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The Microbiome and Epidemiology

Brain-gut-microbiota axis: challenges for translation in psychiatry

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ABSTRACT

Purpose: The accruing data linking the gut microbiome to the development and function of the central nervous system has been proposed as a paradigm shift in neuroscience. The gut microbiota can communicate with the brain via neuroimmune, neuroendocrine, and neural pathways comprising the brain-gut-microbiota axis. Dysfunctional neuroimmune pathways are implicated in stress-related psychiatric disorders.
Methods: Using depression as our primary example, we review both the preclinical and clinical evidence supporting the possible role played by the gut microbiota in stress-related psychiatric disorders. We consider how this can inform future treatment strategies and outline the challenges and necessary studies for moving the field forward.
Results: The role played by the gut microbiota has not been fully elucidated in psychiatric populations. Although tempting to speculate that psychiatric patients may benefit from therapeutic modulation of the brain-gut-microbiota axis, the translational applications of the results obtained in rodent studies have yet to be demonstrated.
Conclusions: Evidence of altered gut microbiota composition and function in psychiatric patients is limited and cannot be regarded as proven. Moreover the efficacy of targeting the gut microbiota has not yet been established, and needs further investigation.

Introduction

Depression is a complex, heterogeneous disorder, which accounts for almost 10 percent of all medical disability, making it the leading cause of medical disability in the United States and Canada, with an economic burden estimated at $210.5 billion dollars [1,2]. Depressive spectrum disorders affect 121 million people and by 2020, the World Health Organization has predicted that depression will be second only to cardiovascular disease as the leading causes of total disease burden worldwide, measured by disability adjusted life years [2]. Depression, frequently comorbid with anxiety [3] is associated with an increased rate of suicide [4] and is an independent risk factor for cardiac morbidity and mortality [5,6].

Studies indicate that the prevalence of depression may be increasing, with an increased lifetime risk for younger cohorts [7,8]. Depression is often recurrent [9] and the risk of recurrence increases with residual symptoms [10] and with longer, more frequent, [11] and more severe episodes [12]. A prospective epidemiologic survey, The Netherlands Mental Health Survey and Incidence Study (NEMESIS), found that 50% of depressed participants recovered within 3 months, 63% within 6 months, 76% within 12 months, whereas 20% did not recover at 24 months [13]. Indeed, current pharmacologic interventions are only effective for some [14–16] and unlike, for example, the field of cancer research, there has been little progress in the identification of biomarkers [17].

Stressful life events are strongly associated with depression and the vast majority of first episodes are preceded by such triggers [18]. Early traumatic events, in particular, increase the risk of depression later in later life [19–21]. From a neurobiological perspective, depression is associated with dysregulated neuroendocrine [22], neuroimmune [23,24], metabolic [25,26], and neurotransmitter systems [27,28]. Emerging evidence, mainly from animal studies, indicates that the some of the same pathways that are dysregulated in depression are modulated by the microbes that inhabit the gut—the gut microbiota.

However, there are a number of challenges faced by psychiatry as it seeks to consolidate this emerging field of microbiome science within the already complex field of brain disorders. These include

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an appreciation of what is meant by a healthy microbiome and the relevant features of dysbiosis that might be implicated in stress-related disorders. Although the preclinical studies are promising, there are both specific challenges in translating this preclinical literature [29] and more generic issues related to the well-established difficulties surrounding modeling neuropsychiatric disorders in rodents [30–33]. Although psychiatry is now familiar with dealing with large data sets from genome-wide association studies [34] and the connectome project [35], the incorporation of next generation sequencing technology and the associated bioinformatics from microbiome research into these fields will also be a significant challenge [36].

Gut microbiota: structure

The human body is composed of a complex ecosystem of more than 90% microbial cells and 10 million microbial genes [37,38]. The gut microbiome is thus a key interface for gene-environment interactions, and although the functional significance of the microbiome has yet to be fully determined [39], it is clear that an interlinked symbiotic physiology exists between host and microbe [40]. The most heavily colonized area of the human body is the gut, with bacterial concentrations ranging from 10^1–10^3 bacteria cells per gram in the upper parts to 10^{11}–10^{12} bacteria per gram in the colon [41,42]. *Firmicutes* (species such as *Lactobacillus*, *Clostridium*, *Enterococcus*) and *Bacteroidetes* (species such as *Bacteroides*) account for most the phyla found in the gut [43–45].

Although the composition of the gut microbiota, in the absence of insults remains relatively stable during adulthood, there are significant interpersonal differences [46,47]. Consequently, there are multiple possible configurations for a healthy microbiome and it is also likely that some stable configurations are associated with disease [48]. This concept of an entire ecosystem as a potential pathogen is a somewhat unfamiliar concept in clinical psychiatry. It is important also to appreciate that the functional output of multiple microbiome configurations may in fact be equivalent, given that concepts of redundancy and pleiotropy can also be applied to specific microbial members of the overall consortium.

