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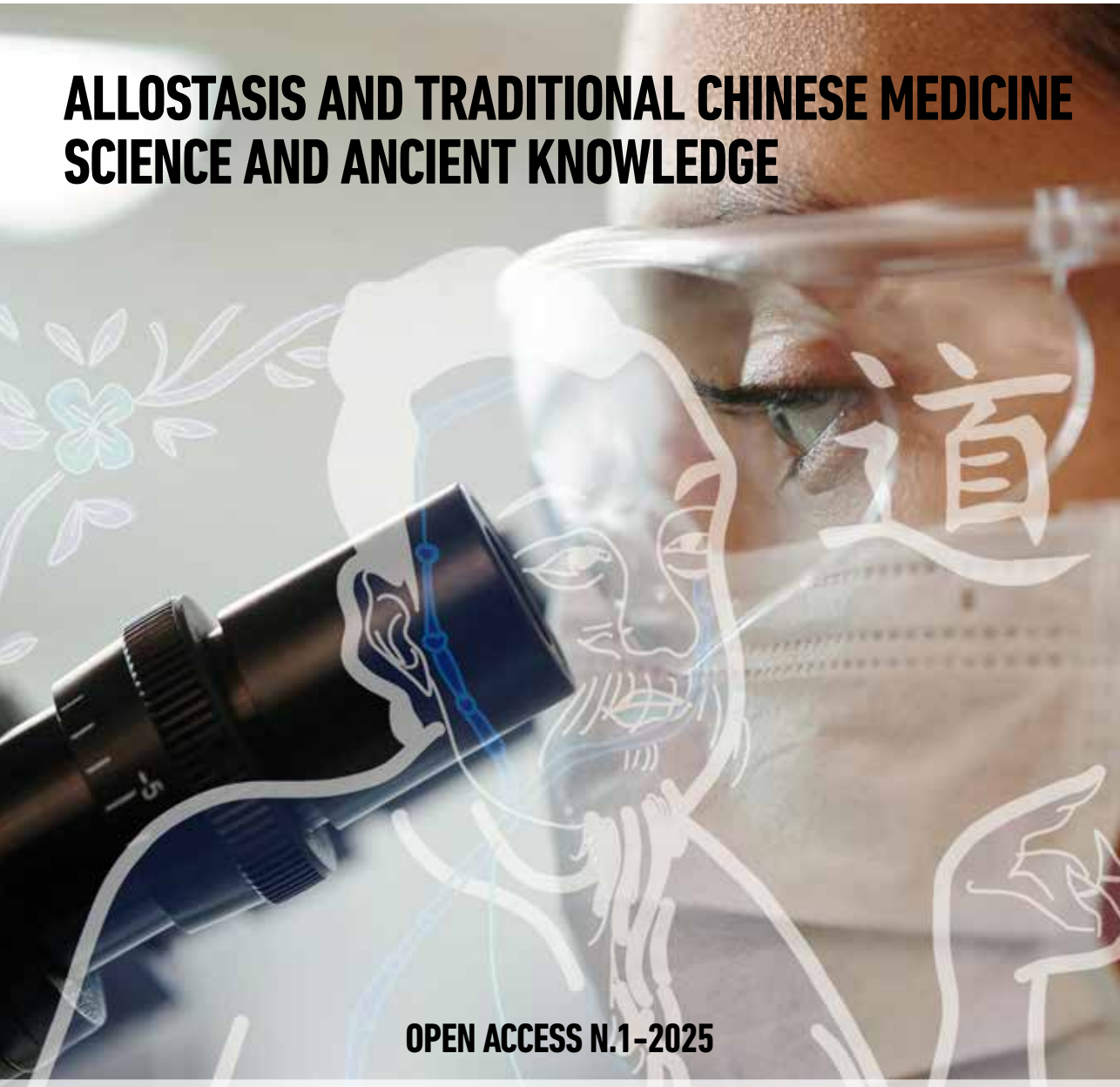
pneireview

Journal of Italian Society of Psychoneuroendocrineimmunology

ALLOSTASIS AND TRADITIONAL CHINESE MEDICINE SCIENCE AND ANCIENT KNOWLEDGE



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Editor in chief Francesco Bottaccioli

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Summary

Francesco Bottaccioli – Pnei Review, *Italian English, open access. A contribution to the community of scholars and health professionals*

Pnei Review, in Italian, was founded in 2013. Four years later, it joined the panel of scientific journals published by Franco Angeli. This year, with the support of the publisher, we are launching a highly innovative project: to make Pnei Review a bilingual scientific journal, in Italian and English, with free access. As the Italian Society of Psychoneuroendocrinoimmunology, we are proud that the project has found supporters and collaborators of high scientific standing at national and international level, as can be seen from the names of the Direction, Scientific Advisors and Editorial Board.

Andrea Minelli, Francesco Bottaccioli, Anna Giulia Bottaccioli – *Psyche and life. Allostasis between the mind-brain predictive system and Traditional Chinese Medicine*

The paradigm of allostasis and traditional Chinese medicine (TCM) share conceptual and pathophysiological principles, as well as a unified view of the relationship between the psychic and biological dimensions. TCM emphasises a profound connection between the body and Qi; in the allostatic model, the representation and regulation of bodily states are at the centre of all our mental faculties.

Massimo Agnoletti, Alessio Fasano – *The funnel effect of the microbiota: how multiple factors converge independently to change the microbiota*

The article presents the concept of the "funnel effect" of the microbiota to describe the convergent and partially independent nature of various factors (nutrition, physical activity, psychological well-being, sleep quality, social support, physical and chemical environmental quality, circadian rhythms) on the composition of the gut microbiota, thereby impacting the overall health of the human organism.

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Marcello Romeo – *Carbohydrate malabsorption and non-coeliac gluten/wheat sensitivity: the role of probiotic biomodulation*

Recent studies suggest the use of strain – specific probiotics to improve fermentative dysbiosis, reducing gas – producing species and promoting the digestion and absorption of carbohydrates, gluten proteins and micronutrients.

Viviana Mucci, Carolina Beppi, Enrico Amato – *Psycho-Neuro-Endocrine-Immunology and Vestibular Disorders: A prospective study*

In this article, the PNEI paradigm is considered in application to various peripheral and central vestibular disorders. Overall, this study offers an overview of holistic approaches to the treatment of patients with vestibular disorders.

Paolo Migone – *The problem of validating psychotherapy*

Some issues concerning the problem of proving the effectiveness of psychotherapy are reviewed and discussed. First, the difference between clinical research and empirical research is examined: the former is conducted by the psychotherapist in their daily work with patients, while the latter is carried out in the experimental laboratory. The article then discusses whether replicability, which is a central feature of the scientific method, is possible in psychotherapy. An overview of the history of the psychotherapy research movement is then provided.

Franco Baldoni – *Perinatal grandparents: a new frontier for caregiving*

We know that a father (or partner, including homosexual partners) who cares for a newborn baby as a caregiver undergoes significant neuroendocrine and epigenetic changes. These changes also occur in the bodies of grandparents when they act as caregivers for a newborn baby.

Bruno Burlando – *Loopomics: a possible breakthrough in understanding and controlling life*

Life sciences struggle to develop theories that allow us to operate on biological systems. This is evident in biomedical research, where many diseases remain obscure despite prolonged efforts to investigate them. The complexity of living systems is often cited as the cause of these problems. To address these challenges, the author proposes a new definition of life, called Loopomics.

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Editorial

Pnei Review, Italian English, open access. A contribution to the community of scholars and health professionals

Francesco Bottaccioli*

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Pnei Review, in Italian, was born in 2013. Fourth years later, became part of the panel of scientific journals published by Franco Angeli. In this year, with the support of the publisher, we are launching a highly innovative project: to make *Pnei Review* a bilingual, Italian English, open-access scientific journal.

As Italian Society of Psychoneuroendocrineimmunology, we are proud that the project has found supporters and contributors of high national and international scientific level, as can be seen from the names of the Editors, Scientific Advisors and Editorial Board.

Starting now, February 2025, we start publishing articles *online first*, ranging in different fields, from topics in clinical medicine, centered on the gut microbiota, to the validation of efficacy of psychotherapy, to topics in scientific theory, such as the connections between allostasis and traditional Chinese medicine, and last but not least, reflections on the necessary shift to a systemic view of life. Different themes but all within the Psychoneuroendocrineimmunology paradigm.

We will continue in the coming months by dealing with the relationship environment, climate change and health, between stress emotions and diseases, of psychological and internal medicine interest.

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When we founded *Pnei Review*, twelve years ago, we motivated the choice thus: «We are convinced of the need for a journal that differs from traditional neuroscience or psychosomatic journals. A journal that is both interdisciplinary (promoting exchange between scientific disciplines) and cross-cultural (promoting exchange between humanistic and scientific cultures)» (*Pnei Review* 2013; 1: 3).

In recent years, those motivations have strengthened.

The basis for the integration of medicine and psychology

It is now clear that only Psychoneuroendocrineimmunology can provide the basis for the integration of medical and psychological sciences and practices. Integration between medicine and psychology, which is scientifically mature and desired by relevant sectors of practitioners and users to overcome the spiral of rising costs-modest efficacy of treatments based on the reductionist drug-centric model. The accumulation of knowledge and experience on the integration of psychology and medicine, in turn, is essential for the development of the Psychoneuroendocrineimmunology (PNEI) paradigm itself.

PNEI, in fact, is not Neuroendocrineimmunology. PNEI describes the relationships of mutual influence between psyche and biological systems, showing the scientific inconsistency of the reductionist dogma that makes the psyche a mere epiphenomenon of brain activity. We are at a stage of research that allows the definitive overcoming of the dualistic conception of the human being without falling into the trap of the mind-brain identity, in the reduction of the psychic dimension to the biological one, from which it undoubtedly originates but on which it influences from the earliest stages of individual life. To this end, it is essential to critique the philosophical basis of contemporary reductionism and, at the same time, present scientific evidence documenting the mutual influence of psyche and biological systems in health and disease (Bottaccioli F., & Bottaccioli A.G., 2024; Bottaccioli A.G., Bologna, Bottaccioli F., 2022).

Pnei Review will host and actively search for works of integrated knowledge on the functioning of the human network, which are essential to understand health and disease dynamics and thus build a pathophysiological vision open both to molecular updates and preventive and therapeutic strategies. In fact, the parcelization of knowledge must be overcome because it is an obstacle to the understanding of pathogenesis and the proposition of personalized therapies, without underestimating, rather enhancing, the study of the molecular dimension, which, with epigenetics, shows us that even the genome is flexible and responsive to the environment and behavior.

Thus, reviews (narrative, scoping, systematic) and original research in human

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pathophysiology and integration between medicine and psychology fields are welcome in *Pnei Review*. Also welcome are those scientific papers documenting the role of behavior (nutrition, physical activity, stress and emotion management, sleep), socio-environmental conditions (inequalities, pollution, climate change), complementary therapeutic methods with scientific evidence (phytotherapy, acupuncture, meditation, mind-body techniques, osteopathy), in prevention and therapy. It will also host and actively seek opinions, comments, and essays on the philosophical and cultural foundations of PNEI and related disciplines (psychology, pedagogy, sociology, philosophy of science).

Articles will undergo rigorous and rapid peer-review and will be free from financial charge.

In short, we believe that as Italian Society of Psychoneuroendocrineimmunology, with the new *Pnei Review*, we can make an original contribution to the international scientific movement that studies and treats human beings in a unified way and that is working hard to overcome the parcelization of knowledge and treatment.

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Psyche and Life: Allostasis between the Predictive brain-mind system and Traditional Chinese Medicine

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***Abstract**: The paradigm of allostasis and Traditional Chinese Medicine (TCM) share foundational conceptual and pathophysiological principles, as well as a holistic perspective on the relationships between psychological and biological dimensions. TCM emphasizes the profound connection between the body and Qi, while the allostatic model places the representation and regulation of bodily states at the core of all mental processes. According to predictive processing theories, the brain-mind system employs internal models to anticipate neurosensory states, continuously comparing predictions with incoming data from external and internal environments. By minimizing predictive errors, the brain-mind system constructs perceptions, plans actions, and regulates allostasis. Disruptions in the balance between predictions and prediction errors can impair allostatic efficiency, leading to clinical consequences. Similarly, imbalances in Qi – stagnation, deficiency, excess – disrupt psychophysical equilibrium and contribute to the development of chronic diseases, notably under prolonged stress conditions. Integrating Western and Eastern paradigms holds promise for developing more effective, patient- centered therapeutic approaches.*

Key words: *Neuroscience, Eastern philosophy, Qi, Chronic stress, Integrated medicine, Chronic diseases.*

This work seeks to identify potential intersections between life sciences, particularly neuroscience as it relates to allostasis, and key principles of Eastern philosophy and Traditional Chinese Medicine (TCM). The aim is to contribute to the development of a shared perspective on the relationships between the psychic and biological dimensions of the human organism.

In Western thought, the dualistic conception of the human being, first articulated in Christian philosophy and theology by Augustine (4th century), was formalized in the 17th century by René Descartes. This perspective, foundational to modern scientific inquiry, separates soul and body, envisaging a res cogitans, an immaterial, eternal substance capable of thought and feeling, and a res extensa, the corruptible material substance that constitutes the individual body (Meditationes de Prima Philosophia, 1641). A few decades later, Spinoza criticized Cartesian dualism and proposed a monistic view in which mind and body, rather than being ontologically separate substances, are considered as two expressions of the same reality and natural order (Ethics, 1677). The dualistic perspective, in its various forms, has prevailed in the evolution of scientific thought, inspiring hypotheses and theories, lines of research, and academic training. It has also permeated popular culture, where the mind is often portrayed as a repository of rational, moral, and spiritual thought. Building on Spinoza's ideas and on contemporary philosophy of complexity (Morin, 2022), we adopt the view that the psychic dimension is an emergent property of living organisms. Evolutionary psychologists and advocates of the embodied mind framework argue that the psyche finds its roots, expressions, and fundamental purposes within biological life (Varela *et al.*, 1991; Barsalou, 2008; Ziemke, 2016). The term "psyche" derives from the Greek word for "breath", "spirit", or "soul" as the vital force. Here, we propose that the foundational essence of the psyche is deeply intertwined with "breath", understood in its literal and physiological meanings, serving as a synecdoche for the continuous flow of the living organism's complex functions. This assertion may seem less audacious if interpreted in light of the principles of Eastern philosophy. A fundamental concept of TCM and Taoist philosophy is *Qi*, the vital force that flows through the universe and all living beings, which ancient texts (such as the Huangdi Neijing, a medical and philosophical treatise written between the 4th and 2nd centuries BC) describe both as a substance and as the driving force of life, closely linked to Yin and Yang, the complementary and opposing forces that govern natural harmony.

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The Qi, the principle that unifies the universe and man

The ancient ideogram for the term *Qi* (pronounced "chi") consists of two parts (or "radicals"): one depicts rising vapor, and the other a grain of rice (Fig. 1). The ideogram symbolizes the fundamental nature of *Qi*: it represents both a dense, material reality (the grain) and a more energetic, ethereal reality (the vapor); in essence, the earth and the heavens.

Fig. 1. The *Qi* Ideogram
The radical at the top right represents swirls of vapor, while the one at the bottom left symbolizes a grain of rice

With the advancement of medicine, *Qi* came to be understood as the fundamental vital principle of human existence: it is what constitutes the human body and, at the same time, unifies it. As such, the *Qi* must be preserved and nourished in alignment with the *Qi* of the heavens, symbolized by the seasons. Otherwise, the flow of *Qi* can become pathological due to its excess, deficiency, stagnation, or improper circulation. Thus, *Qi* is seen as both the foundation of health and a potential source of illness.

As many scholars have observed, this concept serves as a bridge between East and West, appearing in Greek philosophy as *pneuma* and in Indian tradition as *prana*. In humans, it is intimately connected to "breath", therefore to life in its root and most evident expression (Maciocia, 2007; Bottaccioli F., Bottaccioli A.G., 2024a). Without delving too deeply into technicalities, it is essential to understand that *Qi* originates from a dual process: one innate and the other derived from food and breath. The innate component, inherited from one's parents, is known as *jing*, i.e. the vital essence stored in the Kidneys. This essence generates *yuan Qi*, the driving force of *Qi*, which enables its extraction and transformation from food and breath. An essential feature of *Qi*, recognized as early as the Mawangdui manuscripts (2nd century BC), is its close relationship with blood. Blood is moved by *Qi*, and disturbances in *Qi* are the root cause of blood-related disorders.

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Psyche and body: an integral unity in ancient Chinese wisdom

In this perspective, the human organism is a system of interconnected functions rooted in the organs. These functions extend beyond physiology to encompass mental activities, including emotions and consciousness. Each organ (*zang*) is associated with a specific emotion and mental function; in turn, emotions and mental states influence their corresponding organs. The *Ling Shu* explains: «If the blood of the Liver is deficient, there is fear; if it is in excess, there is anger […]. If the Qi of the Heart is deficient, there is sadness; if it is in excess, there is manic behavior». Conversely: «Fear, anxiety, and ruminative thought harm the *Shen* of the Heart […]; rumination linked to the Spleen damage the *Yi*» (cited in Maciocia, 2007).

This interplay between organs and emotions operates in two directions. The first movement goes from organs to emotions: an excess of *Yang* of the Liver can result in anger, a deficient *Qi* of the Lung can lead to sadness, a deficient *Qi* of the Kidney can cause fear, an excess of *Yang* of the Heart may produce manic euphoria, a deficient *Qi* of the Spleen can lead to ruminative or obsessive thoughts. The second movement, in reverse, goes from emotions to organs. Mental imbalances can damage their associated organs, as each organ serves as the seat of specific mental functions: the Heart houses the *Shen* (consciousness, mental vitality, emotional stability, and spiritual connection), the Liver is associated with the *Hun* (the ethereal soul linked to the heavens, to which it returns after death; on a psychological level, it reflects the ability to act outwardly, linked to creativity and action), the Lungs house the *Po* (the corporeal soul, tied to the earth, which decays with the body after death; on a psychological level, it is tied to introspection), the Kidneys are linked to *Zhi* (willpower that knows how to act, determination as desire to act and ability to do so; it is the foundation of a stable personality), the Spleen governs the *Yi* (intellect and cognitive processing). In this unified framework, mental disorders are always interpreted in relation to the energetic imbalances of the organs, while organ dysfunctions are understood to have a psychological component in their origin or clinical manifestations. This perspective avoids the mind-body dualism, rejecting both biological and spiritual reductionism (Bottaccioli, 2020).

Life gives rise to mind: an evolutionary perspective

As surprising as it may seem, the discussion around the definition of life remains still open. In their seminal work, *Autopoiesis and Cognition* (1980), Chilean neuroscientists Humberto Maturana and Francisco Varela argue that living organisms are *autopoietic systems*: self-contained entities, distinct from their environment

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yet in constant exchange with it, describable as networks of heterogeneous components functionally interconnected by organizational patterns largely dictated by genetic programming. These entities transform energy, matter, and information to continuously regenerate the very components that make up their networks, thereby actively maintaining their internal organization. Living beings, from the earliest unicellular organisms, "create" their environment by assigning meaning and significance to external elements based on the repertoire of possible interactions they can have with them, given their internal structure and organization. For instance, a glucose molecule is not a nutrient without a bacterium capable of transforming it into metabolic energy, thus "attributing meaning" to it in relation to its own internal organizational structure. The interaction between a living organism and its environment is, therefore, a process of meaning-making (thus a cognitive process, even in the absence of a mind).

As the complexity of organisms increases, evolving from single cells to multicellular systems, the exchange operations with the environment are managed by a variety of organs and systems, which require efficient coordination to ensure an optimal, integrated regulation of vital functions. The emergence of motor effectors enabling flexible and diversified actions aimed at selected objectives necessitates the development of specialized sensory systems for increasingly refined and informative representations of the environment. This is precisely the role of the nervous system. In the earliest metazoans, even a few neurons sufficed to form rudimentary nervous systems that governed the activity of simple structures responsible for motility, resource acquisition, and waste elimination. Over the course of phylogeny, the nervous system underwent progressive development, culminating in the human brain, the most complex organ in nature. Yet, despite its increasing sophistication, the brain's fundamental task remains the same: to ensure the acquisition and distribution of energy resources, preserving the organism's integrity and supporting adaptive behavior.

As the brain's complexity grows, it acquires the ability to construct internal models of the body and the world; thus, the mind emerges. The brain identifies and encodes the statistical regularities of the organism's interactions with its environment, and it can be regarded as the neurophysiological realization of the causal structure of the world inhabited by the organism, embedded in the spatial and temporal patterns of its neural activity. The more complex and hierarchically organized the brain's structure, the greater its capacity for multimodal integration and abstraction, enabling the construction of increasingly rich and intricate internal models that capture and map the causal structure of the world. Nonetheless, as in the earliest stages of unicellular life, every organism attributes meaning to the world in relation to the repertoire of possible interactions it maintains with it,

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"constructing" reality based on the internal models and interpretative schemas that its brain-mind system projects onto the world. Here, we use the term 'brain-mind system' to underline the interconnected and inseparable nature of mental and physical processes in human functioning, thus emphasizing the ongoing interaction between psychic and bodily aspects in shaping both experience and behavior.

Allostasis and adaptation

In 1970, Conant and Ashby formulated one of the foundational concepts of cybernetics, stating that any regulator, to be effective, must contain a representation of the system it aims to control («a good regulator of a system must be a model of that system»). Using its internal models of the body and world, the brain-mind system integrates current information with its repository of prior knowledge and experiences to anticipate needs and prepare to address them. This predictive regulatory process is known as *allostasis*.

