Research Article

DOI: http://dx.doi.org/10.53043/2347-3894.acam90015

Body NPI Dimensions, the Neural, Perfusional, and Interconnective Matrix

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Asian Journal of Complementary and Alternative Medicine. Volume 09 Issue 3

Published on:17 /09/2021

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Cite this article as: YU, Edwin Chau-Leung. *Body NPI Dimensions, the Neural, Perfusional, and Interconnective Matrix.* Asian Journal of Complementary and Alternative Medicine, Vol 9(3), 71-78:2021.

ABSTRACT

A sustainable body with biological robustness for life is subsumed as it develops with evolutionarily conserved embryogenetic and organogenetic mechanisms. The neural, perfusional, and interconnective elements (NPI) as three dimensions in the contextual assembly of the body provide a basic adaptive mutually sustaining matrix. The fascial connective tissues stabilize and facilitate external-internal body formation while the neural and vascular elements, co-directed since early development, adapt flexibly for new changes over the preset life unit. The interactive array of body NPI dimensions has all along been underemphasized. This paper makes a short description of the makeup of this complex.

Keywords: Body NPI dimensions; Fascia; Connective tissue; Neuro-vascular complexity; Robustness

DEVELOPING A SUSTAINABLE BODY FOR LIFE

Three Basic Dimensions before birth

Human body development after conception proceeds at cellular level proceeds as a consequence of multiple processes including proliferation, differentiation, acquisition of polarity, and cell movement. In order to develop unfailingly a sustainable body for life, embryogenetic and organogenetic mechanisms of development are highly conserved evolutionarily among species at tissue, cellular, and molecular levels [1,2]. Patterning and cellular migration [3] form the complex structures to produce the recognized morphogenesis of embryos and organs. Self-organization depends both on chemical and on physical cues [4-7].

In producing functional tissues and operational organs that match the physiological needs of the organism, it needs a tightly regulated organization in time and space. The neural, perfusional, and the interconnective NPI matrix develop early as three essential dimensions together and spread out their contextual assembly over the body. The NPI three dimensions are mutually enhancing during development. Chemical signals as well as mechanical signals [8,9] mediate information propagation. The mesenchymal interconnective dimension with its biophysical attributes contributes to instructive sculpting of the embryo topology [10] from inside up to the musculoskeletal and mantle frame. Nervous elements and blood vessels, ramifying the same mesenchymal environment, develop in parallel following similar differential cues from the connective tissue environment. Nervous and vascular elements co-directed in an entanglement relationship [11] branch alongside progressively in tree-like network to reach every organ and the periphery. In general, cellular level genetic networks that shape the organs are evolutionarily conserved, while cellular-physical mechanisms workup is a consequence of shared physical organization rather than due to evolutionary descent [12]. With the NPI dimensions, the formation of tissue barriers and boundaries, useful in resisting pushing or pulling forces, is complemented by informational and perfusional elements going around or piercing through them. The setup ensures the ramifying sophistication of body elements in formal order.

Composing the body makeup after birth

The three NPI dimensional elements, along with the hardcore of organ systems under a body mantle, steadfastly maintain and sustain the individual throughout life. Developmental windows open during pregnancy to allow the primal setup varying degrees of adaptations to its environment. The setup at birth endows biological robustness [13] so that individuals sustainably grow and develop in momentum, preserving well innate characteristics and installed assets while overcoming living demands. With biological robustness, doubly assured mechanisms are built in to make sure that the outcomes of biological processes are stereotypical even when environments vary or perturbations arise [14].

The topology of the three NPI dimensions of fascial, circulatory and neurohumoral networks build up biological robustness of the final contextual assembly of the body. The fascia sheets as interconnective matrix would encase, separate and stabilize various parts while sustaining interactively the various body functions. The corresponding development, structural relationship, and functional association between neural and vascular elements are closely related in health and disease [15]. The fascial, circulatory and neurohumoral elements as three dimensions spreading together contribute to shaping interactions between external and internal domains. With their supportive infrastructure, the individual flexibly adapts to new changes over the existing balanced life unit after birth. While the operational organs embody the body hardcore, five self-vitality subsystems consolidate their interactive functions through remodeling with well-patterned dynamics in response to tune in with the environment [16]. The base is thus established for the human being attains the physical, cognitive, and psychosocial development throughout the lifespan.

