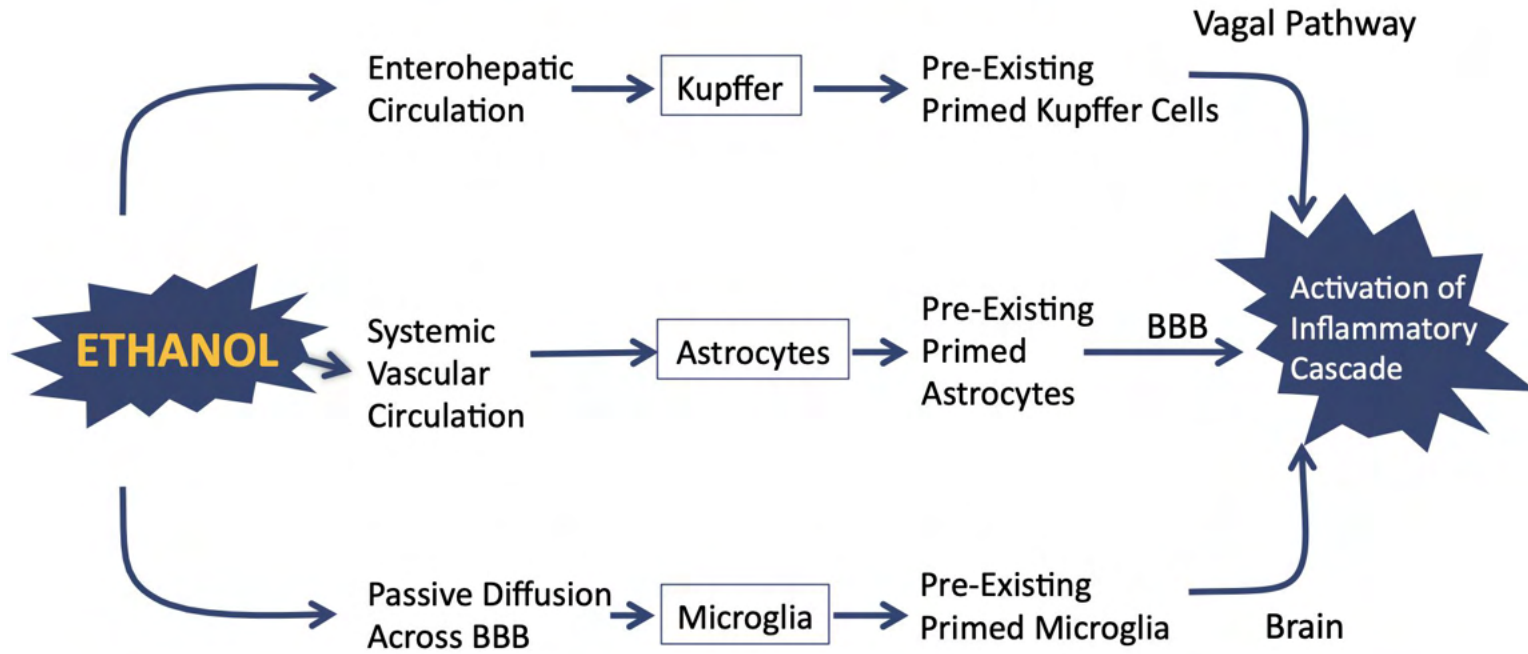
Alcohol

- Do you have a reaction to alcohol? If so - what is it?
 - Dizziness, fatigue, depression, memory loss....
 - Suspect priming
- Some will notice their brain was never the same after a binge episode
 - BBB breach, priming or even AI
- Active NI - avoid alcohol
- Primed patient - should NOT have alcohol - too aggressive of a trigger!
 - It can cause NI and further primed cells
 - Increased BBB permeability even with a little
 - What if the next day you get an infection/injury with open BBB (will predict severity)
- Is it worth it??

