TIMELINE

Ideas about pain, a historical view

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Abstract | The expression 'painful' can be used to describe both an embarrassing moment and a cut on the finger. An explanation for this dichotomy can be found in the convoluted history of ideas about pain. Whether pain is an independent sensation and the product of dedicated neural mechanisms continues to be a topic of debate. This overview concentrates on the issue of specificity together with other notable information regarding pain that has emerged since 1800.

The word 'pain' and its synonyms commonly refer to conscious experiences associated with bodily injury or disease, but are also used to describe discomfort related to other unpleasant feelings. These different circumstances are the bases of a long-standing uncertainty regarding how to think about pain and its mechanisms. This article aims to provide a historical perspective on changing views over the past two centuries.

There is a legacy from distant times. Aristotle (384–322 BC) considered the heart to be the seat of feelings. Taking cognizance of pain's usual importance for disposition, he argued it to be an emotion. Not all ancient Greek philosophers agreed; however, Aristotle's influence on philosophical thought endowed his views with an enduring impact. Centuries later, Galen (AD 130–201), a leading physician–surgeon of Alexandria, used experimental studies along with earlier observations to disagree. Galen recognized the brain as the organ of feeling and placed pain into the sphere of sensation. Avicenna (AD 980–1037), a renowned Muslim philosopher and physician, noted that, in disease, pain can dissociate from touch or temperature recognition, and proposed pain to be an independent sensation[1–3]. Despite much work and thought since these ideas were aired, fundamental issues about pain remain unresolved. Notably, these include whether pain results from the activity of a dedicated neural apparatus or is the product of less specific processes[4].

Much attention was given to nervous system anatomy after the Middle Ages; however, progress in thinking regarding pain awaited developments in understanding of the natural world and scientific tools. For example, until the beginning of the nineteenth century, ideas about sensation were mired in the belief that the senses depend on the transport of an agent from the outside world to the heart or brain. That concept lost favour in the eighteenth century due in part to changing insight into the physical world and proposals by Newton (1642–1727) and Hartley (1705–1757) that neuronal messages were vibrations of substance in nerves[2].

This article highlights the sequence of ideas and observations since 1800 that have contributed to concepts about the nature of pain and its neural mechanisms (TIMELINE). Although it is a focused history, it also provides insight into progress in understanding the function of the mammalian nervous system.

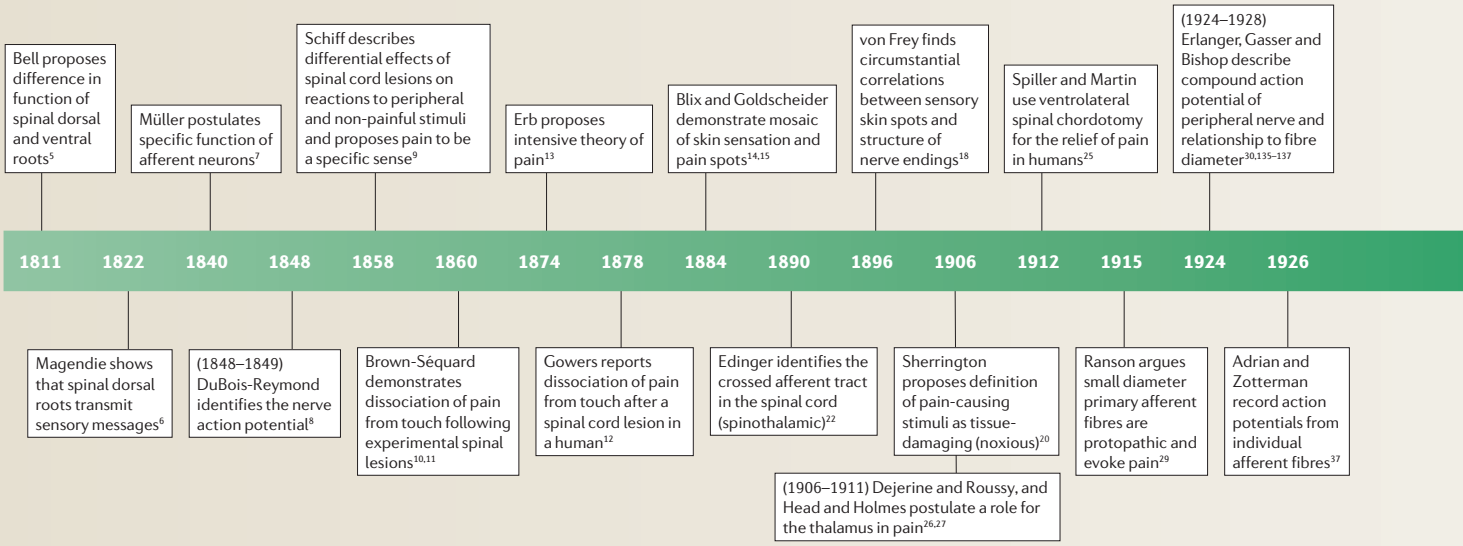
Nineteenth century issues

Afferent pathways for somatic senses. How different information from the body is transmitted to and from the spinal cord and brain was seriously addressed in the nineteenth century. In 1811, Bell, a Scottish physician and anatomist, proposed that the dorsal and ventral spinal roots differ in function, with the ventral roots being responsible for control of muscle contraction[5]. However, Bell was vague about the role of the dorsal roots and Magendie (1822) is generally credited with demonstrating their sensory function[6]. These discoveries provided crucial tools for subsequent experimentation. Bell also expressed the idea that sensory nerves were specialized in their function, that is, particularly adapted to detect and carry information about a given stimulus mode. Later, the concept of sensory nerve specificity was developed by Müller (1840), whose postulates proved both seminally important in subsequent thinking and a focus for criticism[1,2,7]. Müller's proposals were given impact by the contemporary description of the electrochemical nature of the nerve impulse by DuBois-Reymond[8]. If the impulses of different nerve fibres were similar, peripheral and central endings of afferent fibres must provide part of the information about the nature of the stimulus to the brain.

