

SOMATOSENSORY IMPRINTING IN SPINAL REFLEX MODULES

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Understanding how sensory information is used by motor systems for motor commands requires detailed knowledge about how the body shape and biomechanics are represented in the motor circuits. We have used the withdrawal reflex system as a model for studies of sensorimotor transformation. This system has a modular organisation in the adult. Each module performs a detailed and functionally adapted sensorimotor transformation related to the withdrawal efficacy of its output muscle(s). The weight distribution of the cutaneous input to a module is determined by the pattern of withdrawal efficacy of the muscle. Recently, we found that the somatotopic organisation and weight of the cutaneous input to the dorsal horn of the lower lumbar cord is related to this modular organisation. The dorsal horn in the lower lumbar cord thus appears to be organised in a column-like fashion, where each column performs a basic sensorimotor transformation related to the movement caused by a single muscle and the body shape. Since the withdrawal reflex system encodes error signals to the cerebellum through some of the spino-olivo cerebellar pathways, the modular concept is, in fact, a key to understanding sensory processing in higher order motor systems as well. Developmental studies indicate that each module is a self-organising circuitry that uses sensory feedback on muscle contractions to adjust its synaptic organisation. Furthermore, these studies suggest that the spontaneous movements during development, by providing structured sensory information related to movement pattern of single muscles and body shape, are instrumental in shaping the sensorimotor transformation in the spinal cord. These findings and their implications for the understanding of higher motor functions and their clinical aspects will be discussed.

Key words: plasticity, sensorimotor transformation, development, motor control, modular organisation

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MODULAR ORGANISATION OF THE NOCICEPTIVE WITHDRAWAL REFLEX

The withdrawal reflex system has been extensively used as a model system for studies of sensorimotor integration, pain-related mechanisms, learning and memory. For a long time this system was assumed to be organised as a flexion reflex, i.e. a type reflex activating all flexor muscles and inhibiting all extensor muscles simultaneously (1–3). More recent studies in the rat, cat and human instead indicate, for the first time, that this system has a modular organisation (4–7) where each module controls a single or small number of synergistic muscles which have a similar action and receive a multireceptive input from the skin area they withdraw from when the animal is in a standing-like position. Our studies on the characteristics of the sensorimotor transformation performed by each reflex module are summarised below.

Principles for sensorimotor transformation

Since the sensory input arises from an irregular body surface and the muscles perform multi-joint movements, the task of transforming sensory signals from the skin into withdrawal movements is not trivial. To understand the basic principles for this sensorimotor transformation, the 3D movements of the body surface on single muscle contraction were compared with the sensitivity distribution in the receptive fields of withdrawal reflex pathways. In the 3D motion analysis, electrical stimulation of single muscles was performed in anaesthetised rats with the hindlimb in a standing-like position (8–10). The movements of several hundred sites on the skin on muscle contraction were simultaneously measured and expressed relative to the normal vector and the horizontal plane of the skin. Withdrawal movements were thus expressed in relation to the body geometry, and not in relation to external coordinate systems (Fig. 1). Since most mechanoreceptors in the skin signal either loading or unloading of skin surface (movements perpendicular to the horizontal plane, along the normal vector) or skin stretch (movements along the horizontal plane), this movement analysis also provided information about the expected body surface areas to be exposed to sensory feedback by touching external objects, e.g. the ground, on single muscle contractions (see below, ‘Self-organisation and somatosensory imprinting’). Maps of the withdrawal efficacy (defined as the inward movement component perpendicular to the surface) in a

