Published in final edited form as:
Pain. 2014 February ; 155(2): 210–216. doi:10.1016/j.pain.2013.12.010.

Constructing and Deconstructing the Gate Theory of Pain

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Abstract

The Gate Theory of Pain, published by Ronald Melzack and Patrick Wall in *Science* in 1965, was formulated to provide a mechanism for coding the nociceptive component of cutaneous sensory input. The theory dealt explicitly with the apparent conflict in the 1960s between the paucity of sensory neurons that responded selectively to intense stimuli and the well-established finding that stimulation of the small fibers in peripheral nerves is required for the stimulus to be described as painful. It incorporated recently discovered mechanisms of presynaptic control of synaptic transmission from large and small sensory afferents which was suggested to "gate" incoming information depending on the balance between these inputs. Other important features included the convergence of small and large sensory inputs on spinal neurons that transmitted the sensory information to the forebrain as well as the ability of descending control pathways to affect the biasing established by the gate. The clarity of the model and its description gave this paper immediate visibility with numerous attempts made to test its various predictions. Although subsequent experiments and clinical findings have made clear that the model is not correct in detail, the general ideas put forth in the paper and the experiments they prompted in both animals and patients have transformed our understanding of pain mechanisms.

Keywords

Gate Theory; Dorsal root potentials; Presynaptic inhibition; Dorsal horn; TENS; Nociceptor; Substantia Gelatinosa

Introduction

It is approaching the 50th year since the landmark paper advancing the Gate Theory of Pain was published [45]. Although this paper is only one of many very influential papers in the pain field, it holds a special place because of its very clear theoretical position on how pain is coded and its elaboration of a specific model to achieve this based on available electrophysiological evidence. Given its prominence it is valuable to review the findings that led up to its publication. Because Melzack and Wall provided such a clear statement about

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I declare no conflict of interest in connection with this review article.

pain mechanisms, many of the subsequent developments in the field were evaluated with reference to the Gate Theory, and so a discussion of this paper can provide a window into the history of the field at that time and later. The paper made certain predictions that have been influential in the pain field and beyond. Other conclusions in the paper made using available experimental data turned out to be incorrect. A full evaluation of the Gate Theory requires discussion of both its successes and its failures; in so doing we provide a more complete perspective as to its role in the development of modern pain theory.

Early work based largely on lesions and electrical stimulation of peripheral nerves had provided an outline of what could be called a pain pathway projecting from the periphery to the cortex by way of the spinal cord, brainstem and thalamus. Despite this basic information it was not possible to permanently abolish pain in patients surgically or pharmacologically. Beginning with a series of papers by Ronald Melzack, joined later by Patrick Wall, a new conceptual framework for pain was advanced. This framework drew on provocative behavioral observations with important implications for pain mechanisms. Later work made use of new experimental evidence illuminating processing of sensory input by the spinal cord. This led to a simple, elegant mechanism for pain coding that stimulated new modalities of treatment for certain painful conditions. This mechanism, called The Gate, provoked a number of important experiments which advanced the study of pain without necessarily confirming the Gate mechanism.

Early studies

Modern studies leading to the Gate Theory Hypothesis began with the work of Ronald Melzack, a student of DO Hebb at McGill. He noted that dogs maintained in a restricted sensory environment would bump their head on exposed pipes when allowed to run freely and would not avoid these obstacles subsequently. This observation prompted a formal study of the effect of experience on the reaction to stimuli normally causing pain in dogs beginning at 4 weeks of age. The deficit was not in the ability to react immediately to the intense stimuli but rather in the subsequent avoidance behavior. The important conclusion was stated as follows [42]: “The results which have been reported here then, make it difficult to treat behavior related to pain simply in terms of frequency and intensity of stimulations or in terms of imperative reflex responses alone without regard to the earlier perceptual experience of the organism.” This conclusion differs substantially from earlier ideas about pain, notably the iconic picture from Descartes suggesting that pain was an obligatory response to stimulation of elements responsive to the intense stimulus. As he stated “If…fire comes near the foot, the minute particles of this fire…set in motion the spot of the skin of the foot which they touch, and…pulling on the delicate thread…they open up at the same instant the pore against which the delicate thread ends, just as by pulling at one end of a rope one makes to strike at the same instant a bell which hangs at the other end" (from [45]). Apart from details about sensory transduction and axonal conduction, this formulation is identical to what we would now call the labeled line mechanism for pain.