Mid-nineteenth century studies of spinal cord pathways added important insights. Schiff (1858), once Magendie's student, showed that particular lesions of the spinal cord resulted in separate and independent loss of tactile and pain-related reactions[9]. This led Schiff to propose pain to be an independent sensation, mirroring conclusions reached by Avicenna a millennium earlier. Schiff's experimental findings were confirmed and expanded by Brown-Séquard (1860; 1868), who documented the loss of pain sensibility contralateral and distal to a transverse hemisection of the spinal cord[10,11], and Gowers (1878), a prominent English neurologist, who reported similar effects following a lesion in a human[2,12]. By the 1880s there were several lines of support for a spinal pathway essential for conducting information on painful stimuli.

However, not all observers accepted the notion that pain was an independent sensation. The German neurologist Erb (1874), noting that intense sensations are usually disagreeable and involve strong stimuli, proposed pain to be the outcome of vigorous activation of nervous pathways normally concerned with other sensory experiences[13]. Although it had been hinted at earlier, Erb's proposal gave birth to an explicit theory of pain, which presumed that intensity of stimulus and response were the main factors (FIG. 1b).

Timeline | **Important discoveries and concepts for mechanisms related to pain over the past two centuries**



So, near the end of the nineteenth century, three contrasting concepts about the nature and mechanisms of pain prominently and vigorously competed: an emotion (from ancient philosophy, supported by philosophers and some psychologists); a specific sensation with its own sense organs and pathways (formulated by Avicenna and Schiff, supported by physiologists and physicians); and intense activation of afferent systems that serve other sensations (proposed by Erb, supported by many psychologists and some physicians)[1].

New considerations and information came to light at this point. In 1884, Blix[14] and Goldscheider[15] noted cutaneous sensation to be spatially discontinuous. Separate spot-like areas of the skin yielded different sensory experiences (pressure, cold, warmth, pain) when stimulated mechanically with small probes. The observations of von Frey (1896/1897) strongly supported this concept and went further, comparing the relative numbers of particular types of spot to the numbers of histologically defined neural structures in the same regions. From this he deduced relationships between the types of spot and structurally defined neural endings[16–19]. This analysis did much to convince physicians and physiologists that pain is an independent sense. Nonetheless, sceptics remained: Goldscheider swung from supporting the existence of separate pain spots to denying them in favour of a version of the intensive concept, famously battling von Frey in the literature[1]. von Frey's deductions on the correlation between skin spot and nerve terminal histology were particularly in question.

Nociception and neural circuits. One objection to considering pain as a specific sense was its evocation by different types of stimuli (mechanical, thermal and chemical), which differed from accepted sensations. Sherrington (1906), noting that pain commonly originated from tissue injury, suggested labelling stimuli capable of tissue damage as 'noxious' regardless of physical character[20]. He proposed the signalling of noxious events (nociception) to be the function of sense organs responsible for pain. This concept endowed pain with coherent and definable peripheral stimuli.

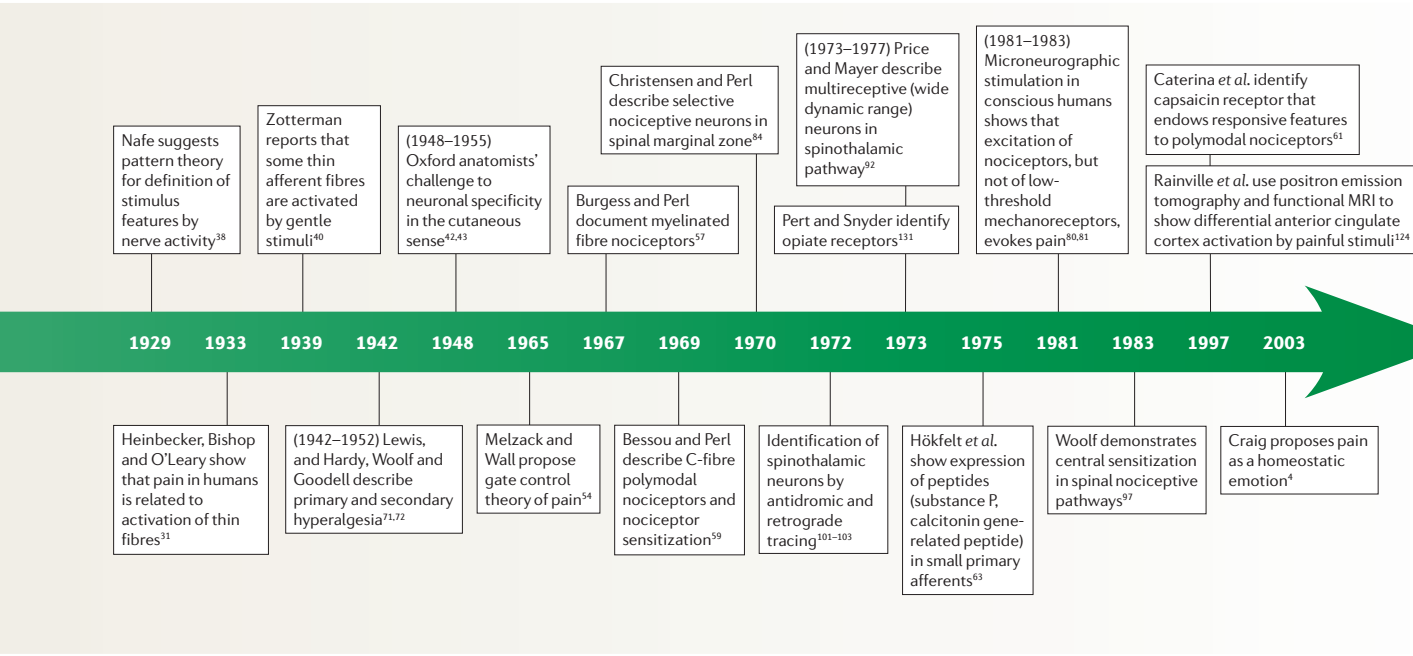
Recognition in the 1890s that the CNS is composed of discrete cells, rather than being a syncytium was another important conceptual step[21]. The concept of synapses as functional connections between cells also supported Sherrington's seminal idea that, in addition to excitation, inhibition of excitability in neural circuits is essential for integrative functioning[20]. So, nervous pathways could be envisioned to consist of neurons with functional connections that could be altered.

