Gut-brain axis or brain-gut axis? Another perspective...

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"Convictions are more dangerous enemies of truth than lies."

Friedrich Nietzsche

Is the throne on which our belly has been placed for a number of years so deserving? Does our belly have such a determining power over our health, our emotions, and our behavior? Can we not dispute this status, or even consider other commanding nerve centers influencing the psychosomatic complexity of the human being?

This article provides some alternative views to these questions and is the premise that I am going to develop. If I give myself the freedom to scratch or relativize some of the conclusions that many researchers and therapists take for granted, I also offer my total respect for these people who advance knowledge, just as I have total respect for the patients who seek solutions to their suffering.

Epistemological considerations

When you read an article on a topic, even if it is based on scientific knowledge and studies, it is, in my opinion, imperative to not absorb everything without having first thoroughly chewed the reported data. Sometimes mixed in with factual information are beliefs, biases, and assumptions the author wanted to convey, consciously or not, and without a bad intention, yet one is at risk of ingesting these.

Too often even a scientist who tends to pride himself on having the most perfect objectivity, when his word is spoken, nothing more should be said. However, epistemology and all studies on how to produce knowledge show unequivocally that subjectivity retains an important place in all scientific research, whether fundamental or applied. In addition one should mention methodological and procedural errors and the multitude of other biases from which no study can fully exonerate itself.

Assumptions, beliefs, conditioning, cognitive distortions, and other mirages (let's not mention the possible financial interests of various forms that might exist) still infiltrate, to varying degrees, the mental processes of the most serious scientists as well as the process of their research.

It is extremely difficult for humans to be free from all this, as it comes from their desire for success or more simply, to be right.

Since the beginning of the pandemic which affected us collectively starting in 2020, the illustration has been made and repeated endlessly, that from the same facts, the

theories and practical outcomes can be multiple and contradictory. We have even witnessed extremely intense confrontations of passion and violence through the media or the social networks. Passion is the emotion that eclipses reason. And where passion shows itself, it becomes obvious that it is the psychological and emotional factors that determine opinions, and no longer the rational intellect.

It must be said that it is quite normal that the acquisition of knowledge and that our understanding of reality progress step by step, after much trial and error and many dead ends. After all, we initially have only five senses to register the information from the outside world, each of which has only a very limited spectrum of frequencies to which it is sensitive. Despite this major limitation, the human brain is capable of prodigious conceptual representations and of adapting in an exceptional way to the world in which we live.

Our limited capacities and our propensity to deceive ourselves are not to be deplored; what is more deplorable is having certainties that do not admit our mental fragility and our ability to misinterpret or to not interpret things well enough. We obviously need representations to adapt to existence, whether they erroneous or not, but we can at the same time keep a constructive and healthy doubt about their veracity or accuracy. The method of Cartesian doubt seems very useful to me. It consists of taking nothing for granted, even what seems obvious at first glance.

Therefore, it is positive doubt that is opposed to skepticism which is by nature negative. And it is a temporary doubt until it breaks against the rock of facts.

This is how it was at the time when it was commonly accepted that the Earth was flat; maps of Europe and the Middle East allowed sailors to successfully navigate from port to port, even with a largely flawed model.

But beware of those who were the first to announce that the Earth was a globe revolving on itself and around the Sun. What fiery debates we would have witnessed if social networks had existed then! At that time, it seemed easier to inflame individuals guilty of ideological subversion.

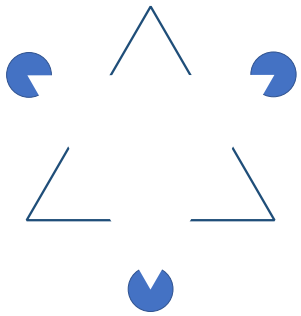
We can understand from this example the first major bias that is imbedded in our intellectual functioning: our senses make us feel unequivocally that the Earth is flat and that the Sun revolves around us from East to West. It took all the focus of powerful and enlightened minds to get out of the illusion of the first observation offered by the senses. So much for the famous saying: I only believe what I see!

The second major bias that I would like to mention is the one that our brain uses to make sense of the concrete things that are presented to it, or of the abstract ones that it is trying to understand. This is because our brain, or that central factor of consciousness called the “self”, has an imperative need to find meaning and

intelligibility whenever possible. Thanks to our learning and conditioning, we have various mental and psychological patterns, neural highways, or even semantic compartments, and everything that comes to us must fit inside these patterns willingly or by force, even if it must be completely deformed. And if it doesn't fit, we have denial, scotomization, or forgetting abilities that come to the rescue. Out of ease and comfort, we indulge in reinforcing our beliefs and opinions with extreme greed. Moreover, the main characteristic of a belief is to believe that it is true – "which was to be demonstrated" (CQFD).

And then, to reinforce everything, as soon as there is a void or some missing information, our brain manufactures, invents, and fills in the holes.

To illustrate this, look at the diagram below:



you see a white triangle which in reality does not exist. What is real, are 3 open angles and 3 incomplete circles.

Our brain manufactures the white triangle.

To extend these insights and apply them to the way scientific ideas are born, developed (and sometimes die invalidated by new data and/or sharper minds), let us consider a well-known example, that of the discovery of the DNA double helix in the 1950's by James Watson and Francis Crick.

