

# Are we Ready for a “Microbiome-Guided Behaviour” Approach?

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**Abstract:** The microbiome is proving to be increasingly important for human brain functioning. A series of recent studies have shown that the microbiome influences the central nervous system in various ways, and consequently acts on the psychological well-being of the individual by mediating, among others, the reactions of stress and anxiety. From a specifically neuroethical point of view, according to some scholars, the particular composition of the microbiome—*qua* microbial community—can have consequences on the traditional idea of human individuality. Another neuroethical aspect concerns the reception of this new knowledge in relation to clinical applications. In fact, attention to the balance of the microbiome—which includes eating behavior, the use of psychobiotics and, in the treatment of certain diseases, the use of fecal microbiota transplantation—may be limited or even prevented by a biased negative attitude. This attitude derives from a prejudice related to everything that has to do with the organic processing of food and, in general, with the human stomach and intestine: the latter have traditionally been regarded as low, dirty, contaminated and opposed to what belongs to the mind and the brain. This biased attitude can lead one to fail to adequately consider the new anthropological conceptions related to the microbiome, resulting in a state of health, both physical and psychological, inferior to what one might have by paying the right attention to the knowledge available today. Shifting from the ubiquitous high-low metaphor (which is synonymous with superior-inferior) to an inside-outside metaphor can thus be a neuroethical strategy to achieve a new and unbiased reception of the discoveries related to the microbiome.

**Keywords:** microbiota; brain-gut axis; fecal transplantation; metaphor; neuroethics

## Introduction

“Follow your gut.” This is no longer just a popular way to justify an emotional choice, but may be the correct (albeit simplified) description of a complex system of interconnected organic subsystems that affect our behavior. “Following one’s gut” used to be considered somewhat negatively, as the prevalence of emotions over reason and impulsivity over reflection, but now things are different. With the new understanding of the role of emotions, the idea is no longer that rationality is abstract, detached from the body and its reactions, but rather that the brain simply plays the main role, while in the past that role was played by a disembodied mind.<sup>1</sup>

It seems that today another problematic shift might occur, especially in the light of the latest scientific discoveries concerning the function performed in humans by the enteric nervous system present in our gut and the microbial population living there—i.e., the microbiota (the microbes populating our body) or microbiome (the genome of such microbes, that is, the most relevant part in the interaction with the host organism), two terms that are often used as synonyms.<sup>2</sup> Indeed, we currently know that, although the concept may seem inadequate, the gastrointestinal system has a “brain” with an “emotional” role superior to that of other organs (such as the heart). The intestine is the only organ that manifests reflected activity irrespective of the input received from the central nervous system and that has its own autonomous nervous system, which is able to mediate reflexes in the absence

of inputs from the brain and the spinal cord, while all the other organs are innervated by the peripheral nervous system that connects to the central one. The human gut’s nervous system is a legacy of our evolutionary past, and if we have kept it, it’s probably because it’s important. It represents a processing and management center that allows us to solve many major and often unpleasant problems without great conscious effort.<sup>3</sup> For example, the visceral sensations of unease or alarm can drive our behavior on many occasions without us being aware of their role in our decisions.

The enteric nervous system (ENS)—made up of two layers of about 100 million nerve cells lining the gastrointestinal tract from the esophagus to the rectum—is an independent neural integration and processing center. Indeed, the ENS can trigger nausea or malaise, can accumulate stress, arouse emotions, and can help fixate food-related memories. And, if it works properly, it does all of the above without reaching the threshold of awareness, as it carries out its functions in ways that are automatic, unconscious and not controlled voluntarily. In other words, they act differently from the vital processes of which we are ordinarily aware, such as the heartbeat.

Inside the intestine there is another “organ”: the microbiome, a microbial ecosystem consisting of thousands of billions of microorganisms—the intestinal microbiota—whose total mass is about 0.2–1 kg in the 70 kg “reference man.”<sup>4</sup> It is estimated that the number of microbial cells in the colon is equal to the total number of nucleated and nonnucleated cells in our body (but excluding red blood cells, the ratio is 10:1) and that it hosts more than one thousand bacterial species, marked by a great genetic variability.<sup>5</sup> The microbiome, among other things, achieves both the recognition and synthesis of neuroendocrine hormones and produces neuroactive factors, capable of communicating not only with the enteric nervous system but also with the central nervous system.

It is well known that there is a relation between irritable bowel syndrome and constipation on the one hand, and anxiety and depression on the other, but the interesting thing is that the latter do not cause the former: it is the other way around. In other words, at least in some cases, depression should be treated in the gut rather than the brain. The activity of the digestive system may even affect cognition.<sup>6</sup> From this perspective, today’s encefalocentric view seems destined to give way to a more integrated and polycentric vision of human nervous and mental functioning.