1900–1965: new approaches

Anatomists (Edinger, 1890, 1892; Bechterew, 1900) provided convincing evidence that a long ascending pathway originated from spinal neurons whose axons crossed the midline and ascended in the lateral white matter to end in the rostral brainstem[22–24]. This pathway was linked to pain by the effects of experimental lesions in both animals and clinical cases[2]. Spiller and Martin (1912) provided a 'proof of concept' by reporting a case in which transection of the ventrolateral spinal cord was used to treat persisting, intractable pain from the opposite side of the body[25]. Observations on clinical syndromes led Dejerine and Roussy (1906) and Head and Holmes (1911) to implicate the thalamus of the rostral brain in the production of pain[26,27].

Müller's proposal in 1840 of specific functions of individual sensory nerves[7] implies that different somatic sensations are served by separate and distinctive nerve fibres. Consistent with this, nineteenth century anatomists had noted that dorsal roots, on joining the spinal cord, separate into a medial division containing large-diameter fibres and a lateral division composed of thin fibres[23]. Observations on the regeneration of transected nerves and the return of sensation led Head and colleagues in 1905 to postulate two different classes of somatic sensory innervation, epicritic (discriminative) and protopathic (crude)[28]. Diffuse, aching pain was of the protopathic genre. A decade later, Ranson proposed that fine, unmyelinated fibres of the lateral dorsal root division are protopathic, and in part represent an afferent limb for pain[29].

Function of individual neurons: electrophysiology. Early in the twentieth century, recording of electrical signals from nerves added a new dimension. Using the cathode-ray



oscilloscope, Erlanger, Gasser and Bishop[30] showed that a brief electrical stimulus to a peripheral nerve evokes a series of conducted electrical waves (FIG. 2). These studies on the compound action potential provided an opportunity to correlate afferent fibre activity with sensory experience.

Studies by Bishop, Gasser and their collaborators showed that selectively exciting or blocking activity in fibres contributing to components of compound potentials implicated thinly myelinated (Aδ-) and unmyelinated (C-) fibres in pain and aversive reactions[31–35]. Furthermore, as Lewis and Pochin later reported, a single brief noxious cutaneous stimulation initiates a double pain experience, with the time between the two pains being proportional to the conduction distance[34,36]. The latter finding indicates that afferent fibres of differing conduction velocities are involved in pain of peripheral origin.

In the mid-1920s, natural stimulation (for example, brushing/stroking of skin, stretching muscles, temperature changes and so on) of peripheral tissue was used to evoke discharges in individual afferent fibres. The early galvanometer records published from Adrian's Cambridge laboratory showed a series of irregular potential deflections evoked in fine nerve filaments by various distinctive stimuli. These records were interpreted to represent selective responses by different nerve fibres to particular forms of stimulation[37]. Nafe (1929), an American psychologist, challenged this view, proposing instead that the pattern of discharge changes with different forms of stimulation[38]. Nafe went on to postulate that the mode of stimulation is signalled by the composite of activity in a population of afferent nerve fibres, thereby creating another hypothesis for the coding of nerve activity leading to bodily sensations — the pattern theory (FIG. 1c).

Between 1930 and 1950, it was established that most rapidly conducting, large-diameter afferent fibres could be excited by a particular form of mechanical stimulation of the skin or subcutaneous tissue. However, recording activity from the finest afferent fibres proved technically challenging. Notably, in 1936, Zotterman concluded that the slowest fibres (C category) in the lingual nerve signal 'pain' because they were excited only by strong stimuli[39]. Three years later, however, he reported that some C-fibres innervating the cat skin were activated by light tactile stimulation[40]. The paucity of these observations raised doubts about the specificity of peripheral afferent neurons conveying activity that produced pain. If pain receptors existed, in 1940 their features remained obscure.

The Oxford challenge to sensory nerve specificity. Between the late 1940s and mid-1950s, members of Oxford University's Department of Anatomy voiced strong exception to the concept of specific signalling by cutaneous afferent fibres. This was based on an absence of correlation between the modality of sensation evocable from the human pinna or cornea and histological analyses of the innervation of these tissues[41–44]. They, like Nafe, proposed that a pattern of nerve impulses in otherwise functionally undifferentiated afferent neurons signalled the nature of stimulation. Wall, who later had an important part in developing concepts regarding pain, was a student at Oxford when these views were generated.

By the mid-twentieth century, electronic equipment capable of amplifying and displaying small electrical signals had markedly improved, facilitating electrophysiological recording from thinly myelinated Aδ fibres and unmyelinated primary afferent C-fibres. In the 1950s and early 1960s, several investigators (Tasaki's group[45], Paintal[46], Bessou and Laporte[47], and Hunt and McIntyre[48,49]) reported that some slowly conducting myelinated afferent fibres required strong (noxious) stimuli for activation. Iggo's notable papers in 1959 and 1960 showed that certain single unmyelinated fibres from the skin give selective responses to noxious stimuli[50,51]; however, the Oxford challenge to specificity could have blunted their impact, even though there were comparable observations by Iriuchijima and Zotterman[52]. The extensive survey of myelinated afferent units serving mammalian skin by Hunt and McIntyre noted only a handful to have high thresholds to mechanical stimulation, a point that later was to figure in an analysis arguing against specific sense organs for pain. Although these studies described afferent neurons responsive only to strong (noxious) stimuli, and therefore could be taken to support the specificity theory, their small numbers, the lack of consistent descriptions and the presence of units responsive to weak stimuli among the thin-fibre population weakened the case.

A review in 1962 on cutaneous sensation by Melzack and Wall accepted the existence of differences in the responsiveness of afferent fibres, but concluded that spatial and temporal patterns of nerve activity form the basis of sensory perceptions from the skin[53]. Their argument emphasized the ambivalence of data correlating given cutaneous sensations with histologically definable primary afferent terminations. Three years later, they elaborated a pattern-based theory (the gate theory) about mechanisms underlying pain, postulating the operation of a neural gate in the dorsal horn of the spinal cord to control activation of ascending projections[54] (FIG. 1d). Absence of specific pain receptors and a lack of dedicated central pathways are core to this proposal. The gate theory was proposed in opposition to the specific-sense concept. It was emphasized that despite many years of study, few primary afferent fibres or CNS cells were reported to be selectively activated by pain-causing stimuli. This was buttressed by reports of the absence of complaints of pain by soldiers at the time of grievous injury and the occurrence of pain in CNS disorders, such as thalamic syndrome, in which noxious stimuli were not involved. The gate theory presumed primary afferent fibres to have differences in adaptation to maintained stimuli and to represent a continuous spectrum of responsiveness. It postulated that afferent signals from thick and thin fibres interact in the substantia gelatinosa of the dorsal horn of the spinal cord. Applying the established principle of control of spinal cord mechanisms by supraspinal centres[20,55,56], their theory included modulation of the gate by higher centres. Despite questions about the validity of the underlying assumptions, the theory was received with excitement and broadly accepted, particularly because it offered possible explanations for aberrant pain after lesions of the nervous system.

