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Pain processing by spinal microcircuits: afferent combinatorics

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Abstract

Pain, itch, heat, cold, and touch represent different percepts arising from somatosensory input. How stimuli give rise to these percepts has been debated for over a century. Recent work supports the view that primary afferents are highly specialized to transduce and encode specific stimulus modalities. However, cross-modal interactions (e.g. inhibition or exacerbation of pain by touch) support convergence rather than specificity in central circuits. We outline how peripheral specialization together with central convergence could enable spinal microcircuits to combine inputs from distinctly specialized, co-activated afferents and to modulate the output signals thus formed through computations like normalization. These issues will be discussed alongside recent advances in our understanding of microcircuitry in the superficial dorsal horn.

Introduction

Pain normally serves to alert us to danger. This is exemplified by people with congenital insensitivity to pain, many of whom succumb to minor injuries or disease because they fail to notice health problems normally evidenced by pain [1]. Pain without overt injury is, however, far more common. Such pain can often be traced back to damage to or dysfunction of the nervous system and is termed “neuropathic” [2]. Unlike nociceptive pain in which noxious stimulation is appropriately perceived as painful, neuropathic pain is associated with mechanical allodynia (pain caused by innocuous touch) and, paradoxically, with hypoesthesia (reduced touch sensation) [3]. Such perceptual anomalies provide valuable insight into how sensory information is processed and what impact that processing has on perception.

Other somatosensory percepts include touch, itch, heat and cold. Many believe that each percept is evoked by stimuli representing distinct (sub)modalities, but the neural signals elicited by different modalities often interact [4–9]. Interactions can be unmasked by careful experimentation (e.g. innocuous cooling can elicit pain, but that pain is typically inhibited by touch [9]) and become more obvious under pathological conditions (e.g. mechanical allodynia). These cross-modal interactions suggest that somatosensory percepts are synthesized from the combination of neural signals representing multiple modalities rather than on the basis of signals representing any one modality.

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Comparison with other sensory systems is revealing: We see an entire rainbow of colors based on the relative activation of three types of cone photoreceptors (trichromacy) [10], and we tend to smell odorant combinations (configural odor perception) rather than the component odorants (elemental odor perception) despite exquisitely specialized olfactory receptor cells [11]. In both cases, as in somatosensation, primary receptor cells transduce specific features of the physical stimulus but we tend to perceive something more synthetic because of subsequent neural processing. Despite this, cross-modal interactions in the somatosensory system are often considered a design fault (i.e. cross-talk between labeled lines) rather than a potentially important design feature. However, processing enabled by cross-modal interactions could, for instance, help disambiguate stimulus quality and intensity, the same way that comparing the relative activation of cones with different spectral sensitivities disambiguates the color and intensity of light [10].

Before delving into spinal microcircuits, we will follow a top-down approach to establish the importance of central pain processing. Then, following a bottom-up approach, we will consider how spinal microcircuits could implement that processing. Given that spinal microcircuits have been the focus of several recent reviews [12**,13**,14–18], we have emphasized theoretical aspects of pain processing and their relation to microcircuit function in the hope of providing a different perspective on this topic.

Pain theories

Several physiological theories of pain have been developed and can be divided into three groups [for detailed history, see 19,20,21]. According to intensity theory, pain occurs when non-specific cells are activated very strongly. This theory denies peripheral specialization (and, for that reason, has been ruled out) but emphasizes the importance of convergence onto and summation by spinal neurons [22], and thus shares some similarities with pattern theory (see below).

According to specificity theory, pain is subserved by cells activated uniquely by noxious stimulation, i.e. nociceptive-specific (NS) cells. For specificity to be maintained throughout the neuraxis, postsynaptic cells in the “pain pathway” receive input exclusively from presynaptic NS cells and are de facto NS. The neural signal conveyed via this labeled line evokes pain upon arrival at some decoder. Other somatosensory percepts are evoked via separate labeled lines. A critical prediction of this theory is that the specificity that exists peripherally (i.e. in primary afferents) is maintained centrally (i.e. in spinal neurons).