In the history of modern Western medicine (biomedicine), the gut has long been considered a peripheral structure of the body, only capable of performing marginal functions, certainly secondary to those of the more noble organs such as the brain and the heart. The recent discovery that the gut is an independent site of neuronal integration and processing has helped disrupt the biomedical view of the separation between body and mind, leading to the epistemological rediscovery and reconsideration of (mainly Oriental) traditional doctrines involving the notion of a “visceral brain” (the gut) affecting the field of organic functions and emotional life.<sup>7</sup>

There are many enteric symptoms of psychiatric disorders: enteric somatizations are a simple yet effective example of psychosomatic disorders that connect brain, mind and gut; some personality disorders have also been associated with the effort to learn to control the sphincter and its intestinal disorders (such as constipation, diarrhea, uncontrollable borborygmus, irritable bowel, dyspepsia, etc.).

These are all attempts to escape the oppressive power of the gut, experienced as a limit to subjective freedom.<sup>8</sup>

### Microbiome-gut-brain Axis: An Upcoming Revolution

Many recent studies in psycho-neuro-immuno-endocrinology seem to point to the existence of an integrated network of command and processing centers inherent in the physiological functions of the body, as well as some pathological conditions of the human body and psyche.<sup>9</sup> This network comprises the gastrointestinal tract, the enteric nervous system, and the brain. There is also growing evidence of the role played by the microbiome in producing individual well-being or causing several illnesses.<sup>10</sup> The presence of serotonergic receptors in the intestinal tract has been well demonstrated and it appears evident that all conditions that may alter the serotonin turnover at the level of enteric nervous system synapses play a primary role in creating functional alterations that have an effect not only locally but also all along the so-called gut-brain axis.

The microbiome is the result of colonization of the human gut during birth and early development by a large variety of microbial species (bacteria, viruses, archaea, and eukaryotic microbes), that differs from individual to individual due to genetic factors and environmental factors, like diet and age. "The number of microbial genes involved in establishing and maintaining the community's ecology is immense, totaling 5,000,000 or more."<sup>11</sup> It appears that gut microbes are largely responsible for the development, maturation and adult function of the enteric nervous system as well as the blood brain barrier, microglia and many aspects of the central nervous system's structure and functioning.<sup>12</sup> It has now been also shown that the microbiome directly affects the neuronal plasticity of both the visceral and the encephalic systems. It is therefore conceivable that what is able to change our microbiome (type of nutrition, fasting, administration of antibiotics, or use of other drugs that can alter or destroy intestinal germs) can indirectly affect our brain and our mind. This gut-brain interaction is supported by several experimental data.<sup>13</sup>

The microbiome may influence the synaptogenesis and regulation of neurotransmitters and neurotrophic factors in the cerebral hemisphere, as it has been shown that it can modulate its autoimmunity by acting favorably or unfavorably on the evolution of several neurological disorders. Probiotic administration (e.g., *Lactobacillus*) and fecal microbiota transplant to treat conditions associated with depression and anxiety are no longer experimental but sound therapeutic means.<sup>14</sup> The relationship between the microbiome and depression has been proven by research on bacterial abnormalities in depression patients.<sup>15</sup> It has also been shown that the administration of some microbial populations (*L. rhammosus*, *B. infantis*, *B. longum*) can improve the mood even in healthy subjects.<sup>16</sup>

The interaction between the gut and the brain has recently been associated with Parkinson's and Alzheimer's disease, autism, anxiety, and depression, through mechanisms related to inflammation, with implication of dopamine.<sup>17</sup> Even various altered metabolic conditions (diabetes mellitus, obesity) seem to be strongly influenced by the microbiome. Recent research has also shown that the microbiome is able to influence behavior and emotions. The reduction of serotonin related to the appearance of mood disorders (depression and bipolar disorder) may be deteriorated or improved by given microbial compositions.<sup>18</sup>

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A recent study, for example, has highlighted the connection between gut bacteria and emotions, according to the profile of the gut microbiota. The researchers found differences between a group of women who had *Bacteroides* versus a group of women who had mainly *Prevotella bacteria*.<sup>19</sup> In the first group, gray matter was thicker in the cortex and insula, and the hippocampus was of greater volume. In the second group, there were more connections between brain areas associated with emotional, attentional and sensory functions, with a reduced brain volume in some regions such as the hippocampus, which was also less active. This second group showed higher levels of negative feelings (anxiety, distress and irritability) after having been exposed to photographs of scenes with perceived negative content.

