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PAIN MECHANISMS: Labeled Lines Versus Convergence in Central Processing

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■ **Abstract** The issue of whether pain is represented by specific neural elements or by patterned activity within a convergent somatosensory subsystem has been debated for over a century. The gate control theory introduced in 1965 denied central specificity, and since then most authors have endorsed convergent wide-dynamic-range neurons. Recent functional and anatomical findings provide compelling support for a new perspective that views pain in humans as a homeostatic emotion that integrates both specific labeled lines and convergent somatic activity.

INTRODUCTION

Pain is an enigma. It differs from the classical senses (vision, hearing, touch, taste, and smell) because it is both a discriminative sensation and a graded motivation (or behavioral drive). It is a leading clinical complaint that can present mystifying symptoms, such as allodynia (sensitization to normally innocuous stimuli), referral from deep tissue to skin, radiation over wide regions, temporal augmentation ("windup"), persistent after-sensations, emotional variability, and hyperpathia (hysterical responses). It can attain intolerable intensity, but it can disappear in the heat of battle. It is a universal human experience that is commonly generalized to psychic suffering of any sort.

Accordingly, the nature of pain has always been controversial. In his book *Pain*, Sir Thomas Lewis (1942), a clinician who differentiated the distinct sensations of first (sharp) and second (burning) pain as well as pain of different tissue origins, pointedly abstained from giving a global definition of pain. The neural basis of pain has been fervently debated from two opposing views—specificity and convergence. The former view posits that pain is a distinct sensation represented by specialized elements both peripherally and centrally, consistent with the idea that the nervous system is evolutionarily and reproducibly well-organized. The latter posits that pain is an integrated, plastic state represented by a pattern of convergent somatosensory activity within a distributed network (a so-called neuromatrix). Historically, these "splitter" and "lumper" views have alternated in dominance.

One should expect that the solution to this puzzle involves both specificity and integration, as found in all other neural systems. A solution has been provided by recent neurobiological findings, which indicate that pain is not part of the exteroceptive somatosensory system that engenders touch, but rather is represented in an unforeseen, novel pathway in humans that is part of a hierarchical system subserving homeostasis, the sense of the physiological condition of the body (interoception), and the subjective awareness of feelings and emotion.

Following a brief historical perspective (based on reviews by Boring 1942; Melzack & Wall 1982; Norrsell et al. 1999; Perl 1984a, 1996; Rey 1995; Sinclair 1967; Willis 1985), the convergent view of central pain processing that has dominated for the past 30 years is summarized and then the new view that incorporates specific labeled lines is elucidated, based on the functional anatomy of the lamina I spino-thalamo-cortical system. Subsequently, the critical arguments between specificity and convergence adherents in the literature are reexamined, and finally a synthesis is presented.

A BRIEF HISTORY OF PAIN

The emotional character of pain, as opposed to pleasure, was emphasized by Aristotle and by Darwin. Early experimental psychologists included pain with other bodily sensations in *Gemeingefühl*, or common sensation. In the late 1800s, Blix in Sweden, von Frey and Goldscheider in Germany, and Donaldson in the United States independently discovered that painful and thermal sensations could be selectively elicited from discrete spots on the skin, and so they considered pain from heat or sharp needles as specific sensations, consistent with Müller's doctrine of specific nerve energies. Subsequently, however, Goldscheider argued for an alternative view that pain is the result of intense stimulation, regardless of modality and tissue origin, with a centrally modifiable threshold; this argument explains the allodynia typically seen in neuropathic pain as a lowering of the central threshold for pain along a mechanical continuum. Soon thereafter the specific view of pain was encouraged by the spinal dissociation of pain and temperature sensations, which ascend with contralateral spinothalamic fibers, from fine touch, which ascends with ipsilateral dorsal column fibers. Thus, Sherrington, in his 1900 review of the German literature on sensation, described pain as part of the sense of "the material me," an extension of common sensation, but later (1948) he codified the view that pain is a special sensation by defining the heuristic category of nociception, that is, sensory activity evoked selectively by noxious stimuli that cause or threaten tissue damage. The pendulum reversed again when Nafe and subsequently Weddell and Sinclair disavowed the functional/structural relationship in primary afferent receptors that von Frey had erroneously asserted, and they professed the view that the various aspects of all bodily sensations, including their quality, intensity, and spatiotemporal characteristics, result from the brain's interpretation of the pattern and intensity of activity across all somatic afferent fibers. The eventual electrophysiological identification of distinct primary afferent nociceptors

and mechanoreceptors by Perl, Iggo, and others in the 1960s negated their arguments and returned the pendulum to specificity. However, the convergent gate control theory, introduced in 1965 by Melzack & Wall, extended pattern/intensity theory into the spinal dorsal horn. They argued particularly against the notion that activity in nociceptors ascending "in a straight-through transmission system to a pain center in the brain" is synonymous with the psychological experience of pain (Wall 1973; Melzack & Wall 1965, 1982). Despite the subsequent discovery of selectively nociceptive neurons in lamina I of the spinal dorsal horn by Christensen & Perl (1970), specialized forebrain substrates were not identified until recently, and the convergent view of pain has dominated the textbooks and research literature.

THE CONVERGENT VIEW OF PAIN

In the gate control theory, small-diameter and large-diameter primary afferents converge on "pain transmission neurons" of the "action system." In particular, the convergent view holds that all somatic afferents, including nociceptors, activate convergent wide-dynamic-range (WDR) cells in the deep dorsal horn (lamina V) that project in the spinothalamic tract (STT) to the main somatosensory thalamus and then to the primary somatosensory cortex (Wall 1973, Price & Dubner 1977, Price 1988, Willis 1985, Willis & Westlund 1997). The activity of the WDR cells is viewed as necessary and sufficient for pain sensation and is characterized as graded throughout the range of tactile sensitivity, so that they respond with progressively greater levels of discharge to brushing hair, light touch, pressure, pinch, and squeeze. The WDR cells also respond to graded noxious heat, noxious cold, and inputs from visceral and deep (muscle, joint) tissues, and these responses are similarly thought to encode pain.

Proponents believe that this view explains the mechanical allodynia and hyperalgesia in neuropathic pain conditions by central sensitization (as in Goldscheider's intensity model). They believe the convergence explains the referral of pain of visceral or deep origin to cutaneous zones, such as in angina. They also believe that plasticity of the forebrain pattern detector can explain the recurrence of pain after a successful block (e.g., after anterolateral cordotomy, a lesion of the STT), that is, in the absence of nociceptor activity.

In addition, gate control theory posits that large-diameter afferents inhibit the small-diameter fiber activation of WDR cells ("close the gate"), which is said to provide the basis for the inhibition of pain by rubbing or vibration. Descending modulation of the "gate" is said to provide the basis for behavioral and stimulation-induced reduction of pain. The phenomenon of counter-irritation (the inhibitory effect of a distant noxious stimulus on local pain sensation) is said to be due to wide-field inhibition of WDR cells. WDR cells have large receptive fields and are not somatotopically organized, so a sombrero-pattern hypothesis based on such inhibition has been proposed in order to explain how the population of lamina V WDR cells encodes stimulus location.

The ascending pathway is thought to match anatomical data showing STT input to human somatosensory thalamus (VP, the ventral posterior nucleus). Projection to primary somatosensory cortex is presumed necessary to provide the substrate for the discriminative aspects (localization, intensity, temporal profile, quality) of pain sensation. Corollary activation of a widespread forebrain network by way of a multisynaptic pathway through the reticular formation and medial thalamus is thought to generate the affective/motivational aspect of pain.

These explanations have satisfied the need of clinicians for a straightforward model of central pain processing (Bonica 1990), despite various discrepancies with neurobiological data and the inherent ambiguity of the convergence/pattern concept (Schmidt 1971, Perl 1984a). Numerous studies in many laboratories have examined WDR lamina V cells (both STT and unidentified) over the past 30 years, as summarized by other investigators (Willis 1985, Willis & Westlund 1997, Price 1988, Foreman 1999, Gebhart & Ness 1991). The critical arguments from that body of work with regard to central pain processing are discussed below.

