

amniotic fluid were sampled and frozen at once (-80°C). Lacteal secretions were milked from non-rabbit species (colostrum from two rats (1 d post partum); colostrum from two ewes (15 h post partum) and milk from two other ewes (8 d post partum); milk from three cows (late gestation); colostrum and milk from six mares (10–15 h and 6 d post partum); milk from one woman (21 d post partum)) and tested on groups of 20 rabbit pups (from four litters, five per litter, aged 2–3 d).

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Correspondence and requests for materials should be addressed to B.S. (schaal@cesg.cnrs.fr).

Spontaneous muscle twitches during sleep guide spinal self-organization

Per Petersson, Alexandra Waldenström, Christer Fåhræus & Jens Schouenborg

Section for Neurophysiology, Department of Physiological Sciences, BMC F10, Lund University, S-221 84 Lund, Sweden

During development, information about the three-dimensional shape and mechanical properties of the body is laid down in the synaptic connectivity of sensorimotor systems through unknown adaptive mechanisms. In spinal reflex systems, this enables the fast transformation of complex sensory information into adequate correction of movements. Here we use a computer simulation to show that an unsupervised correlation-based learning mechanism, using spontaneous muscle twitches, can account for the functional adaptation of the withdrawal reflex system. We also show that tactile feedback resulting from spontaneous muscle twitches during sleep^{1–3} does indeed modify sensorimotor transformation in young rats in a predictable manner. The results indicate that these twitches, corresponding to human fetal movements⁴, are important in spinal self-organization.

The immense computational complexity of generating, coordinating and controlling compound multi-joint movements in mammals has led to the assumption that even relatively simple sensorimotor tasks such as the nociceptive withdrawal reflex (NWR) could be processed only in widely distributed multilayer

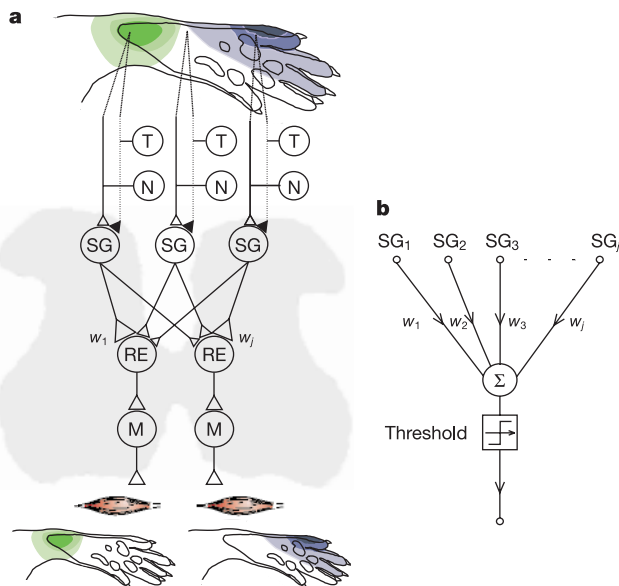


Figure 1 Proposed organization of a reflex module. **a**, The features are as follows. First, many primary afferents feed into the reflex circuit monosynaptically or oligosynaptically (continuous or dotted lines); second, tactile (T) and nociceptive (N) inputs converge in substantia gelatinosa (SG) before reaching the reflex-encoding neurons (RE) located in the deep dorsal horn; third, SG to RE connections are specifically weighted (w_j = synaptic weights); fourth, REs have strong connections to motor neurons activating the muscle(s). The receptive and withdrawal fields of the gastrocnemius (green) and peroneus longus (blue) muscles, respectively, are shown. Filled boutons, inhibitory synapses; open boutons, excitatory synapses. **b**, A Rosenblatt perceptron for comparison.