In the early 1960s Melzack, now at MIT, began collaborating with Patrick Wall whose spinal cord physiology laboratory had been there since the mid-1950s. Their first joint effort was a theoretical paper [44] discussing sensory physiology including pain processing. From

his previous work Melzack was already disposed towards the idea that sensory circuits were not labeled lines such that activation of a particular receptor resulted in a particular sensation- touch receptor/touch; pain receptor/ pain, etc. Wall had similar ideas based on his work on modification of sensory input at the first spinal synapse due to presynaptic inhibition [24, 64, see below]. They noted the ongoing controversy about cutaneous sensory mechanisms with one opinion originating with von Frey that cutaneous modalities were fixed beginning with anatomically distinct cutaneous receptors responsible for different modalities- touch, warm, cold and pain. The other view was championed by Weddell, Sinclair and others based on a lack of correspondence between anatomy and adequate stimulus of receptors. They suggested that stimulus modality was signaled by the spatiotemporal barrage of impulses in sensory fibers (see discussion in [44] for review of these concepts).

Melzack and Wall deconstructed von Frey's theory of specificity into 3 assumptions: Although they accepted the possibility that individual receptors might have a specific anatomy (The Anatomical Assumption) correlated with sensitivity to a specific physical stimulus (The Physiological Assumption), they were skeptical that the "psychological dimension of the somesthetic experience" could be identified with a specific skin receptor type (The Psychological Assumption). They argued in favor of a Pattern Theory where barrages of impulses produced in different sensory fibers initiated a computation in the central nervous system that was decoded into a somesthetic experience based in part on other ongoing brain activity. A corollary was the possibility that interference with the barrage or with the computation of its effects might prevent accurate interpretation, as for example the inability of experience- deprived dogs to react appropriately to intense stimuli.

In this paper Melzack and Wall drew special attention to Goldscheider's original proposal reemphasized by Livingston [11, 35] that central summation is important for generating impulse patterns interpreted as pain. They cited the lack of evidence for individual sensory fibers responding selectively to intense, presumptively painful stimuli. They suggested that pain might arise only when the number of responding fibers as well as their frequency of discharge exceeded some threshold.

Inhibition of cutaneous input to the spinal cord

Two major advances in the late 1950s were very influential in the development of the Gate Theory. The first was a clinical finding from analysis of patients with Herpes zoster. These patients experience excruciating pain in response to gentle stimulation of the affected area. Noordenbos [56] showed that the fraction of large fibers in nerves innervating these areas was diminished. He suggested that large fibers normally inhibit the effects of small fibers, and that this inhibition is reduced in the diseased nerves. This led to the idea, so important in the formulation of the Gate Theory, that the balance between the large and small fiber input was a major factor in determining the painfulness of a stimulus.

A second advance began with the seminal work of Frank and Fuortes [18] who demonstrated long lasting presynaptic inhibition of input to motor neurons elicited by volleys in large afferent fibers. Later, both Wall [65] and Eccles et al [16] both demonstrated that the central effects of volleys in cutaneous afferent fibers were presynaptically inhibited

by conditioning volleys in other segmentally close cutaneous afferents. Up to this point studies of synaptic effects had been largely restricted to the effects of large diameter myelinated afferent fibers. Mendell and Wall [50] investigated the presynaptic effects of activity in small diameter unmyelinated afferent fibers. These were of interest because electrical stimulation of peripheral nerves in human subjects had shown that stimulus intensities high enough to activate unmyelinated fibers were required to elicit pain [9]. Mendell and Wall measured the presynaptic effect of small fiber stimulation by measuring the dorsal root potential (DRP) and by testing the excitability of the terminals of sensory fibers. Presynaptic inhibition is signaled as a negative DRP associated with depolarization of the fiber terminals and as an increase in electrical excitability of the depolarized terminals (reviewed in [57]). When unmyelinated fiber volleys were elicited in isolation using direct current anodal block to prevent conduction in the concomitantly activated large diameter afferents, the DRP was reversed in sign (Figure 1), and the test of terminal excitability revealed a decline. Both of these were indicative of hyperpolarization of the terminals. This was interpreted as presynaptic facilitation.

The requirement to block inputs from large cutaneous Aβ fibers was due to the interference from the large negative DRPs they evoke. This was a technical limitation in these experiments that caused some controversy [76]. In later experiments where muscle nerves were activated, the positive DRP could be unambiguously observed in response to small fiber stimulation without the need for large fiber blockade because large proprioceptive afferent fibers evoke much smaller negative DRPs than large cutaneous afferent fibers [47].

Cells responsible for generating presynaptic inhibition of cutaneous sensory fibers

An important component of the Gate Hypothesis was the suggestion by Wall that cells of the substantia gelatinosa (SG) were responsible for the presynaptic effects [65, 66]. He drew upon anatomical evidence that these cells synapsed only with other cells in the SG in the same segment or in neighboring segments via Lissauer's Tract. This suggested that these cells acted as a modulatory system rather than as a system projecting directly or indirectly to the forebrain. The evidence linking the activity of these cells to presynaptic inhibition was based on correlating the timing of their activity to the generation of the DRP. Crucial was the observation that interrupting intersegmental conduction in the SG by cutting Lissauer's Tract interfered with the spread of the DRP to an adjacent segment. It was hypothesized that cells in the SG made axo-axonic synapses on terminals of sensory fibers in the dorsal horn, but no direct evidence was available on this point. Axo-axonic synapses were first identified in 1962 [19] but there was very little evidence for their distribution in the early 1960s.