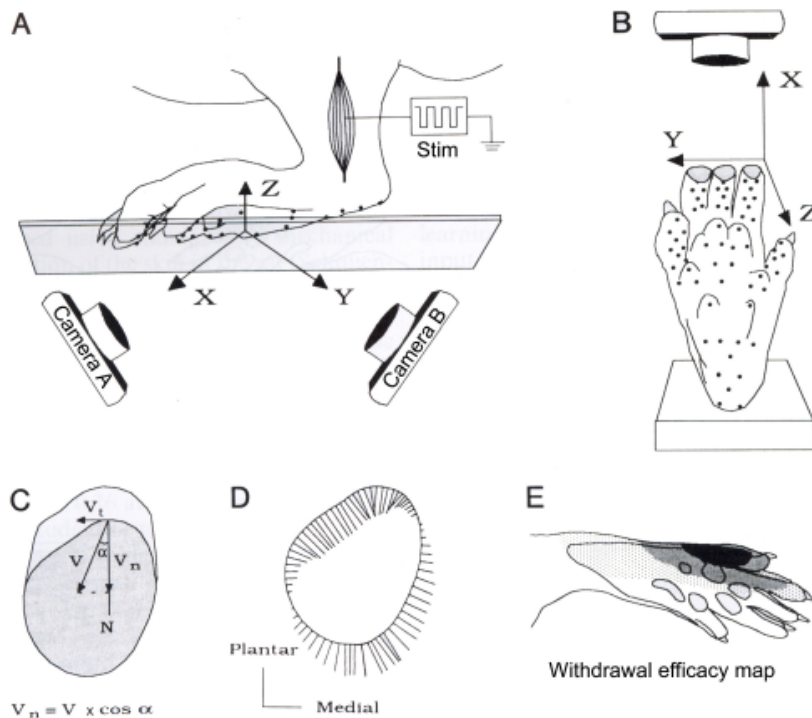


Fig. 1. Method used to document and analyse movements of the body surface in 3D. *A:* Movements of the hindpaw elicited by intramuscular stimulation in deeply anaesthetised rats were documented by two cameras synchronised with a flash of light. Microspheres (black dots), glued to the skin, were used to track movements of the various parts of the hindpaw. *B:* The form and surface co-ordinates of the hindpaw were determined by photographing consecutive sections of a cast made of wax and then digitising the x,y co-ordinates of the contours. *C:* Cross section of a digit segment. Using a computer program written by the author, the movement vector V of several hundred skin sites was decomposed into V_t , the component tangential to the surface, and V_n , the component parallel to the normal (N) of the skin surface. An inward V_n was defined as a withdrawal. *D:* Sample showing V_n (indicated by bars) along the skin surface of the proximal phalanx of digit 5 following contraction in *m. peroneus brevis*. *E:* Distribution of inward V_n (i.e. withdrawal efficacy), based on measurements of 23 segments of the hindpaw, following stimulation of *m. peroneus brevis*. Low, medium and high dot density indicate areas of the skin where the withdrawal efficacy was 0–30%, 30–70% and 70–100% of maximum, respectively. The Kriging algorithm was used to delimit these areas. (Modified from 10).

standing-like position were obtained for six hindlimb muscles. In the receptive field mappings, the response magnitude on stimulation of a large number of skin sites was determined for most of the hindlimb muscles (Fig. 2). Both mechanical and thermal stimulation were used in decerebrate spinal rats and anaesthetised rats. Comparison of the motor output maps with the corresponding sensory input maps of the withdrawal reflexes revealed a striking similarity (Fig. 3). In a sense, the withdrawal efficacy of a single muscle seems to be 'imprinted' on the reflex module acting on the same muscle. Thus, the weight of the input connections from a given skin site to a reflex module is determined by how effective this module is in withdrawing from the skin site when the animal is in the standing position (10). For example, skin sites that are maximally withdrawn by a muscle also exhibit maximal reflex gain. By contrast, there is no relationship between the movement component related to skin stretch (i.e. movements along the skin surface) and the withdrawal reflex receptive fields. Hence, the sensitivity distribution within the excitatory receptive field of a hindlimb muscle is specifically related to the component of the movement that unloads the skin surface on contraction in the muscle in a standing-like position. Analogously, the inhibitory input to the withdrawal reflexes is adapted to movements towards external stimuli, such that the strongest inhibitory effects arise from skin areas that move maximally towards external stimuli on contraction (11–12).

The same principles of sensorimotor transformation as found for rat withdrawal reflexes apply to the cat (13). Interestingly, muscles with different function in the two species exhibit corre-

