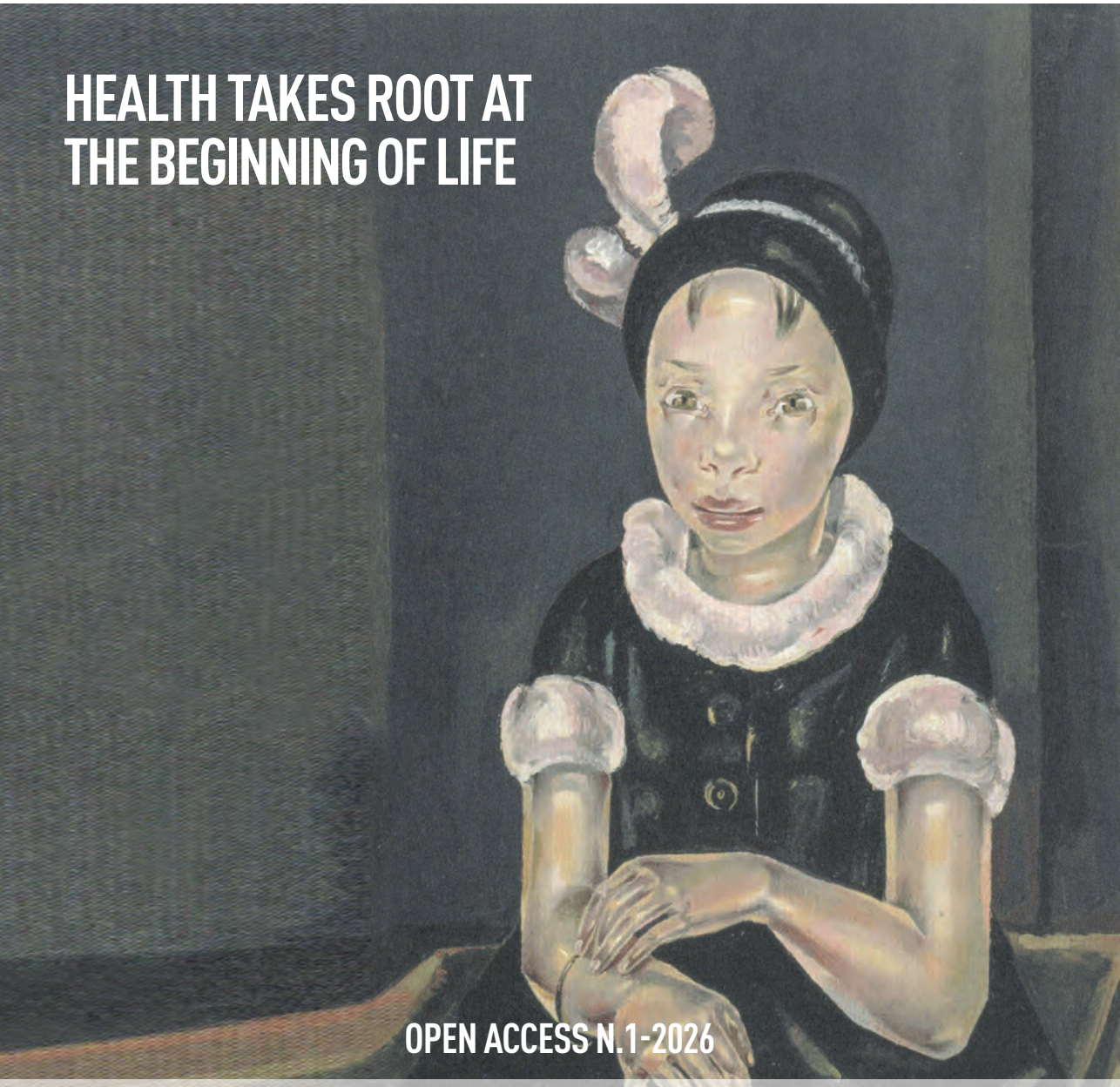
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HEALTH TAKES ROOT AT THE BEGINNING OF LIFE



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pneireview

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Summary

Stefania Carbonella – *Psycho-Neuro-Endocrine-Immunology, DOHaD and mindfulness: towards an integrated model of prenatal salutogenesis*

In the last thirty years, the DOHaD (Developmental Origins of Health and Disease) paradigm has radically transformed the understanding of the etiology of chronic diseases, shifting the focus from genetic determinism to the biological plasticity of the first years of life. This perspective converges with PsychoNeuroEndocrineImmunology (PNEI).

Rossana Terni – *Parenting: the keystone*

The transition to parenthood has undergone a radical structural and conceptual evolution in recent decades, driven by unprecedented demographic changes and rapidly changing family paradigms. These social changes profoundly reshape the psychological and clinical framework of parenting. At the same time, discoveries in cognitive neuroscience and psychoneuroendocrinoimmunology (PNEI) have revealed that this transition represents a unique biological window, characterized by extraordinary adult neuroplasticity and epigenetic vulnerability.

Eleonora Lombardi Mistura – *Gut microbiota: director of the PNEI of the developmental age*

The epistemological transition of modern pediatrics is marked by the overcoming of the reductionist model in favor of a systemic and integrated vision of the human organism. In this scenario, Psychoneuroendocrinoimmunology (PNEI) offers the theoretical framework to understand how adult health is programmed in the very early stages of ontogenetic development and the intestinal microbiota no longer represents an agglomeration of commensal microorganisms but a real dynamic, plastic and systemic psychoneuroendocrinoimmunological organ, capable of acting as the undisputed director of the pathway.

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Rosario Savino – *The trajectories of neurodevelopment: a PNEI and evolutionary path between genetics, epigenetics and integrated clinics*

This article examines in depth the neuro-developmental trajectory of the child from conception to the first years of life, focusing on the critical stages of typical and atypical neurodevelopment. Through the lens of Psychoneuroendocrinoimmunology (PNEI), the overcoming of genetic determinism in favor of a dynamic and probabilistic model, where epigenetics plays a central role, is analyzed. The theoretical frameworks of the exposome and DOHaD (Developmental Origins of Health and Disease) are explored, highlighting the impact of environmental factors, maternal-fetal stress and maternal immune activation (MIA) on brain connectomics and on the genesis of neurodevelopmental disorders (NDD), with particular reference to the autism spectrum (ASD).

Gloria Curati – *Body, movement and physical activity. Opportunities for the evolution of the child through affective and therapeutic touch*

The article explores the fundamental role of affective and therapeutic touch and movement in infant neurobiological development, through the paradigm of Psychoneuroendocrinoimmunology (PNEI). Physical contact is not limited to a mechanical act, but constitutes a pre-verbal language and a primary biological modulator, capable of activating C-tactile fibers and stimulating the release of oxytocin.

Federica Lavista – *The pubertal crisis between metamorphosis and identity, between dependence and independence*

The pubertal crisis constitutes a critical developmental stage in which neurobiological transformations, new hormonal structures and unprecedented relational experiences intertwine, configuring the conditions for a progressive redefinition of identity. From a neurobiological point of view, selective synaptic pruning and progressive myelination remodel the reward circuits – the mesocorticolimbic system with the nucleus accumbens (NAc) and the ventral tegmental area (VTA) – influencing motivation, emotional regulation and behavior.

Silvia Moneti – *Taking care of the environment to take care of the baby: from the delivery room to the classroom*

Through a review of the scientific literature, the article explores the role of the built environment as a determinant of child health and development. The evidence examined demonstrates how specific design characteristics, including acoustic quality, lighting, color, thermo-hygrometric comfort and spatial organization, are able to influence neurobiological processes, sensory development, emotional regulation, learning and social inclusion.

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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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Editorial

Capitalist Societies Are Boiling Pots: Young People, Every Now and Then, Come Out of the Lid

Francesco Bottaccioli*

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The public debate focused, again, on young people. Always with the same name: surprise! The young people, who, in the constitutional referendum, buried the Italian government plan against the judiciary, were a surprise. The pollsters had not seen them. Thus, no one had predicted the violent invasion of the very young in the commercial heart of Milan.

After the images of the looting of fashionable stores, collective theft has become the dominant theme. For the Italian government, teenagers in action are only delinquents to be repressed with yet another security decree. Others, rightly, separate looting from student demonstrations, which have precise political demands, and call for analysis of the social reasons for the apparently blind outbreaks of violence. We make two observations.

First. The damage and looting of shops and other structures, including public ones, is not a new and recent phenomenon. In American history, the most famous episode is that of the 1977 blackout that put New York in total darkness for an entire day, with thousands of shops looted. But the looting also involved large demonstrations of political anger such as after the police assassination of George Floyd. Conclusion: capitalist societies, with their blatant social inequality, which entrusts the poorest and the younger generations to the demons of narcissism, envy, aggression, interhuman competition without ethical constraints, are pots in permanent boiling, which occasionally have outbursts of various violence. For this reason, repression only aggravates the sources of malaise.

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Second. Speaking of adolescents, families and psychologists are invoked at school. But the issue is much more complex. In this issue of PNEI REVIEW we provide an interpretative model of human development and its disorders, which sees all the main aspects: from parenthood to the formation of brain circuits, to nutrition, to the role of physical contact, up to the architectural spaces in which the new human being grows.

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Psycho-Neuro-Endocrine-Immunology, DOHaD and Mindfulness: Towards an Integrated Model of Prenatal Salutogenesis

Stefania Carbonella*

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Abstract: *Over the past thirty years, the DOHaD (Developmental Origins of Health and Disease) paradigm has radically transformed our understanding of the aetiology of chronic diseases, shifting the focus from genetic determinism to the biological plasticity of early life. This perspective converges naturally with Psycho-Neuro-Endocrine-Immunology (PNEI), which interprets the organism not as a collection of isolated systems but as an interconnected network in which the nervous, endocrine, immune and metabolic systems engage in constant dialogue with the psychosocial environment.*

The intersection of these two approaches reveals pregnancy as the temporal window of maximum susceptibility and evolutionary opportunity. Within this scenario, the placenta emerges as a sophisticated interface organ, capable of translating maternal environmental stimuli — including stress signals and adaptive responses — into molecular signals that shape the neurodevelopment, hypothalamic-pituitary-adrenal (HPA) axis and metabolic setting of the offspring.

In this research landscape, mindfulness-based practices are emerging as promising non-pharmacological and transdiagnostic interventions. Although scientific evidence has already validated their efficacy in regulating the stress response, autonomic nervous system balance and low-grade chronic inflammation, the hypothesis that such modulation may directly influence fetal programming remains an unexplored frontier of considerable clinical potential.

The present review aims to bridge this gap by offering a critical synthesis that integrates contemplative neuroscience, polyvagal theory, epigenetics and perinatal medicine. Through the pro-

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posal of an original theoretical model, it explores how maternal neurovegetative regulation — analysed in terms of heart rate variability (HRV) and placental communication — may act as a systemic determinant of health. From this perspective, mindfulness is redefined not merely as a tool for distress reduction, but as an active modulator of salutogenic processes, capable of fostering, from the earliest stages of development, the biological foundations of human resilience.

Keywords: *Developmental Origins of Health and Disease (DOHaD), fetal programming; mindfulness, heart rate variability (HRV), salutogenesis, placenta.*

Introduction

The Developmental Origins of Health and Disease (DOHaD) paradigm has marked a decisive conceptual transition, overcoming genetic determinism in favour of a dynamic model in which adult health is shaped from the earliest stages of development (Barker, 1998; 2004; Gluckman *et al*., 2008). Barker's epidemiological evidence demonstrated that low birth weight is predictive of chronic diseases in adulthood, identifying gestation as a critical window of biological plasticity (Barker, 1990; 1995; Hanson & Gluckman, 2011). Through predictive adaptive responses (PARs), the fetus modulates its phenotype in response to maternal signals; however, a potential developmental mismatch between the prenatal and postnatal environment may convert such adaptations into pathological risk factors (Gluckman & Hanson, 2005).

PNEI defines this programming as a systemic phenomenon mediated by bidirectional communication among the nervous, endocrine, immune and metabolic systems (McEwen, 1998; 2007; Ader, 2007; Bottaccioli & Bottaccioli, 2017). Pregnancy thus becomes a complex ecosystem in which maternal psychophysiological variables — from inflammation to stress regulation — shape fetal development (Van den Bergh *et al*., 2005; 2015; Glover, 2014; O'Donnell & Meaney, 2017).

Adopting Antonovsky's salutogenic perspective, perinatal medicine must evolve toward strengthening maternal-fetal resilience mechanisms, moving beyond mere pathogenic prevention (Antonovsky, 1979; Hanson & Gluckman, 2011). In this context, contemplative neuroscience identifies mindfulness as a systemic modulator capable of influencing the HPA axis, heart rate variability, gene expression and the organisation of neural networks (Kabat-Zinn, 2003; Davidson & McEwen, 2012; Tang *et al*., 2015). Exploring the impact of such practices on fetal programming represents an innovative clinical frontier (Crovetto *et al*., 2023; Nakaki *et al*., 2023). The present review proposes an integrated model of prenatal salutogenesis, synthesising PNEI evidence, polyvagal theory and clinical research on mindfulness-based interventions (Babbar *et al*., 2021).

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DOHaD and Developmental Plasticity: From Fetal Origins of Disease to the Medicine of Salutogenesis

The DOHaD paradigm represents an epistemological turning point in contemporary medicine, having relocated the aetiopathogenesis of chronic diseases from adult maturity phases to the early periods of human development (Barker, 2004). David Barker's epidemiological observations highlighted the correlation between low birth weight and increased incidence of chronic diseases — including ischaemic heart disease, hypertension and metabolic syndrome — in adulthood (Barker, 1990; 1995; 1998). These findings led to the formulation of the Fetal Origins Hypothesis, which postulates that the intrauterine environment exerts a lasting influence on the functional programming of organs and biological systems (Barker, 1995).

The evolution of the DOHaD model, integrated with evolutionary biology, introduced the concept of predictive adaptive responses (Gluckman *et al.*, 2008). Within this framework, the fetus is not a passive organism but a dynamic biological system capable of interpreting maternal environmental signals to adapt its development to anticipated postnatal conditions (Gluckman *et al.*, 2005). The resulting phenotype is the outcome of a continuous interaction between genetic heritage and early biological experience (Gluckman *et al.*, 2008). While such responses are adaptive in predictable contexts (Gluckman & Hanson, 2004), developmental mismatch between the prenatal and postnatal environment may convert these adaptations into factors of pathological susceptibility (Gluckman & Hanson, 2005).

These processes are mediated by epigenetic mechanisms — DNA methylation, histone modifications and microRNA regulation — which modulate gene expression without altering the nucleotide sequence (Meaney & Szyf, 2005; Moore *et al.*, 2013; Meaney, 2010). Within this framework, health is not understood as the mere absence of disease, but as an expression of the organism's adaptive capacity, in accordance with Antonovsky's salutogenic model: whereas the pathogenic paradigm seeks the causes of disease, salutogenesis focuses on the processes that sustain functional stability and resilience in the face of adverse conditions (Antonovsky, 1979).

The current extension of the DOHaD paradigm adopts a life-course perspective, recognising that developmental programming begins in the preconception phase and continues throughout the entire perinatal pathway. PNEI provides the essential theoretical framework for decoding this network of interactions (Bottaccioli & Bottaccioli, 2017): maternal stress is not a mere emotional experience, but a systemic event involving the HPA axis, autonomic nervous system, immune response, energy metabolism and epigenome (McEwen, 1998; 2007; Ader, 2007). This convergence confirms that the intrauterine environment constitutes a dynamic biological ecosystem, constantly shaped by bidirectional communication between mother and fetus (O'Donnell & Meaney, 2017).

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The Placenta: Neuroendocrine, Immune and Epigenetic Hub

The placenta is not a mere passive filter for nutritional exchange, but an organ of biological integration that translates maternal experience into developmental instructions for the fetus. As a neuroendocrine organ, it synthesises crucial mediators such as CRH (corticotropin-releasing hormone), capable of critically modulating the maternal-fetal HPA axis (Bronson & Bale, 2016; Kramer & Bale, 2023; Ragusa *et al.*, 2025). Placental immune function maintains a delicate balance at the maternal-fetal interface via cytokines and decidual cells; alterations in this profile are associated with fetal growth restriction, preeclampsia and neurodevelopmental dysfunctions (Burton & Fowden, 2015).

A fundamental protective mechanism is represented by the enzyme 11β-HSD2, which inactivates maternal cortisol, preventing chronic fetal exposure to glucocorticoids (Seckl & Holmes, 2007). Stress, inflammation and malnutrition may inhibit this enzymatic barrier, altering HPA axis programming and the neurobiological development of the offspring (Hodyl *et al.*, 2017). Concurrently, the placenta serves as an epigenetic interface, sensitive to variations in DNA methylation, microRNA regulation and histone modifications induced by maternal factors such as psychological stress, obesity or exposure to toxins (Kramer *et al.*, 2023).

Systemic integration is completed by the gut-brain-placenta axis, wherein maternal microbiota metabolites modulate trophoblastic function and the gestational immune profile (Cryan *et al.*, 2019). This bidirectional communication positions the placenta at the centre of the systemic pregnancy response (Dinan & Cryan, 2017; Hsiao *et al.*, 2013), defining it as a genuine "sensory organ" capable of transducing endocrine, metabolic and autonomic signals into biological input for the fetus. This view transcends functional reductionism, enshrining the central role of the placenta in mediating fetal plasticity and long-term health trajectories.

Prenatal Stress, HPA Axis and Neurobiological Programming

Maternal stress represents a critical environmental factor for fetal developmental programming, configuring itself, according to the PNEI paradigm, as a systemic event involving the HPA axis, autonomic nervous system and immune response (McEwen, 2007). Although physiological activation of the HPA axis is necessary for fetal pulmonary and metabolic maturation (Van den Bergh *et al.*, 2005), the chronic hyperactivation associated with Early Life Stress (ELS) results in prolonged exposure to glucocorticoids, potentially maladaptive for neurobiological development (Monk *et al.*, 2019; Sandman *et al.*, 2018).

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Under conditions of chronic stress, reduced barrier efficacy of 11β-HSD2 increases transplacental cortisol passage, altering neurogenesis, synaptogenesis and neuronal differentiation (Hodyl *et al.*, 2017). The role of systemic inflammation is additional: the increase in pro-inflammatory cytokines (IL-6, TNF-α) may compromise fetal microglial maturation, conditioning brain developmental trajectories (Slavich & Irwin, 2014). Neuroimaging studies confirm that elevated levels of prenatal stress are associated with structural and functional alterations in the amygdala, hippocampus, prefrontal cortex, cingulate cortex and insula (O'Donnell & Meaney, 2017; Buss *et al.*, 2012; Sandman *et al.*, 2015; Lautarescu *et al.*, 2021; Van den Bergh *et al.*, 2020; Thomason & Hendrix, 2024).

These alterations should not be interpreted as irreversible damage, but rather as modifications of maturational trajectories, intrinsically amenable to remodelling through positive postnatal environmental influences (Glover, 2014; Van den Bergh *et al.*, 2020). Fetal programming indeed creates a probabilistic vulnerability, not an immutable biological fate, confirming the permanent plasticity of the nervous system and validating the opportunity for interventions aimed at promoting biological resilience (Van den Bergh *et al.*, 2020).

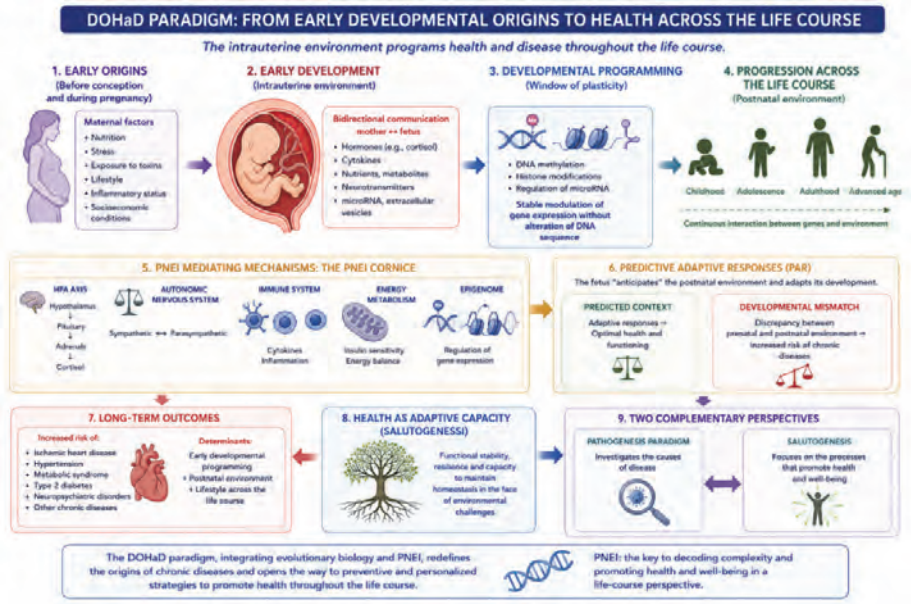


Fig. 1. DOHaD paradigm: from early developmental origins to health across the lifespan

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The Autonomic Nervous System (ANS) as Mediator of Maternal-Fetal Communication

The Autonomic Nervous System (ANS), far from being a mere visceral effector system, is a complex regulatory network that coordinates cardiovascular, endocrine, immune and metabolic activity (Benarroch, 1993; Thayer & Lane, 2009; Critchley & Harrison, 2013). This function is mediated by the Central Autonomic Network (CAN), a network that integrates cognitive, emotional and homeostatic processes through structures such as the prefrontal cortex, insula and amygdala (Benarroch, 1993; Beissner *et al.*, 2013; Valenza *et al.*, 2019; Thayer *et al.*, 2012; 2025). The CAN modulates the dynamic balance between sympathetic and parasympathetic activation, ensuring the resilience and adaptive capacity of the organism (Craig, 2002; Thayer & Lane, 2009; Shaffer & Ginsberg, 2017).

