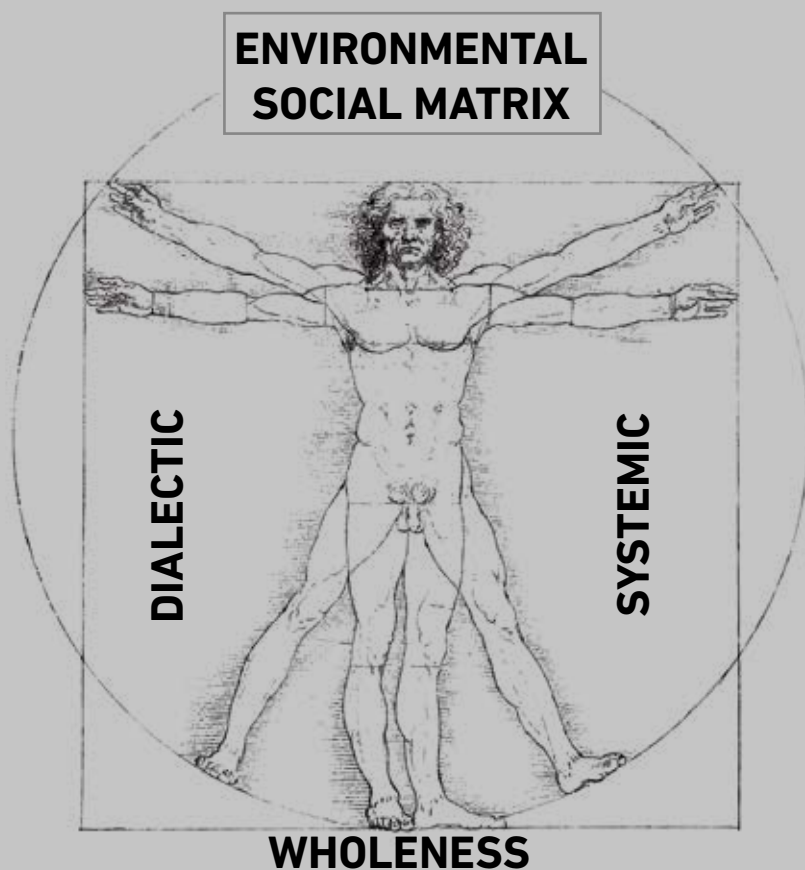


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pneireview

Journal of Italian Society of Psychoneuroendocrineimmunology

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pneireview

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Editor in chief Francesco Bottaccioli

pneireview

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Summary

Gianfranco Porcile – *Systemic Vision in Medicine*

This paper advocates for moving beyond the reductionist biomedical model toward a systemic vision based on Complexity Theory. The author outlines the evolution into Engel's "biopsychosocial" model, which views biological, psychological, and social factors as interconnected in patient health. The text presents the PNEI paradigm as the clinical application of this vision, serving as a bridge between molecular biology and philosophy by scientifically demonstrating the interactions between the organism's systems. Finally, it discusses the "One Health" concept and the "Ecological Model", emphasizing that human health is inseparable from environmental and animal health, thus requiring medicine that integrates personalized care, environmental sustainability, and Medical Humanities.

Ilaria Demori – *The microbiota-immune interaction in the gut-brain axis*

This article explores the crucial role of the immune system (IS) as a coordinator within the microbiota-gut-brain axis. It describes how bacterial metabolites, particularly Short-Chain Fatty Acids (SCFAs), act as signaling molecules that regulate the integrity of both the intestinal and blood-brain barriers, as well as neuroinflammation (by modulating microglia and astrocytes). The author analyzes these dynamics in the context of Parkinson's disease, where dysbiosis and altered SCFA levels contribute to neurodegeneration. The paper concludes by highlighting the therapeutic potential of probiotics, prebiotics, and postbiotics for treating neurological and psychiatric disorders, while noting the need for further clinical studies in humans.

Mauro Bologna – *Environmental causes of disease in the Anthropocene. A paramount PNEI view*

This paper analyzes environmental causes of disease in the current Anthropocene era through the lens of PNEI and the “One Health” concept. The author examines the devastating impact of pollution (air, water, soil), microplastics, and persistent chemicals (such as PFAS) on human health, linking them to endocrine disruption, chronic inflammation, and neurodegeneration. Climate change and risks associated with modern lifestyles (stress, technology, diet) are also discussed. The article concludes with a strong call for primary prevention and social/political responsibility to mitigate the environmental “polycrisis” threatening the global health of all living beings.

Marina Amore, Alessandro Bianchi, Donatella De Colle, Laura Bastianelli, Francesco Bottaccioli, Raffaella Cardone, Ines Romy Cutrona, Emanuela Stoppele, Laura Vaccaro – *Reflections on the physical and biological dimension of the person in psychotherapy and in PNEI-oriented clinical practice*

This paper reflects on integrating physical and biological dimensions into PNEI-oriented psychotherapy. The authors highlight a paradox where, despite growing theoretical attention to the body, it remains marginal in actual clinical practice. The concept of the “organism” as an inseparable mind-body unit is introduced to overcome the fragmentation of different psychotherapeutic models. The article suggests specific technical modifications, such as using interoceptive listening and attending to bodily signals (breathing, muscle tone) within the therapeutic relationship, ultimately proposing integrated training that includes biological competencies for psychotherapists.

Francesco Bottaccioli, Anna Giulia Bottaccioli – *A systemic and dialectical paradigm for Psychoneuroendocrineimmunology and integrated care science*

This paper outlines a philosophical and scientific paradigm for PNEI and integrated care science. The authors critique reductionist models and Cartesian dualism, proposing instead a “systemic and dialectical” approach. Drawing on Yin-Yang dialectics as a framework for biological regulation (e.g., in the immune system), the article explores scientific evidence of bidirectional communication between the psyche and biological systems, citing mechanisms such as stress-induced inflammation and the gut-brain axis. It concludes by emphasizing the need for a new philosophy to guide research and clinical practice toward a true integration of medicine and psychology.

Silvia Moneti – *The Influence of Healthcare Environment Architecture on the Psycho-Neuro-Endocrine-Immunological System*

This article explores the impact of architectural and environmental design on the psycho-neuro-endocrine-immunological (PNEI) system of acute and chronic patients. It outlines operational design guidelines for orientation, accessibility, circadian lighting, acoustics, clinical aromatherapy, and room personalization. Furthermore, it addresses specialized care settings – including labor and breastfeeding rooms, ICUs and NICUs, prosthetic architecture for cognitive impairments, and home-based care – positioning architecture as an integrated therapeutic tool to foster psychophysical health.



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The network as a paradigm

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This issue of *Pnei Review* open access has a common thread that binds the different and, apparently, disparate topics it covers.

Topics of great relevance and scientific and clinical interest. They range from the examination of the influence on health of the organization of physical environments (where we live, work, study, take care of ourselves) to the reconstruction of the pathogenic effects of pollution and more generally of the environmental crisis that grips us, up to the historical and clinical reconstruction of the centrality of the body, as a physical and biological entity, in psychological and psychotherapeutic work.

The common thread is constituted by the demonstration that, in order to understand phenomena, those concerning the individual and also those concerning the physical environment, it is necessary to adopt a systemic paradigm, which grasps the network of interdependent connections.

There is no phenomenon, biological or physical, that exists independently of the context, that is, of the action of other phenomena. This concept, in medicine and psychology, allows us to understand the origin and course of diseases more effectively and, at the same time, hypothesize treatment strategies. It is evident, in fact, that pathologies of psychiatric interest, such as dementia, depression, schizophrenia can be understood and treated within a systemic paradigm that traces the interdependence between nutrition, microbiota, inflammation, stress and trauma, environmental pollution. But even the planetary physical phenomena that are occurring in recent years can only be understood in the logic of the dialectical inter-

connections between the increase in atmospheric CO₂ concentration, climate change, the increase in large fires, the reduction of biodiversity, ocean acidification, just to mention the most striking and worrying phenomena. Scholars of the physical environment now speak of “polycrisis” (Søgaard Jørgensen *et al.*, 2024) to describe the interconnection between phenomena, which can no longer be studied separately.

In this context, a rebirth of philosophical reflection is needed, which deals with life and adopts a systemic and dialectical gaze (Bottaccioli F., Bottaccioli A.G., 2025).

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Systemic Vision in Medicine

Gianfranco Porcile*

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Abstract: Linear thought should give way to the systemic view, from the perspective of Complexity Theory. According to this approach in Medicine disease is considered as part of a larger, interconnected whole. From the “Biomedical” model it is necessary to move to the “Biopsychosocial” model. Today it is time to see the human person within and as an integral part of the ecosystem: this is the concept of “One Health”. Several new paradigms of care and research arise from this kind of vision: the most important to date is the PNEI Paradigm. But other paradigms are especially engaged on the economic and environmental sustainability front. Without detracting from the significant role of technology, increasingly today’s Medicine must reevaluate the fundamental role of the “Medical Humanities”, from bioethics to philosophy, from communication to the integration of knowledge and research.

Key words: Complexity, Biopsychosocial model, Ecological model, One Health, PNEI Paradigm, Systemic Vision

Ayurveda, as a science of life, looks at the man in his totality, not as a set of parts, and states that the maintenance of his health cannot be independent from his social and spiritual context, nor separated from his cosmic connection (Terzani, 2011).

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Introduction

Thomas Kuhn (1922-1996) introduced the concept of the “phases” of science: Preparatory period, Acceptance of the paradigm, Normal science, Birth of anomalies, Crisis of the paradigm, Revolution of the paradigm, New paradigm, Acceptance of the new paradigm. These phases are repeated cyclically (Kuhn, 1962).

For example, the Cultural Paradigm had a particularly important first phase, which we could call “Age of the Reason”: Descartes (1596-1650), Newton (1643-1727), Laplace (1749-1827) had the merit of imposing the scientific method with the so-called “Linear Thought”. Today we call it the “Reductionist Model”: in Medicine this corresponds to the concept of disease considered as an isolated and incidental event.

But in the last century the second phase of the cultural paradigm was imposed: Thought became “Complex Thinking”, and it was the so-called “Age of uncertainty”: Heisenberg (1901-1976) and Godel (1906-1978) were the first exponents of this new paradigm. In Medicine this corresponds to a concept of disease considered as part of a larger and interconnected whole.

The Systemic Vision

When we speak of Systemic Vision, we are referring to a philosophical, scientific, sociological, mathematical, pedagogical concept, and the list could go on. As does the list of exponents who, in addition to the two already mentioned, have contributed to enriching this paradigm continue: Henry Poincaré (1854-1912), Jean Piaget (1896-1980), Gregory Bateson (1904-1980), Alan Turing (1912-1954), Urie Bronfenbrenner (1917-2005), Fritjof Capra (b. 1939), Pier Luigi Luisi (b. 1938), Giorgio Parisi (b. 1948) to mention only the main ones. It is not even possible here to mention what role each of them played in building systemic thought: we can think of each as the indispensable tile in composing a mosaic rich in colors and figures. Soon the contribution of cybernetics, the discipline that studies processes concerning «communication and control in the animal and the machine» (Norbert Wiener, 1894-1964), was also added (Wiener, 1948). Finally, it came to coin the term “Complexity Theory” thanks to the insights of Edgar Morin (b. 1921), (Morin, 1977, 1982, 1985), Ilya Prigogine (1917-2003) (Prigogine, 1985) or, in Italy, by Gianluca Bocchi (1985) and Mauro Ceruti (1985).

Complex is not synonymous with complicated, and simplicity is only one aspect of complexity (Baldoni, 2010, 2024). A complex phenomenon is more understood by what we do not see and cannot describe than by its clear evidence. According to Edgar Morin:

- a) To study complex phenomena without distorting them with arbitrary simplifications, it is necessary to study these phenomena in their environment.
- b) Complex phenomena always depend on their observer. Scientific research, therefore, does not involve knowledge of an absolute and immutable reality (this concept derives from second-order Cybernetics).
- c) Every complex phenomenon is by its nature organized, so it takes on the characteristics of a system.
- d) According to the complexity paradigm, the most useful way to understand the world is through a “network of theories”, which allows us to place ourselves, as appropriate, within one point of view or between one point of view and another, when this is useful. Relationships are not linear. So, fundamental is the ability to tolerate doubt, ambiguity, contradiction, the coexistence of opposing terms such as oneness and dualism, disorder and organization.

The definition of complexity is obviously not simple. Linear reasoning considers the various factors as a relationship of cause and effect in sequence: each factor is effect of another factor and cause of a third factor. But the reality is quite different: today we know that the world is made up of different elements which influence each other continuously. This also applies to the human person constituted by body/soma, mind/psyche and soul (meaning with this term any declination of spirituality, any sense of the sacred). It applies to the entire ecosystem.

It seems appropriate at this point to recall a central aspect of science: the concept of causality, moving from linear (Aristotelian) to multifactorial (common to 20th century medicine) to circular (introduced by general systems theory and cybernetics) and complex (allowing causal relationships to be considered from different perspectives) (Baldoni, 2010, pp. 27-34).

To get a vague idea, it can be helpful to think about the game of chess where on the board insist 32 pieces with different possibilities of movement and action: this can actually give an idea, although simplified, of the situation in real life, in the world today. It is not a coincidence that today, in some educational institutions, the game of chess has become a teaching course. Complexity cannot be eliminated: we must know it and then be able to manage it. Depending on our ability to manage what was previously a difficulty can become an opportunity. The classic example is that of the surfer: the waves of the rough sea become an opportunity for fun and adrenaline thrill. Even sailing can be a valid metaphor: strong wind, in expert hands, can turn into a rewarding sport full of satisfaction.

Literature on this subject is obviously rich, often in the form of books rather than scientific publications. For those who would like to study more carefully, by way of example, we cite two books by F. Capra written each with a different co-author. In the first, the authors propose a different philosophy from the so-called “Decrescita

Felice” (“Happy Decrease”) focusing instead on a Qualitative Growth, and where, among other things, you can read: «The view of the human body as a machine and of the mind as a separate entity is giving way to a view which interprets not only the brain, but also the immune system, bodily tissues and even each cell as a living cognitive system» (Capra *et al.*, 2013). The second book proposes a summa of Systemic Vision ranging from physics to biology to medicine (Capra *et al.*, 2017).

The biopsychosocial model

So far, we have dealt with the subject of complexity from a general point of view. But more particular and sectoral aspects can and must also be seen from a systemic perspective. For example, think to the so-called “War against cancer” which years ago was too simplistically proclaimed by the President of the USA. This technical and scientific aspect has revealed that it is characterized by considerable complexity: already in 2014 were listed ten medical cancer therapy modalities (excluding surgery and radiotherapy) that could interact synergistically but also antagonistically. And certainly, the current advances in medicine today, with the implementation of therapeutic choices, make this complexity even greater. Therefore, the choice between one type of therapy and another must be increasingly carefully considered, in case of relapses of the disease, also the consequences that this choice could have on subsequent treatment possibilities (Hanahan, 2014).

Until now, Medicine has been inspired by the “biomedical” model, which is based on linear thought and a disease-oriented doctor-patient interpersonal relationship. In practice, care of the sick person was analyzed in successive stages almost separate from each other: clinical history, diagnosis, prognosis, therapy, and rehabilitation. Nowadays, this model should be replaced by the “biopsychosocial” model proposed by George Engel (1977), based on systemic theories and a person-centered relationship between the medical team and the sick person, which, together with biological and organic factors, also recognizes the important role played by psychological and social determinants of health.

This model is particularly important in the most sensitive patient groups such as pediatric and elderly patients. Biopsychosocial model means holistic approach, anthropocentric vision (no longer the disease at the center, but the patient, or rather the citizen, the human person), real integration of Medical Humanities with Technological Medicine. It is important to recognize that, if the doctor is the expert on diseases and health techniques, the patient has an equal role, as an expert, just unique, of “his” person, of “his” disease, of “his” expectations. One last aspect must be highlighted in this model: there is no longer a simple doctor-patient relationship, but the doctor is now always part of a multiprofessional team (doctors,

nurses, administrative, volunteers, etc.) and multidisciplinary (collaboration with psychologists, laboratory technicians, anatomical pathologists, organ specialists, etc.): in practice, while the figure of the reference doctor and often the case manager remains important, the patient's relationship is with the whole team, which is also, in practice, responsible, even as a collective, towards the individual consumer/ patient. But also the latter is in reality no longer alone: the family is also becoming increasingly important, both as partners in decisions that are more often shared by the sick person, including with relatives (of course, if he wishes), both as a caregiver and as an important part of care, especially in particular situations such as palliative care and home care (Santosuosso, 1998).

Moreover, in many cases a patient is not able to characterize his condition as a true disease or rather a general life problem, and even the doctor cannot make an exact distinction. Is pain, for example, a symptom or an illness? Psychological, cultural and ethnic aspects strongly influence the perception and communication of pain. The same applies to conditions such as asthenia, fatigue and depression. Since Sigmund Freud published his studies, medicine has developed new branches including psychoanalysis, psychobiology and psychosomatic medicine, with new related interpretations of organic diseases such as gastric ulcers, bronchial asthma and even cancer. But today we increasingly know that there is reciprocal and bidirectional contamination between the organic sphere and the psychological one, so it is wrong to analyze one of these two worlds without taking into careful consideration also the other.

The proposal of this biopsychosocial model is not very recent: today it begins to be known and applied but not as much as would be desirable (Engel, 1977; Bottaccioli, 2024).

In summary, the biopsychosocial perspective starting from systemic assumptions, considers diseases as a result of the complex interaction between factors that distinguish not only different systems (genetic, biochemical, cellular, tissue, metabolic, immunological, psychological, relational, social, environmental), but also levels of different systems (from the molecular to the macrocosm) (Baldoni, 2010).

Perhaps the biopsychosocial model may today seem reductive because it does not take into due consideration some aspects, for example the spiritual dimension. As Susanna Bianchini says «Also the spiritual dimension is an aspect that concerns the life of the human being, meaning by spiritual a constant and dynamic process of care: of one's own inner harmony, of the coherence of life with its own value system and of the relationship with its own soul and with the afterlife. It is a dimension anthropologically studied and that highlights how the theme of spirituality is relevant, since it is considered one of the predictors of psychological well-being, therefore also of mental health» (Bianchini, 2024).

The Biopsychosocial paradigm has rightly influenced other approaches: for example, the new WHO Guidelines (2023) on the comprehensive treatment of chronic low back pain (Barsotti, 2024).

For a long time, medicine was based on the reductionist model: too much time. The genetic reference of J. Monod for a long time has represented a way of interpreting reality which, based on the model of Molecular Biology by Francis Crick, gave us at the same time security and protection (Monod, 1970). But, as we said at the beginning, T. Kuhn soon convinced us that paradigms go periodically into crisis and must be updated and replaced by new paradigms (Kuhn, 1962).

The PNEI Paradigm

It is at this point that the PNEI (psychoneuroendocrinoimmunological) paradigm is placed: his novelty is basically to combine systemic vision and integrated clinical philosophy, with scientific demonstrations of biochemical and biomolecular order.

A fundamental change has been, and continues to be, represented by modern Immunology that, going beyond the concept of *Self* and *Non-self*, presents the immune system as the strategic regulator between our organism and the whole galaxy of microbes (bacteria, viruses, fungi) that colonize our intestines first of all, modulated continuously by the environment, food, drugs, stress. From this point of view, immunology is a bridge organically linking biology and philosophy, two branches which until now have spoken two different languages while ignoring each other (Bottaccioli, 2022). And this is supported by the demonstration that the nervous system and the immune system communicate with each other using the same molecules.

Against the current trend towards more technological medicine, and enthusiastic about research increasingly oriented towards computer science and artificial intelligence, the PNEI paradigm is fully integrated into the philosophy of Systemic Vision applied in clinical practice. It involves attention to analysis, but within the holistic vision. Only with the PNEI paradigm it is possible to see at work the systemic vision, which goes from the affirmation of some general principles (not only Engel but also F. Capra) to the definition of a new pathophysiology and a new integrated treatment. The revolutionary idea of the PNEI paradigm lies in keeping together molecular biology and systemic vision of life, a vision that is therefore rooted in science. It does not remain on the humanistic level, where it does not interfere with biomedicine (just see the zero effect of the so-called Medical Humanities on training in medicine), but works to restructure from the bottom up the life sciences (humanities and biomedical). This is because it is a philosophical and sci-

entific paradigm or, in other words, it is a philosophical paradigm based on science, meaning by science everything that increases verifiable knowledge.

It is important to add that the sciences of care must respond promptly and adequately to the epochal changes taking place. With the advent of Artificial Intelligence and Machine Learning (literally the machines that learn by themselves), today's medicine seems to be facing not so much a great opportunity as an extreme danger. The risk is clearly what already in the 18th century Julien Offray de La Mettrie had synthesized with the name of "*L'homme machine*", describing human physiology as the result of mere activation of mechanical devices. Even the advent of the Medical Humanities did not have much impact on the technological conception of cure. And this is because the two worlds continued to live separated as two rails that they go on, perhaps far away, but without really interfacing.

The great merit of the PNEI paradigm has been and continues to be that it is a bridge between the two approaches, a bridge not only philosophical but based on scientific achievements demonstrated at the biological and chemical level. Thus, the new PNEI paradigm knows and cares for the human being in its entirety, identifies the social and environmental determinants of health, orients molecular research within the systemic vision of the human being, and finally promotes empathy between patients and health care providers.

Let us for example examine the Stress Theory by Hans Selye. His brilliant idea, with the fundamental role of stress, remains confirmed even after many years. But as always happens, there are no longer only cortisol and catecholamines to regulate the body's response: reality is much more complicated, indeed complex. The allostatic load is modulated by a whole series of pro-inflammatory and anti-inflammatory cytokines functionally interconnected into a network of mutual regulation (Bottaccioli, 2017).

An essential element of the PNEI paradigm is the microbiota-gut-brain axis, which would be better described as microbiota-gut-brain-mind axis. Generally, we speak of the "microbiota-gut-brain" axis to connote all possible interactions between these three fundamental systems of the human body (and not only human). Within this definition someone proposes to add, referring to the human context, also the term "mind" because it is not reducible entirely to the neural level as well as each other term of the expression "microbiota-gut-brain" is not entirely reducible to the molecular physico-chemical level of its composition (Agnioletti, 2023).

One possibility that will certainly have a great development of research in the future is that of *Animal Experimentation* and its alternatives. Beyond the right considerations of ethical and bioethical order, even science today realizes that animal testing based on the man-machine model is no longer acceptable: already today there are alternative methods, which will be implemented soon. Consider the use

of imaging (CT, PET, MRI, etc.) and new in vitro methods. A very promising alternative for research into metabolism and toxicokinetic of substances is the use of “organoids” from human tissues, which, using 3D stem cell cultures, simulate the various organs of the human body (Bottaccioli, 2017).

It is interesting how, starting from the analysis of Engel, with its biopsychosocial model, the PNEI paradigm manages to treasure also modern scientific achievements. For example, by incorporating the insights of Carlos E. Sluzki, and integrating neuroscience, genetics, mind, and the social world into a complex of systemic formulations with profound implications for training, practice, and research in the field of family processes and therapy in general. According to this theory, social networks influence biogenetic networks, and, at the same time, the neurobiological system influences the social world and communities. In the light of this co-evolution, the therapist must consider all these processes of adaptation in an integrated vision, and in continuous development, of the human being under the biological, psychological, and social aspect (Sluzki, 2007).

In summary, the biological and cultural revolution of the Third Millennium has led to the birth of profound changes in many approaches and different skills to take care of the human being in all its complex dimensions. Doctors, physicists, biologists and physiologists have seen the appearance of profound changes not only linked to increasing scientific results, but also, and especially, related to new scientific bases in a systemic perspective that transcends the watertight compartments of the different branches and subjects of knowledge and action (Bottaccioli, 2011).

It has been shown that even branches which appear far removed from medicine, such as architecture, can have an important influence on the psycho-neuro-endocrine immunological system (Moneti, 2022).

Complexity and Ecology

The biopsychosocial model, which is still valid today from the point of view of the relationship between physician and patient considered in an expanded context as we have seen to the family and social situation, must evolve today into a model that takes into account the fact that it is now well known that both patient and physician are organic parts of the biosphere. We could call this form of evolution the «ecological model» (Palazzo, 2013).

The “Ecological Model” is biosphere-centric: attention is therefore not only focused on the sick patient or the healthy citizen but must consider the entire Biosphere and the consequences that the doctor’s choices may have on it. Therefore, this model needs a Community of Practice, composed of all the operators, but also with the presence of patients’ representatives, which implements eco-responsible

choices on the potential current and future impact on the human and social environment, and the biosphere.

Meanwhile, we must note the end of anthropocentrism, a concept that has accompanied us wrongly, and here the Catholic Church has played an important role for a long time, too long. The first injury to man's narcissism came a long time ago when Copernicus demonstrated that the Earth was not at the center of the Universe. The second humiliation (the term is from S. Freud) came from Charles Darwin who demonstrated the ineradicability of the animal nature from man. The third came from Sigmund Freud himself, who proved that the self is not master in his own house (Freud, 1916). Finally, the coup de grace was the techno-digital one, with Alan Turing demonstrating that humans are not "alone" to think (Floridi, 2020).

It seems pleonastic to point out that we must not confuse this "ecological" model with what Bronfenbrenner stated when he published his *Ecology of Human Development* (1979): when he describes his theory of ecological systems, distinguishing different levels of systems (micro-, meso-, exo- and macrosystem) he looks specifically to the family, the school environment and society (Bronfenbrenner, 1979).

In summary the Ecological Model must try to reduce the "Ecological Footprint" (that is the damage to the environment, measured as production of CO₂, etc.) for which we are responsible as physicians, just as we are already trying to do as citizens, ordinary men and women (Bonaldi, 2023).

Of course, we must remember that the priority remains the well-being of the patient and the search for the most effective treatment, but in a vision which takes seriously into account the vital and environmental needs of the biosphere.

From these premises was born the concept of "One Health". The One Health approach is a type of holistic methodological approach, which consists in considering the global health of the planet as important as that of individuals: therefore, it proposes to address to the problems with interdisciplinary collaborations. One health = human health + animal health + environmental health. The One Health definition was coined in 2004 at a conference called by the Wild Conservation Society (Manhattan Principles). Initially it was applied mainly to animal health, food safety, zoonotic epidemics, and antibiotic resistance. Today, this approach also takes careful account of a) the pollution of natural resources and the destruction of biodiversity; b) urban planning and spatial, productive and transport planning; c) exploiting the potential of technology and information technology to safeguard the integrity of the planet. In summary "One Health" is a systemic approach aimed at protecting all forms of life on Earth because every life is essential to maintain the balance of the ecosystem: every form of life is useful for the health of other living beings. In summary: a single "HEALTH" (Editorial Lancet, 2023).

Other paradigms

As a result of all these acquisitions, other paradigms have also been born in addition to the PNEI paradigm.

For example, the Slow Medicine movement, a new way of considering health and care, was born in 2011. Founded on a systemic, Network vision, it aims to be a new paradigm, a path of comparison between different approaches to care, meaning by this term more the care and the healthcare than the merely therapeutic side (Bert, 2018) (<https://www.slowmedicine.it/>). One of the key words of Slow Medicine is respect for Appropriateness. In healthcare, appropriateness refers to the correct use, based on scientific evidence and clinical guidelines, of an effective intervention, delivered to the right patient, in the most appropriate way and at the right time, minimizing risks and maximizing benefits (Bobbio, 2017).

Some medical specialties have carried out projects that consider the care and therapeutic aspects from a perspective of systemic vision and environmental sustainability.

For example, the Italian Society of Nephrology has the objective of reducing the ecological footprint of therapies, and in particular dialysis, by saving water, energy, and sustainable waste management (Piccoli, 2020).

Similarly, the CIPOMO (Italian Primary College of Medical Oncology Hospitals) has formed the working group “Green Oncology” with objectives of economic and environmental sustainability (Palazzo, 2010; Bretti, 2014). The experience of Integrated Oncology, while requiring further scientific confirmation, represents a further approach in this direction (Baccetti, 2015).

Following this perspective, which looks in particular to what we have called “ecological model”, we cite the experience of the group of US anesthetists of GAIA (Green Anesthesia Initiatives), which have demonstrated how care can be taken with regard to the environmental impact without harming the health of the patient (Colquhoun, 2025).

But the experiences in this field of interest are numerous: for instance, we recall one more. The “Complexity Institute”, although mainly interested in the world of business and management, is also committed to health: consider the publication of the book “The complexity of an epidemic” at the time of the COVID pandemic (<https://www.complexityinstitute.it/>).

Even an apparent simple topic such as nutrition/diet must be seen today from a systemic perspective. Today we know that the agro-food chain includes several stages: production, distribution, consumption, and waste (including compost). It has close correlations with Economy, Land use, Environment, Health, Work, Chemistry, Social aspects, Culture. And we know that each of these themes com-

prises many other subsystems. A new name has therefore been born: “Agroecology” (Wezel, 2009).

As a conclusion to this short list, we would like to mention psychosomatics: this approach, in a complex conception, is actually proposed not so much as a new paradigm but as a metaparadigm, in the sense that it allows the adoption and integration of different paradigms while accepting any differences and paradoxes (Baldoni, 2010).

The role of SIPNEI

SIPNEI (Society of Psychoneuroendocrineimmunology) has since its birth made a careful study, with its theoretical consideration and research, of new or little explored by the official Medicine territory. Examples include Microbiota and correlations with brain functions and psychiatric pathologies (bowel-brain axis); Epigenetic, (*Pnei Review*, 2023); Lifestyles; Low-grade chronic inflammation; Endocrine disruptors; Therapeutic techniques inspired by oriental culture (relaxation, meditation, acupuncture, plantar reflexology, yoga, Tai Chi, etc.) (Galfano, 2025); Sexuality, Gender and Identity (*Pnei Review*, 2024).

The author does not have the ability to predict, but believes that the challenge will continue in the future in the study of situations still frontier, where a multidisciplinary and multi-professional approach is required, such as: a) Exposome and green prescriptions (Piras, 2021); b) Bioethics; c) Climate Control and Ecological Footprint (Petersen, 2025; Bologna, 2023). But certainly, future projects will also look at other areas of interest and clinical and basic research.

In our opinion, in this activity SIPNEI must continue to move within the challenge of law 833/78: equal treatment for all patients, that is the right to free and universal health care.

Final considerations

Medicine, when referring to clinical aspects, does not necessarily have to be the same for everyone. Otherwise, an algorithm, a robot, the Artificial Intelligence (AI) could be enough. («There is no greater injustice than to make equal parts between inequalities», Scuola di Barbiana, 1967).

In this sense we can hope for a Medicine that is called of the 4P: Precautionary (Preventive), Participatory, Personalized, Predictive (Hood, 2013).

But only on the condition that it will not be a merely digital, computer-based Medicine, prostrate facing the idol of Artificial Intelligence.