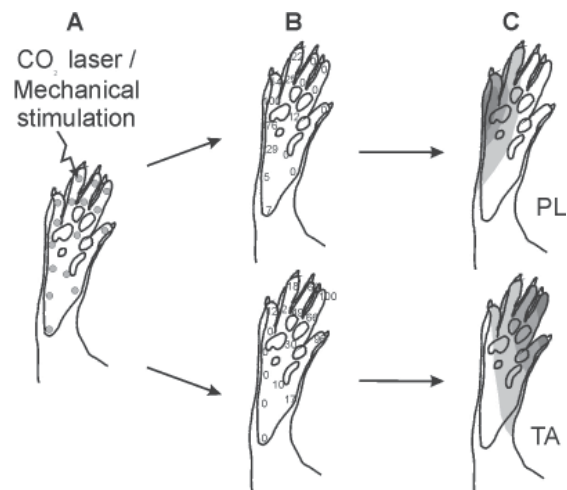


Fig. 2. Mapping of sensitivity distribution in the receptive fields of nociceptive withdrawal reflexes. CO_2 laser stimulation (beam diam. 1 mm, 1W, 5–30 ms) or calibrated pinch (area 1–2 mm², force up to 3.0 N/mm²) was used for noxious thermal or noxious mechanical stimulation, respectively. Pauses of at least 1 min between stimulation of same skin site. Electromyographic recordings from the extensor digitorum longus and peroneus longus (PL) muscles were made using thin steel needles isolated with the exception of about 50 μ m at the tip. *A:* Typical stimulation sites. *B:* Reflex amplitude expressed in percentage of maximal response is plotted on stimulation site. *C:* The receptive field maps of the withdrawal reflexes of tibialis anterior muscle (TA) and PL divided into three levels of sensitivity: Low, medium and high dot density indicate areas of the skin from which the evoked responses were 0–30%, 30–70% and 70–100% of maximal response, respectively. A Kriging algorithm was used to delimit these areas.

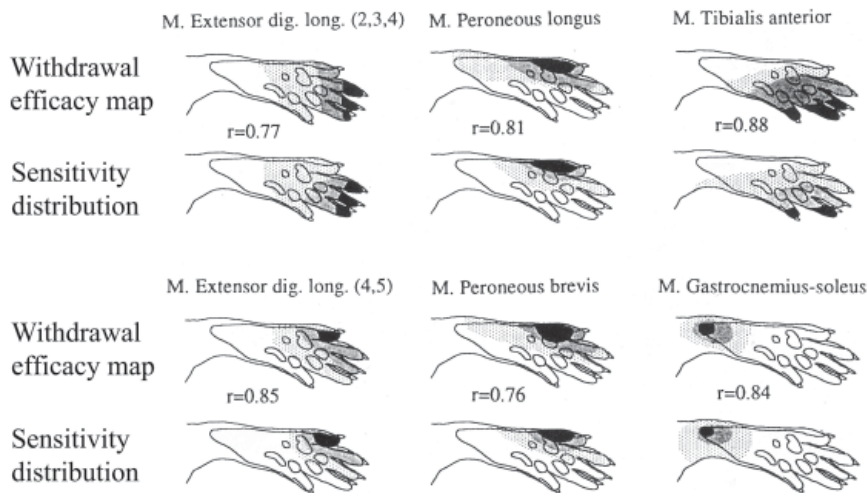


Fig. 3. Relation between excitatory receptive fields of muscles and corresponding maps of withdrawal efficacy. Typical distributions of sensitivity and corresponding withdrawal (here denoted 'withdrawal field') for six muscles are shown. Low, medium and high dot density indicate areas of the skin from which the evoked responses were 0–30%, 30–70% and 70–100% of maximal response, respectively. Spatially unbiased data from 40–50 sites on the paw were used to calculate the correlation coefficient, r , between the reflex response and corresponding withdrawal (linear regression analysis, $p < 0.001$, Student's t -test, modified from 10).

sponding differences in the receptive fields of the withdrawal reflexes. Thus, withdrawal reflexes elicited in dorsiflexors are much weaker in the cat than in the rat and vice versa for reflexes to plantar flexors (14). Cats stand on their digits, whereas rats stand on the whole plantar surface. In the standing position, the dorsiflexors of cat digits are much less effective in withdrawing from the plantar skin than the corresponding muscles in rats, and vice versa for plantar flexors. These findings are consistent with the view that these reflexes consist of adaptive modules (see below).

