Critical Reviews in Clinical Laboratory Sciences

ISSN: 1040-8363 (Print) 1549-781X (Online) Journal homepage: http://www.tandfonline.com/loi/ilab20

Gut microbiota, metabolism and psychopathology: A critical review and novel perspectives

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To link to this article: https://doi.org/10.1080/10408363.2018.1463507

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Published online: 20 Apr 2018.
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ABSTRACT
Psychiatric disorders are often associated with metabolic comorbidities. However, the mechanisms through which metabolic and psychiatric disorders are connected remain unclear. Pre-clinical studies in rodents indicate that the bidirectional signaling between the intestine and the brain, the so-called microbiome-gut-brain axis, plays an important role in the regulation of both metabolism and behavior. The gut microbiome produces a vast number of metabolites that may be transported into the host and play a part in homeostatic control of metabolism as well as brain function. In addition to short chain fatty acids, many of these metabolites have been identified in recent years. To what extent both microbiota and their products control human metabolism and behavior is a subject of intense investigation. In this review, we will discuss the most recent findings concerning alterations in the gut microbiota as a possible pathophysiological factor for the co-occurrence of metabolic comorbidities in psychiatric disorders.

ARTICLE HISTORY
Received 15 November 2017
Revised 15 March 2018
Accepted 8 April 2018
Published online 19 April 2018

KEYWORDS
Gut-brain axis; bile acid; psychiatry; metabolic syndrome; fecal transplantation; germ free; metabolomics; kynurenine; network approach

Introduction
The occurrence of metabolic comorbidities is a common phenomenon in psychiatry. Few psychiatric categories seem to occur in a “pure” form. The nature of psychiatric disorders is therefore dimensional rather than categorical. However, psychiatric disorders do not solely co-occur with each other. In fact, comorbidity between psychiatric and metabolic disorders such as diabetes, cardiovascular disease, and the metabolic syndrome has frequently been reported and is associated with adverse outcomes including higher mortality. The mechanisms through which metabolic and psychiatric disorders are connected remain elusive. One emerging mechanism through which behavior and metabolism may be linked is the so-called microbiome-gut-brain axis. This axis is a complex system of multi-directional signaling between the gut microbes, the immune-, metabolic-, and central nervous systems. Although the exact sequence of mechanisms involved in this axis is still debated, preclinical studies suggest that the gut microbiota can orchestrate this multi-directional communication network and subsequently modulate metabolic homeostasis and psychological wellbeing.

The gastrointestinal (GI) tract harbors the densest microbial population in the body. Despite general knowledge of the presence of these commensals, their possible role in human physiology has been largely ignored until recently. Associations have frequently been reported with diverse common human disease conditions including morbid obesity and the metabolic syndrome, but less so with psychological disorders. Whether the microbiota plays a causal role in the etiology of all these diseases is a matter of controversy. Perhaps the most convincing evidence that the role of the microbiota is not only associative but also causal stems from fecal microbiota transplantation (FMT) intervention studies. Metabolic changes were reported in both rodents and humans treated with FMT and mouse studies have...
suggested a causal link as behavioral changes were observed in addition to physiological changes after FMT [20]. Concerning psychiatric disorders, a first open-label FMT intervention for children with autism spectrum disorder (ASD) found significant improvements in ASD behavioral symptoms and an 80% reduction in GI symptoms for children with ASD eight weeks after the FMT [21]. However, as the intervention did not include a control group with ASD children, results need to be interpreted with care. Although this field is rapidly advancing, illustrated by a surge in publications regarding the potential link between the gut microbiome and metabolic disorders [22–26], evidence concerning an association between gut microbiome composition and psychiatric disorders is lacking. Closing this gap is necessary as research concerning dysregulation of the gut microbiome may present opportunities to investigate whether comorbidities between metabolic and psychiatric disorders is causally related to one another.

In this review we will summarize key findings regarding research on the association between gut microbiome and metabolism and discuss putative links with various psychiatric disorders. In addition, we will consider challenges like the translation into clinical research, variability in findings of clinical studies, and measuring dynamical processes such as the microbiome and psychopathology. With respect to the latter, we will discuss novel approaches such as a network approach to psychopathology that, combined with experience sampling methods, may provide a framework to integrate the dynamic processes with each other.

