The Mind-Body Connection

**Health, Research, & Interventions**

**May, 2025**

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Greeting Keni!

I hope this message finds you well!

You did some FANTASTIC work on your IRB Proposal Project! I left two lengthy comments and I’ve copy/pasted one of them below in the event you find it to be of interest and/or helpful.

What I’m observing broadly is that you’re expressing interests in a few different areas of research/health.

1. One area is in the field of **quantum biology/psychology/neurobiology and quantum healing** (as we discussed previously).
2. A second area is in the field of **the mind-body connection** (e.g., **mind-body phenomenon/health issues and mind-body interventions**).
   1. This is an area of research that falls under the purviews of the National Center for Complementary and Integrative Health (NCCIH) in terms of federal funding (though certainly, research can be done in this area outside of NCCIH funding as well).
   2. The rest of this document will pertain to mind-body research/health findings and systems that may be of interest to you as you continue to move forward on your journey.

# Areas of the Mind-Body Connection Recognized in Biomedicine

Regarding your interests in the mind-body connection, I wonder if some of the following topics might be of interest to you:

## Short- and Prolonged Stress Responses and Systems

## A variety of different internal and external stimuli can evoke stort-, prolonged-, and long-term or even chronic stress responses that are thought to be mediated by neural (brain) activation of the sympatho-adrenal-medullary (SAM) axis and hypothalamic-pituitary-adrenal (HPA) axis. The SAM axis is thought to be associated with immediate/rapid/acute/short-term stress responses, in which rapid activation of the sympathetic nervous system leads to release of adrenaline (epinephrine) and noradrenaline (norepinephrine)

## Of course! The \*\*SAM axis\*\* is activated when the brain perceives a stressor, particularly through the \*\*amygdala\*\*, which processes threats and signals the \*\*hypothalamus\*\* to initiate the response. The hypothalamus then stimulates the \*\*sympathetic nervous system\*\*, leading to the activation of the \*\*adrenal medulla\*\*—the inner part of the adrenal glands—which secretes \*\*adrenaline\*\* (epinephrine) and \*\*noradrenaline\*\* (norepinephrine). These hormones circulate through the bloodstream, preparing the body for immediate action by increasing heart rate, blood pressure, and energy mobilization. The result? A rapid, physiological "fight-or-flight" response to handle acute stress.

## The Hypothalamic-Pituitary-Adrenal (HPA) axis.

**The HPA Axis** coordinates neuroendocrine stress responses. A variety of different stimuli can evoke short-, prolonged-, and longer-term stress responses. Short-term stress response is primarily mediated by the **sympatho-adrenal medullary (SAM) axis**, which rapidly activates the sympathetic nervous system, leading to the release of adrenaline and noradrenaline for immediate fight-or-flight reactions. In contrast, the **hypothalamic-pituitary-adrenal (HPA) axis** governs the prolonged stress response by releasing cortisol, which helps regulate metabolism, immune function, and energy balance over extended periods but can contribute to negative health effects if chronically activated.

(e.g., stress hormones are lipophilic, meaning they can - and do - cross lipid barriers, including the gut membrane, the blood-brain-barrier, and cell membranes. This is one way in which stress hormones (secreted fro the adrenal glands located atop the kidneys bilaterally) can act in the gut and brain as neurotransmitters to alter a variety of different neurotransmission pathways at the rapid (nongenomic) and prolonged (genomic and epigenetic) levels, linking physical and mental health.

### Acute vs Chronic Stress

1. Shchaslyvyi, A. Y., Antonenko, S. V., & Telegeev, G. D. (2024). Comprehensive Review of Chronic Stress Pathways and the Efficacy of Behavioral Stress Reduction Programs (BSRPs) in Managing Diseases. International Journal of Environmental Research and Public Health, 21(8), 1077. <https://www.mdpi.com/1660-4601/21/8/1077>

## The Gut-Brain Axis (AKA The “Gut-Microbiome-Brain Axis”)

I'm still learning the best way to describe the gut-brain axis briefly but here are the basics.