The concept of allostasis, introduced in the late 1980s by Peter Sterling and Joseph Eyer (Sterling, Eyer, 1988; Sterling, 2012), represents an evolution of the homeostatic paradigm developed decades earlier by Walter Cannon. While homeostasis emphasizes the role of reactive and corrective mechanisms aimed at maintaining internal parameters within fixed limits (such as blood oxygen concentration or pH), allostasis recognizes the need for greater flexibility in physiological regulation. Allostasis, that means "achieving stability through change", describes a model of dynamic and predictive regulation of physiological and behavioral states, which anticipate needs and demands and proactively adjust its parameters, ensuring balance and efficiency in response to fluctuating environmental conditions while preventing potential perturbations. An example: in trained individuals, before beginning physical exercise, blood glucose levels, respiratory rate, and cardiac output increase in anticipation of heightened energy demands; simultaneously, heat dissipation and sweating mechanisms are activated in preparation for an imminent rise in metabolic heat production. The allostatic model involves a broad network of brain structures, involving hierarchically advanced regions (such as cortical areas responsible for self-awareness, abstract thinking, and executive functions) and subcortical regions, including the hypothalamus and brainstem, which directly regulate autonomic and neuroendocrine functions. This framework highlights the critical role of psychological and social dimensions, often overlooked in the homeostatic model, in driving allostatic adaptive processes.

Allostatic processes are essential for both acute responses to events and long-term adaptation. However, they carry a cost (McEwen, 1998, 2016). Chronic activation of these mechanisms can lead to *allostatic load*, a term describing the detri-

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mental effects of excessive and prolonged action of allostatic mediators. This cumulative strain results in a gradual wear-and-tear on the systems regulating physiological and psycho- behavioral functions, contributing to the development of a wide range of chronic conditions, including cardiovascular, metabolic, neuropsychiatric, and oncological diseases.

Allostasis and the *Qi*

Although stemming from different cultural and scientific perspectives, allostasis and TCM appear to share a fundamental concept: *dynamic adaptation* as the foundation for maintaining balance and health of the organism. Like allostasis, the *Qi* is dynamic, and it continuously adapts to various internal (emotional states, nutrition) and external (climate, seasons, stress) changes, by balancing *Yin* and *Yang*. The predictive nature of allostatic regulation finds a parallel in the *Qi* of TCM, understood as a proactive element capable of anticipating the body's needs and physiological requirements, thus preventing imbalances in energy flow before they manifest as physical and emotional symptoms, such as fatigue and weakness (associated with *Qi* deficiency), pain and emotional tension (*Qi* stagnation), inflammation or hyperactivity (excess of *Qi*). This capacity for adaptation and regulation highlights the complex and anticipatory nature of *Qi,* in perfect analogy with the principles of allostasis.

In the allostatic model, certain predictive systems are designed to anticipate periodic changes in physiological demands. Many hormones, neurotransmitters, and inflammatory factors exhibit circadian profiles of secretion and activity on target tissues. In fact, the activity of the heart and blood vessels, kidneys, gastrointestinal system, as well as the functions of the liver, pancreas, and spleen, all follow an underlying circadian rhythm. This coordination ensures integrated and efficient multi-system responses to the most probable demands throughout the day. On a longer timescale, seasonal variations in daylight duration allow organisms to anticipate environmental temperature and food availability, regulating behaviors such as migration, mating, and hibernation in many animal species. Similarly, the theory of *Yin-Yang* balance reflects an anticipatory process of cyclic adaptation, in which the *Qi* proactively regulates the mind and body in anticipation of the needs associated with seasonal and circadian rhythms: during winter, the *Qi* tends to concentrate on the internal organs to conserve energy (in preparation for spring); during the day, the *Qi* flows outward to protect the body, while at night it retreats inward to regenerate the organism.

In allostasis, cognitive and emotional states generate anticipatory responses aimed at regulating the activity of bodily systems based on expected needs. Simi-

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larly, in TCM, which views emotions and thoughts as manifestations of *Qi*, the *Qi* "anticipates" how mental states may affect the body and dynamically adjusts to maintain balance in response to shifting environmental influences. The anticipatory nature of *Qi*, whose flow addresses disharmonies before they fully manifest, reflects the principle of preventive health – a fundamental pillar of TCM. A harmonious and balanced flow of *Qi*, like an efficient and flexible allostatic system, is essential for adaptation and for the maintenance of physical and mental well-being. Conversely, interruptions, stagnations, or excesses of *Qi* inevitably lead to illness.

Allostasis and the predictive brain-mind system: the deep roots of self-awareness

An emerging paradigm in neuroscience is the *predictive brain* framework (Clark, 2013; Hohwy, 2016), encompassing a group of theoretical and conceptual approaches that have generated fascinating hypotheses about how the brain constructs experience and plans actions in the service of efficient energy regulation (thus in service of allostasis; Kleckner *et al.*, 2017). Drawing inspiration from Bayesian statistics, this theory suggests that the brain operates as a probabilistic prediction machine, using its internal models to actively generate hypotheses and expectations for inferring the most likely causes of the ambiguous and noisy sensory inputs it receives from the world. This is referred to as *predictive coding*. In the brain-mind system, higher- order hierarchical units constantly send predictive signals to lower-level units that are compared with incoming sensory signals. When descending predictions match incoming input, the contents of the internal models, i.e. the top-down simulations, become perceptions of the external world and action plans for interacting with it. When predictions do not align with sensory inputs, then prediction errors arise, which the brain-mind system must minimize. It does so in two ways: by updating internal models so that new predictions align with incoming input (this is perception), or through action, i.e. keeping models and predictions fixed while moving the body, thus altering the incoming signals to receive the expected inputs (*active inference*; Friston, 2010).

Predictive coding also explains interoception and allostasis. Emotions and awareness of interoceptive states, as well as the visceromotor regulation of bodily parameters, emerge from the brain-mind system's probabilistic predictions which infer the most likely causes of signals originating from the internal environment (Chanes, Barrett, 2016; Seth, Friston, 2016). At the most fundamental (and phylogenetically ancient) level, interoceptive predictions manifest as *affect*, an indistinct and amorphous core of experiences that represent in a non- conceptual manner the

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body's momentary conditions, constantly monitoring the internal physiological states in terms of valence and intensity and signaling the quality and salience of the organism's ongoing interactions with the environment. Primarily, interoceptive predictions serve the function of *interoceptive active inference*, thus allowing the adaptive regulation of internal variables. Simultaneously, however, they generate the pre-cognitive and pre-representational phenomenal experience of "being an embodied living organism", thus forming what can be considered the primitive and foundational core of conscious selfhood (Seth, Tsakiris, 2018). This core, although raw and amorphous, has a profound and pervasive influence on brain activity, reaching the highest hierarchical structures of the neocortex, where the most complex and abstract representations emerge through the maximal integration of multimodal information (Kleckner *et al.*, 2017). These cortico-limbic areas (e.g. anterior insula, anterior cingulate cortex, and orbitofrontal cortex), which are densely connected to deep brain structures that directly regulate bodily functions, serve as high-centrality hubs within the cerebral connectome, facilitating the rapid, large-scale integration of neural information. Collectively, this means that the representation of core affects and bodily states, along with the visceromotor regulation of physiological parameters, is at the center of our mental life (not only emotions, but all psycho-cognitive faculties). In other words, the primary function of the brain is to sustain allostasis. As Spinoza suggested, the psychic and bodily dimensions are two expressions of the same reality. For this reason, signals originating from and regulating the inner body are integral to perception, thought, and decision-making processes. Consider, for instance, Antonio Damasio's «somatic marker hypothesis» (Damasio, 1996), or the extensive experimental evidence demonstrating how internal signals influence exteroceptive perception, spontaneous ideation, and the construction of the embodied self (Azzalini *et al.*, 2019). This also explains why bodily disorders often co-occur with mental disorders (challenging the validity of strictly compartmentalized and hyper-specialized nosography and pathophysiology), and why energy deficits and psychomotor alterations frequently emerge as the primary manifestations of psychological distress.

Abnormal predictive processing and *Qi* imbalances in stress and chronic illness

In the predictive brain, as we have seen, prediction errors are resolved either by updating internal models or by adapting behavior. However, when prediction errors persist or are inadequately resolved, they can foster maladaptive patterns associated with chronic illnesses. There are numerous examples of this. In conditions of chronic pain, such as fibromyalgia, the brain may erroneously predict pain sig-

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nals even in the absence of actual nociceptive input; the persistence of these "false alarms" creates a vicious cycle of sensitization and disability (Apkarian *et al.*, 2009; Tabor, Burr, 2019). In depression, predictive models may overweigh negative information, leading to distorted and catastrophic anticipations of failure and harm (Huys *et al.*, 2016; Shaffer *et al.*, 2022). Similarly, anxiety disorders involve models that generate excessive and abnormal predictions of danger, triggering stress responses which are disproportionate to actual threats (Paulus, Stein, 2006, 2010). Beyond neuropsychiatric conditions, metabolic disorders may also arise. Insulin resistance in type 2 diabetes, for instance, can be conceptualized as a discrepancy between predicted and actual energy needs, resulting in disruptions to glucose metabolism (Burdakov, 2019).

We believe that the negative consequences of altered predictive processing bear similarities to the adverse effects associated with *Qi* imbalances. In predictive coding, disruptions in the delicate balance between predictive signals and prediction errors can perpetuate maladaptive internal models, disturb allostasis, and have clinical implications. Similarly, in TCM, *Qi* imbalances – when the harmonious and dynamic flow of energy is stagnant, insufficient, or excessive – disrupt psychophysical balance and adaptation, thereby promoting the development of chronic diseases (Li *et al.*, 2019). This connection is particularly evident in the case of stress, which is understood as the allostatic response to physical or psychological events perceived – whether real or imagined – as threats to the organism's integrity and well-being, being especially impactful in situations marked by uncertainty and lack of control, where reallocating energy resources to update models and predictions becomes essential. Under chronic stress conditions, dysfunctions in the allostatic mediators and the production of allostatic load create a self-reinforcing cycle; similarly, *Qi* imbalances are viewed both as causes and consequences of systemic dysfunctions that lead to chronic illnesses. In the predictive brain, chronic stress can amplify prediction errors by heightening sensitivity to negative feedback and/or by reinforcing rigid, maladaptive predictive models. Likewise, stress is a critical factor in *Qi* imbalances. Emotional tension, irritability, and chronic pain conditions, such as migraines or musculoskeletal disorders, are commonly associated with *Qi* stagnation (Huys *et al.*, 2016). Conditions such as anemia or chronic fatigue syndrome are described in TCM as consequences of *Qi* deficiency (Kaptchuk, 2000). Disorders such as hypertension and inflammatory diseases may arise from an excess of *Qi*, resulting in hyperactivation of bodily systems (Li *et al.*, 2019; Wang *et al.*, 2022). Prediction errors are central to psycho-affective disorders such as depression and anxiety (Shaffer *et al.*, 2022); similarly, *Qi* stagnation is often linked to emotional disturbances, including frustration and sadness (Huys *et al.*, 2016; Kaptchuk, 2000).

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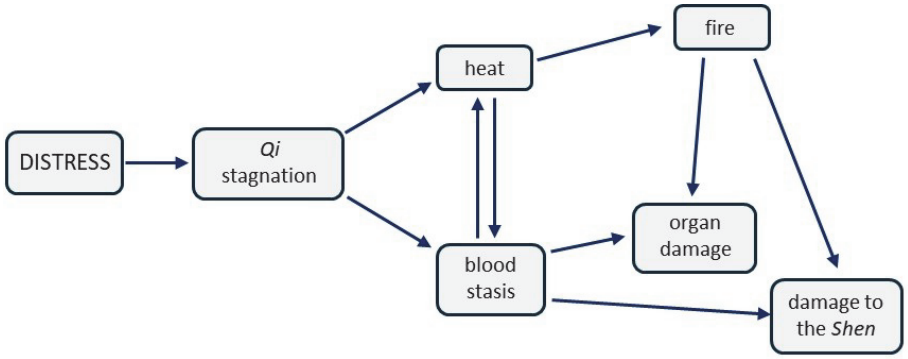

Fig. 2. Negative emotions (distress) in TCM can cause *Qi* stagnation, which in turn leads to blood stagnation (as the blood is no longer moved by *Qi*). This stagnation increases heat, which can transform into fire, causing harm to both the psyche (*shen*) and internal organs. Psychological distress can therefore also lead to biological damage, which in turn exacerbates the distress. This model strongly resonates with current scientific research, which assigns a psychopathogenic role to inflammation (referred to as *heat* or *fire* in ancient Chinese terminology).

In this context, the ancient Chinese medical model provides valuable insights into the integration of the psyche and biological systems in psychiatric disorders. Mood disorders, such as anxiety and depression, exemplify chronic predictive errors, as previously discussed. Psychotherapies like cognitive-behavioral therapy, which focus on helping patients identify and correct faulty thoughts and predictions, can achieve a certain degree of efficacy. However, this framework for understanding psychological suffering overlooks the systemic dimension and the psychopathological impact of biological systems perturbed by the distressed psyche. By contrast, the ancient Chinese model conceptualizes the psychic and biological dimensions as operating in a synergistic relationship – a pathological synergy, as illustrated in Fig. 2. This holistic perspective enables a more accurate understanding of the therapeutic tools required to address both psychological and biological aspects of these conditions.

Towards integration

Both the paradigm of allostasis as explained by predictive brain theories and the concept of *Qi* in TCM highlight the importance of balance and adaptability for human health. Combining these approaches could offer new tools and opportunities to address pathology in an integrated manner, targeting both measurable dysfunctions and subjective experiences (Bottaccioli F., Bottaccioli A.G., 2024a, 2024b). Modern

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healthcare is increasingly challenged by the growing prevalence of chronic illnesses and stress-related disorders. Combined strategies could incorporate pharmacological interventions alongside practices designed to enhance *Qi*, such as acupuncture, Tai Chi, Qi Gong, meditation, and phytotherapy – methods whose efficacy in reducing allostatic load is supported by robust empirical evidence. Moreover, advances in neuroimaging and molecular biology offer promising opportunities to investigate the neurophysiological and epigenetic correlates of these interventions (Kanherkar *et al.*, 2017). Examples of synergy are already emerging. Meditation and mindfulness, deeply rooted in TCM, are increasingly understood through the framework of predictive processing, as practices that recalibrate internal models by improving stress management and enhancing attention (Tang *et al.*, 2015). Similarly, acupuncture serves as a potential bridge between *Qi* and the predictive brain, influencing predictive mechanisms while modulating autonomic regulation and pain perception (Fang *et al.*, 2009; Kong *et al.*, 2009; Napadow *et al.*, 2009; Langevin, Wayne, 2018).

Conclusions

The entirety of our psychic life is founded on affects, thus deeply rooted in the body, and inherently oriented toward preserving vital balance. The human psyche, rising from organism, operates *with* the body, *through* the body, and *for the benefit of* the body. Perhaps it is time to reclaim the etymological meaning of the Greek word "psyche" and reconnect it to "breath", understood in the concreteness of its organic function – a function upon which the preservation of biological life and the fundamental experience of being a living, embodied organism depend. Eastern philosophy and TCM have long emphasized the profound connection between the body and *Qi*, which must remain in harmony to ensure a state of complete well-being. The *Qi* of modern neuroscience appears to reside in the processes of *interoceptive active inference*, i.e. in the interoceptive predictions that, while adaptively regulating bodily states and energy budgets, create the deep affective sense of being alive in a body – which serves as the essential psychological foundation for all other psychic phenomena. We believe that incorporating this knowledge into biomedical education could help bridge the gap between Western and Eastern paradigms, fostering a more patient-centered approach to care (Bottaccioli F., Bottaccioli A.G., 2024a, 2024b).

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The microbiota's funnel effect: How multiple factors independently converge in changing the microbiota

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Abstract: *The science of the microbiota, by revealing the complexity of interactions between the world of microorganisms that colonize us and that of human cells, represents the dawn of a new paradigm in biomedical and psychological sciences. It allows for a more complex yet more promising perspective on human health and disease compared to previous approaches. Scientific literature has now identified specific lifestyle-related factors (nutrition, environmental physical-chemical quality, psychological well-being, etc.) that significantly influence the composition of the microbiota. This paper introduces the concept of the "funnel effect" of the microbiota to describe the convergent and partially independent nature of these factors (nutrition, physical activity, psychological well-being, sleep quality, social support, environmental physical-chemical quality, circadian rhythms) on the composition of the intestinal microbiota, thereby impacting the overall health of the human organism. The "funnel effect" of the microbiota has some highly relevant clinical implications, emphasizing the need for an integrated psycho-neuro-endocrine-immunological approach, in contrast to the highly specialized and molecularly focused approach that is currently widely adopted.*

Key words: *Microbiota, PNEI paradigm, Nutrition, Physical activity, Psychological well-being, Epigenetic.*

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Introduction

At the end of the last century, the massive Human Genome Project aimed to fully map human DNA with the ambition of understanding and potentially solving any human disease. This optimistic expectation stemmed from the theoretical concept of the so-called "central dogma of molecular biology", which posits that a gene (part of the genotype) corresponds to a specific protein (phenotype) and that there can be no informational flow from the phenotype to the genotype – only a unidirectional flow from the gene to the protein structure (Bottaccioli F. & Bottaccioli A.G., 2017; Gottlieb, 2000). Paradoxically, the success of the Human Genome Project in fully sequencing human DNA marked the end of the "central dogma of molecular biology" because it exposed the theoretical inadequacy of this concept considering the data emerging from genetic analysis and the complexity of human bio-psycho-social interactions. A striking example is the fact that a complex organism like a human possesses a genetic heritage of "only" about 25,000 genes, compared to wheat, which has around 150,000, and that the percentage of coding genes is limited to approximately 2% of the entire human genome.

As often happens in the history of science, the partial failure of the ambitious Human Genome Project, on one hand, led to an increasing awareness of the explanatory inadequacy of the "central dogma of molecular biology" in relation to human phenotypic complexity. On the other hand, however, it laid the foundation for two major revolutions – still ongoing – in the scientific landscape. The first revolution concerns epigenetics, the study of factors (both hereditary and non-hereditary) that modify an organism's phenotype without altering the DNA sequence. In other words, it involves studying the flow of information from the environment to the DNA, thereby influencing the expression of the genotype. The second revolution is represented by microbiota science, which examines the trillions of microorganisms (bacteria, fungi, viruses, protozoa) that colonize our bodies.

The effects of microbiota

Thanks to the genetic analysis technologies developed for the Human Genome Project, significant progress has been made in studying the microbiota and understanding the extent to which interactions among its microorganisms affect human cells. This emerging field of study has begun to uncover the astonishing complexity and significant impact of the microorganisms inhabiting our bodies in shaping human health and quality of life. Strengthening this broader perspective – one that includes the microbiota's influence on human bio-psycho-social well-being – there is now substantial evidence showing that the microbial ecosystem colonizing us pro-

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foundly affects complex functions such as nutrient absorption, immune system regulation, and neurodevelopment. It modulates systems like the stress axis and even influences cognitive, emotional, and motivational aspects. The interaction between the microbiota and intestinal permeability plays a particularly crucial role in modulating the immune system and the epigenetic impact on the human host. This makes it a key factor in the development of chronic inflammatory diseases, which have become a true "epidemic" in industrialized countries (Fasano, 2020).

The remarkable influence of the microbiota has shed light on the etiopathogenesis of conditions such as celiac disease, obesity, and ulcerative colitis, as well as psychological disorders, including anxiety, depression, and various psychopathologies such as autism spectrum disorders and schizophrenia (Caio *et al.*, 2019; Cheung *et al.*, 2019; Foster & McVey Neufeld, 2013; Garrett *et al.*, 2007; Li & Zhou, 2016; Mangiola *et al.*, 2016; Rodrigues-Amorim *et al.*, 2018; Sharon *et al.*, 2019; Simpson *et al.*, 2021).

It is important to note that the emergence of the new paradigm, which positions the microbiota as a key player in our health, has been driven precisely by research demonstrating how the microbiota influences neurobehavioral and psychological dimensions – such as anxious or depressive states, sociality, and risk perception (Allen *et al.*, 2017; Ann *et al.*, 2024; Bercik *et al.*, 2011; Bravo *et al.*, 2011; Carloni *et al.*, 2021; Chen *et al.*, 2019; Cheung *et al.*, 2019; Cryan & Dinan, 2012; Cryan & OMahony, 2011; De Palma *et al.*, 2015; Farmer, Randall & Aziz, 2014; Koenig *et al.*, 2011; Ottman *et al.*, 2012; Wu *et al.*, 2021) and how certain phenotypic characteristics of these dimensions can even be transferred from one organism to another through the so-called «microbiota transplantation» (Chinna Meyyappan *et al.*, 2020; Collins *et al.*, 2013; Cryan & Dinan, 2012; Kelly *et al.*, 2016).

It has long been known that the mind can influence intestinal well-being (also because this is intuitively evident from an experiential perspective), but the study of the microbiota has also demonstrated the existence of the opposite causal direction, in which intestinal microorganisms exert an effect on psychosocial dynamics.

The significant impact of the microbiota on the human organism includes endocrine and immunological dynamics, as well as neural and psychological ones, thus affecting the entire complexity of human bio-psycho-social interactions. This is one of the reasons why it would be more appropriate to refer to the "microbiota-gut-brain-mind axis" rather than the reductive, yet widely used, term "microbiota-gut-brain axis", which erroneously considers the mind and brain to be entirely coincident (Agnoletti, 2023a).

The impact of microbiota interaction on human cells is remarkable, considering that the total mass of bacteria alone is estimated to be between 0.2 kg and 1 kg (70% of which are located in the gut), the number of bacteria is estimated to be equal to or greater than that of human cells, and most importantly, the genetic content of bacte-

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ria alone is approximately 100 to 1.000 times greater than that of humans (Sender, Fuchs & Milo, 2016a; Sender, Fuchs & Milo, 2016b).

Given the symbiotic relationship between microbiota and human cells, the microbiome – the collective genetic heritage of the microorganisms that make up the microbiota – represents a variable component of the human genome. In fact, due to its significantly larger genetic contribution compared to the human genome, the microbiota plays a crucial epigenetic role in relation to human cells, making it fundamental in determining human well-being, health, and longevity (Chang *et al.*, 2014; Claesson *et al.*, 2012; Cornuti *et al.*, 2013; Dalile *et al.*, 2019; Kumar *et al.*, 2014; López-Otín *et al.*, 2013; Ottaviani, 2011).