The difference in small and large fiber inputs to the SG demonstrated by Szentagothai [61] played an important part in the elaboration of the Gate Theory. Szentagothai demonstrated that branches of large fibers entering the spinal cord dropped into the deeper laminae of the dorsal horn and then curved dorsally to enter the SG from the ventral side. Small diameter afferents entered SG directly from the dorsal side (Figure 2A). Melzack and Wall distilled the complex figure of Szentagothai focusing on the different patterns of small and large fiber projections to the SG (Figure 2B). They suggested that a single functional set of SG cells with axo-axonal projections to terminals of both large and small sensory fibers could be

excited by large fibers or inhibited by small fibers. There was no specific evidence for this conclusion, but Mendell and Wall [50] had argued that this was the simplest interpretation of the different polarity of presynaptic control exerted by these fibers (Figure 1) as well as the enhancement of the positive DRP during steady enhanced negative DRPs produced by high frequency stimulation of large diameter sensory fibers. Later work [48] indicating that both the negative and positive DRP are blocked by the $GABA_A$ antagonist picrotoxin was supportive of this conclusion although recent studies suggest that the synaptology and transmitters involved may be more complex [22].

These findings were the basis for the iconic gate mechanism diagram published in the 1965 paper (Figure 3). Both large and small sensory fibers were assumed to project to cells (called T-cells) which projected to the forebrain. Selective activation of large fibers should reduce net input to T cells via the presynaptic gate located in the SG. It was proposed that prolonged high intensity stimulation caused an unbalanced small fiber input due to selective adaptation of large fibers (rather than the high threshold of receptors associated with small fibers). This unbalanced small fiber input removed presynaptic inhibition of sensory inputs, i.e., disinhibition which “opened the gate”. Thus, as originally proposed by Noordenbos (see above), the balance between small and large fiber input, ***not*** the activity in in a special class of fibers responding to damage, would determine the output of the T cell via the gate. Once the integrated firing- level of T cells exceeded a critical preset level, the firing would trigger a sequence of responses by the *Action System*. This integrated response would be interpreted as “pain” and would not be an instantaneous response. The Central Control system was proposed to reset the Gate based on external contingencies, including sensory input reaching the brain rapidly via the large fibers in the dorsal columns or the very rapidly conducting spinocervical tract system, and thereby alter control over the sensory input. This implied descending control of the gate mechanism (21), a prediction that was confirmed later (see below).

Implicit in the Gate Control Hypothesis is the idea that pain is evoked when brain activity reaches a certain level due to sensory and/or central inputs. Melzack [39, 40] has expanded this idea into the *Neuromatrix* concept which for pain is a neural network with somatosensory, limbic and cognitive components (41). As in the Gate model, the output or “neurosignature” of the neuromatrix determining the painfulness of a sensory input is modulated by sensory input and differs in different individuals according to genotype and experiential variables. Thus the pain experience is not unique and can differ according to the individual as well as the injury. This was explored by Melzack and Torgerson [43] who classified painful experiences in terms of the words used to describe them. This is useful for investigating the efficacy of treatments in the clinic and led to the more formal McGill Pain Questionnaire [38], used widely in pain clinics.

Tests of closing and opening the gate

A major prediction of the Gate Control Hypothesis was that enhancing input selectively in large fibers would shut the Gate by reducing activity in T- cells; this would diminish any ongoing pain. This was tested initially by Wall and Sweet [70] who reported on 8 patients experiencing pain. Four had conditions indicative of peripheral nerve damage; high

frequency stimulation of the large fibers in that nerve (Transcutaneous Nerve Electrical Stimulation- TENS) produced tingling referred to the distribution of that nerve and relief of the pain for the duration of the stimulation, and for 30 min after cessation of the stimulation. In 4 other cases where peripheral nerve damage was not suspected, stimulation of large diameter afferents also was analgesic but the reappearance of pain after stimulation was much faster, within 5–10 minutes. Pain abolition was attributed to closing the gate by selective stimulation of large fibers. Reappearance of pain was attributed to gradual reopening the gate by ongoing small fiber activity which was less intense in cases where peripheral nerves had been damaged and therefore took longer to be re-established. A similar protocol was attempted in a group of patients suffering from post-herpetic neuralgia and some success was observed in a subset whose pain was moderate [4, 55]. The relief from pain continued for up to 2 hours after the stimulation was stopped. Surprisingly, a few patients reported an improvement in their neuralgia over the course of treatment, and 2 of the patients considered themselves cured (one after 4 months; the other after 3 years of treatment). Because of its potential value in alleviating pain without the use of drugs, TENS has continued to be studied [60] with recent suggestions that its effects may be highly selective, e.g., deep pain vs cutaneous pain [31]. Relief from pain has also been obtained using high frequency stimulation of the dorsal columns [58] which is comprised largely of branches of large myelinated sensory fibers. Although the Gate Theory was the genesis of this treatment modality, it is not clear that it can account for the clinical effects, particularly the lingering after effects of the stimulation.