A fabulous discovery if there ever was one, proof of the genius of the human spirit, this thinking animal which knows how to look down, up, forwards, and backwards, but also within itself, and then again at the infinitely small as at the infinitely large. By the way, I take this opportunity to say that knowing this, there is no reason to be pessimistic about the future of humanity. Our spirit, collectively, is able to solve all challenges, those of nature as well as those that humans impose on themselves.

In the 1970's and 1980's, the scientific community defended the fact that DNA determined everything in the organism and came to believe that when we had sequenced our entire genome, life would not have any more secrets and we would eradicate all the diseases that affect us. The genome weighed overwhelmingly on our destinies.

I remember my professors at the university - I was studying biology at the time - who were zealous about this new genetic science, organizing meetings with students on the "strategy of the gene", and going as far as to show us that it was our genes that directed all our behaviors, which is reminiscent of certain things that we can read about our microbiome. For example, if we humans had sexual desires, this was driven in the background by our genes which programmed us to reproduce, so that

they themselves could duplicate themselves. If the MeToo movement had existed then, that would have been a good argument for today's defendants' lawyers to make: neither responsible, nor guilty, just manipulable...

The human genome project was launched at the end of 1988 and its mission was to establish the complete DNA sequencing of the human genome. It ended in April 2003. The fundraising Telethon, which was part of this promising trend, was also created in 1987; it provided the French Muscular Dystrophy Association with the funds and resources to launch large-scale research.

I do not know how the scientists who pinned all their hopes on this study supposed to give them all Promethean power, reacted when the conclusions of the research were published, but we can assume that they experienced disappointment.

Indeed, as Bruce Lipton[i] reports, the human body being made up of approximately 100,000 different proteins; the researchers expected to count roughly the same number of genes.

Surprisingly, the human genome is composed of only 25,000 genes. So how do you code four times as many proteins as genes, when over and above you also need regulatory genes associated with those that code proteins? More than 80% of the predicted DNA ultimately did not exist!

Therefore, there is a whole assembly of protein material in our body that is not due to our genes. The genes, so to speak, only provide ground plans as well as potentialities, but all the details of the functioning of the organism, as well as its propensity to develop certain diseases or to guard against them, are dependent on other factors. This is when the science of epigenetics was born.

It is very odd that our human organism with its 25,000 genes, which has approximately 3.10^{13} cells (i.e. 30,000 billion!), compares closely with the nematode's genome containing 24,000 genes! The nematode is a small prehistoric worm which is made up of only 969 cells!

Drosophila has a genome of only 15,000 genes, although this insect is much more complex than the nematode.

The complexity of living organisms is not based on the preeminence of genes. It includes many other factors. Epigenetics[ii] has been updated and we better understand that genes are influenced by many factors that make it possible to regulate their expression, or even to block it.

This discovery perfectly illustrates the process of the creation of mental illusions. Considering all the cognitive and psychological biases we have talked about, from certain real and undeniable facts of which there are many others, a conceptual image is created, a representation from which many branches and sub-branches

emanate and formed of extrapolations, abusive generalizations, deviations, hasty conclusions, various applications, sometimes a fad. The whole forms a new paradigm which will be taken up at various levels by other scientists, then by (pseudo-), various and varied specialists, to finally reach a wide audience. The paradigm is no longer being questioned… until sooner or later, it is of course, heard.

Each era has its own mirages: in the 17th century, doctors tried to perform blood transfusions from dog or sheep blood to treat mental illnesses. It may make you smile today, but they were driven by the same convictions as modern scientists.

We should also remember the large number of patients who had a lobotomy performed to treat their mental illness.

In each era, scientific progress generates, at the same time as the increase in knowledge, an excessive pride which makes us believe that from now on "we know". And beware of those who do not fully adhere to the dominant credo!

To conclude on this perspective of how our knowledge is constructed and our intellect functions, I will quote an anonymous author, a great free thinker if ever there was one: “Thinking is first and foremost an exercise in freedom. It is a practice, a certain use of oneself which is called risk, trial, and attempt: the philosophy of freedom, autonomy, and independence. Philosophy also of intuition.” JDR

The paradigm of the microbiome and the second brain

Let us specify again that here we have two very different entities. The microbiome is all the microorganisms living in a given ecosystem, the most documented being that of the intestinal microbiome. What is called the second brain is represented by the clusters of neurons or ganglia present in the muscular and mucous layers of our intestine. Today the second brain is considered as part of the autonomic nervous system, and is regulated by other branches, the most important ones being the parasympathetic branch (in particular the vagus nerve) and the sympathetic branch.

The microbiome and the second brain are two entities which, in my opinion, have been the object of the phenomenon of illusion of which I spoke above, regarding genetics. This illusion was in order to project in the mind of the uninformed public, a single global illusion: the power of our belly.

Any illusion is based on tangible facts and some objective parameters. This is the case with mirages: “The mirage (from the Latin miror, mirari: to look at, to wonder at) is an optical phenomenon due to the deflection of light beams by the superimpositions of air layers of different temperatures. In fact, it is an abnormal propagation of light in an atmosphere where temperature, pressure, and humidity do not vary vertically according to the norm. The deflection of

these rays then gives the impression that the object we are looking at is in a place other than its real location, and can distort the image observed[iii]".