Understanding epigenetic dynamics is essential to grasp the complex interaction between the microbiota and human cells because studying the factors that influence genetic expression allows us to conceptualize the entire microbiota ecosystem as an extra-genetic factor ("extra" in relation to human DNA) that further extends the adaptive capacity of human cells. The additional genetic contribution of the microbiota enables the human holobiont organism (represented by the collaboration between human cells and microorganisms) to adapt more effectively to different environmental conditions, providing clear evolutionary advantages (Agnoletti, 2023b; Gasbarrini, Dionisi & Gasbarrini, 2019; Fasano, 2022). The nature of the genetic contribution of the microbiota represents the greatest factor of interindividual diversity. In fact, while human interindividual genetic heritage is approximately 99,9% identical, the genetic diversity of the microbiota between two individuals can reach as high as 80-90% (Gasbarrini, Dionisi & Gasbarrini, 2019).

The genetic diversity of the microbiota is primarily determined by environmental factors and only marginally by the host's human genetics (Rothschild *et al.*, 2018). Therefore, we can assert that almost the entire contribution of the microbiota to human cells is due to environmental factors rather than human genetic content. Human fitness is thus highly dependent on the epigenetic role of the microbiota, as it significantly expands the body's ability to adapt to variable contexts, such as the food we eat, the physical activity we engage in, the physicochemical quality of the environments we frequent, and the psychosocial stress we experience. Despite these variations, the microbiota still ensures the homeostasis of key physiological systems, including blood pressure, heart rate, blood volume, hydration, pH, bone density, and more.

For the purposes of this discussion, it is important to note that the currently available literature has clearly demonstrated that factors such as:

- Nutrition (Putignani & Dallapiccola, 2016; Valitutti, Cucchiara & Fasano, 2019; Zhang & Zuo, 2018),
- Physical activity (Allen *et al.*, 2018; Aragón-Vela *et al.*, 2021; Mohr *et al.*, 2020),
- Sleep quality (Neroni *et al.*, 2021; Sen *et al.*, 2021; Smith *et al.*, 2019),

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- Circadian rhythms (Bermingham *et al.*, 2023; Thaiss *et al.*, 2014; Voigt *et al.*, 2016),
- Physicochemical environmental quality (De Filippis *et al.*, 2024; Estevinho *et al.*, 2024; Mousavi *et al.*, 2022),
- Perceived social support (Cryan *et al.*, 2019; Kim *et al.*, 2021; Winter *et al.*, 2018),
- Psychological well-being (Chang *et al.*, 2024; Ge *et al.*, 2022; Ilchmann-Diounou & Ménard, 2020), influence the composition of the microbiota, thereby modifying its adaptive contribution – both epigenetic and non-epigenetic – to the entire organism, ultimately affecting human health and quality of life. For the purposes of this discussion, it is particularly interesting to note that the currently available scientific literature does not highlight the dominance of one factor over the others in influencing the microbiota. Instead, it describes a dose-dependent quantitative effect for each of them.

All the factors considered influence one another to some extent (for instance, physical activity affects sleep quality, and circadian rhythms impact the metabolic effects of nutrition). However, each factor also maintains a certain degree of autonomy from the others due to its unique causal mechanism in shaping the microbiota. For example, the management of psychological stress and the physicochemical environmental quality are both factors that influence the microbiota, but they do so at least partially independently of each other, as they follow different causal pathways. The "sensitivity" of the microbiota to multiple factors is thus somewhat independent of the specific nature of the influencing factor itself. In other words, whether it is nutrition, psychological well-being, or physical activity, there will always be an impact on the composition of the microbiota. For instance, dysbiosis may initially stem from a nutritional deficiency, a psychological trauma, or excessive sedentary behavior, even though the causal dynamics linking nutrition, psychological states, and physical activity to the microbiota are at least partially independent of one another.

The fact that various factors converge in modifying the microbiota does not mean that their impact is the same in terms of intensity or frequency. Naturally, the causal pathway resulting from chronic sleep deprivation has a different impact on the microbiota compared to, for example, a single mild exposure to pesticides.

The funnel effect

Considering the diversity and partial independence of the different factors that influence the microbiota, it is equally interesting to highlight the common convergence in modifying the composition of this complex ecosystem that colonizes our body.

For these reasons, the authors propose the concept of the "microbiota funnel effect" to describe the characteristic convergence of the seven main factors identified in the scientific literature (nutrition, physical activity, psychological, sleep-related, so-

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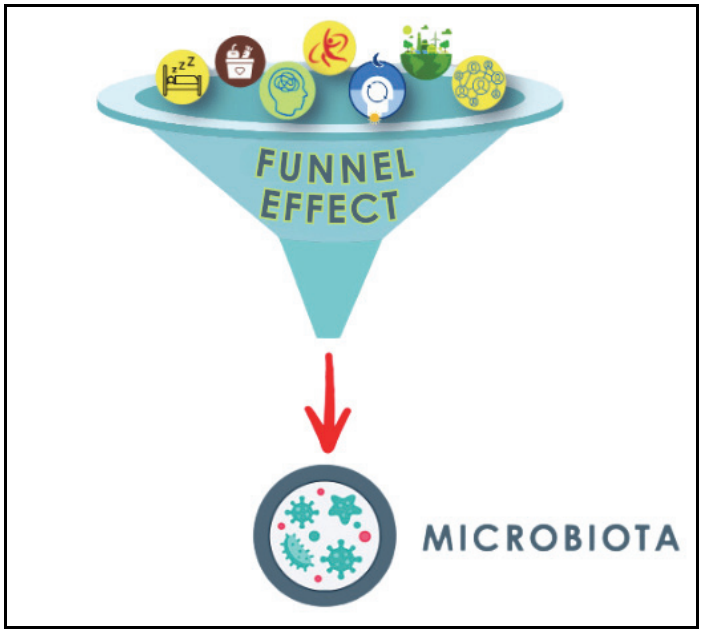
cial, environmental, and circadian), which, in a partially independent manner, contribute to altering the composition of the gut microbiota (see Figure 1).

Fig. 1. The Microbiota's Funnel Effect



The common convergence of the seven lifestyle-related factors on the microbiota has significant implications for peoples well-being and health, highlighting the need for a systemic and holistic approach to promoting well-being and treating suboptimal and pathological conditions.

From a clinical perspective, the "microbiota funnel effect" asserts that, given the high psycho-neuro-endocrine-immunological integration of the considered factors and the significant epigenetic impact of the microbiota on human cell function, the only way to ensure an effective clinical intervention is to adopt a systemic vision that includes a comprehensive evaluation of all factors. Continuing to use a specialist approach that analyses and treats only one (or even some, but not all) of these factors by decontextualizing it from the others is equivalent to adopting a reductionist perspective. This reductionistic approach, by failing to account for the convergent and partially independent nature described by the "microbiota funnel effect", proves to be clinically ineffective, particularly in addressing chronic conditions.

The concept of the "microbiota funnel effect" calls for a radical shift in clinical protocols, as it necessitates at least an initial comprehensive (but not generic) as-

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sessment of the individual factors involved and the patient's gut health (which includes the general state of the microbiota). For any professional whose goal is to enhance human health and well-being, the "microbiota funnel effect" represents a new paradigm that demonstrates the clinical necessity of a truly integrated, holistic, and scientific approach – essential for addressing complex issues involving the microbiota.

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Carbohydrate malabsorption and non-celiac gluten/wheat Sensitivity: The role of probiotic biomodulation

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Abstract: *In recent years, cases of food hypersensitivity reactions in the Western population have significantly increased, with over 50% of patients with functional gastrointestinal disorders (FGID) believing that food triggers their symptoms. The main culprits include FODMAPs (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols) and specific protein components of wheat, such as gluten and amylase/trypsin inhibitors (ATIs).*

Gastrointestinal symptoms related to carbohydrate malabsorption stem from two primary mechanisms. First, unabsorbed carbohydrates can feed certain gut bacteria, leading to fermentative dysbiosis and gas production, which causes bloating and abdominal distension. Second, a diet rich in unabsorbed sugars draws water into the intestinal lumen, accelerating transit and resulting in diarrhea.

Adverse reactions to gluten include celiac disease, wheat allergy, and non-celiac gluten/wheat sensitivity (NCGS/WS). The latter triggers both intestinal and extra-intestinal symptoms, which improve upon gluten withdrawal. Recent studies suggest that, in addition to gluten, other wheat components, such as ATIs and FODMAPs, can contribute to symptom exacerbation. NCGS/WS is associated with intestinal dysbiosis and immune alterations. Although a gluten-free diet is currently considered the only available therapeutic strategy, it may negatively impact gut microbiota and the bioavailability of minerals and vitamins.

Recent research suggests the use of strain-specific probiotics to improve fermentative dysbiosis, reducing gas-producing species and enhancing the digestion and absorption of carbohydrates, gluten proteins, and micronutrients. In conclusion, an integrated approach combining a low-FODMAP diet (LFD) with specific probiotics could be an effective strate-

gy for managing carbohydrate malabsorption symptoms in FGID, restoring intestinal homeostasis, and counteracting associated microbial hyperfermentation.

***Key words**: Carbohydrate Malabsorption, low FODMAP diet, Non-Celiac Gluten/Wheat Sensitivity, Micronutrient malabsorption, Microbiota, Probiotics.*

Microbiota and carbohydrate malabsorption

It is now well known that in a typical Western diet, carbohydrates represent a vital source of energy but, in certain individuals, can pose ongoing challenges in terms of digestion and absorption. Among various dietary factors, the quality of carbohydrates – considering their nature, sugar content, and dietary fiber – has been widely regarded as a potential modulator of the risk of non-communicable chronic diseases (NCDs). Recent systematic reviews of randomized clinical trials (RCTs) and prospective observational studies conducted on adults have found that higher consumption of whole grains, vegetables, and fruits is associated with a reduced risk of NCDs and related mortality.

The World Health Organization (WHO) recommends that carbohydrate intake should primarily come from whole grains, vegetables, fruits, and legumes, with an adult daily intake of at least 400 g/day of vegetables and fruits and 25–35 g/day of dietary fiber. For children, the recommendation includes fruit and vegetable intake ranging from 250 to 400 g/day and fiber intake between 15 and 25 g/day (*Carbohydrate Intake for Adults and Children*, s.d.).

Despite the necessity for regular and consistent intake of adequate amounts of carbohydrates in the diet, they are often reported by patients as potential causes of adverse food reactions. Over the past two decades, cases of adverse food reactions have risen significantly, with 40% to 84% of patients with functional gastrointestinal disorders (FGIDs), particularly those with irritable bowel syndrome (IBS), identifying foods as significant triggers for their symptoms. Carbohydrates are implicated as a source of symptoms in 70% of patients, and gluten-based products are identified as culprits by approximately one in four patients (Makharia *et al.*, 2018).

A recent literature review indicates that, for many patients, in addition to gluten, FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) – particularly lactose – can contribute to bloating and/or abdominal distension associated with pain and alterations in intestinal transit as a consequence of maldigestion and malabsorption (Zingone *et al.*, 2023).

It is believed that the gastrointestinal symptoms of carbohydrate malabsorption are primarily caused by two factors. First, when carbohydrates are not properly

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broken down and absorbed, they may act as fuel for gut bacteria, contributing to fermentative dysbiosis with excessive production of hydrogen, methane, and carbon dioxide, which are responsible for bloating and/or abdominal distension. Second, a diet rich in unabsorbed sugars attracts significant amounts of water, increasing the osmotic load, leading to accelerated transit of the food bolus and diarrhea.

These reactions significantly compromise patients' quality of life and necessitate long-term dietary restrictions. While these restrictions can improve clinical and symptomatic profiles, they expose patients to alterations in gut microbiota biodiversity and the malabsorption of micronutrients (Omer & Quigley E.M.M., 2018).

FODMAPs are short-chain carbohydrates that include lactose, fructose, polyols (sorbitol and mannitol), fructans, galacto-oligosaccharides, stachyose, raffinose and verbascose (RFO) naturally present in a wide range of foods, including fruits, vegetables, cereals, legumes, dairy products, and both natural and artificial sweeteners (Ispiryan *et al.*, 2022).

These molecules are poorly absorbed in the small intestine due to a slow transport mechanism or an ineffective or reduced enzymatic activity. Once ingested, they remain partially undigested in the intestinal lumen, particularly in the colon, where, after fermentation by the gut microbiota, they release gases and attract water through osmotic effects. This process, in predisposed individuals, leads to the onset of bloating and/or abdominal distension, visceral hypersensitivity, abdominal pain, and alterations in transit, particularly diarrhea.

A dietary restriction of FODMAPs can improve symptoms in a large number of patients with irritable bowel syndrome (IBS), and several controlled clinical trials have demonstrated the superiority of the Low-FODMAP Diet (LFD) compared to control diets in IBS patients. The most significant effects of the diet include improvements in bloating and abdominal pain, as well as normalization of bowel habits, with both diarrhea and constipation associated with IBS regressing (Algera *et al.*, 2022; Carbone *et al.*, 2022; Halmos *et al.*, 2014; Holtmann *et al.*, 2017).

Despite the numerous clinical and symptomatic benefits, the Low-FODMAP Diet is not without medium to long-term consequences. In recent years, several authors have investigated the nutritional adequacy of the LFD. Fiber deficiencies are the most common, caused by a reduction in the intake of plant-based foods. Furthermore, calcium intake has been found to be lower when dairy products are excessively excluded. Regarding vitamin intake, the risk of deficiencies is linked to a strict reduction in vegetable and fruit consumption in the diet (Carbone *et al.*, 2022; Sultan *et al.*, 2022; Whelan *et al.*, 2018).

Another highly significant aspect is that the LFD induces alterations in gut microbiota biodiversity, with a significant reduction in the Bifidobacterium genus,

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which is widely considered in the scientific literature as a marker of general eubiosis in the intestinal microbial ecosystem (Rinninella *et al.*, 2019; van Lanen *et al.*, 2021).

Lactose intolerance (LI) is among the most common disaccharidase deficiencies (lactase, sucrase, and maltase). It presents as a clinical syndrome characterized by specific signs and symptoms, including abdominal pain, bloating, and diarrhea triggered by the consumption of this sugar in individuals with lactose malabsorption (LM).

Normally, lactose, a disaccharide, is broken down into glucose and galactose by the enzyme lactase, located on the brush border of the small intestine. Lactase deficiency is common in healthy individuals, resulting in malabsorption when consuming milk or lactose-containing foods, and it can arise from various causes.

The most prevalent cause is "primary lactase deficiency" or "lactase non-persistence", characterized by a gradual decline in lactase enzyme activity with age (Bayless *et al.*, 2017). In addition to this form of hypolactasia, lactose intolerance may also result from "secondary lactase deficiency", caused by conditions such as gastroenteritis, chemotherapy, antibiotic use, celiac disease, inflammatory bowel disease, malnutrition, or conditions that reduce the absorptive surface, such as short bowel syndrome. Lactase deficiency, or hypolactasia, leads to lactose fermentation by the gut microbiota (fermentative dysbiosis), resulting in abdominal discomfort and diarrhea, the latter caused by the osmotic effects of lactose, glucose, and galactose in the colonic lumen (Deng *et al.*, 2015).

Although carbohydrates are a fundamental component of the human diet, providing a vital energy source alongside proteins and fats, studies have shown that certain individuals with fermentative dysbiosis are unable to adequately metabolize them, leading to the onset of gastrointestinal symptoms associated with malabsorption. Nutritional treatment is undoubtedly one of the indisputable aids capable of improving the clinical condition of patients, but dietary modification exposes these individuals to further alterations in microbiota biodiversity and potential nutritional deficiencies.

Recent studies have shown that the integration of probiotic bacteria, depending on their strain-specific actions, can be considered an important aid in modifying microbiota imbalances. This, in turn, contributes to the metabolism of carbohydrates such as fructans and lactose and enhances the bioaccessibility of micronutrients (Markowiak & Śliżewska, 2017).

Certain strain-specific probiotics, due to their biomodulatory capacity on the intestinal microbial ecosystem, can improve the state of hyperfermentative dysbiosis by reducing gas-producing species responsible for the clinical picture typical of carbohydrate malabsorption. Additionally, probiotics may mitigate the adverse effects of the Low-FODMAP Diet by promoting the absorption of micronutrients in

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the intestine, thanks to increased bioaccessibility of vitamins and minerals (Barkhidarian *et al.*, 2021).

The beneficial action of probiotics, particularly species belonging to the genus Lactobacillus, has been demonstrated through the genomic presence of gene loci responsible for lactose digestion and their actual production of beta-galactosidase, specific enzymes for the breakdown of this disaccharide (Ahn *et al.*, 2023).

Microbiota and non-celiac gluten/wheat sensitivity (NCGS/WS)

A specific category of food hypersensitivity is represented by disorders related to gluten ingestion, including celiac disease, wheat allergy, gluten ataxia, and non-celiac gluten/wheat sensitivity (NCGS/WS). Non-celiac gluten/wheat sensitivity (NCGS/WS) is a clinical condition characterized by intestinal and extra-intestinal symptoms triggered by gluten ingestion in the absence of wheat allergy (WA) or celiac disease (CD) (Calabriso *et al.*, 2022).

From a symptomatic perspective, individuals with this condition report intestinal disturbances such as transit alterations (constipation, diarrhea, or alternating bowel habits) associated with abdominal bloating. Many patients also describe sensations of postprandial fullness, gastroesophageal reflux, nausea, and extra-intestinal symptoms such as migraines, mood disturbances, anxiety and/or depression, as well as musculoskeletal manifestations. The clinical-symptomatic picture tends to improve upon gluten withdrawal from the diet and recurs following re-challenge (Caio G. *et al.*, 2020).

Gluten consists of a group of proteins, primarily prolamins and glutelins, found in cereals such as wheat (gliadins and glutenins), rye (secalins), and barley (hordeins). The abundance of glutamine and proline residues in gluten proteins reduces their degradation by human intestinal proteases, limiting their digestibility (Bascuñán *et al.*, 2020; Caio G. *et al.*, 2019).

In addition to gluten proteins, other wheat components have been associated with symptom onset, including alpha-amylase/trypsin inhibitors (ATIs), substances present in cereals as a defense mechanism against pathogens. Recent studies have demonstrated that ATIs exert an indirect effect on the human body by inhibiting the activity of gastrointestinal digestive enzymes and acting as anti-nutritional compounds capable of altering intestinal homeostasis and reducing the bioavailability of various micronutrients (Geisslitz *et al.*, 2021).

In sensitive individuals, these proteins can cause immune dysregulation. It has been demonstrated that gluten interacts with the intestinal epithelium through the CXC Motif Chemokine Receptor 3 (CXCR3), inducing the release of zonulin by en-

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terocytes and allowing the passage of molecules from the intestinal epithelium into the *lamina propria*. Here, wheat proteins activate the innate immune system through Toll-like receptors (TLRs), particularly TLR-2 and TLR-4, inducing the release of pro-inflammatory cytokines.

Recently, in addition to gluten and ATIs, some authors have demonstrated a potential role of FODMAPs in the onset of symptoms reported by patients with NCGS/WS. Specifically, a randomized, double-blind, placebo-controlled study was conducted on 59 patients with NCGS/WS who reported gastrointestinal symptoms following gluten ingestion and were excluded from a diagnosis of celiac disease.

Patients were divided into three groups: the first group consumed 5.7 g of gluten daily for 7 days, the second group consumed 2.1 g of fructans daily, and the third group received a placebo for 7 days. After seven days of diet, patients in each group underwent a seven-day washout period until symptom resolution, followed by crossover to the next group until completing all trials (gluten, fructans, and placebo).

The study results showed that patients who consumed fructans experienced more gastrointestinal symptoms than those who consumed gluten or placebo. Specifically, fructan consumption led to a greater occurrence of abdominal pain, bloating, and bowel transit alterations, both constipative and diarrheal, compared to gluten and placebo, in a statistically significant manner (Skodje *et al.*, 2018).

Recent scientific evidence also suggests an important role of the gut microbiota in regulating innate immune responses in patients with NCGS/WS. It has been shown that the composition of the gut microbiota differs significantly in NCGS/WS individuals compared to healthy subjects, highlighting a state of marked intestinal dysbiosis.

The altered microbiota biodiversity is associated with increased expression of the TLR-2 receptor compared to healthy subjects. In NCGS/WS patients, intestinal dysbiosis correlates with significantly elevated serum levels of lipopolysaccharide-binding protein (LBP) and TLR-2, due to systemic immunity activation by the microbiota (Barbaro *et al.*, 2020; Dieterich *et al.*, 2019).

Currently, a gluten-free (GF) diet is considered the only effective treatment for patients with NCGS/WS. Although gluten exclusion significantly improves the clinical-symptomatic picture, this approach does not always guarantee complete symptom resolution due to patient compliance challenges and the risk of accidental gluten contamination.

Moreover, recent studies show that, in the medium to long term, the GF diet may negatively affect the biodiversity and richness of the intestinal microbiota, reducing beneficial species belonging to the genera *Lactobacillus, Bifidobacterium*, and *Faecalibacterium*, while favoring the growth of pro-inflammatory bacterial species from the *Enterobacteriaceae* family (Caio G. *et al.*, 2020). This can disrupt the intestinal microbial ecosystem, compromising intestinal homeostasis.

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As discussed, research has highlighted a state of intestinal dysbiosis in patients with NCGS/WS, exacerbated by the GF diet, despite its necessity for improving clinical symptoms. Evidence suggests that dysbiosis is linked to the reduced digestibility of wheat proteins, resulting in immune dysregulation and compromised intestinal barrier integrity.

This alteration of intestinal homeostasis, along with the GF diet, is responsible for the malabsorption of specific micronutrients, such as calcium (Ca), iron (Fe), magnesium (Mg), selenium (Se), potassium (K), copper (Cu), zinc (Zn), and vitamins (Skrypnik & Suliburska, 2018; Weyh *et al.*, 2022).

The role of probiotics in the malabsorption of carbohydrates and micronutrients

The growing body of scientific research in this field has demonstrated that strain-specific probiotic supplementation can promote intestinal homeostasis in these patients, primarily by countering intestinal dysbiosis and encouraging the colonization of beneficial bacterial species.

The continuous advancements in scientific research and the increased sensitivity of investigative techniques available today are enabling significant progress in understanding the functions performed by the intestinal microbiota and the role of probiotics in its modulation. This includes both compositional characteristics and the diverse metabolic activities attributed to it.

