Sensorimotor Integration at the Dorsal Column Nuclei

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Interaction among primary afferents, corticofugal fibers, and intrinsic elements allows for sensorimotor integration at the dorsal column nuclei. The interneurons permit the spatial localization, the recurrent collaterals synchronize the activity of projecting cells with overlapping receptive fields, and the corticofugal fibers induce a central zone of activity surrounded by a peripheral zone of inhibition.

Somatosensory ascending activity is linked to movement, in particular to exploratory motor acts. Active exploration of the environment is required for accurate discrimination of texture and for interpretation of complex spatiotemporal patterns of stimuli activating different classes of mechanoreceptors. The interplay between sensory and motor systems culminates in the subjective perception of shape, form, size, surface structure, and mechanical properties of objects as they are actively explored. Elimination of movements that accompany exploration and active touch results in loss of discrimination. When a beaker containing water, treacle, or mercury at identical temperatures is raised over a subject's immobile finger, the subject is unable to discriminate the liquids. However, when allowed to immerse a finger, the subject has no difficulty in discriminating.

In primates, the corticofugal motor fibers allow for more complex limb movements than in lower species; these are under an elaborate feedback from skin, deep muscular, and joint receptors via fibers ascending in the dorsal column system. Sensory feedback from the moving musculature is used to adjust and correct the movement in accordance with varying environmental demands. In bipedal species, the anterior limbs have evolved to generate patterns of manipulation involving the distal musculature. Thus animals with well-developed exploratory and manipulative skills, like the raccoon, have a greater number of dorsal root fibers innervating the forelimb than less dexterous animals, like the cat. Most of these fibers are cutaneous, and a major proportion of cutaneous receptors subserve the forepaws. Also, the monkey has a prevalence of cutaneous primary fibers projecting to the dorsal column nuclei (DCN) compared with primary afferents carrying subcutaneous input. The increase in the number of receptors improves the amount of data collected, and improvement of the motor response serves to better select the peripheral somatosensory inputs to be centrally transmitted.

In this review, we summarize evidence that the sensorimotor integration begins at the level of the second-order neurons of the somatosensory system, at the DCN. At this level, several mecha-

"…corticofugal motor fibers allow for more complex limb movements…."

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nisms enhance the activity of second-order neurons with overlapping receptive fields and inhibit other second-order cells with different receptive fields. These mechanisms include efferent control by the cerebral cortex and positive feedback by collaterals of second-order cells on other second-order neurons.

Organization of the dorsal column nuclei

The primary somatosensory afferents from the limbs and trunk ascending in the dorsal columns terminate in the DCN (cuneate and gracile nuclei). These afferents release glutamate and may contact both projection neurons and intrinsic inhibitory neurons, supporting classical processes of lateral inhibition. In general, the cutaneous afferents travel superficial to the deep (muscular) fibers. About 90% of the fibers terminating in the DCN are primary afferents from dorsal root ganglion neurons. The remaining 10% originate from spinal neurons located mainly in lamina IV. These postsynaptic fibers travel in the dorsal columns between cutaneous and muscle afferents.

The gracile (Goll) nucleus receives its major input from lower thoracic (T_7) and more caudal segments, and the cuneate (Burdach) nucleus, located more laterally, receives its primary afferents from more rostral levels. On the basis of functional and cytoarchitectonic criteria, the cat DCN may be divided into three parts: a rostral reticular region with multisized cells; a middle region with medium-sized, round cells organized into clusters; and a caudal reticular region containing round, medium-sized scattered cells. Neurons in the rostral reticular part have large receptive fields in deep (muscular) structures, neurons in the middle region have small cutaneous receptive fields, and neurons in the caudal reticular region have large receptive fields responding mostly to high-frequency, vibration-sensitive (Pacinian) receptors. The neurons in the three divisions of the DCN differ also in their efferent projections. The rostral reticular part contains both thalamic and cerebellar projecting neurons, some with bifurcating axons to the contralateral medial lemniscus (ML) and the ipsilateral cerebellum. Neurons in the rostral and caudal regions project to different structures including the tectum, the pretectum, the inferior olive, and the spinal cord (3). The middle part of the DCN is more complex (Fig. 1); it consists of a central core receiving predominantly cutaneous input and a shell or peripheral region. The central core has been extensively studied and contains two major types of neurons, glutamatergic cells projecting mostly to the contralateral ML and inhibitory intrinsic neurons (interneurons).