The question of opening the gate by small fiber stimulation has been explored at several different levels. Melzack and Wall proposed explicitly that this occurred by means of a presynaptic control mechanism although they made clear that they were open to other possibilities. Mendell and Wall ([50]- their Figure 6) did demonstrate that large cutaneous afferent fibers could be hyperpolarized but this was demonstrated under conditions where they were initially depolarized by high frequency burst stimulation of another sensory input. In reconsidering the interpretation of this experiment it is possible that the test stimulus interrupted the effects of the burst by presynaptically inhibiting its input, i.e., by closing the gate, rather than by inhibiting tonically active interneurons of the gate mechanism which would open the gate [49]. Furthermore, when intrafiber recording was used to search for changes in polarization from identified afferent fibers in response to peripheral nerve stimulation, the most reliable hyperpolarization was observed in muscle spindle group I afferent fibers of flexor afferents [23, 48] which probably contribute little to conscious pain. Burke and colleagues [49] also questioned the association of presynaptic hyperpolarization with pain by demonstrating that radiant heat stimulation in the noxious range (> 50°C) evoked primary afferent depolarization in cutaneous afferents, not hyperpolarization. So although stimulation of large fibers produced presynaptic depolarization which would be interpreted as closing the gate, the correspondence of gate opening (i.e., presynaptic hyperpolarization) and inputs producing pain was not confirmed.

Nonetheless, it became clear that the firing of second order cells in the spinal cord was selectively enhanced by volleys in small diameter afferents. Furthermore, the repetitive discharge of spinal neurons exhibited a phenomenon called windup [46, 51] whereby it became more prolonged in response to each successive C- fiber stimulus if it occurred

within 4 seconds of the preceding one. At the time this was interpreted in terms of the gate model, i.e., as due to summation of presynaptic facilitation, but now it is recognized as due to the release of peptides by certain small diameter afferents which prolongs the synaptic potential thus allowing temporal summation over a period of seconds [29]; this depolarization activates NMDA receptors whose blockade abolishes windup without eliminating the response to C- fiber stimulation [13]. Windup is an early event in a process leading to central sensitization [72] and represents an increase in gain for the spinal system processing the nociceptive input [73]. Volleys in large diameter afferents also initiate a repetitive discharge in these postsynaptic cells but this is fixed in duration and often followed by a brief silent period [46, 51]. Thus small and large fibers elicit very different central effects that resemble what was suggested in the Gate Theory, but the mechanism responsible for the effects of small fiber stimulation is quite different.

Nociceptors

At the time the Gate Theory was proposed, there was very little evidence for high threshold afferent fibers. Based on reports of very few such fibers [e.g., 25, 27], Melzack and Wall [45] viewed them as the “extreme of a continuous distribution of receptor- fiber thresholds rather than a special category”. The gate circuit was considered to provide a mechanism for enhancing the discharge of central neurons (T-cells) in response to intense stimulation without the need for a population of cells selectively activated by high intensity inputs. The discharge of T-cells was determined by the balance between small and large fiber input; maintained intense stimuli favored the discharge in small diameter afferent fibers because they exhibited little adaptation in contrast to large diameter afferent fibers.

At this time Burgess and Perl [6] published experiments which changed the landscape of the pain field again. They demonstrated a population of small diameter myelinated fibers innervating the skin that were activated only by stimuli that would be damaging to the skin. These became known as High Threshold Mechanoreceptors. Perl and his collaborators went on to describe a population of C-fibers activated by nociceptive stimuli of different modalities (mechanical, thermal and chemical (pH)). These were referred to as Polymodal Nociceptors [5], the term *nociceptor* denoting receptors activated by stimuli that were potentially damaging to the tissue in which they were embedded [59]. Nociceptors were later found to have important physiological properties such as sensitization [29], and to project into the superficial dorsal horn [34] where they synapse upon a population of cells called marginal cells that respond exclusively to noxious stimuli [8]. These cells in the marginal zone were found to contribute to the spinothalamic tract [71, 75] which gave them access to forebrain structures and thus presumably to conscious sensation. A population of nociceptors was also observed to be peptidergic (reviewed in [30]) and thus able to promote Windup.