In recent years, the clinical application of probiotics has been garnering increasing interest within the scientific community to harness their potential molecular strategies. These aim to promote health-associated phenotypes and modulate disease-associated phenotypes. Probiotics are, in fact, regarded as microorganisms capable of contributing to the promotion of human health.

The Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO) define probiotics as «live microorganisms which, when administered in adequate amounts, confer a health benefit on the host» (Hill *et al.*, 2014).

Numerous studies conducted both in vitro and in vivo, particularly using murine models, have identified specific molecular mechanisms that allow probiotic bacterial strains to exert their beneficial effects. These bacteria can secrete a vast number of molecules into the intestinal environment, acting as specific effectors in a complex interplay among the intestinal microbial ecosystem, immune cells, and intestinal epithelial cells.

Probiotic-derived effector molecules released into the intestinal lumen interact primarily with ecosystem components through cross-feeding interactions, altera-

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tions of micro-environmental factors (e.g., pH modulation), competition for epithelial binding sites, and inhibition of pathogenic growth via the production of strain-specific antibacterial compounds. Probiotics also compete continuously for available nutrients within the intestinal environment (Lebeer *et al.*, 2010; Neeser *et al.*, 2000; Schiffrin & Blum, 2002; Verstrepen *et al.*, 2008).

Certain probiotic bacteria, thanks to their strain-specific modes of action, can synthesize specific enzymes (peptidases) targeting wheat proteins. They also exhibit antioxidant properties and contribute to the structural repair of intestinal villi.

Lactobacillus fermentum has demonstrated the ability to mitigate the damage associated with gluten ingestion by degrading gliadin peptides, thereby reducing their immunogenicity and structural damage to intestinal villi (Caminero *et al.*, 2019). Specifically, *Lactobacillus fermentum* has proven to be an effective probiotic in managing issues related to gluten ingestion, such as NCGS/WS, due to its ability to synthesize an x-prolyl dipeptidyl peptidase, known as PepX, with proteolytic activity specific to gluten proteins, particularly gliadin (Heydari *et al.*, 2023).

Furthermore, other studies have shown that *Lactobacillus fermentum* can degrade ATIs, significantly reducing their concentration by over 80% and consequently improving inflammatory parameters and intestinal epithelial damage caused by wheat ingestion (Caminero *et al.*, 2019).

As already emphasized, both individuals with carbohydrate malabsorption (FODMAP and lactose) and those with NCGS/WS often exhibit a pattern of micronutrient malabsorption, essential for their structural role and the many metabolic functions they perform. This deficiency is associated with several factors, including the dysbiotic and inflammatory state of the intestines, which causes an alteration of the intestinal epithelium, as well as adherence to dietary regimens that deprive them of essential food components.

Micronutrients play a crucial catalytic role for hormones, enzymes, and other bioactive components. They are directly linked to the proper functioning of the immune system, and their inadequate absorption influences susceptibility to infections and the development of chronic diseases such as neurodegenerative diseases, osteoporosis, and endocrine-metabolic diseases, including diabetes and thyroid disorders (Nath *et al.*, 2018; Steinbrenner *et al.*, 2022).

Research indicates that the level of minerals in the human body is primarily linked to their dietary intake. At the same time, the human body's functioning is tied not only to the quantity of minerals but also to their proportion and the percentage of absorption.

Recent studies show the direct involvement of the intestinal microbiota in mineral absorption through specific mechanisms that involve the complex interactions between microorganisms, minerals, and host cells (Peredo-Lovillo *et al.*, 2020). As

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demonstrated by recent scientific evidence, an alteration in the biodiversity of the intestinal microbiota significantly impairs mineral absorption with systemic repercussions (Nath *et al.*, 2018).

Targeted probiotic supplementation may represent a complementary approach to addressing mineral deficiencies in individuals with poor intake or reduced absorption, as happens with a GF or LFD diet, or in other conditions such as gastroenteritis, colon diverticulosis, and gastrointestinal resections. Additionally, recent studies have shown that micronutrient malabsorption can also result from long-term pharmacological treatments (Karadima *et al.*, 2016).

Probiotics may offer a complementary approach to addressing mineral deficiencies in individuals with poor intake or absorption of minerals. By increasing the absorption and utilization of minerals, probiotics can counteract these deficiencies, which can have significant health implications. For example, probiotics have been considered for their potential role in improving the absorption of various minerals such as Ca, Se, Zn, Mg, and K. Adequate mineral absorption, especially Ca and Mg, is essential for maintaining optimal bone health to prevent conditions such as osteoporosis (Morato-Martínez *et al.*, 2020).

Probiotic bacteria, depending on their strain-specific action, are involved in mineral metabolism, improving absorption through specific mechanisms. It is important to note that the effects of probiotics on mineral absorption may vary due to many factors, including the specific probiotic strain, the dose and duration of probiotic supplementation, the presence of other nutrients or food components, and individual differences in intestinal microbiota (Bielik & Kolisek, 2021).

Specific probiotic bacteria, belonging to the Lactobacillus genus, can interact with minerals by producing enzymes capable of breaking down complex minerals, thereby making them more accessible for absorption by the host. These probiotic bacteria are among the major producers of phytase, a specific enzyme that our body cannot produce and is necessary for breaking down phytic acid, a compound present in many plant-based foods that can bind to minerals and prevent their absorption. By breaking down phytic acid, these probiotic bacteria can release minerals such as Fe, Ca, Mg, and Zn, making them available for absorption in the small intestine (Priyodip *et al.*, 2017; Scholz-Ahrens *et al.*, 2007; Zhou D. *et al.*, 2021).

Another potential mechanism by which probiotics can influence the bioavailability of minerals is the production of various metabolites resulting from probiotic fermentation of undigested carbohydrates. Among these are short-chain fatty acids (SCFAs: acetic acid, propionic acid, and butyric acid), which promote the solubility of minerals and improve the integrity of the intestinal epithelium.

Among the micronutrients crucial for human well-being, iron is certainly one of the most important. It is involved in oxygen transport, mitochondrial respiration,

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intermediary and xenobiotic metabolism, and cell growth and differentiation. However, today, iron malabsorption in the intestines is one of the most common nutritional problems, leading to an increased risk of iron deficiency in the human body. Iron deficiency is the leading cause of iron deficiency anemia and is associated with dysregulation of the host's immune response (Yilmaz & Li H., 2018). Several scientific studies have demonstrated how strain-specific probiotic supplementation can favor the intestinal luminal absorption of this micronutrient (Dje Kouadio *et al.*, 2024; González *et al.*, 2017; Zakrzewska *et al.*, 2022). In particular, metabolomic analysis of *Lactobacillus fermentum* has shown that it is a microorganism that produces hydroxyphenyl-lactic acid (HPLA), a bioactive metabolite with recognized antioxidant properties and an ability to increase the bioavailability of iron at the intestinal level.

In this regard, a recent study demonstrated that HPLA can promote the luminal intestinal absorption of iron. The mechanism through which HPLA acts is characterized by the reduction of Fe3+, the form typically found in food, into Fe2+, which is more bioavailable. Researchers have shown that hydroxyphenyl-lactic acid in the intestines performs an action similar to that of duodenal cytochrome B (DcytB), a human-origin protein that helps iron enter enterocytes in its reduced form through specific channels (Varvara & Vodnar, 2024).

Some probiotic bacteria can promote the increase of bioaccessibility for other minerals. In particular, the production of SCFAs can influence the absorption of minerals like Ca, improving the architecture of intestinal villi and thus increasing their absorptive surface area. SCFAs can also enhance the metabolism of this trace mineral by increasing the expression of calcium-binding proteins and its paracellular transport. Likewise, a high level of SCFAs can reduce the pH of the cecum and colon, improving mineral solubility. The reduction in pH leads to the dissolution of minerals and the easy release of Ca ions toward epithelial cells via the paracellular route, making it bioavailable for essential metabolic functions, such as the regulation of bone mineral density (Barkhidarian *et al.*, 2021; Beggs *et al.*, 2022; Li C. *et al.*, 2021; Zhou J. *et al.*, 2023). Studies have shown that some probiotics can improve the bioaccessibility and absorption of zinc (Zn). Specific probiotic bacterial strains can modulate the expression of specific proteins involved in its transport across the intestinal wall and contribute to the production of SCFAs, which, by reducing the intestinal pH, promote its solubility. Finally, the bioaccessibility of Zn can also be improved by biotransforming its inorganic form into an organic one, facilitating luminal intestinal absorption and thereby increasing serum levels, as recently demonstrated by researchers using Lactobacillus fermentum (Mohan *et al.*, 2018).

The mechanisms through which probiotics influence magnesium (Mg) absorption, actually, are not fully understood. Possible mechanisms of action may, as with

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other micronutrients already discussed, relate to bacterial production of SCFAs that, by reducing intestinal pH, increase solubility. Some studies suggest that probiotics may improve the expression and activity of specific transport proteins, leading to increased Mg absorption. Finally, probiotics can favor the regulation of tight junction (TJ) proteins, thereby influencing the movement of magnesium ions and other micronutrients across the intestinal epithelium (Chamniansawat *et al.*, 2023; Tribst *et al.*, 2019).

Another trace element whose bioavailability can be influenced by an alteration in intestinal homeostasis (dysbiosis) is selenium (Se). This micronutrient is crucial for the function of certain enzymes called selenoproteins, such as glutathione peroxidase, iodothyronine deiodinase, and thioredoxin reductase, which are recognized for their important metabolic functions. These enzymes exert antioxidant action, capable of reducing the toxic effects of free radicals, decreasing cell death by apoptosis, and modulating thyroid function by contributing to the synthesis of thyroglobulin (TG) and thyroid hormones (T4, T3) (Bielik & Kolisek, 2021; Winther *et al.*, 2020).

As mentioned, the intestinal microbiota can influence selenium metabolism due to the overexpression of its own "selenoproteins". The bacterial species constituting our intestinal microbiota possess a variable number of selenoproteins that they use to ensure their optimal growth. Therefore, the intestinal microbiota, depending on its characteristic composition, can significantly influence the bioavailability of selenium for our organs and tissues.

Recently, some studies have demonstrated that the intestinal microbiota can influence the bioaccessibility, absorption, storage, and utilization of selenium by our cells, affecting the expression of SELP, the selenium transport protein. In conditions of altered microbiota biodiversity and chronic intestinal mucosal inflammation, SELP can undergo progressive down-regulation, preventing adequate absorption and transport of this trace element (Kasaikina *et al.*, 2011; Ramírez-Acosta *et al.*, 2022; Skalny *et al.*, 2025).

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Research

Psycho-Neuro-Endocrine-Immunology and Vestibular Disorders: A prospective study

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Abstract: *Psycho-Neuro-Endocrine-Immunology (PNEI) is a scientific field of study that investigates the link between the bidirectional communication between the nervous, endocrine and immune systems and the correlation of this interaction with physical health. The innovative medical approach of PNEI represents a "paradigm shift" from a "compartmentalized" – strictly biomedical and largely pharmacology-focused – view of health and disease, to a more multi-systemic view, which relies on the integration of interdisciplinary approaches. The key element of the PNEI approach is the concept of a bidirectional dialogue between the psycho-neuro-endocrine and immune systems. In this manuscript, the PNEI hypothesis is considered in application to various*

peripheral and central vestibular disorders. Overall, this study offers an overview of holistic approaches in the treatment of patients with vestibular disorders.

***Keywords**: Balance disorders, vestibular problems, PNEI, hormones, vestibular pathologies – peripheral or central, stress.*

Abbreviations
ACH – Acetylcholine
BVD – Bilateral Vestibular Deafferentation
CGRP – Calcitonin Gene-Related Peptide
fMRI – Functional Magnetic Resonance Imaging
GR – Glucocorticoid Receptors
HPA – Hypothalamic-Pituitary-Adrenal Axis
GCs – Glucocorticoids
MdDS – Debarkation Syndrome or Mal de Débarquement
MD – Ménière's syndrome
MI – Migraine
MR – Mineralocorticoid Receptors
MVN – Medial Vestibular Nucleus
NK – "Natural Killer" cells
PNEI – Psycho-Neuro-Endocrine-Immunology
PPPD – Persistent Postural-Perceptual Syndrome
TVS – Trigeminal Vascular System
UL – Unilateral labyrinthectomy
UVD – Unilateral Vestibular Deafferentation
UVN – Unilateral Vestibular Neurectomy
VC – Vestibular Compensation
VID – Visually Induced Dizziness/Vertigo
VM – Vestibular Migraine

Introduction

The Psycho-Neuro-Endocrine-Immunology (PNEI) is a new theory that studies the bidirectional communication between the nervous system, the endocrine system, the immune system and the psyche (Demori *et al.*, 1975). The dynamic dialogue between these systems results in an overall influence on a patient's health. Scientific evidence suggests that hormones may be involved in vestibular pathophysiology, particularly in peripheral vestibular disorders (Demori *et al.*, 1975). Specifically, steroid, amine and peptide hormones are all implicated in influencing the peripheral vestibular system. For

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example, vasopressin hypersensitivity of the endolymphatic sac is linked to Ménière's syndrome (MD). In addition, modulation of central vestibular pathways by neuroactive steroids may involve effects on the g-aminobutric acid and glutaminergic pathways. The vestibular nuclei also express enzymes that are important in the synthesis of steroids and the modulation of their activities (Seemungal *et al.*, 2001). Steroids mediate stress with both deleterious and beneficial vestibular compensations. This article provides an overview of peripheral and central vestibular conditions, describing their association with and influence on the endocrine system, the immune system and psychological states, within the PNEI model (Ortega *et al.*, 2024; Saman *et al.*, 2020).

The influence of gonadal hormone fluctuations on vestibular function is well documented, although their interactions remain partially unexplored and unorganized to enable direct conclusions and integration into routine clinical practice (C. Ishii *et al.*, 2009; Jeong, 2020; Mucci, Jacquemyn *et al.*, 2018; Price *et al.*, 1994; P. F. Smith *et al.*, 2019). Hormonal fluctuations, especially in women during puberty, the menstrual cycle, pregnancy and menopause, have been shown to modulate vestibular symptoms in several disorders, including Benign Positional Paroxysmal Vertigo (BPPV) (8), Vestibular Migraine (VM) (Tang *et al.*, 2021), MD (Andrews *et al.*, 1992; Jian *et al.*, 2019) and Mal de Débarquement Syndrome (MdDS) (Mucci *et al.*, 2020; Mucci, Jacquemyn *et al.*, 2018).

In addition to hormonal changes, most vestibular patients with a peripheral or central disorder are also known to suffer from secondary mood disorders such as anxiety and stress (Bittar & von Söhsten Lins, 2015; Staab, 2019). In light of this, this manuscript aims to shed light on the main peripheral and central vestibular disorders for which the integration of endocrine, psychological and immunological components supports or fits into the PNEI model.

Methodology

This article reviews the available literature on peripheral and central vestibular disorders, chronic symptoms, the influence of stress, hormonal states and psychological disorders (such as depression and anxiety), to determine their relationship with the PNEI theory and to assess whether this theory is applicable in patients with different vestibular conditions.

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Central vestibular disorders

The central vestibular disorders that we will hereby consider are persistent postural-perceptual vertigo (PPPD) (Indovina *et al.*, 2021; Staab & Ruckenstein, 2007), VM (Formeister *et al.*, 2018; Lempert, 2009; Sacco *et al.*, 2012) and MdDS (Cha *et al.*, 2008; Mucci *et al.*, 2018). These disorders are known to have a clear female pre-dominance and their symptomatic manifestation appears to be related to hormonal fluctuations (P. F. Smith *et al.*, 2019; Stolte *et al.*, 2014). Furthermore, these disorders are associated with secondary mood disorders such as anxiety and major depressive disorder (Furman *et al.*, 2013; Indovina *et al.*, 2021; Mucci *et al.*, 2018; Riccelli *et al.*, 2017; P. F. Smith & Darlington, 2013).

VM is a subtype of migraine (MI) and is one of the most common central vestibular disorders. VM is characterized by episodes of vertigo or dizziness, often associated with typical MI symptoms. The pathophysiology of VM appears to be modulated by gonadal hormones (Tang *et al.*, 2021). In clinical practice, VM is often misdiagnosed and poorly managed, with only 8-20% of patients being correctly identified (Yan *et al.*, 2020). Patients with VM report symptomatic fluctuations due to the impact of gonadal hormones, according to the so-called "oestrogen withdrawal theory" (Sacco *et al.*, 2012). In addition, patients with VM present higher levels of anxiety than MI patients (Kutay *et al.*, 2017) and usually have a clinical history of MI. The main characteristics of patients with VM are similar to those of MI patients, with or without aura (Huang *et al.*, 2019). Studies implementing functional magnetic resonance imaging (fMRI) have demonstrated the presence of brain dysfunction in patients with VM, particularly in relation to pain, vestibular processing and multisensory integration (Zhe *et al.*, 2023). Increased functional connectivity during nociception between vestibular and visual cortex regions has been observed in patients with VM (Mucci *et al.*, 2022; Wang *et al.*, 2014). Furthermore, an abnormal immune response and cytokine dysregulation appear to play a significant role in VM, as well as in other vestibular conditions, including MD. A recent clinical study observed that patients with MI and VM show a type 1 lymphoid cell response, mediated by natural killer (NK) cells, involving an interleukin signaling cascade (IL-1, IL-2, IL-15 and IL-18). Consequently, VM fits perfectly with the theoretical hypothesis of PNEI, which considers how a neuroendocrine imbalance can reflect on the immune system and have a psychological impact. A dysfunction of the neuroendocrine system, evidenced by an immunological and inflammatory response, can therefore manifest itself with a psychological component, e.g. by affecting mood.

The pathophysiology of MI is complex and controversial. In addition to the

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widely accepted theory involving the trigeminal-vascular system (TVS), the relevance of propagated cortical depression (CSD) has re-emerged in recent years (Espinosa-Sanchez & Lopez-Escamez, 2015). CSD is an electrophysiological phenomenon involving a massive transient neural depolarisation, which slowly propagates through the cortex. It has been hypothesised that CSD may be a trigger for MI with silent aura, as aura is not present in most MI patients. According to this theory, MI could be a pathological condition in which alterations of diverse neural networks play a role (Charles, 2013). Headache in migraineurs could result from a dysfunction within diencephalic structures and the brainstem/thalamic nuclei that modulate trigeminal nociceptive and vestibular inputs, thus affecting multisensory integration. In summary, VM involves an interaction between the nociceptive and vestibular pathways.

Considering the PNEI theory, we pose two specific hypotheses:

- A patient with specific comorbidities (such as major depression) might be more prone to develop an altered neuroendocrine system, which in turn triggers an immunological and inflammatory response, manifesting in an altered brain state.
- Alternatively, is there a genetic predisposition that makes such patients more prone to develop a dysfunctional immune system (e.g. neuroinflammation and systemic inflammation)?

This second hypothesis could be a key aetiopathogenic mechanism involved in the onset and development of affective disorders, which could lead or predispose to VM attacks. Although only a hypothesis, this possibility opens up a new view on vestibular disorders (in this case, the pathophysiology of VM): these cannot be understood in isolation, but rather as part of a multisystemic context, involving the dynamic interaction between different factors and systems, in with with the PNEI theory (Ortega *et al.*, 2024). Overall, the discussed evidence suggests that patients with VM require a holistic, and not "compartmental", management approach to address all pathophysiological aspects.

A similar hypothesis can be extended to two other significant central vestibular disorders: PPPD and MdDS. Similarly to VM, PPPD and MdDS also present a female prevalence, with a female-to-male ratio of 2:1 (Bittar & von Söhsten Lins, 2015; Staab & Ruckenstein, 2007). Previous studies have shown how hormonal fluctuations in MdDS (33) influence patients' symptoms. MdDS not only affects significantly more women (approximately 80%), but in particular, women going through a specific hormonal phase: the onset of menopause (Matchock, Levine, Gianaros, 2008). Among patients of reproductive age, a causal relationship between hormonal fluctuations in the menstrual cycle and increased severity of MdDS symptoms and sensitivity to triggers has been reported (Mucci *et al.*, 2020; Mucci, Canceri *et al.*, 2018). Given the clear female predominance (Van Ombergen, Van Rompaey *et al.*, 2016; Van

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Ombergen, Wuyts *et al.*, 2016), recent studies have investigated the role of gonadal hormones in this context (Mucci, Canceri *et al.*, 2018; Mucci, Jacquemyn *et al.*, 2018), showing that hormonal changes correlate with the onset of MdDS, with most patients developing the condition during the menopausal transition phase (Mucci, Canceri *et al.*, 2018).

Moreover, symptoms appear to be more frequent and more severe during menstruation (Mucci, Canceri *et al.*, 2018) and reduce (or resolve completely) during the first two trimesters of pregnancy, as observed in MI patients (Mucci, Canceri *et al.*, 2018). These studies have generated the hypothesis that the pathophysiology of MdDS may be driven by specific hormonal fluctuations and phases (Mucci *et al.*, 2020; Mucci, Jacquemyn *et al.*, 2018). A recent study (Mucci *et al.*, 2020) hypothesised that patients with MdDS may have experienced a specific hormonal phase (low E2) at the time of disease onset that altered their GABAergic system, as well as their calcitonin gene-related peptide (CGRP) levels (Mucci, Jacquemyn *et al.*, 2018). CGRP is known to be implicated in the pathophysiology of MI and is a common comorbidity factor for MdDS (Balaban *et al.*, 2011; Cha, 2015; Mucci, Jacquemyn *et al.*, 2018). Animal studies have also shown that CGRP receptors support vestibular functions (Luebke *et al.*, 2014; Ohno *et al.*, 2016). In particular, CGRP-positive neurons have been found in the vestibular nuclei and in the vestibulo-cerebellum (Ohno *et al.*, 2016), and could therefore be relevant for neuroplasticity mechanisms within the vestibular system, influencing neurotransmitters such as the brain-derived neurotrophic factor (BDNF) (Buldyrev *et al.*, 2006; Wu *et al.*, 2015).