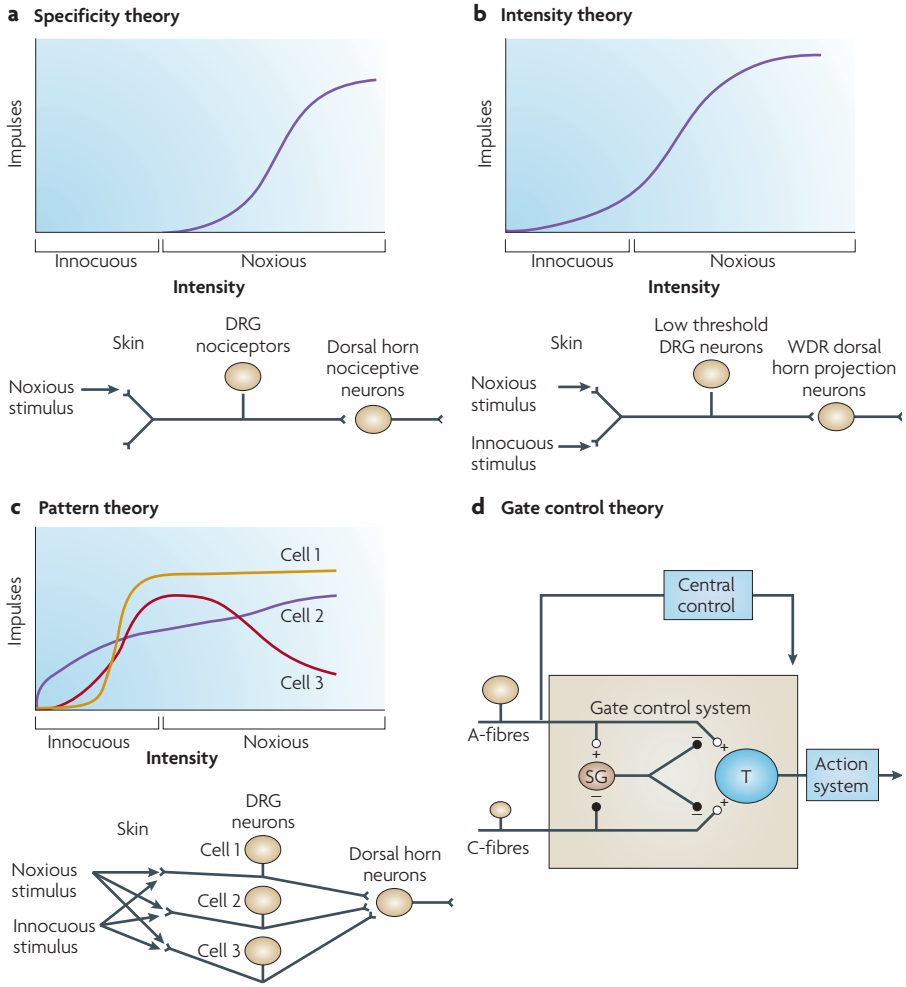


Figure 1 | **Theories of pain.** Diagrams depicting typical assumptions about relationships between stimuli and primary afferent signalling in theories about pain. **a** | According to the specificity theory, specialized sense organs (nociceptors) have thresholds at or near noxious levels, increasing activity with stronger noxious stimuli. These special peripheral afferent neurons have selective connections to particular spinal and brainstem projection neurons. **b** | The intensity theory suggests that peripheral sense organs are not differentiated into low- and high-threshold types. It proposes that afferent fibres transduce innocuous stimuli (for example, skin pressure) by generating a certain level of activity, whereas noxious stimuli are signalled by a greater level of discharge. The intensity-coded primary afferent fibres, in turn, activate projection neurons with a wide dynamic range (WDR). Weak activation of WDR projections indicates innocuous stimuli; strong activation indicates painful (noxious) events. **c** | The pattern theory proposes that somatic sense organs have an extensive range of responsiveness. Individual afferent neurons respond to stimuli with differing relationships to intensity. The mode and locus of stimulation are indicated by the composite pattern of activity in the population of fibres from a particular body region. Central projection neurons code the nature and place of stimulation by the pattern and distribution of their discharges. **d** | According to gate control theory, the spectrum of primary afferent neurons has a range of thresholds, specialized nociceptors and dedicated central pathways do not exist, and large-diameter primary afferent fibres (A-fibres) adapt more quickly to maintained stimuli than thin ones (C-fibres). A presynaptic gate in the substantia gelatinosa (SG) of the spinal dorsal horn between primary afferent and projection neurons is controlled by the balance of activity between the A-fibres and the C-fibres. When the C-fibre input outweighs that of the A-fibres, the gate opens, permitting activation of projection neurons. CNS mechanisms (descending control) are postulated to modulate the gate. DRG, dorsal root ganglion; T, transmission neurons.

Documentation of nociceptors since 1965

The presumption that afferent fibres selectively responsive to tissue injury (nociceptors) do not exist is crucial to the intensive, pattern, and gate theories. This postulate was shown to be untenable in 1967 by Burgess and Perl, who documented a substantial proportion of slowly conducting myelinated fibres in cat cutaneous nerves to have distinct nociceptive characteristics[57]. Such afferent fibres are selectively responsive to strong mechanical stimuli, grading activity proportional to noxious stimulus intensities. Similar nociceptive afferent fibres are present in primates[58]. A subsequent study by Bessou and Perl pointed out that a large proportion of cat cutaneous C-fibres express coherent nociceptive features, being effectively excited by noxious heat, strong mechanical stimuli, and acid[59]. These experiments differed from prior work by utilizing recording methods that sampled peripheral nerve fibres more randomly.

