THE GOOD MICROBES: IMPROVING MENTAL HEALTH THROUGH THE MICROBIOME?

Femke van Hout[1]

[1] Master student Molecular Mechanisms of Disease, Radboud university medical center, Nijmegen, The Netherlands

Critical Appraisal

Already in 1910, George Porter Phillips, physician at London's Bethlem Royal Hospital, stated that: "ranging from a mild attack of depression to a severe case of melancholia, one finds the hub of the disturbance centring itself in the alimentary canal" [1]. He was not alone in this view, as at the beginning of the 20th century, physicians and researchers started to see connections between gastrointestinal and psychological disturbances. Among them was Nobel prize winner Metchnikoff, who recommended to treat such disturbances by taking large quantities of certain microbes, for example, by drinking sour milk [2]. This was in line with his famous belief that we could "modify the flora in our bodies and replace the harmful microbes by useful microbes" [2]. However, their research was mainly hypothetical and small-scale. Not enough scientific support was reached and the idea of microbes influencing our mental health became a taboo until the end of the century [3]. It would take technological developments, such as metagenome sequencing of microbes, and controlled clinical trials, to start up building the scientific capacity and support to bring the fields of microbiology and psychiatry back together. These days, physicians find themselves asking once again: could certain microbes help in treating a patient's depression [4]?

Introduction

Worldwide, mental disorders have a significant consequence on health. According to the World Health Organization, the single largest contributor to global disability is depression [5]. Estimates of the number of people with depression exceed 300 million, with major depressive disorder (MDD) affecting one in five people at some point during their lifetime [5-7]. The MDD symptoms and their severity vary, but often involve decreased energy, low mood, loss of interest and enjoyment, thereby impairing daily functioning and quality of life [5, 8]. Although various pharmacological treatments for MDD are at hand, they can have serious side effects and only 60-70% of patients respond, in various degrees [9]. Therefore, further insight into the complex pathophysiology of MDD is needed to open up the way for new leads of therapy. One of the promising areas of research is the gut microbiome, where the first clinical trials modulating this microbiome have started to show the improvement of depressive symptoms.

The microbiome-gut-brain axis

We have a long and complex history with the microbes living within and on us. According to current estimates, we contain at least as much microbial as human cells [10]. Although these microbial inhabitants have not always been appreciated, we now start to realise more and more how crucial they are to our health and well-being. Our gut microbes perform various physiological roles. Among the first to be elucidated were their abilities to break down indigestible food and to protect against (opportunistic) pathogenic microbes [11]. Even more complex roles were described over the last few decades. As it turns out, our gut microbes can also interact with our central nervous system (CNS). This bidirectional microbiome-gut-brain axis consists of various neural, endocrine, metabolic and immune signalling pathways (Figure 1) [12]. Although the underlying mechanisms are not fully elucidated yet, some interesting examples can already be given. One example is the direct influence of gut microbes on the signalling in the enteric nervous system, that is connected to the CNS through the vagus nerve [13]. Other gut microbes influence the endocrine hypothalamic-pituitary axis involved in cortisol production, thereby altering the stress-response [14, 15]. Regarding metabolic pathways, gut microbes are involved in the production and degradation of neuroactive compounds and their precursors, such as tryptophan, the building block for serotonin [16]. A new mechanism recently proposed involves short-chain fatty acid (SCFA) production by the gut microbes, that can act as epigenetic modulators. When these SCFAs reach the brain, they could alter the gene expression of brain cells, potentially influencing a multitude of processes [17]. The microbiome also affects the production of cytokines, which can induce inflammation in the brain when acting on microglia [18, 19]. Moreover, there is communication from the central nervous system back to the gut as well [20]. Through the release of neurotransmitters and hormones, the gut habitat and physiology can be changed, affecting the microbiome composition.