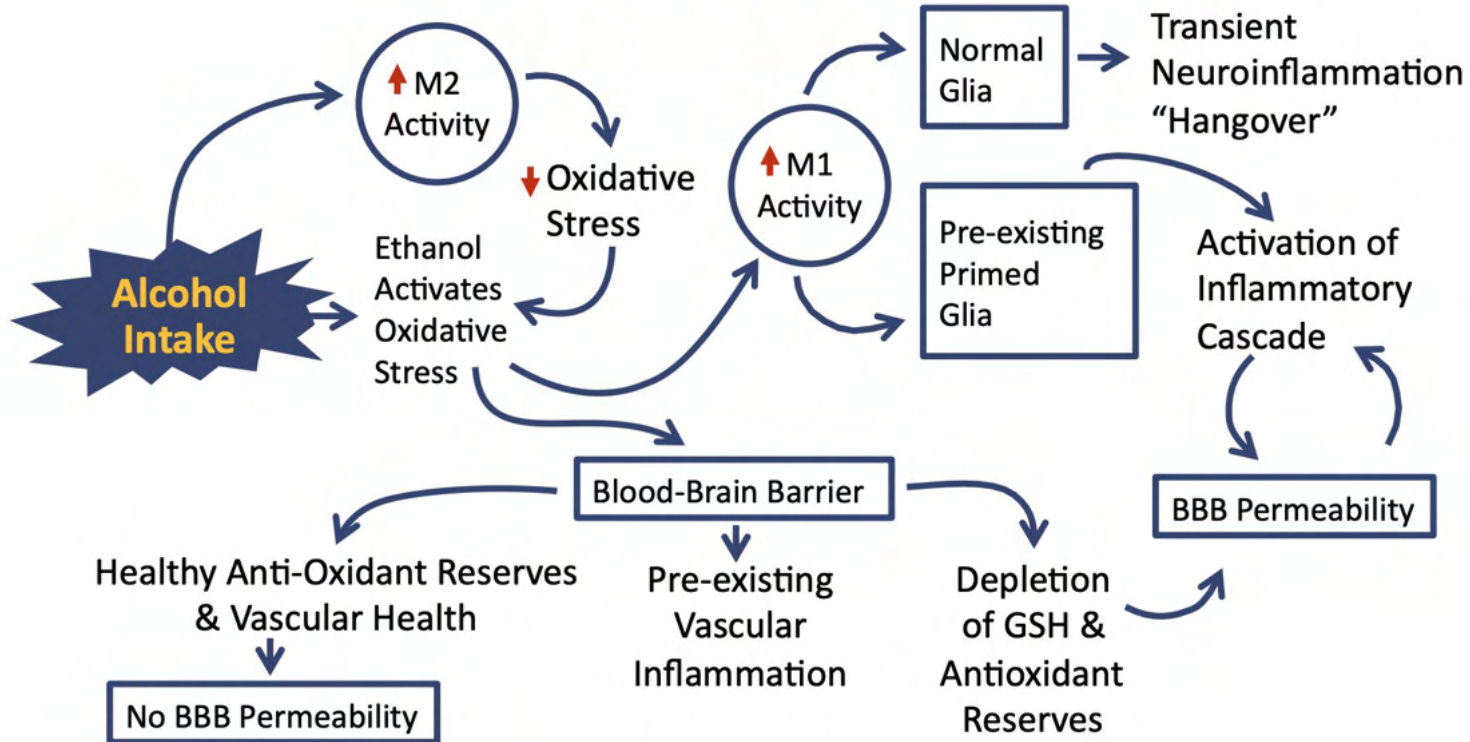
Chronic Alcohol Intake



ETHANOL TARGET SITES



ALCOHOL AND NEUROINFLAMMATION



Exercise

- Has to be part of the treatment plan
- Overall anti-inflammatory and can heal the BBB
- Opioid response from exercise turns on M2
- Overtraining → turns on M1 (more free radicals)
- Initial exercise is both M1,M2 - but then if done well M2 is predominant
- More intense - more M2 activity, releases BDNF, growth hormones
 - HIIT for short intervals better than long sessions of low intensity
- Dramatic potential to heal with exercise!!!!

Exercise

- It will be trial and error to find your sweet spot
- Start slow and low
 - Ex - 3 minutes of jumprope
 - 7 minute workout
- Figure intensity - then intensity duration
 - How did you feel during and after?
 - Fall apart - too much. Can't do each day - too much
- Ideal - 7 minute workout HIIT 1-2 times a day
 - Jump jacks, jump rope, bike, treadmill
- May not be able to start until supplements are on board, help with the gut and brain barriers, or retraining specific areas of the brain

Exercise

- More powerful than any supplement
- Does not have to be time consuming or need any special equipment
- As NI decreases - you can increase time or intensity

EXERCISE INTENSITY LEVELS

Level of Intensity	Maximum Heart Rate (MHR)	Physical Cues
Light	40%-55% of MHR	Does not induce sweating unless it is a hot, humid day. No noticeable change in breathing.
Moderate	55%-69% of MHR	Sweating after 10 minutes. Breathing becomes deeper and more frequent. You can carry on a conversation, but not sing.
High	70% or greater MHR	Will break a sweat after 3-5 minutes. Breathing is deep and rapid. You can only talk in short phrases.