A mirage is an optical illusion, and this can apply to all of our interpretations.

We must be free to question the validity of some conclusions reported in numerous studies and articles that relate to the microbiome and the second brain:

- Is the microbiome really responsible, to the extent stated, for our health, our emotions, and our behavior?

- Are there as many intolerances/sensitivities to gluten or dairy products as we imagine?

- What is the place of the second brain and the microbiome in the global psychosomatic functioning of the human being?

- Are there not other equally important factors, or even more important ones, which could be responsible for our state of health or disease?

There are in these questions a number of facts, even a great number of facts, based on the thousands of studies which are devoted to them, as well as the observations in vitro or in vivo that are completely objective. At least I believe so - I can't do anything but believe it or not - because I have to admit that I have neither the university training nor the ability to do or verify all the experiments carried out, nor to judge the thousands of studies carried out. However, I have enough confidence in science to accept most of the reported facts. On the other hand, I do not accept all the conclusions that derive from it, as I will show.

Where we still recall the genome

Echoing what we reported above about the largely exaggerated conclusions that followed the discovery of the genome, data tells us that, given the diversity of the bacterial families that make up our microbiome, the total of the genetic material is thousands of times larger quantitatively than our own genome.

There may be a shift from observed quantitative facts to a belief expressing an entirely subjective perception of the world, of life, or of the human being. I repeat, the science of epigenetics has shown us to not overestimate the influence of genes. The leeway for maneuver exists and makes the genetic framework in which our being acts, much less rigid than we thought.

Moreover, we cannot simply compare a few million bacterial genes to our 23-25,000 genes. The genome of each type of bacteria does not contain more genes than the human genome. It is simply the addition of the genes of the many varieties and strains forming the microbiome, which leads us to this number. There is no evidence that the purely genetic influence is due to a battalion of genes from all of the microbiome species, all united in a common front to dominate our own genome. Who can say which gene is expressed, when,

how, and under what conditions, and what is the balance sheet of all the genetic expression, bacterial, and human? Obviously, no one can.

Microbiome, autism, and Alzheimer's disease

A first caution is necessary regarding the conclusions of the studies, knowing many of them are carried out on animals devoid of microbiome. This is not a condition found in humans who are seeded with maternal bacteria from the beginning of their existence. Therefore, there is a significant difference, such that the results observed in the laboratory are not necessarily identical to those of a human with a unique microbiome, just as are his fingerprints. The same cause will therefore not generate the same effects from one person to another; it is obvious. Everyone knows, for example, of people who eat large quantities of food,
[iv].

“We need to keep a critical eye on probiotic products and the benefits promoted by their manufacturers. Keep in mind that not all strains are created equal when it comes to effects and effectiveness. Each strain has its own pharmacokinetics and pharmacodynamics which cannot be extrapolated to other strains. In order to act at the intestinal level, the digestive survival of probiotics is essential: they must cross the acid barrier of the stomach, and then resist the bile salts encountered in the small intestine. Their activities and modes of action in situ are then varied, offering

with a daily caloric intake well beyond the norm and who remain perfectly thin, while others gain a kilogram at the slightest glance at a pastry...

Therefore, probiotic supplementation should be put into perspective (at least in the promises that are made) and the reactive terrain of the patient must be considered. In this case more than in others, supplementation responses may not be the same for everyone. How many patients have I had in consultation with various and recurring digestive disorders and who had already received probiotic-based treatments without any convincing, or lasting results?

I would like to quote here the words of Noémie Biard in the conclusion of her thesis, submitted for her State Diploma in Pharmacy

multiple preventive and curative possibilities.

These are still based on many hypotheses and experimental or clinical investigations that are not always sufficient to confirm the "marketing" arguments of manufacturers. We were able to observe that many studies, initially promising, suffered from methodological weaknesses and statistical biases. Research, particularly in vivo in humans, must be continued in order to clarify the modes of action of probiotics, to establish their indications and their dosages”.

Thus, we can see that, despite the thousands of studies conducted on the subject, caution and patience are still required. The interests of the laboratories do not always go hand-in-hand with the greatest integrity, and these always have a stake in blowing on the embers of the anxious hopes of the public to find the miracle solution to their suffering.

To come back to a statement often encountered in the literature on the subject: “the link between the quality of the microbiome and autism or Alzheimer’s is proven”.

We are dealing here, in my opinion, with one of the most frequent shifts encountered in the scientific world. The proof extends most often from a mathematical correlation, to an entire idea, to a concept as well as to possible practical applications. And so, it is implied that a “truth” exists that may not be so, and thereby becomes an approach contrary to scientific logic.

In this case, what has been proven is most certainly that there is a statistical correlation between the quality (impoverished, I imagine?) of the microbiome and the incidence of autism or Alzheimer's disease.

Moreover, this conclusion, which would like to be asserted, excludes from the reflection process all the cases of autism and Alzheimer's disease that present a healthy microbiome. Why this is the case, no one knows, and no one tries to answer it.

Also excluded are all cases of individuals carrying a disturbed microbiome and who are neither autistic nor will develop Alzheimer's disease. Why? It is the same observation.

