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Review

Combining Sensory Experiences with Internal Milieu in the Brain

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Abstract. Understanding the brain is not only intrinsically fascinating to apprehend life's complexity or to further progress in fundamental biosciences, but it is also highly relevant to increase our well-being since the brain exhibits a power over the body that makes it capable both of triggering illness or facilitating the healing process.

Considering the dual role at play by the brain, using ascending and descending pathways to combine information issued from the external world and the internal environment, this review challenges the cerebro-centered vision of the brain. In our daily life, we construct a representation of the outside world by transforming chemical, pressure changes, and light waves into tastes, smells, touches, sounds and sights. In doing so, we create our experience of the external world by interpreting our senses through a process called *exteroception*. But to be compelling, this Descartes' vision of the brain has to be completed by integration of events from inside our body. The way the brain constructs our inner sensations called interoception, is now starting to be unrevealed. As such, brain sciences have undergone, and will undergo, an important revolution, redefining its boundaries beyond the skull to prefer a more holistic vision carried out by the notion of an embodied brain acting as a coincidence detector to combine sensory experiences with corporeal homeostasis.

The goal of this review is to highlight some mechanisms by which the brain activity is controlled by internal cues for better prediction. The gut-brain axis is here taken as a canonical example to discuss about the communication between the *milieu intérieur* and brain functions that shapes how we feel, and how we think.

Keywords: Gut-brain axis, microbiome, plasticity, interoception

THE GUT-BRAIN AXIS

Ivan Pavlov, famous for defining the classical conditioning, was also a pioneer in the field of the gut-brain axis [1]. Remarkably, from a piece of exteriorized dog intestine, he was able to demonstrate the key role of innervation in digestive processes. As such, the descending pathway from brain to gut was anatomically and functionally revealed.

Since the start of the millennium, the gut-brain axis has undergone a revival, gaining popularity once again in the academic and clinical literatures. This new success was due to a full appreciation of the bidirectionality of this axis when it was discovered as an important node for mammalian interoception. For instance, during a meal, the gut provides crucial information to the brain regarding incoming nutrients to allow proper maintenance of energy and essential nutrients homeostasis. These ascending and descending routes were not only recognized by neural routes, but it soon became clear also they encompass endocrine (*i.e.*, various peptides or hormones), humoral, metabolic, and immune routes as well. Indeed, the gut-brain axis signaling molecules use different communication channels. They can enter the blood circulation and act directly on the brain, or they

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can act indirectly via paracrine action on local vagal and spinal afferent neurons that innervate the gut.

Worn by the same wave, the microbes also received a lot of attention, leading to recent discoveries on how the gut microbiota-brain axis participates to brain development and functions, as well as altered emotional, motor, and cognitive behaviors in animals [2]. A new star in Neuroscience was born. The trillions of microbes within the gut, the so-called microbiome, became central to the action of the gut-brain axis.

As it is often the case in Science, it is mainly technological progresses that prompted advents in the field of microbiome. First, it was the possibility of raising mice devoid of all microorganisms that launched this interest, and in particular that of the gut microbiome. Then, reductionist animal approaches became heuristic models helpful to reveal important contributions by gut bacteria to brain activity and behavior. Finally, the microbial profiling using 16 S ribosomal RNA (rRNA) sequencing became a common method for studying bacterial phylogeny and taxonomy. The use of this genetic marker allowed bacterial identification and classification, so launching comparative animal studies in health and disease with their correlates in the brain functions.

Yet, the extent to which these animal data translate to human beings, using causality rules, remains largely unexplored. Number of studies have started revealing correlations between human gut microbiomes and brain activity, but few of them have effectively translated mechanistic findings in animal models to corresponding clinical populations [3, 4].

THE MICROBIOME AND BRAIN CROSSTALK

Over the past twenty years, the recognition that the microbes living inside us outnumber our body's own cells has turned our view of ourselves inside out. This question is rather complex since there is a distinct microbiome in almost every niche of the human body. Furthermore, it is not only the spatial dimension that brings an additional degree of complexity, but the temporal dimension also plays a key role. Right after birth and in early life (<3 years), exposure to microbes gives rise to diverse microbe communities into distinct ecosystems that flourish within the skin, gut, lungs, oral, nasal and vaginal cavities, with most human-associated bacteria harbored in the lower gastrointestinal tract [5]. This early phase is followed by a long period of relative stability that ends with gradual changes associated with advanced age (65+ years) influencing host physiology [6].