However, like any ecosystem, diversity and stability brings resilience and these are some of the key indices for the overall health of a particular gut microbiome. Thus, obesity for example, has been associated with a reduced diversity [49]. Interindividual variation becomes even greater as we age [50] and certain microbiota signatures dependent on diet have been linked to measures of frailty, co-morbidity, and markers of inflammation in this age group [51]. Recently, a Mediterranean diet, suggested as protective for depression, has been associated with beneficial microbiome-related metabolomic profiles [52], and there is increasing awareness of the role of a healthy diet in reducing the risk of depression [53].

Gut microbiota: development

The developmental trajectory of the gut microbiota is compatible with concepts in psychiatry of the early-life period as a vulnerable phase for the subsequent emergence of psychopathology in adulthood [54]. In the initial days of life, the gut microbiota is unstable and of low diversity, shifting in composition over the first few years to resemble an adultlike profile by age 3 years [55]. The effect of mode of delivery and the implications for CNS host development has attracted recent attention [56–58]. Vaginally delivered infants are colonized by the fecal and vaginal bacteria of the mother, most notably *Lactobacilli*, whereas infants delivered by Caesarean section (C-section) are colonized by other bacteria from the skin of the mother and from environmental sources including health-care workers, air, medical equipment, and other newborns [59]. Other factors such as gestational age [60], feeding mode [61,62], antibiotic use, [63] and exposure to family members and pets [57,64–66] also influence the trajectory of microbiota acquisition. The relative importance of these factors in determining the eventual stable microbiota profile has not been fully elucidated.

Recent evidence suggests that prenatal stress also impacts the gut microbiota with implications for physiological outcomes in the offspring [67]. In a mouse model of prenatal stress, maternal stress decreased the abundance of vaginal *Lactobacillus*, resulting in decreased transmission of this bacterium to offspring, which corresponded with changes in metabolite profiles involved in energy balance, and with disruptions of amino-acid profiles in the developing brain [68]. Clinical studies examining the relationship between prenatal stress, and the gut microbiota are starting to emerge but are far from definitive. In one such study, infants of mother's with high self-reported stress and high salivary cortisol concentrations during pregnancy had significantly higher relative abundances of *Proteobacterial* groups known to contain pathogens and lower relative abundances of lactic acid bacteria (*Lactobacillus*) and *Bifidobacteria* [69]. It is currently unclear whether this effect was mediated via maternal microbial transmission or through cortisol-specific effects on the developing gastrointestinal tract. Whatever the mechanism, those infants with altered microbiota composition, exhibited a higher level of maternally reported infant gastrointestinal symptoms and allergic reactions, highlighting the functional consequences of aberrant colonization patterns.

Brain-gut-microbiota axis

A recurring question surrounding the impact of the gut microbiome on the CNS and a possible impediment to integration of this research in psychiatry pertains to the uncertainty surrounding the mechanisms through which this influence can be exerted. The prevailing view currently is that the microbiome recruits the scaffolding provided by the brain-gut axis, a bidirectional communication pathway between the gut and brain [70]. Studies using different but complementary approaches, such as, germ-free rodents (born and raised without microbes), antibiotics, probiotics, gastrointestinal infection studies, and fecal microbiota transplantation studies have shown that the gut microbiota acting via the brain-gut axis contributes to the regulation of brain and behavior [71–73]. There are several putative mechanisms by which the gut microbiota can achieve this; via modulation of the immune system [74], the hypothalamic-pituitary-adrenal (HPA) axis [75], tryptophan metabolism [76], the production of bacterial metabolites [77], via the vagus nerve [78]. Interestingly, the epigenetic factors that play a role in shaping stress-related behaviors could arise as a consequence of host-microbe interactions [79–81].

Gut microbiota: immune regulation

A critical function of the microbiota is to prime the development of the neuroimmune system [82–85]. The luminal surface of the gut is a key interface in this process [41]. Structural components of bacteria interact with the immune system via Toll-like receptors (TLRs) [86]. Different TLRs recognize specific bacterial structures, for example; TLR2 recognizes structures from gram-positive bacteria, whereas TLR4 mediates responses to structures such as lipopolysaccharide primarily from gram-negative bacteria [87]. Activation of TLRs trigger the induction of proinflammatory and anti-inflammatory cytokines [88], and there are a number of routes by which peripheral cytokines can impact the brain [89–91]. Consequently, TLRs may serve as molecular communication channels between gut microbiota alterations and immune system homeostasis [92].