The 'depressed microbiome'

As gastrointestinal and mental health problems often coincide, extensive research has been performed on this connection. With the developments of DNA sequencing techniques, we are now able to identify and characterise the gut microbes and many correlation studies are performed to see whether specific microbes can be associated with specific (medical) conditions. However, research on the directionality of this relation has been limited mainly to animal models, which cannot be translated directly to human health. A remarkable example is given by faecal microbiota transplantation (FMT) studies in mice and rats, where FMT from MDD patients induced dysregulated microbiota in the animals. The developed inflammation and anxiety-like behaviour points towards a causal connection [21, 22]. In humans, studies on the connection between the gut microbiome and mental health have been mainly associative of nature. Although many have focused on depression, a recent meta-analysis showed that based on taxonomy, no consensus can be reached yet on what makes the 'depressed microbiome' [23]. In the taxonomy studies, only one gene is used to identify the bacteria. This strictly prokaryotic gene encodes for the 16S ribosomal RNA (16S rRNA), which is highly conserved in function. Therefore, small differences in the 16S rRNA sequence can be used to identify the different bacterial

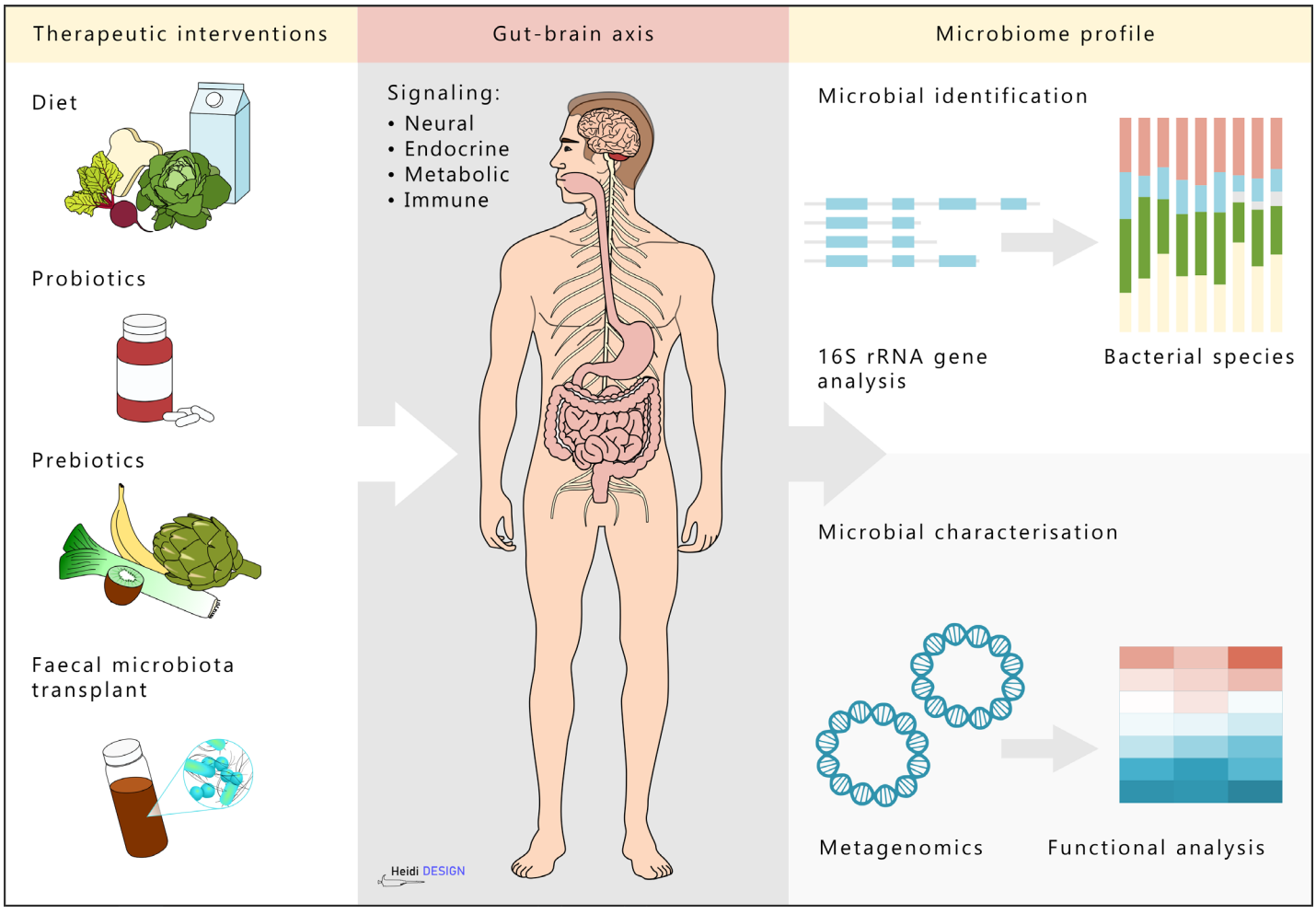

Figure 1: Overview of signalling along the gut-brain axis together with the therapeutic interventions to alter and the methods to profile the gut microbiome
The gut microbiome composition plays a significant role in gut-brain signalling and can be altered through various interventions. These include specific diets, the direct intake of certain microbes (probiotics) or their nutrients (prebiotics) and faecal microbiota transplants. Signalling along the gut-brain axis involves various nerves, hormones, neurotransmitters and cytokines that all contribute to the versatile and extensive communication between the gut microbiome and the central nervous system. The gut microbiome can be profiled through sequencing of only the 16S ribosomal RNA, allowing for taxonomic analysis, or through the total of bacterial genes (metagenomics), allowing for functional analysis.

taxa. As no specific bacterial taxa can yet be pointed out to be the most relevant to depression, it has been suggested that studies of microbial functioning could complement in understanding the gut microbiome in depression [23]. While taxonomic analyses rely on the identification of solely the 16S rRNA genes to identify which bacteria are present, functional metagenomics takes the entire genome of bacteria into account (Figure 1). In this way, the functional potential of the bacteria, including neural, endocrine, metabolic and immune signalling, can be predicted [23-25].