We believe that the possible fifth P of Precision needs to be looked at carefully,

with great caution, if not mistrust. No one denies the benefits of genetic diagnostic kits or monoclonal antibodies for immunotherapy or similar. But the perplexity comes from the risk of losing the concept of the Person as a biological/psychological individual (soma + mind) that only a holistic vision, as we have argued so far, can guarantee. A kind of fatalism would reduce commitment to lifestyles and those determinants of disease/health that are the etiopathogenetic basis of the diseases of this century (Bonaldi, 2018).

In conclusion, the current global situation of conflict and social fragility in many populations makes essential and urgent to have a comprehensive approach that simultaneously guarantees access to care, respect for human rights and economic and financial compatibility: this applies to a serious and widespread disease such as cancer, but this is not true just for the planet cancer (Casolino, 2025).

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Sitography

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The microbiota-immune interaction in the gut-brain axis

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Abstract: *The growing body of evidence on the role of the gut microbiota (GM) in regulating the bidirectional gut-brain axis suggests the existence of a complex network that also involves the immune system (IS). The interaction between GM and IS is crucial for the development and modulation of immune responses, through microbial metabolites such as short-chain fatty acids (SCFAs), which influence both mucosal immunity and neuroinflammation. SCFAs regulate immune homeostasis and the function of the blood-brain barrier (BBB), affecting microglia, astrocytes, and neurons. These mechanisms are particularly relevant in neurological disorders such as Parkinson's disease, where dysbiosis and SCFA alterations contribute to neurodegeneration. Although most results derive from preclinical studies and should be interpreted with caution, the use of probiotics, prebiotics, and postbiotics represents a promising therapeutic approach. The "microbiota-immune-brain" model opens new insights for the prevention and treatment of neurological and psychiatric disorders, although larger and more specific clinical trials are needed to confirm its applicability in humans.*

Key words: *Psychoneuroendocrinology (PNEI), Short-chain fatty acids (SCFA), Intestinal barrier, Blood-brain barrier, Probiotics, Parkinson's disease*

Introduction

The gut-brain interaction has long been a focus of scientific and clinical research, due to its therapeutic potential in gastrointestinal, metabolic, psychiatric, and neurological disorders (Dinan & Cryan, 2017). Bidirectional communication pathways between the gut and the brain are well established and include (Carabotti *et al.*, 2015):

- neural pathways: interactions between the central nervous system (CNS), enteric nervous system (ENS), and the autonomic nervous system;
- endocrine pathways: particularly via the hypothalamic-pituitary-adrenal (HPA) axis and gastrointestinal hormones that regulate food intake;
- microbial pathways: mediated by the activity of the gut microbiota (GM) through its metabolites;
- immune pathways: involving cytokines produced by the gut-associated lymphoid tissue (GALT).

The paradigm of psychoneuroendocrinoimmunology (PNEI) emphasizes that these communication pathways function as an integrated network, supported by signaling molecules recognized by cells across all organs and systems (Bottaccioli & Bottaccioli, 2017). The IS plays a significant role in the gut-brain interaction, both influencing and being influenced by other systems. A key mechanism is the effect of GM-derived metabolites on immune cells, whose production depends on the host's PNEI balance. The IS thus acts as a coordinator in the microbiota-gut-brain communication and represents a potential target for new preventive and therapeutic strategies in mental and neurological health (O'Riordan *et al.*, 2025).

Microbiota and immune system in the gastrointestinal tract

Although until recently the IS was viewed solely as a defense mechanism, within the PNEI framework it is now considered a regulatory system, together with the nervous and endocrine systems. Moreover, the IS acquires the ability to protect the host from pathogenic microbes in part through its interaction with the GM. This interaction, which occurs through various mechanisms throughout life, is essential for the proper and complete development of both the innate and adaptive immune responses (Chung *et al.*, 2012; Ratsika *et al.*, 2023).

Most of our knowledge about the interaction between the IS and the microbiota comes from studies on germ-free (GF) mice (Luczynski *et al.*, 2016), which are born and raised under sterile conditions and therefore lack microbial colonization. GF mice exhibit immature GALT, reduced numbers of intestinal lymphocytes, decreased production of immunoglobulin A (IgA), and impaired secretion of antimicrobial peptides (Round *et al.*, 2009). Many of these deficits can be reversed by re-

colonization of the gut; however, some alterations can only be corrected if colonization occurs during early developmental stages (Hansen *et al.*, 2012).

Conversely, innate immunity contributes to the stabilization of the mutualistic symbiosis between microbiota and host by regulating mucus secretion, antimicrobial peptides, and antibodies along the intestinal epithelium (Kinnebrew & Pamer, 2012). Animal model studies have shown that defects in Toll-like receptor (TLR)-dependent signaling are associated with dysbiosis and intestinal inflammation (Araki *et al.*, 2005). Adaptive immunity also plays a regulatory role on the GM. For instance, mice lacking T and B cells exhibit dysbiosis and reduced microbial diversity (Kwon *et al.*, 2015), while the absence of B cells and antibodies results in altered microbial composition, characterized by a decrease in Clostridiaceae and an increase in the genera *Paracoccus* and *Lactococcus* (Shulzhenko *et al.*, 2011).

Short-chain fatty acids as immunoregulatory molecules

Starting from dietary components and host-derived molecules, the GM synthesizes a vast array of metabolites, some of which act as signaling molecules capable of integrating into the PNEI network, thereby contributing to host physiological regulation. Among the microbial metabolites exerting such regulatory functions, the most prominent examples are short-chain fatty acids (SCFAs), which include, among others, acetate, propionate, and butyrate. SCFAs are produced in the colon through the fermentation of indigestible plant polysaccharides, particularly oligofructose, inulin, pectin, and arabinoxylan (Kumar *et al.*, 2012).

SCFAs generated in the intestinal lumen are absorbed and partially utilized as an energy substrate by intestinal epithelial cells. In the human gastrointestinal tract, the colon contains the highest concentrations of SCFAs, with a typical ratio of 60:20:20 for acetate, propionate, and butyrate, respectively (Cummings *et al.*, 1987). The enzymatic capacity to produce SCFAs varies considerably among microbial taxa. Bacteria belonging to the phylum *Firmicutes* – particularly the genera *Faecalibacterium*, *Clostridium*, *Roseburia*, *Eubacterium*, and *Anaerostipes* – are major butyrate producers. *Bifidobacterium* species mainly produce acetate, whereas both acetate and propionate can be derived from mucus fermentation by mucin-degrading bacteria such as *Akkermansia muciniphila* (Rivière *et al.*, 2016; Derrien *et al.*, 2004).

SCFAs reinforce the integrity of the intestinal epithelial barrier by promoting the assembly of tight junctions (TJs) and supporting the homeostasis of regulatory T (Treg) cells (Kelly *et al.*, 2015; Smith *et al.*, 2013). SCFAs can also reach peripheral organs, where they exert both metabolic and immunomodulatory effects via multiple mechanisms.

First, SCFAs may enter various cell types, including immune cells, through pas-

sive diffusion or via monocarboxylate transporters (MCTs). B cells can absorb and metabolize SCFAs, leading to elevated acetyl-CoA levels that support fatty acid synthesis and fuel the tricarboxylic acid cycle – an essential energy source for immune cell differentiation (Kim *et al.*, 2016).

Second, SCFAs act as key epigenetic regulators. In particular, propionate and butyrate are known inhibitors of histone deacetylases (HDACs), thereby modulating gene expression (Licciardi *et al.*, 2011).

Third, SCFAs function as bona fide signaling molecules. Like hormones, neurotransmitters, and cytokines, they bind to specific membrane receptors, notably G protein-coupled receptors (GPCRs) such as Ffar2 and Ffar3 (Brown *et al.*, 2003). In the IS, Ffar3 is expressed by medullary thymic epithelial cells, B lymphocytes, splenic CD8⁺ dendritic cells, neutrophils, ILC3 Nkp46⁺, and circulating monocytes. Ffar2 is also found on leukocytes including eosinophils, basophils, neutrophils, monocytes, and dendritic cells (Kim *et al.*, 2014). Another SCFA receptor, Olfr78, is expressed by T lymphocytes (CD8⁺, $\gamma\delta$, and NKT cells), B lymphocytes (follicular and germinal center), and ILC2 (Kim, 2021).

Through these combined mechanisms, SCFAs can exert a significant impact on the IS. For instance, they differentially regulate the activity of various innate lymphoid cell (ILC) populations, particularly enhancing ILC3 responses, thereby increasing host resistance to *Clostridium difficile* infection (Kim, 2021).

Microbiota, metabolites, immunity and brain

Alterations in the GM and in the production of microbial metabolites have been associated with a wide range of immune-related neurological disorders, including neurodevelopmental and neurodegenerative conditions (Sittipo *et al.*, 2022). Once again, GF mice have proven instrumental in revealing the importance of the GM in immune and neural functions. These animals display impaired brain function in terms of learning, recognition, and behavior, associated with altered serotonergic neurotransmission and reduced levels of brain-derived neurotrophic factor (BDNF) (Heitz *et al.*, 2011; Bercik *et al.*, 2011).

Moreover, both GF mice and antibiotic-treated dysbiotic mice exhibit abnormalities in the development of the microglia, the main immune cells responsible for CNS homeostasis, as well as dysregulated production of inflammatory cytokines. GF mice also show increased permeability of the blood-brain barrier (BBB), accompanied by decreased expression of TJ proteins, closely resembling the loss of intestinal barrier integrity observed under dysbiosis and inflammation (Braniste *et al.*, 2014). This increased BBB permeability facilitates the entry of harmful molecules into the brain, leading to neuroinflammation. However, microbial colonization or

correction of dysbiosis – particularly when performed during early developmental stages – can restore BBB integrity and reverse the associated dysfunctions (Wang *et al.*, 2018; Erny *et al.*, 2015).

There is now substantial evidence that SCFAs are among the key mediators of microbiota effects on the brain, through mechanisms that often involve immunoregulatory pathways, either directly or indirectly. For instance, by binding to their receptors on enteroendocrine cells, SCFAs stimulate the release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), which not only transmit satiety signals to the brain but also contribute to the regulation of neuroinflammation (Christiansen *et al.*, 2018).

Butyrate supplementation has been shown to prevent BBB disruption and promote neurogenesis via HDAC inhibition (Fessler *et al.*, 2013). Strengthening BBB integrity by SCFAs plays a crucial role in controlling nutrient transport from the bloodstream into the brain and in maintaining CNS homeostasis. Propionate, for example, interacts with the Ffar3 receptor on endothelial cells, providing protection against nonspecific microbial infections and oxidative stress at the BBB (Hoyle *et al.*, 2018).

Monocarboxylate transporters (MCTs), which are abundantly expressed in endothelial and brain tissues, may facilitate SCFA transport across the BBB (Pierre & Pellerin, 2005). Within the CNS, SCFAs can be recognized by microglia, astrocytes, and neurons, which then modulate neurological and behavioral processes (Silva *et al.*, 2020).

In murine models, SCFA treatment induces functional shifts in microglia toward an anti-inflammatory and neuroprotective phenotype. For example, butyrate administration suppresses microglial activation and lipopolysaccharide (LPS)-induced depressive-like behavior (Yamawaki *et al.*, 2017). In cortical astrocytes, acetate upregulates genes involved in anti-inflammatory pathways, while propionate increases IL-22 expression (Spichak *et al.*, 2021). Furthermore, SCFAs promote the proliferation of human neural progenitor cells (Yang *et al.*, 2020). Overall, SCFAs play a key role in the microbiota-gut-brain axis by both modulating BBB integrity and crossing it to directly influence CNS cell populations.

New therapeutic horizons: the example of Parkinson's disease

Recent evidence linking the GM to psychiatric and neurological disorders through the involvement of the IS has led to the development of therapeutic strategies aimed at modulating the GM to influence immune responses and brain function. Several approaches are currently under investigation, including probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation (FMT), ideally combined with dietary education and healthy lifestyle interventions that support long-term efficacy and serve a critical preventive function. Given the data discussed

above, the direct use of microbial metabolites – particularly SCFAs – represents a highly promising strategy deserving of further investigation (O’Riordan *et al.*, 2025).

Parkinson’s disease (PD) offers a compelling pathogenic framework for exploring microbiota-immune-brain interactions in both the development and treatment of the disorder. PD is a progressive, age-related neurodegenerative disease characterized by the accumulation of alpha-synuclein (α -syn), loss of dopaminergic neurons, and consequent motor dysfunction. It is also associated with immune dysregulation and neuroinflammation (Tan *et al.*, 2020). Notably, constipation often arises during the prodromal phase, years before clinical diagnosis, suggesting that intestinal inflammation and dysbiosis may play a role in the pathogenesis (Abbott *et al.*, 2001).

Most PD patients exhibit increased intestinal permeability (Forsyth *et al.*, 2011), and animal models have shown that the GM modulates pathways that promote α -syn aggregation, impairs clearance of insoluble protein aggregates, triggers α -syn-dependent microglial activation, and facilitates motor dysfunction (Sampson *et al.*, 2016). Compared to healthy individuals, PD patients present lower levels of butyrate-producing bacteria such as *Blautia*, *Coprococcus*, *Roseburia*, and *Faecalibacterium* (Keshavarzian *et al.*, 2015). Consistent with this, fecal SCFA concentrations are reduced in PD patients relative to controls (Aho *et al.*, 2021).

Several studies have demonstrated the protective effects of butyrate in murine models of PD, where treatment led to neurobehavioral improvements, prevention of dopaminergic neurodegeneration, improved BBB function, and increased production of intestinal peptides such as GLP-1 (Liu *et al.*, 2017). It is hypothesized that therapies involving probiotics and butyrate may help counteract the detrimental effects of α -syn on Treg differentiation – typically inhibited by α -syn, which promotes Th17 polarization – through histone acetylation regulation and upregulation of anti-inflammatory cytokines such as IL-4 and IL-10 (Troy & Kasper, 2010; Li *et al.*, 2023).

Overall, probiotics, prebiotics, synbiotics, and FMT may alleviate both intestinal and motor symptoms in PD through multiple mechanisms. Neuroprotective effects are thought to involve the reduction of BBB damage, glial cell activation, neuroinflammation, and α -syn aggregation. At the same time, microbial therapies can help restore eubiosis, dampen inflammation, and repair the intestinal barrier, thereby improving mucosal immune responses (Zhang *et al.*, 2023).

However, the role of SCFAs in PD remains complex and controversial. For instance, SCFA administration in GF mice overexpressing α -syn has been shown to induce neuroinflammation by promoting α -syn aggregation, microglial activation, and motor deficits (Sampson *et al.*, 2016). In another murine model, butyrate exacerbated dopaminergic neuronal loss, enhanced neuroinflammation, increased microglial and astrocyte activation, and promoted colonic inflammation (Qiao *et al.*, 2020).

Conclusions

The communication pathways initially known as the “gut-brain axis”, and later refined as the “microbiota-gut-brain axis,” have revealed an increasingly complex level of organization, in which the IS plays a central and integrative role. This has led to the formulation of a network model of microbiota-immune-brain interactions (Figure 1). It is important to reiterate, however, that most of the current knowledge on these interactions derives from animal models, which inherently fail to replicate the full complexity of human physiology. As such, results must be interpreted with caution. Future research should prioritize clinical, observational, and longitudinal studies that incorporate genetic, environmental, social, and cognitive factors unique to the human species to better understand the actual impact of microbiota-immune-brain interactions on human health.

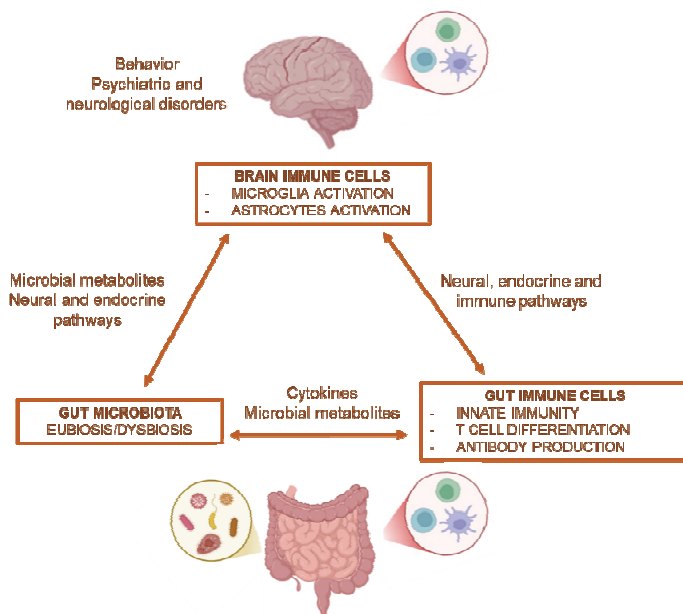


Figure 1. Microbiota-immunity-brain interactions. The GM, primarily through the production of metabolites, shapes the development and function of the IS both at the intestinal and brain levels. In turn, the IS contributes to the establishment and maintenance of a healthy GM (eubiosis) under physiological conditions. Dysbiosis, accompanied by altered microbial metabolite production, is associated with immune dysfunction that, in the brain, involves microglia and astrocytes. In a network-based model, microbiota-immune-brain interactions regulate cerebral homeostasis, whose disruption may lead to behavioral alterations and the onset of psychiatric and neurological disorders. Created with <https://BioRender.com>

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Environmental causes of disease in the Anthropocene.

A paramount PNEI view

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Abstract: *We (the humans) live in a terrestrial environment, where we find and use air, water, food and all the necessary resources for our survival and activity needs. Everyone engages in a daily and intimate relationship with the environment, where one should consider that we are not owners but guests, in a reciprocal, natural and responsible interaction with all other forms of life.*

One World view (in the sense that we all live on the same unique planet) and One Health view (in the sense that all live beings on the planet share many health and disease mechanisms) are the basic philosophical, biomedical and logical paradigms of ecology on Earth: the common house for all live beings, including us, on this planet (the only one available for the known ecosystems so far).

We received terrestrial resources from our ancestors (and their ecological cohabitants), through our parents, and we leave what remains as a basic heritage to our children and descendants, who should hopefully be able to live on Earth in future times with the same chances and quality of life that was offered to each one of us.

The environment however accumulates the consequences of all the preceding insults caused by us and by our human predecessors, who started centuries and centuries ago to extract, construct, modify, pollute every part of the planet, which now carries all the human modifications evident in the present times (Anthropocene).

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Since the industrial revolution (started less than three centuries ago) humans potentiated enormously their capacity to modify the environment, often for improving human life, but almost always by destroying ecosystems and depauperating the natural resources in many aspects.

The PNEI paradigm that inspires us, a group of physicians and health professionals of the 21st century, and also human beings intellectually able to recognize and appreciate the mind-body relationships within each individual, may be very useful to interpret the complex interplay network equilibria existing in the ecological systems between different forms of life and regulating health and disease in every living organism. Such a network-based PNEI paradigm can be, at present, the best basic knowledge to appreciate and correct the environmental causes of disease, before it is too late, for humans and for other forms of life. Climate changes on Earth in the current decades show us that it may be already too late to revert the situation to previous sustainable equilibria.

We shall discuss here some peculiar aspects of these complex but fundamental issues regulating ecosystems, in a One Health perspective and with the PNEI paradigm well in focus.

Key words: *Environment, Anthropocene, One Health, Prevention, Pollution, Climate*

Introduction

Homo sapiens appeared on Earth approximately three hundred thousand years ago and developed on the planet an unprecedented ability to modify its environment with all sorts of extractions, constructions and use of resources. The vast variety of anthropic changes deserved the term of Anthropocene (designating the latest and current geological era, in which very prevalent are indeed the human modifications of the environment). For a more extensive and updated explanation of Anthropocene, see: <https://en.wikipedia.org/wiki/Anthropocene>.

Civilizations and knowledge advances potentiated progressively the human ability to modify the environment until the industrial revolution (XVIII century), when energy control (through carbon and petrol burning, steam engine machines, electricity and new technologies) multiplied enormously the human capacity to build, extract, navigate and change the humanized environment and generally the terrestrial environment in all endeavors.

In such prolonged and intense process of change, all parts of the environment were modified, so that air, water, food, heat production and even climate were affected in their composition, and planetary distribution by human actions.

Pollution is a word and a concept that emerged as early as in the XIVth century (according to the Merriam-Webster Dictionary, 2010 ed.) and indicates the introduction of contaminants into the natural environment that cause harm. This happened, and still happens, mainly in the most industrialized areas of the world, where the changes were and still are, quicker and more evident from all points of view.

But human biology (and the biology of other live beings) does not have sufficient (evolutional) time to adapt to many of these fast environmental changes, so that many discrepancies and pathophysiological consequences emerge, in the form of diseases related to environmental changes. We will screen the most evident changes and the most evident diseases related to them, in the modern integrated view of One World perspective (all species share the basic biological rules of living) and of the One Health perspective (what is good or bad for one species, may be good or bad for other species as well) (Lingiardi, 2025) and inspired by the newest pathophysiological network view called PNEI, Psycho-Neuro-Endocrine-Immunology. PNEI is active in each individual live being and regulates in a wide network organization, indeed, all the most important bodily regulatory systems, involving brain functions, psychic functions, endocrine equilibria and immunological responses (Bottaccioli, 2020, English Edition).

One Health

The evident concept that we have only one planet to live on (so far), together with all other forms of life, is stressed by many authors and is indeed an obvious fact, although it deserves high attention (Berners-Lee, 2021). If there is an alteration of the terrestrial environment, such an alteration may affect the life and pathophysiology of all the living species on Earth. Therefore, the good health of any species may reflect the well-being and the health of many other species. This is the basis of One Health approach, an holistic view considering the global health of the planet together with the good health of each single individual and posing the basis for interdisciplinary collaboration in problem analysis and in problem solving (Capua, 2020). The World Health Organization mentioned the issue and expanded this field of activity in an official document in 2017 and creating afterwards a consulting structure in 2021: the One Health High-Level Expert Panel (OHHLEP). This entity is indeed an advisory group for Quadripartite organizations: the Food and Agriculture Organization of the United Nations (FAO), United Nations Environment Program (UNEP), World Health Organization (WHO) and World Organization for Animal Health (WOAH). For additional informations and details, see reference WHO-One Health (2021).

As already mentioned, humans have modified in a very substantial way the environment, because of their capacity of using all sorts of natural resources (minerals, water, plants, animals, through all forms of technologies starting with agriculture and farming) and potentiating such phenomena with energy availability (coal, petrol, steam, electricity) in almost infinite ways since the industrial revolution of the 18th century and beyond. We must now analyze in general terms the most important environmental changes of our world today and try very quickly to apply

remedies (most of which are already existing); this concept (which is social and political, and involves truth and honest behavior) must be achieved immediately by as many citizens as possible (Berners-Lee, 2025) to avoid very rapidly the completion of the dramatic polychrisis in progress for the humanity. This concept of the current polychrisis is very well described and analyzed in detail by Mike Berners-Lee in his latest book, written and directed to «all those who think about the rest of the world». We highly recommend reading it, together with the relative editorial review by Corriere della Sera (De Carolis, 2025), although we summarize here some of the main concepts presented in this especially important book (Berners-Lee, 2025).

Polychrisis is not only a climate crisis, it is also at the same time a biodiversity crisis, a food security crisis for a rising population, it is a crisis of escalating, permanent pollution and far more. Not to mention the population disparity, super-rich and super poor people, states and economies, with the deriving conflicts.

«Every single year we degrade our environment by an even larger amount than we did the year before».

So, we are all invited to think responsibly, to change our approach and to be honest in analyzing the facts, to be accurate in the political choices and to require honesty by those receiving our votes to manage nations and enterprises. «What can each of us do right now to help? » The most important answers are in the book by Berners-Lee (2025).

Now we must analyze very briefly the elements of the current polychrisis which are most able to affect human and planetary health, to pay appropriately our clinical (medical, psychological, health services) attention to the various aspects of the pathogenic environment and see how to apply our PNEI view to them. Some issues are newly studied and deserve specific attention, like pollution in all forms (air pollution, water pollution, soil pollution, building of waste, micro plastic waste and biological diffusion; forever chemicals – i.e., poorly degradable and non-biologically modifiable chemicals- burning of fuels, etc. etc.). We will specifically mention the most relevant issues in this (partial) list, but we want at the same time to draw the attention of our readers to several key risk factors that can save a decade of life for each individual, according to a very recent and extensive report (Global Cardiovascular Risk Consortium, 2025). If some essential lifestyle changes (mostly quit smoking, lowering blood pressure, cholesterol control, diabetes control and overweight control), are in action, the advantages are indeed very consistent, according to the just mentioned survey, performed on over two million people and across 39 countries. This is indeed a fundamental basis of prevention.

Pollution of air, water and soil

Pollution regards all areas of natural sites, air, water and soil and the living organisms therein. Natural atmosphere on Earth until the industrial revolution was affected only by natural forces (winds, volcanic eruptions, natural burning of grasslands and forests) with local and moderately extensive effects. We know for instance that some important volcanic eruptions may have affected air quality and climate of the planet, by analyzing climate data and Antarctic ice samples revealing tracks of such events.

After the industrial revolution, coal and petrol burning by human activities have enormously increased the production of combustion products and of particles liberated in the air, leading to a local, regional and planetary diffusion of fumes, chemicals and particulate matter (PM) of various sizes. Among the air pollution elements there is also a vast variety of chemicals affecting lung diseases and cardiovascular diseases (CO, Ozone, SO₂, NO_x, etc.) (Rajagoplan, 2021); volatile organic compounds having specific health effects as carcinogens, skin irritants and responsible of gastrointestinal diseases; lead having specific neurotoxic effects and PM of various sizes having mostly pulmonary effects. PM produced are pushed by winds and fall-out on the land surrounding the combustion sites (that is, mostly industrialized areas and towns with intense vehicular traffic and heating plants).

Recent data demonstrate that PM and wildfire smoke (containing small PM of various sizes and derivation) are particularly dangerous not only for lungs but also for brain health (Brooks, 2024). Key facts are that climate change favors the frequency of wildfires, that fine particle pollution from wildfires increases globally and that PM from smoke can affect lung health (asthma, COPD, lung cancer), heart and brain health (Elser, 2025; Du Plessis, 2025). Extensive data are available on the subject, also thanks to computerized models developed for assessing short-term and long-term health effects of PM of various sizes, especially for areas where monitoring station data are not available (Yu, 2023).

A graphic summarizing the most relevant forms of air, water and soil pollution is reproduced in figure 1 (Open source, modified to add the PNEI relationships).

In this vast endeavor, extraordinarily rich in studies and reports, we want to indicate as a reference the extensive report by UNEP (2021) which presents a scientific blueprint for how climate change, biodiversity loss and pollution can be tackled jointly within the framework of the Sustainable Development Goals. The report is a synthesis based on evidence from global environmental assessments.

Plastics and micro plastics

Millions of tons of plastic are produced, used and discarded every year in the world, since early 1950s. Plastic products can contain thousands of different chemicals, most of which are poorly degradable and non-water-soluble; therefore, they are able to concentrate in fat tissues (animal fat, with potential endocrine disturbing effects). The hazards for human health and the environment are already well demonstrated, although they still need to be studied more extensively (Leslie, 2022; Trasande, 2024; Gross, 2025; Yakovenko, 2025).

A major issue in many countries is the presence of plastic waste in the water and soil due to the lack of appropriate disposal and recycling procedures. Enormous amounts of plastic waste are dispersed in landfills, burned in incinerators or casually dispersed and burnt in the fields and finally conveyed by streams and rivers to the seas and the oceans. Presence of plastics and mostly of micro plastics is demonstrated in many organisms and in many human tissues, including the brain (Amato-Lourenço *et al.*, 2024; Zaraska, 2025). This evidence implies probably the penetration of micro plastics directly in the brain via the respiratory bulb from atmospheric exposures; the following neuroinflammatory changes can be observed in exposed animals and in humans. Some neuropsychiatric alterations (anxiety, depression and social deficit) have been described in mice during experiments involving intentional plastic exposure of animals. Such micro plastic-induced neuropsychiatric symptoms may be mediated by microglia and may be the result of neuroinflammation and neurodegeneration (Ma, 2024; Zaraska, 2025).

Airborne microplastics are also ubiquitous and are assumed by respiratory function, particularly in indoor places (Yakovenko, 2025). Airborne suspended micro plastics are inhalable, if in the size range of 1-10 micrometers, and are very prevalent in most indoor places (homes, cars, buildings). Inhaled particles larger than 10 micrometers are generally retained in the upper respiratory tract, while smaller particles can penetrate deeper in the lungs and then even absorbed in the bloodstream. Dietary micro plastics may be assumed by animal and vegetable foods already contaminated, conserved in plastic wrapping, and even from chewing-gums (extraordinarily rich in micro plastics particles).

So, anywhere in the body, the presence of plastic particles can induce inflammation, lipid deposition and endocrine interference.

Some studies have moreover indicated that micro plastics in the bloodstream can induce cerebral thrombosis leading to neurobehavioral abnormalities (Huang, 2025). Concerning cardiovascular effects other reports have found presence of micro plastics in atheromas, where such compounds may play inflammatory and atherogenic roles (Marfella, 2024). Microplastics contribution to pulmonary carcino-

genesis has been studied and data demonstrate that patients with asthma and COPD (chronic obstructive pulmonary disease) are at increased cancer risk from micro plastics (Paplińska-Goryca, 2025).

A further and particularly important issue concerning the diffusion of micro plastics in waters (rivers and oceans) consists in the ability of several bacteria to grow and thrive as biofilms on plastic fragments. Particularly serious is the discovery that some of the bacteria growing on plastic particles are antibiotic-resistant. The possibility exists, therefore, that the ubiquitous presence of plastic debris and of microplastics may favor proliferation and global diffusion of antibiotic-resistant bacteria, particularly in urban waters (Entezari, 2022; Gross, 2025).

Plastics and several chemicals derived from them have moreover a demonstrated effect as endocrine disruptors and even as carcinogens. The issue therefore is really of fundamental importance in modern times. None of those compounds were present in the environment before plastics were synthesized (early 1950s). The decrease in fertility in most industrialized countries is due in part to ED effects of pollutants.

A last-minute fact is the failure of the World Conference on Plastics (Plastic Treaty) held in Geneva in august 2025. A report by Rossano Ercolini, President of Zero Waste Italy, calls for a strong responsibility of the failure by Saudi Arabia and by other petrol exporting countries (including USA, whose actual President, Donald Trump, is one of the principal deniers of climate change and one of the most favorable about unlimited petrol drilling).

Millions of plastic tons are produced yearly from petrol and several of them end up as plastic waste in the oceans and everywhere (as we have mentioned). It is unacceptable that for the gains of few (the petrol producers), many dies of plastic-related diseases and of hydrocarbon carcinogenesis and the ecosystem accumulates amounts of waste impossible to eliminate. Therefore, it is unacceptable that One World and One Health views are systematically ignored and insulted by those few. (Ercolini, 2014; Ercolini, 2025).