networks⁵. However, recent data⁶ instead indicate that the spinal withdrawal reflex system has a modular organization, in which each withdrawal reflex module acts primarily on one muscle (Fig. 1a). For hindlimb reflexes, the sensory input from the skin to a module has a weight distribution that is an imprint of the withdrawal efficiency of the muscle when the limb is in a standing-like position, with the foot in contact with the ground⁶. This imprint is laid down on the reflex pathways through extensive postnatal adjustments; erroneous connections are either eliminated or decreased, and the strength of adequate connections becomes proportional to withdrawal efficiency⁷. This process takes approximately a week in the rat and occurs during the first three postnatal weeks depending on the body part^{7,8} (Fig. 2). The sensorimotor transformation can adapt to neonatally induced alterations of either peripheral innervation⁹ or movement patterns¹⁰.

Here we propose that each module is self-organizing and learns about its withdrawal efficiency by probing the tactile feedback that arises from spontaneous activity in its reflex interneurons, activating the associated principal muscle. The temporal correlation between the initial activity in the reflex interneurons triggering the movement and the ensuing tactile feedback would allow a reversed type of hebbian learning (with the postsynaptic activity in reflex interneurons preceding the afferent input). This unsupervised learning principle is referred to below as motor-directed somatosensory imprinting (MDSI) (Fig. 3b). The bases for this hypothesis are the following observations. First, the developmental adaptation is dependent on tactile input, but independent of nociceptive input⁸. Second, during early development the movement repertoire is dominated by spontaneous muscle twitches³ that occur during sleep^{1,2,11}. The spontaneous twitches, characterized by brief contractions in atonic muscles¹, usually result in increased or decreased skin contact with the environment, causing altered tactile input. Many of these twitches are dominated by a single muscle^{11–13} (see also Supplementary Information). Third, the generators of the spontaneous activity are, at least partly, intrinsic to the spinal cord because spontaneous twitches are unaltered by deafferentation¹⁴ and are not abolished by spinal transection³. Last, the rat brain and its connections with the spinal cord¹⁵ are immature during the first few postnatal weeks. A direct instructive role of supraspinal systems in spinal motor learning is therefore unlikely. However, a permissive role is conceivable because spinal transection at birth interferes with NWR adaptation¹⁶.

To test the plausibility of this hypothesis, a computer simulation of MDSI was performed. The simulation was based on published data on plantar hindpaw excitatory receptive fields of six NWR modules in the rat, and skin displacement patterns due to single hindlimb muscle contractions obtained in a standing-like position⁶

(similar to the normal position of the hindlimbs during twitching; see Supplementary Information). The network organization consisted of an input layer of interneurons in substantia gelatinosa that receive nociceptive and tactile input from the same skin area¹⁷, and an output layer of deep dorsal-horn neurons encoding the strength of the withdrawal reflex, termed reflex encoders, that project to the motor neurons (Fig. 1a). This network architecture is similar to a classical Rosenblatt perceptron¹⁸ (Fig. 1b). Oja's rule¹⁹ (see Methods) was chosen to describe adjustments of the connection weights between substantia gelatinosa and the reflex encoders. This learning rule differs from classical hebbian learning in that it includes a synaptic scaling factor that readjusts synaptic weights gradually when uncorrelated postsynaptic activity is present and is therefore self-normalizing²⁰. Note that in MDSI the relative amplitude, rather than the absolute amplitude, of the tactile feedback determines the change in connection strengths such that connections from skin areas from which stronger tactile input is received after a twitch will weaken compared with those from skin areas with less tactile input. Correlations between synaptic weight maps of the developing receptive fields and the movement pattern of each muscle were calculated at different time points during the adaptation process (Fig. 3a). The learning curves for the six modules that were obtained from the simulation (Fig. 3c) were similar to previous experimental data (Fig. 2b). The model was relatively insensitive to the choice of parameter values (such as twitching probability, learning rate, sensory noise level and initial synaptic weights; see Methods). For the data shown in Fig. 3, inhibitory feedback connections of tactile input to the substantia gelatinosa cells (as shown in Fig. 1) were modelled¹⁷. However, if tactile input instead exerts excitatory effects on the substantia gelatinosa cells²¹ then anti-Ojan learning (replacing η with $-\eta$ in Oja's rule) yields similar relative adult weight distributions and comparable learning curves. By contrast, unsupervised feedforward learning (often assumed to underlie the fine tuning of sensory representations²²) in the same six perceptron-like networks as used in MDSI, based on the same input