“The gut microbiota has been implicated in a variety of stress related conditions including anxiety, depression and irritable bowel syndrome. Experimental alteration of gut microbiota influences stress responsiveness, anxiety-like behaviour, and the set point for activation of the neuroendocrine hypothalamic-pituitary-adrenal (HPA) stress axis.”<sup>20</sup> Indeed, researchers found that mice lacking indigenous bacteria, being raised in sterile environments, showed greater reactions to stress compared to mice with a normal microbiome. When the mice underwent a probiotic-induced bacterial recolonization, their stress levels diminished.<sup>21</sup>

These findings have paved the way to new treatments.<sup>22</sup> “Psychobiotics are beneficial bacteria (probiotics) or support for such bacteria (prebiotics) that influence bacteria-brain relationships. Psychobiotics exert anxiolytic and antidepressant effects characterized by changes in emotional, cognitive, systemic, and neural indices.”<sup>23</sup> Recent studies on mice “strongly suggest a beneficial role of prebiotic treatment for stress-related behaviors. These findings strengthen the evidence base supporting therapeutic targeting of the gut microbiota for brain-gut axis disorders, opening new avenues in the field of nutritional neuropsychopharmacology.”<sup>24</sup>

Instead, “Fecal Microbiota Transplantation (FMT) is the delivery of large amounts of intestinal microbiota (fecal suspension or purified fecal microbiota) from a pre-screened donor into the intestinal tract of a patient,” mainly by colonoscopy.<sup>25</sup> It is deemed a very good therapy for *Clostridium difficile* infection. But it is also used as a treatment for gastrointestinal disorders, obesity, anorexia nervosa, neurodegenerative and neurodevelopmental disorders.<sup>26</sup> It appears to be a natural and organic cure which is safer than traditional antibiotics. There are also instances of a home-based DIY FMT, thanks to methods found online.<sup>27</sup>

As we have seen, the premise is that “our gut has the greater density of microbial communities within our bodies. These gut microbial communities comprise a complex ecosystem of microbiota which can interact with the intestinal mucosa and are responsible for many key physiological functions.”<sup>28</sup> It is therefore believed that some pathological conditions may be prevented or at least improved by microbial manipulation.

Fecal microbiota transplantation has provided evidence that the gut microbiome interacts with the central nervous system, since there have been cases of people who have undergone an FMT and have developed anxiety or depression like the donor.<sup>29</sup> This could occur through neural, endocrine and immune pathways, with possible influences on the receiver’s brain functions and behavior. In mice models, it has been recently shown that the microbial transplant can cause stress and anxiety-related behaviors.<sup>30</sup> Gut microbes may contribute to the synthesis of some neurotransmitters, such as serotonin, and the transfer of such microbes can

create imbalances in the available amount of such neurotransmitters.<sup>31</sup> Healthy mice who have undergone a fecal microbiota transplantation with “depression microbiota” derived from human patients suffering from major depressive disorder manifest typical behaviors of depression, contrary to mice that have instead received “healthy microbiota” derived from healthy individuals.<sup>32</sup>

### A Neuroethical Approach

As briefly shown thus far, there has recently been much progress in understanding the enteric nervous system and its evolution, which seems to show that there is a very close interaction between the enteric nervous system, immunological mechanisms and the central nervous system. Indeed, gut microbiota are largely responsible for the development, maturation and adult functioning not only of the enteric nervous system, but also of the central nervous system.<sup>33</sup> Microbiome alterations induced by a change in diet and, even more so, those caused by the use of antibiotics have direct repercussions on hippocampal neurogenesis and therefore, indirectly, also on cognitive functions, which shows how important the microbiome is for brain functioning.<sup>34</sup>

The presence of such a large community of microorganisms within our body, capable of influencing our behavior, can constitute a challenge to the self understood as “a distinct psycho/phenomenological concept, connoting recognition of the conscious experience of the individual, the subject, and the object of introspection.”<sup>35</sup> If, in some way, the microbial communities that inhabit one’s gut (and also one’s mouth, skin and vagina) are elements of one’s organic make-up, this might support an ecosystem view of the human body, according to which human beings are ecosystems, not individuals in the classical sense of a unitary organism distinct from its environment.<sup>36</sup>

According to some authors, “the ‘holobiont’ concept, defined as the collective contribution of the eukaryotic and prokaryotic counterparts to the multicellular organism, introduces a complex definition of individuality.”<sup>37</sup> There are three traditional biological explanations of the individual self: the immune system, the brain, and the genome. But “evidence show that our resident microbes orchestrate the adaptive immune system, influence the brain, and contribute more gene functions than our own genome.”<sup>38</sup> In fact, recent studies have highlighted “the emergent roles for the gut microbiota in modulating host social and communicative behavior, stressor-induced behavior, and performance in learning and memory task.”<sup>39</sup> The microbiome acts on brain microstructure, gene expression, and neurochemical metabolism in different brain areas, and dysbiosis of the microbiome can be linked to neurobehavioral diseases.