A fundamental concept is therefore the limitation of plastic use, through the industrial planning avoiding plastic packaging and disposable, single use plastic items. Plastic contacts for humans must be limited and mainly the correct disposal of plastic waste (for extensive One Health prevention) must be observed. All physicians and sanitary professionals should know very well these concepts and communicate these facts to the general population (patients, family members, all contacts). Basic for this is to limit and possibly to abandon at once the practice of disposable plastic goods of any kind.

Forever chemicals: PFAS and endocrine disruption

Perfluoroalkyl substances (PFAS) are human made chemicals used in a wide variety of consumer and industrial products characterized by high persistence and limited degradability (waterproof linings of tissues, ignifugous foams, etc.): they are sometimes called “forever chemicals”, because they break down slowly and accumulate in the environment and are traced for long time in animal and human tissues (Aubert, 2025).

In some detail, PFASs have been widely used in industrial products since 1940 and in everyday use objects, because of their water, oil, stain and heat-resistant properties, and they are contained in food wrappers, non-stick cookware, fire-extinguishing foams, water repellent fabrics, paints, personal care products etc. and in contaminated water and soil, since they are very persistent pollutants.

Their metabolism in biological systems (although slow) demonstrates alterations in several critical biological processes, like fat metabolism and thyroid pathophysiology. Effects on developmental disorders, cardiovascular disease, metabolic disease and many types of cancer have been ascertained. A recent study (Goodrich, 2023) shows that PFAS exposure has effects on thyroid hormone function, puberty distress, growth, metabolism, diabetes, obesity, cardiovascular disease and cancer. Further data on thyroid metabolism (Yu, 2025) have evidenced that PFAS exposures may affect peripheral thyroid hormone sensitivity, with several health implications spanning from developmental disturbances to obesity and diabetes.

Presence of PFAS in drinking water and in many environmental sites (mostly near industrial production sites and related wastewater disposals) raises important concerns about public health (Gao, 2024), although it appears that boiling water before drinking it may reduce substantially the active PFAS concentration in the water samples for human and animal use (Dagorn, 2023; Aubert, 2025). Statistic data analysis has identified in Europe at least 20 PFAS producers; 23,000 sites where PFAS contamination has been detected; 232 PFAS industrial users; and over 21,500 presumptive contamination sites (Dagorn, 2023, updated in 2024): therefore, PFAS compounds represent one of the most relevant chemical pollution problems worldwide, mostly in the industrialized regions.

Data about PFAS carcinogenicity has been long debated, but these compounds are now included in group I carcinogens by IARC and are the subject of a very recent IARC Monograph published in February 2025 (IARC, 2025). In their quality of endocrine disruptors, PFAS are of extremely high concern for pathophysiology in humans, animals and ecosystems. Any clinical professional with PNEI basic formation should keep this element in great consideration.

Climate change and related issues

An extensive description of the multiple relationships between climate changes, extreme heat and health may be found in recent review papers published in the last few years in top rated medical journals (Haines, 2019; Perera, 2022; Bell, 2024; Kazi, 2024; Solomon, 2024). Such pathological relationships affect mostly the vulnerable subjects (children and aged people) and deal in particular with cardiovascular diseases (acute coronary syndrome, myocardial infarction, heart failure), kidney diseases (acute renal failure, nephrolithiasis, urinary tract infections), respiratory diseases (asthma and COPD – chronic obstructive pulmonary disease- pulmonary infections and pulmonary edema), mental disorders (anxiety, depression, aggressive behavior, mental fatigue) and adverse birth outcomes (stillbirth, etc.). All these facts impact significantly on morbidity and mortality worldwide.

There is no logical possibility of being doubtful about the causes of climate changes: they are related to the enormous amount of fossil fuels extracted, burnt and used worldwide since the industrial revolution.

In Bell (2024), you can read clearly: «The Intergovernmental Panel on Climate Change (IPCC) concluded unequivocally that human activity, especially the combustion of fossil fuels, is responsible for overall warming of the atmosphere, land, and oceans; that changes in weather extremes driven by climate change are already observed; and that recent extreme heat events are attributable to climate change».

No scientific doubt therefore exists about that, although many politicians have diffused false statements and created antiscientific debates and campaigns about these issues, using inconsistent and scientifically illogical doubt as a weapon against scientists and top-quality scientific research and evidence.

Facts are that increasing temperatures are modifying the habitats and the ecosystems of live beings, in extending or restricting the areas where different species prefer to live and modifying the distribution of diseases on the globe (Thomson, 2022; Semenza, 2023). Therefore, the global distribution of major infectious diseases is involved: Malaria, Dengue, Zika, West Nile, Lyme disease, Chikungunya, Plague, etc. Emergence of new infectious diseases (zoonoses in particular) is also affected (Bologna, 2022). A study calculates that such infectious diseases may reach even London and Paris by 2035 (Radici, 2025). Climate issues, moreover, are interconnected with other fundamental themes, like endocrine disruptors (which increase several health risks, including cancer, neurodevelopmental harm, and infertility) (Woodruff, 2024), and air pollution (Keswani, 2022).

Other issues

We also need to remind here to all readers about some major pathogenic habits, like tobacco smoke, dietary excess of alcohol, of animal derived fats and of red meats. These subjects are not detailed here but remain big pathogenic factors to be always considered for primary prevention of disease and for well-being (Global Cardiovascular Risk Consortium, 2025).

Moreover, there are several additional issues involving exposure to electromagnetic fields and several individual behavioral attitudes with related social stress, very much able to impact on neurophysiological and physical health.

Most of these are old and new self-applied pathogenic factors, like hallucinogenic drugs, ludopathies (compulsive gaming attitudes of all sorts, like video games and lotteries), electronic cigarettes (hiding hundreds of uncontrolled chemical compounds) (Anderer, 2025), tattoos (which chronically stimulate the immune system), smartphones (delightful but dangerous in some aspects), artificial intelligence practice and blind trust, leading to severe damage of personal brain capacities and critical thinking. The mentioned artificial intelligence (AI) and social media themes are studied nowadays even as a possible danger for democracy and political orientation. If I trust blindly the electronic answers by social media and by generative artificial intelligence (like ChatGPT and similar systems), I cannot know any more where my personal culture ends nor how to improve my personal experience and capacities, through personal study and research of truth and facts. This is a very vast and relevant issue at present since it can damage critical thinking and basic education.

“I know that I do not know” is a positive and constructive attitude, meanwhile “I think I have reached knowledge and the truth by AI and social media” is the end of knowledge search, critical thinking and passion for study and culture.

The subjects mentioned all have some possible or ascertained PNEI consequences.

We want here just to stress, for instance, how tattoos can be carcinogenic (for lymphomas) and how psychological stress may be dangerous in many ways. Tattoos are very diffused today and represent a chronic stimulation of the immune system, since they consist of extraneous molecules (not-self) introduced purposely under the skin (therefore beyond the “self” barrier), with the scope of remaining visible for long periods of time (often for the entire lifespan): these not-self components of tattooing inks stimulate the immune reactions chronically, with various consequences. In some cases, even lymphomas have been found in tattooed subjects (Nielsen, 2024). PNEI network influences may also increase the inflammatory status of the subject and modify personal behavior toward various types of psy-

chopathologies (anxiety, depression, aggressive attitudes, sleep disturbances, etc.). Clinicians should be aware of that and take such elements into consideration when confronted with tattooed patients.

One more relevant aspect deals with fertility, mostly on the male side (sperm number and motility): endocrine disturbances by pollutants can have significant effects on limiting the fertility of people in the most polluted areas and with significant exposures to plastic derivatives and PFAS, as mentioned above.

We want also to remember, in this superficial but extensive exploration of the health problems of the Anthropocene, the issue of digital-derived anxiety in young generations. Many adolescents suffer from anxiety because of the judgement they receive in their lives from peers and on social media. They tend to fear the comparison with peers and may develop an avoidant behavior, ending up with extreme phases of total insulation from the social contacts (Hikikomori syndrome). These are serious situations needing special attention from parents, by teachers and by psychologists (Veltroni, 2025).

Finally, we must mention the general stress of modern life, exacerbated by the uncertainty of the current geopolitical situation on a global level. Social stress, geopolitical stress, echo anxiety (everything may hide dangers in daily life) are indeed adding up: only scientific knowledge and savvy counseling by prepared clinicians and teachers can alleviate all this stress of the Anthropocene. Good teachers and good caregivers (physicians, psychologists, health professionals) represent overall the best care and the best medicines themselves.

Most of these themes need to be studied more deeply, under new and continuous scientific advances, but the interactions with the PNEI network make them truly relevant in any individual seeking help for personal health issues (Bottaccioli, 2024). Clinicians must be aware of that.

Conclusion

Modern world in our advanced Anthropocenic Era is full of potential harms due to various kinds of pollutants, linked to physical, chemical and social factors. Scientific knowledge about the pathophysiological consequences of pollutant exposure is growing but still lacks complete knowledge in all the numerous endeavors of pathogenic mechanisms and of different disciplines needing better integration. Primary prevention and caution principles are fundamental. Clinicians can provide advice to patients toward reducing most dangerous exposures, and examining carefully the anamnestic individual data, but policy change by governments is needed to establish legal requirements for comprehensive safety testing and to reduce health threats in particular from petrochemicals. Clinicians are important

advocates for these changes and their formation in the PNEI paradigm can play a substantial role in this process of updating biomedical knowledge and betterment of social and individual care.

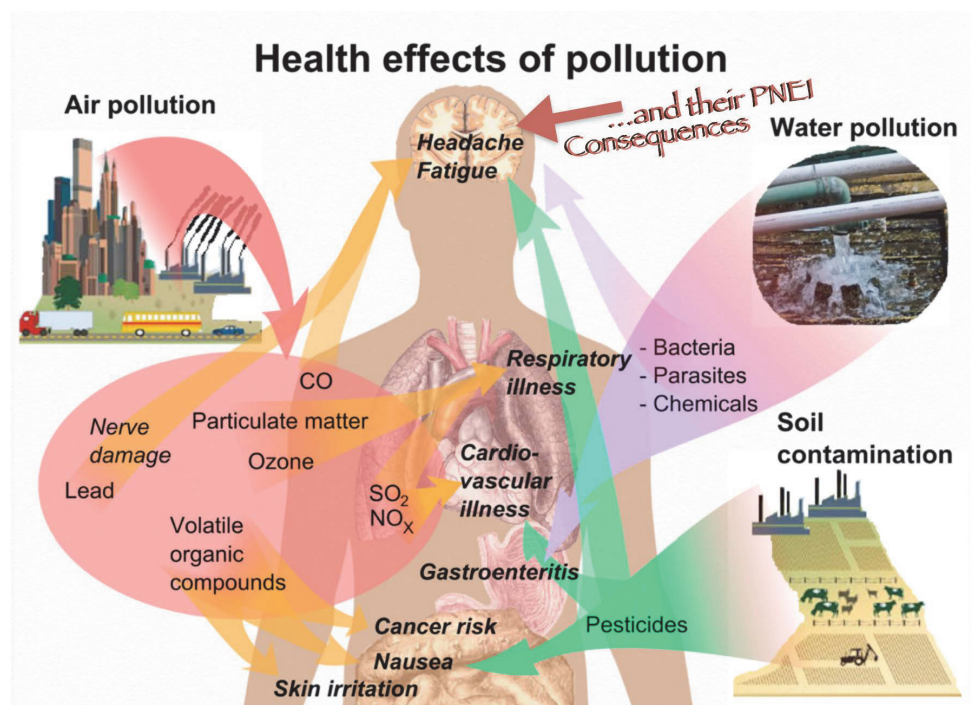


Figure 1 – Scheme synthesizing the environmental causes of disease, modified with the indication of the possible PNEI consequences in many different physiopathological pathways. Modified from: Häggström, Mikael (2014). “Medical gallery of Mikael Häggström 2014”. *WikiJournal of Medicine*, 1 (2). DOI: 10.15347/wjm/2014.008.

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lives and in industrial processes. They are highly resistant and almost indestructible in the environment, and their toxicity is increasingly documented. *Le Monde decoders*, January. https://www.lemonde.fr/en/les-decodeurs/article/2025/01/14/pfas-a-family-of-10-000-forever-chemicals-contaminating-all-of-humanity_6737024_8.html

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Reflections on the physical and biological dimension of the person in psychotherapy and in PNEI-oriented clinical practice

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Abstract: *This paper proposes a reflection on integrating the physical and biological dimensions in PNEI-oriented psychotherapy. Starting from the paradox of a growing theoretical attention to the body in comparison with its marginality in clinical practice, the authors invite us to*

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consider the human being as a unitary organism, in which mind and body constitute an interdependent system. Along the path from Freud through Ferenczi and Reich to contemporary neurosciences, a circular and relational paradigm is outlined, capable of connecting psychic and biological processes. The PNEI perspective is proposed as a framework to overcome the fragmentation of psychotherapeutic models and to promote an integrated vision of health and care. Significant and necessary modifications to both the basic theoretical assumptions and the techniques of intervention and care are derived from this and are discussed.

Keywords: Psychoneuroendocrinoimmunology, Mind-body integrated Psychotherapy, Organism, Relationality, Interoception, Metamodel.

Introduction

The primary objective of this paper is to offer ideas for reflection on how to consider and use the physical and biological dimensions in a PNEI-oriented psychotherapy, independent of the theoretical-clinical reference models. This reflection has become necessary due to the evolution of scientific research over recent decades, which has important theoretical and technical implications for psychology and psychotherapeutic practice. The theoretical-conceptual basis of this paper is outlined in the document *A new paradigm for psychology and psychiatry* (PNEI Review 1/2021), to which we refer.

Our reflections stem from a paradox: the physical and biological dimensions, which, in the current lexicon, define the concept of corporeality, are increasingly present in the theorizations of modern psychotherapies but remain mostly marginal in concrete therapeutic practice. This discrepancy lacks a scientific basis and is inconsistent with the heart of the ongoing paradigmatic evolution; we believe it must be resolved. We add that this discrepancy is part of another, broader one: in the clinical setting, mind and body are still interfaced as separate domains, rather than as the interconnected and unitary systems they actually are.

The very concept of corporeality aims to direct attention to the more discrete bodily manifestations, those directly interceptable and explorable in the psychotherapeutic setting, but which are not always sufficiently observed in relation to psychic content. This paper aims to outline possible directions for resolving these discrepancies. In this regard, we will refer to the concept of the *organism* to indicate the entirety of the psychic, corporeal, and biological dimensions that constitute the human being.

A consequent objective is to offer stimuli to bring the languages of psychotherapies closer together, underscoring the need to build a bridge between different, and often opposing, traditions. The purpose is certainly not to standardize intervention models, nor obviously to define further differentiations between them, but

rather to stimulate clinicians, as a matter of necessity and utility, to cultivate a gaze that contemplates the human subject as an organic whole, whose complex mind-body relationships cannot be reified singularly, neither in the construction and conceptualization of suffering, nor in the healing process.

In particular, the psychoanalytic tradition can be usefully brought into dialogue with the body-psychotherapy tradition, which arose from within it in the 1920s with Wilhelm Reich but was never recognized. Although the latter tradition was born within psychoanalysis, the two traditions subsequently moved far apart. By virtue of the centrality that research recognizes in physiological and sensorimotor manifestations for the development and regulation of affects, and in their conscious and unconscious psychic representations, we believe that reflection on the role of corporeality in development and change is a crucial theoretical and technical vector for a rapprochement between psychotherapies, whose fragmentation determines their main scientific weakness.

The fragmented constellation of psychotherapeutic models indeed constitutes both a theoretical and a technical limitation. Theoretical, because it moves away from the scientific objective of a unitary vision of the development and functioning of the Self. Technical, as the focus on specific aspects of therapeutic work makes treatments non-homogeneous and difficult to compare, and stimulates conflict between psychotherapies, leaving the flank exposed to market logic rather than scientific motivations.

An important limitation is the lack of support for the mind-body integration process, which, across the various models, is often unbalanced in one direction or another, to the detriment of integrating parts into a cohesive sense of self. The absence of a metamodel capable of considering processes in a systemic sense as a means of integrating the access points and focuses of each therapeutic model can lead to the parcelling out of the therapeutic experience itself and to a restructuring that relies solely on bottom-up or top-down processes.

The concept of *circularity* thus seems to us more useful and necessary than ever in approaching complex networks and should be considered as a primary element of observation and intervention. On the level of comparison between psychotherapeutic approaches that refer to very different orientations, greater dialogue could be promoted by the ability, to paraphrase Bromberg (1998), to stand in the spaces that mark the separation between the different psychotherapies by virtue of their differences, and to operate there for their interconnection.

From whatever angle one wishes to observe suffering and whatever techniques one chooses to apply, we believe that the clinical objective can be better achieved if a joint understanding of the psychic and biological processes involved in achieving and maintaining the equilibrium of the subject's body-mind system is guaranteed,

through the clinical interventions necessary to restore the best state of psychic and biological well-being achievable by them. We think that solid bridges, capable of filling the spaces between psychotherapies, can be constituted by sensitive attention to the psychic and somatic processes, simultaneously and circularly active, to promote their integration and support the cohesion of the self, which strictly depends on this integration¹.

The role of the body in the history of psychotherapy

At its origins in psychoanalysis and within the first psychoanalytic community – for Freud himself and his close collaborators, including Groddeck, Reich, and Ferenczi – the body was present in a way that was anything but metaphorical and/or metaphysical, as would instead become characteristic of later theoretical developments. The very notion of *drive* constitutes «a concept on the borderline between the psychic and the somatic, as the psychic representative of the stimuli that originate within the body and reach the psyche, as a measure of the operations demanded of the psychic sphere by virtue of its connection with the bodily one» (Freud, 1915, p. 17).

It was Georg Groddeck, as early as 1923, who first introduced the idea of an original force that shapes human life in all its forms, expressing itself equally in thoughts and in physical symptoms. He called it the *Id* (*Es*), thereby formulating a concept that Freud later adopted. For the German physician, this idea of a primordial force renders any distinction between mind and body superfluous, as he understood them to be interwoven manifestations of a single vital process, two sides of the same coin. According to Groddeck, '(...) for the *Id*, there is no difference between the organic and the psychic, and (...) therefore, if the *Id* can be influenced in some way through analysis, organic illnesses can and, in certain circumstances, must be treated psychoanalytically' (1966, pg. 169). However, Groddeck – nicknamed 'the wild analyst' for his radically integrated approach to cure – always remained on the fringes of the psychoanalytic movement, which in the meantime was consolidating around the charismatic and brilliant figure of Freud.

It was especially Wilhelm Reich, in the 1920s, when he still held a prominent position within the psychoanalytic movement, who advanced a reflection on the problem of the somatic expression of *resistances*, observed and systematized by Freud in his model of the mind as unconscious psychic forces that prevent painful or anxiety-inducing thoughts, emotions, or memories from reaching consciousness. Reich (1949)

¹ The possibility of working simultaneously on the level of the generator, the epiphenomenal level, and the intrapsychic and relational level is proposed in the theorization of the Milan Model, the first constructivist-oriented attempt to apply circularity also among different, yet complementary, intervention foci (Mosconi, 2016).

observed and highlighted how resistances could be directly seen in the patient's bodily attitudes (posture, movements, voice, etc.), and formulated the concepts of *character* and *functional identity* as notions straddling the psychic and the somatic, developing both a theoretical model and a clinical intervention technique directly oriented toward somatic manifestations. At that time, these positions were considered fully coherent with psychoanalytic theory and not yet in conflict with it. The later break between Reich and the psychoanalytic movement – which led to his expulsion in 1934 – was determined by other issues: his interpretation of masochism, namely his critique of the death instinct, and Freud's abandonment of the original theory of trauma, which Reich viewed as a concealment of the social matrix of human suffering. After Reich, psychoanalytic theory turned its attention away from the relations between psychic and somatic manifestations (or more simply between psyche and body), embracing instead a metaphysical, symbolic view of the body, in tune with the conception of the mind – of intrapsychic and monadic matrix – that Freud had meanwhile consolidated with his second topography.

Within this framework, Ferenczi (1931, 1932) maintained his own focus on corporeality by directing attention to the relationship between the analyst's and the patient's corporeality throughout the clinical process. He did so along two main lines: on the one hand, he questioned the concept of technical *neutrality*, emphasizing the analyst's subjectivity and life experience as therapeutic instruments grounded in authenticity and co-participation; on the other, he brought renewed attention to relational trauma, as an alternative to the sole focus on drive conflict, recognizing it as one of the causes of neurotic psychic suffering that often manifests itself through bodily affective states. Ferenczi further stated that cognitive understanding of psychic conflicts is insufficient for healing, particularly in the case of traumatic experiences; in such circumstances, an essential reparative principle in the healing process is the integration of original, normally unconscious emotions into the conscious memory of the traumatic event. This process of integration could, for Ferenczi, be facilitated by the analyst's bodily sensitivity to the patient's affective experiences. His innovative ideas, as had been the case for Reich (and other of Freud's disciples), led to his progressive marginalization within the psychoanalytic movement.

Nevertheless, Reich's contribution gave rise, from the 1960s onward, to the development of the field known as *Body Psychotherapy*, which produced interesting, though heterogeneous, developments – such as in Italy with *Functional Psychology* (Rispoli, L., 1988, 2016) – but which never decisively freed itself from the marginality and exclusion from academic contexts to which the rupture between Freud and Reich had relegated it. This factor also accounts for the limited production of recognized scientific contributions. Despite this weakness, it is now possible to recon-

sider the work of Reich and post-Reichian authors such as Lowen (his student) for its intrinsic richness, which aligns it with the evolution of the PNEI paradigm. Some of its principles can be summarized as follows:

- the indissoluble link between psychotherapy and biology, already present in the early Freud, and the conception of the human being as an integrated organism that unfolds functionally across multiple dimensions, as expressed in the aforementioned concept of *functional identity* and in the theorization of sexuality as a regulatory mechanism of health (for its effects, we might say today, on the *window of tolerance* for stress);
- the rooting of the organismic system within the social and cultural context.
- the attention to etiopathogenesis, recoverable through corporeal signals and expressed in the design within the therapeutic process.
- the location of resistances within the whole organism, placing the focus on the body as an explicit expression of the self, always active in the present within the therapeutic relationship, and as a direct observational datum of organic functioning.

In the second half of the twentieth century, a constellation of contributions from fields relevant to both research and clinical practice – such as infant research, neuroscience, neuropsychanalysis, cognitivism, systemic and relational therapies (to name only the most well-known models) – as well as from certain currents of thought within psychoanalysis itself, rekindled interest in trauma studies and brought about a decisive revaluation of corporeality in the psychotherapeutic process (Solms, 2021).

The mind as an emerging relational phenomenon

Within this timeframe, which witnessed a paradigm shift in understanding the relationship among mind, body, and consciousness, Bateson's (1972) biological-anthropological systemic vision emerged. Bateson conceptualized the mind as a system of relations not confined to a single organism or "entity" – such as the brain, personality, or soul of an individual – but extending beyond, intertwining with the context, and thus transcending the individual subject to acquire the condition of immanence. With the concept of *ecology of mind*, Bateson emphasized the intrinsic relationship between the individual and the environment, which represents a foundation for psycho-organic development. Likewise, Bateson spoke of an *ecology of ideas*, referring to how ideas themselves – products of reflection upon experience – depend on the system in which humans live. The ecology of mind, or of ideas, is thus that form of knowledge capable of grasping the multiple relations and interactions that constitute the mind itself, an immanent and emergent product of the subject's relational networks.

The concept of cybernetics thus defines Bateson's epistemology: every organized system is a set of elements in relation and interaction, whose components coordinate through circular information exchange mechanisms. These continuous exchanges represent communicative processes that bring about state changes in the system's elements, modifying their individual actions. When elements are organized within a system, the interactions among its components endow the whole with properties that do not belong to the elements taken individually. Hence, "*the whole is greater than and not equivalent to the sum of its parts*", since any modification made to one element of the system influences the entire whole, according to the principle of non-summativity.

The principle of non-summativity applies well to this discussion. This schema reflects the functioning of human systems and related psychological and social phenomena, as well as the physical and biological dimensions and cognitive and emotional functions. Therefore, we should not expect to understand the functioning of the human mind by observing only emotional variables. On the contrary, it is necessary to analyse the relationships among various perturbators, physical, emotional, social, and cognitive. Among these, we may consider predictive mind theory, which draws attention to how «*our brain network is always active. Neurons are never simply waiting for some stimulus from the external world to arrive. Rather, all neurons are constantly communicating with one another...*» (Barrett, 2021, p. 41), and how the brain, as a predictive organ, detects signals from various parts of the body (interoception) and from the environment, interpreting them through the lens of culture and experience to efficiently manage the organism's functioning through allostatic processes.

Maintaining homeostasis is a crucial biological process. When illness disrupts homeostasis by triggering an inflammatory response, the organism tends to recalibrate to regain its original equilibrium through allostatic adaptation. The concept of circularity was one of the foundations of the Palo Alto Group's theory. Over time, it evolved primarily on a communicative level, progressively excluding the body as a meaningful element in clinical intervention.

The concept of mind as an emergent phenomenon can be found in the research of those same years: the mind emerges from neural interconnections. According to Damasio, the mind emerges when the activity of small circuits of neurons organizes into networks, giving rise to *transient forms*, configurations of structures that represent and signify external or internal objects and events, or elaborations of other configurations. Thus, a *map* can be defined as the totality of all such representations of objects and events and of their interconnection processes. Damasio identifies precise rules governing the relations among neural processes, both in the construction of the mind and in the formation of self-consciousness, thereby opening a

perspective in which the body is the foundation of a conscious mind, inextricably connected to both mind and consciousness. It should be noted, however, that Damasio's early observations did not conclude the debate on consciousness and the neurobiological processes from which it would emerge. On the contrary, in the past year, the discussion has flared into open conflict between two paradigms: on one side, the integrative vision (Integrated Information Theory - IIT) advanced by a group of scientists led by Giulio Tononi; on the other, a large number of academics rooted in the classical functionalist-computational view, who accused the opposing paradigm of pseudoscience².

Damasio's contribution to more recent research nonetheless represented a cornerstone in recognizing the deep interconnection between cortical and subcortical systems – and their integration with other systems – promoting reflection on a paradigm shift in the conception of health, illness, and their interrelations. Moving away from the Cartesian dichotomy between mind and body, Damasio identifies emotions and bodily processes as fundamental to cognition and reasoning, and introduces the concept of the somatic marker to explain how bodily signals influence decision-making and cognitive processes. In his work, Damasio argues that the Self and consciousness are the product of continuous interaction between the brain and the body, and that the separation between mind and body can lead to cognitive and emotional dysfunctions, contributing to various forms of psychic and physical illness. Although he initially emphasized bottom-up movements from the biological to the psychic, in 2018 the author opened to the possibility of feedback from psyche to biology, thus approaching a PNEI perspective in which mind and body constitute components of a system based on feedback processes, an integrated network: *«The circularity of these operations is remarkable. On the face of it, mind and brain influence the body proper just as much as the body proper can influence the brain and the mind. They are merely two aspects of the very same being»* (Damasio, 2018a). To these considerations, we wish to add that such feedback signals between mind and body underlie the particular aggregation of thought into symbolic forms, a process characteristic also of dream thought and imagination (Zadra & Stickgold, 2021).

In many psychological models, the organism serves as a transversal element at the base of psychic development. It could not be otherwise, since human beings experience the world through their bodies—in health and in illness, from birth to the end of life. At the same time, the body represents one of the main conceptual nodes across theories, as not all align on its role and function in the development of consciousness and in the therapeutic process. The principle of a bidirectional rela-

² For a review of the debate, see the various contributions in *Nature Neuroscience*, volume 28, issue 4, April 2025.

tionship between mind and body, central to Damasio's work, is certainly consistent with the most recent evolution of certain psychotherapeutic orientations—such as constructivism and conversational constructivism—for which corporeality in clinical practice represents not only a symbolic or spatial datum, nor merely an intrapsychic container, but rather a direct key to accessing collicular and limbic dimensions, crucial in the re-elaboration of trauma.

The body in psychotherapy within the theoretical nodes of the paradigm shift

With the evolution of thought in psychotherapy, the representation of the totality of the psychic world (commonly defined as the Self) has undergone a significant transformation. Sometimes explicitly, at other times more implicitly, this evolution revolves around the central issue of the mind-body (or psychic-biological) relationship, which has been carried beyond philosophically oriented debates by neuroscientific research over the past decades. The “psyche” is now irreducibly inscribable within an integrated biological systemic functioning, from which it emerges as part of the system and with which it remains in constant dialogue. We can therefore observe, as a general phenomenon, that—consistent with an integrated perspective coherent with the PNEI framework—the physical and biological dimensions are increasingly receiving attention within the context of psychotherapies. The new paradigm is outlined by several general principles, which we will attempt to summarize here.

Circularity

The organism, in the totality of its functions, fully participates in the processing of the emotional meanings attributed to experience: today, we are witnessing the gradual abandonment of hierarchical visions in favour of psychobiological circularity. The very concept of *mentalization*³, a conceptual and evolutionary apex in cognitivist and psychodynamic theories – often overlapped with the concept of consciousness itself – is no longer understood as the ultimate goal of development or the final aim of therapy, but rather as a function of the mind. Conversely, a distributive concept of consciousness is now supported, articulated between psychic and bodily functions, such that there is no longer reason to speak of “body” and “mind” as independent yet interacting entities, but more correctly of the *organism* – a term that underscores unity and interconnection, and can encompass, while transcending, other frequently used terms such as *body-mind*, *mind-body*, or the more recent *bodymind*.

³ For the concept of “mentalization”, see the work of Peter Fonagy.

Consistently, the paradigm shift in research necessarily entails a revision of the concept of psychotherapy itself, which is reconsidered through the deconstruction of the idea that the process of exploration should be exclusively oriented toward what is present in the conscious mind, in the form of thoughts expressible through verbal communication. This limited approach often results in an endless journey in which some fundamental places of the experience of the self-with-the-other remain unexplored, thus perpetuating dysfunctional or only partially functional configurations.

Relational perspective and interaction between organisms

The progressive affirmation, since the last century, of a relational dimension in psychotherapy has been supported by scientific evidence showing that the actors operating within the clinical setting are organisms in constant interaction. Within developmental research, the Boston Process of Change Study Group has provided extensive evidence of infants' active role in shaping their relationships with caregivers from the very first moments of life. In particular, Daniel N. Stern (1985), one of the most influential figures of the Boston group, made a fundamental contribution to the study of infant development from a psychodynamic and neuroscientific perspective. Stern reformulated the concept of self-development in infants, challenging traditional theories grounded in the Freudian intrapsychic system and proposing a model grounded in early intersubjective experience.