During pregnancy, this balance is fundamental for maternal cardiovascular remodelling and the maintenance of metabolic homeostasis required for fetal development (Braeken *et al.*, 2017; Sharifiheris *et al.*, 2022). Although direct clinical evidence requires further confirmation, a plausible pathophysiological basis exists for the view that maternal autonomic regulation influences uteroplacental function and the fetal environment (Cerritelli *et al.*, 2021; Van den Bergh *et al.*, 2020). Porges' polyvagal theory (2022) underscores how vagal tone reflects the capacity to maintain biological safety and emotional regulation, with elevated parasympathetic activity associated with reduced systemic inflammation.

Heart rate variability (HRV) constitutes the primary non-invasive biomarker of such neurovegetative flexibility (Pinto *et al.*, 2025; Widatalla *et al.*, 2025). Through the cholinergic anti-inflammatory reflex, the vagus nerve modulates inflammation by inhibiting cytokine production (Tracey, 2002). Interventions such as mindfulness and slow breathing, by increasing vagal tone and HRV, offer indirect protective mechanisms for the fetal environment (Lehrer & Gevirtz, 2014; Kramar, 2025; Thayer & Lane, 2009; Braeken *et al.*, 2017; Sharifiheris *et al.*, 2022). Observational studies on maternal-fetal physiological synchrony suggest the existence of co-regulation processes (DiPietro *et al.*, 2006). Although direct causality on fetal programming remains under investigation, the convergence of PNEI data renders it biologically plausible that ANS modulation represents a pillar of prenatal salutogenesis (Van den Bergh *et al.*, 2020; Babbar *et al.*, 2021; Cerritelli *et al.*, 2021).

Contemplative Neuroscience and Neurobiological Regulation

Over the past two decades, contemplative neuroscience has provided important

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evidence on the neurobiological correlates of mindfulness, demonstrating how regular practice is associated with functional modifications in brain networks involved in attention, interoceptive awareness, emotional regulation and cognitive control (Calderone *et al.*, 2024; Rafter *et al.*, 2026; Tang *et al.*, 2015). Neuroimaging studies have identified three principal connectivity systems — the Default Mode Network (DMN), the Salience Network (SN) and the Central Executive Network (CEN) — whose modulation is associated with reduced rumination, enhanced interoceptive awareness and strengthened attentional and emotional regulation (Menon, 2011; Menon & Uddin, 2010; Menon *et al.*, 2023; Bremer *et al.*, 2022; Tang *et al.*, 2015).

Of particular relevance is the down-regulation of the amygdala response, with consequent reduction in stress reactivity and enhanced connectivity with the prefrontal cortex (Taren *et al.*, 2015; Desbordes *et al.*, 2012). These neurofunctional modifications, interpretable as a strengthening of top-down control over limbic circuits, are accompanied by a reduction in cortisol and pro-inflammatory cytokine production, confirming the systemic action of mindfulness (Creswell *et al.*, 2014).

The neurobiological effects of mindfulness also extend to epigenetic modulation. Studies on expert practitioners have documented gene expression modifications, with down-regulation of NF-κB-mediated pro-inflammatory pathways and up-regulation of genes associated with cellular repair and antioxidant response (Kaliman *et al.*, 2014; Buric *et al.*, 2017; Venditti *et al.*, 2020; Venditti, 2025). Such effects have also been observed in the modulation of the epigenetic clock, suggesting a potential impact on biological ageing (Chaix *et al.*, 2017).

Mindfulness in Pregnancy: Clinical Evidence and Mechanisms of Action

The application of mindfulness-based interventions in the perinatal setting has registered significant growth. Randomised clinical trials have demonstrated that programmes such as Mindfulness-Based Childbirth and Parenting (MBCP) significantly reduce anxiety, stress and depression levels in pregnant women (Duncan & Bardacke, 2010; Findik *et al.*, 2025; Gheibi *et al.*, 2020). A meta-analysis by Min *et al.* (2023) confirmed the efficacy of such interventions also in preventing postpartum depression.

At the psychophysiological level, mindfulness during pregnancy is associated with increased HRV and reduced blood pressure, indicative of improved autonomic balance (Braeken *et al.*, 2017; Natarajan, 2023; Barbry *et al.*, 2026). The impact also extends to infant development: the IMPACT BCN study documented favourable effects of mindfulness-based stress reduction (MBSR) on fetal and neonatal brain development, assessed through neuroimaging (Crovetto *et al.*, 2023; Nakaki *et al.*, 2023; Gomez *et al.*, 2025).

Emerging evidence further suggests that maternal mindfulness may modulate

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neonatal autonomic and behavioural reactivity (Noroña-Zhou *et al.*, 2022). These data, albeit preliminary, support the hypothesis that mindfulness represents an epigenetic and neurophysiological modulator capable of influencing developmental trajectories through the regulation of maternal stress response systems (Black & Slavich, 2016; Dunn & Dimolareva, 2022; Bower & Irwin, 2016; Walton *et al.*, 2023).

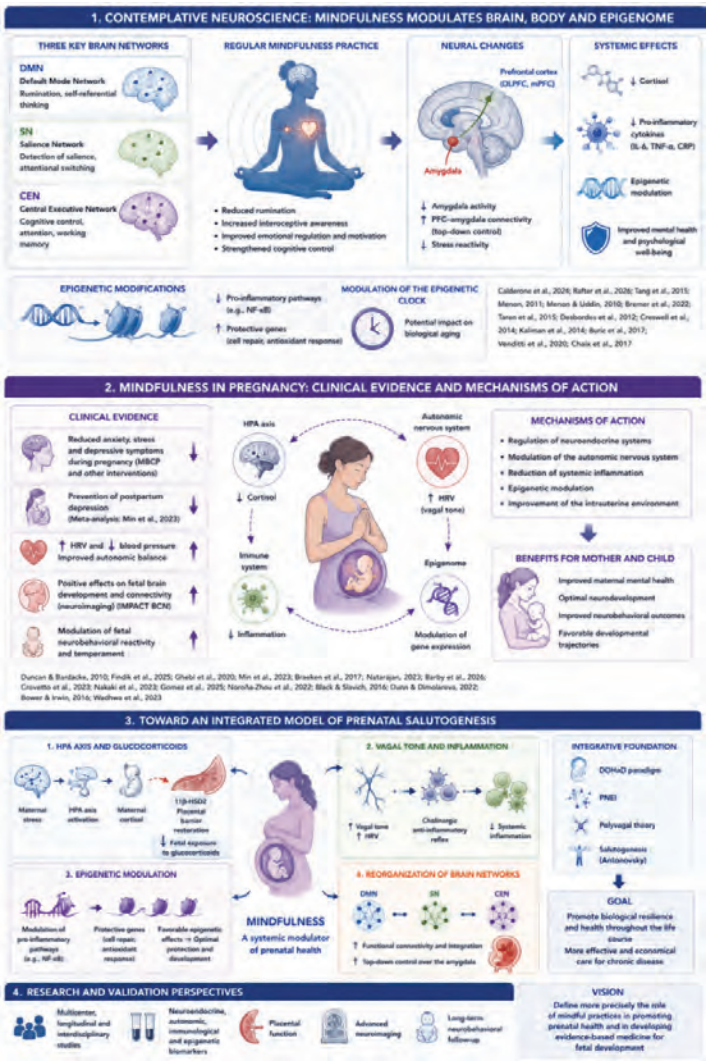


Fig. 2. The PNEI Integrated Model of Prenatal Salutogenesis and Contribution to the Salutogenesis of Meditative Practices

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Towards an Integrated Model of Prenatal Salutogenesis

The evidence reviewed thus far converges in delineating an integrated model in which maternal neurovegetative regulation acts as a systemic determinant of fetal health. Within this framework, mindfulness is configured not merely as an intervention for reducing psychological distress, but as an active modulator of salutogenic processes, capable of influencing the intrauterine environment through neuroendocrine, autonomic, immune and epigenetic mechanisms.

The proposed model rests on four interconnected axes: (1) regulation of the HPA axis and reduction of fetal glucocorticoid exposure, mediated by the restoration of the placental 11β-HSD2 enzymatic barrier; (2) enhancement of vagal tone and HRV, with consequent modulation of the cholinergic anti-inflammatory reflex and reduction of maternal systemic inflammation; (3) epigenetic modulation, with down-regulation of pro-inflammatory pathways and up-regulation of protective genes; (4) functional reorganisation of brain networks involved in emotional and interoceptive regulation, with particular reference to DMN-SN-CEN connectivity and top-down control over the amygdala.

This model finds its foundation in the convergence of the DOHaD paradigm, PNEI and polyvagal theory, and aligns with Antonovsky's salutogenic perspective, according to which promoting biological resilience is more effective and cost-efficient than treating overt pathology.

The clinical validation of this model will require multicentre, longitudinal and interdisciplinary studies integrating neuroendocrine, autonomic, immune and epigenetic biomarkers, measures of placental function, advanced neuroimaging techniques and follow-up of offspring neurobehavioural development. Only through this systemic approach will it be possible to define more precisely the role of integrative medicine interventions in promoting prenatal health and developing a genuinely evidence-based developmental medicine.

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Parenthood: The Keystone. The Parental Brain, Development, and Salutogenesis Parental Functioning as the Conductor of Adult Health Outcomes

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***Abstract**: The transition to parenthood has undergone a radical structural and conceptual evolution in recent decades, driven by unprecedented demographic shifts and rapidly changing family paradigms. These societal changes are profoundly reshaping the psychological and clinical framework of parenthood. Concurrently, discoveries in cognitive neuroscience and psychoneuroendocrinoimmunology (PNEI) have revealed that this transition represents a unique biological window, characterized by extraordinary adult neuroplasticity and epigenetic vulnerability. Neuroimaging studies confirm that entering parenthood triggers extensive anatomical remodeling in both biological and non-biological (or non-gestational) parents.*

However, this heightened neuroplasticity also renders the parental brain highly vulnerable to environmental and psychosocial stressors. Untreated parental distress compromises interactional synchrony and introduces severe transgenerational risks, predicting an increased susceptibility to emotional, behavioral, and even psychotic symptoms in the adult offspring. Furthermore, under the weight of modern socioeconomic pressures and unmitigated stress, parents face the risk of parental burnout.

Therefore, building a robust culture of health and well-being that is both equitable and sustainable requires an intersectoral and multidimensional framework where governmental *institu-*

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tions, healthcare systems, commercial enterprises, local communities, and individual citizens share a collective responsibility.

***Keywords**: Parenthood, matrescence, perinatal depression, parental burnout.*

Scenarios of Parenthood

The term parenthood (or parenting) defines a set of complex, continuously evolving functions and competencies. These pertain to an adult individual's capacity to protect, care for, and affectively and socially regulate – within a relationship – another individual who, due to their developmental stage or specific psychophysical conditions, requires the presence of a figure capable of recognizing and satisfying their needs (Venuti *et al.*, 2018).

In recent decades, the transition to parenthood has assumed distinct characteristics that have substantially altered its nature compared to the recent past. This new configuration is documented by the latest indicators from the National Institute of Statistics (Istat, 2026), which reveal that births in Italy stand at 355,000, marking a 3.9% decrease compared to 2024. The decline in fertility continues, dropping to 1.14 children per woman in 2025, while life expectancy remains high, reaching 81.7 years for men and 85.7 years for women in 2025. Couples with children constitute 28.4% of families, while those without children account for 20.2%. Concurrently, the average age at childbirth has risen to 32.7 years. Over the years, single-parent families have increased, now representing one in ten families; these are predominantly single mothers (8.6%), though cases of single fathers with children are also evident (2.2%).

Likewise, couples' expectations regarding the parental role have shifted; its boundaries are no longer as clearly demarcated and defined as they were in the traditional family, yielding to a fully shared parental responsibility. The pluralization of family forms and the emergence of new family identities have shifted the focus of research and clinical family assessment toward the study of coparenting, as well as paternal and maternal functions that transcend gender definitions. As highlighted in a previous article published in this journal (De Bari, Terni, 2023), research has repeatedly demonstrated that children who do not share a biological bond with their parents do not differ in adjustment from those who do. Similarly, no correlation emerges between parents' sexual orientation and any measure of the child's emotional, psychosocial, or behavioral adjustment. Across diverse family configurations, high levels of parental stress, interparental conflict, and an imbalance between affective and ethico-normative functions are what consistently predict long-term maladjustment in the offspring.

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Becoming Parents is a PNEI experience

The developmental window spanning from conception to the first 6,000 days of life is characterized by extraordinary neuroplasticity and heightened biological vulnerability, driven by intense epigenetic activity and the dynamic, bidirectional processes within the parent-child dyad. Investigating the psychoneuroendocrineimmunological (PNEI) complexity underlying the intersubjective and affective dynamics between parents and their offspring is of paramount importance for promoting long-term well-being and safeguarding health trajectories into adulthood.

During fetal life and the first two years postpartum – a critical phase of profound plasticity – epigenetic mechanisms are highly active. Environmental inputs during this period are capable of altering brain architecture, the composition of the infant's gut microbiota, and endocrine-metabolic and immunological programming, thereby exerting a lasting influence on the behavior of both the child and the future adult. Consequently, it is essential for parents and expectant parents to recognize that a nurturing and supportive environment acts as a primary driver of health promotion, whereas an adverse environment can serve as a factor of systemic vulnerability contributing to the pathogenesis of current or future chronic diseases (Carbonella, Gandini, 2023).

The transition to parenthood is a profound developmental journey marked by complex, interconnected changes that reshape nearly every aspect of a new parent's life. Recent neuroimaging research highlights that entering parenthood involves a remarkable degree of adult brain plasticity and physiological adaptation, demonstrating how these biological processes facilitate and support the highly complex cognitive and behavioral demands of caregiving (Servin-Barthet *et al.*, 2023) and emotional attunement with one's children (Carmona, Vilarroya, 2025).

Structural Brain Plasticity in Matrescence and Patrescence

During pregnancy and the postpartum period, significant neural plasticity occurs within both the structure and function of the adult brain, serving as an essential neurological adaptation for infant care. The "parental brain network" comprises interconnected structures critical for empathy, emotion regulation, executive functions, decision-making, threat assessment, motivation, and reward processing.

The structural and functional mapping of the human parental brain has only recently become a primary focus of cognitive neuroscience. The most robust neuroimaging findings to date concern the specific extent to which gray matter volumes undergo profound anatomical remodeling during pregnancy and the postpartum peri-

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od. Recent prospective studies (Pawluski, 2024) demonstrate that, from the preconception period to the early postpartum weeks, primiparous mothers undergo extensive reductions in gray matter volume – amounting to approximately 1% – localized predominantly within brain regions responsible for social cognition.

The brain structures most affected by pregnancy are those underlying the capacity to mentalize or to cognitively infer the needs of others (Theory of Mind, ToM), rendering these structural changes highly functional and fundamental for effective caregiving. These anatomical modifications are remarkably consistent, with 92% of mothers showing similar patterns of structural remodeling; furthermore, these volumetric reductions correlate strongly with circulating progesterone levels during the third trimester and can persist for several years postpartum (Hoekzema, 2022).

Recent data show that these reductions in gray matter volume accelerate during late pregnancy and can be significantly modulated by the mode of delivery in the immediate postpartum period. For instance, Paternina-Die *et al.* (2024) demonstrated that mothers who underwent a scheduled cesarean section (prior to the onset of spontaneous labor) exhibited a significantly greater increase in cortical volume, thickness, and surface area from pregnancy to the postpartum period compared to mothers who experienced spontaneous labor, independent of gestational age, maternal age, and other potential confounding variables. This clinical evidence suggests that the acute immune and endocrine processes triggered during active labor and delivery exert a direct modulating impact on maternal neurostructural adaptations.

During the early postpartum weeks and months, mothers exhibit a subsequent increase in gray matter volume within subcortical and cortical areas associated with reward, bonding, and ToM, such as the amygdala and the ventral striatum. Conversely, in first-time fathers, longitudinal neuroimaging assessments during pregnancy and the first years of parenthood reveal an approximate 1% reduction in gray matter volume within cortical networks responsible for visual processing, attentional allocation, and empathy.

Although the differential impact of multiple or subsequent pregnancies on these structural brain modifications remains to be fully elucidated in humans, longitudinal animal laboratory models suggest that parity history exerts a cumulative influence on the maternal brain. Straathof *et al.* (2026) conducted a prospective preconception cohort study involving 110 women, utilizing multimodal neuroimaging data to compare the effects of a second pregnancy versus first pregnancies and nulliparous controls. Their analysis evaluated changes in gray matter volume, resting-state functional connectivity, the microstructural organization of white matter tracts, and neuronal metabolite concentrations.

The results highlight distinct volumetric trajectories: both first and second

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pregnancies are associated with widespread reductions in cortical volume compared to nulliparous controls. However, this volumetric reduction is significantly more pronounced in primiparous women (3.1%) compared to multiparous women (2.8%). Furthermore, the common neurostructural alterations shared between the first and second pregnancies are localized primarily within the Default Mode Network (DMN), the frontoparietal network, and the ventral attention network. Crucially, the first pregnancy exhibits more extensive structural alterations across these specific networks, whereas the second pregnancy more selectively involves the somatomotor and dorsal attention networks.

The DMN plays a well-documented role in introspection, self-referential processes, and social cognition (Davey *et al.*, 2016). Together with the cuneus – the primary anatomical region where the differential effects of a first versus a second pregnancy on functional network coherence were observed – it represents the core neural architecture underlying the structural representation of the self. During the transition to parenthood, structural and functional remodeling within these neural networks drives profound modifications in maternal self-perception and enhances the mother's capacity to accurately interpret the physiological needs and emotional states of her offspring (Hoekzema *et al.*, 2022).

Regarding maternal behavior and mental health, Straathof *et al.* (2026) observe that in both first and subsequent pregnancies, these neurostructural adaptations are associated with peripartum depression and psychological distress, although they present distinct temporal profiles. In primiparous women, this correlation culminates during the postpartum period, whereas in multiparous women, it manifests predominantly during gestation. This longitudinal evidence underscores that both first and second pregnancies leave a unique and distinct imprint on the female brain, characterized by specific alterations in gray matter morphology, white matter tracts, and resting-state functional connectivity.

The first pregnancy induces a "primary adaptation" of the neural networks governing introspection, self-perception, and social cognition (DMN and frontoparietal cortex), which is subsequently refined and consolidated during the second pregnancy. Conversely, subsequent pregnancies appear to enhance the neuroplasticity of externally oriented networks, such as the somatomotor and attentional networks, likely to meet the increased behavioral and caregiving demands associated with managing multiple children. Although these pregnancy-induced neural alterations are partially reversible, selected structural modifications can persist for years after childbirth.

Matrescence (Carmona, 2019; 2025) constitutes a fundamental developmental transition encompassing the pre-conception period, pregnancy, childbirth, or alternative pathways to parenthood such as surrogacy and adoption, extending

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through the postnatal period and beyond (Raphael, 1975; Athan, 2024, 2025). This transition is experienced by 80-90% of women globally (Livingston, 2018).

A recent narrative review by Worska *et al.* (2026) synthesized current evidence on the profound hormonal and neuroplastic fluctuations characterizing the maternal brain during pregnancy and the postpartum period, critically evaluating their implications for cognitive function and mental health. The literature demonstrates a U-shaped trajectory in gray matter volume changes, alongside adaptive regional alterations within the hippocampus, amygdala, and prefrontal cortex. These neural dynamics are closely linked to the subjective phenomenon of "mommy brain" (momnesia), which is characterized by forgetfulness, distractibility, and decreased mental clarity. Chief among the contributing factors to this cognitive fog are sleep deprivation, the high mental load of household management, and the hypervigilance required for infant care. Furthermore, executive functions – including planning, cognitive flexibility, and inhibitory control – undergo remodeling secondary to structural changes in the prefrontal cortex.

In fathers, the investigation into structural brain plasticity is a rapidly expanding field (Abraham *et al.*, 2022). Emerging data indicate that during the transition to parenthood, the paternal brain undergoes an approximate 1% reduction in gray matter volume within cortical structures responsible for visual processing, attention, and empathy (Martinez-Garcia *et al.*, 2023). Longitudinal reductions in paternal gray matter volume during the first four months postpartum are positively associated with sensitive and synchronous caregiving behaviors. These changes specifically involve subcortical and cortical regions implicated in reward processes, bonding, and Theory of Mind (ToM), including the amygdala and striatum (Kim *et al.*, 2014).

Fathers who are more deeply engaged in direct childcare exhibit neural activation profiles that mirror maternal brain adaptations. This aligns with preclinical literature demonstrating that paternal neural modifications can be environmentally driven and flexibly activated by direct, prolonged exposure to offspring (Feldman, 2015). Finally, contemporary research indicates that the experience of transitioning to parenthood is associated with widespread reductions in gray matter volume across multiple brain areas in both gestational and non-gestational parents (Pawluski, 2024). While much remains to be elucidated regarding the structural plasticity of the parental brain, it is clear that pregnancy hormones are not the sole drivers of these neural changes; the behavioral experience of parenting itself plays a fundamental role.

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Perinatal Distress, Neurobiological Dysfunction, and Clinical Outcomes

Parent-infant interactions rely on tightly regulated patterns of behavioral activation and deactivation, dictated by the salience of infant cues and the caregiver's capacity to attune to the infant's emotional and physiological needs. This attunement enables parents to provide adaptive responses that are fundamental to infant survival and attachment security. Affective relationships activate emotional salience circuits through the involvement of the basolateral nuclei of the amygdala. By interacting with dopaminergic motivational pathways, this system enhances the salience of infant sensory signals, driving the adult toward proximity-seeking and caregiving behaviors.