According to pattern theory, perception depends on the relative activation of different types of primary afferents – a *spatial* pattern at the population level [23] or, as we propose to refer to it, a combinatorial code. A combinatorial rate code is distinct from temporally patterned spiking at the single cell level [e.g. 24], but the term “pattern” has caused confusion in this regard. Nevertheless, *spatiotemporally* patterned input to spinal circuits is likely to be important, especially given differential conduction velocities among primary afferents. Sensory interaction theory [25] and gate control theory [4*], both of which constitute pattern theories, as well as more recent work [5,26,27*,28**], have all stressed interactions between co-activated inputs. Describing labeled lines as interacting [e.g. 29*,30], despite the inherent self-contradiction, reflects an ongoing effort to reconcile seemingly discrepant observations.

From primary afferent activation to pain – the case for central pain processing

There is unequivocal evidence that primary afferents are specialized to detect certain stimuli [31], e.g. nociceptors detect noxious input. This does not mean that afferents are specialized

to evoke certain percepts. Noxious stimulation activates nociceptors and it evokes pain, but pain is not necessarily evoked via (and only via) nociceptor activation. Nociceptor activation and pain are correlated because they share a common cause – noxious stimulation. This suggests but does not prove causation although most everyone, including us, would concede that nociceptor activation normally evokes pain. Causation is supported by microstimulation studies in humans, which showed that activating single afferents evokes somatosensory percepts consistent with the receptive properties of the afferent [32]. The important points, explained below, are (1) that nociceptor activation does not always evoke pain, and (2) that pain can be evoked independent of nociceptor activation.

With regard to the first point, consider that a given stimulus does not always evoke the same percept. For example, capsaicin can evoke pain or itch depending on how it is applied – punctate application evokes itch [33]. This has been suggested to occur because the peripheral endings of “itch” neurons reach more superficial layers of the skin than other neurons [30], the idea being that “itch” neurons achieve their specificity through a combination of transducer phenotype and anatomy (and that itch is suppressed by pain if/when deeper “pain” fibers are activated). An alternative explanation, consistent with the anomalous percepts elicited by punctate thermal stimulation [27*,34], is that cutaneous stimuli are normally distributed (i.e. not punctate) and thus activate multiple afferents, the exact combination of which dictates the evoked sensation. Indeed, hair follicles are each innervated by multiple types of low-threshold mechanoreceptors (LTMRs), which means mechanical stimulation invariably co-activates more than one type of afferent [28**]. Also, the fact that temperature sensation can be qualitatively altered by differentially blocking conduction in Aδ-cold fibers (relative to thermosensitive C fibers) [7,35] supports the link between afferent co-activation and perception.

With regard to the second point, consider that noxious stimulation, although crucial for normal (i.e. nociceptive) pain, is neither necessary nor sufficient to evoke pain. “Pain signals” can originate centrally, as in central neuropathic pain [36], and peripherally generated “pain signals” can be blocked centrally, as in episodic analgesia [37]. This raises an important point: There is nothing innate to primary afferent nociceptors that endows them, and only them, with the capacity to evoke pain. In apparent contradiction to this, it has been shown in mice that ablating C fibers expressing the G protein-coupled receptor Mrgprd reduces sensitivity to noxious mechanical stimulation without affecting thermal sensitivity, whereas pharmacologically ablating a non-overlapping set of fibers expressing TRPV1 reduces sensitivity to noxious heat without affecting mechanical sensitivity [38]. Those data could be taken to suggest that the former cell type is necessary for mechanical pain whereas the latter is necessary for thermal pain; however, that necessity is true only under certain conditions. For instance, myelinated afferents [39,40,41*] and possibly C-LTMRs [42, but see 43] (neither of which express Mrgprd) contribute to mechanical pain under neuropathic conditions [see also 44] and innocuous temperatures can evoke burning pain without activating TRPV1-expressing neurons (see above). Inability of the primary afferents involved in mechanical allodynia and anomalous temperature sensation to *normally* evoke pain exemplifies how other factors, like downstream microcircuit function and co-activated inputs, are important for perception.