For these reasons, the idea of an individual and bounded human self is being called into question. In fact, the microbiome seems to constitute a relevant part of the systems that contribute to the human being’s biological individuality: so much so that some research is based on the tenet that “the human is contingent on microbes.” The challenge would therefore be to introduce the concept of “microbial humanities,” as a new approach to the “traditional disciplinary divisions between the arts and the science.”<sup>40</sup>

Jonathan Beever and Nicolae Morar have underlined the ethical implications of this challenge to individuality coming from microbial ecology. In fact, individuality is an ontological condition for autonomy.<sup>41</sup> If, rather than being individuals

with a homogeneous constitution, we are complex forms of organic organization where microbial ecological communities play a constitutive part, then autonomy as free rational decisionmaking may have to be rethought. Given the collective biological nature, say Beever and Moran, the self must be understood as an ecosystem, in which—paradoxically—we could be “10% human.”<sup>42</sup> And above all, it is argued, autonomy decreases as the role of those constituent factors increases: those dynamic elements weaken the coherence and unity of the self.

The point seems to be this: if we accept this perspective, therapeutic actions must also find a different explanation. According to the traditional idea of the individual endowed with a homogeneous biological constitution, fecal transplantation is equivalent to an organ transplantation aimed at repairing the organism. From the ecological, multiconstitutive perspective, fecal transplantation is instead an addition of constituent components from one ecological community to another, which in fact would change not only the functioning of the organism but the collaborative organism as such. Beever and Moran’s proposal is a deep challenge to our ontological conception of individuality and, consequently, autonomy.<sup>43</sup> The latter could no longer be normatively presupposed in our social and moral discourse, but would have to become, at best, a useful fiction.

It is evident that this perspective about the microbiome inhabiting human organisms is rather counterintuitive—and certainly debatable. There are indeed two main questions to address: an empirical one and a philosophical one. The first question is related to the effective influence of the microbiota on our mind/brain and behavior; the philosophical one is about the very concept of constitution, of what qualifies an individual as an organism, in addition to the issue of the distinction and interaction between subpersonal processes and personal processes at the mental level.<sup>44</sup> The difficulty of accepting the perspective of a reduced individuality or of a “microbiome-guided behavior” and, in general, a biased reception or a full refusal of applications related to the microbiome therefore appear to fall within the scope of neuroethics, as they concern the social implications of new neurobiological knowledge.<sup>45</sup>

In this vein, the idea that moods, emotional states, effectiveness of cognitive processes and even personality traits are somehow connected to the composition of the microbiome may elicit a biased rejection—or at least a biased reception of the related scientific findings and clinical applications. In fact, everything that is connected to the organic processing of food and in general to the human stomach and intestine has often been considered as low, dirty, contaminated and opposed to what concerns the higher functions of the human being, which were traditionally located in the mind and, later, in the brain. As we shall see, this opposition is mainly, but not only, the result of evolutionary adaptations, aimed at preserving us from possible vehicles of infection.

Many cultures, and the Western one in particular, have constructed narratives that set the gut against the mind. The gut is placed in the lower body, and is the source of irrational decisions, whereas reason is in the head: this is the perspective implicit in the ubiquitous high-low metaphor, synonymous with superior-inferior. Also, physiological functions are given a moral value in relation to the ideas of purity and contamination. This is probably an evolutionary legacy by which humans have learnt to avoid physical contamination and not to break group norms, as both would be detrimental to survival and adaptation to the environment. In the religious field, consider the prescriptions contained in some books of

the Bible, such as *Leviticus* (11–16) and *Deuteronomy* (23, 11–15), or the minor or major ablutions required in the Quran to be able to pray. These mechanisms are implicitly working even in nonbelievers, as shown by many studies of empirical psychology on the connection between physical disgust and moral disgust, in which the simple act of washing hands attenuates the feeling of blame for breaking rules.<sup>46</sup>

However, as discussed earlier, we are now beginning to understand that a significant contribution to the behavioral balance of the human being comes precisely from the belly. Does this mean “lowering” our best intentions and best behaviors, which we have always taken as a result of hard work and education, to the status of random structure of bacterial flora? Could this idea lead to devaluing the effort to build one’s character for the benefit of chemical treatments aimed at improving the microbiome? A balanced consideration of the new discoveries, considered in their context and in their precise scope—the task of a competent neuroethical approach—can help to properly transpose these findings into clinical practice and public discourse, to the benefit of science and society as a whole.<sup>47</sup>

The intestine is considered the core and symbol of well-being, because health, disease and aging are closely related to its state; however, we are not used to linking the gut with the higher functions and the psychological sphere (outside of idiomatic expressions, as seen above). For this reason, even the use of psychobiotics and other microbiota-targeted interventions which might positively affect people’s mental health could be viewed with suspicion or be underestimated. There are critical developmental periods in which the brain is more vulnerable because it is preparing to respond to the outside world. Thus, if the mother’s microbial ecosystem changes, for example due to an infection, stress or an unbalanced diet, this could have an impact on the intestinal microbiome of the newborn, and the effects of this change could last for a lifetime.<sup>48</sup> It is therefore important to make sure that the current cultural attitude will not hinder the search for the most effective treatment.