The Salience Network (SN) is a core intrinsic connectivity network anchored in the anterior insula and the dorsal anterior cingulate cortex (dACC). At the subcortical level, it integrates the amygdala, hippocampus, ventral striatum, ventral tegmental area (VTA), hypothalamus, thalamus, and substantia nigra – structures collectively involved in nurturing behaviors and autonomic responses (Seeley, 2019). Dysregulated SN activity is linked to maladaptive behavioral phenotypes observed across various clinical conditions, including mood disorders, neurodegenerative diseases, autism, schizophrenia, epilepsy, insomnia, chronic pain, and post-traumatic stress disorder (PTSD).

In the parenting context, SN dysregulation disrupts the neural predictive coding of stimuli, compromising parental interoceptive processes and hindering the formation of a secure caregiver-infant bond (Schimmelpfennig *et al.*, 2023). This disruption, in turn, negatively impacts the trajectory and expression of cognitive development in the offspring (Cermakova *et al.*, 2023).

Parental stress – the physiological and psychological response to the ongoing demands of childcare – acts as a critical modulator of parenting-related brain remodeling (Rutherford, Mayes, 2019). Chronically elevated levels of perceived parental stress are strongly associated with perinatal depression, a burden faced by a significant percentage of parents during gestation and the postpartum period (Pawluski *et al.*, 2017).

The most common postpartum emotional disturbance is the "baby blues" which affects the majority of new mothers immediately after delivery. Characterized by transient mood lability, physical exhaustion, anxiety, and role uncertainty, the baby blues typically resolve spontaneously within two weeks. In contrast, clinical perinatal mental disorders exert lasting negative effects on parental health, caregiving dynamics, and child development (Stein *et al.*, 2014).

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During the postpartum period, high maternal stress is linked to reduced functional activity in areas responsible for decision-making and emotion regulation, such as the orbitofrontal gyrus and the amygdala. Specifically, gestational mothers (but not fathers) who report higher levels of stress exhibit reduced neural synchrony with their children (aged 3-4 years) in regions essential for attention, working memory, and cognitive control, including the inferior frontal gyrus and the dorsolateral prefrontal cortex (dlPFC) (Azhari *et al.*, 2019; Nguyen *et al.*, 2021).

From a physiological perspective, mothers who exhibit less reactive circulating cortisol response profiles during the Strange Situation paradigm show a paradoxically increased neural activation to infant distress cues within brain regions governing motivation, empathy, and emotion regulation, such as the striatum, the medial prefrontal cortex (mPFC), the anterior cingulate cortex (ACC), and the insula (Laurent *et al.*, 2011). These data demonstrate a direct link between hypothalamic-pituitary-adrenal (HPA) axis dynamics, maternal neural responsiveness, and parenting quality.

Perinatal depression (PND) represents a highly prevalent complication of the perinatal period, affecting an estimated 10-20% of women. Longitudinal quarterly estimates indicate prevalence rates of 7.4% in the first trimester, 12.8% in the second, and 12.0% in the third, culminating in a cumulative gestational prevalence of 20.4%. Antenatal depression (AND) significantly compromises both maternal well-being and fetal development, adversely altering obstetric outcomes and subsequent child cognitive trajectories. Mothers at high risk for AND frequently present with poor self-care (e.g., nutritional deficiencies, substance abuse), interpersonal conflicts, and an elevated risk of future severe mood disorders or suicide.

Fetal and neonatal risks associated with AND include preterm birth, low birth weight, intrauterine growth restriction (IUGR), and neurocognitive developmental deficits. Infants born preterm or with low birth weight face increased susceptibility to neurocognitive impairments, global developmental delays, and psychomotor deficits (Stoll *et al.*, 2004). Over the long term, children exposed to untreated maternal AND exhibit higher rates of behavioral disorders, cognitive delays, and the onset of clinical depression during adolescence (Stein *et al.*, 2014).

Postpartum depression (PPD) constitutes the most frequent clinical complication of childbirth. A recent review by Wenzel *et al.* (2025) identified distinct cortical thickness alterations among mothers with PPD, particularly within regions responsible for empathy (e.g., the insula) and sensory integration (e.g., the parietal lobe). Postpartum depressive symptoms correlate with increased resting-state activity in the right frontal lobe.

Furthermore, mothers with PPD comorbid with high levels of anxiety exhibit significantly weakened functional connectivity among the amygdala, ACC, dlPFC, and hippocampus compared to healthy postpartum controls. Conversely, increased corti-

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cal thickness is observed in frontal and occipitotemporal regions – including the superior frontal gyrus, the cuneus, the lingual gyrus, and the fusiform gyrus – which regulate emotional processing, visual analysis, and maternal responsiveness.

Task-based fMRI paradigms further reveal altered neural processing of emotionally salient, infant-related stimuli in PPD. When exposed to infant crying, healthy comparison mothers show robust activation of the striatum, thalamus, and ACC, whereas depressed mothers demonstrate reduced activation in these regions. Similarly, when viewing their own infant's face, mothers with PPD show reduced functional connectivity between the amygdala and the right insula, suggesting a selective breakdown in the integration of the Salience Network (Wenzel *et al.*, 2025).

Early postpartum mood symptoms also correlate with a reduced recruitment of prefrontal reward-related circuits, specifically the subgenual and pregenual ACC (Chechko *et al.*, 2023). However, among mothers experiencing high depressive symptomatology, an increased striatal response to emotional cues is predictive of more positive and sensitive caregiving, suggesting a compensatory recruitment of the neural reward system to preserve parenting behavior (Morgan *et al.*, 2017).

Paternal Postpartum Depression and Long-Term Outcomes in the Offspring

A meta-analysis by Álvarez-García *et al.* (2024), involving over one million participants across more than 30 countries, established that paternal postpartum depression is a substantial public health issue, with prevalence rates of 9.76% in the prenatal period and 8.75% in the postnatal period, often persisting beyond the first year after childbirth. Depressed fathers exhibit lower emotional availability, reduced rates of positive interaction, and elevated levels of irritability or withdrawal during caregiving routines.

The offspring of depressed fathers face a significantly higher risk of developing internalizing and externalizing symptoms, including anxiety, oppositional defiant behavior, and emotional dysregulation, particularly when paternal withdrawal coincides with critical developmental windows. A longitudinal cohort study of 1,089 American families demonstrated that paternal depression when the child was 3 years old significantly predicted a higher probability of child neglect by age 5. Similarly, paternal depression correlates with a less synchronous and less positive father-infant interactive style, which acts as a direct predictor of escalating behavioral problems in early childhood (Abraham, Feldman, 2022).

Investigating the long-term transgenerational effects of parental mood disorders, Feibel *et al.* (2026) conducted a prospective longitudinal cohort study tracking the timing of exposure to parental depression (from gestation to early adulthood)

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on the offspring's mental health in adulthood (22-27 years). Their primary findings linked parental depression to specific adult offspring phenotypes: depressive symptoms at age 27, anxiety disorders at age 25, clinical psychotic symptoms at age 24, and alcohol use disorders (AUD) at age 22.

Notably, maternal depression starting from the 32nd week of gestation was strongly associated with clinical depression in the offspring at 18 years of age. Maternal depression occurring from 8 months postnatal onward was uniquely predictive of anxiety symptoms in the offspring at age 21.

Conversely, paternal depression showed a robust and significant association with both depression and anxiety in the offspring, extending from middle childhood (5 years) into early adulthood (21 years). Only prenatal maternal depression at the 32nd gestational week was significantly associated with the emergence of psychotic symptoms in the adult offspring, highlighting a unique window of prenatal vulnerability.

Parenthood in Crisis: Etiology and Dynamics of Parental Burnout

In the modern socioeconomic landscape, parents report lower self-efficacy and higher performance pressures compared to previous generations. When individuals face chronic and unmitigated parental stress that exceeds their internal and external coping resources, they become highly vulnerable to Parental Burnout (PB). This distinct psychological syndrome affects both mothers and fathers and is defined by prolonged physical and psychological exhaustion directly linked to the parental role (Bogdán *et al.*, 2025). This exhaustion is typically accompanied by emotional detachment from one's children, overwhelming weariness, and severe self-doubt regarding one's parenting competence (Roskam, Mikolajczak, 2021).

Risk factors that increase vulnerability to PB include a lack of external support systems, single-parent status, a parent's chronic illness, a high number of dependent children, the extremes of parental age (being very young or older parents), professional burnout, pre-existing mental health conditions (e.g., major depressive disorder or generalized anxiety disorder), or caring for a child with chronic medical or neurodevelopmental needs.

The consequences of PB on the offspring are profound; it significantly increases the risk of child neglect, as well as physical and psychological abuse. Over the long term, children exposed to these environments are more likely to develop post-traumatic stress symptoms, engage in self-harm, develop addiction disorders, and exhibit violent behaviors in adulthood (Haj-Yahia *et al.*, 2019). Epidemiological data indicate that 60-80% of neglected children develop insecure attachment styles

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alongside pervasive deficits in executive functions. These impairments affect cognitive domains such as mental flexibility, goal setting, attentional control, emotional regulation, and inhibitory control, in addition to deeply disturbed emotional processing (Herrero-Roldán, Martín-Rodríguez, 2025).

The prevalence of PB is projected to increase, driven by an increasingly fast-paced global culture and a concomitant reduction in the social and temporal resources available to families. This risk is further amplified for the "sandwich generation" – parents who simultaneously manage the care of dependent children and elderly, chronically ill parents – who face a double burden of physical and psychological stress. Over time, these chronic psychological stressors frequently somatize, and in severe clinical manifestations, parental burnout can precipitate active suicidal ideation.

Early, proactive screening and continuous monitoring of families must be prioritized within modern healthcare and public health systems through holistic and multidisciplinary collaboration. Established protective factors against PB include achieving an optimal work-life balance and the availability of informal support networks, such as members of the extended family (grandparents, aunts, uncles) (Mikolajczak, Roskam, 2018). Furthermore, an effective social buffering effect can be derived from peer friendships and community support (Hosokawa, Katsura, 2024).

Salutogenesis: A Systemic and Multidisciplinary Framework

The establishment of a virtuous cycle of health to support contemporary families depends entirely on the dynamic interaction between individual well-being, robust social support, and favorable environmental conditions. When parents are healthy and backed by adequate socioeconomic, social, and relational resources, they execute their parental roles more effectively, experiencing lower baseline stress and demonstrating greater sensitivity to their children's needs. Supporting functional parenting directly facilitates the harmonious development of children, who grow up in conditions of emotional security, solid physical health, normative cognitive development, and prosocial competencies. This healthy development subsequently mitigates intra-familial stressors, enhances the overall domestic climate, and reinforces parental well-being.

This systemic cycle requires key macro-environmental inputs, including universally accessible healthcare and mental health services, family-centered social policies, population-level health literacy, integrated community networks, and legislative protections for work-life balance. Parenthood can no longer be evaluated solely through the lens of individual responsibility; it must be sustained by an integrated infrastructure of resources and public policies that promote health across the entire lifespan.

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Building a true culture of health and well-being requires fostering equitable and health-supportive communities, where citizens are empowered as active co-producers of healthy lifestyles (Tziraki-Segal *et al.*, 2019). The fundamental components of this paradigm shift include comprehensive health education across all social strata, professional training frameworks, and policies that mandate person-centered care. This care must address well-informed citizens, community advocates, and legislative leaders, while simultaneously reinforcing civic engagement and a shared sense of community.

A central role within this salutogenic model is occupied by the social determinants of health (SDOH), such as education level, stable employment, income security, adequate housing, safe built environments, and structural social cohesion.

High priority must be assigned to citizen empowerment and active aging through personalized, lifelong interventions focused on physical activity, nutritional optimization, and active social participation. This aligns with European public health initiatives aimed at preventing frailty and developing urban and social environments designed to incentivize sustainable and healthy behaviors (CSDH, 2008).

Building a robust culture of health requires an intersectoral and multidimensional framework where governmental institutions, healthcare systems, commercial enterprises, local communities, and individual citizens share a collective responsibility. Future research must focus on identifying scalable and culturally adaptable interventions, evaluating their efficacy across diverse socioeconomic landscapes, and formulating evidence-based public policies designed to maximize well-being, build psychological resilience, and preserve the long-term sustainability of healthcare systems throughout the lifespan.

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Gut Microbiota: PNEI Director of Developmental Age

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Abstract. *The epistemological transition of modern pediatrics is marked by the overcoming of the reductionist model in favor of a systemic and integrated vision of the human organism. In this scenario, Psychoneuroendocrinoimmunology (PNEI) offers the theoretical framework to understand how adult health is programmed during the very early stages of ontogenetic development (Bottaccioli, Bottaccioli, 2020), and the gut microbiota no longer represents a cluster of commensal microorganisms but a true dynamic, plastic, and systemic psychoneuroendocrinoimmunological organ, capable of acting as the undisputed director of the pathway (Lozupone* et al.*, 2012). Through the use of omics sciences (metagenomics, transcriptomics, metabolomics), contemporary research has revealed the functional profile of this microbial ecosystem (Turnbaugh* et al.*, 2009; Milani* et al.*, 2017), demonstrating how its chemical metabolites integrate into the host's regulatory networks. This article delves into the biochemical and molecular mechanisms through which the microbiota modulates the bidirectional communication axes between the gut, immune system, endocrine system, and central nervous system in the first 1000 days of life (Cryan* et al.*, 2019).*

Keywords: *gut microbiota, psychoneuroendocrinoimmunology (PNEI), developmental age, first 1000 days, early dysbiosis, epigenetics.*

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Introduction and Paradigm Shift: PNEI Network and Pediatric Evolution

Contemporary medicine is experiencing a profound conceptual revolution, marked by the progressive decline of the Cartesian biomedical approach, which for centuries compartmentalized the human body into isolated organs and systems. This old reductionist paradigm has proven insufficient to explain the epidemiological explosion of non-communicable chronic diseases (NCDs), neurodevelopmental disorders, allergies, and metabolic dysfunctions that affect the pediatric population at an increasingly early age. Health and disease must be re-read through the lens of systemic complexity (Bottaccioli, Bottaccioli, 2020).

Psychoneuroendocrinoimmunology (PNEI) stands at the center of this paradigm shift as a scientific discipline that studies the bidirectional relationships between the psyche (cognitive and emotional processes) and the major biological regulation systems: the nervous system, the endocrine system, and the immune system (Bottaccioli, Bottaccioli, 2020).

In this integrated scenario, the discovery of the gut microbiota and its characterization as a "PNEI organ" are of extraordinary interest. Indeed, the gut microbiota actively participates in the modulation of the hypothalamic-pituitary-adrenal (HPA) axis (Sudo *et al.*, 2004), regulates the kinetics of inflammatory and anti-inflammatory cytokines (Belkaid, Hand, 2014), synthesizes neurotransmitters (Yano *et al.*, 2015), and exerts strict control over energetic and endocrine metabolism (Cani *et al.*, 2007; Koh *et al.*, 2016). Developmental age, with its maximum biological plasticity, represents the prime temporal window in which this complex interaction is structured.

Intestinal eubiosis represents the cornerstone of the systemic homeostasis of the growing individual (Lozupone *et al.*, 2012).

Omics Sciences and Functional Profile of the Gut Microbiota

The quantum leap in the study of the gut microbiota has been made possible by the advent and spread of latest-generation omics sciences. Until a few years ago, knowledge of gut microorganisms was limited to classical microbiology techniques based on in vitro culture. Since over 80% of the bacterial species in the human gut consist of strict anaerobes that cannot be cultivated under standard conditions, the true entity and diversity of this ecosystem remained unexplored. Today, the metagenomic approach, through 16S ribosomal RNA gene sequencing and shotgun sequencing of the entire microbial genome, allows precise mapping of community

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taxonomy, identifying the phyla, classes, orders, families, genera, and species present (Turnbaugh *et al.*, 2009; Milani *et al.*, 2017). This methodological transition allows us to truly answer the question: "who is in the gut?". However, the true cognitive revolution has come from the possibility of functional analysis supported by transcriptomics, proteomics, and, most notably, metabolomics. Metabolomics studies the set of low molecular weight metabolites produced by bacterial metabolism starting from substrates introduced via diet or secreted by the host. These molecules constitute the true operational arm of the microbiota and the chemical means through which it exercises its remote directing action on the host's target organs (Sharon *et al.*, 2016). Among the most significant PNEI metabolites are short-chain fatty acids (SCFAs, such as acetate, propionate, and butyrate) (Koh *et al.*, 2016), secondary bile acids, indole derivatives (obtained from tryptophan catabolism), polyamines, and a vast array of microbially synthesized neurotransmitters, including gamma-aminobutyric acid (GABA), serotonin, dopamine, and acetylcholine (Cryan *et al.*, 2019). Metabolome analysis makes it possible to establish a direct causal link between the biochemical activity of the microbiota and the physiological or pathological responses of the host, revealing the fine mechanisms of infant homeostasis by studying "what that particular gut bacterial community does" (Milani *et al.*, 2017).

Developmental Age as a Programming Window and the First 1000 Days

David Barker's concept of "fetal and neonatal programming" (Early Life Programming) postulates that the environmental, nutritional, metabolic, toxicological, and psychological stimuli acting during the very early phases of pre- and postnatal development are capable of permanently shaping the structure, physiology, and gene expression of the organism, determining susceptibility to chronic diseases in adulthood (Barker, 1998). Developmental age must therefore not be understood as a mere phase of volumetric and ponderal growth, but rather as the period of maximum biological plasticity of the human being, a critical window in which the individual's "blueprint" is written. International scientific literature identifies this crucial interval in the so-called "first 1000 days" (Wopereis *et al.*, 2014), a time frame spanning from conception to the end of the second year of life. Recently, the PNEI vision has extended this conceptual horizon to the "first 6000 days", including childhood and adolescence, phases marked by further and extremely fine neuronal, endocrine, and immune reorganization, such as late synaptogenesis, cerebral pruning, and the maturation of mesocorticolimbic reward circuits during puberty (Cryan *et al.*, 2019). The gut microbiota fits perfectly into this programming process

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(Tamburini *et al.*, 2016). The development and maturation of the microbial ecosystem occur in parallel with the maturation of the child's biological systems (Koenig *et al.*, 2011). It has been widely demonstrated that the developmental trajectories of the immune system, the central nervous system, and the metabolic axis are intimately guided by signals originating from the microbiota (Gensollen *et al.*, 2016; Foster *et al.*, 2017). If microbial colonization occurs according to physiological timing and modalities, the organism receives the correct inputs to develop immune tolerance, neuroendocrine stability, and metabolic flexibility. Conversely, an alteration of the normal developmental trajectory of the microbiota in this critical temporal window leads to a deviation of the biological program (mis-programming), laying the groundwork for the long-term development of allergies, autoimmune diseases, obesity, metabolic syndrome, and neurobehavioral disorders (Arrieta *et al.*, 2015; Subramanian *et al.*, 2014).

Ecological Succession of the Microbiota in the First 36 Months of Life

The colonization of the newborn's gut follows a rigorous ecological succession that is completed between 30 and 36 months of life (Bäckhed *et al.*, 2015) (Tabella 1). At the end of this pathway, the child's microbiota reaches a complexity, richness, and stability comparable to that of an adult, defining the Community State Type (CST) or definitive enterotype of the subject (Turnbaugh *et al.*, 2009; Lozupone *et al.*, 2012). Although the question of the existence of an intrauterine fetal microbiota is still open, it is undisputed that the moment of birth represents the true microbial "big bang" (Dominguez-Bello *et al.*, 2010). In the first hours and days of postnatal life, the newborn's gut – characterized by a luminal environment with a high redox potential due to the presence of residual oxygen – is colonized by facultative anaerobic microorganisms, mainly enterobacteria such as *Escherichia coli* and streptococci. These pioneers consume free oxygen, modifying the luminal microenvironment and creating the conditions of strict anaerobiosis necessary for the establishment of subsequent colonizers drawn from the maternal environment (Milani *et al.*, 2017). Starting from the first weeks of life and throughout the period of exclusive breastfeeding, the microbiota of the healthy and eubiotic infant undergoes a drastic reduction in overall diversity, being literally dominated by a single phylum: *Actinobacteria*, represented for over 50-70% by the genus *Bifidobacterium* (in particular *B. infantis*, *B. bifidum*, and *B. breve*) (Milani *et al.*, 2017). This bifidobacterial dominance is a fundamental biological characteristic of the human species, phylogenetically selected for the utilization of human milk oligosaccharides (HMOs) (Bode, 2012). Bifidobacteria metabolize HMOs producing large quantities

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of acetate and lactate, molecules that acidify the intestinal luminal pH, exercising a natural barrier action against the establishment of pathogens (such as *Clostridioides difficile* and *Salmonella*) and guiding the early phases of education of the mucosa-associated lymphoid tissue (GALT) (Round, Mazmanian, 2009). The subsequent ecological turning point coincides with weaning and the introduction of solid foods and dietary fiber (Koenig *et al.*, 2011). The transition to a diversified diet deprives the microbiota of the exclusive substrate represented by milk and introduces complex carbohydrates indigestible by the host. This radical change promotes the proliferation of taxa specialized in the degradation of plant fiber, resulting in a progressive relative decline of bifidobacteria and a massive increase in the phyla *Firmicutes* (represented by butyrate-producing genera such as *Faecalibacterium* and *Roseburia*) and *Bacteroidetes* (Bäckhed *et al.*, 2015; Koh *et al.*, 2016). Around three years of life, the ecosystem stabilizes on the typical adult profile, characterized by a dynamic balance composed approximately of 45% *Firmicutes*, 45% *Bacteroidetes*, and the remaining 10% divided among *Actinobacteria*, *Verrucomicrobia* (e.g., *Akkermansia muciniphila*), and minor taxa (Turnbaugh *et al.*, 2009; Lozupone *et al.*, 2012).