### The Gut Microbiome and Symbiotic Gut Microbes

The human body contains 30 trillion human cells and 40 trillion microbe cells, primarily bacteria that live in our guts. We are actually MORE gut microbe than we are human by cell count. We humans have highly symbiotic relationships with our gut microbes. They produce **postbiotics (**"gut microbe poop") that include short-chain fatty acids (SCFAs), neurotransmitter precursors like tryptophan (a precursor for serotonin that can cross the blood-brain barrier to support serotonin synthesis in the brain), inflammatory cytokines (including both anti- and pro-inflammatory cytokines that can reduce and enhance inflammation respectively), and stress hormones. In turn, these **postbiotics** can influence our mood through three main ways.

#### Neurotransmitter precursor postbiotics

Like tryptophan can alter serotonin levels in the gut and brain [sidenote ~80% of our body’s' serotonin supply is synthesized in the gut, not the brain, and I believe a majority of serotonergic receptors exist in the gut too]. In this way, our gut microbes can act as a natural pharmacy!

#### Inflammatory postbiotics

Inflammatory postbiotics can influence inflammatory processes in the gut, body, and brain. This is one way in which the food we eat can induce (cause) inflammation. Separate from this though, ~80% of our bodies’ immune system lives in our guts. Our immune cells interact with the food we eat to determine whether it is “safe/us/of Earth” or “unsafe/not us/not of Earth”). This is actually the primary way in which the food we eat can induce inflammation and immune responses.

Like stress hormones, inflammatory cytokines (immune cells) can cross barriers, including the gut barrier and the blood brain barrier. This, in turn, is a major way in which the food we eat (or don't eat) can result in inflammation that can become systemic (contributing to a host of physical health issues) and can contribute to ***neuroinflammation*** *(inflammatory cytokes (immune cells) activated in the brain),* which can contribute to a host of mental health issues in turn. Neuro-Inflammatory processes can cause cell death which - in the hippocampus and other brain regions - is strongly associated with and predictive AND CAUSATIVE of depression. Inflammation in the amygdala contributes to anxiety states. Of course, inflammation that remains local to the gut can contribute to IBS and IBD, and broadly these can also contribute to a large host of autoimmune disorders.

#### Stress hormone postbiotics.

As above, stress hormones (and other steroid hormones; e.g., reproductive hormones, etc) can cross membranes and barriers, including the gut lining and the blood brain barrier, as well as cell membranes, to induce immediate, non-genomic effects and more long-term genomic (genetic and epigenetic) changes. In the brain, stress hormones can induce cell death (correlated with depression, as described above), they can induce dysregulation of the HPA axis (associated with almost all psycholoigcal states, esp. trauma and stress related disorders, burnout, etc), they can cause hyperactiity in the amygdala associated with fear and panic, they can alter reward neurotransmission (e.g., dopamine release in the nucleus accumbens) associated with ADD/ADHD, attention and motivation issues, and reward processes that contribute to alcohol use disorder, substance related and addictive disorders, addiction-type eating disorders, etc. chronic stres in the brain also tends to inhibit neurogenesis (e.g., new brain cell birth and growth that are known to reverse depression) and neuroplasticity (e.g., LTP/LTD, the mechanism ketamine works on, also known to reverse depression and enable learning and growth and memory). This is mediated in part thorugh the ability of stress to inhibit serotonin production (Li et al., 2015), but also occurs separately from the impacts of stress hormones on serotonin (e.g., Bray et al., 2016, 2018). In the body, stress hormones can induce inflammation and dysregulation of the immune system (the glucocorticoid stress system and the immune system are DEEPLY intertwined), this in turn can contribute to autoimmune disorders. Stress hormones can also dysregulate blood glucose levels and contribute to nearly all phsyical disease and disorder states. In the gut, like inflammation, stress hormones can cause IBS, IBD, and a variety of other issues.

## The Immune-Brain “Axis” (AKA “Psycho-Immuno-Neurobiology”)

The role of the Immune System (and Inflammatory Processes) in the Gut, Brain, Body, and on Physical and Mental Health are mostly described in section 2.1.2 above (“Inflammatory Postbiotics”)).

Approximately 80% of the body’s immune system lives in the gut. Our immune cells interact with the food we eat to determine whether it is “safe/us/of Earth” or “unsafe/not us/not of Earth”). This is the primary way in which the food we eat can induce inflammation and immune responses.