A substantial body of evidence has since accumulated indicating nociceptors to be distinctive afferent units rather than the

limits of a population with a continuum of features. Nociceptors discriminate reliably between noxious and innocuous stimulation, a capability that is missing in low-threshold mechanoreceptive or thermoreceptive afferent neurons[58,60]. Nociceptors differ from low-threshold afferent fibres not only by having elevated thresholds for all stimuli ordinarily affecting a tissue, but also in their membrane constituents[61] and membrane properties, which include action potential shape[62] and cytochemistry[63–65]. Furthermore, they have distinctive termination patterns in the spinal cord[66,67]. A number of tissues have been found to be innervated by more than one category of nociceptor with different responsiveness to various noxious stimuli[65]. Therefore, at the beginning of the twenty-first century, nociceptors are widely accepted as separate classes of primary sensory neurons, with elevated thresholds to all forms of natural stimuli and selectivity in their response to different modes of stimulation.

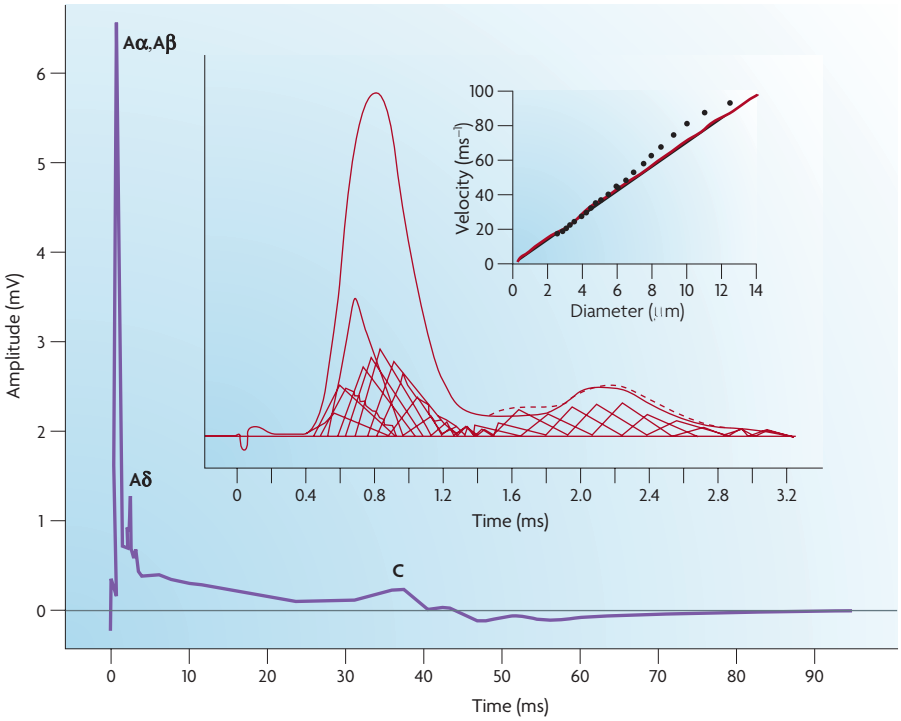


Figure 2 | **The compound action potential.** This composite figure depicts the compound action potential of a mammalian cutaneous nerve. The outer graph is a scale drawing of the compound action potential of a saphenous nerve for a conduction distance of 37 mm. The wave peaks are labelled alphabetically in order of latency[30]. Gasser's and Erlanger's elegant analyses in 1927 established the first peak (A) and its subdivisions (Aα, Aβ, Aδ) to be the summed electrical activity of myelinated fibres[135]. A much delayed (slowly conducting) C deflection was later found to represent the summed action potentials (nerve impulses) of unmyelinated fibres[136]. The speed at which action potentials are conducted was postulated to vary as a positive function of each fibre's cross-sectional diameter. Fibre conduction velocity is distributed around certain modal values, giving rise to the various deflections in the compound potential[137]. The inset shows the compound action potential of myelinated primary afferent fibres (A-fibres) from a saphenous nerve on a faster time base to depict the summation of action potentials of different fibres. Triangles, scaled in amplitude and duration to reflect dimensions of impulses recorded from fibres of particular conduction velocities, were used to represent each fibre of the nerve identified in histological cross-section. The triangles are positioned on the horizontal axis at the latency calculated from the conduction velocity derived from the fibre's measured diameter. Top right graph shows the relationship between fibre diameter (abscissa) and conduction velocity (ordinate) by the line as predicted by assumption and by dots as measured. Reproduction of the compound potential by summing of the triangles closely fit the recorded potential, consistent with validity of the summation and conduction velocity postulates. Modified from REFS 138,139.

Sensitization of nociceptors. It has become increasingly clear that signals transmitted by nociceptive afferents to the CNS are influenced by past events. First described in frogs by Echlin and Propper (1936) and subsequently noted in cats by Witt and Griffin (1962), once they are activated high-threshold afferent fibres exhibit a notable propensity to increase their responsiveness to subsequent stimuli[65,68–70] (FIG. 3). Enhancement of nociceptor responses as a consequence of tissue injury might be at least partially the result of modification of the extracellular milieu by intracellular contents issuing from injured cells (such as protons, potassium ions or ATP). Following tissue damage, the complex process of inflammation adds another set of agents (for example, serotonin, bradykinin, prostaglandins, growth factors[62] and cytokines) and circumstances that alter the responsiveness of peripheral nociceptor terminals. Sensitization of afferent fibres by processes operating on their peripheral terminal is presumed to be partially responsible for increased pain (primary hyperalgesia) in injured tissue[64,65,70–72].

Silent nociceptors. Systematic surveys of slowly-conducting afferent fibres in normal individuals describe some to be unresponsive to any intensity of mechanical or thermal stimulation. This is particularly evident in the innervation of musculoskeletal tissue. As Schaible and Schmidt pointed out, when inflammation is present, the number of inexcitable nerve fibres from joints markedly decreases and the proportion of mechanically excitable fibres increases[73–75]. The colourful names 'sleeping' or 'silent' nociceptors have been given to afferent fibres that are unresponsive under normal conditions. Presumably, they represent a category of sensory nerve fibres lacking mechanical responsiveness until exposed to an inflammatory environment. The recruitment of silent joint nociceptors to an active state is a possible important contributor to arthritic pain.