This series of discoveries was at odds with the philosophy expressed in the Gate Theory since it suggested a labeled line for the projection of nociceptors and thus for “pain”. Some cells in the VPL in thalamus are known to respond selectively to pinch stimuli [20, 32], at least under anesthesia, implying that labeled lines might account for some behavioral responses to nociceptive input. However, there are other cells in the spinal dorsal horn, the

wide dynamic range cells [46],that receive excitatory input from both nociceptive and non-nociceptive sensory inputs. Therefore, it seems unlikely that the presumptive nociceptive circuit is acting in isolation to signal “pain”. In fact, experiments in which pain intensity was rated while recordings were carried out in wide dynamic range cells or in lamina I nociceptive neurons in the medullary dorsal horn suggested that the former were more specialized for coding pain intensity [14]. Lamina I cells have been proposed to serve a homeostatic role with regard to pain by coordinating the organism’s response to nociceptive stimulation in a way that maintains equilibrium [10].

Other gate mechanisms

Although later experiments took issue with some of the specific components of the gate hypothesis and its predictions, the value of the concept has been demonstrated by its extension to other systems. The clearest example of this comes from analysis of descending pathways from the rostroventromedial (RVM) nucleus of the medulla [1, 53]. This nucleus consists of 2 populations of neurons (ON and OFF) projecting to the superficial dorsal horn of the spinal cord. OFF cells are constitutively active and are turned off by nociceptive inputs. ON cells are constitutively silent but are turned on by nociceptive inputs. ON cells enhance transmission from nociceptors to lamina I neurons; OFF cells depress it. When the tail is subjected to an increasingly hot thermal stimulus [17], the motor response (tail flick) is immediately preceded by OFF cells turning off and ON cells turning on. Furthermore, OFF cells are excited by opiates whereas ON cells are inhibited; this is consistent with the antinociceptive effect of opiates. Thus the ON/OFF system acts as an opioid- dependent gate at nociceptor- driven synapses in the spinal dorsal horn.

Anatomy and function of lamina II

One of the major ideas underlying the Gate Theory as originally proposed was that the SG (or lamina II) is a closed network of cells whose activity can be turned on by large myelinated fibers and off by unmyelinated fibers. The other major point was that these cells make axo- axonic synapses on the terminals of incoming afferent fibers. New evidence consistent with the idea that the discharge of cells in the superficial dorsal horn is related to the negative DRP was obtained by Lidierth and Wall [33] who recorded from cells activated by microstimulation of Lissauer’s Tract. They found that most of these cells could also be activated by muscle and skin afferents as well as by inputs from motor cortex. Using spike triggered averaging they demonstrated that the spontaneous discharge of cells activated by Lissauer’s tract stimulation was correlated with the negative DRP. Because these experiments could not establish causation, they concluded that these superficially located neurons activated by Lissauer’s Tract were very promising candidates for generating the negative DRP. It is interesting that in none of this later work was any attempt apparently made to determine the response of these cells to small diameter sensory fiber input.

Recent immunohistochemical work using newly available reagents to identify different populations of neurons within the superficial dorsal horn has made clear that glutamatergic cells in lamina II are activated by small diameter afferents and deliver significant output to projection neurons in lamina I [63], i.e., cells in the SG are part of a projection system. Similar synaptology was observed in electrophysiological studies [62] and further indicate

that the projection from Aβ afferent fibers through lamina II to lamina I projection cells can be inhibited by a postsynaptic inhibitory mechanism.

Additional perspective

We have reviewed the ideas that went into the formulation of the Gate Hypothesis and have evaluated many of the experimental issues in the light of later experiments. It is easy to criticize bits and pieces of the theory as many did. Indeed, in a later paper, partly in answer to a critical review [54], Wall [68] re-evaluated the Gate Theory accepting some but not all of these criticisms. As in an earlier paper [44] he remained dismissive of the labeled line theory of sensation by emphasizing that although the response of sensory receptors is *diagnostic* in indicating the physical stimulus, it is not *prognostic* in predicting the resulting psychological modality.

However, Wall did accept the criticism of one of the initial pillars on which the Gate Theory was constructed, namely the idea initially advanced by Noordenbos from his work on Herpes zoster, that inputs restricted to small sensory fibers are always painful. Several clinical examples of large fiber degeneration e.g., Friederich's ataxia and polyneuropathy of renal failure, were listed where the resulting sensation is not painful [54] (see also [15]). Despite the lack of generality for the painful quality of small fiber inputs, Wall considered the inhibitory effects of large fiber inputs to be well verified by subsequent demonstration of the analgesic effect of TENS and dorsal column stimulation (see above) although the mechanism of that inhibition was still open to question. The iconic diagram published in 1965 indicated a presynaptic inhibitory mechanism, based largely on the then current work in Wall's laboratory, but Melzack and Wall were very careful to point out that postsynaptic inhibition might be responsible [45]. Wall [68] discussed possibilities for postsynaptic inhibition based on literature appearing since publication of the Gate Hypothesis. This change in mechanism gains further currency in a recent account of the Gate Theory by Basbaum and Jessell in the 4th edition of *Medical Neuroscience* textbook [3] where the illustration of the Gate mechanism shows the inhibition as being postsynaptic, not presynaptic.