**Association between microbial metabolism and psychiatric disorders in animal models and humans**

In animal studies, the relationship between microbiota and psychiatric symptoms appears to be bidirectional [27]. There is consensus that stress, which is often associated with psychiatric conditions, notably affects the function and composition of the gut microbiome and host metabolism [28–30]. Conversely, altering the gut microbiota composition with FMT can directly modulate behavior as well as metabolic function [20]. Bercik et al. [20] demonstrated this by colonizing germ-free BALB/c mice (timid strain) mice with commensal bacteria from National Institutes of Health (NIH) Swiss mice (adventurous strain) resulting in increased exploratory behavior. Performing fecal transfers the other way around, thus, transplanting the microbiome of BALB/c mice in NIH Swiss mice led to decreased exploratory behavior. Changes in behavior were associated with differences in hippocampal brain-derived neurotrophic factor (BDNF) levels measured one week after transfer between mice colonized with BALB/c (lower BDNF levels) and mice colonized with NIH Swiss (higher BDNF levels). Even more compelling evidence for the ability of the gut microbiome to directly modulate behavior has been provided by Zheng et al. [31]. They demonstrated that a fecal transfer of microbiota from patients diagnosed with major depressive disorder (MDD) to germ-free mice, resulted in more depression-like behaviors for these mice as compared to germ-free mice that were colonized with healthy individuals’ microbiota. Kelly et al. [32] found the same effect of a fecal transfer from MDD patients to an antibiotics-induced microbiota-depleted rat model. While they failed to observe any significant differences in hippocampal BDNF expression associated with the depression, rats who received the depressive gut microbiota had an increased kynurenine/tryptophan ratio in blood. Lastly, mice that received fecal microbiota from patients with irritable bowel syndrome and symptoms of anxiety were found to also develop anxiety-like behaviors after transplantation [33]. As the mice in these studies experienced alterations in behavior induced by human microbiota [31–33], alterations in gut microbiota may also lead to alterations in human behavior.

Other experimental approaches include gut microbial manipulation with antibiotics, probiotics, or animal models (i.e. germ-free models or models that resemble aspects of psychiatric disorders). The combined findings of these studies also show a range of microbiota related effects such as decreases in depression-like behaviors [34,35] or reduced anxiety-like behavior [36,37] in mice and rats. In an ASD mouse model (maternal immune activation (MIA) model), in which atypical social behaviors were induced by exposing the mother to a virus, the administration of the probiotic *Bacteroides fragilis* resulted in a reduction of some of the observed behavioral abnormalities and reduced gut permeability [38]. Golubeva et al. [39] explored the interactions between gut microbiota, gut physiology, and social behavior in a BTBR T+Ipr3tf/J mouse model of ASD. A reduction in the relative abundance of bile acid-metabolizing *Bifidobacterium* and *Blautia* species was observed in the BTBR gut. Bile acid levels in plasma were decreased suggesting altered absorption, although this was not measured in an experimental set-up. In addition a 50% reduction in serotonin or 5-hydroxytryptamine (5-HT) tissue levels in both small and large intestine of BTBR mice was measured, which was coupled with a down-regulation of tryptophan hydroxylase (*TPH1*) and an up-regulation of the serotonin transporter (*Sert*) gene expression. TPH activity determines the amount of
5-HT which is produced from dietary tryptophan and released from enterochromaffin cells while Sert controls the rate of 5-HT re-uptake and consequent breakdown in enterocytes. These metabolic alterations could be involved in the impaired social interactions in BTBR mice and suggest a mechanistic basis underlying the microbiome-gut-brain axis.

Tryptophan metabolism could play a central role in the microbiota-gut-brain axis. Humans lack the metabolic pathways required to synthesize tryptophan, therefore it must be supplied from the diet. Most of the dietary tryptophan is absorbed in the small intestine via large neutral amino acid transporters and enters the portal circulation to be metabolized in the liver. Kynurenine and kynurenic acid are important intermediates in the kynurenine pathway and have been implicated as biomarkers for MDD [40]. Tryptophan is metabolized by the intestinal microbiota to a variety of compounds including indoles that have been associated with cardiovascular disease [41]. Although a role of tryptophan metabolites in microbiota-induced signaling seems plausible, it cannot be excluded that the primary effect of the microbial activity is the induction of a decrease in plasma tryptophan concentration. This reduction may impact serotonin and melatonin synthesis in the brain and thus secondarily affect brain physiology.