A MORE SPECIFIC VIEW OF PAIN

Recent findings provide a more complete view of the specialized neural system activated by nociceptors, as detailed in prior articles (for complete references, see Craig 2000, 2002a,b). In this view, pain is represented by the forebrain integration of both specific labeled lines and convergent somatic activity in a well-organized, hierarchical system that subserves homeostasis. In this view, pain is one aspect of the representation of the physiological condition of the body (interoception)—as distinguished from fine touch (exteroception)—and it is a homeostatic emotion, that is, both a feeling and a motivation like temperature, itch, thirst, and hunger. This system includes an interoceptive spino-thalamo-cortical pathway, visible only in primates and well-developed only in humans, which provides a direct cortical image of the state of the body and leads to a subjective meta-representation of the feelings from the body that are associated with emotion.

Peripheral Components

Small-diameter primary afferent Aδ- and C-fibers from all tissues of the body terminate in lamina I of the superficial spinal dorsal horn and monosynaptically activate lamina I neurons (Figure 1). (Lamina II, which is less distinct in rat, appears to receive C-fibers only from skin.) These fibers relate information on the physiological status of the tissues—that is, not only damaging mechanical stress, heat and cold, but also innocuous temperature (warm, cool), local metabolism (acidic pH, hypoxia, hypoglycemia, hypo-osmolarity, lactic acid), cell rupture (potassium, ATP, glutamate), parasite penetration (histamine, proteinases), mast cell activation (serotonin, bradykinin, eicosanoids), and immune and hormonal activity (cytokines, somatostatin). Those categorized as nociceptors are selectively sensitive to noxious mechanical stimuli and/or thermal stimuli, and different subtypes

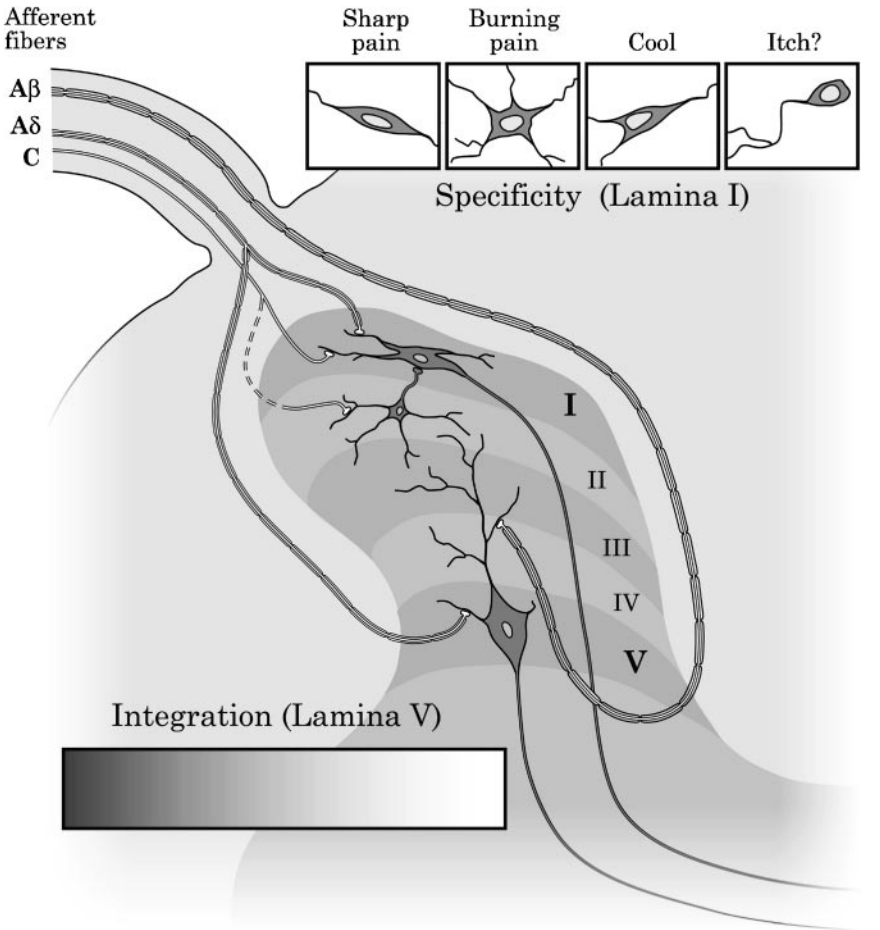

Figure 1 Summary diagram representing the anatomical basis for afferent inputs to specific cells in lamina I and integrative cells in lamina V.

have been identified (Perl 1996, Campbell & Meyer 1996). In particular, cutaneous Aδ mechano-heat-nociceptors that respond to pinch and rapidly to heat >46° (Type II), or pinch and slowly to heat >53°C (Type I), or only to heat have been differentiated in monkey. Similarly, C-nociceptors sensitive to heat, pinch, or both have been identified, although most C-nociceptors respond to several types of noxious stimuli and are termed polymodal nociceptors (in all tissues). Some are insensitive and respond only to subsequent tissue damage or inflammation (Torebjörk 2000).

The cutaneous Aδ- and C-fibers are associated with the distinct sensations of first and second pain, respectively, based on latency, differential stimulation, and nerve blocks. These sensations can be distinguished after a sudden mechanical,

thermal, or electrical stimulus as a rapid sensation of sharp (first) pain followed (1–2 sec later) by a slow, dull, burning (second) pain sensation. Temporally augmenting first pain can be selectively elicited by maintained pressure with a thin (sharp) probe, whereas augmenting second pain can be selectively elicited with brief heat stimuli repeated at intervals of <3 sec (Price 1988, Vierck et al. 1997). The physiological properties of Aδ- and C-nociceptors partially account for these differences (Andrew & Greenspan 1999, Slugg et al. 2000). Thus, the Aδ-fibers show maintained (albeit not augmenting) responses to a maintained mechanical stimulus applied with a thin (sharp) probe, and their responses are graded with the applied force and the size of the probe tip, in parallel with the characteristics of first pain. In contrast, C-nociceptors show an adapting response to sharp probes with little differentiation of force or probe size. Both Aδ- and C-nociceptors show adaptation to repeated brief heat stimuli, so the temporal augmentation of both second pain and first pain must occur centrally.

Particular observations emphasize that the category "nociceptors," while heuristically of enormous value, is actually a theoretical simplification. Microneurographic data (microelectrode recording and stimulation of peripheral nerve fibers in awake humans) indicate that only the summated activation of C-nociceptors causes a conscious perception of pain in humans (Gybels et al. 1979). Consistent with this, C-fibers often have slow (<1 Hz) ongoing discharge without provocation that is apparently not perceived (Campbell & Meyer 1996, Adreani & Kaufman 1998), and that may be related to ongoing tissue metabolic status. It is significant that the empirical mechanical, thermal, and polymodal thresholds of small-diameter afferents extend quite broadly across the pain threshold in all tissues, as expressed clearly by many investigators (Cervero & Jänig 1992, Perl 1996, Mense & Meyer 1985, Torebjörk 2000). These physiological considerations are consistent with the broader concept of viewing small-diameter afferent fibers as homeostatic receptors that relate tissue status, which is also consonant with anatomical and other considerations (see below). In addition, other cutaneous C-fibers are selectively sensitive to weak mechanical stimuli that evoke sensual (limbic) touch, as are particular neurons in lamina I, which is important for reproductive behavior and the emotional status of the body.

The homeostatic role of small-diameter afferent fibers and lamina I neurons is emphasized by their ontogeny, which is temporally coordinated and differentiated from the large-diameter exteroceptive and proprioceptive afferents that project to the deep dorsal horn (Altman & Bayer 1984). The fine afferents originate from small (B) dorsal root ganglion cells and enter the spinal cord in a second wave, through the lateral division of the dorsal root, subsequent to the larger fibers that issue from the A cells and enter in the medial division. Their arrival in the dorsal horn is genetically coordinated to coincide with the arrival of lamina I neurons, and a common transcription factor is activated in the B cells and lamina I neurons at this time. The lamina I cells originate from the progenitors of autonomic interneurons in the lateral horn and migrate to their superficial dorsal position during a ventromedial rotation of the entire dorsal horn that occurs simultaneously

with the arrival of the small-diameter afferents. This rotation enables the entering small-diameter afferent fibers to directly contact lamina I neurons, and it also results in the characteristic recurrent trajectory of the large-diameter fibers, which do not contact lamina I neurons (Woodbury et al. 2001). These observations directly support the view that together the small-diameter afferents and lamina I constitute a cohesive homeostatic afferent system (see Prechtl & Powley 1990).