Tab. 1. Ecological Succession of Intestinal Colonization from 0 to 36 Months

Developmental Phase	*Temporal Epoch*	*Dominant Phyla / Taxa*	*Functional and PNEI Characteristics*
Immediate Neonatal Period	0 - 7 days	*Proteobacteria* (*Enterobacteriaceae*, *E. coli*), *Streptococcaceae*	Consumption of luminal oxygen, shift toward anaerobiosis. Early interactions with innate immunity (Milani *et al.*, 2017).
Exclusive Breastfeeding	1 wk - 6 months	*Actinobacteria* (genus *Bifidobacterium* > 50-70%)	Selective consumption of HMOs, production of acetate and lactate, luminal acidification, anti-pathogen protection (Bode, 2012; Milani *et al.*, 2017).
Weaning	6 months - 24 months	Gradual expansion of *Firmicutes* and *Bacteroidetes*	Adaptation to complex dietary carbohydrates, increase in ecological alpha-diversity (Koenig *et al.*, 2011; Bäckhed *et al.*, 2015).
Adult Maturation and Eubiosis	24 - 36 months	*Firmicutes* (45%), *Bacteroidetes* (45%), *Actinobacteria*/Others 10%	Stabilization of the Community State Type (CST). Massive production of SCFAs (Turnbaugh *et al.*, 2009; Bäckhed *et al.*, 2015).

Note. *Dynamic of colonization and ecological succession associated with metabolic and PNEI regulation functions in the first 36 months of life. HMOs (Human Milk Oligosaccharides); SCFAs (Short Chain Fatty Acids); CST (Community State Type).*

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Early Dysbiosis and Shift toward Gram-Negativity

The delicate process of microbial ecological succession is highly vulnerable and can be perturbed by multiple environmental, iatrogenic, and relational factors, collectively defined as "drivers of early dysbiosis" (Tamburini *et al.*, 2016). The presence of one or more of these drivers alters the physiological trajectory of colonization, inducing a state of lasting imbalance that impacts the child's global programming (Arrieta *et al.*, 2015). The main drivers documented by clinical research include:

- **Cesarean Delivery:** The infant born via vaginal delivery is appropriately colonized by maternal vaginal and fecal microbiota (rich in *Lactobacillus*, *Bifidobacterium*, and *Bacteroides*). Conversely, the infant born via cesarean section is colonized by environmental and hospital skin-derived microorganisms (such as *Staphylococcus*, *Streptococcus*, and *Propionibacterium*), showing a severe delay in the establishment of protective bifidobacteria and a reduced overall biodiversity (Dominguez-Bello *et al.*, 2010; Neu, Rushing, 2011).
- **Prematurity:** Preterm infants present an anatomically and physiologically immature gastrointestinal tract, with a hyper-permeable epithelial barrier and hypomotility. Prolonged hospital stay in Neonatal Intensive Care Units (NICUs), massive exposure to sterile environments, and artificial nutrition hinder normal ecological colonization, favoring the engraftment of opportunistic and endotoxic pathogenic strains and delaying GALT maturation (Milani *et al.*, 2017).
- **Formula Feeding:** Artificial formulas lack the complex bioactive fraction of human milk, including immunoglobulins (secretory IgA), lactoferrin, lysozymes, immunomodulatory cytokines, and above all, the extraordinary variety of HMOs. In the absence of HMOs, the selective substrate for bifidobacterial dominance is lost, leading to premature and unbalanced growth of species typical of the adult microbiota or, worse, potentially pathogenic species (Bode, 2012).
- **Early Antibiotic Therapy:** Intrapartum exposure (maternal antibiotic prophylaxis for group B Streptococcus screening) or direct postnatal exposure to broad-spectrum antibiotics in the first months of life exerts a devastating effect on the intestinal ecosystem. Antibiotics act by wiping out entire populations of sensitive eubiotic bacteria (primarily bifidobacteria) and leaving empty ecological niches that are rapidly occupied by resistant microorganisms or Gram-negative opportunistic pathogens (Arrieta *et al.*, 2015).
- **Early Life Stress (ELS) and Early Life Adversity (ELA):** Stress perceived by the infant or toddler, resulting from maternal deprivation, non-sintonics caregiving, trauma, or alterations in the parental brain, translates biologically into chronic

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hyperactivation of the HPA axis with hypersecretion of cortisol and catecholamines (O'Mahony *et al.*, 2009; Foster *et al.*, 2017). These stress hormones directly alter intestinal motility, reduce mucus production by Goblet cells, and increase the permeability of the epithelial barrier. Furthermore, catecholamines released into the intestinal lumen can act as true molecular growth factors for specific pathogenic bacterial species, modulating the expression of their virulence genes (Foster *et al.*, 2017).

The consequence common to all these dysbiosis drivers is the loss of balance and microbial biodiversity, associated with a shift toward Gram-negativity (Arrieta *et al.*, 2015). Under eubiotic conditions, the infant gut is dominated by Gram-positive bacteria (Milani *et al.*, 2017). When dysbiotic drivers intervene, a massive proliferation of Gram-negative bacteria is observed, belonging primarily to the *Proteobacteria* phylum (such as *Enterobacteriaceae*, *Klebsiella*, *Pseudomonas*, *Serratia*) (Arrieta *et al.*, 2015; Milani *et al.*, 2017). The outer membrane of Gram-negative bacteria is composed for 80% of lipopolysaccharide (LPS), a potent pathogen-associated molecular pattern (PAMP) endowed with extremely high endotoxic and inflammatory activity (Cani *et al.*, 2007). This molecular imbalance represents the *primum movens* of the disruption of infant homeostasis and the activation of systemic inflammatory pathways (Belkaid, Hand, 2014).

Epithelial Cross-Talk, Immune Mechanisms, and Metabolic Endotoxemia

To understand the microbiota as a PNEI organ, it is necessary to examine the biochemical interface where the interaction between microbes and the host takes place: the intestinal epithelial barrier (Belkaid, Hand, 2014). In a healthy wall, enterocytes are tightly welded together by junctional protein complexes known as Tight Junctions (consisting of occludin, zonula occludens-1, claudins), which seal the intercellular space, preventing the uncontrolled paracellular passage of macromolecules, food antigens, and microorganisms. Above the enterocytes lies a continuous layer of hydrophilic mucus, synthesized and secreted by Goblet cells. This mucus acts as a physical and chemical protective shield, within which the eubiotic microbiota resides safely without coming into direct contact with the cellular plasma membrane (Round, Mazmanian, 2009). Below the intestinal epithelium lies the lamina propria, a loose connective tissue that hosts the largest concentration of immune cells in the entire organism, the GALT (Gut-Associated Lymphoid Tissue) (Belkaid, Hand, 2014; Gensollen *et al.*, 2016). The innate immune system and the enterocytes themselves are equipped with specialized pattern recognition receptors, called PRRs (Pattern Recognition Receptors), among which Toll-Like Receptors (specifically TLR-4) stand

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out (Gensollen *et al.*, 2016). Immune cells constantly "sense" the presence of microbes through continuous molecular cross-talk (Round, Mazmanian, 2009). Under eubiosis, weak and tolerogenic signals from bifidobacteria and lactobacilli stimulate dendritic cells to produce regulatory cytokines, such as interleukin-10 (IL-10) and Transforming Growth Factor-beta (TGF-beta), which promote the differentiation of T lymphocytes into regulatory T cells (Treg) (Belkaid, Hand, 2014). Tregs maintain immunological tolerance and stimulate isotype switching and the subsequent synthesis and secretion of secretory Immunoglobulins A (sIgA) into the intestinal lumen, consolidating mucosal protection without triggering severe inflammatory responses (Round, Mazmanian, 2009; Gensollen *et al.*, 2016).

When early dysbiosis with a shift toward Gram-negativity occurs, this delicate tolerance mechanism breaks down (Arrieta *et al.*, 2015). The overproduction of lipopolysaccharide (LPS) massively saturates and activates the TLR-4 receptor expressed on the surface of enterocytes and innate immune cells (Cani *et al.*, 2007). TLR-4 engagement triggers an intracellular signaling cascade mediated by the adapter protein MyD88, culminating in the nuclear translocation of the transcription factor NFKB (Nuclear Factor kappa B). The activation of NFKB induces gene expression and the subsequent release of a storm of pro-inflammatory cytokines, such as Tumor Necrosis Factor-alpha (TNF-alpha), interleukin-1 beta (IL-1beta), and interleukin-6 (IL-6), activating the intracellular inflammasome (Cani *et al.*, 2007; Belkaid, Hand, 2014). These inflammatory cytokines exert a direct cytotoxic effect on Tight Junction proteins, causing their disorganization, dephosphorylation, and degradation. This destabilizes the integrity of the intestinal barrier, configuring the pathophysiological condition known as "increased intestinal permeability syndrome" or Leaky Gut Syndrome. The loss of barrier function allows the massive paracellular passage of bacterial fragments, food antigens, and, above all, LPS itself from the intestinal lumen directly into the bloodstream and lymphatic circulation (Cani *et al.*, 2007). This phenomenon, termed "metabolic endotoxemia", distributes the inflammatory stimulus systemically (Cani *et al.*, 2007). Circulating LPS, by binding to TLR-4 receptors expressed in vascular beds and distant organs (liver, adipose tissue, blood vessels), fuels a state of low-grade chronic inflammation (Low-Grade Chronic Inflammation), which acts as a constant element of disturbance for all integrated biological systems of the growing host (Cani *et al.*, 2007).

The Gut-Microbiota-Brain Axis and the Impact on Neurodevelopment

One of the most fascinating and clinically relevant bidirectional axes from a PNEI perspective is the gut-microbiota-brain axis (Gut-Microbiota-Brain Axis)

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(Cryan *et al.*, 2019). During developmental age, the brain undergoes an extraordinarily rapid and complex phase of development. If at birth the newborn's brain mass represents about one-third of that of an adult, by the second year of life it reaches 80-90% of its final volume, showing unmatched kinetic speed in connectome formation, synaptogenesis, myelination, and synaptic pruning processes (Diaz Heijtz *et al.*, 2011; Sharon *et al.*, 2016). The gut microbiota acts as the occult director of this complex neurological maturation through three main anatomical and biochemical communication pathways (Cryan *et al.*, 2019; Sharon *et al.*, 2016).

- **The Neural Pathway (The Vagus Nerve):** The vagus nerve constitutes the main direct neuroanatomical communication highway between the enteric nervous system (ENS) and the central nervous system (CNS). Vagal afferent fibers terminate at the intestinal mucosa, where they are positioned in immediate proximity to enteroendocrine and enterochromaffin cells. The microbiota, through the production of metabolites and neurotransmitters, electrically stimulates vagal receptors, sending instant signals to the nucleus of the solitary tract in the brainstem, from which information propagates toward limbic and cortical structures responsible for emotional, behavioral, and cognitive regulation (Foster *et al.*, 2017; Cryan *et al.*, 2019).
- **The Endocrine Pathway and Neurotransmitters:** The gut microbiota possesses the enzymatic machinery necessary for the *de novo* synthesis of neurotransmitters or for the regulation of the availability of their amino acid precursors in the host (Cryan *et al.*, 2019). Over 90% of the body's total serotonin (5-HT) is synthesized at the intestinal level by enterochromaffin cells, a process finely regulated by short-chain fatty acids (SCFAs) produced by bacteria (Yano *et al.*, 2015). Although peripheral serotonin is unable to cross the blood-brain barrier (BBB), it regulates intestinal motility and vagal signaling (Yano *et al.*, 2015). Furthermore, the microbiota modulates the systemic availability of tryptophan, the amino acid precursor of serotonin, directing it toward neurotransmitter synthesis or the kynurenine metabolic pathway; early dysbiosis shifts metabolism toward the kynurenine pathway, generating neurotoxic metabolites (such as quinolinic acid) associated with neuroinflammation and behavioral alterations (Clarke *et al.*, 2013; Cryan *et al.*, 2019). Eubiotic bacterial genera such as *Bifidobacterium* and *Lactobacillus* are also known for their ability to secrete high concentrations of GABA, the primary inhibitory neurotransmitter of the CNS, essential for countering excitotoxicity, regulating anxiety states, and stabilizing neuronal excitability (Cryan *et al.*, 2019).
- **The Immune Pathway and Microglial Function:** This represents the biochemical connection pathway most sensitive to dysbiotic states (Erny *et al.*, 2015). Microglia consist of the resident immune cells of the central nervous system, re-

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sponsible not only for anti-infective defense, but above all for synaptic shaping: microglia actively eliminate redundant or non-functioning synapses, allowing the correct configuration of cognitive and emotional neuronal circuits (Erny *et al.*, 2015). Pioneering studies on germ-free animal models (microbe-free) have unequivocally demonstrated that in the absence of a physiological gut microbiota or in the presence of severe early dysbiosis, microglia remain structurally immature, poorly distributed, and functionally dysfunctional (Erny *et al.*, 2015; Cryan *et al.*, 2019). Healthy microbial metabolites, particularly butyrate and propionate, are capable of crossing the blood-brain barrier and guiding the gene and morphological maturation of microglia (Erny *et al.*, 2015; Koh *et al.*, 2016). Conversely, metabolic endotoxemia from LPS activates microglia in a pro-inflammatory sense (M1 phenotype), triggering a silent neuroinflammation process that alters synaptic pruning and heavily interferes with neurodevelopmental trajectories, increasing the biological risk of onset of autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), and learning disorders (LD) (Cani *et al.*, 2007; Erny *et al.*, 2015; Sampson *et al.*, 2016).

Metabolic Regulation, Endocrine Homeostasis, and Epigenetic Markings

The directing action of the gut microbiota extends capillarically to the metabolic and endocrine sphere of the growing subject (Cani *et al.*, 2007; Koh *et al.*, 2016). Hormonal homeostasis in developmental age is a fundamental prerequisite to guarantee not only linear staturo-ponderal growth, but also the correct calibration of circadian rhythms (Bass, Takahashi, 2010; Codoñer-Franch, Gombert, 2018), the neuroendocrine response to stress (Sudo *et al.*, 2004), and future pubertal maturation. The microbiota intervenes in this area by acting as a true "metabolic transducer" (De Vadder *et al.*, 2014; Koh *et al.*, 2016). Through the production of SCFAs, it interacts with specific G protein-coupled receptors (GPR41 and GPR43) expressed on colonic enteroendocrine cells, stimulating the secretion of key peptide hormones such as Glucagon-Like Peptide-1 (GLP-1) and Peptide YY (PYY), central regulators of satiety, insulin sensitivity, and gastric motility (Koh *et al.*, 2016).

Furthermore, the gut microbiota possesses an active metabolic role in the biochemistry and recirculation of systemic hormones. It interferes with the thyroid axis, influencing the absorption of essential micronutrients (iodine, selenium, zinc) and regulating peripheral deiodinase activity; it modulates the adrenal axis, intervening in the kinetics of cortisol degradation and clearance and modifying the glucocorticoid sensitivity set-point (Sudo *et al.*, 2004); finally, it participates in the enterohepatic circulation of estrogens and sex hormones through the enzymatic activ-

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ity of microbial beta-glucuronidase (the so-called "estrobolome"), regulating the fraction of active hormones reabsorbed into circulation and conditioning the timing of adrenarche and gonadarche (Cryan *et al.*, 2019).

The deepest and most lasting molecular mechanism through which the microbiota and its metabolome shape endocrine-metabolic homeostasis is, however, represented by epigenetics (Stilling *et al.*, 2014). Epigenetics encompasses the set of heritable modifications that alter gene expression without changing the primary nucleotide sequence of DNA (Stilling *et al.*, 2014). It is estimated that human health and aging are determined 75% by epigenetic processes influenced by environment and lifestyle (the exposome), and only 25% by inherited genetics (Bottaccioli, Bottaccioli, 2020). The main epigenetic mechanisms include DNA methylation (which typically silences gene expression), histone acetylation/deacetylation (which opens or closes chromatin, regulating RNA polymerase accessibility to gene promoters), and post-transcriptional micro-RNA synthesis (Stilling *et al.*, 2014).

Metabolites produced by a eubiotic microbiota act as powerful epigenetic modifiers (Stilling *et al.*, 2014). Butyrate, for example, is a known and potent natural inhibitor of histone deacetylases (HDACi) (Koh *et al.*, 2016). By inhibiting HDACs, butyrate promotes histone hyperacetylation, keeping chromatin in an open and accessible conformation (euchromatin) that favors the transcription of protective genes, such as tumor suppressor genes, genes involved in metabolic stability, and neurotrophic factors like BDNF (Brain-Derived Neurotrophic Factor), essential for neuronal plasticity and learning (Stilling *et al.*, 2014). Bifidobacteria, through acetate production and the modulation of carbon metabolism and methyl groups (folate pathway), provide the biochemical substrates necessary for DNA methylation processes (Milani *et al.*, 2017). When early dysbiosis occurs with alteration of the microbial metabolome, incorrect epigenetic markings are generated in the nucleus of the growing subject's cells (Stilling *et al.*, 2014). This epigenetic "writing error" can stably silence crucial hormonal receptors or stably activate pro-inflammatory gene promoters, determining biological mis-programming that exposes the child to an exponentially higher risk of developing chronic-degenerative pathologies (type 2 diabetes, atherosclerosis, neurodegeneration, inflammatory bowel diseases) in adulthood (Barker, 1998; Cani *et al.*, 2007).

Clinical Strategies of Primary Prevention and Integrated Therapeutic Intervention

Understanding the gut microbiota as a PNEI director of developmental age requires the development of strategies for systemic and early primary prevention, to be implemented starting from the preconception era (Bottaccioli, Bottaccioli, 2020).

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Since the maternal metabolome regulates and directs fetal programming through the transplacental passage of metabolites and immunomodulatory signals (Barker, 1998; Vuong *et al.*, 2020), caring for the eubiosis, diet, and lifestyle of the pregnant woman represents the first and indispensable preventive medical act. A maternal diet rich in prebiotic fiber (Mediterranean diet), associated with psychological stress control and the reduction of chemical-physical environmental contaminants, favors the structuring of a healthy maternal microbiota, optimizing fetal programming and reducing the risk of adverse neonatal outcomes (Barker, 1998). In the postnatal period, the pediatrician's primary goal must be the protection of the ecological trajectory of the first 30-36 months, minimizing iatrogenic drivers of dysbiosis (Wopereis *et al.*, 2014; Bäckhed *et al.*, 2015). This translates into encouraging vaginal delivery where possible, strenuously promoting exclusive breastfeeding for the first 6 months, and applying criteria of extreme clinical appropriateness and restriction in the use of empirical antibiotic therapy (Dominguez-Bello *et al.*, 2010; Bode, 2012; Arrieta *et al.*, 2015). Should the dysbiotic event prove inevitable (e.g., medically necessary cesarean section, prematurity, maternal hypogalactia, or absolute necessity for antibiotic therapy), it is imperative to intervene promptly through integrated and targeted nutraceutical support, based on the rational use of biotics (Hill *et al.*, 2014; Gibson *et al.*, 2017; Salminen *et al.*, 2021):

- **Prebiotics:** Non-viable substrates selectively utilized by host microorganisms conferring a health benefit. In pediatrics, the use of oligosaccharides such as galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS), capable of partially mimicking the action of human milk oligosaccharides (HMOs), favors the selective expansion of endogenous bifidobacteria and supports luminal acidification, improving barrier function (Gibson *et al.*, 2017).
- **Probiotics:** Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Prescription must not be generic, but strictly guided by strain specificity and clinical evidence (Hill *et al.*, 2014).
- **Synbiotics:** Synergistic formulations combining a live probiotic microorganism and a prebiotic substrate in the same product, optimizing the survival, transit, and engraftment of the administered strain in the host's intestinal lumen (Gibson *et al.*, 2017).
- **Postbiotics:** In accordance with the most recent international scientific consensus definitions (ISAPP, International Scientific Association for Probiotics and Prebiotics), postbiotics consist of preparations of inanimate microorganisms (inactivated, thermally killed, or tyndallized) and/or their structural cellular components (e.g., teichoic acids, peptidoglycans, membrane fragments, surface proteins) that confer a health benefit on the host, whether or not associated with their metabolites (Salminen *et al.*, 2021).

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Conclusions and Future Perspectives

The gut microbiota has demonstrated beyond a reasonable doubt that it exercises an integrated regulatory role in the biological choreography of developmental age (Cryan *et al*., 2019). Through the production of a dynamic metabolome and the generation of bidirectional biochemical signals running along PNEI axes, this microscopic organ modulates the maturation of the immune system, calibrates endocrine-metabolic homeostasis, and directs the child's neurodevelopmental trajectories, impressing stable epigenetic markings that will condition the individual's health for the rest of their existence (Cani *et al*., 2007; Stilling *et al.*, 2014; Cryan *et al*., 2019). The preservation of intestinal eubiosis in the early years of life must no longer be considered complementary or optional, but a fundamental clinical and preventive priority for the public health of the future.