A major hurdle in investigating the mechanisms by which microbiota may influence brain function is the lack of knowledge on the molecular mechanism underlying psychiatric disorders. Despite decades of research, reliable biomarkers are just emerging in the last few years due to the rapid development of liquid chromatography-mass spectrometry based technology enabling measurement of large numbers of metabolites. Major attention has been directed to the possible role of short chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, since SCFAs are the main product of the digestive action of the gut microbiota. Although no direct evidence currently shows that SCFA travel via the blood stream to the brain in humans, findings increasingly support the indirect actions of SCFA. For example, increased production of acetate by an altered gut microbiota in mice and rats leads to activation of the parasympathetic nervous system, which in turn promotes increased glucose-stimulated insulin secretion (GSIS), increased ghrelin secretion, hyperphagia, obesity, and related sequelae [42]. SCFA have been reported to affect host metabolism by various parallel pathways [43,44]. SCFA bind to G protein-coupled receptors (GPR) 41 and 43 [45]. These GPRs are active in neuroendocrine cells in the gut and may therefore influence signaling to the brain [46]. This also seems the most plausible route via which the SCFA exert their function because the systemic concentration is very low [47]. Ongoing developments in complex metabolomics might lead to identification of more bacteria-derived metabolites in host blood and cerebrospinal fluid in the near future. It has been estimated that microbe-derived metabolites contribute up to 10% of the total number of metabolites in blood [48]. Most of these metabolites will not directly influence brain function because they cannot cross the blood brain barrier. However, despite this formidable barrier, the gut-derived metabolites may influence hypothalamic signaling due to the leakiness of the blood brain barrier at this site. The analysis of associations between these metabolite patterns and psychiatric symptoms calls for application of state of the art systems biology approaches and subsequent intervention studies to validate candidate metabolites. Recent advances in analysis of the complete metabolic repertoire of 753 bacterial strains [49] already make it possible to predict which metabolites are produced in ensembles of bacteria allowing development of targeted metabolomics.

Hence, identifying associations of particular bacterial strains with psychiatric disorders may eventually provide insight into the involved metabolites. Below we will review the current knowledge concerning associations between bacteria and a number of psychiatric disorders. Associations amongst most disorders and different bacteria have been found, therefore disorders will be discussed separately. If available, findings based on the comparison of fecal microbiota between clinical populations and non-clinical controls are discussed (see Table 1 for an overview). Otherwise, studies regarding the influence of probiotics or other gut-microbiota related markers are discussed for each disorder.

**Autism spectrum disorder (ASD)**

GI symptoms and increased intestinal permeability are frequently reported in individuals with ASD [50–53]. Hence, it may not be surprising that the majority of studies investigating the microbiome in psychiatric disorders have focused on ASD. This research suggests that ASD is accompanied by alterations in the microbiome [9]. For instance, elevated levels of *Clostridium* bacteria have consistently been observed in patients with ASD [54–56]. However, findings regarding alterations of other specific bacterial species have not been consistent. This may partially be explained by differences in study sample characteristics, the small number of participants included in these studies, or differences in participants’ diet, or use of medication [57].
Another source of variability may be the use of different methodologies to evaluate the microbiome. Nonetheless, even when genome-sequencing methods were comparable, opposing microbiota profiles of the three major phyla (Firmicutes, Bacteroidetes, and Proteobacteria) were found in patients with ASD as compared to controls [58,59], or no difference was found at all [60]. Finegold et al. [59] observed increased ratios of Bacteroidetes and Proteobacteria, but decreased ratios of Firmicutes in ASD patients, while Williams et al. [58] also found increased ratios of Proteobacteria, they observed increased ratios of Firmicutes and decreased ratios of Bacteroidetes as opposed to Finegold et al. [59].

In summary, we cannot infer whether the alterations in gut microbiota composition in ASD patients are an association or related to causation, from these observations. Novel intervention studies (FMT, pre-, and probiotics) might help to identify bacterial strains involved in human behavior that can possibly be isolated and developed as probiotics. Indeed, one recent study performed fecal transplantation in ASD patients, which resulted in statistically significant improvements in both GI and behavioral ASD symptoms that remained at the eight-week follow-up. They also observed an increase of Bifidobacterium and increase in abundance of Prevotella and Desulfovibrio [21]. Interestingly, the same authors observed a significantly lower abundance of Prevotella in samples of children with ASD in a previous investigation [61]. Replications of the FMT results involving a matched control group of children with ASD who receive an autologous fecal transplantation should be carried out to further investigate causality between the gut microbiome and ASD symptoms.

