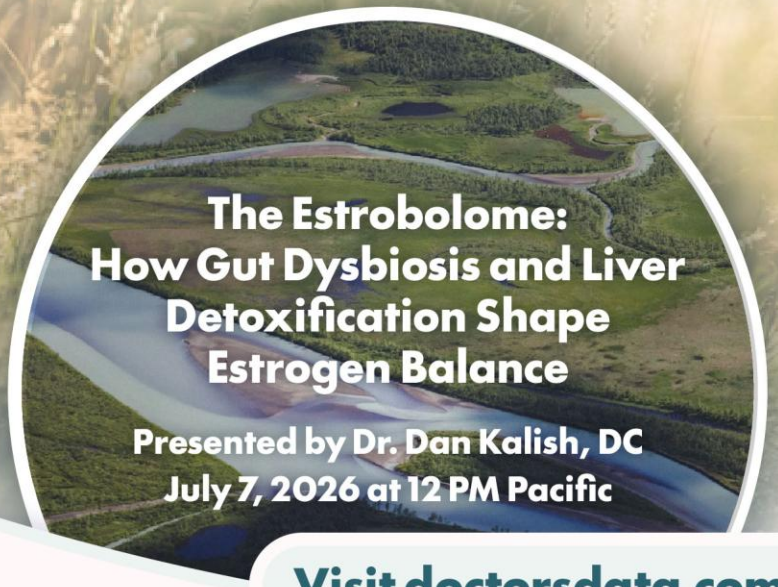
UPCOMING EVENTS



The Estrobolome: How Gut Dysbiosis and Liver Detoxification Shape Estrogen Balance

Presented by Dr. Dan Kalish, DC
July 7, 2026 at 12 PM Pacific

The Hormone-Mitochondria Axis: Linking Endocrinology to Cellular Bioenergetics

Presented by Laura Neville, ND
August 5, 2026 at 12 PM Pacific

Visit doctorsdata.com/Register-for-Webinars

Wellness Wednesday

WILL BEGIN SHORTLY

MORE WEB EVENTS

ADHD in Perimenopause:
The Estrogen-Dopamine Connection and Clinical Implications

Ruth Hobson, ND

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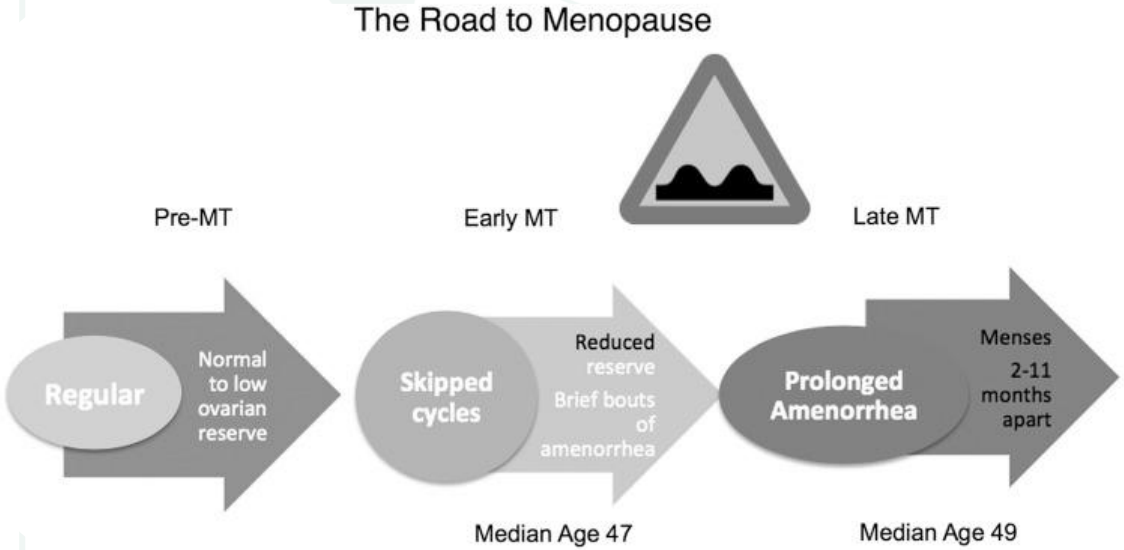
Learning Objectives

- Describe how hormonal fluctuations during perimenopause can influence attention, executive function, mood, and cognition.
- Discuss the relationship between ovarian hormones and neurotransmitter function in women with ADHD.
- Identify key contributors to cognitive dysfunction in perimenopausal women, including hormonal changes, stress, sleep disturbances, and neurotransmitter imbalances.
- Evaluate the potential role of hormone, neurotransmitter, and HPA axis testing in personalized patient care.

Perimenopause

Perimenopause

- “Menopause transition”
- Begins with variation in the menstrual cycle length of >7 days
- Associated with a rise in follicle-stimulating hormone (FSH) and ends 1 year after the final menstrual period
- Often the most symptomatic years for women
- Time of emotional transition
- Affected by stress
- Affected by diet and lifestyle
- Women have different patterns of symptoms



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Peri-Menopause: What does this mean?

- The average age of menopause in the United States is 51. But this means that women are experiencing menopause between the ages of 40 and 58.
- Physical changes begin years before the final menstrual period. This transition phase is called **perimenopause** and may last for 4 to 8 years. It begins with changes in the length of time between periods and ends 1 year after the final menstrual period.
- This means peri-menopause could start at age **32** in some women.

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The North American Menopause Society: https://www.menopause.org/for-women/menopauseflashes/menopause-symptoms-and-treatments/menopause-101-a-primer-for-the-perimenopausal

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This transition towards the end of the reproductive years is often marked by challenging physical and emotional symptoms:

- The lucky few - No symptoms except irregular menstrual periods that stop when menopause is reached.
- Hot flashes & night sweats
- Vaginal atrophy (dryness & thinning)
- Low libido
- Sleep issues
- Mood changes
- Slower metabolism & weight gain
- Aching joints
- Frequent urination
- Memory issues/lack of focus
- Migraines
- Deep fatigue
- Etc.

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Smith, P. W. (2022). *What you must know about women's hormones: your guide to natural hormone treatment for PMS, menopause, osteoporosis, PCOS, and more.* Garden City Park, NY, Square One Publishers.

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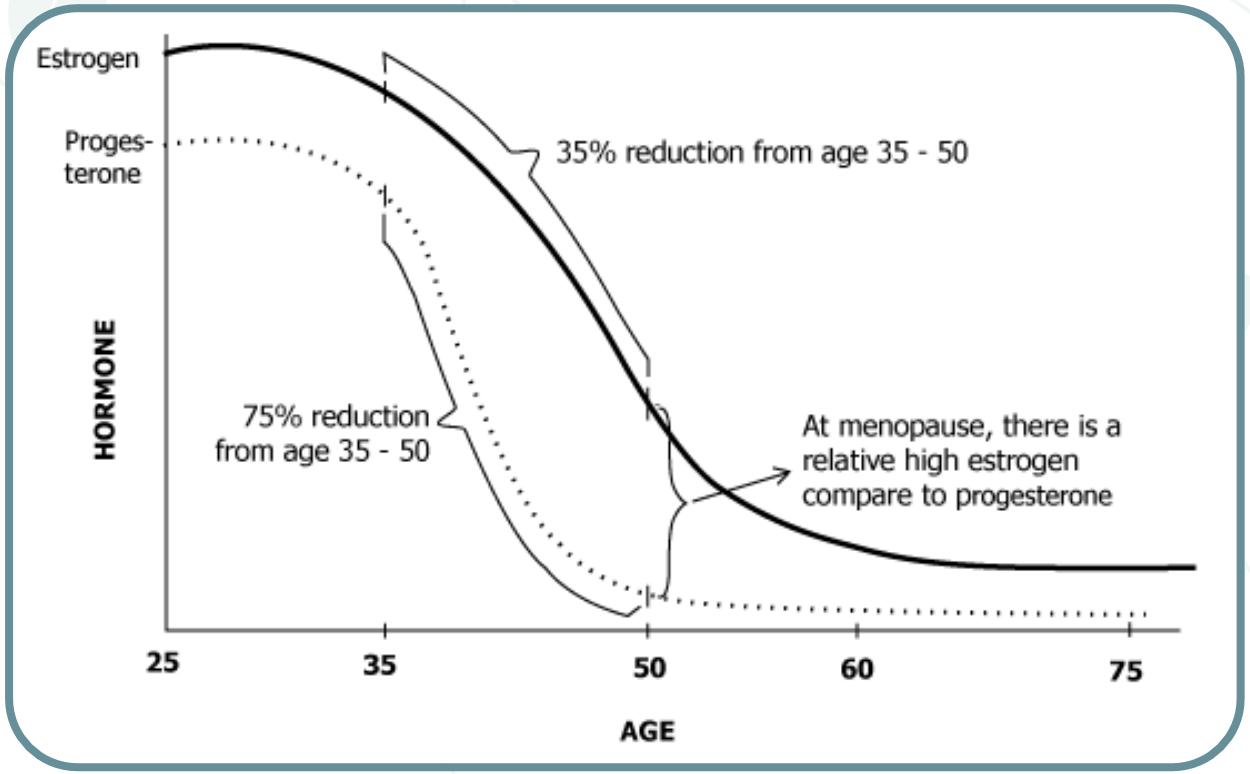
Hormonal decline with peri/menopause

- Estrogen decreases to $^1/_2$ - $^1/_3$ of baseline levels
- progesterone decrease to $^1/_{120}$ of baseline levels.

Estrone (E1)*	19.4	pg/mL	◆	<35
Estradiol (E2)	1.1	pg/mL	◆	0.6–4.5
Estriol (E3)*	30.3	pg/mL	◆	7.5–66
EQ (E3 / (E1 + E2)) Ratio	1.5		◆	≥1.0
Progesterone (Pg)	122	pg/mL	↓	127–446
Pg/E2 Ratio†	111		↓	≥200



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Lee J. What Your Doctor May Not Tell You About Menopause

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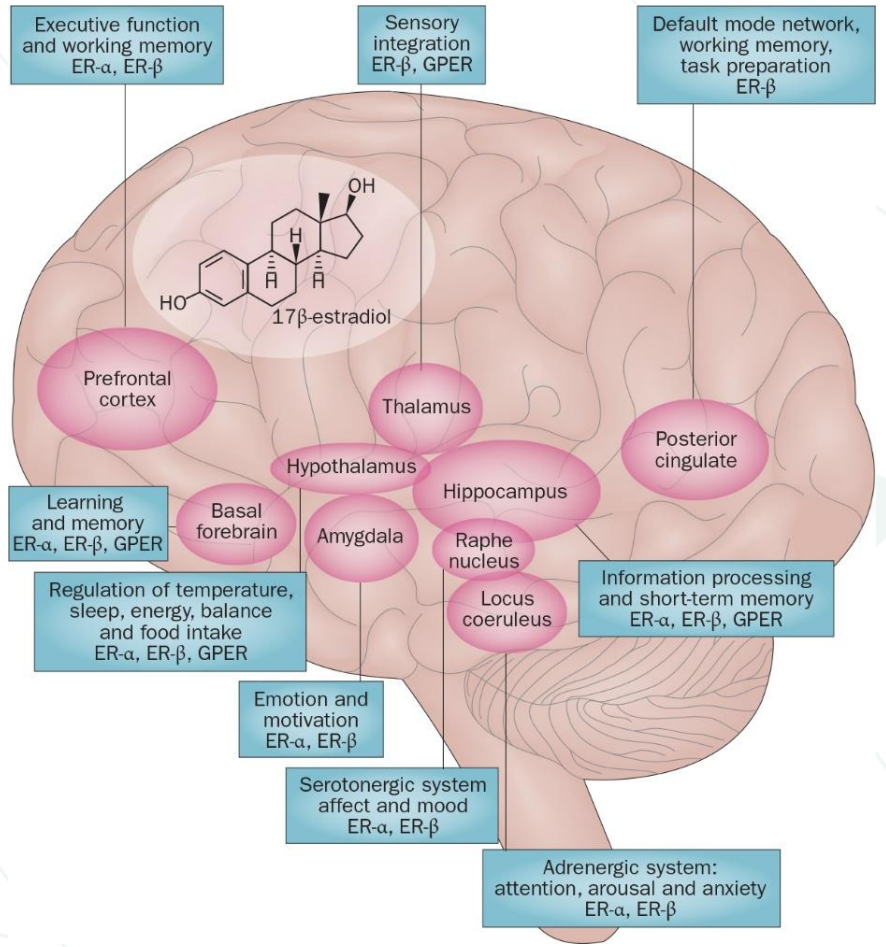
Perimenopause & the Brain