Interneurons encoding the withdrawal reflex strength

Interneurons encoding the withdrawal reflex strength in individual muscles, termed 'reflex encoders', are present in the deep dorsal horn in the L4 and L5 segments (15). These neurons have receptive fields with a sensitivity distribution very similar to those of withdrawal reflex pathways to single muscles and receive a convergent input from tactile A α fibres and nociceptive C fibres (16). In fact, a large proportion of the wide dynamic range neurons, i.e. neurons receiving a convergent input from tactile and nociceptive receptors, appear in the deep layers of the fifth lumbar segment to be of the reflex encoder type. Within this segment, reflex encoders for the interossei, flexor digitorum longus, gastrocnemius, peronei and extensor digitorum longus muscles are located in a mediolateral sequence, reminiscent of the corresponding topographical organisation of the motoneuron columns in the ventral horn. Hence, the reflex encoders appear to be located in discrete pools that have a 'musculotopic' organisation. Whether or not reflex encoders connect monosynaptically with motoneurons has not been determined. However, since they exhibit the same response properties as the withdrawal reflexes recorded from muscles, they would not be necessary from the point of view of information processing. It should also be noted that while there is substantial support for a modular organisation of the withdrawal

reflex system, where each module acts on a single muscle, the existence of weak collaterals to nearby synergistic muscles cannot be ruled out.

Receptors contributing to withdrawal reflex modules

This includes nociceptors and to a lesser extent slowly adapting mechanoreceptors and hair follicle receptors (16). Cutaneous nociceptive C fibres, which provide a major input to the withdrawal reflex circuits in the rat (17), terminate in the superficial layers of the dorsal horn (18–23). Since the dendrites of deep dorsal horn neurons usually do not reach these layers (24), a monosynaptic input to the reflex encoder neurons from nociceptive C fibres does not seem to be significant. Rather, interneurons in the superficial layers¹ may mediate the nociceptive C-fibre input to the reflex encoders. It is known that many of the substantia gelatinosa neurons project to the deeper layers¹ of the dorsal horn (25). However, the exact identity and properties of these first order interneurons have not yet been determined. As regards tactile input, a monosynaptic input to reflex encoders appears likely in view of the short latency for evoked discharges on A α fibre nerve stimulation (26).

The relation between spinal somatotopy and musculotopic organisation of reflex encoders

The relation was studied to further clarify the organisation of the reflex network (23). This somatotopy has been extensively studied previously but not in relation to spinal reflex circuits (19–20). Mapping was done of spinal presynaptic (using cholera toxin and WGA-HRP for staining of coarse and thin afferents, respec-

¹Rexed defined 10 dorsoventral organisational layers (laminae I – X) in the spinal cord.

tively) and postsynaptic somatotopies (using tactile and nociceptive evoked field potentials), in layer¹ II–IV, and of the ‘musculo-topic’ organisation of single ‘reflex encoder’ neurons (using microelectrode recordings) in lamina V (15, 23). The termination patterns of unmyelinated and myelinated afferents in lamina II and laminae III–IV, respectively, were very similar, indicating that their terminations are well aligned in the horizontal plane. This was supported by mappings in the transversal plane of the nociceptive and tactile field potentials and also by previous data obtained using electrical nerve stimulation (18). In the horizontal plane, a complex spinal somatotopy exhibiting a high degree of representational overlap was found. By analysing this overlap with respect to relative input strength from the contributing skin areas, it was found that the weight distribution of the tactile input to circumscribed areas in the fourth and fifth lumbar segments was often very similar to the weight distribution of the nociceptive input to the reflex encoders located 200 μm ventrally in lamina V. Hence, the spinal somatotopic map of laminae III–IV appears to have a specific spatial relation to the topography of reflex interneurons in deeper laminae. The dorsal horn would hence be organised in a column-like fashion (27), where each column performs a basic sensorimotor transformation (Fig. 4). Compatible with such an organisation are the recent results of Tresch et al.

(28), which demonstrate consistent motor responses to spinal microstimulation at different depths in the dorsal horn.

SELF-ORGANISATION AND SOMATOSENSORY IMPRINTING

Evidence for learning-based adaptation of the nociceptive withdrawal reflexes

The withdrawal reflex system has long been assumed to be an innate system that develops independent of experience (29). However, the fact that a map of the withdrawal efficacy is ‘imprinted’ on the receptive fields of the withdrawal reflex network suggests that a learning mechanism is involved. Furthermore, an extensive reorganisation of reflex connections does occur during the early postnatal development in the rat (Fig. 5) (30–32). The withdrawal reflex modules are functionally unadapted at birth, often leading to movements towards the noxious stimulus. Over the first three postnatal weeks, the strengths of the erroneous connections are gradually reduced. Concomitantly, the weight of afferent connections from the skin area that are unloaded by muscle contraction becomes proportional to withdrawal efficacy. Since