The central point of his thesis concerns how subjective experience emerges, from the very first moments of life, out of the infant's sensorimotor interactions with the external world, and how, starting from these, the child progressively and intersubjectively constructs an internal representation of the self, continuously re-adjusted based on subsequent relational experiences throughout development. The attunements between infant and caregiver, essential for the proper functioning of the infant's system, occur through sensorimotor micro-regulations mediated by tone of voice, rhythm of touch, intensity of gaze, and so on.

Drawing on infant research, Stern shows that the infant is not passive in this interaction but intentionally organizes their experiences through the modulation of nonverbal expressions in response to perceptual experiences conveyed by movement, touch, sight, sound, and rhythm in exchanges with others. These exchanges are characterized by dynamic motor coordination patterns defined by perceptual categories such as duration, intensity, and rhythm. To these patterns—which represent the kinetic and emotional quality of the interaction—Stern gives the name *vitality affects*. It is through the repetition and generalization of these exchanges, and the vitality affects they convey, that the child builds the first emotional and relational representations in the form of coherent sensorimotor memory patterns that

have a predictive function for future experiences. Stern calls these generalized psychic models, which serve to organize past experiences and anticipate future ones, *Generalized Event Representations* (RIGs).

Within the attachment paradigm (Bowlby, 1969-1980; Ainsworth, 2006), this same tendency to organize representations of relational experiences in the 12-month-old child is referred to as the *Internal Working Model*. Cassidy (2013) – one of the leading figures in attachment studies – argues that the effects of attachment experiences are embedded in the body and the brain in ways not easily reducible to cognition and should therefore be studied at the physiological level.

Subsequent research has provided further evidence of the presence of active interactional capacities already from the foetal period (Ammaniti & Gallese, 2014). In the first hours of life, infants can imitate facial expressions and mouth movements (Meltzoff & Moore, 1977). This phenomenon suggested the existence of innate neural mechanisms of correspondence between perception and action, which would constitute a sort of prelude to the development of empathic communication among humans. Early imitation of facial and vocal movements by the newborn is a clear example of interpersonal sensorimotor learning. Repeated insufficient or faulty attunements by caregivers (Beebe & Lachman, 2003) lead to disorganized sensorimotor patterns that affect emotional regulation (Tronick, 1989, 2008; Schore, 1994⁴). Consequently, early preverbal traumas remain inscribed in these *being-with schemas*, which guide relational experience and the attribution of meaning in interactions with others, even in adulthood.

Later, Daniel Stern and the Boston Change Study Group (2010) would clearly develop the idea that human consciousness and the sense of self are always embodied, since emotion, cognition, and verbal narration of subjective experience cannot be separated from the perceptual experience of one's body in interaction with the relational context.

In the same years, within the systemic approach, "second-order cybernetics" introduced a paradigm shift: the therapist is an element that perturbs and is perturbed by the family system being treated, thereby influencing and being influenced by the "family games" (Heinz von Foerster, 1981). Likewise, the developments of attachment theory (Bowlby, 1969-1980; Liotti, 1994) – among the most widely applied across different theoretical-clinical models – also converge on the fundamentally bodily and relational grounding of the psyche. The weight of implicit procedural communication among human beings, more than explicit verbal communication, thus takes on the greatest importance in mutual understanding

⁴ From Schore's work, we do not consider the theory of the right brain to be scientifically validated, as it appears to simplify the complex reality of interhemispheric interaction.

and affective attunement. In this sense, psychotherapeutic change itself largely occurs through implicit dialogue, in which what matters most is *how* the two interlocutors relate to one another rather than *what* they say^{5,6}.

The influence of this intersubjective and fully embodied perspective on the development of human consciousness has also reached the more orthodox psychoanalytic context, where—even if technique remains fairly faithful to the original model—the myth of the therapist’s opacity and disembodied stance is no longer relevant. Bucci (2021, p. 343) writes:

«(...) researchers have discovered that some of the nerve cells that activate in a person’s brain when they are touched also activate when they see another person being touched (Keyzers & Gazzola, 2009), when they observe another person showing expressions of disgust or appreciation and when they themselves experience disgusting or pleasant odors (Wicker et al., 2003), when they observe another person’s pain and when they experience it themselves (Singer & Frith, 2005). (...) The implication of these findings is enormously significant for our understanding of the organization of emotional schemas in development and their unfolding in psychotherapy. Just as we are not accustomed to recognizing subsymbolic sensory, bodily, and motor processes as systematic thinking, we are likewise unaccustomed to recognizing that each of us is partially occupied by the perceptions and actions of those with whom we are in contact—and some parts of us are constantly occupied by the people with whom we were in close and continuous contact in our early years. I note here that the concept of projective identification, which has been viewed as somewhat magical and, in some cases, malevolent, acquires a systematic and neutral basis with these new findings».

Neuroscientific research, for its part, irrefutably demonstrates the systemic development of biological networks within a relational dimension in constant communication with the external environment. Rizzolatti, in a recent conference (Rizzolatti, 2023), further expanded the perspective opened by the discovery of mirror neurons toward a systemic vision of their functioning, affirming the existence of broader mirror systems—complex mechanisms of communication and mutual influence between the neural systems of different people, predominantly unconscious.

Studying the structure of the mind within the new paradigm means entering a functional circuit in which the subjective mind does not coincide with an individu-

⁵ Note the resonance with W. Reich’s (1949) concepts of “character” and “functional identity”.

⁶ Daniel Stern (2004) develops a clinical exploration technique based on microanalysis of procedural sequences. In his model, the change process is supported by moments of particular transformative potential between therapist and patient, defined as moments of now, generally arising from a disruption of expectations in the normal course of interaction. Depending on the mutual reactions of the participants to the emergence of an unexpected event in the interaction, moments of now can evolve into so-called moments of meeting: states of intense affective attunement in which the two participants mutually recognize the co-constructed meaning of their experience, implicitly attributing a shared sense to it.

al epiphenomenon but is part of a broader mind. This helps us reflect on the intersubjective “matrix” of which we are made (Bateson, 1984, p. 17). Daniel J. Siegel’s (2001) concept of relational mind builds on the representation of brain structure as a living system, open to environmental influences and dynamic, constantly changing in response to environmental conditions. Interpersonal relationships have a fundamental influence on our brains and minds throughout our lives. The neural circuits mediating social experiences are closely related to those that integrate processes governing meaning-making, the regulation of physiological and organic functions, emotion modulation, memory organization, and communication abilities. Neural circuits develop in ways that are directly linked to their activation. Thus, the development of the mind results from interactions between neurophysiological processes and interpersonal relationships. Our experiences can directly and significantly influence neural connections and brain organization, which is why early-life experiences play a fundamental role. The brain is therefore experience-dependent, as experiences help shape it, while interpersonal relationships facilitate or inhibit the integration of these experiences into coherent representations. In this sense, experiences can consolidate preexisting connections and induce the formation of new synapses, or, conversely, lead to cell death (Demoszi, 2011).

Psychotherapeutic literature has focused extensively on the relational and bodily foundations of the psyche, using a variety of conceptual containers that we will not detail here: body-self, implicit self, body memory, affective-emotional memory, implicit memory, unrepressed unconscious, emotion schemas, pre-verbal psychobiological matrix, alpha function and *rêverie* (...); concepts that in turn connect to broader themes and various research domains: memory mechanisms, unconscious, allostasis, role of sensory and interoceptive systems. Beyond these specific foci and their nomenclature, psychotherapy today generally presents itself as clinical action through a relationship between people, a full organism-to-organism relationship, implying reciprocal transformative processes that aim to restore to the patient transformed experiences (or at least the possibility thereof).

From the perspective of the clinical process, in psychotherapeutic communication – as in all relationships between subjects – alongside verbal and reflective dialogue, a deeper and subtler form of exchange is active, non-intentional, and not fully conscious. This form of communication manifests as a perceptual reverberation among participants through sensory, bodily, and emotional channels. Although it has a strong somatic foundation, this information exchange is not reduced to a mere somatic dynamic; rather, it represents a complex psycho-neuro-biological process that marks affective resonance between bodies and brains in relation (Stern, 2004) and relies on a form of procedural, nonverbal consciousness, which we have already mentioned, termed “implicit” active from a very early stage of life

and operational throughout the lifespan to ensure sensorimotor precision of actions, affective regulation, mentalization, and the construction of meaning from lived experience (Fonagy *et al.*, 2002). Implicit consciousness thus does not coincide with language but precedes it and constantly accompanies it: it represents a constitutive register of experience that evolves through continuity and progressive transformations rather than through discontinuous leaps.

From a PNEI perspective, the link between early relational memories described by Daniel Stern (1985) as RIGs (Representations of Generalized Interactions), the relational schemas described in attachment studies (IWM), and Wilma Bucci's emotion schemas (1997, 2021) is particularly significant. All represent mostly unconscious self-regulation mechanisms based on sensations, perceptions, and affective states largely formed within caregiving relationships. If RIGs or IWMs function as procedural models of interactions, specifically characterized by sensations, perceptions, and "relational moves" learned in the caregiver relationship, Bucci's emotion schemas encode affective patterns associated with such interactions. In other words, emotion schemas include the affective meaning attributed to the original experience and function predictively for all future relationships that share key features with the initial one. For instance, if the caregiver is also a threatening and punitive figure for the child, the expectation of being cared for by others in future relationships will likely also involve physiological activations consistent with feelings of fear and distrust and trigger defensive reactions (fight, flight, freezing), of which the subject is normally unaware, but which may manifest through somatizations. These prototypical relational dynamics tend to be activated in the clinical relationship because memory schemas, marked by affect-action connections, constitute the operative foundation of the self and serve an allostatic adaptive function, aimed at maintaining stability within ongoing change (e.g., they influence the attribution of familiar meanings to new circumstances).

From a neurobiological perspective, RIGs, IWMs, and emotion schemas are unconscious representations of lived experience related to neuroendocrine network calibrations learned in childhood and, through interoceptive monitoring, operate as internal predictive maps and models. They continuously guide and adapt affective and bodily responses to reduce the discrepancy between implicit expectations and environmental stimuli (Barrett & Simmons, 2015; Seth, 2013). These maps support (or fail to support, if experiences have been deficient) the actions and strategies necessary to allostatically manage the various tasks of life. The maps – true psychobiological networks – determine future interactive modes and the potential for deriving satisfaction from them. In the Italian tradition of functional psychotherapy, where the body has a central clinical function, these primary maps and their corresponding biological configurations are referenced in the construct of

Basic Experiences of the Self (BES), which psychotherapy aims to reconstruct (Rispoli, 2016).

Because they are predominantly procedural and unconscious, these schemas are sometimes referred to as “body memories”. However, this expression, if left unspecified, can imply static memories stored in the body, obscuring the brain’s role as an always-active, unitary system for encoding, integrating, preserving, and recalling experience. By “body memory” we mean rather an unconscious processing supported by affect-motor schemas activated by the subjective here-and-now experience and modulated by complex neural networks. These networks involve both subcortical structures (amygdala, insula, thalamus) for emotional and sensory processing, and cortical associative areas (prefrontal, cingulate, and temporo-parietal cortex) for cognitive integration of experience and physiological regulation necessary to sustain that experience. In this perspective, the body actively participates in memory retrieval, always operating in unity with the psyche and brain. The experiential reactivation of a memory, if accompanied by an experience that disconfirms what the memory predicted, can ensure its transformation (Ecker, 2018).

Cristina Alberini’s research (2005, 2011) on the cellular and molecular mechanisms of long-term memory in adults and children also demonstrates that memories are not static traces but dynamic contents susceptible to transformation. This concept of memory plasticity has profound clinical implications, for example, in the treatment of post-traumatic stress disorders (PTSD), where memories are generally reactivated by unconscious sensory traces, which in the clinical context serve as the trigger to begin modifying their emotional charge. Similarly, F. Shapiro (2001) argues that implicit memory representations arise from bodily experiences that subsequently become, through limbic and cognitive interpretation, emotions and cognitions.

In the therapeutic relationship, it is not uncommon – in fact, it is constant if attentively observed – to encounter bodily manifestations of such unconscious processes managed by biological networks. For instance, a consistently lowered gaze conveys the predictive expectation of negative judgment automatically embedded in nonverbal communication patterns, reflecting dysfunctional neurobiological processes learned (if the expected judgment comes from the individual’s early relational experiences) or constructed through an internal defensive dynamic (if the person consciously or unconsciously fears the presumed hostile attitude of the interlocutor). These traces can also be found in posture, breathing, motor behaviours, or various forms of chronic somatic dysregulation. Psychotherapeutic treatments focused on bodily responses are particularly effective in these cases because they address the processing of physical sensations within a safe context of attention and present-moment listening, thereby reducing the emotional charge associated with the original memory.

Analogous resonances may be experienced by the psychotherapist, aspects of countertransference involving the somatic sphere which, far from interfering with treatment, can become valuable signals for understanding the therapeutic relationship in progress.

Perinatal Life and Trauma Reappraisal

Regardless of epigenetic influences and transgenerational transmission, the origin of the sense of self in perinatal relationships is indelibly marked; likewise, the perinatal environment is permeable to environmental stress, understood systemically in all its dimensions (chemical, cultural, family situations, socioeconomic conditions, social climate...). Scientific research over the past twenty years has shown that stress-induced neuroinflammatory processes are linked to a wide range of psychological disorders (Bottaccioli F., Bottaccioli A.G., 2017, 2024a). Environmental stress shapes the maternal and perinatal family environment and can render the developing stress axis particularly dysfunctional, leading to allostatic overload that narrows tolerance windows and alters the development of regulatory mechanisms. Numerous and inescapable scientific evidences establish that life experiences, particularly perinatal life, are decisive for human development, in health or disease, not only due to direct effects but also because of the dysfunctional calibration of biological networks in formation.

Abandoned by Freud in the early years of psychoanalysis, except for the contributions of W. Reich and Ferenczi, trauma has returned to be re-evaluated within psychoanalytic psychotherapy (Gabbard & Westen, 2003; Bromberg, 1998). Recent years have brought new insights from research on ACEs (*adverse childhood experiences*) or ELA/ELS (*early life adversity, early life stress*) as etiopathogenetic factors, with primary focus on the caregiving relationship. Although much research on the relationship between stress and perinatal life, and stress and epidemiology in general, focuses on situations of overt psychosocial stress (poverty, isolation, abuse, illness, conflicts...), the category of “adverse events” should be expanded beyond major traumatic events to include more elusive deficiencies in concrete caregiving relationships, such as those related to contact (Mahler *et al.*, 1978; Beebe & Lachmann, 2002). This expansion makes the reference population universal and opens the way to developments in primary prevention and salutogenesis. The latter, referring to the human organism’s ability to generate and maintain health even under adverse conditions, can also be promoted by caregivers through an open sensitivity to observe simultaneously somatic and psychic functions, and their analogous connections of meaning: somatic symptoms can help identify psychic inclinations, and conversely, psychic symptoms can be related to somatic dispositions. In Western history, the first to establish a systematic relationship between organic

dysfunctions and psychic dysfunctions was Franz Alexander, who is thus considered the founder of psychosomatic medicine (Bottaccioli F. & Bottaccioli A.G., 2024b).

Mind-Body Connections in Health and Disease

Between the 1930s and 1950s, Franz Alexander, a Freudian psychoanalyst who founded the Chicago Psychoanalytic Institute in 1932, developed his own metapsychology on the origins of disease. Starting from the distinction between conversion disorders and genuine organic alterations in which the psychic cause is evident – first termed “psychosomatic” – Alexander proposed an innovative reinterpretation of pathogenetic mechanisms, identifying them, from a complexity perspective, in the dynamic interaction between organic vulnerability, early psychodynamic patterns, and triggering environmental situations. None of these variables alone is considered sufficient to determine disease.

With this approach, the Hungarian physician foresaw the limitations of a dualistic mind-body view, proposing a clinical and scientific method centred on the concept of the organism as a psychobiological unity, thus anticipating one of the most fertile epistemological foundations of the PNEI paradigm (Bastianelli *et al.*, 2021; Bottaccioli F. & Bottaccioli A.G., 2024a). This model proves surprisingly current, capable of integrating two vital dimensions for the sciences and practices of care: the biological and the psychological. Alexander advocated an anti-dualist, holistic philosophy and proposed an integrated approach to pathology – biological, psychological, and socio-environmental – predating Engel. While establishing a solid biological framework, he emphasized the role of psychology as «*the only field capable of explaining human motives*» (Alexander & Selesnick, 1966, p. 402) and as an effective way to influence the organism, complemented by medical analysis and intervention in the biological dimension: «*The basic position of the current psychosomatic approach is that human personality and the body constitute an indivisible whole, and that medicine should address personality problems and their effects on the body with a combination of psychological and somatic treatment methods. The psychological approach is one path to influence the organism. Psychology and biology address the same complex organism representing two different aspects*» (ibid.). The main limitation of his model lies not so much in the “emotional specificity” as a cause of psychosomatic illness – a post-humous simplification attributed to him – but in the cultural limitation arising from the scientific backwardness of his time regarding the functioning of the human organism. Alexander effectively illustrates the influence of the psyche on biology. In contrast, the reverse is understandably absent in his writings, given that the first partial demonstrations of bottom-up communication between the immune

system and the brain only appeared in the 1980s, and only recently has evidence emerged for the influence of inflammation, nutrition, etc., on the psyche.

Already in the 1920s, Ludwig Binswanger sought to overcome the determinism of psychoanalysis in favour of a broader view of human experience. He focused on how humans inhabit the world and, on this basis, developed the concept of existential analysis, integrating Heideggerian phenomenology with psychoanalysis, which he applied to psychiatric practice. Subsequently, Medard Boss (1963⁷) integrated Binswanger's legacy into a structured psychotherapeutic practice model called *Daseinsanalyse*. Boss studied the role of somatic disorders in the subject's existential economy but rejected Alexander's linear causal model linking psychic conflicts to organic pathologies. In line with *Daseinsanalyse*, he approached an existential analysis of illness, in which the symptom is not merely the expression of an unconscious conflict but a mode of being-in-the-world. Boss thus rejects any generic definition of somatic or psychic symptoms, asserting, for example, that there is no general definition of asthma, only "my asthma", i.e., *my asthmatic way of being in the world*.

In medicine, Hans Selye (1936) conducted significant research on the effects of stress, defining the distinction between good and bad adaptation: *eustress* and *distress*. He highlighted how adaptation can function more or less effectively and how diseases result from this process. Prolonged stress responses can create alterations (today called signatures) and predispose the organism to disease, thereby defining the difference between good and bad stress and, more importantly, between activation and allostatic overload. Prolonged stress responses to diverse stimuli can induce an inflammatory state and lead to disease. The capacity for self-regulation – understanding, through proprioceptive and interoceptive mechanisms, the need to modify or vary repetitive dysfunctional response patterns – defines the retroactive modality that allows remaining within one's window of tolerance. The window of tolerance can be defined as the space within which necessary feedback occurs, psychically stimulating and supported by reflective and meta-observational functions on one's actions.

With Selye, research on bidirectional relationships between biological systems and the psyche began, initially between the immune system, the brain, and the psyche, which developed from the 1960s within nascent Psychoneuroimmunology. In 1964, the American psychiatrist George F. Solomon published *Emotion, Immunity, and Disease: A Speculative Theoretical Integration*, in which the term "Psychoimmunology" first appeared. A few years later, he hypothesized that «alterations of

⁷ Swiss psychiatrist, trained in psychoanalysis and analysed by Karen Horney, he was introduced by Binswanger to the work of Heidegger, who became both a friend and a mentor. In 1958, he wrote *Daseinsanalyse e psicoterapia II*, included in the 2018 collection published by Cortina.

the brain during psychic illness could have an immunological reflection and, conversely, it seems conceivable that immune alterations could play a role in the pathogenesis of psychic illness, particularly in schizophrenia». Today, sixty years later, research on severe psychiatric disorders continues to investigate these relationships. The works of Robert Ader, Hugo Besedovsky, and Candace Pert in the 1970s anticipated by decades the mainstream and heterodox science (Damasio, 1994), breaking down the separation between physical-biological systems and the psyche-brain system (Bottaccioli, 2026, in press).

Siegel's contributions are particularly relevant: in trauma clinics, Siegel (1999) defines the window of tolerance as the zone between two levels of arousal: the lower limit, marking hypoactivation dysregulation, and the upper limit, representing hyperactivation dysregulation. Arousal beyond these limits does not favour trauma processing but triggers the dysfunctional re-experiencing of traumatic memories, hindering reflective presence to one's experience. Arousal within the limits, conversely, promotes an observational attitude, self-presence, and awareness of psychic contents and their bodily connections; it allows one to be within memories while observing them externally, as one would observe the landscape from a moving train.

Hyperactivation involves excessive sympathetic activity, with tendencies toward fight-or-flight or avoidance responses, and a disconnection of the prefrontal cortex from limbic circuits. Visible somatic manifestations include tachycardia, sweating, and muscle tension. Traumatic memory fragments activate but cannot be processed due to cortical disconnection. Hypoactivation is characterized by freezing, tonic immobility, and dissociation, a state of emotional distance from one's experience that may extend to derealization and depersonalization. Disconnection of fronto-subcortical circuits results in severe somatic disconnection, a "shutdown" state preventing trauma reprocessing.

Understanding the window of tolerance is useful not only for complex or attachment trauma treatment. It helps clinicians read somatizations from allostatic overload, i.e., when disease arises from prolonged stress-axis maintenance without resolution, i.e., calibration between sympathetic activation and parasympathetic return. It also supports evaluating patient stabilization and monitoring the return of self-regulatory functions within the window of tolerance after clinical interventions. This recalibration process indicates a return from the acute stress response to a resolution phase and the restoration of balance (Sinibaldi & Achilli, 2022). Awareness of these processes allows management of the patient's position relative to the window of tolerance and their reflective and meta-observational capacity. An example of integrated stress measurement is the scale developed in 2000 (Di Nuovo, Rispoli & Genta, 2000), which correlates physiological indices (skin con-

ductance, electromyography, blood pressure, heart rate) with biochemical measures (cortisol, GH, LH, PRL) and the MSP questionnaire.

Rewriting Biochemical Patterns

Considering the human being as an organism, and reevaluating trauma in psychotherapy, as discussed above, implies another significant aspect: the impact of treatment on biochemical patterns. Although findings are not yet conclusive, there is robust evidence regarding the biochemical effects of psychotherapy. One could hypothesize that it is precisely the functional rewriting of these patterns that ensures the long-term stability of psychotherapeutic effects, although research in this area is still evolving. To date, evidence has come primarily from cognitive approaches and, to a lesser extent, from psychodynamic ones.

We have repeatedly emphasized that, within the new paradigm, the body cannot be conceived as an autonomous and isolated entity. Rather, it is a complex organism capable, from the beginning of life, of retaining relational imprints, which remain encoded in implicit memory (more generally, in PNEI functional networks), influence future relationships, and constitute the self as experienced individually, the care of which is ultimately the goal of psychotherapy. Rewriting biochemical patterns can occur through both bottom-up processes (as discussed later via direct interventions, whether internal to or collateral to treatment) and top-down processes, through cognitive and emotional restructuring. These interventions should be understood in a perspective of complementarity and circularity, where micro- and macro-level phenomena represent the same process, albeit at different logical levels.

Current research on the mechanisms of change induced by psychotherapy primarily aims to retrospectively identify the biochemical changes that result from the clinical intervention. We are still far from satisfactory results, but it is hoped that future research may allow the programmatic identification of rewriting targets (i.e., which biochemical or neural mechanisms should be modified to achieve the desired change) and the modalities that explicitly address them (i.e., which therapeutic interventions most effectively act on those mechanisms).

At present, the reduction of chronic inflammation is probably the most promising area of such research and has already been scientifically confirmed (Shields *et al.*, 2020; Ma H. *et al.*, 2022).

Addressing the Broader Systemic Crisis

In addition to the above, there is an urgent need for psychotherapy as well as all health disciplines to intervene in the systemic crisis currently gripping the world,

which has created a pervasive and increasing state of uncertainty and generalized stress. An epiphenomenal pandemic of mistrust, conflict, and social distancing is underway, with already epidemiologically significant effects, particularly following the COVID-19 emergency, converging on a body increasingly prone to dysfunction, whether explosive or implosive⁸.

Of particular concern is the sharp rise in psychological disorders, especially among adolescents, and emerging pathologies related to sensory disorganization, eating disorders, affective blunting, self-harm, anxiety and panic, anti-conservative behaviours, social withdrawal, suicide, and violence. A closely related and highly relevant chapter concerns the use of technology and its impact, especially in developmental stages (Bianchi, 2019).

Intervention in this direction is essential to mitigate the spreading disorders and, above all, to reduce the risk that the chronicity and proliferation of stress may generate dysfunctions whose epigenetic signatures could be transmitted intergenerationally.

Focus on the Bodily Traces of Life Experiences

Psychotherapy, as a therapeutic practice, is concerned with the “traces” of traumatic or dysfunctional life experiences (which in epigenetics may be observed as “signatures”) in order to intervene through specific methodologies. As previously noted, the ongoing trend toward integrated psychotherapy implies an evolution of general psychological theories, in the sense of a systemic reconsideration of the mind-body relationship and a decisive revaluation of the role of the body in the clinical process. This represents an epistemological evolution that brings different psychotherapies closer together.

The traces that psychotherapies consider constitute a kind of theoretical and technical hub, relevant both to the development of a theory of mind and to the re-writing of technical interventions. Regardless of how they are defined, experiential traces have the following characteristics:

- They are primarily written by early relational experiences, conveyed through perceptual and interoceptive information (i.e., the perception of the body’s internal states).
- These experiences leave “imprints” on the body, in the sense that they establish settings within biological networks, particularly the well-studied stress axis (hypothalamic-pituitary-adrenal axis).

⁸ We do not report here the numerous studies in this regard: from COVID-related research to the field of psychotraumatology, to epigenetic studies on generational transmission. Similarly, this applies to the following section concerning the impact of technology.

- They influence subsequent life, affecting emotional and physiological regulation, and if dysfunctional, can generate disturbances throughout the psychobiological continuum.
- Although predominantly unconscious, somatic traces are not repressed and can therefore be accessed and modified through new relational experiences.
- They may become a sensitive locus for the modulation of epigenetic traces that regulate gene activity without altering DNA.

These considerations can stimulate clinicians' reflections in psychotherapy: How are traces inscribed in the organism? Which relational experiences determine them? Are there particularly salient traces that could guide primary prevention and salutogenesis? How do dysfunctional traces act, and through which pathways? Which tools are necessary to detect them in the therapeutic relationship? Which interventions facilitate their rewriting in the organism to promote a new equilibrium of health? Could there be greater convergence among psychotherapies regarding the factors that drive change?

Manipulation of the Body

Social and cultural dynamics, together with vicissitudes in family relations, profoundly influence the organism, forcing it into continuous allostatic adaptations. When tolerance windows are exceeded, the risk of exposure to epigenetic signatures increases, thereby increasing the likelihood that acquired dysfunctions may be transmitted to subsequent generations. For this reason, the PNEI (Psycho-Neuro-Endocrine-Immunology) approach considers it essential that such dynamics be included within the framework of listening and care.

A phenomenon of growing global relevance must be considered. This trend runs counter to the evolutionary direction of science, which seeks to overcome dualism, a principle that underpins this work.

Worldwide, almost 40 million people – and approximately 1 million in Italy –⁹, undergo procedures to modify their bodies through medical and cosmetic surgery. To these numbers must be added a vast but unquantifiable use of tools for more or less permanent body modifications: gym activities, unsupervised diets, tattoos, and piercings. The figures are striking in 2024; the increase over the previous four years was +42.5%. The age group most involved is 35-40 years, predominantly female, though requests from young people (under 24) and men are also rising.

Reading this phenomenon in its complexity, the numerical increase cannot be

⁹ Data drawn from the 2024 Global Annual Survey of the International Society of Aesthetic Plastic Surgery (ISAPS), presented at the ISAPS Olympiad World Congress in Singapore. <https://www.isaps.org/discover/about-isaps/global-statistics/global-survey-2024-full-report-and-press-releases/>

attributed solely to the accessibility of medical technology, which now allows the general population to undergo interventions previously limited to elites. This is a genuine cultural trend.

The ridge-line between a legitimate desire to improve one's appearance and a shortcut to overcoming deep insecurities is both narrow and steep. Leaving aside the biological risks associated with such practices, the phenomenon undoubtedly falls within the domain of psychotherapy, as an expression of generalized identity lability. This identity fragility is evident in many aspects of individual and social life and underlies numerous psychological disorders.

We identify a common thread linking four interactive phenomena: stress in this era of global crisis, uncertainty about individual and social identity, relational difficulties accompanied by distrust and conflict, and the need for compensatory modes of self-affirmation.

In a historical moment in which identity is increasingly less grounded in concrete, shared social actions that leave a meaningful mark in social and relational contexts, the solidity of the self diminishes. Social acceptance, which is indispensable, increasingly relies on the narrow window of apparent image and compliance with – or ostentation of – standards that are themselves becoming more fluid.

The reference mirror becomes increasingly external rather than internal. This same fragility of the Self intertwines with another epochal phenomenon: the exponential expansion of communication technologies, an additional factor in the global crisis.

Just as medical technologies can be understood as opportunities to bypass personal insecurities by directly modifying the body, communication technologies are widely used to seemingly overcome difficulties in concrete relationality, effectively “de-corporizing” the organism. Digital de-corporization can thus be considered a form of bodily manipulation. Non-corporeal relationships are created, developed, and concluded online, often in a very short time span, without direct contact, bypassing the complexity and psychobiological richness of real-life encounters.

The effects, however, are neither ephemeral nor illusory. The organism, interacting through a smartphone, is activated in its full complexity; the stress axis is engaged, often chronically (given the time spent online¹⁰), yet an inability or unwillingness to act within concrete relationality prevents a return to the functional range.

New dysfunctional behaviours reflect this process, such as doomscrolling, the tendency to compulsively and passively scroll through negative news online. First

¹⁰ In Italy, 90% of the population spends an average of nearly 6 hours per day online, according to the 2025 annual Digital report by We Are Social. See: <https://wearesocial.com/uk/blog/2025/02/digital-2025-the-essential-guide-to-the-global-state-of-digital/>

described during the pandemic (Anand *et al.*, 2022), doomscrolling has been associated with anxiety, stress, sleep disturbances, and a general deterioration in psychological and physical well-being. There is clear evidence that digital spaces are often experienced not as opportunities to expand concrete sociality, but rather as substitutes or compensations for it.

This is particularly critical during development, when concrete experiences should calibrate the formation of psychobiological networks. The early introduction of technologies raises genuine concerns about the deprivation of formative experiences in real relationality. It is equally risky to expose children to digital experiences before they are psychobiologically equipped to manage them.

It is urgent that psychotherapy and psychology more broadly engage in deep reflection on these phenomena. Society itself can be seen as an organism in need of care.