- Prefrontal Cortex: executive function and working memory
- Hypothalamus: Regulation of temperature, sleep, energy, balance, and food intake
- Amygdala: Emotion and motivation
- Hippocampus: Information processing and short-term memory
- Raphe Nucleus: Serotonergic system affect and mood
- Locus coeruleus: Adrenergic system: attention, arousal, and anxiety
- Posterior cingulate: working memory and task preparation



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Brinton, R., Yao, J., Yin, F. *et al.* Perimenopause as a neurological transition state. *Nat Rev Endocrinol* 11, 393–405 (2015). https://doi.org/10.1038/nrendo.2015.82

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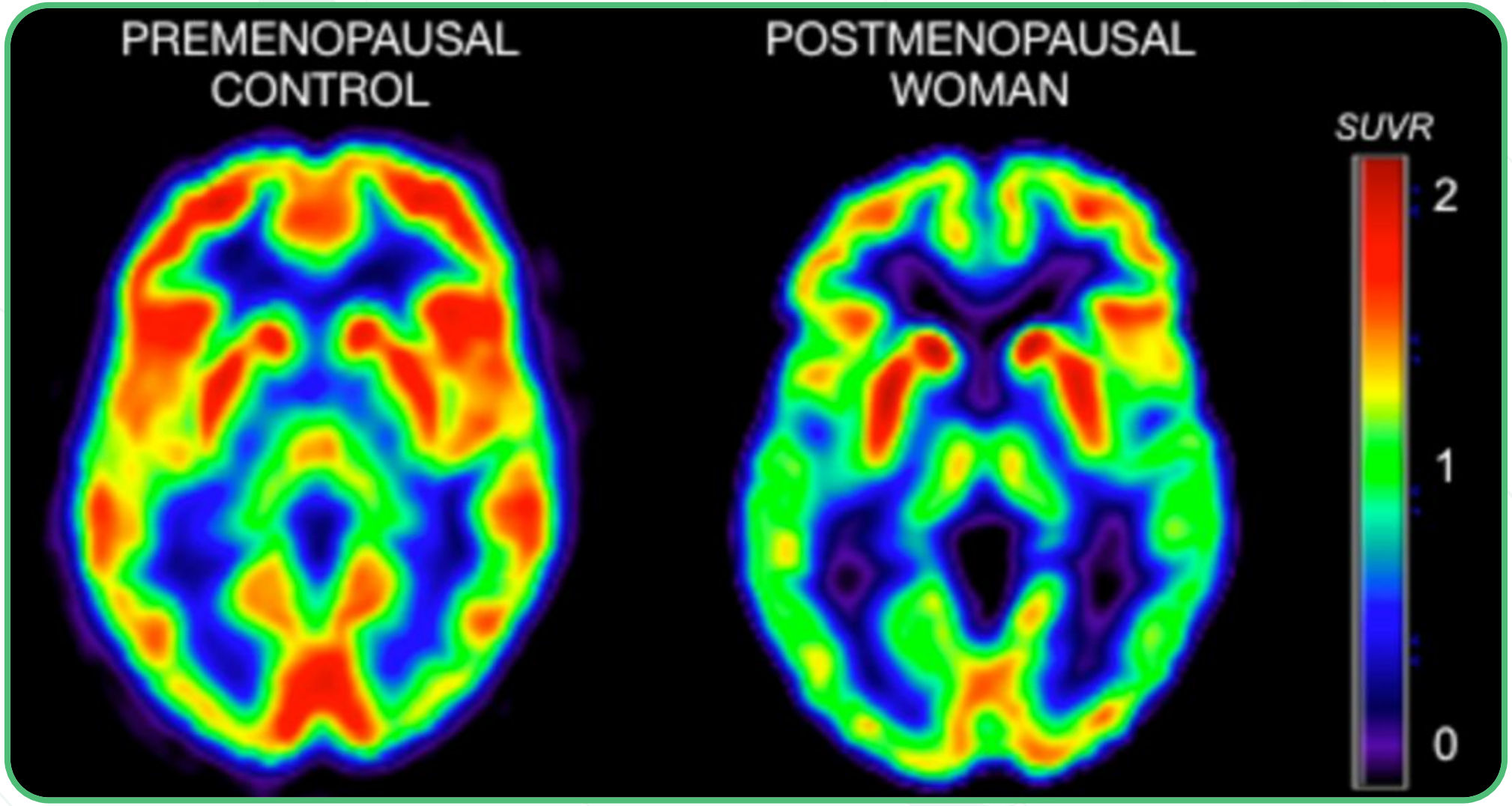

Mosconi et al Neurology 2017; PloS One 2017

ADHD in Primary Care

- 2025, an estimated 22.3 million Americans had a current ADHD diagnosis, approximately 50% of whom received their diagnosis during adult hood.
- According to American Journal of Psychiatry, 13.1 million adults have a current ADHD diagnosis
- 61% of women with ADHD received their diagnosis during adulthood, compared to 40% of men
- Diagnosis of ADHD in women (30-49 yo) nearly doubled from 2020-2022

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- PMCID: PMC11466376 PMID: 39388378 CDC Weekly Mortality and Morbitiy report, 2024
- Epic Research-CBS News: https://www.cbsnews.com/newyork/news/more-and-more-women-being-diagnosed-with-adhd-new-study-finds/ accessed on 7/7/25

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Delayed ADHD diagnosis

- ADHD criteria and teacher training have historically focused on hyperactive behavior typical in boys, leading to under-recognition of girls
- Teachers refer boys 6–9 times more often than girls for ADHD evaluations, even when girls meet diagnostic criteria
- Girls typically exhibit the inattentive subtype (e.g., daydreaming, disorganization, forgetfulness), which is less overt and disruptive compared to the hyperactivity often seen in boys
- Girls often adapt via self-control, perfectionism, and social masking, which delay recognition of underlying challenges
  - This emotional regulation frequently contributes to **anxiety and depression**, which may be diagnosed instead

Ginsberg Y, Quintero J, Anand E, Casillas M, Upadhyaya HP. Underdiagnosis of attention-deficit/hyperactivity disorder in adult patients: a review of the literature. Prim Care Companion CNS Disord. 2014;16(3):PCC.13r01600. doi: 10.4088/PCC.13r01600. Epub 2014 Jun 12. PMID: 25317367; PMCID: PMC4195639.

ADHD Diagnosis On The Rise Adult Women

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ADHD and Hormonal Transitions

- **Adolescence**: The initiation of cyclic hormonal activity can trigger increased emotional sensitivity, distractibility, or anxiety often misinterpreted as typical teenage behavior or mood instability.
- **Reproductive years**: Many women remain undiagnosed until adulthood, when the cumulative demands of work, relationships, and parenting overwhelm prior compensatory strategies. In many cases, a child's diagnosis prompts a retrospective recognition in the mother.
- **Pregnancy and postpartum**: While elevated estrogen during pregnancy may transiently buffer symptoms, the dramatic postpartum drop in estrogen and dopamine is associated with decreased executive dysfunction, overwhelm, and mood disturbances. These are frequently misdiagnosed as postpartum depression, though they may reflect underlying ADHD.
- **Perimenopause and menopause**: This transition is often the tipping point for women who have struggled silently for decades. As estrogen levels decline, dopamine signaling weakens, and previously manageable ADHD symptoms may become heightened. Many women receive their first ADHD diagnosis during this phase.

Quinn PO, Madhoo M. A review of attention-deficit/hyperactivity disorder in women and girls: Uncovering this hidden diagnosis. *Prim Care Companion CNS Disord.* 2014;16(3). doi:10.4088/PCC.13r01596

Estrogen Dominance & Cognitive Instability

- Progesterone drops earlier than estrogen → relative estrogen dominance.
- Estrogen excess may heighten emotional reactivity & mood swings.
- This can intensify ADHD-related emotional dysregulation.

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Brinton, R. D. (2008). *Trends Pharmacol Sci*, 30(4), 212–222. https://doi.org/10.1016/j.tips.2009.01.005

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ADHD: Reproductive Stages

- **Methods**
  - A cross-sectional study was conducted with **602 females (mean age = 39.52**; SD = 10.21), including **377 with self-reported ADHD and 225 without**, recruited through ADHD support groups, social media, Volunteer Ireland, and Prolific. Participants reported their menstrual regularity and completed the Premenstrual Symptoms Screening Tool (PSST). Retrospective postpartum depression levels were measured using the Edinburgh Postnatal Depression Scale (EPDS), and peri- and post-menopausal symptoms were evaluated using the Greene Climacteric Scale (GCS).
- **Results**
  - Females with ADHD exhibited **significantly higher rates of menstrual irregularity** ($\chi 2 = 14.2$, $p < .001$), **more severe premenstrual symptoms** ($\chi 2 = 204.7$, $p < .001$), **elevated postpartum depression levels** ($t = 7.89$, $p < .001$) with increased risk of unplanned pregnancies and pregnancy-related complications, and **greater menopausal symptom severity** ($t = 9.61$, $p < .001$) **compared to their non-ADHD counterparts.**

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Boyd, C., Wrigley, M., Kilbride, K. *et al.* ADHD and the female reproductive stages: menstruation, perinatal and menopause. *Arch Womens Ment Health* 29, 89 (2026). https://doi.org/10.1007/s00737-026-01718-x

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HPA – Axis

ADHD: The role of the stress response

- Emerging research suggests altered stress physiology may also contribute to symptom expression.
- The hypothalamic-pituitary-adrenal (HPA) axis regulates cortisol secretion, influencing:
  - Attention
  - Executive function
  - Emotional regulation
  - Motivation
  - Sleep-wake cycles
- Dysregulation of the HPA axis may help explain why many individuals with ADHD experience:
  - Stress intolerance
  - Emotional dysregulation
  - Sleep disturbances
  - Fatigue despite hyperactivity

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1. Kamradt JM, et al. *A meta-analytic review of the association between cortisol reactivity and ADHD*. J Abnorm Child Psychol. 2018.
2. Chang JPC, Su KP. *Cortisol and inflammatory biomarker levels in youths with ADHD: systematic review and meta-analysis*. Mol Psychiatry. 2021.

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The ADHD–HPA Axis Connection

- Studies suggest individuals with ADHD may demonstrate:
  - Lower basal morning cortisol
  - Blunted diurnal cortisol output
  - Altered cortisol awakening response (CAR)
  - Reduced physiological adaptation to chronic stress

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1. Kamradt JM, et al. *A meta-analytic review of the association between cortisol reactivity and ADHD*. J Abnorm Child Psychol. 2018.
2. Chang JPC, Su KP. *Cortisol and inflammatory biomarker levels in youths with ADHD: systematic review and meta-analysis*. Mol Psychiatry. 2021.
3. Isaksson J, Nilsson KW, Lindblad F. *Early Psychosocial Adversity and Cortisol Levels in Children with ADHD.* Eur Child Adolesc Psychiatry. 2013.

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Cortisol's Effects on the ADHD Brain

Optimal Cortisol levels support:

- Prefrontal cortex activation
- Working memory
- Sustained attention
- Cognitive flexibility

Chronic Dysregulation may contribute to:

- Impaired executive function
- Increased impulsivity
- Emotional lability
- Reduced stress resilience

ADHD symptoms often worsen during periods of psychological stress, sleep deprivation, and hormonal transitions, times when HPA-axis function is most challenged.

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1. Kamradt JM, et al. *A meta-analytic review of the association between cortisol reactivity and ADHD*. J Abnorm Child Psychol. 2018.

