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The Influence of Modern Neurophysiology on the Previous Definitions of "Segment" and "Interference Field" in Neural Therapy

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Keywords
Neural therapy · Interference field · Neuromodulatory trigger · Segment · Autonomic nervous system

Abstract
Background: In neural therapy, local anesthetics are injected for diagnostic and therapeutic purposes. In this process, therapy makes use of the regulatory functions and plastic properties of the nervous system, especially its autonomic part. Up until now, a distinction has been made between "local/segmental neural therapy" and "interference field therapy." This division dating back to the middle of the last century was based on the assumption that anatomical and clinical segments were identical. However, this is only true for the projection symptoms, which are limited to metamerism. All pathophysiological processes beyond this segment were called "interference field events" ("outside of any segmental order" and "not explainable by neuroanatomical circuitry"). ***Summary:*** However, modern neurophysiology no longer recognizes segmental boundaries, taking into account the occurrence of cross-segmental sensitization processes, neuroplastic changes, immune processes, and neurogenic inflammation. In addition, new insights into neuroanatomical circuitry have also contributed to segmental expansion. Thus, in recent years, much of the interference field activity has been assigned to an "extended" segment; however, even there, no segment boundaries can be defined. Thus, the former definition of the interference field effect (considered to be outside any segmental order) is considered obsolete. Nowadays, interference fields are called "neuromodulatory triggers." They can act anywhere, both locally and fairly distant, and even systemically. ***Key Messages:*** Thus, it is no longer tenable to classify interference field therapy as "unscientific" and "not recognized" while local and segmental neural therapy is being scientifically recognized. In the work at hand, the interference fields discovered by the Huneke brothers become scientifically definable as "neuromodulatory triggers" by showing that clinically and pathologically, hardly any segmental boundaries exist.

Der Einfluss der modernen Neurophysiologie auf die bisherigen Definitionen von "Segment" und "Störfeld" in der Neuraltherapie

Schlüsselwörter
Neuraltherapie · Störfeld · Neuromodulatorischer Trigger · Segment · Autonomes Nervensystem

Zusammenfassung
Hintergrund: Bei der Neuraltherapie werden Lokalanästhetika zu diagnostischen und therapeutischen Zwecken injiziert. Dabei werden die Regulationsfunktionen und plastischen Eigenschaften des Nervensystems, insbeson-

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dere des autonomen Anteils, genutzt. Bislang wurde zwischen „lokaler/segmentaler Neuraltherapie“ und „Störfeldtherapie“ unterschieden. Diese aus der Mitte des letzten Jahrhunderts stammende Unterteilung basierte auf der Annahme, das anatomische und das klinische Segment seien identisch. Dies gilt jedoch nur für die Projektionssymptome, die auf die Metamerie beschränkt sind. Alle pathophysiologischen Prozesse jenseits dieses Segments wurden als „Störfeldgeschehen“ bezeichnet („außerhalb jeder segmentalen Ordnung“ und „nicht durch neuroanatomische Verschaltungen erklärbar“). ***Zusammenfassung:*** Die moderne Neurophysiologie kennt aufgrund von segmentübergreifenden Sensibilisierungsprozessen, neuroplastischen Veränderungen, Immunprozessen und neurogenen Entzündungen jedoch keine segmentalen Grenzen mehr. Darüber hinaus haben auch neue Erkenntnisse über neuroanatomische Verschaltungen zur Segmenterweiterung beigetragen. So wurde in den letzten Jahren ein Großteil des Störfeldgeschehens einem „erweiterten“ Segment zugeordnet, wobei auch dort keine Segmentgrenzen definiert werden können. Daher gilt die frühere Definition der Störfeldwirkung (die als außerhalb jeder segmentalen Ordnung liegend betrachtet wurde) als obsolet. Heutzutage werden Störfelder als „neuromodulatorische Trigger“ bezeichnet. Sie können überall wirken, sowohl lokal als auch an weit entfernten Stellen und sogar systemisch. ***Schlüsselbotschaften:*** Es ist also nicht mehr haltbar, die Störfeldtherapie als „unwissenschaftlich“ und „nicht anerkannt“ einzustufen, während die lokale und segmentale Neuraltherapie wissenschaftlich anerkannt wird. In der vorliegenden Arbeit wird das von den Gebrüdern Huneke entdeckte Störfeld als „neuromodulatorischer Trigger“ wissenschaftlich definierbar, indem gezeigt wird, dass klinisch und pathologisch kaum Segmentgrenzen existieren.