The peripheral region consists of a ventral reticular part and a series of neurons at the borders of the nuclei, containing local cells as well as neurons projecting to thalamic and nonthalamic regions. The local circuit neurons are smaller than the cells projecting in the ML (lemniscal neurons, LNs) and appear scattered throughout the DCN. In the central core, they are interspersed between the clusters and, in general, have larger and more proximally located cutaneous receptive fields than the LNs (5).

The DCN projection neurons can be grouped into two main functional populations (3). The first consists of cells sending an axon to the ML and carrying tactile and kinesthetic information related to fine touch, kinesthesia, and orienting behavior. The second consists of neurons projecting to the cerebellum and related structures, constituting a sensorimotor system related to the coordination of activity in muscles during exploratory behavior.

Cortical control of somatosensory input

The sensorimotor cortex receives continuous input during active movement, which provides the sensory feedback required for smooth voluntary movements. Although the sensory route from the periphery to the motor cortex is unclear (4), rodents, felines, and primates have a topographically organized projection from the somatosensory to the motor cortex. Thus most neurons in both the main "motor" and the main "sensory" regions of the arm and leg areas of sensorimotor cortex receive projections from peripheral receptors in the forelimb and hindlimb.

Corticofugal control is a feature common to all the sensory systems and modulates afferent input at subcortical sites; in the somatosensory system part of this modulation occurs at the DCN and spinal cord. The purpose of the cortical control is twofold: *1*) to select certain inputs to the detriment of others, and *2*) to provide input to assure the adequate frequency and duration discrimination for tactile information.

Corticofugal fibers end directly in the DCN. The majority of these terminate in the rostral part of these nuclei and in the ventral part of their middle regions (Ref. 11; see Fig. 1). Most of the corticonuclear neurons are located in lamina V of areas 4 and 3a, with fewer neurons in areas 3b, 1, and 2. The motor cortical projection is mainly to the ventral part of the middle regions, where fibers from area 3a (a cortical zone between the motor and sensory cortexes that receives somesthetic proprioceptive input) also terminate. Because these zones also receive deep peripheral input, the modulatory role of
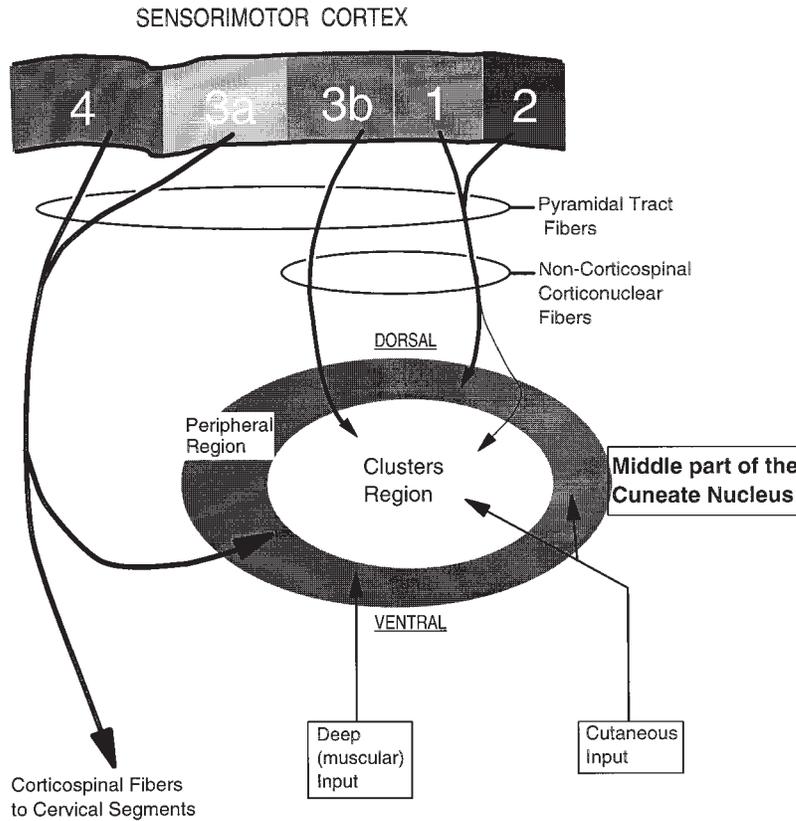
SENSORIMOTOR CORTEX