One of the first studies to look at this functional potential as well is the impressive Flemish Gut Project, with over a thousand of our Belgian neighbours participating [24]. Within this cohort, Belgian and Dutch researchers looked at the associations between gut bacteria, their metabolic potential and the quality of life (QoL). The QoL was assessed with an extensive survey, covering both mental health concepts, such as emotional well-being, and physical health concepts, such as vitality. When first taking a taxonomic approach, they found that certain bacteria, such as *Faecalibacterium* and *Coprococcus*, known for involvement in intestinal barrier function and inflammation, were associated with a higher QoL, while *Dialister* and *Coprococcus* were decreased in participants with depression. Moreover, the researchers looked at the functional potential, by associating the QoL with defined 'gut-brain modules', which are based on microbial pathways of neuroactive potential. With this approach, they found a connection between QoL and the dopamine metabolism of a gut microbiome, more specifically its metabolite 3,4-dihydroxyphenylacetic acid, also known as DOPAC, pointing towards a new target for treatment.

Treating the microbiome

Ever since the first indications of the gut microbiome influencing mental health, people have been trying to mitigate mental health disturbances through alterations of the microbiome [3]. Although no consensus has been reached on the bacterial taxa most relevant to depression, many treatments to improve depressive symptoms through the microbiome have been suggested. Such treatments include certain diets, probiotics, prebiotics and even FMT (Figure 1) [4].

As diet seems to be the major determinant of gut microbiome composition in adults, restriction to a certain diet may change the

microbiome in a beneficial way in terms of gut-brain communication [26]. Although the potential of such nutritional interventions is still under debate, several attempts to show its potential have been made with large trials. An example is the "Supporting the Modification of lifestyle In Lowered Emotional States" trial, also known as SMILES, where adults with MDD switched to a Mediterranean diet for 12 weeks [27]. The Mediterranean diet, with abundant fruits, vegetables and grains, is believed to be a healthy, anti-inflammatory diet and is associated with a lower risk of depression. The 12-week intervention was indeed reported to alleviate MDD symptoms, but other researchers say that the large effect sizes are in part attributable to the study design and therefore, should be critically reviewed [28].