Relationship of nociceptors to sensation. Extensive information connecting activity in nociceptors to sensation has come from correlations between evoked activity (impulses) in nociceptive afferent fibres and behavioural measures[59,76,77]. Whereas nociceptor responses in experimental animals correlate well with descriptions of human pain evoked by the same stimuli, such comparisons depend on an assumption of similarity between species. Hagbarth and colleagues, particularly Torebjörk, established the technique of microneurography — the sampling of electrical activity from individual nerve fibres in conscious human subjects — making direct comparisons in a given person possible[77–79]. Torebjörk described close parallels between the activity of human cutaneous nociceptors and the individual's reports of painful sensations[77].

Using the recording microelectrode in human microneurography to electrically stimulate nerve fibres at the recording locus was suggested by Konietzny *et al.* and by Torebjörk and Ochoa; it provides compelling, albeit controversial, indications that activity in nociceptors, but not low threshold mechanoreceptors, evokes painful experiences[80,81]. The interpretation of such microstimulation studies presumes that weak electrical currents applied through the microelectrode excite the closest fibres, those from which discharges are recorded. Objections to that interpretation by Wall and McMahon focus on the large size of the metal microelectrode tip compared to the diameter of the fine nerve fibres[82]; however, the same size discrepancy exists for the recording of single-fibre traffic with microneurography electrodes[83]. Furthermore, the microneurography stimulation descriptions relate a remarkable correspondence between receptive fields of the recorded afferent fibres and the projected locus of the sensation evoked by intraneural microstimulation[80,81,83].

Late 20th century: CNS arrangements

Documentation of the characteristics of nociceptors provided tools to refine the search for CNS activity related to noxious stimulation. Christensen and Perl (1970) showed that some neurons in spinal lamina I (marginal layer of the spinal dorsal horn) are selectively activated by stimuli exciting nociceptors or thermoreceptors (afferent neurons specifically activated by innocuous warming or cooling)[84]. Craig has presented pivotal evidence that many lamina I neurons projecting to higher centres are selectively responsive to noxious and/or thermal stimuli. The lamina I region has been shown to receive direct input from myelinated- and unmyelinated-fibre nociceptors[66,67,84–86] and also to contain neurons with focused responsiveness to pruritic stimuli[4]. Importantly, both human and animal studies indicate that lamina I neurons contribute to the classical spinothalamic pathway[87–89].

A different and widely studied type of spinal neuron features a multimodal input from primary afferent fibres and is largely found deeper in the dorsal horn (laminae V–VI). Such multimodal neurons evidence weak activation by innocuous mechanical stimulation and more intense excitation by noxious mechanical or thermal stimuli; they are often referred to as wide dynamic range (WDR) neurons[90–92]. Their receptive fields are extensive, involving large regions of a limb or the body, and they respond much as predicted by the intensive theory (FIG. 1). The presence of both selectively nociceptive neurons and the multimodal, WDR type of response in the mammalian spinal dorsal horn has been confirmed and expanded by a number of investigations[4,86].

Both selective and WDR neurons participate in nociceptive and pain-related mechanisms. The differences in their coding of information from the periphery suggest that they serve different functions in the organization of sensory and reflex reactions. Selective responsiveness of lamina I neurons provides a basis for differentiating noxious and innocuous events, a distinction made by the receptive characteristics of the primary afferent neurons. This specificity is presumably carried forward by the focused responsiveness of lamina I neurons. The WDR type of response might concern mechanisms other than those signalling the nature and location of stimuli, although some proposals presume that the convergent WDR neurons could provide the information necessary for both modality and location designation[4,93]. It is possible that the large receptive fields of multimodal projection neurons function in mechanisms that set the responsiveness of higher centres[94].

There is now convincing evidence that projections of both selective and non-selective neurons with nociceptive features reach similar levels in the forebrain[86,95]. Lamina I and laminae V–VI spinal neurons send axons to the midbrain and thalamus[93,95,96]. To some extent these projections might converge. Circumstantial evidence suggests features of WDR-type ascending projections to fit those capable of evoking pain in conscious human subjects[91]. However, spinal chordotomy in humans in which the lateral tracts of the spinal cord are divided surgically to treat otherwise uncontrollable pain from the contralateral body[25] provides a circumstantial link between human lamina I neurons and pain. The segmental distribution of lamina I neurons showing retrograde degeneration from the lesion of the contralateral spinal cord fits closely to the distribution of the lost pain sensitivity[87,88].

Noxious stimulation also evokes enhanced pain in tissue uninjured by the event. This remote effect has been attributed to central nervous mechanisms[72,97,98]. Vigorous activity in certain nociceptive afferents is associated with an increased synaptic activation of spinal neurons; phenomena now labelled 'central sensitization'. Central sensitization could be the product of several different processes. Presynaptic