A scientific study should always be followed by a discussion of possible biases, the limitations of the study, the unanswered questions, and the questions that emerge from the study, etc., before coming to a provisional conclusion.

To explain this statistical correlation which appears between the two parameters (the quality of the microbiome on the one hand, and the development of disease on the other), it is quite possible that there is another factor, or several factors, which determine both the poor quality of the microbiome as well as the appearance or facilitation of certain diseases.

Let us take a completely imaginary example: a sociological study has shown that since the observed boom in the acquisition of luxury second homes, there has been a statistically significant increase in violent thefts. What the study did not take into account is that shortly before this boom and increase, the inequalities between the richest 1% and the poorest 30% had increased by 200% in the space of two years. This is perhaps the common factor between the two variables researched by the study.

This is the kind of sleight of hand or shortcut that leads to premature or incorrect conclusions.

Poor health comes from modern life

Here is another argument heard thousands of times, possessing in certain circles the status of unquestionable truth and about which I reserve the right to put it to the test of Cartesian doubt: our modern diet is unbalanced and along with the competition from antibiotics; our microbiome is impoverished.

However, history shows without reserve, that over the past centuries, more often than not, the small minority of the rich ate too much and too richly... and that the poor did not eat enough, suffered from many deficiencies when they weren't literally starving. Life expectancy is still a parameter that does not deceive; it has increased to reach heights never reached before. Antibiotics and, it can be said in this period of controversy, vaccines have undoubtedly played a major role and extended the lifespan of millions of individuals.

As Voltaire said in his poem Le Mondain,

“For my part, I thank Nature sage,

That she placed me in this age:

Religionists may rail in vain…”

In each era, there are sad slingers to complain about theirs, and to regret the times before, which were necessarily better. What seems to me is that in addition to a longer life, we have never had as much free time as today, with off-peak hours that can only be filled with leisure. Then we have time and the space to feel our bodies and to complain about them, especially if our minds are not engaged in more constructive pursuits.

Of course, in all things, and in all progress, there are abuses, errors, exaggerations, and deviations, and over time we learn to correct our course. Supporting naturopathic ideologies are accurate ideas: better nutrition and less medications; this is a progressive path that we could travel further along.

The focus of attention

Another point that I think is important to raise is when a question begins to attract the interest, of first the scientists, then the decision-making bodies and holders of research funds, then those who will exploit it to derive benefits, and finally the general public, there is a snowball effect on the one hand, and on the other, a tendency for the attention and research to become one-sided.

For more than half a century, and exponentially in recent years, research on the microbiome has been tallied in the hundreds, even the thousands.

However, all these studies have a common focus on the ascending microbiome-brain axis, or more broadly on the intestine-brain axis by considering the famous second brain of the belly.

We cannot deny it; these studies have collected a vast number of facts which we cannot ignore. They have made it possible to raise promising hypotheses and some

tentative therapeutics in the management of many gastrointestinal, rheumatic, and neurodegenerative diseases. Undoubtedly the best is yet to come.

On the other hand, and this should be taken into account, the number of studies on the descending axis, the brain-gut axis (and the brain-microbiome), and even the heart-brain-gut axis are infinitely fewer. However, the conceptual interest and the therapeutic possibilities are no less important than the previous ones. It is well known that you cannot find what you are not looking for, and vice versa, and therefore my argument position is weak.

Let us see if there are any data on which we can rely to understand the descending axis and, thereby, to identify the direct or indirect control and regulating factors of the quality of the microbiome.

The vagus nerve at the interface of the microbiome-gut-brain axis[v]

The conclusions of several studies, carried out by Professor Bruno Bonaz, head of the Gastroenterology Department of the Grenoble University Hospital, are important. Here they are:

"The vagus nerve, due to its role in interoceptive awareness, is able to pick up metabolites from the microbiome through its afferents, to transfer this gut information to the central nervous system where it is integrated into the central autonomic network (I'll address this a bit later) and then to generate an appropriate or inappropriate response. A cholinergic anti-inflammatory pathway has been described through the fibers of the vagus nerve, capable of attenuating peripheral inflammation and of decreasing intestinal permeability, thus most likely modulating the composition of the microbiome (emphasis mine). Stress inhibits the vagus nerve and has deleterious effects on the gastrointestinal tract and the microbiome, and is involved in the pathophysiology of gastrointestinal disorders such as the irritable bowel syndrome (IBS) and the inflammatory bowel disease (IBD) both of which are characterized by dysbiosis. Low vagal tone has been described in patients with IBS and IBD thus, promoting peripheral inflammation. Targeting the vagus nerve, for example, by stimulation of the vagus nerve which has anti-inflammatory properties, would be interesting to restore homeostasis in the microbiome-gut-brain axis".

This is enough to add another light on the too one-sided theory which sees cause and effect links between the microbiome and numerous psychological, neurodegenerative, joint, and intestinal pathologies. The idea that a dysbiosis could be responsible for substantial intestinal porosity, thus allowing into the blood, the transfer of toxic molecules that we find in the brain, certainly has a real basis. However, the reverse is no less true. Good cerebral regulation, correct heart-brain interactions, along with healthy emotional balance, reduce the intestinal porosity and

regulate the proportions of the different bacterial populations of the intestine.