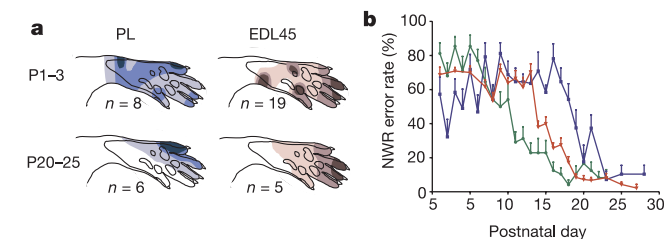


Figure 2 Developmental adaptation of NWRs. **a**, Averaged receptive fields of the PL and EDL45 muscles obtained at different postnatal ages by using CO₂-laser stimulation (intensity twofold the reflex threshold; *n* is the number of rats; see Methods for abbreviations). **b**, Reflex adaptation curves. Graph showing error rate of tail NWRs at different postnatal ages. The tail was stimulated twice, distally, on both lateral sides during P1–P28 in two litters (blue, *n* = 8; green, *n* = 12) and six times on each side in the third litter (red, *n* = 13). (Modified from refs 8, 9.)

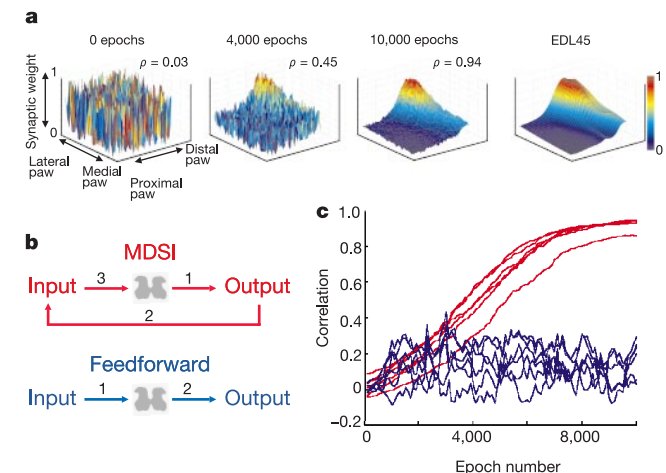


Figure 3 Simulated developmental adaptation of receptive fields for six muscles. **a**, Simulated synaptic weight distributions of a receptive field (EDL45) at different time points during reflex adaptation. **b**, The two simulated learning principles: MDSI and feedforward learning. The sequence of events is numbered. **c**, Simulated reflex adaptation curves. Correlations between synaptic weight maps and movement patterns (597 skin sites) at different time points for the respective muscles with the use of Oja's learning rule for six networks during MDSI (red) or feedforward learning (blue). Simulated (MDSI) and experimental adult correlations, respectively: $r_{EDL23} = 0.94$ and 0.91 , $r_{EDL45} = 0.93$ and 0.95 , $r_G = 0.85$ and 0.95 , $r_{PB} = 0.94$ and 0.88 , $r_{PL} = 0.93$ and 0.91 , $r_{TA} = 0.93$ and 0.90 . (Parameter values and abbreviations are given in Methods.)

patterns and Oja's rule, did not result in correlations stronger than 0.4 (Fig. 3c).