Furthermore, when it comes to fecal microbiota transplantation, often the simple word “fecal” drives people away from treatments based on the microbiome, as it arouses disgust and repugnance. This instinctive reaction to the idea of undergoing a stool transplant is called the “yuck factor,” an expression that generally refers to the influence of instinctive responses to new technologies.<sup>49</sup> In some cases, the patient’s situation is serious enough to overcome the disgust in the hope of improving. Very recently, fecal microbiota transplantation by oral capsules has been tested in treating recurrent *Clostridium difficile* infection (CDI), and 66 percent of the patients rated their experience with the capsules as “not at all unpleasant.”<sup>50</sup> But, in that case, it was a serious and invalidating organic infection without other therapies available, and the alternative route of administration was the colonoscopy. Jonathan Zipursky and colleagues found that “patients recognize the inherently unappealing nature of FMT, but they are nonetheless open to considering it as a treatment alternative for recurrent CDI, especially when recommended by a physician.”<sup>51</sup> However, it must be considered that the small samples of patients of the cited studies are composed of people who had a severe form of CDI. This is why they may consider fecal transplantation the last chance of healing and, therefore, overcome disgust more easily. For patients with psychiatric disorders, the disgust component may be stronger, as some unpublished studies seem to show.

That the symbolic component plays an important role is shown by the fact that some patients choose to use their relatives as donors, so as to reduce the psychological repugnance that is associated with the FMT.<sup>52</sup> And it not just because the “contamination” is somewhat weaker with a relative than with a total stranger, but also because there is a lesser component of social shame connected to the fact that others might find out. Furthermore, and this is very significant, it seems that doctors are also reluctant to handle stools during treatment.<sup>53</sup> Recent research studies on communities of physicians with a precise cultural background show that the component of disgust remains significant, even though scientific knowledge indicates that fecal transplantation can be effective.<sup>54</sup>

So, fear of (physical, but also moral, as we shall see) contamination and shame are generally associated with FMT, and in general with all that concerns the gut and the microbiome. This phenomenon is even stronger when one relates the functionality of the microbiome to the psychological sphere, as in the findings described above. Indeed, these two parts of the body and the person are typically understood in a low/high—inferior/superior and therefore bad/good or even blameworthy/praiseworthy—antithetic relationship.

In short, it can be said that, faced with the FMT treatment of purely organic diseases, such as an infection, the patient might react with: disgust toward the feces as a physical object; fear of contagion or of transmission of pathogens (mainly at the emotional level); and feelings of moral repugnance (on a cognitive level), as if being the subject of an FMT implied a violation of cultural codes and the degradation of human dignity. Obviously, such an assessment does not only concern the personal level, but can also affect interpersonal relationships, due to the fear that having been subjected to a fecal microbiota transplantation—that is, having received another person’s feces—may constitute a social stigma, by which the patient is now physically and morally contaminated. To equate a person with an excrement or to say that they are made of excrements is in fact a widespread way of denigrating and insulting them.

As mentioned, this happens when the FMT is linked to organic diseases, but it can also happen more generally, whenever the gut is taken as a means to cure or improve psychological well-being. If a part of the body can be used to obtain some therapeutic benefit—in this case the gut, to act on psychological functions—this means that the given part of the body affects, at least in part, the functions in question. In other words, the “low” affects the “high.” And this has deep implications for how we generally conceptualize purity, disease and care, especially through the metaphorical apparatus that expresses all this. This seems to happen because these concepts are linked to disgust as an adaptive reaction to direct the behaviors that reduce risk of infection, the so-called parasite avoidance theory. And the pathogen disgust seems to still be an evolutionary feature that continues to play an important role, benefiting those who are more endowed with it.<sup>55</sup> For this, it may be helpful to find cognitive modalities to decrease it in the case of interventions on the microbiome.

### **The Role of the Metaphor**

The metaphor is classically a transfer of meaning, the replacement of a term with a figurative one, following a symbolic transposition of images.<sup>56</sup> In general terms, a metaphor is an analogy. But an important aspect is that the metaphor can pass



from the abstract to the concrete, in order to clarify things, making them compatible with things that are easier to know, through the senses or through intuition.

In fact, according to the substitutive conception of the metaphor proposed by Max Black, the metaphorical expression is used instead of an equivalent literal expression.<sup>57</sup> On the other hand, the comparative conception, instead, sees the metaphor as a condensed or elliptic comparison. Another conception is the interactive one, according to which a metaphor involves at least two cognitive domains, and the relationship between the primary and the secondary subjects generates a meaning that cannot be derived from the single terms (nor from the domains to which they respectively belong), but is produced when a metaphor is formulated, with the restructuring of both the domains involved.

