A systemic and dialectical paradigm for Psychoneuro-endocrineimmunology and integrated care science*

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Received 1 December, accepted 5 December
Online first: 14 January 2026

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Please cite: Bottaccioli F., Bottaccioli A.G. (2025). A systemic and dialectical paradigm for Psychoneuro-endocrineimmunology and integrated care science. *PNEI Review.* DOI: 10.3280/pnei2025oa21668

***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*

[*] A partial version of this article was published in *Brain Behavior and Immunity Integrative*, Volume 12, December 2025, 100138. DOI: 10.1016/j.bbii.2025.100138

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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.

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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-

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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. Withehead 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"

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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-

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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 Patrica 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

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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,

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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 abovementioned 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-

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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).

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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).

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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-

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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 isinfluenced 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

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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".

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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 x 1013) (Sender,

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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 (Dalile *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-κB levels in monocytes. NF-κB 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 NFkB, which activates numerous genes coding for cytokines and other molecules associated with immune activation, including adhesion molecules. The mechanism that increases NFkB 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

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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.

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

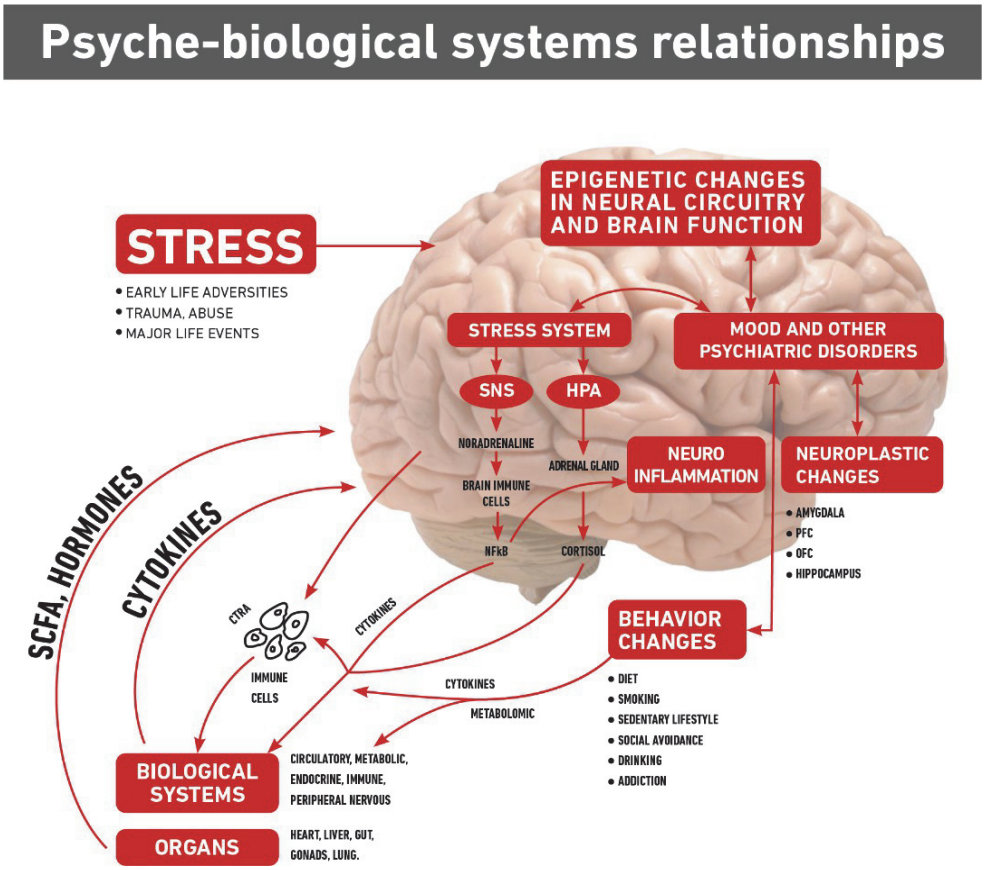

Figure 2 – Bidirectional relations between psyche, brain, immunity, metabolic systems and organs. Chronic psychosocial stress can induce neuroendocrine stress system activation and epigenetic changes in neural circuitry. Simultaneously, the overproduction of noradrenaline induced by the stress reaction 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

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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, noncoding 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-

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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-

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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.