In their 1965 paper [45] Melzack and Wall provided a diagram (their Figure 1) illustrating the many surgical attempts that had been made to treat chronic pain. The inability to permanently abolish pain by cutting various tracts was a taken as evidence against the labeled line pain pathway and served as a stimulus to develop a pattern theory leading to the Gate Theory. We now know that damage to the nervous system or alterations in the sensory barrage due to inflammation can lead to structural and functional changes within the CNS that enhances the nociceptive input [26, 37]. Wall himself was a pioneer in the study of plasticity in the spinal cord [2, 52] dorsal column nuclei [36], and thalamus [69] and stimulated many others to explore these important issues which are central to our understanding of pain. In addition to structural plasticity there have been many new findings of functional plasticity related particularly to the central projections of C-fibers (reviewed in [73]).

Concluding comment

The Gate Theory of Pain was formulated using available physiological observations to explain certain behavioral and psychophysical observations related to pain. The combination of a remarkably clear and incisive paper and some simple diagrams captured the imagination of a generation of clinicians and neuroscientists [12]. Measures of its success are some of the predictions that have been useful clinically. In addition, its broad frame of reference attributing pain to multiple interacting circuits, formalized later by Melzack in the neuromatrix concept, has had numerous offshoots including pain genetics, affective components of pain and environmental contributions to the pain experience. The simple diagram of the gate circuit in the *Science* paper is what is remembered by most, but this was just a small part of discussions in that paper. It forced a re-evaluation of pain mechanisms and it is the outcome of this re-evaluation rather than the simple mechanistic diagram that represents the major significance of the Gate Control Theory. As Wall [67] himself wrote evaluating the Gate Theory in the light of further experiments: “The least, and perhaps the best, that can be said for the 1965 paper is that it provoked discussion and experiment”.

Acknowledgments

I thank Drs. Pablo Rudomin and Rick Koerber for critically reviewing the manuscript and offering helpful comments. LMM was supported by The Christopher and Dana Reeve Foundation and by NIH 5 R01 NS 16996.

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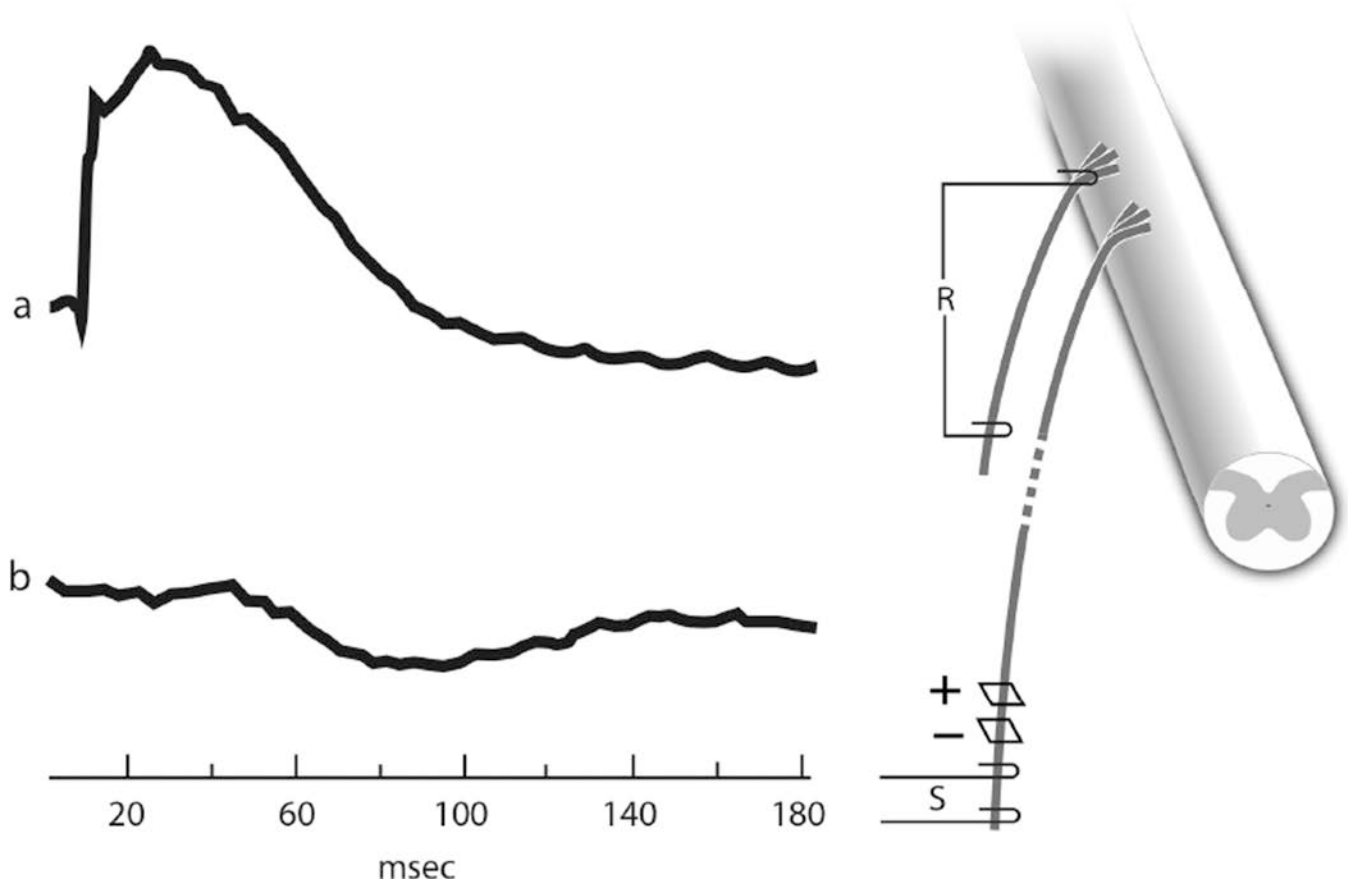

