The Mind as an Epigenetic Hub of the Human Holobiont: The Microbiota as a Biological Mediator of Experience

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Received 30 October, revised 8 November, accepted 10 November
Online first: 18 November 2026

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Please cite: Agnoletti M., The Mind as an Epigenetic Hub of the Human Holobiont: The Microbiota as a Biological Mediator of Experience. *Pnei Review*.
DOI: 10.3280/pnei2026oa24165

Abstract: *This article proposes a conceptualization of the human mind as an epigenetic hub of the biopsychosocial holobiont, in which the experiences of the organism, associated with its human and non-human components, converge, are integrated and selected, and acquire meanings capable of contributing to the regulation of health and disease processes. From this perspective, epigenetics is one of the ways in which experience is biologically embedded, while the gut microbiota represents a point of convergence of multiple exposome factors and a mediator of their influences on the organism. The model also attributes to the mind the function of generating and maintaining a relatively unitary and dynamic sense of identity (self), through which the person organizes experience as their own and participates in the integration of the different teleonomies of the biopsychosocial holobiont. The proposal offers a theoretical framework for interpreting the interactions between experience, meaning and biological regulation, outlining possible developments for research and clinical practice in psychoneuroendocrineimmunology.*

Keywords: *mind, holobiont, gut microbiota, epigenetics, exposome, PNEI.*

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Introduction

Psychoneuroendocrineimmunology (PNEI) studies the reciprocal influence between the psyche and the biological systems of the organism within its physical and social environment (Bottaccioli & Bottaccioli, 2025). Two new paradigms, which developed largely independently of each other, have made this perspective more complex, more concrete and more clinically relevant.

On the one hand, the epigenetic paradigm has provided tools for investigating how environmental signals and the organism's physiological state can modify the regulation of gene activity without altering the DNA sequence; on the other hand, microbiota research has extended the analysis of host functions to the interactions with associated microbial communities, highlighting the need to include these relationships in the description of biological organization.

These fields converge in the possibility of studying the biological embedding of experience as a process that involves both the regulation of human cells and the interactions between host and microorganisms.

The concept of the holobiont provides a framework for addressing this biological complexity and plurality; its integration with the biopsychosocial model makes it possible to situate it within a conception of the person that also encompasses psychological processes and sociocultural relationships (Agnoletti, 2026a).

Such integration, however, requires a distinction between the biological constitution of the organism and the organization of subjective experience. The description of the interdependencies between host and microbiota does not, by itself, explain the processes through which the person maintains a relatively unified sense of self. Identifying the components that contribute to the functioning of the organism and explaining the psychological unity of experience are related, but distinct, problems.

The question therefore concerns the functional and epistemological status of the mind within the biopsychosocial holobiont. In the present contribution, the mind is defined as the organized set of conscious and non-conscious psychological processes through which the person generates, interprets and integrates their own experience. This definition acknowledges the dependence of mental processes on bodily conditions, while preserving the specificity of the categories through which these processes are explained.

Meaning, expectation, intentionality and identity denote relations that cannot be fully explained by identifying their respective neurophysiological correlates. The explanatory autonomy of the psychological and social levels is therefore assumed as an epistemological premise of the model, without postulating a separation of the mind from its biological realization.

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On these grounds, the article proposes to conceive the mind as an integrative and epigenetic hub of the human holobiont. The term hub designates the function through which the biopsychosocial information of the organism, both human and non-human, converges to be selected and processed in ways that support the organism's overall fitness. The term epigenetic, in turn, refers to the mechanisms through which information processed at the psychological level can contribute to modifying the cellular physiology of the organism by means of epigenetic regulatory processes, which therefore alter not the genetic information itself but its expression. In this context, the gut microbiota is regarded as one of the possible mediators of the biological embedding of the organism's experience.

The theoretical contribution also concerns the *self*, conceived as a function of the mind through which the person organizes experience as their own and maintains a dynamic sense of unity and continuity. This function is distinguished from the biological processes of immune individuation and regulation, while remaining connected to them. The challenge of the proposed model therefore lies in explaining how the biological and psychosocial heterogeneity of the holobiont can be integrated into a relatively unitary personal perspective.

The argument proceeds in four steps: epigenetic regulation as one of the modes of biological embedding of the *exposome*; the redefinition of the organism from the holobiont perspective; the evidence on the bidirectional relationships between microbiota and psychological processes; and the formulation of the mind as an integrative hub, with the *self* as one of its functions. The airport metaphor will be used as an illustrative aid for this last proposal, keeping its descriptive usefulness distinct from the empirical support for the relationships considered.