Maximum Heart Rate = 220 - your age in years

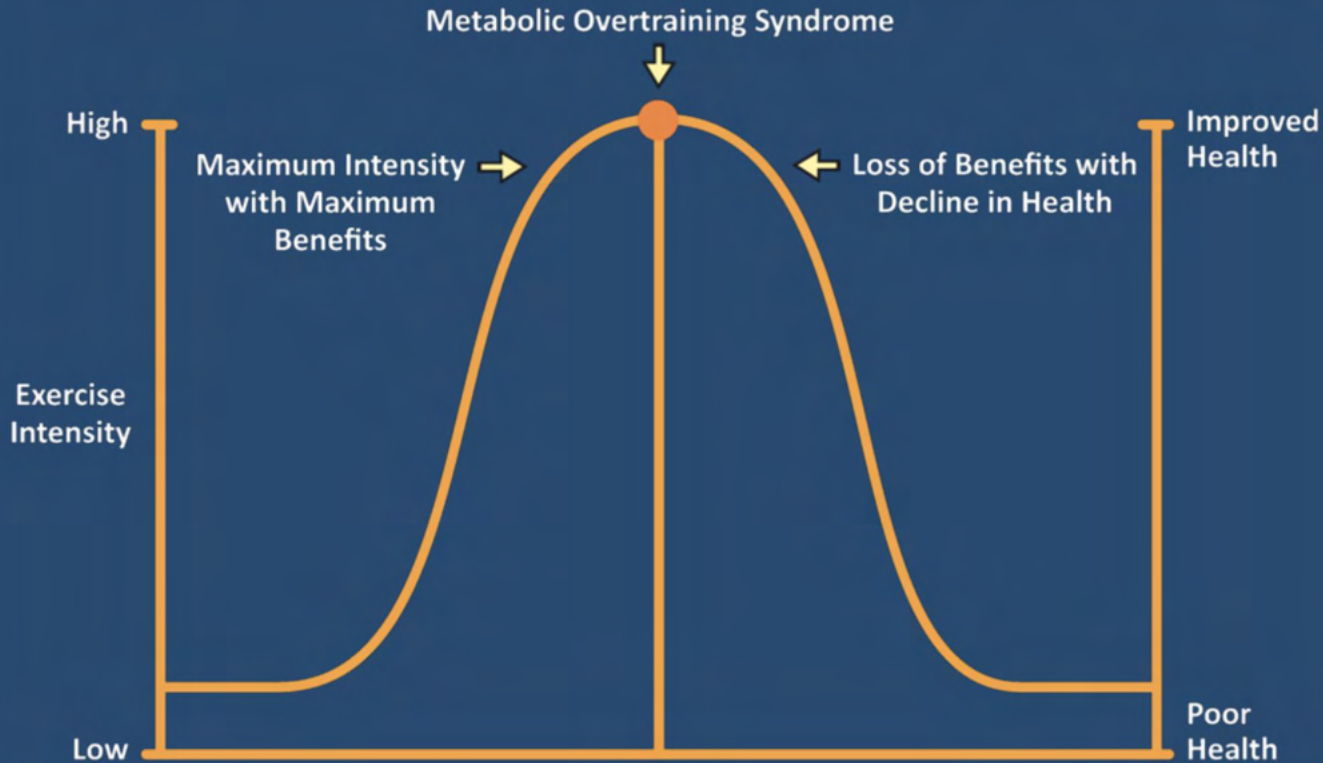


NEUROENDOCRINE-IMMUNE RESPONSES TO EXERCISE INTENSITIES

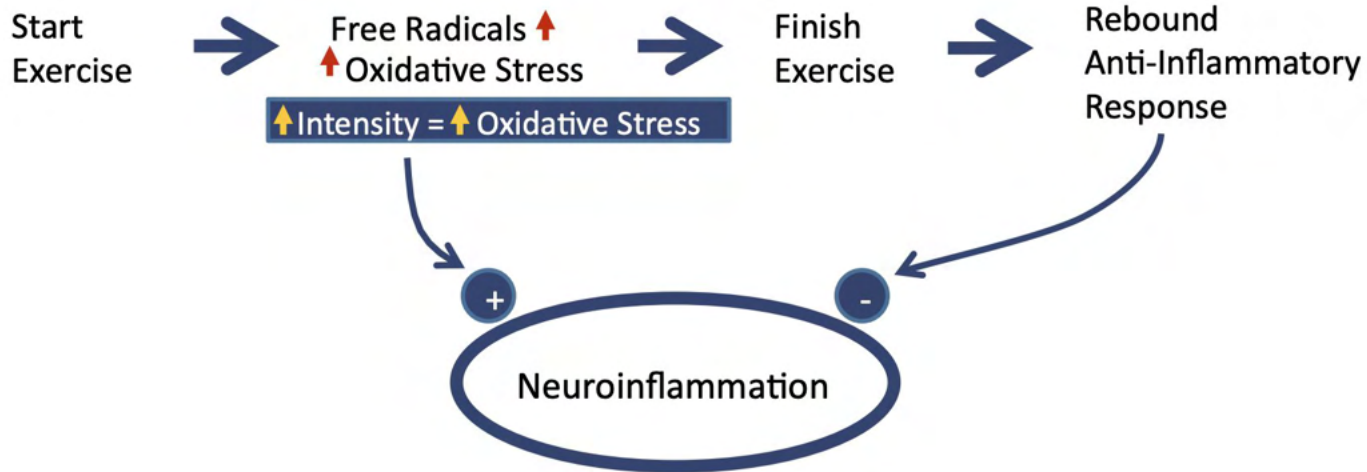
Exercise Outcomes	Light- to Moderate-Intensity Exercise	High-Intensity Exercise
Growth Hormone Release	—	↑ ↑ ↑
Opioid Response	—	↑ ↑ ↑
Nitric Oxide (eNOS) Response	↑, ↑ ↑	↑ ↑ ↑
Brain-Derived Neurotrophic Factor Release	↑, ↑ ↑	↑ ↑ ↑
Insulin Receptor Sensitivity	↑	↑ ↑ ↑
Immune Enhancement	↑	↑ ↑ ↑
Oxidative Stress and Risk for Overtraining Syndrome	↑	↑ ↑ ↑



EXERCISE INTENSITY AND HEALTH OUTCOMES



THE IMPACT OF EXERCISE ON BRAIN INFLAMMATION



Clinical Pearl

- Exercise can be one of the most powerful tools that can be used to reduce neuroinflammation.
- There is a balancing act between intensity and duration to be protective versus neuroinflammatory.

YOU NEED TO FIND IT



Clinical Pearl

- Sometimes the stimulation from exercise causes adverse reactions from an injured area of the brain that cannot handle activation. This is not the same as neuroinflammation caused by exercise intensity.
- If there is an adverse reaction, you may need to determine if this is occurring by trying different type of exercises.