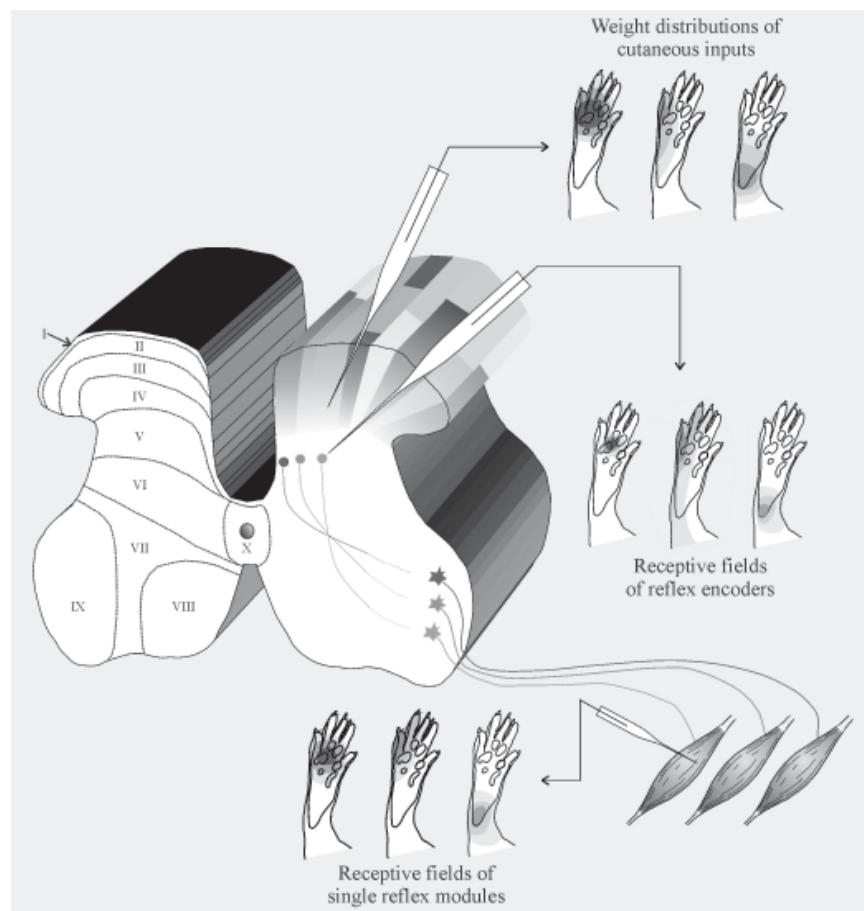


Fig. 4. Schematic figure of proposed organisation of the withdrawal reflex system. Columns of the dorsal horn receive a cutaneous input that has a specific weight distribution. This weight distribution is the same as that of nociceptive input to ‘reflex encoders’ in deep dorsal horn (interneurons that can encode the withdrawal reflex strength of individual muscles, 15). The reflex encoders are assumed to project to single muscles and weigh the input according to the withdrawal efficacy of the output muscle. Left half, schematic indication of Rexed’s laminae.

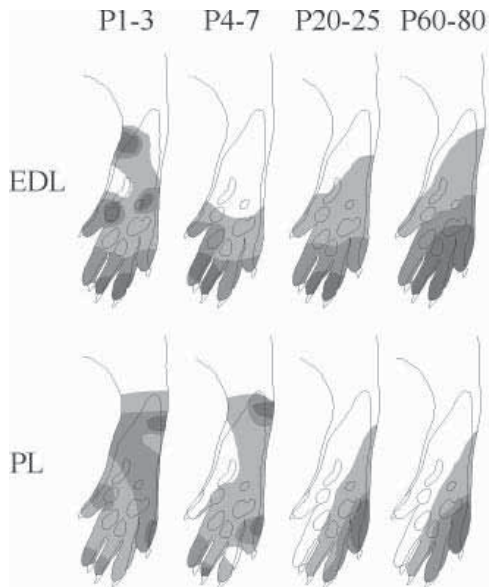


Fig. 5. Functional adaptation of nociceptive withdrawal reflexes during postnatal development in the rat. The sensitivity distribution within the receptive fields of two hindlimb muscles at different postnatal (P) days are shown. Note the gradual disappearance of aberrant foci during the first three weeks. EDL: extensor digitorum longus; PER: peroneus longus and brevis.

this process involves functional specification of the weight of numerous afferent connections to each reflex module, it appears unlikely that this process is specified directly by genetically determined molecular cues.