Coupling DNA sequencing to metatranscriptomics, metabolomics, lipidomics, and proteomics offers have uncovered molecular mediators of the gut microbiota–brain axis [7]. The importance of these microbiome-derived molecules for the blood-brain barrier permeability, the brain development and wiring, the expression of neurotransmitters and their cognate receptors, the myelination and the microglia status, was demonstrated by several means, including germ-free (GF) mice [2, 3, 8]. Even adult neurogenesis and neuroplasticity have been found to be profoundly impaired by changes in the gut microbiota [9–11]. Since then, antibiotic-treated (ABX) mice and other approaches have provided further evidence supporting the importance of a stable and healthy gut microbiota composition in maintaining normal cognitive function and brain development [12]. Without further ado, let's see now what the nature of this communication between microbiome and brain might be.

MICROBIOME-DERIVED SIGNALING

The microbiome composition (including bacteria, archea, fungi, and viruses) differs according to the various niches of the human body, including the skin, the airways, the eyes and ears, the urogenital tract, and the gastrointestinal tract. As for the later, if the communication between the gut and the brain was first awakened by studies on food consumption and digestion, more recently, this communication was extended to more cognitive and psychological functions.

Whatever the niche concerned, the mediation between the microbiota and the brain is ensured by the same building-blocks, including neural, endocrine, metabolic, and immune signaling. For instance, in the context of the gut-brain axis, it has been shown that microbes influence immune cells and inflammatory responses which can affect the brain. In addition, gut microbiome prompts neuropod cells in the gut lining to stimulate the vagus nerve, which connect directly to the brain [2]. Alternatively, substances secreted by gut bacteria into the gut infiltrate blood vessels for a direct ride to the brain, might also represent another facet of the gut-brain axis.

In line with this later hypothesis, the potential role of microbial metabolite pathways acting directly in the brain, has been recently unraveled. We already

knew that the bacteria produce chemical signaling such as GABA in the digestive tract, which may increase GABA levels in the brain. And it was found that GABA producers reduced learned helplessness—a symptom of depression—in animal models [2]. But a recent study reports a new set of data identifying a direct mechanism by which bacteria might control the brain [13]. It demonstrates that bacteria in the mammalian gut can ping the brain to regulate an animal's appetite and body temperature through a well-conserved mechanism that the immune system uses to detect bacterial pathogens in the body. [13] report that bacterial peptidoglycans, a by-product of bacterial cell wall degradation during cell proliferation and cell death, directly inhibit the activity of feeding-promoting neurons in the hypothalamus and ultimately decrease appetite and body temperature. This finding may open new approaches for the treatment of metabolic disorders, including obesity. More generally, the microbiota provides today potential biological markers of microbiota-brain interactions and candidates for the development of therapeutic strategies for the treatment of neurodevelopmental, psychiatric, and metabolic disorders.

CONCLUDING REMARKS

Today, the importance of the bidirectional flow from the gut to the brain, and from the brain to the gut, has been supported by various observations. When this loop dysfunctions, it leads to various pathophysiological consequences described for instance in exacerbated gut inflammation disorders, acute and chronic stress or autism spectrum disorder [2]. After all, with more microbes than cells in our body, it is not so surprising that bacteria and other "body guests" influence our metabolism, immune system, and even our complex behavior.

This review aims at challenging a long history of thinking of bodily regulation as separate from "higher" mental processes. Four centuries ago, René Descartes famously conceptualized the mind as being separate from the body, it is time now to embody our mind. The reductionist approaches have been very successful in this quest when it was demonstrated, using animal models, the key contributions of gut bacteria in settling affective responses, brain activity or behavioral responses.

Yet, considerable efforts are still required to demonstrate how validated these findings are to the human brain and its singularities. Although associations between gut microbiome profiles and human behavior and neurological diseases are quite abundant, human studies still have lagged behind animal research. Longitudinal studies based on large cohorts remain to be launched in order to collect genetic information on the one hand, and environmental and experiential factors, collectively named exposome, on the other hand, to established solid correlations on factors that contribute to brain shaping and responding to gut microbial functions. But all that glitters is not gold! Causation of the gut microbiome on human brain functions requires interventions that modify microbiota-brain crosstalk at both the cellular and molecular levels. It is only at this price that it will be possible to establish rules of distal causality between the composition of the gut microbiome and the normal or pathological functioning of the brain. Without any caution, there is a great threat that this fantastic microbiome will turn into fool's gold.

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CONFLICT OF INTEREST

The author has none to report.

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