New Questions and Directions for Responses in PNEI-Oriented Psychotherapy

The shift in the paradigm regarding the relationships between mind and body, when applied in the clinical realm of psychological theory and practice, inevitably raises broader questions. How does the new scientific paradigm of complexity impact the clinical process of psychotherapy? In this new scenario, how can the psychotherapist integrate the processes of consciousness useful for the development of the clinical process? Given that consciousness is now considered a complex phenomenon emerging from interrelations, interactions, interdependencies, and interferences between mind, body, and interpersonal relationships, how does the concept of narrative and clinical dialogue expand? How can a therapist maintain the centrality of their therapeutic orientation while modifying it to integrate the organism in a meta-level approach? How can verbal therapies be reconciled with body-based therapies while preserving the most significant aspects? How should the organism be conceptualized across different epistemologies? Which interventions aimed at restoring the organism's balance, valid across different theoretical orientations, should be validated and integrated into a meta-model? What training needs might be hypothesized for clinicians?

No longer limited to the verbal domain, in therapy, narratives and dialogues between subjects are also expressed in the explicit and implicit forms, functions, and processes of interacting bodies. Intertwined verbal and non-verbal cues influence mutual listening between patient and therapist. Within this complexity, clinical listening and therapeutic action are enriched when the therapist, beyond verbal exchange, can orient their attunement to those narrative forms unfolding in the

amodal rhythm of verbal and gestural dialogue, easily captured by attention to the external perceptual field; or to those forms articulated in the sensory resonance of organs and viscera, normally muted, detectable only through intentional attention to the internal perceptual field. From this perspective, narrating and dialoguing become true actions that reverberate from one organism to another, from patient to psychotherapist and vice versa (Amore, 2021, 2024).

The complexity of narrative modalities articulated by the organism and its multiple, parallel processes of experience elaboration, as assumed by the Multiple Code Theory (Bucci, 1997), is both verbal and non-verbal, while the intersubjective field of the clinical encounter consists of multidirectional communication between the mind-bodies of two interlocutors who mostly interact through the implicit, non-verbal channel, in addition to the verbal one. In this expanded interactional field, in agreement with Jacobs (1991), we believe that the development of cultivated perceptual sensitivity to bodily experience is necessary for the psychotherapist in training.

This *embodied* vision of the human being constitutes a strong element of scientific evolution and is central to the PNEI paradigm. The theoretical-clinical significance of this premise ensures that the body, as an organism, is not merely a variable to be added to therapeutic protocols, but a central construct that calls for reconsideration of both psychotherapeutic theories and techniques.

From here, we want to highlight the need for more radical reflections on the deconstruction of outdated body-mind relational models that nevertheless guide therapeutic actions, rather than the simpler inclusion of the body within pre-existing models. That is, from the first consultation encounter, a patient's observation should accord the clinician a gaze capable of continuously shifting between psychic and bodily experiences, capturing the functional and meaningful connections within the experiential economy of the person during consultation and throughout their development. In this way, we aim to articulate as closely as possible the subjective sense of human existence in an integrated mind-body-world representation, restoring to the subject the specificity of their complexity. Since dysfunction and illness are now conceived as the result of the unrecognition or dissociation of different aspects of the Self, this constitutes a first, fundamental therapeutic action aimed at integrating the constitutive aspects of the Self normally polarized into psychic and bodily representations. Therefore, *«repairing dissociation implies first operating an integration between mind and body, between somatic and psychic states, tolerating and exploring sensory experiences, thereby fostering the necessary connections for the development of a sense of self-cohesion aligned with self-awareness»* (Amore, 2024, p. 63).

The inevitability of the above has now led almost all models to affirm the cen-

trality of the body in psychotherapy; however, these statements carry very different connotations, referring to underlying theoretical frameworks and corresponding intervention methodologies. The impression remains that the significance of this shift in vision is not yet fully grasped (or is overlooked), and that pre-existing theoretical-clinical models are updated without substantial modification, as if the body could be treated as a simple additional variable enriching therapeutic practice. Scientific progress cannot advance in a fragmented manner; the evolution has been significant, but it is still weak. A strong meta-model is necessary, one that synergistically captures scientifically validated evidence and represents a renewed stimulus for research arising from the abandonment of unvalidated views.

PNEI Proposals for Incorporating the Body into Technique

Expanding Assessment

Generally, across different assessment modalities, the body is investigated as an anamnesis datum: narratives about bodily vicissitudes are collected for diagnostic purposes but often do not involve exploration of the body in its relational functions.

The gamut of information collected ranges from past and/or present disorders to related medical therapies. Less frequently, it includes subtler experiences related to past and current developmental history. There is no consensus on which elements are the most significant for observation and collection. Likewise, regarding the meaning of the collected data and its therapeutic use, the range of possibilities is broad.

Somatic symptoms are consistently included in assessment questionnaires and in many DSM criteria. Yet, their deeper meaning is often overlooked, and a vision that frames their etiopathogenetic origins and developmental consequences is missing. From this emerges the need to conceive of a simultaneously dual care of the Person, defined in the roles of physician and psychologist. Their different professional backgrounds should converge to collect significant content relevant to both domains. This joint approach allows the construction of a hypothesis of functioning that considers both the organic-psycho and the psycho-organic dimensions (where “psycho” here also refers to social and cultural levels).

In terms of process, it is more appropriate to avoid assigning hierarchical salience to the collection of anamnesis information, as this would imply maintaining a non-integrated system view. Conversely, a common perspective is necessary by recognizing the specificity of each exploratory logic without subordinating one to the other. Collaboration between psychologists and physicians must be based on a

shared communicative code, allowing a parallel and integrated approach to patient care. This means professionals should work together not only chronologically but also through a multidimensional reading of the case. Each specialist maintains their own level of access and competence, but they decode phenomena in an integrated manner.

For example, suppose we consider an eating disorder to be an expression of systemic inflammation caused by intestinal dysbiosis, maintained by prolonged emotional and psychosocial stress, in this scenario. In that case, therapeutic interventions should converge on multiple fronts:

- Emotional regulation: Techniques such as biofeedback (e.g., breathing, increased heart rate variability) and mindfulness.
- Interventions on gut health: Detailed dietary prescriptions by the physician, including natural remedies to reduce inflammation.
- Psychotherapy and psychotraumatology: To address emotional causes and traumas.
- Internal medicine guidance: Specific medical treatments.

For this approach to work, professionals will have to share a common language and understand the intricate psycho-neuro-endocrino-immunological connections and their manifestations. This will require a position of humility and cooperation among all involved figures.

The Body in the Anamnesis

Let us take as an example a data collection form proposed by the Order of Psychologists of Tuscany in June 2024. The form is divided into three sections: Personal History, Clinical History, and Analysis of the Request. Bodily data appear in the *personal history* as “current and/or past organic diseases” (and related pharmacology), “dietary habits”, “sleep-wake rhythm”, and use of “alcohol, smoking, or drugs”; but there are no references to bodily data in the *clinical history* (in the family and personal anamnesis sections), while they are indirectly included in the subsection *analysing life skills and personal resources*, such as “stress management” and “effective/assertive communication”. Bodily data are more present in the *analysis of the request*, within the section dedicated to the *physical examination*, in dimensions such as “clothing, self-care, speech, motor activity, agitation, etc.”.

Yet, the form can be considered advanced in some respects: it is transversal to theoretical models (although it does ask for identification of attachment style at one point); it considers dietary habits; it records bodily aspects in the physical examination; and it addresses the topic of stress. However, no reference is made to the body in the person’s life history, such as birth details or possible breastfeeding experiences. Sexuality is also largely absent. Finally, there is no guidance on how

to observe the few collected data, which, from our perspective, are elements that influence and define epigenetics.

For a PNEI-oriented psychotherapist who interfaces with a person whose personal history is traceable through the organism's functioning, it is necessary to go beyond such data collection. The assessment should include minimal aspects of historical-developmental anamnesis (e.g., breastfeeding, crawling, Early Life Adversity (ELA), early motor characteristics, sports activities, etc.) together with objective observations collected in the here-and-now of the encounter (non-verbal patterns, but also indicative data of possible alterations: skin tone, temperature, tachycardia, breathing patterns, etc.). At this stage, a more in-depth anamnesis would be useful, including the evaluation of potential biological and epigenetic markers. Particular attention should be given to those related to inflammatory mediators (cytokines, chemokines, histamine, etc.) and to data on gut microbiota health, now recognized as an active part of the immune system, along with any alterations. The psychotherapist alone can collect and integrate some of this information systematically; however, collaboration with a physician would allow deeper investigation through specific analyses, providing a more useful and truly integrated clinical picture.

The collection should also include experiences of sexuality, both as lived and narrated by the subject, and as objective data potentially influenced by dysfunctions or complications (see the Dis.Men Commission document on sexuality published in PNEI Review: Vaccaro *et al.*, 2024). Finally, all these data should be framed within the context of the subject's birth and development. This framework includes the place of birth, socio-cultural context, myths and assumptions of the social and family system, occupational positions, and everything relevant to the life context.

Regarding data collection, it is also relevant today to reflect on technology-mediated modalities. There is a growing tendency to replace physical co-presence in clinical encounters with virtual platforms, and the criticality of this phenomenon is noted, especially during development (Bianchi, 2019). This vast, complex, and controversial topic will be addressed in a future reflection.

The Body in the Relationship

The patient's learned relational patterns are directly observable in their approach to the therapist through nonverbal communication. Observed patterns should be placed within a systemic view, including familial, social, and cultural levels of relational experience. Only by considering this framework can current observations of posture, musculoskeletal flexibility, bodily modes of emotional regulation, and inferences about traces left by past experiences in the construction of the Self gain meaning.

These data can be considered “macro” epiphenomena of processes and traces inscribed at the “micro” level. Frequently, observable data in the here-and-now reveal alterations in emotional and stress regulation processes and simultaneously constitute potential access points.

From the body psychotherapy tradition, some useful parameters to expand the physical examination to include the relational sense of non-verbal language are highlighted:

- *Breathing.* Breathing is a general regulatory factor and has been scientifically demonstrated to be linked to major biological, emotional, and cognitive systems, particularly in stress management. Biochemical traces of alteration (subject to re-writing or correction) are also reflected in breathing. When unaltered, breathing promotes interoceptive listening, maintaining contact with sensations, and supporting bodily awareness, perception, and emotional expression. Ancient practices, such as meditative techniques (both static and in motion), as well as many modern physiotherapeutic and rehabilitative approaches, share the use of mindful breathing as a privileged gateway to the autonomic nervous system and to physiological-affective regulation. All these techniques, within different theoretical frameworks, converge in considering the respiratory rhythm a basic tool for promoting self-regulation and the development of self-awareness.

- *Posture, voice tone, gaze.* These data make the relational modes of openness, closure, or withdrawal, conveying emotional experiences, more evident. Life skills from anamnesis forms can thus also be captured directly, beyond what the patient reports.

- *Muscle tone.* Alterations in muscle tone within the hyper- and hypotrophy ranges are very common. Beyond causing disorders, muscle tone quality, perceptible through movement flexibility/fluidity, indicates why the organism has calibrated its relational defences toward rigidity or softness, opposition or adaptation.

- *Movement quality.* Characteristics defining specific ways of moving in the world, i.e., sensorimotor patterns, are multiple. The organism interacts with the world and with relationships through learned motor abilities, which, in turn, affect relational possibilities. Each individual develops a personal repertoire of gestures and motor patterns. A person gesturing broadly and decisively may be perceived as extroverted or passionate, whereas someone using contained and cautious gestures may appear more introverted or reserved. These motor patterns are not random; they are learned and shaped by early relational experiences and influence how we are perceived and how others choose to interact with us. The body psychotherapy tradition suggests observing these dynamic elements from the first moment of care, as they form the self-other motor patterns. The RIGs, to use Stern’s term.

Expanding the Technique repertoire

After the data collection phase, the psychotherapist translates the observed data into an intervention plan, often developed implicitly, that guides clinical interaction. The clinical attention to the body spans a continuum of lesser or greater therapist involvement. Even without a shared integrated vision, bodily symptoms or signals during sessions are increasingly recognized by theories as emerging from the relationship. However, except in body-mediated psychotherapies, bodily events generally remain in the background of verbal discourse: even when noticed and considered, clinical exchange focuses on verbal content rather than bodily manifestations. Occasionally, when specific symptomatology brings them prominently to the forefront (e.g., DAP, PTSD), bodily events are addressed through brief-focused interventions (as in some CBT protocols). Nonetheless, except for certain techniques (EMDR, DBR, or some hypnosis practices), these events are not directly and systematically explored, nor are their connections with accompanying emotional experiences investigated.

For the PNEI-oriented psychotherapist, the body is present constantly, not only when symptoms or somatic dysregulations forcibly attract attention. There is ample scope to integrate coherent practices across different therapeutic models that involve the body more directly¹¹. The following are proposals for reorientations that are useful for defining psychotherapy from a PNEI perspective.

Interoceptive listening

In therapeutic dialogue practice, it is useful to implement interoceptive listening techniques, which are already used in some clinical practices. Since the psychotherapeutic encounter itself structures an intersubjective field, consciousness promoted by the psychotherapeutic process emerges also from non-verbal clinical dialogue and is experienced by both participants primarily as an embodied experience in implicit sensorimotor forms. Especially when consciousness cannot access the experience, and verbal forms are unavailable to narrate it, the sensory and proprioceptive states of both remain available for exploration. In these cases, the psychotherapist's body, like a tuning fork, can resonate with the patient's unconscious subjective experience. The clinician's participation can take the form of sensory experiences or enactments¹² in the here-and-now of the clinical encounter (Ogden,

¹¹ Regarding the psychoanalytic orientation, we refer to the works of Marina Amore.

¹² Enactment, first conceptualized by Theodor Jacobs (1986), describes an unconscious response of the therapist to the implicit perception of dissociated or unmentalized content belonging to the patient's experience. This response may manifest in verbal or behavioural actions that disrupt the therapeutic setting, creating discontinuities in how the patient experiences the therapist. Once recognized, enact-

1997; Bromberg, 1998, 2011). The ability to access their own sensory experience and the routine practice of microanalytic monitoring often represent key competencies for those working with patients whose body language precedes or substitutes verbal language. The therapist's interoceptive observation can become the sensory basis for attuning to the patient's sensorimotor experience, initiating exploration that promotes the patient's awareness of affective states—a first step toward expanding consciousness. Based on the clinical work of authors from various theoretical orientations, the empirical utility of sensory focus for both partners in the therapeutic dyad is considered transversal, aiming to amplify the patient's sensory experience in the here-and-now of clinical dialogue and as a facilitator for verbal expression (Ogden, 2006, 2021; Amore, 2012, 2021; Frank, 2001).

Direct Bodily Interaction

Physical contact between therapist and patient, while historically utilized in the early stages of psychoanalysis, later became taboo and was practiced only by so-called heretics. With the collapse of the myth of opacity and the advent of the relational turn, theoretical assumptions shifted. Nevertheless, apart from certain exceptions such as Gestalt therapy, psychodrama, and the composite area of body-oriented psychotherapy, practice in most psychotherapies remains predominantly verbal. In light of new data, the distinction between verbal and body-based therapy should fade; yet this distinction still persists as a lingering dichotomy. Considering the human being as a circular organism, why not render the therapeutic relationship circular in its technical possibilities as well?

Once again, body-oriented psychotherapy offers illustrative examples. For this therapeutic orientation, as previously highlighted, attention to the body occupies a central place in the care process, and interventions using various “body” techniques may involve physical contact between therapist and patient. Direct contact in therapy can be categorized into two types (Bianchi A., 2018):

- *Diagnostic touch*: aimed at highlighting asymmetries in different areas of the body, contractures, temperature, perceptual thresholds, pain, mobility, and alarm reactions.
- *Reconstructive touch*: aimed at directly acting on altered planes and functions, according to the therapeutic phase, to expand mobility, increase body awareness, modify muscle tone, access ancient and regressive sensorimotor patterns, and reconnect them with other experiential contents (such as emotions and memories).

ment can serve as a powerful pathway to access the patient's dissociated affective experiences and become a potent instrument for transformation in therapy.

Within body-oriented psychotherapy, the therapeutic program unfolds simultaneously through verbal and non-verbal channels to integrate the two levels of consciousness. For example, to work on assertiveness and stabilize the biochemical changes that support it, targeted techniques that re-establish open, strong movements, an open posture, diaphragmatic breathing, direct gaze, and an appropriate voice tone are useful.

Direct work on the body takes advantage of interoceptive listening, the ability to perceive internal bodily sensations. Interoception serves as a direct channel to access unconscious memories and contents, as occurs spontaneously during sleep. Dream construction and the ensuing narrative emerge from this circular process of perceiving and amplifying somatic sensations, which occurs automatically and below the threshold of awareness. Similarly, bodily signals during the session – muscle tension, posture, breathing, motor quality, sensations, and somatic symptoms – can be intercepted and explored. Like the elements of a dream, these signals provide access to the patient's implicit narrative and allow for its deeper meaning to be decoded (Amore, 2021, 2022).

We can envisage a trend in the evolution of psychotherapeutic technique that, starting from the verbal definition of experiential contents, initiates processes that amplify interoceptive traces within a multidimensional experiential framework, aiming to integrate the emotional, cognitive, and sensorimotor planes in the here-and-now of the clinical relationship. Through interoceptive listening, each psychotherapeutic orientation can explore these traces according to its clinical tools, which may involve forms of contact and movement in functional psychotherapy or microanalytic verbal exploration of bodily occurrences in psychoanalytic settings. Naturally, the use of interoceptive listening must take into account certain limitations and caution in the case of patients with specific characteristics (traumatized individuals hypersensitive to physical contact, those prone to affective dysregulation, or individuals with disabilities).

The body in therapy is also the main pathway for experimenting with new behaviours: in experiential approaches, such as Gestalt therapy, experiences proposed by the therapist and lived by the patient within the safety of the setting and therapeutic relationship engage the organism as a whole, allowing the exploration of new behaviours that can reconsolidate previously dysfunctional patterns. Continuous guidance from the therapist to attend to interoceptive signals while experiencing new behaviour or emotionally significant experiences in the session promotes the integration of unconscious experiences and the exploration of new possibilities.

The primary route to understanding the boundaries of action and the most effective therapeutic approaches at any one stage of the clinical process remains the

relationship. Attention to observable aspects within the relational context protects against the risk of rigidly applying standardized protocols and ensures individualized pathways aimed at reconstructing injured aspects of the Self.

The first question arises: *if it is legitimate and sometimes necessary to administer questionnaires or tests, why not also test movements, postures, breathing, or pain thresholds?*

The second question: *as a more immediate example, why not work on restoring diaphragmatic breathing in therapy (given its known link to stress), as part of a more complex rewriting of biochemical states?*

Integrated Therapy: Our Proposal

Renewed attention to the role of the body in psychotherapy has led to increasingly widespread adoption of techniques of a somatic nature, in cognitive behavioural therapies and in the psychoanalytic ambit. EMDR, Sensory Motor, DBR (Deep Brain Reorienting), and hypnosis, or through the growing in-session use of specific techniques as supplements to the protocols in use across various therapeutic models. This represents undeniably a step forward, but a feeble step rather than a real rethinking of psychotherapy as an instrument capable of taking care of the complexity of all the dysregulated manifestations – psychic and somatic – of the whole organism.

Inserting a few somatic techniques into the process risks just scratching the surface of that self-sufficiency with which psychotherapy has traditionally defended its territory, claiming specialist knowledge, in parallel with the fragmented competencies of the many specialisations in Western medicine. Change in this way is just partial and superficial, lacking the will to accept the – sometimes unavoidable – necessity of involving professionals from other contexts, in the medical field or other complementary disciplines. Without this further step, the therapeutic relationship will miss the chance to accompany the patient in the conquest of a cohesive representation of the Self, which should include somatic functioning as well as psychic functioning.

What would be preferable is an expansion of the network of cooperation, allowing the psychotherapist to engage in dialogue with a richer constellation of professionals. Not just with the psychiatrist – with whom collaboration is well established – or with teachers in the case of developmental contexts where dialogue is often sought reciprocally. A more choral form of treatment, which has a greater possibility of generating deep and lasting change.

From a PNEI perspective, in aiming to define a metamodel which integrates both synchronous attention to biological and psychic processes and cooperation across disciplines, it is valuable to co-construct with other professionals – and to-

gether with the patient – the lines of intervention necessary to restore a state of health consistent with the patient’s psychic and somatic needs. The strength of integrated therapy emerges when diverse therapeutic indications come out of a shared vision among caregivers.

In the PNEI sense, integrated therapy consists of proposing a unified diagnostic process (medical and psychological) with correlated, progressively monitored, specific interventions (Bottaccioli F. & Bottaccioli A.G., 2024a). This perspective must include the creation of a shared language regarding biopsychological mechanisms to facilitate communication between psychotherapists and specialists from other biological disciplines. A shared diagnostic foundation encourages rapprochement between healthcare professions, requiring all parties to broaden the scope of their diagnostic evaluations while maintaining the specificity of their interventions. For the physician, this involves opening up to a non-reductive organicist view. At the same time, the psychotherapist benefits from foundational knowledge of the connections between biological and psychic processes in order to guide clinical exploration of the patient’s lifestyle, dietary habits, physical activity, and so on.

Within this perspective, it is useful to consider with the patient options among well-being practices, such as meditation (for its known effects on emotional regulation and mindful attention), acupuncture, homeopathy, herbal medicine, music therapy, Tai Chi Chuan, Qigong, and others aligned with the organism’s need for repair.

In summary, all health professionals should learn to read and contextualize, and to intervene according to their specific expertise at the emotional, cognitive, bodily, and social levels in a recursive manner.

Expanding Training

The proposal of an integrated PNEI-based therapy, therefore, implies, for the psychotherapist, the need to access integrated training aimed at sensitizing clinical listening and attention to the complexity of communication levels at play between individuals, and to the necessity of their interconnection on the level of conscious awareness, in order to promote the optimal development of the change process.

Below are some directions for training to be implemented, summarized in bullet points. One key point is the development of the psychotherapist’s capacity to perceive themselves as an interconnected organism, mind, and body, and to understand the implications of this interconnection in the exercise of clinical practice. This condition is encapsulated by the concept of *embodiment*, coined by Varela to express the embodied state of cognition¹³.

¹³ The term has commonly been translated as “embodied cognition”, although the correct translation would be “incorporated cognition”, which we prefer.

Outside the tradition of body-oriented psychotherapy, the psychotherapist generally knows less about their own body than the patient's body. In the history of psychoanalysis, we can trace a line of reflections which, starting with Ferenczi and Reich and continuing through the attention that Bion and Ogden paid to the presymbolic and implicitly embodied dimensions of experience, has repeatedly highlighted the need to include the body in our understanding of the analytic process. In this perspective, Theodore Jacobs, as early as 1991, pointed out that the psychoanalytic tradition had long privileged the listening to verbal communication at the expense of what is conveyed through the body, gesture, and the infinitesimal, unspoken vibration of experience. According to the author, the lack of training attuned to the nonverbal level creates a kind of blind spot in the analyst-in-training. This ingrained perceptual habit tends to take root and be transmitted from one generation of analysts to the next as a technical shortcoming of the discipline, thus making a renewal of analytic technique desirable. In 1998, the volume edited by Aron and Sommer Anderson, *The Body in Relational Psychoanalysis*, represented an important point of convergence among different clinical contributions aimed at restoring centrality to the bodily dimension within relational psychoanalysis; however, the issue of training analysts in this regard remained largely unexplored.

The idea of a renewed psychotherapy resonates deeply with the concept of the embodied mind, which lies at the heart of Francisco Varela's epistemological perspective (1992), oriented toward understanding the mind as an embodied and relational process and conceiving the transformation of consciousness as an experience rooted in the body-in-relation¹⁴. We maintain that, to realize such a project, each school, regardless of orientation, should include in its training program attention to certain dimensions necessary for developing in the psychotherapist the sensitivity for integral listening and the skill to use data gathered from their own interoception to guide clinical work. We consider a broad reflection on the bodily intersubjectivity of the therapeutic relationship to be useful, one that examines key elements that help in conceiving a meta-model within which the specificities of each orientation can be referenced.

Below, we propose some key elements for such a reflection, which we believe can serve as a cornerstone for this debate.

¹⁴ Varela introduced a revolutionary way of thinking about the mind, moving it out of the brain and into the body, relationships, and lived experience. His work laid the foundations for neurophenomenology, influencing contemporary neuroscience, psychology, and philosophy.

The Therapist's Body

During training, the therapist should have the opportunity to explore their own body's experience to develop certain listening sensitivities that support the cultivation of conscious awareness. Therefore, part of the training program should include activities aimed at:

- Raising awareness of sensory experience and discernment regarding its use within the clinical dialogue: the experiences that each clinician has of the therapeutic relationship are never purely cognitive but always involve sensory perception. This is often spontaneously prominent when the therapeutic field hosts dissociated and/or unformulated affective organizations that tend toward consciousness, and whose processing is necessary for therapeutic progress. In these cases, the therapist must develop a foundational disposition for both verbal and non-verbal listening to guide therapeutic action.
 - Ensuring increased attention to symptoms as potential indicators of biological alterations and medical pathologies, as well as to traces for understanding dysfunctional relational organizing principles.
 - Ensuring basic knowledge of biological functioning and the relational setting of regulatory systems and processes, particularly stress, including an awareness of epigenetic markers and their effects on psychobiological networks.
 - Developing knowledge of the impact of lifestyle and nutrition on hormonal cycle alterations and gut microbiota functions, and how such alterations influence emotional and cognitive manifestations.
 - Acquisition of a shared clinical language that allows communication not only with psychiatrists but also with internists, general practitioners, and specialists from other biological disciplines.
 - Learning basic clinical interventions for somato-emotional regulation that may be necessary during the session, both to reduce stress in the here-and-now if it exceeds the window of tolerance and as autonomous tools for the patient to decrease inflammatory response and support the organism in restoring and maintaining emotional balance. Techniques such as diaphragmatic breathing and meditation are examples.
- Additional key aspects for good practice include:

The therapist's attention to their own well-being

Just as ongoing cognitive training (ECM) is mandatory and valued, the training program should also offer practices aimed at the therapist's well-being to maintain functional stress regulation capacities, which are normally challenged during professional activity. Consequently, the therapist's equilibrium requires constant attention and monitoring.

Beyond validating the importance of personal psychotherapy aimed at understanding one's own functioning – currently required only in dynamic-oriented training models¹⁵ – it is important to maintain ongoing attention to personal well-being and health. Like their patients, therapists should consistently evaluate the use of tools and practices (previously mentioned) that promote functional integration of the organism.

Multidisciplinary supervision sessions should complement individual work in line with the PNEI paradigm.

Expanded conception of countertransfert

Often insufficiently considered, although increasingly reflected upon, is the therapist's self-observation of signals emerging from their own body, both inside and outside the session. These signals and experiences, often initially without meaning, are frequently perceived by therapists as interference rather than explored as clinical tools.

This issue has a historical context. In 1958, Heinrich Racker, a Polish psychoanalyst who emigrated to Argentina to escape Nazism, wrote: *«It is important that the analyst perceives their own facial expression, frames it as a countertransference response to the transference, and, after controlling for the personal factors it expresses, reintegrates that part of their personality onto the patient via interpretation»* (Racker, 1968, p. 45).

In 1988, in the first comprehensive text on body-centred psychotherapy that would soon become Functional Psychotherapy, Barbara Andriello and Luciano Rispoli, referencing Racker, added:

«...facial expression is only one aspect of the bodily self that, beyond our conscious intentions, impacts relational configurations... the inner phantasmatic world, which heavily influences countertransference actions, is not triggered solely by impulses generated internally; nor does it originate exclusively from a mechanical concatenation between the patient's thoughts and images... and the therapist's fantasies. Input channels include all perceptual levels to which the therapist's sensory world is exposed, both exogenous and endogenous. These messages produce a complex network of resonances, not all of which belong explicitly to conscious awareness. Exploring this vibration of emotional, bodily, and cognitive strings constitutes a therapeutic use of expanded countertransference» (pp. 248-249).

In addition to images and thoughts, during the session, the therapist can often register somatically marked experiences: repulsion, disgust, withdrawal, empathy,

¹⁵ When referring to dynamically oriented models, we do not mean exclusively psychoanalysis and psychoanalytic psychotherapies, but also other approaches that share an emphasis on unconscious and relational dynamics, such as Gestalt therapy and Transactional Analysis.

tenderness, alarm, and sometimes tensions or pains, as well as interoceptive and exteroceptive sensations whose nature may not be immediately clear. If recognized in their connection with the current relationship, even ancient bodily experiences – such as a migraine – can transform from obstacles into signs of therapeutic evolution.

The gaze of a psychotherapist oriented by the PNEI perspective, regardless of their clinical model of reference, should be able to perceive the whole and the continuity between the patient's verbal and non-verbal expressions, integrating their shared meaning to foster greater cohesion in the sense of self. The patient's bodily signals, conveyed through the implicit channels of communication, are reflected in the therapist's bodily experience, who perceives their echo through the multiple signals discussed above. For psychotherapists trained in verbal therapies, it may be necessary to develop and integrate skills not normally addressed in training for "talk therapies". These skills should primarily concern the ability to intercept and identify, in a microanalytic way, how the dynamics of the here-and-now of the therapeutic relationship resonate in one's own bodily experience as a representation of the patient's past relational dynamics, and, subsequently, to learn to use one's sensory resonances as traces to promote exploration in clinical dialogue.

We consider it highly useful for training institutions to take into account the need to sensitize trainees to sensory-motor forms of listening that require a different register of perception and information processing than that required by traditional listening to verbal content brought by the patient in therapy. This sensitization would require psychotherapy training programs to include the development of intersubjective listening through dedicated activities.

Regarding integrated listening, where does psychotherapy training stand today? We believe that, for many orientations and for many individual professionals, progress in this direction is still hindered by action schemes that rely, to paraphrase Daniel Stern's central concept, on old theoretical-clinical RIGs that struggle to be deconstructed in favour of *new ways of being-with*.

At the same time, we observe in society a progressive movement that, increasingly rapidly, is moving toward a disembodiment of relational experience. We wish to believe that psychotherapy, as care for the human subject in their entirety, can still intervene to counteract this dehumanizing tendency of humanity. This is also the *project for psychotherapy* that Jacobs hoped for in 1991¹⁶, and which refers to the concept of the *embodied mind* that characterized the central epistemological po-

¹⁶ Despite what Jacobs still hoped for in 1991, to date, training schools with this orientation in Italy normally do not include in their curriculum educational activities specifically aimed at developing interoceptive sensitivity in clinical listening. The only exception is represented by the newly established School of Specialization in Psychosomatic Psychotherapy with a PNEI orientation.

sition on the idea of consciousness transformation in Francisco Varela's theory in 1992¹⁷.

Conclusions

The evolution of scientific knowledge, which underlies PNEI (psycho-neuro-endocrine-immunology), demonstrates that to understand the human being in health and disease, it is necessary to adopt a systemic perspective. This vision recognizes the individual as a complex organism in which biological and psychological dimensions constantly communicate bidirectionally.