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

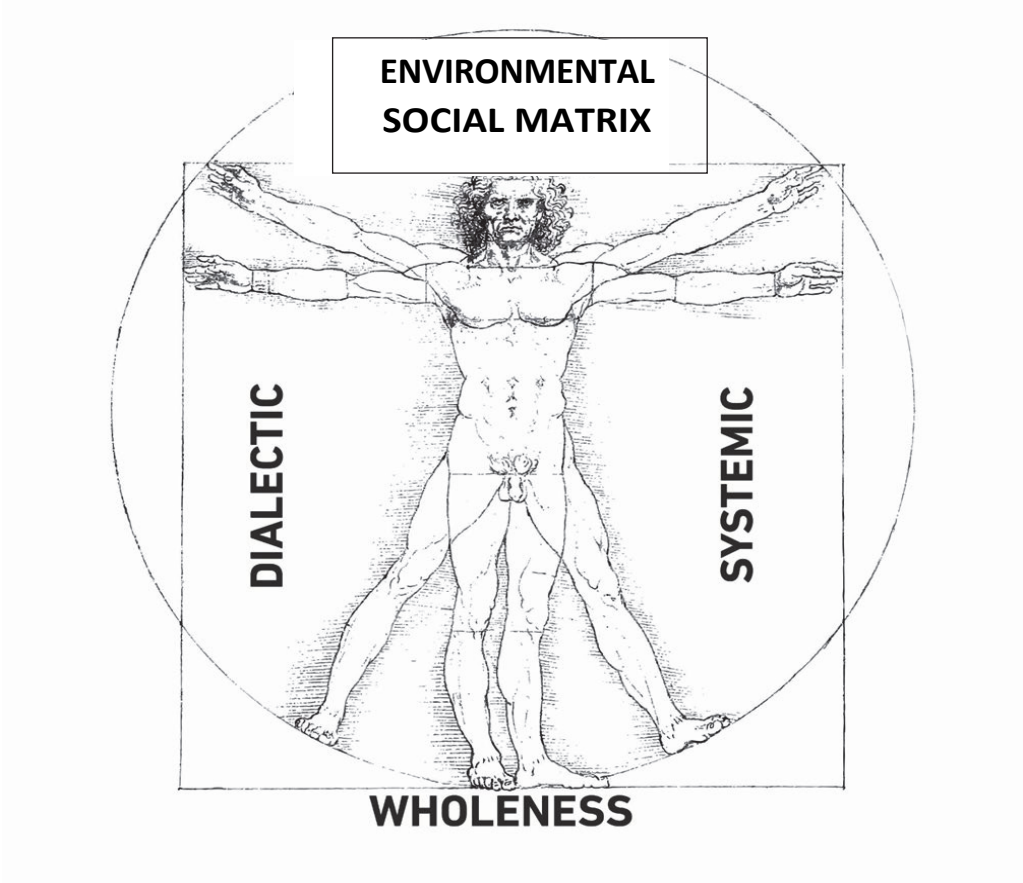

Figure 3 – The philosophical cornerstones of the PNEI paradigm: to see the human being as a whole, fully immersed in the environmental and social matrix, to study the relationships between the psychic, nervous, endocrine and immune systems, which operate dialectically, i.e. bidirectionally, in networks.

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

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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 paradigmof 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).

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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.

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

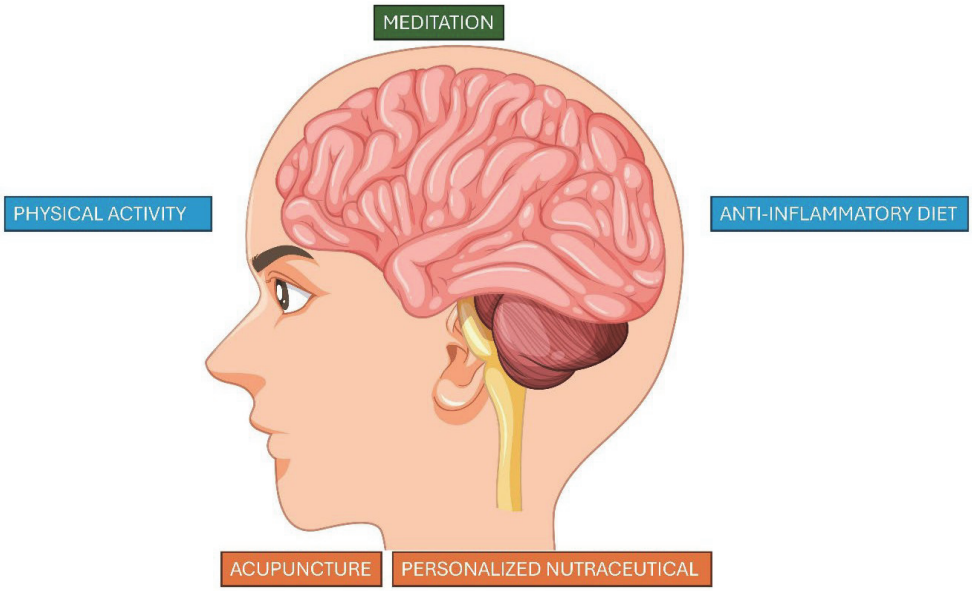

Figure 4 – From: Bottaccioli, Bologna, Bottaccioli, 2025. The integrated therapy followed by patient GB affected by severe chronic major depression. Note that GB preferred to discontinue psychotherapy, which she had been following for years and with different psychotherapists, in favor of learning meditative 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

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa21668

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 thegap 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).

Author Contributions: Conceptualization: F.B. and A.G.B; writing—original draft preparation, F.B. and A.G.B.; writing—review and editing, F.B and A.G.B. All authors have read and agreed to the published version of the manuscript.
Funding: This research received no external funding. Conflicts of Interest: The authors declare no conflicts of interest.
Data Availability Statement: Data are contained within the article Acknowledgments: We thank the reviewers who, with their suggestions, have significantly improved the publication.

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