Spinal Components

LAMINA I Lamina I neurons comprise several distinct, modality-selective classes that receive input from particular subsets of small-diameter fibers and relate the ongoing physiological status of the tissues of the body. These classes of neurons can be termed virtual labeled lines because they differ physiologically, morphologically, and biochemically, and because their activity corresponds with distinct sensations, albeit after integration in the forebrain (Han et al. 1998, Craig et al. 2001). Based on cutaneous stimulation (and the heuristic category of nociception), two classes of nociceptive lamina I STT cells can be distinguished that correlate with sharp (first) pain and burning (second) pain, respectively (Craig & Andrew 2002, Andrew & Craig 2002). There are two types of thermoreceptive lamina I STT cells that respond selectively to cooling or to warming, distinct types of chemoreceptive cells that respond selectively to histamine or to noxious chemicals, and other classes that respond selectively to muscle or joint afferents or to mechanical slow brush (sensual touch). The selectivity inherent in this pathway is convincingly highlighted by the histamine-responsive cells that constitute a labeled line for the sensation of itch (Andrew & Craig 2001): Such cells receive input only from a specific subset of very slowly conducting C-fibers that are selectively responsive to histamine; they are distinct with respect to ongoing activity (none), central conduction velocities, and thalamic projections; their temporal response profile parallels itch sensation in humans; and their axons in the lateral STT seem to be critical for the sensation of itch. The thermoreceptive-specific lamina I STT cells are similarly unique in their functional and anatomical characteristics, and their properties directly correspond with the characteristics of human thermal sensation. An additional type that remains to be clarified is viscероceptive lamina I cells (Cervero & Jänig 1992, Gebhart & Ness 1991, Foreman 1999). Most of those examined to date had convergent cutaneous input, which could certainly provide a substrate for referred sensation. However, sensitization by repeated visceral search stimuli seems likely, and anatomical data suggest that distinct types of viscероceptive lamina I cells probably exist that even distinguish renal artery from renal vein occlusion by responding selectively to renal osmoreceptors or mechanoreceptors (Rosas-Arellano et al. 1999).

The two nociceptive cell types, termed nociceptive-specific (NS) and polymodal nociceptive (HPC, for heat, pinch, and cold), have significantly different ongoing discharge, conduction velocities, membrane properties, somatal shapes, and thresholds to noxious heat and pinch. They receive predominantly Aδ-nociceptor

and polymodal C-nociceptor inputs, respectively, and they have little (HPC) or almost no (NS) ongoing discharge. By using the maintained mechanical stimulus paradigm with a graded series of fine probes that produces a selective sensation of first pain and the repeated brief contact heat stimulus paradigm that produces a selective sensation of augmenting second pain, the NS lamina I STT neurons (which are fusiform cells) have been definitively associated with first pain, and the HPC neurons (which are multipolar cells) with second pain. Thus, only the NS cells show maintained responses to fine probes that differentiate force and probe size, and only the HPC cells show temporal augmentation to repeated brief contact heat stimuli with characteristics corresponding to the temperatures, intervals, and temporal profile of the human psychophysics.

The polymodal nociceptive HPC lamina I STT cells deserve particular attention. They are insensitive to low-threshold mechanical stimulation (with a thermoneutral probe), and they respond to graded noxious mechanical, heat, and cold stimuli (Christensen & Perl 1970, Craig et al. 2001). The correspondence of their responses with the characteristics of the second pain sensation elicited by repeated brief contact heat includes a striking "reset" phenomenon, in which the omission of a single stimulus in a train of brief contacts causes the temporal augmentation to begin again from baseline—in both the human pain reports and the HPC responses (Vierck et al. 1997, Craig & Andrew 2002). The HPC cells can uniquely explain not only burning pain due to noxious heat, but also the burning sensation elicited by noxious cold or by the thermal grill illusion of pain (Craig et al. 2001). For an explanation of the thermal gill illusion of pain, see Craig 2002a,b.

Notably, HPC lamina I STT cells have static thresholds to cold that extend over a broad span in the innocuous range (28.7°C–12.5°C), with a median of ~24°C (~75°F; their dynamic sensitivity begins just below skin temperature). Their maintained response to cold accelerates at noxious temperatures (<15°C). Thus, many HPC cells are sensitive to mechanical contact by probes at room temperature (but not at neutral skin temperature), which suggests that such cells very likely were miscategorized as WDR cells in many prior studies that did not use cold stimuli for unit identification. This confound can explain discrepancies in the earlier literature that are significant for the issue of specificity, as detailed below.

It is important to recognize that the sensitivity of HPC cells to noxious cold is graded below ~24°C, corresponding to our increasing thermoregulatory discomfort below this neutral ambient temperature. This emphasizes that pain is not a binary (yes or no) modality. It compels the conceptual shift of viewing the role of polymodal C-nociceptors and the HPC lamina I neurons that convey their activity as a homeostatic afferent pathway, rather than simply a nociceptive pathway. It is significant that the linear static sensitivity of cooling-sensitive (COOL) thermoreceptive-specific lamina I STT cells begins at approximately normal skin temperature (~34°C) but plateaus at ~15°C, i.e., at the mean temperature reported as painfully cold by humans and at which the polymodal nociceptive HPC cells are increasingly active. This suggests that it is an increase in HPC activity beyond COOL cell activity that signals burning pain. This inference is directly supported by the observation that an artificial reduction in COOL activity (by a peripheral nerve

block of cooling-sensitive Aδ-fibers or by simultaneous warming in the thermal grill illusion of pain) produces cold allodynia or burning pain at normally innocuous cool temperatures. Thus, the perception of thermal distress (unpleasantness) or burning pain depends on the integration of these two sensory channels in the forebrain (Craig et al. 1996), as well as on core temperature (Mower 1976), and this conclusion is consistent with the view that it is a homeostatic motivation. In other words, homeostasis, rather than the heuristic simplification nociception, does indeed appear to be the fundamental role of the small-diameter afferent fiber/lamina I system.

In order to directly address the role of lamina I in homeostasis, we recently examined the responses of lamina I neurons to static muscle contraction. We found one class that responded selectively and another that had cutaneous HPC responses and convergent input from muscle (Wilson et al. 2002). Some cells responded during and some after the contraction, consistent with the properties of the muscle Aδ- and C-fibers that activate these lamina I cells. Some of these receptors are sensitive to contraction, whereas others are sensitive to lactic acid and other metabolites released during muscular exercise; these can be viewed as ergoreceptors and metaboreceptors that relate tissue metabolic needs and continuously drive a variety of regional and whole-body homeostatic adjustments to muscular work, including the so-called exercise pressor reflex (Adreani & Kaufman 1998, LeDoux & Wilson 2001). It is important to recognize that muscles normally produce ongoing homeostatic adjustments without the behaviorally motivating signal of pain, yet large increases in such activity cause muscles to ache or burn, and synchronous activation causes a painful cramping sensation (Simone et al. 1994). These observations clearly confirm the role of lamina I in ongoing homeostasis, and they substantiate the concept that it comprises modality-selective labeled lines that relate the current physiological condition of all tissues of the body.

LAMINA V Lamina V neurons are large cells with dendrites that extend across much of the dorsal horn. They receive large-diameter (myelinated) primary afferent input from cutaneous and deep sources, as well as direct Aδ-nociceptor input and polysynaptic C-fiber input. They provide a representation of all primary afferent input, including mechanoreceptive and proprioceptive as well as nociceptive activity (Milne et al. 1982, Surmeier et al. 1988). They generally have large receptive fields (e.g., most of a limb) and high ongoing discharge [which is related to limb position (Milne et al. 1982; A.D. Craig, unpublished observations)]. Deeper (laminae VI–VII) neurons are even more responsive to limb movement than to cutaneous input and have complex receptive fields.

Almost all lamina V neurons are WDR cells, though some respond better to innocuous stimulation, and others better to noxious stimulation. They show graded responses to pressure (applied with von Frey hairs), noxious heat, noxious cold, and noxious deep and visceral stimulation. Their sensitization by intracutaneous capsaicin or deep stimulation has been compared to the hyperalgesia and allodynia these stimuli produce in humans, and consequently these paradigms have been used to address the pharmacology of dorsal horn sensitization in WDR lamina V cells

(e.g., Simone et al. 1991), which are relatively easy to isolate with microelectrodes (Wall 1973).