Introduction

In neural therapy, local anesthetics are used for diagnostics and therapy. The injection treatment makes use of the regulatory functions and plastic properties of the nervous system, especially its autonomic part. Targeted stimuli (set by the needle prick) and the simultaneous, short-term selective deletion of engrams (by the local anesthetic) in the sense of a “reset” influence both the organization in the nervous system and the tissue perfusion. In the pain process, with the normalization of the engrammatically stored pathological irritability of the sympathetic and nociceptive systems in the peripheral-spinal and (indirectly) supraspinal reflex arcs, a vicious circle can be broken. Therefore, the therapeutic effect usually outlasts the duration of action of the anesthesia by far [1]. Historically, two types of therapy have been differentiated for decades: local and segmental neural therapy on the one hand and interference field therapy on the other [2–6]. With the present work we point out that the previous division of neural therapy into segment therapy and interference field therapy no longer reflects current neurophysiological and neuroanatomical knowledge which shows that “segment” goes far beyond the limits of the previous (anatomical) definition.

Previous Definitions of Neural Therapy

Local and Segmental Neural Therapy

In neural therapy, injections are made into the skin (wheals), into myofascial trigger points, painful tendon insertions, joints, etc. While these injections are performed “loco dolendi” in local therapy, segmental therapy is based on the polysegmental reflexive interconnections of skin, musculoskeletal system, and internal organs. Furthermore, infiltrations on nerves, peripheral arteries and their periarterial sympathetic plexus as well as on sympathetic ganglia are also considered to be part of segmental therapy. Knowledge of the segmental (metameric) organization pattern of the body is a powerful tool in diagnosis and treatment of many diseases. Thus, projection symptoms (see below) are part of viscerocutaneous reflexes (i.a.) and represent the underlying base in a variety of medical procedures such as neural therapy and manual medicine.

Local (most commonly used) and segmental neural therapy is classified as conventional medicine [7–11].

Interference Field Therapy

The interference field defined by the Huneke brothers is a chronic source of irritation after formerly diseased or injured tissue potentially in any part of the organism. The stimulus is subliminal, so that usually, the interference field itself is free of symptoms. However, the pathological impulses emanating from the interference field can lead suprasegmentally to pain, dysfunction, or inflammation up to generalized diseases “outside” the formerly diseased or injured segment, i.e., “far away” from the interference field [2–6]. Common potential interference fields are chronic tonsillitis, displaced or impacted wisdom teeth, ostitis in the tooth root area, periodontitis, certain scars, intestinal diseases, chronic irritations in the urogenital area, etc. Impulses and their clinical consequences in interference field events were considered unexplainable in terms of anatomical neural structures [2, 3]; thus, the “interference field” became part of the “realm of the unexplained,” i.e., not ascertainable by known science. With progressive findings concerning neuroanatomical circuitry as well as pathophysiological events – especially in

chronic pain – much pertaining to the interference field had to be reassigned to an "extended segment," i.e., to polysegmental reflexes [5, 12]. However, this could not completely solve the problem of differentiation between segment and interference field.

Embryology, Anatomy, and Pathophysiology of the Segment

Embryology – Segmental Organization

During embryologic development, as in all mammals, the human body shows a segmental organization, which is attributed to the interaction of the mesoderm with the ectoderm (neural tube), resulting in the formation of the somites. During this period neuronal segmentation and the innervation of somites begins. Somites are derivatives of the paraxial mesoderm and contain progenitors of the axial skeleton, trunk musculature (and tendons), trunk dermis, endothelial cells, and meninges of the spinal cord. Each somite can be differentiated into dermatome, myotome (splits into dorsal epimere and ventral hypomere), and sclerotome.

The spinal nerve contains efferent, e.g., somatomotor and visceromotor (sympathetic) as well as afferent (viscero-somatosensory) fibers. The development process is common to cervical, thoracic, lumbar, sacral, and coccygeal segments and reflects the segmental or metameric organization of the body [13].

About the Anatomy of the Segment

Accordingly, a spinal cord segment is understood as a "slice" of the spinal cord with the associated gray matter and root filaments that unite to form a spinal nerve pair. The spinal nerves, with their various fiber qualities supply a specific region of the body, the peripheral segment. Thus, the peripheral segment is the projection of a spinal cord segment to a particular body region. This includes:

- the segmental (radicular) skin innervation (dermatome)
- the segmental (radicular) muscle innervation (myotome)
- the segmental (radicular) periosteal/bone innervation (sclerotome)
- the segmental (radicular) visceral innervation (viscerotome)

On a horizontal level, this segmental "slice" of the spinal cord interconnects the dermatome, myotome, sclerotome, and viscerotome through afferent and efferent reflexes. On the vertical level, each spinal cord segment is connected to the brain stem and the superior vegetative centers by means of feedback. The sympathetic nervous system with its sympathetic trunk plays an important role in this process.