In a metaphor, only some characteristics of a given domain are selected and emphasized (*homo homini lupus*, for example), but the difference of meaning between domains remains irreducible: this makes the metaphor extremely effective both from a linguistic and from a conceptual point of view, and any paraphrase or literal reduction involves a great loss of meaning. This is a central point: the metaphor adds meaning and illocutionary force. In interactive theories there is no alternative literal meaning, nor is there a similitude that explains the meaning of the metaphor. The metaphor is the center of the very possibility of understanding reality.

According to the conceptual theory of the metaphor, to understand the world we live in, we need to represent it with reference points that allow us to make predictions, act, communicate, and so forth. Our first representations are perceptive and sensorial in nature (*image schemata*), and are based on a literal and direct relationship with the environment. We literally think of physical entities such as limbs, rocks, animals, which we know based on direct bodily-sensory experience. For example, orientation metaphors are constrained by the position of our sense organs, our postural characteristics and perceptual and motor experience, so that up/down becomes positive/negative. Metaphors are our way of thinking, and they seem not to be arbitrary, because they depend mainly on how our bodies are made. They are therefore shared by multiple languages and cultures.

A conceptual metaphor is made up of correspondences that link a source domain to a target domain, even if these correspondences are predominantly of a partial nature (for example, an argument is like a journey: we proceed step by step). Consider the source domain of vertical spatial orientation, where two extreme and opposite conditions are possible: the condition of being at the top is related—in the (emotional) target domain—to the idea of happiness, while the opposite condition of being low is linked to the idea of unhappiness. But these definitions in the spatial universe also correspond to moral positions, linking the high to the positive, the good, or the right, and the low to the negative, the bad, and the unjust. There are many metaphors that refer to vertical spatial orientation and conceptualize feelings of happiness and sadness. All refer to the basic concepts of up and down and relate height (both absolute and relative, i.e., being high as opposed to something else) to positivity (understood as pleasure or moral good), while being low is linked to both concrete and ideal negativity.

There is a correlation between the posture of those who are healthy, who stand tall and look at things from above, and the posture of those who are sick, suffering or even tired: the latter are slightly bent down, with their eyes on the floor or even lying down and looking at things from below. In general, from the top you can

have control over the surrounding environment, while at the bottom you are more exposed to dangers that you may not be prepared for. Hence also, the value judgment attributed to the high-low dichotomy. Consider the value given to the higher functions, i.e., the psychological sphere linked to the mind/brain, as opposed to the inferior functions related to the gut. Those who are happy, in fact, "have their spirits up" or are even "high," whereas those who are sad "are down"; we also speak of "falling so low" to express a negative moral condition; think of "being knocked down" and "pulling oneself up," or the fact that happiness is associated with "flying" or "jumping," whereas "sinking," and "being at the bottom" are metaphors of depression and shame. "Falling" and "plummeting" are abrupt changes from positive to negative, while "rising" means rebirth. Even references to the earth are typical of lower situations, while the positive ones are those that mention the sky, heaven, lightness and immateriality.

Why is the metaphor so relevant? What is its scope as a cognitive tool? George Lakoff and Mark Johnson are convinced that the conceptual system based on which we think and act is essentially metaphorical in nature.<sup>58</sup> The metaphor allows us to experience a thing in terms of another. Thus, for example, if we accept the metaphor according to which "argument is war," we will actually begin to think of the discussion as an armed conflict and act accordingly (elaborating strategies, attacking weak points, destroying other people's arguments, etc.). This phenomenon is even more evident if we consider, as already seen, the so-called orientation metaphors, which organize an entire system of concepts in terms of another and are called this way because they often have to do with spatial orientation (up-down, inside-outside, front-back, deep-superficial, etc.).

"Such metaphorical orientations are not arbitrary. They have a basis in our physical and cultural experience. Though the polar oppositions up-down, in-out etc., are physical in nature, the orientational metaphors based on them may vary from culture to culture."<sup>59</sup> The physical component therefore plays a fundamental role in the organization of our conceptual system: "we generally conceptualize the non-physical in terms of the physical, that is, we conceptualize the less clearly delineated in terms of the more clearly delineated."<sup>60</sup>

According to Lakoff and Johnson, most of our conceptual system is intrinsically metaphoric. We see the high as better and the low as worse because there is a natural correlation between our posture and our evaluative system. In this sense, mental images acquire particular value in new situations in order to increase the amount of information available to the subject and orientate and frame her conceptual understanding (moral assessment is also affected).<sup>61</sup> Furthermore, different metaphoric experiences have different gradual salience in terms of how easy access to mental lexicon in a given context facilitates processing and comprehension (and the efficacy of the metaphor).