In brief, somatosensory afferents are specialized to encode certain modalities and intensities of stimulation. There is, however, no one-to-one relationship between afferent activation and perception, contrary to what labeled lines predict. Instead, numerous observations speak to the importance of central processing and suggest that co-activated inputs converge and interact within spinal circuits. We will focus on circuits in the superficial dorsal horn (laminae I and II) because of their established importance in pain processing and because they are better understood than those in deeper laminae.

Dorsal horn circuitry

Input

Sensory information is conveyed to the spinal cord dorsal horn via primary afferents. Different types of primary afferents terminate in different laminae (Fig. 1) [45]. Large myelinated fibers also send collaterals into the dorsal columns. Apart from sensory input, the spinal dorsal horn also receives descending modulation including serotonergic fibers from the nucleus raphe magnus, noradrenergic fibers from the locus coeruleus, and GABAergic fibers from the rostral ventromedial medulla [for review see 12].

Intrinsic components

Projection neurons (see *Output*) comprise as few as 5% of all neurons in lamina I of rat lumbar segments [46] and lamina II contains no projection neurons, meaning local interneurons predominate. About one third are GABAergic based on immunocytochemistry [47], and a subset of those co-express glycine, but the majority are excitatory, consistent with paired recordings [48, but see 49]. The neuronal population is, to say the least, heterogeneous [50–54] (Fig. 2). This heterogeneity reflects the distinct ways in which different spinal neurons process information [55,56,57*]. Inclusion within the same circuit of single-spiking neurons that behave as near-optimal coincidence detectors (comparable to those in the auditory midbrain [e.g. 58]) and tonic-spiking neurons that behave as diametrically opposite integrators is intriguing, but the implications for somatosensory processing await further investigation. Below, we highlight our current knowledge of spinal circuitry. For comprehensive reviews, see [12**,13**,14–18].

Using transgenic mice that express GFP selectively in (subsets of) GABAergic neurons, intrinsic spiking patterns of inhibitory neurons have been identified [59–62,63*] and include tonic-, transient- (phasic-) and single-spiking [e.g. 62]. The same genetic tools have not been used to target excitatory interneurons but immunocytochemical studies provide interesting correlations; for instance, Kv4 channels (responsible for the A-type potassium current) are not co-expressed with GABA [64,65] and are thus present in excitatory interneurons and some projection neurons [66]. The A-type current is associated with several spiking patterns including delayed-, gap-, single- and reluctant-spiking [50,52–54,67]. Delayed-spiking can be accounted for by the inactivation kinetics of the A-type potassium current, whereas single-spiking is accounted for by a separate, noninactivating low-threshold potassium current [57]; gap- and reluctant-spiking arise from interactions between those two currents (unpublished observations; SR and SAP). However, tonic- and transient-spiking patterns have also been described in excitatory interneurons [48] which, given the patterns observed in inhibitory interneurons (see above), suggests there is no simple electrophysiological way of delineating excitatory neurons from inhibitory neurons. Notably, Kv4.2 has been shown to play an important role in pain plasticity [68]. Protein kinase C γ, which is expressed in a subset of excitatory interneurons [69], also plays an important role in neuropathic pain [70].