Exposome and Epigenetics

The term *exposome* was proposed to denote the totality of environmental exposures to which an individual is subject from conception onwards, as a necessary complement to the genome in the study of health and disease (Wild, 2005). From a PNEI perspective, the *exposome* should be understood in a broad sense, encompassing environmental physical and chemical exposures, diet, physical activity and the psychological and social experiences of the organism.

Epigenetics, in turn, describes the mechanisms through which these experiences leave a biological trace, a memory, in the organism. Alongside the classical concept of Waddington (1942/2012) and the molecular definition of Bird (2007), this paper proposes an experience-centered definition: epigenetics is the study of how experiences can modify gene expression, without altering the underlying DNA sequence, through changes that may or may not be heritable. DNA methylation, histone

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modifications and non-coding RNAs regulate the activation or silencing of genes, thereby contributing to the definition of the phenotype, understood also as the state of health or disease of the cell or of the organism. Epigenetics thus represents the mechanism through which experience is biologically embedded in the cell or in the organism, creating genuine biological memories (Agnoletti, 2026b).

This perspective draws on Denis Noble's critique of genetic determinism. The principle of biological relativity holds that no level of organization possesses, a priori, a privileged causal role: the functioning of genes must be understood within the cellular, tissue and organismal networks that condition their activity (Noble, 2012, 2013). The genome is thus an indispensable component of biological organization, but not a self-sufficient explanation of the phenotype. Epigenetic regulation is situated within this multilevel causality, through which the conditions of the organism and its interactions with the environment contribute to modulating the use of genetic information. This approach makes it possible to consider the *exposome* in relation to an organism actively involved in the regulation of its own responses, moving beyond an exclusively unidirectional representation from gene to function (Noble & Noble, 2025).

A further perspective on the relationship between information, context and epigenetics is offered by Ervin Laszlo and Pier Mario Biava (2019) in their book *Information Medicine*. Reference to this proposal makes it possible to emphasize the processes by which genetic information is regulated, via epigenetic mechanisms, in the cell or in the organism.

Among the experiences capable of producing this embedding, psychological experiences play a prominent role. Epigenetic psychology is, in fact, the study of the influences that psychological factors, in their cognitive, emotional and motivational components, exert on the expression of genetic information (Agnoletti, 2018). Research indicates that maternal care epigenetically programs the stress response (Weaver *et al.*, 2004); that mental practices such as meditation rapidly modify the expression of epigenetic and inflammatory genes (Kaliman *et al.*, 2014); and that the meaning attributed to a treatment produces, through the placebo effect, measurable physiological changes (Benedetti, 2014). The pathways through which psychological states are translated into biological molecules have now been largely described (Bottaccioli, Bologna & Bottaccioli, 2022; Bottaccioli & Bottaccioli, 2023).

This perspective, however, requires specifying which conception of the organism is adopted.

The Human Holobiont

The World Health Organization's definition of health as "a state of complete

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physical, mental and social well-being" (World Health Organization, 1946) and the biopsychosocial model of Engel (1977) extended the boundaries of the organism beyond biology alone. The so-called *microbiota revolution* calls for a further extension: every person is a biopsychosocial holobiontic organism. The concept of the holobiont, introduced by Margulis (1991) to denote a host and its symbionts as a biological unit, was subsequently extended by the *hologenome* theory, according to which host and microbiota constitute a unit upon which selection acts (Zilber-Rosenberg & Rosenberg, 2008; Bordenstein & Theis, 2015). From this perspective, the human organism is not a biologically monolithic entity, but a system characterized by functional interactions between host cells and associated microorganisms (Gilbert, Sapp & Tauber, 2012).

The human microbiota comprises bacteria, viruses, fungi, archaea and protozoa, and reaches its highest density in the gut. The ratio of bacterial to human cells is estimated at approximately 1.3:1, for a total bacterial mass of about 0.2 kg, comparable to that of a kidney (Sender, Fuchs & Milo, 2016); the bacterial gene pool is approximately 360 times larger than the human one (Human Microbiome Project Consortium, 2012). This genetic repertoire participates directly in the epigenetic regulation of the host by modulating gene expression in numerous tissues (Stilling, Dinan & Cryan, 2014; Krautkramer *et al.*, 2016). It follows that the biological embedding of experience concerns not only the human genome, but the *hologenome*.