### **From the Up-Down to the Inside-Outside Metaphor**

The idea of studying both the doctor's and the patient's use of images and metaphors is not new in the medical field: it has also relevant pragmatic goals in terms of how the patient experiences illness and recovery. In fact, it is well known that the patient's psychological attitude and the trust that she puts in the treatment are often key elements for the therapy to work. The general context of the treatment, the patient's understanding of it—even imperfect but sufficient for the

patient to believe in the possibility that it may be effective—are therefore of great importance.

Recent research in applied linguistics shows that it is possible to empirically test the persuasiveness and effectiveness of the metaphors used.<sup>62</sup> Furthermore, one could argue that there are different appropriate metaphors for different contexts.<sup>63</sup> As for the issue of the microbiome and its influence over the psychic sphere, the typical up-down/higher-lower metaphor is likely to perpetuate the reaction of disgust or rejection associated with it. It certainly makes it hard to accept that there is a strict relationship between gut microbiota and psychological well-being, and therefore to embrace therapies or prevention methods that rely on the gut.

So, it could be hypothesized that conceiving of care, health and wellbeing with different metaphors might have a *nocebo* effect on patients under microbiome-related therapies.<sup>64</sup> In fact, if the main metaphor is that by which the gut is physically and morally “lower” and therefore “inferior,” the patient could be unconsciously led to devalue the therapy and/or believe it to be ineffective or even harmful. Indeed, the up-down metaphor sets something of low value (the gut) against something that has great value and should be protected from all kinds of physical and moral contamination (our psyche). If the main metaphor is the higher-lower one, the patient might be (perhaps unconsciously) made unconfident toward the therapy—and this, as a result of neurophysiological processes, might make the therapy itself less effective.

Hence the need to conceptualize the microbiome with a different metaphor: that based on the inside/outside dichotomy. According to Lakoff and Johnson, our conceptual system makes it easy for us to apply the container metaphor to a number of different things.<sup>65</sup> This probably happens because it is a clear and intuitive structure, which belongs to everyday life and is able to convey more complex and less immediate concepts. Time, for example, is a container (something we are in); the body is a container in many senses, in that we are our body but can also be “beside ourselves,” when we are furious or act inconsistently with our usual behavior. Emotions are normally seen as something that lies inside something else (the mind, the body or the heart): hence the notions of “bursting” into tears or laughter, “crying one’s heart out,” being “out of one’s mind,” etc.

So the container is what keeps the flow of emotions in check, so to speak. To contain can also mean to restrain, or curb. Another way to do this is to “transfer” something that can no longer be kept inside into another, more socially appropriate, container: such as when one vents one’s frustration in sport. The emotional flow has a given temperature: one can “get heated” or “cool down”; also, the container can be filled up, so that one is “filled with joy” or else “bring out the best.” And the emotional flow is a bearer of energy and positivity: it is not stagnant, and it takes a great quantity of it to provoke uncommon feelings of complete contentment. Of course, one can also be full of sadness, regrets or pain, but these feelings do not lead to a sense of “fullness” or even an “explosion,” but rather lead the person to a sense of emptiness and inwardness (apart from some notable exceptions).

The inside-outside metaphorical duality can also be traced back to a general psychological attitude. In particular, the inside-outside dichotomy can be brought back to the different “loci of control.” The psychological construct of the “internal / external locus of control” was introduced by Julian Rotter.<sup>66</sup> It indicates the way in

which an individual believes that the events of her life are mainly produced by her behavior or actions, or by external causes independent of her will. The internal locus of control is characteristic of those individuals who believe in their ability to control what happens to them. These subjects attribute their successes or failures to factors directly related to the exercise of their skills, will and ability. The external locus of control is typical of those who believe that specific events, especially social and relational ones such as rewards or punishments, are not the result of the direct exercise of their personal skills, but rather the outcome of unpredictable external factors, such as chance or destiny; they believe that, in any case, the actions of others have more consequence in their lives than their own.

In this sense, using the inside/outside metaphor could help one regard one's gut and bodily functions (considered inferior in the up/down metaphor) as simply what is inside of us. Thus, looking after the gut would be a way of taking control of one's health and, therefore, of one's psychological situation, given that the microbiome has some influence on the biochemical structures of the brain. Thus, the metaphorical shift from *low* to *inside* could be a conceptual strategy to achieve a change of attitude toward health treatments based on, or including, actions on the microbiome.

The "inside" and the "container" metaphors are also functional to account for the ideal of purity that is opposed to that of contamination.<sup>67</sup> And it can also help overcome resistance to the very idea that our health is partly based on the presence of microbial species, sometimes potentially dangerous, resident in our gut.<sup>68</sup> What is low can hardly be pure, while what is within us, what is contained inside us, can more easily be assimilated to the positive aspects that characterize us. If the psychic element that is typically considered superior is inside us, then the other elements that are contained within us can also enjoy the same positive characterization. The point is to no longer think in terms of up and down, higher and lower, but rather to see what is "naturally" inside us as at least potentially homogeneous, interconnected, and part of a positive process in which each side plays an important role. In this metaphorical perspective, all the elements of our body are characterized by being equally "inside" us, located in the valuable container of each individual.