FIGURE 1. The middle cuneate nucleus is formed by a core or clusters region (white) and a peripheral region (gray). Primary afferents running in the dorsal column and corticofugal fibers running in the pyramidal tract are segregated in this part of the nucleus. The majority of fibers from cortical areas 4 and 3a enter the peripheral region ventrally to the clusters zone, where deep peripheral input prevails. The fibers from area 3b are directed mainly to the clusters region, and those from areas 1 and 2 terminate mostly in the peripheral region.

areas 4 and 3a is directed to DCN neurons receiving proprioceptive input. The projection from area 3a is more abundant in cats than in monkeys (2), indicating a greater dependence on proprioception in the cat and a major role by cutaneous input in monkeys. Corticofugal fibers from areas 4 and 3a may also influence the cutaneous cells in the clusters region through DCN interneurons. Fibers from areas 3b, 1, and 2 terminate dorsally in the same region (see Fig. 1). Area 3b, a cortical zone receiving cutaneous input, has a focal projection to the clusters region whereas areas 1 and 2 project mostly to regions surrounding the clusters zone, which receives cutaneous and proprioceptive inputs.

The corticonuclear pathway has at least two components, 1) corticonuclear cells whose axons do not reach the spinal cord and 2) corticospinal cells projecting mainly to cervical segments and whose axons send collateral branches into the DCN (2, 12). Therefore, corticospinal fibers sending collateral branches to the DCN exert their control on spinal neurons mostly at the cervical cord and, at the same time, influence the sensory input at the level of the DCN, implying that the cortical

coordination is directed to forelimb movements. Consistent with this, lesions of the dorsal column in monkeys lead to deficiencies in fine motor acts involving the forelimbs, with no or minimal deficiencies in grasping with the hindlimbs (14). Obviously, the hindlimbs are used more for postural support than for tactile exploration.

Noncorticospinal corticonuclear neurons have slow-conducting axons, in comparison with those of the corticospinal neurons involved in fast movements, and exhibit tonic and sustained activity during movement. Because the cortical influence on DCN projecting neurons is mainly inhibitory (1, 5), it may prevent any sensory input during movement from reaching the cortex. Only DCN projecting neurons receiving strong sensory input during movement would be able to overcome this inhibition so that during movement, distracting sensory information is eliminated.

The somatic afferent fibers exert a powerful monosynaptic excitatory action on DCN projecting neurons that can be seen extracellularly as unitary prepotentials preceding the spikes. The excitatory postsynaptic potentials (EPSPs) induced by stimulating primary afferent fibers

"The corticonuclear pathway has at least two components...."