Potential Adverse Reactions with Impaired Brain Regions

BRAIN REGIONS

SENSITIVITY TO TYPE OF EXERCISE

Cerebellum



- Balance exercises (Yoga)
- Core platform exercises (BOSU)
- Lots of ups and downs (Burpees)

Vestibular



- Excessive motion in environment (crowded gym)
- Unstable ground (treadmill)

Frontal Cortex



- Exercise that requires focus and concentration

Auditory Context/Tectum



- Environments that are very loud



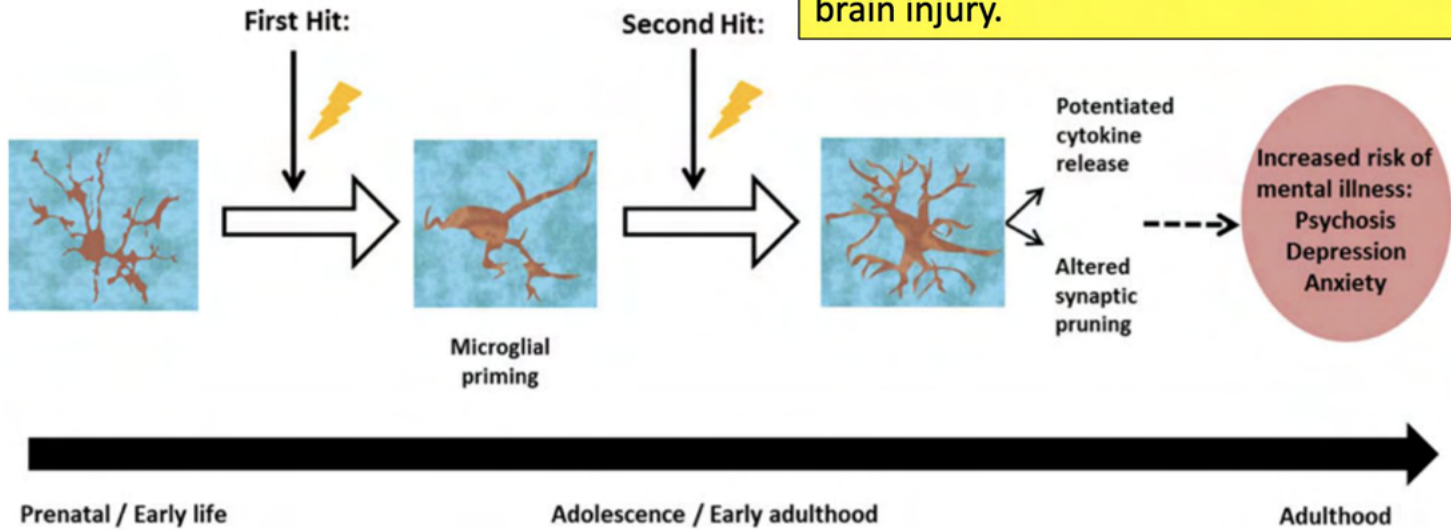
Stress

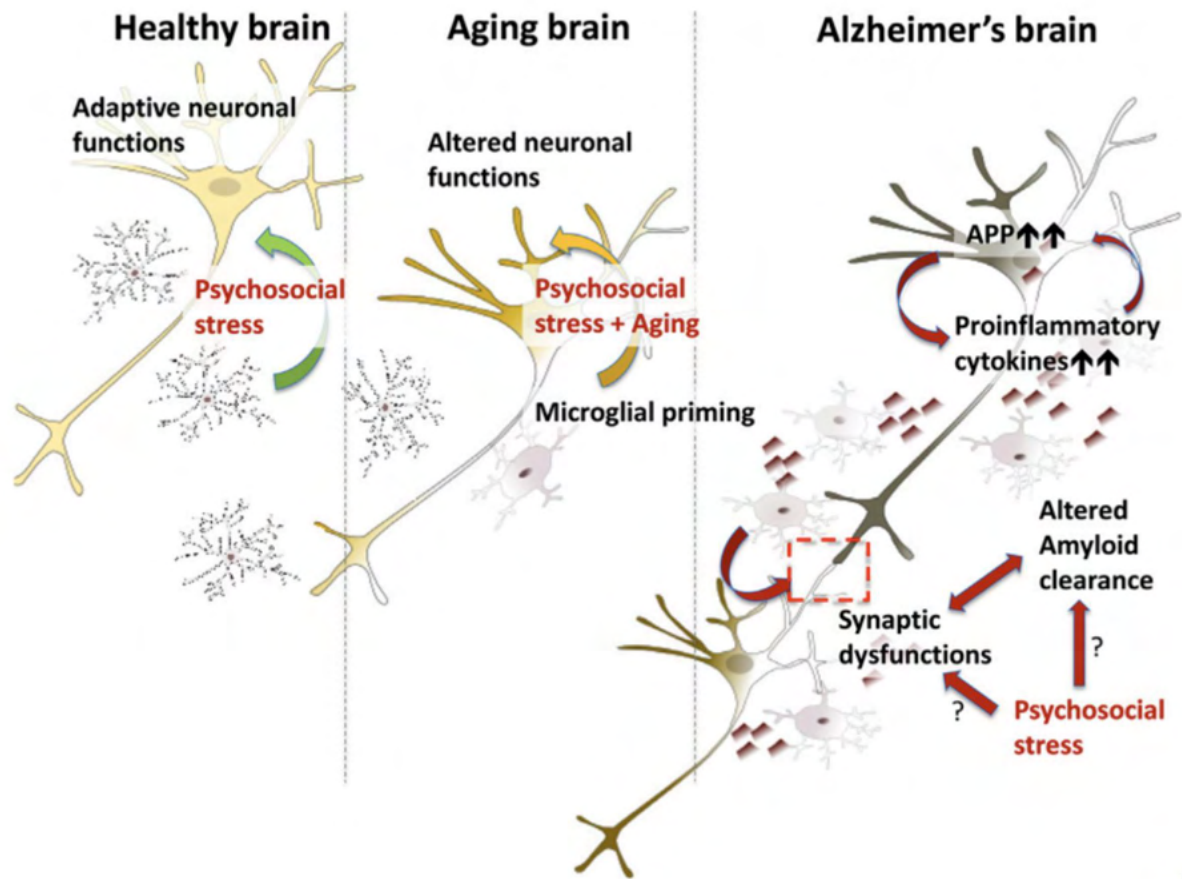
- It can directly affect the brain!!
- Creates inflammatory pathways
- Can prime glial cells and reactive already primed cells
- You have to manage stress to heal the brain!
 - That may mean changing jobs, relationships, other things in your life
 - That may mean counseling, or other modalities to help
- You need to come up with multiple ways to calm down and manage stress in the moment. Practice so these tools are available.
- Adaptogens won't help!!
- Unless you manage this - you will not heal.
- Primed glial cells and ongoing stress - will continue the inflammatory process