### Major depressive disorder (MDD)

Six studies have compared fecal microbiota of depressed patients with those of (healthy) control participants [31,32,62–65]. Jiang et al. [65] found significantly greater fecal microbial diversity based on the Shannon Index (which takes into account abundance and evenness of species) in a sample of 46 patients with MDD compared to 30 healthy controls. MDD was associated with higher levels of Bacteroidetes, Proteobacteria, and Actinobacteria, whereas levels of Firmicutes were significantly reduced. Faecalibacterium were negatively correlated with the severity of depressive symptoms. Using a different control group, Naseribafrouei et al. [64] compared a sample of 37 MDD patients with 18 non-depressed patients from a neurological outpatient unit and found lower levels of Bacteroidales to be associated with depression. Underrepresentation of Bacteroidales has also been associated with obesity [26]. Whether decreased levels of Bacteroidales may also play a role in comorbidity between depression and obesity requires further investigation. Zheng et al. [31], who investigated the effects of a fecal transfer from MDD patients to mice, also compared gut microbiota composition between MDD patients (n = 58) and matched healthy controls (n = 53). The relative abundance of Actinobacteria at the phylum level was increased in MDD patients, whereas the abundance of Bacteroidetes was decreased. Kelly et al. [32] found no significant differences in the relative abundance of gut microbiota between depressed patients and healthy controls, but found various differences in relative proportions of microbiota at the family level (see Table 1).
One study investigated whether any correlations existed between repeated assessments (three visits) of fecal microbiota and depression scores in a period of one month [62]. Ten patients who experienced continuous reductions in depression scores (over these three visits) were compared to 10 healthy controls. At the phylum level they found no significant differences in gut microbiota compositions across the three visits, but at the genus level they found Klebsiella to have significantly decreased over time. Like Zheng et al. [31] they observed lower proportions of Bacteroidetes in patients with MDD as compared to controls, but in contrast to Jiang et al. [65] they found higher proportions in phylum Firmicutes in patients as compared to controls. Lastly Aizawa et al. [63] compared specifically Bifidobacterium and Lactobacillus counts in fecal samples of MDD patients and healthy controls. Only the Bifidobacterium counts were significantly lower in patients.

In summary, the combined findings of these studies are rather inconsistent in terms of which species of microbiota are correlated with depression and whether an over- or underrepresentation of these species is observed (see Table 1). The observed inconsistencies may be partially related to the different samples that were used or inter-individual variability in terms of health status, age, treatment, or diet which all influence gut bacteria composition [65]. Diet is specifically important to consider in MDD, because opposing dietary patterns (increased appetite/weight gain versus decreased appetite/weight loss) are observed in depressed patients and are considered as features of the MDD subtypes: atypical and melancholic depression. The atypical subtype, characterized by increased appetite/weight gain, has been previously associated with metabolic abnormalities [66]. Future research should take the variability in dietary patterns as part of the symptom presentation of MDD into account, as this may differentially influence the gut microbiota composition of MDD patients.

Anxiety disorders

We are unaware of any clinical studies that compared the composition of microbiota in patients with anxiety disorders to healthy controls. However, a growing number of studies investigating the effects of pre- and probiotic diets in healthy individuals suggest a positive effect both on mood and anxiety [37,67].

For instance, a double-blind, randomized, placebo controlled study showed that 30-day consumption of a probiotic mixture containing Lactobacillus helveticus and Bifidobacterium longum had a small but significant effect on participants’ levels of anxiety and depression [37]. Participants who had received the daily administration of bacteria showed improvement in scores related to perceived stress, anxiety, and depression and had reduced levels of the stress hormone cortisol in comparison to participants receiving the placebo.

However, a study that administered a mixture of probiotics, including Bifidobacterium animalis subsp. Lactis, Streptococcus thermophilus, Lactobacillus bulgaricus, and Lactococcus lactis subsp. Lactis, to healthy female volunteers for four weeks [67] observed changes in brain activity in regions associated with processing of emotion and sensation, but found no changes in mood or anxiety symptom reports. In summary, research on microbiota composition associated with anxiety disorders is lacking. Preliminary research on the effects of probiotics for anxiety seems positive, although conflicting results have been reported.