Like stress hormones, inflammatory cytokines (immune cells) can cross barriers, including the gut barrier and the blood brain barrier. This, in turn, is a major way in which the food we eat (or don't eat) can result in inflammation that can become systemic (contributing to a host of physical health issues) and can contribute to ***neuroinflammation*** *(inflammatory cytokes (immune cells) activated in the brain),* which can contribute to a host of mental health issues in turn. Neuro-Inflammatory processes can cause cell death which - in the hippocampus and other brain regions - is strongly associated with and predictive AND CAUSATIVE of depression. Inflammation in the amygdala contributes to anxiety states. Of course, inflammation that remains local to the gut can contribute to IBS and IBD, and broadly these can also contribute to a large host of autoimmune disorders.

## The Immune-Adrenal-Gut-Brain Axis (or Adrenal-Immune-Gut-Brain Axis)

Although the HPA axis (above), the Gut-brain axis (above) and the immune-brain “connection” (above, e.g., Psycho-immuno-neurobiology) are all areas with strong empirical support and ongoing empirical investigation, I don’t see the term “immune-gut-brain axis” used in PubMed ever (with only one single exception). I suspect this is because the immune system is not regarded as an “axis” in the same way the HPA axis and Gut-Brain axis are. At any rate, there IS a strong base of research that confirms, addresses and explores the interconnections of these

### Immune-Adrenal-Gut-Brain Resources

I tend to consider Risch, Layden, & Dugas’ 2023 review to be the most comprehensive “holy grail” on the Immune-Adrenal-Gut-Brain Connection. It has some nice figures though it IS comprehensive (AND LONG).

1. **Warren, A., Nyavor, Y., Beguelin, A., & Frame, L. A. (2024, 2024-May-02). Dangers of the chronic stress response in the context of the microbiota-gut-immune-brain axis and mental health: a narrative review [Review]. *Frontiers in Immunology, Volume 15 - 2024*.**[**https://doi.org/10.3389/fimmu.2024.1365871**](https://doi.org/10.3389/fimmu.2024.1365871)
2. **Rusch, J. A., Layden, B. T., & Dugas, L. R. (2023). Signaling cognition: the gut microbiota and hypothalamic-pituitary-adrenal axis. *Frontiers in endocrinology*, *14*, 1130689.** [**https://doi.org/10.3389/fendo.2023.1130689**](https://doi.org/10.3389/fendo.2023.1130689)
3. Marano, G., Mazza, M., Lisci, F. M., Ciliberto, M., Traversi, G., Kotzalidis, G. D., De Berardis, D., Laterza, L., Sani, G., Gasbarrini, A., & Gaetani, E. (2023). The Microbiota-Gut-Brain Axis: Psychoneuroimmunological Insights. *Nutrients*, *15*(6), 1496. <https://doi.org/10.3390/nu15061496>
4. Mázala-de-Oliveira, T., Silva, B. T., Campello-Costa, P., & Carvalho, V. F. (2023, Oct 10). The Role of the Adrenal-Gut-Brain Axis on Comorbid Depressive Disorder Development in Diabetes. *Biomolecules, 13*(10). <https://doi.org/10.3390/biom13101504>

## The Immune-Adrenal-Brain Axis

You can pretty much skip this section, as it’s largely covered in section 4 above. That said, I’m including it, since you’ll find more information and resources here (and in each of the separate components of the Immune-Adrenal-Gut-Brain axis) as compared to the immune-adrenal-gut-brain axis altogether.