To me, it seems wise to keep in mind that nature has given us protective mechanisms to counter or to minimize the deleterious effects of the microbiome. Otherwise, we would never have been able to successfully pass the tests of natural selection and become one of the dominant species on this planet. The faculties of adaptation and self-healing that we have are simply extraordinary. So let us not be too afraid of those bacteria with which we co-developed.

Professor Bonaz discusses the pernicious effects of stress on the beneficial action of the vagus nerve and, therefore, promoting inflammation and many ailments. Stress! This is an adversary that should not be overlooked, as well as what greatly favors it: the mismanagement of our emotions. It is not absurd to think that being prey to recurring anger, irritation, frustration, jealousy, disappointment, sadness, fear... ends up altering our microbiome. So, would cultivating joy, equanimity, gratitude, hindsight, and a dose of stoicism be the best probiotic?

In another study[vi], Professor Bonaz clarifies the action of the vagus nerve a little further: "The vagus nerve is a key element of the neuro-immune and brain-gut axes thanks to a bidirectional communication between the brain and the gastrointestinal tract. A dual anti-inflammatory role of the vagus nerve is observed using either vagal afferents, targeting the hypothalamic-pituitary-adrenal axis, or vagal efferents, targeting the cholinergic anti-inflammatory pathway. The sympathetic nervous system and the vagus nerve act synergistically, via the splenic nerve, to inhibit the release of tumor necrosis factor alpha (TNF*α*) from macrophages in peripheral tissues and the spleen. Due to its anti-inflammatory effect, the vagus nerve is a therapeutic target in the treatment of chronic inflammatory disorders where TNF*α* is a key component."

Coming from an eminent specialist of the digestive tract, we can only lend an attentive ear to his statements: the vagus nerve, in addition to its anti-inflammatory role (also playing a protective role in cancers, in particular by reducing the progression of tumors and by slowing the spread of metastases[vii]) is able to influence the microbiome in a positive way, as well as reducing intestinal permeability, responsible for so many food intolerances. With his patients and in order to offer them a regular, autonomous practice, Professor Bonaz uses daily electrical stimulation of the vagus nerve over a period of at least three months, as well as he teaches them how to manage stress and emotions and to apply cardiac coherence. When necessary, he does not shy away from suggesting psychotherapeutic approaches.

The brain is essential in gut regulation

One of the arguments commonly put forward to support the major role that our belly and our bacteria have, is that the information which goes from the belly to

the brain is, quantitatively, much more important than that which goes from the brain to the belly.

We know that the vagus nerve is made up of 80% sensory fibers (carrying information from the organs of the neck, thorax, and abdomen to the brain) against 20% motor fibers (carrying motor orders from the centers of cerebral regulation towards our organs).

Despite its purely accounting logic, this argument is still speculative. Opposing two quantitative values says nothing about the qualitative aspects.

Let us take an analogy: to ensure the security of the nation, the State needs a highly developed intelligence network, comprising a large number of intelligence agents, informants, liaison officers, etc.

However, the decisions taken to preserve the security only come from a limited number of people and the chain of command (which corresponds to the descending axis) is much less important quantitatively. The precision of the orders and actions to be implemented also requires a certain concentration of powers. Why wouldn't it be the same in the regulation of our body?

Make no mistake, I'm not against using probiotics as a palliative, to fight symptoms and try to help people feel better. This is a highly commendable step. What I challenge are the mirages that surround the facts, and the belief that our health, moods, and behaviors are all inside our abdomen.

Another piece of evidence that highlights that there is top-down regulation of the belly by the brain is this one: researchers have identified a bidirectional link between traumatic brain injury and consequent gut changes[viii].

Brain damage may contribute to an increase in bacterial infections of the gastrointestinal tract in patients, and these may also worsen chronic brain damage.

This bacterial infection can in turn increase post-traumatic brain inflammation and associated tissue loss.

The increase in bacterial infections of the gastrointestinal tract is in conjunction with an imbalance of the microbiome. The brain, as well as everything that happens inside our black box, is therefore in a diplomatic relationship with our bacteria! If diplomacy fails, there is war with its pathological consequences.

In another article[ix], the various functions of the vagus nerve are discussed that make it an attractive target in the treatment of psychiatric and gastrointestinal disorders. There is preliminary evidence that vagus nerve stimulation is a promising complementary treatment for treatment-resistant depression, post-traumatic stress disorder, and inflammatory bowel disease. Treatments that target the vagus nerve increase vagal tone and inhibit cytokine production. Both are important resilience

mechanisms. Stimulation of vagal afferent fibers in the gut influences monoaminergic brain systems in the brainstem that play a crucial role in major psychiatric conditions, such as mood disorders and anxiety. Additionally, there is preliminary evidence that gut bacteria have a beneficial effect on mood and anxiety, in part by affecting vagus nerve activity. Since vagal tone is correlated with the ability to regulate stress responses (as we will see in the next paragraph) and can be influenced by breathing, increasing this tone through meditation and yoga likely contributes to the resilience and alleviation of mood and anxiety symptoms. Therefore, we have at our disposal here again tools that strengthen our vagal tone and all central cerebral regulation as we will now detail.