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Neurodevelopmental Trajectories: A PNEI and Developmental Pathway Linking Genetics, Epigenetics and Integrated Clinical Care

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Abstract. *This article examines the child's neurodevelopmental trajectory from conception to the early years of life, focusing on the critical stages of typical and atypical neurodevelopment. Through the lens of Psychoneuroendocrinoimmunology (PNEI), the article analyzes the shift from genetic determinism to a dynamic and probabilistic model in which epigenetics plays a central role. The theoretical frameworks of the exposome and DOHaD (Developmental Origins of Health and Disease) are explored, highlighting the impact of environmental factors, maternal-fetal stress and maternal immune activation (MIA) on brain connectomics and on the genesis of neurodevelopmental disorders (NDDs), with particular reference to autism spectrum disorder (ASD). The article examines the molecular mechanisms of neuronal migration, microglia-mediated synaptic pruning and alterations of the gut-brain axis. Finally, it discusses the functional meaning of atypical sensory profiles and stereotypies, proposing a therapeutic paradigm shift based on brain plasticity, environmental modification and early clinical intervention aimed at relational and sensory enrichment.*

Keywords: *Neurodevelopment, Neurodevelopmental disorders, DOHaD, Exposome, Sensory profiles, PNEI.*

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Introduction: A Paradigm Shift in Neurodevelopment

The human brain is the most complex non-linear biological system known to science. Historically, developmental biology and child neuropsychiatry have operated under the hegemony of genetic determinism, a reductionist model that regarded DNA as a rigid and immutable program – an "architectural blueprint" capable of univocally determining the structural and functional destiny of the individual. Within this older framework, neurodevelopmental disorders were interpreted almost exclusively as the product of intrinsic errors in the genetic code.

Modern neuroscience, integrated with the paradigm of Psychoneuroendocrinoimmunology (PNEI), has radically dismantled this static view. As the biologist Richard Strohman (2003) clearly put it, DNA is not a program of action but a vast vocabulary. The genetic code contains the words, but it is the environment, experience, relationships and metabolic context that write a narrative endowed with biological and psychological meaning. The genome thus emerges not as a destiny but as a field of molecular possibilities, constantly modulated by external and internal signals.

Neurodevelopment is not a linear process of structural accumulation but a dynamic developmental trajectory that begins at the very moment of conception and reaches its peak of vulnerability and plasticity during intrauterine life and the first postnatal year. In these critical time windows, the constant interaction between genome and epigenome shapes the configuration of neural networks. Understanding neurodevelopment today means abandoning the obsolete dichotomy between nature and nurture in favor of a systemic view in which the child's biology is co-constructed, moment by moment, through interaction with the environment and with the maternal relational matrix.

The Architecture of the Mind: Connectome, Interactome and Emergence

The child's brain does not develop as a set of isolated anatomical modules maturing independently, but as a complex network of synaptic and structural connections known as the "connectome" (Sporns, Tononi & Kötter, 2005). Brain connectomics studies the brain as a complex graph made up of nodes (specialized brain areas) and edges (the white matter tracts and synapses connecting them).

In the early years of life, brain architecture undergoes a profound dynamic transition. Before the age of seven, the pediatric connectome features so-called hyperconnected cortical "hubs", located mainly in the primary sensory and motor areas. These hubs act as convergence zones for information arriving from the outside

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world. As neurodevelopmental maturation proceeds, the interactome – the totality of molecular and cellular interactions governing these networks – expands, allowing a shift from predominantly local connectivity to long-range connectivity linking posterior to anterior (frontal and prefrontal) regions, which are required for higher executive functions, emotional regulation and social cognition.

A key concept of this architecture is emergence. In complex systems theory, emergent properties are functions of a global system that cannot be traced to its individual components but arise solely from their dynamic interactions. The mind, consciousness, empathy and the capacity to integrate sensory stimuli do not reside in a single neuron or in an isolated brain area; they are emergent properties of the brain interactome.

In neurodevelopmental disorders, and in autism spectrum disorder (ASD) in particular, this network architecture is altered. A fragmentation of the connectome is frequently observed, characterized by short-range local hyperconnectivity (especially in primary sensory areas) together with long-range hypoconnectivity (between the prefrontal cortex and posterior or limbic regions). This imbalance prevents the proper integration of information, turning the flow of environmental stimuli into a disorganized and chaotic whole that lacks central coherence.

Phases of Brain Development: From Embryogenesis to Adolescence

The neurodevelopmental trajectory unfolds through a sequence of biological events tightly orchestrated in time and space, each representing both a marvel of evolutionary engineering and a window of potential vulnerability to epigenetic insults.

Neurogenesis and Cell Proliferation

During the first months of gestation, the ventricular zone of the fetal neural tube is the site of massive neuronal proliferation. Billions of neural stem cells divide symmetrically and asymmetrically to generate the neurons and glial cells that will make up the brain. This phase requires a perfect energetic and metabolic balance.

Neuronal Migration and Positioning

Once generated, neurons must migrate from their deep site of origin towards the outer surface to form the cerebral cortex, which is organized into six distinct layers. This journey takes place along radial glial processes and requires the coor-

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dinated action of molecular adhesion and signaling complexes, among which NEGR1 (Neuronal Growth Regulator 1) and FGFR2 (Fibroblast Growth Factor Receptor 2) stand out.

If these molecular guidance mechanisms are disrupted (for instance by an inflammatory state or by environmental toxicants), neurons fail to reach their correct destination and come to a halt in the deep layers. This mispositioning leads to the formation of atypical neural networks (Belmonte *et al.*, 2004) that receive incoherent input and fail to integrate into the global connectome – a pathological finding frequently reported in neuroanatomical models of autism.

Explosive Synaptogenesis

Between the last trimester of pregnancy and the first two postnatal years, the child's brain undergoes an unprecedented synaptic explosion. Trillions of redundant connections are deliberately created. The brain produces an excess of connections to ensure that, whatever the environment into which the child is born, the structural bases for learning and adaptation are in place.

Experience-dependent synaptic pruning

This phase, which extends into adolescence, marks the crucial transition from the potential brain to the functional brain. Pruning consists in the selective elimination of redundant, weak or unused synapses, guided by experience and environmental stimuli. The true architects of this process are microglial cells, the resident macrophages of the central nervous system. Microglia do not merely perform immune defense functions; they act as genuine "gardeners" of the brain: they recognize less active synapses through molecular complement signals and phagocytose them, optimizing neural circuits and reducing the organ's energy consumption.

If pruning is deficient or delayed, the brain remains flooded with an overabundance of immature and weak synapses. This phenomenon underlies the pathophysiology of autism: the absence of proper pruning generates high background noise in brain circuits (Holiga *et al.*, 2019). Neural networks fail to specialize; information is dispersed across countless synaptic rivulets, preventing the system from distinguishing the relevant signal from incidental stimuli.

Myelination

In parallel with pruning, oligodendrocytes wrap axons in myelin sheaths, increasing the conduction velocity of nerve impulses up to a hundredfold. Mye-

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lination proceeds in a caudo-rostral direction (from posterior motor and sensory areas towards the anterior frontal lobes) and is completed only in early adulthood, marking the full maturation of planning and inhibitory control abilities.

Epigenetics, the Exposome and the DOHaD Framework

To understand the heterogeneity of developmental profiles, modern medical research has had to integrate three revolutionary scientific concepts: the exposome, epigenetics and the DOHaD theory.

Epigenetics comprises the set of molecular mechanisms through which the exposome communicates with the genome, altering gene expression without modifying the underlying nucleotide sequence. The main epigenetic mechanisms include:

DNA methylation: the addition of methyl groups at CpG islands, which generally silences gene transcription.

Histone modification: acetylation or methylation of histone tails, which alters chromatin compaction, making DNA more or less accessible to the transcriptional machinery.

Non-coding RNAs (miRNAs): small RNA molecules that degrade target mRNA or block its translation in the cytoplasm.

Through these biochemical switches, an experience of severe stress or exposure to environmental toxicants can "switch off" protective genes (such as those involved in the synthesis of neurotrophic factors like BDNF) or "switch on" pro-inflammatory genes.

The exposome (Wild, 2005) represents the totality of non-genetic exposures to which an individual is subjected over the entire life course, starting from conception. It includes not only exposure to chemical and physical factors (air pollutants, heavy metals, endocrine disruptors, microplastics, drugs, nutrients) but also exposure to psychological and social factors (maternal stress, trauma, socioeconomic deprivation, quality of the attachment relationship). The exposome concept recognizes that the environment constantly penetrates our biology and modifies it.

The DOHaD theory (*Developmental Origins of Health and Disease*), originally formulated by the epidemiologist David Barker (1995), postulates that the environmental and metabolic conditions experienced during crucial phases of fetal development and early childhood durably program the structure, function and metabolism of organs, thereby determining susceptibility to chronic metabolic, cardiovascular and neuropsychiatric diseases in adulthood. In this context, as Barker himself stated, «the womb may be more important than the home» (as cited in Burgio, 2015, p. 1).

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Fetal programming is the mechanism through which the fetus "reads" the mother's biochemical state (via the placental transfer of stress hormones such as cortisol, cytokines and nutrients) and adapts its own gene expression to prepare for the external environment (Burgio, 2015). If the mother is immersed in a hostile, stressful or pollutant-saturated environment, the fetus will receive continuous alarm signals. This alters the development of the unborn child's hypothalamic-pituitary-adrenal (HPA) axis, inducing a state of stress hyperreactivity, remodeling amygdala circuits and predisposing the child to atypical developmental trajectories.

Primary prevention must therefore focus decisively on safeguarding maternal and child health during the first 1000 days (from conception to two years of age), reducing maternal-fetal distress and minimizing exposure to environmental pollution, since protecting proper cellular programming in this early phase is the only way to safeguard the health of future generations.

Maternal Immune Activation (MIA) and Persistent Neuroinflammation

One of the most groundbreaking discoveries of contemporary neuroscience concerns the role of the maternal immune system in guiding or diverting fetal brain development. Maternal immune activation (MIA) (Estes & McAllister, 2016) is a pathophysiological model that applies when the mother undergoes a systemic immune insult during gestation, due to infections (viral or bacterial), autoimmune diseases or acute and prolonged psychological stress.

In response to these conditions, the maternal immune system releases high concentrations of pro-inflammatory cytokines into the bloodstream, including interleukin-6 (IL-6), interleukin-17 (IL-17) and tumor necrosis factor alpha (TNF-α). These molecules can cross the placental barrier (Nugent & Bale, 2015) and enter the fetal compartment, where they interact directly with receptors expressed on neural stem cells and on fetal microglial cells that are still differentiating.

The impact of MIA on the developing brain is profound:

it alters neuronal proliferation and migration, contributing to structural cortical abnormalities;

it induces a phenotypic shift of microglia towards a persistently activated, pro-inflammatory state (M1 phenotype).

This state of persistent neuroinflammation does not end at birth but may become chronic within the child's central nervous system for years.

The clinicopathological demonstration of this phenomenon lies in the landmark studies by Vargas and colleagues (Vargas *et al.*, 2005). Through post-mortem analy-

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sis of brain tissue from individuals with ASD aged 5 to 44 years, the researchers documented marked and widespread microglial and astrocytic activation in the cerebral cortex, white matter and cerebellum. Increased production of specific chemokines and cytokines was found in the cerebrospinal fluid and brain tissue of these patients, notably monocyte chemoattractant protein-1 (MCP-1) and transforming growth factor beta-1 (TGF-β1).

This study demonstrated unequivocally that autism is not a static, purely "neuro-architectural" disorder but an active, dynamic and chronic neuroinflammatory process, mediated by an innate immune response of the central nervous system that continues to disrupt synaptic homeostasis throughout life. Moreover, this underlying immune vulnerability creates susceptibility to a postnatal "second hit". Subsequent infections, severe intestinal dysbiosis or early psychosocial stress may act on microglia already primed by MIA, triggering an amplified and destructive inflammatory response that results in clinical regression or worsening of neuropsychiatric symptoms.

Sensory Profiles and Autism Spectrum Disorder (ASD)

The clinical picture of neurodevelopmental disorders, and of autism in particular, is not limited to deficits in social communication and emotional reciprocity but is intrinsically rooted in a profound alteration of sensory processing. This evidence has been formally incorporated into the DSM-5 diagnostic criteria (American Psychiatric Association, 2013), which list hyper- or hyporeactivity to sensory input, or unusual interest in sensory aspects of the environment, among restricted and repetitive behaviors.

Neuropsychological models, in particular the Sensory Profile framework (Ermer & Dunn, 1998), show that each individual has a specific neurological threshold for responding to stimuli and a specific mode of behavioral response. In children with ASD, the processing of sensory stimuli (visual, auditory, tactile, olfactory, gustatory, vestibular and proprioceptive) is marked by extreme atypicality and fluctuation, which manifests in three main profiles:

Hyperreactivity (hypersensitivity): characterized by an extremely low neurological threshold. Ordinary environmental stimuli (the hum of a fluorescent lamp, the texture of a fabric, background noise in a room, a faint odor) are perceived by the child's brain as painful, threatening or overwhelming signals. The behavioral response is often avoidance, intolerance or an acute anxiety crisis (meltdown).

Hyporeactivity (hyposensitivity): characterized by a pathologically high neurological threshold. The child appears not to register stimuli from the outside world: does not respond to their name, shows apparent insensitivity to physical pain or extreme

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temperatures, and requires stimuli of massive intensity to elicit a neural response.

Sensory seeking: the child has a high threshold but, unlike the hyporeactive profile, adopts an active behavioral strategy to reach the necessary level of neurological arousal. This translates into a relentless search for intense stimulation: watching rotating objects, systematically sniffing surfaces, producing continuous vocal noises, seeking deep pressure contact.

Clinical studies using standardized instruments such as the Sensory Profile show that sensory abnormalities in the autistic population have high predictive value for the onset of severe behavioral problems such as emotional dysregulation, irritability and aggression (Fabbri-Destro *et al.*, 2022).

The biological link between the altered connectome and the sensory profile lies, as mentioned above, in the failure of synaptic pruning. The "background noise" generated by the excess of unpruned synapses allows primary sensory networks (which mature first and are metabolically very robust) to retain an absolute competitive advantage within the brain, dominating its electrical activity. As a result, higher integrative networks (fronto-parietal and prefrontal) fail to modulate and filter incoming stimuli in a top-down manner. The child is thus at the mercy of an environment perceived as unpredictable, threatening and chaotic (Ayres, 2005).

Within this neurobiological framework, the phenomenon of stereotypies (repetitive movements such as rocking, hand flapping or the repetition of words) takes on an entirely new meaning. Historically regarded as bizarre symptoms to be eliminated or suppressed pharmacologically or behaviorally, stereotypies are in fact remarkable tools for bottom-up self-regulation. When the child's brain is overwhelmed by sensory background noise and by the anxiety generated by an unpredictable external environment, performing a rhythmic, repetitive movement entirely under the child's control produces a pure sensory input that is 100% predictable. This coherent stimulus acts as a neural "anchor", reducing sympathetic nervous system activation, lowering cortisol levels and allowing the system to restore a semblance of homeostatic balance. Forcibly interrupting a stereotypy without first modifying the sensory environment means depriving the child of their only neurofunctional survival strategy against sensory collapse.

The Gut-brain Axis and the Role of the Microbiome

The systemic perspective of PNEI requires us to regard the central nervous system not as an isolated entity enclosed within the skull, but as an organ in constant bidirectional communication with the rest of the body's biology. The clearest example of this interconnection is the gut-brain axis (Dinan & Cryan, 2017), a com-

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plex communication network linking the central nervous system, the neuroendocrine system, the immune system and the enteric nervous system (the so-called intestinal "second brain").

At the center of this axis lies the gut microbiome, the vast community of trillions of microorganisms (bacteria, viruses, fungi) that co-evolves with humans and performs fundamental metabolic, immune and neurochemical functions. The microbiome may be regarded as the epigenetic organ *par excellence* (Woo & Alenghat, 2022): it produces signaling molecules capable of travelling via the vagus nerve, altering the blood-brain barrier and directly influencing brain gene transcription and microglial activation.

In people with neurodevelopmental disorders, and in ASD in particular, the prevalence of chronic gastrointestinal symptoms (abdominal pain, persistent constipation, diarrhea, altered intestinal permeability) is markedly higher than in the neurotypical population, as confirmed by clinical meta-analyses (McElhanon *et al.*, 2014). This clinical finding reflects the frequent co-occurrence of intestinal dysbiosis in autism spectrum disorders, i.e. a qualitative and quantitative alteration of microbiome composition (Zheng *et al.*, 2026), often characterized by reduced microbial biodiversity, an increased Firmicutes/Bacteroidetes ratio and the proliferation of pathogenic or opportunistic bacterial species (such as certain *Clostridia* or *Sutterella* strains).

Intestinal barrier integrity: dysbiosis reduces the production of short-chain fatty acids (SCFAs) such as butyrate, which nourish colonocytes and maintain the integrity of tight junctions. Loss of this barrier results in the so-called leaky gut syndrome.

Endotoxin translocation: through the permeable gut, toxic bacterial fragments such as lipopolysaccharide (LPS) pass into the systemic circulation, triggering low-grade inflammation that aggravates central neuroinflammation (Hughes *et al.*, 2018) and alters blood-brain barrier permeability.

Neurotransmitter synthesis: gut bacteria are responsible for the synthesis or modulation of precursors of key neurotransmitters such as serotonin (90% of which is produced in the gut by enterochromaffin cells stimulated by the microbiome) and GABA. A dysbiotic microbiome alters the balance between excitatory (glutamate) and inhibitory (GABA) neurotransmission in the brain – a bioelectrical trait typical of the autistic brain, characterized by cortical hyperexcitability.

Therapeutic interventions aimed at restoring intestinal eubiosis – through specific nutritional protocols, the rational use of prebiotics and targeted probiotics and, in the most severe cases, fecal microbiota transplantation (FMT), which is under investigation in international research – do not simply aim to resolve a digestive problem; they represent a bottom-up therapy capable of reducing circulating

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inflammatory cytokine levels, modulating microglial activation and, consequently, significantly improving the child's behavioral symptoms, attention, hyperactivity and relational availability.

Clinical Interventions, Neural Plasticity and Environmental Enrichment

Accepting the dynamic, PNEI-based model of neurodevelopment radically transforms the approach to clinical therapy in pediatrics. If the brain is not a computer rigidly hard-wired at birth but a plastic system in constant co-construction with the environment, early diagnosis and intervention become absolute ethical and clinical imperatives.

In autism spectrum disorder, the golden therapeutic window coincides with the preschool years (before 3-4 years of age). During this period, synaptic pruning and myelination are at their peak of flexibility, and network connectivity has not yet become rigidly set in stable pathological configurations. The goal of modern neuropsychiatric and rehabilitative therapy is not "to correct a mechanical defect" but to steer the competition between neural networks towards functional and resilient outcomes.

Clinical interventions of proven efficacy are based on the principles of experience-dependent neuroplasticity and environmental enrichment, and are organized along three fundamental lines.

Adapting the Sensory and Relational Environment

To reduce overload in hyperreactive children, the environment must be made structured, predictable and low in simultaneous stimuli. This means slowing the pace of communicative interaction, using visual supports to make daily routines predictable, and modulating lighting and acoustics in everyday settings. By reducing chaotic external stimulation, the metabolic and electrical demand on hyperactive sensory hubs is lowered, allowing the nervous system to emerge from a state of constant sympathetic alarm.

Amplifying Functional Connections

Through relationship-based and ecological play-based therapies such as the Early Start Denver Model (Rogers & Dawson, 2010), or developmental-relational approaches, therapists and parents use contingent affective and empathic interaction as a powerful neurobiological stimulus. The coherent repetition of attuned

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communicative exchanges simultaneously activates the child's sensory, motor and emotional areas, driving the connectome to create and strengthen long-range synapses linking the prefrontal cortex (involved in reciprocity) with posterior areas.

Modifying Competition between Networks

By placing the child in a context of warm, predictable and attuned relational experiences, higher integrative networks – previously "silent" or hypofunctioning because of excessive background noise – are progressively recruited and activated. The brain system thus regains a dynamic equilibrium: prefrontal networks resume their top-down control over sensory and limbic modulation, and the subsequent process of synaptic pruning can finally select and eliminate weak connections adaptively.

The clinical approach must therefore move beyond purely training-based techniques focused on the mere extinction of overt behavior, and embrace interventions that address the child's biology as a whole: reducing systemic inflammation (gut-brain axis), clearing the exposome of pollutants and toxic stress, and enriching the relational matrix, thereby transforming a trajectory of vulnerability into a path of deep neurodevelopmental resilience.

Conclusions

The fascinating and complex journey of neurodevelopment, read through the modern frameworks of Psychoneuroendocrinoimmunology, connectomics and epigenetics, offers a profoundly renewed vision of pediatric health and disease.

In our view, neurodevelopmental disorders and autism spectrum disorder can no longer be regarded as unalterable genetic sentences written in the cell nucleus from conception, nor as psychopathological conditions isolated from the rest of the body. They represent the dynamic, plastic and probabilistic outcome of complex developmental trajectories in which epigenetic events, maternal immune activation, persistent neuroinflammatory states (Hughes *et al.*, 2018) and alterations of the gut-brain axis divert the proper maturation of the brain connectome.

Far from generating a sense of medical helplessness, this awareness conveys a message of deep hope and responsibility. If environment and experience have the biological power to influence the developmental trajectory negatively, they also possess, through epigenetic and plastic mechanisms, the extraordinary power to heal and reshape it. The challenge for modern medicine lies in primary prevention during the first thousand days of life: for example, by implementing in clinical practice procedures and protocols for the observation and clinical assessment of

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early infant motor development (Caruso *et al.*, 2020); by protecting the biological and psychological health of pregnant women; by reducing the impact of the toxic exposome to a minimum; and, at the same time, by activating early and appropriate habilitative interventions tailored to each child, which use relational attunement and metabolic care to guide the infant's brain towards its full developmental potential.