have been shown to be unusually large and to elicit bursting activity (1). This is possible because these fibers possess large presynaptic knobs containing round glutamatergic vesicles. The synaptic contacts are so powerful that a single primary afferent fiber can generate pairs or triplets of output spikes from several target DCN neurons (8) without the need of temporal or spatial summation for reliable transmission (10). This high degree of synaptic security allows the dorsal column-ML system to encode high rates of afferent stimulation. Recent work by Vierck and colleagues suggests that the dorsal column-ML system may be particularly important for frequency and duration discrimination of tactile information. Thus it was shown that *1*) the distal extremity movement depends crucially on dorsal column-lemniscal input (14); *2*) when the fasciculus cuneatus is interrupted, monkeys are unable to control the position of their fingers and the fine motor activities are impaired (9); and *3*) transection of the dorsal columns of monkeys spares detection, localization, and discrimination between spatial attributes of tactile stimuli, but the performances requiring tactile direction sensitivity and frequency discrimination are impaired. Also, interruption of the ipsilateral dorsal column makes the monkeys unable to detect repetitive cutaneous stimulation. These deficits appear to be caused by the impairment of inhibiting mechanisms within the primary somatosensory cortex as a consequence of contralateral dorsal column interruption (15).
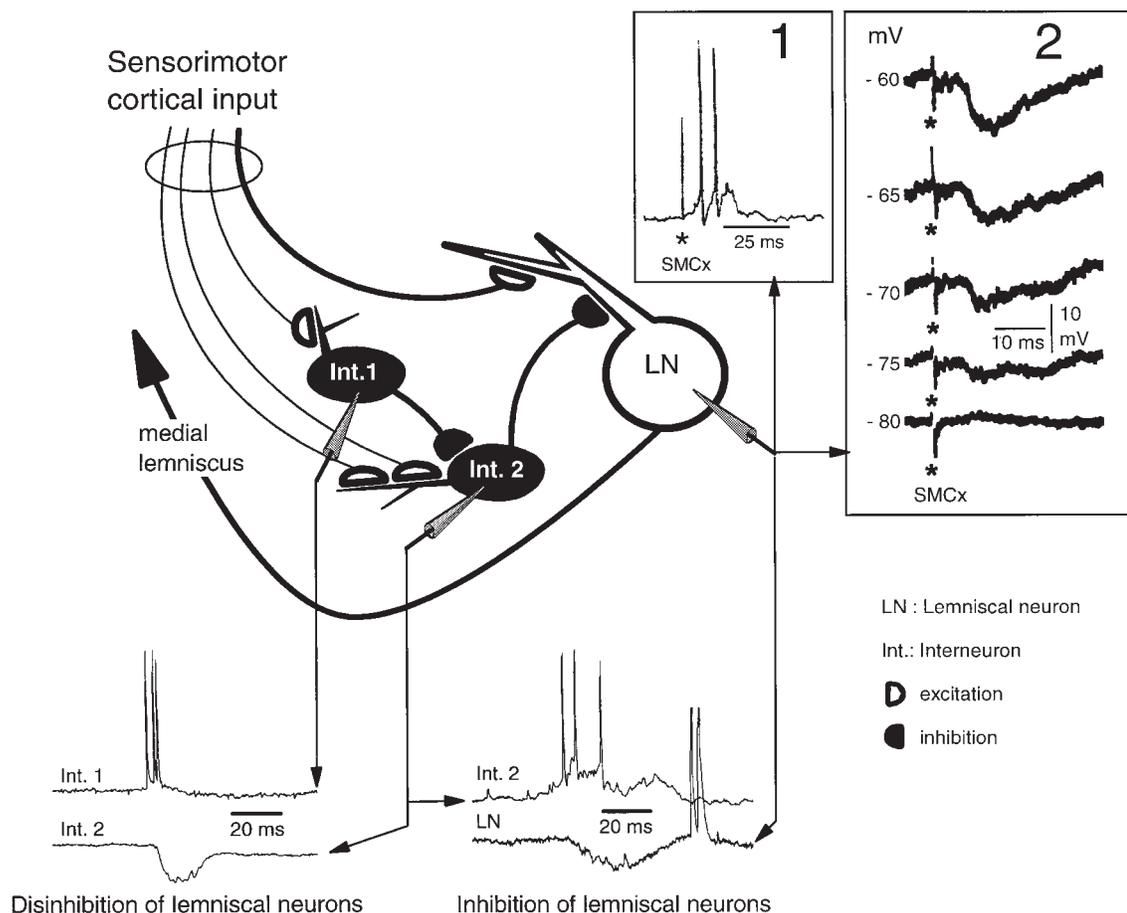
It was postulated in the early 1960s (1) that the synaptic mechanisms involved in the cortical modulation of LNs include presynaptic axo-axonic contacts between corticonuclear terminals and primary sensory terminals reaching the DCN and postsynaptic inhibition via DCN interneurons. However, subsequent anatomic studies demonstrating that corticonuclear fibers terminate on small- to medium-sized dendrites of DCN neurons without establishing axo-axonic contacts (6) make cortical presynaptic inhibition unlikely. The evidence on postsynaptic inhibition in the nuclei in response to sensorimotor cortical stimulation is, however, unequivocal. The inversion in the polarity of inhibitory postsynaptic potentials evoked on LNs by sensorimotor cortical stimulation on intracellular injection of negative current unambiguously indicates the synaptic nature of the inhibition (see *inset 2* in Fig. 2). Data from the feline cuneate nucleus demonstrated that sensorimotor cortical stimulation mostly inhibits LNs and activates interneurons (1, 5); however, some other interneurons are also inhibited. Because the corticofugal fibers are excitatory, the inhibition of some interneurons