By combining immunocytochemistry and electrophysiology, Todd and colleagues have shown that inhibitory neurons comprise mostly islet, central and vertical morphologies with mostly tonic spiking, whereas excitatory neurons comprise mostly radial and vertical morphologies with various spiking patterns associated with A-type current (see above) plus central morphology associated with transient spiking [52*]. This is generally consistent with paired recording work by Perl and colleagues (Fig. 3). Tonic-spiking islet cells inhibit transient-spiking central cells [49]. Transient-spiking central cells excite delayed-spiking vertical cells, which in turn excite lamina I projection neurons [71]. Tonic-spiking central cells form reciprocal inhibitory connections with tonic-spiking islet cells and also inhibit vertical and possibly transient-spiking central cells [63*]. In general, excitatory connections

tend to depress whereas inhibitory connections facilitate [72]. The two types of inhibitory interneurons receive different C fiber input [63*] and are differentially modulated by serotonin [73]. Opposite effects of noradrenaline on inhibitory interneurons have been reported [73,74]. Yoshimura and colleagues have shown that islet and central cells (both putative inhibitory interneurons) receive monosynaptic excitation uniquely via C fibers (although the former also receive polysynaptic Aδ) and GABAergic inhibition, whereas radial and vertical cells (both putative excitatory interneurons) receive monosynaptic C and Aδ input and mixed GABA/glycinergic inhibition [75*]. Excitatory neurons selectively receive input from TRPA1-expressing C fibers [76]. Notably, all cell types except islet cells receive monosynaptic input from Mrgprd-expressing C fibers [77*], which are purportedly critical for mechanical nociception (see *From primary afferent activation to pain – the case for central pain processing*). A subset of inhibitory neurons also receive Aβ input [78]. Overall, it appears that most dorsal horn cell types receive convergent input from multiple types of primary afferents.

Output

A subset of neurons in all laminae except lamina ll send projections to supraspinal targets including the thalamus and brainstem [79,80], with some neurons innervating more than one projection site [for review see 12]. Lamina I projection neurons constitute a large fraction of the spinothalamic tract, conveying information related to pain, itch and temperature. This cell population includes NS neurons (responsive to pinch and/or noxious heat) [81] as well as COLD neurons (responsive to innocuous cooling and inhibited by warming) and HPC neurons (responsive to heat, pinch and cold) [82]. Itch-specific neurons (i.e. selectively activated by histamine) have also been described [83, but see 84]. Notably, however, dorsal horn neurons have inhibitory receptive fields (mapped by innocuous peripheral stimulation) that are larger than their excitatory receptive fields ([85–87]. Moreover, the excitatory receptive field can expand and contract rapidly [88], suggesting that it is dynamically regulated by microcircuit function rather than being hard-wired [see also 89]. Furthermore, lamina I NS cells become responsive to innocuous stimulation after nerve injury, and this can be acutely reproduced by experimental manipulations [90*]. These data demonstrate that pre-existing polysynaptic pathways carrying low-threshold input to “NS” lamina I neurons can be unmasked [see also 91,92,93]. In short, the dynamic multi-modal tuning of spinal projection neurons demonstrates the importance of microcircuit function and argues against labeled lines. Please note that evidence against labeled lines does not equate with evidence against peripheral specialization – this misappropriation has caused too much confusion not to be mentioned here.

Microcircuits and putative computations

The emerging picture is one of spinal circuits composed of numerous excitatory and inhibitory interneurons that (i) have diverse intrinsic coding properties, (ii) receive different patterns of primary afferent input, (iii) connect preferentially to other spinal cell types, and (iv) are differentially modulated. Despite these advances, we are still a long way from understanding exactly how spinal circuits contribute to pain processing. Here, in the hopes of stimulating more research in this direction, we speculate on how microcircuits could implement some simple but potentially important computations.