Stress

- Environment is critical
- The brain is extremely sensitive to stress - and has to be addressed!!!
- Goal - get away from those things that cause stress
 - Extra curricular activities
 - Job
 - Relationships
- For those that you absolutely can't change - engage in activities to decrease stress
- If you have been working in many ways to heal and you are not better - it could be stuck stress patterns
- Stress also affects the gut → affects the brain

The impact of a psychological second hit can be as significant as a traumatic brain injury.





Alternate Nostril Breathing (Pranayama)

- Using your right thumb, softly close the right nostril, and inhale as slowly as you can through the left nostril, then close it with your ring finger. Pause. Open and exhale slowly through the right nostril.
- With the right nostril open, inhale slowly, then close it with the thumb. Pause. Exhale through the left nostril. Once your exhalation is complete, inhale through the left. Pause before moving to the right.
- Repeat this pattern five to ten times, and then release the right hand to the right knee. Ease back into normal breathing.



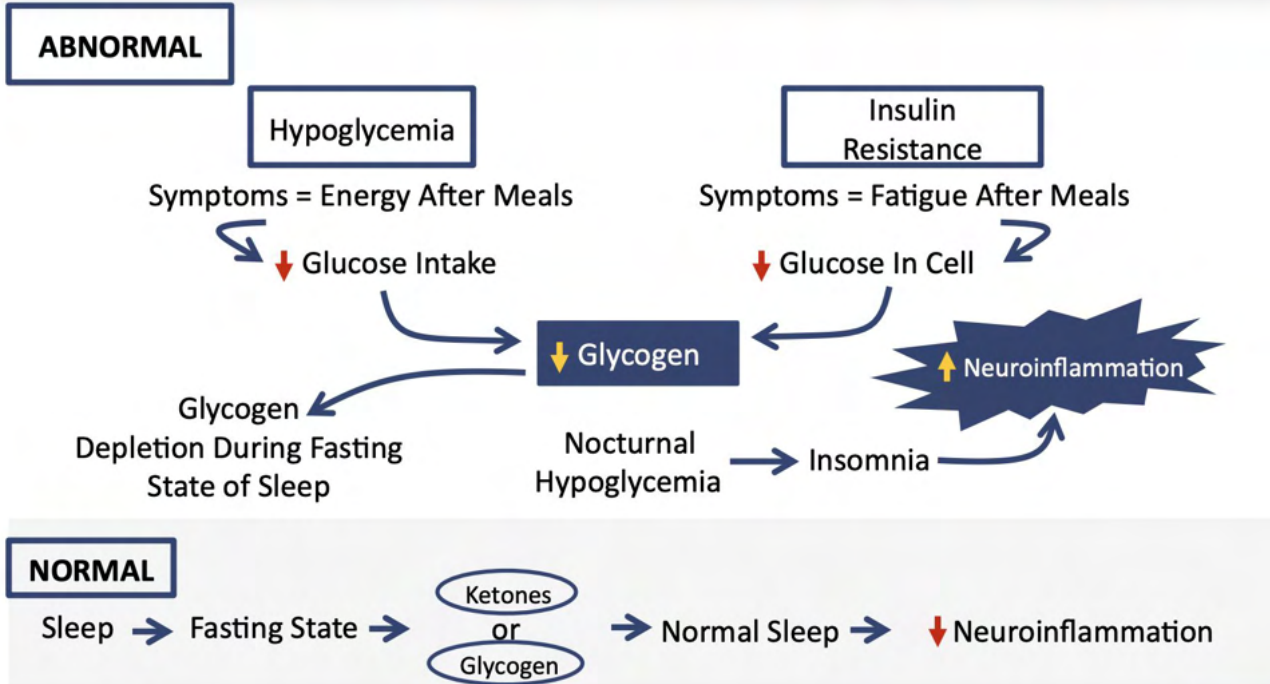
Primed Glial Cells

- Critical to manage stress
- If you need to quit, rid relationships, need to do it to heal
- Use techniques where you cannot change the stress