The model proposed by Mucci *et al.* (2020) describes how a specific neurochemical imbalance, involving the GABAergic network, can lead to imbalances in the inhibitory transmission or to disproportions in the levels of CGRP and BDNF (e.g. low levels of oestrogen and high levels of CGRP and BDNF), predisposing susceptible and vulnerable individuals (Mucci *et al.*, 2020). While this hypothesis has been proposed mainly in relation to MdDS, similar mechanisms could also be involved in VM and PPPD, likewise predisposing susceptible and vulnerable individuals (Mucci *et al.*, 2020; Mucci, Jacquemyn *et al.*, 2018). The PNEI model aligns closely with the theory previously proposed by Mucci (Mucci, Jacquemyn *et al.*, 2018), according to which patients with MdDS report a potential inflammatory response and neuroendocrine dysregulation that could influence multisensory integration in the vestibular nuclei. The immunological component, in specific relation to MdDS and PPPD, remains unexplored. Further research is needed to consider the application of the PNEI theory to the discussed pathologies.

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Peripheral vestibular disorders

Ménière's syndrome: MD describes a condition of the labyrinth of the inner ear whereby there is an accumulation of endolymphatic fluid. MD is responsible for tinnitus, vertigo, hearing loss and a feeling of air pressure, aka "fullness within the ear". The syndrome is related to conditions of excessive stress that can generate neural hyperactivity of the autonomic sympathetic system. Stress can consequently impact hormonal regulation and the immune response, leading to a progression and exacerbation of the syndrome (Horner & Cazals, 2003; M. Ishii *et al.*, 2022; S.-H. Lee & Kim, 2010; Söderman *et al.*, 2004). If chronicised, stress can alter the production and release of hormones – including cortisol – that can affect the immune response, in turns accentuating ear inflammation (Saman *et al.*, 2012). Steroids, known for their anti-inflammatory properties, have been used to manage MD symptoms. In this context, one study (Barrs *et al.*, 2001) showed that intratympanic steroid injections (specifically, 4 mg/mL dexamethasone for 4 weeks) may offer temporary relief of persistent vertigo in patients with MD. Moreover, relief was maintained in 52% of cases at 3 month follow-up, and in 43% of cases at 6 month follow-up. This suggests that modulation of the immune response may relieve symptoms.

Similarly, a more recent study (Barrs *et al.*, 2001) showed that intratympanic therapy with gentamicin or dexamethasone is an effective approach to treat MD symptoms (incl. the "fullness within the ear" sensation), with negligible side effects. Specifically, the former shows greater efficacy than the latter, if one selectively considers the complete control of vertigo. In contrast, dexamethasone causes higher improvements in tinnitus, albeit without statistical significance. Gentamicin, on the other hand, seems to cause more hearing loss than dexamethasone at high frequencies. Using methylprednisolone and/or dexamethasone, another study (Dodson *et al.*, 2004) supports that intratympanic steroid injections are, in approximately 50% of MD patients, an effective treatment for temporary symptom relief, but that they do not result in relief of vertigo and hearing loss in the long-term. Overall, the evidence supports the PNEI theory, emphasising the interrelation between psychological stress, the immune function and the clinical manifestations of MD. The low long-term efficacy of monofactorial treatments in some studies may suggest that holistic, i.e. multisystemic, approaches are needed to achieve more significant and sustained effects over time. A patient with MD might therefore benefit from complementing mere pharmacological interventions with multisystemic interventions aimed at reducing the patient's stress level, e.g. by introducing mindfulness, physical exercise and a targeted diet (Koukoulithras *et al.*, 2022; Oğuz *et al.*, 2021).

Benign Paroxysmal Positional Vertigo: BPPV is a disorder of the inner ear caused by small calcium carbonate crystals (otoliths) that, when displaced, cause disturbances

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such as episodes of vertigo of short duration (<60-sec) depending on the head's position and angle. Additional disturbances include nausea and nystagmus. When patients with BPPV develop visual-induced dizziness (VID), we refer to postural instability associated with peripheral vestibular conditions. Although BPPV is considered a purely mechanical disorder, patients with anxiety disorders have a higher risk of developing BPPV, highlighting the link between psyche and vestibular function (Chen *et al.*, 2016). Furthermore, chronic stress can influence the immune response and hormonal regulation, potentially aggravating BPPV symptoms (Saman *et al.*, 2020; L. J. Smith *et al.*, 2024).

The interaction between the endocrine system and vestibular syndromes is twofold. Vestibular deficits can cause hormonal changes at different times, such as during acute crises or compensation phases. Specific hormonal profiles may also increase susceptibility to vertigo. For instance, the prevalence of BPPV increases with age, particularly in postmenopausal women due to decreased levels of oestrogen and progesterone, which affect the microcirculation of the inner ear. Diabetic patients are more likely to develop BPPV, with 46% of patients with type 2 diabetes affected, compared to 37% without diabetes. Hyperglycaemia is a risk factor for recurrence of BPPV. BPPV is also linked to thyroid disorders such as goiter (i.e. thyroid volumetric increase), thyroiditis, hypothyroidism and hyperthyroidism. MD, common in anxious individuals, can be induced by stress-related increases in vasopressin. Hypothyroidism has also been associated with MD. Hormonal changes have been observed at different stages of vestibular pathology. The syndrome begins with an acute crisis characterised by dizziness and anxiety, followed by a phase of functional recovery mediated by vestibular compensation. The vestibular system's connections with the hypothalamic-pituitary-adrenal (HPA) axis lead to changes in the stress hormone profile, demonstrated by altered levels of cortisol and acetylcholine (ACH). Central vestibular compensation varies between patients and is slower in those experiencing stress.

Vestibular neuritis is an inflammation of the vestibular nerve, which is part of the peripheral vestibular system. It causes intense vertigo and a sudden loss of balance, although without affecting hearing. The symptoms of unilateral vestibular neurectomy (UVN) can cause stress and activate the HPA, leading to postural, oculomotor, perceptual and neurovegetative syndromes. In a 2003 study on guinea pigs, unilateral vestibular deafferentation (UVD) (n=6) and sham intervention (n=6) were compared. The UVD intervention resulted in a significant increase ($P<0.05$) in nocturnal cortisol concentrations compared to pre-operative salivary cortisol concentrations, also showing a significant interaction ($P<0.05$) between nocturnal cortisol concentration and time. No significant difference was shown in terms of morning salivary cortisol concentrations between pre- and post- UVD surgery, nor between pre- and post- sham surgery. This suggested that the oculomotor and postural imbalances might cause activation of the HPA (Gliddon *et al.*, 2003).

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Another study in adult cats showed that prolonged activation of the HPA is a likeable index of the chronic stress experienced by the animals. This stress corresponds to the duration required for complete vestibular compensation and is no longer evident when the animals are completely free of postural-locomotor symptoms at 90 days (Tighilet *et al.*, 2009). The development of vestibular compensation after unilateral labyrinthectomy (UL) is significantly influenced by stress and stress-related steroids, as well as by conditions such as anxiety and major depression, which alter the normal HPA function. Glucocorticoids (GCs) released from the adrenal cortex, in response to stress-induced HPA activation, exert extensive actions throughout the body. In addition, they have significant modulatory effects on neurons and synapses within the brain. GCs can have a direct impact on membrane ion channels and neurotransmitter receptors to regulate their function or alter gene expression in neurons via specific intracellular receptors, including glucocorticoid receptors (GR) and mineral corticoid receptors (MR). Moreover, GCs can be rapidly converted by various enzymes into active neurosteroids. Neurosteroids derived from sex steroid progesterone also influence neuronal and synaptic function in the vestibular system and the cerebellum.

Several studies indicate that glucocorticoids and neurosteroids can modulate the vestibular system's function and compensation. Anxiety and stress in patients with vertigo substantially delay recovery from vestibular symptoms. In contrast, treatment with the GR steroid methylprednisolone has been reported to improve vestibular compensation. The acute stress that accompanies behavioural symptoms immediately after UL could facilitate cell plasticity in medial vestibular nucleus (MVN) neurons. An essential site of glucocorticoid action during vestibular compensation (VC) appears to be the cerebellar flocculus. However, an optimal level of GR activation seems to be necessary in that additional stress, such as restraint applied to a compensatory animal after UL, may hinder behavioural recovery.

The interactions between HPA, glucocorticoids and vestibular plasticity have potentially important implications for the treatment and management of patients with balance disorders. The effectiveness of vestibular rehabilitation exercises in promoting VC may be partly due to the acute stress resulting from initially aversive movements, which facilitate the brain plasticity mechanisms required for VC. It is also possible that patients who fail to compensate adequately after UL may either (A) have pre-existing alterations in their HPA function due to depression or anxiety or (B) develop changes in their HPA due to vestibular dysfunction and associated symptoms. This could cause inappropriate stress responses to vestibular, visual and postural challenges, impeding the necessary cellular plasticity in vestibular pathways for VC. Further investigations are needed to shed light on the cellular mechanisms of stress steroids on VC in animal models and to study the function of the

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HPA in patients with balance disorders (Dutia & Straka, 2009). In addition to this, there is to consider that the contrast to the effects of UVD, following bilateral vestibular deafferentation (BVD) in rats, where their serum corticosterone was not elevated when compared to sham surgery at 3 weeks (59) or 6 months (Russell *et al.*, 2006) or 9 months (Zheng *et al.*, 2008). However a reduction in anxiety was observed in animals after BVD (Zheng *et al.*, 2008) suggesting that the interactions between the vestibular and limbic systems are chronically altered (Saman *et al.*, 2012).

Stress modulation and symptoms

It is crucial to understand the interaction between the vestibular and endocrine systems. There is an urgent need to determine how hormonal profiles influence patients with vertigo and their vestibular conditions. Preclinical and clinical studies are essential to develop diagnostic tools to identify different types and stages of vestibular disorders and to create targeted therapies. These therapies aim to prevent vestibular disorders, reduce vertigo attacks and promote rapid recovery. There is currently a lack of information on the proportion of vestibular disorders linked to hormonal factors or profiles. Filling these gaps in the scientific knowledge could significantly improve the management and clinical outcomes of patients with vertigo and instability (El Khiati *et al.*, 2023).

Stress has been shown to influence vestibular symptoms (3). Whether one considers peripheral or central disorders, the vestibular system is influenced by stress responses (i.e. activation of the HPA, and the autonomic nervous system, through the release of "stress mediators" such as neuropeptides, steroids and monoamine hormones). The activation of the stress response may be necessary for vestibular compensation (Ortega *et al.*, 2024). However, excessive stress may adversely affect compensation (Saman *et al.*, 2012), highlighting the fine line separating healthy and pathological states. It is known that, in patients with MdDS, stress causes an aggravation of symptoms (Mucci *et al.*, 2018). Similarly, in PPPD, (Popkirov *et al.*, 2017) psychological distress modulates symptoms (Bittar & von Söhsten Lins, 2015; J. O. Lee *et al.*, 2018). When considering peripheral disorders, stress not only influences symptomatology, but also prevents vestibular compensation mechanisms and thus a complete recovery of functionality.

Future studies for hypothesis-validation

Based on the discussed evidence, we propose to determine whether the PNEI theory may apply to central and peripheral vestibular disorders. To this end, it would be necessary that future studies examine patients with a multidisciplinary approach. Immunological studies and genetic assessments of vestibular patients would be of particular relevance, as the literature in this context is still very scarce. For example, it is assumed

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that, in the presence of the glucocorticoid polymorphism, patients report higher levels of anxiety and cortisol. It would hence be important to determine whether patients suffering from chronic vertigo and vestibular symptoms have a higher prevalence of polymorphisms that prevent them from fully compensating, thus predisposing them to developing secondary mood disorders (i.e. anxiety and depression).

As discussed, women are more prone to various vestibular disorders (including VM, PPPD and MdDS) and kinetosis. Therefore, another key research question would be to investigate how gonadal hormones, stress and dysfunctions of neuroendocrine modulation might influence the symptomatology or pathophysiology of vestibular disorders. In conclusion, these abovementioned aspects highlight the association between immunoendocrine and psychological factors in vestibular disorders, as well as the importance of a combined "mind-and-body" management in patient care.

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The problem of validation of psychotherapy

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***Abstract**: Some issues concerning the problem of efficacy of psychotherapy are reviewed and discussed. The difference between clinical research and empirical research is examined, also with some philosophical considerations. Clinical research and empirical research are very different: the former is conducted by the psychotherapist in the daily work with patients, while the latter is performed in the experimental laboratory. It is then discussed whether replicability, which is a central characteristic of the scientific method, is possible in psychotherapy. An overview of the history of the psychotherapy research movement is then traced: a first phase has been mainly dedicated to outcome research, while a second phase concerns mostly process research. Finally, some recent research on the efficacy of psychoanalysis is summarized, where it increasingly emerges that psychoanalysis and dynamic psychotherapy are not inferior, but sometimes even superior, to cognitive-behavioral therapy.*

***Key words**: Efficacy of psychotherapy, Replicability, Psychotherapy and science, Research in psychotherapy, History of the psychotherapy research movement, Efficacy of psychoanalysis.*

What practical use do the results of experimental research in psychotherapy have for the daily work of the clinician? And, vice versa, what scientific value do they have and how generalizable are the observations made on single cases? Is there an impossible gap to fill, or can these two types of knowledge, so different, somehow interface and contribute to building a unitary science? Let us first clarify what is generally meant by research in psychotherapy, with references to some philosophical implications, and let's briefly review the history of the psychotherapy research movement, also referring to previous works (Migone, 1995, 1996, 1998, 2006, 2021, 2024).

Research in psychotherapy does not mean "clinical research", a term that refers to a type of observations and hypotheses made by the therapist within the clinical situation. The therapist can share his observations with colleagues or in study groups, he can also make predictions and look for possible confirmations. He can write articles on these hypotheses, and some of them can be subjected to experimental validation in studies conducted with different methodologies, which belong precisely to what is commonly called "psychotherapy research", also called "empirical" or "experimental" research. Some of its main features are the following.

First of all, with a term that has come into common use after Grünbaum's (1984) philosophical critique of psychoanalysis, these methodologies are "extra-clinical", not just "intra-clinical". This means that they rely on technical tools and on the observations of independent judges, external to the therapy and sometimes "blind" to the method used, who can use rating scales based for example on videotaped sessions. These rating scales, which are standardized, can concern various aspects: diagnosis (and there are different diagnostic methods; Migone, 2011, 2013), size of change, with the possibility that it may have been caused by events external to therapy, degree of "adherence" to the psychotherapy manual that the therapist had committed himself to follow, and so on. Not only that, but these external researchers can also conduct epidemiological studies to seek confirmation of certain hypotheses. Finally, and this last is one of the most important aspects, the data must always be subjected to an investigation of statistical significance.

"Extra-clinical" research (i.e., empirical or experimental) is therefore very different from clinical research because it uses sophisticated technologies that clinicians do not use, and performs quantitative assessments, generally on samples of many subjects, who are then subjected to statistical analysis. These assessments are not intuitive or "subjective" but, as we can say, "objective" (a term that, in a way, is inappropriate because it does not refer to a supposed "truth" or to a greater adherence to reality, but to the degree of agreement between multiple observers – as Freud himself said, reality as such is unknowable, we only see what our observation tools allow us to see).

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Having clarified how these two types of research are different, we would be fooling ourselves if we thought we had solved all the problems. Indeed, it can be said that the real problems begin right here. In fact, we could ask ourselves: how do these two types of research relate to each other? Are they placed on irreconcilable levels or are they conceivable within a single hierarchical system? And furthermore: why is there a need to do extra-clinical or empirical research? Couldn't traditional clinical research be enough to guide the therapist, especially in a field as complex and not "objectivable" as psychotherapy?

Behind these questions lie age-old problems that have been widely debated throughout the 20th century, which are also reflected in other well-known dichotomies that have characterized the history of philosophy (Migone, 1998). First of all, there is the dichotomy, attributed to Dilthey, of the "two sciences", the natural sciences (*Naturwissenschaften*) and the human sciences (*Geisteswissenschaften*), the latter also called historical (Rickert called them *Kulturwissenschaften*, and Windelband *Geschichte*). Parallel to this dichotomy is the one between "explaining" (*Erklären*) and "understanding" (*Verstehen*), and also between "causes" and "reasons" of a behavior. This issue has been taken up by hermeneutics, which emerged in the psychoanalytic debate in the United States in the 1970s and 1980s (the best-known hermeneutic psychoanalysts were Roy Schafer [1976, 1992] and Donald Spence [1982], in the wake of some European philosophers, essentially Ricoeur and Habermas). Another dichotomy that in some ways follows the previous ones is that between "quantitative" and "qualitative" research, and yet another, perhaps even better known, is that between "nomothetic" and "idiographic" sciences, proposed by Windelband. Nomothetic sciences aim to construct general laws (the Greek term *nomos* means "law"), and therefore to make it possible to predict certain phenomena (typically, nomothetic are the natural sciences), while idiographic sciences study those unique phenomena (*idios* means "particular"), unrepeatable (an example is the study of personality or, indeed, of psychotherapy), for which the methods of nomothetic sciences would not only not find easy application, but would even prevent us from seeing new phenomena, blinded as they are by their own limited methods of observation. In a certain sense, it can be said that nomothetic methods risk discovering only what is already known, while idiographic ones, even if not very reliable, can sometimes lead to unexpected discoveries (think, in this regard, of the difference between objective and projective tests).

If we look closely, the complex question behind these dichotomies concerns the very concept of science: should it be characterized by its method, or by the field of application to which the method must adapt?

In the first case, there would be a single method (called scientific), which could adapt better to certain fields rather than others. As some critics of this concept of

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science argue, the classical scientific method (characterized by experimentation, prediction, replicability, etc.) would lend itself more to the study of "natural" phenomena (for example physical) than to subjectivity where the complex variables at play make it difficult to use the traditional scientific method; furthermore, psychotherapy sometimes employs methods that are not easy to investigate experimentally, such as introspection or intuition. If – some critics continue – we force the observation of the data of psychotherapy through the lenses of this method, we risk distorting them or losing something that perhaps constitutes the very essence of the phenomenon we want to study (an example can be represented by behaviorism, which in fact, even according to many of its own exponents, has shown its limits as a form of psychotherapy). The result would be a reductive or even distorted image of the object studied.

In the second case, that is, if we adopt a conception of science according to which it is the method that must adapt to the field of observation, we would have many scientific methods, many "sciences", with the result that the dichotomies we were talking about would reappear, and a fragmentation of knowledge would be created, with complex implications, some of which are precisely those we are discussing.

This is certainly not the place to resolve these issues, but only to stimulate some reflections. It can be argued that in recent decades, thanks also to a greater knowledge of the scientific method (even on the part of many philosophers, who had an abstract conception of it and not grounded in the concrete practice of research), a sort of reshuffling of the cards has occurred with respect to these dichotomies, in the sense that they are no longer as clear and sharp as they once were. For example, the belief that the nomothetic/idiographic opposition is a false dichotomy, originating from a romantic reaction to a 19th-century conception of science that is now outdated, is increasingly widespread. This is, for example, the position taken by Robert Holt, a research psychoanalyst, later David Rapaport's successor and leader of his group, in a work he wrote in 1962 in which he criticized the legitimacy of the idiographic method. At the time, Holt was a student of Gordon Allport, who was a strong supporter of the idiographic method in personality theory. Holt, clashing with his master, came to the conclusion that, as soon as we simply observe and describe a phenomenon idiographically, we cannot help but use certain conceptual categories that no longer belong to this method. Without these categories, we could not even communicate our observations to other colleagues. According to Holt, the idiographic method would therefore have only artistic, not scientific, purposes, since it is limited to understanding and not to prediction and control (see Holt, 1989; Holt *et al.*, 1994).

To return to psychotherapy research, to say that there has been a reshuffling of

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the cards between the dichotomies mentioned above does not mean that the difference between clinical and extra-clinical research disappears, or that clinical research should be abandoned in favor of empirical-experimental research only. On the contrary: it would be a mistake to neglect, as many research programs and scientific journals unfortunately do, clinical studies on single cases, because they have enormous heuristic implications, and sometimes even the power to falsify certain hypotheses. Let us not forget that a good part of psychotherapeutic hypotheses originated from a number of clinical cases that can be counted on the fingers of one hand, studied in depth by Freud, Binswanger and others.

The history of both medicine and psychiatry presents countless examples of how the method based on "clinical experience" and single cases has led to errors. We know that, for example, at the end of the 19th century most medical interventions were useless if not harmful, and yet they continued to be practiced with a rich series of self-confirmations and with respect coming from the "scientific" community of the time (Migone, 1995, ch. 6). A striking example in this regard is psychosurgery, whose successes were boasted by a generation of psychiatrists and neurologists, as well as by nurses and patients' families, all convinced of its extraordinary efficacy, so much so that in 1949 its inventor, Egas Moniz, was awarded the Nobel Prize. But the scientific community was greatly embarrassed when the progress of research made psychosurgery disappear overnight: it emerged that the vaunted therapeutic successes were self-deceptions, based on observations without independent control (Pressman, 1998). This is not surprising, after all, if one considers that the first published randomized controlled trial (RCT), i.e., controlled by placebo in a double-blind condition, was the English study on streptomycin for tuberculosis in 1948, so in recent times. In certain cultures, harmful or useless methods have continued to be used for centuries or millennia (just think of bloodletting), and it is not clear why this cannot also happen for psychotherapy. It was only with the generalization of the advances of scientific revolution that a dramatic improvement was made in the identification of the most effective therapies, leading to the eradication of many diseases and saving entire populations from epidemics. The scientific method, based on double-blind controlled studies and on specific extra-clinical methodologies, allows us to break the daily self-deception that is always lurking in front of the clinician. And to the extent that the experimental method allows us to circumvent, at least partially, this constant self-deception fostered by our unconscious expectations, in this respect it is reminiscent, in some ways, of the psychoanalytic method, because it helps us to combat our false consciousness, to see what we sometimes defensively do not want to see.