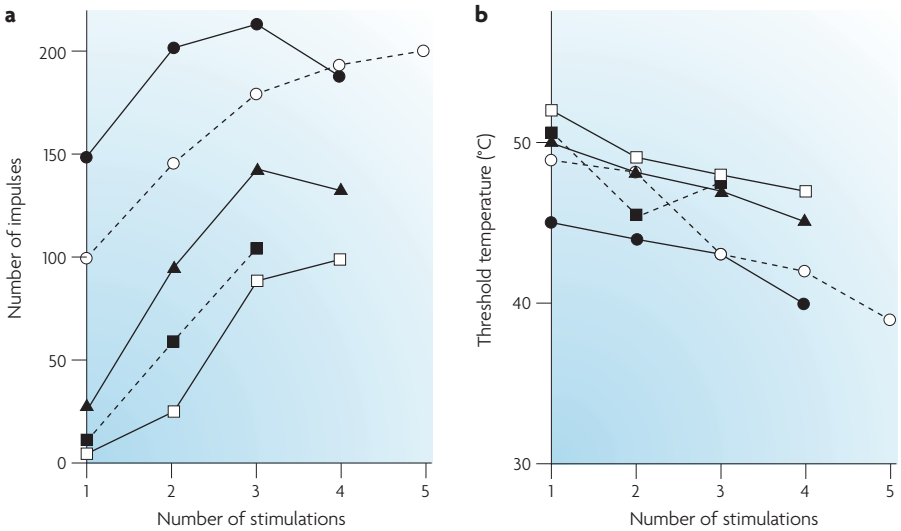


Figure 3 | **Peripheral sensitization of nociceptors.** Exposure to noxious heat is associated with an increased response and a decrease in heat threshold by mammalian single unmyelinated (C-) fibre nociceptors. Action potentials from C-fibres from primate polymodal nociceptors were isolated by mechanically teasing a cutaneous nerve. A small contact thermode was used to produce a sequence of temperature increases to stimulate the skin (stepping in equal increments from 30–53°C in ~90 s followed by quick cooling to the 30°C holding temperature). Identical stimulus programs were repeated at 200 s intervals. **a** | The total number of impulses between the start of the heating program and the start of the next heating cycle. **b** | The temperature threshold for evoked impulses in each run. The symbol indicating a given fibre also applies to both panels. Note the increase in number of impulses generated during a given cycle and the decrease in the threshold temperature on successive applications of the heat stimuli. The increased response and lowering of threshold is evident in some units after a single stimulus cycle. Reproduced, with permission, from REF. 140 © (1977) American Physiological Society.

terminals of many neurons, including some primary afferent fibres, contain more than one excitatory synaptic mediator. One mediator (for example, glutamate) could be released on infrequent to moderate activation, with another (such as a peptide or ATP) being released when there are high levels of presynaptic activity[99]. Secondary mediators could enhance the response to other agents or increase excitability of postsynaptic neurons[100]. Alternatively, a given mediator such as glutamate can activate different postsynaptic excitatory receptors — for example, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), NMDA (*N*-methyl-D-aspartate) and metabotropic receptors — again on an activity-dependent basis. Activation of NMDA receptors induces a persisting facilitation, part of a process leading to the generation of long-term potentiation of synaptic effectiveness. Involvement of NMDA receptors in the central sensitization of nociceptive connections has been argued by Woolf and his colleagues to indicate a mechanism similar to memory processing in the hippocampus[98].

Central ascending pathways. Fibres in the lateral and ventral spinal white matter form an important ascending pathway for nociceptive and pain-related activity from the opposite side of the body. However, much evidence has accumulated supporting a far more complex arrangement than a single invariant and dedicated tract. Fibres of the crossed ventrolateral spinal pathway were established to reach the thalamus, giving rise to the designation 'spinothalamic.' Willis and his colleagues have utilized antidromic activity evoked by electrical stimulation in thalamic structures to uncover functional characteristics of neurons contributing to ventrolateral tracts. Importantly, modern histochemical (anterograde and retrograde transported markers)[101,102] and physiological (antidromic) tracing[86,93,103] have shown that axons in the same spinal regions also to project to more caudal brain stem nuclei[95,104,105].

Information projected rostrally by the ventrolateral tracts is complex, and details remain the subject of debate[4]. Ventrolateral projection neurons in spinal lamina I include selectively nociceptive categories conveying activity from a single or several types of primary afferent nociceptor. Other lamina I ventrolateral projection neurons receive excitation from a combination of nociceptors and thermoreceptors[4]. Ventrolateral projection neurons from deeper dorsal horn laminae have more multireceptive characteristics, fitting the WDR category[95]. How this mix of signals and cell groups is organized to provide a sensation remains unknown.

The crossed ventrolateral pathway is not the sole ascending spinal projection to carry nociceptive information; however, in general, there is a lack of convincing evidence for important contributions from other major ascending pathways in normal nociceptive reactions and pain[86]. An exception is the relatively recent uncovering by Willis and colleagues of a role for the spinal dorsal columns in transmitting pain-related information from pelvic viscera to higher centres[106–108]. This dorsal spinal pathway helps to explain the clinical observation that a lesion of the spinal cord in the dorsal midline, separating the dorsal columns, can alleviate visceral pain[109].

Whereas certain nuclear groups of the thalamus are a principal target of the spinal ventrolateral system, direct connections from neurons of several spinal regions to other higher centres including the hypothalamus and parts of the amygdala have been established[110–112]. The amygdala and hypothalamus are usually considered to participate in affective and homeostatic functions rather than somesthesis, raising the possibility that special pathways subserve nociceptive mechanisms other than sensation (see below). Nociceptive signals also reach higher brain centres via multisynaptic routes by way of connections in subthalamic brainstem nuclei.

The thalamus and cerebral cortex. The crossed ventrolateral pathway terminates in both lateral and medial thalamic nuclei[4,95]. The lateral component contributes terminals to several nuclei of the ventral posterior thalamus, a main somatosensory zone with spatial and modality characteristics suggestive of a role in discrimination[64,95,96]. By contrast, the medial thalamic ventrolateral projection targets neurons in nuclei usually associated with affective or motivational reactions. However, one projection of spinal lamina I to a thalamic ventral medial region proposed by Craig and colleagues in 1994 has been reported to feature cells showing selective excitation by localized noxious or thermal stimuli. The thalamic zone of this projection was reported to be marked by calbindin labelling[113]; however, these findings have been challenged by Jones's laboratory, which questions the distinctiveness of the region defined by calbindin immunocytochemistry[114].

Early in the twentieth century, pain was suggested to be a product of thalamic mechanisms, discounting a contribution by the cerebral cortex based on absence of selective alteration in pain perception after lesions or electrical stimulation[26,27,115,116]. However, there were also reports of a persisting loss of capacity to recognize painful stimulation in restricted body regions after localized cortical injuries in the central sulcus region. These earlier observations and modern imaging analyses strongly support the concept that the cerebral cortex has an important role in pain processing[117–120].

Imaging. The last decade of the twentieth century saw an explosion of information from imaging blood flow and fluid changes in the intact, functioning human brain using positron emission tomography (PET) and functional MRI (fMRI). The fundamental tenet in these studies is that blood flow and fluid changes in the brain parallel local neuronal activity. An increase in the net metabolism of a group of neurons is generally a consequence of excitation; however, synchronous activation of inhibitory linkages will leave metabolic traces as well. This burgeoning field of *in vivo* investigation so far lacks convincing resolution at the cellular level. Nonetheless, brain imaging spearheaded by several groups (Bushnell; Derbyshire; Davies) demonstrates the extent and pliability of the cerebral neural networks that become active after a noxious stimulus and emphasizes the complexity of the system. Such studies make it clear that processing of information in the neural systems associated with nociception and pain partly occurs in several brain regions operating in parallel.