Figure 1.

Negative (upward going) and positive (downward going) dorsal root potentials produced by stimulating large (A-) and small (C-) fibers. The diagram illustrates the dorsal root potential recording (R), and sural nerve stimulation (S). The square electrodes (+ and −) on the peripheral nerve illustrate the arrangement to produce selective anodal block of the large A-fibers that permitted the effects of C-fibers to be observed (from [50] with permission).

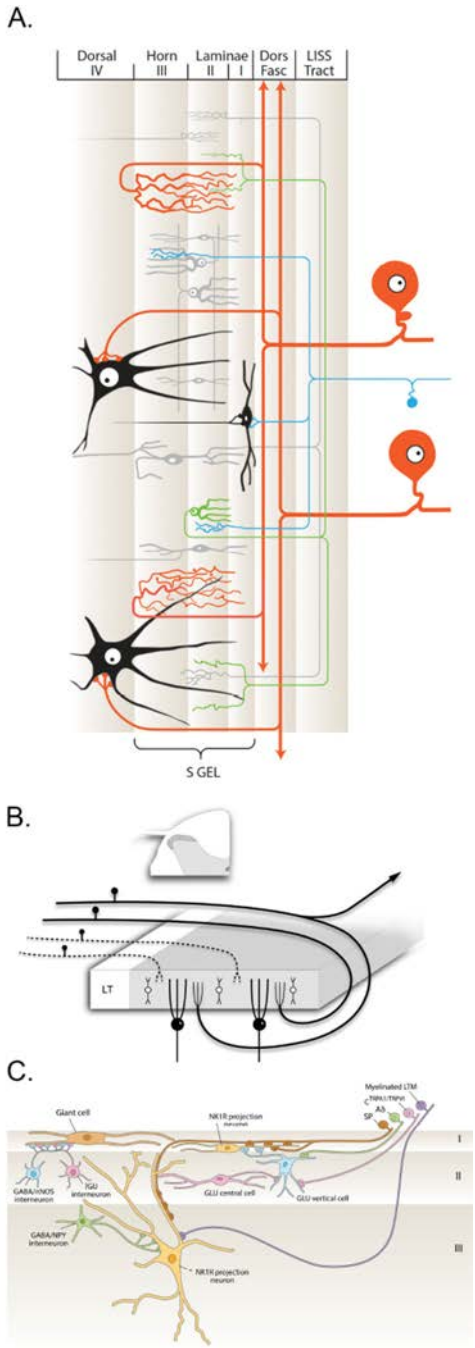

Figure 2.

Arrangement of small and large fiber inputs to the SG in the dorsal horn. A. Sagittal view of the lumbar dorsal horn (laminae I to IV) modified from Figure 3 of [61]- with permission). The original figure was a schematic drawing of the cells observed in the superficial dorsal horn. Here we emphasize certain features of that schematic to illustrate the concepts used by Melzack and Wall in their elaboration of the Gate Theory. Large DRG axons (orange) run rostrocaudally in dorsal columns (Dors Fasc) and drop to below the SG to terminate on large cells in lamina IV (shown most ventrally). They also recurve dorsally and enter SG from the ventral surface. Small DRG axons (blue) run rostrocaudally in Lissauer's tract (LISS Tract) and enter the SG (S GEL) from the dorsal surface. They also terminate on cells of lamina I. A single SG cell (green) is shown to project to other segments

of SG via Lissauer's tract; this cell does not project outside SG in keeping with the idea that SG is a modulatory system rather than a projecting system (but see text). Other SG cells in the original Szentagothai schematic are in background (gray). Note that SG is shown to be in laminae II and III; more recently this structure has been considered to be restricted to lamina II. B. Inputs to SG as illustrated in [45]. Here the SG is shown as a horizontal slab. Four sensory afferents are shown entering from the dorsal roots. Two large fibers (solid) curve around the slab and enter from the ventral surface. Two small fibers (dashed) enter from the dorsal surface. Lissauer's tract (LT) is shown laterally as are 2 cells in deeper lamina of the dorsal horn. The inset illustrates the dorso- ventral location of the slab in cross section (dotted structure). Redrawn from [45], with permission). C. Recent analysis of inputs to and outputs from lamina II. In contrast to the Szentagothai picure, cells in lamina II terminate on projection neurons in laminae I and IV. Redrawn from [63], with permission.