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Body, Movement, and Physical Activity: Opportunities for Child Evolution Through Affective and Therapeutic Touch

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Abstract. *This paper explores the fundamental role of affective and therapeutic touch and movement in child neurobiological development through the paradigm of Psychoneuroendocrineimmunology (PNEI). Physical contact is not merely a mechanical act but constitutes a preverbal language and a primary biological modulator capable of activating C-tactile fibers and stimulating the release of oxytocin. The latter acts as a core mediator in stress reduction, regulation of the HPA axis, modulation of the anti-inflammatory immune response, and the structuring of predictive models of social cognition. By integrating the osteopathic, physiotherapeutic, and psychological approach, touch and its subsequent evolution into structured movement – an essential driver for BDNF production and brain plasticity – offer a multidisciplinary care model. This approach promotes interpersonal synchronization and caregiver empowerment, establishing itself as a highly effective preventive and evolutionary medicine strategy for long-term health.*

Keywords: *PNEI, Therapeutic Touch, C-Tactile Fibers, BDNF, Oxytocin, Pediatric Osteopathy*

Touch represents the first form of communication experienced by human beings, a pre-verbal language that precedes the structuring of the self and the symbolic comprehension of the world (Montagu, 1986). In the context of early devel-

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opment, physical contact is not merely a mechanical act, but a powerful modulator of homeostasis, capable of radically influencing the child's brain architecture and immune response (Feldman, 2012).

Within the paradigm of Psychoneuroendocrineimmunology (PNEI), therapeutic is conceived as a systemic intervention: it acts not only on the musculoskeletal level, but promotes synchronization between the biological systems of the child and the caregiver (Ader, 2007; McGlone *et al.*, 2014). Recent scientific literature emphasizes how affectionate touch is a biological necessity, a catalyst that enables the transition from a state of basal reactivity to one of dynamic regulation, essential for facing the challenges of growth (Uvnäs-Moberg, 2003). In this process, oxytocin acts as the core biochemical mediator, a molecule capable of transforming a tactile mechanical signal into a complex physiological response, guaranteeing the cohesion of the osteopath-parent-child triadic system (Carter, 1998; Accardi *et al.*, 2023).

Oxytocin as the System's Architect: Neurobiology and Regulation

The role of oxytocin in affective touch transcends the classical function linked to childbirth and lactation. In neonatal development, it serves as the interface between the external world and internal equilibrium (Uvnäs-Moberg, 2003). Through the activation of unmyelinated C-tactile fibers – low-threshold receptors sensitive to slow, rhythmic caresses – touch sends preferential signals to the brain areas dedicated to affective regulation, in particular the posterior insular cortex and the somatosensory cortex (S1) (Löken *et al.*, 2009; McGlone *et al.*, 2017).

This afferent stimulation induces an endogenous release of oxytocin, which exerts an inhibitory modulation on the amygdala circuits, reducing the alert response of the hypothalamic-pituitary-adrenal (HPA) axis (Heinrichs *et al.*, 2009). This is where the central role of oxytocin lies: it not only attenuates the stress response but actively participates in T-cell development and the modulation of the immune response, promoting the expression of an anti-inflammatory profile.

Oxytocin essentially acts as a "linking molecule" between the central nervous system and the immune system (Gouin *et al.*, 2010). In the presence of adequate tactile stimulation, a suppression of inflammatory cytokines and an enhancement of innate immune functions areobserved, such as increased Natural Killer cell activity. This neuro-immunological tuning process is fundamental for the developing child, since contact with the caregiver's skin represents not only a source of warmth, but a true "information ecosystem" that actively contributes to the colonization of the skin microbiota and, consequently, to the maturation of the systemic immune system (Gilbert *et al.*, 2018).

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If biologically oxytocin modulates homeostasis, neurocognitively it constitutes the fundamental substrate for the construction of "social cognition". The child is not a passive receptor of stimuli, but an organism that constantly attempts to predict the dynamics of its environment (Friston, 2010). In this framework, affectionate touch mediated by oxytocin allows for the "calibration" of the predictive models that the infant brain builds regarding the caregiver and the surrounding world (Fotopoulou & Tsakiris, 2017).

The adoption of the active inference framework – central to recent reflections in neonatology and osteopathic practice – allows us to understand how therapeutic touch is not merely a corrective action, but a process of "precision" communication within the child's generative models (Pezzulo *et al.*, 2015). The brain, interpreted as an inference machine, seeks to reduce prediction error (the discrepancy between what is expected and what is perceived) (Clark, 2013). When a child, especially one in a condition of developmental fragility, experiences unpredictable or invasive touch, their predictive system goes into crisis, generating alarm signals.

Oxytocin, produced in response to reassuring and rhythmic touch, acts by reducing the noise in the system, lowering the precision attributed to negative prediction error signals and simultaneously facilitating the updating of models toward a perception of safety (Fonagy & Target, 2002; Addabbo *et al.*, 2025). In this sense, the osteopath and the parent become active agents of neurobiological scaffolding: through rhythmic repetition and the affective quality of contact, they help the child stabilize internal models in which the relationship is perceived as a source of support rather than a threat (Mercuri, 2025).

Interpersonal synchrony – understood as temporal and dynamic coordination between the biological rhythms of parent and child – is the ultimate outcome of this oxytocin-mediated process (Feldman, 2012). This is not merely a psychological state, but a measurable neurophysiological phenomenon that fosters secure attachment (Bowlby, 1982). Recent studies confirm that the frequency and quality of maternal touch directly predict the resting-state activity and connectivity of the "social brain" networks in the child (Atzil *et al.*, 2011; Brauer *et al.*, 2016).

Oxytocin not only modulates reward (making social interaction intrinsically rewarding), but facilitates the processing of social information, allowing the child to tune into the facial expressions, vocalizations, and intentions of the other (Insel, 2010). In a clinical intervention, the osteopath who facilitates this attunement, is in effect, using touch as an "endogenous biological drug" (Frymann, 1998; Accardi *et al.*, 2023). This approach breaks the cycle of isolation and fear, fostering resilient social cognition even in contexts of genetic complexity or motor development delays, where conventional communication pathways may appear compromised.

Although in clinical practice the two dimensions are intrinsically overlapping

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– especially in the pediatric setting – it is appropriate to analyze the peculiarities that define affective touch versus therapeutic touch, both cited as pillars in recent systematic reviews on neonatal and pediatric manual therapy (McGlone *et al.*, 2017).

Affective Touch

Affective touch is defined by its non-intentional nature in the clinical-rehabilitative sense, but is essentially relational (McGlone *et al.*, 2014). As highlighted, it is mediated by C-tactile (CT) fibers, a population of unmyelinated low-threshold afferent fibers that respond optimally to slow stimulations, with a velocity between 1 and 10 cm/s, and a neutral skin temperature (Olausson *et al.*, 2002; McGlone *et al.*, 2017).

From a neurobiological standpoint, affective touch acts as social glue. Its primary function is the regulation of emotional state and the promotion of the affiliative bond (Dunbar, 2010). It does not aim at resolving a biomechanical dysfunction, but at affective stability. The oxytocin released in response to this type of touch is not just a neurotransmitter, but a signal of "biological safety" that allows the child to modulate their stress response (Uvnäs-Moberg, 2003). In terms of active inference, affective touch reduces the weight (or precision) of the environmental prediction error, reassuring the child of the caregiver's presence and availability (Fotopoulou & Tsakiris, 2017; Addabbo *et al.*, 2025).

Therapeutic Touch: Clinical Intentionality

Therapeutic touch, as practiced in pediatric osteopathy and physiotherapy, adds a dimension of intentional precision to the affective component (Franke 2022). Here, touch is not merely a caress, but a therapeutic gesture aimed at modulating muscle tone and fascial mobility (Tozzi, 2015).

- **Autonomic System Modulation:** While affective touch induces generalized relaxation, therapeutic touch can be used to finely tune the balance between the sympathetic and parasympathetic systems (Porges, 2011). Studies indicate that manipulative osteopathic treatments (OMT) in preterm infants show a reduction in autonomic stress markers, a result that goes beyond the simple "calming" effect of contact (Manzotti *et al.*, 2022).
- **Sensory Integration:** Therapeutic touch acts as a form of guided sensory input (Ayres, 2005). In cases of motor development delays, touch is not only affective, but "informative". It provides the child's central nervous system with proprioceptive and kinesthetic feedback that, in the absence of such intervention,

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would not be adequately integrated, thereby facilitating motor learning and reducing stereotypical or dysfunctional movement patterns (Shumway-Cook & Woollacott, 2017).

- **Synergy in the Multidisciplinary Approach:** The strength of therapeutic touch lies in its capacity to integrate the clinician's technical competence with the relational quality of affectivity (Degenhardt *et al.*, 2014). The clinician does not merely manipulate a body, but "accompanies" the child's biological system toward a state of greater order (entropy reduction) through interpersonal synchronization (Feldman, 2012; Accardi *et al.*, 2023). In this sense, the professional becomes a mediator of exogenous-endogenous oxytocin: the quality of their touch modulates the small patient's biochemical response, creating the necessary physiological conditions for rehabilitative strategies to be received and integrated by the nervous system.

This distinction does not intend to separate the two domains, but rather to highlight how the expert integration of these two modalities is the beating heart of modern pediatric intervention. The clinician who understands the neurobiology of C-tactile fibers knows that, even when performing a maneuver of a technical nature, the "affective" quality of the contact is what ultimately determines the success of therapeutic reception by the child's neurobiological system (McGlone *et al.*, 2017).

The approach based on therapeutic touch and affective tuning is not exhausted by clinical efficacy on the individual patient, but projects itself as a strategy of significant value for the entire healthcare system (Langevin *et al.*, 2001). Recent literature, including systematic studies on manipulative osteopathy, has demonstrated how targeted interventions in pediatric and neonatal settings can produce a measurable impact on the economic sustainability of care (Lanaro *et al.*, 2017).

A finding of particular relevance for health planning is the capacity of osteopathic intervention to reduce the duration of hospital stay, especially in Neonatal Intensive Care Units (NICU) (Lanaro *et al.*, 2017). Studies indicate that manual treatments focused on autonomic nervous system regulation and stress reduction correlate significantly with early discharge of preterm infants (Lanaro *et al.*, 2017; Manzotti *et al.*, 2022). The reduction in length of stay represents not only an improvement in patient outcomes – avoiding prolonged exposure to a medicalized and potentially stressful environment – but translates into a direct reduction in costs for public healthcare facilities, freeing up precious resources (WHO, 2013).

The Model of Multidisciplinarity

The complexity of developmental disorders requires a response that overcomes

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the fragmentation of traditional medical skills (Engel, 1977). The PNEI paradigm offers the ideal common ground for this integration: physicians, psychologists, physiotherapists, and osteopaths can converge toward a shared objective: the optimization of the child's developmental trajectory (Ader, 2007; Accardi *et al.*, 2023).

The figure of the professional utilizing therapeutic touch serves, in this context, as an interdisciplinary "bridge". Integrating touch into clinical practice does not mean adding a procedure, but adopting a vision in which biology (immune and endocrine systems), psychology (attachment and social cognition), and body physics (movement and muscle tone) are considered as a single functional unit (Bottaccioli & Bottaccioli, 2017). This approach is particularly necessary in the treatment of rare pathologies or neurodiversity conditions, where protocol standardization often fails to capture the specificity of the individual child's needs and those of their family.

The Family as Part of the Care System

A central aspect, often overlooked by classical medicine, is the role of the caregiver within the therapeutic process (Minuchin, 1974). Therapeutic touch teaches parents to use affective contact not only to comfort, but to actively "regulate" their child's biological system (Schore, 2001; Accardi *et al.*, 2023). This process of parent empowerment, supported by the osteopath, transforms the home into an environment of continuous care (Dunst *et al.*, 2002).

When parents learn the importance of C-tactile fibers and interpersonal synchrony, treatment does not end with the session, but continues in everyday life, exponentially multiplying the efficacy of the rehabilitative intervention (Feldman, 2012; Mercuri, 2022).

The challenge for future public healthcare lies in recognizing and institutionalizing neurobiologically-based practices that value touch as a resource for care (WHO, 2013). Scientific literature today provides the foundations to validate therapeutic touch no longer as a "complementary practice", but as an integral component of pediatric care, capable of promoting not only immediate well-being, but also long-term health through the protection and development of the child's "social brain" (McGlone *et al.*, 2017).

Movement and Physical Activity: Catalysts of Neuro-Motor Development and Resilience

Touch does not represent the sole mode of engaging the biological system within the PNEI paradigm; it finds its natural evolution in movement. Physical activity, in

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fact, constitutes the terrain upon which sensory integration is consolidated and the motor and social competence of the child and adolescent is defined (Gallahue *et al.*, 2012). Recent studies, including those focused on sports-based integration, highlight how structured movement is not merely a matter of musculoskeletal efficiency, but a powerful driver for the development of complex skills (Diamond, 2000).

Movement, Stress, and Brain Plasticity

Beyond the motor component, physical activity acts as a formidable modulator of the stress axis (Sapolsky, 2004). Through constant practice, the nervous system learns to regulate the sympathetic response and mitigate excessive cortisol activation, offering the child effective tools for managing frustration and intense emotions (Ratey, 2008). This self-regulation process is closely linked to the production of neurotrophic factors: physical activity stimulates the synthesis of BDNF (Brain-Derived Neurotrophic Factor), a crucial protein that acts as "fertilizer" for the brain (Cotman & Berchtold, 2002).

BDNF plays a decisive role in neurogenesis, particularly at the level of the hippocampus, a structure dedicated to memory and learning (Erickson *et al.*, 2011). Thanks to the increase in physical activity-induced BDNF levels, neuronal proliferation and strengthening of synaptic connections are observed, translating clinically into a tangible improvement in selective and sustained attention capacities, as well as greater efficiency in memorization processes (Hillman *et al.*, 2008). In this sense, movement not only prepares the body for action, but predisposes the nervous system to learning, making cognitive functions more plastic and reactive to environmental stimuli (Diamond, 2013).

Physical activity acts in synergy with touch: if the latter provides the basis of affective security and autonomic regulation (mediated by oxytocin), movement allows the child to test their limits, experience intentional action, and build their bodily identity in the world (Rizzolatti & Sinigaglia, 2006). This process is vital for the development of social skills: engagement in shared dynamic activities promotes synchrony, improves motor control, and fosters greater competence in interactions with peers (Brauer *et al.*, 2016).

In this framework, BDNF produced through movement becomes the "nutrient" of plasticity, allowing the brain to consolidate active inference models learned within the care relationship (Friston, 2010). Physical activity, therefore, is not an addition to therapy, but a dynamic continuation of the tuning pathway initiated with touch, essential for the child's social participation and their capacity to face developmental crisis not as a traumatic event, but as a manageable challenge (Feldman, 2012).

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The proposed reflection leads to an unequivocal synthesis: therapeutic and affective touch cannot be relegated to a marginal role in pediatric practice, but must be integrated as a fundamental pillar of neurobiological development (McGlone *et al.*, 2017). Convergent evidence from PNEI sciences demonstrates that child maturation is an intrinsically relational process (Ader, 2007; Accardi *et al.*, 2025). The skin is not simply the anatomical boundary separating the subject from the world, but the primary interface through which the nervous, endocrine, and immune systems communicate with the external environment (Montagu, 1986).

Oxytocin confirms itself, in this synthesis, as the fulcrum around which the entire developmental dynamic revolves (Uvnäs-Moberg, 2003). Through the modulation of the immune response – from T-lymphocyte proliferation to cytokine regulation – and the protection of the central nervous system against excessive HPA stress activation, it acts as a guarantor of infant homeostasis. The capacity of touch to trigger and sustain this biochemical cascade makes manual intervention a powerful non-pharmacological modulator, capable of orienting developmental trajectories toward outcomes of greater resilience and health (Manzotti *et al.*, 2022).

Multidisciplinarity, far from being an optional choice, proves to be the necessary condition for this approach to express its potential (Bottaccioli & Bottaccioli, 2017). The convergence between osteopathic, physiotherapeutic, medical, and psychological competencies allows for reading the child's biological "signal" coherently, translating the complexity of symptoms into a care strategy that views parents not as simple spectators, but as an integral and active part of therapeutic synchrony (Feldman, 2012; Accardi *et al.*, 2023).

Take Home Messages: Towards a Clinical Practice Centered on Relationship and Movement

In conclusion of this theoretical and clinical journey, key points are proposed to guide the practice of professionals dealing with developmental age:

- **Touch is information:** Every tactile stimulus is a communication. The quality of the stimulus, mediated by C-tactile fibers, is decisive for secure predictive models and for the development of social cognition (McGlone *et al.*, 2017).
- **Centrality of the regulation system:** The objective of intervention is the tuning of biological rhythms. The oxytocin produced is the principal mediator of healing and immune protection (Uvnäs-Moberg, 2003).
- **Movement as the continuity of touch:** Physical activity and structured movement are fundamental catalysts of neuro-motor and social development. Integrating movement means allowing the child to pass from the "security of contact" to "competence in action" (Gallahue *et al.*, 2012; Brauer *et al.*, 2016).

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- **Overcoming fragmentation:** The PNEI approach requires constant dialogue among osteopaths, physiotherapists, physicians, and psychologists to ensure sensory and motor stimulation is always coherent (Bottaccioli & Bottaccioli, 2017; Accardi *et al*., 2023).
- **The caregiver as a resource:** Supporting parents means potentiating the most powerful therapeutic resource, transforming the home into an environment of continuous care (Dunst *et al*., 2002; Mercuri, 2022).
- **Ethics of care:** Investing in an approach that unites touch and movement means protecting the neurobiological bases of human development, promoting health and resilience from the earliest phases of life (WHO, 2013).

Ultimately, affective and therapeutic touch stands as the most advanced form of preventive medicine. Recognizing oxytocin as the protagonist of this process transforms our professional practice into a mission of care that goes beyond the body, literally touching the roots of future human development (Montagu, 1986; Uvnäs-Moberg, 2003; Accardi *et al*., 2023; McGlone *et al*., 2017).

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The Pubertal Crisis between Metamorphosis and Identity, between Dependence and Independence

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Abstract. *The pubertal crisis constitutes a critical developmental stage in which neurobiological transformations, new hormonal configurations, and unprecedented relational experiences intertwine, shaping the conditions for a progressive redefinition of identity. From a neurobiological standpoint, selective synaptic pruning and progressive myelination reshape the reward circuits – the mesocorticolimbic system with the nucleus accumbens (NAc) and the ventral tegmental area (VTA) – influencing motivation, emotional regulation, and behavior. The reduction in baseline dopaminergic tone generates a mesolimbic-prefrontal asymmetry that is adaptive but that also exposes, among other things, to massive vulnerability to addiction. The endocannabinoid system, a key mediator of pleasure regulation and synaptic plasticity, takes on particular relevance in adolescence. Early Life Stress experiences interfere with the maturation of these systems, predisposing to lasting alterations. Alongside the neurobiological dimension, the pubertal crisis must be read as a complex relational process: the peer group takes on a rewarding function comparable to biologically salient stimuli. An interdisciplinary reading offers tools to guide prevention, care, and educational support.*

Keywords: *Pubertal Crisis, Endocannabinoid System, Reward Circuit, Early Life Stress, Identity, Addiction*

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Introduction

The Greek term krisis – a key term in the context of the SIPNEI 2026 congress year – etymologically indicates the concept of a crossroads, discernment, the possibility of choice. It is in this original sense, and not in its meaning closer to danger, that the pubertal crisis should be read: an obligatory passage toward a new possible form. A laboratory, a suspended time of continuity and antithesis.

Puberty, together with the adolescence that follows, constitutes one of the most extraordinary and most exposed periods of an entire existence. Neurobiological transformations of comparable proportions occur only in the context of perinatal neurodevelopment, and they intertwine with an affective, relational, and identity-related reorganization without precedent in life. The brain reshapes itself, the body transforms, the world changes meaning. Young people find themselves having to become something that has not yet existed, while at the same time ceasing to be something that already was.

This paper offers an integrated reading of these processes, moving from neurobiology, passing through psychological and clinical aspects, and dwelling on some of the most characteristic and urgent expressions of adolescent suffering in our time: the hikikomori phenomenon, the world of psychonauts, and the question of gender fluidity. Phenomena that are apparently distant from one another, but united by a certainly useful interpretive possibility.

Peripubertal Metamorphosis from a PNEI Perspective

From a neurobiological standpoint, puberty represents the second critical window of brain development – the first being the perinatal one – characterized by processes of selective pruning and progressive myelination (Fagiolini & Hensch, 2000). Synaptic pruning is a process of eliminating weak synapses and optimizing the most used and efficient neural networks, according to the principle of use it or lose it. An intelligent pruning, guided by experience, that consolidates the most active circuits and eliminates the least efficient ones, sculpting the neural architecture that will support adult functioning in its best possible version.

The protagonist of this transformation is the mesocorticolimbic reward system. It is here that the most important game of this stage of life is played, because it is here that the capacity to attribute motivational salience to stimuli, to feel pleasure, to desire, and therefore to choose, is built or diverted. It is, in the fullest sense, the very essence of the crossroads (Barendse *et al.*, 2024).

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The Mesocorticolimbic Reward Circuit: Anatomy and Function

The reward circuit refers to the group of neural structures responsible for the motivation to seek, desire, and crave rewarding stimuli, as well as for learning positive emotions in association with the experiences themselves. The system chiefly involves the basal ganglia in the mesencephalic portion, the prefrontal cortex (PFC), and a large part of the limbic system, with the nucleus accumbens (NAc) and the ventral tegmental area (VTA) as main stations (Nair-Roberts *et al.*, 2008).

The primary role belongs to dopaminergic neurons, which give rise to the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular pathways, each with specific functions that contribute, synergistically and in a coordinated way, to structuring the emotional and behavioral disposition – as well as the entire systemic configuration – for which dopamine is responsible, given its specific biological significance, which has to do with taste, with the gratification deriving primarily from social behavior and, even earlier, from the primary relationship. The association between a stimulus and the gratification that derives from it motivates the search for the stimulus itself, encoding its salience: the motivational urgency, the more or less strong drive to act on a behavior in response. The pathophysiology of many conditions related to impulse dyscontrol and addiction is conditioned precisely by a deviation from the physiology of these structures (Tan *et al.*, 2012).