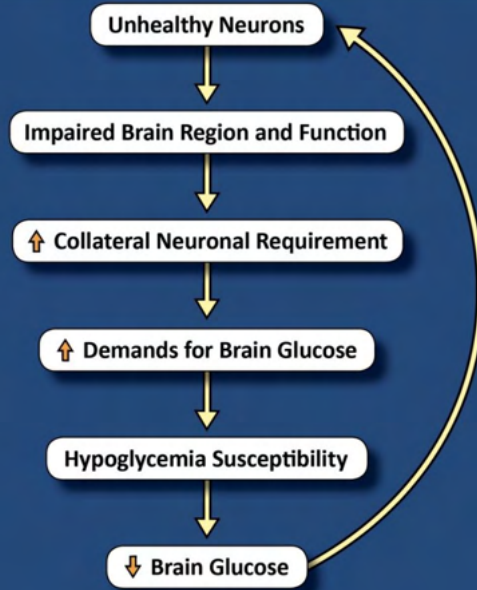
Sleep

- Critical with NI, primed glial cells, and many other health conditions
- An inflamed brain needs more fuel to work - increase glucose need
- This leads to hypoglycemia - especially at night
 - This can cause you to wake up at 3am....
 - Need adequate glycogen and ketones to support the brain during sleep
- Prone to hypoglycemia (need to have bs stable)
- Many also have decreased appetite which worsens the picture
- Need steady fuel all day long
 - Eat frequently and avoid simple sugars (protein and fat)
 - Some need keto to fix this
 - Some can't get into keto due to too much NI

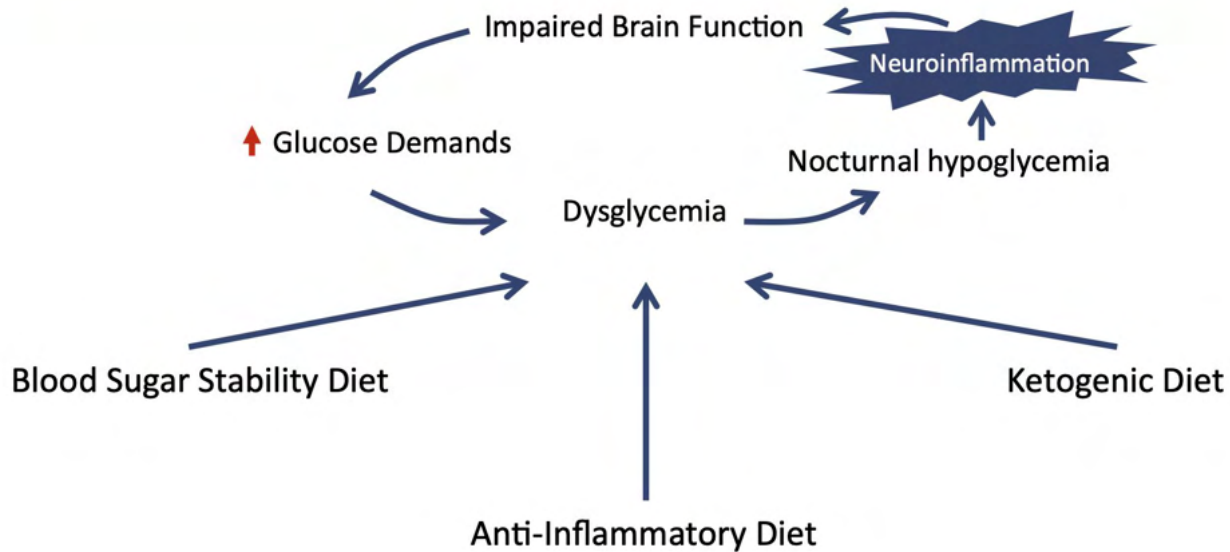
DYSGLYCEMIA, SLEEP, AND NEUROINFLAMMATION