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Circadian Rhythm

ADHD, Sleep & Circadian Rhythm Dysregulation

- Sleep problems are highly prevalent in ADHD across the lifespan.
- Adults with ADHD commonly show:
  - Longer sleep onset latency
  - Delayed sleep timing
  - Increased evening chronotype (“night owl” pattern)
  - Many individuals show features consistent with Delayed Sleep-Wake Phase Disorder (DSWPD)

1. Snitselaar MA, et al. *Sleep and circadian rhythmicity in adult ADHD.* J Atten Disord. 2017
2. Bijlenga D, et al. *The role of the circadian system in ADHD.* ADHD Atten Deficit Hyperact Disord. 2019
3. Coogan AN, et al. *Circadian rhythm dysfunction in ADHD.* Atten Defic Hyperact Disord. 2017

Circadian Phase Delay in ADHD

- ADHD is strongly associated with evening chronotype
  - Delayed dim light melatonin onset (DLMO)
  - Later sleep onset and wake times
  - Delayed circadian phase (~1–1.5 hours in adults)

- Evidence suggests circadian rhythm disorder phenotype in ADHD

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1. Coogan AN & McGowan NM. *A systematic review of circadian function in ADHD.* Atten Defic Hyperact Disord. 2017.
2. Van Veen MM et al. *Circadian rhythm in adult ADHD.* Expert Rev Neurother. 2010.
3. Bijlenga D et al. *ADHD and delayed sleep phase syndrome prevalence and circadian delay.* 2019 review

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Melatonin and ADHD: Circadian reset

- Melatonin is a key regulator of circadian timing, not simply a sedative hormone.
- Individuals with ADHD commonly show:
  - Delayed melatonin onset (delayed circadian phase)
  - Evening chronotype (“night owl” pattern)
  - Sleep-onset insomnia and circadian misalignment
- In ADHD, melatonin is used primarily to:
  - Advance sleep phase (shift biological clock earlier)
  - Reduce sleep-onset latency
  - Improve total sleep time

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1. Coogan AN, McGowan NM. *A systematic review of circadian function, chronotype and chronotherapy in ADHD.* Atten Defic Hyperact Disord. 2017.
2. Hoebert M, van der Heijden KB, et al. *Long-term melatonin treatment in children with ADHD and chronic sleep onset insomnia.*

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Sleep Disturbance as a Driver of ADHD Symptoms

- Sleep deprivation directly impacts:
  - Prefrontal cortex function (attention, inhibition, working memory)
  - Emotional regulation
  - Impulse control
- Sleep loss can mimic or amplify ADHD symptoms
- Bidirectional relationship:
  - ADHD → sleep disruption
  - Sleep disruption → worse ADHD symptoms

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1. Gruber R et al. *Sleep processes and neurobehavioral functioning in ADHD.* Brain Sci. 2023.
2. Díaz-Román A et al. *Sleep in adults with ADHD: systematic review and meta-analysis.* Sleep Med Rev. 2018.
3. Kamradt JM et al. *Cortisol reactivity and ADHD (stress-sleep interaction context).* J Abnorm Child Psychol. 2018

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Sleep & ADHD

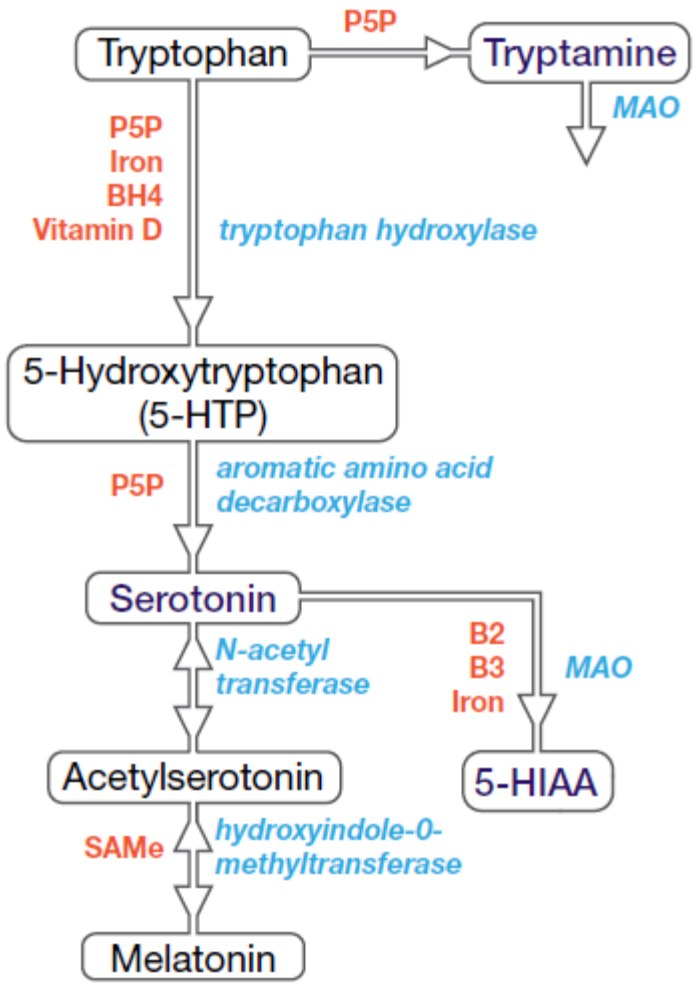
- ADHD sleep dysfunction is influenced by:
  - Circadian delay (melatonin timing)
  - HPA-axis dysregulation (cortisol rhythm disruption)
  - Neurotransmitter imbalance (dopamine / norepinephrine)
- Common contributing factors:
  - Evening light exposure / screen use
  - Irregular wake times
  - Stress physiology activation at night
  - Perimenopausal hormone shifts

1. Coogan AN et al. *Circadian rhythm and chronotherapy in ADHD.* 2017.
2. Snitselaar MA et al. *Sleep and circadian rhythmicity in adult ADHD.* 2017.
3. Korman M et al. *ADHD, circadian clock genes, and sleep/wake cycle.* Review 2020.

Hormones & NTs

Analyte	Result	Unit per Creatinine	L	WRI	H	Reference Interval
Phenethylamine (PEA)	20	nmol/g				42 – 160
Tyrosine	48	µmol/g				70 – 180
Tyramine	3.4	µmol/g				2.8 – 8.5
Dopamine	258	µg/g				175 – 500
3,4-Dihydroxyphenylacetic acid (DOPAC)	1520	µg/g				540 – 1850
3-Methoxytyramine (3-MT)	151	nmol/g				122 – 278
Norepinephrine	17.6	µg/g				29 – 69
Normetanephrine	195	µg/g				112 – 400
Epinephrine	1.9	µg/g				2.1 – 14.5
Metanephrine	84	µg/g				60 – 158
Norepinephrine / Epinephrine ratio	9.3					< 13
Tryptamine	0.4	µmol/g				0.65 – 1.6
Serotonin	84.4	µg/g				79 – 235
5-Hydroxyindoleacetic acid (5-HIAA)	5913	µg/g				2500 – 9000
Glutamate	23	nmol/g				18.0 – 70.0
Gamma-aminobutyrate (GABA)	5	nmol/g				2.6 – 8.0
Glycine	966	nmol/g				700 – 2500
Histamine	12	µg/g				14 – 51
Taurine	428	µmol/g				420 – 1400
Creatinine	73.1	mg/dL				25 – 180

Urinary Neurotransmitter Profile



Serotonin

- Biochemically derived from the amino acid tryptophan.
- Serotonin is primarily found in:
  - GI tract
    - 80-90% of the body's serotonin
  - Platelets and CNS
    - the remaining 10-20%

- King MW. "Serotonin". *The Medical Biochemistry Page*. Indiana University School of Medicine. Retrieved 2009-12-01.
- Berger M, Gray JA, Roth BL (2009). "The expanded biology of serotonin". *Annu. Rev. Med.* **60**: 355–66.

Imbalanced Serotonin

- Physical changes such as:
  - Vasomotor symptoms
  - Aches/pains
  - Bowel/bladder issues
- Mood concerns: depression/anxiety
- Thoughts of suicide
- Insomnia
- Racing/troublesome thoughts

- Emotional numbness
- Crying and/or angry outbursts
- Thoughts of escaping your current circumstances
- Obsessive/compulsive traits such as paranoia about germs and disease

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Berger M, et al. The expanded biology of serotonin. *Annu Rev Med*. 2009; 60: 355-66.

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Appetite change

- Moderately low serotonin can cause your appetite to change.
- Symptoms may include a lack of interest in eating, or cravings for sweets and carbohydrates.
- The brain tries to use sweets and carbohydrates to increase serotonin levels.

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Wurtman RJ, et al. Brain serotonin, carbohydrate-craving, obesity and depression. *Obes Res*. 1995 Nov;3 Suppl 4:477S-480S.

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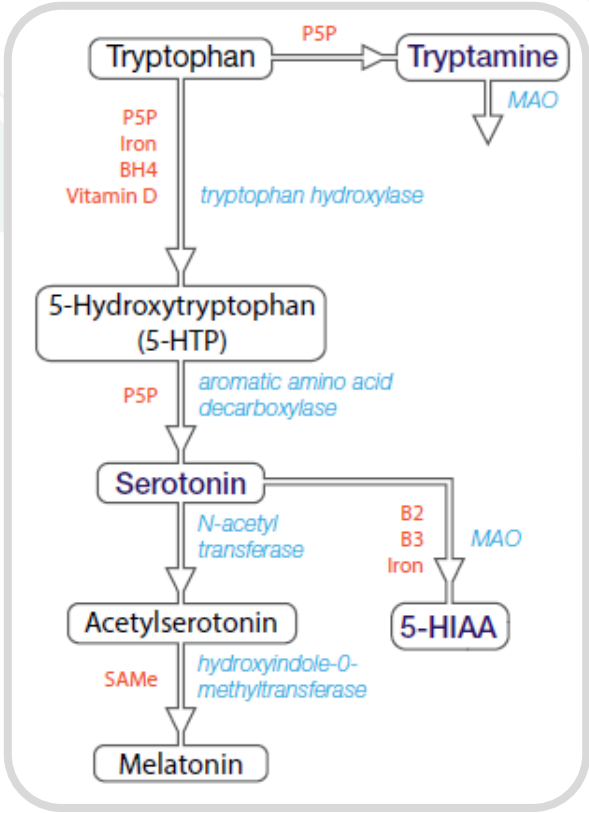
Estrogen and Emotional Regulation

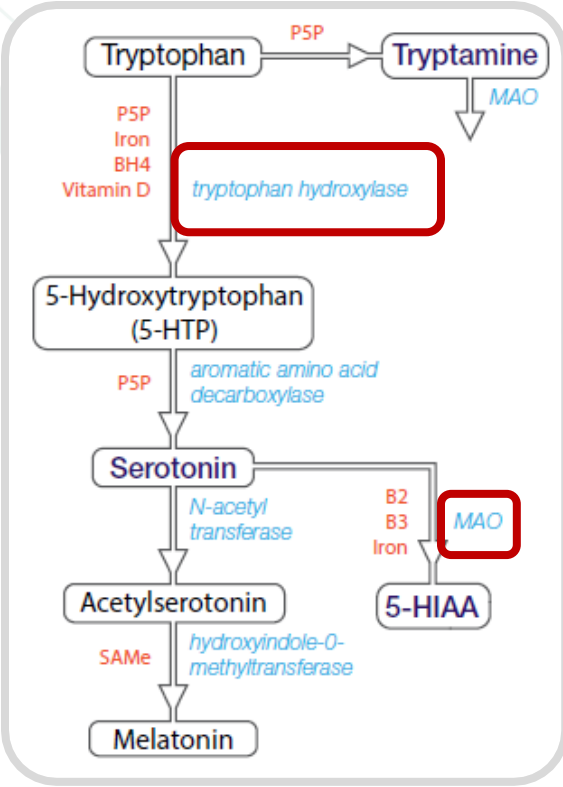
- Estrogen modulates the serotonin synthesis, impacting mood, anxiety, and impulse control.
- As estrogen declines, serotonin levels may also drop increasing emotional lability, irritability, and mood swings.
- These effects mirror or amplify ADHD related emotional dysregulation.



