Microbes and Geriatric Mental Health: Past, Present, and Future

Eleonora D. Vaccariello, M.Sc.¹ and Tanya T. Nguyen, Ph.D.¹,²,³

¹ Department of Psychiatry, University of California San Diego, California
² Sam and Rose Stein Institute for Research on Aging, University of California San Diego, California
³ Veterans Affairs San Diego Healthcare System, California

Correspondence should be addressed to:
Tanya T. Nguyen, Ph.D.
Assistant Professor of Psychiatry
Stein Institute for Research on Aging
University of California San Diego
9500 Gilman Drive #0664
La Jolla, CA 92093
Phone: (858)-246-5347
Fax: (858)-543-5475
ttn050@health.ucsd.edu
The existence of a complex interplay between the gastrointestinal and central nervous systems is no stranger to the world of medicine and psychiatry. Some of the earliest reports hinting at the relationship between these distal organs date back to the early 19th century (Bested, Logan and Selhub, 2013). During this period, several high-profile physicians and scientists speculated that the contents of the colon and its microbial residents may contribute to general malaise, fatigue, melancholia, and neuroses. It was believed that a process of “autointoxication” – in which the putrid contents of the colon could over time infect the body – was to blame. Military physicians of the era proposed that the acute stress of war could lead to autointoxication and accelerate mental health deterioration in soldiers. With very little scientific validity behind these claims at the time, this term became controversial in the 20th century and was shunned by many prominent scientists. After nearly 70 years, the technological advances of the last decade have brought forth an explosion of renewed interest in the notion that the gut may be of relevance to both physical and mental health.

The human microbiome consists of diverse microorganisms, such as bacteria, fungi, archaea, microbial eukaryotes, viruses, and their corresponding genes, that live on different surfaces of the human body. The large intestine has the largest concentration of these organisms. Budding evidence suggests that the microbiome plays a fundamental role in several aspects of human physical and mental health. When an imbalance of the gut microbiota takes place, it can result in a state of sustained hyperactivation of the immune system (Clemente et al., 2012). Chronic inflammation has long been known to have a deleterious effect on physical health, although the exact mechanisms are not fully understood. Modern studies have noted increased inflammatory markers in a number of diseases, many of which are also associated with advanced age, such as arthritis, cancer, cardiovascular disease, and frailty (Chung et al., 2009). Studies have revealed that features of the gut microbiota could distinguish or even predict healthy aging and longevity in humans (Badal et al., 2020; Wilmanski et al., 2021). Prolonged activation of the intestinal immune system may also have detrimental effects on the brain and mental health. This occurs, in part, by an increase in circulating inflammatory cytokines that can destabilize neurochemistry, making some individuals more prone to stress, anxiety, and depression. Elevated inflammatory cytokines and alterations in gut microbiota have been noted in severe mental illnesses, such as bipolar disorder and schizophrenia (Nguyen et al., 2019; Nguyen, Eyler, and Jeste, 2018).
turns out that the early theory of autointoxication may have not been as far-fetched as previously believed.

These observations bring forth an important, yet underexplored question: what is the relationship between the microbiota and mental health during aging? Nineteenth-century scientist Elie Metchnikoff was one of the first to suggest that the microbiota may be associated with physical and cognitive aging. In his work, Metchnikoff studied whether administration of health-promoting bacteria *Lactobacillus* could slow down age-related ailments such as arteriosclerosis and improve overall emotional well-being. Despite some methodological shortcomings, Metchnikoff’s research later paved the way for modern research into “psychobiotics,” a term referring to substances that exert a microbiota-mediated effect on the brain or behavior (Dinan, Stanton, and Cryan, 2013). Most commonly, this term is used in reference to probiotics and prebiotics, though some have argued that dietary interventions, antibiotics, and even psychotropic medications could fall into this category as well. It has been speculated that age-associated changes in the gut microbiota may reflect poor nutrition that results from a decreased appetite and gastrointestinal functioning with aging, consequently leading to impoverished diversity of the gut ecosystem (Oriach et al., 2016). Paradoxically, this outcome may pose a silver lining, as reduced microbial diversity may make the microbiota of older adults more malleable to psychobiotic intervention. Indeed, preliminary evidence exists suggesting that probiotic and/or dietary intervention may reduce systemic inflammation and mitigate certain late-life conditions, such as frailty and cardiovascular disease (De Filippis et al., 2016; Theou et al., 2019). A recent systematic review on the effects of nutrition on geriatric depression revealed that proper nutritional intake had positive effects on depression symptomology (Klimova, Novotny, and Valis, 2020). Positive changes were particularly associated with increased intake of Vitamin B and ω-3 fatty acid supplements, both of which have been associated with healthy immune functioning and promotion of anti-inflammatory activity (Yoshii et al., 2019). The current evidence in support of dietary intervention as a potential therapeutic approach is promising.