A direct consequence of this paradigm is that the physical and biological elements of the person and their interrelations have become central and indispensable material in psychotherapy and clinical practice as well.

The overcoming of the mind-body dichotomy has represented a long process in the evolution of psychotherapeutic thought, from the origins of psychoanalysis throughout the twentieth century.

The present work has described the key stages of this long process: from the historical authors within early psychoanalysis – Reich, Ferenczi, and Groddeck – to the first school of psychosomatics with Alexander; from contributions coming from neuroscience and infant research, to the internal evolutions of the main psychotherapeutic models: psychodynamic, cognitive-behavioural, relational-systemic, psychocorporeal, and Gestalt.

Although there is a clear tendency to revalue corporeality in psychotherapy, this often translates into eclectic solutions that fail to grasp the depth of the change required. Due to their specificity linked to a particular orientation model, such approaches are unable to provide a connected and unified understanding.

The PNEI approach addresses all areas of psychotherapy. It does not merely constitute a simple update but requires even radical modifications of the basic theoretical assumptions and technical modalities of intervention.

It has been highlighted how outdated and scientifically unfounded conceptualizations must be abandoned in favour of new assumptions. The physical and biological elements of corporeality convey inescapable meanings, just like thoughts and experiences that can be communicated verbally, with which they are deeply intertwined. They must therefore fully become material for therapeutic action, as they constitute historical traces of the relational and bodily foundation of the psy-

¹⁷ Varela introduced a revolutionary way of thinking about the mind, taking it out of the brain and into the body, the relationship, and lived experience. His work laid the foundations for neurophenomenology, influencing contemporary neuroscience, psychology, and philosophy.

che, dating back to early attachment experiences. These traces, predominantly unconscious but not repressed, have a primarily procedural nature and, in our view, are generally unsatisfactorily defined as “body memories”. They pertain to the perceptual and sensory sphere, to gestures, body attitudes, somatic symptoms, and the underlying settings of psychobiological networks.

As in any intersubjectivity, the therapeutic relationship too develops as a relationship between organisms in the fullest sense, implying reciprocal transformative processes aimed at returning elaborated and transformed experiences to the patient.

It has been suggested that even the dimension of therapeutic techniques should adapt, transversally across models, to intercept and use physical and biological elements from the assessment phase onward.

It has been emphasized that interoception constitutes a direct channel for accessing unconscious memories and contents. Similarly, bodily signals present during the session (muscle tension, posture, breathing, sensations, and somatic symptoms) can not only be intercepted and explored but can also become the object of direct therapeutic intervention. To this end, suggestions have been offered both for the expansion of assessment and for the recovery of techniques derived from the tradition of body-oriented psychotherapy.

It has also been urged that each therapeutic model reflect on appropriate modifications in training. PNEI proposes to implement biological training for psychotherapists as well, always embedded within a meta-model of interpretation. This would allow equal collaboration with medical colleagues, envisaging the desired possibility of joint care.

Finally, it has been reiterated how social and cultural dynamics profoundly influence the organism, forcing it into continuous and sometimes difficult allostatic adaptations. The ongoing global crisis (in its systemic, political, health, and ecological aspects) correlates with increasing identity lability, manifested in phenomena such as the reification of one’s own body, contrary to the evolutionary direction of science, which has led to the overcoming of the mind-body dichotomy. Such phenomena include the increase of forms of body manipulation and digital decorporealization in the exponential use of new communication technologies, with consequent risks also at the epigenetic level, which health sciences must and will increasingly address, both in terms of care and prevention.

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A systemic and dialectical paradigm for Psychoneuroendocrineimmunology and integrated care science*

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Abstract: *The integrated care needs of a philosophical paradigm. Psychoneuroendocrineimmunology can be it, provided that a consensus is created on its profound meaning. What is Psychoneuroendocrineimmunology (PNEI)? It is not Neuroendocrinoimmunology. PNEI (also called PNI, Psychoneuroimmunology) describes the relationships of mutual influence between the psyche and biological systems and between the whole organism and the physical and social environment, showing the scientific inconsistency of the reductionist dogma that makes the psyche a mere epiphenomenon of brain activity. We are in a phase 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. To this end, it is essential to critique the philosophical foundations of contemporary reductionism, while, at the same time, highlighting the theoretical-conceptual paradigm that underlies PNEI research and the practice of treatments that integrate medicine and psychology, which descend from this paradigm.*

Key words: *Psychoneuroendocrineimmunology; Dialectical and systemic philosophy; Reductionism; Materialism; Integrated care; Medicine and Psychology Unity*

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Introduction

The integration of care is becoming increasingly interesting for the scientific community, but there is a lack of reflection on the philosophical paradigm that supports this integration. Recently, Jording and Hoffman (2024) examine four models: Interactionism, Materialism, Functionalism, Complementarity. According to the authors, none of these, we agree, is able to solve the “mysterious mind-body problem”, although the Complementarity model would allow a better application in current PNEI research.

According Jording and Hoffmann, Interactionism is internal to the Cartesian paradigm, describing both mind and body as two separate substances, with body being a material substance and the mind being a mental substance, interactionism is held together by the idea of a causal relationship between the two substances incommensurable with each other. The second model examined by the authors is Materialism, which thinks it solves Cartesian dualism by eliminating the mind from scientific investigation. A paradigm that is clearly not usable by PNI, which instead studies the relationships between psyche and biological systems. The third model is Functionalism which, although radically critical of materialism, according to the authors, cannot be useful to the PNI since “while functionalism is concerned with causation, it is still not concerned with the nature of the relation”. In the next paragraph we examine in detail the main paradigms used during the twentieth century to describe the mind and mind-body relationships.

From Cartesian dualism to the philosophy of mind. Behaviourism, logical neopositivism, analytical philosophy and eliminativist materialism

An opinion, very widespread among scientists, traces back to the French philosopher and scientist, active in the first half of the seventeenth century, René Descartes (known in the Latin world of the time as Cartesius) the birth of the dualist paradigm, which characterizes the human being composed of two substances, mind (*res cogitans*) and body (*res extensa*), of an incommensurable nature. If we stick to this scholastic definition, it is impossible to understand the functioning of the human being, composed of two substances that are not commensurable and therefore not communicable. The solution to the problem, which ridicules Cartesian reflection, is offered by the English philosopher Gilbert Ryle (1949), according to whom the mind, in the Cartesian model, would function «like a ghost inside the machine» of the body.

In essence, Descartes, a proponent of dualism, was also a sophisticated philosopher who demonstrated a noteworthy aptitude for biological and mathematical domains. In the 6th Meditation of his most famous work, *Meditationes de prima philosophia* (1641), Descartes wrote: «Nature teaches me that I am not purely present to my body as a commander is to his vessel but am joined to it very closely and almost mingled (*permixtum*) so as to form a unity (*unum*) with it». This and other analogous statements in his final work *The Passions of the Soul* (1649) are evidently incongruous with his theory of the two incommensurable substances, which he rejected, but to understand this contradiction it is necessary to contextualize Descartes' philosophical work. The dualist paradigm did not originate with this philosopher, but rather finds its most illustrious antecedent in the thought of the Greek philosopher Plato (fourth century BC): the body is the prison of the soul, which, immortal, will be freed only with the death of the corruptible body. Despite its lack of success in ancient Greece, this model of human nature was adopted in the first centuries of the Christian era by both pagan and Christian philosophers (Bottaccioli, 2020). The recovery of Platonic dualism, in its late antique version, and of the vision of earthly life, as premise and promise for the "true life" after death, will serve as the foundational principle upon which Augustine will build the Christian paradigm, which will dominate western culture from the fourth-fifth centuries AD until the present day. This was the centuries-old cultural context, founded on the considerable power of the Church, including its political influence, against which revolutionaries in the fields of medicine (e.g. Vesalius), the physical sciences (e.g. Galileo), and philosophy (e.g. Descartes) would clash. Indeed, there is no doubt that the medical researchers of the seventeenth and eighteenth centuries took advantage of the Cartesian model, which excluded the mind, identified with the soul, from the study of the human being. This research, mainly anatomical and physiological, provided the scientific basis for the development of modern medicine. A development that in the nineteenth century took advantage of the positivist paradigm, which explicitly excluded the soul from scientific investigation. The materialist solution to the contradiction inherent in the Cartesian model will, in various forms, permeate the study of human nature in the twentieth century.

Analytical Behaviourism

In the first three decades of the twentieth century, a strong current emerged among scholars of the mind and mind-body relations that would mark the entire century and the current state of the debate. The American psychologist John B. Watson and the German philosopher Rudolf Carnap, to name two very representative scholars, converge in rejecting the psychic or mental dimension, as they

call it. Watson inaugurated behaviourism in psychology, which aimed to be the scientific version of psychology. For Watson, scientific psychology could only take into account observable data, i.e. patterns of response, the behaviour of a subject in the face of environmental stimuli. Input and output. Nothing in between, a black box of no interest to the psychologist. Thoughts, fantasies, emotions are implicit behaviours, habits, automatic mechanisms inscribed in the organism. If a psychologist were to study mental states, it would be like an astronomer studying astrology, i.e. superstition, wrote the founder of behaviourism.

«The behaviourist ignores mental states in the same way that the chemist ignores alchemy, the astronomer ignores astrology, the psychologist ignores telepathy. The behaviourist has no interest in mental states because, as the river of science widens and becomes deeper, these old concepts are sucked up never to reappear» (Watson, 1920). It is a truly spectacular paradox: scientific psychology is based on the amputation of the psyche, on the excision of the psyche from the human being!

This paradox was to be ennobled and sustained by the reflection of a philosophical current that was to be highly regarded in the 1920s and 1930s: that of the so-called “Vienna Circle”, a club of intellectuals from various backgrounds (philosophers, physicists, mathematicians, sociologists) who met both in Vienna and in Berlin in two periods separated by war: from 1907 to 1914 and then from 1924 to 1938. Their practice was one of collective study and debate. In 1929 they published their manifesto entitled *The Scientific Conception of the World* (Hahn, Neurath, Carnap, 1929). Its most prominent exponents were the philosophers of science Moritz Schlick and Rudolf Carnap, the sociologist and economist Otto Neurath, and the mathematical logicians Philipp Frank and Kurt Gödel. There were three closely intertwined programmatic goals: 1) the realisation of a model that would allow the formation of a unified science; 2) the criticism of traditional philosophy and metaphysics by demonstrating the meaninglessness of the fundamental propositions on which it is based; 3) the realisation of the unity of knowledge through the unity of the natural and psycho-sociological sciences.

In this framework, philosophy is not conceived as a form of knowledge. Its fundamental function is to clarify concepts and control language, especially that used by science. In this sense, but only in this sense, philosophy is, according to Schlick, the queen of the sciences. Sciences that have a centre around which everything is summed up: physics, which, especially in the theories of Otto Neurath, is the fundamental science whose universal language is capable of encompassing the contents of all other scientific languages (physicalism).

It is this view that leads Carnap (who also developed a different way of thinking and was critical of Neurath’s universal physicalism) to write that the lan-

guage of psychology must also be reduced to that of physics. In fact, according to Carnap (1935), the analysis of the mind does not require psychological concepts, but only those of physics. Consequently, the claims of psychology are physicalist claims.

Psychology thus becomes an integral part of physics. Physicalist reductionist claims which, as we shall see, will be taken up by other philosophers of mind.

The Vienna Circle's interest in the analysis of language, mentioned above, is the spirit of the age: it stems from Bertrand Russell's studies in logic, who published a famous text on logic, *Principia Mathematica*, with Alfred N. Whitehead in 1910, and from Russell's encounter, from 1911, with Ludwig Wittgenstein, a young Austrian engineer from the upper middle classes who had gone to Cambridge to study philosophy.

In 1918 Russell published *Philosophy of Logical Atomism*, while Wittgenstein had just finished writing his only completed work, the *Tractatus logico-philosophicus*, begun in Cassino prison, where he had been imprisoned as a soldier of the Austrian troops, and which, thanks only to Russell's support, would be published in a proper editorial version in 1922.

Both texts emphasise the need for philosophy to engage in the analysis of language, albeit with very different emphases. For Russell, the analysis of language had the primary aim of furthering the progress of scientific knowledge by means of appropriate logical tools, while Wittgenstein's aim was primarily to demonstrate, through the analysis of language, the inconsistency of certain problems in which philosophy had become entangled over the centuries. Famous is the compelling and lapidary final sentence of the *Tractatus*, which reads: «On what one cannot speak, one must keep silent», precisely in order to avoid the linguistic errors that condition the presentation of philosophical problems and render them insoluble.

Texts on the history of contemporary philosophy trace these writings, together with some by the mathematical philosopher Gottlob Frege, to the origins of analytic philosophy, as a diverse philosophical field of British origin that would later have a strong development in the United States in the middle of the century, including the philosophy of language and, what interests us most here, the philosophy of mind.

In *Philosophical Investigations*, Wittgenstein (1968) states that ordinary language is completely detached from reality, it follows its own rules which depend on its use, on what he calls "language games", which are apparently typical of children and elementary forms of language, but which in fact constitute the whole structure of language. Language is not a unified phenomenon. In a part of the *Investigations*, Wittgenstein develops arguments about "private thought"

and thus also about individual sensations, which are sometimes rather obscure and leave room for different interpretations, but after all, as he himself states in the ante litteram preface (dated January 1945) to the book to be published posthumously, «the philosophical observations contained in this book are, so to speak, a collection of landscape sketches (...) so this book is really just an album» (Wittgenstein, 1968).

The aim of the “clippings” that make up the album, which express his latest philosophy, is to “let the fly out of the cage”, that is, to free philosophy from the linguistic cage that has been built up over the centuries.

It is not possible here to explore in depth the jagged thought of the late Wittgenstein; we will merely point out that the thread of reasoning can be summarised and simplified as follows: there is no private thought, there is no direct connection between thought and language in the sense that language does not interpret thoughts and feelings, feelings are given.

From analytical behaviourism to mind-brain identity

The reception of the argument for the non-existence of private thought and subjective feeling itself in the British philosophical milieu took place within the behaviourist and anti-mentalist paradigm that already dominated Anglo-American psychological culture.

In 1949, long after Wittgenstein had retired from teaching at Cambridge, an Oxford professor of philosophy, Gilbert Ryle, published the book that is considered to have established the “philosophy of mind” as an autonomous discipline. The Concept of Mind, the title of Ryle’s book, has two targets, Cartesian dualism and mentalism, which are then reduced to one: the liquidation of autonomy and the concept of mind, which, in Ryle’s opinion, is based on a categorical error, on the consideration of mental events as causes of behaviour. In a metaphor that will become famous among philosophers, Ryle writes that we must get rid of “the dogma of the ghost in the machine”. There is no mind (the ghost) present in the body (the machine) and determining its behaviour. Then what is mind? «My mind means the ability or tendency to do certain kinds of things, not a personal device without which I could not do them» (Ryle, 1949).

Behaviourism, also called “analytical behaviourism”, would later be developed by a philosophical current that would resolve in its own way the difficulties inherent in Ryle’s argument and in behaviourism in general (the negation of the mind) by proposing a strong thesis: the mind-brain identity. For these philosophers, Herbert Feigl, a direct student of Ryle’s, Jack Smart and David Armstrong, the subjective feelings and personal thoughts denied by Ryle do exist; they cannot be denied. But dualism can be avoided, they argue, by reducing mental activ-

ity to brain activity. According to Armstrong, it is possible to think of each type of state or mental process as corresponding to a type of brain state or process. This theory is called “type identity”.

A theory that has been philosophically opposed and crumbled by scientific verification.

However, the thesis of the reduction of the mind to the brain has, according to some, gained increasing acceptance in recent decades under the banner of “eliminative materialism”.

The eliminativist materialism

The two philosophers who have been developing the eliminative materialist approach for several decades are Paul and Patricia Churchland. Eliminative means that the mental dimension can be eliminated from scientific investigation. Not in the sense that there are no feelings, desires, consciousness, and everything else that describes what Churchland calls “Folk Psychology” (common sense psychology). Rather, in the sense that it is wrong to interpret states of the brain using the categories of psychology.

Paul and Patricia Churchland argue that common sense psychology is a complete misrepresentation of our internal states and activities. Beliefs and desires are therefore unreal, and as science progresses, we will relate to them in the same way we relate to witchcraft or phlogiston today: superstitions that will also be abandoned by psychology, which will then turn definitively into neurophysiology (Churchland 1986, 1994).

The liquidation of psychology as a science and a field of study. But on what arguments are they based? There are two central arguments that lead to a conclusion in favour of eliminative materialism.

First. A physical phenomenon can only be moved by another physical phenomenon. Since the psyche is not physical in nature, it cannot act on the brain and thus play a role in the body. This argument is usually referred to as the “closure of the physical world”. The second argument claims that neuroscience has fully confirmed eliminativism. Edelman and LeDoux are cited in this regard (Nannini, 2018, 2021).

Thus, eliminative materialism is the only acceptable paradigm because argument 1 (the closure of the physical world) liquidates both dualism and functionalism and, above all, its most dangerous rival, emergentism. All three paradigms, for different reasons, would violate the closure of the physical world.

The argument for the closure of the physical world is based on a conception of physical reality established by Descartes, that dualist so abhorred by eliminativists. For the French philosopher, the physical world had, first and foremost, one

fundamental characteristic: it consisted of extended objects: *res extensa* was distinguished from *res cogitans* precisely because the former, unlike the latter, occupied space. Similarly, eliminativists judge psyche, which does not occupy space, to be a non-physical reality, and since nothing exists that is not physical, they conclude that psyche does not exist. This is the syllogism.

As is well known, syllogism is a procedure of ancient logic whose conclusions can only be true if the premise is true. But is the Cartesian premise true? In the light of twentieth-century physics (from electromagnetism to relativity to quantum physics), there are objects that make up physical reality that have no extension or, to use the language of physics, no mass. Photons are among them; others acquire mass as a result of the decay-transformation of elementary particles. We therefore have a continuous transformation of mass into energy and vice versa: changes in the state of what we call matter, but which, with Bertrand Russell and in the light of contemporary physics, we should not forget is a «logical construction» (Russell, 1921), the dynamics of which the sciences try to describe and know, using theoretical and instrumental paradigms of various kinds.

In this respect, the psyche is a state of the brain, or rather of the whole organism. It is a dynamic state that depends on brain energy and can in turn influence its dynamics. Thus, in this sense, the psyche is a physical reality, not a supernatural substance, which has ways of connecting to and influencing the brain and organismic network from which it arises.

But according to eliminativists, this thesis, which has gone down in the history of philosophy of mind as “emergentist”, is not supported by neuroscience, which on the contrary would support eliminative materialism. In support of this claim, two eminent scientists are cited, Gerald Edelman and Joseph LeDoux. Of the latter, the metaphor «you are your synapses» (LeDoux, 2002) is used to enlist the New York neuroscientist in the ranks of eliminative materialism. This does not seem to be the case. One only has to read pages 319-320 of LeDoux’s text to be convinced.

In this part of his book, LeDoux addresses the crucial aspect of brain plasticity, i.e. the ability of brain circuits to change, to alter the strength of connections between cells and to establish new ones, when he writes: «If cells processing sensory events can undergo plasticity as a result of the kind of activity, those events trigger in sensory systems then why cannot cells processing a thought change the connections of the cells with which they communicate? Obviously, they do» (LeDoux, 2002). LeDoux is describing the feedback of mental activity on the brain, and to make the concept clear he emphasises: «The downward mobility of thought provides a powerful means by which parallel plasticity in neural systems is coordinated» (LeDoux, 2002). In other words, thought, mental activity,

has a retroactive power over the plasticity of the brain. This is an undeniable fact based on empirical research and, according to LeDoux, a fundamental resource in the hands of each of us. «With thoughts empowered this way, we can begin to see how the way we think about ourselves can have powerful influences on the way we are» (LeDoux, 2002), i.e. on how we build our synapses, to stay with the metaphor.

So LeDoux is not supporting eliminative materialism, he is supporting its opponent, emergentism, the dialectical view of the two-way mind-brain relationship.

Now we look at Gerald Edelman. The Nobel Prize winner in medicine, who like Francis Crick switched from biology to neuroscience, in the last book summarising his thinking before his death, entitled “Second Nature. Brain Science and Human Knowledge”, he explicitly criticises both the eliminative materialism of Skinner and Churchland and the sociobiology of Wilson (Edelman, 2006). The programme of his book is to «heal the rift between the two cultures», the humanistic and the scientific, by making it clear that «science is a fundamental basis, but it is neither unique nor exhaustive of knowledge» (Edelman, 2006). In short, the exact opposite of the eliminativist dogma according to which the real facts are only those that can be known by science. In the book, Edelman illustrates the mind’s great capacity for metaphor, which is linked to the associative power of brain circuits that he defines as “degenerate”, i.e. not fixed to single functions, but rather generic and adaptable (Edelman, 2006). This is a very long way from eliminative materialism.

It is true that Edelman clings to the idea, expressed in the past in his famous books on neural Darwinism and consciousness of the inability of the mind to produce effects on the brain. To think otherwise, he writes in Second Nature, «is one of many useless illusions» (Edelman, 2006). Here Edelman brings into play a dogma of traditional logic, which Russell (1921) also recalls in his above-mentioned book on the analysis of the mind: if there is a causal relationship between A and B, i.e. If there is a causal relationship between A and B, i.e. B depends on A, then knowing A we can explain B, but not vice versa, and, above all, B cannot have a retroactive effect on A. It is a dogma of mechanistic logic that is incapable of explaining anything substantial about what happens in the physical world, other than the banality that one body hitting another is the cause of the latter’s movement (the logic of billiard balls). Above all, it explains nothing about the biological world.

In medicine and psychology, one usually starts from B to infer A, i.e. from the manifested data (symptom or sign) to hypothesise the cause. Moreover, feedback from B to A has been known in modern medicine since 1865, since Bernard’s ex-

periments and theories on homeostasis. In the last 100 years, the knowledge of the physiological functioning of the organism can only be carried out with a retroactive and systemic logic, i.e. by sharing different forms of knowledge.

At this point, let's examine the complementary model.

Complementarity

We believe that the concept of Complementarity, as presented by Jording and Hoffman, has its critical issues, but above all we want to try to extract from the PNEI research programme the philosophical foundations that we believe are dialectical and systemic, capable of shedding light on the mind-body problem and, above all, of placing research and clinical practice in a more advanced and innovative dimension than the reductionist standard.

Complementary means to integrate, to complete. Two things are complementary because they complement each other. In fact, this is the meaning of the term, which Jording and Hoffman take from Niels Bohr, who proposed it in the second half of the 1920s to solve the dilemma of whether light consists of waves or particles. Bohr proposed that the two dimensions, wave and particle, are different, even opposite, but complementary in the sense mentioned above, i.e. both are essential for understanding the phenomenon, which therefore consists of two dimensions. Dimensions that can be highlighted by changing the reference system. Jordin and Hoffman rightly demonstrate the usefulness of this paradigm in order not to run the risk of studying one dimension, the psychic, with inappropriate instruments, in this example with the instruments of biology and vice versa.

What the authors fail to consider, we believe, is that the two dimensions are not the product of observational schemes, but the reality of the phenomenon that has both dimensions.

This is where the ancient Chinese philosophy comes to our aid. With the theory of yin and yang, it shows that one phenomenon can be antagonistic to the other, but at the same time contain the root of the other, in the sense that one is dialectically derived from the other: in the greatest Yang is Yin and vice versa.

It does not seem to be a coincidence that Niels Bohr explicitly refers to Chinese philosophy on the subject of complementarity in his writings (Bohr, 1960). Nor does it seem a coincidence that when the great scientist had to choose a coat of arms on the occasion of receiving Denmark's highest honor, the Order of the Elephant, he chose the Yin-Yang symbol (see Figure 1) (Pais, 1991).



Figure 1 – Coat of arms of Niels Bohr with Yin-Yang and Latin motto “CONTRARIA SUNT COMPLEMENTA” (“THE OPPOSITES ARE COMPLEMENTS”) & collar of the Danish order of the Elephant. Source: https://it.wikipedia.org/wiki/File:Coat_of_Arms_of_Niels_Bohr.svg

Yin-Yang dialectic

One of the fundamental qualities of the Yin-Yang relationship applied to human physiology is that every phenomenon has both a yin and a yang aspect. This is not to say that we are faced with an indistinctness or ambiguity: there is always a prevalence of one or the other; thus, one can connote the phenomenon as yin or as yang. However, one cannot exist without the other, for one is the root of the other. «The yin is located inside, but it is the yang that keeps it there; the yang is located outside, but it is the yin that allows it to act», (the “Great Treatise on the Correspondence of Yin-Yang Phenomena” in Su Wen Huangdi Nei Jing, the Yellow Emperor’s Classic of Internal Medicine, 1995).

On the contrary, and this is another fundamental characteristic, one is transmuted into the other. Transmutation is possible because in the maximum yang there is still yin, and vice versa. Therefore, we are faced with a dynamic and dialectical vision different from classical Western logic based on the principle of identity and non-contradiction (A is not B) the Yin-Yang dialectic is dynamic and adaptive. It is dynamic because the yang and yin are not in opposition; they are two polarities of the life process, whose dominance alternates in cosmology (day and night, summer and winter, sun and moon), physiology (activity and rest) and in pathology (illnesses from yang excess and yin deficit and vice versa).

The Yin-Yang dialectic is also adaptive in that a moderation of the weight of each polarity is possible i.e., it is possible to moderate the yang, if in excess, by nourishing the yin, and vice versa. The Yin-Yang dialectic, unlike classical Western logic and even Hegelian dialectic, allows the researcher to understand biological dynamics, particularly those of the immune system, in a more penetrating way. We will return to these considerations later by describing the insertion of the Yin-Yang dialectic into a new dialectical vision that integrates and transcends the traditional Hegelian vision.

Yin and Yang are complementary: a phenomenon always contains these two dimensions. Thus, the human organism is at the same time biology and psyche, which together constitute it and represent its manifestations: physiological, pathological, behavioural.

Reducing complementarity to a point of view, to a system of reference, as Jording and Hoffman's argument seems to suggest, means, in our opinion, failing to understand Bohr's concept and, above all, failing to develop it by applying it to the study of the human being. Half a century of research in the field of PNEI and related disciplines (neuroendocrinology, neuroimmunology, neuroscience, psychology and, more recently, neurogastroenterology) has gradually built up a picture clarifying the connections within the human psychobiological network and, increasingly, the molecular mechanisms by which psychological phenomena influence the cellular and genetic machinery and vice versa. Indeed, the pathways and mechanisms by which biological systems influence emotion, cognition and behaviour are emerging.

Communication pathways in the human network and mechanisms

In recent decades, scientific exploration has yielded irrefutable evidence that substantiates the notion of communication between systems. This finding challenges the prevailing dogma that posited an absence of such communication be-

tween the central nervous system and the immune system (Blalock, 1989; Hoffman 1998, 2009; Ader, 2007; Del Rey, Besedovsky, 2013; Dantzer, 2018; Huh, Veiga-Fernandes, 2019; Schiller, Ben-Shaanan, Rolls, 2020; Salvador, Kipnis, 2023).

There is compelling evidence in the form of monographs, special sections, and extensive reviews in prominent scientific journals that communication between biological systems is a significant area of research. Editorials and commentaries have also been published expressing surprise at the observation that the immune system not only participates in the genesis and development of relevant psychiatric and nervous system pathologies (Kwon, 2022; Castellani *et al.*, 2023) – such as neurodegeneration, psychosis, depression and neurodevelopmental disorders – but also plays an essential role in brain development and functioning (Talbot *et al.*, 2016). Therefore, the action of immunity in the brain constitutes not only a source of pathology, but also of physiology: in the absence of exposure to a well-functioning immune system, the brain does not develop and function properly.

The historical development of the dichotomy between central nervous system (CNS) and the immune system has been an extensive one. Let's quote some crucial passages. Niels Jerne, a pioneering figure in the field of immunology, was awarded the Nobel Prize in 1984 for his seminal work on the Theory of the Immune Network. In a paper published in the *Annals of Immunology of the Pasteur Institute*, Jerne draws parallels between the immune and nervous systems, noting their shared capacity to infiltrate most body tissues. However, he also observes that, despite this similarity, the immune and nervous systems appear to avoid each other's presence, a phenomenon he attributes to the presence of the blood-brain barrier (Jerne, 1974). The proposal of this separation can be traced back to the 1940s, thus giving rise to the theoretical concept of the brain as an immune-privileged organ. This theory is, to this day, still included in some textbooks used for medical students. The communication pathways between immunity and CNS are multiple and concern both the blood, nerve and lymphatic pathways. The communication pathways between the immune system and the central nervous system (CNS) are intricate and encompass the blood, nerve, and lymphatic pathways. In the Preface to the latest edition of the primary international textbook of immunology (Flajnik *et al.*, 2023), "neuroimmunology" is listed among the topics of the new edition, to which a chapter is dedicated (Chapter 39). This chapter details the history of the decline of the theory on brain as an immune-privileged organ and provides a overview of the main evidence of communication between the two systems.

This is indicative of a collapse of the reductionist dogma surrounding the immune system as a potential opponent of the brain, which systematically keeps the immune system outside the blood-brain barrier. We now have evidence that communication between the neuroendocrine and immune systems is operational even

among simple organisms such as invertebrates (Kemenade, *et al.* 2017). Indeed, physiology, at every level of life evolution, is integration. Without integration between systems, there is no life (Godinho-Silva, Cardoso, Veiga-Fernandes, 2019).

In the domain of human physiology, the concept of integration assumes even greater complexity. The levels of integration among biological systems encompass psychic regulation, a phenomenon that, contrary to the prevailing scientific reductionist perspective of the past two centuries, is not confined to the domain of “relationship life” or separable from organic or biological life. The immune system is influenced by mental processes, and in turn, these processes are influenced by the immune system’s activity. Exposure to emotional stress or living conditions characterised by loneliness, depression or social suffering has been demonstrated to increase the immune system’s inflammatory activity.

Conversely, inflammation, which can reach the brain either through the immune system or directly by immune cells that are an integral part of brain tissue, increases the brain’s sensitivity to the various experiences of “relationship life”. The result of this process is that motivational processes can be immersed in an inflammatory brain matrix, causing dysfunctional behaviour and states of psychic distress, from which full-blown psychiatric disorders can also result (Bottaccioli, Bottaccioli, Minelli, 2019).

Cytokines, the molecules that regulate immune system function, follow three distinct routes to reach the brain. The first is a humoral route that transports them via the bloodstream. The second is a nervous route that involves the afferent nerve network, particularly the vagus nerve. The third is a meningeal lymphatic route, the existence of which was recently discovered by Antoine Louveau’s research group in 2015. This was, in fact, a rediscovery, since the meningeal lymphatic system had already been described by the Italian anatomist Paolo Mascagni in 1786, but as Salvador and Kipnis write: «However, these observations were undermined and discounted by the scientific mainstream, which maintained that the central nervous system (CNS) was immune privileged and had no ability to communicate with the peripheral immune system, in part due to the absence of a lymphatic system that would drain the CNS. In 2015, a detailed structural and functional characterization of the meningeal lymphatic system emerged and challenged this dogma» (Salvador *et al.*, 2024).