DEVELOPMENT OF THE THREE BASIC DIMENSIONS

The NPI interactive array of neural, perfusional, and interconnective elements as three dimensions provide a basic adaptive mutually sustaining matrix. In the fascial connective system woven with the circulatory and neurohumoral elements, the living organism is in fact building up a network with paths for the transportation of energy signals including Meridians [17]. Nei Jing describes how the parts of mind and body are interacting with the environment through the energy processes (Qi), circulatory channels and blood as well as fascial system to consolidate related Zang organs, vitalized by meaningful ideas and intention up to the enduring will, well bred-in-the-bone [18].

Fascial dimension

During embryonic development, different forms of connective tissues (CTs) originated from undifferentiated mesenchymal cells derived from mesodermal and mesectodermal (neural crest) cells. CTs have different forms as bones, cartilage, tendons, ligaments, and irregular connective tissue [19]. Mesenchymal stem cells were noted for many years for their ability to differentiate into more than one type of the cells that form connective tissue in many organs [20]. These cells migrate and diffuse throughout the body of the embryo. Cells belonging to different germ layers, mediated by mesenchymal determinants, direct the role and functions [21] as specific key transcription factors or signaling molecules direct CTs differentiation into different types. The Sox5/6/9, Runx2/Osx, Scx/Mkx/Egr1, and Tcf4/Tbx5/Osr1 genes induce mesenchymal stem cell differentiation into either cartilage, bone, tendon or irregular connective tissue [22].

The fascial system can be viewed as sheets and bundles of CTs that interpenetrates and surrounds all the various organs, muscles and bones and cartilage as well as nerves and vessels [23]. The bones and cartilage are notably specialized CTs. Taking aside *loose connective tissue* as that filling unfilled spaces, CTs in this fascial system could be viewed in two groups for a more effective understanding of the body.

1. CTs along the body tendomuscular frame, where tendons, muscles and bones provide a biomechanical system in actions. Ligaments from bone to bone and tendons from muscle to bone are two main types of CTs that enforce the muscular-skeletal system in actuating movements. In particular, their alignment to transmit forces over a distance is consolidated by *dense regular connective tissue*.
2. CTs penetrating and surrounding the various organs, where *dense irregular connective tissue* predominates. The dense irregular connective tissue embeds and scaffolds different body organs as a protective envelop, with scattered cells embedded in high extracellular matrix content. Dense irregular connective tissue also wraps around the body under the mantle and includes joint capsules, periosteum, and aponeuroses. As it forms a stroma and provides structural support, fiber orientation is multidimensional.

To start with, during development of both dense regular CT and irregular CT, Type I and type III collagen are expressed. During maturation, type I collagen predominates in adult tendons with dense regular CT. On the other hand, both type III and type VI collagen are still expressed in mature irregular CT [24-27].

The fascial system enfolds the tendons, muscles and bones and ligaments. CTs are important in this tendomuscular frame: CTs exist between every cell, fiber, and fascicle of the muscle, bones of the skeleton as specialized connective tissue are held firmly together by ligaments, muscles are attached to bone by tendons, and tendons with dense connective tissue in parallel array of fibre bundles provide great tensile strength. This broad presence of CTs in the breadth of interactive musculoskeletal framework allows for effective and powerful muscle contraction over joints (which cartilage is also one of CTs with an abundant intercellular substance facilitating gliding movements), while tendons transmit forces generated by muscle contractions to bones for joint movements maintaining articular stability. Simply, different forms of CTs make up this interconnectivity array.

Evidence indicate more underlying interactive biological mechanisms around this CT continuum as each part develops its special role and usage. CTs are important in the regulation of developmental and regenerative myogenesis, and defect in connective tissue-muscle interactions can lead to related human pathology [22]. Dense regular connective tissue of tendons induces muscle development. For example, tendon is implicated in the final patterning and position of muscles at least in the mouse forelimb [28]. Bi-directional muscle-CT communication directs a correct assembly of the musculoskeletal system during development and up maintaining adult muscle health. Vice versa, tenogenic and ligamentogenic differentiation starts with inductive signals from nearby sclerotome and myotome [29,30]. Tendons require muscle to fully develop embryologically [31]. From head to axis, axial tendon initiation is dependent of muscle, while for head and limb tendons, muscles are required full differentiation, though not for tendon initiation [22]. All these CTs development in the musculoskeletal system highlight their important interactive information signaling necessary for proper morphogenesis of a tensile system.