Figure 4 contrasts the input-output transformation that could be implemented by different circuit motifs. Pure labeled lines, represented by motif 1, do not interact, meaning input *a* gives output *A* and input *b* gives output *B* regardless of whether inputs *a* and *b* are co-activated. By comparison, co-activation of multiple inputs is important in motifs 2–5. Motif 2 shows lateral inhibition between the top and bottom pathways; in this scenario, only the optimally activated pathway will relay output if weak (non-optimal) excitation is

overpowered by inhibition [94]. Inclusion of reciprocal inhibition (i.e. between inhibitory interneurons; not shown) could improve categorization [95]. In motif 3, co-activated inputs converge onto a common inhibitory interneuron whose inhibition is therefore proportional to the net input; in this scenario, each output is normalized by total input [96]. In effect, motifs 2 and 3 allow ratios of different inputs to be calculated. Notably, inhibition may not be evident except through its modulation of concurrent excitation, meaning interactions between pathways are likely to be overlooked unless multiple inputs are co-activated. In experiments, co-activation is typically avoided by using stimuli designed to isolate individual inputs. This reductionist tendency may seriously limit our understanding given that realistic stimuli are likely to be complex, and thus conducive to co-activating multiple inputs which could then interact.

In motifs 2 and 3, output in each pathway is scaled by activity in the neighboring pathway but it is not qualitatively altered – one could argue that the pathways still qualify as labeled lines. Motif 4 shows the subtle way in which labeling can be compromised by cross-excitation. Input *b* (without *a*) will give output *B* in the bottom pathway and could excite the top pathway polysynaptically, but polysynaptic excitation will not be evident if B^*/B' is subliminal. Under pathological conditions, B^*/B' may become supraliminal, in which case the top pathway will respond to input *b*. Even under normal conditions, co-activation of inputs *a* and *b* may render input B^*/B' supraliminal; thus, cross-modal interaction would only be (normally) evident when co-activating inputs *a* and *b*. It is not clear how such mixing could be useful, but it does seem to occur, as evidenced by mechanical allodynia induced by disinhibition. Motif 5 shows convergent input onto an excitatory interneuron that behaves as a coincidence detector (e.g. single-spiking neuron). Because such a neuron requires simultaneous input from both pathways, it can multiply its input firing rates [97] or implement a logical AND operation, thus enabling its output (which represents the conjunction of inputs) to "color" the regular output of each pathway. This last example highlights the importance of intrinsic cell properties. To continue that theme, consider that normalization is best implemented by inhibitory interneurons that behave as integrators (e.g. tonic-spiking neurons). Our postulated connection between spiking pattern and cell types (i.e. inhibitory vs. excitatory interneuron) is consistent with available data (see *Dorsal horn circuitry*).

Conclusions

Like in other sensory systems, primary somatosensory afferents are specialized to encode elemental stimulus features. According to specificity theory, the initial neural representation should remain unchanged as the signal passes to postsynaptic neurons along a labeled line, implying a one-to-one relationship between stimulation, primary afferent activation, and perception – evidence does not support this. The same peripheral specialization that is cited as supporting specificity theory (without due regard for exclusive synaptic connectivity to central neurons) is also required for the combinatorial coding proposed here – spinal microcircuits could not calculate the relative activation of different types of primary afferents if the primary afferent population was homogeneous. Such computations require an array of variably specialized afferents and some degree of central convergence. Both requirements seem to be fulfilled.

For now, we can only speculate that spinal microcircuits carry out computations that are known to be important in other sensory systems but which, to date, have attracted little attention in the context of pain processing. Identifying those computations and determining how spinal microcircuits implement them will require much more work, but we are moving closer. What is clear is that information processing by spinal microcircuits is important for

how we perceive somatosensory stimuli and that improper processing can produce debilitating perceptual anomalies like mechanical allodynia.

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Highlights

- Primary somatosensory afferents are specialized to detect different modalities and intensities of stimulation.
- Signals carried by different types of primary afferents converge in the dorsal horn of the spinal cord.
- Central convergence compromises central specificity but enables cross-modal interactions.
- Spinal circuits may exploit convergence to transform input signals (representing elemental stimulus features) into output signals that are more closely related to perception.

