

The Intersection of the Microbiome-Gut-Brain Axis, PTSD, and Ayahuasca in Veterans

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A COMMON THEME AMONG THOSE who eventually make their way toward psychedelic medicine is the realization that the current standard of care for mental health provides few reliably effective treatment options. Many of these same individuals acknowledge how little the lay audience and scientific communities seem to understand about what it means to be mentally healthy. For American military veterans, coming to terms with these kinds of realizations has become a painful and standard part of one's transition process, not to mention the endless paperwork and severely protracted timelines associated with their attempts to receive care within the U.S. Department of Veterans Affairs (VA). In large part, due to the groundbreaking research from the Multidisciplinary Association for Psychedelic Studies (MAPS), the scientific community is reevaluating the use of certain illicit substances like MDMA and ayahuasca, leading to the reemerging discussion of psychedelic-assisted therapy. The tremendous potential of these substances is providing hope for countless individuals who seek peace from their traumas. Heroic Hearts Project (heroicheartsproject.org) was founded to solve this disconnect between the mental health systems of the VA and exciting breakthroughs that are happening in psychedelic research.

Given the extreme nature of the profession, members of the military are at much higher risk for experiencing trauma and struggling with mental health issues such as posttraumatic stress disorder (PTSD), depression, anxiety, and addiction than their civilian peers. Because of this, the veteran population is a good barometer for measuring just how effective current treatment options are at helping individuals work through and beyond their traumas and improving mental health. It won't come as a surprise to most people that the current options are severely lacking. According to the latest VA report, veterans are 1.5 times more likely to die by suicide than Americans who never served in the military. For female veterans, the risk factor jumps to 2.2 times more likely (U.S. Department of Veterans Affairs, 2019). These numbers have stayed elevated for over 15 years, and despite billions of dollars in funding for a variety of federal initiatives, the VA has not been successful at effectively addressing veteran suicide. In fact, the veteran suicide epidemic may be getting worse: the total number of suicides among veterans has increased steadily during four of the last five years on record (U.S. Department of Veterans Affairs, 2019).



In May 2019, the Heroic Hearts veterans group participate in ayahuasca ceremonies in this maloka in Tarapoto, Peru. Photo Credit: Jeremy Lock

The VA's current standard of care for mental health issues like PTSD includes a form of psychotherapy and medication. Unfortunately for many veterans, the approach for determining mental health diagnoses is an overly simplistic psychological evaluation. Based on the answers provided, a veteran will receive a percentage rating based on the detected severity of PTSD. However, there is rarely any discussion of other important factors in a veteran's life, like their diet, sleep, quality of life, current employment, social support network, and other contributing elements. All of our interactions with veterans in the Heroic Hearts program strongly suggest that these are all important considerations for how well a veteran will adjust to a post-military life.

There are other factors that play a significant role in influencing a veteran's overall mental health, including brain trauma, toxic exposures, and pre-military trauma. Standard assessments fail to consider and/or measure these factors, which is critical because we now know that many symptoms of traumatic brain injury (TBI), specifically military-related blast trauma, and PTSD overlap, leading to the misdiagnosis of PTSD in those suffering from brain injuries. There are a cluster of symptoms collectively known as "Operator Syndrome," of which TBI and PTSD can be a part, but it's a complex collection of many factors, and it's affecting our special operations community at an alarming rate (Stewart & Trujillo, 2020). A partner veteran organization, HunterSeven Foundation (hunterseven.org), has been dedicated to bringing attention to the nuanced mental and physical health issues that veterans often face due to the extreme impact that toxic exposures from burn pits and other occupational hazards have on the body. It's nearly impossible to consider every exposure, every blast, every night of missed sleep that a service member accumulates over his or her career, but these examples should highlight the numerous ways in which the current assessments are falling short and potentially leading to misdiagnosing and misunderstanding serious issues.

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Many of the veterans who go through our program share similar stories about their frustrating experiences with the VA. For perspective, the following is one such account from a veteran in the Heroic Hearts program.