On the other hand, CTs penetrating and surrounding the various organs are dense irregular connective tissue which provide support and reserves. These include the CTs of peritoneum and CTs of fibrous pericardium which provide resilience to forces stretching from many different directions. Finally, loose areolar connective tissue is widely distributed, and relatively unspecialized. Some embed adipose tissue, a form of connective tissue with cells are specialized for energy-rich reserves. Various stationary cells and migrating cells are found in their high extracellular matrix content.

Collagens are large, triple-helical proteins that form fibrils and network-like structures in the extracellular matrix. The collagen triple helix as a module through oligomerization acts as a structural organizer that is relatively resistant to proteases and also establishes multivalent supramolecular networks. The collagens may have participated in the evolution as early as in metazoans. Collagen IV is ancient, highly conserved through evolution and present in all mammals. Its presence enables the assembly of a fundamental architectural unit for tissue formation [32]. With specialized high-avidity collagen-receptor integrins, the body of chordates probably through these cell adhesion receptors have evolved out bone, cartilage, circulatory and immune systems [33]. The emergence of collagen I in vertebrates provide an advantageous increase in stiffness for support of long-range force propagation in a tensile system and the development of low-compliant tissues necessary for vertebrate traits including pressurized circulation and renal filtration [34].

All forms of CTs are composed of extracellular fibres, ground substance, and stationary and migrating cells. The proportions of these components would vary from one part of the body to another depending on the local structural requirements. Major functions of CTs include binding and supporting, protecting, insulating, storing reserve fuel, and transporting substances within the body. Moreover, understanding that development and orientation of CTs are closely associated with nervous and perfusional elements expand our understanding of their dynamic functions.

Neural and vascular dimensions

While the fascial connective tissues stabilize and facilitate body formation be adapted external-internally, the co-directed neural and vascular elements adapt flexibly for new changes over life for a balanced snug and fit outcome. Its complexity is recently described at length [11]. Nerves and vasculature since early development go in parallel following similar differential cues from the mesenchymal connective tissue. Neural and vascular branching are closely associated alongside and patterned together throughout development and up to adulthood.

Starting embryologically, pericytes present around the endothelial cells in every vascularized tissue in the body generate early microvascular structures before recruiting endothelial cells to line these vessels [35]. Positive blood vessel patterning signals are initiated by the embryonic neural tube [36]. Growth cones for neurons and for vasculature project onwards, sharing receptor expression [37] and other features [38].

In the periphery, nerve-artery congruence is established through nerve-derived signals that direct arterial differentiation and regulate patterns of angiogenic remodeling [39]. In the developing brain, pericytes appear early during vascular development [40], and neural tube-derived signals regulate sprouting capillaries to induce formation of blood brain barrier characteristics in the neural tube vasculature. Their symbiotic relationship is demonstrated by the close association between nerves and blood vessels as neurovascular bundles in the periphery and as neurovascular unit in the brain [41] as well as the correlation between neuronal and vascular cells [42,43]. Information and perfusional resources go together to suit spatial and temporal needs.

NEURAL, PERFUSIONAL, AND INTERCONNECTIVE ELEMENTS CO-PLAY TO LIVE

The three dimensions as a whole in the body

An overview of the body described it comprehensively for a functional-anatomical whole [16]. Four layers are described with the mantle as borderzone, the underlayer interface as interactional zone, the core with organ systems, and the deep biostratum of resources, all subjected to constant changes. The hardcore consist of operational organ systems - cardiovascular system, lymphatic system, respiratory system, digestive system, nervous system, endocrine system, urinary system, and reproductive systems. The whole musculoskeletal system is anchored together with the integumentary system to enable the body to move about. Taking advantage of biological robustness endowed in early life, the individual sustains his body through living with well-patterned dynamics remodeled integrally and recurrently to suit environment [44]. Self-vitality subsystems [16] continually remodeled the buildup of well-coordinated dynamics patterned for the core-vs-match necessities of life in individual environment.

Bound outside by the mantle, the body is subjected to surrounding physical and biochemical changes. As the body borderzone stabilizes, acts, reacts, and shape overall outer feeling and reaction, a correspondence mechanism is set up between the body and the outside world, through processes including traction, immune surveillance, border sensing, heat transfer, and microbiome sampling. The fascia sag of the whole body, from the mantle to the inner organs, are formed as multiple sets of different connective tissue in the transfer of this correspondence, also aligning itself with the tendo-musculo-skeletal frame. Nervous and vascular elements, following similar differential cues from the environment of CTs, have their growth cones in the embryo extending filopodia and dissolving confronted obstructions by secreting proteases to project onwards [45,46]. Consequently, they ramify the body by neurovascular bundles that penetrate many structures, even tunneling through clammed complexes of CTs, and also reach the periphery by piercing the deep fascia out to the superfices.