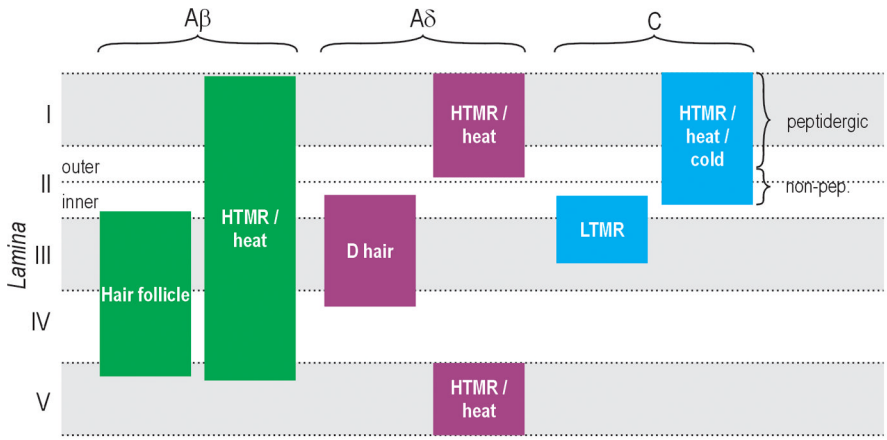

Figure 1. Afferent termination patterns in the spinal dorsal horn

Primary afferents are routinely categorized as Aβ (thickly myelinated), Aδ (thinly myelinated), and C (unmyelinated) fibers based on conduction velocity, and can be further divided according to their responsiveness to different modalities and intensities of stimulation. The spinal dorsal horn is divided into laminae (indicated along left margin). Different types of afferents terminate in different laminae. HTMR, high-threshold mechanoreceptor. LTMR, low-threshold mechanoreceptor. Modified from [45].