The agreement between the simulation and experiments indicated that our model had high validity. Nevertheless, the role of spontaneous muscle twitches during sleep for spinal self-organization had to be evaluated experimentally. This was done in behavioural experiments in which artificial sensory feedback was given shortly after spontaneous muscle twitches. For technical reasons we studied tail NWRs in these experiments. An automatic imaging system that triggered air-puff stimulation was developed. This stimulation was directed to either side of the tail upon detection of isolated, rapid tail movements. Before training began, the animals were randomized to either air-puff stimulation from the side of the set-up that the tail was moving towards or from the side it was moving away from. Because an adequate NWR can cause an increased input from the skin area moving towards external objects but should not cause an increased input from the skin area withdrawn, these two air-puff stimulations are referred to as 'normal' and 'aberrant', respectively (Fig. 4a). Rats were trained in the system for 2 h a day (mean \pm s.d., 944 ± 526 stimulations) during the period when adequate tail NWRs are normally learned (postnatal ages 12–17 days (P12–P17))⁸. The effect of training was examined by comparing the error rate of NWR responses before (less than 1 h) and after (less than 10 min) each training session. Reflexes were elicited by cutaneous nociceptive CO₂-laser stimulation of either side of the tail in the horizontal plane. Reflex movements towards the laser source were classified as erroneous. After aberrant air-puff conditioning (895 ± 493 stimulations), the mean NWR error rate was increased by 9.2% per training session (Kruskal–Wallis and Dunnett's test, $P < 0.01$; Fig. 4b), whereas normal air-puff stimulation (1032 ± 593) had no significant effect. However, if the change in error rate was adjusted to account for the amount of feedback that the animals had received—calculated as $\sum[\Delta(\text{error rate}) \times N_{\text{twitches}}] / \sum N_{\text{twitches}}$ —there was a tendency for normal air-puff stimulation to reduce the error rate (Wilcoxon signed-rank test, $P < 0.087$). Uncorrelated air-puff stimulation (1159 ± 833) had no effect on NWR adaptation (Wilcoxon signed-rank test, $P = 0.65$; Fig. 4b). Thus, the behavioural data prove that NWR adaptation can indeed be guided by spontaneous muscle twitches.

The simulations show that the postulated reflex network is able to self-organize, guided solely by local learning rules without defined error signals. Each module extracts the relevant feedback information efficiently by assuming a 'learning mode' only in conjunction with its own twitches, given limited co-activity (see Methods and Supplementary Information). A system performance that asymptotically approaches zero error is achieved by multiple learn-

ing cycles, where each cycle causes a small change in synaptic weights. These learning principles result in a much lower error rate than classical hebbian learning in a feedforward network architecture, the latter often being assumed to underlie the spatial organization of sensory representations²³. The behavioural experiments also confirm that tactile input can be used to adjust the connection strengths functionally in the nociceptive spinal withdrawal reflex circuits⁸, but only when tactile input is correlated with spontaneous twitches. The stronger effect of aberrant as opposed to normal feedback in the behavioural study (Fig. 4b) was predicted by simulation of MDSI using aberrant and normal feedback (see Supplementary Information.).

In many sensory systems, spontaneous activity is known to be essential for the refinement of topographical representations: the projections of patches of synchronously discharging afferent neurons are strengthened centrally and those of unsynchronized (uncorrelated) inputs are weakened, thereby refining initial topographical representations that were relatively crude²⁴. Note, however, that the ensuing pattern of afferent input on spontaneous muscle twitches provides more complex functional information, integrating aspects of the complex body-surface, biomechanics and movement patterns. To our knowledge, MDSI has not been established in any other sensorimotor system, although it has been shown that active tactile exploration is needed for the maturation of normal vibrissa representation within the rat somatosensory system²⁵ (see also ref. 26).