Three recent studies support this view: 1) Withdrawal reflex receptive fields with normal sensitivity distribution develop despite altered innervation of the skin (33). In these experiments

the plantar skin was reinnervated by collateral sproutings of nearby nerves after plantar nerve transection at birth (Fig. 6). 2) The sensorimotor transformation of withdrawal reflex circuits can adapt to altered withdrawal movement patterns caused by neonatal tendon transfer (34). In these experiments the distal tendons of digit dorsiflexors and pronators were transferred to new insertion points, thereby changing the movements caused by these muscles. This adaptation appears to be restricted to sensory input from the normal adult receptive field of the muscles. Shifting the withdrawal focus outside the normal adult receptive field did not result in the generation of a new focus of sensitivity. Instead, there was a marked reduction of responses from the normal receptive field. Moreover, despite overlapping receptive fields of withdrawal reflex pathways acting on muscles with similar action, only the reflex pathway to the manipulated muscles is affected, indicating that each module is adapted independently of other modules (Fig. 7). 3) Blocking sensory input from the skin during the postnatal third week arrests the withdrawal reflex adaptation and can erase previous adaptation, indicating that the adaptation is dependent on sensory information (35). In these experiments, tail anaesthesia was accomplished by a combination of EMLA salve and hair removal. Following recovery of sensation, the withdrawal reflex adaptation recommenced, showing that the adaptive mechanisms were not abolished. Control experiments showed that the EMLA treatment did not cause general analgesia.

Learning mechanisms

The findings that the sensorimotor transformations of reflex modules are adjusted independently of each other during development and that the sensitivity distribution in the receptive field of a module mimics the distribution on the skin of its withdrawal efficacy indicate that each reflex module must receive sensory

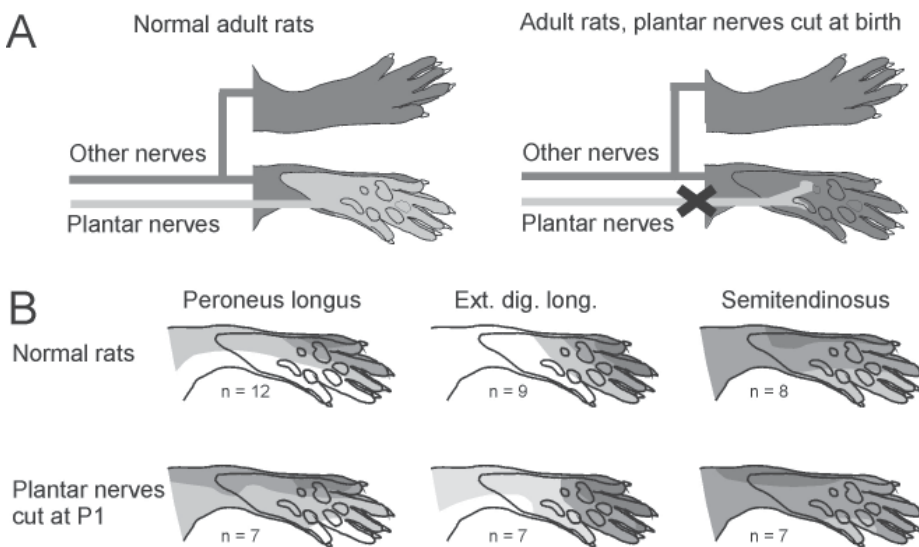


Fig. 6. Effects on withdrawal reflex receptive fields of altered peripheral innervation. A: Innervation of the paw in normal adult rats and in adult rats whose plantar nerves were transected at birth. Following neonatal transection, the plantar nerves degenerate almost completely and the plantar skin is subsequently reinnervated by adjacent nerves through collateral sprouting. B: Averaged receptive fields of mm. peroneus longus and brevis, extensor digitorum longus, and semitendinosus in normal adult rats (upper row) and in rats subjected to transection of the plantar nerves at birth (bottom row). n = number of rats. Calibrated noxious pinch was used to map the receptive fields. Cross indicates site of neuroma. Conventions as in Fig. 2. (Modified from 33).