On the Present Pathophysiology of the Segment

The importance of segmental organization in diagnosis and treatment of many diseases was first recognized by Head [14] and Mackenzie [15]. For instance, Head found that certain areas of the skin developed tenderness (allodynia) in the course of visceral disease and herpes zoster neuralgia. It is assumed that these Head zones represent dermatomes and are based on viscerocutaneous reflexes. These reflexes arise from the convergence of viscero- and somatoafferent nerve fibers on dorsal horn cells of the spinal cord and subsequently on the projection onto segmental efferent somato- or visceromotor (sympathetic) nerve fibers [16].

Therefore, in case of a nociceptive stimulus in such a segment, skin, musculoskeletal system, and viscera react collectively [3, 5, 17, 18]. Accordingly, clinically, combined projection symptoms appear, such as changes in blood circulation, increases in skin turgor, sensory disturbances, increase in muscle tone, and dysregulation of the metamerically (segmentally) associated internal organ. Depending on the individual threshold, pain and/or inflammation develop. Often, however, the clinical segment must be seen much more broadly, as will be illustrated in the following section.

Findings That Lead to the Expansion of the Clinical (Metameric) Concept of Segments

Overview

Our cumulative knowledge on the interaction of the autonomic nervous system with the sensory system as well as with the immune system and the brain implies that many diseases do show much more than a clear segmental (metameric) nature.

Before certain findings in present-day neurophysiology in connection with the known neuroanatomical fundamentals, "suprasegmental" or generalized diseases (pain, inflammation, functional disorders) originating from a stimulus source were being assigned to so-called interference field activity in neural therapy. However, if a suprasegmental, pathophysiological event is to be distinguished from a segmental event, then segmental boundaries have to be defined. Up until now, mostly, the extent of the anatomical segment has served as the boundary of the segment, but that turns out to be increasingly problematic [4, 12, 19–21]. Taking into account neuroanatomical circuitry as well as pathophysiological events, especially in chronic pain or inflammation, it has to be recognized that clinical symptoms which do not "stop" at the anatomical segment boundaries do not constitute a distinct etiological and pathogenetic entity. Accordingly, the clinical interpretation of the segment must be broader than the anatomical segment itself. To escape this dilemma, we began