The mechanisms that initiate the muscle twitches, and thus MDSI, in the reflex circuits are not known. However, cells located in the deep dorsal horn, some of which are presumably reflex encoders, exhibit Ca²⁺-dependent plateau potentials that greatly increase firing frequency and the duration of after-discharges²⁷. These plateau potentials might drive the spontaneous twitches and at the same time switch the membrane properties of the reflex interneurons from a 'transmission mode' to a 'learning mode'. Interestingly, spontaneous muscle twitches occur preferentially during REM-like sleep^{1,2,11}, indicating that MDSI is influenced by the brain's state. This would be consistent with the concept that the brain has a permissive role in this learning¹⁶. Sleeping and dreaming are known to promote learning²⁸ and also influence the functional development of sensory systems in young animals²⁹. The notion of using test pulses to probe the biomechanical properties of the system bears similarities to impulse response analysis, which is used abundantly to characterize linear time-invariant systems, for example in control theory³⁰. MDSI in self-learning systems could potentially be of great value in applications related to the design of prosthetics and in robotics.

The present results, which identify the role of spontaneous

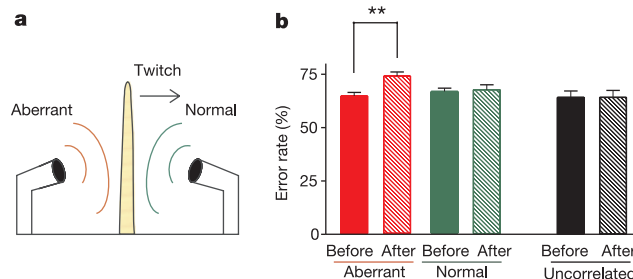


Figure 4 Behavioural experiments. **a**, Schematic training set-up depicting the aberrant and normal training protocols. **b**, NWR error rate before and after aberrant, normal or uncorrelated stimulation; results are means \pm s.e.m. The NWR error rate was significantly increased (** $P < 0.01$) in rats given aberrant tactile feedback (49 training

sessions); normal air-puff stimulation (54 training sessions) had no significant effect (Kruskal–Wallis and Dunnett's test). Controls with random air-puff stimulation (23 training sessions) or no stimulation (23 training sessions; not shown) did not affect NWR adaptation ($P = 0.65$ and $P = 0.37$, respectively; Wilcoxon signed-rank test).

movements in the functional adaptation of spinal sensorimotor systems, provide a key to the understanding of how these basic circuits can incorporate information about the individual's bodily constitution and thereby perform the remarkably complex computations needed for accurate motor output. Many sensorimotor systems could have this strategy in common. □