Rubinow, D. R., & Schmidt, P. J. (2006). Gonadal steroid regulation of mood: the lessons of premenstrual syndrome. *Front Neuroendocrinol*, 27(2), 210–216. https://doi.org/10.1016/j.yfrne.2006.03.002

Estradiol increases serotonin synthesis & decreases its breakdown

- Higher levels of estradiol inhibit MAO leading to more serotonin available in the synapse.
- Estradiol supplementation increases tryptophan hydroxylase
- Increased serotonin activity improves cognitive performance and mood.



- Amin Z, Canli T, Epperson CN. Effect of estrogen-serotonin interactions on mood and cognition. *Behav Cogn Neurosci Rev*. 2005; 4: 43-58.
- Epperson CN, Amin Z, Ruparel K, et al. Interactive effects of estrogen and serotonin on brain activation during working memory and affective processing in menopausal women. *Psychoneuroendocrinology*. 2012; 37(3); 372-382
- Klaiber EL, Broverman DM, Vogel W, et al. Effects of estrogen therapy on plasma MAO activity and EEG driving responses of depressed women. Am J Psychiatry. 1972 Jun;128(12):1492-8.
- Paredes S, Cantillo S, Candido KD, Knezevic NN. An Association of Serotonin with Pain Disorders and Its Modulation by Estrogens. *Int J Mol Sci*. 2019;20(22):5729. Published 2019 Nov 15.

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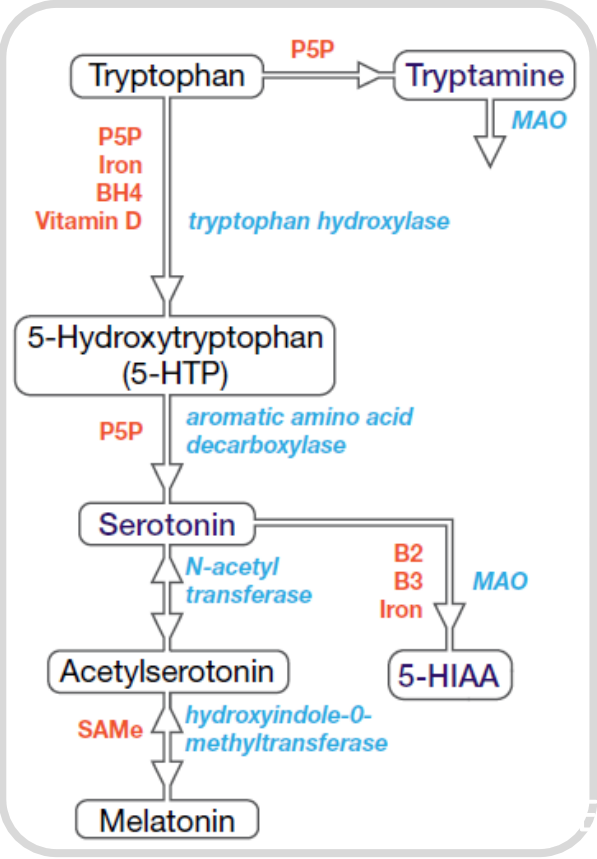
Supporting Serotonin

Low serotonin

- Tryptophan
  - 500-2,000 mg
- 5 HTP
  - 50-600 mg
- **HRT** (Estrogen)
- Rhodiola 100-300mg
- Melatonin
  - 0.5-3mg
- L-theanine
  - 100-500 mg bid
- Cofactors
  - Iron 25-50 mg (citrate or bisglycinate)
  - P5P 10-50 mg
  - Vitamin D 2,000-10,000 IU
  - BH4
    - Vitamin B3: 50 mg
    - Vitamin C 1,000-3,000 mg
    - SAMe: 100-500 mg
    - Molybdenum: 250-500 mcg
    - Zinc: 15-30 mg



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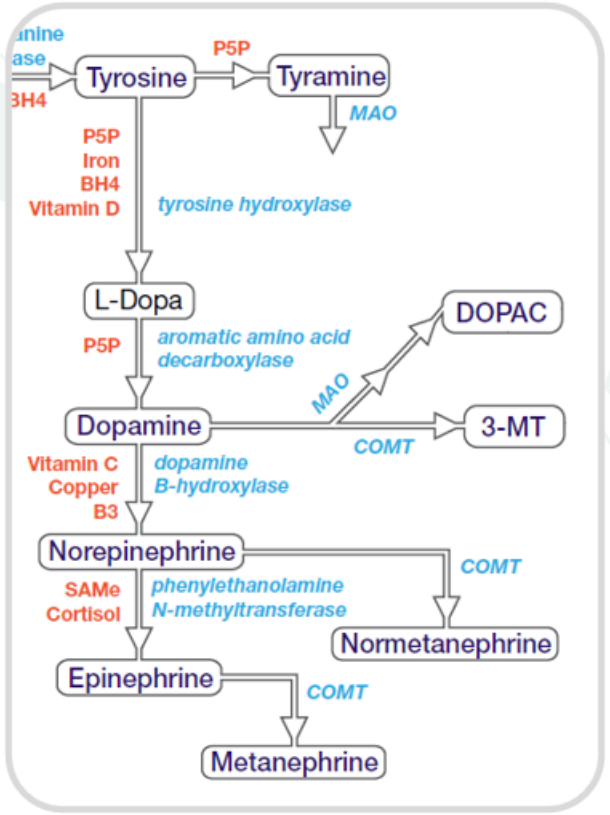
Dopamine

- Enhances the reward response, especially if the reward is perceived as greater than expected.
- Stimulates pleasure centers
- Enables us not only to see rewards, but to take action to move towards them
- Motivation
- Behavior and cognition
- Sleep
- Mood
- Attention and learning
- Locomotion and coordination of movement



Schultz W. Dopamine signals for reward value and risk: basic and recent data. *Behav Brain Funct*. 2010; 6: 1-9.

Dopamine Deficiency

- Mood swings/depression/anxiety
- Isolation
- Loss of interest
- Issues with motivation. Inability to finish tasks. Drop in sex drive.
- Forgetfulness
- Other pathological states have also been associated with dopamine dysfunction, such as schizophrenia, autism, and **attention deficit hyperactivity disorder**, restless legs syndrome

Dopamine, the “Motivation Molecule”

Lab mice that are dopamine deficient are so apathetic they’ll literally starve themselves to death, even when food is readily available — that’s how important dopamine is to motivation

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Angier, Natalie. “Molecule of Motivation, Dopamine Excels at its task. *The New York Times*. Oct. 26, 2009.

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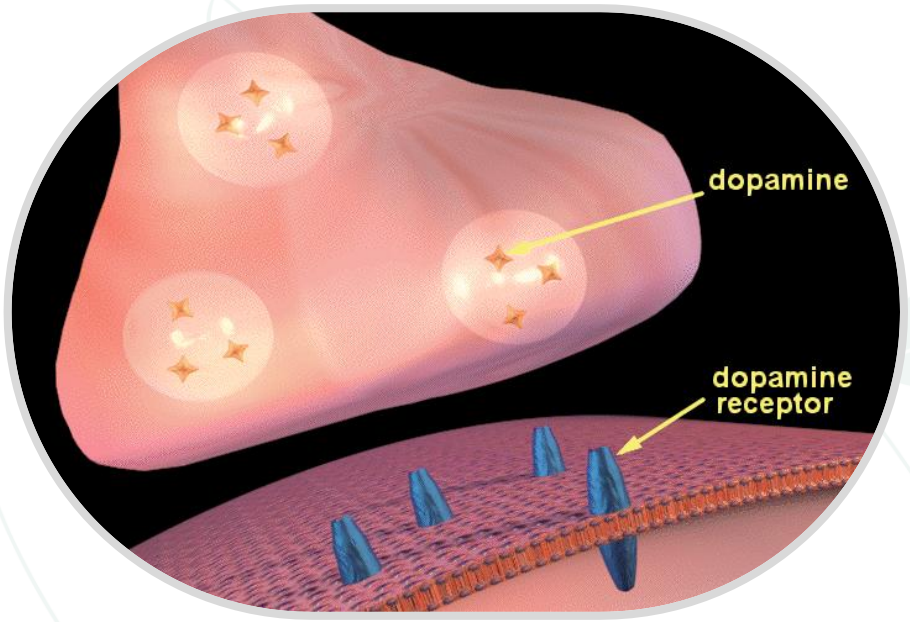
Estrogen & Dopamine

- Estrogen enhances dopamine synthesis, release, and receptor sensitivity, particularly in the prefrontal cortex.
- Dopamine regulates executive function, attention, and working memory.
- Fluctuating or low estrogen disrupts these functions → brain fog, distractibility, poor focus.

Jacobs, E., & D'Esposito, M. (2011). Estrogen shapes dopamine-dependent cognitive processes: implications for women's health. *J Neurosci*, 31(14), 5286–5293. https://doi.org/10.1523/JNEUROSCI.5404-10.2011

Progesterone & Dopamine

- Progesterone modulates dopamine transporters and receptors.
- Decline may reduce dopaminergic tone → worsened motivation, reward response, and focus.
- Midlife ADHD symptoms may shift toward executive dysfunction.



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Becker, J. B., & Chartoff, E. (2019). *Neuropsychopharmacology*, 44(1), 166–183. https://doi.org/10.1038/s41386-018-0125-6

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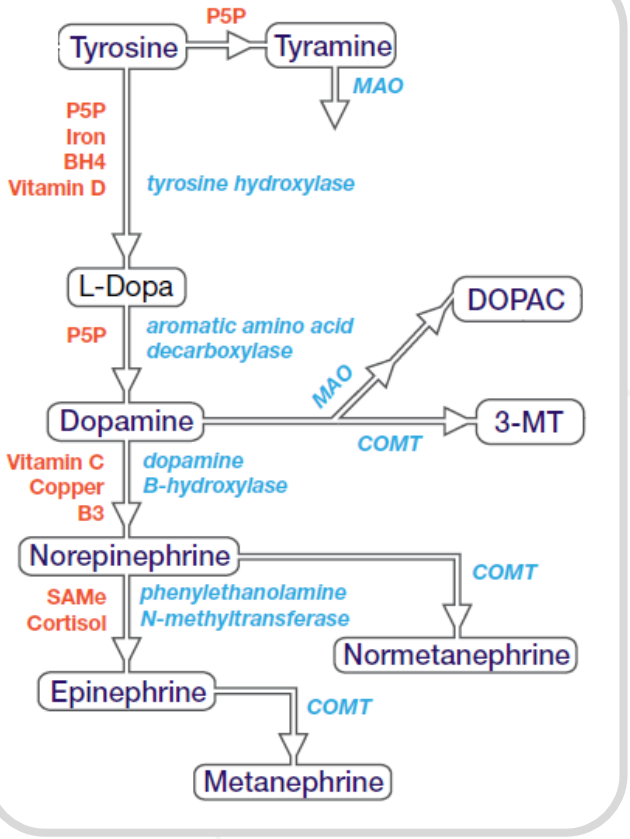
Supporting Dopamine



Low dopamine

- N-acetyl l-tyrosine
  - 250-1,500 mg
- Macuna pruriens
  - 200-800 mg
- HRT (Estrogen / Progesterone)
- Rhodiola 100-300mg
- L-theanine
  - 100-500 mg bid
- Cofactors
  - Vitamin D 1,000-10,000 IU
  - Iron 25-50 mg
  - P5P 10-50 mg
  - BH4
    - Vitamin B3 50 mg
    - Vitamin C 1-3 gm
    - SAMe: 100-500 mg
    - Molybdenum: 250-500 mg
    - Zinc: 15-30 mg

High dopamine

- L-theanine
  - 100-500 mg bid
- Rhodiola (Rhodiola rosea) Root Extract (4% Rosavins, 1% Salidroside)
  - 1,000-2,000 mg
- Co-factors for MAO/COMT
  - Vitamin B2: 50 mg
  - Vitamin B3: 100 mg
  - Iron: 25-50 mg
  - SAMe: 250-500 mg
  - Magnesium: 150-500 mg
  - MTHF: 400 – 5,000 mcg
  - Methylcobalamin: 1000 – 5000 mcg
- Support conversion to Norepi if needed