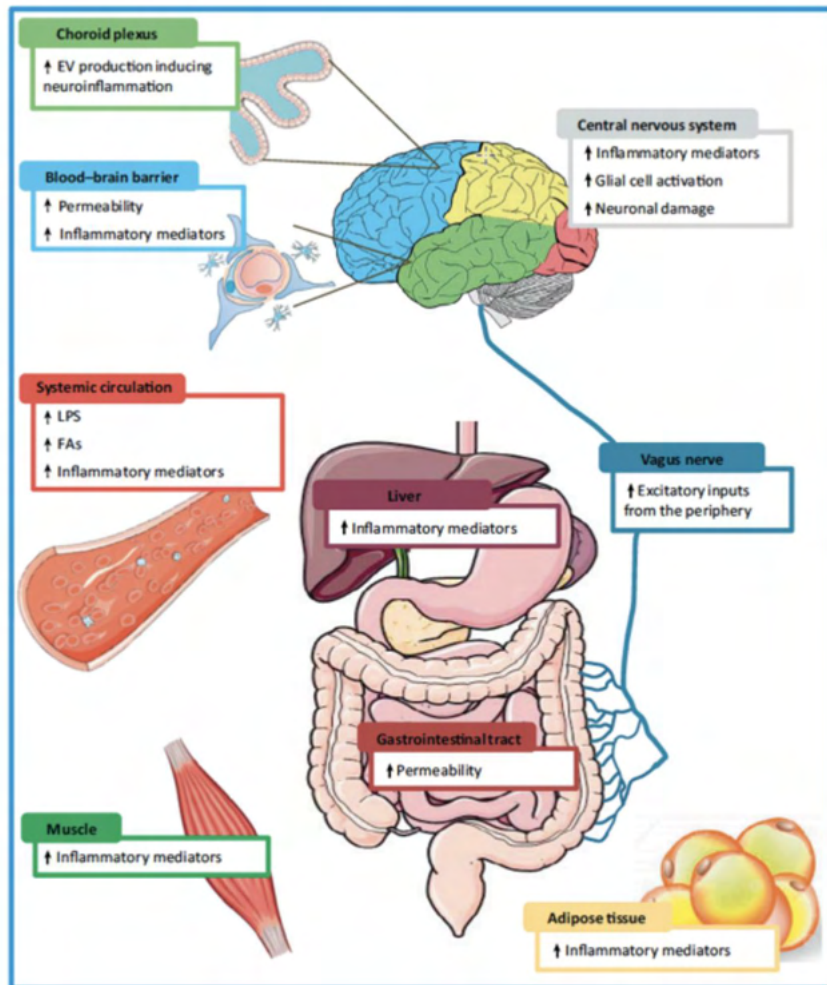


IMPAIRED NEURONAL HEALTH— DYSGLYCEMIC MECHANISMS



VICIOUS CYCLE OF DYSGLYCEMIA, INSOMNIA, AND NEUROINFLAMMATION

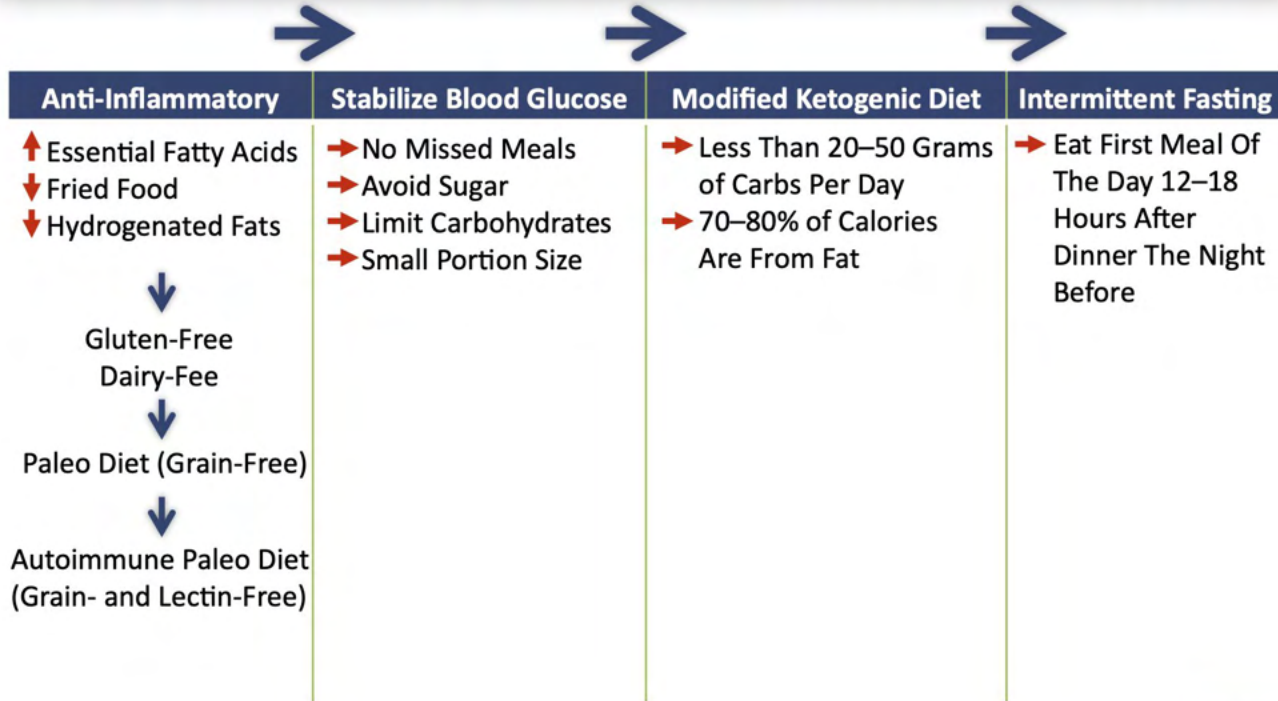




Diet

- Food impacts glial cells!!
- Goal M1→ M2
- SAD (high in long chain saturated fats, sugars) - very neuroinflammatory
- High BMI - increases NI. High insulin - increases NI
 - More body fat - more NI and increased glial priming
 - Insulin turns on glial cells
- IF turns on M2
- Keto and IF is the easiest and quickest way to decrease NI

DIETARY INTERVENTIONS FOR NEUROINFLAMMATION





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Ketone Bodies as Anti-Seizure Agents

Timothy A. Simeone¹, Kristina A. Simeone¹, and Jong M. Rho^{2,3}

There is growing evidence that ketone bodies (KB)—derived from fatty acid oxidation and produced during fasting or consumption of high-fat diets—can exert broad neuroprotective effects.