After my own issues were starting to negatively impact my life I decided to go to the VA in order to seek professional therapy. Hours later, I ended up walking out of the office, having achieved nothing. I was told that I would have to learn to live with PTSD. They informed me that they could provide me with three therapy sessions but after that I would have to be open to going on medication if I wished to continue. I wasn't interested in medication, so I left. There was no discussion about any other aspects of my life or any real assessment of the issues I was struggling with.

Unfortunately, stories like these and stories of veterans finding themselves with more than ten prescription medications are far too common.

Through our work at Heroic Hearts Project, we have come to realize the breadth of what "mental health" really means. Although there can be commonalities among the symptoms that veterans experience, each person is unique and should be treated as such. Additionally, veterans and all individuals should have more agency with regard to their preferences for treatment rather than being told what to do. Currently available prescription medications are certainly a powerful tool and should be considered as an option for some, but psychedelics provide an alternative that may be more effective in some cases.

Over the years, our proprietary veteran program has evolved around this concept, which has primarily focused on helping veterans with PTSD find healing through ayahuasca.

However, we quickly began to realize that many of the veterans who came to us for healing displayed some, but not all, of the symptoms required for a PTSD diagnosis according to the Clinician-Administered PTSD Scale (CAPS-5) from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), and yet they were still struggling mightily. What the veterans were experiencing was more complex and nuanced than what the CAPS-5 assessment was measuring, and each person had multiple influencing factors that contributed to how he or she dealt with trauma. What we witnessed was in stark contrast to our culture's stereotype that "problems"

with veterans are psychological in nature and all stem from one or more uniquely stressful or horrific events that imprinted on the individual's mind and subsequently affected behavior.

Service-related traumatic events often do play a major role in the psychological health of a veteran, but stopping here at the explanation is only a partial measure. The majority of the veterans in our program have had some form of combat-related trauma, but again, addressing just combat-related experiences falls short of a holistic approach to health. We believe that in order for veterans to fully heal and experience long-lasting results, more comprehensive approaches to physical, mental, and spiritual health are needed.

It's an exciting time to be participating in and studying psychedelic research. The field continues to grow, and new preclinical and clinical studies are being pursued on a regular basis. However, restrictions and legalities have made the research on these important medicines difficult or impossible in many parts of the world. With regard to ayahuasca, randomized, placebo-controlled clinical trials are few and far between. Observational research studies and anecdotal reports predominate in the literature, but even these are hard to come by. Thus, new empirical studies are increasingly important to pursue. Our team believes that ayahuasca, when administered in a traditional ceremonial setting, can be extremely effective for helping veterans overcome mental health challenges, including PTSD, and we have observed as much in our few short years of existence as an organization. "During the ayahuasca journey, individuals can explore sensations, emotions, and thoughts associated with trauma, so that symptoms are discharged and resolved. Ayahuasca also guides victims to resolve events that predispose them to PTSD" (Nielson & Megler, 2014).

The authors of this paper primarily focus on providing alternative options for healing to veterans in need. The authors also feel compelled to better understand how ayahuasca can benefit veterans struggling with PTSD, but also those struggling with TBI or other mental or physical health issues. To that end, this team has undertaken a novel study to investigate how ayahuasca consumption can lead to changes in the gut microbiome in veterans with PTSD, and how psychological, biological, and physiological biomarkers are correlated with these changes. This research is ongoing and preliminary data will be available in early 2021.

When Dr. Kate Pate, an author of this paper, initially approached Dr. Christopher Lowry, another author of this paper, about working with Heroic Hearts Project to evaluate and understand the intersection of ayahuasca, the gut microbiome, and PTSD, he jumped at the opportunity. His laboratory is grounded in the desire to develop novel therapeutic strategies to the prevention and treatment of anxiety disorders, affective disorders, and trauma- and stressor-related disorders, such as PTSD. In particular, Dr. Lowry shares a common interest in complementary and integrative health approaches to the treatment of trauma- and stress-related disorders, in part because these approaches tend to be more acceptable to many veterans, and, while the jury is still out, these complementary and integrative health approaches appear to hold great promise.



