Psychobiotics: Shaping the Mind With Gut Bacteria

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Abstract: Preclinical and a few clinical studies have demonstrated the existence of a brain-gut-microbiome axis in which bacterial signals can modulate affective behavior, brain activity, and central gene expression profiles. The study by Wang et al. in this issue (Wang H, Braun C, Murphy EF, et al. Bifidobacterium longum 1714™ strain modulates brain activity of healthy volunteers during social stress. Am J Gastroenterol 2019;114:1152–62.) contributes to a growing body of literature demonstrating that probiotics that alter behavior in animal models—termed "psychobiotics"—can induce changes in human brain networks involved in emotional or cognitive responses. Although there are still many unknowns about the potential of existing probiotics to induce clinically relevant effects, these findings support continued investigation into interventions acting on the brain-gut-microbiome axis for affective, cognitive, and behavioral disorders.

Am J Gastroenterol 2019;114:1034–1035. https://doi.org/10.14309/ajg.0000000000000281

There is a growing recognition—largely based on studies performed in laboratory animals—that the intestinal microbiome can have wide-ranging effects on the brain. Germ-free mice (i.e., lacking all bacteria) have been found to have altered social, sensorimotor, exploratory, and stress response behaviors that are associated with neurophysiological abnormalities in diverse regions of the brain, including the prefrontal cortex, amygdala, hypothalamus, and hippocampus (1). Human microbiome studies have also found associations of microbiome composition and function with neurobehavioral and affective disorders, as well as with brain neuroimaging parameters (2,3). The specific channels of communication between gut bacteria and the brain have begun to be elucidated. These include vagal nerve signaling, activation of enteric nerves, stimulation of enteroendocrine and enterochromaffin cells, release of neuroactive products into the circulation, and modulation of neuroimmune responses (4). This bidirectional interaction has been termed the brain-gut-microbiome axis.

The emerging understanding of this axis has led to interest in modifying behavioral and cognitive properties with live microorganisms, which in this context have been termed "psychobiotics" (5). The great majority of strains under investigation belong to the *Lactobacillus* and *Bifidobacterium* genera, reflecting the historical interest in these bacteria as probiotics which dates back to a century ago (6). The rationale is to introduce bacteria that either directly engage one or more brain-gut-microbiome circuits or alter recipients' existing gut microbiota to modulate their signals to the brain. Such effects may occur whether the microorganisms permanently colonize the host or only survive transiently after ingestion, as is the case with most probiotics. There is now an extensive preclinical literature documenting the effects of some microorganisms on behavioral endpoints, neurotransmitters, and neurophysiological parameters in rodent models (7). In humans, there have been several randomized placebo-controlled trials (RCTs) of probiotics for conditions such as depression and anxiety, but interpretation has been hampered by inconsistent clinical outcomes and a lack of biological readouts to demonstrate mechanisms (8).

A recent development in the brain-gut-microbiome field has been the use of brain imaging techniques in probiotic studies to identify changes in brain networks at rest and during tasks that require emotional or cognitive responses. In a pivotal initial proof-of-concept RCT of 25 healthy subjects, Tillisch et al. (9) found that consumption of a multispecies probiotic for 4 weeks was associated with altered response of the affective, viscerosensory, and somatosensory cortices to an emotional face recognition task. A second RCT of a multispecies probiotic involving 45 healthy subjects found changes in the default mode, salience, and middle/superior frontal gyrus networks in the resting state after 4 weeks and alterations in activity in the cingulate cortex, precuneus, inferior parietal lobule, thalamus, and parahippocampal gyrus in response to emotional triggers (10,11). A third RCT of a multispecies probiotic involving 58 healthy subjects did not identify shifts in brain responses to emotion reactivity, emotion regulation, and cognitive control testing after 4 weeks but did observe a change in the prefrontal cortex during stress-induced working memory testing (12). In addition to these healthy subject trials, there has been one published RCT of 44 patients with irritable bowel syndrome treated with *Bifidobacterium longum* NCC3001 that found reduced activity in the

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Received April 10, 2019; accepted April 25, 2019; published online May 28, 2019

amygdala, frontal, and temporal cortices and heightened activity in the occipital regions in response to fear stimuli (13).

In this issue, Wang et al. (14) add to these previous studies with a RCT of *B. longum* 1714 in 40 healthy subjects. This strain was previously reported to improve performance of mice in cognitive tasks, particularly those involving memory and response to fear (15). The authors used magnetoencephalography to record the electrical activity throughout the brain in response to a validated laboratory stressor ("Cyberball game") in which the subjects were either socially included or excluded in a virtual ball throwing game. This was the first study to examine a probiotic in the context of a social stress situation, as previous studies had used images or backward number counting to induce responses. The authors found that although 4 weeks of probiotic usage did not significantly change self-reported social stress or social/emotional well-being, it was associated with changes in resting activity in the frontal cortex, cingulate cortex, fusiform gyrus, hippocampus, temporal cortex, and cerebellum as well as altered social stress-induced activity in the frontal cortex, cingulate cortex, and supramarginal gyrus. These neurophysiological changes were associated with self-reported vitality and perceived social stress severity, suggesting potential psychological correlates of the observed brain responses.

Collectively, these studies from different laboratories support the premise that human brain activity may be modulated by ingestion of certain microorganisms. However, the affected brain parameters and regions have varied across studies and have generally not been associated with behavioral changes and clinical outcomes, making it impossible to identify which specific brain mechanisms are affected. These results may reflect variation in strain composition/dosage, patient populations, functional imaging techniques (including choice of tasks used to elicit responses), and small sample size. These issues highlight the need for larger follow-up studies and standardization of functional imaging protocols to facilitate comparison across studies.

There are many uncertainties about the clinical application of psychobiotics, even if subsequent studies can demonstrate reproducible neurophysiological responses and clear clinical outcomes. Mechanisms that mediate the effect of probiotics on brain functions have not been identified. It is also unclear whether neurological responses require continued usage or are durable after cessation of treatment. Moreover, given the wide range of brain regions reported to change in response to probiotics, there is the possibility of unanticipated psychological effects not captured by questionnaires in these short-term studies. Furthermore, response to these interventions will likely depend greatly on the microbiome, diet, genetics, and preexisting neuroanatomy of recipients. Finally, major skepticism is warranted regarding a clinically relevant effect of such interventions on human emotion, cognition, and behavior, considering the widespread use of probiotics around the world without reported significant psychological effects. Despite these limitations, it is hoped that clinical evaluation of interventions that target the gut microbiome to modulate normal and abnormal emotional states will continue to expand. Such research holds the potential to yield novel microbial therapies that leverage the brain-gut-microbiome axis to shape behavior, emotion, and cognition.

CONFLICTS OF INTEREST

Guarantor of the article: Jonathan P. Jacobs, MD, PhD.
Specific author contributions: J.P.J. and E.A.M. both contributed to the writing of this editorial.
Financial support: J.P.J. is supported by a VA Career Development Award (IK2CX001717). E.A.M. is supported by NIH/NIDDK R01 DK048351 and P50 DK064539.
Potential competing interests: J.P.J. has no potential competing interests to disclose. E.A.M. is a member of the scientific advisory boards of Danone, Viome, Amare, Prolacta, Axial Biotherapeutics, Whole Biome, uBiome, Bloom Science, and Mahana Therapeutics.

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