Methods

Computer simulation and model parameters

Simulations were implemented in MATLAB (MathWorks; see Supplementary Information for the program code). Movement patterns produced by the activation of five different muscles (peroneus longus (PL), peroneus brevis (PB), tibialis anterior (TA), gastrocnemius (G) and two subunits of the extensor digitorum longus with tendon insertions on digits 2 and 3 (EDL23) and digits 4 and 5 (EDL45), respectively) were represented in 28 × 61 matrices (597 of these matrix elements represented sites of the plantar skin and were used in the simulation, representing >1.5 pixels mm⁻² in an adult). The data were sampled by optical three-dimensional movement analysis yielding the velocity component perpendicular to the skin surface for 40–50 individual skin sites. Matrix values for intermediate sites were interpolated by spatial low-pass filtering⁶. These patterns were assumed to describe the pressure changes on the plantar skin in the hindlimb in standing position and consequently the pattern of afferent input from mechanoreceptors responding to skin pressure on muscle contraction. Quantified and normalized NWR receptive fields (intramuscular electromyographic recordings) of the muscles were obtained from previous studies⁶. For each learning epoch, muscles were activated at random with a specified probability. On co-activation of muscles, the withdrawal movement was approximated as the sum of the normalized withdrawal patterns of the individual activated muscles. The possible error in correlation coefficient caused by simple summation of movement patterns on co-activation was estimated to be less than 3.5% for a twitch probability per muscle of 0.045 (as calculated by using only the contaminating movement patterns on co-activation). The cutaneous feedback, which was represented on the same coordinates as the withdrawal efficiency, is conveyed by parallel afferents reaching 597 first-order interneurons in substantia gelatinosa (SG_i). These, in turn, act on six reflex-encoding deep dorsal-horn neurons (RE^k). Hence, 597 connection weights (w_{ij}^k) between substantia gelatinosa neurons and reflex encoders for each of the six modules were updated in each learning epoch. A total of 10,000 epochs was estimated to correspond roughly to the observed number of tail twitches during the adaptation period¹⁴. Oja's rule, Δw_{ij}^k = ηRE^k(SG_i - RE^kw_{ij}^k), where η is the learning rate, was used for synaptic weight adjustments (w_{ij}^k normalizes to w_{ij}^k ∈ [0, 1])^{19,20,23,24}. In MDSI, a learning epoch is initiated by a burst in the reflex-encoding neuron (RE^k ≠ 0). Parameter values in the simulation shown in Fig. 3a, c had the following settings: a learning rate of 0.008, a twitch probability per module for each epoch of 0.045 (resulting in ~1/4 of the epochs containing twitch activity in at least one of the six modules and ~11% co-activity), sensory noise ∈ [-0.5, 0.5] (±50% of maximum tactile input), and initial synaptic weights were randomly drawn from a uniform distribution U[-0.8, 0.8]. The model was effective within a relatively wide range of parameter values. Mean adult correlations of at least 0.8 were reached for η ∈ [0.0053, 0.043], twitching probability ∈ [0.03, 0.24] (yielding 7.5–55% co-activity), sensory noise ∈ [-3.9, 3.9] and initial synaptic weights drawn from U[-3.2, 3.2] if these parameters were altered one at a time. Using only the contaminating movement patterns on co-activation, 0.11 is the maximum twitch probability that still satisfies a mean adult correlation of more than 0.80.

In the simulation of unsupervised feedforward learning, learning occurs when the postsynaptic activity in the reflex-encoding neurons exceeds ~15% of the maximum response. Increasing the activation probability did not improve adult correlations. When activated, weight adjustments were performed exactly as in MDSI learning.

Animals used

Wistar rats (P12–P17) of both sexes (n = 84 from 13 litters) were used.

Conditioning stimulation

Spontaneous twitches were detected by an optical system consisting of a complementary metal-oxide semiconductor sensor camera (CCi4; C-Cam Technologies, acquisition rate ~180 images s⁻¹) with software written in LabVIEW 5.2 (National Instruments Corp.) on a PC. Twitches with a lateral deviation of the midsection of the tail more than 9.2 radians s⁻¹ (~0.28 m s⁻¹) after more than 300 ms of immobility triggered an air-puff directed to the side of the tail (Fig. 4a). These criteria were selected after a careful qualitative evaluation of the system's classification of different movement patterns. The air-puff had a peak pressure of ~20 kPa and stimulation latency from twitch initiation of ~40 ms at normal tail position. The time-point and direction of stimulation were stored by the system. Conditioning stimulation was given for 2–3 days per animal. The uncorrelated stimulation was given at random to either side of the tail. Trained animals did not differ from untrained animals of the same litter with regard to body weight or overall behaviour.

NWR testing

Every test included 10 stimulations (25-ms CO₂-laser pulses, 5 W, beam width 3 mm) to each side of the distal tail; the persons performing the analyses were blinded to the type of conditioning stimulation used. Response latencies were monitored in all NWR testing experiments; owing to the increase in animal size, the mean latencies increased from 156 to 179 ms during the P12–P17 period (mean of the s.e.m. = 2.1 ms), indicating C-fibre-

evoked reflexes. Only tail-tip movements of more than 0.02 radians (~1 mm) were considered. Data were discarded from the study (53 sessions) if the error rate was less than 20% or more than 80% before conditioning, to allow the detection of both improvements and deteriorations (mean of the s.d. within a given testing session ≈ 13%).

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Correspondence and requests for materials should be addressed to P.P. (per.petersson@mphy.lu.se).