The first dose of ayahuasca during a ceremony with a Heroic Hearts veteran group in Tarapoto, Peru, in May 2019. Photo Credit: Jeremy Lock

But why study the gut microbiome in association with ayahuasca as treatment for PTSD? The interest is founded in our growing understanding that the microbiome-gut-brain axis plays a role in both physical and mental health. The authors are particularly interested in the relationship between the gut microbiome, inflammation, and mental health. To understand why, it's important to grasp a few tenets.

First, inflammation prior to or at the time of trauma exposure increases the risk of developing PTSD symptoms. For example, in a seminal study, the Marine Resiliency Study of 2,600 war zone-deployed Marines, those who had higher blood concentrations of C-reactive protein, a biomarker of inflammation, at boot camp had higher risk of post-deployment PTSD symptoms (Eraly et al., 2014).

Second, trauma and stressor exposures can alter the gut microbiome in ways that favor increases in inflammation. The mechanisms involved are not completely understood, but some are becoming more clear. One mechanism is through reduction of what is called "alpha diversity" of the microbiome. The consensus is that a microbiome characterized by high alpha diversity is a healthy microbiome (McBurney et al., 2019), and that stress, by decreasing alpha diversity, makes the gut microbiome more vulnerable to opportunistic pathogens. Opportunistic pathogens can cause gut inflammation, "leaky gut," resulting in translocation of bacteria from the gut into the body, and subsequently, systemic inflammation (which can be detected by increases in biological signatures of inflammation, including C-reactive protein; Myers et al., 2004). A second mechanism is that trauma and stressor exposures can increase proliferation of "pathobionts", microorganisms that typically behave themselves, but under some conditions become pathogenic (Chow et al., 2011; Reber et al., 2016;), leading to the cascade of effects described above, culminating in increased inflammation.

Inflammation increases stress-induced fear learning and impairs acquisition and recall of fear extinction

Although confirmation in human studies is needed (Michopoulos et al., 2017), evidence suggests that inflammation increases stress-induced fear learning and impairs acquisition and recall of fear extinction (Doenni et al., 2017; Jones et al., 2015; Quiñones et al., 2016; Young et al., 2018). Together, these studies suggest that targeting inflammation is a rational strategy for both the prevention and treatment of PTSD.

Hope for microbiome-based interventions

Dr. Lowry and colleagues have recently shown in mouse models that immunization with a soil-derived bacterium with anti-inflammatory and immunoregulatory properties can prevent development of a PTSD-like syndrome (Reber et al., 2016). These findings led his laboratory to conduct, together with the Rocky Mountain MIRECC in Denver, Colorado, a randomized, double-blind, placebo-controlled clinical trial evaluating the feasibility, acceptability, and safety of an eight-week administration of an anti-inflammatory and immunoregulatory probiotic in U.S. veterans with PTSD and mild TBI (Brenner et al., 2020). Although additional studies with larger group sizes are needed, the results show a trend for the probiotic to reduce plasma C-reactive protein concentrations, and a highly significant effect to reduce stress reactivity during a psychosocial stress test (Brenner et al., 2020). An alternative approach to probiotic administration is whole dietary intervention. Whole dietary interventions that increase intake of fruits and vegetables, nuts, seeds, and olive oil (essentially, an anti-inflammatory diet) decrease anxiety and depressive symptoms (Firth et al., 2019). Although the mechanisms through which whole dietary interventions decrease anxiety and depressive symptoms are not clear, increased consumption of diverse plants increases the alpha diversity of the gut microbiome (McDonald et al., 2018), and therefore may promote stress resilience.

Ayahuasca, the gut microbiome, and PTSD

The impact of ayahuasca on the gut microbiome is unknown. However, the anecdotal reports of the transformative effects of ayahuasca on PTSD symptoms lead us to believe that ayahuasca may impact the gut microbiome, either increasing the diversity of the gut microbiome, eliminating pathobionts, or preventing inflammatory responses to pathobionts, and that an altered microbiome may play a role in the transformative effects of ayahuasca. Thanks to the individuals involved in this collaboration, we can begin this journey of discovery, find answers, and, hopefully, help those in need.