Psychotic disorders

One study has investigated whether differences exist in fecal microbiota composition between first episode psychotic patients and matched, healthy controls [68]. They found no significant differences between cases and controls, which the authors attributed to the high inter-individual variation and limited sample size. However, within the patient group, the authors did observe symptom severity to positively correlate with bacterial numbers in various groups such as Lactobacillus, Lachnospiraceae, Ruminococcaceae, and Bacteroides spp. Moreover, they observed that the patients whose microbiota profiles clustered with controls were more likely to experience remission after 12 months. At baseline, when the fecal samples were collected, all but two patients were treated with antipsychotics. To what extent this may have impacted the findings is unclear, but antipsychotics have been found to influence microbiota composition [69–71].

Besides this single study, a role of gut microbiota in psychotic disorders has mostly been suggested based on associations between a history of Toxoplasma gondii infection and higher risk of onset of schizophrenia [72]. A Danish cohort-based study showed that Toxoplasma gondii immunoglobulin G (IgG) levels were significantly associated with schizophrenia risk (odds ratio [OR] = 1.79). A potential mechanism could be by the parasite induced disruptions of the microbiota, resulting in a dysregulation of the bidirectional microbiome-gut-brain-axis [73]. Other support is based on the association between inflammatory markers and the incidence of schizophrenia. Levels of serological markers of bacterial translocation, such as soluble CD14, were
found to be significantly elevated in patients with schizophrenia and bipolar disorders as compared to controls [74]. In summary, there is a paucity of research on dysbiosis in psychosis, but indirect evidence suggests a link.

**Eating disorders**

Anorexia nervosa (AN) is a severe mental disorder with an estimated mortality rate of 10% [75]. Dysbiosis in the gut microbiota is thought to be an important environmental factor involved in the pathophysiology of AN [76]. Significant differences in total number of bacteria and relative abundances of bacterial taxa were found in multiple small studies. A small study in nine patients with AN, found an increased concentration of *Methanobrevibacter smithii* (a methane-producing archaeon) compared to normal weight and obese controls [77]. Patients harboring an increased concentration of *M. smithii*, showed a negative correlation ($r = -0.20$) with body mass index. Morita et al. [76] compared the fecal microbiota composition of AN patients ($n = 25$) with healthy controls. Patients with AN had significantly lower amounts anaerobes (*C. coccoides* group, *B. fragilis*, *C. leptum* and *Streptococcus*) and total bacteria. Lastly, Kleiman et al. [78] studied a sample of acute AN patients ($n = 16$) of whom fecal samples were assessed before and after hospital-based nourishment. Although they observed significant changes in microbiota composition associated with nourishment, microbiota diversity remained significantly lower as compared to healthy control participants. The researchers also observed a significant negative association between levels of depression and the number of observed bacterial species, meaning that higher levels of depression were associated with lower microbiome diversity. The mechanism via which the microbiota exerts effects on AN is still an enigma. Interestingly, some of the effects on microbiota in AN may be persistent. A recent study demonstrated that weight gain in AN patients did not correct the fecal microbiota profiles [79]. In summary, there is evidence for dysbiosis in AN but most questions still remain unanswered.

**Limitations of preclinical and clinical studies**

Evidence for a causal role of gut microbiota in metabolic and psychiatric disorders has mostly been obtained in studies on germfree animals. These animal models have various limitations. It is unclear to what extent findings based on rodent models translate to the human experience of the modeled psychiatric disorder and how the rodent gut microbiome relates to the human gut microbiome [80]. There are additional limitations specifically related to the use of germfree animals. These rodents have altered gut motility and physiology [81], multiple immune deficits [82], altered brain chemistry [83,84], reduced peripheral 5-HT production [85], and increased blood brain barrier permeability [86]. Hence, this may confound the findings and complicate the interpretation of results.

Clinical studies show the potential of the microbiome-gut-brain axis in further elucidating the nature of psychiatric disorders. However, the observations made in these studies also stress some of the challenges that lie ahead. For instance, the findings concerning alterations in specific types of microbiota associated with the various disorders (e.g. in ASD and MDD) were not always consistent. As previously mentioned, this may be explained by the use of different techniques for evaluating the microbiome. Another putative confounding factor is the influence of the subjects’ dietary habits in the different studies. It has been shown that the type of diet has a major effect on microbiome composition and hence most probably on the metabolites secreted by the microbiome [87]. In disorders such as AN, MDD, and ASD, the effect of the disease on diet and GI physiology will certainly control the microbiome and influence the cause or effect question. Along the same lines, use of medication may influence the microbiome composition [69,70] and should be taken into account when analyzing data from studies in which the subjects were not drug naive. Another challenge pertains to whether observed alterations in gut microbiota are unique to specific types of psychiatric disorders. If so, the microbiome may function as a predictive biomarker for a specific disorder. Although, a controlled investigation studying different psychiatric populations has yet to be conducted, some preliminary evidence suggests there may be some similarities across disorders. For example, the increased levels of *Alistipes* in depressed patients observed by Jiang et al. [65], have also been found in chronic fatigue [88] and in irritable bowel syndrome [89]. This suggests that there might be a common metabolite produced by the microbiota that drives microbiome-gut-brain mechanisms across disorders.