implies the existence of at least two inhibitory interneurons synaptically linked. Consistent with that, it is now known that there are glycinergic and GABAergic interneurons similarly distributed throughout the DCN and expressing different subtypes of glutamatergic receptors. The consequences of interneuronal inhibition by the cerebral cortex are functionally important because the cortical inhibition of inhibitory interneurons that, in turn, synapse with LNs allows the cortex to disinhibit the sensory transmission through specific LNs (see Fig. 2).

In addition, electrical stimulation of the monkey´s pericentral cortex induces monosynaptic excitatory responses on contralateral LNs, and recent data obtained in our laboratory from the cat middle cuneate nucleus demonstrated that ~21% of the LNs are monosynaptically activated by stimulation of the somatosensory cortex and that these excitations are the fastest responses induced from the cerebral cortex. This indicates that these excitatory effects are produced by collateral branches of corticospinal cells because the cortico-DCN axons originated from noncorticospinal neurons have slow conduction speeds (12). The cortical activation of particular sets of DCN neurons constitutes a positive feedback to differentially select the sensory input to be transmitted as necessary during active exploratory behavior. The data of Bentivoglio and Rustioni (2) showing that the corticospinal fibers branching into the DCN are considerably more numerous in monkeys than in cats suggest that the increase in corticospinal collateral branches to the DCN allows for greater tactile resolution and manipulation skills.

In summary (Fig. 2), the slow-conducting corticonuclear fibers impose a tonic inhibition over the DCN (with inhibition of some inhibitory interneurons) whereas the fast subset activates the projection neurons mostly during movements of the distal musculature, thus overcoming the underlying inhibition and favoring the transmission of sensory feedback generated by the movement itself. Such a circuit will operate during manipulative and exploratory behavior, shaping the receptive fields of the DCN LNs, making them more discrete, and allowing faithful transmission of high-frequency inputs by specifically depolarizing and disinhibiting the appropriate LNs (Fig. 3*C*).

Thus recent experimental findings related to prior data indicate that the corticofugal influence on the function of the DCN may not require presynaptic inhibiting mechanisms and could serve not only to shape the peripheral receptive fields but also to improve the high-frequency following capability of the LNs.