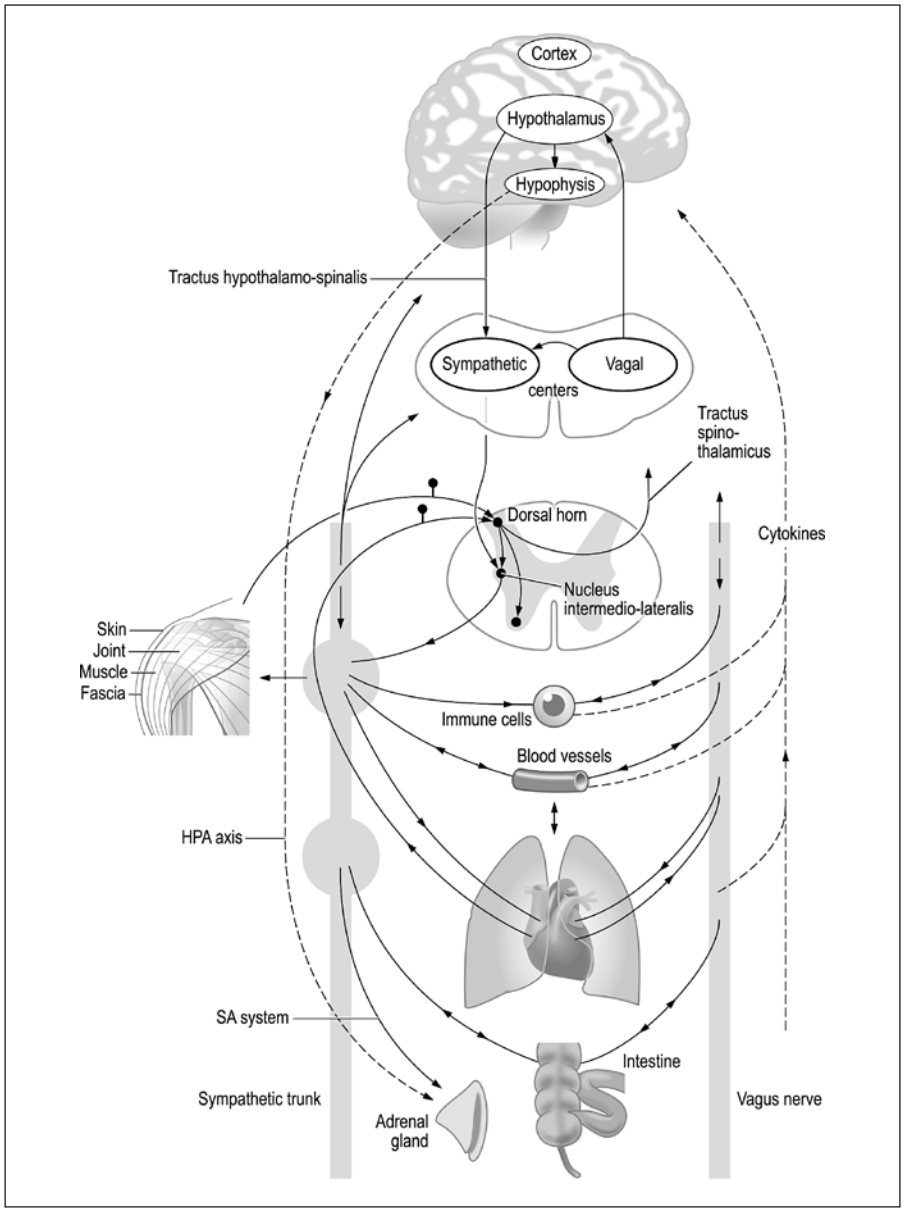

Fig. 1. The coordinating function of the autonomic nervous system (ANS). Schematic, highly simplified representation. The inseparability of internal organs, skin, musculature, nervous system, and interstitium (microcirculation, immune and inflammatory system) is illustrated. Afferents from internal organs, the skin and the musculoskeletal system converge on the same dorsal horn cells. Then, the impulses are conducted in a spinal reflex arc back to the periphery, but also to the brain via the tractus spinothalamicus. Vagal and sympathetic centers in the brainstem complete the reflex arc there. Further cranially, cortex, hypothalamus, and pituitary gland are integrated into another reflex arc. Efferent sympathetic centers in the brainstem receive information from vagal projection nuclei on the one hand, and from the hypothalamus (tractus hypothalamo-spinalis) on the other. Thus, the sympathetic nucleus-of-origin in the spinal cord (nucleus intermedio-lateralis) simultaneously receives information from centers in the brain and from the periphery (internal organs, musculoskeletal system, skin, interstitium). The complexity is further increased by the regulatory intervention of the hypothalamo-pituitary-adrenal (HPA) system from the pituitary gland, as well as the sympatho-adrenal (SA) system via the sympathetic trunk. The ANS and the immune system communicate with each other both peripherally and centrally. This communication regulates where and to what extent inflammation or a change in microcirculation should occur. This occurs via the reflex arcs described above. They consist of neuronal (mainly autonomic), but also of non-neuronal (e.g., cytokines) components. In this complex feedback system, the same neuronal and non-neuronal components may have an activating or inhibitory effect, depending on timing or prior loads. The principal modes of reaction are always the same, regardless of whether the initial stimulus was, for example, a tissue injury, a viral infection, or psychological stress. Only the most integrated organs or organ systems then show the clinical picture. From the point of view of neurophysiology, there are no isolated processes in a segment in which the system does not react as a whole. It is also obvious that every part of the system must be informed about every other part. In this sense, the figure also shows that an "end" of the segment cannot be defined and that the separation of segment and "interference field" is artificial. Rather, an "interference field" can act as a neuromodulatory trigger at any point in the organism and trigger corresponding subsequent reactions (sensitization processes, neuroplastic changes). Modified from Fischer et al. [66].

using the term "extended segment" in 1998 [5]. However, with further scientific findings on neuroanatomical connections and neuroplastic changes, clinical segment boundaries can often no longer be defined, at all.

In the following, the expansion or even dissolution of segmental boundaries is illustrated using the example of chronic pain and inflammation.

Expansion of the Segment Concept for Neuroanatomical Reasons

Ubiquitous Basic Regulatory System

Via the basic regulatory system [22–24], which permeates the entire extracellular space, information conduction and storage in the sense of a "ubiquitous synapse" is possible across all segment boundaries. Therefore, we propagate that the basic regulatory system is used not only to explain neural therapeutic interference field events as before, but also as one of the justifications for the disintegration of the segment boundaries. This system can be considered as the most peripheral level of the autonomic nervous system while also being a part of the immune system [4, 5, 18, 22–24]. The "results" of the complex, partly autoregulatory interactions of the autonomic nervous system with the immune system are conducted to the central nervous system via sensory nerve fibers or, e.g., via cytokines [25–29]. After being "processed" in the brain, the information is fed back to the basic system via sympathetic and vagal efferents (shown in Fig. 1).

