Gut microbiota’s effect on physical and mental health (MyNewGut)

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Did you know we are almost more bacteria than human? There are over 100 trillion bacteria residing inside our large intestine, making up our gut microbiota.[1] These bacteria encode over 100 times more genes than the human genome.

Our physical and mental health can be strongly affected by ‘our microbes’, or so to say, the small organisms (such as bacteria) which form the microbial ecosystem in our gut. This ecosystem is known as our gut *microbiota*. Disrupting that ecosystem (so-called 'dysbiosis’*) may be dangerous for our health. In fact, dysbiosis is associated with disorders like obesity, metabolic syndrome, type 2 diabetes, and mental diseases. But how exactly do these tiny ‘gut bugs’ control different body and brain functions and how can we use this knowledge to prevent diseases?

The EU-funded project MyNewGut has delved into the gut microbiota universe and tried to find an answer to these questions by:

- Investigating the role of the gut microbiota and its specific components in metabolism and energy balance.
- Identifying specific gut microbiota components and the metabolic functions that contribute to and predict obesity, eating and emotional disorders and associated conditions.
- Understanding the influence of environmental factors on the gut microbiota, in pregnancy and during a baby’s development, and its impact on brain, immune and metabolic long-term health.
- Developing new food ingredients and food prototypes, by collaborating with the EU food industry, that target the gut ecosystem and contribute to reducing the risks of metabolic- and mental-related disorders.

Over the last 5 years, the MyNewGut partners have published 45 papers with many more to come. The published papers include human, animal and *in vitro* studies, as well as extensive literature reviews.

These studies have not only confirmed many existing hypotheses surrounding the role of the gut microbiota, but also produced various promising new discoveries. Let's have a look at them in detail!

New gut bacteria may help fight obesity and mental disorders

Bacteria account for >90% of the microorganisms found in our gut.[2] The MyNewGut project has discovered bacterial species and strains in healthy people that seem to be effective against obesity, metabolic and mood disorders. They do so by influencing the endocrine and immune pathways that have an impact on both our physical and mental health. For instance, the bacterial strain '*Bacteroides uniformis* CECT 7771' has shown pre-clinical efficacy on metabolic and immune dysfunctions in obesity, reducing for example serum triglyceride levels, glucose intolerance and body weight gain.[3,4] . Furthermore, the MyNewGut partners have also identified a *Bifidobacterium longum* bacteria strain, which had a positive impact on perceived stress, sleep quality and cortisol release. These strains could potentially be next generation probiotics that could in the future be used to help tackle obesity and stress-related disorders (e.g. impairments in cognitive task performance like reduced attention, learning ability; or mood disorders like depression).

How diet has an influence on our gut microbiota

Diet appears to be a major factor that influences the composition and function of the human gut microbiota.[5,6] MyNewGut experts have conducted several human intervention trials to investigate dietary health effects potentially mediated by the microbiota and they are publishing a range of position papers that will show evidence on how we could inform future dietary recommendations. These position papers are based on both project results and other recent insights regarding the role of the gut microbiota and its interaction with the diet on health related outcomes. MyNewGut partners have specifically looked into the role played by proteins, fats and fibres on the gut microbiota.

How high intake of proteins or a high fat diet harm the gut microbiota

Protein intake benefits weight management and some aspects of metabolic health, but, unlike carbohydrates, high intake levels also seem to have negative effects. MyNewGut partners found out that high protein consumption, which increases protein fermentation in the large intestine, generates some of the toxic metabolites (products of amino acid metabolism) linked to diseases such as colorectal cancer. In the 3-week human high-protein dietary intervention by Beaumont and colleagues also the source of the protein (animal or plant) appeared to lead to significant differences in the metabolites that were generated.[7] This makes protein source an important factor for future research particularly in relation to the possible different long-term effects of high protein diets on microbiota and derived metabolites. Wolters and colleagues concluded that a **high fat diet**, especially when rich in saturated fatty acids, may have negative effects on the gut microbiota, characterised by a lower number of microbes and a lower variety of microbial species. Diets rich in omega 3 or omega 6 polyunsaturated fatty acids do not seem to negatively affect the microbiota, whereas the effects of monounsaturated fatty acids are less consistent (submitted for publication).