Cytokine signalling from the body’s periphery to the brain is part of the more general concept of interoception, i.e. the process by which the nervous system perceives and integrates information about the body’s internal state (Chen, Schloesser, Arensdorf *et al.*, 2021). A multitude of cortical and subcortical brain areas are implicated in this process, with the posterior insular cortex playing a pivotal role in the processing of emotional and biological signals. For instance, research has

demonstrated an alteration in the insula in patients diagnosed with depression, particularly in individuals with a history of suicidal behaviour (Jung, Choi, Han, 2020). In addition, there is evidence that this area of the brain is highly sensitive to inflammation and can map an inflammatory state in a distant area of the body, for example in the gut. In experimental animals, the induction of colonic inflammation has been shown to induce a corresponding activation in the cerebral insula, which is involved in memory and has been termed an engram. Alterations in neural circuits, such as light stimuli, have been used to deconstruct this phenomenon (the optogenetics technique). This has been demonstrated to reduce inflammation in the gut, thereby underscoring the existence of a robust bidirectional connection between the body and brain (Koren, Yifa, Amer *et al.*, 2021).

The connection between the brain and the rest of the body is provided by the peripheral nervous system, which is organised into the somatic and neurovegetative nervous system. The latter has significant effects on the following: vessels, cellular activities and, in particular, the immune system.

Neuropeptides and neurotransmitters, which are released by nerve fibres, provide immune cells with signals that can either stimulate or inhibit them. These signals influence the activation and progression of the inflammatory response.

As was first demonstrated by the group of neuroanatomists David Felten, Felten, Carlson and others, there exists a connection between the nervous and immune systems (Felten, Felten, Carlson *et al.*, 1985). The researchers found that the immune system is closely connected to the nervous system in the lymphoid organs, where immune cells are produced and matured in response to antigenic stimuli. The connection between these cells and the nervous system is so close that researchers call it a “neuroimmune synapse”. In the decades that followed, a significant number of other researchers documented the anatomical connection between the autonomic nervous system and immune cells in lymphoid organs (Bellinger, Nance, Lorton, 2013).

A significant contribution to the study of the relationship between psyche and biological systems was provided by the research on stress, of which Hans Selye (1956, 1976) was the most important exponent until his death in 1982. Two fundamental concepts underpin his research. Firstly, stressors (emotional and environmental in nature) can produce either a beneficial or a detrimental adaptation. In the latter case, the organism is damaged by the accumulation of products of biological activity.

This suggestion, which is critical of the homeostatic conception attributed to Selye, will be extensively developed with the concept of allostasis by Peter Sterling (1988) and allostatic load by Bruce S. McEwen (1998). According to Sterling, allostasis is a complex physiological process that “achieves stability through change”.

McEwen (2004) has implemented allostasis in medicine, also working on the definition of models for measuring allostatic load to use it as a predictive model of disease (Fava, McEwen et al, 2019). The research conducted over several decades by McEwen's laboratory at Rockefeller University in New York has contributed to our understanding of the impact of stress on the brain and, more broadly, on the biological systems of the human body. According to the findings of the research, chronic stress has the capacity to induce structural remodelling in key areas of the brain, including the hippocampus, the prefrontal cortex, and the amygdala. This remodelling involves the activation of atrophic processes in the first two areas and hypertrophic processes in the latter, resulting in alterations to emotional and behavioural cognitive functions (McEwen, 2007; McEwen *et al.*, 2012).

It is important to note the research that utilises the revival of epigenetic investigations, begun in the 1940s (Waddington, 1942) and obscured by reductionist genetics until the end of the last century (Crick, 1970), to document the molecular effects of negative, toxic social environments on the brain and immune system (McEwen, McEwen, 2017).

The primary social environment of the human individual is the maternal environment. Recent research, integrating molecular, epigenetic and observational studies, has yielded unexpected insights into the long-term implications of early-life experiences, starting with pregnancy (Weaver et al, 2004). Maternal stress has been demonstrated to be associated with an internal inflammatory environment that epigenetically marks the stress axis and some key molecules in the foetus, including cortisol, serotonin, oxytocin, and neurotrophic factors (Palma-Gudiel *et al.*, 2015). The outcome for children and adults may lead to psychiatric, cognitive and metabolic disorders (see Szyf, 2021 and Bottaccioli *et al.*, 2023 for details).

This knowledge provides a more profound comprehension of the aetiology of diseases. For instance, it has been demonstrated that psychological stress, which results in the release of noradrenaline, adrenaline and cortisol, can modify immune surveillance towards tumours, thereby promoting their growth and spread (Ma, Kroemer, 2024; Globig, Zhao, Roginsky *et al.*, 2023). The association between psychological stress and the onset and progression of various major diseases, including psychiatric, cardiovascular, autoimmune, and infectious diseases, is becoming increasingly evident.

Finally, in this brief overview of the network of connections within the organism, it should be mentioned that a relevant communication pathway between the immune system and the psyche/brain system is the bidirectional microbiota-gut-brain axis.

It has been estimated that the total number of bacteria, viruses and fungi in the mucous membranes and skin of an adult human is 38 trillion (3.8×10^{13}) (Sender,

Fuchs, Milo, 2016), while for other researchers it is even higher: 90 per cent of these microorganisms are found in the gut. A mutualistic symbiosis is established between the organism and the microbiota. The organism provides food for the microbes, and the microbes provide life-supporting substances, including short-chain fatty acids (SCFAs), vitamins (K and B) and neurotransmitters such as norepinephrine, glutamate and gamma-aminobutyric acid (GABA). Recent research documents the impact of intestinal microbiota-derived substances (particularly short-chain fatty acids) on both the immune system (Mann *et al.*, 2024) and the brain (Dallile *et al.*, 2019). These substances have been shown to affect mood and cognitive function (Yang *et al.*, 2024).

What pathways does a psychic phenomenon follow in order to produce biological changes? Stress-induced inflammation and neuroinflammation

The first controlled experimental demonstration in humans that an emotional stimulus activates an inflammatory mechanism is more than 20 years old. This pioneering study was conducted by researchers at the Medical Faculty of Trier in Germany (ancient Treviri) on a group of healthy students. The students were subjected to a typical acute stress scenario, involving public speaking, rapid question-answering and arithmetic calculations (Bierhaus, Wolf, Andrassy *et al.*, 2003). The present study investigates the levels of the stress hormones cortisol and norepinephrine in students before and after a test, as well as NF- κ B levels in monocytes. NF- κ B is a nuclear transcription factor that is responsible for regulating various physiological processes. It is involved in the transfer of information from the cell surface to the nucleus and the genes contained therein. Emotional stress in students has been shown to induce an increase in stress hormones (cortisol and noradrenaline) and a significant rise in the concentration of NF κ B, which activates numerous genes coding for cytokines and other molecules associated with immune activation, including adhesion molecules. The mechanism that increases NF κ B activity and thus inflammation is centred on noradrenaline, whose signal is received by the immune cell via specific (beta-adrenergic) membrane receptors. The aforementioned phenomenon may be observed in the brain, where norepinephrine, which is synthesised under conditions of stress by the locus coeruleus neurons located in the brain stem, activates microglia. Microglia represent a class of immune cells analogous to macrophages, and these cells are present in the brain since its embryonic development (Sugama, Kakinuma, 2021).

Activated microglia produce inflammatory cytokines resulting in a pathological phenomenon, that is currently the focus of scientific research on neurodegenerative

and psychiatric diseases, known as neuroinflammation (Bottaccioli, Bottaccioli, Minelli, 2019; Cai, Liu, Wang *et al.*, 2022; Thakur, Dhapola, Sarma *et al.*, 2023).

Inflammation of the brain can thus be induced by alterations originating from other parts of the body, as in the case of dysbiosis or inflammation in the gut or other organs and tissues. However, it can also be induced directly in the brain through the activation of brain immune cells (Fig. 2). In this regard, it is important to acknowledge the recent shift in the field of immunology, which has begun to recognise and study the immune system intrinsic to the brain. This area of research has been given a new focus, under the watchword “changing ideas about the brain’s immune system”, as highlighted in a recent article in *Science* (Castellani, Croese, Peralta Ramos, Schwartz, 2023).

The consequences of psychic suffering on the brain and other biological systems have been summarised by research under the term “psychic stress”. This term refers to adversity in the early phases of life, such as trauma or abuse, as well as major life events which exceed an individual’s internal and external resources. These effects are now also evident at the molecular level.

Steve Cole, director of the UCLA Social Genomics Core Laboratory, has made a significant contribution to this field of research. He has documented the effects of loneliness and social isolation on the immune system in healthy and sick subjects. The study revealed that loneliness elicits a “conserved transcriptional response to adversity” (CTRA) in immune cells. This is characterized by increased expression of pro-inflammatory genes (IL-1, IL-6 and TNF- α) and decreased expression of anti-viral and antibody genes (e.g., IFNs) (Cole, 2015; Bower *et al.*, 2018). A meta-analysis of controlled studies on loneliness and social isolation found an association between loneliness and increased IL-6 concentration and between social isolation and fibrinogen (Smith *et al.*, 2020).

The present focus of research in neurodevelopmental, psychiatric and neurodegenerative disorders is on neuroinflammation. We conducted a recent review of the relationship between inflammation, both of central and peripheral origin, and major depression, with the aim of proposing a new pathophysiological framework on which to base a truly integrated treatment. This treatment would evaluate the person presenting the disorder in its complexity, originating from a combination of biological and psychological factors. For a more comprehensive overview of the role of psychological interventions in this context, we direct the reader to the aforementioned review, which also highlights the biological effects of psychological interventions on the immune system (Bottaccioli *et al.*, 2025). These effects are demonstrated by a systematic review and network meta-analysis (Ballesio *et al.*, 2023), which also shows that psychological interventions can reduce certain inflammatory markers.

Psyche-biological systems relationships

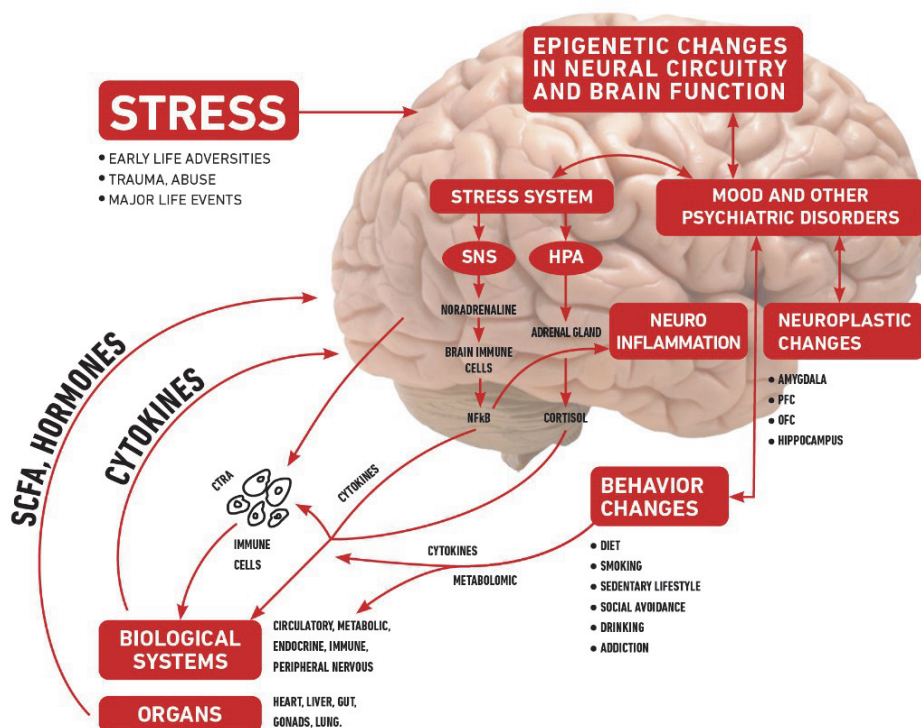


Figure 2 – Bidirectional relations between psyche, brain, immunity, metabolic systems and organs. Chronic psychosocial stress can induce neuroendocrine stress system activation and epigenetic changes in neural circuitry. Simultaneously, the overproduction of noradrenaline induced by the stress reaction activates the brain's immune cells (microglia), which in turn causes neuroinflammation. Brain epigenetic changes and neuroinflammation drive mood and other mental and psychological changes, which, in turn, strengthen epigenetic signatures and feed neuroplastic changes in key brain areas for emotional and cognitive functions, increasing the risk of developing psychiatric disorders. Chronic stress induces a "Conserved Transcriptional Response to Adversity" (CTRA) in peripheral immune cells. This is characterized by increased expression of proinflammatory genes (i.e., IL-1, IL-6, and TNF- α) and decreased expression of antiviral- and antibody-related genes, exposing the body to the risk of viral infections and tumours. The release, by biological systems and organs, of cytokines, hormones and metabolites produced by the gut microbiota, such as short-chain fatty acids (SCFA), reaches the brain, affecting cognitive and emotional functions.

Source (modified) Bottaccioli AG, Bottaccioli F, Minelli A. Stress and the psyche-brain-immune network in psychiatric diseases based on Psychoneuroendocrineimmunology: a concise review. *Ann N Y Acad Sci.*, 2019 Feb; 1437(1): 31–42. DOI: 10.1111/nyas.13728. Epub 2018 May 15. PMID: 29,762,862. With John Wiley and Sons licence

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This substantial and expanding corpus of scientific research cannot be explained by the materialist-reductionist paradigm, but neither can it be explained by a weakversion of complementarity. It is evident that an alternative philosophy is required to provide a comprehensive explanation. However, prior to an exposition of its fundamental aspects, it is considered helpful to trace a brief history of the philosophical models that have represented human nature: from Cartesian dualism to the contemporary philosophy of mind. For reasons of space we have included this part as supplementary material, to which we refer readers interested in the history of the philosophy of mind.

Philosophy for Psychoneuroendocrineimmunology and science of integrated care

Eliminativist philosophers of mind claim that their theories are based on neuroscience and biological research, but they use only ancient logic, some apodictic assumptions, and mental experiments that have no connection with scientific research. PNEI is not based on mental experiments or unsubstantiated assertions, but on a multitude of examples from experimental and epidemiological research that document the constant dialectical relationship between the psychic dimension – which includes emotional, intellectual, relational, social and behavioural life – and the human biological network.

PNEI research (Rezaei, Yazdanpanah, 2024) documents the effects of chronic stress, traumatic events, mental suffering, psychiatric disorders, inequality and loneliness on specific brain areas such as the hippocampus, hypothalamus (stress axis), amygdala, prefrontal cortex, as well as on the immune system and other physiological regulatory systems. At the same time, other research is documenting the feedback of biological systems on the psyche, opening up new diagnostic and therapeutic avenues for mental disorders (Bottaccioli *et al.*, 2022).

This research increasingly combines tools from different fields of knowledge: a state of psychological suffering or an internal disorder can be studied by combining structured psychological reactants, inflammatory biochemical markers (cortisol, cytokines) and epigenetic markers (methylation of single genes, non-coding RNAs, epigenetic clocks). The combination of these tools is based on a unified and integrated vision of the human being, which sees its dimensions in mutual dialectical influence.

Without this paradigm, it would make no sense to study depression or an autoimmune, cardiac or neoplastic disease by combining psychological and biological tools. Nor would it make sense to propose a combination of biological, psychological and behavioural interventions in prevention and therapy, stress management or psy-

chotherapy in the treatment of an internal disease, as is done in the most advanced international research and clinical centres.

One paradigm is superior to another if it produces new and useful knowledge. The PNEI paradigm, based on epigenetics and molecular biology, has these characteristics. The philosophy on which it is based is neither reductionist nor vulgarly materialist: on the contrary, it recognises the fundamental role of the psyche, which is not conceived as a cerebral epiphenomenon without history, but rather as a dimension of identity endowed with its own language, its own modes of cultural transmission, its relative autonomy from the biological context from which it emerges and, above all, its capacity to act, consciously or unconsciously, on the other systems of the human network.

Nor is the philosophy of the PNEI paradigm spiritualist or culturalist, since it does not presuppose a divine or mysterious origin of the psyche, nor its alienation from the human biological systems from which it derives. It is a dialectical, systemic, complex philosophy in constant dialogue with scientific research and healing practices.

A systemic and dialectical approach makes it possible to overcome a pillar of Western culture of the last two centuries: the idea that biological and even economic-social phenomena follow linear automatisms that guarantee equilibrium. In biology, the traditional concept of homeostasis explains the restoration of an equilibrium that may have been disturbed by stressors. Homeostasis, proposed by Cannon in the 1920s, was superseded by the concept of allostasis, introduced in the late 1980s by Peter Sterling and Joseph Eyer, and later elaborated, as mentioned above, by Bruce S. McEwen.

Allostasis means achieving stability through change and describes a model of dynamic and predictive regulation of physiological and behavioural states that change in anticipation of needs and demands to ensure the balance and efficiency of the organism. A dynamic physiology therefore replaces a static physiology.

In economics, the “invisible hand of the market” of Adam Smith and contemporary liberal and neoliberal schools has been invoked to imagine the automatic capacity of the mercantile economy to guarantee the free flow of trade and social relations. In this view, disturbances in the economic system are occasional factors, like a viral infection, which the homeostatic invisible hand of the market will eradicate. There are also influential voices in economics, such as Nobel Prize winner Joseph Stiglitz (2024), author of a sharp critique of neoliberalism and market automatisms.

In mechanistic thought, there are no systemic dynamics between seemingly very different and distant systems, for example, in economics between the rise of the Earth’s temperature and the development of international finance, or in medicine between a state of social isolation experienced by a person and the alteration of his or her an-

tiviral immune circuitry. There is no reciprocal, dialectical relationship of influence between stress, which alters the microbiota, and an inflamed mind.

It therefore seems appropriate to examine more closely a philosophical concept revised in the light of the science of Psychoneuroendocrineimmunology.

Dialectics, a new lecture

Dialectics, after Hegel had developed the idealist version and Marx the materialist one, and after it had become the official philosophy of the international communist movement in the twentieth century (so-called dialectical materialism, “Diamat” in the acronym), disappeared from the scene with the collapse of the Soviet Union. But Diamat had long since been heavily criticised by leftist and Marxist-inspired intellectuals and philosophers (Adorno, 1958). It is certainly not our intention to reanimate the corpse of the Diamat, but rather to show how certain categories of dialectical thought elaborated by Hegel and Marx are useful in representing the functioning of the human organism.

The concept of the whole or totality. The vision of the whole human being is one of the cornerstones of the PNEI paradigm, in open polemic with the reductionist view discussed above. For Hegel (1807), «the true is the whole». Individual elements separated from the whole, Hegel and Marx argue, are abstractions which therefore contain little cognitive content. The whole is true because it is concrete, that is, it is the product of a multiplicity of determinations that are related to each other, that have grown together (from the Latin *concretus* from *con-cresco*, I grow together). But is it possible to know the whole without knowing its parts, the individual elements that make it up? Hegel, and especially Marx, rejected an undifferentiated holistic view. Hegel’s polemic against his contemporary Schelling, who was accused of conceiving of the whole without knowing its specific determinants, as «the night when all the cows are black» (Hegel, 1807), is well known.

For Marx, knowing the parts as precisely as possible is the practice of the scientific method, which he holds in high esteem and uses throughout his writings to understand and criticise capitalist political economy. After all, science is, by definition, knowledge of the elements of reality, physical, social, individual. But how do we know the whole and its parts at the same time? If we start from the individual components of the whole, we fall into the reductionist approach based on induction from the individual to the whole.

We can know the whole – here we find another fundamental category – because the whole is a system, it is the set of relations of the parts among themselves and between them and the whole. Truth, i.e. adequate knowledge, is the result of the dialectical process of relations that structure and reveal the whole, which is therefore a historical and complex phenomenon that must be known as

it unfolds. In the case of the sciences and practices of care, the reconstruction of the patient's history, in its psychological, biomedical and social dimensions, allows the therapist to have an initial pregnant vision of the whole, which makes it possible to study the individual salient phenomena.

Examination that must be done not in isolation, not by seeing the data as fixed and immobile, but by grasping their inner dynamism and grasping the connection that binds the individual phenomena to the whole. Dialectical thinking is thus the opposite of reified thinking, which sees the individual elements as separate from one another and with an immobile identity (Hegel, 1807).

Hegel's observation that the elements are not immobile, but have an internal dynamic, has been confirmed by many contemporary scientists. One example is research into T regulatory (Treg) lymphocytes, cells that have the fundamental task of switching off inflammation. Well, if these cells receive a signal from the context (i.e. from the whole) that changes their epigenetic state (from hypomethylation to hypermethylation of the FOXP3 gene), they can turn into their opposite, T-helper (TH)-17 cells, which are highly inflammatory. We can say, dialectically, that this element, the Treg lymphocyte, contains the thesis and the antithesis, and that its opposite effects depend on the whole.

In the "Introduction" to the "Critique of Political Economy" (1857), Marx, while criticising the idealist approach, i.e. the «Hegelian illusion of conceiving the real as the result of self-moving thought» (Marx, 1857), endorses the dialectical procedure by which thought appropriates knowledge of the whole. Marx says that the real, concrete element is the whole that we intuitively represent to ourselves. We then deepen our knowledge of the elements through a series of abstractions, which always presuppose the connection with the whole. Finally, we go back from the abstract to the concrete, from the individual elements to the whole, which thus becomes rich in determinations and can really be known (Marx, 1857).

To summarize, adequate knowledge is knowledge of the whole, which is a system, a concrete manifold, constructed in a complex way, which must be studied in its historical dynamics and in its parts, seeing the evolution of the relations between them, which are not rigid identities but are endowed with an intrinsic dynamism, and seeing the connections that bind the parts to the whole. The "true", knowledge, is the result of this dialectical process. Finally, it seems useful to us to correct in depth a metaphysical and scholastic vision of dialectics (which finds its nourishment in the basic theological inspiration of Hegel's own thought) that hinges on the thesis-antithesis-synthesis triad. The correction may come from the transplantation into Western dialectics of the dialectics of ancient Chinese philosophy, which sees the dynamics of two polarities, yin and yang, one of

which is the root of the other, and which therefore, while defining a clear predominance of both yang and yin in the phenomenon, are not mutually exclusive: in the maximum yang there is the minimum yin, and vice versa. Moreover, this philosophical approach contains neither theology nor teleology and thus proves to be a useful tool for scientific investigation. We have developed these and other concepts extensively in a recent paper published in this journal (Bottaccioli, Bottaccioli, 2024a) and favourably reviewed by Li & Kelley (2024), where we demonstrate the usefulness of ancient Chinese philosophy for the study of the functioning of the immune system. Our article cites several examples of the Yin-Yang dialectic in immunology: 1) The brake of Th1: The yin is in the yang. Numerous examples are given on the self-regulation of Th1 cells that in a first phase produce IL-12 and IFN- γ (yang), then after a few days produce the opposite signal IL-4 (yin) that curbs Th1 in favour of Th2. Similar phenomena are indicated for the role of IFN- γ ; 2) From regulatory T to inflammatory T: The yang is in the yin.

Recent research has documented that if the main anti-inflammatory lymphocyte cell, the regulatory T-cell (Treg), receives context signalling that changes the epigenetic status of an area of the Foxp3 gene from hypo- to hypermethylation, it also changes its function from anti- to inflammatory, thus turning into a Th17 cell, which is highly inflammatory; 3) IL-6: A Yin-Yang cytokine. Interleukin-6 (IL-6) has been the focus of ongoing research and clinical trials on COVID-19 as a significant increase in cytokine concentration has been found in severe forms of the disease. However, high concentrations of IL-6 are found in people's blood after intense aerobic physical activity. In this case, the significance of IL-6 is not its inflammatory ability. On the contrary, it is clearly anti-inflammatory. In the context of aerobics and controlled physical activity, IL-6, instead of activating an inflammatory response, elicits an anti-inflammatory one by reducing the concentration of TNF- α , whose activity is clearly inflammatory, and stimulates the production of other anti-inflammatory molecules resulting in positive effects on various biological systems, including the brain and cognitive functions.

Therefore, IL-6 can be yin or yang, responding in an inflammatory or anti-inflammatory direction depending on contextual signals. In Bottaccioli, Bottaccioli 2024a, the reader can find the references of cited studies and other examples of the application of the Yin-Yang dialectic to the study of the immune system.

The dialectic thus outlined can guide scientific research into the functioning of the human being in health and disease, because the starting hypothesis is systemic (the study of the human being as a psychobiological network) and the determinants identified by the various scientific investigations, both in the biological and psychological fields, are always related to the whole. The same method can

be used in the diagnosis and treatment of an individual, studying his or her life and health history, relating events and molecular data to each other and to the person's development. Molecular studies are indeed indispensable for knowing the pathophysiology of an individual, but in isolation (abstracted from the whole) they do not constitute knowledge. When medicine uses reductionist knowledge to guide treatment (cholesterolemia, hypertension, prostate-antigen, serotonin, etc.), it errs with serious consequences, leading to the chronicisation of disorders and even to fatal iatrogenic effects.

The dialectic also makes it possible to link psychology, biomedicine and the social sciences in a powerful way and to achieve what is probably the most important objective: to link theory to empirical research and care practices, making it alive, flexible and antidogmatic. Figure 3 summarises the main philosophical concept of the PNEI paradigm.

It seems to us that this philosophical perspective can contribute to outlining an alternative to the «general difficulty experienced by twentieth-century philosophy», mentioned by the philosopher Roberto Esposito (2012), who sees its three main currents in crisis: analytic philosophy, Frankfurt's critical theory, and postmodern philosophy. We need a new philosophy that supports and stimulates the process of unification of knowledge, which can also be seen in the molecular sciences (epigenetics, immunology, neurochemistry). We need a philosophy that measures itself in relation to science in its making and unmaking, without feelings of inferiority and foreignness, at a time when the horizon has collapsed into a confused present devoid of human meaning. The crisis of the great narratives of the nineteenth and twentieth centuries, which should have freed philosophy from the ballast of ideological systems, has not produced its renewed connection with life, the only possibility, in our opinion, of recovering, if not the "legislative" role of the past, of which Zygmunt Bauman (1993) speaks, at least a crucial position in the intellectual and cultural universe of the twenty-first century. On the contrary, in the new millennium, philosophical reflection seems to be carving out a "modest" space for itself, one that does not envisage contrasting the "desertification of the future" following the collapse of the great narratives. To get out of this state, the relationship with science seems crucial. For philosophy and for science.

For philosophy, whose aim is to break out of the ghetto of a form of knowledge for initiates by constructing itself instead as an ideal place for public discussion. For science, whose fundamental advances coincide with paradigmatic crises when «more and more scientists turn to philosophical analysis», as Thomas Khun (1996) points out.

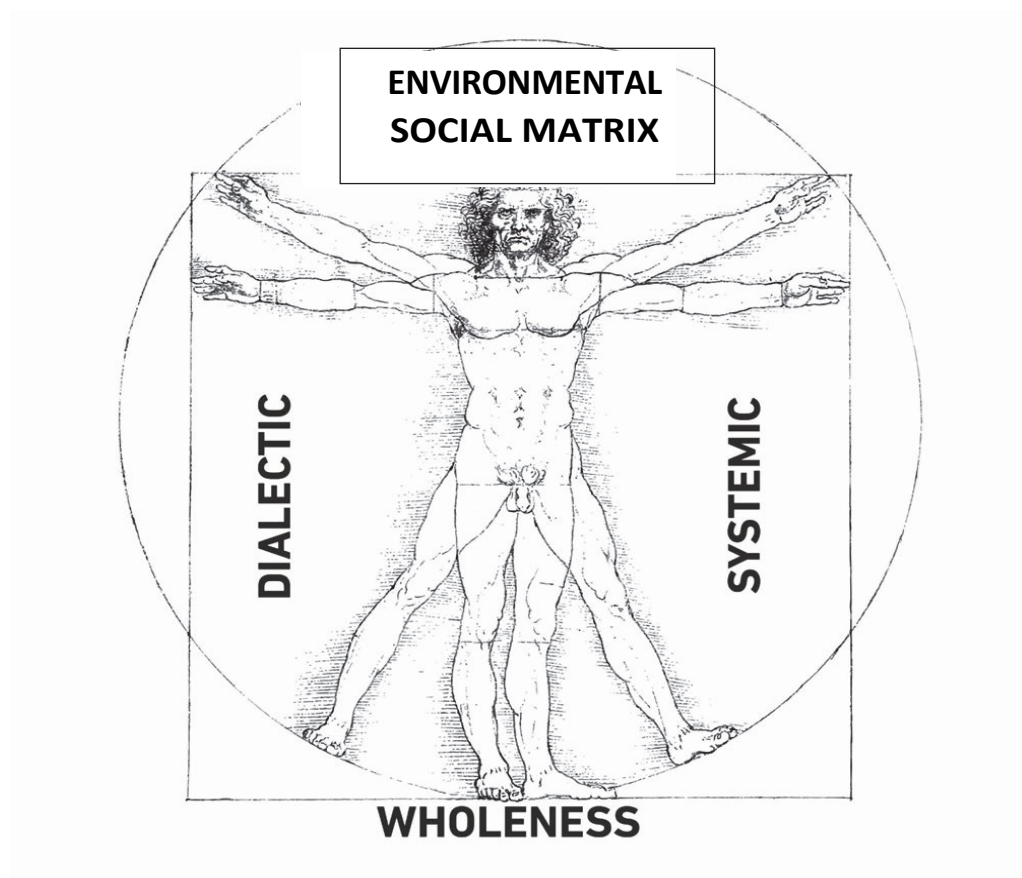


Figure 3 – The philosophical cornerstones of the PNEI paradigm: to see the human being as a whole, fully immersed in the environmental and social matrix, to study the relationships between the psychic, nervous, endocrine and immune systems, which operate dialectically, i.e. bidirectionally, in networks.

Conclusions

Psychoneuroendocrineimmunology is not the study of relationships between biological systems. In fact, the philosophy of PNEI requires a dialectical, systemic paradigm that studies the human being as a whole and embedded in the environmental matrix, physical and social.

The vision of dialectics presented in this paper is a profound correction of a metaphysical and scholastic vision of Hegelian dialectics that has since been criticised by Karl Marx and especially by Antonio Gramsci. A more profound correction could come from the transplantation into Western dialectics of the dialectics of ancient

Chinese philosophy, which sees the dynamics of two polarities, yin and yang, one of which is the root of the other, and which are therefore not mutually exclusive, even though they define in the phenomenon a clear predominance of both yang and yin.