Somatic versus Sympathetic Segment

The sympathetic nuclei are not distributed throughout the spinal cord, but only located in the thoracolumbar section (C8–L3). However, from there, they supply the whole body by means of sympathetic fibers. Thus, there is no segmental correspondence (especially in the head and extremities) between the somatic and sympathetic nervous systems [5, 30].

The particular topographical location of the sympathetic nuclei-of-origin has a clinical significance which, unfortunately, is all but ignored: the sympathetic nuclei-of-origin only present in the thoracolumbar part of the spinal cord receive afferent impulses (via the posterior horn by way of interneurons) segmentally from the internal organs, the locomotor system, and the skin (convergence in the posterior horn) [31, 32]. After spinal and supraspinal modulation, the sympathetic efferences originating from the nuclei-of-origin influence not only "their" thoracolumbar segments, but also body regions such as extremities, cervical and head regions. Thus, according to today's knowledge, and under the clinically necessary consideration of the autonomic nervous system, the definition of "segment" is not to be restricted to the somatic part alone, but to be applied much more broadly. The designation "interference field" thus becomes largely explicable by means of segmental connections [33, 34]. Depending on the case of illness, often, the segmental boundaries are to be viewed as having indefinite extent, especially due to new findings that the ubiquitously present sympathetic nervous system can maintain and even initiate pain and inflammation [29, 35–38].

Ganglia of the Autonomic Nervous System

The ganglia supply larger areas, which furthermore disrupts the somatic segmental order. In the paravertebral sympathetic ganglia, there are connections via rr. interganglionares to cranial and caudal ganglia, which in turn influence further segments [30]. Likewise, the right and left sympathetic trunks are connected to each other horizontally. In addition, there are, for example, connections from the stellate ganglion via rr. communicantes to vagal fibers (overview in [39]) and from the supercervical ganglion to the vagus nerve via the jugular nerve, and thus, for example, to the heart and lungs as well as to the abdominal organs. Irritation states of ganglia can lead to complex, suprasegmental symptoms of disease via the mentioned connections. These symptoms were previously assigned to the interference field. With today's knowledge, however, where the segment "ends" can no longer be determined.

Complex Projections of Inner Organs

Internal organs respond to nociceptive stimuli often with projection symptoms beyond the putative segmental boundaries due to different neuroanatomical connections:

1. Into the thoracic segments (partly also into the lumbar and sacral segments), mediated via the segmental reflexes of the sympathetic nervous system. Caudally and cranially, other segments may be affected via the sympathetic trunk;
2. into the neck/shoulder segments (C3/C4/C5) by sensory fibers along the phrenic nerve from the pleural, pericardial, and peritoneal regions;
3. into the supply area of the trigeminal nerve, mediated by sensory fibers in the vagus nerve (for example from the upper abdominal organs), which establish connections to efferent vagal nuclei as well as to efferent sympathetic centers in the brain stem on the one hand, and to the afferent core areas of the trigeminal nerve on the other hand. Via the trigeminal nerve's nucleus tractus spinalis, neck pain can arise and be maintained in addition to 2. It is therefore plausible that the cause of neck pain described here may be eliminated by treating the upper abdominal organs ("erasing" engrams in the coeliac plexus). This procedure used to be assigned to interference field therapy, but with knowledge of the interconnections, the segment expands "randomly" here as well.

Role of the Axial Division of the Skeletal System

In the case of metameric nociceptive stimuli, the axial musculoskeletal system is often involved in the development of the syndrome. This can occur, for example, if a motion segment is blocked, leading to increased positive feedback in the pain process [5]. In case of persistent stimuli, a cross-over can also take place and thus influence the segmental reflexes of the opposite side; possibly via lateral cross-over connections of the sympathetic nervous system (rr. communicantes interganglionares). With time, segments located both cranially and caudally become affected as well, with metameric segmental reflexes of their own. Here, too, there is a concatenation (even changeover) of segmental connections (which can explain the interference field as polysegmental event in this example).