However, WDR cells are modality-ambiguous; they do not differentiate any particular modality of innocuous or noxious stimulation or the afferent tissue of origin (e.g., Carstens 1997). As a population, their activity represents the integration of all afferent input to the dorsal horn or an "intensive trajectory" (Wall 1973, Surmeier et al 1988). In contrast to lamina I neurons, they are not somatotopically organized, and their complex excitatory and inhibitory receptive fields can be regarded as musculotopically organized (Schouenborg et al. 1995, Levinsson 2002). These characteristics are consistent with the long-standing proposal that they have a fundamental role in flexor withdrawal mechanisms and sensorimotor integration (Perl 1984b, Lundberg et al. 1987, Levinsson 2000), which is also supported by their anatomical connections. The contention that they have a fundamental role in pain sensation is specifically addressed in the Critical Arguments section below.

Supraspinal Connections

The propriospinal and bulbar projections of lamina I neurons in cat and monkey directly indicate their role in homeostasis (Figure 2) (Craig 2002b). They project strongly to the sympathetic cell columns of the thoracolumbar spinal cord (intermediolateral and intermediomedial regions) and to the major homeostatic integration sites in the brainstem. The latter include regions that also receive parasympathetic afferent activity (by way of the solitary nucleus) and are heavily interconnected with the hypothalamus and amygdala [e.g., caudal and rostral ventrolateral medulla, catecholamine cell groups A1-2 and A5-7, parabrachial nucleus (PB), periaqueductal gray]. These lamina I projections substantialize (provide the anatomic substrate for) the hierarchical somato-autonomic reflexes activated by small-diameter afferents that are critical for homeostatic functions (Sato & Schmidt 1973). In turn, lamina I receives descending modulation directly from brainstem preautonomic sources, and most striking, lamina I and the autonomic motor nuclei are the only spinal regions that receive descending input directly from the hypothalamus.

The deep laminae contain many premotor interneurons (Hoover & Durkovic 1992), and they have extensive propriospinal projections to intermediate zone and ventral horn neurons. They also have strong projections to the cerebellum (in the ventral spinocerebellar tract) and the brainstem reticular formation (Verburgh et al. 1990), where they can affect somatomotor coordination, behavioral state, postural set, and descending modulatory systems. Laminae V–VII receive strong descending inputs from a variety of sources, such as the corticospinal, rubrospinal, bulbospinal, and vestibulospinal fibers.

Lamina I and laminae V–VII each provide about half of the STT. Anatomic data indicate that lamina I STT axons course in the middle of the lateral funiculus, that is, in the classical lateral STT, whereas laminae V–VII STT axons are concentrated in the ventral (anterior) funiculus in the anterior STT. These bundles

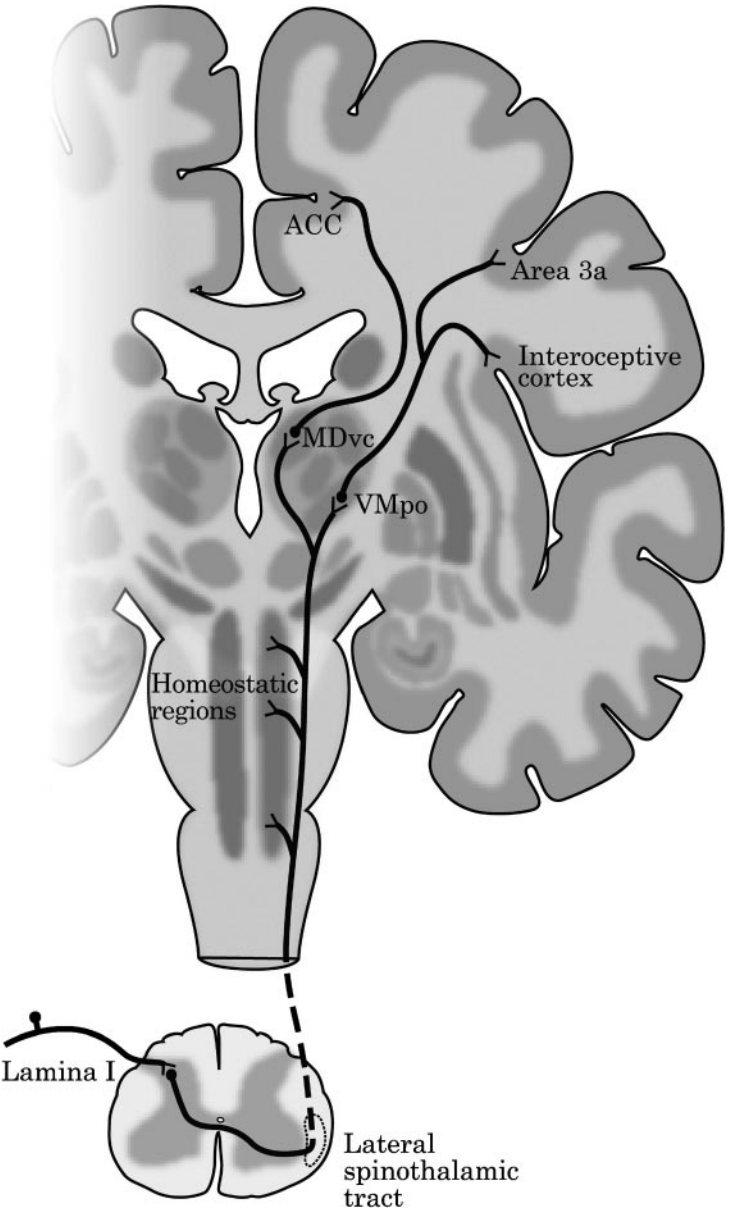

Figure 2 Summary diagram of the ascending projections of the lamina I spino-thalamo-cortical system.

are also distinguished by their immunoreactivity for calbindin and parvalbumin, respectively (Craig et al. 2002). Cordotomy lesions that involve the lateral STT specifically reduce pain, temperature, itch, and sensual touch, whereas lesions of the anterior STT reportedly affect crude touch and movement.

THALAMIC SUBSTRATES In primates, lamina I STT neurons project heavily to a recently distinguished nucleus in the posterolateral thalamus, the posterior part of the ventral medial nucleus (VMpo) (Craig et al. 1994). There is also weak lamina I input to VP (in the form of boutons of passage), some input to the ventral posterior inferior nucleus (VPI), and significant input to the ventral caudal portion of the medial dorsal nucleus (MDvc). The anatomical characteristics of VMpo are those of a specific thalamic relay nucleus; dense clusters of large, glutamatergic lamina I boutons are organized topographically (in the rostrocaudal direction) within cytoarchitectonically distinguishable cell nests and terminate in triadic arrangements with GABAergic presynaptic dendrites and proximal relay cell dendrites. It receives spinal input only from lamina I. Whereas the VMpo is diminutive in the macaque monkey thalamus and only primordially represented in subprimates, it is proportionately very large in the human thalamus (Blomqvist et al. 2000). The cytoarchitectonically and immunohistochemically identified location of VMpo in human thalamus coincides with the region caudal to VP where STT terminal degeneration occurs most densely following cordotomy (Craig & Blomqvist 2002).

Specifically nociceptive and thermoreceptive neurons with properties similar to lamina I neurons have been identified in VMpo in macaque and owl monkeys, and similar neurons have also been recorded in the region of VMpo in awake humans (Lenz & Dougherty 1997, Davis et al. 1999). Significantly, it has repeatedly been shown that microstimulation within this region of the thalamus in awake humans elicits discrete, well-localized pain or cooling or visceral sensations (Hassler & Reichert 1959, Dostrovsky 2000, Lenz & Dougherty 1997, Davis et al. 1999). Thus, the VMpo constitutes a dedicated lamina I spino-thalamo-cortical relay nucleus that specifically represents pain and temperature, fulfilling the conjecture Head & Holmes (1911) made based on analyses of central (thalamic) pain patients and the expectation of the specific view of pain.