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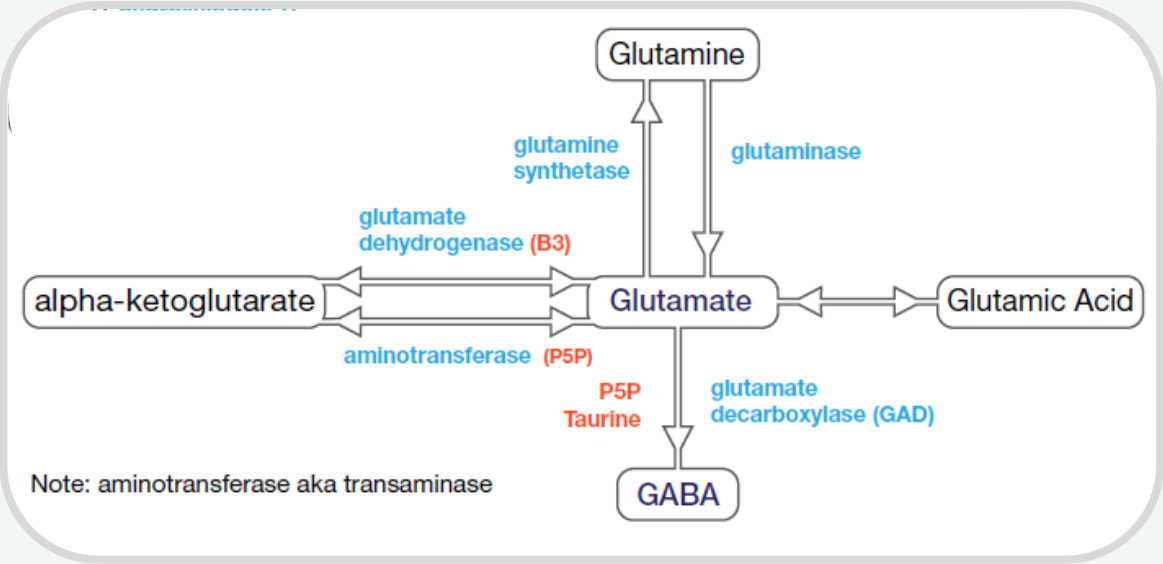
GABA



- The major inhibitory neurotransmitter
- Relaxing and calming
- Synthesized from glutamate and P5P
- Predominant receptor
  - GABA A
    - Utilized by neuroactive drugs like benzodiazepines
    - Often used to treat anxiety, seizures, act as sedative or muscle relaxant

Progesterone & GABA – Calming the Brain

- Progesterone's metabolite, allopregnanolone, enhances GABA-A activity
- Low levels reduce anxiolytic, sedative, and mood-stabilizing effects.
  - Women may experience increased anxiety, agitation, and sleep disruption worsening ADHD

Progesterones		Result	Unit	L WRI H	Reference Interval
Progesterone‡	(P4)	<dl	ng/mg Creat/Day		0.00 – 0.22
5α-Pregnanediol‡	(5A-PD)	117	ng/mg Creat/Day		5 – 25
5β-Pregnanediol‡	(5B-PD)	1660	ng/mg Creat/Day		70 – 320
Allopregnanolone‡	(ALLOP)	28	ng/mg Creat/Day		1.4 – 4.8
21-Hydroxyprogesterone‡	(21-OHP)	1.0	ng/mg Creat/Day		0.3 – 1.4
17-Hydroxyprogesterone‡	(17-OHP)	0.20	ng/mg Creat/Day		0.12 – 0.65
5-pregnenetriol‡	(5-PT)	107	ng/mg Creat/Day		35 – 120

Wellness Wednesday

Backstrom, T. et al. (2014). *Prog Neurobiol*, 113, 88–94. https://doi.org/10.1016/j.pneurobio.2013.09.013

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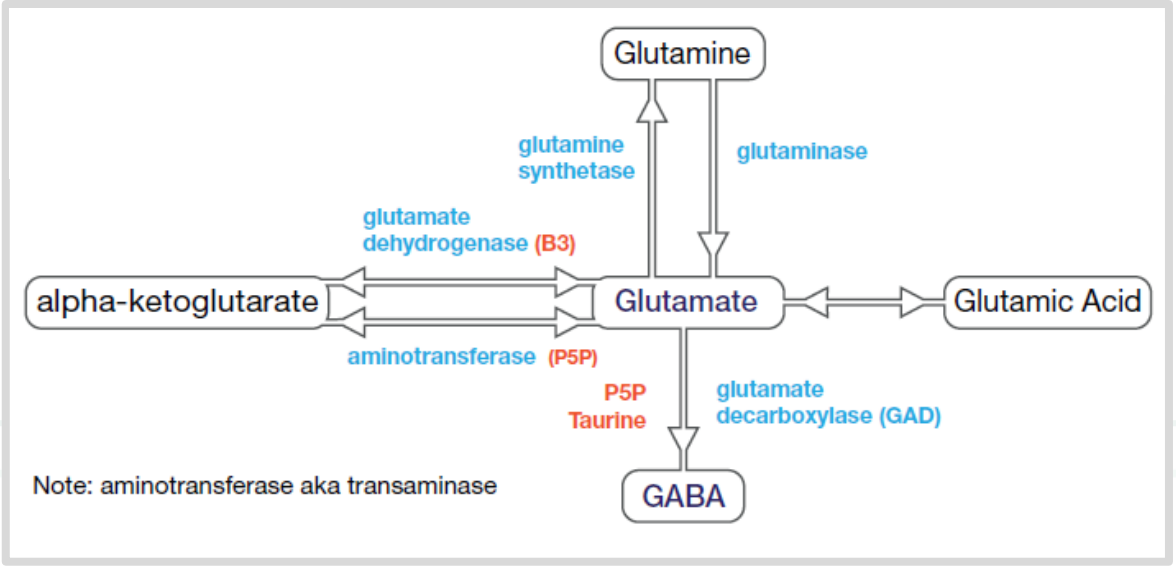
Addressing GABA

Low GABA

- L-theanine
  - 100-500 mg bid
- GABA
  - 500-2,000 mg
- Taurine
  - 500- 1500 mg
- Glutamine
  - 1,000-3,000 mg
- Co-factors
  - P5P: 10-50 mg

High GABA

- L-theanine
  - 100-500 mg bid



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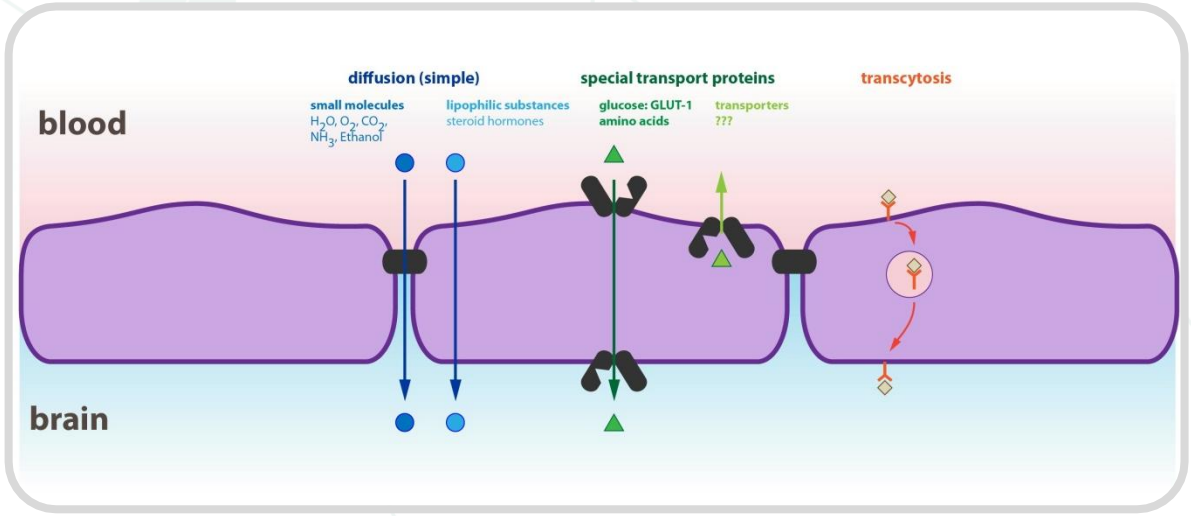
Inflammation & the BBB

- BBB is designed to allow only nano-sized particles in or out as needed, and to keep unhealthy things out.
- BBB is extremely vulnerable to inflammation



Kharrazian, Datis DHSc, DC, MS. *Why Isn't My Brain Working?* Carlsbad: Elephant Press, 2013. Print.

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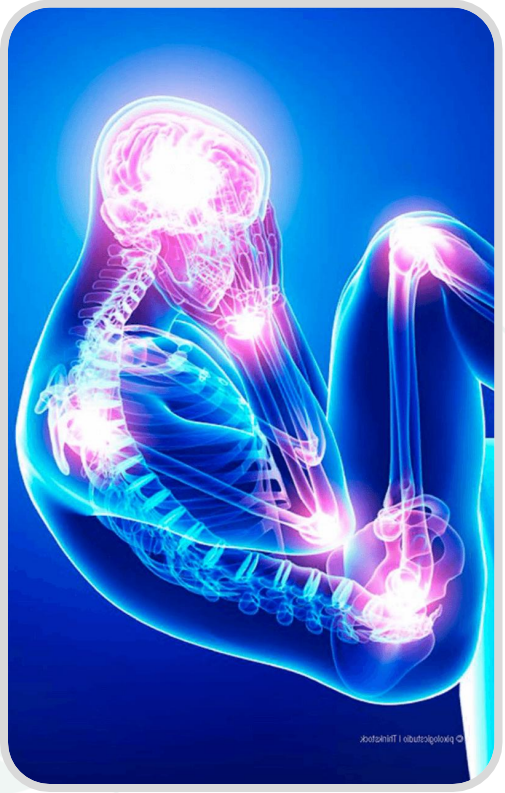
Inflammation: Perimenopause + ADHD



- ADHD and estrogen decline both linked to low-grade neuroinflammation.
- Systemic inflammation releases cytokines. These cytokines send messages across the BBB that activate inflammation in the brain, which alters function and can destroy brain tissue.
- Likewise, inflammation in the brain can activate the body's immune system and trigger systemic inflammation which can manifest as joint pain, gut pain, skin disorders, etc.

- Kharrazian, Datis DHSc, DC, MS. *Why Isn't My Brain Working?* Carlsbad: Elephant Press, 2013. Print.
- Backstrom, T. et al. (2014). *Prog Neurobiol*, 113, 88–94. https://doi.org/10.1016/j.pneurobio.2013.09.013

Cytokine effects on neurotransmitters

- Once cytokine signals reach the brain, they have the capacity to influence the synthesis, release, and reuptake of serotonin, dopamine, and norepinephrine.

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Miller AH, et al. Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression. *Biol Psychiatry*. 2009 May 1; 65(9): 732-741.

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Omega-3s to the Rescue

- Omega-3s reduce pro-inflammatory cytokines and protect against estrogen deficiency related neural inflammation.
- Omega-3s enhance dopaminergic transmission in the prefrontal cortex, improving attention and working memory
- EPA, in particular, increases dopamine release and reduces reuptake.

Wellness Wednesday

Freeman, M. P. et al. (2006). Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry*, 67(12), 1954–1967. https://doi.org/10.4088/JCP.v67n1217

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Omega-3 Fatty Acids: ADHD

- **Meta-analysis of 10 RCTs**: Omega-3s improve attention and reduce hyperactivity.
  - Participants: 699 children and adults diagnosed with ADHD
  - Small-to-moderate improvement in ADHD symptoms with omega-3s vs placebo.
  - Most benefit seen in **inattention symptoms** vs hyperactivity
  - Benefits attributed primarily to **EPA**, not DHA

Wellness Wednesday

Chang, J. P. C. et al. (2018). *Neuropsychopharmacology*, 43(3), 534–545. https://doi.org/10.1038/npp.2017.160

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EPA to DHA ratios matter

- Children with ADHD who had higher baseline EPA levels in red blood cells showed greater clinical improvement.
- EPA (not DHA) correlated more strongly with **reduction in ADHD symptoms**, particularly **inattention**.
- Supports the concept that **EPA dominant formulations** (EPA:DHA ≥ 2:1) are more effective.