Trigeminocervical Reflexes (Nucleus Paratrigeminalis)

The so-called Adler-Langer pressure points in the cervical spine [40–42] are pressure-dolent points (possibly also spontaneously painful) in the area of the transverse processes. Empirically, they have been associated with various pathologies in the head/neck region (e.g., pathologies in the dental/jaw region, chronic sinusitis, chronic tonsillitis). The explanation lies in the fact that afferents of the trigeminal nerve (e.g., sinuses/teeth) and glossopharyngeal nerve (e.g., tonsillar nerve) as well as the vagus nerve (e.g., from the pharyngeal plexus, from the thoracic and abdominal organs) together project onto the nucleus of the spinal nerve tract of the trigeminal nerve in the cervical medulla [4–6, 43–45]. Further clarification of such connections was provided by the description of the "trigeminocervical complex" [46] and the nucleus paratrigeminalis [47], which connects the segmental order (medulla spinalis) at level C1–C3 with NON-segmental structures (medulla oblongata, pons, mesencephalon, vegetative centers).

The triggering pathologies in the head/neck area or the thoracic or abdominal area used to be assigned to interference field activities. Today, with advanced knowledge of modern neuroanatomy and neurophysiology, these pathologies of the trigeminocervical complex are considered polysegmental-reflectory events.

Myofascial Trigger Points and Referred Pain

Myofascial trigger points or joint dysfunctions can arise – among other mechanisms – from nociceptive stimuli of the skin, the internal organ, or the musculoskeletal system (reflexes via the spinal cord). The musculature reacts as a polysegmentally interconnected, cross-segmental functional chain. Along this chain pseudoradicular symptoms (referred pain) can be found [12, 17, 18, 48]. Pathophysiologically, the most diverse "combinations" (also with internal organs) are possible. Some of them were formerly considered as interference field. Nowadays, they are definable as polyreflectory events.

Further Relationships

From many multisegmental connections, arbitrary examples have been picked below: innervation of the urinary bladder is sympathetic via the inferior hypogastric plexus and its afferents from thoracic and lumbar segments. Parasympathetic innervation occurs via the lateral horn cells from S1–S3. Voluntary innervation also occurs via sacral parts (pudendal nerve S2–S4). Thus, sensory and efferent reflex processes can cause sensory disturbances of the skin and painfully tense muscles in the back and legs when the nervous system of the bladder is irritated.

The supply of the heart is similar: the parasympathetic innervation comes from the brain (brain stem) via the nuclei-of-origin of the vagus nerve, whereas the sympathetic supply comes from the nuclei-of-origin of the thoracic spinal cord via the sympathetic trunk and the sympathetic cervical ganglia. The sympathetic and vagal nuclei-of-origin are in turn indirectly dependent on sensory impulses from the most diverse regions (for example, sensory fibers of the vagus nerve not only from the heart and lungs, but also, for example, from the intestine). These sensory fibers of the vagus nerve project in the brain stem onto the nucleus tractus solitarius (NTS) (shown in Fig. 1). From this nucleus, connections run to efferent vagus nucleus areas (nucleus ambiguus and nucleus dorsalis n. vagi) and to efferent sympathetic centers (hypothalamus, rostral ventrolateral medulla [RVLM]) [49]. Thus, the vagus nerve also connects with the sympathetic nervous system in the brain (not only peripherally). From these efferent centers, the hypothalamo-spinal tract influences the sympathetic nuclei in the spinal cord and, via para- and prevertebral ganglia, the organs, the vessels, and the interstitium (basic system), thus also influencing microcirculation, the immune system, and inflammatory mechanisms. The hypothalamo-pituitary-adrenal (HPA) axis and the sympatho-adrenal (SA) system constitute further sympathetic efferents. Peripherally, sympathetic and vagal/parasympathetic efferents and sensory fibers form plexuses in front of the organs. This results in feedback loops. With pathological impulses ("neuromodulatory triggers") at arbitrary places in these feedback loops, such connections are comprehensible with circuits of neural structures and are therefore by definition not to be considered as interference field events (in contrast to the former view). Here, too, the segment expands almost without limits, but is explainable by means of neural circuits. This example shows especially well that the distinction between segment and interference field is no longer sensible, at all.

Jänig and Green [50] show complex activation and inhibition mechanisms in knee arthritis via different neuronal circuits of the autonomic nervous system. These arthritis-modulating circuits are found both peripherally-spinally and in the brain. In addition to nociceptive afferents from the arthritis area, afferents in the vagus nerve, e.g., from the gastrointestinal tract (!), can also have a central modulatory effect and influence the efferent "control" of arthritis via the following systems: 1. HPA system; 2. SA system; 3. sympatho-neural system. Thus, the reflex arc is closed, which also includes central integration mechanisms. The neural therapeutic control of arthritis via the gastrointestinal tract both in the case of illness and its therapeutic regulation (via the coeliac plexus) used to be regarded as interference field therapy. With the reflex mechanisms mentioned here via neuroanatomical circuitry, it is again apparent that no segmental boundary can be drawn – the "segment" has become "holistic" and ubiquitous. This "holism" used to be "reserved" for the definition of "interference field."