### Immune-Adrenal-Brain Resources

1. Straub, R. H., & Cutolo, M. (2018). Psychoneuroimmunology—developments in stress research. *Wiener Medizinische Wochenschrift, 168*, 76-84. <https://studynotesunisa.co.za/wp-content/uploads/2018/12/StraubandCutulo_2017_psychoneu.pdf>
2. Hassamal, S. (2023). Chronic stress, neuroinflammation, and depression: an overview of pathophysiological mechanisms and emerging anti-inflammatories [Review]. *Frontiers in Psychiatry, Volume 14 - 2023*. <https://doi.org/10.3389/fpsyt.2023.1130989>
3. Katrinli, S., Oliveira, N. C. S., Felger, J. C., Michopoulos, V., & Smith, A. K. (2022). The role of the immune system in posttraumatic stress disorder. *Transl Psychiatry, 12*(1), 313. <https://doi.org/10.1038/s41398-022-02094-7>
4. Sun, Y., Qu, Y., & Zhu, J. (2021). The Relationship Between Inflammation and Post-traumatic Stress Disorder. *Front Psychiatry, 12*, 707543. <https://doi.org/10.3389/fpsyt.2021.707543>
5. Song, H., Fang, F., Tomasson, G., Arnberg, F. K., Mataix-Cols, D., De La Cruz, L. F., Almqvist, C., Fall, K., & Valdimarsdóttir, U. A. (2018). Association of stress-related disorders with subsequent autoimmune disease. *Jama, 319*(23), 2388-2400.
6. Niharika, L., Sharma, M., Babu, V. S., & Chahare, V. W. (2024). The Mind-Body Connection in Stress and Immunity: A Systematic Review. *European Journal of Cardiovascular Medicine, 14*, 303-306. <https://www.healthcare-bulletin.co.uk/article/the-mind-body-connection-in-stress-and-immunity-a-systematic-review-2577/>

# Summer Reading ☺

Here are a few publications you like to get you started (of course, no pressure):

## Adrenal-Gut-Brain Axis

The hypothalamic-pituitary-adrenal (HPA) axis and the gut-brain axis (AKA the “Gut-Brain-Microbiome Axis”) are both topics with strong empirical support and ongoing investigation. I consider Risch, Layden, & Dugas’ 2023 review to be the most comprehensive “holy grail” on the topic. It has some nice figures though it IS comprehensive (AND LONG).

1. **Warren, A., Nyavor, Y., Beguelin, A., & Frame, L. A. (2024, 2024-May-02). Dangers of the chronic stress response in the context of the microbiota-gut-immune-brain axis and mental health: a narrative review [Review]. *Frontiers in Immunology, Volume 15 - 2024*.**[**https://doi.org/10.3389/fimmu.2024.1365871**](https://doi.org/10.3389/fimmu.2024.1365871)
2. **Rusch, J. A., Layden, B. T., & Dugas, L. R. (2023). Signaling cognition: the gut microbiota and hypothalamic-pituitary-adrenal axis. *Frontiers in endocrinology*, *14*, 1130689.** [**https://doi.org/10.3389/fendo.2023.1130689**](https://doi.org/10.3389/fendo.2023.1130689)
3. Marano, G., Mazza, M., Lisci, F. M., Ciliberto, M., Traversi, G., Kotzalidis, G. D., De Berardis, D., Laterza, L., Sani, G., Gasbarrini, A., & Gaetani, E. (2023). The Microbiota-Gut-Brain Axis: Psychoneuroimmunological Insights. *Nutrients*, *15*(6), 1496. <https://doi.org/10.3390/nu15061496>
4. Mázala-de-Oliveira, T., Silva, B. T., Campello-Costa, P., & Carvalho, V. F. (2023, Oct 10). The Role of the Adrenal-Gut-Brain Axis on Comorbid Depressive Disorder Development in Diabetes. *Biomolecules, 13*(10). <https://doi.org/10.3390/biom13101504>

## Immune-Adrenal-Brain Axes (Pycho-neuro-immuno-endocrinology):

1. Straub, R. H., & Cutolo, M. (2018). Psychoneuroimmunology—developments in stress research. *Wiener Medizinische Wochenschrift, 168*, 76-84. <https://studynotesunisa.co.za/wp-content/uploads/2018/12/StraubandCutulo_2017_psychoneu.pdf>
2. Hassamal, S. (2023). Chronic stress, neuroinflammation, and depression: an overview of pathophysiological mechanisms and emerging anti-inflammatories [Review]. *Frontiers in Psychiatry, Volume 14 - 2023*. <https://doi.org/10.3389/fpsyt.2023.1130989>
3. Katrinli, S., Oliveira, N. C. S., Felger, J. C., Michopoulos, V., & Smith, A. K. (2022). The role of the immune system in posttraumatic stress disorder. *Transl Psychiatry, 12*(1), 313. <https://doi.org/10.1038/s41398-022-02094-7>
4. Sun, Y., Qu, Y., & Zhu, J. (2021). The Relationship Between Inflammation and Post-traumatic Stress Disorder. *Front Psychiatry, 12*, 707543. <https://doi.org/10.3389/fpsyt.2021.707543>
5. Song, H., Fang, F., Tomasson, G., Arnberg, F. K., Mataix-Cols, D., De La Cruz, L. F., Almqvist, C., Fall, K., & Valdimarsdóttir, U. A. (2018). Association of stress-related disorders with subsequent autoimmune disease. *Jama, 319*(23), 2388-2400.
6. Niharika, L., Sharma, M., Babu, V. S., & Chahare, V. W. (2024). The Mind-Body Connection in Stress and Immunity: A Systematic Review. *European Journal of Cardiovascular Medicine, 14*, 303-306. <https://www.healthcare-bulletin.co.uk/article/the-mind-body-connection-in-stress-and-immunity-a-systematic-review-2577/>