To a considerable degree, PET and fMRI determinations of human brain regions activated by painful stimuli are consistent with expectations from modern morphological and physiological tracing and projection studies of spinal ventrolateral pathways. Noxious stimulation evokes prominent signs of localized metabolic increases in several distinct cerebral cortical areas including the anterior insula, the anterior cingulate cortex (ACC) and somatosensory II regions[121,122]. Less consistent, more context-influenced or smaller activations occur in other cortical regions[4,123–126]. Mental state, attention and disposition modify the pattern and details of imaged cortical responses to noxious input[121,124,127]. There seems to be agreement that activity in the ACC detected by PET and fMRI, evoked by pain-causing stimuli, is related to emotion and motivation[124,127,128].

Descending control. Modulation of spinal mechanisms by activity descending from rostral brain centres was documented in Sherrington's classical neurophysiological studies[20]. Intrinsic neural mechanisms controlling pain were given sharp focus by Reynold's 1969 article describing rodent surgery during analgesia produced by electrical stimulation in the midbrain periaqueductal grey[129]. Activation of a number of other brainstem nuclei produces potent suppression of pain-related spinal activity. This prompted numerous studies of 'stimulation-produced anaesthesia' and descending 'analgesia' pathways[86,93]. Descending inhibition of spinal pain-related activity is produced by neurons utilizing different chemical mediators, including serotonin, catecholamines, and endogenous opioids.

Investigators who concentrate on pain have tended to categorize descending systems and their effects as specifically anti-nociceptive or analgesic arrangements. However, there is remarkable similarity in the nuclei involved and the mediators employed, between those implicated in analgesic effects and those involved during sleep and stress[64,130]. It seems reasonable to view descending control of spinal reflex and afferent mechanisms in a more general context than simply modifying nociception and pain.

Opioid receptors. Opioid derivatives from the poppy plant have been used by man for centuries, although often not for amelioration of pain. However, morphine and other opiates continue to be extremely important agents for pain relief. Even though it was long suspected that opiates acted on particular receptive structures in cells and tissues, an opioid receptor in neural tissue was only definitively identified in 1973 by Pert and Snyder[131]. A specialized molecular receptor for opioid compounds strongly suggested the existence of an endogenous ligand. Shortly after the identification of opiate receptors, enkephalin was shown by Hughes and Kosterlitz[132,133] and Simantov and Snyder[134] to be one of a series of endorphins (endogenous morphine). Activation of opiate receptors by morphine or synergists produces changes in behaviour and suppresses nociceptive reactions, among other actions. Certain anti-nociceptive opioid actions involve the suppression of synaptic effectiveness by primary afferent fibres at their central terminations.

Sensation–emotion and homeostasis. The primary evidence for considering pain from noxious stimulation as a discriminative sense, rather than an emotion, is its dissociation from other body sensations in disorders of the nervous system. However, the discomfort or suffering usually related to the recognition of a painful event are strong feelings of the type categorized as emotions. So what is pain? Its ordinary expression has attributes and an underlying neural organization of both a specific sensation (detecting, signalling and recognizing noxious stimuli) and those of an emotion. Should pain be considered both a specific sense and an emotion? Given these two sides, it is no wonder that there has been debate and uncertainty about the nature of pain over the ages. Modern neuron tracing and human brain imaging observations showing connections and activity consistent with a discriminative sense and an affective reaction certainly can be argued to reflect such duality.

In considering labelled line (that is, dedicated sense organs and neural pathways) and convergent-intensity (that is, quantitatively controlled, nonspecific neural arrangements) models for the central organization of nociceptive and pain systems, Craig (2003) concluded that pain was a homeostatic emotion[4]. However, homeostasis implies holding an organism and its systems to a stable state, a concept that is difficult to reconcile with some concomitants of nociception and pain. These include marked increases in respiration, heart rate and arterial pressure. Such functional alterations could be appropriate reactions when tissue is injured, but they poorly fit the usual concept of homeostasis.

Chronic pain. Present-day clinicians call pain that persists beyond the usual time associated with injury of a tissue 'chronic', often regardless of presumed cause. This implies a difference from the usual relationship between tissue injury and rapid pain or nociceptive reactions. There are unquestionable changes in neural functioning secondary to persistent nociceptive input. Moreover, long-lasting aberrant CNS-generated activity that triggers the perception of pain also produces plastic alterations in behaviour and nervous function. In addition to phenomena such as sensitization of peripheral nociceptors or central neurons, rearrangements of activity and possibly neuronal connections are reported. Some processes leading to these rearrangements might take place at the genetic level. Principal factors in clinical circumstances are the emotional and motivational concomitants of persisting pain symptoms. This is not to suggest that the mechanisms discussed in this article do not apply to the chronic situation; however, long-term pain-related activity might be associated with other profound alterations in reactions, including sensory experience and pathological functions in other organ systems. These situations are beyond the scope of the present perspective.

Conclusions

In summary, the past two centuries have seen major alterations in thinking regarding pain, which have paralleled a great expansion in understanding of nervous mechanisms. During the last 40 years, incontrovertible evidence has accumulated to show that specialized peripheral sense organs act as detectors of tissue-damaging events, and that activity in these nociceptors normally initiate pain. Their signals have been shown to be partially segregated in transmission to multiple rostral brain centres including the thalamus and the cerebral cortex. However, it has become apparent that activity in neuronal pathways characterized by the convergence of primary afferent input has a role in the processes associated with nociception and pain. Considerable importance has been attached to activity-dependent changes in nociceptive neuronal systems and to higher centre control of ascending pathways, even though the latter might not be unique to pain. Finally, current evidence from human imaging studies emphasises parallel processing of sensory information in complex reactions, including pain.

With the benefit of the past two centuries of scientific work and thought, can one define pain? Considering the evidence, it seems reasonable to propose pain to be both a specific sensation and an emotion, initiated by activity in particular peripheral and central neurons. Pain shares features with other sensations, but the strong association with disposition is special. The mechanisms of pain include specialized receptive organs, selective and convergent pathways, plasticity of responsiveness and interactive modulation. No single theory (emotion, specific, intensive, pattern or gate) fits the present evidence by itself, although a combination of ideas answers most issues. Reason suggests an integration of features is the best choice for a working hypothesis.

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Competing interests statement

The author declares no competing financial interests.

FURTHER INFORMATION

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