Expansion of the Segment as a Result of Functional and Plastic Changes in the Nervous System

A sharp separation from the previous section is not possible. In addition, many processes run simultaneously.

Peripheral and Central Sensitization and Neurogenic Inflammation

Nociceptors and nociceptive fibers as well as sensory neurons in the sympathetic trunk and vagus nerve can be sensitized by strong (e.g., trauma, pathogens, toxins) or long-lasting stimuli (e.g., neuromodulatory triggers ["interference fields"]) and initiate an inflammatory cascade. The activated sensory nerves can now release proinflammatory neuropeptides such as substance P and cytokines (!). This results in neurogenic inflammation with plasma extravasation [14, 38, 51–56]. Surprisingly, these proinflammatory substances released by nerve fibers can in turn stimulate cytokine production in immune cells [57–60], thereby amplifying the inflammatory response. A positive feedback loop has now been created in which the sympathetic nervous system plays an important role. The consequences of inflammation are: lowering of the stimulus threshold; increased impulse number following a stimulus; development of spontaneous activity at the nociceptor [61]. In addition, previously silent nociceptors can be recruited [38]. This increases the active receptive fields, and subsequently, neuroplastic changes can occur [38, 62]. By this peripheral sensitization, too, the clinical segment is "expanded."

As a consequence of peripheral sensitization of nociceptors, central sensitization may develop. In addition to sensitization of nociceptor sites, inhibitory and excitatory synaptic influences of interneurons and descending inhibitory and excitatory influences are involved [38]. Inflammatory mediators (prostaglandins), cytokines, neuropeptides, neurotrophic factors, glial cells, and signal molecules of the immune system are involved in inflammatory processes [35, 63]. These processes, in addition to the development and maintenance of spontaneous pain, hyperalgesia, and allodynia, lead to an enlargement of receptive fields beyond anatomical segmental boundaries. Over time, altered information processing occurs in the spinal cord, brainstem, and cortex based on altered neural structures. Thus, a "pain memory" (neuroplasticity) has developed [38], which can expand depending on additional factors (including the influence of emotions, stress) and can affect any number of segments (without boundaries) in the periphery.

Neuroimmunological Interaction and Neurogenic Inflammation

On the one hand, the sympathetic nervous system influences immunological processes; on the other hand, it can cause and maintain inflammation [25, 35, 38, 64–66].

The following interactions between the autonomic nervous system and the immune system [25, 27, 35] show the problems of "segment limitation" – which concern most diseases; after all, these are general principles [66].

Sympathetic postganglionic fibers innervate the vascular smooth muscle cells as well as the parenchyma of the thymus, bone marrow, spleen, lymph nodes, and mucosa-associated lymphoid tissue (MALT) [67, 68]. Noradrenergic varicosities closely appose many types of immune cells such as macrophages, lymphocytes, eosinophils, mast cells, dendritic cells, thymocytes, bone marrow hematopoetic stem cells, and others [65]. The sympathetic fibers secrete norepinephrine (NE) (as the major transmitter), but also ATP, neuropeptide Y, and nitric oxide. All neurotransmitters act on immune cells, although NE is best characterized in this respect. NE is either secreted by postganglionic sympathetic nerve fibers localized in lymphoid organs or by the adrenal medulla. NE can act via regulating blood or lymph flow or by modulation of proinflammatory peptide release. The sympathetic nerve system can act pro- or anti-inflammatory (in the late phase) [36, 69, 70]. Thus, during local injury, sympathetic fibers may boost regional immune responses [71, 72]. The sympathetic modulation remains uncertain and seems to be influenced by baseline levels of sympathetic activity [73]. Tracey [28], too, sees a modulation of the immune system by the sympathetic nervous system and the parasympathetic nervous system of the vagus nerve. He postulates a physiological, neural "set point" (homeostasis) for the protective immune response. In the presence of a preload an "increased set point" arises. Then, an infection or a neuromodulatory trigger can lead to such neural overactivity with an exces-