The neurovisceral integration model[x]:

This model postulates that cardiac vagal tone, as evidenced by Heart Rate Variability (HRV), can indicate the functional integrity of a whole network of neurons involved in emotion-cognition interactions.

HRV is associated with ascending and descending cognitive processes of emotional stimuli. High resting HRV is associated with enhanced adaptive and functional descending and ascending cognitive modulation of the emotional stimuli, which may facilitate effective emotion regulation. Conversely, low resting HRV is associated with hyper-vigilant and maladaptive cognitive responses to emotional stimuli, which can impair emotional regulation.

Self-regulation refers to the ability to regulate thoughts, emotions, and behaviors, thereby enabling one to choose appropriate responses to different situations. Several neural mechanisms associated with cognitive, emotional, and autonomic nervous system self-regulation have been identified, one of which is the central autonomous network (CAN). The CAN has been involved in creating adaptive and flexible visceromotor, neuroendocrine, and behavioral responses to various environmental demands. CAN structures include the anterior cingulate gyrus, the insula, the ventromedial prefrontal cortex, the central nucleus of the amygdala, the paraventricular nucleus and the related nuclei of the hypothalamus, the periaquaductal gray matter, the nucleus of the solitary tract (NTS), the ambiguous nucleus, and the medullary neurovegetative fibers. The brain structures of the CAN are reciprocally connected, and information can flow efferently and afferently.

In particular, the prefrontal-subcortical inhibitory circuits within the CAN play a critical role in the auto-regulatory function. Under normal circumstances, the prefrontal cortex identifies safety cues from the environment and exerts its inhibitory control over subcortical sympatho-excitatory circuits, including the central nucleus of the amygdala. This prefrontal regulation allows an organism to provide optimal responses to different situational

demands. In threatening and uncertain situations, prefrontal inhibitory regulation decreases and subcortical sympatho-excitatory circuits provide a default response to the threats.

Reduced prefrontal regulation can result in overactive subcortical activity, resulting in prolonged activation of defensive behavior mechanisms, including hypervigilance and obsessive cognition (e.g., worry or rumination). Unsurprisingly, disruption of subcortical prefrontal circuits has been associated with a wide range of psychopathologies, including depression, anxiety, schizophrenia, and addictive behaviors.

According to the neurovisceral integration model, the functioning of the subcortical prefrontal inhibitory circuits essential for self-regulation are linked to the heart via the vagus nerve which provides inhibitory inputs to the heart.

Clearly, there is a link between the HRV and the subcortical prefrontal circuits essential for cognitive and emotional self-control.

Several pharmacological and neuro-imaging studies have demonstrated the link between subcortical prefrontal inhibitory circuits and HRV-indexed cardiac vagal tone at rest.

Powerful and flexible vagal activity is therefore one of the keys to this regulatory system, the starting point for all the afferent regulation of our organs in particular, but also of all the tissues of the body by the control of the level of inflammation.

We have many studies that have shown the preventive and/or curative role of good vagus nerve activity in many conditions. For example, the increased inflammatory state in the body determines the pathogenesis of sepsis, atherosclerosis, obesity, cancer, lung disease, inflammatory bowel disease, neurodegeneration, multiple sclerosis, and rheumatoid arthritis (Nathan and Ding, 2010).

With regard to the painful scourge of cancer, we already have at our disposal several studies[xi] which confirm the protective and beneficial role of the vagus nerve, and therefore of the afferent regulations of the heart-brain-rest of the body.

According to Stephen Porges[xii], a high HRV is under the control of the most evolved branch of the vagus nerve (called the ventral vagus nerve). The ventral vagus nerve functions optimally when our central nervous system identifies safety signals and when the connection we have with the environment, with others, and with ourselves is satisfactory.

Thus, a positive, serene, committed, joyful, and empathetic emotional state determines an optimal afferent regulation of our viscera and is a factor of health and of the best possible regulation.

Good vagal activity controls inflammation as much as possible, the intestinal

permeability to toxic and allergenic molecules, and the protection of the enteric nervous system. Good vagal activity is also the antidote to the possible deleterious effects of the microbiome, by regulating the balance of the different bacteria strains.

Emotion

As we have just seen, the quality of our emotional balance and the regulating power of the ventral vagus nerve are two things that go hand-in-hand.

While external means to strengthen the vagus nerve are of course useful, the essential, primary, and most causal factor is that of the emotions. I talked about it a lot in my book[xiii] and develop the subject in depth in an online training[xiv], and I will only say a few words about it here.

Obviously, at the current stage of human evolution, the central factor for the majority of individuals is that of the emotions. It is what conditions our whole psyche, including our thoughts and opinions, and in the background of which stand psychological complexes, emotions, and passions.

Humans stand torn between the past and the future. Sad passions, like nostalgia for the past when days and nights were more beautiful than now; sad passions linked to regrets, remorse, or even to traumas suffered.

Imaginative anticipations sterilizing our power to be and to act in the present:

- On the one hand, hopes for better days which imply that I deserve better than what I have today, hopes of becoming something else, someone else, rid of my emotional handicaps, my inhibitions, my physical, mental, or intellectual limitations.