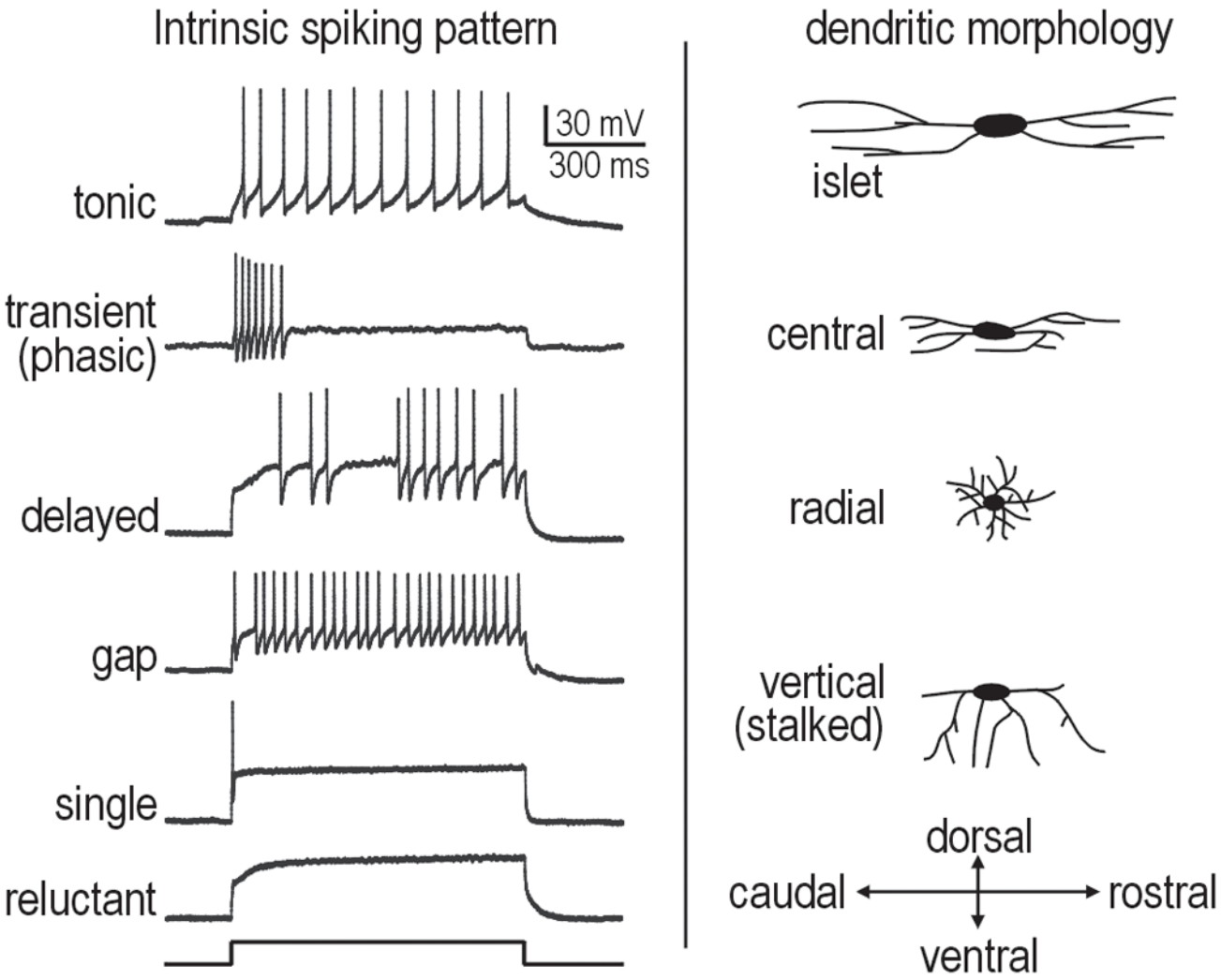

Figure 2. Classification of neurons in the superficial dorsal horn

Left column shows sample spiking patterns elicited by current injection into the cell body. Right column shows cartoon representation of differences in dendritic morphology.

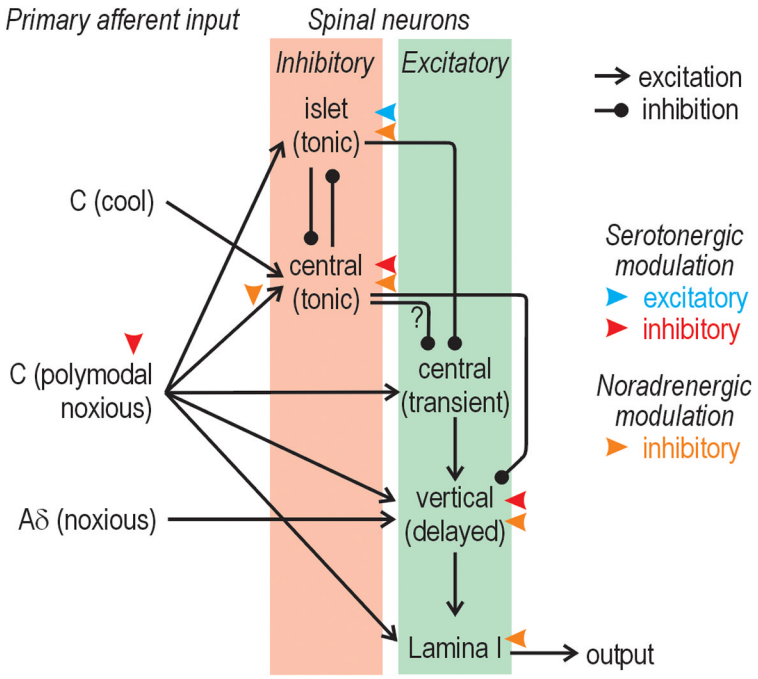

Figure 3. Circuitry in the superficial dorsal horn

Summary of what is currently known about synaptic input to and connectivity between different types of spinal neurons based primarily on paired recording data [49,63,71,73]. Notably, ref. 63 reports that tonic central cells receive input from TRPM8-expressing C fibers (which have fast conduction velocities relative to other C fibers) whereas ref 49 reports that islet cells receive fast C fiber input (relative to transient central cells); this figure depicts the former results, which are arguably more definitive. Also, this figure does not depict input from Mrgprd-expressing C fibers to all cell types other than islet cells [77], input from TRPA1-expressing C fibers to excitatory interneurons [76], or input from Aβ fibers onto some inhibitory interneurons [78], not to mention the full extent of polsynaptic connections.