The Microbiota as a Biological Mediator of Experience

Sleep, circadian rhythms, diet, physical activity, environmental quality, social relationships and psychological well-being act, at least partly independently, on the composition of the gut microbiota. This phenomenon has been described as the "funnel effect" (Agnoletti & Fasano, 2025): heterogeneous *exposome* factors converge on the microbiota, which in turn exerts both epigenetic and non-epigenetic effects on the host. The clinical implication is significant: an alteration in just one of these factors may be sufficient to induce dysbiosis. The microbiota can therefore be regarded as a point of biological convergence of the organism's experiences.

Research indicates that the microbiota can causally influence mental states: the absence of microbiota alters the development of the stress axis (Sudo *et al.*, 2004); microbiota transplantation can transmit anxiety-like behavioral phenotypes (Bercik *et al.*, 2011) and, when the microbiota derives from patients with major depression, it induces depressive-like behaviors in recipient animals (Kelly *et al.*, 2016; Zheng *et al.*, 2016). The vagus nerve is one of the main routes of this bidirectional communication between non-human and human cells (Bravo *et al.*, 2011; Cryan & Dinan, 2012), to the extent that, under conditions of increased intestinal permeability, it

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even appears to allow the passage of live bacteria from the gut to the brain (Thapa *et al.*, 2026), a finding that, if confirmed, would represent a further paradigm shift.

The mind, too, can causally influence the microbiota. Psychosocial stress reduces the abundance of intestinal lactobacilli (Galley *et al.*, 2014) through a circuit that has now been described in detail: the central nucleus of the amygdala controls, via the vagus nerve, mucus secretion by the duodenal Brunner's glands, on which the proliferation of lactobacilli depends; chronic stress inhibits this circuit, promoting dysbiosis and impairing intestinal barrier function and immunity (Chang *et al.*, 2024). The alteration of tight junctions and of intestinal permeability, in turn, constitutes a gateway to systemic inflammation (Fasano, 2011). The survival of lactobacilli in the gut can therefore also be influenced by the emotional states of the host, through the physiological responses associated with them.

The relationship between mind and microbiota is thus causal in both directions. The aphorism attributed to Hippocrates, according to which all disease begins in the gut (Fasano, 2020), may be replaced by a more precise formulation: diseases, particularly chronic ones, *pass through* the gut, and some of them reach it from the mind.

The complexity of these interactions requires an interpretative framework consistent with the biopsychosocial holobiont model. The terms *gut-brain axis* and *microbiota-gut-brain axis*, while identifying fundamental components of biological communication, do not make explicit the specificity of the psychological level. It has therefore been proposed to adopt, in the human context, the term *microbiota-gut-brain-mind axis* (MGBM), in order to acknowledge the role of experiences, cognitive appraisals, emotions and sociocultural meanings in the dynamics of the organism (Agnoletti, 2026c). The inclusion of the mind does not introduce a component separate from biology, but makes explicit a level of organization and explanation that cannot be regarded as equivalent to the mere description of neural activity.

The clinical relevance of this approach finds convergent support in the recent Rome V documents of the Rome Foundation. In the introductory contribution, Drossman, Chang & Tack (2026) explicitly state that the optimal therapeutic management of patients with disorders of gut-brain interaction requires a biopsychosocial approach. This indication is developed in the chapter devoted to the biopsychosocial aspects of these disorders in adults and children, which integrates psychological assessment, social context and therapeutic interventions (Elsenbruch *et al.*, 2026). These documents do not formally adopt the MGBM terminology, but they support the need for a clinical understanding that systematically includes psychological and social dimensions: an orientation consistent with the epistemological rationale of the terminological proposal discussed here.

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The Airport Metaphor

To define the position of the mind within the holobiont, this paper proposes a metaphor. Imagine the organism as a large international airport. Like the organism, the airport is an open complex system that continuously exchanges matter, energy and information with its environment. Thousands of actors operate within it: airlines, crews, baggage handlers, refueling services and security staff. Each pursues its own objectives; none of them, alone, can ensure the functioning of the whole.

Within this complexity, not everything is equally important. Losing three pieces of luggage is not the same as losing contact with three aircraft on final approach. A system of this kind therefore requires a function that selects relevant information, establishes hierarchies among priorities and coordinates the activities of the various operators so as to ensure the functioning of the whole: the control tower. Most airport operations proceed automatically, according to established protocols; only some require explicit decisions. Similarly, the mind comprises non-conscious processes, which handle most of the regulation, and conscious processes, which intervene when experience requires an appraisal suited to the context and functional to the priorities defined by the organism.