In this light, Freud's statement in a 1934 letter to the psychologist Saul Rosenzweig, who had sent him the results of his experimental studies in favor of

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the theory of repression, is surprising: «Dear Dr. Rosenzweig, I have examined with interest your experimental studies on the scientific validity of psychoanalytic assertions. I cannot attach much value to these confirmations because the abundance of reliable observations on which these assertions rest makes them independent of empirical verification. However, they cannot do any harm» (cited in: Wallerstein & Fonagy, 1999, p. 91). On another occasion Freud stated, with ill-concealed sarcasm: «These critics who limit their studies to methodological investigations remind me of those who spend their time cleaning their spectacles rather than wearing them to look» (cited in: Jacoby, 1983). But perhaps Freud underestimated the self-deceptions mentioned above, and the possibility that research could invalidate a given theory (he himself, moreover, consistently modified his own theories in the light of new clinical experiences).

Here the underlying philosophical problem is that of inductivism, that is, the possibility of inducing, starting from particular observations, general laws that – through deduction – then allow us to make predictions about other cases. Needless to say, there has been a heated debate in this regard that has seen opposing positions, a debate that cannot be said to have completely died down. I am referring, for example, to the harsh attack by Grünbaum (1984) on Popper (1957) – who never responded – which cannot be summarized here (see Migone, 1995, ch. 11).

The challenge, in short, is to see if it is possible in some way to bridge, as mentioned before, the gap between clinical and experimental research, a gap – the "great divide", as some have called it (see Carere-Comes & Migone, 2001-03) – that unfortunately still separates the world of clinicians from that of researchers. In fact, clinicians often shy away from empirical research, saying that they don't need it, that it doesn't interest them, that for them research is only clinical research, based on their "experience", or that psychotherapy is an art. The difficult coexistence of these two worlds has been debated countless times (for a debate that lasted several years, which ended with disagreements, see Carere-Comes & Migone, 2001-03; see Luyten *et al.*, 2006). This great divide should be bridged in some way, following, for example, the research path of David Rapaport's group (Blatt, 2004, 2006, 2008; Holt, 1989; Migone, 1998, 2015; Rapaport, 1942-60; Rubinstein, 1952-83). In fact, both research methods should be used because, in a complementary way, they contribute to the progress of knowledge, and it is not correct to see the two methods in dichotomous terms, but as a *continuum* of ways of knowing. These methods have different purposes, and correspond to different types of cognitive functioning, different ways in which our mind processes information, and as such both should be valued. It could be argued that the clinical method can correspond to a first phase of research, of an inductive type, in which it is essential to formulate hypotheses that can then be tested with the experimental method, which however does not

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lead to the "truth", which by definition should never belong to science (if anything, the problem of truth concerns philosophy); science, even for its limited horizons of investigation, is characterized by great modesty and awareness of its own ignorance, and this has always been its strength.

Not only that, but if we look closely, the problem of the coexistence of different "sciences" or methods of investigation does not exist only with regard to the relationship between human sciences and natural sciences, since it already exists within the latter, where we have many research methods, each of which – as argued by the Italian philosopher Evandro Agazzi (2006) – produces or "constructs" its own "scientific *object*", to the point that the problem remains, it only shifts. For example, with regard to the different methodologies of studying the psychotherapy process, we could ask ourselves: how do all these methods relate to each other? Is there a "better" or hierarchically "superior" method, or one that measures the "true" therapeutic process? If by science we do not mean, in a reductive way, only a method that is applied to objects that lend themselves to being investigated with that method, it does not depend on the type of objects it deals with but on the "way" in which it deals with them. As Agazzi (2006) argues, this method can be called "scientific" to the extent that it satisfies certain criteria such as "rigor" (giving reason for what is stated, not necessarily through quantification, measurement, etc., and using a specific language and logic), "testability", "objectivity", "protocolarity", etc. Each approach to knowledge, however, as has been said, constructs its own "scientific object" which is different from those produced by other approaches. Again according to Agazzi, this scientific object should not be confused with a "thing", in the sense that the same thing can be the "object" of different sciences, so a thing is transformed into a "bundle" of potentially infinite objects: for example, the fact that new methodologies are always being created that study a certain thing does not mean that the number of things in the world has increased, but that new "points of view" on that thing have been identified (for example, the mind can be studied with the methods of neuroscience, with projective tests, with introspection, and so on; in the same way, psychotherapy can be studied with a purely clinical methodology or by quantifying certain variables). Therefore, each scientific approach, understood as a "point of view", cuts out or reduces reality according to its own methods, building a different *object*. From this comes the fact that, concretely, each approach, that is, each point of view, translates itself into the identification of its own methods of investigation. This is important because – as Agazzi (2006, pp. 64-65) argues – it helps us understand that the dispute between different schools with the mutual accusation of being unscientific is meaningless. This dispute would make sense if opposing methods dealt with the same object, while this is not the case: each method deals with different "scientific objects", it carves out its own

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object, so «adhering to one methodological choice rather than the other simply means deciding to deal with something more or less different or, if you want, to do another psychology» (p. 65). To give an example, it makes no sense for the behaviorist to accuse of methodological incorrectness those who use introspection, in fact the conflict between different methods is «only apparent when it is understood that it translates into a differentiation of objects and is not a fight about how to take possession of a single and identical object» (p. 65). Moreover, this problem is not new nor does it belong only to psychology, but also to the "hard" sciences: think of physics, where once it was believed that there was only Newtonian mechanics, but then it was realized that there is also electromagnetism, quantum physics, etc., all disciplines that deal with the same things but construct different scientific objects; they are "many physics", even if they coexist within physics as a discipline.

It could be said, therefore, that psychology from an epistemological point of view finds itself in the same condition as physics (which would also go against the division between soft and hard sciences), and the same obviously also applies to psychotherapy, which is an application of psychology: the problems that the epistemologist finds himself having to face when he reflects on the way in which the different psychotherapeutic schools relate to each other would be the same ones he faces when he reflects on the way in which the different "physics" that coexist in physics relate to each other. And the problem of the relationship that the different "scientific objects" of psychotherapy have between them is not easy to solve, and above all it should not be forgotten that each of them does not completely reveal the "truth", since they are all bearers of partial and reductive knowledge, useful only for the purposes for which these "scientific objects" were "constructed" (for a criticism of Agazzi see, however, Fornaro, 2013).

If we take this point of view to its extreme consequences, not only could the plurality of psychotherapeutic models be a good thing, because each of them legitimately explores an aspect of the patient's reality, but, one could say, it would also be a good thing to never arrive at a single psychotherapeutic model that is "truer" or "better" than the others, because this could mean that we have come to know the patient's ultimate reality, when we know that reality by definition is unknowable (as has been said, this was also Freud's position). In other words, flattening our field with a single model could inhibit the process of knowledge, which is interminable (Migone *et al.*, 2012).

It should not be forgotten that the experimental method can also lead to errors, because there are various ways of implementing a research and analyzing the results, and further research can also correct previous results. And it must be said that a therapeutic practice guided only by empirical research data is premature because too many data still escape most of research. The fact that something has not

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yet been demonstrated does not mean that it cannot be demonstrated in the future, and certain reviews of the literature seem to imply that if a technique has not yet been studied this means that *it has already been proven ineffective*. We must therefore be very careful not to draw hasty conclusions from research, also because there are many biases and a large "halo effect" created by the way in which certain data are publicized by mass media. In this regard, Westen, Novotny & Thompson-Brenner (2004) have made a magisterial criticism of the methodology that produced the lists of Empirically Supported Treatments (EST) (Chambless & Ollendick, 2001), whose logic is derived from the RCTs of Evidence Based Medicine (EBM). Westen and colleagues have shown that the assumptions on which the EST methodology is based are not theoretically neutral but reflect the fundamental assumptions of cognitive-behavioral therapy of the 1960s and 1970s (and these assumptions are no longer accepted today by many exponents of the cognitive-behavioral therapy movement itself), and that these assumptions are empirically testable but, paradoxically, many of them have never been tested; among those tested, some *have been shown to be false* precisely on the basis of empirical research itself. Also important in this regard are the criticisms of Wachtel (2010) and Shedler (2018); see also Migone (2021, ch. 6 and 7).

With regard to the EBM paradigm, it should be noted that to the extent that its explicit statute proposes to eliminate any type of intuition or "clinical experience" but to rely solely on controlled research (De Girolamo, 1997), it seems to commit the same and opposite error of the paradigm it seeks to combat: if on the one hand we have a clinical practice that is only intuitive, on the other it recommends an impersonal and automated practice, without any integration or dialectic of the two poles and therefore with an impoverishment of real clinical practice which by its nature is based on complex cognitive operations (see Sackett *et al.*, 1996).

The issue of replicability

Replicability, perhaps more than other aspects, characterizes science. Without wanting to delve deeply into the age-old debate on the "theory of demarcation" between science and non-science, if the word science has any meaning it must refer to a phenomenon that is to a certain extent replicable, experimentally controllable. Curiously, however, as argued by the physicist Bersani (2008), even in the "hard" sciences (such as physics, chemistry, etc., and not only in the soft sciences such as psychotherapy) there is no experiment that is perfectly replicable, due to a thousand variables that continually modify the conditions of the experiment. We would therefore have one more reason to question a clear difference between hard and soft sciences, because these would be experiments that are more or less perfectly

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replicable. In certain physical phenomena, it is not possible to predict the movement of individual particles (that would be hard to replicate), but it is possible to predict fairly well the macroscopic phenomena produced by the sum of those same microscopic particles. An example is that of a gas, whose general laws can be studied but the movements of individual particles cannot; another example, which is part of everyday life, is the porcelain cup fallen on the floor that breaks into a thousand pieces – a phenomenon certainly replicable – of which we cannot, however, predict the number, the dimensions or the distribution on the floor.

This brings to mind the well-known "uncertainty principle" developed by Werner Heisenberg in the 1920s, according to which infinitesimal particles do not have a position and a velocity defined simultaneously: the greater the precision with which their position is determined, the less precision is established with which their velocity is established. In other words, the observer influences the observed object, and this is the reason why Heisenberg's uncertainty principle is often cited by those psychotherapists who sympathize with relational or intersubjective approaches. But these psychotherapists are wrong because Heisenberg's uncertainty principle does not apply to macroscopic phenomena but only to microscopic ones (to molecular phenomena but not to "molar" ones, one might say; see Pauri, 2000), and this difference seems to be counterintuitive because one might think that macroscopic phenomena are more complex than microscopic ones and therefore less controllable. But here comes into play the "theory of complexity", according to which in complex and "chaotic" phenomena there are regularities that are not easily explained by the detailed analysis of the individual components.

Apart from this, it should be noted that there are interesting examples of "scientific" discoveries that were later unmasked and demonstrated to be "pseudo-scientific" (Bersani, 2008, p. 67). However, if we use the term "pseudo-science", we automatically put ourselves in the position of those who believe in science as different from something that it is not, so we are back to square one, that is, the question of demarcation arises again. And if we had previously said that perfect replicability does not exist, the problem of establishing what we mean by science arises again.

It seems that we are therefore faced with an impasse, but it is only apparent, since some form of replicability must exist, and not only in the hard sciences, but also in psychotherapy, otherwise it would not be teachable. Certainly, this replicability is never perfect, but to some extent it is there, certainly at a macroscopic level. We can give many examples in which certain patient behaviors are reproduced regularly due to certain traumas as well as certain more or less structured and "replicable" therapeutic interventions, called precisely psychotherapy (for a detailed clinical example in which one can see how in psychotherapy one can make

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hypotheses and then test them empirically, see Migone, 2021 pp. 29-34, 2008b pp. 79-83).In short, psychotherapy would be a natural phenomenon, that can be studied just like in medicine. It should also be remembered, as mentioned above, that psychotherapy and medicine are not two sciences but two "applications" of basic sciences, in which complicated factors intervene such as the interpersonal relationship, which is the core of psychotherapy and which makes it more complex in terms of scientific experimentation.

Notes on the history of the psychotherapy research movement

Trying to understand which hypothesis is the most probable among rival hypotheses is the aim of the psychotherapy research movement, especially starting from Eysenck's healthy provocation of 1952 according to which the effect of psychotherapy is irrelevant, useless. Incidentally, Eysenck was careful never to say that psychotherapy is harmful, otherwise he would have been forced to admit that it could be effective. According to Eysenck, improvements occurred only thanks to the "mere passage of time", that is, by "spontaneous remission" of diseases due to the natural oscillations of their course. This hypothesis implies that therapists, when sooner or later they encounter the positive oscillation of the disease (so the longer a therapy, the better it serves this purpose), take credit for it. According to this hypothesis, one could say that therapy works because of the "streetlight effect": we put the patient for an hour a week sitting on a bench lit by a streetlight, and it is the streetlight that heals the patient, who, when he feels better, gets up from the bench-couch and goes home, happy to have been healed by the streetlight-analyst.

Well, it was not easy to prove that Eysenck was wrong, thirty years of research were needed, in fact the first data emerged only from the studies made by Smith, Glass & Miller in 1980 (Smith *et al.*, 1980). However, in what is considered the first phase of psychotherapy research, defined as "outcome research", an embarrassing situation was reached, which was called the "equivalence paradox": all psychotherapies on average obtained the same results. In other words, «everyone wins and everyone deserves a prize» (Luborsky *et al.*, 1975, 2002; Rosenzweig, 1936) as the Dodo bird said after calling a race in *Alice in Wonderland*. This equivalence is known as the "Dodo verdict", and it continues to be a specter that haunts researchers, especially those who have a faith in one of the many psychotherapy schools. One of the causes of the Dodo verdict lies in the difficulty of identifying methods capable of measuring change with sufficient precision.

It is because of the Dodo verdict that we have moved on to a second phase in

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the history of the psychotherapy research movement, called "process research", in which research on outcome has been abandoned, considered useless since it was not known which "process" produced the outcome. In other words, we studied what really happens in the therapeutic interaction, since it is not enough for a therapist to say that he does a "psychoanalysis" (or a "cognitive therapy", etc.) to be certain that he does it; indeed, it has often been shown that at times a therapist does something completely different from what he says he does. Westen, Novotny & Thompson-Brenner (2004), for example, show that sometimes patients improve thanks to interventions that belong to another technique. One study showed not only that both cognitive and psychodynamic therapists used techniques from the other approach, but that in both cases the outcome was correlated with interventions typical of psychodynamic therapy, that is, the fact that cognitive therapists used cognitive techniques was not correlated with outcome (Westen *et al.*, 2004, p. 639, p. 124 in the 2021 edition).

It is for this reason that in the second phase of psychotherapy research, there was a boom in the manualization of various techniques, precisely to ensure that therapists were doing exactly what they claimed to do and not something else. The first psychoanalytic manual for research was Luborsky's 1984 manual for "supportive-expressive" treatment, and many others followed, such as Inter-Personal Therapy (IPT) by Klerman *et al.* (1984), Transference-Focused Psychotherapy (TFP) by Clarkin, Yeomans & Kernberg (1999), Dialectical Behavior Therapy (DBT) by Marsha Linehan (1993), and so on (the names of the manuals generally refer to specific techniques, not to general theories; in fact, the same theory – for example, psychoanalysis – can inspire different manuals depending on the author who constructs them, the target diagnosis, etc.). The first manuals to be built were naturally those of behavior therapy, because they were simpler (they become almost preestablished algorithms of interventions, the so-called "procedures"). Manuals are built only for research, often *ad hoc* for a specific study, and should not be confused with books on clinical technique: as examples of books on psychoanalytic technique for clinical practice, think of Menninger (1958), Greenson (1967), Etchegoyen (1986), etc. – books on psychoanalytic technique for clinical practice are not very many, and not by chance precisely because of the difficulty in explaining or "prescribing" detailed interventions that are valid for the entire course of treatment (in fact, as Freud [1913, p.123] said, treatment is a bit like a game of chess, in which the opening and closing moves – checkmate – can be described, but it is very difficult to predict the intermediate moves). It is no coincidence that some have defined psychoanalytic technique manuals as "collections of errors" (and the errors can be much greater in research manuals, because they are much more detailed; see Migone, 1986). In this regard, it is quite interesting a beautiful statement by

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Helmut Thomä, which Kernberg, with wisdom and self-irony, wanted to use as an epigraph to his own therapy manual for borderline patients: «This treatment book should be memorized, and then forgotten» (Clarkin *et al.*, 1999, p. V).

Manualization is only one aspect of the phase of process research; there are other aspects, for example the construction of several rating scales, even very sophisticated ones, precisely to measure the process: today the best known are at least twenty (see Dahl *et al.*, 1988; Dazzi *et al.*, 2006; Levy *et al.*, 2012; Migone, 1995, p. 225 note 15 of the 2010 edition) just think of Luborsky's *Core Conflictual Relationship Theme* (CCRT), which is an "operationalization" of transference for research purposes, a sort of bridge between the qualitative and the quantitative (Luborsky & Crits-Christoph, 1990), Wilma Bucci's *Referential Activity* (1997, 2019), the scale to measure the reflective function studied by Fonagy *et al.* (2002), the *Shedler-Westen Assessment Procedure* (SWAP) by Shedler & Westen (2003) which allows a narrative formulation of the clinical case, and so on.

To return to psychotherapy manuals, they have advantages and disadvantages. The main advantage is that they allow one to do research, identifying a phenomenon that can be replicated, while the disadvantages are many: think of the excessive rigidity that can go as far as to distort psychotherapy itself, or the "efficacy" which however is achieved at the price of a low "effectiveness", that is, poor results are obtained in the phase of "exporting" the technique from the laboratory to real clinical practice (what can also be called "external validity"), in which the patients are not selected and therefore for example present a comorbidity that was not present in the research sample (so much so that, ironically, one can say that research is on a third of the patients while clinicians see the remaining two thirds, the most difficult ones and excluded from the researches' rigid criteria). In short, there seems to be a curious paradox: the better a research is done, the less useful it is to the clinician, in the sense that the required methodological rigor distances too much from real clinical practice, which necessarily is not very rigorous and is "contaminated" by a thousand factors.

For further information, I refer to the article by Westen, Novotny & Thompson-Brenner (2004), cited above, and to other reviews (see Migone, 1996, 2006). Among the main international reviews on psychotherapy research, we can mention that of Roth & Fonagy (1996), and the "bible" of researchers, the *Bergin and Garfield's Handbook of Psychotherapy and Behavior Change*, now in its seventh edition (Barkham *et al.*, 2021). An important manual is that of Levy, Ablon & Kächele (2012), which has the subtitle "evidence-based practice and practice-based evidence", which offers an in-depth overview.

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The efficacy of psychoanalysis

After this overview of some problems in psychotherapy research, one might ask: what is the evidence of the efficacy of psychoanalysis? It is certainly not possible here to carry out a detailed review of the literature, so only some general observations will be made that summarize the trends that emerge from research. From many quarters – in books, journals, conferences, and in the mass media that act as a sounding board – it is often stated that cognitive-behavioral therapy is the most effective, as if this were an incontrovertible fact. But in recent years more and more evidence has accumulated showing that therapies derived from psychoanalysis are effective. The superiority of cognitive-behavioral therapy may have seemed true years ago when there was not yet enough research on psychodynamic therapy – and, as has been said, many made the mistake of believing that if it had not yet been studied it meant that it had been proven ineffective – but when the psychoanalytic movement entered into the arena of empirical research, things soon changed: not only did psychodynamic therapy prove to be not inferior to cognitive-behavioral therapy, but it was shown that at times the results of psychodynamic therapy can increase over time, as if the patient internalizes certain abilities whose effects mature gradually.

It should also be considered that cognitive-behavioral therapy, in a way, does not exist, there are different types, in the same way that psychoanalysis does not exist but there are *many psychoanalyses*. It is therefore necessary to be clear about the meaning of the terms. For example, within the cognitive-behavioral therapy movement, the so-called "third wave" is very popular (the importance of "acceptance" of the patient's emotional states is recognized, the technique of mindfulness and other practices derived from Eastern philosophies have spread, and so on; see Migone, 2008a), a phenomenon that can also be read as the rediscovery of psychodynamic ideas and therefore as a sign of crisis or rethinking in the cognitive-behavioral movement (moreover – as important exponents of cognitive therapy itself have admitted, for example Kazdin (2007, p. 8) – the low efficacy of cognitive therapy had already been recognized, as it focused on cognitions while underestimating emotions). In short, we are witnessing hybridizations and assimilations of ideas and techniques taken from other approaches, often without recognizing their debt.

And if we must specify the terms we use, what is then meant by "psychodynamic therapy"? This term is not intended to be understood in a generic but precise way, and not based only on theoretical but empirical research. In fact, this term refers to a technique based on psychoanalytic principles and defined by "seven distinctive characteristics" as they emerged from empirical studies capable of reliably distinguishing it from other techniques, such as cognitive-

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behavioral therapy (Shedler, 2010 pp. 98-100, pp. 48-51 of the 2021 edition). And just as cognitive-behavioral therapy is generally defined with the acronym CBT, the research community has decided to use the acronym PDT for psychodynamic therapy, but in a more precise way than for CBT which, as we have seen, is an "umbrella" term that includes different techniques, some of which also include techniques derived from psychoanalysis (think of Schema Therapy, which is considered a CBT technique but avowedly uses techniques derived from Gestalt therapy, psychoanalysis, etc.).

The now famous review by Shedler (2010), which reports the "effect size" of various types of psychotherapy, shows the efficacy of psychodynamic therapy on the basis of several "meta-analyses", i.e. "analysis of analyses". And this research by Shedler was followed by others (see, for example, Cuijpers *et al.*, 2021). Regarding depression, which is one of the most common disorders, it is also interesting to compare it with antidepressant drugs, that on average have a decidedly lower efficacy (Migone, 2005), which implies that a treatment for depression that favors the use of drugs – as unfortunately often happens – is in fact malpractice. Vast sectors of academic culture and many specialty schools of psychiatry, to the extent that they emphasize the use of drugs and neglect the importance not only of psychotherapy but also of the patient/therapist relationship, are complicit in this antiscientific approach, based on ignorance of research. There are many studies on the efficacy of psychodynamic therapies that could be mentioned here (among the many references, see for example Steinert *et al.*, 2017; Leichsenring & Steinert, 2017; Leuzinger-Bohleber & Kächele, 2015; Leuzinger-Bohleber & Target, 2018; Levy *et al.*, 2012; Migone, 2021; etc.). Also very useful is the third edition of the *Open Door Review* of the *International Psychoanalytic Association* (IPA) (Leuzinger-Bohleber & Kächele, 2015), with introductory interventions in which some epistemological issues of research in psychoanalysis are discussed.

