The Law of Specific Nerve Energies and Sensory Spots

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Aristotle distinguished five special senses: vision, hearing, smell, taste, and ‘touch’ or feeling. Studies of the physiology of sensation started with Johannes Müller (1801–1858) who devised the Law of Specific Nerve Energies in the second edition of his *Handbuch* [1]. He was professor at Berlin, whose students included Helmholtz, DuBois-Reymond, Schwann, Virchow, Kölliker and Remak.

‘The same cause, such as electricity, can simultaneously affect all sensory organs, since they are all sensitive to it; and yet, every sensory nerve reacts to it differently; one nerve perceives it as light, another hears its sound, another one smells it; another tastes the electricity, and another one feels it as pain and shock. One nerve perceives a luminous picture through mechanical irritation, another one hears it as buzzing, another one senses it as pain ... He who feels compelled to consider the consequences of these facts cannot but realize that the specific sensibility of nerves for certain impressions is not enough, since all nerves are sensitive to the same cause but react to the same cause in different ways ... Sensation is not the conduction of a quality or state of external bodies to consciousness, but the conduction of a quality or state of our nerves to consciousness, excited by an external cause.’

He thought that the type of sensation was different for each stimulus; sensation was a function of the nerve, not the stimulus; pain was a function of a unitary sensory system.

Sensory Spots

Sensory spots on the skin surface can be shown to be selectively sensitive to one of four sensory qualities in decreasing order of density: pain, touch, cool and warm. The presence of such spots was observed virtually simultaneously in the early 1880s by three independent investigators. Two papers on punctate sensitivity of the skin were published in 1882 and 1883 by Magnus Blix of Uppsala University [2]; three papers in 1884 by Alfred Goldscheider, a German physician, and one in 1885 by Henry Donaldson of Johns Hopkins, Maryland. Blix’s and Goldscheider’s experiments were based on Johannes Müller’s concept of ‘The Specific Energies of Nerves, 1838’ and the extension of this idea to sensory function by others, including Hermann von Helmholtz. The discovery of different types of sensory spots has only recently been substantiated by electrophysiological experiments.

Blix was the first to demonstrate the modal character of cutaneous sensory messages in 1882–1883 [3, 4]. He had found that electrical stimulation of different points on the skin surface evoked distinct, cool or warm sensations. He then constructed the temperature stimulator with which he showed that a lowered skin temperature induced cool sensations from spots located on separate skin locations, and raised temperature induced warm sensations from different sites. Investigations with his tactile stimulator showed special touch spots, located between the cool and warm spots.

Alfred Goldscheider of Berlin asserted that the particular patterns of nerve impulses that evoke pain are produced by the summation of skin sensory inputs. Pain results when the total output of the cells surmounts a critical level owing to excessive stimulation of receptors that are normally fired by non-noxious stimuli. Henry H. Donaldson confirmed and extended Blix's findings in 1884–1885 and acknowledged his priority.

Von Frey's Specific Receptors

Between 1894 and 1896, Max von Frey discovered in human skin discrete pain points or '*Schmerzpunkte*' when probing the skin at threshold intensity for sensory detection with fine sharp needles or plant spicules. Von Frey (1894) stated that each sensory modality has a specific receptor – indicating that the skin contained minute, highly specialized areas. He believed that the skin comprises a mosaic of four types of sensory spots: touch, cold, warmth and pain. He subsumed Meissner's corpuscles, Ruffini's cylinders, Paccinian corpuscles, Krause's end bulbs, and the free nerve endings that he believed transmitted pain.

Von Frey's single hair was placed on the skin and pressed down; by varying the size of hairs, he determined the threshold force needed to produce the sensation of touch. Probes were used to localize cold-, warm- and pain-sensitive spots. Sensory spots could also be demonstrated by applying electrical stimulation to discrete points on the skin. He thus showed sensory points sensitive to pressure, pain, and temperature.

This discovery predicated von Frey's theory (1894) of *receptor sensitivity* to account for sensory stimuli distinguishing pain from other sensory modalities [5–7]. Struhold [8], his student, found approximately 150–200 pain points/cm² on the lower arm and leg and on the back of the hand and of the foot. He reported that the number of pain points increased when increasing the force, which suggested that the presence of a pain point depended on the stimulus intensity.

Pattern Theory

Weddell et al. [9] and Sinclair [10] in 1955 developed the *pattern theory* that pain is produced by intense stimulation of non-specific receptors [23]. The pattern theory suggested that pain perception was the interpretation of the spatial and temporal patterns of stimuli, and the multisynaptic modification system (Noordenbos).

Nociceptive Units

Years later, recordings from single nociceptive afferents were achieved, in particular from polymodal C-fibre units, first in animal experiments and then with micro-neurography in human volunteers [11]. Nociceptor units, it was discovered, do not form single sensory spots in the skin, but have extended innervation territories (receptive fields). Free nerve endings serve several somatosensory modalities. Histological research showed that thin afferent nerve fibres comprised extended, terminal branching and complex innervation territories [12, 13]. Moreover, the 'naked nerve endings' are characterized by multiple 'sensory beads' spread over the whole terminal axon, forming a structural substrate for the sensitive spots within the receptive fields [14]. The afferent C fibres, subserving sensation, appear separate from the sympathetic fibres innervating the same regions.

Somatosensory modalities are processed by receptors that encompass localization, spatial, temporal and tactile discrimination, and are elaborated centrally by memory and affective responses.

Transducer Mechanisms. Three types of transducer mechanisms are: mechanoreceptors, thermoreceptors, and chemoreceptors. Mechanoreceptors consist of both free nerve endings, epidermal (Merkel's disk), and encapsulated endings, which include Paccinian corpuscles, Ruffini's cylinders, and Meissner's corpuscles. The encapsulated endings serve as mechanical filters, and account for responses of the receptors. Mechanoreceptor transduction is not, however, fully understood.

Transduction involves: (1) the mechanical response of the skin to the stimulus is transferred to the receptor (coupling); (2) deformation of the receptor generating an electrical potential, and (3) transformation of the generator potential to neural firing.

Receptor Systems

Free nerve endings have surface membrane receptors associated with second messenger chemoreceptor systems. Endogenous substances that act on chemoreceptors include bradykinin, cytokines, and prostaglandins. The initial trigger is the release of bradykinin, which acts on

Table 1. Nerve fibre type and sensory quality

	Nerve fibre type			
	'A' δ small myelinated	'A' β larger, myelinated	'C' small unmyelinated	'B'
Sensory quality	Sharp pricking pain and temperature	Tactile and kinaesthesia	'Slow' burning pain and temperature	Autonomic function

β_2 -receptors, which then synthesize arachidonic acid, which in turn is metabolized to prostaglandins. The change in membrane potential results from blocking calcium-dependent potassium channels due to activation of a cyclic AMP-dependent protein kinase. This causes depolarization because the ionic potassium channel blocked has a hyperpolarizing function.

Most skin receptors are thermoreceptors and probably occupy free nerve endings (table 1). Temperature transduction is thought to involve thermal effects on temperature-sensitive ion pump mechanisms. Cold and warm dis-

tinguishable by cold receptors being associated with 'A' δ fibres (small myelinated) while warm receptors are associated with 'C' fibres. The final transmission to the brain is via afferent fibres bearing.

Each sensory modality is associated with functionally distinct receptors and separate neural pathways. Thus, skin has a dense innervation of multiple layers of nociceptive endings, which allows for substantial spatial summation in response to noxious stimuli, together with a somatotopic organization for noxious events distributed throughout the nervous system.

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