There is a paucity of research that investigates the effects of first-line treatments for depression, such as psychotropic medications, on the gastrointestinal system or microbiota. The article by Lee and colleagues (2021) in this current issue addresses this question, building upon the
growing body of research. The investigators examined the gut microbiota as a predictor of treatment response to levomilacipran, a serotonin-norepinephrine reuptake inhibitor (SNRIs), and remission in geriatric depression. The gut microbiome is a major producer of several neurotransmitters such as serotonin, dopamine, gamma-aminobutyric acid (GABA), and norepinephrine. Up to 90-95% of serotonin is produced in the gut and plays a principal role in regulating GI functioning, such as motility (O’Mahony et al., 2015). However, the role of peripheral neurotransmitters on the brain or how the microbiota may interact with medication response is less known. In the Lee study, subjects were grouped into remitters vs. non-remitters, regardless of their initial randomization group, due to the high drop-out rate in the clinical trial. Although groups did not differ in in alpha-diversity or beta-diversity, remission following 12-weeks was predicted by the higher relative abundance of Faecalibacterium, Agathobacter, and Roseburia at baseline. These genera have been associated with the production of short-chain fatty acids (SCFA), gut peptides that are critical for colonic motility and immune maintenance and have anti-inflammatory properties (Venegas et al., 2019). SCFA production may be increased in long-living older adults ages 90 and older (Badal et al., 2020). As such, these microbes and related SCFA metabolites might be important in alleviating depression and promoting successful aging in older adults. There were also longitudinal changes in several genera among clinical remitters, although it is still unclear what the specific role of these bacteria are.

The bulk of current studies have focused on the “bottom-up” effects of the microbiota-gut-brain axis, or in other words, how modulation of the gut influences brain health. Fewer studies have assessed the alternative “top-down” effect, that is, whether treatments that focused on brain function or behavior such as psychotherapy or even brain stimulation might modulate gut functioning or the microbiota. Although in its infancy, this avenue of research is beginning to show promising results. For example, both cognitive behavioral therapy and mindfulness-based therapies have been associated with subsequent decreases of inflammatory markers (Shields, Spahr, and Slavich, 2020; González-Moret et al., 2020). The Lee and colleagues’ study lies in between: not only do SNRIs act on neural chemical messengers but also, they have been found to alter the gut microbiota (2021). Another important consideration is that intra-individual differences in gut microbiota composition can alter drug bioavailability (Weersma, Zhernakova,
and Fu, 2020), suggesting that the microbiota might determine the efficacy of psychotropic treatment, further highlighting the complex nature of this relationship.

Lee and colleagues were unable to separate the effects of medication from those of placebo (2021). Due to the small sample size, both treatment groups were included within the remitter and non-remitter groups; thus, it is impossible to conclude whether symptom improvement was due to subjects’ microbiota at baseline, medication effect, or another factor altogether. Another possibility is that positive psychological or lifestyle factors may contribute to improved depression. We have shown that psychosocial factors such as loneliness, wisdom, social support, and social engagement are associated with the diversity of the gut microbiota (Nguyen et al., 2021). This is a nascent field of research, and several questions remain. Future studies will need to further characterize how various protective and risk factors interact with the microbiota in geriatric depression to improve treatment. As previously discussed, one promising therapeutic venue may be the addition of psychobiotic treatment (e.g., probiotic, prebiotic, dietary intervention) in conjunction with pharmacological treatment. Considering the inter-individual variability in microbiota composition of older adults, some individuals may respond better to a combination of one or more of these treatment methods. The gut microbiome provides an exciting opportunity for individualized precision medicine that may improve the quality of life for older adults.
References