## Conclusion

The microbiome is proving to be increasingly important for our immune system, brain, and genome. Its role in shaping physiological reactions to the environment in a symbiotic relationship with the organism is a challenge to the notion of self and individuality as they have been traditionally understood. Our "inner self," as it has been called, is made of evolving microbial-host associations and relations.<sup>69</sup> Whatever the self may be, though, it can still act on its organic bases with different strategies. And since the microbiome evolves decisively in the early stages of individual development, the role of caregivers and of society in shaping the balance of the organism and the self through interventions on the microbiome becomes increasingly important. In fact, the child does inherit a simple microbiome from his mother, but over time feeding (breastfeeding is important here) and environmental influences lead from the neonatal period to the early-stage maturation, to puberty (in which sex hormones and gender specific microbial populations play a significant part), up to adulthood.<sup>70</sup>

And even in adulthood the microbiome is very sensitive to environmental perturbations. Recent studies indicate that “the gut microbiome is not significantly associated with genetic ancestry, and that host genetics have a minor role in determining microbiome composition.”<sup>71</sup> Instead, there are “significant similarities in the compositions of the microbiomes of genetically unrelated individuals who share a household, and that over 20 percent of the inter-person microbiome variability is associated with factors related to diet, drugs, and anthropometric measurements.” This would seem to suggest that we are not uniquely driven by the microbiome, but that we can somehow also guide this part of natural evolution. As is well known, the same is also happening with other aspects of environmental pressure that used to shape adaptation and selection mechanisms. Today, thanks to technology (which allows us, for example, not to suffer from temperature variations, changes in agricultural productivity or epidemics), environmental elements no longer significantly affect the evolutionary mechanisms of the human being.

Indeed, there are many new potential treatments that can affect the gut microbiota and therefore the functions of the organism and the brain. In addition to special dietary regimes and prebiotics (nondigestible nutrients), a well known intervention, whose effectiveness is still controversial, involves probiotics (live microorganisms).<sup>72</sup> However, the use of specific bacteria to obtain mind-altering effects—via changes in the levels of neurotransmitters, immunological functions or hormonal signals—has been called psychobiotics.<sup>73</sup> Personalized medicine is also beginning to take the shape of targeted nutrition along with bacterial products called postbiotics.<sup>74</sup>

But the idea that moods, emotional states, cognitive processes and even personality traits should be linked to the arrangement of the microbiome may elicit a biased rejection. In fact, everything that is related to the organic processing of food and, in general, to the human stomach and gut has often been regarded as low, dirty, contaminated and opposed to that which is proper of the mind (later, the brain), and considered higher and pure.

The metaphors about our intestinal functions show a general attitude of distrust which dates back to our evolutionary history (it was aimed to avoid infections carried by excrements) but has then developed also at a cultural and social level. Such rooted metaphors may cause patients (and medical personnel as well) to reject this new clinical approach. In particular, as we have seen, the idea of physical and moral contamination may discourage the use of the microbiome, lead to the rejection of specific treatments and trigger nocebo effects for those same treatments. Furthermore, the new idea of human individuality that could emerge from the study of the interactions between microbiome and host risk being misunderstood, misconceived or denied due to this implicit bias. In other words, it might be hard to accept that the “inhabitants” of our gut may challenge the way we see ourselves. A reconsideration of the metaphorical framework of the gut could therefore be useful to achieve a nonbiased philosophical reception of the discoveries on the microbiota. However, in our view this does not imply that our idea of self should be radically revised.

Metaphors may change and it is possible to inaugurate a different metaphorical discourse. Several aspects of the same bodily experiences can be used selectively for the creation of metaphors, and some bodily experiences could be overshadowed by specifically cultural aspects. Lakoff and Johnson, on whose theory of metaphor we have based our argument, acknowledge that cultural assumptions,

values, and attitudes are always part of our experience of the world we live in: there is therefore a continuous interconnection and exchange between the cultural and the natural.<sup>75</sup> Studies on metaphor in another, more established field of medicine—that of cancer treatment—provide further useful elements to propose a neuroethical view able to tackle the question of whether we are ready for a “microbiome-guided behavior” approach. In this paper, we have suggested a shift of focus from up/down to inside/outside metaphors. This would hopefully make the clinical approach—in psychology, psychiatry and neurology—less biased when it comes to interventions on the microbiome, also making the anthropological-philosophical research more attuned with scientific findings on the relation between microbiota and human organisms.

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