- On the other hand, fears and anxiety about what is to come; fear insinuating itself through all possible interstices: my own future, that of my children, that of my country, that of the world.

The economic, societal, health-related, and geopolitical difficulties that we are currently experiencing only reinforce these fears; it might be that it is our collective psychic immaturity that is the cause of these difficulties. One way or another, a solid vicious circle exists.

The ventral vagus nerve is called by Stephen Porges the nerve of social engagement. This means that its proper functioning depends on the quality of the relationships that we are able to weave with others and with ourselves. In other words, if our psychic constitution is healthy, if our emotions are easily regulated and do not turn into long-term feelings, crystallized in the form of passions[xv] and character traits or, to put it another way, if we know how to protect ourselves from the tyranny of emotions, so we can be in harmony with ourselves, with each other, and with the world, whatever the difficulties we may encounter. Because life is never free of difficulties, we can simply “Be”, be with a sufficient measure of freedom in the midst of the world, however

difficult it may be. On the level of our physiology, we release the power of our vagus nerve to the maximum of its capacities. It is of different levels in various individuals no doubt, because this is determined by our individual genetics, history, medical and psychological histories, environment, etc.

Of course, we live in a polluted environment; we consume unbalanced food containing pesticides and other nicotinoids, low in fiber and vitamins. The law of the jungle is rampant in our intestine where certain aggressive bacterial strains proliferate at the expense of other wise but weakened one. But... but during this time we ignore the world where the most terrible pollution reigns, the one infested with the most powerful toxins: that of our own individual emotions, which, with all those of the other individuals, form the emotional field of humanity.

Our emotions must acquire the “organic” label, by refining themselves, by rising towards the beautiful and the good, as Plato already suggested: “Beauty is the splendor of truth”.

And Félix-Antoine Savard adds: “The true, the beautiful, the good, wherever they come from, are the treasures of humanity”.

Is it hard to imagine that a living, embodied philosophy, in other words true wisdom, can lead to inner harmony, coupled with the ability to be part of the world creatively with as a consequence, and not as a goal or in vain hope, the balance in our organism where our bacteria are left to their own devices, free to perform the biological functions for which the evolution of life and the species has given them?

Synthesis

It seems judicious to me to have caution regarding all the conclusions that flow from the scientific data available to us today, conclusions that are too often used out of context, broadened, and generalized beyond reason, by those who are not the authors of the studies, but are the users, as is the case of laboratories and some health practitioners, for example.

Here is a list of elements that any research on the microbiome, as well as any therapeutic application of the conclusions that seem valid to date, should take into account:

• Pharmacological treatments acting on inflammation or on the microbiome show indisputable effects. However, no one can discern between causes and consequences. Many discoveries on the microbiome result largely from animal experiments, often even involving animals genetically selected for their abnormal characteristics (mice devoid of microbiome, for example), and the results announced should not turn into a generalized belief: prudence and humility are the keys of the genuine scientific mind.

• Treating the consequences is nevertheless useful and beneficial to patients whose disease has already reached a certain

degree of severity. It evolves on its own account and can be very difficult to reverse.

• As a preventive measure, and for patients who are still in a functional state, or for those more severely affected who have more solid psychic resources, would it not be in our interest to change the paradigm and to move the status of the patient to that of actor?

• Could we continue to explore various and more comprehensive methods and find new means that lead to equally convincing results, and capable of preventing the occurrence of more serious conditions?

• Science and medicine could make major discoveries if, in addition to focusing on the study of diseases and their mechanisms – the how? – they decided to try to understand why so many individuals remain in good health, among those who eat poorly, who smoke, who are in contact with viruses and bacteria without developing symptoms, etc. Genes cannot explain everything, as we have seen.

Antithesis

One can only develop an idea correctly if, after having developed one's thesis, one does not dispense with the antithesis.

In fact, it is impossible for most people to properly regulate their emotions. The evolutionary development in which we are currently does not allow this; it is enough to observe how the majority of humans function. My practice as an osteopath confirms the fact that most of the patients I see for disorders that could be classified as those directly or indirectly linked to an imbalance of the microbiome do not reach this state of inner balance and sufficient emotional management to allow the full deployment of the functions of their ventral vagus nerve and the satisfactory physiological and microbiotic homeostasis.

I am therefore forced to admit that the means that I propose, as well as the progressive acquisition of a practical philosophy of wisdom, are not accessible to everyone, far from it.

But we must also admit that it is the same with an ascending approach, one that targets dietetics and the ingestion of pro- or prebiotics. I also see many patients who do not improve from this approach, or only in the short-term.

However, the sick must be helped and cared for: when their ground is too fragile, their illness too advanced, their psychic resources exceeded, they need all the outside help that science and medicine are capable of giving them, with where science and medicine are in their understanding and knowledge. We are not guilty of what we still do not understand or misunderstand.

Conclusion

Having started this article on epistemological considerations, I can only end it bearing in mind the thought of the great epistemologist that was Karl Popper. According to him, the true scientific

approach consists not in a “verificationist” approach, but in that of refuting hypotheses. The first seeks in observations or experiments to prove its hypothesis, while the second tries by all means to determine if there is at least one factor that invalidates it. In this case, the hypothesis is false, or at least incomplete.