Finally, a mention of psychiatry is necessary. There is strong empirical evidence showing that a psychiatry based solely on a "technological paradigm" (privileged use of drugs, instrumental tests, etc.) is less effective than a psychiatry based instead on careful listening to the patient and understanding the symptoms within his life history and interpersonal relationships. It is a big misunderstanding to think that psychiatry is a medical specialty comparable to high-tech specialties such as anesthesiology or ophthalmology (and moreover it has been demonstrated that also in medicine – even in surgery – attention to the psychological relationship with the patient has an impact on improvement); the "specialty" of psychiatry also consists in the fact that, as Michael Balint (1956) once said – the psychiatrist administers himself as a drug, that is, it is a matter of working carefully on the variables of the interpersonal relationship, because it is from relationships that most mental

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disorders originate. In short, thinking that complex psychological or personality problems can improve only with the administration of some pharmacological "potions" is a myth, well fueled by multiple interests that are intertwined: the identity insecurity of psychiatrists in such a difficult profession, the need for illusion of many patients, and above all the propaganda of pharmaceutical companies that heavily influence the culture of the field (Migone, 2017). There are many contributions that could be mentioned here (American Psychological Association, 2013; Angell, 2011a, 2011b; Bracken *et al.*, 2012; Whitaker, 2010).

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Review

Perinatal grandparents: A new frontier for caregiving

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Abstract: *In the contemporary nuclear family, fewer children are born, both parents work, and it is rare for other relatives (such as parents, siblings, uncles, or other elderly family members) to live in the household. Both partners share the responsibilities of raising and caring for their children. When a child is born, today's parents often find themselves alone. As both parents work, raising a newborn becomes more challenging, necessitating support from other adults. The absence of a network of women who, in patriarchal societies, could provide assistance (such as sisters, aunts, and cousins) makes it necessary to seek help elsewhere. In families where grandparents are available, they constitute a crucial resource and become indispensable, at least during the early years. As caregivers, they take care of newborns by feeding, bathing, changing diapers, rocking, dressing, holding, putting them to sleep, escorting them to and from daycare or school, educating, telling stories, talking and playing with their grandchildren, and protecting them both inside and outside the home. While for many individuals becoming grandparents is one of the most fulfilling experiences in life, making them feel younger and more energetic, for others, it represents a challenging existential transition. Some refuse to embrace grandparenthood as it is perceived as a narcissistic wound, symbolizing aging, a loss of power, and the approach of death.*

It is well established that fathers (or partners, including same-sex partners) who assume caregiving responsibilities for a newborn exhibit significant neuroendocrine and epigenetic changes. These changes also occur in grandparents when they undertake caregiving roles for an infant. To date, as far as we know, research has only focused on grandmothers, with no studies conducted on grandfathers. Research in mothers, fathers, and grandmothers has led to the hy-

pothesis of a Global Parenting Caregiving System in our species, which is activated even in non-maternal caregivers (allomothers) and involves at least ten brain regions along with endocrine and epigenetic modifications.

Key words: *Caregiving, grandparents, grandfather, psychoneuroendocrinology, newborn, grandmaternal gatekeeping.*

From the patriarchal family to the nuclear family

Over the past eighty years, particularly since the second post-war period, the structure of Western families has undergone profound transformations. Families traditionally organized in a patriarchal manner – especially in small towns and rural areas but also in urban settings – have gradually evolved into what can be termed the «contemporary nuclear family» (Baldoni, 2025; Baldoni & Giannotti, 2022; Quilici, 2010). Several factors have contributed to this shift, including population migration to large cities, a decline in birth rates, and the widespread entry of women into the workforce.

In patriarchal family life, the patriarch (a grandfather or father) played the role of protecting and guiding the family. Extended family members often lived in close proximity. The division of labor between men and women was distinct, with privileges typically granted to males. Women were responsible for household tasks (cooking, cleaning) and were supported in maternity and child-rearing by a network of other women (their mothers, sisters, grandmothers, aunts, cousins, and wet nurses). Families tended to have many children (sometimes ten or more). Fathers and other male relatives (such as grandfathers and uncles), who were engaged in work and family economics, were involved in child-rearing primarily in educational, social, or religious aspects. Abuse or violence were not inherent to patriarchal life, whose primary aim was to protect the family; rather, such behaviors stemmed from specific cultural or social conditions.

In the contemporary nuclear family, fewer children are born (often none, and rarely more than one), both parents work, and it is uncommon for other relatives (parents, siblings, uncles, or elderly family members) to live in the household. Both partners share the responsibilities of raising and caring for their children. In this context, as extensively documented in contemporary research (Abraham & Feldman, 2022; Feldman, 2023; Feldman *et al.*, 2019; Bakermans-Kranenburg *et al.*, 2019; Lotz *et al.*, 2020; Baldoni & Giannotti, 2022; Baldoni, Ancora, & Latour, 2021), fathers who assume caregiving responsibilities for a newborn exhibit significant endocrine and neurobiological changes. These changes manifest as early as pregnancy and persist

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throughout the perinatal period, including reductions in testosterone and estradiol, increases in oxytocin, prolactin, and vasopressin, as well as fluctuations in cortisol levels. Epigenetic modifications that alter gene expression and offspring phenotype have also been described (Mashood, & Champagne, 2014). These physiological modifications are accompanied by neural adaptations in the central nervous system and, in some cases, perinatal affective disorders such as depression, anxiety, and behavioral issues (Baldoni, 2016, 2024, 2025; Baldoni & Giannotti, 2020, 2022).

Grandparents as caregivers

When a child is born, today's parents often find themselves alone. Both parents work, making it more challenging to raise a newborn. Assistance from other adults becomes necessary. With the absence of a network of women who, in patriarchal societies, could provide support (such as sisters, aunts, and cousins), parents must seek help elsewhere. When financially feasible, families turn to nannies and babysitters, and as soon as possible, the child is enrolled in daycare and later in preschool for part of the day. In families where grandparents are available, they serve as an important resource and often become indispensable, at least during the early years. As caregivers, grandparents take care of newborns, feeding, bathing, changing diapers, rocking, dressing, holding, putting them to sleep, escorting them to and from daycare or school, educating, storytelling, conversing, playing with their grandchildren, and protecting them both inside and outside the home.

Grandmothers, in most cultures – including non-Western and primitive societies – have traditionally assisted mothers during childbirth and in the early care of the newborn (Sansone, 2021). Perinatal research has shown that grandmothers engaged as caregivers and allomothers promote mothers' perinatal mental health (for example, by moderating perinatal depression) and influence grandchildren's development (Manzari *et al.*, 2019; Riem, & van Der Stratten, 2024).

Historically, grandfathers were exempt from these duties. However, like fathers, grandfathers today, along with grandmothers, increasingly participate in caring for their grandchildren.

The phenomenon of grandparents involved in neonatal care is widespread in Western countries, particularly in Italy (Zamberletti *et al.*, 2018). Several considerations can be made regarding the condition of contemporary grandparents, especially during the perinatal period:

- Despite their age, many grandparents remain relatively young. Many drive, are energetic, maintain decent health, and often contribute financially to the family. Some grandparents are still working and must manage their time accordingly (Polvere *et al.*, 2018). The increasing retirement age may negatively impact their

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availability. In other cases, health issues may force them to choose between self-care and fulfilling their role as grandparents (Taylor *et al.*, 2017). Some have a partner who is unwell, no longer self-sufficient, and requires assistance, such as transportation to medical appointments, clinical exams, and treatments. In such cases, grandparents find themselves in a paradoxical situation, acting as caregivers on two fronts: for their partner and their grandchildren.

- Life narratives, such as those shared in psychotherapy or through semi-structured attachment interviews (Adult Attachment Interview), reveal that many grandparents become attachment figures by providing stability and security, particularly when both parents are frequently absent due to work or in cases of separated or divorced families. The death of a grandparent is often the first experience of significant loss in life, introducing to the concept of mortality.
- A perinatal loss affects the entire family – parents, siblings, and grandparents – like an emotional avalanche. Some manage to cope constructively, while others struggle, leading to disrupted intergenerational relationships (O'Leary *et al.*, 2011). For parents, the most crucial aspect is recognizing the ongoing intergenerational relationship with the deceased child. However, for grandparents, as well as for siblings, the perinatal death of a newborn is an emotionally challenging and often underestimated experience (Murphy & Jones, 2014).
- Grandparents sometimes have to divide their time and energy among multiple children and grandchildren, which can lead to conflicts. Relationship issues may arise between grandparents as a couple, between grandparents and their children, between siblings, and among grandchildren (e.g., jealousy, envy, and competition). In such cases, grandparents and parents must navigate and mediate these dynamics skillfully.
- In some situations, grandparents must interact with a non-biological father (or partner), who may be of a different gender, ethnicity, religion, or social background. Cultural, religious, or ideological biases can create serious acceptance challenges. In some cases, grandparents assume full parental roles, obtaining legal custody of their grandchildren (De Toledo & Brown, 1995), particularly when their children face difficulties such as rejecting parenthood, psychiatric disorders, substance abuse, or criminal activity. The phenomenon of "skipped-generation" families (Holman, 2011), in which grandchildren are raised by grandparents rather than their parents (Goodman, 2007; Zimmer & Treleaven, 2020), can lead to the transmission of distinctive behaviors or traits from grandparents to grandchildren without passing through the parents. Additionally, conflicts may arise within grandparent couples due to jealousy, envy, or competition. Some grandparents care for multiple grandchildren from different children, sometimes in different locations, making it impossible to provide

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equal attention to all. In such cases, parents must mediate sibling relationships and manage expectations.

- Some grandparents are currently cared for and supported by their children and grandchildren, who, in turn, become caregivers and attachment figures (Patrick *et al.*, 2023). Italy appears to be the leading European country for teenage caregiving of grandparents (D'Amen *et al.*, 2020), to the extent that the government has proposed a "grandchild bonus" to financially support them (Salvia, 2017).

The significant role of grandparents as caregivers has led to the development of perinatal educational programs aimed at supporting them in this role and fostering an "interdependent" family environment (Polomeno, 1999a, 1999b).

The role of grandparents often assumes importance in family therapy. Many contemporary families consist of two working parents. When children are born, they must be cared for as infants, taken to daycare and school, and protected at home. Systemic family therapists have been addressing the role of grandparents for years, encouraging a three-generational perspective (Baldoni, 2025; see Fig. 1). One author who has highlighted this aspect through dedicated seminars is Maurizio Andolfi (2021).

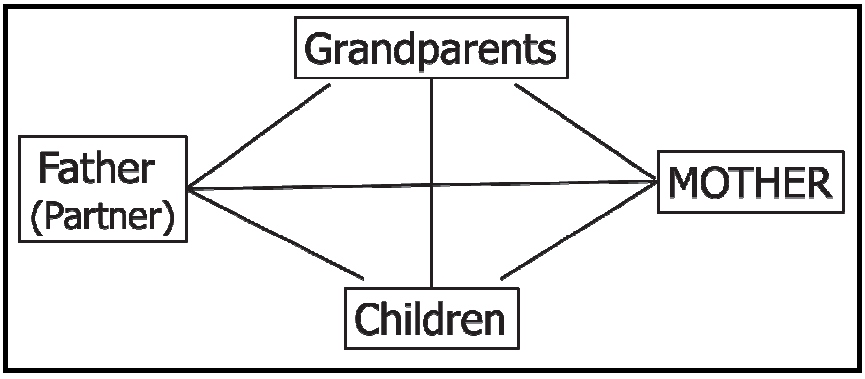

Fig. 1 – A trigenerational perspective (from Baldoni, 2025)

Experience in psychotherapy with individuals and their families teaches that becoming a grandparent can be the most beautiful period of life (which is still worth living). It makes you discover that even the elderly can be useful and feel loved by grandchildren and children. Grandchildren make us understand the importance of stories and narration of stories, the testimony of the family's past (when the parents were small or of their own parents, that is, the great-grandparents). For grandparents, the exercise of creativity and imagination is very important: inventing fun and exciting fairy tales and stories, new and old games, teaching how to cook, to love

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cinema, music or to play a musical instrument (Baldoni 2025). But above all, they can create an atmosphere of safety and stability, becoming attachment figures vicarious to those of the parents. In this, grandchildren play a fundamental and active role: they stimulate, guide, move, have requests, make observations, attract attention, provoke, play, joke and cry. This complex relationship with grandchildren involves the transmission of an ethical model (not based on social networks, TV or the Internet), which the new generations, as Lorenz (1973) rightly argued, need. They can therefore provide an affective, gender, ethical and social human model that integrates with that offered by parents. Becoming a grandparent, moreover, can also teach you to withdraw into the background, leaving space for the new generations without competing with your children. Faced with the looming danger represented by Artificial Intelligence (AI), grandparents can therefore represent an important element of compensation, as they report their own experience, offer life models and tell of a past in which the Internet, social networks and smartphones were unknown and were not a source of information.

Dysfunctional grandparents

Although for many people becoming a grandparent is one of the most beautiful experiences in life, which makes them more youthful and vital, for others it is a very difficult existential transition. Some refuse to be called grandparents (they prefer *daddy*, *papy*, *mamy*, or their own name) and do not accept becoming grandparents because it is the expression of a narcissistic wound, a sign of old age, loss of power and the approach of death.

Today, many adults are not prepared to face aging and society does not value those who take care of young people and in young people and adults it fosters a dysfunctional narcissism (see social networks, sports fanaticism, politicians, musical models, mass phenomena and gatherings in stadiums). These are business and marketing problems. Money is made on the narcissistic needs of young people and adults (Lash, 1979).

Many elderly people and parents today do not want to grow old and do not devote themselves sufficiently to their successors, there is a tendency to live in the present and a primary objective is the fulfillment of oneself and one's immediate needs, with the consequent loss of the sense of historical continuity and social responsibility (Selvini Palazzoli *et al*., 1998; Baldoni, 2025). Today parents want to appear younger, similar to their children, and no longer recognize themselves in the behavioral models of previous generations. They present themselves to their children more as friends or brothers (Bly, 1996), unconsciously denying their own role and parental responsibilities. The family, social and cultural function of the el-

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derly, as a result, is increasingly devalued, a phenomenon already recognized by Konrad Lorenz (1973) with the name of demolished tradition, and they are unable to use the experience of past generations as a model.

Other grandparents, while actively taking care of their grandchildren, tend to replace their parents or compete with them on how to care for and educate them, criticizing, devaluing or not recognizing (verbally or non-verbally, sometimes generating double bind phenomena) the role of parents of their children, see the phenomenon of enmeshment described by Minuchin (Minuchin, Rosman & Baker, 1978). An example could be a grandmother who explicitly or implicitly disapproves of her daughter for how she deals with pregnancy or for the way she cares for, feeds or educates her grandchildren. This can exacerbate a conflict of adolescent origin between grandmother and daughter, making the latter feel unjustified and favoring the manifestation of a perinatal affective disorder in her (Baldoni, 2025). Obviously, this problem can also manifest itself for the grandfather towards his own son, but also towards a daughter.

It may sometimes be necessary to relate to a non-biological father (or partner) of the same or different sex, or of a different ethnic or social origin. Cultural, religious or ideological prejudices can create serious acceptance problems.

Maternal and grandmaternal gatekeeping

The importance of the father is often underestimated by health workers (pediatricians, gynecologists, neonatologists, midwives, nurses), who tend to consider pregnancy and childbirth as exclusively female matters (Ireland *et al.*, 2016).

This attitude, called *maternal gatekeeping* (Allen & Hawkins, 1999; Gaunt, 2008; Baldoni, 2024), is often favored and shared by mothers themselves and leads to excluding fathers or legitimizing their disengagement towards mother and newborn. In patriarchal families it was considered normal and supported by women themselves who defended their role in the home from male privileges.

The phenomenon derives from an unconscious sedimentation of normative principles that date back to the Middle Ages. Historically and culturally, therefore, childbirth has always been a "woman's affair". Over the years it has led to significant discrimination between men and women, considering mothers as the main responsible for their children's developmental problems, as in the case of the first theories on autism or the idea of a schizophrenogenic mother in the case of psychosis. In families of the past and today, *grandmaternal gatekeeping* is also possible (Baldoni, 2024), when grandmothers exclude grandfathers and male children because they are considered less competent as caregivers. This attitude can lead to conflicts and competition in the grandparental couple.

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Neuroendocrine changes in grandparents

We know that a father (or a partner, even a homosexual one) who takes care of a newborn as a caregiver shows significant changes on a neuroendocrine and epigenetic level (Mashood, & Champagne, 2014; Fisher *et al.*, 2018; Feldman, Braun, Champagne, 2019; Bakermans-Kranenburg *et al.*, 2019; Lotz *et al.* 2020; Baldoni and Giannotti, 2022; Baldoni, 2024). The phenomenon manifests itself in both directions, both in the caregiver and in the newborn, influencing its development. What favors these changes is precisely the experience of perceptual contact (touching, hugging, warmth, smell, sight, hearing). The first research that highlighted the importance of perceptual experience was carried out by Myron Hofer first on rats, then extended to humans (1995, 2006). These changes also manifest themselves in the organism of grandparents, when they perform the functions of caregiver of a newborn. Currently, to our knowledge, the only research has been conducted on grandmothers, but none on male grandfathers.

A study on 50 caregiver grandmothers (Rilling, Gonzalez, & Lee, 2021), assessed through functional magnetic resonance imaging and self-report questionnaires, subjected them to stimuli such as photographs of their grandchildren and other newborns, invited to observe the figures and discriminate the child's emotion. The grandmothers were compared with 30 fathers studied with the same procedure. The results highlighted in grandmothers a more intense activation than that of the father in several areas involved in caregiving (medial orbitofrontal cortex, insula, right precentral cortex) with greater capacity for empathy and motivation. In fact, the central nervous system of grandmothers tends to change in a similar way to that of mothers and more intensely than that of fathers. These changes could favor an extension of the female life cycle for decades after the end of fertility (Hawkes, & Coxworth, 2013). Other contributing factors are: 1) the greater longevity of mothers' parents compared to the past (Coall, Hertwig, 2010) and the greater investment of mothers in caregiving (because they have few children). With the increase in separations and divorces, the help of grandmothers as caregivers has become more essential (Buchanan, & Rotkirch, 2018).

Grandchildren could therefore constitute a stimulus for grandmothers' brains, extending their post-reproductive longevity and this should also apply to other non-maternal caregivers (Rilling, Gonzalez, & Lee, 2021).

Research on paternal caregiving experiences (nutritional, hormonal, toxic, social, stress), has shown that they cause significant variations in the gene expression and phenotype of the offspring, which can persist for generations, also involving grandchildren (Mashood, & Champagne, 2014). These environmentally induced epigenetic modifications occur in gametes and epigenetic reprogramming is main-

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tained after fertilization by modifying the genes and phenotype of the offspring through potential alterations in DNA methylation. These modifications are transmitted to subsequent generations through the germ line.

Studies on hormonal modifications of caregivers are still few, and, once again, have been carried out mainly on grandmothers (Byrd-Craven, & Rankin, 2022), with the aim, for example, of deepening the endocrine aspects of relationships between women.

A *Global Parental Caregiving System*

Research on the neuroendocrine changes in mothers, fathers and grandmothers has led to the hypothesis of a *Global Parenting Caregiving System* in our species that is also activated in non-maternal caregivers (allomothers) (Abraham, Feldman, 2018; Rilling, Gonzales, & Lee, 2021). This system involves at least 10 brain areas underlying emotional empathy and motivation, including: medial orbitofrontal cortex, ACC (anterior cingulate cortex), IFG (inferior frontal gyrus), Insula, VTA (ventral tegmental area) and MPOA (medial preoptic area). On the endocrine level, the main changes are in: testosterone, estradiol, oxytocin, vasopressin, prolactin and cortisol (see Fig. 2.0). As mentioned, these changes are influenced by the perceptual experience of caregiving and no differences have been found in the relationship with biologically related or unrelated, foster or adapted newborns.

Currently, there are virtually no studies of this type on male grandparents and other allomothers (uncles, siblings, babysitters, wet nurses, adoptive and foster parents) (Abraham, Feldman, 2018; Rilling, Gonzales, & Lee, 2021; Feldman, 2023; Abraham *et al.* 2014; Bakermans-Kranenburg *et al.*, 2019; Baldoni, 2024) and could constitute a new perspective for research.

Endocrine changes	>testosterone, estradiol, >oxytocin, vasopressin, prolactin, cortisol
Neural Correlates	10 brain areas underlying emotional/cognitive empathy and motivation, including: medial orbitofrontal cortex, anterior cingulate cortex (ACC), (inferior frontal gyrus (IFG), Insula, ventral tegmental area (VTA), and medial preoptic area (MPOA)

Fig. 2 – Global Parenting Caregiving System

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Conclusions

After having studied the psychoneuroendocrine aspects of the father, research in recent years has also focused on grandparents. For now, the few scientific data concern grandmothers, but inevitably future studies will also consider grandparents and all other non-maternal caregivers (allomothers). These studies will allow us to better understand the adaptive skills of our species and to identify the best conditions for the growth and education of offspring. The results of the most recent research make it necessary to reformulate evolutionary theories that consider the psychobiological plasticity of our species, and specifically parental ones, not only in cultural terms, but also neuroendocrine and epigenetic.