Dopaminergic Reorganization in Puberty: Mesolimbic-Prefrontal Asymmetry

During puberty and into adolescence, dopaminergic neurotransmission undergoes a profound reorganization (McNeilly *et al.*, 2022). There is a progressive reduction in baseline dopamine tone, with a consequent, paradoxical reduction in the capacity to feel gratification from ordinary stimuli, associated with increased reactivity to highly rewarding stimuli, novelty, and social stimuli. This condition – analogous, in a way, to the dopaminergic dysregulation observed in Attention Deficit Hyperactivity Disorder (ADHD) – generates a mesolimbic-prefrontal asymmetry that does not constitute a developmental defect: it is the biological drive that pulls the human cub away from the family of origin, that opens it to exploration, that allows it to feel attracted to what is new, big, intense. It is, in a word, adaptive.

A role of great interest in the regulation of the reward system is played by the GABAergic neurons of the VTA, which act as a gating mechanism for dopaminergic activity, proving sensitive to stress – therefore to Early Life Stress – but also to early exposure to highly potent rewarding stimuli, such as psychoactive substanc-

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es. Each of these transformations affecting the neurotransmission systems carries a fine biological meaning that is still open to interpretation: it is one of the areas of research in which the PNEI perspective is most prolific.

The Endocannabinoid System: A Crucial Player in Adolescence

Alongside that of dopamine, a role of extraordinary interest – and still largely unexplored in clinical practice – must be recognized for the endocannabinoid system (Pacher *et al.*, 2006). This system operates according to a logic with no equivalent in classical neurotransmission: it is a retrograde system. Its endogenous ligands, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are synthesized on demand by the postsynaptic neuron and migrate backward toward the presynaptic terminal, where they bind to CB1 and CB2 receptors, modulating neurotransmitter release. It is an arbiter of synaptic excitability, a fine feedback system that, in adolescence, finds itself managing one of the most active neural construction sites of existence.

CB1 receptors in the prefrontal cortex reach, at this stage, the highest density of the entire lifespan: a feature necessary to facilitate prefrontal plasticity during the critical window, but one that also makes this very young brain extraordinarily sensitive to exogenous interference. 2-AG actively drives synaptic pruning and the transition of NMDA glutamate receptor subunits – a fundamental biochemical process for the emergence of certain mature cognitive functions – which exogenous cannabinoids, and even more so synthetic cannabinoids, can disturb in a lasting way if exposure occurs during this critical window.

Anandamide shows a peak in the prepubertal phase, then decreases as puberty progresses: this decrease is part of the mechanism that unlocks the hypothalamic-pituitary-gonadal axis, serving as a neuroendocrine gate on the onset of puberty. Estradiol cyclically reduces the activity of certain enzymes involved in this process, producing sex-specific oscillations in endocannabinoid tone, which help explain some gender differences in anxiety regulation and stress response that emerge precisely with puberty (Bigos *et al.*, 2009; Taylor *et al.*, 2000). In the basolateral amygdala, moreover, 2-AG is necessary for the extinction of conditioned fear – that capacity to learn safety which, in many adolescents with a history of Early Life Stress, is structurally compromised.

Endocannabinoids, Dopamine, and Cortisol: A PNEI Triad

The endocannabinoid system directly intersects the dopaminergic system, through CB1 receptors on the GABAergic interneurons of the VTA. Their activa-

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tion reduces the inhibitory tone on dopaminergic neurons, producing a net effect of increased dopamine release in the NAc. This mechanism is the pathway through which biologically significant experiences activate the reward circuit. It is also the mechanism that explains the rewarding effect of exogenous cannabinoids and its amplification in adolescents with a hypersensitive NAc and an immature PFC. A polymorphism of the FAAH enzyme (C385A), present in about 30% of the Caucasian population, produces systematically higher anandamide levels and an amplified mesolimbic response to pleasurable stimuli, with a reward-sensitivity profile that, in adolescence, translates into greater vulnerability to addictive conditioning (Calipari *et al.*, 2017).

The third link in this triad of effects is the dialogue with the hypothalamic-pituitary-adrenal axis. Under physiological conditions, elevated cortisol induces the production of 2-AG in the hippocampus and PFC, which acts retrogradely on CRH neurons, suppressing their release: an endocannabinoid buffer that allows a return to homeostasis after every acute stress. Early Life Stress structurally alters this system, reducing CB1 receptor density and lowering anandamide tone – a hypotonic endocannabinoid system, unable to dampen cortisol and unable to help produce an adequate level of gratification through physiological pathways.

The adolescent with a history of trauma arrives at the window of maximum vulnerability with a biologically determined deficit in pleasure regulation, and the path of external reward becomes proportionally more attractive (Peña *et al.*, 2019).

Sleep in Puberty: A Multiplier of Vulnerability

These aspects cannot be addressed without any reference to sleep regulation, which is systematically sacrificed in young people. Puberty involves a physiological shift in circadian rhythm, mediated by changes in melatonin secretion and by modifications of clock genes (McClung *et al.*, 2005), together with a slowing of homeostatic sleep pressure that tends to delay sleep onset and compress the duration of rest. What is sometimes mistakenly attributed to laziness is the expression of a circadian reprogramming of neurobiological origin.

The VTA and NAc are true extra-suprachiasmatic-nucleus (SCN) oscillators with intrinsic circadian properties, and their regulation is closely connected to sleep quality (Eban-Rothschild *et al.*, 2016). Sleep deprivation in adolescence reduces PFC activity and increases ventral striatum activity in response to rewarding stimuli, amplifying precisely that mesolimbic-prefrontal asymmetry already characteristic of this stage. It reduces D2/D3 receptors in the NAc, lowering the threshold for seeking intense gratification. It dysregulates the HPA axis, with alterations in the cortisol profile that constitute an independent risk factor for the develop-

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ment of mood disorders and addictive behaviors. A further consideration must be added regarding evening exposure to electronic devices: light stably alters sleep architecture, and the continuous stimulation of the dopaminergic system produced by digital content – through a variable-interval reinforcement mechanism – further amplifies sleep-onset insomnia. Sleep deprivation in adolescence is, in short, a multiplier of vulnerability: a brain already physiologically predisposed to seeking strong stimuli, deprived of rest, becomes even more vulnerable to any source of immediate and intense gratification.

The Two-Speed Brain: The Developmental Paradox

The maturational asymmetry between the limbic system, expanding and hyperreactive to emotional and rewarding stimuli, and the prefrontal cortex, still developing until about age 25, produces what can be defined as a two-speed brain. The PFC is the neurological substrate of some of the most sophisticated executive functions: impulse control, planning, risk assessment, delay of gratification. In adolescence it works less well not because it is damaged, but because it has not yet completed its development.

This imbalance serves the precise evolutionary purpose mentioned above: to make the human cub bold enough to move away from the family, sensitive enough to peer-group signals to find new systems of belonging, reactive enough to stimuli to invest in new and potentially rewarding experiences. It is the biologically necessary price of acquiring independence and, under conditions of vulnerability, the ideal ground for the development of addictions of every kind.

Dopaminergic neurons, in adolescence, respond to rewards differently than in adulthood, with amplified sensitivity to rewarding stimuli and a greater ease in structuring new and lasting adaptations, including addictive ones. Epigenetic modifications at the level of histone tails in several regions of the mesolimbic system, induced by exposure to intense rewarding stimuli at this stage of life, can have long-lasting molecular consequences, forming the neurobiological basis of addiction and making the scale of risk in the developmental age significantly higher than in later periods.

Dopamine does not discriminate: it is activated in the same way in the face of meaningful human contact or compulsive activity on social networks, in response to a strongly significant stimulus in an affective relationship or to the intake of a synthetic cannabinoid. Addictions generate feelings of gratification that overlap with those obtained from authentic relational experiences, building reward systems that are progressively more autonomous and self-referential, with significant consequences for clinical framing and treatment strategies.

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Early Life Stress, Oxytocin, and Glucocorticoids

Early adverse experiences – from neglect to abuse, from insecure attachment patterns to genuine relational traumas, including early and particularly marked sleep dysregulation – interfere with the maturation of the VTA and NAc, altering the morphology and functioning of dopaminergic circuits, GABAergic inhibition of dopaminergic neurons, and the dopaminergic response to stress (Baram *et al.*, 2012; Gunnar & Quevedo, 2007). The neurobiological consequence is a reduced sensitivity to natural rewarding stimuli, with states of anhedonia and chronic dysphoria, alongside an amplified reactivity to intense rewarding stimuli (Hanson *et al.*, 2017): a documented ground of predisposition to addictions and mood disorders.

Examining the reciprocal relationships between the oxytocin affiliative system, the dopamine reward system, and the glucocorticoid stress-response system – a cornerstone of the PNEI paradigm – is the way to understand how early affective experience becomes inscribed in the neural architecture and conditions, for years, how the young person seeks and finds gratification (Siegel, 2001; Nakazawa, 2015). Oxytocinergic neurons, which connect the hypothalamus with the mesocorticolimbic system, facilitate reward responses to affective and social cues: the secure bond is neurobiologically protective, and its absence or discontinuity increases the risk that the adolescent will seek elsewhere the gratification that the relationship failed to provide adequately.

The Self Under Construction

Alongside the neurobiological dimension, the pubertal crisis must be read as a relational and affective process of extraordinary complexity. The new sexed body becomes the site of identity redefinition, through phases of discontinuity and, at times, of estrangement from oneself.

The adolescent is called upon to come to terms with the mourning of childhood objects (Winnicott, 1965), to renegotiate attachment bonds with primary figures, to build a self-image that confronts and often clashes with a radically transformed body. Professor Gustavo Pietropolli Charmet, who has devoted his entire professional life to understanding the emotional movements of adolescents, teaches how intensely this process is experienced, an intensity that adults often underestimate: boredom, shame, enthusiasm, a sense of omnipotence, and narcissistic collapse alternate with a speed that defies any attempt at categorization (Pietropolli Charmet, 2008).

The progressive loosening of dependence on primary objects does not proceed linearly: it is accompanied by regressive movements, sudden idealizations and devaluations, and new affective investments that primarily involve the peer group.

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The peer group activates the reward circuits to an extent comparable to biologically salient stimuli: social approval is a primary reinforcer, mediated by dopamine, which in the adolescent takes on an almost imperative valence (Erikson, 1968). Where the adult's normative function becomes fragile – where the parent struggles to maintain the function of limit-setting and containment – the search for recognition within the peer group or in virtual communities takes on the character of a genuine urgency.

Hikikomori: When Withdrawal Becomes the Solution

Among the turmoils of adolescence, the hikikomori phenomenon deserves specific attention today, since it embodies, in an emblematic way, the trajectory that runs from isolation to addiction, passing through the identity crisis. The Japanese term – literally "to stay apart, to isolate oneself" – describes the condition of very young people, but also young adults, who withdraw from social life in a radical and prolonged way, confining themselves to their own room for months, sometimes years, living a parallel and solitary existence, mediated almost exclusively by the internet and electronic devices. Italy's National Centre for Addictions and Doping at the National Institute of Health (Istituto Superiore di Sanità) estimated in 2024 around 66,000 cases in Italy, with a significant prevalence in the 11-to-13 age bracket, placing this phenomenon precisely in the peripubertal period.

From the young person's point of view, withdrawal is not a symptom, it is a solution. A strategy to regulate a reward system and a stress-response system that cannot be managed in any other way. The outside world – school, comparison with peers, family expectations – becomes a source of unbearable suffering, while the room, the screen, and the permanent connection offer a form of gratification that is accessible, extremely rapid, predictable, and controllable. Gaming, social networks, streaming platforms, and virtual worlds operate on a variable-interval reinforcement mechanism – the same scheme used by slot machines – in which the unpredictability of the next rewarding stimulus produces a dopaminergic response that is intermittent but intense, highly resistant to extinction.

Internet and gaming addiction, in these young people, is a superstructure built on pre-existing suffering, which nonetheless progressively reinforces it, making the return to real contact ever more distant and intolerable. From the family's point of view, the hikikomori young person is a painful and often misunderstood enigma: parents oscillate between overprotective attitudes and a paralyzing sense of guilt. The parental function of limit-setting and containment, essential to the structuring of the Self at this stage of life, risks being completely suspended, aggravating the withdrawal process instead of containing it.

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The on-life dimension – that is, life lived indistinguishably between the physical and the virtual, without interruption – is a generational specificity that cannot be ignored in the clinical reading of these cases. For these young people, identity is sometimes built online even before it is built in the body: relationships, sense of belonging, and social recognition pass through screens, profiles, and above all filters. When this space is the only one left, dependence on it stops being a choice and becomes an adaptive response to a context that has made contact with reality unbearable.

Psychonauts and New Psychoactive Substances

The phenomenon of psychonauts introduces an even more specific and neurobiologically relevant variant: that of the adolescent – sometimes even preadolescent – who explores altered states of consciousness through New Psychoactive Substances (NPS), always alone and at home, in an experimental intent that has its own distinctive characteristics and generates a wholly peculiar form of addiction. The term psychonaut, from the Greek psychē (soul) and nautēs (sailor), evokes an image used with pride within the relevant community: the navigator of the mind, the explorer of inner spaces through the skillful use of chemistry.

NPS constitute a continuously expanding universe: to date, more than 4,000 synthetic psychotropic molecules have been identified, belonging to different pharmacological categories. Hallucinogens act on 5-HT2A serotonin receptors, producing perceptual alterations of extraordinary intensity. Dissociatives block NMDA glutamate receptors, inducing states of depersonalization and derealization. Synthetic cathinones act on dopamine and noradrenaline reuptake. Synthetic cannabinoids bind to CB1 and CB2 receptors with an affinity far greater than natural THC, producing much more potent and unpredictable effects. New synthetic opioids act on mu and kappa receptors. New-generation entactogens modulate the release of serotonin, dopamine, and noradrenaline.

The reason these experiences are particularly attractive to adolescents lies in the specific neurobiological configuration already described: a still-immature PFC, a dopaminergic system hyperreactive to rewarding stimuli, but above all a natural tendency to search for meaning and for answers to the great existential questions – who am I? what really matters in life? The adolescent is not merely seeking a high; not infrequently, they are seeking meaning (Frankl, 1963). And when a substance produces what the young person experiences as an inner illumination, a sudden understanding of self and world, the risk that it will be attributed a motivational salience of the very highest order is very high.

To this is added a clinically crucial identity dynamic: the psychonaut becomes

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the expert. In the psychonaut community, active in forums and online groups, expertise about substances builds a paradoxical form of functional identity. In an era in which identity is by definition fragile, the possibility of being recognized as an expert answers the real need to feel like someone, to have a place, to be seen. It is the same neurobiological logic of social reinforcement, with the difference that the recognition is built on expertise in a potentially deadly domain.

Gender Fluidity and New Identity Guises

The topic of gender fluidity in pre-adolescence is among the most debated, and most poorly framed, in contemporary public and clinical discourse. It is necessary to distinguish precisely, and without prejudice, between different phenomena that are too often confused, with consequences that are not without risk for the young people encountered in clinical practice.

Gender dysphoria, according to the clinical meaning attributed to it by the DSM-5, describes a marked and persistent incongruence between experienced or expressed gender and gender assigned at birth, accompanied by clinically significant distress and clear impairment of functioning. It is a real condition, with identifiable neurobiological bases, but certainly not as frequent as the number of young people who today present to services requesting transition would suggest. Data from specialized clinics indicate that early-onset dysphoria, the kind that manifests clearly in early childhood, undergoes spontaneous reorganization in 80% of cases before puberty (Zucker, 2017). It is late-onset dysphoria – the kind that begins or intensifies with puberty – that requires more structured attention, with careful clinical evaluation of any associated comorbidities: social phobia, depression, eating disorders, among others.

What is observed with increasing frequency, and which should not be confused with dysphoria, is a broad gallery of expressions of fluidity in the experience of one's own gender, readable through the concept of an identity gymnasium: attempts by the transforming Self to find forms of coherence and recognition, to explore one's own sense of belonging, to give voice and shape to an identity that does not yet have defined contours. The PNEI perspective offers a specific contribution here: the adolescent nervous system is extraordinarily sensitive to social validation, and the approval of a particular identity by the community powerfully and directly activates the reward circuits. In an era in which online communities make identity solutions immediately available – identities that are, to a certain extent, similar to one another in terms of aesthetics, language, and self-narratives – it is understandable that many adolescents try on this broad and colorful gallery of guises the way one tries on a garment, in a healthy and lively search for the one that best fits a Self still far from being defined.

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The clinical risk is not fluidity itself, but that the identity fragility it may conceal goes unrecognized, and that a purely medicalizing response obscures a need for care with deeper roots. Clinical work with these young people requires a double gaze: recognizing and respecting the exploratory process underway, while at the same time carefully assessing the presence of any structured dysphoria or comorbidities that might benefit from a psychotherapeutic path, before any intervention on the body.

Crisis as Therapeutic Space

The pubertal crisis is the second developmental window, after the perinatal one, in which the brain is extraordinarily plastic, experiences leave deep traces, and preventive and therapeutic interventions can have a significant impact on the future trajectory. Understanding how the reward systems function at this stage, the vulnerability of the immature PFC in the face of highly rewarding stimuli, the role of all the neurotransmitter systems in regulating pleasure and stress, the centrality of social recognition in identity construction, and the weight of early attachment as a neurobiological programmer, is the foundation for guiding prevention and treatment strategies that are effective and respectful of the specificity of this stage of life.

On the therapeutic side, what emerges strongly from the evidence is the primary role of relationship. Addiction – to a substance, to a device, to a closed room – builds reward systems that progressively exclude authentic relationship. Care cannot do without relational exchange: it must contribute to the development of a new experience in which the feeling of well-being can again be achieved within the context of ongoing relationships. The body of work highlighting the countless facets and importance of the oxytocin system, at any age, and its complex interaction with the dopamine system and numerous other neurotransmission systems, in support of a powerfully health-promoting effect of relationship, is becoming ever more detailed.

Work with the family remains essential. The parental function – the one most at risk of fragility in the current cultural and social context – is the first tool of prevention. A parent who manages to maintain the limit-setting function, who is able to tolerate the child's anguish without removing or amplifying it, who offers a containing space in the right measure, is the most powerful protective factor known to the literature.

Finally, the body must not be forgotten. In an era in which most anxieties and uncertainties coalesce around the body, physical activity – especially when carried out in nature and in a group, in a dimension of pleasure rather than performance –

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is an extraordinary therapeutic tool, PNEI in the fullest sense of the term. Setting the body in motion restores endorphin, dopaminergic, and endocannabinoid balance, generating experiences of pleasure not mediated by technology. Physical exercise increases circulating endocannabinoid levels, helping to generate a sense of well-being that reactivates the perception of the body as a place of belonging to oneself, a biologically grounded response to the hardship of the crisis.

Conclusions

The pubertal crisis, multiform and dissonant, remains what it has always been: a fundamental space for the construction of the Self. The crossroads, in its fullest sense, possibility. It is essential that clinical, educational, and relational interventions, whatever the need, be timely, calibrated, and respectful of the neurobiological and psychological specificity of this stage. Our task, as clinicians, as researchers, and as health professionals working from a PNEI perspective, is to contribute with strength and confidence to keeping this space of transformation open: with the strength needed to hold the limit firm, and the confidence essential to preserving young people's freedom to explore who they are and who they can become.

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Designing the Environment to Care for the Child: From the Delivery Room to the Classroom

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Abstract. *This contribution draws upon the concepts developed in the volume Archi-Therapeia. The Influence of Architecture on the Mind–Body Psycho-Neuro-Endocrine-Immune (PNEI) System by Silvia Moneti, teacher architect, and holder of a Master's degree in Psycho-Neuro-Endocrine-Immunology and Integrated Care Science. The topics addressed herein were further explored during the SIPNEI–ELCA (Early Life, Childhood and Adolescence) pre-congress meeting, held in Rome on 23 May 2026 and dedicated to the theme Changing in Order Not to Succumb: Supporting Developmental Crises Through Resources and Opportunities.*

Through a review of the scientific literature, this article examines the role of the built environment as a determinant of health and child development. The evidence reviewed demonstrates that specific design features, including acoustic quality, lighting, color, thermal and hygrometric comfort, and spatial organization, can influence neurobiological processes, sensory development, emotional regulation, learning outcomes, and social inclusion.

Particular attention is devoted to perinatal environments, neonatal intensive care units, educational settings, and design strategies aimed at supporting children with special needs.

The findings suggest that appropriate architectural design can positively influence the children's mind–body PNEI system, positioning architecture as a genuine form of integrated therapy. These considerations highlight the need for interdisciplinary collaboration between healthcare professionals and design practitioners to promote well-being and support harmonious development from the earliest stages of life.

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Keywords: *Architecture, Pnei, Child Health, Neuro-sensory Development, Therapeutic Environments, School Inclusion*

Introduction

This article is inspired by the concepts developed in the volume *Archi-Therapeia. The Influence of Architecture on the Mind–Body Psycho-Neuro-Endocrine-Immune (PNEI) System*, authored by Silvia Moneti, architect, teacher, and holder of a Master's degree in Psycho-Neuro-Endocrine-Immunology and Integrated Care Science. In this work, the author examines the relationship between the built environment and psychophysical health, highlighting how architecture can actively contribute to health promotion.

Child health is the result of a complex interaction among biological, psychological, social, and environmental factors. Among these, the built environment has gained increasing recognition in the scientific literature as a significant determinant of health, influencing neuro-sensory, cognitive, and emotional development from the earliest stages of life. From delivery rooms to neonatal intensive care units, and from domestic settings to educational environments, architecture helps shape the conditions within which children grow, learn, develop autonomy, and establish meaningful social relationships.

Scientific and medical studies have demonstrated that factors such as lighting, acoustics, color, temperature, spatial quality, and environmental organization can directly affect developmental processes and children's psychophysical well-being. Within this framework, designing for childhood requires moving beyond a purely functional conception of space and recognizing architecture as a preventive resource and a health-promoting tool throughout the individual's developmental trajectory.