The impressive close association of this interlocking inter-woven matrix of the three body NPI dimensions demonstrates how they significantly interact for the individual as a whole.

Microenvironment facilitating interactions together

Starting in the embryo, the body is endowed from genetic, epigenetic and developmental programs to prepare for life. After birth, the real world involves fluctuating levels of both internal and environmental perturbations, and the NPI dimensions embody adaptable coordinative setup poised for requisite changes for successful survival.

Nutrients and waste products are exchanged in tissues in the organ systems. While cells in CTs maintain the extracellular spaces with conditions that facilitate this exchange, the exchange must traverse perivascular spaces in them. Nervous elements supports and directs the development of blood vessels to carry necessary nutrients, oxygen, proteins to all organs via the interstitial space. Immunity cells migrate out from the blood vessels. Fibroblasts in the connective tissue could generate mesenchymal stem cells [47,48]. Fibroblasts in CTs act as stromal cells and as parenchymal cells in several specialized connective tissues. Fibroblasts are more than collagen-producing cells and in fact remarkably diverse in different tissues across the body, and even within the same tissue [49]. Fibroblasts in most organs are actively involved in regeneration apart from repair [50].

The setup of the NPI dimensions is a crucial body framework for its adaptivity. The surrounding physical stimuli amongst other chemical, biological and social cues and demands are reacted upon and acted through their interplay. Fibroblasts when migrated to tissues with different tension would change into different cellular phenotypes accordingly [51]. The mechanical properties of the extracellular matrix (ECM), including the fiber density [52,53], fiber orientation [54], and cell–substrate adhesiveness [55,56] can influence cell migration. On the other hand, cells can inducing permanent strain in the ECM [57,58] can significantly remodel the matrix, forming bundles of aligned densified collagen fibers [58]. These bilateral influences between cells and CT have been well studied [59-62].

Physical forces and changes in the mechanical properties of cells and tissues contribute to development, cell differentiation, physiology, and disease. Even in vascular tissues, adherens junctions supporting the integrity of the vascular tube and regulating tensile forces comprise the basic cellular adhesions between endothelial cells. Mechanical and chemical cues and stimuli should be considered together. The extracellular matrix

(ECM) serves as a scaffolding for cells including stationary cells and cells migrated in. Adherence of cells to the ECM facilitates migration. Stimulated fibroblasts during injury and inflammation migrate into the site with formation of new collagen profusely for scar formation. Mast cells migrated in from the blood contain granules with histamine and heparin which affects vascular permeability and delay blood clotting.

The NPI fascial, circulatory and neurohumoral elements are woven together to shape interactions between external and internal domains. Stem cells reside within stem cell niches in extracellular matrix proteins that provide signals to govern the stem cells. A growth factor nrg-7, produced by neurons, stimulates stem cell proliferation, and increases after removal of collagen IV [63]. Mesenchymal stem cells, even for their small numbers in adult tissues, contribute to tissue cell turnover and also respond to tissue damage [64,65]. Maintenance of potency of adult stem cells require physical interactions with ECM [66]. Even in the bones, skeletal stem cells are essential for development, growth, and maintenance of the skeleton [67]. Physical cues through the fascia regulate stem cell fate and function during embryonic development and in adult tissues [67].

More than simply repair, regenerative functions can be seen [50]. In adults, resident stem cells allow recovery from mild damage in tissues and organs. In highly regenerative organs such as the intestine, fibroblast are actively maintaining the stem cell niche [68]. Fibroblasts activated after injury would secrete growth factors and mitogens in remodeling structural components of ECM to restore normal tissue architecture in the liver with proliferation of differentiated cells [69].

In the adult, endothelial cells still show significant growth potential, even for regenerative or pathological processes [70,71]. Neurogenesis and angiogenesis are closely associated, with endothelial cells in vascular niches releasing cues for neural stem cells [72,73]. Mesenchymal cells located within or in proximity to the blood vessels wall, including pericytes, adventitial fibroblasts and mesenchymal stromal cells, are well coordinated so that their responses contribute well to inflammatory states or else fibrotic problems [74]. Blood vessels and vascular niches in bone are also critically important in regulating bone development and physiology [75].