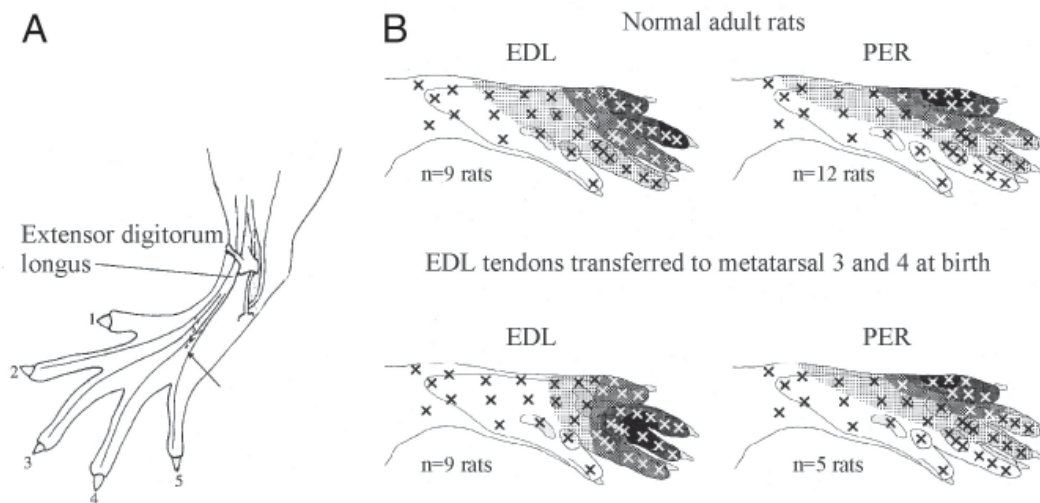


Fig. 7. Effects on withdrawal reflex receptive fields of altered withdrawal efficacy pattern (modified from 34). *A*. Schematic to show the rearrangement of tendons caused by neonatal surgery. The withdrawal efficacy was altered at birth by transferring the distal tendons of m. extensor digitorum longus (EDL) to the third and fourth metatarsal bones. The normal course of tendons is indicated by continuous lines. The course of the tendons after transfer is indicated by a dashed line. Arrow indicates new insertion site of EDL. *B*. Averaged withdrawal reflex receptive fields of EDL and peroneus longus (PL) in normal adult rats (top) and in adult rats whose EDL tendons were transferred to the third and fourth metatarsal bone at birth (bottom). Each site was stimulated once with calibrated noxious pinch. Low, medium and high dot densities indicate areas of the skin from which the evoked responses were 0–30%, 30–60%, 60–85% of maximal response, respectively. Black represents 85–100% of maximal response (referred to as receptive field focus). Note the shift in sensitivity distribution for the withdrawal reflex of manipulated EDL, i.e. shift of focus from the distal digits to the proximal part of the digits and central pads and the lack of effect on the receptive field of PL. These adaptive changes did not occur unless the tendon surgery actually resulted in a change of withdrawal movement pattern. Crosses indicate stimulation sites.

input related to the withdrawal efficacy of its own output muscle(s) during the learning. This could be achieved if sensory feed-back following muscle twitches evoked by ‘spontaneous’ discharges in individual reflex modules provide the necessary information (Fig. 8) (10, 34, 36). This self organisation mechanism has been termed ‘somatosensory imprinting’ (34). By contrast, sensory feedback following stimulus-produced withdrawal reflex responses would not be adequate since it provides information on the concerted action of all activated reflex modules with overlapping receptive fields. Spontaneous non-reflexogenic motility (37–40) is a common feature of normal development and a substantial fraction of the spontaneous movements appear to be due to single muscle contractions (37, 39, 41–50). The spontaneous movements occur during active sleep (38). In this situation the animal is atonic and the hindpaws are usually in contact with the ground, i.e. a similar position as used to document the withdrawal efficacy of single muscles (10, see also above). Indeed, artificial sensory feedback on spontaneous motility has recently been shown to modify the sensorimotor transformation in the withdrawal reflex modules in the proposed way (50). It is also conceivable that mechanisms similar to those proposed in the adaptation of the withdrawal reflex modules are involved in the developmental adaptation of other motor systems. If so, ‘spontaneous’ movements during prenatal and early postnatal life may constitute the observable effects of developmental ‘test pulses’ emitted from different central motor systems.