The Heroic Hearts veteran group gathers around the opening fire ceremony, discussing intentions for their ayahuasca experience in Tarapoto, Peru, in May 2019. Photo Credit: Jeremy Lock

References

- Brenner, L. A., Forster, J. E., Stearns-Yoder, K. A., ... Lowry, C. A. (2020). Evaluation of an immunomodulatory probiotic intervention for Veterans with co-occurring mild traumatic brain injury and posttraumatic stress disorder: A pilot study. *Frontiers in Neurology, 11*:1015. Retrieved from: <https://doi.org/10.3389/fneur.2020.01015>
- Chow, J., Tang, H., & Mazmanian, S. K. (2011). Pathobionts of the gastrointestinal microbiota and inflammatory disease. *Current Opinion in Immunology, 23*:473-480. Retrieved from: <https://doi.org/10.1016/j.coi.2011.07.010>
- Doenni, V. M., Song, C. M., Hill, M. N., & Pittman, Q. J. (2017). Early-life inflammation with LPS delays fear extinction in adult rodents. *Brain, Behavior, and Immunity, 63*:176-185. Retrieved from: <https://doi.org/10.1016/j.bbi.2016.11.022>
- Eraly, S. A., Nievergelt, C. M., Maihofer, A. X., ... Baker, D. G. (2014). Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. *JAMA Psychiatry, 71*(4):423-431. Retrieved from: <https://doi.org/10.1001/jamapsychiatry.2013.4374>
- Firth, J., Marx, W., Dash, S., ... Sarris, J. (2019). The effects of dietary improvement on symptoms of depression and anxiety: A meta-analysis of randomized controlled trials. *Psychosomatic Medicine, 81*(3):265-280. Retrieved from: <https://doi.org/10.1097/PSY.0000000000000673>
- Jones, M. E., Lebonville, C. L., Barrus, D., & Lysle, D. T. (2015). The role of brain interleukin-1 in stress-enhanced fear learning. *Neuropsychopharmacology, 40*:1289-1296. Retrieved from: <https://doi.org/10.1038/npp.2014.317>

McBurney, M. I., Davis, C., Fraser, C. M., ... Latulippe, M. E. (2019). Establishing what constitutes a healthy human gut microbiome: State of the science, regulatory considerations, and future directions. *The Journal of Nutrition*, *149*(11):1882-1895. Retrieved from: <https://doi.org/10.1093/jn/nxz154>

McDonald, D., Hyde, E., Debelius, J. W., ... Knight, R. (2018). American gut: An open platform for citizen science microbiome research. *mSystems*, *3*(3). Retrieved from: <https://doi.org/10.1128/mSystems.00031-18>

Michopoulos, V., Powers, A., Gillespie, C. F., ... Jovanovic, T. (2017). Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. *Neuropsychopharmacology*, *42*:254-270. Retrieved from: <https://doi.org/10.1038/npp.2016.146>

Myers, G. L., Rifai, N., Tracy, R. P., ... AHA. (2004). CDC/AHA workshop on markers of inflammation and cardiovascular disease: Application to clinical and public health practice: Report from the laboratory science discussion group. *Circulation*, *110*(25):e545-e549. Retrieved from: <https://doi.org/10.1161/01.cir.0000148980.87579.5e>

Nielson, J. L. & Megler, J. D. (2014). Ayahuasca as a candidate therapy for PTSD. In Labate, B. C. & Cavnar, C. (Eds.), *The therapeutic use of ayahuasca* (pp. 41-58). Springer, Berlin, Heidelberg. Retrieved from: <https://doi.org/10.1007/978-3-642-40426-9>

Quiñones, M. M., Maldonado, L., Velazquez, B., & Porter, J. T. (2016). Candesartan ameliorates impaired fear extinction induced by innate immune activation. *Brain, Behavior, and Immunity*, *52*:169-177. Retrieved from: <https://doi.org/10.1016/j.bbi.2015.10.017>