FIGURE 2. Proposed sensorimotor cortico-cuneate interactions. The inhibitory interneurons receive direct corticofugal excitatory input and make synaptic contact among them and with cells projecting to the medial lemniscus (LNs), thus inducing disinhibition and inhibition on LNs, respectively. Some LNs also receive monosynaptic cortical excitatory input (*inset 1*). *Inset 2* shows the responses of a LN to sensorimotor cortex stimulation (SMCx) during sequential membrane hyperpolarization from –60 to –80 mV. The inhibitory postsynaptic potential reversed in polarity at membrane potentials between –75 and –80 mV. The artifacts of SMCx stimulation are marked by asterisks. *Inset 2* data are from Ref. 5.

Repetitive activity and synchronization of DCN neurons

One form of normal spontaneous activity in DCN neurons is a high-frequency bursting of two to five spikes. Histological observations have demonstrated that the LNs emit short recurrent collateral branches to neighboring DCN cells. Consistent with the histological data, stimulation of the ML induces antidromic spikes in LNs followed by one to three transynaptic action potentials at latencies suggesting the existence of one synapse between recurrent collaterals and the recorded lemniscal cell. These transynaptic effects could be induced by descending fibers activated by spread of current when the ML is stimulated. However, in many cases the transynaptic responses have the same or even lower thresholds than the antidromic responses, thus indicating that they were indeed induced through recurrent collaterals because there are no known fibers descending in the ML. The result of this interaction is that a given DCN LN activated by stimulation of its receptive field tends to impose its pattern of activity on neighboring cells. This is so because the LNs are somatotopically organized so that neurons devoted to the processing of a single sensory modality and submodality are adjacent to each other (7). Accordingly, neighboring LNs receive synchronous excitatory input from dorsal column fibers and from the recurrent collaterals of other LNs, thus
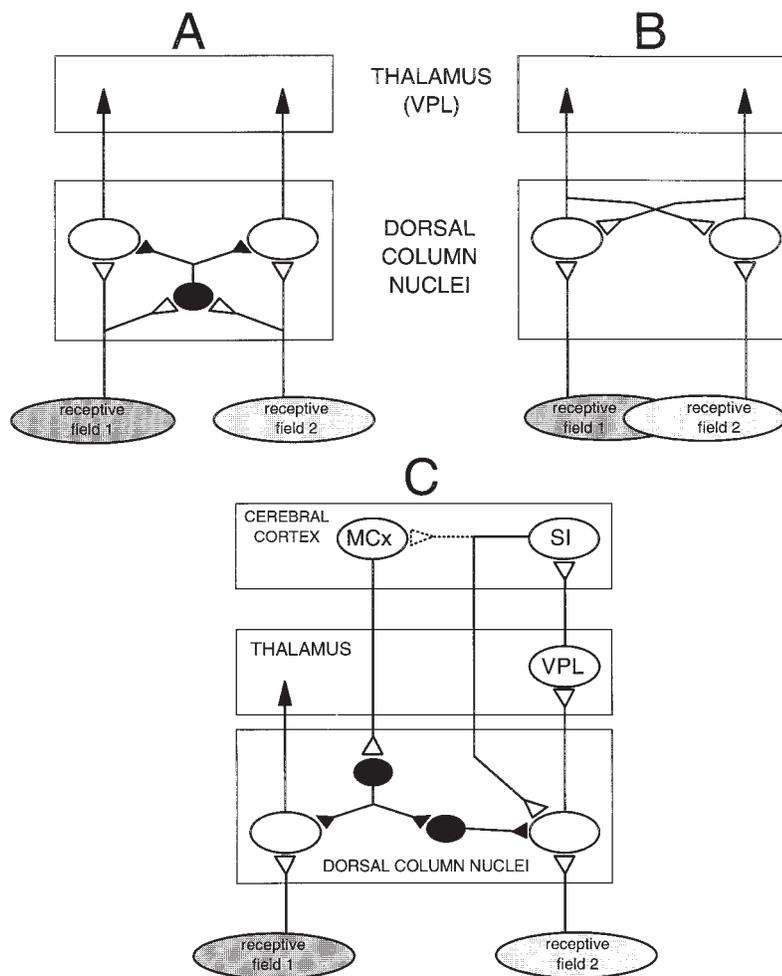
FIGURE 3. The presence of intranuclear inhibitory interneurons (in black) allows for lateral inhibition (*A*) and for somatotopic sensorimotor cortical excitation and disinhibition (inhibition of inhibitory cells) of specifically activated channels while inhibiting the surround and thus also assuring the capability of the cortically activated lemniscal projection cells to follow high-frequency cutaneous input (*C*). The existence of focused recurrent collateral branches permits synchronization among neighboring lemniscal neurons (*B*). MCx, primary motor cortex or area 4; SI, primary somatosensory cortex; VPL, thalamic ventroposterolateral nucleus.