Nonetheless, consideration of the evidence indicates a broader view. The VMpo is contiguous with the basal part of the ventral medial nucleus, or VMb (which for historical reasons is denoted by some as the parvicellular part of the ventral posterior medial nucleus, or VPMpc, though it does not project to somatosensory cortex like VPM proper does), which in primates receives direct input from the nucleus of the solitary tract (NTS) that conveys visceral and gustatory afferent activity (Beckstead et al. 1980). Thus, encephalization in primates produced a cohesive substrate (VMpo and VMb together) that represents all homeostatic afferent inflow (i.e., both sympathetic and parasympathetic) and forms a rostrocaudally organized column that is orthogonal to the mediolateral orientation of the exteroceptive and proprioceptive representations in VP, to which they are connected at the representation of the mouth. By contrast, in subprimates, only integrated (rather than direct) homeostatic afferent activity reaches the forebrain by way of input to a

primordial VMb from the brainstem parabrachial nucleus. In other words, VMpo represents lamina I activity as part of a direct homeostatic afferent pathway in primates, consistent with the broader view that pain and temperature are aspects of interoception.

Lamina V STT axons terminate in VP, VPI, and the ventral lateral nucleus (i.e., motor thalamus), as well as in the intralaminar nuclei (which project to the basal ganglia and to motor and parietal cortices). Their terminations in VP occur in separate bursts predominantly along the borders of the lemniscal VP subnuclei, where WDR neurons have been recorded with properties very much like lamina V WDR STT cells (Willis & Westlund 1997, Treede et al. 2000). The available evidence suggests that such neurons are immunohistochemically distinct within VP (Rausell et al. 1992). WDR neurons are also found in VPI, where lamina V and lamina I STT terminations converge.

CORTICAL SUBSTRATES Anterograde tracing data indicate that VMpo and VMb project with a rostrocaudal topography to the middle layers of a cytoarchitectonically distinct field in the fundus of the superior limiting sulcus at the dorsal margin of insular cortex (Craig 2002a). A corollary projection from each terminates in area 3a at the fundus of the central sulcus. The MDvc projects to area 24c in the fundus of the anterior cingulate sulcus (ACC).

Although few recordings from nociceptive units in the dorsal posterior insula have been obtained in anesthetized monkeys, stimulation of dorsal posterior insula in awake humans causes well-localized pain (Ostrowsky et al. 2002). Lesions of the parieto-insular region centered on the dorsal posterior insula critically reduce pain and temperature sensation (Schmahmann & Leifer 1992, Greenspan et al. 1999). In area 3a, clusters of nociceptive neurons have been recorded that show augmenting responses to repeated brief contact heat stimuli (Tommerdahl et al. 1996; A.D. Craig, unpublished observations).

Functional imaging results in awake humans verify that dorsal insular cortex is activated by pain and also by temperature and other interoceptive modalities that cause distinct feelings from the body (Craig 2002b). It is the only site that is linearly activated by graded innocuous cooling stimuli; with this modality, there is no activation in somatosensory cortices. This substantiates the concept that temperature and other bodily feelings (including pain) are interoceptive sensations, rather than exteroceptive sensations associated with touch. The interoceptive cortex in the dorsal posterior margin of insular cortex is activated in every study using (graded) noxious heat or cold (e.g., Derbyshire & Jones 1998, Hofbauer et al. 2001, Brooks et al. 2002). It is active in chronic pain patients (Kupers et al. 2000) and in neuropathic pain patients during allodynic pain (Petrovic et al. 1999, Peyron et al. 2000). It is also activated during itch, isometric and dynamic exercise, blood pressure manipulations, air hunger, hypoglycemia (hunger), and hyperosmolarity (thirst) (for more references see Craig 2002b). The delimitation of this cortical field by labeling for receptors for corticotropin releasing factor confirms its homeostatic nature (Sanchez et al. 1999). The dorsal insular cortex more rostrally is activated by gustatory stimuli. In addition, C-fiber-induced tactile

stimulation associated with an indistinct pleasant sensation activates interoceptive cortex, consistent with an essential role for lamina I and the lateral STT in sensual (limbic) touch (Olausson et al. 2002). Finally, preliminary fMRI activation by noxious cold in the anesthetized monkey is located precisely in the anatomically identified lamina I spino-thalamo-cortical projection targets in dorsal posterior insula, area 3a, and area 24c (see Figure 10 in Craig 2002a).

Virtually all functional imaging studies of pain show ACC activation (Derbyshire & Jones 1998). Lesions of the ACC can reduce the affect of pain clinically. Nociceptive units in the ACC in awake humans (Hutchison et al. 1999) and in anesthetized rabbits have been recorded. PET (positron emission tomography) activation in humans by the thermal grill illusion indicates a selective association with thermal distress, integrated with thermal afferent activity (Craig et al. 1996), and a relationship of PET activation with unpleasantness has been shown using hypnotic modulation (Rainville et al. 1997), consistent with ACC involvement in homeostatic behavioral motivation. Many imaging studies have documented the role of the ACC in behavioral drive and volition (for references see Craig 2002b). Despite the absence of direct lamina I input in rats, behavioral data substantiate a primordial role of the ACC in homeostatic motivation, probably owing to brainstem (parabrachial) input to medial thalamus (Johansen et al. 2001; A.D. Craig, unpublished observations). In short, the sensory aspect of pain is represented in interoceptive cortex, and the motivational aspect is represented in the ACC.

The VP neurons that receive lamina V STT input apparently project to area 3b—the S1 cortical region proper (Kaas 1993)—and area 1, though apparently to the superficial layers rather than to the middle layers, which suggests a modulatory role (Rausell et al. 1992). Neurons in VPI project to the parietal opercular (S2/PV) region, but VPI also appears to be a source of input to the parieto-insular vestibular cortex (retroinsular). Nociceptive units in areas 3b and 1 in monkeys (see Treede et al. 2000) have been reported—in one study as many as one third of the recorded units—but this contrasts starkly with considerable microelectrode and imaging data documenting the role of these areas in fine touch (Mountcastle 1984, Bodegard et al. 2001). Nociceptive units in the S2/PV region in monkeys (Robinson & Burton 1980) were rarely recorded. Nearly all functional imaging studies of pain report activation of an area labeled "S2," but the activation site is probably interoceptive cortex (see below). About half of these studies report activation of an area labeled "S1," but it seems likely that this activation is in area 3a (see below).

THE CRITICAL ARGUMENTS

This section compares the details of the convergent view and the more specific view with regard to the experimental and clinical characteristics of pain sensation.

Psychophysical Correlations with STT neurons

LOCALIZATION Sharp pain and burning pain as well as fine touch can be localized (Schlereth et al. 2001). Lamina V neurons have large receptive fields, and they

are musculotopically organized; accordingly, a population pattern hypothesis was conjectured to explain how lamina V WDR cells could encode stimulus location (Price 1988). In contrast, lamina I neurons have small receptive fields, and the entire lamina I spino-thalamo-cortical projection pathway is somatotopically organized. Therefore, it can readily provide the basis for accurately localized sensations of pain, temperature, and itch, obviating the presumption that the lemniscal somatosensory system is required for the localization of pain.

DISTINCT SENSATIONS Pain arising from different tissues and different modes of stimulation certainly involves different sensations. Lamina I STT cells differentiate these modalities, but WDR lamina V STT cells do not. In particular, first and second pain sensations are readily distinguishable (Campbell & Mayer 1996, Price 1988). The lamina I STT projection comprises virtual labeled lines (the NS and HPC subpopulations) that correspond directly with these sensations. The correspondence of HPC cells with second pain includes a particularly striking reset phenomenon that clearly differs from the characteristics of WDR lamina V cells. In contrast, WDR cells show maintained windup to repetitive C-fiber stimulation, which has been claimed to be related to central sensitization, secondary hyperalgesia, and neuropathic pain (e.g., see Lin et al. 1999). One study concluded that WDR cells differentiate first and second pain with early and late responses (Price 1988), but they produce a plateau response to repeated heat stimuli, without augmentation, and they do not display the reset phenomenon (Craig & Andrew 2002; A.D. Craig, unpublished observations); thus, they cannot underlie second pain. Similarly, modality-selective lamina I STT cells, but not WDR lamina V STT cells, can distinguish pain of different tissue origins, and HPC lamina I cells, but not WDR lamina V cells, can explain the illusory burning sensation elicited by the thermal grill (Craig et al. 2001; A.D. Craig, unpublished observations).