Furthermore, psychiatric disorders are highly heterogeneous (e.g. 227 different symptom patterns all qualify as MDD [90,91]). Hence it is unlikely that one disease mechanism is relevant to all phenotypes. Besides within-disorder heterogeneity, patients with a psychiatric disorder may frequently fit multiple diagnoses [92] or do not fit one particular diagnosis at all [93]. In addition, traditional diagnostic labels assume that psychiatric symptoms are stable over time. However, psychopathological symptoms are known to wax and
wane over time within the individual [94–96] and vary dimensionally instead of simply being present or absent [97–99]. Alternative approaches to conceptualize psychiatric disorders, such as the network approach, do address the complexity of psychiatric disorders [100]. In this framework psychopathology is hypothesized to develop dynamically as a complex dynamic system of interacting symptoms [100–104], which may also shed new light on comorbidity [105]. The stronger symptoms trigger each other, the more likely a vicious circle of co-occurring symptoms will emerge [106,107] that could become a psychiatric disorder [103]. The network approach has not yet been connected to metabolic networks or microbiota composition. It will be very interesting to investigate whether the periodicity in psychopathological symptoms correlate to time-related patterns in microbiota composition.

**Opportunities in research on gut-microbiome, metabolic, and psychiatric disorders**

**Dynamic assessment of psychopathology and gut microbiome**

Fluctuations in psychopathological symptoms or mood states may be captured by means of ecological momentary assessment (EMA) techniques, such as the experience sampling method (ESM) [108,109]. The ESM technique is a structured diary technique, which allows for time-intensive, real-time assessment of self-reports concerning affective states, thoughts or behaviors, and the contexts in which these occur [110,111]. Due to the technological advances in mobile technology, participants may receive the questionnaires and enter their responses electronically by means of personal digital assistants or smartphones. With relative ease, multiple momentary assessments may be collected for each individual in an ecologically valid manner. Subsequently, this vast amount of data per person can accommodate personalized analyses [112–114]. Direct coupling of such an approach to collection of microbiota analysis will be difficult because of the difference in time scales. Collection and metabolomics analysis of urine and in the future exhaled air may, however, monitor microbiota metabolism quite accurately allowing coupling of the different data sets. Ultimately, dynamic psychiatric-metabolic symptom-interconnections may be modeled for each individual, including his or her specific risk factors like alterations in the gut microbiome. Two examples of external factors or innate vulnerability that were modeled directly as influencing dynamic symptom interrelationships, instead of on the level of the complete disorder involved genetic variants. The researchers found variations in the BDNF and catechol-O-methyl transferase gene to be associated with dynamic connections between social stress and negative effect [115] and with the dynamic connections between experiencing pleasant activities and positive effect [116]. Likewise, alterations in a complex system like the microbiome could be added to network models in a similar fashion to study its influence on interconnections between symptoms/mental states.

**Conclusion**

There is a need for increased insight into the comorbidity between metabolic and psychiatric disorders, to ameliorate burden of disease associated with comorbidity, and to improve the course and outcome of such comorbidities. Since both types of disorders can be linked to gut health, a more thorough investigation of the latter is of vital importance. However, research in this field is hampered by methodological challenges. New studies should combine the dynamic changes in the gut microbiota composition and their metabolic effects with a network approach to psychopathology. By mapping the microbiome and fluctuations in the microbiome on a daily basis and connecting to fluctuations in symptoms, it may become possible to untangle the order of these processes in humans. Consequently, the gut microbiome may provide insight into the complex interaction between body and mind, perhaps resulting in novel therapies for both physiological and psychological disorders.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

**Funding**

R. N. Groen was supported by the Dutch Organisation for Scientific Research [NWO Talent Grant; 406.16.507].

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