The metaphor makes it possible to highlight four properties of the mind. The first is convergence: signals from all sectors of the airport reach the control tower, just as nervous, endocrine, immune and microbial signals reach the mind, together with those originating from the physical and social environment. The second is integration: the tower does not merely receive signals, but composes them into a unified picture of the situation. The third is the attribution of meaning: the same radar signal may indicate a routine flight or an emergency, and the response of the entire airport depends on this appraisal; likewise, the biological response of the organism also depends on the meaning that the mind attributes to the information it receives. The fourth is the coordination of actors/agents with their own, partly autonomous, goals: the tower neither owns the airlines nor flies their aircraft, but makes their trajectories compatible through communication and coordination.

Like all metaphors, the one proposed here has a limitation that should be made explicit. The control tower is a structure physically distinct from the other areas of the airport; the mind is not. The mind is not an observer external to the organism, but a property of the organism itself, embodied in it and continuously modified by its dynamics, including those associated with the microbiota. The metaphor should therefore not be read in a dualistic sense: the tower is made of the same materials as the airport, and its functioning depends on what happens on the runways and in all the other areas of the airport complex.

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The Mind as an Epigenetic Hub of the Holobiont

In the vocabulary of communication networks, and in air transport itself, a hub is the node through which most flows pass and which enables their redistribution. A hub does not command the system unilaterally; it makes the system's coherence possible by facilitating the coordination of information flows. The gut microbiota and the mind are both points of convergence within the holobiont, but with qualitatively different functions. The microbiota behaves like a funnel: it sums and transmits the effects of the *exposome* to the host, without interpreting them. The mind behaves like a hub: in addition to convergence, it integrates, attributes meaning, coordinates and remembers.

This distinction makes it possible to address an objection. The gut has its own nervous system, with several hundred million neurons (Furness, 2012), but it does not have a mind of its own. The enteric nervous system regulates motility and secretion largely autonomously; it does not generate psychological experience. Expressions such as "I have butterflies in my stomach" or "I can't stomach this situation" describe an experience of the mind that involves the gastrointestinal system (Mayer, 2011); they are not the product of two separate minds. Only the mind, at least in the human species, generates psychological experience, understood as an embodied and relational process that regulates the flow of energy and information within the organism and between the organism and others (Siegel, 2012).

Each component of the holobiont, whether human or microbial, is endowed with its own teleonomy, that is, an internal purposiveness produced by evolution and inscribed in its biological program (Pittendrigh, 1958; Monod, 1970). These teleonomies may converge or come into conflict (Agnoletti, 2004).

The immune system, too, constructs its own *self*, which enables it to distinguish what must be tolerated from what must be attacked (*non-self*) because it is potentially dangerous to the organism; this, however, is an exclusively biological *self*. The *self* produced by the mind integrates this level with the psychological and social levels.

The following definition can thus be proposed: the human mind is an epigenetic hub that enables the various biopsychosocial teleonomies (human and non-human) of the organism to converge and integrate in order to optimize its adaptive capacity, providing this complexity with a global sense of identity (*self*).

The mind is an *epigenetic* hub because the meaning it attributes to experience is translated into neuroendocrine and immune signals that modify host gene expression and, through circuits such as the amygdala-vagus nerve-Brunner's glands pathway, the composition and hence the collective gene expression of the microbiota. The microbiota thus acts as a biological mediator of experience, helping to

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translate its effects, including those shaped by psychological meaning-making processes, into changes in the hologenome. At the same time, it conveys information about the state of the holobiont to the mind.

A distinctive feature of the human mind is that it also represents the point of encounter and mediation between two evolutionary processes: biological evolution, which produced the holobiont, and cultural evolution, which provides information and meanings to human experience (Laland, Odling-Smee & Myles, 2010). The present paper is itself one of many examples of this sociocultural process. The proposed model of the mind seeks to move beyond both reductionist interpretations, which reduce the explanation of the psyche to the description of brain activity, and dualist conceptions, which separate the mind from its biological realization (Bottaccioli & Bottaccioli, 2025).

Conclusions

Considering the mind as an epigenetic hub of the holobiont has at least two important consequences. For research, psychological variables should not be regarded solely as confounding factors, but also as possible determinants and mediators of the observed dynamics. For clinical practice, interventions on the microbiota, from nutrition to psychobiotics (Dinan, Stanton & Cryan, 2013), and interventions on the mind, from psychological support to stress-regulation techniques, are neither marginal nor alternative, but act in a complementary manner on different nodes of the same network. Many of the causal findings discussed derive from animal models and require further verification in humans. Nevertheless, the emerging picture is consistent with the PNEI paradigm and identifies the mind as the level of the holobiont at which experience becomes meaning and meaning becomes biology once again.

Funding: This research received no external funding. Conflicts of Interest: The author declares no conflict of interest.

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PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2026oa24165
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PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2026oa24165
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