GRADED MECHANICAL RESPONSES One study compared superficial NS and deep WDR cells using maintained, graded mechanical stimuli with large probes on the rat's tail and concluded, using a ratiometric analysis, that NS responses correspond better with psychophysical reports (Cervero et al. 1988). Recent data obtained with fine probes clearly confirm a role of NS lamina I STT cells in mechanical (first) pain (Andrew & Craig 2002). Comparable data for WDR lamina V STT neurons are needed to complete this comparison, although their responses to low-threshold stimuli and their ongoing sensitivity to limb position preclude a direct role in graded first pain sensation. Nonetheless, NS lamina I STT responses alone do not explain the temporal augmentation of maintained mechanical pain (Andrew & Craig 2002), and WDR cell activity could conceivably contribute to this intensity-related temporal phenomenon by integration at the level of the forebrain.

PROLONGED HEAT RESPONSES One study challenged the role of superficial NS neurons in pain using prolonged (45 min) repetitive (5 s on/off) heat stimulation (Coghill et al. 1993a). They reported that NS responses habituated over time, but

WDR and psychophysical responses did not. Coghill et al. provocatively concluded: "WDR neurons alone are sufficient to evoke both sensory intensity and affective responses to prolonged pain. Furthermore, because subjects could localize and qualitatively describe pain at times when responses of NS neurons were minimal, WDR neurons alone can encode some spatial and qualitative aspects of pain." Their results are compatible with the dissociation of NS lamina I STT cells from second pain; however, the inability of WDR neurons to encode or to localize second pain, as described above, invalidates their conclusion. The correspondence of HPC lamina I STT cells, but not WDR lamina V STT cells, with the human sensation of burning pain predicts that HPC responses to the prolonged heat stimuli used by Coghill et al. (1993a) underlie the psychophysical reports.

BEHAVIORAL RESPONSES IN TRAINED MONKEYS An essential role in pain sensation was claimed for a highly responsive subset of WDR trigeminothalamic cells, based on correlations between their discharge activity and the operant response speeds of well-trained monkeys to incremental changes in noxious heat stimuli (Bushnell et al. 1984, Maixner et al. 1989). In those studies, less responsive WDR cells and NS cells were not correlated as well with motor performance. As in most quantitative studies of WDR cells, the correlations were enhanced by subtracting background activity levels, "to exclude the contributions of spontaneous activity and mechanical responsiveness." The background activity of WDR lamina V STT cells is related to limb position (Milne et al. 1982; A.D. Craig, unpublished observations), so this analytical step posits an implausibly complicated pattern detector at thalamocortical levels.

However, the "WDR" cells could well have been miscategorized HPC cells. Most of the WDR trigeminothalamic cells in those studies were apparently located in lamina I, rather than lamina V, and the illustrated antidromic electrode placement probably included VMpo [see Figures 2 and 3 in Bushnell et al. (1984) and Figure 2 in Maixner et al. (1989)]. HPC cells can indeed have very steep stimulus-response functions to heat (without subtracting ongoing activity) (Craig et al. 2001), and in one study that did use cold stimulation for unit characterization, the lamina I "WDR" characteristics were very HPC-like (Ferrington et al. 1987). Sensitization due to the repetitious noxious heat stimuli was certainly a distinct confound and a cause of increased ongoing discharge. A role in sensorimotor integration could explain the activity of the few lamina V cells reported.

Ascending Pathway

THE LATERAL STT Several studies claimed that lamina I STT axons ascend in the dorsolateral funiculus (DLF) and thereby could not play a significant role in pain sensation because they would not be involved in cordotomy lesions that critically reduce pain and temperature sensation (see references in Craig et al. 2002). The idea originated from work in rats, where the corticospinal tract is shifted from the DLF to the dorsal columns, so that lamina I axons do ascend in the DLF, in

stark contrast to cats, monkeys, and humans. Similar claims were made in cat and monkey, based on retrograde labeling following white matter lesions that split the lateral STT in the middle of the lateral funiculus. However, recent evidence from anterograde labeling, antidromic mapping, and immunohistochemical staining studies convincingly demonstrate that lamina I STT axons form the classical lateral STT in cats, monkeys, and humans, coinciding precisely with the location of cordotomy lesions that critically reduce pain, temperature, itch, and sensual touch sensations.

ELECTRICAL STT STIMULATION A unique study used electrical stimulation of STT axons to directly compare the roles of NS lamina I and WDR lamina V STT neurons in human pain (Mayer et al. 1975). Single- and double-pulse stimuli were delivered through a macroelectrode used surgically to perform C1-2 percutaneous cordotomy in chronic pain patients, and the evoked pain reports were compared with the electrophysiological properties of single STT units characterized in monkeys using similar stimuli. Greater pain was elicited with pulse pairs that just exceeded the axonal refractory period of lamina V cells (but not that of the more slowly conducting NS lamina I cells), and so the authors concluded that activation of WDR lamina V STT cells was sufficient to produce pain.

The authors later revealed that at subthreshold intensities, the patients reported localized sensations of cool or warm (Coghill et al. 1993b), which indicates that the electrode must have been properly positioned to excite thermoreceptive-specific lamina I axons in the lateral STT. The later report also clarified that the stimulation-induced pain was generally a well-localized burning sensation. These observations strongly suggest that the electrical stimuli excited HPC lamina I axons in the lateral STT, which were not recognized at the time of the study. The myelinated axons of HPC lamina I STT cells conduct just slower than those of COOL cells, but much faster than unmyelinated NS axons, so they would be excited at slightly greater stimulus intensities than COOL cells and show refractory periods similar to those of lamina V axons. Only the activity of HPC cells corresponds with a well-localized, burning pain sensation. In contrast, the spatio-temporal population pattern across WDR lamina V STT cells that would be required for topographic localization (Price 1988) could not have been produced by the synchronous electrical activation.

Role of VP

Convergence proponents believe that the lemniscal VP nucleus is necessarily involved in discriminative pain sensation. Several studies reported WDR and a few NS neurons in VP (for references see Willis & Westlund 1997). The neurons were roughly somatotopically organized, though presumed to receive input from musculotopic WDR lamina V STT cells. Units in VP that were correlated with the motor performance of trained monkeys were found.

However, electrical stimulation in VP of awake humans elicits reports of topographically localized paraesthetic sensations (buzzing, tingling), not pain. In fact,

stimulation of VP is often used to alleviate chronic pain, similar to rubbing a bruised area (cf. Tommerdahl et al. 1996). In stark contrast, microstimulation in the region immediately posterior and inferior to VP, i.e., VMpo, can elicit discrete, localized sensations of sharp pain, burning pain, cooling, or visceral sensations (see above), and nociceptive- and thermoreceptive-specific units in this region in humans, and not in VP, have been recorded (Lenz & Dougherty 1997, Davis et al. 1999).

In neuropathic and central pain patients, electrical stimulation in VP can elicit reports of pain, which could indicate important functional changes (Dostrovsky 2000). However, such pain reports are topographically out of register with the somatic representation in VP and therefore could represent enhanced excitability of passing thalamo-cortical axons from VMpo—which is itself significantly more sensitive to stimulation in such patients (Lenz & Dougherty 1997)—because those fibers ascend in a dispersed fashion directly through VP (A.D. Craig, unpublished observations).

Ironically, it has recently been claimed that VP must be important for pain because it receives strong lamina I STT input (Willis et al. 2001). Many lamina V and few lamina I cells from lateral, hindlimb VP in one monkey were retrogradely labeled, but a larger injection that spread medially to "VPM" labeled many lumbar lamina I cells, which the authors claimed must project to hindlimb VP. The first case is consistent with anterograde tracing evidence (Craig et al. 1994), and the second case can be explained by spread to VMpo, which is easily misidentified as VPM (see below).

Role of the Somatosensory Cortices

In the convergent view, activation of somatosensory cortices is required for the discriminative aspects of pain. The S1 and S2/PV cortical areas receive lemniscal input from VP and provide a precise mechanoreceptive representation that is important for active touch and movement. Electrical stimulation of postcentral somatosensory cortex (S1) or the lateral operculum (S2/PV) in awake humans elicits reports of tactile paraesthesia and almost never pain. In contrast, electrical stimulation of the dorsal posterior insular cortex can elicit localized pain sensations in patients (Ostrowsky et al. 2002).