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Loopomics: A possible breakthrough in the understanding and control of life

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Abstract: *Life sciences face challenges in developing theoretical frameworks for operating on biological systems. This is evident when considering disappointing results in biomedicine, as many diseases remain poorly understood despite decades of intensive efforts. The complexity of living systems is often cited as the reason for these shortcomings. To address these challenges, I have proposed a new definition of life, which I call Loopomics. According to this new paradigm, life is defined as any natural entity consisting of agents that produce physical changes, interconnected through chains of interactions that form closed loops. These loops create nonlinear systems whose dynamics are known to be characterized by single equilibrium points or transitions between different equilibrium points. The number of equilibrium points is determined by the kind of loop but is modified by bifurcation parameters, whose variation over time can significantly alter the behavior of the system. Thus, bifurcation parameters are key targets for interventions aimed at acquiring control of these systems. Biological loops give rise to ordered and predictable accumulations of materials that realize epiphenomena, including subcellular organelles, cells, tissues, organs, and organisms. These epiphenomena do not help in conceptualizing life and can be only used to identify, map, and manipulate the loop systems. The verification of the Loopomics hypothesis can be carried out by developing loop models of pathogenesis, identifying bifurcation parameters, and addressing them as therapeutic targets. If this approach is successful, it would provide positive validation for the hypothesis and could chart a new direction for biomedical research and applied biology.*

Key words: *Bifurcation parameters, Biodiversity, Biouniformity, Closed loops, Nonlinear dynamical systems, Life complexity, Unsolved diseases.*

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Introduction

Complexity is a term frequently used in scientific literature related to life sciences. Unsurprisingly, the book by Nobel laureate Erwin Schrödinger, *What Is Life* (Schrödinger, 1944), is considered a precursor to complexity theory (Portugali, 2023). One of the key concepts analyzed in the book is delayed entropy, which refers to a living organism's ability to postpone thermodynamic equilibrium, i.e. death, through its metabolism. In this paper, I present a new perspective on life, which reveals that Schrödinger's viewpoint is fundamentally misleading. However, this is not a flaw specific to Schrödinger himself but rather reflects a widely held belief among scientists. The specific mistake I highlight in the concept of delayed entropy, and concomitantly in the interpretation of life itself, is a confusion between the process of life and the products that it produces. These products give rise to epiphenomena, such as an organism and its lifetime, while life is an underlying phenomenon that transcends these epiphenomena. Within life, entropy is neither delayed nor abolished, it is simply present, just as it is in all other physical processes. The most critical point to address when analyzing life is how it achieves a self-sustaining process that continues indefinitely, as long as boundary conditions permit. My analysis clarifies this essential characteristic of life by providing a precise definition and exploring its implications.

Life is undeniably complex. Living beings are highly diversified, both among themselves and within their own structures (Campbell, 2003). This complexity is why modeling life is so challenging, particularly when using mathematical tools (Vittadello & Stumpf, 2022). It is also likely why our ability to interact with and engineer living systems is far more limited compared to inorganic objects. Despite the development of genetic engineering and biotechnology, the ability to control biological systems, even at the level of single cells, remains considerably lower compared to the achievements in physics and chemistry. These latter fields have given rise to technological advancements such as electronics, photonics, chemical synthesis, and materials science. In contrast, progress in the engineering ability of life sciences has been dramatically slow, as evidenced by the challenges faced in biomedicine. Despite decades of intense global efforts, backed by substantial financial investment, the results have been disappointingly limited. The rise of high-throughput analyses in the form of bio-omics, along with the concurrent development of systems biology, has not yet resulted in a significant acceleration in this area (Naylor & Chen, 2010). A staggering number of diseases still lack models for pathogenesis and the identification of effective therapeutic targets, while at the same time, biomedicine continues to seek an appropriate scientific approach to adopt (Rocca & Anjum, 2020).

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The debate on the problems of biomedicine seems inextricably linked to the complexity of biological systems, and therefore, complexity weighs as some sort of original sin for this area. Hence, overcoming such difficulty could imply the removal of complexity in the conceptualization of these systems. I have proposed an approach to the analysis of living systems that reaches this goal by starting from a definition of life that is totally non-conformist (Burlando, 2017).

Defining life is challenging

Despite the extreme diversification of living beings, the notion has long been established that these entities represent a unified phenomenon with a common origin, also known as the Last Universal Common Ancestor, or LUCA (Jheeta, 2017). However, as mentioned above, life is complex, and this is reflected in the various attempts by different authors to define the phenomenon (Benner, 2010; Cleland, 2019; Dhar & Giuliani, 2010). The definitions that have been proposed lack conciseness and are scarcely effective on an operational level, the one where they should enable the solving of practical problems. So, the core issue we face is determining whether it is possible to eliminate complexity in defining life.

I have proposed that the definition of life, or, in other words, its fundamental conceptual modeling, should focus on the interactions observed in the phenomenon, rather than on the elements that interact with each other and are ultimately produced through these interactions. The chemistry of life is extraordinarily diverse, with thousands of different compounds being present within a single cell (Naylor & Chen, 2010). The combination of some of these substances into insoluble aggregates (membranes, cytoskeleton, chromosomes, etc.) creates an astonishing variety of objects at subcellular (organelles), cellular (cell types), extracellular (matrix), and supracellular levels (tissues). Eventually, whole organisms are formed (bacteria, fungi, algae, plants, animals, etc.) whose individuality (worms, spiders, dogs, etc.) or coloniality (corals, superorganism plants, fungal mycelia, etc.) varies in prominence.

According to my proposal, all theoretical and practical problems faced by life sciences stem from prioritizing objects over processes. In contrast, I categorize life into two levels: one pertaining to interactions and the other to the epiphenomena produced by these interactions. Focusing on epiphenomena inevitably entangles us with the vast complexity of life, whereas focusing on interactions can eliminate the burden of complexity. An analogy can help clarify the problem. Flocks of birds form striking shapes in the sky, sometimes resembling familiar objects. These shapes are connected to bird flight through cause-effect relationships. However, if we attempted to study bird flight by analyzing these shapes, we would gain no

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useful information. While these shapes are highly diverse, they are always rooted in the same mechanical activity of individual birds. It is this dynamic activity that we should focus on to understand bird flight rather than the epiphenomena that emerge from it. In my opinion, a similar drawback affects our understanding of life as a natural process, leading to negative consequences across all applied fields of the life sciences, including the management of human health.

The Nobel laureate Richard Feynman stated that it is not possible to define anything precisely (Feynman *et al.*, 1963). This is quite correct, as any definition of a physical entity is affected by vagueness, and therefore, we can have various definitions for a specific physical entity. However, this does not mean that all possible definitions are equivalent. We can distinguish between good definitions and poor definitions, with the former allowing to acquire control of physical processes with higher efficiency than the latter. In physics and chemistry, it has been possible to formulate good definitions of physical entities, enabling various technological developments. Conversely, the current definitions of life are unsatisfactory, not because of their vagueness, but rather because they do not allow for operating on life processes with high efficiency, thus leaving many problems unsolved.

Loopomics: a new definition of life

The definition of life that I have proposed is characterized by the attempt to eliminate any element that could introduce complication or require additional distinctions. Therefore, my definition avoids referencing any physical or chemical feature of life, aiming to capture the essential traits that distinguish this natural phenomenon (Burlando, 2017). I started from the evidence that living systems are characterized by entities able to produce physical changes, which I will term agents. A typical example is provided by enzymes, which promote and sustain the intense chemical activity of living systems, known as metabolism. Another well assessed notion is the establishing of series of interactions among agents, or chains. To distinguish living from non-living entities, I hypothesize that any biological agent controls the activity of other agents and is reciprocally controlled by the same or different agents. Therefore, given an obvious non-infinity of agents, it follows that all chains are closed, i.e. they have the shape of closed loops. Branched chains are also present, but they are hypothesized to be part of closed loops too. Hence, a living being is defined as any entity where the above conditions are satisfied, irrespective of its physical nature. I have termed this kind of arrangement Loopomics (Burlando, 2017), where the suffix "-omics" emphasizes the global nature of the loop arrangement. However, unlike other omics, it does not signify multiplicity but rather, as we will see, uniformity.

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My definition of life is very concise compared to those we generally find in the literature (Gómez-Márquez, 2021). However, it explains various basic features of biological systems and provides distinct operational guidelines for design-based manipulation and control of these systems. The interactions between biological agents are generally nonlinear, i.e., the relationship between the input and output is not described by a straight line. In most cases, such interactions can be suitably modeled by Hill functions, as demonstrated by extensive data spanning from ligand-to-receptor binding (Gesztelyi *et al.*, 2012), to interneuron modulatory activities (Silver, 2010).

Nonlinear dynamical systems arranged as closed loops have been extensively studied in Systems and Control Theory. Given a series of agents mutually interacting in a closed chain, we have a negative loop if there is an odd number of inhibitory steps, or a positive loop if this number is even or zero (Blanchini *et al.*, 2014). Negative loops give rise to dynamical systems characterized by single equilibrium points or limit cycles, i.e., producing hoemostasis or confined oscillations. In contrast, positive loops can be multistationary, i.e. with multiple equilibrium points, allowing the possibility of switching from one equilibrium point to another upon suitable stimuli (Domijan & Pécou, 2012) (Fig. 1).

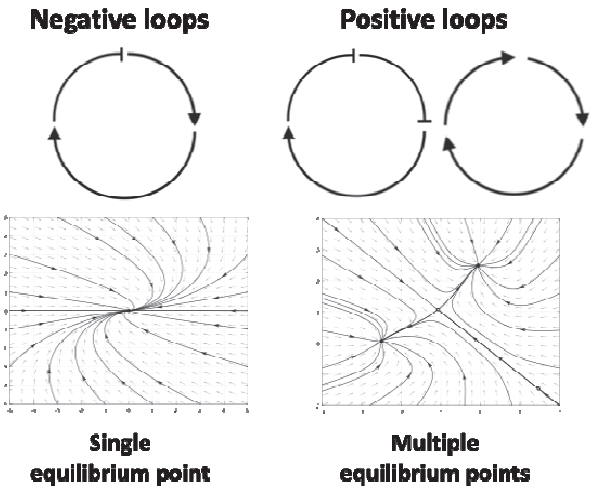

Figure 1. Different loop systems (above) and their dynamics depicted in phase space diagrams (below). Negative loops consist of closed series of interactions with an odd number of inhibitory steps (T-bar lines) and admit single equilibrium points. Positive loops have no inhibitory steps or an even number of them and admit multiple equilibrium points. Created in Matlab, version R2024b, MathWorks, Natick, MS, USA, https://it.mathworks.com/matlabcentral/fileexchange/110785-phase-portrait-plotter-on-2d-phase-plane, Copyright (c) 2022, Yu Zhang, Copyright (c) 2021, Erik A. Johnson.

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My definition of life involves a completely new perspective that simplifies the complexity of biodiversity into biouniformity. Within this framework, biodiversity is understood as a vast collection of epiphenomena resulting from the ordered accumulation of materials and their ongoing transformation (Fig. 2). These objects are considered ancillary when it comes to understanding the principles governing the phenomenon of life. On the other hand, the complex interactions among biological agents are viewed as nonlinear systems arranged topologically as closed loops, adhering to a very limited set of rules that constrain the behaviors of positive and negative loops.

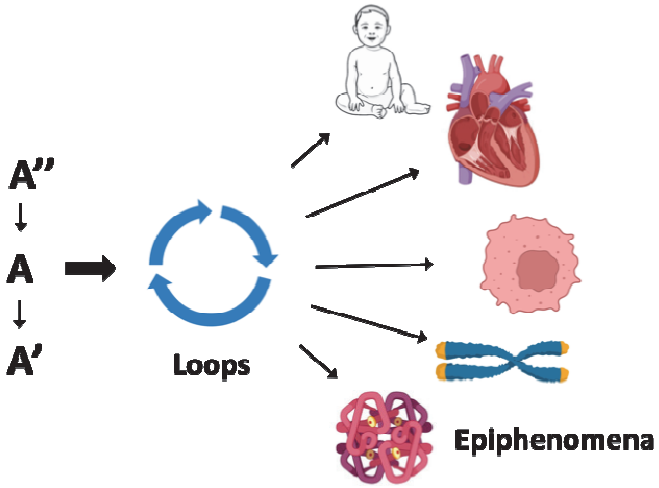

Figure 2. Schematic representation of a hypothetical definition of life. Life consists of agents (A) capable of producing physical changes, each of which interacts upstream with at least one other agent and downstream with at least one other agent. As a result, agents form closed loops of interactions. These loops are the essential phenomena of life, while the observable entities – such as macromolecules, supramolecular structures, cells, organs, organisms, etc. – are epiphenomena arising from the activity of loops. Created in Biorender.com, https://app.biorender.com (last visited 01-21-2025).

Limitations and advantages of Loopomics

Loopomics is currently a theoretical hypothesis awaiting experimental evaluation. However, it could offer several advantages. First, by adhering to the Loopomics conceptualization, life becomes fully analyzable on a mathematical basis. Thus, Loopomics could fulfill the prediction made by Uri Alon, one of the pioneers of systems biology, that biology has the potential to become a truly quantitative science through the application of mathematical tools (Alon, 2019). Such a revolution-

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ary shift in biological research could potentially lay the groundwork for designing operational interventions with the same precision and efficacy as those based on the principles of physics and chemistry, potentially ushering in a new era for the control and engineering of biological systems and addressing inherent challenges, such as diseases.

Second, Loopomics provides an explanation for an apparently paradoxical feature of life: the exact predictability of its epiphenomena. Based on the relatively precise estimate of the number of cells in the human body (Bianconi *et al.*, 2013), and the number of chemical reactions per second occurring in a single cell (Hołyst *et al.*, 2024), a rough estimate suggests at least 10^{25} (ten trillions of trillions) chemical reactions take place during human prenatal life. Even so, while a mother might feel anxious that anything proceeds well, once she has assumed that everything will go well, she is never concerned about the result of her pregnancy. She is absolutely confident that a baby with all the expected features of a newborn human will be born. Of course, a mother is generally unaware of biological mechanisms and places her confidence in the overwhelming case history of human births. However, and most surprisingly, even qualified neonatologists are quite certain that no butterfly effect, i.e., chaotic behavior (Lorenz, 1993), will occur during the baby's development. Yet, cellular processes are subject to thermal fluctuations and are inherently chaotic. Despite such thermodynamic constraints, an astonishing number of chemical reactions proceeds in perfect coordination, leading to cell division and differentiation. Furthermore, billions of cells carry out these activities under perfect harmony, allowing for tissue and organ development (Hołyst *et al.*, 2024). Many experts will seek answers in the human genome, but although genes direct the development, it is like a dog chasing its own tail because the genome and its metabolism are not external to the aforementioned thermodynamics. Conversely, on the Loopomics ground, everything seems quite reasonable. Loop systems allow for equilibrium points which represent poles of attraction for their dynamics (Luenberger, 1979). Then, if we assume that everything happening in a living being results from the activity of this kind of systems, then each biological event represents the attainment of some equilibrium point. In other words, only events corresponding to equilibrium points can occur, and therefore, given a specific starting point, the dynamics will proceed from one equilibrium point to another in a strictly predictable manner. This is why, without exception, a child develops from a fertilized human egg, or a wheat plant grows from the germination of a grain seed.

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Proving the Loopomics hypothesis

Nonlinear dynamical systems with loop arrangements have been identified in a wide range of biological processes (Angeli *et al.*, 2004; El-Samad, 2021), but a comprehensive theory in this sense has yet to be developed. Additionally, it is not yet understood that these systems represent the essence of life processes and that their analysis is the only way to comprehend the meaning of life processes and determine the most effective ways to manipulate them. The Loopomics hypothesis asserts these ideas but, as said above, it still requires experimental validation before being eventually acknowledged as a scientific theory.

By searching for a way to prove the hypothesis on an experimental basis, we could, for example, attempt to demonstrate that following its principles makes it possible to manipulate a biological system with an efficiency level not yet achieved. The wide array of diseases that affect the human body offers many opportunities in this regard. Several diseases remain problematic due to a lack of knowledge about their pathogenesis, pathophysiology, and therapeutic targets. This challenging category includes not only idiopathic and rare diseases but also a long list of common disorders, such as autoimmune, neurodegenerative, infectious, malignant, neurological, psychiatric, and metabolic diseases. Many of these diseases have been studied for decades with limited progress in developing cures, as evidenced by numerous examples: rheumatoid arthritis (Watanabe *et al.*, 2022), Alzheimer's disease (Anderson *et al.*, 2017), amyotrophic lateral sclerosis (Petrov *et al.*, 2017), and chronic pain (Maiarú *et al.*, 2023), among others. Therefore, the search for effective treatments for these challenging diseases could represent a testing ground for Loopomics.

Together with a group of co-authors, I have developed pathogenesis models for some challenging diseases based on loop systems of interacting biological agents. These pathogenesis models include fibromyalgia (Demori *et al.*, 2022), Alzheimer's disease (Burlando *et al.*, 2022), amyotrophic lateral sclerosis (Burlando *et al.*, 2020), and mal de debarquement syndrome (Burlando *et al.*, 2020). Like their inspiring Loopomics hypothesis, these results remain theoretical but nonetheless provide innovative insights. They demonstrate that it is possible to approach the triggering events of widely different pathological conditions using essentially the same kind of model. Moreover, these theoretical models are consistent with a range of data related to the corresponding pathological conditions. The case study of fibromyalgia is emblematic because it has been possible to extend the pathogenesis model through theoretical analysis up to the formulation of a potential treatment based on neurosteroid drugs (Burlando & Demori, 2024; Demori *et al.*, 2024).

The seminal idea of this kind of analysis is the obvious consideration that the

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development of any disease must involve some change in an organism's functioning. As mentioned earlier, the Loopomics hypothesis proposes that any phenomenon occurring in a living being reflects the nonlinear dynamics of loop systems. Specifically, the occurrence of changes is attributed to multistationary positive loops that undergo transitions from one equilibrium point to another under the action of certain stimuli (Rombouts & Gelens, 2021). The possibility of undergoing transitions depends on the variation of specific factors known as bifurcation parameters. As these parameters vary, the system's behavior changes abruptly in correspondence of bifurcation points, for example shifting from monostable to bistable or vice versa (Tsumoto *et al.*, 2012). Additionally, if multiple equilibrium points exist, their importance can vary depending on changes in the extension of their basins of attraction in the system's phase space, i.e. the space representing all possible functional states. Under the Loopomics framework, bifurcation parameters are viewed as the control buttons that offer the potential to gain influence over a specific biological process.

The fibromyalgia model mentioned above is based on a thalamocortical loop in which GABAergic transmission functions as a bifurcation parameter (Demori *et al.*, 2022). When GABAergic strength decreases, the system changes from monostable to bistable, acquiring a new pathogenic equilibrium point whose basin of attraction expands as GABA weakens further. As a result, the system becomes increasingly prone to settle on the pathogenic equilibrium point upon the action of stimuli such as signals from the spinothalamic tract. This model explains why gabapentinoids rate among the most effective pharmacological treatments for fibromyalgia. Gabapentinoids reduce the release of excitatory neurotransmitters, notably glutamate, thus potentially offsetting the weakening of GABAergic transmission. Additionally, the model is consistent with the poor efficacy of benzodiazepines, despite their role as positive modulators of specific GABA receptor subtypes. Conversely, it suggests that other positive modulators of GABA receptors, such as neurosteroids, which have never been considered for this disorder, could be an excellent therapeutic option (Burlando & Demori, 2024).

A unifying model for pathogenesis processes

Various studies have attempted to model diseases by using loop systems (Glass, 2015). However, these investigations have been always conducted on a case-by-case basis, without any effort to establish a unifying theoretical framework. The Loopomics hypothesis offers such unifying principles. If all changes in biological systems result from the dynamics of positive loops, and if diseases represent changes in the functioning of specific biological systems, then at the root of any

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disease there must be a multistationary positive loop that transitions between different equilibrium points (Burlando, 2022). Thus, Loopomics provides a unifying model for understanding the pathogenesis of the extraordinarily diverse range of human diseases, effectively transforming complexity into uniformity.

These ideas lead to the consideration of all diseases as essentially a single type of event, which is observed as a multitude of different conditions due to the diversification of biological epiphenomena. This perspective is highly unconventional respect to current opinions in biomedicine and clinical practice. More significantly, it is apparently in contrast with the innovative precision medicine, which views each patient as a unique case based on genetic traits, lifestyle, and environmental factors, thus aiming at tailored treatments on which great hopes are being placed (Evans W. *et al.*, 2024). However, this contrast is only superficial and, once again, arises from the confusion between fundamental life processes and their epiphenomena.

To understand the effective contribution Loopomics can bring to the medical field, it is helpful to divide health sciences into two classes of activities, viz. patient management and disease management. By patient management, I mean a set of activities including patient intake, diagnostic tests, prescriptions, hospitalization, surgery, psychological and nutritional help, and any other interaction between the patient and medical or paramedical staff. This complex system of operations requires significant effort and financial resources but offers satisfaction and rewards as it continuously evolves and incorporates technological innovations. On the other hand, by disease management I mean assuming control of a biological system that has switched between different functioning regimes, thus leading to an epiphenomenon generally referred to as a pathological condition. Secondary events, such as symptom proliferation, tissue degeneration, and interpersonal variations, generally create confusion in disease management. Instead, the focus should be on the primary event that marks the transition from physiological to pathological condition. Unlike patient management, disease management is a slowly advancing field of research. Furthermore, its progress remains relatively uncoupled from technological advancements, which, in my view, is the clearest evidence of the underlying conceptual limitations.

Loopomics is a genuine biological field that does not directly contribute to patient management. This latter addresses epiphenomena, ranging from anatomical details to whole organisms, including their essence as human emotional beings and social identities. By contrast, Loopomics could provide crucial support to disease management, as this field needs to address the biological events underlying pathogenic processes with an appropriate conceptual framework.

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Conclusions

In summary, this study argues that the current conceptualization and modeling of life are insufficient, offering limited opportunities to effectively manage biological processes. This shortcoming is evident in the challenges biomedicine faces when studying a wide range of diseases. To overcome this stagnation, I have previously proposed the Loopomics hypothesis. This hypothesis suggests that observable life is a collection of diverse epiphenomena generated by the activity of loop systems, which can be conceptually unified within a single framework. As such, Loopomics provides a pathway to navigate the complexity of life, by focusing on abstract constructs, such as interaction patterns, rather than on physical objects. These patterns are then represented through mathematical models as loop systems with nonlinear dynamics, ultimately identifying equilibrium points and bifurcation parameters. The physical counterparts of bifurcation parameters can then be targeted to gain control over biological processes. Loopomics offers insights into fundamental questions about life, such as the paradox between the vast array of life events and their precise predictability in the absence of butterfly effects. Although still theoretical, this framework could be validated through experimental evidence. If Loopomics successfully addresses biomedicine's current struggles to resolve health challenges, the hypothesis would be confirmed. Therefore, experimentally validating this hypothesis represents a worthwhile pursuit.

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