Wellness Wednesday

Barragán, E., Breuer, D., Döpfner, M. (2017).
"Efficacy and safety of omega-3/6 fatty acids in children with ADHD: A double-blind, randomized, placebo-controlled trial."
Journal of Attention Disorders, 21(8), 667–676.
https://doi.org/10.1177/1087054713518238

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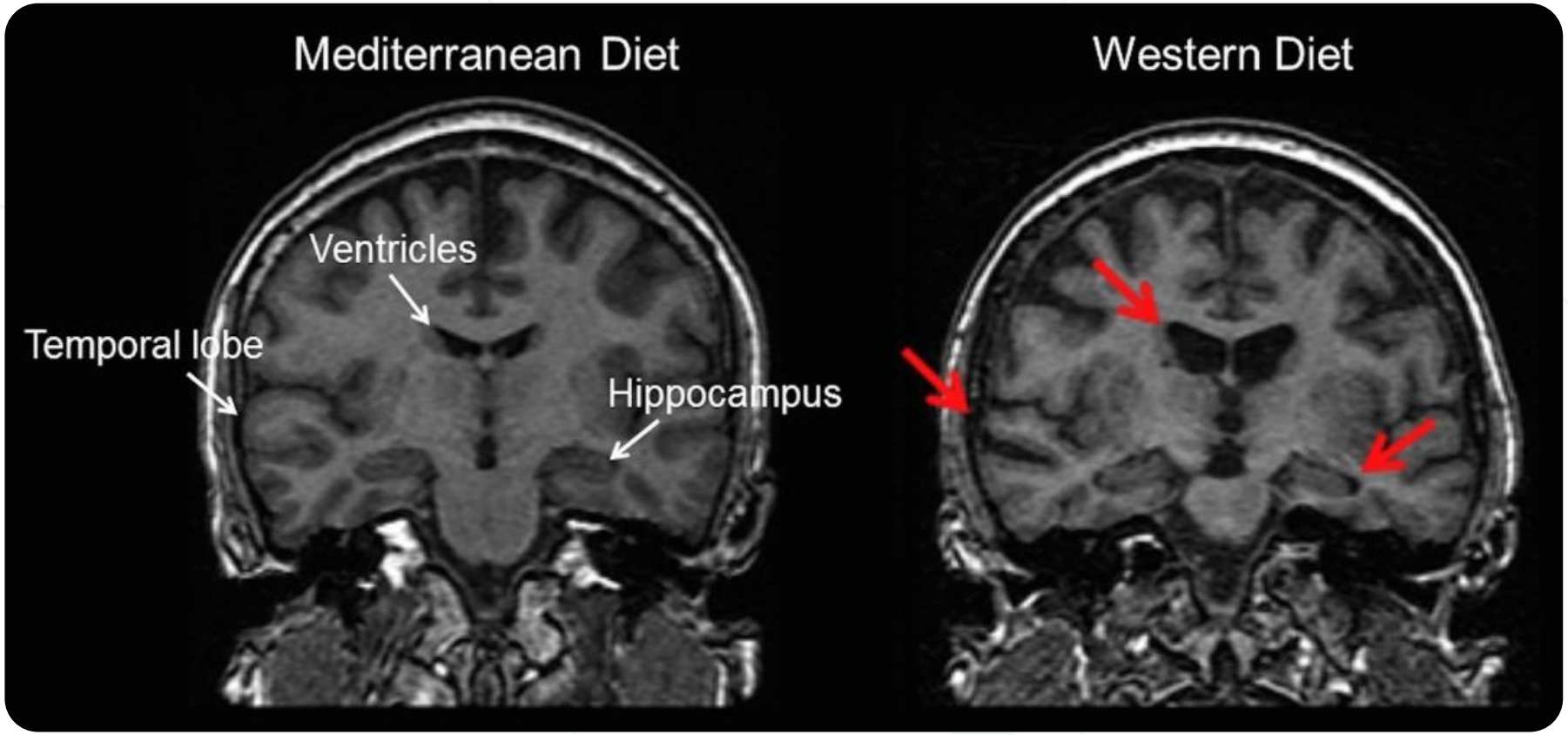
Life Style intervention: Mediterranean Diet

- Emphasis on fruits, vegetables, bread and other grains, potatoes, beans, nuts and seeds
- Limited dairy, eggs
  - Goat and sheep vs cow dairy
- Emphasis on fish and limited red meat
- Wine consumed with meals regularly
- Fruit as dessert
- Olive oil
  - Phenolic compounds (simple phenols, hydroxytyrosol and tyrosol, and the secoiridoids, oleuropein, oleocanthal, and ligstrosideconfer) antioxidant and anti-inflammatory properties
- Confounding factor of European Food standards, seasonal, local foods and “meals with others” (similar to hunter-gatherer diets)

Diet Is Immensely Influential



https://www.lisamosconi.com/projects. Accessibility verified 3/28/24.

Lifestyle Intervention: Exercise

1. Boosting Dopamine & Norepinephrine
   - Aerobic exercise stimulates dopamine and norepinephrine release, particularly in the prefrontal cortex, mimicking stimulant medication effects

2. Improving Neuroplasticity, Cognitive Control, Neuroinflammation
   - Exercise elevates BDNF, IGF, and synaptic proteins, supporting growth in the hippocampus & prefrontal cortex **study in children
   - Moderate-to-high intensity workouts produce anti-inflammatory effects by reducing IL-6 and TNF-α

Wellness Wednesday

1. Dastamooz S, Sadeghi-Bahmani D, Farahani MHD, Wong SHS, Yam JCS, Tham CCY, Sit CHP. The efficacy of physical exercise interventions on mental health, cognitive function, and ADHD symptoms in children and adolescents with ADHD: an umbrella review. EClinicalMedicine. 2023 Aug 10;62:102137. doi: 10.1016/j.eclinm.2023.102137. PMID: 37599910; PMCID: PMC10432969.
2. Chan YS, Jang JT, Ho CS. Effects of physical exercise on children with attention deficit hyperactivity disorder. Biomed J. 2022 Apr;45(2):265-270. doi: 10.1016/j.bj.2021.11.011. Epub 2021 Nov 29. PMID: 34856393; PMCID: PMC9250090.

DOCTOR'S DATA INC

Role of the Gut Microbiome

- Nutrition; Synthesize vitamins and nutrients
  - Compromised nutrient absorption (Vitamin D, calcium, magnesium, omega-3 FAs)may be associated with inflammation
- Metabolism; energy metabolism, glucose, lipid homeostasis
  - Aberrant glucose metabolism, mitochondria function and lipid metabolism are associated with inflammation
- Influence satiety and dietary patterns (GLP-1)
  - Incretin mimetics glucagon-like peptide-1 (GLP-1) receptor agonists Mounjaro (terzepatide) and Ozempic (semaglutide)
    - Reduce inflammation in the liver, kidneys and heart
- Immune Regulation
  - Informs and regulates self tolerance as human biology meets the external environment
    - T lymphocytes , CD4+ Th1 vs Th2 balance is associated with allergies and autoimmunity
- Influences innate and adaptive immune systems
  - T lymphocytes , CD4+ Th1 vs Th2 balance is associated with allergies and autoimmunity
- Gut associated lymphoid tissue (GALT) 70% of immune system resides in the gut
  - GALT is involved in the regulating intestinal immune responses during homeostasis and inflammatory bowel disease (IBD).
  - GALT is key to adaptative immune response, production of autoantibodies and gut inflammation

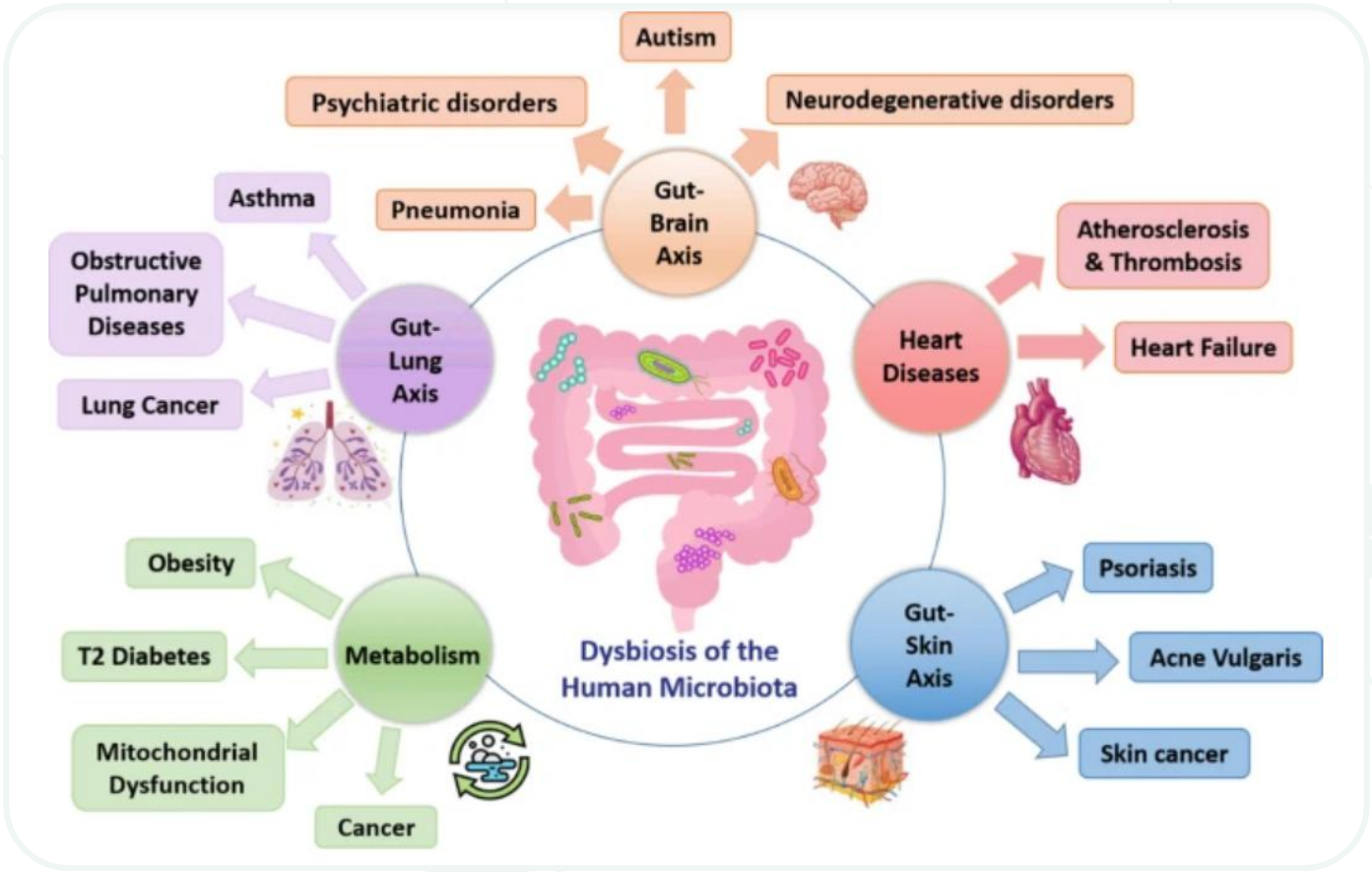
https://www.nature.com/articles/d41586-024-00118-4#:~:text=Evidence%20suggest%20that%20the%20drugs%20classified%20as%20GLP-1,reduce%20inflammation%20in%20the%20liver%2C%20kidneys%20and%20heart.
Pushpa Tandon, Natalie D. Abrams, Danielle M. Carrick, Preethi Chander, Johanna Dwyer, Rebecca Fuldner, Gallya Gannot, Maren Laughlin, George McKie, Mercy PrabhuDas, Anju Singh, Shang-Yi Anne Tsai, Merriline M. Vedamony, Chiayeng Wang, Christina H. Liu; Metabolic Regulation of Inflammation and Its Resolution: Current Status, Clinical Needs, Challenges, and Opportunities. J Immunol 1 December 2021; 207 (11): 2625–2630. https://doi.org/10.4049/jimmunol.2100829