Large lesions of the postcentral gyrus do not affect pain sensation in humans (Head & Holmes 1911), which once led to the mistaken suggestion that pain sensation occurs in the thalamus. Small lesions that reportedly involved area 3a at the fundus of the central sulcus have caused permanent, topographic reductions in pain sensibility (see Perl 1984a). One recent report attributed the loss of discriminative pain sensation (without loss of pain affect) to a large lesion involving both S1 and S2 (Ploner et al. 1999), but the documentation clearly showed involvement of the dorsal posterior insular cortex (consistent with the patient's contralateral thermanesthesia). Perhaps the loss of both interoceptive cortex and area 3a in that case was particularly significant. The residual pain affect described in that patient is consistent with the role of the ACC.

The strongest evidence for a role of somatosensory (or perhaps better, sensorimotor) cortices in pain comes from functional imaging work. About half of all imaging studies of cutaneous pain show no activation in S1 cortex, like studies of visceral and deep pain, but the other half do (Derbyshire & Jones 1998, Bushnell et al. 1999). Attempts have been made to reconcile these different findings by comparing methodological details, by direct comparisons with low-threshold activation or by modulation of attention to discriminative features (e.g., Ploner et al. 2000, Hofbauer et al. 2001, Chen et al. 2002). The activation is ascribed to WDR lamina V STT input by way of VP, which is certainly a possibility. However, a more likely possibility is that the activation near the central sulcus actually occurs in area 3a, where VMpo projects, rather than in areas 3b and 1, where VP projects. Optical imaging data in the monkey directly support this view; repeated noxious heat stimuli (which activate HPC lamina I neurons) produce infrared activation in area 3a and suppress mechanically induced emission in area 3b (Tommerdahl et al. 1996). Temporally augmenting multiunit responses in area 3a were also recorded in that study [and confirmed in this laboratory (A.D. Craig, unpublished observations)]. The imaging findings in monkey also indicate that the supragranular WDR lamina V input to areas 3b and 1 does not cause macroscopic infrared activation. Consistent with these findings, fMRI activation by noxious cold in the anesthetized monkey has been observed only in the dorsal insula, ACC, and area 3a, as noted above. Thus, nociceptive activation near the central sulcus in humans probably occurs in area 3a, but its localization is below the level of PET resolution. Although not noted by the authors, data illustrated in a recent fMRI study using noxious heat show the focus at the fundus of the central sulcus in 3 of 4 subjects (see Figure 3 in Chen et al. 2002). Similarly, the medial shift of pain-related activity from the low-threshold S1 activation site recorded magnetoencephalographically in humans (Ploner et al. 2000) mirrors that reported by Tommerdahl et al. (1996) in the monkey.

A few reports have suggested that S1 cortex is involved in phantom limb pain. A medial shift of the evoked potential from electrical stimulation of the lip into the hand area was found in upper limb amputees, which correlated with pain magnitude and which reversed with reduction of pain during local anesthesia (see Karl et al. 2001). The medial shift in evoked potential could well be related to the medial topographic shift of pain-related activation in area 3a (Tommerdahl et al. 1996), similar to the changes in the motor cortical map (cf. Karl et al. 2001) produced by altered afferent input, such as rhizotomy or even changes in limb position (Sanes & Donoghue 2000, Juottonen et al. 2002).

Most imaging studies report activation in S2, and laser-evoked potential studies indicate this is the first pain-related site activated in cortex (Treede et al. 2000). Unfortunately, in human atlases, the VMpo projection target in the dorsal margin of insular cortex is included with the parietal operculum as part of S2. This misinterpretation originates from the anatomic literature prior to the recognition of VMpo; an injection placed in "VPM" that produced terminal labeling in the dorsal margin of the insula was actually located in VMpo (Burton & Jones 1976; see

Figure 2.4 in Jones 1985, p. 72, in which VMpo is labeled "VPM"). That mistake is revealed by the topography of S2/PV, which is mediolaterally aligned (Disbrow et al. 2000), orthogonal to the rostrocaudal topography in the interoceptive cortical field, with the face represented most laterally, adjacent to S1, and not medially in the dorsal insula. The pain-related activation site labeled "S2" in imaging reports is actually interoceptive cortex. For example, the S2 site in a recent PET study (Hofbauer et al. 2001) occurred at the coordinates [36, −12, 19], which is nearly identical (slightly anterior) to the coordinates of interoceptive cortex identified in our thermosensory PET regression analysis [36, −22, 24] (Craig et al. 2000). Similarly, the ultralate (C-fiber) laser-evoked potential was centered near the same site (Opsommer et al. 2001). Although a role in pain for the VPI projection to S2 or retroinsular cortex is still possible, recent fMRI data clearly confirm that heat pain-related activation from the hand is focused in the dorsal margin of the insula, that is, in interoceptive cortex (Brooks et al. 2002), and pain-related activation from the head appears to be more rostrally located in the dorsal insula (Bucher et al. 1998), consistent with the topography of interoceptive cortex.

Clinical Characteristics

REFERRED PAIN In the convergent view, the convergence of inputs from deep (muscle, joint), visceral and cutaneous inputs on WDR lamina V cells is said to provide a basis for referred pain that NS neurons cannot provide. For example, convergence proponents reported that lamina I cells did not respond to muscle input (Foreman et al. 1977). Yet, lamina I is the main target of deep small-diameter afferent input, and lamina I cells responsive to deep small-diameter afferent input have been identified, some with selective input and some with convergent cutaneous input (Wilson et al. 2002). Similarly selective and convergent visceroceptive lamina I subpopulations seem likely. Such cells can explain both the subjective identification of specific tissue origin as well as referred sensation.

SENSITIZATION, ALLODYNIA, AND HYPERALGESIA In the convergent view, the sensitized responses of WDR cells to innocuous stimuli subsequent to strong noxious stimuli provides a basis for the allodynia and hyperalgesia that occurs in humans. (This view presumes a well-informed pattern detector, i.e., a central observer, that differentiates such activity from the normal WDR responses to low-threshold stimulation and from ongoing discharge). Allodynia and hyperalgesia are clinically perplexing characteristics of neuropathic pain, and there has been enormous interest in comparing similarities in the pharmacology of WDR sensitization with the pharmacology of behavioral models of pain (Willis &Westlund 1997). These similarities include an essential dependence on NK-1 (substance P) receptors, which ironically are present virtually only on lamina I neurons in the monkey (Yu et al. 1999, Khasabov et al. 2002). Some reports even claim that "superficial STT neurons" do not show such sensitization (referring in a misleading fashion to cells recorded superficially in the deep dorsal horn; see Lin et al. 1999), despite clear

descriptions of sensitization in NS lamina I STT neurons by prior studies (see Craig 2000).

The sensitization paradigm that has mainly been used is based on intracutaneous injection of capsaicin, which causes intense burning pain in humans for 3–5 min and distinct mechanical allodynia, hyperalgesia, and lingering pain for at least 30 min. Simone et al. (1991) reported that WDR lamina V STT cells in monkey show comparable responses but that NS lamina I STT cells do not. Capsaicin drives primarily C-nociceptors, and accordingly, recent data in this laboratory confirm that HPC cells show robust activation and sensitization in response to capsaicin (A.D. Craig, unpublished observations). Secondary hyperalgesia to pinprick, however, is mediated by Aδ-fibers following capsaicin (Ziegler et al. 1999), for which the contributions of NS and WDR neurons have yet to be compared.

A second sensitization paradigm is based on recordings of ventral root or flexor reflex activity, which show windup with stimuli that cause strong C-fiber activity (e.g., Wall et al. 1988). Of course, this does not measure sensation (cf. Garcia-Larrea et al. 1993), though it is likely relevant to the role of lamina V cells in the flexor reflex and sensorimotor integration. Notably, dysfunction of the reset phenomenon demonstrated in HPC activity with the repeated brief contact heat paradigm could explain the important windup pain often described in neuropathic and central pain patients (Staud et al. 2001, Craig and Andrew 2002).