WITHDRAWAL REFLEX MODULES AS MULTIPURPOSE ERROR DETECTORS

It is well known that the transmission in withdrawal reflex circuitry is controlled by numerous supraspinal centres (51). This fact suggests that these reflex modules have other functions than the purely protective. Furthermore, spinal circuits with movement-related receptive fields such as the withdrawal reflex system would be ideal for mediating and servo-assisting supraspinal commands to unload/load the pressure on the skin. For example, if withdrawal reflex modules are addressed to unload a given skin surface from contact, the modules will receive an excitatory feedback and inhibitory input proportional to the error of the task. That way the modules that are best suited to unload the skin surface will automatically be facilitated by the sensory feedback. Furthermore, since the weighted cutaneous input would inform about the degree of the motor error, the reflex modules may serve an additional important role as error detectors. The latter role as error detectors may be of particular relevance for the climbing fibre input to the cerebellum known to be involved in motor learning. Recent studies indicate that the climbing fibres projecting to the cerebellar C1, C3 and Y zones inform about the activity in the withdrawal reflex circuits (14). These findings thus suggest that an experience-dependent weighting of somatosensory input according to loading/unloading of receptors reflects a general principle for sensorimotor transformation.

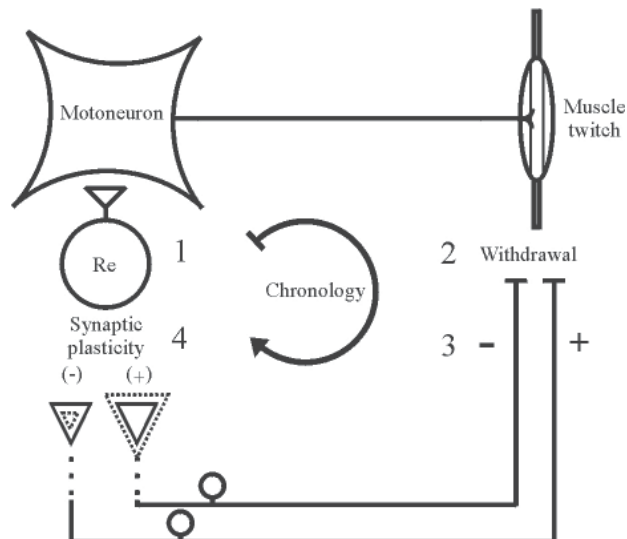


Fig. 8. Proposed self-organising circuitry that uses sensory information related to withdrawal efficacy to adjust the strength of nociceptive connections (35). One 'test' cycle consists of the following chain of events: 1) spontaneous bursts in 'reflex encoders' (Re: interneurons encoding the reflex strength of a module, (15)). Neurons in this region exhibit spontaneous Ca^{2+} -dependent bursts during postnatal development (57); 2) motoneuron activation leads to a muscle twitch; 3) altered tactile sensory input to first order interneurons, and 4) strength of erroneous connections (receiving increased mechano-receptive input) between first order interneurons and reflex encoders is weakened (-) and that of appropriate ones (receiving reduced mechanoreceptive input) is strengthened (+). It is known that temporally correlated pre- and postsynaptic activity may cause altered synaptic efficacy (58–59).

CONCLUDING REMARKS AND CLINICAL IMPLICATIONS

The embryonic development of the spinal cord is characterised by a ventral to dorsal temporal sequence. Appearance of motoneurons precedes that of interneurons which in turn precedes primary afferent ingrowth (52). It is thus of interest that there is a specific spatial relation between the topography of motoneuron pools and lamina V 'reflex encoders' (15) and between the weight distribution of cutaneous input to the dorsal horn and the receptive fields of the reflex encoders. Taken together, these findings may suggest an instrumental role of motoneurons and the sensory feedback caused by spontaneous motility in the functional assembly of the dorsal horn.

Although repairing the spinal cord after injury has so far been relatively unsuccessful, some advances indicate that regeneration across spinal lesions is possible and that some functional recovery may occur after such regeneration (53–55). A major problem, once the obstacle of limited regeneration has been overcome, will be to eliminate the erroneous connections arising from regeneration. Such connections may be devastating for the patient. For example, patients with partially transected spinal cords often report chronic pain that is very difficult to alleviate (56). In a

situation where regeneration after spinal injury has been accomplished it would be useful to revive the 'sensorimotor imprinting' self-organising mechanisms underlying withdrawal reflex adaptation and possibly other motor systems as well that eliminate erroneous connections and weight the correct connections according to function during development.

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