sive immune response (e.g., cytokine storm) and hyperinflammation [66]. This in turn is consistent with Speranski's experiments in 1950 [74]: He called the preload "first strike" and an additional load such as an infection or dental interference field (neuromodulatory trigger) "second strike" [66]. Preloads include i.a. hypertension [75], obesity, and stress. The sites of inflammation depend on situational communication between the brain and the immune system: for example, sensory fibers of the truncus sympathicus or the vagus nerve can transmit local concentration changes of immune cell messengers (such as cytokines) to the brain in the form of action potentials [27, 28]. As a result, the autonomic centers in the brain now have the information about where the inflammation is located (e.g., in the lungs), which would not be possible via the blood pathway [52]. Thus, it becomes clear that such inflammations "topographically" depend on the distribution pattern of the autonomic nervous system (or are generalized) rather than on the somatic metameric segmental order. An example of that is complex regional pain syndrome (CRPS), which is thought to be related to the sympathetic nervous system [37, 64]. The current understanding indicates an interaction between sensory and sympathetic nerve fibers as well as the immune system [76]. Further, CRPS is associated with increased sensitivity of blood vessels to catecholamines and the development of adrenergic sensitivity by nociceptive neurons rather than excessive sympathetic outflow to the skin [77]. Otherwise, nociceptive neurons may be sensitized by sympathetic afferent coupling that can result in secretion of neuropeptides (substance P) from c-fibers. CRPS is an example of how the interaction between the sympathetic nerve system, immune system, and inflammation can lead to neuroplastic changes in the cortex [78, 79].

Sympathetic-Afferent Couplings

Under pathological conditions (e.g., peripheral sensitization), a short-circuit-like coupling between sympathetic efferents and nociceptive afferents can occur in the periphery [35, 38]. It can be assumed that these couplings follow the distribution pattern of the sympathetic nervous system rather than the somatic metameric segment. Assuming that these couplings continuously take place at anatomical segment boundaries, here too, a transgression of the segment boundaries takes place with time.

Sympathetic Sprouting

Increased spontaneous activity (e.g., due to peripheral sensitization) or inflammatory processes can cause sympathetic fibers to sprout (structural neuroplasticity), forming basket-like structures around nociceptive afferents of dorsal root ganglia [80–82]. This results in positive feedback with sensitization processes and subsequent neuroplastic changes in the central nervous system, which can have a "segment-expanding" effect in the periphery.

Wide Dynamic Range Neurons

Wide dynamic range (WDR) neurons (also termed "trigger, lamina V-type, class 2, multireceptive, and convergent neurons") are localized to the spinal dorsal horn. They are targets of nociceptive as well as non-nociceptive nerve fibers from skin, visceral organs, and muscles. Moreover, they include interneurons that are involved in polysynaptic reflexes and neurons projecting in pathways such as the spinothalamic and spinoreticular tracts. Remarkably, these neurons may remain active after withdrawal of a nociceptive stimulus. On the other hand, it was also observed that they remain active following the activation of inhibitory mechanisms [83]. Taken together, a WDR cell receives information from Aβ, Aδ, and C fibers as well as excitatory and inhibitory information. WDR neurons display plasticity in that receptive fields may enlarge, for instance, after recruitment of quiescent synapses, transient electrical stimulation of C-fibers, injury, noxious stimulation of viscera or muscles, and others [83]. The WDR neurons are thought to be responsive for wind-up phenomena and/or long-term potentiation and central sensitization [84]. On the other hand, wind-up can be dependent for example on substance P alone. At least, wind-up is changed after inflammation and central sensitization [85]. These changes in the WDR neurons are further factors in the expansion of the "segment" affected by pain and inflammation.

Conclusion

The historical separation into "local and segmental therapy" and "interference field therapy" in the middle of the last century had its reason in the fact that based on the knowledge of that time the clinical segment was more or less equated with the anatomical, somatic segment (metamerism). This equation is still correct when projection symptoms are limited to metamerism. All pathophysiological processes which exceeded this "narrowly," anatomically defined segment were called "interference field events," i.e., the interference field impulses had an effect far away from the interference field "outside any segmental order" and were "not explicable by neuroanatomical circuitry" [2, 3]. However, these early definitions can no longer be upheld with new neuroanatomical and neurophysiological findings, because in view of sensitization processes, neuroplastic changes, immune and inflammatory processes, segmental boundaries all but vanish or "expand" almost arbitrarily, respectively, and the interference field events become scientifically explainable.

The term "neuromodulatory trigger" is already used synonymously for the term "interference field" or "interference field impulse" [34, 86–88]. This is in accordance with the Scientific Advisory Board of IFMANT (International Federation of Medical Associations of Neural Therapy).

This clarification of the nomenclature and "abolition" of the clinical segment boundaries in chronic pain and inflammation processes on the basis of modern neurophysiological findings have not changed the basic approach in neural therapy.

Therefore, there is no longer any reason to scientifically separate interference field therapy from segmental therapy (i.e., to classify interference field therapy as unscientific), since with the new findings there is, in principle, no difference. There is a unified explanatory model for neural therapy which knows no "arbitrary" (segmental) boundaries: the (holistic!) neurophysiology and neuroanatomy.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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