Reber, S. O., Siebler, P. H., Donner, N. C. ... Lowry, C. A. (2016). Immunization with a heat-killed preparation of the environmental bacterium *Mycobacterium vaccae* promotes stress resilience in mice. *Proceedings of the National Academy of Sciences*, *113*(22):E3130-E3139. Retrieved from: <https://doi.org/10.1073/pnas.1600324113>

Stewart, W. & Trujillo, K. M. (2020). Modern warfare destroys brains: Creating awareness and educating the force on the effects of blast traumatic brain injury. *National Security Fellows Program; Belfer Center for Science and International Affairs, Harvard Kennedy School*. Retrieved from: <https://www.belfercenter.org/sites/default/files/2020-07/ModernWarfareDestroysBrains.pdf>

U.S. Department of Veterans Affairs, Office of Mental Health and Suicide Prevention. (2019). *2019 National Veteran Suicide Prevention Annual Report*. Retrieved from: https://www.mentalhealth.va.gov/docs/data-sheets/2019/2019_National_Veteran_Suicide_Prevention_Annual_Report_508.pdf

Young, M. B., Howell, L. L., Hopkins, L., ... Marvar, P. J. (2018). A peripheral immune response to remembering trauma contributes to the maintenance of fear memory in mice. *Psychoneuroendocrinology*, *94*:143-151. Retrieved from: <https://doi.org/10.1016/j.psyneuen.2018.05.012>

JESSE GOULD is a military veteran leader in psychedelics. As Founder and President of the Heroic Hearts Project, he has spearheaded the research and acceptance of ayahuasca and other psychedelic therapy programs for military veterans. Jesse has raised over \$400,000 in scholarships from donors including Dr. Bronner's, partnered with the world's leading ayahuasca treatment centers, and is researching psychiatric applications with the University of Colorado Boulder and the University of Georgia. His mission is to help military veterans struggling with mental trauma and spread awareness of the benefits that ayahuasca therapies offer as an alternative treatment to pharmaceuticals. Jesse has spoken globally about the benefits of psychedelics on mental health and has been featured in the New York Times and Rolling Stone magazine and recognized as one of the Social Entrepreneurs To Watch For In 2020 by Cause Artist. The mission of Heroic Hearts Project has expanded internationally and represents the voices of veterans across the U.S., the United Kingdom, and Canada: heroicheartspj.org.

KATE PATE, PH.D., is a neurophysiologist, lover of mountain sports, entrepreneur, integration coach, and yogi. She has a broad scientific background, having spent over 15 years conducting research in a variety of fields within academic and industry settings. She is also the CEO and Founder of Coruna Medical, a military-specific medical device company. For the past five years, Kate's research has focused solely on military trauma medicine and mental health. She comes from a military family and has always been passionate about helping military service members and veterans in whatever capacity she could. This passion, coupled with her interest in plant-based medicines and her journey to find ways to heal from her own traumas, led her to cross paths with Heroic Hearts Project. Kate joined Heroic Hearts Project as the Director of Research in January of 2019 and has been working closely with the team to investigate the ways in which ayahuasca can benefit veterans suffering from traumatic brain injury, PTSD, and other mental health issues, and how changes in the gut microbiome following ayahuasca consumption may be correlated with long-term psychological and behavioral changes.

CHRISTOPHER A. LOWRY, PH.D., is an Associate Professor in the Department of Integrative Physiology, Center for Neuroscience, and Center for Microbial Exploration at the University of Colorado Boulder, with a secondary appointment in the Department of Physical Medicine and Rehabilitation and Center for Neuroscience at the University of Colorado Anschutz Medical Campus; a Principal Investigator in the Department of Veterans Affairs Eastern Colorado Health Care System, VA Rocky Mountain Mental Illness Research, Education, and Clinical Center; and Director of the Behavioral Neuroendocrinology Laboratory at CU Boulder. He is Co-Director, with Dr. Lisa Brenner, of the Military and Veteran Microbiome Consortium for Research and Education. Dr. Lowry's research program focuses on understanding stress-related physiology and behavior with an emphasis on the role of the microbiome-gut-brain axis in stress resilience, health, and disease.