Role of the Gut Microbiome

- Gut-Brain-Axis
  - Influences neurotransmitters (gut derived and neuronal derived via Vagus n.)
    - Cross-talk along the gut-brain axis regulates inflammatory nociception, inflammatory responses, and immune homeostasis
    - Intestinal permeability may be an indicated of compromised blood brain barrier
- Process complex carbohydrates and produce SCFAs
  - SCFAs, especially butyrate, anti-inflammatory properties
    - SCFAs act as microbial mediators and influence systemic physiology
    - Gut microbiota regulates susceptibility to extra-intestinal autoimmune diseases, such as multiple sclerosis, type 1 diabetes, arthritis and allergy
    - Gut dysbiosis plays a role in in chronic inflammatory diseases

https://www.nature.com/articles/d41586-024-00118-4#:~:text=Evidence%20suggest%20that%20the%20drugs%20classified%20as%20GLP-1,reduce%20inflammation%20in%20the%20liver%2C%20kidneys%20and%20heart. Pushpa Tandon, Natalie D. Abrams, Danielle M. Carrick, Preethi Chander, Johanna Dwyer, Rebecca Fuldner, Gallya Gannot, Maren Laughlin, George McKie, Mercy PrabhuDas, Anju Singh, Shang-Yi Anne Tsai, Merriline M. Vedamony, Chiayeng Wang, Christina H. Liu; Metabolic Regulation of Inflammation and Its Resolution: Current Status, Clinical Needs, Challenges, and Opportunities. J Immunol 1 December 2021; 207 (11): 2625–2630. https://doi.org/10.4049/jimmunol.2100829

Gut Microbiome Dysbiosis & Health



Wellness Wednesday

Gebrayel, P., Nicco, C., Al Khodor, S. *et al.* Microbiota medicine: towards clinical revolution. *J Transl Med* 20, 111 (2022). https://doi.org/10.1186/s12967-022-03296-9

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Gut Brain Axis (GBA)

Bidirectional communication system between the gastrointestinal tract and the central nervous system (CNS), involving:

- Neural pathways (Vagus nerve)
- Immune Signaling
- Microbial metabolites (Short Chain Fatty Acids)
- Neurotransmitter Production (Serotonin, Dopamine)

This axis allows the gut microbiota to influence neurodevelopment, mood, cognition, and behavior

Menopausal Changes: Less Microbiome diversity

- Premenopausal women have a robust gut microbiome with many different gut flora—our microbiome diversity peaks around age 40. After menopause, it starts to decline, and women's gut population begins to look more like that of men. A more diverse gut microbiome is beneficial because it helps better protect against germs and bacteria that can cause disease.
- In a 2023 study, researchers at the University of Oxford found that the more kinds of good flora you have, the quicker they can shut down invading bacteria.

Wellness Wednesday

- de la Cuesta-Zuluaga J, Kelley ST, Chen Y, Escobar JS, Mueller NT, Ley RE, McDonald D, Huang S, Swafford AD, Knight R, Thackray Sex-Dependent Patterns of Gut Microbial Diversity in Human Adults. mSystems. 2019 May 14;4(4):e00261-19. doi: 10.1128/mSystems.00261-19. PMID: 31098397; PMCID: PMC6517691.
- Frances Spragge et al. Microbiome diversity protects against pathogens by nutrient blocking.Science382,eadj3502(2023).DOI:10.1126/science.adj3502

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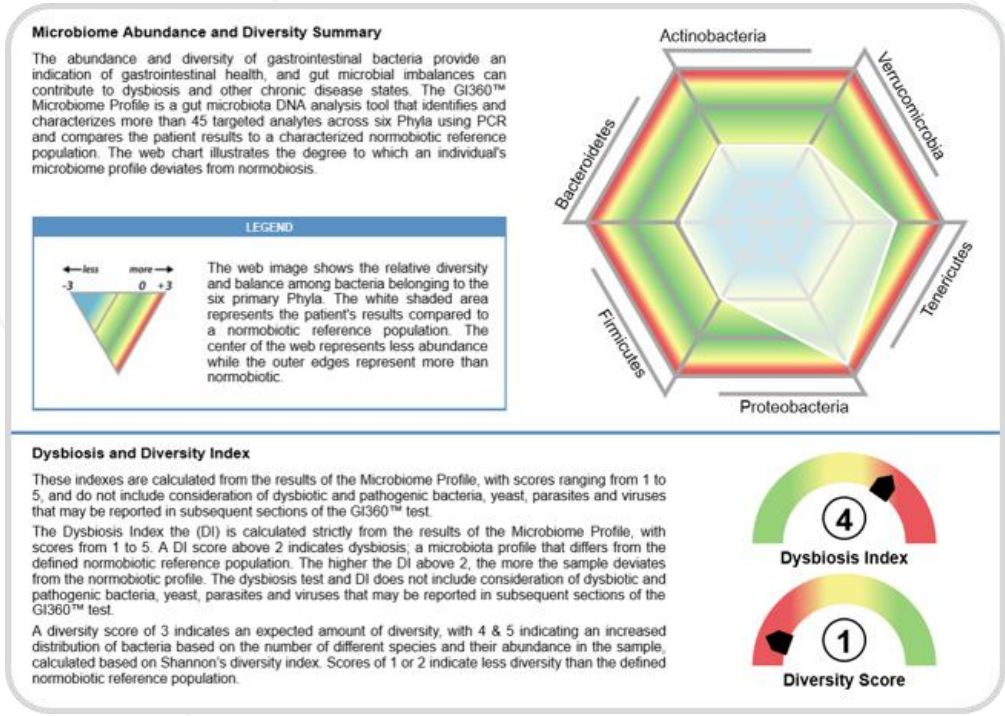
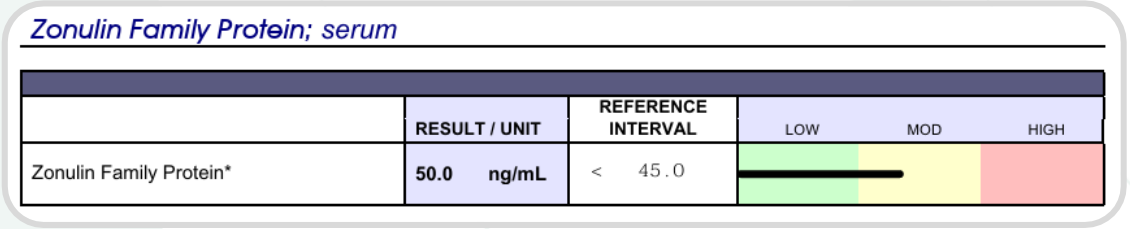
Dysbiosis & Its Role in ADHD Pathophysiology

1. Dysbiosis is an imbalance in the composition or function of the gut microbiota. In individuals with ADHD, dysbiosis is often characterized by:
    - **Decreased** microbial **diversity**
    - **Overgrowth** of potentially pro-inflammatory taxa such as **Bacteroides, Proteobacteria, and Clostridium**
    - **Reduced** beneficial strains like **Bifidobacterium and Faecalibacterium prausnitzii**



Aarts, E. et al. (2017). *Gut microbiome in ADHD and its relation to neural reward anticipation*. Microbiome, 5(1), 82. https://doi.org/10.1186/s40168-017-0301-5

Dysbiosis & Its Role in ADHD Pathophysiology



Zonulin Family Protein; serum

	RESULT / UNIT	REFERENCE INTERVAL	LOW MOD HIGH
Zonulin Family Protein*	**50.0** ng/mL	< 45.0	

2. Increased Intestinal Permeability ("Leaky Gut")
    - Dysbiosis can compromise the gut barrier, allowing lipopolysaccharides (LPS) and other bacterial endotoxins to enter systemic circulation.
    - This activates:
        - Toll-like receptor 4 (TLR4) on immune cells
        - Production of pro-inflammatory cytokines (e.g., IL-6, TNF-α)
        - Microglial activation in the brain, leading to neuroinflammation

Neuroinflammation is associated with altered dopaminergic function, impaired executive function, and behavioral dysregulation in ADHD

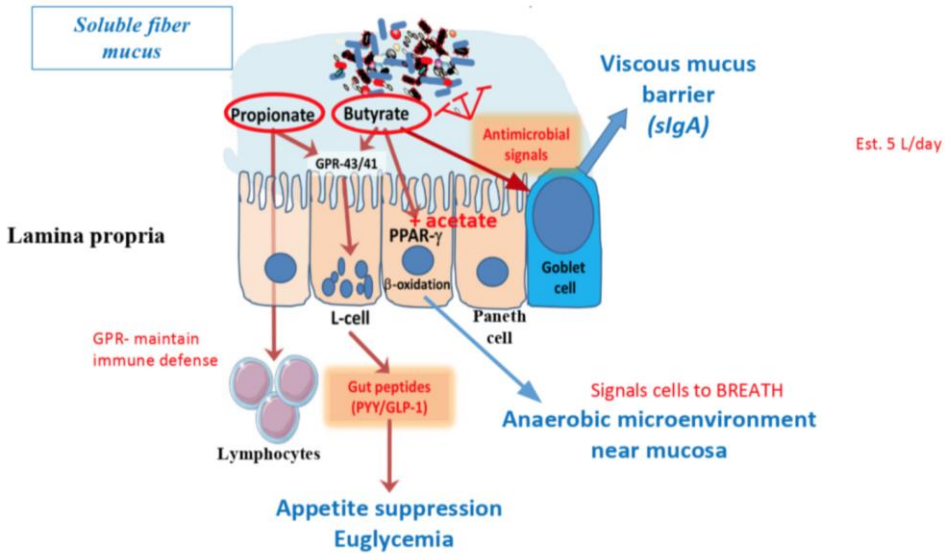
Prehn-Kristensen, A. et al. (2018). *Role of the gut microbiota in ADHD – A systematic review.* **Neurosci Biobehav Rev**, 92, 422–431. https://doi.org/10.1016/j.neubiorev.2018.06.016

Healthy microbial host crosstalk

Key Findings

Butyrate producing bacteria		Consistency, Abnormal	β-glucuronidase, Low
Gut barrier protective bacteria		Lactoferrin, Very High	*Pichia manshurica*, Cultured
Gut intestinal health marker		Lysozyme, High	
Pro-inflammatory bacteria		Calprotectin, Very High	
Gut barrier protective bacteria vs. opportunistic bacteria		Secretory IgA, Very Low	
		% Acetate, Low	