Besides changing the overall diet to alter the gut microbiome, one could also directly take the microbes that confer a health benefit or take certain nutrients, such as fibres, that specifically enhance their growth. These are, respectively, termed probiotics and prebiotics. Many studies on their use in mental health have been performed, but differ in study design, including the type, dose and duration of pre-or probiotic treatment, the cohort, the read-out of depressive symptoms and many more. Meta-analyses of these controlled trials report that, although prebiotics do not significantly mitigate depression, probiotics can positively affect depressive symptoms [29, 30]. Over the last years, it has, therefore, become widely accepted that at least some probiotic treatments can help in reducing the depression burden [29-32]. To help clinicians and patients in their search for these scientifically proven treatments, the International Scientific Association for Probiotics and Prebiotics offers a clinical guide [33].

Another suggested treatment is the FMT, where the faecal microbiota from a healthy donor would be given to an MDD patient. The FMT was first reported in medical literature in 1958 and is best known for its treatment of *Clostridium difficile* enterocolitis [34, 35]. Currently ongoing clinical studies on FMT in MDD have yet to be completed before data on its effectiveness can be analysed. However, similar studies in inflammatory bowel syndrome patients seem promising. Patients with this syndrome that received a healthy donor FMT showed improvement in terms of depression and anxiety [36]. Yet, it should be noted that it is currently not clear whether it is mainly the microbes themselves, certain bacterial products or even bacteriophages, mediating these effects [37].

Limitations

Although research in animal models and the first human studies may look very promising, caution is warranted as well. Critical evaluation of study design is required to assess the value of given results and their translation to specific patient groups. For example, the famous Yakult bacterium *Lactobacillus casei Shirota* as probiotic intervention only showed mood improvements for those people at the lowest end of the mood scale [38]. Therefore, researchers in the field emphasise that it is of great importance to be aware of the selected participants of each study [29]. The inclusion of healthy participants that have little room for improvement in terms of depressive symptoms may limit evidence for a real antidepressant potential in patients or sub-clinical populations. The performed human trials also vary in the exact treatment type, for example the (combinations of) bacteria strains in probiotic studies, the dosage and duration and the way in which depression severity is assessed. Moreover, many studies are too small in size or do not account for confounding factors such as diet, medical comorbidities and medication impacting the gut microbiome, including antibiotics [23, 24, 32]. Only when cohorts are large enough to control for confounding factors and the above-mentioned parameters of study design become more standardised, will clinical trials be able to give conclusive results.

Conclusion

More than a century after the ideas of Porter and Metchnikoff a crucial role for the gut microbiome in our mental health can no longer be denied. These microbes influence our central nervous system through various neural, endocrine, metabolic and immune signalling pathways. Specific microbiome features have been linked to depression and gave way to new targets for treatment such as probiotics. Although animal studies look very promising in terms of causality and treatment successes, human studies are lagging behind. Only with standardised large clinical trials can the role of the microbiome and the effectiveness of microbiome-targeting treatments in human mental health be fully elucidated.

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EXAM QUESTIONS

As RAMS aims to enlighten both students and professionals, we would like to present you two exam questions. Find out if you can remember what you have learned during your bachelor's!

We challenge you!

Question 1

The cerebral lobes cannot only be distinguished by anatomical location, but also according to their function. In which lobe can the primary motor cortex be found?

A. Frontal lobe
B. Parietal lobe
C. Temporal lobe

(Topic from Q6-1 MGZ Nervous System, 2018)

Question 2

After a stroke, a patient suffers from paralysis of their right hand. The mobility of the hand is controlled by a nerve tract emerging from the contralateral motor cortex of the brain. In what structure of the central nervous system does this nerve tract cross to the contralateral side of the nervous system?

A. Capsula interna
B. Medulla oblongata
C. Spinal cord
D. Thalamus

(Topic from Q6-2 MGZ Nervous System, 2019)

The answers to these questions can be found on page 17 in this journal.