## Psychoneuroimmunology

1. Heather Zwickey's done quite a bit of work in this area.
   1. My colleague Matthew Hicks (MS, ND, who was just appointed to the Oregon Psilocybin Advisory Board) used to run a podcast and had Heather on; unfortunately, I think that podcast is no longer being hosted as it got too $$. In leu of that podcast, here are a few resources of Heather’s that might be helpful.
      1. I mention Matthew here b/c I know you expressed interests in psychedelics as well. I know I mentioned NUNM’s MS in Clinical Research Program; one of my ND/MSR students at NUNM, Payton Follestad is pioneering some work on Ayahuasca right now and Dr. Hicks has quite a bit of ongoing research on psilocybin and shaman psychedelic medicine practices.
   2. Gustafson C. **Heather Zwickey, PhD: Neuroimmunomodulation-A Driving Force Behind the Need for a Holistic Approach to Medicine**. Integr Med (Encinitas). 2017 Aug;16(4):24-26. PMID: 30881253; PMCID: PMC6415636. <https://pmc.ncbi.nlm.nih.gov/articles/PMC6415636/>
   3. **PODCAST:** Ep 6 - Immunology, Gut Microbes, and You. (2022, November 4, 2022). In *Ep 6 - Immunology, Gut Microbes, and You*. Can be accessed here:
      * + <https://podcasts.apple.com/us/podcast/inherited-wellness/id1624398725?i=1000585067597>
        + <https://inheritedwellness.substack.com/p/ep-6-your-immunology-story-gut-microbes>
2. Murphy, T. F. (2024). Psychoneuroimmunology. *Psychology Fanatic*. <https://psychologyfanatic.com/psychoneuroimmunology/>
3. MADDEN, K. S., BELLINGER, D. L., & ACKERMAN, K. (2003). PSYCHONEUROIMMUNOLOGY: INTERACTIONS BETWEEN THE BRAIN. *Neuropsychiatry*, 245. <https://animalmedicalresearch.org/Vol.14_Issue-2_December_2024/PSYCHO-NEURO-IMMUNO-ENDOCRINOLOGY.pdf>

## Mind-Body Interventions

1. Niharika, L., Sharma, M., Babu, V. S., & Chahare, V. W. (2024). The Mind-Body Connection in Stress and Immunity: A Systematic Review. *European Journal of Cardiovascular Medicine, 14*, 303-306. <https://www.healthcare-bulletin.co.uk/article/the-mind-body-connection-in-stress-and-immunity-a-systematic-review-2577/>
2. Khanpour Ardestani, S., Karkhaneh, M., Stein, E., Punja, S., Junqueira, D. R., Kuzmyn, T., Pearson, M., Smith, L., Olson, K., & Vohra, S. (2021). Systematic Review of Mind-Body Interventions to Treat Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Medicina, 57*(7), 652. <https://www.mdpi.com/1648-9144/57/7/652>
   * This is a systematic review specific to myalgic encephalomyelitis/chronic fatigue syndrome, so some parts won't be super relevant, but it can at least provide a nice taster.

## Acute vs Chronic Stress

1. Shchaslyvyi, A. Y., Antonenko, S. V., & Telegeev, G. D. (2024). Comprehensive Review of Chronic Stress Pathways and the Efficacy of Behavioral Stress Reduction Programs (BSRPs) in Managing Diseases. International Journal of Environmental Research and Public Health, 21(8), 1077. <https://www.mdpi.com/1660-4601/21/8/1077>

# Plug for NUNM’s Clinical Research MS Program

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