Indeed, recent data from behavioral models in rat strongly support the role of lamina I neurons in allodynia and hyperalgesia (for references see Blomqvist & Craig 2000, Craig 2002a). Abolition of lamina I cells bearing NK-1 (substance P) receptors or knockout of NK-1 receptors caused behavioral hypoalgesia. Knockout mice lacking dynorphin in the superficial dorsal horn showed reduced allodynia in the formalin test. Mechanical allodynia (pain behavior in response to brushing) after nerve injury was correlated with c-fos activation of lamina I and parabrachial neurons. Chemical lesions of the deep dorsal horn that spared lamina I produced allodynic behavior indicative of spinal cord injury pain but not the converse.

POST-CORDOTOMY PAIN The occurrence of ongoing pain after lesions that disrupt evoked pain and temperature sensibility, such as an anterolateral cordotomy, was a core argument made against the existence of a specific neural representation of pain (Melzack & Wall 1965, 1982). After cordotomy, the original pain can remain if the lesion does not include the lateral STT, or in the case of visceral pain, unless a bilateral lesion is made (Villanueva & Nathan 2000); however, if the lesion is successful, a central pain condition can arise, which is a distinct phenomenon (Pagni 1998).

Central pain is a paradoxical syndrome, in which ongoing burning, ice-like pain occurs in the area that has been rendered hypoalgesic and thermanesthetic (by cordotomy, tractotomy, infarct, or sclerosis). Lesions that cause this syndrome interrupt the ascending lamina I spino-thalamo-cortical pathway, including interoceptive cortex itself (Boivie 1994, Schmahmann & Leifer 1992). As recognized by Head & Holmes (1911), the phenomenon of central (or thalamic) pain

demonstrates, first, that a specific substrate representing pain and temperature as discriminative sensations can indeed be lost, and, second, that this loss can unmask the existence of a distinct neural substrate representing pain as a motivation.

The two aspects, sensation and motivation, exist in humans for all interoceptive modalities, or "feelings" from the body, because they are emotions related to the physiological condition of the body that inherently cause homeostatic adjustments. The affective/motivational aspect of such feelings is the perceptual correlate of the essential behavioral drive required for homeostasis. For example, consider the pleasantness/unpleasantness of a thermal stimulus, which is the affect corresponding to the motivation for behavioral thermoregulation (a primal vertebrate homeostatic drive). This can be readily distinguished psychophysically from the discriminative thermal sensation (Mower 1976); imagine touching a cool object when your body is overheated versus when your body is deeply chilled—in each case the temperature can be accurately described, but the affective responses are opposite (pleasant in the first instance, unpleasant in the second) because your body's needs are opposite. This motivational drive is also exactly what the thermal grill unmasks or what one feels by pouring warm water on a foot that is numb with cold. This motivation involves the medial lamina I spino-thalamo-cortical pathway through MDvc and the ACC (Craig et al. 1996, Craig 2002a, b), and this is what remains in the central pain syndrome.

Such considerations have led to the thermosensory disinhibition hypothesis, which proposes that central pain is dysfunctional thermoregulatory motivation: Loss of discriminative cooling sensibility results in imbalanced cortical control of brainstem (parabrachial) integration, leading to homeostatic drive engendered in the ACC (Craig 2000, 2002a,b). In other words, cold inhibits pain (as used daily therapeutically and as demonstrated by the thermal grill), and if the pathway for cooling (and with it usually pain) sensation is lost, then pain as a behavioral drive is disinhibited. This concept is supported by considerable data [for example, imaging evidence that ongoing and central pain are correlated with activation of the ACC and interoceptive cortex (Petrovic et al. 1999, Olausson et al. 2001)], and it provides a concrete explanation for central pain, in contrast to the convergent view that specific neural pathways for pain do not exist.

A MORE INTEGRATIVE VIEW OF PAIN

The lamina I spino-thalamo-cortical pathway provides a specialized neural system that can explain almost all of the characteristics of pain. The recognition of the polymodal nociceptive (HPC) class of neurons, in particular, resolves several discrepancies in the earlier literature, and it adds physiological significance to the anatomical evidence that this pathway is first of all a homeostatic afferent pathway. These data indicate that pain is one aspect of the physiological condition of the body, which homeostatic (autonomic, neuroendocrine, and behavioral) mechanisms serve to maintain in an optimally balanced state (for survival). Viewing

pain as a homeostatic emotion with both a sensory and a motivational aspect obviates several concerns of the convergence proponents. Most important, this concept can explain the variability of clinical pain because homeostasis is a dynamic, hierarchic process that continuously integrates all aspects of the body's condition in a time-varying manner (Cannon 1939). This perspective offers new prospects for understanding mysterious pain conditions, such as fibromyalgia (deep aches and pain), that may depend on homeostatic dysfunction instead of outright tissue damage (e.g., see Staud et al. 2001).

The neural substrates underlying pain sensation in this model include both specific sensory channels (virtual "labeled lines") from lamina I and the convergent intensity-related pathway from lamina V. Integration of these multiple ascending pathways in the brainstem and the forebrain is necessary for homeostatic control, for integrated perception, and for behavioral arousal. The essential conceptual difference between the prior convergent model and the more specific view described in this review stems from the fundamental recognition that the various feelings from the body represented in the STT are all aspects of the sense of the body's physiological condition, referred to as interoception, whereas the lemniscal fine touch and positional senses provide information about the relationship between the body and the external environment, that is, exteroception and proprioception. The distinction begins in the dorsal roots and the dorsal horn, where specific interoceptive information is represented in lamina I and integrative, intensity-related sensorimotor activity is represented in lamina V.

The evidence indicates that in primates the dorsal margin of insular cortex contains a primary sensory representation of the small-diameter afferent activity carried in the lamina I spino-thalamo-cortical pathway that relates the physiological condition of the entire body (Craig 2002b). This area constitutes an interoceptive image of homeostatic afferents. It provides the cortical representations of several highly resolved, distinct, specific sensations, including temperature (cool, warm), first and second pain, itch, muscular and visceral sensations, and sensual touch, along with hunger, thirst, air hunger, and other feelings from the body. The ancillary projection to area 3a may provide an important adjunctive representation for pain, which could potentially be integrated across sensorimotorcortex with lamina V WDR input to areas 3b and 1. Enhanced convergent activity in lamina V cells could have particularly important effects on forebrain integration in neuropathic pain conditions, but this idea needs closer study. In addition, there is in primates a direct, medial lamina I spino-thalamo-cortical pathway that is integrated with brainstem inputs that generate homeostatic behavioral drive (motivation) in the ACC. Together these engender the specific sensory and the integrated affective aspects of the emotion of pain.

Notably, the absence of the direct cortical interoceptive representation and the direct medial motivational pathway in subprimates implies that they cannot experience feelings from the body in the same way that humans do, particularly pain. The available data indicate that emotional behavior in subprimates reflects behavioral drive generated by homeostatic integration and arousal mechanisms in the

brainstem and hypothalamus (for references, see Norrsell & Craig 1999, Swanson 2000, Johansen et al. 2001, and Craig 2002b).

Finally, in humans, successive re-representations of interoceptive cortex lead to a meta-representation in the right (nondominant) anterior insula that seems to provide the basis for subjective awareness of the material self as a feeling (sentient) entity (Craig 2002b). Activation in this area is correlated with subjective thermal sensation, with attention to pain, with subjective judgments of trust, disgust, anger, and happiness, and with sexual arousal, romantic love, and musical enjoyment. This is consistent with the idea that the feelings from the body provide the basis for emotions and self-awareness (James 1890), which is the essence of the somatic marker hypothesis of consciousness (Damasio 1993). This also provides a ready neuroanatomical explanation for the interactions of pain with emotional state—a primary concern of convergence proponents—and for psychosomatic disorders. For example, recent imaging data indicate that placebo analgesia is associated with conjoined activation of the right anterior insula and the ACC (Petrovic et al. 2002), which from this perspective reflects limbic motor modulation (by the behavioral agent, the ACC) of the cortical image of subjective pain (in the representation of the feeling self, the right anterior insula).

Thus, the neural representation of pain involves both specificity and integration. Pain as a homeostatic emotion is, in humans, both a specific interoceptive sensation and an integrated affective behavioral drive caused by a physiological imbalance that automatic (subconscious) homeostatic systems alone cannot rectify. This recognition solves the inconsistencies between the polarized views of the past, it makes explicit predictions that can be tested, and it suggests new directions to examine that could have strong impact on the treatment of clinical pain.

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