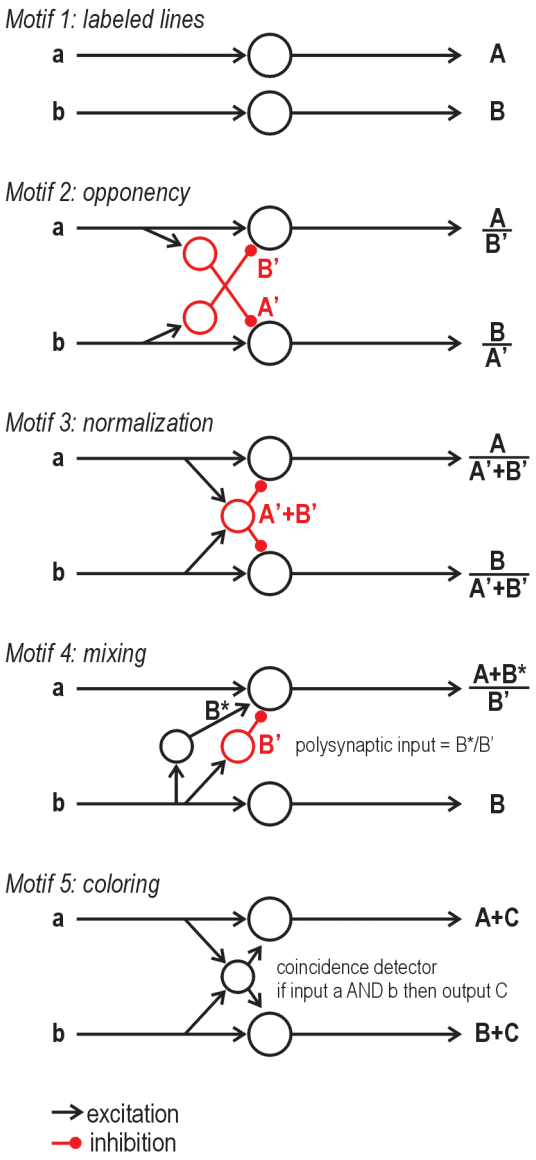

Figure 4. Putative microcircuits and their computational role

Motif 1: Pure labeled lines do not interact, meaning input *a* gives output *A* in the top pathway and input *b* gives output *B* in the bottom pathway even when inputs *a* and *b* are co-activated. ***Motif 2:*** Opponency is implemented by lateral inhibition, meaning output *A* is modulated by inhibition B' and output *B* is modulated by inhibition A' if inputs *a* and *b* are co-activated. ***Motif 3:*** Normalization is implemented when inputs *a* and *b* converge (perhaps via an excitatory interneuron; not shown) on an inhibitory interneuron whose output $A'+B'$ modulates outputs *A* and *B*. ***Motif 4:*** Mixing is implemented by an excitatory interneuron relaying excitation B^* to the top circuit, which, if combined with polysynaptic inhibition B', would give output $(A+B^*)/B'$. This is the first example in which two letters occur in the numerator of the output, which is to say that the labeled line has been corrupted. ***Motif 5:*** Coloring is implemented when an excitatory interneuron's output *C* indicates that input *a* and *b* have occurred together. Output *C* thus gives context to, or "colors", outputs *A* and *B*. In this example, the excitatory interneuron must behave as a coincidence detector. See text for additional discussion.