Dietary fibres are the main fuel for our gut microbiota

Fibres are carbohydrates that are not digested by our digestive enzymes, and thus reach our large intestine intact. They get fermented by gut bacteria, which form short-chain fatty acids (SCFA: acetate, propionate and butyrate). These substances play an important role in gut health; for example, they help protect the cells lining our gut, they also trigger hormones involved in appetite and glucose metabolism and reduce inflammation.[2] Carbohydrate fermentation is thus considered beneficial for overall gut health and beyond. Recent studies suggest that intake of fibre at levels above current dietary recommendations (25-30 g fibre/day) could be necessary to achieve some of the microbiome-related beneficial effects, such as reducing makers of gut inflammation.[8]

High fat or high fibre diets are oppositely associated with depression

The interaction between diet and gut microbiota has also been found to modulate the gut-brain axis in mice fed a high-fat diet, and ultimately negatively influence brain function.[9] More precisely, studies conducted by MyNewGut partners showed that Western diets rich in saturated fat resulted not only in obesity, but also in depressive behaviour. We know that these effects are mediated by the gut microbiome, since they were reduced by antibiotic-treatment. These results are only a starting point, and new research would have to confirm the findings in humans.[10] A review of other research shows that high fibre diets are also associated with fewer symptoms of depression, whereby prebiotic fibres shape microbiota composition which could influence behaviour.[11]

The role of the gut in metabolic health: mechanistic clues

Studies in animal models conducted by project partners have revealed new mechanisms whereby the microbiota could impact metabolic health. The consortium showed that peptidase activity (DPPIV) responsible for the degradation of enteroendocrine hormones produced in the gut, which regulate appetite and glucose homeostasis (like glucagon-like peptide I [GLP-I]), are of bacterial origin.[12] This means that the presence of specific bacteria producing these new enzymes can influence appetite, food intake and body weight gain.

Gut microbiota: we are all different

The MyNewGut project has also explored innovative interventions, including Faecal Microbiota Transplants (FMT) for restoring dysbiosis-associated disorders. In FMT, the microbiota of a healthy donor is transferred to an individual suffering from some form of dysbiosis. In MyNewGut studies, the donor's microbiota was transferred to human subjects with metabolic syndrome.[5] In this study, the responsiveness to treatment depended on the individual's gut microbiota profile, suggesting a need for personalised intervention strategies. This study also demonstrates that the individual's microbiota directly impacts neural systems that could mediate the impact of food intake on metabolic health (paper in preparation).

The impact of early life microbial imbalance on health

MyNewGut has demonstrated how important it is to better understand the role of environmental factors and the diet on the gut microbiota at critical development periods, such as infancy and childhood. During these periods, different organs and systems are under development and maturation making it a crucial time for developing a diverse gut microbiota. Dietary changes that favourably influence the microbiota are thought to have a higher and longer-lasting effect during stages of development, emphasising the importance of diet during early life for long-term health in adulthood.[2] MyNewGut partners specifically investigated whether effects of environmental factors in early life and childhood also impact health outcomes in later stages of life in humans. For example, they conducted a unique longitudinal study in children to determine the role of the microbiota, the lifestyle (diet, exercise, etc.) and other individual factors (immune and metabolic profile) in the development of overweight. The study revealed that specific microbiota configurations were indeed correlated to inflammatory markers and dietary patterns, and subsequently to the development of obesity. MyNewGut's partners have also showed that the type of birth, a factor that influences the maturation of the microbiota early in life and may contribute to health programming, also influences vulnerability to stress in young adulthood in humans. Birth by caesarean section adversely impacts inflammatory markers and stress response.

What's next for gut health research?

To conclude, the MyNewGut project findings have demonstrated that our gut 'has a mind of its own' and that further research is needed to understand how it functions and influences our health. The project has provided precious insights into the role of our gut microbiota both in metabolic and mental health. The MyNewGut findings will play a fundamental role in the future development of more effective interventions targeting the gut - to fight obesity, metabolic syndrome, and behavioural disorders, like eating and mood/emotional disorders. In three words: mind your gut!

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