For example, if I hypothesize that rainy weather systematically increases the pain of osteoarthritis of the knee, I must not content myself with carrying out a study which would establish that this occurrence is verified in 70% of cases, an unassailable statistical study of support. If there were only one percent of the cases that did not support the hypothesis, that would be enough to invalidate it in its present form and cause me to reconsider it, or to look for the factors that may contradict it.

With regards to the subject that concerns us here, while it is indisputable that numerous studies demonstrate that there are ascending gut-brain relationships, it is not scientific to develop a paradigm and a praxis (the therapeutic response) ignoring the other side of the issue, that of the descending heart-brain-gut relationships. And the remark also applies to my point of view; I would be wrong to ignore what has already been highlighted.

But since there are two-way interactions, studies must therefore focus equally on these two directions. For the time being, the focus is mainly on the ascending gut-brain interactions.

The descending relationships correspond better to the conception that I have of the human being, and that is why I wanted to defend this cause, which still remains the poor cousin of the collective interest.

Understanding the conditioning and the major impact of the brain, the autonomic nervous system, or the bacteria of the intestine, does not mean that the human subject is only the product or the puppet of biology.

To abdicate one's capacity to be and to choose for the benefit of our bacteria, seems to me an absolute despair.

However, to know what limits us, what weighs on us, what acts in the depths of our flesh, is to allow our mind, if not to completely free itself from it, to at least know the rules of the game of our body and to use it to realize ourselves as thinking, conscious and… loving human beings.

[i] Lipton B. “The Biology of Belief: Unleashing the Power of Consciousness, Matter and Miracles”. Hay House Inc., 2005.

[ii] Epigenetics is the branch of biology which studies the nature of the mechanisms modifying in a reversible, transmissible and adaptive way, the expression of genes without changing the nucleotide sequence (DNA).

[iii] Source: Wikipedia.

[iviviv] Biard N. “Le mircrobiote intestinal, les probiotiques et leur place dans les pathologies digestives basses du nourrisson”. Sciences pharmaceutiques. 2016. Hal-0173070.

[v] Bonaz B, Bazin T, Pellissier S. “The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis”. Front Neurosci. 2018; 12:49.

[vi] Bonaz B, Sinniger V, Pellissier S. “The Vagus Nerve in the Neuro-Immune Axis: Implications in the Pathology of the Gastrointestinal Tract”. Front. Immunol., 02 November 2017.

[vii] Thayer J, Sternberg E. “Neural Aspects of Immunomodulation: Focus on the Vagus Nerve”. 2010 (11 p.).

[viii] Ma EL, Smith AD, Desai N, Cheung L, Hanscom M, Stoica BA, Loane DJ, Shea-Donohue T, Fadena AI. “Bidirectional Brain-Gut Interactions and Chronic Pathological Changes After Traumatic Brain Injury in Mice”. Brain, Behavior and Immunity. Published online Nov. 2017. doi:/10.1016/j.bbi.2017.06.018.

[ix] Breit S, Kupferberg A, Rogler G, Hasler G, “Vagus Nerve as Modulator of the Brain-Gut Axis in Psychiatric and Inflammatory Disorders”. Front. Psychiatry. March 13, 2018.

[x] Thayer JF, Lane RD. “A Model of Neurovisceral Integration in Emotion Regulation and Dysregulation”. Jan. 2001, Journal of Affective Disorders 61(3):201-16.

[xi] Consult these:

- De Couck M, Caers R, Spiegel D, Yea G. “The Role of the Vagus Nerve in Cancer Prognosis: a Systematic and Comprehensive Review”. 2018.
- Thayer J, Sternberg E. “Neural Aspects of Immunomodulation: Focus on the Vagus Nerve”. 2010: (11 p.).
- Magnon C, Hall S, Jea L. “Autonomic Nerve Development Contributes to Prostate Cancer Progression”. 2013: 341.
- Tracey K-J, Pavlov V-A. “The Vagus Nerve and the Inflammatory Reflex: Linking Immunity and Metabolism”. 2014 (743-54 pp.).
- Zhou X, Ma Z, Zhang L. “Heart Rate Variability in the Prediction of Survival in Patients with Cancer: A Systematic Review and Meta-Analysis”. 2016: 89: (20-5 pp.).
- Fadul N, Strasser F, Palmeretal J. “The Association Between Autonomic Dysfunction and Survival in Male Patients With Advanced Cancer: a Preliminary Report”. 2010; 39: (283-90 pp.).
- Guo Y, Palmer J, Strasser F, Yusuf S, Bruera E. “Heart Rate Variability as a Measure of Autonomic Dysfunction in Men With Advanced Cancer”. 2013: (9 p.).

[xii] Porges SW. “The Polyvagal Theory: Neurophysiological Foundations of Emotions, Attachment, Communication, and Self-Regulation”. New York: WW Norton, 2011.

[xiii] Marlien É. “New Approach to the Vagus Nerve and the Autonomic Nervous System”. Barral Productions, 2021.

[xiv] Marlien É. “Invitation au voyage transpersonnel”. https://geopse-formation.fr/.

[xv] Passion literally means that which obscures our reason.