NEURAL AND VASCULAR ACTIVITIES ADAPTIVELY UNDER THE FASCIAL SUPPORTIVE COVERAGE

It can be said that the connecting tissues provide the grounding base for neural and vascular fronts. Pushing forward, information and perfusional resources go hand in hand. Environmental cues would input as patterning signals. These NPI dimensions secure for the individual in his forward thrust with perfusional support, and also provide innate vascular and connective cells with proliferation and significant growth potential ready for tissue repair and regeneration when required. Responsive to mechanical cues and with the nerve-vascular entanglement governing appropriate microvascular density towards needs, nervous activity and perfusion go together to meet forwarding fronts. Maintenance of resources to vital tissues in satisfactory levels through vasodilation and vasoconstriction allow nervous activities be well protected by perfusion.

A number of neuro-vascular functionalities are in place to provide resourceful support. During and after assertion, appropriate microvascular density towards nervous-directed needs and redistribution for coordinated neuro-vascular regulation in effective patterns for the whole body are needed [11]. These include neuro-vascular coupling with fascial support at tissue level, autoregulation at regional levels to maintain stable blood flow to a region over a wide range of systemic conditions, recruitment of the hepatic splanchnic circulation during assertive activities at whole body level, and patternable metabolism and perfusion through body pacemakers matching for daily patterned activities [76].

During activity, blood flow needs to reach the local tissues at the right time and place and in the right amount. The fascial system ground an orderly matrix for support. Well-patterned dynamics provide for ready and matching mechanisms to act and react to surrounding variations and disturbances [44]. Execution with assured dynamics would be controlled by fine-tuning itself to match for discrepancies at task over a stabilized core to sustain and maintains the individual formation as a whole. The better the matching responses, the stronger would be the individual to function.

In continuing more demanding activities, extra effort is deemed necessary. The individual needs to exert beyond basic levels of functioning or attempt alternative strategies or recruit other resources to maintain performance. The fascial system with repeated strains and torsions would be mal-aligned to the best effective formation. The neuro-vascular coordination may be strained accordingly. Clinically, the complexion should show up. Sometimes continual demands may call even for shifts or new body changes even in constitutions, psychotypes and adaptive structural types. Unsuccessful accomplishment, poor core-to-match environment, or incongruent restitution causes problems which can alter the orderly or well-patterned contextual assembly of the three dimensions. As blocks and blood stasis even with bruising manifestations are prominent pathologies in Chinese medicine, the consideration of the interactivity of the NPI dimensions is pertinently required clinically.

SUSTAINABILITY WITH BODY SNUG AND FIT

With the NPI contextual assembly well-ordered and with resources carried along nervous and perfusional elements, all kinds of activities can spring forth. Survival quality depends both on fitness and snug of the individual. The core formation needs be kept integrally robust while the individual fits well with the surrounding demands. Conserving biological and physiological synchrony between the individual and environment in interactions produce snug [11]. Even since birth, the body is equipped with processes that the body core can continually match its environment without losing the core formation and strength. Above the hardcore operational organs, all five self-vitality subsystems [16] evolve with repeated remodeling as they mature, and the three NPI dimensions tune in with a setup correspondingly.

While lives of any organism depend upon the entire ecosystems, the body developed pertinent energy efficient mechanisms. Energy efficiency is an important principle for optimizing physiological functions within organisms [77]. For effective living and actuation modes in different terrains, this energy efficient state depends on the central nervous well in disposition, the body fascial system toned up, and activities handled by well-patterned functions wherewith reserves are never over-drained. Maturation of body habits and brain circuits, nervous-circulation coordination, and associated physiological regulation and autonomic responses follow. All these support self-actualization with social engagement, living strong with adaptive body and assets as the individual actuates, self-vitality subsystems remodel, whereas the NPI dimensions restitute and re-pattern to re-attain snug while reaching out for being fit.

Retrospectively, the understanding of hardcore organs systems through last few centuries have opened up a clinical approach starting with specific therapies for lesions as a clinical problem. The understanding of the NPI dimensions under the remodeling self-vitality subsystems should initiate re-understanding another clinical approach for multi-system disorders which have nowadays been viewed as chronic diseases. The disorderly contextual assembly and static/blocked interactions of the three dimensions could amount up to layers of burden, diminishing quota for reserves, and rings on rings of maladjustment. With more direct remedy towards the NPI dimensions rather than detour treatment of the hardcore organs, another perspective would be open for effective treatment.

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