This dialectic makes it possible to study the psychobiological network and its components, the macro movements, e.g. psyche-brain-immune system relations, and the micro movements, e.g. epigenetic signatures induced by psychic or biological states.

The reductionist paradigm, in the various versions examined in this article, which has dominated science to date, has, on the one hand, accumulated a mass of molecular knowledge of undoubted scientific importance, which has provided research and clinical practice with the discovery of pathological molecular markers, improving diagnosis. Furthermore, without this remarkable accumulation of molecular knowledge, it would not have been possible to advance research into the relationships between the psyche and biological systems, and therefore it would not have been possible to establish the new paradigm of Psychoneuroendocrineimmunology, which we can define as a molecular-based systemic paradigm. However, on the other hand, the reductionist paradigm has been an obstacle to the progress of scientific knowledge about human beings and to the improvement of the effectiveness of treatments. Three examples suffice to illustrate the serious obstacles to research and clinical studies created by the reductionist paradigm, which presupposes a separation between the sciences.

For half a century, Alzheimer's research has focused on the molecular mechanisms of amyloid plaque aggregation, ignoring the role of the immune system, both endogenous (microglia) and peripheral. This line of research, which has improved diagnosis at the molecular level, has been a complete failure in terms of treatment. Now, the link with the immune system, both central and peripheral, is opening up new avenues, also of a clinical nature (Heneka *et al.*, 2015; Ramanan *et al.*, 2023).

For many decades, cancer research has focused on the molecular and genetic mechanisms that control the transformation of the normal cell into a malignant cell, with poor results. The reductionist paradigm of cancer excluded the immune system as capable of recognising and controlling malignant transformation and also excluded the role of the psyche and nervous system in carcinogenesis and the progression of oncological disease. The first exclusion has been reversed in recent years with the growing development of cancer immunotherapy (Rosenberg, 2024; Chen *et al.*, 2024). The second has been overturned in recent years by the demonstration of the carcinogenic role of stress hormones and nerve fibres: the former suppress the anticancer lymphocyte (Th1) circuit, the latter envelop the initial tumour mass and are arranged at the service of its development and metastatic spread (Magnon & Hondermarck, 2023; Amit *et al.*, 2024; Park & Lee, 2024).

Depression is a major health problem worldwide, especially in countries with higher industrialization. Despite decades of pharmacological research and a massive and increasing prescription of antidepressants, less than half of the treated subjects (48%) showed improvement (symptom remission) after 6 months of treatment, a percentage that drops to 34% if functional remission is assessed (Scheehan *et al.*, 2011). The origin of this poor treatment efficacy stems from the reductionist model of depression as a chemical imbalance, neglecting the complex origin of the disorder, which has its sources in biology, behavior and affective and social relationships. The new lines of research highlight the central role of inflammation (Pariante, 2017), however it must be clear that the origin of inflammation is multiple: the immune system can be activated both by antigenic and behavioral means (inflammatory diet, disturbed sleep, sedentary lifestyle, pollution) and by emotional stress. Depression is therefore a disorder of the person as a whole, its sources are multiple and personal, which must be recorded in detail in a joint medical and psychological assessment, on which to base an effective integrated treatment that cannot be reduced to the addition of anti-inflammatory to antidepressants drugs. We have recently published an extensive article on the subject, which also illustrates the clinic based on the PNEI paradigm (Bottaccioli, Bologna, Bottaccioli, 2025). In this paper, we present also a clinical case of severe chronic depression. The assessment and treatment of the patient was guided by the PNEI paradigm. The first visit was conducted jointly by FB (psychologist) and AGB (medical doctor). She suffered from Major Depression for more than 15 years and was under standard treatment: psychotherapy in combination with medication. She was severely overweight, had uncontrolled thyroiditis (elevated TSH) despite hormone therapy and uncontrolled osteoporosis (fractures) despite drug therapy with bisphosphonates and vitamin D; blood tests also showed a plasma cortisol value on the high end of the range, an inversion of neutrophil: lymphocytes ratio and a frank folic acid deficiency.

We found that the inducer of the process of change towards healing was neither drug nor psychotherapy, but a mix of biological and psychological actions. The biological actions, obtained by various tools (nutrition, precision nutraceuticals, acupuncture), provided energy to the patient and lowered inflammation by regulating the immune system. So, a new interoceptive state was realized. On this new perception of self, learning meditative and stress management practices facilitated the implementation of self-management of emotions and the practice of new health behavior. At follow-up at 8 months, she showed psychological rebalancing, new behavior, a strong reduction in physical symptoms and weight, a biological rebalancing of thyroid hormones, cortisol, insulin, and neutrophil: lymphocytes ratio.

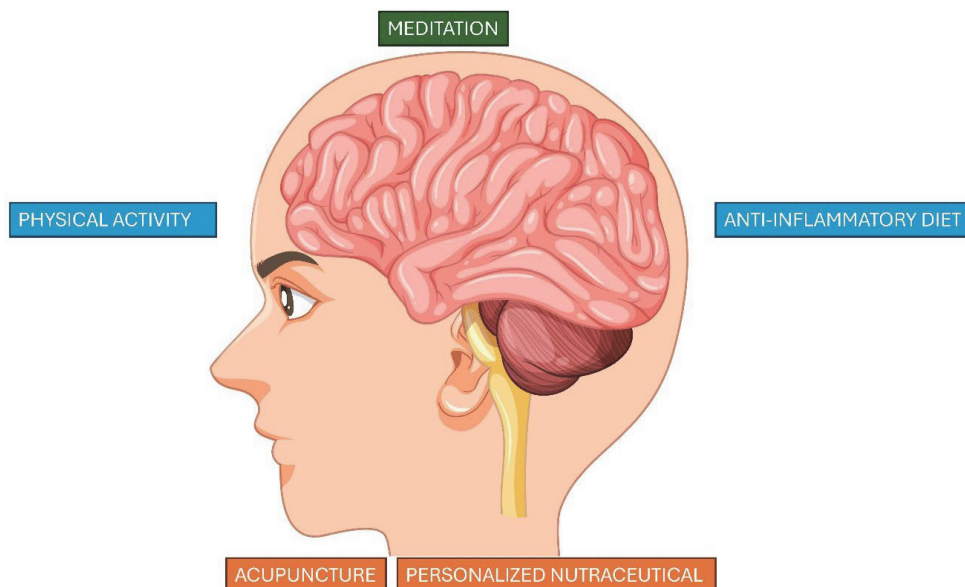


Figure 4 – From: Bottaccioli, Bologna, Bottaccioli, 2025. The integrated therapy followed by patient GB affected by severe chronic major depression. Note that GB preferred to discontinue psychotherapy, which she had been following for years and with different psychotherapists, in favor of learning meditative practice. Obviously, this was GB's preference, and others find themselves very well with psychotherapy and benefit from it.

Since the middle of the last century, the main alternative model to the reductionist paradigm has been the biopsychosocial model, proposed by George Engel (1977) on the basis of the research and theories of psychosomatic medicine (Alexander, 1950). Both Franz Alexander and George Engel are fundamentally critical of the biomedical model. The three fundamental errors on which this model is based, according to Engel, are: the reduction of complex phenomena to simple determinants (reductionism), the separation of biological phenomena from psychosocial phenomena (mind-body dualism), the interpretation of vital phenomena in physical-chemical terms (physicalism). Alexander's criticism of the reductionist model led him to conclude that progress in science and treatment could only be achieved by uniting medicine and psychology in both the assessment and treatment of the patient, regardless of whether the symptomatology was predominantly biological or psychological: «Progress in modern medicine consists specifically in the co-operation of the psychiatric and non-psychiatric specialists both in diagnosis and in treatment» (Alexander, 1950 p.264). The scientific programme of Alexander and Engel found one of its main obstacles in the backwardness of the available scientific knowledge to justify their claims about the reciprocal influence of the psyche and biological systems of a subject embedded

in a social context that shapes not only culture and behaviour but also individual biology.

The paradigm of Psychoneuroendocrineimmunology is the heir of this scientific and philosophical tradition (Bottaccioli, Bottaccioli, 2024c), which, on the basis of the new systemic and molecular knowledge of the functioning of the human organism accumulated over the last five decades, closes the gap between the quest for a systemic approach to health and disease and the molecular and clinical evidence.

Based on the PNEI paradigm, the treatment could be effectively integrated, combining biomedical and psychological sciences, using very modern therapeutic means and very ancient scientifically valid means. The health professional could have a profound knowledge of the body's internal language, its words made up of hormones, neurotransmitters and cytokines. He could know how to master the powerful substances coming out of the current scientific revolution, but he could also use words, meditative techniques, hands, herbs and natural substances. Ultimately, by mastering the PNEI paradigm, he will be a good technician and an excellent educator in the preservation of life (Bottaccioli, 2005; Bottaccioli, Bottaccioli, 2024b).

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The Influence of Healthcare Environment Architecture on the Psycho-Neuro-Endocrine-Immunological System

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Abstract: *This article is a re-elaboration based on the book Archi-Therapeia. The Influence of Architecture on the PNEI Mind-Body System authored by Silvia Moneti, Architect and Teacher with a Master's degree in PNEI and Integrated Care Science.*

In particular, reference is made to the chapter concerning design guidelines for healthcare facilities, with the aim of presenting a set of strategies that can be implemented within care environments to promote patients' psychophysical well-being.

The initial sections address issues related to orientation, accessibility, social interaction, spatial organization and personalization of the patient room.

The discussion then proceeds with the presentation of guidelines concerning lighting, acoustics and clinical aromatherapy.

The final sections focus on the design of labor and breastfeeding rooms, intensive care units and spaces for home-based care.

The article concludes with the hope that the collected evidence may be translated into future architectural projects for healthcare facilities and care environments, while continuing to promote Architecture as a discipline within the PNEI framework and as a form of integrated therapy in its own right.

Keywords: *Architecture, PNEI, Healthcare Facilities, Labor Room, Intensive Care Unit, Home Care*

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Introduction

This article is derived from the book *Archi-Therapeia. The Influence of Architecture on the PNEI Mind-Body System*, and in particular from the chapter addressing design guidelines for healthcare facilities.

Its aim is to present a range of architectural strategies that can be implemented to promote the psychophysical well-being of patients undergoing treatment for specific pathologies, whether in acute or chronic phases.

The article is therefore intended for both Healthcare Professionals and Technical Professionals, who are called upon to engage in dialogue and collaboration in order to promote the health of a “shared patient”.

Orientation and Accessibility

Spatial perception can be defined as the individual’s ability to interpret the surrounding environment and to understand the relationship between physical space and the position of one’s own body within it. The concept of accessibility, by contrast, refers to the extent to which an environment can be used by individuals with diverse functional characteristics, including those with sensory, motor or cognitive impairments, whether temporary or permanent.

The study *Patient-Friendly Hospital Environments: Exploring the Patients’ Perspective* (Calbert and Mary, 2004) investigated how fifty patients admitted to departments of Internal Medicine, Surgery, Geriatrics and Maternity perceived hospital spaces. The findings highlighted that a significant number of participants experienced difficulties in orienting themselves within the healthcare facility, resulting in increased anxiety, reduced perceived control and a loss of personal autonomy.

Evidence from research on so-called place cells suggests that a clear and recognizable characterization of environments may enhance spatial orientation processes, as the presence of distinctive elements facilitates the stabilization of cognitive spatial representations generated within neural circuits involving the hippocampus and entorhinal cortex. Conversely, environments lacking spatial cues may promote persistent activation of the physiological stress response, which is associated with immunosuppression, delayed wound healing and an increased severity and frequency of viral infections (Vedhara *et al.*, 1999; Glaser and Kiecolt-Glaser, 2005; Sternberg, 2006).

In the field of healthcare architecture, the concept of “hospital wayfinding” has been developed, encompassing a set of design and communication strategies aimed at facilitating user orientation within hospital settings. Commonly adopted measures include the use of differentiated color-coding systems, the installation of interactive digital information devices and the integration of Braille signage.

Social Interaction

Some patients exhibit a more marked reduction in stress levels when hospitalization occurs in single rooms, environments characterized by lower exposure to acoustic and visual stimuli and a higher degree of privacy. For other individuals, however, staying in shared environments (such as double or four-bed rooms) may be psychologically more beneficial, as the presence of other patients reduces the perception of isolation. Preferences for a specific type of accommodation are not determined solely by individual personality traits but are also influenced by the type of ward and the expected length of stay (Calbert and Mary, 2004).

For patients who retain an adequate level of psychophysical autonomy, the availability of common spaces dedicated to recreational activities is particularly relevant. Such environments promote social interaction and contribute to the stimulation of cognitive and motor functions. In several healthcare settings, dedicated indoor spaces have been designed, including libraries, tea rooms and small screening areas. In parallel, some healthcare institutions, particularly in the United States and Northern Europe, have established collaborations with local museums to organize guided cultural visits for patients who are able to temporarily leave the hospital.

These initiatives fall within the therapeutic paradigm known as “Art on Prescription”, an approach that involves the use of artistic experiences as complementary interventions aimed at improving psychophysical well-being. Numerous studies have shown that this practice can enhance patient’s awareness of their clinical condition and encourage a more active role in managing their own health.

A significant contribution in this field derives from a study conducted in Australia, which evaluated the psychophysiological responses of patients with dementia participating in a cultural visitation program at the National Gallery of Australia (D’Cunha *et al.*, 2019). After six weeks of participation in the museum-based therapy program, several beneficial effects were observed, including increased dynamism of the circadian cortisol rhythm (indicative of improved functioning of the hypothalamic-pituitary-adrenal axis), more effective blood pressure regulation, reduction in depressive symptoms, improvements in memory performance and verbal fluency, enhanced self-esteem, higher levels of empowerment and a greater propensity for social interaction.

The “Art on Prescription” approach has recently also been applied in the prevention and treatment of depression associated with prolonged hospitalization (Monsuez *et al.*, 2019). In Paris, the Louvre Museum established a collaboration with several city hospitals to develop a cultural program for long-term patients admitted to Geriatrics, Psychiatry and Palliative Care wards. Over the course of

one year, sculptures were installed in patient gardens, reproductions of renowned paintings were displayed in common areas and educational art history sessions were organized for patients, caregivers and healthcare staff. The results observed at the end of the study indicated that approximately 80% of patients reported a significant reduction in perceived stress, while more than 90% reported benefiting from the artistic experience in terms of improved quality of life during hospitalization. Furthermore, the joint participation of patients, caregivers, and healthcare professionals contributed to the creation of a relational climate characterized by greater trust, familiarity and collaboration.

Spatial Arrangement

In 2019, MacAllister and colleagues conducted a study on patient satisfaction in relation to the spatial arrangement of hospital rooms, titled *Exploring the Relationships Between Patient Room Layout and Patient Satisfaction*. Rooms located at an intermediate distance (10-20 meters) from the nursing station, with the entrance positioned on the patient's right side and the head of the bed not visible from the doorway, were found to be the most appreciated. These configurations were valued because they were close enough to healthcare staff to allow prompt assistance if needed, while simultaneously providing privacy and a restful environment.

Personalization

It has been observed that, as the length of hospital stay increases, patients exhibit a growing need to intervene in their surrounding environment through forms of personalization that help reinforce their sense of identity and belonging (Andersson, 2017).

From this perspective, Andersson and colleagues (2019) propose various design and organizational strategies, including the possibility of displaying family photographs in frames provided by the facility, installing a magnetic board for posting drawings, posters or personal notes, providing a small writing desk, allowing the introduction of personal objects from home, offering potted flowers or plants that patients can care for themselves, enabling individual control of room lighting, distributing books and newspapers on a daily basis and granting access to personal devices for listening to music or viewing visual content.

The implementation of these interventions aims to create a more humanized care environment, capable of supporting the patient's psychological well-being during hospitalization and fostering a greater sense of control over their temporary living space.

Lighting and Circadian Rhythm

Visible light represents one of the primary environmental cues through which humans synchronize their biological clock. Circadian rhythms are physiological oscillations with an approximately 24-hour periodicity that regulate numerous biological functions, including body temperature, hormone secretion, the sleep-wake cycle and cognitive performance.

In 1998, specific photoreceptors were identified in the human eye, known as intrinsically photosensitive retinal ganglion cells (ipRGCs), which express the photopigment melanopsin. This pigment allows the transmission of information to the suprachiasmatic nucleus (SCN), which serves as the body's central clock, aligning internal biological rhythms with external environmental cycles (Wahl *et al.*, 2019).

Blue light (wavelength between 380 and 435 nm; correlated color temperature between 5000 and 7000 K) is one of the most potent synchronizers of the circadian system. Exposure to this spectral component during daytime contributes to melatonin suppression, increased body temperature, heart rate and blood pressure. Additionally, it is associated with heightened alertness, improved concentration, and enhanced cognitive performance, while reducing perceived effort during mental tasks (Zauner, 2020).

Conversely, prolonged exposure to low-intensity blue light during nighttime hours (LAN – Light At Night) can disrupt normal circadian function, impair sleep quality, and potentially contribute to adverse psychophysical health outcomes, including increased risk of oncological (Haus and Smolensky, 2006) and diabetic pathologies (Kreier *et al.*, 2007), cognitive decline (Stevens *et al.*, 2007), reproductive dysfunction (Mahoney, 2010), obesity (Bass and Takahashi, 2010), as well as gastrointestinal issues and alterations in gut microbiota composition (Codoñer-Franch and Gombert, 2018).

Based on this evidence, Giménez and collaborators (2017) proposed a model for optimized circadian lighting in hospital patient rooms, integrating guidelines for color temperature and illuminance levels throughout the day. According to this model, during daytime hours, light sources with a high blue-light component (approximately 4000-6500 K) are recommended to enhance mood, cognitive performance and physiological activation. Under these conditions, average illuminance should be around 300 lux, with possible peaks up to approximately 1500 lux between roughly 10 a.m. and 1 p.m. In the evening, the color temperature should be progressively reduced and maintained below 3000 K to promote melatonin secretion and facilitate sleep onset. Simultaneously, illuminance should decrease to a maximum of around 100 lux in the early evening, and further reduced to between 5 and 10 lux during nighttime rest periods.

Acoustics and Soundscape

The topic of acoustics in hospital settings is addressed in a particularly comprehensive and insightful manner in the article *Exploring the Effect of Sound and Music on Health in Hospital Settings: A Narrative Review*, published in 2016 by the research group led by Timothy Onosahwo Iyendo. The authors first emphasize the importance of distinguishing between the notions of sound and noise, introducing the concept of the soundscape, defined as the ensemble of acoustic components perceived within a specific environment.

Noise is generally defined as any auditory stimulus perceived as unwanted and is considered a significant stressor, capable of producing negative psychological and physiological effects (Plack, 2013). Exposure to intrusive sound sources represents one of the most frequently reported environmental problems by both patients and staff in healthcare facilities. Since the 1960s, there has been a progressive increase in sound pressure levels within hospitals: during daytime hours, average levels range between 57 and 72 dB (comparable to a busy restaurant or an urban street), while nighttime levels typically range from 42 to 60 dB (similar to the noise produced by an operating household appliance) (Busch-Vishniac *et al.*, 2005). These levels exceed by approximately 20-30 dB the recommended limits for background environmental noise in healthcare facilities set by the World Health Organization (Berglund *et al.*, 1999).

Numerous studies have shown that prolonged exposure to unwanted noise can produce adverse effects in hospitalized patients, including increased urinary cortisol levels, headaches, and heightened pain sensitivity (Melamed and Bruhis, 1996), elevated blood pressure, increased risk of cardiovascular disease, potential alterations in neonatal development and modifications of immune responses (Segerstom and Miller, 2004). Additionally, high noise levels have been associated with longer hospital stays (Bailey and Timmons, 2005), deficits in memory functions and psychomotor agitation (Short *et al.*, 2011).

In contrast, a growing number of studies have highlighted the beneficial effects of music on patient's psychophysical health, preferably listened to through personal devices at sound levels below approximately 60 dB. Reported benefits include reductions in preoperative pain and anxiety (Chaput-McGovern and Silverman, 2012), improved management of behavioral and psychological symptoms in patients with dementia (Ueda *et al.*, 2013) and enhanced motor and communication skills in individuals with Parkinson's disease (Pohl *et al.*, 2013).

Clinical Aromatherapy

Aromatherapy is a discipline within the field of phytotherapy that utilizes natural essential oils with the goal of promoting an individual's psychophysical well-being.

According to the article *Clinical Aromatherapy* (Farrar A.J. and Farrar F.C., 2020), the historical origins of aromatherapy cannot be attributed to a single cultural context, as practices involving the use of aromatic plant substances were widespread across numerous ancient civilizations. Among the most significant records is the *Ebers Papyrus*, dated around 2800 BC, considered one of the principal documents of Ancient Egyptian medicine, containing instructions on the therapeutic use of resins, balms, and scented oils. Around the same period, the *Shennong Manuscript*, attributed to the Chinese deity associated with agriculture, describes over 350 plant species along with their medicinal properties. In Europe, the Greek philosopher and botanist Theophrastus (a student of Aristotle) is traditionally regarded as the founder of scientific botany; in the 4th century BC, he authored *Historia Plantarum*, documenting the characteristics and medicinal uses of more than four hundred plant species. With the spread of Christianity in Europe, some practices involving aromatic plants were associated with pagan rituals, leading Pope Gregorio Magno in the 6th century AC to prohibit their use.

The modern scientific rediscovery of essential oils occurred in the 1920s, when French chemist René Maurice Gattefossé coined the term “aromatherapy” after studying the wound-healing properties of lavender essential oil during experiments conducted in military hospitals. Later, during World War II, French surgeon Jean Valnet significantly contributed to the diffusion of aromatherapy in medical practice, using essential oils to treat soldiers' wounds and manage trauma-related psychological disorders. In 1961, the nurse and naturopath Marguerite Maury published *Le Capital de Jeunesse*, analyzing the effects of essential oils on the central nervous system and cellular regeneration processes.

Currently, clinical aromatherapy is administered through three main modalities: topical application, oral ingestion, and inhalation. Depending on the patient's clinical needs, aromatherapy may serve as a complementary therapeutic intervention with multiple purposes, including antibacterial, antifungal, antiviral, analgesic, antiseptic, anti-inflammatory, antioxidant, anticoagulant, antipyretic, antidepressant, detoxifying, decongestant and muscle-relaxing effects (Kaufmann, 2018).

The influence of aromatherapy on the PNEI system is evident when considering the path of essential oil molecules: once inhaled, the molecules reach the olfactory bulb and then the amygdala and hippocampus, facilitating the retrieval of positive memories and emotions associated with specific scents. Simultaneously, the molecules travel from the respiratory system into the bloodstream, reaching organs and

tissues that can benefit from their therapeutic properties (Farrar A.J. and Farrar F.C., 2020; Vora *et al.*, 2024).

Despite the potential benefits of clinical aromatherapy, its use requires specialized expertise and adherence to strict safety protocols. Essential oils are highly concentrated and flammable substances that must be stored in cool environments, preferably in amber glass bottles to minimize exposure to ultraviolet light. Additionally, prior to topical application, preliminary allergy testing is recommended to prevent potential skin reactions, dermatitis or photosensitization.

Labor and Breastfeeding Rooms

Between 2005 and 2007, Osborne Park Hospital in Western Australia hosted a research program focused on the implementation of controlled multisensory environments, used as spaces for labor and breastfeeding.

The first published study, titled *Women's Experiences of Using a Snoezelen Room During Labour in Western Australia* (Hauck *et al.*, 2008a), examined the experiences of sixteen women who used a labor room designed to provide multisensory stimuli under the direct control of the birthing women. The room featured floors and walls painted in warm, muted tones, natural fabrics, comfortable furnishings, and adjustable lighting with individualized control over intensity and color temperature. Obstetric care could be continuous or intermittent, depending on the woman's preferences. Pain management and relaxation strategies included immersion in warm-water tubs, acupuncture, aromatherapy, music therapy, massage, and transcutaneous electrical nerve stimulation (TENS). Post-experience interviews revealed that participants perceived the environment as an active factor enhancing their sense of control and self-efficacy while significantly reducing pain perception.

Subsequently, the same space at Osborne Park Hospital was used as a breastfeeding room. The results of this second research phase were published in *A Qualitative Study of Western Australian Women's Perceptions of Using a Snoezelen Room for Breastfeeding During Their Postpartum Hospital Stay* (Hauck *et al.*, 2008b). The study aimed to evaluate the influence of the architectural environment on the breastfeeding experiences of eleven new mothers who exhibited high levels of anxiety or difficulties in establishing intimate bonding with their newborns. At the conclusion of the experience, all participants expressed a positive assessment, highlighting the benefits of being able to step away from the traditional hospital environment and access a space with an intimate and welcoming atmosphere. Privacy reduced external distractions and direct control over environmental conditions promoted maternal relaxation, reinforced self-esteem and facilitated a more enjoyable breastfeeding experience.

Intensive Care and NICU

In recent years, numerous studies have examined the impact of ICU architectural design on clinical outcomes and patient well-being. These investigations have compared traditional intensive care units with innovative design models featuring single-patient rooms, neutral color schemes, eco-friendly materials, noise-reducing technologies, circadian rhythm-aligned lighting systems, and the possibility of including personalized elements such as photographs and personal objects (Andersson *et al.*, 2019).

Patients admitted to traditional ICUs, even when sedated or in a state of reduced consciousness, often report fragmented memories of their hospitalization, frequently characterized by unpleasant auditory perceptions, disturbing visual images, and feelings of disorientation and vulnerability (Johansson *et al.*, 2012; Olausson *et al.*, 2013; Baumgarten and Poulsen, 2015). From a pathophysiological perspective, these conditions may be associated with spatial-temporal disorientation, increased risk of persistent cognitive deficits, elevated heart rate and blood pressure, sleep disturbances and delayed wound healing. More favorable outcomes have been observed in studies conducted in ICUs designed according to innovative principles, where patients reported lower distress levels, improved pain management and reduced risk of infectious complications (Andersson *et al.*, 2019; Tronstad *et al.*, 2023).

Designing Neonatal Intensive Care Units (NICUs) requires even greater consideration, as the physical environment can significantly influence the neuro-sensory development of preterm infants. Dr. Stanley Graven was the first to introduce the concept of a “critical period”: a temporal window during which the physical environment exerts a particularly significant effect on the visual and auditory systems of premature infants (Graven, 2000; Robinson and Pallasmaa, 2017).

The critical auditory period begins approximately 10-12 weeks before birth and extends until the second year of life. Follow-up studies of preterm infants exposed to inadequate acoustic conditions during NICU hospitalization have shown potential long-term negative outcomes, including delays in language development, difficulties in auditory discrimination, and reduced ability to recognize complex acoustic patterns (Wright *et al.*, 1983). These findings highlight the necessity of designing an appropriate soundscape within NICUs, one that simulates the acoustic conditions of the uterine environment. Operationally, this involves maintaining average sound pressure levels below 50 dB and emphasizing frequencies below 250 Hz (Graven and Browne, 2008), thereby promoting physiological stability, weight gain, sleep quality and reducing long-term language development disorders (Graven, 2000).

The critical visual period begins immediately after birth, when the combination of light and visual stimuli activates the primary visual cortex and related neural networks. Assessment of visual development in neonates relies on multiple interde-

pendent functional parameters, each maturing at different rates: visual acuity, horizontal visual field, color perception and binocular vision (Niessen, 2006). NICUs are not always optimized to support proper visual system maturation in preterm infants. For example, prolonged exposure to high-intensity artificial light can cause retinal damage proportional to wavelength, intensity and duration of exposure. Even natural light entering through large windows may exceed neonatal tolerance, as eyelids do not yet provide full protection. Another frequently overlooked aspect is the alternation of light and dark periods: appropriate modulation of environmental lighting is essential to promote circadian rhythm synchronization in neonates.

Prosthetic Architecture

Prosthetic architecture is designed to compensate, much like a prosthesis, for certain physical or cognitive disabilities. Creating a prosthetic environment requires a thorough understanding of the patient who will benefit from it, including personal characteristics and medical history, as well as an assessment of deficits and the development of compensatory strategies to ensure a good quality of life.

Most studies conducted to date on prosthetic architecture have focused on patients with Alzheimer's disease. This condition, even in its early stages, involves reduced environmental control due to diminished visual fields and eye movements, impaired depth and distance perception, decreased contrast sensitivity and reduced ability to detect moving objects and cool-colored stimuli.

A well-designed prosthetic environment can enhance residual autonomy and preserve patient dignity while minimizing risks and caregiver burden-effectively functioning as a "Non-Human Caregiver". Key principles for designing such environments include:

- furniture and furnishings: these should be easy to use and create an intimate, homelike atmosphere. Since certain behavioral disturbances may result from misinterpreted reflections, mirrors should be easily removable or obscurable;
- spatial readability: to facilitate perception of the surrounding environment, corners and edges should be highlighted in contrasting colors. Horizontal and vertical surfaces should be distinguished using different colors for floors, baseboards, walls and ceilings. Flooring should be uniform throughout and black-and-white checkerboards should be avoided, as dark tiles may be perceived as gaps or holes in the floor;
- orientation aids: the use of photographs, labels, and stylized signage on doors and walls can enhance wayfinding and clarify the functional purpose of each space. To support temporal orientation, large clocks and calendars should be installed at a height no greater than 170 cm, as individuals with dementia often have visual field deficits in the upper-middle range.

These design strategies aim to create environments that support autonomy, reduce disorientation, and provide a safe, comprehensible space tailored to the cognitive and sensory capacities of the patient.

Impact of Architecture on Home-Based Care

As reported in *L'infermiere. Manuale teorico-pratico di infermieristica* (Fabbri and Montalti, 2011), home-based care encompasses all healthcare and support interventions delivered directly at the patient's residence, aiming to reduce hospitalization while ensuring continuity of care. From an integrated medicine perspective, home care services must provide adequate support not only to the patient but also to their family unit.

Within the framework of the Individualized Care Plan (Piano Assistenziale Individualizzato, PAI), it is therefore necessary to include not only diagnostic and therapeutic interventions but also actions aimed at:

- preserving functional autonomy: enhancing the patient's residual abilities to maintain independence in daily activities;
- improving quality of daily life: creating conditions that promote comfort, well-being and meaningful engagement in routine tasks;
- supporting and training caregivers: guiding family members in the administrative management of care, as well as in the proper use of medical devices and equipment present in the home;
- organizing the domestic space: adapting the home environment to meet specific clinical needs without compromising its emotional and symbolic value.

These principles underscore the importance of considering architecture and environmental design as integral components of home-based care, where the physical space itself becomes a therapeutic and supportive element for both patients and caregivers.

Conclusions

The article concludes with the hope that the scientific evidence presented will be translated into future architectural projects for healthcare facilities and care environments. Architecture, conceived as an integrated therapeutic tool, has the potential to significantly and effectively promote patient health, both in preventive and curative contexts. By embedding evidence-based design principles into healthcare settings, future projects can transform the built environment into an active agent of well-being, supporting recovery, enhancing quality of life and fostering a truly holistic approach to patient care.

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