Moreover, ketone bodies appear to exert both epigenetic and anti-inflammatory effects.

Notwithstanding this limitation, there is growing evidence that ketone bodies are more than just cellular fuels, and can exert profound biochemical, cellular, and epigenetic changes favoring an overall attenuation in brain network excitability.

and mitochondrial permeability transition). Moreover, BHB appears to exert both epigenetic (i.e., inhibition of histone deacetylases or HDACs) and anti-inflammatory (i.e., peripheral modulation of hydroxycarboxylic acid receptor and inhibition of the NOD-like receptor protein 3 or NLRP3 inflammasome) activity. While the latter two effects of BHB have yet to be directly linked to ictogenesis and/or epileptogenesis, parallel lines of evidence indicate that HDAC inhibition and a reduction in neuroinflammation alone or collectively can block seizure activity. Nevertheless, the notion that KB are themselves anti-seizure agents requires clinical validation, as prior studies have not revealed a clear correlation between blood ketone levels and seizure control. Notwithstanding this limitation, there is growing evidence that KB are more than just cellular fuels, and can exert profound biochemical, cellular and epigenetic changes favoring an overall attenuation in brain network excitability.

Keto Food Plan

- Higher fat food plan
 - <20 carbs/day
- Profound anti-inflammatory effect on the brain
- Provides ketones as fuel and healing - turn on M2
- Has even shown to help with remyelination
- Burns body fat and decreases insulin
- Needs to be smart and done correctly
 - There is a lot of bad keto out there
- GF/DF!! Layer in AI if needed for your situation (no whey protein)
- Moderate medium fats - coconut. Plenty of EVOO, avocado (SCFA)

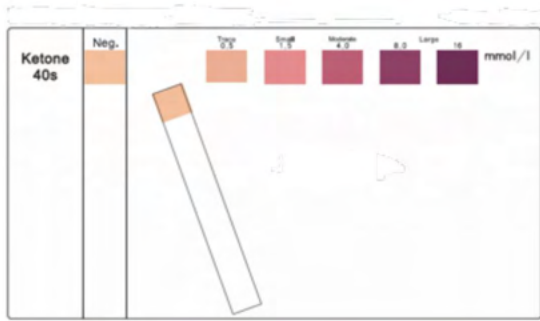
Keto

- For those with severe NI, primed cells - keto is the best way to start healing
- Measure ketones with strips (usually takes 2-3 days)
- After 6-8 weeks you will be keto-adapted and your body uses the ketones well
 - So urine strips will be negative
- Then you can start IF at this point
- The combination can be extremely helpful
- Will want to follow some basic labs in keto
- Goal 6-8 weeks or longer until the NI is cooled down
- Then decide - cycle in carbs, continue, etc...
- Key - keep diversity!!
- Microbiome mash-up is great here!
- Fibers: flax seed, shirataki noodles, veggie mashup

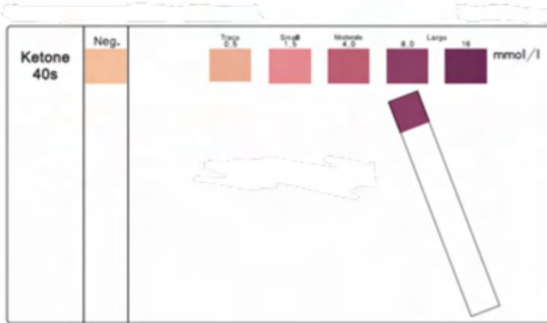
Clinical Pearl

- Do not start intermittent fasting until the patient is "Keto-Adapted."
- Keto-Adapted occurs when the patient no longer exhibits ketones with urinary ketone strips.

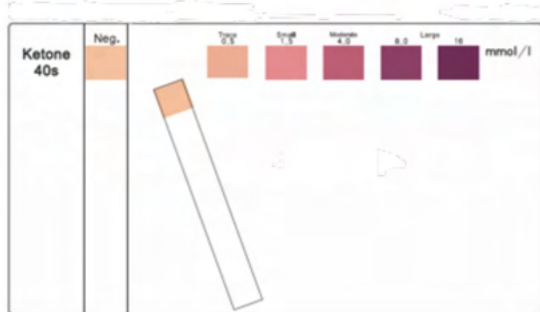




Not in Ketosis



Ketosis



Keto-Adapted
During Ketogenic Diet



Ketones

- Ketones are SCFA (short chain fatty acids) - decrease inflammation
- These have effects in the gut also
 - Probably more important than probiotics
- Butyrate, proprionate and acetate are also SCFA - decrease NI via the vagal pathway
- If you have transient brain fog - may not need to go all the way to keto
- If you have alot of brain issues and are primed - keto!
 - It may be one of the only ways out of severe NI
- Very least -
 - GF/DF, then cut common foods that bother the brain: GMO, corn, soy , egg

Summary

- We can have huge effects on neuroinflammation with lifestyle
 - This is primary!
- But there are also nutraceuticals that can increase M2, decrease M1
- Goals:
 - Increase M2, decrease M1
 - Decrease overall inflammation (increases NI and primed cells)
 - Deal with oxidative stress
 - Prevent neurological disease (we are in a fight to prevent future issues)
- Not only NI and primed cells - but the mitochondria shut down
 - Mito uncouples and then can damage the neuron

TRIGGERING EVENT