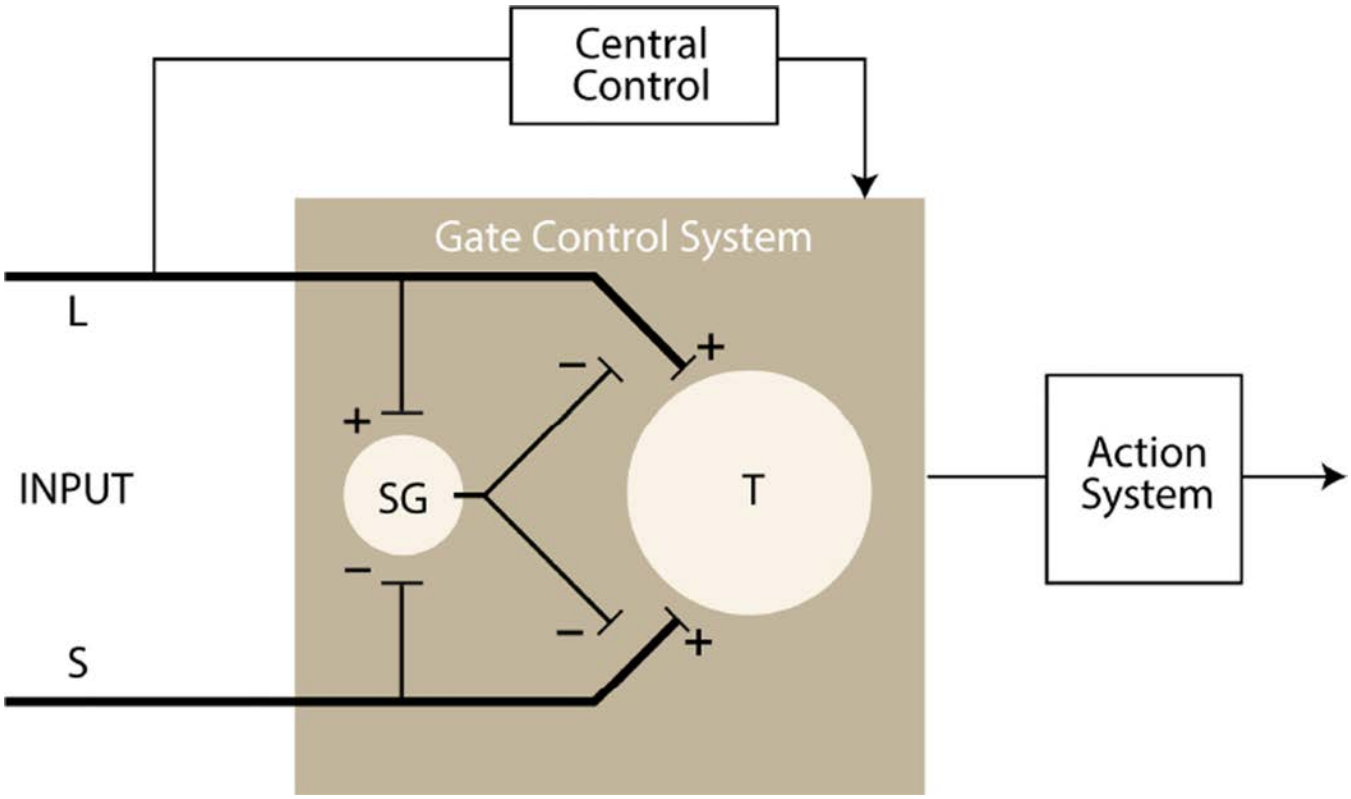

Figure 3.

The Gate Theory of Pain model published by Melzack and Wall [45]. Large (L) and small (S) sensory fibers excite T- (transmission) cells in the dorsal horn where they engage the "Action System". However, they differ in their projections to cells of the SG. Large afferent fibers excite SG cells and elicit presynaptic inhibition of sensory inputs, both from small and large inputs. Small afferent fibers inhibit SG cells and remove presynaptic inhibition, in effect eliciting presynaptic facilitation. Thus the Gate will be open or closed depending on the balance between the large and small fiber input. Central control is envisioned as a descending system activated by rostral projections of large fiber input via the dorsal columns. Further details in the text. From [45], with permission.