generating the repetitive and synchronous activity normally observed in DCN neurons.

That the corticonuclear cells are engaged in a true feedback was demonstrated by Towe and Zimmerman (13), who showed that the mass discharge evoked in the cuneate nucleus either by peripheral cutaneous stimulation or by direct stimulation of the dorsal column fibers is followed by a second late discharge that disappears upon cortical removal. Cutaneous stimulation produces a double discharge in the DCN, the first due to the ascending afferent volley and the second due to a transcortical volley descending in the pyramidal tract. Thus, although there is no doubt that the corticonuclear fibers can induce bursting activity, it is still unknown whether these bursts are induced directly on lemniscal projection neurons and/or generated through inhibitory

interneurons that, in turn, induce postinhibitory rebound discharges on LNs. Both phenomena are theoretically possible and not incompatible given the spatial focusing of the cortico-DCN projections. Intracellular recordings from projection cells and interneurons while the motor and somatosensory cortexes were stimulated were necessary to evaluate this question. Recently, we demonstrated that the cortex induces both direct excitatory and indirect postinhibitory bursting discharges on LNs (see Fig. 2). This explains the generally reported observation that upon stimulation of the sensorimotor cortex, the lemniscal gross activity shows an early excitation followed by an inhibitory period and a late excitation. Repetitive activity can also be produced by EPSPs crossing threshold during sufficient time to allow various action potentials to be produced.

Conclusions

According to the available data, the inhibitory interneurons within the DCN allow for a precise spatial localization of the peripheral stimuli through lateral inhibition (Fig. 3*A*). Although the neurons activated by stimulation of a certain peripheral receptive field (for example, field 1) are able to overcome the underlying inhibition, other neurons not activated from the periphery (correspondent to field 2) are not (Fig. 3*A*). The existence of short, recurrent collateral branches from LNs that contact other neighboring LNs allows for repetitive activity and for synchronizing LNs with overlapping receptive fields (Fig. 3*B*). Finally, the cortex serves as a positive feedback by directly activating LNs from the primary somatosensory receiving area. At the same time, corticofugal fibers from the motor cortex disinhibit the same cells and inhibit other LNs with different receptive fields (Fig. 3*C*). Different cortical sites induce distinct responses on DCN neurons, and it would be expected that those cortical cells activated from the periphery affect the LNs excited by the same peripheral stimulus. Thus the cerebral cortex would induce a central zone of activity surrounded by a peripheral zone of inhibition. Neighboring LNs have similar receptive fields (7) and send axons to adjacent thalamocortical cells that, in turn, activate clusters of cortico-DCN neurons. The sensorimotor cerebral cortex can thus discriminate wanted from unwanted sensory information at the level of the DCN by producing excitation and disinhibition on LNs whose peripheral receptive fields are strongly activated, while inducing inhibition on distinct LNs with less activated peripheral receptive fields. This focused cortical activation and removal of inhibition also assures the reliable transmission of high-frequency tactile inputs through LNs strongly activated from the periphery.

"…discriminate wanted from unwanted sensory information…."

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