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 stimulation environments designed for use as labour and breastfeeding spaces.

The first study, entitled *Women's Experiences of Using a Snoezelen Room During Labour in Western Australia* (Hauck *et al*., 2008a), investigated the experiences of sixteen women who used a labour room specifically designed to provide multisensory stimuli under the direct control of the expectant mother. The room featured floors and walls painted in soft warm tones, natural fabrics, comfortable furnishings, and user-controlled lighting systems allowing adjustment of both illuminance

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levels and color temperature. Midwifery care was provided either continuously or intermittently, according to each woman's preferences. Pain management and relaxation strategies included immersion in warm-water baths, acupuncture, aromatherapy, music therapy, massage therapy, and transcutaneous electrical nerve stimulation (TENS). Postpartum interviews revealed that participants perceived the environment as an active therapeutic component that enhanced their sense of control and self-efficacy while substantially reducing pain perception.

Subsequently, the same environment at Osborne Park Hospital was also used as a breastfeeding room. The findings from this second phase of research were published in the article *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 aim of the study was to evaluate the influence of the architectural environment on the breastfeeding experiences of eleven postpartum women admitted to the facility who reported high levels of anxiety or difficulties in establishing an adequate mother–infant bond. At the conclusion of the study, all participants expressed positive evaluations, emphasizing the benefits of temporarily distancing themselves from the conventional hospital environment and accessing a space characterized by a warm, intimate, and supportive atmosphere. Privacy, reduced external distractions, and direct control over environmental conditions promoted maternal relaxation, enhanced self-confidence, and contributed to a more positive breastfeeding experience.

Neonatal Intensive Care Units (NICU)

The design of Neonatal Intensive Care Units (NICUs) warrants careful consideration, as these environments can significantly influence the neuro-sensory development of preterm infants. Over recent decades, Dr. Stanley Graven of the Department of Community and Family Health at the University of Florida has contributed extensively to understanding the impact of NICU environments, particularly on the visual and auditory systems of premature newborns.

Human sensory maturation is known to follow a biologically predetermined sequence, beginning with tactile development, followed by auditory maturation and culminating in visual development. Premature birth does not alter this developmental sequence. Targeted sensory stimulation, when provided at a stage compatible with the maturation of a given sensory system, may facilitate its development; conversely, premature or excessively intense stimulation may disrupt normal neurofunctional organization and maturation processes (Graven, 2000). In this regard, developmental biology recognizes the existence of so-called "critical periods," during which external environmental influences exert a particularly strong

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effect on neuronal connectivity and sensory system development (Graven, 2000; Robinson and Pallasmaa, 2017).

The auditory critical period begins approximately 10–12 weeks before birth and extends through the second year of life. Follow-up studies of preterm infants exposed to inappropriate acoustic conditions during NICU hospitalization have reported persistent adverse outcomes, including delayed language development, impaired auditory discrimination, and reduced ability to recognize complex acoustic patterns (Wright *et al*., 1983). These findings highlight the importance of designing an acoustic environment within NICUs that closely replicates the auditory conditions of the intrauterine environment. From a practical standpoint, this involves maintaining average sound pressure levels below 50 dB and prioritizing frequencies lower than 250 Hz (Graven and Browne, 2008). Such conditions have been associated with improved physiological stability, enhanced weight gain, better sleep quality, and a reduced risk of long-term language disorders (Graven, 2000).

The visual critical period begins immediately after birth, when exposure to light and visual stimuli activates the primary visual cortex and associated neural networks. Assessment of visual development in newborns relies on several interdependent functional parameters characterized by distinct maturation timelines, including visual acuity, horizontal visual field, color perception, and binocular vision (Niessen, 2006). NICUs may not always provide environments conducive to the optimal maturation of the visual system in preterm infants. For example, prolonged exposure to high-intensity artificial lighting may induce retinal damage, the extent of which is related to wavelength, intensity, and duration of exposure. Likewise, natural daylight entering through large glazed surfaces may exceed the infant's tolerance threshold, as neonatal eyelids do not yet provide complete protection from intense light. Another often-overlooked factor concerns the alternation of light and dark periods. Appropriate modulation of environmental lighting is essential for promoting circadian rhythm entrainment and supporting healthy neurodevelopment in newborns.

Chromotherapy and the Use of Colour

To promote children's psychophysical health during growth, it is essential to consider the environments in which they live and study, selecting appropriate colors, lighting conditions, and thermal parameters.

Chromotherapy, a discipline that exploits wavelengths within the visible spectrum (380-740 nanometers) for therapeutic purposes, employs application methods such as exposure to light of specific spectral qualities or the use of pigments on

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walls and furnishings. However, since color perception is influenced by subjective factors and color does not constitute an intrinsic property of objects, the adoption of objective criteria for its assessment and reproduction has become necessary. To this end, the chromatic standardization method developed by the Commission Internationale de l'Éclairage (CIE) in 1931, known as the CIE Diagram, remains the reference framework for color classification based on measurable parameters such as hue, saturation, and luminance, where saturation refers to the purity of a color and luminance indicates the proportion of white or black in its composition.

Studies conducted by Wilms and Oberfeld (2018) have shown that the presence of specific color tones within an environment can modulate skin conductance responses and heart rate, thereby influencing individuals' psychophysiological states. Furthermore, it has been demonstrated (Franklin *et al*., 2010; Palmer and Schloss, 2010) that children tend to prefer colors such as red and yellow, although these hues are associated with increased arousal and heightened alertness. Conversely, young adults show a preference for green and blue, colors that are associated with relaxation, improved study performance, and enhanced concentration (Costa, 2018).

Lighting and Circadian Rhythm

To effectively employ lighting in therapeutic architectural design, it is essential to recognize that visible light is the primary environmental cue through which humans synchronize their biological clock. Circadian rhythms are physiological oscillations with an approximate 24-hour periodicity that regulate numerous biological functions, including core body temperature, hormonal secretion, sleep-wake cycles, and cognitive performance.

In 1998, specific photoreceptors in the human eye were identified, known as intrinsically photosensitive retinal ganglion cells (ipRGCs), which express the photopigment melanopsin. These cells enable the transmission of environmental light information to the suprachiasmatic nucleus (SCN), which ensures the alignment between internal biological rhythms and external environmental cycles (Wahl *et al*., 2019).

Blue light (wavelengths between 380 and 435 nm and correlated color temperature (CCT between 5000 and 7000 K) represents one of the most potent synchronizing agents of the circadian system. Exposure to this spectral component during daytime hours contributes to melatonin suppression, increases in core body temperature, heart rate, and blood pressure, and is associated with enhanced alertness, improved concentration, and better cognitive performance, as well as a reduction in perceived mental effort (Zauner, 2020).

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Conversely, prolonged exposure to low-intensity blue light during nighttime hours (light at night, LAN) may disrupt normal circadian functioning, reducing sleep quality and producing adverse psychophysiological effects. These include significant suppression of melatonin secretion and delayed onset of REM sleep (Bruni, 2015), impaired cognitive processes and reduced academic performance (Fredriksen *et al*., 2004; Gruber *et al*., 2012), as well as associations with oncological conditions (Haus and Smolensky, 2006), metabolic disorders such as diabetes (Kreier *et al*., 2007), cognitive decline (Stevens *et al*., 2007), reproductive dysfunction (Mahoney, 2010), obesity (Bass and Takahashi, 2010), and gastrointestinal disturbances alongside alterations in gut microbiota composition (Codoñer-Franch and Gombert, 2018).

On the basis of these findings, Giménez and colleagues (2017) proposed a circadian-optimized lighting model applicable to living environments, integrating recommendations on color temperature and illuminance levels across the day. According to this model, daytime lighting should employ sources with higher CCT values (approximately 4000-6500 K) to support mood regulation, cognitive performance, and physiological activation. Under these conditions, average illuminance should be around 300 lux, with potential increases up to approximately 1500 lux during the late morning hours (approximately 10:00 a.m. - 01:00 p.m.). In the evening, color temperature should be progressively reduced and maintained below 3000 K to facilitate melatonin secretion and sleep readiness. Concurrently, illuminance should decrease to a maximum of approximately 100 lux in the early evening, and further decline to values between 5 and 10 lux during the nocturnal rest period.

Temperature and Relative Humidity

Temperature and relative humidity are two fundamental parameters in the design of healthy indoor environments capable of promoting well-being. Studies addressing this topic typically distinguish three thermal conditions:

- cold environments (below 17°C);
- thermo-neutral environments (approximately 22°C);
- hot environments (above 30°C).

A 2018 study (Xiong *et al*.) evaluated the impact of temperature and relative humidity (RH) on learning processes, memory, concentration, and problem-solving in environments with an illuminance of 300 lux, sound levels not exceeding 50 dB, and 50% relative humidity. Participants achieved the highest levels of learning efficiency and problem-solving performance in the thermo-neutral condition (22°C), whereas exposure to cold temperature (17°C) was associated with en-

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hanced concentration and attentional focus. Conversely, it has been demonstrated (Lan *et al*., 2011) that indoor temperatures above 30°C may lead to reduced cognitive performance and increased anxiety states, even in individuals who have psychologically adapted to thermal discomfort.

Montessori Furniture

The same level of care should be applied in the design of school buildings, with the aim not only of supporting educational attainment, but also of fostering students' autonomy, self-efficacy, and stress reduction.

A significant example in this regard is represented by the "Children's Houses", conceived by Maria Montessori starting in 1907 for children aged 3 to 6 years. These facilities were not limited to traditional classroom spaces but also included areas dedicated to meals, rest, and creative activities, under the supervision of trained educators. The environments, designed to be welcoming and well-lit, recreated a domestic-like atmosphere and were organized into interconnected thematic areas arranged according to a sequential logic. Teaching materials and furnishings, preferably made of natural materials such as wood, paper, and fabric and treated with non-toxic substances, were positioned according to rigorous criteria of spatial and temporal organization, consistent with their function and aimed at ensuring maximum safety.

Special attention should be given to the Montessori line of furniture, increasingly widespread in both domestic and educational settings due to their functional characteristics. These elements are designed to adapt dynamically to children's growth, fostering decision-making abilities, curiosity, and autonomy.

Among the most relevant furnishings is the Montessori floor bed, introduced from approximately 18 months of age, characterized by a mattress slightly raised from the floor and the absence of side rails. These features allow the child to independently climb in and out of bed while reducing the risk of falls. The structure often presents a hut-like form, which can be covered with fabric strips to create a more enclosed and protective environment, thereby enhancing the child's sense of security.

The Montessori mirror accompanies child development from as early as 6 months, a stage in which infants begin to recognize themselves in their reflection. Initially, the mirror is mounted horizontally on the wall, allowing the infant to observe themselves even in a lying position. Later, when the child acquires the ability to stand and walk, a support bar may be added to enable standing practice and balance exploration.

The Montessori wardrobe is designed at a height that facilitates independent

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access for the child, allowing them to reach each compartment autonomously. The structure does not include doors, as clothing, shoes, and accessories are displayed visibly, either hung or placed in transparent or clearly labelled containers. The adult, whether parent or educator, pre-selects the items made available, thereby encouraging the child to make conscious and autonomous choices.

The Montessori stool, usable from approximately 18 months of age, represents a versatile tool that allows children to actively participate in daily activities alongside adults, such as food preparation or personal care. Thanks to its adjustable height, children can safely reach standard work surfaces (such as desks or kitchen counters) without risk of falling, thereby learning to wash their hands, open drawers, or collaborate safely with adults.

School Architecture and Hearing Impairment

School environments can represent concrete tools for inclusion for students with visual and hearing impairments, helping to overcome the barriers that these conditions may impose on communication and active participation in educational pathways.

Deafness, whether total or partial (hearing loss), does not in itself constitute an insurmountable obstacle to the transmission and acquisition of knowledge. From a communicative perspective, content delivery can be ensured through alternative channels, particularly visual-gestural modalities, which compensate for the student's auditory and vocal deficits (*Dizionario di Pedagogia Speciale*, 2019). The effectiveness of inclusive education for students with hearing impairment therefore depends on the deliberate design of didactic and environmental strategies that facilitate access to information and reduce associated discomfort. Among the most common design shortcomings in classrooms intended for students with hearing loss are inadequate functional layout, excessive background noise, prolonged acoustic reverberation, and suboptimal lighting conditions. These factors may generate cognitive and physical fatigue, distraction, reduced academic performance, and difficulties in social interaction.

Regarding spatial layout, the seating position of students with hearing impairment should be predetermined and shared among all teachers within the class council. Placing the student's desk at a distance greater than four meters from the teacher's desk is not advisable, as this would result in a reduction of approximately 20 dB in sound intensity, with a consequent decrease in speech intelligibility and reduced ability to lip-read the instructor.

Environmental noise, originating from both external and internal sources, represents an additional barrier to accessibility. Careful spatial planning is essential in

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order to separate high-noise areas (such as gyms, music rooms, or recreational spaces) from standard classrooms, which require lower noise exposure. This can be achieved by introducing acoustic buffer zones such as corridors or storage areas.

Reverberation time, defined as the persistence of an acoustic signal within an enclosed space, is a critical parameter for classroom acoustic quality. According to current standards, the optimal reverberation time in school classrooms should range between 0.4 and 0.6 seconds, whereas empirical measurements (Caroselli, 2012) have reported values between 3.25 and 5.37 seconds, indicating poor acoustic performance. Mitigation strategies include the installation of sound-absorbing panels on ceilings and walls, replacement of windows, use of wooden storage units, and elimination of metallic furnishings, which, in addition to increasing reverberation, may generate electromagnetic fields potentially detrimental to cochlear implant devices.

Lighting plays a crucial role in optimizing lip-reading and the visibility of interactive whiteboards. For this reason, doors with transom windows should be avoided, curtains should be installed to regulate natural light, and artificial lighting should be designed to ensure uniform illumination without glare or excessive contrast, thereby guaranteeing optimal visual conditions.

A further aspect concerns the communication of school announcements, which are often transmitted exclusively through auditory signals such as bells or fire and earthquake alarms. To ensure autonomy and safety for students with hearing impairment, these systems should be integrated with visual signalling devices, such as light-based displays with color-coded indicators corresponding to different types of alerts, ensuring equitable and accessible access to information.

School Architecture and Visual Impairment

The term visual impairment encompasses both total blindness and low vision, the latter defined as a qualitative and quantitative impairment of visual function. As highlighted in *Disabilità sensoriali a scuola* (AA.VV., 2015), it is essential that children with visual impairment are encouraged from early childhood to develop sensory substitutions, interacting with their environment through the auditory channel, movement, and haptic exploration. The latter, in particular, consists of the preliminary analysis of details through tactile perception, enabling the child to construct a comprehensive mental representation of surrounding objects.

To facilitate school inclusion, it is advisable to accompany the student in exploring the environment prior to the start of educational activities. This practice may reduce anxiety, feelings of loss of control, and disorientation, particularly in contexts involving peer groups. Within the school setting, signage systems can be op-

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timized both horizontally and vertically by integrating visual and tactile elements. The use of chromatic variations on walls or flooring allows differentiation of functional areas, while the provision of Braille signage and multisensory 3D maps enhances accessibility. Furthermore, the use of object cues at classroom entrances can indicate functional spaces: in early childhood education, for instance, three-dimensional objects such as a scented soap may be used to identify bathrooms, or a spoon to indicate the dining area, whereas in higher educational levels these are typically replaced by embossed symbols. To further improve orientation, door locks, light switches, and electrical outlets should be marked with high-contrast colors or contrasted against the background, and doors may be painted in different colors on each side so that low-vision students can more easily determine whether they are open or closed.

Similarly to what occurs in domestic environments, the spatial arrangement of classroom furnishings should remain stable over time, preventing the student from continuously reorganizing spatial references. To support mobility and autonomy, the student's desk, the teacher's desk, and storage units may be marked using high-contrast colors, small meaningful tactile objects attached to surfaces, Braille labels, or large-print signage. These measures support not only environmental navigation and material management but also the development of autonomy, self-esteem, and self-efficacy.

Given the size and operational requirements of certain tiflological assistive devices (such as magnifiers or screen readers), it may be necessary to provide a secondary support desk adjacent to the student's main desk, with both surfaces covered in non-slip materials to prevent the falling of objects. Traditional desks often force visually impaired students into poor postural habits, such as excessive forward bending, which may lead to progressive postural deformities. A more appropriate solution consists of a height-adjustable desk with an inclinable surface, preferably made of matte-finished metal to reduce glare and allow stable fixation of books and notebooks using magnetic supports.

Autism, TEACCH, and Structured Teaching

Autism is a neurodevelopmental disorder characterized by significant impairments in social communication and interaction, as well as the presence of restricted, repetitive patterns of behaviour, interests, or activities (*Dizionario di Pedagogia Speciale*, 2019). Among the main difficulties associated with this condition are cognitive inflexibility, limited adaptive capacity, and impaired understanding of environmental context. In order to address the specific needs of individuals with autism spectrum disorder (ASD), the TEACCH Program was developed in the 1960s

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as an integrated and comprehensive intervention model supporting individuals across the entire lifespan, with the aim of promoting the development of motor skills, self-efficacy, cognitive flexibility, behavioral regulation, and the achievement of the highest possible level of autonomy in personal, social, and occupational domains (Fretti, 2020).

The TEACCH Program is based on structured teaching, a methodological approach that involves the reorganization of the physical environment, carefully calibrated sensory input, the use of visual supports, and the structuring of tasks, in order to compensate for deficits in adaptation and contextual understanding. Within this framework, structuring space means translating the educator's verbal and abstract instructions into concrete environmental cues, based on furnishings, objects, and tangible materials that directly communicate to the individual with ASD clear information about the space they are in and the activities they are expected to perform within it. A truly inclusive school should therefore provide distinct and specifically designed environments dedicated to individual work, group activities, and relaxation, each immediately recognizable and functionally organized.

The individual work area is typically arranged with a central desk and side shelving units: the left shelf is used by the educator to place assigned materials, while the right shelf is used by the student with ASD to store completed tasks. Group activity spaces, on the other hand, are organized with circular tables surrounded by four to six chairs, identical in shape but differentiated by color, enabling the student to identify their assigned seat based on a predetermined color code. When necessary, the teacher may sit alongside the students using a clearly distinguishable chair. Finally, relaxation spaces should be located in quiet areas, equipped with adjustable artificial lighting and shading systems for natural light, in order to reduce sensory overload that may trigger emotional dysregulation or challenging behaviors. It is also advisable to include soft flooring such as carpets, along with sofas, poufs, and cushions, and to allow access to preferred low-volume music.

Research conducted by Schopler has shown that many individuals with ASD fall within the category of "visual learners", meaning that they acquire and consolidate skills more effectively through graphic and visual means rather than verbal instruction. For this reason, it is essential to integrate visual supports into both school and home environments, providing detailed information about daily activities, required tools, and people they will encounter. This approach makes each situation more predictable, reducing stress associated with routine changes and unexpected events. Furthermore, visual schedules help mitigate deficits in attention and memory, compensate for communicative difficulties, foster student independence, and enhance self-motivation (Schopler *et al*., 1998).

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Snoezelen Room

The term "Snoezelen" refers to a controlled multisensory stimulation approach, developed in the 1970s by healthcare professionals working in a Dutch centre specialized in the care of individuals with intellectual disabilities. Initially conceived as a purely recreational space, the Snoezelen Room has progressively demonstrated its therapeutic potential, particularly when used under the supervision of a trained healthcare professional (Nasser *et al*., 2004).

Over the past two decades, the scientific literature has produced numerous studies documenting the positive effects of Snoezelen Rooms in individuals with a range of conditions, including children and adults with autism spectrum disorder (ASD), intellectual disabilities, and learning disorders.

From a structural and environmental perspective, the Snoezelen Room is typically characterized by a surface area of approximately 30 m^2, with walls and floors covered by padded panels and soft color schemes. The environment is windowless and relies exclusively on artificial lighting sources, carefully calibrated to prevent sensory overstimulation. The equipment within the room is designed to provide multisensory input across the visual, auditory, olfactory, and tactile modalities, including wall-mounted projectors generating dynamic light effects, large containers with moving colored liquids, mirrors producing modulated reflections, aromatherapy diffusers releasing mild fragrances, music therapy devices, ceiling-mounted swings, cushioned seating of various geometric forms, as well as pillows and blankets aimed at promoting relaxation.

Interviews conducted with parents and siblings of individuals with autism spectrum disorder following exposure to a Snoezelen Room environment revealed that this setting promoted a greater sense of family intimacy, fostering feelings of protection and safety in relation to the external world. Parents reported experiencing increased serenity and engagement during shared activities, while siblings demonstrated more active and motivated participation, to the extent that they requested more frequent sessions. Concurrently, the child with ASD exhibited enhanced responsiveness and communicative behaviour towards family members, alongside increased self-sufficiency and improved pain management abilities, suggesting a positive impact not only at the relational level but also in terms of emotional regulation and behavioral functioning.

Conclusions

The evidence presented supports the view that architecture cannot be regarded as a mere "container" for healthcare, domestic, or educational activities, but rather

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constitutes an active component of care processes and health promotion. Environments designed according to scientifically grounded criteria can support neuropsychological development, reduce stress, enhance autonomy, and promote the well-being of children and their families.

Within this framework, architecture assumes the role of a genuine form of integrated therapy, capable of complementing clinical and educational interventions through the modulation of environmental conditions. Achieving this objective requires stable collaboration among physicians, psychologists, educators, and architects, who are called upon to integrate different competencies and disciplinary languages in response to the needs of a single "patient": the child. Only through an interdisciplinary approach will it be possible to create environments that do not merely host care, but actively contribute to its generation.

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