= Expected = Imbalanced



Modified from Gut (2018)67:1716–1725. doi:10.1136/gutjnl-2018-316723

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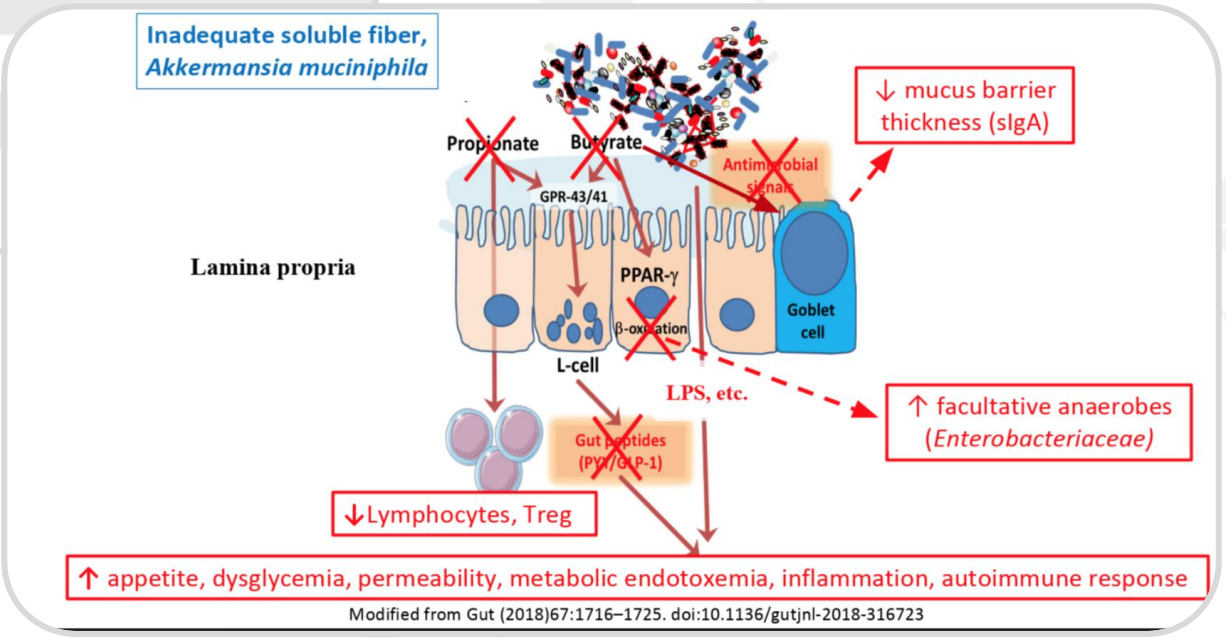
Dysbiosis induced breakdown

Key Findings

Butyrate producing bacteria		% Propionate, Low	*Klebsiella pneumoniae*, Cultured
Gut barrier protective bacteria		% Butyrate, High	*Proteus mirabilis*, Cultured
Gut intestinal health marker		% Valerate, Low	
Pro-inflammatory bacteria		Total SCFA's, Low	
Gut barrier protective bacteria vs. opportunistic bacteria		β-glucuronidase, Low	
		Occult Blood, Detected	

= Expected = Imbalanced



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Dysbiosis & Its Role in ADHD Pathophysiology

3. Microbial Influence on Neurotransmitters

Gut microbes synthesize or modulate key neurotransmitters:

- Dopamine: Influenced by microbial metabolism of tyrosine
- Serotonin: 90% of peripheral serotonin is produced in the gut
- GABA: Produced by Lactobacillus and Bifidobacterium strains

- Dysbiosis reduces production or availability of these neurotransmitters, leading to:
  - Inattention and impulsivity (dopamine)
  - Mood dysregulation (serotonin, GABA)
  - Sleep disturbances, often comorbid with ADHD

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Strandwitz, P. (2018). *Neurotransmitter modulation by the gut microbiota.* **Brain Research**, 1693, 128–133.

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Dysbiosis in ADHD

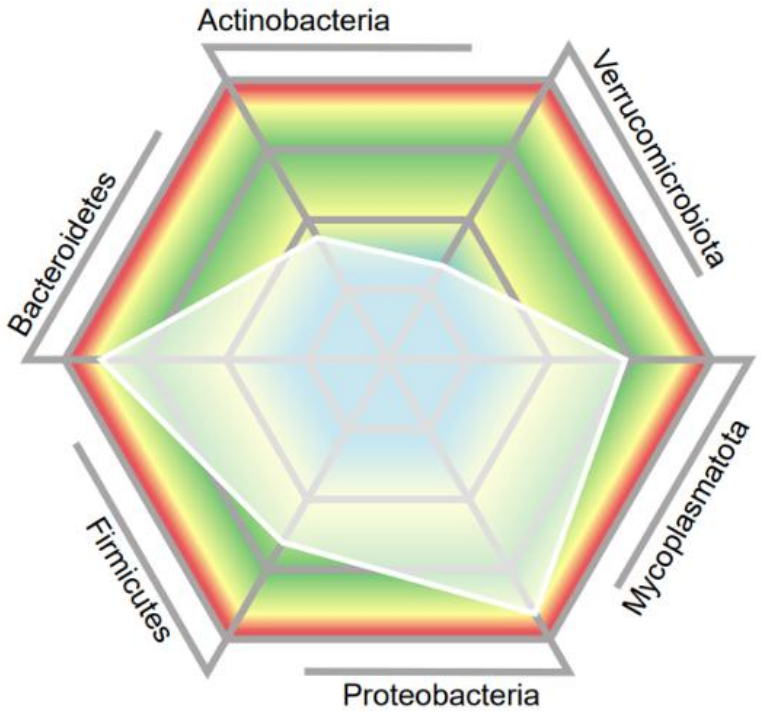
- Children with ADHD have altered microbial metabolites, including changes in short-chain fatty acids (SCFAs) like butyrate, which modulate brain inflammation and blood–brain barrier integrity.
  - Wang, L. J. et al., 2020. Brain, Behavior, and Immunity, 89, 418–429
- Germ-free mice display hyperactivity and reduced dopamine receptor expression, which are partially reversed by microbiota transplantation from healthy controls.
  - Hsiao, E. Y. et al., 2013. Cell, 155(7), 1451–1463

Gut Health Matters in ADHD

Mechanism	Microbial Contribution	Effect on ADHD
Neuroinflammation	LPS, cytokines, microglial activation	Impaired cognition, hyperactivity
Neurotransmitter imbalance	Dysregulated dopamine, serotonin, GABA	Inattention, impulsivity, anxiety
Barrier dysfunction	Leaky gut, endotoxin translocation	Systemic and CNS inflammation
Metabolite disruption	Low SCFAs (e.g., butyrate)	Blood–brain barrier compromise

Inflammatory Gut Bacteria in ADHD

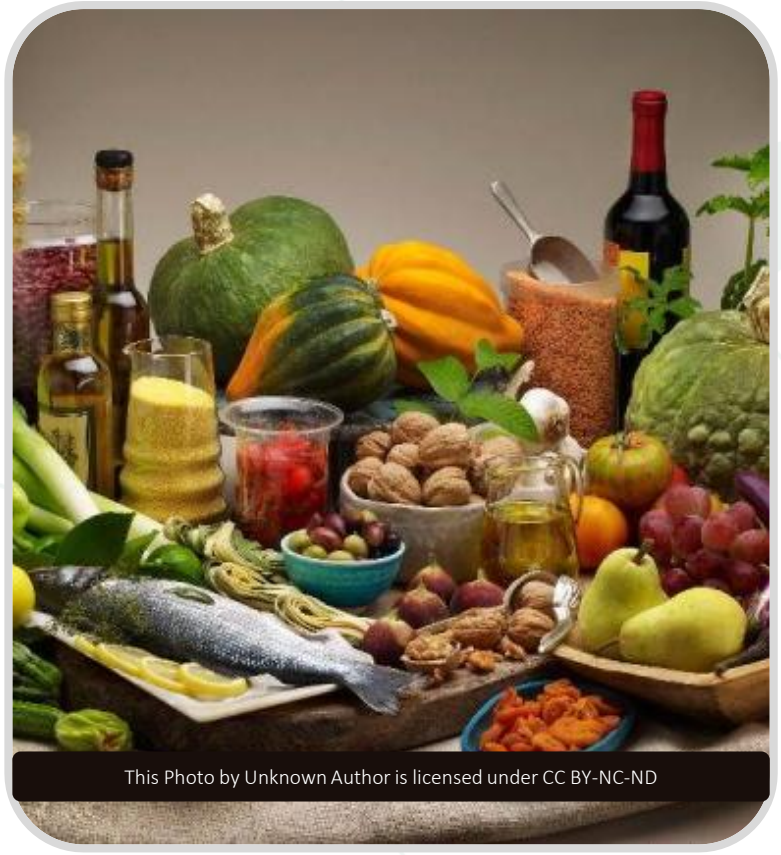
- ADHD microbiomes
  - Reduced : Bifidobacterium
  - Increased: Bacteroides, Clostridium, or Proteobacteria.



- Aarts, E. et al. (2017). Gut microbiome in ADHD: Distinct microbial signatures. *Microbiome*, 5, 82. https://doi.org/10.1186/s40168-017-0301-5
- Prehn-Kristensen, A. et al. (2018). Microbiota and ADHD: a review. *Neurosci Biobehav Rev*, 92, 422–431. https://doi.org/10.1016/j.neubiorev.2018.06.016

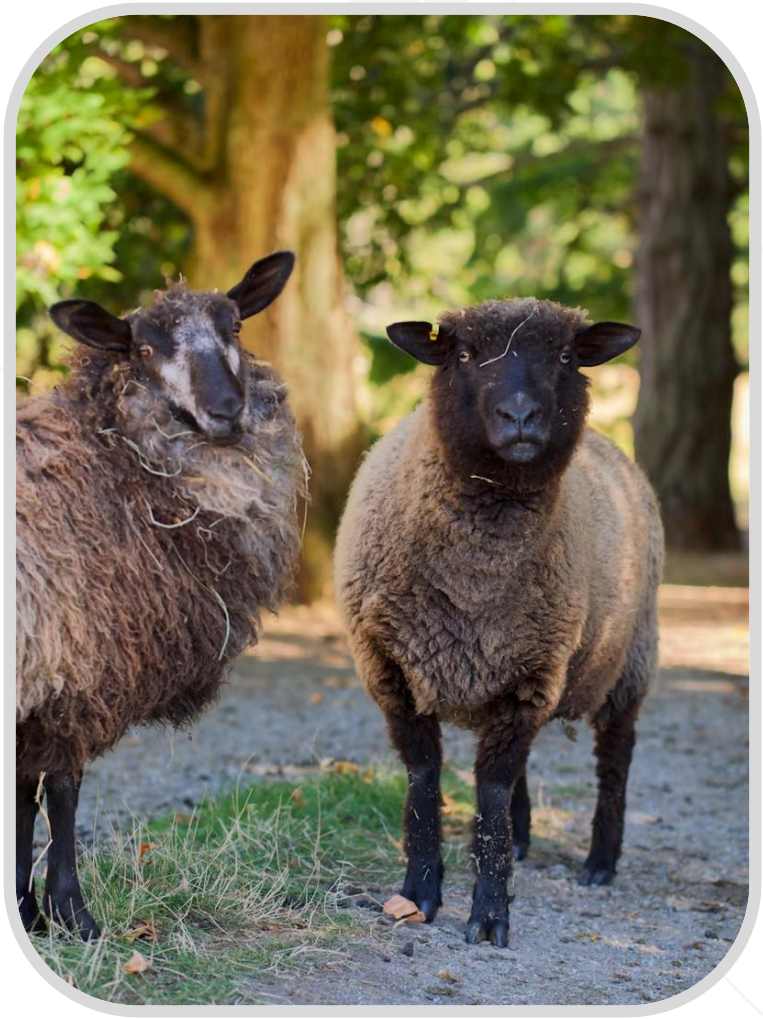
Anti-inflammatory Gut Bacteria

- ***Bifidobacterium spp.***
  - One of the primary colonizers of the human gut microbiome
  - Considered amongst the most beneficial commensal bacteria in the human gut
  - Provides health benefits directly through interactions with the host, and indirectly through interactions with other microorganisms
  - Involved in production and adsorption of vitamins, such as vitamins K and B12, biotin, folate, thiamine, riboflavin, and pyridoxine.
  - Also involved in lipid absorption and metabolism, glucose and energy homeostasis, and regulating intestinal barrier function
  - Polyphenols and anthocyans derived from red berries, chocolate, green tea, blackcurrant, red wine and grape seed extracts have been shown to increase *Bifidobacterium* species.
- ***Faecalibacterium prausnitzii***
  - One of the most prevalent bacteria within the human gastrointestinal tract
  - Recognized as a major butyrate producer and can promote anti-inflammatory processes and intestinal barrier function.
  - Lower levels of *Faecalibacterium prausnitzii* in the intestines have been associated with gastrointestinal and metabolomic disorders.



Anti-Inflammatory Diets & the Gut Microbiome

- Fermented Foods
- Fiber
- Produce
- Polyphenols
- Olive Oil
- Add herbs and spices
- Avoid processed foods



Questions?